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Short- and long-term outcomes of laparoscopic *vs* open surgery for T2 gallbladder cancer: A systematic review and meta-analysis

Abstract

BACKGROUND

With the development of laparoscopic techniques, gallbladder cancer (GBC) is no longer a contraindication to laparoscopic surgery (LS). Although LS is recommended for stage T1 GBC, the value of LS for stage T2 GBC is still controversial.

AIM

To evaluate the short- and long-term outcomes of LS, in comparison to those of open surgery (OS), for stage T2 GBC.

METHODS

We searched the PubMed, Embase, Cochrane Library, Ovid, Google Scholar, and Web of Science databases for published studies comparing the efficacy of LS and OS in the treatment of stage T2 GBC, with a cut-off date of September 2022. The Stata 15 statistical software was used for analysis. Relative risk (RR) and weighted mean difference (WMD) were calculated to assess binary and continuous outcome indicators, respectively. Begg's test and Egger's test were used for detecting publication bias.

RESULTS

A total of 5 studies were included, with a total of 297 patients, 153 in the LS group and 144 in the OS group. Meta-analysis results showed that the LS group was better than the OS group in terms of operative time [WMD = -41.29, 95% confidence interval (CI): -75.66 to -6.92, *P* = 0.02], estimated blood loss [WMD = -261.96, 95%CI: -472.60 to -51.31, *P* = 0.01], and hospital stay [WMD = -5.67, 95%CI: -8.53 to -2.81, *P* = 0.0001], whereas there was no significant difference between the two groups in terms of blood transfusion [RR = 0.60, 95%CI: 0.31-1.15, *P* = 0.13], complications [RR = 0.72, 95%CI: 0.39-1.33, *P* = 0.29], number of lymph nodes retrieved [WMD = –1.71, 95%CI: -4.27 to -0.84, *P* = 0.19], recurrence [RR = 0.41, 95%CI: 0.06-2.84, *P* = 0.36], and 3- and 5-year overall survival [RR = 0.99, 95%CI: 0.82-1.18, *P* = 0.89 and RR = 1.02, 95%CI: 0.68-1.53, *P*

= 0.92; respectively] and disease-free survival [RR = 1.01, 95%CI: 0.84-1.21, *P* = 0.93 and RR = 1.15, 95%CI: 0.90-1.46, *P* = 0.26; respectively].

CONCLUSION

The long-term outcomes of LS for T2 GBC are similar to those of OS, but LS is superior to OS in terms of operative time, intraoperative bleeding, and postoperative hospital stay. Nevertheless, these findings should be validated *via* high-quality randomized controlled trials and longer follow-ups.

Key Words: Gallbladder cancer; T2 stage; Laparoscopic cholecystectomy; Oncological outcome; Meta-analysis

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Core Tip: With the development of laparoscopic techniques, gallbladder cancer (GBC) is no longer a contraindication to laparoscopic surgery (LS). Although LS is recommended for stage T1 GBC, the value of LS for stage T2 GBC is still controversial. This study evaluated the safety and efficacy of LS, in comparison to those of open surgery (OS), for stage T2 GBC. We searched the PubMed, Embase, Cochrane Library, Ovid, Google Scholar, and Web of Sci-ence databases for published studies comparing the efficacy of LS and OS in the treatment of stage T2 GBC, with a cut-off date of September 2022. The Stata 15 statistical software was used for analysis. Finally, a total of 5 studies were included, with a total of 297 patients, 153 in the LS group and 144 in the OS group. Meta-analysis results showed that the LS group was better than the OS group in terms of operative time, estimated blood loss, and hospital stay, whereas there was no significant difference between the two groups in terms of blood transfusion, complications, number of lymph nodes retrieved, recurrence, and 3- and 5-year overall

and disease-free survival rates. The long-term outcomes of LS for T2 GBC are similar to those of OS, but LS is superior to OS in terms of operative time, intraoperative bleeding, and postoperative hospital stay.

INTRODUCTION

Gallbladder cancer (GBC) is one of the most common malignancies of the biliary system and has the 6th highest incidence among gastrointestinal tumors[1]. Radical resection is the only potentially curative treatment for GBC[2-4]. Traditional open extended cholecystectomy, including regional lymph-node dissection and wedge resection of the gallbladder bed, is the standard radical surgery for stage T2 GBC[5,6]. Since the late 1980s, laparoscopic surgery (LS) has been widely used to treat benign gallbladder disease, and GBC has been considered to be a contraindication to LS[7,8]. With the continuous improvement of devices and techniques in recent years, curative resection of gastrocolic cancer and liver cancer in difficult sites and even pancreaticoduodenectomy can be conducted laparoscopically. Additionally, LS is increasingly employed in radical resection of stage T1a GBC, and thus GBC is no longer a contraindication to LS[9]. However, the short- and long-term outcomes of LS for stage T2 GBC are still controversial.

Although there are still concerns about the efficacy of laparoscopic radical surgery of stage T2 GBC, LS has already been exploratively applied to treat patients with T2 GBC, and even T3 GBC, at several large medical institutes. There has been a rapid increase in incidental GBC with the widespread use of laparoscopic techniques in benign gallbladder disease, especially in patients with T2 GBC[10,11]. It has become a point of debate whether LS is safe for the treatment of T2 GBC and whether OS is required.

Previous studies on T2 GBC have been limited to case reports or small-sample retrospective single-arm case series on the technical feasibility, safety, and oncological outcomes. Several recent studies have reported long-term outcomes of laparoscopic treatment of stage T2 GBC[12-16]. As there is still a lack of evidence from high-quality multicentre random controlled trials (RCTs), we believe that it is necessary to conduct a

meta-analysis to provide an evidence-based reference for laparoscopic radical surgery of T2 GBC.

MATERIALS AND METHODS

This meta-analysis was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses[17]. The data used in this study were derived from published studies and are anonymous. This study did not need informed consent from patients or a review by an institutional ethics committee. This meta-analysis was registered under the registration number CRD42022367334 on the systematic review registration platform PROSPERO (https://www.crd.york.ac.uk/PROSPERO/).

Search strategy

The Pubmed, Medline, Cochrane library, Ovid, Google Scholar, and Web of Science databases were searched with a cut-off date of September 2022. The search topics were "laparosco*", "open", "extended cholecystectomy", "open surgery", and "T2 gallbladder cancer". The search strategy for each database is described in Supplementary material. We also conducted an expanded search based on the references of the retrieved publications. Table 1 lists the basic characteristics of the included studies.

Inclusion criteria

(1) Population: Stage T2 GBC; (2) Intervention: LS; (3) Comparison: Open surgery (OS); (4) Study sample size: Unlimited; (5) Type of studies: RCTs, and prospective or retrospective cohort studies; (6) Follow-up time: Unlimited; (7) Language type of the publications: Unlimited; (8) Study type: Human studies; and (9) Primary outcomes: Overall survival, disease-free survival, recurrence, and the number of lymph nodes removed. Secondary outcomes: Operative time, intraoperative blood loss, hospital stay, and postoperative complications.

Exclusion criteria

(1) Studies with unknown follow-up times, or incomplete data and no response from the contact author; and those not peer-reviewed; (2) Single-arm studies with LS or OS; and (3) Robots, reviews, case reports, and animal studies.

Quality assessment

The quality of the cohort studies (retrospective or prospective) was assessed using the Newcastle-Ottawa Scale (NOS), which specifically included study population selection (selection), comparability (comparability), and exposure (exposure) evaluation or outcome (outcome) evaluation. The RCTs were conducted for the risk assessment according to the "risk assessment tool" recommended by the Cochrane Collaboration Network[18-20].

Statistical analysis

The meta-analysis was performed using the STATA SE 13 software. Relative risk (RR) and weighted mean difference (WMD) were used to calculate the pooled statistics for binary and continuous data, respectively, and the 95% confidence interval (CI) was reported for each. Heterogeneity was assessed using the chi-square test, with the significance level set at $P = 0.05$. This meta-analysis was carried out using a random-effects model. $P < 0.05$ was considered to indicate statistical significance[21]. Begg's test and Egger's test were performed using the Stata 15 software to quantitatively assess each outcome for publication bias. Funnel plots were drawn to qualitatively and visually assess the outcomes for publication bias.

RESULTS

Search results and study selection

After searching the publication databases and excluding duplications, 47 articles remained. We then excluded the reviews (including systematic reviews), case reports, and meta-analyses, as well as the studies that were not relevant based on their titles or

abstracts, finally leaving 5 publications to be employed in this meta-analysis. The detailed steps of the publication retrieval are shown in Figure 1. These five publications involved one study from Japan and four studies from South Korea. The basic characteristics of the included studies are shown in Table 1. The included studies were all cohort studies and were quality-evaluated using the NOS. The NOS scores are attached to Supplementary Table 1.

Results of the meta-analysis

We compared LS and OS for T2 GBC in 11 postoperative outcomes, each of which was analysed for sensitivity. The results of the meta-analysis are summarised in Table 2. Random-effects models were used to obtain the effect sizes.

Operative time, intraoperative blood loss, and hospital stay: Five studies reported the operative time with moderate heterogeneity [WMD = -41.29, 95%CI: -75.66 to -6.92), P = 0.02][12-16]. Four studies reported the intraoperative blood loss with moderate heterogeneity [WMD = -261.96, 95%CI: -472.60 to -51.31), P = 0.01][12,14-16]. Five studies reported the hospital stays with high heterogeneity [WMD = -5.67, 95%CI: -8.53 to -2.81), P = 0.0001][12-16]. Operative time (min), intraoperative blood loss (mL), and length of hospital stay (day) were significantly lower in LS than in OS (Figures 2A and 2B).

Number of lymph nodes retrieved, recurrence, blood transfusion, and complications: Five studies reported the number of lymph nodes retrieved with high heterogeneity [WMD = -1.71, 95%CI: -4.27 to 0.84, P = 0.19]. Three studies reported the intraoperative blood transfusion with low heterogeneity [RR = 0.56, 95%CI: 0.29-1.09, P = 0.09][12,14,15]. Five studies reported the complication rate with low heterogeneity [RR = 0.72, 95%CI: 0.39-1.33), P = 0.29][12-16]. Two studies reported the recurrence rate with moderate heterogeneity [RR = 0.41, 95%CI: 0.06-2.84, P = 0.36][12,16]. There was no significant difference between the LS and OS groups in the number of lymph nodes retrieved, recurrence, blood transfusion, or complications (Figures 2B and 2C).

3- and 5-year overall and disease-free survival rates: Three studies reported the 3-year overall survival rate with moderate heterogeneity [RR = 0.99, 95%CI: 0.82-1.18, *P* = 0.89][12-14]. Three studies reported the 5-year overall survival rate with high heterogeneity [RR = 1.02, 95%CI: 0.68-1.53, *P* = 0.92][12,14,15]. Three studies reported the 3-year disease-free survival rate with low heterogeneity [RR = 1.01, 95%CI: 0.84-1.21, *P* = 0.93][12-14]. Three studies reported the 5-year disease-free survival rate with moderate heterogeneity [RR = 1.15, 95%CI: 0.90-1.46, *P* = 0.26][12,14,15]. There was no statistical difference between the LS and OS groups in terms of 3- and 5-year overall and disease-free survival rates (Figure 2D).

Sensitivity analysis and publication bias

The sensitivity analysis showed that our meta-analysis was stable and no reversal of the meta-analysis results was found. Publication bias was qualitatively assessed using funnel plots. The funnel plots were largely symmetrically distributed, with no significant extreme values (Supplementary Figure 1). Neither Begg's test nor Egger's test revealed any significant publication bias (Supplementary Table 2).

DISCUSSION

Recently, LS for patients with stage T2 GBC has become feasible in high-volume medical centres and has shown similar outcomes to those of OS[16,22-25]. However, the value of LS for T2 GBC remains controversial. The current guidelines, such as those of the National Comprehensive Cancer Network and the Japanese Society of Hepatobiliary and Pancreatic Surgery, do not recommend LS for T2 GBC[9]. Previous studies referenced by the guidelines have shown that LS is associated with a higher risk of tumor spread and incisional recurrence than OS[7,26,27]. However, tumor spread is not a complication specific to LS and can also occur in OS[28]. Currently, since specimens are often intraoperatively obtained using plastic internal bags, which can prevent tumor

spread and incision-site recurrence in GBC[29,30], there is no statistically significant difference in the incidence of incisional implants between LS and OS[31].

LS follows the principles of OS. Lymph-node dissection and R0 rate are two important indicators to evaluate radical surgery for GBC. One study has found that the rate of lymph-node metastasis in stage T2 GBC is 46%[32,33]. It has been suggested that LS is superior to OS for lymph-node dissection because of the unique magnified surgical field of view[22]. However, the results of this meta-analysis showed no significant difference between the two procedures. R0 resection is also an important prognostic factor for postoperative patients. Among the analysed studies, only the study by Lee *et al*[12] reported the R0 resection rate to be similar between the LS and OS groups, with no statistical difference.

Although oncological outcomes based on surgical procedures, such as R0 rates and number of lymph nodes removed, were not significantly different between the LS and OS groups, the therapeutic effect should be based on more direct clinical evidence, such as improved survival, improved quality of life, or reduced tumor-related symptoms. These clinical benefits sometimes cannot be assessed based on intraoperative or short-term outcomes. Therefore, we explored long-term survival and found that postoperative recurrence, and 3- and 5-year overall and disease-free survival rates are not significantly different between the LS and OS groups.

In addition, our findings suggest that LS is associated with lower operation time, intraoperative blood loss, and length of hospital stay than OS. Although a random-effects model was used to combine the effect sizes, there was a high degree of heterogeneity in operative time, intraoperative bleeding, and length of hospital stay, which significantly weakens the explanatory effect of the results and may cause confounding bias. The high heterogeneity may be explained by the fact that surgeons are still at the learning-curve stage. As these results are prone to bias, they need to be validated *via* high-quality RCTs.

CONCLUSION

LS for T2 GBC has similar long-term survival outcomes to those of OS but is superior to OS in terms of operative time, intraoperative bleeding, and length of hospital stay. Additional high-quality RCTs and long follow-ups are needed to further evaluate the effectiveness of LS for stage T2 GBC.

ARTICLE HIGHLIGHTS

Research background

Although laparoscopic surgery (LS) is recommended for stage T1 gallbladder cancer (GBC), the value of LS for stage T2 GBC is still controversial.

Research motivation

This study evaluated the short- and long-term outcomes of LS, in comparison to those of open surgery (OS), for stage T2 GBC.

Research objectives

As there is still a lack of evidence from high-quality multi-centre random controlled trials, we believe that it is necessary to conduct a meta-analysis to provide an evidence-based reference for laparoscopic radical surgery of T2 GBC.

Research methods

We searched the PubMed, Embase, Cochrane Library, Ovid, Google Scholar, and Web of Science databases for published studies, with a cut-off date of September 2022.

Research results

A total of 5 studies were included, with a total of 297 patients, 153 in the LS group and 144 in the OS group. Meta-analysis results showed that the LS group was better than the OS group in terms of operative time, estimated blood loss, and hospital stay, whereas there was no significant difference between the two groups in terms of blood

transfusion, complications, number of lymph nodes retrieved, recurrence, and 3- and 5-year overall survival and disease-free survival.

Research conclusions

The long-term outcomes of LS for T2 GBC are similar to those of OS, but LS is superior to OS in terms of operative time, intraoperative bleeding, and postoperative hospital stay.

Research perspectives

Our meta-analysis is the first to assess the efficacy of laparoscopic approach in the treatment of stage T2 GBC and to provide a reference for clinical management.

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