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REVIEW ARTICLE

Comparison of clinical outcomes of laparoscopic versus open surgery for recurrent hepatocellular carcinoma: a meta-analysis

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Abstract

Background The purpose of this study is to compare the clinical outcomes of laparoscopic liver resection versus open liver resection for recurrent hepatocellular carcinoma (RHCC).

Methods Published studies which investigated laparoscopic versus open liver resection for RHCC were identified, and meta-analysis was used for statistical analysis.

Results Six studies were analyzed by meta-analysis method, and cumulative 335 cases were included in this study. Laparoscopic liver resection was performed in 145 cases, and open liver resection was performed in 190 cases. Meta-analysis showed that there was no difference in operative time and 90-day mortality between the laparoscopic group and the open group ($p = 0.06$ and $p = 0.06$ respectively); Nevertheless, compared with the open group, the laparoscopic group resulted in significantly lower rate of in-hospital complication ($p < 0.0001$), much less blood loss ($p < 0.0001$) and shorter postoperative hospital stay ($p = 0.002$).

Conclusion Laparoscopic liver resection for RHCC offers a benefit of lower in-hospital complication rate, less blood loss, shorter postoperative hospital stay, while similar operative time and 90-day mortality as the open liver resection. Laparoscopic liver resection is feasible with satisfactory postoperative outcomes and can be a safe alternative treatment strategy to open procedure for RHCC.

Keywords Recurrent hepatocellular carcinoma · Laparoscopic liver resection · Open liver resection · Meta-analysis

The incidence of hepatocellular carcinoma (HCC) has risen, which ranks as the fifth most common carcinoma in men, the seventh most common in women and has become the third most frequent cause of cancer-related death all over the world [1, 2]. For HCC in patients with good liver function, hepatic lobe resection is an effective and only potentially curative treatment method [3]. However, the clinical outcomes of liver resection are often undermined by high rates of recurrence (more than 70%), and recurrence in intrahepatic is reported about 80% of these patients [4, 5]. Hence, further salvage treatment is extremely necessary. Up to now, liver-repeated resection has been shown to be an effective

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treatment for recurrent HCC (RHCC) with a satisfactorily and acceptably low morbidity and mortality rate [6, 7].

With the dramatic innovation in laparoscopic techniques and instruments in the past decade, the role of laparoscopic liver resection has been established in the treatment of HCC. Benefit from its advantages of less invasiveness, the similar oncologic clearance and survival rate compared with traditional open surgery, it is increasingly adopted worldwide for treatment of HCC [6, 8]. However, due to formation of intra-abdominal adhesions, change in anatomy, and other adverse conditions caused by the primary operation, laparoscopic liver resection for RHCC presents more technical challenges. So far, there are only a few studies with small numbers on the application of laparoscopic liver resection for RHCC, and the safety and efficacy of the minimally invasive surgical approach is still controversial.

Hence, we performed this systematic review and meta-analysis to compare the clinical outcomes of laparoscopic liver resection versus open liver resection for RHCC, so that the best treatment strategy for the RHCC patients could be chosen.

Materials and methods

This article is a meta-analysis, which extract data from the published articles to make further statistical analysis, so Institutional Review Board approval is not needed for this paper.

Search strategy

The following databases were systematically searched without time restrictions using the English language in December 2018: the electronic database Medline (PubMed), EMBASE, and Web of Science. "recurrent hepatocellular carcinoma", "recurrent hepatoma" combined with "laparoscopic surgery", "laparoscopic hepatectomy", "laparoscopic liver resection" and "laparotomy", "open surgery" were used as key words, using the Boolean operators AND, OR. To prevent missing relevant publications, the references of publication and reviews were hand searched.

Inclusion criteria and data extraction

Studies were included in this meta-analysis if they met the following criteria: (1) patients were diagnosed as RHCC by contrast-enhanced computed tomography (CT) angiography or magnetic resonance (MR) angiography combined with tumor marker (AFP or Ca199, Ca242, Ca125); (2) patients had been treated by one of these 2 approaches (laparoscopic surgery or open surgery); (3) all publications have complete and clear comparative data; and (4) all publications must have reported at least one evaluation result of the following: operative time, blood loss, in-hospital complication rate, postoperative hospital stay, and 90-day mortality, or sufficient data to estimate one of them. We excluded the studies that were of repetition, poor quality, or had little information.

Data were extracted independently by two researchers (W.C. and Z.L.) from each study as follows: the first author's surname, the year of publication, the nationality of the first author, the number of patients treated by laparoscopic surgery and open surgery, follow-up time and evaluation results. Disagreements were resolved by discussion and were checked by the third researcher (Q.L.).

Assessment of study quality

Study quality was assessed independently by two researchers (W.C. and Z.L.) by means of a predefined form. It included the following criteria: (1) whether the study reported inclusion and exclusion criteria; (2) whether the study data were prospectively or retrospectively gathered; (3) whether the patient's characteristics were sufficiently described; (4) whether the method used to measure the clinical outcomes of these two approaches was sufficiently described; (5) whether the start point and endpoint of the study was provided; (6) whether the follow-up time of patients in the study was described; and (7) whether the study reported how many patients were lost to follow-up and the percentage should be below 10%. Studies with a total score of 7 were considered to show the highest study quality, and a zero score indicated the lowest quality. The median quality score of these included studies was 5 (range 4–7).

Statistical analysis

Statistical analysis was carried out using Comprehensive Meta-analysis software (RevMan version 5.0). Data were derived from the included studies. When the clinical outcome was mentioned, but there were no enough data to take statistical analysis, we would try to contact the author to get the original data. 95% confidence intervals (CIs) was used for continuous and dichotomous data, while odds ratio (ORs) was only used for dichotomous data in this meta-analyses. Q-test and I^2 statistic were used to estimate the heterogeneity between these studies. If the I^2 statistic was $\leq 50\%$, we thought these studies had little heterogeneity and the fixed effects model was used in this meta-analysis; but if the I^2 statistic was $> 50\%$, it meant that these studies had great heterogeneity and then we would try our best to find the cause of heterogeneity. These studies would be divided into subgroups, Q-test and I^2 statistic were used to estimate the heterogeneity in the subgroup, if the subgroup still

had statistical heterogeneity, but they did not have clinical heterogeneity, or the difference between them had no statistical significance, the random effect model would be used in this meta-analysis. Potential publication bias was evaluated through a funnel plot, which was further investigated by Egger's and Begg's test. All tests were two sided and p values < 0.05 were considered to be statistically significant.

Results

Characteristics of the included studies

A total of six studies were subjected to final analysis and 335 patients were included [9–14]. Among these studies, there were 145 cases in the laparoscopic group and 190 cases in the open group. These cases came from two countries (Japan and China). The general information of the included studies are summarized in Table 1.

Operative time

All these six studies had reported the operative time, and these studies analyzed using Q test showed that they had little heterogeneity ($p = 0.21$, $I^2 = 30\%$), therefore, the fixed effects model was used in this meta-analysis. The results showed that there was no statistical difference between these two groups (MD = − 13.56, 95% CI − 27.50 to 0.38, $p = 0.06$), which meant that though laparoscopic liver resection presented more technical challenges, the operative time was not markedly increased in the laparoscopic group (Fig. 1).

Blood loss

All these six studies had reported the blood loss. Q test showed that these studies had great heterogeneity ($p = 0.0008$, $I^2 = 76\%$), and therefore, the random effects model was used and the results showed that there was a statistically significant difference between these two groups (MD = − 330.22, 95% CI − 486.10 to − 174.35, $p < 0.0001$) (Fig. 2). Then, these studies were reviewed and we found

Table 1 The general information of the included studies in this meta-analysis

Author	Year	Country	Group	Number	Follow-up (months)	Outcomes measured
Kanazawa [9]	2013	Japan	LG	20	NR	OT, BL, IHC, PHS, NDM
			OG	20	NR	
Chan [10]	2014	China	LG	11	NR	OT, BL, IHC, PHS
			OG	22	NR	
Zhang [11]	2016	China	LG	31	17	OT, BL, PHS
			OG	33	17	
Liu [12]	2017	China	LG	30	35	OT, BL, IHC, PHS, NDM
			OG	30	35	
Noda [13]	2018	Japan	LG	20	NR	OT, BL, IHC, PHS
			OG	48	NR	
Ome [14]	2018	Japan	LG	33	NR	OT, BL, IHC, PHS, NDM
			OG	37	NR	

LG laparoscopic group, *OG* open group, *NR* not reported, *OT* operative time, *BL* blood loss, *IHC* in-hospital complication, *PHS* postoperative hospital stay, *NDM* 90-day mortality

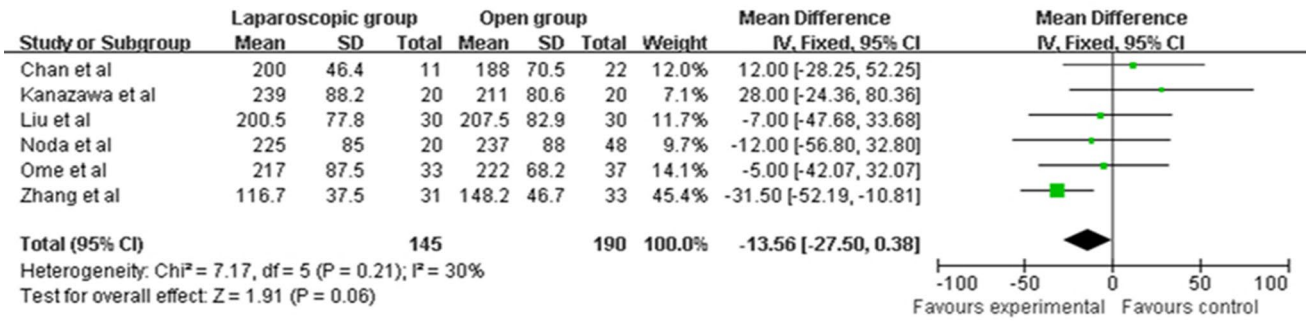

Fig. 1 The comparison of the operative time between the laparoscopic group and the open group. We found that there was no statistical difference between these two groups ($p = 0.06$)

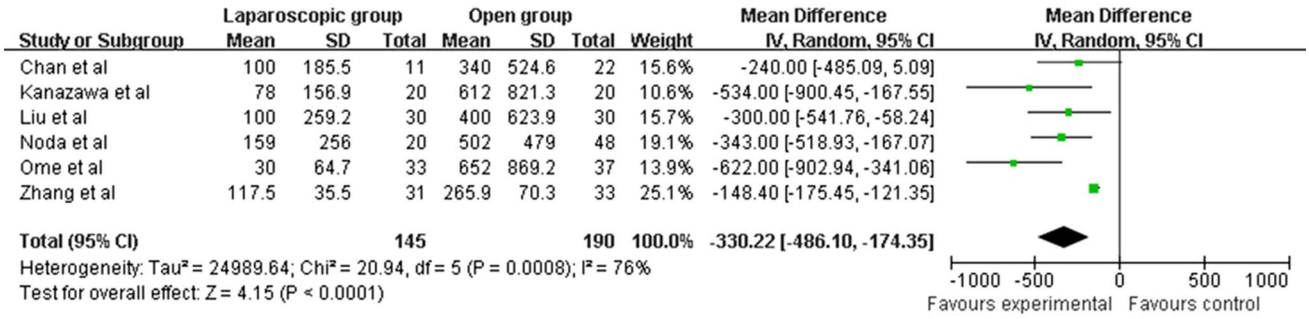

Fig. 2 The comparison of the blood loss between the laparoscopic group and the open group. We found that the laparoscopic group had much less blood loss compared with the open group ($p < 0.0001$)

that, except for hepatectomy, 9 patients and 5 patients were further treated by Transcatheter Arterial Chemoembolization (TACE) and local thermal ablation, respectively, before reoperation in Zhang [11] study. Therefore, five studies were analyzed and Q test showed no statistical significance of heterogeneity ($p = 0.25$, $I^2 = 25\%$). Finally, the fixed effects model was used in this analysis and the results showed there was a statistically significant difference between these two groups (MD = − 372.09, 95% CI − 479.81 to − 264.37, $p < 0.00001$) (Fig. 3). This meant that the laparoscopic liver resection group had much less blood loss, which may have absolutely benefited the patients' recovery.

In-hospital complication rate

In the included six studies, five studies had reported in-hospital complications, which included bile leak, subphrenic collection, intra-abdominal hemorrhage, surgical site infection, ascites, hepatic failure, renal failure, heart failure and delayed gastric emptying. These five studies had little heterogeneity ($p = 0.18$, $I^2 = 36\%$), and therefore, the fixed effects model was used in this meta-analysis. The results showed that there was a statistically significant difference between these two groups (OR 0.16, 95% CI 0.07–0.38, $p < 0.0001$), which meant that the patients had much less in-hospital complications after laparoscopic liver resection (Fig. 4).

Postoperative hospital stay

The postoperative hospital stay was referred in all these six studies. Q test showed that these studies had great heterogeneity ($p = 0.00001$, $I^2 = 91\%$), so we prudently reviewed these studies again, but no abnormalities were found. Finally, the random effects model was used and the results showed that there was a statistically significant difference between these two groups (MD = − 3.32, 95% CI − 5.44 to − 1.21, $p < 0.002$), which meant the patients could be discharged earlier after surgery in the laparoscopic liver resection group (Fig. 5).

Ninety-day mortality

Three of the included six studies had reported 90-day mortality. These three studies had little heterogeneity ($p = 0.31$, $I^2 = 3\%$), and therefore, the fixed effects model was used in this meta-analysis. The results showed that there was no difference in the 90-day mortality between these two groups (OR 1.06, 95% CI 0.15–7.57, $p = 0.96$) (Fig. 6).

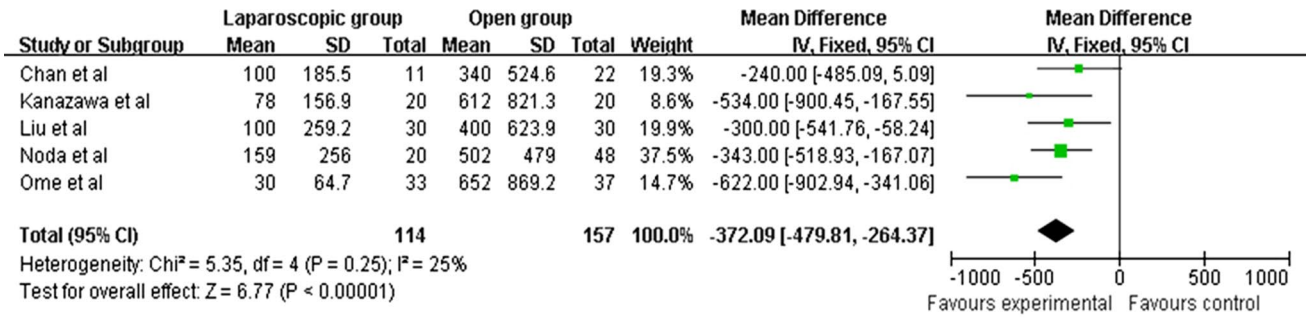

Fig. 3 The comparison of the blood loss of five little heterogeneity studies between the laparoscopic group and the open group. We found that the laparoscopic group had much less blood loss compared with the open group ($p < 0.00001$)

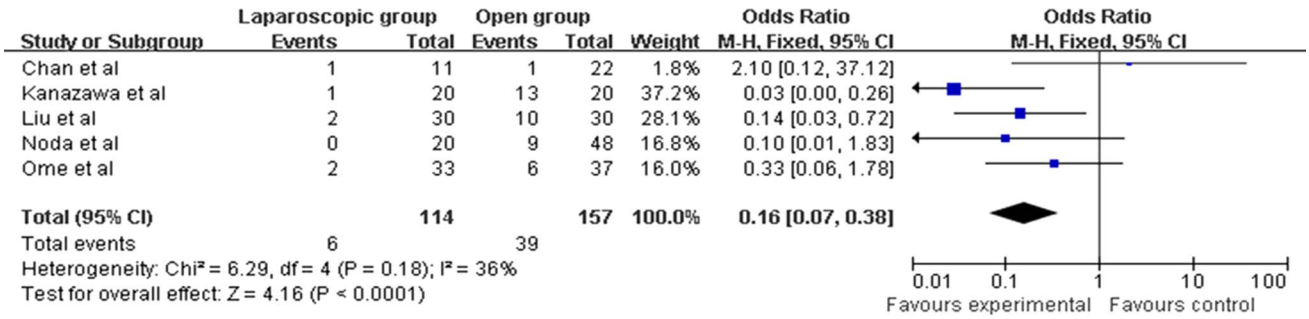

Fig. 4 The comparison of the in-hospital complication rate between the laparoscopic group and the open group. We found that the laparoscopic group had a significant lower in-hospital complication rate compared with the open group ($p < 0.0001$)

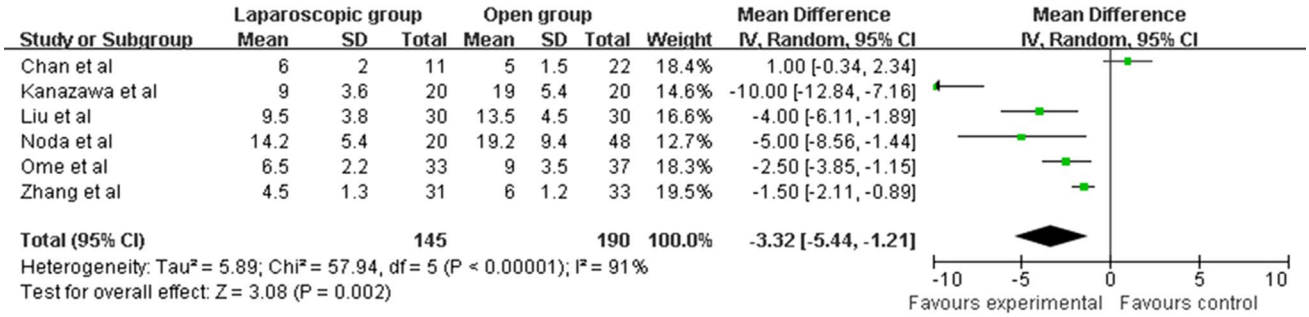

Fig. 5 The comparison of the postoperative hospital stay between the laparoscopic group and the open group. We found that patients in the laparoscopic group had a much shorter hospital stay after operation compared with patients in the open group ($p < 0.002$)

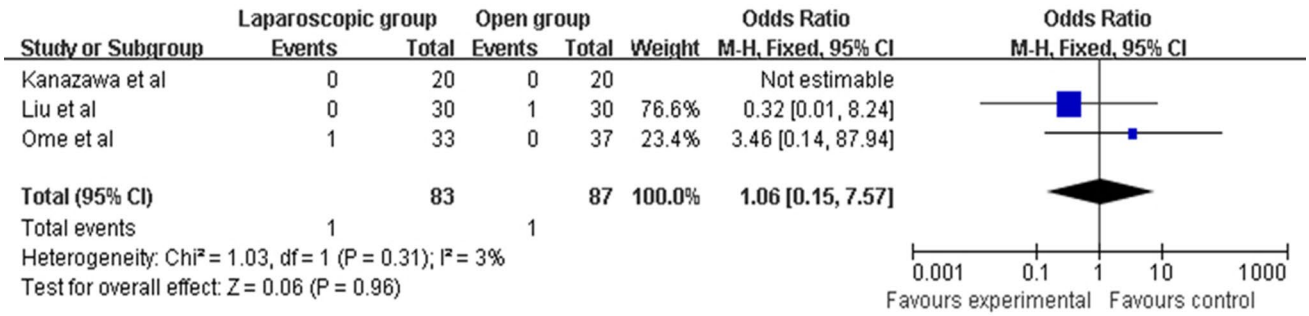

Fig. 6 The comparison of the 90-day mortality between the laparoscopic group and the open group. We found that there was no difference between these two groups ($p = 0.96$)

Sensitivity analysis and publication bias

Publication bias was investigated using a funnel plot. When reviewing the funnel graph, we found that all plots were scattered in the funnel, but not symmetrically, which meant that there was some publication bias in this meta-analysis (Fig. 7). We considered that the publication bias could originate from three sources: the authors, the sponsor of the study, and the editors or reviewers of the journal to which the article was submitted. They were more likely to publish the studies which reported statistically significant results [15–17].

Discussion

After actively improving liver function, liver resection is still an effective treatment method for RHCC. In 1991, Reich reported the first successful and complete laparoscopic liver resection [18]. Since then, laparoscopic liver resection has gradually gained popularity. Especially, as the laparoscopic

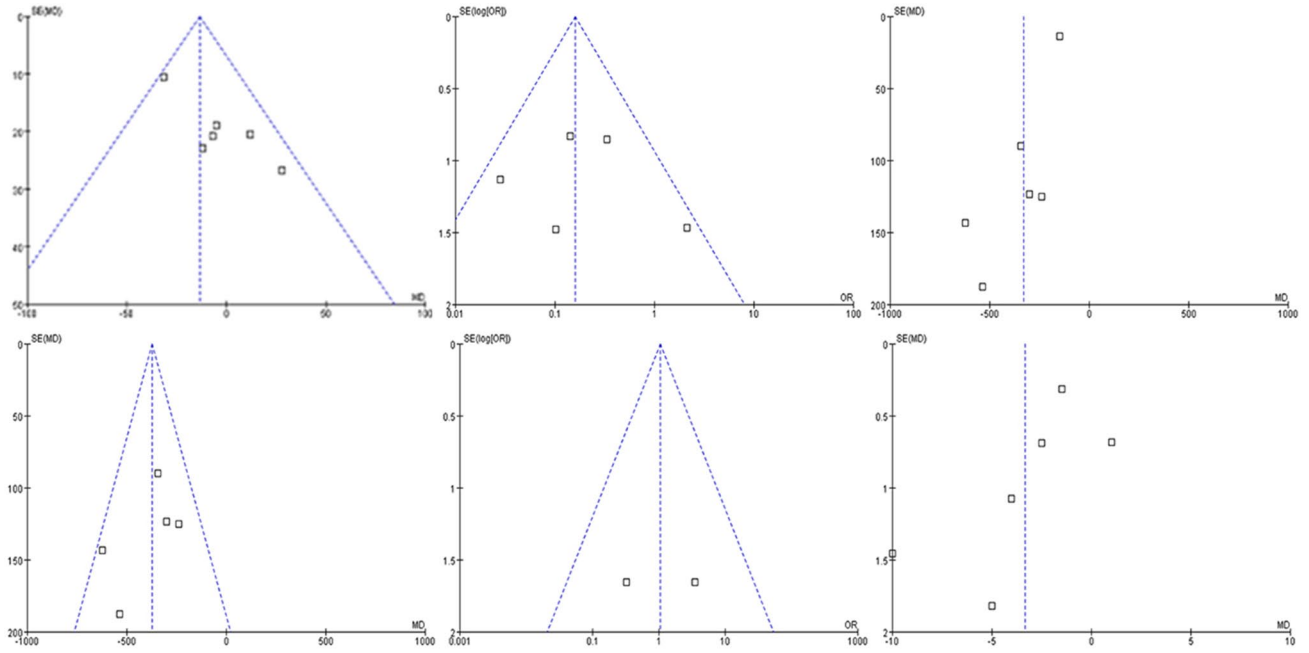

Fig. 7 Funnel plot of publication bias. From the funnel plot, we could find that there was some publication bias in this meta-analysis

surgical techniques and instruments have improved and surgeons have been more experienced, laparoscopic liver resection has become increasingly common in clinical practice [19–22].

However, due to the presence of intra-abdominal adhesions, laparoscopic liver resection for RHCC presents more technical challenges. The intra-abdominal adhesions are inevitable after laparotomy (70–95% of patients) [23, 24]. Its degree and range cannot be predicted. Besides, due to the possibly severe portal hypertension in HCC patients, the venous collateral circulation is more likely formed between the abdominal wall and the omentum [25]. The dense and hypervascularized intra-abdominal adhesions make laparoscopic liver resection more challenging, and usually lead to more intraoperative bleeding. When performing laparoscopic liver resection for RHCC, surgeons must dissect additional intra-abdominal adhesions to obtain an optimized surgical field, which might increase the blood loss, operative time, and in-hospital complications including risk of bowel injury [26].

For the above reasons, a history of abdominal surgery was once considered a contraindication for laparoscopic liver resection. However, laparoscopic surgical techniques and instrument improvement allow for laparoscopic liver resection to be safely applied in the selected RHCC patients. Recently, bioresorbable anti-adhesion products are reported to effectively reduce abdominal adhesions after abdominal surgery. The routine application of these anti-adhesion products in clinical practice may help surgeons achieve laparoscopic liver resection for RHCC patients [27–29]. Besides, Hu reported that complete dissection of abdominal adhesions can be avoided in laparoscopic liver resection, if the abdominal adhesions do not affect the current procedure [30]. Belli reported that the laparoscopic approach ensured a more meticulous and easier dissection of abdominal adhesions in 2009. Once the pneumoperitoneum was established, the increased intraperitoneal pressure strained the abdominal adhesions to get a large laparoscopic-operating field, which facilitated the dissection of the abdominal adhesions. Besides, he also reported the selection criteria for laparoscopic liver resection for the RHCC patients: a well-preserved liver function, no signs of severe portal hypertension, single tumor with a maximum size of 5 cm, and tumor location limited in segment 2–6 [25].

In this study, the results showed that the volume of blood loss, the rate of in-hospital complication and the length of the postoperative hospital stay in the laparoscopic liver resection group was significantly decreased compared with the open liver resection group. Moreover, the operative time and 90-day mortality was similar between these two groups. These results promise the laparoscopic liver resection as an effective and safe alternative treatment strategy for RHCC.

Transcatheter arterial chemoembolization (TACE) and micro-wave ablation are also important treatments for recurrent HCC [31]. However, they have their own shortcomings. The therapeutic effect of TACE is usually compromised by higher metastasis and recurrence rates, besides, it has certain impairment on liver function. The therapeutic effect of micro-wave ablation is usually cut down by blood flow in the liver, because the faster blood

flow will take away the heat generated by micro-wave. Thus, Hirooka has reported TACE combined with microwave ablation is more conducive to the improvement of patients' survival and quality of life [32].

Benefit from its total removal of tumors and cure for underlying cirrhosis, salvage liver transplantation has gained popularity in recent years for recurrent HCC [33]. Chan has reported salvage liver transplantation is a safe, feasible and effective therapy with a 5-year disease-free rate of 67%, 5-year overall survival rate of 62%, morbidity rate of 34% and morality rate of 6.34% for recurrent HCC [34]. However, Guerrini has reported short- and long-term outcomes of both laparoscopic and open liver resection appear not to be inferior to that of salvage liver transplantation [35], besides, few liver donors and high cost limit its application in clinical practice.

In addition to the publication bias, there are several other types of bias [36, 37]. When finding the published studies, because PubMed began indexing articles in 1966, those published earlier will not be in the database, or when studies whose results are published in a series of articles are more likely to be sampled than those published only once, they may contribute to a biased retrieval of studies. If the inclusion criteria is inappropriate, which may not be so specific as to dictate which studies are included or excluded or even exclude some important studies, this may cause inclusion criteria bias and selector bias. When the data are not extracted accurately from the studies, extractor bias may occur. Besides, Rosenthal has also reported recording error bias, which originates from the difference between the actual study results and the recorded results in the published article [38]. For this paper, because all the six included studies were retrospective research, whatever the types of operation such as segmentectomy, lobectomy, or extended lobectomies, the recurrent HCC patients who had underwent laparoscopic or open liver resection were included in the study and divided into laparoscopic group or open group. The basis for grouping did not consider the specific types of operation. This may lead to a selection bias.

Based on the results of this review of patients from six studies, we demonstrate that laparoscopic liver resection is a feasible and safe alternative for RHCC patients. Compared with the conventional open liver resection, laparoscopic liver resection of RHCC has the advantages of lower in-hospital complication rate, less blood loss, similar operative time and 90-day mortality, which undoubtedly result in a faster recovery and a shorter postoperative hospital stay.

This paper has just systematically reviewed six retrospective studies to summarize the short-term and mid-term outcomes of laparoscopic versus open surgery for recurrent HCC, and multicenter-controlled randomized clinical trial need to be further carried out to verify long-term outcomes.

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Compliance with ethical standards

Disclosures Drs. Wenwu Cai, Zhide Liu, Yangyan Xiao, Weichang Zhang, Da Tang, Boran Cheng and Qinglong Li have no conflicts of interest or financial ties to disclose.

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