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Effects of Hepatitis B Virus Load on Hepatectomy

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Abstract

Background: To investigate the impact of preoperative hepatitis B virus status, as well as postoperative antiviral therapy, on the risk of recurrence-free survival (RFS), overall survival (OS) after curative resection of hepatitis B virus-related hepatocellular carcinoma (HCC) within milan criteria (MC).

Patients and methods: A retrospective studies regarding hepatitis B virus-related HCC patients within MC undergoing curative resection from 2007 to 2012 were analysed. Two groups were compared according to preoperative virus status (using 1,000 copies/ml of hepatitis B virus DNA level as cut-off value). Prognostic factors for OS and RFS were evaluated. Additionally, subgroup analysis was conducted in patients with positive hepatitis B virus-DNA (HBV-DNA) to investigate prediction of postoperative antiviral therapy on the long-term prognosis.

Results: Patients with positive HBV-DNA had lower OS rates (1 year, 3 year, and 5 year: 91.7%, 77.4%, and 69.6%, respectively) as compared to those with negative HBV-DNA (1-year, 3-year, and 5-year: 95.0%, 82.3%, and 74.6%, respectively) (P=0.041). There were significant differences in RFS rates of the positive vs. negative HBV-DNA group (1-year, 3-year, 5-year: 70.8%, 49.3%, 32.8% vs. 73.7%, 53.7%, 41.8%, respectively) (P=0.032). Multivariate analysis revealed that preoperative positive HBV-DNA was an independent risk factor affecting OS (P<0.001) and RFS (P<0.001). The subgroup analysis revealed that postoperative antiviral therapy independently improved OS and RFS (P<0.001).

Conclusions: Preoperative positive HBV-DNA of Hepatitis B virus-related HCC patients within MC led to a poor overall and recurrence-free survival than those with negative HBV-DNA after curative resection. To prevent postoperative recurrence, antiviral therapy should be initiated if HBV-DNA ≥ 1,000 copies/ml.

Keywords: Hepatocellular carcinoma; Milan Criteria; Hepatitis B virus; Hepatic resection; Antiviral therapy

Abbreviation

HCC: Hepatocellular Carcinoma; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; HDV: Hepatitis D Virus; HIV: Human Immunodeficiency Virus; LT: Liver Transplantation; MC: Milan Criteria; HR: Hepatic Resection; AFP: Alpha-Fetoprotein; OS: Overall Survival; RFS: Recurrence-Free Survival; DNA: Deoxyribonucleic Acid; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; RFA: Radiofrequency Ablation; PEI: Percutaneous Ethanol Injection; TACE: Transcatheter Arterial Chemoembolization; CI: Confidence Interval; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; AASLD: The American Association for the Study of Liver Diseases

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third most common cause of death due to cancer around the world [1-3]. It has been estimated that more than 50% of HCC worldwide is etiologically associated with hepatitis B virus (HBV), and more than 80% of HBV-related HCC are in developing countries, especially in China [4].

Liver transplantation (LT) is the gold standard therapy for patients with HCC within milan criteria (MC) [5]. While in the current era of limited supply of donor organs [6], worldwide scarcity of donor liver grafts is a limitation of this management [7]. Approximately 20-30% of patients with HCC drop off the waiting list because of tumor progression [8-11]. Hence hepatic resection (HR) in time is still an effective treatment for HCC patients who are indicated for this procedure [12,13]. And some recent researches indicate HR and LT provide similar short and long survival rates, but HR offer significantly lower recurrence-free survival rates [14].

Previous studies have noted that factors contributing to short and long term survival and HCC recurrence after curative resection include the following: Child-Pugh scores; tumor size; tumor number; tumor differentiation; alpha-fetoprotein (AFP) level; intraoperative transfusion[15,16]. With regard to HBV-related HCC, recent studies have evaluated viral replication status, particularly HBV viral load as a predictor of long-term prognosis [17-20]. However, these findings were limited in that most investigators focused on tumor recurrence as the only or primary end point and associations with overall survival or mortality after resection have not been reported. In addition, the efficacy of antiviral therapy in reducing the risk of HBV-related HCC recurrence and death after resection is far from clear [21].

Herein, we conducted a retrospective study to elucidate prognostic factors for overall survival (OS) and recurrence-free survival (RFS) after HR by univariate and multivariate analyses, and to clarify the efficacy of postoperative antiviral therapy on the risk of tumor recurrence and mortality after resection in patients with positive HBV-DNA.

Patients and Methods

Screening patients and grouping

From February 2007 to April 2012, in our center, 1237 patients were diagnosed as HCC according to pathological examination after hepatic resection. Patients who satisfied the conditions such as: HBV-related HCC, meeting Milan criteria (For patients with a single HCC, the tumor could not exceed 5 cm in diameter. In patients with multiple tumors, there could be no more than three tumors, none exceeding 3 cm in diameter. Patients in whom tumor invasion of big blood vessels or lymph nodes, or extrahepatic metastasis was evident or suspected were excluded [22].), were enrolled. Patients who were excluded as follows: age<18 years, co-infected with HCV, not underwent their first curative hepatic resection for HCC, not had the HBV-DNA test either before or after surgery, with residual tumor at the excision margin according to pathological examination, underwent liver transplantation (Figure 1). Ultimately, 274 patients were enrolled in this retrospective study.

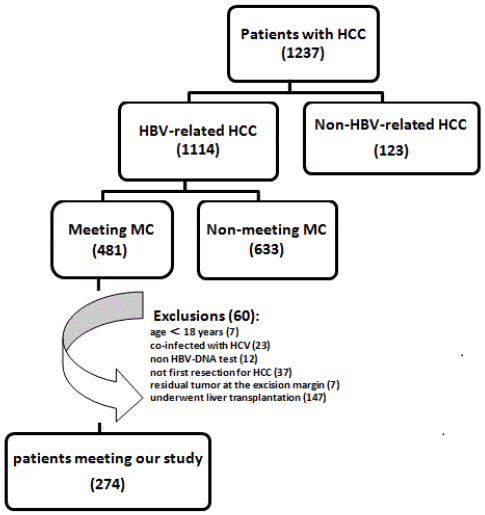

Figure 1: A study flowchart to screen the patients who meeting our study.

HBsAg, HbsAb, HBeAg, HbeAb and HBcAb were determined for all these patients by the microparticle enzyme immunoassay (Abbott Laboratories, Chicago, IL). Serum HBV-DNA tests were measured routinely within a week before surgery using the Digene hybrid capture assay (Roche Diagnostics, Branchburg, NJ) (lower limit of detection: 500 copies/ml).

Using 1,000 copies/ml of HBV-DNA level as cut-off value, patients were divided into the following two groups: the negative HBV-DNA group (<103 copies/ml) and the positive HBV-DNA group (≥ 103 copies/ml). According to the viral load, the positive HBV-DNA group was divided into the low viral load group (≥ 103 copies/ml and <105 copies/ml) and the high viral load group (≥ 105 copies/ml) [23]. The protocol was approved by the Clinical Research Ethics Committee of West China Hospital of Sichuan University.

Use of antiviral therapy and follow-up

All the curative HRs was defined as macroscopically complete removal of the tumor, with a pathologically tumor-free surgical margin [21]. After curative resection of HBV-related HCC in our center, in principle, adjuvant antiviral therapy with lamivudine 100 mg, adefovir dipivoxil 10 mg, or entecavir 0.5 mg orally, on daily basis was commenced within a week after operation or after discharge for all patients regardless the HBV-DNA status. For patients with renal insufficiency, the daily lamivudine or adefovir dipivoxil dose was adjusted according to creatinine clearance.

According to whether patients with positive HBV-DNA received regular antiviral therapy. The positive HBV-DNA group was divided into the regular antiviral therapy group and the irregular antiviral therapy group. In positive HBV-DNA patients with regular antiviral therapy, some patients had negative HBV-DNA after a period of treatment, but other patients still had positive HBV-DNA. Using 6 months as cut-off value [24], positive HBV-DNA patients with regular antiviral therapy were divided to the HBV-DNA became negative within six months group and the HBV-DNA stayed positive within six months group.

Patients were followed up in our clinic at postoperative 1 month, and then every 3 months during postoperative year. The HBV-DNA status, AFP assay and liver ultrasonography were performed during each visit. A computed tomography (CT) scan of the abdomen was performed every 6 months. If recurrence was suspected, CT or magnetic resonance imaging (MRI) was immediately performed to confirm the finding. Patients with confirmed recurrence were subjected to further treatment. If the recurrent tumor was localized, a second liver resection, radiofrequency ablation (RFA), or percutaneous ethanol injection (PEI) was suggested; if the recurrent tumor was multiple or diffused; transcatheter arterial chemoembolization (TACE) was the choice [25].

The OS was calculated from the day of surgery until the day of HCC-related death or lost contact. The RFS was defined as the time from the day of surgery to the day of confirmed tumor recurrence for recurrent patients, or from the day of surgery to the day of death or lost contact for non-recurrent patients.

Statistical methods

Data were expressed as percentage, mean with standard deviation, or median with 95% confidence interval (95% CI). The clinicopathologic and operative parameters were compared between two groups using Student's t-test or the Mann-Whitney test, or χ^2 test as appropriate. OS and RFS were calculated by the Kaplan-Meier method and differences were compared by the log-rank test.

18 parameters of patients at enrollment in this study were selected for their potential relation to the prognosis on the basis of the previous studies. For the laboratory parameters, the cut-off values were the upper limit of the normal values in West China hospital. After the univariate analysis, only the significant variables were used in the multivariate analysis using the Cox proportional hazard model. P<0.05

was considered to be statistically significant. Statistical analysis was carried out using SPSS software version 19.0 (SPSS, Chicago, IL, USA).

Results

Patient characteristics

Of all 274 patients in the present study, 240 were male and 34 were female, with the median age of 51 years (range, 22 years-78 years). Based on the preoperative serum HBV-DNA level, 123 (44.9%) had negative HBV-DNA, and 151 patients (55.1%) had positive HBV-DNA. Patient characteristics are summarized in Table 1. Liver function was relatively good in the majority of all patients at the time of surgery (260 with Child-pugh criteria A; 14 with Child-pugh criteria B), and confirmed cirrhosis in 174 patients histologically.

	Total (N=274)	Negative HBV-DNA group (N=123)	Positive HBV-DNA group (N=151)	P value
Sex				
Male	240 (87.6%)	105 (85.4%)	135 (89.4%)	0.081
Female	34 (12.4%)	18 (14.6%)	16 (10.6%)	
Age (years)	51 (22-78)	51 (24-78)	50 (22-77)	0.431
Cirrhosis	174 (63.5%)	58 (47.2%)	116 (76.8%)	<0.001
Child-Pugh grade				
A	260 (94.9%)	121 (98.4%)	139 (92.1%)	0.001
B	14 (5.1%)	2 (1.6%)	12 (7.9%)	
Positive Serum AFP(≥ 8 ng/ml)	207 (75.5%)	99 (80.5%)	108 (71.5%)	0.149
Total bilirubin (μmol/l)	14.1 (4.2-117.2)	13.9 (4.2-112.5)	14.2 (5.9-117.2)	0.943
ALT (U/l)	40.1 (8.3-567.1)	38.0 (8.3-341.6)	41.9(9.5-567.1)	<0.001
AST (U/l)	37.6 (11.5-471.9)	36.4 (11.5-381.9)	38.6 (12.1-471.9)	0.001
Albumin (g/l)	41.3 (28.7-53.0)	42.5 (30.1-53.0)	40.2 (28.7-52.7)	<0.001
Platelet count (× 10^9/l)	147 (35-427)	158 (109-427)	137 (35-415)	0.013
Prothrombin time (s)	12.6 (10.4-17.3)	11.4 (10.4-16.2)	13.6 (11.3-17.3)	<0.001
Positive HBeAg	129 (47.1%)	47 (38.2%)	82 (54.3%)	<0.001
Tumor number				
Solitary	234 (85.4%)	108 (87.8%)	126 (83.4%)	0.244
Multiple	40 (14.6%)	15 (12.2%)	25 (16.6%)	
Tumor size				
≤ 3 cm	217 (79.2%)	96 (78.0%)	121 (80.1%)	0.489
>3 cm	57 (20.8%)	27 (22.0%)	30 (19.9%)	
Tumor differentiation				
Well or moderately	211 (77.0%)	96 (78.0%)	115 (76.2%)	0.372
Poorly	63 (23.0%)	27 (22.0%)	36 (23.8%)	
Intraoperative blood loss (ml)	300 (50-2000)	300 (50-800)	350 (50-2000)	0.053
Intraoperative transfusion	18 (6.6%)	8 (6.5%)	10 (6.6%)	0.051
Regular hepatic lobectomy	217 (79.2%)	101 (82.1%)	116 (76.8%)	0.931

Table 1: Patient characteristics and comparisons of the negative vs. positive HBV-DNA group.

Comparison of clinical characteristics

There was no significant difference in terms of sex distribution, age, serum AFP levels, tumor-pathologic parameters, and operative findings between the negative HBV-DNA group and the positive HBV-DNA group (Table 1). Laboratory datas were compared between the two groups to investigate the effect of HBV-DNA status on liver function status at study entry. As shown in Table 1, patients with positive HBV-DNA had significantly lower serum platelet count (P=0.013), more increased prothrombin time (P<0.001), lower serum albumin level (P<0.001), and higher serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels (ALT: P<0.001; and AST: P=0.001, respectively). And also in comparision with the negative HBV-DNA group, the positive HBV-DNA group had significantly higher HBeAg positive rate (54.3% vs. 38.2%, P<0.001), higher incidence of cirrhosis (76.8% vs. 47.2%, P<0.001), and poor Child's grade (7.9% of Child-pugh criteria B vs. 1.6%, P=0.001).

Comparisons of OS, RFS, and mortality

Within a median follow-up duration of 50 months (range, 1 month-74 months), recurrences were found in 118 patients (43.1%) and deaths occurred in 44 patients (16.1%). 7 patients suffered from perioperative death in total; 3 patients (2.4%) from the negative HBV-DNA group, owing to hepatic failure(n=2) and cardiovascular disease(n=1); 4 patients (2.6%) from the positive HBV-DNA group, owing to hepatic failure(n=4). So far, 21 patients failed to follow-up, of which 8 patients before recurrence.

Among 118 recurrences, 70 patients were from the positive HBV-DNA group and 48 patients were from the negative HBV-DNA group. Similarly, among a total of 44 deaths, 26 patients were from the positive HBV-DNA group and 18 patients were from the negative HBV-DNA group.

The OS and RFS curves between the positive HBV-DNA group and the negative HBV-DNA group are shown in Figure 2 and 3, both demonstrating a significant difference between the two groups. Patients with positive HBV-DNA had lower OS rates (1-year, 3-year, and 5-year: 91.7%, 77.4%, and 69.6%, respectively) as compared to those with negative HBV-DNA (1-year, 3-year, and 5-year: 95.0%, 82.3%, and 74.6%, respectively) (P=0.041). Consistent with the OS results, there were significant differences in RFS rates between the positive HBV-DNA group and the negative HBV-DNA group (1-year, 3-year, 5-year: 70.8%, 49.3%, 32.8% vs. 73.7%, 53.7%, 41.8%, respectively) (P=0.032).

Among 151 patients with positive HBV-DNA, 60 patients (39.7%) had high viral load and 91 patients (60.3%) had low viral load. Among 70 recurrences of patients with positive HBV-DNA, 36 patients were from the high viral load group and 34 patients from the low viral load group. Similarly, among a total of 26 deaths, 14 patients were from the high viral load group and 12 patients from the low viral load group.

Figure 4 and 5 demonstrates a significant difference of OS and RFS between the two groups, respectively. The high viral load group had lower OS rates (1-year, 3-year, and 5-year: 89.2%, 76.6%, and 62.8%, respectively) as compared to the low viral load group (1-year, 3-year, and 5-year: 93.1%, 81.5%, and 70.1%, respectively) (P=0.001). There were also significant differences in RFS rates between the high viral load group and the low viral load group (1-, 3-, 5-year: 67.2%, 40.6%, 23.8% vs. 71.1%, 49.7%, 38.1%, respectively) (P=0.017).

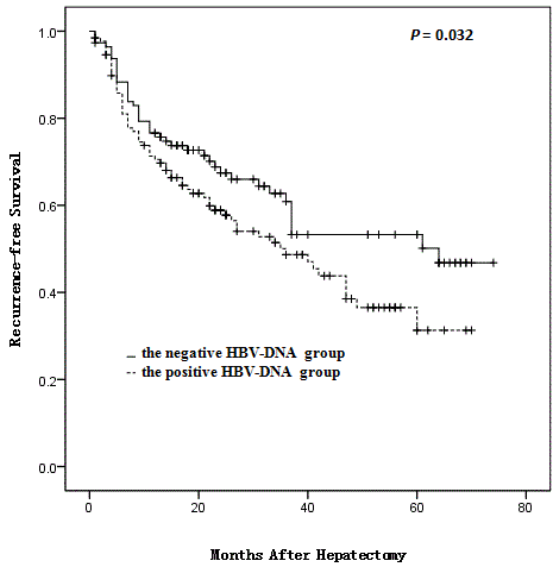

Figure 2: The RFS and OS curves between the positive HBV-DNA group and the negative HBV-DNA group.

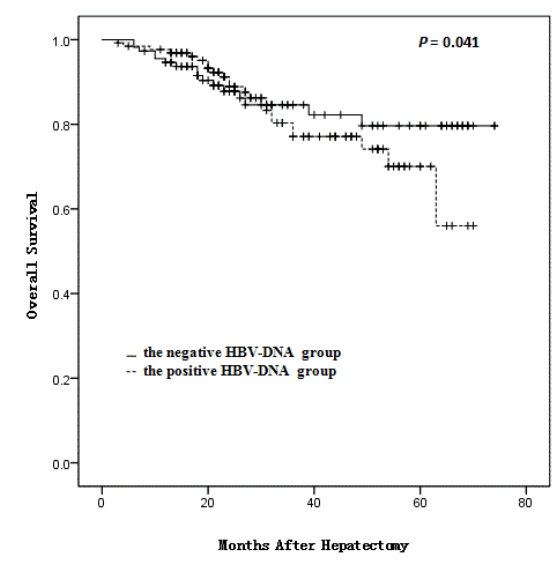

Figure 3: The RFS and OS curves between the positive HBV-DNA group and the negative HBV-DNA group.

Prognostic factors for OS and RFS

Univariate analyses for prognostic factors of OS and RFS after curative resection of HBV-related HCC are shown in Table 2. Multivariate analyses (Table 3) revealed that multiple tumors, maximum tumor size>3 cm, intraoperative transfusion, and irregular hepatic lobectomy were independently associated with poor OS and RFS.

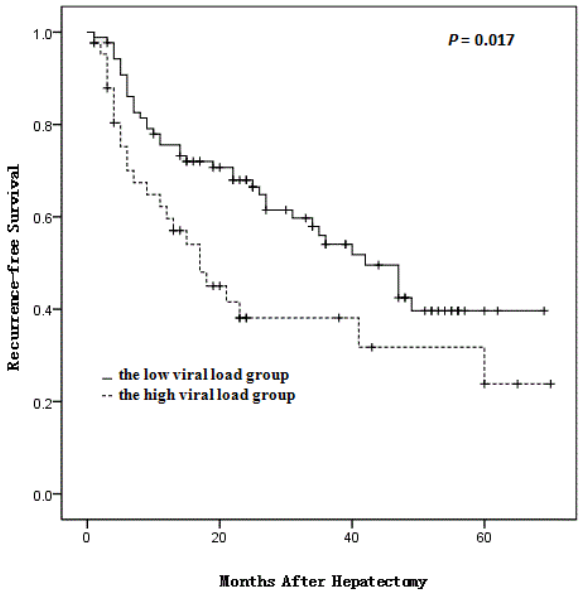

Figure 4: The RFS and OS curves between the high viral load group and the low viral load group.

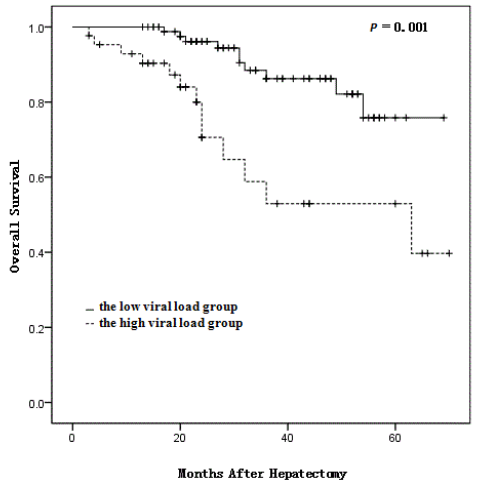

Figure 5: The RFS and OS curves between the high viral load group and the low viral load group.

Notably, preoperative positive HBV-DNA was also confirmed to be independently related to poor survival outcome (OS: P<0.001, odd ratio 2.401, 95% CI 1.476-2.813; RFS: P<0.001, OR 1.783, 95% CI 1.342-1.904). In addition, platelet counts<100 × 10^9/l, serum total bilirubin levels>17 mmol/l, and serum albumin levels<35 g/l were also independent factors for OS.

	Recurrence	P value for RFS	Died	P value for OS
Male	114	0.531	39	0.714
Age>50 years	63	0.736	27	0.597
Cirrhosis	81	0.032	33	<0.001
Child-Pugh grade				
A	115	0.241	39	<0.001
B	3		5	
Serum AFP level ≥ 8 ng/ml	74	0.026	26	<0.001
Total bilirubin>17 μmol/l	59	0.791	28	0.031
ALT>50 U/l	68	0.672	19	0.317
AST>40 U/l	81	0.041	22	<0.001
Albumin<35 g/L	63	0.413	26	<0.001
Platelet count<100 × 10^9/l	55	0.927	26	<0.001
Prothrombin time>14 s	65	0.591	21	0.002
Positive HBeAg	74	0.044	27	<0.001
HBV viral load ≥ 10^3 copies/ml	70	<0.001	26	<0.001
Multiple tumor	75	<0.001	20	<0.001
Tumor size>3 cm	78	<0.001	27	<0.001

Poorly tumor differentiation	73	0.003	17	0.051
Intraoperative blood loss ≥ 800 ml	7	<0.001	7	<0.001
Intraoperative transfusion	4	<0.001	5	<0.001
Irregular hepatic lobectomy	28	<0.001	39	<0.001

Table 2: Univariate analysis of prognostic factors for recurrence-free and overall survival.

	RR	95% CI		P
		Low	High	
Overall survival				
Positive HBV-DNA	2.401	1.476	2.813	<0.001
Total bilirubin>17 μmol/l	1.352	1.009	1.976	0.027
Albumin<35 g/l	1.652	1.470	2.093	0.045
Platelet count<100 × 10^9/l	1.892	1.329	2.118	0.031
Multiple tumor	1.672	1.327	2.228	<0.001
Tumor size>3 cm	1.727	1.562	2.761	<0.001
Intraoperative transfusion	1.826	1.483	2.430	0.021
Irregular hepatic lobectomy	1.753	1.560	2.551	0.002
Recurrence-free survival				
Positive HBV-DNA	1.783	1.342	1.904	<0.001
Multiple tumor	1.674	1.236	2.128	<0.001
Tumor size>3 cm	1.868	1.598	2.305	<0.001
Intraoperative transfusion	1.544	1.388	2.622	0.003
Irregular hepatic lobectomy	1.127	0.936	1.872	<0.001

Table 3: Multivariate analysis of risk factors for poor overall survival and recurrence-free survival.

Effects of antiviral therapy on OS and RFS

A further study on the efficacy of postoperative antiviral therapy in patients with positive HBV-DNA was conducted. 151 patients were enrolled in the subgroup analysis, including 50 patients (33.1%) who had received irregular antiviral drugs after surgery or discharge from hospital, and 101 patients (66.9%) who received the regular administration of oral antiviral drugs.

Among 70 recurrences of patients with positive HBV-DNA, 31 patients were from the regular antiviral therapy group and 39 patients from the irregular antiviral therapy group. Similarly, among a total of 26 deaths, 11 patients from the regular antiviral therapy group and 15 patients from the irregular antiviral therapy group.

As shown in Figure 6 and 7, the regular antiviral therapy group had higher OS rates (1-year, 3-year, and 5-year: 94.0%, 80.0%, and 72.4%, respectively) as compared to the irregular antiviral therapy group (1-year, 3-year, and 5-year: 88.1%, 71.7%, and 60.4%, respectively) (P<0.001). There were also significant differences in RFS rates between the regular antiviral therapy group and the irregular antiviral therapy group (1-year, 3-year, 5-year: 74.2%, 50.7%, 42.1% vs. 66.3%, 39.6%, 20.8%, respectively) (P<0.001).

101 positive HBV-DNA patients who received regular antiviral therapy were monitored. After six months, 55 patients (54.5%) had negative HBV-DNA, and 46 patients (45.5%) still had positive HBV-DNA.

Among 31 recurrences of positive HBV-DNA patients who received regular antiviral therapy, 14 patients were from the HBV-DNA became negative within six months group and 17 patients were from the HBV-DNA stayed positive within six months group. Similarly, among a total of 11 deaths, including 3 patients from the HBV-DNA became negative within six months group and 8 patients from the HBV-DNA stayed positive within six months group.

As shown in Figure 8 and 9, the HBV-DNA became negative within six months group had higher OS rates compared to the HBV-DNA stayed positive within six months group (1-year, 3-year, 5-year: 97.6%, 82.4%, 74.0% vs. 89.6%, 76.5%, 67.4%, respectively) (P=0.001). It also demonstrated significant differences in RFS rates between the HBV-

DNA became negative within six months group and the HBV-DNA stayed positive within six months group (1-year, 3-year, 5-year: 79.6%, 52.4%, 44.8% vs. 71.1%, 46.7%, 31.1%, respectively) (P<0.001).

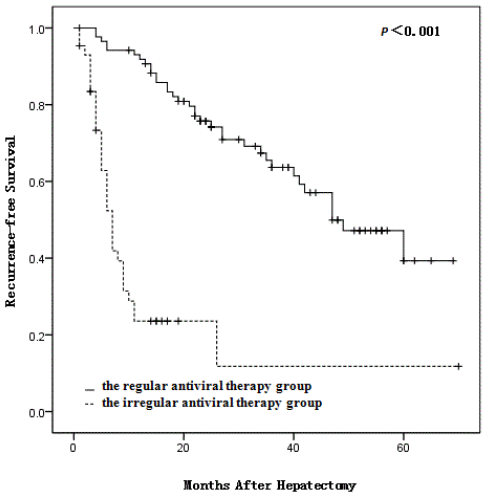

Figure 6: The RFS and OS curves between the regular antiviral therapy group and the irregular antiviral therapy group.

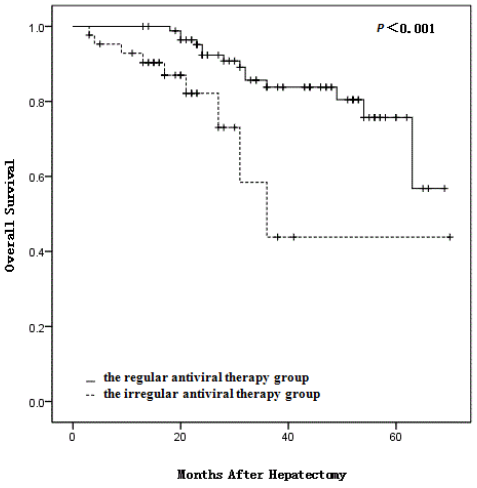

Figure 7: The RFS and OS curves between the regular antiviral therapy group and the irregular antiviral therapy group.

Discussion

General comment about our study

This study is on recurrence-free survival, overall survival and prognostic factors after curative resection of HBV-related HCC within milan criteria. Our data added strength to the viewpoint that HBV-DNA status at study entry is associated with tumor recurrence after resection of HBV-related HCC, which has been previously confirmed in only a few studies with relatively small sample sizes [17-20]. And our results showed that higher viral load led to lower PFS and OS. We evaluated the relationship between HBV-DNA status and overall survival and mortality after curative resection, and clearly showed that postoperative antiviral therapy significantly decreased recurrence and improved recurrence-free survival in patients with positive HBV-DNA at study entry, which was implied in several studies previously [18-20,26].

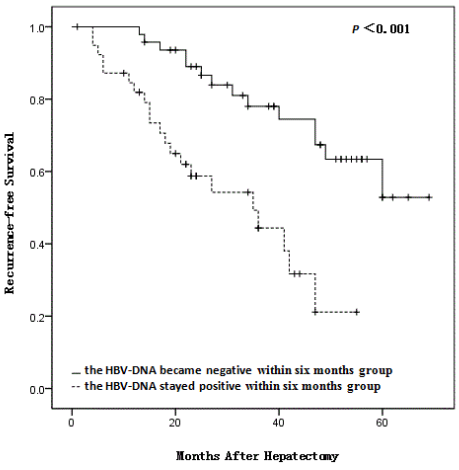

Figure 8: The RFS and OS curves between the HBV-DNA became negative within six months group and the HBV-DNA stayed positive within six months group.

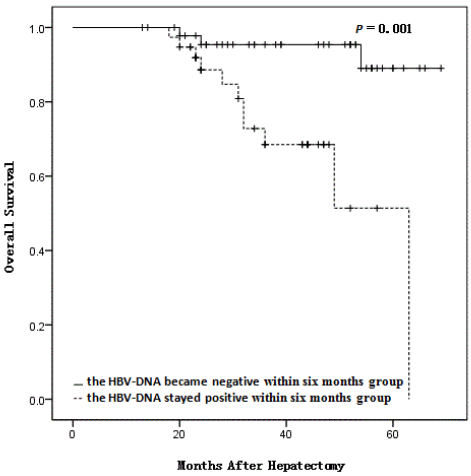

Figure 9: The RFS and OS curves between the HBV-DNA became negative within six months group and the HBV-DNA stayed positive within six months group.

In this current study, we investigated patients who received regular antiviral therapy and who received irregular antiviral therapy during the follow-up, and we did collect full information on the fluctuation of HBV-DNA, including degree of suppression by antiviral treatment, presence of HBeAg seroconversion which may be associated with

long-term prognosis after curative resection. The most important contribution of this study is that we, demonstrated for the first time, curative regular antiviral therapy within a relative short time has significantly improved PFS and OS of HBV-related HCC within Milan Criteria after HR.

Overview of literature

Some authors have suggested that HBV DNA levels of 1,000 copies/ml or more is the strongest predictor of future HCC risk [27,28], and some studies have already confirmed that positive HBV-DNA is a major risk factor for the development of HCC in patients with chronic HBV infection [27-29]. In a recent study on the recurrence of HCC after surgical resection [17-20], patients with positive HBV-DNA at study entry had a significantly higher risk of HCC recurrence when compared to those with negative HBV-DNA, which is consistent with the findings of our current study.

Although the precise mechanism by which HBV DNA induces hepatocarcinogenesis is unclear, it is possible that the upregulation of adhesion molecules on the cells lining the sinusoids in patients with high viral load may enhance tumor progression [17]. In addition, another possible mechanism is that an increased viral load may contribute to the carcinogenic process, probably caused by the augmented, direct oncogenic potential of HBV and the accompanying necroinflammatory process resulting from high viral load [30].

Effects of antiviral therapy on survival

The american association for the study of liver diseases (AASLD) practice guidelines recommend that antiviral therapy be initiated in all patients with compensated cirrhosis and serum HBV DNA>1,000 copies/ml [31]. Actually, adjuvant antiviral therapy was commenced within a week after operation or after discharge for all patients' regardless HBV-DNA status in our center [24]. However, because of poor medical and health education, unsound medical system [21], Chinese patients do not always follows doctor's advice and treatment regime, which made our present study possible. In addition, in Mainland China, there is still no official guideline to indicate that antiviral treatment for HBV patients could prevent HCC recurrence. Hence, no ethical issue.

It is now clear that active HBV replication is the key driver of liver injury and disease progression, thus sustained viral suppression is of paramount importance [32]. Therefore, the primary aim of treatment for HBV-related HCC after HR is to permanently suppress HBV replication. This decreases infectivity and pathogenicity of the virus, reducing the pathogenicity of the virus results in reduced hepatic necroinflammation. Clinically, the short-term goal of treatment is to achieve "initial response" in terms of HBV-DNA suppression, and prevention of hepatic decompensation; to ensure "maintained/ sustained response" to reduce hepatic necroinflammation and fibrosis during/after therapy. The ultimate long-term goal of therapy is to achieve "durable response" to prevent hepatic decompensation, reduce or prevent progression to cirrhosis and/or HCC, and prolong survival [24].

Of note, high levels of viral load at study entry are not only a major risk factor for long-term prognosis but also the risk factor most amenable to modification. It is anticipated that the implementation of strategies for antiviral use, that results in a durable suppression of HBV replication will ultimately lead to a reduction in the recurrence and death due to HCC. A recent, small, non-randomized study on the use of antiviral therapy after resection of HBV-related HCC patients with positive HBV-DNA suggested that antiviral therapy may be effective in improving recurrence-free survival[33]. Our current analysis in a subgroup of patients with positive HBV-DNA showed that postoperative antiviral therapy did significantly decrease tumor recurrence rate, with prolonged median RFS and OS. Therefore, we believe that antiviral therapy should improve prognosis, especially including recurrence-free survival after resection of HCC with positive HBV-DNA [34].

Limitations of the present study

Even though this is a retrospective study, one of the limitations of this study is based on determinations of HBV-DNA status at a single time point rather than at multiple time points. We prospectively collected all the information of patients in West China hospital from electronic medical record within the time period of 2007 to 2012. Also, HBV genotypes [28], HBV mutations [29], and concurrent infection with HCV, HDV, or HIV [30] were not evaluated in the present study. These factors are all well-recognized virological predictors associated with HCC incidence in patients with chronic HBV infection. And we did not investigate various effects and types of antiviral drugs, whether there is any difference among them such as lamivudine, adefovir dipivoxil, and entecavir. All these shortcomings require further randomized controlled clinical trials to confirm.

Conclusion

In conclusion, we have shown that preoperative positive HBV-DNA (HBV-DNA ≥ 1,000 copies/ml) is associated with poor overall and recurrence-free survival after curative resection of HBV-DNA related HCC within MC. Apart from other clinicopathological and operative factors that are potentially associated with long-term prognosis, HBV-DNA status, and antiviral therapy are also very important in comprehensive assessments. To improve long-term prognosis of HBV-related HCC after resection, we recommend that curative antiviral therapy be initiated in HBV- related HCC patients with positive HBV-DNA as soon as possible.

Conflict of interest

The authors indicates no potential conflicts of interest.

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