Digestive Surgery

Review Article

Dig Surg 2021;38:1–13
DOI: 10.1159/000506104

Received: October 1, 2019
Accepted: January 22, 2020
Published online: November 5, 2020

Clinical Outcomes of Proximal Gastrectomy versus Total Gastrectomy for Proximal Gastric Cancer: A Systematic Review and Meta-Analysis

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Keywords
Proximal gastric cancer · Proximal gastrectomy · Total gastrectomy · Survival · Meta-analysis

Abstract
Introduction: The extent of optimal gastric resection for proximal gastric cancer (PGC) continues to remain controversial, and a final consensus is yet to be met. The current study aimed to compare the perioperative outcomes, postoperative complications, and overall survival (OS) of proximal gastrectomy (PG) versus total gastrectomy (TG) in the treatment of PGC through a meta-analysis. ***Methods:*** We systematically searched PubMed, Embase, The Cochrane Library, and Web of Science for articles published in English since database establishment to October 2019. Evaluated endpoints were perioperative outcomes, postoperative complications, and long-term survival outcomes. ***Results:*** A total of 2,896 patients in 25 full-text articles were included, of which one was a prospective randomized study, one was a clinical phase III trial, and the rest were retrospective comparative studies. The PG group showed a higher incidence of anastomotic stenosis (OR = 2.21 [95% CI: 1.08–4.50]; $p = 0.03$) and reflux symptoms (OR = 3.33 [95% CI: 1.85–5.99]; $p < 0.001$) when compared with the TG group, while no difference was found in PG patients with double-tract reconstruction (DTR). The retrieved lymph nodes were clearly more in the TG group (WMD = −10.46 [95% CI: −12.76 to −8.17]; $p < 0.001$). The PG group was associated with a better 5-year OS relative to TG with 11 included studies (OR = 1.35 [95% CI: 1.03–1.77]; $p = 0.03$). After stratification for early gastric cancer and PG with DTR groups, however, there was no significant difference between the 2 groups (OR = 1.35 [95% CI: 0.59–2.45]; $p = 0.62$). ***Conclusion:*** In conclusion, PG was associated with a visible improved long-term survival outcome for all irrespective of tumor stage, while a similar 5-year OS for only early gastric cancer patients between the 2 groups. Future randomized clinical trials of esophagojejunostomy techniques, such as DTR following PG, are expected to prevent postoperative complications and assist surgeons in the choice of surgical approach for PGC patients.

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Introduction

Gastric cancer remains a world-wide cancer with the third most frequent cause of cancer-related deaths [1]. Although the overall incidence of gastric cancer has been declining in some countries, the incidence of carcinoma of the proximal third of the stomach has been increasing at an alarming rate in recent years [2–4]. Consequently, the optimal surgical selection has received considerable attention for proximal gastric cancer (PGC).

To date, the optimal extent of gastric resection for PGC patients, that is, proximal gastrectomy (PG) or total gastrectomy (TG), remains controversial. Several studies have shown that PG was a considerable resection procedure that provided equivalent oncological outcomes compared with conventional TG, although more than half of these studies are defined as early PGC [5–18]. Proponents of TG, however, have argued that TG was associated with better overall survival (OS) as well as less postgastrectomy disturbances [19–21]. Definitely, most studies were too small to evaluate the surgical outcomes of PG adequately. Thus, the purpose of the current study was to compare the perioperative outcomes, postoperative complications, and OS of PG versus TG and the reconstruction types following PG procedure in the treatment of PGC, through a systematic review and meta-analysis of published studies.

Methods

Study Selection and Study Strategy

We systematically searched PubMed, Embase, The Cochrane Library, and Web of Science databases. The search strategy of PubMed was as follows and was applied to other databases also: ("proximal gastric cancer" [Tiab] OR "proximal gastric carcinoma" [Tiab] OR "PGC" [Tiab] OR "upper-third gastric adenocarcinoma" [Tiab] OR "upper-third gastric cancer" [Tiab] OR "proximal third gastric cancer" [Tiab] OR "adenocarcinoma of the upper third of the stomach" [Tiab] OR "cancer of the cardia and esophagogastric junction" [Tiab] OR "cancer of the cardia" [Tiab] OR "cardia adenocarcinoma" [Tiab]) AND ("proximal gastrectomy" [Tiab] OR "PG" [Tiab]) AND ("total gastrectomy" [Tiab] OR "TG" [Tiab]). All articles published in English since database establishment to October 2019 were included.

Inclusion and Exclusion Criteria

Inclusion criteria were described as follows: (1) studies that compared PG with TG for PGC; (2) human studies; (3) studies with at least one of the outcomes mentioned; (4) PG or TG that was performed with either laparoscopy-assisted or open gastrectomy; and (5) any type of comparative study. Excluded criteria were described as follows: (1) abstracts, letters, editorials, expert opinions, case reports, reviews, and studies lacking control groups; (2) studies for benign lesions and gastrointestinal stromal tumors; (3) studies including only subgroup analyses comparing PG with TG; (4) studies without necessary data for statistical analysis; and (5) duplicate research based on author or center.

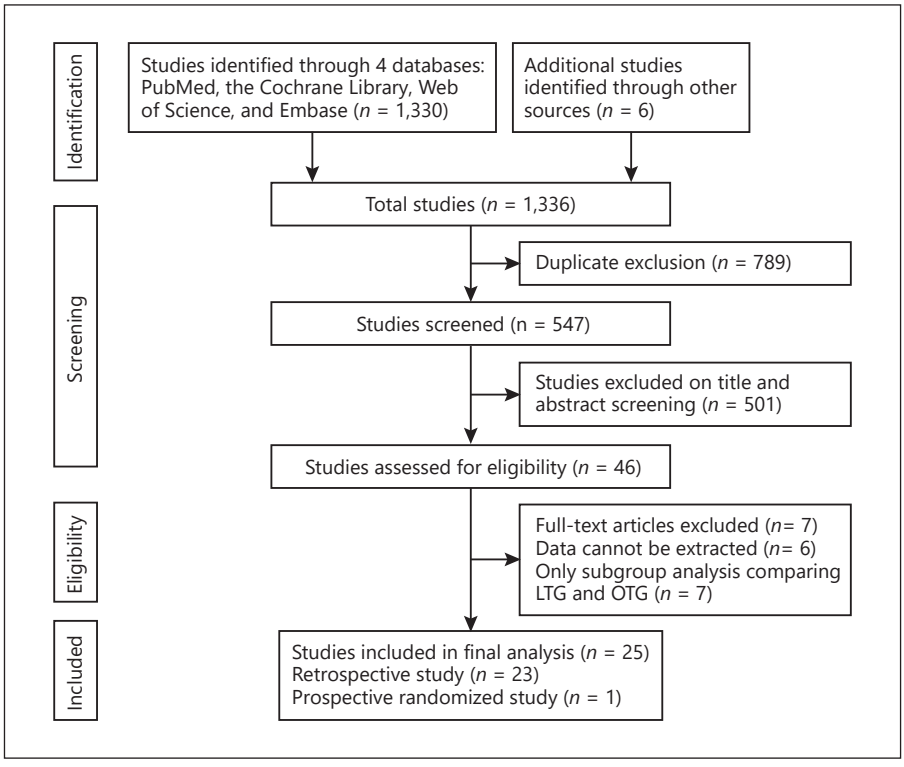

Fig. 1 The flow diagram of the research process until October 2019.

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Table 1. Clinicopathological characteristics of included 25 studies

Author	Country	Design	Population included	Group	Patients, *n*	Age, years	Gender (M/F)	BMI at diagnosis, kg/m^2	Pathological stage			Tumor size, cm	Adjuvant therapy	NOS score
									I	II–III	IV			
Yoo et al. [16]	Korea	Retrospective study	All stage (I, II, III, IV)	PG-EG	74	54.5±10.8	55/19	–	–	–	–	5.6±2.8	–	6
				TG-RY	185	54.2±12.7	126/59	–	–	–	–	6.5±3.5	–	
Yoo et al. [41]	Korea	Prospective randomized study	Staged T1–3	PG-JI	25	52.6±10.9	21/4	–	–	–	–	–	–	9
				TG-RY	26	55.4±11.2	19/7	–	–	–	–	–	–	
Kim et al. [21]	Korea	Retrospective study	All stage (I, II, III, IV)	PG-EG	43	55.93±13.31	25/18	–	12	28	3	4.84±2.53	–	6
				TG-RY	104	57.14±11.57	70/34	–	27	61	16	5.19±3.07	–	
Kondoh et al. [32]	Japan	Retrospective study	Early gastric cancer	PG-EG	10	67.8±5.9	9/1	23.6±1.8	–	–	–	2.0±1.0	–	8
				TG-RY	10	61.4±8.5	9/1	24.1±2.7	–	–	–	2.6±1.2	–	
Ooki et al. [35]	Japan	Retrospective study	Staged T1–3	LAPG-EG	37	57.4±9.0	26/11	–	36	1	0	3.8±1.1	–	6
				LATG-RY	81	59.3±11.0	58/23	–	75	6	0	4.1±2.3	–	
Ikeguchi et al. [11]	Japan	Retrospective study	Early gastric cancer	PG-EG/JI/DTR	51	64.8	38/13	–	47	4	0	3.0±1.5	–	8
				TG-RY	35	67.2	31/4	–	31	4	0	5.4±3.1	–	
Ichikawa et al. [29]	Japan	Retrospective study	Early gastric cancer	PG-EG	39	64	25/14	–	–	–	–	3	0	8
				TG-RY	45	62	34/11	–	–	–	–	4	0	
Nozaki et al. [7]	Japan	Retrospective study	Staged T1–2	PG-RG	102	67 (44–85)	79/23	–	89	13	0	2.5 (0.5–10)	–	8
				TG-RY	49	71 (34–86)	36/13	–	34	15	0	5 (0.7–21)	–	
Ahn et al. [26]	Korea	Retrospective study	Early gastric cancer	LAPG-EG	50	58.8±12.1	36/14	24.2±3.7	–	–	–	2.8±1.3	–	7
				LATG-RY	81	59.7±11.8	56/25	23.6±3.4	–	–	–	4.0±2.7	–	
Son et al. [9]	Korea	Retrospective study	Early gastric cancer	PG-EG	64	58.0±13.3	43/21	–	64	0	0	2.63±1.00	–	6
				TG-RY	106	61.3±10.3	76/30	–	106	0	0	3.46±1.95	–	
Kosuga et al. [33]	Japan	Retrospective study	Early gastric cancer	LAPG-EG	25	66 (41–80)	17/8	22.3	–	–	–	–	–	6
				LATG-RY	52	67 (40–89)	45/7	23.6	–	–	–	–	–	
Sugoor et al. [17]	India	Retrospective study	Staged I, II, and III	PG-EG	43	53 (29–74)	37/6	–	9	28	0	–	36	7
				TG-RY	32	59 (23–85)	24/8	–	3	27	0	–	29	
Hosoda et al. [10]	Japan	Retrospective study	Early gastric cancer	LAPG-EG	40	68.4±8.3	32/8	23.5±2.4	36	4	0	–	0	7
				LATG-RY	59	66.5±11.0	41/9	23.3±3.5	45	14	0	–	0	

Table 1 (continued)

Author	Country	Design	Population included	Group	Patients, *n*	Age, years	Gender (M/F)	BMI at diagnosis, kg/m^2	Pathological stage			Tumor size, cm	Adjuvant therapy	NOS score
									I	II–III	IV			
Jung et al. [31]	Korea	Retrospective study	Early gastric cancer	PG-DRT	92	59.8±11.4	77/15	23.5±2.7	92	0	0	2.4±1.3	0	9
				TG-RY	156	58.7±10.8	120/36	23.9±3.3	156	0	0	3.2±1.9	0	
Hayami et al. [28]	Japan	Retrospective study	Early gastric cancer	LAPG-EG	43	72 (37–90)	31/12	23.7 (18.2–36.2)	39	3	0	2.5 (0.8–7)	4	6
				LATG-RY	47	69 (41–84)	34/13	22.4 (16.4–30.6)	44	3	0	3.45 (0.7–10.5)	3	
Nishigori et al. [34]	Japan	Retrospective study	Early gastric cancer	LAPG-EG	20	66.2±13.4	15/5	23.4±3.8	–	–	–	–	0	8
				LATG-RY	42	64.4±12.2	28/14	22.8±3.6	–	–	–	–	0	
Rosa et al. [36]	Italy	Retrospective study	Staged I, II, III, and IV	PG-EG	75	–	57/18	–	26	48	1	3.6±5.1	0	7
				TG-RY	75	–	55/20	–	23	43	9	4.8±5.6	0	
Sugiyama et al. [38]	Japan	Retrospective study	Early gastric cancer	PG-DRT	10	65.6±3.8	7/3	21.3±1.0	9	1	0	–	–	8
				TG-RY	20	68.6±2.7	17/3	23.7±0.7	17	5	0	–	–	
Cho et al. [27]	Korea	Retrospective study	Early gastric cancer	LAPG-DTR	38	55.8±11.6	32/6	24.2±3.1	38	0	0	2.14±1.71	0	8
				LATG-RY	42	59.3±11.6	31/11	23.5±5.0	42	0	0	3.25±2.71	0	
Ushimaru et al. [39]	Japan	Retrospective study	Early gastric cancer	PG-EG	39	67 (44–83)	32/7	23.0 (18.3–28.0)	37	2	0	2.5 (0.45–6.0)	–	8
				TG-RY	39	69 (34–83)	31/8	22.7 (16.6–30.9)	35	4	0	2.5 (0.5–5.5)	–	
Asaoka et al. [43]	Japan	Retrospective study	Early gastric cancer	PG-EG	39	66 (38–86)	33/6	23.2±3.10	37	2	0	3.12±1.89	2	8
				TG-RY	73	70 (46–86)	57/16	23.4±3.20	57	16	0	5.34±3.58	10	
Park et al. [44]	Korea	Retrospective study	Early gastric cancer	LAPG-EG	34	64.1±12.2	26/8	23.1±3.2	30	4	0	2.1±1.1	3	8
				LATG-RY	46	56.7±11.8	22/24	22.9±3.4	39	7	0	3.2±1.9	2	
Kano et al. [45]	Italy	Retrospective study	Early gastric cancer	LAPG-EG/JI/DTR	72	67 (30–88)	47/25	–	67	5	0	2.8 (0.2–12.5)	–	9
				LATG-RY	78	66 (41–84)	66/12	–	74	4	0	3.0 (0.1–7.5)	–	
Katai et al. [46]	Japan	Clinical phase III trial	Early gastric cancer	LAPG-JI/DTR	49	67 (31–80)	173/72	22.8 (16.1–29.2)	–	–	–	3.0 (0.6–18.0)	–	9
				LATG-RY	195				–	–	–		–	
Ko et al. [42]	Korea	Retrospective study	Early gastric cancer	PG-DTR	52	61.5±12.3	35/17	23.7±3.1	45	8	0	2.8±1.6	–	8
				TG-RY	52	63.0±9.2	35/17	23.4±2.9	40	14	0	3.9±2.8	–	

PG, proximal gastrectomy; TG, total gastrectomy; LAPG, laparoscopy-assisted proximal gastrectomy; LATG, laparoscopy-assisted total gastrectomy; EG, esophagojejunostomy; JI, jejunal interposition; DTR, double-tract reconstruction.

Table 2. Subgroup meta-analysis of comparison between PG and TG

Subgroup	Included studies	Included patients	I^2, %	Effect model	OR/WMD	95% CI	*p* value
For all gastric cancer patients							
5-year OS	11	1,695	36	Fixed	1.35	1.03–1.77	0.03
Basic characteristics							
Age, year	14	1,599	47	Fixed	−0.51	−1.57 to 0.55	0.35
Male	24	2,652	29	Fixed	1.05	0.88–1.26	0.61
BMI at diagnosis, kg/m^2	10	966	77	Random	−0.18	−0.97 to 0.62	0.67
Tumor size, cm	13	1,705	42	Fixed	−0.93	−1.12 to −0.73	<0.001
Pathological stage I	17	1,968	0	Fixed	1.69	1.25–2.29	<0.001
Pathological stage II–IV	17	1,968	0	Fixed	0.56	0.42–0.76	<0.001
Adjuvant therapy	10	1,080	5	Fixed	0.76	0.36–1.61	0.48
Perioperative outcomes							
Operative time, min	9	834	87	Random	−4.80	−22.82 to 13.21	0.6
Estimated blood loss, mL	7	664	88	Random	−50.13	−103.38 to 3.13	0.07
Retrieved lymph nodes, *n*	11	1,389	63	Random	−10.46	−12.76 to −8.17	<0.001
Splenectomy	11	1,226	88	Random	0.40	0.09–1.79	0.23
Postoperative stay, day	7	496	10	Fixed	0.07	−0.48 to 0.62	0.8
Complications							
Hospital mortality	10	1,222	30	Fixed	1.11	0.46–2.68	0.82
Reflux symptoms	8	866	21	Fixed	3.33	1.85–5.99	<0.001
Reflux esophagitis	12	1,375	70	Random	1.36	0.59–3.13	0.47
Anastomotic leakage	19	2,201	0	Fixed	0.73	0.45–1.19	0.21
Anastomotic stenosis	18	2,257	59	Random	2.21	1.08–4.50	0.03
Internal hernia	5	659	0	Fixed	0.30	0.08–1.91	0.09
Cholecystitis	6	586	0	Fixed	0.81	0.27–2.48	0.71
Ileus	11	1,439	0	Fixed	0.39	0.20–0.78	0.007
Abdominal abscess	10	1,183	41	Fixed	0.36	0.19–0.69	0.002
Pancreatitis	6	839	16	Fixed	0.50	0.18–1.38	0.18
Pneumonia	7	919	0	Fixed	0.55	0.25–1.21	0.14
Reoperation	4	539	31	Fixed	1.51	0.38–5.96	0.55
For early gastric cancer patients							
5-year OS	7	988	50	Random	1.20	0.59–2.45	0.62
Retrieved lymph nodes, *n*	9	1,188	65	Random	−11.31	−13.18 to −8.79	<0.001
Reflux symptoms	8	866	21	Fixed	3.33	1.85–5.99	<0.001
Anastomotic stenosis	13	1,499	42	Fixed	1.69	1.07–2.67	0.02
For PG patients with DTR							
5-year OS	4	588	67	Random	1.06	0.29–3.83	0.93
Reflux symptoms	4	518	0	Fixed	1.98	0.66–5.94	0.23
Anastomotic stenosis	6	792	13	Fixed	0.66	0.25–1.71	0.39

PG, proximal gastrectomy; TG, total gastrectomy; WMD, weighted mean difference; CI, confidence interval; OR, odds ratio; OS, overall survival; DTR, double-tract reconstruction.

Quality Assessment of the Studies

The Newcastle-Ottawa Quality Assessment Scale (NOS) was used to evaluate the quality of our included studies by 2 independent reviewers (Table 1) [22]. There were 9 elements in the NOS to assess patient population and selection, study comparability, follow-up, and outcome of interest. Each study was graded as either low quality (0–5) or high quality (6–9). A consensus reviewer resolved any discrepancies.

Data and Statistical Analysis

Effects were expressed as weighted mean difference (WMD) with corresponding 95% confidence interval (CI) for continuous variables and odds ratio (OR) with corresponding 95% CI for categorical variables. Heterogeneity was evaluated using the χ^2 test, and p value <0.1 was considered significant, while I^2 values were used for the evaluation of statistical heterogeneity [23]. Random effects models were used owing to the high heterogeneity of the studies; otherwise, fixed-effects models were used [24, 25]. Sensitivity analyses were performed by removing individual studies from the dataset and analyzing the effect on the overall results to identify sources of significant heterogeneity. Meta-analysis was performed using the Review Manager Version 5.3 software (The Cochrane Collaboration, Oxford, UK). A 2-tailed value of $p \leq 0.05$ was considered significant.

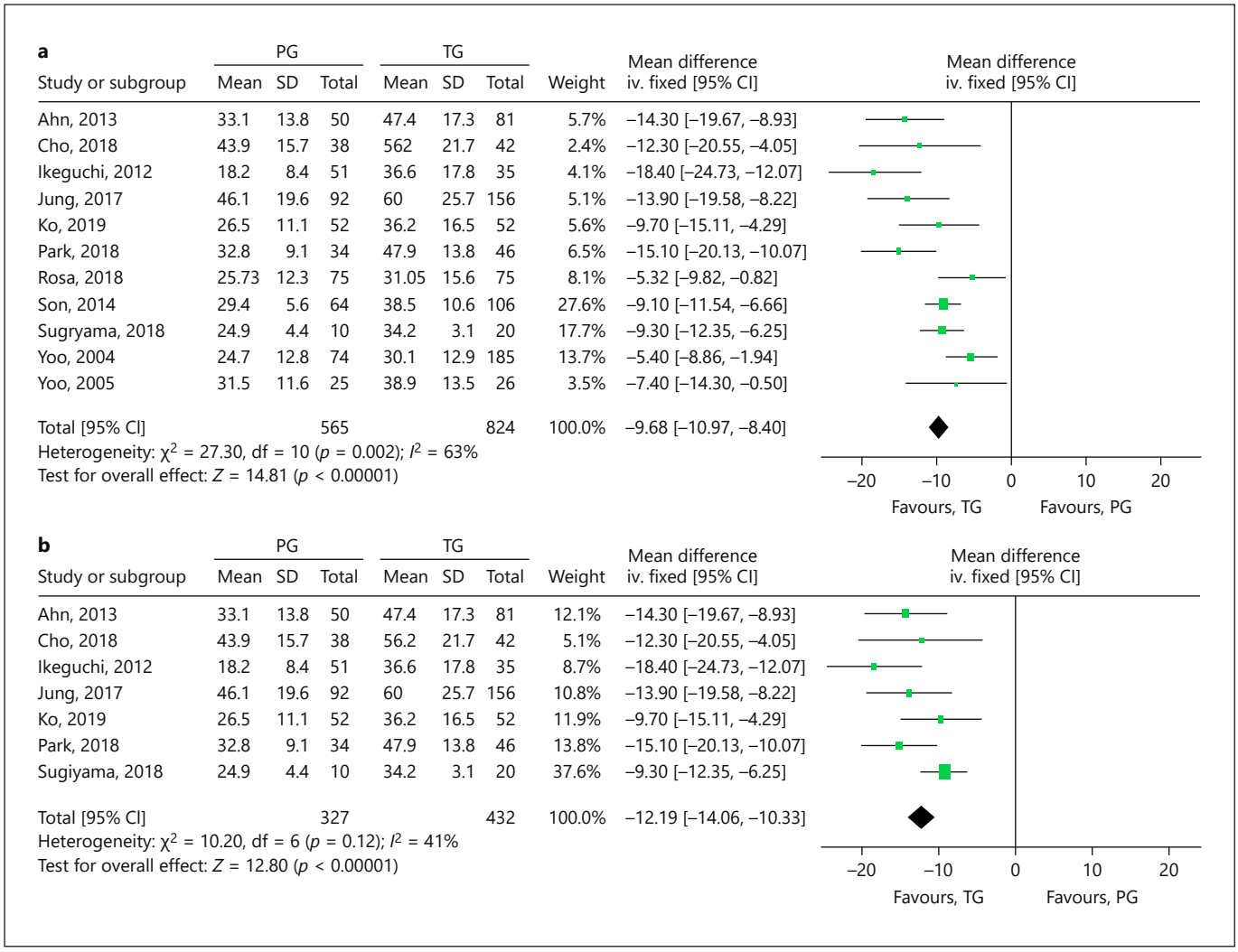

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Fig. 2 The number of retrieved lymph nodes of gastrectomy between PG and TG groups. **a** For all gastric cancer patients irrespective of stage. **b** For only early gastric cancer patients. PG, proximal gastrectomy; TG, total gastrectomy.

After the meta-analyses for all included gastric cancer patients irrespective of tumor stage, we further analyzed 2 detailed subgroups: 1 group consisting of only early gastric cancer patients, and the other for only the PG group with double-tract reconstruction (DTR). Early gastric cancer was defined as clinical early gastric cancer or clinical stage I tumor as defined in the original studies.

Results

Selected Studies

Figure 1 shows the flow diagram of the research process. The search strategy generated 1,336 clinical studies mentioned PG versus TG for PGC. After screening the titles, abstracts, full-text, or a combination of these, we selected articles based on the inclusion and exclusion criteria. Finally, a total of 2,896 patients in 25 full-text articles [7, 9–11, 17, 21, 26–45] were identified for further investigation, of which one [40] was a prospective randomized study, one [45] was a clinical phase III trial, and the rest were retrospective comparative studies. Table 1 presents the characteristics and quality assessment scores of the included studies.

Perioperative Outcomes

There were 24 studies that provided information on surgery (Table 2; see online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000506104). The meta-analysis showed that the operation time was

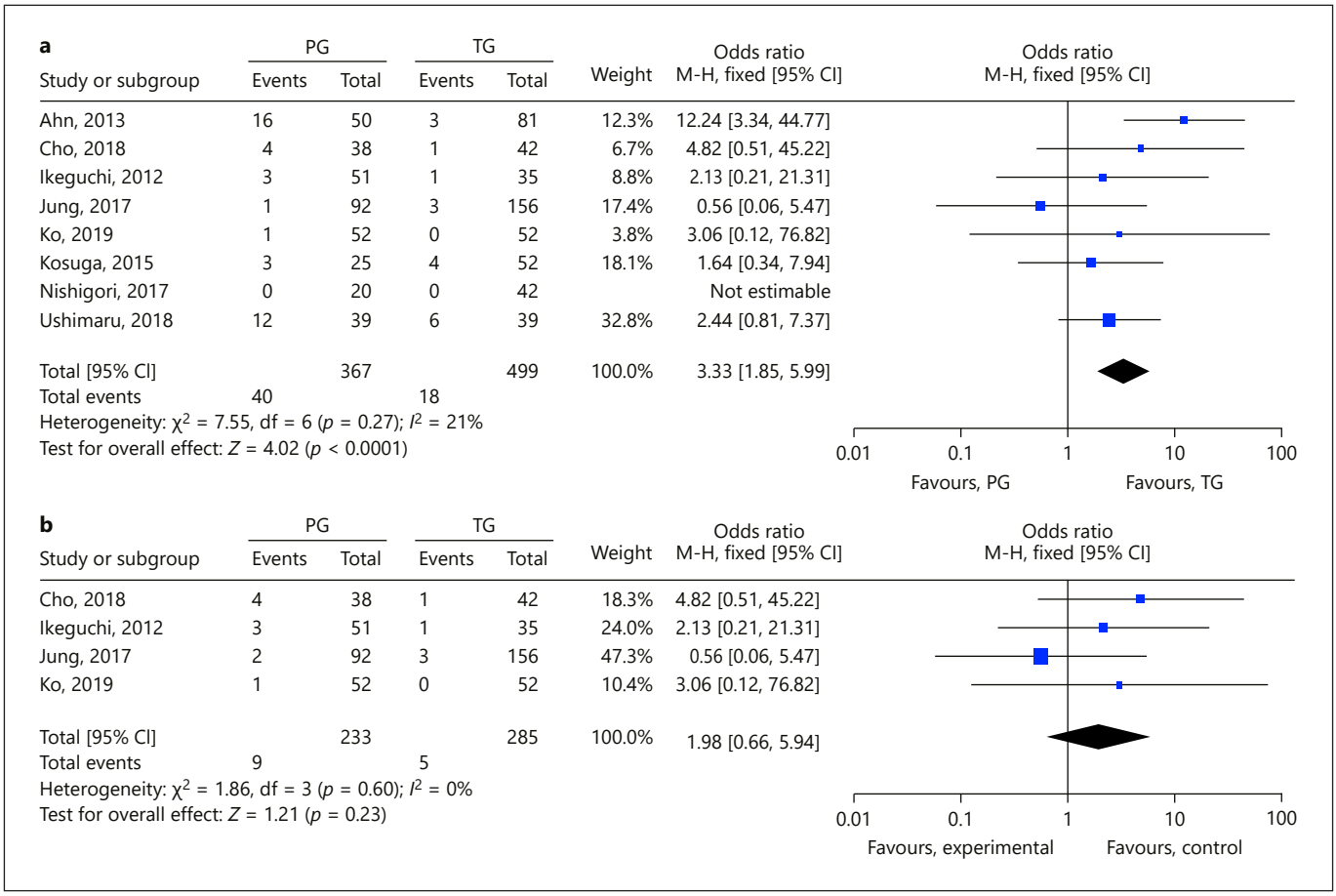


Fig. 3 The incidence of reflux symptoms of gastrectomy between the PG and TG groups. **a** For all gastric cancer patients, which were all studies of early gastric cancer patients. **b** For only the PG group with DTR. PG, proximal gastrectomy; TG, total gastrectomy; DTR, double-tract reconstruction.

comparable between the PG and TG groups (WMD = −4.80 [95% CI: −22.82 to 13.21]; $p = 0.60$). The heterogeneity between the 2 groups was significant ($I^2 = 87\%$) (online suppl. Fig. 1). There was also no significant difference in the estimated blood loss during gastrectomy between the 2 groups (WMD = −50.13 [95% CI: −103.38 to 3.13]; $p = 0.07$) (online suppl. Fig. 2).

Eleven of the 25 studies reported the number of retrieved lymph nodes of the gastrectomy. The results showed that the harvested lymph nodes were more in the TG group than in the PG group (WMD = −10.46 [95% CI: −12.76 to −8.17]; $p < 0.001$). The heterogeneity between the 2 groups was also significant ($I^2 = 63\%$) (Fig. 2a). This benefit of retrieved lymph nodes for the TG procedure was also seen in the detailed groups for early gastric cancer patients (WMD = −11.31 [95% CI: −13.18 to −8.79]; $p < 0.001$) (Table 2; Fig. 2b).

Eleven studies showed the perioperative outcome of splenectomy. The meta-analysis revealed similar outcomes (OR = 0.40 [95% CI: 0.09–1.79]; $p = 0.23$) and significant heterogeneity between the PG and TG groups ($I^2 = 88\%$) (online suppl. Fig. 3). The fixed model ($I^2 = 10\%$) of postoperative stay showed no significant differences between the 2 groups (WMD = 0.07 [95% CI: −0.48 to 0.62]; $p = 0.80$) (online suppl. Fig. 4).

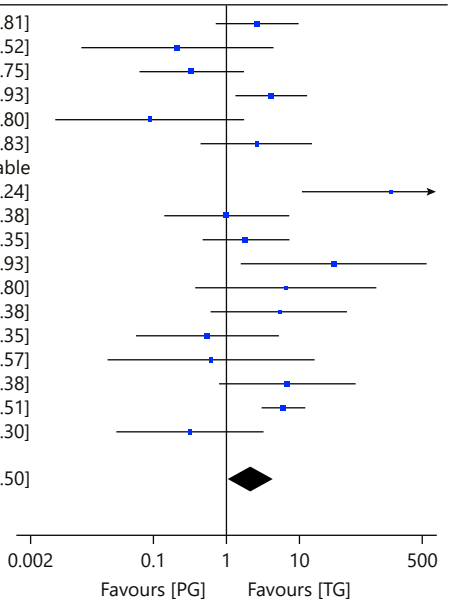
Postoperative Complications

Table 2 and online suppl. Table 2 show the postoperative complications of the included 25 studies. Among these morbidities, there were no differences in the frequencies of hospital mortality, anastomotic leakage, internal hernia, cholecystitis, pancreatitis, pneumonia, and reoperation ($p > 0.05$).

a

Study or subgroup	PG Events	PG Total	TG Events	TG Total	Weight	Odds ratio M-H, random [95% CI]
Ahn, 2013	6	50	4	81	8.3%	2.63 [0.70, 9.81]
Cho, 2018	0	38	2	42	3.7%	0.21 [0.01,4.52]
Hayami, 2017	2	43	6	47	7.1%	0.33 [0.06,1.75]
Hosoda, 2016	11	40	5	59	8.9%	4.10(1.30,12.93]
Ikeguchi, 2012	0	51	3	35	3.8%	0.09 [0.00,1.80]
Jung, 2017	3	92	2	156	6.7%	2.60(0.43, 15.83]
Katai, 2019	0	49	0	195	4.1%	Not estimable
Kim, 2006	20	43	0	104	6.1%	182.32 [10.64, 3,123.24]
Ko, 2019	2	52	2	52	8.0%	1.00(0.14, 7.38]
Kosuga, 2015	4	25	5	52	3.9%	1.79 [0.44, 7.35]
Nishlgori, 2017	5	20	0	42	4.0%	30.16(1.57, 577.93]
Nozaki, 2013	6	102	0	49	5.6%	5.67 (0.37, 120.80]
Rosa, 2018	5	75	1	75	5.3%	5.29 [0.60, 46.38]
Son, 2014	1	64	3	106	3.3%	0.54 [0.06, 5.35]
Sugiyama, 2018	0	10	1	20	5.6%	0.62 [0.02,16.57]
Ushimaru, 2018	6	39	1	39	10.4%	6.91 (0.79, 60.38]
Yoo, 2004	26	74	15	185	5.2%	6.14(3.01,12.51]
Yoo, 2005	1	25	3	26	100.0%	0.32 (0.03, 3.30]
Total [95% CI]		892		1,365		2.21 [1.08, 4.50]
Total events	98		53			

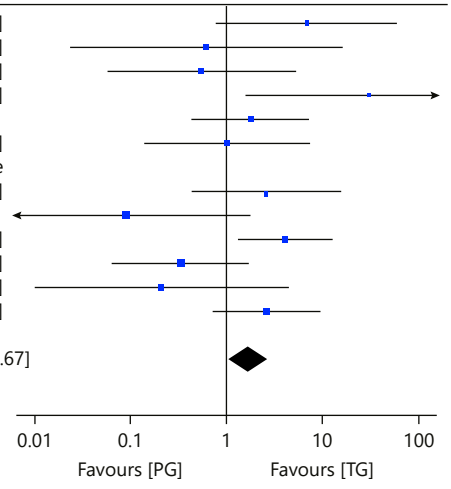
Heterogeneity: $\tau^2 = 1.13$, $\chi^2 = 39.00$, df = 16 ($p = 0.001$); $I^2 = 59\%$
Test for overall effect: $Z = 2.18$ ($p = 0.03$)



b

Study or subgroup	PG Events	PG Total	TG Events	TG Total	Weight	Odds ratio M-H, random [95% CI]
Ushimaru, 2018	6	39	1	39	3.0%	6.91 [0.79, 60.38]
Sugiyama, 2018	0	10	1	20	3.5%	0.62 [0.02, 16.57]
Son, 2014	1	64	3	106	8.0%	0.54 [0.06, 5.35]
Nishigori, 2017	5	40	0	42	0.9%	30.16 [1.57, 577.93]
Kosuga, 2015	4	25	5	52	9.8%	1.79 [0.44, 7.35]
Ko, 2019	2	52	2	52	6.9%	1.00 [0.14, 7.38]
Katai, 2019	0	49	0	195		Not estimable
Jung, 2017	3	92	2	156	5.1%	2.60 [0.43, 15.83]
Ikeguchi, 2012	0	51	3	35	14.7%	0.09 [0.00, 1.80]
Hosoda, 2016	11	40	5	59	10.5%	4.10 [1.30, 12.93]
Hayami, 2017	2	43	6	47	19.6%	0.33 [0.06, 1.75]
Cho, 2018	0	38	2	42	9.6%	0.21 [0.01, 4.52]
Ahn, 2013	6	50	4	81	4.1%	2.63 [0.70, 9.81]
Total [95% CI]		573		926	100.0%	1.69 [1.07, 2.67]
Total events	40		34			

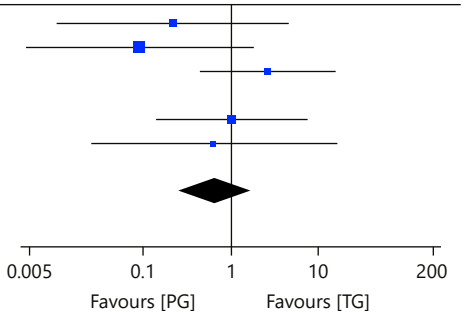
Heterogeneity: $\chi^2 = 18.91$, df = 11 ($p = 0.006$); $I^2 = 42\%$
Test for overall effect: $Z = 2.26$ ($p = 0.02$)



c

Study or subgroup	PG Events	PG Total	TG Events	TG Total	Weight	Odds ratio M-H, random [95% CI]
Cho, 2018	0	38	2	42	21.8%	0.21 [0.01, 4.52]
Ikeguchi, 2012	0	51	3	35	38.0%	0.09 [0.00, 1.80]
Jung, 2017	3	92	2	156	13.3%	2.60 [0.43, 15.83]
Katai, 2019	0	49	0	195		Not estimable
Ko, 2019	2	52	2	52	17.8%	1.00 [0.14, 7.38]
Sugiyama, 2018	0	20	1	20	9.1%	0.62 [0.02, 16.57]
Total [95% CI]		292		500	100.0%	0.66 [0.25,1.71]
Total events	5		10			

Heterogeneity: $\chi^2 = 4.60$, df = 4 ($p = 0.33$); $I^2 = 13\%$
Test for overall effect: $Z = 0.86$ ($p = 0.39$)



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The incidence of reflux symptoms (OR = 3.33 [95% CI: 1.85–5.99]; $p < 0.001$) was significantly higher in the PG group than in the TG group (Fig. 3a). Reflux esophagitis of 12 included studies, however, was comparable between the PG and TG groups (OR = 1.36 [95% CI: 0.59–3.13]; $p = 0.47$) (online suppl. Fig. 5). The heterogeneity of reflux symptom rate and reflux esophagitis between the 2 groups was significant ($I^2 = 21$ and 70%, respectively). This meta-analysis also revealed that the incidence of anastomotic stenosis between the PG and TG groups was also different (OR = 2.21 [95% CI: 1.08–4.50]; $p = 0.03$) (Fig. 4a, b), and the heterogeneity was significant ($I^2 = 59\%$). In contrast, there was no significant difference between the 2 groups for detailed PG patients following DTR in terms of reflux symptoms and anastomotic stenosis ($p = 0.23$ and $p = 0.39$, respectively) (Table 2; Figs. 3b, 4c).

Eleven homogenous ($I^2 = 0.0\%$) studies (1,439 patients) provided data of ileus. According to the fixed-effects model, the TG group showed a higher ileus rate than the PG group (OR = 0.30 [95% CI: 0.20–0.78]; $p = 0.007$). The result also revealed that patients who underwent TG had more possibility of abdominal abscess (OR = 0.36 [95% CI: 0.19–0.69]; $p = 0.002$) (Table 2).

Long-Term Survival Outcomes

Our result showed that the PG group was associated with a better 5-year OS relative to TG with 11 included studies (OR = 1.35 [95% CI: 1.03–1.77]; $p = 0.03$) (Fig. 5a). After stratification for early gastric cancer and PG-DTR groups, however, there was no significant difference between the 2 groups (OR = 1.35 [95% CI: 0.59–2.45]; $p = 0.62$) (Fig. 5b, c).

Discussion

To date, the extent of optimal gastric resection for PGC continues to remain controversial, and a final consensus has yet to be met. Realistically, many surgeons are now actively applying PG to PGC due to the advantages of preservation of the gastric remnant. Our study used a meta-analysis way, a total of 2,896 patients from 25 studies, to investigate how the gastrectomy type was associated with perioperative complications and prognosis of PGC patients. To our best knowledge, this analysis represented the largest evaluation that targeted this issue.

Surgical resection was the preferred treatment for gastric cancer patients [46]. Our analyses indicated that the PG group showed equivalent outcomes of the operative time and estimated blood loss duration gastrectomy when compared with the TG group. The published randomized controlled study, however, demonstrated that the volume of intraoperative blood loss was obviously more by TG than the PG procedure as it was universally acknowledged [40]. A critical reason for this difference was the technical development for PG surgery nowadays. Concerning neo-/adjuvant therapy, an essential factor for survival, there was no significant difference between the 2 groups. In addition, our study also revealed TG enabled a more completed nodal dissection, which was concordance with all published studies [47, 48]. The extent of lymphadenectomy was another important consideration when TG and PG are compared, especially the dissection of #4d, #5, and #6, which are usually excluded in PG. However, Yura et al. [49] following 202 locally advanced gastric cancer patients indicated that the metastatic rate of these lymph nodes was really low (#4d, 0.99%; #5, 0%; and #6, 0%), while the nodes with high metastatic rate for PGC, like #3, #2, and #1, were included in PG. This may suggest that oncological safety would be ensured by PG, without the need for TG when targeting for nodal dissection.

Recently, postoperative quality of life has received significant attention in addition to oncological outcomes. This was mainly because the incidence of postgastrectomy disturbances in patients who underwent PG was high as previously reported, including some meta-analyses [17, 29, 47, 48, 50]. In our experience, the PG group showed a higher rate of anastomotic stenosis and reflux symptoms but similar reflux esophagitis when compared with TG. More investigations are needed to clarify this issue in future studies. Luckily, PG patients with DTR of our study did not have a higher rate for postoperative complications, including anastomotic stenosis and reflux symptoms. The esophagojejunostomy techniques, such as that done with jejunal interposition (JI) or DTR, are now thought to be alternatives to esophagogastrostomy (EG) reconstruction after PG to prevent postoperative complications [7, 51, 52]. For example, Li et al. [53] showed that there was no difference statistically in anastomotic stenosis and reflux esophagitis between laparoscopy-assisted proximal gastrectomy (LAPG) with DTR and laparoscopy-assisted total gastrectomy (LATG), which showed an optimistic prospect for PG feasibly.

Fig. 4 The incidence of anastomotic stenosis of gastrectomy between the PG and TG groups. **a** For all gastric cancer patients irrespective of stage. **b** For only early gastric cancer patients. **c** For only the PG group with DTR. PG, proximal gastrectomy; TG, total gastrectomy; DTR, double-tract reconstruction.

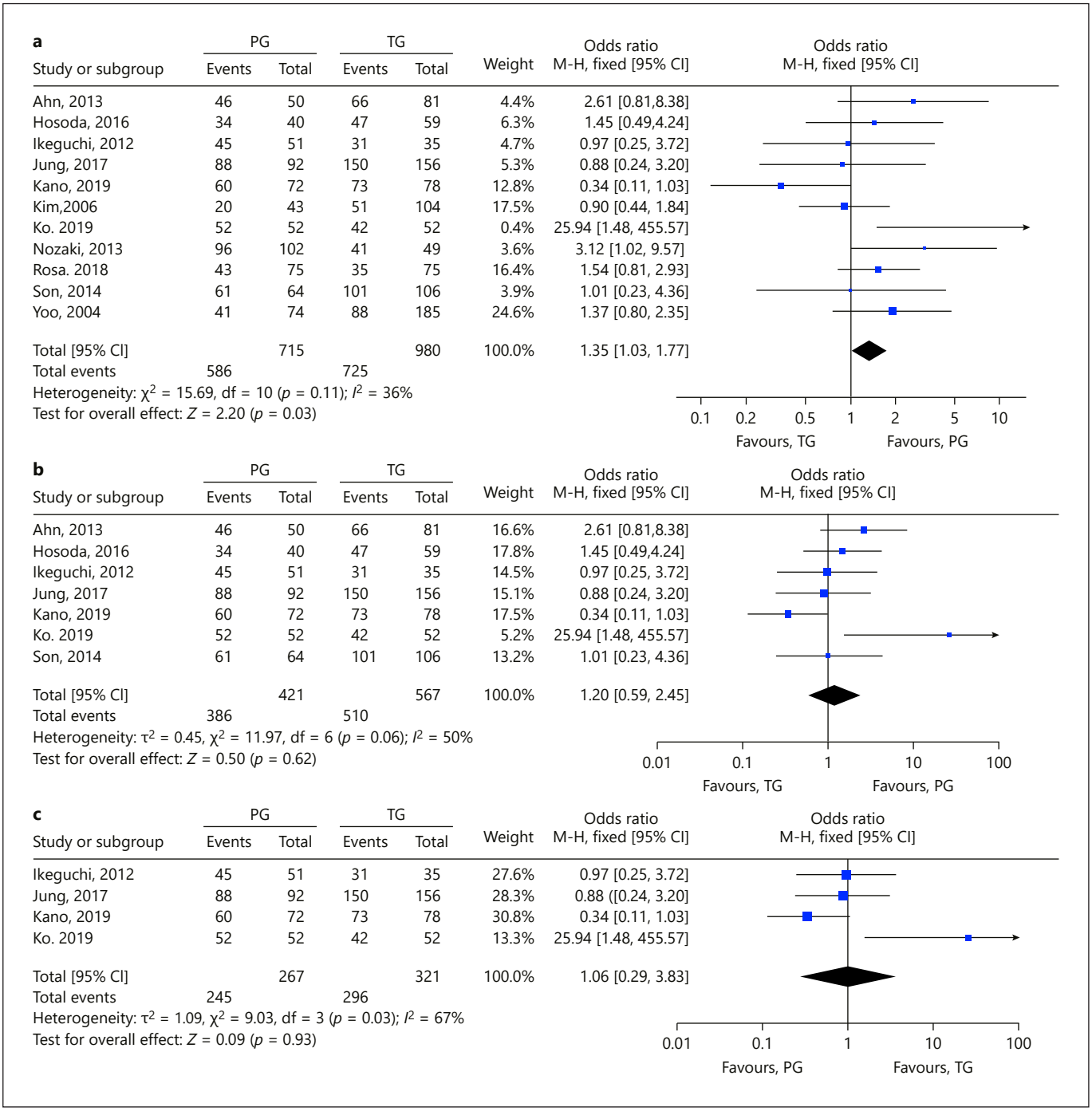

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Fig. 5 The 5-year OS for PGC with PG or TG. **a** For all gastric cancer patients irrespective of stage. **b** For only early gastric cancer patients. **c** For only the PG group with DTR. OS, overall survival; PGC, proximal gastric cancer; PG, proximal gastrectomy; TG, total gastrectomy; DTR, double-tract reconstruction.

Shreds of evidence for the prognosis effect of PG have been inconsistent. The published "Japanese Gastric Cancer Treatment Guidelines 2014" commended that PG was only suitable for some certain early stage diseases (such as clinical T1a), while TG should be recommended for advanced PGC to achieve the standard lymph node dissections [46]. On the other hand, some recent meta-analyses showed no significant difference in long-term survival in

both early and locally advanced gastric cancer between PG and TG groups in past years [17, 47, 48, 50]. Different from these meta-analyses, our study provided that PG had a prominent improved OS than TG for all gastric cancer patients irrespective of stage, while a similar 5-year OS for only early gastric cancer patients. This may suggest that the PG approach with DTR could be considered under well-established protocols for resectable PGC patients. There were some possible reasons for this survival difference. Firstly, compared with the previous meta-analyses, we have included the latest articles targeting this issue until October 2019. Ko et al. [41] even presented that 5-year OS rates were 100 and 81.6% for PG with DTR and TG patients ($p = 0.02$), respectively. Secondly, the PG group appeared to present at an earlier stage (higher rate of pathological stage I, $p < 0.05$) when compared with the TG group, which may have a survival bias for outcomes. Furthermore, a possible reason for the favorable survival for all patients but not in the subgroup of early stage patients was that the patients with stage II–IV cancers are more likely to be older, who would receive more benefits of stomach-function preserving of PG than TG, thus keeping a stable nutritional status [26].

Strengths and limitations should be considered when interpreting the study results. The study had several advantages. Above all, it might have the reference value as the number of this meta-analysis was the largest to date to compare the clinical outcomes between PG and TG groups. Moreover, we assessed the effect of PG on perioperative results, postgastrectomy disturbances, and long-term survival outcomes. Nevertheless, there are some limitations. Firstly, 23 of 25 studies were clinical observational trials, and only one was a clinical phase III trial. Secondly, the heterogeneities of the operation time, blood loss, number of retrieved lymph nodes, and other variables were all significant. This result may be mainly attributed to the selection bias. Thirdly, nutrition and body weight indexes after gastrectomy were not included in this meta-analysis for limited data reported in the original articles.

In conclusion, PG was associated with a visible improved long-term survival outcome for all irrespective of tumor stage, while a similar 5-year OS for only early gastric cancer patients between the 2 groups. Future randomized clinical trials of esophagojejunostomy techniques, such as DTR following PG, are expected to prevent postoperative complications and assist surgeons in the choice of surgical approach for PGC patients.

Disclosure Statement

The authors have declared no conflicts of interest.

Funding Sources

This study was funded in part by the National Key R&D Program of China (Grant No. 2017YFC0908300).

Author Contributions

Lulu Zhao and Rui Ling contributed equally to this work. All authors made substantial contributions to the intellectual content of this paper. Yingtai Chen: concept; Lulu Zhao: design; Jinghua Chen: supervision; Fuhai Ma: resources; Anchen Shi: materials; Changpeng Chai: data collection and processing; Dongbing Zhao: analysis and interpretation; Jinghua Chen: literature search; Rui Ling and Lulu Zhao: manuscript writing; and Yingtai Chen: critical review.

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