RESEARCH ARTICLE

Robotic versus Laparoscopic Gastrectomy for Gastric Carcinoma: a Meta-Analysis of Efficacy and Safety

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Abstract

Purpose: To systematically review efficacyand safety of robotic gastrectomy (RG) compared with conventional laparoscopic gastrectomy (LG) for gastric carcinoma. Materials and Methods: A systematic literature search was carried out using PubMed, Cochrane Library, CBM, CNKI, WanFang, VIP and other sources like relevant references to obtain comparative studies assessing the effectiveness and safety between RG and LG published between 2013 and 2016. Then the literature was screened and the data were extracted by 2 independent reviewers. The quality of the literature was assessed, and the data analyzed using Stata/SE 14 software. Fixed effects or random effects models wereapplied according to heterogeneity. Results: A total of 12 non-randomized observational clinical studies involving 3,580 patients were included, of which 1,096 had undergone RG and 2,484 had received LG. The results of the meta-analysis showed in terms of effectiveness, RG was associated with less blood loss, less time to first flatus and greater number of harvested lymph nodes, but there were no significant differences in proximal and distal resection margins, compared with LG. In terms of efficiency, RG was associated with shorter hospital stay, but longer operative time. In terms of safety, there were no statistically significant differences in complications, mortality and conversions between RG and LG. Conclusions: RG can achieve comparable or better short-term and radical effects than LG, with respect to effectiveness, efficiency and safety in treatment of gastric carcinoma. Future studies involving RG should focus on decreasing operative time and reducing cost. Moreover, there is a need for randomized controlled trials comparing the two techniques with long-term follow-up.

Keywords: Gastric carcinoma - Da Vinci robot - laparoscopy - radical gastrectomy - meta-analysis

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Introduction

Gastric carcinoma is the 4th most common malignancy and a leading cause of carcinoma death in the world (Torre et al., 2015). Surgical excision is regarded as the gold standard of treatment for gastric carcinoma (Wu et al., 2011). Since Kitano et al. reported firstly LG for gastric carcinoma in 1994, LG had been widely applied to the treatment of gastric carcinoma. Compared with open gastrectomy (OG), LG has lots of unique predominance such as less blood loss, reduced invasiveness, rapider postoperative recovery and less complication (Kim et al., 2008; Lee et al., 2009; Vinuela et al., 2012; Yasunaga et al., 2013; Deng et al., 2015). However, LG has also limitations of itself including lack of flexibility, 2-D imaging, limited ranges of instrument movement and amplification of hand tremor (El-sedfy et al., 2014). Application of robotic surgical system has overcome the limitations of LG as an emerging technique (Hashizume et al., 2002; Son et al.,2014; Suda et al., 2015; Obama et al., 2016). Hashizume et al. reported firstly RG in 2002, which confirmed the feasibility of RG for gastric carcinoma. Since then, many surgeons have reported the benefits of RG for treatment of gastric carcinoma such as high definition 3-D stereo video, short learning curve, tremor suppression, and stable picture (Vinuela et al., 2012; Kang et al., 2012; Eom et al., 2012; Park et al., 2012; Uyama et al., 2012; Nakauchi et al., 2016).

Although some studies have reported the effectiveness and safety of RG, due to small samples size included single study and low test efficiency, there has been no definite conclusion whether RG can achieve an equal or even better surgical effect to LG and can spread widely. So we do the meta-analysis to systematically review effectiveness and safety of RG.

Materials and Methods

Search Strategy

A systematic literature search was performed in PubMed, Cochrane Library, WanFang, CBM, CNKI and VIP for clinical research published between January

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2013 and May 2016 that compared RG and LG, using the following major terms: gastric cancer, gastrectomy, da Vinci, robotic, laparoscopic. Meanwhile, the relevant references were also carried out to broaden the search. Only the studies with full-text articles were included.

Inclusion and exclusion criteria

Included studies must meet the following criteria: *i*). The studies comparing RG and LG were limited to patients with gastric carcinoma. The studies have clear case characteristics, selection criteria and group description. *ii*). The studies provided the original data of evaluation index. *iii*). For repeated studies, the higher quality was included in the analysis). The mean age of the patients in included studies was restricted to between 50 and 70 years old. Comments, meeting papers, review articles and animal experimental studies were excluded.

Data extraction and quality assessment of included studies

Two reviewers extracted carefully data from all included studies independently according to the inclusion and exclusion criteria, and checked across the result. The controversial results were determined by discussing, and explaining the reasons of exclusion. The extracted data included patient and study characteristics, perioperative, postoperative and oncological outcomes. The methodological quality of the non-randomized studies was estimated according to the Newcastle-Ottawa Scale (NOS) (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp).

Statistical analysis

Meta-analysis was performed by using Stata/SE 14 software. Dichotomous variables were analyzed by using estimation of odds ratio (OR) with a 95% confidence interval (95% CI) and continuous variables using weighted mean difference (WMD) with a 95% CI. A fixed effect model was adopted unless there was evidence of significant unexplained heterogeneity, in which case, a random effects model was adopted. I^2 was used to evaluate the heterogeneity. $I^2<25\%$, $25\%\leq I^2\leq 50\%$ and $I^2>50\%$ indicated low, moderate and high heterogeneity. If the heterogeneity was high ($I^2>50\%$ or $P<0.05$), a random effect model was used for analysis. Otherwise, a fixed effect model was used for analysis. $P<0.05$ was considered to be statistically significant.

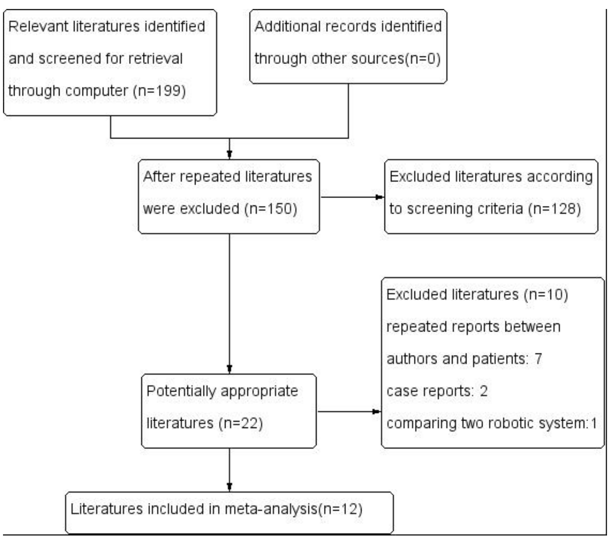

Figure 1. Flow Chart of Literatures Selection

Results

Study Characteristics

12 literatures involving 3580 patients were selected from 199 potentially relevant literatures, of which 1096 had undergone RG and 2484 had received LG. The basic characteristics and quality assessment of all included studies were showed in Table 1. In the meta-analysis, we found there was no statistical difference in mean sex composition and BMI. However, in terms of mean age, we found statistical significance between the two groups.

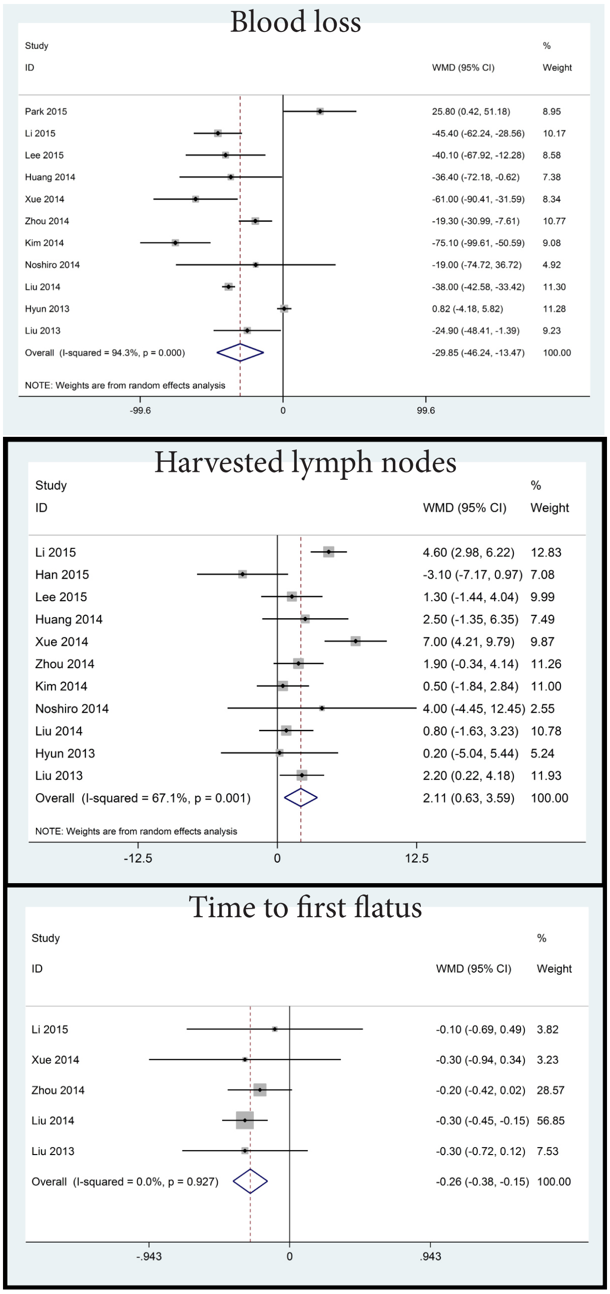

Figure 2. Forest plots comparing effectiveness of RG vs LG (blood loss, harvested lymph nodes, time to first flatus)

Meta-analysis of effectiveness

Data from eleven studies (Hyun et al., 2013; Liu et al., 2013; Huang et al., 2014; Xue et al., 2014; Zhou et al., 2014; Kim et al., 2014; Noshiro et al., 2014; Liu et al., 2014; Park et al., 2015; Li et al., 2015; Lee et al., 2015) were pooled together to obtain the mean operative blood loss in the two groups. Because of significant heterogeneity (I^2=94.3%, P<0.05), a random effect model was used. Meta-analysis revealed that RG group had a significantly less blood loss compared with LG group (WMD=-29.855, 95% CI=-46.236~-13.474, P<0.05).

There were eleven studies (Hyun et al., 2013; Liu et al., 2013; Huang et al., 2014; Xue et al., 2014; Zhou et al., 2014; Kim et al., 2014; Noshiro et al., 2014; Liu et al.,

Table 1. Characteristics and quality scoreof studies included in the meta-analysis?

Study	Year	Country	Design	Group	Number	Sex	Age	BMI(kg/m^2)	Score
Park et al.	2015	Korea	non-RCT	RG	145	*	54.5±11.6	23.9±3.3	7
				LG	612	*	58.3±11.8	23.9±3	
Li et al.	2015	China	non-RCT	RG	126	70/56	56.7±9.9	21.4±3.8	6
				LG	124	64/60	57±10.6	22.2±3.7	
Han et al.	2015	Korea	non-RCT	RG	68	31/37	50.6±8.3	22.7±2.4	7
				LG	68	31/36	49.8±11.5	22.8±3	
Lee et al.	2015	Korea	non-RCT	RG	133	85/48	53.6±13.2	23.2±2.7	8
				LG	267	154/113	59.2±11.7	23.7±2.8	
Huang et al.	2014	China	non-RCT	RG	72	40/32	67.7±15.1	24.1±3.3	6
				LG	73	42/31	66±13.5	24.2±3.3	
Xue et al.	2014	China	non-RCT	RG	50	37/13	56.9±10.6	24.4±2.8	6
				LG	64	42/22	56±13.8	23.8±3.7	
Zhou et al.	2014	China	non-RCT	RG	120	90/30	54.7±10.1	21.6±2.8	7
				LG	394	276/118	55.6±11.8	21.7±2.6	
Kim et al.	2014	Korea	non-RCT	RG	172	103/69	55.2±14	23.7±2.9	7
				LG	481	294/187	61.3±11.9	23.6±2.9	
Noshiro et al.	2014	Japan	non-RCT	RG	21	14/7	66±10	22.8±3.1	7
				LG	160	102/58	69±12	21.8±2.8	
Liu et al.	2014	China	non-RCT	RG	100	59/41	66.4±5.7	22.7±1.8	6
				LG	100	63/37	67.8±4.8	23.1±1.2	
Hyun et al.	2013	Korea	non-RCT	RG	38	25/13	54.2±12.7	23.8±2.6	8
				LG	83	55/28	60.3±12.3	23.8±2.9	
Liu et al.	2013	China	non-RCT	RG	48	41/7	51.8±10.5	21.2±2.1	6
				LG	48	40/8	52.1±10.2	21±1.6	

Table 2. Results of Meta-analysis Comparing RG versus LG

Outcomes	"No.of studies	No.of RG	No.of LG	OR/WMD (95% CI)	P value	I^2	P value HG
Baseline characteristics							
Age	12	1096	2484	-2.16 (-3.66,-0.67)	0.005	0.695	<0.0001
Gender ratio	11	951	1872	1.09 (0.92,1.29)	0.341	0	0.963
BMI	12	1096	2484	-0.137 (-0.334,0.06)	0.173	0	0.448
Effectiveness							
Blood loss (ml)	11	1028	2416	-29.855 (-46.236,-13.474)	<0.0001	0.943	<0.0001
Harvested lymph nodes	11	951	1872	2.11 (0.63,3.59)	0.005	0.671	0.001
Time to first flatus (day)	5	444	730	-0.264 (-0.379,-0.148)	<0.0001	0	0.927
Proximal resection margin	5	374	693	-0.104 (-0.307,0.099)	0.314	0	0.758
Distal resection margin	5	374	693	-0.176 (-0.413,0.062)	0.147	0.278	0.236
Efficiency							
Operative time	12	1096	2484	42.437 (31.82,53.053)	<0.0001	0.897	<0.0001
hospital stay	10	1008	2337	-0.465 (-0.741,-0.19)	0.001	0.203	0.256
Safety							
Complication	12	1096	2484	1.019 (0.786,1.32)	0.889	0	0.954
Mortality	3	389	1166	0.607 (0.119,3.101)	0.548	0	0.901
Conversion	4	314	920	1.55 (0.6,4.02)	0.364	0.179	0.301

OR, odds ratio; WMD, weighted mean difference; CI, confidence interval; HG, heterogeneity

2014; Han et al., 2015; Li et al., 2015; Lee et al., 2015) that reported the number of harvested lymph nodes. Significant heterogeneity was found in the studies (I2=67.1%, *P*<0.05), so a random effect model was adopted. Meta-analysis showed that there was difference in the number of harvested lymph nodes (WMD=2.11, 95% CI=0.63~3.59, *P*<0.05). However, in terms of the proximal and distal resection margin, there was no statistical difference between the two groups when data from five studies were pooled(WMD=-0.104, 95% CI=-0.307~0.099, *P*>0.05; WMD=-0.176, 95% CI=-0.413~0.062, *P*>0.05).

Five studies (Liu et al., 2013; Xue et al., 2014; Zhou et al., 2014; Liu et al., 2014; Li et al., 2015) reported time to first flatus. There was no significant heterogeneity (I2=0, *P*>0.05), so a random effect model was used. Meta-analysis showed that patients in RG group had a shorter time to first flatus compared with LG group (WMD=-0.264, 95% CI=-0.379~-0.148, *P*<0.05).

Meta-analysis of efficiency

All the studies (Hyun et al., 2013; Liu et al., 2013; Huang et al., 2014; Xue et al., 2014; Zhou et al., 2014; Kim et al., 2014; Noshiro et al., 2014; Liu et al., 2014; Park et al., 2015; Li et al., 2015; Lee et al., 2015; Han et al., 2015) reported operative time. Because of significant heterogeneity (I^2=89.7%, *P*<0.05), a random effect model was adopted. Meta-analysis revealed that RG group had a longer operative time compared with LG group (WMD=42.437, 95% CI=31.82~53.053, *P*<0.05).

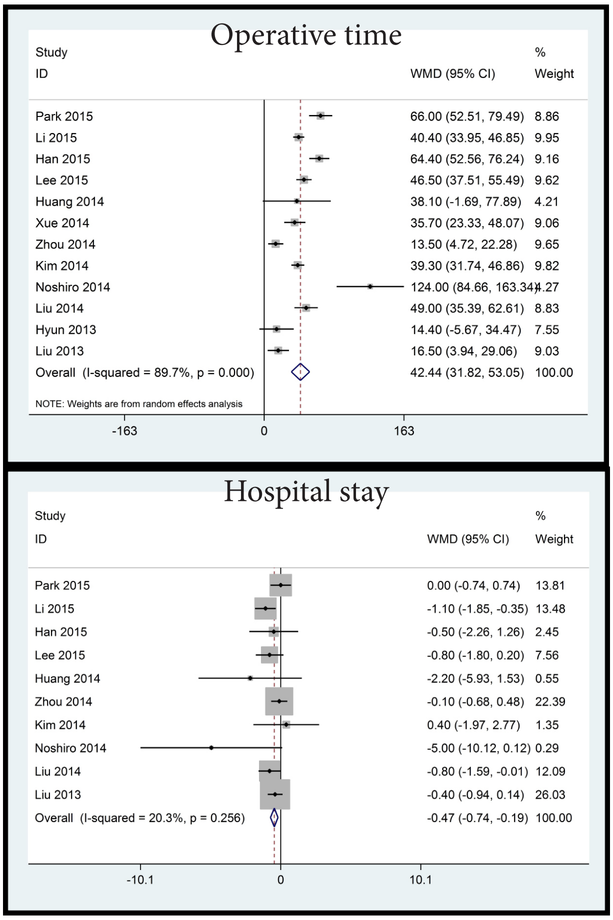

Figure 3. Forest Plots Comparing Efficiency Of RG vs. LG (operative time, hospital stay) Complication

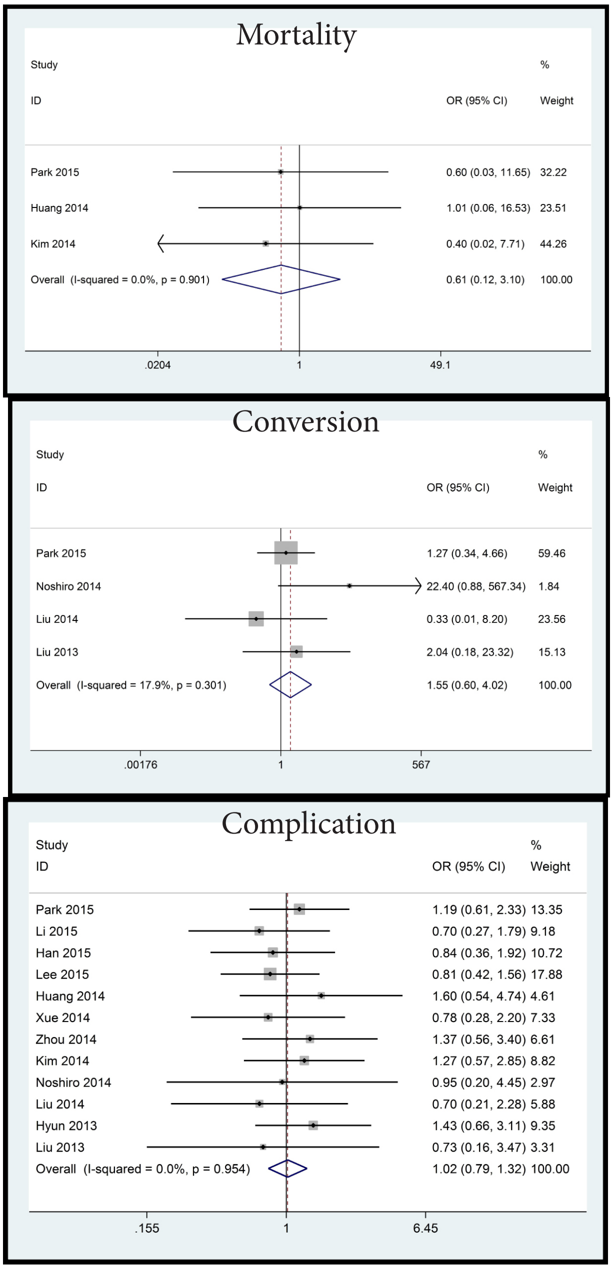

Figure 4. Forest plots comparing safety of RG vs. LG (complication, mortality, conversion)

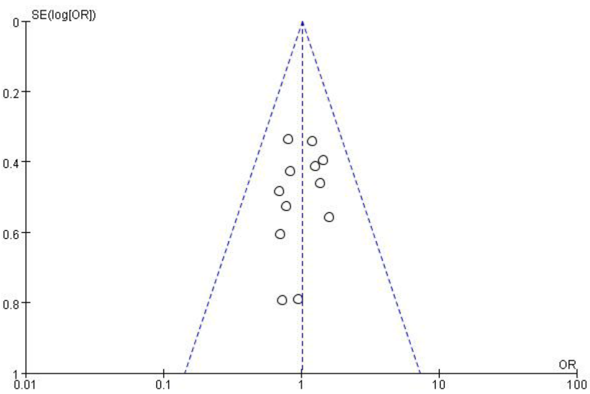

Figure 5. Funnel Plot of Comparing Postoperative Complication Rate between RG and LG, Which Showed No Publication Bias. OR, odds ratio; SE, standard error

However, in term of hospital stay (Liu et al., 2013; Huang et al., 2014; Zhou et al., 2014; Kim et al., 2014; Noshiro et al., 2014; Liu et al., 2014; Park et al., 2015; Li et al., 2015; Lee et al., 2015; Han et al., 2015), meta-analysis suggested that RG group had a shorter hospital stay compared with LG group (WMD=-0.465, 95% CI=-0.741~-0,19, P<0.05), with a no significant heterogeneity (I^2=20.3%, P>0.05).

Meta-analysis of safety

All the studies (Hyun et al., 2013; Liu et al., 2013; Huang et al., 2014; Xue et al., 2014; Zhou et al., 2014; Kim et al., 2014; Noshiro et al., 2014; Liu et al., 2014; Park et al., 2015; Li et al., 2015; Lee et al., 2015; Han et al., 2015) reported total postoperative complication. Analysis of the index showed no statistical difference between the two techniques (OR=1.019, 95% CI=0.786~1.32, P>0.05). According to mortality (Huang et al., 2014; Kim et al., 2014; Park et al., 2015), meta analysis revealed that LG group had a higher mortality than RG group, although there was no statistical difference (OR=0.607, 95% CI=0.119~3.101, P>0.05). Four studies (Liu et al., 2013; Noshiro et al., 2014; Liu et al., 2014; Park et al., 2015) reported conversion to LG or OG, which was described in six cases in RG group and twelve cases in LG group. There was no statistical difference (OR=1.55, 95% CI=0.6~4.02, P>0.05).

Sensitivity analysis

Sensitivity analysis was performed by the alternating method between random effect model and fixed effect model. The results revealed that all the evaluation indexes were consistent with the conclusion of alternating analysis, and that the study stability was good, and that the analytical result was reliable.

Publication bias

Publication bias was examined base on the total postoperative complication with funnel plot method. All included studies were inside the 95% CI and symmetrical around the vertical.

Discussion

Radical gastrectomy is regarded as gold standard of treatment for gastric carcinoma (Wu et al., 2011). The technique has obtained a revolutionary application in gastrectomy with the development of minimally invasive surgery. However, minimally invasive surgery had an altercation over complication and mortality for gastric carcinoma. Minimally invasive surgery increases the quality of life, but it should be guaranteed that this technique can reduce complication and mortality (Zeng et al., 2012), especially the new technique-RG. The present data was still incomplete to support the widespread application of RG for gastric carcinoma (Katsios et al., 2010).

In the meta-analysis, we compared the effectiveness and safety of RG and LG. Regarding the effectiveness, result of meta-analysis revealed that RG was associated with less blood loss, more number of harvested lymph nodes and shorter time to first flatus, compared with LG. Blood loss in minimally invasive gastrectomy occurs mostly during lymph node harvest and is caused by vascular injury. The application of the new techniques (3D video, EndoWrist® and filter tremor) (Hanly et al., 2004; Pugliese et al., 2010; Chen et al., 2013; Suda et al., 2015; Obama et al., 2016) in RG can contribute to more acute operation and lymph node harvest with less blood loss in a large part. It is no doubt that extended lymph node harvest is the basic criterion of treatment for gastric carcinoma with a high risk of node metastasis. In terms of exposure, identification and harvest of lymph node, RG is more convenient and accurate, so that the number of lymph node harvest is more in RG group, which reduces further the risk of lymph node metastasis (Jayaraman et al., 2009; Son et al., 2014).The result of meta –analysis showed that there was significant difference in time to first flatus, and RG had a less time to first flatus than LG, which may be associated with minimal invasion and small stress response of RG (Park et al., 2012). As a pathological parameter, the proximal resection margin was similar in the two group because of no statistical difference, and the distal resection margin was also.

Regarding the efficiency, result of meta-analysis revealed that RG was associated with shorter hospital stay, compared with LG, which might have a close relation to fewer trauma and rapid recuperation. However, the results of meta-analysis suggested that RG required a longer operative time than LG. The reason might come from time of preparing for robotic surgery (Huang et al., 2012). With experience obtained, Zhang et al. reported that the set up time was reduced rapidly to 15.9±8.9 min. Another cause might be from the difference of surgeons' experience (Kang et al., 2012; Eom et al., 2012). The operative time was distinctly affected by surgeons' learning curve. Huang et al. reported that the mean operative time was 467.0 min for the initial 25 patients in RG group. As experience obtained, the operative time was stringently reduced to 286.9 min.

Regarding the safety, analysis of the pooled data of the included studies revealed that complication, mortality and conversion did not differ significantly between RG and LG in the meta-analysis. The postoperative complication rate is an important indicator of surgical procedures, the incidence of complications in RG group was less than in LG group, although no statistical difference. There was only a death in RG group, which was less than LG group (7 deaths).

The results of the meta-analysis should be explicated with caution because of limitations. *i*). The meta-analysis included a large number of patients, but they are non-randomized controlled study, which affect the quality of meta-analysis. *ii*). The postoperative long-term curative effect needs to be further analyzed, because of lack of long-term follow-up, such as the quality of life, recurrence rate and survival rate after operation. *iii*). We find significant heterogeneity in terms of operative time, blood loss and lymph node harvested, and these parameters can be affected by surgeons' experience.

In summary, RG is an effective and safe method in treatment of gastric carcinoma, and makes up for the limitations of laparoscopy, which make patients have fewer trauma, rapid recuperation and a significant advantage in the recent effect. Because of lack of long-term curative effect analysis, it is not sure that the overall effect of RG is better than LG. So multi-center, large sample and high quality randomized controlled trials are needed to evaluate the long-term effect of RG in the treatment of gastric carcinoma in order to provide clinical evidence support for RG. Meanwhile, the future work should focus on reducing the operative time and cost, so that RG can be widely applied in clinical practice.

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