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REVIEW ARTICLE

Is lymph node dissection necessary for resectable intrahepatic cholangiocarcinoma? A systematic review and meta-analysis

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Abstract

Background: The objective of this meta-analysis was to evaluate the effectiveness and safety of lymph node dissection (LND) in patients with intrahepatic cholangiocarcinoma (ICC).

Methods: A literature search with a date range of January 2000 to January 2018 was performed to identify studies comparing lymph node dissection (LND+) with non-lymph node dissection (LND-) for patients with ICC. The LND + group was further divided into positive (LND + N+) and negative (LND + N-) lymph node status groups based on pathological analysis.

Results: 13 studies including 1377 patients were eligible. There were no significant differences in overall survival (OS) (HR 1.13, 95% CI 0.94–1.36; P = 0.20), disease-free survival (DFS) (HR 1.23, 95% CI 0.94–1.60; P = 0.13), or recurrence (OR 1.39, 95% CI 0.90–2.15; P = 0.14) between LND + group and LND-group. Postoperative morbidity was significantly higher in the LND + group (OR 2.67, 95% CI 1.74–4.10; P < 0.001). A subset analysis showed that OS was similar between LND + N- and LND-groups (HR 1.13, 95% CI 0.82–1.56; P = 0.450). However when comparing, OS of the LND-group to the LND+N+ group there was a significant increase in OS for the LND-group (HR 3.26, 95% CI 1.85–5.76; P < 0.001).

Conclusions: LND does not seem to positively affect overall survival and is associated with increased post-operative morbidity.

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Introduction

Intrahepatic cholangiocarcinoma (ICC) is rare in most parts of the world,[1] but has a high incidence in many parts of Asia. Nonetheless, the incidence of ICC has been steadily increasing worldwide.[2] Hepatic resection with or without bile duct resection is the recommended treatment for those with resectable disease.[3] However, the recurrence rates are high owing to vascular invasion or metastases within the lymphatic system.[4] The prognosis following resection for patients with ICC is heavily influenced by the presence of vascular invasion, number of tumours, and lymph node metastases (LNM).[5,6] LNM have been reported to be one of the most prominent adverse prognostic factors for patients with ICC, raising the question regarding the role for nodal dissection.[7]

LND has been an established approach for resection in several types of hepatobiliary malignancy including gallbladder cancer,[8]

extrahepatic hilar cholangiocarcinoma,[9] and fibrolamellar hepatocellular carcinoma.[10] However, the benefits of LND in primary resectable ICC remains debatable. A recent expert consensus statement on ICC recommended that regional lymphadenectomy be performed in patients undergoing resection.[11] de Jong *et al.* demonstrated that among patients who underwent routine lymphadenectomy, patients with LNM had a worse median survival.[12] However, there exists some disagreement regarding LND, with some studies reporting the number of LNs retrieved affects patient survival.[13–15] However, owing to the lack of a definitive controlled study, there is still no consensus about the prognostic significance of LND in ICC with or without LNM. In addition, it is unclear what is a standard LND given the multiple potential lymphatic drainage pathways for intrahepatic malignancies. Some Guidelines and Consensus[11,16] statements recommend routine hilar lymph node dissection, but there's lack of long-time survival data to support these statements.

In this study, a meta-analysis of the published literature was performed to assess the effect of LND on morbidity and overall survival for patients with resectable ICC.

Methods

The study protocol was published on PROSPERO, the international prospective register of systematic reviews (reference: CRD42017078091; http://www.crd.york. ac.uk/PROSPERO). The search and analysis were performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Statement[17] and Cochrane Handbook for Systematic Reviews of Interventions.[18]

Literature search and selection criteria

The online databases of PubMed/Medline, EMBASE, Web of Science, and the Cochrane Library were searched for all levels of evidence published in print or electronically from January 2000 to January 2018 without limitations in terms of language. The following Medical Subject Headings terms were used: "intrahepatic cholangiocarcinoma," "intrahepatic bile duct carcinoma," "intrahepatic biliary cancer," and "lymph node dissection," "lymphadenectomy," and "lymphatic clearance." In order to broaden the other potentially relevant citations, a manual search of reference lists from identified trials and related review articles was performed.

Article were included if: they were comparative studies, including retrospective investigations and prospective studies, conducted to evaluate the effectiveness and safety of LND in the surgical treatment of ICC; and patients had a histological diagnosis as ICC.

The exclusion criteria were as follows: (i) patients diagnosed as hepatocellular carcinoma, mixed type ICC, or tumour site in another part of the bile duct by pathologic examination; (ii) the provided information was non-comparable or insufficient for data extraction or quality assessment, such as conference abstracts, letters to the journal editors, and review articles.; (iii) if the reports came from the same medical centre, only the most complete data were included unless the relevant outcomes were used in different groups of analysis.

Data extraction

Two independent researchers (Zhou and Lu) reviewed the studies; disagreements regarding eligibility, data extraction, and quality assessment were resolved via discussion and consensus. The same reviewers extracted data from each study using prepared extraction forms independently: general information (first author, year of publication, study design) and characteristics of included studies (number of patients enrolled in the surgery, reason for and area of LND, resection margin, matching criteria). The primary outcome was the overall survival and disease-free survival. The secondary outcome was the post-operative morbidity and the probability of recurrence. Investigators were contacted to provide key data that was missing.

Quality assessment

The methodological quality of the observational studies was assessed using the Newcastle-Ottawa scale (NOS).[19] This assessment scale consists of three factors: patient selection, comparability of groups, and assessment of outcomes. A score of 0–9 was allocated to each study, which was estimated by two independent reviewers. Disagreements were resolved by discussion or adjudication of the third author. Observational studies which achieved a score of >6 were considered to be of a higher quality.

Statistical analysis

The patients were categorized into two groups according to the extent of lymph node dissection: non-lymph node dissection (LND-) group and lymph node dissection (LND+) group. Given the influence of LNM, the LND + group was further classified. Patients who underwent lymphadenectomy with lymph node metastases at final pathology (LND + N+), and patients who underwent lymphadenectomy without lymph node metastases (LND-N-).

Hazard ratio (HR) was used as a summary statistic for time-to-event and censored outcomes (overall survival and disease-free survival) as described by Parmar *et al.*[20] HR and its standard error was estimated and calculated according to a method as described by Tierney *et al.*[21] The odds ratio (OR) was used for statistical analysis of dichotomous variables (post-operative morbidity and recurrence). For the purpose of this study, the OR indicated the odds of an adverse event. A pooled HR and OR of <1 favoured the LND + group or LND + N- group or LND+N+ group, and the beneficial effect of the surgical treatment was considered statistically significant if the P value < 0.05 or the 95% confidence interval (CI) did not overlap 1.

Statistical heterogeneity between studies was assessed on the basis of the χ^2 and I^2 statistic, the interpretation of which was

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guided by the Cochrane Handbook.[18] A random-effects model was used, if the heterogeneity between studies was considered present (P <0.1 or $\mathbf{I}^2$ >50%). Otherwise, a fixed-effects model was used. Funnel plots were used to detect the presence of publication bias risk. A two-tailed P value < 0.05 was considered statistically significant. A sensitivity analysis was conducted to explore the sources of heterogeneity as well as evaluate the reliability of the result obtained using the pooled data.

Review Manager v5.2 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen 2012) and STATA v11.0 (StataCorp, College Station, TX, USA) was used for the statistical analysis.

Results

Study search results

The search result summary is shown in Fig. 1. In total, 13 eligible studies[7,14,15,22–31] including 1377 patients were identified for inclusion. There was no disagreement between the two researchers in terms of the inclusion and exclusion of the studies.

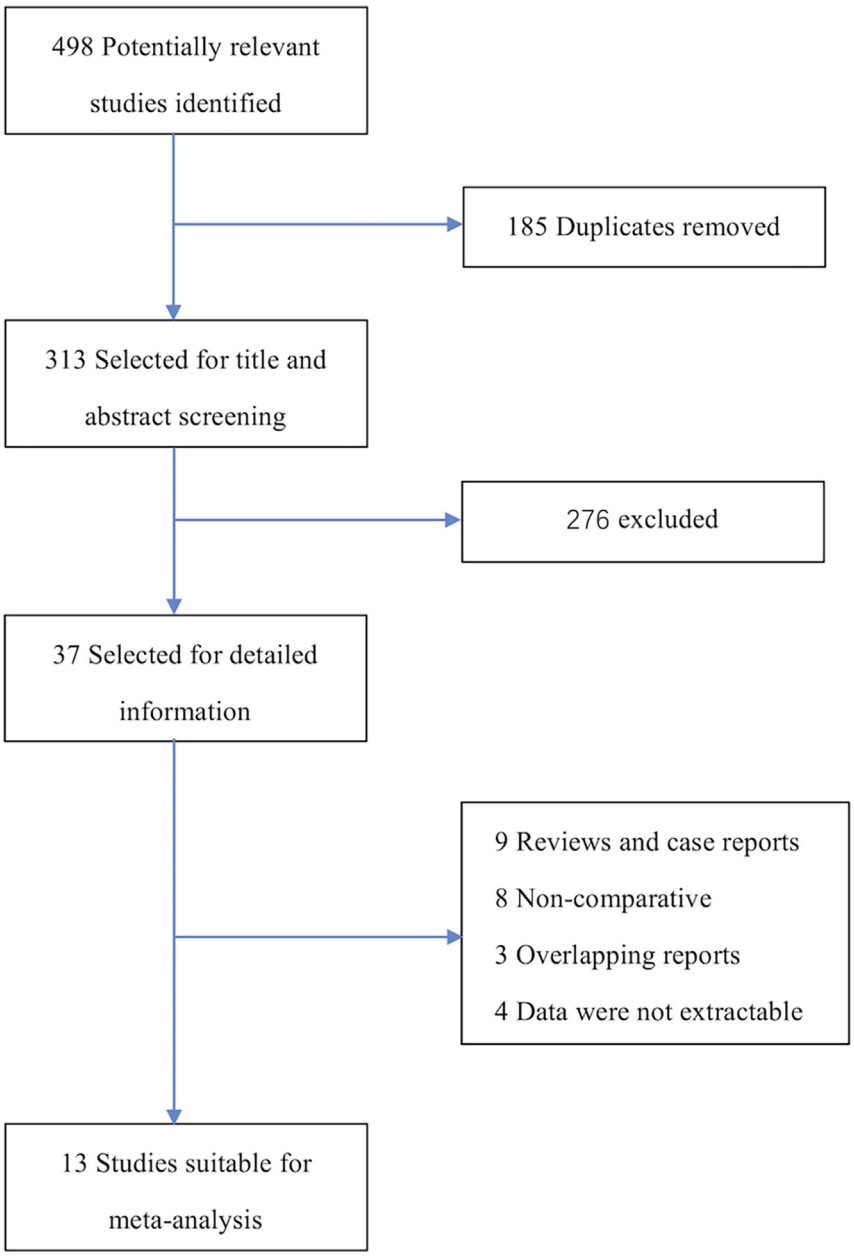

Figure 1 Diagram of literature search and study selection

Characteristics of eligible studies

The characteristics, survival outcomes, matching criteria, and quality scores of the 13 studies included are summarized in Supplementary Table 1. The included studies[7,14,15,22–31] were all retrospective cohort trials (9 from the east of Asia, 4 from the US and Europe), and the publication dates ranged from 2009 to 2018. The largest multi-centred retrospective analysis[24] involved >400 patients and used the Surveillance, Epidemiology, and End Results (SEER) database wherein the removal of >3 LNs was regarded therapeutic LND. Thus, patients who underwent therapeutic LND were included in the LND + group in the current meta-analysis. Eight studies[7,14,22–24,26,29,30] compared the histological characteristics and surgical outcomes between the LND + group and LND-group, but only five[7,14,22,24,26] could be used in the meta-analysis owing to the availability of extractable data for the survival curve. Five studies[22,26–29] compared a LND+N+ group and LND-group. Seven studies[15,23,25,27–30] used the LND + N- group as an experimental group to compare with the LND-group in order to evaluate the survival outcomes. Two included studies[25,26] had an overlapping population in the same centre, but involved different outcome investigations. With regard to the indications for LND, most studies recommended complete LND owing to a high suspicion of LNM. Two studies, one conducted in Korea[14] and the other in the US,[28] LND was adopted according to the surgeon's decision and performed routinely, respectively.

Survival outcomes and meta-analysis

The summary of study outcomes are shown in Table 1.

Five studies[7,14,22,24,26] allowed for pooling of the data to access the overall survival of 760 patients (Fig. 2a), which showed no significant difference between the LND+ and LND-groups. Four studies[7,14,22,28] were used to describe disease-free survival (Fig. 2b). There was no significant difference between the two groups.

Eight studies[15,22,23,25,27–30] that compared overall survival between the LND + N- and LND-groups were suitable for data pooling (Fig. 3a), and five studies[22,26–29] involved in the assessment of overall survival between LND+N+ and LND-groups (Fig. 3b). There was a significant difference in favour of the LND-group by compared with LND+N+ in terms of overall survival, and no significant difference between LND + N- and LND-groups.

Four studies[7,14,15,29] were further pooled, which reported postoperative recurrence, and showed no significant difference in recurrent rate between the groups (Fig. 4a). Additionally, Li *et al.*[15] assessed recurrence by comparing the LND + N- and LND-groups and found no statistically significant difference. Postoperative morbidity data were available in four included studies[14,22,29,31] (Fig. 4b). Significantly higher morbidity was found in the LND + group than in the LND-group.

The result of sensitivity analysis was shown in Table 2. High quality that scored >6 on the NOS,[14,15,22,23,26,28–30] extended dissection area (more than HDL),[7,14,15,22,25,26,29,30] greater sample sizes,[14,15,22–24,26–29] the publication date after 2012[7,14,15,22–27] and surgical margin[7,14,23,25,28,30] were assessed, respectively.

Publication bias

The funnel plots of the studies included in this meta-analysis did not show any asymmetry for most outcomes, indicating no obvious publication bias (Supplementary Fig. 1).

Discussion

This study performed a quantitative analysis of the effectiveness and safety of LND in ICC patients. These patients all received attempted curative surgical treatment without a pathological assessment of nodal status via preoperative imaging or the surgeon's discussion. No survival benefit in patients who underwent

Table 1 Results of Meta-analysis comparing LND+/LND + N-/LND+N+ versus LND-

	Studies	LND + Patients	LND + N-Patients	LND + N + Patients	LND- Patients	Total patients	pooled HR/OR (95%CI)	p value	Study heterogeneity			
									χ^2	d.f.	I^2	p
Survival(Group A/Group B)												
OS(LND+/LND-)	5	394	–	–	388	782	1.13 (0.94–1.36)	0.20	6.45	4	38%	0.17
OS(LND + N-/LND-)	8	–	170	–	256	426	1.13 (0.82–1.56)	0.45	3.43	7	0%	0.84
OS(LND + N+/LND-)	5	–	–	55	126	181	3.26 (1.85–5.76)	<0.001	3.63	4	0%	0.46
DFS(LND+/LND-)	4	182			167	349	1.23 (0.94–1.60)	0.13	1.27	3	0%	0.74
Postoperative outcomes (Group A/Group B)												
Postoperative recurrences (LND+/LND-)	4	132	–	–	122	391	1.39[a](0.90–2.15)	0.14	0.90	3	0%	0.83
Postoperative morbidity (LND+/LND-)	4	78	–	–	64	497	2.67[a](1.74–4.10)	<0.001	2.49	3	0%	0.48

OR, odd ratio. HR, hazard ratio. OS, overall survival. DFS, disease-free survival. CI, confidence interval. LND, lymph node dissection. N, lymph node status. d.f. = degrees of freedom.
[a] OR.

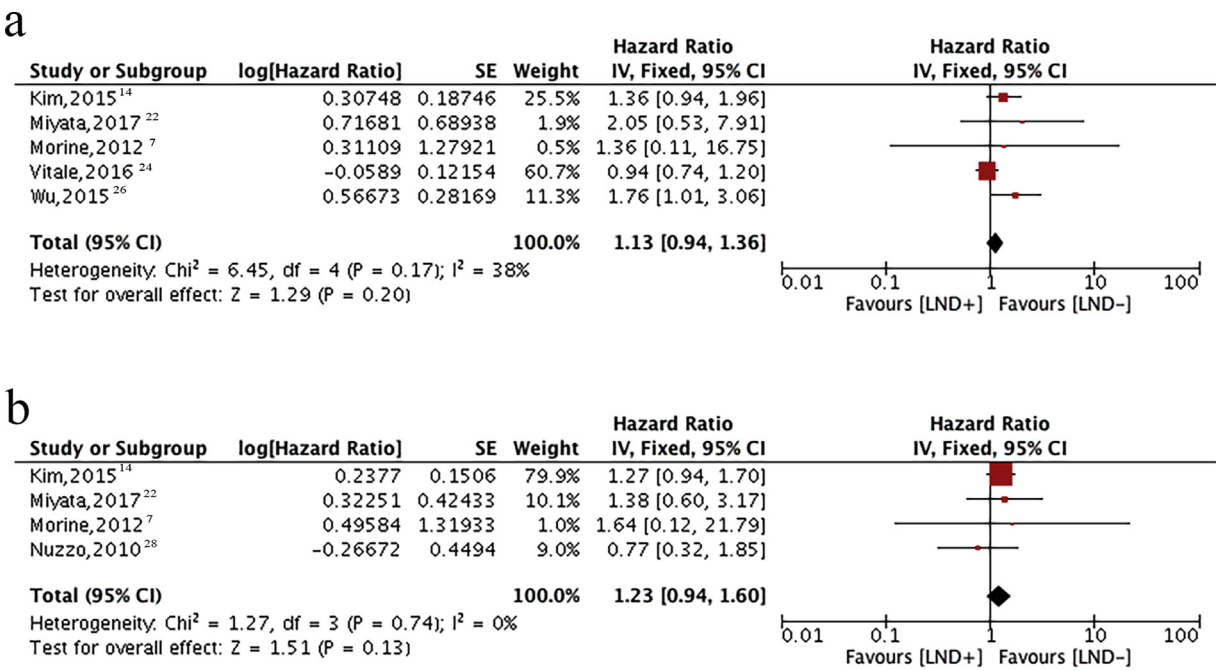

Figure 2 Forest plot comparing overall survival (a) and disease-free survival (b) in LND+ and LND-groups. LND lymph node dissection. IV inverse variance method. CI confidence interval. SE standard error

LND when compared with those who did not was observed. Likewise, the result of a subset analysis showed that LND may not improve overall survival in patients with or without LNM. A further analysis concerning postoperative events showed an increased risk of morbidity with an elevated incidence of postoperative complications in patients who underwent LND. In the sensitivity analysis for the assessment of the quality of studies included, a significant difference in favour of the LND-group was found; however, these results should be interpreted with caution because of the limitation of the number of patients included.

Several methodological differences were observed between studies. In the largest retrospective study, conducted by Vitale *et al.*,[24] although a matched-group assessment was performed, large amount and specific details of patients with ICC such as margin status, tumour histology, and the receipt of adjuvant therapies were not available within the SEER database, which may have introduced greater heterogeneity in this meta-analysis. Heterogeneity decreases when this study was excluded (Table 2). Upon exclusion of this study owing to the unknown quality, the overall survival between the LND+ and LND-groups showed significant differences.

At present, surgical resection of the liver is considered the only curative treatment for patients with ICC to achieve long-term survival.[32,33] The majority of the studies considered LNM as the most important determinant of prognosis,[32,34,35] which may be the reason why surgeons paid more attention to the effectiveness and safety of LND in patients with ICC. The current findings suggest that LND may not prolong survival in patients with ICC regardless the LN status. The negative conclusion may be challenged because a LND was done only if LN metastases were suspected. That is the reason why a further analysis is conducted according to their LN status after surgery. Several studies have noted that when the nodal status was adequately assessed, the incidence of LNM ranged from 30% to 40%.[12,30,36] Thus the rationale for why LN dissection may not improve survival is due to representing systemic metastatic disease rather than true loco-regional spread.

The extent of LND still remains controversial. Currently, although there is insufficient evidence to demonstrate that LND can improve long-term survival in ICC patients with radical resection, the 2017 NCCN Guidelines[16] and the Consensus on American Association of Hepatobiliary and Pancreatic Surgery[11] recommend routine hilar lymph node dissection. In general, conventional or standard LND usually refers to the removal of lymph nodes along the hepatoduodenal ligament and the area also includes lymph node in lesser curvature or left gastric artery, when the tumours located in the left lobe of the liver. However, there are multiple lymphatic drainage pathways from the liver and therefore further research potentially including the concept of sentinel nodes are required. Alternatively LN sampling may be able to provide the same information with regard to staging but reduced morbidity.[30]

Postoperative morbidity was lower in the LND-group than in the LND+. Some studies reported that postoperative complications such as bile leakage, infection, and ileus were associated with a decrease in tumour surveillance, increased risk of disease

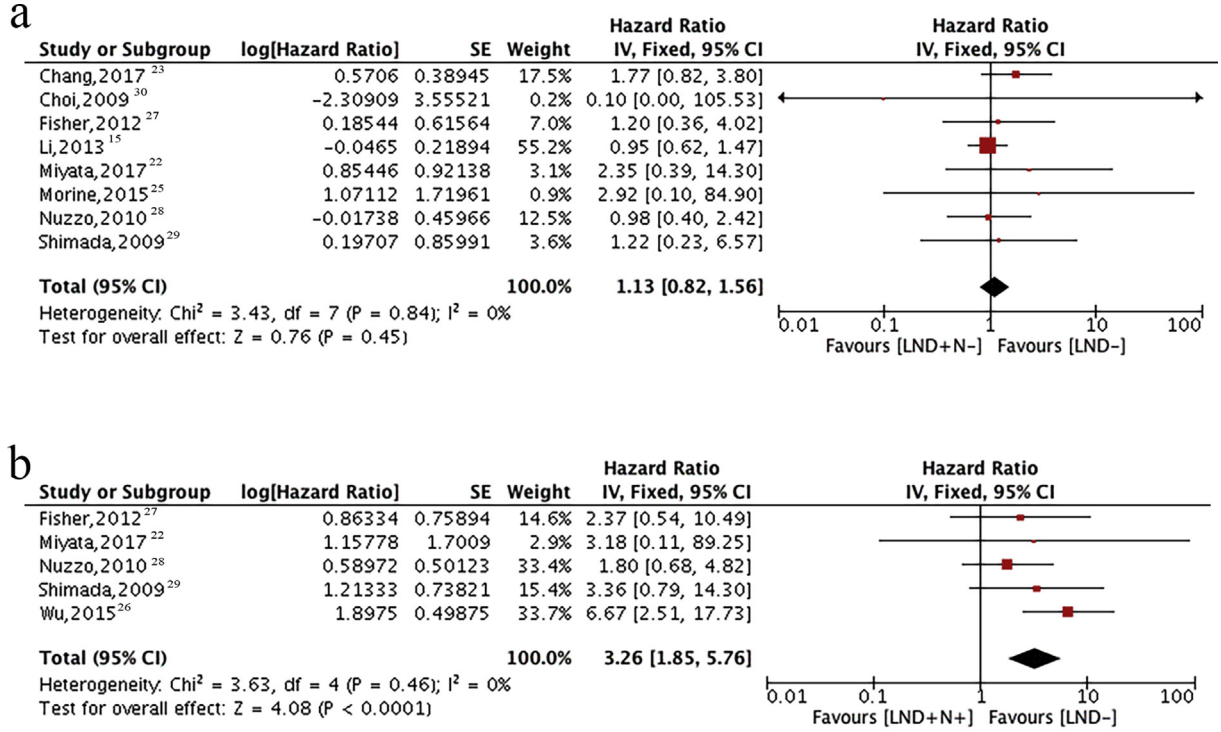

Figure 3 Forest plot comparing overall survival in LND + N- group (a) and LND+N+ group (b). LND lymph node dissection. N lymph node status. IV inverse variance method. CI confidence interval. SE standard error

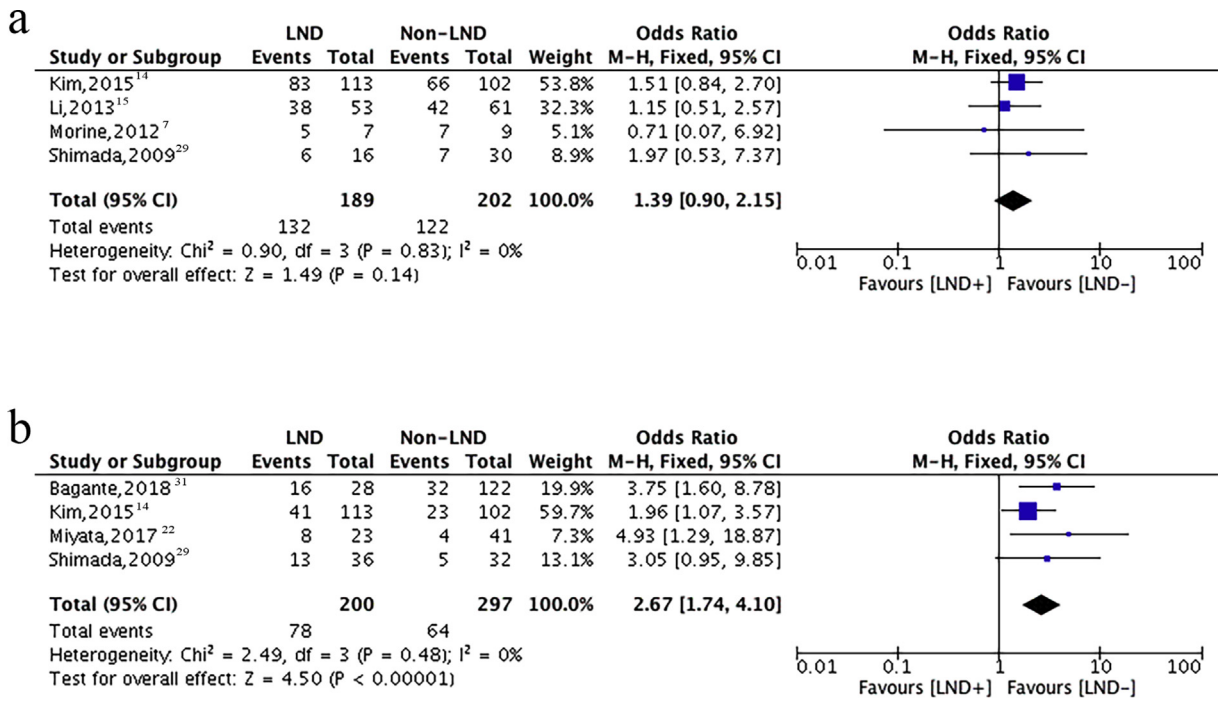

Figure 4 Post-operative outcomes following LND + versus LND-in terms of recurrence (a) and post-operative morbidity (b). LND lymph node dissection. M–H Mantel-Haenszel method. CI confidence interval

Table 2 Sensitivity analysis among groups

	Studies	Patients	Total	pooled HR (95%CI)	p value	Study heterogeneity			
						χ^2	df	I^2	p
High-quality studies (score>6)									
OS(LND+/LND-)	3	186/178	364	1.50 (1.11–2.02)[b]	0.008	0.80	2	0%	0.67
OS(LND + N-/LND-)	6	131/212	343	1.12 (0.80–1.55)	0.52	3.11	5	0%	0.68
OS(LND + N+/LND-)	4	42/106	148	3.45 (1.87–6.37)	<0.001	3.42	3	12%	0.33
DFS(LND+/LND-)	3	175/158	333	1.22 (0.94–1.59)	0.14	1.22	2	0%	0.54
Studies with sample size greater than 50									
OS(LND+/LND-)	4	387/379	766	1.27 (0.91–1.77)	0.17	6.43	3	53%	0.09
OS(LND + N-/LND-)	3	78/167	245	1.14 (0.79–1.65)	0.48	2.55	2	22%	0.28
DFS(LND+/LND-)	3	175/158	333	1.22 (0.94–1.59)	0.14	1.22	2	0%	0.54
Studies published after 2012									
OS (LND+/LND-)	5	394/388	782	1.13 (0.94–1.36)	0.20	6.45	4	38%	0.17
OS (LND + N-/LND-)	5	117/205	322	1.16 (0.82–1.64)	0.41	2.85	4	0%	0.58
OS (LND + N+/LND-)	3	29/94	123	4.77 (2.16–10.54)	<0.001	1.36	2	0%	0.51
DFS (LND+/LND-)	3	142/152	294	1.28 (0.97–1.69)	0.08	0.07	2	0%	0.97
Studies with surgical margin of R0 + R1									
OS (LND+/LND-)	3	321/312	633	1.05 (0.86–1.28)	0.61	2.73	2	27%	0.26
OS (LND + N-/LND-)	4	74/113	187	1.39 (0.78–2.46)	0.26	1.69	3	0%	0.64
OS (LND + N+/LND-)[a]	3	30/89	119	3.47 (1.76–6.83)	0.0003	3.42	2	42%	0.18
DFS (LND+/LND-)	3	159/126	285	1.21 (0.92–1.60)	0.18	1.19	2	0%	0.55
Studies with LND area more than HDL									
OS (LND+/LND-)	4	193/187	380	1.49 (1.11–2.01)[b]	0.008	0.81	3	0%	0.85
OS (LND + N-/LND-)	5	100/154	254	1.02 (0.68–1.52)	0.92	1.76	4	0%	0.78
OS (LND + N+/LND-)	3	28/91	119	5.23 (2.38–11.48)	<0.001	0.68	2	0%	0.71
DFS (LND+/LND-)	3	147/152	299	1.28 (0.97–1.69)	0.08	0.07	2	0%	0.97

HR, hazard ratio. OS, overall survival. DFS, disease-free survival. CI, confidence interval. LND, lymph node dissection. N, lymph node status. HDL, hepatoduodenal ligament. d.f. = degrees of freedom.
[a] Because of the limited number of studies, we used surgical margin of R0 instead.
[b] Result changed significantly.

recurrence, and disease-specific death.[37] Therefore, given the current lack of benefit it cannot be recommended as part of a routine resection.

No effectiveness of LND in terms of decreasing the probability of recurrence using the pooled data from the four studies was identified. Because of the small sample size and moderate proportion of patients with LN metastasis after pathological tests, the question of whether LND provides a lower rate of recurrence in patients with ICC cannot be completely answered via this meta-analysis. Some authors have suggested a therapeutic benefit of LND in terms of decreased locoregional recurrence, because the LN is the most frequent recurrent site of ICC.[11,29] The possible beneficial effect will be more apparent if LND with a negative resection margin (R0) is performed in patients without LNM.

The present meta-analysis has several limitations. Firstly, the included studies were almost single-centred and retrospective, which involved selection bias and missing data. In fact, the differences in surgical expertise, pathological characteristics of the tumour, perioperative adjuvant therapy, and other factors among the studies might be responsible for the high heterogeneity. Secondly, there was no standard practise and guidelines regarding LND for ICC treatment. The indication for and extent of LND was decided by surgeons according to their clinical experience and preoperative imaging examination findings. Thus, the patients who did not undergo LND may have not had lymphadenopathy or other high risk and concerning features at the time of their operation. Similarly, the LN status for patients who did not undergo LND cannot be ascertained. Thirdly, some studies[25,27,29] failed to provide descriptions of critical information on methodology, surgical process, and detailed results, making it difficult to extract data for the meta-analysis.

In conclusion, the current evidence indicates that LND does not significantly improve the survival of patients with ICC regardless of the LN status. The patients who underwent LND demonstrated higher postoperative morbidity and similar

probability of recurrence compared with those who did not. Routine or prophylactic LND cannot currently be recommended owing to the uncertain survival benefit. Further prospective randomized clinical trials are needed to clarify the influence of LND on survival in ICC.

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Conflicts of interest

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2018.12.011.