Antiviral Therapy Reduces Hepatocellular Carcinoma Recurrence in Patients With Low HBV-DNA Levels

A Randomized Controlled Trial

Gang Huang, MD, Peng-peng Li, MD,* Wan Yee Lau, MD, FRCS, FACS, FRACS(Hon),*† Ze-ya Pan, MD,* Ling-hao Zhao, MD,* Zhen-guang Wang, MD,* Meng-chao Wang, MD,* and Wei-ping Zhou, MD**

Background: Despite antiviral treatment has been shown to reduce hepatocellular carcinoma (HCC) recurrence after curative treatment for hepatitis B virus (HBV)-related HCC in patients with high preoperative HBV-DNA levels, it is still unclear whether antiviral therapy is useful in reducing recurrence in patients with low preoperative HBV-DNA levels.

Methods: In this randomized controlled trial, 200 patients who underwent curative resection for HCC with low baseline HBV-DNA levels were randomly assigned to receive preemptive antiviral therapy or not. The primary endpoints were recurrence-free survival. This study was censored on March 31, 2015 when all surviving patients had a minimum follow-up of 60 months. The analysis was done on an intention-to-treat basis.

Results: The baseline clinical, laboratory, and tumor characteristics of the 2 groups were comparable. The 1-, 3-, and 5-year recurrence-free survival rates for the antiviral group and the control group were 85.9%, 55.2%, and 52.0% and 80.6%, 40.9%, and 32.3%, respectively. The corresponding overall survival rates for the 2 groups were 94.0%, 75.7%, and 64.1% and 90.0%, 62.4%, and 43.7%, respectively. The recurrence-free survival and overall survival for the antiviral group were significantly better than the control group ($P = 0.016$, $P = 0.004$, respectively). After adjusting for confounding prognostic factors in a Cox model, the relative risks of recurrence and death for antiviral treatment were 0.601 [95% confidence interval (CI), 0.409–0.884; $P = 0.010$] and 0.509 (95% CI, 0.333–0.778; $P = 0.002$), respectively. Antiviral therapy was an independent protective factor of late tumor recurrence (hazard ratio [HR] = 0.316, 95% CI 0.157–0.637; $P = 0.001$) but not of early tumor recurrence (HR = 0.782, 95% CI, 0.493–1.240; $P = 0.296$).

Conclusions: In patients with low preoperative HBV-DNA levels, antiviral therapy significantly reduced HCC recurrence after R0 hepatic resection.

Keywords: antiviral therapy, hepatectomy, hepatitis B virus, hepatocellular carcinoma, prognosis

(*Ann Surg* 2018;268:943–954)

Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world and the third leading cause of cancer-related death.[1]

From the *Eastern Hepatobiliary Surgery Hospital, National Innovation Alliance for Hepatitis and Liver Cancer, Shanghai, China; and †Faculty of Medicine, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong SAR, People's Republic of China.

G.H. and P.L. contributed equally to this work.

This study was funded by the Project of Science and Technology Commission of Shanghai Municipality: 14411967800; National Science Foundation of China: 81572941; National Key Basic Research Program of China: 2014CB542102; and Creative Research Groups Grant: 81221061.

The authors declare no conflicts of interest.

Reprints: Wei-ping Zhou, MD, Gang Huang, MD, Department of Hepatic Surgery, Eastern Hepatobiliary Surgery Hospital, National Innovation Alliance for Hepatitis and Liver Cancer, No. 225 Changhai Rd., Shanghai 200438, China. E-mail: ehphwp@126.com; squaror@163.com.

ISSN: 0003-4932/18/26806-0943

DOI: 10.1097/SLA.0000000000002727

Hepatitis B virus (HBV) infection is a major risk factor for HCC.[2] Surgical resection is the first-line therapeutic option for patients with resectable tumors and preserved liver function.[3] However, a significant proportion of patients develop tumor recurrence, which together with concomitant hepatic decompensation in a background of cirrhosis, are the main causes of death on long-term follow-up.[4,5] Thus, the long-term prognosis after liver resection remains unsatisfactory, and prevention of recurrence via adjuvant treatments is an important, though unmet medical need, in patients with HCC.

In addition to tumor and surgical factors, host factors such as presence of cirrhosis and hepatitis viral load have also been shown to be risk factors of recurrence after curative resection of HCC.[6] Results from our previously reported randomized controlled trial showed antiviral treatment with nucleotide analogues reduced the risk of tumor recurrence in patients with high preoperative HBV-DNA levels.[7] Whether antiviral therapy reduces tumor recurrence and improves postoperative survivals in patients with low preoperative HBV-DNA levels (HBV-DNA <2000 IU/mL) are still unclear.

This randomized controlled trial was conducted to investigate whether preemptive antiviral therapy improves survivals after liver resection for HBV-related HCC in patients with low preoperative viral levels.

METHODS

Study Design and Participants

The study was designed as a prospective, single-center, randomized controlled study to test the efficacy of postoperative antiviral therapy in patients with HBV-related HCC with low preoperative HBV-DNA levels. Eligible patients were randomly assigned in a 1:1 ratio via computer-generated allocation to either the antiviral group or the control group. The Barcelona Clinic Liver Cancer (BCLC) stage was used as a stratification factor before randomization. Patients had to wait for the postoperative pathologic results (4–6 days after surgery) before they were assigned. Using the 2007 guideline as approved by the American Association for the Study of Liver Diseases, telbivudine was chosen as the antiviral drug. Telbivudine has a low treatment cost with good effects in suppressing the wild type HBV.[8,9] Patients in the antiviral group received telbivudine tablets (Sebivo, Novartis, Beijing Novartis Pharma Ltd, Beijing, China) 600 mg/day orally starting from 4 to 7 days after surgery; those in the control group did not receive any antiviral treatment. Antiviral treatment was continued unless there was unacceptable toxicity or withdrawal of consent. The study was approved by the Ethics Committee of the Eastern Hepatobiliary Hospital, and the study enrollment was carried out after a written informed consent was obtained from each patient. The study was investigator designed and investigator driven, and it received no support from any pharmaceutical companies. This research was under the effective ethical review of a member of the executive oversight committee. The study has been registered in the Chinese Clinical Trials

Registry (ChiCTR) at http://www.chictr.org.cn and the registration number isChiCTR-IPR-15006587.

From November 2008 to March 2010 consecutive patients with newly diagnosed HBV-related HCC who had received R0 liver resection at the Hepatic Surgery Center, the Eastern Hepatobiliary Surgery Hospital were eligible for enrollment. The diagnosis of HCC was based on histopathological study of the resected specimens.

The inclusion criteria for this study were: (1) age 18 to 70 years; (2) positive test for hepatitis B surface antigen (HBsAg) and negative tests for antibodies to hepatitis C virus (HCV-Ab) or to human immunodeficiency virus; (3) serum HBV-DNA level <2000 IU/mL; (4) BCLC stage 0, A or a solitary tumor with a diameter >5 cm; (5) no extrahepatic metastasis; (6) no radiologic evidence of invasion into major portal/hepatic venous branches; (7) good liver function with Child - Pugh Class A and baseline serum alanine aminotransferase (ALT) level less than 2 times the upper limit of normal (reference range <40 IU/L), with no history of encephalopathy, ascites refractory to diuretics, esophagogastric variceal bleeding; (8) good renal function (a serum creatinine level <133 μmol/L); (9) no previous treatment of HCC; (10) no previous treatment of hepatitis B with nucleoside or nucleotide analogues or both; no previous treatment with interferon or other immunomodulators; (11) negative resection margin (R0 resection); and (12) histopathological result of the resected specimens being HCC.

Eligible patients were excluded if they refused to participate.

Preoperative Data

All patients had a chest x-ray, ultrasonography of abdomen, and contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) of abdomen. Laboratory blood tests including HBsAg, hepatitis B e antigen (HBeAg) and its antibody, HCV-Ab, serum alpha-fetoprotein (AFP), carcinoembryonic antigen, carbohydrate antigen 19-9, serum albumin, serum total bilirubin, aspartate aminotransferase, ALT, and prothrombin time were obtained, and the Pugh modification of Child's criteria was determined. All the patients were monitored twice before the operation at an interval which varied from 1 to 4 weeks. The HBV-DNA was also tested 1 week after operation. As treatment for HCC should be given soon after diagnosis, we were unable to monitor the HBV-DNA levels for a prolonged time period before the operation. Quantitative analysis of serum HBV-DNA was performed using the real-time polymerase chain reaction (PCR) method (ABI 7300, Applied Biosystems, CA) with a linear range of quantification of 200 to 2,000,000 IU/mL.

The preoperative diagnosis of HCC was based on the diagnostic criteria for HCC used by the European Association for the Study of the Liver.[10] Further investigations were performed only when there was clinical suspicion of extrahepatic metastases. The tumor was staged by the BCLC staging system.[11,12]

Cirrhosis was clinically defined based on the findings on US, CT, upper gastrointestinal endoscopy, and laboratory tests. Radiological evidences of cirrhosis in patients with a background of chronic liver disease included decreased liver size, bluntness of liver edge, coarseness of liver parenchyma, nodulation of liver surface, and increased spleen size. The group of patients who were classified to have cirrhosis included those who had radiological evidences of (1) cirrhosis or (2) patients who had a background of chronic liver disease and was associated with thrombocytopenia (<150 K/mm^3) and/or esophageal varices. If the clinical diagnosis of cirrhosis was equivocal, the patient was allocated to the "without cirrhosis" group.

Surgical Procedure

All surgeries were performed by the same surgical team with the same standard technique. Surgery was performed through a bilateral subcostal incision. The abdominal cavity was carefully searched for extent of local disease and extrahepatic metastases. Intraoperative ultrasound was performed to assess the number and the size of the lesions, and to assess the relationship of the tumor to vascular structures. Pringle's maneuver was applied to occlude the blood inflow of the liver with cycles of 15 minutes clamp time and 5 minutes unclamped time. Liver resection was carried out by a clamp-crushing method.

Assessment of Outcomes and Follow-up

All patients were followed-up at the outpatients clinic once every month for the first year and then once every 3 months thereafter. Serum HBV-DNA levels were quantified at each time point. The undetectable HBV-DNA level was restricted to our technology and equipment at the time. The quantitative analysis of serum HBV DNA in this study was performed using the real-time-PCR method and the instrument used was ABI 7300 (Applied Bio systems, CA), which has a linear range of quantification of 200 to 2,000,000 IU/mL. So the undetectable HBV-DNA level was less than 200 IU/mL.

Patient histories, physical examinations, and venipuncture samples for laboratory assessments were obtained at screening, at baseline, and at each follow-up visit after the operation. Serum HBV-DNA levels were quantified at each time point.

The primary endpoints of the study were recurrence-free survival, which was defined as the time from randomization to the first documented disease recurrence; and overall survival (OS), which was defined as the time from randomization to death by any cause. The secondary endpoints included the rate of HBV reactivation within 1 year, patient tolerance of antiviral treatment, virologic response, and liver function. Prescription cards for antiviral treatment were issued and patients were asked to record each drug dose taken. All patients were followed-up at the outpatients clinic once every month for the first year and then once every 3 months thereafter. At each follow-up visit, adverse effects were documented and blood tests were taken for HBV-DNA, complete blood counts, coagulation profile, renal and liver function, creatine kinase, AFP, and ultrasonography. Hepatitis B virus serology, including HBsAg, HBeAg, chest radiography, and contrast-enhanced 3-phase CT or MRI scan were performed once every 3 months.

Tumor recurrence was suspected on detection of new hepatic lesions on ultrasound or by a progressive and continuous elevation of serum AFP (>100 ng/mL). If the AFP level of the patient had fallen to normal after operation, or the patient had a normal AFP level before operation, the serum AFP levels of these patients were also regularly monitored. The diagnosis of recurrence was confirmed by dynamic CT scan or MRI. Further investigations (such as chest CT, full-body bone scan, and positron emission tomography-CT) were performed when there was clinical suspicion of extrahepatic metastases. Patients with tumor recurrence were actively treated with repeat hepatic resection, percutaneous radiofrequency ablation, percutaneous microwave coagulation therapy, systemic chemotherapy, radiotherapy, and/or transcatheter arterial chemoembolization, depending on the extent of the disease, the liver function, and the general condition of the patients.

HBV reactivation was defined as a greater than 10-fold increase in serum HBV-DNA when compared with the baseline level. Postoperative hepatitis due to HBV reactivation was defined as a sustained 2-fold or greater increase in serum ALT to a level that exceeded 80 IU/L(reference range <40 IU/L) during or after HBV reactivation in patients in the absence of clinical features of tumor progression, hepatotoxic drugs, treatment-related hepatic damage, or other systemic infections.[13–15] Patients who developed hepatitis caused by HBV reactivation were given antiviral therapy or a change in the antiviral treatment. Postoperative liver failure after partial

hepatectomy was defined using the criteria on the peak serum bilirubin concentration greater than 7 mg/dL.[16] Persistently undetectable HBV-DNA was defined as undetectable HBV-DNA on 2 or more consecutive occasions, and the assays were carried out at least 3 months apart. HBeAg seroconversion was present if 2 consecutive samples taken at least a month apart were positive for hepatitis B e antibody and negative for HBeAg. As recommended by Pawlotsky et al,[17] a nonresponse to antiviral treatment was assumed when HBV-DNA failed to decrease for more than 1 log after 12 weeks of treatment. The presence of drug viral resistance was actively looked for in patients who were put on prolonged antiviral therapy but with persistently detectable viremia, or in patients with an increase in HBV-DNA of at least 1 log following an initial decline in HBV-DNA level when these patients were put on antiviral treatment. When a suboptimal response was identified, the type of mutation was actively identified, and antiviral treatment was added/switched to a more potent nucleos(t)ide analogue accordingly. Patients who were refractory to telbivudine were switched to entecavir.

Patients who achieved a complete response with undetectable HBV-DNA, and seroconversion to anti-HBe were offered to continue the antiviral therapy. During this time, periodic monitoring of HBV-DNA and HBeAg were continued as relapse remained a possibility.

This study was censored on March 31, 2015 when all surviving patients had a minimum follow-up of 60 months.

Sample Size Calculation

Based on the results from a previous study on the effects of lamivudine on survival outcomes after resection of HCC in patients with high serum concentrations of HBV-DNA,[18] the 5-year tumor-free survival rate was approximately 80.0% in the lamivudine group, and the corresponding rate was approximately 30.0% in the control group. Using an alpha risk of 0.05 and a power of 80%, a sample size of 20 patients in each group was required. However, the main drawbacks of this study are its retrospective design, a small sample size and patients with high HBV-DNA levels. In another previously reported study,[19] the 3-year recurrence rate was 35.1% in the lamivudine group, and the corresponding rate was 53.2% in the control group. Consequently, a sample size of 80 patients in each group was calculated using an alpha risk of 0.05 and a power of 80%. Considering the difference between these studies and our new study and assuming the possibility of some violation from protocol and loss to follow-up after randomization, 100 patients were randomized into each study arm in our study.

Statistical Analysis

Continuous data were expressed as mean values ± standard deviations. The non-normal distribution data were given as median values with ranges. The serum HBV-DNA levels were expressed on a logarithmic scale. Statistical analyses were performed using the Statistical Program for Social Sciences (SPSS 18.0 for Windows). Quantitative values were compared using the Student *t* test or the Mann-Whitney nonparametric *U* test. Categorical variables were tested by the Chi-square or Fisher exact tests. OS and recurrence-free survivals were calculated by the Kaplan-Meier method and the differences were compared by the log-rank test. Univariate and multivariate analyses were performed by the Cox proportional hazards regression model with stepwise selection of variables. A statistical significance was defined at a P value of less than 0.05. All analyses were performed on an intention-to-treat basis.

RESULTS

Patients

From November 2008 to March 2010, 772 patients underwent hepatic resection for hepatitis B-related HCC at the Department of Liver Surgery, Eastern Hepatobiliary Surgery Hospital, China. There were 322 patients who had a preoperative HBV-DNA level <2000 IU/mL.

A total of 104 patients were excluded from this study because of: previous antiviral therapy (n = 31); previous treatment by regional or systemic chemotherapy (n = 12); age less than 18 or more than 70 years (n = 11); seropositivity for both HBsAg and HCV-Ab (n = 6); portal vein tumor thrombosis (n = 15); poor liver function (n = 10); poor renal function (n = 2); histopathological result being not HCC (n = 13); and residual tumor at the resection margin by postoperative histopathology (n = 4). Eighteen patients who fulfilled the inclusion criteria refused to participate. Finally, 200 consecutive patients were randomized to the 2 treatment groups (Fig. 1).The median follow-up was 60 months for all surviving patients. However, the range of follow-up was 2 to 77 months when patients who died and were loss to follow-up were included. Seven patients were lost to follow-up (3 patients in the antiviral group and 4 patients in the control group). On follow-up, 17 patients were given oral antiviral therapy for hepatitis due to HBV reactivation in the control group. In the antiviral group, 1 patient developed primary nonresponse, 18 patients developed viral resistance to telbivudine and 1 patient discontinued treatment because of myopathy. The therapy of these patients was then switched to entecavir 0.5 mg/day.

Six patients stopped taking antiviral treatment without authorization from clinicians on months 15, 24, 24, 28, 33, and 36 after operation, respectively, in the antiviral group. Except for these 6 patients, all patients in the antiviral group and all patients who were treated with antiviral treatment for hepatitis due to HBV reactivation in the control group were continued with antiviral treatment up to the date when this study was censored. All patients who were shifted to receive entecavir did not develop antiviral drug resistance and entecavir was continued up to the date when this study was censored.

The baseline characteristics and operative data of the patients are presented in Table 1. There were no significant differences in the parameters between the 2 groups.

Virologic Changes and Hepatitis B Virus Reactivation

The pretreatment HBV-DNA levels of the antiviral and the control groups were comparable (Table 1). At years 1, 3, and 5 during therapy, the corresponding rates of undetectable HBV-DNA (HBV-DNA <200 IU/mL) for the 2 groups were 95.7%, 94.4%, and 96.6% and 54.8%, 58.3%, and 69.8%, respectively. Twenty-five (25.0%) patients in the control group and 3 (3.0%) patients in the antiviral group developed viral reactivation (P <0.001) within 1 year after operation. Of the 25 patients who developed HBV reactivation in the control group, 17 (68.0%) patients developed clinical hepatitis due to viral reactivation. After administration of telbivudine (in 3 patients, the drug was switched to entecavir because of development of resistance to telbivudine in the control group) and glutathione, these patients recovered rapidly. The patients in the antiviral group who developed HBV reactivation received entecavir for primary nonresponse or resistance to telbivudine therapy. All these patients recovered well. They were all censored at the end of the study.

Recurrence and Survival

At the time of censor, 112 (56.0%) patients had developed tumor recurrence and 94 (47.0%) patients had died. Of the patients who had died, 88 (93.6%) patients (54 in the control group and 34 in the antiviral group) died from tumor recurrence, and 6 (6.4%) patients (4 in the control group and 2 in the antiviral group) died from liver failure. The 1-, 3-, and 5-year recurrence-free survival rates for the antiviral group and the control group were 85.9%, 55.2%, and 52.0% and 80.6%, 40.9%, and 32.3%, respectively. The

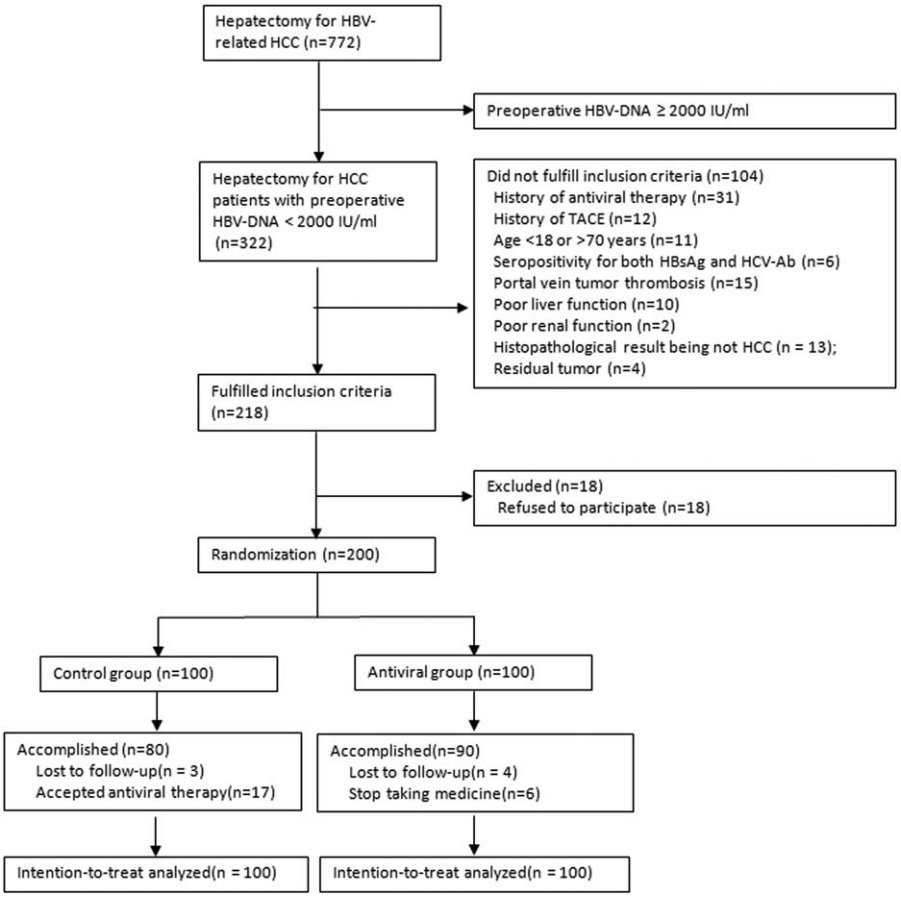

FIGURE 1. Patient numbers for the intention-to-treat analysis.

corresponding OS rates for the 2 groups were 94.0%, 75.7%, and 64.1% and 90.0%, 62.4%, and 43.7%, respectively. At 5-year follow-up, the recurrence-free survival and OS for patients who received antiviral therapy were significantly better than those who did not receive antiviral therapy ($P = 0.016$, $P = 0.004$) (Figs. 2 and 3).

The parameters which were significantly associated with tumor recurrence on univariate analysis were entered into multivariate analysis. Antiviral treatment ($P = 0.010$, hazard ratio [HR] = 0.601, 95% confidence interval [CI] 0.409–0.884) and tumor encapsulation ($P = 0.019$, HR = 0.611, 95% CI 0.404–0.923) were independent prognostic factor that were associated with a decreased risk of HCC recurrence. In contrast, tumor size of more than 5 cm ($P = 0.003$, HR = 1.814, 95% CI 1.224–2.678), presence of satellite nodules ($P = 0.004$, HR = 1.920, 95% CI 1.238–2.978), presence of microvascular infiltration ($P = 0.001$, HR = 1.979, 95% CI 1.302–3.008), high Ishak inflammation score ($P = 0.029$, HR = 1.647, 95% CI 1.054–2.573), and high Ishak fibrosis score ($P = 0.026$, HR = 1.554, 95% CI 1.054–2.289) were independent prognostic factors that were associated with an increased risk of HCC recurrence after liver resection (Table 2). On multivariate analysis, 6 significant factors were associated with postoperative OS: tumor size of more than 5 cm ($P = 0.029$, HR = 1.605, 95% CI 1.049–2.455), tumor encapsulation ($P = 0.025$, HR = 0.603, 95% CI 0.387–0.939), presence of satellite nodules ($P = 0.024$, HR = 1.697, 95% CI 1.074–2.683), presence of microvascular infiltration ($P < 0.001$, HR = 2.981, 95% CI 1.924–4.619), high Ishak fibrosis score ($P = 0.029$, HR = 1.654, 95% CI 1.052–2.603), and antiviral treatment ($P = 0.002$, HR = 0.509, 95% CI 0.333–0.778) (Table 3). Antiviral therapy was not only an independent protective factor of tumor recurrence, but also an independent protective factor of death.

Early and Late Recurrences

Of 200 patients, 73 patients (33 in the antiviral group and 40 in the control group) developed early HCC recurrence within 2 years of liver resection. On multivariate analysis, tumor size of more than 5 cm, absence of encapsulation, presence of satellite nodules, and presence of microportal vein tumor thrombus were significantly associated with early tumor recurrence. Antiviral therapy was not associated with a low risk of early tumor recurrence (HR = 0.782, 95% CI, 0.493–1.240; $P = 0.296$) (Table 4). There were 39 patients (14 in the antiviral group and 25 in the control group) who developed late tumor recurrence. On analysis of the risk factors associated with late recurrence in the remaining 121 patients (excluding 73 patients with early tumor recurrence and 6 patients without early tumor recurrence but who had died or lost to follow-up within 2 years), antiviral therapy was an independent protective factor of late tumor recurrence (HR = 0.316, 95% CI 0.157–0.637; $P = 0.001$) (Table 5).

Subgroup Analysis on Patients With Cirrhosis

A total of 79 patients (40 in the antiviral group and 39 in the control group) were diagnosed with cirrhosis. There were no significant differences in the rates of cirrhosis between the 2 groups (40% vs 39%, $P = 0.885$) (Table 1). Cirrhosis was not significantly associated with tumor recurrence (HR = 1.236, 95% CI, 0.850–1.797; $P = 0.267$) and death (HR = 1.444, 95% CI, 0.962–2.167; $P = 0.076$) (Tables 2 and 3). We also analyzed the effect of viral suppression in

TABLE 1. Baseline Characteristics and Operative Data of the Patients

Characteristics	Control Group (n = 100)	Antiviral Group (n = 100)	*P*
Patient characteristics			
Age (yr)	52 (39)	51 (50)	0.569
Sex (M/F)	86/14	87/13	0.836
HBeAg positivity	19 (19.0%)	18 (18.0%)	0.856
HBV-DNA level (IU/mL)			
≤200	71 (71%)	72 (72%)	0.876
200-1999	29 (30%)	28 (28%)	
Cirrhosis	39 (39%)	40 (40%)	0.885
Normal ALT levels	84 (84%)	77 (77%)	0.212
Ishak inflammation score	4 (12)	4 (13)	0.712
Ishak fibrosis score	3 (5)	3 (5)	0.701
Alcohol abuse	9 (9%)	11 (11%)	0.637
History of smoking	20 (20%)	22 (22%)	0.728
Family history of HCC	11 (11%)	10 (10%)	0.818
Body mass index (BMI)	23.6 ± 3.6	23.1 ± 3.2	0.297
Diabetes	14 (14%)	12 (12%)	0.674
Hypertension	14 (14%)	18 (18%)	0.440
Preoperative laboratory tests			
Hemoglobin (g/L)	143.5 ± 15.2	143.8 ± 16.6	0.915
Platelet count (10^9/L)	154.1 ± 51.5	157.3 ± 52.8	0.663
Prothrombin time (s)	12.1 ± 1.3	12.0 ± 1.3	0.343
Bilirubin (μmol/L)	14.7 ± 4.3	14.4 ± 4.9	0.569
Albumin (g/L)	42.5 ± 5.0	42.5 ± 4.6	0.968
Alanine aminotransferase (IU/ L)	28.3 ± 14.6	29.7 ± 14.1	0.480
Creatinine (μmol/L)	70.6 ± 12.5	68.7 ± 11.6	0.264
Creatine kinase (U/L)	66.1 ± 19.8	67.5 ± 19.3	0.616
Tumor characteristics			
AFP (ng/mL) median (range)	60.7 (0.6–1210.0)	72.2 (1.9–1210.0)	0.821
Tumor diameter (cm)	4.6 ± 1.9	4.7 ± 2.3	0.674
BCLC stage			
0	8 (8.0%)	9 (9.0%)	0.894
A	56 (56.0%)	58 (58.0%)	
Solitary tumor with diameter >5 cm	36 (36.0%)	33 (33.0%)	0.861
Satellite nodule (n)			
Yes	21 (21.0%)	20 (20.0%)	0.747
No	79 (79.0%)	80 (80.0%)	
Microvascular infiltration (n)			
Yes	25 (25.0%)	27 (27.0%)	
No	75 (77.0%)	73 (73.0%)	
Operative data			
Type of resection (n)			
Minor	74 (74.0%)	70 (70.0%)	0.529
Major	26 (26.0%)	30 (30.0%)	
Operating time (min)	177.9 ± 46.4	175.8 ± 41.8	0.737
Clamp Time (min)	23.2 ± 12.3	22.7 ± 11.6	0.777
Blood loss (mL)	300 (100–2600)	300 (100–4500)	0.720
Transfusions (n)			
Yes	13 (13.0%)	12 (12.0%)	0.831
No	87 (87.0%)	88 (88.0%)	

these patients with cirrhosis. We found that the 1-, 3-, and 5-year recurrence-free survival rates for the antiviral group and the control group were 84.6%, 53.8%, and 45.5% and 78.4%, 35.1%, and 27.0%, respectively. Analysis of survival in the patients with cirrhosis, however, revealed that the recurrence-free survival rates were slightly higher in the antiviral group compared with controls, although the differences were not significant ($P = 0.126$).

DISCUSSION

Partial hepatectomy is universally accepted as a curative treatment option for HCC, but the long-term prognosis remains unsatisfactory due to the high rate of recurrence. Several investigators reported that a high HBV-DNA level was a risk factor of recurrence after curative resection of HCC.[6,20] It is well known that antiviral treatment reduces the incidence of HCC in patients who are HBsAg positive,[21–24] and antiviral treatment is important in reducing HCC recurrence and improving survival after curative liver resection for HBV-related HCC in patients with a high preoperative HBV-DNA load.[25–27] Our previous studies showed antiviral therapy to be useful in reducing postoperative HCC recurrence in patients with high preoperative HBV-DNA levels, and antiviral therapy was an independent prognostic factor of long-term survival (HR, 0.651; 95% CI: 0.451–0.938).[7] The guidelines put forward by the American Association for the Study of Liver Diseases, European Association for the Study of the Liver, and Asian Pacific Association for the Study of the Liver recommend treatment when the HBV-DNA levels are high (>2000 IU/mL).[28–30] Whether patients with low HBV-DNA levels

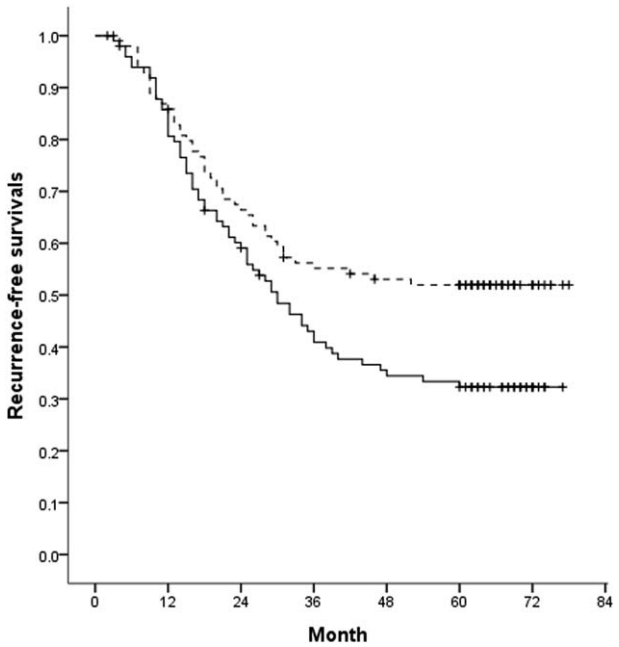

FIGURE 2. Comparison of recurrence-free survivals between the 2 groups. Dotted line: the antiviral group (n = 100), solid line: the control group (n = 100), log-rank test: $P = 0.016$.

should be treated with antiviral therapy, especially in patients who undergo partial hepatectomy for HBV-related HCC, is unclear. This study was conducted to find out the answers to these questions.

Many tumor characteristics are factors which are irreversible. However, the HBV status can be altered by antiviral therapy. Our previously reported study showed reactivation of viral replication to occur quite commonly after liver resection in patients with low preoperative HBV-DNA levels and prophylactic antiviral treatment very efficiently prevented HBV reactivation.[31] Another recent study even reported that HBV reactivation occurred in patients with HBsAg negativity.[32] This observation can be explained by the facts that the cut-off point (2000 IU/mL) for giving antiviral therapy or not is arbitrarily set and that the HBV-DNA levels in a patient can fluctuate.[33] A low preoperative baseline serum HBV-DNA level cannot be used to reliably identify patients who have a persistently low HBV-DNA level at all time points.[34] Furthermore, even when the serum HBV-DNA levels are at all the time points low, liver disease can still be in progress.[35]

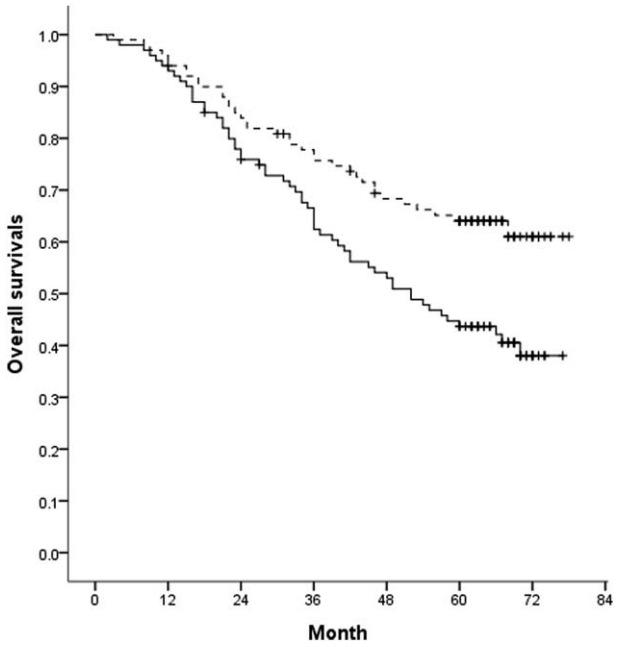

FIGURE 3. Comparison of overall survivals between the 2 groups, dotted line: the antiviral group (n = 100), solid line: the control group (n = 100), log-rank test: $P = 0.004$.

This study showed that the risk of HCC recurrence was not low for patients with low preoperative HBV-DNA levels. The 5-year cumulative HCC recurrence rate was 67.7% for patients with a low viral load at baseline. Antiviral treatment for these patients not only prevented HBV reactivation, but also improved postoperative survival. The HCC recurrence rate of the antiviral group was significantly lower than the control group of patients (Fig. 2). Thus, our data suggested that patients with HBV-related HCC with low viral loads should also be considered for prompt antiviral treatment after hepatectomy.

Imamura et al[36] suggested that recurrence of HCC should be divided into early and late recurrences according to the time of recurrence after liver resection. Early recurrence (within 2 years) was associated with tumor-related factors, including the presence of microvascular invasion and satellite lesions, whereas late recurrence (after 2 years) was related to the background of liver disease, such as hepatic inflammation and liver damage.[37] Our study showed early recurrence was associated with tumor size more than 5 cm, absence of encapsulation, presence of satellite nodules, and presence of microportal vein tumor thrombus. On the contrary, the risk factors of late recurrence were presence of satellite nodules, high Ishak fibrosis scores, and no antiviral treatment. Antiviral therapy improved both recurrence-free and OS after R0 resection for HCC. This study also demonstrated that antiviral treatment had no protection against early HCC recurrence. Our previously reported randomized trial[7] also showed that antiviral treatment could not reduce early HCC recurrence in patients with high baseline HBV-DNA levels. This study also showed antiviral treatment reduced the incidences of late tumor recurrence. These observations can be explained by the facts that specific tumor factors are known to be associated with early tumor recurrence and oral antiviral treatment has no direct antitumorous effect.

The main therapeutic effects of antiviral treatment were to prevent HBV reactivation, inhibit hepatitis activity, reduce inflammation in liver remnants, and reverse cirrhosis.[38] Active replication of HBV initiates hepatocarcinogenesis via both the direct and indirect carcinogenic mechanisms.[39,40] Sustained viremia has been shown to impair tumor immune surveillance resulting in a higher likelihood to develop multicentric carcinogenesis in the liver remnant,[41,42] and to upregulate adhesion molecules on cells lining liver sinusoids in patients with viral replication to enhance tumor development and spread.[41] Our results showed that the rate of undetectable HBV-DNA was significantly higher in antiviral group than in control group during follow-up. Restricted to our technology and equipment at the time, the undetectable HBV-DNA level was less than 200 IU/mL in our study. This level of 200 IU/mL is now considered to be too loose endpoint to define undetectable HBV-DNA level. Our current undetectable HBV-DNA level is less than 30 IU/mL. By today's standards, the rate of undetectable HBV-DNA should decrease in the control group and the differences of this rate between the 2 groups might become more obvious.

The hepatitis activity in the nontumorous liver has also been shown to be associated with tumor recurrence after hepatectomy,[43,44] especially for late recurrence. The putative mechanisms of how

TABLE 2. Univariate and Multivariate Analyses for Recurrence of Hepatocellular Carcinoma in Patients Who Underwent R0 Hepatic Resection

	No. Patients	Univariate Analysis		Multivariate Analysis	
Factors		**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Sex					
Male	173 (86.5%)	1.382 (0.759–2.518)	0.290		
Female	27 (13.5%)				
Age					
>60	40 (20.0%)	1.069 (0.680–1.679)	0.773		
≤60	160 (80.0%)				
Detectable HBV DNA					
Yes	58 (29.0%)	1.280 (0.859–1.905)	0.225		
No	142 (71.0%)				
HBeAg positivity					
Yes	37 (18.5%)	1.256 (0.794–1.987)	0.330		
No	163 (81.5%)				
ALT (IU/I)					
≥40	39 (19.5%)	1.126 (0.700–1.811)	0.624		
<40	161 (80.5%)				
TBIL (μmol/L)					
≥17	44 (22.0%)	1.374 (0.896–2.109)	0.146		
<17	156 (78.0%)				
PT (s)					
≥13	33 (16.5%)	1.114 (0.680–1.824)	0.669		
<13	167 (83.5%)				
Alb (g/L)					
<35	22 (11.0%)	1.443 (0.824–2.528)	0.199		
≥35	178 (89.0%)				
AFP (ng/mL)					
>100	93 (46.5%)	1.331 (0.919–1.929)	0.130		
≤100	107 (53.5%)				
Cirrhosis					
Yes	79 (39.5%)	1.236 (0.850–1.797)	0.267		
No	121 (60.5%)				
Liver Resection					
Major	56 (28.0%)	1.261 (0.845–1.880)	0.256		
Minor	144 (72.0%)				
Tumor diameter (cm)					
>5	69 (34.5%)	1.912 (1.316–2.778)	0.001	1.814 (1.224–2.687)	0.003
≤5	131 (65.5%)				
Clamp time (min)					
>30	50 (25.0%)	1.175 (0.777–1.778)	0.445		
≤30	150 (75.0%)				
Operation time (min)					
>180	122 (61.0%)	1.241 (0.843–1.826)	0.275		
≤180	78 (39.0%)				
Blood loss (mL)					
>1000	16 (8.0%)	1.562 (0.838–2.913)	0.160		
≤1000	184 (92.0%)				
Transfusion					
Yes	25 (12.5%)	1.690 (1.020–2.802)	0.042	1.214 (0.716–2.056)	0.472
No	175 (87.5%)				
Capsule					
Yes	144 (72.0%)	0.604 (0.410–0.890)	0.011	0.611 (0.404–0.923)	0.019
No	56 (28.0%)				
Presence of satellite nodules					
Yes	41 (20.5%)	2.409 (1.595–3.641)	<0.001	1.920 (1.238–2.978)	0.004
No	159 (79.5%)				
Presence of microvascular infiltration					
Yes	52 (26.0%)	2.569 (1.729–3.818)	<0.001	1.979 (1.302–3.008)	0.001
No	148 (74.0%)				
Ishak inflammation score					
>6	38 (19.0%)	1.709 (1.113–2.625)	0.014	1.647 (1.054–2.573)	0.029
≤6	162 (81.0%)				
Ishak fibrosis score					
≥4	75 (37.5%)	1.528 (1.053–2.218)	0.026	1.554 (1.054–2.289)	0.026
<4	125 (62.5%)				
Antiviral treatment					
Yes	100 (50.0%)	0.636 (0.437–0.926)	0.018	0.601 (0.409–0.884)	0.010
No	100 (50.0%)				

PT, prothrombin time; TBIL, total bilirubin.

TABLE 3. Univariate and Multivariate Analyses for Overall Survival for Hepatocellular Carcinoma Patients Who Underwent R0 Hepatic Resection

		Univariate Analysis		Multivariate Analysis	
Factors	**No. of patients**	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Sex					
Male	173 (86.5%)	1.326 (0.688–2.557)	0.400		
Female	27 (13.5%)				
Age					
>60	40 (20.0%)	0.994 (0.600–1.645)	0.981		
≤60	160 (80.0%)				
Detectable HBV DNA					
Yes	58 (29.0%)	1.518 (0.992–2.321)	0.054		
No	142 (71.0%)				
HBeAg positivity					
Yes	37 (18.5%)	1.474 (0.914–2.377)	0.112		
No	163 (81.5%)				
ALT (IU/I)					
≥40	39 (19.5%)	1.427 (0.878–2.321)	0.152		
<40	161 (80.5%)				
TBIL (μmol/L)					
≥17	44 (22.0%)	1.331 (0.832–2.132)	0.233		
<17	156 (78.0%)				
PT (s)					
≥13	33 (16.5%)	1.399 (0.846–2.315)	0.191		
<13	167 (83.5%)				
Alb (g/L)					
<35	22 (11.0%)	1.815 (1.027–3.207)	0.040	1.431 (0.767–2.671)	0.260
≥35	178 (89.0%)				
AFP (ng/mL)					
>100	93 (46.5%)	1.037 (0.691–1.555)	0.861		
≤100	107 (53.5%)				
Cirrhosis					
Yes	79 (39.5%)	1.444 (0.962–2.167)	0.076		
No	121 (60.5%)				
Liver resection					
Major	56 (28.0%)	1.305 (0.845–2.013)	0.230		
Minor	144 (72.0%)				
Tumor diameter (cm)					
>5	69 (34.5%)	1.658 (1.104–2.492)	0.015	1.605 (1.049–2.455)	0.029
≤5	131 (65.5%)				
Clamp time (min)					
>30	50 (25.0%)	1.248 (0.798–1.952)	0.331		
≤30	150 (75.0%)				
Operation time (min)					
>180	122 (61.0%)	1.247 (0.817–1.905)	0.306		
≤180	78 (39.0%)				
Blood loss (mL)					
>1000	16 (8.0%)	1.177 (0.570–2.429)	0.660		
≤1000	184 (92.0%)				
Transfusion					
Yes	25 (12.5%)	1.521 (0.876–2.643)	0.136		
No	175 (87.5%)				
Capsule					
Yes	144 (72.0%)	0.591 (0.388–0.899)	0.014	0.603 (0.387–0.939)	0.025
No	56 (28.0%)				
Presence of satellite nodules					
Yes	41 (20.5%)	2.399 (1.545–3.723)	<0.001	1.697 (1.074–2.683)	0.024
No	159 (79.5%)				
Presence of microvascular infiltration					
Yes	52 (26.0%)	3.524 (2.327–5.338)	<0.001	2.981 (1.924–4.619)	<0.001
No	148 (74.0%)				
Ishak inflammation score					
>6	38 (19.0%)	1.557 (0.972–2.494)	0.066		
≤6	162 (81.0%)				
Ishak fibrosis score					
≥4	75 (37.5%)	1.853 (1.235–2.779)	0.003	1.654 (1.052–2.603)	0.029
<4	125 (62.5%)				
Antiviral treatment					
Yes	100 (50.0%)	0.549 (0.362–0.832)	0.005	0.509 (0.333–0.778)	0.002
No	100 (50.0%)				

PT, prothrombin time; TBIL, total bilirubin.

TABLE 4. Univariate and Multivariate Analyses for Early Recurrence of Hepatocellular Carcinoma in Patients Who Underwent Hepatic Resection

		Univariate Analysis		Multivariate Analysis	
Factors	**No. Patients**	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Sex					
Male	173 (86.5%)	1.206 (0.579–2.514)	0.617		
Female	27 (13.5%)				
Age					
>60	40 (20.0%)	1.051 (0.604–1.830)	0.860		
≤60	160 (80.0%)				
Detectable HBV DNA					
Yes	58 (29.0%)	0.969 (0.584–1.609)	0.904		
No	142 (71.0%)				
HBeAg positivity					
Yes	37 (18.5%)	1.167 (0.661–2.060)	0.594		
No	163 (81.5%)				
ALT (IU/I)					
≥40	39 (19.5%)	1.292 (0.742–2.250)	0.366		
<40	161 (80.5%)				
TBIL (μmol/L)					
≥17	44 (22.0%)	1.392 (0.825–2.349)	0.215		
<17	156 (78.0%)				
PT (s)					
≥13	33 (16.5%)	1.170 (0.642–2.131)	0.607		
<13	167 (83.5%)				
Alb (g/L)					
<35	22 (11.0%)	1.550 (0.795–3.022)	0.198		
≥35	178 (89.0%)				
AFP (ng/mL)					
>100	93 (46.5%)	1.344 (0.849–2.127)	0.207		
≤100	107 (53.5%)				
Cirrhosis					
Yes	79 (39.5%)	1.199 (0.754–1.907)	0.443		
No	121 (60.5%)				
Liver resection					
Major	56 (28.0%)	1.315 (0.807–2.143)	0.272		
Minor	144 (72.0%)				
Tumor diameter (cm)					
>5	69 (34.5%)	1.852 (1.170–2.932)	0.009	2.088 (1.283–3.399)	0.003
≤5	131 (65.5%)				
Clamp time (min)					
>30	50 (25.0%)	1.083 (0.642–1.827)	0.765		
≤30	150 (75.0%)				
Operation time (min)					
>180	122 (61.0%)	1.489 (0.908–2.441)	0.114		
≤180	78 (39.0%)				
Blood loss (mL)					
>1000	16 (8.0%)	1.179 (0.511–2.718)	0.699		
≤1000	184 (92.0%)				
Transfusion					
Yes	25 (12.5%)	1.572 (0.846–2.920)	0.152		
No	175 (87.5%)				
Capsule					
Yes	144 (72.0%)	0.514 (0.322–0.819)	0.005	0.516 (0.313–0.851)	0.010
No	56 (28.0%)				
Presence of satellite nodules					
Yes	41 (20.5%)	2.420 (1.475–3.972)	<0.001	1.716 (1.029–2.862)	0.038
No	159 (79.5%)				
Presence of microvascular infiltration					
Yes	52 (26.0%)	3.069 (1.924–4.895)	<0.001	2.384 (1.469–3.869)	<0.001
No	148 (74.0%)				
Ishak inflammation score					
>6	38 (19.0%)	1.496 (0.879–2.548)	0.138		
≤6	162 (81.0%)				
Ishak fibrosis score					
≥4	75 (37.5%)	1.187 (0.745–1.893)	0.470		
<4	125 (62.5%)				
Antiviral treatment					
Yes	100 (50.0%)	0.782 (0.493–1.240)	0.296		
No	100 (50.0%)				

PT, prothrombin time; TBIL, total bilirubin.

TABLE 5. Univariate and Multivariate Analyses for Late Recurrence of Hepatocellular Carcinoma in Patients Who Underwent Hepatic Resection

		Univariate Analysis		Multivariate Analysis	
Factors	**No. Patients**	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Sex					
Male	103 (85.1%)	1.747 (0.621–4.916)	0.291		
Female	18 (14.9%)				
Age					
>60	24 (19.8%)	1.105 (0.508–2.404)	0.801		
≤60	97 (80.2%)				
Detectable HBV DNA					
Yes	32 (26.4%)	2.142 (1.122–4.088)	0.021	1.915 (0.919–3.991)	0.083
No	89 (73.6%)				
HBeAg positivity					
Yes	19 (15.7%)	1.454 (0.668–3.164)	0.345		
No	102 (84.3%)				
ALT (IU/I)					
≥40	19 (15.7%)	0.806 (0.315–2.061)	0.653		
<40	102 (84.3%)				
TBIL (μmol/L)					
≥17	22 (18.2%)	1.339 (0.635–2.821)	0.443		
<17	99 (81.8%)				
PT (s)					
≥13	19 (15.7%)	1.008 (0.422–2.407)	0.985		
<13	102 (84.3%)				
Alb (g/L)					
<35	11 (9.1%)	1.234 (0.438–3.472)	0.691		
≥35	110 (90.9%)				
AFP (ng/mL)					
>100	55 (45.5%)	1.308 (0.698–2.451)	0.402		
≤100	66 (54.5%)				
Cirrhosis					
Yes	45 (37.2%)	1.308 (0.694–2.464)	0.406		
No	76 (62.8%)				
Liver resection					
Major	32 (26.4%)	1.159 (0.577–2.328)	0.679		
Minor	89 (73.6%)				
Tumor diameter (cm)					
>5	34 (28.1%)	2.033 (1.074–3.851)	0.029	1.873 (0.973–3.607)	0.060
≤5	87 (71.9%)				
Clamp time (min)					
>30	31 (25.6%)	1.358 (0.688–2.682)	0.377		
≤30	90 (74.4%)				
Operation time (min)					
>180	70 (57.9%)	0.903 (0.479–1.700)	0.751		
≤180	51 (42.1%)				
Blood loss (mL)					
>1000	8 (6.6%)	2.524 (0.986–6.460)	0.054		
≤1000	113 (93.4%)				
Transfusion					
Yes	11 (9.1%)	1.974 (0.827–4.714)	0.126		
No	110 (90.9%)				
Capsule					
Yes	92 (76.0%)	0.857 (0.418–1.759)	0.674		
No	29 (24.0%)				
Presence of satellite nodules					
Yes	16 (13.2%)	2.385 (1.129–5.036)	0.023	2.578 (1.209–5.496)	0.014
No	105 (86.8%)				
Presence of microvascular infiltration					
Yes	17 (14.0%)	1.610 (0.710–3.651)	0.254		
No	104 (86.0%)				
Ishak inflammation score					
>6	20 (16.5%)	2.237 (1.089–4.599)	0.028	2.176 (0.968–4.888)	0.060
≤6	101 (83.5%)				
Ishak fibrosis score					
≥4	43 (35.5%)	2.445 (1.301–4.593)	0.005	2.198 (1.148–4.209)	0.017
<4	78 (64.5%)				
Antiviral treatment					
Yes	65 (53.7%)	0.429 (0.223–0.825)	0.011	0.316 (0.157–0.637)	0.001
No	56 (46.3%)				

PT, prothrombin time; TBIL, total bilirubin.

antiviral therapy reduce HCC risks include downregulation of hepatic inflammation and related nuclear signaling pathways that lead to neoplastic transformation at the cellular level, and reversal of fibrosis and reduction of regenerative stimuli at the tissue level. Antiviral therapy also reduces the expression of the HBx protein to levels insufficient to promote HCC development, acts at a genomic level by preventing HBV-DNA integration into host chromosomes, or affects its malignant potential.[45–47]

Also, antiviral therapy significantly enhances tolerance to therapy against disease recurrence and leads to increased OS. We, therefore, suggest the concept of antiviral therapy to change from ''close monitoring'' to ''the lower the better and the earlier the better,'' for patients with HCC with low preoperative HBV-DNA levels, especially for patients who are to undergo liver resection.

Studies involving patients with chronic hepatitis B from Asia showed that the beneficial effect of antiviral treatment was apparent in both patients with and without cirrhosis.[22,23,48,49] However, the results of a Greek nationwide cohort study showed that antiviral therapy with lamivudine did not significantly affect the incidence of HCC in patients with cirrhosis.[50] The inconsistency can be explained by the differences in the patient populations, for example, in HBV genotype distribution. The lack of treatment effect on cirrhotic patients in our study may also be due to insufficient statistical power relating to a small sample size of patients with cirrhosis and a relatively short follow-up.

In conclusion, prophylactic oral antiviral therapy after partial hepatectomy in patients with low preoperative HBV-DNA levels reduced HBV reactivation, reduced late HCC recurrence, and enhanced the chance to receive treatment for recurrence. All these eventually improved survivals of these patients with HBV-related HCC. This study suggested that patients with a low serum HBV-DNA load should also receive early and effective antiviral treatment without delay after partial hepatectomy.

REFERENCES

1. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. *Lancet*. 2003;362:1907–1917.
2. Bruix J, Llovet JM. Hepatitis B virus and hepatocellular carcinoma. *J Hepatol*. 2003;39(suppl 1):S59–S63.
3. European Association for the Study of the Liver, European Organisation for Research and Treatment of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol*. 2012;56:908–943.
4. Poon RT, Fan ST, Lo CM, et al. Long-term survival and pattern of recurrence after resection of small hepatocellular carcinoma in patients with preserved liver function: implications for a strategy of salvage transplantation. *Ann Surg*. 2002;235:373–382.
5. Lim KC, Chow PK, Allen JC, et al. Systematic review of outcomes of liver resection for early hepatocellular carcinoma within the Milan criteria. *Br J Surg*. 2012;99:1622–1629.
6. Hung IF, Poon RT, Lai CL, et al. Recurrence of hepatitis B-related hepatocellular carcinoma is associated with high viral load at the time of resection. *Am J Gastroenterol*. 2008;103:1663–1673.
7. Huang G, Lau WY, Wang ZG, et al. Antiviral therapy improves postoperative survival in patients with hepatocellular carcinoma: a randomized controlled trial. *Ann Surg*. 2015;261:56–66.
8. Lai CL, Gane E, Liaw YF, et al. Telbivudine versus lamivudine in patients with chronic hepatitis B. *N Engl J Med*. 2007;357:2576–2588.
9. Hou J, Yin YK, Xu D, et al. Telbivudine versus lamivudine in Chinese patients with chronic hepatitis B: results at 1 year of a randomized, double-blind trial. *Hepatology*. 2008;47:447–454.
10. Bruix J, Sherman M, Llovet JM, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. *J Hepatol*. 2001;35:421–430.
11. Bruix J, Sherman M, Practice Guidelines Committee AAftSoLD. Management of hepatocellular carcinoma. *Hepatology*. 2005;42:1208–1236.
12. Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. *Semin Liver Dis*. 1999;19:329–338.
13. Jang JW, Choi JY, Bae SH, et al. Transarterial chemo-lipiodolization can reactivate hepatitis B virus replication in patients with hepatocellular carcinoma. *J Hepatol*. 2004;41:427–435.
14. Jang JW, Choi JY, Bae SH, et al. A randomized controlled study of preemptive lamivudine in patients receiving transarterial chemo-lipiodolization. *Hepatology*. 2006;43:233–240.
15. Yeo W, Lam KC, Zee B, et al. Hepatitis B reactivation in patients with hepatocellular carcinoma undergoing systemic chemotherapy. *Ann Oncol*. 2004;15:1661–1666.
16. Mullen JT, Ribero D, Reddy SK, et al. Hepatic insufficiency and mortality in 1,059 noncirrhotic patients undergoing major hepatectomy. *J Am Coll Surg*. 2007;204:854–862.
17. Pawlotsky JM, Dusheiko G, Hatzakis A, et al. Virologic monitoring of hepatitis B virus therapy in clinical trials and practice: recommendations for a standardized approach. *Gastroenterology*. 2008;134:405–415.
18. Kubo S, Tanaka H, Takemura S, et al. Effects of lamivudine on outcome after liver resection for hepatocellular carcinoma in patients with active replication of hepatitis B virus. *Hepatol Res*. 2007;37:94–100.
19. Kuzuya T, Katano Y, Kumada T, et al. Efficacy of antiviral therapy with lamivudine after initial treatment for hepatitis B virus-related hepatocellular carcinoma. *J Gastroenterol Hepatol*. 2007;22:1929–1935.
20. Qu LS, Jin F, Huang XW, et al. High hepatitis B viral load predicts recurrence of small hepatocellular carcinoma after curative resection. *J Gastrointest Surg*. 2010;14:1111–1120.
21. Cho JY, Paik YH, Sohn W, et al. Patients with chronic hepatitis B treated with oral antiviral therapy retain a higher risk for HCC compared with patients with inactive stage disease. *Gut*. 2014;63:1943–1950.
22. Liaw YF, Sung JJ, Chow WC, et al. Lamivudine for patients with chronic hepatitis B and advanced liver disease. *N Engl J Med*. 2004;351:1521–1531.
23. Wu CY, Lin JT, Ho HJ, et al. Association of nucleos(t)ide analogue therapy with reduced risk of hepatocellular carcinoma in patients with chronic hepatitis B: a nationwide cohort study. *Gastroenterology*. 2014;147:143.e5–151.e5.
24. Wang JP, Kao FY, Wu CY, et al. Nucleos(t)ide analogues associated with a reduced risk of hepatocellular carcinoma in hepatitis B patients: a population-based cohort study. *Cancer*. 2015;121:1446–1455.
25. Chan AC, Chok KS, Yuen WK, et al. Impact of antiviral therapy on the survival of patients after major hepatectomy for hepatitis B virus-related hepatocellular carcinoma. *Arch Surg*. 2011;146:675–681.
26. Wu CY, Chen YJ, Ho HJ, et al. Association between nucleoside analogues and risk of hepatitis B virus-related hepatocellular carcinoma recurrence following liver resection. *JAMA*. 2012;308:1906–1914.
27. Lee TY, Lin JT, Zeng YS, et al. Association between nucleos(t)ide analog and tumor recurrence in hepatitis B virus-related hepatocellular carcinoma after radiofrequency ablation. *Hepatology*. 2016;63:1517–1527.
28. European Association for the Study of the Liver. EASL clinical practice guidelines: management of chronic hepatitis B virus infection. *J Hepatol*. 2012;57:167–185.
29. Liaw YF, Kao JH, Piratvisuth T, et al. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2012 update. *Hepatol Int*. 2012;6:531–561.
30. Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology*. 2009;50:661–662.
31. Huang G, Lai EC, Lau WY, et al. Posthepatectomy HBV reactivation in hepatitis B-related hepatocellular carcinoma influences postoperative survival in patients with preoperative low HBV-DNA levels. *Ann Surg*. 2013;257:490–505.
32. Hung HH, Su CW, Wu JC, et al. Reactivation of hepatitis B virus after transarterial chemo-embolization for hepatocellular carcinoma in one patient with negative hepatitis B surface antigen. *J Hepatol*. 2010;52:463–465.
33. Korean Association for the Study of the Liver. KASL clinical practice guidelines: management of chronic hepatitis B. *Clin Mol Hepatol*. 2012;18:109–162.
34. Yim SY, Um SH, Jung JY, et al. Role of hepatitis B surface antigen (HBsAg) in identifying true inactive HBsAg carriers infected with genotype C hepatitis B virus. *J Clin Gastroenterol*. 2014;48:166–171.
35. Tseng TC, Liu CJ, Yang HC, et al. High levels of hepatitis B surface antigen increase risk of hepatocellular carcinoma in patients with low HBV load. *Gastroenterology*. 2012;142:1140.e3–1149.e3.
36. Imamura H, Matsuyama Y, Tanaka E, et al. Risk factors contributing to early and late phase intrahepatic recurrence of hepatocellular carcinoma after hepatectomy. *J Hepatol*. 2003;38:200–207.
37. Wu JC, Huang YH, Chau GY, et al. Risk factors for early and late recurrence in hepatitis B-related hepatocellular carcinoma. *J Hepatol*. 2009;51:890–897.

38. Marcellin P, Gane E, Buti M, et al. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. *Lancet*. 2013;381:468–475.
39. Lupberger J, Hildt E. Hepatitis B virus-induced oncogenesis. *World J Gastroenterol*. 2007;13:74–81.
40. Chen JD, Yang HI, Iloeje UH, et al. Carriers of inactive hepatitis B virus are still at risk for hepatocellular carcinoma and liver-related death. *Gastroenterology*. 2010;138:1747–1754.
41. Kubo S, Hirohashi K, Tanaka H, et al. Effect of viral status on recurrence after liver resection for patients with hepatitis B virus-related hepatocellular carcinoma. *Cancer*. 2000;88:1016–1024.
42. Kubo S, Hirohashi K, Tanaka H, et al. Virologic and biochemical changes and prognosis after liver resection for hepatitis B virus-related hepatocellular carcinoma. *Dig Surg*. 2001;18:26–33.
43. Ko S, Nakajima Y, Kanehiro H, et al. Significant influence of accompanying chronic hepatitis status on recurrence of hepatocellular carcinoma after hepatectomy. Result of multivariate analysis. *Ann Surg*. 1996;224:591–595.
44. Shirabe K, Takenaka K, Taketomi A, et al. Postoperative hepatitis status as a significant risk factor for recurrence in cirrhotic patients with small hepatocellular carcinoma. *Cancer*. 1996;77:1050–1055.
45. But DY, Lai CL, Yuen MF. Natural history of hepatitis-related hepatocellular carcinoma. *World J Gastroenterol*. 2008;14:1652–1656.
46. Arzumanyan A, Reis HM, Feitelson MA. Pathogenic mechanisms in HBV- and HCV-associated hepatocellular carcinoma. *Nat Rev Cancer*. 2013;13:123–135.
47. Kew MC. Hepatitis B virus x protein in the pathogenesis of hepatitis B virus-induced hepatocellular carcinoma. *J Gastroenterol Hepatol*. 2011;26(suppl 1):144–152.
48. Yuen MF, Seto WK, Chow DH, et al. Long-term lamivudine therapy reduces the risk of long-term complications of chronic hepatitis B infection even in patients without advanced disease. *Antivir Ther*. 2007;12:1295–1303.
49. Yang SC, Lee CM, Hu TH, et al. Virological response to entecavir reduces the risk of liver disease progression in nucleos(t)ide analogue-experienced HBV-infected patients with prior resistant mutants. *J Antimicrob Chemother*. 2013;68:2154–2163.
50. Papatheodoridis GV, Manolakopoulos S, Touloumi G, et al. Virological suppression does not prevent the development of hepatocellular carcinoma in HBeAg-negative chronic hepatitis B patients with cirrhosis receiving oral antiviral(s) starting with lamivudine monotherapy: results of the nationwide HEPNET. Greece cohort study. *Gut*. 2011;60:1109–1116.