Problems of Lymph Node Dissection in Intrahepatic Cholangiocarcinoma: A Multicenter Retrospective Study Using Inverse Probability of Treatment Weighting.

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Research

Keywords: Lymph node dissection, Intrahepatic Cholangiocarcinoma, IPTW, Surgery

Posted Date: December 30th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-136506/v1

Abstract

Background

Lymph node dissection (LND) is considered to improve the prognosis of patients with intrahepatic cholangiocarcinoma (ICC). Although the National Comprehensive Cancer Network (NCCN) guidelines recommend routine LND in ICC, the role of LND remains controversial. This study aimed to explore the effect of LND on the prognosis of patients with ICC from two Chinese centers.

Methods

Patients were identified in two Chinese academic centers. Inverse probability of treatment weighting (IPTW) was used to reduce bias. Kaplan–Meier curves and Cox proportional hazards models were used to compare overall survival (OS) and disease-free survival (DFS).

Results

Of 251 patients, 189 (75.2%) underwent LND, and 72 (38%) had metastatic lymph nodes. A minimum of 6 lymph nodes were dissected in 67 patients (35.5%). Lymph node metastasis (LNM) was a risk factor with a high hazard ratio. There was no association between LND and OS after IPTW; however, LND may affect the DFS. Tumors in the LNM group were more malignant, and surgical trauma was greater in the LNM group.

Conclusions

Only a few LNDs meet the NCCN guidelines' requirements. LND did not improve prognosis, with higher surgical trauma. The best approach for LND requires further discussion.

Synopsis

The role of Lymph Node Dissection in ICC is controversial. We used inverse probability of treatment weighting (IPTW) to reduce bias, and found that LND did not improve prognosis. Only a few LNDs meet the NCCN guidelines' requirements.

Introduction

Bile duct cell carcinoma (BCC) is a highly malignant tumor originating from the bile duct epithelium. Depending on the site, it can be classified as intrahepatic cholangiocarcinoma (ICC), hilar cholangiocarcinoma, and distal cholangiocarcinoma[1]. ICC originates above the secondary branches of the bile duct. ICC comprises about 10% of the primary malignant tumors of the liver, and is the second commonest in this group of tumors[1]. The onset of ICC is insidious. Surgery is the only effective treatment for ICC; however, only about 20% of the patients are eligible for resection at the time of diagnosis[2]. The prognosis of ICC is poor; the median postoperative survival is about 30 months, and the 5-year survival rate is approximately 30%[3, 4]. The postoperative recurrence rate is high, and the median disease-free survival (DFS) is only 20 months. Pathogenic factors, tumor size, tumor number, lymph node metastasis (LNM), vascular infiltration, degree of differentiation, and cancer antigen (CA) 19 – 9 levels are related to ICC prognosis[5–11]. LNM is an important confirmed risk factor of ICC[5–7, 11].

Lymph node dissection (LND) has been used in ICC for many years. The 7th edition of the American Joint Committee on Cancer (AJCC) staging system, released in 2010 is the first independent staging system of ICC. The 8th edition of the AJCC staging system recommends the dissection of at least 6 lymph nodes in ICC for an accurate N staging[12]. LND plays an important role in determining the lymph node status in ICC and in assessing the prognosis more accurately. Many studies have focused on the relationship between prognosis and the number and location of LNMs[13, 14]. Lymph node dissection has been suggested to improve ICC prognosis. However, whether LND can improve the survival of patients with ICC remains controversial. This study aimed to explore the effect of LND on the prognosis of patients with ICC from two Chinese centers.

Methods

1. Data Collection

Patients with pathologically confirmed ICC, who underwent a therapeutic surgery from 2003 to 2018, at the Cancer Hospital and Peking Union Hospital were included in this study. Patients who underwent non-primary surgeries, had no follow-up data, had other cancers, or an overall survival (OS) ≤ 1 month were excluded. Finally, 147 patients from Nation Cancer Center/Cancer Hospital and 104 patients from Peking Union Hospital were included in this study (N = 251).

2. Statistical method

SPSS 25 (IBM, Armonk, NY, USA) and RStudio (RStudio, Vienna, Austria) were used for statistical analysis. Categorical variables were compared using the chi-square test. Inverse probability of treatment weighting (IPTW) was used to reduce the confounders of multi-center data and was implemented using RStudio. The best cutoff values were found using the X-tile software (Yale School of Medicine/Pathology/Rimm Lab, New Haven, USA), with the minimum P value method. Survival analysis and verification were performed using the Kaplan-Meier method and log-rank test, respectively. Multivariate analysis was performed using the Cox proportional hazards regression model. P values < 0.05 were considered statistically significant. All P values in this paper are derived from unilateral tests

3. The study variables

Sex, age, Hepatitis B Virus status (defined as hepatitis B surface antigen-positive), LND, LND area (within or above the hepatoduodenal ligament), LNM area (within or above the hepatoduodenal ligament), number of dissected lymph nodes, number of LNMs, operation time, length of postoperative hospital stay (POD time), blood loss, intraoperative blood transfusion, tumor size, carcinoembryonic antigen (CEA) levels, CA 19 − 9 levels, multiple disease, margin, differentiation, vascular invasion, nerve invasion, adjuvant therapy, and T stage. The cutoffs for some of the variables were: X-tile: number of LNM≥3, CA 19 − 9 ≥75 U/mL, CEA≥7 ng/mL, POD time > 9 days, operation time > 235 minutes, blood loss≥300 mL, tumor size > 6 cm, and age > 60 years. The cutoff of the number of dissected lymph nodes was 6, based on the 8th edition of the AJCC cancer staging system. The patients were divided in 2 groups: those who underwent LND (LND group) and those who did not (nLND group). The LND group was further divided into the LN-negative and LN-positive group based on the presence of LNMs.

Results

1. Patient characteristics

Of the 251 patients, 189 (75.2%) underwent LND, and 72 (38%) had at least one LNM. A minimum of 6 lymph nodes were dissected in 67 patients (35.5%). The LND area of 116 patients (61.4%) was limited to the hilar area (hepatoduodenal ligament). There were significant baseline differences between the two groups (Table 1). POD time, operative time, intraoperative blood loss, and intraoperative blood transfusion were all higher in the LND group.

Table 1
Characteristics of Patients with Intrahepatic Cholangiocarcinoma which underwent surgery (N = 251)

		LND(N = 189,75.2%)	nLND(N = 62,24.8%)	P value
Sex				
	Male	97(51.3)	43(69.3)	**0.01**
	Female	92(48.7)	19(30.1)	
Age(Year)				
	≤ 60	111(58.7)	36(58.0)	0.93
	60	78(41.3)	26(42.0)	
LND area				
	Hilar	116(61.4)	NA	
	Beyound hilar	73(38.6)		
LNM area				
	Hilar	39(20.6)	NA	
	Beyound hilar	31(16.4)		
	Negative	119(63.0)		
LNM +				
	Yes	72(38.0)	NA	
	No	117(62.0)		
LND number				
	<6	122(64.5)	NA	
	≥ 6	67(35.5)		
LNM number				
	0	139(73.5)	NA	
	1 to 3	41(21.7)		
	>3	9(4.8)		
POD time(day)				
	≤ 9	84(44.4)	40(64.5)	**<0.01**
	>9	105(55.6)	22(35.5)	
HbsAg +				
	Yes	33(21.1)	9(14.5)	0.59
	No	156(78.9)	53(85.5)	
CEA(ng/mL)				
	≤ 7	145(76.7)	50(80.6)	0.4

		LND(N = 189,75.2%)	nLND(N = 62,24.8%)	P value
	>7	33(17.5)	7(11.3)	
	UK	11(5.8)	5(8.1)	
CA199(U/mL)				
	≤ 75	81(42.8)	38(61.3)	**<0.01**
	>75	95(50.2)	12(19.3)	
	UK	13(7.0)	12(19.3)	
Operation time(min)				
	≤ 235	89(47.3)	48(77.4)	**<0.01**
	>235	99(52.7)	14(22.6)	
Blood loss(mL)				
	≤ 300	92(48.7)	44(71.0)	**<0.01**
	>300	97(51.3)	18(29.0)	
Intraoperative blood transform				
	No	115(60.8)	48(77.4)	**0.02**
	Yes	74(39.2)	14(22.6)	
Tumor size(cm)				
	≤ 6	110(58.2)	41(66.1)	0.27
	>6	79(41.8)	21(33.9)	
Multi-disease				
	Yes	35(18.5)	9(14.5)	0.47
	No	154(81.5)	53(85.5)	
Margin+				
	Yes	22(11.6)	3(4.8)	0.12
	No	167(88.4)	59(95.2)	
Differentiation				
	Poorly	72(38.1)	24(38.7)	0.48
	Moderately	93(49.2)	35(56.5)	
	Well	24(12.7)	3(4.8)	
Vascular invasion				
	Yes	91(48.1)	21(33.9)	**0.05**
	No	98(51.9)	41(66.1)	
Nerve invasion				
	Yes	61(32.3)	9(85.5)	**<0.01**

		LND(N = 189,75.2%)	nLND(N = 62,24.8%)	P value
	No	128(67.7)	53(14.5)	
T stage				
	T1	108(57.1)	52(83.9)	**<0.01**
	>T1	81(42.9)	10(16.1)	
Adjuvant therapy				
	Yes	84(44.4)	26(41.9)	0.73
	No	105(55.6)	36(58.1)	
UK = Unknown,POD time = Postoperative hospital stay, adjuvant therapy represent of chemotherapy, radiotherapy and interventional therapy				

2. Prognostic factor analysis

The median follow-up time was 19 months. The total median OS was 28 months, and the 5-year OS rate was 33.0%. The total median DFS was 13.5 months, and the 5-year DFS rate was 26.8%. The 5-year OS of the nLND group and LND group was 51.6% vs. 24.9%, and the median OS was 61 vs. 21 months (95% confidence interval [CI] 34.9–87.1 months vs. 14.5–27.4 months, P < 0.01). The DFS of the nLND group was better than that of the LND group; the 5-year DFS was 39.7% vs. 22.1%, respectively, and the median DFS was 31 vs. 11 months, respectively (95% CI 13.8–48.2 months vs 8.6–13.4 months, P < 0.01).

LND, POD time > 9 days, CEA > 7 ng/mL, CA 19 − 9 > 75 U/mL, operation time > 235 min, blood loss > 300 mL, intraoperative blood transfusion, tumor size > 6 cm, multi-disease, positive margin, vascular invasion, nerve invasion, and T stage > T1 were risk factors for OS in univariate analysis. These variables were included in the multivariate analysis; CA 19 − 9 > 75 U/mL, CEA > 7 ng/mL, positive margin, and T stage > T1 were statistically significant (Table 2).

Table 2
Univariate and multivariate analyses of OS and DFS

		OS				DFS			
		Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
		HR	P	HR	P	HR	P	HR	P
LND									
	No	1	**<0.01**	1	0.82	1	**<0.01**	1	0.19
	Yes	1.75(1.19–2.56)		0.95(0.59–1.52)		1.82(1.25–2.65)		1.36(0.85–2.17)	
Sex									
	Female	1	0.98			1	0.88		
	Male	1.00(0.72–1.38)				1.02(0.75–1.40)			
Age(Year)									
	≤ 60	1	0.48			1	0.46		
	>60	0.90(0.64–1.24)				0.89(0.65–1.21)			
POD time(day)									
	≤ 9	1	**<0.01**	1	0.28	1	**0.02**	1	0.56
	>9	2.06(1.48–2.86)		1.27(0.82–1.96)		1.44(1.06–1.96)		1.13(0.75–1.69)	
HbsAg +									
	No	1	0.45			1	0.48		
	Yes	0.84(0.54–1.32)				1.15(0.78–1.71)			
CEA(ng/mL)									
	≤ 7	1	**<0.01**	1	**<0.01**	1	**<0.01**	1	**0.03**
	>7	3.79(2.54–5.67)		2.43(1.53–3.87)		2.45(1.62–3.69)		1.71(1.06–2.75)	
CA199(U/mL)									
	≤ 75	1	**<0.01**	1	**0.01**	1	**<0.01**	1	0.2
	>75	2.44(1.72–3.46)		1.67(1.13–2.46)		1.90(1.37–2.65)		1.28(0.876–1.86)	
Operation time(min)									
	≤ 235	1	**<0.01**	1	0.08	1	**<0.01**	1	0.27
	>235	2.0(1.44–2.76)		1.47(0.95–2.28)		1.64(1.20–2.24)		1.26(0.84–1.90)	
Blood loss(mL)									

		OS				DFS			
	≤ 300	1	**<0.01**	1	0.69	1	**<0.01**	1	0.8
	>300	2.07(1.50–2.87)		1.11(0.67–1.82)		1.62(1.19–2.21)		1.06(0.71–1.58)	
Intraoperative blood transform									
	No	1	**<0.01**	1	0.71	1	0.12		
	Yes	1.93(1.39–2.68)		0.91(0.54–1.52)		1.29(0.93–1.77)			
Tumor size(cm)									
	≤ 6	1	**0.03**	1	0.08	1	**0.04**	1	0.16
	>6	1.43(1.03–1.97)		1.38(0.96–1.99)		1.37(1.01–1.87)		1.29(0.91–1.82)	
Multi-disease									
	No	1	**<0.01**	1.49(0.92–2.43)	0.11	1	**<0.01**	1	**0.03**
	Yes	2.01(1.38–2.91)				1.80(1.24–2.62)		1.71(1.07–2.75)	
Margin+									
	No	1	**<0.01**	1	**<0.01**	1	**<0.01**	1	0.08
	Yes	2.63(1.65–4.20)		2.80(1.60–4.90)		1.99(1.26–3.17)		1.65(0.94–2.90)	
Differentiation									
	Poorly	1				1			
	Moderately	0.92(0.65–1.30)	0.62			0.78(0.57–1.08)	0.14		
	Well	1.26(0.75–2.10)	0.39			0.70(0.40–1.21)	0.2		
Vascular invasion									
	No	1	**0.01**	1	0.55	1	**<0.01**	1	0.49
	Yes	1.70(1.23–2.34)		1.14(0.74–1.74)		1.51(1.11–2.06)		1.16(0.77–1.74)	
Nerve invasion									
	No	1	**0.02**	1	0.16	1	**<0.01**	1	0.06
	Yes	1.70(1.20–2.41)		1.36(0.88–2.09)		1.61(1.15–2.23)		1.46(0.98–2.18)	
T state									
	T1	1	**<0.01**	1	**0.03**	1	**<0.01**	1	0.6

		OS			DFS		
	>T1	2.32(1.68–3.21)		1.67(1.05–2.66)	1.53(1.11–2.10)		0.89(0.57–1.39)
Adjuvant therapy							
	No	1	0.12		1	0.53	
	Yes	0.77(0.56–1.07)			0.91(0.66–1.24)		
POD time = Postoperative hospital stay, adjuvant therapy = chemotherapy, radiotherapy and interventional therapy							

LND, POD time > 9 d, CEA > 7 ng/mL, CA 19 − 9 > 75 U/mL, operation time > 235 min, blood loss>300 mL, tumor size > 6 cm, multi-disease, positive margin, vascular invasion, nerve invasion, and T stage > T1 were the primary factors influencing DFS. CEA and multi-disease were independent risk factors in multivariate analysis (P < 0.05) (Table 2).

3. Effects of LND on prognosis——IPTW

There were significant differences in patient characteristics between the LND and nLND groups. To further determine whether LND improved ICC prognosis, we used IPTW to minimize confounders. LNM or related variables were not included because they were unclear in the LND group. The adjustments are shown in **Fig. 1a**. The standardized mean differences showed that IPTW effectively balanced the between-group differences. The median OS and DFS were 61 months vs. 57 months (P = 0.75) and 34 months vs. 17 months (P = 0.10), respectively (nLND vs. LND, **Fig. 1b-1e**).

Further, we compared nLND with patients who underwent LND and were LNM-negative using the same method (Fig. 2a); Similarly, the difference in the OS and DFS were significant between the two groups; these differences were eliminated by IPTW (Fig. 2b-e**)**. The nLND and LND ≥ 6 groups were also compared at the same time (Fig. 3a, **Fig. 3b-e**). The IPTW-adjusted analysis showed that in all the groups, LND had a greater effect on DFS than on OS, and the DFS of the LND ≥ 6 group was significantly worse than that of the nLND group.

4. LND subgroup analysis

A subgroup analysis of LND was conducted to investigate whether the range, LND number, and LNM number affected prognosis. LN positivity was a risk factor for both OS and DFS, with a high hazard ratio. CA 19 − 9, CEA, tumor size, T stage, positive margin, and LNM were all risk factors for OS. Tumor size, LNM, and LND numbers were significant for DFS.

A relationship was observed between LNM area and OS, but not between LNM area and DFS. LNM number > 3 affected OS and DFS; however, there was no statistical significance (Table 3).

Table 3
Subgroup analysis of LND group

		OS				DFS			
		Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
		HR	P	HR	P	HR	P	HR	P
Sex									
	Female	1	0.87			1	0.49		
	Male	1.03(0.72–1.49)				1.13(0.80–1.60)			
Age(Year)									
	≤ 60	1	0.83			1	0.83		
	>60	0.96(0.66–1.40)				0.96(0.68–1.37)			
CEA(ng/mL)									
	≤ 7	1	**<0.01**	1	**<0.01**	1	**0.01**	1	0.35
	>7	3.20(2.04-5.00)		2.1(1.26–3.59)		1.76(1.11–2.80)		1.29(0.76–2.21)	
CA199(U/mL)									
	≤ 75	1	**<0.01**	1	**<0.01**	1	**<0.01**	1	0.22
	>75	2.38(1.59–3.57)		1.85(1.19–2.87)		1.69(1.17–2.45)		1.29(.86-1.95)	
Tumor size(cm)									
	≤ 6	1	0.12	1	**0.03**	1	**0.01**	1	**0.02**
	>6	1.33(0.92–1.92)		1.56(1.04–2.41)		1.343(0.95–1.90)		1.55(1.06–2.26)	
T stage									
	T1	1	**<0.01**	1	**<0.01**	1	**0.01**	1	0.38
	>T1	2.26(1.56–3.27)		1.88(1.17–3.02)		1.35(0.95–1.91)		1.2(0.80–1.81)	
Margin									
	Negative	1	**<0.01**	1	**0.04**	1	0.08		
	Positive	2.30(1.40–3.77)		1.90(1.05–3.45)		1.54(0.93–2.54)			
Multi-disease									
	No	1	**0.03**	1	0.41	1	0.24		
	Yes	1.57(1.03–2.40)		1.24(0.74–2.09)		1.29(0.84–1.98)			
LND area									

		OS				DFS			
	Hilar	1	0.13	1	0.2	1	0.33	1	0.95
	Beyond Hilar	0.74(0.50–1.10)		0.73(0.44–1.20)		1.19(0.83–1.69)		1.01(0.66–1.56)	
LN positive									
	No	1	**<0.01**	1	**<0.01**	1	**<0.01**	1	**<0.01**
	Yes	3.31(2.26–4.86)		2.35(1.44–3.84)		2.31(1.60–3.34)		2.13(1.36–3.35)	
LND number									
	<6	1	0.77	1	0.09	1	**0.04**	1	**0.04**
	≥ 6	1.06(0.72–1.55)		1.51(0.94–2.42)		1.43(1.00-2.03)		1.6(1.03–2.50)	
LNM area	**Only analysis in LNM group(N = 72)**								
	Hilar	1	0.77	1	0.58	1	**0.01**	1	**0.02**
	Beyond Hilar	0.930.55–1.58)		0.87(0.494–1.49)		2.00(1.16–3.45)		1.97(1.11–3.49)	
LNM number									
	1 to 3	1	0.26	1	0.23	1	0.3	1	0.86
	>3	1.40(0.76–2.58)		1.47(0.78–2.78)		1.35(0.74–2.44)		1.06(0.57–1.98)	
LNM = lymph nodes metastasis, The hilar representation is confined to the hepatoduodenal ligament									

5. Characteristics of the LN-negative and LN-positive groups

To identify the predictors and characteristics of LNM, we compared the LN-positive and LN-negative groups and found that the LN-positive group had higher CEA levels, CA 19 − 9 levels, and T stages, as well as a higher proportion of vascular and nerve invasion, and positive margins. Meanwhile, POD time, blood loss, and operation time were significantly higher in the LN-negative group (Table 4).

Table 4
Characteristics of Patients of different lymph nodes metastasis state

		LN negative(N = 114,61.3%)	LN positive(N = 72,38.7%)	P value
Sex				
	Male	57(50)	38(52.8)	0.71
	Female	57(50)	34(47.2)	
Age(Year)				
	≤ 60	71(62.3)	38(52.8)	0.2
	>60	43(37.7)	34(47.2)	
LND area				
	Hilar	73(64.0)	40(55.6)	0.25
	Beyound hilar	41(36.0)	32(44.4)	
LND number				
	<6	76(66.7)	43(59.7)	0.34
	≥ 6	38(33.3)	29(40.3)	
POD time(day)				
	≤ 9	58(50.9)	23(31.9)	**0.01**
	>9	56(49.1)	49(68.1)	
HbsAg +				
	Yes	25(21.9)	8(11.1)	0.06
	No	89(78.2)	64(88.9)	
CEA(ng/mL)				
	≤ 7	96(92.3)	46(64.8)	**<0.01**
	>7	8(7.7)	25(35.2)	
CA199(U/mL)				
	≤ 75	59(57.3)	21(30.0)	**<0.01**
	>75	44(42.7)	49(70.0)	
Operation time(min)				
	≤ 235	63(55.8)	25(34.7)	**<0.01**
	>235	50(44.2)	47(65.3)	
Blood loss(mL)				
	≤ 300	64(56.1)	27(37.5)	**0.01**
	>300	50(43.9)	45(62.5)	
Intraoperative blood transform				
	No	74(64.9)	39(54.2)	0.14

		LN negative(N = 114,61.3%)	LN positive(N = 72,38.7%)	P value
	Yes	40(35.1)	33(45.8)	
Tumor size(cm)				
	≤ 6	68(59.6)	39(54.2)	0.46
	>6	46(40.4)	33(45.8)	
Multi-disease				
	Yes	21(18.4)	13(18.1)	0.95
	No	93(81.6)	59(81.9)	
Margin+				
	Yes	8(7.0)	14(19.4)	**0.01**
	No	106(93.0)	58(80.6)	
Differentiation				
	Poorly	42(36.8)	28(38.9)	0.84
	Moderately	56(49.1)	36(50.0)	
	Well	16(14.0)	8(11.1)	
Vascular invasion				
	Yes	44(38.6)	45(62.5)	**<0.01**
	No	70(61.4)	27(37.5)	
Nerve invasion				
	Yes	26(22.8)	38(52.8)	**<0.01**
	No	88(77.2)	34(47.2)	
T state				
	T1	79(69.3)	28(38.4)	**<0.01**
	>T1	35(30.7)	44(61.1)	
Adjuvant therapy				
	Yes	48(42.1)	33(45.8)	0.62
	No	66(57.9)	39(54.2)	

Discussion

ICC is a malignant disease with a poor prognosis. The goal of surgery is complete (R0) resection. The prevalence of LNM in ICC is as high as 17%-39.1%[15, 16], and LND is considered as part of R0 resection. Many surgeons believe that LND improves ICC survival. However, some researchers found that LND is only a staging operation and has little effect on prognosis[4, 17]. In our study, the initial analysis showed a poorer prognosis in the LND group, which might be explained by the incongruity of the baseline characteristics. Variables were better adjusted using IPTW than propensity score matching (PSM); there was no significant difference in OS between the groups. This is not consistent with the findings of some prior studies. Yoh et al. compared the effect of LND on prognosis in patients with no suspected LNM before surgery[15]. This indicated that LND improved both DFS and OS in the nLND group. Only 112 patients were included, and some deviations in preoperative imaging

assessment may exist. Ma et al.[18] found that patients who underwent extensive LND in the R0 resection group and group without distant metastases had a better prognosis, even after PSM. However, there was no difference in the whole cohort. Kim et al. obtained a results in the LND ≥ 6 and nLND groups, the former's OS is better[19]. However, the sample size was only 68, and the OS in this study was much longer than those in other studies. We also verified this conclusion using IPTW. Unlike OS, DFS was better in the nLND group. LNM status was unknown in the nLND group; therefore, we could not include it in any match. Although many possible variables were included in IPTW to address this problem, it could not completely balance the LNM situations of the two groups. Generally, our research supported the hypothesis that LND has no prognostic benefit, but it may be related to DFS in ICC.

However, this does not render LND unmeaningful. The prevalence of LNM in ICC is high (approximately 31.9. -58.0%)[20, 21]. Since LNM is a predictor of poor prognosis in ICC, LND should be performed routinely as it is the only means to assess the LN status. The best approach for LND is controversial. The 8th edition of the AJCC cancer staging system suggests routine LND and removal of at least 6 LNs. This system also clearly defines regional LNs[22]. In addition to hilar nodes (common bile duct, hepatic artery, portal vein, and cystic duct nodes), regional LNs include the inferior phrenic and gastrohepatic lymph nodes in the left liver lobe. The right lobe covers the periduodenal and peripancreatic LN areas. Extraregional LNM like distant metastases are contraindications to surgery according to the NCCN guideline. [23]. Although the NCCN guidelines recommend only the dissection of the hilar area[24], the LND extent is insufficient. In our data, 75.2% underwent LND, and 35.5% had a sufficient number of dissected lymph nodes, of which 61.4% were hilar lymph nodes. This indicates that the N stage of more than half of the patients may not be exact, and the assessments in some patients with LNM are incorrect because LND is not performed or poorly done. However, some improvements in these rates have been observed. The proportion of qualified LND is increasing, though it is still not satisfactory[25]. The large difference in baseline data also showed that many surgeons perform LND, which is consistent with previous studies[14, 26, 27]. Generally, the tumors of the LND group were more malignant, with higher tumor marker levels, T stage, vascular invasion, and nerve invasion. Surgery was indicated in these patients because the surgeons suspected that they would have more LNMs; this was confirmed by the LND subgroup analysis (LN-positive vs. LN-negative). Unfortunately, this did not change the fact that LND could not improve the prognosis. Given that LND rendered surgery more challenging, caution should be taken when selecting this procedure in some patients.

Another question was the best number and area of LND. In a large multicenter study published by Zhang et al., the dissection of 6 lymph nodes was the best for obtaining a better overall survival[13]. This was not confirmed in our data. In fact, we did not find a significant cutoff LND number for survival using X-tile software. This requires further study. Concurrently, the LND area was not significantly different in our study. From our findings, LND did not improve survival; further studies should preferably focus more on the relationship between LND and LNM detection rate, than on that between LND and OS. To obtain very accurate results, LND should be routine and standardized, instead of just removing the LNs which were probed intraoperatively. Although this has been recommended by the AJCC, there is still need for further research.

The current N staging system seems to be a little simplistic. A cutoff of 1 (i.e., LNM-positive and negative) has been shown to effectively differentiate the patients' prognoses[9, 11, 18, 28–31]. Zhang et al. put forward a new N stage model: N0 (LNM 0), N1 (LNM 1–2), and N2 (LNM > 2); they found that their model performed better in patients with at least 6 dissected lymph nodes[13]. In our study, we grouped patients with LNM 1–3 and LNM ≥ 3, and found a difference (14 months vs. 9 months); however, the difference was not statistically significant, regardless of the cutoff value. There was no significant difference in the LND ≥ 6 subgroup. We tried to correct this result using IPTW but failed, because the sample size was not large enough. Further studies focusing on a better N staging system should be conducted.

This study had some limitations. First, the sample size was small. Data was collected by many people and may have produced incorrect results. LND was recorded only by the surgeon who performed the operation, which may make it less objective. The analysis methods in this study could not eliminate the differences between groups. Despite these limitations, we provide researchers with reference data for ICC surgery, prognostic model, and staging system, through in-depth data analysis.

Conclusions

LNM was a significant prognostic factor of ICC, and the LNM area was associated with DFS. Only a few LNDs met the guidelines' requirements. There was no significant improvement in the OS and DFS after adjusting for LND in each group. The LND group had a higher degree of malignancy than the nLND group, making surgery more difficult and traumatic. The best approach to LND should be explored further.

Abbreviations

LND= Lymph node dissection, nLND=did not undergo LND, BCC=Bile duct cell carcinoma, AJCC=American Joint Committee on Cancer, ICC= intrahepatic cholangiocarcinoma, NCCN=National Comprehensive Cancer Network, IPTW=Inverse probability of treatment weighting, LNM= Lymph node metastasis, UK= Unknown，POD time= Postoperative hospital stay, OS= Overall survival, DFS= Disease-free survival.

Declarations

1. **Ethics approval and consent to participate**

The Cancer Hospital and Peking Union Hospital Institutional Review Board granted this study exemption due to its retrospective nature.

2. **Consent for publication**

Not applicable.

3. **Availability of data and materials**

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

4. **Competing interests**

The authors declare that they have no competing interests.

5. **Funding**

This work was supported by the State Key Project on Infection Diseases of China (2017ZX10201021-007-003); The National The capital health research and development of special (2018-1-4021); The National Natural Science Foundation of China (81672461); The National Natural Science Foundation of China (81972311); Supported by Sanming Project of Medicine in Shenzhen（No.SZSM202011010）.

6. **Authors' contributions**

HH conducted data analysis, and was the major contributor in writing the manuscript. HH and XG collected the clinical information of the patients. LZ provides statistical technical support. All authors read and approved the final manuscript.

7. **Acknowledgement**

Not applicable.

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Figures

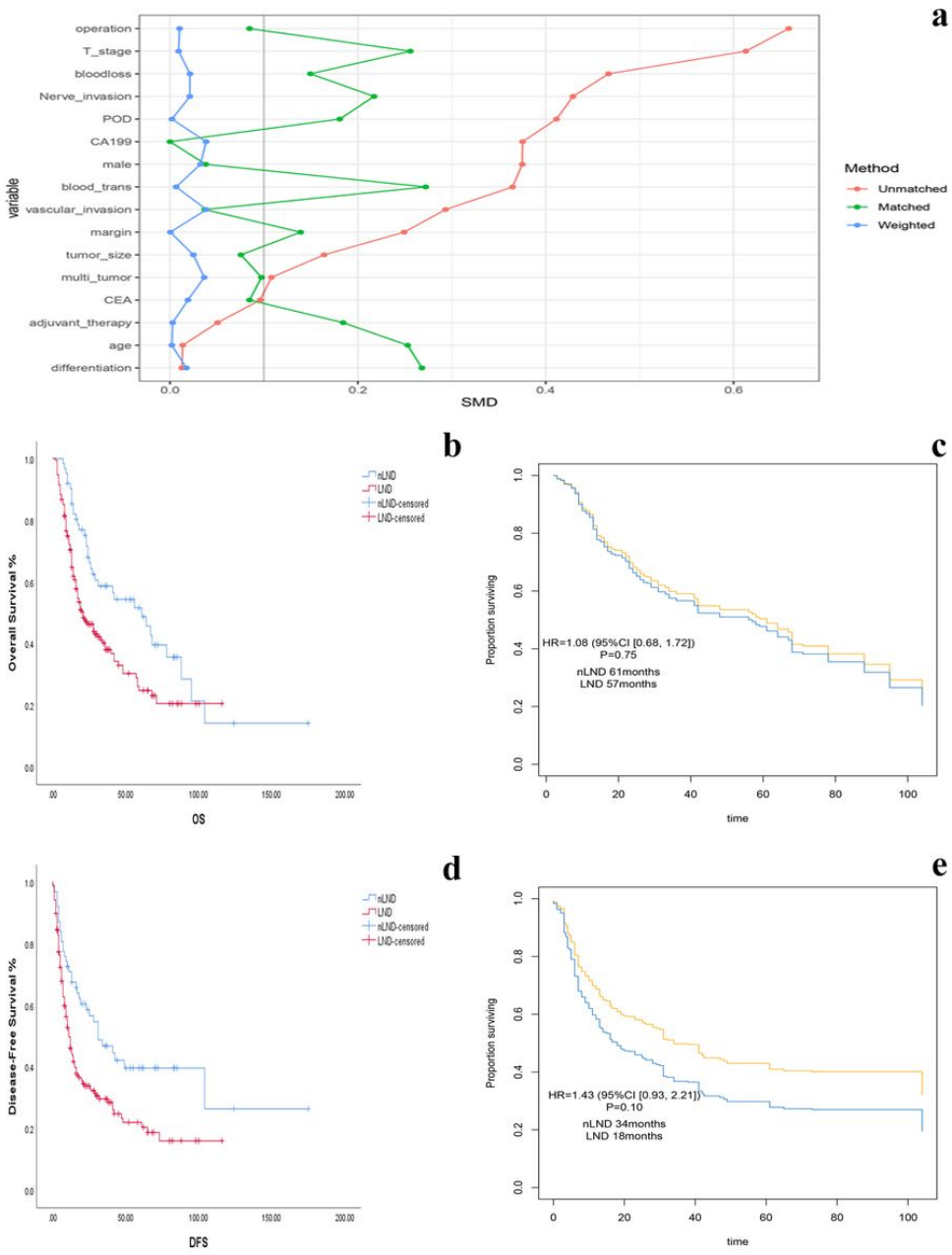

Figure 1

nLND vs. LND. The adjustment of variables (a); The Median OS without (b) and with (c) adjustment; The Median DFS without (d) and with (e) adjustment;

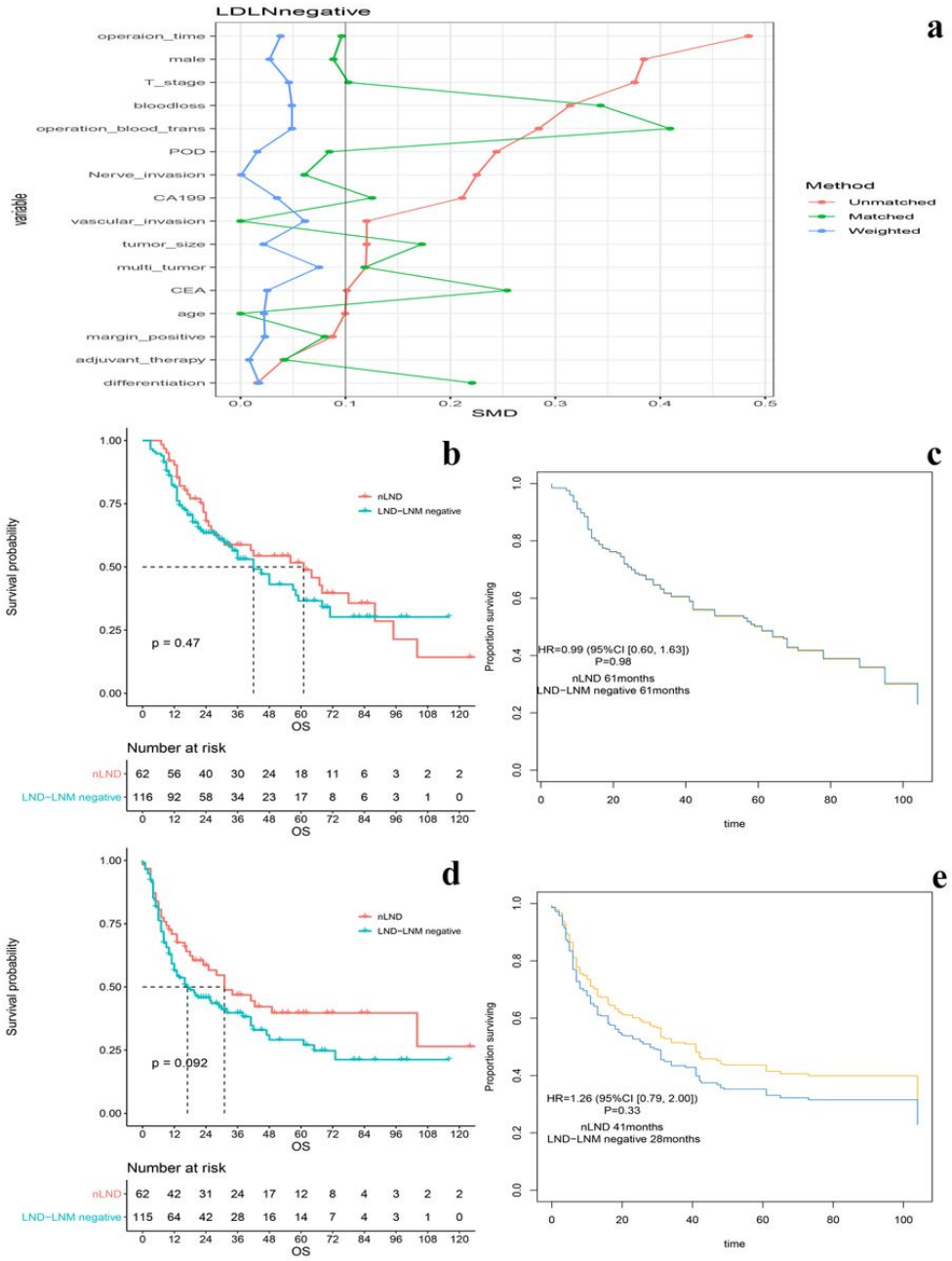

Figure 2

nLND vs. LND-LNM negative. The adjustment of variables (a); The Median OS without (b) and with (c) adjustment; The Median DFS without (d) and with (e) adjustment;

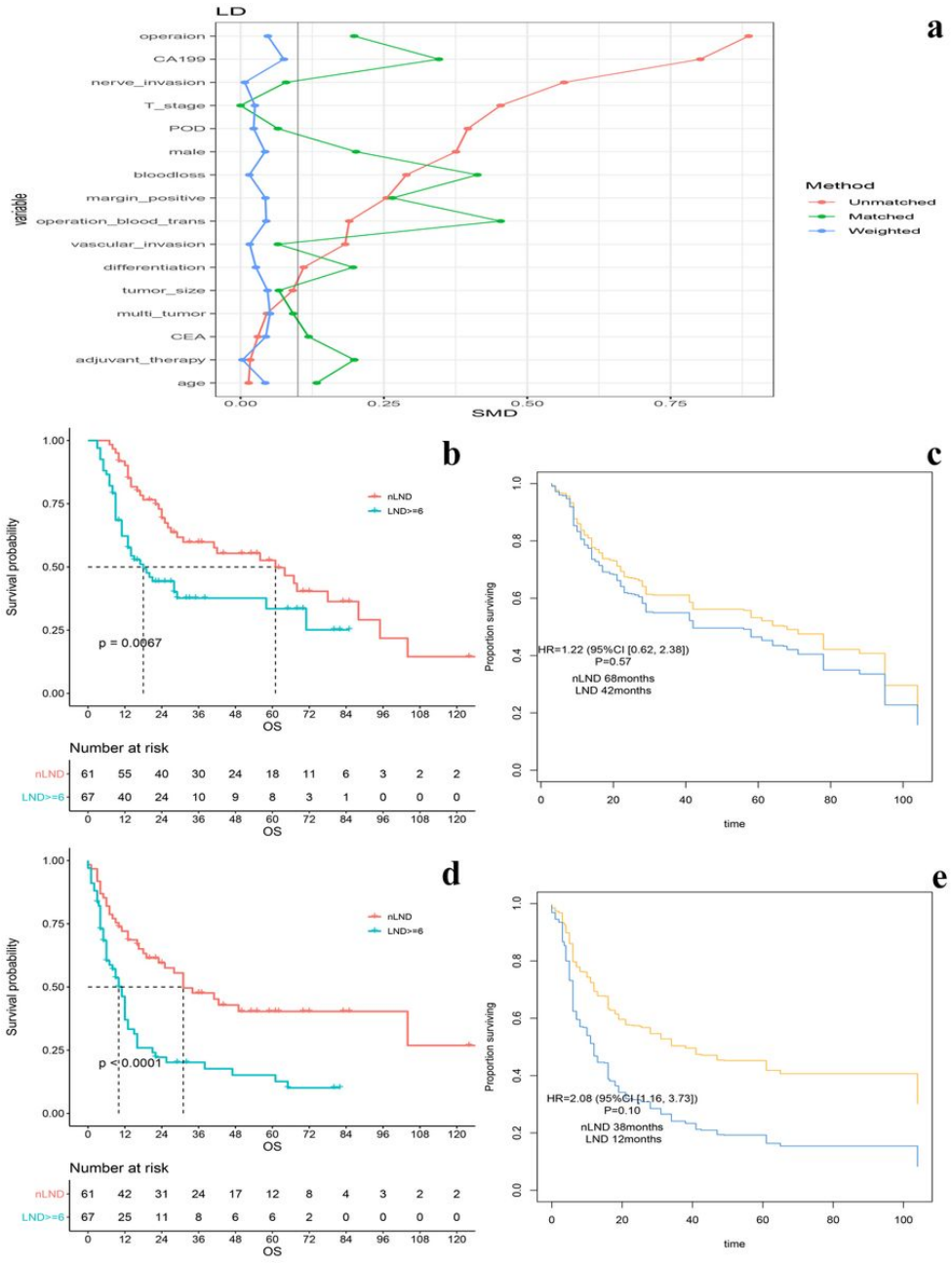

Figure 3

nLND vs. LND>=6. The adjustment of variables (a); The Median OS without (b) and with (c) adjustment; The Median DFS without (d) and with (e) adjustment.