

Format for ANSWERING REVIEWERS



April 20, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 10161-review.doc).

Title: Laparoscopic versus open D2 gastrectomy for locally advanced gastric cancer: a meta-analysis

Authors: Zhen-Hong Zou, Li-Ying Zhao, Ting-Yu Mou, Yan-Feng Hu, Jiang Yu, Hao Liu, Hao Chen, Jiaming Wu, Shengli An, Guoxin Li

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ESPS Manuscript NO: 10161

The manuscript has been improved according to the reviewers' suggestions:

1 Format has been updated.

2. We would like to express our sincere gratitude to the reviewers for their constructive and positive comments.

Revisions have been made according to the reviewer's suggestions

Reviewer 1:

1A) However, supplementary explanation about characteristics of included trials and more detailed results of surgical outcomes and survivals could be needed.

1B) Could you show the ratio of stage IB cancer, adjuvant chemotherapy, and reconstruction type of included trials? That will help to give homogeneity to the studies.

The details of tumor stage, surgical extensions (distal gastrectomy/proximal gastrectomy/total gastrectomy),

and reconstruction type are presented in Tables S1 and S2 (Supplement files), respectively. However, majority of studies did not include details on adjuvant chemotherapy.

Table S1 Details for tumor stages

Studies	L/O					
	Tis	IA	IB	II	III	IV
Hur <i>et al</i> ^[19]	-	-	11/6	9/9	4/8	2/2
Du <i>et al</i> ^[20]	1/0	3/2	5/7	27/30	37/40	5/11
Du <i>et al</i> ^[21]	-	-	3/6	36/31	43/57	-
Huang <i>et al</i> ^[22]	-	5/3	13/13	21/21	26/30	1/2
Cai <i>et al</i> ^[23]	-	-	14/11	13/17	22/19	-
Scatizzi <i>et al</i> ^[24]	-	-	-	12/10	18/20	-
Shuang <i>et al</i> ^[25]	-	-	10/9	15/13	10/13	-
Zang <i>et al</i> ^[26]	-	-	13/10	50/43	88/97	-
Chen <i>et al</i> ^[27]	-	-	40/25	99/51	85/36	-
Hamabe <i>et al</i> ^[28]	-	-		66/101		-
Sato <i>et al</i> ^[29]	-	-	18/42	12/36	6/52	-
Wang <i>et al</i> ^[30]	-	-	34/29	53/46	118/97	5/8
Kim <i>et al</i> ^[31]	-	-	32/28	35/33	21/27	-
Shinohara <i>et al</i> ^[32]	-	70/43		49/33	48/41	19/6

Tis: Tumor in situ; L: Laparoscopic gastrectomy; O: Open gastrectomy.

Table S2 Details for type of gastrectomy and reconstruction

Studies	Type of gastrectomy(L/O)			Reconstruction(L/O)			
	PG	DG	TG	BI	BII	Roux-en-Y	EG
Hur <i>et al</i> ^[19]	-	26/25	-	0/2	25/20	1/3	-
Du <i>et al</i> ^[20]	-	78/90	-	29/√	49/√	-	-
Du <i>et al</i> ^[21]	-	-	82/94	-	-	82/94	-
Huang <i>et al</i> ^[22]	-	66/69	-	-	66/69	-	-
Cai <i>et al</i> ^[23]	26/29	19/17	4/1	√	√	√	-
Scatizzi <i>et al</i> ^[24]	-	30/30	-	-	-	30/30	-
Shuang <i>et al</i> ^[25]	-	35/35	-	-	35/35	-	-
Zang <i>et al</i> ^[26]	-	-	156/156	-	-	156/156	-
Chen <i>et al</i> ^[27]	-	118/51	106/61	101/37	16/14	107/61	-
Hamabe <i>et al</i> ^[28]	-	45/66	21/35	23/59	0/2	43/40	-
Sato <i>et al</i> ^[29]	√	√	√	√	√	√	-
Wang <i>et al</i> ^[30]	20/24	66/54	124/102	√	√	√	-
Kim <i>et al</i> ^[31]	1/0	69/58	18/30	49/28	20/30	18/30	1/0
Shinohara <i>et al</i> ^[32]	5/9	119/76	662/38	√	√	√	-

L: Laparoscopic gastrectomy; O: Open gastrectomy; PG: Proximal gastrectomy; DG: Distal

gastrectomy; TG: Total gastrectomy; EG: Esophagogastrostomy.

2. It will be better that you suggest sub-divided complication rates into surgical extensions (disital gastrectomy/ proximal gastrectomy/ total gastrectomy).

Subgroup analyses, with regard to surgical extensions (disital gastrectomy/ proximal gastrectomy/ total gastrectomy), showed no significant differences between LGD2 and OGD2 groups in major surgical site complications (anastomotic stenosis, anastomotic leakage, duodenal stump leakage, pancreatic fistula/pancreatitis, or intra-abdominal bleeding) as shown in Figures S1-S5 (Supplemental files).

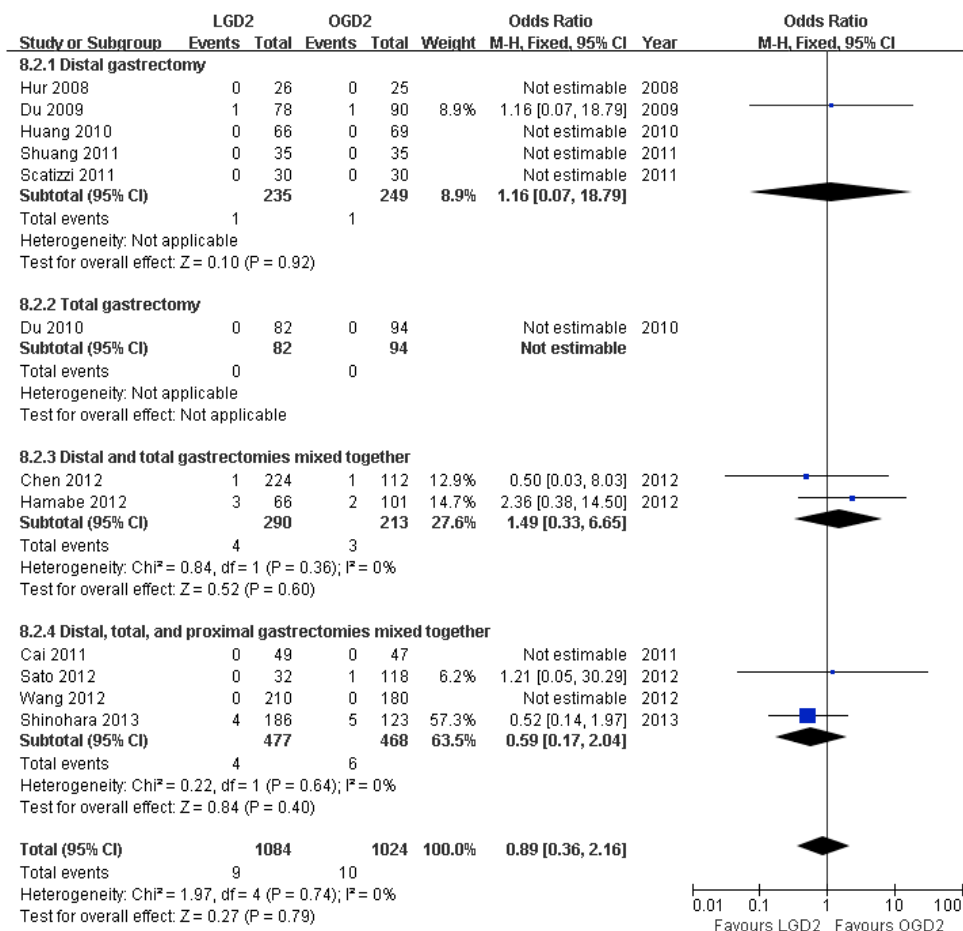


Figure S1 Meta-analysis of anastomotic stenosis grouped by surgical extensions.

LGD2: Laparoscopic gastrectomy with D2 lymphadenectomy; OGD2: Open gastrectomy with D2 lymphadenectomy; CI: Confidence interval.

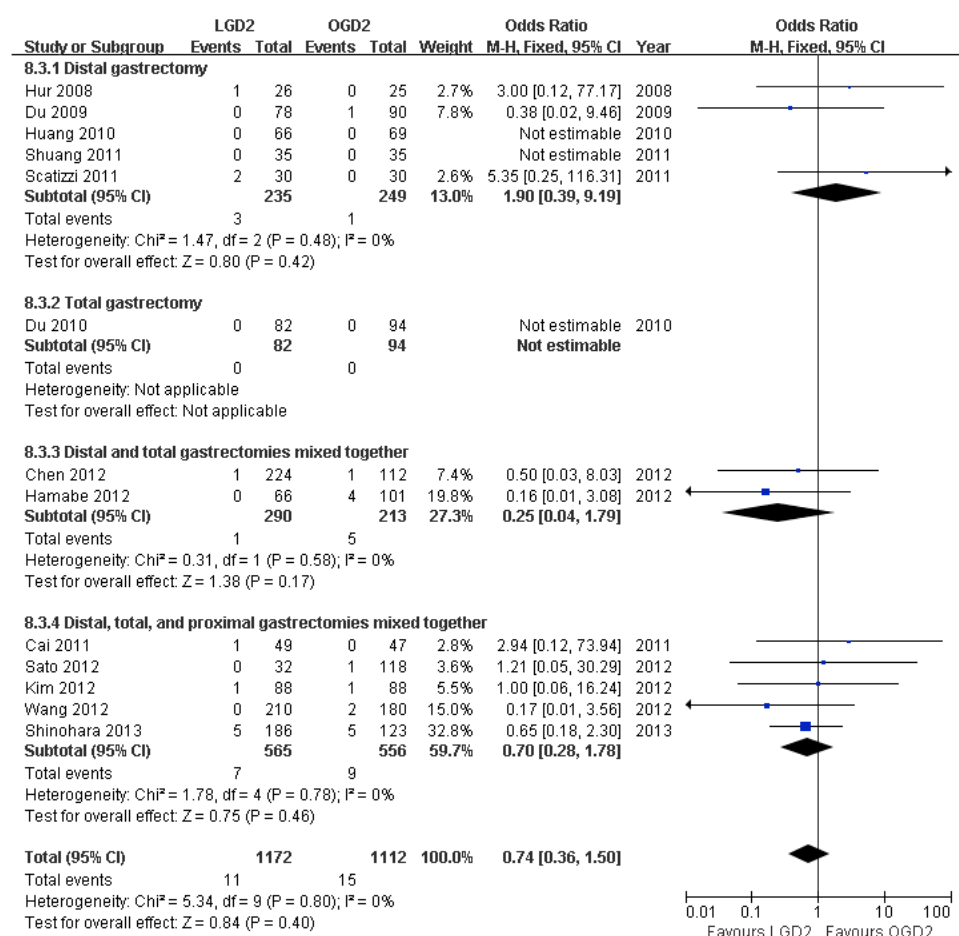


Figure S2 Meta-analysis of anastomotic leakage grouped by surgical extensions.

LGD2: Laparoscopic gastrectomy with D2 lymphadenectomy; OGD2: Open gastrectomy with D2 lymphadenectomy; CI: Confidence interval.

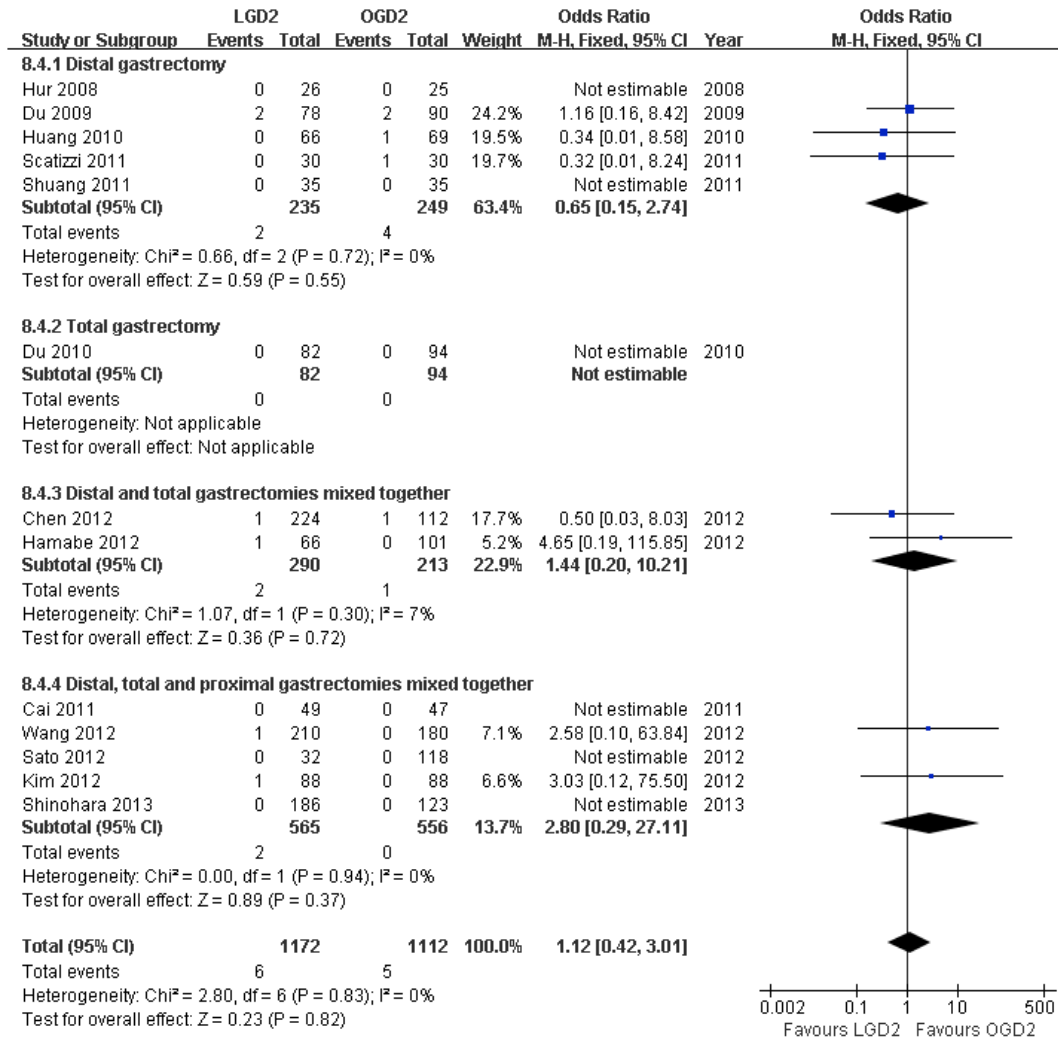


Figure S3 Meta-analysis of duodenal stump leakage grouped by surgical extensions.

LGD2: Laparoscopic gastrectomy with D2 lymphadenectomy; OGD2: Open gastrectomy with D2 lymphadenectomy; CI: Confidence interval.

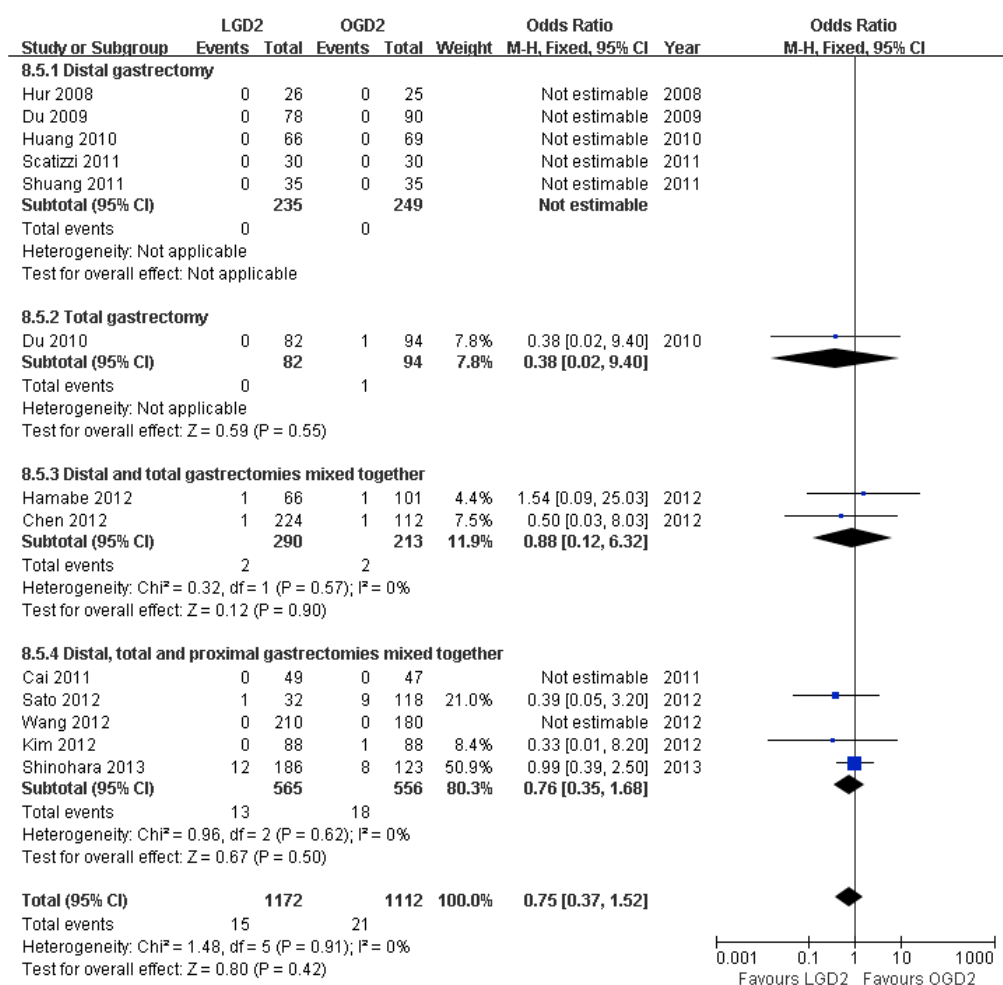


Figure S4 Meta-analysis of pancreatic fistula or pancreatitis grouped by surgical extensions.

LGD2: Laparoscopic gastrectomy with D2 lymphadenectomy; OGD2: Open gastrectomy with D2 lymphadenectomy; CI: Confidence interval.

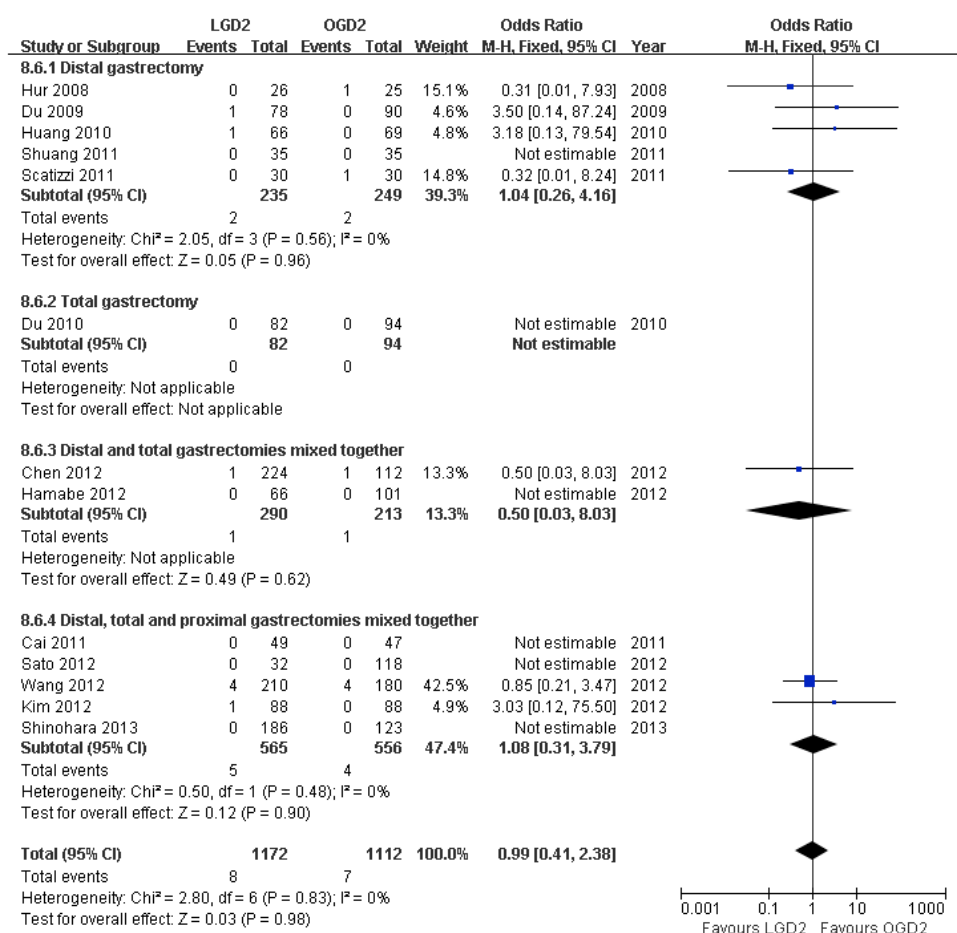


Figure S5 Meta-analysis of intra-abdominal bleeding grouped by surgical extensions.

LGD2: Laparoscopic gastrectomy with D2 lymphadenectomy; OGD2: Open gastrectomy with D2 lymphadenectomy; CI: Confidence interval.

3. The survivals also could be subdivided into stages.

Among the included studies, only Shinohara et al^[32] presented calculated disease-free survival (DFS) and overall survival rates (OS) based on different tumor stages. The results of this study were as follows: “The calculated 5 year DFS rates for the patients after laparoscopic and open D2 gastrectomy: 94.3 % (95 % CI: 88.0–100 %) vs 91.8 % (95 % CI: 81.0–100 %) for the patients with stage IB disease ($P = 0.760$); 71.3 % (95 % CI: 58.6–84.0 %) vs 61.0 % (95 % CI: 41.8–80.2 %) for the patients with stage II disease ($P = 0.836$); 51.7 % (95 % CI: 36.0–67.4 %) vs 45.8 % (95 % CI: 29.1–62.5 %) for the patients with stage III disease ($P = 0.457$); 0 % vs 0 % for the patients with stage IV disease ($P = 0.629$), respectively. There were no differences between the groups with regard to tumor stage. The calculated 5 year OS rates for the patients after laparoscopic and open D2 gastrectomy were: 95.9 % (95 % CI: 90.4–100 %) vs 95.8 % (95 % CI: 87.8–100 %) for the patients with stage IB disease ($P = 0.944$); 78.1 % (95 % CI: 65.0–91.2 %) vs 61.9 % (95 % CI: 38.0–85.8 %) for the patients with stage II disease ($P = 0.896$); 54.1 % (95 % CI: 36.5–71.7 %) vs 47.1 % (95 % CI: 25.0–69.0 %) for the patients with stage III disease ($P = 0.393$); 0 % vs 16.7 % (95 % CI: 0–46.0 %) for the patients with stage IV disease ($P = 0.787$), respectively. There were no differences between the groups with regard to tumor stage as shown below in Figure 3 and Figure 5.

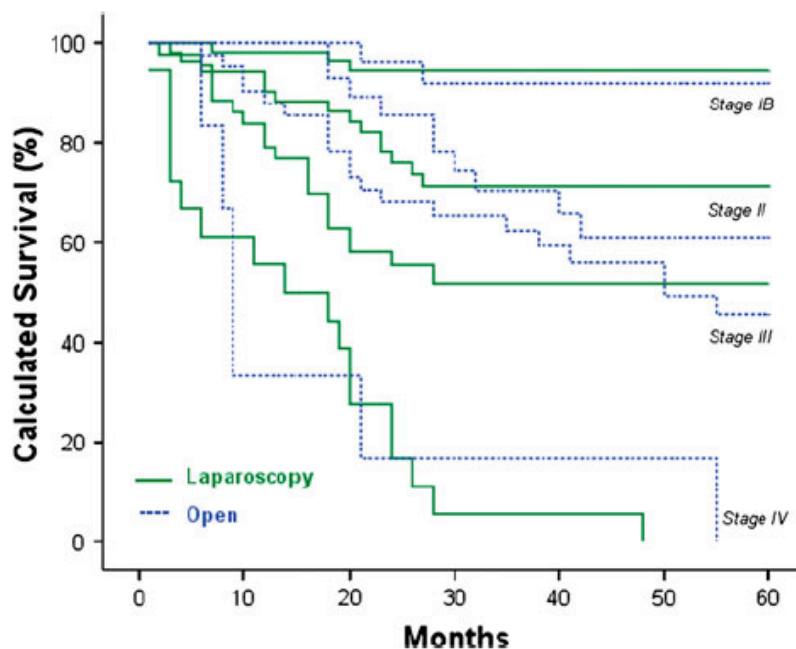


Fig. 3 Kaplan–Meier curves for DFS between the laparoscopic gastrectomy and the open gastrectomy groups according to pathology of UICC staging

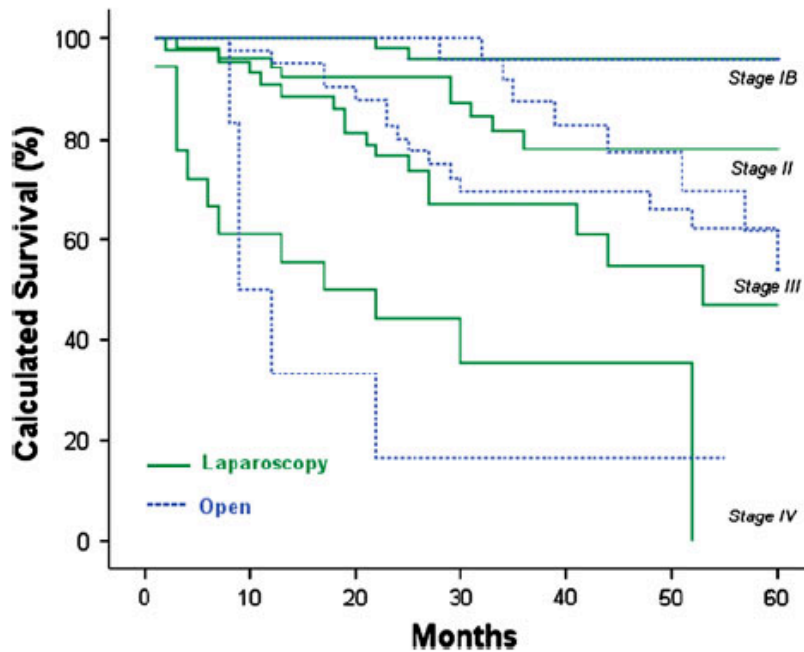


Fig. 5 Kaplan–Meier curves for OS between the laparoscopic gastrectomy and the open gastrectomy groups according to pathology of UICC staging

Reviewer 2:

Laparoscopic gastrectomy in early gastric cancer already has been demonstrated stability and effectiveness. Recently, interests increase in the safety and efficacy of laparoscopic gastrectomy for advanced gastric cancer. Recently, some paper reported that there was no statistical difference in overall survival and disease-free survival between laparoscopic gastrectomy and open gastrectomy. In addition, there are large-scale RCTs is ongoing for two group and this paper don't have something new factor. More than all, predictable conclusion is disappointed.

The Japanese Gastric Cancer Association guidelines stipulate D2 gastrectomy to be required for the treatment of advanced gastric cancer. However, the application of laparoscopic D2 gastrectomy (LGD2) for advanced gastric cancer remains questionable due to its technical difficulty and the lack of long-term results, which drove us to perform this meta-analysis. Our meta-analysis demonstrated that despite LGD2 being a technically demanding and time-consuming procedure, it should be considered as an acceptable alternative to OGD2 for locally advanced gastric cancer. Furthermore, LGD2 has comparable oncological results and better short-term prognoses than OGD2. We strongly believe that this meta-analysis provided new insights regarding the value of LGD2 in treatment of locally advanced gastric cancer. First, this being a meta-analysis included 14 studies providing a higher level of evidence compared with a single retrospective study. Second, we found

significantly lower incidences of overall morbidity, wound problems, and pneumonia in the LGD2 than OGD2 group, with no significant differences in incident rates in major surgical site complications including anastomotic stenosis, anastomotic leakage, duodenal stump leakage, pancreatic fistula/pancreatitis, and intra-abdominal bleeding. Above all, we strongly believe that conclusion based on the ongoing large-scale RCTs provides invaluable and relevant information in regard to treatment of advanced gastric cancer.

Reviewer 3:

This meta-analysis of 14 articles comparing LGD2 with OGD2 for AGC shows clearly that Although LGD2 is a technically demanding and time-consuming procedure, it is a safe, feasible alternative to OGD2 for locally AGC, with lower overall morbidity, enhanced postoperative recovery, and comparable oncological outcomes. The paper is well organized and structured, keeps the focus on important details and draws the right conclusion from the data presented. Therefore the paper is very important and should be published in his current form.

We want to thank you for your valuable insight and comments.

Reviewer 4:

The main problem with the papers that some relevant data are based on a fraction of the 14 papers object of the meta analysis: - 4/14 for 3 years disease free interval - 3/14 for 5 years disease free interval - 3/14 for 5 years survival. The conclusion that the long term prognosis after the lap procedure is comparable to the open one may not be sustainable. In addition to the limitations denounced as the most important is the "operative technique heterogeneity" which introduces an uncontrollable factor.

The existing evidence was organized in way to illustrate the long-term oncologic outcomes comparing LGD2 with OGD2. Consequently, only 5 studies could be included for meta-analysis to further evaluate 3/5-years disease free or overall survival, and the meta-analysis demonstrated that there were no significant differences between LGD2 and OGD2 regarding 3/5-years disease free or overall survival ($P > 0.05$). Our conclusion was not a definitive conclusion; instead we concluded that LGD2 may yield comparable oncologic results, as the level of evidence was limited by all retrospective studies included.

As you suggest, operative technique heterogeneity might have an undesirable effect on the results. Hence the addition of details regarding surgical extension and reconstruction, as well as subgroup analyses with regard to

surgical extensions (distal gastrectomy/ proximal gastrectomy/ total gastrectomy). All of these results showed no significant differences between LGD2 and OGD2 groups in major surgical site complications (anastomotic stenosis, anastomotic leakage, duodenal stump leakage, pancreatic fistula/pancreatitis, or intra-abdominal bleeding) as shown in Figures S1-S5 (Supplemental files). As such, we suggest that the operative technique heterogeneity may not have a very important effect on the results.

3. References and typesetting were edited.

We would like to thank you again for considering publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

Guo-Xin Li, MD, PhD, Professor
Department of General Surgery
Semmelweis University
No. 1838, North Guangzhou Avenue
Guangzhou 510515, Guangdong Province, China
Fax: +86-20-61641683
E-mail: gzlguoxin@163.com