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ORIGINAL ARTICLE

Comparison of the prognostic accuracy of the sixth and seventh editions of the TNM classification for intrahepatic cholangiocarcinoma

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Abstract

Background: The seventh TNM edition introduced a new, specific staging structure for intrahepatic cholangiocarcinoma (IHC).

Objective: To compare the accuracy of the sixth and the new seventh edition to predict survival after hepatectomy for IHC.

Methods: In all, 434 consecutive patients who underwent hepatectomy at 16 tertiary-care centres (1990–2008) were identified. End points were overall (OS) and recurrence-free survival (RFS) for both T cohorts and stage strata.

Results: After a median follow-up of 32.4 months, 3- and 5-year OS and RFS estimates were 47.1% and 32.9%, and 26.5% and 19.1%, respectively. Overall, both the editions were statistically significant discriminators of OS and RFS ($P < 0.05$). However, the survival curves of the new T2a and T2b cohorts appear superimposed. Conversely, the old T2 and T3 cohorts accurately stratify patients into distinct prognostic groups ($P < 0.01$). The seventh edition does not show monotonicity of gradients (the T4 category demonstrates significantly better OS and RFS compared with T2 patients). The seventh edition stage I and II are significantly different whereas the old stage I and II were not.

Conclusions: The new seventh edition of the *AJCC/UICC Staging System* proved to be adequate although further studies are need to confirm its superiority compared with the previous edition.

Keywords

intrahepatic cholangiocarcinoma, hepatic resection, prognosis, staging, TNM classification

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Introduction

Intrahepatic cholangiocarcinoma (IHC) is the second commonest primary malignant neoplasm of the liver, originating from the epithelium of the second-order or more proximal bile ducts. Although rising incidence rates, paralleled by mortality rates, have been documented in most areas worldwide,[1,2] IHC remains a rare disease when compared with hepatocellular carcinoma (HCC). Data from the 17th nationwide follow-up survey of primary liver cancer in Japan indicate that IHC accounts for only 4.1% of the newly diagnosed liver tumours.[3] In non-endemic geographical regions, such as the United States, this proportion is estimated to be slightly higher (approximately 10%).[1] The rarity of the disease and the frequency with which patients present at a late, unresectable stage (80–85%),[4] had hampered an in-depth understanding of the prognostic factors associated with poor survival after resection. In western countries, the severity or stage of an individual's cancer has traditionally been evaluated on the basis of the TNM staging system which classifies cancers by the size and extent of the primary tumour (T), involvement of regional lymph nodes (N) and the presence or absence of distant metastases (M). In 1988, in the 3rd edition of the TNM staging manual, the American Joint Committee on Cancer (AJCC) and the International Union for Cancer Control (UICC) devised a separate staging system for primary liver cancers, which applied to both HCC and IHC. However, this original staging algorithm as well as all subsequent revisions was based only on data obtained from patients resected for HCC. Nonetheless, HCC and IHC differ significantly in pathogenesis, tumour behaviour and prognosis after surgical resection. Therefore, after two decades, the development of a separate staging with specific relevance to IHC was critical as information derived from staging not only provides data regarding prognosis, but also dictates patient stratification in clinical research. Based on the analysis of data obtained form The Surveillance, Epidemiology, and End Results (SEER) database on 598 unselected patients who had undergone surgery for IHC, Nathan *et al.*[5] proposed a new staging schema which was adopted in the seventh edition of the *TNM Staging Manual*.[6] However, this novel staging system, which is independent of the staging systems for HCC and extahepatic bile duct malignancy, has not been externally validated nor compared with the sixth edition classification schema.[7] The purpose of the present study was to compare the prognostic accuracy of the sixth and the new seventh edition of the AJCC/UICC staging systems to predict survival after liver resection for IHC in a large series of patients treated at tertiary hepatobiliary centres.

Methods

In all, 434 consecutive patients treated with curative intent liver resection for IHC between March 1990 and December 2008 at 16 tertiary hepatobiliary centres were identified from each institution's prospectively collected database. Pathological data of all patients were reviewed to confirm the diagnosis of IHC which was based on the histopathological examination of haematoxylin and eosin (H&E) and cytokeratin-stained sections. Patients with mixed IHC/HCC and hilar (Klatskin) adenocarcinomas were considered ineligible for entering this study. Before surgery, all

Table 1 sixth and seventh edition of the AJCC/UICC TNM classification algorithm for intrahepatic cholangiocarcinoma (IHC)

sixth edition		seventh edition	
T1	Solitary tumour without vascular invasion	T1	Solitary tumour without vascular invasion
T2	Solitary tumour with vascular invasion or multiple tumours, none more than 5 cm	T2a	Solitary tumour with vascular invasion
T3	Multiple tumours more than 5 cm or tumour involving a major branch of the portal or hepatic veins	T2b	Multiple tumours, with or without vascular invasion
T4	Tumour(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum	T3	Tumour(s) perforating the visceral peritoneum or involving the local extra hepatic structures by direct invasion
		T4	Tumour with periductal invasion
N0 no regional lymph node metastases		N0 no regional lymph node metastases	
N1 regional lymph node metastases		N1 regional lymph node metastases	
M0 no regional lymph node metastases		M0 no regional lymph node metastases	
M1 regional lymph node metastases		M1 regional lymph node metastases	
Stage		*Stage*	
I	T1 N0 M0	I	T1 N0 M0
II	T2 N0 M0	II	T2 N0 M0
IIIa	T3 N0 M0	III	T3 N0 M0
IIIb	T4 N0 M0	IVa	T4 N0 M0, Any T N1 Mo
IIIc	Any T N1 M0	IVb	Any T, Any N, M1
IV	Any T, Any N, M1		

patients received routine clinical evaluation including medical history, physical examination, assessment of serum laboratory tests, colonoscopy and upper gastrointestinal (GI) endoscopy and appropriate imaging studies [e.g. computed tomography (CT) or magnetic resonance imaging (MRI) scan of the abdomen and chest radiography or a chest computed tomography] at the discretion of the treating physician. After surgery, patients were followed at regular intervals of 3 to 6 months according to each institution protocols. Follow-up data were prospectively recorded until 31 October 2009. Relevant clinicopathological features were collected for each patient. Specifically, these variables included: age; gender; pre-operative serum CEA and CA19.9 concentration; type of surgical procedures; tumour size (in patients with multiple IHCs the largest tumour was used as the index lesion); tumour number (as we could not retrospectively differentiate between satellitosis, intrahepatic metastasis and multiple primary tumours, tumours were classified as solitary vs. multiple); histological differentiation; presence of microscopic or major vascular invasion; lymph node status; invasion of adjacent organs; and presence of distant metastases. Patients were classified separately according to the criteria of the sixth and the new seventh edition of the *AJCC/UICC Staging System* (Table 1).

In the present study, the primary end points used to evaluate the stratification ability of the two staging systems were OS and RFS. Rates for these outcome measures were estimated using the Kaplan–Meier methodology measuring time from the date of surgery to the date of death or last follow-up, and the date of tumour relapse at any site, respectively. For estimation of RFS, patients who were alive and without tumour recurrence at the time of last contact were censored. As the aim of the present study was to investigate the performance of the two staging systems in stratifying the long-term prognosis, patients who died in the post-operative period (i.e within 90 days after surgery or during the same hospital stay) were excluded. The capacity of each staging system to distinguish categories of patients with significantly different survival rates was evaluated by comparing the survival distributions within single categories using the log-rank test. Cox's proportional hazard regression was used to assess the monotonicity of gradients (i.e. the median survival, either overall or recurrence free, of patients classified within earlier stages is longer than the survival of patients in more advanced stages). Two sets of analyses were performed. The first focused on the evaluation of the T categories while the second analysed the stage strata. Of note, statistical comparisons ware made only between groups of a minimum informative sample size of 20 patients. Statistical significance was set at P-values of <0.05. The R environment (version 2.10.1) software package was used for statistical analyses.

Results

Patients characteristics and survival

The descriptive characteristics of the 434 patients included in the study are summarized in Table 2. Patients were evenly distributed

Table 2 Clinical and pathologic features of the study population

Variable	Value	%
Age (years)	65 (29–85)	
Gender (male/female)	243/191	56/44
Pre-operative serum concentration		
CEA (ng/ml)	2.3 (0–36 000)	
CA19.9 (U/ml)	57.1 (0.2–27 000)	
Type of resection		
Extended hepatectomy	84	19.4
Major hepatectomy	220	50.7
Minor hepatectomy	130	29.9
Lymph node dissection		
None	121	27.9
Sampling	43	9.9
Standard	157	36.2
Extended	113	26.0
Additional abdominal procedures	134	30.9
Macroscopic type classification		
Mass forming	390	89.9
Periductal infiltrating or mixed mass forming + periductal	39	9.0
Intraductal	5	1.1
Tumour size (cm)	60 (10–250)	
Tumour number		
Single	293	67.5
Multiple	140	32.3
NA	1	0.2
Tumour grade		
Well/moderately differentiated	259	59.7
Poorly or undifferentiated	147	33.9
NA	28	6.4
Presence of vascular invasion		
Present	211	48.6
Absent	187	43.1
NA	36	8.3
Presence of perineural invasion		
Present	163	37.5
Absent	183	42.2
NA	88	20.3
Lymph node status		
pNx	121	27.9
pN0	193	44.5
pN1	113	26.0
NA	7	1.6
Distant metastases	14	3.2

Continuous variable are reported as median (range); NA, not available.

as to gender (male/female ratio 1.27 : 1) with a median age of 65 (range 29–85) years. Seventy per cent of patients underwent major (n = 220) or extended (n = 84) hepatectomies. In addition to hepatic resection, 313 patients (72.1%) underwent hepatic pedicle lymph node (LN) sampling (n = 43) or regional LN dissection (n = 270). This was extended to second echelon LN in 113 patients (41.8%). Therefore, 121 patients (27.9%) were classified as pNx. Nodal status was pN0 in 193 patients (44.5%) whereas 113 patients (26.0%) were found to have lymph nodes metastases (the pN status was uncertain for 7 patients who had undergone lymphadenectomy). In all, 134 patients (30.9%) underwent 159 additional major intraabdominal procedures of which 84 (52.8%) were bile duct resections and 22 (13.8%) were vascular resections. Twenty-three patients died within 90 days (mortality rate 5.3%), leaving, for the purpose of this study, a final cohort of 411 patients.

At the time the data were censored, 218 patients (53.0%) had died, with a median follow-up for the survivors of 36.5 (range 1 to 181) months. Overall median survival was 33 months [95% confidence interval (CI) 27.0–39.1], and the 1-, 3- and 5-years overall survival estimates were 82.3%, 47.1%, and 32.9%, respectively. Recurrence occurred in 237 patients (57.7%) after a median of 15 months, with the liver involved in 174 patients (73.4%). In 129 (54.4%) patients this was isolated to the liver and in 45 (19.0%) it was with disseminated disease. At last follow-up, disease recurrence could not be ascertained in 33 patients (8.0%), while for an additional 13 patients (3.1%) who developed recurrence, the exact date of recurrence could not be obtained. Therefore, these patients were not considered for the estimation of the RFS. Median RFS was 15.2 months (95% CI, 12.8–18.7), and the 1-, 3- and 5-years RFS estimates were 56.1%, 26.5% and 19.1%, respectively.

Staging system comparison

Patient distribution by T classification for each system and stage migration is shown in Table 3. Figure 1 depicts the Kaplan–Meier estimated OS and RFS curves, according to the two different staging systems. When comparison of survival distribution was made using the log-rank test, both staging systems were statistically significant discriminators of both overall OS and RFS (both $P < 0.001$). Only the sixth edition showed monotonicity of gradients; in fact, in the seventh edition, T4 patients had a better survival than patients classified as T2a and T2b (Table 4). In addition, the survival curves of the new T2a and T2b cohorts appear superimposed. On the contrary, the old T2 and T3 cohorts accurately stratify patients into two distinct prognostic groups ($P < 0.01$) (Fig. 1 and Table 4). Similar results were obtained when the analysis of OS was restricted to patients without nodal or metastatic disease (pN0 M0) (data not shown). In the same subset of patients, however, analysis of RFS did not show statistically significant differences.

In order to assess the precision of prognostication of the stage grouping of the two systems, survival analysis was restricted to 284 patients. In fact, 127 patients who survived their hepatic resection had no pathological information on the N status and could not be assigned to a specific stage. Figure 2 depicts the Kaplan–Meier estimated OS and RFS curves for the two systems strata. Both systems showed an overall significant difference in the probability of OS across the different stages ($P < 0.001$) and a monotonicity of gradients (Table 4). However, in neither edition a significant stepwise discrimination of all stages could be demonstrated. In particular, in the sixth edition stage I and II were not sequentially different (Table 4). Because of the small number of patients in stages IIIb ($n = 4$) and IV ($n = 12$), no meaningful conclusions can be driven by the comparison of stages III and IV. However, when stage IIIa was compared with stage IIIc, OS of stage IIIc patients was not statistically worse (P = 0.286). Conversely, the seventh edition adequately stratified stages I and II into two distinct prognostic groups, albeit the difference was marginally significant (P = 0.049). Again, stage III and IVb were too small to allow for statistical analysis. When stage II was compared with stage IVa a significant discrimination between patients was observed ($P = 0.01$).

Overall both staging systems were significant discriminators for RFS ($P < 0.001$) and showed monotonicity of gradients for representative strata (i.e. strata with more than 20 patients) (Table 4). With consideration of the statistical constraints related to stages IIIb and IV (sixth edition) and III and IVb (seventh

Table 3 Patients distribution by T classification in each system

		seventh edition							
	T	1	2a	2b	3	4	NA	n*	%
sixth edition	1	122				14		**136**	33.1
	2		99	38		15		**152**	37.0
	3		12	82		7		**100**	24.3
	4				10	2		**12**	2.9
	NA						11	**11**	2.7
	n*	**122**	**110**	**120**	**10**	**38**	**11**	**411**	
	%	29.7	26.8	29.2	2.4	9.2	2.7		

*n, number of patients; T, category T; NA, not available.

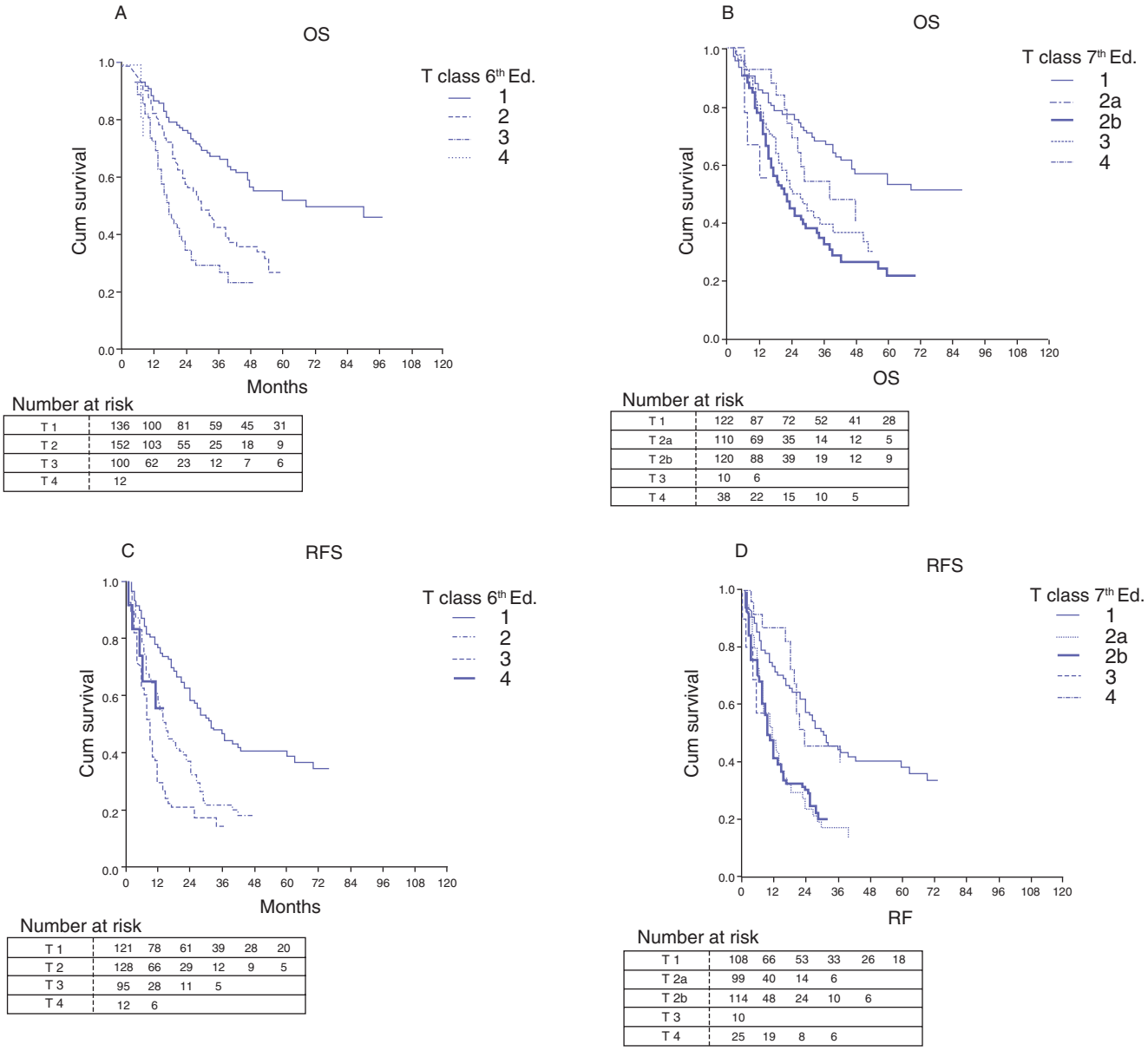

Figure 1 Kaplan–Meier estimated overall (OS) (A and B) and recurrence-free survival (RFS) (C and D) curves stratified for T categories according to the sixth and seventh editions of the *TNM Staging System*. Survival curves have been truncated when the number at risk is less than 10% of the starting denominator or less than 5

edition), the sixth edition accurately discriminates sequential stages I and II, whereas stage IIIa did not differ from stage II. The new seventh edition performed similarly with almost identical survival estimates of stages II and IVa.

Discussion

Accurate staging after surgical resection of any cancer type is essential to evaluate the results of treatments and clinical trials, to provide data regarding the prognosis and to serve as a basis for clinical and translational cancer research or registries. Over the past 20 years, staging of IHC has traditionally been defined on the basis of an algorithm specifically developed for HCC. However, the appropriateness of a single staging system applying to both primary liver cancers is questionable because of the inherent differences in the aetiology and the biological behaviour of the two diseases.[8] Previous attempts to design a specific staging algorithm for IHC resulted in the proposal of two distinct staging systems.[8,9] However, both systems were devised after analysis of a relatively small series of patients. This may be problematic because the

Table 4 Survival estimates stratified for groups in the two staging systems

	sixth edition								seventh edition							
	Class	n*		Median (95% CI)	3-year estimates (%)	5-year estimates (%)	Hazards Ratio	*P* value[a]	Class	n*		Median (95% CI)	3-y estimates (%)	5-y estimates (%)	Hazards Ratio	*P* value[a]
Overall survival	T1	136	91	44.2–137.7	68.1	55.7	1		T1	122	91	43.7–138.3	68.2	53.5	1	
	T2	152	30	23.7–36.2	42.8	24.7	1.89	<0.001	T2a	110	28	20.5–35.5	39.4	23.4	2.11	<0.001
	T3	100	18	14.1–21.9	29.6	20.2	3.26	0.002	T2b	120	22	16.8–27.1	34.7	21.9	2.58	0.265
	T4	12	–	–	–	–	–	–	T3	10	–	–	–	–	–	–
									T4	38	39	15.8–62.1	54.2	32.1	1.42	0.030
	I	67	60	20.9–99.1	68.3	47.8	1		I	56	60	11.6–108.3	66.2	48.0	1	
	II	69	40	16.6–63.3	57.3	35.8	1.32	0.277	II	95	39	24.2–53.7	50.8	28.2	1.61	0.049
	IIIa	32	20	12.1–27.8	35.4	17.7	2.65	0.034	III	3	–	–	–	–	–	–
	IIIb	4	–	–	–	–	–	–	IVa	117	19	14.6–23.3	31.3	19.0	2.63	0.420
	IIIc	100	17	14.2–19.8	23.6	13.8	3.51	0.339	IVb	12	–	–	–	–	–	–
	IV	12	–	–	–	–	–	–								
Recurrence-free survival	T1	121	32	22.1–40.9	46.5	38.5	1		T1	108	31	22.4–39.6	44.5	38.2	1	
	T2	128	15	11.2–18.7	21.6	10.8	2.19	<0.001	T2a	99	12	9.3–14.7	17.2	4.3	2.71	<0.001
	T3	95	9	7.6–10.3	14.1	7.5	3.58	0.001	T2b	114	10	8.1–11.9	18.5	11.6	2.54	0.700
	T4	12	–	–	–	–	–	–	T3	10	–	–	–	–	–	–
									T4	25	24	4.1–43.9	45.5	31.2	1.21	0.019
	I	61	27	16.4–37.5	44.9	34.9	1		I	50	24	13.9–34.0	37.5	31.2	1	
	II	62	18	12.4–23.5	24.2	13.4	1.75	0.010	II	89	15	10.6–19.3	19.4	12.2	1.82	0.008
	IIIa	31	10	7.3–12.6	12.7	0	2.63	0.065	III	3	–	–	–	–	–	–
	IIIb	4	–	–	–	–	–	–	IVa	107	11	7.5–14.4	24.5	13.0	2.11	0.682
	IIIc	91	8	5.9–10.3	16.7	6.7	3.11	0.809	IVb	9	–	–	–	–	–	–
	IV	9	–	–	–	–	–	–								

n* = number of patients; [a]*P*-values are calculated with respect to the preceding category. Survival data, HR and *P*-values are not reported for categories of less than 20 patients.

development of a staging system should rely on the identification of individual variables that consistently predict survival. Yet, in patients with IHC reports on the significance of various predictors of poor outcome are still conflicting.[8–16] To overcome this limitation, Nathan and colleagues[5] utilized the SEER database to select a large series of patients who had undergone liver resection for IHC. By analysing the survival data of 598 patients, the investigators found that tumour size had no independent effect on survival. Because a tumour size >5 cm had no prognostic relevance, the sixth edition AJCC/UICC T classification failed to stratify T2 and T3 cohorts into two distinct prognostic groups. In this study, the Cox model also revealed that both vascular invasion and multiplicity of tumour number significantly impacted prognosis with no additive or synergistic effect of the two factors. These findings were integrated into a simplified staging system that omits tumour size as a parameter to define the T categories. Although simpler, the resulting model demonstrated similar prognostic accuracy to the sixth edition classification scheme and represented the basis for designing a new staging structure independent of that for HCC. This new algorithm was incorporated into the seventh edition of the AJCC/UICC TNM staging manual. However, since its introduction in clinical practice, this new staging schema has not been independently validated. Using the largest, prospectively collected series of IHC resected at tertiary referral centres we sought to critically evaluate the prognostic accuracy of the sixth and seventh editions of the TMN classification systems.

Unexpectedly, the most significant finding of the present study was that the old T2 and T3 categories accurately stratify patients into two distinct prognostic groups for both OS and RFS. This is in contrast with the results of Nathan *et al.*[5] and may be attributed to our cohort selection from highly specialized hepatobiliary centres. In fact, in the current series the 5-year OS was twice that observed in Nathan's study (32.9%, vs. 18%). This might suggest substantial differences in the baseline characteristics between the two studies' populations. However, the percentage of individuals with LN metastases, multiple tumours, poorly differentiated or undifferentiated tumours was similar. Likewise, the distribution of patients after stratification for tumour diameter (2–5 cm and >5 cm) was comparable, with a higher proportion of small IHC (<2 cm) in the SEER population (16.5% vs. 5.1%). In a retrospective study analysing the outcome of 172 patients resected for mass-forming IHC, tumour size <2 cm was found to be the most important determinant of survival after multivariate analysis.[8] Therefore, the substantial number of patients with small IHC in the study by Nathan *et al.*[5] might counterbalance the higher proportion of patients with distant metastases observed in their series (19.2% vs. 4.2% in the current series). In addition, from the methodological standpoint, within the current series all pathological data were retrospectively reviewed to confirm the diagnosis of IHC and the consistency of the data recorded in each prospectively collected database for the variables of interest. Therefore, the number of missing values was reduced, usually because of a lack in

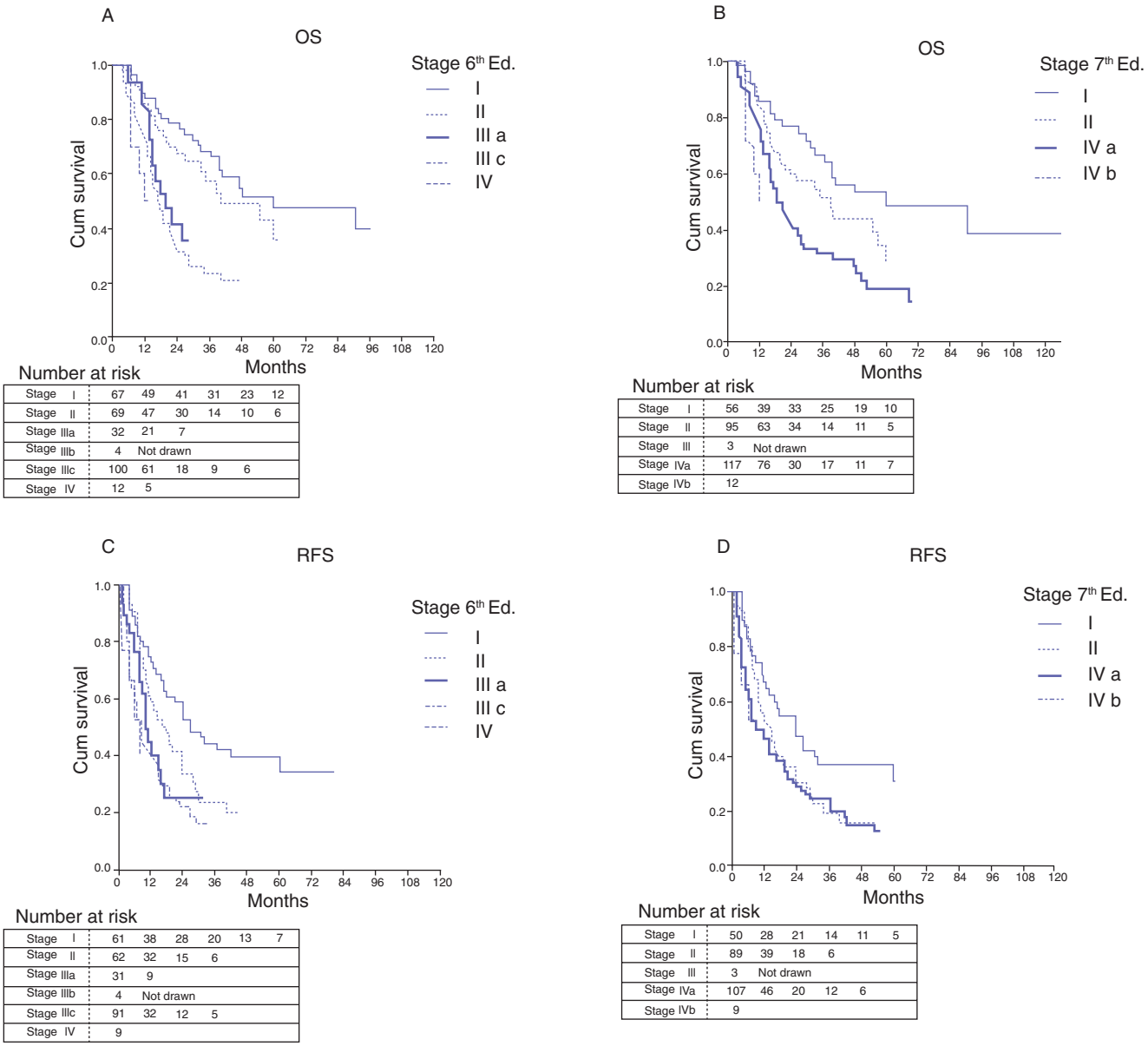

Figure 2 Kaplan–Meier estimated overall (OS) (A and B) and recurrence-free survival (RFS) (C and D) curves stratified for stage classes according to the sixth and seventh editions of the *TNM Staging System*. Survival curves have been truncated when the number at risk is less than 10% of the starting denominator or less than 5

the original pathology report, to an average of 6–8%. In contrast to this, within the SEER dataset the proportion of missing values for the most important variables was as high as 61%.

After elimination of tumour size as a parameter to designate the T subgroups, in the seventh edition patients with multiple tumour or vascular invasion – the old T2 and T3 patients – were combined into a unique, broad T2 category which is sub-classified into 2a and 2b. In the TMN philosophy, subdivisions of the main designators should provide more specific prognostic information. The current data indicate that these two sub-categories do not differ with respect to long-term survival questioning the prognostic appropriateness of such a separation. Nevertheless, the T2a and T2b sub-classification might be relevant to define what type of tumour the patient has rather than simply allocating them into a broad category.

For representative strata, the sixth edition staging algorithm showed monotonicity of gradients (i.e. the median survival of patients classified within earlier stages is longer than the survival of patients in more advanced stages) for both the T classification and stage groupings whereas the seventh edition did not. In fact, within the current series a significantly better OS and RFS of patients classified as T4 as compared with patients classified as T2a or T2b

was observed. The provision of a separate classification into the T4 category of patients with a specific IHC subtype, the periductal-infiltrating, represents the second characteristic feature of the new AJCC/UICC TNM staging system. However, although limited data definitely demonstrate a more aggressive biology of this tumour subtype, in the seventh edition periductal-infiltrating tumours were coded as T4 which should denote the greatest cancer extent usually associated with the poorest survival. In addition, the inclusion of the T4 category into the stage grouping IVa, which includes any patients with LN metastases, points out that the TMN reviewers postulated that in such patients the prognosis is independent to the presence or absence of LN metastases. Yet, this assumption remains to be demonstrated. One may argue that the current results should be cautiously interpreted. Indeed, several series from Japan have reported that the prevalence of the periductal infiltrating subtype or mixed tumours, usually mass-formingplus periductal-infiltrating, is significantly higher than the one observed in our population.[15,16] Although it is possible that some patients have been misdiagnosed with an underestimation of the mixed forms, a fact that might have determined a stage migration, it is also possible that the gross pathology of IHC in Eastern and Western countries differ significantly. Evidences suggests that in Europe IHC are almost exclusively of the mass forming subtype.[17,18] While the prognostic significance of the new T4 category remains uncertain the introduction of this specific T class might facilitate the acquisition of oncologic information for future investigations.[19]

A limitation of the present study is that it was not possible to compare all T classes and stage strata because of the limited number of patients with 'Tumour(s) perforating the visceral peritoneum or involving the local extra hepatic structures by direct invasion' (the sixth edition T4 and seventh edition T3 categories corresponding, in pN0 patients, to stages IIIb and III, respectively). Nonetheless, the rarity of such patients has been previously recognized.[18] One possible explanation is that, in western countries, an accurate reporting of the serosal invasion is lacking or that such locally advanced tumours are rarely resected because, at this stage of disease, the frequency with which peritoneal implants are present is extremely high.

In conclusion, although the seventh edition of the TMN staging system has introduced important changes resulting in a better contrast, albeit marginally significant, between early stages and the provision of a specific reporting of IHC of the periductal-infiltrating subtype, its superiority to the sixth edition remains to be confirmed.

Conflicts of interest

None declared.

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