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Original Paper

Microvascular Invasion and a Size Cutoff Value of 2 cm Predict Long-Term Oncological Outcome in Multiple Hepatocellular Carcinoma: Reappraisal of the American Joint Committee on Cancer Staging System and Validation Using the Surveillance, Epidemiology, and End-Results Database

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Keywords
Hepatocellular carcinoma · Surgery · Prognostic prediction · Staging system

Abstract
Introduction: For prognostication of hepatocellular carcinoma (HCC), the optimal size cutoff value and the significance of microvascular invasion (mvi) remain inconclusive. ***Objective:*** This study sought to revisit the inconclusive components of current American Joint Committee on Cancer (AJCC) staging system and to develop a new practical prognostication model for patients with HCC based on 2 large cohorts. ***Method:*** In 1,175 patients who underwent resection for HCC (training cohort), prognostic significance of mvi, and optimal size cutoff value were revisited and a new staging model was established. Then, its performance was validated using 5,249 patients derived from a population-based database (validation cohort). ***Results:*** The optimal size cutoff value was 2 cm in multiple HCC, similar to that for solitary HCC. Multivariate analyses confirmed that mvi, a size >2 cm, and multiple lesions were independent predictors with similar weights for disease-specific survival. Based on these results, earlier stages of HCC were reclassified according to the number of the following factors: multiple tumors, >2 cm in diameter, and presence of mvi. Also, given the similar prognosis of Stages IIIB and IVA according to the AJCC 8th edition, these groups were reclassified into the same stage. This

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new staging model had a better performance than the AJCC 8th edition in both training cohort (c-statistics, 0.648 vs. 0.629) and the validation cohort (c-statistics, 0.646 vs. 0.645) regardless of the presence of cirrhosis. ***Conclusions:*** Inclusion of a size cutoff value of 2 cm and mvi could reclassify the current version of the AJCC staging system and offer an alternative prognostication model using a single size-cutoff value of HCC.

Introduction

Prognostication of patients with hepatocellular carcinoma (HCC) remains a challenge because the patients suffer from both HCC itself and underlying liver disease, both of which are prognostic factors. Incorporating components of the anatomical extent of the tumor and the degree of the underlying liver disease has led to multiple staging and scoring systems with differing options [1]. However, the oncological extent of the tumor and underlying liver disease should ideally be assessed independently, since a mixture of tumor stages and a treatment algorithm that is influenced by the hepatic functional reserve could result in a significant discrepancy in the prognosis of patients with the same cancer stage among regions and countries because of geographic heterogeneity in cancer management and preferences and/or expertise in specific treatments.

Among several staging systems, the American Joint Committee on Cancer (AJCC) staging system [2] and the Liver Cancer Study Group of Japan (LCSGJ) staging system [3] have conventionally been used to describe the pure anatomical extents of the diseases. By incorporating clinical factors strongly associated with the prognosis of HCC, these staging systems have regularly been revised to reflect the updated clinical outcomes of populations [4, 5] and/or published evidence [6, 7]. While the AJCC staging system and the LCSGJ staging system include similar clinical factors for prognostication, there have been slight differences in the weights of the clinical factors and the cutoff values for tumor size between these 2 staging systems [8]. These differences are partly derived from differences in the baseline characteristics of patients, basic policies for patient management, and treatment algorithms between Japan and Western countries. However, for the comparison of clinical outcomes and the standardization of optimal patient management, a universally available staging model is needed. Therefore, this study sought to revisit the inconclusive components of the current AJCC staging systems and to develop a new simple and practical prognostication model for patients with HCC based on 2 large cohorts.

Patients and Methods

Study Population

From a prospective hepatobiliary database maintained by the Department of Gastroenterological Surgery, Toranomon Hospital, Tokyo, Japan, a total of 1,175 consecutive patients who had undergone curative resection for HCC between January 1995 and October 2017 were identified as a training cohort. In addition, 5,249 patients aged ≥20 years old with histologically confirmed HCC undergoing surgical resection were identified using the surveillance, epidemiology, and end-results (SEER) database from 1995 to 2015 inclusive as a validation cohort. The International Classification of Disease 3rd edition was used to identify HCC using site code C22.0 and the corresponding histology code of 8170 hepatocellular carcinoma. All the analyses in the current study were performed in accordance with the ethical guidelines for clinical studies in Japan, SEER research data use agreement, and Declaration of Helsinki under approval of Institutional Review Board of Toranomon Hospital (No. 1823). Written informed consent was waived because of the retrospective design.

Table 1. Baseline characteristics

Characteristic	Training cohort (*n* = 1,175)	Validation cohort (*n* = 5,249)	*p* value
Age, years, median (range)	65 (28–87)	64 (20–93)	0.0054
Gender, male	880 (74.9)	3,791 (72.2)	0.0647
Tumor size, cm, median (range)*	22 (2–180)	50 (1–200)	<0.0001
Number of tumor*			<0.0001
Solitary	1,010 (86.0)	3,748 (77.9)	
Multiple	165 (14.0)	1,069 (22.1)	
Microscopic vascular invasion*	303 (25.8)	1,252 (26.8)	0.4785
Major vascular invasion*	30 (2.5)	235 (4.7)	0.0013
Direct invasion or perforation*	9 (0.8)	197 (3.8)	<0.0001
Nodal involvement*	5 (0.4)	87 (1.7)	0.0006
Distant metastases*	3 (0.3)	126 (2.4)	<0.0001
Histologic grade*, [a]			<0.0001
Well differentiated	161 (14.3)	1,008 (21.5)	
Moderately differentiated	755 (66.8)	2,504 (53.5)	
Poorly differentiated	214 (18.9)	1,069 (22.8)	
Undifferentiated	0 (0)	98 (2.1)	
Cirrhosis*, [b]			0.0007
No	555 (47.2)	966 (53.6)	
Yes	620 (52.8)	836 (46.3)	
Type of resection*			
Minor	1,121 (95.4)	2,569 (54.7)	<0.0001
Major	54 (4.6)	2,129 (45.3)	

Values in table are number of patients (percentage) unless indicated. * Missing data are excluded. [a] Edmondson grade [11]. [b] Desmet's classification [13] grade 4 for the training cohort and Ishak score [12] F5 or F6 for the validation cohort.

Indications for Liver Resection and Follow-Up

The indications for surgery were based on an algorithm that included the presence/absence of ascites, the serum total bilirubin level, and the results of indocyanine green clearance tests [9, 10]. Follow-up protocols were reported elsewhere [9] including regular screening for recurrence by monitoring the plasma levels of alfa-fetoprotein and des-gamma-carboxyprothrombin every 1–2 months, abdominal ultrasound every 3 months, and dynamic computed tomography or magnetic resonance imaging every 6 months. Recurrence was aggressively treated appropriately based on the recommendations at a multidisciplinary discussion.

Pathological Diagnosis

The histological grade of differentiation of the tumor, the degree of fibrosis in the background liver, and the presence/absence of vascular invasion were assessed microscopically based on the classification system proposed by the LCSGJ [3] for Japanese cohort. Tumor grade and degree of fibrosis were described according to Edmondson grade [11] and Ishak score [12], respectively in the SEER database. Diagnosis of liver cirrhosis was based on histopathologic evidence of grade 4 fibrosis according to Desmet's classification [3, 13] in the training set and F5–6 according to Ishak score in the validation set.

Statistical Analysis

A statistical analysis was performed using JMP 14.0 software (SAS Institute Japan, Tokyo, Japan). The continuous variables were compared using the Mann-Whitney U test. Categorical variables were compared using the Pearson chi-square test or the Fisher exact test, as appropriate. Statistical analysis was two-tailed, and p values of <0.05 were considered to be statistical significance. Survival curves were generated using the Kaplan-Meier method and were compared using the log-rank test.

In addition to the currently adopted cutoff value for solitary HCC [6], an optimal size cutoff value for multiple HCC was also determined based on the results of the minimum p value approach for disease-specific

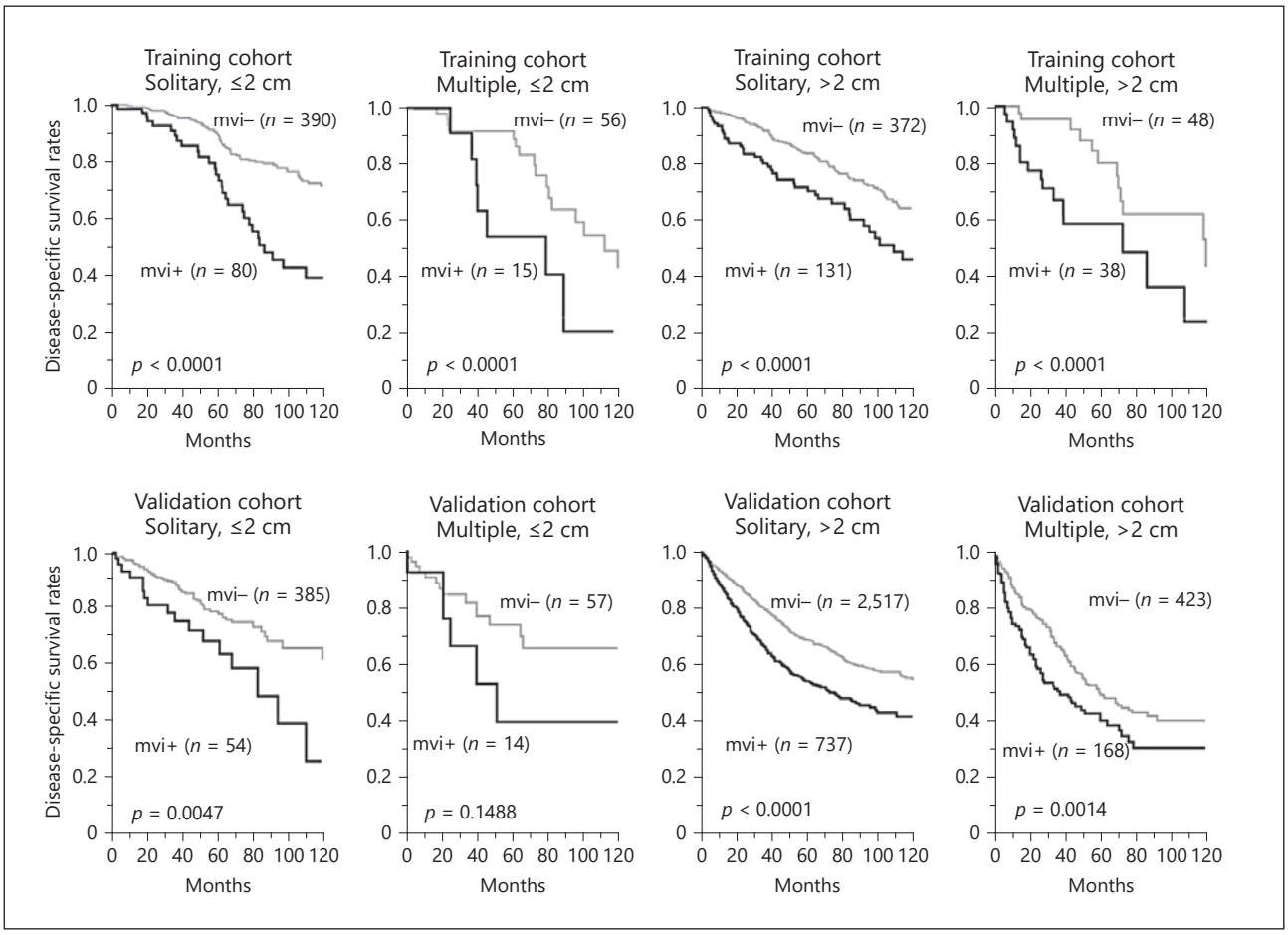

Fig. 1. Disease-specific survival rates according to the size, number, and presence of microvascular invasion in HCC. mvi, microvascular invasion.

survival after surgery. A new staging model was established based on the results in the training cohort, and its performance was then tested using the validation cohort. Harrel's c-statistic was used to determine the performance of each staging model.

Results

Baseline Characteristics

The baseline characteristics of the training cohort and the validation cohort are summarized in Table 1. The distributions of age and gender were similar between the 2 cohorts. However, the tumor size was significantly larger, and the presence of multiple lesions was more frequent in the validation cohort. Although the prevalence of microvascular invasion (mvi) was similar, the validation cohort included more cases of advanced disease, and a major hepatectomy was selected more frequently.

Prognostic Impact of mvi

The prognostic impact of mvi was compared in Figure 1 according to size (≤2 vs. >2 cm) and tumor number (solitary vs. multiple). The rationale for adopting a cutoff value of 2 cm for multiple HCC was based on the results of a minimum *p* value approach to predict disease-

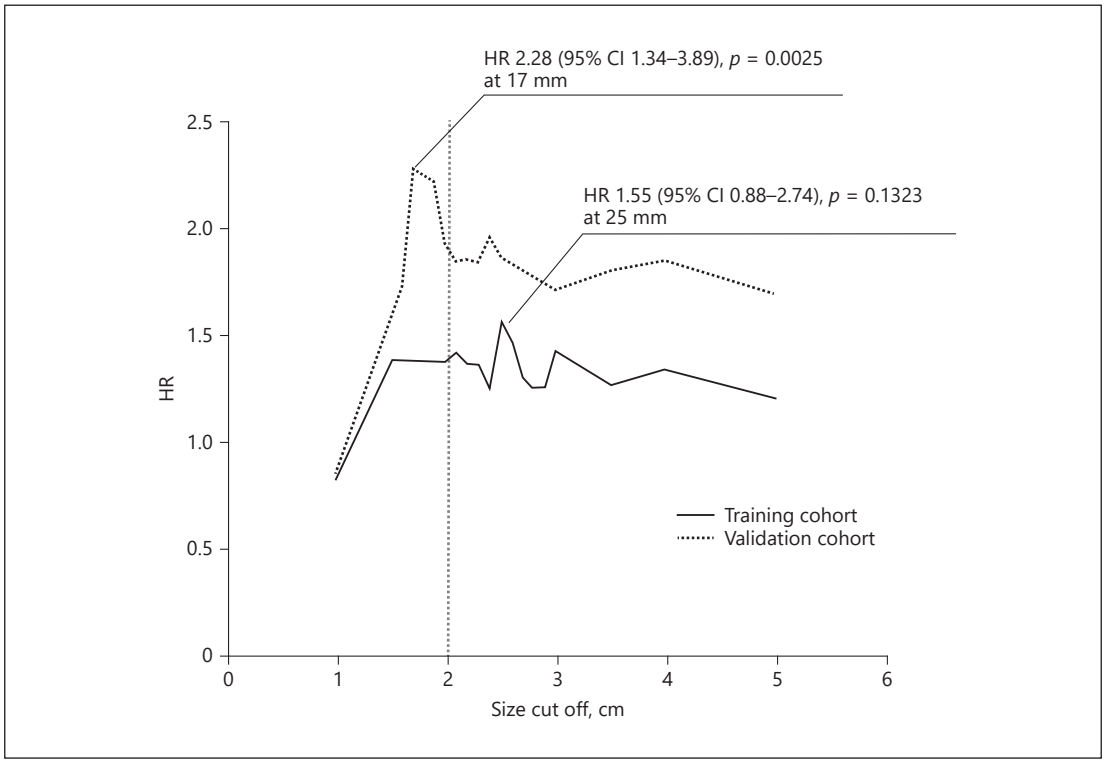

Fig. 2. Optimal size cutoff values for multiple lesions estimated by minimum-*p* value approach. HR, hazard ratio.

Table 2. Multivariate analysis for disease-specific survival

	Wald χ^2	HR	95% CI	*p* value
Training cohort				
mvi	48.2	2.41	1.88–3.09	<0.0001
Cirrhosis[a]	30.8	2.01	1.57–2.57	<0.0001
Multiple lesions	11.2	1.69	1.24–2.31	0.0008
Size >2 cm	7.1	1.38	1.09–1.76	0.0078
Poor differentiation[c]	6.9	1.44	1.10–1.90	0.0085
Age >65	5.4	1.32	1.05–1.68	0.0201
Validation cohort				
mvi	17.6	1.65	1.30–2.08	<0.0001
Multiple lesions	15.4	1.67	1.29–2.15	<0.0001
Poor differentiation[c]	14.3	1.59	1.25–2.02	0.0002
Cirrhosis[b]	12.6	1.47	1.19–1.82	0.0004
Size >2 cm	11.7	2.07	1.36–3.14	0.0006

Multivariate Cox-hazard regression was applied with stepwise backward selection. Initially, all factors were included in the model. Then factors that showed no or limited statistically significant association ($p > 0.1$) with disease-specific survival adjusted for the remaining factors were deleted from the model in stepwise fashion. The 7 factors tested were as follows: age (> vs. ≤65), gender, maximum tumor size (> vs. ≤2 cm), number of tumor (multiple vs. solitary), microvascular invasion (presence vs. absence), cirrhosis (presence vs. absence), and tumor differentiation (poor vs. well/moderate). HR, hazard ratio; mvi, microvascular invasion. [a] Desmet's classification [13] grade 4. [b] Ishak score [12] F5 or F6. [c] Edmondson grade 3 or 4 [11].

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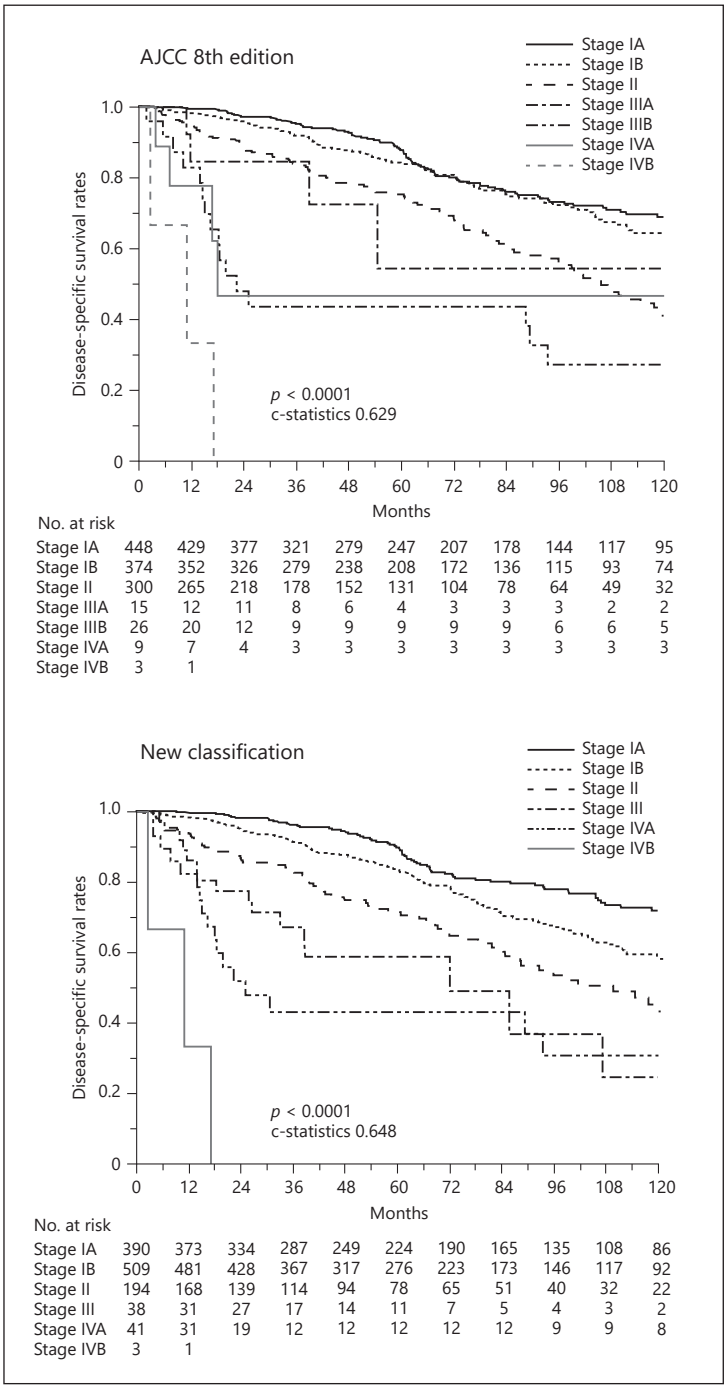

Fig. 3. Disease-specific survival rates stratified by the AJCC 8th edition and the new classification in the training cohort. AJCC, American Joint Committee on Cancer.

specific survival after surgical resection. The hazard ratio (HR) was highest and the *p* value was lowest at 2.5 cm in the training cohort (HR 1.55; $p = 0.132$) and 1.7 cm in the validation cohort (HR 2.28; $p = 0.0025$), respectively, when sliding the cutoff value from 1.1 through 5.0 cm (Fig. 2). When focusing on the group of patients without direct invasion to surrounding organs, tumor rupture, major vascular invasion, nodal involvement, or distant metastases, the presence of mvi had prognostic value in each group in both the training cohort and the validation cohort.

Table 3. Definition of staging systems and survival outcomes

	T criteria	N category	M category	DSS, months, median (95% CI)	Five-year DSS, %
AJCC 8th					
Stage IA	Solitary tumor ≤2 cm	N0	M0	210.5 (178.9–NE)	87.7
Stage IB	Solitary tumor >2 cm without mvi	N0	M0	159.4 (131.8–NE)	83.7
Stage II	Solitary tumor >2 cm with mvi or multiple tumors, none >5 cm	N0	M0	105.7 (92.8–119.8)	75.2
Stage IIIA	Multiple tumors, at least one of which is >5 cm	N0	M0	NE	54.4
Stage IIIB	Single tumor or multiple tumors of any size involving a major branch of the portal vein or hepatic vein, or tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum	N0	M0	22.3 (15.0–93.4)	43.6
Stage IVA	Any T	N1	M0	18.0 (3.8–161.5)	46.7
Stage IVB	Any T	Any N	M1	11.0 (2.6–17.1)	0
New staging					
Stage IA	None of following factors	N0	M0	219.7 (187.9–NE)	89.7
Stage IB	One of following factors	N0	M0	137.2 (122.9–NE)	83.0
Stage II	Two of following factors	N0	M0	114.8 (88.6–154.0)	72.7
Stage III	Three of following factors • Size >2 cm • Multiple tumors • mvi	N0	M0	72.2 (33.2–NE)	58.7
Stage IVA	Single tumor or multiple tumors of any size involving a major branch of the portal vein or hepatic vein, or tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum	N0	M0	30.6 (18.0–161.5)	47.1
	Any T	N1	M0		
Stage IVB	Any T	Any N	M1	11.0 (2.6–17.1)	0

DSS, disease-specific survival; AJCC, American Joint Committee on Cancer; NE, not estimated; mvi, microvascular invasion.

Cutoff values of tumor size for predicting mvi estimated by receiver operating characteristics curve analysis were 53 mm for solitary HCC and 50 mm for multiple lesions, respectively. In a multivariate analysis of prognostic factors for disease-specific survival rates, however, a size >2 cm, multiple lesions, and mvi were independent prognostic factors in both the training cohort and the validation cohort, and their degrees of contribution to disease-specific survival were comparable (HRs 1.4–2.4; Table 2).

Establishment of New Staging Models and Validation

When the AJCC 8th edition was applied to the training cohort, the survival outcomes were not well stratified with the overlapping survival curves for several stages. Based on these observations and the aforementioned clinical outcomes, a new staging model was established using (1) equivalent weighting for size, number, and mvi for the classification of earlier stages of HCC and (2) the reclassification of Stages IIIB and IVA into the same group (Fig. 3, Table 3). Because the purpose of the present study was to investigate the possibility of reclassification

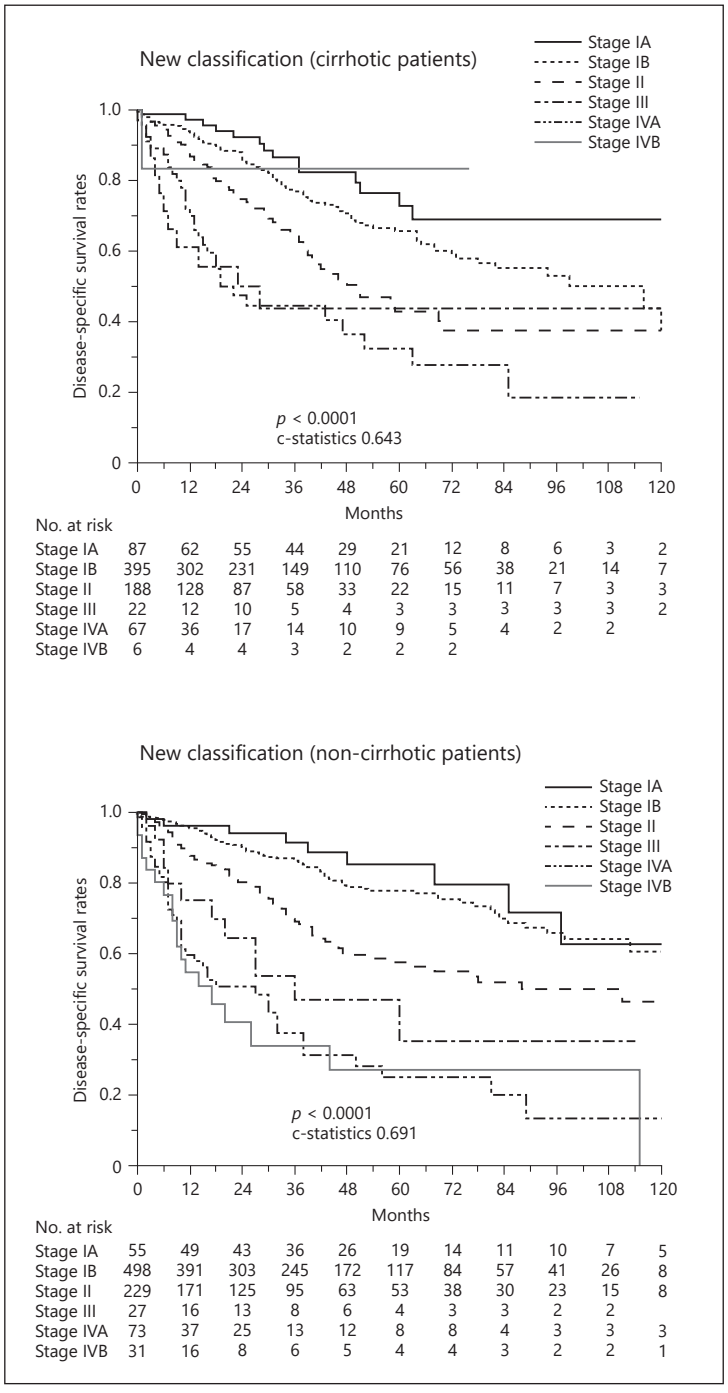

Fig. 4. Disease-specific survival rates according to the presence of cirrhosis by the new classification model in the validation cohort.

for the current version of the AJCC staging system, only clinical parameters used for the AJCC 8th edition were included in the new prognostication model, and the performance of the new model was then tested according to the presence of cirrhosis or tumor grade.

The performance of the new classification was better than that of the AJCC 8th edition or the AJCC 7th edition in the training cohort (c-statistics, 0.648 vs. 0.629 vs. 0.632 for disease-specific survival; 0.606 vs. 0.596 vs. 0.594 for overall survival; and 0.592 vs. 0.586 vs. 0.583 for time-to-interventional failure [14]). This tendency was also confirmed in the validation cohort. The discriminatory power of the new classification for disease-specific survival

(c-statistics, 0.646) was comparable or even better than that of the AJCC 8th edition (0.645) or the AJCC 7th edition (0.639; online suppl. Fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000504193).

Performance of the New Classification According to Underlying Liver Status and Tumor Grade

Figure 4 shows disease-specific survival curves according to the presence of cirrhosis in the validation cohort. In cirrhotic patients, the new classification showed better performance than the AJCC 8th edition in both the training cohort (c-statistics, 0.643 vs. 0.615) and the validation cohort (0.643 vs. 0.642). This tendency was also confirmed in noncirrhotic patients (training set, 0.696 vs. 0.692; validation set, 0.691 vs. 0.686).

Similarly, when stratified by tumor grade, the new classification showed comparable to better performance compared with the AJCC 8th edition in both the training cohort (0.620 vs. 0.598) and the validation cohort (0.634 vs. 0.631) for well to moderately differentiated HCC. Comparable performance between the AJCC 8th edition and new classification was also confirmed for poorly differentiated or undifferentiated HCC (training set, 0.709 vs. 0.693; validation set, 0.635 vs. 0.640; online suppl. Fig. 2).

Discussion

In this study, we revisited the influence of tumor size and mvi on the disease-specific survival of 1,175 patients with HCC. The optimal size cutoff value for multiple HCC was around 2 cm, which was similar to that adopted in the current version of the AJCC staging system for solitary HCC. Our findings indicate that mvi is a significant prognostic factor irrespective of the size and number of tumors. By incorporating these new findings, a new prognostication model was established, and its discriminatory performance was confirmed in 5,249 patients derived from the SEER database.

In the current version of the AJCC staging system, a solitary lesion measuring up to 2 cm in diameter is subclassified as T1a based on the results of a previous international multicenter study [6]. In this study, mvi or tumor differentiation showed no significant contribution to survival in patients with small HCC. Indeed, the prognostic difference was not significant when the "overall" survival of patients with solitary HCC measuring up to 2 cm was examined in the current SEER population (p = 0.0693, data not shown), while a significant difference in disease-specific survival was confirmed, as shown in Figure 1 (p = 0.0047). Because the population of patients with HCC has a relatively advanced age and may have underlying liver diseases, overall survival does not always reflect the oncological prognosis of patients because of the relatively high incidence of other causes of death [15]. As such, disease-specific survival would be more suitable for prognostication of this unique cancer.

Interestingly, while the median tumor size was approximately 5 cm in the validation cohort, the optimal size cutoff value for prognostication of multiple HCC was around 2 cm, which is similar to that for solitary HCC (Fig. 2). Although the current AJCC staging system uses 5 cm for the staging of multiple HCC, 5 cm is an empirical cutoff value for predicting the presence of mvi. In the current SEER population, size cutoff value for mvi was estimated around 5.0–5.3 cm in a receiver-operating characteristics curve analysis. Given the close association between a tumor size of >5 cm and mvi, the new cutoff value of 2 cm would be better to balance the weighting of the listed prognostic factors for the prediction of disease-specific survival in patients with HCC.

The new classification model uses a similar method for staging in earlier stages of HCC, compared with the LCSGJ staging system, while the LCSGJ uses "macrovascular invasion" instead of mvi for staging. As confirmed in the multivariate analysis, the degrees of the contri-

butions to disease-specific survival among size, number, and mvi were similar (Table 2). Importantly, the current classification model showed acceptable performance in both cirrhotic and noncirrhotic patients (Fig. 4). Because presence of cirrhosis independently influences treatment outcomes and prognosis of patients with HCC [16], staging model should be effective apart from the presence of underlying liver disease. Although the actual performance of the new classification was almost comparable to or slightly better than the current version of the AJCC staging system, the current method could be an alternative model that effectively predicts survival outcomes using a "single" size cutoff value.

From a clinical standpoint, a 2 cm cutoff is important because various therapeutic options can be selected, including resection, ablation, and transplantation for solitary or small number of HCCs [17, 18]. Although the treatment of advanced stages of HCC remains challenging even in the era of multidisciplinary treatment, the new classification would better stratify patients who are candidates for curative treatment. As such, the current model could further improve the current version of the AJCC staging system in line with our actual clinical practice. Given the different policy in prognostication between the AJCC staging system (pathological staging system based on the surgical cohort) and the LCSGJ staging system (clinical staging system based on both surgical and medical cohorts), there remain several issues to be solved to create a universally acceptable oncological staging systems for HCC. However, current results indicate the possibility to merge these 2 staging models using the same size cutoff value and similar weight for prognostication and also highlight the next process of discussion including the issue of vascular invasion (macrovascular vs. microvascular), tumor grade (well to moderate differentiation vs. poor differentiation), or status of underlying liver (cirrhosis vs. noncirrhosis) to establish a universal prognostication model.

The limitations of this study include its retrospective nature and selected population. Also, several items of information were not accessible in the SEER database, including underlying liver disease, hepatic function, surgery detail, site of recurrence and repeated treatment, and so on, and accordingly, it is difficult to establish a completely new prognostication model using parameters not listed in the current version of AJCC staging system. However, the new model was established using prospectively collected data at a high-volume center in Japan, and the reproducibility of the results was confirmed using Western population-based data. In addition, the present validation cohort had similar baseline characteristics compared to the international multicenter database, which was used to establish the current version of the AJCC staging system: median tumor size, 50 vs. 52 mm; multiple tumors, 22.2 vs. 32.9%; mvi, 26.8 vs. 40.2%; cirrhosis 46.3 vs. 47.1%; and tumor grade (well differentiated/moderately differentiated/poor differentiated/ undifferentiated), 21.5/53.5/22.8/2.1 vs. 16.4/53.4/29.7/0.4% (personal communication). Therefore, the present results may warrant an international multicenter validation study to strengthen the current outcomes.

In conclusion, a size cutoff value of 2 cm and mvi were equally prognostic for both solitary and multiple HCC regardless of the presence of cirrhosis. The inclusion of these factors could be an alternative prognostication model using a single size-cutoff value for HCC.

Acknowledgment

None.

Statement of Ethics

The Institutional Review Board of Toranomon Hospital approved this study protocol (No. 1823). This study was conducted according to the guidelines for human studies and the Declaration of Helsinki.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

J.S.: study conception. J.S., Y. Kobayashi., Y. Kawamura.: analysis and interpretation of data. All authors: acquisition of data, drafting of manuscript, and final approval.

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