Article

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ORIGINAL REPORT

Intrahepatic Cholangiocarcinoma: An International Multi-Institutional Analysis of Prognostic Factors and Lymph Node Assessment

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ABSTRACT

Purpose
To identify factors associated with outcome after surgical management of intrahepatic cholangiocarcinoma (ICC) and examine the impact of lymph node (LN) assessment on survival.

Patients and Methods
From an international multi-institutional database, 449 patients who underwent surgery for ICC between 1973 and 2010 were identified. Clinical and pathologic data were evaluated using uni- and multivariate analyses.

Results
Median tumor size was 6.5 cm. Most patients had a solitary tumor (73%) and no vascular invasion (69%). Median survival was 27 months, and 5-year survival was 31%. Factors associated with adverse prognosis included positive margin status (hazard ratio [HR], 2.20; $P < .001$), multiple lesions (HR, 1.80; $P = .001$), and vascular invasion (HR, 1.59; $P = .015$). Tumor size was not a prognostic factor (HR, 1.03; $P = .23$). Patients were stratified using the American Joint Committee on Cancer/International Union Against Cancer T1, T2a, and T2b categories (seventh edition) in a discrete step-wise fashion ($P < .001$). Lymphadenectomy was performed in 248 patients (55%); 74 of these (30%) had LN metastasis. LN metastasis was associated with worse outcome (median survival: N0, 30 months *v* N1, 24 months; $P = .03$). Although patients with no LN metastasis were able to be stratified by tumor number and vascular invasion (N0; $P < .001$), among patients with N1 disease, multiple tumors and vascular invasion, either alone or together, failed to discriminate patients into discrete prognostic groups ($P = .34$).

Conclusion
Although tumor size provides no prognostic information, tumor number, vascular invasion, and LN metastasis were associated with survival. N1 status adversely affected overall survival and also influenced the relative effect of tumor number and vascular invasion on prognosis. Lymphadenectomy should be strongly considered for ICC, because up to 30% of patients will have LN metastasis.

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INTRODUCTION

Cholangiocarcinoma can be anatomically classified into intrahepatic (ICC), hilar (Klatskin tumors), and distal bile duct types according to their location in the biliary tree.[1] Unlike extrahepatic bile duct cancers, ICC occurs within the hepatic parenchyma, where it frequently presents as a mass lesion in the absence of jaundice or other constitutional symptoms.[2] ICC is the second most common primary liver malignancy after hepatocellular carcinoma (HCC).[3] Although ICC was historically considered the least common of the bile duct cancers, incidence of ICC has been increasing.[4,5] No distinction was made in the sixth edition of the American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC) staging manual between ICC and HCC, in part because of the relative rarity of the disease.[6] The sixth edition AJCC/UICC staging system used tumor size, tumor number, and presence of vascular invasion as major prognostic criteria to establish the T-category

subgroups. However, combining ICC and HCC into a single staging system may be problematic, because ICC and HCC have distinct mechanisms of carcinogenesis, underlying risk factors, and biologic and clinical behaviors.[7,8]

Recently, our group used the Surveillance, Epidemiology, and End Results (SEER) data set to assess the predictive accuracy of several ICC staging systems, including the sixth edition of the AJCC/UICC staging manual.[9] We reported that the sixth edition AJCC/UICC T-category subgroups failed to accurately stratify patients with ICC. Instead, we proposed a simplified T-category system more able to risk-stratify patients into discrete prognostic groups. In part on the basis of our work, the seventh edition of the AJCC/UICC staging manual has incorporated a new distinct staging system for ICC based on prognostic factors including tumor number and vascular invasion but not tumor size.[10] Like other staging systems for solid malignancies, the seventh edition AJCC/UICC staging system also requires ascertainment of nodal status. However, the role of lymphadenectomy for ICC remains controversial, with many surgeons not performing lymph node (LN) evaluation.[11] Given that the seventh edition ICC staging system was only recently published, data to support its widespread adoption and use are lacking. Furthermore, data on the role of lymphadenectomy for ICC and its impact on prognosis are also inadequate. As such, the objective of the current study was to identify factors associated with outcome after surgical management of ICC. More specifically, we sought to validate the new seventh edition AJCC/UICC ICC T-category scheme as well as examine the impact of LN assessment and nodal status on survival.

PATIENTS AND METHODS

Using an international multi-institutional database, 449 patients with ICC who underwent surgical resection with curative intent between October 1973 and February 2010 at one of 11 institutions (Johns Hopkins School of Medicine, Baltimore, MD; Duke Medical Center, Durham, NC; University of Pittsburgh School of Medicine, Pittsburgh, PA; Massachusetts General Hospital, Boston, MA; University of Virginia, Charlottesville, VA; University Hospital Essen, Essen, Germany; Fundeni Clinical Institute of Digestive Disease, Bucharest, Romania; Hôpitaux Universitaires de Genève, Geneva, Switzerland; Ospedale San Raffaele, Milan, Italy; Cliniques Universitaires Saint Luc, Brussels, Belgium; and Curry Cabral Hospital, Lisbon, Portugal) were identified. The institutional review board of each respective institution approved this study. Only patients with histologically confirmed ICC who received their initial treatment for ICC at a study center were included.

Data Collection

Standard demographic and clinicopathologic data were collected, including sex, age, and primary tumor characteristics. Specifically, data were collected on primary tumor location, size, and number as well as morphologic subtype and presence of vascular invasion, defined as minor and/or major. Data on treatment-related variables, such as type of surgery, receipt of lymphadenectomy, and adjuvant therapy, were also obtained. Resection was classified as less than hemihepatectomy, hemihepatectomy, or extended hepatectomy.[12] Margin and nodal status were ascertained based on final pathologic assessment. Date of last follow-up and vital status were collected on all patients.

Statistical Analyses

Summary statistics were obtained using established methods and presented as percentages, mean, or median values. Overall survival time was calculated from date of surgery to date of last follow-up. Cumulative event rates were calculated using the Kaplan-Meier method.[13] Univariate analyses were performed using the χ^2 or log-rank test to compare differences between categorical groups and the Mann-Whitney U test for continuous variables. Cox proportional hazards models[14] were developed using relevant clinicopathologic variables to determine the association of each with overall survival. Relative risks were expressed as hazard ratios (HRs) with 95% CIs. Significance levels were set at $P < .05$; all tests were two sided. All statistical analyses were performed using SPSS version 17.0 (Chicago, IL).

RESULTS

Patient and Primary Tumor Characteristics

Table 1 lists the clinicopathologic features of the 449 patients with pathologically confirmed ICC who were included in the study. A majority of patients presented with a solitary tumor (n = 329; 73.3%), and the median size of the largest lesion was 6.5 cm (range, 7 to 25.0 cm). Only a minority of patients were treated with adjuvant systemic chemotherapy (n = 125; 27.8%) or radiation therapy (n = 31; 6.9%) after surgical resection.

Table 1. Patient Demographics and Clinicopathologic Characteristics

	Patients (N = 449)	
Variable	No.	%
Age, years		
Median	61	
Range	23-85	
Sex		
Male	209	46.5
Race		
White	412	91.9
Bilateral involvement	135	30.1
Tumor size, cm		
Median	6.5	
Range	0.7-25.0	
Presence of multiple tumors	120	26.7
Concomitant extrahepatic disease	22	4.9
Type of liver resection		
< Hemihepatectomy	110	24.4
Hemihepatectomy	189	42.1
Extended hemihepatectomy	139	31.0
Central hepatectomy	8	1.8
Uknown	3	0.7
Lymphadenectomy performed	248	55.2
No. of lymph nodes harvested		
Median	3	
Range	1-76	
Resection margin		
R0	364	81.1
R1	70	15.6
R2	12	2.7
Unknown	3	0.6
Lymph node disease	74	16.5
No. of lymph node metastases		
Median	1	
Range	1-25	
Invasion		
Vascular	140	31.2
Perineural	52	11.6
Biliary	57	12.7

Table 2. Factors Associated With Overall Survival Stratified by Nodal Status

Prognostic Factor	All Patients Irrespective of N Status (N = 449)			Patients With N0 Status (n = 165)			Patients With N1 Status (n = 63)		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Tumor size	1.03	0.98 to 1.07	.23	1.00	0.94 to 1.07	.97	1.03	0.90 to 1.19	.66
Multiple tumors	1.80	1.28 to 2.52	.001	1.53	1.18 to 7.65	.021	3.01	0.94 to 2.47	.09
Positive resection margin	2.20	1.52 to 3.17	< .001	2.53	1.53 to 4.18	< .001	1.15	0.26 to 4.98	.85
Vascular invasion	1.59	1.10 to 2.32	.015	2.11	1.30 to 3.42	.003	1.22	0.36 to 4.17	.75
Direct invasion of adjacent organs	1.13	0.65 to 1.96	.15	0.69	0.31 to 1.52	.36	3.31	0.97 to 11.24	.055
Biliary invasion	0.70	0.42 to 1.15	.15	0.81	0.36 to 1.85	.62	0.98	0.33 to 2.95	.97

Abbreviation: HR, hazard ratio.

At the time of surgical resection, the extent of hepatic resection was less than a hemihepatectomy (n = 110; 24.5%), central hepatectomy (n = 8; 1.8%), hemihepatectomy (n = 189; 42.1%), and extended hepatectomy (n = 139; 31.0%). On final pathologic analysis, 12 patients (2.7%) had a macroscopically positive margin (R2); margin status was microscopically positive (R1) in 70 patients (15.6%) and microscopically negative (R0) in 364 patients (81.1%). On final pathologic analysis, 140 patients (31.2%) had vascular invasion, whereas 57 patients (12.7%) had biliary invasion.

Overall Survival: Prognostic Factors and Assessment of Seventh Edition AJCC/UICC T Category

Median overall survival after surgical resection of ICC was 27.3 months. One-, 3-, and 5-year overall survival was 77.5%, 44.3%, and 30.7%, respectively. On univariate analysis, factors influencing survival included tumor number (HR, 1.82; 95% CI, 1.40 to 2.39; $P < .001$) and presence of vascular invasion (HR, 1.69; 95% CI, 1.28 to 3.53; $P < .001$). Median survival for patients with solitary ICC was 36.0 months compared with 19.0 months for patients with multiple ICC lesions ($P < .001$). Similarly, presence of vascular invasion was associated with worse survival; patients who had no vascular invasion had a median survival of 41.0 months versus 20.0 months for those patients with vascular invasion ($P < .001$). Tumor size was also associated with survival on univariate analysis (HR, 1.05; 95% CI, 1.02 to 1.08; $P = .019$). Other factors, such as presence of biliary invasion or direct invasion of adjacent organs, were not associated with survival ($P > .05$ for both). On multivariate analysis, tumor number and presence of vascular invasion remained associated with poor outcome (multiple tumors: HR, 1.80; 95% CI, 1.28 to 2.52; $P = .001$; presence of vascular invasion: HR, 1.59; 95% CI, 1.10 to 2.32; $P = .015$). In contrast, tumor size had no impact on survival after surgical resection of ICC (HR, 1.03; 95% CI, 0.98 to 1.07; $P = 0.23$; Table 2).

We then examined the new T categories of the seventh edition AJCC/UICC staging system relative to overall survival and prognosis. Patients were unevenly distributed across T categories, with most patients classified as T1 (n = 140; 31.2%), T2a (n = 64; 14.3%), or T2b (n = 102; 22.7%). A small number of patients in the study cohort were classified as T3 or T4, and therefore, these subgroups were not further analyzed. Analysis of the AJCC/UICC T1, T2a, and T2b subgroups stratified patients with regard to prognosis. Patients with T1 tumors (ie, those with a solitary tumor plus no vascular invasion) had a 5-year survival of 46.7% versus 25.0% and 12.0% for patients with T2a (ie, those patients with solitary tumor plus vascular invasion) and T2b tumors (ie, those patients with multiple tumors with or without vascular invasion), respectively (Fig 1).

Lymphadenectomy: Incidence of LN Metastasis and Impact of Nodal Status

Of the 449 patients who underwent surgical resection for ICC, 248 (55.2%) had a lymphadenectomy performed. In contrast, 201 patients (44.8%) did not have the locoregional LN basin evaluated (Nx) at time of surgery. Of those patients who underwent LN evaluation, the median number of LNs harvested was three (range, one to 76). Of the 248 patients who underwent a lymphadenectomy, 74 had metastatic nodal disease. Therefore, among patients who had LN evaluation, the incidence of N1 disease was 29.8%.

Both vascular (HR, 2.89; 95% CI, 1.56 to 5.35; $P = .001$) and biliary invasion (HR, 4.03; 95% CI, 1.94 to 8.36; $P < .001$) were strongly associated with increased risk of N1 disease. Of note, however, was the finding that incidence of LN metastasis was still 9.1% and 20.7%, respectively, among patients with no vascular or biliary invasion. Other factors, such as tumor number and size as well as

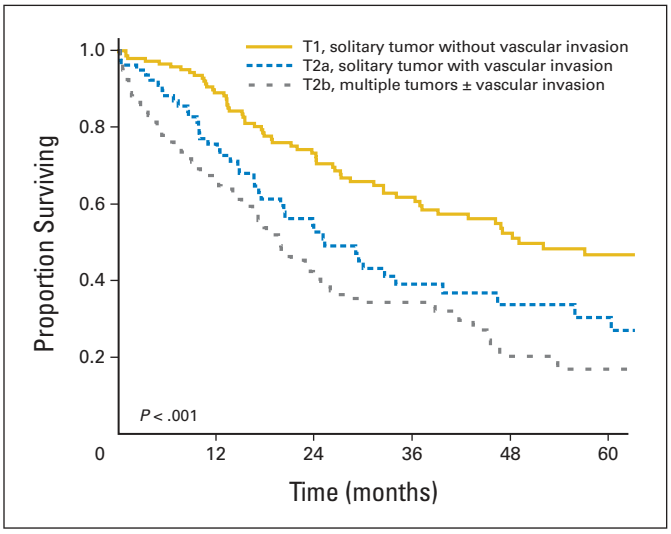

Fig 1. Overall survival stratified by T1 (patients with solitary tumor without vascular invasion), T2a (patients with solitary tumor with vascular invasion), and T2b (patients with multiple tumors with or without vascular invasion), seventh edition American Joint Committee on Cancer/International Union Against Cancer categories.

mass-forming morphology and direct invasion of adjacent organs were not associated with increased risk of LN metastasis ($P > .05$ for all; Table 3).

The finding of N1 disease affected overall survival, with N0 patients having a median survival of 30.1 months versus 22.9 months for patients with N1 disease ($P = .03$). Using the three independent variables associated with outcome—tumor number, presence of vascular invasion, and N1 disease—patients were stratified with regard to prognosis. Patients lacking all three risk factors had longer median survival (46.9 months) compared with patients with either one factor (29.5 months) or two or three risk factors (20.3 months; $P = .002$). Five-year survival for patients with none, one, or two to three risk factors was 38.3%, 27.3%, and 18.1%, respectively ($P < .001$). When patients were then stratified according to nodal status, tumor number and presence of vascular invasion were able to stratify patients with no LN metastasis (N0) with regard to prognosis ($P < .001$; Fig 2A). In contrast, among patients with N1 disease, presence of multiple tumors or vascular invasion either alone or together failed to discriminate patients into discrete prognostic groups ($P = .34$; Fig 2B). Specifically, when we examined the impact of LN status on tumor number, tumor number was only a predictor of survival among patients with N0 disease ($P = .004$; Fig 3A). In contrast, patients with N1 disease had the same overall survival whether they had multiple tumors or a solitary lesion ($P = .45$). The same effect was seen with vascular invasion. Although vascular invasion was a predictor of outcome among patients with N0 disease ($P = .009$), it failed to act as a prognostic marker among patients with LN metastasis ($P = .30$; Fig 3B).

DISCUSSION

Although its incidence has been increasing over the last three decades, ICC has historically been a relatively uncommon disease with a poor prognosis.[4] ICC now accounts for 5% to 30% of all primary liver malignancies, and some reports have noted an improved trend in the prognosis of patients with ICC who undergo surgical resection.[4,15] In part, as a consequence, there has been increasing clinical interest in ICC as well as a greater focus on research surrounding this disease.[16] In the sixth edition of the AJCC/UICC staging manual, ICC was staged identically to HCC. In the newly released seventh edition of the AJCC/UICC staging manual, ICC now has a separate, unique staging system,[10] guided in part by data derived from the SEER data set published by our group.[9] Unfortunately, there remains a paucity of prognostic data for ICC, with most data derived from small single-institution studies or administrative data sets.[9,17,18] The current study is important, because it reports one of the largest multi-institutional experiences on the surgical management of ICC. We report that overall survival after surgical resection of ICC was approximately 30% to 35%. Although tumor number and vascular invasion both significantly affected prognosis, tumor size was not a relevant prognostic factor, consistent with the newly proposed seventh edition AJCC/UICC T-category schema. In addition, we report that incidence of LN metastasis associated with surgically resected ICC was 20% to 30%. N1 status not only adversely affected overall survival but also influenced the relative effect of tumor number and vascular invasion on prognosis.

Our previous ICC study that used the SEER data set was noteworthy, because it was the first, to our knowledge, that was aimed at

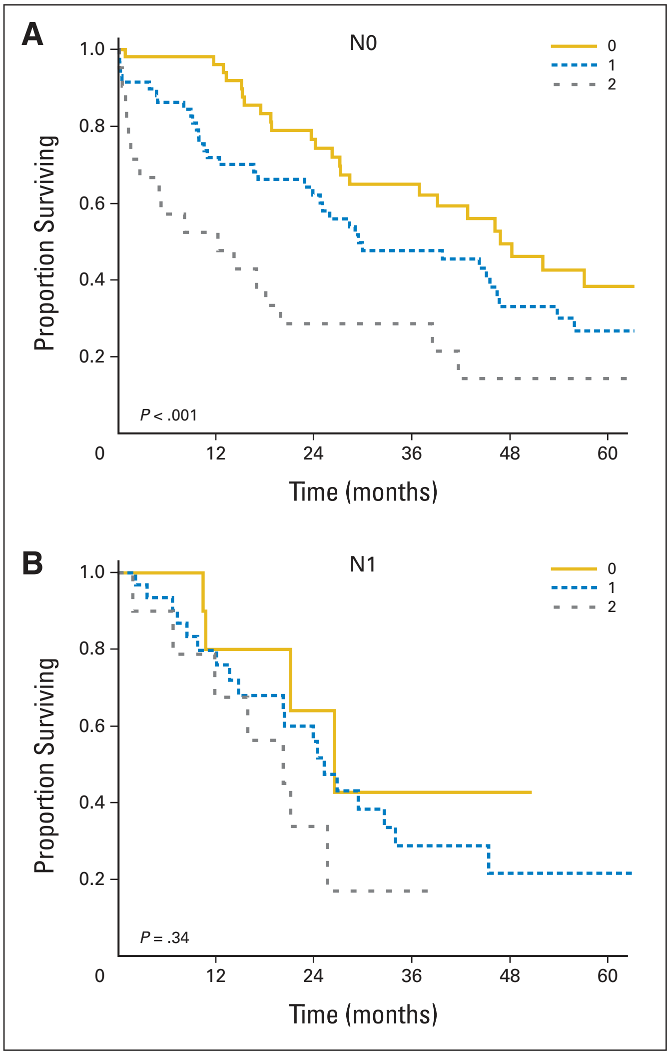

Fig 2. Impact of tumor number and presence of vascular invasion stratified by nodal status. Although tumor number and presence of vascular invasion were able to stratify patients with (A) no lymph node metastasis (N0), these factors either alone or together failed to discriminate (B) N1 patients into discrete prognostic groups.

Table 3. Factors Associated With Increased Risk of Lymph Node Metastasis (n = 248)*

Prognostic Factor	OR	95% CI	P
Size of largest lesion (continuous)	0.99	0.92 to 1.07	.80
Multiple tumors	1.56	0.81 to 3.02	.19
Vascular invasion	2.89	1.56 to 5.35	.001
Direct invasion of adjacent organ	1.74	0.68 to 4.47	.25
Perineural invasion	1.87	0.78 to 4.49	.16
Billiary invasion	4.03	1.94 to 8.36	< .001
Morphologic subtype			
Mass forming		Reference	
Papillary	0.65	0.15 to 2.74	.55
Periductal infiltrating	0.19	0.02 to 1.56	.12
Mass forming plus periductal infiltrating	0.15	0.65 to 2.74	.55

Abbreviation: OR, odds ratio.
*Univariate analysis.

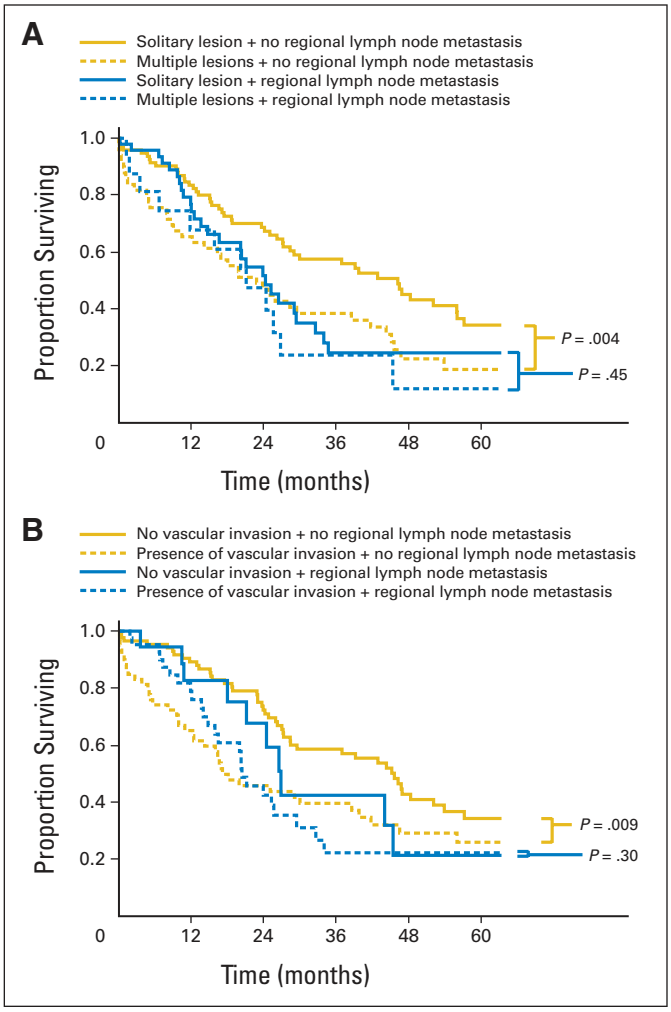

Fig 3. (A) Tumor number was predictor of survival only among patients with N0 disease ($P = .004$), whereas patients with N1 disease had same overall survival whether they had multiple tumors or solitary lesion ($P = .45$). (B) Same effect was seen with vascular invasion. Although vascular invasion was predictor of outcome among patients with N0 disease ($P = .009$), it failed to act as prognostic marker among patients with lymph node metastasis ($P = .30$).

developing an independent Western staging system for ICC.[9] The most significant finding from that study was that tumor size had no independent effect on survival. Previous studies had demonstrated conflicting results regarding the role of tumor size in ICC and were limited by both insufficient sample size and a failure to separate the effect of tumor size from the effects of other negative prognostic factors (eg, multiple tumor, vascular invasion) that tend to be more common in larger tumors.[19] In the current study, using multicenter institutional data, we confirmed our earlier finding that tumor size was not a relevant prognostic factor after accounting for other competing risk factors (Table 2). Rather, tumor number and presence of vascular invasion were the dominant clinicopathologic factors associated with survival after surgical resection of ICC. In turn, when we examined the new T categories of the seventh edition AJCC/UICC staging system, we noted that the T1, T2a, and T2b subgroups stratified patients in a discrete step-wise fashion (Fig 1). Farges et al[20] also recently validated the ICC staging systems proposed by Nathan et al[9] and the seventh edition AJCC/UICC staging manual.[10] In aggregate, data from the current study as well as those from others confirm that the morphologic and pathologic criteria used to define the new AJCC/UICC T categories are prognostically relevant and accurate when used to predict outcome among patients undergoing surgical resection of ICC.

Although LN status is included in the staging of ICC in the seventh edition AJCC/UICC staging system, the role of routine lymphadenectomy for ICC remains controversial. The fact that many surgeons do not routinely perform LN evaluation was highlighted in the current study; only approximately one half of patients undergoing surgery at any of the major hepatobiliary centers had their LNs evaluated. However, data herein presented serve to emphasize the potential importance of including lymphadenectomy as part of the surgical procedure for ICC. Specifically, we noted that roughly one third of patients (29.8%) who had their LNs evaluated had metastatic disease found in the nodal basin. These data are consistent with previous reports that have similarly described an incidence of LN metastasis of 35% among patients with ICC undergoing lymphadenectomy.[20,21] To better assess the true possible range of LN metastasis, patients who did not undergo lymphadenectomy were also considered. For example, if the entire cohort was considered, and all Nx patients were assumed to have had N0 disease, the most conservative estimate of the incidence of LN metastasis would be 16.5%. Therefore, data from the current study are important, because we empirically establish the incidence of LN metastasis in a large cohort of patients and report it to range from 20% to 30%. Given this, we believe that routine LN evaluation should strongly be considered in patients undergoing resection of ICC.

Although the removal of metastatic nodes may decrease locoregional recurrence, the implication of removing these nodes may be more important for accurate staging. In addition to certain primary tumor factors, LN status has traditionally been strongly associated with prognosis after resection of most solid malignancies. Indeed, in the current study, patients with ICC and LN metastasis had a median survival that was roughly two thirds the median survival noted among patients with ICC and no nodal disease. In fact, when we examined the cumulative effect of the three main risk factors (ie, multiple tumors, vascular invasion, and N1 disease), we found that patients who had none of these risk factors had 5-year survival of 38.3% compared with 27.3% for patients with one and 18.1% for patients with two or three risk factors. Perhaps more importantly, LN status had a significant impact on the relative prognostic power of the other clinicopathologic factors. When patients were stratified according to nodal status, among patients with no LN metastasis, the other two risk factors were still able to stratify patients with regard to prognosis. In contrast, when patients with N1 disease were examined, we noted that presence of multiple tumors or vascular invasion either alone or together failed to discriminate patients into discrete prognostic groups. Specifically, when we examined the impact of LN status on tumor number and presence of vascular invasion, patients with N1 disease had the same overall survival whether they had multiple tumors versus a solitary lesion as well as whether they had no vascular invasion versus vascular invasion (Figs 3A, 3B). Collectively, these data suggest that the morphologic and pathologic criteria for the AJCC/UICC T1 and T2 categories were only prognostically relevant among patients with N0 disease. In turn, using these T categories in patients with either N1 disease or unknown nodal status may inaccurately stratify patients, which may have important implications for guiding treatment recommendations and predicting prognosis.

The current study had several limitations. We were only able to examine the validity of the T1, T2a, and T2b categories. However, theobjective of the current study was to evaluate general prognostic factors associated with survival after surgical resection. In particular, we sought to evaluate those factors traditionally included in the staging of ICC and HCC: tumor size, tumor number, and vascular invasion. In addition, because our study was retrospective in nature, there may have been a selection bias in how patients were selected for lymphadenectomy. As such, the current study cannot definitively comment on the true incidence of LN metastasis among all patients undergoing surgery for ICC. We therefore report a possible range of LN metastasis for patients with ICC that includes not only those patients undergoing LN evaluation but also the entire cohort (eg, patients undergoing lymphadenectomy plus patients with Nx disease).

In conclusion, data from the current study demonstrate that although tumor size provides no prognostic information, tumor number, vascular invasion, and LN metastasis were associated with survival after surgical resection of ICC. The new seventh edition AJCC/UICC T categories accurately discriminate patients with ICC into cohorts with distinct prognoses. LN status is an important factor in AJCC/UICC staging of patients with ICC. N1 status not only adversely affected overall survival but also influenced the relative effect of tumor number and vascular invasion on prognosis. Similar to fibrolamellar HCC and gallbladder cancer, routine lymphadenectomy of the hepatoduodenal ligament area should be considered for ICC, because up to 30% to 35% of patients may have LN metastasis. As such, lymphadenectomy for ICC may play an important role in the accurate classification and risk stratification of patients with ICC for future clinical trials.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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Collection and assembly of data: All authors
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors

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