Original Article

Pylorus-preserving gastrectomy versus distal gastrectomy in oncology for the patient with early gastric cancer: a meta-analysis

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Background: The purpose of this study is to evaluate the early and late outcomes after pylorus-preserving gastrectomy (PPG) compares with distal gastrectomy (DG) in early gastric cancer (EGC).

Methods: We used PubMed, EMBASE, and the Cochrane Library to conduct a comprehensive search up to March 2016. All suitable studies comparing PPG with DG were included. Weighted mean difference (WMD), odds ratio (OR) and hazard ratio (HR) with corresponding 95% confidence intervals (95% CIs) were calculated in this meta-analysis.

Results: Sixteen studies of 2,066 EGC patients that compared PPG (n=685) with DG (n=1,381) were analyzed. As for early outcomes, analysis of PPG versus DG showed that PPG had shorter operative time (WMD =−12.84; 95% CI: −16.76 to −8.91, P<0.01). However, no significant differences were found for intraoperative blood loss (P=0.63), postoperative hospital stay (P=0.26), overall complication rate (P=0.67), or number of retrieved lymph nodes (P=0.21). In addition, analyses of late outcomes, including overall survival (OS), recurrence-free survival (RFS), recurrence and metastasis, indicated that all these outcomes had no significant difference between PPG and DG.

Conclusions: PPG has the advantage over DG in shorter operative time in EGC. Besides, there were no significant differences between PPG and DG in intraoperative blood loss, postoperative hospital stay, overall complication rate, number of retrieved lymph nodes, OS, RFS, recurrence and metastasis. More high quality trials are required to better evaluate early and late outcomes.

Keywords: Gastrectomy; early gastric cancer (EGC); pylorus-preserving gastrectomy (PPG); meta-analysis

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Introduction

Due to the advances in diagnostic modalities, the gastric cancer is allowed to be detected earlier and the occurrence of early gastric cancer (EGC) has been raising, even in asymptomatic patients. Patients who have EGC usually get a satisfactory prognosis after surgical treatment, with overall 3-year survival rate of 97.8% and disease-specific 3-year survival rate of 99.3% reported by Jiang *et al.* (1) This has drawn attention of surgeons to function-preserving surgery which can minimize postgastrectomy problems such as dumping syndrome, alkaline reflux, gastroesophagitis, nutritional deficit, and weight loss, while maintaining an excellent level of radicality (2).

Pylorus-preserving gastrectomy (PPG) which was

firstly adopted at the therapy of peptic ulcers with content outcomes by Maki *et al.* (3) and has since been introduced as a function-preserving treatment for EGC (4-7). So far, many studies have reported that PPG has advantages versus distal gastrectomy (DG) with Billroth I reconstruction by functional conserving (8-10).

Among these studies, the surgical and oncological safety of PPG has still no consensus. Besides, most studies on PPG have only reported fragmentary results, and the patients with long-term results after PPG are not enough to provide credible evaluation for oncological outcome. Thus, we performed a meta-analysis to systematically and objectively assess the possible advantage of PPG comparing with DG in the outcomes of EGC.

Methods

Search strategy

By searching the major medical databases, PubMed, EMBASE, and the Cochrane Library, we identified relevant publications up to March 26, 2016. We used the MeSH form strategy for PubMed as follows: ((stomach neoplasms (Mesh)) OR (stomach neoplasms) OR (stomach neoplasm) OR (stomach carcinoma) OR (stomach cancer) OR (stomach cancers) OR (stomach tumor) OR (cancer of stomach) OR (cancer of the stomach) OR (gastric neoplasms) OR (gastric neoplasm) OR (gastric carcinoma) OR (gastric cancer) OR (gastric cancers) OR (gastric tumor)) AND ((pylorus-preserving gastrectomy) OR (function-preserving gastrectomy)). The publication language was limited in English, Chinese and Japanese.

The references of relevant articles and previous meta-analyses were manually searched to identify additional relevant articles. In order to check for additional studies, we also used authors' names as search terms and the "related articles" function in PubMed database.

Outcome measures

The primary outcomes were recurrence, metastasis and survival, including overall survival (OS) and recurrence-free survival (RFS). The secondary outcomes were operative time, intraoperative blood loss, postoperative hospital stay, overall complication rate, and number of retrieved lymph nodes. OS was defined from surgery to death for any reason. RFS was defined from surgery to the first occurrence of disease progression or relapse due to the primary cancer.

Inclusion and exclusion criteria

All studies involved in this meta-analysis should meet the following criteria: (I) studies that compared PPG versus conventional DG for EGC; (II) patients diagnosed with primary gastric adenocarcinoma; (III) data that included the primary and secondary outcomes. Two exclusion criteria were applied: (I) gastrointestinal stromal tumors or benign gastric diseases or advanced gastric cancer; (II) publication with overlapped data or insufficient data for the analyses.

Three of the authors (Tao Chen, Ziyu Chen and Li Zhen) assessed the eligibility of all studies searched from the databases according to the selection criteria, independently. The risk of bias in each study was evaluated according to the Newcastle-Ottawa Scale for observational studies.

Data extraction

Three researchers (Tao Chen, Ziyu Chen and Li Zhen) used a structured sheet to extract data from each study, which were then entered into a database. Another author (Xiaolong Qi) reviewed this process. Disagreements were resolved through discussion and consensus of the study team.

Statistical analysis

We used the software Review Manager (RevMan) ver. 5.0 by the Cochrane Collaboration (Nordic Cochrane Center, Copenhagen, Denmark) to conduct this meta-analysis. Odds ratio (OR) for dichotomous variables and weighted mean differences (WMD) for continuous outcome measures were calculated with 95% confidence intervals (CIs). Hazard ratio (HR) was calculated as a summary statistic for censored outcomes (OS and RFS) as described by Tierney *et al.* (11) Three investigators used Engauge Digitizer version 4.1 to read the Kaplane-Meier curves independently in order to reduce reading variability and estimated the HRs and the 95% CIs. Heterogeneity of the results across studies was evaluated by Higgins I^2 and chi-square tests, while an I^2 value of greater than 50% and a P value of chi-square less than 0.10 are considered as indicative of substantial heterogeneity. If there is no heterogeneity, fixed-effects model was applied, otherwise, the random effects model was used. We obtained the standard deviation by extracting the estimated standard deviation from the P value, or

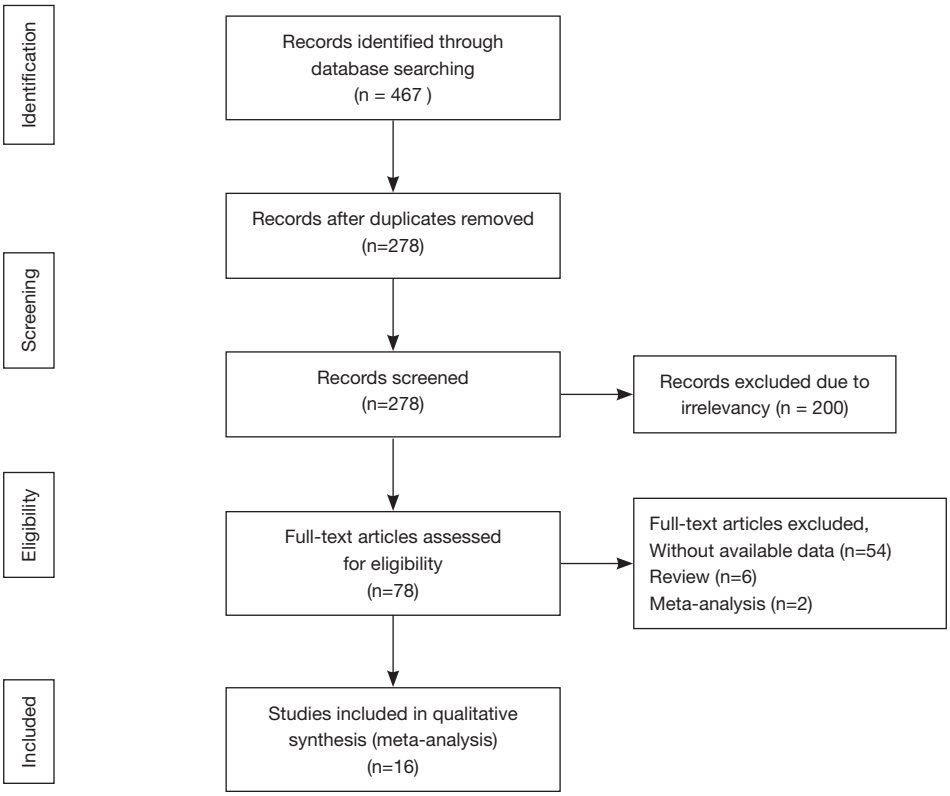

Figure 1 Flow diagram of included studies for this meta-analysis

contacting the authors by e-mail. Begg's funnel plot was carried out to estimate the potential publication bias in the studies. The risk of bias for cohort studies was assessed by the Newcastle-Ottawa scale, while risk for randomized controlled trials (RCT) was assessed based on the Cochrane risk of bias tool.

Results

In total, 16 articles (8,10,12-25) were included on the basis of our inclusion and exclusion criteria (*Figure 1*). Two studies (12,17) are multicenter randomized control trial (RCT), others are non-randomized, non-blinded, retrospective cohort studies. *Table 1* shows the characteristics of the sixteen included articles are shown in.

A total of 2,066 patients diagnosed as EGC were analyzed, including 685 patients who underwent PPG, 1,381 patients who underwent DG. The risk of bias of included studies is shown in *Tables 2* and 3.

Early outcomes after the surgery

These outcomes include operative time, intraoperative blood loss, postoperative hospital stay, overall complication rate and number of retrieved lymph nodes. The pooled results were shown in *Table 4*. Shibata *et al.* (17) reported that the operative time was shorter in PPG than DG (WMD =−12.00; 95% CI: −16.29 to −7.71, P<0.01). Likewise, our analysis of the operative time demonstrated a significant difference between PPG and DG (WMD =−12.84; 95% CI: −16.76 to −8.91, P<0.01) in a fixed effect model (P=0.12, I^2 =45%; *Figure 2*), and PPG took shorter operative time. The intraoperative blood loss was less in PPG than DG, but without statistical significance (WMD =−10.62; 95% CI: −53.92 to 32.68, P=0.63) in a fixed effect model (P=0.17, I^2=46%; *Figure 2*). Additionally, there was no significant difference in postoperative hospital stay (WMD =0.37; 95% CI: −0.28 to 1.01, P=0.26) and overall complication rate (OR =0.90; 95% CI: 0.57 to 1.44, P=0.67) between the two groups in a fixed effect model (P=0.12, I^2=45%;

Table 1 Selected studies

Study	Journal	Country	Language	Number of patient (PPG)	Number of patient (DG)	No. 1/5/6/7 lymph node was dissected in PPG
Kodama *et al.* 1995	World Journal of Surgery	Japan	English	35	29	NS/N/Y/Y
Sawai *et al.* 1995	Am J Surg	Japan	English	25	33	Y/N/Y/Y
Imada *et al.* 1998	Surgery	Japan	English	20	25	N/N/Y/N
Zhang *et al.* 1998	Arch Surg	Japan	English	15	28	Y/Y/Y/P
Hotta *et al.* 2001	Surg Today	Japan	English	19	45	Y/N/Y/N
Shibata *et al.* 2004	World J Surg	Japan	English	36	38	P/Y/Y/P
Urushihara *et al.* 2004	Surg Endosc	Japan	English	26	26	NS/NS/NS/NS
Nomura *et al.* 2005	Japanese Journal of Gastroenterological Surgery	Japan	Japanese	71	262	Y/P/Y/Y
Park *et al.* 2008	World Journal of Surgery	Korea	English	22	17	Y/Y/Y/Y
Hu *et al.* 2010	Zhonghua Wei Chang Wai Ke Za Zhi	China	Chinese, only survival	52	159	Y/N/Y/P
Ikeguchi *et al.* 2010 [1]	Surg Today	Japan	English	46	87	Y/N/Y/Y
Ikeguchi *et al.*2010 [2]	Indian J Surg	Japan	English	24	30	Y/N/Y/Y
Lee *et al.* 2010	J Am Coll Surg	Japan	English	148	305	P/NS/P/P
Tomikawa *et al.* 2012	Surg Today	Japan	English	9	12	Y/NS/Y/Y
Kim *et al.* 2013	Ann Surg Oncol	Korea	English	21	109	Y/Y/Y/Y
Suh *et al.* 2014	Annals of Surgery	Korea	English	116	176	Y/N/Y/Y

PPG, pylorus-preserving gastrectomy; DG, distal gastrectomy; "N", no; "Y", yes; "P", partial; "NS", not stated.

Figure 2) and a random effect model (P=0.09, I^2=41%; *Figure 2*). The number of retrieved lymph nodes was lower in PPG compared with DG, though without a statistically significant difference (WMD =−4.68, 95% CI: −12.07 to 2.71, P=0.21) in a random effect model (P =0.05, I^2=66%; *Figure 2*).

Late outcomes after the surgery

Three studies (19-21) reported OS, only one study (25) investigated RFS. There was not a significant difference in OS with PPG compared with DG (HR =3.77; 95% CI: 0.84 to 16.99, P=0.08) in a fixed effect model (P=0.93, I^2=0%; *Figure 3*). The same non-significant outcome RFS (HR =2.31; 95% CI: 0.08 to 64.78, P=0.62; *Figure 3*) was noted when including only one data. Additionally, the two comparative surgical approaches did not differ significantly in regards to local recurrence and metastasis (OR =1.12; 95% CI: 0.41 to 3.00, P=0.83; *Figure 3*); (OR =1.55; 95% CI: 0.45 to 5.38, P=0.49; *Figure 3*); respectively.

Discussion

Extent of lymphadenectomy

Although many investigators has recommended PPG as a function-preserving surgery for EGC (26), the inconsistency of procedures still exist in different institutions. The main controversy is relation with the extent of lymphadenectomy. Firstly, to prevent from the schemic of pylorus and preserve the vagal nerves, one of the pitfall of PPG is considered to be insufficient lymphadenectomy for N0.5 station, which has potential risks against oncological safety and prompted many to advocated strict and limited indications for PPG (26). However, in Nakajima's previous study (27), only

Table 2 The assessment of the risk of bias in each study using the Newcastle-Ottawa scale

Study (Cohort studies)	Selection (0–4)				Comparability (0–2); outcome (0–3)					Total
	REC	SNEC	AE	DO	SC	AF	AO	FU	AFU	
Sawai *et al.* 1995	*	*	*	*			*		*	6
Imada *et al.* 1998	*	*	*	*			*		*	6
Zhang *et al.* 1998	*	*	*	*			*		*	6
Hotta *et al.* 2001	*	*	*	*			*	*	*	7
Urushihara *et al.* 2004	*	*	*	*			*		*	6
Nomura *et al.* 2005	*	*	*	*			*		*	6
Park *et al.* 2008	*	*	*	*			*	*	*	7
Hu *et al.* 2010	*	*	*	*			*		*	6
Ikeguchi *et al.* 2010 [1]	*	*	*	*			*	*	*	7
Ikeguchi *et al.* 2010 [2]	*	*	*	*			*		*	6
Lee *et al.* 2010	*	*	*	*			*		*	6
Tomikawa *et al.* 2012	*	*	*	*			*		*	6
Kim *et al.* 2013	*	*	*	*			*		*	6
Suh *et al.* 2014	*	*	*	*			*	*	*	7

REC, representativeness of the exposed cohort; SNEC, selection of the non-exposed cohort; AE, ascertainment of exposure; DO, demonstration that outcome of interest was not present at start of study; SC, study controls for age, sex, marital status; AF, study controls for any additional factors; AO, assessment of outcome; FU, follow-up long enough for outcomes to occur; AFU, adequacy of follow-up of cohorts. *Asterisk means that the study is satisfied the item, and no asterisk means the opposite situation.

Table 3 The assessment of the risk of bias in randomized controlled trials based on the Cochrane risk of bias tool

Study	Random sequence generation	Allocation concealment[#]	Blinding	Incomplete outcome data addressed	Selective reporting
Kodama *et al.* 1995	Low risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Shibata *et al.* 2004	Low risk	Low risk	Unclear risk	Unclear risk	Unclear risk

[#], factors considered: age, gender, TNM stage, tumor size, tumor location, follow-up period.

a 0.2% rate of metastases of No. 5 station in 3,646 case of T1 (mucosal or submucosal) cancer located in middle of the body of stomach. Other retrospective analysis reported that 0.0–0.5% of T1 gastric cancers showed lymph node metastases to No. 5 station (7,28). Based on these dates, Hiki (26) imply that patients who are diagnosed clinically as T1N0 could be candidates for PPG without suprapyloric lymphadenectomy, if the preoperative diagnosis of T1N0 is accurate. In our meta-analysis, eight studies report lymphadenectomy without No. 5 in PPG procedure, conversely only four studies with No. 5 all of which report the preservation of pyloric branch simultaneously except one not. In this exceptional study, Zhang *et al.* (15) demonstrated No. 5 lymphadenectomy excluding preservation of pyloric branch accompanying PPG didn't negate these benefits in postoperative gastric function and can be safely performed if infrapyloric artery is preserved. But more studies are need for further verification. Secondly, the dissection of No. 6 lymph node is frequently incomplete in order to reserve the infrapyloric vessels that may also be worrisome in terms of oncologic safety. But in consider of the present and previous studies, No. 6 lymph nodes are sufficiently dissected in PPG procedure compared to DG, and the micrometastasis and macrometastasis are very rare in No. 6 station (8,28).

Table 4 Outcomes

Observed outcomes	Number of study	PPG patients	DG patients	HR/OR/WMD (95% CI)	P	Study heterogeneity	
						I^2 (%)	P value
Early outcomes							
Operative time	5	207	277	−12.84 (−16.76 to 8.91)	<0.01	45	0.12
Intraoperative blood loss	2	35	38	−10.62 (−53.92 to 32.68)	0.63	46	0.17
Postoperative hospital stay	5	204	301	0.37 (−0.28 to 1.01)	0.26	45	0.12
Overall complication rate	10	525	1000	0.90 (0.57 to 1.44)	0.67	41	0.09
Number of retrieved lymph nodes	2	60	115	−4.68 (−12.07 to 2.71)	0.21	66	0.05
Late outcomes							
Overall survival	3	168	500	3.77 (0.84 to 16.99)	0.08	0	0.93
Recurrence-free survival	1	116	176	2.31 (0.08 to 64.78)	0.62	–	–
Recurrence	5	257	546	1.12 (0.41 to 3.00)	0.83	0	0.96
Metastasis	2	74	176	1.55 (0.45 to 5.38)	0.49	24	0.25

Thirdly, there are still some debates regarding the dissection of No. 7. On the ground of celiac branch anatomic relation with left gastric artery, dissection of No. 7 with the preservation of celiac branch is still a difficult technology which is a battery for the previant of PPG, because in 81.8% of cases, celiac branch lay closer to the left gastric artery (29). In our meta-analysis, only six studies show the preservation of celiac branch. However, for experienced surgeon, even in laparoscopic pylorus-preserving gastrectomy (LAPPG) procedure, the celiac branch can be preserved regardless of its anatomical variation during the dissection of No. 7 lymph nodes (5,29). In brief, more comparative clinical studies are needed to demonstrate the oncological safety of the preservation of the nerves and vessels with or without the extent of No. 5, 6, 7 lymphadenectomy.

Perioperative course

Our meta-analysis demonstrated that PPG take shorter time compared with DG. Other perioperative results, including intraoperative blood loss, postoperative hospital stay, overall complication rate, and number of retrieved lymph nodes, were found to have no significant statistical difference. These results meant PPG had the advantage over DG during perioperative period.

Oncological safety of PPG

The 5-year survival rate for patients with EGC after gastrectomy with radical lymph node dissection ranges from 93% to 98% (30). Morita *et al.* (9) reported the first overall 5-year survival rate for 611 T1 gastric cancer patients after PPG (96.3%) which seems comparable to the outcome of open DG for EGC. However, the prognosis of PPG comparing with DG is still a contentious issue. Recently, Hiki *et al.* (31) reported a 98% overall 5-year survival and 0% gastric cancer-related deaths in 305 patients treated using PPG and it demonstrated that PPG may provide a long-term survival benefit for patients with clinically diagnosed T1N0 gastric cancer in the middle one-third of the stomach, only when the accuracy of preoperative diagnosis can be assured.

The results in our meta-analysis revealed that there was no significant difference in OS and RFS between PPG and DG. As for recurrence and metastasis, there was no significant difference between the two operations, either. Previous meta-analysis conducted by Song *et al.* (32) suggested that PPG provided a better life quality over DG. Thus, PPG might could be considered as a better operation for EGC.

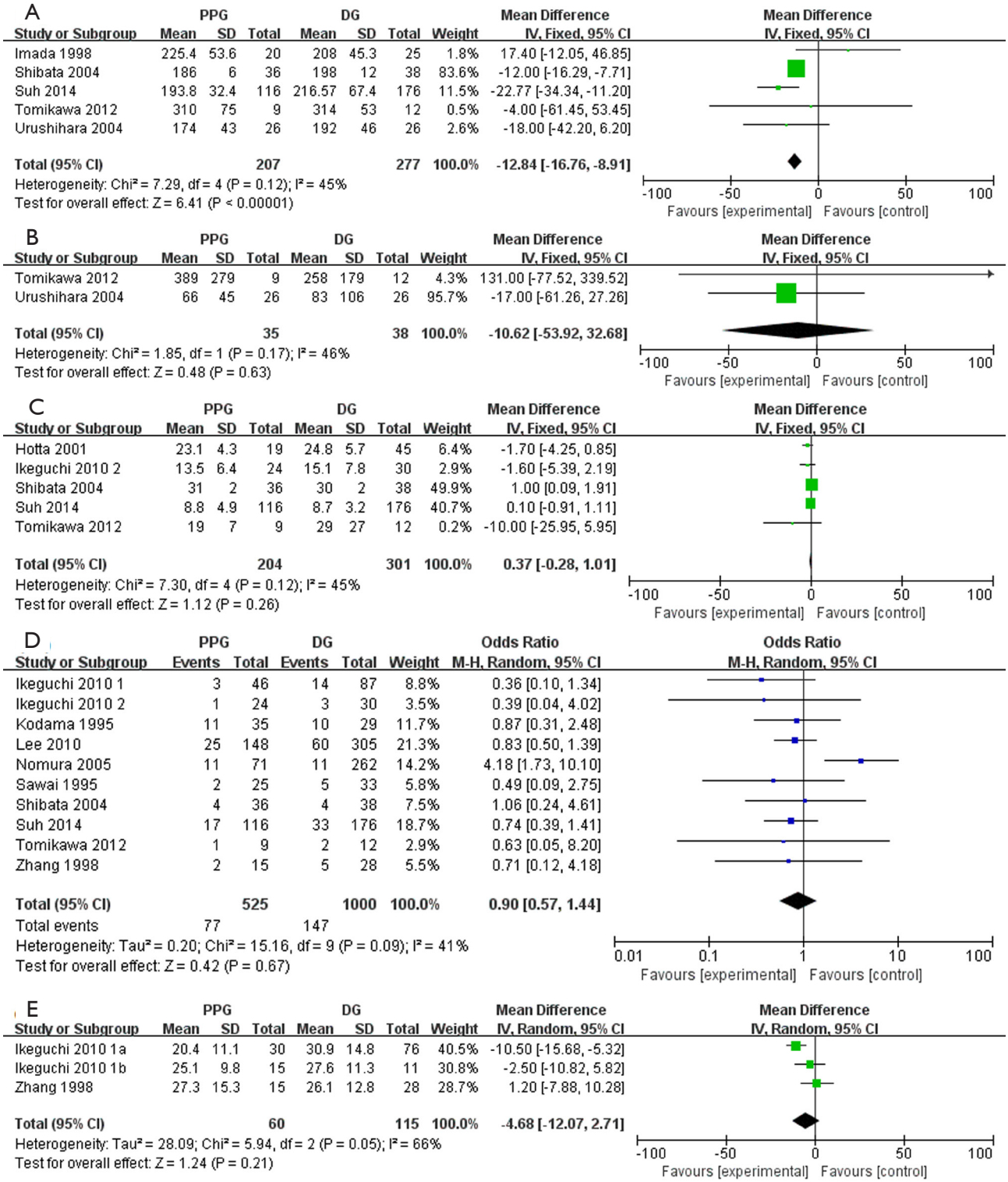

Figure 2 Pylorus-preserving gastrectomy (PPG) vs. distal gastrectomy (DG): early outcomes. (A) operative time; (B) intraoperative blood loss; (C) postoperative hospital stay; (D) overall complication rate; (E) number of retrieved lymph nodes. SD, standard deviation; CI, confidence interval; df, degree of freedom.

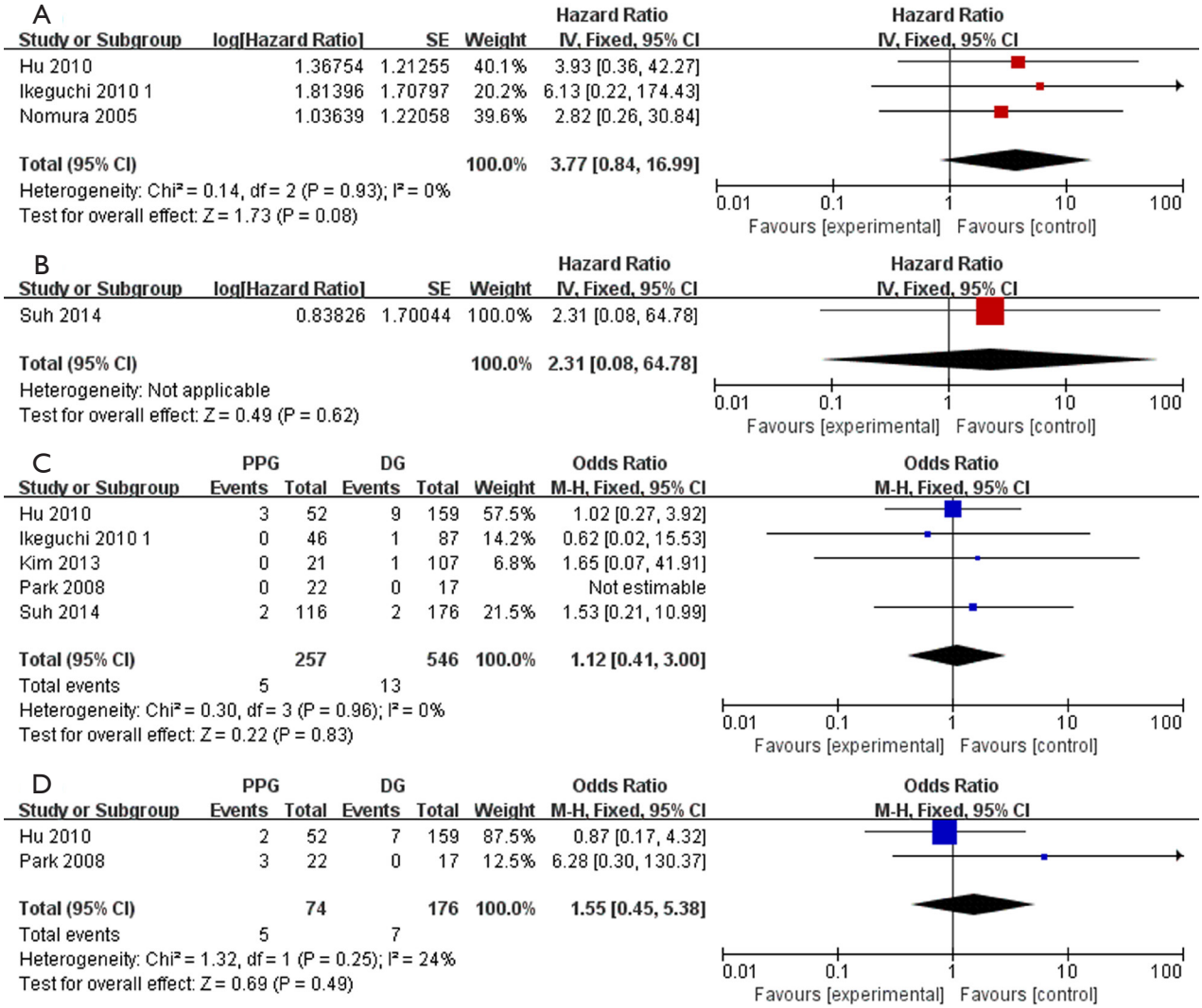

Figure 3 Pylorus-preserving gastrectomy (PPG) vs. distal gastrectomy (DG): late outcomes. (A) Overall survival; (B) recurrence-free survival; (C) recurrence; (D) metastasis. SD, standard deviation; CI, confidence interval; df, degree of freedom.

Conclusions

To sum up, comparing with DG, PPG has shorter operative time for EGC. However, other outcomes such as Intraoperative blood loss, postoperative hospital stay, overall complication rate, number of retrieved lymph nodes, OS, RFS, recurrence and metastasis don't differ significantly. Moreover, higher quality trials are needed to evaluate PPG's clinical and oncological outcomes.

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Footnote

Conflicts of Interest: The authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/amj.2017.05.15). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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