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The different effects of adefovir dipivoxil and telbivudine on the prognosis of hepatitis b virus-related hepatocellular carcinoma patients after curative resection

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Abstract

Numerous studies suggested that antiviral therapy could reduce the recurrence in hepatocellular carcinoma (HCC) patients after hepatectomy. The impact of nucleotide and nucleoside analogues on prognosis of chronic hepatitis B (CHB) related HCC remains to be explored. We aimed to investigate the role of the telbivudine and adefovir dipivoxil on the prognosis of CHB-related HCC patients after hepatectomy.

One hundred eighty-eight CHB-related patients who received hepatectomy from February 2010 to February 2017 were divided into telbivudine (LdT) and adefovir dipivoxil (ADV) groups. The characteristics and survival information of both groups were retrospectively compared and analyzed.

One hundred eleven and 77 patients received telbivudine and adefovir dipivoxil monotherapy, respectively. Alanine aminotransferase (ALT), total bilirubin level, status of hepatitis B e antigen (HBeAg), serum HBV-DNA level were compared between groups. OS and DFS in ADV-treatment group were significantly better than it in LdT-treatment group ($P < .05$). In the subgroups analysis, we found that ADV treatment was significantly associated with better DFS and OS among patients with cirrhosis, HBeAg-negative patients, or those with detectable HBV-DNA.

CHB-related HCC patients receiving long-term ADV-treatment had a better OS and DFS than patients receiving LdT-treatment after hepatectomy.

Abbreviations: ADV = adefovir dipivoxil, AFP = alpha-fetoprotein, ALT = alanine aminotransferase, anti-HCV = antibodies against hepatitis C virus, CHB = Chronic hepatitis B, DFS = disease-free survival, HBeAg = hepatitis B e antigen, HBsAg = hepatitis B surface antigen, HBV-DNA = HBV-deoxyribonucleic acid, HCC = hepatocellular carcinoma, HR = hazard ratio, ISGs = induced interferon-stimulated genes, LdT = telbivudine, NsA = nucleosides, NtA = nucleotides, OS = overall survival, RCTs = randomized controlled trials, TDF = tenofovir.

Keywords: adefovir disoproxil, chronic hepatitis b, hepatocellular carcinoma, nucleo(t)side analogues, telbivudine

1. Introduction

In Asia, hepatocellular carcinoma (HCC) commonly occurred in the underlying hepatitis B virus (HBV)-related liver disease.[1] Curative therapies like liver transplantation, hepatectomy, and radiofrequency ablation could improve the prognosis of HCC patients. With the advances in surgical techniques and perioperative management, the 5-year survival rates after curative therapy has reached 50%.[2] However, tumor recurrence after curative therapy remains high with a 5-year recurrence rate >70%.[3,4] To date, no effective postoperative treatment has been available to prevent HCC recurrence.

Chronic HBV infection is the main cause of HCC in Asia. The risk for HCC development is increased for patient with HBV infection.[5,6] Recent studies also showed that tumor recurrence after curative treatment of HCC was increased with the level of HBV-DNA and alanine aminotransferase (ALT).[7] Studies of large cohorts from China Hong Kong, China Taiwan, and Japan have confirmed that concomitant antiviral therapy with curative treatment reduced the recurrence of HCC.[8–11] However, there was no consensus about which kind of oral antiviral treatment was the best option in the prevention of HBV related HCC recurrence after curative treatment. Therefore, we conducted this study to investigate the different effects of adefovir dipivoxil

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(ADV) and telbivudine (LdT) on the prognosis of HBV-related HCC after curative resection. As a result, we found that OS and DFS in ADV-treatment group were significantly longer than it in LdT-treatment group. In the subgroups, we found that ADV treatment was significantly associated with increased DFS and OS among patients with cirrhosis, HBeAg-negative patients, and those with detectable HBV-DNA. So we concluded that patients receiving long-term ADV treatment had a better OS and DFS than patients receiving LdT treatment.

2. Materials and methods

This study complied with the standards of the Helsinki Declaration and current ethical guidelines and was approved by the Ethics Committee of West China Hospital, Sichuan University.

2.1. Patients

From February 2010 to February 2017, a total of 317 consecutive patients with newly diagnosed HCC according to the Milan criteria (i.e., a single tumor <5 cm or up to 3 nodules <3 cm) who underwent R0 resection at the Department of Liver Surgery and Liver Transplantation Centre of the West China Hospital of Sichuan University were prospectively enrolled and followed up. The diagnosis of HCC was confirmed by a postoperative histopathologic examination (CL, Lu). Preoperatively, all patients underwent chest radiography and at least 2 dynamic imaging examinations (contrast-enhanced ultrasound, contrast-enhanced computed tomography or magnetic resonance imaging). Hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg), HBV-deoxyribonucleic acid (HBV-DNA) load, antibodies against hepatitis C virus (anti-HCV), alpha-fetoprotein (AFP), liver function, and hematological parameters were serologically examined within 1 week before surgery. All medical records from our prospectively maintained database were reviewed retrospectively.

Inclusion criteria for this study were as follows: age 18 to 75 years; a positive test for HBsAg and a negative test for antibodies against hepatitis C virus or human immunodeficiency virus; the use of either nucleosides (NsA) (LdT, 600 mg/d) or nucleotides (NtA) (ADV, 10 mg/d) for postoperative anti-viral treatment; no previous treatment HCC; no extra-hepatic metastasis; no radiologic evidence of invasion into major portal/hepatic venous branches; good liver function with Child-Pugh Class A and no history of encephalopathy, ascites refractory to diuretics, or esophagogastric variceal bleeding; and good renal function (a serum creatinine level <124 mmol/L).

Exclusion criteria for this study were as follows: other etiologies of HCC, such as primary biliary cirrhosis, non-alcoholic fatty liver disease, alcoholic liver disease, and cryptogenic HCC; the use of other antiviral therapies, such as Entecavir (ETV), Lamivudine (LAM); drug resistance: NsA combined with NtA (LdT+ADV) or NtA (NsA) followed by NsA (NtA); and treatment naïve and poor compliance.

2.2. Nucleotide/nucleoside analogues treatment of chronic hepatitis B

The choice of treatment strategies for chronic hepatitis B was based on the updated management guidelines for chronic hepatitis B,[12–16] drug resistance, and the patient's financial conditions.

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

2.3. Follow-up

All the patients received follow-up monitoring 1 month after the operation, every 3 months thereafter during the first 3 years, and then every 6 months in subsequent years.

Physical examination, blood cell and differential counts, liver function tests, AFP levels, HBV markers and HBV-DNA levels, and imaging examinations were included in the follow-up examinations when necessary. Overall survival (OS) time was defined as the interval between the operation and death or the last follow-up. Disease-free survival (DFS) time was defined as the interval between the operation and the 1st incidence of detectable recurrence. The last follow-up date was the end of July 2017.

Tumor recurrence was diagnosed based on the identification of a new lesion on at least 2 radiological examinations and increased AFP levels. Patients with tumor recurrence were actively treated with salvage liver transplantation, repeat hepatic resection, radiofrequency ablation, transcatheter arterial chemoembolization, sorafenib, and/or chemotherapy, depending on the extent of the disease, the liver function, and the general condition of the patient. The study was approved by West China Hospital of Sichuan University Research Ethical Committee. All experiments were performed according to relevant guidelines and regulations. Informed consent was obtained from all participants for the experiments.

2.4. Statistical analysis

Continuous variables are expressed as the mean ± standard deviation and were compared between groups using the *t* test or the Mann–Whitney *U* test for variables with an abnormal distribution. Categorical data were compared using the chi-squared test or Fisher exact test. The OS rates were analyzed using the Kaplan–Meier method, and the differences were analyzed using the log-rank test. The Cox proportional hazard model was used for univariate and multivariate analyses of prognostic factors after surgery. Two-tailed *P* values ≤.05 were considered statistically significant. Calculations were performed using the SPSS package (SPSS, Inc., Chicago, IL).

3. Results

3.1. Baseline information of both groups

Based on our inclusion and exclusion criteria, a total of 188 patients were excluded from the present study. Ultimately, 188 consecutive patients with HBV-related HCC who had undergone antiviral treatment with either ADV (n = 111) or LDT (n = 77) after surgery and who met our criteria were included in this retrospective analysis (Fig. 1).

The baseline characteristics, serologic parameters, tumor characteristics, and operative data are summarized in Table 1. There were no significant differences in the parameters of the 2 groups except that the ADV group had a higher ratio of HBeAg-positive patients than the LdT group (97/111 vs 55/77, $P = .006$). At the time of data collection, 94 (50.0%) patients had had an

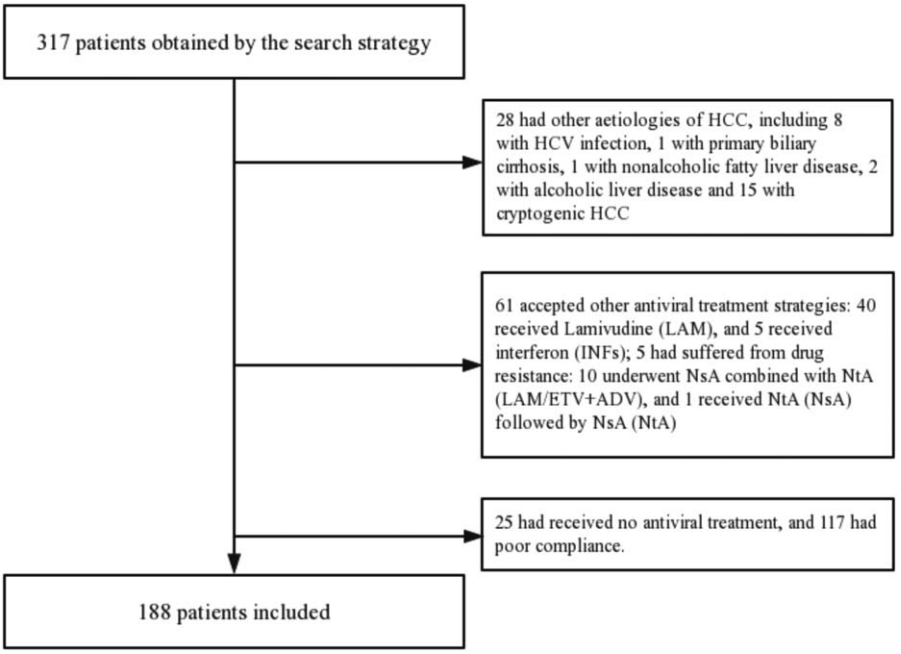

Figure 1. Flowchart of the process for patients' selection.

HCC recurrence, and 56 (29.8%) of them died. In addition, no adverse effects of the use of NtA or NsA were reported.

3.2. The different effects of NtA and NsA on the prognosis of HBV-related HCC

The 1-, 3-, and 5-year OS rates for the ADV group and the LdT group were 96.3%, 84.9%, 77.5% and 92.1%, 71.2%, 51.9%, respectively. The OS of patients who received ADV treatment was significantly better than that of those who received LdT treatment ($P=.002$, Fig. 2A).

The corresponding 1-, 3-, and 5- year DFS rates for the ADV group and the LdT group were 83.6%, 66.0%, 50.4% and 59.0%, 43.7%, 30.9%, respectively. The DFS of patients who received ADV treatment was significantly better than that of those who received LdT treatment ($P=.001$, Fig. 2B)

3.3. The different effects of NtA and NsA in patients with a cirrhotic background

A total of 168 (89.4%) patients had a cirrhotic background (Ishak fibrosis score ≥ 5), including 71 in the ADV group and 97 in the LdT group. The 1-, 3-, and -5 year OS rates for the LdT group and the ADV group were 88.6%, 70.2%, 53.4% and 95.7%, 86.5%, 78.0%, respectively. Patients who underwent ADV treatment had a significantly higher OS than those who underwent LdT treatment ($P=.002$, Fig. 3A).

The 1-, 3-, and 5-year DFS rates for the LdT group and the ADV group were 61.1%, 46.0%, and 35.0% and 82.3%, 66.4%, and 50.6%, respectively. Patients who underwent ADV treatment had a significantly higher DFS than those who underwent LdT ($P=.01$, Fig. 3B).

When OS and DFS were compared for the patients with a non-cirrhotic background (14 in the ADV group and 6 in the LdT group), they did not differ significantly between the 2 groups (Supplementary figure S1, http://links.lww.com/MD/C816).

3.4. The different effects of NtA and NsA in patients with detectable HBV-DNA

Eighty seven patients had undetectable HBV-DNA (HBV-DNA <1000 copies/mL), including 57 in the ADV group and 30 in the LdT group. No significant difference was found between the ADV and LdT groups for OS and DFS.

The 1-, 3-, and 5-year DFS rates for the LdT group and the ADV group were 65.9%, 58.9%, 54.0% and 82.3%, 69.8%, 61.5%, respectively ($P=.368$, Supplementary figure S2A, http://links.lww.com/MD/C816). And the 1-, 3-, and 5-year OS rates for the LdT group and the ADV group were 93.1%, 74.3%, 69.0% and 94.4%, 83.4%, 74.3%, respectively ($P=.539$, Supplementary figure S2B, http://links.lww.com/MD/C816).

One hundred one patients had detectable HBV-DNA (HBV-DNA ≥ 1000 copies/mL), including 54 in the ADV group and 47 in the LdT group.

The 1-, 3-, and 5-year DFS rates for the LdT group and the ADV group were 50.2%, 34.5%, 20.0% and 85.1%, 63.8%, 44.5%, respectively. Patients who received ADV treatment had a more favorable DFS rate than those who received LdT treatment ($P=.001$, Fig. 4A).

The 1-, 3-, and 5-year OS rates for the LdT group and the ADV group were 91.5%, 69.9%, 42.5% and 98.1%, 86.6%, 80.2%, respectively. Patients who received ADV treatment had a more favorable OS rate than those who were treated with LdT ($P=.001$, Fig. 4B)

3.5. The different effects of NtA and NsA in HBeAg-negative patients

A total of 152 patients were HBeAg negative (97 in the ADV group and 55 in the LdT group), and 36 patients were HBeAg positive (14 in the ADV group and 22 in the LdT group). The OS and DFS of the HBeAg-negative patients were significantly better than those of the HBeAg-positive patients (1-, 3-, and 5-year DFS rates: 77.9%, 60.8%, 47.2% vs 54.7%, 39.5%, 26.3%,

Table 1

Comparison of baseline variables in patients receiving LdT and ADV.

Factors	LDT (n=77)	ADV (n=111)	P
Gender (male/female)	67/10	90/21	.276
Age, y	47.74±1.393	50.87±1.024	.094
TBIL, mmol/L	18.00±2.57	15.28±0.64	.231
ALT, U/L	49.18±4.58	40.24±5.16	.22
Tumor size, cm, n, %			.941
≤2	17 (22.1)	24 (21.6)	
>2	60 (77.9)	87 (78.4)	
BCLC, n, %			.724
0 stage	14 (18.2)	18 (16.2)	
A stage	63 (81.8)	93 (83.8)	
MVI, n, %			.187
Yes	47 (61.0)	78 (70.3)	
No	30 (39.0)	33 (29.7)	
Differentiation, n, %			.104
High	1 (1.3)	5 (4.5)	
Moderate	31 (40.3)	68 (61.3)	
Low	45 (58.4)	38 (34.2)	
Cirrhosis, n, %			.292
Yes	71 (92.2)	97 (87.4)	
No	6 (7.8)	14 (12.6)	
HBV-sAg, n, %			.132
Positive	74 (96.1)	111 (100)	
Negative	3 (3.9)	0 (0)	
HBV-eAg, n, %			.006
Positive	55 (71.4)	97 (87.4)	
Negative	22 (28.6)	14 (12.6)	
AFP, ng/mL, n, %			.123
≥400	32 (41.6)	34 (30.6)	
<400	45 (58.4)	77 (69.4)	
HBV-DNA			.094
<10^3, IU/mL	30 (39.0)	57 (51.4)	
≥10^3,IU/mL	47 (61.0)	54 (48.6)	
Complication, n, %			.133
Yes	61 (79.2)	97 (87.4)	
No	16 (20.8)	14 (12.6)	

ADV = adefovir disoproxil, AFP = alpha fetoprotein, ALT = alamine aminotransfera, BCLC = Barcelona Clinic Liver Cancer, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, LDT = telbivudine, MVI = microvascular invasion, TBIL = total bilirubin.

respectively, $P=.008$, Fig. 5A; the 1-, 3-, and 5-year OS rates: 95.9%, 80.8%, 68.0% vs 83.2%, 70.1%, 54.7%, respectively, $P=.033$, Fig. 5B).

For the HBeAg-negative patients, the 1-, 3-, and 5-year DFS rates of the LdT group and the ADV group were 57.6%, 44.2%, 34.9% and 87.5%, 70.6%, 54.7%, respectively. The patients who received ADV had a more favorable DFS rate than those who received LdT ($P=.010$, Fig. 5C).

The 1-, 3-, and 5-year OS rates for the LdT group and the ADV group were 94.4%, 74.5%, 52.4% and 96.8%, 85.2%, 79.1%, respectively. The patients who received ADV had a more favorable DFS than those who received LdT ($P=.009$, Fig. 5D).

When OS and DFS were compared among the subgroups of HBeAg-positive patients, there were no significant differences (Supplementary figure S3, http://links.lww.com/MD/C816).

3.6. Prognostic factors for patients with HBV-related HCC

The parameters that were significantly associated with a high cumulative risk of death and recurrence in the univariate analysis were entered into the multivariate analysis. For OS, HBeAg positive status (hazard ratio [HR]=1.882 95% confidence [CI]: 1.041–3.403, $P=.036$), high albumin level (ALT, HR=1.004, 95%CI: 1.00–1.008, $P=.043$), poor tumor differentiation (HR=1.723, 95%CI: 1.005–2.953, $P=.048$), high total bilirubin level (TBIL, HR=1.01, 95%CI: 1.000–1.021, $P=.046$), andnone antiviral treatment (HR=0.418, 95%CI: 0.243–0.719, $P=.001$) significantly predicted a poor prognosis (Table 2). The multivariate analysis revealed that 5 prognostic factors were significantly associated with tumor recurrence: HbeAg-positive status (HR=1.617, 95% CI: 1.006–2.601, $P=.047$), HBV-DNA positive status (HR=1.581, 95% CI: 1.035–2.416, $P=.034$), AFP level (HR=2.115, 95% CI: 1.378–3.247, $P=.001$), poor tumor differentiation (HR=1.985, 95% CI: 1.323–2.979, $P=.001$), BCLC staging (HR=2.395, 95%CI: 1.249–4.593, $P=.008$), and antiviral treatment (HR=0.569, 95% CI: 0.377–0.859, $P=.007$); (Table 3).

4. Discussion

As we know, liver resection has been widely considered as the standard treatment for HCC patients. However, recurrence rate is as high as ≥70% at 5 years.[3] Risk factors for recurrence and long-time survival are multiple and prevalent. Consistent with previous research, we confirmed differentiation, HBeAg, liver function, and antiviral treatment were independent risk factors for overall survival of HBV-HCC patients. As for tumor

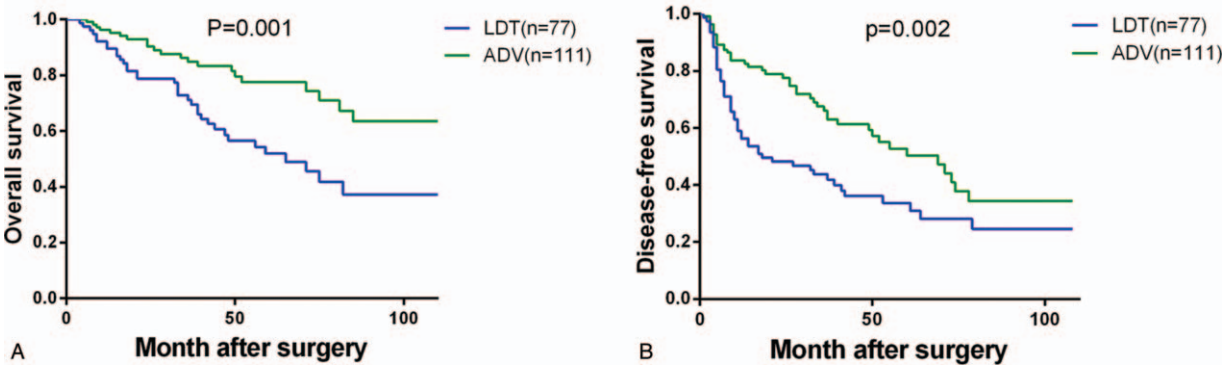

Figure 2. A. The overall survival of CHB-related HCC patients after surgery. The comparison of cumulative HCC development probability between LdT group (blue) and ADV group (green). *X*-axis represented time (month), *Y*-axis represented overall survival. B. The disease-free survival of CHB-related HCC patients after surgery. The comparison of cumulative HCC development probability between LdT group (blue) and ADV group (green). *X*-axis represented time (month), *Y*-axis represented disease-free survival. ADV = adefovir dipivoxil, CHB = chronic hepatitis B, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, LdT = telbivudine.

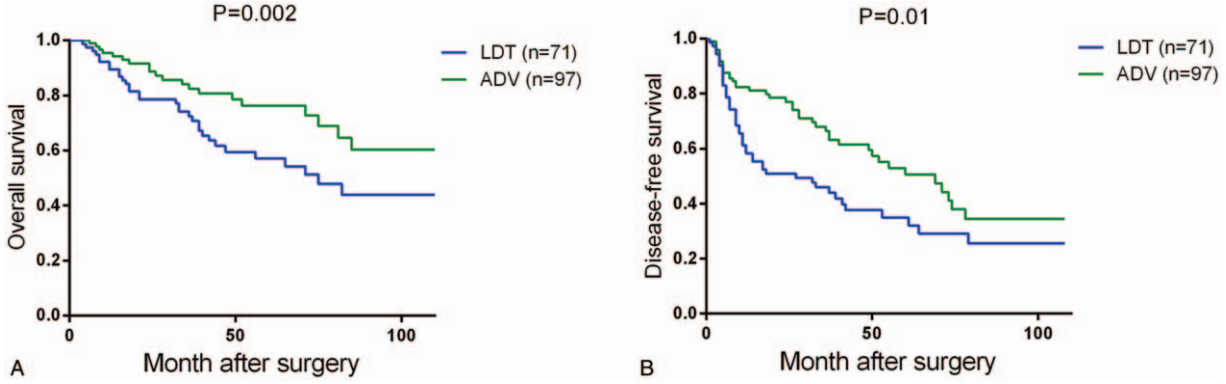

Figure 3. A and B. The overall survival and disease-free survival of CHB-related HCC patients with a cirrhotic background after surgery. The comparison of cumulative HCC development probability between LdT group (blue) and ADV group (green). *X*-axis represented time (month), *Y*-axis represented overall survival or disease-free survival. ADV = adefovir dipivoxil, CHB = chronic hepatitis B, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, LdT = telbivudine.

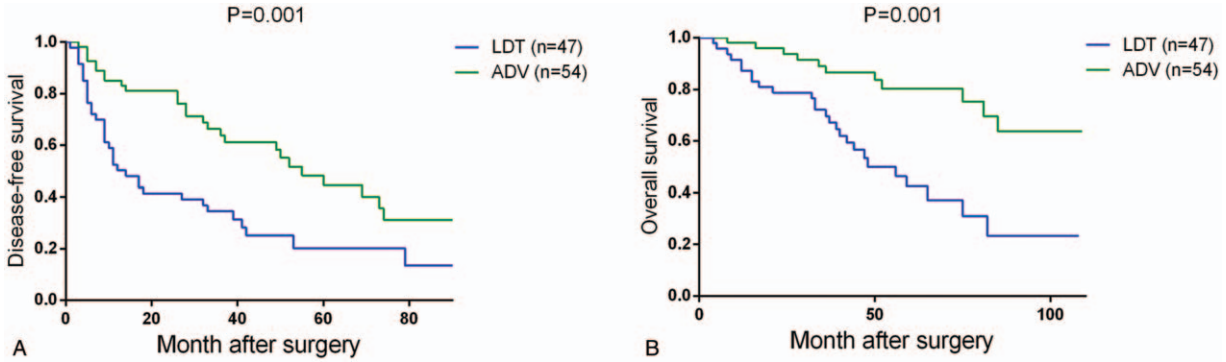

Figure 4. A and B. The disease-free survival and overall survival of CHB-related HCC patients with detectable HBV-DNA. The comparison of cumulative HCC development probability between LdT group (blue) and ADV group (green). *X*-axis represented time (month), *Y*-axis represented overall survival or disease-free survival. ADV = adefovir dipivoxil, CHB = chronic hepatitis B, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, LdT = telbivudine.

recurrence, we found differentiation, HBeAg, AFP, HBV-DNA, BCLC staging, and antiviral treatment are all prognostic factors. In previous researches,[17] prognosis after HCC resection has been shown to be affected by tumor invasiveness, HBV infection, and liver function, which is similar to our results. Moreover, previous researches found that about 60% to 90% cases are with cirrhosis,[18,19] about 15% to 45% cases are multifocal.[18–20] Therefore, even in small HCC, 5-year RFS rate is only about 40%.[21] So improvements in preventing recurrence and prolonging OS are essential. In previous studies, active HBV replication was found significantly associated with the recurrence of hepatocellular carcinoma after surgery.[22] Although continuous suppression of HBV has been proved to be effective in reducing the incidence and recurrence of HCC with solid evidence. Systematic antiviral treatment with nucleoside and nucleotide analogues has seemed to be a potential adjuvant therapy for patients with HBV-related HCC, but no universally effective adjuvant antiviral drugs have been found to have better disease-free survival. Recently, the results of 2 randomized controlled trials (RCTs) from Shanghai (China) showed that patients who received continuous treatment with ADV or LAM had a more favorable DFS and OS than patients who did not receive antiviral treatment after surgery.[23,24] However, no evidence in the literature has indicated which is the superior antiviral treatment for patients with HBV-related HCC after curative resection, and no recommendations regarding postoperative nucleotide/nucleoside treatments was found in current clinical practice guidelines for the management of HBV-related HCC.[25–27] Thus, we conducted the present study and found that NtAs provided a better long-term outcome than NsAs for patients with HBV-related HCC. Recently, Murata et al[28] revealed that NtAs, but not NsAs, had the novel additional pharmacological effect of inducing IFN-λ3. They reported that serum IFN-λ3 was upregulated by NtA administration, and furthermore, the induced IFN-λ3 in turn induced interferon-stimulated genes (ISGs), which contributed to the inhibition of viral mRNA translation and to RNA degradation and synthesis[29] in hepatoma cells and inhibited HBsAg production. With their additional pharmacological effect of inducing IFN-λ3 production, NtAs provide novel options for HBV treatment. Additionally, IFNs yield has a variety of other biological properties, including immunomodulatory, anti-proliferative, and antiangiogenic effects.[30,31] Moreover, interferon-λ3 has been demonstrated to be involved in modulation of immunity during virus infection or autoimmune diseases.[32] Inflammation is determined to have a strong association with carcinogenesis and recurrence of HCC.[33] Thus, we supposed that NtAs such as ADV might regulate the immunity through induction of interferon-λ3 to improve the survival of CHB-related HCC patients in our study. However, it requires further studies to prove our hypothesis.

In this study, we found that CHB-related HCC patients received ADV after surgery have better OS and DFS, compared with patients received LdT. Furthermore, we stratified the

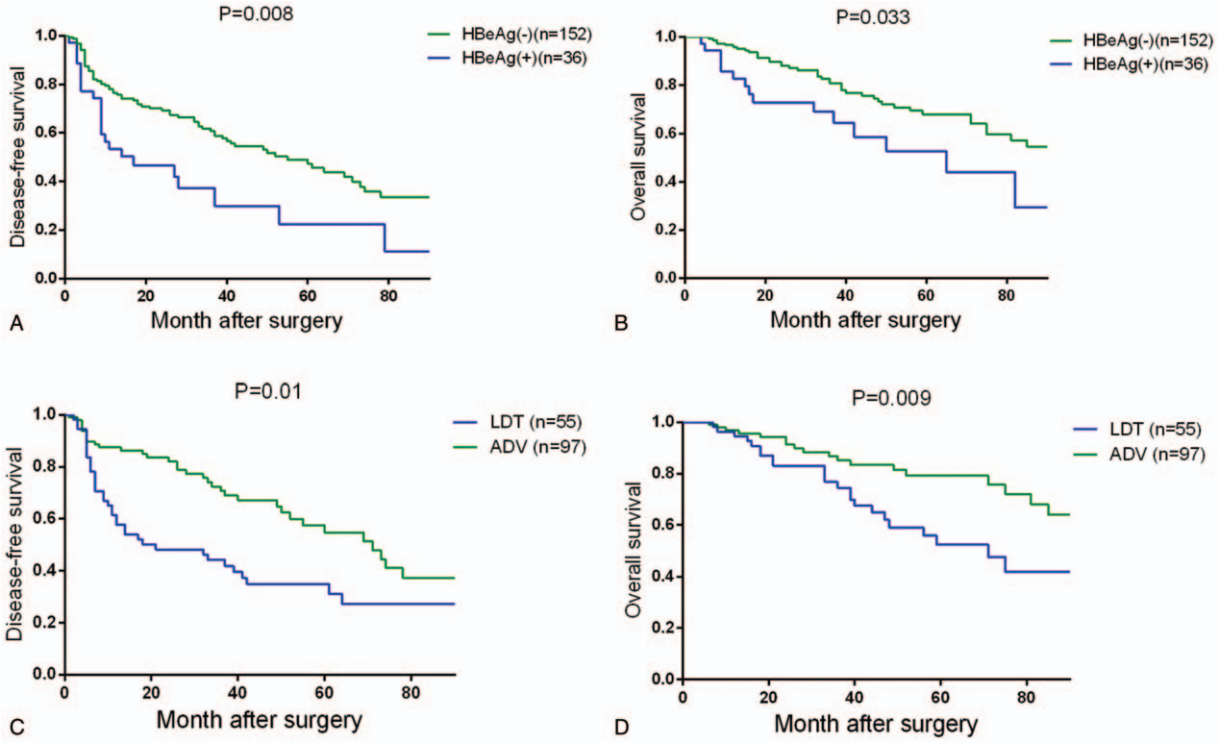

Figure 5. A and B. The disease-free survival and overall survival between HBeAg-negative patients and HBeAg-positive patients. The comparison of cumulative HCC development probability between LdT group (blue) and AdV group (green). *X*-axis represented time (month), *Y*-axis represented overall survival or disease-free survival. C and D. The disease-free survival and overall survival for HbeAg-negative patients. The comparison of cumulative HCC development probability between LdT group (blue) and ADV group (green). *X*-axis represented time (month), *Y*-axis represented overall survival or disease-free survival. ADV = adefovir dipivoxil, CHB = chronic hepatitis B, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, LdT = telbivudine.

patients into 3 variables within the LdT and ADV groups to evaluate the effects of ADV treatment on postoperative prognosis in each stratum. We found that ADV treatment was significantly associated with increased DFS and OS among patients with cirrhosis, HBeAg-negative patients, and those with detectable HBV-DNA, whereas antiviral treatment did not significantly increase RFS and OS in non-cirrhosis patients, HBeAg-positive patients, and those with undetectable HBV-DNA.

Our study has several limitations. First, since it was a retrospective study, there was some selection bias. Second,

Table 2

Univariate and multivariate analyses of prognostic factors for OS of 188 small HCC patients after liver resection.

	Univariate	Multivariate		
Factors	***P***	**HR**	**95% CI**	***P***
Gender (F/M)	.085			
Age (>60 vs <60 y)	.771			
Differentiation (well, moderate, poor)	.041	1.723	1.005–2.953	.048
MVI (yes vs no)	.219			
Tumor size, cm (≤2 vs >2)	.152			
Cirrhosis (yes vs no)	.879			
HBV-eAg (yes vs no)	.033	1.882	1.041–3.403	.036
AFP, ng/mL (<400 vs <400)	.089			
Transfusion (yes vs no)	.573			
TBIL, mmol/L	.033	1.01	1.000–1.021	.046
ALT, U/L	.038	1.004	1.000–1.008	.043
Complication (yes vs no)	.197			
HBV-DNA (positive vs negative)	.325			
BCLC staging (0 vs A)	.101			
Antiviral treatment (LdT vs ADV)	.001	0.418	0.243–0.719	.002

ADV = adefovir disoproxil, AFP = alpha fetoprotein, ALT = alamine aminotransfera, BCLC = Barcelona Clinic Liver Cancer, CI = confidence interval, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, LdT = telbivudine, MVI = microvascular invasion, TBIL = total bilirubin.

Table 3

Univariate and multivariate analyses of prognostic factors for DFS of 188 small HCC patients after liver resection.

	Univariate	Multivariate		
Factors	***P***	**HR**	**95% CI**	***P***
Gender (F/M)	.516			
Age (>60 vs <60y)	.622			
Differentiation (well, moderate, poor)	<.001	1.985	1.323–2.979	.001
MVI (yes vs no)	.181			
Tumor size, cm (≤2 vs >2)	.143			
Cirrhosis (yes vs no)	.737			
HBV-eAg (yes vs no)	.009	1.617	1.006–2.601	.047
AFP, ng/mL (400 vs <400)	.001	2.115	1.378–3.247	.001
Transfusion (yes vs no)	.573			
TBIL, mmol/L	.098			
ALT, U/L	.194			
Complication (yes vs no)	.552			
HBV-DNA (positive vs negative)	.033	1.581	1.035–2.416	.034
BCLC staging (0 vs A)	.03	2.395	1.249–4.593	.008
Antiviral treatment (LDT vs ADV)	.002	0.569	0.377–0.859	.007

ADV = adefovir disoproxil, AFP = alpha fetoprotein, ALT = alamine aminotransfera, BCLC = Barcelona Clinic Liver Cancer, CI = confidence interval, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, LdT = telbivudine, MVI = microvascular invasion, TBIL = total bilirubin.

because of the study's retrospective nature, we cannot identify whether serum IFN-λ3 levels increase after ADV administration. However, Murata et al[28] described this phenomenon in their study. A large multicenter randomized and controlled study is needed to confirm the additional pharmacological effect of inducing IFN-λ3 and the favorable DFS and OS associated with ADV treatment. The results of the present study could provide supportive evidence for subsequent RCTs and basic experiments. Third, the sample sizes of the subgroups were small, which could affect the validity of these findings. The results should be validated in a future study with a large sample size. Fourth, the American Association for the Study of Liver (AASLD) adopted Entecavir (ETV) and tenofovir (TDF) as first-line treatment for hepatitis B in 2015, so LdT and ADV might have their limitations due to the emergence of antiviral-resistant HBV mutants.[34] Finally, some patients who received ADV treatment also experienced relapse. It is known that IFNs are less effective for the treatment of genotype C HBV;[35–37] However, the association between the relapse of patients who received ADS and the HBV genotype need further study.

In conclusion, our study suggested the ADV had advantages over LdT in term of prognosis of CHB-related HCC patients, especially for the patients with cirrhotic background, detectable HBV-DNA, and negative HBeAg. Antiviral treatment with NtAs might be the superior choice for patients with HBV-related HCC after curative resection.

Author contributions

Wen Tianfu, He Linye, and Zhang Xiaoyun designed the experiments. Shen Junyi, Li Chuan, and Xia Zijing collected and analyzed the data. He Linye and Xiazijing wrote the manuscript.
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