

Robot-assisted vs laparoscopy-assisted gastrectomy for gastric cancer: A meta-analysis based on 3518 subjects

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Abstract

AIM: To compare the short-term clinical outcomes of robot-assisted gastrectomy (RAG) with laparoscopy-assisted gastrectomy (LAG) in gastric cancer patients.

METHODS: Articles were identified through a literature search of Pubmed, EMBASE, Scopus, Web of Science, Chinese National Knowledge Infrastructure and the Cochrane Library. Weighted mean differences (WMDs) and odds ratios (ORs) were selected as effect sizes for quantitative variables and qualitative variables, respectively. And 95%CIs were also calculated.

RESULTS: A total of 13 studies with 3518 patients were included. RAG was associated with longer operative time (WMD = 46.26 min, 95%CI: 31.89-60.63, $P < 0.00001$), less blood loss [WMD = -37.19 mL, 95%CI:

-60.16(-14.23), $P = 0.002$] and shorter postoperative hospital stay [WMD = -0.65 d, 95%CI: -1.24(-0.05), $P = 0.03$] than LAG. No significant difference in the numbers of retrieved lymph nodes was found between the two groups (WMD = 1.46, 95%CI: -0.19-3.10, $P = 0.08$). There was no significant difference in mortality (OR = 1.55, 95%CI: 0.49-4.94, $P = 0.45$), overall complications (OR = 1.00, 95%CI: 0.80-1.26, $P = 0.98$), anastomosis leakage (OR = 1.02, 95%CI: 0.62-1.65, $P = 0.95$) and anastomosis stenosis rates (OR = 0.54, 95%CI: 0.18-1.57, $P = 0.25$).

CONCLUSION: RAG is effective and safe in the treatment of gastric cancer. RAG is a promising alternative to laparoscopic surgery. Long-term randomized controlled studies with large scale and improved designs are needed to further evaluate the long-term outcomes.

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Key words: Gastric cancer; Robot; Laparoscopy; Gastrectomy; Meta-analysis

Core tip: A total of 13 studies with 3518 patients were included in this meta-analysis. The results indicated that robot-assisted gastrectomy was associated with longer operative time (WMD = 46.26 min, 95%CI: 31.89, 60.63, $P < 0.00001$), less blood loss [WMD = -37.19 mL, 95%CI: -60.16(-14.23), $P = 0.002$] and shorter postoperative hospital stay [WMD = -0.65 d, 95%CI: -1.24(-0.05), $P = 0.03$] than laparoscopy-assisted gastrectomy. Robot-assisted gastrectomy is effective and safe in the treatment of gastric cancer and will be a promising alternative to laparoscopic surgery. Long-term randomized controlled studies with large scale and improved designs are needed to further evaluate the long-term outcomes.

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INTRODUCTION

Gastric cancer is the fourth leading cancer and second leading cause of cancer death in the world^[1,2]. At present, radical gastrectomy with lymph node (LN) dissection is still the mainstay of treatment for gastric cancer^[3]. Since 1994, the laparoscopy-assisted gastrectomy (LAG) has become widely accepted in Asian countries because it offers less invasiveness and pain, speedier recovery, milder morbidity and shorter hospital stay^[4-7]. According to the report of Japanese Society of Endoscopic Surgery, the total number of patients who had undergone LAG for gastric cancer was 34645 until 2013^[8]. However, the instruments of LAG have a limited range of motion and are usually associated with a long learning curve, especially in LN dissection^[9].

Another minimally invasive approach for gastric cancer seems to be more promising. Hashizume *et al*^[10] had performed distal gastrectomy successfully with the assistance of the da Vinci computer-enhanced surgical system in 2002. They found that the robotic system enhanced visualization of both the operative field and precision of the necessary techniques. It may therefore help surgeons overcome many of the difficulties associated with the endoscopic approach. Since then, several studies^[11-15] have been conducted to evaluate the safety and efficacy of robot-assisted gastrectomy (RAG) for gastric cancer. However, most of them were case control studies and their sample sizes were rather small. Therefore, in this study, we conducted a meta-analysis to compare the short-term clinical outcomes of RAG with LAG in gastric cancer patients.

MATERIALS AND METHODS

Search strategy

We performed an electronic search of Pubmed, EMBASE, Scopus, Web of Science, Cochrane Library and Chinese National Knowledge Infrastructure from the inception to December 13th, 2013. The following search terms were used: gastric cancer, gastric carcinoma, gastrectomy, robotic, robot, laparoscopy and laparoscopic. Only English and Chinese articles were considered. We also searched additional articles through the reference lists of related papers. Two investigators screened the articles independently.

Study selection

Two investigators identified appropriate articles and conducted data extraction independently. Eligible studies should match all of the following: (1) study design: prospective or retrospective cohort studies, randomized or nonrandomized controlled studies, case-control studies;

(2) study population: gastric cancer patients who received RAG or LAG; (3) grouping: RAG group *vs* LAG group; and (4) outcomes: intraoperative outcome (operative time, blood loss, number of retrieved LNs, conversion to open gastrectomy) and postoperative outcome (overall complications, anastomosis leakage, anastomosis stenosis, bleeding, intestinal obstruction, mortality and postoperative hospital stay). Meeting abstracts, case reports, editorials and reviews were excluded.

Data extraction and quality assessment

We extracted the study type, country, patient characteristics, age, clinical outcomes, operating cost and the number of cases for each article. The quality of the included studies was evaluated by Newcastle-Ottawa quality assessment (NOS) scale^[16]. A study can be awarded a highest score of nine. Data extraction was completed independently by two investigators.

Statistical analysis

All statistical tests were performed with Review Manager 5.1 software (Cochrane Collaboration, Copenhagen, Denmark). In this study, I^2 was used to investigate the heterogeneity. In the analysis process, if $I^2 \geq 50\%$, we ran a random-effect model. On the other hand, a fixed-effect model was chosen if $I^2 < 50\%$. In the analysis of quantitative variables (operative time, blood loss, number of retrieved LNs and postoperative hospital stay), we chose weighted mean difference (WMD) with 95%CI as summary statistics. As for qualitative variables (overall complications, anastomosis leakage, anastomosis stenosis, bleedings, intestinal obstruction, conversion to open gastrectomy and mortality), odds ratios (ORs) with 95% CIs were used accordingly. A value of $P < 0.05$ (two-tailed test) was considered statistically significant.

RESULTS

Study selection

At the beginning of search process, 535 publications were reviewed. After a screening process, 11 retrospective studies^[1,3,6,9,11-15,17,18], one nonrandomized prospective study^[19] and one randomized control trial^[20] were included (Figure 1). Twelve studies^[1,3,6,9,11-13,15,17-20] were from Asia and one^[14] from Europe. Totally, 3518 patients with gastric cancer were included in this meta-analysis. Among them, 1143 cases were in RAG group, the other 2375 patients received LAG (Table 1). Ten studies^[1,3,9,12-15,17-19] were published in English, and three^[6,11,20] published in Chinese. No significant publication bias was found (Figure 2).

Comparison of intraoperative outcomes between RAG and LAG group

In this pooled analysis, operative time, blood loss and number of retrieved LNs were included. In total, there were 13 studies^[1,3,6,9,11-15,17-20] which reported of the operative time, 12 studies^[1,3,6,9,11-14,17-20] reported of blood loss

Table 1 Main characteristic of the included studies

Ref.	Country	Group	No. of patients	Age (yr)	Males (%)	BMI (kg/m ²)	TNM stage (I / II / III / IV)	NOS score
Eom <i>et al</i> ^[17]	South Korea	RAG	30	52.8	70	24.2	25/3/2/0	6
Huang <i>et al</i> ^[9]	Taiwan China	RAG	62	57.9	66.1	24.1	56/6/0/0	6
		LAG	39	65.1	48.7	24.2	29/7/3/0	
Hyun <i>et al</i> ^[18]	South Korea	RAG	64	65.6	67.2	24.7	55/9/0/0	7
		LAG	38	54.2	65.8	23.8	30/5/3/0	
Kang <i>et al</i> ^[12]	South Korea	RAG	83	60.3	66.3	23.8	67/9/7/0	6
		LAG	100	53.2	63	23.7	82/11/7/0	
Kim <i>et al</i> ^[5]	South Korea	RAG	282	58.8	67.7	23.6	NR	7
		LAG	436	54.2	60.8	23.6	350/51/32/0	
Kim <i>et al</i> ^[13]	South Korea	RAG	861	58.8	63.9	23.5	714/96/43/0	6
		LAG	16	53.8	62.5	21.3	NR	
Liu <i>et al</i> ^[6]	China	RAG	11	57.9	90.9	25.3	NR	7
		LAG	48	51.8	85.4	21.2	14/5/27/2	
Noshiro <i>et al</i> ^[19]	Japan	RAG	48	52.1	83.3	21	16/6/23/3	6
		LAG	21	66	66.7	22.8	18/-/-/-	
Pugliese <i>et al</i> ^[14]	Italy	RAG	160	69	63.8	21.8	113/-/-/-	7
		LAG	16	71	NR	28.8	NR	
Woo <i>et al</i> ^[11]	South Korea	RAG	48	71	NR	28.8	NR	6
		LAG	236	54	57.6	23.5	236/0/0/0	
Yoon <i>et al</i> ^[15]	South Korea	RAG	591	58.3	61.6	23.5	591/0/0/0	7
		LAG	36	53.9	50	23.2	29/7/0/0	
Zhang <i>et al</i> ^[11]	China	RAG	65	56.9	47.7	23.6	55/7/3/0	7
		LAG	97	56.1	68	22.5	23/22/52/0	
Zhao <i>et al</i> ^[20]	China	RAG	70	54.8	70	21.7	8/17/45/0	8
		LAG	30	71.8	73.3	23.6	2/18/9/1	
		LAG	30	72.4	76.7	23.9	1/25/3/1	

BMI: Body mass index; TNM: Tumor node metastases; NOS: Newcastle-ottawa quality scale; RAG: Robot-assisted gastrectomy; LAG: Laparoscopy-assisted gastrectomy; NR: Not Reported.

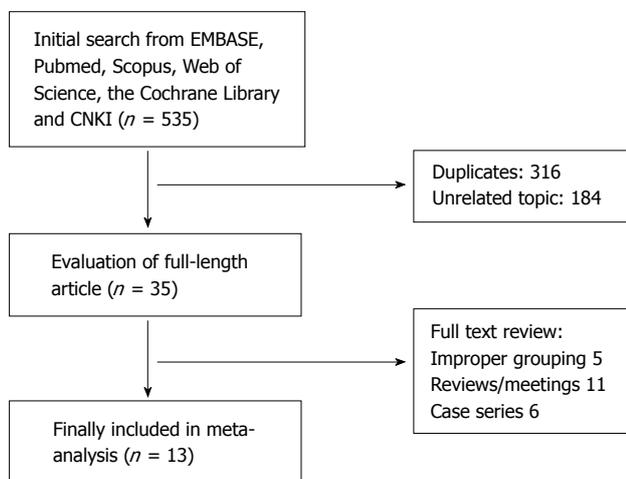


Figure 1 Flow chart of literature search for meta-analysis.

and 12 studies^[1,3,6,9,11,13-15,17-20] reported of the number of retrieved LNs. In the heterogeneity tests of operative time, blood loss and number of retrieved LNs, *I*² were 91%, 94% and 70%, respectively. Accordingly, we chose the random-effect model.

As shown in Figure 3A, the mean operative time for the RAG group was on average 46 min longer than the LAG group (WMD = 46.26 min, 95%CI: 31.89-60.63, *P* < 0.00001), while mean blood loss was significantly less in the RAG group [WMD = -37.19 mL, 95%CI:

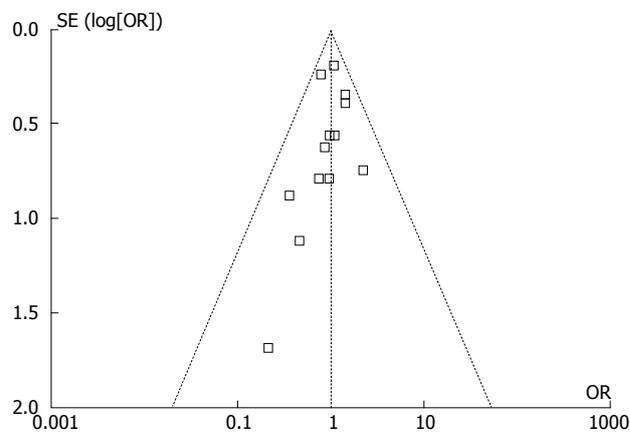
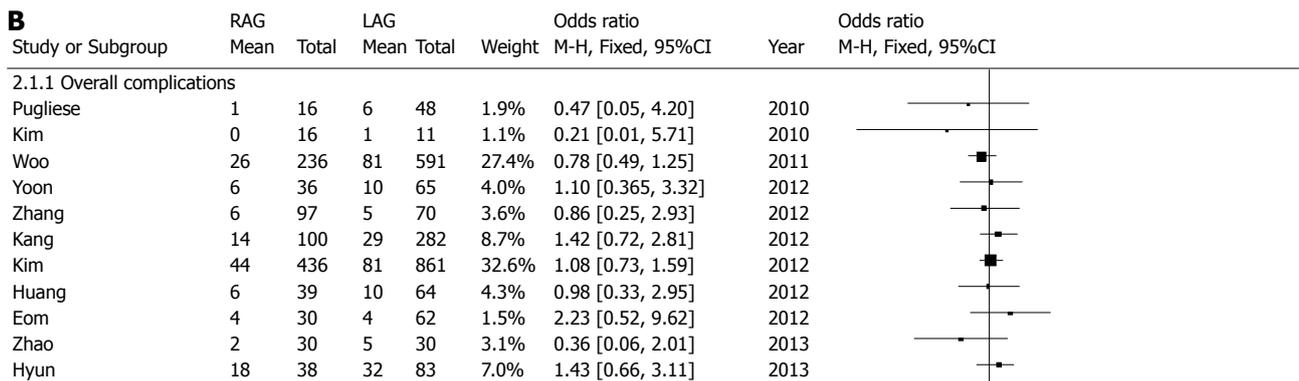
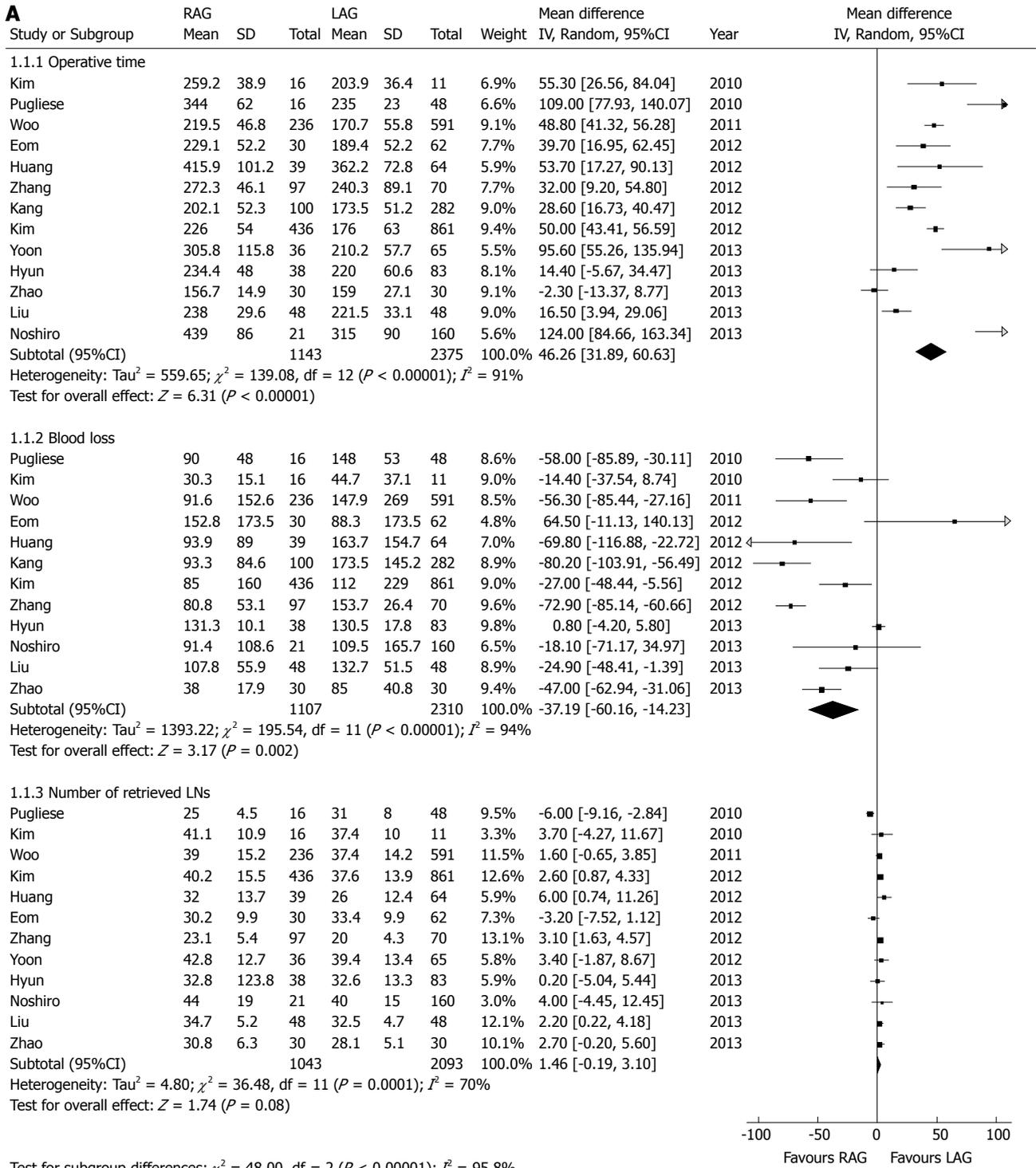


Figure 2 Funnel plot of included studies in this meta-analysis.

-60.16-(-14.23), *P* = 0.002]. The pooled results also indicated that there was no significant difference in the number of retrieved LNs between the two groups (WMD = 1.46, 95%CI: -0.19-3.10, *P* = 0.08).

Comparison of postoperative outcomes between RAG and LAG group

Overall complications, anastomosis leakage and anastomosis stenosis were included for analysis. Information in detail is shown in Figure 3B. Thirteen studies^[1,3,6,9,11-15,17-20] which reported of the overall complications were included. No statistical heterogeneity was found in this analysis



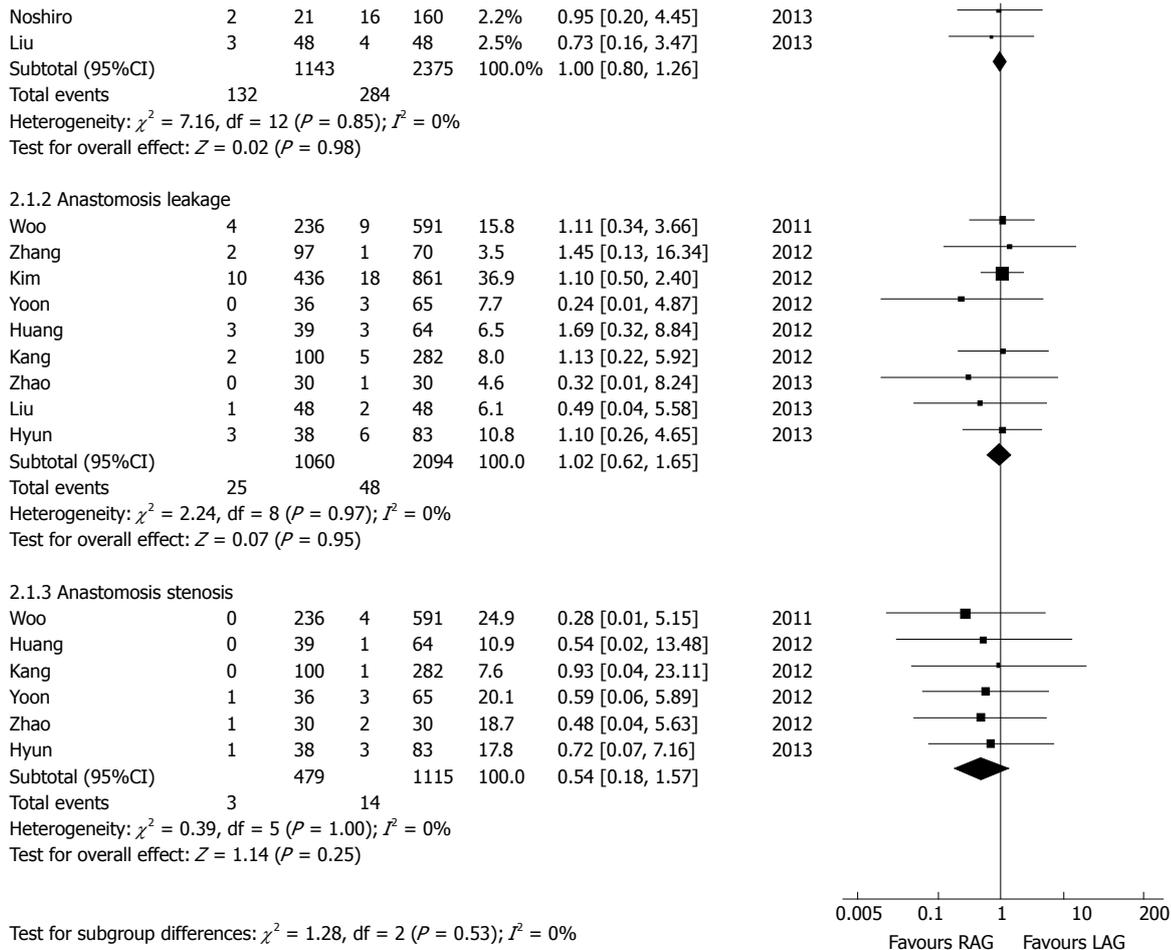


Figure 3 Forest plot comparing intraoperative (A) and postoperative (B) outcomes between robot-assisted gastrectomy and laparoscopy-assisted gastrectomy. RAG: Robot-assisted gastrectomy; LAG: Laparoscopy-assisted gastrectomy.

($I^2 = 0\%$). A fixed-effect model was selected. No significant difference between RAG and LAG group was found in the comparison of the incidences of overall complications (11.5% vs 12.0%, OR = 1.00, 95%CI: 0.80-1.26, $P = 0.98$).

The incidences of anastomosis leakages were reported in 9 studies^[1,3,6,9,11,12,15,18,20]. In total, 1060 patients were treated with RAG and 2094 patients received LAG. No statistical heterogeneity was found ($I^2 = 0\%$). There was no significant difference between RAG and LAG group in the comparison of the incidences of anastomosis leakages (2.4% vs 2.3%, OR = 1.02, 95%CI: 0.62-1.65, $P = 0.95$).

Six studies^[1,9,12,15,18,20] involving 1594 subjects were included in the analysis of anastomosis stenosis rates. No statistical heterogeneity was found in this analysis ($I^2 = 0\%$) and a fixed-effect model was selected. The results didn't indicate statistical difference between the two groups in the comparison of the anastomosis stenosis rates (0.6% vs 1.3%, OR = 0.54, 95%CI: 0.18-1.57, $P = 0.25$).

Comparison of other clinical outcomes between RAG and LAG group

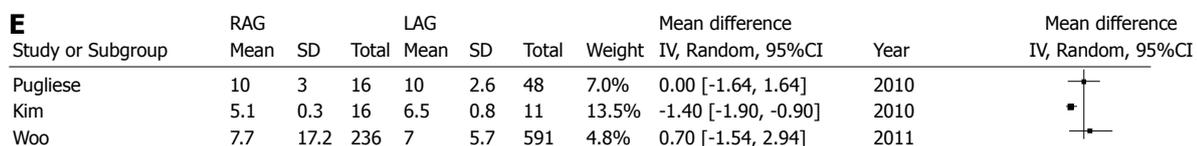
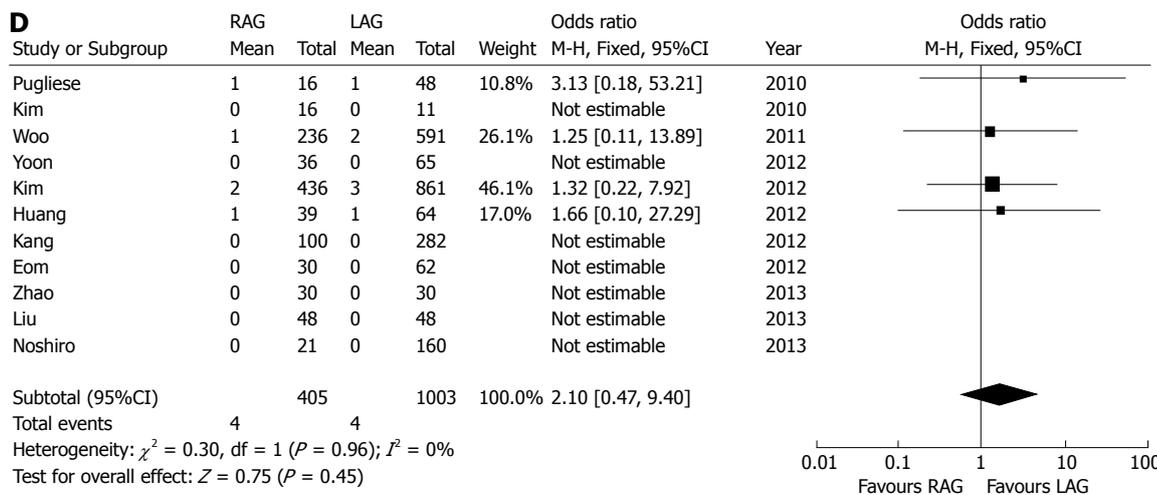
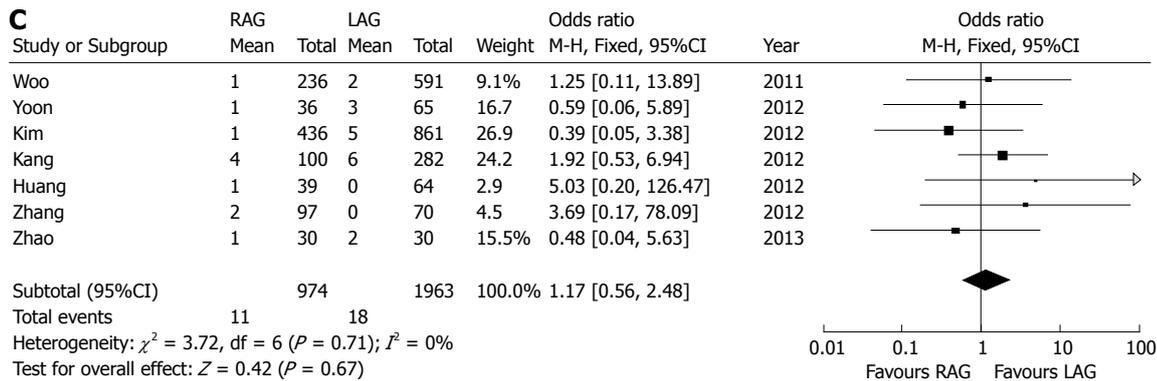
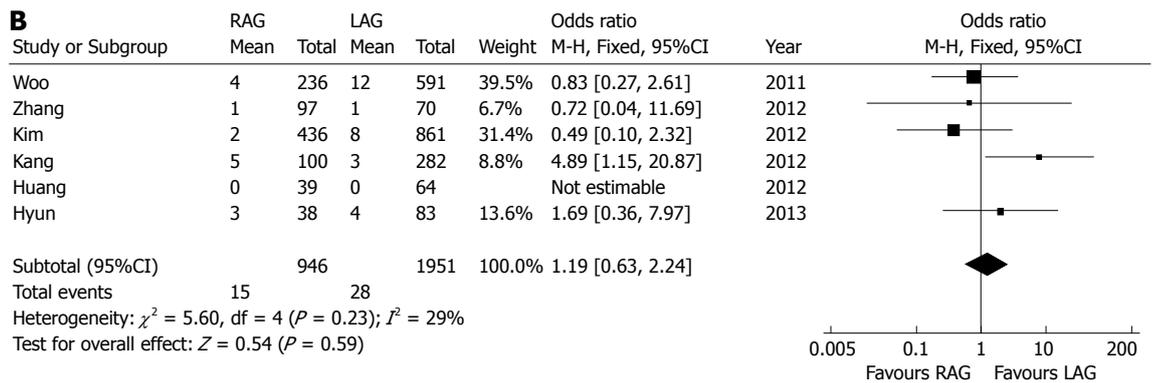
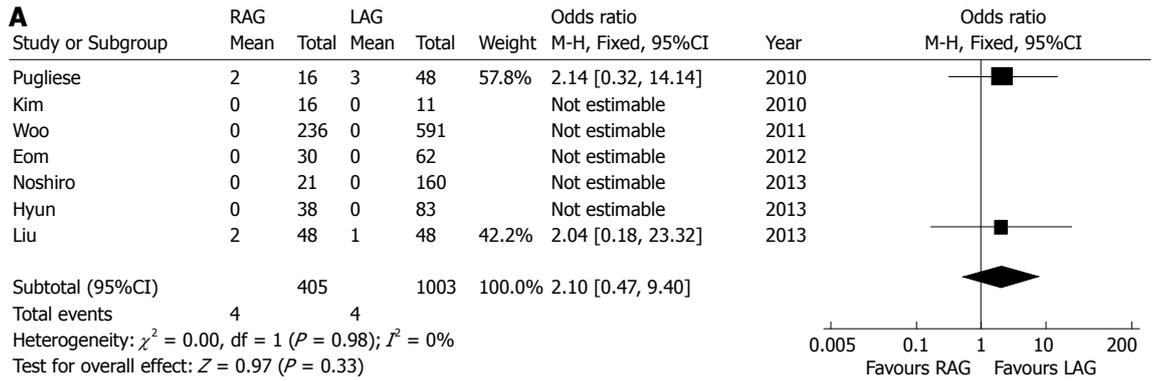
There were 7 studies^[1,6,13,14,17-19] which reported of num-

bers of patients in LAG or RAG group who converted to open gastrectomy (Figure 4A). No statistical heterogeneity was found ($I^2 = 0\%$). There was no statistical difference in the comparison of conversion to open gastrectomy between the two groups (OR = 2.10, 95%CI: 0.47-9.40, $P = 0.33$).

The incidences of bleeding events after operation were reported in 6 studies^[1,3,9,11,12,18], involving 2897 subjects. No statistical heterogeneity was found in this analysis ($I^2 = 29\%$) and a fixed-effect model was selected (Figure 4B). The results indicated that there was no significant difference in the comparison of bleeding rates (1.6% vs 1.4%, OR = 1.19, 95%CI: 0.63-2.24, $P = 0.59$).

Seven studies^[1,3,9,11,12,15,20] involving 2937 patients were included in the analysis of intestinal obstruction (Figure 4C). A fixed-effect model was selected ($I^2 = 0\%$). No significant difference was found in the comparison of intestinal obstruction rates (1.1% vs 0.9%, OR = 1.17, 95%CI: 0.56-2.48, $P = 0.67$).

Eleven studies^[1,3,6,9,12-15,17,19,20] had reported the mortalities (Figure 4D). There were 3230 subjects included (1008 in RAG group and 2222 in LAG group). No statistical heterogeneity was found ($I^2 = 0\%$). The results indicated no significant difference of mortality between the two



Eom	7.9	0.27	30	7.8	0.27	62	14.8	0.10 [-0.02, 0.22]	2012
Kang	9.8	12.2	100	8.1	4.1	282	4.3%	1.70 [-0.74, 4.14]	2012
Kim	7.5	13.7	436	7.8	8.5	861	8.2%	-0.30 [-1.71, 1.11]	2012
Huang	11.3	14.4	39	17.2	13.3	64	1.1	-5.90 [-11.47, -0.33]	2012
Zhang	6.1	2.6	97	6.9	2.3	70	12.1	-0.80 [-1.55, -0.05]	2012
Yoon	8.8	3.3	36	10.3	10.8	65	3.4	-1.50 [-4.34, 1.34]	2012
Hyun	10.5	5.9	38	11.9	10.3	83	3.3	-1.40 [-4.30, 1.50]	2013
Noshiro	8	5	21	13	30	160	1.3	-5.00 [-10.12, 0.12]	2013
Liu	7.5	1.3	48	7.9	1.4	48	13.3	-0.40 [-0.94, 0.14]	2013
Zhao	4	0.9	30	5.4	1.5	30	12.8	-1.40 [-2.03, -0.77]	2013
Subtotal (95%CI)			1143			2375	100.0%	-0.65 [-1.24, -0.05]	
Heterogeneity: Tau ² = 0.63; χ^2 = 70.30, df = 12 ($P < 0.00001$); I^2 = 83%									
Test for overall effect: Z = 2.11 ($P = 0.03$)									

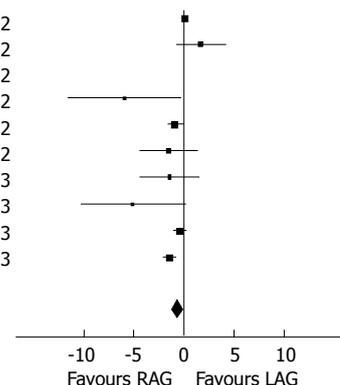


Figure 4 Forest plot. A: Comparing conversion to open gastrectomy between RAG and LAG; B: Comparing bleeding events between RAG and LAG; C: Comparing intestinal obstruction between RAG and LAG; D: Comparing mortality between RAG and LAG; E: Comparing postoperative hospital stay between RAG and LAG. RAG: Robot-assisted gastrectomy; LAG: Laparoscopy-assisted gastrectomy.

groups (0.5% vs 0.3%, OR = 1.55, 95%CI: 0.49-4.94, $P = 0.45$).

Thirteen studies^[1,3,6,9,11-15,17-20] involving 3518 patients were included in the analysis of postoperative hospital stay (Figure 4E). A random-effect model was selected ($I^2 = 83%$). The RAG group had a shorter mean postoperative hospital stay than the LAG group [WMD = -0.65 d, 95%CI: -1.24(-0.05), $P = 0.03$].

DISCUSSION

The findings from our meta-analysis suggest that RAG is effective and safe for gastric cancer compared to LAG. Overall, combining the available data RAG was associated with longer operative time, less blood loss and shorter postoperative hospital stay than LAG. Moreover, there was no significant difference in mortality, conversion, overall complications, postoperative bleeding events, intestinal obstruction, anastomosis leakage and anastomosis stenosis rates. There was also no significant difference in the numbers of retrieved LNs during the operation between RAG and LAG.

Previous studies have reported the application of RAG for the treatment of gastric cancer. Yoon *et al*^[15] included 36 patients who underwent RAG and 65 patients who underwent LAG at the National Cancer Center in South Korea. The operative data, postoperative morbidity, and pathologic data were analyzed. They found that the mean postoperative hospital stay was 8.8 ± 3.3 d in the RAG group and 10.3 ± 10.8 d in the LATG group ($P = 0.416$). The mean operative time was 305.8 ± 115.8 min in the RAG group and 210.2 ± 57.7 min in the LAG group ($P < 0.001$). No significant differences were found in the comparison of mean number of dissected LNs and incidence of postoperative complications. Some other studies^[6,18,20] and meta-analysis^[21,22] have reported similar results. However, these studies have limited samples and most of them were retrospective. Therefore, we pooled relevant studies and conducted a meta-analysis to compare the short-term clinical outcomes of RAG with LAG systematically. Finally, 13 studies involving 3815 subjects

were included. The quality of these studies was relatively high because their NOS scores ranged from 6 to 8. There was a significant heterogeneity among the included studies in the analysis of intraoperative outcomes. This may be explained by the differences in the stage of gastric cancer, resection scope, operation skill, gastric resection approach, extension of LN dissection and the standards for discharge among the studies. Further, according to the funnel plot, the publication bias was acceptable.

According to the results of our analysis, the operative time is much longer in RAG group. It may be related to the increased set-up time to position and the inexpert skill of surgeons. RAG was also associated with less estimated blood loss compared with LAG. It's more convenient for hemostatic treatment because RAG provides an excellent and stable visualization of the operative field^[9,11]. Even though the mean postoperative hospital stay is 0.65 d shorter in RAG, we think that it is of little practical significance because it's too short. Moreover, there are no differences between RAG and LAG in the comparison of retrieved LNs and postoperative outcomes. Briefly, the results in the current study indicate that RAG is as safe and effective as LAG in the treatment of gastric cancer.

However, the costs of RAG are much higher than those of LAG. The mean cost of RAG is about \$6000 to \$11400 for gastric cancer, while only \$2000 to \$6000 in LAG group^[9,11,17]. Consequently, before surgeons and patients make the decision, patients' economic condition should also be taken into consideration.

However, this study had some potential limitations. Firstly, there might be a certain degree of language bias because only publications in Chinese or English were searched in the databases. And then, the number of included subjects was relatively few in this study, which may lead to low statistical power. Moreover, most of them were retrospective designed and long-term outcomes were not reported. More high-quality randomized clinical studies are deserved to better evaluate both short and long-term outcomes of RAG. Further, the end points predetermined in the included studies were different. We can only partly extract the information from these

studies. As for study population, most participants were Asian. Studies in Western countries were relatively rare. Lastly, the differences in population characteristics (stage of gastric cancer, age, gender ratio, diabetes mellitus, hypertension, *etc.*), device and the duration of follow up among the included studies may also lead to a bias in a certain degree.

In conclusion, the synthesis of available evidence indicates that RAG is effective and safe in the treatment of gastric cancer. RAG is a promising alternative to laparoscopic surgery. Long-term randomized controlled studies with large scales and improved designs are needed to further evaluate the long-term outcomes.

ACKNOWLEDGEMENTS

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COMMENTS

Background

Gastric cancer is the fourth leading cancer and second leading cause of cancer death in the world. Robot-assisted gastrectomy (RAG) is a new approach for gastric cancer and is reported to be safe and efficient. However, most of the studies were case control studies and their sample sizes were rather small.

Research frontiers

The purpose of this study was to perform a meta-analysis to compare the short-term clinical outcomes of RAG with laparoscopy-assisted gastrectomy (LAG) in gastric cancer patients systematically.

Innovations and breakthroughs

In the present study, the results indicate that RAG is associated with longer operative time [weighted mean difference (WMD) = 46.26 min, $P < 0.00001$], less blood loss (WMD = -37.19 mL, $P = 0.002$) and shorter postoperative hospital stay (WMD = -0.65 d, $P = 0.03$) than LAG. So far, this is a meta-analysis with most included studies and largest number of included subjects.

Applications

RAG is effective and safe in the treatment of gastric cancer. RAG is a promising alternative to laparoscopic surgery.

Terminology

RAG: Robot-assisted gastrectomy. Robot-assisted surgery is a kind of minimally invasive approaches. It can be used in gastrectomy and may enhance visualization of both the operative field and precision of the necessary techniques. The most popular one is da Vinci computer-enhanced surgical system.

Peer review

Lin *et al* in their manuscript present an interesting meta-analysis. This is a well done study.

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