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ABOUT COVER

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AIM AND SCOPE

World Journal of Gastrointestinal Oncology (*World J Gastrointest Oncol*, *WJGO*, online ISSN 1948-5204, DOI: 10.4251) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJGO covers topics concerning carcinogenesis, tumorigenesis, metastasis, diagnosis, prevention, prognosis, clinical manifestations, nutritional support, molecular mechanisms, and therapy of benign and malignant tumors of the digestive tract. The current columns of *WJGO* include editorial, frontier, diagnostic advances, therapeutics advances, field of vision, mini-reviews, review, topic highlight, medical ethics, original articles, case report, clinical case conference (Clinicopathological conference), and autobiography. Priority publication will be given to articles concerning diagnosis and treatment of gastrointestinal oncology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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META-ANALYSIS

Comparison between laparoscopic and open surgery for large gastrointestinal stromal tumors: A meta-analysis

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Author contributions: Cui JX, Gao YH and Xi HQ contributed equally to this work; Wei B and Chen L conceived the project; Cui JX and Gao YH independently searched references and took charge of data extraction and statistical analysis; Xi HQ searched references and extracted the parameters from each study; Cai AZ, Zhang KC and Li JY participated in the manuscript revision; all authors read and approved the final manuscript.

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Abstract

AIM

To investigate whether laparoscopic surgery is as safe and feasible as open resection for patients with larger gastrointestinal stromal tumors (GISTs) ($\geqslant$ 5 cm).

METHODS

A systematic search of PubMed, EMBASE, Web of Science and the Cochrane Library database was performed. Relevant studies of laparoscopic and open surgery for GISTs of > 5 cm published before December 2016 were identified from these databases. The quality of the studies was assessed by the Newcastle-Ottawa Quality Assessment Scale. The tumor size, operation time, blood loss, postoperative hospital stay, complication rate, and disease-free survival rate were assessed. The software Stata (version 12.0) was used for the meta-analysis.

RESULTS

Five clinical trials comprising 209 patients with GISTs of similar larger sizes were evaluated. The pooled analysis of 100 patients in the laparoscopic resection group and 109 patients in the open resection group demonstrated that laparoscopic surgery was significantly associated with a shorter postoperative hospital stay (P < 0.001)

and less blood loss (P = 0.002). Moreover, there were no statistically significant differences in the operation time (P = 0.38), postoperative complication rate (P = 0.88), or disease-free survival rate (P = 0.20) between two groups.

CONCLUSION

Our findings revealed that for patients with large GISTs of comparable sizes, laparoscopic surgery did not significantly influence the operation factors or clinical outcomes compared with open surgery. This suggests that laparoscopic resection is as acceptable as open surgery for treatment of large gastric GISTs.

Key words: Laparoscopic resection; Open resection; Gastrointestinal stromal tumor; Meta-analysis; Clinical outcome

Core tip: Whether laparoscopic resection is also effective and feasible for treatment of larger gastric gastrointestinal stromal tumors (GISTs) (> 5 cm) remains unknown. This meta-analysis collected up-to-date clinical data of comparison of laparoscopic and open resection for larger gastric GISTs (> 5 cm). Our results showed that laparoscopic resection is an upgraded minimal invasive technique with a shorter postoperative hospital stay and less intraoperative blood loss compared with open surgery in treating patients with larger GISTs.

Cui JX, Gao YH, Xi HQ, Cai AZ, Zhang KC, Li JY, Wei B, Chen L. Comparison between laparoscopic and open surgery for large gastrointestinal stromal tumors: A meta-analysis. *World J Gastrointest Oncol* 2018; 10(1): 48-55 Available from: URL: http://www.wjgnet.com/1948-5204/full/v10/i1/48.htm DOI: http://dx.doi.org/10.4251/wjgo.v10.i1.48

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most common gastrointestinal sarcomas. They usually arise from the interstitial cells of Cajal and regulate gastrointestinal motility[1,2]. GISTs are often characterized by cellular markers such as CD117 (a receptor tyrosine kinase protein also known as tyrosine-protein kinase Kit). The stomach is the most prevalent location of GISTs, and the proximal stomach is involved in about two-thirds of suffering patients[3]. It is well accepted that the malignant potential of GISTs depends on the tumor size, cell mitotic rate, and tumor location[4].

Although substantial advances have been made in the targeted therapies for these tumors, surgical resection is still the most important component in the treatment of primary GISTs with no evidence of metastasis. Because wide margins (> 5 cm) and lymph node dissection are not necessary in the surgical management of GISTs[5], laparoscopic surgery seems to be more suitable for resection of these tumors. Various types of laparoscopic procedures for GISTs have been performed in a few specialized centers, including wedge resection of the stomach, intragastric tumor resection, and combined endoscopic–laparoscopic resection, *etc*. However, during laparoscopic surgery, these tumors must be handled with great care because rupture of their capsule confers a near 100% risk of recurrence.

Several studies and meta-analyses have shown that laparoscopic resection for gastric GISTs is as safe and efficacious as open surgery; additionally, laparoscopy is associated with less blood loss, less morbidity, and quicker recovery[6-8]. The long-term survival of patients with GISTs mainly depends on the tumor progression, and laparoscopic surgery does not increase the risk of tumor relapse and metastasis. The clinical practice guidelines for the management of GISTs released by the National Comprehensive Cancer Network and the Japanese Study Group on GIST note that laparoscopic surgical resection is the preferred therapy for relatively small GISTs with a diameter of < 5 cm[9].

However, most cohort studies have focused on laparoscopic surgery for relatively smaller tumors; few have been designed for evaluation of larger GISTs (> 5 cm)[10-14]. Although the size limit was not clearly stated, the practice guideline of the European Society for Medical Oncology recommends application of laparoscopic procedures in patients with large GISTs[15]. However, the complex surgical skills and long learning curve associated with laparoscopic surgery might prevent its application to larger GISTs to some extent[16]. Therefore, the feasibility and safety of laparoscopic surgery for GISTs of > 5 cm remains unclear. Additionally, whether 5 cm is the most appropriate cutoff for performance of minimally invasive procedures in patients with larger GISTs remains controversial. This meta-analysis was performed to assess the short- and long-term results of patients with larger gastric GISTs (> 5 cm) undergoing laparoscopic surgery.

MATERIALS AND METHODS

Literature search

Systematic electronic searches of PubMed, EMBASE, the Cochrane Library, the Clinical Trials Database, Web of Science, and Google Scholar were performed to identify relevant articles published up to 30 December 2016, utilizing the following search terms: "gastrointestinal stromal tumor," "GIST," "laparoscopic," "laparoscopy," "open resection," "gastrectomy," and "stomach". Citations and references of identified studies were also reviewed for additional literature and trials. The language of the publications was limited to English.

Table 1 Main characteristics of enrolled trials

Ref.	Region	Year	Study design	Study period	Sample size		Tumor size (cm)		CS	Follow-up (mo)
					LAP	Open	LAP	Open		
Kim *et al*[10]	South Korea	2012	OCS (R)	1998-2011	24	14	6.1 ± 1.3	7.2 ± 1.7	0	49.3 (8.4-164.4)
Lin *et al*[11]	China	2014	OCS (R)	2007-2012	23	23	7.2 ± 1.6	7.3 ± 1.5	1	34.0 (6-78)
Hsiao *et al*[12]	Taiwan	2015	OCS (P)	2002-2012	18	37	6.1 ± 1.0	6.0 ± 0.9	0	43.2 (16.8-133.2)
Takahashi *et al*[13]	Japan	2015	OCS (R)	1995-2011	12	15	7.5 ± 1.9	5.5 ± 0.73	3	63 (7-154)
Khoo *et al*[14]	Japan	2016	OCS (R)	2002-2015	23	36	NA	NA	1	45

OCS: Observational clinical study; R: Retrospective study; P: Prospective study; NA: Not available; CS: Convention surgery.

Study selection

The inclusion criteria were as follows: (1) The studies involved patients with gastric GISTs larger than 5 cm; (2) The specific interventions were laparoscopic and open surgical resection; (3) The clinical outcomes were the operation time, intraoperative blood loss, conversion rate, length of hospital stay, adverse events, and long-term outcomes (overall survival, disease-specific survival, or recurrence rate); (4) Controlled studies (randomized controlled trials, cohort studies, and case-control studies) were included for the pooled analysis. However, case reports and case series were included for the systematic review; and (5) The informative data and full text of the articles were available.

The exclusion criteria were as follows: (1) The patients had GISTs that were located outside of the stomach or complicated with mixed disease; (2) Duplicate publications; (3) the size of the GIST was not specifically stated; (4) The article was a case report or review; and (5) The publication was in a language other than English.

Data extraction and management

Two reviewers independently screened the titles and abstracts of the publications. Once deemed acceptable, the whole manuscripts were obtained and screened. Controversial issues were resolved by discussion or referred to a third reviewer. Another two reviewers independently extracted the data using a unified form and resolved any discrepancies through discussion. The variables of interest included the author, study period, number of patients, tumor size, operation time, blood loss, length of postoperative hospital stay, complication rate, and long-term outcome (namely disease-free survival). In addition, if the original studies included the median, range, and size of a sample, we estimated the mean and variance using the methods described by Hozo *et al*[12].

The quality of the included papers was assessed using the Newcastle-Ottawa Quality Assessment Scale[17]. This scale ranges from 0 to 9 points; studies with a score of $\geqslant$ 6 were considered methodologically sound.

Statistical analysis

The meta-analysis was performed using weighted mean differences (WMDs) for continuous variables, odds ratios for dichotomous variables, and hazard ratios for time-to-event variables. Statistical heterogeneity was assessed by performing χ^2 tests and calculating the Higgins I^2 statistic, and a value of P < 0.10 or I^2 > 50%, indicated statistical significance. A fixed-effects model was generally employed. If the heterogeneity was statistically significant, a random-effects model was adopted. Publication bias was evaluated by Begg's test. A P value of < 0.05 was considered significant. Statistical analyses were performed using Stata software (version 12.0; StataCorp, College Station, TX, United States).

RESULTS

Enrolled studies and quality assessment

No eligible randomized controlled trials were identified, but 5 nonrandomized trials were analyzed (209 patients with GISTs of similar size). Overall, 100 patients underwent laparoscopic resection and 100 underwent open resection. A flow chart of the search strategy is illustrated in Figure 1. The main characteristics and quality assessment results of the included studies are shown in Tables 1 and 2, respectively.

Tumor size

Four studies reported no statistically significant differences in tumor size between the laparoscopy and open group, while Kim *et al*[10] reported that the tumor size in the open group was significantly larger than that in the laparoscopy group. Additionally, in the pooled data from a fixed-effects model with no significant heterogeneity (I^2 = 53.3%, P = 0.073) (Table 3), no significant difference was identified in the total analysis [WMD = -0.038 cm, 95% confidence interval (95%CI): -0.699 to 0.362, P = 0.632] (Figure 2).

Operative factors

All enrolled studies provided data for analysis of the operation time. The results showed no significant difference between the two groups (WMD = 7.17 min, 95%CI: -56.02 to 70.36, P = 0.824) (Figure 3A). Because obvious heterogeneity was detected (I^2 = 92.9%, P = 0.000) (Table 3), a random-effects model was employed.

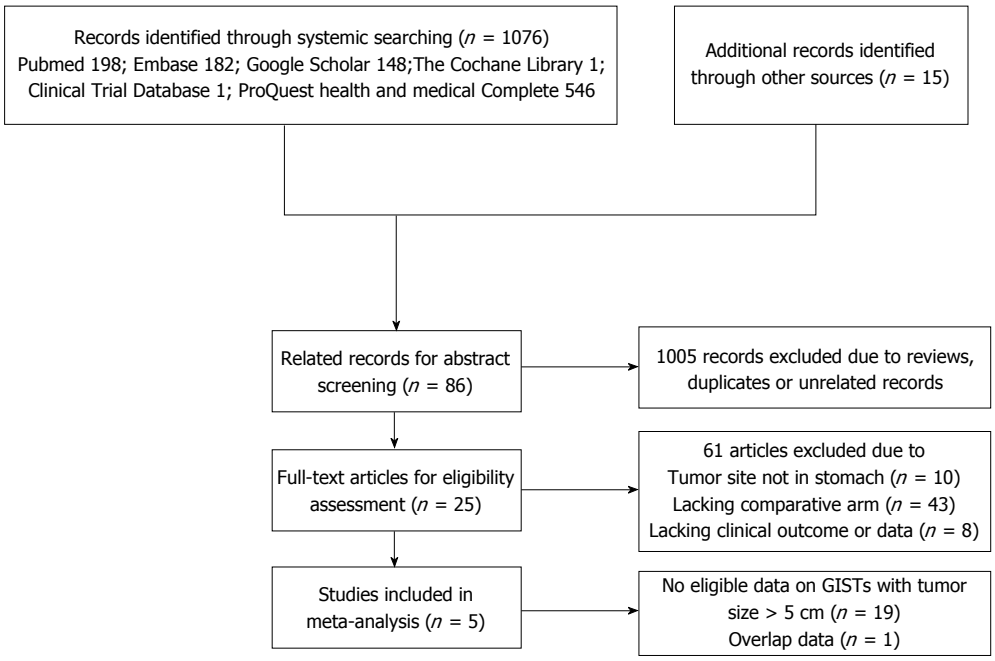

Figure 1 Flow chart of study selection process. GISTs: Gastrointestinal stromal tumors.

Table 2 Newcastle-Ottawa Scale Assessment of enrolled studies

Ref.	Selection (0-4)				Comparability		Outcome (0-3)			Total
	REC	Snec	AE	OINP	SCB	SCA	AO	FU	AFC	
Kim *et al*[10]	1	1	1	1	1	0	1	1	1	8
Lin *et al*[11]	1	1	1	1	1	1	1	1	0	8
Hsiao *et al*[12]	1	1	1	1	1	0	1	1	1	8
Takahashi *et al*[13]	1	1	1	0	1	0	1	1	1	7
Khoo *et al*[14]	1	1	1	1	1	1	1	1	1	9

REC: Representativeness of the exposed cohort; SNEC: Selection of the no exposed cohort; AE: Ascertainment of exposure; OINP: Outcome of interest not presented in the start of study; SCB: Study controls for basic characteristics; SCA: Study controls for additional factor; AO: Assessment of outcome; FU: Follow-up; AFC: Adequacy of follow up.

Table 3 Summary results of meta-analysis of clinical outcomes

Outcomes	No. of studies	Effect value	95%CI of effect	Heterogeneity	
				I^2 (%)	*P* value
Tumor size	4	WMD = -0.0.38	-0.699 to 0.362	53.3	0.073
Operation time	5	WMD = 7.17 min	-56.02 to 70.36	92.9	0.000
Blood loss	4	WMD = -47.47 mL	-93.20 to -1.73	63.2	0.043
Postoperative complications	5	OR = 0.93	0.34 to 2.50	0.0	0.858
Postoperative stay	5	WMD = -2.81 d	-3.68 to -1.94	38.7	0.163
Progression-free survival	5	HR = 0.64	0.35 to 1.19	0.0	0.553

WMD: Weighted mean differences.

Four studies reported data regarding intraoperative blood loss; Lin *et al*[11] reported that laparoscopic surgery was associated with less blood loss. The heterogeneity between the studies was significant (I^2 = 63.2%, *P* = 0.043); therefore, the analysis was performed with a random-effects model. In the pooled data, a significant difference was found among these three groups (WMD = -47.47 mL, 95%CI: -93.20 to -1.73 mL, *P* = 0.042) (Figure 3B).

Among all enrolled studies, five patients in the laparoscopy group reportedly underwent conversion to open surgery. One conversion resulted from the surgeons' initial learning curve for laparoscopy, one was due to dense adhesion to liver, and the other three occurred because of failure to secure the tumor in the visual field of the laparoscope.

Short-term outcomes

All five studies reported postoperative complications. The pooled data revealed no significant difference

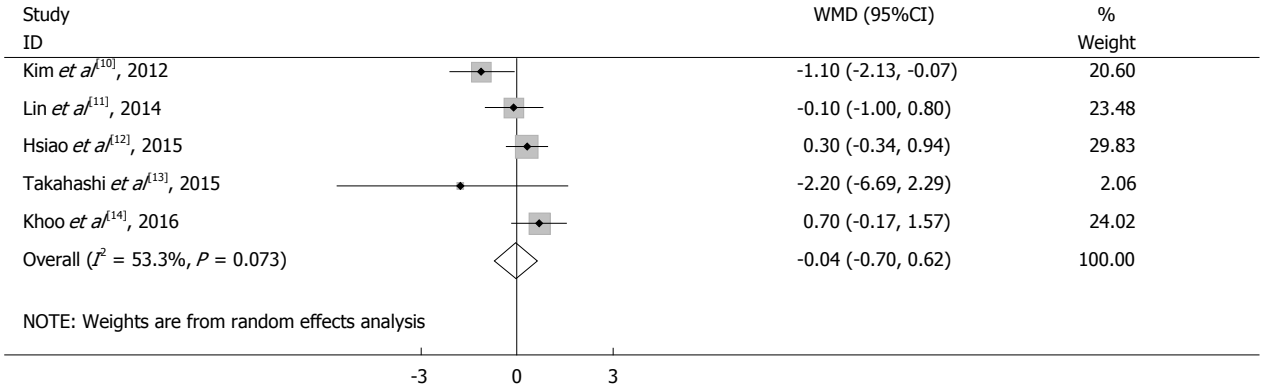

Figure 2 Meta-analysis of tumor size in laparoscopic surgery and open surgery groups.

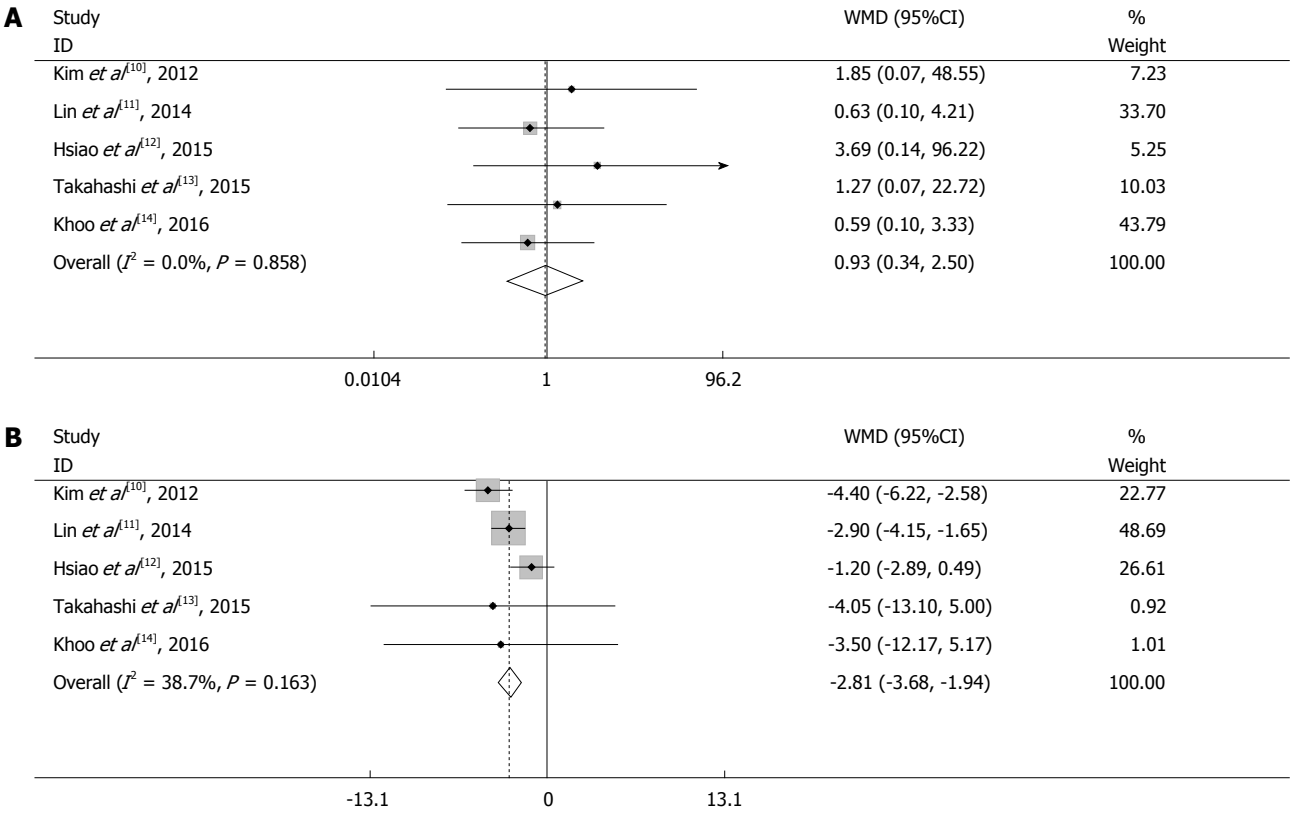

Figure 3 Meta-analysis of operative factors in laparoscopic surgery and open surgery group. A: Pooled analysis of operation time; B: Pooled analysis of blood loss.

between the two groups (odds ratio = 0.93, 95%CI: 0.34 to 2.50, P = 0.88) (Figure 4A). A fixed-effects model was used because of the lack of significant heterogeneity (I^2 = 0.0%, P = 0.858).

Five studies reported data regarding the postoperative hospital stay. A fixed-effects model was employed because of insignificant heterogeneity (I^2 = 38.7%, P = 0.163). The postoperative hospital stay was significantly shorter in the laparoscopy than open group (WMD = -2.81 d, 95%CI: -3.68 to -1.94, P < 0.001) (Figure 4B).

Long-term outcomes

All eligible studies reported the progression-free survival of patients. Figure 5 shows a forest plot of disease-free survival and the results of the meta-analysis. No significant difference was observed in patients with larger GISTs who underwent laparoscopic *vs* open surgery (hazard ratio = 0.64, 95%CI: 0.35 to 1.19, P = 0.157). No obvious heterogeneity was observed in this study; therefore, a fixed-effects model was applied in the survival meta-analysis (I^2 = 0.0%, P = 0.553) (Figure 5).

Publication bias

Publication bias was evaluated based on the postoperative hospital stay using Begg's and Egger's tests. No publication bias was identified in the five studies (Begg's test, P = 0.773; Egger's test, P = 0.825) (Figure 6).

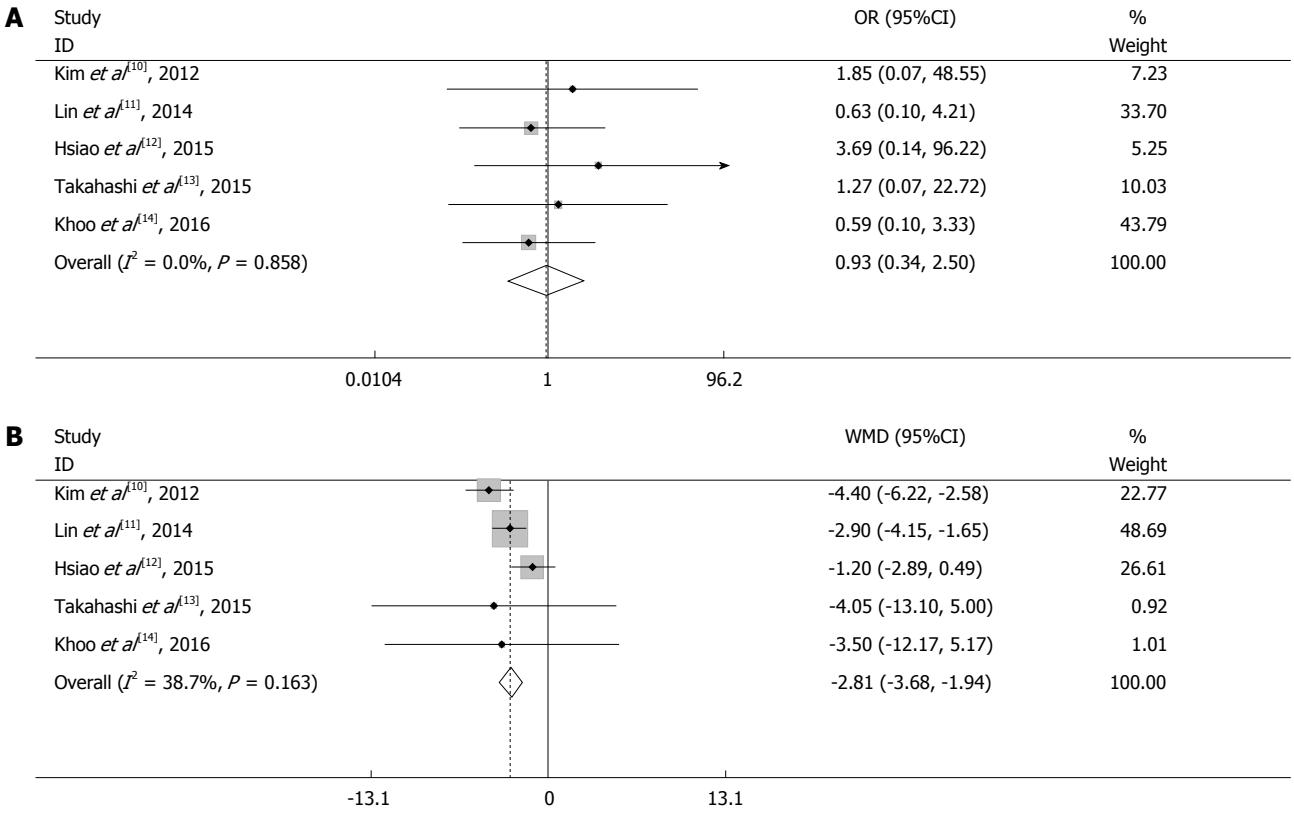

Figure 4 Meta-analysis of short-term outcomes in laparoscopic surgery and open surgery groups. A: Pooled analysis of postoperative complications; B: Pooled analysis of postoperative hospital stay.

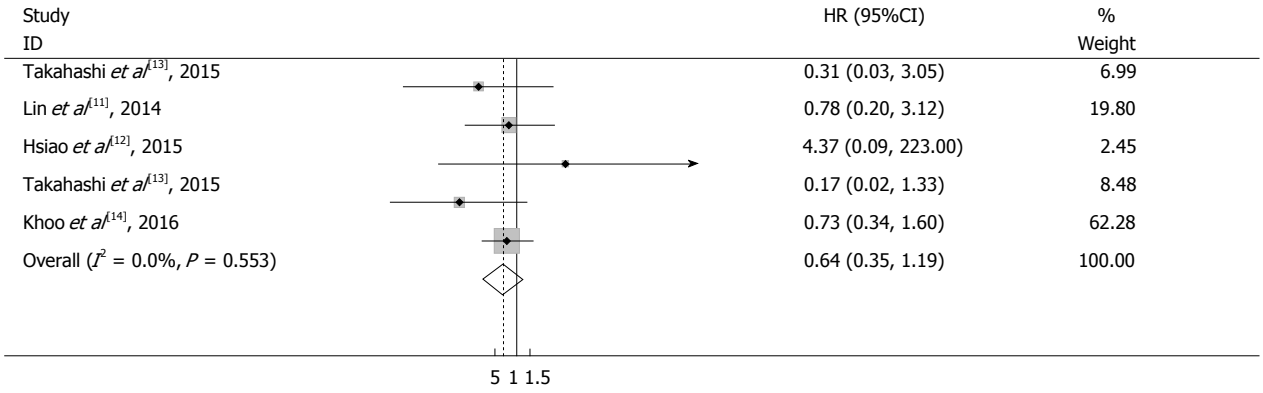

Figure 5 Meta-analysis of progression-free survival in laparoscopic surgery and open surgery groups.

DISCUSSION

Recent studies have suggested that the prognosis of GISTs is mainly based on the tumor size and histological features rather than achievement of wide resection margins[18]. Therefore, laparoscopic resection is more frequently performed for treatment of patients with GISTs using the advances currently being made in surgical techniques.

Although randomized controlled trials are the first choice for high-quality meta-analyses, we failed to enroll any randomized controlled trials in this study. There are several obstacles to design and perform randomized controlled trials, such as ethical issues and organization difficulty[19]. Finally, five nonrandomized controlled studies (one prospective and four retrospective) were enrolled; all were assessed according to the Newcastle-Ottawa Quality Assessment Scale and scored > 6, ensuring their high quality.

Our pooled analysis demonstrated faster recovery and less blood loss in the laparoscopy than open surgery group. Less trauma caused by laparoscopic surgical intervention, only a mild acute inflammatory response, and earlier postoperative activities are considered to contribute to the shorter postoperative hospital stay. Although the blood loss volume might have varied according to the different methods used among the studies, the results of our work indicate

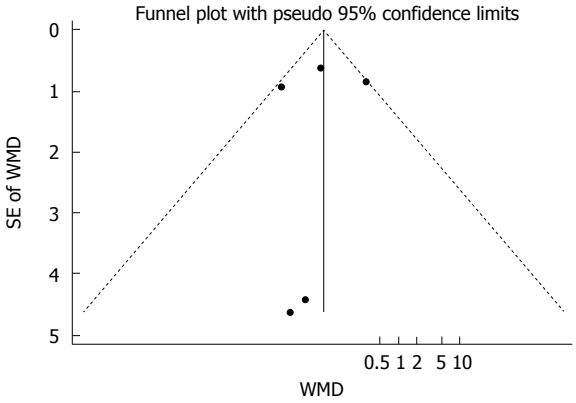

Figure 6 Funnel plot of postoperative hospital stay in laparoscopic surgery and open surgery groups. WMD: Weighted mean difference.

that laparoscopic surgery might reduce patients' surgical trauma to some extent. Furthermore, there was no difference in the postoperative complications between the two groups, adding to the safety of laparoscopic surgery in patients with larger GISTs.

Our review also indicated that laparoscopic resection for larger GISTs is feasible with a conversion rate of 5%, which is similar to other laparoscopic procedures such as laparoscopic gastrectomy[20,21]. The oncological outcome is one of the most concerning problems that prevents application of laparoscopy to the surgical treatment of larger GISTs[22]. Our results showed no difference in the disease-free survival of patients with larger GISTs who underwent laparoscopy *vs* open surgery (hazard ratio = 0.643, 95%CI: 0.349 to 1.185, $P = 0.157$), suggesting that the performance of a laparoscopic procedure does not profoundly influence the oncological outcome compared with open surgery.

Several limitations in our study should be addressed. First, the limited number of patients might affect the reliability of the results (209 patients across 5 studies). Second, most of the patients' tumor sizes ranged from 5 to 10 cm; therefore, the results might not be suitable for patients with GISTs of > 10 cm. Third, treatment of larger GISTs in laparoscopic surgery requires greater surgical skill to prevent tumor rupture and gain adequate resection margins. Therefore, the inclusion of single-center studies with various levels of surgical techniques might have contributed to the bias of our meta-analysis. Finally, the use of different risk classifications and drug therapies within the groups might have also contributed to the bias of recurrence or progression-free survival[23].

In conclusion, this meta-analysis has demonstrated that laparoscopic surgery is as safe and feasible as open surgery for resection of larger GISTs (> 5 cm, mainly 5-10 cm). Moreover, laparoscopic surgery might offer the advantage of faster recovery and less trauma over open surgery in patients with GISTs. More multicenter randomized controlled clinical trials are needed to clarify and confirm the role of laparoscopic surgery in patients with larger GISTs.

ARTICLE HIGHLIGHTS

Research background

Laparoscopic resection of relatively small gastric gastrointestinal stromal tumors (GISTs) is currently well-accepted and has been proven as safe and feasible as traditional open surgery. However, whether laparoscopic resection is also effective and feasible for treatment of larger gastric GISTs (> 5 cm) remains unknown.

Research motivation

The authors aimed to explore whether laparoscopic resection is also effective and feasible for treatment of larger gastric GISTs (> 5 cm), just as the same situation in smaller GISTs.

Research objectives

Laparoscopic resection for small GISTs is now well-accepted. However, whether laparoscopic surgery is as safe and feasible as open resection for patients with larger GISTs (⩾ 5 cm) remains controversial.

Research methods

A systematic search of PubMed, EMBASE, Web of Science and the Cochrane Library database was performed. Relevant studies of laparoscopic and open surgery for GISTs of > 5 cm published before December 2016 were identified from these databases. The meta-analysis was performed using Stata (version 12.0) applying weighted mean differences for continuous variables, odds ratios for dichotomous variables, and hazard ratios for time-to-event variables.

Research results

In terms of operative and oncological factors, our research demonstrated that laparoscopic surgery was significantly associated with a shorter postoperative hospital stay ($P < 0.001$) and less blood loss ($P = 0.002$) in resecting larger GISTs. Moreover, there were no statistically significant differences in the operation time ($P = 0.38$), postoperative complication rate ($P = 0.88$), or disease-free survival rate ($P = 0.20$) between two groups.

Research conclusion

This research stands as the first meta-analysis focusing on this specific type of GISTs. The meta-analysis has demonstrated that laparoscopic surgery is as safe and feasible as open surgery for resection of larger GISTs (> 5 cm, mainly 5-10 cm). Moreover, laparoscopic surgery might offer the advantage of faster recovery and less trauma over open surgery in patients with GISTs.

Research perspectives

Laparoscopic resection is as acceptable as open surgery for treatment of large gastric GISTs.

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