EUROPEAN JOURNAL OF CANCER XXX (2009) XXX–XXX

available at www.sciencedirect.com

journal homepage: www.ejconline.com

Applicability of staging systems for patients with hepatocellular carcinoma is dependent on treatment method – Analysis of 2010 Taiwanese patients

Chien-Hung Chen[a], *Fu-Chang Hu*[b,c], *Guan-Tarn Huang*[a], *Po-Huang Lee*[d], *Yuk-Ming Tsang*[e], *Ann-Lii Cheng*[a,f], *Ding-Shinn Chen*[a,g,h], *Jung-Der Wang*[a,i], *Jin-Chuan Sheu*[a,*]

[a]*Department of Internal Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, 7, Chung-Shan South Road, Taipei 10016, Taiwan*

[b]*Department of Medical Research, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan*

[c]*Statistical Consulting Clinic, National Center of Excellence for General Clinical Trial and Research, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan*

[d]*Department of Surgery, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan*

[e]*Department of Medical Imaging, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan*

[f]*Department of Oncology, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan*

[g]*Graduate Institute of Clinical Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan*

[h]*Hepatitis Research Center, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan*

[i]*Institute of Occupational Medicine and Industrial Hygiene, College of Public Health, National Taiwan University, Taipei, Taiwan*

ARTICLE INFO

Article history:
Received 15 December 2008
Accepted 18 December 2008

Keywords:
Hepatocellular carcinoma
Staging
Scoring
Prognosis
Taiwan

ABSTRACT

The aim of this study was to compare six prognostic staging systems (Okuda stage, TNM stage, CLIP score, BCLC stage, JIS score and Tokyo score) in predicting survival in patients with hepatocellular carcinoma (HCC). A total of 2010 Taiwanese HCC patients were included. Demographic, laboratory and tumour characteristics were determined at diagnosis. Predictors of survival included serum levels of albumin, total bilirubin, alkaline phosphatase, α-fetoprotein, ascites, tumour size and portal vein invasion. The Tokyo score was the most informative one for predicting the survival of HCC patients as a whole, receiving surgical resection, or receiving transarterial chemoembolisation. CLIP score was the best fit system for HCC patients receiving chemotherapy or supportive care. Each staging system showed a significant difference in predicting the probability of survival across different stages. The applicability of staging systems for patients with HCC was dependent on treatment methods.

1. Introduction

Hepatocellular carcinoma (HCC) is the fifth most common solid tumour in the world, and there are about 500,000 deaths each year.[1] Since 1984, HCC has been the leading cause of cancer death in Taiwan[2]; annually around 7000 people die of HCC and around 8000 new HCC cases are diagnosed (Taiwan Cancer Registration System. http://crs.cph.ntu.edu.tw/). Over

* *Corresponding author:* Tel.: +886 2 23123456x66579; fax: +886 2 23819723.
E-mail address: sheuhcc@ntuh.gov.tw (J.-C. Sheu).

0959-8049/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ejca.2008.12.025

the last 5–8 years, accumulated evidence has shown that the incidence of HCC is rising in different countries.[3] Great efforts have been made to improve the survival rates of HCC patients. Regular sonographic examination can help detect small HCC early,[4] and many therapeutic modalities are available for HCCs.[3] However, despite these scientific advances and the implementation of measures for early HCC detection in patients at risk, patient survival has not improved during the last three decades.[5]

Staging systems are used to define prognosis and treatment options. Several staging or scoring systems for HCC have been proposed, such as the Okuda staging system[6] (Table 1), GRETCH (Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire) scoring system,[7] CUPI (Chinese University Prognostic Index) staging system,[8] simplified staging system,[9] TNM staging system[10] (Table 2), CLIP (Cancer of the Liver Italian program) scoring system[11] (Table 3), BCLC (Barcelona Clinic Liver Cancer) staging system[12] (Table 4), JIS (Japan Integrated Staging) staging system[13] (Table 5) and Tokyo scoring system[14] (Table 6). The variables used in these staging systems can be grouped into four aspects: (1) tumour factors, such as tumour size, portal vein thrombosis and alpha-fetoprotein (APF), (2) underlying liver function (such as Child-Pugh stage), (3) overall health of the patient (such as performance status) and (4) efficacy of treatment. Although the American Association for the Study of Liver Disease suggests that BCLC might be the most suitable staging system for HCC,[3] the prediction of prognosis in HCC patients is very complex because the underlying liver function also affects prognosis. Thus, there is no worldwide consensus on the use of any given HCC staging system.[3]

In this study, we built a Taiwanese HCC patients cohort, which represented early to advanced stages. The aims of this study were to identify independent predictors of survival at the time of HCC diagnosis in a single centre and to compare the applicability of different staging systems in predicting survival in a cohort of patients with HCC undergoing different treatments.

Table 1 – Definition of the Okuda staging system for hepatocellular carcinoma.

Variables	Score	
	0	1
Tumour size	≦50% of liver	>50% of liver
Albumin (g/dl)	≧3	<3
Bilirubin (mg/dl)	<3	≧3
Ascites	No	Yes

Table 2 – Definition of TNM staging system (6th edition, 2002) for hepatocellular carcinoma.

Stage	Tumour	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

T1, single tumour without vascular invasion.
T2, single tumour with vascular invasion, or multiple tumours, none >5 cm.
T3, multiple tumours, any >5 cm, or tumours involving major branch of portal or hepatic veins.
T4, tumours with direct invasion of adjacent organs other than the gallbladder, or perforation of visceral peritoneum.
N1, regional lymph node metastasis.
M1, distant metastasis.

Table 3 – Definition of the Cancer of the Liver Italian Program (CLIP) scoring system for hepatocellular carcinoma.

Variables	Score		
	0	1	2
Child-Pugh stage	A	B	C
Tumour morphology	Uninodular and extension ≦50%	Multinodular and extension ≦50%	Massive or extension >50%
AFP (ng/mL)	<400	≦400	
Portal vein thrombosis	No	Yes	

AFP, alpha-fetoprotein.

Table 4 – Definition of BCLC staging system for hepatocellular carcinoma.

BCLC stage	PST	Tumour stage	Liver function status (Child-Pugh)
Stage 0 (very early)	0	Single and <2 cm	A
Stage A (early)	0	Single and ⩽5 cm 3 tumours and each ⩽3 cm	A–B
Stage B (intermediate)	0	Large, multinodular	A–B
Stage C (advanced)	1–2	Vascular invasion or extrahepatic spread	A–B
Stage D (terminal)	3–4	Any	C

PST, performance status.

Please cite this article in press as: Chen C-H et al., Applicability of staging systems for patients with ..., *Eur J Cancer* (2009), doi:10.1016/j.ejca.2008.12.025

Table 5 – Definition of the Japan Integrated Staging (JIS) scoring system for hepatocellular carcinoma.

Variables	Score			
	0	1	2	3
Child-Pugh class	A	B	C	
TNM stage by LCSGJ	I	II	III	IV
TNM stage by liver Cancer Study Group of Japan (LCSGJ) criteria				
Factors	I. Single	II. Size <2 cm		III. No vessel invasion
T1	Fulfilling three factors			
T2	Fulfilling two factors			
T3	Fulfilling one factor			
T4	Fulfilling 0 factors			
Stage I	T1N0M0			
Stage II	T2N0M0			
Stage III	T3N0M0			
Stage IV-A	T4N0M0 or Any TN1M0			
Stage IV-B	Any T N0 or N1M1			

Table 6 – Definition of the Tokyo scoring system for hepatocellular carcinoma.

Variables	Score		
	0	1	2
Albumin (g/dl)	>3.5	2.8–3.5	<2.8
Bilirubin (mg/dl)	<1	1–2	>2
Tumour size (cm)	<2	2–5	>5
Tumour number	⩽3		>3

2. Patients and methods

2.1. Patients

The medical records with a diagnosis of HCC in the National Taiwan University Hospital from January 1981 to June 2000 were retrospectively reviewed. Those who received their initial treatments for HCC at other hospitals were excluded. A total of 3593 Taiwanese HCC patients were collected. The ratio of male to female patients was 4.04 (2880/713). The overall mean age was 56.3 ± 14.0 years. The diagnosis of HCC was confirmed by histopathological examination of either surgical samples or needle biopsy specimens in 1773 patients (49.4%), by typical image pictures plus -fetoprotein (AFP) higher than 400 ng/mL in 967 patients (26.9%) and by typical image pictures in 853 patients (23.7%).

The initial treatments were classified into four categories: (i) surgical resection, (ii) percutaneous ethanol injection therapy (PEIT), (iii) transcatheter arterial chemoembolisation (TACE) and (iv) chemotherapy or supportive care. Generally speaking, all patients were first evaluated for the possibility of curative treatment (surgical resection or local treatment). If the HCC was not suitable for curative treatment and patients had preserved liver function and portal vein was patent, TACE was considered. Patients who were not qualified for TACE were considered for investigational protocols using systemic chemotherapy or best supportive care. Before the year 2000, very few of our patients received liver transplantation for HCCs in our hospital.

2.2. Variables collection

The following variables at the time of HCC diagnosis were collected: name, sex, chart number, national citizen identification number, birthday, address, zip code, WBC, haemoglobin, platelet, prothrombin time, albumin, bilirubin, aspartate aminotransferases (ASTs), alanine aminotransferase (ALT), alkaline phosphatase (ALP), blood urea nitrogen (BUN), creatinine, serum alpha-fetoprotein (AFP), hepatitis B surface antigen (HBsAg), antibody for hepatitis C virus (anti-HCV), presence of liver cirrhosis, ascites, encephalopathy, evidences of portal vein invasion, tumour size, tumour location, diagnostic criteria for HCC, date of HCC diagnosis, modality of initial treatment, date of first recurrence and distant metastases. The cirrhosis was confirmed histologically in surgical patients. For most of the non-surgical patients, the presence of cirrhosis was assessed via clinical and radiological image studies. Okuda stage (Table 1), TNM stage (Table 2), CLIP score (Table 3), BCLC stage (Table 4), JIS score (Table 5) and Tokyo score (Table 6) were calculated using these variables. Because we wanted to compare the six staging systems in our patients, only records with complete data that could be staged for all of the six staging systems were enrolled for the final analysis.

2.3. Searching for fatalities

To verify patients' deaths, we used the national citizen identification (ID) number of patients with HCC to search the mortality data bank established by the Statistics Office, Department of Health, Taiwan. The mortality data bank includes data from the certificate of death, which contains the demographic data of the patient; the time, place and cause of death; and the name of the person who issued the document. The mortality data bank included patients expired before 31st December 2001. Thus, cases that still survived after 31st December 2001 were right censored.

Please cite this article in press as: Chen C-H et al., Applicability of staging systems for patients with ..., *Eur J Cancer* (2009), doi:10.1016/j.ejca.2008.12.025

2.4. Univariate and multivariate analysis to identify predictors of survival

Descriptive statistical analysis was conducted. The log-rank test was used for univariate analysis of potential predictors of survival of HCC patients. Statistically significant variables at univariate analysis were further analysed using a multivariate Cox proportional hazard regression model with stepwise selection of variables. In addition, an all-possible-subset regression approach was taken to find the best eight variables for the purpose of prediction. Statistical significance was set at 0.05. An adjusted generalised R-square (R^2_G) was computed and the Gronnesby-Borgan goodness-of-fit test (X^2_{GB}) was conducted to assess the adequacy of the fitted Cox proportional hazard regression models.

2.5. Comparisons of different staging systems

The performance of a prognostic staging or scoring system has been shown to be related to homogeneity, discriminatory ability and monotonicity of gradients.[15,16] The statistics were done as described before.[16] In brief, a Cox proportional hazard regression model was used to calculate the likelihood ratio (LR) χ^2 test to determine homogeneity. High homogeneity indicates small differences in survival among patients in the same stages. The linear trend χ^2 test for staging was then used to measure the discriminatory ability of each staging system. A smaller value of Akaike information criterion (AIC) indicates a better fit of a staging system.

All statistical analyses were performed using the SAS software, Version 8 (Statistical Analysis System, Cary, NC, United States).

3. Results

The final cohort included 2010 HCC patients who did not have any missing data for the six staging systems, including 1566 male and 444 female patients. The HBsAg positive rate was 67%, while the anti-HCV positive rate was 33.6%. The tumour was larger than 5 cm in 48.1% of these HCC patients (Table 7). The initial treatment was surgical resection in 984 patients (49%), PEIT in 30 patients (1.5%), TACE in 518 patients (25.8%) and chemotherapy or supportive care in 478 patients (23.8%). The overall median survival among the 2010 Taiwanese HCC patients was 18.2 months, and the 1-, 2-, 3-, 5- and 10-year survival rates were 57.3%, 43.6%, 35.8%, 23.9% and 13.5%, respectively. Those who received surgical resection or PEIT had best survival, followed by TACE and supportive/chemotherapy (Fig. 1).

3.1. Baseline predictors of survival

Univariate analysis identified that HBsAg, anti-HCV, albumin, bilirubin, AFP, AST, ALP, creatinine, ascites, tumour size, tumour number, portal vein thrombosis and metastasis were significant baseline predictors of survival in patients with HCC (Table 7). In the multivariate Cox proportional hazard regression model, an all-possible-subset regression approach was taken to find the best eight predictors of survival. We

Table 7 – Univariate analysis of predictors of survival in 2010 Taiwanese patients with hepatocellular carcinoma.

Characteristics	No. of patients (%)	Median survival (months)	P-Value*
Age (years)			0.669
<40	212 (10.6)	10.0	
40–65	1197 (59.6)	18.0	
>65	601(29.9)	22.1	
Sex			0.1548
Male	1566 (77.9)	16.8	
Female	444 (22.1)	22.5	
Virology			
HBsAg (+)/(–)	1302 (67.0)/ 641 (33.0)	15.1/ 25.8	0.0004
Anti-HCV (+)/(–)	606 (33.6)/ 1198 (66.4)	25.8/15.3	0.012
Biochemical values			
Albumin (g/dL)			<0.0001
<2.8	174 (8.7)	3.8	
2.8–3.4	569 (28.3)	10.2	
≧3.5	1267 (63.0)	30.3	
Bilirubin, total (mg/dL)			<0.0001
<2	1717 (85.4)	22.2	
2–3	148 (7.4)	7.6	
>3	145 (7.2)	2.2	
AFP (ng/mL)			<0.0001
≦20	655(32.6)	30.1	
20–400	507 (25.2)	25.2	
≧400	848 (42.2)	9.1	
AST			<0.0001
<2 ULN	1314(65.4)	25.7	
≧2 ULN	696(34.6)	8.6	
ALT			0.8756
<2 ULN	1579 (78.6)	17.9	
≧2 ULN	431 (21.4)	20.4	
ALP			<0.0001
<2 ULN	1760 (87.6)	22.2	
≧2 ULN	250 (12.4)	3.7	
Creatinine (mg/dL)			0.0002
<1.5	1805(89.8)	18.5	
≧1.5	205 (10.2)	12.7	
Ascites			<0.0001
Yes	280 (13.9)	4.1	
No	1730 (86.1)	22.8	
Child-Pugh class			<0.0001
A	1666 (82.9)	24.6	
B	305 (15.2)	5.2	
C	39(2)	1.6	
Liver cirrhosis			0.0011
Yes	1331 (66.2)	18.4	
No	679 (33.8)	20.3	
Tumour number			<0.0001
Single	1274 (63.4)	21.6	
Multiple	736 (36.6)	14.5	
Size of tumour (cm)			<0.0001
≦3	591 (29.4)	38.7	
3–5	453(22.5)	29.2	
> 5	966 (48.1)	8.1	

Table 7 (continued)

Characteristics	No. of patients (%)	Median survival (months)	P-Value*
Portal vein thrombosis			<0.0001
Yes	388 (19.3)	4.2	
No	1622 (80.7)	25.7	
Metastasis			<0.0001
Yes	95 (4.7)	5.7	
No	1915 (95.3)	19.5	

HBsAg, hepatitis B surface antigen; Anti-HCV, antibodies to hepatitis; AFP, alpha-fetoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ULN, upper limit of normal; ALP, alkaline phosphatase.

* Log-rank test.

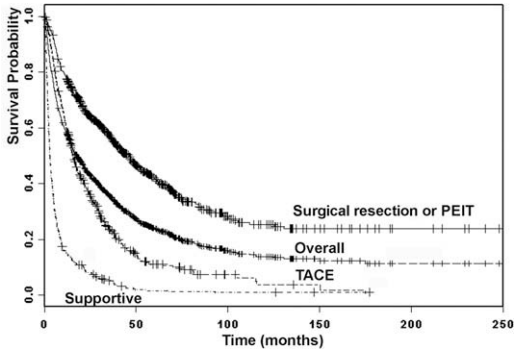

Fig. 1 – Kaplan–Meier estimated survival curves of 2010 HCC patients stratified according to initial treatment methods. PEIT, percutaneous ethanol injection therapy; TACE, transarterial chemoembolisation.

found that serum albumin level, serum total bilirubin levels, serum ALP level, serum AFP level, ascites, tumour size and portal vein invasion were statistically significant predictors of HCC patients' survival. We then generated the following equation, risk score = $2 \times (0.63 \times \text{alb1} + 0.98 \times \text{alb2} + 0.40 \times \text{alp} + 0.65 \times \text{as} + 0.44 \times \text{afp} + 0.05 \times \text{bil} + 0.58 \times \text{pvt} + 0.63 \times \text{size})$ to estimate the risk scores of HCC patients and called it the NATURE (NAtional Taiwan University Risk Estimation) scoring system (for the coding of each variable, see Table 8). A larger score indicates a higher risk of dying.

Using this risk scoring system, we categorised our HCC patients into the following four groups: NATURE 1, score $\leqslant 1$, NATURE 2, $1 < \text{score} \leqslant 2$, NATURE 3, $2 < \text{score} \leqslant 3$, NATURE 4, $3 < \text{score} \leqslant 4$, NATURE 5, $4 < \text{score} \leqslant 5$, NATURE 6, $5 < \text{score} \leqslant 6$ and NATURE 7, score $\geqslant 7$. As shown in Fig. 2, NATURE scores showed a significant difference in the probability of survival across different stages.

3.2. *Staging systems for HCC patients as a whole*

To compare different staging systems, we plotted the Kaplan–Meier survival curves for the Okuda, TNM, CLIP, BCLC, JIS and Tokyo staging systems. A comparative analysis of the NATURE scoring system with other scoring systems using the same cohort of patients from which the NATURE scoring system is derived is not fair. Obviously, NATURE might always win in the cohort from which it was derived. Thus, we did not include NATURE score in the comparison of staging systems.

As shown in Fig. 3, each staging system showed a significant difference in predicting the probability of survival across different stages. However, most of the staging systems had less differentiating power of survival at the advanced stages, such as Tokyo 5–8, JIS 4–5 and CLIP 4–6. For the HCC patients as a whole, Tokyo scoring system had the highest homogeneity, indicating small differences in survival among patients within the same stages (Table 9). The Tokyo staging system, followed by JIS staging, had the lowest AIC value, indicating that it was the most informative one for predicting the survival of HCC patients. In contrast, TNM systems had the lowest homogeneity and the lowest AIC value. If we stratified our patients on the basis of time of diagnosis, years 1980–1990 and years 1991–2000, the trend of AIC would have been the same (data not shown).

3.3. *Staging systems for HCC patients stratified by different treatments*

Because different staging systems have been developed using a set of HCC patients with advanced stages or are based on patients with earlier diseases, each staging system might have different predictive powers for HCC patients undergoing different treatments. Thus, we classified our HCC patients

Table 8 – The NATURE scoring system.

Predictors	0	1
alb_1	Albumin $\geqslant$ 3.5 (g/dL)	Albumin < 3.5 (g/dL)
alb_2	Albumin $\geqslant$ 2.8 (g/dL)	Albumin < 2.8 (g/dL)
alp	ALP < 2 × ULN	ALP $\geqslant$ 2 × ULN
as	No ascites	Ascites positive
afp	AFP < 400 ng/mL	AFP $\geqslant$ 400 ng/mL
bil	Bilirubin $\leqslant$ 3 (mg/dL)	Bilirubin > 3 (mg/dL)
pvt	Portal vein thrombosis (–)	Portal vein thrombosis (+)
size	Tumour size $\leqslant$ 5 cm	Tumour size > 5 cm

NATURE score = $2 \times (0.63 \times \text{alb\_1} + 0.98 \times \text{alb\_2} + 0.40 \times \text{alp} + 0.65 \times \text{as} + 0.44 \times \text{afp} + 0.05 \times \text{bil} + 0.58 \times \text{pvt} + 0.63 \times \text{size})$.
ULN, upper limit of normal; ALP, alkaline phosphatase; PVT, portal vein thrombosis; AFP, alpha-fetoprotein.

Please cite this article in press as: Chen C-H et al., Applicability of staging systems for patients with ..., *Eur J Cancer* (2009), doi:10.1016/j.ejca.2008.12.025

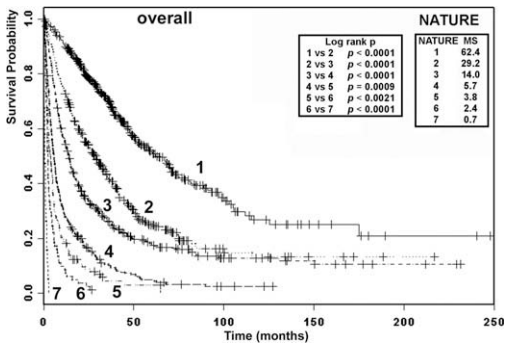

Fig. 2 – Kaplan–Meier estimated survival curves of 2010 HCC patients stratified by NATURE staging systems. MS: median survival (months).

according to the treatment modality. Our results demonstrated that the fitness of each staging system was not equal for patient groups stratified to different treatment methods (Table 9). For surgical patients, Tokyo scores, followed by CLIP scores, had the lowest AIC value. The TNM staging system had the highest AIC value (Table 9 and Fig. 4). Because only 30 patients received PEIT, we did not include this group of patient in the comparison of staging system. For HCC patients receiving TACE, Tokyo scores, followed by Okuda staging system, had the lowest AIC value (Table 9 and Fig. 5). For HCC patients receiving supportive or chemotherapy, CLIP scores, followed by BCLC staging system, had the lowest AIC value. Tokyo was only slightly better than TNM in this group of patients (Table 9 and Fig. 6).

4. Discussion

In this study, we used data from a large (n = 2010) cohort of patients with HCC that included different aetiologies of underlying chronic liver diseases, variable treatment methods and different stages: The HBsAg, albumin, bilirubin, AFP, AST, ALP, creatinine, ascites, tumour size, tumour number, portal vein thrombosis and metastasis as independent baseline predictors in our cohort. These independent predictors of survival for the HCC patients could be grouped into two major categories, those related to underlying liver reserve and those related to the tumour factors. These predictors were in collaboration with other predictors reported previously.[6–9,11–14]

Using Kaplan–Meier analysis, we showed that all staging systems revealed a progressive decrease in survival from the earliest to the most advanced stage. Among these staging systems, Tokyo system was the best at discriminating survival of HCC patients as a whole in different stages and had the greatest homogeneity of survival among patients within the same stage. However, if we stratified the HCC patients according to the treatment method, the ranking of fitness of each staging system changed. Tokyo system was much less informative for patients undergoing supportive care or chemotherapy. As the authors discussed in their manuscript, the applicability of the Tokyo score was limited by the fact that it was established and validated on the basis of HCC patients treated by medical ablation or surgical resection.[14] Therefore, it was not unexpected that Tokyo scoring system was of less use in predicting the survival of HCC patients with advanced diseases.

CLIP system[11] has been externally validated in Canadian,[17] Italian[18] and Japanese cohorts.[15] We found that CLIP system was the most suitable staging system for HCC patients receiving chemotherapy or supportive care. In the CLIP score, tumour morphology was divided into three categories: uninodular and extension ⩾50% of the size of the liver (score 0); multinodular and extension ⩽50% of the size of the liver (score 1) and massive or extension >50% of the size of the liver (score 2). Our result supported the concept that the tumour morphology criteria in CLIP are too general to apply to patients with HCC in countries where many early stage HCCs can be detected.[13] In addition, it has been demonstrated that

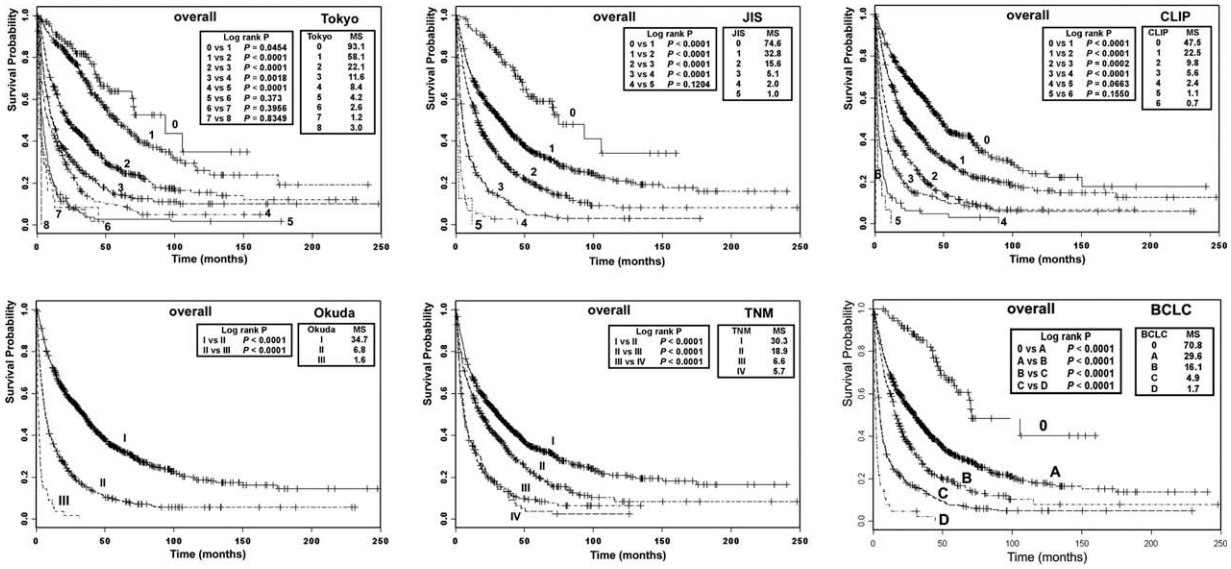

Fig. 3 – Kaplan–Meier estimated survival curves of 2010 HCC patients as a whole stratified by Tokyo, JIS, CLIP, Okuda, TNM and BCLC staging systems. MS: median survival (months).

Table 9 – Comparison of different HCC staging systems among 2010 HCC patients.

Staging system	Linear trend χ^2 value	LR χ^2 value	AIC
All patients (N=2010)			
Tokyo	279.1	552.2	19383.7
JIS	213.3	443.5	19492.3
CLIP	205.3	427.5	19508.3
BCLC	191.2	395.8	19540.1
Okuda	184.7	384.1	19551.7
TNM	93.3	153.0	19782.9
Surgical resection (N = 984)			
Tokyo	74.7	92.8	6630.5
CLIP	43.2	50.6	6672.7
Okuda	44.5	48.5	6674.8
BCLC	28.1	31.0	6692.4
JIS	21.9	26.1	6697.2
TNM	7.6	11.8	6711.5
TACE (N = 518)			
Tokyo	30.6	79.4	4547.9
Okuda	24.5	60.6	4566.7
CLIP	20.3	38.1	4589.2
JIS	21.6	29.2	4598.1
BCLC	8.3	16.0	4611.4
TNM	3.3	3.9	4623.4
Supportive (N = 478)			
CLIP	2.9	66.1	4799.1
BCLC	3.2	40.7	4824.5
Okuda	1.6	36.5	4828.6
JIS	2.4	33.9	4831.2
Tokyo	0.9	29.9	4835.2
TNM	0	0.7	4864.5

LR, likelihood ratio, AIC, Akaike information criterion, TACE, transarterial chemoembolisation.

patients in the same CLIP stage might be heterogeneous.[19] The difference in the survival of patients in the same stage might be due to the intragroup heterogeneity, not due to the effect of different treatments. Thus, it was not unexpected that CLIP score was more suitable for advanced HCC in our cohort.

American Association for the Study of Liver Diseases (AASLDs) endorsed BCLC staging system because BCLC could be used to guide the choice of treatments and estimate the life expectancy, while the other staging systems could only be used to predict survival.[3] However, there were substantial differences in the treatment algorithm between Japan guideline[38] and BCLC guideline.[3] The principle of HCC treatment in our institution was similar to those described in Japan guideline.[39] Several recent studies showed that surgical resection for HCC patients beyond BCLC criteria could offer better survival.[39–42] Thus, if the choice of treatment for HCC was not done according to BCLC guideline, the usefulness of predicting the survival by BCLC could be compromised. This might partially explain why BCLC was the best staging system to predict survival of HCC patients mostly in western countries, but not in eastern countries.

We demonstrated that the applicability of staging systems for patients with HCC was dependent on treatment methods. Because the staging systems have been developed using a set of HCC patients with advanced stages[8] or are based on patients with earlier diseases,[11,14] there may be different predictive powers using these current staging systems to predict prognosis for different patient groups. This implied that different staging systems might be needed for early versus advanced HCCs. Since the clinical presentation of HCC is tremendously heterogeneous, it is necessary to consider all known predictive factors from early to advanced stage in building a staging system that may serve as the best tool for prognostic prediction.[20]

Several studies have compared the predictive power of staging systems for the survival of patients with HCCs. As summarised in Table 10, different staging systems had different predictive powers of survival for patients with HCC in dif-

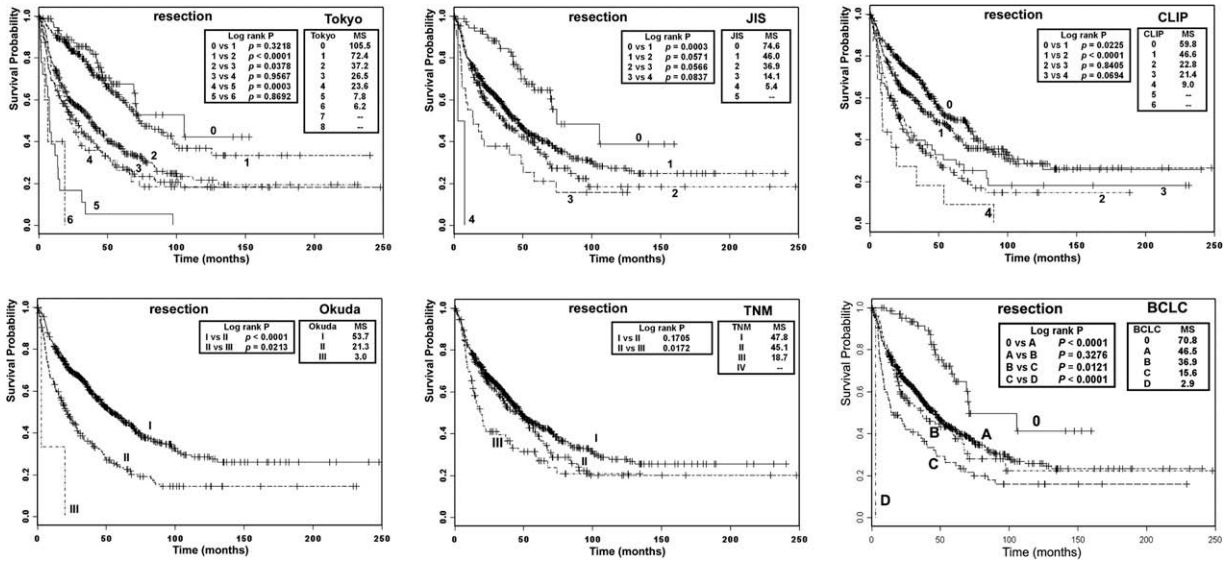

Fig. 4 – Kaplan–Meier estimated survival curves of HCC patients who underwent surgical resection stratified by Tokyo, JIS, CLIP, Okuda, TNM and BCLC staging systems. MS: median survival (months).

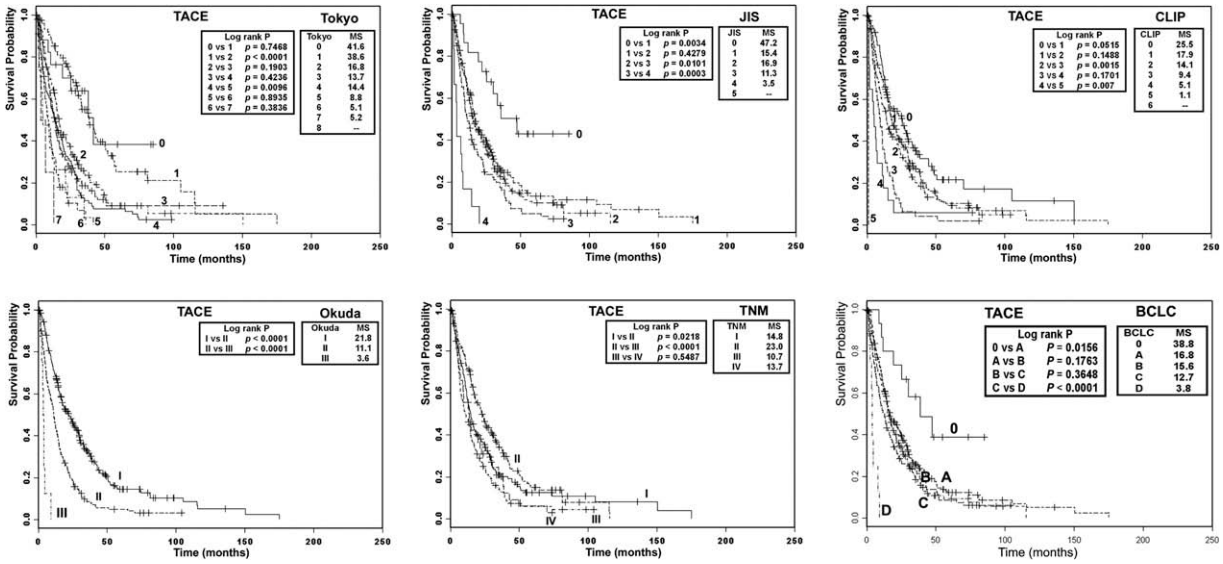

Fig. 5 – Kaplan–Meier estimated survival curves of HCC patients who underwent TACE stratified by Tokyo, JIS, CLIP, Okuda, TNM and BCLC staging systems. MS: median survival (months), TACE: transarterial chemoembolisation.

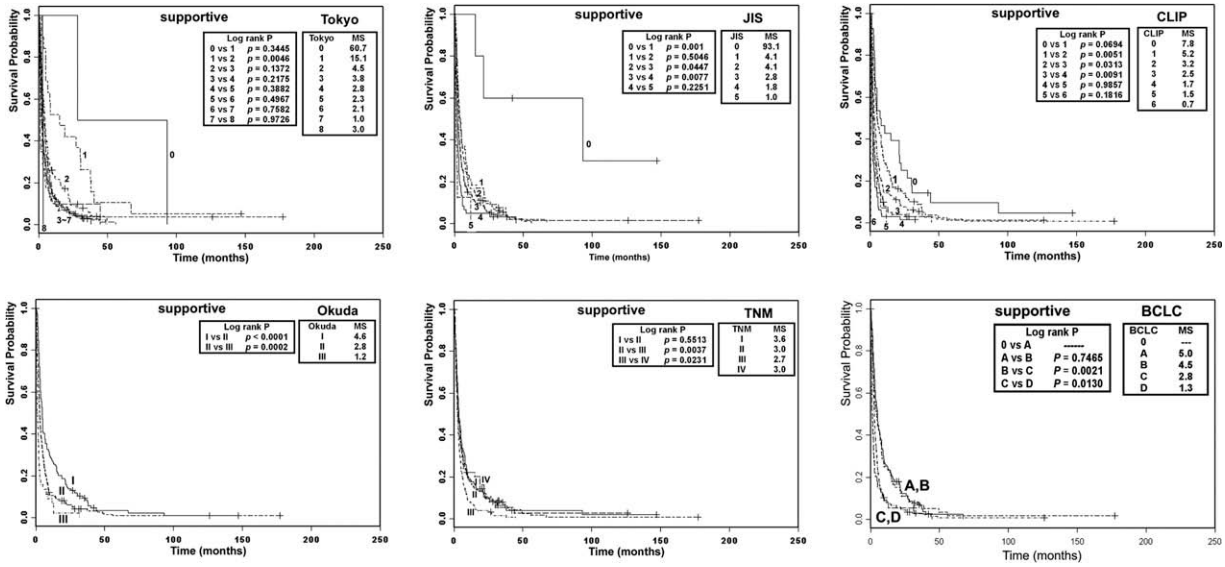

Fig. 6 – Kaplan–Meier estimated survival curves of HCC patients who received chemotherapy or supportive care stratified by Tokyo, JIS, CLIP, Okuda, TNM and BCLC staging systems. MS: median survival (months).

ferent countries. In eastern countries, most studies from Japan concluded JIS or modified JIS was the best staging system for their HCC patients.[21–24] Studies from China, Korea and Taiwan favoured either TNM[25–27] or CLIP[28–30] as the better staging system. In contrast, most studies from western countries concluded that either BCLC[16,31–35] or CLIP[17,36,37] was the best staging system for their HCC patients. It seemed that the best staging system for HCC patients in a certain country was the system developed from the country. However, such observation was debatable because each study enrolled different subgroups of HCC patients. The items of staging systems that are to be compared were also different among studies. Therefore, it was difficult to reach a very solid conclusion from these heterogeneous studies.

In conclusion, each staging system showed a significant difference in predicting the probability of survival across different stages. The Tokyo staging system was the most informative one for predicting the survival of HCC patients as a whole. The applicability of staging systems for patients with HCC was dependent on treatment methods. The best fit staging system for HCC patients receiving surgical resection or TACE was Tokyo staging system, and while it was CLIP

Please cite this article in press as: Chen C-H et al., Applicability of staging systems for patients with ..., *Eur J Cancer* (2009), doi:10.1016/j.ejca.2008.12.025

Table 10 – Comparison of different HCC staging systems in the literature.

Country	Published year	Case number	patient population	Comparison of staging systems	Ref.
Eastern country					
China	2008	234	Surgery	TNM > CLIP, CUPI, Okuda	[25]
Japan	2004	4525	All	JIS > CLIP	[43]
Japan	2005	210	Surgery	CLIP > JIS > Japan TNM > AJCC TNM	[44]
Japan	2005	1508	All	JIS > CLIP > BCLC	[21]
Japan	2006	230	Surgery	Modified JIS > modified CLIP > JIS > CLIP > Japan TNM	[22]
Japan	2007	235	Surgery	JIS > CUPI > BCLC > modified JIS > Tokyo > GRETCH > CLIP	[24]
Japan	2008	290	All	JIS > BCLC > Tokyo	[23]
Korea	2007	305	Radiotherapy	TNM > JIS, CLIP, Okuda	[26]
Korea	2008	131	TACE	CLIP > JIS > modified CLIP > modified JIS > Okuda > Child-Pugh score > BCLC	[28]
Taiwan	2005	599	Surgery	TNM > JIS, CLIP, Okuda	[27]
Taiwan	2007	382	Surgery	CLIP > JIS > BCLC > Okuda > CUPI > AJCC	[29]
Taiwan	2007	430	All	CLIP > JIS > BCLC	[30]
Western country					
Canada	2002	257	All	CLIP > Okuda	[17]
French	2008	538	Advanced	CLIP > BCLC, Okuda	[36]
Italy	2004	187	All	BLCL > CLIP > Okuda > French > CUPI	[31]
Italy	2005	268	Early to intermediate	BCLC $\geqslant$ CLIP > Okuda	[32]
Italy	2006	195	All	BCLC > TNM 6th > Okuda > CLIP > JIS	[33]
Italy	2008	406	All	CLIP > BCLC > GRETCH	[37]
Italy	2008	112	RFA	BCLC > Okuda > GRETCH > CUPI > JIS > TNM > CLIP	[34]
Spain	2006	115	All	BCLC > CLIP > Okuda > French	[35]
USA	2005	244	All	BCLC > GRETCH > Okuda > TNM > CLIP > CUPI > JIS	[16]
USA	2006	172	TACE	Child-Pugh scores > Okuda, CLIP, BCLC, GRETCH, CUPI, JIS, LCSGJ, Tokyo, TNM, MELD	[45]

>, indicates 'better than'; Ref, reference; RFA, radiofrequency ablation; TACE, transarterial chemoembolisation; GRETCH, Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire; CUPI, Chinese University Prognostic Index; CLIP, Cancer of the Liver Italian program; BCLC, Barcelona Clinic Liver Cancer; JIS, Japan Integrated Staging; MELD, model for end-stage liver disease; LCSGJ, Liver Cancer Study Group of Japan.

scores for HCC patients receiving chemotherapy or supportive care.

Conflict of interest statement

None declared.

Acknowledgements

This study was financially supported by the grants from the Department of Health, Taiwan (DOH90-HP-1002), the National Health Research Institute, Taiwan (NHRI-EX94-9204PP) and the Liver Disease Prevention and Treatment Research Foundation, Taiwan. We are indebted to our colleagues at the Cancer Registry, Office of Medical Record, NTUH, for their excellent work in the cancer registry system and to the physicians for their care of the patients. We also appreciate Miss Yu-Jen Lin's help for the statistical analyses.

REFERENCES

1. Parkin DM. Global cancer statistics in the year 2000. *Lancet Oncol* 2001;**2**:533–43.
2. Chen CH, Chen DS. Hepatocellular carcinoma: 30 years' experience in Taiwan. *J Formos Med Assoc* 1992;**91**(Suppl. 3): S187–202.
3. Bruix J, Sherman M. Management of hepatocellular carcinoma. *Hepatology* 2005;**42**:1208–36.
4. Sheu JC, Sung JL, Chen DS, et al. Early detection of hepatocellular carcinoma by real-time ultrasonography. A prospective study. *Cancer* 1985;**56**:660–6.
5. Blum HE. Treatment of hepatocellular carcinoma. *Best Pract Res Clin Gastroenterol* 2005;**19**:129–45.
6. Okuda K, Ohtsuki T, Obata H, et al. Natural history of hepatocellular carcinoma and prognosis in relation to treatment. Study of 850 patients. *Cancer* 1985;**56**:918–28.
7. Chevret S, Trinchet JC, Mathieu D, Rached AA, Beaugrand M, Chastang C. A new prognostic classification for predicting survival in patients with hepatocellular carcinoma. Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire. *J Hepatol* 1999;**31**:133–41.
8. Leung TW, Tang AM, Zee B, et al. Construction of the Chinese University Prognostic Index for hepatocellular carcinoma and comparison with the TNM staging system, the Okuda staging system, and the Cancer of the Liver Italian Program staging system: a study based on 926 patients. *Cancer* 2002;**94**:1760–9.
9. Vauthey JN, Lauwers GY, Esnaola NF, et al. Simplified staging for hepatocellular carcinoma. *J Clin Oncol* 2002;**20**:1527–36.
10. Greene FL, Page DL, Fleming ID, et al. *AJCC cancer staging manual*. 6th ed. Chicago, USA: Springer; 2002.
11. The Cancer of the Liver Italian Program (CLIP) investigators. A new prognostic system for hepatocellular carcinoma: a retrospective study of 435 patients. *Hepatology* 1998;**28**:751-5.
12. Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. *Semin Liver Dis* 1999;**19**:329–38.
13. Kudo M, Chung H, Osaki Y. Prognostic staging system for hepatocellular carcinoma (CLIP score): its value and limitations, and a proposal for a new staging system, the

Japan Integrated Staging Score (JIS score). *J Gastroenterol* 2003;**38**:207–15.
14. Tateishi R, Yoshida H, Shiina S, et al. Proposal of a new prognostic model for hepatocellular carcinoma: an analysis of 403 patients. *Gut* 2005;**54**:419–25.
15. Ueno S, Tanabe G, Sako K, et al. Discrimination value of the new western prognostic system (CLIP score) for hepatocellular carcinoma in 662 Japanese patients. Cancer of the Liver Italian Program. *Hepatology* 2001;**34**:529–34.
16. Marrero JA, Fontana RJ, Barrat A, et al. Prognosis of hepatocellular carcinoma: comparison of 7 staging systems in an American cohort. *Hepatology* 2005;**41**:707–16.
17. Levy I, Sherman M. Staging of hepatocellular carcinoma: assessment of the CLIP, Okuda, and Child-Pugh staging systems in a cohort of 257 patients in Toronto. *Gut* 2002;**50**:881–5.
18. Farinati F, Rinaldi M, Gianni S, Naccarato R. How should patients with hepatocellular carcinoma be staged? Validation of a new prognostic system. *Cancer* 2000;**89**:2266–73.
19. Lin CY, Kee KM, Wang JH, et al. Is the Cancer of the Liver Italian Program system an adequate weighting for survival of hepatocellular carcinoma? Evaluation of intrascore prognostic value among 36 subgroups. *Liver Int* 2009;**29**:74–81.
20. Huo TI, Wu JC, Lee SD. Comparison of staging systems for HCC: one more positive answer or mission impossible? *Hepatology* 2005;**42**:238–9.
21. Toyoda H, Kumada T, Kiriyama S, et al. Comparison of the usefulness of three staging systems for hepatocellular carcinoma (CLIP, BCLC, and JIS) in Japan. *Am J Gastroenterol* 2005;**100**:1764–71.
22. Nanashima A, Sumida Y, Abo T, et al. Modified Japan Integrated Staging is currently the best available staging system for hepatocellular carcinoma patients who have undergone hepatectomy. *J Gastroenterol* 2006;**41**:250–6.
23. Chung H, Kudo M, Takahashi S, et al. Comparison of three current staging systems for hepatocellular carcinoma: Japan integrated staging score, new Barcelona Clinic Liver Cancer staging classification, and Tokyo score. *J Gastroenterol Hepatol* 2008;**23**:445–52.
24. Kondo K, Chijiiwa K, Nagano M, et al. Comparison of seven prognostic staging systems in patients who undergo hepatectomy for hepatocellular carcinoma. *Hepatogastroenterology* 2007;**54**:1534–8.
25. Lu W, Dong J, Huang Z, Guo D, Liu Y, Shi S. Comparison of four current staging systems for Chinese patients with hepatocellular carcinoma undergoing curative resection: Okuda, CLIP, TNM and CUPI. *J Gastroenterol Hepatol*, in press.
26. Seong J, Shim SJ, Lee IJ, Han KH, Chon CY, Ahn SH. Evaluation of the prognostic value of Okuda, Cancer of the Liver Italian Program, and Japan Integrated Staging systems for hepatocellular carcinoma patients undergoing radiotherapy. *Int J Radiat Oncol Biol Phys* 2007;**67**:1037–42.
27. Huang YH, Chen CH, Chang TT, et al. Evaluation of predictive value of CLIP, Okuda, TNM and JIS staging systems for hepatocellular carcinoma patients undergoing surgery. *J Gastroenterol Hepatol* 2005;**20**:765–71.
28. Cho YK, Chung JW, Kim JK, et al. Comparison of 7 staging systems for patients with hepatocellular carcinoma undergoing transarterial chemoembolization. *Cancer* 2008;**23**:1874–8.
29. Chen TW, Chu CM, Yu JC, et al. Comparison of clinical staging systems in predicting survival of hepatocellular carcinoma patients receiving major or minor hepatectomy. *Eur J Surg Oncol* 2007;**33**:480–7.
30. Huo TI, Lin HC, Hsia CY, et al. The model for end-stage liver disease based cancer staging systems are better prognostic models for hepatocellular carcinoma: a prospective sequential survey. *Am J Gastroenterol* 2007;**102**:1920–30.
31. Cillo U, Bassanello M, Vitale A, et al. The critical issue of hepatocellular carcinoma prognostic classification: which is the best tool available? *J Hepatol* 2004;**40**:124–31.
32. Grieco A, Pompili M, Caminiti G, et al. Prognostic factors for survival in patients with early-intermediate hepatocellular carcinoma undergoing non-surgical therapy: comparison of Okuda, CLIP, and BCLC staging systems in a single Italian centre. *Gut* 2005;**54**:411–8.
33. Cillo U, Vitale A, Grigoletto F, et al. Prospective validation of the Barcelona Clinic Liver Cancer staging system. *J Hepatol* 2006;**44**:723–31.
34. Guglielmi A, Ruzzenente A, Pachera S, et al. Comparison of seven staging systems in cirrhotic patients with hepatocellular carcinoma in a cohort of patients who underwent radiofrequency ablation with complete response. *Am J Gastroenterol* 2008;**103**:597–604.
35. Pascual S, Zapater P, Such J, et al. Comparison of staging systems to predict survival in hepatocellular carcinoma. *Liver Int* 2006;**26**:673–9.
36. Collette S, Bonnetain F, Paoletti X, et al. Prognosis of advanced hepatocellular carcinoma: comparison of three staging systems in two French clinical trials. *Ann Oncol* 2008;**19**:1117–26.
37. Camma C, Di Marco V, Cabibbo G, et al. Survival of patients with hepatocellular carcinoma in cirrhosis: a comparison of BCLC, CLIP and GRETCH staging systems. *Aliment Pharmacol Ther* 2008;**28**:62–75.
38. Makuuchi M, Kokudo N, Arii S, et al. Development of evidence-based clinical guidelines for the diagnosis and treatment of hepatocellular carcinoma in Japan. *Hepatol Res* 2008;**38**:37–51.
39. Ho MC, Huang GT, Tsang YM, et al. Liver selection improves the survival of patients with multiple hepatocellular carcinomas. *Ann Surg Oncol*, in press.
40. Wang JH, Changchien CS, Hu TH, et al. The efficacy of treatment schedules according to Barcelona Clinic Liver Cancer staging for hepatocellular carcinoma – survival analysis of 3892 patients. *Eur J Cancer* 2008;**44**:1000–6.
41. Ishizawa T, Hasegawa K, Aoki T, et al. Neither multiple tumors nor portal hypertension are surgical contraindications for hepatocellular carcinoma. *Gastroenterology* 2008;**134**:1908–16.
42. Torzilli G, Donadon M, Marconi M, et al. Hepatectomy for stage B and stage C hepatocellular carcinoma in the Barcelona Clinic Liver Cancer classification: results of a prospective analysis. *Arch Surg* 2008;**143**:1082–90.
43. Kudo M, Chung H, Haji S, et al. Validation of a new prognostic staging system for hepatocellular carcinoma: the JIS score compared with the CLIP score. *Hepatology* 2004;**40**:1396–405.
44. Nanashima A, Omagari K, Tobinaga S, et al. Comparative study of survival of patients with hepatocellular carcinoma predicted by different staging systems using multivariate analysis. *Eur J Surg Oncol* 2005;**31**:882–90.
45. Georgiades CS, Liapi E, Frangakis C, et al. Prognostic accuracy of 12 liver staging systems in patients with unresectable hepatocellular carcinoma treated with transarterial chemoembolization. *J Vasc Interv Radiol* 2006;**17**:1619–24.

Please cite this article in press as: Chen C-H et al., Applicability of staging systems for patients with ..., *Eur J Cancer* (2009), doi:10.1016/j.ejca.2008.12.025