

Meta-Analysis of Laparoscopy-Assisted Distal Gastrectomy With D2 Lymph Node Dissection for Gastric Cancer

JIE DING, MD, GUO-QING LIAO, MD,* HE-LI LIU, MD, SHENG LIU, MD, AND JING TANG, MD
Department of Gastrointestinal Surgery, Xiangya Hospital, Central South University, Changsha, Hunan Province, China

Background: To assess the value of laparoscopy-assisted distal gastrectomy with D2 dissection for treatment of gastric cancer.

Methods: We collected studies that have compared laparoscopy-assisted distal gastrectomy (LADG) and open distal gastrectomy (ODG) with D2 dissection for treatment of gastric cancer in the past 15 years. Data of interest for LADG and ODG were subjected to meta-analysis using a fixed-effect and random-effect model.

Results: We analyzed 8 studies that included 1,065 patients. There were significant differences in operating time, blood loss, time to first flatus and first eating, postoperative hospital stay, and postoperative complications between the LADG and ODG groups. Compared with the ODG group, blood loss and complications in the LADG group decreased, time to recovery of gastrointestinal function and hospitalization period were shorter, but operating time was longer. There were no significant differences in the number of harvested lymph nodes, mortality, and rate of recurrence between the groups.

Conclusions: Compared with ODG, LADG with D2 dissection has the advantages of minimal invasion, faster recovery, and fewer complications, and it can achieve the same degree of radicality and short-term prognosis as ODG. The drawbacks are that the operating time is slightly longer and long-term prognosis is not clear.

J. Surg. Oncol. 2012;105:297–303. © 2011 Wiley Periodicals, Inc.

KEY WORDS: laparoscopy-assisted distal gastrectomy; open distal gastrectomy; D2 dissection; gastric neoplasm; gastric carcinoma

INTRODUCTION

At present, the operating method, extent of resection, and level of radicality of gastric cancer surgery still involve many controversies [1]. “Gastric Cancer Treatment Guidelines in Japan” were implemented in 2010 and define standard radical gastrectomy as: more than two-thirds of proximal, distal, or total gastrectomy associated with D2 dissection, and recommend laparoscopic-assisted distal gastrectomy (LADG) with D2 dissection temporarily for clinical research. In fact, the implementation of LADG with D2 dissection is already technically feasible, but when the extent of dissection is extended, 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 radicality as open surgery.

We performed a meta-analysis of data from case–control studies that have compared LADG with open distal gastrectomy (ODG) with D2 dissection over the past 15 years, to assess systematically and objectively the value of LADG for treatment of gastric cancer.

MATERIALS AND METHODS

Search Strategy

The publications were identified by searching the major medical databases such as MEDLINE, EMBASE, and Cochrane Library for relevant articles published between January 1995 and October 2010. The search strategy was as follows: (“Laparoscopic assisted gastrectomy” OR “Laparoscopy assisted gastrectomy”) and “D2” and (“Gastric cancer” OR “Stomach cancer”).

Inclusion and Exclusion Criteria

Inclusion criteria were: (1) clinical studies that compared LADG versus ODG with D2 dissection for treatment of gastric cancer

between 1995 and 2010; (2) patients with primary distal gastric cancer; and (3) raw data included most of the following: operation time, blood loss, number of harvested lymph nodes, time to first flatus, time to first oral intake, hospital stay, complications, mortality, and recurrence. Exclusion criteria were: (1) LADG with D1 or D1 + α or D1 + β or D2+ or D3 dissection, and laparoscopic-assisted total gastrectomy or laparoscopic-assisted proximal gastrectomy; (2) no ODG as a control; (3) recurrent gastric cancer, nonprimary gastric cancer, or benign gastric diseases; and (4) duplicate publication or the publication did not provide sufficient data.

Definitions

D2 lymphadenectomy was performed according to the lymph node classification of the Japanese Gastric Cancer Association [2]. When carcinoma is located in the middle third of the stomach, the no. 1, 3, 4d, 4sb, 5, 6, 7, 8a, 9, 11p, and 12a lymph nodes should be dissected, and when carcinoma is located in the lower third of the stomach, the no. 1, 3, 4d, 5, 6, 7, 8a, 9, 11p, 12a, and 14v lymph nodes should be dissected. The complications were defined as 30-day complications, and the mortality was defined as 30-day mortality.

*Correspondence to: Liao Guoqing, MD, Department of Gastrointestinal Surgery, Xiangya Hospital, Central South University, Changsha 410008, Hunan Province, China. Fax: 86-0731-84327332.
E-mail: liaoguoqing@medmail.com.cn

Received 13 February 2011; Accepted 22 August 2011

DOI 10.1002/jso.22098

Published online 22 September 2011 in Wiley Online Library (wileyonlinelibrary.com).

TABLE I. Characteristics of the Selected Eight Case–Control Studies

References	Year	Country	Study style	Number of patients		Extent of lymphadenectomy	Depth of invasion	Reconstruction
				LADG	ODG			
Noshiro et al. [4]	2005	Japan	RNT	37	31	D2	EGC, AGC	BI, Roux-en-y
Song et al. [5]	2007	Korea	RNT	44	31	D2	EGC, AGC	BI, BII
Hur et al. [6]	2008	Korea	RNT	26	25	D2	AGC	BI, BII, JPI
Kawamura et al. [7]	2008	Japan	RNT	53	67	D2	EGC, AGC	BI
Lee et al. [8]	2008	Chinese Taipei	RNT	34	34	D2	EGC, AGC	BII, Roux-en-y
Du et al. [9]	2009	China	RNT	78	90	D2	EGC, AGC	BI, BII
Lee et al. [10]	2009	Korea	RNT	106	105	D2	EGC	BI, BII, Roux-en-y
Wang et al. [11]	2010	China	RNT	132	172	D2	EGC, AGC	BI, BII, Roux-en-y

AGC, advanced gastric cancer; BI, Billroth I; BII, Billroth II; EGC, early gastric cancer; JPI, jejunal pouch interposition; RNT, retrospective nonrandomized trial.

Quality of Literature

We used a star scoring system [3] based on criteria related to study design, comparability of patient groups, and outcome assessment to assess literature quality. 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).

Data Extraction

Three researchers extracted data from each study using a structured sheet and entered the data into a database. The extracted information comprised: author, year of publication, source journal, sample size, research design, operative time, blood loss, number of harvested lymph nodes, time to first flatus, time to first oral intake, length of hospital stay, number of complications, mortality, and rate of recurrence. Mortality was defined as 30-day mortality.

Statistical Analysis

Meta-analysis was performed using weighted mean differences (WMDs) for continuous variables and odds ratios (ORs) for dichotomous variables. Data for continuous variables in the form of means

and standard deviation allowed statistical analysis. Random-effects models were used to identify heterogeneity between the studies. Heterogeneity was assessed using the χ^2 test. The 95% confidence intervals (CIs) were established. $P < 0.05$ was considered to indicate statistical significance. Statistical analyses were performed using the Review Manager Version 4.2 provided by the Cochrane Collaboration.

RESULTS

According to the search strategy and inclusion criteria, a total of 8 retrospective case–control studies [4–11] that included 1,065 distal gastrectomies with D2 lymph nodes resection (510 LADG and 555 ODG) were considered suitable for meta-analysis. The characteristics of the eight case–control studies are shown in Table I. Quality assessment of the reported studies is shown in Table II, and each study had a score of >6 points.

Operative Time

Six studies had data on operative time, and four showed that it was significantly longer for LADG than for ODG. The heterogeneity test showed that there was heterogeneity in the operative time of the six studies; therefore, the random-effect model was used to combine the data. This model showed that there was a significant difference between LADG and ODG for operative time. In the pooled data, the operative time for LADG was longer than for ODG (WMD: 36.51, 95% CI: 15.55–57.46, $P < 0.05$; Fig. 1).

Blood Loss

Seven studies had data on intraoperative blood loss, and six estimated that intraoperative blood loss was significantly less for LADG than ODG. The random-effect model was used to combine the data due to evident heterogeneity. In the pooled data, the intraoperative blood loss for LADG was less than for ODG (WMD: –114.73, 95% CI: –160.46 to –69.01, $P < 0.05$; Fig. 2).

Number of Harvested Lymph Nodes

Seven studies had data on number of harvested lymph nodes, and the heterogeneity test showed that there was heterogeneity for this parameter, therefore, the random-effect model was used to combine the data. Only one of the seven studies showed that the number of harvested lymph nodes was significantly smaller for LADG than ODG [10]. In the pooled data, there were no significant differences in the number of harvested lymph nodes between LADG and ODG (WMD: –0.59, 95% CI: –3.41 to 2.23, $P = 0.68$; Fig. 3).

TABLE II. Quality Assessment Scoring of Studies

References	Selection			Comparability of groups		Outcomes		Total
	1	2	3	4	5	6	7	
Noshiro et al. [4]	*	*	*	**	**	*	*	9*
Song et al. [5]	*	*	*	**	*	*	*	7*
Hur et al. [6]	*	*	*	*	**	*	*	6*
Kawamura et al. [7]	*	*	*	*	**	*	*	6*
Lee et al. [8]	*	*	*	*	**	*	*	8*
Du et al. [9]	*	*	*	*	**	*	*	6*
Lee et al. [10]	*	*	*	**	**	*	*	9*
Wang et al. [11]	*	*	*	*	**	*	*	7*

Selection for treatment: 1: inclusion criteria reported; 2: representability of patients undergoing LADG to population undergoing surgery for distal gastric cancer; 3: representability of patients undergoing ODG to population undergoing surgery for distal gastric cancer. Comparability between groups (if yes to all, 2 stars; if one of these characteristics was not reported, 1 star; no star if the two groups differed): 4: age, sex, body mass index; 5: tumor site, tumor histological type, tumor size, tumor stage. 6: Outcome assessment: >8 outcomes clearly recorded; 7: quality of follow-up: 1 star if >90 patients were followed up for 5 years.

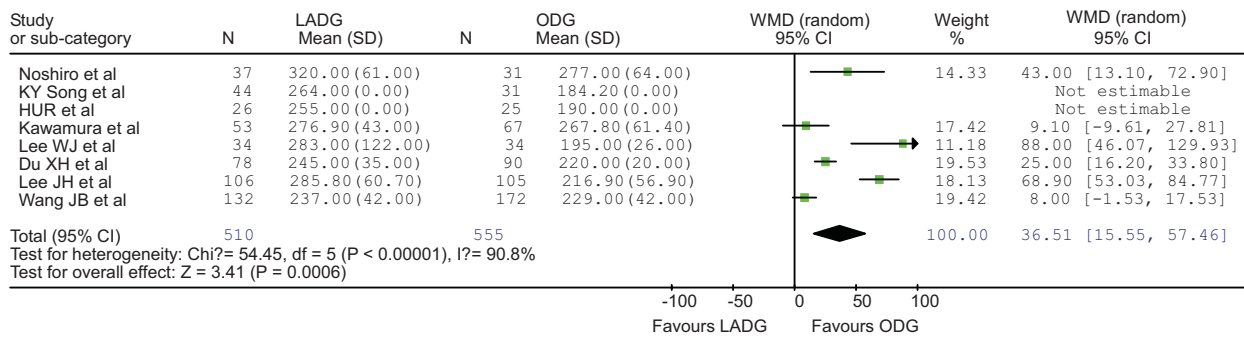


Fig. 1. Operative time (minutes). [Color figure can be seen in the online version of this article, available at <http://wileyonlinelibrary.com/journal/jso>]

Time to First Flatus

Five studies reported time to first flatus. The random-effect model was used to combine the data due to evident heterogeneity. In the pooled data, the time to first flatus for LADG was significantly earlier than for ODG (WMD: -1.01 , 95% CI: -1.44 to -0.57 , $P < 0.05$; Fig. 4).

Time to First Oral Intake

Three studies reported the time to first oral intake, and no heterogeneity was evident, therefore, the fixed-effect model was used to combine the data. In the pooled data, the time to oral intake for LADG was significantly earlier than for ODG (WMD: -0.95 , 95% CI: -1.19 to -0.71 , $P < 0.05$; Fig. 5).

Postoperative Length of Hospital Stay

Six studies had data on postoperative length of hospital stay. In five studies, length of stay was significantly shorter after LADG than ODG. The random-effect model was used to combine the data due to evident heterogeneity. In the pooled data, the length of hospital stay after LADG was significantly shorter than after ODG (WMD: -3.28 , 95% CI: -4.16 to -2.39 , $P < 0.05$; Fig. 6).

Number of Complications

All eight studies had data on the number of complications. Three studies showed that the number of complications was significantly less after LADG than ODG. The fixed-effect model was used to combine the data because heterogeneity was not evident. The number of complications after LADG was significantly lower than after ODG (OR: 0.61, 95% CI: 0.42–0.88, $P < 0.05$; Fig. 7).

Mortality Rate

Three studies had data on mortality rate and showed no significant difference between LADG and ODG. The fixed-effect model was used to combine the data because heterogeneity was not evident. In the pooled data, there were no significant differences in rate of mortality between LADG and ODG (OR: 0.64, 95% CI: 0.19–2.13, $P = 0.46$; Fig. 8).

Rate of Recurrence

Five studies had data on rate of recurrence and showed no significant difference between LADG and ODG. The fixed-effect model was used to combine the data because heterogeneity was not evident. In the pooled data, there were no significant differences in rate of mortality between LADG and ODG (OR: 0.87, 95% CI: 0.51–1.49, $P = 0.62$; Fig. 9).

DISCUSSION

Currently, the development of endoscopy has penetrated into all areas of surgical treatment. Laparoscopic-assisted gastrectomy has aroused interest among many surgeons since its inception, and it has the advantages of minimal invasion and low levels of pain; it is conducive to recovery, and it has gradually received general approval [12]. However, compared with open surgery, it is not clear whether laparoscopic surgery is able to achieve adequate lymphadenectomy (D2 dissection is required for radical surgery for gastric cancer), whether it increases the number of complications, and whether it can achieve a good prognosis. We identified eight case-control studies that have compared LADG versus ODG with D2 lymph node dissection, and conducted a meta-analysis of relevant features of the surgery, recovery of gastrointestinal function, hospital stay,

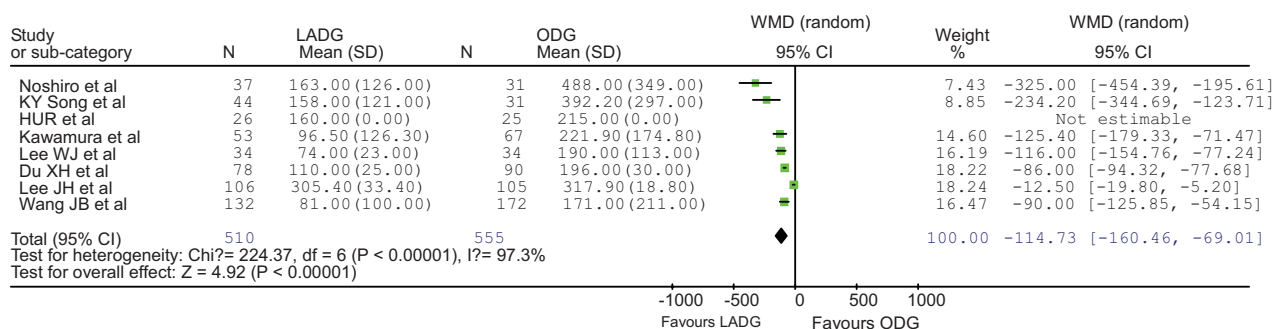


Fig. 2. Blood loss (ml). [Color figure can be seen in the online version of this article, available at <http://wileyonlinelibrary.com/journal/jso>]

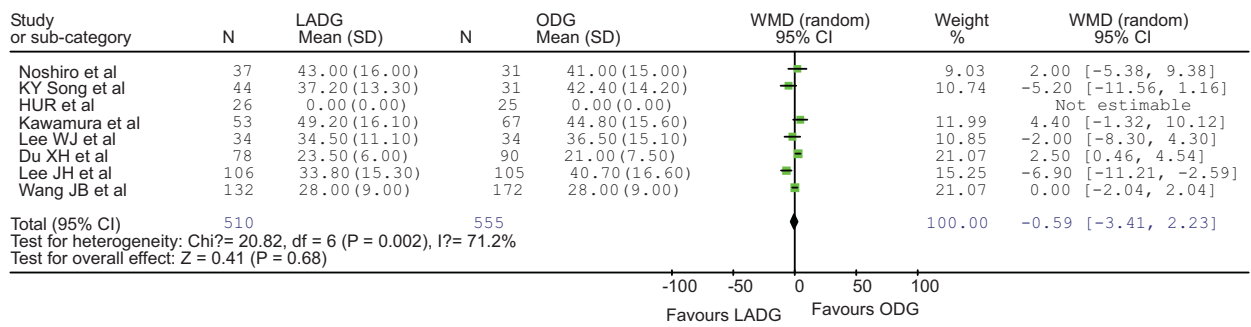


Fig. 3. Number of harvested lymph nodes. [Color figure can be seen in the online version of this article, available at <http://wileyonlinelibrary.com/journal/jso>]

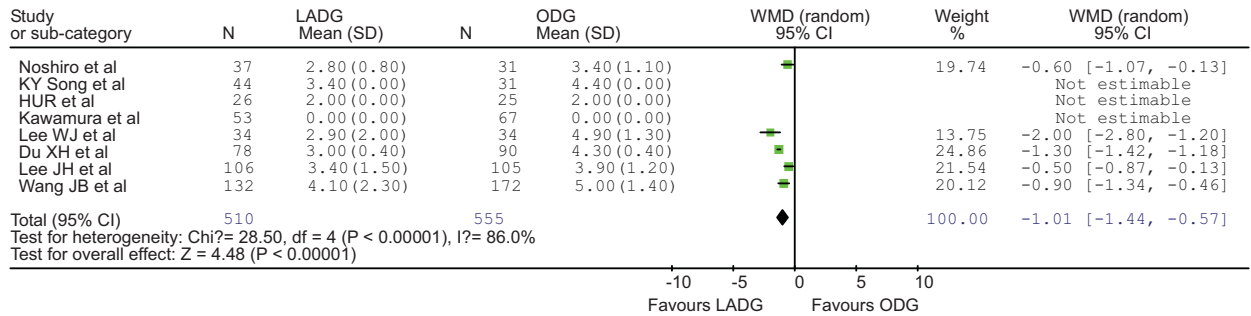


Fig. 4. Time to first flatus (days). [Color figure can be seen in the online version of this article, available at <http://wileyonlinelibrary.com/journal/jso>]

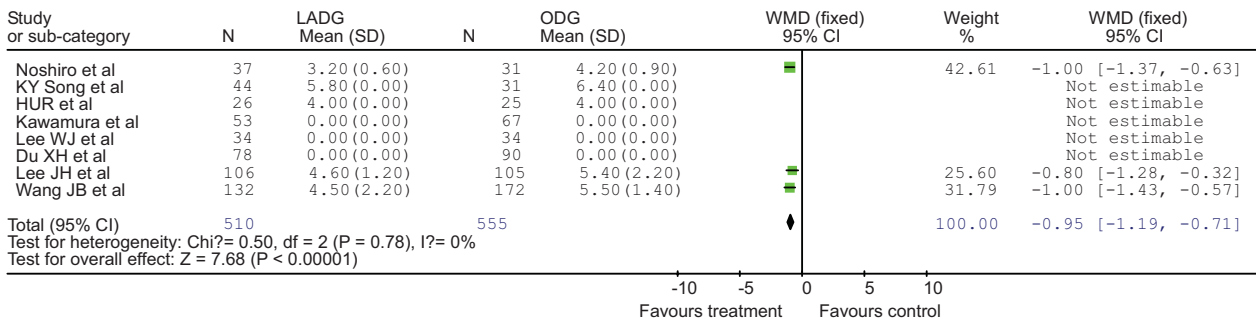


Fig. 5. Time to oral intake (days). [Color figure can be seen in the online version of this article, available at <http://wileyonlinelibrary.com/journal/jso>]

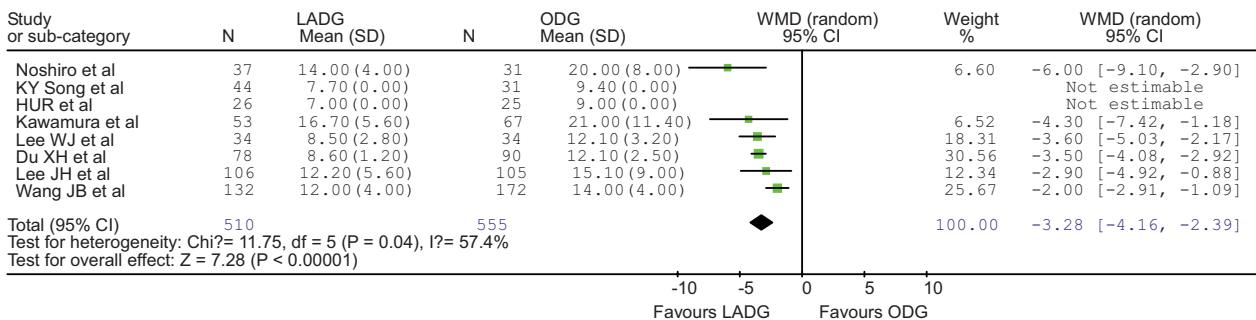


Fig. 6. Postoperative period of hospital stay (days). [Color figure can be seen in the online version of this article, available at <http://wileyonlinelibrary.com/journal/jso>]

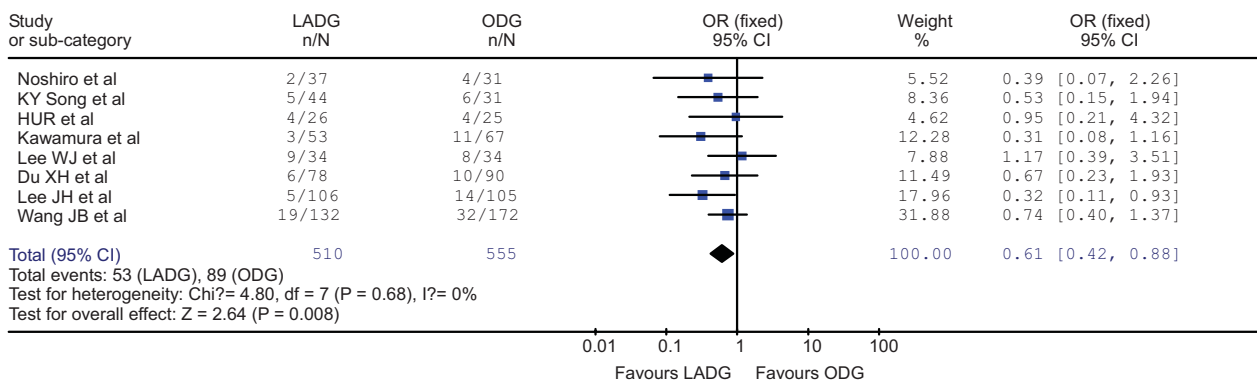


Fig. 7. Rate of complication. [Color figure can be seen in the online version of this article, available at <http://wileyonlinelibrary.com/journal/jso>]

complications, mortality, and recurrence rate, to investigate the value and safety of LADG with D2 lymph node dissection for treatment of gastric cancer.

The meta-analysis of eight case-control studies revealed that operative time for LADG was longer than that for ODG. Fujiwara et al. [13] have considered that this is due to the lack of tactile sensation, complexity, and the advanced techniques required for LADG that involve systemic lymphadenectomy. This requires a long learning curve, an accumulation of cases, the surgeon's familiarity with the endoscopic instruments, and cooperation of the whole therapeutic team [14]. It can be expected that with proficiency in laparoscopic technique and continuous improvement of equipment, the time required for laparoscopic-assisted gastrectomy will become shorter [15].

Our meta-analysis revealed that blood loss during LADG was significantly less than that during ODG. Ohtani et al. [15] attributed this to the enlarged laparoscopic surgical field, which could have exposed and identified the vessels better. In addition to this, we believe that the use of special equipment, including the ultrasonic scalpel, and ligatures also contributed to this outcome. A reduction in the amount of bleeding in patients with gastric cancer is desirable, because it reduces the likelihood or amount of transfusion, and reduces the immunosuppression caused by transfusion and cancer recurrence [16].

Lymph node dissection is an important part of radical gastrectomy, and our meta-analysis revealed that there was no evident difference in the number of lymph nodes dissected between LADG and ODG, which was different from previous meta-analyses [15,17]. Previous studies have shown that the number of lymph nodes dissected

was related to the prognosis of gastric cancer [18], and a number of studies have also shown that the difference in the number of harvested lymph nodes between LADG and ODG was not sufficient to cause any difference in 5-year survival rate [15,17,19]. Moreover, as operative technique has developed, the number of lymph nodes dissected by LADG has gradually increased [10,20]. Therefore, we suggest that the reason why our study differed from previous ones lies in improved technical accomplishment of D2 lymph node dissection in LADG. We also noted that the number of harvested lymph nodes by D2 lymphadenectomy differed between countries. In Japan, the number of harvested lymph nodes during LADG was significantly higher than in China and Korea, but does this necessarily mean that the surgical technique is performed better by Japanese surgeons?

Our meta-analysis revealed that time to first flatus, time to first oral intake, and hospital stay were all shorter for LADG than ODG. Time to flatus is an objective indicator for recovery of gastrointestinal function, which is seldom interfered with by subjective factors [21], and this indicated that LADG was more conducive to recovery of gastrointestinal function. Kang et al. [22] have considered that recovery was faster because the laparoscopic procedure allowed a more subtle operative technique and reduced the level of invasion. In addition to this, Braga et al. [23] have found that gut oxygen tension was significantly higher in the laparoscopic group than in the open group during the entire surgical procedure. Many factors could explain this, such as the less-traumatic abdominal incision, less traction on the mesentery, and the relatively low-pressure pneumoperitoneum that was used. It can be speculated that the higher oxygen tension during laparoscopic surgery plays an important role in improving the systemic host response and early recovery of gut function.

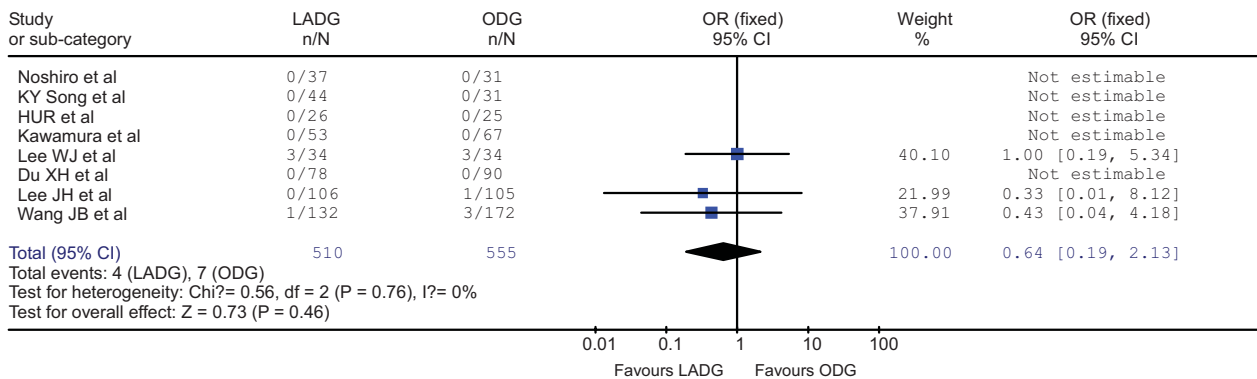


Fig. 8. Rate of mortality. [Color figure can be seen in the online version of this article, available at <http://wileyonlinelibrary.com/journal/jso>]

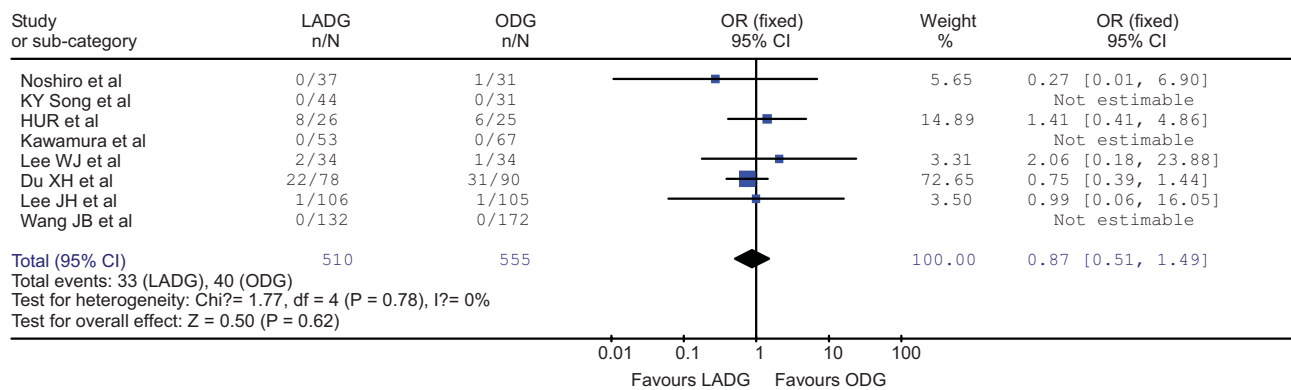


Fig. 9. Rate of recurrence. [Color figure can be seen in the online version of this article, available at <http://wileyonlinelibrary.com/journal/jsj>]

Our meta-analysis revealed that complications were fewer with LADG than ODG. Frequent complications after LADG and ODG included: atelectasis, wound infection, pancreatic injury, fistula, and abdominal abscess. Kitano et al. [24] have reported that lung injury induced by LADG was less severe than that with ODG. Lee et al. [20] have reported that the incidence of atelectasis after LADG was significantly lower compared with that after ODG (2/24 vs. 7/23). This phenomenon might have been due to relatively mild postoperative pain, and patients in the LADG group were more willing to get out of bed early and expectorate to reduce pulmonary complications. This was different from the past concern that pneumoperitoneum might affect lung function and aggravate lung injury; this concern could be subverted completely [25]. The faster recovery of gastrointestinal function and the lower number of postoperative complications led to a shorter period of hospitalization.

Our meta-analysis revealed that there was no significant difference in mortality and recurrence rate in the two groups. In other words, LADG did not increase perioperative mortality and achieved an equivalent short-term prognosis to that of ODG. The long-term prognosis could not be evaluated because 5-year survival rate was not mentioned in the studies analyzed.

In summary, LADG with D2 dissection has the advantages of minimal invasion, faster recovery and fewer complications, and it can achieve the same degree of radicality and short-term prognosis as ODG. The drawbacks are that the operative time is slightly longer, which requires improved technical ability of the surgeon and further improvement of laparoscopic instruments, and the long-term prognosis is not clear. All the studies included in our meta-analysis were retrospective studies, which could have led to some selection bias. Therefore, more prospective randomized controlled trials are expected to be published to allow a more convincing evaluation.

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