ORIGINAL ARTICLE

Proposed modification of the eighth edition of the AJCC staging system for intrahepatic cholangiocarcinoma

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Abstract

Background: To improve the prognostic accuracy of the 8th edition of the American Joint Committee on Cancer (AJCC) staging system for intrahepatic cholangiocarcinoma (ICC) with establishment and validation of a modified TNM (mTNM) staging system.

Methods: Data on patients who underwent curative-intent resection for ICC was collected from 15 high-volume centers worldwide (n = 643). An external validation dataset was obtained from the SEER registry (n = 797). The mTNM staging system was proposed by redefining T categories, and incorporating the recently proposed N status as N0 (no lymph node metastasis [LNM]), N1 (1–2 LNM) and N2 (≥3 LNM).

Results: The 8th AJCC TNM staging system failed to stratify overall survival (OS) of stage II versus IIIA, stage IIIB versus IV, as well as overall stage III versus IV among all patients from the two databases, as well as stage I versus II, and stage III versus III among patients who had ≥6 LNs examined. There was a monotonic decrement in survival based on the proposed mTNM staging classification among patients derived from both the multi-institutional (Median OS, stage I 69.8 vs. II 37.1 vs. III 18.9 vs. IV 16.4 months, all $p < 0.05$), and SEER (Median OS, stage I 87.0 vs. II 29.3 vs. III 17.7 vs. IV 14.2 months, all $p < 0.05$) datasets, which was also verified among patients who had ≥6 lymph node harvested from both databases.

Conclusion: The modified TNM staging system for ICC using the new T and N definitions provided an improved means to stratify patients relative to long-term OS versus the 8th AJCC staging.

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Introduction

Accurate assessment of tumor stage is important to estimate patient survival, provide information to guide postoperative surveillance, as well as direct decisions around adjuvant therapy. The staging of patients with intrahepatic cholangiocarcinoma (ICC) has traditionally lagged behind other cancers, including

hepatocellular carcinoma (HCC). In fact, there was no distinct staging system for ICC until 2010 when the American Joint Committee on Cancer (AJCC) staging manual first introduced a unique TNM staging system specific to ICC.[1] The initial staging system contained in the 7th edition of AJCC staging manual was established largely based on data from the Surveillance, Epidemiology, and End Results (SEER) registry.[2] As such, related analyses were limited by the quality and granularity of the data, with the 7th edition ICC AJCC staging system subsequently being questioned by multiple investigators.[3–5]

In 2017, the updated 8th edition of AJCC staging system made several significant changes including the incorporation of tumor size ≤5 cm versus >5 cm, redefining of T categories, as well as downstaging of lymph node metastasis (LNM) IVA to IIIB.[6,7] In turn, studies have sought to validate the 8th versus 7th edition of AJCC staging system noting that the prognostic accuracy of the 8th edition was only partially improved or comparable to the 7th edition.[3–5] In particular, several studies suggested that the definition of T3 as tumor perforation of the visceral peritoneum may be problematic, as patients with T3 disease often had a better survival outcome than patients with T1b or T2 disease.[4,5,8,9] In addition, several studies have also reported failure of the 8th AJCC staging system to distinguish survival of patients with stage II disease from stage III disease, as well as individuals with stage III versus stage IV disease.[10,4,5,9,11]

The association between LNM, number of LNM and prognosis following resection of ICC has also been debated. LNM is identified in roughly 40% of patients with ICC, and can be associated with tumor recurrence and poor outcomes after curative resection.[12–14] In other types of biliary cancer, such as gallbladder carcinoma, hilar cholangiocarcinoma and distal cholangiocarcinoma, nodal staging has been subdivided into N0, N1 and N2.[6] To this end, our research group recently proposed a new nodal staging for ICC: N0 (no nodal metastasis), N1 (1–2 LNM), and N2 (≥3 LNM), which was associated with a stepwise increased hazard of death.[14] This new nodal system has not, however, been widely adopted.

Given the ongoing debate around the current AJCC 8th staging system, the objective of the current study was to examine the prognostic accuracy of the 8th edition of AJCC staging system using a large international multi-institutional database. In addition, we sought to develop a modified TNM (mTNM) staging system that consisted of new T categories, as well as the recently proposed novel N categories, using the international cohort.[14] This novel mTNM staging system was then externally validated in the SEER dataset to assess the prognostic stratification of patients following resection of ICC.

Patients and methods

Study cohort and data collection

Patients who underwent curative-intent resection (R0/R1) for ICC between November 1999 and August 2017 were identified from a database involving 15 major hepatobiliary centers in North America, Europe, Australia and Asia.[14] All patients were diagnosed with ICC confirmed by histological examination. The Institutional Review Board of each participating institution approved the study.

A standardized datasheet was created for collection of clinicopathologic and surgical information. Tumor-related characteristics, including maximal tumor diameter, number, location, tumor morphology, histological grade, invasion of adjacent organs, major vascular invasion, microvascular/perineural invasion, satellite lesions, total number of lymph node (LN) examined (TNLE), as well as number of metastatic LNs evaluated based on final pathology were obtained. Pathologic staging was assigned according to the 8th edition of the AJCC staging guidelines (Table 1).[15] Specifically, multiple tumors were defined as multifocal tumors, as well as a tumor with satellite lesions or intrahepatic metastasis; vascular invasion included both macro- and microvascular invasion.[15] The morphological status of ICC was grouped as mass forming (MF)/intraductal growth (IG) and periductal infiltrating (PI) ± MF sub-types. For all cases, the imaging and pathological data were reviewed to determine the macroscopic morphologic sub-types. Patients who underwent palliative resection (n = 18), who were lost during follow-up (n = 37), as well as individuals who had no information on pathologic nodal information (n = 671) were excluded. Patients were regularly followed after surgery with ultrasound, abdominal CT and/or MRI scanning. Overall survival (OS) was calculated from the date of surgery to the date of death or last follow-up.

Data collection from the SEER registry

The SEER database was used to identify ICC patients between 1975 and 2016 using the 3rd edition International Classification of Disease for Oncology (ICD-O-3). Patients with ICC were identified by using the primary site code for liver (22.0) and the histology code for cholangiocarcinoma (8160), as well as by the primary site code for intrahepatic bile duct (22.1) with the histology codes for malignant neoplasm (8000), malignant tumor cells (8001), carcinoma (8010), undifferentiated carcinoma (8020), adenocarcinoma (8140), and cholangiocarcinoma (8160). TNM information was retrieved based on the following codes: collaborative stage (CS) tumor size (2004–2015), CS extension (2004–2015), CS lymph nodes (2004–2015), CS mets at DX (2004–2015), extent of disease (EOD) 10-size (1988–2003), EOD 10-extent (1988–2003), EOD 10—nodes (1988–2003) and regional metastatic nodes (1988+). M1 disease was defined as disease found at the time of surgery or metastatic disease that presented with 90 days of surgery.

Using this algorithm, 17,266 patients with ICC were identified. Only patients with microscopically confirmed primary ICC and patients who underwent cancer-directed surgery (surgery of primary site codes 20–80) were included (n = 2226). Patients with no data on lymphadenectomy (n = 1137) were excluded. Moreover, patients who did not have

Table 1 The 8th edition AJCC definition and modified definition for Intrahepatic Cholangiocarcinoma staging

7th AJCC Staging System for ICC		8th AJCC Staging System for ICC	
T1	Solitary tumor without vascular invasion	T1	Solitary tumor without vascular invasion, ≤5 cm, or >5 cm
T2a	Solitary tumor with vascular invasion	T1a	Solitary tumor ≤5 cm without vascular invasion
T2b	Multiple tumors, with or without vascular invasion	T1b	Solitary tumor >5 cm without vascular invasion
T3	Tumor perforating the visceral peritoneum or involving structures by direct invasion	T2	Solitary tumor with intrahepatic vascular invasion or multiple tumors, with or without vascular invasion
		T3	Tumor perforating the visceral peritoneum
T4	Tumor with periductal invasion	T4	Tumor involving local extrahepatic structures by direct invasion
N0	No regional lymph node metastasis	N0	No regional lymph node metastasis
N1	Regional lymph node metastasis present	N1	Regional lymph node metastasis present
M0	No distant metastasis	M0	No distant metastasis
M1	Distant metastasis	M1	Distant metastasis

Modified 8th AJCC Staging System for ICC	
T1	Solitary tumor ≤5 cm without vascular invasion
T2	Solitary tumor >5 cm without vascular invasion
T3	Solitary tumor with vascular invasion
T4	Multiple tumors, or tumors with periductal infiltrating, or tumor involving local extrahepatic structures by direct invasion
N0	No regional lymph node metastasis
N1	1-2 regional lymph node metastasis
N2	≥3 regional lymph node metastasis
M0	No distant metastasis
M1	Distant metastasis

7th AJCC for ICC		8th AJCC for ICC		Modified 8th AJCC for ICC	
I	T1N0M0	IA	T1aN0M0	IA	T1N0M0
II	T2N0M0	IB	T1bN0M0	IB	T2N0M0
III	T3N0M0	II	T2N0M0	IIA	T3N0M0
IVA	T4N0M0, T_{Any}N1M0	IIIA	T3N0M0	IIB	T4N0M0, T1-2N1M0
IVB	T_{Any} N_{Any}M1	IIIB	T4N0M0, T_{Any}N1M0	III	T3-4N1M0, T1-2N2M0
		IV	T_{Any} N_{Any}M1	IV	T3-4N2M0, $T_{Any}N_{Any}$M1

Staging systems		Multi-institutional database				SEER registry			
		8th AJCC				8th AJCC			
		I	II	III	IV	I	II	III	IV
Modified AJCC	I	111	3	23	0	248	0	7	0
	II	6	145	115	0	0	92	54	0
	III	0	0	139	0	0	0	136	0
	IV	0	0	67	34	0	0	50	46

complete data to allow re-staging per the 8th edition of the AJCC classifications and the modified 8th AJCC classifications, including T stage, nodal status, distant metastases, and follow-up data were also excluded. As the SEER registry did not code tumor growth patterns before 2010, data of morphological types were unavailable. Overall, a total of 797 patients with ICC were identified in the SEER dataset who met criteria.

Statistical analysis

Continuous variables were expressed as medians with interquartile ranges (IQR) and were compared with student *t* test or Mann–Whitney U test. Statistical comparisons for categorical variables were made using χ^2 test or Fisher's exact test. Overall survival (OS) was analyzed using the Kaplan–Meier method and compared using log-rank tests to evaluate the staging system. Factors associated with OS were identified using univariable and

multivariable Cox proportional hazards regression models. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated. The receiver-operating characteristic curve (ROC) analysis was used to investigate the discriminatory ability of the AJCC and modified TNM staging system, and the area under the curve (AUC) were compared using Z statistics. The variables with a p value less than 0.05 on univariate analysis were included in the multivariable models. Statistical analyses were performed using SPSS version 21.0 (IBM SPSS Inc., Chicago, IL, USA) for multi-institutional database, whereas STATA 14.0 software (StataCorp, College Station, TX) was utilized for the SEER database analyses. A 2-tailed P value of <0.05 was considered statistically significant.

Results

Baseline characteristics

Among 643 patients who underwent curative-intent resection and simultaneous LND, median age was 62 (IQR 52–70) years and 307 (47.7%) patients were male (Table 2). Median tumor size was 6.0 (IQR 4.5–9.0) cm and 202 (31.4%) patients had multiple tumors; median TNLE was 4 (IQR 2–8) and 270 (42.0%) patients had LNM on histopathologic examination. Among patients who had LNM on pathologic examination, 188 (29.2%) had 1 to 2 LNM, whereas 82 (12.8%) had 3 or more LNM. Morphological subtypes included MF (n = 485, 75.4%), PI ± MF (n = 122, 17.6%) and IG (n = 13, 2.0%). A majority (n = 540, 84.0%) of patients underwent R0 resection. A subset of patients (n = 238, 37.0%) received adjuvant chemotherapy following resection. Overall median, 1-, 3- and 5-year OS were 30.6 months, 76.5%, 44.9% and 29.7%, respectively.

Among 797 patients who underwent curative-intent resection and LND identified from the SEER registry, median age was 63 (IQR 53–71) years and 365 (45.8%) patients were male (Table 2). Median tumor size was 5.5 (IQR 3.5–8.0) cm and 196 (24.6%) patients had multiple tumors. Median number of LNs examined was 3 (IQR 1–6) and 270 (33.9%) patients had LNM; 196 (24.6%) had 1 to 2 LNM, whereas 74 (9.3%) patients had 3 or more LNM. Among patients in the SEER cohort, 388 (48.7%) patients received adjuvant chemotherapy. Overall median, 1-, 3- and 5-year OS were 32.0 months, 78.8%, 46.3% and 33.5%, respectively.

AJCC staging classification and survival

The 8th edition of the AJCC staging system failed to stratify OS among patients with stage II versus stage IIIA (median OS, 37.8 vs. 50.8 months, $p = 0.314$), stage IIIB versus stage IV (median OS, 18.9 vs. 17.0 months, $p = 0.256$), and overall stage III versus stage IV (median OS, 20.7 vs. IV 17.0 months, $p = 0.058$) disease (Fig. 1) among patients in multi-institutional cohort, as well as patients in the SEER registry (median OS, stage II 33.0 vs. IIIA 88.8 months, $p = 0.636$; IIIB 18.0 vs. IV 15.5 months, $p = 0.858$; III 18.9 vs. IV 15.5 months, $p = 0.779$) (Fig. 2). On multivariable analysis, compared with AJCC stage IA disease, patients with stage IIIA disease (tumor perforating the visceral peritoneum with no nodal or distant metastasis) had comparable long-term survival as patients with stage IA (HR 1.5, 95% CI 0.7–3.3, $p = 0.329$) in the multi-institutional database (Supplementary Table 1), as well as in the SEER registry (HR 1.4, 95% CI 0.5–4.6, $p = 0.512$).

Modified AJCC staging on survival

Given the poor discriminatory power of the 8th edition AJCC staging system, a modified TNM staging system was established with a new definition for T and N (N0, no LNM; N1, 1–2 LNM; N2, ≥3 LNM) categories.[14] Among tumor-associated factors, tumor size (>5 vs. ≤ 5 cm, HR 1.6, 95% CI 1.2–2.0), number (multiple vs. single, HR 1.6, 95% CI 1.3–2.1, $p < 0.001$), direct invasion of extrahepatic structures (HR 1.7, 95% CI 1.1–2.6, $p = 0.012$), macrovascular (HR 1.6, 95% CI 1.2–2.1, $p < 0.001$) and microvascular invasion (HR 1.3, 95% CI 1.0–1.6, $p = 0.036$), as well as PI ± MF types (referent MF/IG types, HR 1.7, 95% CI 1.0–1.6, $p < 0.001$), rather than perforation of visceral peritoneum (HR 1.2, 95% CI 0.9–1.6, $p = 0.219$), were associated with increased risk of patient death (Supplementary Table 1). As such, a modified definition of T (mT) categories was generated according to the median OS of patients with certain tumor-associated characteristics (Supplementary Fig. 1a) (Table 1). For example, patients with PI-type ICC, multiple ICC, and ICC with direct invasion of a local extrahepatic structure had similar worse median OS (19.5 months, 20.9 months, and 22.2 months, respectively; p > 0.05); as such, ICC tumors with these characteristics were classified as modified T4 (mT4). A solitary tumor ≤5 cm or >5 cm without vascular invasion were defined as mT1 and mT2, respectively, whereas a solitary tumor with vascular invasion was defined as mT3 (Supplementary Fig. 1a).

According to the new definition of T and N categories, the median OS of patients with modified T, N and M status were compared (Supplementary Fig. 1b). The median OS of patients with the same stage according to the current 8th AJCC staging system varied widely among different substages. For example, patients with LNM were classified as stage IIIB in the 8th edition AJCC staging system with median survival time varying widely among patients with T1-2N1 (1–2 LNM) M0, T3-4N1M0/T1-2N2 (≥3 LNM) M0, as well as T3-4N2M0. As such, the substages were regrouped into a new proposed modified TNM staging system according to the median OS of patients in each substage (Table 1) (Supplementary Fig. 1b).

According to the mTNM staging system, patients with stage IA (T1N0M0) had a comparable OS with stage IB (T2N0M0) (median OS, IA 101.4 vs. IB 66.3, $p = 0.179$) in both the multi-institutional (Fig. 1c) and SEER datasets (median OS, IA 73.0 vs. IB 88.1, $p = 0.848$) (Fig. 2c). In contrast, patients with stage IIA had equivalent survival to stage IIB (median OS, IIA 45.2 vs. IIB 31.7, $p = 0.354$) in the multi-institutional database (Fig. 1c), yet a more favorable OS than IIB in the SEER registry (median OS, IIA

Table 2 Characteristics of patients undergoing hepatic resection and regional lymphadenectomy for intrahepatic cholangiocarcinoma in the multi-institutional and SEER databases

Variables	*n* (%)/median (IQR)	
	Multi-institutional data (n = 643)	SEER data (n = 797)
Age (years)	62 (52–70)	63 (53–71)
Male gender	307 (47.7%)	365 (45.8%)
Nodal metastasis on preoperative imaging	192 (29.9%)	/
Liver cirrhosis	89 (13.8%)	/
Tumor size (cm)	6.0 (4.5–9.0)	5.5 (3.5–8.0)
Multiple lesions (≥2)	202 (31.4%)	196 (24.6%)
Bilobar tumor	128 (19.9%)	/
Major vascular resection	104 (16.2%)	/
Bile duct resection	160 (24.9%)	/
Total number of lymph nodes examined	4 (2–8)	3 (1–6)
Nodal metastasis	270 (42.0%)	270 (33.9%)
1-2 LNM	188 (29.2%)	196 (24.6%)
≥ 3 LNM	82 (12.8%)	74 (9.28%)
Intraoperative blood loss	550 (300–1000)	/
Operation time (min)	298 (190–439)	/
Vascular invasion		
Macro	123 (19.1%)	/
Micro	254 (39.5%)	/
Perineural invasion	173 (26.9%)	/
Direct invasion of adjacent organs	37 (5.8%)	102 (12.8%)
Biliary invasion	118 (18.4%)	/
AJCC staging		
IA	33 (5.1%)	127 (15.9%)
IB	84 (13.1%)	121 (15.2%)
II	148 (23.0%)	206 (25.9%)
IIIA	73 (11.4%)	8 (1.0%)
IIIB	271 (42.1%)	289 (36.3%)
IV	34 (5.3%)	46 (5.8%)
Histological grade		
Well to moderate	447 (69.5%)	470 (59.0%)
Poor to undifferentiated	152 (23.6%)	225 (28.2%)
Missing	44 (6.8%)	102 (12.8%)
Morphological type		
Mass-forming	485 (75.4%)	/
Periductal infiltrating	48 (7.5%)	/
Intraductal papillary	13 (2.0%)	/
MF + periductal infiltrating	64 (10.0%)	/
Missing	33 (5.1%)	/
R0 margin	540 (84.0%)	/
Postoperative complications	257 (40.0%)	/
Adjuvant chemotherapy	238 (37.0%)	388 (48.7%)

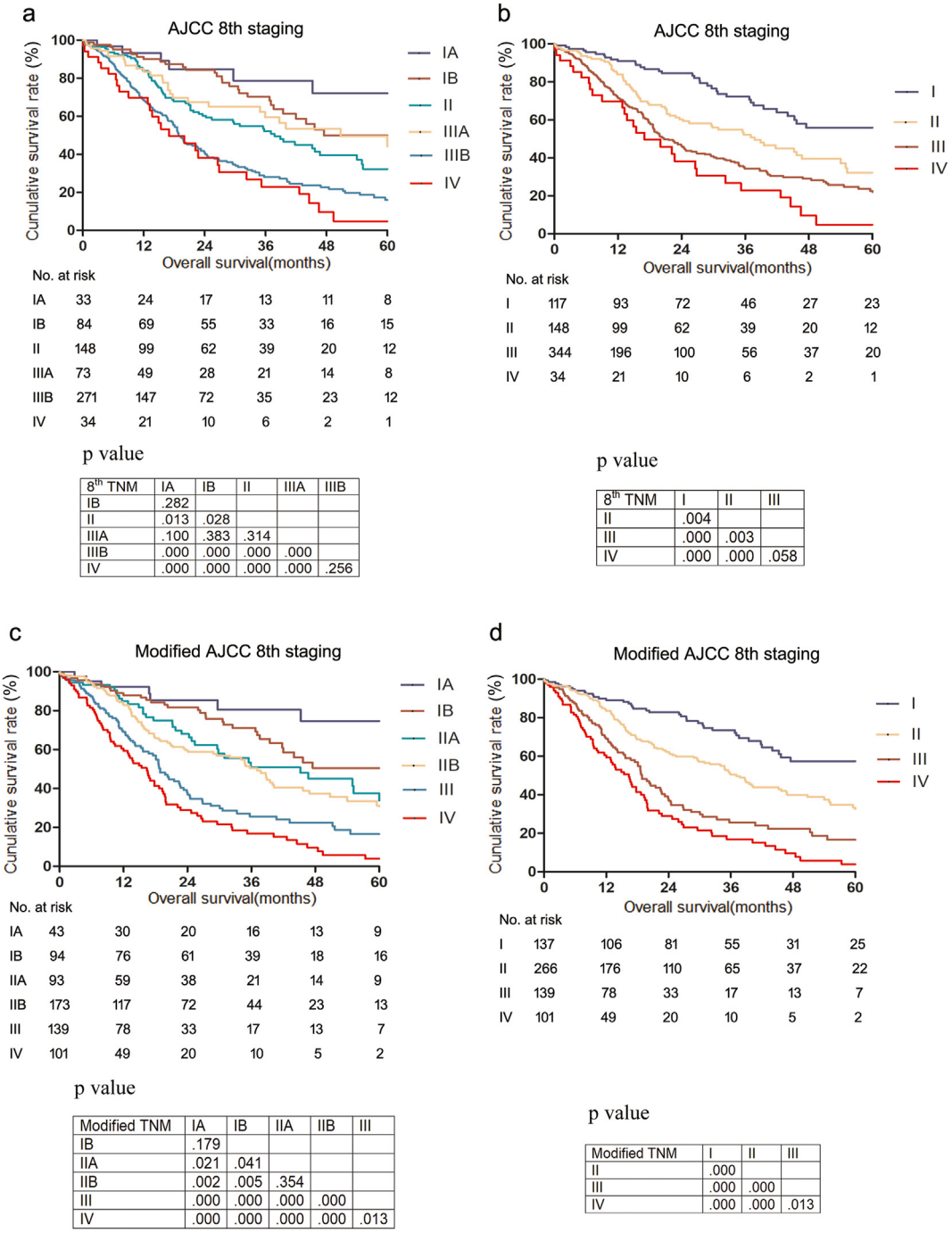

Figure 1 Survival of patients undergoing curative-intent resection for intrahepatic cholangiocarcinoma in the multi-institutional database stratified by the 8th American Joint Committee on Cancer (**a and b**), as well as the proposed modified new staging system (**c and d**)

46.0 vs. IIB 26.5, $p = 0.002$) (Fig. 2c). Of note, there was worsening survival as patients were upstaged (median OS, I 69.8 vs. II 37.1 vs. III 18.9 vs. IV 16.4 months, all $p < 0.05$) in the multi-institutional database (Fig. 1d), as well as in the SEER registry (median OS, I 87.0 vs. II 29.3 vs. III 17.7 vs. IV 14.2 months, all $p < 0.05$) (Fig. 2d). In addition, on multivariable analysis, mTNM staging was strongly associated with prognosis, as the hazard of death increased incrementally with each stage among patients in both the multi-institutional (Referent IA, IB: HR 1.6, 95% CI 0.8–3.4, $p = 0.188$; IIA: HR 2.3, 95% CI 1.1–4.7, $p = 0.028$; IIB: HR 2.9, 95% CI 1.5–5.8, $p = 0.003$; III: HR 4.8, 95% CI 2.4–9.5, $p < 0.001$; IV: HR 7.0, 95% CI 3.5–13.9,

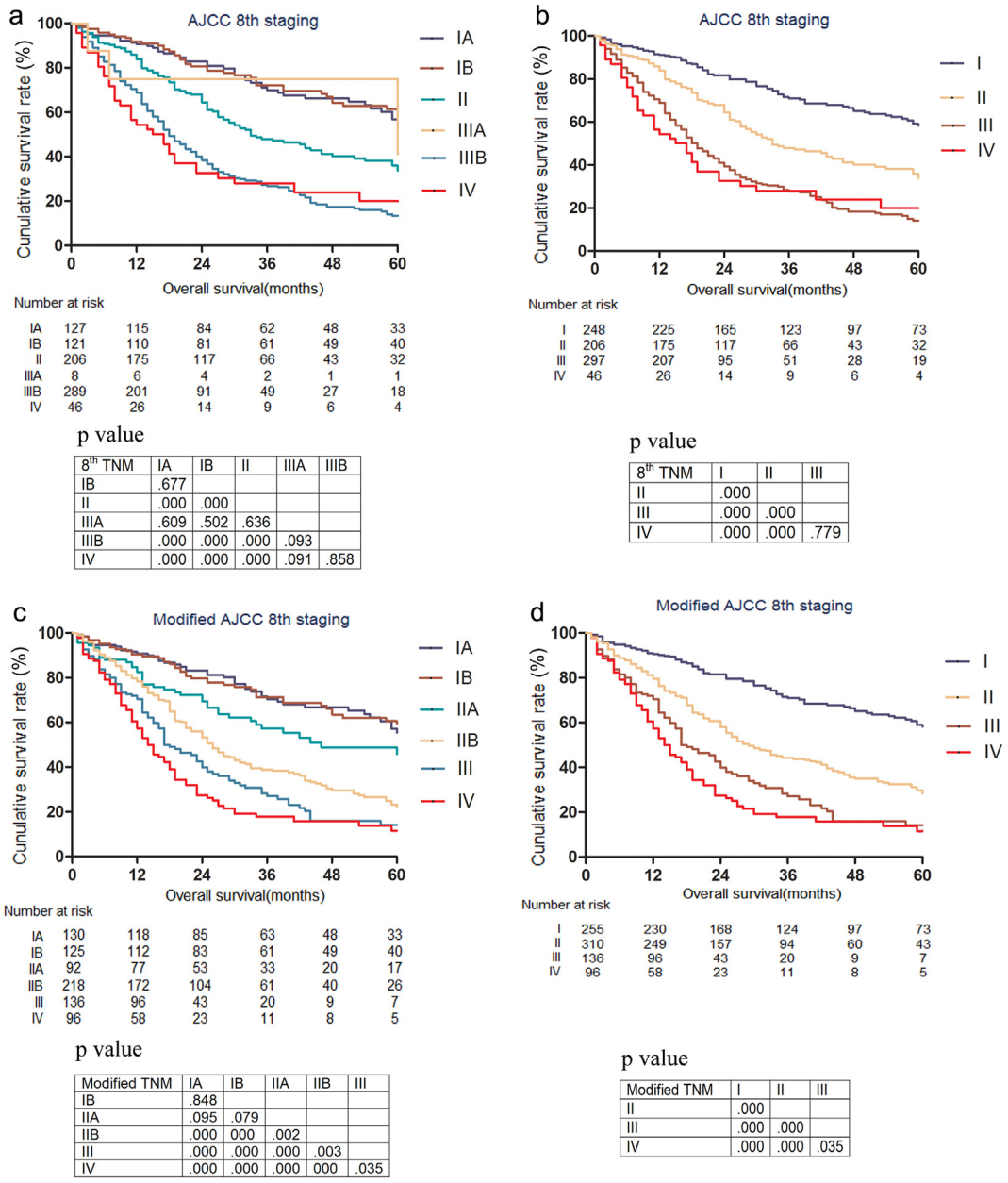

Figure 2 Survival of patients with intrahepatic cholangiocarcinoma (ICC) from SEER registry stratified by the 8th American Joint Committee on Cancer (**a and b**), as well as the proposed modified new staging system (**c and d**)

$p < 0.001$) (Supplementary Table 1), as well as in the SEER (Referent IA, IB: HR 1.0, 95% CI 0.6–1.5, $p = 0.851$; IIA: HR 1.4, 95% CI 1.0–1.9, $p = 0.035$; IIB: HR 2.5, 95% CI 1.7–3.5, $p<0.001$; III: HR 3.6, 95% CI 2.5–4.5, $p < 0.001$; IV: HR 4.6, 95% CI 3.1–6.3, $p < 0.001$) datasets. Of note, the mTNM outperformed the 8th edition AJCC staging system in the multi-institutional (mTNM, AUC 0.669, 95% CI 0.631–0.705 vs. AJCC, AUC 0.635, 95% CI 0.597–0.673, $p = 0.003$), as well as the SEER (mTNM, AUC 0.690, 95% CI 0.656–0.722 vs. AJCC, AUC 0.676, 95% CI 0.642–0.708, $p = 0.042$) database.

Impact of number of LNs examined on staging performance

As the AJCC staging manual recommended a minimum number of 6 LNs be examined for accurate nodal evaluation, further validation of the proposed TNM staging was performed among patients with ≥6 TNLE from both the multi-institutional (n = 250, 38.9%) and SEER (n = 199, 25.0%) databases. Of note, the current 8th edition AJCC staging system failed to differentiate survival outcome among patients with stage I versus stage II (median OS: multi-institutional data, stage I not attained

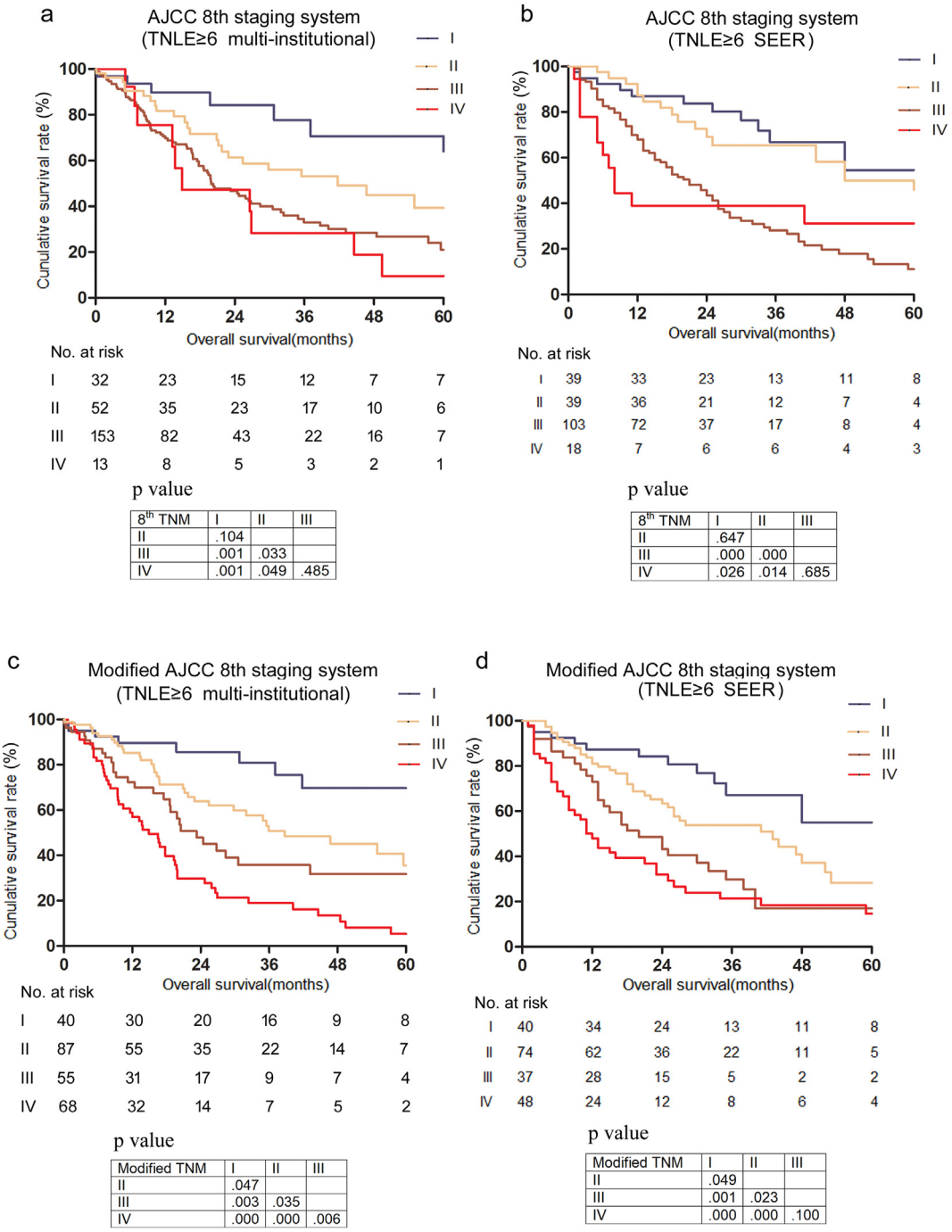

Figure 3 Validation of the prognostic accuracy of the AJCC 8th (**a and b**) and mTNM (**c and d**) staging system among patients who had ≥6 lymph nodes examined from the multi-institutional (**a and c**) and SEER database (**b and d**)

vs. II 41.8 months, $p = 0.104$; SEER data, stage I 72.0 vs. II 48.0 months, $p = 0.647$), as well as stage III versus stage IV (median OS: multi-institutional, III 19.9 vs. IV 14.9 months, $p = 0.485$; SEER, III 21.0 vs. IV 8.0 months, $p = 0.685$) disease (Fig. 3a and b). In contrast, the mTNM staging discriminated survival among patients with adequate nodal sampling (median OS: multi-institutional, I 69.8 vs. II 38.7 vs. III 23.3 vs. IV 14.9 months, all $p < 0.05$; SEER, I 72.0 vs. II 43.2 vs. III 20.8 months, all $p < 0.05$; III 20.8 vs. IV 11.5 months, $p = 0.100$) (Fig. 3c and d) (AJCC, 0.641, 95% CI 0.578–0.700 vs. mTNM, AUC 0.694, 95% CI 0.633–0.751, $p = 0.005$; SEER, AJCC, 0.685, 95% CI 0.615–0.749 vs. mTNM, AUC 0.723, 95% CI 0.655–0.784,

p = 0.030). In contrast, among patients who had <6 LNs examined, both the AJCC and mTNM staging systems failed to stratify OS among patients with stage III versus IV disease (median OS: multi-institutional, AJCC, III 22.6 vs. IV 20.0 months, p = 0.154; mTNM, stage III 18.1 vs. IV 16.4 months, p = 0.293; SEER, AJCC, stage III 18.0 vs. IV 17.0 months, p = 0.652; mTNM, stage III 17.4 vs. IV 15.1 months, p = 0.156).

Discussion

Cancer staging remains a cornerstone in the estimation of patient prognosis, cohorting of patients with similar outcomes, as well as the stratification of patients for adjuvant therapy and/or clinical trials. The staging of patients with ICC has evolved only over the last decade, and has been the topic of considerable debate.[10,4,5,8,9,11] The current study was important as the data demonstrated that the 8th edition AJCC staging system failed to stratify patients with stage II versus IIIA, stage IIIB versus IV, and overall stage III versus IV disease relative to long-term OS in both a large multi-institutional cohort, as well as the SEER database. In turn, we specifically sought to expand on our previous work and develop a proposed mTNM staging for ICC that incorporated the new N status (N0 [no nodal metastasis], N1 [1–2 LNM], N2 [≥3 LNM]) with redefined T categories and overall stage classification.[14] In particular, on multivariable analysis, perforation of visceral peritoneum was not associated with patient survival and thus was removed from the T definition. In contrast, multiple tumors, PI subtype ICC, and ICC with direct invasion of extrahepatic structures were defined as T4 in the mTNM staging system due to similar prognoses. In turn, the new T and N categories resulted in a mTNM staging system that more accurately stratified patient survival in both the development and validation cohorts. Of note, in both the development and validation cohorts, the proposed mTNM was associated with a strong stepwise increase in hazard of death as patients were upstaged. While the mTNM performed well among patients who had adequate LND (≥6), it did not perform as well among patients who had <6 LNs examined.

Several previous studies had questioned the validity of the current 8th edition AJCC staging system to stratify outcomes of ICC patients. For example, using the SEER registry, Kim *et al.* reported no improvement in the prognostic accuracy of the 8th over the previous 7th edition AJCC staging system.[3] In addition, studies from our own group and others have demonstrated that the 8th edition AJCC T3 (perforation of the visceral peritoneum) category was paradoxically associated with a better OS than either T1b or T2 disease; in addition, patients with stage IIIa (T3N0M0) had a comparable long-term survival as patients with stage Ib disease.[4,5] As such, both the 7th and 8th edition T categories remain problematic.[4] The reasons for this are likely multifactorial, yet may relate to the fact that invasion of the liver capsule is often affected by tumor location. As such, perforation of the visceral peritoneum may not truly reflect ICC tumor biology unlike other factors such as tumor size, vascular invasion, or morphologic types.[16,4,5] Consistent with this hypothesis, we failed to note an impact of visceral perforation of the peritoneum on long-term survival of patients after curative resection for ICC. Rather, tumor size, number, vascular invasion, and PI type were drivers of worse long-term outcomes. Based on the median OS of patients with these risk factors, we proposed new definitions for the T categories. Periductal invasion was defined as T4 disease – as it had been in the 7th edition AJCC staging. In addition to data in the current study, several studies had demonstrated that patients with PI subtype ICC routinely had worse outcomes versus patients with MF or IG subtypes.[17,16,18,19] In fact, ICC morphology has been associated with differences in cellular origin, molecular features, risk factors, as well as distinct tumor biologic progression.[20,21,18] PI ± MF ICC subtype ICC has been associated with hepatolithiasis, and more often originate from large bile duct epithelium and peribiliary glands with more aggressive signatures.[22,20,21,23] In contrast, the MF ICC subtype is more often induced by hepatitis, and typically arises from peripheral small bile ducts or hepatic progenitor cells with a growth pattern like HCC.[22,20,21,23] In addition, the PI ICC subtype more frequently is characterized by the Kirsten rat sarcoma viral oncogene (KRAS) mutation than other subtypes.[24] In the current study, the median OS of patients with PI ± MF type ICC was 19.5 months, which was comparable to patients with multiple lesions (median OS, 20.9 months) and/or tumor invasion of extrahepatic structures (median OS, 22.2 months) and thus these factors were collectively defined as mT4 disease.

The inclusion of tumor size in ICC staging has also been debated.[25–27] In fact, tumor size was not included in the first ICC staging system in the 7th edition manual, only being added to the 8th edition.[6] Currently, a single tumor ≤5 cm and a solitary lesion >5 cm with no vascular invasion are classified as T1a and T1b disease, respectively, in the 8th edition of AJCC staging. In the current study, we proposed modifying a single tumor ≤5 to T1 and solitary lesion >5 cm with no vascular invasion to T2, respectively, because patients with the proposed mT1 had a much more favorable survival than patients with mT2 (median OS, mT1 101.4 vs. mT2 44.0 months, respectively). In addition, patients with multiple tumors were reclassified from T2 disease in the 8th AJCC staging system to T4 in the mTNM staging system. Consistent with our findings, Yamamoto *et al.* also proposed reclassifying multiple tumors as T4, as patients with multiple ICCs had a 5-year disease-specific survival of only 4.7%, which was markedly worse than patients with a single ICC (52.4%).[11] In fact, some studies have demonstrated patients with multiple ICC (T2b, 7th edition of AJCC) had an even worse survival than patients with perforation of the liver capsule or extrahepatic invasion (T3, 7th edition of AJCC) or PI subtype (T4, 7th edition of AJCC) ICC.[16,5] The definition of "multiple" ICC included multifocal tumors, as well as a tumor with satellite lesions or intrahepatic metastasis. In fact, multifocal tumors may be uncommon in ICC patients with intrahepatic metastasis being

relatively more common.[10,16,11] In general, the progression of ICC typically involves primary tumor invasion of intrahepatic vessels prior to the development of intrahepatic metastasis. As such, intrahepatic metastasis should be categorized as a more aggressive stage than vascular invasion.[10,16,11]

In addition to redefining T categories, data from the current study were used to inform a new modified TNM staging system based on the median OS of patients with different T, N and M status.[14] In contrast to the current 8th AJCC staging system, the mTNM staging system was able to differentiate the survival of patients in both the multi-institutional and SEER database more accurately. As the number of LNs examined strongly affects the incidence of LNM identified, insufficiency of LNs retrieved may lead to understaging.[28] As such, the 8th edition of the AJCC staging manual recommends that ≥6 LNs should be evaluated from the regional nodal stations to obtain adequate pathologic staging.[6,14] Of note, the mTNM staging discriminated the long-term survival of patients with adequate nodal sampling in the multi-institutional (median OS, I 69.8 vs. II 38.7 vs. III 23.3 vs. IV 14.9 months), as well as the externally validated SEER (median OS, I 72.0 vs. II 43.2 vs. III 20.8 vs. IV 11.5 months) datasets.

Several limitations should be considered when interpreting data in the current study. Although use of multi-institutional data increased the generalizability of the results, there were likely variations in patient selection, surgical procedures, postoperative surveillance, as well as consideration of adjuvant therapies. In addition, no data of morphologic subtypes of ICC were available in the SEER validation dataset, making validation of ICC subtype not feasible. The current study utilized OS rather than recurrence-free survival to mitigate any potential differences related to detection or management of recurrent disease. Moreover, in the current study, the proposed new staging system was based on two surgical databases. As such, the data only pertain to patient with ICC that was amenable to surgical resection, and not patients with advance unresectable disease. While the purpose of the current study was not to develop a clinical staging system for patient with unresectable ICC, future studies are needed to determine which factors impact the clinical staging of patients with advanced ICC disease.

In conclusion, there were paradoxical survival outcomes among patients with different ICC disease stages based on the 8th edition AJCC staging system in both the multi-institutional and SEER cohorts. Using empirical analyses, the T categories were redefined and combined with new nodal categories into a proposed novel mTNM staging system. The mTNM staging system better stratified the long-term survival of patients than the current 8th edition AJCC staging system among patients in both the training and validation cohorts. These data should be strongly considered for potential adoption in the next AJCC staging manual to more accurately stratify long-term outcomes of patients following surgical resection of ICC.

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Conflicts of interest

None declared.

References

1. Edge SB, Compton CC. (2010 Jun) The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol* 17:1471–1474.
2. Nathan H, Aloia TA, Vauthey JN, Abdalla EK, Zhu AX, Schulick RD *et al*. (2009 Jan) A proposed staging system for intrahepatic cholangiocarcinoma. *Ann Surg Oncol* 16:14–22.
3. Kim Y, Moris DP, Zhang XF, Bagante F, Spolverato G, Schmidt C *et al*. (2020 Jun) Evaluation of the 8th edition American Joint Commission on Cancer (AJCC) staging system for patients with intrahepatic cholangiocarcinoma: a surveillance, epidemiology, and end results (SEER) analysis. *J Surg Oncol* 107:854–864.
4. Spolverato G, Bagante F, Weiss M, Alexandrescu S, Marques HP, Aldrighetti L *et al*. (2017 May) Comparative performances of the 7th and the 8th editions of the American Joint Committee on Cancer staging systems for intrahepatic cholangiocarcinoma. *J Surg Oncol* 115: 696–703.
5. Kang SH, Hwang S, Lee YJ, Kim KH, Ahn CS, Moon DB *et al*. (2018 Apr) Prognostic comparison of the 7th and 8th editions of the American Joint Committee on Cancer staging system for intrahepatic cholangiocarcinoma. *J Hepato-Biliary-Pancreatic Sci* 25:240–248.
6. Amin MB. (2017) *American Joint committee on cancer: AJCC cancer staging manual*, 8th ed. New York: Springer.
7. Lee AJ, Chun YS. (2018 Oct) Intrahepatic cholangiocarcinoma: the AJCC/UICC 8th edition updates. *Chin Clin Oncol* 7:52.
8. Sasaki K, Margonis GA, Andreatos N, Chen Q, Barbon C, Bagante F *et al*. (2018 Oct) Serum tumor markers enhance the predictive power of the AJCC and LCSGJ staging systems in resectable intrahepatic cholangiocarcinoma. *HPB Offic J Int Hepato Pancreato Biliary Assoc* 20: 956–965.
9. Cheng Z, Lei Z, Si A, Yang P, Luo T, Guo G *et al*. (2019 Dec) Modifications of the AJCC 8th edition staging system for intrahepatic cholangiocarcinoma and proposal for a new staging system by incorporating serum tumor markers. *HPB : Offic J Int Hepato Pancreato Biliary Assoc* 21:1656–1666.
10. Uenishi T, Ariizumi S, Aoki T, Ebata T, Ohtsuka M, Tanaka E *et al*. (2014 Jul) Proposal of a new staging system for mass-forming intrahepatic cholangiocarcinoma: a multicenter analysis by the Study Group for Hepatic Surgery of the Japanese Society of Hepato-Biliary-Pancreatic Surgery. *J Hepato-Biliary-Pancreatic Sci* 21:499–508.
11. Yamamoto Y, Sugiura T, Okamura Y, Ito T, Ashida R, Ohgi K *et al*. (2020 Apr) The evaluation of the eighth edition of the AJCC/UICC staging system for intrahepatic cholangiocarcinoma: a proposal of a modified new staging system. *J Gastrointest Surg : Offic J Soc Surg Alim Tract* 24:786–795.
12. Asakura H, Ohtsuka M, Ito H, Kimura F, Ambiru S, Shimizu H *et al*. (2005 May-Jun) Long-term survival after extended surgical resection of intrahepatic cholangiocarcinoma with extensive lymph node metastasis. *Hepato-Gastroenterology* 52:722–724.
13. Choi SB, Kim KS, Choi JY, Park SW, Choi JS, Lee WJ *et al*. (2009 Nov) The prognosis and survival outcome of intrahepatic cholangiocarcinoma

following surgical resection: association of lymph node metastasis and lymph node dissection with survival. *Ann Surg Oncol* 16:3048–3056.

14. Zhang XF, Xue F, Dong DH, Weiss M, Popescu I, Marques HP *et al*. (2020 Jan 14) Number and station of lymph node metastasis after curative-intent resection of intrahepatic cholangiocarcinoma impact prognosis. *Ann Surg*. EPub ahead of print.
15. MB A. (2017) American Joint committee on cancer. In: *AJCC cancer staging manual Chicago, American Joint committee on cancer*. Springer.
16. Sakamoto Y, Kokudo N, Matsuyama Y, Sakamoto M, Izumi N, Kadoya M *et al*. (2016 Jan 1) Proposal of a new staging system for intrahepatic cholangiocarcinoma: analysis of surgical patients from a nationwide survey of the Liver Cancer Study Group of Japan. *Cancer* 122:61–70.
17. Shimada K, Sano T, Sakamoto Y, Esaki M, Kosuge T, Ojima H. (2007 Oct) Surgical outcomes of the mass-forming plus periductal infiltrating types of intrahepatic cholangiocarcinoma: a comparative study with the typical mass-forming type of intrahepatic cholangiocarcinoma. *World J Surg* 31:2016–2022.
18. Bagante F, Spolverato G, Weiss M, Alexandrescu S, Marques HP, Aldrighetti L *et al*. (2017 May 02) Impact of morphological status on long-term outcome among patients undergoing liver surgery for intrahepatic cholangiocarcinoma. *Ann Surg Oncol* 24:2491–2501.
19. Zhang XF, Lv Y, Bagante F, Weiss M, Popescu I, Marques HP *et al*. (2019) Should utilization of lymphadenectomy vary according to morphologic subtype of intrahepatic cholangiocarcinoma? *Ann Surg Oncol* 26:2242–2250.
20. Sia D, Tovar V, Moeini A, Llovet JM. (2013 Oct 10) Intrahepatic cholangiocarcinoma: pathogenesis and rationale for molecular therapies. *Oncogene* 32:4861–4870.
21. Liau JY, Tsai JH, Yuan RH, Chang CN, Lee HJ, Jeng YM. (2014 Aug) Morphological subclassification of intrahepatic cholangiocarcinoma: etiological, clinicopathological, and molecular features. *Mod Pathol : Offic J United States Canad Acad Pathol Inc.* 27:1163–1173.
22. Aishima S, Kuroda Y, Nishihara Y, Iguchi T, Taguchi K, Taketomi A *et al*. (2007 Jul) Proposal of progression model for intrahepatic cholangiocarcinoma: clinicopathologic differences between hilar type and peripheral type. *Am J Surg Pathol* 31:1059–1067.
23. Aishima S, Oda Y. (2015 Feb) Pathogenesis and classification of intrahepatic cholangiocarcinoma: different characters of perihilar large duct type versus peripheral small duct type. *J Hepato-Biliary-Pancreatic Sci* 22:94–100.
24. Ohashi K, Nakajima Y, Kanehiro H, Tsutsumi M, Taki J, Aomatsu Y *et al*. (1995 Nov) Ki-ras mutations and p53 protein expressions in intrahepatic cholangiocarcinomas: relation to gross tumor morphology. *Gastroenterology* 109:1612–1617.
25. de Jong MC, Nathan H, Sotiropoulos GC, Paul A, Alexandrescu S, Marques H *et al*. (2011 Aug 10) Intrahepatic cholangiocarcinoma: an international multi-institutional analysis of prognostic factors and lymph node assessment. *J Clin Oncol : Offic J Am Soc Clin Oncol* 29: 3140–3145.
26. Bagante F, Spolverato G, Merath K, Weiss M, Alexandrescu S, Marques HP *et al*. (2019 Dec) Intrahepatic cholangiocarcinoma tumor burden: a classification and regression tree model to define prognostic groups after resection. *Surgery* 166:983–990.
27. Brustia R, Langella S, Kawai T, Fonseca GM, Schielke A, Colli F *et al*. (2020 Apr) Preoperative risk score for prediction of long-term outcomes after hepatectomy for intrahepatic cholangiocarcinoma: report of a collaborative, international-based, external validation study. *Eur J Surg Oncol : J Eur Soc Surg Oncol Br Assoc Surg Oncol* 46(4 Pt A):560–571.
28. Feinstein AR, Sosin DM, Wells CK. (1985 Jun 20) The Will Rogers phenomenon. Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. *N Engl J Med* 312: 1604–1608.

Appendix A. Supplementary data

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