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Intrahepatic cholangiocarcinoma tumor burden: A classification and regression tree model to define prognostic groups after resection

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ABSTRACT

Background: Tumor burden is an important factor in defining prognosis among patients with primary and secondary liver cancers. Although the eighth edition of the American Joint Committee on Cancer staging system has changed the criteria for staging patients with intrahepatic cholangiocarcinoma to better define the effect of tumor burden on prognosis, the impact of intrahepatic cholangiocarcinoma tumor burden on overall survival has not been examined using a machine-learning tool.

Methods: Patients who underwent resection of intrahepatic cholangiocarcinoma at 1 of 14 participating international hospitals between 1990 and 2015 were identified. Classical survival models and the Classification and Regression Tree model were used to identify groups of patients with a homogeneous risk of death and investigate the hierarchical association between variables and overall survival.

Results: Among 1,116 patients included in the analysis, tumor size was ≤5 cm in 447 (40.1%) patients and >5 cm in 669 (59.9%) patients. Although 82.9% ($n = 926$) of patients had a single intrahepatic cholangiocarcinoma, 9.9% ($n = 110$) and 7.2% ($n = 80$) of patients had 2 and ≥3 tumors, respectively. Patients with intrahepatic cholangiocarcinoma tumors ≤5 cm and >5 cm had a 5-year overall survival of 51.7% and 32.6%, respectively ($P < 0.001$). Five-year overall survival decreased from 44.6% among patients with a single intrahepatic cholangiocarcinoma to 28.1% and 14.2% among patients with 2 and ≥3 intrahepatic cholangiocarcinomas, respectively ($P < 0.001$). Among the combinations of tumor size and intrahepatic cholangiocarcinoma tumor number used to estimate tumor burden, logarithmic transformation of tumor size (log tumor size) and intrahepatic cholangiocarcinoma tumor number had the highest concordance

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index. The Classification and Regression Tree model identified 8 classes of patients with a homogeneous risk of death, illustrating the hierarchical relationship between tumor burden (log tumor size and number of intrahepatic cholangiocarcinomas) and other factors associated with prognosis.
Conclusion: Intrahepatic cholangiocarcinoma tumor size and number demonstrated a strong nonlinear association with survival after resection of intrahepatic cholangiocarcinoma. A log-model Classification and Regression Tree–derived tumor burden score may be a better tool to estimate prognosis of patients undergoing curative-intent resection of intrahepatic cholangiocarcinoma.

Introduction

Intrahepatic cholangiocarcinoma (ICC) is a rare malignancy that arises from the epithelium lining and peribiliary glands of the intrahepatic biliary tree, as defined by the anatomic landmark of the portal system (ie, the umbilical portion of the left portal vein and the origin of the right posterior portal vein).[1,2] Although surgery is the only potentially curative treatment for patients with ICC, the clinicopathological characteristics associated with long-term survival among patients undergoing hepatectomy for ICC have not been fully defined. In turn, there remains a poor ability to identify patients at high risk of recurrence and to predict patient prognosis.[3]

Although overall tumor burden has been identified as an important factor in assessing prognosis among some patients with primary and secondary liver cancers (ie, metro ticket for hepatocellular carcinoma [HCC] and tumor burden score [TBS] for colorectal liver metastasis), the relationship between tumor burden, clinical decision making, and prognosis among patients with ICC has not been thoroughly investigated.[4–7] Although some surgeons consider multifocal ICC as a contraindication to surgery, the proportion of patients undergoing liver resection for multiple ICCs can range from 20% to 30% at high-volume hepato-biliary centers.[8–11] Moreover, the American Joint Committee on Cancer (AJCC) revised the criteria for staging patients with ICC in the eighth edition of the AJCC staging manual in an effort to better identify the effect of tumor burden on the prognosis of patients with ICC.[12] Although the seventh edition of the AJCC system staged all patients with solitary tumors as having T1 disease, the eighth edition of the AJCC now includes a tumor cut-off size of 5 cm to discriminate between T1a (solitary tumor $\leq$5 cm) versus T1b (solitary tumor >5 cm) disease.[12,13] Furthermore, according to the eighth edition of the AJCC staging system, the T2 category includes patients with both multiple tumors and presence of vascular invasion (solitary tumor with intrahepatic vascular invasion or multiple tumors with or without vascular invasion), essentially classifying patients with >1 ICC as having the same risk of death as patients with macroscopic vascular invasion.[12] Although the new T categories in the eighth edition of the AJCC staging system for ICC may represent an improvement, the optimal association between ICC size, tumor number, and other pathological factors to predict prognosis has not been fully defined.[14] Therefore, the objective of the current study was to characterize the impact of overall ICC tumor burden on patient prognosis relative to other clinicopathological factors using a machine-based approach applied to a large, multi-institutional cohort of patients who underwent curative-intent resection of ICC.

Methods

Study population and data collection

Patients who underwent curative-intent hepatectomy for ICC at 1 of 14 participating international tertiary referral hepatobiliary centers between 1990 and 2015 were identified. Patients undergoing surgical resection with curative intent (negative [R0] or microscopically positive [R1] margins) for a pathologically confirmed ICC without evidence of extrahepatic metastasis (M0) were included in the analytic cohort. Patients who underwent palliation, radioembolization, or transarterial chemoembolization or surgical resection with a macroscopic residual margin (R2) were excluded. Standard demographic and clinicopathologic characteristics included age, sex, and American Society of Anesthesiologist (ASA) status. Pathological characteristics included number and size of ICCs, cirrhosis/liver fibrosis, invasion of adjacent organs, liver capsule involvement, lymph node status (negative [N0], positive [N1], and unknown [NX]), surgical margin status, grade of tumor differentiation, morphological subtype (mass forming [MF], intraductal growth [IG], periductal infiltrating [PI], and mix type [MF+PI]), vascular, lympho-vascular, and perineural invasion. Treatment-related variables, such as extent of hepatic resection, lymphadenectomy, and receipt of neoadjuvant and adjuvant chemotherapy, were also recorded. Tumor stage (T1a/T1b stages versus T2/T3/T4 stages) was categorized according to the eighth edition of the AJCC staging manual.[12] The institutional review board of each participating institution approved the study.

Statistical analysis

Continuous variables were reported as medians with interquartile ranges; categorical variables were recorded as totals and frequencies. The χ^2 test or Fisher exact test were used to compare categorical variables, as appropriate. The primary outcome for the survival analysis was overall survival (OS), which was defined as the time interval between the date of surgery and the date of death; OS was censored at the date of the last follow-up for patients who remained alive. OS was estimated by Kaplan-Meier methodology, and survival curves were compared using the log-rank test. Cox proportional hazards regression analysis was used to evaluate any association among variables and survival outcomes, with the coefficients reported as hazard ratios (HRs) and corresponding 95% confidence intervals (CIs). Variables with a P value <0.1 on univariable analysis were included in the final multivariable model; a P value <0.05 was considered statistically significant. The concordance index (c-index) was used to assess the predictive abilities of different methods to estimate tumor burden. C-index is a statistic comparable to the area under the receiver operator characteristic curve used for the binary classifier systems varying from 50% (no discrimination) to 100% (perfect discrimination). The Tukey transformation was used to re-express variables using a power transformation to increase the power of the statistical tests that required variables be normally distributed. The Classification and Regression Tree (CART) model, a machine-learning and data-mining recursive algorithm, was used to identify groups of patients with a homogeneous risk of death and investigate the hierarchical association between variables and OS. All analyses were performed using Stata, version 12.0 (Stata Corporation, College

Station, TX) and R software, version 3.5.1, for statistical computing (R Foundation for Statistical Computing; R Core Team, Vienna, Austria), with the following additional packages: survival, Hmisc, party, and rcompanion.

Results

Demographics and clinicopathologic features

Among 1,116 patients undergoing liver resection for ICC who were included in the analysis, 55.3% ($n = 617$) of patients were male, 62.5% ($n = 698$) of patients were aged <65 years, 43.9% ($n = 490$) of patients had an ASA score of 3 to 4, and the incidence of cirrhosis was 12.1% ($n = 117$) (Table I). The vast majority of ICCs were MF/IG ($n = 920$ [86.9%]), whereas the incidence of the PI/MF+PI ICC subtype was considerably lower ($n = 139$ [13.1%]). Utilization of neoadjuvant chemotherapy was uncommon ($n = 81$ [9.0%]). A total of 399 (39.4%), 388 (38.3%), and 226 (22.3%) patients underwent minor, major, and extended hepatectomy, respectively. On final pathological assessment, 139 (12.6%) patients had an R1 surgical margin, whereas 205 (18.4%) and 66 (6.5%) patients had invasion of the liver capsule or invasions of adjacent organs, respectively. Tumor size was ≤5 cm in 447 (40.1%) patients and >5 cm in 669 (59.9%) patients. Although 926 (82.9%) patients had a single ICC, 110 (9.9%) and 80 (7.2%) patients had 2 and ≥3 tumors, respectively. A total of 862 (82.4%) patients had a well-to-moderately–differentiated ICC, whereas 184 (17.6%) patients had a poorly/undifferentiated tumor. Among individuals who had at least 1 lymph node examined, the incidence of lymph node metastasis was 38.2% (190 of 497 patients who underwent lymphadenectomy); 619 (55.5%) patients did not undergo lymphadenectomy. A total of 511 (45.8%) patients had stage T1a/T1b disease, whereas 605 (54.2%) patients had stage T2/T3/T4.

OS analyses and comparison among different approaches to estimate tumor burden

With a median follow up of 2.4 years (interquartile range 1.2–4.3), 3- and 5-year OS was 52.4% (95% CI 49.1–55.8) and 40.5% (95% CI 37.0–44.4), respectively. On univariate analysis, ASA score, tumor morphology subtype, extent of resection, surgical margin status, invasion of adjacent organs, tumor grade, major vascular invasion, lymphovascular invasion, perineural invasion, lymph node status, and T stage were each associated with OS (Table I). Patients with ICCs ≤5 cm and >5 cm had a 5-year OS of 51.7% (95% CI 45.7–57.4) and 32.6% (95% CI 28.0–37.3), respectively ($P < 0.001$). Of note, the 5-year OS decreased from 44.6% (95% CI 40.4–48.7) among patients with a single ICC to 28.1% (95% CI 17.6–39.6) among patients with 2 ICCs and to 14.2% (95% CI 6.8–24.2) among patients with ≥3 ICCs ($P < 0.001$).

To assess various approaches to estimating tumor burden, ICC size and number were examined as continuous values; logistic transformations, the Tukey transformation ladder, and overall TBS were used as well (Supplementary Table I). Using the Cox regression model, risk of patient death increased by 5% for each 1-cm increase in size, whereas the risk of death increased by 20% for each ordinal increase in the number of ICC tumor lesions (tumor size, HR 1.05 [95% CI 1.03–1.08]; number of ICCs, HR 1.20 [95% CI 1.13–1.28]; both P values <0.001). After logarithmic transformation, the HR for tumor size (log tumor size) and number of ICC lesions (log number of ICC) increased to 1.52 (95% CI 1.29–1.79) and 1.74 (95% CI 1.46–2.06), respectively (both P values <0.001). The λ values for the Tukey transformation resulted in values of 0.25 and −0.825 for tumor size and ICC number, respectively. After the Tukey transformation, the HR for tumor size (T tumor size) and ICC lesion number (T number of ICCs) increased to 2.89 (95% CI 2.03–4.13) and 2.92 (95% CI 1.94–4.40), respectively (both P values <0.001). Moreover, risk of patient death increased by 7% for each increase in the TBS (HR 1.07 [95% CI 1.05–1.09]; $P < 0.001$) (Supplementary Table I). The six combinations of tumor size and ICC lesion number used to estimate overall tumor burden were tested by comparing the c-index calculated at 1 to 5 years after surgery (Table II; Fig 1). Log tumor size and ICC lesion number had the highest c-index, ranging from 61.4% when estimated at 2 years to 60.0% when estimated at 3 years; TBS c-index was 61.2% and 58.8% at 2 and 3 years, respectively.

Multivariable OS analyses and CART model

In the multivariable Cox regression model, the risk of death increased by 58% for each increase in log tumor size (about 2.7 cm, HR 1.58 [95% CI 1.32–1.89]; $P < 0.001$) and 19% for each additional ICC lesion among patients who had multifocal disease (compared with a single ICC, HR 1.19 [95% CI 1.12–1.27]; $P < 0.001$). Although PI/MF+PI morphological subtype (HR 1.41 [95% CI 1.09–1.83]; $P = 0.008$), positive surgical margins (HR 1.43 [95% CI 1.10–1.87]; $P = 0.008$), and poorly/undifferentiated tumor grade (HR 1.49 [95% CI 1.19–1.88]; $P < 0.001$) were associated with an increased risk of death, lymph node status was the strongest predictor of OS among ICC patients. Compared with patients who did not have lymph node metastasis, individuals who had metastatic lymph nodes and patients who did not undergo lymphadenectomy (NX) had a 2.4-fold (HR 2.45 [95% CI 1.85–3.23]; $P < 0.001$) and 1.6-fold (HR 1.56 [95% CI 1.24–1.97]; $P < 0.001$) increased risk of death, respectively (Table III). A sensitivity analysis including only the 957 (86%) patients who underwent surgery after 2005 was performed and the results were comparable with those obtained when the whole cohort was analyzed (Supplementary Table I).

A CART algorithm was used to investigate the relationship between the 2 variables identified as the best estimators of ICC tumor burden (log tumor size and ICC lesion number), with other variables identified as being associated with long-term prognosis (Fig 2). The CART algorithm used both categorical and continuous variables to identify a rule (ie, a cut-off value for continuous variables or a set of values for categorical variables) to better differentiate patients into groups with a homogeneous risk of death. As in the multivariable Cox's model, lymph node status was the first variable selected by the CART algorithm (N0/Nx versus N1) as the most important variable associated with prognosis. The CART model identified 8 terminal nodes (ie, terminal branches of the CART model) as 8 classes of patients with a homogeneous risk of death (Table IV; Fig 2). Classes 1 and 2 included patients with no lymph node metastasis or patients who did not undergo lymphadenectomy (N0/Nx) who had small ICCs (cutoff identified for log tumor size 1.6, approximately 5 cm) that was either the MF or PI/MF+PI ICC subtype. Patients in classes 3, 4, and 5 had ≤2 tumors >5 cm (log tumor size >1.6). Moreover, patients in class 3 included individuals who had a lymphadenectomy with no nodal metastasis on pathology (N0); patients in class 4 did not undergo lymphadenectomy (NX) and had 1–2 tumors measuring ≤7.5 cm (log tumor size 2.01); patients in class 5 did not undergo lymphadenectomy (NX) and had 1–2 tumors >7.5 cm (log tumor size >2.01). Class 6 included patients without lymph node metastasis (N0/NX), large ICC size (log tumor size >1.6, >5 cm), and multifocal disease (>2 tumors). Patients in classes 7 and 8 had the worst predicted prognosis. Specifically, patients who had metastatic lymph nodes and negative (R0)

Table I
Baseline characteristics and 5-year OS of 1,116 patients undergoing liver resection for ICC

Variables	$N = 1,116$	5-Year OS	95% CI	P value
Sex				.33
Female	499 (44.7%)	43.7%	38.1–49.2	
Male	617 (55.3%)	38.0%	33.1–42.9	
Age (y)				.82
<65	698 (62.5%)	40.5%	35.9-45.0	
≥65	418 (37.5%)	40.4%	34.0-46.7	
ASA score				.012
1–2	626 (56.1%)	41.0%	35.9–46.1	
3–4	490 (43.9%)	39.4%	34.1–44.7	
Cirrhosis				.23
Yes	117 (12.1%)	38.9%	28.6–49.2	
No	852 (87.9%)	42.3%	37.7–46.9	
NA	147	—	—	
Tumor morphology type				<.001
MF	920 (86.9%)	42.6%	38.4–46.7	
PI/MF+PI	139 (13.1%)	26.1%	17.8–35.2	
NA	57	—	—	
Neoadjuvant chemotherapy				.92
No	823 (91.0%)	44.3%	39.7–48.7	
Yes	81 (9.0%)	46.3%	31.6–59.8	
NA	212	—	—	
Extent of resection				.008
Minor hepatectomy	399 (39.4%)	44.9%	38.4–51.2	
Major hepatectomy	388 (38.3%)	41.0%	35.0–46.9	
Extended hepatectomy	226 (22.3%)	35.0%	26.8–43.3	
NA	103	—	—	
Margins				<.001
Negative	968 (87.4%)	42.7%	38.5–46.4	
Positive	139 (12.6%)	26.5%	17.6–36.4	
NA	9	—	—	
Liver capsule involvement				.22
No	911 (81.6%)	40.9%	36.7–45.1	
Yes	205 (18.4%)	38.7%	30.9–46.4	
Invasion of adjacent organs				<.001
No	853 (93.5%)	43.7%	39.6–47.7	
Yes	66 (6.5%)	14.7%	6.4–26.5	
NA	197	—	—	
Tumor size (cm)				<.001
≤5	447 (40.1%)	51.7%	45.7–57.4	
>5	669 (59.9%)	32.6%	28.0–37.3	
Number of tumors				<.001
1	926 (82.9%)	44.6%	40.4–48.7	
2	110 (9.9%)	28.1%	17.6–39.6	
≥3	80 (7.2%)	14.2%	6.8–24.2	
Tumor grade				<.001
Well to moderately	862 (82.4%)	44.3%	39.9–48.5	
Poorly to undifferentiated	184 (17.6%)	23.4%	16.1–31.4	
NA	70	—	—	
Major vascular invasion				<.001
Not present	956 (86.4%)	42.9%	38.9–46.9	
Present	150 (13.6%)	24.6%	15.7–34.5	
NA	10	—	—	
Lymphovascular invasion				.007
Not present	755 (68.8%)	43.7%	39.3–48.1	
Present	342 (31.2%)	33.4%	26.5–40.4	
NA	19	—	—	
Perineural invasion				.001
Not present	789 (79.0%)	42.6%	38.3–46.8	
Present	210 (21.0%)	23.9%	15.6–33.3	
NA	117	—	—	
Lymph node status				<.001
Negative	307 (27.5%)	46.5%	39.1–53.7	
Positive	190 (17.0%)	16.7%	9.7–25.3	
Not assessed	619 (55.5%)	44.0%	39.1–48.8	
T stage (AJCC eighth edition)				<.001
T1a/T1b	511 (45.8%)	49.1%	43.5–54.5	
T2/T3/T4	605 (54.2%)	33.1%	28.4–37.9	

surgical margins were categorized as class 7; patients who had metastatic lymph nodes with a positive (R1) surgical margin were classified as class 8. Compared with patients in class 1 (N0/NX, log size ≤1.6/5 cm, MF ICC), the risk of death increased by over 4-fold for patients in class 6 (N0/NX, log size >1.6/5 cm, number of ICCs >2) and 6-fold for patients in class 8 (N1, R1) (referent class 1: class 6, HR 4.63 [95% CI 3.25–6.59]; class 8, HR 6.11 [95% CI 4.09–9.12]; all $P < 0.001$) (Table IV; Fig 2).

Table II
C-index values calculated at 1, 2, 3, 4, and 5 years after surgery comparing the different approaches to estimating ICC tumor burden

Variables	Time After Surgery				
	1 year	2 years	3 years	4 years	5 years
Size and number	61.0%	61.1%	59.8%	60.1%	60.1%
Log size and log number	61.0%	61.3%	59.9%	60.2%	60.1%
Size and log number	60.8%	61.1%	59.7%	59.9%	60.0%
Log size and number	61.2%	61.4%	60.0%	60.4%	60.2%
Tukey transformation	60.6%	60.0%	58.8%	59.5%	59.1%
TBS	60.8%	61.2%	59.8%	60.0%	60.0%

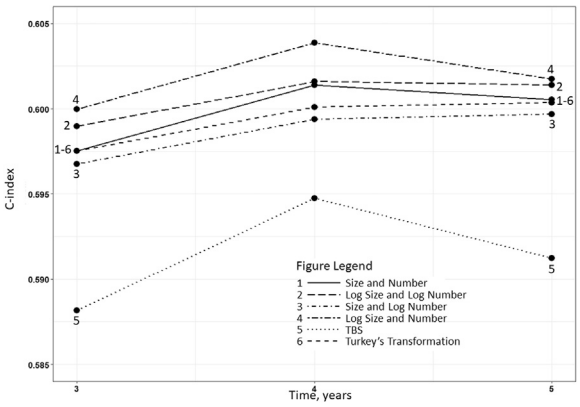

Fig 1. Trends of c-index values calculated for the different approaches to estimating ICC tumor burden.

Discussion

Although surgery is the only potentially curative treatment option for patients with ICC, the 2018 National Comprehensive Cancer Network guidelines for hepatobiliary cancers recommend that surgical resection for ICC should only be performed in select cases among individuals with "limited" disease. To this point, Wright et al[8] reported no benefit of surgery compared with intra-arterial therapy among patients with a large burden of disease. Other groups, however, have reported a 5-year OS of 19% among patients undergoing hepatic resection for large (≥7 cm) or multifocal (≥2) ICC tumors.[8,15] As such, the role of surgery, and long-term prognosis, among patients with varying degrees of ICC tumor burden remain poorly defined and debated. In the 8th edition of the AJCC staging system for ICC, 2 separate categories, T1a (single ICC ≤5 cm) and T1b (single ICC >5 cm), were introduced to underline the effect of tumor size on the prognosis of patients with a single ICC, while the T2 category includes both patients with multifocal ICCs and patients with vascular invasion.[12] Among the 1,116 patients included in the current study who underwent surgical resection of ICC, 60% ($n = 669$) of patients had ICC tumors >5 cm, but only 10% and 7% of patients had 2 and >2 tumors, respectively. Of note, both ICC size and number were independently associated with OS, and these factors were the most predictive of long-term prognosis when the number of ICC lesions was combined with the logarithmic transformation of tumor size. The current study was novel and important because we used a CART machine-based learning model to better understand the relationship between ICC tumor burden and patient prognosis. Specifically, the CART model was used to estimate the hierarchical relationships between ICC size and number relative to other variables that were associated with long-term prognosis. Using this technique, we were able to identify and define 8 distinct prognostic groups of patients based on ICC tumor size and number in addition to other clinicopathological characteristics, such as nodal status and morphologic subtype.

In a retrospective analysis that included 1,556 patients, Mazzaferro et al[16] demonstrated that HCC tumor size and number (modelled as continuous variables by the 3-knot restricted cubic splines method) and microvascular invasion could be combined into an HCC metro-ticket prognostic tool to predict survival after liver transplantation better than the Milan criteria.[16,17] In a separate study, Sasaki et al[6] proposed a new metro-ticket tool for colorectal liver metastases (CRLM) based on tumor size and number to predict patient prognosis. After the paradigm shift from dichotomous to continuous prognostic stratification proposed for HCC by Mazzaferro et al,[16] Sasaki et al[7] used the Pythagorean theorem to combine maximum tumor size and number of CRLM into a single value denoted as the TBS.[6,7] As reported by the authors, TBS for CRLM outperformed both maximum tumor size and number of tumors to predict OS (area under the receiver operator curve: TBS, 0.67; maximum tumor size, 0.62 [$P = 0.012$]; number of tumors, 0.59 [$P < 0.001$]).[6] Analyses in the current study expand on this previous work in that we assessed various combinations and mathematical transformations of tumor size and ICC number to determine the best manner to estimate long-term prognosis following resection of ICC. In contrast to HCC metro ticket and CRLM TBS, ICC TBS did not result in the best clinical tool to predict patient prognosis after surgery. The reason for these disparate results may be due to the different biologic and natural histories of the diseases. For example, although multifocal CRLM and HCC may represent the presence of multiple tumors growing simultaneously, multifocal ICC often implies intrahepatic metastasis and more advanced disease. According to this hypothesis, in the current CART model, tumor number was not selected as a prognostic variable for small ICC tumors (ie, early disease tended not to be associated with intrahepatic metastasis); in contrast, tumor number was an important prognostic factor among patients with large ICC tumors.

In the multivariable model, several variables affected prognosis, including tumor morphology (PI//MF+PI, HR 1.46, $P = 0.004$), margin status (positive, HR 1.47, $P = 0.004$), tumor grade (poor/undifferentiated, HR 1.49, $P < 0.001$), and lymph node metastasis (positive, HR 2.32, $P < 0.001$). Moreover, a CART model was used to investigate how the association of these variables influenced the prognosis of patients by identifying the hierarchical relationship among clinicopathological features and tumor burden. Of note, lymph node status was the strongest predictor of survival in both the "classical" survival analysis and in the CART model. Interestingly, tumor size and ICC number were associated with OS among patients with pathologically negative lymph nodes (N0) and patients who did not undergo lymphadenectomy (NX). In contrast, among patients with N1 disease, the only variable associated with survival was surgical margin status. In a meta-analysis by Tang

Table III
Multivariable Cox proportional hazards regression analysis of risk factors associated with OS for patients undergoing liver resection for ICC

Variables	HR	95% CI	*P* Value
Tumor morphology type			
MF/IG	Reference	—	—
PI/MF+PI	1.41	1.09–1.83	.008
Margins			
Negative	Reference	—	—
Positive	1.43	1.10–1.87	.008
Tumor size (logistic transformation) (cm)	1.58	1.32–1.89	<.001
Number of tumors	1.19	1.12–1.27	<.001
Tumor grade			
Well to moderate	Reference	—	—
Poor to undifferentiated	1.49	1.19–1.88	<.001
Lymph node status			
Negative	Reference	—	—
Positive	2.45	1.89–3.23	<.001
Not assessed	1.56	1.24–1.97	<.001

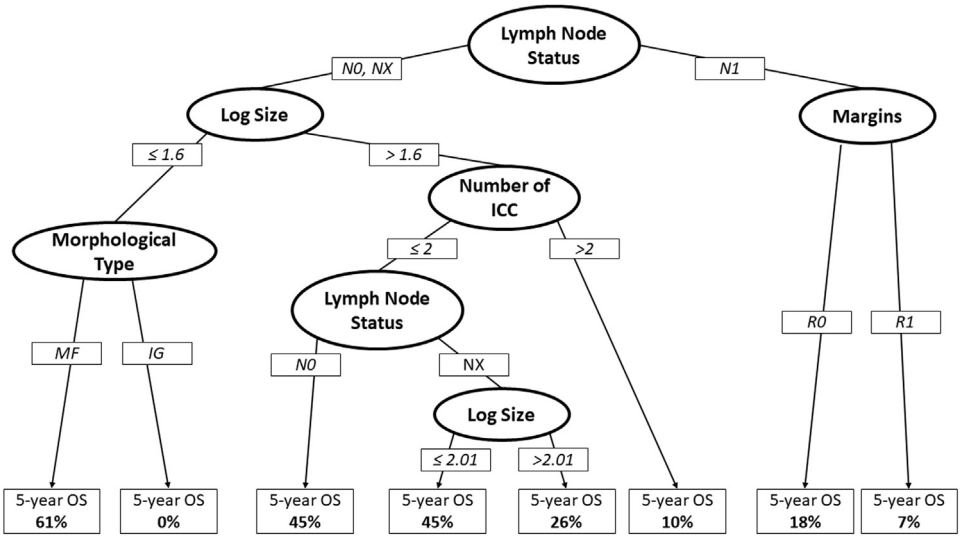

Fig 2. CART model representing the hierarchical association between tumor burden (log tumor size and number of tumors) and the other clinicopathological variables to predict patients' survival.

et al[18] that examined the impact of surgical margins on OS after resection of ICC, positive margins (<10 mm) were associated with an increased risk of death compared with negative margins (≥10 mm); however, in a sensitivity analysis that included only patients who did not have lymph node metastasis (N0/NX), no difference was noted among surgical margin–negative (R0) versus surgical margin–positive (R1) patients. Similar to the results of this meta-analysis, margin status was not associated with survival among patients who were N0/NX in the CART model. In contrast, among patients with lymph node metastasis (N1), patients with negative margins (R0) had a 5-year OS of 18% compared with a 7% OS among patients with positive margins (R1) ($P < 0.001$).

Among N0/NX patients, tumor size (log tumor size) was the most important variable selected by the CART model, with 5 cm as the optimal cut-off value to discriminate between large and small ICC tumors. This cut-off value was consistent with the new tumor-size category introduced in the eighth edition of the AJCC staging system to define T1a and T1b disease as patients with a single ICC tumor that is ≤5 cm versus >5 cm.[12] In a meta-analysis that examined ICC prognostic factors, Mavros and al[19] reported that although larger tumor size was not predictive of recurrence-free survival, it was associated with shorter OS (HR 1.09 for each 1-cm increment). Importantly, in the current analysis, the CART model demonstrated that small ICC tumors (≤5 cm) were associated with a favorable prognosis only among patients with MF/IG ICC subtypes. In fact, among patients without metastatic lymph nodes who had small ICC tumors (classes 1 and 2), patients with MF/IG ICC (class 1) had a 5-year OS of 61%, whereas no patients with PI/MF+PI (class 2) survived 5 years after surgery ($P < 0.001$). Although morphological subtype was removed from the eighth edition of the AJCC staging system as a criteria for the T4 category, more recent data have demonstrated that patients with PI/MF+PI subtypes likely have a worse prognosis compared with patients who have the MF/IG ICC subtype.[20–23] Based on the current study and previous data, ICC tumor burden should likely be interpreted in light of morphological ICC subtype.

The role of lymphadenectomy at the time of surgery for ICC remains debated. In general, lymphadenectomy is only performed roughly half the time among patients undergoing surgery for ICC. Even more surprisingly, data from our own group have demonstrated that among patients who did not undergo lymphadenectomy (NX), two-thirds had a preoperative radiological diagnosis of

Table IV
Classes of risk identified by the CART model

Classes	*N* (%)	5-year OS (95% CI)*	HR (95% CI)†	*P* Value†
1. N0-NX, log size ≤1.6, MF/IG	283 (25.4%)	61.3% (54.5–69.0)	Reference	Reference
2. N0-NX, log size ≤1.6, PI/MF+PI	23 (2.1%)	—	2.96 (1.65–5.30)	<.001
3. N0, log size >1.6,‡ ≤2	198 (17.7%)	45.3% (36.7–55.8)	1.44 (1.07–1.95)	.017
4. NX, log size 1.6 − 2.01,‡ ≤2	210 (18.8%)	44.9% (37.9–53.2)	1.82 (1.39–2.39)	<.001
5. NX, log size >2.01,‡ ≤2	161 (14.4%)	25.8% (18.0–36.9)	2.99 (2.25–4.00)	<.001
6. N0NX, log size >1.6,‡ >2	51 (4.6%)	9.6% (0.4–23.7)	4.63 (3.25–6.59)	<.001
7. N1, R0	153 (13.7%)	17.6% (10.4–29.6)	3.38 (2.53–4.50)	<.001
8. N1, R1	37 (3.3%)	7.4% (2.1–26.4)	6.11 (4.09–9.12)	<.001

Log size, logarithmic transformation of tumor.
* Kaplan Meier estimation.
† Cox regression model.
‡ Number of tumors.

negative lymph node, yet almost one third had some evidence of a suspicious or metastatic node on preoperative imaging.[24] In the current analysis, preoperative radiological status of lymph nodes was not included in the CART model; rather, NX patients were initially grouped with N0 patients. Of note, there were no major differences in long-term prognosis among NX and N0 patients among patients with small ICC tumors (≤5 cm; class 1 and 2), yet nodal status (NX vs N0) was an important factor to differentiate prognosis among patients with larger ICC tumors (>5 cm). In particular, for patients with ≤2 large ICC tumors, the CART model distinguished three groups: class 3 (N0 large and ≤2 ICC lesions) patients who underwent a formal lymphadenectomy with nodal negative disease (N0) and classes 4 and 5, which included NX patients who had a log tumor size ≤2.01 and >2.01 (approximately 7.5 cm), respectively. Collectively, the CART machine-learning model with a recursive data-mining algorithm allowed for the identification of groups of patients with a homogeneous risk of death and long-term prognosis using a broad array of clinic-pathological data.

The present work had several limitations. Owing to the retrospective and multicentric nature of the study, patient selection and treatment protocols may have varied at the different centers. Moreover, tumor size was based only on the largest lesion in the case of multifocal disease. An assessment of tumor burden that included the size of all the lesions might further improve the ability to assess the association between tumor burden and prognosis. Of note, although our CART model demonstrated a good ability to identify groups of patients with different prognoses (ie, 5-year OS rates ranging from 61% for N0-NX, log size ≤1.6, MF/IG patients to 7% and 0% for N1, R0 and N0-NX, log size ≤1.6, PI/MF+PI patients, respectively), an external validation will be required to confirm our results. In addition, all patients with >1 ICC tumors were included in the same category as having multifocal disease. We did not record the patterns of distribution of ICC among patients (eg, single tumors [pattern type I], single tumors with satellites in the same liver segment [pattern type II], or multifocal tumors [pattern type III]).[11] Moreover, the exact location of ICC within the liver (ie, bilobar vs unilobar disease; superficial vs deep within the liver parenchyma) was not recorded. Additional studies investigating the molecular characteristics of multifocal disease might refine the classification of the tumor burden among ICC patients to further discriminate the prognosis of patients. While the use of machine-learning algorithms such as CART models might improve our ability to predict patient prognosis, in the last year integrative genomic analyses have identified molecular profiles of cholangiocarcinoma, providing information that will need to be integrated in future prognostic models to improve their accuracy.[25,26]

In conclusion, although tumor size and lesion number have been reported to have the same “weight” in predicting prognosis among patients with HCC and CRLM, the relationship of these tumor-specific factors was more complex among ICC patients. Specifically, tumor size and number of ICC tumors demonstrated a strong nonlinear association with survival after resection of ICC. A machine-learning–based analytic approach demonstrated variable effects on long-term prognosis of nodal status and morphologic subtypes relative to other factors, such as tumor size and number. In turn, the derived CART model was able to classify patients into 8 distinct prognostic groups to estimate prognosis after curative-intent resection of ICC. This log-model CART–derived tumor burden score may be a better tool to estimate prognosis of patients undergoing curative-intent resection of ICC.

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Conflict of interest/Disclosure

The authors have no personal conflicts of interest to declare.

Supplementary materials

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