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ORIGINAL RESEARCH

Evaluation of the AJCC 8th Edition Staging System for Pathologically Versus Clinically Staged Intrahepatic Cholangiocarcinoma (iCCA): a Time to Revisit a Dogma? A Surveillance, Epidemiology, and End Results (SEER) Analysis

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Abstract

Background Recently, the AJCC has released its 8th edition changes to the staging system for intrahepatic cholangiocarcinoma (iCCA). This study sought to validate the proposed changes to the 8th edition of AJCC system for T and N classification of iCCA using a population-based data set.

Methods Using the Surveillance, Epidemiology, and End Results (SEER) database (1998–2013), patients undergoing resection or non-surgical management for non-metastatic iCCA were identified. Overall survival was estimated using the Kaplan-Meier method and compared using log-rank tests. Concordance indices (c-indices) calculated from Cox proportional hazards models were calculated to evaluate discriminatory power.

Results The study included 2630 patients resected (37%) or non-surgically managed (63%) for iCCA. Nodal staging was performed in 56%, of whom 31% had positive nodes. For all patients with iCCA, the median 5-year survival by AJCC T classification for T1a, T1b, T2, T3, and T4 was 32, 21, 14, 10, and 10 months, respectively ($p < 0.001$). The concordance index for the staging system was 0.57 for all patients, 0.62 for those who underwent resection, and 0.54 for patients who did not undergo resection.

Conclusion In summary, the new AJCC 8th edition staging system is comparable to the 7th edition and valid in stratifying patients with iCCA. However, the performance of the staging system is better in patients undergoing surgical resection than those undergoing non-surgical management. These findings further highlight the need for improved accuracy of radiological imaging in clinically staging patients to guide prognosis.

Keywords Intrahepatic cholangiocarcinoma · Staging · Surgery · Survival · SEER

Introduction

Intrahepatic cholangiocarcinoma (iCCA) is the second most common primary liver cancer, accounting for 10–15% of all primary liver cancers [1, 2]. The incidence of iCCA is increasing, accounting for 0.7 cases per 100,000 adults in the USA [3]. Despite advances in multimodality treatment, long-term survival is only seen in 10–20% of patients. Surgical resection remains the only potentially curative therapy for patients with iCCA; however, only 30–60% of patients are candidates for surgical resection [4]. Even in patients who undergo successful resection and adjuvant therapy, 5-year survival is 20–40% and median survival is 9 months [4, 5]. To improve patient outcomes, clinical trials to evaluate novel therapeutic strategies are needed. Clinicians also require tools to appropriately counsel patients regarding prognosis. Hence, accurate and improved staging systems are essential.

The American Joint Committee on Cancer (AJCC) introduced several changes into the 8th edition staging system of iCCA (Table 1). Three major modifications were made from the 7th edition staging system (Table 2), resulting in new definitions for T classifications, but none for the N classifications [6]. The current T1 classification was further stratified to account for prognostic impact of tumor size (T1a ≤ 5 cm vs

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Table 1 AJCC 8th edition staging system for intrahepatic cholangiocarcinoma

Primary tumor (T)		Regional lymph nodes (N)		Distant metastases (M)	
T1a	Solitary tumor ≤ 5 cm without vascular invasion	Nx	Regional lymph nodes cannot be assessed	M0	No distant metastasis
T1b	Solitary tumor > 5 cm without vascular invasion	N0	No regional lymph node metastasis		
T2	Solitary tumor with intrahepatic vascular invasion or multifocal tumors with or without vascular invasion	N1	Metastasis in regional lymph nodes	M1	Distant metastasis
T3	Tumor perforating the visceral peritoneum				
T4	Tumor involving local extrahepatic structures by direct invasion				
Stage					
Stage IA		T1a	N0	M0	
Stage IB		T1b	N0	M0	
Stage II		T2	N0	M0	
Stage IIIA		T3	N0	M0	
Stage IIIB		T4	N0	M0	
		Any T	N1	M0	
Stage IV		Any T	Any N	M1	

T1b > 5 cm). Furthermore, T2 tumors were defined as solitary or multifocal tumors with vascular invasion. Instead of denoting T4 according to tumor growth pattern, the current staging system has defined T4 tumors as extensions to local extrahepatic structures, including the retrohepatic vena cava, hepatoduodenal ligament, and visceral structures.

Despite this, this new staging system has not been validated and validation using a nationally representative data set is required. Hence, this study sought to evaluate the discriminative ability of the AJCC 8th edition staging system and study the impact of T and N classification changes on stratification of survival using nationally representative registry data.

Methods

Data Source and Study Cohort

Prospectively collected data from the Surveillance, Epidemiology, and End Results (SEER) database maintained

Table 2 AJCC 7th edition staging system for intrahepatic cholangiocarcinoma

Primary Tumor (T)		Regional Lymph Nodes (N)		Distant Metastases (M)	
T1	Solitary tumor without vascular invasion	Nx	Regional lymph nodes cannot be assessed	M0	No distant metastasis
T2a	Solitary tumor with vascular invasion	N0	No regional lymph node metastasis	M1	Distant metastasis
T2b	Multifocal tumors, with or without vascular invasion	N1	Metastasis in regional lymph nodes		
3	Tumor(s) perforating the visceral peritoneum or involving the local extra hepatic structures by direct invasion				
T4	Tumor with periductal invasion				
Stage					
Stage I		T1	N0	M0	
Stage II		T2	N0	M0	
Stage III		T3	N0	M0	
Stage IVA		T4	N0	M0	
		Any T	N1	M0	
Stage IVB		Any T	Any N	M1	

by the National Cancer Institute were used for analysis in this study. The SEER database has grown to include 21 cancer registries, representing 28% of the US population. As compared to the general US population, the SEER population is slightly more urban and has a slightly higher percentage of foreign-born individuals. Available data included patient demographics (e.g., age, gender, race), tumor data (histology, grade, stage), and treatment data (surgery, radiation). Some data elements (e.g., AJCC staging, details of surgical therapy, tumor size, lymph node involvement) are consistently available only in more recent time periods.

This study identified patients aged > 18 years old with histologically confirmed iCCA undergoing surgical resection using the Surveillance, Epidemiology, and End Results (SEER) database from 1988 to 2013 inclusive. The International Classification of Disease 3rd edition (ICD-O3) was used to identify iCCA using site code C221 and corresponding histology codes such as 8160, 8161, 8470, and 8980. Other variants of iCCA such as neuroendocrine tumors and non-specific histologies (e.g., "neoplasm" or "carcinoma, NOS") were excluded from the analysis. Likewise, cases with vague histology codes of "neoplasm" (8000–8003), "carcinoma, NOS" (8010–8013), and "carcinoma undifferentiated, NOS" (8120–8122) were excluded (NOS, not otherwise specified). Cases with another malignancy preceding 5 years before diagnosis of iCCA were excluded. The SEER database provides reliable TNM staging information for cases from 1988 onwards based on the AJCC 3rd and 6th editions. Hence, patients had to be restaged to the 8th and 7th edition classifications using definitions as listed in Tables 1 and 2 respectively.

Statistical Analysis

Categorical variables were compared using the chi-squared test. Non-normally distributed data were analyzed using the Mann-Whitney *U* test. Survival was estimated using the Kaplan-Meier survival curves and compared using the log-rank test. A concordance index (c-statistic) was calculated to evaluate the discriminatory power of each staging system. A value of 0.5 indicates chance alone is as predictive as the staging system, whereas a level of 1.0 signifies perfect concordance. A Cox proportional hazards model was used with stage coded as indicator variables to obtain hazard ratios (HR), and the concordance index was calculated from this Cox model. Cox proportional hazards modeling was used to assess the relative impacts of T and N classification on survival. A separate model adjusting for potential confounding variables including sex, age, and race was also assessed. A p value of < 0.05 was considered to be statistically significant. Data analysis was performed using R Foundation Statistical software (R 3.2.1) with TableOne, ggplot2, Hmisc, and survival packages (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline Demographics

This study identified 2630 iCCA patients with complete staging from 1988 to 2013, of which 37% underwent liver resection and 63% did not undergo resection. Patient characteristics are presented in Table 3. Patients undergoing liver resection were more likely to be younger with well/moderate tumor grades and early tumor stage at presentation. In patients undergoing liver resection, the rate of lymphadenectomy was 56%, of which 14% (132/975) had ≥ 6 lymph nodes examined. In patients with lymph nodes examined, 31% (169/547) had positive lymph nodes.

Overall Survival by T Classification

For all patients with iCCA, the median 5-year survival by AJCC T classification for T1a, T1b, T2, T3, and T4 was 32, 21, 14, 10, and 10 months, respectively ($p < 0.001$, Fig. 1a). Cox regression for N0 and Nx tumors demonstrated significant differences in survival between the new AJCC 8th edition T classifications (Table 4). The corresponding c-index for the 8th edition T classification was 0.57 ($CI_{95\%}$ 0.54–0.60), similar to that for the 7th edition (0.57, $CI_{95\%}$ 0.55–0.61). In patients undergoing surgical resection for iCCA, the median 5-year survival by AJCC T classification for T1a, T1b, T2, T3, and T4 was NR, 60, 34, 19, and 18 months, respectively ($p <$ 0.001, Fig. 1b). Cox regression for N0 and Nx tumors demonstrated significant differences in survival between the new AJCC 8th edition T classifications (Table 4). The corresponding c-index for the 8th edition T classification was 0.62 ($CI_{95\%}$ 0.61–0.63), similar to that for the 7th edition (0.62, $CI_{95\%}$ 0.60–0.65). In patients undergoing non-surgical treatment for iCCA, the median 5-year survival by AJCC T classification for T1a, T1b, T2, T3, and T4 was 13, 11, 9, 7, and 8 months, respectively ($p < 0.001$, Fig. 1c). The corresponding c-index for the 8th edition T classification was 0.54 ($CI_{95\%}$ 0.52–0.56), similar to that for the 7th edition (0.54, $CI_{95\%}$ 0.51–0.57).

Outcomes of Subgroups of T1 Tumors

The new staging system stratified T1 tumors according to tumor size, T1a (≤ 5 cm) and T1b (> 5 cm). In the entire cohort, there were 558 patients with solitary tumors ≤ 5 cm and 437 patients with solitary tumors > 5 cm. The 5-year (24 vs 22%) and median (32 vs 21 months, all $p = 0.062$, Fig. 2a) survival were not significantly longer for patients with T1a as compared to T1b tumors. In patients undergoing surgical resection, there were 222 patients with solitary tumors ≤ 5 cm and 180 patients with solitary tumors > 5 cm. The 5-year (42 vs 41%) and median (not reached vs 60 months, all $p = 0.2$,

Table 3 Clinicopathologic variables of intrahepatic cholangiocarcinoma

	Overall, $n = 2630$	No resection, $n = 1655$	Liver resection, $n = 975$	p value
Age at diagnosis				
18–69	1532 (58.3)	867 (52.4)	665 (68.2)	< 0.001
70–79	715 (27.2)	464 (28.0)	251 (25.7)	
> 80	383 (14.6)	324 (19.6)	59 (6.1)	
Sex, female	1310 (49.8)	819 (49.5)	491 (50.4)	0.695
Ethnicity				
White	2037 (77.5)	1259 (76.1)	778 (79.8)	0.088
Other	590 (22.4)	394 (23.8)	196 (20.1)	
Unknown	3 (0.1)	2 (0.1)	1 (0.1)	
Grade of tumor				
Well/moderate	878 (33.4)	325 (19.6)	553 (56.7)	< 0.001
Poor/anaplastic	547 (20.8)	288 (17.4)	259 (26.6)	
Unknown	1205 (45.8)	1042 (63.0)	163 (16.7)	
Radiation therapy				
None	2432 (92.5)	1626 (98.2)	806 (82.7)	< 0.001
Neoadjuvant	20 (0.8)	4 (0.2)	16 (1.6)	
Adjuvant	176 (6.7)	25 (1.5)	151 (15.5)	
Others	2 (0.0)	0 (0.0)	2 (0.2)	
AJCC 8th T classification				
T1a	558 (21.2)	336 (20.3)	222 (22.8)	< 0.001
T1b	437 (16.6)	257 (15.5)	180 (18.5)	
T2	1146 (43.6)	727 (43.9)	419 (43.0)	
T3	288 (11.0)	213 (12.9)	75 (7.7)	
T4	201 (7.6)	122 (7.4)	79 (8.1)	
Lymph node examined				
0	1981 (75.3)	1553 (93.8)	428 (43.9)	< 0.001
1–5	469 (17.8)	54 (3.3)	415 (42.6)	
≥ 6	180 (6.8)	48 (2.9)	132 (13.5)	
AJCC 8th N classification				
N0	416 (15.8)	38 (2.3)	378 (38.8)	< 0.001
N1	233 (8.9)	64 (3.9)	169 (17.3)	
Nx	1981 (75.3)	1553 (93.8)	428 (43.9)	

Fig. 2b) survivals were not significantly longer for patients with T1a as compared to T1b tumors. In patients undergoing non-surgical management, there were 336 patients with solitary tumors ≤ 5 cm and 257 patients with solitary tumors > 5 cm. The 5-year (6 vs 5%) and median (13 vs 11 months, all $p = 0.011$, Fig. 2c) survivals were not significantly longer for patients with T1a as compared to patients withT1b tumors.

Outcomes of Subgroups of T2 Tumors

In the AJCC 8th edition staging, T2 tumors include both solitary tumors with vascular invasion and multifocal tumors with/without vascular invasion.

In the entire cohort, there were 651 patients with solitary tumors with vascular invasion, and 495 patients with multifocal tumors with/without vascular invasion. The 5-year (22 vs 8%) and median (15 vs 13 months, all $p = 0.024$) survivals were significantly longer for patients having solitary tumors with vascular invasion as compared to those with multifocal tumors with/without vascular invasion. In patients undergoing surgical resection, there were 256 patients with solitary tumors with vascular invasion, and 163 patients with multifocal tumors with/without vascular invasion. The 5-year (26 vs 19%) and median (37 vs 28 months, all $p = 0.2$) survivals were not significantly longer for patients having solitary tumors with vascular invasion as compared to those with multifocal tumors with/without vascular invasion. In patients undergoing non-surgical management, there were 395 patients with solitary tumors with vascular invasion, and 332 patients with multifocal tumors with/without vascular invasion. The 5-year (3% vs 1%) and median (9 vs 9 months, all $p = 0.1$)

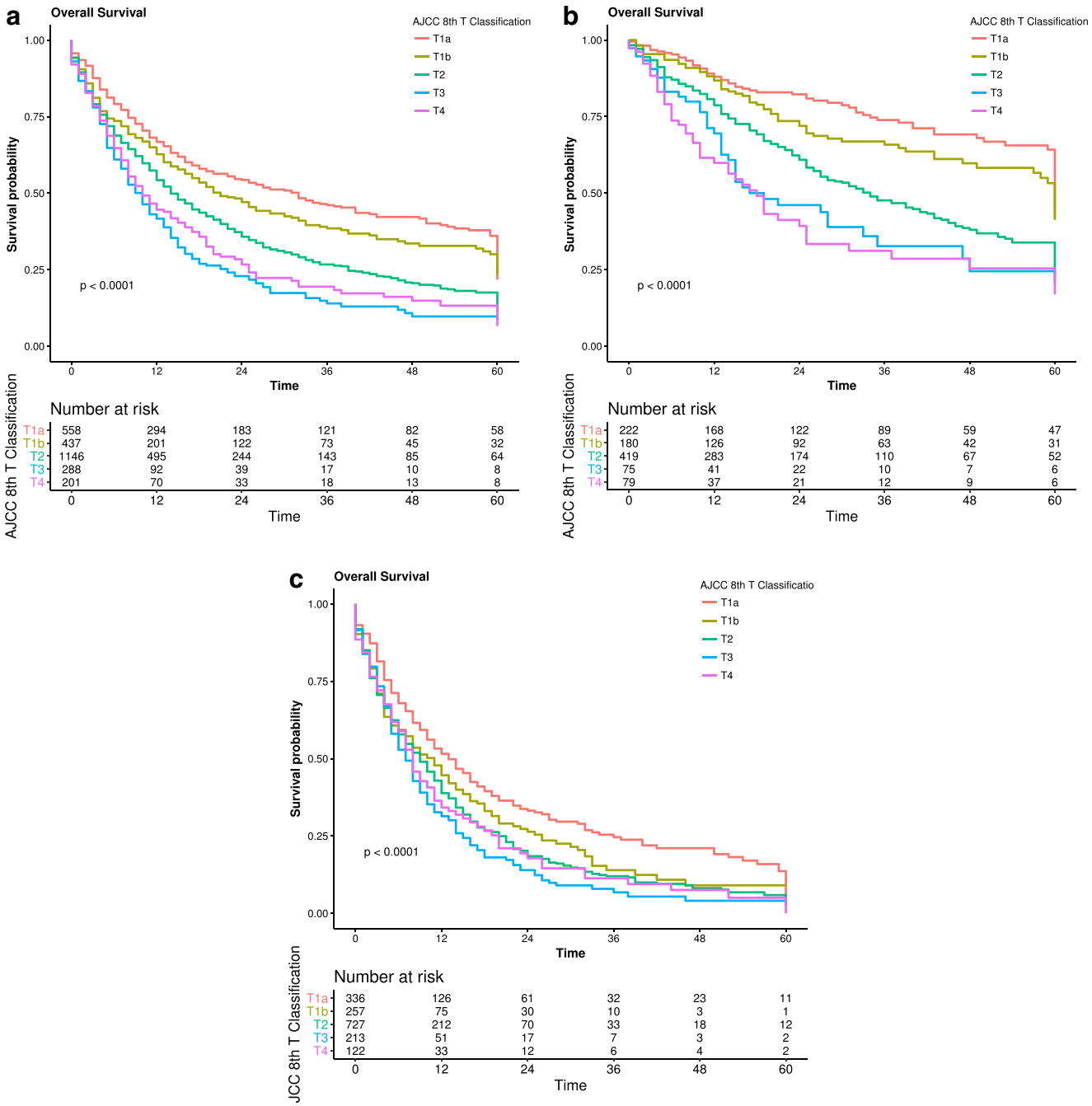

Fig. 1 Overall survival of patients with intrahepatic cholangiocarcinoma stratified by the AJCC 8th edition T classification. **a** All patients. **b** Surgical resection. (**c**) Non-surgical management

survivals were not significantly longer for patients having solitary tumors with vascular invasion as compared to those with multifocal tumors with/without vascular invasion.

Outcomes of Vascular Invasion in Multifocal Tumors

In the AJCC staging system for iCCA, multifocal tumors with/without vascular invasion were grouped together. In the entire cohort, there were 208 patients with multifocal tumors without vascular invasion, and 285 patients without vascular invasion. The 5-year (14 vs 4%) and median (15 vs 12 months, all $p = 0.088$) survivals were not significantly longer for patients having multifocal tumors without vascular invasion as compared to those with vascular invasion. In patients undergoing surgical resection, there were 77 patients with multifocal tumors without vascular invasion, and 85 patients with vascular invasion. The 5-year (28 vs11%) and median (33 vs 25 months, all $p = 0.2$) survivals were not significantly longer for patients having multifocal tumors without vascular invasion as compared to those with vascular invasion. In patients

Table 4 Cox proportional hazards model evaluating independent impact of T and N classification on survival

		All patient		N0		Nx	
		HR ($CI_{95\%}$)	*p* value	HR ($CI_{95\%}$)	*p* value	HR ($CI_{95\%}$)	*p* value
All patients	T1a	REF		REF		REF	
	T1b	1.18 [0.99, 1.40]	0.066	0.89 [0.52, 1.52]	0.667	1.33 [1.10, 1.61]	0.004
	T2	1.58 [1.38, 1.81]	< 0.001	1.65 [1.08, 2.52]	0.021	1.65 [1.41, 1.92]	< 0.001
	T3	2.15 [1.79, 2.58]	< 0.001	1.72 [0.90, 3.27]	0.098	2.24 [1.83, 2.74]	< 0.001
	T4	1.95 [1.59, 2.38]	< 0.001	2.38 [1.38, 4.11]	0.002	2.34 [1.84, 2.96]	< 0.001
	c-stats	0.57		0.60		0.57	
Resection	T1a	REF		REF		REF	
	T1b	1.24 [0.88, 1.74]	0.21	1.55 [0.98, 2.43]	0.059	1.49 [0.94, 2.37]	0.091
	T2	2.05 [1.57, 2.69]	< 0.001	1.86 [0.95, 3.64]	0.071	1.96 [1.33, 2.88]	0.001
	T3	2.85 [1.93, 4.19]	< 0.001	2.69 [1.52, 4.79]	0.001	3.17 [1.74, 5.77]	< 0.001
	T4	3.35 [2.32, 4.85]	< 0.001	–	–	5.14 [2.68, 9.88]	< 0.001
	c-stats	0.62		0.61		0.62	
Non-resection	T1a	REF		REF		REF	
	T1b	1.29 [1.05, 1.59]	0.014	1.84 [0.37, 9.25]	0.46	1.32 [1.07, 1.63]	0.01
	T2	1.43 [1.22, 1.68]	< 0.001	3.14 [0.80, 12.31]	0.101	1.44 [1.22, 1.70]	< 0.001
	T3	1.68 [1.37, 2.07]	< 0.001	0.90 [0.09, 9.40]	0.928	1.74 [1.40, 2.15]	< 0.001
	T4	1.53 [1.19, 1.95]	0.001	0.38 [0.04, 3.70]	0.408	1.71 [1.32, 2.20]	< 0.001
	c-stats	0.54		0.67		0.55	

undergoing non-surgical management, there were 131 patients with multifocal tumors without vascular invasion and 200 patients with vascular invasion. The 5-year (2% vs 0%) and median (9 vs 9 months, all $p = 0.9$) survivals were not significantly longer for patients having multifocal tumors without vascular invasion as compared to those with vascular invasion.

Discussion

This validation study using a national database demonstrated that the new AJCC 8th edition staging system for iCCA is comparable to the AJCC 7th edition and valid for prognostication in patients. However, the new staging system performs much better for undergoing surgical resection as compared to patients undergoing non-surgical management. Considering the T2 tumors, both solitary and multifocal tumors have a similar survival and vascular invasion does not impact on survival in patients with multifocal tumors. Validation of this new staging system allows counseling of patients of survival in both surgical and non-surgically managed patients.

The revised T classification incorporates tumor size for further stratifying prognosis in solitary tumors without vascular invasion. To date, literature on the impact of tumor size have been inconclusive; certain studies demonstrate no survival difference [7–12], while other authors have suggested that tumor size may indeed be prognostically important following hepatic resection [13–15]. A recent systematic review by Mavros et al., examining 4756 patients undergoing hepatic resection across 57 studies, demonstrated that large tumor size was associated with poor long-term outcomes [16]. In this study, tumor size was prognostic in patients undergoing non-surgical management but not for those undergoing surgical management.

Previous studies have established multifocal tumors and vascular invasion as poor prognostic factors in iCCA [10, 13, 17]. Hyder et al. demonstrated that tumor number (HR = 1.58, $p < 0.001$) and vascular invasion (HR = 2.1, $p < 0.001$) were both notable risk factors of poor outcome following a curative intent resection of iCCA [13]. Similarly, the Wang et al. nomogram also identified tumor number and vascular invasion as important in determining survival [17]. However, the new staging system has reclassified previous T2a (solitary tumor with vascular invasion) and T2b (multifocal tumor with/without vascular invasion) classification as T2. In this study, there were no significant differences in survival between patients with solitary and multifocal tumors, both in patients undergoing surgical and non-surgical management. Furthermore, vascular invasion was not prognostic in patients with multifocal tumors which may be due to inherent aggressive tumor biology associated with multifocal tumors.

Limitations of this study include the lack of information on resection margin status and underlying etiology. However,

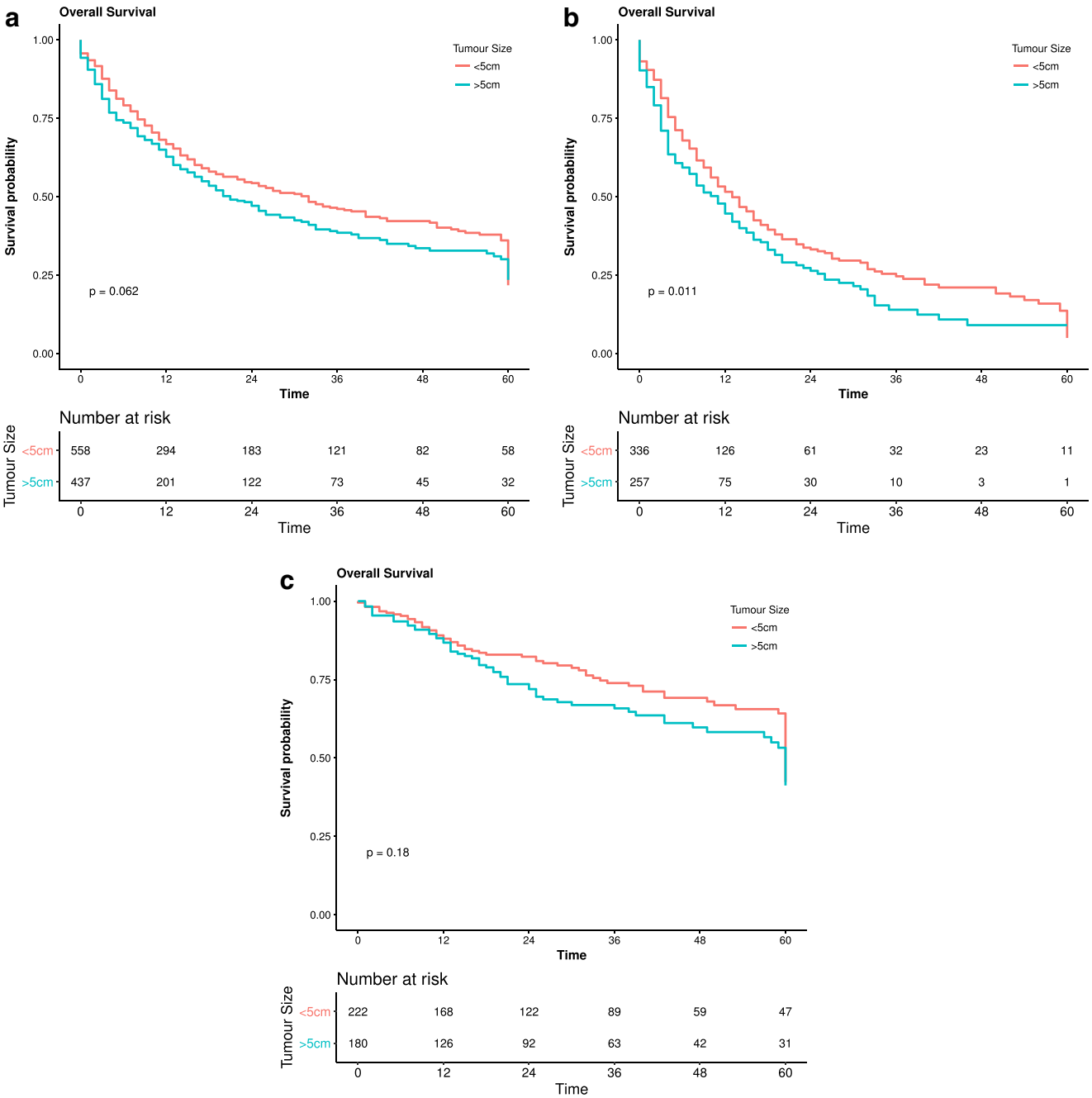

Fig. 2 Overall survival of patients with T1 intrahepatic cholangiocarcinoma stratified by tumor size. **a** All patients. **b** Surgical resection. **c** Non-surgical management

these are not variables that have been historically included in the iCCA staging system, even though they may have some prognostic impact. There was no centralized pathologic review of tumor specimens in this cancer registry-based study. Despite this, previous studies have reported good agreement between the histologic subtypes of cancer reported by SEER and those assigned by independent reviewers [18]. Notable strengths of our study include the large population included and the robust long-term follow-up of survival provided by SEER.

Conclusion

In summary, the new AJCC 8th edition staging system is comparable to the 7th edition and valid in stratifying patients with iCCA. However, the performance of the staging system is better in patients undergoing surgical resection than those undergoing non-surgical management. These findings highlight the need for improved accuracy of radiological imaging in clinically staging patients to guide prognosis and further management.

Compliance with Ethical Standards

Conflict of Interest The author declares that there is no conflict of interest.

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