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Original Article

Evaluation of prognostic factors and implication of lymph node dissection in intrahepatic cholangiocarcinoma: 10-year experience at a tertiary referral center

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Abstract

Background: Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver malignancy, and surgical resection remains the only potentially curative treatment. However, the existing literature indicates that those prognostic factors associated with outcome after surgery remain poorly defined.

Methods: Data were retrospectively collected from 103 patients with ICC who underwent surgical resection between 2005 and 2014. The patients were divided into two groups: one with (D1) and one without (D0) lymph node dissection of hepatic hilum according to the surgery performed. Thereafter, the prognostic values of clinicopathological characteristics were evaluated.

Results: The median overall survival (OS) after surgical resection of ICC was 43.9 months [95% confidence interval (CI), 11.6−76.2 months]. The 1-, 3-, and 5-year OS rates were 85.5%, 52.8%, and 45.6%, respectively. Multivariable analysis showed that lymph node metastases [hazard ratio (HR), 6.70; 95% CI, 2.18−20.55], positive resection margins (HR, 2.67; 95% CI, 1.14−6.23), periductal infiltration (HR, 3.64; 95% CI, 1.27−10.44), and poor differentiation (HR, 2.90; 95% CI, 1.41−5.95) were independently associated with poor survival. There were no significant differences in clinicopathological characteristics between D1 and D0 groups, except for vascular invasion ($p = 0.018$) and perineural invasion ($p = 0.008$). In the D1 group, lymph node metastases were associated with late T stages, multiple tumors, and elevated serum carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) levels.

Conclusion: Regional lymph node metastasis, positive resection margin, periductal infiltration, and poor differentiation were poor prognostic factors in patients with ICC after curative surgery. Lymph node dissection did not show survival benefits, but was useful for nodal staging. However, lymph node metastases were strongly associated with late T stages, multiple tumors, and elevated serum CEA and CA19-9 levels.

Keywords: cholangiocarcinoma; lymph node dissection; prognostic factors

Conflicts of interest: The authors declare that they have conflicts of interest related to the subject matter or materials discussed in this article.

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1. Introduction

Intrahepatic cholangiocarcinoma (ICC) originates from either the small intrahepatic ductules, or the large intrahepatic ducts proximal to the bifurcation of the right and left hepatic ducts. ICC accounts for 10−15% of all liver cancers, and is the second most common primary malignancy of the liver after hepatocellular carcinoma.[1,2] Surgical resection remains the only potentially curative treatment for ICC. However, only 30−40% of patients present with resectable disease at the time of diagnosis.[3] High recurrence rates have contributed to a poor 5-year survival, which ranges from 14% to 40%.[4,5] Recently, a multicenter international study of ICC patients reported a median postoperative overall survival (OS) of only 14.8 months.[6] Accurate staging may therefore be helpful to select suitable patients to undergo surgery or receive earlier chemotherapy.

The 6th edition of the American Joint Committee on Cancer (AJCC) cancer staging system did not separate ICC from hepatocellular carcinoma, whereas the staging system referenced in the 7th edition of the AJCC introduced a separate TNM (tumor, node, metastasis) classification for ICC.[7] The latest classification focuses on multiple tumors, vascular invasion, and lymph node metastases. However, several studies found additional prognostic factors, including age, positive surgical margins, tumor sizes, and tumor differentiation.[4,8,9] Prognostic nomograms, including additional factors, might be more accurate than the conventional AJCC staging system for predicting outcomes.[10] In this study, we analyzed 103 ICC patients who received surgical resection with curative intent at the Taipei Veterans General Hospital in Taiwan. We aimed to identify additional prognostic factors and evaluate the effect of lymph node dissection (LND) on prognosis in this cohort of ICC patients.

2. Methods

2.1. Patients and collection of clinicopathological data

This study enrolled a total of 103 patients with ICC who received surgical resection with curative intent at the Taipei Veterans General Hospital, Taiwan, between April 1, 2005 and December 31, 2014. The study was approved by the Institutional Review Board of this hospital. Patients were evaluated by recording the baseline history, physical examination, serum laboratory tests, and appropriate imaging studies [e.g., computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen and pelvis and radiography or CT of the chest] at the discretion of the treating surgeon. A diagnosis of ICC was confirmed by pathologic evaluation of the resected specimen. LND of hepatic hilum was performed at the discretion of the surgeon, based on preoperative imaging and intraoperative findings. Patients were divided into two groups: one with LND of the liver hilum (D1) and one without (D0). The LND was performed by dissecting along the hepatoduodenal ligament and removing the lymph nodes. For surgical margin status, R0 was defined as free surgical cut margin without residual tumor cell microscopically. R1 resection was defined as unclear surgical margin with residual tumor cells observed only under microscopic examination. R2 resection was defined as incomplete tumor resection with grossly residual tumor on surgical cut surface. The pathologic sides were reviewed by a single pathologist (Y.C. Yeh), and the pathological factors—including tumor numbers, tumor sizes, resection margins, nodal status, tumor-growth types, tumor differentiation, vascular invasion, and perineural invasion were reevaluated. Tumors were restaged using the 7th edition of the AJCC TNM classification according to each patient's pathological review. Patients with combined hepatocellular−cholangiocarcinoma were excluded.

2.2. Follow-up study

After surgery, all patients were followed up routinely in our clinics. The follow-up evaluation included a physical examination and blood chemistry tests at each visit, as well as measurement of serum levels of carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9). The remnant livers were examined by ultrasound every 3 months. CT of the abdomen or magnetic resonance cholangiopancreatography were performed when a new lesion was detected by ultrasound, or when elevated levels of CEA or CA19-9 were noted. Moreover, when patients complained of bone pain, whole body bone scans were performed to detect bone metastases. If any of the abovementioned follow-up mechanisms indicated recurrences, the patient received a more comprehensive assessment, including angiographic evaluation. The date of the last follow-up, death, and recurrence were recorded for all patients. Recurrences or metastases of ICC were defined as the appearance of newly detected tumors with typical radiologic features on CT, MRI, or positron emission tomography scan, or with pathological confirmation by tissue biopsy. The OS time was defined as the interval between the date of surgery and either the date of death or the date of the last follow-up. The disease-free survival time was defined as the interval between the date of surgery and the date of recurrence.

2.3. Statistical analysis

Demographic and clinicopathologic characteristics were described as summary statistics obtained using established methods and were presented as percentages or median values. Univariate survival curves were estimated using the Kaplan−Meier method, and compared by means of the log-rank test. Continuous variables, such as serum concentration of total bilirubin and sizes (diameter) of the tumor, were transformed into binary categorical variables. For continuous variables, the cutoff point showing the lowest p value was retained if the value reached significance. Variables that were statistically significant as predictors were further analyzed using a multivariate Cox proportional hazards regression model, except for cases involving missing data that comprised a variable in >10% of cases. The chi-square test was applied to compare differences in demographic and clinicopathologic characteristics between the two groups of patients with

different status of LND (D1 vs. D0). All statistical analyses were carried out using IBM PASW Statistics 22.0 (SPSS Inc., Chicago, IL, USA). A p value < 0.05 was considered statistically significant.

3. Results

3.1. Demographic and clinicopathologic characteristics

Of the 103 patients included in the study cohort, approximately half were male [54 (52.4%)], with a median patient age of 64.3 years (Table 1). Some patients had hepatolithiasis (21 [20.4%]). A minority of patients were diagnosed with liver abscesses [10 (9.7%)]. Most patients had a solitary tumor [75 (72.8%)]. More than half of the patients did not receive LND [67 (65.0%)]. Node status was available for 36 patients, and 17 patients (16.5%) had N1 diseases. Most patients had early T1–T2 category tumors [69 (67.0%)]. The median tumor size was 5.5 cm. Most patients had tumors that were smaller than 6 cm [61 (59.2%)]. Most patients had R0 surgical margins [78 (75.7%)], 15 (14.7%) had R1 margins, and nine (8.8%) had R2 margins.

Table 1
Demographic and clinicopathologic characteristics of patients with intrahepatic cholangiocarcinoma ($n = 103$).

	Number of patients (%)
Age (y)	
<60	37 (35.9)
≥60	66 (64.1)
Sex	
Male	54 (52.4)
Female	49 (47.6)
AJCC, T status	
T1	15 (14.6)
T2	54 (52.4)
T3	19 (18.4)
T4	14 (13.6)
Missing	1 (1.0)
AJCC, N status	
Nx	67 (65.0)
N0	19 (18.4)
N1	17 (16.5)
Hepatolithiasis	
Positive	21 (20.4%)
Negative	82 (79.6%)
Cirrhosis	
Positive	15 (14.6)
Negative	88 (85.4)
Liver abscess	
Positive	10 (9.7)
Negative	93 (90.3)
Preoperative drainage	
Positive	7 (6.8)
Negative	96 (93.2)
HBsAg	
Positive	31 (49.5)
Negative	51 (30.1)
Missing	21 (20.4)
Anti-HCV Ab	
Positive	10 (9.7)
Negative	69 (67.0)
Missing	24 (23.3)
Total bilirubin	
<1.5 mg/dL	94 (91.3)
≥1.5 mg/dL	7 (6.8)
Missing	2 (1.9)
CEA	
Median (IQR)	2.60 (1.97–4.46)
<6 ng/mL	69 (67.0)
≥6 ng/mL	15 (14.6)
Missing	19 (18.4)
CA19-9	
<35 U/mL	26 (25.2)
≥35 U/mL	54 (52.4)
Missing	23 (22.3)
AFP	
<2.48 ng/mL	10 (9.7)
≥2.48 ng/mL	73 (70.9)
Missing	20 (19.4)
Tumor size	
<6 cm	61 (59.2)
≥6 cm	41 (39.8)
Missing	1 (1.0)
Single tumor	
Yes	75 (72.8)
No	27 (26.2)
Missing	1 (1.0)
Resection margin	
R0	78 (75.7)
R1	15 (14.7)
R2	9 (8.8)
Tumor growth pattern	
Mass-forming	80 (77.7)
Periductal	14 (13.6)
Intraductal	8 (7.8)
Missing	1 (1.0)
Tumor differentiation	
Well	5 (4.9)
Moderate	67 (65.0)
Poor	31 (30.1)
Vascular invasion	
Positive	84 (81.6)
Negative	18 (17.5)
Missing	1 (1.0)
Perineural invasion	
Positive	47 (45.6)
Negative	55 (53.4)
Missing	1 (1.0)

AFP = alpha fetoprotein; AJCC = American Joint Committee on Cancer; CA19-9 = carbohydrate antigen 19-9; CEA = carcinoembryonic antigen; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; IQR = interquartile range; N0 = no lymph node metastases; Nx = no LND; N1 = lymph node metastases.

3.2. Assessment of OS

The median OS after surgical resection of ICC was 43.9 months (95% CI, 11.6–76.2 months). The 1-, 3-, and 5-year OS rates were 85.5%, 52.8%, and 45.6%, respectively. We analyzed this cohort according to the 7th edition AJCC/Union for International Cancer Control staging system. The

median OS was not reached in stage I and II patients, was 51.4 months in stage III patients, and 13.9 months in stage IV patients (Fig. 1).

3.3. Univariate and multivariate analyses of prognostic factors

Possible prognostic factors that were selected from the database included age at diagnosis, sex, AJCC stage, nodal status, hepatolithiasis, cirrhosis of the liver, liver abscesses, preoperative drainage, total bilirubin levels at diagnosis, CEA levels at diagnosis, CA19-9 levels at diagnosis, hepatitis B virus status, hepatitis C virus status, tumor sizes, tumor numbers, resection margins, tumor growth patterns, tumor differentiation, vascular invasion, and perineural invasion (Table 2). Univariable analysis showed 12 factors that were significantly related to OS. Multivariable analysis identified four factors that were most significantly associated with survival: lymph node metastases [hazard ratio (HR), 6.70; 95% CI, 2.18−20.55], positive resection margins (HR, 2.67; 95% CI, 1.14−6.23), periductal infiltration (HR, 3.64; 95% CI, 1.27−10.44), and poor differentiation (HR, 2.90; 95% CI, 1.41−5.95).

Fig. 1 shows that the 7th AJCC TNM stages were significantly related to OS ($p < 0.001$). Patients were divided into three groups based on nodal status. These included N0 (no lymph node metastases), Nx (no LND), and N1 (lymph node metastases). Tumor differentiation was divided into two categories: well to moderate and poor. Resection margins were defined as positive (R1 + R2) or negative (R0). Prognostic discrimination was performed by nodal status, resection margins, tumor growth patterns, and tumor differentiation. These factors were then used to plot Kaplan−Meier curves (Fig. 2). It is important to note that there was no significant difference in survival rates between Nx and N0 (Table 2 and Fig. 2A).

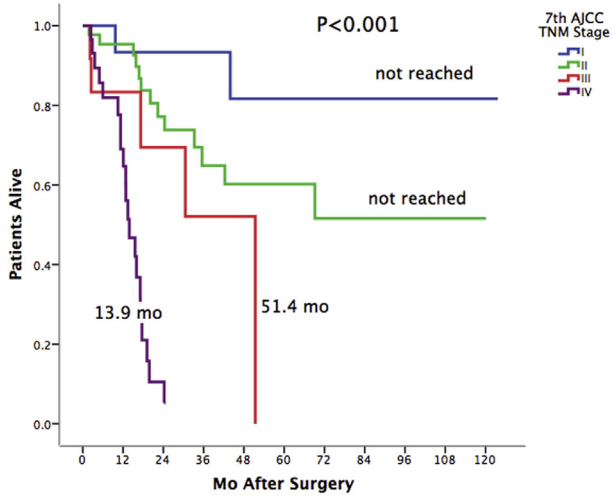

Fig. 1. Kaplan−Meier survival curves with median overall survival of patients diagnosed with intrahepatic cholangiocarcinoma according to the 7th AJCC staging system. (5-year survival rates were 81.7% on stage I and 60.2% on stage II.) AJCC = American Joint Committee on Cancer; TNM = tumor node metastasis.

Table 2
Univariable and multivariable analysis of prognostic factors for overall survival ($n = 103$).

	Univariable		Multivariable	
	Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	p
Sex	0.89 (0.49−1.65)	0.721		
Age, 60 y	1.49 (0.77−2.88)	0.239		
AJCC, TNM stage		<0.001		
Stage I	1.00 (Reference)			
Stage II	3.,46 (0.78−15.39)			
Stage III	7.29 (1.39−38.30)			
Stage IV	32.04 (6.82−150.56)			
AJCC, N status				
N0	1.00 (Reference)		1.00 (Reference)	
Nx	0.76 (0.32−1.78)	0.524	1.10 (0.41−2.93)	0.848
N1	3.68 (1.42−9.55)	0.007	6.70 (2.18−20.55)	0.001
Hepatolithiasis	2.21 (1.12−4.34)	0.018	1.21 (0.54−2.71)	0.645
Cirrhosis	0.64 (0.25−1.64)	0.349		
Liver abscess	2.45 (1.01−5.90)	0.040	0.88 (0.25−3.02)	0.833
Preoperative drainage	0.57 (0.08−4.16)	0.573		
Total bilirubin, 1.5 mg/dL	1.15 (0.27−4.78)	0.853		
CEA, 6 ng/mL	4.55 (2.04−10.17)	<0.001		
CA19-9, 35 U/mL	3.01 (1.23−7.35)	0.011		
HBsAg	1.14 (0.80−1.64)	0.468		
Anti-HCV Ab	1.54 (0.75−3.16)	0.223		
Tumor size, 6 cm	1.85 (1.00−3.40)	0.045	1.71 (0.85−3.44)	0.132
Single tumor	1.10 (0.78−1.55)	0.588		
Resection margin	2.97 (1.55−5.69)	0.001	2.67 (1.14−6.23)	0.024
Tumor growth pattern				
Mass-forming	1.00 (Reference)	<0.001	1.00 (Reference)	
Intraductal	1.35 (0.32−5.73)		1.15 (0.24−5.52)	0.857
Periductal	5.23 (2.37−11.51)		3.64 (1.27−10.44)	0.016
Tumor differentiation				
Well to moderate	1.00 (Reference)	0.008	2.90 (1.41−5.95)	0.004
Poor	2.28 (1.22−4.27)			
Vascular invasion	7.58 (1.82−31.63)	0.001	2.74 (0.58−12.84)	0.201
Perineural invasion	2.60 (1.37−4.96)	0.003	1.55 (0.68−3.56)	0.297

AFP = alpha fetoprotein; AJCC = American Joint Committee on Cancer; CA19-9 = carbohydrate antigen 19-9; CEA = carcinoembryonic antigen; CI = confidence interval; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; N0 = no lymph node metastases; Nx = no LND; N1 = lymph node metastases; TNM = tumor, node, metastasis.

3.4. Incidence of lymph node metastases and impact of nodal status and LND

Of the 103 patients enrolled in this study, 67 (65.0%) were in the D0 group and 36 (35.0%) were in the D1 group. There was no significant difference in demographic characteristics (age and sex) between the two groups (Table 3). AJCC T status (T1−T2 and T3−T4) tended to differ significantly between D0 and D1 groups ($p = 0.054$). Other clinicopathological characteristics did not differ significantly except for vascular invasion ($p = 0.018$) and perineural invasion ($p = 0.008$). There were more patients in the LN (D1) group who had tumors with vascular invasion and perineural invasion. Among the patients in the D1 group, lymph node metastases were significantly associated with late T stages ($p = 0.042$), multiple tumors ($p = 0.042$), elevated serum

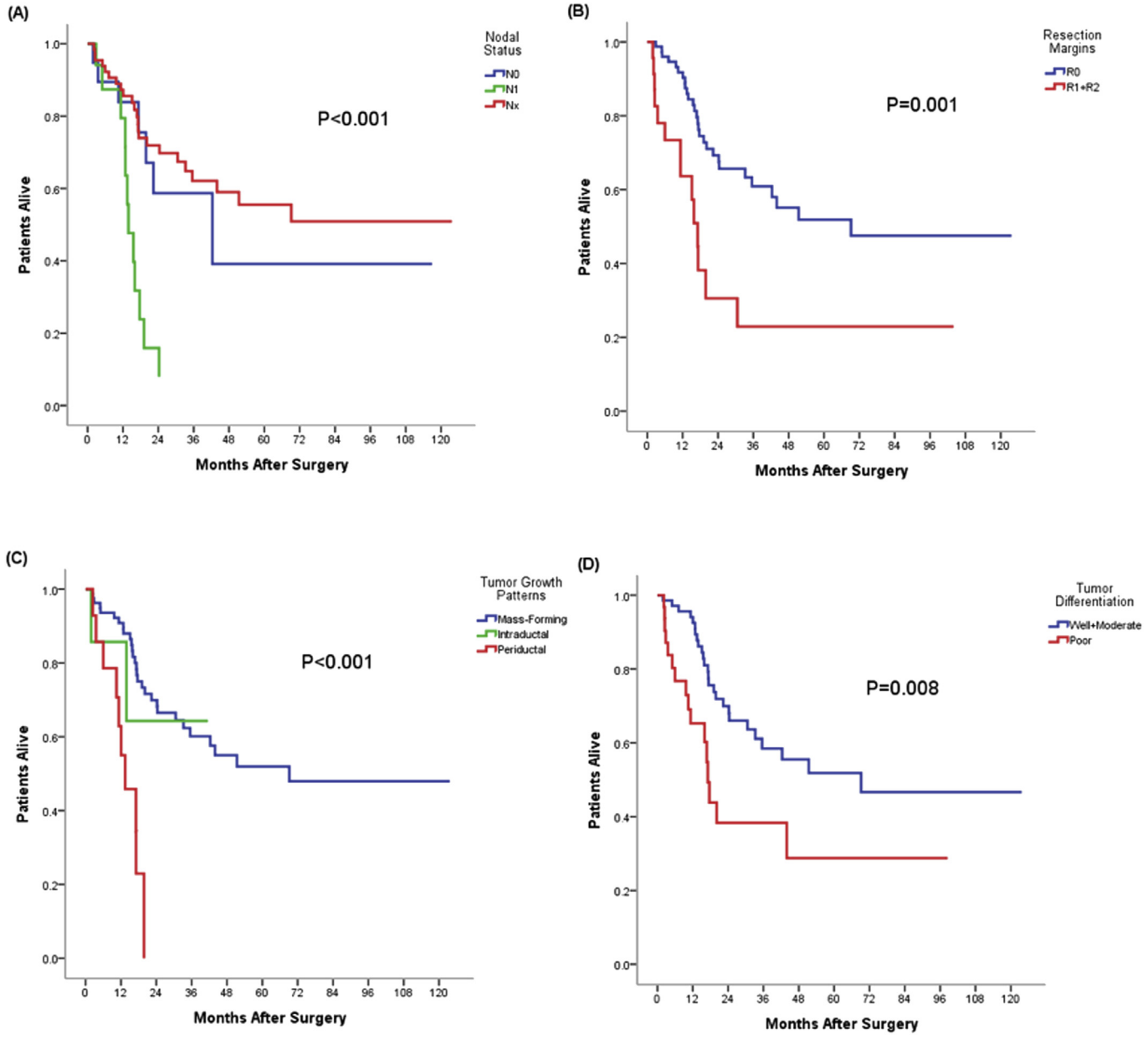

Fig. 2. Kaplan−Meier survival curves of patients diagnosed with intrahepatic cholangiocarcinoma according to (A) nodal status, (B) resection margins, (C) tumor growth patterns, and (D) tumor differentiation.

CEA levels ($p = 0.012$), and elevated serum CA19-9 level ($p = 0.050$) (Table 4). Larger tumors (>6 cm) tended to be related to lymph node metastases ($p = 0.095$).

4. Discussion

ICC represents an aggressive malignancy arising from the intrahepatic biliary tree.[3] Recent years have seen a dramatic increase in the incidence of ICC, making it the second most common primary liver cancer.[1,2] Prognosis of ICC remains poor, with 5-year OS rates ranging from 14% to 40%.[4,5] This study was a review of OS in ICC patients after surgery in a Taiwan medical center over a period of 10 years. Our data showing 5-year OS rates of 45.6% are similar to results from recent studies.[6,9,11−16]

Surgical resection of the liver is the only curative treatment for patients with ICC that achieves long-term survival.[17,18] Accurate information on prognostication is important for decision making and counseling of patients. Widely used prognostication systems, such as the AJCC TNM classification, include a limited number of tumor-related variables, and lack flexibility in terms of allowing physicians to tailor prognostication for specific patients.[6] We therefore reviewed the known prognostic factors of ICC and evaluated correlations between demographic and clinicopathological characteristics and survival (Table 1).[6,10,13,18] As this study was a retrospective analysis, missing data did exist in some variables. For a more accurate analysis, we excluded CEA levels and CA19-9 levels with missing data in >10% of cases for our multivariable analysis. We used univariable analysis to show that lymph

Table 3
Demographic and clinicopathologic characteristics of patients with or without lymph node dissection ($n = 103$).

Characteristics	D0 ($n = 67$)	D1 ($n = 36$)	p
Age (range), y	63.76 (35–88)	65.25 (46–82)	0.497
Sex, n (%)			0.109
Male	39 (58.2%)	15 (41.7%)	
Female	28 (41.8%)	21 (58.3%)	
AJCC, T status, n (%)			0.054
T1–T2	49 (74.2%)	20 (55.6%)	
T3–T4	17 (25.8%)	16 (44.4%)	
Hepatolithiasis, n (%)	14 (20.9%)	7 (19.4%)	0.862
Cirrhosis, n (%)	11 (16.4%)	4 (11.1%)	0.467
Liver abscess, n (%)	6 (9.0%)	4 (11.1%)	0.725
Preoperative drainage, n (%)	4 (6.0%)	3 (8.3%)	0.650
HBsAg, n (%)	23 (42.6%)	8 (28.6%)	0.214
Anti-HCV Ab, n (%)	6 (11.5%)	4 (14.8%)	0.678
Total bilirubin (mg/dL ± SD)	0.82 ± 0.58	0.76 ± 0.60	0.631
CEA (ng/mL ± SD)	9.24 ± 28.47	8.48 ± 23.00	0.900
CA19-9 (U/mL ± SD)	3068.43 ± 10,310.5	5897 ± 28,943.4	0.531
AFP (ng/mL ± SD)	18.70 ± 65.75	5.91 ± 5.78	0.161
Tumor size (cm ± SD)	5.38 ± 2.74	6.31 ± 2.57	0.113
Single tumor, n (%)	50 (75.8%)	25 (69.4%)	0.490
Resection margin			0.818
Negative	50 (75.8%)	28 (77.8%)	
Positive	16 (24.2%)	8 (22.2%)	
Tumor growth pattern			0.501
Mass-forming	54 (81.8%)	26 (72.2%)	
Periductal	8 (12.1%)	6 (16.7%)	
Intraductal	4 (6.1%)	4 (11.1%)	
Tumor differentiation			0.707
Well to moderate	46 (68.7%)	26 (72.2%)	
Poor	21 (31.3%)	10 (27.8%)	
Vascular invasion	50 (75.8%)	34 (94.4%)	0.018
Perineural invasion	24 (36.4%)	23 (63.9%)	0.008

AFP = alpha fetoprotein; AJCC = American Joint Committee on Cancer; CA19-9 = carbohydrate antigen 19-9; CEA = carcinoembryonic antigen; D0 = without lymph node dissection; D1 = with lymph node dissection; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; SD = standard deviation.

Table 4
Differences of clinicopathological factors in patients with lymph node dissection ($n = 36$).

	N0 ($n = 19$)	N1 ($n = 17$)	p
AJCC, T status, n (%)			0.042
T1	2 (10.5%)	0 (0%)	
T2a	9 (47.4%)	4 (23.5%)	
T2b	0 (0%)	5 (29.4%)	
T3	4 (21.1%)	6 (35.3%)	
T4	4 (21.1%)	2 (11.8%)	
Single tumor, n (%)			0.042
Yes	16 (84.2%)	9 (52.9%)	
No	3 (15.8%)	8 (47.1%)	
Tumor size			0.095
<6 cm	12 (63.2%)	6 (35.3%)	
≥6 cm	7 (36.8%)	11 (64.7%)	
CEA			0.012
<6 ng/mL	16 (100%)	10 (66.7%)	
≥6 ng/mL	0 (0%)	5 (33.3%)	
CA19-9			0.050
<35 U/mL	6 (37.5%)	1 (7.1%)	
≥35 U/mL	10 (62.5%)	13 (92.9%)	

AJCC = American Joint Committee on Cancer; CA19-9 = carbohydrate antigen 19-9; CEA = carcinoembryonic antigen; N0 = no lymph node metastases; N1 = lymph node metastases.

node metastases, hepatolithiasis, liver abscesses, high CEA and CA19-9 levels, and large tumor diameters were adverse preoperative prognostic factors. Similarly, positive resection margins, periductal infiltration, poor differentiation in tumors, vascular invasion, and perineural invasion were adverse postoperative prognostic factors (Table 2). It is especially notable that hepatolithiasis and liver abscesses adversely influenced survival of ICC. Su et al[19] reported that patients with hepatolithiasis-associated cholangicarcinoma including ICC had a significantly worse survival compared to patients with only cholangiocarcinoma. In a study of 66 patients with hepatolithiasis-associated ICC, radical resection was possible in only 38 patients.[20] Liver abscesses may mask ICC leading to delayed diagnosis.[21] Our multivariable analysis identified lymph node metastases, positive resection margins, periductal infiltration, and poor differentiation in tumors as independent prognostic factors of ICC. These results were consistent with the recent studies that evaluated prognosis of resectable ICC.[6,9,11,13]

Although several clinicopathologic factors have been reported to influence survival after resection for ICC, nodal status may be the most strongly predictive.[3,12,14,22–24] In this study, the presence of lymph node metastases was an independent negative predictor of OS in multivariate analysis. Despite several national guidelines advocating the removal of clinically suspicious lymph nodes, there are wide practice variations regarding routine LND among patients without clinically suspicious lymph nodes.[4,12,25,26] In our study group, there was no significant difference in survival between Nx (no LND) and N0 (no lymph node metastases). We therefore performed a further analysis of demographic and clinicopathologic characteristics of patients with or without LND (Table 3). Patients in the D1 (with LND) group tended to have more late T stages (T3–T4) compared to patients in the D0 (without LND) group. Furthermore, among the patients in the D1 group, lymph node metastases were associated with late T stages, multiple tumors, and elevated serum CEA and CA19-9 levels (Table 4). Marubashi et al[27] found that patients with solitary lesions less than 5 cm in diameter and peripheral-type ICC showed a very low probability of lymph node metastasis. Similarly, Miwa et al[17] also suggested that patients with tumors less than 4.5 cm in diameter located in the peripheral liver had less lymph node metastases. Moreover, there was a higher incidence of vascular and perineural invasion in the D1 group compared to the D0 group. A retrospective study in a tertiary institution revealed that a significantly greater proportion of patients with lymph node metastases had lymphovascular or perineural invasion.[27] This study result suggested the finding that LND of liver hilum may not lead to survival benefits, but was useful for nodal staging, which is an essential prognostic factor of ICC. In addition, later T stages, multiple tumors, and high preoperative serum tumor marker levels were associated with lymph node metastases. Those might be preoperative indicators for LND.

This study had several limitations. First, the retrospective design had selection bias and missing data. Second, the number of patients was small. Third, our institution had no

standardized practice for LND during ICC treatment. This lack of standardization reflects the absence of guidelines, attributable to contradictory evidence in the literature.

In conclusion, our data showed that lymph node metastases, positive resection margins, periductal infiltration, and poor differentiation in tumors were independent adverse factors predicting survival in ICC patients. LND of liver hilum may not result in survival benefits, but was useful for nodal staging. Late T stages, multiple tumors, and high serum CEA and CA19-9 levels might be preoperative indicators for LND. Further prospective randomized studies are necessary to clarify the role of LND.

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