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EDITORIAL

7963 *Exophiala dermatitidis*

Usuda D, Higashikawa T, Hotchi Y, Usami K, Shimozawa S, Tokunaga S, Osugi I, Katou R, Ito S, Yoshizawa T, Asako S, Mishima K, Kondo A, Mizuno K, Takami H, Komatsu T, Oba J, Nomura T, Sugita M

REVIEW

7973 Gastric neuroendocrine neoplasms: A review

Köseoğlu H, Duzenli T, Sezikli M

MINIREVIEWS

7986 Coronavirus disease 2019 and renal transplantation

Nassar M, Nso N, Ariyaratnam J, Sandhu J, Mohamed M, Baraka B, Ibrahim A, Alfishawy M, Zheng D, Bhangoo H, Soliman KM, Li M, Rizzo V, Daoud A

7998 Impact of COVID-19 on liver

Su YJ, Chang CW, Chen MJ, Lai YC

ORIGINAL ARTICLE**Case Control Study**

8008 Association of gestational anemia with pregnancy conditions and outcomes: A nested case-control study

Sun Y, Shen ZZ, Huang FL, Jiang Y, Wang YW, Zhang SH, Ma S, Liu JT, Zhan YL, Lin H, Chen YL, Shi YJ, Ma LK

Retrospective Cohort Study

8020 Clinical stages of recurrent hepatocellular carcinoma: A retrospective cohort study

Yao SY, Liang B, Chen YY, Tang YT, Dong XF, Liu TQ

Retrospective Study

8027 Accuracy of ultrasonography in diagnosis of fetal central nervous system malformation

Pang B, Pan JJ, Li Q, Zhang X

8035 Analysis of ocular structural parameters and higher-order aberrations in Chinese children with myopia

Li X, Hu Q, Wang QR, Feng ZQ, Yang F, Du CY

8044 Radial nerve recovery following closed nailing of humeral shaft fractures without radial nerve exploration: A retrospective study

Yeh KL, Liaw CK, Wu TY, Chen CP

8051 Bridging therapy and direct mechanical thrombectomy in the treatment of cardiogenic cerebral infarction with anterior circulation macrovascular occlusion

Ding HJ, Ma C, Ye FP, Zhang JF

- 8061** Endu combined with concurrent chemotherapy and radiotherapy for stage IIB-IVA cervical squamous cell carcinoma patients

Zhao FJ, Su Q, Zhang W, Yang WC, Zhao L, Gao LY

CASE REPORT

- 8071** Primary pancreatic paraganglioma harboring lymph node metastasis: A case report

Jiang CN, Cheng X, Shan J, Yang M, Xiao YQ

- 8082** Retraction of lumbar disc herniation achieved by noninvasive techniques: A case report

Wang P, Chen C, Zhang QH, Sun GD, Wang CA, Li W

- 8090** Mixed neuroendocrine carcinoma of the gastric stump: A case report

Zhu H, Zhang MY, Sun WL, Chen G

- 8097** Diploic vein as a newly treatable cause of pulsatile tinnitus: A case report

Zhao PF, Zeng R, Qiu XY, Ding HY, Lv H, Li XS, Wang GP, Li D, Gong SS, Wang ZC

- 8104** Acute myocardial infarction and extensive systemic thrombosis in thrombotic thrombocytopenic purpura: A case report and review of literature

Şalaru DL, Adam CA, Marcu DTM, Şimon IV, Macovei L, Ambrosie L, Chirita E, Sascau RA, Stasescu C

- 8114** Limited thoracoplasty and free musculocutaneous flap transposition for postpneumonectomy empyema: A case report

Huang QQ, He ZL, Wu YY, Liu ZJ

- 8120** Paraneoplastic focal segmental glomerulosclerosis associated with gastrointestinal stromal tumor with cutaneous metastasis: A case report

Zhou J, Yang Z, Yang CS, Lin H

- 8127** Acute coronary syndrome with severe atherosclerotic and hyperthyroidism: A case report

Zhu HM, Zhang Y, Tang Y, Yuan H, Li ZX, Long Y

- 8135** Gastric cancer with calcifications: A case report

Lin YH, Yao W, Fei Q, Wang Y

- 8142** Value of eosinophil count in bronchoalveolar lavage fluid for diagnosis of allergic bronchopulmonary aspergillosis: A case report

Wang WY, Wan SH, Zheng YL, Zhou LM, Zhang H, Jiang LB

- 8147** Asymptomatic gastric adenomyoma and heterotopic pancreas in a patient with pancreatic cancer: A case report and review of the literature

Li K, Xu Y, Liu NB, Shi BM

- 8157** Successful treatment of gastrointestinal infection-induced septic shock using the oXiris® hemofilter: A case report

Li Y, Ji XJ, Jing DY, Huang ZH, Duan ML

- 8164** Streptococcal pneumonia-associated hemolytic uremic syndrome treated by T-antibody-negative plasma exchange in children: Two case reports
Wang XL, Du Y, Zhao CG, Wu YB, Yang N, Pei L, Wang LJ, Wang QS
- 8171** Subclavian steal syndrome associated with Sjogren's syndrome: A case report
Hao LJ, Zhang J, Naveed M, Chen KY, Xiao PX
- 8177** Metachronous mixed cellularity classical Hodgkin's lymphoma and T-cell leukemia/lymphoma: A case report
Dong Y, Deng LJ, Li MM
- 8186** Duodenal perforation after organophosphorus poisoning: A case report
Lu YL, Hu J, Zhang LY, Cen XY, Yang DH, Yu AY
- 8192** Surgical treatment of abnormal systemic artery to the left lower lobe: A case report
Zhang YY, Gu XY, Li JL, Liu Z, Lv GY
- 8199** Madelung's disease with alcoholic liver disease and acute kidney injury: A case report
Wu L, Jiang T, Zhang Y, Tang AQ, Wu LH, Liu Y, Li MQ, Zhao LB
- 8207** Anesthetic technique for awake artery malformation clipping with motor evoked potential and somatosensory evoked potential: A case report
Zhou HY, Chen HY, Li Y
- 8214** Multiple hidden vessels in walled-off necrosis with high-risk bleeding: Report of two cases
Xu N, Zhai YQ, Li LS, Chai NL
- 8220** Non-small-cell lung cancer with epidermal growth factor receptor L861Q-L833F compound mutation benefits from both afatinib and osimertinib: A case report
Zhang Y, Shen JQ, Shao L, Chen Y, Lei L, Wang JL
- 8226** Successful removal of two magnets in the small intestine by laparoscopy and colonoscopy: A case report
Oh RG, Lee CG, Park YN, Lee YM
- 8232** Acute lower extremity arterial thrombosis after intraocular foreign body removal under general anesthesia: A case report and review of literature
Jeon S, Hong JM, Lee HJ, Kim E, Lee H, Kim Y, Ri HS, Lee JJ
- 8242** Low-intensity extracorporeal shock wave therapy for midshaft clavicular delayed union: A case report and review of literature
Yue L, Chen H, Feng TH, Wang R, Sun HL
- 8249** Treatment of bilateral granulomatous lobular mastitis during lactation with traditional Chinese medicine: A case report
Li ZY, Sun XM, Li JW, Liu XF, Sun ZY, Chen HH, Dong YL, Sun XH
- 8260** Early acute fat embolism syndrome caused by femoral fracture: A case report
Yang J, Cui ZN, Dong JN, Lin WB, Jin JT, Tang XJ, Guo XB, Cui SB, Sun M, Ji CC

- 8268** Combined fascia iliaca compartment block and monitored anesthesia care for geriatric patients with hip fracture: Two case reports
Zhan L, Zhang YJ, Wang JX
- 8274** Bell's palsy after inactivated COVID-19 vaccination in a patient with history of recurrent Bell's palsy: A case report
Yu BY, Cen LS, Chen T, Yang TH

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Retrospective Cohort Study

Clinical stages of recurrent hepatocellular carcinoma: A retrospective cohort study

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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 ($\chi^2 = 70.144$, $P < 0.05$); no statistically significant difference was noted between group A and group B ($\chi^2 = 2.659$, $P > 0.05$), although there were statistically significant differences between group A and group C and between group B and group C ($\chi^2 = 62.110$, 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 ($\chi^2 = 38.949$, $P < 0.05$); 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 ($\chi^2 = 9.577, 37.172, \text{ and } 7.183, \text{ respectively; } P < 0.05$).

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

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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 ≤ 30 mm 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 \pm 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 ($\chi^2 = 70.144$, $P < 0.05$); no statistically significant difference was noted 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 ($\chi^2 = 62.110$ 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 ($\chi^2 = 38.949$, $P < 0.05$); there were statistically significant differences between group A and group B, group A and group C, and group B and group C ($\chi^2 = 9.577$, 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.

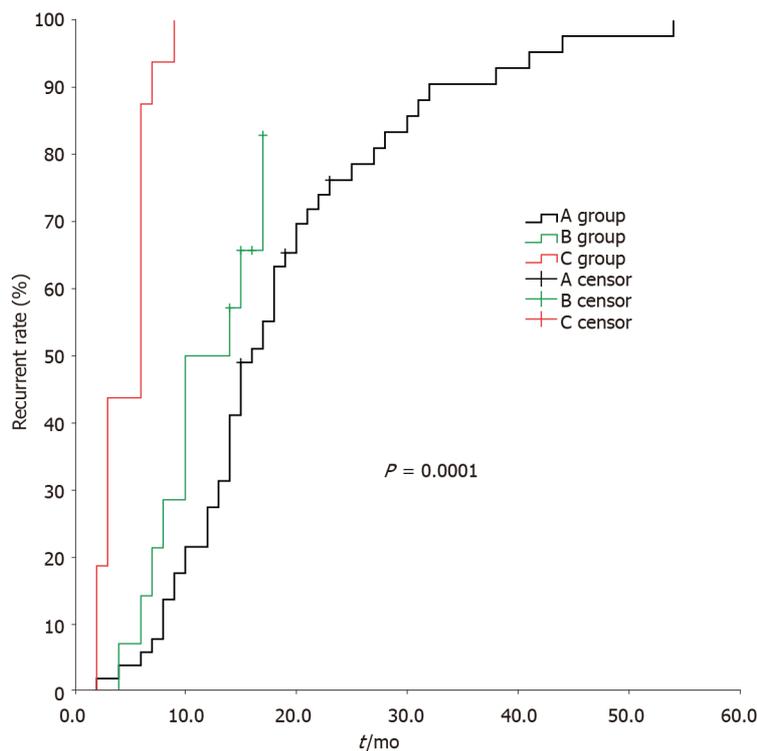


Figure 1 Recurrence curve of recurrent hepatocellular carcinoma.

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.

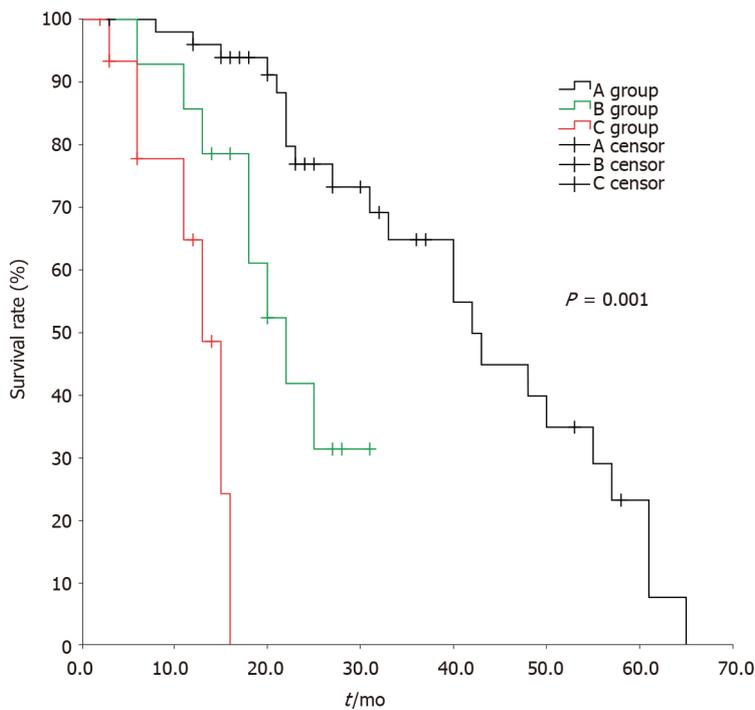


Figure 2 Overall survival curve of recurrent hepatocellular carcinoma.

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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