RESEARCH ARTICLE

Analysis on Postoperative Efficacy of Radical Hepatectomy for Patients with Non-HBV/HCV Hepatocellular Carcinoma

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Abstract

Objective: Patients with hepatocellular carcinoma (HCC) in stage Barcelona Clinic Liver Cancer (BCLC)-A were grouped based on whether they were accompanied with hepatitis B virus (HBV) infection or not so as to explore the clinical characteristics and prognostic conditions of HCC patients with non-HBV/hepatitis C virus (HCV). Materials and Methods: Clinical data of 64 stage BCLC-A HCC patients with non-HBV/HCV infection (observation group) who received radical hepatectomy in the Affiliated Cancer Hospital of Guangxi Medical University from January, 2006 to November, 2014 were retrospectively analyzed and compared with those of 409 stage BCLC-A HCC patients with HBV infection (control group) in corresponding period. Results: The postoperative 1-, 3- and 5-year recurrent rates of the observation group were 25%, 38.6% and 48.8%, with postoperative mean and median disease-free survival time being 49.1 months and 62.0 months, respectively. Additionally, the postoperative 1-, 3- and 5-year survival rates of observation group were 90.1%, 72.7% and 62.0%, with the mean and median survival times being 54.4 months and 70.0 months, respectively. Conclusions: The 1-year recurrent rate is the highest in HCC patients with non-HBV/HCV, and almost half of the patients have recurrence within 1 year, after which the recurrent rate decreases along with the time.

Keywords: Non-HBV/HCV infection - hepatocellular carcinoma - hepatectomy

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors in clinic, whose morbidity increases annually around the globe (dead patients>625 thousand/year), ranking the 5th of the malignant tumors. In addition, the number of patients died of HCC is close to 600 thousand/year, ranking the 3rd of the tumor-related death (Zhu et al., 2013; Jeng et al., 2014; Maida et al., 2014). However, HCC is high in heterogeneity between Asian countries (except Japan and Indonesia) and western countries, in which there are significant differences in etiology, stages, biological malignant behaviors, diagnosis (therapeutic concepts and clinical practice guidance) and prognosis, etc (Kar, 2014; Ramesh, 2014). So far, Barcelona Clinic Liver Cancer (BCLC) and therapeutic methods have been the most popular ones in western countries (Graf et al., 2014; Kim et al., 2015; Liu et al., 2015). Nonetheless, there is significant difference in the background of HCC between western countries and China, and most of the HCC patients are accompanied with hepatitis B virus (HBV) infection in China. On this basis, patients with non-HBV/hepatitis C virus (HCV) in China were grouped based on BCLC stages and compared with those with HBV infection who were treated with surgeries in corresponding period in order to explore the clinical characteristics of HCC patients with non-HBV/HCV infection. Therefore, in this study, the clinical data of 64 stage BCLC-A HCC patients with non-HBV/HCV infection undergoing radical hepatectomy were retrospectively analyzed and compared with those of 409 stage BCLC-A HCC patients with HBV infection in corresponding period, and the results are reported as follows.

Materials and Methods

General data

A total of 64 HCC patients with non-HBV/HCV infection at stage BCLC-A who received radical hepatectomy in *The Affiliated Cancer Hospital of Guangxi Medical University* from January, 2006 to November, 2014 were selected as observation group. All patients had complete clinical records and were pathologically diagnosed as HCC. Another 409 stage BCLC-A HCC patients with HBV infection undergoing radical hepatectomy in corresponding period served as control group. No patient received chemotherapy or radiotherapy before operation.

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Inclusion criteria

(1) Patients who received radical hepatectomy and were diagnosed as stage BCLC-A clinically; (2) Patients who were pathologically diagnosed as HCC after operation; (3) Patients without radiotherapy or chemotherapy before operation; (4) Patients without distant metastasis; (5) Patients whose postoperative recurrent time >2 months.

Surgical methods

All patients were treated with radical hepatectomy. Of the 41 patients with regular hepatectomy in observation group, 13 were on left half liver, 16 on right half liver, 6 on left lateral lobe and 6 on right lateral lobe. The range of excised liver was determined according to the size and range of the tumor, the hepatic function and the residual liver volume.

Criteria for radical resection

(1) The visible tumors were completely excised without residual cancerous tissues on tissue margin; (2) Tumor number ≤3 and was limited in a segment or a lobe of the liver; (3) There was no cancerous thrombus in the main and first-grade branch of portal vein and the main and first-grade branch choledochal duct as well as the main branch of hepatic vein and inferior vena cava; (4) There was no hepatic portal lymph node metastasis; (5) There was no extra-hepatic distant metastasis.

Criteria for postoperative recurrence after radical resection

Patients who were conformed with the criteria of radical resection combined with one of the following conditions were considered to be concurrent: (1) Imageology showed new or metastatic nidi in liver; (2) Continuous increase of alpha fetal protein (AFP) level after operation; (3) The AFP level decreased after operation and then increased again.

Follow up

Patients in both groups were followed up till January 31th, 2015. Survival time was expressed by months and defined as the time from the surgical day to day of death or the terminal follow-up time. The clinical follow-up data were obtained through the hospitalized or outpatient re-examination and letters or phone calls. The arrangement of follow-up time: 1 time/month within the first 3 months after operation, and then 1 time every 3 months. The follow-up contents including: (1) The clinical physique and blood biochemical indexes were examined in each follow up, including the determination of serum AFP level, hepatic functional examination, abdominal B-ultrasound, upper abdominal computed tomography (CT) and chest X-ray images, etc., and spiral CT scan on upper abdomen or magnetic resonance imaging (MRI)- or B-ultrasound-guided hepatic puncture biopsy were performed to some suspicious cases when necessary; (1) Survival conditions, etc.

Statistical data analysis

SPSS16.0 software was applied for all data analysis. The survival rate was calculated with Kaplan-Meier method, with the significant test level α=0.05.

Results

Clinical data

In observation group, there were 53 males (82.8%) and 11 females (17.2%), aged 36~74 years with median age being 53.4 years, in which patients ≤40 years, 40~60

Table 1. Comparison of Clinical Characteristics between Two Groups

Clinical characteristics	Stage BCLC-A HCC		χ^2 value	*P* value
	Observation group	Control group		
Gender				
Female	11	36	4.348	0.037
Male	53	373		
Age (year)				
≥60	13	62	16.573	0.000
40~60	44	197		
≤40	7	150		
Preoperative ALT (U/L)				
<40	59	314	7.887	0.005
≥40	5	95		
Preoperative AST (U/L)				
<40	59	319	6.945	0.008
≥40	5	90		
Child-pugh class of hepatic function				
Class B	1	88	14.424	0.000
Class A	63	321		
AFP level (ng/ml)				
<20	49	214	62.782	0.000
≥20	15	195		
Tumor size (cm)				
≤5cm	20	87	3.148	0.076
>5cm	44	322		
Tumor capsule				
No	12	107	1.614	0.204
Yes	52	302		
Adjacent tissue invasion				
No	57	323	3.566	0.059
Yes	7	86		
Preoperative tumor rupture				
No	62	392	0.153	0.696
Yes	2	17		
Regular resection				
Yes	41	122	28.716	0.000
No	23	287		
Distance from tumor to incisal margin (cm)				
<1	25	203	2.477	0.116
≥1	39	206		
Injection of absolute alcohol on incisal margin				
No	52	267	6.427	0.011
Yes	12	142		
Postoperative blood transfusion				
No	47	301	0.001	0.979
Yes	17	108		
Pathological differentiation				
Other differentiation	17	199	10.886	0.001
High-high and moderate differentiation	47	210		

Table 2. Mean and Median Values of DFS

Groups	Mean value				Median value			
	Estimated value	Standard error	95% CI Upper limit	95% CI Lower limit	Estimated value	Standard error	95% CI Upper limit	95% CI Lower limit
Control group	36.754	1.510	33.794	39.714	37.000	3.150	30.826	43.174
Observation group	49.082	4.459	40.344	57.821	62.000	16.046	30.550	93.450
Total	38.966	1.524	35.980	41.952	37.000	2.105	32.875	41.125

Note: CI: Confidence Interval

Table 3. Mean and Median Values of Postoperative Survival Time

Groups	Mean value				Median value			
	Estimated value	Standard error	95% CI Upper limit	95% CI Lower limit	Estimated value	Standard error	95% CI Upper limit	95% CI Lower limit
Control group	44.616	1.181	42.302	46.930	45.000	1.746	41.579	48.421
Observation group	54.414	2.142	50.215	58.613	70.000	2.861	64.393	75.607
Total	46.931	1.053	44.866	48.996	50.000	2.555	44.992	55.008

Note: CI: Confidence Interval

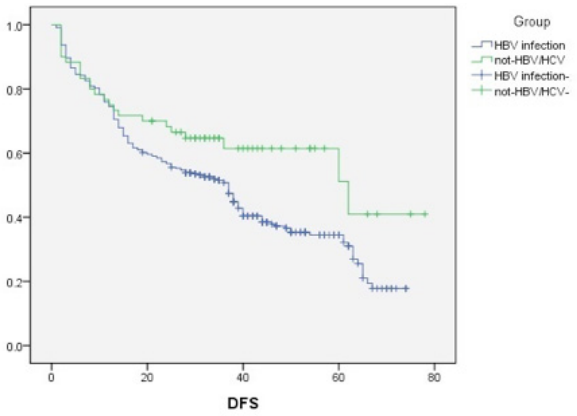

Figure 1. Postoperative DFS between Two Groups

years and ≥60 years accounted for 10.9% (7/64), 68.8% (44/64) and 20.3% (13/64), respectively. In control group, there were 373 males (91.2%) and 36 females (8.8%), aged 19~74 years with median age of 48.3 year, in which patients ≤40 years, 40~60 years and ≥60 years accounted for 36.7% (150/409), 48.2% (197/409) and 15.1% (62/409) , respectively.

In observation group, the average tumor size was 7.44 cm, in which patients with diameter ≤5 cm and >5 cm accounted for 31.2% (20/64) and 68.8% (44/64); those with and without tumor capsule for 81.3% (52/64) and 18.7% (12/64); those with alanine transaminase (ALT) <40 U/L and ≥40 U/L for 92.2% (59/64) and 7.8% (5/64); those with aspartate aminotransferase (AST) <20 ng/mL and ≥20 ng/mL for 76.6% (49/64) and 23.4% (15/64); those with preoperative Chlid-Pugh class A and B for 98.4% (63/64) and 1.6% (1/64); those with distance from tumor to incisal margin <1 cm and ≥1 cm for 39.1% (25/64) and 60.9% (39/64); those with and without injection of absolute alcohol on incisal margin for 18.7% (12/64) and 81.3% (52/64); and those with high to high-moderate differentiation and other differentiation for 73.4% (47/64) and 26.6% (17/64), respectively.

In observation group, the average tumor size was 6.73 cm, in which patients with diameter ≤5 cm and >5 cm accounted for 21.3% (87/409) and 78.7% (322/409); those with and without tumor capsule for 73.8% (302/409) and 26.2% (107/409); those with ALT <40 U/L and ≥40 U/L for 84.1% (314/409) and 25.9% (95/409); those with AST <20 ng/mL and ≥20 ng/mL for 78% (319/409) and 75.6% (301/409); those with preoperative Chlid-Pugh class A and B for 78.4% (321/409) and 21.6% (88/409); those with distance from tumor to incisal margin <1 cm and ≥1 cm for 49.6% (203/409) and 50.4% (206/409); those with and without injection of absolute alcohol on incisal margin accounted for 34.7% (142/409) and 65.3% (267/409); and those with high to high-moderate differentiation and other differentiation for 51.3% (210/409) and 48.7% (199/409), respectively. The comparison of the clinical characteristics between two groups was shown in Table 1.

Postoperative recurrent rates and tumor-free survival time

The 1-, 3- and 5-year recurrent rates were 25.0%, 38.6% and 48.8% in observation group, and were 25.4%, 49.2% and 65.5% in control group, respectively. The average and median DFS were 49.1 and 62.0 months in observation group, and were 36.8 and 37.0 months in control group, respectively (Table 2 and Figure 1).

Accumulated survival rates and survival time

As shown in Table 3 and Figure 2, the 1-, 3- and

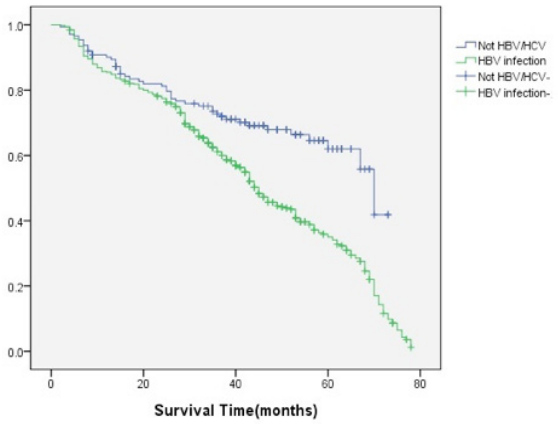

Figure 2. Postoperative Survival Time between Two Groups

5-year survival rates were 90.1%, 72.7% and 62.0% in observation group, and were 85.5%, 61.1% and 35.0% in control group, respectively. The average and median survival time were 54.4 and 70.0 months in observation group, and were 44.6 and 45.0 months in control group, respectively

Discussion

There is significant difference in the morbidity of HCC, and approximately 90% of HCC patients are accompanied with hepatic cirrhosis all over the world (Dai et al., 2013; Xu et al., 2014). Hepatic cirrhosis is closely associated with HBV and HCV infection, and the development of 80% of HCC is in connection with chronic HBV and HCV infection (Bruix et al., 2004; Fattovich et al., 2004). In China, most HCC patients are accompanied with HBV infection (significantly more than those with HCV infection), so there were less number of patients with HCV infection in the included objects in *The Affiliated Cancer Hospital of Guangxi Medical University*, who were then excluded from this study.

In this study, the postoperative recurrence of HCC patients was defined as the development of recurrent nidi >2 months after operation because patients who had postoperative recurrence within 2 months already had disseminated tumor nidi in liver before operation (Carr et al., 2015; Yamamoto et al., 2015). Therefore, the inclusion criteria were determined 2 months after operation so as to exclude the patients with recurrence due to the undefined recurrent nidi in liver before operation.

BCLC, which is related with therapeutic indications, has been widely used in clinic as a decisional therapeutic tool. It also considers multiple variables such as tumor stages, hepatic functional reserve, general condition and tumor-related symptoms, etc. In this study, HCC patients in stage BCLC-A were selected aiming to reduce the factors influencing prognostic evaluation (Bruix et al., 2004).

In this study, the minimum and median ages were 19 and 48.3 years in control group and 36 and 53.4 years in observation group, respectively, indicating that patients in control group showed younger trend than those in observation group, which was in potential association with the early HBV infection in the families. As to the male/female ratio, the females accounted for 17% (11/64) in observation group but for 8.8% (36/409) in control group, suggesting that the ratio of females increased in HCC patients with non-HBV/HCV infection, and drinking alcohol was a common adjuvant factor for HCC (Calle et al., 2003; Li et al., 2014), which was potentially correlated with the fact that the number of females who drank was less than that of males, thus reducing the ratio of females in HCC patients with HBV infection.

This study found that there were significant differences between two groups in preoperative ALT and AST levels and the Child-pugh class of hepatic function, demonstrating that HCC patients with HBV infection were frequently accompanied with hepatitis and different-degree hepatic cirrhosis. In addition, hepatic functional reserve often impacts the surgeons in selecting surgical patterns. It was found in this study that patients with regular resection accounted for 64% (41/64) in observation group but for 29.8% (122/409) in control group, so it was believed that there was significant difference between two groups in the regular resection. At present, it was proposed that resection of liver segment was superior to non-anatomical resection in removing HCC from oncological aspect, and the resection of portal vein branch of liver segment could also remove the potential metastatic lymph nodes (Poon et al., 2000; Norsa'adah et al., 2013). Moreover, the difference of regular resection may also trigger great influence on the tumor recurrence (Morise et al., 2014; Yang et al., 2015). Additionally, patients with injection of absolute alcohol on incisal margin accounted for 18.7% (12/64) and 34.7% (142/409) in observation group and control group respectively, revealing that there was contradiction for physicians in maintaining liver parenchyma and in assuring enough tumor-free incisal margin.

It was found in this study that the positive rate of serum AFP expression accounted for only 23.4% (15/64) in observation group but for 47.7% (195/409) in control group, indicating that it was evidently lower in patients with non/HBV/HCV infection. And the postoperative pathological detection of tumor tissues showed that patients with high to high-moderate differentiation of tumor tissues accounted for 73.4% (47/64) and 51.3% (210/409) in observation group and control group, and there was significant difference, demonstrating that the differentiation of tumor tissues were better in HCC patients with non-HBV/HCV infection than those with HBV infection, which could lead to the predication that in the carcinogenesis procession of HCC, HBV-induced cancerous cell differentiation was relatively more original and easy to develop recurrence and metastasis, which was consistent with the results of Oyunsuren' study (Oyunsuren et al., 2006).

In this study, the 1-, 3- and 5-year recurrent rates were 25.0%, 38.6% and 48.8% in observation group and 25.4%, 49.2% and 65.5% in control group. The 1-year recurrent rate was the highest in observation group, and nearly half of the recurrent patients had recurrence within 1 year, after which it showed decreasing trend along with the time. In control group, the 1-year recurrent rate was similar to that in observation group, but most patients had recurrence within 3 years, and the 5-year recurrent rate was still higher than the 3-year rate by 16.3%, illustrating that the postoperative recurrent rate did not decrease significantly along with the time in HCC patients with HBV infection. In addition, the average and median DFS were 49.1 and 62.0 months in observation group, and were 36.8 and 37.0 months in control group, and there was significant difference, demonstrating that HCC patients with non-HBV/HCV infection had lower recurrent rate and longer DFS than those with HBV infection.

In this study, the 1-, 3- and 5-year survival rates were 90.1%, 72.7% and 62.0% in observation group and were 85.5%, 61.1% and 35.0% in control group. The 1-year survival time was similar between two groups, but the difference increased markedly along with the time. The average and median survival time were 54.4 and 70.0

months in observation group and were 44.6 and 45.0 months in control group, revealing that the clinical efficacy was better in the treatment of patients with non-HBV/HCV infection.

In conclusion, the 1-year recurrent rate was the highest in observation group, and nearly half of recurrent patients had recurrence within 1 year, after which it showed decreasing trend along with the time. Additionally, HCC patients with non-HBV/HCV infection had obviously lower recurrent rate and longer survival time than those with HBV infection.

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