DR. JONGGI CHOI (Orcid ID : 0000-0002-7470-5850)
PROF. YOUNG-SUK LIM (Orcid ID : 0000-0002-1544-577X)

Article type : Original

Tenofovir vs. Entecavir on Recurrence of Hepatitis B Virus-Related Hepatocellular Carcinoma after Surgical Resection

Short Title: Tenofovir vs. Entecavir on HCC Recurrence

Jonggi Choi, MD, PhD,[1]* Chanyoung Jo, MD,[2]* Young-Suk Lim, MD, PhD[1]

[1]Department of Gastroenterology, Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea
[2]Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

*J Choi and C Jo contributed equally to this work and deserve co-first authorship.

Correspondence to:
Young-Suk Lim, MD, PhD
Professor, Department of Gastroenterology
Asan Medical Center, University of Ulsan College of Medicine
88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Republic of Korea
Tel.: +82-02-3010-5933; Fax: +82-02-485-5782
E-mail: limys@amc.seoul.kr

Word counts:

- Abstract: 271 words
- Main text: 5,464 words (including references)

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/HEP.31289

Number of figures and tables:

- Three tables and two figures
- One supplementary material

Financial Support: There was no funding or support from industry for this study. The interpretation and reporting of the data were the sole responsibility of the authors.

This study was supported by grants from the Korean Health Technology R&D Project, Ministry of Health & Welfare (HI19C0790); National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIT, 2017R1A2B4011233); and the Technology Innovation Program (10079271) funded by the Ministry of Trade, Industry & Energy (MOTIE) of the Republic of Korea.

Declaration of interests: No industry funded or supported this study. The interpretation and reporting of the data were the sole responsibility of the authors. Y-S.L. is an advisory board member of Bayer Healthcare and Gilead Sciences and receives investigator-sponsored research funding from Bayer Healthcare and Gilead Sciences. No other disclosures are declared.

List of Abbreviations: AHR, adjusted hazard ratio; ALT, alanine aminotransferase; anti-HBe, hepatitis B e antibody; BCLC, Barcelona Clinic Liver Cancer; CHB, chronic hepatitis B; CI, confidence interval; CT, computed tomography; ETV, entecavir; HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; HR, hazard ratio; MR, magnetic resonance; NUC, nucleos(t)ide analogues; OS, overall survival; PY, person-year; RFA, radiofrequency ablation; RFS, recurrence-free survival; TDF, tenofovir disoproxil fumarate.

Author Contributions: All authors have full access to all data used in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. J.C., C.J. and Y-S.L. were responsible for the conception and design of the study; acquisition, analysis, and interpretation of data; and drafting of the manuscript. J.C. performed statistical analyses. All authors approved the final version of the manuscript.

ABSTRACT

Studies have suggested that tenofovir disoproxil fumarate (TDF) treatment is associated with a significantly lower risk of hepatocellular carcinoma (HCC) occurrence when compared to entecavir (ETV) therapy in chronic hepatitis B patients. We aimed to compare HCC recurrence and survival of patients treated with TDF or ETV after surgical resection for hepatitis B virus (HBV)-related HCC. This historical cohort study included 1,695 consecutive patients treated with ETV (n=813) or TDF (n=882) after curative-intent hepatectomy for HBV-related HCC of Barcelona Clinic Liver Cancer stage 0 or A in Korea between 2010 and 2018. HCC recurrence and overall survival of patients were compared between ETV and TDF groups by propensity score-matched and multivariable-adjusted Cox regression analyses from the date of hepatectomy for HCC. Mean age of the study patients was 54.8 years and 1,294 patients (76.3%) were male. During median follow-up duration of 37.6 months with continued ETV or TDF therapy, 561 (33.1%) patients developed HCC recurrence, 144 (8.4%) died, and 22 (1.3%) received liver transplant. Compared with ETV, TDF therapy was associated with significantly higher recurrence-free (*P*=0.02) and overall survival (*P*=0.03) rates by propensity score-matched analysis. By multivariable-adjusted analysis, TDF group was associated with significantly lower rates of HCC recurrence (HR, 0.82; 95% CI, 0.68-0.98; *P*=0.03), and death or transplantation (HR, 0.62; 95% CI, 0.44-0.88; *P*=0.01). TDF therapy was an independent protective factor for both early (<2 years; HR, 0.79; *P*=0.03) and late (≥2 years; HR, 0.68; *P*=0.03) postoperative HCC recurrence.

***Conclusion*:** Among patients who underwent curative hepatectomy for HBV-related HCC, TDF therapy was associated with a significantly lower risk of HCC recurrence and better overall patient survival compared to ETV therapy.

Keywords: Chronic hepatitis B; Comparative effectiveness; Liver cancer; Nucleos(t)ide analogues; Tenofovir disoproxil fumarate.

INTRODUCTION

Chronic hepatitis B virus (HBV) infection (CHB) is a leading cause of hepatocellular carcinoma (HCC) which is the second largest cause of cancer mortality in the world.(1, 2) The prognosis of the patients with HCC is poor, even after a curative treatment, mainly because of the high rate of intrahepatic HCC recurrence.(3, 4) High levels of HBV viremia are associated with high rates of HCC recurrence after surgical resection in patients with HBV-related HCC.(5, 6) In contrast, reducing HBV load through the treatment with nucleos(t)ide analogues (NUCs) may lower the risk of HCC recurrence and improve the survival of patients after hepatectomy.(7-11)

Entecavir (ETV) and tenofovir disoproxil fumarate (TDF) are equally recommended as first-line NUCs for CHB in clinical practice guidelines because of their similarly high antiviral efficacy and low rate of resistance.(12-14) However, our group recently reported that CHB patients treated with TDF was associated with a significantly lower risk of HCC occurrence compared to those treated with ETV.(15) Although results are controversial in the subsequent studies, no studies so far have shown opposite results with favourable outcomes for ETV therapy over TDF treatment.(16-21) Nevertheless, it is not clear whether TDF and ETV have different effects on HCC recurrence in patients receiving curative hepatectomy for HBV-related HCC.

Therefore, in this large-scale historical cohort study, we aimed to compare the effectiveness of ETV vs. TDF on HCC recurrence and overall survival of patients after curative hepatectomy for HBV-related HCC.

METHODS

Study Design & Subjects

This was a historical cohort study of patients who were treated with either TDF or ETV for CHB after curative hepatectomy for early stage (Barcelona Clinic Liver Cancer [BCLC] stage 0 or A) HCC.

The source population was obtained from a historical cohort of 3,367 consecutive patients who received curative-intent hepatectomy for HBV-related HCC between January 2010 and December 2018 at Asan Medical Center, a 2,700-bed academic tertiary referral hospital in Seoul, Korea (Figure 1). Of these, 1,695 patients who were treated with either ETV (n=813) or TDF (n=882) were included in the analysis as the study population.

ETV was first approved in January 2007 and TDF in December 2012 in Korea. However, during the entire study period, both of the drugs have been equally recommended for the treatment of CHB by local practice guidelines. The patients in each treatment group continued their initial treatment regimen (i.e., ETV or TDF) during the study period without change, because the change of the treatment regimen was not reimbursed by the National Health Insurance Service if there is no clear medical reason for the change (e.g., adverse events or drug-resistance, etc.). Furthermore, the patients who changed their treatment regimen were censored at the time of the change.

Patients meeting any of the following criteria were excluded: any previous treatment for HCC via other modalities; history of non-HCC malignancy; co-infection with hepatitis C virus; simultaneous treatment with resection and radiofrequency ablation; gross vascular invasion; intermediate or advanced BCLC stage HCC; lymph node involvement; extrahepatic metastasis; less than 3 months of follow-up; previous treatment with antiviral drugs other than ETV or TDF; initiation of ETV or TDF therapy $\geq$3 months after hepatectomy; or treatment with combination of NUCs.

Information regarding baseline patient and tumor characteristics was obtained from the electronic medical records of Asan Medical Center. All included patients tested positive for serum HBsAg for at least 6 months, and have been taking either ETV or TDF at hepatectomy or initiated the medication within 3 months after the operation. Serum HBV DNA levels were measured at the time of hepatectomy or within 1 month before the surgery using a real-time PCR assay (linear dynamic detection range, 15 IU/mL to 1 x 10^9 IU/mL; Abbott Laboratories, Chicago, IL).

All study patients had pathologically proven HCC of BCLC stage 0 or A. Tumor characteristics were derived from findings from resected specimens by certified pathologists. Histologic grade of tumor differentiation was assessed according to the

Edmondson-Steiner (E-S) classification. Cirrhosis was also defined histologically by findings of resected liver specimens.

This study was approved by the institutional review boards of Asan Medical Center, Seoul, South Korea (IRB No. 2019-1013).

Outcomes and Follow-up Evaluation

The primary outcome measure of this study was HCC recurrence, and the secondary outcome was all-cause mortality or liver transplantation.

The index date was defined as the date of hepatectomy for HCC. Each patient's recurrence-free survival (RFS) and overall survival (OS) were computed from the index date to the confirmation of recurrence, death, liver transplantation, or date of last follow-up (July 1st, 2019). To validate the completeness of follow-up data, information about vital status was verified using the database of the National Health Insurance Service, which is the single-payer national health insurance system in Korea.

All patients were advised to continue the treatment with ETV or TDF. The routine follow-up protocol was identical between patients receiving ETV or TDF treatment. It included 4-phase dynamic computed tomography (CT) imaging, biochemical liver function tests, and serum levels of alpha-fetoprotein and des-gamma-carboxy prothrombin every 3 months for the first 2 years after hepatectomy and then every 3–6 months thereafter. Gadoxetic acid-enhanced magnetic resonance (MR) imaging was performed when a recurrence of HCC was not confirmatory by dynamic CT imaging during follow-up.

Definition of HCC Recurrence

Intrahepatic HCC recurrence was defined using the same criteria as for the diagnosis of HCC with dynamic CT or MR imaging showing typical features of HCC, i.e., a nodule larger than 1 cm with arterial hypervascularity and portal- or delayed-phase washout.(22, 23) There were no changes in techniques or instrumentation for the acquisition of CT or MR images throughout the study period. Although the final diagnostic decision was left to the radiologist's judgment, they generally used the pre-defined criteria of our institution as described above.

Statistical Analysis

All study patients who met the eligibility criteria at baseline were included in the analyses, and their data were analyzed based on intention-to-treat principle. OS was defined as the patient survival free of death or liver transplantation.

Propensity score-matched analysis was used to reduce the effect of selection bias and potential confounding between the two groups. Multiple imputation was used to estimate the missing values, which comprised 1.0% to 7.4% of the baseline laboratory data. Propensity scores were computed using the following 20 variables: age; sex; diabetes; hypertension; hemoglobin, platelet, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, total bilirubin, prothrombin time, and serum HBV DNA levels; HBeAg-positivity; BCLC stage; tumor size and E-S grade; and presence of background cirrhosis, microvascular invasion, capsular invasion, and satellite nodules. For propensity score matching, a nearest-neighbor 1:1 matching scheme with a caliper size of 0.1 was used. (Supplementary Figure 1) RFS and OS were compared between the two groups in a propensity score-matched cohort by a log-rank test.

Multivariable analyses were performed using a Cox proportional hazard (PH) model, which was fitted using the backward selection approach. Adjusted hazard ratios (AHRs) and 95% confidence intervals (CIs) for HCC recurrence and death/transplant were estimated with competing risk and multivariable analyses.

Competing risk analyses were conducted to evaluate the cumulative recurrence rates of HCC, adjusting for the possibility of death or liver transplantation in the entire cohort.(24)

All statistical analyses were performed using R statistical software, version 3.4 (R Foundation for Statistical Computing; https://www.R-project.org/). The R packages *MatchIt*, *cmprisk*, and *crrSC* were used to construct the matched cohort and for the competing risk analysis. All reported *P* values are two-sided, and $P < 0.05$ was considered significant.

RESULTS

Baseline Characteristics of the Study Patients

Among a total of 1,695 patients included in this study, 813 (48.0%) patients were treated with ETV and 882 (52.0%) were treated with TDF (Table 1). At baseline, i.e. at curative hepatectomy for HBV-related HCC, the mean age of the study patients was 54.8 years and 1,294 (76.3%) patients were male. The median size of HCC was 2.8 cm, and all patients had BCLC stage 0 (n=426, 25.1%) or A (n=1269, 74.9%). Cirrhosis was histologically confirmed, and was present in 996 (58.8%) patients. While most of the patients had initiated antiviral treatment before surgery, 72 (4.2%) started the treatment within 3 months after receiving the liver resection (median 1 month).

Compared with the ETV group, the TDF group had significantly more patients with higher levels of serum HBV DNA (≥2,000 IU/mL; 24.2% vs. 39.5%; P<0.001), higher levels of ALT (28 IU/mL vs. 33 IU/mL; P<0.001), larger tumor size (2.7 cm vs. 2.8 cm; P=0.01), more patients with BCLC stage A (72.4% vs. 77.1%; P=0.03), and more patients with microvascular invasion of HCC (25.5% vs. 32.4%; P=0.002), but fewer patients with BCLC stage 0 (27.6% vs. 22.9%; P=0.03) and fewer patients with cirrhosis (63.8% vs. 54.1%; P<0.001; Table 1).

The median duration of follow-up was 3.1 years. The median follow-up period in the TDF group was shorter compared with that of the ETV group (2.6 years vs. 4.4 years), due to the later approval of the TDF in Korea.

To minimize the effect of potential confounders in the comparison of HCC RFS and overall survival rates between the ETV and TDF groups, we generated 567 pairs of patients by propensity score-matching. Of the 567 pairs of propensity score-matched patients, the ETV and TDF groups did not differ significantly in baseline characteristics with the absolute standardized mean difference between the two groups <0.1 (Table 1 and Supplementary Figure 2), and it was considered that covariate balance was achieved.(25, 26)

HCC Recurrence

During follow-up with continued ETV or TDF therapy, 561 (33.1%) developed HCC recurrence among the 1,695 entire study population. The 1-, 3-, and 5-year cumulative recurrence rates of HCC were 15.7%, 33.0% and 44.5%, respectively.

For the 567 propensity score-matched pairs, the TDF group had significantly better RFS rate than the ETV group (hazard ratio [HR], 0.77; 95% confidence interval [CI], 0.62-0.95; *P*=0.02; Figure 2A). The Kaplan-Meier plots for RFS began to diverge between the two groups after 1 year of follow-up. The estimated 3-year RFS rates were 73.2% in the TDF group and 64.1% in the ETV group.

The TDF group showed a significantly lower rate of intrahepatic recurrence compared with the ETV group (33.6% vs. 44.5% at 5-year by Kaplan-Meier estimate; *P*=0.008) in the matched pairs of patients (Supplementary Figure 3). In contrast, the rates of extrahepatic metastasis did not significantly differ between the matched pairs of TDF and ETV groups (6.7% vs. 6.8% at 5-year by Kaplan-Meier estimate; *P*=0.99; Supplementary Figure 4).

In the multivariable Cox PH model including the entire cohort of 1,695 patients, the TDF group was associated with a significantly lower risk of HCC recurrence than the ETV group (adjusted hazard ratio [AHR], 0.82; 95% confidence interval [CI], 0.68-0.98; *P*=0.03), which was independent to other predictive factors (Table 2).

Other significant factors associated with HCC recurrence were older age (AHR, 1.01; *P*=0.01), male sex (AHR, 1.70; *P*<0.001), HBeAg-positivity (AHR, 1.46; *P*<0.001), cirrhosis (AHR, 1.21; *P*=0.04), larger tumor size (AHR, 1.09; *P*<0.001), microvascular invasion (AHR, 1.65; *P*<0.001), capsular invasion (AHR, 1.43; *P*=0.006), and presence of satellite nodules (AHR, 2.11; *P*<0.001; Table 2).

Overall Patient Survival

During the study period, 166 (9.8%) patients died (n = 144) or received liver transplantation (n = 22). Overall transplant-free survival rates at 1-, 3-, and 5-year for the entire cohort were 98.0%, 91.6%, and 86.8%, respectively.

Among the 567 propensity score-matched pairs, the TDF group had significantly better overall survival than the ETV group (HR, 0.63; 95% CI, 0.42-0.96; *P*=0.03; Figure 2B). The Kaplan-Meier plots for RFS began to diverge between the two groups after 1 year of follow-up. The estimated 3-year overall survival rates were 93.3% in the TDF group and 90.0% in the ETV group.

In the multivariable Cox PH model including the entire cohort of 1,695 patients, the TDF group was associated with a significantly lower risk of death or transplantation (AHR, 0.62; 95% CI, 0.44-0.88; *P*=0.01) than the ETV group, which was independent from other predictive factors (Table 2).

Other significant factors associated with death or transplantation were male sex (AHR, 1.67; *P*=0.02), HBeAg positivity (AHR, 1.54; *P*=0.01), cirrhosis (AHR, 1.52; *P*=0.02), larger tumor size (AHR, 1.12; *P*<0.001), microvascular invasion (AHR, 2.22; *P*<0.001), capsular invasion (AHR, 1.81; *P*=0.004), and satellite nodules (AHR, 2.44; *P*<0.001; Table 2).

Competing Risk and Sensitivity Analyses

During the study period, 23 patients died (n=19) or received liver transplantation (n=4) before the recurrence of HCC in the entire cohort. With the competing risk analysis, TDF therapy was again associated with a significantly lower risk of HCC recurrence than ETV therapy (HR, 0.82; 95% CI, 0.68-0.99; *P*=0.04; Supplementary Table 1 and Supplementary Figure 5).

To exclude confounding effect of extrahepatic metastasis on overall survival, a sensitivity analysis for overall survival between the TDF and ETV groups was conducted with censoring at the time of extrahepatic metastasis. In this analysis, TDF treatment was again significantly associated with a better overall survival compared with ETV treatment (*P*=0.03; Supplementary Figure 6).

Factors Related with Early (< 2 years) and Late (≥ 2 years) HCC Recurrence

Among the total of 561 patients with HCC recurrence, 392 (69.9%) and 169 (30.1%) patients had early (< 2 years) and late (≥ 2 years) postoperative recurrences, respectively. Risk of HCC recurrence after liver resection was highest during the first year after liver resection, and then gradually decreased during next two postoperative years (Supplementary Figure 7). However, the risk of recurrence and its difference between the ETV and TDF groups increased gradually after 3 postoperative years (Supplementary Figure 7-8).

TDF treatment was an independent factor that was significantly associated with lower risk of both early recurrence (AHR, 0.79; 95% CI, 0.64-0.97; *P*=0.03) and late

recurrence (AHR, 0.68; 95% CI, 0.47-0.97; *P*=0.03) when compared with ETV therapy by the multivariable Cox analysis in the entire cohort (Table 3).

Baseline factors that were significantly associated with higher risk of early recurrence were male sex (AHR, 1.33; *P*=0.04), BCLC stage A (AHR, 1.39; *P*=0.03), cirrhosis (AHR, 1.42; *P* =0.002), larger tumor size (AHR, 1.10; *P*<0.001), microvascular invasion (AHR, 1.66; *P*<0.001), capsular invasion (AHR, 1.37; *P*=0.04), presence of satellite nodules (AHR, 1.69; *P*=0.003), higher levels of total bilirubin (AHR, 1.38; *P*=0.03), high levels of serum HBV DNA ≥ 2,000 IU/mL (AHR, 1.35; *P*=0.02), and high levels of serum alpha-fetoprotein ≥ 20 ng/mL (AHR, 1.23; *P*=0.05; Table 3).

Factors other than TDF treatment that were significantly associated with late recurrence were older age (AHR, 1.02; *P*=0.04), capsular invasion (AHR, 1.86; *P*=0.02), and high AST levels of > 40 IU/mL (AHR, 1.64; *P*=0.01; Table 3).

DISCUSSION

This historical cohort study analysed 1,695 consecutive patients who were treated with ETV (n=813) or TDF (n=882) after curative hepatectomy for HBV-related HCC of early stage (BCLC stage 0 or A). We found that TDF treatment was associated with a significantly lower risk of HCC recurrence and better overall survival after curative liver resection compared to ETV therapy, which was consistently observed in propensity score-matched, multivariable-adjusted, and competing risk-adjusted analyses. TDF therapy was an independent protective factor for both early (<2 years) and late (≥2 years) post-operative HCC recurrence.

For most patients with HCC, surgical resection or liver transplantation is the only curative option. Nonetheless, HCC recurrence occurs in up to 41–50% of patients within 2 years after resection (early recurrence) and in up to 20 % of patients more than 2 years later (late recurrence).(13) High pre-operative HBV load has been reported to be associated with higher risk of HCC recurrence and worse overall survival after curative resection.(6, 27, 28) It was suggested that high viral load and hepatic inflammatory activity may lead to necrosis and subsequent regeneration of remaining hepatocytes,

which may induce DNA mutations and instability, eventually leading to higher rates of HCC recurrence.

NUC therapy has been consistently reported to be associated with decreased HCC recurrence after resection.(8, 29-31) A nationwide cohort study from Taiwan of 4,051 untreated versus 518 NUC-treated CHB patients with resected HCC found that the risk of HCC recurrence was lower in the patients treated with NUC therapies such as ETV, lamivudine, telbivudine, etc. (43.6% untreated vs. 20.5% treated, P<0.001).(8) In that Taiwan study, NUC therapy was independently associated with a significantly lower HCC recurrence risk (HR 0.67, 95 % CI 0.55–0.81, P<0.001).(8) In a randomized trial, even in patients with low-level viremia (HBV DNA < 2,000 IU/mL), NUC therapy was associated with better RFS (P=0.016) and OS (P=0.004).(32) A meta-analysis also demonstrated the beneficial effects of NUC therapy with regards to HCC recurrence (odds ratio [OR]: 0.59, 95 % CI: 0.35–0.97, P=0.04) and liver-related mortality (OR: 0.13, 95 % CI: 0.02–0.69, P=0.02).(30) Therefore, many international and local clinical practice guidelines recommend that NUC should be given to patients with HBV-related HCC before and/or after curative therapy of HCC to prevent disease progression and reduce the risk of HCC recurrence.(12, 13, 33)

Treatment with highly potent NUCs with high genetic barriers to drug-resistance (i.e., ETV or TDF) have been found to be associated with significantly higher RFS than treatment with low-potency and low-barrier drugs (i.e., lamivudine, clevudine, or telbivudine) after surgical resection or radiofrequency ablation (RFA).(34) However, so far, only single small-scale retrospective study has compared recurrence rates of HCC after liver resection in patients treated with ETV vs. TDF, which reported lower risk of HCC recurrence in the TDF group.(35) Although that study was limited by the low number and heterogeneity of the study population and lack of relevant information for tumor characteristics, the results were consistent with ours.

We recently reported that CHB patients treated with TDF was associated with a significantly lower risk of HCC occurrence compared to those treated with ETV in a nationwide cohort, which was validated by a hospital cohort.(15) Although the issue is debatable, it is notable that the subsequent studies that compared the risk of HCC occurrence between TDF and ETV therapies have indicated one direction favouring TDF

or no difference.(16-21) No studies, so far, has reported the opposite direction of favouring ETV over TDF.

The underlying mechanism of our findings showing lower rates of HCC recurrence with TDF therapy compared with ETV needs to be elucidated by future studies. However, a recent study found that higher serum interferon-λ3 levels were induced in patients treated with TDF, but not in those treated with ETV.(36) Interferon lambda has shown potent antitumor activity in murine models of cancer, including HCC,(37-39) and this antitumor activity could presumably contribute to the difference in the risks of HCC occurrence and recurrence. A subsequent in vitro study also demonstrated that pretreatment of peripheral blood mononuclear cells with TDF inhibited enteric lipopolysaccharide-mediated production of interleukin (IL)-10, but induced production of IL-12p70 and tumor necrosis factor-α in a dose-dependent manner, which was not observed with ETV.(40) IL-10 inhibit antigen-specific CD8+-T cells. Therefore, downregulation of IL-10 may restore the function of T cells and NK cells. In contrast, IL-12 directly stimulates T cells and NK cells to induce IFN-γ, and upregulation of IL-12 restores the normal function of exhausted CD8+-T cells. Our clinical observations may be in line with those in vitro findings that TDF modulates cytokine profiles.

It is generally accepted that most early recurrence within 2 years of hepatectomy results from dissemination of the primary tumor, while most late recurrence after 2 years of hepatectomy stems from *de novo* recurrence of tumors spontaneously arising in the remaining liver.(3, 4, 41) Notably, RFS rates between the TDF and ETV groups started to diverge from 1 year after liver resection in our present study. Although treatment with TDF was significantly associated with lower risk of both early and late HCC recurrence compared with ETV therapy, the magnitude of risk difference for late recurrence (HR, 0.68) was more prominent than that for early recurrence (HR, 0.79). These findings suggest that the differences in recurrence rates between the two treatment groups might stem from their differences in the preventive effect on *de novo* HCC recurrence. In these regards, we considered that it would not be appropriate to include the patients who received RFA in the comparison of preventive effect of TDF vs. ETV therapies on the recurrence of HCC. The rate of early intrahepatic HCC recurrence after RFA has been consistently reported to be significantly higher than that after surgical resection,(42) even in the patients with very early stage (BCLC stage 0) HCC,(43) mainly because of the

incomplete tumor ablation. The high rate of early recurrence by the dissemination of the incompletely ablated primary tumor may obscure the preventive effect of anti-HBV therapies on the *de novo* recurrence of HCC.

It is also noteworthy that occurrence of extrahepatic metastasis did not significantly differ between patients treated with TDF (6.7% at 5-year) vs. ETV (6.8% at 5-year), while intrahepatic recurrence was less likely to develop in the TDF group (33.6% at 5-year) compared with the ETV group (44.5% at 5-year). To exclude confounding effect from extrahepatic metastasis on OS, we conducted a sensitivity analysis for OS between the TDF and ETV groups censoring the patients at the time of extrahepatic metastasis. As a result, TDF treatment was significantly associated with a better OS compared with ETV (P=0.03). This implies that better survival in the TDF group than the ETV group resulted from lower risk of intrahepatic recurrence.

The major limitation of the present study is that it was based on observational data, which may be subject to bias and confounding. To overcome this issue, we used multiple strategies (propensity-score matching, multivariable adjustment, and competing risk-adjusted analysis, and sensitivity analysis) to adjust for the differences in baseline susceptibility to the outcomes of interest in a large number of study patients with large number of outcome events. We also applied strict inclusion and exclusion criteria and collected pathologically proven tumor characteristics data to adjust for well known risk factors for HCC recurrence in the analysis, thereby enhancing the comparability between TDF and ETV groups. Nonetheless, unmeasured biases and confounders might exist, which is an inherent limitation of observational studies. Second, there was some heterogeneity in the time of antiviral agent initiation in our study patients. While most of the patients had initiated antiviral treatment before surgery that may be associated with a better long-term prognosis,(10) 72 (4.2%) started antiviral treatment within 3 months after receiving the liver resection. Third, there was a disparity in the follow-up periods between the 2 groups owing to the later approval of TDF. However, the annual risk of HCC recurrence was found to be the highest during the first 3 years after the surgery, and the difference in the RFS rates between the two groups was statistically significant at 3 years. Lastly, as a single center study, our results are limited in terms of generalization. Most patients in our study were assumed to be infected with genotype C HBV acquired through vertical transmission,(44) which may be associated with enhanced risk of HCC.

Genotype C HBV is predominant in many Asian countries, where the majority of people in need of HBV treatment live. The findings of this study should be validated in CHB patients of other ethnicities and HBV genotypes.

In conclusion, among patients who underwent curative hepatectomy for HBV-related HCC, TDF treatment was associated with significantly lower rate of HCC recurrence and better overall patient survival than ETV therapy. Given the high rate of post-operative recurrence of hepatitis B virus-related HCC and poor prognosis of the patients who developed HCC recurrence, our findings may have considerable clinical implications in the prevention of the cancer recurrence in the patients.

ACKNOWLEDGEMENTS

We also thank the Scientific Publications Team at Asan Medical Center for the editorial assistance in preparing this manuscript. None of them received compensation for their work.

REFERENCES

1. Global Burden of Disease Cancer C, Fitzmaurice C, Abate D, Abbasi N, Abbastabar H, Abd-Allah F, Abdel-Rahman O, et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-Years for 29 Cancer Groups, 1990 to 2017: A Systematic Analysis for the Global Burden of Disease Study. JAMA Oncol 2019:Epub ahead of print.
2. Global Burden of Disease Liver Cancer C, Akinyemiju T, Abera S, Ahmed M, Alam N, Alemayohu MA, Allen C, et al. The Burden of Primary Liver Cancer and Underlying Etiologies From 1990 to 2015 at the Global, Regional, and National Level: Results From the Global Burden of Disease Study 2015. JAMA Oncol 2017;3:1683-1691.
3. Imamura H, Matsuyama Y, Tanaka E, Ohkubo T, Hasegawa K, Miyagawa S, Sugawara Y, et al. Risk factors contributing to early and late phase intrahepatic recurrence of hepatocellular carcinoma after hepatectomy. J Hepatol 2003;38:200-207.
4. Poon RT, Fan ST, Ng IO, Lo CM, Liu CL, Wong J. Different risk factors and prognosis for early and late intrahepatic recurrence after resection of hepatocellular carcinoma. Cancer 2000;89:500-507.
5. Kim BK, Park JY, Kim DY, Kim JK, Kim KS, Choi JS, Moon BS, et al. Persistent hepatitis B viral replication affects recurrence of hepatocellular carcinoma after curative resection. Liver Int 2008;28:393-401.
6. **Yang T, Lu JH**, Zhai J, Lin C, Yang GS, Zhao RH, Shen F, et al. High viral load is associated with poor overall and recurrence-free survival of hepatitis B virus-related hepatocellular carcinoma after curative resection: a prospective cohort study. Eur J Surg Oncol 2012;38:683-691.
7. Chan AC, Chok KS, Yuen WK, Chan SC, Poon RT, Lo CM, Fan ST. 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.
8. Wu CY, Chen YJ, Ho HJ, Hsu YC, Kuo KN, Wu MS, Lin JT. Association between nucleoside analogues and risk of hepatitis B virus-related hepatocellular carcinoma recurrence following liver resection. JAMA 2012;308:1906-1914.
9. **Yin J, Li N**, Han Y, Xue J, Deng Y, Shi J, Guo W, et al. Effect of antiviral treatment with nucleotide/nucleoside analogs on postoperative prognosis of hepatitis B virus-related

hepatocellular carcinoma: a two-stage longitudinal clinical study. J Clin Oncol 2013;31:3647-3655.
10. Huang G, Lau WY, Wang ZG, Pan ZY, Yuan SX, Shen F, Zhou WP, et al. Antiviral therapy improves postoperative survival in patients with hepatocellular carcinoma: a randomized controlled trial. Ann Surg 2015;261:56-66.
11. Wong GL, Tse YK, Chan HL, Yip TC, Tsoi KK, Wong VW. Oral nucleos(t)ide analogues reduce recurrence and death in chronic hepatitis B-related hepatocellular carcinoma. Aliment Pharmacol Ther 2016;43:802-813.
12. European Association for the Study of the Liver. Electronic address eee, European Association for the Study of the L. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017;67:370-398.
13. Sarin SK, Kumar M, Lau GK, Abbas Z, Chan HL, Chen CJ, Chen DS, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol Int 2016;10:1-98.
14. Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, Brown RS, Jr., et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 2018;67:1560-1599.
15. **Choi J, Kim HJ**, Lee J, Cho S, Ko MJ, Lim YS. Risk of Hepatocellular Carcinoma in Patients Treated With Entecavir vs Tenofovir for Chronic Hepatitis B: A Korean Nationwide Cohort Study. JAMA Oncol 2019;5:30-36.
16. Yip TC, Wong VW, Chan HL, Tse YK, Lui GC, Wong GL. Tenofovir Is Associated With Lower Risk of Hepatocellular Carcinoma Than Entecavir in Patients With Chronic HBV Infection in China. Gastroenterology 2020;158:215-225 e216.
17. Zhang Z, Zhou Y, Yang J, Hu K, Huang Y. The effectiveness of TDF versus ETV on incidence of HCC in CHB patients: a meta analysis. BMC Cancer 2019;19:511.
18. Choi J, Lim YS. Comparison of risk of hepatocellular carcinoma between tenofovir and entecavir: One direction or no direction. J Hepatol 2019;71:846-847.
19. Hsu YC, Wong GL, Chen CH, Peng CY, Yeh ML, Cheung KS, Toyoda H, et al. Tenofovir Versus Entecavir for Hepatocellular Carcinoma Prevention in an International Consortium of Chronic Hepatitis B. Am J Gastroenterol 2020;115:271-280.
20. **Lee SW, Kwon JH**, Lee HL, Yoo SH, Nam HC, Sung PS, Nam SW, et al. Comparison of tenofovir and entecavir on the risk of hepatocellular carcinoma and

mortality in treatment-naive patients with chronic hepatitis B in Korea: a large-scale, propensity score analysis. Gut 2019:Epub ahead of print.
21. **Kim SU, Seo YS**, Lee HA, Kim MN, Lee YR, Lee HW, Park JY, et al. A multicenter study of entecavir vs. tenofovir on prognosis of treatment-naive chronic hepatitis B in South Korea. J Hepatol 2019;71:456-464.
22. Heimbach JK, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, Zhu AX, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology 2018;67:358-380.
23. European Association for the Study of the Liver. Electronic address eee, European Association for the Study of the L. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 2018;69:182-236.
24. Zhang X, Zhang MJ, Fine J. A proportional hazards regression model for the subdistribution with right-censored and left-truncated competing risks data. Stat Med 2011;30:1933-1951.
25. Harder VS, Stuart EA, Anthony JC. Propensity score techniques and the assessment of measured covariate balance to test causal associations in psychological research. Psychol Methods 2010;15:234-249.
26. McCaffrey DF, Griffin BA, Almirall D, Slaughter ME, Ramchand R, Burgette LF. A tutorial on propensity score estimation for multiple treatments using generalized boosted models. Stat Med 2013;32:3388-3414.
27. Hung IF, Poon RT, Lai CL, Fung J, Fan ST, Yuen MF. 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.
28. Wu JC, Huang YH, Chau GY, Su CW, Lai CR, Lee PC, Huo TI, et al. Risk factors for early and late recurrence in hepatitis B-related hepatocellular carcinoma. J Hepatol 2009;51:890-897.
29. Chong CC, Wong GL, Wong VW, Ip PC, Cheung YS, Wong J, Lee KF, et al. Antiviral therapy improves post-hepatectomy survival in patients with hepatitis B virus-related hepatocellular carcinoma: a prospective-retrospective study. Aliment Pharmacol Ther 2015;41:199-208.
30. **Wong JS, Wong GL**, Tsoi KK, Wong VW, Cheung SY, Chong CN, Wong J, et al. Meta-analysis: the efficacy of anti-viral therapy in prevention of recurrence after curative

treatment of chronic hepatitis B-related hepatocellular carcinoma. Aliment Pharmacol Ther 2011;33:1104-1112.

31. **Lao XM, Luo G**, Ye LT, Luo C, Shi M, Wang D, Guo R, et al. Effects of antiviral therapy on hepatitis B virus reactivation and liver function after resection or chemoembolization for hepatocellular carcinoma. Liver Int 2013;33:595-604.

32. **Huang G, Li PP**, Lau WY, Pan ZY, Zhao LH, Wang ZG, Wang MC, et al. Antiviral Therapy Reduces Hepatocellular Carcinoma Recurrence in Patients With Low HBV-DNA Levels: A Randomized Controlled Trial. Ann Surg 2018;268:943-954.

33. Korean Association for the Study of the L. KASL clinical practice guidelines for management of chronic hepatitis B. Clin Mol Hepatol 2019;25:93-159.

34. **Cho H, Ahn H**, Lee JH, Jung YJ, Chang Y, Nam JY, Cho YY, et al. Entecavir and tenofovir reduce hepatitis B virus-related hepatocellular carcinoma recurrence more effectively than other antivirals. J Viral Hepat 2018;25:707-717.

35. Zhang M, Wang D, Liu H, Li H. Tenofovir decrease hepatocellular carcinoma recurrence in chronic hepatitis B patients after liver resection. Infect Agent Cancer 2018;13:19.

36. **Murata K, Asano M**, Matsumoto A, Sugiyama M, Nishida N, Tanaka E, Inoue T, et al. Induction of IFN-lambda3 as an additional effect of nucleotide, not nucleoside, analogues: a new potential target for HBV infection. Gut 2018;67:362-371.

37. Abushahba W, Balan M, Castaneda I, Yuan Y, Reuhl K, Raveche E, de la Torre A, et al. Antitumor activity of type I and type III interferons in BNL hepatoma model. Cancer Immunol Immunother 2010;59:1059-1071.

38. Sato A, Ohtsuki M, Hata M, Kobayashi E, Murakami T. Antitumor activity of IFN-lambda in murine tumor models. J Immunol 2006;176:7686-7694.

39. Yan Y, Wang L, He J, Liu P, Lv X, Zhang Y, Xu X, et al. Synergy with interferon-lambda 3 and sorafenib suppresses hepatocellular carcinoma proliferation. Biomed Pharmacother 2017;88:395-402.

40. Murata K, Tsukuda S, Suizu F, Kimura A, Sugiyama M, Watashi K, Noguchi M, et al. Immunomodulatory Mechanism of Acyclic Nucleoside Phosphates in Treatment of Hepatitis B Virus Infection. Hepatology 2019:Epub ahead of print.

41. Chen YJ, Yeh SH, Chen JT, Wu CC, Hsu MT, Tsai SF, Chen PJ, et al. Chromosomal changes and clonality relationship between primary and recurrent hepatocellular carcinoma. Gastroenterology 2000;119:431-440.
42. **Xu XL, Liu XD**, Liang M, Luo BM. Radiofrequency Ablation versus Hepatic Resection for Small Hepatocellular Carcinoma: Systematic Review of Randomized Controlled Trials with Meta-Analysis and Trial Sequential Analysis. Radiology 2018;287:461-472.
43. Chu HH, Kim JH, Kim PN, Kim SY, Lim YS, Park SH, Ko HK, et al. Surgical resection versus radiofrequency ablation very early-stage HCC (</=2 cm Single HCC): A propensity score analysis. Liver Int 2019;39:2397-2407.
44. **Kim H, Jee YM**, Song BC, Shin JW, Yang SH, Mun HS, Kim HJ, et al. Molecular epidemiology of hepatitis B virus (HBV) genotypes and serotypes in patients with chronic HBV infection in Korea. Intervirology 2007;50:52-57.

FIGURE LEGENDS

Figure 1. Study flow diagram.

Figure 2. Recurrence-free and overall survival of the propensity score-matched cohort of patients who were treated with either tenofovir disoproxil fumarate or entecavir for hepatitis B after curative hepatectomy for hepatocellular carcinoma of BCLC stage 0 or A.

A. Recurrence-free survival

B. Overall patient survival

Table 1. Baseline characteristics of patients treated with entecavir vs. tenofovir disoproxil fumarate after curative hepatectomy for hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC).

Characteristics	Entire cohort (n = 1,695)			Propensity score-matched cohort (567 pairs)		
	Entecavir (n = 813)	Tenofovir (n = 882)	*P* Value	Entecavir (n = 567)	Tenofovir (n = 567)	SMD
Demographic characteristics						
Age, years	55.0 ± 8.7	54.6 ± 9.1	0.30	54.6 ± 8.6	54.7 ± 9.3	0.02
Male sex, n (%)	623 (76.6)	671 (76.1)	0.83	430 (75.8)	433 (76.4)	0.01
Diabetes mellitus, n (%)	122 (15.0)	133 (15.1)	0.99	86 (15.2)	88 (15.5)	0.01
Hypertension, n (%)	248 (30.5)	240 (27.2)	0.15	155 (27.3)	171 (30.2)	0.06
Laboratory findings						
HBeAg-positive, n (%)	189 (23.2)	248 (28.1)	0.03	137 (24.2)	149 (26.3)	0.05
HBV DNA, log_{10}IU/mL	1.7 ± 2.2	2.8 ± 2.4	< 0.001	2.2 ± 2.3	2.3 ± 2.4	0.03
HBV DNA			< 0.001			0.01
Undetectable	448 (55.1)	263 (29.8)		238 (42.0)	236 (41.6)	
DNA < 2,000 IU/mL	168 (20.7)	271 (30.7)		151 (26.6)	150 (26.5)	
DNA ≥ 2,000 IU/mL	197 (24.2)	348 (39.5)		178 (31.4)	181 (31.9)	
Hemoglobin*, g/dL	14.3 [13.2-15.1]	14.2 [13.2-15.1]	0.78	14.3 [13.2-15.1]	14.2 [13.2-15.1]	0.02
Platelets*, x1000/mm^3	149 [120-181]	160 [128-198]	< 0.001	153 [125-187]	158 [126-194]	0.06
AST*, IU/mL	29 [23-37]	32 [26-42]	< 0.001	30 [24-40]	31 [25-39]	0.06
ALT*, IU/mL	28 [20-41]	33 [24-46]	< 0.001	31 [21-43]	31 [22-42]	0.04
Albumin*, g/dL	3.8 [3.6-4.1]	3.8 [3.6-4.0]	0.009	3.8 [3.6-4.0]	3.8 [3.6-4.0]	0.01
Total bilirubin*, mg/dL	0.6 [0.5-0.9]	0.6 [0.4-0.8]	< 0.001	0.6 [0.4-0.8]	0.6 [0.4-0.8]	0.05
PT*, INR,	1.0 [1.0-1.1]	1.1 [1.0-1.1]	< 0.001	1.0 [1.0-1.1]	1.0 [1.0-1.1]	0.04
AFP*, ng/mL	16.6 [3.8-147.5]	15.8 [4.5-173.7]	0.26	16.2 [4.0-132.9]	15.7 [4.4-162.6]	0.04
AFP			0.71			
AFP < 20 ng/mL	424 (52.2)	469 (53.2)		297 (52.4)	296 (52.2)	0.01
AFP ≥ 20 ng/mL	389 (47.8)	413 (46.8)		270 (47.6)	271 (47.8)	
Pathologic findings						
BCLC stage						
Very early (0)	224 (27.6)	202 (22.9)	0.03	151 (26.6)	142 (25.0)	0.04
Early (A)	589 (72.4)	680 (77.1)		416 (73.4)	425 (75.0)	
Single tumor, n (%)	773 (95.1)	837 (94.9)	0.96	545 (96.1%)	540 (95.2%)	0.02
HCC Size*, cm	2.7 [2.0-3.8]	2.8 [2.0-4.3]	0.01	2.7 [2.0-4.0]	2.8 [2.0-4.1]	0.06
ES grade, worst, n (%)			0.45			0.06
I	11 (1.4)	8 (0.9)		7 (1.2)	7 (1.2)	
II	212 (26.1)	215 (24.4)		154 (27.2)	139 (24.5)	

III	423 (52.0)	454 (51.5)		281 (49.6)	294 (51.9)	
IV	167 (20.5)	205 (23.2)		125 (22.0)	127 (22.4)	
ES grade, background, n (%)			0.17			0.01
I	31 (3.8)	22 (2.5)		21 (3.7)	13 (2.3)	
II	504 (62.0)	542 (61.5)		353 (62.3)	360 (63.5)	
III	272 (33.5)	304 (34.5)		190 (33.5)	186 (32.8)	
IV	6 (0.7)	14 (1.6)		3 (0.5)	8 (1.4)	
Microvascular invasion, n (%)	207 (25.5)	286 (32.4)	0.002	157 (27.7)	148 (26.1)	0.04
Capsular invasion, n (%)	73 (9.0)	79 (9.0)	0.99	49 (8.6)	45 (7.9)	0.03
Satellite nodule, n (%)	34 (4.2)	29 (3.3)	0.40	22 (3.9)	22 (3.9)	0.001
Cirrhosis, n (%)	519 (63.8)	477 (54.1)	< 0.001	340 (60.0)	333 (58.7)	0.03
Follow-up period*, years	4.4 [2.1-6.5]	2.6 [1.5-3.8]	< 0.001	4.4 [2.1-4.3]	2.6 [1.4-4.0]	0.53

Presented as mean and standard deviation. *Presented as median and interquartile ranges.

AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC; Barcelona Clinic Liver Cancer staging system; ES, Edmondson-Steiner; HCC, hepatocellular carcinoma; INR, international normalized ratio; SMD, standardized mean difference.

Table 2. Multivariable analysis for hepatocellular carcinoma (HCC) recurrence and overall mortality/transplant following curative hepatectomy in the entire cohort.

Variables	HCC Recurrence			Death or transplantation		
	AHR	95% CI	*P* value	AHR	95% CI	*P* value
Antiviral treatment						
Entecavir	1	Reference		1	Reference	
Tenofovir disoproxil fumarate	0.82	0.68-0.98	0.03	0.62	0.44-0.88	0.01
Age, *per 1-year increase*	1.01	1.00-1.02	0.01			
Male sex	1.70	1.36-2.13	< 0.001	1.67	1.10-2.56	0.02
HBeAg, positivity	1.46	1.21-1.76	< 0.001	1.54	1.10-2.15	0.01
BCLC stage						
Very early	1	Reference				
Early	1.20	0.95-1.53	0.13			
Hypertension				1.31	0.95-1.83	0.10
Cirrhosis	1.21	1.01-1.45	0.04	1.52	1.07-2.15	0.02
Size, *per 1 cm increase*	1.09	1.06-1.13	< 0.001	1.12	1.07-1.17	< 0.001
Microvascular invasion	1.65	1.37-2.00	< 0.001	2.22	1.56-3.15	< 0.001
Capsular invasion	1.43	1.11-1.86	0.006	1.81	1.20-2.72	0.004
Satellite nodule, *present*	2.10	1.50-2.92	< 0.001	2.44	1.51-3.93	< 0.001
Albumin, *per 1 g/dL increase*	0.86	0.67-1.10	0.23			
HBV DNA						
Undetectable	1	Reference		1	Reference	
DNA < 2,000 IU/mL	1.03	0.82-1.30	0.79	1.49	0.98-2.29	0.06
DNA ≥ 2,000 IU/mL	1.11	0.89-1.40	0.33	1.11	0.73-1.67	0.63
AST						
≤ 40 IU/L	1	Reference				
> 40 IU/L	1.36	1.11-1.66	0.003			
AFP						
< 20 ng/mL	1	Reference				
≥ 20 ng/mL	1.06	0.89-1.26	0.54			

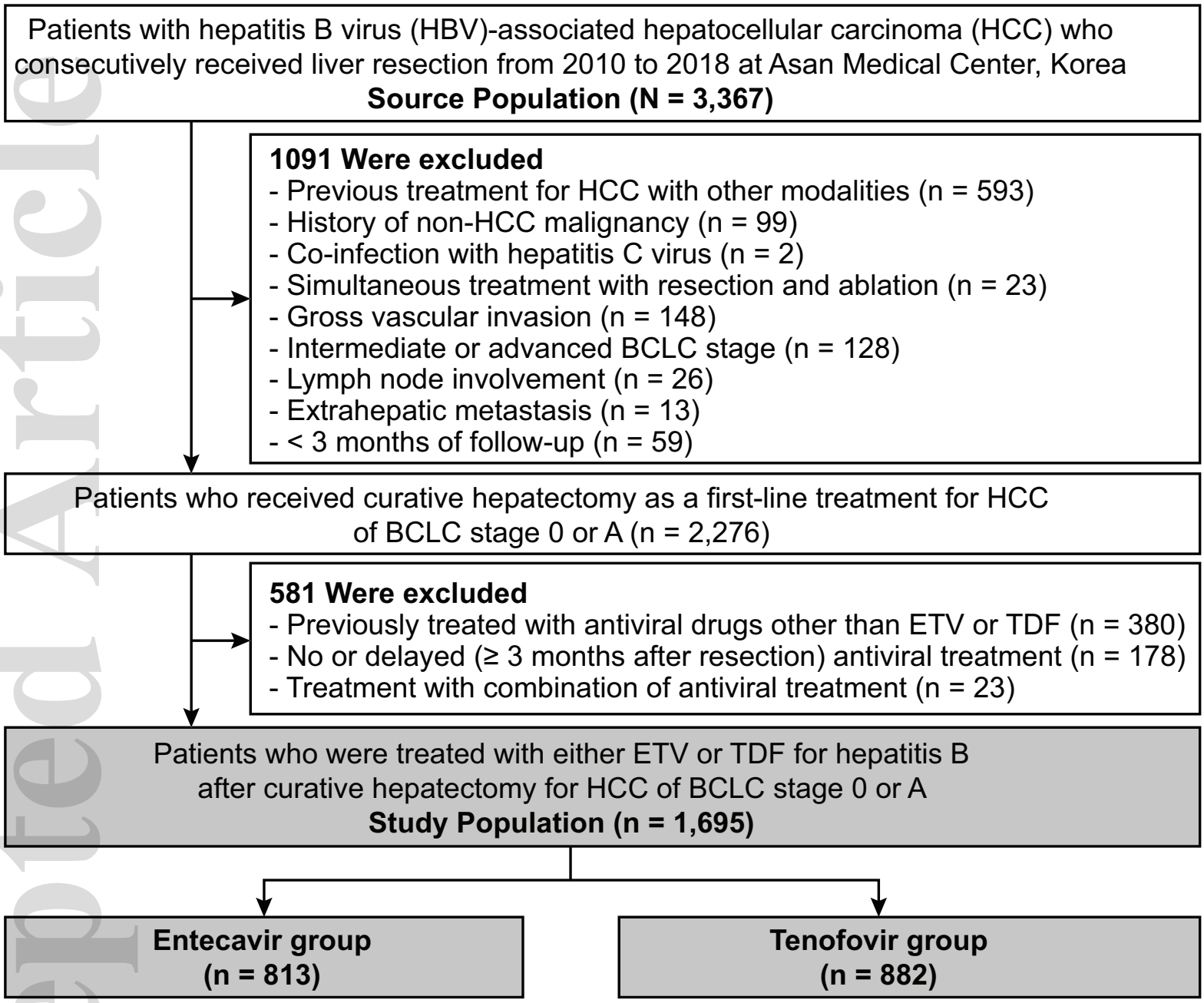
Total number of patients, 1695; number of patients with HCC recurrence, 561; number of death or transplantation, 166.
AFP, alpha-fetoprotein; AHR, adjusted hazard ratio; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer staging system; CI: confidence interval.

Table 3. Multivariable analysis for factors associated with early and late HCC recurrence after curative hepatectomy.

Variables	Early recurrence (< 2 years)			Late recurrence (≥ 2 years)		
	AHR	**95% CI**	***P* value**	**AHR**	**95% CI**	***P* value**
Antiviral treatment						
Entecavir	1	Reference		1	Reference	
Tenofovir disoproxil fumarate	0.79	0.64-0.97	0.03	0.68	0.47-0.97	0.03
Age, *per 1-year increase*				1.02	1.00-1.04	0.04
Male sex	1.33	1.02-1.75	0.04	1.42	0.97-2.10	0.12
HBeAg, positivity	1.20	0.96-1.49	0.11			
BCLC stage						
0 (Very early)	1	Reference		1	Reference	
A (Early)	1.39	1.03-1.84	0.03	1.39	0.95-2.02	0.11
Cirrhosis	1.42	1.14-1.77	0.002	1.27	0.91-1.79	0.16
Size, *per 1 cm increase*	1.10	1.06-1.13	< 0.001			
Microvascular invasion	1.66	1.34-2.06	< 0.001	1.32	0.91-1.90	0.14
Capsular invasion	1.37	1.01-1.84	0.04	1.86	1.12-3.09	0.02
Satellite nodule, *present*	1.69	1.19-2.40	0.003			
Total bilirubin, *per 1 mg/dL increase*	1.38	1.04-1.84	0.03			
HBV DNA						
Undetectable	1	Reference		1	Reference	
DNA < 2,000 IU/mL	0.98	0.74-1.29	0.87	1.03	0.69-1.57	0.86
DNA ≥ 2,000 IU/mL	1.35	1.04-1.76	0.02	1.01	0.69-1.52	0.92
AST ≤ 40 IU/L	1	Reference		1	Reference	
AST > 40 IU/L	1.14	0.89-1.45	0.31	1.64	1.13-2.38	0.01
AFP < 20 ng/mL	1	Reference		1	Reference	
AFP ≥ 20 ng/mL	1.23	1.00-1.51	0.05	0.87	0.63-1.19	0.38

Total number of patients, 1695; number of patients with early HCC recurrence, 392; number of patients with late HCC recurrence, 169.

AFP, alpha-fetoprotein; AHR, adjusted hazard ratio; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer staging system; CI, confidence interval.



hep_31289_f1.eps