

Surgical and oncological outcomes of distal gastrectomy compared to total gastrectomy for middle-third gastric cancer: A systematic review and meta-analysis

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Abstract. Distal gastrectomy (DG) and total gastrectomy (TG) are the most common types of radical surgery for patients with middle-third gastric cancer (MTGC). However, the indications and benefits of the two procedures still remain controversial. The present meta-analysis aimed to compare the surgical and oncological outcomes of DG and TG in the treatment of MTGC. A rigorous literature review was performed in the databases of PubMed, Embase, Web of Science, China National Knowledge Infrastructure and Chinese BioMedical Literature to retrieve studies published up to February 2022. The Newcastle-Ottawa Scale was used to assess the quality of included studies and a meta-analysis was performed using

RevMan 5.3 software. A total of 12 retrospective studies performing comparisons of DG and TG were included in the present meta-analysis. For patients who underwent DG, a lower rate of overall post-operative complications, anastomosis leakage and intro-abdominal infection was determined. No significant difference was observed between DG and TG in the 5-year overall survival when the proximal resection margin ranged from 3 to 5 cm. Although DG was associated with a higher 5-year overall survival rate when compared to TG, there was no significant difference in the stratified analyses by TNM stage. In conclusion, the prognosis of MTGC did not depend on the extent of gastrectomy. With lower complications and acceptable oncological outcomes, DG was a safe and feasible surgical procedure for MTGC when a negative proximal margin was confirmed.

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Abbreviations: DG, distal gastrectomy; TG, total gastrectomy; MTGC, middle-third gastric cancer; CNKI, Chinese National Knowledge Infrastructure; LN, lymph node; OS, overall survival; PRM, proximal resection margin; NOS, Newcastle-Ottawa Scale; OR, odds ratio; CI, confidence interval; OG, open gastrectomy; LAG, laparoscopic-assisted gastrectomy; JGCTG, Japanese gastric cancer treatment guidelines; RCT, randomized controlled trial

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Key words: middle-third gastric cancer, total gastrectomy, distal gastrectomy, meta-analysis, outcomes

Introduction

Gastric cancer has become the fifth most common and the third most lethal malignant tumor type, with >1 million cases diagnosed throughout the world in 2020 (1). Numerous patients had lymph node (LN) or distant metastasis of cancer, leading to poor prognosis and posing a major threat to their lives (2). Radical gastrectomy was the dominant surgical therapy for gastric cancer and the extent of surgical resection was mainly determined by tumor size, tumor location and resection margin distance. Distal gastrectomy (DG) and total gastrectomy (TG) were recommended as the standard methods for radical resection of lower-third and upper-third gastric cancer, respectively (3). However, the optimal resection extent for middle-third gastric cancer (MTGC) still remains controversial.

Studies suggested TG as the best choice for surgical treatment of MTGC due to the possibility of a more thorough lymphadenectomy and lower incidence of remnant gastric cancer (4,5). Several other reports indicated that DG was a reasonable procedure for MTGC with less weight loss, better nutritional status and a lower post-operative complication

rate than TG (6-8). Further research discovered a similar post-operative survival for DG and TG (9,10). In addition, the study by Zheng *et al* (11) clarified that prophylactic clearance of the no. 10 LN was not essential for MTGC. Therefore, it is still being debated whether DG or TG is the more beneficial procedure for MTGC.

Previous meta-analyses were performed to explore the clinical efficacy and benefits of DG vs. TG, but the majority of cases included were patients with lower-third gastric cancer, which inevitably decreased the credibility of the analytical results for MTGC (12-14). Hence, the present meta-analysis was performed to compare the surgical and oncological outcomes between DG and TG only in MTGC.

Materials and methods

Search strategy. Studies published in English and Chinese were retrieved from the electronic databases PubMed (<https://pubmed.ncbi.nlm.nih.gov/>), Web of Science (<https://www.webofknowledge.com>), Embase (<https://www.embase.com>), Chinese National Knowledge Infrastructure (CNKI; <https://www.cnki.net>) and Chinese BioMedical Literature (<http://www.sinomed.ac.cn>) from inception to February 2022. The key words for the search were as follows: 'Gastric cancer or middle-third or gastrectomy', 'gastric carcinoma or middle-third or gastrectomy', 'gastric cancer or distal gastrectomy or total gastrectomy' and 'gastric cancer or subtotal gastrectomy or total gastrectomy'. Papers unable to be directly found on the internet were obtained via manually searching the other publications of all of the authors of the studies already retrieved.

Inclusion and exclusion criteria. All of the studies included were required to meet the following criteria: i) Studies focused on the comparison of short- or long-term outcomes between DG and TG; ii) patients in the studies were diagnosed with MTGC; iii) at least one concerned outcome was reported in the studies, such as operation time, blood loss, retrieved LNs, hospital stay, post-operative complications and 5-year overall survival (OS); and iv) studies with available data.

Studies fulfilling the following criteria were excluded from the present analysis: i) Studies not assessing the clinical efficacy of DG and TG in patients with MTGC; ii) non-case-control studies; iii) studies identified to be reviews, case reports, brief communications or letters to editors; iv) studies without extractable data of clinical outcomes; and v) repeatedly published studies.

Data extraction. A total of two authors (YJ and FY) extracted the data from each included study independently. In the case of any discrepancy, a third author was involved in this process until a final agreement was reached. The data for extraction were as follows: Author, publication year, study design, study period, sample size, median age, gender distribution, surgical procedure of gastrectomy and lymphadenectomy, numbers of cases of each TNM stage, median follow-up, blood loss, numbers of LNs, hospital stay, post-operative morbidity (overall morbidity rate, anastomosis leakage, anastomosis stenosis, duodenal stump fistula, intra-abdominal infection, wound problems and post-operative bleeding), 5-year OS,

5-year stage-specific OS and the 5-year OS according to the width of the proximal resection margin (PRM).

Quality assessment. The quality of each selected study was determined using the Newcastle-Ottawa-Scale and the scoring criteria contained three aspects of selection of patients, comparability and exposure (14). Studies with a score ≥ 6 were considered high-quality studies, while those with a score < 6 were considered low-quality studies.

Statistical analysis. The dichotomous variables and continuous variables were described as the odds ratio (OR) and weighted mean difference and the two types of variables were reported with the 95% confidence interval (CI). $P < 0.05$ was considered to indicate a statistically significant difference. I^2 statistics were performed to calculate the heterogeneity among the studies; if there was no significant heterogeneity ($I^2 < 50\%$, $P > 0.1$) observed in the results, the fixed-effects model was used, while the random-effects model was used when significant heterogeneities ($I^2 > 50\%$, $P < 0.1$) were detected. Funnel plots were generated to evaluate any possible publication bias. All of the statistical analyses of the present meta-analysis were performed by Review Manager version 5.3 software (Nordic Cochrane Centre).

Results

Clinical characteristics. A total of 330 articles were retrieved in the initial literature search. Subsequently, 143 papers were excluded due to duplicated data. In the second screening, 131 papers with irrelevant topics were excluded. Furthermore, 44 papers met the exclusion criteria and were removed after the third screening. Finally, 12 retrospective studies were included in this present meta-analysis after rigorous literature screening (10,15-25). The flowchart for the literature selection process is displayed in Fig. 1. Among these studies, 9 pertained to conventional open gastrectomy and 3 to laparoscopic-assisted gastrectomy (LAG). Of the enrolled patients, 1,077 underwent DG and 1,502 underwent TG. The clinical characteristics were summarized in detail in Table I. The assessment process of the methodological quality of selected studies is presented in Table II; each study reached a score ranging from 6 to 8, which indicated that all of the included papers were high-quality studies.

Surgical outcomes. Comparisons of the duration of surgery were provided by 4 of the studies included (10,18,19,24). A significantly longer operative time was observed in the TG as compared with that in the DG group (random-effects model; I^2 : 72%; OR, 17.95; 95% CI, 5.69-30.20; $P = 0.004$; Fig. 2A). A total of three studies reported on the estimated blood loss and the analysis revealed comparable results for the DG and TG groups (10,18,19) (random-effects model; I^2 : 93%; OR, 39.75; 95% CI, -3.71 to 83.20; $P = 0.07$; Fig. 2B). Data of LN extraction were recorded in 6 studies and a significant difference was detected with a higher number of LNs extracted in the TG group (10,16,18,19,24,25) (random-effects model; I^2 : 66%; OR, 5.32; 95% CI, 3.39-7.26; $P < 0.001$; Fig. 2C). Furthermore, data on the post-operative hospital stay were provided by 4 studies and the pooled analysis indicated that the TG group

Table I. Detailed characteristics of patients from the included studies.

First author	Year	Population	Study design	Study period	Sample size		Age, years		Sex, males/females		Surgical procedure	Lymphadenectomy	Tumor stage (I/II/III/IV)		Median, follow-up months	5-year overall survival, %	
					TG	DG	TG	DG	TG	DG			TG	DG		TG	DG
Jang	2010	South Korea	Retrospective study	1993-2005	178	148	53.42±13.07	54.41±13.65	101/77	95/53	OG	D1, D2	17/37/89/35	36/41/62/9	-	58.4	67.8
Lee	2010	South Korea	Retrospective study	2000-2006	63	62	56.2	58	43/20	39/23	OG	-	5/13/40/5	29/13/19/1	-	38.1	69
Wang	2012	China	Retrospective study	2001-2006	98	47	-	-	57/41	31/16	OG	D1, D2, D2+	6/19/67/6	10/15/21/1	40	25.5	63.8
Li	2013	China	Retrospective study	2010-2012	50	58	62.1±5.4	61.2±6.8	35/15	38/20	OG	D1, D2, D3	16/14/13/7	10/15/28/5	-	49	59
Tao	2013	China	Retrospective study	1998-2005	156	66	56.9±11.5	55.8±9.8	130/26	43/23	OG	D2	15/19/122/0	18/13/35/0	-	49.8	63.9
Lu	2014	China	Retrospective study	2000-2007	194	86	54.7±10.2	56.3±11.3	157/37	54/32	OG	-	24/32/138/0	27/25/34/0	-	47.6	64.3
Zhou	2014	China	Retrospective study	2003-2008	85	32	-	-	-	-	OG	-	6/18/61/0	15/7/10/0	-	48.2	66.8
Gao	2015	China	Retrospective study	2003-2008	104	53	58.87±11.45	59.56±10.97	60/44	34/19	OG	D1, D2, D2+	8/20/69/7	12/17/23/1	48	24	64.2
Ji	2017	China	Retrospective study	2005-2011	195	144	-	-	132/63	94/50	OG	D1, D2	17/38/132/8	36/25/64/19	41.8	47	65
Li	2018	China	Retrospective study	2005-2014	146	146	55.95±10.84	55.48±11.60	103/43	103/43	LAG	D2	18/59/69/0	20/59/67/0	54	61	64.4
Wang	2018	China	Retrospective study	2007-2013	188	188	57.9 ± 11.1	57.3 ± 11.4	151/37	146/42	LAG	D2	49/40/99/0	45/40/103/0	44.8	41.8	55.6
Liu	2020	China	Retrospective study	2013-2017	45	47	58.0 ± 9.9	57.0 ± 11.1	17/28	11/36	LAG	D2	11/16/18/0	18/10/19/0	41	-	-

TG, total gastrectomy; DG, distal gastrectomy; OG, open gastrectomy; LAG, laparoscopic-assisted gastrectomy; -, not mentioned.

Table II. Results of quality assessment with the Newcastle-Ottawa scale tool.

Author (year)	Selection				Comparability	Exposure			Total score	(Refs.)
	1	2	3	4	5	6	7	8		
Jang (2010)	+	+	-	+	+	+	+	-	6	(16)
Lee (2010)	+	+	-	+	+	+	+	+	7	(15)
Wang (2012)	+	+	-	+	++	+	+	+	8	(20)
Li (2013)	+	+	-	+	+	+	+	+	7	(24)
Tao (2013)	+	+	-	+	+	+	+	-	6	(21)
Zhou (2014)	+	+	-	+	+	+	+	+	7	(22)
Lu (2014)	+	+	-	+	+	+	+	-	6	(25)
Gao (2015)	+	+	-	+	++	+	+	+	8	(23)
Ji (2017)	+	+	-	+	+	+	+	+	7	(17)
Li (2018)	+	+	-	+	++	+	+	+	8	(10)
Wang (2018)	+	+	-	+	++	+	+	+	8	(18)
Liu (2020)	+	+	-	+	++	+	+	+	8	(19)

Items: 1, Representativeness of exposed cohort; 2, Selection of non-exposed cohort; 3, Ascertainment of exposure; 4, Outcome of interest was not present at start of study; 5, Comparability of cohorts on the basis of the design or analysis; 6, Assessment of outcomes; 7, Follow-up long enough for outcomes to occur; 8, Adequacy of follow-up.

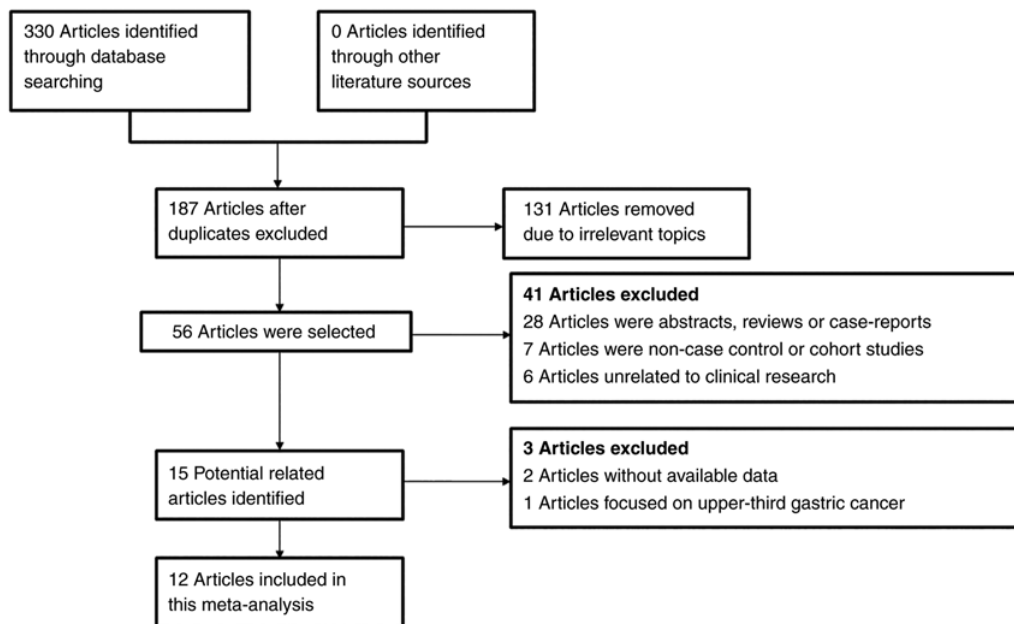


Figure 1. Flow chart for the literature search.

had a longer hospital stay when compared with that of the DG group (10,18,19,24) (fixed-effects model; I^2 :12%; OR, 1.01; 95% CI, 0.76-1.26; P <0.001; Fig. 3).

Post-operative complications. Post-operative complication rates were reported by 5 studies (10,17-19,24). Regarding overall complications, DG was associated with a significantly lower incidence rate than TG (fixed-effects model; I^2 : 0%; OR, 1.69; 95% CI, 1.23-2.31; P =0.001; Fig. 4A). When analyses were stratified by the various types of complications, it was observed that the incidence of duodenal stump fistula,

anastomosis stenosis, post-operative bleeding and wound problems were reported by 3, 4, 3 and 3 of the included studies, respectively (10,17-19). The results did not indicate any significant differences in these specific complications between the two groups (fixed-effects model; I^2 : 0%; P >0.05; Fig. 4D-G). Of note, subgroup analyses focusing on anastomosis leakage (fixed-effects model; I^2 :0%; OR, 3.38; 95% CI, 1.23-9.28; P =0.02) and intro-abdominal infection (fixed-effects model; I^2 : 0%; OR, 2.24; 95% CI, 1.18-4.26; P =0.01) suggested that TG was associated with a higher incidence of both of the two complications (Fig. 4B and C).

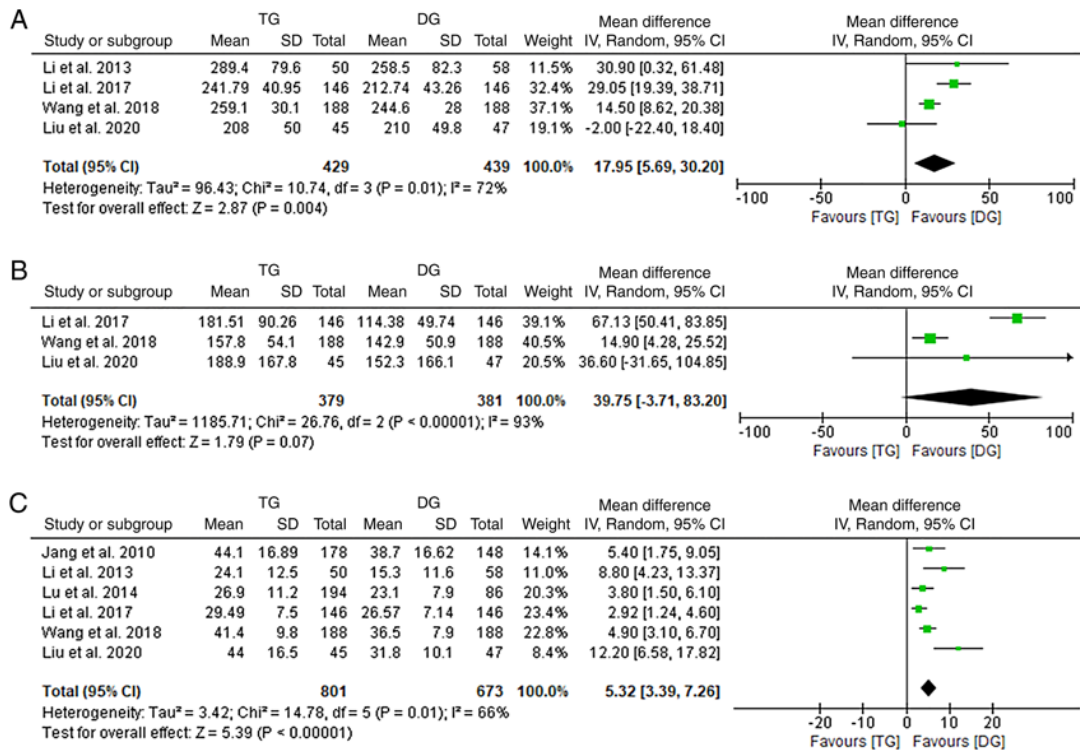


Figure 2. Forest plot for the comparisons of intra-operative parameters between TG and DG. (A) Intra-operative time; (B) estimated blood loss; and (C) retrieved lymph nodes. TG, total gastrectomy; DG, distal gastrectomy; SD, standard deviation; IV, inverse variance; df, degrees of freedom.

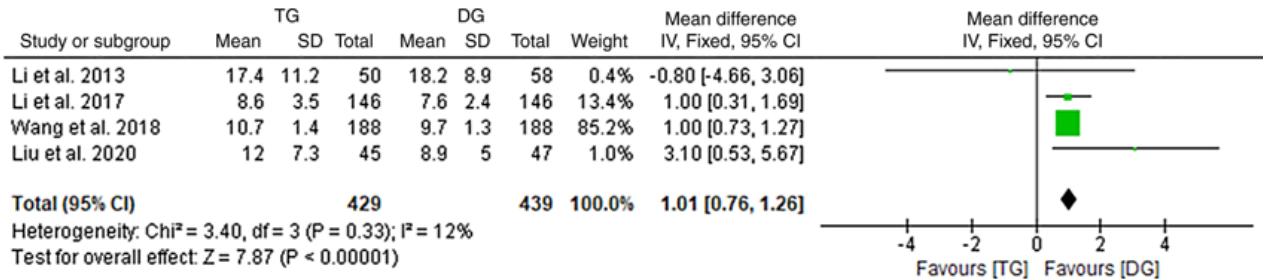


Figure 3. Forest plot for the comparison of post-operative hospital stay between TG and DG groups. TG, total gastrectomy; DG, distal gastrectomy; SD, standard deviation; IV, inverse variance; df, degrees of freedom.

Impact of the distance to PRM on prognosis. A total of five studies comprehensively explored the associations of the distance to the PRM with the prognosis of patients with MTGC (15,16,21,22,25). Among these studies, 3 defined 3 cm as the standard and 5 defined 4 and 5 cm as the standards. No significant difference was discovered in the 5-year OS between the groups if the standard for the PRM was set as 3, 4 and 5 cm (fixed-effects model; I²: 0%; P>0.05; Fig. 5A-C).

Post-operative survival. Data on post-operative survival were provided by 11 of the included studies (10,15-24). A significantly lower 5-year OS was observed in the TG group as compared with that in the DG group (random-effects model; I²: 60%; OR, 0.47; 95% CI, 0.36-0.62; P<0.001; Fig. 6). However, when further analyses with stratification by TNM stage (I, II, III or IV) were performed, no significant differences were obtained between the TG and DG groups (fixed-effects model; I²: 0%; P>0.05; Fig. 7A-D).

Discussion

During the past two decades, the proportion of patients diagnosed with upper or MTGC was gradually elevated (26). Recently, an increasing morbidity of advanced MTGC with poor survival was also reported by statistics from the USA (27). According to the 5th Japanese gastric cancer treatment guidelines (JGCTG), pylorus-preserving distal gastrectomy is only suggested for cases with cT₁N₀M₀ stage malignant tumor arising in the middle-third of the stomach if a macroscopically negative distal margin of at least 4 cm was feasible (28). TG and DG are the two major surgical treatments for MTGC. However, the results regarding short- and long-term outcomes of the two procedures in the different studies were inconsistent. Certain studies recommended TG for MTGC as a means of prevention for tumor recurrence and gastric stump cancer. However, it was clarified that DG was associated with better post-operative functional outcomes with its lesser disruption

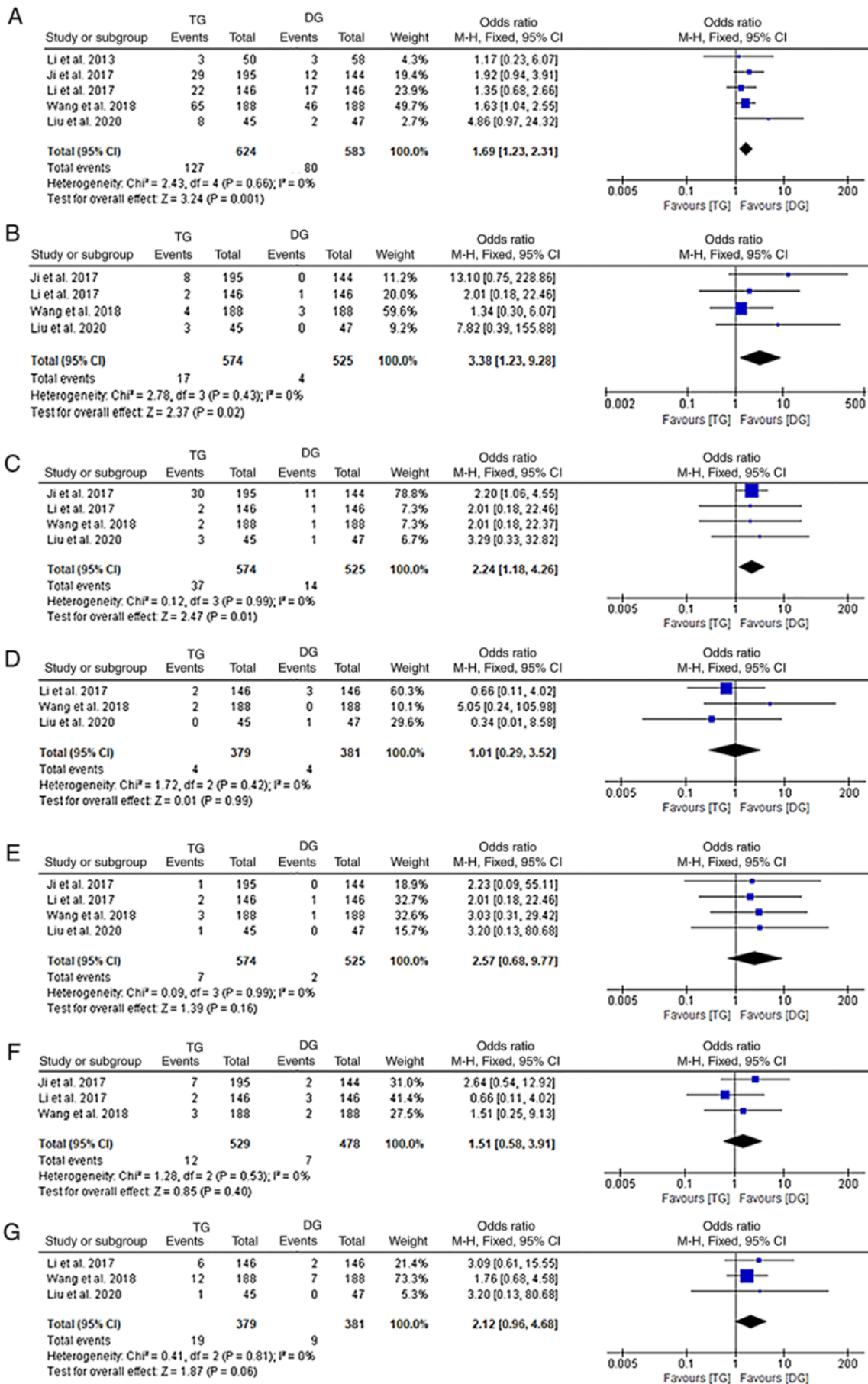


Figure 4. Forest plot for the comparison of post-operative complications between TG and DG groups. (A) Overall complications; (B) anastomosis leakage; (C) intra-abdominal infection; (D) duodenal stump fistula; (E) anastomosis stenosis; (F) post-operative bleeding; and (G) wound problems. TG, total gastrectomy; DG, distal gastrectomy; SD, standard deviation; M-H, Mantel-Haenszel; df, degrees of freedom.

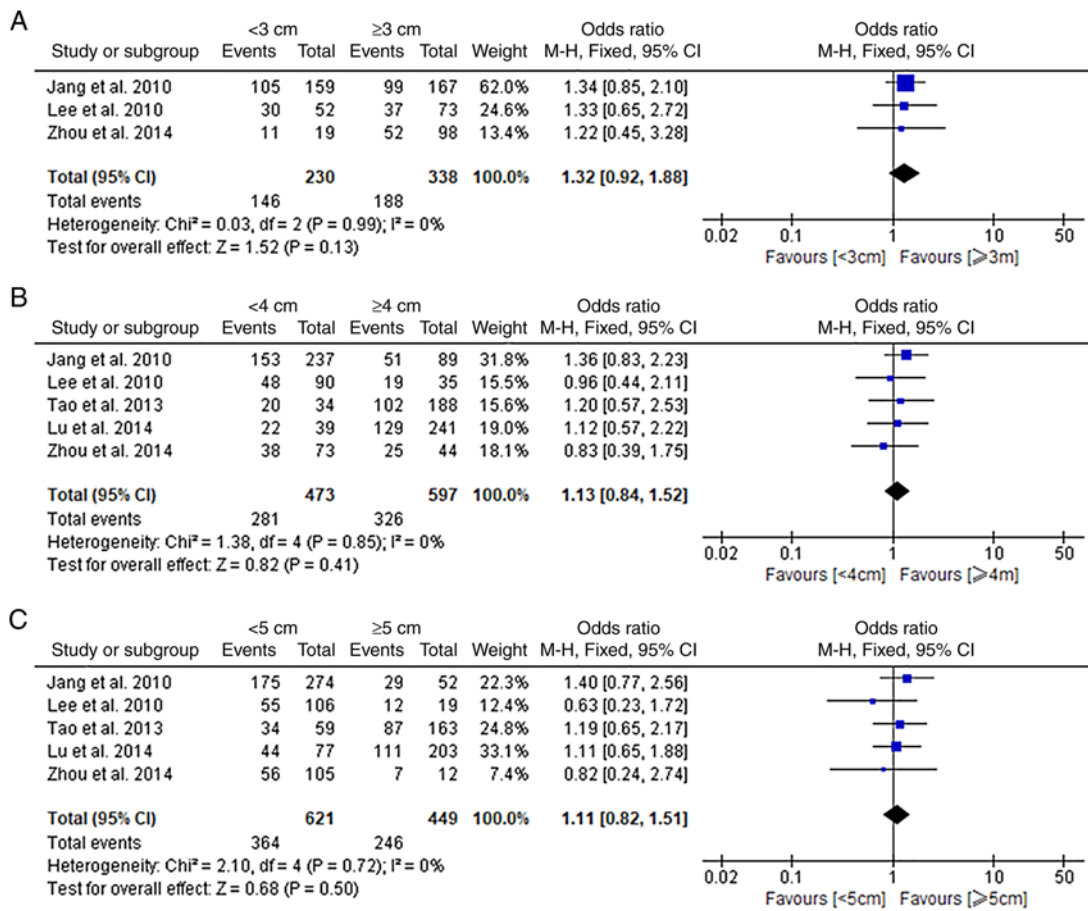


Figure 5. Forest plot for the comparison of 5-year overall survival when the PRM ranged from 3 to 5 cm. (A) PRM=3 cm; (B) PRM=4 cm; (C) PRM=5 cm. TG, total gastrectomy; DG, distal gastrectomy; M-H, Mantel-Haenszel; df, degrees of freedom; PRM, proximal resection margin.

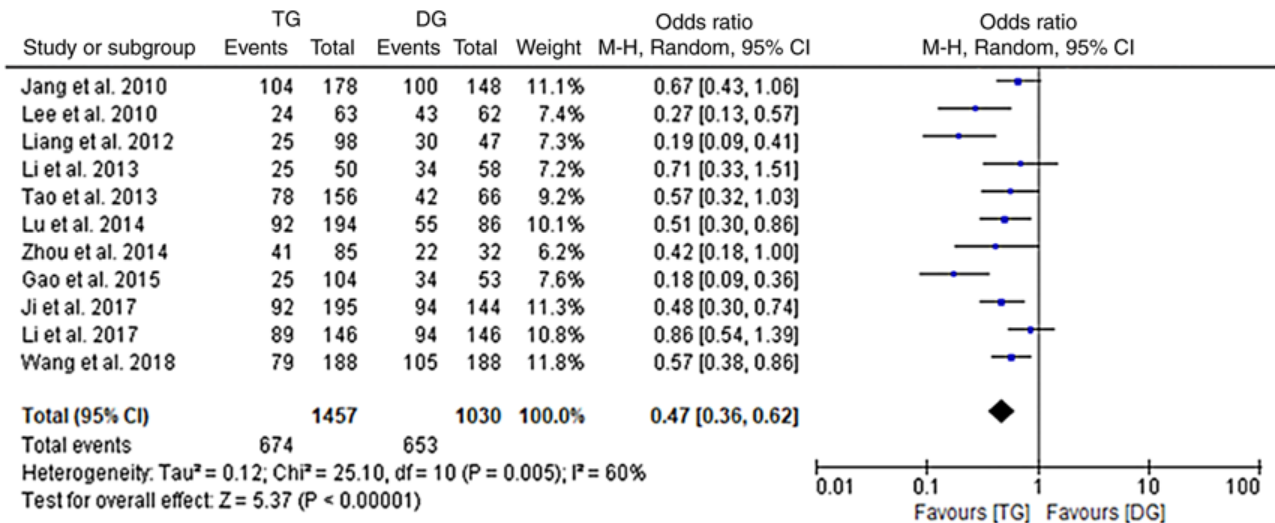


Figure 6. Forest plot for the comparison of 5-year overall survival between TG and DG groups. TG, total gastrectomy; DG, distal gastrectomy; M-H, Mantel-Haenszel; df, degrees of freedom.

of the digestive tract, which probably enhanced the post-operative recovery (29). The present meta-analysis was performed to determine the potential optimal surgical procedure for MTGC.

Surgical performance data are important for the assessment of post-operative short-term outcomes. In the present study,

TG was determined to be associated with a larger extent of lymphadenectomy and a longer operative time. In the scenario of standard lymphadenectomy in DG, an added stage of no. 2, 4sa and 11d LNs was necessary to be dissected in TG with D2 LN dissection to meet the criteria of the 5th JGCTG (30), which may appropriately explain the significantly larger

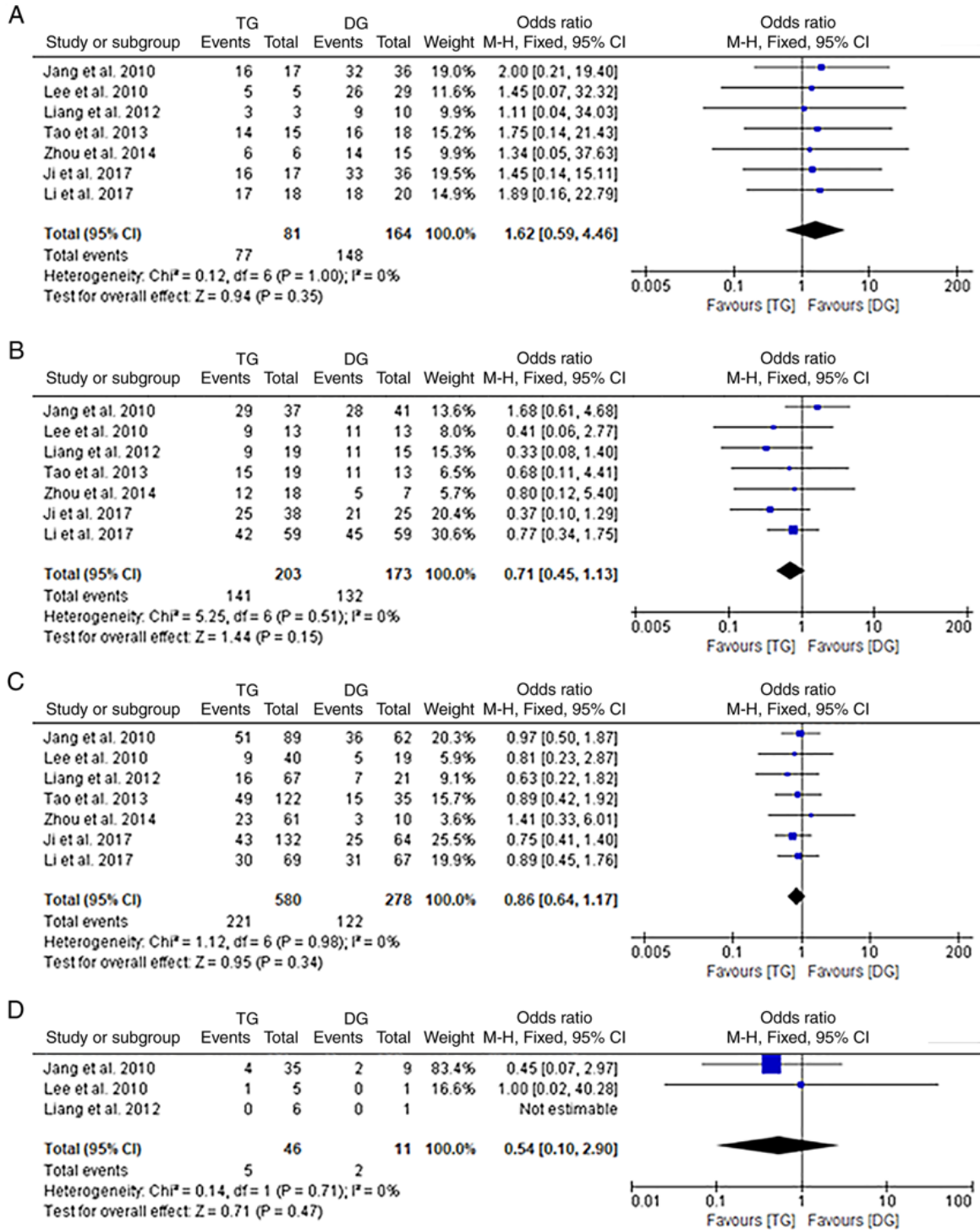


Figure 7. Forest plot of the comparison between TG and DG in the 5-year overall survival by TNM stage. (A) Stage I; (B) stage II; (C) stage III; (D) stage IV. TG, total gastrectomy; DG, distal gastrectomy; M-H, Mantel-Haenszel; df, degrees of freedom.

number of retrieved LNs determined in the TG group. The technical complexity may be another factor responsible for the extended operative time in TG. Lee *et al* (31) detected a positive association between longer operative time and higher morbidity rate and another study reported a trend toward post-operative aspiration and bacterial infection induced by prolonged anesthesia (32). Since DG was associated with a shorter operative time in the present study, its possible benefit in reducing the morbidity rate may raise the interest of

clinicians. A similar blood loss was detected between the DG and TG groups; however, a significant heterogeneity existed in the analysis and certain studies focused on the comparisons between TG and DG in distal gastric cancer and obtained a different result (33,34). As previously reported, when TG was performed, the larger surgical region and more complex reconstruction of the digestive tract increased the proneness to bleeding (17). Thus, the comparison of blood loss requires to be further estimated. A significantly longer hospital stay in TG

as compared to DG was also determined in the present study. TG requires more stretching and pulling of organs, possibly resulting in post-operative inflammatory response and then extending the post-operative intestinal recovery time (35).

The post-operative complication rate is a crucial factor for judging the safety of a surgical procedure and closely affects post-operative recovery and prognosis (36). In the present study, a higher overall complication rate was present in the TG group and a similar result was also obtained in a previous meta-analysis focusing on distal gastric cancer (37). To explore the specific origin of the significant difference, further stratified analyses were performed and a higher morbidity for anastomotic leakage was observed in TG. Oesophago-jejunal anastomosis has been rarely performed in DG; however, it was a key process in TG. As previously reported, in oesophago-jejunal anastomosis, it was more difficult to maintain the integrity and reduce the tension of anastomosis instead of gastro-jejunal anastomosis, resulting in a possible fragile reconstruction of the digestive tract in TG (38), which may explain the significantly different anastomotic leakage rate between the two procedures. In addition, since the application of LAG was first reported in 1994 (39), although minimally invasive surgery was widely used, its feasibility and safety were confirmed by numerous studies. Of note, a Dutch study revealed a higher anastomotic leakage risk in minimally invasive TG than conventional open TG (40). It is well recognized that anastomotic leakage is prone to causing secondary abdominal infection and the present meta-analysis detected a higher abdominal infection rate in TG (41). Besides the factor of anastomotic leakage, it may be reasoned that the greater extent of resection and longer operative time also contributed to the increased occurrence of abdominal infection. Duodenal stump fistula is a life-threatening complication, but no significant difference was found in the comparison of this rate between the two groups. However, the duodenal stump may be absent in certain reconstructions for DG, such as Billroth-I anastomosis and results pertaining to this aspect are expected to be provided by future well-designed studies.

Another key factor for determining the surgical procedure in gastric cancer was the PRM. Particularly in DG for MTGC, an inadequate PRM not meeting the R0 resection probably results in post-operative cancer recurrence. However, it is difficult to warrant a completely clear PRM without remaining cancer cells, even with the aid of intraoperative freezing detection (17,19,20). The 5th JGCTG from 2018 suggested that a PRM of >3 cm should be ensured in gastrectomy for localized T2-T4b cancer and for tumors of the infiltrative type, the criterion is a PRM of >5 cm (30). Furthermore, a western multicenter randomized controlled trial (RCT) recommended DG as an alternative surgical therapy for MTGC when the free PRM was limited to 3-6 cm (6). The results of the present meta-analysis indicated no significant effect of the length of the PRM on post-operative 5-year OS when the PRM ranged from 3 to 5 cm, which further confirmed similar findings from South Korea (15,16).

Previous studies also compared the long-term outcomes between TG and DG. The study by Bozzetti *et al* (42) indicated a comparable 5-year OS for both the two procedures, while Chen *et al* (43) reported a significantly superior 5-year OS of patients with DG compared with that

of patients who underwent TG in the same period. Further multivariate analyses considered the resection extent as an independent factor for post-operative survival (44-46); however, this was not supported by the evidence provided in certain other studies (47,48). In the present study, it was explored whether the 5-year OS of patients with MTGC differed between those receiving TG and DG. A significantly higher 5-year OS was determined for DG; however, when patients were stratified by TNM stage, the benefit disappeared and the 5-year OS in the TG and DG groups was similar for stages I, II, III and IV. Indeed, certain surgical oncologists tend to perform TG in order to achieve a curative PRM, particularly for more advanced-stage tumors (13), indicating that the factor most likely to impact oncological outcomes for MTGC is the TNM stage rather than resection extent.

Despite the rigorous design of the present study and thorough analysis, several inevitable limitations should be recognized. First, all of the studies included in the present meta-analysis were retrospective studies and the absence of RCTs may have affected the strength of the evidence of the results. Furthermore, the included studies were only performed in East Asian countries, such as China and Korea, while corresponding data from other countries and ethnicities, particularly Japanese, Caucasian and African populations, were not available. In addition, the publication language was limited to English and Chinese at the step of literature search and relevant studies published in other languages may not be retrieved, resulting in a potential publication bias. Finally, the sample size of the present meta-analysis was relatively small and the findings require to be confirmed in further studies with large samples.

In conclusion, the present meta-analysis indicated that DG as a surgical treatment for MTGC resulted in a comparable 5-year OS, but a shorter hospital stay and a lower post-operative complication rate compared to TG, which suggested that if a negative PRM of >3 cm was ensured, DG was an effective, safe and promising option for curative resection of MTGC.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

Study conception and design, interpretation of data and critical revision: FY, GL and YJ. Literature review and data analysis: JM, NZ, CZ, ZL, FY and YJ. Drafting of the manuscript: FY, YJ and ZL. Revision of the manuscript: YJ. Revision of the manuscript for important intellectual content: ZL. All authors read and approved the final manuscript. YJ and FY checked and confirmed the authenticity of the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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