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BRIEF ARTICLE

Staging systems for predicting survival of patients with hepatocellular carcinoma after surgery

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Abstract

AIM: To compare the staging systems for stratifying and predicting the prognosis of patients with hepatocellular carcinoma (HCC) after partial hepatectomy (PH).

METHODS: Clinical data about 438 HCC patients who underwent PH from January 1991 to December 2004 at our hospital were retrospectively analyzed. Tumor stage was evaluated following the Chinese tumor node metastasis (TNM) and barcelona clinic liver cancer (BCLC) staging systems, respectively. Survival curves for the HCC patients were plotted using the Kaplan-Meier method and differences were compared by the log-rank test. The accuracy of each system for predicting death of HCC patients was evaluated by calculating the area under the receiver operating characteristic curve.

RESULTS: The HCC patients were classified into stages Ⅰ-Ⅲ, stages Ⅰ-Ⅳ and stages A-C, according to the 3 staging systems, respectively. Log-rank test showed that the cumulative survival rate was significantly different for the HCC patients at 3 Chinese system stages, TNM stages Ⅰ and Ⅱ, TNM stages Ⅲ and Ⅳ, and 3 BCLC stages ($P < 0.05$). However, no significant difference was found in the HCC patients at TNM stages Ⅱ and Ⅲ. The accuracy of the Chinese and BCLC staging systems was higher than that of the TNM staging system for predicting the survival rate of HCC patients.

CONCLUSION: The Chinese and BCLC staging systems are better for stratifying and predicting the prognosis of HCC patients after PH than the TNM staging system.

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INTRODUCTION

Hepatocellular carcinoma (HCC), one of the most common cancers in the world, especially in Eastern Asia, with a poor prognosis[1], is the first leading cause of cancer-related death in the southeast of China[2]. Treatment modalities for HCC are strongly dependent on tumor stage

and the underlying liver diseases. Surgical intervention is the only potentially curative modality for it at present. However, the long-term prognosis of HCC patients remains dismal even after radical excision or liver transplantation[3].

Staging systems are used to define the prognosis of HCC and its treatment[4]. Generally, a better clinical staging system can stratify patients according to their survival time, and is reliable and useful for comparing the curative effects on HCC. Several HCC staging systems have been proposed, such as the Okuda staging system[5], tumor node metastasis (TNM) staging system of the American Joint Committee on Cancer (AJCC)[6], cancer of the liver Italian program (CLIP) scoring system[7], Barcelona clinic liver cancer (BCLC) staging classification[8], Japan integrated staging (JIS) score[9], and Tokyo score[10]. However, no worldwide consensus has been reached on the use of any given HCC staging systems. Therefore, more accurate classification of HCC patients with a homogeneous prognosis would at minimum improve the application of currently available treatment modalities.

The Chinese staging system, established by the Chinese Society of Liver Cancer (CSLC) in 1999[11,12], combines the tumor-related factors and liver function reserve. However, its application in stratifying and predicting the prognosis of HCC patients remains to be defined. This study was to evaluate and compare the Chinese staging system, the AJCC TNM staging system (7th edition) and the BCLC staging system for stratifying and predicting the prognosis of a large cohort of Chinese HCC patients after partial hepatectomy (PH).

MATERIALS AND METHODS

Patients
Four hundred and thirty-eight patients with HCC who underwent PH from January 1991 to December 2004 at our hospital were included in this study. The diagnosis of HCC was pathologically confirmed. Clinicopathological features and survival rates of the patients were analyzed. The study was approved by the Ethical Committee of Sun Yat-Sen Memorial Hospital and in accordance with the Helsinki Declaration of 1975. Written informed consent was obtained from the patients or their guardians.

Tumor stage
HCC was divided into different stages following the criteria for the Chinese, TNM and BCLC staging systems, respectively. The detailed definition and criteria for the Chinese staging system are listed in Table 1.

Treatment
All patients underwent non-anatomical resection. According to the Couinaud's nomenclature for liver segmentation, minor hepatectomy (1-2 segments), major hepatectomy (≥ 3 segments), and wedge resection were performed in 179 (40.9%), 47 (10.9%), and 212 (48.2%) patients, respectively. Of the 438 patients, 24 (5.5%) with

Table 1 Definition and criteria of Chinese staging system for hepatocellular carcinoma (1999)

Stage	Tumor	Thrombi	CLN metastasis	Distant metastasis	Child-Pugh score
I a	Solitary ≤ 3 cm	No	No	No	A
I b	Solitary or two ≤ 5 cm in single lobe	No	No	No	A
II a	Solitary or two ≤ 10 cm in single lobe, or two ≤ 5 cm in bilateral lobes	No	No	No	A
II b	Solitary or two > 10 cm in single lobe, or two > 5 cm in bilateral lobes	No	No	No	A
	Any	PV-branch, HV or BD	No	No	A
	Any	No	No	No	B
III a	Any	PV-trunk or IVC	Yes/No	Yes/No	A/B
	Any	Yes/No	Yes	Yes/No	A/B
	Any	Yes/No	Yes/No	Yes	A/B
III b	Any	Yes/No	Yes/No	Yes/No	C

CLN: Celiac lymph nodes; PV: Portal vein; HV: Hepatic vein; BD: Bile duct; IVC: Inferior vena cava.

unresectable HCC underwent surgery after trans-catheter hepatic arterial chemoembolization (TACE, down-staged). Moreover, HCC patients with inoperable intrahepatic recurrence or extrahepatic metastases received combined therapies, including TACE, radiofrequency ablation (RFA), microwave coagulation therapy (MCT), percutaneous ethanol injection (PEI), and biotherapy or traditional Chinese therapy.

Follow-up
During the first 6 mo after operation, the patients were re-examined every 1-2 mo followed by every 3-6 mo. The clinical, laboratory and radiological (abdominal computed tomography scan and chest X-ray) data were collected at each follow-up. Three hundred and ninety-two (89.5%) HCC patients were followed-up until the end of January 2005 or death, while 46 (10.5%) HCC patients were lost during the follow-up. The median follow-up time was 21 mo (range 1-156 mo).

Statistical analysis
Statistical analysis was conducted with the SPSS software package (version 13.0, SPSS, Chicago, IL). Quantitative data were presented as mean ± SE. Survival curves for the HCC patients were plotted using the Kaplan-Meier method and examined by the log-rank test. The accuracy of each system for predicting the 1-, 3-, and 5-year rates of HCC patients was evaluated by calculating the area under the receiver operating characteristic curve. Patients censored before 1, 3 and 5 years were excluded from the analysis. $P < 0.05$ was considered statistically significant.

Table 2 Characteristics of hepatocellular carcinoma patients enrolled in this study

Characteristics	n (%)
Sex	
Male	380 (86.8)
Female	58 (13.2)
Age (yr)	
≤ 50	235 (53.6)
> 50	203 (46.4)
Child-Pugh score	
Class A	391 (89.3)
Class B	47 (10.7)
Tumor number	
Single	374 (85.4)
Two	29 (6.6)
Multiple	35 (8)
Tumor size (cm)	
≤ 5	166 (37.9)
> 5	272 (62.1)
Tumor location	
Single lobe	389 (88.8)
Bilateral lobes	49 (11.2)
Capsular invasion	
With	346 (79)
Without	92 (21)
Vascular invasion	
With	84 (19.2)
Without	354 (80.8)
Lymph node metastasis	
With	11 (2.5)
Without	427 (97.5)
Extra-hepatic metastasis	
With	7 (1.6)
Without	431 (98.4)
Histological grade	
G1	129 (29.5)
G2	188 (42.9)
G3	121 (27.6)

Table 3 Overall survival rates of hepatocellular carcinoma patients according to their tumor stage

Tumor stage	n	Survival rate (%)		
		1-yr	3-yr	5-yr
CS				
I	132	0.916	0.760	0.693
II	265	0.622	0.426	0.281
III	41	0.330	0.126	0.126
TNM				
I	271	0.825	0.652	0.548
II	67	0.521	0.354	0.216
III	82	0.437	0.235	0.153
IV	18	0.278	/	/
BCLC				
A	178	0.870	0.678	0.602
B	165	0.756	0.574	0.402
C	95	0.375	0.182	0.142

CS: Chinese staging; TNM: Tumor node metastasis; BCLC: Barcelona clinic liver cancer.

Table 4 Accuracy of three staging systems for the death of hepatocellular carcinoma patients 1, 3 and 5 years after partial hepatectomy

System	AUC (95% CI)		
	1-yr death	3-yr death	5-yr death
CS	0.709 (0.658-0.761)	0.703 (0.645-0.761)	0.720 (0.648-0.791)
TNM	0.718 (0.662-0.774)	0.702 (0.646-0.759)	0.695 (0.629-0.760)
BCLC	0.730 (0.675-0.785)	0.701 (0.644-0.757)	0.710 (0.645-0.776)

AUC: Area under the receiver operating characteristic curve; CI: Confidence interval; CS: Chinese staging; TNM: Tumor node metastasis; BCLC: Barcelona clinic liver cancer.

RESULTS

Clinicopathological features and survival of HCC patients

The general characteristics of the 438 HCC patients are summarized in Table 2. The mean and median ages of the patients were 50.0 ± 0.6 years and 49.0 years (range: 35-68 years), respectively. By the end of follow up, 223 HCC patients (50.9%) died. The 1-, 3- and 5-year postoperative overall survival rates were 72.2%, 53.5% and 43.3%, respectively, for the patients after PH.

Prognosis stratification according to the three clinical staging systems

The 438 HCC patients were classified into stages I -III, stages I -IV and stages A-C according to the Chinese, TNM and BCLC staging systems, respectively. The log-rank test showed that the cumulative survival rate was significantly different for the HCC patients at 3 Chinese system stages, TNM stages I and II, TNM stages III and IV, and 3 BCLC stages (Table 3 and Figure 1, $P < 0.05$). However, no significant difference was found in the HCC patients at TNM stages II and III ($P > 0.05$).

Accuracy of the three clinical staging systems for predicting survival rate of HCC patients

The accuracy of 3 staging systems for predicting the survival rate of HCC patients 1, 3 and 5 years after PH is summarized in Table 4. The accuracy of the Chinese and BCLC staging systems was higher than that of the TNM staging system for predicting the survival rates of HCC patients (Figure 2).

DISCUSSION

HCC is the second most lethal cancer after pancreatic ductal adenocarcinoma, leading to about 600 000 deaths every year worldwide, with nearly 55% of the deaths occurred in China alone[3]. The long term prognosis of HCC patients is extremely dismal and the incidence of HCC is continuously growing globally[1,13,14]. In the southeast of China, HCC is the leading cause of cancer-related death despite aggressive conventional therapies[2]. Surgery remains the most effective treatment of HCC with a curative potential[15,16]. However, HCC patients even after curative resection of the tumor often have a high rate of relapse.
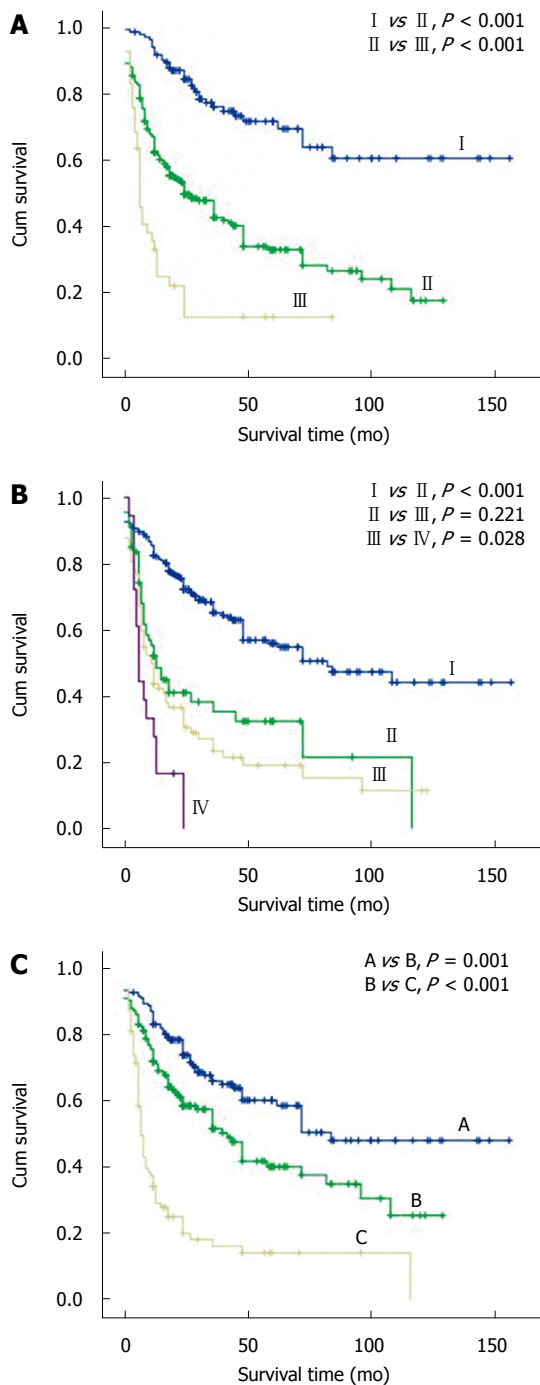
Figure 1 Survival curves for hepatocellular carcinoma patients according to the Chinese staging system (A), tumor node metastasis staging system (B), barcelona clinic liver cancer staging system (C).
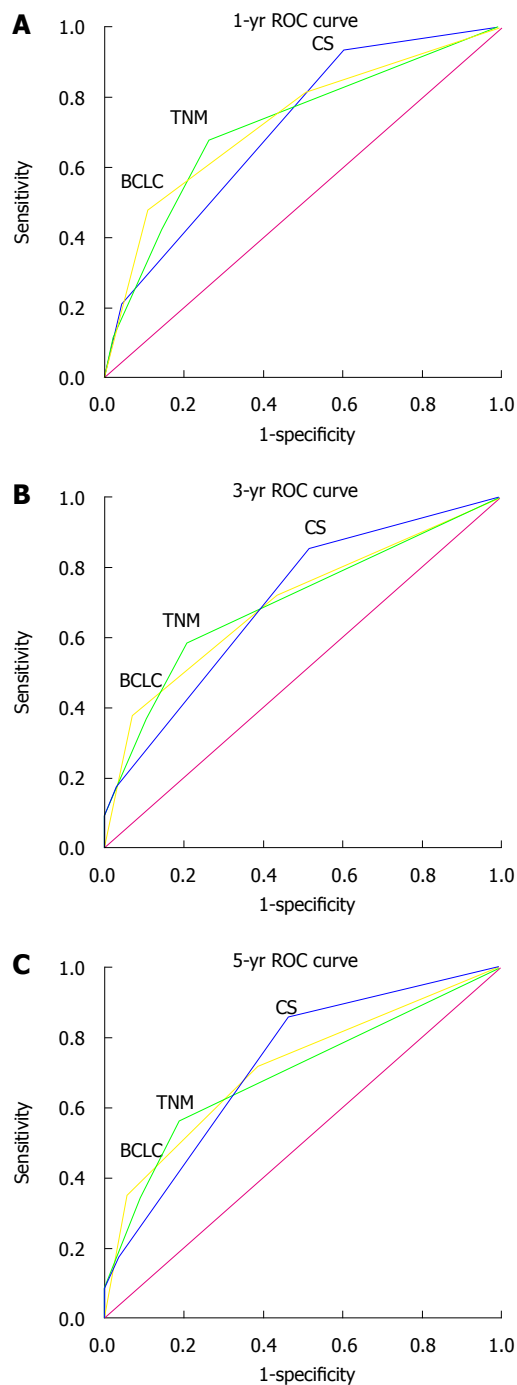

Figure 2 Accuracy of the three staging systems for predicting the 1-year (A), 3-year (B), 5-year (C) survival rates of hepatocellular carcinoma patients. ROC: Receiver operating characteristic curve; CS: Chinese staging; TNM: Tumor node metastasis; BCLC: Barcelona clinic liver cancer.

Therefore, tools that can be used to stratify the prognosis of HCC patients after therapy are urgently needed. Gene-expression analysis has led to the successful molecular classification of HCC according to its prognosis, aetiology and intra-hepatic recurrence[17]. However, it has not been widely accepted due to its high cost.

Staging systems are often used to select primary and adjunctive therapies and to assess their outcome. Generally, a well defined clinical staging system not only can classify HCC patients and predict their survival time, but

also can be generally applied globally. Increasing evidence shows that liver function reserve and tumor-related factors can also significantly influence the prognosis of HCC patients[4]. Chen *et al*[18] reported that a better staging system can provide more valid tumor-related factors and liver function parameters. Therefore, both tumor-related features and liver function reserve should be included in the clinical staging systems for HCC[19].

Several clinical staging systems are available for pre-

dicting the prognosis of HCC patients after PH at present. However, no worldwide consensus has been reached on which staging system is the best for predicting the prognosis of HCC patients after surgery[20]. Although the Okuda staging system[5], CLIP scoring system[7], JIS score[9], and Tokyo score[10] are widely used, they have been mostly applied to unresectable HCC, and none is universally accepted[21]. The TNM staging system is the most widely used system worldwide at present[21]. However, the AJCC TNM staging system does not include any measurement of liver functions and is thus not widely used[20]. Llovet *et al*[22] reported that the AJCC TNM staging system fails to adequately stratify HCC patients and predict their prognosis. Lu *et al*[23] also reported that the TNM staging system provides inadequate information for the prognosis of HCC patients.

In the present study, application of the CS system in stratifying and predicting prognosis of a large cohort of Chinese HCC patients ($n = 438$) after PH was investigated and compared to that of the AJCC TNM and BCLC staging systems. The log-rank test showed that the cumulative survival rate was significantly different for HCC patients at Chinese system stages, TNM stages Ⅰ and Ⅱ, TNM stages Ⅲ and Ⅳ, and 3 BCLC stages, while no significant difference was found in the cumulative survival rate of HCC patients at TNM stages Ⅱ and stage Ⅲ. The accuracy of the Chinese and BCLC staging systems was higher than that of the TNM staging system for predicting the long-term survival (3- and 5-year) rates of HCC patients after PH, indicating that the Chinese and BCLC staging systems are better than the TNM staging system for stratifying and predicting the prognosis of HCC patients after PH. In our study, the AJCC TNM staging system could not accurately stratify the HCC patients with multiple nodules or vascular/peripheral invasion.

In conclusion, the Chinese and BCLC staging systems are better than the AJCC TNM staging system for stratifying and predicting the prognosis of HCC patients after PH. Further studies are needed to establish a single, worldwide staging system that can stratify and predict the prognosis of HCC patients after PH.

COMMENTS

Background
Staging systems are used to define the prognosis and treatment of hepatocellular carcinoma (HCC) patients. Several staging systems are available for predicting the prognosis of HCC patients, but no worldwide consensus has been reached on the use of any given HCC staging systems. Therefore, more accurate classification of HCC patients with homogeneous prognosis is urgently needed.

Research frontiers
Although the Okuda and cancer of the liver Italian program scoring systems, Japan integrated staging score, and Tokyo score are widely used, they have been mostly applied to unresectable HCC patients. The tumor node metastasis (TNM) staging system for HCC does not include any measurement of liver functions and is thus not widely used. The Chinese staging system for stratifying and predicting the prognosis of HCC patients remains to be defined.

Innovations and breakthroughs
The Chinese staging system was studied for stratifying and predicting the prognosis of HCC patients. Furthermore, the applicability of the Chinese staging system was compared with other staging systems for stratifying and predicting the prognosis of HCC patients after partial hepatectomy.

Applications
The results of this study demonstrate that the Chinese staging system can be used for predicting the prognosis of HCC patients after partial hepatectomy.

Peer review
The authors evaluated and compared the Chinese, American Joint Committee on Cancer (AJCC) TNM and Barcelona clinic liver cancer (BCLC) staging systems for stratifying and predicting the prognosis of a large cohort of Chinese HCC patients after partial hepatectomy. The results reveal that the Chinese and BCLC staging systems are better than AJCC TNM staging system for stratifying and predicting the prognosis of HCC patients after partial hepatectomy.

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