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RESEARCH ARTICLE

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Comparative performances of the 7th and the 8th editions of the American Joint Committee on Cancer staging systems for intrahepatic cholangiocarcinoma

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Background: We sought to evaluate and validate the 8th edition of the AJCC classification using a multi-institutional cohort of patients with intrahepatic cholangiocarcinoma (ICC).

Methods: Patients undergoing curative-intent hepatic resection for ICC between 1990 and 2015 at 14 major hepatobiliary centers were included and were staged according to 7th and 8th editions AJCC criteria.

Results: A total of 1154 patients underwent liver resection for ICC. When patients were staged using the AJCC 7th edition, T2a, T2b, and T4 patients had a higher hazard ratio (HR) of death compared with T1 (T2a, HR 1.43, $P = 0.004$; T2b, HR 1.99, $P < 0.001$; T4, HR 2.20, $P < 0.001$). T3 patients had a higher HR of death compared with T1 patients (HR 1.30, $P = 0.029$) but lower than T2a and T2b. According to AJCC 8th edition, T1b, T2, and T4 patients were at higher risk of death compared with T1a patients (T1b, HR 1.91, $P < 0.001$; T2, HR 2.29, $P < 0.001$; T4, HR 4.16, $P < 0.001$). As in the AJCC 7th edition, AJCC 8th edition T3 patients had a higher HR of death compared with T1 patients (HR 1.65, $P = 0.001$) but lower than T1b and T2. AJCC 8th edition.

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T-category performed slightly better than AJCC 7th edition with a C-index of 0.609 versus 0.590.

Conclusions: A staging system that perfectly discriminates between stages has not yet been developed, but the AJCC 8th edition was able to better stratify the risk of death of Stage III and T3 patients.

KEYWORDS

8th edition, AJCC, ICC, surgery, staging

1 | INTRODUCTION

Although intrahepatic cholangiocarcinoma (ICC) has historically been considered a relatively uncommon disease, its incidence is increasing worldwide. As a consequence, a growing body of evidence on factors associated with long-term outcomes of ICC patients has emerged.[1–8] The importance of ICC has been recently recognized by the American Joint Committee on Cancer (AJCC) with the 7th edition of the AJCC Staging Manual incorporating a tumor-node-metastasis (TNM) staging system for ICC distinct from hepatocellular carcinoma (HCC) and extrahepatic bile duct malignancies.[9] In the AJCC 7th edition, T-category was based on three major prognostic factors including tumor number, vascular invasion, and direct extrahepatic extension derived from the work of Nathan et al.[10] N-category was based on the presence or absence of metastasis in one or more regional lymph nodes; specifically, for a left-sided ICC, nodal disease in the common bile duct, hepatic artery, portal vein, and cystic duct nodes, while for a right-sided ICC, the nodal basins of interest were hilar, periduodenal, and peripancreatic. The 7th edition of the AJCC staging system was subsequently validated in several different cohorts.[11–16] Over time, however, several groups proposed modifications to the staging system. For example, Igami et al advocated for replacing periductal invasion with multiple tumors for T4 disease, as well as categorizing nodal metastasis in the gastrohepatic lymph node basin as distant metastasis.[13]

Recently, the 8th edition of the AJCC staging manual was published.[17] In this edition, ICC staging remained independent of the staging systems for HCC and extrahepatic bile duct cholangiocarcinomas, yet mixed hepato-cholangio carcinomas and rare intrahepatic primary neuroendocrine tumors were included in the staging system. Importantly, the 8th edition of the AJCC staging system introduced several notable changes to the T-category classification schema. In particular, T1 disease has been modified to account for the prognostic impact of tumor size (T1a, solitary tumor ≤5 cm vs. T1b, solitary tumor >5 cm). T2 has been revised to reflect the equivalent prognostic effect of tumor number and vascular invasion (T2, solitary tumor with intrahepatic vascular invasion or multiple tumors, with or without vascular invasion). In addition, T4 disease, which previously was based on tumor growth pattern, has been excluded from the 8th edition.

Given the recent introduction of this new staging system, the objective of the current study was to evaluate and validate the new edition of the AJCC staging system using a large multi-institutional cohort of patients with ICC.

2 | MATERIALS AND METHODS

2.1 | Patient demographic and clinical data

Patients undergoing curative-intent hepatic resection for ICC between 1990 and 2015 at 14 major hepatobiliary centers in the United States, Europe, Australia, and Asia (Johns Hopkins Hospital, Baltimore, MD; Stanford University, Stanford, CA; University of Virginia, Charlottesville, VA; Emory University, Atlanta, GA; Fundeni Clinical Institute of Digestive Disease, Bucharest, Romania; Curry Cabral Hospital, Lisbon, Portugal; Ospedale San Raffaele, Milan, Italy; Royal Prince Alfred Hospital, University of Sydney, Sydney, Australia; Eastern Hepatobiliary Surgery Hospital, Shanghai, China; Beaujon Hospital, Clichy, France; University of Ottawa, Ottawa, Ontario, Canada; Erasmus University Medical Centre, Rotterdam, Netherlands; Yokohama City University School of Medicine, Yokohama, Japan; University of Verona, School of Medicine, Verona, Italy) were identified. Only patients with histologically confirmed ICC were included. Patients with metastatic disease and those who underwent a R2 resection were excluded. Patients who underwent a palliative operation, those who underwent only ablation or intra-arterial therapy (IAT) were also excluded. The Institutional Review Board of each institution approved the study.

Standard patient demographic and clinicopathologic data were collected including age, sex, American Society of Anesthesiologists (ASA) classification and presence of cirrhosis. Serum level of carcinoembryonic antigen (CEA) and Cancer Antigen (CA) 19-9 were also collected. Data regarding treatment were collected including receipt of neoadjuvant chemotherapy, type of surgery, and receipt of adjuvant treatments. Resection margin status was classified as microscopically negative (R0) or microscopically positive (R1). Tumor-specific characteristics including tumor size and number, liver capsule involvement, histological grade, morphological type, number of lymph nodes achieved, and number of metastatic lymph nodes were included. Even if it can be difficult to determine the local extent of disease on radiological imaging, the major prognostic factors, including tumor size and number, vascular

invasion, perforation of the visceral peritoneum, and regional lymph node involvement, as defined by high-resolution cross-sectional imaging, biopsy tissue and surgical pathology.[17] Presence of vascular/perineural/biliary invasion, and direct invasion of contiguous organs were also recorded. Data on tumor stage were collected according to both the 7th and the 8th edition AJCC staging systems.[9] Perioperative complications and mortality were considered within 90 days from the operation.[18]

2.2 | Statistical analysis

Continuous variables were summarized as medians with interquartile ranges (IQR) while categorical variables were reported as whole numbers and percentages. The outcome for survival analyses was overall survival (OS), defined as the time interval between the date of surgery and the date of death. Time was censored at the date of last follow-up for living patients. OS estimates were calculated using the Kaplan-Meier method. Cox proportional hazards models were used to evaluate associations between tumor stage and OS. The coefficients from the Cox models were subsequently reported as hazard ratios (HR) with corresponding 95% confidence intervals (CI). In order to assess the performance of the 7th and the 8th edition AJCC staging systems, the concordance index (C-index) was utilized.[19] Standard errors, CI, and *P* values for the C-index were computed by assuming asymptotic normality.[20,21]

3 | RESULTS

3.1 | Clinicopathologic characteristics of the study group

A total of 1154 patients underwent liver resection for ICC. The majority of patients were male (*n* = 638, 55.3%) and median age was 60.4 years old (IQR, 51.7-69.0; Table 1). Preoperatively, median CA 19-9 and CEA were 49 U/mL (IQR, 16.9-218.0) and 2.4 ng/mL (IQR, 1.4-4.3), respectively. Cirrhosis, HBV, and HCV infections were present in 118 (10.2%), 205 (17.8%), and 31 (2.7%) patients, respectively. The majority of patients had a single ICC (*n* = 941, 81.5%) and median tumor size was 6 cm (IQR, 4.0-8.5). Major vascular invasion was noted in 156 (13.5%) patients and liver capsule involvement in 209 (18.1%) patients. The majority of patients underwent a major hepatectomy (*n* = 708, 61.4%), whereas 289 (25.0%) patients underwent a minor hepatectomy and 157 (13.6%) a wedge resection. ICC was well differentiated in 147 (13.6%) patients, moderately differentiated in 739 (68.9%), and poorly/un-differentiated in 188 (17.5%). Surgical margins of the resected specimen were negative (R0) in 992 (87.2%) patients, while 146 (12.8%) patients were R1. Lymph-vascular invasion was present in 356 (30.8%) patients and perineural invasion in 215 (21.1%). Overall, 200 (17.3%) patients had lymph nodes metastasis, while 315 (27.3%) patients had no lymph node metastasis; lymphadenectomy was not performed in 639 (55.4%) patients.

TABLE 1 Baseline characteristics of the study cohort (*n* = 1154)

Variables	*N* (%)
Gender	
Female	516 (44.7)
Male	638 (55.3)
Age, median (IQR)	60.4 years (51.7-69.0)
ASA	
≤2	634 (54.9)
>2	520 (45.1)
Cirrhosis	
No	1036 (89.8)
Yes	118 (10.2)
HBV infection	
No	949 (82.2)
Yes	205 (17.8)
HCV infection	
No	1123 (97.3)
Yes	31 (2.7)
Neoadjuvant chemotherapy	
No	1070 (92.7)
Yes	84 (7.3)
Morphological type	
Mass-forming (MF)	941 (87.0)
Periductal-infiltrating (PI)	54 (4.9)
MF + PI	88 (8.1)
NA	71
Ca 19-9, median (IQR)	49 U/mL (16.9-218.0)
CEA, median (IQR)	2.4 ng/mL (1.4-4.3)
Type of surgery	
Wedge resection	157 (13.6)
Minor hepatectomy	289 (25.0)
Major hepatectomy	708 (61.4)
Margins	
Negative	992 (87.2)
Positive	146 (12.8)
NA	16
Liver capsule involvement	
No	945 (81.9)
Yes	209 (18.1)
Tumor size, median (IQR)	6.0 cm (4.0-8.5)
Lesion	
Unifocal	941 (81.5)
Multifocal	213 (18.5)
Grade	
Well	147 (13.6)
Moderate	739 (68.9)
Poor-undifferentiated	188 (17.5)
NA	82
Major vascular invasion	

(Continues)

TABLE 1 (Continued)

Variables	*N* (%)
Not present	998 (86.5)
Present	156 (13.5)
Lymph-vascular invasion	
Not present	771 (69.2)
Present	356 (30.8)
NA	27
Perineural invasion	
Not present	805 (78.9)
Present	215 (21.1)
NA	134
Radiological nodal status	
Negative	608 (52.7)
Suspicious	118 (10.2)
Positive	59 (5.1)
Not reported	369 (31.9)
Pathological lymphnode status	
Negative	315 (27.3)
Positive	200 (17.3)
Not harvested	639 (55.4)

NA, not available.

3.2 | Comparison of AJCC 7th and 8th editions T-categories

A total of 487 (42.2%) patients had a solitary ICC without vascular invasion (T1 AJCC 7th ed.) while 207 (17.9%) and 123 (10.7%) patients had a solitary ICC with vascular invasion (T2a AJCC 7th ed.) or multiple ICC with or without vascular invasion (T2b AJCC 7th ed.), respectively. There were 195 (16.9%) patients with ICC perforating the visceral peritoneum or involving the local extra-hepatic structures by direct invasion (T3 AJCC 7th ed.), while 142 (12.3%) patients had ICC with periductal invasion (PI and MF + PI; T4 AJCC 7th ed.). When the AJCC 7th edition T-staging system was used, 5-year OS was 49.3% (95% Confidence Interval, 43.4-54.9) in T1 patients, 35.7% (95% CI, 26.7-44.8) in T2a patients, 20.9% (95% CI, 12.4-31.0) in T2b patients, 42.5% (95% CI, 34.2-50.6) in T3 patients, and 25.5% (95% CI, 17.3-34.4) in T4 patients (Table 2 and Fig. 1a).

A total of 249 (21.6%) patients had a solitary ICC without vascular invasion measuring ≤5 cm (T1a AJCC 8th ed.) while 270 (23.4%) patients had a solitary ICC without vascular invasion >5 cm (T1b AJCC 8th ed.). About one third of patients (n = 402; 34.8%) had a solitary ICC with vascular invasion or multiple ICC with or without vascular invasion (T2 AJCC 8th ed.). There were 167 (14.5%) patients with ICC perforating the visceral peritoneum (T3 AJCC 8th ed.) and there were 66 (5.7%) with ICC involving local extra hepatic structures by direct invasion (T4 AJCC 8th ed.). According to AJCC 8th edition, 5-year OS was 60.8% (95% CI, 52.6-68.0) in T1a patients, 36.7% (95% CI, 29.2-44.2) in T1b, 29.3% (95% CI, 23.3-35.5) in T2, 45.8% (95% CI, 36.6-54.4) in T3, and 14.7% (95% CI, 6.4-26.5) in T4, respectively (Table 2 and Fig. 1b).

TABLE 2 Comparison between the 7th and the 8th edition of the AJCC T staging systems—Kaplan-Meier analysis

	N = 1154 (%)	5-year (%)	95% CI
AJCC 7th ed. T-category			
T1	487 (42.2)	49.3	43.4-54.9
T2a	207 (17.9)	35.7	26.7-44.8
T2b	123 (10.7)	20.9	12.4-31.0
T3	195 (16.9)	42.5	34.2-50.6
T4	142 (12.3)	25.5	17.3-34.4
AJCC 8th ed. T-category			
T1a	249 (21.6)	60.8	52.6-68.0
T1b	270 (23.4)	36.7	29.2-44.2
T2	402 (34.8)	29.3	23.3-35.5
T3	167 (14.5)	45.8	36.6-54.4
T4	66 (5.7)	14.7	6.4-26.5

When patients were categorized using the AJCC 7th edition T-category system, T2a, T2b, and T4 patients had a higher HR of death compared with T1 (AJCC 7th ed., T2a vs. T1, HR 1.43 95% CI, 1.12-1.83 P = 0.004; T2b vs. T1, HR 1.99 95% CI, 1.52-2.59, P < 0.001; T4 vs. T1, HR 2.20 95% CI, 1.72-2.82 P < 0.001; Fig. 1a). Of note, T3 patients had a higher HR of death compared with T1 patients (AJCC 7th ed. T3 vs. T1, HR 1.30 95% CI, 1.03-1.66 P = 0.029) but lower than T2a and T2b patients. According to AJCC 8th edition, T1b, T2, and T4 patients were at higher risk of death compared with T1a patients (AJCC 8th ed., T1b vs. T1a, HR 1.91 95% CI, 1.45-2.50 P < 0.001; T2 vs. T1a, HR 2.29 95% CI, 1.78-2.96, P < 0.001; T4 vs. T1a, HR 4.16 95% CI, 2.92-5.94 P < 0.001; Fig. 1b). As in the AJCC 7th edition, AJCC 8th edition. T3 patients had a higher HR of death compared with T1 patients (AJCC 8th ed. T3 vs. T1, HR 1.65 95% CI, 1.22-2.24 P = 0.001), but lower than T1b and T2 patients.

A validation analysis was performed to compare the ability of the two editions of AJCC T-staging systems to stratify patients based on risk of death. AJCC 7th edition T-category had a C-index of 0.590 compared with a C-index of 0.609 for the AJCC 8th edition T-category (Table 3).

3.3 | Comparison of AJCC 7th and 8th editions

According to the AJCC 7th edition, 93 (18.1%) patients were classified as Stage I and had a 5-year OS of 58.8% (95% CI, 44.9-70.3; Table 4 and Fig. 2a). According to the AJCC 8th edition, 15 (5.1%) patients were classified as Stage Ia and 18 (6.1%) as Stage Ib with a 5-year OS of 90.0% (95% CI, 47.3-98.5) and 50.6% (95% CI, 19.9-75.0), respectively (Fig. 2b). Based on the AJCC 7th edition, 110 (21.4%) patients were classified as Stage II with a 5-year OS of 38.8% (95% CI, 26.5-51.0), while 37 (12.5%) patients were classified as Stage II according to the AJCC 8th edition with a 5-year OS of 55.1% (95% CI, 34.5-71.7). According to the AJCC 7th edition, 70 (13.6%) patients were classified as Stage III and had a 5-year OS of 39.7% (95% CI, 24.1-54.9); conversely, 22 (7.4%) and 204 (16.2%) patients were defined as Stages IIIa and b according to the AJCC 8th

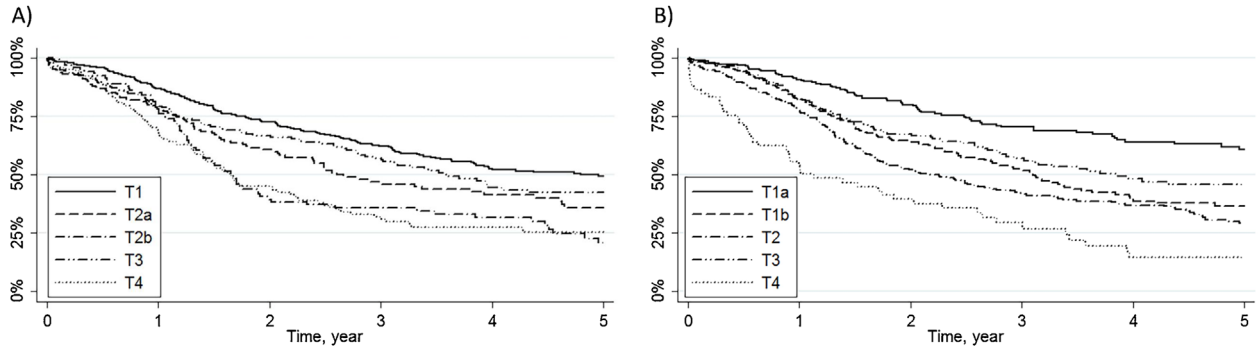

FIGURE 1 A) Kaplan-Meier overall survival curves stratified by AJCC 7th T-category. B) Kaplan-Meier overall survival curves stratified by AJCC 8th T-category

edition, and had a 5-year OS of 49.7% (95% CI, 16.6-76.2) and 16.2% (95% CI, 9.5-24.5), respectively. Moreover, according to AJCC 7th edition, 242 (46.9%) patients were classified in Stage IVa with a 5-year OS of 18.4% (95% CI, 11.9-26.1).

Compared with AJCC 7th edition Stage I, patients in AJCC 7th edition Stages II and IVa were at higher risk of death (AJCC 7th ed., II vs. I, HR 1.89, 95% CI, 1.17-3.06 $P = 0.010$; IVa vs. I, HR 3.63, 95% CI, 2.38-5.53 $P < 0.001$). Of note, AJCC 7th edition Stage III patients had a higher HR of death compared with Stage I patients (AJCC 7th ed. III vs. I, HR 1.69 95% CI, 0.99-2.89 $P = 0.053$) but lower than Stage II. Compared with AJCC 8th edition Stage I, patients in AJCC 8th edition Stages Ib, II, IIIa, and IIIb were at higher risk of death (AJCC 8th ed., Ib vs. Ia, HR 6.42, 95% CI, 0.77-53. 4 $P = 0.085$; II vs. Ia, HR 5.89, 95% CI, 0.77-45.0, $P = 0.088$; IIIa vs. Ia, HR 7.39 95% CI, 0.91-60.2 $P = 0.061$; IIIb vs. Ia, HR 16.4, 95% CI, 2.29-117.4 $P = 0.005$; Table 5). Of note, AJCC 8th edition Stages Ib, II, and IIIa patients had a higher HR of death compared with Stage Ia patients, but the difference was not statistically significant.

A validation analysis was performed to compare the two editions of the AJCC staging system. AJCC 7th edition had a C-index of 0.637 compared with a C-index of 0.607 of the AJCC 8th edition (Table 5).

3.4 | Comparison of AJCC 7th and 8th editions including patients with lymph node staging assessed by radiological imaging

Given the high number of patients who did not undergo lymphadenectomy (Nx), we performed a sensitivity analysis. To further assess the performance of the 7th and 8th staging systems based on both preoperative radiological imaging and the pathological specimen. The total number of patients included in the sub-set analysis was 932. According to the AJCC 7th edition, 356 (38.2%) patients were classified as Stage I and had a 5-year OS of 55.0% (95% CI, 48.0-61.4; Table S1). According to the AJCC 8th edition, 178 (19.1%) patients were classified as Stage Ia and 196 (21.0%) as Stage Ib with a 5-year OS of 69.2% (95% CI, 59.8-76.8), and 40.9% (95% CI, 31.6-49.9), respectively. Based on the AJCC 7th edition, 197 (21.2%) patients were classified as Stage II with a 5-year OS of 36.8% (95% CI, 27.7-45.8), while 222 (23.8%) patients were classified as Stage II according to the AJCC 8th edition with a 5-year OS of 35.9% (95% CI, 27.2-44.7). According to the AJCC 7th edition classification, 128 (13.7%) patients were classified as Stage III and had a 5-year OS of 54.4% (95% CI, 43.6-64.1); conversely,

TABLE 3 Comparison between the 7th and the 8th edition of the AJCC T staging systems—Validation

	HR	95% CI	*P*-value	C-index
AJCC 7th ed. T-category				0.619
T1	–	–	–	
T2a	1.43	1.12-1.83	0.004	
T2b	1.99	1.52-2.59	<0.001	
T3	1.30	1.03-1.66	0.029	
T4	2.20	1.72-2.82	<0.001	
AJCC 8th ed. T-category				0.644
T1a	–	–	–	
T1b	1.91	1.45-2.50	<0.001	
T2	2.29	1.78-2.96	<0.001	
T3	1.65	1.22-2.24	0.001	
T4	4.16	2.92-5.94	<0.001	

TABLE 4 Comparison between the 7th and the 8th edition of the AJCC staging systems—Kaplan-Meier analysis

	N (%)	5-year (%)	95% CI
AJCC 7th edition[a]			
I	93 (18.1)	58.8	44.9-70.3
II	110 (21.4)	38.8	26.5-51.0
III	70 (13.6)	39.7	24.1-54.9
IVa	242 (46.9)	18.4	11.9-26.1
AJCC 8th edition[b]			
Ia	15 (5.1)	90.0	47.3-98.5
Ib	18 (6.1)	50.6	19.9-75.0
II	37 (12.5)	55.1	34.5-71.7
IIIa	22 (7.4)	49.7	16.6-76.2
IIIb	204 (68.9)	16.2	9.5-24.5

[a]*N* = 515.
[b]*N* = 296.

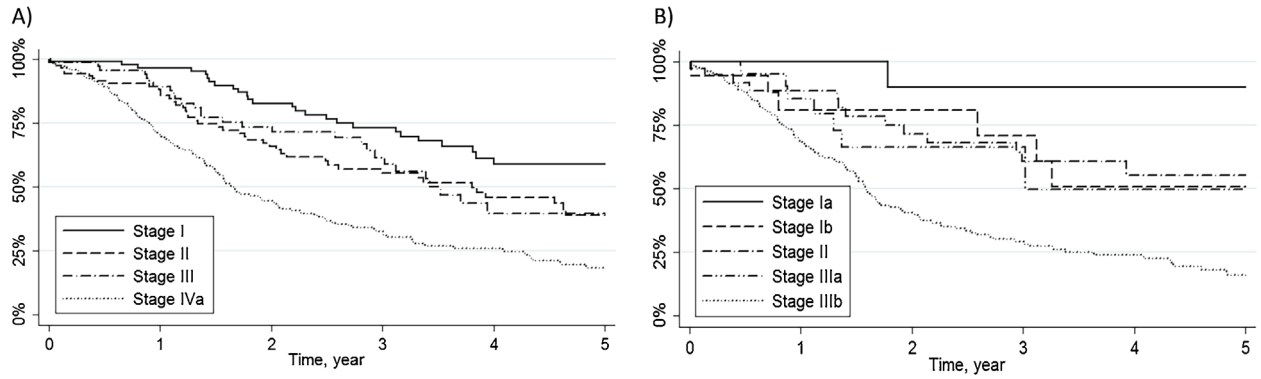

FIGURE 2 A) Kaplan-Meier overall survival curves stratified by AJCC 7th edition tumor staging. B) Kaplan-Meier overall survival curves stratified by AJCC 8th edition tumor staging

109 (11.7%) and 227 (24.4%) patients were defined as Stages IIIa and b according to the AJCC 8th edition edition classification and had a 5-year OS of 60.0% (95% CI, 48.4-69.8) and 16.3% (95% CI, 9.9-24.0), respectively. Moreover, according to AJCC 7th edition, 251 (26.9%) patients were classified in Stage IVa with a 5-year OS of 19.5% (95% CI, 12.7-27.2).

Compared with AJCC 7th edition Stage I, patients in AJCC 7th edition Stages II and IVa were at higher risk of death (AJCC 7th ed., II vs. I, HR 1.49, 95% CI, 1.14-1.97 $P = 0.003$; IVa vs. I, HR 2.63, 95% CI, 2.07-3.34 $P < 0.001$). Conversely, AJCC 7th edition Stage III patients did not have a higher HR of death compared with Stage I patients (AJCC 7th ed. III vs. I, HR 1.05 95% CI, 0.76-1.45 $P = 0.78$). Compared with AJCC 8th edition Stage I, patients in AJCC 8th edition Stages Ib, II, and IIIb were at higher risk of death (AJCC 8th ed., Ib vs. Ia, HR 2.32, 95% CI, 1.61-3.34 $P < 0.001$; II vs. Ia, HR 2.41, 95% CI, 1.69-3.45, $P < 0.001$; IIIb vs. Ia, HR 4.53, 95% CI, 3.22-6.39 $P < 0.001$; Table S2). Of note, AJCC 8th edition Stage IIIa patients had a higher HR of death compared with Stage Ib patients (AJCC 8th ed. IIIa vs. Ib, HR 1.49 95% CI, 0.97-2.30 $P = 0.07$), but lower than Stages Ib and II.

TABLE 5 Comparison between the 7th and the 8th edition of the AJCC staging systems—Validation

	HR	95% CI	*P*-value	C-index
AJCC 7th edition[a]				0.637
I	–	–	–	
II	1.89	1.17-3.06	0.010	
III	1.69	0.99-2.89	0.053	
IVa	3.63	2.38-5.53	<0.001	
AJCC 8th edition[b]				0.607
Ia	–	–	–	
Ib	6.42	0.77-53.4	0.085	
II	5.89	0.77-45.0	0.088	
IIIa	7.39	0.91-60.2	0.061	
IIIb	16.4	2.29-117.4	0.005	

[a]$N = 515$.
[b]$N = 296$.

A validation analysis was performed to compare the two editions of the AJCC staging system. AJCC 7th edition had a C-index of 0.642 compared with a C-index of 0.667 of the AJCC 8th edition ($P = 0.98$; Table S2).

4 | DISCUSSION

Staging of ICC has historically mirrored the staging system for HCC and extrahepatic cholangiocarcinoma, largely due to the fact that ICC is a relatively uncommon disease. However, over the last decade there has been an increased recognition of ICC as a distinct clinical entity. Following the introduction of the first unique staging system for ICC in the 7th edition AJCC staging manual, the staging of ICC has continued to evolve.[11–16] Several staging systems have been proposed; for example, in addition to the AJCC staging system in Western Countries, the Liver Cancer Study Group of Japan (LCSGJ) has proposed a distinct staging system that is used in many Eastern Countries.[9,22] In the newly released 8th edition of the AJCC staging manual, while ICC remained a separate unique staging system, several new revisions to the staging of ICC were introduced. Specifically, in the 8th edition, T1 disease has been revised to include tumor size (≤5 cm vs. >5 cm); T2 was also modified to reflect an equivalent prognostic value of vascular invasion and multifocal disease. In addition, 7th edition T4 disease that described tumor growth pattern was excluded from staging with T4 disease now defined as involving local extrahepatic structures by direct invasion. The current study is important because it is one of the first reports to validate the newly proposed 8th edition ICC stating. In addition, unlike many other small single institution case series, the current study utilized a large, international, multi-institutional cohort of patients undergoing curative-intent surgery for ICC to evaluate the 8th edition of the AJCC staging system.

In examining the T categories, the AJCC 8th edition discriminated prognosis with variable effectiveness (Fig. 1b). Specifically, while T1b patients had a better 5-year OS (36.7%) than T2 patients (29.3%), T3 patients paradoxically had a better 5-year OS than either of these lower T categories (45.8%). Interestingly, in AJCC 7th edition T3 patients similarly had a better 5-year OS (42.5%) compared with T2b (20.9%) and T2a (35.7%) patients. Interestingly, as in the AJCC 7th edition, AJCC 8th

edition T3 patients had a higher HR of death compared with T1 patients (AJCC 8th ed. T3 vs. T1, HR 1.65 95% CI, 1.22-2.24 $P = 0.001$) but lower than T1b and T2 patients. As such, neither the 8th nor the 7th edition accurately stratified patients into distinct prognostic T categories. Moreover, the major revision that involved the addition of tumor size, which had been omitted from the previous 7th AJCC T staging, did not seem to add much additional prognostic information, as reflected in the minimal improvement in the C-index (AJCC 7th ed., C-index 0.590 vs. AJCC 8th ed., C-index 0.609; $P = 0.39$).

In addition, the overall staging groups based on the 8th edition had a C-index of 0.607, which was actually worse than the previous 7th edition that had a C-index of 0.637 ($P = 0.18$). Of note, according to the AJCC 8th edition, higher tumor stage was associated with an expected generally lower 5-years OS (Fig. 2b). However, Stage II patient had an improved 5-year OS of 55.1% compared with Stage Ib patients who had a 5-year OS of 50.6%. In addition, Stage IIIa patients had a 5-year OS of 49.7% that was comparable to Stage Ib patients. These data were similar when the previous 7th edition AJCC staging schema was examined. Specifically, Stage III patients had a 5-year OS of 39.7% versus 38.8%, and 58.8% for Stages II and I patients, respectively. In the validation analysis of the AJCC 8th edition staging system, Stage IIIa patients had a higher risk of death versus Stage Ia patients, but the difference was not statistically significant. This finding is in line with the comparison between AJCC 7th edition Stages III and I patients ($P > 0.05$). These data suggest that perforation of the visceral peritoneum may not carry as poor a prognostic impact as tumors characterized by vascular invasion.

A major shortcoming of ICC staging is that many patients do not undergo a routine lymphadenectomy, and therefore, were classified as Nx. To overcome this shortcoming, in part, we performed additional analyses comparing the two editions of the AJCC staging system based on lymph node status data obtained from by either preoperative radiological imaging and/or final pathology. Of note, in this analysis, Stage IIIa patients had a 5-year OS of 60.0% versus 35.9%, and 40.9% for Stages II and Ib patients, respectively. In addition, AJCC 8th edition Stage IIIa patients had a higher HR of death compared with Sage Ib patients (AJCC 8th ed. IIIa vs. Ib, HR 1.49 95% CI, 0.97-2.30 $P = 0.07$), but lower than Stages Ib and II. AJCC 8th edition staging did not seem to add much additional prognostic information, as reflected in the minimal improvement in the C-index (AJCC 7th ed., C-index 0.642 vs. AJCC 8th ed., C-index 0.667; $P = 0.24$).

The current study had several limitations. Due to the retrospective nature of the study, there may have been selection and confounding bias. However, such biases were unlikely to affect comparison of performance of the 7th versus 8th edition staging systems. Although the multi-institutional nature of the study was a strength, it also likely led to heterogeneity in treatment approach.

In conclusion, although the AJCC 8th edition was able to better stratify the risk of death of Stage III patients and T3 patients, the revised staging system still fails to discriminate prognosis for a subset of patients. Further improvements and refinements in the T- and overall staging for ICC will be necessary.

POTENTIAL CONFLICTS OF INTEREST

Nothing to disclose.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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