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Review

Long-term oncological outcomes in laparoscopic versus open gastrectomy for advanced gastric cancer: A meta-analysis of high-quality nonrandomized studies

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ABSTRACT

Background: Multicenter randomized controlled trials (RCTs) and several meta-analyses have confirmed that laparoscopic gastrectomy (LG) is a safe and feasible procedure for patients with locally advanced gastric cancer (AGC) in terms of short-term outcomes. However, the long-term oncological outcomes of LG for AGC are still needed for further evaluation. This study aimed to compare the long-term oncological outcomes of LG with open gastrectomy (OG) for patients with AGC.

Methods: We performed a systematic literature search in various databases from January 1997 to August 2018. Studies comparing the long-term oncological outcomes between LG with OG were evaluated and data were extracted accordingly. We performed the meta-analysis using RevMan 5.3 software.

Results: Fifteen studies with 4494 patients (2273 in LG group and 2221 in OG group) were included. The 5-year overall survival (OS) rate (HR 0.95, 95% CI 0.86 to 1.05, P = 0.28), disease-free survival (DFS) rate (HR 0.93, 95% CI 0.81 to 1.06, P = 0.27), and recurrence rate (OR 0.87, 95% CI 0.72 to 1.04, P = 0.13) were comparable in LG and OG. Subgroup analysis showed the publication year, study region, sample size, extent of resection, extent of lymphadenectomy, retrieved lymph nodes, proportion of stage III, and patients with serosa-positive (pT4a) did not influence the estimates.

Conclusions: For patients with AGC, LG is a feasible surgical procedure alternative to OG in terms of long-term oncological outcomes.

Introduction

Laparoscopic gastrectomy (LG) has been increasingly performed since it was first reported in 1994 by Kitano et al.[1] Based on the experience accumulation of LG for early gastric cancer (EGC), some experienced surgeons in high-volume centers have applied the laparoscopic procedure for patients with locally advanced gastric cancer (AGC).[2] A growing number of studies have demonstrated the technical feasibility and safety of LG for AGC.[3–5] Till date, several meta-analysis had reported that patients underwent LG always had better short-term outcomes are compared with those underwent open gastrectomy (OG).[6–9] Long-term oncological outcomes are key indicator for assessing oncological safety and regard as a major concern in clinical practice. Currently, the long-term outcomes of LG for locally AGC still remain controversial due to the lack of solid evidence from randomized controlled trials (RCTs). Studies that reported long-term oncological outcomes of LG and OG were always restricted to single-center, low-quality, small simple size, or limited follow-up. Therefore, the long-term oncological outcomes of LG for AGC are still needed for further evaluation. The aim of this study is to perform a comprehensive evaluation of all the available high-quality published nonrandomized studies, comparing long-term oncological outcomes of LG and OG for AGC.

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Methods

Literature search

A systematic literature was searched from PubMed, MEDILNE, EMBASE, the Cochrane Library, and Web of Science from January 1997 to August 2018. Search terms "gastric carcinoma", "gastric cancer", "stomach neoplasms", "gastric neoplasm", "stomach cancer" "laparoscopic", "laparoscopy", "open gastrectomy", and "conventional gastrectomy" were used in combination with the Boolean operators AND or OR. The reference lists of articles obtained were also reviewed to find relevant literature. Two authors (Li ZY and Zhao Y) individually conducted the literature search and cross-checked their search results.

Inclusion and exclusion criteria

Included criteria for this meta-analysis were as follows[1]: histologically confirmed gastric cancer[2]; published studies comparing LG with OG for AGC[3]; the follow-up period is at least 5 years or 60 months[4]; studies that reported at least one of the following outcomes, including 5-year overall survival (OS), 5-year disease-free survival (DFS), or recurrence. The excluded criteria were[1]: studies such as reviews, comments, letters, case reports, or cohort studies including fewer than ten patients[2]; studies published in a language other than English.

Data extraction and quality assessment

Data were extracted independently by two reviewers (Li ZY and Zhao Y) independently using predefined standards and cross-checked, and discrepancies were adjudicated by a third reviewer (Zhao QC). The following data were extracted from each study: first author, publication year, Region, sample size, extent of resection, lymph node dissection, mean or median follow-up, and long-term oncological outcomes (5-year OS, 5-year DFS, and recurrence). All included studies were methodologically assessed using the Newcastle–Ottawa Scale (NOS), which has been widely used for the assessment of the quality of non-randomized (nRCTs) studies in meta-analyses.[10] The high-quality trials should score $\geq$7 of a maximum score of 9.

Statistical analysis

Data analyses were performed with the Review Manager software (RevMan version 5.3; Cochrane Collaboration). Hazard ratios (HRs) were used with a generic inverse variance method to analyze time to event outcomes (OS and DFS). The HR was estimated using the method introduced by Tierney et al.[11] Odds ratio (OR) was used to calculated dichotomous variables (recurrence), and both were reported with 95% confidence intervals (CIs). I^2 statistics were used to quantify the heterogeneity among studies. If data was not significantly heterogeneous ($P > 0.05$ or $I^2 < 50\%$), the pooled effects were calculated using a fixed model. Otherwise, the random effects analysis would be performed. Publication bias was evaluated by a funnel plot. The results were regarded as statistically significant at two-sided $P < 0.05$.

Results

Study selection

We conduct this systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[12] Finally, 15 non-randomized controlled studies were eligibly included in the pooled analysis.[13–27] The detailed search steps are presented in Fig. 1.

The characteristics and quality of the studies

Table 1 summarizes the characteristics of included studies, which were published from 2011 to 2018. These articles are from China, Japan, Korea, and Italy. A total of 4494 patients were included in the meta-analysis, among which 2273 cases in the LG group and 2221 in the OG group. The quality assessment outcomes of nRCTs are summarized in Table 2.

Five-year overall survival

Fifteen studies involving 4494 patients were identified to investigate the 5-year OS according to LG versus OG. The pooled analysis of these studies showed that there is no significant difference in 5-year OS between LG and OG (HR 0.95, 95% CI 0.86 to 1.05, $P = 0.28$), no significant heterogeneity ($I^2 = 0\%$, $P = 1.00$) (Fig. 2). Subgroup analysis showed the publication year, study region, sample size, extent of resection, extent of lymphadenectomy, retrieved lymph nodes (LNs), proportion of stage III, and patients with serosa-positive (pT4a) did not influence the estimates. Table 3 shows the results of subgroup analysis.

Five-year disease-free survival

In the nine studies[16,17,19–21,23,24,26,27] involving 2127 patients, the 5-year DFS between LG and OG are investigated via Kaplan–Meier survival curves. The pooled analysis showed there is no significant difference in 5-year DFS between the LG and OG groups (HR 0.93, 95% CI 0.81 to 1.06, $P = 0.27$), with no significant heterogeneity ($I^2 = 0\%$, $P = 0.95$) (Fig. 3).

Tumor recurrence rate and recurrence patterns

Nine studies[13–17,20,23,24,27] involving 2367 patients reported data on tumor recurrence. Overall, 383 cases in LG group and 403 cases in OG group experienced recurrence. There was no significant difference in recurrence rate between the LG and OG groups (OR 0.87, 95% CI 0.72 to 1.04, $P = 0.13$), with low heterogeneity ($I^2 = 48\%$, $P = 0.05$) (Fig. 4). Further analysis revealed that the recurrence pattern was similar between the LG the OG groups (Fig. 5).

Sensitivity analysis and publication bias

Sensitivity analyses were conducted by exclusion of the highest weighted study in each pooled analysis. These exclusions did not alter the results obtained in cumulative analyses. Funnel plots were performed to assess publication bias. No significant publication bias was detected by visual inspection of the funnel plot (Fig. 6).

Discussion

With better short-term outcomes, LG for gastric cancer have garnered tremendous popularity over open gastrectomy. Several meta-analysis studies have demonstrated patients underwent LG had better early postoperative and comparable long-term outcomes when compared with those underwent OG.[28–30] However, these studies mainly focused on early gastric cancer, and some included studies in previous meta-analyses were always restricted to single-center, low-quality, small simple size, or limited follow-up. At present, there is only one RCT report 5-year survival outcomes concerning LG for distal gastric cancer. However, the series

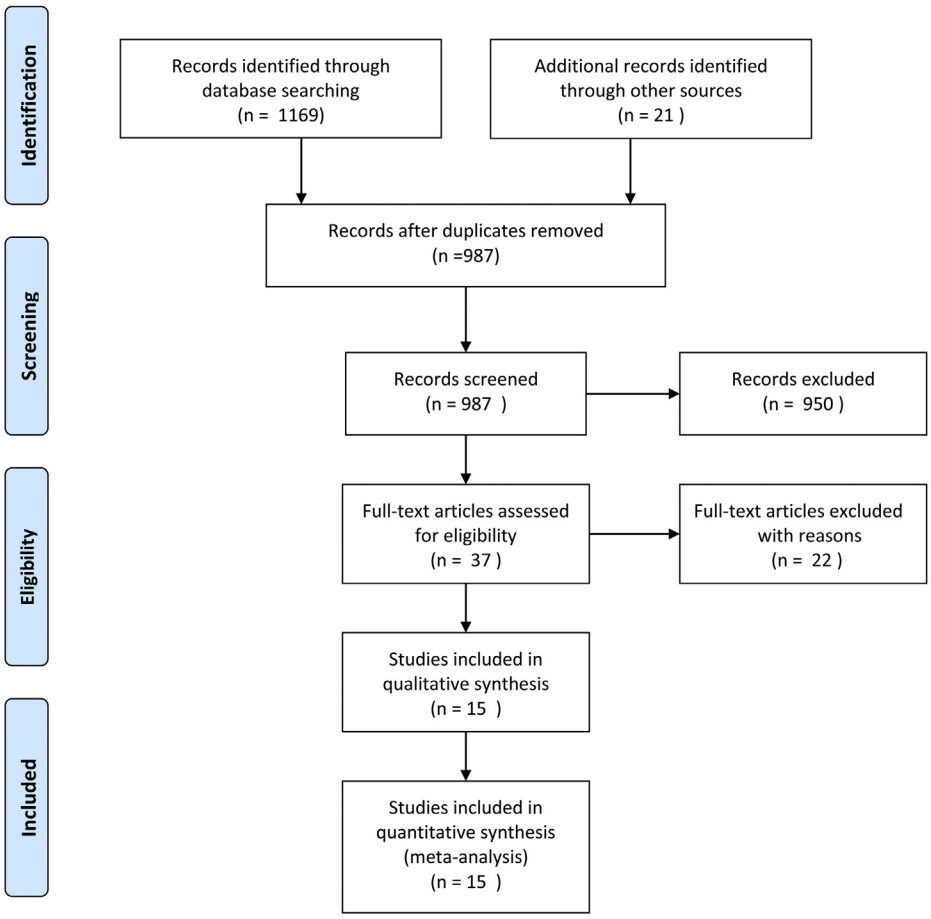

Fig. 1. PRISMA flow diagram of the meta-analysis.

Table 1
Characteristics of included studies.

Study	Year	Region	No. of patients		Extent of resection	Extent of lymphadenectomy	Follow-up (months) (mean or median)
			LG	OG			
Zhao	2011	China	346	313	DG,	D1 + α/β, D2	37
Sica	2011	Italy	22	25	SG TG	D1, D2	38
Chun HT	2012	Korea	52	67	DG	D2	LG:53.2 OG:60.4
Hamabe A	2012	Japan	66	101	DG,TG	D2	LG:30.4; OG:53.5
Kim KH	2012	Korea	88	88	DG, TG	D2	53.7
Bo T	2013	China	117	117	TG	D2	61.2
Shinohara	2013	Japan	186	123	DG,PG,TG	D2	48.8
Son	2014	Korea	39	22	SG TG	D1+, D2	64
Zhang	2015	China	86	86	DG	D2	LG:40; OG:38
Lin	2015	China	539	539	DG, TG	D2	45
Zhang	2016	China	92	92	DG, TG	D2	LG:38; OG:40
Xu	2017	China	67	67	DG, TG	D2	22
Zhang	2017	China	111	119	SG, TG	D2	37
Inokuchi	2018	Japan	52	52	DG, TG	D2	62.2
Li	2018	China	410	410	DG, TG	D2	46.2

DG, distal gastrectomy; SG, subtotal gastrectomy; TG, total gastrectomy.

Table 2
Newcastle-Ottawa Scale assessment of non-randomized studies.

Study	Selection				Comparability		Outcome			Total
	1	2	3	4	5	6	7	8	9	
Zhao	*	*	*	*	*		*	*	*	8
Sica	*	*	*	*	*		*	*	*	8
Chun HT	*	*	*	*	*		*	*	*	8
Hamabe A	*	*	*	*	*		*	*	*	8
Kim KH	*	*	*	*	*		*	*	*	8
Bo T	*	*	*	*	*	*	*	*	*	9
Shinohara	*	*	*	*	*		*	*	*	8
Son	*	*	*	*	*		*	*	*	8
Zhang	*	*	*	*	*		*	*	*	8
Lin	*	*	*	*	*	*	*	*	*	9
Zhang	*	*	*	*	*		*	*	*	8
Xu	*	*	*	*	*	*	*	*	*	9
Zhang	*	*	*	*	*		*	*	*	8
Inokuchi	*	*	*	*	*	*	*	*	*	9
Li	*	*	*	*	*	*	*	*	*	9

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. Study controls for age, sex, and marital status; 6. Study controls for any additional factors; 7.Assessment of outcomes; 8. Follow-up long enough for outcomes to occur; 9. Adequacy of follow-up.

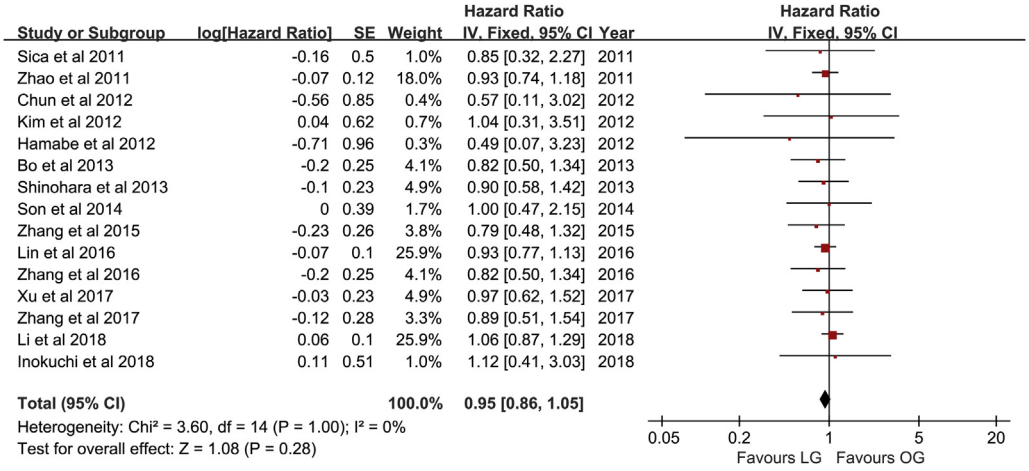

Fig. 2. Forest plot of 5-year overall survival.

Table 3
Subgroup analyses of 5-year OS.

Subgroup	Study No.	HR	(95% CI)	P_s	I^2 (%)	P_t
Publication year						
≤2012	5	0.92	0.73,1.14	0.94	0%	0.43
>2012	10	0.95	0.85,1.07	0.98	0%	0.41
Region						
Japan	3	0.91	0.61, 1.36	0.75	0%	0.65
Korea	3	0.94	0.51, 1.72	0.82	0%	0.44
China	8	0.95	0.86, 1.06	0.92	0%	0.34
Sample size						
≤200	9	0.88	0.70, 1.11	0.99	0%	0.29
>200	6	0.96	0.86, 1.07	0.89	0%	0.48
Extent of resection						
Distal gastrectomy	3	0.90	0.73, 1.11	0.74	0%	0.33
Others	12	0.95	0.85, 1.06	0.99	0%	0.37
Extent of lymphadenectomy						
D2	12	0.95	0.85, 1.06	0.98	0%	0.37
D1/D1+/D2	3	0.93	0.75, 1.16	0.97	0%	0.54
Retrieved LNs						
≤30	6	0.97	0.85, 1.12	0.58	0%	0.70
>30	9	0.91	0.78, 1.07	0.99	0%	0.26
Proportion of tumor stage						
III ≤ 50%	9	0.97	0.84, 1.14	0.93	0%	0.74
III > 50%	6	0.92	0.80, 1.06	0.88	0%	0.27
T4a	3	0.95	0.71, 1.28	0.95	0%	0.75

P_s P value for heterogeneity, P_t test for overall effect.

of 59 patients in this RCT was relatively small and consisted of with both EGC and AGC patients.[31] In some eastern Asian countries, high percent of patients are diagnosed at advanced stage. Currently, two ongoing RCT studies from China (CLASS-01) and Japan (JLSSG0901) have demonstrated the technical safety of LADG for AGC only in terms of short-term surgical morbidity and mortality.[4,5]

The long-term oncological outcomes were major concerns in clinical practice and it also important for the wide application of LG in AGC. Recently, several high-quality articles compared LG with OG have been published. Therefore, we perform this updated meta-analysis with more sufficient evidence to compare the oncological of LG with OG for AGC. The long-term results including OS, DFS, and recurrence could be directly used to evaluate the effects of surgical procedures. The present meta-analysis includes studies comparing LG with OG for patients with AGC from 2011 to 2018. The results of this study showed no significant difference between LG and OG groups in OS, DFS, and the recurrence rate. These results indicate LG is a feasible surgical procedure for AGC in terms of long-term oncological outcomes.

For patients with gastric cancer, tumor recurrence still occurred in some patients in the 4th or 5th year postoperatively. Therefore, the reliability of results will increase due to the sufficient follow-up duration.[32] Compared to previously published meta-analyses, the

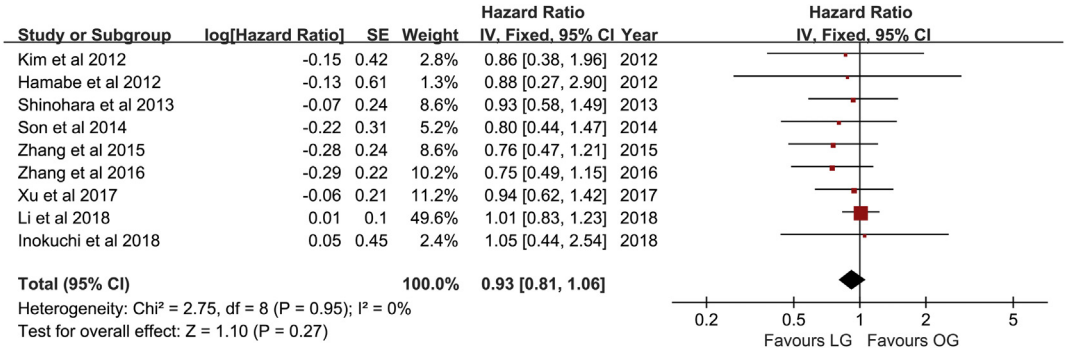

Fig. 3. Forest plot of 5-year disease-free survival.

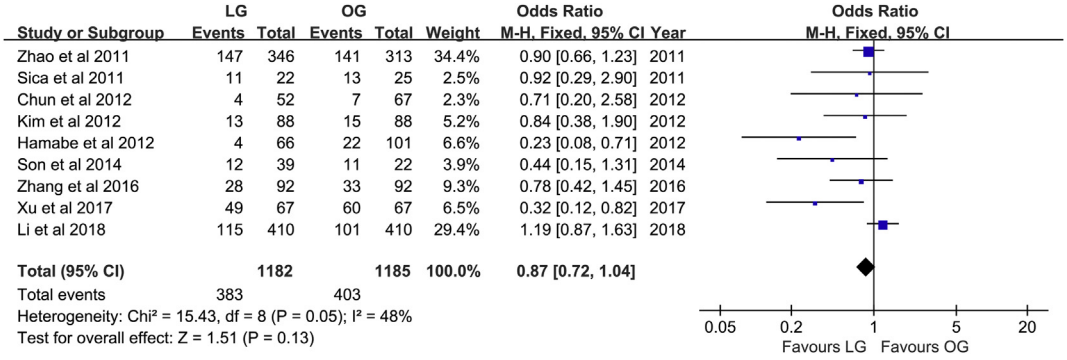

Fig. 4. Forest plot of recurrence rate.

follow-up period of the included studies in the present meta-analysis is at least 5 years. Till date, several large cohort studies have reported the 5-year survival outcomes.[14,19,22,27] For studies with different sample size, the subgroup analysis revealed no significant differences in the 5-year OS between LG and OG groups. Except for sample size, several factors such as the publication year, study region, surgical extension, lymphadenectomy extent, retrieved LNs, and tumor stage are potential factors which may influence the long-term survival outcome. Our results also showed no significant difference between the LG and OG groups in the subgroup analysis based on these factors. In some East Asian countries, LG is indicated for serosa-negative tumors. Laparoscopic surgery is considered to be controversial for gastric cancer with serosa invasion (T4a).[33] Currently, although some retrospective studies have reported that the long-term survival outcomes of AGC patients underwent LG are similar with those treated with OG. However, few of them reported the stage-specific survival outcomes of patients in pT4a stage. The subgroup analysis of this meta-analysis showed LG and OG groups had similar survival 5-year OS for patients with pT4a gastric cancer.

Although gastrectomy with sufficient lymph node dissection remains the cornerstone of curative treatment for patients with gastric cancer, recurrence and metastasis occur in 20–60% of patients, and survival remains low even after curative resection.[34–36] Compared with previous meta-analysis, our study evaluated the recurrence rates of LG and OG for AGC. With reference to recurrence patterns, a study of 1417 patients after LG from multicenter stated the most common recurrence pattern after LG was hematogenous, followed by peritoneal and locoregional.[37] Another study of 1304 gastric cancer patients reported the recurrence rate was 60.8% (793/1304), and the distant metastasis is the most common recurrence pattern, followed by local-regional recurrence and peritoneum implanting.[38] Our recent study showed that the recurrence rate was 28.0% after LG with a median follow-up period of 69 months, and peritoneal were the most common recurrence pattern, followed by locoregional recurrence and hematogenous recurrence. Our results showed that the recurrence rate and pattern did not differ between the LG and OG groups during the follow-up stage.[27] In the present meta-analysis, the results confirmed the comparable recurrence types between LG and OG groups. These demonstrated that LG do not increase peritoneal metastasis of patients with AGC. Port site metastasis associated with pneumoperitoneum and laparoscopic tumor handling has also been regard as one of the major concern in clinical practice, although it is actually quite rare based on current evidence.[8,39] Several reports stated that laparoscopic surgery does not promote port site metastasis of gastric cancer.[14,20] In this meta-analysis, three studies reported the follow-up results about port-site metastasis, and two of them did not observe this incident.[14,19,20] Zhao et al.[14] found one patients experienced port site metastasis in the LG group during the follow-up period. However, it was not a unique event to LG, because two cases of implantation metastasis were also observed in the OG group. These studies stated that laparoscopic surgery does not promote port site metastasis of gastric cancer.

Although our meta-analysis included nRCTs with high quality to draw a reasonable conclusion, there were still two major limitations need to be noted. First, most of the included studies were from Eastern Asia. Thus, the limited generalizability to other populations

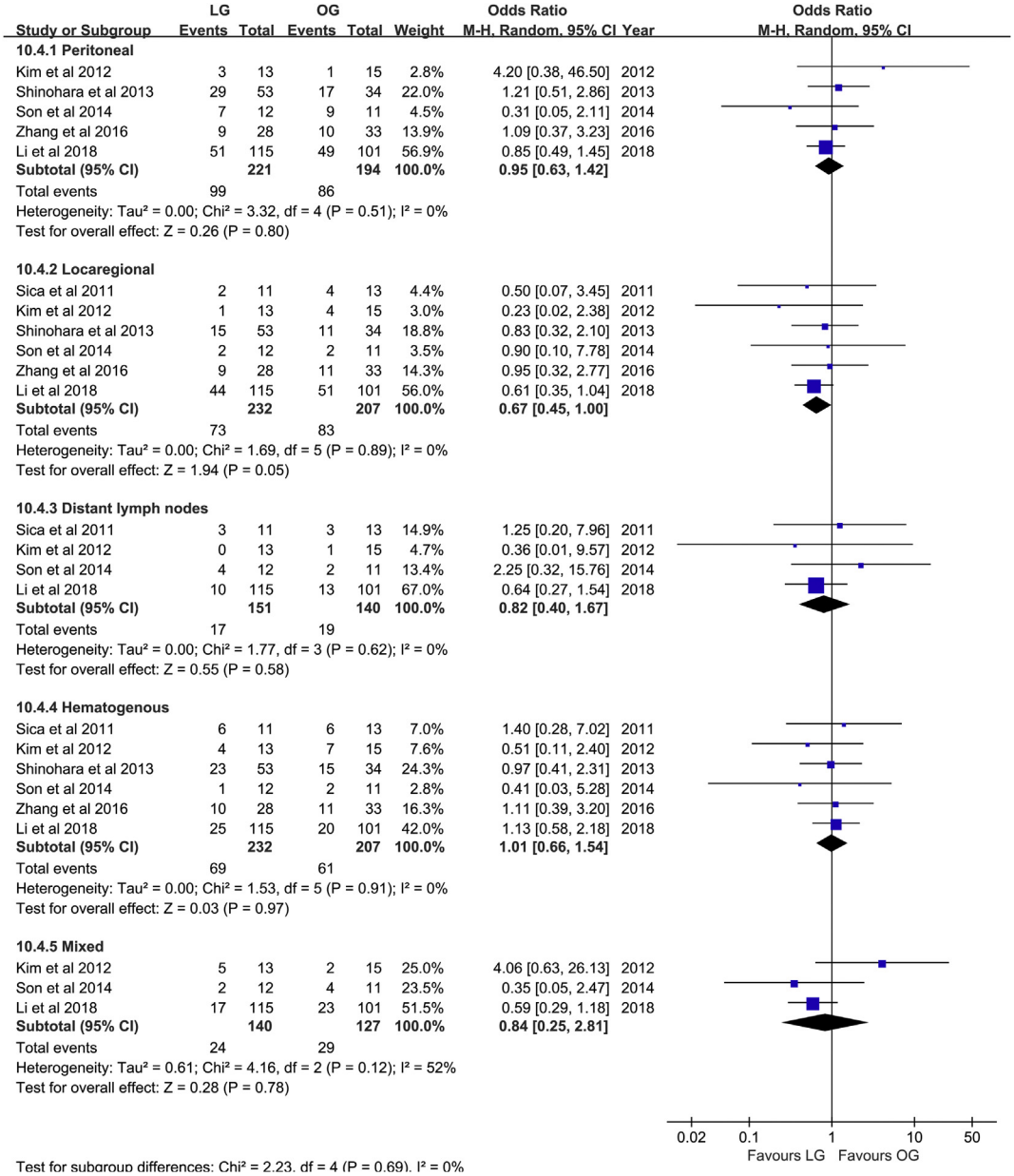

Fig. 5. Forest plot of recurrence pattern.

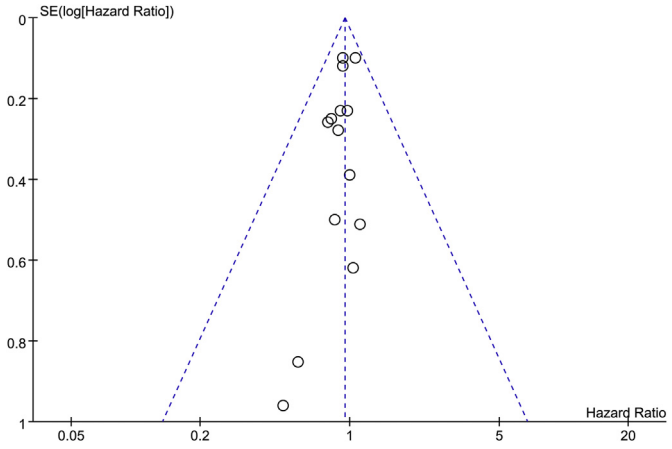

Fig. 6. Funnel plots of 5-year overall survival.

should be taken into consideration when interpreting our findings. Second, the survival outcomes may be influenced by learning curve, follow-up period, and varied baseline data among included studies which is impossible to be quantified.

Conclusion

In conclusion, the results show that LG could achieve comparable oncological outcomes with OG for AGC patients. We hope the ongoing multicenter RCTs will provide definitive evidence on this topic in the near future.

Compliance with ethical standards

Disclosures

Zhengyan Li, Yan Zhao, Bo Lian, Yezhou Liu, and Qingchuan Zhao have no conflicts of interest or financial ties to disclose.

Authors' contributions

Zhengyan Li and Qingchuan Zhao conceived the study and drafted the manuscript. Zhengyan Li and Yan Zhao identified and screened the search findings for potentially eligible studies of the meta-analysis. Yan Zhao and Bo Lian independently extracted the data using a unified datasheet, and the Qingchuan Zhao was consulted when controversial issues were presented. Yezhou Liu and Zhengyan Li performed the statistical analyses and gave an interpretation of the results. Zhengyan Li and Qingchuan Zhao revised and supervised the study. All authors read and approved the final manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjsurg.2019.01.020.

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