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META-ANALYSIS

Systematic review and meta-analysis of laparoscopy-assisted and open total gastrectomy for gastric cancer

Ke Chen, Xiao-Wu Xu, Ren-Chao Zhang, Yu Pan, Di Wu, Yi-Ping Mou

Ke Chen, Xiao-Wu Xu, Ren-Chao Zhang, Yu Pan, Di Wu, Yi-Ping Mou, Department of General Surgery, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou 310016, Zhejiang Province, China
Author contributions: Chen K and Xu XW wrote the manuscript; Zhang RC, Pan Y and Wu D collected literatures and conducted the analysis of pooled data; Mou YP proofread and revised the manuscript; all authors have approved the version to be published.
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Correspondence to: Yi-Ping Mou, MD, PhD, Professor, Department of General Surgery, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, 3 East Qingchun Road, Hangzhou 310016, Zhejiang Province, China. mouyiping2002@163.com
Telephone: +86-571-86006445 Fax: +86-571-86044817
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Abstract

AIM: To evaluate the safety and efficacy of laparoscopy-assisted total gastrectomy (LATG) and open total gastrectomy (OTG) for gastric cancer.

METHODS: A comprehensive search of PubMed, Cochrane Library, Web of Science and BIOSIS Previews was performed to identify studies that compared LATG and OTG. The following factors were checked: operating time, blood loss, harvested lymph nodes, flatus time, hospital stay, mortality and morbidity. Data synthesis and statistical analysis were carried out using RevMan 5.1 software.

RESULTS: Nine studies with 1221 participants were included (436 LATG and 785 OTG). Compared to OTG, LATG involved a longer operating time [weighted mean difference (WMD) = 57.68 min, 95%CI: 30.48-84.88; $P < 0.001$]; less blood loss [standard mean difference (SMD) = -1.71; 95%CI: -2.48 - -0.49; $P < 0.001$]; earlier time to flatus (WMD= -0.76 d; 95%CI: -1.22 - -0.30; $P < 0.001$); shorter hospital stay (WMD = -2.67 d; 95%CI: -3.96 - -1.38, $P < 0.001$); and a decrease in medical complications (RR = 0.41, 95%CI: 0.19-0.90, $P = 0.03$). The number of harvested lymph nodes, mortality, surgical complications, cancer recurrence rate and long-term survival rate of patients undergoing LATG were similar to those in patients undergoing OTG.

CONCLUSION: Despite a longer operation, LATG can be performed safely in experienced surgical centers with a shorter hospital stay and fewer complications than open surgery.

Key words: Laparoscopy; Total gastrectomy; Gastric cancer; Complications; Meta-analysis

Core tip: This study evaluated the safety and efficacy of laparoscopy-assisted total gastrectomy (LATG) and open total gastrectomy (OTG) for gastric cancer through systematic review and meta-analysis. The existing research shows that LATG is safe and feasible, which can achieve similar lymph node dissection effects as OTG, characterized by such advantages as less pain, fewer postoperative complications, and rapid recovery, and which is expected to achieve the same effect in oncological treatment as OTG.

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INTRODUCTION

Since it was first reported in 1994[1], laparoscopy-assisted distal gastrectomy (LADG) for gastric cancer has undergone rapid development and gained popularity in the past 20 years. Compared to traditional open gastrectomy, most studies have reported that LADG can achieve better cosmesis, shorter hospital stay, faster postoperative recovery, and better postoperative quality of life[2-6]. However, laparoscopy-assisted total gastrectomy (LATG) is technically demanding and the incidence of upper gastric carcinoma is relatively low in East Asia[7,8]. Therefore, although LADG has been accepted worldwide for tumors located in the lower stomach, LATG for upper and middle gastric cancer has not been generalized. In fact, there are only a few reports on the technical feasibility and safety of LATG and its long-term oncologic outcomes[9-12]. Although several meta-analyses and systematic reviews have been published for LADG[13-19], such studies have not been conducted for the potential benefits and disadvantages of LATG.

In order to assess accurately the current status of LATG, we strictly limited inclusion criteria by focusing exclusively on LATG and carried out a comprehensive meta-analysis. We believe that such research will contribute to a more systematic and objective evaluation of the safety of the LATG in cancer treatment.

MATERIALS AND METHODS

Search strategy

We searched PubMed, Cochrane Library, Web of Science and BIOSIS Previews for literature comparing LATG and open total gastrectomy (OTG) published between January 1995 and March 2013, and broadened the search range by browsing the related summary, methods, and references of retrieved articles. The following keywords were used: "laparoscopy", "laparoscopic", "gastric cancer", "gastric carcinoma", and "gastrectomy". The language of the publications was confined to English. Two investigators reviewed the titles and abstracts, and assessed the full text to establish eligibility.

Inclusion and exclusion criteria

All clinical studies should meet the following criteria for the meta-analysis: (1) published in English with data comparing LATG and OTG; (2) clear case selection criteria, containing at least the following information: the number of cases, surgical methods and perioperative data; and (3) if there was overlap between authors or centers, the higher quality or more recent literature were selected. However, articles from the same authors or centers but with different patient cohorts were included. The papers containing any of the following were excluded: (1) totally laparoscopic, laparoscopic hand-assisted, or robot-assisted gastrectomy; (2) non-gastric carcinoma cases; (3) palliative resection cases; and (4) extent of lymphadenectomy was not required for grouping in this study, but the articles with significant differences between the two groups in the extent of lymphadenectomy were excluded.

Data extraction and quality assessment

Two authors independently extracted the data using a unified datasheet, and decided upon the controversial issues through discussion. Extracted data included: author, study period, geographical region, number of patients, operating time, blood loss, number of retrieved lymph nodes, proximal and distal margin distance, time to flatus, time to oral intake, length of hospital stay, morbidity and mortality. Postoperative complications were classified as medical (cardiovascular, respiratory, or metabolic events; nonsurgical infections; deep venous thrombosis; and pulmonary embolism) or surgical (any anastomotic leakage or fistula, any complication that required reoperation, intra-abdominal collections, wound complications, bleeding events, pancreatitis, ileus, delayed gastric emptying, and anastomotic stricture). This classification system is based on the Memorial Sloan-Kettering Cancer Center complication reporting system[20]. If necessary, the first authors were contacted to retrieve further information. Selected documents were rated according to the grading of the Centre of Evidence-Based Medicine (CEBM, Oxford, United Kingdom; http://www.cebm.net), which, in brief, assigns level 1 to randomised controlled trials (RCTs), level 2 to cohort studies, level 3 to case-control studies, level 4 to case series or poor quality observational study and level 5 to expert opinion.

Statistical analysis

The meta-analysis was performed in line with recommendations from the Cochrane Collaboration and the Quality of Reporting of Meta-Analyses guidelines[21,22]. Continuous variables, when both means and standard deviations were presented, were assessed using weighted mean difference (WMD) or standard mean difference (SMD), the postoperative morbidity and mortality were analyzed using the risk ratio (RR), and the risk difference (RD) was used to evaluate cancer recurrence because there may be no recurrence events in either groups during follow-up. When heterogeneity test showed no significant differences ($P > 0.05$), we used a fixed-effects model to calculate the summary statistics. When the heterogeneity test showed statistically significant differences ($P < 0.05$), we used a random effects model based on the DerSimonian and Laird method. Subgroup analysis of intraoperative outcomes, such as operating time, blood loss, and number of retrieved lymph nodes, was conducted for the number of LATG cases performed (40 cases were used as a cut-point), because the learning curve may have an impact on the operative outcomes. Potential publication bias was determined by conducting informal visual inspection of funnel plots based on the complications. Data analyses were performed using Review Manage Version 5.1 (RevMan 5.1) software downloaded from Cochrane Library. $P < 0.05$ was considered statistically significant.

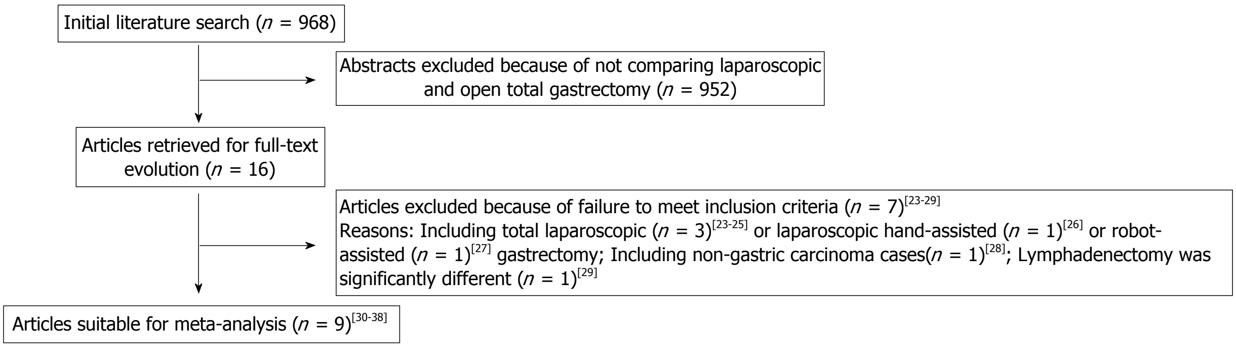


Figure 1 Flow chart of literature search strategies.

Table 1 Characteristics of included studies

Ref.	Nation	Study type	Study period	Sample size		Stage	Level of lymphadenectomy	Follow-up (mo)		Level of evidence
				LATG	OTG			LATG	OTG	
Kim *et al*[30]	South Korea	Retro	2004-2006	27	33	EC + AC	D1 + α/β, D2	NR	NR	2b
Mochiki *et al*[31]	Japan	Retro	1999-2007	20	18	EC + AC	D1 + β	31 (3-60)	46 (13-60)	2b
Sakuramoto *et al*[32]	Japan	Retro	2003-2007	30	44	EC + AC	D1 + β, D2	30		4
Kawamura *et al*[33]	Japan	Retro	2003-2008	46	35	EC	D2	NR	NR	4
Du *et al*[34]	China	Retro	2005-2009	82	94	AC	D2	25 (2-44)		2b
Kim *et al*[35]	South Korea	Pros	2009-2010	63	127	EC + AC	D2	NR	NR	2b
Kunisaki *et al*[36]	Japan	Pros	2002-2008	27	30	EC + AC	D1 + β	NR	NR	3b
Eom *et al*[37]	Korea	Retro	2003-2008	100	348	EC + AC	D2	52.6 (0.3-95.7)		4
Guan *et al*[38]	China	Pros	2007-2010	41	56	EC + AC	D2	NR	NR	3b

Retro: Retrospective observational study; Pros: Prospective observational study; EC: Early gastric cancer; AC: Advanced gastric cancer; NR: Not reported; LATG: Laparoscopy-assisted total gastrectomy; OTG: Open total gastrectomy.

RESULTS

Studies selected

The initial search strategy retrieved 968 publications in English. After the titles and abstracts were reviewed, papers without comparison of LATG and OTG were excluded, which left 16 comparative studies, seven[23-29] of which did not meet the inclusion criteria and were excluded. This left a total of nine comparative observational studies[30-38]. A flow chart of the search strategies is illustrated in Figure 1.

Study characteristics and quality

A total of 1221 patients were included in the analysis with 436 undergoing LATG (35.7%) and 785 undergoing OTG (64.3%). Only one study reported a case converted to open surgery because of extensive abdominal adhesions[38]. Regarding the tumor stage, only one study was limited to early stage cancer[33]. In another study, only patients with advanced gastric cancer were described[34]. The other seven studies included both populations. All studies had Asian data from Japan, South Korea and China. In the included studies, four studies was considered as level of evidence 2b, two studies as level of evidence 3b, and the remaining three as level of evidence 4 (according to the grading of the CEBM). The characteristics and methodological quality assessment scores of the included studies are shown in Table 1.

Intraoperative effects

Most of the studies considered suitable for the meta-analysis reported a longer operating time for LATG than for OTG. The mean operating time of LATG was 57.68 min longer than for OTG (WMD = 57.68 min; 95%CI: 30.48-84.88, P < 0.001) (Figure 2A). Two studies[31,32] used grams but the others[33-36,38] used milliliters as the unit of measurement for intraoperative blood loss, therefore, SMD was used to synthesize the data. The intraoperative blood loss was lower in LATG than OTG (SMD = -1.71; 95%CI: -2.48 - -0.94, P < 0.001) (Figure 2B). All studies contained the number of retrieved lymph nodes. The difference in the mean number of retrieved lymph nodes between LATG and OTG was not significant in the pooled data (WMD = -1.41; 95%CI: -3.15 - 0.32, P = 0.11) (Figure 2C). Two studies described the proximal and distal margin distances[35,38]. Meta-analysis of the distal margin distance showed no significant difference between the two groups (WMD = 0.46 cm; 95%CI: -0.40 - 1.32, P = 0.29). However, the proximal margin distance of OTG was longer than that of LATG with a marginal difference (WMD = -0.40 cm; 95%CI: -0.82 - 0.02, P = 0.06). All intraoperative effect outcomes are summarized in Table 2.

Subgroup analysis for learning curve

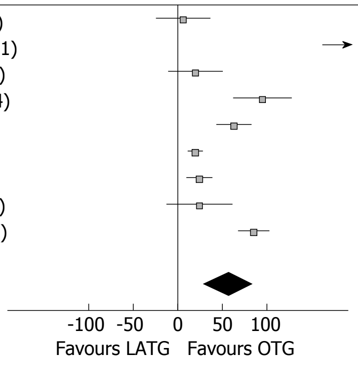
The overall effects of operating time and blood loss remained unchanged in subgroups, although performing

A

Study or subgroup	LATG Mean	LATG SD	LATG Total	OTG Mean	OTG SD	OTG Total	Weight	Mean difference IV, random, 95%CI
Mochiki *et al*[31]	254	44.7	20	248	50.9	18	10.8%	6.00 (-24.61, 36.61)
Kim *et al*[30]	527.5	95.7	27	320.9	75.8	33	9.4%	206.60 (162.19, 251.01)
Kawamura *et al*[33]	291.9	59.4	46	272.1	76.8	35	10.8%	19.80 (-10.89, 50.49)
Sakuramoto *et al*[32]	313	81	30	218	53	44	10.6%	95.00 (62.06, 127.94)
Du *et al*[34]	275	78	82	212	51	94	11.8%	63.00 (43.22, 82.78)
Kim *et al*[35]	150.8	31.2	63	131.2	21.6	127	12.4%	19.60 (11.03, 28.17)
Guan *et al*[38]	235.7	38.5	41	211.5	33.2	56	12.1%	24.20 (9.55, 38.85)
Kunisaki *et al*[36]	286.4	68	27	262.1	74.9	30	10.2%	24.30 (-12.80, 61.40)
Eom *et al*[37]	283.7	84.1	100	198.5	59.7	348	11.9%	85.20 (67.56, 102.84)
Total (95%CI)			436			785	100.0%	57.68 (30.48, 84.88)

Heterogeneity: Tau² = 1535.02; χ^2 = 127.63, *df* = 8 (P < 0.00001); I^2 = 94%

Test for overall effect: Z = 4.16 (P < 0.0001)

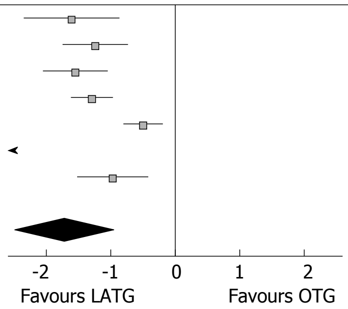


B

Study or subgroup	LATG Mean	LATG SD	LATG Total	OTG Mean	OTG SD	OTG Total	Weight	Mean difference IV, random, 95%CI
Mochiki *et al*[31]	299	223.6	20	758	330.9	18	13.5%	-1.61 (-2.35, -0.87)
Sakuramoto *et al*[32]	134	98	30	407	270	44	14.5%	-1.24 (-1.75, -0.73)
Kawamura *et al*[33]	54.9	45.3	46	304.3	237.3	35	14.5%	-1.55 (-2.05, -1.05)
Du *et al*[34]	156	112	82	339	162	94	15.1%	-1.29 (-1.62, -0.97)
Kim *et al*[35]	179.7	123.8	63	272.7	209.6	127	15.1%	-0.50 (-0.80, -0.19)
Guan *et al*[38]	104.2	42.9	41	355.6	51.3	56	13.0%	-5.20 (-6.05, -4.35)
Kunisaki *et al*[36]	155	138.8	27	422.4	350.4	30	14.3%	-0.97 (-1.52, -0.42)
Total (95%CI)			309			404	100.0%	-1.71 (-2.48, -0.94)

Heterogeneity: Tau² = 0.99; χ^2 = 109.49, *df* = 6 (P < 0.00001); I^2 = 95%

Test for overall effect: Z = 4.36 (P < 0.0001)

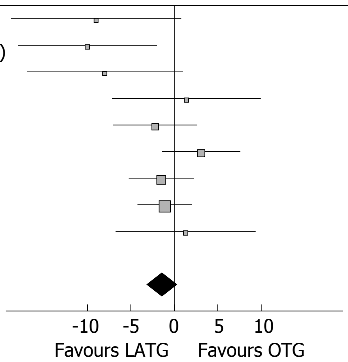


C

Study or subgroup	LATG Mean	LATG SD	LATG Total	OTG Mean	OTG SD	OTG Total	Weight	Mean difference IV, fixed, 95%CI
Mochiki *et al*[31]	26	13.4	20	35	17	18	3.1%	-9.00 (-18.81, 0.81)
Kim *et al*[30]	27.2	15.7	27	37.2	15.7	33	4.7%	-10.00 (-17.99, -2.01)
Sakuramoto *et al*[32]	43.2	17.2	30	51.2	22.1	44	3.7%	-8.00 (-16.97, 0.97)
Kawamura *et al*[33]	48.5	16.3	46	47.1	21.5	35	4.1%	1.40 (-7.14, 9.94)
Du *et al*[34]	34.2	13.5	82	36.4	19.1	94	12.8%	-2.20 (-7.04, 2.64)
Kim *et al*[35]	38.7	15.7	63	35.6	13.1	127	14.9%	3.10 (-1.40, 7.60)
Eom *et al*[37]	48.3	16.4	100	49.8	18.4	348	21.4%	-1.50 (-5.25, 2.25)
Guan *et al*[38]	23.1	8	41	24.2	7.5	56	30.5%	-1.10 (-4.24, 2.04)
Kunisaki *et al*[36]	38.1	13.9	27	36.8	17.1	30	4.6%	1.30 (-6.76, 9.36)
Total (95%CI)			436			785	100.0%	-1.41 (-3.15, 0.32)

Heterogeneity: χ^2 = 13.67, *df* = 8 (P = 0.09); I^2 = 41%

Test for overall effect: Z = 1.60 (P = 0.11)

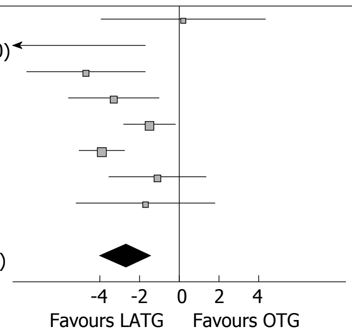


D

Study or subgroup	LATG Mean	LATG SD	LATG Total	OTG Mean	OTG SD	OTG Total	Weight	Mean difference IV, random, 95%CI
Kim *et al*[30]	16.2	7.1	27	16	9.3	33	7.1%	0.20 (-3.95, 4.35)
Mochiki *et al*[31]	19	13.4	20	29	12.7	18	2.2%	-10.00 (-18.30, -1.70)
Sakuramoto *et al*[32]	13.5	2.7	30	18.2	9.6	44	10.9%	-4.70 (-7.70, -1.70)
Kawamura *et al*[33]	15.5	3.3	46	18.8	6.3	35	14.5%	-3.30 (-5.59, -1.01)
Kim *et al*[35]	8.1	3.8	63	9.6	5.3	127	20.9%	-1.50 (-2.82, -0.18)
Guan *et al*[38]	9.7	2.2	41	13.6	3.6	56	21.9%	-3.90 (-5.06, -2.74)
Kunisaki *et al*[36]	14.5	3.5	27	15.6	5.8	30	13.5%	-1.10 (-3.56, 1.36)
Eom *et al*[37]	12.6	15.5	100	14.3	16.7	348	9.0%	-1.70 (-5.21, 1.81)
Total (95%CI)			354			691	100.0%	-2.67 (-3.96, -1.38)

Heterogeneity: Tau² = 1.63; χ^2 = 16.04, *df* = 7 (P = 0.02); I^2 = 56%

Test for overall effect: Z = 4.05 (P < 0.0001)

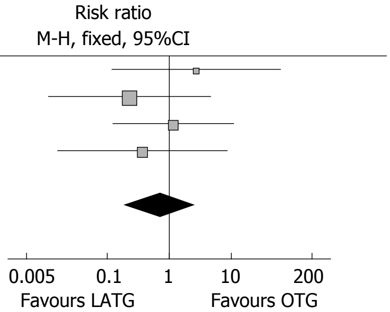


E

Study or subgroup	LATG Events	LATG Total	OTG Events	OTG Total	Weight	Risk ratio M-H, fixed, 95%CI
Mochiki *et al*[31]	1	20	0	18	9.3%	2.71 (0.12, 62.70)
Du *et al*[34]	0	82	2	94	41.5%	0.23 (0.01, 4.70)
Eom *et al*[37]	1	100	3	348	23.8%	1.16 (0.12, 11.03)
Kunisaki *et al*[36]	0	27	1	30	25.3%	0.37 (0.02, 8.69)
Total (95%CI)		229		490	100.0%	0.72 (0.20, 2.57)
Total events	2		6			

Heterogeneity: χ^2 = 1.58, *df* = 3 (*P* = 0.66); I^2 = 0%

Test for overall effect: *Z* = 0.51 (*P* = 0.61)

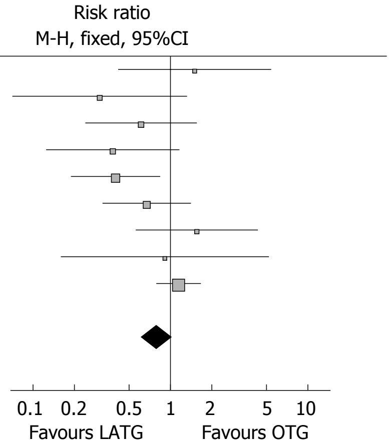


F

Study or subgroup	LATG Events	LATG Total	OTG Events	OTG Total	Weight	Risk ratio M-H, fixed, 95%CI
Mochiki *et al*[31]	5	20	3	18	2.9%	1.50 (0.42, 5.41)
Kim *et al*[30]	2	27	8	33	6.5%	0.31 (0.07, 1.32)
Sakuramoto *et al*[32]	5	30	12	44	8.8%	0.61 (0.24, 1.56)
Kawamura *et al*[33]	4	46	8	35	8.2%	0.38 (0.12, 1.16)
Du *et al*[34]	8	82	23	94	19.4%	0.40 (0.19, 0.84)
Kim *et al*[35]	8	63	24	127	14.4%	0.67 (0.32, 1.41)
Kunisaki *et al*[36]	7	27	5	30	4.3%	1.56 (0.56, 4.33)
Guan *et al*[38]	2	41	3	56	2.3%	0.91 (0.16, 5.20)
Eom *et al*[37]	27	100	82	348	33.2%	1.15 (0.79, 1.67)
Total (95%CI)		436		785	100.0%	0.79 (0.61, 1.02)
Total events	68		168			

Heterogeneity: χ^2 = 13.42, *df* = 8 (*P* = 0.10); I^2 = 40%

Test for overall effect: *Z* = 1.83 (*P* = 0.07)

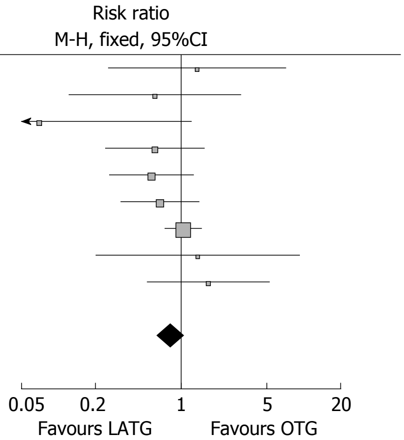


G

Study or subgroup	LATG Events	LATG Total	OTG Events	OTG Total	Weight	Risk ratio M-H, fixed, 95%CI
Mochiki *et al*[31]	3	20	2	18	2.1%	1.35 (0.25, 7.19)
Kim *et al*[30]	2	27	4	33	3.6%	0.61 (0.12, 3.09)
Kawamura *et al*[33]	0	46	5	35	6.2%	0.07 (0.00, 1.22)
Sakuramoto *et al*[32]	5	30	12	44	9.6%	0.61 (0.24, 1.56)
Du *et al*[34]	8	82	16	94	14.7%	0.57 (0.26, 1.27)
Kim *et al*[35]	8	63	24	127	15.7%	0.67 (0.32, 1.41)
Eom *et al*[37]	29	100	97	348	42.8%	1.04 (0.73, 1.48)
Guan *et al*[38]	2	41	2	56	1.7%	1.37 (0.20, 9.30)
Kunisaki *et al*[36]	6	27	4	30	3.7%	1.67 (0.53, 5.28)
Total (95%CI)		436		785	100.0%	0.83 (0.64, 1.08)
Total events	63		166			

Heterogeneity: χ^2 = 8.14, *df* = 8 (*P* = 0.42); I^2 = 2%

Test for overall effect: *Z* = 1.39 (*P* = 0.16)

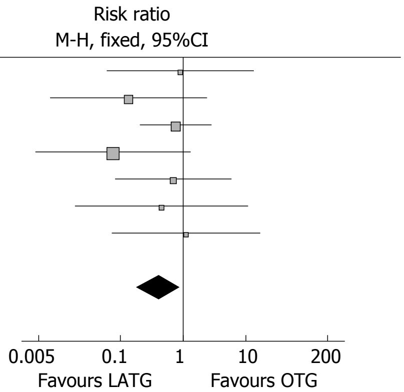


H

Study or subgroup	LATG Events	LATG Total	OTG Events	OTG Total	Weight	Risk ratio M-H, fixed, 95%CI
Mochiki *et al*[31]	1	20	1	18	5.0%	0.90 (0.06, 13.36)
Kim *et al*[30]	0	27	4	33	19.3%	0.13 (0.01, 2.40)
Kawamura *et al*[33]	4	46	4	35	21.5%	0.76 (0.20, 2.83)
Du *et al*[34]	0	82	7	94	33.1%	0.08 (0.00, 1.32)
Eom *et al*[37]	1	100	5	348	10.6%	0.70 (0.08, 5.89)
Guan *et al*[38]	0	41	1	56	6.0%	0.45 (0.02, 10.83)
Kunisaki *et al*[36]	1	27	1	30	4.5%	1.11 (0.07, 16.91)
Total (95%CI)		343		614	100.0%	0.41 (0.19, 0.90)
Total events	7		23			

Heterogeneity: χ^2 = 3.84, *df* = 6 (*P* = 0.70); I^2 = 0%

Test for overall effect: *Z* = 2.21 (*P* = 0.03)



I

Study or subgroup	LATG Events	LATG Total	OTG Events	OTG Total	Weight	Risk difference M-H, fixed, 95%CI
Mochiki *et al*[31]	1	20	1	18	11.1%	-0.01 (-0.15, 0.14)
Sakuramoto *et al*[32]	1	30	3	44	20.9%	-0.03 (-0.13, 0.06)
Du *et al*[34]	19	82	23	94	51.3%	-0.01 (-0.14, 0.11)
Kunisaki *et al*[36]	0	27	2	30	16.7%	-0.07 (-0.17, 0.04)
Total (95%CI)		159		186	100.0%	-0.03 (-0.10, 0.05)
Total events	21		29			

Heterogeneity: χ^2 = 0.71, *df* = 3 (*P* = 0.87); I^2 = 0%

Test for overall effect: *Z* = 0.70 (*P* = 0.49)

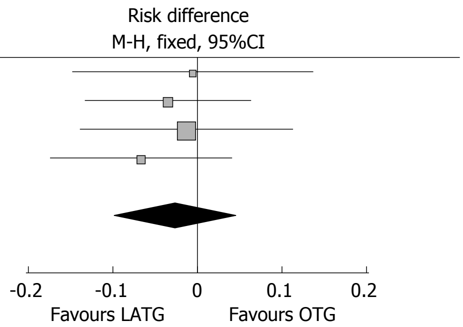


Figure 2 Meta-analysis. A: The pooled data: operating time; B: The pooled data: intraoperative blood loss; C The pooled data: number of retrieved lymph nodes; D: The pooled data: duration of hospital stay; E: The pooled data: mortality; F: The pooled data: overall postoperative complications; G: The pooled data: surgical complications; H: The pooled data: medical complications; I: The pooled data: recurrences.

Table 2 Results of meta-analysis

Outcome	No. of study	Sample size LATG	Sample size OTG	Heterogeneity (*P*, I^2)	Overall effect size	95%CI of overall effect	*P* value
Operating time (min)	9	436	785	< 0.001, 94%	WMD = 57.68	30.48-84.88	< 0.001
Blood loss	7	309	404	< 0.001, 95%	SMD = -1.71	-2.48 - -0.94	< 0.001
Retrieved lymph nodes	9	436	785	0.09, 41%	WMD = -1.41	-3.15 - 0.32	0.11
Proximal margin (cm)	2	163	475	1.00, 0%	WMD = -0.40	-0.82 - 0.02	0.06
Distal margin (cm)	2	163	475	0.67, 0%	WMD = 0.46	-0.40 - 1.32	0.29
Analgesics given	4	221	300	< 0.001, 93%	SMD = -0.86	-1.62 - -0.11	0.02
Duration of fever (d)	2	112	138	0.47, 0%	WMD = -1.58	-1.80 - -1.37	< 0.001
Time to first flatus (d)	7	316	419	< 0.001, 91%	WMD = -0.76	-1.22 - -0.30	0.001
Time to oral intake (d)	4	161	257	0.04, 63%	WMD = -0.81	-1.26 - -0.35	< 0.001
Hospital stay (d)	8	354	691	0.02, 56%	WMD = -2.67	-3.96 - -1.38	< 0.001
Overall complications	9	436	785	0.10, 40%	RR = 0.79	0.61-1.02	0.07
Surgical complications	9	436	785	0.42, 2%	RR = 0.83	0.64-1.08	0.16
Medical complications	7	343	614	0.70, 0%	RR = 0.41	0.19-0.90	0.03
Mortality	4	229	490	0.66, 0%	RR = 0.72	0.20-2.57	0.61

WMD: Weighted mean difference; SMD: Standard mean difference; LATG: Laparoscopy-assisted total gastrectomy; OTG: Open total gastrectomy.

> 40 LATG cases demonstrated a moderate reduction in operating time and blood loss. Lymph node retrieval was lower in the subgroup with < 40 LATG cases performed (WMD = -6.12; 95%CI: -10.42 - -1.81, *P* = 0.005). However, there was no difference when > 40 LATG procedures were performed (WMD = -0.50; 95%CI: -2.4 - 1.39, *P* = 0.60). The outcomes of subgroup analysis are summarized in Table 3.

Postoperative outcome

Flatus is one of the outcome measures for evaluating postoperative recovery of gastrointestinal functions. The mean time to first flatus was shorter in LATG than in OTG (WMD= -0.76 d; 95%CI: -1.22 - -0.30, *P* = 0.001), as was the time to restart oral intake after surgery (WMD = -0.81 d; 95%CI: -1.26 - -0.35, *P* < 0.001). Postoperative analgesic consumption was less in LATG than in OTG (SMD = -0.86; 95%CI: -1.62 - -0.11, *P* = 0.02). A shorter hospital stay was also observed in the LATG group (WMD = -2.67 d; 95%CI: -3.96 - -1.38, *P* < 0.001) (Figure 2D). All postoperative outcomes are summarized in Table 2.

Two studies reported inflammatory response index such as white blood cell (WBC) count and C-reactive protein (CRP)[32,33]. A significantly lower WBC count for LATG compared with OTG was found on postoperative days 1, 3, 7[32,33] and 10[33], and lower CRP for LATG was found on postoperative day 1 in both studies[32,33].

Mortality was described in four studies, and there was no significant difference in postoperative mortality (RR = 0.72, 95%CI: 0.20-2.57, *P* = 0.61) (Figure 2E). Morbidity was addressed and specified in all studies with exception of Kunisaki's study[36]. We contacted the authors of this study to get information about the specific complications. The rate of overall postoperative complications was lower for LATG with a marginal difference (RR = 0.79, 95%CI: 0.61-1.02, *P* = 0.07) (Figure 2F). Visual inspection of the funnel plot revealed symmetry, indicating no serious publication bias (Figure 3). After further analysis, surgical complications were similar between the two groups (RR = 0.83, 95%CI: 0.64-1.08, *P* = 0.16) (Figure 2G), without the exception of any specific complications such as anastomotic leakage, intra-abdominal collections, bleeding, or anastomotic stricture. LATG was associated, however, with a significant reduction in medical complications (RR = 0.41, 95%CI: 0.19-0.90, *P* = 0.03) (Figure 2H) with a

Table 3 Subgroup analysis for learning curve using a cut-point of 40 laparoscopy-assisted total gastrectomy cases

Outcome	No. of study	Sample size LATG	Sample size OTG	Heterogeneity (P, I^2)	Overall effect size	95%CI of overall effect	P value
Operating time (min)							
< 40 LATG cases	4	104	125	< 0.001, 95%	WMD = 81.99	1.47-162.5	0.05
> 40 LATG cases	5	332	660	< 0.001, 93%	WMD = 42.53	16.23-68.82	0.002
Blood loss							
< 40 LATG cases	3	77	92	0.40, 0%	SMD = -1.22	-1.55 - -0.88	< 0.001
> 40 LATG cases	4	232	312	< 0.001, 97%	SMD = -2.07	-3.35 - -0.79	0.002
Retrieved lymph nodes							
< 40 LATG cases	4	104	125	0.20, 36%	WMD = -6.12	-10.42 - -1.81	0.005
> 40 LATG cases	5	332	660	0.47, 0%	WMD = -0.50	-2.4 - 1.39	0.60

LATG: Laparoscopy-assisted total gastrectomy; OTG: Open total gastrectomy; WMD: Weighted mean difference; SMD: Standard mean difference.

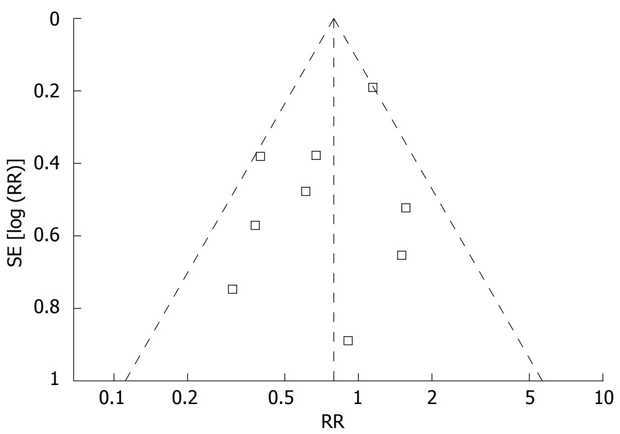


Figure 3 Funnel plot of the overall postoperative complications.

possible contribution from respiratory complications (RR = 0.34, 95%CI: 0.11-1.03, P = 0.06). The outcomes of mortality and morbidity are summarized in Table 2.

Recurrence and long-term survival rate

During the follow-up period, cancer recurrence was observed in four studies[31,32,34,36]. The recurrence risk in LATG was 13.2% (21/159) and 15.6% (29/186) in OTG, but the difference between LATG and OTG was not significant (RD = -0.03, 95%CI: -0.10-0.05, P = 0.49) (Figure 2I).

Three trials reported the long-term survival rate[31,36,37]. Mochiki *et al*[31] have reported that there was no significant difference in the cumulative or disease-specific 5-year survival rates between LATG and OTG (cumulative: 95% in LATG, 90.9% in OTG; disease-specific: 100% in LATG, 91.7% in OTG, P = 0.81). Eom *et al*[37] have reported that the survival rates were similar between groups; the hazard ratio of LATG *vs* OTG was 0.43 (95%CI: 0.15-1.20; P = 0.107) for overall survival and 0.47 (95%CI: 0.19-1.18; P = 0.106) for disease-free survival. Kunisaki *et al*[36] also have reported that there was no significant differences in overall and disease-specific survival between groups.

DISCUSSION

RCTs are the most ideal tools for meta-analysis. However, no RCTs on LATG have yet been conducted because the history and popularity of LATG are insufficient compared with LADG, due to the fact that it is difficult to dissect splenic hilar lymph nodes and mobilize the esophagus under a laparoscope, while it is demanding to perform Roux-en-Y esophagojejunostomy through mini-laparotomy. Thus, our meta-analysis synthesized the existing observational studies with strictly limiting inclusion and exclusion criteria. The included studies were primarily derived from the countries with the most widespread use of laparoscopic gastrectomy (four from Japan, three from Korea, and two from China), and all published in the past 5 years (2008-2012), and the total number of cases incorporated in the study was 1221. The meta-analysis conducted based on this point will contribute a more comprehensive and objective evaluation for the current LATG surgical status.

Similar to most reports comparing laparoscopic and open surgery in many different clinical situations, the intraoperative blooding in the LATG group was less than that in the OTG group, as is the need for transfusions. The reduced length of incision wound and the application of energy-dividing devices, such as the Harmonic Scalpel and Ligasure, contribute to the reduction in blood loss. Lack of blood is a common problem faced by many hospitals, especially in developing countries such as China. Therefore, less-invasive laparoscopic surgery can reduce the clinical requirement for blood and lower the rate of complications associated with blood transfusions such as virus infection and allergic reaction. In addition, some researchers have suggested that transfusions are associated with increased perioperative mortality and morbidity[39].

Regarding the operating time, LATG is more time-consuming than OTG. LATG combined with lymphadenectomy is a complex operation and needs a lot of technical expertise. Almost all of the studies included in this meta-analysis demonstrated prolonged operating time in LATG, despite significant heterogeneity. Learning curve which related to the surgeon's experience, familiarity with instruments, and assistant compliance could influence some outcomes studied, such as operating time or lymph node retrieval[40]. Because several of the researches included in this study reported on their initial experience, so we performed a subgroup analysis using 40 LATG cases as a cut-point and demonstrated a moderate reduction in LATG operating time. Another reason for the prolonged operating time for LATG may be related to the reconstructive step, which is more difficult to complete through minilaparotomy than open surgery because of the narrow operating window for manual suture or anvil insertion and application of other instruments, especially in obese patients. To overcome these potential problems, various modified techniques have been reported, such as laparoscopic purse-string suture technique using Endo Stitch (Covidien, Mansfield, MA, United States)[41], Endo-PSI (Hope Electronics Co., Ltd, Shenzhen, China)[42], or a hemi-double stapling technique[43]. Another two intracorporeal reconstruction methods may be most representative; one using a transorally inserted anvil (OrVil; Covidien) to make an end-to-side esophagojejunostomy[44], the other using linear staplers to make a side-to-side anastomosis[45]. These methods not only avoid auxiliary incision, but also help to simplify the procedure of reconstruction and shorten the operating time[46,47].

The inflammatory stress reaction is an inevitable outcome of operative trauma and is an important index for measuring its extent. Some studies have compared inflammatory cytokines such as interleukin (IL)-6, IL-10 and CRP in plasma of patients who have undergone laparoscopic or laparotomic resection for gastroenteric cancer. The postoperative level of IL-6, IL-10 and CRP increased but the levels in the laparoscopic group are significantly lower than in the laparotomic group[48-50]. A meta-analysis of laparoscopic colectomy has also demonstrated that the postoperative IL-6 level of laparotomic group patients was significantly lower than that of laparotomic group[51]. The studies included in this research show that the WBC count and CRP of patients in the LATG group were lower than those in the OTG group, and serum protein was higher[32,33], indicating that LATG imposes few inflammatory stimuli on patients and consumes less protein. Kawamura *et al*[33] have also found that postoperative blood glucose in OTG patients is significantly higher than that in LATG patients when the same amount of calories was ingested, indicating that LATG has a lower effect on sugar metabolism.

The most striking finding was a reduced number of complications in the LATG *vs* OTG group, which may have resulted from a reduction in medical complications. It was conceivable that surgical complications were similar between groups because LATG results in the same organ and lymphatic resection as OTG. However, it is worth noting that some studies have found that there is a high risk of anastomotic stricture after LATG[10,52], whereas our study found morbidity associated with anastomotic stricture was similar between the two groups. Prevention of anastomotic stricture has long been one of the main tasks in total gastrectomy and also should not be ignored in LATG. Some researchers hold that side-to-side esophagojejunostomy could be used to reduce the risk of anastomotic stricture because a larger anastomotic stoma can be made from it[45,53]. Besides, the significantly decreased medical complications could be explained by the reduced invasiveness of the laparoscopic technique and less postoperative pain. We also found that respiratory complications occurred in LATG less often than in OTG, although the difference was not significant (P = 0.06). The pain caused by large incision as well as the use of tension sutures and abdominal bandages after laparotomy can make it difficult for patients to cough, expectorate and perform exercise breathing effectively, thus leading to such complications as pulmonary infection[54]. Pain after surgery was less serious in LATG than in OTG due to the shorter duration or the lower dosage of analgesic application[32-35]. The time to first flatus was also earlier in LATG than in OTG, which indicated a rapid recovery of gastrointestinal function after LATG. Reduced use of analgesic drugs, shortened time of abdominal cavity exposure, alleviated inflammatory reactions, and earlier postoperative activities are considered to be the main reasons for earlier gastrointestinal recovery from LATG; all of which may also contribute to shortening the duration of postoperative hospital stay.

The adequacy of the radical resection should be evaluated by the extent of lymph node dissection performed and the number of harvested lymph nodes, as well as the length of the resection margins. We found that fewer lymph nodes were obtained after LATG than in OTG, even though the difference was not significant. However, the subgroup analysis with 40 cases in LATG showed that the difference was shrinking. The number of laparoscopic lymph nodes dissected was closely related to the level of surgical technique. In recent years, with increasingly mature techniques, some researchers have reported not only a similar number of overall retrieved lymph nodes between LADG and open distal gastrectomy, but also a similar number of specific lymph nodes, such as group 7, 8a, 9, 11p, 12a and 14v, which used to be considered difficult for laparoscopic dissection[55,56]. Splenic hilar lymph node dissection is one of the difficulties in radical total gastrectomy, which is because the splenic vessels run circuitously, and the branches vary substantially and they are in a narrow space at a very deep location. It is easy to cause hemorrhage because of splenic vascular injury or cause spleen ischemia and further necrosis by accidental cutting of the splenic artery branches of when dissecting the lymph nodes in this area. Compared to laparotomy, laparoscopy allows the operator to complete the spleen hilum lymph node dissection under a clear field of view and helps to improve surgical safety[57].

With regard to the length of the resection margin, we found that the proximal margin in LATG was shorter than that of OTG. Such result may relate to the nature for LATG which should resect specimen and make reconstruction all through mini-laparotomy; and it is difficult to pull the proximal stomach using a narrow incision, which may influence the distance of proximal margin. Therefore, patients with smaller neoplasms are more likely to receive LATG instead of OTG, thus allowing the surgeon to choose a smaller excision extension.

Cancer recurrence and long-term survival rate are two critical outcomes for evaluating surgical interventions in oncological therapy. LATG is not superior to LADG in both history and popularity, and only three studies have compared the long-term survival rate between the two groups[31,36,37], and another two have performed a descriptive analysis of cancer recurrence[32,34]. Based on these data, postoperative cancer recurrence and long-term survival rate in LATG were similar to those in OTG. However, as the cases in the studies included in our analysis were mostly concerned with early gastric cancer, the effect of LATG for early gastric cancer should be affirmed. Some RCTs and meta-analyses have demonstrated that long-term follow-up outcome of laparoscopic gastrectomy for advanced gastric cancer is similar to that of laparotomy[58,59]. Recently, Park *et al*[60] have analyzed the follow-up results of 239 cases of advanced gastric cancer treated with laparoscopic radical gastrectomy. Among these cases, 130 were T_2 stage, 63 were T_3, and 46 were T_4, and the 5-year survival rates were 86.6%, 77.4% and 58.7%, respectively. The result is similar to that for concurrent laparotomy and is encouraging. However, there should be an attitude of caution for laparoscopic resection of advanced gastric cancer because relevant studies and clinical evidence are still deficient.

During our research, a similar article by Haverkamp *et al*[61] was published, which had several limitations. The clinical heterogeneity could have been caused by the different underlying conditions and interventions. It is well known that gastric submucosal tumors (SMTs) such as lymphoma, leiomyosarcoma, and gastrointestinal stromal tumors are significantly different from adenocarcinoma in terms of biological characteristics, clinical diagnosis, and treatment. In our study, only patients who underwent gastrectomy for gastric adenocarcinoma were included, but Haverkamp *et al* included 8 patients undergoing total gastrectomy for *SMTs*; this may influence the reliability the results[28]. The difference in surgical methods is a major cause of clinical heterogeneity. In laparoscopy-assisted gastrectomy (LAG), an incision is almost always required for extracting a relatively large specimen and involves some complicated steps. However, totally laparoscopic gastrectomy (TLG) is considered to be incisionless, except for the trocar wounds, and it is a laparoscopic approach for intracorporeal anastomosis without auxiliary incision and touching the tumor. Hence, these are two different operative methods. Furthermore, some studies have shown that TLG may be less invasive than LAG, with the disadvantage of prolonged operating time[47,62-66]. Therefore, it is inappropriate to pool trials that differ in terms of these two methods in a meta-analysis. However, the existing meta-analysis included a study in which the TLG was performed using a totally laparoscopic method[23]. In addition, for the trials without the mean and standard deviation, Haverkamp *et al* used the median and range to estimate them based on the Hozo method[67]. However, this method may lead to deviation, especially when the sample size is small or the samples exhibit serious skewness. In the study of Topal for example[23], the median intraoperative blood in the laparoscopic group (n = 38) was 10 (5-400) mL, so the estimated mean blood loss was 10 mL. In fact, however, even the minimum mean blood loss could be 15.4 mL, which differed from the estimated value. Besides, since the study by Haverkamp *et al*[61] was published, several clinical observational studies have become available. The larger the number of patients in a meta-analysis, the greater its power to detect a possible treatment effect. Therefore, our comprehensive meta-analysis will contribute to a more systematic and objective evaluation for the safety and cancer treatment of LATG.

In conclusion, the existing research shows that LATG is safe and feasible, which can achieve similar lymph node dissection effects as OTG, characterized by such advantages as less pain, fewer postoperative complications, and rapid recovery, and which is expected to achieve the same effect in oncological treatment as OTG. However, most of the published studies were retrospective, the sample sizes were relatively small, most of the cases were early gastric cancer, the follow-up periods were not long enough, and the results exhibited substantial heterogeneity. Therefore, the results mentioned above should be subject to verification by strictly designed, large-sample, multicenter, RCTs.

COMMENTS

Background

Since it was first reported in 1994, laparoscopy-assisted distal gastrectomy (LADG) for gastric cancer has undergone rapid development and gained popularity in the past 20 years. Compared with traditional open gastrectomy, LADG can achieve better cosmesis, shorter hospital stay, faster postoperative recovery, and better postoperative quality of life. Although LADG has been accepted worldwide for tumors located in the lower stomach, laparoscopy-assisted total gastrectomy (LATG) for upper and middle gastric cancer has not been generalized. Although several meta-analyses and systematic reviews have been published for LADG, such studies have not been conducted for the potential benefits and disadvantages of LATG.

Research frontiers

In order to assess accurately the current status of LATG, the authors strictly limited inclusion criteria by focusing exclusively on LATG and carried out a comprehensive meta-analysis. This will contribute to a more systematic and objective evaluation of the safety of the LATG in cancer treatment.

Innovations and breakthroughs

LATG is safe and feasible, which can achieve similar lymph node dissection effects as open total gastrectomy (OTG), characterized by such advantages as less pain, fewer postoperative complications, and rapid recovery, and which is expected to achieve the same effect in oncological treatment as OTG.

Applications

Despite a longer operation, LATG can be performed safely in experienced surgical centers with a shorter hospital stay and fewer complications than open surgery.

Peer review

This is a well written paper which will add a great deal to the literature on the subject. One of the most significant conclusions from this work is the lack of randomised controlled trials surrounding the field. Future research should compare LADG and LATG to further verify the safety and feasibility of LATG.

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