



Review

Laparoscopic versus open liver resection for colorectal liver metastases: A systematic review and meta-analysis of studies with propensity score-based analysis



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H I G H L I G H T S

- Laparoscopic liver resection (LLR) versus open liver resection (OLR) on colorectal liver metastases (CRLM).
- LLR is a beneficial alternative to OLR in selected patients.
- LLR is superior to OLR in improving short-outcomes in CRLM patients.

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Background: This meta-analysis collected studies with propensity score matching analysis (PSM) and focused on comparing the short-term and oncological outcomes of patients with colorectal liver metastases (CRLM) who underwent laparoscopic liver resection (LLR) versus open liver resection (OLR), to provide relatively high-level evidence of the additional value of LLR in treating patients with CRLM in comparison with OLR.

Methods: A systematic literature search was performed using the PubMed, Embase and Cochrane Library databases. Bibliographic citation management software (EndNote X7) was used for literature management. Quality assessment was performed based on a modified version of the Newcastle-Ottawa Scale. The data were analyzed using Review Manager (Version 5.1), and sensitivity analysis was performed by omitting one study in each step. Dichotomous data were calculated by odds ratio (OR) and continuous data were calculated by weighed mean difference (WMD) with 95% confidence intervals (CI).

Results: Overall, 10 studies enrolling 2259 patients with CRLM were included in the present meta-analysis. The pooled analysis suggested that LLR was associated with significantly less overall morbidity (OR, 0.57; 95% CI 0.40 to 0.80; $I^2 = 57\%$; $P < 0.001$), reduced blood loss (WMD, -124.68 ; 95% CI, -177.35 to -72.01 ; $I^2 = 83\%$; $P < 0.00001$), less transfusion requirement (OR, 0.46; 95% CI 0.35 to 0.62; $I^2 = 0\%$; $P < 0.00001$), shorter length of hospital stay (WMD, -2.13 ; 95% CI, -2.68 to -1.58 ; $I^2 = 0\%$; $P < 0.00001$), but longer operative time (WMD, 39.48; 95% CI, 23.68 to 55.27; $I^2 = 66\%$; $P = 0.04$). However, no significant differences were observed in mortality (OR, 0.50; 95% CI 0.21 to 1.2; $I^2 = 0\%$; $P = 0.12$). For oncological outcomes, no significant differences were observed in negative surgical margins (R0 resection), tumor recurrence, 3-year disease-free survival, 5-year disease-free survival, 5-year overall survival between the approaches. Nevertheless, LLR tended to provide higher 3-overall survival rate (OR, 1.37; 95% CI 1.11 to 1.69; $I^2 = 0\%$; $P = 0.003$). The pooled OR for overall morbidity in each subgroup analysis was consistent with the overall pooled OR. Additionally, the pooled OR for overall morbidity varied from (0.63; 95% CI 0.45 to 0.88; $I^2 = 49\%$; $P = 0.007$) to (0.51; 95% CI 0.37 to 0.69; $I^2 = 39\%$; $P < 0.0001$) in sensitivity analysis.

Conclusion: LLR is a beneficial alternative to OLR in select patients, and provides more favorable short-term outcomes such as less overall morbidity, shorter length of hospital stay, less blood loss, lower blood transfusion rate. Simultaneously, LLR does not compromise oncological outcomes including surgical margins R0, tumor recurrence, disease-free survival, 5-overall survival, as well as even yielding

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better 3-overall survival. Considering unavoidable bias from non-randomized trials, high-quality RCTs are badly needed to determine whether LLR can become standard practice for treating patients with CRLM.

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1. Introduction

Colorectal cancer is the second most common cause in Western Europe and America, and 15%–25% patients with colorectal cancer have synchronous liver metastases [1,2]. Colorectal liver metastases (CRLM) has been widely recognized as an absolute indication for liver resection and the complete resection of primary colorectal cancer (CRC) and CRLM still offers the greatest curative potential, although there are many choices including ablative therapy, cryotherapy, perioperative chemotherapy, and hepatic artery infusion [3,4]. In recent years, a large body of literature has highlighted the added values of laparoscopic liver resection (LLR) versus open liver resection (OLR) in terms of reduced blood loss, lower morbidity rate, shorter length of hospital stay and earlier return to functional activities [5–12]. Furthermore, LLR was even thought to provide superior oncological outcomes to patients with CRLM [13].

However, the positive results from LLR have to be interpreted discreetly due to the potential role of selection bias and small sample size that may lead to inauthentic evaluation of outcomes and uncertain conclusions in that the majority of relevant data were merely extracted from case series, case-control studies or meta-analyses of these studies [14–21]. Consistent with the perceived benefits from the studies above, in 2014, the Second International Consensus Conference on LLR (ICLLR) in 2014 concluded that minor LLR had become standard practice and that major liver resections were still innovative procedures in the exploration phase that should be practiced with continued caution. However, the only low-level evidence available for scrutiny, and higher-quality evaluative studies are badly needed to determine the place of LLR in treating liver lesions [22]. Currently, two ongoing clinical trials, the Oslo CoMet trial (NCT01516710) and the multinational Orange II Plus trial (NCT01441856), have randomized patients with resectable CRLM to LLR or OLR, but the final results of both trials have not yet been reported. However, treading on the heels of the second ICLLR and lacking data from RCTs, the researchers in this field have conducted numerous high-quality non-randomized trials based on propensity score matching (PSM) analyses to assess the additional value of LLR in patients with CRLM compared with OLR. The propensity score (PS) method is a successful tool for minimizing treatment selection bias in the context of observational studies and the recent literature even indicated that non-randomized studies with suitable PSM analysis could provide comparable evidence to that from randomized controlled trials (RCT) [23]. In these PSM analysis-dependent studies comparing the outcomes of CRLM patients undergoing LLR versus OLR, propensity score adjustment was performed on variables such as baseline characteristics, tumor characteristics, preoperative chemotherapy and type of liver resection, which are known to influence the choice of treatment approach and prognosis. To date, most of the studies with propensity score matching analysis suggested that LLR for CRLM may provide oncological outcomes comparable to those from OLR, as well as better short-term outcomes including less blood loss, lower blood transfusion rate, lower overall morbidity, and shorter hospital stay in selected patients [24–27]. Conversely, some of these studies indicated that there was no significant difference regarding incidence of morbidity and

mortality [13,28] and that LLR have even resulted in improved oncological outcomes [13]. The sample size from each trial ranged from 36 to 450, which indicated that small sample issues may partly explain the inconsistencies across different trials and influence the confidence level of the evidence from these studies via PSM analysis [13,24–27,29–33]. The most recently published meta-analysis comparing the effects of LLR and OLR in CRLM patients was conducted by Tian ZQ et al., but the meta-analysis only included two studies with PSM, which mean that the quality of evidence was rather low-level [19]. Therefore, this meta-analysis of high-quality studies with PSM analysis is indispensable and was conducted to provide the current best evidence supporting LLR in treating patients with CRLM.

2. Methods

The current meta-analysis was undertaken according to the Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [34,35].

2.1. Literature search

The PubMed, Embase, and Cochrane Library were searched from inception until Apr. 2017. The electronic searches were performed using exploded medical subject headings (MeSH) and the corresponding terms, including “laparoscop*”, “minimally invasive”, “open”, “liver metastas*”, “hepatic metastas*”, “colorectal metastas*”, “colon metastas*”, “rectal metastas*”, and “rectum metastas*”. In addition, the references of relevant reviews and included studies were checked to retrieve any other possible eligible studies.

2.2. Study selection

We selected all clinical studies comparing short-term and oncological results of patients with CRLM who underwent laparoscopic and open liver resection. Additionally, all the studies included in the current meta-analysis had to fulfill the criteria [1]: designed with PSM analysis [2] published as full-length articles. Furthermore, the following studies were also excluded [1]: abstracts, letters, protocol, comments, reviews, non-matched studies and matched studies without PSM analysis [2]. studies that lack clearly reported outcomes of interest [3]; studies that evaluated patients with benign lesions or malignant non-CRLM.

2.3. Data extraction and quality assessment

The following parameters were extracted from each study and tabulated by two reviewers (Xue-liang Zhang and Dan Zhang): first author names, year of publication, study design, number of patients in each group, patient baseline characteristics, and outcomes of interest. The primary outcome was overall postoperative morbidity. The secondary outcomes were operative time, blood loss, blood transfusion requirement, length of hospital stay, 90-day mortality and oncological outcomes including surgical margins R0, tumor recurrence, 3-year disease-free survival, 5-year disease-free

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