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ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Tumor Burden Dictates Prognosis Among Patients Undergoing Resection of Intrahepatic Cholangiocarcinoma: A Tool to Guide Post-Resection Adjuvant Chemotherapy?

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ABSTRACT

Introduction. While tumor burden (TB) has been associated with outcomes among patients with hepatocellular carcinoma, the role of overall TB in intrahepatic cholangiocarcinoma (ICC) remains poorly defined.

Methods. Patients undergoing curative-intent resection of ICC between 2000 and 2017 were identified from a multi-institutional database. The impact of TB on overall (OS) and disease-free survival (DFS) was evaluated in the multi-institutional database and validated externally.

Results. Among 1101 patients who underwent curative-intent resection of ICC, 624 (56.7%) had low TB, 346 (31.4%) medium TB, and 131 (11.9%) high TB. OS incrementally worsened with higher TB (5-year OS; low TB: 48.3% vs medium TB: 29.8% vs high TB: 17.3%, $p < 0.001$). Similarly, patients with low TB had better DFS compared with medium and high TB patients (5-year DFS: 38.3% vs 18.7% vs 6.9%, $p < 0.001$). On multivariable analysis, TB was independently associated with OS (medium TB: HR = 1.40, 95% CI 1.14–1.71; high TB: HR = 1.89, 95% CI 1.46–2.45) and DFS (medium TB, HR = 1.61, 95% CI 1.33–1.96; high TB: HR = 2.03, 95% CI 1.56–2.64). Survival analysis revealed an excellent

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prognostic discrimination using the TB among the external validation cohort (3-year OS; low TB: 44.8%, medium TB: 29.3%; high TB: 23.3%, $p = 0.03$; 3-year DFS: low TB: 32.7%, medium TB: 10.7%; high TB: 0%, $p < 0.001$). While neoadjuvant chemotherapy was not associated with survival across the TB groups, receipt of adjuvant chemotherapy was associated with increased survival among patients with high TB (5-year OS: 24.4% vs 13.4%, $p = 0.02$).

Conclusion. Overall TB dictated prognosis among patients with resectable ICC. TB may be used as a tool to help guide post-resection treatment strategies.

Intrahepatic cholangiocarcinoma (ICC) ranks second among primary liver cancers with an increasing incidence in the United States over the last three decades.[1,2] Despite improvements in the understanding of the biological behavior of ICC and advances in perioperative care, ICC still carries dismal prognosis, ranging from 15 to 40 months among patients with resectable tumors and 6–13 months among patients with unresectable ICC.[2–4] Of note, approximately 60% of patients with resectable tumors will recur within 2 years of surgery, while one in four patients will recur in the first 6 months after curative-intent resection.[5] As such, better risk stratification schemas are needed to optimize patient selection and identify individuals who will benefit the most from an operative approach.

Tumor burden has been an important predictor of outcomes among patients with primary or secondary liver cancers [Milan criteria, tumor burden score for hepatocellular carcinoma (HCC) and colorectal liver metastasis (CRLM) etc.].[6–9] The impact of overall tumor burden on outcomes of patients with ICC has not, however, been formally investigated. The 8th edition of the American Joint Committee on Cancer (AJCC) staging manual highlights the importance of tumor size relative to prognosis as patients with solitary ICC ≤ 5 cm are categorized as T1a, while individuals with solitary tumors > 5 cm are categorized as T1b.[10] In fact, a classification and regression tree (CART) recently proposed by our own group identified tumor size (≤ 5 cm and > 5 cm) and tumor number (1, 2–3, > 3 lesions) as the two most important predictors of long-term survival among patients with ICC.[11] Nevertheless, this categorization may be too "vague," as tumor size was examined using a categorical cutoff (5 cm). Recently, Bagante et al.[12] reported that different combinations of tumor size and tumor number may be a better way to define ICC tumor burden (logarithm [natural] of tumor size + the number of lesions). A detailed analysis of long-term outcomes using a tumor burden metric among a large cohort of patients is still lacking. In addition, whether ICC tumor burden may help guide pre- and postoperative treatment strategies among patients undergoing surgery for ICC remains unknown. As such, the objective of the current study was to evaluate the impact of tumor burden among patients undergoing resection for ICC. In addition, we sought to examine whether tumor burden could serve as a tool to identify individuals who may benefit the most from pre- and post-resection treatment strategies (i.e., neoadjuvant or adjuvant chemotherapy).

METHODS

Study Population and Inclusion Criteria

Patients undergoing curative-intent liver resection for ICC between 2000 and 2017 were identified using the International Intrahepatic Cholangiocarcinoma Study Group database incorporating data from 15 tertiary hepatobiliary institutions worldwide.[13,14] Patients were excluded if they did not undergo curative-intent resection, had R2 resection, had missing data on size and number of lesions, or had missing follow-up data. The institutional review boards of all participating institutions approved this study.

Variables and Outcomes of Interest

The following variables were analyzed: age, sex, American Society of Anesthesiologists (ASA) class, preoperative serum CA19-9, albumin-bilirubin (ALBI) grade, history of cirrhosis, extent of disease (i.e., unifocal or multifocal), type of resection (i.e., minor or major), N stage (i.e., N0: negative, N1: positive, Nx: not evaluated), tumor size, number of tumors (i.e., single, multiple), resection margin status (i.e., R0, R1), morphologic sub-type (i.e., MF: mass-forming; IG: intraductal growth; or PI: periductal infiltrating), tumor differentiation grade, presence of micro- or major vascular invasion, as well as receipt of adjuvant chemotherapy. Resection of ≥ 3 Couinaud segments was defined as major hepatectomy.[15] Invasion of the first- and second-order branches of the portal vein or hepatic arteries, or invasion of ≥ 1 hepatic veins, were defined as major vascular invasion. In contrast, microvascular invasion was defined as intraparenchymal vascular involvement identified on histological examination.[10] The ALBI grade was calculated as previously reported.[16,17] Tumor burden was defined as the logarithm (natural) of tumor size plus the number of lesions [ICC tumor burden = $\log_e$(tumor size) + number of lesions], as defined previously by Bagante et al.[12].

The primary outcomes were overall survival (OS) and disease-free survival (DFS). OS was defined as the time interval between the date of liver resection and the date of

death or last follow-up. DFS was defined as the time interval between the date of hepatectomy and the date of recurrence or last follow-up. Secondary outcomes were 1-year death, early recurrence (i.e., recurrence within 2 years following resection) and very early recurrence (i.e., recurrence within 6 months following resection). The primary independent variable was the ICC tumor burden, which was categorized as low, medium, or high using X-tile software.[18] X-tile software determines appropriate cutoffs of different markers to subset the population into clinically relevant groups and is a valuable tool for outcomes based cut-off generation. Cut-points were made in X-tile and were cross validated with Monte-Carlo simulations.[18] Cross-validation with 1000 random populations in the multi-institutional cohort was performed to identify the appropriate thresholds to define low, medium, and high tumor burden. In turn, these cut-offs were validated using an external validation cohort consisting of patients treated at Cleveland Clinic (Cleveland, Ohio) and the First Affiliated Hospital of Xi'an Jiaotong University (Xi'an, China).

External Validation Cohort

Data on patients who underwent curative-intent hepatectomy for ICC between 2006 and 2017 at the Cleveland Clinic (Cleveland, Ohio) and the First Affiliated Hospital of Xi'an Jiaotong University (Xi'an, China) were used to validate the proposed categorization of low, medium and high ICC tumor burden. The external validation cohort included patients who met the same inclusion criteria as the patients in the test cohort.

Statistical Analysis

Continuous variables are presented as median [interquartile range (IQR)], and categorical variables as frequency (%). Categorical variables were compared using the Chi square test and continuous variables using Kruskal–Wallis one-way analysis of variance. Bivariate survival analyses were performed using the Kaplan–Meier method and the log-rank test. Clinicopathologic variables that were found to be significant on bivariate analysis (p value < 0.05) were entered into the multivariable model to assess their impact on OS and DFS following resection of ICC. The performance of the multivariable models incorporating tumor burden and then tumor size and tumor number separately was examined using Harrell's concordance index (c-index). The impact of ICC tumor burden on OS and DFS was validated in an external validation cohort. Patients who were censored within 1 year, 2 years, and 6 months following resection of ICC were excluded from the calculation of the positive predictive value of tumor burden class relative to the risk of 1-year death, early recurrence, and very early recurrence, respectively. The level of statistical significance was $p < 0.05$. All statistical analyses were performed with SPSS, v26 (IBM Corp. Armonk, NY, USA) and JMP v14 (SAS Institute Inc., Cary, NC, USA) statistical packages.

RESULTS

Demographics of the Analytic Cohort

A total of 1101 patients underwent curative-intent resection for ICC and were included in the multi-institutional cohort (Table 1). Median patient age was 60 years (IQR: 51–69), most patients were male (n = 610, 55.5%), and had an ASA class ≤ 2 (n = 607, 65.9%). Median tumor size was 6.0 cm (IQR: 4.0–8.5) and 18.0% (n = 183) of patients had metastatic nodal disease (N1). Only a minority of patients had multifocal ICC (n = 193, 19.2%). Most patients underwent an R0 resection (n = 953, 87.0%), had the MF or IG ICC subtype (n = 921, 88.0%), and a well- to moderately differentiated tumor (n = 838, 81.1%). A small subset of individuals had major vascular (n = 151, 13.8%) or microvascular invasion (n = 338, 31.2%). Receipt of neoadjuvant or adjuvant chemotherapy was noted in 7.6% (n = 68) and 32.1% (n = 340) of patients, respectively (Table 1). Overall, 56.7% (n = 624) of patients had low tumor burden ($\leq$ 3.00), 31.4% (n = 346) had medium tumor burden (3.00–3.99) and 11.9% (n = 131) of patients had high tumor burden ($\geq$ 4.00) (Fig. 1). Differences among low, medium, and high tumor burden groups are summarized in Table 1.

Impact of Tumor Burden on OS and DFS

After a median follow-up of 20.3 months (IQR: 10.5–40.4), 5-year OS and DFS following curative-intent liver resection for ICC were 38.8% and 28.3% among the entire cohort, respectively. Of note, ICC tumor burden was able to stratify prognosis as OS incrementally worsened with higher tumor burden (5-year OS; low tumor burden: 48.3% vs medium tumor burden: 29.8% vs high tumor burden: 17.3%, $p < 0.001$; unadjusted HR; ref: low tumor burden; medium tumor burden: HR = 1.49, 95% CI 1.23–1.80; high tumor burden: HR = 2.31, 95% CI 1.82–2.92, Fig. 2a). In addition, tumor burden was associated with DFS as a higher TB correlated with worse DFS (5-year DFS; low tumor burden: 38.3% vs medium tumor burden: 18.7% vs high tumor burden: 6.9%, $p < 0.001$; unadjusted HR; ref: low tumor burden; medium tumor burden: HR = 1.67, 95% CI 1.40–2.00; high tumor burden: HR = 2.31, 95% CI 1.81–2.95, Fig. 2b).

TABLE 1 Baseline characteristics of patients with low, medium, and high tumor burden

Variable	Overall (n = 1101)	Low tumor burden (n = 624)	Medium tumor burden (n = 346)	High tumor burden (n = 131)	p value
Age, median (IQR)	60 (51–69)	59 (51–68)	61 (51–69)	60 (52–69)	0.64
Male	610 (55.5%)	378 (60.7%)	167 (48.3%)	65 (49.6%)	< **0.001**
ASA					**0.004**
≤2	607 (65.9%)	365 (68.9%)	189 (65.4%)	53 (52.0%)	
>2	314 (34.1%)	165 (31.1%)	100 (34.6%)	49 (48.0%)	
CA19-9, UI/ml	49.4 (17.0–215.0)	39.4 (15.0–171.7)	62.0 (20.1–285.0)	98.5 (23.9–300)	**0.001**
ALBI grade					**0.005**
1	485 (65.5%)	318 (69.9%)	130 (59.1%)	37 (56.1%)	
2/3	256 (34.5%)	137 (30.1%)	90 (40.9%)	29 (43.9%)	
Cirrhosis	115 (12.1%)	75 (13.5%)	32 (10.6%)	8 (8.7%)	0.26
Location					< **0.001**
Unifocal	810 (80.8%)	501 (88.4%)	246 (75.9%)	63 (56.3%)	
Multifocal	193 (19.2%)	66 (11.6%)	78 (24.1%)	49 (43.8%)	
Type of resection					< **0.001**
Minor resection	402 (40.2%)	275 (48.7%)	104 (32.1%)	23 (20.7%)	
Major resection	598 (59.8%)	290 (51.3%)	220 (67.9%)	88 (79.3%)	
AJCC 8th edition N stage					< **0.001**
N0	271 (26.7%)	131 (22.8%)	105 (32.4%)	35 (30.4%)	
N1	183 (18.0%)	93 (16.2%)	59 (18.2%)	31 (27.0%)	
Nx	560 (55.3%)	351 (61.0%)	160 (49.4%)	49 (42.6%)	
Tumor size (cm)	6.0 (4.0–8.5)	4.7 (3.2–6.0)	9.0 (7.9–11.0)	8.5 (7.0–11.0)	< **0.001**
Multiple tumors	190 (17.2)	2 (0.3%)	59 (17.1%)	129 (98.5%)	< **0.001**
Margin status					**0.008**
R0	953 (87.0%)	557 (89.7%)	284 (82.8%)	112 (85.5%)	
R1	142 (13.0%)	64 (10.3%)	59 (17.2%)	19 (14.5%)	
Morphologic type					**0.04**
MF, IG	921 (88.0%)	523 (87.6%)	294 (91.0%)	104 (82.5%)	
PI, MF + PI	125 (12.0%)	74 (12.4%)	29 (9.0%)	22 (17.5%)	
Grade					< **0.001**
Well/moderate	838 (81.1%)	507 (87.0%)	255 (77.3%)	76 (63.3%)	
Poor/undifferentiated	195 (18.9%)	76 (13.0%)	75 (22.7%)	44 (36.7%)	
Major vascular invasion	151 (13.8%)	76 (12.2%)	48 (14.1%)	27 (20.6%)	**0.04**
Microvascular invasion	338 (31.2%)	165 (26.8%)	115 (33.8%)	58 (45.7%)	< **0.001**
Adjuvant chemotherapy	340 (32.1%)	167 (27.6%)	114 (34.9%)	57 (47.1%)	< **0.001**
Neoadjuvant chemotherapy	68 (7.6%)	34 (6.4%)	21 (7.2%)	13 (16.3%)	**0.008**
Tumor burden					–
Low	624 (56.7%)	624 (100%)	–	–	
Medium	346 (31.4%)	–	346 (100%)	–	
High	131 (11.9%)	–	–	131 (100%)	

Bold values denote statistical significance

IQR, interquartile range; ASA, American Society of Anesthesiologists; CA, carbohydrate antigen; MF, mass-forming; IG, intraductal growth; PI, periductal infiltrating; ALBI, albumin-bilirubin

On multivariable analysis, after adjusting for competing risk factors, patients with medium (HR = 1.40, 95% CI 1.14–1.71, p = 0.001) and high tumor burden (HR = 1.89, 95% CI 1.46–2.45, $p < 0.001$) had 40% and 89% higher hazards of death compared with patients with low ICC tumor burden, respectively (Table 2). Similarly, higher

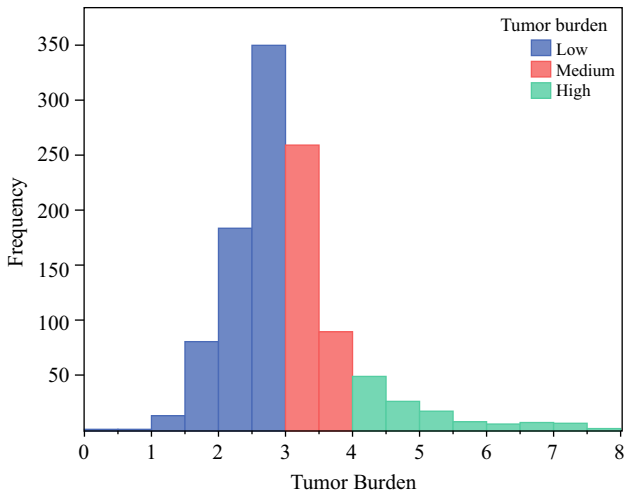

FIG. 1 Distribution of tumor burden in the multi-institutional cohort

tumor burden independently predicted worse DFS following resection of ICC (referent low tumor burden; medium tumor burden: HR = 1.61, 95% CI 1.33–1.96, $p < 0.001$; high tumor burden: HR = 2.03, 95% CI 1.56–2.64, $p < 0.001$) (Table 2). The accuracy of the models that included tumor burden was higher than that of the models incorporating tumor size and tumor number separately when predicting OS (c-index: 0.721 vs 0.716) and DFS (c-index: 0.652 vs 0.643).

The positive predictive value of medium/high and high tumor burden relative to 1-year mortality was 27.4% and 33.1%, respectively. The positive predictive value of different tumor burden classes relative to early (≤ 2 years) and very early (≤ 6 months) recurrence is summarized in Table 3.

External Validation: Tumor Burden Accurately Stratifies OS and DFS

The ability of ICC tumor burden to stratify prognosis among patients undergoing curative-intent resection for ICC was validated using an external cohort from the First Affiliated Hospital of Xi'an Jiaotong University (Xi'an, China) ($n = 104$) and Cleveland Clinic (Cleveland, Ohio) ($n = 74$). The distribution of ICC tumor burden in the external validation cohort was: low ($n = 120$, 67.4%), medium ($n = 48$, 27.0%), and high tumor burden ($n = 10$, 5.6%).

Survival analysis revealed an excellent prognostic discrimination using the tumor burden among the external validation cohort. Specifically, patients with low, medium, and high tumor burden had incrementally worse OS following resection of ICC (3-year OS; low tumor burden: 44.8%, medium tumor burden: 29.3%; high tumor burden: 23.3%, $p = 0.03$, unadjusted HR; ref: low tumor burden; medium tumor burden: HR = 1.50, 95% CI 1.10–2.45; high tumor burden: HR = 2.52, 95% CI 1.14–5.58, Fig. 3a). Similarly, DFS incrementally worsened with higher ICC tumor burden (3-year DFS: low tumor burden: 32.7%, medium tumor burden: 10.7%; high tumor burden: 0%, $p < 0.001$; unadjusted HR; ref: low tumor burden; medium tumor burden: HR = 1.70, 95% CI 1.09–2.65; high tumor burden: HR = 4.37, 95% CI 1.84-10.4, Fig. 3b).

Adjuvant Chemotherapy Is Associated with Increased Survival Among Patients with High Tumor Burden

The impact of neoadjuvant and adjuvant chemotherapy on OS was examined relative to the different tumor burden classes. Of note, neoadjuvant chemotherapy was not associated with an OS benefit across all tumor burden groups (5-year OS: neoadjuvant vs no neoadjuvant; low tumor burden: 39.7% vs 51.2%, $p = 0.06$; medium tumor burden: 21.3% vs 34.7%, $p = 0.97$; high tumor burden: 20.0% vs 18.1%, $p = 0.36$). In contrast, receipt of adjuvant chemotherapy was associated with increased survival among patients with high tumor burden disease (5-year OS: adjuvant vs no adjuvant; low tumor burden: 44.0% vs 50.4%, $p = 0.48$; medium tumor burden: 30.2% vs 30.7%, $p = 0.20$; high tumor burden: 24.4% vs 13.4%, $p = 0.02$, Fig. 4a–c). When analyzing tumor size alone, receipt of adjuvant chemotherapy was not associated with survival among patients with tumors < 5 cm (5-year OS: adjuvant

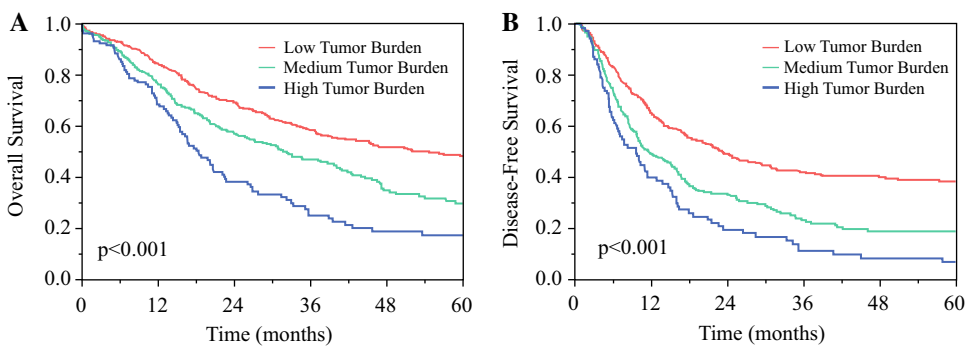

FIG. 2 Kaplan-Meier curves demonstrating differences in OS (**a**) and DFS (**b**) among patients with low, medium, and high tumor burdens in the multi-institutional cohort

TABLE 2 Bivariate and multivariable analysis of overall survival (OS) and disease-free survival (DFS)

Variables	Overall survival				Disease-free survival			
	Bivariate HR, 95% CI	*p* value	Multivariable HR, 95% CI	*p* value	Bivariate HR, 95% CI	*p* value	Multivariable HR, 95% CI	*p* value
Age (> 65)	1.00 (0.83–1.20)	0.98	–	–	0.78 (0.65–0.94)	**0.008**	0.74 (0.61–0.90)	**0.002**
Sex (male)	1.11 (0.93–1.31)	0.24	–	–	1.09 (0.92–1.28)	0.32	–	–
ASA class (> 2)	1.27 (1.06–1.53)	**0.01**	1.20 (0.98–1.46)	0.08	1.24 (1.03–1.49)	**0.02**	1.17 (0.96–1.44)	0.12
Cirrhosis	1.14 (0.86–1.49)	0.36	–	–	1.03 (0.79–1.35)	0.81	–	–
CA 19-9 (> 200)	2.45 (1.98–3.04)	< **0.001**	2.32 (1.82–2.96)	< **0.001**	1.47 (1.19–1.82)	< **0.001**	1.31 (1.03–1.67)	**0.03**
AJCC 8th edition N stage								
N0	Ref		Ref		Ref		Ref	
N1	2.58 (1.99–3.33)	< **0.001**	2.19 (1.66–2.88)	< **0.001**	1.74 (1.36–2.22)	< **0.001**	1.53 (1.17–1.99)	**0.002**
Nx	1.25 (1.00–1.56)	0.05	1.74 (1.34–2.24)	< **0.001**	0.93 (0.76–1.14)	0.51	1.17 (0.92–1.49)	0.21
Tumor burden								
Low	Ref		Ref		Ref		Ref	
Medium	1.49 (1.23–1.80)	< **0.001**	1.40 (1.14–1.71)	**0.001**	1.67 (1.40–2.00)	< **0.001**	1.61 (1.33–1.96)	< **0.001**
High	2.31 (1.82–2.92)	< **0.001**	1.89 (1.46–2.45)	< **0.001**	2.31 (1.81–2.95)	< **0.001**	2.03 (1.56–2.64)	< **0.001**
Margin status (R1)	1.88 (1.49–2.38)	< **0.001**	2.06 (1.57–2.71)	< **0.001**	1.33 (1.04–1.71)	**0.02**	1.29 (0.98–1.70)	0.07
Morphologic type								
MF, IG	Ref		Ref		Ref		Ref	
PI, MF + PI	1.72 (1.35–2.19)	< **0.001**	1.43 (1.09–1.89)	**0.011**	1.37 (1.06–1.76)	**0.01**	1.08 (0.81–1.44)	0.59
Grade (poor/undiff)	1.71 (1.40–2.09)	< **0.001**	1.56 (1.26–1.95)	< **0.001**	1.55 (1.26–1.89)	< **0.001**	1.27 (1.02–1.59)	**0.03**
Major resection	1.23 (1.02–1.48)	**0.031**	0.81 (0.64–1.03)	0.08	1.20 (1.01–1.43)	**0.04**	0.83 (0.66–1.03)	0.09
Microvascular invasion	1.31 (1.09–1.57)	**0.004**	1.13 (0.92–1.38)	0.26	1.35 (1.13–1.60)	**0.001**	1.22 (1.00–1.49	**0.048**
Adjuvant chemotherapy	1.04 (0.87–1.25)	0.65	–	–	1.57 (1.32–1.86)	< **0.001**	1.22 (0.99–1.51)	0.06

Bold values denote statistical significance

ASA, American Society of Anesthesiologists; CA, carbohydrate antigen; MF, mass-forming; IG, intraductal growth; PI, periductal infiltrating; AJCC, American Joint Committee on Cancer; HR, hazard ratio; CI, confidence interval

TABLE 3 Sensitivity, specificity and positive predictive value of different tumor burden cut-offs relative to 1-year mortality, early (≤ 2 years) and very early recurrence (≤ 6 months) following resection of ICC

Tumor burden		1-year mortality	Early recurrence	Very early recurrence
Medium/high vs low	Sensitivity*	55.0% (48.0–61.9%)	50.3% (45.8–54.8%)	54.6% (47.3–61.7%)
	Specificity*	60.5% (56.9–63.4%)	68.8% (62.8–74.4%)	61.8% (58.1–65.4%)
	PPV	27.4%	75.3%	28.7%
High vs medium/low	Sensitivity*	18.7% (13.6–24.6%)	14.9% (11.8–18.3%)	18.4% (13.2–24.5%)
	Specificity*	89.8% (87.4–91.8%)	94.2% (90.7–96.7%)	91.4% (89.0–93.4%)
	PPV	33.1%	82.9%	37.5%

PPV, positive predictive value; ICC, intrahepatic cholangiocarcinoma

*Expressed as value (95% CI)

vs no adjuvant: 39.3% vs 56.7%, $p = 0.09$), 5–10 cm (35.6% vs 28.6%, $p = 0.051$) or > 10 cm (27.6% vs 29.1%, $p = 0.46$). Similarly, when analyzing number of tumor lesions only, adjuvant chemotherapy was again not associated with survival (5-year OS: adjuvant vs no adjuvant; single: 39.4% vs 45.4%, $p = 0.96$; multiple: 25.6% vs 17.9%, $p = 0.08$).

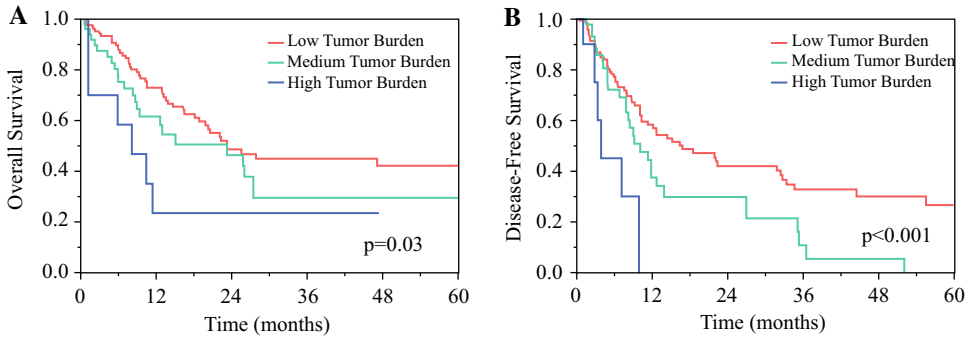

FIG. 3 Kaplan–Meier curves demonstrating differences in OS (**a**) and DFS (**b**) among patients with low, medium, and high tumor burden in the external validation cohort

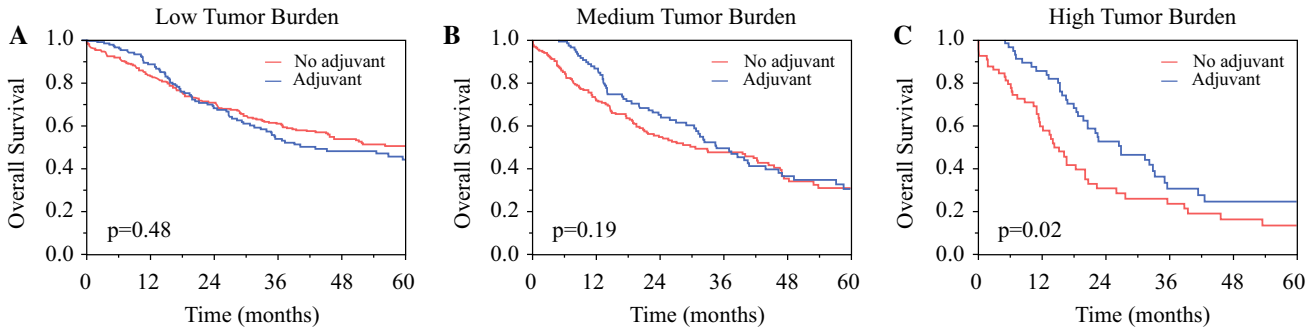

FIG. 4 Kaplan–Meier curves demonstrating differences in OS relative to the receipt of adjuvant chemotherapy among patients with low (**a**), medium (**b**), and high (**c**) tumor burden disease

DISCUSSION

ICC is an aggressive malignancy associated with a poor prognosis.[2,4] Surgery is considered the best chance for long-term survival among patients with resectable ICC, yet only one in ten patients will achieve long-term "cure" even after curative-intent resection.[19] To this end, there is a need for better patient selection of surgical candidates and more precise risk stratification in the pre- and postoperative setting. Tumor burden appears to be a powerful predictor of outcomes among patients with hepatobiliary malignancies, especially HCC and CRLM.[6–9] Nevertheless, the impact of tumor burden among patients with ICC is not well understood to date. The current study was important because we demonstrated that tumor burden (logarithm [natural] of tumor size + the number of lesions)[12] dictated outcomes of patients following resection of ICC. Of note, both OS and DFS incrementally worsened with higher ICC tumor burden, resulting in a 5-year OS and DFS of only 17.3% and 6.9% among individuals within the high tumor burden group (approximately 10% of the cohort). Importantly, tumor burden remained an independent predictor of outcomes even after adjusting for all relevant clinicopathologic characteristics, and was able to stratify prognosis accurately in an external validation cohort. In addition, tumor burden was able to identify individuals who might benefit the most from adjuvant chemotherapy (i.e., individuals with high tumor burden). To our knowledge, this is the first study to utilize ICC tumor burden to stratify outcomes of patients following resection of ICC.

Tumor burden has been considered to be a powerful predictor of outcomes among patients with liver cancer.[6–9] Although traditionally assessed using cut-off values of tumor size or tumor number, more recent tools have evaluated tumor burden in a continuous rather than a categorical fashion, which may improve prognostication and increase statistical power.[20,21] For example, Mazzaferro et al.[9] suggested a "metro-ticket" tool based on HCC tumor size and number to predict survival after liver transplantation, and noted that this tool was superior to the traditional Milan criteria. In a separate study, Sasaki et al.[7] proposed a novel "tumor burden score" (TBS) consisting of tumor size and number based on the principles of the Pythagorean theorem to predict prognosis following resection of CRLM, which was later validated in the setting of HCC.[6] Nevertheless, the "optimal" definition of tumor burden for ICC remains largely unknown. Recently, Bagante et al.[12] examined a number of combinations and mathematical transformations using size and tumor number to determine the most accurate prediction of prognosis after ICC resection. Notably, TBS showed sub-optimal performance in ICC, and the best definition of ICC tumor burden was considered the logarithmic transformation of size plus the number of lesions.[12] As such, tumor burden may need

to be defined differently to achieve an "optimal" risk stratification among patients with hepatobiliary malignancies, depending on the specific diagnosis. The current study expanded on this previous work and suggested categories to stratify patients as low, medium, and high relative to ICC tumor burden. Importantly, OS and DFS incrementally worsened as tumor burden increased and was particularly poor among patients with the highest tumor burden. In fact, individuals with a high tumor burden had a 5-year OS and DFS of only 17.3% and 6.9%, respectively, with almost one-third of patients dying within the first year following resection of ICC (positive predictive value of 1-year mortality: 33.1%, Table 3), suggesting that these patients might be better treated with alternative treatment strategies, including neoadjuvant therapy or other non-surgical treatment modalities. Importantly, the suggested ICC tumor burden categories accurately discriminated OS and DFS in both the multi-institutional (development cohort), as well as the external validation cohorts (Figs. 2, 3) confirming the generalizability of the findings. Tumor burden remained an independent predictor of both OS and DFS among patients with resectable ICC even after adjusting for relevant clinicopathologic characteristics (Table 2). Collectively, the data suggest that tumor burden is an important predictor of outcomes among patients undergoing resection for ICC. Given the extremely poor outcomes of patients with high ICC tumor burden, these patients may be better treated with alternative treatment options, including neoadjuvant chemotherapy prior to resection or other loco-regional treatment strategies, rather than upfront resection.

The role of adjuvant chemotherapy among patients with resectable ICC remains debatable. Of note, the BILCAP study demonstrated that adjuvant chemotherapy with capecitabine improved outcomes after resection of biliary tract cancers,[22] whereas the PRODIGE trial did not reveal a survival benefit with adjuvant gemcitabine and oxaliplatin (GEMOX) despite an acceptable safety/tolerance profile.[23] Although the etiology for these disparate results is likely multifactorial, heterogeneity in patient populations enrolled in these trials may account for these differences. For example, there was a greater number of patients with node-positive disease and R1 resection margins in the BILCAP versus PRODIGE trial, which might suggest that adjuvant therapy potentially is more beneficial among patients with adverse prognostic factors (i.e., LN metastasis and R1 margins) as opposed to individuals with favorable clinicopathologic characteristics. In line with this hypothesis, two recent meta-analyses reported that adjuvant chemotherapy following ICC resection was more beneficial among patients with positive resection margins and lymph node metastasis.[24,25] Of note, the current study demonstrated that despite poor outcomes among patients with high ICC tumor burden, adjuvant chemotherapy was associated with increased survival among these individuals (5-year OS: 24.4% vs 13.4%, $p = 0.02$, Fig. 4c). Interestingly, patients with high ICC tumor burden more frequently had an R1 resection and lymph node metastasis compared with individuals with low tumor burden (Table 1), which further supports the hypothesis of a beneficial effect of adjuvant chemotherapy among patients with adverse clinicopathologic characteristics. As such, apart from accurate prognostication, tumor burden may also help identify individuals who would benefit the most from adjuvant chemotherapy following ICC resection. Taken together, data from the current study suggest that patients with high tumor burden had poor outcomes following resection and should be better considered for alternative and adjuvant treatment strategies.

Certain limitations should be considered when interpreting the findings of the current study. Selection bias was possible due to the retrospective nature of the study. In addition, the criteria for patient selection for surgery and surgical techniques may have varied among different participating centers. Also, the impact of adjuvant and neoadjuvant chemotherapy among patients with different ICC tumor burdens could not be assessed in the external validation cohort due to the limited number of patients receiving perioperative treatment. Finally, pathologic assessment of tumor size and number may have slightly varied at different centers, although these variations were unlikely to be clinically significant.[26]

In conclusion, tumor burden dictated prognosis among patients undergoing surgery for ICC. Patients with high tumor burden had an extremely dismal prognosis after resection of ICC. The proposed tumor burden classification was also able to predict outcomes accurately in an external validation cohort. While neoadjuvant chemotherapy was not associated with survival across the tumor burden groups, receipt of adjuvant chemotherapy was associated with increased survival among patients with high tumor burden. Estimating the tumor burden of ICC patients may help clinicians in the preoperative treatment selection process, and can help guide post-resection treatment strategies among high-risk patients (i.e., adjuvant chemotherapy for high ICC tumor burden patients).

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