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Validation of clinical AJCC/UICC TNM staging system for hepatocellular carcinoma: Analysis of 5,613 cases from a medical center in southern Taiwan

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This study was aimed to validate the 5th and 6th editions of tumor-node-metastasis (TNM) system for patients with hepatocellular carcinoma (HCC), and attempted to improve prognostic stratification by modifying the 6th edition according to vascular invasion and tumor size. From 1986 to 2002, a total of 5,613 HCC cases from Kaohsiung Chang Gung Memorial Hospital in southern Taiwan were enrolled. The 6th edition was modified by dividing stage I into stages IA (single tumor, ≤2cm) and IB (single tumor, >2cm), and by dividing stage II into IIA (multiple tumors, none >5cm) and IIB (tumor with segmental macro vascular invasion). The Akaike information criteria (AIC), within a Cox proportional hazard regression model were used; lower AIC value indicated a better discriminatory ability for staging system. The 1-, 3-, 5-, and 7-year overall survival rates were 45.6, 25.9, 17.9, and 13.4%, respectively. Significant differences in survival curve existed in the 5th, 6th, and modified 6th edition TNM systems. For the modified 6th edition TNM, survival differed significantly between stages IA and IB, and between stage IIA and IIB. The AIC values of 5th (72,328), 6th (72,188), modified 6th (71,991) edition TNM system were decreasing. This investigation demonstrated better prognostic stratifications for the 6th edition than the 5th edition TNM staging system. Moreover, the modified 6th edition staging system demonstrated better prognostic prediction than the former two. Pretreatment staging and simple classification of current modified 6th edition TNM staging can be applied to all HCC patients and are clinically useful.

Key words: hepatocellular carcinoma; TNM staging; survival

Hepatocellular carcinoma (HCC) ranks the fifth as most common cancer in the world. Since Taiwan is an endemic area for hepatitis B, HCC is the most common cancer in Taiwan.[1] Various staging systems have been used to predict survival for HCC patients, this includes tumor-node-metastasis (TNM),[2] Okuda,[3] the Cancer of the Liver Italian Program (CLIP),[4] Japan Integrated Staging (JIS)[5] and Barcelona Clinic Liver Cancer (BCLC)[6] staging systems. American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC) staging system stratifies HCC patients using a TNM classification. This classification considers tumor size and number, vascular invasion, bilobar involvement and extra-hepatic metastasis. Liver function is an important factor for survival of HCC patients. The Okuda, CLIP and JIS staging systems includes both tumor extension and liver functions for prognostic evaluation. Beside, BCLC staging system categories patients according to the tumor stage, liver function and general health. The tumor classifications in JIS and BCLC systems were similar to TNM. To date, BCLC staging system is the sole system used for treatment assignment and provide a guide for therapy of HCC patients.

The AJCC/UICC published the 5th edition TNM staging system in 1997.[7] In 2002, Vauthey *et al.*[8] observed that tumor size and vascular invasion are key prognostic factors in pathological TNM staging for HCC patients receiving hepatic resection. The new 6th edition TNM staging system[2] redefined the T-classification and vascular invasion for HCC. In some studies, the new 6th edition TNM staging appears to have better prognostic stratification than the 5th edition TNM staging.[9–11] In the 6th edition TNM system, single tumor without vascular invasion were classified into T1, this pathological staging was primarily applied for patients who received hepatic resection. However, postoperative histopathological staging has limited the usefulness of the TNM staging system for HCC patients. Most studies on the validation of TNM system have been limited to patients receiving hepatic resection. Less than 30% of tumors are surgically resectable upon diagnosis of HCC,[12] and patients who had not received surgical intervention were not enrolled in the analysis. Clinical staging for TNM system with image study has not been widely used. The prognostic value of the TNM staging system for all HCC patients remains controversial.

In fact, prognoses differ markedly between small and large tumors. Several studies have identified that tumor size and pathological grade are correlated with microvascular invasion.[13–15] The risk of vascular invasion and poor prognosis that can be predicted increases with tumor size.

This study was aimed to validate the prognostic stratification ability of the 5th and 6th editions of the AJCC TNM staging system for all HCC patients. Moreover, this study redefines T-classification and vascular invasion based on TNM systems and attempts to design a better model of prognostic stratification for TNM staging.

Patients and methods

Patients

A total of 5,613 consecutive patients diagnosed with hepatocellular carcinoma (HCC) between 1986 and 2002 were included in this study. The study populations came from Kaohsiung Chang Gung Memorial Hospital, located in Southern Taiwan. Sufficient information was available for all patients to analyze tumor-node-metastasis (TNM) staging. Patients were classified using the 5th (Table I) and 6th (Table II) edition AJCC/UICC TNM staging system. Vascular invasion was defined as tumor invasion of the portal or hepatic veins. Macroscopic vascular invasion was confirmed *via*

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TABLE I – FIFTH EDITION UICC TNM CLASSIFICATION OF HEPATOCELLULAR CARCINOMA (1997)

T1	Solitary, ≤2 cm, without vascular invasion
T2	Solitary, ≤2 cm, with vascular invasion, or multiple, one lobe, ≤2 cm, without vascular invasion, or solitary, >2 cm, without vascular invasion
T3	Solitary, >2 cm, with vascular invasion or multiple, one lobe, ≤2 cm, with vascular or multiple, one lobe, >2 cm, with or without vascular invasion
T4	Multiple, more than one lobe, or invasion of major branch of portal vein or hepatic veins, or invasion of adjacent organs other than the gallbladder, or perforation of visceral peritoneum
N1	Regional lymph node metastasis
M1	Distant metastasis

Stage	Tumor	Node	Metastasis
I	T1	N0	M0
II	T2	N0	M0
IIIA	T3	N0	M0
IIIB	T1, T2, T3	N1	M0
IVA	T4	Any N	M0
IVB	Any T	Any N	M1

TABLE II – SIXTH EDITION UICC TNM CLASSIFICATION OF HEPATOCELLULAR CARCINOMA (2002)

T1	Single tumor without vascular invasion
T2	Single tumor with vascular invasion, or multiple tumors, none >5 cm
T3	Multiple tumors, any >5 cm, or tumors involving major branch of portal or hepatic veins
T4	Tumors with direct invasion of adjacent organs other than the gallbladder, or perforation of visceral peritoneum
N1	Regional lymph node metastasis
M1	Distant metastasis

Stage	Tumor	Node	Metastasis
I	T1	N0	M0
II	T2	N0	M0
IIIA	T3	N0	M0
IIIB	T4	N0	M0
IIIC	Any T	N1	M0
IV	Any T	Any N	M1

TABLE III – CHARACTERISTICS OF THE 5,613 PATIENTS WITH HEPATOCELLULAR CARCINOMA INCLUDED IN THE STUDY

Variables	Value	%
Age (years, mean ± SD)	57.9 ± 12.7	
Sex, *n*		
Male	4,357	77.6
Female	1,256	22.4
Cause of liver disease		
HBV	2,361	42.1
HCV	1,456	25.9
HBV + HCV	470	8.4
Non-B, non-C	573	10.2
Others	753	13.4
Tumor size		
≤2 cm	739	13.2
>2–5 cm	1,878	33.4
>5 cm	2,996	53.4
Single	2,982	53.1
Multiple	2,631	46.9
Tumor location		
Unilobar	4,102	73.1
Bilobar	1,511	26.9
Initial therapeutic modality		
No	2,432	43.3
Yes		
Surgery	537	9.6
Percutaneous ablation therapy[1]	231	4.1
TAE	2,119	37.8
Radiotherapy	294	5.2

TAE, transcatheter arterial embolization; HBV, hepatitis B virus; HCV, hepatitis C virus.

[1]Percutaneous ablation therapy including radiofrequency ablation, percutaneous ethanol injection, percutaneous acetic acid injection and percutaneous microwave coagulation therapy.

dynamic computed tomography (CT) or angiography. Extrahepatic metastasis was assessed by bone scan, chest X-ray and chest CT.

Diagnosis of HCC

The diagnostic criteria of HCC were arbitrarily classified as 1 to 4. Criterion 1 indicated diagnosis of HCC verified by either pathology or cytology. Criterion 2 indicated diagnosis of HCC based on an α-fetoprotein level higher than 400 ng/mL plus at least 1 imaging study showing a typical HCC image. Criterion 3 indicated diagnosis of HCC that initially did not fit Criteria 1 or 2, but did fit either Criteria 1 or 2 during the follow-up period. Criterion 4 indicated that diagnosis of HCC was based on typical image studies, but did not fit Criteria 1 to 3.

Identification of mortality

We obtained the national citizen identification number of the studied patients to match with the national mortality datasets up to the end of 2004, established by the Statistics Office, Department of Health, Taiwan. The national mortality datasets were based on death certificate data, including time, place and cause of death, and details of the individual on whose behalf the document was issued. The underlying cause of death was classified according to the International classification of disease (ICD = 155). The study protocol was approved by the Institutional Review Board of Chang Gung Memorial Hospital, Taiwan.

Establishing a new modified 6th TNM staging system

This study tried to design a new prognostic model based on the tumor size and vascular invasion base for 6th edition TNM staging systems. For tumor ≤2 cm, there was low probability of vascular invasion and a large chance of receiving curative treatments, including percutaneous tumor ablation, liver transplantation and surgical resection.[16–20] Stage I was thus divided into stage IA (single tumor ≤2 cm) and IB (single tumor >2 cm without vascular invasion). Vascular invasion is a well known poor prognostic factor for survival. For multiple tumors (none >5 cm) without vascular invasion having higher survival rates if compared with vascular invasion.[15,21–23] Stage II was thus divided into stages IIA (multiple tumors, none >5 cm and without vascular invasion) and IIB (tumor with segmental macroscopic vascular invasion).

Statistical analysis

Univariate survival curves were analyzed using the Kaplan-Meier method, and differences between curves were assessed using the log-rank test. Survival curves that did not differ significantly were combined into a single curve. According to Ueno *et al.*,[24] the performance of the TNM system was as follows: (*i*) homogeneity within subgroups (small differences in survival among patients with the same stage); (*ii*) discriminatory ability measured by differences among subgroups; (*iii*) monotonicity of gradients shown in the correlation between stages and survival rates (patients in earlier stages have longer survival than those in later stages within the same system). The likelihood ratio (LR) χ^2 test was used to assess homogeneity within each classification system, and to estimate gradient monotonicity. The Akaike information criteria (AIC)[25] within a Cox proportional hazard regression model were used to demonstrate the discriminatory ability of the given model for staging system. A smaller AIC value indicates a more desirable model for predicting outcome. A value of $p < 0.05$

TABLE IV – PATIENTS DISTRIBUTION ACCORDING TO 5TH AND 6TH EDITION TNM STAGING SYSTEM

	TNM stage	5th edition				Total
		I	II	III	IV	
6th edition	I	439 (18.9%)	1886 (81.1%)	0 (0%)	0 (0%)	2325 (41.4%)
	II	0 (0%)	178 (14.1%)	721 (57.0%)	365 (28.9%)	1264 (22.5%)
	III	0 (0%)	0 (0%)	521 (26.7%)	1427 (73.3%)	1948 (34.7%)
	IV	0 (0%)	0 (0%)	0 (0%)	76 (100%)	76 (1.4%)
Total		439 (7.8%)	2064 (36.8%)	1242 (22.1%)	1868 (33.3%)	5613 (100%)

Wilcoxon signed ranks test shows 5th TNM staging is larger than the 6th TNM staging ($p < 0.001$).

was considered statistically significant. Statistical analysis was performed using SPSS 10 for Windows (SPSS, Chicago, IL).

Results

Patient characteristics

Table III lists the clinical characteristics of the 5,613 subjects. Diagnosis of HCC was confirmed in 2,366 patients (42.2%) *via* histopathological examination and 1,565 patients (27.9%) were diagnosed *via* AFP >400 ng/mL combined with typical image finding of HCC, 193 patients (3.4%) were diagnosed *via* either 1 of prior diagnostic criteria following more than 6 months follow-up, and the remaining 1,489 patients (26.5%) were diagnosed based on typical image findings. Table IV lists patient stage migration for reclassifying patients from the 5th to the 6th staging system. The Wilcoxon signed ranks test showing that 5th edition TNM staging exceeds the 6th edition TNM staging ($p < 0.001$).

Prognosis stratification according to 5th, 6th and modified 6th TNM staging system

Table V lists the patient distribution and survival rates. The 1-, 3-, 5- and 7-year overall survival rates were 45.6, 25.9, 17.9 and 13.4%, respectively.

Figures 1–3 illustrate the Kaplan-Meier survival curves and AIC values of HCC patients based on the 5th, 6th and modified 6th TNM staging systems. In the 5th edition TNM staging system, significant differences in survival curves existed between each of the stages (I, II, III, IV) (Figs. 1*a*–1*c*). AIC value was lower when dividing stages III and IV into IIIA and IIIB, and IVA and IVB, respectively. Otherwise, Stage IIIB and IVA showed similar survival rates (Table VI).

In the 6th edition TNM staging system (Figs. 2*a* and 2*b*), significant differences existed in the survival curves in each stage. Notably, AIC value was lower in the 6th edition than the 5th edition (Table VI, Figs. 1–3). Owing to the lack of difference in survival rates between stages IIIA, IIIB and IIIC, these 3 sub-stages were combined into stage III.

In the modified 6th edition (Figs. 3*a*–3*c*) stages IA and IB, and stages IIA and IIB differed significantly. However, survival rates did not differ significantly between stages IB and IIA. AIC values decreased after subdividing stages I and II. The primary stage IA was thus defined as modified stage I, stages IB and IIA as modified stage II, stage IIB as modified stage IIIA, and stage III as modified stage IIIB (Fig. 3*c*). The modified 6th TNM staging system is simplified into 4 stages and illustrated in Table VII. The AIC value was lowest for the new modified 6th edition TNM staging system, which represented the optimum prognostic stratification.

TABLE V – PATIENT DISTRIBUTION AND SURVIVAL RATES ACCORDING TO 5TH, 6TH, AND MODIFIED 6TH EDITION TNM STAGING SYSTEM

Staging system	*N*	(%)	Survival				
			1-year	3-year	5-year	7-year	Median (mo)
5th edition							
I	439	7.8	80.6	50.7	38.1	24.9	3.08
II	2,064	36.8	62.0	37.6	26.2	19.6	1.72
III	1,242	22.1	40.4	20.5	13.4	11.1	0.68
IV	1,868	33.3	22.9	10.7	7.0	5.2	0.25
6th edition							
I	2,325	41.4	64.2	39.0	27.7	20.6	1.92
II	1,264	22.5	54.7	30.0	18.7	12.2	1.25
III	1,948	34.7	19.1	8.5	6.2	5.5	0.23
IV	76	1.4	7.9	1.3	1.3	1.3	0.21
Modified 6th edition							
I	439	7.8	80.6	50.7	38.1	24.9	3.08
II	2,804	50.0	62.7	36.9	24.5	17.8	1.76
IIIA	346	6.2	21.4	8.3	7.1	6.5	0.32
IIIB	1,948	34.7	19.1	8.5	6.2	5.5	0.23
IV	76	1.4	7.9	1.3	1.3	1.3	0.21

Discussion

HCC is a major disease, accurate and useful staging system will benefit for providing a better prognostic prediction and even a guide for patient management. The TNM staging system for HCC is mainly used for prognostic prediction rather than treatment assignment. Most previous studies on the validation of TNM staging system were restricted to patients who received hepatic resection,[8,9–11] who comprised just 20–30% of all HCC patients.[12] These studies mainly focused on pathologic TNM staging. Microscopic vascular invasion, which may represent a more important prognostic prediction could be identified in patients who received operation. However, the usefulness of postoperative staging and microscopic findings in all HCC patients is limited. This cannot be applied for majority of HCC patients, who have not undergone surgery. Current study, which is based on macroscopic findings for TNM staging, included all HCC patients for survival analysis. This large-scale retrospective study demonstrated significant prognostic stratification of the 5th, 6th and modified 6th clinical TNM staging system for all HCC patients. The optimum prognostic stratification occurred in modified 6th edition TNM staging.

In the current study, we simply modified present 6th edition TNM system by reconsidering the tumor size and vascular invasion, no new variable was added. This study showed signification prognostic discrimination if we use 2 cm as cut-off level. Owing to microscopic vascular invasion not being identified, overestimation of the survival rates of this group of patients may be a concern. However, a previous large-scale study in Japan demonstrated the number of cases with tumors smaller than 2 cm and with vascular invasion was too small to be included in a staging classification.[26] This reflected that very low risk of microvascular invasion and low tumor grade could be expected for small size HCC.[16,17] Additionally, such patients may have high curative rates after treatment, including percutaneous tumor ablation, partial hepatectomy and liver transplantation.[17–20] The BCLC and JIS score staging systems used 2 cm as cut-off for staging and demonstrated significant prognostic prediction. Since Taiwan is an endemic area for HBV, routine screening with ultrasonography and α-fetoprotein for patients with chronic liver disease could have higher detection rates of small size HCC.[27] A study investigating the long-term survival rates of HCC patients in Taiwan[28] revealed that improved survival of HCC in recent years, earlier

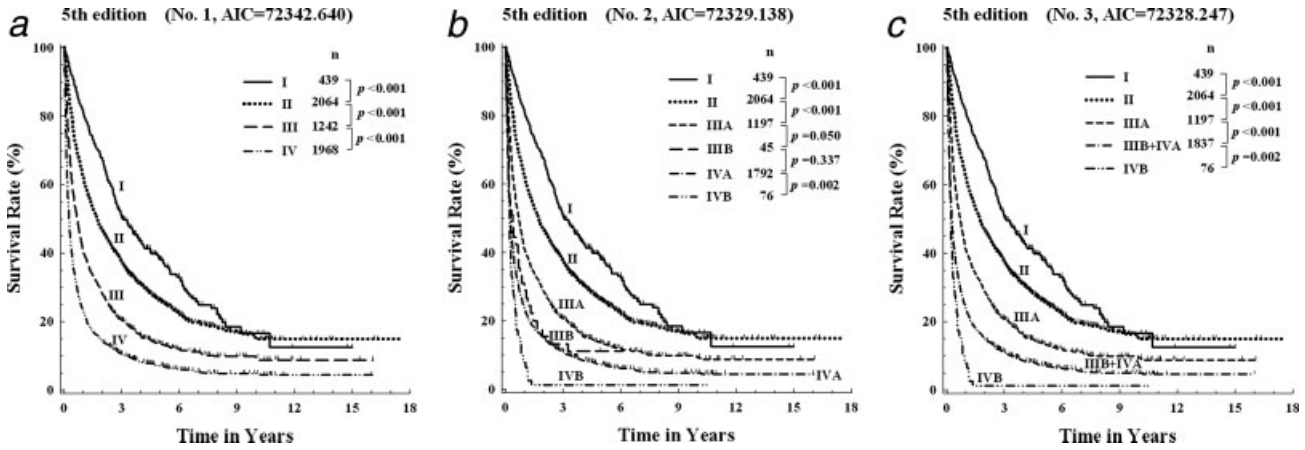

FIGURE 1 – Kaplan-Meier survival curves of 5613 HCC cases classified by 5th edition TNM system. (*a*) Classified as 4 major stages, (*b*) Classified as all 6 sub-stages, (*c*) Merge the sub-stages without statistical difference. The AIC values were decreasing from A, B to C.

TABLE VI – PROGNOSTIC STRATIFICATION OF 5TH, 6TH AND MODIFIED 6TH EDITION TNM STAGING SYSTEM

TNM staging	No.	Figure	Model	Linear trend χ^2	LR χ^2	AIC
5th edition	1	1A	I, II, III, IV	911.99	963.09	72,343
	2	1B	I, II, IIIA, IIIB, IVA, IVB	974.11	994.17	72,329
	3	1C	I, II, IIIA, IIIB+IVA, IVB	935.49	992.35	72,328
6th edition	4	2A	I, II, IIIA, IIIB, IIIC, IV	988.84	1229.99	72,189
	5	2B	I, II, III, IV	1054.03	1223.33	72,188
Modified 6th edition	6	3A	IA, IB, II, III, IV	1000.19	1248.07	72,153
	7	3B	IA, IB, IIA, IIB, III, IV	1224.71	1418.42	71,993
	8	3C	IA(I), IB + IIA(II), IIB(IIIA), III(IIIB), IV	1333.35	1418.16	71,991

AIC, Akaike information criteria; LR, Likelihood ratio. The lower AIC value represented better model for discriminatory ability; No. 6–8 shows modified 6th edition TNM staging. *p* value between each stage of edition is demonstrated at corresponded figure shown in table.

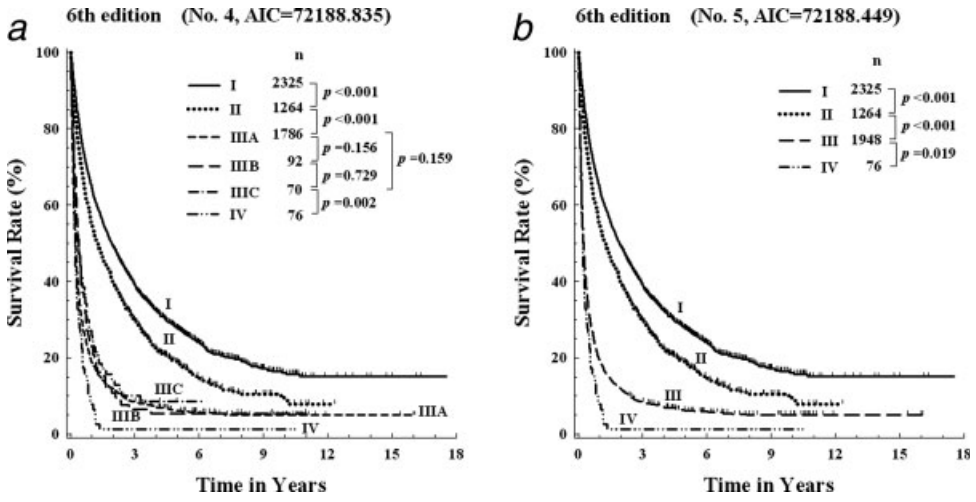

FIGURE 2 – Kaplan-Meier survival curves of 5613 HCC cases classified by 6th edition TNM system. (*a*) Classified as all 6 sub-stages, (*b*) Stage IIIA, IIIB and IIIC was combined as stage III due to no statistical difference. The AIC values were decreasing from *a* to *b*.

detection of HCC and improved treatments may play an important role.

This study found better prognosis in tumors with <5 cm without vascular invasion than in those with segmental vascular invasion. Macroscopic vascular invasion has been shown to be a more important prognostic factor than microvascular invasion following hepatectomy of HCC.[29–31] Macroscopic vascular invasion is also a strong predictor of both survival and tumor recurrence in patients with cirrhosis who received liver transplantation for HCC.[32] The risks of intrahepatic and extrahepatic metastasis were higher for HCC with macroscopic vascular invasion. Meanwhile, multiple tumors may result from multicentric or intrahepatic metastasis. As previously reported, tumor size larger than 5 cm has poor prognosis and is a predictive factor for early tumor recurrence.[8,21,23] Higher risk of vascular invasion and higher tumor grade may occur in larger tumors, especially those larger than 5 cm.[13–15] Relatively, multiple tumors in both lobes with size less than 5 cm may have lower risk of occult vascular invasion and intrahepatic metastasis. Additionally, survival rates were better after treatment in these patients.[8,22]

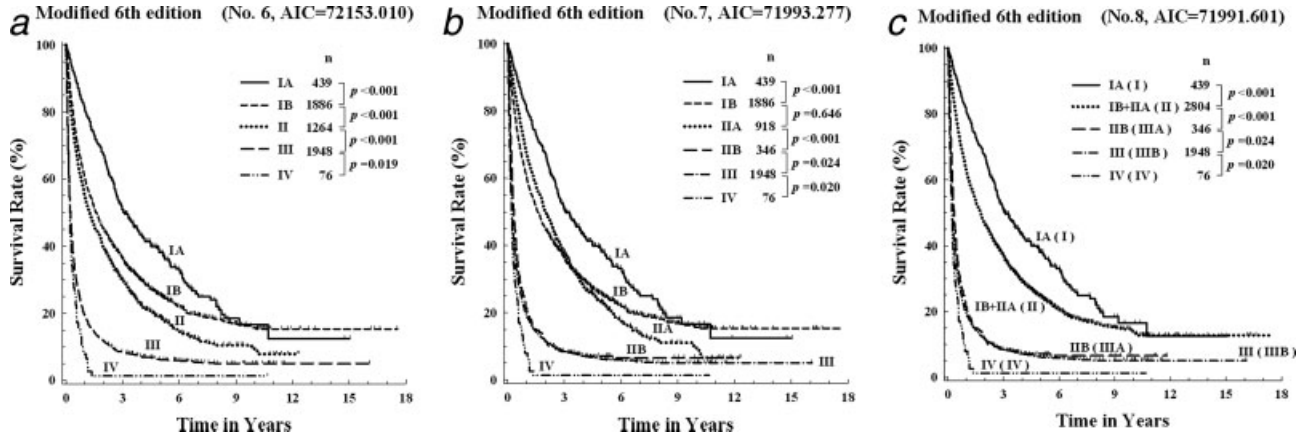

FIGURE 3 – Kaplan-Meier survival curves of 5613 HCC cases classified by modified 6th edition TNM system. (*a*) Significant difference between stage IA and IB ($p < 0.001$). (*b*) Significant difference between stage IIA and IIB ($p < 0.001$). (*c*) Merge the sub-stages without statistical difference. Re-define staging into 4 major stages. The AIC values were decreasing from *a*, *b* and *c*.

TABLE VII – MODIFIED 6TH EDITION TNM CLASSIFICATION OF HEPATOCELLULAR CARCINOMA

T1	Solitary, ≤2 cm, without vascular invasion
T2	Solitary or multiple, >2 cm and ≤5 cm, without vascular invasion
T3	Solitaty, ≤5 cm, involving segmental branch of portal or hepatic veins
T4	Multiple, any >5 cm, or tumors involving major branch of portal or hepatic veins, or tumors with direct invasion of adjacent organs other than the gallbladder, or perforation of visceral peritoneum
N1	Regional lymph node metastasis
M1	Distant metastasis

Stage	Tumor	Node	Metastasis
I	T1	N0	M0
II	T2	N0	M0
IIIA	T3	N0	M0
IIIB	T4	N0	M0
	Any T	N1	M0
IV	Any T	Any N	M1

This study demonstrated that there was no significant difference in survival rates between major vascular invasion, multiple tumors larger than 5 cm and lymph nodes metastasis. Therefore this study combined these 3 subgroups of primary 6th edition stage III into modified stage IIIB. This might indicate that survival rates for major vascular invasion are very poor, with the median survival of such patients generally being less than 3 months.[33–35] The survival curves of stage I and II crossing (Fig. 3*c*) 10 years after diagnosis of HCC. This may occur due to several reasons. First, majority of HCC patients are combined with advance liver disease, hepatic decompensation with liver failure is an important factor of survival in these patients. Some patients have poor liver functions even in early stage of HCC, half of HCC patients may die in hepatic failure. In addition, antiviral treatment for chronic hepatitis B and C were not widely used during studied period. Second, the majority HCC patients are old age (mean age, 57.9 ± 12.7 years), patients may have died due to aging and other diseases 10 years after HCC diagnosed.

This study demonstrated that improved prognostic stratification could be achieved by stratified staging by reconsidering tumor size and macroscopic vascular invasion. Additionally, this modified 6th TNM staging system can be applied to pretreatment staging of all HCC patients, which is important in clinical practice.

In conclusion, this study showed better prognostic stratifications of 6th edition than 5th edition TNM staging system. Moreover, modified 6th edition demonstrated better prognostic prediction than the other 2 systems. Pretreatment staging and simple classification of current modified 6th edition TNM staging can be applied to all HCC patients and would be useful in clinical practice.

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