# Comparison of laparoscopic versus open gastrectomy with D2 lymph node dissection for advanced gastric cancer: A meta-analysis

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## ABSTRACT

For many decades, D2 procedure has been accepted in the far-east as the standard treatment for both early (EGC) and advanced gastric cancer (AGC). In case of AGC, the debate on the extent of nodal dissection has been open for many years in order to highlight the safety and efficacy of treatment, hence this study.

A comprehensive literature research was performed in PubMed to identify studies that compared laparoscopic- assisted gastrectomy (LAG) and open gastrectomy (OG) with D2 lymph node dissection (D2-LND) for treatment of AGC for the last five years. Data of interest were checked and subjected to meta-analysis with RevMan 5.3 software. The pooled risk ratios (RR) and weighted mean difference (WMD) with 95% confidence intervals (CI) were calculated.

Overall, 19 studies were included in this meta-analysis. LG had some advantages over OG, including shorter hospitalization (WMD -2.31; 95% CI -4.09 to -0.53; P = 0.01), less blood loss (WMD -120.49; 95% CI -174.27 to -66.71; P < 0.01), faster bowel recovery (WMD -0.55; 95% CI -0.86 to -0.24; P < 0.01) and earlier ambulation (WMD -0.75; 95% CI -1.38 to -0.11; P = 0.02). In terms of surgical and oncological safety, LG could achieve similar lymph nodes (WMD, -0.94, 95% CI, -2.95 to 1.06; P=0.36), a lower complication rate [odds ratio (OR)=0.80; 95%CI, 0.68-0.97; P=0.02], and overall survival (OS) and disease-free survival (DFS) comparable to OG.

In conclusion, for AGCs both techniques (LAG and OG) appeared comparable in short- and long-term results. More time was needed to perform LAG; nonetheless, it had some advantages in achieving faster postoperative recovery over OG. In order to clarify this controversial issue ongoing trials and future studies are needed.

Keywords: **Advanced gastric cancer, Laparoscopic gastrectomy, Open gastrectomy, D2 lymph node dissection, meta-analysis**

## Introduction

With the third highest rate of mortality, cancer of the stomach is one of the most malignant tumors in the world[1]. In fact, around three-quarters of all new cases and deaths occur in Eastern Asia, Eastern Europe and South America, and almost close to half (42 %) in China[2]. Despite considerable progress in the diagnosis and treatment of gastric cancer, it remains a major health problem and requires a multidisciplinary approach in which surgery is the cornerstone in the treatment of gastric cancer[3], which includes conventional open gastrectomy (OG) and laparoscopy-assisted gastrectomy (LAG).

For a long time in history, conventional open gastrectomy (OG) surgery remains the treatment of choice for gastric cancer. A complete resection along with lymph node dissection was recognized as broad as the only one cure for gastric cancer [4].

But since its first description in 1991 by Kitano[5], laparoscopic gastrectomy (LG) has experienced rapid development and has been widely accepted and widely used to treat EGC nowadays, especially in East Asia( China, Japan and Korea)[6,7].

With curative intent, the D2 lymph node dissection has been widely applied in traditional open surgery for locally advanced gastric cancer (AGC)[8], however, the use of this procedure in LG for AGC is discussed. The oncological safety of LG in AGC treatment has not been well evaluated, and it remains to be confirmed whether laparoscopic surgery can still guarantee the advantage of minimal invasion, whether it increases perioperative complications and mortality, and whether it can achieve the same degree of radicalism as open surgery. To this end, we conducted a meta-analysis by comparing LAG with OG with D2 lymph node dissection for AGC with regard to their short- and long-term outcomes in order to determine the current status of LAG.

## Materials & Methods

### Search strategy:

A comprehensive PubMed search from January 2011 to February 2016 was performed using the following Mesh search headings and text words: “laparoscopy-assisted gastrectomy”, “laparoscopic-assisted gastrectomy”, “open gastrectomy”, “conventional gastrectomy”, “gastric cancer”, “gastric carcinoma”, “advanced gastric cancer”, “D2 dissection”. Logical combinations of these and related terms (stomach, neoplasm) were used to maximize sensitivity and only studies published in English were included. Title and abstracts of each identified publication were screened, and only publications that reported the full texts for the clinical outcomes of this analysis were further retrieved. Reference lists of systematic reviews or meta-analysis were additionally checked to identify potential eligible studies.

### Study eligibility:

Studies following below criteria were selected:

(1) RCTs and nonrandomized comparative studies

(2) Patients with advanced gastric carcinoma and/or with locally advanced were acceptable, without limitations for race, age or gender and where the patients in the LG and OG groups were compared; and the staging system was based on the individual reports

(3) Studies comparing the short and long-term outcomes of LADG and OG with D2 LND.

Exclusion criteria included:

(1) robot-assisted gastrectomy

(2) no OG as a control

(3) abstract only

(4) recurrent gastric cancer or palliative resection cases

(5) duplicate publication or publications with sufficient data.

### Data extraction:

EndNote (Version X7, Thomson Reuters) was used to merge the search results and remove duplicate records of the same report. Titles and abstracts were screened. Articles deemed potential for inclusion were reviewed by two reviewers independently and data extracted in predefined forms. Disagreement was resolved by discussion with the two other reviewers. Relevant data included: first author, year of publication; geographical region; study period; type of study; sample size for each technique, laparoscopic technique. The short-term outcomes included operation time, blood loss, harvested lymph nodes, tumor size, first flatus time, oral diet time (soft or liquid), post-operative hospital stay, ambulation, morbidity (or the incidence of postoperative complications), mortality (here defined as hospital mortality). Postoperative complications were classified as surgical complications and medical complications. The long-term outcomes included cancer recurrence and survival rate.

### Quality assessment:

For all the included studies[9], to assess their quality we used the modified Newcastle–Ottawa Scale. The total score was 9 stars, and the quality of each study was graded as level 1 (0-5 stars) or level 2 (6-9 stars). Studies ≥ 5 stars were considered as high-quality studies.

### Data synthesis and statistical analysis:

The “Review Manager 5.3” software from the Cochrane collaboration was used for statistical analysis. For all statistical calculations, RRs was used for dichotomous variables and WMDs for continuous variables with a 95% confidence interval (CI). For this latter, data in the form of means and standard deviation allowed statistical analysis. A random-effect model was used to avoid statistical heterogeneity between the studies owing to the high heterogeneity of the studies; otherwise, fixed-effects model was used. Heterogeneity was calculated by $Chi^2$ and the $I^2$ test. The fixed effect model was used if no significant heterogeneity was observed among the included studies ($P > 0.1$, $I^2 < 50$ %). Publication bias was evaluated by a funnel plot. For all analyses, $P \leq 0.05$ was considered statistically significant. For dichotomous outcomes, the Mantel-Haenszel method was used for both fixed effect analysis and random effect (DerSimonian)[10] analysis. For continuous data, an inverse variance method was used.

## Results

A total of 19 studies[11-29] that included 4949 (2534 in LAG and 24155 in OG) gastrectomy with D2 lymph node resection for AGC were considered eligible for our meta-analysis. For every study, analysis of the demographics and clinic-pathological characteristics of patients treated by LG and OG did not differ from each other. Among the 19 articles, twelve studies originated from China[11-22], three from Korea[23-25], three from Japan[26-28], and one from Italy[29]. Selected studies were published within 5 years, from 2011 to 2016, and case numbers varied from 18 to 1078. Proximal, distal, total and subtotal gastrectomies were used as surgical options. Gastrointestinal tract reconstruction modalities included Billroth-I/II, Roux-en-Y anastomosis, eosophago-gastrostomy, and eosophago-jejunostomy. None of the studies had reported the use of neo-adjuvant chemo-radiotherapy, but one study[28] reported the use of chemo-radiotherapy in postoperative period. The follow-up ranged from 30 days to 5 years. Detailed information on study characteristics is shown in **Table 1** and quality assessment in **Table 2**, all study had a score of ≥ 6 stars.

The quality of each study was graded as low level (total score 0–5) or high level (total score 6–9).

a) *Selection: (1)* Assignment for treatment: One star was assigned if details of criteria for assignment of patients to treatments provided. (2) One star was assigned if the laparoscopic-assisted distal gastrectomy group was representative of patients for gastric cancer; no star was assigned if groups of patients were selected or selection of the group was not described. (3) One star was assigned if the open distal gastrectomy group was representative of patients for gastric cancer; no star was assigned if groups of patients were selected or selection of the group was not described.

b) *Comparability:* Comparability variables were as follows: 1, age; 2, sex; 3, depth of tumor invasion on preoperative diagnosis; 4, extent of lymphadenectomy; 5, median or mean follow-up; 6, American Society of Anesthesiologists status; 7, tumor size; 8, postoperative pathologic stage; and 9, histological type. (4)

**Table 1:** Baseline characteristics of studies included in the meta-analysis

| References | Country | Publication year | Study period | Study design | Patients Total | LADG | OG | Tumor stages of AGCs | Surgical extension | Construction methods | Median Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Cai et al [11] | China | 2011 | 2008/03-2009/12 | RCT | 96 | 49 | 47 | Ib-IIIb | PG,DG,TG | B-I/II | 22.1 months |
| Jeong et al [23] | Korea | 2011 | 2005/01-2007/12 | Retro | 185 | 109 | 76 | Ib-IV | DG,TG | B-I/II, R-Y | 36.8 months |
| Scatizzi et al [29] | Italy | 2011 | 2006/01-2009/09 | Retro | 60 | 30 | 30 | II-IIIb | SG | R-Y | 18 months |
| Shuang et al. [12] | China | 2011 | 2005/08-2007/12 | Retro | 70 | 35 | 35 | Ib-IIIb | DG | B-II | 35 months |
| Chen et al [13] | China | 2012 | 2008/01-2010/12 | Retro | 336 | 224 | 112 | Ib-IIIb | DG,TG | B-I/II, R-Y | 19 months |
| Chun et al [24] | Korea | 2012 | 2004/01-2009/12 | Retro | 119 | 52 | 67 | Ib-IIIa | DG | B-I/II, R-Y | 5 years |
| Hamabe et al [26] | Japan | 2012 | 2000/01-2009/12 | Retro | 167 | 66 | 101 | Ib-IIIb | DG,TG | B-I/II, R-Y | 5 years |
| Kim et al [25] | Korea | 2012 | 1999/08-2007/06 | Retro | 176 | 88 | 88 | Ib-IIIc | PG,DG,SG | B-I/II, R-Y, EG | 5 years |
| Shinohara et al [27] | Japan | 2013 | 1997/10-2008/12 | Retro | 309 | 186 | 123 | cT2- T4 | PG,DG,TG | B-I, R-Y | 48.8 months |
| Lin et al [14] | China | 2013 | 2008/01-2010/12 | Retro | 166 | 83 | 83 | Ib-IIIb | DG,TG | B-I/II, R-Y | 23 months |
| Bo et al [15] | China | 2013 | 2004/01-2010/12 | Retro | 234 | 117 | 117 | Ib-IIIb | TG | R-Y | 61.2 months |
| Fang et al [16] | China | 2013 | 2009/08-2011/01 | Retro | 112 | 50 | 62 | NR | NR | B-I/II | 18 months |
| Yamanaka et al [28] | Japan | 2013 | 2000/01-2010/12 | Retro | 18 | 9 | 9 | IV | DG,TG | NR | 20.5 months |
| Li et al [17] | China | 2013 | 2009/03-2011/06 | Retro | 239 | 106 | 133 | Ib-IIIc | DG,TG | B-I/II, R-Y | 15 months |
| Fang et al [18] | China | 2014 | 2005/04-2009/10 | Retro | 174 | 87 | 87 | Ib-IIIc | DG,TG | EJ, GI | 44 months |
| Zhang et al. [19] | China | 2015 | 2007/01-2014/12 | Retro | 172 | 86 | 86 | Ib-IIIc | NR | NR | 39 months |
| Li et al [20] | China | 2016 | 2012/04-2014/12 | Retro | 202 | 101 | 101 | II-IIIb | DG,TG | NR | NR |
| Hu et al. [21] | China | 2016 | 2012/09-2014/12 | Retro | 1036 | 517 | 519 | Ib-Iv | DG,TG | B-I/II, R-Y | 30 days |
| Lin et al [22] | China | 2016 | 2005/01-2011/12 | Retro | 1078 | 539 | 539 | Ib-IIIc | DG,TG | NR | 45 months |

NR not reported, DG distal gastrectomy, RCT randomized controlled trial, Retro retrospective, PG proximal gastrectomy, TG toal gastrectomy, SG subtotal gastrectomy, B-I Billroth-I, B-II Billroth II, R-Y Roux-en-Y, EG eosophagogastrostomy, EJ eosophagojejunostomy

**Table 2:** Quality assessment of included studies

| Reference | Selection | | | Comparability of group | | Outcomes | | Total |
|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | |
| Cai et al. | * | * | * | ** | * | * | | ******* |
| Jeong et al. | * | * | * | * | * | * | | ****** |
| Scatizzi et al. | * | * | * | ** | * | * | * | ******** |
| Shuang et al. | * | * | * | ** | | * | * | ******* |
| Chen et al. | * | * | * | ** | ** | * | * | ********* |
| Chun et al. | * | * | * | ** | * | * | * | ******** |
| Hamabe et al. | * | * | * | ** | * | | * | ******* |
| Kim et al. | * | * | * | ** | * | | * | ****** |
| Shinohara et al. | * | * | * | ** | ** | * | * | ********* |
| Lin et al. | * | * | * | ** | * | * | * | ******** |
| Bo et al. | * | * | * | ** | * | * | | ******* |
| Fang et al. | * | * | * | ** | * | * | | ******** |
| Yamanaka et al. | * | * | * | ** | * | * | | ******* |
| Li et al | * | * | * | ** | * | | * | ******* |
| Fang et al. | * | * | * | ** | ** | | * | ******** |
| Zhang et al. | * | * | * | * | * | | * | ****** |
| Li et al | * | * | * | * | ** | * | * | ******** |
| Hu et al. | * | * | * | ** | ** | * | | ******** |
| Lin et al. | * | * | * | ** | ** | | * | ******** |

Two stars were assigned if the groups were all comparable for the variables 1–5; 1 star was assigned if one of these five characteristics was not reported, even if there were no other differences between the groups, and other characteristics had been controlled for; and no star was assigned if the two groups differed. (5) Two stars were assigned if the groups were all comparable for the variables 6-9; 1 star was assigned if one of these four characteristics was not reported, even if there were no other differences between the groups, and other characteristics had been controlled for; and no star was assigned if the two groups differed.

c) *Outcome assessment:* (6) one star was assigned if primary outcome parameters were clearly reported. (7) One star was assigned if more than 90% of patients were followed up.

### 1) Comparison of intraoperative effects

The duration of operation time in LAG group was 59.61 min longer than that in OG group (WMD 59.61; 95% CI 28.43, 90.79; $P < 0.01$) with the random-effect model due to significant heterogeneity ($I^2$ = 100%)**.** With 12 studies included**,** the results of estimated blood loss were in favor of LAG group, with a reduction of 120.49 ml than OG (WMD -120.49; 95% CI -174.27, -66.71; $P < 0.01$)**,** same as the patients needed transfusion is less in LAG group compared to the OG (WMD 0.40; 95% CI 0.22, 0.72; $P < 0.01$)**.** Concerning the dissected LNs, LAG could achieve the same radical dissection effect as OG (WMD, -0.94, 95 % CI, -2.95, 1.06; $P = 0.36$) with the random-effect model due to marked heterogeneity ($I^2 = 94\%$) **(Figure 1).** Furthermore, both procedures yielded comparable proximal (WMD, -0.34, 95 % CI, -0.86, 0.19; $P = 0.21$), marked heterogeneity ($I^2$ = 80%) and distal (WMD, -0.05, 95 % CI, -0.27, 0.18; $P = 0.68$**)** resection margin distance where the level of heterogeneity was not worthy ($I^2$ = 17%), so the fixed effect model was used**.** Similar size of tumor was found between LAG group and OG group (WMD = 0.61; 95% CI -5.83, 7.05; $P = 0.85$) with the random-effect model due to significant heterogeneity ($I^2$ = 100%)**.**

Results of analyses of intraoperative effects are shown in **Table 3**.

LG laparoscopic-assisted gastrectomy, OG open gastrectomy, LN lymph node, WMD weighted mean difference

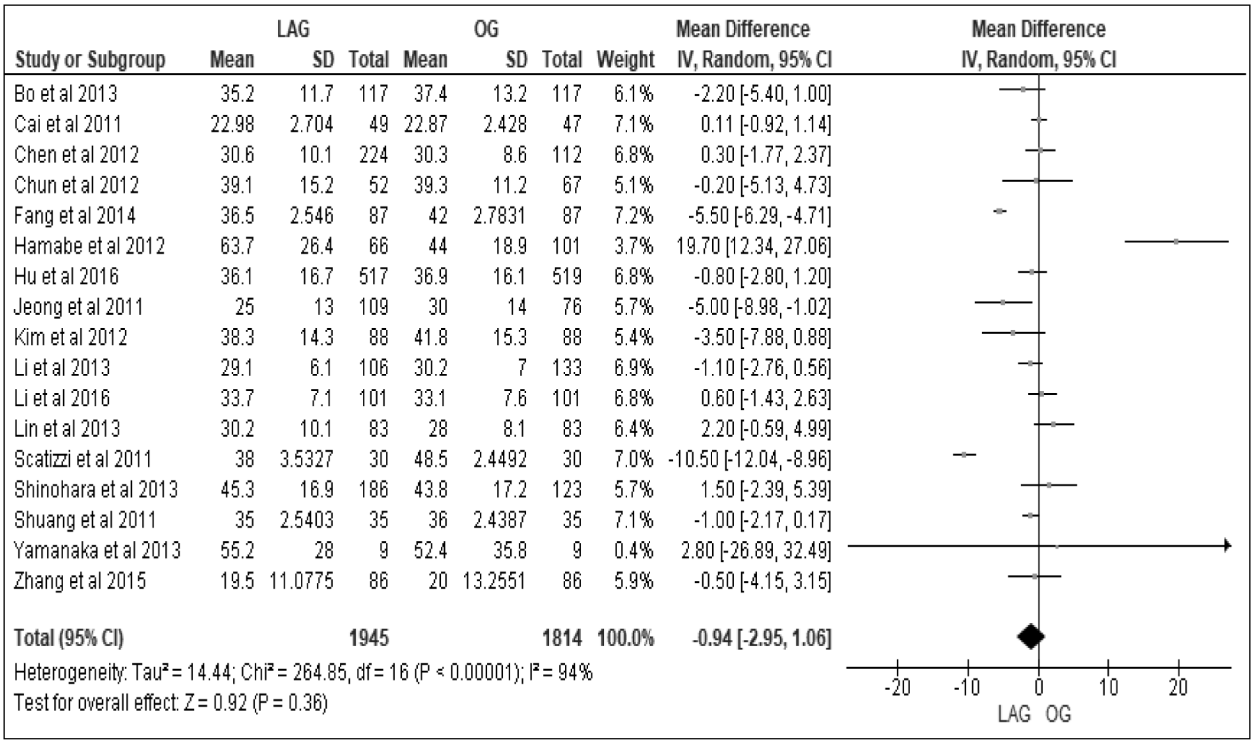


**Figure 1**: Harvested lymph nodes

**Table 3:** Comparisons of intraoperative surgical effects

| Outcomes | Included studies | Patients | | Heterogeneity ($I^2$, P) | Overall effect WMD (95% CI) | P value |
|---|---|---|---|---|---|---|
| | | LAG | OG | | | |
| Operation time, min | 18 | 1995 | 1876 | 100%, P < 0.01 | 59.61 28.43,90.79 | **< 0.01** |
| Estimated blood loss | 12 | 1657 | 1544 | 100%, P < 0.01 | -120.49 -174.27,-66.71 | **< 0.01** |
| Needed transfusion | 7 | 802 | 681 | 57%, 0.03 | 0.40 0.22,0.72 | **< 0.01** |
| Retrieved LNs | 17 | 1945 | 1814 | 94%, P < 0.01 | -0.94 -2.95,1.06 | 0.36 |
| Tumor size | 12 | 1719 | 1740 | 100%, P < 0.01 | 0.61 -5.83,7.05 | 0.85 |
| Proximal resection margin Distance | 5 | 883 | 867 | 80%, P < 0.01 | -0.34 -0.86,0.19 | 0.21 |
| Distal resection margin Distance | 5 | 816 | 812 | 17%, 0.31 | -0.05 -0.27,0.18 | 0.68 |

## 2) Analyses of short-term results

Laparoscopic surgery has certain advantages compared to open surgery such as less pain, shorter hospitalization, quicker bowel function recovery, earlier resumption of body movement. In agreement with this, we found patients undergoing LAG had: shorter mean time for use of analgesic drugs (WMD -1.87; 95% CI -2.57, -1.18; P < 0.01)**,** shorter hospital stay with 2.31 days (WMD -2.31; 95% CI -4.09, -0.53; P = 0.01). Also, shorter mean time to first flatus with 0.55 day earlier (WMD -0.55; 95% CI -0.86, -0.24; P < 0.01), and resumed oral intake much earlier in both soft diet (WMD -1.60; 95% CI -2.18, -1.01; P < 0.01) and fluid diet (WMD -0.48; 95% CI -0.90, -0.06; P = 0.03) than those undergoing OG with 1.60 and 0.48 days earlier respectively. In addition, patients treated with LAG needed less time to ambulation than those with OG (WMD -0.75; 95% CI -1.38, -0.11; P = 0.02). The perioperative complication rate was also compared. Overall complication rate for LAG was 15%, significantly lower than the rate of 17.6% of OG (OR, 0.81; 95% CI 0.68, 0.97; P = 0.02) **(Figure 2).** To be specific, the rates of surgical complications, including leakage, wound infection, bleeding and anastomotic stricture (OR, 0.72, 95 % CI, 0.55, 0.94; P = 0.02), and medical complications such as respiratory or cardiovascular events, pulmonary embolism, deep venous thrombosis and non-surgical infections (OR, 0.48, 95 % CI, 0.31, 0.74; P = 0.001) were both in favor of LAG. Moreover, in

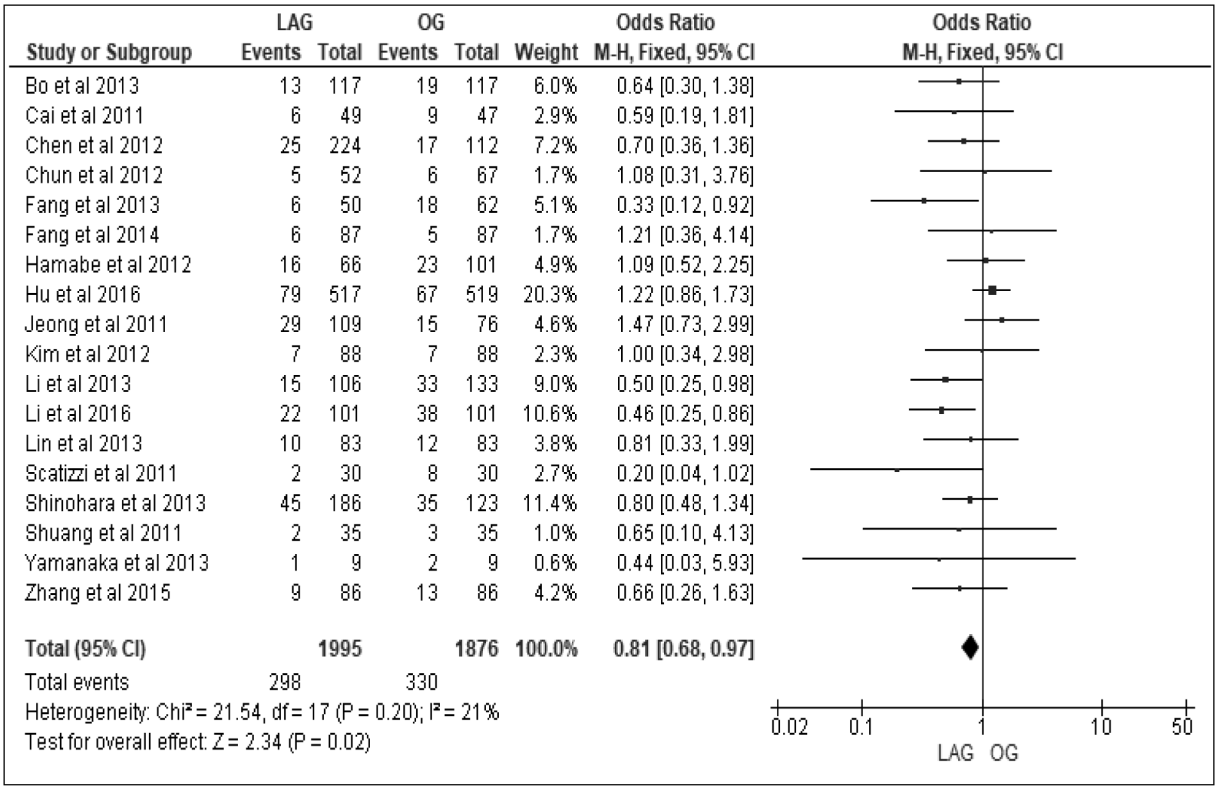


**Figure 2:** Forest plot of pooled odds ratio of overall complication

terms of mortality, there is no significant differences between the two procedures (OR, 0.68, 95 % CI, 0.46, 1.02; P = 0.06).

The comparison outcomes of short- term results between LG and OG is summarized in **Table 4**.

LG laparoscopic-assisted gastrectomy, OG open gastrectomy, WMD weighted mean difference, OR odds ratio

### 3) Analyses of long-term effects

Seven studies reported data on tumor recurrence, with a moderate heterogeneity observed. The recurrence rate in LAG was 23.45 %, which was significantly lower than the rate of 25.23% in OG (RR, 0.83, 95 % CI, 0.55, 1.24; P = 0.36) **(Figure 3)**. Thirteen studies[13–19, 22, 24–28] reported long-term follow-up ranging from 1 year to 5 years. Five studies[13-14,16-17,28] reported 1-year OS; two studies[16,22] reported 3-year OS, and seven[15,18-19,24-27] reported 5-year OS. No significant differences were seen in 1-, 3-, or 5-year OS between LAG and OG [1-year: Risk ratio(RR)=1.02, 95% CI, 0.97-1.08; P=0.42; 3-year: RR=0.97, 95%CI, 0.88-1.07; P=0.53; 5-year: RR=1.08, 95%CI, 1.00-1.16; P=0.04] respectively. Regarding RFS, two studies[18,26] reported 5-year RFS.

**Table 4**: Comparisons of short-term results

| Outcomes | Included studies | Patients | | Heterogeneity ($I^2$, P) | Overall effect WMD (95% CI) | P value |
|---|---|---|---|---|---|---|
| | | LAG | OG | | | |
| Hospital stay | 17 | 1907 | 1788 | 97%, P < 0.01 | -2.31 -4.09,-0.53 | **< 0.01** |
| First flatus | 11 | 1476 | 1373 | 91%, P < 0.01 | -0.55 -0.86,-0.24 | **< 0.01** |
| Oral diet (soft) | 6 | 633 | 458 | 85%, P < 0.01 | -1.60 -2.18,-1.01 | **< 0.01** |
| Fluid intake | 4 | 496 | 409 | 72%, P < 0.01 | -0.48 -0.90,-0.06 | 0.03 |
| Use of analgesic drugs | 5 | 352 | 352 | 83%, P < 0.01 | -1.87 -2.57,-1.18 | **< 0.01** |
| Ambulation, days | 7 | 1206 | 1031 | 98%, P < 0.01 | -0.75 -1.38,-0.11 | 0.02 |
| Overal complication | 18 | 1995 | 1876 | 21%, 0.20 | 0.81 0.68,0.97 | 0.02 |
| Surgical complication | 10 | 1014 | 914 | 0%, 0.67 | 0.72 0.55,0.94 | 0.02 |
| Medical complication | 7 | 813 | 663 | 21%, 0.27 | 0.48 0.31,0.74 | 0.001 |
| Mortality | 10 | 1458 | 1345 | 0%, 0.49 | 0.68 0.46,1.02 | 0.06 |

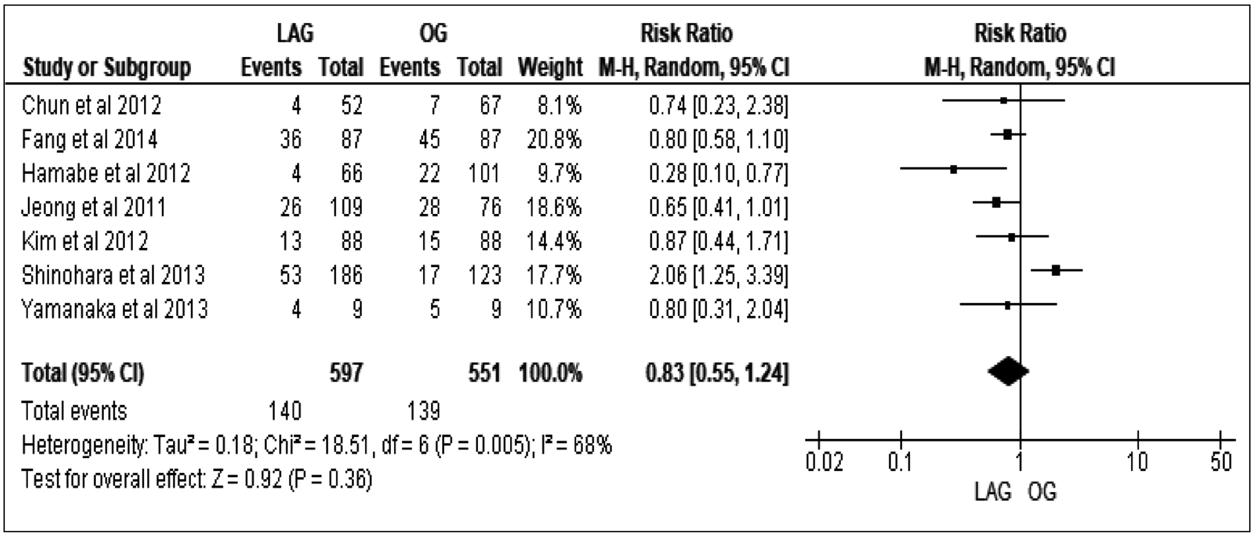


**Figure 3:** Recurrence rate.

The 5-year RFS of LAG and OG were 53.6 % and 34.6 % respectively (RR=1.67, 95 % CI, 1.32-2.11; P < 0.01). About DFS, three studies[19,25,27] reported 5-year DFS. The 5-year DFS of LAG and OG were 66.66 % and 62.62 % respectively (RR=1.07, 95 % CI, 0.96–1.19; P=0.25).

Results of meta-analysis of long-term effects are presented in **Table 5**.

**Table 5**: Comparisons of long-term results

| Outcomes | Included studies | Patients | | Heterogeneity ($I^2$, P) | Overall effect RR (95% CI) | P-value |
|---|---|---|---|---|---|---|
| | | LG | OG | | | |
| Recurrence | 7 | 597 | 551 | 68%, 0.36 | 0.83, 0.55-1.24 | 0.005 |
| 1-year OS | 5 | 472 | 399 | 20%, 0.29 | 1.02, 0.97-1.08 | 0.42 |
| 3-year OS | 2 | 589 | 601 | 0%, 0.97 | 0.97, 0.88-1.07 | 0.53 |
| 5-year OS | 7 | 682 | 669 | 0%, 0.47 | 1.08, 1.00-1.16 | 0.04 |
| 5-year RFS | 2 | 153 | 188 | 0%, 0.53 | 1.67, 1.32-2.11 | < 0.01 |
| 5-year DFS | 3 | 360 | 297 | 0%, 0.88 | 1.07, 0.96-1.19 | 0.25 |

LG laparoscopic gastrectomy, OG open gastrectomy, OS overall survival, RFS recurrence-free survival, DFS disease-free survival, RR risk ratio

## Discussion

Important advantages, such as less blood loss, less pain, faster postoperative recovery, reduced hospital stay and early return to normal bowel function are offered by laparoscopic resection over open surgical procedures for patients with gastric cancer[30,31]**.** Laparoscopic D2 LND for AGC was first reported by Uyama et al.[32] in 2000. While the technical feasibility remains controversial, Desiderio et al. described the application of minimally invasive surgery (MIS) regarding the short-term outcomes in AGC patients[33,34]. It is for this reason that we decided to conduct this meta-analysis in order to shed more light on the value of the LAG with D2 LND for AGC.

In our study, we can observe that LAG demonstrated several advantages for AGC treatment. LAG group patients showed significantly less blood loss, faster recovery, earlier ambulation and shorter hospital stay compared to those treated by OG. These advantages are consistent with the findings of fast track surgery and benefits to AGC patient's recovery[35,36]. Less blood loss found in LAG group is same as for scholars who found that it could reduce the risk of adverse effects such as acute lung injury, hypothermia[37]. Faster bowel function recovery and shorter postoperative hospital findings are identical with previous meta-analysis done by Ding, Wang, Qiu and Huang[38-41].

We also found in this study that the operation time for LAG is longer, explainable by the skill and the familiarity of surgeons with the laparoscopic system influencing the length of operation time. Some studies reporting the learning curve of LAG in AGCs claimed that LG could be done as quickly as OG, if and only if, experienced surgeons, likely about after 40 cases, do it the operation time could reach a plateau[42-46]. Another important finding was the surgical and oncological safeties of LAG. The latter were comparable with or even superior to those of OG, thus, supporting the application of LAG with D2 LND for AGC.

In this study, we found that both, overall and specific complication rates in LAG groups were much lower. As we already know, LG has the inherent benefit of minimal invasiveness, reducing the risk of causing massive tissue and organ damage during an operation, therefore, would lead to fewer complications (15% in LAG group versus 17.6% in OG group). Similarly, compared to OG group, we found fewer medical complications in LAG group - medical complications such as respiratory and cardiovascular events, pulmonary embolism, deep venous thrombosis and non-surgical infections are potential life threatening events. Here, we found a rate of 4.67 % medical complication for LG patients, which is significantly lower compared to 8.9 % in OG group. This difference could also be attributed to the benefits of laparoscopic surgery as, not only the LG patients had lesser hospital stay and quicker recovery, but also lesser probability to acquire a nosocomial infection[47]; also these sunsets of patients were capable of early mobilization/ambulation than OG patients, thereby reducing the risk of developing hypostasis and deep venous thrombosis[48].

From the oncology security standpoint, LG is comparable to OG. In fact, at specific stages of the disease, an adequate LN dissection is very important for prognosis in the treatment of gastric cancers not only to reduce the possibility of recurrence and metastasis[49], but also renders survival benefits[50]. As D2 Lymphadenectomy is already considered as a method of choice for treating AGC in East Asia[51], it leads us to believe that the success of this practice is an essential part of the radical resection for the AGC treatment[52]. And as we found in our meta-analysis, the number of LNs retrieved in LG with D2 lymphadenectomy did not differ much from that observed in the OG suggesting that LG had lymphadenectomy efficiency comparable to that of OG, which matched with Ding's[38] Wang's[39] and Quan's[53] meta-analysis.

Another variable that also affects the oncological results is resection margin distance. It is well established that the main objective of radical resection is complete removal of tumor mass and that, in many cancers, a close correlation exists between positive resection margin and increased risk of local recurrence and consequently, decreased OS and DFS[54]. As suggested by recent studies, the status of surgical margin could be considered as an independent prognostic factor for GC patients[55,56] thereby ensuring complete resection of the tumor tissues by a sufficient distance between the edge of the tumor and the resection margin, and also reduced the risk of a positive resection margin[57]. Thus it may in part reflect the possibility of healing of surgical procedures in the evaluation of the distance of the resection margin. Here, we found that there is no difference in the distance between the proximal and distal resection margin for the two techniques, suggesting that both, LAG and OG, possessed comparable curability and oncological safety. Deng et al.[58] suggested in their study that the size of the tumor should also be considered an important clinic pathology factor in order to improve the accuracy of the prediction of the prognosis of the GC patients. When compared to Quan's meta-analysis[53], we observed that the tumor size in OG was much larger than in LG. There is significant heterogeneity among the articles in terms of tumor sizes.

For long-term results, in order to evaluate the direct effects of surgical interventions, OS, DFS and recurrence were used. Our study showed that different types of survival seemed almost the same for LG as for OG. The results for 1-, 3-, and 5-year OS and 5-year RFS and 5-year DFS were separately compared, showing that the effects of treatment with LAG were no comparable to OG. Unlike Chen et al. analysis[59], recurrences observed in LG Group was less, which apparently corresponded to the studies performed by Huang[41] and Quan[53] and we theorize that this variation in finding is relative to the nature of the studies included for the analysis. In order to broaden the case pool and eliminate confounding bias at the same time, only recently published articles were included and rejected those where EGC and AGC were treated together.

And as for the interpretation of the conclusions of this study, we do not overlook certain limitations which are as follow. Firstly, only one RCT was included in our meta-analysis and most of the studies were carried out retrospectively. Secondly, ranging from a total of 8 to 1078 patients, the case volumes of the selected studies varied greatly. In such cases, the experience of surgeons would greatly influence the comparisons of surgical results, leading to a misinterpretation of the results of surgical procedures, and explains the high heterogeneity among the studies. This scenario necessitates future trials with prospective design and multi-center participation.

## Conclusions

This study has allowed us to demonstrate that in both short- and long-term, LG with D2 LND could be as effective as OG to treat AGC patients. It has also been shown that LG had several advantages such as minimal invasion, faster recovery and shorter hospitalization. Currently, there are ongoing RCTs studying the value of LG over OG, but in the waiting of the publication of their findings, and based on our analysis, as well as the previous meta-analyses, we can conclude that LG may very well be applied for the treatment of AGC, especially if experienced surgeons perform it.

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