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Editorial Board Member of *World Journal of Clinical Cases*, Sunil Kumar Gupta, MBBS, MD, Reader (Associate Professor), Department of Dermatology, Venereology and Leprology, All India Institute of Medical Sciences, Gorakhpur, Gorakhpur 273008, Uttar Pradesh, India. dr.sunil_30@yahoo.co.in

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ORIGINAL ARTICLE

Retrospective Cohort Study

Clinical stages of recurrent hepatocellular carcinoma: A retrospective cohort study

Si-Yang Yao, Bin Liang, Yuan-Yuan Chen, Yun-Tian Tang, Xiao-Feng Dong, Tian-Qi Liu

ORCID number: Si-Yang Yao 0000-0001-5693-0002; Bin Liang 0000-0002-3250-3011; Yuan-Yuan Chen 0000-0002-8528-1731; Yun-Tian Tang 0000-0002-5266-4090; Xiao-Feng Dong 0000-0003-2099-2652; Tian-Qi Liu 0000-0002-8114-2566.

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Si-Yang Yao, Bin Liang, Yuan-Yuan Chen, Yun-Tian Tang, Xiao-Feng Dong, Tian-Qi Liu, Department of Hepatobiliary-Pancreatic-Splenic Surgery, The People's Hospital of Guangxi Zhuang Autonomous Region, Nanning 530021, Guangxi Zhuang Autonomous Region, China

Corresponding author: Tian-Qi Liu, PhD, Chief Doctor, Department of Hepatobiliary-Pancreatic-Splenic Surgery, The People's Hospital of Guangxi Zhuang Autonomous Region, No. 6 Taoyuan Road, Nanning 530021, Guangxi Zhuang Autonomous Region, China. gxljrqt@163.com

Abstract

BACKGROUND

Hepatocellular carcinoma (HCC) is the second leading cause of cancer-related death worldwide, and has relatively high recurrence rates. Few studies have been published on the clinical stages of recurrent HCC.

AIM

To assess the applicability of the Barcelona Clinic Liver Cancer (BCLC) staging for recurrent HCC and the need to establish clinical stage criteria for recurrent HCC.

METHODS

The clinicopathological data of 81 patients with recurrent HCC who were admitted to the Hospital of Guangxi Zhuang Autonomous Region from January 2013 to December 2017 were collected. The patients were divided into three groups according to the BCLC staging system as follows: (1) Group A with BCLC stage A, 51 patients; (2) Group B with BCLC stage B, 14 patients; and (3) Group C with BCLC stage C, 16 patients. The median time to tumor recurrence and the median overall survival were compared.

RESULTS

The median time to tumor recurrence in groups A, B, and C was 16 ± 1.5 mo, 10 ± 2.8 mo, and 6 ± 0.5 mo, respectively, with a statistically significant difference among them (χ^2 = 70.144, P < 0.05); no statistically significant difference was noted between group A and group B (χ^2 = 2.659, P > 0.05), although there were statistically significant differences between group A and group C and between group B and group C (χ^2 = 62.110, and 19.972, P < 0.05). The median overall survival in groups A, B, and C were 42 ± 5.1 mo, 22 ± 3.1 mo, and 13 ± 1.8 mo, respectively, with a statistically significant difference among them (χ^2 = 38.949, P < 0.05); there were statistically significant differences between group A and group B, group A

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and group C, and group B and group C (χ^2 = 9.577, 37.172, and 7.183, respectively; $P < 0.05$).

CONCLUSION

There are different prognoses in recurrent HCC patients according to the BCLC staging. Therefore, BCLC staging is applicable to recurrent HCC and it is essential to formulate clinical stage criteria for recurrent HCC.

Key Words: Clinical stages; Recurrent hepatocellular carcinoma; Barcelona Clinic Liver Cancer staging system

Core Tip: We analyzed the clinical and pathological data of 81 patients who developed recurrent hepatocellular carcinoma (HCC), with an aim to evaluate the applicability of the Barcelona Clinic Liver Cancer (BCLC) staging system for recurrent HCC. Our results indicate that BCLC staging is applicable to recurrent HCC and it is essential to formulate clinical stage criteria for recurrent HCC.

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INTRODUCTION

In 2012, there were 782500 patients with newly diagnosed hepatocellular carcinoma (HCC) (ranked 6th worldwide) and 745500 patients who died (ranked 2nd worldwide) [1]. The radical treatment methods for HCC include liver transplantation, surgical resection (SR), and radiofrequency ablation (RFA). Numerous studies have shown that although many patients receive curative treatment, tumor recurrence is quite common. For very early stage HCC patients, the 5-year disease-free survival (DFS) rates are 40.7% for SR and 29.3% for radiofrequency ablation. For early stage HCC patients, the 5-year DFS rates are 50.8% for SR and 14.1% for radiofrequency ablation[2]. However, even in patients who undergo liver transplantation, the tumor recurrence rate is up to 15%–20%[3]. Therefore, how to manage recurrent HCC is important in improving overall survival. To date, there have not been criteria of clinical stages for recurrent HCC. The Barcelona Clinic Liver Cancer (BCLC) staging system is regarded as the most reasonable staging criteria for primary HCC. However, whether it is suitable for recurrent HCC remains unclear. The aim of this study was to assess the applicability of the BCLC staging for recurrent HCC and the need to establish clinical stage criteria for recurrent HCC, and analyze the factors affecting the prognosis of recurrent HCC patients.

MATERIALS AND METHODS

Patients

Three hundred and fifty-six recurrent HCC patients who received curative hepatic resection or RFA as an initial treatment at the People's Hospital of Guangxi Zhuang Autonomous Region between January 2013 and December 2017 were considered candidates for this study. The inclusion criteria were as follows: (1) Pathological diagnosis of HCC; (2) No other malignant tumors or pregnancy-related disease, which may influence survival; (3) BCLC stage A, B, or C; (4) Child-Pugh level A or B; and (5) Complete clinicopathological data. Finally, 81 patients met these criteria and were enrolled. This study did not require approval from the institutional ethics committee or informed consent, and complied with the principles of the Declaration of Helsinki.

The patients were stratified into three groups based on BCLC criteria: A (performance status score = 1, single tumor or multiple tumors with a maximum diameter ≤ 30mm and tumor number ≤ 3), B (tumor number > 3 or multiple tumors with a maximum diameter > 30 mm), and C (radiological evidence of vascular invasion or extrahepatic metastasis).

Follow-up and definition of recurrence

All patients were regularly followed to identify recurrence by assessing the level of the tumor marker alpha-fetoprotein (AFP) or performing ultrasonography (US) or contrast-enhanced computed tomography (CT) every 3 mo in the first year after radical treatment and every 6 mo in the subsequent years thereafter. If recurrence was suspected, contrast-enhanced CT, contrast-enhanced US (CEUS), or contrast-enhanced magnetic resonance imaging (MRI) was performed to confirm the diagnosis. Recurrence was defined as: (1) Histopathological confirmation; and (2) Two or more imaging diagnoses of liver cancer.

Data collection

Clinical and pathological characteristics, including age, gender, AFP, HBsAg, HBV-DNA, tumor location, liver cirrhosis, tumor cell differentiation, treatment modalities, time to recurrence from last treatment, number of recurrences, and time of survival were collected from our electronic medical records or by telephone follow-up. All the patients were given antiviral treatment once they have positive HBV-DNA according to the guidelines of prevention and treatment for chronic hepatitis B (2010 version, China)[4].

Statistical analysis

Continuous variables were assessed for normality and are expressed as the mean ± SD, and comparisons among groups were evaluated by ANOVA. Categorical variables were compared by Chi-square test or Fisher's exact test with small expected frequencies (< 5). Survival time is presented in months. Survival curves and recurrence curves for recurrent HCC patients were analyzed by the Kaplan-Meier method and the differences were analyzed by the log-rank test. All statistical analyses were performed using SPSS for Windows version 19.0 and P values < 0.05 were considered significant.

RESULTS

Baseline data comparison

We identified 81 patients, and all of them underwent a complete follow-up. The follow-up time ranged from 2 to 65 mo, with an average follow-up time of 23 ± 15 mo. There were 72 males and 9 females, with a mean age of 53 years (range, 25–82 years). There were 51 cases in group A, 14 cases in group B, and 16 cases in group C. No significant differences were detected among the three groups with respect to age, gender, AFP, HBsAg, HBV-DNA, tumor location, liver cirrhosis, tumor cell differentiation, treatment modalities, time to recurrence from last treatment, or number of recurrences (Table 1).

Recurrence and survival

The median time to tumor recurrence for group A, group B, and group C was 16 ± 1.5 mo, 10 ± 2.8 mo, and 6 ± 0.5 mo, respectively, with a statistically significant difference among them (χ^2 = 70.144, P < 0.05); no statistically significant difference was noted between group A and group B (χ^2 = 2.659, P > 0.05), but there were statistically significant differences between group A and group C, and group B and group C (χ^2 = 62.110 and 19.972, respectively, P < 0.05) (Figure 1).

The median time of overall survival for group A, group B, and group C was 42 ± 5.1 mo, 22 ± 3.1 mo, and 13 ± 1.8 mo, respectively, with a statistically significant difference among them (χ^2 = 38.949, P < 0.05); there were statistically significant differences between group A and group B, group A and group C, and group B and group C (χ^2 = 9.577, 37.172, and 7.183, respectively, P < 0.05) (Figure 2)

Table 1 Comparison of clinicopathological features among the three groups

Variable	Group A (*n* = 51)	Group B (*n* = 14)	Group C (*n* = 16)	χ^2 value/*F* value	*P* value
Gender (male/female)	44/7	13/1	15/1	0.622	0.784
Age (yr)	54 ± 13 (33-82)	48 ± 11 (25-67)	52 ± 10 (39-67)	1.028	0.461
AFP (μg/L)	353.5 ± 104.5 (143.5-563.4)	121.9 ± 47.5 (19.2-224.6)	326.9 ± 90.6 (133.8-519.9)	0.769	0.467
HBsAg (negative/positive)	4/47	2/12	1/15	0.968	0.728
HBV-DNA (negative/positive)	39/12	7/7	8/8	5.956	0.051
Tumor location (left lobe/right lobe/both lobe)	9/37/5	0/10/4	2/9/5	7.459	0.089
Liver cirrhosis (negative/positive)	23/28	8/6	6/10	1.180	0.554
Tumor cell differentiation (well/moderate/poor)	9/32/10	4/8/2	2/10/4	1.655	0.832
Treatment modality (RFA/RFA + PEI/TACE/LR)	21/20/1/9	4/6/1/3	7/2/4/3	10.933	0.064
Time to recurrence from last treatment (mo)	26.6 ± 3.9 (18.6-34.5)	22.6 ± 4.1 (13.7-31.6)	17.3 ± 5.3 (5.9-28.5)	0.856	0.429
Number of recurrences (first/second)	43/8	10/4	11/5	2.632	0.285

Data are expressed as the mean ± SD. AFP: Alpha-fetal protein; HBsAg: Hepatitis B surface antigen; HBV-DNA: Hepatitis B virus deoxyribonucleic acid; RFA: Radiofrequency ablation; PEI: Percutaneous ethanol injection therapy; TACE: Transarterial chemoembolization; LR: Liver resection.

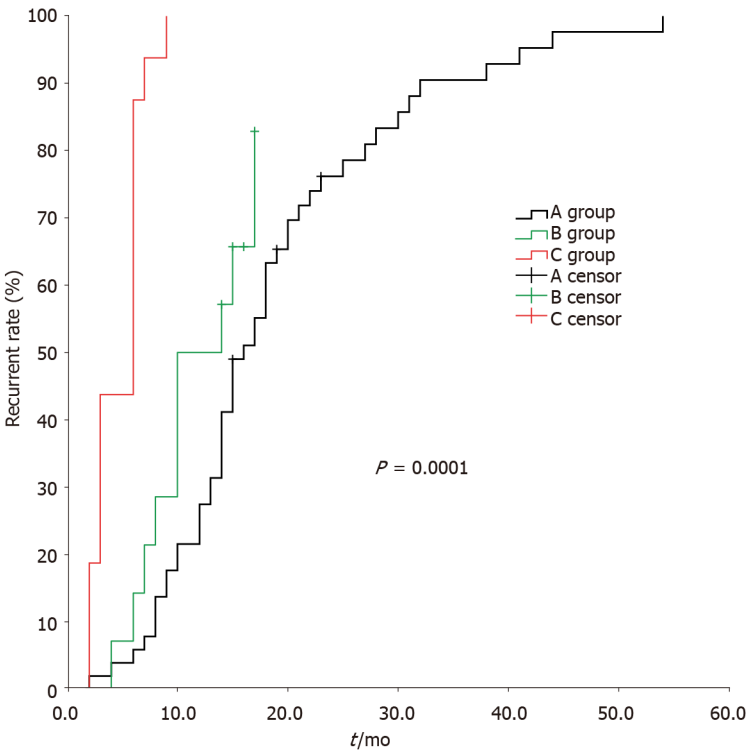

Figure 1 Recurrence curve of recurrent hepatocellular carcinoma.

DISCUSSION

Since the BCLC staging system was put forward in 1999, it has been confirmed by a large number of clinical studies and is considered to be the most reasonable liver cancer staging criteria by combining tumor status, liver function, and treatment strategies.

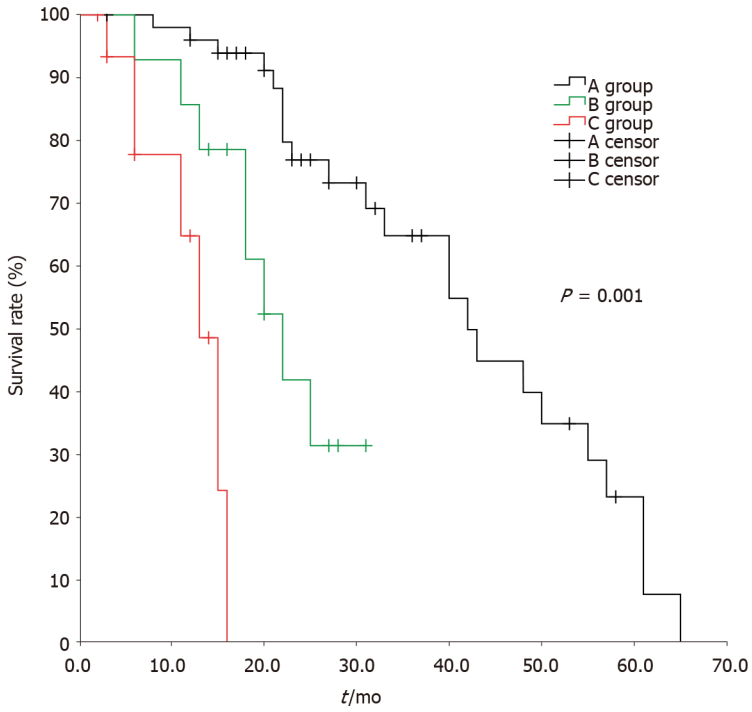

Figure 2 Overall survival curve of recurrent hepatocellular carcinoma.

Recurrence is one of the most important reasons why the prognosis of HCC is difficult to improve. At present, there have been guidelines for primary liver cancer, but for recurrent liver cancer, there is still much controversy[5,6]. Some researchers consider that the treatment for recurrent HCC can refer to that for primary HCC, including repeat hepatectomy, liver transplantation, local ablation, interventional therapy, radiotherapy, and systemic therapy[7,8]. Although SR is the best treatment option for patients with HCC, the 3-year recurrence rate is still as high as 50%-70%[9]. The treatment modalities for recurrent HCC include liver transplantation, SR, RFA, transcatheter arterial chemoembolization, and targeted therapy. Several studies show that 10%-30% of recurrent HCC patients underwent repeated SR, with a 5-year survival rate of 22%-83%, which is similar to that with first time hepatectomy[10,11]. Sun *et al*[12] found that in small recurrent HCC after SR, RFA achieved a similar overall survival and disease-free survival compared with repeated SR and resulted in a shorter hospital stay. Another meta-analysis showed contrary results, reporting that the 3-year survival after repeated SR is higher than that after RFA[13]. To date, how to manage recurrent HCC patients remains confusing, and there has not been a unanimous opinion about the treatment of recurrent HCC. Therefore, it is essential to establish clinical stages for recurrent HCC, which can provide more precise and individual treatment plans for recurrent HCC patients.

Is the Barcelona Clinic Liver Cancer (BCLC) staging system applicable to recurrent HCC? In our study, the median time to tumor recurrence for group A, group B, and group C was 16 ± 1.5 mo, 10 ± 2.8 mo, and 6 ± 0.5 mo, respectively, with a statistically significant difference among them ($P < 0.05$); there was no statistically significant difference between group A and group B ($\chi^2 = 2.659$, $P > 0.05$), but there were statistically significant differences between group A and group C, and group B and group C ($P < 0.05$). Meanwhile, the median time of overall survival for group A, group B, and group C was 42 ± 5.1 mo, 22 ± 3.1 mo, and 13 ± 1.8 mo, respectively, with a statistically significant difference among them ($P < 0.05$); there were statistically significant differences between group A and group B, group A and group C, and group B and group C ($P < 0.05$). Our study showed the BCLC staging system is applicable to recurrent HCC, and there are different prognoses in recurrent HCC patients with different stages classified by BCLC, which is just similar to that for primary HCC. It is essential to formulate the standard of clinical stages for recurrent HCC, which would contribute to the development of more precise and individual treatment plans for recurrent HCC patients, and, improve the therapeutic efficacy for recurrent HCC. Our study showed as well that the regular examination and follow-up are important because they can increase the rate of early diagnosis and treatment for recurrent HCC. Further research is needed to provide a more exact staging basis for recurrent HCC.

The limitations of our study included its non-prospective nature and small cohort size, which would lead to recall bias. Therefore, there is clearly a need for larger sample, prospective, multicenter clinical trials to confirm our conclusion in the future, and it is essential to formulate a better clinical staging system for recurrent HCC.

CONCLUSION

There are different prognoses in recurrent HCC patients with different stages classified by BCLC, which is just similar to that for primary HCC. BCLC staging system is applicable to recurrent HCC, but not precisely enough. It is essential to formulate the standard of clinical stages for recurrent HCC, which would contribute to the development of more precise and individual treatment plans for recurrent HCC patients, and, improve the therapeutic efficacy for recurrent HCC.

ARTICLE HIGHLIGHTS

Research background

Hepatocellular carcinoma (HCC) is the second leading cause of cancer-related death worldwide, and has relatively high recurrence rates. At present, there has not been a unanimous opinion for the treatment of recurrent HCC, and clinical stages of recurrent HCC remain controversial.

Research motivation

This study showed that the Barcelona Clinic Liver Cancer (BCLC) staging system is applicable to recurrent HCC, and it is essential to formulate the standard of clinical stages for recurrent HCC, which would contribute to the development of more precise and individual treatment plans for recurrent HCC patients.

Research objectives

The aim of this study was to assess the applicability of the BCLC staging for recurrent HCC and the need to establish clinical stage criteria for recurrent HCC.

Research methods

The clinicopathological data of 81 patients with recurrent HCC were collected. The patients were divided into three groups according to the BCLC staging system as follows: (1) Group A with BCLC stage A, 51 patients; (2) Group B with BCLC stage B, 14 patients; and (3) Group C with BCLC stage C, 16 patients. The median time to tumor recurrence time and the median overall survival were compared.

Research results

The median time to tumor recurrence in groups A, B, and C was 16 ± 1.5 mo, 10 ± 2.8 mo, and 6 ± 0.5 mo, respectively, with a statistically significant difference among them; no statistically significant difference was noted between group A and group B, although there were statistically significant differences between group A and group C and between group B and group C. The median overall survival time in groups A, B, and C was 42 ± 5.1 mo, 22 ± 3.1 mo, and 13 ± 1.8 mo, respectively, with a statistically significant difference among them; there were statistically significant differences between group A and group B, group A and group C, and group B and group C.

Research conclusions

There are different prognoses in recurrent HCC patients according to the BCLC. Therefore, BCLC staging is applicable to recurrent HCC and it is essential to formulate clinical stage criteria for recurrent HCC.

Research perspectives

Recurrent HCC patients with different clinical stages have different prognoses, and it is essential to formulate more precise clinical stage criteria for recurrent HCC.

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