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Original Article

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Impact of Lymph Node Dissection for Patients With Clinically Node-Negative Intrahepatic Cholangiocarcinoma: A Multicenter Cohort Study

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Abstract

Background: Lymph node status is a prominent prognostic factor for intrahepatic cholangiocarcinoma (ICC). However, the prognostic value of performing lymph node dissection (LND) in patients with clinical node-negative ICC remains controversial. The aim of this study was to evaluate the clinical value of LND on long-term outcomes in this subgroup of patients.

Methods: We retrospectively analyzed patients who underwent radical liver resection for clinically node-negative ICC from three tertiary hepatobiliary centers. The propensity score matching analysis at 1:1 ratio based on clinicopathological data was conducted between patients with and without LND. Recurrence-free survival (RFS) and overall survival (OS) were compared in the matched cohort.

Results: Among 303 patients who underwent radical liver resection for ICC, 48 patients with clinically positive nodes were excluded, and a total of 159 clinically node-negative ICC patients were finally eligible for the study, with 102 in the LND group and 57 in the non-LND group. After propensity score matching, two well-balanced groups of 51 patients each were analyzed. No significant difference of median RFS (12.0 vs. 10.0 months, P = 0.37) and median OS (22.0 vs. 26.0 months, P = 0.47) was observed between the LND and non-LND group. Also, LND was not identified as one of the independent risks for survival. Among 51 patients who received LND, 11 patients were with positive lymph nodes (lymph node metastasis (LNM) (+)) and presented significantly worse outcomes than those with LND (-). On the other hand, postoperative adjuvant therapy was the independent risk factor for both RFS (hazard ratio (HR): 0.623, 95% confidence interval (CI): 0.393 - 0.987, P = 0.044) and OS (HR: 0.585, 95% CI: 0.359 - 0.952, P = 0.031). Furthermore, postoperative adjuvant therapy was associated with prolonged survivals of non-LND patients (P = 0.02 for RFS and P = 0.03 for OS).

Conclusions: Based on the data, we found that LND did not significantly improve the prognosis of patients with clinically node-negative ICC. Postoperative adjuvant therapy was associated with prolonged survival of ICC patients, especially in non-LND individuals.

Keywords: Intrahepatic cholangiocarcinoma; Liver resection; Lymph node dissection; Lymph node metastasis

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Introduction

Intrahepatic cholangiocarcinoma (ICC), the second most common primary liver malignancy, has increased dramatically across the world in the past decades [1]. Radical surgery remains the potential curative treatment that improves survival outcomes [2, 3]. However, the 5-year overall survival (OS) rate of patients was barely at 30% even after curative liver resection [4, 5]. For locally advanced or metastatic ICC, the latest guidelines have recommended the use of gemcitabine- or capecitabine-based chemotherapy to provide survival advantage [6], however, the median OS was still far from satisfactory. Recently, several clinical trials including targeted therapies and immune checkpoint inhibitors, are currently evaluating the role of novel therapeutic approaches in patients with advanced ICC [7-9]. The studies are still ongoing, and the results are yet to be conclusively confirmed whether to provide survival benefits.

Among all the risk factors, lymph node status is acknowledged as one of the most prominent prognostic factors associated with tumor recurrence and poor outcomes [10]. Therefore, TNM staging system recommends the dissection of lymph nodes for accurate staging and better outcomes [11]. In clinical practice, standard lymph node dissection (LND) has been widely accepted in patients with preoperative evidence of lymph node metastasis (LNM) (clinically node-positive) [12]. However, it remains controversial to perform LND in patients without preoperative evidence of LNM (clinically node-negative) [13]. The main reason is the lack of evidence of its impact on survival benefits [14]. Besides, additional LND for clinically node-negative patients may lead to hepatic injury or chylous leak that increases risk of postoperative complications [15].

Since most retrospective studies focused on prognostic value of LND in ICC patients regardless of preoperative lymph node status, the goal of our study is to evaluate the long-term outcomes of LND for patients with clinically node-negative ICC. In addition, we also aimed to identify which subgroup of patients may benefit most from the surgery.

Materials and Methods

Patient selection

Patients who underwent radical hepatectomy for ICC between January 2007 and December 2019 were retrospectively evaluated from three tertiary referral centers in China (Renji Hospital, Shanghai; the Second Affiliated Hospital of Xi'an Jiaotong University, Shanxi; the First People's Hospital of Yancheng, Jiangsu). Patients were enrolled in the study meeting the inclusion criteria: 1) Pathological confirmation of ICC; 2) No LNM or extrahepatic metastasis identified by preoperative imaging tests; 3) Hepatectomy performed with R0 resection. Patients who received preoperative adjuvant therapy were excluded from the study. In addition, postoperative death within 1 month was also excluded (Fig. 1). The Institutional Review Board has approved and confirmed the study. This study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration.

Definition of clinically node-negative ICC

Clinically node-negative ICC was defined as patients with no suspicious or positive LNM evaluated by preoperative radiology findings [16]. Presence of lymph nodes > 1 cm, contrast enhancement at computed tomography (CT) or magnetic resonance imaging (MRI) and central necrosis or extra-nodal extension was proposed as clinically node-positive ICC [17, 18]. Patients without LND were defined as non-LND, while patients receiving LND were divided into LNM (+) and LNM (-) according to postoperative pathological status of lymph nodes (Fig. 2).

Operation and treatment strategy

The operative strategies were determined by senior surgeons on the basis of patients' clinical conditions including size, number and location of tumor, vascular involvement, liver function reserve and volume of residual liver. LND was performed when: 1) Patients were suspicious of LNM at a weekly multidisciplinary team discussion before operation; or 2) Enlarged lymph nodes were detected during surgical findings. The extent of LND in the present study included: 1) Lymph nodes located around the hepatoduodenal ligament and the common hepatic artery (station 12 and 8); 2) Retro-pancreatic lymph nodes (station 13, for right-sided tumors); and 3) Lymph nodes around the cardiac portion of the stomach and along the lesser curvature (station 7, for left-sided tumors) (Fig. 3).

Postoperative adjuvant therapy was determined by multidisciplinary team discussion on a case-by-case basis. Generally, the regimen included transarterial chemoembolization, four to six courses of cisplatin or gemcitabine-based chemotherapy, radiotherapy or chemoradiotherapy.

Data collection and follow-up

Demographic data were collected including gender, age, hepatitis virus infection, Karnofsky Performance Status (KPS) score, cirrhosis and carbohydrate antigen 19-9 (CA 19-9) levels. Tumor characteristics through radiological and pathological findings included tumor size, tumor number, vascular invasion, tumor grade, perineural invasion, number of harvested lymph nodes and resection margin. In addition, intra- and postoperative parameters of surgical time, blood loss, hospital stays, and major complications were also collected. The Dindo-Clavien classification was used to evaluate postoperative complications which were considered as "major" when graded > II [19].

All patients were followed-up once per 3 months within 2 years after surgery and once per 6 months thereafter. The clinical monitoring consisted of physical assessment, liver function tests, CA 19-9 level, as well as abdominal ultrasound. CT or MRI scans of the chest and abdomen were performed once every 6 months to detect early recurrence. The positron emission tomography-computed tomography (PET-CT) was conducted when tumor recurrence was highly suspected. OS was calculated as the interval between the date of surgery and the date of death, while recurrence-free survival (RFS) was calculated as interval between surgery and presence of tumor recurrence at any site.

Statistical analysis

Propensity score matching (PSM) was conducted to minimize the bias between LND group and non-LND group [20]. Variables including gender, age, hepatitis virus infection, KPS score, cirrhosis, CA 19-9 level, tumor diameter, tumor number, vascular invasion, tumor grade and perineural invasion underwent 1:1 nearest-available matching of the propensity score with a caliper width of 0.20. Categorical variables are presented as numbers with percentage, and continuous variables are expressed as median with interquartile range. The correlations between LND and clinicopathological characteristics were estimated with χ^2 or Fisher exact test before and after

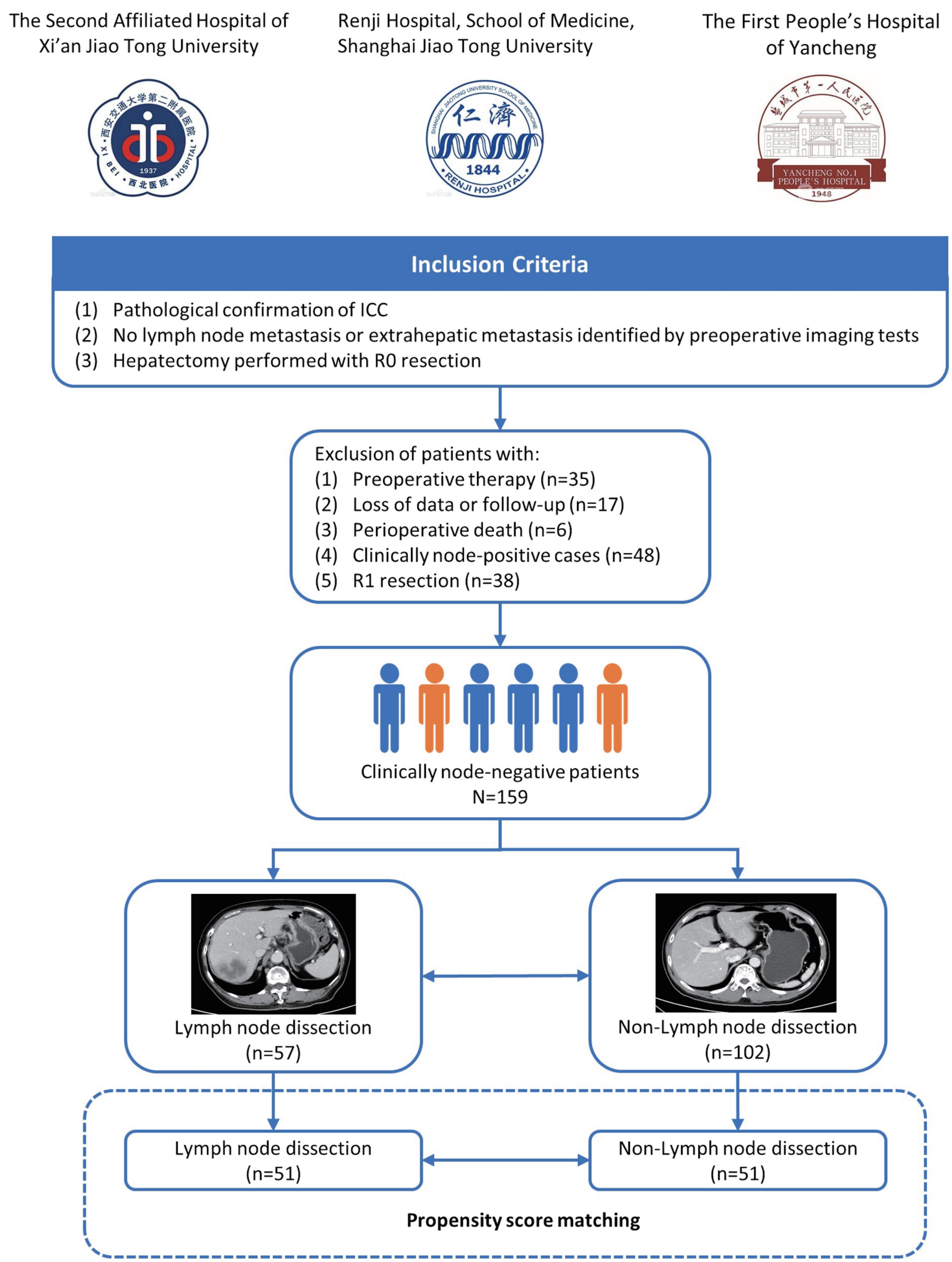


Figure 1. Flowchart of patients' enrollment. ICC: intrahepatic cholangiocarcinoma.

PSM. Continuous variables of intra- and postoperative outcomes were compared using Student's *t*-test or Mann-Whitney U test. Cox hazards proportional regression was performed to identify independent risk factors associated with RFS and OS. Kaplan-Meier analysis and log-rank test were used to estimate and compare survival curves. All analyses were performed using SPSS (version 24.0) with P value < 0.05 determined as statistical significance.

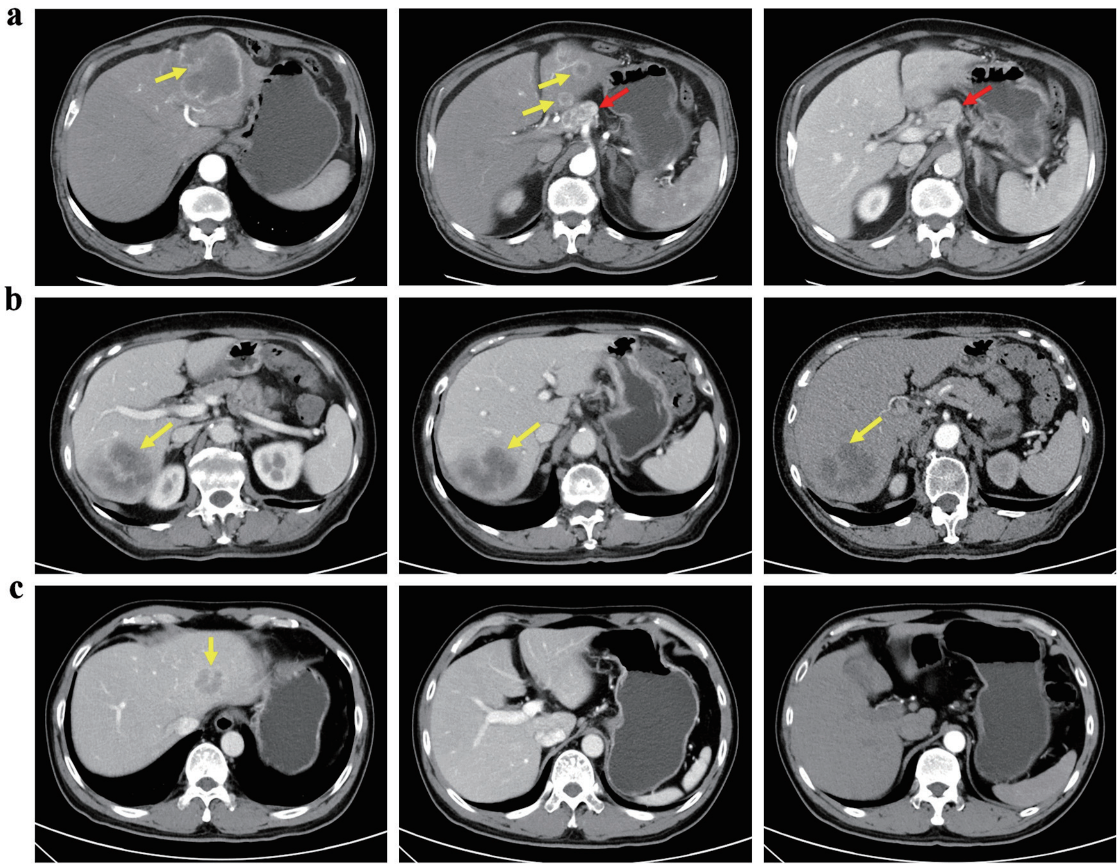


Figure 2. Patients with different lymph node status of ICC. (a) A patient with clinically node-positive ICC received left hemihepatectomy and lymph node dissection. (b) A patient with clinically node-negative ICC underwent both liver resection and lymph node dissection based on suspicion of lymph node metastasis at multidisciplinary team discussion. Postoperative pathology confirmed no lymph node metastasis. (c) A patient with clinically node-negative ICC underwent liver resection only. Yellow arrows: tumor; red arrows: lymph node.

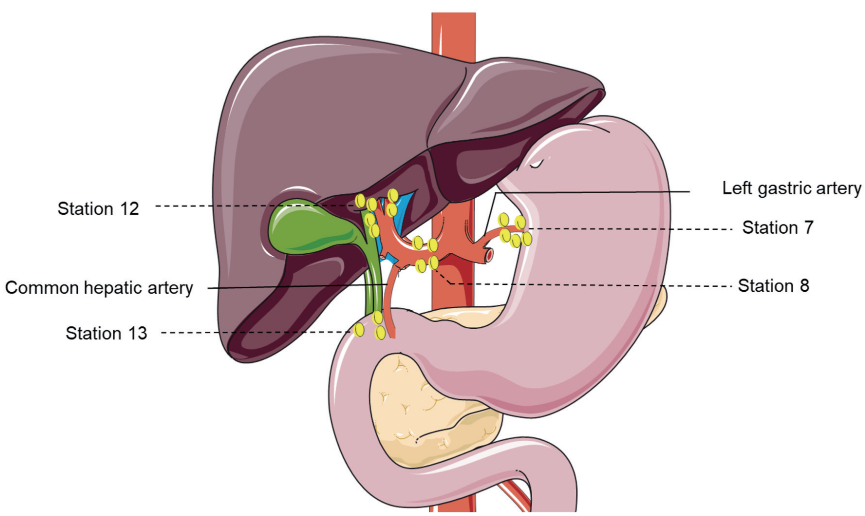


Figure 3. The lymph node dissection map of patients with suspected positive lymph nodes. Including: 1) Lymph nodes located around the hepatoduodenal ligament and the common hepatic artery (stations 12 and 8); 2) Retro-pancreatic lymph nodes (station 13, for right-sided tumors); and 3) Lymph nodes around the cardiac portion of the stomach and along the lesser curvature (station 7, for left-sided tumors).

Results

Initially, 303 patients who underwent curative-intent resection for ICC between January 2007 and December 2019 were screened for the study. Fifty-eight patients were excluded due to preoperative therapy (n = 35), loss of data or follow-up (n = 17) and perioperative death (n = 6) based on the study criteria. Of the remaining patients, 48 patients with clinically positive nodes and 38 patients who underwent R1 resection did not meet the selection criteria. Finally, a total of 159 patients with clinically node-negative ICC were enrolled in the present study.

Patient clinicopathological characteristics

Of the 159 patients included in the study, 57 underwent LND and 102 did not. The baseline clinicopathological characteristics of patients were summarized in Table 1. Before PSM, presence of cirrhosis was significantly higher in the LND group than that in the non-LND group (P < 0.001). After PSM, 11 selected variables (gender, age, hepatitis B virus (HBV) infection, cirrhosis, KPS score, CA 19-9 level, tumor diameter, number, differentiation, vascular invasion and perineural invasion) showed no significant difference between the two groups (all P > 0.05).

Intra- and postoperative outcomes

The median retrieval of lymph nodes was 4 in the LND group (range 1 - 21). As shown in Table 2, surgical time, blood loss and incidence of major complications related to surgery did not differ between LND group and non-LND group before and after PSM (all P > 0.05). Nearly half of patients received postoperative adjuvant therapy both in the LND and non-LND group. No significant difference was observed in the proportion of postoperative treatment before and after PSM (P > 0.05). It is noted that hospital stay was longer in the LND group than that in the non-LND group before PSM (10 days vs. 9 days, P = 0.021). The difference still exists after PSM (10 days vs. 9 days, P = 0.049).

Survival outcomes

In the crude cohort, median RFS was similar between the LND group and non-LND group (12.0 vs. 10.0 months, P = 0.37) (Fig. 4a). For median OS, it was slightly shorter in the LND group than that in the non-LND group with no significant difference (22.0 vs. 26.0 months, P = 0.47) (Fig. 4b). The 1-, 3- and 5-year survival rates in the two groups were 82.4% vs. 60.8%, 33.9% vs. 43.0% and 26% vs. 38.6%, respectively.

Among 51 patients who received LND, 11 patients presented with positive lymph nodes (LNM (+)) and 40 patients presented with LNM (-) confirmed by pathological findings. The presence of LNM significantly affected RFS and OS. Patients with LNM (-) showed significantly better outcomes than those with LNM (+), with a median RFS of 17.0 vs. 10.0 months (P = 0.03) and a median OS of 27.0 vs. 15.0 months (P = 0.02) (Fig. 5a, b). Of note, no significant difference of RFS or OS was observed between patients with non-LND and LNM (-) (P = 0.65 and 0.60, respectively) (Fig. 5c, d).

Independent prognostic factor associated with survival

In the matched cohort, tumor diameter, tumor number, vascular invasion and postoperative adjuvant therapy were identified to be related with RFS through univariate analysis (Table 3). These factors were further evaluated using multivariate analysis. It turns out that only tumor diameter (hazard ratio (HR): 2.027, 95% confidence interval (CI): 1.231 - 3.338, P = 0.005) and postoperative adjuvant therapy (HR: 0.623, 95% CI: 0.393 - 0.987, P = 0.044) were independent risk factors for RFS. For OS, tumor diameter (HR: 2.172, 95% CI: 1.304 - 3.618, P = 0.003), tumor number (HR: 2.130, 95% CI: 1.223 - 3.711, P = 0.008) and postoperative adjuvant therapy (HR: 0.585, 95% CI: 0.359 - 0.952, P = 0.031) were determined as independent risk factors through univariate and multivariate analysis (Table 4). It is noted that LND was not prognostic factors for either RFS or OS.

Effect of postoperative treatment of ICC

In the matched cohort, 44 patients received postoperative adjuvant therapy, including 22 patients in the non-LND group, 16 patients in the LNM (-) group and six patients in the LNM (+) group. Patients who received adjuvant therapy showed significantly longer RFS (22.0 vs. 9.5 months, P = 0.04) and OS (36.0 vs. 17.0 months, P = 0.04) than those without adjuvant therapy (Figs. 6a, 7a). Further stratified analysis found that patients in the subgroup of non-LND benefited most from postoperative therapy (P = 0.02 for RFS, and P = 0.03 for OS) (Figs. 6b, 7b). However, no significant benefits of RFS or OS were observed by postoperative treatment in the subgroups of LNM (-) and LNM (+) (all P > 0.05) (Figs. 6c, d and 7c, d).

Discussion

Lymph node status is one of the most crucial factors for accurate staging and predicting long-term outcomes of ICC [21, 22]. However, LND has long been debated in the surgical resection of ICC, especially for clinically node-negative tumors [23]. Our present study evaluated the prognostic value of LND for patients with clinically node-negative ICC based on patients from three tertiary referral centers in China. The results revealed that LND did not bring survival benefits for patients with clinically node-negative ICC. While postoperative adjuvant therapy for non-LND patients was associated with prolonged survival of ICC patients.

Routine LND of clinically node-negative ICC has not come to consensus in the guidelines, resulting in heterogeneous practices in ICC operation [24]. In the current study, there

Table 1. Correlation Between Lymph Node Dissection and Clinicopathological Characteristics in Patients Matched by LND Before and After PSM

Characteristics	Before PSM			After PSM		
	Non-LND (n = 102)	LND (n = 57)	P value	Non-LND (n = 51)	LND (n = 51)	P value
Gender						
Female	39 (38.2%)	19 (33.3%)	0.538	17 (33.3%)	17 (33.3%)	1.000
Male	63 (61.8%)	38 (66.7%)		34 (66.7%)	34 (66.7%)	
Age						
≤ 50 years	18 (17.6%)	13 (22.8%)	0.431	13 (25.5%)	11 (21.6%)	0.641
> 50 years	84 (82.4%)	44 (77.2%)		38 (74.5%)	40 (78.4%)	
HBV infection						
Absent	65 (63.7%)	43 (75.4%)	0.129	39 (76.5%)	37 (72.5%)	0.650
Present	37 (36.3%)	14 (24.6%)		12 (23.5%)	14 (27.5%)	
KPS score						
> 60	88 (86.3%)	50 (87.7%)	0.796	43 (84.3%)	45 (88.2%)	0.565
≤ 60	14 (13.7%)	7 (12.3%)		8 (15.7%)	6 (11.8%)	
Cirrhosis						
Absent	74 (72.5%)	55 (96.5%)	< 0.001	48 (94.1%)	49 (96.1%)	0.647
Present	28 (27.5%)	2 (3.5%)		3 (5.9%)	2 (3.9%)	
CA 19-9 level						
≤ 55 U/mL	54 (52.9%)	30 (52.6%)	0.970	26 (51.0%)	27 (52.9%)	0.843
> 55 U/mL	48 (47.1%)	27 (47.4%)		25 (49.0%)	24 (47.1%)	
Tumor diameter						
≤ 5 cm	59 (57.8%)	27 (47.4%)	0.204	22 (43.1%)	23 (45.1%)	0.842
> 5 cm	43 (42.2%)	30 (52.6%)		29 (56.9%)	28 (54.9%)	
Tumor number						
Single	84 (82.4%)	45 (78.9%)	0.599	40 (78.4%)	42 (82.4%)	0.618
Multiple	18 (17.6%)	12 (21.1%)		11 (21.6%)	9 (17.6%)	
Vascular invasion						
Absent	76 (74.5%)	35 (61.4%)	0.084	36 (70.6%)	34 (66.7%)	0.670
Present	26 (25.5%)	22 (38.6%)		15 (29.4%)	17 (33.3%)	
Differentiation						
Well and moderate	51 (50.0%)	36 (63.2%)	0.110	30 (58.8%)	32 (62.7%)	0.685
Poor	51 (50.0%)	21 (36.8%)		21 (41.2%)	19 (37.3%)	
Perineural invasion						
Absent	84 (82.4%)	51 (89.5%)	0.229	47 (92.2%)	45 (88.2%)	0.505
Present	18 (17.6%)	6 (10.5%)		4 (7.8%)	6 (11.8%)	
Postoperative adjuvant therapy						
Absent	55 (53.9%)	29 (50.9%)	0.712	29 (56.9%)	28 (54.9%)	0.842
Present	47 (46.1%)	28 (49.1%)		22 (43.1%)	23 (45.1%)	

P values were calculated using Chi-square test for categorical variables. PSM: propensity score matching; LND: lymph node dissection; KPS: Karnofsky Performance Status; HBV: hepatitis B virus; CA 19-9: carbohydrate antigen 19-9.

was no significant difference of median RFS and OS between patients in LND and non-LND group, which was coincident with previous study. While, Japanese and another Chinese Fujian cohort reported survival benefits and advocated the LND for patients with ICC [25, 26]. The difference can be attributed to several reasons as follows: Firstly, in Fujian cohort, 40.6% of patients with clinically negative ICC receiving LND were confirmed to be LNM postoperatively. The high false-negative

Table 2. Intra- and Postoperative Outcomes in Patients Matched by LND Before and After PSM

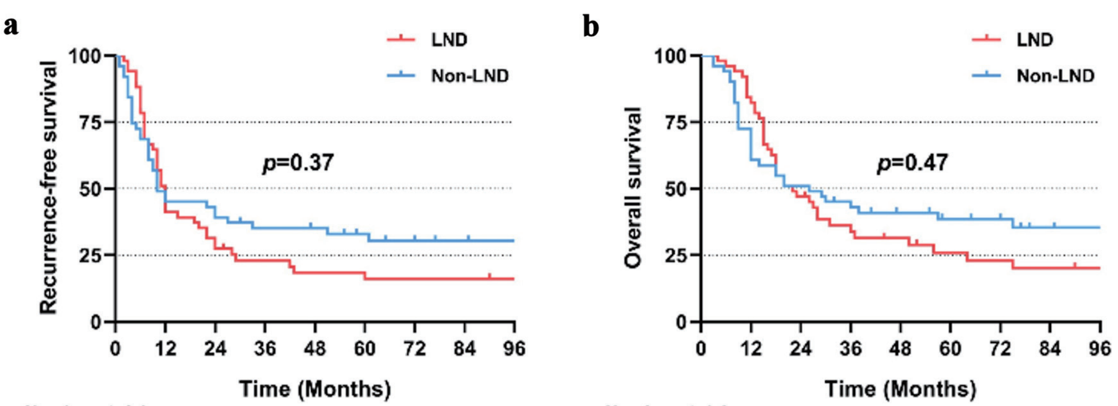
Characteristics	Before PSM			After PSM		
	Non-LND (n = 102)	LND (n = 57)	P value	Non-LND (n = 51)	LND (n = 51)	P value
Surgical time (min)	160 (100, 180)	160 (120, 190)	0.319	180 (140, 200)	170 (130, 200)	0.521
Blood loss (mL)	200 (50, 300)	200 (100, 300)	0.752	200 (100, 300)	200 (100, 200)	0.454
Postoperative hospital stays (days)	9 (7, 11)	10 (8, 12)	0.021	9 (8, 11)	10 (8, 13)	0.049
Major complications	13 (12.7%)	8 (14.0%)	0.818	8 (15.7%)	7 (13.7%)	0.780
Postoperative adjuvant therapy	47 (46.1%)	28 (49.1%)	0.712	22 (43.1%)	23 (45.1%)	0.842

Data were median (interquartile range) and n (%) for continuous and categorical variables. P values were calculated using nonparametric test and Chi-square test for continuous and categorical variables. PSM: propensity score matching; LND: lymph node dissection.

rate significantly lowered the survivals of patients in the LND group, while the rate in our cohort was only 21%. Second, at least six lymph nodes are recommended to be harvested according to the Eighth American Joint Committee on Cancer (AJCC) guidelines [27]. In the current study, the median retrieval nodes in the LND group were only 4 (range 1 - 21) due to different surgeon experiences. Inadequate LND and potential nodal metastasis may impact the survival rate. In addition, a higher proportion of postoperative adjuvant therapy (22 of 51, 43.1%) was reported in our non-LND group. More antitumor therapy may inhibit hidden tumor cells and bring survival benefits [28].

Though the present study did not show survival benefits by LND, this is not to deny the role of preoperative lymph node staging for ICC. Actually, in our study, clinically node-negative patients with postoperative LNM (+) showed significantly worse outcomes than those with LNM (-). The result confirms the importance of preoperative evaluation for lymph node status [29]. Under this setting, it highlights the accuracy of preoperative imaging evaluation. However, previous studies reported that the sensitivity and specificity of CT/MRI varied from 35.0% to 78.2% [30, 31], which strongly calls for more precise detection methods. Recent studies reported that 18-F fluorodeoxyglucose (FDG) PET-CT [32, 33] showed significantly higher sensitivity, specificity and accuracy than conventional CT/MRI in diagnosing regional LNM, which may facilitate tumor staging in ICC. Besides, artificial intelligence-based radiomics [34, 35] also performed well in metastatic nodal discrimination, enabling accurate N staging of ICC and patient risk stratification.

Postoperative adjuvant therapy is another important issue to discuss. Our study showed postoperative adjuvant therapy was the independent risk factor for both RFS and OS. Patients who received adjuvant therapy revealed significantly better outcomes than those without adjuvant therapy. It is interesting to further find that patients in the subgroup of non-LND benefited most from postoperative therapy. The results were consistent with the current Eighth National Comprehensive Cancer Network (NCCN) guidelines that suggested systemic therapy or gemcitabine-/capecitabine-based chemotherapy for patients with low-risk resected ICC [36-38]. It is reported that more than 50% of recurrences occurred in liver only even after adequate LND [27], which implies that most hidden tumor cells exist within the liver or bloodstream rather than lymph nodes [39]. This may explain why patients with non-LND get better outcomes from adjuvant therapy to eliminate residual disease. It also suggests a potential reevaluation of surgical strategies in favor of less invasive approaches complemented



Number at risk (a)									
LND	51	26	16	10	8	8	7	7	6
Non-LND	51	25	22	17	16	13	11	9	8

Number at risk (b)									
LND	51	43	24	15	12	9	8	7	6
Non-LND	51	37	26	22	18	14	13	9	8

Figure 4. Recurrence-free (a) and overall (b) survival of patients receiving lymph node dissection or not after propensity score matching (PSM). LND: lymph node dissection.

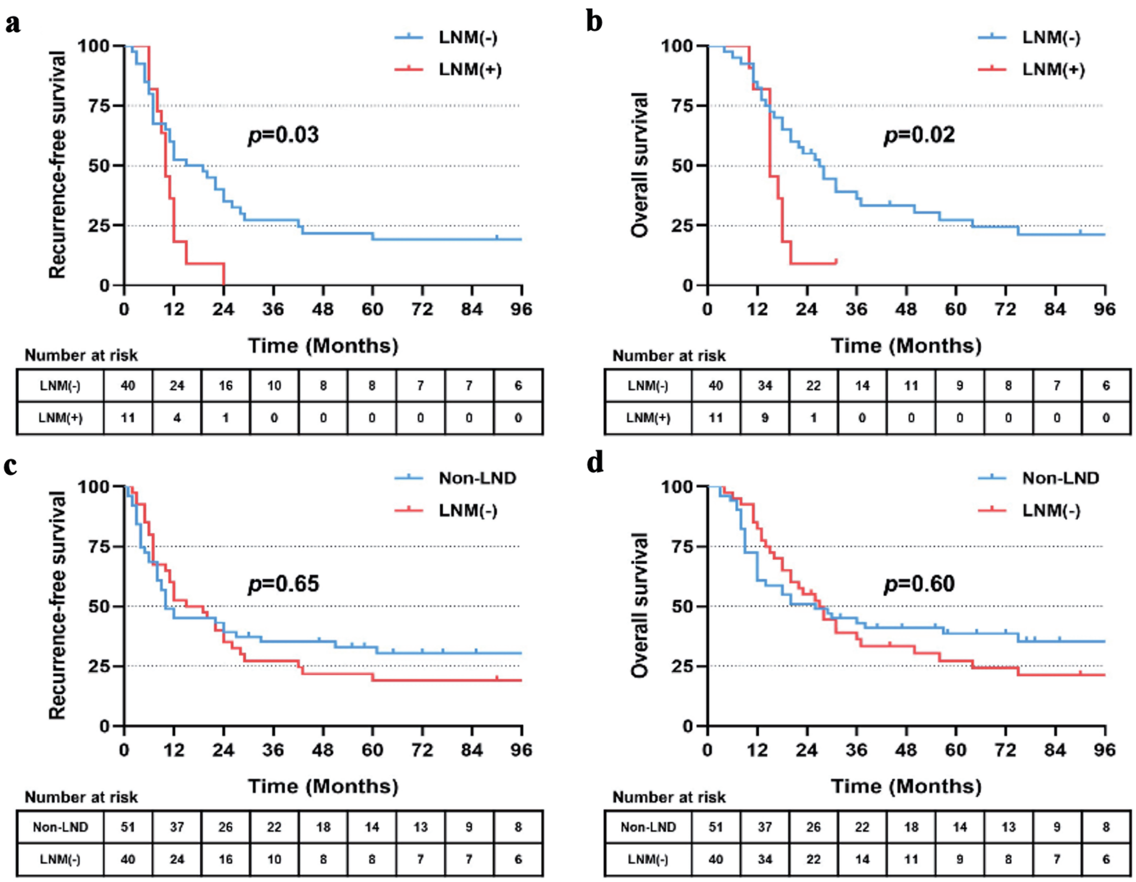


Figure 5. Recurrence-free (a) and overall (b) survival of patients with lymph node metastasis (LNM (+)) and no lymph node metastasis (LNM (-)). Recurrence-free (c) and overall (d) survival of patients with hepatectomy alone (non-LND) and LNM (-). LND: lymph node dissection.

Table 3. Univariate and Multivariate Analysis of Prognosis Factors for Recurrence-Free Survival in Patients Who Underwent Resection for ICC After PSM

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age (≤ 50 vs. > 50)	1.608	0.914 - 2.830	0.099			
Gender (male vs. female)	1.491	0.913 - 2.437	0.111			
HBV infection (absent vs. present)	0.807	0.471 - 1.384	0.436			
KPS score (> 60 vs. ≤ 60)	1.509	0.758 - 2.618	0.278			
Cirrhosis (absent vs. present)	1.576	0.574 - 4.326	0.377			
Preoperative CA19-9 (U/mL) (≤ 55 vs. > 55)	1.187	0.759 - 1.858	0.452			
Tumor diameter (≤ 50 mm vs. > 50 mm)	2.353	1.461 - 3.789	< 0.001	2.027	1.231 - 3.338	0.005
Tumor number (single vs. multiple)	1.754	1.018 - 3.021	0.043	1.493	0.860 - 2.591	0.154
Vascular invasion (absent vs. present)	1.772	1.110 - 2.827	0.016	1.517	0.940 - 2.447	0.088
Histologic differentiation (well/moderate vs. poor)	1.465	0.930 - 2.309	0.100			
Perineural invasion (absent vs. present)	1.386	0.690 - 2.784	0.358			
Lymph node dissection (absent vs. present)	1.222	0.778 - 1.919	0.385			
Postoperative adjuvant therapy (absent vs. present)	0.619	0.392 - 0.978	0.040	0.623	0.393 - 0.987	0.044

KPS: Karnofsky Performance Status; HBV: hepatitis B virus; CA19-9: carbohydrate antigen 19-9; HR: hazard ratio; CI: confidence interval.

Table 4. Univariate and Multivariate Analysis of Prognosis Factors for Overall Survival in Patients Who Underwent Resection for ICC After PSM

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age (≤ 50 vs. > 50)	1.863	1.000 - 3.471	0.050			
Gender (male vs. female)	1.360	0.818 - 2.262	0.236			
HBV infection (absent vs. present)	0.826	0.466 - 1.462	0.511			
KPS score (> 60 vs. ≤ 60)	1.692	0.923 - 3.100	0.089			
Cirrhosis (absent vs. present)	1.865	0.675 - 5.151	0.229			
Preoperative CA19-9 (U/mL) (≤ 55 vs. > 55)	1.342	0.838 - 2.149	0.221			
Tumor diameter (≤ 50 vs. > 50 mm)	2.383	1.443 - 3.936	0.001	2.172	1.304 - 3.618	0.003
Tumor number (single vs. multiple)	2.330	1.349 - 4.022	0.002	2.130	1.223 - 3.711	0.008
Vascular invasion (absent vs. present)	1.389	0.841 - 2.295	0.199			
Histologic differentiation (well/moderate vs. poor)	1.605	0.997 - 2.583	0.051			
Perineural invasion (absent vs. present)	1.527	0.757 - 3.082	0.237			
Lymph node dissection (absent vs. present)	1.189	0.740 - 1.909	0.474			
Postoperative adjuvant therapy (absent vs. present)	0.578	0.357 - 0.936	0.026	0.585	0.359 - 0.952	0.031

KPS: Karnofsky Performance Status; HBV: hepatitis B virus; CA19-9: carbohydrate antigen 19-9; HR: hazard ratio; CI: confidence interval.

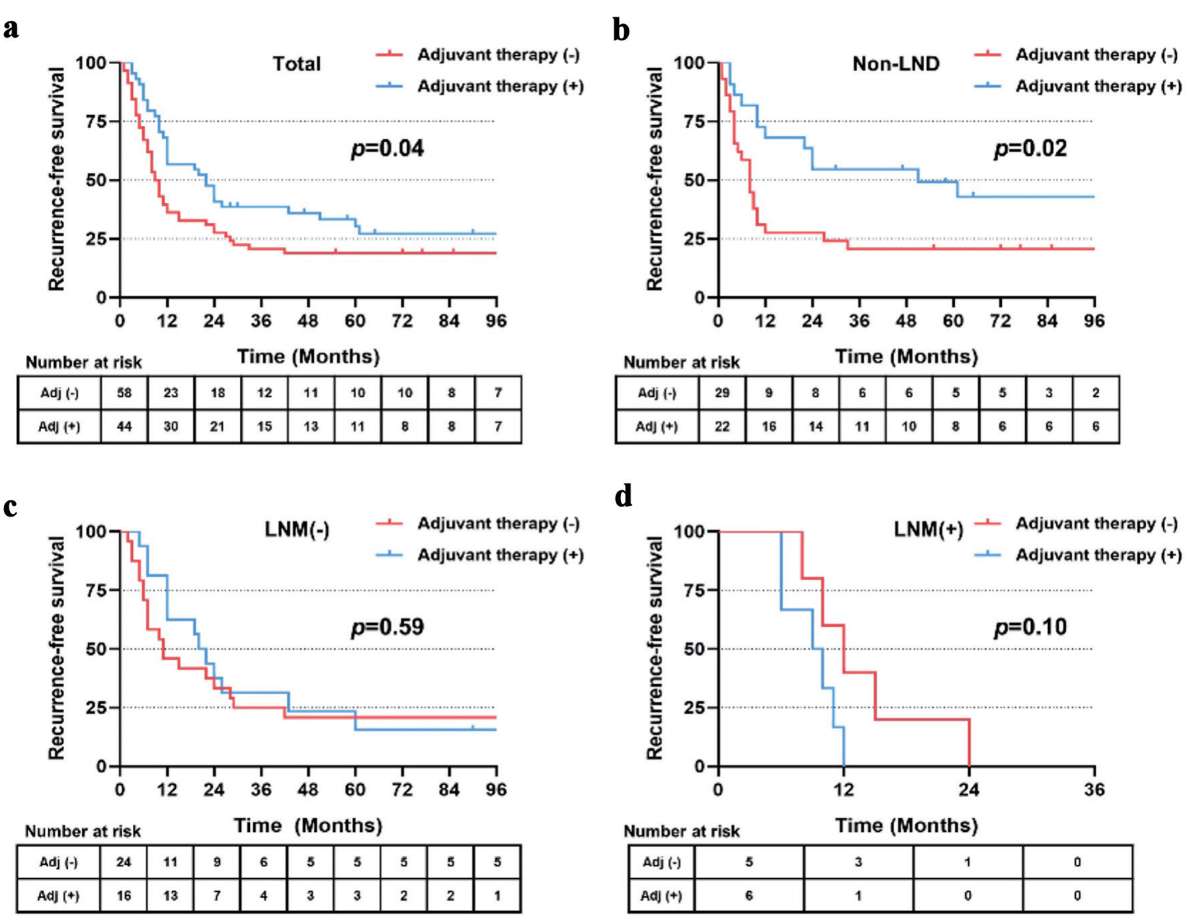


Figure 6. (a-d) Recurrence-free survival of patients in total, with non-LND, LNM (-) and LNM (+) receiving postoperative adjuvant therapy or not after PSM. LND: lymph node dissection; LNM: lymph node metastasis; PSM: propensity score matching.

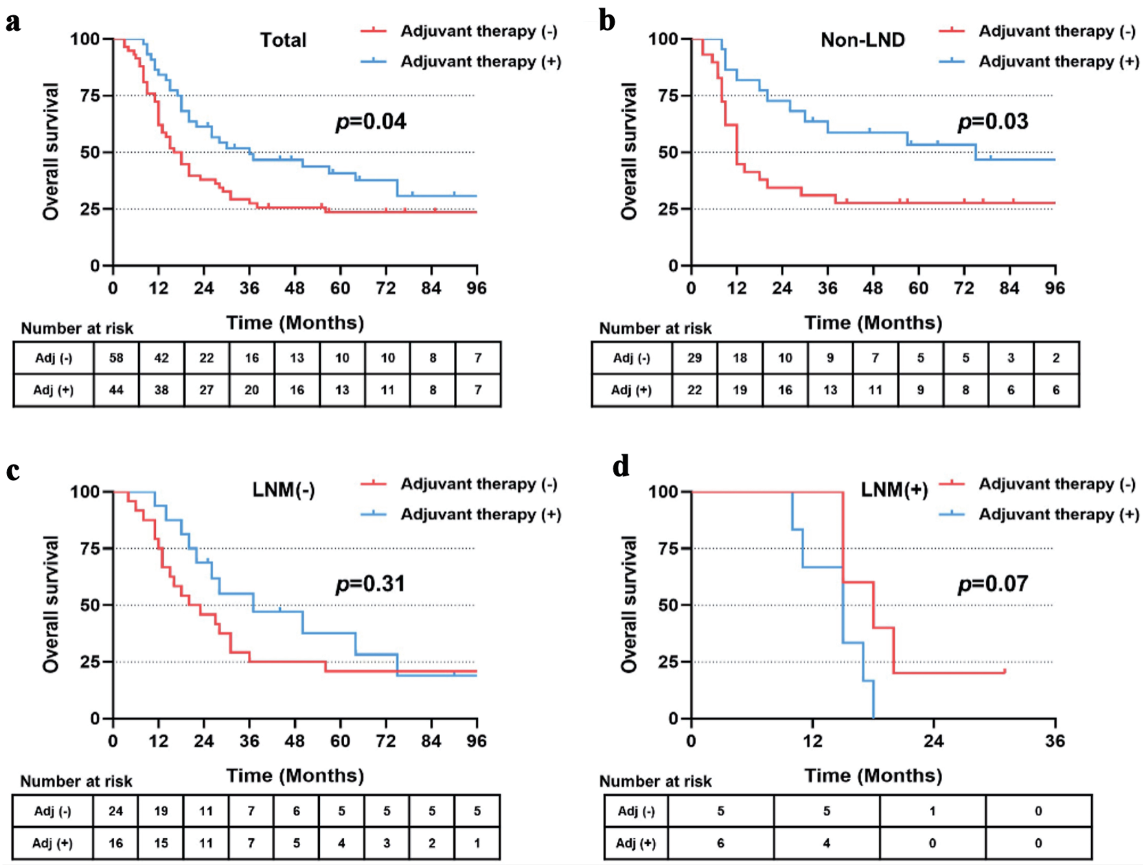


Figure 7. (a-d) Overall survival of patients in total, with non-LND, LNM (-) and LNM (+) receiving postoperative adjuvant therapy or not after PSM. LND: lymph node dissection; LNM: lymph node metastasis; PSM: propensity score matching.

by adjuvant therapies. On the other hand, survival outcomes did not differ in patients of LND (+) with and without adjuvant therapy. It was supported by the recent STAMP trial [40], which revealed that adjuvant gemcitabine plus cisplatin did not improve survival outcomes in resected lymph node-positive cholangiocarcinoma. However, it is noted that the limited number of patients in the LNM (-) subgroup of our study may impede the evaluation of postoperative treatment in these patients. Additionally, detailed protocol of adjuvant therapy varied between each center, which calls for prospective clinical trials of consistent adjuvant regimen. Currently, rapid developments in systemic therapy, including immune checkpoint inhibitors and multi-kinase inhibitors, have demonstrated convincing effects for ICC [41, 42]. More promising adjuvant therapy approaches will improve the prognosis of ICC in future.

Our study has some potential limitations. Firstly, the retrospective nature of the study unavoidably introduces biases in data collection and patient selection. Although a PSM analysis was conducted to minimize the drawback, the limited number of patients may impact the statistical power of the study and the generalizability of the findings. Secondly, precise evaluation of imaging in determining lymph node status is difficult to made based on the current methods. Imaging modalities can sometimes fail to detect microscopic metastases, leading to a potential underestimation of the actual nodal involvement. Thus, it strongly calls for more accurate detection methods such as PET-CT or machine learning-based radiomics. The third limitation was the extent of LND. Although we have established the principles of LND as previously described, the extent of LND was mostly determined by each surgeon. The median retrieval of lymph nodes was 4 in the LND group, which was far from at least six nodes based on the latest guideline. Inadequate LND may lead to misinterpretation of pathological results and affect survival outcomes. Additionally, detailed data on postoperative chemotherapy drugs and doses, radiotherapy dosage and treatment after recurrence were lacking. Last but not least, the study was conducted in three tertiary hepatobiliary centers, which may cause concerns regarding the generalizability of the findings to other settings, particularly those with less specialized expertise in ICC management.

Despite the limitations above, our study focused on patients with clinically node-negative ICC to evaluate the necessity of LND, which was different from previous studies. We discussed the prophylactic LND in various aspects of survival outcomes, accurate N staging and adjuvant therapy. The results suggest that routine LND may not be applied in patients with clinically node-negative ICC. Postoperative adjuvant therapy is recommended to prolong survivals of ICC patients, especially in non-LND individuals. With more accurate preoperative imaging methods, future prospective, multicentered, largescale studies are expected to confirm the value of LND for patients with clinically node-negative ICC. Also, it is required to further confirm the effect of postoperative adjuvant therapy in different subgroups of ICC patients.

Conclusions

Based on our data, we found that LND did not significantly improve the prognosis of patients with clinically node-negative ICC. Postoperative adjuvant therapy was associated with prolonged survival of ICC patients, especially in non-LND individuals.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Informed Consent

The patients provided their written informed consent.

Author Contributions

Conception and design: Meng Sha and Jie Cao. Provision of study materials or patients: Cheng Lin Qin, Jian Zhang and Jie Cao. Collection and assembly of data: Meng Sha and Zhe Li. Data analysis and interpretation: Meng Sha, Chao Fan and Lei Xia. Manuscript writing: all authors.

Data Availability

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

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