

# Long-term clinical outcomes of laparoscopy-assisted distal gastrectomy versus open distal gastrectomy for early gastric cancer

## A comprehensive systematic review and meta-analysis of randomized control trials

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### Abstract

The objective of this study was to compare long-term surgical outcomes and complications of laparoscopy-assisted distal gastrectomy (LADG) with open distal gastrectomy (ODG) for the treatment of early gastric cancer (EGC) based on a review of available randomized controlled trials (RCTs) evaluated using the Cochrane methodology.

RCTs comparing LADG and ODG were identified by a systematic literature search in PubMed, Cochrane Library, MEDLINE, EMBASE, Scopus, and the China Knowledge Resource Integrated Database, for papers published from January 1, 2003 to July 30, 2015. Meta-analyses were performed to compare the long-term clinical outcomes.

Our systematic literature search identified 8 eligible RCTs including 732 patients (374 LADGs and 358 ODGs), with low overall risk of bias. Long-term mortality and relapse rate were comparable for both techniques. The long-term complication rate was 8.47% in LADG groups and 13.62% in the ODG group, indicating that LADG was associated with lower risk for long-term complications (RR = 0.63; 95%CI = 0.39–1.00;  $P = 0.03$ ).

In the treatment of EGC, LADG lowered the rate of long- and short-term complications and promoted earlier recovery, with comparable oncological outcomes to ODG.

**Abbreviations:** AGC = advanced gastric cancer, CI = confidence interval, CONSORT = CONSolidated Standards of Reporting Trials, EGC = early gastric cancer, FVC = forced vital capacity, GRADE = Grading of Recommendations Assessment, Development, and Evaluation, LADG = laparoscopy-assisted distal gastrectomy, ODG = open distal gastrectomy, QOL = quality of life, RCT = randomized controlled trial, RD = relative difference, RR = risk ratio, SD = standard deviation, SMD = standardized mean difference.

**Keywords:** clinical outcomes, early gastric cancer, laparoscopy-assisted distal gastrectomy, meta-analysis, open distal gastrectomy

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## 1. Introduction

With the popularization and rapid advance in endoscopy surveillance, the proportion of early gastric cancer (EGC) had been elevated during the past decade.<sup>[1]</sup> Different from advanced gastric cancer (AGC), EGC had an excellent prognosis, and the 5-year survival rate exceeds 90%.<sup>[2]</sup> Therefore, postoperative complication and recovery become a major concern of the surgical outcomes to EGC patients. Laparoscopic surgery results in small incisions, less scarring, and faster recovery and therefore has been widely used for decades for the management of benign diseases. With recent advances in technology and surgical technique, laparoscopic surgery has been increasingly used for the treatment of EGC.<sup>[3]</sup> However, the clinical outcomes of this procedure have not been substantially evaluated.

Laparoscopy-assisted distal gastrectomy (LADG), introduced by Kitano et al<sup>[3]</sup> in 1995, is one of the most consistently used laparoscopic techniques for surgical resection of gastric carcinomas. With the recent rapid advancement in technique, application of laparoscopy to treat EGC had gained wide acceptance. More than 30 retrospective studies and several randomized control trials (RCTs) have been conducted to evaluate the feasibility of LADG in the clinical management of EGC.<sup>[4]</sup> Previous meta-analyses<sup>[4–9]</sup> comparing the short-term outcomes of LADG with open distal gastrectomy (ODG) provide limited evidence to guide practice due to some methodological concerns. Findings from individual RCTs<sup>[10,11]</sup> are inconsistent and inconclusive, partly due to the small sample size of each individual study.

Therefore, the aim of our study was to compare oncological and surgical outcomes and complications of LADG with ODG for the treatment of EGC based on a systematic review of available RCTs using the best practices for systematic review and meta-analysis to generate high quality evidence to inform practice. We strictly adopted the guidelines for preferred reporting items for systematic reviews and meta-analyses (PRISMA),<sup>[12,13]</sup> evaluated the quality of RCTs, including risk of bias, as defined by the Cochrane working group,<sup>[14]</sup> and assessed the quality of available evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.<sup>[15,16]</sup> Applying the principles of the CONSolidated Standards of Reporting Trials statement,<sup>[17,18]</sup> we also provide a summary of current limitations of available evidence to shed light on the design of future RCTs.

## 2. Methods

### 2.1. Eligibility criteria

We applied the following criteria to determine study eligibility: patients were diagnosed with EGC; patients underwent LADG in the treatment group, and ODG in the control group; outcomes of interests included long- and short-term complication; and the studies were RCTs. Short-term complications were defined as the complications that occurred within 30 days postoperation, regardless of whether they were related to the operation or not. Long-term complications were defined as the complications related to the operation that occurred from 30 days postoperation to the end of the follow-up. Studies were excluded if robot-guided surgery was used, if a pylorus-preserving gastrectomy was performed, if surgery was performed on an emergency basis, or if measured outcomes included data for cases of malignant stromal tumors, benign disease, or were based on a high proportion of patients with AGC. Studies in which only

pooled data were reported, or from which necessary data could not be extracted, were also excluded. When multiple studies by the same research group were identified, we used data merged from different reports with the same trial number.

### 2.2. Literature search strategies

A structured literature search was conducted in Pubmed, Cochrane Library, MEDLINE, EMBASE, the Scopus, and the China Knowledge Resource Integrated Database, for papers published from January 1, 2003 to July 31, 2015 to identify eligible RCTs. The following terms were used in the search ([laparoscop\* OR (minimal invasive)] AND gastrectomy AND [(early gastric) OR (early stomach)] AND [cancer OR carcinoma OR adenocarcinoma OR malignan\*]). The search was slightly adjusted according to the requirement of different databases. A cursory review of titles and abstracts were performed (WL and JG), followed by a detailed review of potentially relevant publications. Disagreement on inclusion/exclusion of RCTs was resolved through consensus. The search was limited to papers published in English or Chinese.

### 2.3. Data extraction

Data were extracted independently by 2 researchers (WL and YZ) using a prepared data extraction form. Continuous variables were expressed as the mean and standard deviation (SD). To pool continuous data in which only the median and range were available, estimates of the mean and SD were calculated using the methods of Hozo et al.<sup>[19]</sup> If the mean and SD were not reported directly, these data were extracted from published figures using Engauge Digitizer version 4.1 (<http://digitizer.sourceforge.net/>) to calculate the means and SDs. Disagreement was resolved by consultation with a senior author (YL).

### 2.4. Assessment of bias and quality of evidence

Risk of bias was assessed independent by 2 reviewers (WL and JG) according to the Cochrane methodology,<sup>[21]</sup> which includes 6 domains: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other potential sources of bias. When there was insufficient information to allocate a high or low score, an “unclear” risk score was allocated. Disagreements in score allocations were resolved through group discussion. Publication bias was assessed using funnel plots and Egger regression, with  $P \leq 0.1$  indicative of reporting biases.<sup>[20]</sup>

The quality of evidence of each study was assessed (WL and JG) according to the guidelines of the GRADE Working Group (<http://www.gradeworkinggroup.org/index.htm>), using the GRADE profiler (version 3.6.1, <http://ims.cochrane.org/revman/gradepro>) and GRADE Handbook to determine the quality of evidence and strength of recommendation.<sup>[21]</sup>

### 2.5. Data synthesis

Risk ratio (RR) and the associated 95% confidence interval (CI) were used to compare postoperative complications between LADG and ODG. Alternatively, when there was no event in either groups during the follow-up, we used relative difference (RD), defined as the difference in the incidence rate of the LADG group from that in the ODG group. Mortality was evaluated using RD. RRs were pooled using a random-effects model.

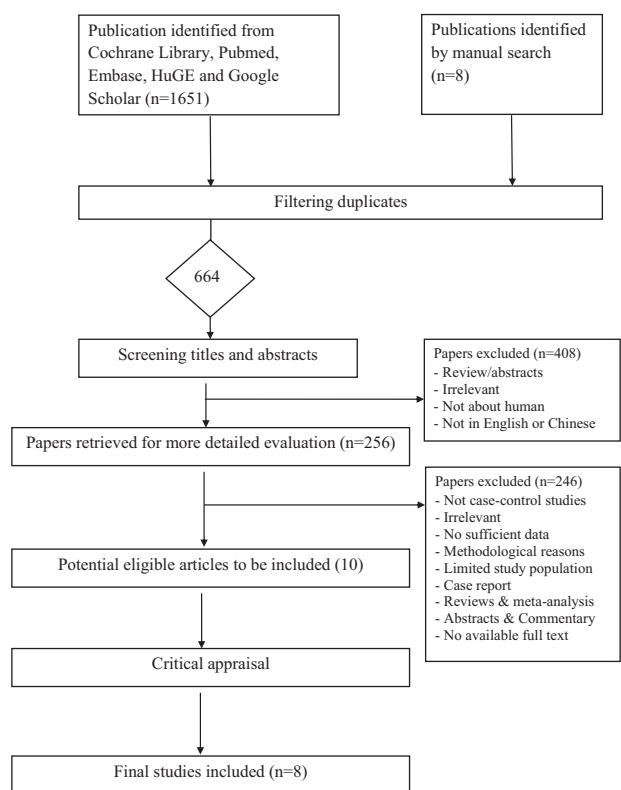


Figure 1. Flow chart of literature selection.

Standardized mean differences (SMDs) were pooled by using an inverse variance model. Statistical heterogeneity among studies was assessed by using the Q statistic and  $I^2$ .<sup>[22]</sup> Meta-analyses were performed using Review Manager Version 5.3.<sup>[23]</sup> All additional analyses were performed by using Stata/MP 12.1 (Stata Corp, College Station, TX). A  $P$ -value  $< 0.05$  was set as the threshold of statistical significance. As a systematic review and meta-analysis, ethical approval of this study is not needed.

### 2.6. Sensitivity, subgroup analysis, and meta-regression

For meta-analysis with  $I^2 > 70\%$ , if sufficient trials were available, sensitivity analyses were conducted by excluding or subgrouping studies to reduce the potential confounding effects of age, sex, body mass index, concurrent illness, surgical type, year of publication, country of the trial, and tumor location, size, histology, and tumor, node, metastasis (TNM) stage. The log of the estimate of the study effect was set as the dependent variable in a general linear model, and  $I^2$  and  $P$ -value were recalculated. Differences in the slopes of the linear regression models for the original and subgrouped data were used to predict contributions of these potential confounding factors on the measured outcomes.

## 3. Results

### 3.1. Study selection and characteristics

Our initial literature search identified 664 possible publications; 408 studies were excluded after the initial screening of titles and abstracts. We retrieved the full text of the 256 studies and further excluded 246 studies after full-text review. Of the 10 remaining

Table 1 Patient and tumor meta-characteristics.

Outcome	No. studies	LADG	ODG
Age (years, mean $\pm$ SD)	8	56.32 $\pm$ 10.87	57.94 $\pm$ 10.90
BMI (kg/m <sup>2</sup> , mean $\pm$ SD)	8	23.82 $\pm$ 3.22	23.56 $\pm$ 3.16
Tumor size (cm, mean $\pm$ SD)	6	4.15 $\pm$ 4.53	4.69 $\pm$ 5.86
Tumor location (n/%)	3		
Body		33/56.9%	34/58.7%
Antrum		25/43.1%	24/41.3%
Sex (n/%)	8		
Male		225/60.2%	225/62.8%
Female		149/39.8%	133/37.2%
Comorbidities (n/%)	6		
Present		170/61.2%	145/55.3%
Absent		108/38.8%	117/44.7%
Histology (n/%)	6		
Well differentiated		95/54.3%	90/52.9%
Poor differentiated		80/45.7%	80/47.1%
TNM stage (n/%)	7		
Stage I		182/93.3%	187/95.9%
Stage II		12/6.2%	6/3.1%
Stage III		1/0.5%	2/1.0%

BMI=body mass index, LADG=laparoscopy-assisted distal gastrectomy, ODG=open distal gastrectomy, SD=standard deviation, TNM=tumor, node, metastasis.

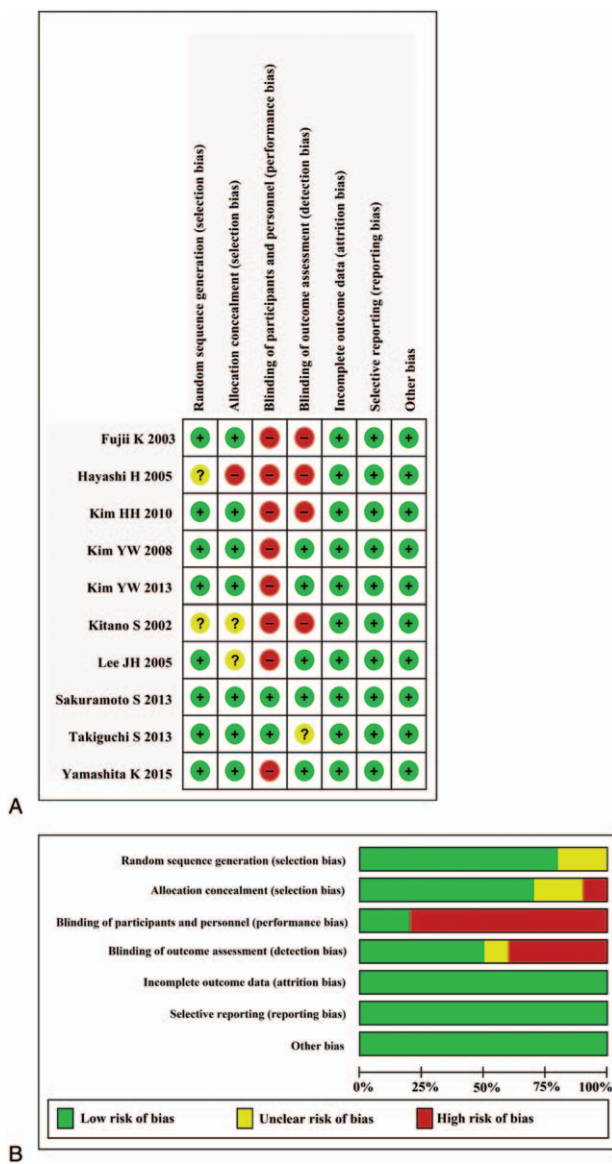
studies, 2 RCTs reported short- and long-term outcomes separately in 2 articles. Both articles were retained in the corresponding meta-analysis. Finally, 8 RCTs reported in 10 articles were included in our meta-analysis. The flow chart for the selection of eligible studies is presented in online Fig. 1.<sup>[24-33]</sup>

As a result, our meta-analysis included data of 732 patients (374 LADG and 358 ODG). All 8 RCTs were conducted in Asia between 1998 and 2008, with their data published between 2002 and 2015. The sample size ranged from 20 to 342 patients. Overall, in 97.1% of the patients, tumors were classified as TNM stage I and were located in the body and antrum of the stomach. The distribution of the stages and locations of the tumors for the remain patients are as follows: 2.5% (18/732) with stage II tumors, 12 allocated to the LADG group and 6 to the ODG group; and 0.4% (3/732) with stage III tumors, 1 allocated to the LADG group and 2 to the ODG group. Six trials recorded the number of lymph node harvested. Patients in 3 trials consented to D2 lymphadenectomy and in another 3 trials, to D1 or D1<sup>+</sup> resection. In the remaining 2 trials, patients consented to elective dissection. Patients and tumor characteristics of the included studies are presented in Table 1.

### 3.2. Assessment of quality of randomized controlled trials, risk of bias, and quality of evidence

Overall, the included RCTs had low risk of bias (Fig. 2). Two of the 8 studies did not report random sequence generation and were considered as having unclear risk of bias. Regarding allocation concealment, we found no significant between-group differences in the distribution of TNM tumor stages ( $P=0.315$ ). Due to the inherent difficulty in performing a blinded trial of LADG and ODG, there is a risk of bias in some reported outcomes. The main characteristics of the included trials, including risk study quality, are summarized in online Supplementary Table 1, <http://links.lww.com/MD/B92>.

The funnel plot was symmetrical (Fig. 3), indicating the absence of reporting bias between trials included in our meta-analyses ( $P=0.119$ , Egger test). The GRADE evaluation of level



**Figure 2.** Bias assessment of the included studies. (A) Risk of bias summary for each individual study included in the meta-analyses; and (B) summary of risk of bias across all of the included studies. +, low risk of bias; -, high risk of bias; and ?, unclear risk of bias.

of evidence for each outcome, including reasoning, is summarized in Table 2. Briefly, we evaluated a total of 20 outcomes. Of the 9 critical outcomes, 7 were considered to be of strong recommendation grade, including mortality rate, relapse rate, complication rate, number of resected lymph nodes in D2 resection, reoperation rate, and blood loss. Of the 11 important outcomes, 2 were considered to be of strong recommendation grade, including operation time and hospital stay. The remaining outcomes were considered to be of weak recommendation grade.

**3.3. Primary short-term clinical outcome**

Overall, short-term complications were reported in 58/374 patients in the LADG group (15.5%) and in 101/358 in the ODG group (28.2%), with a lower RR of complications in the LADG group compared with ODG (RR=0.57; 95% CI, 0.44–0.76;

$P < 0.0001$ ). We found low heterogeneity among the trials ( $\chi^2 = 3.73$ ;  $I^2 = 0\%$ ;  $P = 0.81$ ; Fig. 4).

Comparison of individual complications between LADG and ODG is summarized in Table 3. Short-term mortality was reported in only 1 trial, which found that 2 patients died of chronic hepatitis B virus infection or liver cirrhosis within 31 days in the LADG group.<sup>[30]</sup>

The number of lymph nodes harvested was reported in 6 trials involving 185 patients (Fig. 5). Our meta-analysis found no difference in the number of harvested lymph nodes (SMD = -0.32; 95% CI: -0.65–0.01;  $P = 0.06$ ), with significant heterogeneity ( $\chi^2 = 4.02$ ;  $I^2 = 53\%$ ;  $P = 0.06$ ). Suspecting that the difference might be due to the heterogeneity between the studies, we performed subgroup analysis by strength of lymphadenectomy procedure as defined by the Japanese Classification of Gastric Cancer.<sup>[34]</sup> The number of retrieved lymph node was significantly lower in the LADG group compared to that in the ODG group in studies in which most of the participants (92.9%, 222/239) accepted D2 resection (SMD = -0.39; 95% CI: -0.65 to -0.14;  $P = 0.003$ ), with no significant heterogeneity ( $\chi^2 = 1.84$ ;  $I^2 = 0\%$ ;  $P = 0.40$ ). There was no significant difference between groups in studies in which participants accepted less than D2 resection (SMD = -0.36, 95% CI, -1.11 to -0.39;  $P = 0.35$ ).

The duration of postoperative hospital stay was significantly shorter for the LADG group (SMD = -0.67; 95% CI: -1.24 to -0.11;  $P = 0.02$ ), with significant heterogeneity ( $\chi^2 = 28.98$ ;  $I^2 = 83\%$ ;  $P < 0.0001$ ). Meta-regression identified that the heterogeneity was contributed by 1 trial.<sup>[24]</sup> Excluding the data from this trial yielded a similar but more significant between-group difference (SMD = -0.70; 95% CI: -1.01 to -0.39;  $P < 0.0001$ ), with no significant heterogeneity ( $\chi^2 = 4.37$ ;  $I^2 = 31\%$ ;  $P = 0.22$ ; online Supplementary Figure 1, <http://links.lww.com/MD/B93>).

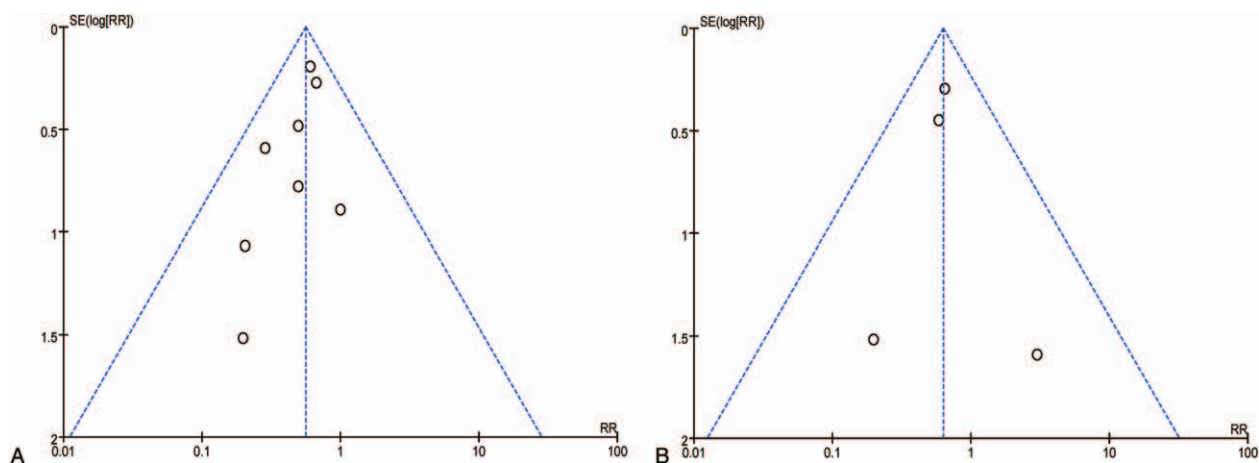
**3.4. Secondary short-term clinical outcomes**

We found that LADG was associated with less intraoperative blood loss (SMD = -0.94; 95% CI: -1.38 to -0.49;  $P < 0.0001$ ) and ODG with shorter operative time (SMD = 2.66; 95% CI: 1.91–3.40;  $P < 0.0001$ ). We also found significant differences in time to 1st postoperative flatus (SMD = -0.94; 95% CI: -1.58 to -0.29;  $P = 0.005$ ), postoperative analgesic consumption (SMD = -0.79; 95% CI: -1.55 to -0.22;  $P = 0.04$ ), and pain visual analog scale score at day 7 (SMD = -1.66, 95% CI: -3.23 to -0.10,  $P = 0.04$ ), but not earlier. We found no significant differences in time to 1st postoperative oral intake (SMD = -0.41; 95% CI: -1.14–0.33;  $P = 0.28$ ). LADG was also associated with shorter duration of postoperative fever (SMD = -1.03; 95% CI: -1.79 to -0.28;  $P = 0.007$ ; 131 patients) and lower increase in WBC (day 3, SMD = -0.23, 95% CI: -0.46 to -0.01,  $P = 0.04$ ; day 7, SMD = -0.35, 95% CI: -0.60 to -0.09,  $P = 0.007$ ). However, we found no significant difference in blood albumin, C-reactive protein, interleukin 6 level, forced expiratory volume in 1 second, and forced vital capacity (see online Supplementary Table 2, <http://links.lww.com/MD/B92>).

**3.5. Long-term clinical outcomes**

We found no significant differences in rate of mortality (RD = 0.01, 95% CI: -0.01–0.02;  $P = 0.82$ ), with no heterogeneity between trials ( $\chi^2 = 3.68$ ;  $I^2 = 0\%$ ;  $P = 0.47$ ). Similarly, relapse rate was comparable for both groups (RD = -0.01, 95% CI:



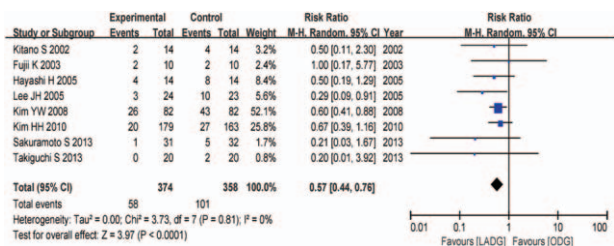


**Figure 3.** Funnel plot for comparison of short- and long-term postoperative complications between LADG and ODG. (A) Short-term complications, and (B) long-term complications. LADG=laparoscopy-assisted distal gastrectomy, ODG=open distal gastrectomy.

**Table 2**  
Rating the quality of evidences by GRADE.

Outcomes	Studies	No of participants		Effect		Quality	Importance	Recommendation grade
		LADG	ODG	RR/RD (95% CI)	Absolute			
Overall mortality rate	8	5/374 (1.3%)	5/358 (1.4%)	RD 0.01 (-0.01 to 0.02)	1 Fewer per 1000 (from 10 fewer to 33 more)	⊕⊕⊕⊕ High	Critical	Strong
Disease related mortality rate	8	2/374 (0.5%)	2/358 (0.6%)	RD -0.01 (-0.04 to 0.02)	0 Fewer per 1000 (from 10 fewer to 10 more)	⊕⊕⊕⊕ Moderate	Critical	Strong
Relapse rate	4	1/151 (0.7%)	2/151 (1.3%)	RD 0.00 (-0.01 to 0.01)	7 Fewer per 1000 (from 40 fewer to 20 more)	⊕⊕⊕⊕ Moderate	Critical	Strong
Overall long-term complications rate	3	24/281 (8.5%)	38/265 (14.3%)	RR 0.61 (0.38 to 0.98)	60 Fewer per 1000 (from 10 fewer to 110 fewer)	⊕⊕⊕⊕ High	Critical	Strong
Overall short-term complications rate	8	58/374 (15.5%)	101/358 (28.2%)	RR 0.57 (0.44 to 0.76)	121 Fewer per 1000 (from 68 fewer to 158 fewer)	⊕⊕⊕⊕ High	Critical	Strong
Lymph node (D2 resection)	3	120	119	-	SMD 0.39 lower (0.65 to 0.14 lower)	⊕⊕⊕⊕ Moderate	Critical	Strong
Lymph node (less than D2 resection)	3	65	66	-	SMD 0.36 lower (1.11 lower to 0.39 higher)	⊕⊕⊕⊕ Low	Critical	Weak
Reoperation rate	6	3/268 (1.1%)	4/253 (1.6%)	RR 0.75 (0.18 to 3.09)	4 Fewer per 1000 (from 13 fewer to 31 more)	⊕⊕⊕⊕ Moderate	Critical	Weak
Blood loss	8	374	358	-	SMD 0.94 lower (1.38 to 0.49 lower)	⊕⊕⊕⊕ High	Critical	Strong
Hospital stay	4	151	151	-	SMD 0.7 lower (1.01 to 0.39 lower)	⊕⊕⊕⊕ Moderate	Important	Strong
Operation time	7	195	195	-	SMD 2.66 higher (1.91 to 3.4 higher)	⊕⊕⊕⊕ Moderate	Important	Strong
Flatus	6	185	185	-	SMD 0.94 lower (1.58 to 0.29 lower)	⊕⊕⊕⊕ High	Important	Weak
VAS pain score (day 7)	4	147	148	-	SMD 2.43 lower (4.52 to 0.33 lower)	⊕⊕⊕⊕ Low	Important	Weak
Analgesic usage	4	83	83	-	SMD 0.79 lower (1.55 to 0.02 lower)	⊕⊕⊕⊕ Moderate	Important	Weak
WBC (day 7)	5	157	158	-	SMD 0.35 lower (0.60 to 0.09 lower)	⊕⊕⊕⊕ Low	Important	Weak
Albumin (day 7)	3	137	137	-	SMD 0.07 higher (0.17 lower to 0.31 higher)	⊕⊕⊕⊕ Very low	Important	Weak
CRP (day 7)	4	147	148	-	SMD 0.17 lower (0.40 lower to 0.06 higher)	⊕⊕⊕⊕ Low	Important	Weak
FEV1	2	96	96	-	SMD 0.27 higher (0.12 lower to 0.67 higher)	⊕⊕⊕⊕ Very low	Important	Weak
Fever	3	65	66	-	SMD 1.03 lower (1.79 to 0.28 lower)	⊕⊕⊕⊕ Very low	Important	Weak
Wound length	4	140	139	-	SMD 7.4 lower (10.05 to 4.76 lower)	⊕⊕⊕⊕ Low	Important	Weak

CI=confidence interval, CRP=C-reaction protein, FEV1=forced expiratory volume in 1 second first, GRADE=Grading of Recommendations Assessment, Development, and Evaluation, LADG=laparoscopy-assisted distal gastrectomy, No=number, ODG=open distal gastrectomy, RD=relative difference, RR=risk ratio, SMD=standardized mean difference, VAS=visual score, WBC=white blood cell.



**Figure 4.** Meta-analysis of rate of short-term complications after LADG in comparison to ODG for the treatment of early gastric cancer. CI=confidence interval, LADG=laparoscopy-assisted distal gastrectomy, ODG=open distal gastrectomy, OR=odds ratio.

−0.04–0.02;  $P=0.67$ ), with no heterogeneity between trials ( $\chi^2=0.16$ ;  $I^2=0\%$ ;  $P=0.98$ ). The LADG group had significantly fewer long-term complications (RR=0.63, 95% CI: 0.39–1.01,  $P=0.03$ ) with no significant heterogeneity ( $\chi^2=3$ ,  $I^2=0\%$ ,  $P=0.67$ ; Fig. 6). Quality of life (QOL) was considered in only 2 trials, which reported better QOL for the LADG group; however, data from these 2 trials could not be pooled for meta-analysis.

#### 4. Discussion

In this study, we conducted a systematic review of RCTs to compare oncological and surgical outcomes and complications of LADG and ODG for the treatment of EGC. We found no significant between-group differences in oncological outcomes and in lymph node harvesting with D1 or D1+ resections. We found significantly lower long- and short-term complications and shorter postoperative hospital stay in the LADG group. LADG also improved outcomes by reducing blood loss and wound length, and accelerated postoperative recovery, with no evidence of influencing systemic inflammatory reaction and respiratory function. Our meta-analysis provided evidence for the beneficial effect of laparoscopic surgery in treating EGC.

Several meta-analyses have been conducted to compare LADG with ODG for the treatment of EGC. The 1st one, conducted in 2006, found that LADG was superior to ODG in short-term outcomes.<sup>[5]</sup> Findings from most subsequent meta-analyses also favor LADG in the evaluation of short-term clinical outcomes.<sup>[4,6–11,35,36]</sup> Meta-analysis of long-term clinical

outcome is scarce, and most of these studies did not assess the quality of evidence. Further, existing meta-analyses included mixed RCTs and non-RCTs publications (online Supplementary Table 3a,3b, <http://links.lww.com/MD/B92>). By adopting the best practices for systematic review and meta-analysis of RCTs, our study provided some key updates with high fidelity on the superiority of LADG over ODG in optimizing long-term survival and complications.

Although laparoscopic surgery elongated operation time, which may increase the surgical stress of the patients, we found no significant difference in C-reactive protein and interleukin 6 level between the 2 groups. Previous research indicated that laparoscopic surgery resulted in smaller wound, which can promote recovery.<sup>[37]</sup> In day 1 and day 3 after surgery, we found no significant difference in pain visual analog scale score ( $P=0.11$  and  $0.09$ , respectively). However, patients in the LADG group had significantly less pain when intravenous analgesic intervention was withdrawn on day 7 ( $P=0.04$ ). As a result, patients might experience less mental stress from smaller wound and less pain. With the development of modern laparoscopic surgery instruments, we can anticipate that laparoscopic surgery might exhibit more advantages due to a better field of vision and a more detailed observation by visual magnification. However, it has to be acknowledged that LADG is demanding to the surgeons with respect to skills and experiences.

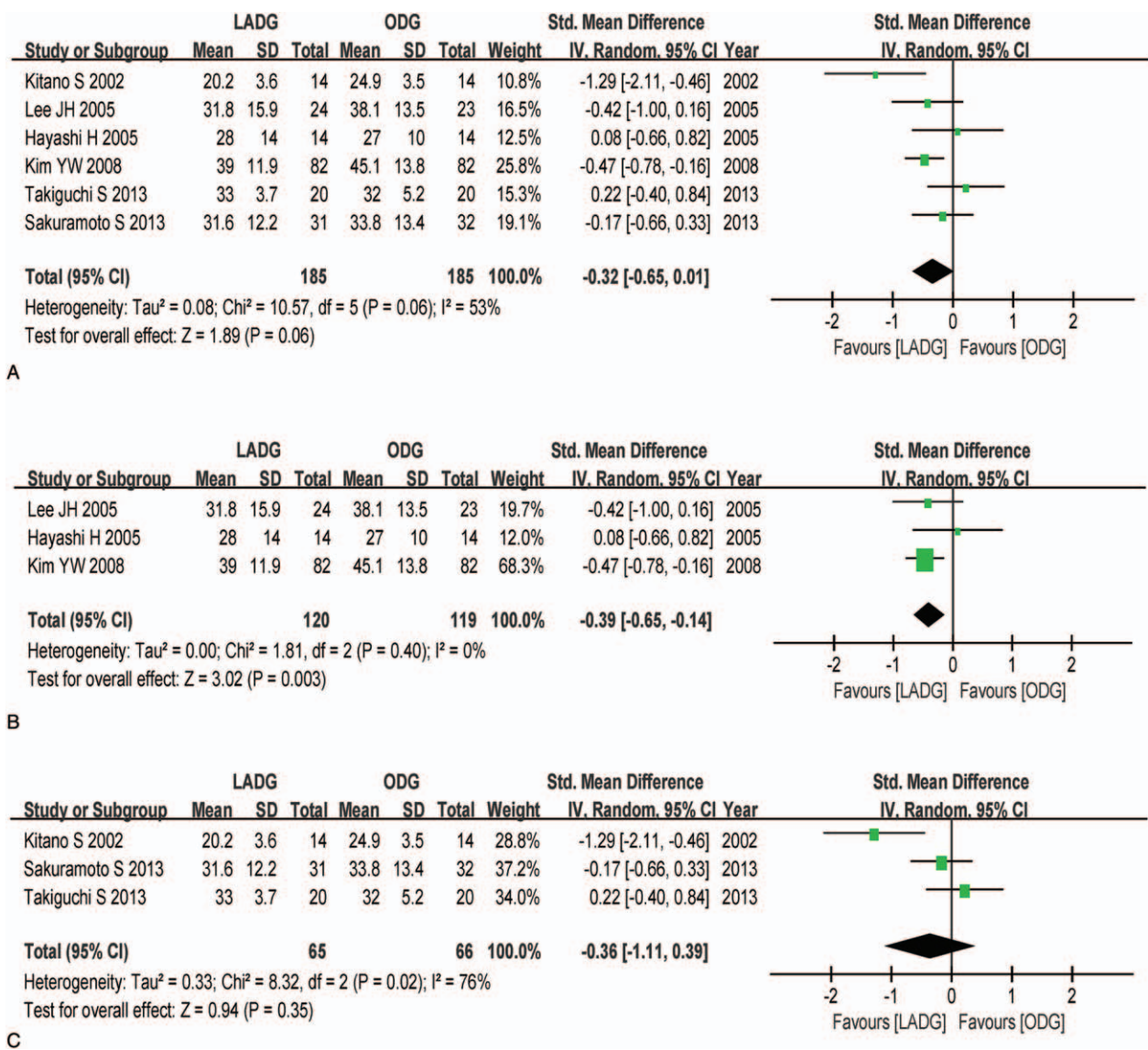
We also highlight the difficulty in lymph nodes clearance with LADG in D2 lymphadenectomy. Previous studies noticed that LADG might be inferior in lymph node clearance, which may limit the application of LADG.<sup>[6,10]</sup> A previous meta-analysis reported that there was no significant difference in lymph node clearance between LADG and ODG, but the results were based on a mixture of retrospective studies and RCTs.<sup>[38]</sup> Another meta-analysis found that laparoscopic surgery was inferior in lymph node clearance, but this analysis suffered the same limitation of including only retrospective studies.<sup>[39]</sup> We found no difference in lymphadenectomy of less than D2 resection between LADG and ODG. However, there was significantly lower efficiency in lymph node clearance in the LADG group when D2 lymphadenectomy was applied. Although this did not appear to influence the oncological outcomes of patients with EGC, the difference between laparoscopic and open harvesting of lymph nodes could play a pivotal role in the surgical treatment of AGC.<sup>[40]</sup> In such cases, ODG might be a more suitable treatment

**Table 3**  
Meta-analysis of subtypes of LADG complications in comparison with ODG.

Complication type/no. of studies	Case number		Incidence rate		Z	Difference			Heterogeneity		
	LADG	ODG	LADG	ODG		RR	95% CI	P-value	Chi-squared	I <sup>2</sup> , %	P-value
Respiratory system/7	8/292	17/276	2.14%	4.75%	1.92	0.49	0.23–1.01	<b>0.05</b>	2.19	0	0.70
Digestive system/7	3/292	4/276	0.80%	1.12%	0.41	0.75	0.19–2.97	0.68	0.22	0	0.64
Abdominal/8	9/292	18/276	3.08%	6.52%	1.78	0.52	0.25–1.07	0.08	3.23	0	0.66
Post operation bleeding/7	3/268	5/253	0.80%	1.40%	0.75	0.60	0.16–2.29	0.46	0.75	0	0.39
Wound complication/7	2/292	8/276	0.53%	2.23%	1.80	0.28	0.07–1.12	0.07	1.13	0	0.57
Other/7	7/292	6/276	1.87%	1.68%	0.11	1.06	0.36–3.10	0.91	—	—	—
Reoperation/6*	3/268	4/253	0.80%	1.12%	0.44	0.73	0.18–2.93	0.66	0.29	0	0.59
Overall short-term complications/8	58/374	101/358	15.51%	28.21%	4.14	0.56	0.42–0.74	<b>&lt;0.0001</b>	3.73	0	0.81
Overall long-term complications/4	25/295	38/279	8.47%	13.62%	1.94	0.63	0.39–1.00	<b>0.03</b>	1.57	0	0.67

Significant values are in boldface type. Respiratory system complications include atelectasis, pneumonia, and pleural effusion. Digestive system complications include delayed gastric emptying, constipation, hiccups, diarrhea, and dumping. Abdominal complications include anastomotic leakage, chyle leakage, ileus, anastomotic stenosis, intraabdominal abscess, and fluid collection. Wound complications include wound bleeding, wound infection, and wound dehiscence. Other complications include urinary tract infection, renal complication, liver function abnormality, and herpes zoster. CI=confidence interval, LADG=laparoscopy-assisted distal gastrectomy, ODG=open distal gastrectomy, RR=risk ratio.

\*Reoperations due to abdominal complications were not included in the calculation of the number of complications.



**Figure 5.** Meta-analysis of the number of lymph nodes harvested with LADG in comparison with ODG in patients with early gastric cancer. (A) D1 and D2 lymphadenectomy, (B) D2 lymphadenectomy, and (C) D1 lymphadenectomy. CI = confidence interval, LADG = laparoscopy-assisted distal gastrectomy, ODG = open distal gastrectomy, SD = standard deviation.

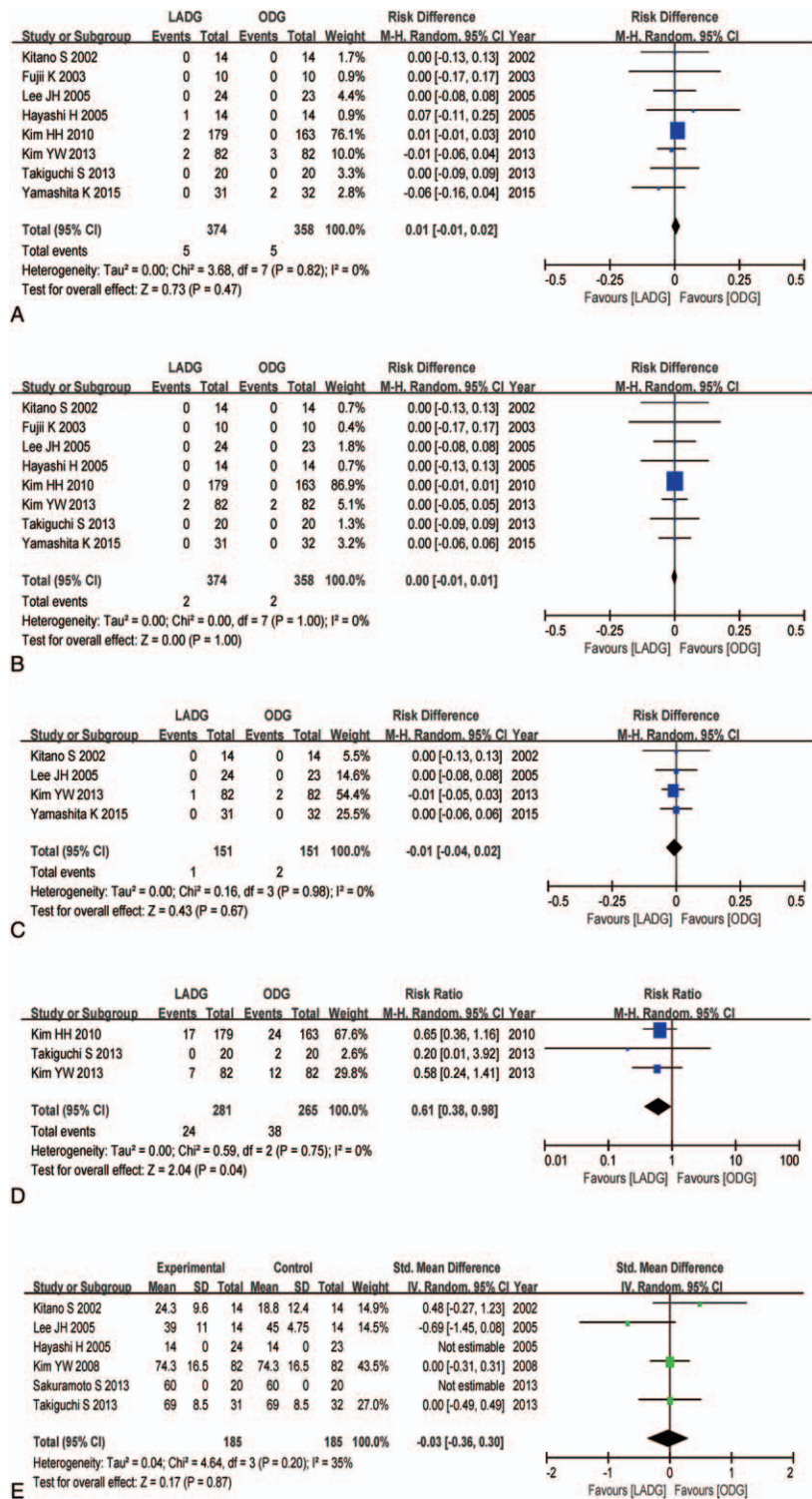
approach. Future studies are warranted to further evaluate the role of LADG in lymph node harvesting.

The lower need for analgesic medication has been claimed to be an advantage of LADG.<sup>[5]</sup> However, we found that the evidence supporting this claim to be of low quality due to the wide variation in type and administration of analgesic drug. These heterogeneities prevented meaningful pooling of data across RCTs for meta-analysis of the need for analgesic medication. Moreover, we found no significant difference in postoperative pain until day 7 after surgery, when patients in the LADG group reported significantly lower levels of pain. We noticed a trend of including QOL, financial expenditure, and patient satisfaction as outcome variables in more recent studies. QOL, a major index of the long-term effect of LADG and ODG, is often reported using various classification systems with different scopes and domains, therefore lowering the feasibility of pooling data for meta-analysis. We hope that future studies can adopt a single, validated QOL classification system such that meta-analysis can be

conducted across studies. Again, the evidence supporting a beneficial effect of LADG on postoperative pain is deemed to be of low quality due to the high level of between-trial heterogeneity. More homogeneous studies are needed to further evaluate the effect of LADG on postoperative pain.

Our study has several limitations. Although the included studies were all RCTs and strictly selected for surgical methods and study population, there was still a high-level of heterogeneity, as illustrated above. Despite our efforts to conduct a literature search as systematic and comprehensive as possible, the sample size is still limited, compared to the previous meta-analysis not limited to the inclusion of only RCTs.<sup>[36]</sup> This prevented us from performing some subgroup analysis. For example, although overall survival and disease-free survival are pivotal outcomes, we were unable to perform meta-analysis on these factors because the very low incidence of mortality made it impossible to discriminate between the surgical groups. Similarly, we could not analyze postoperative QOL and patients' satisfaction because





**Figure 6.** Meta-analysis of rate of long-term complication and long-term mortality after LADG versus ODG for the treatment of early gastric cancer. (A) Long-term overall mortality, (B) long-term disease related mortality, (C) long-term overall relapse, (D) long-term complication rate, and (E) follow-up time (month). CI= confidence interval, LADG=laparoscopy-assisted distal gastrectomy, ODG=open distal gastrectomy, SD=standard deviation.

few of the included studies monitored these features. Moreover, all RCTs included in our meta-analyses were conducted in 2 East Asian countries (Korea and Japan), and it is not clear whether the findings can be generalized to other countries or other ethnic groups.

### 5. Conclusions

In summary, we conducted a systematic and comprehensive literature review and performed meta-analyses to compare LADG with ODG for the treatment of EGC. We found that LADG is beneficial regarding long-term and/or short-term



complications and hospital stay. However, it was associated with fewer harvested lymph node during D2 lymphadenectomy. Further larger and more homogeneous RCTs that take into account the effect of age, ethnicity, body mass index, and comorbidity are needed to validate our findings. Future meta-analysis taking advantage of a larger sample size from more available RCTs will also be informative to compare the clinical outcomes between LADG and ODG in the treatment of EGC.

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