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ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Tumor Necrosis Impacts Prognosis of Patients Undergoing Resection for T1 Intrahepatic Cholangiocarcinoma

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ABSTRACT

Background. The prognostic impact of tumor necrosis among patients undergoing resection for intrahepatic cholangiocarcinoma (ICC) remains ill-defined.

Methods. Patients who underwent curative-intent resection for ICC between 2000 and 2017 were identified using a multi-institutional database. The association of pathologic tumor necrosis with overall survival (OS) and recurrence-free survival (RFS) was examined.

Results. Among 757 patients who underwent resection for ICC, tumor necrosis was present in 384 (50.7%) patients (no necrosis: $n = 373$, 49.3%; <50% necrosis: $n = 291$, 38.4%; ≥50% necrosis: $n = 93$, 12.3%). Tumor necrosis was associated with worse OS (5-year OS: no necrosis 39.3% vs. <50% necrosis 34.7% and ≥50% necrosis 24.0%; $p = 0.03$) and RFS (5-year RFS: no necrosis 25.7% vs. <50% necrosis 13.9% and ≥50% necrosis 18.8%; $p < 0.001$). After stratifying by T stage, tumor necrosis was able to further stratify prognosis among patients with T1a ICC (5-year RFS: T1a and no necrosis 46.7% vs. T1a and necrosis 36.1%; $p = 0.02$), and T1b ICC (5-year RFS: T1b and no necrosis 31.1% vs. T1b and necrosis 11.2%; $p = 0.006$), but was not associated with outcomes among patients with more advanced T2–T3 disease. Patients with T1a ICC and tumor necrosis had similar 5-year RFS as individuals with T1b ICC and no tumor necrosis (36.1% vs. 31.1%; $p = 0.66$).

Conclusion. Tumor necrosis was associated with worse prognosis among patients with T1 ICC. Tumor necrosis for T1 ICC should be considered as an important factor to

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further stratify outcomes of patients with early T-stage ICC.

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver cancer with an increasing incidence over the last three decades worldwide.[1, 2] Despite originating from the same organ, ICC displays a much more aggressive behavior compared with hepatocellular carcinoma (HCC).[3, 4] In fact, even after curative intent resection, median survival among individuals with ICC ranges from 15 to 37 months, whereas the respective figures among individuals with HCC range between 26 and 55 months depending on the extent of resectable disease.[5, 6] Given the poor prognosis associated with ICC, efforts have recently focused on improving prognostication and optimizing selection criteria to identify the best candidates for surgery.[7] In addition, investigators have focused on developing perioperative strategies (i.e. neoadjuvant or adjuvant chemotherapy) that could potentially improve long-term survival among individuals with resectable, high-risk tumors.[7, 8]

Traditional predictors of outcomes among patients with resectable ICC include tumor burden (i.e. size and number), differentiation/grade, macro- and microvascular invasion, presence of lymph node metastasis (LNM), margin status, and tumor-specific markers (i.e. carbohydrate antigen [CA] 19-9 and, less importantly, carcinoembryonic antigen [CEA] levels).[7, 8] Of note, the American Joint Committee on Cancer (AJCC) 8th edition staging system incorporates tumor size and number, vascular invasion, as well as LNM and presence of distant metastases to define staging in ICC.[9] Nevertheless, the traditional AJCC staging system, as well as other available prognostic scores, have been suboptimal in accurately predicting prognosis of patients with ICC.[10, 11] In particular, significant variations in outcomes may exist among patients within the same pathologic stage, suggesting that other factors might also have a prognostic value among individuals with ICC.[10, 11]

Tumor necrosis has been associated with worse prognosis among individuals with a variety of solid tumors, including HCC and pancreatic and breast cancer.[12–14] Due to the rarity of the disease, there is a paucity of data regarding the association of tumor necrosis with long-term outcomes among patients with resectable ICC.[15] To this end, the objective of this study was to define the prognostic impact of tumor necrosis among patients who underwent resection of ICC utilizing a large multi-institutional database. In addition, we sought to examine whether a modified T classification that incorporates tumor necrosis in the existing AJCC staging schema could better stratify outcomes among individuals undergoing resection for ICC.

METHODS

Inclusion and Exclusion Criteria

Patients who underwent curative-intent liver resection for ICC between the years 2000 and 2017 were identified using the International Intrahepatic Cholangiocarcinoma Study Group database that incorporates data from 15 major hepato-pancreatico-biliary (HPB) centers worldwide.[16, 17] Patients who underwent palliative resection, had R2 resection, had missing follow-up data, or did not have available histopathologic data on tumor necrosis were excluded from the analytic cohort (Supplementary Fig. 1). The Institutional Review Board of all participating institutions approved this study.

Variables Examined

Demographic and clinicopathologic data included age, sex, American Society of Anesthesiologists (ASA) performance score, history of cirrhosis, preoperative serum CA19-9, extent of resection (i.e. minor or major), uni- or multifocality, T and N stage, resection margins (i.e. R0, R1), morphological ICC subtype (i.e. mass-forming [MF], intraductal growth [IG], or periductal infiltrating [PI]), tumor grade, presence of micro- or macrovascular invasion, and receipt of adjuvant chemotherapy.

Major hepatectomy was defined as resection of three or more Couinaud segments,[18] and tumor staging (T and N stage) was defined according to the AJCC 8th edition staging manual.[9] Presence of tumor necrosis was prospectively evaluated by pathologists at each of the participating centers and was classified as absent, moderate ($\leq$50% extent), or extensive necrosis (>50% extent). In cases where patients had multiple lesions, tumor necrosis status was defined according to the lesion with the most severe necrosis.

Statistical Analysis

Descriptive statistics were presented as median (interquartile range [IQR]) and frequency (%) for continuous and categorical variables, respectively. Bivariate analyses included the Wilcoxon rank-sum test for continuous variables and Chi-square test or Fisher's exact test for categorical variables, as appropriate. Overall survival (OS) was defined as the time interval between the date of liver resection and the date of death or last follow-up, while recurrence-free survival (RFS) was defined as the time interval between the date of liver resection and date of recurrence or last follow-up. RFS was deemed the primary outcome of this study given that this outcome is disease-specific and is not affected by other factors such as

performance status and treatment of recurrent disease. After stratifying by T stage, bivariate survival analyses were performed using Kaplan–Meier curves and log-rank test to assess the impact of tumor necrosis on RFS. Due to the limited number of patients after stratifying both by T stage and tumor necrosis (absent, <50% extent, >50% extent), tumor necrosis was evaluated as a binary variable (absent/present).

A new proposed T classification that incorporates tumor necrosis was evaluated by means of Cox regression analysis to assess whether the proposed T classification was independently associated with RFS after adjusting for all other relevant clinicopathologic characteristics. Clinicopathologic variables significant on bivariate analysis ($p < 0.05$) were entered into the multivariable models to assess the current versus proposed AJCC T stage relative to RFS following resection of ICC. Model fit was calculated and compared using the corrected Akaike information criterion (AICc) and was also assessed visually via Kaplan–Meier plots for each model; the lowest AICc value indicated a better fit for the prognostic model.[19, 20] The level of statistical significance for all tests was set at $\alpha = 0.05$. All statistical analyses were performed using the SPSS version 26 (IBM Corporation, Armonk, NY, USA) and JMP version 14 (SAS Institute Inc., Cary, NC, USA) statistical packages.

RESULTS

Demographics of the Analytic Cohort

A total of 757 patients underwent curative-intent resection for ICC and met the inclusion criteria (Table 1). Patients had a median age of 62 years (IQR 54–70), an ASA class ≤2 ($n = 370$, 53.7%), and most patients were female ($n = 392$, 51.9%). Median CA19-9 levels prior to surgery were 80.6 UI/mL, and 21.4% ($n = 162$) of patients had LNM. Only a minority of patients had a history of cirrhosis ($n = 38$, 6.2%). The majority of patients underwent an R0 resection ($n = 619$, 82.3%), had MF or IG ICC subtype ($n = 576$, 81.9%), and had well to moderately differentiated tumors ($n = 525$, 72.6%). Approximately one-third of patients had microvascular invasion on pathology ($n = 234$, 35.7%), and 47.2% ($n = 289$) of patients received adjuvant chemotherapy following liver resection (Table 1).

On pathology, tumor necrosis was present in 384 (51.0%) patients (no necrosis: $n = 373$, 49.0%; necrosis <50%: $n = 219$, 38.4%; necrosis >50%: $n = 93$, 12.3%). Of note, tumor necrosis was associated with a number of clinicopathologic characteristics. Specifically, patients with tumor necrosis on pathology were younger (median age: 60 years [IQR 51–69] vs. 64 years [IQR 56–71]), had higher preoperative CA19-9 levels (median: 120.2 [IQR 34.7–300.0] vs. 53.2 [IQR 19.0–236.0]), larger tumors (size >5 cm: 67.4% vs. 57.4%), and more frequently had poor/undifferentiated tumor grade (32.8% vs. 21.8%) and received adjuvant chemotherapy following resection (52.1% vs. 43.5%) [all $p < 0.05$] (Table 1).

Impact of Tumor Necrosis on Long-Term Outcomes

Median and 5-year OS following liver resection for ICC in the entire cohort was 34.6 months (95% confidence interval [CI] 29.8–39.5) and 35.6%, respectively, while median and 5-year RFS following ICC resection was 14.3 months (95% CI 12.4–16.2) and 20.8%, respectively. ICC tumor necrosis was associated with both OS (5-year OS: no necrosis, 39.3%; necrosis <50%, 34.7%; necrosis >50%, 24.0%) and RFS (5-year RFS: no necrosis, 25.7%; necrosis <50%, 22.6%; necrosis >50%, 13.9%) [both $p < 0.001$] (Figs. 1a, b). Among patients who experienced a recurrence, individuals with tumor necrosis on pathology had a higher incidence of simultaneous intra- and extrahepatic recurrence (26.8% vs. 17.5%; $p = 0.01$), as well as a higher incidence of very early recurrence (i.e. recurrence within 6 months following resection) [34.9% vs. 22.7%; $p = 0.01$].

Impact of Tumor Necrosis on Recurrence-Free Survival by T Stage and Proposal for Modification of American Joint Commission on Cancer T stage

After stratifying by AJCC T stage, tumor necrosis was able to further stratify prognosis among patients with T1a ICC (5-year RFS: T1a and no necrosis, 46.7% vs. T1a and necrosis, 36.1%; $p = 0.02$) and T1b ICC (5-year RFS: T1b and no necrosis, 31.1% vs. T1b and necrosis, 11.2%; $p = 0.006$); however, tumor necrosis was not associated with outcomes among patients with more advanced T2 (5-year RFS: T2 and no necrosis, 19.6% vs. T2 and necrosis, 20.0%; $p = 0.34$) or T3 disease (5-year RFS: T3 and no necrosis, 8.7% vs. T3 and necrosis, 5.9%; $p = 0.93$) (Fig. 2). Of note, patients with T1a ICC and tumor necrosis had similar RFS as individuals with T1b ICC and no tumor necrosis (5-year RFS: T1a and necrosis, 36.1% vs. T1b and no necrosis, 31.1%; $p = 0.66$) (Fig. 3).

Based on these data, we proposed a new T-stage classification (T_n) that incorporated pathologic tumor necrosis into the current staging system: $T1a_n$, T1a tumors without necrosis; $T1b_n$, T1a with necrosis or T1b without necrosis; $T2_n$, T1b with necrosis or previous T2; $T3_n$, similar to T3 (Table 2). Of note, the proposed T classification was able to better stratify RFS compared with the current T classification (proposed T_n classification, 5-year RFS: $T1a_n$ 46.6%, $T1b_n$ 32.6%, $T2_n$ 16.3%, $T3_n$ 7.5%, $p < 0.001$, AIC

TABLE 1 Baseline characteristics of patients with and without tumor necrosis on pathology

Variable	Overall [$N = 757$]	No tumor necrosis [$n = 373$, 49.3%]	Tumor necrosis [$n = 384$, 50.7%]	p-value
Age, years [median (IQR)]	62 (54–70)	64 (56–71)	60 (51–69)	**<0.001**
Female	392 (51.9)	196 (52.5)	196 (51.2)	0.38
ASA				0.20
≤2	370 (53.7)	171 (51.2)	199 (56.1)	
>2	319 (46.3)	163 (48.8)	156 (43.9)	
CA19-9, UI/mL	80.6 (23.9–290.0)	53.2 (19.0–236.0)	120.2 (34.7–300.0)	**0.003**
Cirrhosis	38 (6.2)	16 (5.2)	22 (7.2)	0.30
Location				0.66
Unifocal	572 (76.0)	280 (75.3)	292 (76.6)	
Multifocal	181 (24.0)	92 (24.7)	89 (23.4)	
Type of resection				0.92
Minor resection	185 (24.6)	92 (24.8)	93 (24.5)	
Major resection	566 (75.4)	279 (75.2)	287 (75.5)	
AJCC 8th edition N stage				0.18
N0	289 (38.3)	154 (41.5)	135 (35.2)	
N1	162 (21.4)	78 (21.0)	84 (21.9)	
Nx	306 (40.4)	139 (37.5)	165 (43.0)	
AJCC 8th edition T stage				0.03
T1a	128 (16.9)	71 (19.0)	57 (14.8)	
T1b	138 (18.2)	74 (19.8)	64 (16.7)	
T2	393 (51.9)	173 (46.4)	220 (57.3)	
T3/T4	98 (12.9)	55 (14.7)	43 (11.2)	
Size >5 cm	474 (62.6)	215 (57.6)	259 (67.4)	**0.005**
Multiple tumors	133 (17.6)	64 (17.2)	69 (18.0)	0.77
Margin status				0.65
R0	619 (82.3)	303 (81.7)	316 (82.9)	
R1	133 (17.7)	68 (18.3)	65 (17.1)	
Morphologic type				**0.001**
MF, IG	576 (81.9)	253 (76.9)	323 (86.4)	
PI, MF+PI	127 (18.1)	76 (23.1)	51 (13.6)	
Tumor grade				**0.001**
Well/moderate	525 (72.6)	277 (78.2)	248 (67.2)	
Poor/undifferentiated	198 (27.4)	77 (21.8)	121 (32.8)	
Microvascular invasion	234 (35.7)	134 (36.2)	100 (35.0)	0.74
Adjuvant chemotherapy	289 (47.2)	150 (43.5)	139 (52.1)	**0.03**

Bold p-values indicate statistical significance

The percentages derive from the number of patients with each of the above characteristics divided by the number of patients with data available on the respective variable shown in this table

IQR interquartile range, *ASA* American Society of Anesthesiologists, *CA* carbohydrate antigen, *AJCC* American Joint Committee on Cancer, *MF* mass-forming, *IG* intraductal growth, *PI* periductal infiltrating

4380; current T classification: T1a 42.0%, T1b 21.2%, T2 17.4%, T3 7.5%, $p < 0.001$, AIC 4392) (Fig. 4). When assessing OS, the proposed T classification was also able to better stratify OS compared with the current T classification (Supplementary Fig. 2).

On multivariable analysis after adjusting for relevant clinicopathologic characteristics, the current 8th edition AJCC T classification was not associated with RFS (ref T1a; T1b: hazard ratio [HR] 1.48, 95% CI 0.87–2.53; T2: HR 1.28, 95% CI 0.80–2.03; T3: HR 1.57, 95% CI 0.90–2.74). In contrast, the modified T classification was independently associated with RFS, with higher T_n stage predicting incrementally worse RFS after adjusting for other relevant covariates (ref $T1a_n$; T1bn: HR 1.95, 95% CI 0.94–4.02; $T2_n$: HR 1.93, 95% CI 1.01–3.68; $T3_n$: HR 2.28, 95% CI 1.11–4.67) (Table 3).

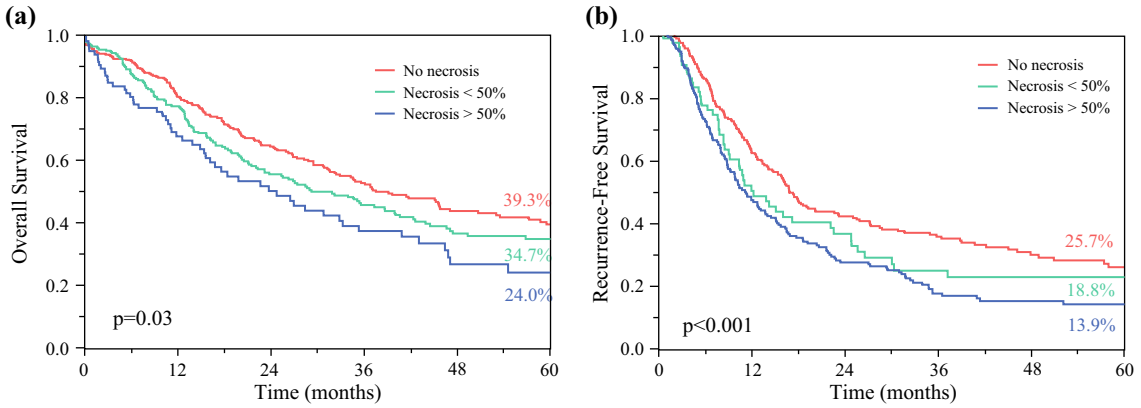

FIG. 1 Kaplan–Meier curves demonstrating differences in (**a**) overall survival and (**b**) recurrence-free survival among patients without tumor necrosis versus patients with moderate or extensive tumor necrosis

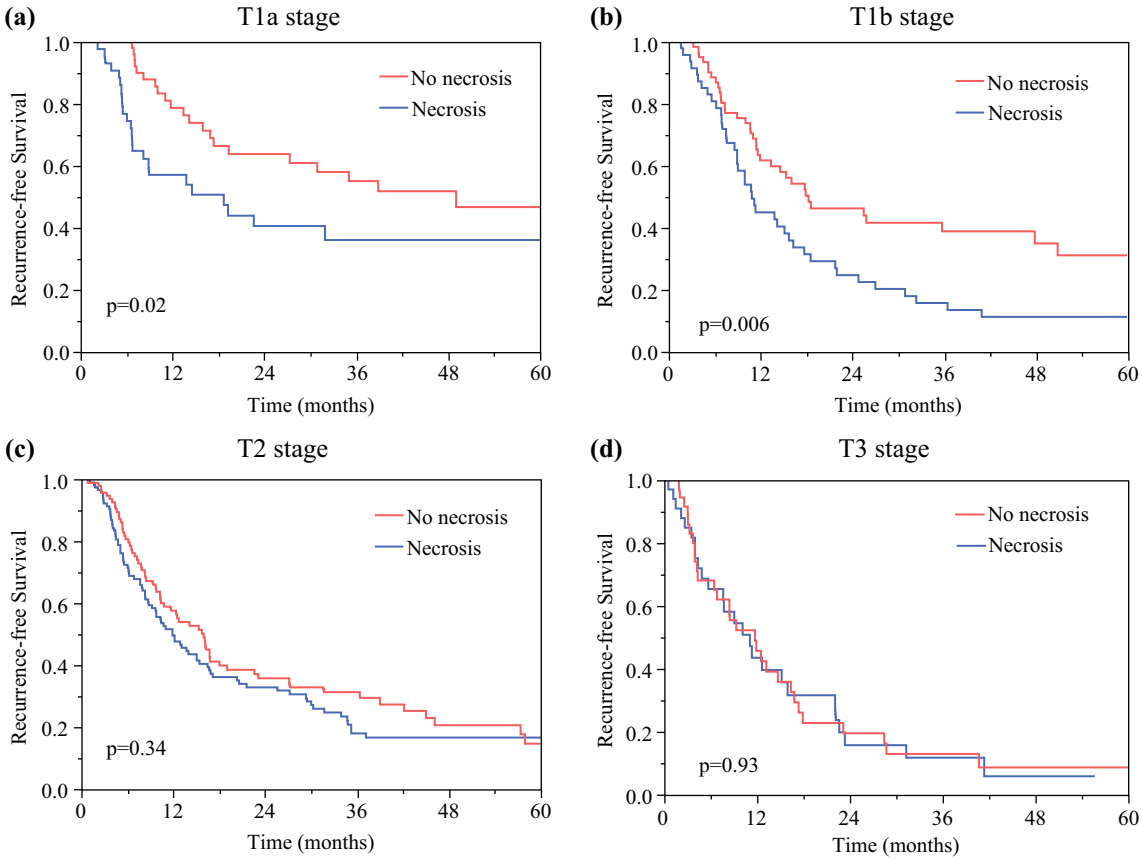

FIG. 2 Kaplan–Meier curves demonstrating differences in recurrence-free survival among (**a**–**d**) individuals with or without tumor necrosis per T stage

DISCUSSION

Although the impact of tumor necrosis on long-term outcomes among individuals with solid tumors has been previously investigated for certain tumors, the association of tumor necrosis with outcomes among patients with hepatobiliary tumors, and in particular ICC, remains ill-defined. In turn, the current study was important because we specifically examined the impact of tumor necrosis on long-term outcomes among individuals with resectable ICC utilizing an international, multi-institutional database. Of note, the data suggested that the presence of tumor necrosis on pathology was associated with adverse outcomes (both OS and RFS) among individuals who had

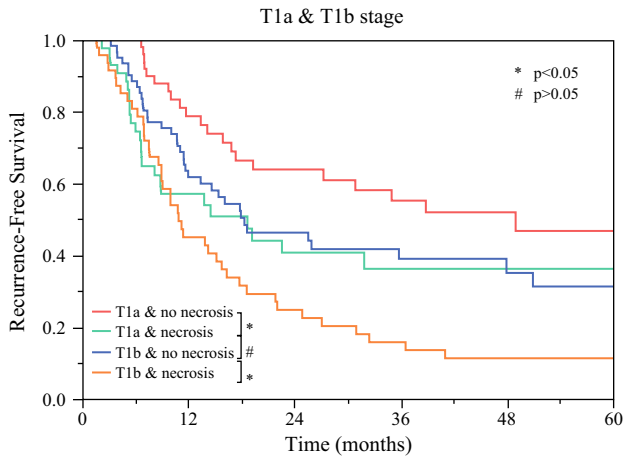

FIG. 3 Kaplan–Meier curves demonstrating differences in recurrence-free survival among individuals with T1a and T1b intrahepatic cholangiocarcinoma with or without tumor necrosis

undergone resection for ICC. Importantly, tumor necrosis was associated with a higher incidence of simultaneous intra- and extrahepatic recurrence, as well as a higher incidence of very early recurrence following resection. In particular, the impact of tumor necrosis on outcomes was more pronounced among individuals with early T-stage tumors (T1a, T1b), yet not associated with outcomes among patients with more advanced T2–T3 disease. In fact, individuals with T1a ICC and tumor necrosis had similar outcomes as patients with T1b tumors without necrosis. A proposed T classification that incorporated tumor necrosis better stratified RFS compared with the current AJCC 8th edition T classification. To the best of our knowledge, this is the largest study to examine the impact of tumor necrosis relative to prognosis among patients with ICC.

Tumor necrosis, characterized by the presence of dead cells with preservation of the tissue architecture, has been considered a poor predictor of outcomes among individuals with a number of solid malignancies. For example, Sengupta et al. noted that tumor necrosis was an independent predictor of outcomes for renal cell carcinoma, suggesting that this information should be routinely used in clinical practice to guide clinical decision making.[21] In analyzing 348 patients with pancreatic adenocarcinoma, Hiraoka et al. demonstrated that histologic necrosis was a simple, accurate, and reproducible predictor of postoperative

TABLE 2 Proposed AJCC T-staging modification

Current 8th edition AJCC staging		Proposed AJCC T-stage changes	
T1a	Solitary tumor ≤5 cm without vascular invasion	$T1a_n$	T1a without necrosis
T1b	Solitary tumor >5 cm without vascular invasion	$T1b_n$	T1a with necrosis or T1b without necrosis
T2	Solitary tumor with intrahepatic vascular invasion or multiple tumors, with or without vascular invasion	$T2_n$	T1b with necrosis or previous T2
T3	Tumor perforating the visceral peritoneum	$T3_n$	Same as T3

AJCC American Joint Committee on Cancer

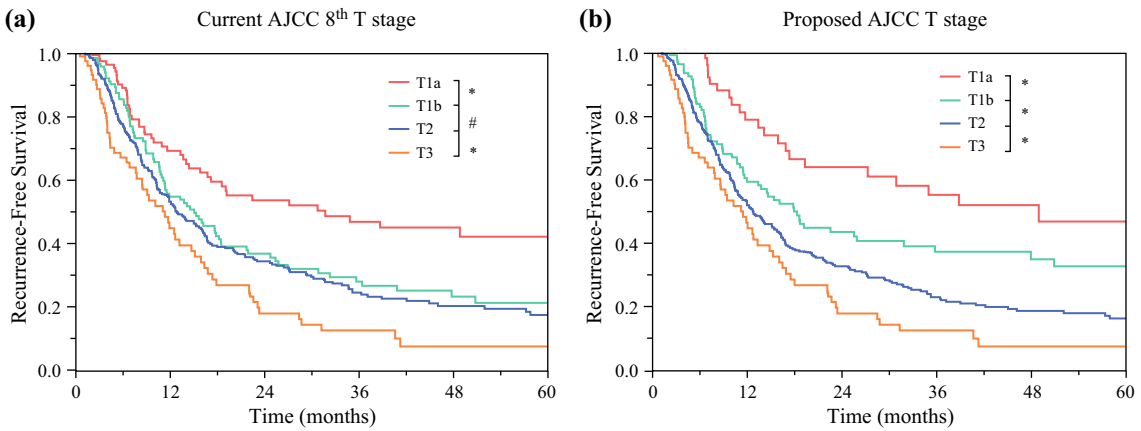

FIG. 4 Kaplan–Meier curves demonstrating differences in recurrence-free survival per T stage based on the **a** current 8th edition AJCC T stage and **b** proposed AJCC T stage. *AJCC* American Joint Committee on Cancer

TABLE 3 Multivariable analysis: current and proposed modification of AJCC 8th edition T stage

Variables	Current AJCC 8th edition T stage				Proposed AJCC T stage			
	HR	95% CI		*p*-value	HR	95% CI		*p*-value
Age >65 years	0.739	0.550	0.992	**0.044**	0.726	0.543	0.971	**0.031**
Morphology (PI, MF/PI)	1.179	0.800	1.738	0.404	1.142	0.777	1.678	0.50
Poor/undifferentiated tumor grade	1.411	1.036	1.923	**0.029**	1.402	1.025	1.918	**0.035**
CA19-9 >200 ng/mL	1.503	1.121	2.015	**0.006**	1.490	1.110	1.999	**0.008**
AJCC N0	Ref				Ref			
AJCC Nx	1.340	0.939	1.911	0.106	1.341	0.940	1.913	0.105
AJCC N1	1.680	1.208	2.337	**0.002**	1.651	1.189	2.293	**0.003**
AJCC T1a	Ref				Ref			
AJCC T1b	1.483	0.870	2.528	0.148	1.947	0.942	4.021	0.072
AJCC T2	1.278	0.804	2.031	0.300	1.929	1.010	3.681	**0.046**
AJCC T3	1.574	0.903	2.744	0.109	2.281	1.113	4.674	**0.024**

Bold p-values indicate statistical significance

AJCC American Joint Committee on Cancer, *HR* hazard ratio, *CI* confidence interval, *Ref* reference, *MF* mass-forming, *PI* periductal infiltrating, *CA* carbohydrate antigen

outcomes.[14] In another single-center analysis, Richards et al. reported that tumor necrosis was associated with worse cancer-specific survival among individuals who underwent resection for colorectal cancer over a 10-year period.[22]

The exact mechanism contributing to poor prognosis among individuals with solid malignancies and tumor necrosis remains unclear. One possible explanation is that rapid tumor growth may contribute to the relative hypoperfusion in the core areas of tumors leading to hypoxia, and subsequent cell death.[12, 14, 23] Necrotic cells release cellular contents, which may then act as proinflammatory and tumor-promoting cytokines. Tumor necrosis attenuates local and systemic inflammatory response, remodeling the tumor microenvironment to promote immune evasion.[24, 25] Tumor necrosis might also interfere with the process of neo-angiogenesis in cancer, providing routes for tumor cells to disseminate.[26] Hypoxia may induce genomic instability and alter DNA damage pathways, resulting in increased tumor resistance to treatment and, in turn, poor outcomes.[25] In line with these findings, individuals with tumor necrosis experienced worse RFS and OS compared with individuals without histologic necrosis. In particular, patients with tumor necrosis were more likely to have simultaneous intra- and extrahepatic recurrence, as well as very early recurrence following ICC resection, which has been associated with a median survival of 13.8 months.[7]

To date, only a few studies have examined the impact of tumor necrosis on hepatobiliary tumors. For example, Wei et al. recently demonstrated the prognostic impact of tumor necrosis among 919 patients who underwent curative-intent resection for HCC.[12] In this study, tumor necrosis was a strong predictor of poor outcomes following HCC resection irrespective of T stage.[12] In another study, Atanasov et al. demonstrated that tumor necrosis was the only independent prognostic factor among individuals with resected hilar cholangiocarcinoma ($n = 47$) after adjusting for other clinicopathologic characteristics.[27] The same group later reported on the impact of tumor necrosis among 88 patients with ICC in a single-center analysis.[15] The current study utilized a large multi-institutional database to assess the impact of tumor necrosis on outcomes of patients with ICC. In the current study, tumor necrosis was identified in 51% of ICC tumors following curative-intent resection. Of note, this percentage was lower than the incidence reported among patients with pancreatic cancer (64.1%),[14] yet higher than individuals with HCC (40%)[12] or breast cancer (42.2%).[28] Although the explanation behind this finding is likely multifactorial, ICC is typically a poorly vascularized tumor, which may have contributed to the relatively higher incidence of tumor necrosis. In addition, ICC displays an aggressive biologic behavior and growth that could at least in part explain the higher incidence of tumor necrosis on pathology versus HCC or breast cancer. In line with this hypothesis, tumor necrosis was associated with worse clinicopathologic characteristics, including higher CA19-9 levels, larger tumors, and poor/undifferentiated tumor grade, all known to be adversely related to long-term survival.[7, 8] Of note, tumor necrosis was associated with younger patient age, which has previously been shown to be a risk factor for early recurrence among individuals with ICC.[7]

The AJCC 8th edition staging system incorporates tumor size and number and vascular invasion, as well as lymph node metastases and presence of distant metastases, to define staging of ICC. Of note, the data from the current

study demonstrated that the presence of necrosis on pathology 'upstaged' patients with early T1-stage tumors. In particular, patients with T1a ICC and tumor necrosis had comparable RFS as individuals with T1b ICC without tumor necrosis, while patients with T1b tumors with necrosis had similar RFS as T2 patients. Based on these findings, a modified T classification was proposed that incorporated tumor necrosis in early T1-stage tumors (Table 2). The modified T classification was able to better stratify outcomes among individuals with ICC compared with the current 8th edition AJCC T stage. On multivariable analysis, after adjusting for relevant clinicopathologic characteristics, the modified T was independently associated with RFS, with higher T stage predicting incrementally worse RFS, which was not seen with the current 8th edition T stage (Table 3). Collectively, patients with tumor necrosis on pathology were at increased risk for recurrence and adverse outcomes. The modified T stage may enhance prognostication among patients with early T-stage ICC and help identify individuals with early-stage disease who are at high risk for recurrence following resection.

Several limitations should be considered when interpreting the findings of the current study. Selection bias as to which patients had available data on pathologic tumor necrosis was possible. The limited number of patients with T4 tumors and data available on tumor necrosis ($n = 9$) did not allow us to perform further analyses on this particular patient group. We also did not directly compare the presence of tumor necrosis with other factors such as CA19-9, morphologic type, and tumor grade. As such, the relative impact of these factors on AJCC T category will need to be assessed in the future. In addition, patient selection and surgical techniques may have varied among different participating institutions. Furthermore, only major HPB centers contributed data to this study—tumor specimens were evaluated for necrosis by experienced hepatopathologists at each of the participating centers following standard pathologic assessment guidelines.

CONCLUSION

Tumor necrosis was present in approximately one in two patients who underwent curative-intent resection for ICC. Tumor necrosis was associated with OS and RFS as well as simultaneous intra- and extrahepatic recurrence following curative-intent resection of ICC. The presence of tumor necrosis upstaged patients with T1a and T1b tumors, yet did not impact the outcomes of individuals with more advanced T2–T3 disease. A modified T classification that incorporates tumor necrosis can further stratify the outcomes of patients with early T-stage ICC.

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