

## Peer Review File

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### Reviewer A

The authors assessed the prognostic value of the number of metastatic lymph nodes on the long-term survival of intrahepatic cholangiocarcinoma (ICC) using the SEER database. The authors reported that the prognosis gets worse with an increasing number of metastatic lymph nodes, and that more than six lymph nodes need to be dissected to accurately staging. These results led to Western patients with ICC were confirmed to have worse prognosis with an increasing number of metastatic.

The following issues need to be thoroughly reviewed.

Major problems

1. The term of Extended lobectomy is not clear. Was the extra bile duct resection with hepatectomy included in "Extended lobectomy"?

- Reply

According to the "SEER 2003+ Site-Specific Surgery of Primary Site Codes," an extended lobectomy is defined as the "resection of a single lobe along with a segment of another lobe." Therefore, when coding for extended lobectomy, the focus should be on the extent of resection of the hepatic lobe rather than the additional resection of the bile duct. We have modified our text as advised. (see page 5 line 141, table 1)

Changes in the text: page 5 & table 1

(line 141) 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.

Table1.

Types of surgery	
Wedge resection or <b>segmentectomy</b>	179 (27.2%)
<b>Hemihepatectomy</b>	261 (39.7%)
<b>Extended hemihepatectomy</b>	134 (20.4%)
Excision of bile duct with partial hepatectomy	84 (12.8%)

2. "Excision of bile duct with partial hepatectomy" should be removed because partial resection with resection of the extrahepatic bile duct is a procedure for perihilar cholangiocarcinoma not for ICC. Biology is completely different between the two diseases.

- Reply

A total of 84 patients received treatment with "Excision of bile duct with partial hepatectomy." The SEER database defines this procedure as "Excision of a bile duct for an intra-hepatic bile duct primary only." In other words, it refers to the resection of intra-hepatic bile ducts within the liver parenchyma surrounding ICC lesions rather than the excision of the extrahepatic bile ducts. Therefore, it would be challenging to consider these procedures as radical surgery for perihilar cholangiocarcinoma. We have modified our text as advised. (see page 5 line 137)

Changes in the text: page 5

(line138) 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 intra-hepatic bile duct primary only**) with or without partial hepatectomy, and liver transplantation.

3. More details need to be included on the treatment of after surgery. Postoperative adjuvant chemotherapy has been reported to improve prognosis. The presence or absence of adjuvant chemotherapy should be included in the analysis.

4. Can the author show the status of margins positive or negative? This is another important prognostic factor and should be clearly stated.

- Reply

We have added information regarding the use of chemotherapy and radiotherapy. The coding for chemotherapy and radiation therapy in the SEER database has certain limitations. In terms of chemotherapy, as shown in Table 1, 48.9% of patients received chemotherapy it combines patients who did not receive treatment with those for whom it is unknown or not recorded as "None/Unknown." Similarly, for radiation therapy, there is a category of "None/Unknown" coding. Furthermore, the database includes patients coded as "Refused" and "Recommended, Unknown if Administered," making it challenging to determine whether patients received radiotherapy accurately and 17% of patients received radiotherapy. We included this variable in both univariable and multivariable analyses. However, no significant differences were observed, as demonstrated in a supplementary table (where chemotherapy and radiotherapy were included in the multivariable analysis) below. This lack of differentiation may likely be attributed to the inclusion of patients for whom it is uncertain whether they received treatment. In addition, as mentioned by the reviewer, the status of the margin can be an important prognostic factor. However, we could also not confirm this information in the SEER database. We have modified our text as advised.

Consequently, in the revised manuscript, we decided not to include chemotherapy and radiotherapy status in Table 2 and discuss these points in the limitation section. We have modified our text as advised. (see table 1, page 5 line 144 and page 10 line 290)

Changes in the text: table 1, page 5 and 10

<b>Radiotherapy</b>	
Yes	113 (17.2%)
No/Unknown	545 (82.8%)
<b>Chemotherapy</b>	
Yes	322 (48.9%)
No/Unknown	336 (51.1%)

(line 145) The information on chemotherapy and radiotherapy was also collected from the SEER database.

(line 302) 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.

### Supplementary table for reviewer

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

(chemotherapy and Radiotherapy included in Multivariable analysis)

Variables (N=658)	Univariable analysis			Multivariable analysis		
	HR	95% CI	p value	HR	95% CI	p value
Sex (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	1.828	1.418-2.358	<0.001
T3	2.616	1.489-4.597	0.001	2.324	1.312-4.118	0.004
T4	2.952	2.045-4.260	<0.001	2.313	1.567-3.416	<0.001
Radiotherapy (ref: No/Unknown)	1.095	0.837-1.433	0.506	1.049	0.786-1.401	0.744
Chemotherapy (ref: No/Unknown)	1.079	0.872-1.336	0.484	0.823	0.651-1.042	0.105
Metastatic LN (Increment 1)	1.300	1.225-1.379	<0.001	1.257	1.179-1.340	<0.001

## Minor problems

1. In Table1, the designation of the procedure for hepatic resection should be given according to the Brisbane 2000 nomenclature of liver anatomy and resections or the New World Terminology.

### - Reply

We have revised the terminology of the procedures coded in the SEER database in the manuscript by the Brisbane 2000 Nomenclature of Liver Anatomy and Resections. We have modified our text as advised. (see page 5 line 137 and table 1)

Changes in the text: page 5, table 1

(line 137) 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 intra-hepatic 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.

Table 1

Types of surgery	
Wedge resection or <b>segmentectomy</b>	179 (27.2%)
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## **Reviewer B**

This article assesses the number of positive lymph nodes in association with recurrence and survival after resection for cholangiocarcinoma.

Unfortunately, this is a well known finding in the literature. The number of metastatic lymph nodes has long been correlated with an increased recurrence and worse survival. Thus, this study approach does not add any new data to the current literature and the thought that this would be different in Eastern or Western populations is not significant enough to warrant additional re-investigation. As such I must recommend that this study be rejected.

### - Reply

As the reviewer mentioned, Zhang et al. reported in a multicenter study involving hospitals in Western countries, demonstrating that the number of metastatic lymph nodes does impact prognosis. They also performed external validation using the SEER database to support these results.

Despite this background, there is significance in fully utilizing this population database and confirming through multivariable analysis that, as the number of lymph nodes increased one by one, the Hazard Ratio (HR) significantly worsened survival. Additionally, when lymph node dissection was insufficient, we made efforts to predict prognosis based on other lymph node-related indicators such as LODDS and LNR. This demonstrates our commitment to further exploring the impact of lymph node metastasis on predicting survival prognosis

We have modified our text as advised. (see page 4 line 100 and page 10 line 273)

Changes in the text: page 4 and 10

(line 100) Zhang et al reported in multicenter study involving hospitals in Western countries, demonstrating that the number of metastatic lymph nodes does impact 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 on reconfirming the prognostic impact of the number of metastatic lymph nodes 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 8<sup>th</sup> edition of the AJCC, we decide to check how different long-term survival depends on the number of LN metastases when at least six LNs are retrieved.

(line 282) Zhang et al also used SEER database to validate the association between number of metastatic LN and prognosis. (24) We have reaffirmed the significance of the number of metastatic lymph nodes using the SEER database. Considering lymph node count as a continuous variable and demonstrating the increment-based Hazard Ratio (HR) with population-based data is, to the best of our knowledge, a novel aspect of this study.

I would also recommend the authors utilize a program such as Grammarly for future research to improve the quality of the writing.

- Reply

We regret that the reviewer felt the need to improve the quality of the writing despite receiving professional English editing. After revising the manuscript, we have undergone another round of English editing.

## Reviewer C

The SEER database has been queried at least nine times to examine the management of intrahepatic cholangiocarcinoma.<sup>1–9</sup> Some of these studies specifically examined the role of lymph node dissection.

1. Shinohara ET, Mitra N, Guo M, Metz JM. Radiation Therapy Is Associated With Improved Survival in the Adjuvant and Definitive Treatment of Intrahepatic Cholangiocarcinoma. *Int J Radiat Oncol Biol Phys.* 2008;72(5):1495-1501. doi:10.1016/j.ijrobp.2008.03.018
2. Clark CJ, Wood-Wentz CM, Reid-Lombardo KM, Kendrick ML, Huebner M, Que FG. Lymphadenectomy in the staging and treatment of intrahepatic cholangiocarcinoma: a population-based study using the National Cancer Institute SEER database. *HPB (Oxford).* 2011;13(9):612-620. doi:10.1111/j.1477-2574.2011.00340.x
3. Vitale A, Moustafa M, Spolverato G, Gani F, Cillo U, Pawlik TM. Defining the possible therapeutic benefit of lymphadenectomy among patients undergoing hepatic resection for intrahepatic cholangiocarcinoma. *J Surg Oncol.* 2016;113(6):685-691. doi:10.1002/jso.24213
4. Kim Y, Moris DP, Zhang X-F, et al. Evaluation of the 8th edition American Joint Commission on Cancer (AJCC) staging system for patients with intrahepatic cholangiocarcinoma: A surveillance, epidemiology, and end results (SEER) analysis. *J Surg Oncol.* 2017;116(6):643-650. doi:10.1002/jso.24720
5. Zhang XF, Chen Q, Kimbrough CW, et al. Lymphadenectomy for Intrahepatic Cholangiocarcinoma: Has Nodal Evaluation Been Increasingly Adopted by Surgeons over Time? A National Database Analysis. *J Gastrointest Surg.* 2018;22(4):668-675. doi:10.1007/s11605-017-3652-2
6. Altman AM, Kizy S, Marmor S, Huang JL, Denbo JW, Jensen EH. Current survival and treatment trends for surgically resected intrahepatic cholangiocarcinoma in the United States. *J Gastrointest Oncol.* 2018;9(5):942-952. doi:10.21037/jgo.2017.11.06
7. Chen X, Rong D, Zhang L, et al. Evaluation of nodal status in intrahepatic cholangiocarcinoma: a population-based study. *Ann Transl Med.* 2021;9(17):1359. doi:10.21037/atm-21-2785
8. Hu H, Zhao H, Cai J. The role of lymph node dissection and a new N-staging system for intrahepatic cholangiocarcinoma: a study from the SEER database. *J Int Med Res.* 2021;49(6):3000605211012209. doi:10.1177/03000605211012209
9. Zhang XF, Xue F, Dong DH, et al. Number and Station of Lymph Node Metastasis after Curative-intent Resection of Intrahepatic Cholangiocarcinoma Impact Prognosis. *Ann Surg.* 2021;274(6):E1187-E1195. doi:10.1097/SLA.0000000000003788

The *J Gastrointest Oncol* published an article in 2018 that included 1,263 patients from 2000-2014 with the aim of determining the incidence and adequacy of lymph node dissection.<sup>6</sup> Lymph nodes were removed in 49% of patients, but in only 10% the lymph node dissection met the criteria of the American Joint Committee on Cancer (≥6 lymph nodes). Positive lymph nodes were found in 29% of patients. The authors concluded that lymph node dissection was inadequate and this most likely resulted in under-staging.<sup>6</sup>

That year, a separate analysis concurred with the previous findings, adding that lymph node dissection harvesting ≥6 lymph nodes showed an upward trend over the years, although only



reaching a modest 14.3% at the end of the study period.<sup>5</sup>

A recent study compared patients undergoing resection with curative intent for intrahepatic cholangiocarcinoma at 15 centers worldwide with patients from the SEER database.<sup>9</sup> The study found that patients with no (N0), 1-2 (N1), or  $\geq 3$  (N2) positive lymph nodes had worse overall and progression-free survival.

## Introduction

Page 2, lines 11-13:

The phrase "These studies have been mainly published in East Asian countries and studies in Western countries are insufficient." does not accurately reflect the facts (see comments above).

### - Reply

As the reviewer mentioned, Zhang et al. reported in a multicenter study involving hospitals in Western countries, demonstrating that the number of metastatic lymph nodes does impact prognosis. They also performed external validation using the SEER database to support these results.

Despite this background, there is significance in fully utilizing this population database and confirming through multivariable analysis that, as the number of lymph nodes increased one by one, the Hazard Ratio (HR) significantly worsened survival. We have modified our text as advised. (see page 4 line 98)

Changes in the text: Page 4.

(line 98) 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 in multicenter study involving hospitals in Western countries, demonstrating that the number of metastatic lymph nodes does impact 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 on reconfirming the prognostic impact of the number of metastatic lymph nodes on survival.

## Results

After excluding those who did not meet the criteria, the study included 658 patients operated on between 2000-2018. Six or more lymph nodes were harvested in 159 patients (24.2%). Only 29 patients (4.4%) had  $\leq 4$  positive lymph nodes. From year three, one or no patients with  $\leq 4$  positive lymph nodes remained alive in the survival study. The increase in the number of positive lymph nodes was independently associated with survival (HR 1.245, 95% CI 1.169 - 1.326,  $p < .001$ ). Subgroup analysis is limited by the small number of patients with  $\leq 6$  lymph nodes harvested and, above all, by the small number of patients with  $\leq 4$  positive lymph nodes.

### - Reply

Our analysis has limitations due to the small number of patients with four or more confirmed lymph node metastases. We mentioned this limitation in the discussion section. (see page 10 line 285)

Changes in the text: page 10

(line 294) 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 lymph node metastases.

Page 6, lines 22-28:

The following comments, at the end of Discussion, do not give due credit to the referenced study: “Zhang et al (18) also used SEER database to validate the association between number of metastatic LN and prognosis. Although previous studies also provided useful information about LN metastasis in ICC patients, this study focused on efforts to reflect the details of treatment and tumor staging as much as possible. The number of metastatic LN increased; it was associated with significantly increased risk for CSS in the multivariable analysis. Since no other institution has confirmed that the risk for CSS increased gradually as the number of metastatic LNs increased, it might help to develop a new standard for LN staging for ICC.” It is not true that no other institution has confirmed that survival increases gradually with the number of positive lymph nodes (see the study by Zhang).

### - Reply

As noted by the reviewer, previous studies have also conducted subgroup analyses, revealing that patients with more metastatic lymph nodes exhibited a worse prognosis. However, to the best of our knowledge, considering lymph node count as a continuous variable and demonstrating the increment-based Hazard Ratio (HR) with population-based data is a novel aspect of this study. We have modified our text as advised. (see page 10 line 273)

Changes in the text: Page 10

(line 282) Zhang et al also used SEER database to validate the association between number of metastatic LN and prognosis. (24) We have reaffirmed the significance of the number of metastatic lymph nodes using the SEER database. Considering lymph node count as a continuous variable and demonstrating the increment-based Hazard Ratio (HR) with population-based data is, to the best of our knowledge, a novel aspect of this study.

The main finding of the study: "Western patients with ICC were confirmed to have worse prognosis with an increasing number of metastatic LNs." has been previously published.

- Reply

We comprehend the reviewer's concern that the academic contribution of this study might be somewhat diminished due to previously published findings. We'd prefer not to specify "Western patients" and instead state that "we have reaffirmed the significance of the number of metastatic lymph nodes using the SEER database." (see page 10 line 273)

-Changes in the text: Page 10

(line 282) Zhang et al also used SEER database to validate the association between number of metastatic LN and prognosis. (24) We have reaffirmed the significance of the number of metastatic lymph nodes using the SEER database. Considering lymph node count as a continuous variable and demonstrating the increment-based Hazard Ratio (HR) with population-based data is, to the best of our knowledge, a novel aspect of this study.

## Reviewer D

The paper by Juwan Kim et al. reported the prognostic value of the number of metastatic lymph nodes on the long-term survival of intrahepatic cholangiocarcinoma using the SEER database. The author showed that the number of metastatic lymph nodes appeared to be a prognostic factor of intrahepatic cholangiocarcinoma using SEER database. In addition, when it was divided between  $N < 4$  and  $4 \leq N$  group according to the number of metastatic LNs, it was associated with significantly increased risk in  $4 \leq N$  group. However the patients who were harvested less than 6 LNs had no statistical difference between  $N < 4$  and  $4 \leq N$  group. The author stated that six or more LNs should be harvested during surgery. I have some comments as listed below.

Major Comment:

1. How did the author divide the number of LNs into  $N < 4$ ,  $N \geq 4$ , as shown in Table 1, and did the author have any data or previous literature related it? Could the classification have been made as in the guidelines for perihilar and distal cholangiocarcinoma, but is it applicable to intrahepatic cholangiocarcinoma? If so, would the prognosis be better for the number of one or two LN metastases compared to  $N \geq 4$  LNs metastases?

- Reply

We previously presented the survival rate differences between patients with four or more lymph node metastases and those with fewer than four in “Kim SH et al. Prognostic impact of the metastatic lymph node number in intrahepatic cholangiocarcinoma. *Surgery*. 2022;172(1):177-83.” Based on prior research conducted at our institution, we divide the number of LNs into  $N < 4$  and  $N \geq 4$  as other biliary cancers. Figure 3 shows distinct differences between the two groups in the overall patient population and in the subgroup where six or more lymph nodes were retrieved. We added information as advised. (see page 6 line 166)

Changes in the text: Page 6

(line 172) In addition, the enrolled patients were divided into 3 groups based on the number of metastatic LNs (N0: no metastasis; N1 [N+ <4]: 1 to 3 metastatic LNs; N1 [N+  $\geq$ 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)

2. In the cases which the LN dissection was performed, was lymph node dissection performed in a case with a positive preoperative diagnosis of lymph node when the LN size is greater than 0.2 mm. The LN size of 0.2 mm seems quite little, but is there any evidence for this in the past literature?

- Reply

Under the SEER database, we defined lymph node metastasis based on the following criteria. "Lymph nodes with only isolated tumor cells (ITCs) are NOT counted as positive lymph nodes. Only lymph nodes with metastases greater than 0.2mm (micrometastases or larger) should be counted as positive. If the pathology report indicates that nodes are positive, but the size of the metastases is not stated, assume the metastases are > 0.2mm and code the lymph nodes as positive in this field." We have modified our text as advised (see page 5 line 152)

Changes in the text: Page 5

(line 152) In addition, the SEER database used the 'regional nodes positive' code to record lymph node metastasis. Lymph node positive is defined as the presence of a tumor measuring 0.2mm or larger, confirmed through pathological examination in the SEER database.

3. The author stated that more than 6 lymph nodes needed to be dissected. Is there any data for the extent of LN dissection or the type of LNs, such as hepatoduodenal ligament or around common hepatic artery, needed to be harvested?

- Reply

In a prior study conducted at our institution, we recommended an extensive lymph node dissection (LND) encompassing at least stations no. 12 (hepatoduodenal ligament) and 8 (common hepatic artery) for accurate staging in patients with intrahepatic cholangiocarcinoma (ICC). This recommendation is held regardless of the tumor's location (Kim SH, Han DH, Choi GH, Choi JS, Kim KS. "Extent of Lymph Node Dissection for Accurate Staging in Intrahepatic Cholangiocarcinoma." J Gastrointest Surg. 2022 Jan;26(1):70-76. doi: 10.1007/s11605-021-05039-5. Epub 2021 Jun 7. PMID: 34100250).

However, the SEER database did not provide information regarding the specific regions of lymph node dissection. Consequently, we could not include an analysis of this aspect in our current research.

Minor Comment :

1. As the author showed in Fig,2, the number of cases with LN dissection was about 30% in 2015 - 2018. Why such a low ratio, even though the guidelines indicate it? Is it because lymph node dissection is not considered very important? If there is a reason, the author should indicate it in the Discussion

- Reply

That ratio reflects many possible reasons. The clinical significance of lymph node dissection in intrahepatic cholangiocarcinoma (ICC) has been suggested by several studies. However, it wasn't until 2015 that it was officially endorsed in an expert consensus statement. Furthermore, between 2015 and 2018, there was no consensus regarding the minimum number of lymph nodes required for accurate staging. Additionally, in cases where distinguishing between hepatocellular carcinoma (HCC) and ICC before surgery proves challenging, lymph node dissection may not have been performed based on the presumption that the lesion is HCC. Consequently, these could be the reasons for the low rate of adequate lymph node dissection (involving retrieving more than 6 lymph nodes) between 2015 and 2018. (see page 9 line 244)

Changes in the text: Page 9

(line 246) The clinical significance of lymph node dissection in intrahepatic cholangiocarcinoma (ICC) had been suggested by several studies, but it wasn't until 2015 that it was officially endorsed in an expert consensus statement.(33) The rate of appropriate lymph node dissection might have seen a gradual increase only following the establishment of a consensus on lymph node dissection in ICC.

2. As shown in Fig.3, the more lymph nodes are dissected, the better the prognosis seems to be, but are there any data on prolonged operation time or increased complication rate due to LN dissection?

- Reply

Unfortunately, the SEER database did not provide information regarding the duration of the operation or postoperative complications. Consequently, we could not include an analysis of this aspect in our current research.

3. If the author has a rationale for more than 6 LNs dissection, do more than 10 LNs dissection have better prognosis?

- Reply

In this study, the evidence for lymph node dissection improving survival rates is unclear. This is because, in the Cox model, there was no significant difference in survival rates between groups with fewer than 6 lymph nodes removed and those with 6 or more lymph nodes removed. Therefore, it is more appropriate to interpret that performing sufficient lymph node dissection can assist in determining staging based on the number of lymph node metastases and guide future treatment directions after surgery rather than viewing it as a concept primarily aimed at cytoreduction. In addition, we discussed the controversy that regional lymphadenectomy can improve survival after surgery. (see page 8 line 233)

## Reviewer E

JW Kim et al. Used the SEER database to investigate the association between the number of metastatic lymph nodes and the prognosis of ICC patients in Western countries. The authors included 658 ICC patients who underwent hepatectomy and lymph node dissection between 2000 and 2018, and searched for the proportion of ICC patients with more than six LN metastases. The authors divided patients into three groups based on the number of metastatic lymph nodes and further compared etiologically specific survival (CSS). To identify the number of metastatic LN as a prognostic factor in ICC patients, the authors performed survival analyses of the three sets of data and compared whether the differences between subgroups were significant. These results lead the authors to conclude that the prognosis of ICC patients in the West deteriorates as the number of metastatic lymph nodes increases.

Although some of these observations are well documented and persuasive, this study leaves much to be desired. The data selected in the SEER database cannot fully represent the overall level of ICC patients in Western countries. At the same time, due to the setting of inclusion criteria, a small number of patients were finally selected for the study, which may have a large bias. In addition, the manuscript lacked regression analyses for prognostic indicators of ICC patients, such as the presence or absence of stones, degree of differentiation, vascular invasion, histological grade, AFP, and CA19-9. If the number of metastatic lymph nodes in ICC patients from certain hospitals in Western countries can be added for a retrospective study, the credibility of the study will be increased. Some of the other major issues are listed below. In order to represent a significant contribution, these observations should be addressed substantively.

### - Reply

We agree that the SEER database may not represent patients in Western countries. Therefore, we have revised the manuscript to avoid mentioning that the SEER database represents ICC patients in Western countries.

As a population-based database with a diverse representation of various races, it has the potential to be more representative of the disease compared to multi-institutional studies. However, missing data is inevitable, and this limitation may result in the exclusion of many patients, potentially introducing significant bias. Additionally, we could not collect sufficient data, such as CA19-9 or AFP levels, already known as prognostic factors. We fully acknowledge these study limitations and will explicitly address them in the discussion section. (see Page 10, line 274)



Changes in the text: Abstract, page 10

(line 47) Patients with ICC in the SEER database were reaffirmed to have worse prognosis with an increasing number of metastatic LNs.

(line 278) Zhang et al also used SEER database to validate the association between number of metastatic LN and prognosis. (24) We have reaffirmed the significance of the number of metastatic lymph nodes using the SEER database.

Major points:

1. More background information on intrahepatic cholangiocarcinoma (ICC) can be provided in the Introduction section, such as introducing the incidence and mortality of ICC in Eastern and Western countries and explaining why lymph node dissection and intraoperative collection are important for the prognosis of ICC patients.

- Reply

We have modified our text as advised. (see page 3 line 67)

Changes in the text: Page 3

(line 67) Globally, cholangiocarcinoma exhibits an average annual incidence of 2 cases per 100,000 individuals. 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. Within the spectrum of cholangiocarcinoma, extrahepatic cholangiocarcinoma has displayed a relatively stable incidence pattern in recent decades. In contrast, intrahepatic cholangiocarcinoma 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.

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

Since the introduction of the 7<sup>th</sup> edition of the American Joint Committee on Cancer (AJCC) staging system, significant endeavors have been undertaken to differentiate intrahepatic cholangiocarcinoma from other intrahepatic tumors, aiming to refine prognosis prediction. Precise prognosis prediction plays a pivotal role in determining the necessity for supplementary adjuvant therapies such as chemotherapy or radiotherapy. Furthermore, lymph node metastasis in intrahepatic cholangiocarcinoma stands as a prominent prognostic determinant.

2. Page 1, 10: The phrase of “cause specific survival (CSS)” should be convert to “cause-specific survival (CSS)”.

- Reply

We have modified our text as advised (see page 1 line 42)

Changes in the text: page 1

(line 42) The patients were then divided into three groups according to their metastatic LN numbers (N0: no metastatic LNs; N<sup>+</sup><4: 1-3 metastatic LNs; N<sup>+</sup>≥4: ≥4 metastatic LNs), and cause-specific survival (CSS) was compared.

3. Page 2, 2; Page3, 12: There are no explanations or descriptions of the abbreviation “HBP” and “NOS”, respectively.

- Reply

We have modified our text as advised. (see page 3 line 87 and page 5 line 139)

Changes in the text: page 3 and 5

(line 87) Since it is a relatively rare disease in the field of Hepato-Biliary-Pancreatic Surgery, almost all ICC studies are single-institutional.

(line 139) 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 intra-hepatic bile duct primary only) with or without partial hepatectomy, and liver transplantation.

4. Page 2, 28: Authors need to use quotes in the same format, 'malignant neoplasm (8000)'.

- Reply

We have modified our text as advised. (see page 4 line 119)

Changes in the text: Page 4

(line 119) the histology code of 'malignant neoplasm (8000)', 'malignant tumor cells (8001)', 'carcinoma (8010)', 'undifferentiated carcinoma (8020)' and 'cholangiocarcinoma (8160)' were collected.

5. Page 3, 33 : There are grammatical errors in this paragraph, such as replacing the words “In additions” with “In addition”.

- Reply

We have modified our text as advised. (see page 6 line 167)

Changes in the text: Page 6

(line 168) The hazard ratio (HR) according to the increasing number of metastatic LNs was calculated. In addition, the enrolled patients

6. Page 4, 31: There’s a grammatical problem that you need to add “a” before the word “significant”.

- Reply

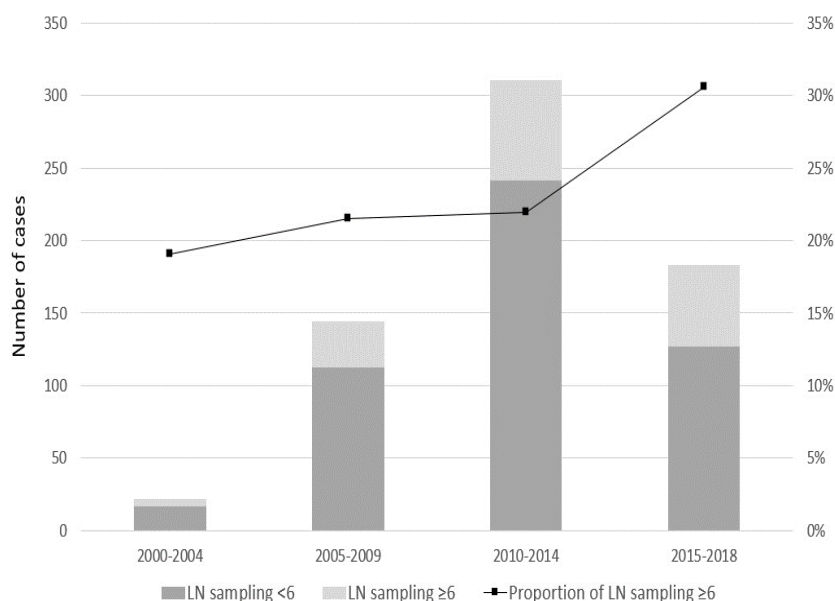
We have modified our text as advised. (see Page 7 line 204)

(line 204) the number of metastatic LNs was also a significant prognostic factor with T stage.

7. Figure 2 : A line chart can be added to better show the LN sampling 6 or more, and the difference between different periods should be shown. If possible, please add the data from 2019 to 2023.

- Reply

We could not include data for ICC patients from the SEER database for 2019 to 2023. However, we have modified our figure as advised.



8.General: The whole study excluded too much data that could not collect specific information because of insufficient information, so we can choose to expand the sample size or adjust the exclusion criteria to reduce the incidence of bias.

- Reply

The study aimed to evaluate survival differences based on lymph node dissection. The exclusion criteria for this study included missing data, distant metastasis, and other treatments such as non-curative resection or liver transplantation. These criteria could not be altered, given the significance of lymph node dissection in patients with ICC who underwent curative resection.

9. There are several articles relevant to your research, please add 2 references from the list below.

1) The influence of 18F-fluorodeoxyglucose positron emission tomography/computed tomography on the N- and M-staging and subsequent clinical management of intrahepatic cholangiocarcinoma. (doi: 10.21037/hbsn-21-25. PMID: 36268256; PMCID: PMC9577996)

2) Cholangiocarcinoma: a review of the literature and future directions in therapy. (doi: 10.21037/hbsn-20-396. PMID: 36016753; PMCID: PMC9396092)

3) Epigenome-wide development and validation of a prognostic methylation score in intrahepatic cholangiocarcinoma based on machine learning strategies. (doi: 10.21037/hbsn-21-424. PMID: 37601000; PMCID: PMC10432305)

- Reply

We added those 2 references as advised.