

## Research Article

# Long-Term Survival Outcomes of Laparoscopy-Assisted Versus Open Gastrectomy for Advanced Gastric Cancer: A Meta-Analysis

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Received: December 11, 2017; Accepted: January 09, 2018; Published: February 08, 2018

## Abstract

**Background:** Laparoscopy-Assisted Gastrectomy (LAG) has been accepted to treat early gastric cancer. The technical feasibility and favorable short-term surgical outcomes of laparoscopic gastrectomy for Advanced Gastric Cancer (AGC) have been confirmed by several meta-analyses, but the long-term survival outcome of LAG for AGC still remains controversial. This study aimed to compare the Overall Survival (OS) rate, Disease-Free Survival (DFS) rate and recurrence of LAG with OG for AGC.

**Methods:** Pub med, Embase, the ISI Web of Science and The Cochrane Library were searched (up to October 10, 2016) systematically. Prospective or retrospective studies comparing the clinical efficacy of LAG with OG for advanced gastric cancer were included to assess their survival and recurrence outcomes. Statistical analyses were carried out using RevMan 5.3 software.

**Results:** Ten studies with 2205 patients (1111 LAG, 1094 OG) were included in the analyses. There was no statistical difference in overall survival (OR=1.15, 95% confidence interval (CI):0.96, 1.38, P=0.13) and disease-free survival OR=1.15, 95% CI: 0.91, 1.44, P=0.25) between the two groups.

**Conclusion:** This meta-analysis demonstrated that LAG for AGC provided an acceptable prognosis with similar long-term survival outcomes and recurrence as OG.

**Keywords:** Laparo Scopic Gastrectomy; Advanced Gastric Cancer; Long-term Survival Meta-analysis

## Introduction

Laparoscopy-Assisted Gastrectomy (LAG) has been accepted as one of best treatments for Early Gastric Cancer (EGC) since it was first reported by Kitano in 1994 [1]. The analysis of Randomized Clinical Trials (RCTs) and multiple high-quality studies have described the safety of laparoscopic surgery for early gastric cancer [2-7]. In several medical centers, LAG gastrectomy for advanced gastric cancer has been carried out as a selection of operation for several years [8-13]. A growing number of reports and meta-analyses demonstrated that LAG was technically feasible and safety for locally advanced gastric cancer [14-18]. However, meta-analysis regarding long-term outcomes of AGC has been seldom reported. This meta-analysis performs an updated evaluation of all the available high-quality published trials aimed to compare the 5-year survival and recurrence outcomes of LAG with OG for AGC.

## Methods

### Literature search

A systematic literature search (up to October 10, 2016) was carried out using the Pub Med, Embase, the ISI Web of Science and The Cochrane Library data base restricted to articles published in English, using the following search keywords: "gastric carcinoma Or gastric cancer" And "laparoscopy OR laparoscopic" And "gastrectomy". In

addition, the reference lists of all included studies were also searched. Three authors (Zheng-yan LI, Chuan LI and Zi-yan Luo) individually conducted the literature search and cross-checked their search results.

### Study selection criteria

Studies were included if they meet the following criteria: (1) randomized or nonrandomized comparative studies were considered (2) The patients who underwent gastrectomy for advanced gastric cancer were acceptable; (3) the patients in the LG and OG groups were compared; (4) extent of lymphadenectomy from D1, D1+, D2 and D2+ was acceptable; (5) all the potentially eligible studies should report at least one of the primary outcome measures, including the 5-year overall survival (OS), tumor recurrence and gastric cancer-related death rates. If there was an overlap between authors or centers we selected the higher quality or more recent literature. Studies cannot provide relevant data were excluded.

### Data extraction and quality assessment

The following information was recorded for each eligible trial: authors' names, study.

Design, the publication year, duration of follow-up, number of patients, general patient characteristics, 5-year overall survival (OS) rate, disease-free survival (DFS) rate and recurrence rate. The methodological quality of each included non-randomized control

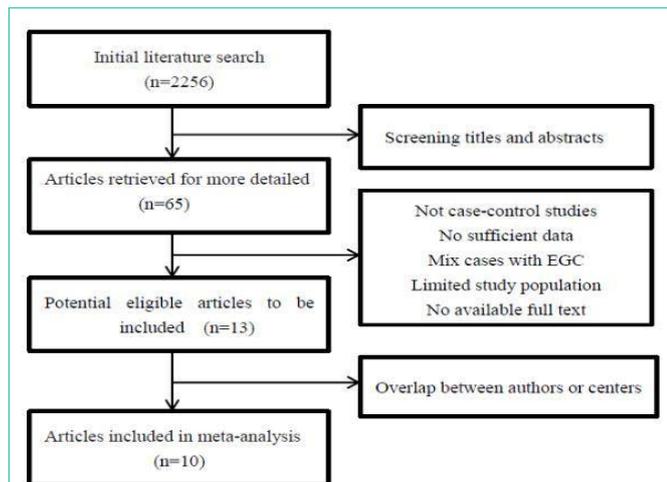


Figure 1:

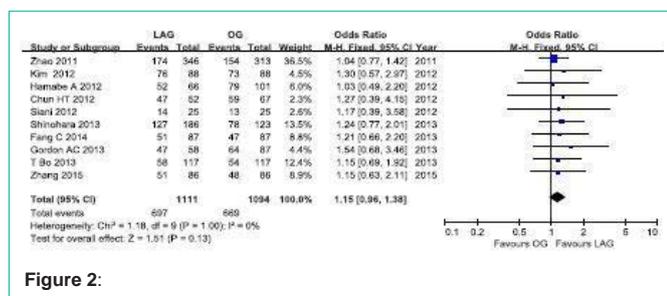


Figure 2:

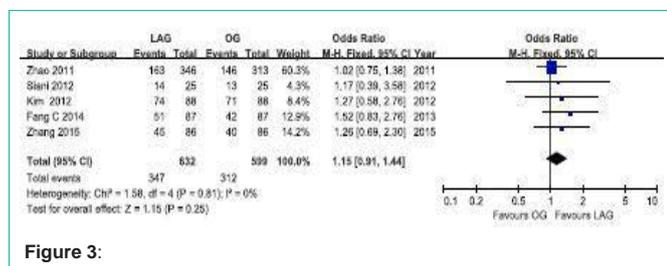


Figure 3:

trial was assessed by the Newcastle-Ottawa scale (NOS). A score of 0 to 9 was assigned to each study.

**Statistical analysis**

This meta-analysis was carried out using the Review Manager (RevMan) software, version 5.3. Dichotomous variables were analyzed using Odds Ratios (OR) and 95% Confidence Interval (CI). We considered heterogeneity to be present if the I2 value was greater than 50% and a random effect model was applied. However, if I2 statistic was less than 50%, we used a fixed effect model. The presence of reporting bias was evaluated according to the symmetry of the funnel plot. For all analyses, P < 0.05 was considered statistically significant.

**Results**

**Study characteristics**

Finally, 10 retrospective non-randomized controlled studies [19-28] were included in the present meta-analysis. The flow chart of the selecting process of articles is shown in (Figure 1). In all, our meta-analysis includes 2205 cases (1111 patients underwent LAG, and

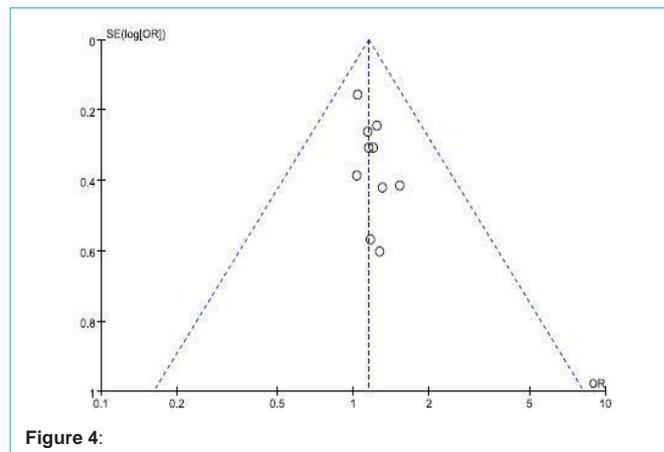
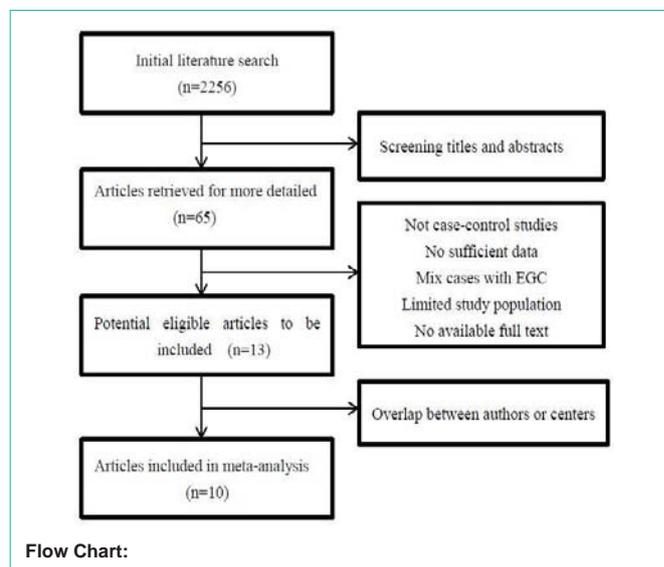


Figure 4:



Flow Chart:

1094 patients underwent OG) with Advanced Gastric Cancer (AGC). The detailed characteristics of the selected articles are summarized in Table 1.

**Five-year overall and survival**

10 studies reported (1111 cases in LAG group, and 1094 cases in OG group) 5-year overall survival outcomes. Visual inspection of the funnel plot revealed symmetry, indicating no serious publication bias, and none of the studies lay outside the limits of the 95% CI. (Figure 2). The result demonstrated that there was no significant difference between the LAG and OG groups (OR=1.15, 95% CI 0.96, 1.38, P=0.13), and no heterogeneity was presented (Figure 3). 5 studies reported (632 cases in LAG group, and 599 cases in OG group) 5-year overall survival outcomes. Meta-analysis of these available data showed that the Disease-Free Survival (DFS) rate was not significantly different in participants who received LAG compared with OG, and no heterogeneity was presented (Figure 4).

**Subgroup analyses**

In order to remove several factors which may influence the results of survival results, we made the Subgroup analyses. All of the subsets are comparable between the two groups, including the

**Table 1:** The detailed characteristics of the selected articles.

Study	Year	Region	Study type	Sample size		LN dissection	Surgical extension	Number of retrieved lymph node	Quality score
				LG	OG				
Zhao	2011	China	RNT	346	313	D1 + $\alpha/\beta$ , D2	DG,	33.2(12.5)/32.8(15.6)	9
Chun HT	2012	Korea	RNT	52	67	D2	DG	39.1(15.2) / 39.3(11.2)	9
Hamabe A	2012	Japan	RNT	66	101	D2	DG,TG	63.7(26.4) / 44.0(18.9)	7
Kim KH	2012	Korea	RNT	88	88	D2	DG, TG	38.3(14.3) / 41.8(15.3)	9
Siani	2012	Italy	RNT	25	25	D1 + $\alpha/\beta$ , D2	TG	35(18) / 40(16)	8
Bo T	2013	China	RNT	117	117	D2	TG	35.2(11.7) / 37.4(13.2)	9
Gordon AC	2013	Japan	RNT	66	135	D1 + $\alpha/\beta$ , D2	DG	35.92(12.60) / 36.59(14.48)	7
Shinohara	2013	Japan	RNT	186	123	D2	DG,PG,TG	45.3(16.9) / 43.8(17.2)	9
Fang C	2014	China	RNT	87	87	D2	DG, TG	16.3 / 17.2	8
Zhang	2015	China	RNT	86	86	D2	DG	20(16-23) / 21(17-23)	8

RNT: Retrospective Non-Randomized Controlled Study; DG: Distal Gastrectomy; TG: Total Gastrectomy

**Table 2:** The 5-year overall survival outcomes of different subsets.

Subgroup	Study No.	OR	(95% CI)	P	Model	I-Squared	P
<b>Publication year</b>							
≤2012	5	1.08	[0.84, 1.40]	0.54	Fixed	0%	0.99
>2012	5	1.22	[0.95, 1.58]	0.13	Fixed	0%	0.98
<b>Region</b>							
Japan	3	1.24	[0.87, 1.79]	0.24	Fixed	0%	0.78
Korea	2	1.29	[0.66, 2.54]	0.46	Fixed	0%	0.98
China	4	1.10	[0.88, 1.37]	0.41	Fixed	0%	0.97
<b>Sample size</b>							
<100	7	1.22	[0.91, 1.63]	0.18	Fixed	0%	1.00
≥100	3	1.11	[0.88, 1.39]	0.38	Fixed	0%	0.83
<b>Surgery extension</b>							
Distal only	4	1.11	[0.87, 1.43]	0.40	Fixed	0%	0.84
Total only	2	1.15	[0.72, 1.84]	0.55	Fixed	0%	0.97
<b>Lymphadenectomy</b>							
D2/D2+only	7	1.19	[0.93, 1.50]	0.16	Fixed	0%	1.00
D1/D1+ (>20%)	2	1.40	[0.73, 2.69]	0.31	Fixed	0%	0.70
<b>Nodes harvested</b>							
<30	2	1.18	[0.77, 1.81]	0.45	Fixed	0%	0.92
≥30	8	1.14	[0.94, 1.39]	0.19	Fixed	0%	0.99
<b>Tumor stage</b>							
I+II>50%	6	1.23	[0.93, 1.63]	0.15	Fixed	0%	0.99
I+II≤50%	4	1.09	[0.87, 1.38]	0.45	Fixed	0%	0.97

publication year, study region, sample size, surgery extension, lymphadenectomy, Number of retrieved lymph node and proportion of tumor stage ( $P<0.05$ ). The 5-year overall survival outcomes of different subsets are summarized in Table 2.

### Recurrence and stage-specific survival analyses

6 studies reported (825 cases in LAG group, and 779 cases in OG group) recurrence during the follow-up period. The result suggested that there was no significant difference between the LAG and OG

groups (OR=0.82, 95% CI 0.65, 1.02,  $P=0.24$ ). We made stage-specific analyses aim to make a precise analysis of survival outcomes. We also found that the results obtained are comparable between the two groups in stage II–III. Results of stage-specific analyses of 5-year overall survival outcomes are shown in Table 3.

### Discussion

The long-term survival outcomes are key factor to evaluate the clinical efficacy and feasibility of an operation [7,29]. The present

**Table 3:** Five-Year Recurrence and Stage-Specific Analyses of the 5-Year Overall Survival.

Subgroup	Study No.	OR	(95% CI)	P	Model	I-Squared	P
Recurrence	6	0.82	[0.65,1.02]	0.07	Fixed	26%	0.24
Overall survival	10	1.15	[0.96,1.38]	0.13	Fixed	0%	0.51
Stage I	2	0.75	[0.18,3.09]	0.69	Fixed	0%	0.56
Stage II	2	2.07	[0.99,4.35]	0.05	Fixed	0%	0.81
Stage III	2	1.32	[0.62,2.83]	0.48	Fixed	0%	0.84

meta-analyses are a specific analysis of long-term survival outcomes and aim to make a precise analysis of relevant factors. The results indicate that the 5-year OS, recurrence is comparable between LAG and OG. Several factors such as the publication year, study region, sample size, Surgery extension, lymphadenectomy, Number of retrieved lymph node, and proportion of Tumor stage do not influence the results. What's more, when we further study the OS outcomes by stage-specific analysis. We also found that the results obtained are comparable between the two groups. This updated meta-analysis confirms the results of several previous studies [30-33]. The results of 1 RCT conducted by Cai et al [11], show that the survival rate of the LAG group is slightly higher than that of the OG group though with no statistical significance. Zhao et al [19], reported the 5-year survival rate in the LG group was similar to the OG group which is consistent with the result of studies by Shinohara et al [26], and Bo T et al. [25]. A recent large-scale samples study conducted by Hao et al [31], reported that there was no significant difference in the stage-stratified survival rates between the two groups.

Perigastric lymphadenectomy is an important part of radical resection for gastric cancer patients [34-36]. Now, D2 has been acknowledged as the standard procedure for AGC by the European Society of Surgical Oncology (ESSO), the European Society for Medical Oncology (ESMO), and the European Society of Radiotherapy and Oncology (ESTRO) guidelines. Two meta-analyses reported that gastrectomy with D2 lymphadenectomy improves prognosis compared with D1. Our meta-analysis further evaluate the 5-year OS of different Lymphadenectomy subsets. 7 studies included in this meta-analysis were performed by gastrectomy with D2 or D2+lymphadenectomy. Mean while, Two studies included in this meta-analysis were performed by gastrectomy with D1/D1+>20% subset lymphadenectomy. No significant difference was shown with regard to the different extent of the dissection between the two groups.

The stage-specific analysis suggests that the long-term survival rates are comparable from Stage I to Stage III between the two groups. Moreover, we found that the studies in china present a higher recurrence rates than that in Japan and Korea. The primary reason for the differences is likely that over 80% of patients were diagnosed at advanced stage [19]. Therefore, studies in china may include more stage III patients which have poor prognosis than that in stage I or stage II. Meanwhile the follow-up period of these studies are various which may lead to the difference of the recurrence rates. Regarding recurrence rates we found no significant difference between the two groups and these results suggest no inferiority of the long-term results for LAG compared with those for OG.

A multicenter retrospective study with large-scale cases suggest that the hematogenous recurrence pattern was most common in the

LAG group, followed by the loco regional pattern [37]. The recurrence sites in these study are similar, included the peritoneum, liver, lymph node metastasis, and remnant stomach. Several studies stated that the peritoneum was the most common recurrence sites [23, 31,37]. Huang et al [38] reported port-site recurrence was occurred in one patient 10 month later after LG.

The majority of previous studies about LAG mainly included cases with T2 or T3 depth. Therefore, a general concern that laparoscopic surgery for AGC with serosa invasion (T4a ) may be lead an increased incidence of peritoneal seeding of malignant cells and port site recurrence. In previous studies, 25.9% patients (45/174) were diagnosed to have T4a depth of invasion. Recurrence was detected in 14 cases (16.1%) in the LAG group and 16 cases (18.4%) in the OG group which appeared to be not significantly different [27]. Till now, studies for patients with serous membrane invasion are rare and still needed to further investigate.

Some limitations of our present study need to be noted. First, no RCTs are included in the meta-analyses. Second, some subgroups such as stage-specific analyses of the 5-year OS only include the data of two studies which may limit the strength of the stage-specific analyses. What's more, the survival outcomes may be influenced by learning curve, follow-up period and different baseline data of the two groups which is impossible to quantified.

## Conclusion

In conclusion, our meta-analysis demonstrated that LAG for advanced gastric cancer provided an acceptable prognosis with similar long-term survival outcomes compared with OG. These findings support the acceptance and application of LAG for AGC. However, large-scale prospective RCT studies with long follow-up are still needed to further investigate the clinical outcomes of the two surgical procedures.

## Authors' Contributions

Zhengyan Li and Qingchuan Zhao designed the study. Zhengyan Li wrote the manuscript. Jipeng Li, Bin Bai and Deliang Yu performed the literature review, extraction of the data, and analysis of the pooled data. Gang Ji and Jipeng Li revised the manuscript. All authors read and approved the final manuscript.

Financial support: no

Ethics approval and consent to participate section: All analyses were based on previous published studies, thus no ethical approval and patient consent are required.

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