European Journal of Surgical Oncology xxx (xxxx) xxx

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Prognostic value of lymphadenectomy in node-negative intrahepatic cholangiocarcinoma: A multicenter, retrospectively study

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A R T I C L E I N F O

Article history:
Received 1 July 2022
Received in revised form
24 September 2022
Accepted 3 November 2022
Available online xxx

Keywords:
Intrahepatic cholangiocarcinoma
Lymph node dissection
Node-negative
Total number of lymph nodes examined
Curative intent resection

A B S T R A C T

Background: This study aimed to evaluate the prognostic value of lymph node dissection (LND) in node-negative intrahepatic cholangiocarcinoma (ICC) and identify the appropriately total number of lymph nodes examined (TNLE).

Methods: Data from node-negative ICC patients who underwent curative intent resection in ten Chinese hepatobiliary centers from January 2010 to December 2018 were collected. Overall survival (OS), relapse-free survival (RFS) and postoperative complications were analyzed. Propensity score matching (PSM) was performed to reduce the bias due to confounding variables in LND group and non-lymph node dissection (NLND) group. The optimal TNLE was determined by survival analysis performed by the X-tile program using the enumeration method.

Results: A total of 637 clinically node-negative ICC patients were included in this study, 74 cases were found lymph node (LN) positive after operation. Among the remaining 563 node-negative ICC patients, LND was associated with longer OS but not RFS before PSM (OS: 35.4 vs 26.0 months, $p = 0.047$; RFS: 15.0 vs 15.4 months, $p = 0.992$). After PSM, patients in LND group had better prognosis on both OS and RFS (OS: 38.0 vs 23.0 months, $p < 0.001$; RFS: 15.0 vs 13.0 months, $p = 0.029$). There were no statistically differences in postoperative complications. When TNLE was greater than 8, OS (48.5 vs 31.1 months, $p = 0.025$) and RFS (21.0 vs 13.0 months, p = 0.043) were longer in the group with more dissected LNs.

Conclusion: Routinely LND for node-negative ICC patients is recommended for it helps accurate tumor staging and associates with better prognosis. The optimal TNLE is more than 8.

1. Introduction

Intrahepatic cholangiocarcinoma (ICC) arises from the peripheral bile ducts within the liver parenchyma, proximal to the secondary biliary radicals. Recent epidemiological studies have shown that its worldwide incidence has increased almost threefold in the last three decades, especially in Southeast Asia [1]. Meanwhile survival of ICC patients is still disappointing, probably due to the aggressive malignancy natural history of disease characterized by

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https://doi.org/10.1016/j.ejso.2022.11.008
0748-7983/

Please cite this article as: C. Chen, J. Su, H. Wu *et al.*, Prognostic value of lymphadenectomy in node-negative intrahepatic cholangiocarcinoma: A multicenter, retrospectively study, European Journal of Surgical Oncology, https://doi.org/10.1016/j.ejso.2022.11.008

early lymph node involvement, distant metastasis and resistance to systemic chemotherapy [2–4]. Although kinds of adjuvant therapies, such as chemotherapy, radiotherapy and targeted therapy have been conducted gradually to improve the prognosis, surgical resection is still the most preferred treatment for patients with ICC [5]. The 5-year overall survival rate after surgical resection is 15%–40% [6–9]. However, up to 60% of ICC patients presented with disease tending to be advanced or even lethal upon diagnosis, who were not suitable for curative resection [10].

Studies have shown that lymph node metastasis is one of the strongest predictors of poor overall survival (OS) and relapse-free survival (RFS) for ICC patients [11–13]. The complete surgical en-bloc resection with negative margins, both macroscopic and microscopic, as well as the adequate lymph node dissection (LND) in patients with lymph node metastasis are decisive criteria regarding long-term survival [14,15]. The 7th edition of the American Joint Committee on Cancer (AJCC) tumor-node-metastasis manual proposed the isolation of ICC from hepatocellular carcinoma for the first time and recommended the inclusion of lymph node status in staging system [16]. In addition, the 2020 edition of the National Comprehensive Cancer Network (NCCN) clinical practice guidelines on hepatobiliary cancers recommended that lymphadenectomy should be considered for accurate staging [17]. Adequate LND could not only improve the accuracy of staging, but also prolong overall survival [18]. The total number of lymph nodes examined (TNLE) could provide additional prognostic value [19].

However, despite the importance of LND, it is not routinely performed in ICC patients without preoperatively suspected positive lymph nodes. The clinical benefit of LND in node-negative ICC remains controversial, LND is reportedly associated with an increased operative risk, and some investigators have argued that LND does not provide prognostic benefit [20–23]. Therefore, the present study aimed to evaluate the prognostic value of LND in node-negative ICC, we compared the long-term survival of node-negative ICC who underwent radical resection with or without LND, the postoperative complications of LND were analyzed, and the optimal TNLE for node-negative ICC patients was investigated.

2. Materials and methods

2.1. Patients and data collection

Data from the respective institutional databases for all consecutive patients with ICC who underwent curative intent resection at 10 hospitals in China (the First Affiliated Hospital of Xi'an Jiaotong University, Eastern Hepatobiliary Hospital Affiliated to Naval Medical University, West China Hospital of Sichuan University, Tianjin Medical University Cancer Hospital, the First Hospital Affiliated to Army Medical University, Hunan Provincial People's Hospital, the First Affiliated Hospital of Zhengzhou University, Zhongda Hospital of Southeast University, Affiliated Hospital of North Sichuan Medical College, Xinhua Hospital Affiliated to Shanghai Jiaotong University School of Medicine) between January 2010 and December 2018 were collected. The institution review board of each institution approved this study. Unified CRF (Case Report Form) was distributed to these ten centers, standard demographic, laboratory, and clinicopathologic data were collected and the data were uniformly assigned.

The inclusion criteria were as follows: (1) Postoperatively pathological diagnosed as ICC; (2) Lymph node negative, preoperatively clinically node-negative was defined as without any evidence of positive LNs determined by imaging examinations including computed tomography, ultrasound, PET-CT and magnetic resonance imaging; (3) Underwent curative intent resection; (4) Without definite distant metastases; (5) With follow up data. The exclusion criteria included : (1) Patients with a prior or concurrent other malignancy; (2) Preoperatively imaging evidence of positive LNs; (3) Postoperative 30-day mortality; (4) Incomplete clinical data; (5) M1 disease, distant LN such as the para-aortic lymph nodes metastasis was considered as M1; (6) Underwent neoadjuvant therapy.

The diagnosis and pathological evaluation were according to the World Health Organization (WHO) defining criteria (2010). Hepatectomy, which based on Couinaud's segments, was carried out according to tumor diameter, location, presence or absence of cirrhosis, and estimated volume of the future liver remnant. Major hepatectomy was defined as bi-sectionectomy or more. The scope of lymph node dissection involved hepatoduodenal ligament and retro-pancreatic and/or para-aortic area.

Standard demographic, perioperative clinicopathological, and tumor-related characteristics were collected. T classification, tumor location, vascular invasion and surgical procedure were determined by preoperative examination and intraoperative exploration. Postoperative characteristics, including tumor size, surgical margin, TNLE, pathological differentiation, microvascular/perineural invasion and multiple tumors, were collected based on final pathology reports.

To verify the safety of surgery, we collected the postoperative complications and classified it according to Clavien-Dindo Classification. Besides these, we also collected the amount of intraoperative blood loss and postoperative hospital stay. Whether postoperative chemotherapy was performed was also recorded. Deadline of follow-up was December 2020.

2.2. Assessment of LND impact using propensity score matching

There is a bias in whether lymphadenectomy is performed in node-negative ICC patients. The value of standardized mean difference of T classification, surgical procedure, tumor location and vascular invasion were bigger than 0.100 meant imbalance between LND group and NLND group. Therefore, we used the factors including age, T stage, surgical procedure, tumor location and vascular invasion as the matched factors to implement PSM based on multivariable logistic regression model and identified 221 pairs of node-negative ICC patients with LND or NLND who had comparable baseline clinical and pathologic characteristics.

2.3. Statistical analysis

We compared nominal data using χ^2 tests or Continuity Correction, continuous parametric data using T tests, and non-parametric data using MannWhitney tests. Log-rank test was used in univariate analysis. Cox regression model was adopted for multivariable analysis using all statistically significant factors performed by univariate analysis. Propensity score matching (PSM) was used to mitigate bias, and propensity score analysis was performed with 1:1 exact matching [24]. All statistical analyses were performed with the SPSS 25.0 (SPSS, Chicago, IL, United States) software package. A standardized mean difference of <0.100 indicates very small differences. A P-value of <0.05 was defined as statistically significant. The cut-off value of TNLE was determined by the X-tile program. (https://medicine.yale.edu/lab/rimm/research/software/).

3. Results

A total of 950 ICC patients were collected , according to inclusion and exclusion criteria, 637 clinically node-negative ICC patients were enrolled, 74 cases were found lymph nodes positive after operation. Among the remaining 563 node-negative ICC patients, 261 cases underwent LND and 302 cases were in the NLND group (Fig. 1). The median TNLE was 6 and the range interquartile was 2–8 in patients underwent LND. Multiple tumors were presented in a minority of patients (19.2%). Among those with tumor invasion, 80 patients (14.2%) had vascular invasion, 76 patients (13.5%) had microvascular invasion, and 75 patients (13.3%) had perineural invasion. After surgical resection, 199 patients (35.3%) received adjuvant treatments, including adjuvant chemotherapy and radiation therapy (Table 1). Median OS of node-negative ICC patients was 29.0 months (95% CI, 25.2–32.8 months). The 1-, 3- and 5-year overall survival rates were 81.1%, 43.1% and 25.3%, respectively. 422 patients have collected RFS, and median RFS was 15.3 months (95% CI, 13.7–16.8 months). The 1-, 3- and 5-year RFS rates were 59.8%, 24.7% and 15.3%, respectively.

3.1. Long-term outcomes and recurrence in node-negative ICC patients

Univariate analysis showed that poor tumor differentiation, vascular invasion, microvascular invasion, advanced T classification, without lymphadenectomy, positive surgical margin (R1) and complications were associated with shorter OS (all $p < 0.05$; Table 1). Multivariate analyses showed that T classification (HR = 1.30, 95%CI: 1.02–1.67), vascular invasion (HR = 1.84, 95%CI: 1.35–2.52), surgical margin (HR = 1.78, 95%CI: 1.07–2.97) and tumor differentiation (HR = 1.38, 95%CI: 1.07–1.76) were independent prognostic risk factors, and LND (HR = 0.69, 95%CI: 0.55–0.88) were prognostic protective factors (Table 1). Univariate analysis showed that poor tumor differentiation, vascular invasion and advanced T classification were associated with shorter RFS (all $p < 0.05$; Table 1). Multivariate analyses showed that vascular invasion (HR = 1.86, 95%CI: 1.37–2.54) and T classification (HR = 1.65, 95%CI: 1.26–2.15) were independent prognostic factors for tumor recurrence (Table 1).

3.2. Comparison of clinicopathological features and survival between LND group and NLND group

The patients in the LND group had higher T classification ($p = 0.025$), more major hepatectomy ($p < 0.001$), more vascular invasion ($p < 0.001$) and less well-moderately tumor differentiation ($p = 0.017$) compared with NLND group. It is worth mentioning that there was no significant difference in intraoperative blood loss and Clavien-Dindo classification between two groups ($p = 0.332$ and $p = 0.785$). The discharge days in NLND group were longer than that in LND group ($p = 0.012$). The detailed comparisons between two groups are summarized in Table 2.

The LND group had longer OS with 35.4 months than the NLND group with 26.0 months ($p = 0.047$) (Fig. 2A). The RFS of the LND group was similar to that of the NLND group (15.0 months vs 15.4 months, $p = 0.992$) (Fig. 2C).

After PSM, the OS of LND group and NLND group were 38.0 months and 23.0 months, respectively ($p < 0.001$) (Fig. 2B). Due to the absence of RFS in some patients, data were available for 141 cases in the NLND group after matching 179 cases in the LND group. After PSM, the RFS of LND group was 15.0 months, which was longer than 13.0 months with NLND group ($p = 0.029$) (Fig. 2D).

3.3. Optimal total number of lymph nodes examined for node-negative ICC

The optimal cut-off value of TNLE in patients with node-negative ICC was 8, which was determined by the X-tile program. Brighter green squares were the intersections which divide the continuity variables into two groups with the greatest differences in survival (Fig. 3A). There were 207 patients with TNLE ≤8 and 54 patients with TNLE > 8. These two groups had the similar OS and RFS (OS: 48.5 vs 33.0 months, $p = 0.088$; RFS: 21.0 vs 14.5 months, $p = 0.214$) (Fig. 3B&D). There was no statistically significant difference in prognosis between the two groups before PSM. To reduce

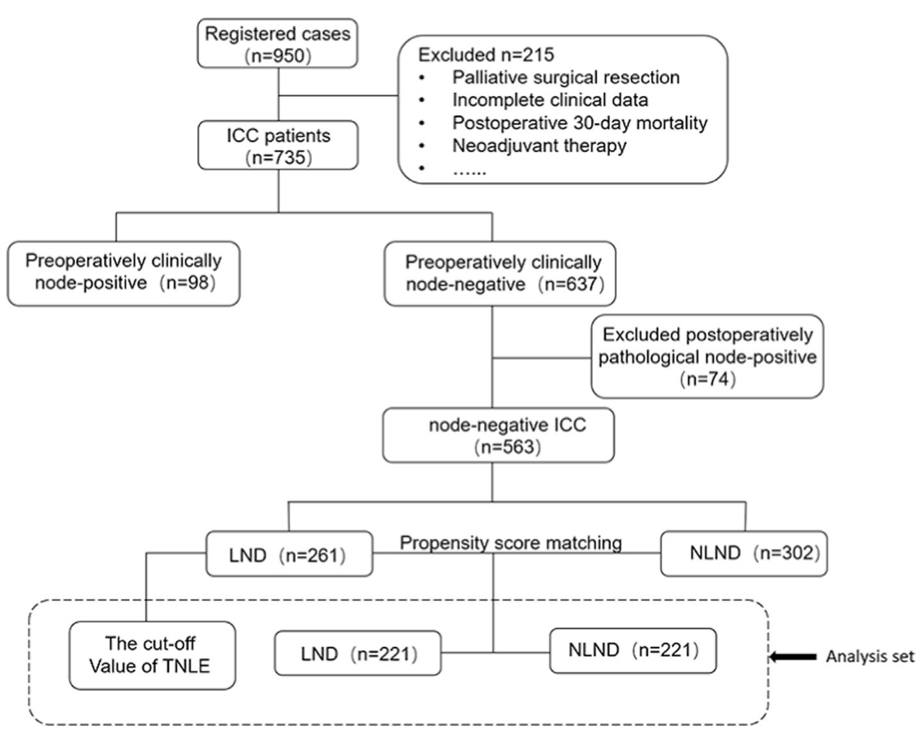

Fig. 1. Flowchart of the patient selection and group assignment processes.

Table 1
Univariate and multivariate analysis of prognostic factors on overall survival and relapse-free survival of ICC patients with negative lymph nodes.

Factors	Overall survival (OS)					Relapse-free survival (RFS)				
	cases	Univariate analysis		Multivariate analysis		cases	Univariate analysis		Multivariate analysis	
		Median OS (95%CI)	P values	Hazard ratio (95% CI)	P values		Median RFS (95%CI)	P values	Hazard ratio (95% CI)	P values
Gender										
Male	295	27.0 (23.3–30.7)	0.085			216	15.3 (12.4–18.2)	0.152		
Female	268	31.1 (25.0–27.1)				206	15.1 (12.9–17.4)			
Age (years)										
< 60	302	32.0 (25.1–38.9)	0.327			227	15.0 (12.4–17.6)	0.664		
≥60	261	28.0 (24.2–31.8)				195	16.0 (14.1–17.9)			
Child-Pugh stage										
A	520	29.7 (26.0–33.5)	0.101			397	15.0 (13.3–16.7)	0.674		
B & C	43	22.0 (11.1–32.9)				25	18.0 (15.1–20.9)			
Differentiation										
Moderately/Well	386	32.0 (27.1–36.9)	<0.001	1.38 (1.07–1.76)	0.012	287	18.0 (15.7–20.3)	0.002		
Poorly	177	23.0 (18.2–27.8)				135	12.0 (9.5–14.5)			
Tumor location										
Left	265	26.0 (21.7–30.3)	0.137			202	15.0 (12.2–17.8)	0.446		
Right	298	32.0 (26.5–37.5)				220	15.4 (13.0–17.8)			
Tumor size (cm)										
≤5	323	28.0 (20.9–25.1)	0.357			247	15.4 (13.3–17.4)	0.959		
>5	240	30.2 (25.4–35.1)				175	15.0 (12.6–17.4)			
Multiple tumor										
No	455	29.0 (23.9–34.1)	0.274			342	15.4 (13.9–17.0)	0.123		
Yes	108	31.0 (22.2–39.8)				80	12.0 (9.3–14.7)			
Vascular invasion										
No	483	32.0 (27.3–36.7)	<0.001	1.84 (1.35–2.52)	<0.001	358	17.0 (15.1–18.9)	<0.001	1.86 (1.37–2.54)	<0.001
Yes	80	19.7 (14.7–24.8)				64	9.0 (7.4–10.6)			
Perineural invasion										
No	488	30.2 (25.7–34.7)	0.122			360	15.3 (13.6–17.0)	0.503		
Yes	75	23.3 (17.9–28.8)				62	14.9 (12.0–17.9)			
Microvascular invasion										
No	487	30.0 (25.0–35.0)	0.016			360	15.4 (13.6–17.1)	0.294		
Yes	76	25.0 (16.3–33.7)				62	13.0 (5.8–20.2)			
T stage										
1–2	393	32.0 (26.8–37.2)	0.004	1.30 (1.02–1.67)	0.037	325	17.0 (15.1–18.9)	<0.001	1.65 (1.26–2.15)	<0.001
3–4	170	21.5 (16.8–26.2)				97	11.0 (7.5–14.5)			
Lymphadenectomy										
No	302	26.0 (22.7–29.3)	0.047	0.69 (0.55–0.88)	0.003	213	15.4 (13.3–17.5)	0.992		
Yes	261	35.4 (28.7–42.1)				209	15.0 (12.5–17.5)			
Surgical margin										
R0	537	30.0 (25.7–34.3)	0.023	1.78 (1.07–2.97)	0.027	407	15.3 (13.7–16.8)	0.378		
R1	26	20.0 (13.7–26.3)				15	13.0 (5.5–20.5)			
Adjuvant therapy										
No	364	30.0 (25.8–34.2)	0.729			249	15.3 (13.6–17.0)	0.654		
Yes	199	28.0 (22.0–34.0)				173	15.3 (12.2–18.3)			

bias, we performed propensity matching scores using match variables showed in Table 3.

PSM was utilized to identify 51 pairs of patients with TNLE ≤8 or TNLE > 8, and the standardized mean difference between the two groups of matching variables after matching was less than 0.1. There was a significant difference between OS in these two groups (48.5 vs 31.1 months, $p = 0.025$) (Fig. 3C). In addition, RFS of the TNLE >8 group (44 cases) was longer significantly than that of the TNLE ≤8 group (37 cases) (RFS: 21.0 vs 13.0 months, log-rank test: $p = 0.124$, breslow test: $p = 0.043$) (Fig. 3E).

The amount of intraoperative blood loss in group of TNLE ≤8 was more than that in group of TNLE >8 ($p = 0.023$). There was no significant difference in Clavien-Dindo classification and discharge days between the two groups ($p = 0.630$ and $p = 0.287$).

4. Discussion

Previous studies have reported prognostic factors after radical surgery for ICC, including tumor size, multiple lesions, cirrhosis, tumor differentiation, vascular invasion, perineural invasion, tumor markers and lymphadenectomy [25–27]. Among them, lymphadenectomy is beneficial to accurate staging and associated with better overall survival proved in some studies [17,22]. There is no controversy about that the regional lymphadenectomy could enhance the survival in ICC patients with lymph node metastasis [18].

However, whether lymphadenectomy is routinely used in radical resection of ICC remains controversial. Kim's study which using PSM showed that there was a marginally significant difference between the LND and NLND groups with respect to the disease-free survival, and overall survival was significantly better in the LND group [28]. Utilizing an augmented version of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program database, Kizy et al. even showed that surgical resection for patients with LN-positive ICC may not improve survival compared to chemotherapy alone [23]. More studies have argued the need for routine lymphadenectomy in ICC patients with negative lymph nodes. In a study of 103 patients, there was no significant difference in survival between Nx (no LND) and N0 (no lymph node metastases) [29]. A systematic review and meta-analysis including 1377 patients has reported that LND does not seem to positively affect overall survival of patients with negative

Table 2
Clinical pathological characteristics and operative outcomes in node-negative ICC patients before and after matching.

	Before PSM			After PSM		
	NLND	LND	P value	NLND	LND	P value
Variables to be balanced						
Age (≥60 years)	141 (46.7%)	120 (46.0%)	0.866	104 (47.1%)	104 (47.1%)	1.000
T stage						
1-2	223 (73.8%)	170 (65.1%)	0.025	159 (71.9%)	159 (71.9%)	1.000
3-4	79 (26.2%)	91 (34.9%)		62 (28.1%)	62 (28.1%)	
Surgical procedure						
Minor hepatectomy	127 (42.1%)	66 (25.3%)	<0.001	60 (27.1%)	60 (27.1%)	1.000
Major hepatectomy	175 (57.9%)	195 (74.7%)		161 (72.9%)	161 (72.9%)	
Tumor location						
Left	128 (42.4%)	137 (52.5%)	0.017	107 (48.4%)	107 (48.4%)	1.000
Right	174 (57.6%)	124 (47.5%)		114 (51.6%)	114 (51.6%)	
Vascular invasion	28 (9.3%)	52 (19.9%)	<0.001	25 (11.3%)	25 (11.3%)	1.000
Postoperative variables						
Perineural invasion	43 (14.2%)	32 (12.3%)	0.491	38 (17.2%)	23 (10.4%)	0.039
Microvascular invasion	42 (13.9%)	34 (13.0%)	0.760	36 (16.3%)	23 (10.4%)	0.069
Multiple tumor	66 (21.9%)	42 (16.1%)	0.083	52 (23.5%)	34 (15.4%)	0.031
Tumor size (cm)	4.00 [3.00–6.13]	5.10 [3.45–7.20]	<0.001	5.00 [3.00–7.00]	5.10 [3.20–7.05]	0.191
Differentiation (Poorly)	78 (25.8%)	99 (37.9%)	0.002	63 (28.5%)	75 (33.9%)	0.218
Surgical margin (R1)	20 (6.6%)	6 (2.3%)	0.015	17 (7.7%)	3 (1.4%)	0.001
Intraoperative blood loss (ml)	300 [200–600]	300 [200–600]	0.332	300 [200–600]	300 [200–600]	0.781
Clavien-Dindo Classification						
0/I-II	248 (82.1%)	212 (81.2%)	0.785	175 (79.2%)	180 (81.4%)	0.550
III-IV	54 (17.9%)	49 (18.8%)		46 (20.8%)	41 (18.6%)	
Discharge days	12 [9–15]	11 [7–15]	0.012	12 [9–16]	11 [7–15]	0.010
Adjuvant therapy	72 (23.8%)	127 (48.7%)	<0.001	51 (23.1%)	104 (47.1%)	<0.001

Categorical data are presented in the form of numbers and percentages and continuous data are presented as the median [range], unless otherwise indicated.

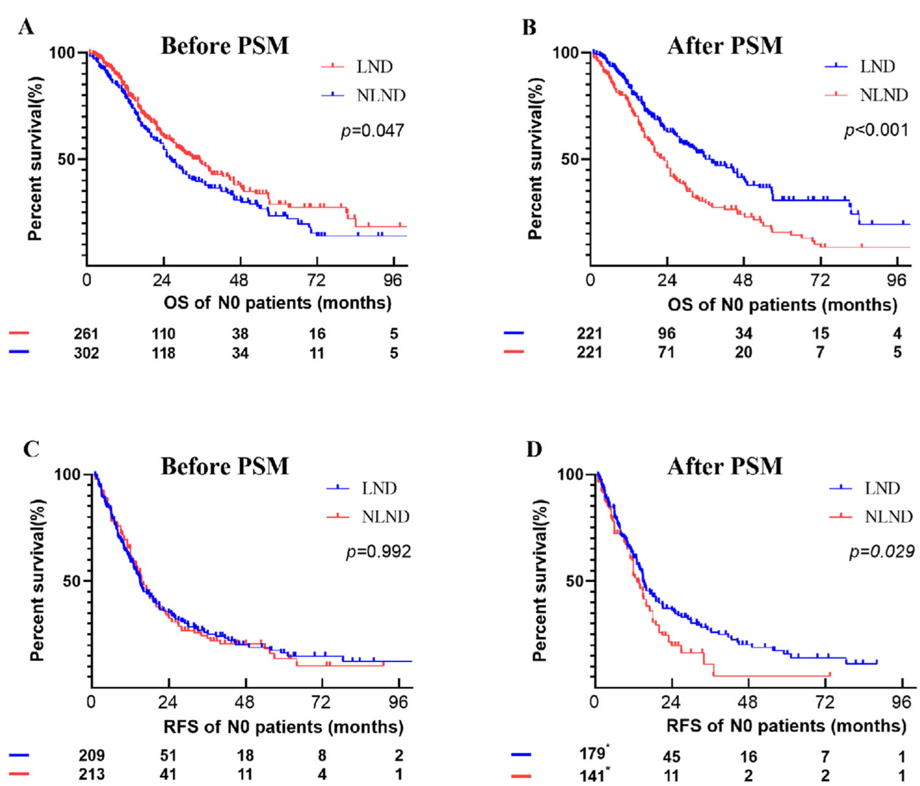

Fig. 2. Long-term outcomes between the node-negative ICC patients who underwent lymph node dissection and those who did not: Overall survival (A) and relapse-free survival (C) of the patients with node-negative ICC between LND group and NLND group. Overall survival (B) and relapse-free survival (D) of the patients with node-negative ICC between LND group and NLND group in the matched cohort.

lymph nodes and is associated with increased post-operative morbidity [20].

In our study, lymphadenectomy was an independent risk factor for overall survival, and it associated with improved OS (HR = 0.69, $p = 0.003$) in ICC patients with negative lymph nodes. After mitigating the bias by PSM, difference between LND patients and NLND

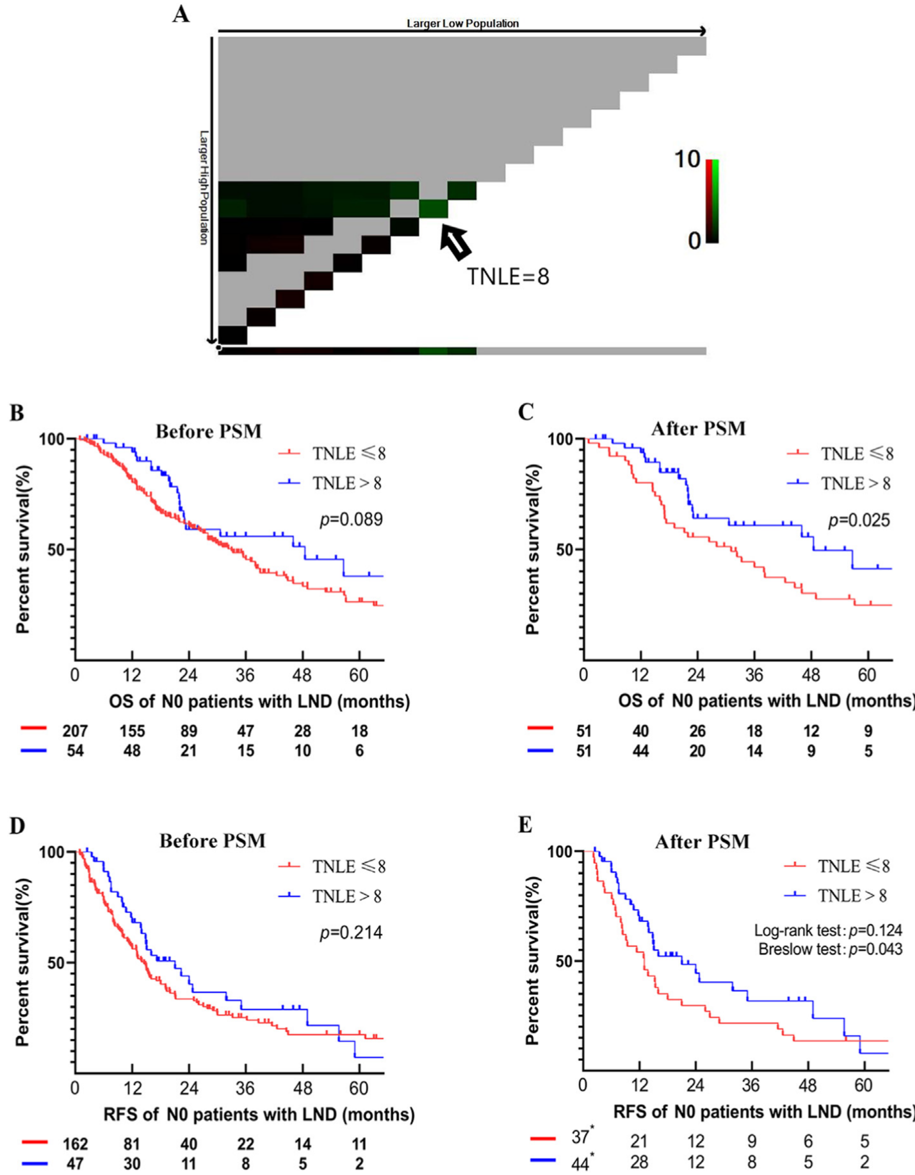

Fig. 3. The cut-off value for TNLE and long-term outcomes between the node-negative ICC patients with LND whose TNLE ≤8 and >8: X-tile program converts the continuity variable to a second classification variable and compares the differences in survival (A). The brighter the block looks, the greater the difference in the cut-off value. Overall survival (B) and relapse-free survival (D) of the patients with LND. Overall survival (C) and relapse-free survival (E) of the patients with LND in the matched cohort.

patients both existed in OS ($p < 0.001$) and RFS ($p = 0.029$). The results were similar to Yoh's study which using PSM in a 1:1 ratio showed that lymphadenectomy associated with better long-term outcomes in patients with node-negative ICC, though they included only 192 clinical node-negative ICC patients [30]. Other studies in support of lymphadenectomy emphasized the role of LND in accurate staging [24,31]. In the current study , 74 cases clinically node-negative ICC patients were found LN positive after LND, which indicates that LND in clinically node-negative ICC not only improving the long-term prognosis, but also improving the accuracy of tumor staging.

There was also a lack of evidence-based recommendation on the number of harvested lymph nodes with ICC patients. Based on PSM, we recommend dissection of more than 8 lymph nodes in ICC patients with negative lymph nodes. By using US National Cancer Database, Brauer et al. found that within the 631 patients undergoing R0 resection with pN0 disease, maximal chi-square testing identified ≥3 LNs as the threshold most closely associated with overall survival, but multivariable survival analysis showed no threshold of LNs was associated with overall survival [31]. Zhang's study showed that standard LND of at least 6 LNs was strongly recommended and should include examination beyond station 12 to have the greatest chance of accurate staging [32]. Kim et al. attempted to identify the minimum number of harvested LNs required for ICC by using a Bayesian Weibull model, and their results suggested that at least 5 LNs should be harvested in patients who undergo radical surgery for ICC to promote accurate staging. However, there were only 142 patients in their study [33]. This study demonstrates that dissection of more than 8 lymph nodes is associated with better patients' outcomes, not just accurate staging. The more TNLE recommended may be related to the selection of patient population. Only more dissection may reduce the possibility of lymph node negative patients with tumor metastasis through lymph nodes. In addition, LND does not increase the

Table 3
Clinical pathological characteristics and operative outcomes in node-negative ICC patients underwent LND before and after matching.

	Before PSM			After PSM		
	TNLE≤8	TNLE>8	P value	TNLE≤8	TNLE>8	P value
Variables to be balanced						
Age (≥60 years)	97 (46.9%)	23 (42.6%)	0.575	21 (41.2%)	21 (41.2%)	1.000
T stage						
1-2	138 (66.7%)	32 (59.3%)	0.309	31 (60.8%)	31 (60.8%)	1.000
3-4	69 (33.3%)	22 (40.7%)		20 (39.2%)	20 (39.2%)	
Surgical procedure						
Minor hepatectomy	52 (25.1%)	14 (25.9%)	0.904	12 (23.5%)	12 (23.5%)	1.000
Major hepatectomy	155 (74.9%)	40 (74.1%)		39 (76.5%)	39 (76.5%)	
Tumor location						
Left	110 (53.1%)	27 (50.0%)	0.681	24 (47.1%)	24 (47.1%)	1.000
Right	97 (46.9%)	27 (50.0%)		27 (52.9%)	27 (52.9%)	
Vascular invasion	39 (18.8%)	13 (24.1%)	0.391	10 (19.6%)	10 (19.6%)	1.000
Postoperative variables						
Perineural invasion	24 (11.6%)	8 (14.8%)	0.520	4 (7.8%)	7 (13.7%)	0.338
Microvascular invasion	29 (14.0%)	5 (9.3%)	0.356	5 (9.8%)	5 (9.8%)	1.000
Multiple tumor	35 (16.9%)	7 (13.0%)	0.482	10 (19.6%)	7 (13.7%)	0.425
Tumor size (cm)	5.80 [3.20–7.70]	5.00 [4.00–6.10]	0.426	6.00 [3.20–8.50]	5.00 [4.00–6.00]	0.345
Differentiation (Poorly)	76 (36.7%)	23 (42.6%)	0.428	18 (35.3%)	20 (39.2%)	0.682
Surgical margin (R1)	4 (1.9%)	2 (3.7%)	0.792	1 (2.0%)	2 (3.9%)	1.000
Intraoperative blood loss (ml)	300 [200–600]	200 [200–400]	0.017	500 [300–800]	200 [200–400]	0.023
Clavien-Dindo Classification						
0/I-II	169 (81.6%)	43 (79.6%)	0.736	39 (76.5%)	41 (80.4%)	0.630
III-IV	38 (18.4%)	11 (20.4%)		12 (23.5%)	10 (19.6%)	
Discharge days	11 [8–15]	10 [7–13]	0.106	12 [8–15]	10 [7–13]	0.287
Adjuvant therapy	99 (47.8%)	28 (51.9%)	0.598	26 (51.0%)	25 (49.0%)	0.843

Categorical data are presented in the form of numbers and percentages and continuous data are presented as the median [range], unless otherwise indicated.

postoperative complications and discharge days.

There are some limitations in this study. Firstly, this is a retrospective study, preoperative and intraoperative assessment of lymph node status may not fully reflect the status of the lymph node. Secondly, the harvested LNs of specific location cannot be obtained from some patients' records. Finally, we could not get the specific information of recurrence position, which is important data to validate the significance of lymph node dissection. More prospective studies with detailed follow-up are needed in the future.

5. Conclusion

Our analysis suggests routinely lymphadenectomy for nodes-negative ICC, which helps accurate tumor staging and associates with better prognosis. Lymphadenectomy does not associate with incidence of complications. At the same time, we recommend the removal of more than 8 lymph nodes, which plays an important role in possessing better OS and RFS, and does not increase incidence of postoperative complications and length of postoperative hospital stay.

Credit authors statement

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Declaration of competing interest

Disclosure: The authors declare no conflict of interest.

Acknowledgements

Chen Chen and Jingbo Su contributed equally to this work. The study was supported by the National Natural Science Foundation of China (No. 81772521, No. 62076194); Multicenter Clinical Research Project of Shanghai Jiaotong University, School of Medicine (No.DLY201807); Clinical Training Program of Shanghai Xinhua Hospital Affiliated to Shanghai Jiaotong University, School of Medicine (No. 17CSK06). The authors thank the three foundations.

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