Journal of Gastrointestinal Surgery (2021) 25:1156–1163
https://doi.org/10.1007/s11605-020-04720-5

ORIGINAL ARTICLE

Predicting Lymph Node Metastasis in Intrahepatic Cholangiocarcinoma

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Received: 4 May 2020 / Accepted: 28 June 2020 / Published online: 14 July 2020

Abstract

Background The objective of the current study was to develop a model to predict the likelihood of occult lymph node metastasis (LNM) prior to resection of intrahepatic cholangiocarcinoma (ICC).

Methods Patients who underwent hepatectomy for ICC between 2000 and 2017 were identified using a multi-institutional database. A novel model incorporating clinical and preoperative imaging data was developed to predict LNM.

Results Among 980 patients who underwent resection of ICC, 190 (19.4%) individuals had at least one LNM identified on final pathology. An enhanced imaging model incorporating clinical and imaging data was developed to predict LNM (https://k-sahara.shinyapps.io/ICC_imaging/). The performance of the enhanced imaging model was very good in the training data set (c-index 0.702), as well as the validation data set with bootstrapping resamples (c-index 0.701) and outperformed the preoperative imaging alone (c-index 0.660). The novel model predicted both 5-year overall survival (OS) (low risk 48.4% vs. high risk 18.4%) and 5-year disease-specific survival (DSS) (low risk 51.9% vs. high risk 25.2%, both $p < 0.001$). When applied among Nx patients, 5-year OS and DSS of low-risk Nx patients was comparable with that of N0 patients, while high-risk Nx patients had similar outcomes to N1 patients ($p > 0.05$).

Conclusion This tool may represent an opportunity to stratify prognosis of Nx patients and can help inform clinical decision-making prior to resection of ICC.

Keywords lymph node · metastasis · ICC · survival

Introduction

Intrahepatic cholangiocarcinoma (ICC) represents approximately 10–20% of all primary liver cancers with an increasing incidence worldwide.[1, 2] Surgery remains the mainstay of treatment for the majority of patients with resectable ICC.[3, 4] Apart from resection of the tumor, lymph node dissection (LND) is also necessary to appropriately stage the disease and inform conversations around prognosis.[5, 6] Despite advances in patient selection, surgical techniques, and perioperative care, the prognosis of patients with ICC is still dismal even after an appropriate oncologic resection at major hepatopancreatobiliary (HPB) centers.[2, 7]

Lymph node metastasis (LNM) has been one of the strongest predictors of poor outcomes among patients undergoing surgery for ICC.[6, 8, 9] Previous studies have suggested a median OS of 7 to 14 months among patients with at least one metastatic LN following resection for ICC.[8–10] The location as well as the number of metastatic lymph nodes (LNs) have also been associated with the outcomes of ICC patients.[9] Our group recently reported that patients with 0, 1–2, or ≥ 3 LNM had incrementally worse disease-specific and recurrence-free survival following curative-intent resection of ICC.[9] To this end, the latest American Joint Committee

Presented as an Oral Presentation at the AHPBA 2020 Annual Meeting, Miami, FL, March 2020

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11605-020-04720-5) contains supplementary material, which is available to authorized users.

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Extended author information available on the last page of the article on Cancer (AJCC) guidelines recommended at least six LNs be assessed to accurately stage the disease.[11] Despite evidence suggesting the importance of LNM on patient outcomes, less than half of patients have concomitant LND at the time of ICC resection.[2, 10] In turn, a considerable amount of Nx patients are mis- or under-staged leading to heterogeneous and incorrect prognostic classification.[12] As such, preoperative imaging is important to characterize patients at risk for LNM who should definitely be offered LND. The accuracy of preoperative imaging to detect LNM, however, remains questionable especially for the periductal infiltrating subtypes of ICC.[5] To this end, the objective of the present study was to assess the accuracy of preoperative imaging to detect LNM. In addition, we sought to develop a novel model to enhance the accuracy of preoperative imaging and more accurately identify LNM in the preoperative setting. To facilitate clinical applicability of the model, an easy-to-use online calculator was developed to predict the risk of LNM among individuals with resectable ICC prior to resection.

Methods

Study Population and Inclusion/Exclusion Criteria

Patients undergoing curative-intent liver resection for ICC between January 2000 and August 2017 were identified in the International Intrahepatic Cholangiocarcinoma Study Group database.[13, 14] Patients were excluded who (1) did not undergo curative-intent resection, (2) underwent ablation only, (3) had missing data on preoperative imaging, (4) had macroscopically positive margins (R2 resection), (5) died within 30 days following surgery, and (6) had missing follow-up data. The Institutional Review Board of all participating institutions approved the present study.

Variables and Definitions

Demographic data and clinicopathologic data included age, sex, American Society of Anesthesiologist (ASA) classification, presence of cirrhosis, tumor location (i.e., uni- or multifocal), preoperative carbohydrate antigen (CA) 19-9 levels, body mass index (BMI), neutrophil-to-lymphocyte ratio (NLR), albumin-bilirubin (ALBI) grade, tumor size and number, extent of resection, preoperative LN status on imaging (i.e., negative, suspicious, positive), T- and N-stage, margin status, morphological subtype (MF, mass-forming; IG, intraductal growth; PI, periductal infiltrating), tumor grade, presence of micro-vascular invasion, and receipt of adjuvant chemotherapy.

The ALBI score was calculated using the following formula: $[\log_{10} \text{bilirubin } (\mu\text{mol/L}) \times 0.66] + [\text{albumin } (\text{g/L}) \times -0.085]$, and patients were categorized into three groups: grade $1 \leq -2.60$, grade $2 \geq -2.60$ and ≤ -1.39, and grade $3 \geq -1.39$, as previously described.[13] Tumor stage was defined according to the AJCC 8th edition staging manual.[11] Major liver resection was defined as the resection of three or more Couinaud segments.[15] Microvascular invasion was defined as intraparenchymal vascular involvement identified on histological examination.[11] Margin status was categorized as R0 and R1 for microscopically negative and positive resection margins, respectively. Preoperative LN status was determined by imaging studies including CT, MRI, and/or PET-CT.[5] Patients with negative LN status on imaging and metastatic LNs on pathology (N1), as well as individuals with suspicious/metastatic LN status on imaging but non-metastatic LNs on pathology (N0) were categorized as having a discordant radiologic–pathologic assessment.

Statistical Analysis

Descriptive statistics were presented as median (interquartile range (IQR)) and frequency (%) for continuous and categorical variables, respectively. Differences in survival among different groups were assessed using the Kaplan–Meier method and log-rank test. Overall survival (OS) was defined as the time interval between the date of liver resection for ICC and the date of death of any cause or last follow-up. Disease-specific survival (DSS) was defined as the time between resection of ICC and the date of death from disease or last follow-up. The association of preoperatively available variables with LNM was evaluated by means of logistic regression analysis among patients who underwent LND. Variables significant on bivariate analysis ($p < 0.05$) were entered into the multivariable logistic regression model. The β coefficients of the variables in the multivariable model were utilized to develop weighted risk scores. Two risk scores to predict LNM were created; one risk score included only with clinical factors (clinical risk score (CRS)) and the other risk score had clinical factors along with preoperative LN assessment on imaging (enhanced imaging). The optimal cutoff to estimate low versus high risk for LNM was determined using the Youden index.[16, 17] To assess the performance of the risk scores, the C-index was calculated in the training data set followed by a bootstrapping resample method ($n = 2000$) (internal validation). The level of statistical significance was set at $\alpha = 0.05$. All analyses were performed with the SPSS, v25 (IBM Corp. Armonk, NY, USA) and JMP, v14 (SAS Institute Inc., Cary, NC, USA) statistical packages.

Results

Baseline Characteristics of the Entire Cohort

A total of 980 patients underwent curative-intent resection for ICC and were included in the analytic cohort. Median patient age was 59.0 years (IQR 50.0–68.0); most patients were male (n = 556, 56.8%) and had an ASA class ≤ 2 (n = 635, 69.9%). The majority of patients had unifocal disease (n = 812, 83.3%) with a median tumor size of 6.0 cm (IQR 4.0–8.3). Median BMI was 24.8 kg/m2 (IQR 22.1–27.6) and median CA19-9 was 53.0 UI/mL (IQR 19.3–227.1). On preoperative imaging, 760 patients (77.6%) had negative LNs, whereas 141 (14.4%) and 79 (8.0%) had suspicious or metastatic LNs, respectively (Table 1). On final pathology, 25.9% (n = 254) and 19.4% (n = 190) had N0 and N1 disease, respectively, whereas LND was not performed among 54.7% (n = 536) of patients. The majority of patients underwent an R0 resection (n = 853, 87.6%), had MF or IG morphologic ICC subtype (n = 834, 89.3%), well to moderately differentiated tumors (n = 756, 79.9%), and no microvascular invasion (n = 641, 72.7%). Roughly one third of patients received adjuvant chemotherapy (n = 261, 29.9%). The median follow-up for the entire cohort was 20.8 months (IQR 10.0–39.7).

Table 1 Baseline characteristics of patients undergoing curative-intent surgery for ICC

Variable	Total (N = 980)
Age (years)	59.0 (50.0–68.0)
Sex	
Male	556 (56.8)
Female	424 (43.2)
ASA class	
≤ 2	635 (69.9)
> 2	274 (30.1)
Cirrhosis	
No	791 (87.7)
Yes	111 (12.3)
Location	
Unifocal	812 (83.3)
Multifocal	163 (16.7)
CA19-9 (UI/mL)	53.0 (19.3–227.1)
BMI	24.8 (22.1–27.6)
NLR	2.7 (2.1–3.9)
ALBI grade	
1	492 (62.7)
2/3	293 (37.3)
Tumor size (cm)	6.0 (4.0–8.3)
Lesion number	1 (1–1)
Major resection	566 (58.0)
LN status on imaging	
Negative	760 (77.6)
Suspicious	141 (14.4)
Positive	79 (8.0)
AJCC 8th ed. N stage	
N0	254 (25.9)
N1	190 (19.4)
Nx	536 (54.7)
Margin status	
R0	853 (87.6)
R1	121 (12.4)
Morphologic type	
MF, IG	834 (89.3)
PI, MF + PI	100 (10.7)
Tumor grade	
Well to moderate	756 (79.9)
Poor to undifferentiated	190 (20.1)
Microvascular invasion	
No	641 (72.7)
Yes	241 (27.3)
Adjuvant chemotherapy	
No	613 (70.1)
Yes	261 (29.9)

ASA American Society of Anesthesiologists, *CA* carbohydrate antigen, *MF* mass-forming, *IG* intraductal growth, *PI* periductal infiltrating, *AJCC* American Joint Committee on Cancer, *NLR* neutrophil-to-lymphocyte ratio, *ALBI* albumin-bilirubin, *BMI* body mass index

Prediction of LNM with or without preoperative imaging

Among patients who underwent LND (n = 444), a total of 152 patients (34.2%) had discordant radiologic–pathologic LN status. Specifically, 87 out of 276 patients (31.5%) with preoperative node-negative disease ultimately had LNM on pathology. In contrast, 103 out of 168 patients (61.3%) with preoperative suspicious/metastatic LNs had pathologically confirmed LNs.

A number of preoperative factors were assessed relative to the association with LNM among patients who underwent LND. On bivariate analysis, higher number of lesions (OR 1.21, 95% CI 1.01–1.45, p = 0.04), suspicious or metastatic LNs on imaging (OR 3.44, 95% CI 2.31–5.14, p < 0.001), preoperative CA19-9 levels >200 UI/mL (OR 2.02, 95% CI 1.34–3.04, p = 0.001) and ALBI grade 2/3 (OR 1.47, 95% CI 1.01–2.15, p = 0.04) were associated with a higher odds of LNM, whereas older age (OR 0.98, 95% CI 0.96–0.99) was associated with lower odds of LNM (Table 2). Two risk scores—with (enhanced imaging model) and without radiologic LN assessment (pure CRS)—were developed based on the β coefficients of the factors in the respective multivariable models (Table 2).

The performance of the enhanced imaging model was very good in the training data set (c-index 0.702, 95% CI 0.653–0.751), as well as the validation data set with bootstrapping resamples (c-index 0.701, 95% CI 0.652–0.751). The enhanced imaging model outperformed the preoperative imaging alone (c-index 0.660, 95% CI 0.608–0.713), as well as the pure CRS (c-index 0.637, 95% CI 0.583–0.688; bootstrapping resamples; 0.635, 95% CI 0.583–0.688) (Fig. 1). To facilitate clinical applicability of the enhanced imaging model, a convenient online calculator to calculate the probability of LNM was developed (Supplemental Fig. 1), which is available online (https://k-sahara.shinyapps.io/ICC_imaging/).

Association of Enhanced Imaging and Pathologic LN Status with Oncologic Outcomes

Based on the enhanced imaging model, patients were categorized into risk groups for LNM: low risk (n = 188, 42.3%) versus high risk (n = 256, 57.7%) (Youden index

Table 2. Bivariate and multivariable logistic regression analysis of factors associated with LNM among patients who underwent liver resection and LND for ICC (*n* = 444)

	Bivariate analysis		Multivariable analysis			
			Enhanced imaging		CRS	
Variable	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	0.98 (0.96–0.99)	0.013	0.98 (0.97–1.01)	0.08	0.98 (0.96–0.99)	0.011
Sex (male)	1.18 (0.81–1.72)	0.38				
ASA class > 2	0.84 (0.57–1.25)	0.39				
Liver cirrhosis	1.23 (0.51–2.95)	0.65				
BMI	0.97 (0.92–1.01)	0.12				
NLR	0.95 (0.88–1.02)	0.13				
Tumor size (cm)	0.99 (0.94–1.04)	0.73				
Number of lesions	1.21 (1.01–1.45)	0.04	1.16 (0.95–1.41)	0.14	1.14 (0.95–1.38)	0.17
LNs on imaging						
Negative	Ref					
Suspicious or positive	3.44 (2.31–5.14)	<0.001	3.14 (2.08–4.74)	<0.001		
CA19-9 > 200	2.02 (1.34–3.04)	0.001	1.67 (1.08–2.59)	0.021	1.91 (1.25–2.90)	0.003
ALBI grade 2/3	1.47 (1.01–2.15)	0.04	1.41 (0.94–2.11)	0.094	1.39 (0.94–2.06)	0.095

Enhanced imaging = 1.23 − 0.016 × Age + 0.146 × Number of lesions + 1.143 × (LNs on Imaging Suspicious or positive: 1, negative: 0) + 0.514 × CA19-9 (> 200: 1, ≤ 200: 0) + 0.345 ALBI grade (grade 2/3: 1, grade 1: 0)

CRS = 1.76 − 0.022 × Age + 0.132 × Number of lesions + 0.645 * CA19-9 (> 200: 1, ≤ 200: 0) + 0.333 ALBI grade (grade 2/3: 1, grade 1: 0)

ASA American Society of Anesthesiologists, *CA* carbohydrate antigen, *NLR* neutrophil-to-lymphocyte ratio, *ALBI* albumin-bilirubin, *BMI* body mass index, *CRS* clinical risk score

0.8857). While preoperative LN status did not adequately discriminate OS (5-year OS; negative 32.8%, suspicious 33.7%, positive 18.3%, p = 0.003, Fig. 2a), the enhanced imaging model (5-year OS; low risk 48.4% vs. high risk 18.4%, p < 0.001, Fig. 2b) was able to stratify prognosis in a way that closely resembled actual pathologic LN status (5-year OS; N0 45.4% vs. N1 8.6%, p < 0.001, Fig. 2c). Similarly, while preoperative LN imaging was not able to discriminate DSS (5-year DSS; negative 38.3%, suspicious 40.7%, positive 25.6%, p = 0.09, Fig. 2d), the enhanced imaging model could predict DSS (5-year DSS; low risk 51.9% vs. high risk 25.2%, p < 0.001, Fig. 2e) similar to actual pathologic LN status (5-year DSS; N0 53.8% vs. N1 13.1%, p < 0.001, Fig. 2f).

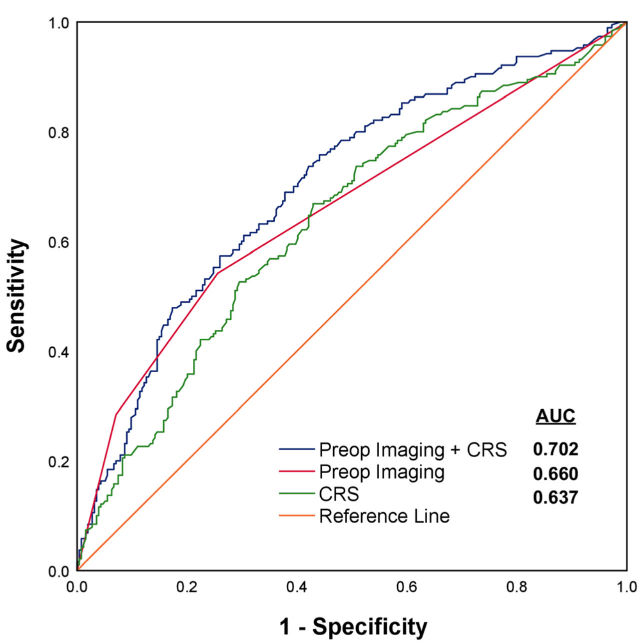

Fig. 1 Performance of the enhanced imaging model, preoperative imaging, and clinical risk score

Application of the Enhanced Imaging Model in Nx Patients

The enhanced imaging model was further applied to patients who underwent curative-intent resection of ICC who did not have LN status assessed (Nx). Of note, 5-year OS and DSS among Nx patients with low risk for LNM was comparable with that of N0 patients (5-year OS 55.1% vs. 47.2%, p = 0.10; 5-year DSS 60.1% vs. 53.8%, p = 0.34, Fig. 3a). Similarly, 5-year OS and DSS of Nx patients with high risk for LNM was similar to that of N1 patients (5-year OS 27.2% vs. 8.6%, p = 0.08; 5-year DSS 32.0% vs. 13.1%, p = 0.19, Fig. 3b).

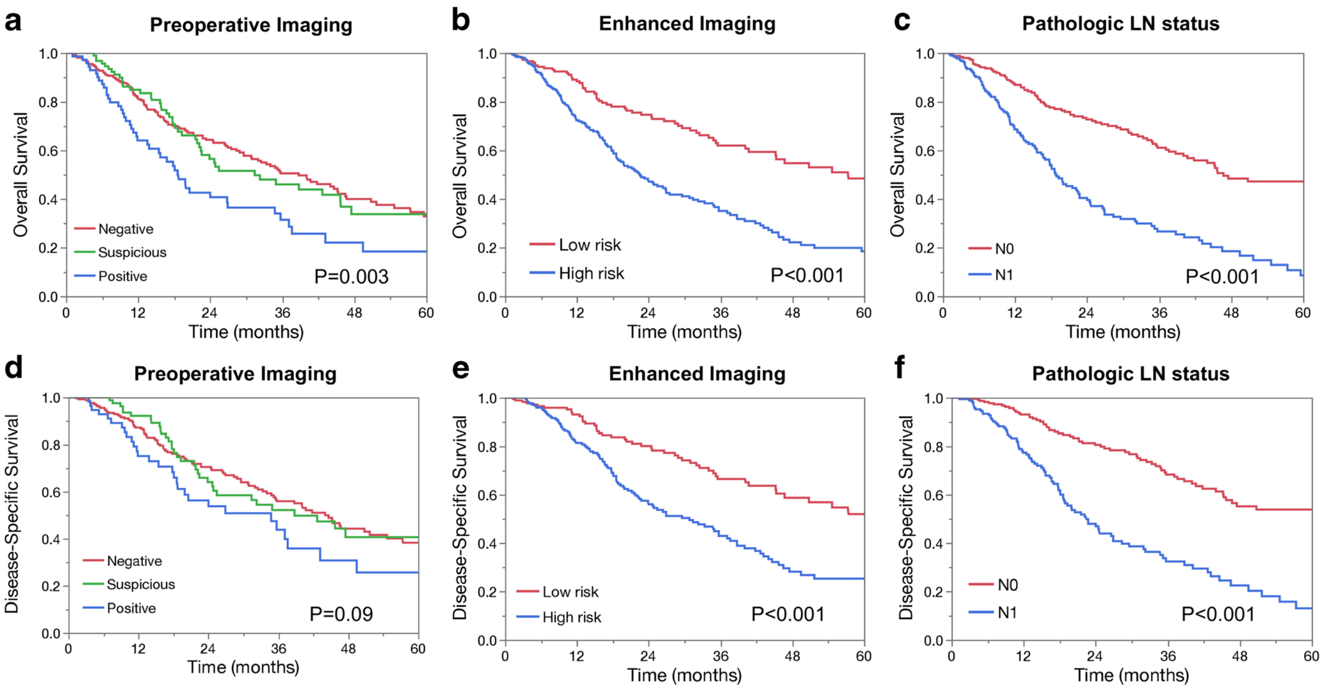

Fig. 2 Kaplan–Meier curves demonstrating differences in OS based on preoperative imaging (**a**), enhanced imaging model (**b**), and pathologic LN status (**c**). Kaplan–Meier curves demonstrating differences in DSS based on preoperative imaging (**d**), enhanced imaging model (**e**), and pathologic LN status (**f**)

Discussion

ICC is a relatively rare liver malignancy with an aggressive tumor biology.[4] Even after curative-intent resection, the long-term prognosis of ICC patients is dismal with an estimated 5-year OS of only 30–35%.[4, 14] Prognosis is even worse among patients with at least one metastatic LN identified after resection with a median OS ranging from 7 to 14 months.[6] Due to the tendency of ICC to metastasize to the regional LNs, LND is essential to adequately stage the disease and guide decisions around adjuvant chemotherapy.[18] Nevertheless, up to 50% of patients do not have concomitant LND at the time of surgery.[2, 12] In turn, a large number of patients with ICC are frequently mis- or under-staged further compromising their outcomes.[6] Accurate preoperative assessment of LNs is necessary to guide decision treatment making and categorize patients at risk for LNM who should definitely be offered LND. Preoperative assessment of the nodal basin has, however, been challenging in ICC.[5] The current study was important because it demonstrated that approximately one third of patients (34.2%) who underwent LND had a discordant radiologic–pathologic assessment of the nodal basin. A novel enhanced imaging model was developed that incorporated clinical and imaging data to predict the probability of LNM in the

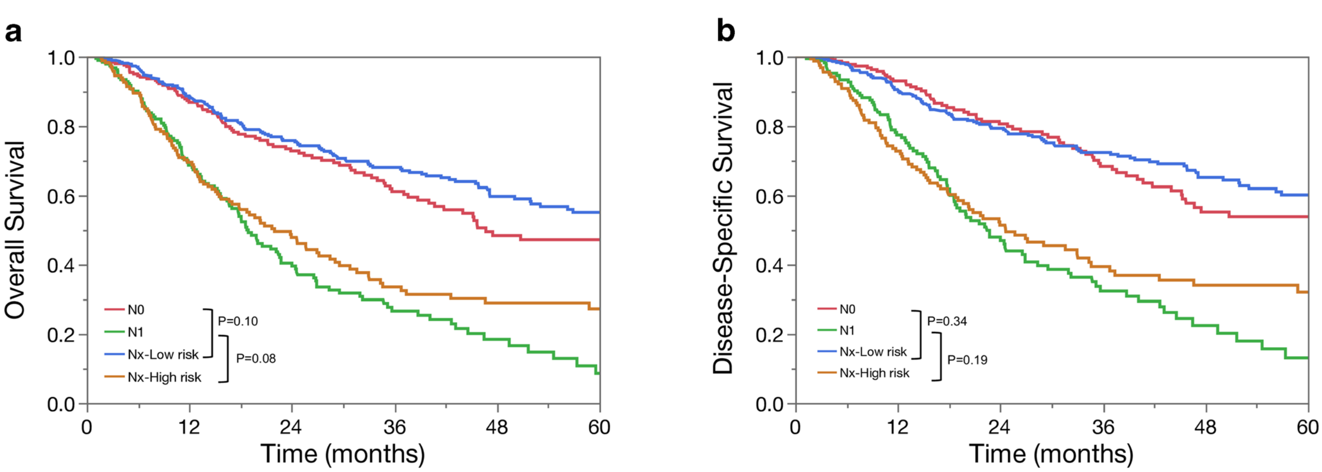

Fig. 3 Kaplan–Meier curves demonstrating differences in OS (**a**) and DSS (**b**) among patients with N0, N1, and Nx (low- or high-risk) disease

preoperative setting. Using this tool, patients were categorized into low- and high-risk groups for LNM with an incrementally worse 5-year OS and DSS (5-year OS; low risk 48.4% vs. high risk 18.4%; 5-year DSS; low risk 51.9% vs. high risk 25.2%, both $p < 0.001$). When the model was applied in Nx patients, low-risk Nx patients had comparable outcomes with N0 patients, whereas high-risk Nx patients had similar outcomes with N1 patients. The enhanced imaging model performed very well in the test and internal validation datasets and outperformed preoperative imaging alone, as well as the pure CRS. To further enhance the applicability of this novel tool, an easy-to-use online calculator was developed to calculate the individualized probability of LNM among patients with ICC in the preoperative setting.

Although LND has been well accepted for extrahepatic cholangiocarcinoma, the role of routine LND has been a matter of debate for ICC.[6, 10, 19] Recent data from the National Cancer Database noted that only half of patients have pathologic evaluation of at least one regional LN,[20] although LNM is universally cited as an important adverse prognostic factor.[4, 6, 8, 10] Of note, the number as well as the station of LNM have been associated with outcomes among patients with ICC.[9] Proponents of LND note the importance of accurate staging of the disease, which in turn may guide decisions around adjuvant chemotherapy.[18] In contrast, possible higher morbidity rates associated with LND have limited its routine use in the clinical setting.[6] In addition, the moderate accuracy of preoperative imaging to detect LNM prior to surgery has also added to the low rates of LND among patients with resectable ICC.[21, 22] Similar to previous studies,[5, 6, 8, 10] the current study confirmed an overall low use of LND (45.3%) even among major HPB centers. In turn, this might have led to mis- or under-staging and incorrect prognostic classification of a considerable number of patients.[12] As such, better preoperative tools are necessary to predict the likelihood of LNM among patients with ICC and characterize patients at risk of LNM who should definitely be offered LND.

Preoperative assessment of the nodal basin in ICC has been challenging.[5] Previous data have suggested a low accuracy of CT and MRI scan to identify LNM, with a sensitivity of only 40–50% and specificity of 77–92%.[21, 22] In addition, although PET-CT has somewhat improved the accuracy of LNM detection, its use to identify LNM in the clinical setting has been limited.[23] The current study revealed a notable 34.2% discordance rate between radiologic and pathologic assessment of LNs, highlighting the need for more accurate assessment of LN status in the preoperative setting. Previous investigators have attempted to preoperatively predict LNM associated with ICC.[24, 25] Meng and colleagues proposed a nomogram that was based on preoperative CA19-9 levels, primary tumor site, size of LNs on CT imaging, and tumor growth pattern to predict LNM in ICC.[24] Another group suggested a radiomics nomogram that incorporated eight LN status–related features and preoperative CA19-9 to predict LNM and facilitate clinical decision-making.[25] Yet, both of these nomograms were highly dependent on radiologists (i.e., LN size, tumor growth pattern) and specialized technicians (i.e., radiomics signatures) to obtain clinically useful information.

The current study developed an easy-to-use, enhanced imaging model to predict LNM following resection for ICC. By incorporating factors that are readily available (i.e., age, number of lesions, CA19-9 levels, and ALBI grade) along with the preoperative LN assessment into a single model, the current study developed a novel risk score (enhanced imaging model, c-index 0.702) that significantly improved the accuracy of preoperative imaging alone (c-index 0.660). In addition, the enhanced imaging model outperformed the CRS that was based solely on clinical data (c-index 0.637, Fig. 1). Of note, by incorporating age, number of lesions, CA19-9 levels, and ALBI grade along with the radiologic assessment of LNs, the enhanced clinical model was able to stratify patients according to the risk for LNM (low risk, 42.3%; high risk, 57.7%). While preoperative imaging did not adequately discriminate OS and DSS, the enhanced imaging model stratified prognosis in a way that closely resembled that of actual pathologic LN status (Fig. 2). Specifically, 5-year OS was 48.4% among low risk for LNM patients versus 18.4% among high-risk individuals ($p < 0.001$). Similarly, N0 patients had a 5-year OS of 45.4% vs. 8.6% among N1 patients ($p < 0.001$). Another interesting finding of the current study was that the enhanced clinical model could also stratify prognosis among patients who were not offered LND (Nx). Indeed, 5-year OS and DSS among Nx patients with low risk for LNM was comparable with that of N0 patients, while high-risk Nx patients had similar outcomes with N1 patients (Fig. 3). Taken together, the current study suggests that incorporating clinical data into the radiologic assessment can significantly enhance the prediction of LNM and, thus, can be particularly helpful for surgeons treating patients with ICC. In turn, by using the online calculator proposed in the current study (https://k-sahara.shinyapps.io/ICC_imaging/), surgeons can preoperatively estimate the individualized probability of a specific patient to have LNM. While lymphadenectomy is generally recommended for all patients at the time of ICC resection, the enhanced imaging model when used in the preoperative setting may help define whether LNs likely harbor metastatic disease and inform physicians to perform lymphadenectomy at the time of surgery. The enhanced imaging model may also be helpful to identify high-risk patients who may benefit from neoadjuvant chemotherapy prior to resection, although future clinical trials are needed to investigate this approach. Data from the current study suggest, however, that the enhanced imaging model may represent an opportunity to stratify prognosis of patients who did not undergo LND (Nx).

The results of the current study should be interpreted in light of certain limitations. As with all retrospective studies, selection bias was possible. Patients with more aggressive tumor biology may have been underrepresented because these patients likely were less likely to be offered resection. In addition, surgical techniques and perioperative management may have varied among the participating institutions. Furthermore, the decision to perform LND at the time of resection may have varied according to the individual surgeon and institutional practices. While preoperative LN assessment was based on CT, MRI, or PET-CT, variations in the evaluation of positive/suspicious LNs may also exist depending on the method of assessment and the operator expertise among the different centers. The current study, however, included data from 15 high-volume international centers and, thus, provide a good representation of the surgical practice of ICC at major HPB centers worldwide.

In conclusion, approximately one third of patients undergoing curative-intent resection of ICC had discordant radiologic–pathologic assessment of the nodal basin. A novel, easy-to-use enhanced imaging model was developed based on both clinical and imaging data to predict LNM prior to resection. The enhanced imaging model demonstrated a very good accuracy on internal validation and outperformed preoperative imaging alone. A convenient online calculator was developed to enhance clinical applicability of the model. This tool may aid in the clinical decision-making prior to resection of ICC and may represent an opportunity to more accurately stratify prognosis of Nx patients.

Acknowledgments none

Funding none

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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