Risk factors for hepatitis B virus reactivation after conformal radiotherapy in patients with hepatocellular carcinoma

Wei Huang,1,5 Wei Zhang,2,5 Min Fan,1 Yanda Lu,3,4 Jian Zhang,1 Hongsheng Li1 and Baosheng Li1

1Department of Radiation Oncology VI, Shandong Cancer Hospital, Shandong Academy of Medical Sciences, Shandong’s Key Laboratory of Radiation Oncology, Jinan; 2Department of Radiation Oncology, Yuhuangding Hospital, Yantai; 3Cancer Center, The Third People's Hospital of Jinan, Jinan, China

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Correspondence
Baosheng Li, Department of Radiation Oncology VI, Shandong’s Key Laboratory of Radiation Oncology, Shandong Cancer Hospital, 440 Jiyan Road, Jinan 250117, Shandong Province, China.
Tel: +86-531-67626161; Fax: +86-531-67626161; E-mail: baoshli@yahoo.com

This study investigated whether conformal radiotherapy affects hepatitis B virus (HBV) reactivation, and the risk factors for HBV reactivation in patients with HBV-related hepatocellular carcinoma (HCC). Sixty-nine patients with HCC were included in this retrospective study. Before radiotherapy (RT), all patients underwent imaging examinations and some baseline examinations, including CBC, liver function test, renal function test, α-fetoprotein level, hepatitis B (HB) surface antigen, HB surface Ab, HB e antigen, HB e Ab, and serum HBV DNA quantification. During the period of RT and at least 16 weeks after the end of RT, CBCs were carried out weekly and the other tests were monitored monthly or more frequently if necessary. The clinical features and dosimetric parameters of RT were recorded. Univariate and multivariate logistic regression algorithms were used to analyze the risk factors of HBV reactivation. The incidence of complications in the study population was as follows: radiation-induced liver disease, 17.4%; HBV reactivation, 24.6%; and HBV reactivation-induced hepatitis, 21.7%. The HBV DNA level and dose volume parameters including normal liver volume, V20, and mean dose were associated with HBV reactivation. There was a relatively high incidence of HBV reactivation in HCC patients after the end of conformal RT. The serum HBV DNA level and some dosimetric parameters related to normal liver, including normal liver volume, V20, and mean dose, were the prognosis factors of HBV reactivation and should be carefully considered before conformal RT.

Hepatocellular carcinoma is particularly prevalent in South China and approximately 85% of patients are infected with chronic HBV(1,2) as the cause. Reactivation of HBV is a well-recognized complication in infected HCC patients who undergo chemotherapy.(3) The clinical implications of HBV reactivation can be hepatitis without any symptoms or serious hepatitis accompanied by deterioration of liver function, which may be fatal. The reactivation of HBV has often been reported in patients undergoing chemotherapy, especially those with malignant lymphoma who are receiving combination chemotherapy involving rituximab.(4,5) The incidence of hepatitis caused by HBV reactivation, mostly attributed to chemotherapy, has been reported to be 60%. (6) In recent years, 3-DCRT and IMRT have been generally used in advanced HCC patients(7,8) who are not suitable for surgical resection, with RILD as a common complication.(9,10) Although it has been observed that HBV reactivation occurs after the end of RT in a way similar to that after cytotoxic chemotherapy, questions such when does RT cause HBV reactivation, and what are the risk factors of HBV reactivation, are still unanswered. We undertook this study to answer these questions.

Materials and Methods

Patients. Between June 2009 and June 2011, 81 HBV-related HCC patients (69 were specifically selected and 12 were excluded) treated with conformal RT at three centers were enrolled in this retrospective study. The study was carried out after obtaining patient consent and under protocols approved by the institutional review boards. All patients were diagnosed with HCC by pathology or cytology, and all were followed-up until September 2012 with a median follow-up time of 24.7 months.

Inclusion criteria. The inclusion criteria included: (i) positive HBsAg with positive or negative HBeAg; (ii) predictive lifespan of more than 6 months; (iii) Karnofsky Performance Status score ≥70; (iv) patient could undergo RT safely without too many diffuse lesions in the liver; (v) grade A Child–Pugh classification of liver function; (vi) favorable renal function with blood creatinine level in serum <1.4 mg/dL; (vii) intolerance to or disagreement with surgery; and (viii) completed and submitted informed consent form.

Exclusion criteria. The exclusion criteria included: (i) antiviral therapy within 6 months prior to the study; (ii) chemotherapy...
and transcatheter hepatic arterial chemoembolization within 1 month prior to the study, due to inadequate recovery of hepatic function; (ii) HBV DNA level in serum \( \geq 1 \times 10^5 \) copies/mL; (iv) positive results for serum antibodies against the hepatitis C virus antigen; (v) any distant organ metastases; (vi) grade B or C Child–Pugh classification of liver function; (vii) inability to confirm the tumor border through imaging methods; (viii) previous radiotherapy for liver cancer; and (ix) inability to complete the entire course of study.

**Methods.** The prior RT work-up consisted of a complete medical history and examinations, including physical examination, AFP level, liver function test, renal function test, HBsAg, HBsAb, HBeAg, HBeAb, and HBV DNA quantification, abdominal ultrasonography, and CT evaluation of chest and abdomen for primary tumor and exclusion of distant organ metastasis. Hepatitis B virus markers and HBV DNA level in serum were tested by ELISA and an autofluorescent quantitation instrument for PCR, respectively. Test kits were the same in the three hospitals laboratories and were provided by Beijing Sichuan Bioengineering Factory and Beijing DaAn Gene Company. The lower detection limit of HBV DNA assay in serum was \( 1.0 \times 10^3 \) copies/mL. The CBCs were carried out weekly. The liver function including ALP and ALT values, HBeAg status, HBV DNA quantitative, and abdominal ultrasonography to detect ascites were monitored every 4 weeks from the beginning of RT to at least 16 weeks after the end of RT. If abdominal ultrasonography showed there was ascites, puncture guided by ultrasound and CT examinations, they were considered to be benign ascites and puncture was not implemented. If ascites grew quickly there were considered to be malignant. Exclusion of primary tumor progression and distant organ metastasis were assessed by CT after completion of RT every 2 months for the first year, 3–4 months during the second year, and 4–6 months thereafter.

For better tumor contouring, contrast phases of simulation CT were needed. All patients were given conformal RT, either 3-DCRT or IMRT, over a period of 5–7 weeks, which was delivered with linear accelerators using 6 or 15-MV X-rays. Twenty-nine patients in Shandong Cancer Hospital were treated with the active breathing control technique to reduce the motion of the liver. Treatment techniques typically included initial anterior–posterior beams followed by oblique off-cord beams. Most plans used four to eight fields and the prescribed dose was at the 90–95% isodose line. Each patient was delivered a daily fraction of 1.8–2.0 Gy up to total dose of 45–64 Gy in five fractions per week up to 25–32 fractions. The median prescription dose was 55.8 Gy. Several dosimetric parameters were calculated from the DVH, which was generated from the computerized treatment plan using the Pinnacle3 Planning System (Philips Medical Systems, Fitchburg, WI, USA) for each patient. Gross tumor volume was defined as the hepatic tumor volume, visualized by 3-D computation of contrast CT-defined contours. Planning target volume included GTV and margins of 10–20 mm for primary tumors. Normal liver volume was defined as the total liver volume minus the GTV; \( V_D \) was the relative volume of normal liver receiving more than a threshold dose \( D \) of radiation, and \( D_{\text{mean}} \) was the mean dose of normal liver. Figure 1 shows typical examples of dose distribution image and DVH analysis in one patient who underwent RT.

**Definitions of terminology.** Classic RILD was defined as non-malignant ascites and a serum ALP level \( \geq 2 \)-fold the ULN, or ALT \( \geq 5 \)-fold the ULN. Non-classic RILD was without non-malignant ascites. There was no tumor progression detected by imaging examinations. Reactivation of HBV was defined as increased HBV DNA levels compared with pre-RT in serum \( \geq 10 \)-fold the baseline level, or HBeAg becoming positive in HBeAg-negative patients. The HBV reactivation-induced hepatitis was defined as increased ALT \( \geq 3 \)-fold the ULN in patients with HBV reactivation or \( \geq 100 \) U/L (normal value, \( < 33 \) U/L), excluding tumor progression and hepatotoxicity drugs. According to elevated ALT levels compared with pre-RT, three degrees of hepatitis were as follows: mild, \( \leq 3 \)-fold ULN; midrange, \( > 3 \)-fold to \( \leq 5 \)-fold ULN; and severe, \( > 5 \)-fold ULN.

**Results.**

**Clinical features.** In this study, 12 of the 81 patients were excluded due to the exclusion criteria. Among these 12 patients, four underwent lamivudine antiviral therapy in 6 months, four underwent chemotherapy and transcatheter hepatic arterial chemoembolization therapy in 4 weeks, three had HBV DNA assay in serum of \( \geq 10^5 \) copies/mL, and one was hepatitis C virus antigen positive. The clinical features of the 69 patients enrolled in this study are shown in Table 1.**

**Incidence rate and sequelae of RILD.** The RILD incidence rate was 17.4% (12/69), with 10.1% (7/69) diagnosed as classic RILD and 7.3% (5/69) as non-classic RILD. The peak probability of RILD happened at 8 weeks after the end of RT, which was 7.2% (5/69). The cumulative RILD rates at 4, 8, 12, and 16 weeks after the end of RT were 4.3% (3/69), 11.6% (8/69), 15.9% (11/69), and 17.4% (12/69), respectively (Fig. 2). Of 12 RILD patients, protection of liver function was efficient in seven patients who lived up to the follow-up endpoint, but was inefficient in five patients who died of liver function failure 4 months after the end of RT.

**Incidence rate and sequelae of HBV reactivation.** The HBV reactivation rate was 24.6% (17/69), with 4.3% (3/69) occurring at 4 weeks, 11.6% (8/69) at 8 weeks, and 8.6% (6/69) at 12 weeks after the end of RT. The cumulative HBV reactivation rates at 4, 8, 12, and 16 weeks after the end of RT were 4.3% (3/69), 15.9% (11/69), 24.6% (17/69), and 24.6% (17/69), respectively (Fig. 2).

**Incidence rate and sequelae of HBV reactivation-induced hepatitis.** Of the 69 patients, five were with elevated HBV DNA or ALT levels compared with pre-RT, but not diagnosed as RILD or HBV reactivation according to their diagnostic criteria. This might be caused by chronic hepatitis. The HBV reactivation-induced hepatitis was 21.7% (15/69). Among these 15 patients, nine suffered moderate hepatitis and six had severe hepatitis. The highest probability of HBV reactivation-induced hepatitis also occurred at 8 weeks after the end of RT, which
Fig. 1. Representative example of dose distribution image and dose-volume histogram analysis in a patient with hepatitis B virus-related hepatocellular carcinoma.
HBV DNA, copies/mL

TNM staging, UICC 2002

PVTT

⁄

3-DCRT

Treated with ABC

⁄

<

Tumor size, cm (AFP, ng/mL)

⁄

HBeAg (positive/negative)

AFP, ng/mL (<400→≥400)

Tumor size, cm (<5→<10→≥10)

Treated with ABC/none

PVT/N/none

3-DCRT/IMRT

TNM staging, UICC 2002

T2/T3/T4

HBV DNA, copies/mL

<1.0 × 10^3/1.0 × 10^3–10^5/≥1.0 × 10^5

Radiotherapy dose, Gy

<50/50–60/≥60

3-DCRT, 3-D conformal radiotherapy; ABC, active breathing control; AFP, α-fetoprotein; HbeAg, hepatitis B e antigen; IMRT, intensity-modulated radiation therapy; PVT/N, portal vein tumor thrombosis; UICC, International Union Against Cancer.

was 7.2% (5/69). The cumulative rates at 4, 8, 12, and 16 weeks after the end of RT were 4.3% (3/69), 14.5 (10/69), 21.7% (15/69), and 21.7% (15/69), respectively (Fig. 2).

All 15 patients received lamivudine antiviral therapy (100 mg/day) when they were diagnosed with HBV reactivation-induced hepatitis. The median antiviral therapy time was 14 weeks (range, 2–30 weeks). The HBV DNA and ALT levels in serum both descended to normal levels in nine patients 3 weeks after antiviral therapy. The HBV DNA levels in three patients changed to normal, but ALT was still higher than the baseline level. Three patients were unresponsive to antiviral therapy and died of liver function failure within 4 months of the end of RT.

Correlation factors of HBV reactivation. The univariate analysis in this study revealed that HBV reactivation had no correlation with age, gender, HBeAg positivity, AFP level, ALT, ALP, tumor size, portal vein tumor thrombosis, RT technique, TNM staging, total liver volume, and V40, but did have a correlation with HBV DNA level, radiation dose, NLV, GTV, V5, V10, V20, V30, and Dmean (Tables 2,3). The multivariate logistic regression showed that HBV DNA level, NLV, V20, and Dmean were significantly correlated with HBV reactivation.

The ORs were 1.345, 6.588, 4.331, and 5.187, respectively (Table 4).

Discussion

Hepatitis B virus infection is prevalent in East Asia, especially in China, with over 10% of the adult population chronic carriers. Reactivation of HBV caused by cytotoxic chemotherapy is a well-recognized complication and has been increasingly observed in HCC patients with HBV infection. However, there are few studies of HBV reactivation after the end of RT. Immunosuppression-enhanced viral replication, with destruction of infected hepatocytes on restoration of the immune system, is considered the pathogenesis of HBV reactivation during chemotherapy. Nevertheless, this hypothesis does not apply to the pathogenesis of radiation-induced HBV reactivation. Conformal radiotherapy usually focuses radiation on only a small part of the liver. Therefore, local radiotherapy may have less effect on immune function than systemic chemotherapy. A previous study disclosed that radiation-induced liver toxicity with HBV reactivation arises from bystander effect on irradiated endothelial cells releasing cytokines, including interleukin-6, through the STAT3 signal transduction pathway. So the risk factors for HBV reactivation after radiotherapy should be different from chemotherapy. In recent years, 3-DCRT and IMRT have been widely and increasingly used in HCC patients. In 2007, Kim et al. (22) from the Korean National Cancer Center carried out a retrospective study with 48 unresectable HCC patients who underwent 3-DCRT. Their study showed that the cumulative RILD, HBV reactivation, and chronic hepatitis B exacerbation rates were 21.8%, 21.8%, and 12.6%, respectively. However, HBV reactivation did not correlate with age, gender, AST or ALT level, HBeAg positivity, serum HBV DNA level, radiation dose, or modified UICC stage (P > 0.05). This negative finding might have resulted from a retrospective study, the small study population, strict criteria of HBV reactivation, and/or the use of a relatively insensitive solution–hybridization assay for HBV DNA. Another important reason might be, as pointed out in Cheng’s comments on Kim et al.’s study, that the only dosimetric factor included was the prescribed radiation dose, which was homogeneous in these patients (53.9 ± 0.5 Gy). Several dosimetric parameters that showed effectiveness in predicting RILD were not assessed in Kim’s study.

Based on the above issues, we carried out a retrospective study to assess the occurrence condition and risk factors for...
HBV reactivation in HCC patients after the end of RT. In our study, the association of HBV reactivation with radiation was analyzed with dose–volumetric parameters in detail. Furthermore, the HBV DNA assay in serum has a lower detection limit of $1.0 \times 10^3$ copies/mL. Some patients have large tumors or multiple lesions, so the GTVs are large or irregular. It is difficult to escalate the dose of RT for certain patients because of the dose limitation of organs at risk. The prescribed dose for each patient differed significantly in our study, ranging from 45 to 64 Gy. However, the multivariate logistic regression analysis of our study showed that only HBV DNA level, NLV, V20, and $D_{\text{mean}}$ were significantly correlated with HBV reactivation and were prognostic factors of HBV reactivation. All these DVH parameters were generated from the dose–volume data of liver, in contrast to the prescribed dose to the tumor.\(^{(24,25)}\) From the data in Table 2, HBV reactivation was found in 6/26 (22%) in CRT and 13/43 (30%) in IMRT. Mostly, IMRT is superior to CRT technologies in some aspects. However, IMRT involves more fields, and DVHs show that, as a consequence, a larger volume of normal tissue is exposed to lower doses. Moreover, biologic data disclosed radiation-induced HBV reactivation through the bystander effect of exposed liver rather than tumor tissue.\(^{(26)}\) So, it might be the reason that IMRT didn’t contribute to avoid HBV reactivation at all, but rather than a little risky numerically.

Radiation-induced liver disease is the main adverse reaction of HCC patients treated with RT. The incidence rate of RILD is closely related to radiation volume, dose, and liver function.\(^{(6,8)}\) Of the 69 HCC patients with HBV infection in our study, the RILD incidence rate was 17.4% (12/69), with 10.1% (7/69) diagnosed as classic RILD and 7.2% (5/69) as non-classic RILD. Hepatitis B virus reactivation was defined as a rebound of serum HBV DNA ≥10-fold the baseline level, which means a narrow criterion of reactivation. Such a definition is used for viral breakthrough under the antiviral therapy of chronic hepatitis B. The natural course of HBV chronic hepatitis shows waxing and waning of HBV DNA levels within the range of $<2 \log_{10}$ copies/mL. Therefore, some RILD patients may be classified into HBV hepatitis exacerbation. In our study, five patients had elevated ALT levels and HBV DNA levels, which was consistent with the diagnostic criteria of HBV reactivation-induced hepatitis. Their serum HBV DNA levels changed to normal 4 weeks after antiviral therapy, but ALT levels did not return to baseline level, which may be due to overlapping disease and should be identified by hepatic tissue biopsy. However, these patients often had hepatic cirrhosis, hepatic insufficiency, and clotting mechanism disorder, which are intolerable with hepatic tissue biopsy. Yankelevitz et al.\(^{(26)}\) tried to use MRI to diagnose RILD. With regard to RILD patients, the MRI showed a signal potentialization region on T2 phase, which was completely consistent with an irradiated region of the liver. However, it was still difficult to distinguish RILD from HBV reactivation-induced hepatitis of HCC patients who underwent RT, especially to distinguish non-classic RILD from severe HBV reactivation-induced hepatitis using imaging methods, because of the limitations of the technology. Some patients might have had overlapping disease. There are no specific therapies for RILD and the treatments.

### Table 2. Univariate analysis of measurement data associated with hepatitis B virus (HBV) reactivation

| Factors | Total | HBV reactivation | OR value | P-value |
|---------|-------|------------------|----------|---------|
| Gender, male/ female | 38/71 | 9/8 | 1.169 | 0.261 |
| HBeAg, ± | 29/40 | 7/10 | 0.495 | 0.615 |
| Treated with | 29/40 | 8/9 | 0.834 | 0.244 |
| ABC/none | 33/36 | 7/10 | 0.427 | 0.370 |
| PVTT/none | 26/43 | 6/13 | 0.592 | 0.731 |
| TNM staging | | | | |
| T2 | 9 | 2 | 0.624 | 0.538 |
| T3 | 39 | 8 | | |
| T4 | 21 | 7 | | |
| HBV DNA, copies/mL | <1.0 $\times 10^3$ | 25 | 4 | 1.215 | <0.001 |
| 1.0 $\times 10^3$–1.0 $\times 10^5$ | 21 | 4 | | |
| ≥1.0 $\times 10^5$ | 23 | 9 | | |

ABC, active breathing control; CRT, conformal radiotherapy; HBeAg, hepatitis B antigen; IMRT, intensity-modulated radiation therapy; OR, odds ratio; PVTT, portal vein tumor thrombosis.

### Table 4. Multivariate analysis of risk factors associated with hepatitis B virus (HBV) reactivation

| Parameter | B | SE | Wald | Sig. OR | 95% CI for OR |
|-----------|---|----|------|---------|-------------|
| Radiotherapy | 0.436 | 0.086 | 14.895 | 0.252 | 0.591 | 1.273–1.882 |
| HBV DNA | 0.135 | 0.048 | 12.421 | <0.001 | 1.345 | 1.062–1.535 |
| Dmean, Gy | 0.328 | 0.126 | 10.192 | 0.001 | 1.399 | 1.057–1.871 |

CI, confidence interval; Dmean, mean dose; GTV, gross tumor volume; NLV, normal liver volume; OR, odds ratio; SE, standard error; Sig., significance; Wald, wald chi square.

### Table 3. Univariate analysis of measurement data associated with hepatitis B virus (HBV) reactivation

| Parameter | Mean ± SD | OR value | P-value |
|-----------|-----------|----------|---------|
| Age, years | 52.4 ± 6.5 | 0.571 | 0.476 |
| AFP, µg/mL | 653.1 ± 502.3 | 0.638 | 0.371 |
| ALT, IU/mL | 25.5 ± 12.3 | 1.562 | 0.654 |
| ALP, IU/mL | 133.9 ± 57.6 | 1.621 | 0.771 |
| Tumor size, cm | 8.4 ± 6.7 | 0.985 | 0.143 |
| Radiotherapy dose, Gy | 56.2 ± 7.6 | 1.449 | 0.036 |
| TLV, cm³ | 1656.0 ± 695.2 | 3.591 | 0.058 |
| NLV, cm³ | 15790.0 ± 664.7 | 4.512 | 0.001 |
| GTV, cm³ | 3137.7 ± 296.1 | 1.473 | 0.023 |
| V5 (%) | 64.5 ± 18.2 | 1.620 | 0.017 |
| V10 (%) | 56.3 ± 11.9 | 3.412 | 0.008 |
| V20 (%) | 43.7 ± 10.4 | 2.626 | 0.003 |
| V30 (%) | 36.2 ± 11.4 | 1.872 | 0.008 |
| V40 (%) | 29.0 ± 9.8 | 2.910 | 0.163 |
| $D_{\text{mean}}$, Gy | 1483.5 ± 616.3 | 6.811 | 0.009 |

AFP, α-fetoprotein; ALP, alkaline phosphatase; ALT, alanine aminotransferase; $D_{\text{mean}}$, mean dose; GTV, gross tumor volume; NLV, normal liver volume; OR, odds ratio; TLV, total liver volume.
were mainly protecting liver function and alleviating symptoms.

In our study, the rate of HBV reactivation and HBV reactivation-induced hepatitis was 24.6% (17/69) and 21.7% (15/69), respectively. The 15 patients diagnosed as HBV reactivation-induced hepatitis all accepted antiviral therapy of lamivudine 100 mg/day, and the median time of antiviral therapy was 14 weeks (range, 2–30 weeks). The serum HBV DNA and ALT levels reached normal levels in nine patients 3 weeks after antiviral therapy. The HBV DNA levels in three patients changed to normal with their ALT level still higher than baseline level. Three patients were unresponsive to antiviral therapy and died of liver function failure, a fatality rate of 20.0% (3/15). Results showed that, although the patients with HBV reactivation-induced hepatitis accepted antiviral therapy in time, their prognosis was still not good. Although the effect is not very satisfactory in our study, antiviral therapy was still necessary to treat HBV reactivation-induced hepatitis. It was more important to prevent HBV reactivation.

In conclusion, HBV reactivation is a clinical problem deserving attention for patients with HCC receiving conformal RT. Our study showed that there was a relatively high rate of HBV reactivation in those patients and whose prognosis was unfavorable. The serum HBV DNA level and some dosimetric parameters (normal liver volume, V20, and Dmean) were the prognostic factors for HBV reactivation and should be considered carefully before CRT. Further studies are needed to clarify whether antiviral therapy could prevent/reduce HBV reactivation before/during CRT. Furthermore, in future work, we want to provide details on the threshold for serum HBV DNA levels and dosimetric parameters related to normal liver that can cause the rate of reactivation to be high. A prediction model would help to give clinicians an idea of which patients they treat are at risk of reactivation.

**Disclosure Statement**

The authors have no conflict of interest.

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**Abbreviations**

- 3-DCRT: 3-D conformal radiotherapy
- AFP: α-fetoprotein
- ALP: alkaline phosphatase
- ALT: alanine aminotransferase
- CBC: complete blood cell counts
- CI: confidence interval
- CRT: conformal radiotherapy
- CT: computed tomography
- Dmean: mean dose
- DVH: dose-volume histogram
- GTV: gross tumor volume
- HbeAg: hepatitis B e antigen
- HBV: hepatitis B virus
- IMRT: intensity-modulated radiation therapy
- NLV: normal liver volume
- OR: odds ratio
- RILD: radiation-induced liver disease
- UICC: International Union Against Cancer
- ULN: upper limit of normal

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