The prognostic value of the number of metastatic lymph nodes on the long-term survival of intrahepatic cholangiocarcinoma using the SEER database

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Background: In the 8th edition of the American Joint Committee on Cancer, the nodal staging of intrahepatic cholangiocarcinoma (ICC) is classified as N0 and N1 in accordance with lymph node (LN) metastases. Recently, several studies have reported that the number of metastatic LNs is associated with prognosis in patients with ICC. However, the majority of these studies were published in Eastern countries, and there are few available data for Western countries. This study aimed to investigate the association between metastatic LN number and prognosis in ICC patients using the Surveillance, Epidemiology, and End Results (SEER) database.

Methods: Data from 658 ICC patients in the SEER database who underwent hepatectomy with LN dissection from 2000 to 2018 were retrospectively reviewed. Hazard ratios (HRs) according to increasing numbers of metastatic LN were calculated. The patients were then divided into three groups according to their metastatic LN numbers (N0: no metastatic LNs; $N^+ <4$: 1–3 metastatic LNs; $N^+ \geq 4$: ≥4 metastatic LNs), and cause-specific survival (CSS) was compared.

Results: Metastatic LN number was a prognostic factor of oncologic survival [CSS: HR =1.300; 95% confidence interval (CI): 1.225–1.379; $P<0.001$]. In survival analysis, an increasing number of metastatic LNs was significantly correlated with poorer oncologic outcomes [CSS: N0 *vs.* $N^+ <4$ *vs.* $N^+ \geq 4$: 40.856 (95% CI: 38.806–42.919) *vs.* 22.000 (95% CI: 18.283–25.717) *vs.* 15.000 (95% CI: 11.520–18.480) months, $P<0.001$]. In post hoc analysis, a significant difference was found between adjacent groups (N0 *vs.* $N^+ <4$, $P<0.001$; $N^+ <4$ *vs.* $N^+ \geq 4$, $P=0.004$).

Conclusions: Patients with ICC in the SEER database were reaffirmed to have worse prognosis with an increasing number of metastatic LNs.

Keywords: Cholangiocarcinoma (CC); lymph node excision (LN excision); lymphatic metastasis; Surveillance, Epidemiology, and End Results program (SEER program); survival analysis

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Introduction

Cholangiocarcinoma (CC) is a malignant tumor that occurs at various locations in the biliary tree and is classified according to the anatomic location of the occurrence. Intrahepatic cholangiocarcinoma (ICC) is a CC that occurs at the proximal level of the second-order bile duct (1,2). Globally, CC exhibits an average annual incidence of two cases per 100,000 individuals (3). However, marked regional disparities exist, particularly in certain Asian nations like Thailand, where the reported rates surpass the global average by over 40-fold, reaching an annual incidence of 96 cases per 100,000 people (3). Within the spectrum of CC, extrahepatic CC has displayed a relatively stable incidence pattern in recent decades (4,5). In contrast, ICC is experiencing a consistent and progressive increase worldwide, with notable rises observed in Europe, North America, Asia, Japan, and Australia over the past two decades (4).

Complete tumor resection is the only curative treatment option for CC (5-7). Nevertheless, the 5-year overall survival rate following surgery ranges from a modest 15% to 40%, with recurrence observed in approximately two-thirds of patients (8). Therefore, selecting the appropriate surgical treatment and predicting the prognosis of patients after surgery are crucial.

Since the introduction of the 7th edition of the American

Highlight box

Key findings
- The number of metastatic lymph nodes (LNs) appears to be a prognostic factor of intrahepatic cholangiocarcinoma (ICC) in the Surveillance, Epidemiology, and End Results (SEER) database.

What is known and what is new?
- American Joint Committee on Cancer 8th staging system suggested N stage as N0 and N1 in ICC, however, previous studies have reported that the number of metastatic LNs is associated with a long-term prognosis in ICC patients.
- This study reconfirmed the prognostic impact of the number of metastatic LNs on survival in the SEER database.
- It was difficult to accurately determine the prognosis of patients with less than six LN resection even by examining various values about LN status.

What is the implication, and what should change now?
- A revised N staging system that accounts for the quantity of metastatic LNs is needed for more accurate prognosis prediction in ICC patients.
- For accurate staging of ICC, six or more LNs should be harvested during surgery.
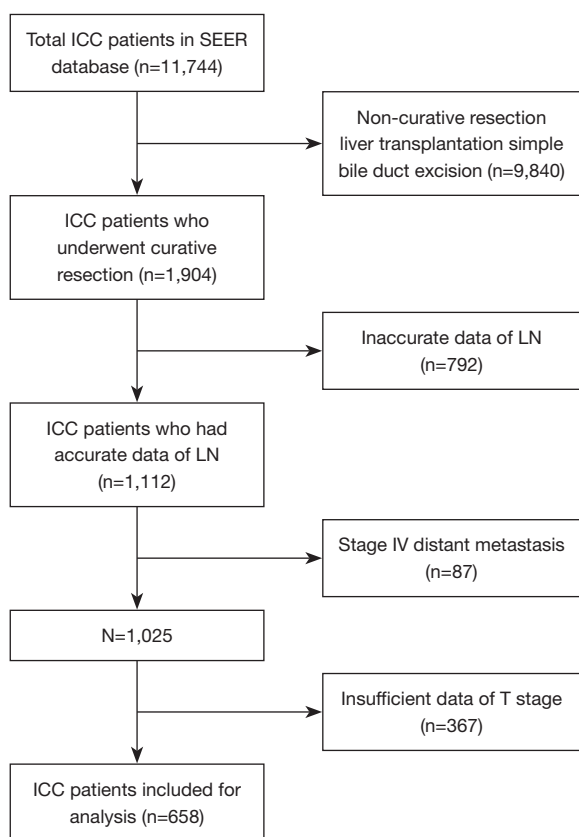

Joint Committee on Cancer (AJCC) staging system, significant endeavors have been undertaken to differentiate ICC from other intrahepatic tumors, aiming to refine prognosis prediction (9). Precise prognosis prediction plays a pivotal role in determining the necessity for supplementary adjuvant therapies, such as chemotherapy or radiotherapy. Furthermore, lymph node (LN) metastasis in ICC stands as a prominent prognostic determinant (10-14).

In the 8th edition of AJCC, although ICC is recommended to sample more than six LNs during the surgery, objective evidence is insufficient (9,15-17). Since it is a relatively rare disease in the field of hepato-biliary-pancreatic surgery, almost all ICC studies are single-institutional. The discussion of appropriate surgical treatment is ongoing, and especially the necessity of lymphadenectomy is still under discussion. In addition, debates on the appropriate number of LN retrieval and the appropriate extent of LN resection have not yet been concluded. Our institution also previously published a couple of studies on the appropriate number of LN sampling and the appropriate extent of LN dissection to reduce recurrence (11,12,18,19).

Moreover, nodal staging of ICC in the AJCC 8th guidelines is classified only into N0 without LN metastasis and N1 with LN metastases, unlike perihilar CC or extrahepatic CC (10,15,20-22). For the other biliary tract cancers, N2 is classified when four and more metastatic LNs are retrieved according to the AJCC 8th edition. There is still room for an improvement in the prognosis according to the metastatic state of the LNs in ICC. Several studies have reported that the number of metastatic LNs is associated with a long-term prognosis in ICC patients (10,12,23,24). These studies have been mainly published in East Asian countries. Zhang *et al.* reported a multicenter study involving hospitals in Western countries, demonstrating that the number of metastatic LNs does impact the prognosis (24). They also performed external validation using the Surveillance, Epidemiology, and End Results (SEER) program to support these results (24).

Since the SEER program collects cancer incidence data from population-based cancer registries and encompasses a diverse range of ethnicities, there is significance in fully utilizing this population database to reconfirm the prognostic impact of the number of metastatic LNs on survival. This study focused on efforts to reflect the details of treatment and tumor staging as much as possible. In addition, as recommended by the 8th edition of the AJCC, we decided to check how different long-term survival depends on the number of LN metastases when at least six

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Figure 1 Flow chart of ICC patient inclusion and exclusion. ICC, intrahepatic cholangiocarcinoma; SEER, Surveillance, Epidemiology, and End Result; LN, lymph node.

LNs are retrieved. We present this article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-580/rc).

Methods

Subjects' identification and inclusion criteria

This study was conducted with a database collected from the 18 registries from 2000 to 2018 among several databases registered in the SEER program. In the SEER database, the diagnostic name is coded according to the International Classification of Oncology Measures (3rd Edition, ICD-O-3) (25). To collect information on ICC patients, patients corresponding to 'liver (22.0)' in the topography code and 'cholangiocarcinoma (8160)' in the histology code were collected. Furthermore, patients with the topography code of 'intrahepatic bile duct (22.1)' and the histology code of 'malignant

neoplasm (8000)', 'malignant tumor cells (8001)', 'carcinoma (8010)', 'undifferentiated carcinoma (8020)', and 'cholangiocarcinoma (8160)' were collected. A total of 11,744 patients diagnosed with ICC were included through this search result.

Among them, patients diagnosed after the age of 100 were excluded. Patients who underwent surgery with curative aim were included in the inclusion criteria using the 'surgery of Primary Site Code' and patients who received liver transplantation or only excision of bile duct were excluded. A total of 1,904 patients were included. Patients with accurate records of the number of LNs recovered after surgery and the number of metastatic LNs were selected using the 'regional node examined' and 'regional node positive' codes (n=1,112). In addition, patients with distant metastasis and stage IV according to AJCC 8th edition staging were excluded. A total of 1,025 patients were included. Finally, 658 patients were included in the inclusion criteria, excluding 367 patients who could not be classified as T-staging due to lack of information such as tumor size and degree of invasion of blood vessels. The flowchart of inclusion criteria was shown in *Figure 1*. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Identification of general characteristics and procedure

The SEER database collects information such as the gender of the patients, the age at the time of diagnosis, race, and year of diagnosis. In addition, the SEER database collects information about the surgery that patients have obtained with 'surgery of Primary Site Code'. Using this code, the SEER database codes patients who did not undergo surgery, patients who received only local therapy, such as ablation, and patients who underwent surgery such as wedge resection, segmentectomy, hemihepatectomy, extended hemihepatectomy, excision of the bile duct (for an intrahepatic bile duct primary only) with or without partial hepatectomy, and liver transplantation. In this study, the types of surgery were classified into wedge resection or segmentectomy, hemihepatectomy (right or left), extended hemihepatectomy, which is defined as the resection of a single lobe along with a segment of another lobe, and excision of the bile duct with partial hepatectomy. The information on chemotherapy and radiotherapy was also collected from the SEER database. The information such as CA19-9 level or tumor growth pattern for bile duct infiltration, which was known to be associated with prognosis, was collected under

J Gastrointest Oncol 2023;14(6):2511-2520 | https://dx.doi.org/10.21037/jgo-23-580

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the code 'CS site specific factor' through the 'Collaborative stage date set', but the information was not collected adequately and excluded from this study.

Assessment of LN metastasis and LN dissection rate

The SEER database has collected the status of LN metastasis since 1988, and the LN was examined by a pathologist and the number of LNs recovered was coded as 'Regional Nodes examined'. In addition, the SEER database used the 'regional nodes positive' code to record LN metastasis. LN positive is defined as the presence of a tumor measuring 0.2 mm or larger, confirmed through pathological examination in the SEER database.

During the study period, the AJCC staging classification was revised three times from the 6th edition to the 8th edition in 2004, 2010, and 2017. The AJCC staging of the patients was recorded according to the edition at the time of each diagnosis, so the 'CS tumor size' code and the 'CS Extension' code were referred to change it to AJCC 8th edition. Cases with insufficient information corresponded to the exclusion criteria and were excluded. Basis on these definitions, the rate of proper LN dissection accordance with AJCC (at least 6 LNs) was calculated by period.

Assessment of the impact of metastatic LN number and its survival

Patients diagnosed with ICC from 2000 to 2018 were followed, and the study cut-off date was December 2018. In the SEER data, there is an algorithm that collects information on the cause of death and obtains cause-specific survival (CSS) by excluding deaths from other causes than the disease.

The hazard ratio (HR) according to the increasing number of metastatic LNs was calculated. In addition, the enrolled patients were divided into three groups based on the number of metastatic LNs [N0: no metastasis; N1 (N^+ <4): 1 to 3 metastatic LNs; N1 (N^+ ≥4): 4 or more metastatic LNs], using the same nodal staging as other biliary tract cancers, such as perihilar CC or extrahepatic CC, consistent with the findings of a previous study conducted by our institution (12). CSS among the three groups was compared. Moreover, in the subgroup analysis, these groups were subdivided into two groups based on the harvested LN number (<6 vs. ≥6), and their CSS was also compared.

Statistics analysis

Statistical analysis was performed using SPSS Version 24 (IBM, Chicago, IL, USA) and R.3.6.3. Continuous variations are represented by median and interquartile range (IQR) and nominal variables in numbers and percentage. Univariate and multivariate survival analysis was conducted using the Cox proportional hazard model. Survival analysis according to the subgroup was conducted through the Kaplan-Meier method and log-rank test. In the subgroup survival analysis, CSS was compared with median and IQR in cases when death (event) occurred in more than 50% of patients, and medium and IQR in cases of less than 50%. In all tests, when the P value <0.05, it was set to be statistically significant. Akaike information criterion (AIC) and Harrell concordance index (C-index) were calculated by Stata software, version 12.0 (StataCorp, College Station, TX, USA).

Results

General characteristics of patients with ICC in SEER data

In this study, a total of 658 patients correspond to the inclusion criteria, and the general characteristics of the patients are shown in *Table 1*. The age of 60–69 years was the age of peak in ICC patients. The median number of harvested LNs was 3.0 [IQR, 1.0–5.0], and six or more LNs were retrieved in 159 (24.2%) patients. LN metastasis was not reported in 472 (71.7%) patients. One hundred and fifty-seven patients (23.9%) reported more than one and three or less LN metastases, and 29 patients (4.4%) reported more than four LN metastases. The median CSS was 36.000 [IQR, 30.755–41.245] months.

Trend of LN dissection rate according to periods

The proportion of ICC patients with more than six LNs retrieved increased slightly over the years, but there was no statistical difference (P=0.120) (*Figure 2*).

Analysis of risk factors for survival in patients with ICC

The HR of each variable with CSS was investigated in the enrolled patients. In the univariate analysis, the number of LNs with metastasis increased by one and the HR was 1.300 [95% confidence interval (CI): 1.225–1.379], (P<0.001). In

Table 1 General characteristics of intrahepatic cholangiocarcinoma patients in inclusion criteria (n=658)

Variables	Values
Sex (male:female)	295:363 (1:1.2)
Age (years), n (%)	
<40	28 (4.3)
40–49	77 (11.7)
50–59	159 (24.2)
60–69	227 (34.5)
70–79	142 (21.6)
>80	25 (3.8)
Race and origin, n (%)	
White	446 (67.8)
Black	47 (7.1)
Asian or Pacific Islander	77 (11.7)
Hispanic all races	82 (12.5)
American Indian/Alaska Native	6 (0.9)
Types of surgery, n (%)	
Wedge resection or segmentectomy	179 (27.2)
Hemihepatectomy	261 (39.7)
Extended hemihepatectomy	134 (20.4)
Excision of bile duct with partial hepatectomy	84 (12.8)
Number of harvested LNs, median [interquartile range]	3.0 [1.0–5.0]
Radiotherapy, n (%)	
Yes	113 (17.2)
No/unknown	545 (82.8)
Chemotherapy, n (%)	
Yes	322 (48.9)
No/unknown	336 (51.1)
LN sampling, n (%)	
<6	499 (75.8)
≥6	159 (24.2)
Number of metastatic LNs, n (%)	
None	472 (71.7)
1–3	157 (23.9)
≥4	29 (4.4)

Table 1 (continued)

Table 1 (continued)

Variables	Values
T stage, n (%)	
T1a	129 (19.6)
T1b	118 (17.9)
T2	321 (48.8)
T3	19 (2.9)
T4	71 (10.8)
N stage, n (%)	
N0	472 (71.7)
N1	186 (28.3)
AJCC 8th stage, n (%)	
Ia	110 (16.7)
Ib	97 (14.7)
II	213 (32.4)
IIIa	9 (1.4)
IIIb	229 (34.8)
Follow-up duration (months), median [interquartile range]	36.000 [30.755–41.245]

LN, lymph node; AJCC, American Joint Committee on Cancer.

the multivariate analysis, the number of metastatic LNs was also a significant prognostic factor with T stage (metastatic LN: HR =1.245, 95% CI: 1.169–1.326, P<0.001; T stage: T1 *vs.* T2: HR =1.772, 95% CI: 1.378–2.278, P<0.001; T1 *vs.* T3: HR =2.220, 95% CI: 1.259–3.915, P=0.006; T1 *vs.* T4: HR =2.240, 95% CI: 1.525–3.291, P<0.001) (*Table 2*).

Survival analysis of ICC patients according to number of LN metastasis

In the CSS analysis, the mean survival in the N0 group was 40.856 (95% CI: 38.806–42.919) months, the median survival in the N$^+$ <4 group was 22.000 (95% CI: 18.283–25.717) months, and the median survival in the N$^+$ ≥4 group was 15.000 (95% CI: 11.520–18.480) months and showed statistical difference (P<0.001). In addition, each subgroup also showed statistical differences (N0 *vs.* N$^+$ <4, P<0.001; N$^+$ <4 *vs.* N$^+$ ≥4, P=0.004) (*Figure 3A*).

For the subgroup analysis, the survival analysis was performed to find out how the prognosis differs depending on the number of metastatic LNs in patients with more
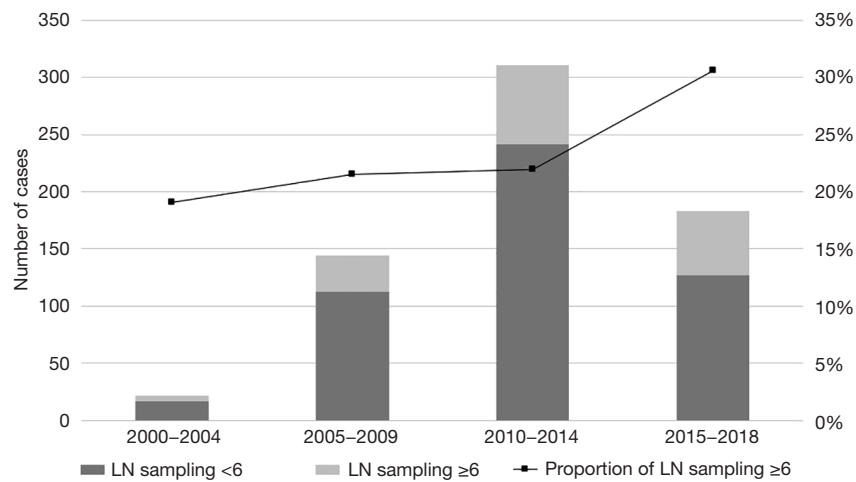
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Figure 2 The trend of LN dissection accordance with year at diagnosis. LN, lymph node.

Table 2 Univariable and multivariable analysis of risk factors of survival of intrahepatic cholangiocarcinoma patients

Variables	Univariable analysis			Multivariable analysis		
	HR	95% CI	P value	HR	95% CI	P value
Male	1.094	0.883–1.354	0.412			
Race and origin						
Hispanic		Reference		–	–	–
Asian and Pacific islander	1.221	0.785–1.898	0.376	–	–	–
Black	1.455	0.897–2.359	0.128	–	–	–
White	0.979	0.695–1.380	0.904	–	–	–
American Indian/Alaska Native	0.709	0.219–2.298	0.567	–	–	–
LN sampling						
<6		Reference		–	–	–
≥6	1.108	0.864–1.423	0.418	–	–	–
T stage						
T1		Reference			Reference	
T2	1.902	1.483–2.440	<0.001	1.772	1.378–2.278	<0.001
T3	2.616	1.489–4.597	0.001	2.220	1.259–3.915	0.006
T4	2.952	2.045–4.260	<0.001	2.240	1.525–3.291	<0.001
Metastatic LN (increment 1)	1.300	1.225–1.379	<0.001	1.245	1.169–1.326	<0.001

HR, hazard ratio; CI, confidence interval; LN, lymph node.

than six LNs retrieved and patients with less than six. For patients with less than six LNs retrieval, there was significant difference between the groups [N0 vs. N^+ <4 vs. N^+ ≥4: 48.000 (95% CI: 37.733–58.267) vs. 20.000 (95% CI: 16.476–23.524) vs. 14.000 (95% CI: 4.388–23.612)

months, P<0.001]. In post hoc analysis, however, N^+ <4 and N^+ ≥4 group did not show statistically significant difference (P=0.099) (*Figure 3B*). For patients with six or more LNs retrieval, there was significant difference between the groups including post hoc analysis [N0 vs. N^+ <4 vs. N^+
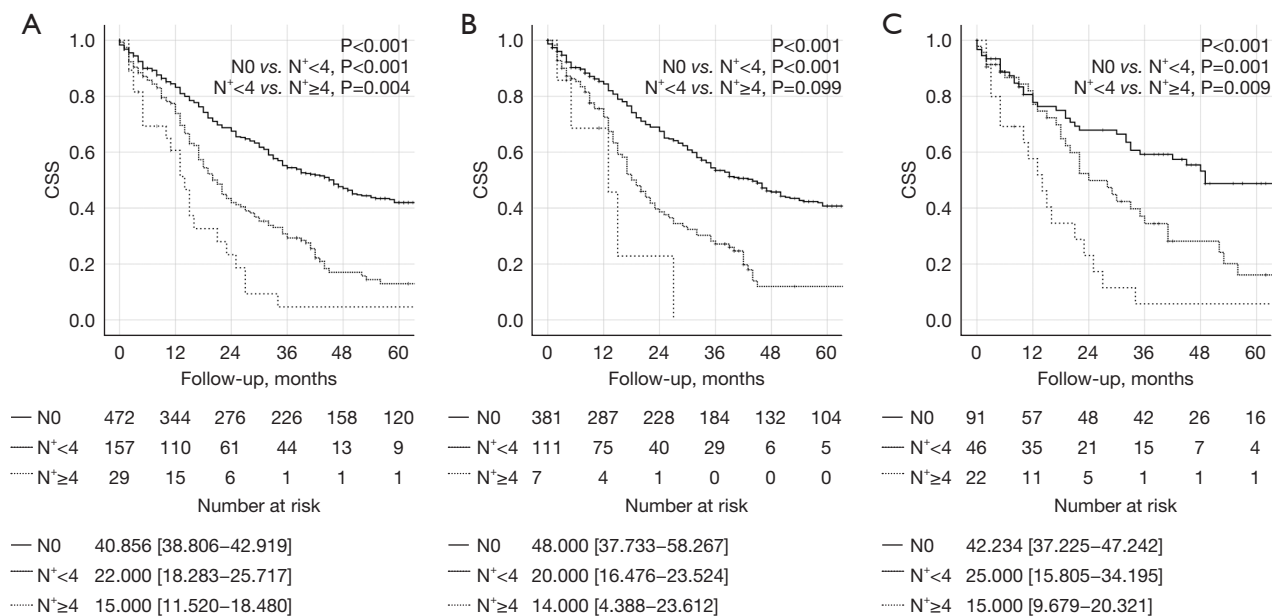
Figure 3 Survival analyses for ICC patients according to harvested LNs status. (A) CSS analysis according to number of metastatic LN. (B) CSS analysis according to metastatic number of LN in subgroup which is sampling LNs less than six. (C) CSS analysis according to metastatic number of LN in subgroup which is sampling LNs equal or more than six. CSS, cause-specific survival; ICC, intrahepatic cholangiocarcinoma; LN, lymph node.

≥4: 42.234 (95% CI: 37.225–47.242) *vs.* 25.000 (95% CI: 15.805–34.195) *vs.* 15.000 (95% CI: 9.679–20.321) months, P<0.001] (*Figure 3C*).

Discussion

In this study, the association between the number of metastatic LNs and the prognosis of patients after surgery was investigated by the SEER database. Although the rate of retrieving six or more LNs was relatively low (24.2%), patients in the SEER database were also confirmed to have a worse prognosis depending on the number of metastatic LNs. Additionally, there was a statistically significant difference in prognosis when the LN status was classified according to the number of LN metastases of N0, N^+ <4, and N^+ ≥4, such as perihilar CC and distal CC. In addition, the HR according to the number of metastatic LNs increased in this study.

Discussion of the significance of lymphadenectomy in ICC patients is still ongoing (11,26-30). Several studies have been published that regional lymphadenectomy can improve survival after surgery (11,27,28). However, some studies reported that lymphadenectomy could not improve survival but also increase complication rate

(30,31). Even though there are many controversies, it is a consensus that LN resection as a staging operation, so that it helps to accurate staging and planning further treatment (8,32,33).

The AJCC staging had been revised to the 8th edition and recommends sampling at least six LNs (15). However, according to Zhang *et al.*, SEER database from 2000 to 2013 showed no significant change in the rate of LN resection in the United States, up to 50% (34). The percentage of patients who had more than six LNs increased slightly but it was still about 14.3% from 2009 to 2013 (34). Within the inclusion criteria of this study, although the rate of patients who had more than six LNs retrieved increased, only about 30% of ICC patients did from 2015 to 2018. The clinical significance of LN dissection in ICC had been suggested by several studies, but it was not until 2015 that it was officially endorsed in an expert consensus statement (33). The rate of appropriate LN dissection might have seen a gradual increase only following the establishment of a consensus on LN dissection in ICC. When including patients with inaccurate LN status who did not underwent LN dissection, it is expected that the actual proportion of patients with less than six LNs retrieved is much lower. On the other hand, a multicenter study from Korea and Japan reported 63.7%

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of patients underwent LN dissection (10). It was a relatively higher rate than the West.

In some studies, when dividing subgroups according to the number of metastatic LNs, more LN metastasis group had statistically worse prognosis (10,12,23,24). Furthermore, in this study, as the number of metastatic LN increased, it was associated with significantly increased risk for CSS in the multivariable analysis. However, among the patients who were harvested less than six LNs, there was no statistical difference in CSS between N$^+$ <4 and N$^+$ ≥4 group. There were two possible reasons for this. First, within the patients who retrieved less than six LN, N$^+$ ≥4 group were only seven patients. Due to the lack of subjects, the difference between two groups could not be statistically significant. It was also possible that patients who should be included in the N$^+$ ≥4 group were under-staged, as they did not receive sufficient lymphadenectomy. For this reason, the prognostic difference could be more evident in the group with sufficient LNs retrieved.

Since there are many patients who have less than six resected LNs, it was examined whether the prognosis could be analyzed with information on their LN status. In previous studies, some prognostic values about LN status were suggested to predict the prognosis of ICC (35,36). log odds of metastatic lymph nodes (LODDS) and lymph node ratio (LNR) already showed better prognostic performance than the AJCC 7th N stage in a previous study (35). Therefore, we investigated these values and AJCC 8th N stage in patients with less than six LNs retrieved. The cut-off value of LNR and LODDS were calculated by X-tile plot (37). Although dividing the subgroups according to the metastatic LN showed the lowest AIC; 2,902.5, its C-index was 0.58. Moreover, the other variables showed similar C-index that were under 0.6 (Table S1). That was to say, it was difficult to accurately determine the prognosis of patients with less than six LN resection even by examining various values about LN status. Retrieving more than six LNs is important to predict the patient's prognosis.

In 2011, Clark *et al.* had already conducted a study on the effectiveness of lymphadenectomy in patients with ICC using the SEER database (38). Since the evaluation of lymphatic nodes was only performed in about 13.5% of all patients, there was a limit to the data to reach conclusions about the efficacy of lymphadenectomy. Zhang *et al.* also used the SEER database to validate the association between the number of metastatic LN and the prognosis (24). We have reaffirmed the significance of the number of metastatic LNs using the SEER database. Considering LN count as

a continuous variable and demonstrating the increment-based HR with population-based data is, to the best of our knowledge, a novel aspect of this study. It might help to develop a new standard for LN staging for ICC. In addition, this study investigated alternative nodal status parameters, such as LNR and LODDS, for patients in whom fewer than six LNs were harvested during ICC surgery. However, statistically significant alternative parameters were not shown. Six or more LNs dissection must still be performed during ICC surgery for accurate staging.

This study has several important limitations. First, although this study used large-sized registry data, the number of patients corresponding to the inclusion criteria was relatively small compared to all ICC patients in the SEER database. Only about 5% of data were used for this study, and selection bias may have occurred in the process of identifying the patients in the inclusion criteria. In addition, subgroup analysis was limited by the small number of patients with less than six LNs retrieval and, above all, by the small number of patients with four or more confirmed LN metastases. Second, several parameters, such as the status of resection margin, histologic grade, and CA19-9, that were related to oncologic outcomes for ICC could not collected due to the limitation of retrospective registry data. In the SEER database, the coding for patients received chemotherapy included 'None/Unknown', referring to patients who did not receive treatment and those for whom it was unknown or not recorded. Similarly, for radiation therapy, there were categories of 'None/Unknown', 'Refused', and 'Recommended, Unknown if Administered'. These limitations made it challenging to analyze the exact effect of chemotherapy or radiotherapy on survival. In addition, although the status of the resection margin is one of the significant prognostic factors, we were unable to confirm this information in the SEER database. Third, due to the lack of information about recurrence, we could not conduct the analysis about the association between the number of metastatic LNs and disease-free survival. Nonetheless, strength of this study is that it shows the prognostic value of the number of metastatic LNs itself with a long-term population-based database by using western public data that showed comparatively low rate of lymph node dissection.

Conclusions

In conclusion, the number of metastatic LNs appears to be a prognostic factor of ICC in the SEER database. However,

for accurate staging, six or more LNs should be harvested during surgery. Further studies for detailed nodal staging of ICC in terms of a cut-off level for the adequate number of harvested LN metastasis needed in the future.

Acknowledgments

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-580/rc

Peer Review File: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-580/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-580/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Approval was waived by the local ethics committee, as SEER data is publicly available and de-identified. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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Table S1 AIC value and C statics of variable nodal parameters for ICC subgroup which is sampling LNs less than six

Nodal parameters	Cut off point	AIC	C-index
AJCC 8th N stage	0	2,902.5	0.58
N0 vs. N+ <4 vs. N+ ≥4	Lower: 0, higher: 3	2,902.6	0.58
LNR (%)	Lower: 0, higher: 66.67	2,903.6	0.58
LODDS	Lower: −0.69897, higher: 0.477	2,904.3	0.59

AIC, Akaike information criterion; ICC, intrahepatic cholangiocarcinoma; LN, lymph node; C-index, Harrell concordance index; AJCC, American Joint Committee on Cancer; LNR, lymph node ratio; LODDS, log odds of metastatic lymph nodes.