Ann Surg Oncol (2019) 26:2242–2250
https://doi.org/10.1245/s10434-019-07336-5

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Should Utilization of Lymphadenectomy Vary According to Morphologic Subtype of Intrahepatic Cholangiocarcinoma?

Xu-Feng Zhang, MD, PhD[1,2], Yi Lv, MD, PhD[1], Matthew Weiss, MD[3], Irinel Popescu, MD[4], Hugo P. Marques, MD[5], Luca Aldrighetti, MD[6], Shishir K. Maithel, MD[7], Carlo Pulitano, MD[8], Todd W. Bauer, MD[9], Feng Shen, MD[10], George A. Poultsides, MD[11], Oliver Soubrane, MD[12], Guillaume Martel, MD[13], B. Groot Koerkamp, MD[14], Endo Itaru, MD[15], and Timothy M. Pawlik, MD, MPH, PhD[2,16]

[1]Department of Hepatobiliary Surgery and Institute of Advanced Surgical Technology and Engineering, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China; [2]Department of Surgery, The Urban Meyer III and Shelley Meyer Chair for Cancer Research, The Ohio State University Wexner Medical Center, Columbus, OH; [3]Department of Surgery, Johns Hopkins Hospital, Baltimore, MD; [4]Department of Surgery, Fundeni Clinical Institute, Bucharest, Romania; [5]Department of Surgery, Curry Cabral Hospital, Lisbon, Portugal; [6]Department of Surgery, Ospedale San Raffaele, Milan, Italy; [7]Department of Surgery, Emory University, Atlanta, GA; [8]Department of Surgery, Royal Prince Alfred Hospital, University of Sydney, Sydney, NSW, Australia; [9]Department of Surgery, University of Virginia, Charlottesville, VA; [10]Department of Surgery, Eastern Hepatobiliary Surgery Hospital, Shanghai, China; [11]Department of Surgery, Stanford University, Stanford, CA; [12]Department of Hepatobiliopancreatic Surgery and Liver Transplantation, AP-HP, Beaujon Hospital, Clichy, France; [13]Division of General Surgery, Department of Surgery, University of Ottawa, Ottawa, ON, Canada; [14]Department of Surgery, Erasmus University Medical Centre, Rotterdam, The Netherlands; [15]Gastroenterological Surgery Division, Yokohama City University School of Medicine, Yokohama, Japan; [16]Department of Surgery, Oncology, Health Services Management and Policy, The Ohio State University Wexner Medical Center, Columbus, OH

ABSTRACT

Objective. We sought to evaluate the utilization of lymphadenectomy (LND) and the incidence of lymph node metastasis (LNM) among different morphologic types of intrahepatic cholangiocarcinoma (ICC).

Methods. Clinical data of patients undergoing curative-intent resection for ICC between 1990 and 2017 were collected and analyzed. The preoperative nodal status was evaluated by imaging studies, and the morphologic and lymph node (LN) status was collected on final pathology report.

Results. Overall, 1032 patients had a mass-forming (MF) or intraductal growth (IG) ICC subtype, whereas 150 patients had a periductal infiltrating (PI) or MF + PI subtype. Among the 924 patients with MF/IG ICC subtype who had nodal assessment on preoperative imaging, 747 (80.8%) were node-negative, whereas 177 (19.2%) patients were suspicious for metastatic nodal disease. On final pathological analysis, 71 of 282 (25.2%) patients who had preoperative node-negative disease ultimately had LNM. In contrast, 79 of 135 (58.5%) patients with preoperative suspicious/metastatic LNs had pathologically confirmed LNM (odds ratio [OR] 4.2, $p < 0.001$). Among the 129 patients with PI/MF + PI ICC subtype and preoperative nodal information, 72 (55.8%) were node-negative on preoperative imaging. In contrast, 57 (44.2%) patients had suspicious/metastatic LNs. On final pathologic examination, 45.3% ($n = 24$) of patients believed to be node-negative on preoperative imaging had LNM; 68.0% ($n = 34$) of patients who had suspicious/positive nodal disease on imaging ultimately had LNM (OR 2.6, $p = 0.009$).

Electronic supplementary material The online version of this article (https://doi.org/10.1245/s10434-019-07336-5) contains supplementary material, which is available to authorized users.

First Received: 10 December 2018;
Published Online: 29 March 2019

T. M. Pawlik, MD, MPH, PhD
e-mail: tim.pawlik@osumc.edu

Conclusion. Given the low accuracy of preoperative imaging evaluation of nodal status, routine LND should be performed at the time of resection for both MF/IG and PI/MF + PI ICC subtypes.

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver cancer after hepatocellular carcinoma (HCC). Surgical resection remains the only potentially curative treatment option.[1] Based on the classification of the Liver Cancer Study Group of Japan, ICC can be classified into three subtypes: mass-forming (MF), periductal infiltrating (PI), and intraductal growth (IG).[2] Several studies have demonstrated that morphological status can impact the long-term outcomes of ICC patients.[3–6] For example, Bagante et al.[3] demonstrated that the PI/MF + PI ICC subtype was associated with worse overall survival (OS) compared with the MF/IG subtype. In a separate study, Shimada et al.[4] reported that MF + PI ICC had a higher risk of local recurrence. In fact, ICC morphology may be associated with differences in pathogenesis and cellular origin, as well as distinct biological progression.[3,7–10] For example, the PI and MF + PI ICC subtypes have been associated with hepatolithiasis, primary sclerosing cholangitis, and choledochal cyst, as well as origination from large bile duct epithelium and peribiliary glands with a higher incidence of extrahepatic bile duct/major vascular invasion and lymph node metastasis (LNM).[7–9,11] In contrast, the MF ICC subtype is more often induced by chronic hepatitis and typically arises from peripheral small bile ducts or hepatic progenitor cells characterized by more expansive HCC-like growth patterns and a lower risk of lymphatic and perineural invasion.[7–9,11]

The role of lymphadenectomy (LND) at the time of surgery for ICC remains controversial as some surgeons perform LND routinely, whereas other surgeons only perform LND selectively.[12,13] Given the questionable sensitivity and specificity of imaging to detect LNMs, some surgeons advocate systematic removal of lymph nodes (LNs) for accurate staging and potential decrease in local recurrence.[1,14–16] Morphologic status of ICC may be an important determinant in LND utilization as some investigators have recommended omission of LND for the MF or IG ICC subtypes due to a suspected lower ICC incidence of LNM.[17–22] However, these data have been questioned as most previous studies were small, single-institution case series.[17–19,21,22] Therefore, the objective of the current study was to investigate the impact of ICC morphologic status on LND utilization, as well as define the incidence of LNM stratified by preoperative imaging-based nodal status. In addition, we sought to characterize the incidence of LNM among patients with the MF/IG versus PI/MF + PI ICC subtypes using a large, multi-institutional database.

PATIENTS AND METHODS

Study Cohort

Patients undergoing curative-intent resection (R0/R1) for ICC between April 1990 and August 2017 were identified from a multi-institutional database from 15 hepatobiliary centers in North America, Europe, Australia, and Asia. The Institutional Review Boards at each participating institution approved the study.

Data Collection

A standardized datasheet was created for collection of the clinicopathologic and surgical information. Preoperative LN status was evaluated by imaging studies including computed tomography (CT), magnetic resonance imaging (MRI), and/or positron emission tomography-computed tomography (PET-CT). 'Suspicious' or 'positive' LNs were defined as nodes abnormally shaped or swollen, as detected by imaging studies such as CT, MRI, etc. Tumor-related characteristics, including maximal tumor diameter, number, location, tumor morphology, histological grade, invasion of adjacent organs, major vascular invasion, microvascular/perineural invasion, satellite lesions, number of LNs harvested, and number of metastatic LNs were collected based on final pathology. Pathologic staging was assigned according to the 8th edition of the American Joint Committee on Cancer (AJCC) staging guidelines.[23] The morphological status of ICC was grouped as MF/IG and PI/MF + PI ICC subtypes. For all cases, the imaging and pathological data were reviewed to determine the macroscopic morphologic subtypes. LND was defined as nodal harvested in hepatoduodenal ligaments, with or without common hepatic artery, celiac artery, and/or peripancreas. Resection margin status was defined as R0 for a tumor margin that was microscopically negative, and R1 for a tumor margin that was microscopically positive.

Statistical Analysis

Continuous variables were expressed as medians with interquartile ranges (IQRs) and compared using the Mann–Whitney U test or Kruskal–Wallis test as appropriate. Categorical variables were expressed as number and percentages and compared using the Chi square test or Fisher's exact test. Kaplan–Meier curves were used to estimate median OS, and the log-rank test was used to assess differences in OS. Factors associated with utilization of LND and LNM among MF/IG and PI/MF + PI ICC patients were identified using univariate and multivariate logistic regression models. Odds ratios (OR) and 95% confidence intervals (CI) were estimated. Variables with a

p value < 0.05 on univariate analysis were included in the multivariate models. A two-tailed p value of < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 21.0 (IBM SPSS Inc., Chicago, IL, USA).

RESULTS

Patient Characteristics and Nodal Assessment

Among 1182 patients who underwent curative-intent resection, 999 (84.5%) had the MF subtype, 33 (2.8%) had the IG subtype, 66 (5.6%) had the PI subtype, and 84 (7.1%) had the MF + PI subtype. The OS of patients with the IG subtype was similar to patients with the MF subtype after surgery (median OS, IG 37.0 vs. MF 37.0 months, $p = 0.944$), while the OS of patients with the PI or MF + PI subtypes was worse (median OS, PI 17.0 months, MF + PI 19.9 months, $p < 0.05$, vs. IG or MF subtype). As such, patients were classified as MF/IG subtype ($n = 1032$) and PI/MF + PI ICC subtype ($n = 150$). Obviously, patients with the PI/MF + PI ICC subtype had more aggressive tumor characteristics (e.g. higher incidence of vascular invasion, nodal metastasis, etc.) and underwent more aggressive resection (e.g. higher percentage of major vascular/bile duct resection and LND, longer operation time, higher intraoperative blood loss, etc.) (electronic supplementary Table 1).

Among the 924 patients with the MF/IG ICC subtype who had nodal assessment on preoperative imaging, 747 (80.8%) were classified as node-negative, whereas 177 (19.2%) patients had regional LNs that were suspicious or believed to be positive for metastatic disease. Patients who had suspicious or metastatic nodes on preoperative imaging were more likely to undergo LND at the time of surgery (76.3%) compared with patients who had nodes deemed normal on preoperative imaging (37.8%; OR 5.3, 95% CI 3.6–7.7, $p < 0.001$) (Fig. 1a). On final pathological analysis, 71 of 282 (25.2%) patients who were preoperatively considered to have node-negative disease ultimately had LNM. In contrast, 79 of the 135 (58.5%) patients with preoperative suspicious/metastatic LNs ultimately had pathologically confirmed LNM (OR 4.2, 95% CI 2.7–6.5, $p < 0.001$) (Fig. 1b). Therefore, the specificity and sensitivity of preoperative imaging examination to detect pathological nodal metastasis among patients with the MF/IG ICC subtype were 74.8% and 58.5%, respectively.

Among the 129 patients with the PI/MF + PI ICC subtype who had detailed information on preoperative nodal assessment, 72 (55.8%) were deemed to be node-negative on preoperative imaging. In contrast, 57 (44.2%) patients had suspicious/metastatic LNs. Utilization of LND among patients with PI/MF + PI was only slightly higher among individuals who had preoperatively suspicious/metastatic LNs (87.7%) versus individuals with nodal disease that was not suspicious (73.6%; $p = 0.076$) (Fig. 1c). On final pathologic examination, among patients with the PI/MF + PI ICC subtype, 45.3% ($n = 24$) believed to be node-negative based on preoperative imaging were ultimately noted to have LNM; 68.0% ($n = 34$) of patients who were thought to have suspicious/node-positive disease on preoperative imaging ultimately had LNM (OR 2.6, 95% CI 1.2–5.7, $p = 0.009$) (Fig. 1d). As such, the specificity and sensitivity of preoperative imaging to detect nodal metastasis among patients with the PI/MF + PI ICC subtype were 54.5% and 68.0%, respectively.

Factors Associated with Performance of Lymphadenectomy and Risk of Lymph Node Metastasis

Patients with no use of LND (Nx) had less-aggressive tumor characteristics and underwent less-aggressive procedures than patients with N0 or N1 status (electronic supplementary Tables 2 and 3). Several factors were associated with the performance of LND on multivariate analysis. Specifically, patients who had suspicious LNs or nodes deemed to be metastatic on preoperative imaging (OR 4.9, 95% CI 3.2–7.6), as well as patients who had more advanced T (T1a referent: T2; OR 3.3, 95% CI 1.8–6.1) and bilateral (OR 1.8, 95% CI 1.1–2.8) disease were more likely to undergo LND (all $p < 0.05$) (Table 1). Overall, patients who had the PI/MF + PI ICC subtype had a higher odds of LND compared with patients who had the MF/IG subtype (OR 4.4, 95% CI 2.9–6.7; $p < 0.001$). Among patients with PI/MF + PI ICC subtype, performance of LND correlated with bile duct resection (OR 4.1, 95% CI 1.1–15.4) (Table 2), while major hepatic resection (OR 3.0, 95% CI 2.2–4.2) and concomitant bile duct resection (OR 3.1, 95% CI 1.6–5.8) were associated with LND among patients with the MF/IG ICC subtype (all $p < 0.05$) (Table 1). Of note, nodal status based on preoperative imaging evaluation was associated with LND utilization among patients with the MF/IG subtype, but not patients with the PI/MF + PI ICC subtype (Tables 1, 2).

The risk of LNM on final pathology was associated with certain preoperative and tumor-related factors. On multivariate analysis, preoperative imaging that suggested suspicious or metastatic nodal status (OR 3.8, 95% CI 2.0–7.1), preoperative carcinoembryonic antigen (CEA) > 10 ng/mL (OR 5.1, 95% CI 1.6–16.2), and major vascular invasion (OR 3.5, 95% CI 1.2–10.2) were each strongly associated with the risk of LNM among patients with the MF/IG ICC subtype ($p < 0.05$) (Table 3). Among patients with PI/MF + PI ICC, bilateral disease (OR 3.3,

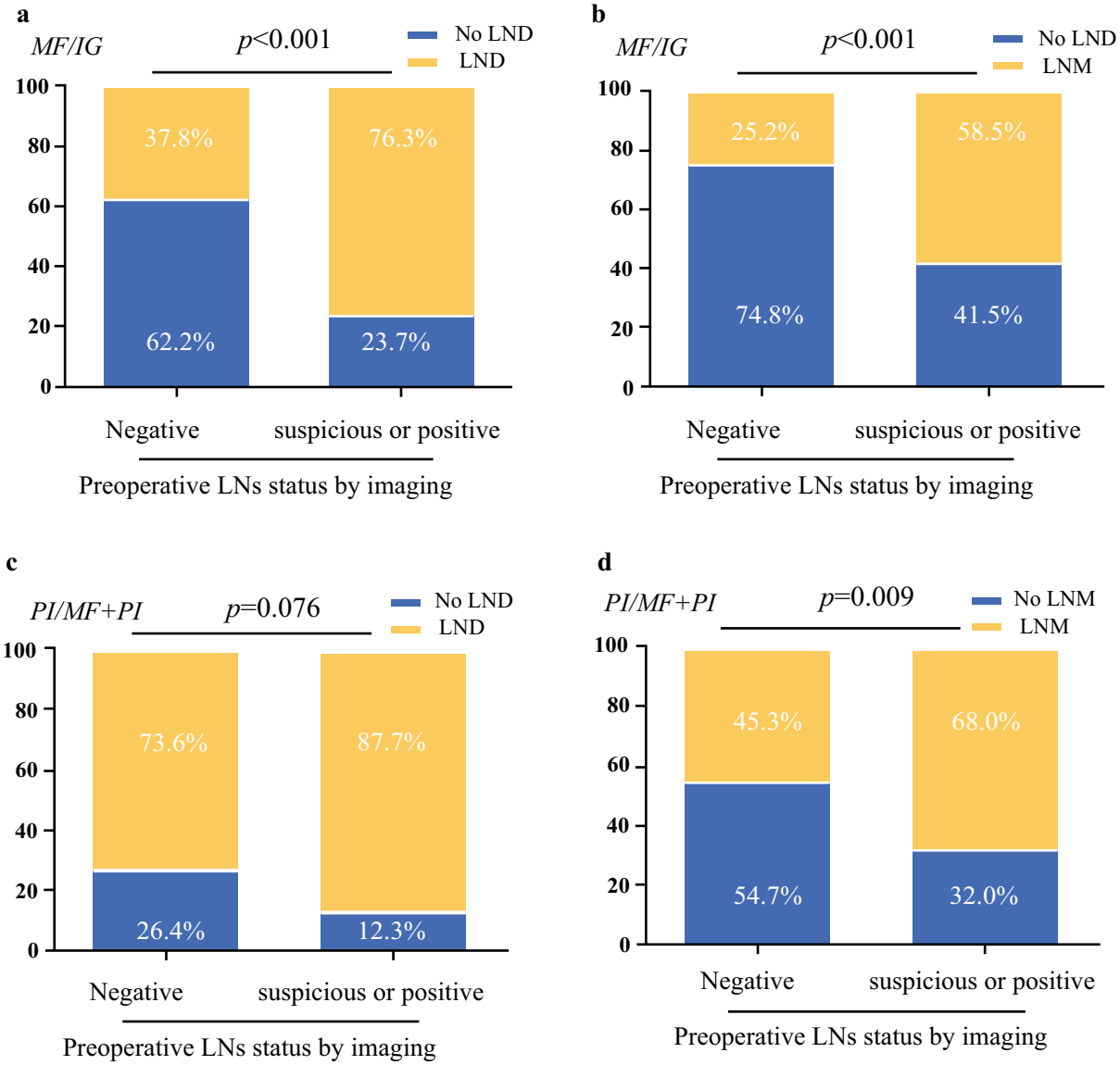

FIG. 1 **a** Performance of LND and **b** incidence of LNM stratified by nodal status on preoperative imaging among patients with MF or IG ICC subtypes. **c** Performance of LND and **d** incidence of LNM stratified by nodal status on preoperative imaging among patients with PI or MF + PI ICC subtypes. *MF* mass-forming, *IG* intraductal growth, *ICCs* intrahepatic cholangiocarcinomas, *PI* periductal infiltrating, *LND* lymphadenectomy, *LNM* lymph node metastasis, *LNs* lymph nodes

95% CI 1.2–9.1) and six or more nodes harvested (OR 2.0, 95% CI 1.1–3.9) were independently associated with the likelihood of finding LNM on final pathology (both $p < 0.05$), however preoperative imaging that suggested suspicious or metastatic nodal status was not (OR 1.9, 95% CI 0.8–4.5; $p = 0.148$) (Table 4).

Additionally, patients who did not undergo nodal dissection (Nx) had worse OS than patients with N0 disease among both the MF/IG ICC subtype (median OS, Nx 43.0 vs. N0 46.0, $p = 0.042$) (electronic supplementary Fig. 1a) and the PI/MF + PI ICC subtype (median OS, Nx 12.0 vs. N0 34.0, $p < 0.001$) (electronic supplementary Fig. 1b).

DISCUSSION

The role of LND for ICC remains controversial, despite the fact that several groups have reported an incidence of LNM ranging from 17 to 65%.[1,19,24–27] In fact, studies have revealed that different ICC tumor morphologies can be associated with distinct cellular origin, clinicopathologic characteristics, and outcomes,[3,7–10] As such, some authors recommended omission of routine LND in MF or IG ICC subtypes as these two subtypes always present with a low incidence of nodal metastasis, and thus good prognosis after resection.[17–22] Data on the incidence of LN disease, and whether LND should be performed relative to ICC

TABLE 1 Pre- and intraoperative factors associated with decision of lymphadenectomy for MF/IG ICC in a logistic regression model

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Preoperative nodal evaluation		< 0.001		< 0.001
Negative	Reference		Reference	
Suspicious or positive	5.3 (3.6–7.7)		4.9 (3.2–7.6)	
Tumor size, cm		< 0.001		0.323
≤ 5	Reference		Reference	
> 5	1.9 (1.5–2.5)		1.3 (0.8–2.3)	
AJCC T stage				
T1a	Reference		Reference	
T1b	1.9 (1.4–2.6)	< 0.001	1.3 (0.6–2.5)	0.489
T2	4.4 (3.0–6.4)	< 0.001	3.3 (1.8–6.1)	< 0.001
T3	3.1 (2.0–4.8)	< 0.001	1.2 (0.3–5.7)	0.852
T4	2.5 (1.3–4.7)	0.006	0.8 (0.3–2.4)	0.740
Multiple tumors	1.7 (1.2–2.4)	0.006	1.6 (0.4–6.7)	0.534
Bilobar tumors	2.7 (1.9–3.9)	< 0.001	1.8 (1.1–2.8)	0.012
Major vascular invasion	2.8 (1.8–4.5)	< 0.001	0.9 (0.4–1.9)	0.807
Direct invasion of adjacent organs	1.4 (0.8–2.6)	0.257		
Satellite lesions	1.3 (0.9–1.8)	0.186		
Surgical procedure		< 0.001		< 0.001
Minor hepatectomy	Reference		Reference	
Major hepatectomy	4.7 (3.6–6.3)		3.0 (2.2–4.2)	
Major vascular resection	3.5 (2.2–5.7)	< 0.001	1.6 (0.7–3.4)	0.226
Bile duct resection	6.6 (3.9–11.2)	< 0.001	3.1 (1.6–5.8)	0.001

MF mass-forming, *IG* intraductal growth, *ICC* intrahepatic cholangiocarcinomas, *OR* odds ratio, *CI* confidence interval, *AJCC* American Joint Committee on Cancer

tumor morphology, remain poorly defined. The current study was important because we specifically characterized LND utilization, as well as the incidence of LNM relative to ICC morphological subtype. In addition, preoperative nodal imaging was assessed relative to final pathology to estimate the overall accuracy to predict LNM. Among patients with MF/IG ICC subtype, only approximately one-third underwent LND if preoperative imaging suggested node-negative disease. However, among MF/IG patients who were suspected, preoperatively, of being node-negative yet underwent LND, one in four ended up having nodal metastasis on final pathologic examination. Interestingly, most patients (73.6%) with the PI/MF + PI subtype underwent LND regardless of preoperative imaging nodal status. In turn, approximately half of the patients with PI/MF + PI who had no suspicious disease on preoperative imaging had LNM on final pathology. Collectively, these data strongly suggest that the incidence of LNM ranged from 25 to 50% regardless of ICC morphologic subtype, and preoperative imaging was not accurate in identifying which patients had metastatic disease to the nodal basin.

Patients with the MF and IG subtypes have been reported to have a better prognosis, with a lower incidence of perineural, vascular, and lymphatic invasion. In contrast, PI and MF + PI tumors have been suggested to have a higher tendency of vascular and LN involvement along Glisson's sheath.[3,8,9,11] In addition, distinct cells of origin may be associated with different morphologic subtypes, with MF arising from hepatic precursor cells and adult hepatocytes.[8,9,28,29] As such, some investigators have argued that the MF ICC subtype is more like HCC and does not warrant routine LND.[17–19] In the current study, the overall incidence of LNM among patients with MF/IG was actually fairly high at 35.9%. Interestingly, the incidence of LNM among patients with MF/IG ICC was not too dissimilar to the incidence of LNM reported among patients with fibrolamellar HCC.[30,31] Given the 30–40% incidence of nodal metastasis for fibrolamellar HCC, routine LND for this disease has been widely adopted.[30,31] The incidence of LNM was even higher among patients with PI/MF + PI (56.3%). As such, given the comparable incidence of LNM among patients with MF/IG ICC and fibrolamellar HCC, as

TABLE 2 Pre- and intraoperative factors associated with decision of lymphadenectomy for PI/MF + PI ICC in a logistic regression model

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Preoperative nodal evaluation		0.052		0.079
Negative	Reference		Reference	
Suspicious or positive	2.6 (1.0–6.7)		3.4 (0.9–12.9)	
Tumor size, cm		0.501		
≤ 5	Reference			
> 5	0.8 (0.3–1.7)			
AJCC T stage				
T1a	Reference			
T1b	2.5 (0.6–11.0)	0.213		
T2	2.1 (0.7–6.8)	0.201		
T3	3.3 (0.4–30.7)	0.285		
T4	0.4 (0.1–1.2)	0.086		
Multiple tumors	0.7 (0.2–2.3)	0.546		
Bilobar tumors	1.1 (0.4–2.9)	0.826		
Major vascular invasion	1.3 (0.5–3.9)	0.601		
Direct invasion of adjacent organs	0.2 (0.1–0.4)	< 0.001	0.1 (0.0–0.3)	< 0.001
Satellite lesions	0.4 (0.1–1.0)	0.042	0.5 (0.2–1.6)	0.248
Surgical procedure		0.044		0.797
Minor hepatectomy	Reference		Reference	
Major hepatectomy	3.3 (1.0–10.4)		1.3 (0.2–8.0)	
Major vascular resection	1.9 (0.7–5.4)	0.242		
Bile duct resection	4.9 (1.8–13.0)	0.002	4.1 (1.1–15.4)	0.037

PI periductal infiltrating, *MF* mass-forming, *ICC* intrahepatic cholangiocarcinomas, *OR* odds ratio, *CI* confidence interval, *AJCC* American Joint Committee on Cancer

well as the high rate of LNM among patients with PI/MF + PI, routine LND for all patients with ICC should strongly be considered.

Data from the current study demonstrate that reliance on preoperative imaging to identify patients with LNM may be misplaced. The specificity and sensitivity of preoperative imaging analysis for LNM were only 74.8% and 58.5% among patients with the MF/IG subtype, and 54.5% and 68.0% among individuals with PI/MF + PI ICC, respectively. These findings were consistent with previous studies that preoperative imaging assessment for LN metastasis by CT or MRI scan is unsatisfactory. For example, the accuracy of CT and MRI to identify LNM was low, with a sensitivity of only 40–50% and specificity of 77–92%.[14,32] Although PET-CT has somewhat improved the accuracy of LNM detection, it remains useless for identification of metastatic nodes in clinical settings.[32] In fact, the incidence of LNM by final histological assessment was high among MF/IG (25%) and PI/MF + PI ICC subtype patients (45%) who had negative nodes on preoperative imaging yet underwent LND. While several factors were associated with the risk of LNM (e.g. CEA level, bilateral disease), predictive models to predict LNM preoperatively have not performed well.[15] As such, routine histological assessment by LND appears to be the only accurate way to diagnose LNM and provide accurate staging, and may reduce the risk of local recurrence.[14,15,27]

Another interesting finding in the current study was that utilization of LND was much lower among patients with MF/IG versus PI/MF + PI ICC (46.4% vs. 72.0%). In addition, surgeons seemed to rely more on preoperative nodal imaging to decide whether to perform LND among patients with MF/IG ICC, but not PI/MF + PI ICC. These data suggest that surgeons tended to use LND more selectively among MF/IG tumors, but had more liberal use of LND for PI/MF + PI ICC. In addition, bile duct resection was associated with utilization of LND at the time of resection for both MF/IG and PI/MF + PI ICC subtypes. To achieve curative resection for ICC, concomitant bile duct or vascular resection is occasionally performed in up to 20% and 5% of cases, respectively.[33,34] When LND was performed and LNMs were detected, the impact of LN status was comparable among patients regardless of morphologic tumor type. Specifically, patients with N1 disease had a markedly worse prognosis compared with patients who had N0 disease, regardless of

TABLE 3 Pre- and intraoperative factors predicting lymph nodes metastasis of MF/IG ICC in a logistic regression model

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age, years		0.145		
≤ 65	Reference			
> 65	0.7 (0.5–1.1)			
Sex, male versus female	0.9 (0.6–1.3)	0.582		
Preoperative nodal evaluation		< 0.001		< 0.001
Negative	Reference		Reference	
Suspicious or positive	4.2 (2.7–6.5)		3.8 (2.0–7.1)	
CA19-9, U/mL		0.015		0.550
≤ 50	Reference		Reference	
> 50	1.7 (1.1–2.7)		1.2 (0.6–2.3)	
CEA, ng/mL		< 0.001		0.006
≤ 10	Reference		Reference	
> 10	5.5 (2.2–14.0)		5.1 (1.6–16.2)	
Tumor size, cm		0.045		0.327
≤ 5	Reference		Reference	
> 5	1.5 (1.0–2.2)		1.6 (0.6–4.1)	
Multiple tumors	1.2 (0.8–1.9)	0.393		
Bilobar tumors	0.9 (0.5–1.4)	0.602		
Major vascular invasion	2.0 (1.2–3.5)	0.009	3.5 (1.2–10.2)	0.024
Direct invasion of adjacent organs	2.7 (1.1–6.3)	0.024	1.1 (0.2–6.2)	0.901
AJCC T stage				
T1a	Reference		Reference	
T1b	1.3 (0.7–2.2)	0.393	− 0.6 (0.2–2.1)	0.401
T2	1.7 (1.0–2.9)	0.073	0.5 (0.2–1.8)	0.323
T3	1.5 (0.8–2.9)	0.229	1.2 (0.4–4.2)	0.752
T4	3.5 (1.3–8.8)	0.010	1.9 (1.0–2.1)	0.123
Number of lymph nodes harvested		0.001		0.550
1–5	Reference		Reference	
≥ 6	1.8 (1.3–2.5)		1.5 (0.8–2.8)	

MF mass-forming, *IG* intraductal growth, *ICC* intrahepatic cholangiocarcinomas, *OR* odds ratio, *CI* confidence interval, *CA19-9* cancer antigen 19-9, *CEA* carcinoembryonic antigen, *AJCC* American Joint Committee on Cancer

whether the morphologic subtype was MF/IG or PI/MF + PI. In addition, the long-term survival of patients who did not undergo LND (Nx) was worse than N0 patients among both the MF/IG and PI/MF + PI subtypes, suggesting that these patients were understaged. In turn, Nx patients likely represent a heterogeneous cohort that included both patients with node-negative and metastatic disease. Therefore, regional LND is needed to stage patients accurately in order to stratify patients with regard to prognosis, as well as consideration for adjuvant therapy.[35]

The current study had several limitations. Although preoperative imaging data on nodal evaluation was documented based on CT, MRI, or PET-CT, there likely was inconsistency in the diagnostic criteria for nodal swelling among each modality and among different institutions. As a retrospective study, the indication for LND also likely varied among each center and may have been impacted by factors other than those accounted for in the current study (e.g. preoperative nodal status, tumor morphologic subtype, etc.). However, data from the current study included 15 international high-volume centers and therefore provide a general good representation of current surgical practice of ICC worldwide at major hepatobiliary centers.

CONCLUSION

The MF/IG subtype differs from the PI/MF + PI subtype of ICC in clinicopathologic features, as well as surgical outcomes. Preoperative imaging evaluation of

TABLE 4 Pre- and intraoperative factors predicting lymph nodes metastasis of PI/MF + PI ICC in a logistic regression model

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age, years		0.403		
≤ 65	Reference			
> 65	1.4 (0.6–2.9)			
Sex, male versus female	0.8 (0.4–1.7)	0.620		
Preoperative nodal evaluation		0.021		0.148
Negative	Reference		Reference	
Suspicious or positive	2.6 (1.2–5.7)		1.9 (0.8–4.5)	
CA19-9, U/mL		0.399		
≤ 50	Reference			
> 50	1.5 (0.6–3.6)			
CEA, ng/mL		0.876		
≤ 10	Reference			
> 10	1.1 (0.3–4.4)			
Tumor size, cm		0.010		0.092
≤ 5	Reference		Reference	
> 5	0.4 (0.2–0.8)		0.5 (0.2–1.4)	
Multiple tumors	1.7 (0.5–6.0)	0.411		
Bilobar tumors	2.4 (1.0–5.9)	0.047	3.3 (1.2–9.1)	0.023
Major vascular invasion	1.9 (0.8–4.8)	0.201		
Direct invasion of adjacent organs	1.3 (0.4–4.4)	0.642		
AJCC T stage				
T1a	Reference			
T1b	0.3 (0.1–1.0)	0.059		
T2	1.4 (0.5–4.0)	0.474		
T3	1.3 (0.3–5.9)	0.694		
T4	1.2 (0.3–4.9)	0.769		
Number of lymph nodes harvested		0.018		0.034
1–5	Reference		Reference	
≥ 6	2.0 (1.1–3.5)		2.0 (1.1–3.9)	

PI periductal infiltrating, *MF* mass-forming, *ICC* intrahepatic cholangiocarcinomas, *OR* odds ratio, *CI* confidence interval, *CA19-9* cancer antigen 19-9, *CEA* carcinoembryonic antigen, *AJCC* American Joint Committee on Cancer

nodal status had low accuracy in predicting nodal metastasis among either type of ICCs. One in four patients undergoing resection of MF/IG ICC subtypes with LND, and almost half of the patients undergoing resection of PI/MF + PI ICC subtypes with LND had nodal metastasis, even when preoperative imaging suspected no nodal disease. Data from the current study suggest that routine LND should be performed at the time of resection for both MF/IG and PI/MF + PI ICC subtypes to achieve curative resection of ICC, clear the locoregional LN basin, and provide accurate staging to guide adjuvant therapy.

ACKNOWLEDGMENT Xu-Feng Zhang was supported by the Clinical Research Award of the First Affiliated Hospital of Xi'an Jiaotong University of China (No. XJTU1AF-CRF-2017-004).

DISCLOSURE Xu-Feng Zhang, Yi Lv, Matthew Weiss, Irinel Popescu, Hugo P. Marques, Luca Aldrighetti, Shishir K. Maithel, Carlo Pulitano, Todd W. Bauer, Feng Shen, George A. Poultsides, Oliver Soubrane, Guillaume Martel, B. Groot Koerkamp, Endo Itaru, and Timothy M. Pawlik have no financial or commercial interests to disclose.

REFERENCES

1. de Jong MC, Nathan H, Sotiropoulos GC, et al. Intrahepatic cholangiocarcinoma: an international multi-institutional analysis of prognostic factors and lymph node assessment. *J Clin Oncol.* 2011;29:3140-5.
2. Yamasaki S. Intrahepatic cholangiocarcinoma: macroscopic type and stage classification. *J Hepatobiliary Pancreat Surg.* 2003;10:288–91.
3. Bagante F, Spolverato G, Weiss M, et al. Impact of morphological status on long-term outcome among patients undergoing liver

surgery for intrahepatic cholangiocarcinoma. *Ann Surg Oncol.* 2017;24:2491–501.
4. Shimada K, Sano T, Sakamoto Y, Esaki M, Kosuge T, Ojima H. Surgical outcomes of the mass-forming plus periductal infiltrating types of intrahepatic cholangiocarcinoma: a comparative study with the typical mass-forming type of intrahepatic cholangiocarcinoma. *World J Surg.* 2007;31:2016–22.
5. Ohtsuka M, Ito H, Kimura F, et al. Results of surgical treatment for intrahepatic cholangiocarcinoma and clinicopathological factors influencing survival. *Br J Surg.* 2002;89:1525–31.
6. Yamamoto M, Takasaki K, Yoshikawa T, Ueno K, Nakano M. Does gross appearance indicate prognosis in intrahepatic cholangiocarcinoma? *J Surg Oncol.* 1998;69:162–7.
7. Aishima S, Oda Y. Pathogenesis and classification of intrahepatic cholangiocarcinoma: different characters of perihilar large duct type versus peripheral small duct type. *J Hepatobiliary Pancreat Sci.* 2015;22:94–100.
8. Liau JY, Tsai JH, Yuan RH, Chang CN, Lee HJ, Jeng YM. Morphological subclassification of intrahepatic cholangiocarcinoma: etiological, clinicopathological, and molecular features. *Mod Pathol.* 2014;27:1163–73.
9. Sia D, Tovar V, Moeini A, Llovet JM. Intrahepatic cholangiocarcinoma: pathogenesis and rationale for molecular therapies. *Oncogene.* 2013;32:4861–70.
10. Wei M, Lu L, Lin P, Chen Z, Quan Z, Tang Z. Multiple cellular origins and molecular evolution of intrahepatic cholangiocarcinoma. *Cancer Lett.* 2016;379:253–61.
11. Aishima S, Kuroda Y, Nishihara Y, et al. Proposal of progression model for intrahepatic cholangiocarcinoma: clinicopathologic differences between hilar type and peripheral type. *Am J Surg Pathol.* 2007;31:1059–67.
12. Shimada H, Endo I, Togo S, Nakano A, Izumi T, Nakagawara G. The role of lymph node dissection in the treatment of gallbladder carcinoma. *Cancer.* 1997;79:892–9.
13. Kitagawa Y, Nagino M, Kamiya J, et al. Lymph node metastasis from hilar cholangiocarcinoma: audit of 110 patients who underwent regional and paraaortic node dissection. *Ann Surg.* 2001;233:385–92.
14. Morine Y, Shimada M. The value of systematic lymph node dissection for intrahepatic cholangiocarcinoma from the viewpoint of liver lymphatics. *J Gastroenterol.* 2015;50:913–27.
15. Zhang XF, Chakedis J, Bagante F, et al. Trends in use of lymphadenectomy in surgery with curative intent for intrahepatic cholangiocarcinoma. *Br J Surg.* 2018;105:857–66.
16. 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;22:668–75.
17. Miwa S, Miyagawa S, Kobayashi A, et al. Predictive factors for intrahepatic cholangiocarcinoma recurrence in the liver following surgery. *J Gastroenterol.* 2006;41:893–900.
18. Marubashi S, Gotoh K, Takahashi H, et al. Prediction of the postoperative prognosis of intrahepatic cholangiocarcinoma (ICC): importance of preoperatively- determined anatomic invasion level and number of tumors. *Dig Dis Sci.* 2014;59:201–13.
19. Shimada K, Sano T, Nara S, et al. Therapeutic value of lymph node dissection during hepatectomy in patients with intrahepatic cholangiocellular carcinoma with negative lymph node involvement. *Surgery.* 2009;145:411–6.
20. Shimada M, Yamashita Y, Aishima S, Shirabe K, Takenaka K, Sugimachi K. Value of lymph node dissection during resection of intrahepatic cholangiocarcinoma. *Br J Surg.* 2001;88:1463–6.
21. Kim DH, Choi DW, Choi SH, Heo JS, Kow AW. Is there a role for systematic hepatic pedicle lymphadenectomy in intrahepatic cholangiocarcinoma? A review of 17 years of experience in a tertiary institution. *Surgery.* 2015;157:666–75.
22. Li DY, Zhang HB, Yang N, Quan Y, Yang GS. Routine lymph node dissection may be not suitable for all intrahepatic cholangiocarcinoma patients: results of a monocentric series. *World J Gastroenterol.* 2013;19:9084–91.
23. Reames BN, Ejaz A, Koerkamp BG, et al. Impact of major vascular resection on outcomes and survival in patients with intrahepatic cholangiocarcinoma: a multi-institutional analysis. *J Surg Oncol.* 2017;116:133–9.
24. Jutric Z, Johnston WC, Hoen HM, et al. Impact of lymph node status in patients with intrahepatic cholangiocarcinoma treated by major hepatectomy: a review of the National Cancer Database. *HPB (Oxford).* 2016;18:79–87.
25. Bagante F, Gani F, Spolverato G, et al. Intrahepatic cholangiocarcinoma: prognosis of patients who did not undergo lymphadenectomy. *J Am Coll Surg.* 2015;221:1031-40.e1-4.
26. Amini N, Ejaz A, Spolverato G, Maithel SK, Kim Y, Pawlik TM. Management of lymph nodes during resection of hepatocellular carcinoma and intrahepatic cholangiocarcinoma: a systematic review. *J Gastrointest Surg.* 2014;18:2136–48.
27. Bagante F, Spolverato G, Weiss M, et al. Assessment of the lymph node status in patients undergoing liver resection for intrahepatic cholangiocarcinoma: the new eighth edition AJCC staging system. *J Gastrointest Surg.* 2018;22(1):52–59.
28. Palmer WC, Patel T. Are common factors involved in the pathogenesis of primary liver cancers? A meta-analysis of risk factors for intrahepatic cholangiocarcinoma. *J Hepatol.* 2012;57:69–76.
29. Sekiya S, Suzuki A. Intrahepatic cholangiocarcinoma can arise from Notch-mediated conversion of hepatocytes. *J Clin Invest.* 2012;122:3914–8.
30. Lafaro KJ, Pawlik TM. Fibrolamellar hepatocellular carcinoma: current clinical perspectives. *J Hepatocell Carcinoma.* 2015;2:151–7.
31. Mayo SC, Mavros MN, Nathan H, et al. Treatment and prognosis of patients with fibrolamellar hepatocellular carcinoma: a national perspective. *J Am Coll Surg.* 2014;218:196–205.
32. Seo S, Hatano E, Higashi T, et al. Fluorine-18 fluorodeoxyglucose positron emission tomography predicts lymph node metastasis, P-glycoprotein expression, and recurrence after resection in mass-forming intrahepatic cholangiocarcinoma. *Surgery.* 2008;143:769–77.
33. Weber SM, Ribero D, O'Reilly EM, Kokudo N, Miyazaki M, Pawlik TM. Intrahepatic cholangiocarcinoma: expert consensus statement. *HPB (Oxford).* 2015;17:669–80.
34. Ribero D, Pinna AD, Guglielmi A, et al. Surgical approach for long-term survival of patients with intrahepatic cholangiocarcinoma: a multi-institutional analysis of 434 patients. *Arch Surg.* 2012;147:1107–13.
35. Reames BN, Bagante F, Ejaz A, et al. Impact of adjuvant chemotherapy on survival in patients with intrahepatic cholangiocarcinoma: a multi-institutional analysis. *HPB (Oxford).* 2017;19(10):901–909.