Proximal gastrectomy with anti-reflux anastomosis for patients with adenocarcinoma of the esophagogastric junction: The simple and safe triangle-valve technique

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Abstract. A simple and safe triangle-valve technique (TVT) was applied in proximal gastrectomy (PG) in order to prevent postoperative gastric reflux among patients with adenocarcinoma of the esophagogastric junction (AEG). The clinical outcomes were evaluated in comparison to those of canonical total gastrectomy (TG). This retrospective study of 74 AEG patients compared two surgical procedures, PG-TVT (n=44) and TG (n=30), in terms of surgical outcomes, postoperative complications and nutritional status. The Reflux Disease Questionnaire (RDQ) was used to evaluate reflux esophagitis, and patients with an RDQ score of ≥12 points were diagnosed with gastroesophageal reflux disease (GERD). The mean operative time was significantly shorter in the PG-TVT group (242.6 min) compared with that in the TG group (288.1 min). The overall postoperative complication rate did not differ significantly between the PG-TVT and TG groups. All the patients were followed up for 6 months, and none developed cancer recurrence in distant organs, gastric remnant, or lymph nodes. The GERD incidence was similar between the PG-TVT and TG groups. The mean levels of total protein and albumin within 6 months were significantly higher in the PG-TVT group compared with those in the TG group after adjustingtthe time effect and the interaction of time and surgical methods. The level of total protein significantly increased within 6 months in the PG-TVT group, but decreased in the TG group. Therefore, PG-TVT has several advantages over TG for patients with AEG, including a shorter operative time and better postoperative nutritional status, whereas the incidence of GERD was found to be similar between the two techniques.

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Introduction

Adenocarcinoma of the esophagogastric junction (AEG), an entity distinct from non-cardiac gastric cancer, is defined as a type of cancer located within 2 cm proximal and distal of the anatomical cardia (1). In recent decades, there has been a notable increase in the incidence of AEG, not only in Western (2,3), but also in Asian countries (4-6). In China, a significantly increasing trend in the incidence of AEG was reported from 1988 to 2013 in a population-based study, while the incidence of non-cardiac gastric cancer decreased (7).

Although Siewert and Stein proposed an AEG classification system, including types I-III, to aid clinicians in deciding on the surgical approach (8), the surgical strategies for AEG cases remain controversial. Total gastrectomy (TG) is considered as a standard procedure, with the benefits of sufficient resection margins and more radical lymphadenectomy (9). Some recent studies have reported that proximal gastrectomy (PG) achieves survival rates equivalent to those of TG, while preserving the physiological functions of the gastric remnant (10-14). However, others questioned whether the advantages of PG outweigh the functional drawbacks of esophageal reflux, which markedly affects the quality of life of the patients (15,16), as several reconstruction methods after PG, including esophagogastrostomy and jejunal interposition, may carry a high risk of reflux esophagitis and gastroesophageal anastomotic stenosis (16-20). Hayami *et al* applied a novel double-flap technique, invented by Kamikawa *et al* (21), to laparoscopic proximal gastrectomy (LPG-DFT) in order to prevent reflux. Their results indicated

that LPG-DFT is a better surgical procedure for upper-third early gastric cancer compared with laparoscopic TG in terms of morbidity, postoperative hospital stay and postoperative nutritional status (22). In addition, Tanioka *et al* indicated that LPG may be more beneficial compared with laparoscopic TG (LTG) in terms of perioperative and nutritional outcomes for early-stage gastric cancer (23). However, the operative time was significantly longer in the LPG-DFT group due to the complexity of valvuloplasty, which requires masterful intracorporeal suturing.

The aim of the present study was to investigate a simple and safe anti-reflux anastomosis technique, the triangle-valve technique (TVT), in PG. This valve technique was designed to prevent reflux. It was hypothesized that the TVT may be time-saving due to its easiness and simplicity and, if the clinical outcomes of PG-TVT and TG were found to be comparable in terms of postoperative complications, PG-TVT may improve their nutritional status by conserving half of the stomach.

Materials and methods

Patients. A total of 74 patients with AEG (Siewert II or III) were recruited consecutively at the First Affiliated Hospital of Zhengzhou University between July 2013 and December 2017. From May 2015 to December 2017, PG-TVT was performed on 44 patients with a clinical diagnosis of $T_{1-4}N_{0-3}M_0$ AEG at the preoperative evaluation according to the 8th edition of American Joint Committee on Cancer-TNM Staging System of Gastric Carcinoma (24). A total of 30 patients with $T_{1-4}N_{0-3}M_0$ AEG located in or involving the upper third of the stomach who received TG between July 2013 and December 2015 were considered as the control group. Between January 2016 and January 2017, TG was also performed in a further 17 patients with the same indications as in the previous period. However, the latter period was not included, as the number of TG-TVT cases had gradually increased during that period. Certain settings, including the surgeon's preference in relation to adopting the procedure, had been taken into consideration to avoid selection bias. All the procedures were performed by the same surgical team.

All the patients were in stable condition and were considered as operable. Written informed consent was obtained from each patient. This was a retrospective study using clinicopathological, surgical and follow-up data, and the study protocol was approved by the Institutional Review Board at the First Affiliated Hospital of Zhengzhou University (Zhengzhou, China).

Surgical procedure of PG and PG-TVT reconstruction. Lymph node dissection was performed laparoscopically and the TVT reconstruction was performed with an open technique. The detailed surgical procedure of PG and PG-TVT reconstruction is described below (Fig. 1). After lymph node dissection is completed, the first step of the procedure is to locate the tumor lesion and determine the area of resection, including upper (G1) and lower (G2) resection margins. As shown in Fig. 1A, an example of a primary tumor lesion (indicated by the white circle) located along the lesser curvature is used to present the resection region with the G1 and G2 margins at a distance of no less than 2 and 5 cm, respectively, from the tumor. The aforementioned distances are measured on the tension-free gastric body. Based on the after-mentioned estimation of the resection area, the upper resection line is defined with cutting line G1 (black), and then a lower resection line is defined with the first cutting line L1, which was perpendicular to the greater curvature, and the second cutting line L2, which is at an angle of 30˚ relative to L1 (both indicated with white dotted lines; Fig. 1B). The crossing point of line L2 on the lesser curvature must be no less than 8 cm from the pyloric sphincter. Consequently, a solid linear path of L1 and L2, as shown in Fig. 1B, indicates the lower resection line. A proximal gastrectomy is then performed along the aforementioned solid linear path with a linear cutting closure (Fig. 1B). Third, as shown in Fig. 1C, on the exposed flattened side of the remnant gastric body, a curved line (yellow continuous line) is drawn 2 cm from the greater curvature, with 3 parallel lines (red dotted lines, 2 cm from each other) perpendicular to it. The midpoints of those three parallel lines are marked with yellow dots (Fig. 1C). A similar curved line, three parallel lines and midpoints are also marked on the posterior side of the remnant gastric body (not shown in the figure). Then, three stitches are made along these midpoints on both sides (Fig. 1D), so that the gastric wall between those midpoints of both sides will be folded towards the gastric cavity to form a triangle-valve shaped bulge when those sutures are knotted (Fig. 1E and F). Finally, the distal gastric remnant is anastomosed to the esophageal end through point H (Fig. 1E). The triangle valve-shaped bulge (Fig. 1F) functions similarly to the cardia as an anti-reflux mechanism.

Surgical procedure of TG and Roux-en-Y (R-Y) reconstruction. Radical TG was performed following the Japanese gastric cancer treatment guidelines (25). The resection distance from the upper and lower margins of the tumor was ≥2 cm, and D2 lymph node dissection was ensured (26,27). After that, Roux-en-Y reconstruction was completed (28). The jejunum was separated 20 cm below the ligament of Treitz and esophageal-distal jejunal anastomosis was performed. subsequently, the proximal jejunum was anastomosed with the distal jejunum 40 cm below the esophagojejunal anastomosis.

Clinical parameters and surgical outcomes. The patients' clinical characteristics, including age, sex, body mass index (BMI), Siewert type, tumor size, histological type, pathological TNM stage, history of abdominal surgery, preoperative chemotherapy and postoperative adjuvant chemotherapy, were obtained from their medical records. Surgical parameters, such as operative time, estimated blood loss, laparoscopy assistance, extent of lymph node dissection, number of retrieved lymph nodes, residual tumor (R), postoperative complications and postoperative hospital stay, were also retrieved from the medical records.

Follow-up and postoperative nutritional status. All the patients were followed up for 6 months. The Reflux Disease Questionnaire (RDQ) was used to evaluate reflux esophagitis. Information on the frequency and severity of upper gastrointestinal symptoms (heartburn, regurgitation and non-cardiogenic chest pain) were obtained in the 6 months after surgery. Patients with RDQ scores of ≥12 points were

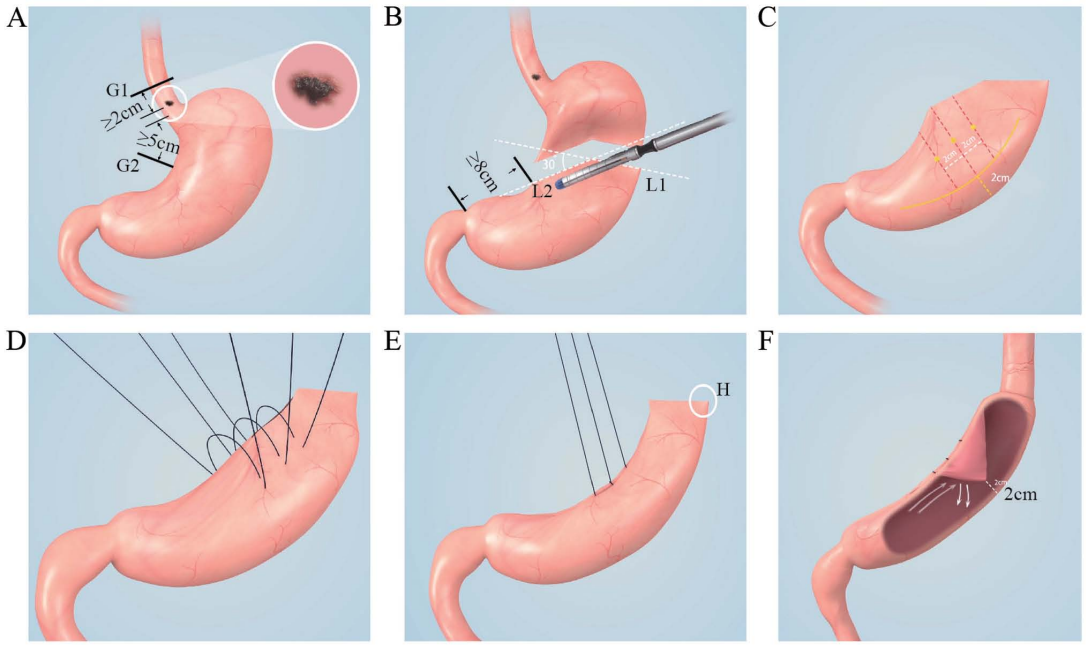

Figure 1. Schematic illustration of reconstruction using proximal gastrectomy with triangle-valve technique. (A) An example of a primary tumor lesion. (B) Resection of the proximal stomach. (C) Marking suture point. (D) Three stitches are made along these midpoints on both sides. (E) A triangle-valve shaped bulge when those sutures are knotted. (F) The triangle valve-shaped bulge functions similarly to the cardia as an anti-reflux mechanism.

diagnosed with gastroesophageal reflux disease (GERD) (29). To evaluate postoperative nutritional status, changes in body weight and biochemical data, such as serum concentrations of total protein (TP), albumin (Alb), hemoglobin (Hb) and prealbumin (PA), were examined at 7 days and at 6 months after surgery.

Statistical analysis. Categorical variables were compared by using the χ^2 test or Fisher's exact test, and continuous data were compared by using the Student's t-test or Mann-Whitney U test. Postoperative changes in weight, TP, Alb, Hb and PA were compared using repeated measures ANOVA and the Least-Significant Difference method was used for pairwise comparisons. All analyses were conducted using RStudio software (version 1.1.456, 2009-2018 RStudio Inc.). All statistical tests were two-sided, and $P<0.05$ was considered to indicate statistically significant differences.

Results

Patient characteristics. The characteristics of the patients are listed in Table I. There were no significant differences in age, sex, BMI, previous abdominal operations, Siewert type, histological type, pathological TNM stage, preoperative and postoperative chemotherapy between the two groups. The median tumor size was significantly larger for patients with TG (4.6 cm) compared with those undergoing PG-TVT (3.5 cm).

Surgical outcome. The operative and early postoperative outcomes of patients undergoing PG-TVT and TG are shown in Table II. The mean operative time was significantly shorter in the PG-TVT group (242.6 min) compared with that in the TG group (288.1 min). There was no significant difference in the estimated blood loss, transfusion, laparoscopy assistance, extent of lymph node dissection or the number of retrieved lymph nodes between the two groups. R0 resection was performed in all patients and no fatalities were recorded. The overall postoperative complication rate did not differ significantly between the PG-TVT and TG groups (22.7 vs. 20.0%, respectively; P=1.000), including the frequency of anastomotic complications, infection and lymphatic fistula. The mean postoperative hospital stay of the patients was shorter in the PG-TVT group (16 days) compared with that in the TG group (17 days), but the difference was not statistically significant.

Follow-up and postoperative nutritional status. All the patients were followed up for 6 months. None of the patients developed cancer recurrence in distant organs, gastric remnant, or lymph nodes. As regards the incidence of GERD within 6 months after PG-TVT and TG, GERD was observed in 7 of the 44 PG-TVT patients (15.9%), compared with 4 of the 30 TG patients (13.3%), but the difference was not statistically significant (P=1.00).

The mean weight loss of the patients at 6 months was 1.9 kg in the TG group and 2.0 kg in the PG-TVT group, but the difference was not statistically significant (P=0.743, data not shown). The means of Hb, Alb, TP and PA at 3 timepoints (pre-operatively, and at 1 week and 6 months postoperatively) in the PG-TVT and TG groups are shown in Fig. 2. Adjusting the time effect and interaction of time and surgical methods, the mean levels of TP and Alb in 6 months were significantly higher in the PG-TVT compared with those in the TG group. Furthermore, the level of TP was significantly increased at 6 months in the PG-TVT group and decreased in the TG group. The mean levels of Hb and PA at 6 months were also higher in the PG-TVT group compared with those in the TG group, but the difference was not statistically significant. As shown in Fig. 2, the levels of all the biomarkers decreased after surgery,

Table I. Characteristics of the study population.

Characteristics	PG-TVT (n=44)	TG (n=30)	P-value[a]
Age (years)	64 (45-79)	62 (37-77)	0.574
Sex (male/female)	35/9	28/2	0.182
BMI (kg/m^2)	23.8 (17.3-28.4)	24.5 (19.8-29.0)	0.216
Siewert (II/III)	27/17	16/14	0.655
Preoperative chemotherapy			0.336
Yes	5 (11.4)	6 (20.0)	
No	39 (88.6)	24 (80.0)	
Previous abdominal surgery			0.336
Yes	5 (11.4)	6 (20.0)	
No	39 (88.6)	24 (80.0)	
Tumor size (cm)	3.5 (0.6-10.0)	4.6 (1.0-10.0)	<0.001
T stage[b]			0.095
T1	13 (29.5)	3 (10.0)	
T2	8 (18.2)	5 (16.7)	
T3	7 (15.9)	3 (10.0)	
T4	16 (36.4)	19 (63.3)	
N stage[b]			0.507
N0	27 (61.4)	20 (66.6)	
N1	5 (11.4)	2 (6.7)	
N2	5 (11.4)	6 (20.0)	
N3a/N3b	7 (15.8)	2 (6.7)	
M stage[b]			1.000
M0	44 (100.0)	30 (100.0)	
Proximal resection margin, cm	4.6 (2.5-10.0)	4.9 (2.0-10.0)	0.796
Distal resection margin, cm	7.4 (2.5-10.5)	7.0 (2.0-15.0)	0.093
Histological grading			1.000
Well-differentiated	6 (13.6)	4 (13.3)	
Moderately differentiated	21 (47.7)	14 (46.7)	
Poorly differentiated	17 (38.6)	12 (40.0)	
Postoperative adjuvant chemotherapy			0.210
Yes	28 (63.6)	24 (80.0)	
No	16 (36.4)	6 (20.0)	

[a]t-test, Mann-Whitney U test, Fisher's exact test, or χ^2 test; [b]According to the 8th edition of the American Joint Committee on Cancer TNM Staging System of Gastric Carcinoma. Values are expressed as n (%) or mean (range). PG-TVT, proximal gastrectomy with triangle-valve technique; TG, total gastrectomy; BMI, body mass index.

but gradually increased over 6 months in the PG-TVT group. However, the levels of all the biomarkers, with the exception of Alb, decreased over 6 months in the TG group. Detailed information is provided in supplementary Table SI.

Discussion

In the present study, the operative time for PG-TVT was markedly shorter compared with that for TG. The nutritional status of patients in the PG-TVT group was superior to that of the TG group. There were no significant differences between the two groups in the frequency of complications, including reflux esophagitis, and the postoperative weight loss at 6 months. Thus, PG-TVT achieved a good clinical result in patients with AEG.

PG for patients with AEG is controversial. Important considerations include curability and prognosis related to the surgical treatment, as well as the development of complications and postoperative quality of life. It was widely believed that PG reduces postoperative weight loss (11) due to conserving half of the stomach and achieves survival rates equivalent to those of TG (30). The reported incidence of anastomotic leakage was 1.5-7.4% and that of stricture 3.4-21.2% after gastrectomy (31,32). In the present study, the incidence of leakage and stricture were also in this range. However, several studies reported that PG was associated with a markedly

Table II. Surgical outcomes of patients undergoing PG-TVT and TG.

Characteristics	PG-TVT (n=44)	TG (n=30)	P-value[a]
Operative time (min)	242.6±55.3 (85-355)	288.1±58.3 (210-470)	0.002
Estimated blood loss (ml)	239±208 (50-1200)	297±214 (100-1000)	0.100
Transfusion			
Yes	2 (4.5)	4 (13.3)	0.215
No	42 (95.5)	26 (86.7)	
Laparoscopy assistance			
Yes	41 (93.2)	24 (80.0)	0.146
No	3 (6.8)	6 (20.0)	
Lymph node metastasis			
Positive	27 (61.4)	20 (66.7)	0.826
Negative	17 (38.6)	10 (33.3)	
No. of retrieved lymph nodes	32±13 (9-70)	36±17 (18-87)	0.585
R0 resection	44 (100)	30 (100)	
Morbidity	10 (22.7)	6 (20.0)	1.000
Anastomotic complications	9 (20.5)	5 (16.7)	
Bleeding	2 (4.5)	2 (6.7)	
Leakage	3 (6.8)	1 (3.3)	
Stricture	4 (9.1)	2 (6.7)	
Infection	1 (2.3)	0 (0)	
Lymphatic fistula	0	1 (3.3)	
Mortality	0	0	
Postoperative hospital stay (days)	16±7 (8-41)	17±7 (8-36)	0.663

[a]Mann-Whitney U test, or Fisher's exact test. Values are expressed as n (%) or mean ± standard deviation (range). PG-TVT, proximal gastrectomy with triangle-valve technique; TG, total gastrectomy; BMI, body mass index.

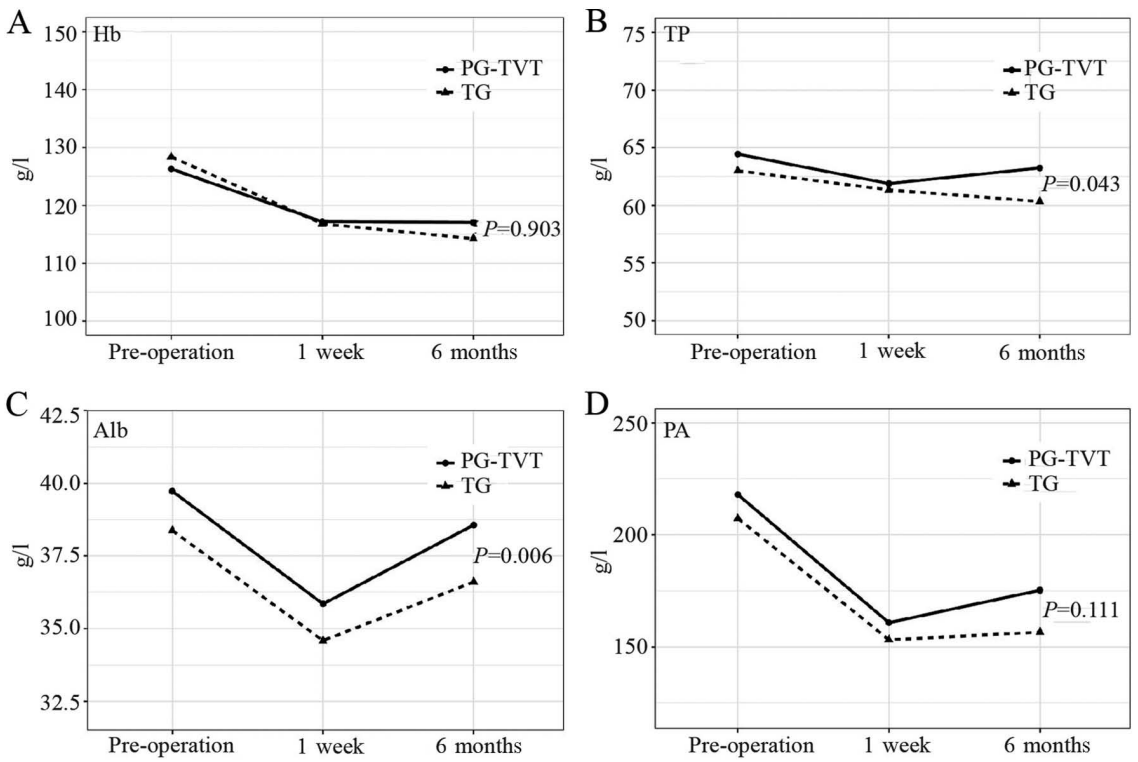

Figure 2. Comparison of changes in nutritional parameters between PG-TVT and TG. (A) Hb, (B) TP, (C) Alb, (D) PA. Hb, hemoglobin; TP, total protein; Alb, albumin; PA, pre-albumin. PG-TVT, proximal gastrectomy with triangle-valve technique; TG, total gastrectomy.

higher complication rate and the functional drawbacks of gastroesophageal reflux, which substantially affects the quality of life, compared with the TG (16-20). However, the postoperative morbidity of the PG-TVT group did not differ from that of the TG group in the present study.

The most common reported problem after PG is reflux. Kim *et al* reported the rate of reflux esophagitis at 48% after PG (33), and Katsoulis *et al* reported that 100% of patients experienced reflux symptoms after PG (15). In a recent study, Hayami *et al* reported no severe reflux esophagitis observed after the novel double-flap technique, LPG-DFT (22). In the LPG-DFT procedure, valvuloplasty preserves the backflow prevention valve embedded between the submucosal layer and the seromuscular flap of the stomach. However, due to the complex valvuloplasty, it demands masterful intracorporeal suturing and the operative time was notably longer compared with that of the TG.

In the present study, TVT was applied in PG, and no patients developed reflux esophagitis in the PG-TVT group in 6 months of follow-up, compared to 3 patients in the TG group. TVT was designed based on the anti-reflux principle. The stomach wall on the side of the lesser curvature was sewed into the stomach to form a triangular valve, resembling the cardia, which prevents gastric juice reflux through the narrow threshold. When the stomach is dilated, the valve resembles a peaked hillock, which has anti-reflux function. When the gastric fluid flows upwards, according to physics principles, the collision with the peak generates a vortex phenomenon, which greatly reduces the reflux and also prevents the gastric juice from irritating the relatively fragile anastomotic region. The procedure of TVT is simple and easy to perform, and does not demand complex suturing skills; therefore, the operative time for PG-TVT was markedly shorter compared with that for TG.

In terms of the nutritional status, the postoperative levels of TP and Alb were significantly higher in the PG-TVT compared with those in the TG group. No significant difference in Hb and PA was observed between the two groups. However, the Hb level increased slightly within 6 months in the PG-TVT group and decreased in the TG group, which is one of the benefits of the presence of the gastric remnant. The levels of several hormones, such as ghrelin and gastrin, decrease after gastrectomy (34,35). However, the reduction in the serum levels of vitamin B12 and these hormones is less notable in the PG-TVT group. In addition, the patients' appetite improves due to the lower incidence of GERD. These results indicate that PG-TVT had important advantages compared with TG. Tanioka *et al* also suggested that LPG may be more beneficial compared with LTG in terms of perioperative and nutritional outcomes for early-stage gastric cancer (23).

Although weight loss and other biomarkers did not differ significantly between the two groups, there was a positive trend observed in the PG-TVT group. These results are consistent with those of other studies (22). However, as the patients were only followed up for 6 months in the present study, long-term follow-up evaluation is also required.

There were certain limitations to the present study. First, this was a retrospective study with a small sample size that was conducted in a single institution. However, the two operative procedures were performed by the same surgical team in the same institution. Clinicopathological and treatment factors, Siewert type, degree of lymph node dissection and the degree of lymph node involvement were similar between the two groups studied. Thus, the bias from patients and surgeons were minimized. Second, a randomized clinical trial with equivalent background characteristics among the reconstructions after PG is required to further analyze the advantages of PG-TVT. Third, as shown in Table I, the maximum proximal resection margins for both operations were 10 cm. The reason for this is that the actual measurements demonstrated that the length of the lesser curvature was ~22-28 cm, and the length of the greater curvature was ~25-32 cm. The center of Siewert III AEG is located 2-5 cm below the dentate line. If the upward infiltration distance of the tumor is not long, the resection distance of the upper margin may be 10 cm, provided that sufficient residual stomach (lesser curvature ≥10 cm) and a safe resection distance of the upper margin are ensured. Another limitation was the relatively short follow-up time. A longer follow-up period and more nutritional indices should be included in future analyses.

In conclusion, PG-TVT has several advantages over TG for patients with AEG, including a shorter operative time, better postoperative nutritional status, with a similar incidence of GERD. Further randomized clinical trials with a larger sample size are required to fully investigate the comparative benefits of PG-TVT. In addition, further evaluation of the patients' quality of life and survival analysis compared with that after traditional TG should be performed in future studies.

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Availability of data and materials

The datasets generated and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

JS and YG performed the surgical procedures and wrote the manuscript. YZ helped to analyze the data. YG, JS, YC, YZ, PC, LZ, JHu, JHa and XC designed this study. YC performed a linguistic review and editing of the manuscript. All the authors have read and approved the final manuscript.

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University. All clinical samples were obtained from patients who had provided written informed consent.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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