

Clinical Outcomes of Gastric Cancer Patients Who Underwent Proximal or Total Gastrectomy: A Propensity Score-Matched Analysis

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Abstract

Background Total gastrectomy (TG) and proximal gastrectomy (PG) are used to treat upper-third early gastric cancer. To date, no consensus has been reached regarding which procedure should be selected. The aim of this study was to validate the usefulness of preserving the stomach in early upper-third gastric cancer.

Methods Between 2004 and 2013, 201 patients underwent PG or TG at our institution for treatment of upper-third early gastric cancer. According to the defined inclusion and exclusion criteria, 192 cases were enrolled in this study. One-to-one propensity score matching was performed to compare the outcomes between the two groups.

Results The operation time was shorter in the PG group. Although no significant difference was observed, the PG group had less bleeding and fewer postoperative complications. R0 resection rate was 100%, and no surgery-related deaths were observed. The frequencies of reflux symptoms and anastomotic stenosis were significantly higher in the PG group, but could be controlled by balloon dilation and drug therapy. The maintenance rates of body mass index and lean body mass were significantly higher in patients who underwent PG than TG. The total protein and serum albumin values were higher in the PG group than in the TG group and remained statistically superior.

Conclusion PG group exhibited better perioperative performance. Furthermore, better nutritional results were obtained in the PG group. Although the late stenosis and reflux symptoms must be addressed, the PG is a preferable surgical procedure for the treatment of early proximal gastric cancer.

Introduction

Despite a declining incidence in Western countries, gastric cancer remains the third most frequent cause of cancer-related deaths and the fifth most common type of malignancy worldwide [1, 2], and surgical resection is the mainstay of curative treatment. While its overall incidence appears to be decreasing, the frequency of cancers in the upper third of the stomach and the gastroesophageal

junction has been increasing in both Western and Asian countries [3–10].

Two surgical procedures, total gastrectomy (TG) and proximal gastrectomy (PG), are used to treat early-stage gastric cancer located in the upper stomach as the standard therapies [11–13]. To date, no consensus has been reached regarding which procedure should be selected, although several comparative analyses of TG and PG have been performed regarding postoperative disorders and nutritional benefits [14–18].

To date, no prospective randomized comparative study of the outcomes of PG and TG has been published. In clinical practice, performing a prospective randomized study to compare the outcomes between different surgical procedures is difficult. Propensity score matching (PSM)

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has been proposed as a method to overcome selection bias and increase the evidence level in observational non-randomized studies [19, 20]. Therefore, PSM analysis has been widely used to estimate the effects of exposure using observational data.

In our institute, TG has been routinely performed to treat early-stage proximal gastric cancer, and PG with esophagogastrotomy [21] has been performed only when more than half of the distal stomach can be preserved. In this study, we intended to compare the short- and long-term postoperative complications and nutritional outcomes between PG and TG and assess the advantages of both surgical procedures.

Materials and methods

Patients

Between 2004 and 2013, a total of 1563 gastric cancer patients were admitted to the Department of Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases. During this period, 201 patients who underwent PG or TG for clinical early-stage upper-third gastric cancer (cT1N0M0, Clinical Stage I) were identified in a retrospectively maintained database. TNM staging was based on the Japanese Classification of Gastric Carcinoma, 3rd English Edition [22]. The clinicopathological features of these patients were reviewed retrospectively using hospital records. Only PG patients who underwent esophagogastrotomy reconstruction (EG) were enrolled in this study, and only TG patients who underwent Roux-en-Y reconstruction were included in this study. The reasons for exclusion from PSM analysis were as follows: double tract reconstruction ($n = 5$), interposition reconstruction ($n = 2$), double tract reconstruction with another malignancy ($n = 1$), and a combined operation ($n = 1$). Finally, 43 PG and 149 TG patients were enrolled in this study. The clinical characteristics and short-term and long-term nutritional outcomes were compared between the PG and TG groups.

Surgical approach

All operations were performed with curative intent. All the cases were performed by open laparotomy with D1 + lymph node dissection, and preserved the celiac branch of vagal nerve. In the PG group, esophagogastrotomy anastomosis was performed using a circular stapler (diameter 25 mm) in an end-to-side EG at the anterior wall 2 cm from the lesser curvature and 3 cm from the top of the remnant stomach to function as the new fundus. After TG, esophagojejunostomy with a circular stapler (diameter

25 mm) was used routinely for Roux-en-Y reconstruction. Proximal and distal resection margins were evaluated intraoperatively to confirm freedom from disease in all patients.

Definitions and procedure of follow-up

We conducted follow-up examination in all cases for 1 month, 3 months, 6 months, 12 months after surgery, and then every half year. Blood tests and radiograph were taken at all outpatient visits. As a postoperative surveillance, we performed a computerized tomography once a year. In the PG group, gastroduodenal endoscopy (GDE) was performed once a year after surgery to eliminate residual gastric cancer. In the TG group, GDE for postoperative surveillance was not conducted. Additional GDE was performed to all patients who had gastrointestinal symptoms such as acid reflux and stasis. Reflux symptoms were evaluated using the Visick score at 6 months postoperatively under no medication, and reflux esophagitis was assessed using the Los Angeles (LA) classification [23, 24].

PSM analysis

PSM analysis was conducted using a logistic regression model and the following covariates: age, sex, American Society of Anesthesiologists physical status classification (ASA-PS), body mass index (BMI), tumor size, histology, and preoperative laboratory data (total lymphocyte count (TLC), total protein (TP), and serum albumin (ALB)).

Postoperative complications and nutritional outcomes

The clinical features (age, sex, performance status, ASA-PS, height, weight, BMI, tumor size, histology), postoperative early complications (0–30 days), postoperative late complications (after 30 days), nutritional status, body weight, body mass index (BMI), lean body mass (LBM), and laboratory data such as the TLC, TP, ALB, hemoglobin, and prognostic nutritional index (PNI) of patients were analyzed based on information gathered from retrospectively collected gastric cancer databases in our hospital. Anthropometric-based prediction equations such as the Deurenberg equation were used to calculate the LBM of patients [25]. The anthropometric-based prediction equations are shown below: $\text{Body fat (\%)} = (1.2 \times \text{BMI}) + (0.23 \times \text{Age}) - (10.8 \times \text{Sex}) - 5.4$ (Male = 1, Female = 0). All patients were followed for at least 36 months.

Statistical analysis

All statistical calculations were performed with JMP® PRO software (JMP version 13.1.0, SAS Institute, Cary, NC). The demographic and clinicopathological characteristics are summarized using descriptive analysis, and all qualitative values are presented as means and standard deviations unless otherwise specified. Student's *t* test or the Mann–Whitney *U* test and Pearson's χ^2 test were used to compare continuous and categorical variables, respectively. All values were two-tailed, and *P*-values < 0.05 were considered significant. We used a caliper width of 0.2 of the pooled standard deviation of the logit of the propensity score for PSM.

Results

Patient characteristics after PSM analysis

The study flowchart is summarized in Fig. 1. A total of 78 patients with upper-third early gastric cancer were included in the study; 39 patients were included in the PG group, and the remaining 39 patients were included in the TG group. The baseline characteristics of the PG and the TG groups are summarized in Table 1. No significant differences were observed between the two groups with respect to all the preoperative background. Because we studied only upper-third early gastric cancer in this study, it was possible to operate PG similarly for patients who performed TG. The mean duration of postoperative follow-up period was 36 months or more, and no significant difference between two groups (*P* = 0.41).

Short-term outcomes

The surgical outcomes of patients undergoing PG and TG are detailed in Table 2. In the comparison of surgical characteristics, the median operation time was shorter in the PG group than in the TG group (*P* < 0.001). No significant difference in blood loss was observed between the two groups (*P* = 0.182).

Surgical complications classified as Clavien–Dindo grade II or higher are described in Table 2. The postoperative 30-day mortality rate was 0%. Concerning early postoperative complications, more cases (10 cases, 25.6%) were observed in the TG group than in the PG group (4 patients, 10.3%), but the difference was not statistically significant. One patient in the PG group (2.6%) and three patients in the TG group (7.7%) had Clavien–Dindo class III or higher complications. One patient in the PG group had angina pectoris. In the TG group, one case of anastomotic leakage, one case of dehiscence due to pancreatic fistula and an abdominal abscess secondary to pancreatic fistula were observed, and two cases of wound dehiscence and suture failure required reoperation. Curative resection (R0) was performed in all patients.

Long-term outcomes

The long-term outcomes are detailed in Table 3. The rate of patients with late complications was 7.7% in the TG group and 25.6% in the PG group. The incidence rates of reflux esophagitis and anastomotic stricture were greater in the PG group than in the TG group. Postoperative GDE was performed in all cases in the PG group and in 9 patients with digestive symptoms in the TG group.

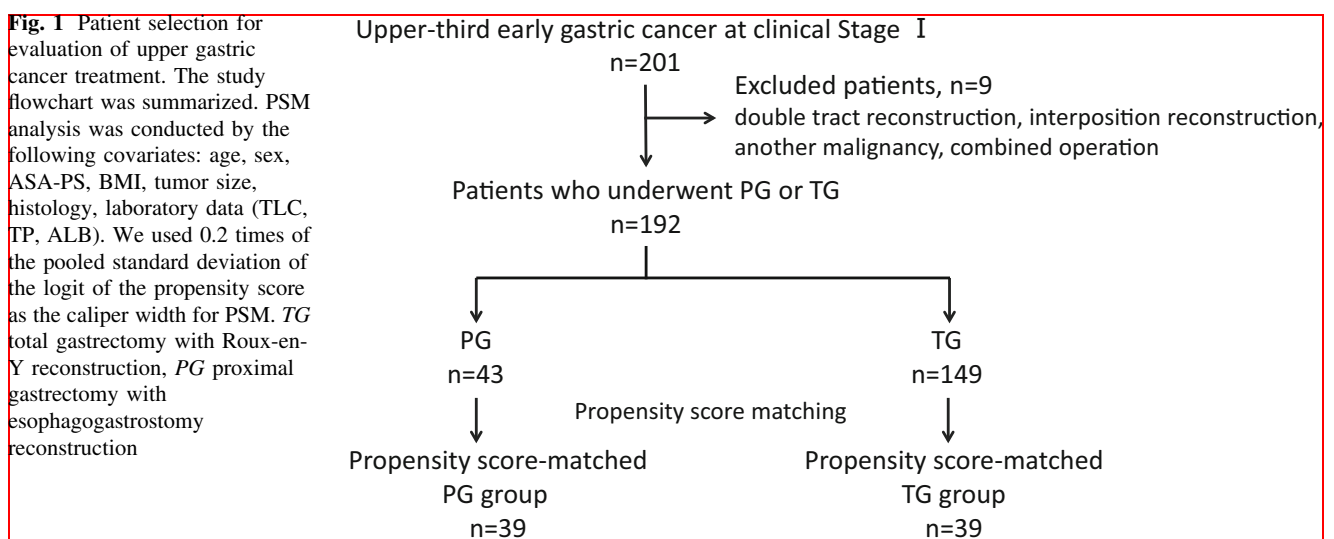


Table 1 Patient characteristics after PSM

	PG (<i>n</i> = 39)	TG (<i>n</i> = 39)	<i>P</i> value
Age	67 (44–83)	69 (34–83)	1.000
Sex (M:F)*	32 (82.1%):7(17.9%)	31 (79.5%):8 (20.5%)	0.774
PS (0:1:2)*	36 (92.3%):3 (7.7%):0 (0%)	36 (92.3%):3 (7.7%):0 (0%)	1.000
ASA-PS(1:2:3)*	17 (43.6%):21 (53.9%):1 (2.6%)	20 (51.3%):16 (41.0%):3 (7.7%)	0.374
Height (cm)	164.3 (148.7–181)	165 (145–180)	0.858
Weight (kg)	62 (45.3–79.5)	63 (43.9–82.4)	0.743
Body mass index (kg/m ²)	23.0 (18.3–28.0)	22.7 (16.6–30.9)	0.799
Lean body mass (kg)	45.5 (33.6–55.6)	45.8 (32.7–57.3)	0.860
Total lymphocyte count (cells/mm ³)	1865 (700–3368)	1898 (731–3326)	0.821
Serum total protein (g/dl)	7.0 (6.3–8.1)	7.0 (6.4–8.2)	0.836
Serum albumin (g/dl)	4.2 (3.5–4.8)	4.3 (3.2–5)	0.405
Serum hemoglobin (mg/dl)	14.0 (9.9–17.0)	13.8 (10.7–16.9)	0.611
Prognostic nutritional index	50.4 (38.6–61.4)	49.7 (42.2–55.9)	0.497
Clinical stage IA	39 (100%)	39 (100%)	1.000
Pathological stage (IA/IB/IIA)	34 (87.2%)/3 (7.7%)/2 (5.1%)	31 (79.5%)/4 (10.3%)/4 (10.3%)	0.618
Tumor size (mm)	25 (4.5–60)	25 (5–55)	0.852
Lauren classification (diffuse/intestinal)*	5 (12.8%)/34 (87.2%)	5 (12.8%)/34 (87.2%)	1.000

*Values are presented as medians (min–max) or number (%)

PG proximal gastrectomy; TG total gastrectomy; ASA-PS American Society of Anesthesiologists physical status classification

P = 0.05 was considered statistically significant

Table 2 Short-term outcomes after PSM

	PG (<i>n</i> = 39)	TG (<i>n</i> = 39)	<i>P</i> value
<i>Short-term outcomes</i>			
Operation time (min)*	214 (140–460)	263 (179–488)	<0.001*
Blood loss (ml)*	373 (150–1060)	420 (50–4200)	0.182
Early complications**	4 (10.3%)	10 (25.6%)	0.073
Clavien–Dindo > III	1 (2.6%)	3 (7.7%)	0.294
Anastomotic leakage	0	2 (5.1%)	0.152
Pancreatic fistula	0	2 (5.1%)	0.152
Bleeding	1 (2.6%)	0	0.314
Surgical site infection	2 (5.1%)	2 (5.1%)	1.000
Chylorrhea	0	1 (3.0%)	0.314
Reoperation	0	2 (5.1%)	0.152
Postoperative mortality	0	0	–
R0 resection	39 (100%)	39 (100%)	–

*Values are presented as medians (min–max) or numbers (%)

**Early complications describe Clavien–Dindo classification grade ≥ II

PG proximal gastrectomy; TG total gastrectomy

P = 0.05 was considered statistically significant

The presence or absence of reflux symptoms according to the Visick score was not significantly different between the two groups (*P* = 0.234). However, reflux esophagitis

classified as grade A or higher was observed in patients who underwent PG (9 cases, 23.8%) and TG (2 cases, 5.1%); this result was statistically significant (*P* = 0.019). Specifically, in 2 cases in the PG group and 1 case in the TG group, severe reflux esophagitis of LA classification C and D was observed, but no statistically significant difference was found (*P* = 0.556). Patients in the PG group (6 cases, 15.4%) suffered anastomotic stenosis more frequently than those in the TG group (1 case, 2.6%) (*P* = 0.038). The proportion of patients with anastomotic strictures requiring endoscopic balloon dilatation was significantly higher in the PG group than in the TG group (6/39, 18% vs. 1/39, 2.6%; *P* = 0.038). No cancer recurrence, including remnant gastric cancer, was observed in either the PG or TG groups.

Parameters of nutritional status

The body weight was significantly higher in the PG group than in the TG group at all observation points, as shown in Fig. 2a. The body weight in the TG group gradually decreased, but it gradually increased in the PG group after 6 months. The LBM was significantly lower in the TG group than in the PG group at all observation points (Fig. 2b). The rate of decrease in LBM was small compared to that in body weight. The rate of decrease was smaller in the PG group than in the TG group. No

Table 3 Long-term outcomes after PSM

	PG (n = 39)	TG (n = 39)	P value
<i>Long-term outcomes</i>			
Late complications	10 (25.6%)	3 (7.7%)	0.030 *
Severe esophagitis (LA classification C or D)	2 (5.1%)	1 (2.6%)	0.556
Stenosis	6 (15.4%)	1 (2.6%)	0.038 *
Ileus	2 (5.1%)	2 (5.1%)	1.000
Cholecystitis	0	0	–
Reflux symptoms	12 (30.8%)	6 (15.4%)	0.104
Visick score (I/II/III/IV)	0 (0%)/11 (28.2%)/1 (2.6%)/0 (0%)	0 (0%)/5 (12.8%)/1 (2.6%)/0 (0%)	0.234
Use of anti-reflux medicine	19 (48.7%)	0	<0.001*
Endoscopic balloon dilatation	6 (15.4%)	1 (2.6%)	0.038*
Recurrence	0	0	–
Follow-up	39 (100%)	39 (100%)	–

*Values are presented as medians (min–max) or numbers (%)

**Early complications describe Clavien-Dindo classification grade ≥ II

PG proximal gastrectomy; TG total gastrectomy; PPI proton pump inhibitor

P = 0.05 was considered statistically significant

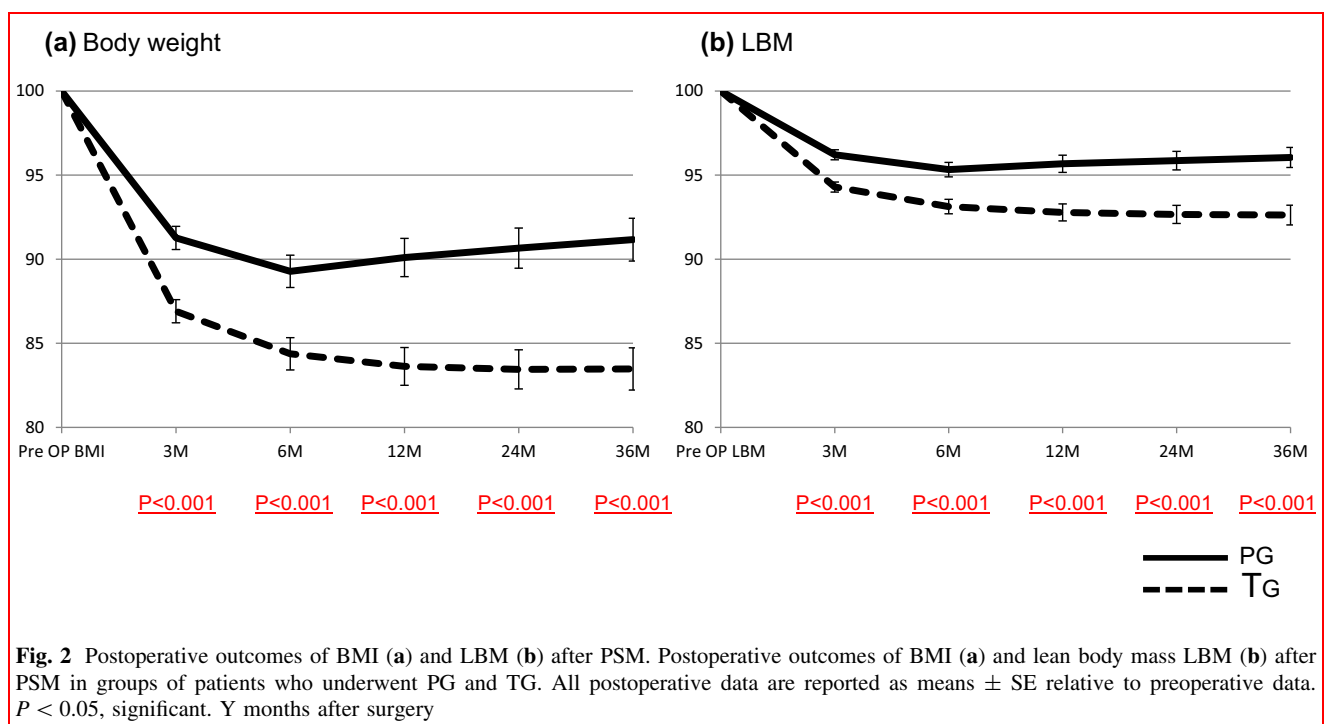


Fig. 2 Postoperative outcomes of BMI (a) and LBM (b) after PSM. Postoperative outcomes of BMI (a) and lean body mass LBM (b) after PSM in groups of patients who underwent PG and TG. All postoperative data are reported as means ± SE relative to preoperative data. P < 0.05, significant. Y months after surgery

difference was observed between the two groups regarding the TLC after surgery (Fig. 3a). The changes in TP and serum ALB levels showed similar tendencies (Fig. 3b, c). A significant decrease in TP was observed in the TG group within 1 year after surgery, and no significant differences were observed at other observation points after 1 year (Fig. 3b). A significant decrease in the ALB level was observed in the TG group only at 3 months after surgery,

and no significant differences were observed at other observation points. The PNI showed a similar trend to the ALB level (Fig. 3c). The serum hemoglobin level decreased in both groups immediately after surgery (Fig. 3d). Specifically, the value was lowest at 3 months after surgery; thereafter, it gradually recovered. The recovery rate was small in the TG group and roughly leveled off; however, the level in the PG group gradually

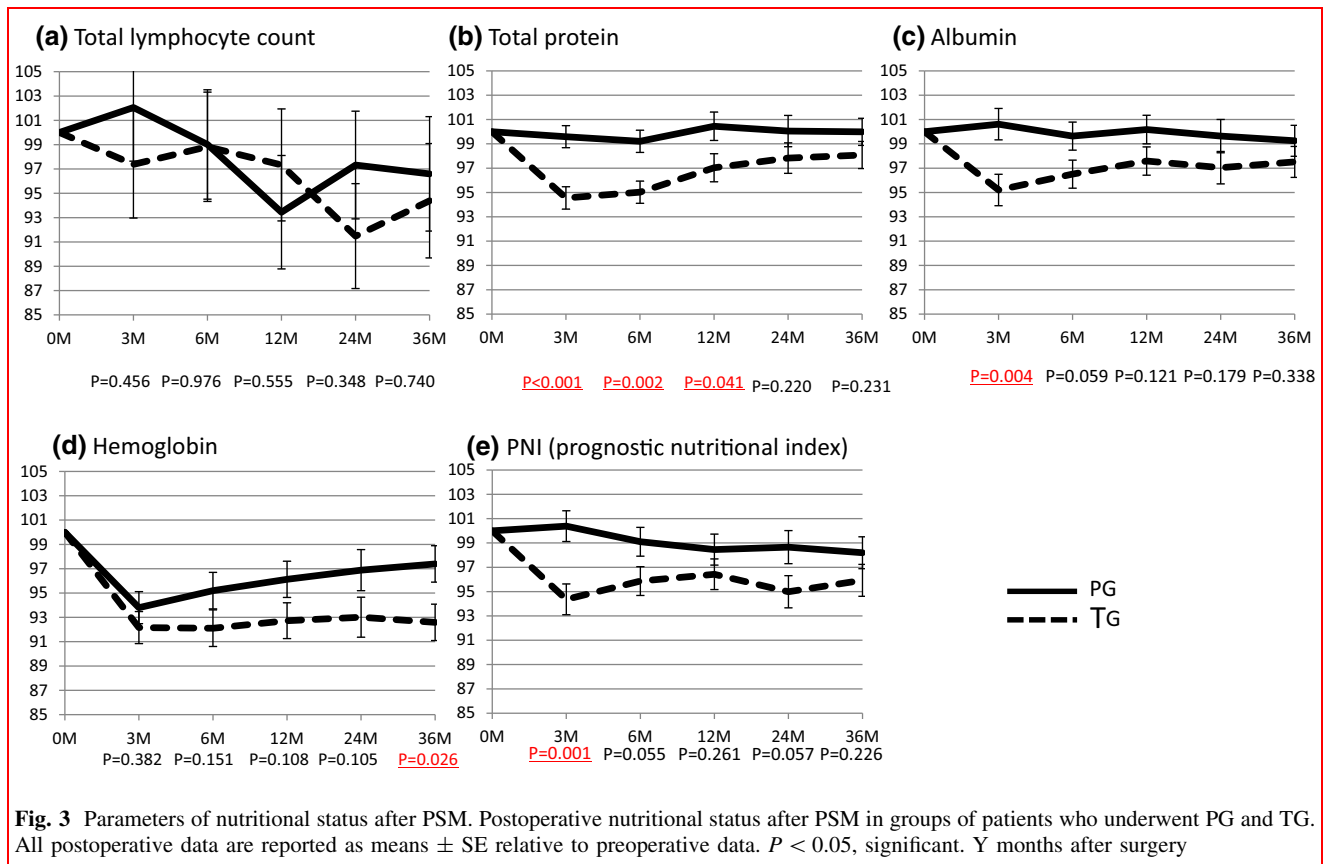


Fig. 3 Parameters of nutritional status after PSM. Postoperative nutritional status after PSM in groups of patients who underwent PG and TG. All postoperative data are reported as means \pm SE relative to preoperative data. $P < 0.05$, significant. Y months after surgery

increased, but 36 months after the operation, the recovery rate had not returned to the preoperative level. A significant difference was found only at 36 months after the operation in the PG group. Focus on PNI, a significant difference was observed only at 3 months after surgery, but no significant difference was noted after 6 months (Fig. 3e).

Discussion

The superiority of PG or TG during the perioperative period is controversial. Huh et al. [15] reported that patients who underwent PG suffered fewer complications after surgery than those who underwent TG. Other studies have reported that the TG procedure required an obviously longer operation time and caused greater intraoperative blood loss [17, 18, 26]. However, PG procedures involved a higher risk of late complications such as reflux symptoms and anastomotic stenosis. An et al. [14] reported rates of esophagogastric anastomosis-site stricture and reflux esophagitis of 38.2 and 29.2% after PG, respectively. Although we cannot perform a simple comparison because the PG group included various reconstruction methods, Masuzawa et al. [27] reported that both a bloated feeling (PG vs. TG 16.3 vs. 2.5%) and heartburn (PG vs. TG 18.4

vs. 11.5%) were more frequent in the PG group than in the TG group. Furthermore, others have concluded that reflux symptoms after PG were worse than after TG, and PG should be avoided for adenocarcinoma of the gastric cardia, except for early-stage cancer [28]. In this study, the PG procedure had an obviously lower risk of Clavien–Dindo class III or higher surgical complications. The operation time was significantly shorter in the PG group than in the TG group. R0 resection could be performed, and the postoperative mortality rate was 0% in all patients. Of the 39 patients who underwent PG, 23.1% suffered from dysphagia due to gastroesophageal anastomotic stenosis, and 30.8% presented with epigastric soreness and reflux esophagitis diagnosed by endoscopy. These rates were similar to or slightly lower than those in previous reports. After TG, stenosis of esophagojejunostomy and reflux esophagitis occurred in only 5.1 and 15.4% of patients, respectively. Endoscopic balloon dilatation could effectively manage anastomotic stenosis in most patients, which is consistent with other reports [29, 30], and reflux symptoms were relieved by medication such as proton pump inhibitors.

In the postoperative nutritional evaluation, differences were found among the two treatment groups in terms of postoperative transitions. The laboratory data related to

nutritional evaluation were generally good in the PG group. Specifically, body weight changes are a matter of grave concern after gastrectomy, and difficulty in maintaining body weight is a defining characteristic of post-gastrectomy syndrome. However, a change in body weight is an indicator of nutritional status in patients that can be easily evaluated [31]. Additionally, LBM is associated with immunity and quality of life, and a decrease of 5% or more after gastrectomy leads to increased drug toxicity such as that produced by adjuvant chemotherapy [32, 33]. Previous studies have reported that PG offers no advantage over TG in terms of weight preservation [14, 18]. However, Son et al. [34] reported that the PG group had a higher body weight than the TG group at the 2-, 3-, and 5-year post-operative follow-up evaluations, and the PG group showed an increasing tendency, whereas the TG group showed a decreasing tendency. In this PSM study, the PG group had a significantly lower weight loss rate than the TG group. Likewise, LBM was low in the PG group, and a decrease of 5% or more, which is said to be particularly high with regard to drug toxicity, was not observed in the PG group.

The present study has several limitations. First, the analysis was based on retrospective data collected at a single institution. Due to the retrospective nature of this study, a selection bias existed between the PG and TG groups. To reduce this bias as much as possible, statistical analysis was performed using PSM. Second, the study did not include assessments of patient symptoms or quality of life using validated questionnaires after surgery. Third, only the Visick score and LA classification were used for grading postoperative esophageal reflux. Therefore, a precise comparison may not have been performed between the two groups. Although some limitations were present, no RCT comparing PG and TG has been published, and by conducting the statistical analysis using PSM, the data could be rigorously examined and compared with past studies.

In conclusion, the PG group exhibited better perioperative performance than the TG group. Furthermore, better nutritional results were obtained in the PG group than in the TG group. Although late complications such as reflux and stenosis were observed in the PG group, they could be well managed by balloon dilation or drug administration. Therefore, this study provides important baseline data on the use of PG for minimally invasive treatment and functional maintenance of early-stage gastric cancer.

Compliance with ethical standards

Conflict of interest Drs. Yuki Ushimaru, Yoshiyuki Fujiwara, Yuji Shishido, Yoshitomo Yanagimoto, Jeong-Ho Moon, Keijiro Sugimura, Takeshi Omori, Hiroshi Miyata, and Masahiko Yano have no conflicts of interest or financial ties to declare.

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