Systematic Review and Meta-Analysis

Medicine®

OPEN

Proximal versus total gastrectomy for proximal early gastric cancer

A systematic review and meta-analysis

Yixin Xu, MD, Yulin Tan, MD, Yibo Wang, MD, Cheng Xi, MD, Nianyuan Ye, MD, Xuezhong Xu, MD*

Abstract

Background: Recently, the incidence of proximal early gastric cancer (EGC) has been rising rapidly. Prevalent surgical methods are proximal gastrectomy (PG) and total gastrectomy (TG); however, which method is superior remains controversial. We conducted a systematic review and meta-analysis of original articles to compare the short- and long-term clinical outcomes of PG with TG for proximal EGC.

Methods: Databases, including PubMed, Embase, Web of Science, and Cochrane Library were searched up to October 2018. The Newcastle-Ottawa scale was utilized to conduct quality assessments, and publication bias was evaluated using Egger test. STATA version 14.0 was used to perform the meta-analysis.

Results: A total of 2036 patients with proximal EGC in 18 studies were included in the meta-analysis. The results showed that PG was potentially superior to TG regarding operation time, intraoperative blood loss volume, and long-term nutritional status. Overall survival between the PG and TG groups was not significantly different. PG was associated with a high incidence of 2 kinds of postoperative complications: anastomotic stenosis and reflux esophagitis. However, the incidence of these complications associated with esophagojejunostomy with double-tract reconstruction (DTR) was comparable with that of TG.

Conclusions: PG has several advantages over TG for the treatment of proximal EGC, including surgical outcomes and long-term nutritional status. However, anastomotic stenosis and reflux esophagitis frequently occurred in patients undergoing PG. Esophagojejunostomy with DTR could offer a solution to reducing the incidence of these complications.

Abbreviations: CI = confidence interval, DTR = double-tract reconstruction, EGC = early gastric cancer, EJ = esophagojejunostomy, EMR = endoscopic mucosal resection, ESD = endoscopic submucosal dissection, GJ = gastrojejunostomy, HR = hazard ratio, JJ = jejunojejunostomy, NOS = Newcastle-Ottawa Scale, OR = odds ratio, OS = overall survival, PG = proximal gastrectomy, TG = total gastrectomy, WMD = weighted mean differences.

Keywords: long-term nutritional status, postoperative complications, proximal early gastric cancer, proximal gastrectomy, surgical outcomes, total gastrectomy

1. Introduction

Gastric cancer is the most common cancer worldwide, resulting in the third-highest number of cancer-related deaths.[1] With advances in medical techniques, early diagnoses of gastric cancer are increasing. Nowadays, many doctors choose endoscopic techniques, including endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), to treat early gastric cancer (EGC). However, both of these have limitations. Moreover, EMR is recommended only in cases of EGC less than 20 mm in diameter and without ulcer findings.[2]

The incidence of lymph node metastasis ranges from 3% to 5% for EGC limited to mucosa and 16% to 25% for submucosal involvements.[3,4] Because of the risk of lymph node metastasis, curative resection, including proximal (PG) and total gastrectomy (TG), is still the standard therapy procedure for proximal EGC.[5,6] Both of these techniques have their own merits and demerits.[7,8] As a result, no consensus has been reached regarding which surgical method is superior. Thus, the purpose of this study was to assess the surgical outcomes, postoperative complications, overall survival (OS), and long-term nutritional status of PG and TG in patients with proximal EGC by performing a systematic review of the literature and a meta-analysis. To the best of our knowledge, this is the first meta-analysis comparing of PG and TG for proximal EGC.

2. Methods

2.1. Literature search strategy

A systematic literature search was performed in PubMed, Embase, Web of Science, and Cochrane Library (up to October 1, 2018). In

Editor: Neil Merrett.

The authors have no funding and conflicts of interest to disclose.

Department of General Surgery, Wujin Hospital Affiliated to Jiangsu University, Changzhou, Jiangsu Province, China.

* Correspondence: Xuezhong Xu, Wujin Hospital Affiliated to Jiangsu University, Changzhou, Jiangsu, China (e-mail: xxz197001@sina.com).

Medicine (2019) 98:19(e15663)

Received: 20 November 2018 / Received in final form: 27 March 2019 / Accepted: 20 April 2019

http://dx.doi.org/10.1097/MD.0000000000015663

each database, the following terms were combined as keywords: (total gastrectomy) and (proximal gastrectomy) and (early gastric cancer). After searching, we identified 53 relevant results in PubMed, 71 in Embase, 11 in Cochrane Library, and 191 in Web of Science. All the articles were reviewed carefully, including the abstracts, studies, and references. Articles in the reference list were screened to identify any potentially relevant studies.

This study was conducted in accordance with guidelines of the 1975 *Declaration of Helsinki*. This study and protocol were designed with permission by our institutional review board.

2.2. Inclusion criteria

The inclusion criteria for the studies were as follows:

1. patients with EGC (stage I);
2. TG or PG was performed as the primary treatment method;
3. patients enrolled in the studies were divided into TG and PG groups; and
4. preoperative comorbidities and/or postoperative complications and/or mortalities and/or long-term survival outcomes and/or nutritional status were mentioned.

2.3. Exclusion criteria

The studies would be excluded if they met the following criteria:

1. articles that reported case reports, reviews, letters, and comments;
2. studies that did not provide precise data about clinicopathological features;
3. non-English publications; and
4. the sample size was smaller than 20.

If 2 studies were reported by the same institution, the one with the smaller sample size was excluded.

2.4. Data extraction and quality assessment

All studies were carefully reviewed. Data were extracted from each study by 2 independent researchers, including study ID (first author's name and publication year), country, sample size, postoperative complications, long-term survival outcomes, and nutritional status. Any inconsistencies between reviewers were resolved by a third investigator through discussion. Weighted mean differences (WMD) with 95% confidence intervals (CIs) were used to analyze continuous variables. Data presented as means with ranges were converted into means with standard deviations.[9] Dichotomous data were measured using odds ratios (ORs). Some studies used line charts to show changes in nutritional status; these charts did not provide precise data such as means and standard deviations. As a result, an email was sent to the author asking for the original data. If studies only provided Kaplan-Meier curves for long-term survival outcomes (original data were not available), hazard ratios (HRs) with their corresponding 95% CIs were extracted using Engauge Digitizer version 4.1 (http://markummitchell.github.io/engauge-digitizer/).

The Newcastle-Ottawa Scale (NOS) was used to assess the quality of retrospective studies. The NOS evaluates studies based on the selection of the study groups, comparability between the groups, and the determination of exposure/outcomes using a scale from 0 to 9. Studies that scored ≥6 were deemed to be of high quality.[10]

2.5. Outcomes of interest

First, surgery-related features (operation time, intraoperative blood loss volume, and quantity of harvested lymph nodes), postoperative morbidities, and OS were compared between the TG and PG groups. Second, postoperative nutritional status (1 and 2 years after surgery) was examined.

2.6. Statistical analysis

In this study, we used STATA version 14.0 (StataCorp., College Station, TX) to perform the meta-analysis. Heterogeneity among studies was tested using Cochran's Q and Higgins' I^2 statistics. If there was no heterogeneity ($I^2 < 50\%$, $P > .10$), a fixed-effects model was used. Otherwise, a random-effects model was applied. Sensitivity analysis was carried out when the heterogeneity was higher than 50%. Studies were sequentially omitted at each step. If the result did not change, the pooled studies were considered to be stable. Publication bias was evaluated using Egger test. The results were defined as statistically significant for P values $< .05$.

3. Results

3.1. Search strategy

Three hundred twenty-six articles were identified after searching PubMed, Embase, Web of Science, and Cochrane Library. After duplicates were removed, 84 articles were screened. Twelve articles were excluded for reasons of being non-English publications, containing irrelevant subjects, or using grouping standards that were different from those under consideration. After reading the full-text articles, those that could not provide a precise number of outcomes of interest were excluded. Finally, 18 articles were included in this meta-analysis (Fig. 1).

3.2. Cohort characteristics and quality of the studies

Eighteen studies were finally included in our analysis.[11–27] Sample sizes varied from 20 to 349 participants. With respect to the study region, 11 studies were performed in Japan and seven in Korea. The publication dated ranged from 2012 to 2018. Fourteen studies provided surgery-related features, 9 provided postoperative nutritional status, and 5 reported long-term survival outcomes (OS). According to the NOS, 1 article received a score of 6, 3 were scored 7, 1 received a score of 8, and 3 were scored 9. All studies were retrospective case-control studies. The characteristics and quality assessment scores of the included studies are presented in Table 1.

3.3. Surgery-related features

3.3.1. *Operation time.* Twelve studies (1283 patients) provided data on operation time. Because of the moderate heterogeneity ($I^2 = 72.9\%$, $P = .000$), the random-effects model was used. Operation time in the TG group was longer than in the PG group (WMD = −29.777; 95% CI: −41.813, −17.741; $P = .000$) (Table 2). In the subgroup analysis, the open surgery and laparoscopic surgery groups showed similar results. However, the difference between the laparoscopic surgery with double tract group and the TG group was not statistically significant (WMD = −8.079; 95% CI: −28.312, 12.153; $P = .434$) (Fig. 2A).

3.3.2. *Intraoperative blood loss volume.* Thirteen studies (1431 patients) reported intraoperative blood loss volume.

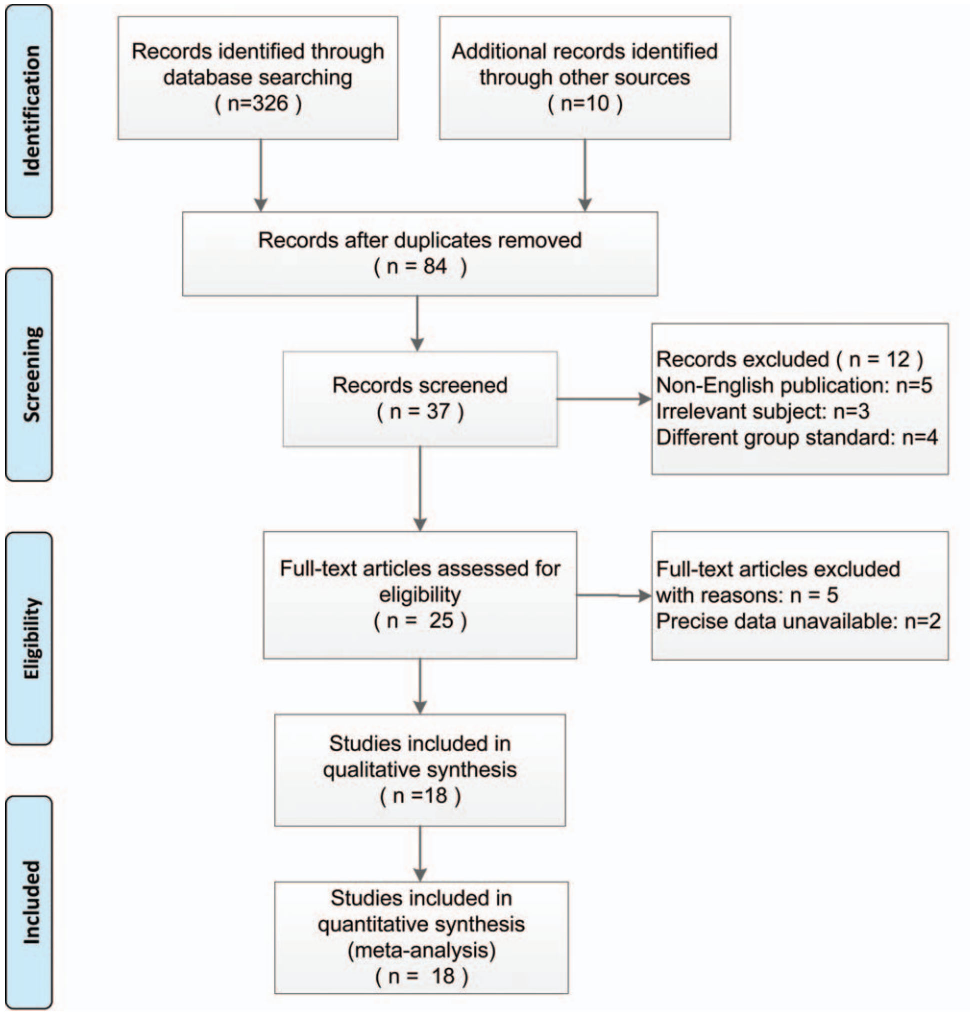

Figure 1. Flow diagram for study selection.

Intraoperative blood loss volume was higher in the TG group than in the PG group (WMD=−33.773; 95% CI: −63.055, −4.490; P=.024); however, the heterogeneity between the studies was significant (I^2=78.5%, P=.000) (Table 2). The 2 groups showed similar results, except for the laparoscopic surgery with double tract group (WMD=3.657; 95% CI: −74.207, 81.522; P=.927) (Fig. 2B).

3.3.3. Postoperative hospital stay. Ten homogenous (I^2=0.0%, P=.975) studies (1310 patients) provided data of postoperative hospital stay. According to the fixed-effects model, there was no significant difference between the 2 groups (WMD=−0.404; 95% CI: −1.308, 0.499; P=.380) (Table 2).

3.3.4. Harvested lymph nodes. The quantities of harvested lymph nodes were included in 9 studies (949 patients) with moderate heterogeneity (I^2=33.5%, P=.150). The overall effect size favored the TG group (WMD=11.035; 95% CI: 9.528, 12.541; P=.000) (Table 2).

3.3.5. Overall survival. Five homogenous (I^2=0.0%, P=.784) studies (885 patients) reported long-term survival outcomes (OS). The results revealed that patients who had undergone either TG or PG had similar OS rates (HR=0.676; 95% CI: 0.325, 1.026; P=.430) (Table 2).

3.4. Postoperative complications

Among the postoperative morbidities, there were no differences in the frequencies of anastomotic leakage, bleeding, and pancreatic fistula (Table 2). The incidence of reflux (OR=2.696; 95% CI: 1.729, 4.206; P=.000) and anastomotic stenosis (OR=2.010; 95% CI: 1.315, 3.072; P=.001) was significantly higher in the PG group than in the TG group (Table 2).

In the subgroup analysis, different from conventional anastomosis, the incidence of reflux (OR=1.010; 95% CI: 0.209, 4.875; P=.990) and anastomotic stenosis (OR=0.849; 95% CI: 0.265, 2.726; P=.784) between the PG with double-tract reconstruction (DTR) and TG groups was not significantly different (Fig. 3A and B).

3.5. Postoperative nutritional status

We selected 5 variables to measure postoperative nutritional status, including albumin, body-weight loss, hemoglobin, total cholesterol,

Table 1

Characteristics of studies included in meta-analysis.

Author	Year	Country	Group	Cases	Age range (yr)	Gender (male/female)	Surgical procedure	Anastomotic method	Follow-up	NOS Score
Kondoh	2007	Japan	PG	10	67.8±5.9	9/1	open	EG	Up to 5 years	8
			TG	10	61.4±8.5	9/1		RY		
Ushimaru	2017	Japan	PG	39	44–83	32/7	open	EG	Up to 36 months	8
			TG	39	34–83	31/8		RY		
Ahn	2012	Korea	PG	50	58.8±12.1	36/14	laparoscopic	EG	Up to 3 years	7
			TG	81	59.7±11.8	56/25		RY		
Park	2018	Korea	PG	34	64.1±12.2	26/8	laparoscopic	EG	Up to 24 months	8
			TG	46	56.7±11.8	22/24		RY		
Kosuga	2015	Japan	PG	25	41–80	17/8	laparoscopic	EG	Up to 2 years	9
			TG	52	40–89	45/7		RY		
Ohashi	2015	Japan	PG	65	37–77	55/10	open	JI	NA	7
			TG	117	30–84	83/34		RY		
Huh	2015	Korea	PG	192	59.7±11.2	130/62	open	EG	Up to 100 months	7
			TG	157	57.4±11.9	115/42		RY		
Sugiyama	2018	Japan	PG	10	65.6±3.8	7/3	laparoscopic	DTR	NA	8
			TG	20	68.6±2.7	17/3		RY		
Jung	2017	Korea	PG	92	59.8±11.4	77/15	laparoscopic	DTR	Up to 2 years	8
			TG	156	58.7±10.8	120/36		RY		
Kim	2016	Korea	PG	17	64.7±9.9	14/3	laparoscopic	DTR	Up to 24 months	9
			TG	17	60.9±12.9	10/7		RY		
Nozaki	2012	Japan	PG	102	44–85	79/23	open	EG	Up to 3 years	8
			TG	49	34-86	36/13		RY		
Ichikawa	2013	Japan	PG	49	36-80	34/15	open	EG	Up to 5 years	8
			TG	35	42-87	29/6		RY		
Son	2014	Korea	PG	64	58.0±13.3	43/21	open	EG	Up to 60 months	6
			TG	106	61.3±10.3	76/30		RY		
Hosoda	2015	Japan	PG	40	69.2±8.2	32/8	laparoscopic	EG	Up to 2 years	8
			TG	59	67.7±8.4	41/18		RY		
Ikeguchi	2012	Japan	PG	49	64.8	38/11	open	EG/JI/DTR	NA	9
			TG	35	67.2	31/4		RY		
Furukawa	2017	Japan	PG	27	59–84	22/5	laparoscopic	EG/DTR	Up to 12 months	8
			TG	48	44–84	35/13		RY		
Cho	2018	Korea	PG	38	55.8±11.6	32/6	laparoscopic	DTR	Up to 24 months	8
			TG	42	59.3±11.8	31/11		RY		
Nishigori	2017	Japan	PG	20	66.2±13.4	15/5	laparoscopic	EG	Up to 12 months	8
			TG	42	64.4±12.2	28/14		RY		

DTR=double-tract reconstruction, EG=esophagogastrostomy, JI=jejunal interposition, NOS=Newcastle-Ottawa Scale, PG=proximal gastrectomy, RY=Roux-en Y reconstruction, TG=total gastrectomy.

and total protein. Each variable was divided into 2 parts (1 and 2 years after surgery). The results revealed that the overall effect size of albumin did not favor either the PG or TG group. Patients in the TG group had a higher loss of body weight and lower hemoglobin levels than those in the PG group. The above results did not change over time. In contrast, total cholesterol and total protein were lower in the TG group 1 year after surgery and equal between the 2 groups, 2 years after surgery (Table 3).

Table 2

Meta-analysis results of operation and complications status.

Measured outcome	Studies	Patients	OR, WMD,HR	95%CI		*P*	Heterogeneity test I^2	Heterogeneity test *P*	*Pr*>|t|
Operation time	12	1283	–29.777	–41.813	–17.741	.000	72.9%	.000	.670
Intraoperative blood loss	13	1431	–33.773	–63.055	–4.490	.024	78.5%	.000	.605
PO Hospital stay	10	1310	–0.404	–1.308	0.499	.380	0.0%	.975	.685
Harvested lymph nodes	9	949	11.035	9.528	12.541	.000	33.5%	.150	.089
OS	5	885	0.841	0.549	1.287	.430	12.0%	.337	.696
PO complications									
Anastomotic leakage	13	1569	0.729	0.421	1.263	.260	0.0%	.901	.454
Bleeding	5	609	1.138	0.329	3.933	.838	0.0%	.919	.008
Pancreatic fistula	5	376	0.567	0.196	1.640	.295	0.0%	.862	.329
Reflux	7	810	2.696	1.729	4.206	.000	36.8%	.147	.577
Anastomotic stenosis	15	1785	2.010	1.315	3.072	.001	20.3%	.227	.348

OS=overall survive, PO=post operation.

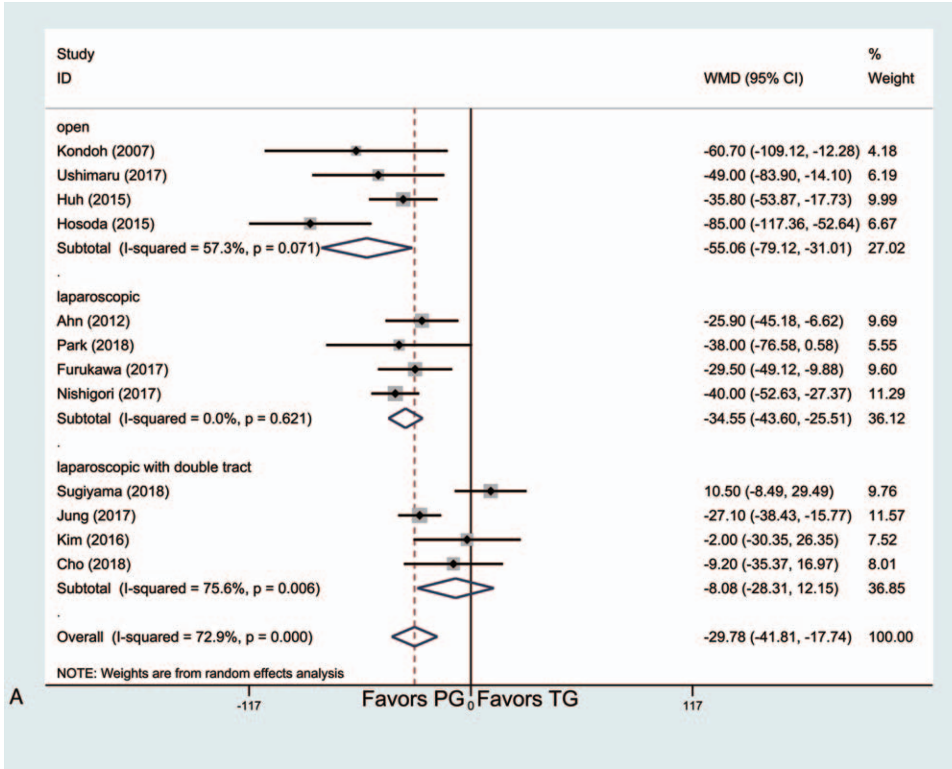

Figure 2. A. Meta-analysis forest plots for comparison of operation time between PG and TG group. 2B. Meta-analysis forest plots for comparison of intraoperative blood loss volume between PG and TG group.

3.6. Publication bias and sensitivity analysis

We assessed the publication bias in every outcome according to Egger test. No publication bias was found except for postoperative bleeding ($P=.008$). A Galbraith plot was used to identify the source of the heterogeneity. We excluded those studies and analyzed the data of the remaining articles. However, the result did not change.

4. Discussion

In the present study, PG was proven to be superior to TG in several ways. First, PG was associated with shorter operation time, a lower volume of intraoperative blood loss, and a shorter length of hospital stay.[14] In the subgroup analysis of operation time and intraoperative blood loss volume in our study, we obtained the same result as the study by Kei in which LPG and LTG were compared, despite the differences in surgical procedure between the studies.[14] However, we found that the PG and TG groups had a similar length of postoperative hospital stay. Second, our study showed that TG was superior regarding the quantities of harvested lymph nodes. However, OS between the 2 groups was not significantly different. The reason for this finding might be that EGC located in the upper third of the stomach is not associated with metastasis to the lower lymph nodes.[28] Most of the lymph nodes harvested during TG were negative.

Due to early diagnosis and the advanced surgical techniques now available, EGC patients have markedly longer survival times than in earlier years. As a result, great importance has been attached to the long-term nutritional status and quality of life of patients with EGC. In the present study, we found that PG is better than TG in terms of long-term nutritional status, including body weight loss, hemoglobin, total cholesterol, and total protein. There are several possible reasons for this result. First, the gastric fundic gland region which secretes gastric acid and Castle intrinsic factors is preserved in PG. Thus, vitamin B12 deficiency rarely occurs in patients who have undergone PG.[29] Second, the duodenal passage plays an important role in the absorption of dietary iron during food intake,[30] and it is also preserved in PG. Finally, the distal stomach and pylorus are preserved during surgery, which is also of great benefit to digestion and absorption. Some previous studies have shown that body weight is closely associated with immunologic function, and a decrease of more than 5% in the lean body weight leads to an increase in the toxicity of adjuvant chemotherapy drugs.[31]

Although PG has obvious advantages in preserving long-term nutritional status, there is still a high incidence of postoperative complications, including anastomotic stenosis and reflux esophagitis. In view of these 2 main complications, we carried out a corresponding analysis. The result revealed that patients who had undergone PG suffered these 2 kinds of complications more frequently than those who had undergone TG. The mechanism underlying anastomotic stenosis is still unclear. The most likely reason is reflux esophagitis and a discrepancy in wall thickness between the esophagus and the stomach. The prevalent treatment method for stenosis is endoscopic balloon dilatation which has been proven to be well-tolerated and effective. Meanwhile, it appears that reflux symptoms after PG cannot be avoided completely. Surgeons have improved the operation procedures to overcome reflux, including jejunal interposition, gastric tube

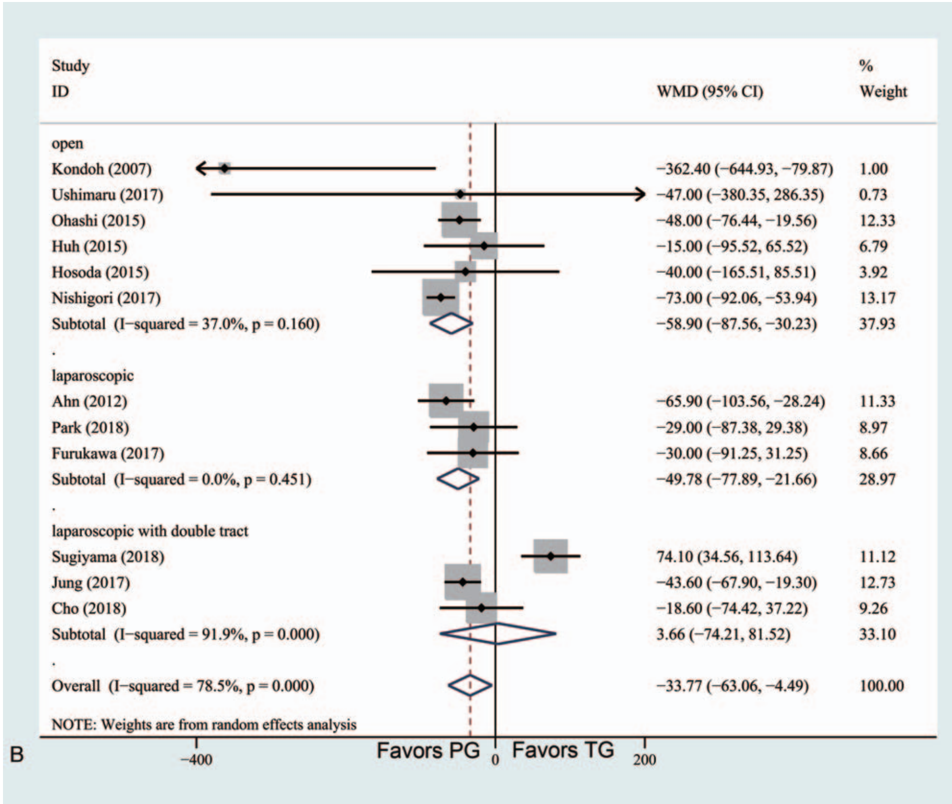

Figure 2. Continued

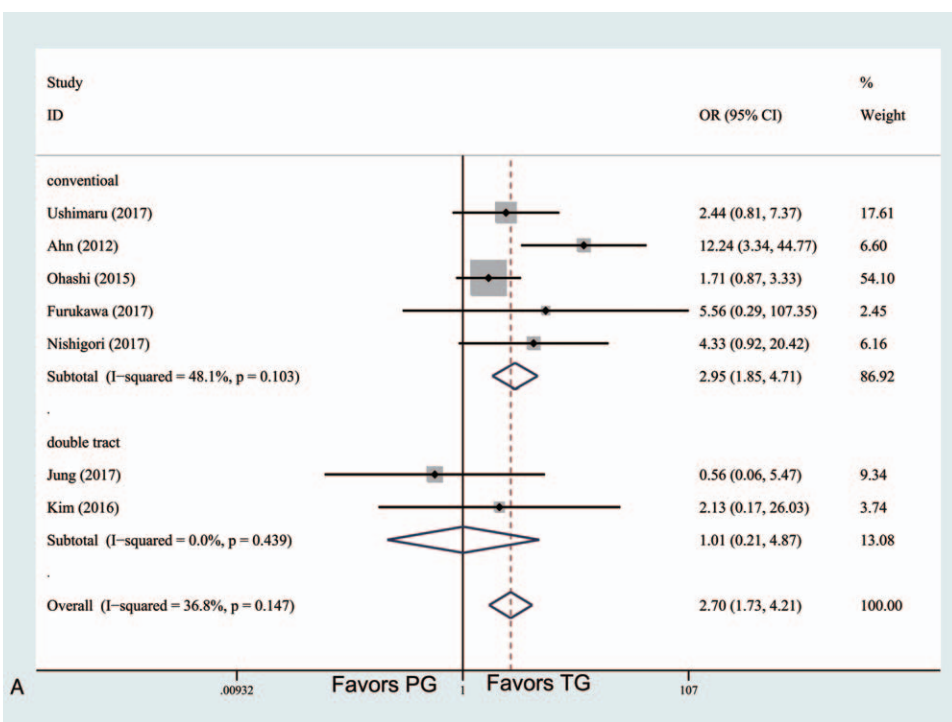

Figure 3. A. Meta-analysis forest plots for comparison of incidence of reflux between PG and TG group. B. Meta-analysis forest plots for comparison of incidence of anastomotic stenosis between PG and TG group.

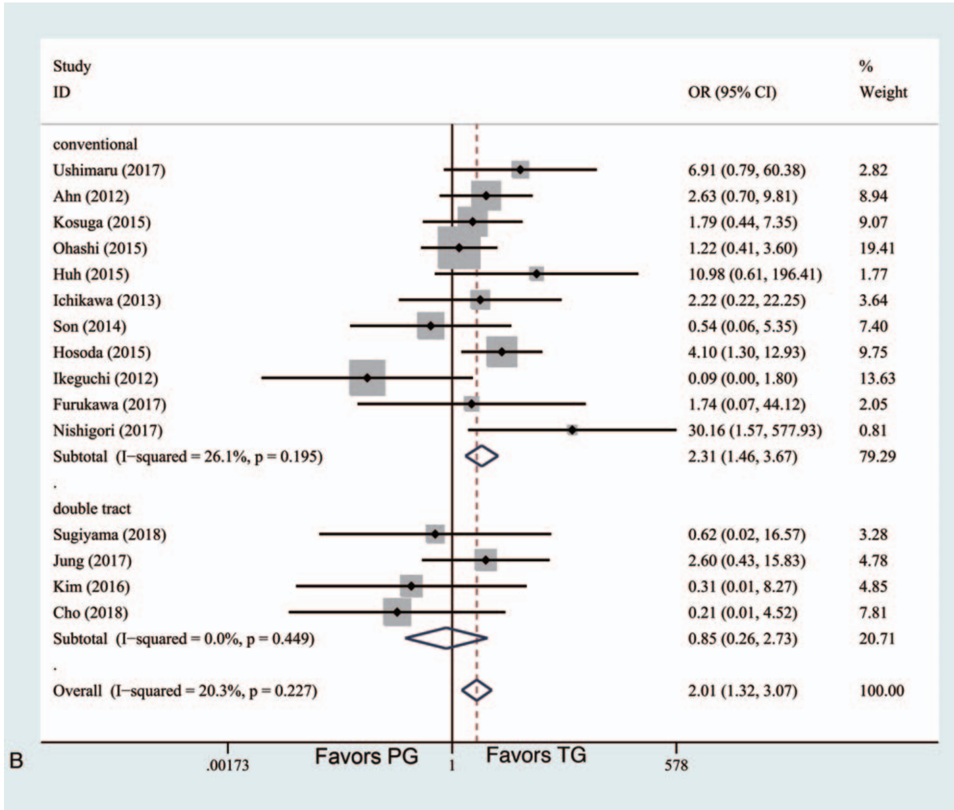

Figure 3. Continued.

esophagogastrostomy, lower esophageal sphincter-preserving esophagogastrostomy, and DTR. However, some of these techniques have been proven to be inefficient, and others are considered to be technically complex, especially under laparoscopy.[32,33]

Esophagojejunostomy (EJ) with DTR was first reported in 1988 by Aikou et al.[34] It can be described briefly as follows: after stomach resection and lymph node dissection, EJ is carried out intracorporeally using a tubular stapler; gastrojejunostomy (GJ) is performed distally to the EJ; and jejunojejunostomy (JJ) is performed distally to the GJ. The distance between anastomotic stomas (EJ to GJ and GJ to JJ) varies according to the surgeon's habits. This reconstruction method is shown in Figure 4. EJ with DTR was originally designed to allow for a smooth transfer of larger food fragments through the duodenal passage. Theoretically, compared to TG, this surgical procedure has 3 advantages. First, food can move through 2 passageways: the jejunal alimentary limb and the remnant stomach to the duodenum. This is important for iron absorption[35]; laboratory data about iron absorption have been reported previously.[25] Second, the

Table 3

Meta-analysis results of postoperative nutritional status.

Characteristics	Studies	Patients	PO time (yr)	WMD	95%CI		*P*	Heterogeneity test		*Pr* > |t|
								I^2	*P*	
Albumin	6	586	1	0.008	–0.098	0.114	.877	89.4%	.000	.223
			2	0.026	–0.122	0.174	.729	94.0%	.000	.917
Body weight loss	9	816	1	–4.333	–5.988	–2.678	.000	96.8%	.000	.710
	7	679	2	–4.843	–7.617	–2.068	.001	98.3%	.000	.822
Hemoglobin	6	586	1	–0.312	–0.471	–0.152	.000	50.4%	.073	.646
			2	–0.504	–0.902	–0.105	.013	89.5%	.000	.138
Total cholesterol	4	421	1	–7.372	–14.503	–0.240	.043	51.1%	.105	.745
			2	–6.344	15.763	3.075	.187	71.2%	.015	.953
Total protein	6	586	1	–0.084	–0.116	–0.053	.000	44.8%	.107	.401
			2	–0.016	–0.106	0.074	.727	76.9%	.001	.240

PO = post operation.

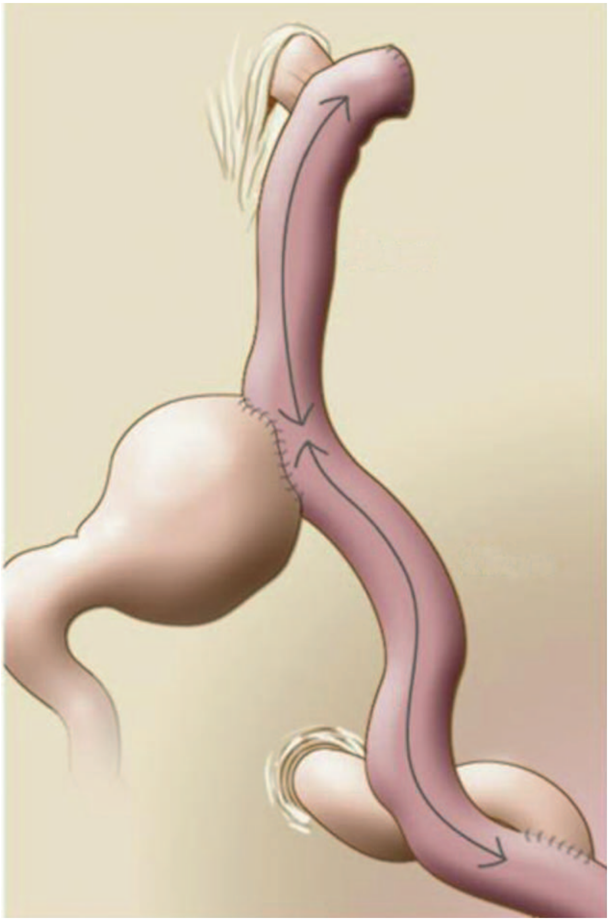

Figure 4. Illustration of proximal gastrectomy with double tract reconstruction.

gastric antrum and distal stomach are preserved during the surgery, which means increased food intake and more potential sources of intrinsic factors. Third, the distance of the anastomosis between GJ and EJ reduces the incidence of reflux symptoms. As we found in the present study, PG with DTR had a similar incidence of anastomotic stenosis and reflux esophagitis to TG. Moreover, the surgical outcomes of PG with DTR, such as operation time and intraoperative blood loss volume, were comparable to those of TG.

There are some limitations which should be declared here. First, all the included studies were retrospective which might have led to an additional selection and information bias. Second, comparing the incidence of postoperative complications and long-term nutritional status without similar physical histories always results in a significant selection bias. Third, the number of studies about PG with DTR is small; thus, our findings may be unreliable. Finally, all enrolled patients were from Asia. Therefore, it is not known whether the results are similar for patients from western countries.

In conclusion, compared to TG, PG is superior regarding operation time, intraoperative blood loss volume, quantities of harvested lymph nodes, and long-term nutritional status, despite the surgical method used (laparotomy or laparoscopic surgery). Furthermore, the disadvantages of PG are also obvious, mainly concerning 2 kinds of complications: anastomotic stenosis and reflux esophagitis. However, these 2 complications appear to be improved by EJ with DTR, a finding that should be confirmed by large multicenter prospective clinical trials. Since, the incidence of complications associated with PG with DTR is comparable to that with TG and the long-term nutritional status of PG with DTR is superior to that of TG, PG with DTR might be accepted by surgeons as the optimal surgical procedure for proximal EGC.

Acknowledgments

We thank Dr Peng Jiang and Dr Haifeng Tang for their critical reading and informative advice during the process of study. Meanwhile, we would like to thank Editage (www.editage.com) for English language editing.

Author contributions

Conceptualization: Xuezhong Xu.
Validation: Yulin Tan, Yibo Wang.
Visualization: Yixin xu, Nianyuan Ye.
Writing – original draft: Yixin xu, Cheng Xi.
Writing – review & editing: Xuezhong Xu.

References

[1] Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.
[2] Eguchi T, Gotoda T, Oda I, et al. Is endoscopic one-piece mucosal resection essential for early gastric cancer? Dig Endosc 2010;15:113–6.
[3] Oñate-Ocaña LF, Aiello-Crocifoglio V, Mondragón-Sánchez R, et al. Survival benefit of D2 lymphadenectomy in patients with gastric adenocarcinoma. Ann Surg Oncol 2000;7:210–7.
[4] Gore RM, Levine MS, Ghahremani GG, et al. Gastric cancer. Radiologic diagnosis. Radiol Clin North Am 1997;35:311–29.
[5] Ooki A, Yamashita KS. Clinical significance of total gastrectomy for proximal gastric cancer. Anticancer Res 2008;28:2875.
[6] Ichikawa D, Komatsu S, Kubota T, et al. Long-term outcomes of patients who underwent limited proximal gastrectomy. Gastric Cancer 2014; 17:141–5.
[7] An JY, Youn HG, Choi MG, et al. The difficult choice between total and proximal gastrectomy in proximal early gastric cancer. Am J Surg 2008;196:587–91.
[8] Shiraishi N, Adachi Y, Kitano S, et al. Clinical outcome of proximal versus total gastrectomy for proximal gastric cancer. World J Surg 2002;26:1150.
[9] Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range,;1; and the size of a sample. BMC Med Res Methodol 2005;5:13.
[10] Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;283:2008–12.
[11] Ahn SH, Lee JH, Park DJ, et al. Comparative study of clinical outcomes between laparoscopy-assisted proximal gastrectomy (LAPG) and laparoscopy-assisted total gastrectomy (LATG) for proximal gastric cancer. Gastric Cancer 2013;16:282–9.
[12] Cho M, Son T, Kim HI, et al. Similar hematologic and nutritional outcomes after proximal gastrectomy with double-tract reconstruction in comparison to total gastrectomy for early upper gastric cancer. Surg Endosc 2018.
[13] Furukawa H, Kurokawa Y, Takiguchi S, et al. Short-term outcomes and nutritional status after laparoscopic subtotal gastrectomy with a very small remnant stomach for cStage I proximal gastric carcinoma. Gastric Cancer 2018;21:500–7.
[14] Hosoda K, Yamashita K, Katada N, et al. Potential benefits of laparoscopy-assisted proximal gastrectomy with esophagogastrostomy for cT1 upper-third gastric cancer. Surg Endosc 2015;30:3426–36.
[15] Huh YJ, Lee HJ, Oh SY, et al. Clinical outcome of modified laparoscopy-assisted proximal gastrectomy compared to conventional proximal gastrectomy or total gastrectomy for upper-third early gastric cancer

with special references to postoperative reflux esophagitis. J Gastric Cancer 2015;15:191–200.
[16] Ikeguchi M, Kader A, Takaya S, et al. Prognosis of patients with gastric cancer who underwent proximal gastrectomy. Int Surg 2012;97:275–9.
[17] Jung DH, Lee Y, Kim DW, et al. Laparoscopic proximal gastrectomy with double tract reconstruction is superior to laparoscopic total gastrectomy for proximal early gastric cancer. Surg Endosc 2017; 31:3961–9.
[18] Kim DJ, Kim W. Laparoscopy-assisted proximal gastrectomy with double tract anastomosis is beneficial for Vitamin B12 and iron absorption. Anticancer Res 2016;36:4753–8.
[19] Kondoh Y, Okamoto Y, Morita M, et al. Clinical outcome of proximal gastrectomy in patients with early gastric cancer in the upper third of the stomach. Tokai J Exp Clin Med 2007;32:48–53.
[20] Kosuga T, Ichikawa D, Komatsu S, et al. Feasibility and nutritional benefits of laparoscopic proximal gastrectomy for early gastric cancer in the upper stomach. Ann Surg Oncol 2015;22 Suppl 3:S929–935.
[21] Nishigori T, Okabe H, Tsunoda S, et al. Superiority of laparoscopic proximal gastrectomy with hand-sewn esophagogastrostomy over total gastrectomy in improving postoperative body weight loss and quality of life. Surg Endosc 2017;31:3664–72.
[22] Nozaki I, Hato S, Kobatake T, et al. Long-term outcome after proximal gastrectomy with jejunal interposition for gastric cancer compared with total gastrectomy. World J Surg 2013;37:558–64.
[23] Ohashi M, Morita S, Fukagawa T, et al. Functional advantages of proximal gastrectomy with jejunal interposition over total gastrectomy with Roux-en-Y esophagojejunostomy for early gastric cancer. World J Surg 2015;39:2726–33.
[24] Park JY, Park KB, Kwon OK, et al. Comparison of laparoscopic proximal gastrectomy with double-tract reconstruction and laparoscopic total gastrectomy in terms of nutritional status or quality of life in early gastric cancer patients. Eur J Surg Oncol 2018;44:1963–70.
[25] Son MW, Kim YJ, Jeong GA, et al. Long-term outcomes of proximal gastrectomy versus total gastrectomy for upper-third gastric cancer. J Gastric Cancer 2014;14:246–51.
[26] Sugiyama M, Oki E, Ando K, et al. Laparoscopic proximal gastrectomy maintains body weight and skeletal muscle better than total gastrectomy. World J Surg 2018;42:3270–6.
[27] Ushimaru Y, Fujiwara Y, Shishido Y, et al. Clinical outcomes of gastric cancer patients who underwent proximal or total gastrectomy: a propensity score-matched analysis. World J Surg 2018;42:1477–84.
[28] Kitamura K, Nishida S, Yamamoto K, et al. Lymph node metastasis in gastric cancer in the upper third of the stomach–surgical treatment on the basis of the anatomical distribution of positive node. Hepatogastroenterology 1998;45:281–5.
[29] Hu Y, Kim HI, Hyung WJ, et al. Vitamin B(12) deficiency after gastrectomy for gastric cancer: an analysis of clinical patterns and risk factors. Ann Surg 2013;258:970–5.
[30] Lee JH, Hyung WJ, Kim HI, et al. Method of reconstruction governs iron metabolism after gastrectomy for patients with gastric cancer. Ann Surg 2013;258:964–9.
[31] Aoyama T, Sato T, Segami K, et al. Risk factors for the loss of lean body mass after gastrectomy for gastric cancer. Ann Surg Oncol 2016; 23:1963–70.
[32] Kim JH, Park SS, Kim J, et al. Surgical outcomes for gastric cancer in the upper third of the stomach. World J Surg 2006;30:1870–6. discussion 1877-1878.
[33] Katsoulis IE, Robotis JF, Kouraklis G, et al. What is the difference between proximal and total gastrectomy regarding postoperative bile reflux into the oesophagus? Dig Surg 2006;23:325–30.
[34] Aikou T, Natsugoe S, Shimazu H, et al. Antrum preserving double tract method for reconstruction following proximal gastrectomy. Jpn J Surg 1988;18:114–5.
[35] Fleming RE, Bacon BR. Orchestration of iron homeostasis. N Engl J Med 2005;352:1741–4.