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ORIGINAL ARTICLE

Comparison of laparoscopic versus open gastrectomy for advanced gastric cancer: an updated meta-analysis

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Abstract
Background Laparoscopic gastrectomy (LG) has been used as an alternative to open gastrectomy (OG) to treat early gastric cancer. However, the use of LG for advanced gastric cancer (AGC) has been in debate.
Methods Literature retrieval was performed by searching PubMed, EMBASE, and the Cochrane library up to July 2014. Potential studies comparing the surgical effects between LG with OG were evaluated and data were extracted accordingly. Meta-analysis was carried out using RevMan. The pooled risk ratio and weighted mean difference (WMD) with 95 % confidence interval (95 % CI) were calculated.
Results Overall, 26 studies were included in this meta-analysis. LG had some advantages over OG, including shorter hospitalization (WMD, −3.63, 95 % CI, −4.66 to −2.60; $P < 0.01$), less blood loss (WMD, −161.37, 95 % CI, −192.55 to −130.18; $P < 0.01$), faster bowel recovery (WMD, −0.78, 95 % CI, −1.05 to −0.50; $P < 0.01$), and earlier ambulation (WMD, −0.95, 95 % CI, −1.47 to −0.44; $P < 0.01$). In terms of surgical and oncological safety, LG could achieve similar lymph nodes (WMD, −0.49, 95 % CI, −1.78 to 0.81; $P = 0.46$), a lower complication rate [odds ratio (OR), 0.71, 95 % CI, 0.59 to 0.87; $P < 0.01$], and overall survival (OS) and disease-free survival (DFS) comparable to OG.
Conclusions For AGCs, LG appeared comparable with OG in short- and long-term results. Although more time was needed to perform LG, it had some advantages over OG in achieving faster postoperative recovery. Ongoing trials and future studies could help to clarify this controversial issue.

Keywords Laparoscopic gastrectomy · Open gastrectomy · Advanced gastric cancer · Meta-analysis

Introduction

Gastric cancer is the fourth most frequently occurring cancer and the second most common cause of cancer-related death worldwide, accounting for 8 % of total and 10 % of annual cancer deaths globally [1, 2]. Despite advances in chemoradiotherapy and targeted therapy, surgery remains the only curative method for gastric cancer [3]. Complete removal of macroscopic and microscopic malignant lesions along with regional or extended lymphadenectomy represents the optimal treatment of choice for resectable localized gastric cancer.

For a long time, conventional open gastrectomy (OG) has been the only choice for gastric cancer surgery. In recent decades, however, minimally invasive surgeries, namely, endoscopic and laparoscopic procedures, have been increasingly used. For early gastric cancer (EGC) patients with negligible risk of lymph node (LN) metastasis, endoscopic surgeries such as endoscopic mucosal

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resection (EMR) and endoscopic submucosal dissection (ESD) have become the primary treatment of choice in Japan and Korea [4]. Of note, laparoscopic gastrectomy (LG) for EGC was first introduced by Kitano in 1994 [5]; since then, it has undergone rapid development and is widely used to treat EGC nowadays. Compared to OG, LG is associated with less blood loss, fewer surgical complications, faster bowel function recovery, shorter hospital stay, and an equivalent rate of postoperative tumor recurrence [6–8]. Although the long-term oncological effects of LG for EGC still need to be validated by two ongoing phase III trials [9, 10], laparoscopic surgery for EGC is largely accepted and increasingly used in East Asia (China, Japan, and Korea).

However, the use of LG for advanced gastric cancer (AGC) has been controversial. The oncological safety of LG in AGC treatment has not been thoroughly evaluated, and it is largely unknown whether the long-term follow-up of LG is comparable with that of OG. Nevertheless, LG is attracting more and more attraction and is widely used for AGC by surgeons in East Asia, despite the lack of evidence concerning its safety and efficiency. To this end, we compiled this updated meta-analysis to compare the intraoperative effects, morbidity and mortality, and short- and long-term results between LG and OG, trying to find some proof for the use of LG in AGC treatment.

Methods

Literature search

A comprehensive literature search strategy was made by retrieving the keywords “advanced gastric cancer”, “laparoscopic gastrectomy”, and “open gastrectomy” in the electronic databases of PubMed, EMBASE, and the Cochrane library from the inception until July 2014. Only studies published in English were included. To avoid omitting any potential studies, we manually checked the references of included literature. Two authors (Quan and Huang) individually conducted the literature search and cross-checked their search results. Full texts of included studies were downloaded accordingly from these databases.

Study selection

Duplicated search results were first excluded. Studies were included in this meta-analysis if they met the following criteria: having compared the two surgical procedures, namely, LG and OG; having reported detailed/available data of the surgical results, including short- and/or long-term results; patients in the studies were diagnosed with AGC or data of AGC patients were presented separately from EGC patients. If there were two or more studies derived from the same authors or centers, only the study with the largest sample size/highest quality or the more recent one was chosen. In case of studies from the same authors or centers with different patients enrolled, they were all included. Conference abstracts were deleted because no detailed information could be retrieved. Study selection was done by two authors (Ye and Xu) separately, and selection results were mutually checked. In case of discrepancies, a third author (Min) was asked to discuss to reach a consensus.

Data extraction

Data were extracted by two authors (Zhuang and Zhang) independently using predefined standards and cross-checked. Data extracted included study characteristics (author, publication year, region, study period, design, case number), patient demographics (age, gender, tumor stage), and surgical results (operation time, intraoperative blood loss, retrieved LNs, length of hospital stay, time to first flatus, onset of oral diet, time to ambulation, perioperative complication and death rates, tumor size, proximal and distal resection margin distance, tumor recurrence, and overall and disease-free survival). Perioperative complications were categorized as surgical or nonsurgical complications using previously reported criteria [11]. Corresponding authors were contacted if further information was needed. In case of discrepancies, a third author (Yu) was asked to discuss until a consensus was reached.

Statistical analysis

This meta-analysis was conducted under the guidelines of preferred reporting items for systematic reviews and meta-analyses (PRISMA) 2009 [12]. Data analyses were performed with the software Review Manager (RevMan) Version 5.2 (http://ims.cochrane.org/revman). Generally, because of the heterogeneity and the different risk profiles of patients operated on by surgeons from different centers, the random effects model was first employed to calculate the weighted mean difference (WMD) (continuous data) or risk ratio (dichotomous data) and their 95 % confidence interval (95 % CI). Heterogeneity was calculated by Cochran’s χ^2 and the I^2 test. If no significant heterogeneity was observed among the included studies ($P > 0.1$, $I^2 < 50$ %), the fixed effect model was used. Publication bias was evaluated by a funnel plot. For all analyses, $P < 0.05$ was considered statistically significant.

Results

Outcome of literature search and study selection

The literature search strategy identified a total of 501 studies. Ninety-two non-English written publications and 64 repetitive search items were first excluded; 268 studies were deleted on the basis of reviewing the titles and abstracts. After reading the full texts of the remaining papers, 24 studies [13–36] were removed as they only reported the outcomes of LG for AGC whereas no controlled or matched cases treated by OG were available. Among the remaining articles, 19 studies [37–55] were excluded because EGC cases were mixed with AGCs in the cohort studies and data on AGCs were not extractable. Eight studies were further deleted for the following reasons: 2 studies were ongoing randomized controlled trials (RCTs) that only described study design and patient enrollment criteria without results reported [56, 57]; 2 studies had overlapped enrollments with former research [58, 59]; 1 study reported incomplete data that were not suitable for analysis [60]; and 3 studies discussed other issues irrelevant to the topic of this meta-analysis [61–63]. Finally, a total of 26 studies that compared the short-term and/or long-term results of AGCs treated by LG with those of OG were included [64–89]. Figure 1 depicts the literature search and selection process of this meta-analysis.

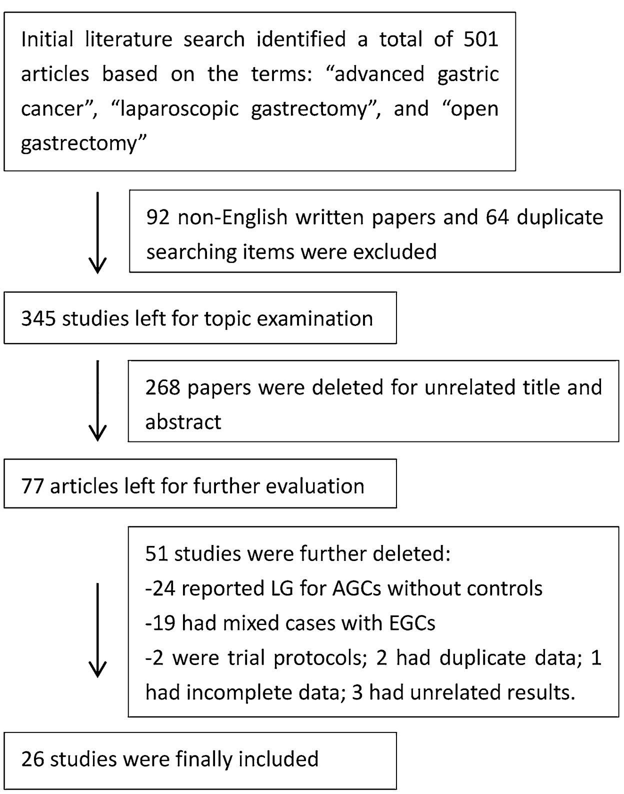

Fig. 1 Flowchart of literature search and study selection process

Characteristics of included studies

Overall, a total of 5061 AGC patients were included in this meta-analysis; among them, 2193 (43.3 %) patients were treated by LG and 2868 (56.7 %) patients underwent OG. For each study, the demographics and clinicopathological characteristics of patients treated by LG and OG did not differ from each other. Of the 26 included articles, 10 studies originated from China, 7 from Korea, 5 from Japan, 2 from Italy, and 1 each from Chile and Canada, respectively. The research period ranged from 1997 to 2011, and most studies were published within the past 3 years. Case numbers varied among included studies, from as few as 18 to as many as 799. Distal and total gastrectomy were frequently used surgical options, although proximal and subtotal gastrectomy were also adopted in some studies. Gastrointestinal tract reconstruction modalities included Billroth-I/II, Roux-en-Y anastomosis, jejunal pouch interposition, esophagogastrostomy, and esophagojejunostomy. None of the studies had used neoadjuvant chemoradiotherapy, and postoperative chemoradiotherapy was prescribed for some of the patients in some studies. Most studies reported follow-up ranging from 15 months to 5 years. Detailed information on study characteristics is shown in Table 1.

Comparison of intraoperative effects

We first compared the intraoperative results between LG and OG. Consistent with the pronounced benefits of laparoscopic surgery, the estimated blood loss was much less for LG than OG (WMD, −161.37, 95 % CI, −192.55 to −130.18; $P < 0.01$). In contrast, the mean operation time of LG was longer than OG (WMD, 51.86, 95 % CI, 35.82–67.91; $P < 0.01$). In terms of dissected LNs, LG could achieve the same radical dissection effect as OG (WMD, −0.49, 95 % CI, −1.78 to 0.81; $P = 0.46$) (Fig. 2); specifically, we compared studies that adopted D2 LN dissection, which showed that LG had similar LN production with OG as well (WMD, −0.69, 95 % CI, −2.31 to 0.93; $P = 0.41$). Furthermore, both procedures yielded comparable proximal (WMD, −0.10, 95 % CI, −0.38 to 0.18; $P = 0.49$) and distal (WMD, 0.14, 95 % CI, −0.01 to 0.29; $P = 0.06$) resection margin distance; however, the average tumor size in LG was slightly larger than that in OG (WMD, −0.35, 95 % CI, −0.63 to −0.07; $P = 0.02$). Results of analyses of intraoperative effects are shown in Table 2.

Analyses of short-term results

The advantages of laparoscopic surgery over open surgery also included less pain, shorter hospitalization, quicker

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

References	Country	Publication year	Study period	Study design	Patients		Tumor stages of AGCs	Surgical extension	Level of lymphadenectomy	Construction methods	Mean/median follow-up
					LG	OG					
Lee et al. [64]	Korea	2006	2003/05–2004/12	Retro	16	90	NR	DG	D1 + α/β, D2	B-I/II, R-Y	NR
Hur et al. [65]	Korea	2008	2004/04–2007/03	Retro	26	25	T2b	DG	D2	B-I/II, JPI	3 years
Hwang SI [66]	Korea	2009	2004/11–2007/06	Retro	45	83	Ib–IIIb	DG	D1 + α/β, D2	B-I/II	23.6 months
Du et al. [67]	China	2010	2005/11–2009/05	Retro	82	94	Ib–IIIb	TG	D2	NR	22.5 months
Cai et al. [68]	China	2011	2008/03–2009/12	RCT	49	47	Ib–IIIb	PG, DG, TG	D2	B-I/II	22.1 months
Jeong et al. [69]	Korea	2011	2005/01–2007/12	Retro	109	76	Ib–IV	DG, TG	D2	B-I/II, R-Y	36.8 months
Scatizzi et al. [70]	Italy	2011	2006/01–2009/09	Retro	30	30	II–IIIb	SG	D2	R-Y	18 months
Shuang et al. [71]	China	2011	2005/08–2007/12	Retro	35	35	Ib–IIIb	DG	D2	B-II	35 months
Sica et al. [72]	Italy	2011	2000/02–2004/09	Longi	22	25	Ib–IV	TG, SG	D1 + β, D2	B-II, R-Y	38 months
Zhao et al. [73]	China	2011	2004/01–2009/06	Retro	346	313	Ib–IV	DG	D1/ + α/β, D2	B-I/II	37 months
Chen et al. [74]	China	2012	2008/01–2010/12	Retro	224	112	Ib–IIIb	TG, DG	D2	B-I/II, R-Y	19 months
Chun et al. [75]	Korea	2012	2004/01–2009/12	Retro	52	67	Ib–IIIa	DG	D2	B-I/II, R-Y	5 years
Hamabe et al. [76]	Japan	2012	2000/01–2009/12	Retro	66	101	Ib–IIIb	DG, TG	D2	B-I/II, R-Y	NR
Kim et al. [77]	Korea	2012	1999/08–2007/06	Retro	88	88	Ib–IIIc	PG, TG, SG	D2	B-I/II, R-Y, EG	5 years
MacLellan et al. [78]	Canada	2012	2000/01–2009/11	Retro	21	182	T2b+	PG, TG, DG, SG	NR	NR	3 years
Moisan et al. [79]	Chile	2012	2005/05–2010/08	Retro	19	18	Ib–IIIc	TG, SG	D1 + α/β, D2	B-II, R-Y	50 months
Sato et al. [80]	Japan	2012	2001/01-2010/12	Retro	36	130	Ib-III	PG, DG, TG	D2	NR	43 months
Bo et al. [81]	China	2013	2004/01–2010/12	Retro	117	117	Ib–IIIb	TG	D2	R-Y	61.2 months
Fang et al. [82]	China	2013	2009/08–2011/01	Retro	50	62	NR	NR	D2	B-I/II	18 months
Gordon et al. [83]	Japan	2013	1999/01–2010/03	Retro	66	135	Ib–IIIc	DG	D1/ + α/β,D2/ + α	B-I/II, R-Y	49.2 months
Li et al. [84]	China	2013	2009/03–2011/06	Retro	106	133	Ib–IIIc	DG, TG	D2	B-I/II, R-Y	15 months
Lin et al. [85]	China	2013	2008/01-2010/12	Retro	83	83	Ib–IIIb	DG, TG	D2	B-I/II, R-Y	23 months
Shinohara et al. [86]	Japan	2013	1997/10–2008/12	Retro	186	150	cT2–T4	PG, DG, TG	D2	B-I, R-Y	48.8 months
Yamanaka et al. [87]	Japan	2013	2000/01–2010/12	Retro	9	9	IV	DG, TG	D2	NR	20.5 months
Fang et al. [88]	China	2014	2005/04–2009/10	Retro	87	87	Ib–IIIc	DG, TG	D2	EJ, GI	44 months
Lee et al. [89]	Korea	2014	2003/05–2009/12	Retro	223	576	Ib–IIIc	NR	D1+, D2	NR	5 years

NR not reported, *DG* distal gastrectomy, *retro* retrospective, *PG* proximal gastrectomy, *TG* total gastrectomy, *SG* subtotal gastrectomy, *B-I* Billroth-I, *B-II* Billroth-II, *R-Y* Roux-en-Y, *JPI* jejunal pouch interposition, *EG* esophagogastrostomy, *RCT* randomized controlled trial, *longi* longitudinal prospective nonrandomized trial, *GI* gastrointestinal anastomosis, *EJ* esophagojejunostomy

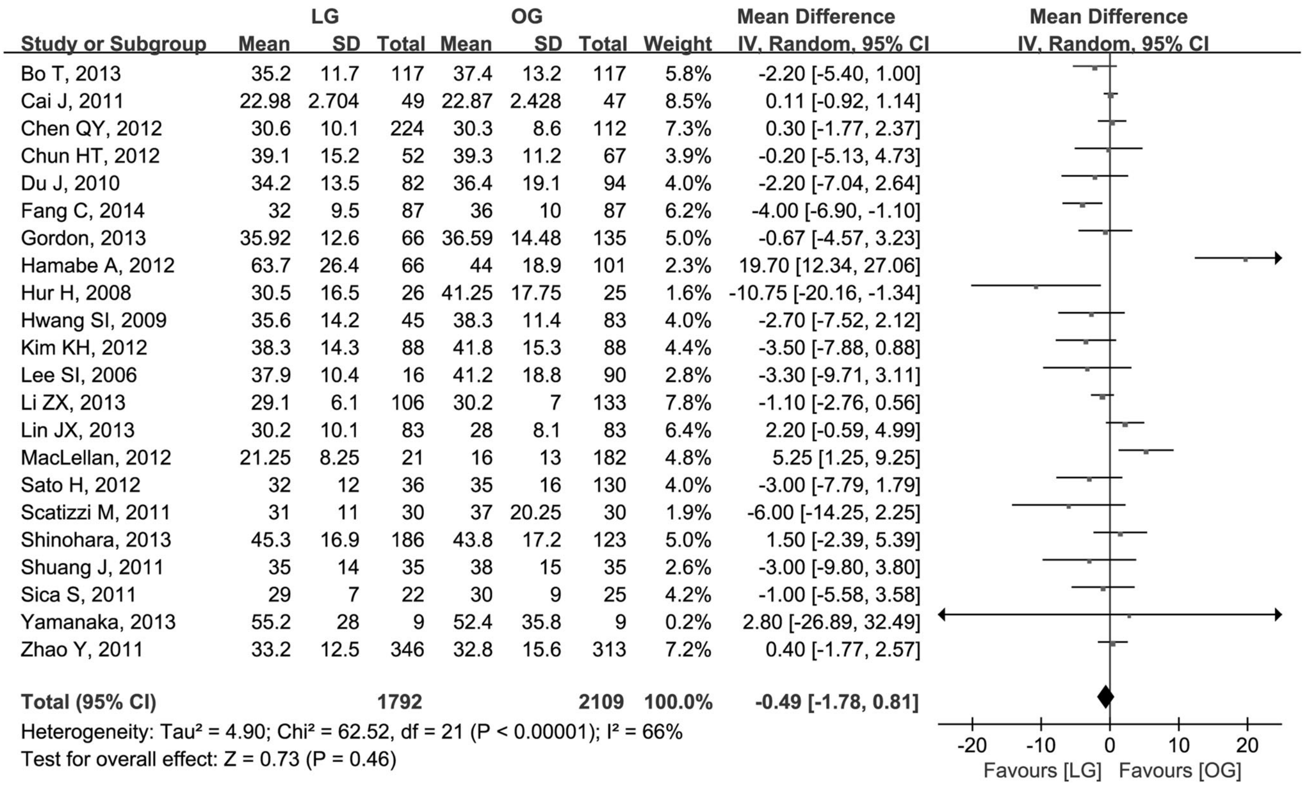

Fig. 2 Forest plot showing the meta-analysis results of retrieved lymph nodes. The estimates of the weighted mean difference in each study correspond to the *middle* of *each square* and the *horizontal line* gives the 95 % CI. Pooled effect is represented by the *middle* of the *solid diamond*

Table 2 Comparisons of intraoperative surgical effects

Outcomes	Included studies	Patients		Heterogeneity (I^2, P)	Overall effect WMD (95 % CI)	P value
		LG	OG			
Estimated blood loss	16	1563	1627	88 %, <0.01	−161.37 (−192.55, −130.18)	<0.01
Operation time	20	1783	1874	94 %, <0.01	51.86 (35.82, 67.91)	<0.01
Retrieved LNs	22	1792	2109	64 %, <0.01	−0.49 (−1.78, 0.81)	0.46
Retrieved LNs of D2 lymphadenectomy	16	1276	1281	72 %, <0.01	−0.69 (−2.31, 0.93)	0.41
Tumor size	14	1277	1233	67 %, <0.01	−0.35 (−0.63, −0.07)	0.02
Proximal resection margin distance	8	775	805	58 %, 0.02	−0.10 (−0.38, 0.18)	0.49
Distal resection margin distance	5	618	624	0 %, 0.86	0.14 (−0.01, 0.29)	0.06

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

bowel function recovery, and earlier resumption of body movement. In agreement with this, we found patients undergoing LG had shorter hospital stay (WMD, −3.63, 95 % CI, −4.66 to −2.60; $P < 0.01$), shorter mean time to first flatus (WMD, −0.78, 95 % CI, −1.05 to −0.50; $P < 0.01$), and resumed oral intake much earlier (WMD, −0.89, 95 % CI, −1.20 to −0.59; $P < 0.01$) than those undergoing OG. Also, patients treated with LG needed less time to ambulation than those with OG (WMD, −0.95, 95 % CI, −1.47 to −0.44; $P < 0.01$). The perioperative complication rates were also compared: overall complication rate for LG was 13.2 %, significantly lower than the rate of 18.0 % of OG (OR, 0.71, 95 % CI, 0.59–0.87; $P < 0.01$) (Fig. 3). To be specific, the rates of surgical complications, including leakage, bleeding, wound infection, and anastomotic stricture (OR, 0.69, 95 % CI, 0.53–0.88; $P = 0.003$), and medical complications such as respiratory or cardiovascular events, deep venous thrombosis, pulmonary embolism, and nonsurgical infections (OR, 0.51, 95 % CI, 0.32–0.81; $P = 0.004$), were both lower in the LG patients than in OG patients. In terms of mortality, no significant differences were seen between the

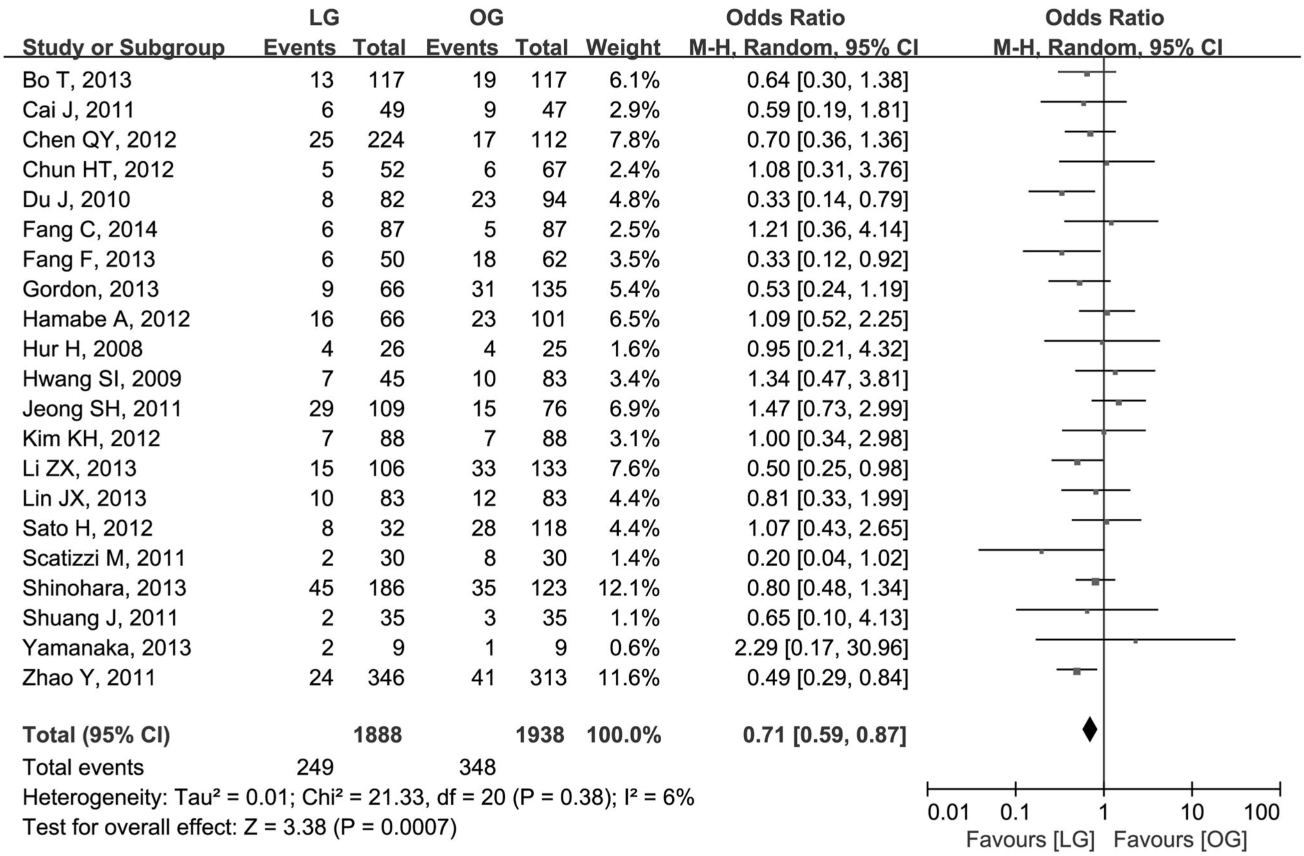

Fig. 3 Forest plot of pooled odds ratio of overall complication

Table 3 Comparisons of short-term results

Outcomes	Included studies	Patients		Heterogeneity (I^2, P)	Overall effect WMD/RR (95 % CI)	P value
		LG	OG			
Hospital stay	18	1593	1652	86 %, <0.01	−3.63 (−4.66, −2.60)	<0.01
First flatus	15	1373	1398	89 %, <0.01	−0.78 (−1.05, −0.50)	<0.01
Oral diet	12	1237	1165	72 %, <0.01	−0.89 (−1.20, −0.59)	<0.01
Ambulation	9	1162	1002	97 %, <0.01	−0.95 (−1.47, −0.44)	0.0003
Overall complication	21	1888	1938	6 %, 0.38	0.71[a] (0.59, 0.87)	0.0007
Surgical complication	13	1404	1318	0 %, 0.61	0.69[a] (0.53, 0.88)	0.003
Medical complication	11	1023	970	8 %, 0.37	0.51[a] (0.32, 0.81)	0.004
Mortality	11	1230	1225	0 %, 0.89	0.67[a] (0.25, 1.77)	0.42

LG laparoscopic gastrectomy, *OG* open gastrectomy, *WMD* weighted mean difference, *RR* risk ratio

[a] RR

two procedures (OR, 0.67, 95 % CI, 0.25–1.77; $P = 0.42$). Table 3 summarizes the comparison outcomes of short-term results between LG and OG.

Analyses of long-term effects

The long-term results including recurrence, overall survival (OS), and disease-free survival (DFS) were analyzed. Fourteen studies reported data on tumor recurrence, with no significant heterogeneity observed. The recurrence rate in LG was 27.1 %, which was significantly lower than the rate of 30.6 % in OG (OR, 0.80, 95 % CI, 0.66–0.96; $P = 0.02$). In all, 24 studies [65–75, 77–89] reported long-term follow-up ranging from 1 year to 5 years. Four studies [73, 74, 82, 85] reported 1-year OS; 7 studies [65, 68, 70, 73, 78, 79, 82] reported 3-year OS, and 9 [72, 73,

Table 4 Comparisons of long-term results

Outcomes	Included studies	Patients		Heterogeneity (I^2, P)	Overall effect RR (95 % CI)	P value
		LG	OG			
Recurrence	14	1184	1391	0 %, 0.69	0.80 (0.66, 0.96)	0.02
1-year OS	4	674	543	0 %, 0.88	0.98 (0.68, 1.40)	0.90
3-year OS	7	527	661	0 %, 0.83	1.19 (0.92, 1.53)	0.18
5-year OS	9	1008	992	0 %, 0.62	1.20 (0.99, 1.46)	0.06
3-year DFS	3	66	225	58 %, 0.09	1.25 (0.44, 3.55)	0.67
5-year DFS	5	773	712	13 %, 0.33	1.22 (0.95, 1.57)	0.11

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

75–77, 81, 83, 86, 88] reported 5-year OS. No significant differences were seen in 1-, 3-, or 5-year OS between LG and OG [1-year: risk ratio (RR) = 0.98, 95 % CI 0.68–1.40, $P = 0.90$; 3-year: RR = 1.19, 95 % CI 0.92–1.53, $P = 0.18$; 5-year: RR = 1.20, 95 % CI 0.99–1.46, $P = 0.06$]. Regarding DFS, 3 [65, 78, 79] studies reported 3-year DFS and 5 studies [73, 76, 77, 86, 88] reported 5-year DFS. The 3-year DFS of LG and OG were 65.2 % and 58.2 %, respectively (OR, 1.25, 95 % CI, 0.44–3.55; $P = 0.67$); the 5-year DFS of LG and OG were 60.7 % and 57.9 %, respectively (OR, 1.22, 95 % CI, 0.95–1.57; $P = 0.11$). Meta-analysis results of long-term effects are presented in Table 4.

Discussion

Laparoscopic surgery has several advantages over conventional open surgery, such as faster recovery, shorter hospitalization, less pain, and less blood loss [90]. In the past two decades, the use of laparoscopy has been continuously increasing, and its indications have also expanded, from benign diseases to malignant tumors [91, 92]. Laparoscopic gastrectomy has long been used to treat EGC, and in the past decade, attention has been paid to the feasibility and safety of LG for AGC. Although several clinical trials have been initiated to evaluate the effectiveness of LG [9, 10, 56, 57], currently we do not have enough evidence to support this surgical procedure in AGC management. To this end, we conducted this meta-analysis trying to find some clues.

In the current study, we observed that LG demonstrated several advantages when it was used for AGC treatment. Compared to AGC patients treated by OG, patients in the LG group showed significantly shorter hospital stay, less blood loss, faster postoperative recovery, and earlier ambulation. These advantages were in agreement with the conceptions of fast track surgery and benefits to AGC patient recovery [93, 94]. We also found longer operation time for LG in this study. Although laparoscopy could provide a wide operation field, restriction in trocar number [95], insufficient training [96], and lack of tactile feedback [97] made the surgical process less flexible and more complicated than open surgery. For AGC, gastrectomy combined with D1 or D2 lymphadenectomy was more difficult than gastrectomy alone, which possibly resulted in the longer operation time in LG. However, according to studies that reported the learning curve of LG in AGCs, the operation time could reach a plateau after about 40 cases, and by experienced surgeons, LG could be done as quickly as OG [98–100].

Another major finding that supported the use of LG for AGC was that the surgical and oncological safety of LG were comparable with or even superior to those of OG. In the present study, we found both the overall and specific complication rates of LG were much lower. As already mentioned, LG has the inherent benefit of minimal invasiveness, and this certainly reduced the chance of causing massive tissue and organ damage during an operation, which would result in fewer surgical complications as a consequence. Similarly, a smaller incision and the use of techniques such as hemolock, titanium clip, and ultrasonic scalpel reduced the incidence of wound infection and bleeding. Moreover, under laparoscopy, surgeons could sufficiently dissect the duodenum to make anastomosis without tension so as to avoid stomal leakage and stricture. We also observed fewer medical complications in LG than OG. For postoperative inpatients, medical complications such as respiratory or cardiovascular events, deep venous thrombosis, and pulmonary embolism are potential threats. In this study, the medical complication rate of LG patients was 4.1 %, significantly lower than the rate of 7.8 % of OG. This change could also be attributed to the benefits of laparoscopic surgery because patients needed less hospitalization time to recovery, which reduced the risk of acquiring a nosocomial infection [101]; further, LG patients were able to resume body movements earlier than OG patients, thus lowering the risk of hypostasis and deep venous thrombosis [102].

In terms of oncological safety, LG achieved comparable results with OG. To reduce the possibility of recurrence and metastasis, adequate LN dissection is important in gastric cancer treatment [103] and confers survival benefits for gastric patients at specific stages [104]. One major concern about the use of laparoscopy in AGC was its efficiency for lymphadenectomy: whether this technique could harvest enough LNs for pathology evaluation and reach the same radicality as open surgery remained controversial. In this meta-analysis, we found LG could retrieve as many LNs as did OG, possibly resulting from the increasing use of LG and improvements in laparoscopy facilities and surgical methodology. Importantly, a recent study by Lee et al. showed that for experts of OG, in cases in which surgical time extension could be accepted willingly, the radicality in lymphadenectomy could be also achieved even during the learning period of LG [105]. Specially, D2 lymphadenectomy is generally recommended as the standard procedure to treat AGCs in East Asia [106]. Successful D2 lymphadenectomy is thus an essential part of radical resection for AGC [107]. We found the number of LNs retrieved in LG with D2 lymphadenectomy did not differ from that of OG, suggesting LG had lymphadenectomy effectiveness comparable with that of OG.

Resection margin distance is another variable that affects oncological results. It is well established that complete removal of tumor mass is the primary goal of radical resection and that positive resection margin correlates with increased risk of local recurrence and decreased OS and DFS in many cancers [108]. Recent studies suggested that surgical margin status could be considered as an independent prognostic factor for GC patients [109, 110] and that sufficient distance between resection margin and tumor edge assured the complete removal of the tumor tissues and also decreased the risk of positive resection margin [111]. Thus, evaluation of resection margin distance could partially reflect the curability of surgical procedures. Hereby, we found both the proximal and distal resection margin distances did not differ between LG and OG, indicating LG possessed curability and oncological safety comparable to that of OG. It is proposed that tumor size should also be recommended as an important clinicopathological factor to enhance the accuracy of the prognostic prediction of GC patients [112]. Previous meta-analyses rarely made comparisons about this factor. Unexpectedly, we observed that the tumor size in LG was much larger than that of OG, which suggested a prognostic benefit of LG. Although moderate heterogeneity was seen among the included studies, this difference led us to believe LG might have better curability than OG and that future studies should pay additional attention to this field.

The long-term results including OS, DFS, and recurrence could be directly used to evaluate the effects of surgical procedures. In this study, different types of survival were similar between LG and OG. The 1-, 3-, and 5-year OS and 3- and 5-year DFS were comparable, indicating the treatment effects of LG at least were not inferior to OG. Interestingly, less recurrence was observed in LG, which contradicted the results of a former meta-analysis [113], and we believed this difference might be attributed to the studies included for analysis. The presented study included several recently published trials and also excluded some studies with both EGC and AGC patients, which enlarged the case pool and eliminated confounding bias at the same time. Port-site metastasis is proposed to be one disadvantage of laparoscopic surgery and could occur in different kinds of malignant cancers [114]; moreover, port-site metastasis might indicate a harbinger of progressive disease [115]. Although it occurred rarely in LG for EGCs, the incidence of port-site metastasis after LG in AGCs is largely unknown [116]. In this meta-analysis, only two studies reported port-site metastasis [66, 73]. This type of complication could be avoided if surgeons would carefully perform LG with standard laparoscopic procedures, minimize tumor touch, and protect the incision with a plastic bag during tumor extraction [117].

Some limitations exist that should not be neglected when interpreting the conclusions of this study. First, most studies included in this meta-analysis were performed retrospectively whereas only one prospective RCT was included. Generally, RCTs are much more suitable than other types of trials for meta-analysis; with only one RCT included in this meta-analysis, the quality and confidence level might be questioned. Second, there was no analysis of survival based on chemoradiotherapy status. It is well known that chemoradiotherapy following surgery is the standard treatment for AGC patients; thus, the long-term follow-up results of LG and OG could be better evaluated if patients were stratified by chemoradiotherapy status or modality. Third, the case volumes of the included studies varied greatly, which could significantly affect the results of surgical procedures and lead to high heterogeneity among studies. In such a case, comparisons of surgical results would be influenced by surgeons' experience. Future trials with prospective design and multi-center participation are needed.

Conclusively, the current study presented convincing evidence to show that LG could achieve comparable results with OG for AGC patients in terms of short- and long-term effects. Moreover, LG demonstrated some advantages over OG, including faster recovery and shorter hospitalization time. Although ongoing RCTs have not yielded clear answers on this issue up to now, based on the results of this and other former meta-analyses, as well as previous trials, we believe AGC could be safely treated with LG by experienced surgeons under standard laparoscopic principles.

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