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ORIGINAL ARTICLE

Effects of radiofrequency ablation combined with transarterial chemoembolization and antiviral therapy on the prognosis and quality of life in primary chronic HBV-related liver cancer

Baoling Lu*, Liying Zhu*, Xiaofang Wang, Lihua Zhong, Yu Cheng, Jian Fan, Lei Yu

Department of Infectious Disease, the fourth Hospital of Harbin Medical University, Harbin 150001, China.

*Baoling Lu and Liying Zhu contributed equally to this work

Summary

Purpose: *To investigate the effects of radiofrequency ablation (RFA) combined with transarterial chemoembolization (TACE) and antiviral therapy on the prognosis and quality of life in primary chronic hepatitis B virus (HBV)-related liver cancer.*

Methods: *A total of 80 hepatitis B patients complicated with hepatocellular carcinoma treated in our hospital from March 2016 to February 2018 were selected and divided into the control group (n=40) and the observation group (n=40) using a random number table. The patients in the control group were treated with RFA combined with TACE, while those in the observation group were additionally treated with entecavir. The HBV-DNA load and alpha fetoprotein (AFP) level during intervention and the liver function before and after intervention were compared between the two groups. The patients were followed up for 2 years after treatment, the clinical therapeutic effects in both groups were recorded, and the correlations of HBV-DNA load, AFP level and alanine aminotransferase (ALT) level with the survival time of patients were analyzed.*

Results: *At 1 and 3 months after intervention, the HBV-DNA load in the observation group was significantly lower than that before intervention (p<0.05), and it was also significantly lower than in the control group (p<0.05). At 1 and 3 months after intervention, the AFP level was lowered in both groups compared with that before the intervention (p<0.05), and it was also lower in the observation group than in the control group (p<0.05). After intervention, the levels of total bilirubin (Tbil), aspartate aminotransferase (AST) and ALT in the observation group were lower than those before the intervention (p<0.05), and they were also lower than those in the control group (p<0.05). Moreover, the disease progression in the observation group was significantly lower than in the control group, and the 1-year and 2-year survival in the observation group was longer compared with the control group. The HBV-DNA load, AFP level and ALT level were negatively correlated with the survival of patients (p<0.05).*

Conclusions: *The RFA combined with TACE and regular antiviral therapy for HBV-related liver cancer is of significance in reducing the HBV-DNA load and tumor markers, improving the liver function, promoting the overall clinical therapeutic effect and prolonging the survival of patients.*

Key words: *antiviral therapy, entecavir, radiofrequency ablation, transarterial chemoembolization, hepatitis B, hepatocellular carcinoma*

Introduction

Infection with hepatitis B virus (HBV) is the most important cause of hepatocellular carcinoma, and about 10% population (nearly 130 million people) in China are carriers of HBV [1]. With the extended course of disease, HBV infection will develop into fatty liver and liver cirrhosis, ultimately resulting in liver cancer [2]. The development process from hepatitis B to liver cancer is relatively hidden,

Corresponding author: Lei Yu, MD. Department of Infectious Disease, the fourth Hospital of Harbin Medical University, 37 Yiyuan Street, Nangang District, Harbin, 150001 Heilongjiang, China.
Tel: +86 013804535457, Email: widedoor@sina.com
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and the course of disease is longer, so the patients do not pay attention to it. As a result, the disease has been mostly in the middle-advanced stage with a poor prognosis once there are liver cirrhosis and even clinical manifestations of liver cancer [3].

Hepatocellular carcinoma has a high mortality rate, the survival of patients is short and the quality of life is low after onset [4]. Studies have revealed that the effective control of hepatitis B has great value in promoting the therapeutic effect in liver cancer, reducing the risk of recurrence and metastasis, improving the prognosis and prolonging the survival of HBV-infected patients with hepatocellular carcinoma [5]. Due to the hidden onset of hepatocellular carcinoma, some patients have lost the opportunity for surgical resection when diagnosed. At this time, hepatic arterial chemoembolization combined with RFA is of important significance in reducing tumor size, prolonging survival and improving the patient quality of life [6]. During treatment, however, immune dysfunction may occur in the body, thus activating HBV and leading to tumor recurrence. In the present study, therefore, antiviral therapy was combined in the treatment, so as to inhibit the activity of HBV and improve the clinical therapeutic effect.

Methods

General data

A total of 80 hepatitis B patients complicated with hepatocellular carcinoma treated in our hospital from March 2016 to February 2018 were selected. All patients were diagnosed with hepatitis B *via* biochemical examination, and definitely diagnosed with hepatocellular carcinoma *via* biopsy. The expected survival time of patients enrolled was more than 6 months. All patients signed informed consent before enrollment, and this study was approved by the Ethics Committee of our hospital. Patients complicated with severe cardiopulmonary insufficiency, renal insufficiency, obvious tumor cachexia when enrolled, other types of hepatitis virus infection or mental diseases or who were illiterate were excluded. The patients enrolled were divided into the control group (n=40) and the observation group (n=40) using a random number table.

In the observation group, there were 31 males and 9 females aged 51-70 years (mean 64.1±2.1). In terms of educational level, there were 24 cases below primary school and 16 cases above primary school. The course of hepatitis B was 3-40 years (mean 16.7±1.1). The course of diagnosis with liver cancer was 1-6 months (mean 2.1±0.2).

In the control group, there were 32 males and 8 females aged 50-70 years (mean 64.0±2.0). In terms of educational level, there were 25 cases below primary school and 15 cases above primary school. The course of hepatitis B was 3-40 years (mean 16.8±1.1). The course of diagnosis with liver cancer was 1-6 months (mean 2.0±0.2). There were no statistically significant differences in the gender, age, educational level, history of hepatitis B and course of diagnosis with liver cancer between the two groups ($p>0.05$).

Methods

The patients in the control group were treated with RFA combined with TACE. First, the femoral artery was punctured using the Seldinger technique, and hepatic arteriography was performed to determine the site, shape and number of tumors and understand the main blood supply of the tumor. Then, the guide wire and catheter were inserted till the main feeding artery of the tumor under fluoroscopic guidance, and the gelatin sponge and/or lipiodol was injected to occlude the main feeding artery of the tumor. Then, a number of chemotherapeutic drugs were injected into the end of the occluded tumor vessels, including lobaplatin (40 mg/m^2, NMPN H20050309, Hainan Changan International Pharmaceutical Co., Ltd., Haikou, China) and pirarubicin (50 mg/m^2, NMPN H10910093, Shenzhen Wanle Pharmaceutical Co., Ltd., Shenzhen, China). After that, the electrode needle was punctured under ultrasonic guidance for RFA (about 15 min for one tumor lesion). The effect was evaluated at 3 months after treatment, and the above treatment was repeated at an interval of 3 months. The patients in the observation group were additionally treated with entecavir (0.5 mg/time/d, NMPN H20080798, Bristol-Myers Squibb, New York, NY, USA) based on the treatment in the control group.

Observation indexes

All patients were followed up for 2 years. The HBV-DNA load and AFP level during intervention and the liver function before and after intervention were compared between the two groups. The patients were followed up for 2 years after treatment, the clinical therapeutic effects in both groups were recorded, and the correlations of HBV-DNA load, AFP level and ALT level with the survival time of patients were analyzed.

Evaluation criteria

The HBV-DNA load (normal value in adults: ≤500 copy/mL) in patients with hepatitis B was detected *via* fluorescence quantitative polymerase chain reaction (qPCR). AFP (normal value in adults: 0-25 μg/L) was detected *via* radioimmunoassay. The liver function-related indexes included total bilirubin (Tbil, normal value in adults: 3.4-20 μmol/L), aspartate aminotransferase (AST, normal value in adults: ≤40 U/L) and ALT (normal value in adults: ≤40 U/L). The clinical efficacy in both groups was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST):

Complete remission (CR): The liver cancer lesion disappeared in imaging and AFP returned to normal.

Partial remission (PR): The liver cancer lesion shrank by more than 30% in imaging, and AFP significantly declined but still did not return to normal.

Progressive disease (PD): The diameter of liver cancer lesion was increased by more than 20% in imaging, and/or new lesions appeared.

Stable disease (SD): The liver cancer lesion shrank by less than 30% or increased by less than 20%, and the AFP level was increased.

Statistics

SPSS 20.0 software (IBM, Armonk, NY, USA) was used for statistical analyses. Measurement data, such as HBV-DNA load, AFP level and liver function-related indexes before and after intervention, were expressed as mean ± standard deviation (x±s). T-test was adopted for the comparison of means between two groups, one way analysis of variance (ANOVA) was used for the comparison of means within the group at different time points, and the clinical therapeutic effect was expressed as [n (%)]. Chi-square test was performed for statistical processing. The patients were followed up for 2 years after treatment, the survival status was analyzed *via* Life Table Analysis, and the correlations of HBV-DNA load, AFP level and ALT level with the survival time of patients were analyzed *via* Pearson correlation analysis. Kaplan-Meier method was utilized to generate survival curves, and Log-Rank test was carried out for analyzing the survival rate. P<0.05 suggested that the difference was statistically significant.

Results

Changes in HBV-DNA load in both groups during intervention

The HBV-DNA load had no statistically significant difference between the two groups before intervention (p>0.05). At 1 and 3 months after intervention, the HBV-DNA load in the observation group was significantly lower than that before intervention (p<0.05), and it was also significantly lower than that in the control group (p<0.05) (Table 1).

Changes in AFP level in both groups during intervention

The AFP level had no statistically significant difference between the two groups before intervention (p>0.05). At 1 and 3 months after intervention, the AFP level was lowered in both groups compared with that before intervention (p<0.05), and it was also lower in the observation group than that in the control group (p<0.05) (Table 2).

Comparison of liver function between the two groups before and after intervention

Before intervention, the levels of Tbil, AST and ALT were 29.8±4.6 μmol/L, 90.6±3.9 U/L and 109.8±4.3 U/L, respectively, in observation group, and 29.9±4.5 μmol/L, 90.5±3.8 U/L and 109.9±4.4 U/L, respectively, in the control group. At 3 months after intervention, the levels of Tbil, AST and ALT were 15.1±1.6 μmol/L, 40.6±0.9 U/L and 39.5±1.0 U/L, respectively, in the observation group, and 21.1±1.9 μmol/L, 54.5±1.5 U/L and 46.5±1.5 U/L, respectively, in the control group. It can be seen that there were no statistically significant differences in the levels of Tbil, AST and ALT between the two groups before intervention. After intervention, the levels of Tbil, AST and ALT in the observation and the control group were all lower than those before intervention (t=19.082, 79.008 and 100.712, p<0.05;

Table 1. Changes in HBV-DNA load in both groups during intervention (copy/mL, x±s)

	Before intervention	*1 month after intervention*	*3 months after intervention*	*F*	*p*
Observation group	16114.2±45.1	7326.2±21.9	1327.2±12.1	17.879	0.000
Control group	16115.3±44.9	17312.5±33.1	18111.3±21.2	10.291	0.000
t	0.109	475.875	1757.736	-	-
p	0.913	0.000	0.000	-	-

Table 2. Changes in AFP level in both groups during intervention (μg/L. x±s)

	Before intervention	*1 month after intervention*	*3 months after intervention*	*F*	*p*
Observation group	879.2±34.2	324.5±19.9	33.2±2.1	29.291	0.000
Control group	880.1±34.3	678.9±23.1	109.3±3.9	17.118	0.000
t	0.118	73.515	108.659	-	-
p	0.907	0.000	0.000	-	-

Table 3. Comparison of clinical therapeutic effect between the two groups within 2-year follow-up after treatment

	CR	*PR*	*SD*	*PD*
Observation group	3	11	9	17
Control group	1	4	8	27

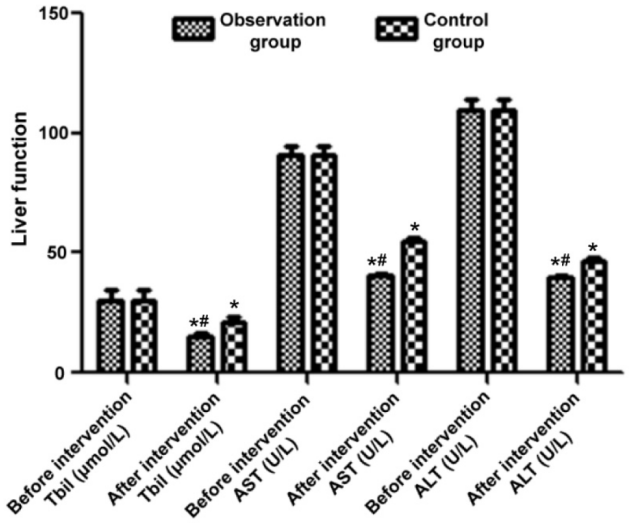

Figure 1. Comparison of liver function between the two groups before and after intervention. After intervention, the levels of Tbil, AST and ALT in both groups were all lower than those before intervention (p<0.05), and they were also lower in the observation group than those in control group (p<0.05). *p<0.05, compared with before intervention; #p<0.05, compared with control group.

t=11.394, 55.732 and 86.257, p<0.05), and they were also lower in the observation group than those in the control group after intervention (t=15.277, 50.256 and 24.558, p<0.05) (Figure 1).

Comparison of clinical therapeutic effect between the two groups within 2-year follow-up after treatment

Within 2-year follow-up after treatment, the progression rate of disease in the observation group (42.5%) was significantly lower than that in the control group (67.5%) (x^2=5.051, p=0.025) (Table 3).

Survival analysis in both groups within 2 years after treatment

In the observation group there were 31 1-year survival cases (77.5%) and 25 2-year survival cases (62.5%). In the control group, there were 23 1-year survival cases (57.5%) and 18 2-year survival cases (45.0%). It can be seen that the 1- and 2-year survival time in the observation group was longer than that in the control group (Figure 2).

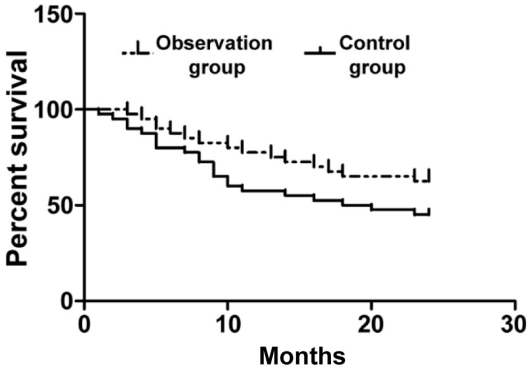

Figure 2. Survival analysis in both groups within 2 years after treatment. The results showed that the 1- and 2-year survival time in the observation group was longer than that in the control group (p<0.05).

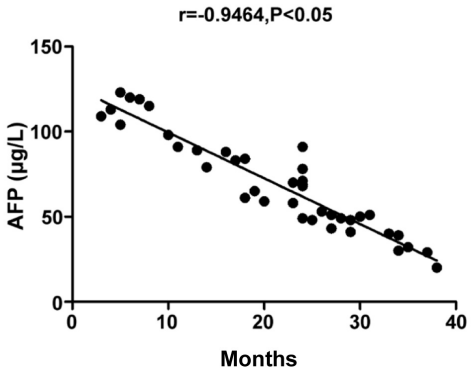

Figure 4. Correlation between AFP level and survival time of patients. The results of this figure showed that the AFP level was negatively correlated with the patient survival (r=-0.9464, p<0.05).

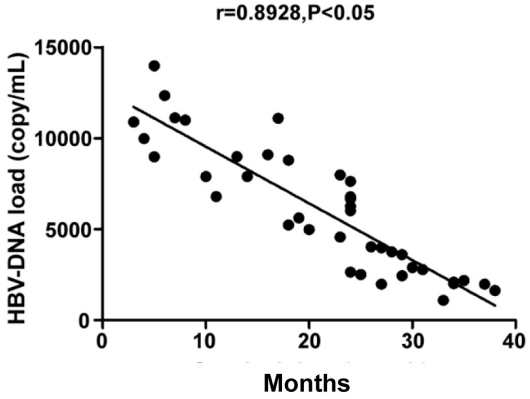

Figure 3. Correlation between HBV-DNA load and survival time of patients. The results of this figure showed that the HBV-DNA load was negatively correlated with the patient survival (R=-0.8928, p<0.05).

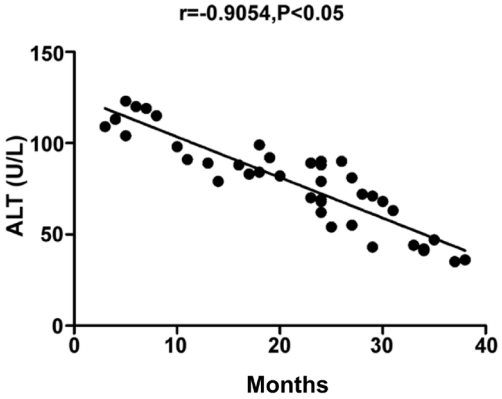

Figure 5. Correlation between ALT level and survival time of patients. The results of this figure showed that the ALT level was negatively correlated with the patient survival (r=-0.9054, p<0.05).

Correlation analysis of HBV-DNA load, AFP level and ALT level with survival time of patients

The HBV-DNA load, AFP level and ALT level were negatively correlated with the patient survival (r=-0.8928, -0.9464 and -0.9054, p<0.05) (Figures 3-5).

Discussion

HBV-related liver cancer often has a long duration, and patients are resistant to antitumor and antiviral drugs [7]. Hepatic arterial chemoembolization combined with RFA [8] applied for HBV-infected patients with hepatocellular carcinoma create certain damage to normal liver tissue and a greater impact on liver function [9] while killing malignant tumor cells. Moreover, it will also activate the sterile inflammatory response, reduce the immunity, induce activation of HBV and enhance its replication activity, and even cause liver failure and death in patients in severe cases [10]. Therefore, the drug administration after local embolization can improve the local antitumor efficiency, but its impact on normal liver cells cannot be ignored [11]. It induces massive release of sterile inflammatory cytokines and reduces the immune function, ultimately leading to tumor recurrence and metastasis [12]. In addition, antiviral therapy is very necessary for HBV-infected patients with hepatocellular carcinoma [13].

RFA combined with TACE were performed for HBV-related liver cancer in the control group, while antiviral therapy with entecavir was given in the observation group based on the treatment in the control group. The comparison of changes in HBV-DNA load between the two groups during intervention revealed that at 1 and 3 months after intervention, the HBV-DNA load in the observation group was significantly lower than that before intervention, and it was also significantly lower than that in the control group, indicating that RFA combined with TACE and regular antiviral therapy for HBV-related liver cancer has great value in reducing the HBV-DNA load. Besides, the comparison of change in the AFP level between the two groups during intervention showed that at 1 and 3 months after intervention, the AFP level was lowered in both groups compared with that before intervention, and it was also lower in the observation group than in the control group, suggesting that regular antiviral therapy for liver cancer has great significance in reducing the levels of tumor markers. At the same time, the comparison of liver function between the two groups before and after intervention manifested that the levels of Tbil, AST and ALT in the observation group at 6-month follow-up were lower than those before intervention and those in the control group after intervention, further indicating that RFA combined with TACE and regular antiviral therapy for HBV-related liver cancer is of great importance in improving the patient liver function.

All patients were followed up for 2 years and the clinical therapeutic effect and survival status were recorded. What was found was that the progression rate of disease in the observation group was significantly lower than in the control group, and the 1- and 2-year survival time in the observation group was longer than in the control group, suggesting that RFA combined with TACE and effective antiviral therapy has positive significance in promoting the clinical therapeutic effect and improving the prognosis of patients. Finally, the correlation analysis of HBV-DNA load, AFP and ALT level with survival of patients showed that these 3 parameters were negatively correlated with the survival of patients, indicating that effective antiviral therapy for HBV-related liver cancer is of important significance in reducing the HBV-DNA load and tumor markers and protecting the liver function.

In the present study, the regular antiviral therapy was performed in the observation group based on the RFA combined with TACE in the control group. Entecavir application effectively reduced the activation of HBV induced by arterial embolization and lowered the HBV-DNA load, thus improving the immunity [14]. Entecavir, as triphosphate [15], used in the observation group can effectively inhibit the activity of HBV polymerase and suppress the HBV replication [16]. Entecavir is the most potent antiviral drug for hepatitis B, which can effectively block the extension of viral DNA strand [17], while inhibiting the activity of viral polymerase. Moreover, entecavir takes effect quickly [18] with a low drug resistance rate in antiviral therapy and high safety [19], which relieves the super-strong immune response in the body, thus alleviating the damage of HBV to the liver and promoting the hepatocyte regeneration and repair [20].

Conclusions

In conclusion, RFA combined with TACE and regular antiviral therapy for HBV-related liver cancer is of significance in reducing the HBV-DNA load and tumor markers, improving the liver function, promoting the overall clinical therapeutic effect and prolonging the survival of patients.

Conflict of interests

The authors declare no conflict of interests.

References

1. 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;5:30-6.
2. Dong H, Xiao J, Zhu R et al. Serum sphingosine 1-phosphate in hepatocellular carcinoma patients is related to HBV infection. JBUON 2018;23:1711-6.
3. Han J, Wang S, Kwong T, Liu J. Dermatomyositis as an extrahepatic manifestation of hepatitis B virus-related hepatocellular carcinoma: A case report and literature review. Medicine (Baltimore) 2018;97:e11586.
4. Zhang S, Yue M, Shu R, Cheng H, Hu P. Recent advances in the management of hepatocellular carcinoma. JBUON 2016;21:307-11.
5. Liu B, Yang XF, Liang XP et al. Expressions of MiR-132 in patients with chronic hepatitis B, posthepatitic cirrhosis and hepatitis B virus-related hepatocellular carcinoma. Eur Rev Med Pharmacol Sci 2018;22:8431-7.
6. Aktas G, Kus T, Emin KM et al. Sorafenib with TACE improves the survival of hepatocellular carcinoma patients with more than 10 cm tumor: a single-center retrospective study. JBUON 2017;22:150-6.
7. Sotiropoulos GC, Kostakis ID, Machairas N, Kykalos S, Kouraklis G. Safety and efficacy of liver resections in elderly patients. JBUON 2017;22:1180-5.
8. Tang L, Covert E, Wilson E, Kottilil S. Chronic Hepatitis B Infection: A Review. JAMA 2018;319:1802-13.
9. Yoo J, Hann HW, Coben R, Conn M, DiMarino AJ. Update Treatment for HBV Infection and Persistent Risk for Hepatocellular Carcinoma: Prospect for an HBV Cure. Diseases 2018;6 (PMID: 29677098, DOI: 10.3390/diseases6020027)
10. Guo X, Wu J, Wei F et al. Trends in hepatitis B virus resistance to nucleoside/nucleotide analogues in North China from 2009-2016: A retrospective study. Int J Antimicrob Agents 2018;52:201-9.
11. Kelling M, Sokol L, Dalia S. Hepatitis B Reactivation in the Treatment of Non-Hodgkin Lymphoma. Cancer Control 2018;25:1146203143.
12. Hashimoto M, Taguchi K, Ishiguro T et al. Pharmacokinetics studies of 4'-cyano-2'-deoxyguanosine, a potent inhibitor of the hepatitis B virus, in rats. J Pharm Pharmacol 2018;70:723-31.
13. Ogura N, Ogawa K, Watashi K, Ito T, Wakita T. Novel stable HBV producing cell line systems for expression and screening antiviral inhibitor of hepatitis B virus in human hepatoma cell line. Biochem Biophys Res Commun 2018;498:64-71.
14. Reviakine I. When a transmembrane channel isn't, or how biophysics and biochemistry (mis)communicate. Biochim Biophys Acta Biomembr 2018;1860:1099-1104.
15. Balsitis S, Gali V, Mason PJ et al. Safety and efficacy of anti-PD-L1 therapy in the woodchuck model of HBV infection. PLoS One 2018;13:e190058.
16. Sun D, Zhu L, Yao D, Chen L, Fu L, Ouyang L. Recent progress in potential anti-hepatitis B virus agents: Structural and pharmacological perspectives. Eur J Med Chem 2018;147:205-17.
17. Hall S, Shaikh A, Teh K et al. Hepatitis B screening before rituximab therapy: a multicentre South Australian study of adherence. Intern Med J 2018;48:936-43.
18. Cho H, Ahn H, Lee DH et al. Entecavir and tenofovir reduce hepatitis B virus-related hepatocellular carcinoma recurrence more effectively than other antivirals. J Viral Hepat 2018;25:707-17.
19. Hsu YC, Ho HJ, Lee TY et al. Temporal trend and risk determinants of hepatocellular carcinoma in chronic hepatitis B patients on entecavir or tenofovir. J Viral Hepat 2018;25:543-51.
20. Liu XF, Zhang T, Tang K, Sui LL, Xu G, Liu Q. Study of Preoperative Antiviral Treatment of Patients with HCC Negative for HBV-DNA. Anticancer Res 2017;37:4701-6.