Prognosis of Hepatocellular Carcinoma: Comparison of 7 Staging Systems in an American Cohort

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Currently there is no consensus which staging system is best in predicting the survival of patients with hepatocellular carcinoma (HCC). The aims of this study were to identify independent predictors of survival and to compare 7 available prognostic staging systems in patients with HCC. A total of 239 consecutive patients with cirrhosis and HCC seen between January 1, 2000, and December 31, 2003, were included. Demographic, laboratory, and tumor characteristics and performance status were determined at diagnosis and before therapy. Predictors of survival were identified using the Kaplan–Meir test and the Cox model. Sixty-two percent of patients had hepatitis C, 56% had more than 1 tumor nodule, 24% had portal vein thrombosis, and 29% did not receive any cancer treatment. At the time of censorship, 153 (63%) patients had died. The 1- and 3-year survival of the entire cohort was 58% and 29%, respectively. The independent predictors of survival were performance status ($P < .0001$), MELD score greater than 10 ($P = .001$), portal vein thrombosis ($P = .0001$), and tumor diameter greater than 4 cm ($P = .001$). Treatment of HCC was related to overall survival. The Barcelona Clinic Liver Cancer (BCLC) staging system had the best independent predictive power for survival when compared with the other 6 prognostic systems. In conclusion, performance status, tumor extent, liver function, and treatment were independent predictors of survival mostly in patients with cirrhosis and HCC. The BCLC staging system includes aspects of all of these elements and provided the best prognostic stratification for our cohort of patients with HCC. (HEPATOLOGY **2005;41:707–716.**)

Hepatocellular carcinoma (HCC) is the fifth most common tumor worldwide. In the United States, the incidence of HCC has been rising,[1] and it is the tumor with the largest increase in incidence over the last 12 years.[2] Furthermore, the overall survival of patients with HCC has not improved over the last 20 years, with the incidence rate almost equal to the death rate.[3] It is projected that the increase in incidence of HCC will continue over the next 20 years in the United States.[4] Therefore, it is important to understand the factors that predict survival of patients with HCC.

Clinical staging of cancers provides a guide to assess prognosis and to direct therapeutic interventions. Well-defined, widely accepted prognostic staging systems are available for many solid tumors, including cancer of the colon[5] and prostate.[6] These staging systems have been invaluable in designing tumor surveillance programs and in comparing the efficacy of new therapies. Four key factors that may affect the prognosis of patients with HCC have been identified[7]: (1) tumor stage at diagnosis; (2) overall health of the patient; (3) hepatic synthetic function; and (4) efficacy of treatment. Several prognostic staging systems have been proposed for HCC (Table 1),[8-14] and recently there has been much debate regarding which prognostic staging system is the best. The lack of a consensus on an HCC staging system is in part related to the heterogeneity in diagnostic criteria of HCC when histological confirmation is not available.[7,15] Nonhisto-

Abbreviations: HCC, hepatocellular carcinoma; BCLC, Barcelona Clinic Liver Cancer; CT, computed tomography; MRI, magnetic resonance imaging; AFP, alpha-fetoprotein; UNOS, United Network of Organ Sharing; ALT, aminotransferase; AST, aspartate aminotransferase; CTP, Child-Turcotte-Pugh; MELD, model for end-stage liver disease; TNM, tumor node metastasis; CLIP, Cancer of Liver Italian Program; JIS, Japanese integrated system; GRETCH, Groupe d'Etude de Traitement du Carcinoma Hepatocellulaire; CUPI, Chinese university prognostic index; LR, likelihood ratio.

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Table 1. Variables Included in Seven Staging Systems for HCC

Staging System	Hepatic Function	Alpha-fetoprotein	Performance Status	Tumor Staging
Okuda	Ascites, albumin, and bilirubin	No	No	Tumor greater or less than 50% of cross-sectional area of liver
TNM	No	No	No	Number of nodules, tumor size, presence of portal vein thrombosis, and presence of metastasis
CLIP	CTP	<400 or ≥400 ng/mL	No	Number of nodules, tumor greater or less than 50% area of liver, and portal vein thrombosis
BCLC	CTP	No	Yes	Tumor size, number of nodules, and portal vein thrombosis
CUPI	Bilirubin, ascites, alkaline phosphatase	<500 or ≥500 ng/mL	Presence of symptoms	TNM
JIS	CTP	No	No	TNM
GRETCH	Bilirubin, alkaline phosphatase	<35 or ≥35 μg/L	Yes	Portal vein thrombosis

logical criteria for diagnosis of HCC were proposed at a European Association for the Study of the Liver conference,[7] but these criteria are not adhered to universally. There is also a lack of standardization regarding the tests needed to determine tumor burden and extent of spread of HCC, which impede accurate staging. The absence of a consensus on a HCC staging system may hinder progress in critical areas of HCC research, such as evaluation of biomarkers for early detection of HCC and development of new therapeutic modalities.

The aims of this study were to identify independent predictors of survival at the time of HCC diagnosis in a single center and to compare the ability of 7 existing HCC staging systems in predicting survival in a cohort of patients with HCC.

Patients and Methods

Patients. Consecutive patients with HCC seen in the Liver Clinics at the University of Michigan Medical Center were enrolled into a database that was approved by the Institutional Review Board. Data were extracted from the records of patients seen between January 1, 2000, and December 31, 2003. Follow-up was censored on May 31, 2004. Diagnosis of HCC was based on histology in 192 patients and on nonhistological criteria in 52 patients.[7] The nonhistological criteria were two imaging studies—computed tomography (CT) or magnetic resonance imaging (MRI)—showing an arterial enhancing mass greater than 2 cm (n = 21), or one imaging study (CT or MRI) showing an arterial enhancing mass greater than 2 cm and an alpha-fetoprotein (AFP) greater than 400 ng/mL (n = 31). A treatment algorithm was followed (Fig. 1) in which all patients were first assessed for resection; if deemed ineligible, liver transplantation was considered if the patient met United Network of Organ Sharing (UNOS) criteria. Patients who were not candidates for surgical therapy received radiofrequency ablation if they had no more than 3 tumor nodules and the maximum diameter of each nodule was less than 5 cm. Patients with diffuse or more extensive tumors were considered for intra-arterial chemoembolization if they had preserved liver function and portal vein was patent. Patients who did not qualify for intra-arterial chemoembolization were considered for investigational protocols using radiation, systemic chemotherapy, and/or investigational therapies after a multispecialty group evaluation.

For all patients, demographic information, etiology of liver disease as previously defined,[16] biochemical data, hematological data, assessment of hepatic function based on Child-Turcotte-Pugh(CTP) and model for end-stage liver disease (MELD) score, and performance status were recorded. All data, including staging of the tumors, were determined at the time of HCC diagnosis and before therapy. Presence of underlying cirrhosis was assessed histologically (n = 188) or via clinical and radiological evidence of portal hypertension (n = 56). Available

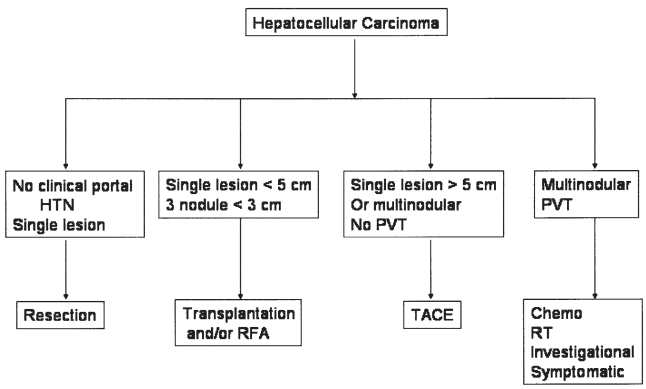

Fig. 1. Treatment algorithm of patients with hepatocellular carcinoma at the University of Michigan. HTN, hypertension; RFA, radiofrequency ablation; PVT, portal vein thrombosis; TACE, transarterial chemoembolization; RT, radiation therapy.

abdominal CT or MRI scans at the time of diagnosis were reviewed by 2 radiologists; the number and location of nodules, maximum diameter of the largest nodule, and any evidence of portal vein thrombosis were recorded. Extrahepatic metastasis was evaluated via chest CT (n = 209), bone scan (n = 232), and/or chest X ray (n = 35).

The date of death was determined by the Social Security Death Index if more than 3 months had elapsed since the last follow-up visit and death did not occur in our hospital or was not reported by the family. The predominant cause of death was extracted from the medical record. Death was attributed to tumor progression in patients with a more than 25% increase in size of any tumor nodule or an increase in the number of nodules based on imaging at the time of death compared with the imaging at diagnosis. Death was attributed to hepatic failure in patients who had a more than twofold increase in bilirubin, international normalized ratio, or development of ascites, variceal hemorrhage, or hepatorenal syndrome at the time of death. If patients had evidence of hepatic failure and tumor progression, the cause of death was considered to be a combination of both.

Statistical Considerations. Continuous data were expressed as the mean ± SD. A univariate analysis to identify predictors of survival at the time of HCC diagnosis (baseline) was performed using the Kaplan–Meier method of survival function.[17] The baseline variables evaluated were:

1. demographics: age, sex, ethnicity (non-Hispanic white or not);
2. etiology of liver disease (hepatitis C or not);
3. laboratory values: platelet, international normalized ratio, bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, alkaline phosphatase, creatinine, AFP;
4. hepatic function as determined by CTP classification and MELD score;
5. tumor characteristics: number of nodules, maximum tumor diameter, portal vein thrombosis, extrahepatic metastasis; and
6. Eastern Cooperative Oncology Group performance status.

For continuous variables, median values were used to determine the cutoff. Variables other than tumor staging with an alpha less than 0.10 were included in a forward Cox proportional regression model[18] to identify independent predictors of survival.

We next set out to determine which staging systems were the best at predicting survival in our cohort of patients with HCC. Tumor staging was performed in 209 patients who had chest CT. This included the following systems: UNOS-modified tumor node metastasis (TNM), Barcelona Clinic Liver Cancer (BCLC), Cancer of Liver Italian Program (CLIP), Japanese Integrated System (JIS), Groupe d'Etude de Traitement du Carcinoma Hepatocellulaire (GRETCH), Chinese University Prognostic Index (CUPI), and the Okuda staging system. The performance of a prognostic system has been shown to be related to homogeneity (small differences in survival among patients in the same stage within each system), discriminatory ability (greater differences in survival among patients in different stages within each system), and monotonicity of gradients (the survival of patients in earlier stages is longer than the survival of patients in more advanced stages within the same system).[19] To determine whether each of the staging systems could predict survival, we used the Kaplan–Meier method as the initial analysis. The Cox regression model was then used to calculate the likelihood ratio (LR) χ^2 to determine homogeneity.[20] In the LR test, we used the ordinary prognostic score rather than using dummy variables.[19] The linear trend χ^2 was then used to measure the discriminatory ability of each of the staging systems.[21] Both the LR χ^2 and linear trend χ^2 were also used to measure the monotonicity of gradients of survival, and the degrees of freedom was 1 so that two prognostic systems with different number of stages could be compared. In addition, the results of the Cox regression were expressed using the Akaike information criterion, which shows how the explanatory variable (staging systems) affect the dependent variable (survival of HCC)—the lower the Akaike information criterion, the more explanatory it is and the more informative the model is.[22] Lastly, the independent contribution of each staging system to overall prediction of survival in the Cox model was evaluated by comparing the LR test in the full model (all systems included) and in a reduced model when one staging system was removed.[23] All statistical analyses were performed using SAS version 8.1 (Cary, NC), and all graphs were created using MedCalc 7.4 (Mariakerke, Belgium).

Results

Patient Characteristics. A total of 244 HCC patients were seen during the time period. Table 2 shows the demographic, clinical, and tumor information for all patients. The majority of the patients were men (73%) and non-Hispanic white (74%); the mean age was 57 years. Almost all (n = 239, 98%) met criteria of having cirrhosis, the most common cause being hepatitis C (62%). One hundred five (43%) patients were CTP class A. One hundred thirty-seven (56%) patients had more than 1 tumor nodule, 60 (24%) had portal vein thrombosis, and 13 (5%) had evidence of extrahepatic metastases. Ninety-

Table 2. Demographic, Clinical, and Tumor Staging Information of 244 Patients With HCC

Demographics	
Age	57 ± 10
Sex (M:F)	177:67
Ethnicity, n (NHW/AA/Hispanic/Asian/other)	181/22/12/11/18
Etiology, n (HCV/HCV-Alc/HBV/Crypto/Alc/other)	79/73/10/38/28/16
Cirrhosis, n (%)	239 (98)
Laboratory values	
AFP ng/mL (median) (range), n (%)	6231 ± 51184 (44) (1-974220)
≤20	93 (38)
21–200	67 (27)
≥200	84 (35)
Albumin g/dL	3.3 ± 1.2
AST (IU/mL)	114 ± 45
ALT (IU/mL)	98 ± 51
Alkaline phosphatase (IU/mL)	248 ± 203
Total bilirubin (mg/dL)	2.7 ± 3.1
Creatinine (mg/dL)	1.0 ± 0.7
International normalized ratio	1.3 ± 0.4
Platelet (/mm^3)	131 ± 88
CTP score	8 ± 2
MELD score	13.1 ± 13
Tumor characteristics	
Number meeting Milan criteria	86
Single <5 cm	51
<3 each <3 cm	35
Number of nodules	2.4 ± 2
Type (unifocal, multifocal, diffuse), n	107/127/10
Maximum tumor diameter (cm) (range)	5.4 ± 3.7 (1.2-22)
Location (right/left/both lobes)	164/58/22
Portal vein thrombosis, n (%)	60 (24%)
Extrahepatic metastasis, n (%)	13 (5%)
Staging (%)	
BCLC (A/B/C/D)	28/25/31/16
TNM (I/II/III/IV)	4/31/36/29
Okuda (1/2/3)	19/44/37
CLIP (0–5)	19/31/15/13/14/8
JIS (0–5)	9/25/19/17/19/11
GRETCH (A/B/C)	19/42/39
CUPI (L/I/H)*	19/44/37
Treatment, n (%)	
None	71 (29)
Resection†	10 (4)
Liver transplantation	51 (21)
Radiofrequency ablation	46 (19)
Chemoembolization	23 (9)
Radiation	14 (6)
Systemic chemotherapy	29 (12)
Performance status (0/1/2)	65/101/78

NOTE. Values are the mean ± SD unless otherwise noted.

Abbreviations: M, male; F, female; NHW, non-Hispanic white; AA, African American; HCV, hepatitis C virus; HCV-Alc, hepatitis C virus + alcohol; HBV, hepatitis B virus; Alc, alcohol.

*L, low; I, intermediate; H, high-risk.

†Includes 5 patients without cirrhosis.

three (38%) patients had an AFP level of 20 ng/mL or less. Ten (4%) patients had surgical resection, 51 (21%) underwent liver transplantation, 46 (19%) had radiofrequency ablation, 23 (9%) had chemoembolization, and 43 (18%) had other therapies. Seventy-one (29%) did not receive cancer treatment because of advanced tumor stages (51%), hepatic decompensation (21%), and patient refusal (28%). The following analysis is based on the 239 patients with cirrhosis.

Survival. At the time the data were censored, 153 (63%) patients had died. The overall median survival of the entire cohort was 16.4 months (95% CI 12.9-19.8 mo) (Fig. 2A) and the 1- and 3-year probability of survival was 58% and 29%, respectively. The causes of death were tumor progression (n = 65, 42%), hepatic failure (n = 38, 24%), combined tumor progression/hepatic failure

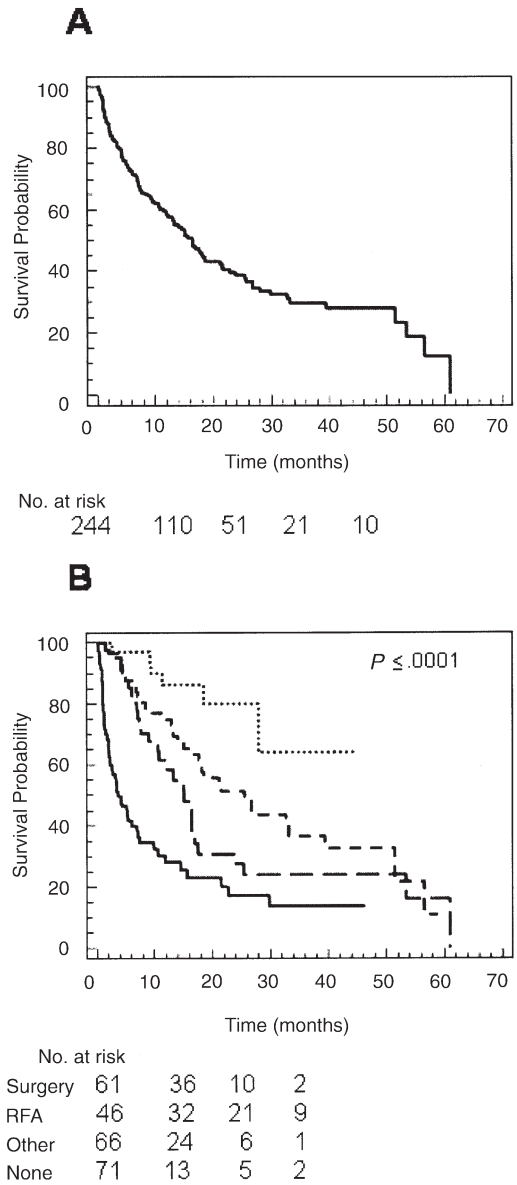

Fig. 2. Probability of survival (A) in all patients in the entire cohort and (B) according to treatment. Resection/orthotopic liver transplant (· · ·· · ·), radiofrequency ablation (––), other treatments such as chemoembolization, radiation and systemic chemotherapy (- - -), did not undergo treatment (- - - -). RFA, radiofrequency ablation.

Table 3. Univariate Analysis of Baseline Predictors of Survival in 239 Patients With Cirrhosis and HCC

Variables	Number of Patients	Median Survival (mo)	*P* Value
Age			
<57	115	16.4	.482
≥57	124	15.2	
Sex			
Male	113	17.1	.933
Female	66	14	
Ethnicity			
Non-Hispanic white	176	16.4	.911
Others	63	22.1	
Etiology			
HCV	151	17.4	.211
Non-HCV	88	18.5	
Ascites			
Present	20	14.7	.318
Absent	219	17.9	
AFP			
<44	119	29.8	<.0001
≥44	120	10.6	
AST			
<110	122	19.4	.357
≥110	117	17.5	
ALT			
<95	125	17.6	.548
≥95	114	18.9	
Alkaline phosphatase			
<220	109	22.5	.010
≥220	130	12.4	
International normalized ratio			
<1.2	153	19.2	.06
≥1.2	86	11.6	
Bilirubin			
<1.5	110	17.6	.283
≥1.5	129	13.3	
Creatinine			
<1.0	148	17.8	.031
≥1.0	91	11.3	
Albumin			
<3.3	118	16.7	.751
≥3.3	121	17.3	
Platelet			
<118	128	16.8	.43
≥118	111	17.9	
MELD			
<10	110	18.5	.020
≥10	129	11.3	
CTP class			
A	100	18.5	.030
B	98	16.5	
C	41	10.5	
Detected by surveillance			
Yes	129	17.2	.875
No	110	14.3	
Number of tumor nodules			
<2	165	18.5	.010
≥2	74	10.1	
Maximum tumor diameter (cm)			
<4	122	33.4	<.0001
≥4	117	7.5	
Portal vein thrombosis			
Yes	60	5.5	<.0001
No	179	25.4	
Extrahepatic metastasis*			
Yes	13	7.7	.004
No	196	17.5	
Performance status			
0	63	29.1	<.0001
1	198	16.4	
2	78	6	
BCLC			
A	64	–	<.0001
B	60	17.1	
C	76	9.9	
D	39	5.1	
TNM			
I	6	–	.0003
II	75	22.5	
III	87	16.4	
IV	71	5.9	
CLIP			
0	43	53.1	.001
1	74	16.2	
2	36	12.4	
3	32	10.8	
4	34	3.4	
5	20	1.7	
Okuda			
1	42	18.4	.001
2	107	15.3	
3	90	5.4	
JIS			
0	18	39.8	.0004
1	60	15.8	
2	46	17.2	
3	42	10.6	
4	46	3.3	
5	27	1.8	
GRETCH			
A	41	32.3	.003
B	102	17.3	
C	96	6.2	
CUPI†			
L	41	20.5	.001
I	108	17.3	
H	90	7.8	

NOTE. A dash (–) indicates that the median survival could not be calculated because the last cumulative survival was greater than 50%.
Abbreviation: HCV, hepatitis C virus.
*Staging information was available in 209 patients.
†L, low; I, intermediate; H, high-risk.

(n = 19, 13%), infections (n = 19, 13%), and unknown (n = 12, 8%).

Baseline Predictors of Survival. Univariate analysis showed that AFP, alkaline phosphatase, international normalized ratio, creatinine, MELD score, CTP class, number of nodules, maximum tumor diameter, portal vein thrombosis, extrahepatic metastasis, and performance status were significant baseline predictors of survival in patients with HCC (Table 3). Patients who received treatment for HCC had significantly better sur-

Table 4. Independent Predictors of Survival

Variables	Hazard Ratio (95% CI)	*P* Value
All patients (n = 244)		
Performance status		
0	0.07 (0.02-0.16)	<.0001
1	0.46 (0.31-0.69)	<.0001
MELD >10	1.9 (1.3-2.8)	.001
Portal vein thrombosis	2.2 (1.4-3.3)	.001
Tumor diameter >4 cm	2.4 (1.5-3.9)	.001
Nontransplant (n = 193)*		
Performance status		
0	0.15 (0.03-0.32)	.03
1	0.59 (0.38-0.81)	.001
MELD >10	2.0 (1.4-3.4)	.008
Portal vein thrombosis	2.5 (1.3-4.2)	<.0001
Tumor diameter >4 cm	2.3 (1.4-2.8)	.02

*Patients who underwent liver transplantation were not included in the analysis.

vival compared with those who did not receive treatment (log rank $P < .0001$), but there were significant differences between these two groups. Patients who did not receive treatment had significantly more advanced tumors compared with those treated: maximum tumor diameter, 6.9 ± 3.6 cm versus 5.1 ± 3.4 cm ($P = .0001$), portal vein thrombosis 46% versus 20% ($P = .0002$), and poorer performance status (% Eastern Cooperative Oncology Group 0/1/2: 18/41/41 vs. 31/43/25) ($P = .01$). However, there was no difference with regard to hepatic synthetic function as measured by MELD ($P = .745$) or CTP class ($P = .132$). After controlling for differences in baseline factors and MELD (to also control for hepatic function), a significantly better survival persisted among the patients who received treatment (those treated had a median survival of 13.2 mo vs. 2.8 mo in those untreated; $P < .0001$). Figure 2B shows the survival according to treatment adjusted for tumor size, portal vein thrombosis, performance status, and MELD score; patients who underwent liver transplantation had the best survival. Treatment was not included in the multivariate analysis because it is not a variable obtained at diagnosis.

Cox regression analysis identified performance status ($P < .0001$), MELD score ($P = .001$), maximum tumor diameter ($P = .001$), and portal vein thrombosis ($P = .001$) as independent baseline predictors of survival for the entire cohort of HCC patients (Table 4). Performance status of 0 and 1 were protective with hazard ratios of 0.07 (95% CI 0.02-0.16) and 0.46 (95% CI 0.31-0.69), respectively.

Staging Systems and Survival. When the seven prognostic staging systems were analyzed separately using Kaplan–Meier survival analysis (n = 244), each staging system showed a significant difference in the probability of survival across the different stages (Fig. 3). Figure 3

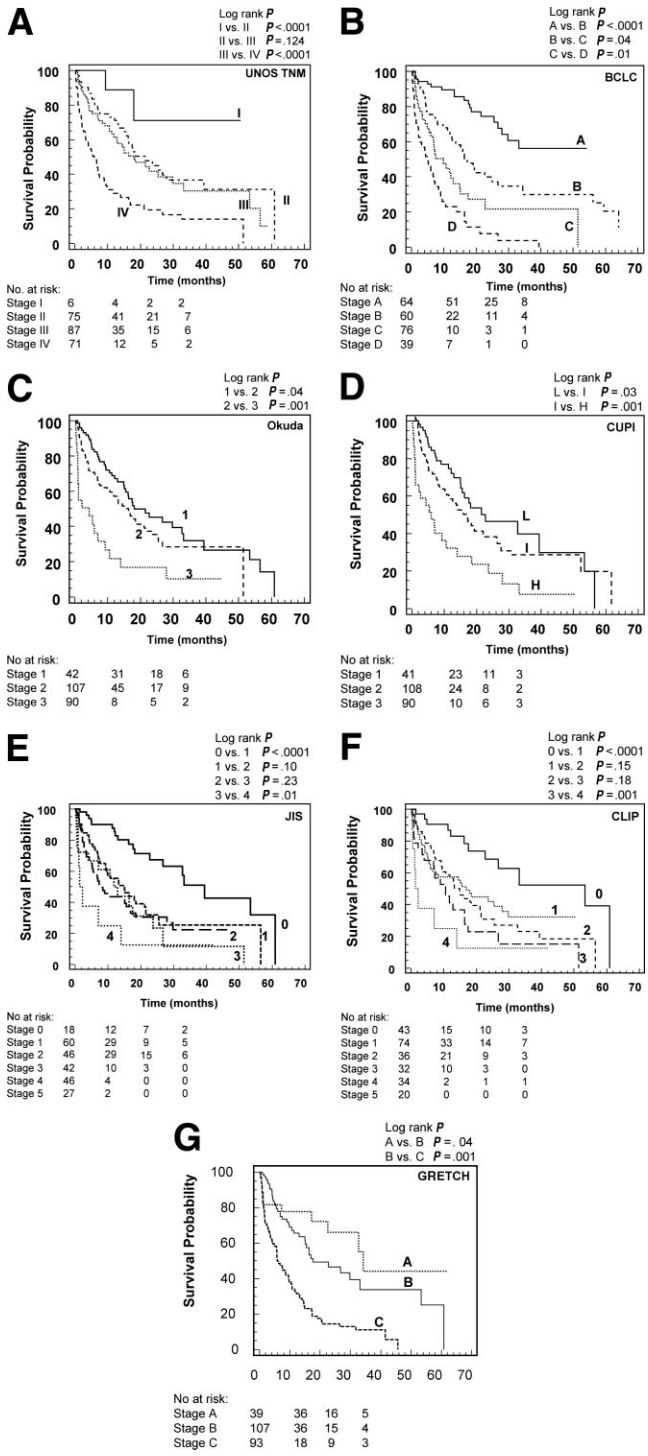

Fig. 3. Probability of survival according to (A) UNOS TNM, (B) BCLC, (C) Okuda, (D) CUPI, (E) JIS, (F) CLIP, and (G) GRETCH. UNOS TNM, United Network of Organ Sharing tumor node metastasis; BCLC, Barcelona Clinic Liver Cancer; CUPI, Chinese university prognostic index; JIS, Japanese integrated system; CLIP, Cancer of Liver Italian Program; GRETCH, Groupe d'Etude de Traitement du Carcinoma Hepatocellulaire.

Table 5. Comparison of Prognostic Stratification of Seven HCC Staging Systems

Model	Discriminatory Ability Linear Trend χ^2	Homogeneity LR χ^2 Test	Akaike Information Criterion
All patients (n = 244)			
BCLC	28.7	76.8	943.7
GRETCH	16.3	59.2	970.4
Okuda	11.2	52.9	974.4
CLIP	9.4	51.9	981.5
JIS	8.4	49.7	994.0
TNM	7.2	54.3	978.5
CUPI	9.8	52.3	990.8
With transplantation (n = 51)			
BCLC	12.7	23.8	407.1
GRETCH	6.7	10.3	422.5
CUPI	2.9	3.2	427.7
Okuda	2.8	5.3	431.7
CLIP	1.9	2.1	427.3
JIS	0.6	1.8	433.8
TNM	1.1	2.3	425.4
Without transplantation (n = 193)			
BCLC	22.8	38.7	534.2
GRETCH	16.2	31.4	549.2
CLIP	11.9	21.3	558.1
TNM	11.1	20.8	560.9
JIS	10.2	16.7	569.4
Okuda	9.8	17.5	566.3
CUPI	8.7	14.3	569.9

shows that the TNM (stages II and III), JIS (stages 1, 2, and 3), CLIP (stages 1, 2, and 3), and GRETCH (stages B and C) systems had poor stratification of survival at the intermediate stages, while the BCLC, Okuda, and CUPI systems had a better stratification of survival across all stages. The BCLC system had the highest homogeneity (LR χ^2 76.8), indicating small differences in survival among patients in the same stages (Table 5). The BCLC classification also had the highest discriminatory score (liner trend χ^2 28.7) compared with other systems. The BCLC classification had the best monotonicity of gradient based on the LR χ^2 and linear trend χ^2. The Akaike information criterion was the lowest for the BCLC system, indicating that the model containing the BCLC system was the most informative when explaining the survival of HCC patients (see Table 5). Further evidence that the BCLC system provided the best prediction of survival in our cohort was its contribution to the Cox model. The BCLC was the only staging system that had a significant impact on the Cox survival model when it was removed from the model containing all other staging systems (−Log likelihood = 903.1; LR χ^2 42.7; $P < .0001$). Therefore, it was the only prognostic staging system that had independent predictive value on survival in our cohort.

Prediction of Survival in "Non-Transplant" Patients. Liver transplantation can improve survival in patients with HCC by removing the tumor as well as the underlying cirrhosis. To eliminate the beneficial effects conferred by removal of a liver with cirrhosis, predictors of survival were reanalyzed after patients who underwent transplantation were removed from the analysis. The median survival of the 188 patients who did not undergo liver transplantation was 11.3 months (95% CI 9.6-15.4) with a mean of 18.8 months; the median survival for the 51 patients who underwent transplantation was more than 50 months, and the mean was 42.8 months, respectively (95% CI, 30-48.9; $P < .0001$). The 1- and 3-year probability of survival was 48% and 19% for all patients who did not undergo transplantation , respectively, and 90% and 74% for those patients who did undergo transplantion, respectively. Cox regression analysis identified the same independent predictors of survival in the patients who did not undergo transplantion as the entire cohort, but the hazard ratios were slightly different (see Table 4).

Kaplan–Meier analysis of the patients who did not undergo transplantation (n = 193) showed that each staging system—except the JIS—demonstrated significant differences in survival across the different tumor stages (data not shown). The LR χ^2 and the linear trend χ^2 for the BCLC system were the highest among the 7 tumor prognostic staging systems for the patients who did not undergo transplantation (38.7 and 22.8, respectively) (see Table 5), indicating better homogeneity and discriminatory ability compared with the other systems. The Akaike information criterion was the lowest for the BCLC system, indicating that this system is a more informative model of survival compared with the other systems. The BCLC system had the highest and only significant contribution to the Cox model (−Log likelihood = 468; LR $\chi^2 = 23.9$; $P = .001$) compared to the other systems in patients who did not undergo tranplantation.

Discussion

Recently there has been much debate regarding which of the existing tumor staging systems has the best prognostic value for HCC. Design of a tumor staging system relies on the identification of individual variables that can predict survival of patients with HCC. In this study, we used data from a large (n = 239), well-characterized cohort of patients with HCC balanced between early (35% TNM stage I/II) and advanced disease (24% portal vein thrombosis and 56% multifocal/diffuse tumors), and a substantial number of untreated patients (29%) to allow us to study prognostic factors. The extent of tumor (tumor size and portal vein involvement), hepatic function (MELD score), and overall well-being of the patient (performance status)] were independent baseline predictors in our en-

tire cohort as well as the subset of patients who did not undergo transplantation. In addition, we also showed that HCC treatment was related to higher overall probability of survival. Therefore, the four key factors affecting HCC prognosis were important in our cohort of patients.

Performance status had been shown to be an independent predictor of survival in a study on the natural history of untreated HCC and in other solid tumors.[24,25] Almost all our patients had underlying cirrhosis, so it is not surprising that survival was related to hepatic function. We found that MELD score was a better predictor of survival compared with CTP classification and individual laboratory tests of hepatic function. Recent studies also found that MELD is a better predictor of survival than CTP classification in patients waiting for a liver transplantation.[26] Portal vein thrombosis had been found to be a poor prognostic variable in multiple studies.[27] Microscopic and macroscopic portal vein involvement is one of the major modes of spread of HCC, leading to recurrence after resection[28] and transplantation.[29] In addition, portal venous thrombosis can lead to complications of portal hypertension such as ascites, variceal hemorrhage, and worsening hepatic function in HCC patients.[30] Tumor burden had also been shown to be an important prognostic indicator, but the cutoff used in previous studies has varied from more than 5 cm diameter of the largest nodule to a tumor involving more than 50% of the liver.[31,32] As expected, patients who were eligible for some form of treatment had better survival than those who were too moribund for any treatment. Nevertheless, treatment in general significantly improved survival even after performance status, MELD score, portal vein thrombosis, and tumor size were controlled for.

Using Kaplan–Meier analysis, we showed that all seven tumor staging systems currently in use for HCC revealed a progressive decrease in survival from the earliest to the most advanced stage. However, the BCLC system was the best at discriminating survival of patients in different stages and had the greatest homogeneity of survival among patients within the same stage. In addition, the BCLC system provided the largest contribution to the Cox model, indicating that it has the best prognostic power for survival compared with the other systems. The superiority of the BCLC system over other tumor staging systems persisted when separate analyses were performed for patients who did not undergo liver transplantation, indicating that it provided better stratification of HCC patients at both intermediate and advanced stages. We believe that the BCLC system had the best prognostication in our cohort because it included the independent predictors of survival we identified: performance status, measure of hepatic function, and tumor stage (size and portal thrombosis). Although the BCLC system does not include treatment as a variable, it has the advantage of stratifying patients into treatment groups. The superiority of the BCLC system was also demonstrated in a recent study of 187 Italian patients with surgically treated HCC.[33]

Two staging systems, CUPI and GRETCH (see Table 1), also include performance status, measures of hepatic function, and tumor staging. However, hepatic function was based on bilirubin, presence of ascites, and elevated alkaline phosphatase; the latter has not been shown to be a sensitive marker of liver function. The CUPI system was derived from a cohort of Chinese patients, most of whom had chronic hepatitis B, while the GRETCH system was based on a multicenter French study of patients with alcoholic liver disease. Both CUPI and GRETCH included AFP, which had no prognostic value in our cohort because more than one third of our patients (38%) had an AFP level of less than 20 ng/mL, and only 32% had an AFP level of 500 ng/mL or more. We believe that the Okuda, JIS, and UNOS TNM systems were not predictive of survival in our cohort because they included only extent of tumor and a limited assessment of hepatic function.

The CLIP system has been externally validated in Canadian,[34] Italian,[35] and Japanese cohorts.[19] CLIP was recently endorsed by a consensus conference on HCC staging because it was the only staging system externally validated.[36] However, one potential limitation of these validation studies is that the other prognostic systems were not studied. Studies that have evaluated more than three systems have shown an advantage of BCLC[33] or equality of the BCLC, GRETCH, and CLIP systems.[37] In our cohort, CLIP was able to discriminate survival of patients with stage 0 from those with stages 4, 5, and 6 (log rank $P = .0001$ in Fig. 3). However, it could not differentiate patients with stages 1, 2, and 3, which comprised 59% of our cohort (poor discriminatory ability). The suboptimal performance of CLIP in our cohort may be related to the inclusion of AFP in the CLIP system. Another limitation of the CLIP system is that treatment decisions often involve overlapping stages. In our cohort, 46% of patients in stage 0, 29% in stage 1, and 42% in stage 2 underwent liver transplantation.

There are several limitations in our study. This is a single-center study, and the results may not be generalizable. There may be referral bias, because patients who are moribund may not be referred to a tertiary center. On the other hand, being a tertiary referral center with protocols for investigational treatment, patients with advanced tumors are often referred to us as a last resort. Although our treatment algorithm is based on published literature and

recommendations from consensus conference, different centers may have different practice. It is also possible that our results may not apply to patients with HCC in other countries because of differences in demographics, underlying cause of liver disease, and proportion of patients with cirrhosis. However, the strengths of our study are the complete data in a large number of patients; a full spectrum of patients with early, intermediate, and advanced tumors at diagnosis; and uniformity with regard to the diagnostic and treatment algorithms. In addition, the epidemiological characteristics of our cohort are consistent with that reported in other studies of American patients with HCC.[38,39]

In conclusion, our study shows that measures of hepatic function (MELD score), performance status, tumor characteristics (size and presence of portal vein thrombosis), and the effect of treatment are predictors of survival in cirrhotic patients with HCC. We show that among the seven prognostic staging systems available for HCC, the BCLC system provided the best independent prediction of survival. The superior performance of BCLC may be related to the fact that it includes the same characteristics that had been identified as independent predictive variables in our cohort. Our results should be confirmed in a larger multicenter cohort to study the effect of multiple etiologies, ethnicity, and the effect of various treatments on overall survival. A consensus in prognostic staging for HCC is urgently needed to assure progress in the development of biomarkers for early detection and novel therapies.

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