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REVIEW ARTICLE

Laparoscopic versus open gastrectomy with D2 lymph node dissection for advanced gastric cancer: a systematic review

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Summary

Purpose: *Review of the literature collecting trials comparing laparoscopic (LGD2) and open D2 gastrectomies (OGD2) for the treatment of advanced gastric cancer (AGC).*

Methods: *Randomized control trials (RCTs) and non-RCTs comparing LGD2 with OGD2 for AGC treatment, published between 1 January 2000 to 30 November 2017 were identified by searching the PubMed, EMBASE and Cochrane Library databases. Primary endpoints included operative outcomes (operative time, intraoperative blood loss, number of transfused patients and conversion rates), postoperative outcomes (postoperative analgesic consumption, time to first ambulation, time to first flatus, time to first oral intake, length of postoperative hospital stay, postoperative morbidity, incidence of reoperation and postoperative in-hospital mortality), and oncologic outcomes (number of harvested lymph nodes, tumor recurrence, disease-free rates and overall survival rates). The modified Newcastle-Ottawa scale was used to assess the quality of RCTs and non-RCTs in the study.*

Results: *Two RCT and 10 non-RCTs with a total of 2732 patients were included in the review. LGD2 when compared to OGD2 demonstrated significant lower intraoperative blood loss, shorter duration of analgesic administration, shorter times to first ambulation, flatus and oral intake, shorter postoperative hospital stay, lower incidence of nonsurgical complications. No significant differences were observed between LGD2 and OGD2 for the following criteria: postoperative in-hospital mortality, number of harvested lymph nodes, tumor recurrence, 5-year disease-free survival rates and five- or three-year overall survival rates. However, LGD2 had longer operative times.*

Conclusion: *Although a technically demanding and time-consuming procedure, LGD2 offers the advantages of minimal invasion and can achieve the same degree of radical resections, harvested lymph nodes and short- or long-term prognosis for the treatment of locally AGC.*

Key words: *gastrectomy, laparoscopy, gastric cancer, D2 dissection*

Introduction

On a worldwide basis, gastric cancer is considered the third most common cancer and the second leading cause of cancer-related deaths, despite the great advances in the diagnosis and treatment in the field [1,2]. Nowadays, radical gastrectomy along with lymph node dissection is the mainstay of treatment for patients with gastric cancer [3,4]. Indeed, over the past decades radical gastrectomy has contributed to the increased survival rates for such patients.

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The Japanese Gastric Cancer Association (JGCA) guidelines recommend D2 gastrectomy for the treatment of advanced gastric cancer (AGC) [5,6]. According to the same guidelines, stations 12a or 10 D2 dissection is technically demanding due to an increasing risk of organ injury or leakage (bile or pancreatic) [7,8]. Besides open surgery, laparoscopic approach has been also recommended. The first laparoscopic gastrectomy (LG) was reported by Kitano et al, who performed a Billroth I procedure to treat early gastric cancer [9]. In 2000, Uyama et al. first reported LG with D2-extended lymph node dissection (LGD2) for the treatment of AGC [10]. Ultimately, in 2002, Coh et al. reported laparoscopy-assisted D2 radical gastrectomy for advanced gastric cancer [11].

The advances in the minimally invasive era led to a dramatic increase in the number of such procedures performed laparoscopically worldwide. Currently, laparoscopic gastrectomy with D2 lymph node dissection has become a reliable alternative to open approach for the treatment of gastric cancer. However, several reasons have hindered its wider application; a: concerns about oncological safety that is determined mainly through a R0 resection and the extent of lymph node dissection; b: steep learning curve, especially for the reconstruction of the alimentary tract; c: the absence of a large-scale prospective randomized trial clearly favoring this procedure.

Therefore, we sought to compare the short- and long-term outcomes of LAG through a systematic review of the literature and draw conclusions on which approach is superior in terms of safety and oncologic outcomes.

Methods

Literature search

All trials (RCTs and non-RCTs) and meta-analyses were identified by searching the PubMed, EMBASE and Cochrane Library databases for studies published between 1 January 2000 to 30 November 2017. Only articles published in English were included in this review. The following MeSH terms were used in various combinations: "stomach neoplasms"; "stomach cancer"; "gastric cancer"; "laparoscopy"; "laparoscopic"; "laparoscopy-assisted gastrectomy"; "laparoscopic-assisted gastrectomy"; "minimally invasive"; "open gastrectomy"; "conventional gastrectomy"; "D2 lymph node dissection"; "D2 gastrectomy"; "extended"; "radical". Additional relevant articles were identified using references of relevant articles and previous meta-analyses.

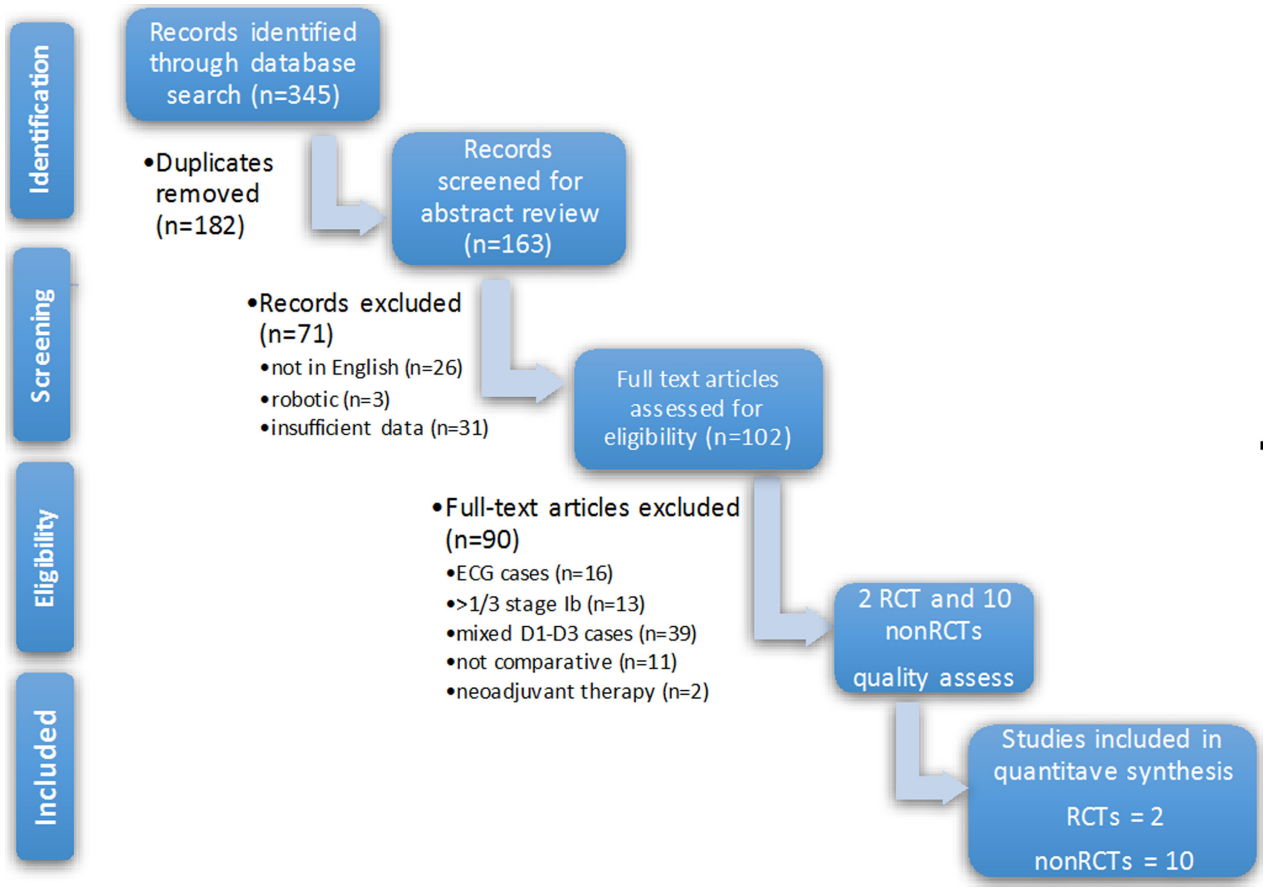

Figure 1. Flow chart of the search strategy.

Method of review

Two authors (AM, MCM) evaluated all retrieved studies to determine whether they met the criteria, assessed the quality of the included studies and extracted the data. The extracted variables were as follows: study features, clinical, surgical and pathological parameters (sample size, age, BMI, tumor size, extend of lymphadenectomy, type of GI reconstruction, conversion rate, tumor stage), operative time, intraoperative bleeding, number of resected and positive lymph nodes, time to first flatus, time to liquid diet, postoperative hospital stay, complications, morbidity and mortality. Any disagreements were resolved by team consensus.

Inclusion and exclusion criteria

Inclusion criteria were as follows: a: RCTs or non-RCTs reporting on LGD2 and OGD2 in patients with AGC (stage Ib-III); b: no evidence of local and distant metastasis; c: no prior neoadjuvant therapy; d: stage: Ib < 1/3 of all cases; e: compared short and long-term outcomes of LADG and ODG with D2 dissection; f: recorded the majority of the following: age, BMI, tumor size, serosa invasion status, number of HLNs, positive LN rate; g: were published in English.

The exclusion criteria were as follows: a: early gastric cancer (EGC) cases; b: malignant stromal tumors; c: combined D1-D3 lymphadenectomy; d: >1/3 of cases be stage Ib; e: hand-assisted, robotic surgery, emergency operations; f: neoadjuvant therapy, g. recurrent gastric cancer or palliative resection cases; h: insufficient data; i: duplicate publications.

Quality assessment of the included studies

The (modified) Newcastle-Ottawa Quality Assessment star scoring system was used to evaluate the quality of all the included studies. The scale is comprised of seven elements that assess patient population and selection, study comparability, follow-up and outcome of interest. In assessing comparability between groups, focus was on the variables that might affect primary endpoints such as patient age and sex, pathologic tumor-node-metastasis stage, type of gastrectomy, resection margin, tumor size, histologic type, reconstruction, and adjuvant treatment. Studies were scored using an ordinary star scale so as to compare their quality, with higher scores representing higher quality. A maximum of one star was awarded to a study for each numbered item within the selection and outcome assessment. A maximum of two stars was awarded for the comparability of the two groups. The total score was 9 stars and the quality of each article was graded as level 1/low quality (0-5 stars) or level 2/high quality (6-9 stars).

RCTs were evaluated by the Jadad composite scale. High-quality trials scored more than 2 out of a maximum possible score of 5.

Table 1. Study characteristics

First author	*Study design*	*Country*	*Journal, year*	*Study period*	*LADG2 ODG2*	*Type of gastrectomy*
Fang C	nonRCT	China	Am J Surg 2014	2005-2009	87 - 87	46 / 46 Distal 41 / 41 Total
Lin J	nonRCT	China	Chin Med J (Engl) 2014	2009-2011	58 - 58	58 / 58 Total
Cai J	nonRCT	China	Hepatogastroenterology 2013	2008-2011	41 - 43	25 / 27 Total 16 / 16 Prox
Li ZX	nonRCT	China	J BUON 2013	2009-2011	106 - 133	22 / 31 Distal 84 / 102 Total
Lin JX	nonRCT	China	World J Surg Oncol 2013	2008-2010	83 - 83	37 / 37 Total 46 / 46 Distal
Chen QY	nonRCT	China	World J Surg Oncol 2012	2008-2012	224 - 112	106 / 61 Total 118/ 51 Distal
Kim KH	nonRCT	Korea	Dig Surg 2012	1999-2007	88 - 88	18 /30 Total 69 / 58 Distal 1 / 0 Proximal
J. Cai D	RCT	China	Dig Surg 2011	2008-2009	49 - 47	4 / 1 Total 19 / 17 Distal 26 / 29 Prox
Scatizzi M	nonRCT	Italy	Updates Surg 2011	2006-2009	30 - 30	30 / 30 Distal
Shuang J	nonRCT	China	J Gastrointest Surg 2011	2005-2007	35 - 35	35 / 35 Distal
Du J	nonRCT	China	Hepatogastroenterology 2010	2005-2009	82 - 94	82 / 94 Total
Hu Y	RCT	China	Journal of clinical oncology	2012-2014	519-520	11/13 Total 508/507 Distal
Total					2732 (1402-1330)	930 Total 1714 Distal 88 Proximal

Definitions

AGC was defined as malignant neoplastic growth beyond the submucosal layer of the stomach. Locally AGC is the subgroup which does not include stage IV. LG was defined as total LG or laparoscopy-assisted gastrectomy. In all included studies, D2 lymph node dissection was performed according to the JGCA lymph node classification [12], which state that lymph node numbers 1, 3, 4sb, 4d, 5, 6, 7, 8a, 9, 10, 11p, 11d and 12a should be dissected.

The endpoints were classified as operative outcomes (operative time, intraoperative blood loss, conversion rate), postoperative outcomes (postoperative analgesic consumption, time to first ambulation, time to first flatus, time to first oral intake, length of postoperative hospital stay, incidence of reoperation, postoperative

Table 2. Clinicopathological characteristics (LADG2 / ODG2)

First author	*Age, years*	*BMI*	*Tumor size (cm)*	*Pathological stage (Ib:II:III)*	*% Ib*	*Adjuvant therapy*	*Follow-up (months)*	*Follow-up rate*
Fang C	57 (33-82) / 56 (33-79) [p NS]	23.3 (18.3-31.6) / 22.9 (18.3-31.6)	NR	19:38:30 / 9:29:39	21.8% / 21.8%	NR	44 (1-82)	96.6% / 94.8%
Lin J	61.4 ± 9.2 / 60.9 ± 9.4 [p 0.853]	22.0 ± 2.6 / 22.0 ± 2.7 [p 0.981]	5.3 ± 1.9 / 5.4 ± 2.7 [p 0.896]	7:21:30 / 9:21:28	12.1% / 15.5%	NR	24.0 (2-50)	NR
Cai J	61.9 ± 9.1 / 60.1 ± 9.2 [p 0.362]	22.2 ± 3.0 / 23.0 ± 2.7 [p 0.215]	3.3 ± 1.1 / 3.7 ± 1.2 [p 0.135]	3:15:23 / 1:25:17	7.3% / 2.3%	YES	24 (4-54)	NR
Li ZX	62.3 ± 8.4 / 63.0 ± 8.8 [p 0.252]		4.1 ± 2.5 / 4.4 ± 2.6 [p 0.185]	NR	≤17.9% / ≤15.8%	NR	15 (3 -39)	92.1%
Lin JX	61.6 ± 10.3 / 61.1 ± 10.5 [p 0.777]	22.3 / 21.5 [p 0.113]	4.6 ± 2.1 / 4.4 ± 2.2 [p 0.631]	16:26:31 / 16:38:30 [p 0.958]	19.3% / 19.3%	YES	23.0 (12 - 50)	96.40%

Table 3. Modified Newcastle-Ottawa scale and Jadad composite scale for quality assessment of nonRCTs and RCTs respectively

First author	*Selection*[a]			*Comparability*[b]		*Outcomes*[c]		*Total score*
	1	*2*	*3*	*4*	*5*	*6*	*7*	
Fang C	*	*	*	**	**	*		8*
Lin J	*	*	*	**	*	*	*	8*
Cai J	*	*	*	**	**	*		8*
Li ZX	*	*	*	*	*	*	*	7*
Lin JX	*	*	*	**	*	*	*	8*
Chen QY	*	*	*	**	**	*	*	9*
Kim KH	*	*	*	**	**	*	*	9*
Scatizzi M	*	*	*	**	*	*	*	8*
Shuang J	*	*	*	**	*	*		7*
Du J	*	*	*	**	**	*	*	9*

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

[b] Comparability: Comparability variables were as follows: 1. age; 2. sex; 3. depth of tumor invasion on preoperative diagnosis; 4. extent of lymphadenectomy; 5. median or mean follow-up; 6. American Society of Anesthesiologists status; 7. tumor size; 8. postoperative pathologic stage; and 9, histological type. (4) Two stars were assigned if the groups were all comparable for the variables 1–5; 1 star was assigned if one of these five characteristics was not reported, even if there were no other differences between the groups. and other characteristics had been controlled for; and no star was assigned if the two groups differed. (5) Two stars were assigned if the groups were all comparable for the variables 6–9; 1 star was assigned if one of these four characteristics was not reported, even if there were no other differences between the groups. and other characteristics had been controlled for; and no star was assigned if the two groups differed.

[c] Outcomes: (6) One star was assigned if primary outcome parameters were clearly defined. (7) One star was assigned if more than 90% of patients were followed up.

morbidity and mortality) and oncologic outcomes (number of harvested LNs, tumor recurrence and metastasis, disease-free and overall survival rates). The primary endpoints were postoperative morbidity and mortality and overall survival rates.

Morbidity was defined as the incidence of 30-day postoperative complications and the mortality as 30-day mortality. Postoperative complications were classified as organ injury, intra-abdominal bleeding, anastomotic leakage, duodenal stump fistula, lymphorrhea, ileus, pancreatitis, intra-abdominal abscess, anastomotic stenosis, wound infection. Pneumonia, pleural effusion, cardiocerebral vascular complications were classified as nonsurgical.

Table 4. Operative outcomes of the studies included in our analysis

First author	*LADG2*	*ODG2*	*p*
A. Operative time (min)			
Fang C	337 (240-650)	224 (145-500)	<0.01
Lin J	235.7 ± 67.2	245.4 ± 54.5	0.118
Cai J	269.2 ± 49.2	188.7 ± 44.4	0.001
Li ZX	268 ± 51	261 ± 49	0.142
Lin JX	212.7 ± 57.2	226.4 ± 63.5	0.214
Chen QY	207.2 ± 137.3	213.0 ± 54.7	0.667
Kim KH	228.3 ± 49.4	183.6 ± 42.7	<0.0001
J. Cai D	270.51 ±55.27	187.66 ± 40.18	<0.0001
Scatizzi M	240 (160-90)	180 (120-240)	0.001
Shuang J	320 (260-570)	210 (138-300)	<0.01
Du J	275 ± 78	212 ± 51	<0.001
B. Blood loss (ml)			
Fang C	220 (50-400)	310 (100-600)	<0.05
Lin J	74.0 ± 80.1	218.4 ± 195.2	0.001
Cai J	219.5 ± 125.4	303.3 ± 163.6	0.01
Li ZX	134.0 ± 66	289 ± 139	0001
Lin JX	78.4 ± 77.9	200.4 ± 218.3	0.001
Chen QY	82.7 ± 101.3	213.0 ± 54.7	0.001
J. Cai D	293.67 ± 164.49	344.47 ± 219.65	0.205
Shuang J	200 (100-600)	300 (100-1100)	<0.05
Du J	156 ± 112	339 ± 162	<0.001
C. Number of transfused patients			
Lin J	2	3	0.648
Li ZX	5	19	0.001
Lin JX	3	11	0.025
Chen QY	4	8	0.029
D. Conversion rates			
Li ZX	2.80%		
J. Cai D	3.28% (2)		
Scatizzi M	6.67% (2)		
Du J	0%		

Results

Descriptive assessment and study characteristics

Of the publications identified in the initial literature search, 12 trials (2 RCTs, 10 non-RCTs) were included in this analysis, published between 2010 and 2017 [13-24]. A total of 2732 participants (1402 in the LGD2 group and 1330 in the OGD2 group) were included in the study (Figure 1, Table 1). Ten studies were conducted in China, 1 in Korea and 1 in Italy. In the laparoscopic group, all procedures were laparoscopically-assisted. Out of the 2732 gastrectomies, 930 were total gastrectomies, 1714 were distal and 88 were proximal, almost equally distributed for either group (laparoscopic/open).

Clinicopathological characteristics

The mean age was 60.57 years for the LDG2 group and 60.23 years for the OGD2 group (Table 2). Eleven studies reported on the BMI status and all of them showed no significant difference between the two groups.

Two of the 9 trials which recorded the tumor size, demonstrated that this was statistically different between the laparoscopic and open group.

Of the patients that were included in this review no one had EGC. The maximum percentage of Ib disease was 33.4 %, while in 7 out of the 11 studies this percentage was <20%.

Study quality

The quality of all 10 non-RCTs was level 2 (6-9 stars) on the modified Newcastle-Ottawa scale and good for the RCTs according to the Jadad composite scale (Table 3).

Analysis of operative outcomes

Operative time was provided by all studies. Eight of them showed significantly longer operative time in the laparoscopic group [22, 14, 24, 15, 21, 17, 16, 19, 23], whereas in the largest study of Hu [13] the mean difference was 31 min.

Blood loss was reported in 10 studies. Nine of them revealed significantly lower blood loss in the laparoscopic group [23, 19, 16, 17, 25, 15, 24, 20, 14, 22]. The number of transfused patients was recorded in 4 studies, 3 of which showed a significant difference against the OGD2 group [26, 19, 17, 18].

Conversion rates were documented in 5 studies, ranging from 0 to 6.67%. The authors reported the following reasons for converting to open procedures: uncontrolled bleeding (n=2); overlarge tumor (n=1); lack of pneumoperitoneum (n=1); technical difficulties (n=1); hardly distinguished

posterior stomach wall from the pancreas (n=1); hard to dissect no. 7, 8 and 11 lymph nodes (n=1) [8, 19, 27, 28].

Table 4 summarizes the operative outcomes of the studies included in our analysis.

Analysis of post-operative outcomes

Duration of analgesic administration was reported in 4 articles included in this study. All showed a significantly shorter duration of analgesic use in the laparoscopic compared to the open group [7, 23, 19, 24].

The time to first ambulation was documented in 7 studies [23, 19, 16, 24, 20, 14, 22]. Only 2 of them revealed significant difference between the two groups, with the patients in the OGD2 group ambulating later compared to the LGD2.

The time to first flatus was reported in 9 studies [23, 19, 16, 17, 29, 24, 20, 14, 22]. All but 3 showed significantly shorter time in the LGD2 than in the OGD2 group.

The time to first oral intake was found in 7 papers [23, 19, 16, 17, 20, 14, 22]. Five of them demonstrated a significantly shorter time in the LGD2 group than in the OGD2 patients.

The length of postoperative hospital stay was reported in 10 articles [7, 23, 19, 16, 17, 29, 15, 20, 14, 22]. Seven studies revealed significant advantage of the laparoscopic group over the open group. Furthermore, two of the remaining 3 studies showed no statistical difference between the two groups when complications occurred postoperatively, but a significant advantage of the LAGD2 group when the postoperative course was uncomplicated.

The postoperative morbidity rates were reported in 11 studies and none revealed a significant difference between the two groups [7, 23, 19, 16, 17, 29, 15, 24, 20, 14, 22]. However, the subgroup analyses in 4 of the trials demonstrated significantly lower incidence rates of nonsurgical (cardiovascular, pulmonary) complications after LADG2.

Table 5. Postoperative outcomes of the studies included in our analysis

First author	*LADG2*	*ODG2*	*p*
A. Duration of analgesic administration (days)			
Lin JX	3.1 ± 1.2	5.8 ± 2.0	0.006
Scatizzi M	3 (1-10)	4.5 (3-11)	0.048
Shuang J	3 (0-5)	4 (1-6)	<0.01
Du J	1.3 ± 1.2	3.8 ± 1.4	<0.001
B. Time to first ambulation (days)			
Lin J	2.7 ± 1.0	2.8 ± 1.1	0.458
Cai J	4.2 ± 1.5	5.0 ± 1.1	0.014
Lin JX	2.6 ± 1.1	2.7 ± 1.1	0.577
Chen QY	2.7 ± 1.2	2.9 ± 1.2	0.099
J. Cai D	4.78 ± 2.09	4.89 ± 1.54	<0.753
Scatizzi M	1 (0-3)	1 (1-5)	0.659
Du J	2.4 ± 1.1	4.9 ± 1.4	<0.001
C. Time to first flatus (days)			
Lin J	2.6 ± 1.1	3.7 ± 1.1	0.028
Cai J	3.9 ± 1.5	4.3 ± 1.1	0.118
Li ZX	3.4 ± 0.9	5.0 ± 1.4	0.000
Lin JX	2.9 ± 1.2	2.9 ± 1.2	0.038
Chen QY	2.6 ± 1.1	3.2 ± 1.1	0.001
Kim KH	3.2 ± 0.9	3.7 ± 0.9	<0.0001
J. Cai D	3.89 ± 1.65	4.21 ± 1.25	0.293
Scatizzi M	2 (1-4)	3 (2-5)	0.036
Du J	3.5 ± 0.8	5.3 ± 1.3	<0.001

NA: not available

Continued on the next page

First author	*LADG2*	*ODG2*	*p*
D. Time to first oral intake (days)			
Lin J	4.2 ± 1.5	5.5 ± 2.3	0.031
Cai J	7.0 ± 1.7	7.2 ± 2.0	0.692
Li ZX	7.3 ± 1.3	8.1 ± 1.4	0.031
Lin JX	4.1 ± 1.5	5.5 ± 2.3	0.041
Chen QY	4.7 ± 1.5	5.1 ± 1.8	0.034
J. Cai D	6.85 ± 1.81	6.47 ± 1.67	<0.277
Scatizzi M	3 (1-5)	4 (1-10)	0.020
E. Length of postoperative hospital stay (days)			
Fang C	12 (5-36)	18 (7-45)	<0.01
Lin J	14.2 ± 6.9	18.1 ± 5.3	0.012
Cai J	12.2 ± 3.3	11.8 ± 2.2	0.463
Li ZX	12.8 ± 6.9	14.5 ± 3.1	0.001
Lin JX	14.2 ± 7.2	17.2 ± 5.0	0.001
Chen QY	13.3 ± 5.7	17.4 ± 5.0	0.001
Kim KH	uncomplicated 7.0 ± 1.3	uncomplicated 10.4 ± 7.1	<0.0001
	complicated 9.5 ± 14.7	complicated 10.3 ± 6.9	0.618
J. Cai D	11.63 ± 2.95	11.43 ± 1.17	0.65
Scatizzi M	7 (6-50)	9 (6-23)	0.029
Shuang J	12 (5-36)	17 (8-45)	<0.01
F. Postoperative morbidity			
Fang C	6.9%	5.7%	NA
Lin J	12.1%	15.5%	0.744
Cai J	14.6%	23.3%	0314
Li ZX	non-surgical complications 14.2%	non-surgical complications 24.8%	0.029
	surgical complications NSD	surgical complications NSD	NA
Lin JX	12%	14.4%	0.819
Chen QY	11.1%	15.3%	0.266
Kim KH	8%	8%	0.605
J. Cai D	non-surgical complications 4.1%	non-surgical complications 17.0%	0.038
	surgical complications 12.24 %	surgical complications 19.15%	0.357
Scatizzi M	non-surgical complications 0%	non-surgical complications 20%	0.048
	surgical complications 6.67%	surgical complications 6.67%	1.0
Shuang J	5.7%	8.6%	NA
Du J	9.8%	24.5%	0.214
G. Postoperative in-hospital mortality			
Fang C	0%	0%	
Lin J	0%	1.7%	1.000
Cai J	0%	0%	
Li ZX	0%	0%	
Lin JX	1.2%	2.4	1.000
Chen QY	0.9%	1.8%	0.859
Kim KH	0%	0%	
Du J	0%	2.1%	NA

NA: not available

No difference in the incidence rate of major surgical site complications, such as anastomosis stenosis, anastomotic leakage, duodenal stump leakage, pancreatic fistula, pancreatitis and intra-abdominal bleeding, was found between the two groups except for the study by Hu et al. which demonstrated 1.9% anastomotic leakage in the laparoscopic group versus 0.6% in the open group [13].

The postoperative in-hospital mortality rates were reported in 8 studies with no significant difference in the rate between the LGD2 and OGD2 groups [19, 16, 17, 21, 15, 24, 20, 14].

Table 5 summarizes the postoperative outcomes of the studies included in our analysis.

Analysis of oncologic outcomes

The number of lymph nodes harvested was reported in 10 studies with no difference between the two groups [7, 23, 19, 16, 17, 21, 24, 20, 14, 22].

Tumor recurrence was documented in 4 studies, which all demonstrated no significant difference [16, 29, 15, 24].

One study of 176 patients provided 5-year disease-free survival rates [21] and another one with

Table 6. Oncologic outcomes of the studies included to our analysis

First author	*LADG2*	*ODG2*	*p*
A. Number of harvested lymph nodes			
Lin J	30.8 ± 10.6	29.0 ± 8.3	0.114
Cai J	23.3 ± 2.9	22.3 ± 1.5	0.051
Li ZX	29.1 ± 6.1	30.2 ± 7.0	0.100
Lin JX	30.2 ± 10.1	28.0 ± 8.1	0.103
Chen QY	30.6 ± 10.1	30.3 ± 8.6	0.786
Kim KH	38.3	41.8	NA
J. Cai D	22.98 ± 2.70	22.87 ± 2.43	0.839
Scatizzi M	31 (16-60)	37 (8-89)	0.174
Shuang J	35 (7-63)	38 (6-66)	NA
Du J	34.2 ± 13.5	36.4 ± 19.1	0.331
B. Tumor recurrence			
Fang C	41.4%	51.7%	NA
Lin J	NSD	NSD	NA
Kim KH	17.1%	14.8%	0.837
Du J	23.2%	24.5%	NA

C. Disease free survival rates

	5-year			*44-month*		
	LADG2	*ODG2*	*p*	*LADG2*	*ODG2*	*p*
Fang C				59%	48%	0.205
Kim KH	84.6%	81.1%	0.415			

D. Overall survival rates

	5-year			*3-year*			*2-year*		
	LADG2	*ODG2*	*p*	*LADG2*	*ODG2*	*p*	*LADG2*	*ODGG2*	*p*
Cai J							58.5%	60.5%	NA
Kim KH	85.9%	83.1%	0.463						
J. Cai D				67.1%	53.8%	0.911			
Scatizzi M				70.91%	56.77%	0.449			

	44-month			*15-month*		
	LADG2	*ODG2*	*p*	*LADG2*	*ODG2*	*p*
Fang C	59%	54%	0.525			
Li ZX				100%	99.3%	>0.05

NA: not available

174 patients provided disease-free survival rates during a mean follow-up of 44 months. The study showed no significant difference between the two groups [15].

One trial involving 176 patients provided 5-year overall survival rates [30] and 2 trials with 156 patients provided 3-year overall survival rate [14,23]. Three further studies including 174, 84 and 239 patients with 44, 24 and 15 months follow-up respectively, provided overall survival rates [17,15,14]. None of these studies demonstrated significant differences between the two groups regarding the overall survival rates.

Table 6 summarizes the oncologic outcomes of the studies included in our analysis.

Discussion

Nowadays LDG has gained popularity for the treatment of gastric cancer mainly due to the clinical benefits over conventional, open surgery such as less blood loss, less postoperative pain, accelerated recovery, shorter hospital stay, reduced postoperative morbidity [31,32,29,30,33-35]. LADG with limited lymphadenectomy (D1 or D1+) has been adopted worldwide as the mainstay of treatment in patients with AGC. Furthermore, with the development of the laparoscopic instruments and techniques in complex gastric surgery, an increasing percentage of surgeons prefer to perform total gastrectomy laparoscopically [31,36,37]. Nevertheless, debate on the oncological safety and postoperative outcomes render the use of LGD2 for AGC still debatable taken also into consideration the difficulty of D2 lymph node dissection. Therefore, in this systematic review we sought to assess the value of LAGD2 for AGC. In order to achieve more accurate results regarding the survival rates we only included studies that had no AGC cases and a maximum proportion of 33.3% of stage Ib disease.

Our literature review identified 2 RCT and 10 non-RCTs that met our criteria. No significant difference in regards to the baseline characteristics - such as age, BMI and tumor size- were found between the two groups, indicating that the two groups were comparable. Our results suggest that despite LGD2 being a technically demanding and time-consuming procedure with longer operative times and acceptable conversion rates, it can be used to achieve short- and long-term prognosis.

Indeed, the comparison between LGD2 and OGD2 revealed similar numbers of harvested lymph nodes, tumor recurrence, disease-free and overall survival rates. Moreover, LGD2 provides better short-term prognoses with lower postoperative pain, faster recovery and shorter hospital stay. There was also a lower postoperative non-surgical related morbidity associated with LDG2.

The main reasons for long operative times in LGD2 are the long learning curve, time for setting up the laparoscopic equipment, lack of tactile sensation, the extent of lymphadenectomy and the postresectional gastrointestinal tract reconstruction. Longer procedures are associated with prolonged anesthesia and pneumoperitoneum, which may have a negative impact on the mortality and morbidity rates, especially in elderly patients with comorbidities [38].

In estimating the oncological safety and efficacy of LGD2, the number of lymph nodes is fundamental [39]. Cancer recurrence and long-term survival rates are of critical importance when evaluating such interventions in oncological therapy. Laparoscopic surgeons must overcome the complexity of the technique and focus on the adequacy of the D2 lymph node dissection in order to fulfill the aspects of an oncologically safe D2 operation [40,41]. Indeed, the majority of clinical studies correlate the quality of the procedure taking into account the number of the lymph nodes in both LADG and ODG. An accepted D2 lymph node dissection should be considered the harvesting of a minimum of 15 lymph nodes for pathologic examination, but usually an average of 25 nodes is harvested.

In our review, most studies were conducted in eastern countries due to the preference of the majority of the Asian surgeons to perform D2 dissection. It has to be noted that baseline characteristics of patients across the world differ significantly with Asian patients generally being younger, thinner and healthier compared with the corresponding patients from Western countries [42]. These may play a significant role in the associated postoperative outcomes in favor of open gastrectomy in Asian patients compared to the Western population [43-45].

It is widely accepted that at least 30 cases of LADG with D1 resection are needed in order for a surgeon to overcome the learning curve [25,28,46]. Yoo et al. [47] concluded that after completing 50 LADG cases, the operative time shortened, but without analogous reduction in complications. It is true that laparoscopic D2 surgery is considered much more difficult for less experienced surgeons, especially when dealing with major vascular structures. Thus, LGD2 is generally not recommended in low-volume centers. The relationship of surgical experience and patient safety is well-documented with some studies indicating a high frequency of postoperative complications mainly in the very early learning period [26,27]. Indeed, training for

laparoscopic second-tier lymph node dissection under a two-dimensional video is demanding in terms of selecting a reasonable surgical approach and achieving *en bloc* resection [46,48].

The present study has several limitations. First, a meta-analysis was not performed, due to the heterogeneity of the included studies, thus limiting the results in narratively describing the findings of individual studies. Second, all but one of the included trials were observational. Third, most of the included studies were conducted at tertiary centers and major institutions in East Asia (10 in China, 1 Korea and 1 in Italy). Hence, the results of the studies may not be representative of the general population.

In conclusion, although LGD2 is a technically demanding and time-consuming procedure, evidence shows that it may be an acceptable alternative to OGD2 for locally AGC with comparable oncologic outcomes. More clinical trials are needed to confirm the advantages of LGD2, in terms of perioperative morbidity and long-term survival.

Conflict of interests

The authors declare no conflict of interests.

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