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Systematic review of laparoscopy-assisted versus open gastrectomy for advanced gastric cancer*

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Abstract: Objective: The study compared laparoscopy-assisted gastrectomy (LAG) with open gastrectomy (OG) in the management of advanced gastric cancer (AGC). Methods: Literature search was performed in the Medline, Embase, and Cochrane Library databases to identify control studies that compared LAG and OG for AGC. A meta-analysis was conducted to examine the surgical safety and oncologic adequacy, using the random-effect model. Results: Seven eligible studies including 815 patients were analyzed. LAG was associated with less blood loss, less use of analgesics, shorter time of flatus and periods of hospital stay, but longer time of operation. The incidence of most complications was similar between the two groups. However, LAG was associated with a lower rate of pulmonary infection (odds ratio (OR) 0.19; 95% confidence interval (CI) 0.05 to 0.68; $P<0.05$). No significant differences were noted in terms of the number of harvested lymph nodes (weighted mean difference (WMD) 1.165; 95% CI −2.000 to 4.311; $P>0.05$), overall mortality (OR 0.65; 95% CI 0.39 to 1.10; $P>0.05$), cancer-related mortality (OR 0.64; 95% CI 0.32 to 1.25; $P>0.05$), or recurrence (OR 0.62; 95% CI 0.33 to 1.16; $P>0.05$). Conclusions: LAG could be performed safely for AGC with adequate lymphadenectomy and has several short-term advantages compared with conventional OG. No differences were found in long-term outcomes. However, these results should be validated in large randomized controlled studies (RCTs) with sufficient follow-up.

Key words: Gastric cancer, Laparoscopic gastrectomy, Meta-analysis, Mortality, Recurrence
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1 Introduction

Laparoscopy-assisted gastrectomy (LAG) has gained popularity since Kitano *et al.* (1994) reported their first LAG including lymphadenectomy. The principal advantages of laparoscopic surgery are the minimal trauma, low complication rate, and quick recovery.

In the recent randomized controlled trials (RCTs), Kitano *et al.* (2002), Lee *et al*. (2005), and Hayashi *et al.* (2005) have reported several benefits of LAG for treating early gastric cancer (EGC), compared with the open gastrectomy (OG) in short-term outcomes. Meanwhile, after five-year follow-up, Huscher *et al.* (2005) and Kim *et al.* (2008) showed no significant difference in the five-year outcomes, such as tumor recurrence or overall mortality. Therefore, LAG is considered to be accepted for EGC, although the long-term results of the multi-institutional randomized prospective trials are yet to be published, such as Korean Laparoscopic Gastrointestinal Surgery Study Group (KLASS) (Kim *et al.*, 2010).

However, many controversies remain on whether this technique could be applied in advanced gastric cancer (AGC), including the technical difficulty of extraperigastric lymphadenectomy and insufficient data related to the procedure's oncologic

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adequacy. There are few reports related to the efficacy of LAG in the management for AGC. Regarding the inclusion criteria used to select studies, the recent reports (Hosono *et al.*, 2006; Liang *et al.*, 2011; Ding *et al.*, 2012; Vinuela *et al.*, 2012) included patients with EGC. AGC has rarely been evaluated rigorously in a study. Therefore, we performed a systematic review by comparing LAG with OG with regard to their short- and long-term outcomes to elucidate the current status of LAG. Since only one RCT has been published, no meta-analysis of only RCTs can be performed. However, it is believed that estimates derived from high-quality non-randomized controlled trials (NRCTs) may be as accurate as those from RCTs in comparing surgical procedures (MacLehose *et al.*, 2000; Abraham *et al.*, 2010). This study is not only confined solely to RCTs but also includes retrospective, observational trials that have compared LAG with OG.

The aim of the study is to perform an updated systematic review including all the available randomized and observational trials limited solely to AGC, providing the initial experience of LAG in the treatment of AGC.

2 Materials and methods

2.1 Literature search methodology

Primary studies were searched for in the Medline, Embase, and Cochrane Library databases. Trial registries and databases were also explored to retrieve results from ongoing clinical trials. Finally, we manually reviewed the reference lists of the publications retrieved and obtained the entire text of publications that possibly could be included in the over review. The search terms used were 'gastric cancer/carcinoma', 'laparoscopy-assisted/laparoscopic-assisted', and 'gastrectomy'. Logical combinations of these and related terms (stomach and neoplasm) were used to maximize sensitivity. The search was limited to studies published in English.

2.2 Selection criteria of trials

Studies considered potentially eligible were then reviewed for inclusion in the analysis based on the following criteria:

1. Study type included RCTs and NRCTs;

2. Studies described the surgical treatment in patients undergoing LAG and OG;

3. The manuscript was written in English;

4. Outcome assessment of studies included short- and long-term outcomes;

5. The study was limited to AGC.

Studies were excluded from the analysis if:

1. Duplicate publication or the publication that did not provide sufficient data;

2. No OG as a control;

3. They reported on gastric surgery for benign lesions, recurrent gastric cancer, or non-primary gastric cancer;

4. Patients initially had non-curative factors such as hepatic metastasis, peritoneal metastasis, or distant metastasis.

2.3 Clinical appraisal and data extraction

Clinical appraisal and data extraction were conducted independently by two authors. Whenever possible, contact was made with principal investigators of each included trial to resolve any ambiguities. An evidence table was prepared including authors' names, year of publication, study design (sample size, follow-up, randomization, and analysis performed), and characteristics of the laparoscopic technique studied. The short-term outcomes examined were related to the surgery (duration of operation, number of nodes removed, estimated blood loss) and postoperative recovery (pain, time to food intake, time to bowel function, and length of hospital stay). The long-term outcomes examined were rate of mortality, cancer-related mortality, and disease recurrence. Studies with complication data were also included to assess the safety of LAG (Reza *et al.*, 2006).

2.4 Quality assessment

For the purpose of assessing quality, we decided to use a star scoring system (Ding *et al.*, 2012). The main parameters were study design, comparability of patient groups, and outcome assessment to assess literature quality (Table 1). The total score was nine stars, and the quality of each study was graded as Level 1 (0–5 stars) or Level 2 (6–9 stars).

2.5 Statistical analysis

All statistical calculations were performed using the Stata software (Version 10.0; Stata Corporation, College Station, TX, USA). Kaplan-Meier curves were read by Engauge Digitizer Version 2.11 (free software downloaded from http://sourceforge.net). Estimated effect measures were weighted mean differences (WMDs) for continuous data and odds ratios (ORs) for event-related outcomes. When the trials had reported medians and ranges instead of means and standard deviations (SDs), we assumed that the difference in medians is equal to that in means, and the estimated SD was considered equivalent to a quarter of the reported range. If neither a range nor any other measure of dispersion was available, then the SD was estimated by halving the mean or the median. A random-effect model was used to avoid statistical heterogeneity. All the *P*-values were for two-sided analysis and values of $P<0.05$ were considered statistically significant. Heterogeneity was evaluated by using the χ^2 test; $P<0.1$ was considered significant for heterogeneity.

3 Results

The search strategy identified that one RCT and six NRCTs met the inclusion criteria and were selected for analysis (Fig. 1). We performed a systematic review of all the seven studies using the data obtained from 815 patients (365 and 450 patients who underwent LAG and OG, respectively). All of included studies showed short- and long-term outcomes and were reported by Eastern authors (China, Japan, and Korea). With respect to the tumor staging of these seven studies, the vast majority of cases were local AGC, with 1 (0.12%) case in Stage 0 and 13 (1.60%) cases in Stage IA (0 indicates TisN0M0, IA indicates T1N0M0) according to the sixth edition of the American Joint Committee on Cancer Staging Manual (Edge and Compton, 2010). The characteristics of the studies included in our meta-analysis are listed in Table 2.

3.1 Short-term outcomes

All studies had compared the operating time between the groups, and six studies had reported estimated blood loss and the lymph nodes excised. Table 3 shows the surgical outcomes of both types of

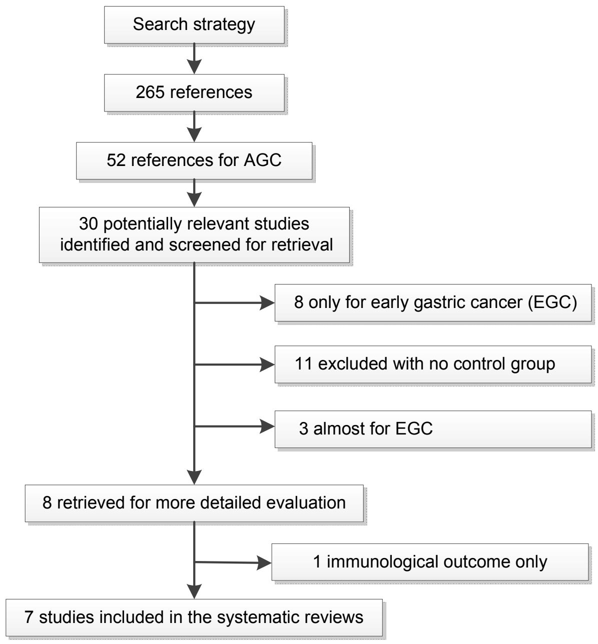

Fig. 1 Identification flow diagram of potentially eligible studies

Table 1 Quality assessment scale of studies

Reference	Selection			Comparability of groups		Outcome		Total number of stars
	S1	S2	S3	C1	C2	O1	O2	
Hamabe *et al*., 2012	*	*	*	*	**	*	*	8
Cai *et al*., 2011	*	*	*	**	**	*		8
Shuang *et al*., 2011	*	*	*	**	*	*		7
Huang *et al*., 2010	*	*	*	*	*	*		6
Hwang *et al*., 2009	*	*	*	*	**	*		7
Du *et al*., 2009	*	*	*	*	**	*		7
Hur *et al*., 2008	*	*	*	*	**			6

Quality was assessed using a star scoring system. Selection for treatment: S1, inclusion criteria reported; S2, representability of patients undergoing LAG to population undergoing surgery for AGC; S3, representability of patients undergoing OG to population undergoing surgery for AGC. Comparability of groups (if yes to all, 2 stars; if one of these characteristics was not reported, 1 star; if the two groups differed, no star): C1, age, sex, and body mass index; C2, tumor site, tumor histological type, tumor size, and tumor stage. Outcome assessment: O1, >8 outcomes clearly recorded, 1 star; O2, quality of follow-up, 1 star if >90 patients were followed up for five years

Table 2 Characteristics of studies in the meta-analysis

Reference	Follow-up	Number of patients			Level of lymph node dissection	Laparoscopy technique
		Total	LAG	OG		
Hamabe *et al*., 2012	5 years	167	66	101	D2	LAG
Cai *et al*., 2011*	4–36 months	96	49	47	D2	LAG
Shuang *et al*., 2011	23–50 months	70	35	35	D2	LADG
Huang *et al*., 2010	1–19 months	135	66	69	D2	LADG
Hwang *et al*., 2009	9–40 months	128	45	83	D2, D1+α, D1+β	LADG
Du *et al*., 2009	4–58 months	168	78	90	D2	LADG
Hur *et al*., 2008	6–47 months	51	26	25	D2	LADG

* RCT study. LAG: laparoscopy-assisted gastrectomy; LADG: laparoscopy-assisted distal gastrectomy

Table 3 Surgical outcomes of laparoscopy-assisted gastrectomy (LAG) and open gastrectomy (OG)

Reference	Operating time (min)		Estimated blood loss (ml)		Lymph nodes excised	
	LAG	OG	LAG	OG	LAG	OG
Hamabe *et al*., 2012*	283.1	225.9			63.7[a]	44.0
Cai *et al*., 2011*	270.51	187.66	293.67	344.47	22.98	22.87
Shuang *et al*., 2011#	320[a]	210	200[a]	300	35	38
Huang *et al*., 2010*	266.05[a]	223.78	131.91[a]	342.30	25.81	27.47
Hwang *et al*., 2009*	255.5[a]	208.3	333.3[a]	440.6	35.6	38.3
Du *et al*., 2009*	245	220	110[a]	196	23.5	21.0
Hur *et al*., 2008#	255[a]	190	160[a]	215	30.5	35.0

[a] Statistically significant difference vs. OG. * Values are means; # Values are medians

surgery. The duration of LAG was longer than that of OG in all studies, but only significantly (by 40–80 min) in four studies (Hur *et al.*, 2008; Hwang *et al.*, 2009; Huang *et al.*, 2010; Shuang *et al.*, 2011). Five studies demonstrated that LAG was significantly associated with less blood loss (by 80–210 ml) in the operation (Du *et al.*, 2009; Hwang *et al.*, 2009; Huang *et al.*, 2010; Cai *et al.*, 2011; Shuang *et al.*, 2011).

Seven publications have reported the number of retrieved lymph nodes in LAG with D2 dissection as similar to that in OG with D2 dissection (Hur *et al.*, 2008; Du *et al.*, 2009; Hwang *et al.*, 2009; Huang *et al.*, 2010; Cai *et al.*, 2011; Shuang *et al.*, 2011; Hamabe *et al.*, 2012). Only one study showed that the number of harvested lymph nodes was significantly higher for LAG than for OG (Hamabe *et al.*, 2012). The number of lymph nodes in our analysis showed that LAG could produce satisfactory lymph node dissection, suggesting that oncologically appropriate D2 lymph node dissection could be carried out with laparoscopic surgery (WMD 1.165; 95% CI −2.000 to 4.311; $P>0.05$; Fig. 2) (Hur *et al.*, 2008; Du *et al.*, 2009; Hwang *et al.*, 2009; Huang *et al.*, 2010; Cai *et al.*, 2011; Shuang *et al.*, 2011; Hamabe *et al.*, 2012).

LAG is also superior to OG in terms of postoperative recovery (Table 4). Patients who underwent LAG experienced less postoperative pain. Three studies reported the number of days of postoperative analgesic and narcotic medication to be shorter with LAG (Hwang *et al.*, 2009; Huang *et al.*, 2010; Shuang *et al.*, 2011). Bowel function returned earlier after LAG (Du *et al.*, 2009; Hwang *et al.*, 2009; Huang *et al.*, 2010), but some studies did not find a statistically significant difference between LAG and OG (Hur *et al.*, 2008; Cai *et al.*, 2011). Five individual studies (Du *et al.*, 2009; Hwang *et al.*, 2009; Huang *et al.*, 2010; Shuang *et al.*, 2011; Hamabe *et al.*, 2012) reported a significantly shorter hospital stay after LAG than after OG.

3.2 Surgical safety

All the studies provided data regarding the overall postoperative complications. The overall postoperative morbidity associated with LAG (38/365, 10.4%) was similar to that associated with OG (60/450, 13.3%; $P>0.05$; Fig. 3). The most common complications for both types of procedure were wound infection, anastomotic leakage, and

Table 4 Recovery outcomes of laparoscopy-assisted gastrectomy (LAG) and open gastrectomy (OG)

Reference	Use of analgesic (d)		First flatus (d)		Soft diet (d)		Hospital stay (d)		Conversion to OG (%)
	LAG	OG	LAG	OG	LAG	OG	LAG	OG	
Hamabe *et al.*, 2012*							19.8[a]	23.5	0
Cai *et al.*, 2011*			3.8900	4.2128	6.8571	6.4681	11.6327	11.4255	3.28
Shuang *et al.*, 2011#	3.0[a]	4.0					12[a]	17	
Huang *et al.*, 2010*	1.33[a]	3.50	3.18[a]	4.50	6.53	7.64	9.20[a,b]	11.35	0
Hwang *et al.*, 2009*	2.9[a]	4.1	3.3[a]	3.7	6.7[a]	7.8	9.8[b]	11.1	4
Du *et al.*, 2009*			3.04[a]	4.25			8.6[a,b]	12.1	0
Hur *et al.*, 2008#			2	2	4	4	7	9	0

[a] Statistically significant difference vs. OG. [b] Postoperative hospital stay. * Values are means; # Values are medians

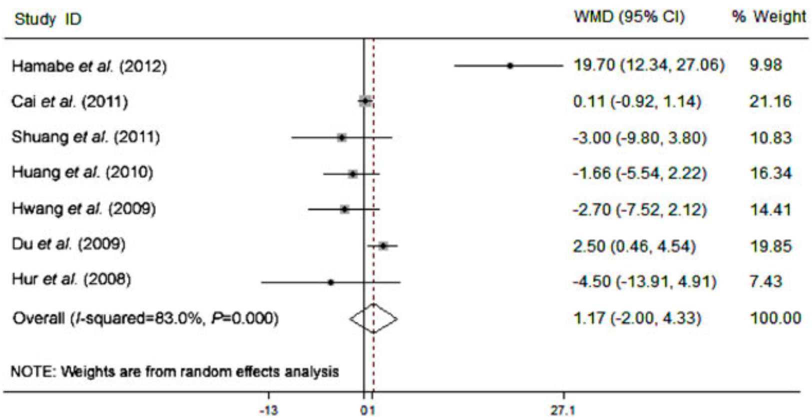

Fig. 2 Meta-analysis of harvested lymph nodes after laparoscopy-assisted gastrectomy (LAG) versus open gastrectomy (OG) for advanced gastric cancer (AGC)

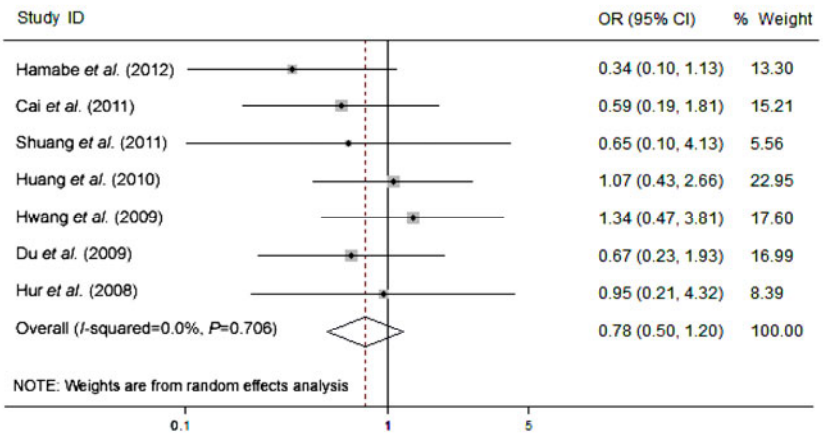

Fig. 3 Meta-analysis of overall complications after laparoscopy-assisted gastrectomy (LAG) versus open gastrectomy (OG) for advanced gastric cancer (AGC)

pulmonary infection. Five of the studies (Hur *et al.*, 2008; Du *et al.*, 2009; Huang *et al.*, 2010; Cai *et al.*, 2011; Shuang *et al.*, 2011) that examined wound infection rates found no significant differences between LAG (5/254; 2.0%) and OG (10/266; 3.8%) (P=0.262). The incidence of anastomotic leakage was not different between LAG (2/219; 0.9%) and OG (5/263; 1.9%) (P=0.767) in four studies (Hur *et al.*, 2008; Du *et al.*, 2009; Cai *et al.*, 2011; Hamabe *et al.*, 2012). However, pulmonary infection observed in three studies (Hur *et al.*, 2008; Huang *et al.*, 2010; Cai *et al.*, 2011) was less frequent in LAG (2/141; 1.4%)

than in OG (13/141; 9.2%) (*P*=0.011). There was no difference in postoperative ileus between LAG (2/210; 1.0%) and OG (5/260; 1.9%) (*P*=0.653) in three studies (Du *et al.*, 2009; Huang *et al.*, 2010; Hamabe *et al.*, 2012). Similarly, the anastomotic stenosis described in two studies (Du *et al.*, 2009; Hamabe *et al.*, 2012) was not significantly different between the LAG (4/144; 2.8%) and OG (3/191; 1.6%) (*P*=0.411; Table 5).

3.3 Long-term outcomes

All seven studies reported the rate of overall mortality, and six studies with 745 patients were included in this meta-analysis. One study was discarded from this analysis because no definite rate of overall mortality was reported (Hwang *et al.*, 2009). Six studies examined overall mortality, and reported rates of 0%–32.7% for LAG and 0%–34.0% for OG, respectively (Hur *et al.*, 2008; Du *et al.*, 2009; Huang *et al.*, 2010; Cai *et al.*, 2011; Shuang *et al.*, 2011; Hamabe *et al.*, 2012). No significant differences were found (OR 0.65; 95% CI 0.39 to 1.10; *P*>0.05; Fig. 4).

In three trials, cancer-related mortality was lower after LAG (Hur *et al.*, 2008; Hwang *et al.*, 2009; Cai *et al.*, 2011), but in a fourth study, it equaled that after OG (Huang *et al.*, 2010). There was no significant difference between LAG and OG with respect to this outcome (OR 0.64; 95% CI 0.32 to 1.25; *P*>0.05; Fig. 5).

Four studies reported that disease recurrence did not differ significantly between LAG and OG (6.1%–30.8% and 21.8%–34.4%, respectively) (Hur *et al.*, 2008; Du *et al.*, 2009; Hwang *et al.*, 2009; Hamabe *et al.*, 2012). No significant difference was found between the two techniques in this outcome (OR 0.62; 95% CI 0.33 to 1.16; *P*>0.05; Fig. 6).

Table 5 Analysis of postoperative morbidity

Outcome	n_{trial}	n_{event}		$n_{patient}$		OR (95% CI)	Interpretation	Test for heterogeneity
		LAG	OG	LAG	OG			
Overall complications	7	38	60	365	450	0.78 (0.50, 1.202) Z=1.14, P=0.256	LAG=OG	χ^2=3.78, df=6, p=0.706, I^2=0
Wound infection	5	5	10	254	266	0.55 (0.19, 1.57) Z=1.12, P=0.262	LAG=OG	χ^2=0.29, df=4, p=0.991, I^2=0
Anastomotic leakage	4	2	5	219	263	0.79 (0.16, 3.81) Z=0.30, P=0.767	LAG=OG	χ^2=2.63, df=3, p=0.452, I^2=0
Pulmonary infection	3	2	13	141	141	0.19 (0.05, 0.68) Z=2.54, P=0.011	LAG<OG	χ^2=0.05, df=2, p=0.976, I^2=0
Ileus	3	2	5	210	260	0.71 (0.16, 3.13) Z=0.45, P=0.653	LAG=OG	χ^2=1.34, df=2, p=0.513, I^2=0
Anastomotic stenosis	2	4	3	144	191	1.89 (0.41, 8.67) Z=0.82, P=0.411	LAG=OG	χ^2=0.17, df=1, p=0.679, I^2=0

n_{trial}: number of trials; n_{event}: number of events; $n_{patient}$: number of patients; LAG: laparoscopy-assisted gastrectomy; OG: open gastrectomy

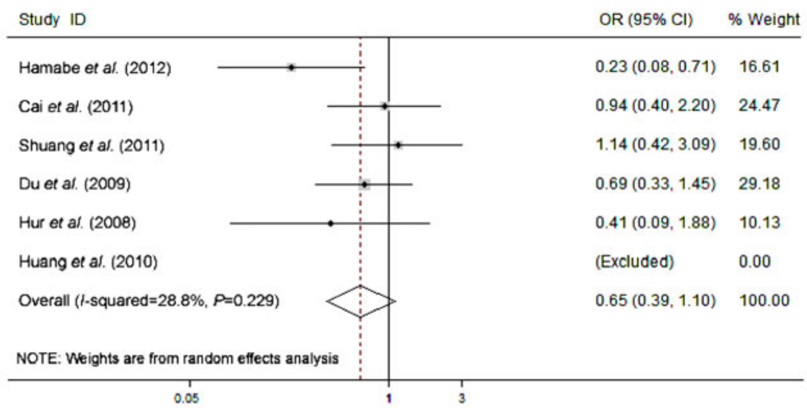

Fig. 4 Meta-analysis of overall mortality after laparoscopy-assisted gastrectomy (LAG) versus open gastrectomy (OG) for advanced gastric cancer (AGC)

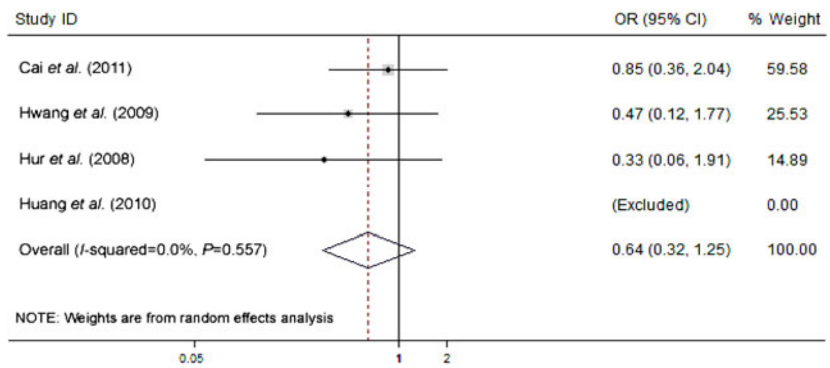

Fig. 5 Meta-analysis of cancer-related mortality after laparoscopy-assisted gastrectomy (LAG) versus open gastrectomy (OG) for advanced gastric cancer (AGC)

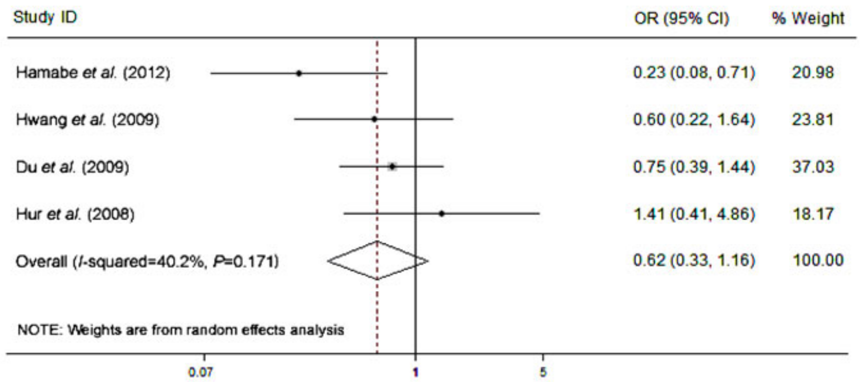

Fig. 6 Meta-analysis of recurrence after laparoscopy-assisted gastrectomy (LAG) versus open gastrectomy (OG) for advanced gastric cancer (AGC)

4 Discussion

Laparoscopic gastrectomy is an emerging surgical approach, especially in Eastern countries, for the high incidence of gastric cancer. This study summarizes the data comparing LAG to OG for AGC. The present study reveals that short-term results favor the use of LAG over OG, except duration of operation. Significant reductions in the use of analgesics and narcotics, more rapid recovery of intestinal movement, and faster return to normal diet in LAG group together contribute to a reduction in hospital stay, although local hospital policies are different worldwide. These results concur with previous published analyses (Hosono *et al.*, 2006; Liang *et al.*, 2011; Ding *et al.*, 2012; Vinuela *et al.*, 2012), making the meta-analysis of short-term outcomes unnecessary. This study (815 patients) focused on the surgical safety and oncologic results for LAG with extended lymphadenectomy of seven studies comparing laparoscopic with open surgery for mainly AGC; and confirmed that LAG for AGC achieved equivalent morbidity rates.

Overall postoperative complications from this analysis have not demonstrated any significant difference. This is consistent with the first prospective, randomized and multicenter trial in Korea, KLASS (Kim *et al.*, 2010). However, significantly decreased surgical complications in the LAG group were found in Vinuela *et al.* (2012)'s study (OR 0.59; 95% CI 0.47 to 0.745; P<0.001), which included more patients from Western countries. This might suggest that patients from Western countries have higher morbidity rates after open gastric surgery compared to their Eastern counterparts, due to unfavorable characteristics, such as age, comorbidities, and obesity (Strong *et al.*, 2010). In our study, the rates of wound infection, anastomotic leakage, postoperative ileus, and anastomotic stenosis between the LAG and OG groups were comparable. However, pulmonary infection has been observed significantly less frequently in LAG than in OG. This might be owing to less pain and suppression in the laparoscopic group, which led to reduced risks of restraints of diaphragmatic movement and pulmonary function (Frazee *et al.*, 1991; McMahon *et al.*, 1993). Some advantages of laparoscopic procedures in the reduction of complications such as incisional hernias (Strong *et al.*, 2009) and adhesive bowel obstructions (Mochiki *et al.*, 2002) are factors in favor of LAG that should be taken into account, although they are not evaluated in our study.

Despite the favorable short-term and safety results of LAG, many doubts still remain about oncology adequacy, the compliance rate for number of harvested lymph nodes and long-term prospective data, which is the most critical issue when proposing the laparoscopic treatment of gastric cancer. Although D1 dissection in the management of EGC is currently accepted according to the Gastric Cancer Treatment Guidelines in Japan (Nakajima, 2002), D2 dissection is thought to be a more appropriate treatment for patients with advanced disease (Songun *et al.*, 2010). In our study, the D2 lymphadenectomy was routinely performed except in Hwang *et al.* (2009)'s study, who performed D1+α (D1+No. 7) or D1+β (D1+Nos. 7, 8a, and 9) lymphadenectomy in older and in high-risk patients. Some reports argue that conventional open surgery is superior to laparoscopic surgery (Miura *et al.*, 2004; Liang *et al.*, 2011) in extraperigastric lymphadenectomy, especially the second tier nodes, station Nos. 7, 8, 9, and 11, along the branches of celiac artery. The results in the meta-analysis by Hosono *et al.* (2006), the significantly higher number of lymph nodes in OG group, likely support this opinion. However, this conclusion may be unreliable, because they included some studies with less than 15 nodes harvested. These observations may be conducted in the learning curve of laparoscopic D2 dissection and represent a lower proficiency with the technique (Powell *et al.*, 2002; Crew and Neugut, 2004). Therefore, it is believed that D2 lymphadenectomy should be applied only in large specialized centers with experienced surgeons, so the learning curve can be completed more effectively (Tokunaga *et al.*, 2009). No study shows that the mean number of dissected lymph nodes obtained by LAG is less than 20 in our study. The reasonable explanation for this is that studies included in our analysis were not conducted in their initial learning phase of LAG. The extent of the lymph node dissection was sufficient for AGC and our results are not influenced by learning curve issues.

The long-term results in LAG group were similar with those in OG group because laparoscopic technique, although LAG was less invasive, conducts the same organ and lymphatic resection as the open procedure. A higher overall mortality rate had been reported in patients undergoing OG compared to LAG, but statistically there was no real difference. Neither was any significant difference found in terms of cancer-related mortality or disease recurrence. These results in LAG group were comparable to those in the large-scaled multicenter retrospective study about LAG for AGC in Korea (Park Do *et al.*, 2012).

In the present study, the number of retrieved lymph nodes was considered to be oncologically acceptable. No significant differences were found in the complication rates and mortality rates in our study. Thus, LAG for AGC can be regarded as technically feasible and safe. However, the long-term results are still lacking. These results should be validated in some large RCTs with enough follow-up.

Peritonitis carcinomatosa was observed in both LAG (4%–6%) and OG (0%–2%) (Hur *et al.*, 2008; Hamabe *et al.*, 2012). Hwang *et al.* (2009) reported that one patient (pT3N1M0, IIIA) had port-site recurrence 10 months after surgery (LAG). There is a belief that laparoscopic curative surgery for serosa-exposed (T3) AGC is not yet an acceptable treatment method, because there could be peritoneal seeding of malignant cells in dealing with possible metastatic lymph nodes or a risk of port-site recurrence (Lee *et al.*, 2007). Several in vivo studies have also shown that laparoscopy with carbon dioxide insufflations seems to stimulate the growth of dormant tumor cells into overt liver metastases (Gutt *et al.*, 2001; Kim *et al.*, 2002). However, some studies in colon and gallbladder cancer refuted this risk (Kim *et al.*, 1998; Goetze and Paolucci, 2006). Regard to these results, the possibility of peritoneal or port site seeding of malignant cells remains unknown.

In consideration of these possibilities, most reports mainly concerned cases with T2 or lower depth of invasion, the number of T3 cases in the literature was very small. In Cai *et al.* (2011)'s study, according to the subclassification for the depth of tumors, the overall survival rates were 100%, 75%, and 51.2% in patients with T2a, T2b, and T3 tumors in LAG group, respectively, and there was a statistically significant difference. However, Shuang *et al.* (2011)'s study, in which 42 (60.0%) patients were T3, yields good oncologic outcomes including the similar complication and the cumulative survival rates between the two groups after 50 months of follow-up. There was no significant difference between the two groups in depth of invasion, and 24.3%, 15.7%, and 60.0% of all the patients were T2a, T2b, and T3, respectively. Owing to the insufficient data, the indications in T stages for LAG in patients with AGC require further investigation.

Currently, most studies focused on distal gastric cancer. The explanations may be: (1) The low incidence of proximal gastric cancer. Distal gastric cancers predominate in Asia compared to North America and Europe (Parkin and Muir, 1992; Corley and Buffler, 2001), although Cai *et al.* (2011) and Hamabe *et al.* (2012) described the ratio of the proximal gastric cancer is 58.3% and 24.6%, respectively in their area. (2) The more difficult proximal gastric laparoscopic surgical procedure. Cai *et al.* (2011) claimed that for proximal gastric cancer, traditional open surgery has difficulties on No. 4sb and No. 2 lymph nodes dissection and laparoscopy has more advantages. (3) The homogeneity of lymphadenectomy as well as gastric resection. For the time being there are only limited published cases regarding laparoscopic gastrectomy in AGC. In this study, we included not only distal gastric cancer but also the proximal gastric cancer to conduct a more comprehensive result. However, the mix-up of LAG and laparoscopy-assisted distal gastrectomy (LADG) techniques may be a weak point of this analysis.

Nevertheless, our study has several limitations. Firstly, most studies published in the English literature analyzing both LAG and OG for the treatment of AGC are non-randomized retrospective trials. To overcome the lack of RCTs, we include NRCTs. The drawbacks of methodology, such as possible selection bias, short periods of follow-up, and small object numbers, may cause the heterogeneity although no heterogeneity was observed (Petitti, 1994; Shapiro, 1994). To conduct a conservative result, we employed the random effects model in this meta-analysis. Furthermore, some studies about laparoscopic surgery for gastric cancer cannot distinguish the EGC and AGC preoperatively (Cai *et al.*, 2011), since accurate preoperative staging based on the current auxiliary examination is still difficult. Finally, it largely represents the experience of Eastern countries with AGC because of the low incidence of gastric cancer in Western countries. Patients from Western countries often have a higher body mass index (BMI) compared to Eastern counterparts, and are prone to have higher mortality and morbidity rates. The paucity of studies from Western countries may underestimate the rate of postoperative complications.

5 Conclusions

In conclusion, after analyzing seven studies, the indications for LAG with extended lymphadenectomy could be expanded in the treatment of locally AGC. In China, where most gastric cancers present at an advanced stage, the results are encouraging. For LAG to be widely accepted, concerns for feasible and oncologic results must be addressed, which indicates that this surgical approach maintains surgical safety and curability. A larger RCT in multicenter comparing the LAG with OG will be recommended.

Compliance with ethics guidelines

Long-yun YE, Da-ren LIU, Chao LI, Xiao-wen LI, Ling-na HUANG, Sheng YE, Yi-xiong ZHENG, and Li CHEN declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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