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ORIGINAL ARTICLE **CME**

Impact of Fractionated Stereotactic Body Radiotherapy on Liver Function in Patients with Hepatitis B Virus–related Hepatocellular Carcinoma: Clinical and Dosimetric Analysis

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ABSTRACT

Objectives: *To investigate the impact of fractionated stereotactic body radiotherapy (SBRT) on liver function and identify any dosimetric parameters that may predict deterioration of liver function in patients with hepatitis B (HBV)–related hepatocellular carcinoma (HCC).*

Methods: *Thirty-six eligible patients with HBV-related HCC who were treated with fractionated SBRT between January 2008 and December 2010 were assessed. The treatment prescription ranged from 20 to 40 Gy (median, 32 Gy) in 5 to 10 fractions over 1 to 2 weeks. All the patients received pre-emptive antiviral therapy. The median gross tumour volume was 509 cm^3 (range, 2-3088 cm^3). Four liver toxicity endpoints were assessed: (1) rate of HBV reactivation; (2) rate of chronic hepatitis B exacerbation; (3) rate of radiotherapy-induced liver disease; and (4) rate of deterioration in Child-Pugh class. Clinical and dosimetric parameters were evaluated to identify the significant predictors of liver toxicity.*

Results: *No patient developed HBV reactivation, chronic hepatitis B exacerbation, or radiotherapy-induced liver disease within 3 months after SBRT. Four (11%) experienced Child-Pugh class deterioration. On univariate analysis, no clinical and dosimetric parameters were identified as predictors of Child-Pugh class deterioration.*

Conclusion: *SBRT with individualised dosing of up to 40 Gy in 10 fractions can be delivered safely to patients with large unresectable HBV-related HCC in palliative setting. Pre-emptive antiviral therapy is probably mandatory to prevent HBV-related complications in this setting.*

Key Words: *Carcinoma, hepatocellular; Hepatitis B virus; Radiosurgery*

中文摘要

乙型肝炎病毒相關性肝細胞癌患者中分次立體定向放射治療對肝功能的影響：臨床和劑量學分析

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目的：探討分次立體定向放射治療（SBRT）對肝功能的影響，並在乙型肝炎病毒（HBV）相關性肝細胞癌患者中，找出可能預測肝功能惡化的劑量參數。

方法：篩選並評估36名在2008年1月至2010年12月期間進行分次SBRT的HBV相關性肝細胞癌患者。治療方案為患者於一至兩週內接受5至10次放療，總劑量從20 Gy至40 Gy不等（中位數：32 Gy）。

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所有患者在放療前先接受抗病毒治療。腫瘤大致體積的中位數為509 cm^3（介乎2-3088 cm^3）。分別有四項肝毒性評估點：（1）HBV再活率；（2）慢性乙型肝炎的惡化率；（3）放射性肝損傷的發病率；和（4）Child-Pugh分級的惡化率。然後評估臨床和劑量參數以確定肝毒性的有效預測因子。

結果：進行SBRT後三個月，無患者出現HBV再激活、慢性乙型肝炎惡化或因放療導致的肝病。4名患者（11.1%）的Child-Pugh分級出現惡化。單因素分析顯示並無臨床及劑量參數可以預測Child-Pugh分級惡化。

結論：對於因瘤體大不能手術切除，而採取姑息治療的HBV相關性肝癌患者來說，分10次接受總劑量達40 Gy的個體化SBRT是安全的。患者放療前應先接受強制性的抗病毒治療，以防止HBV相關的併發症。

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common cancer in the world and is the third most common cause of cancer death.[1] It is most prevalent in Asia where chronic hepatitis B virus (HBV) infection accounts for 75 to 80% of cases.[2] The majority of HCC patients present with unresectable disease and are treated with either local ablative therapies (mostly radiofrequency ablation[3] or transarterial chemoembolisation [TACE])[4,5] or systemic therapy with sorafenib.[6,7] The role of radiotherapy for primary HCC has been increasing in the past decade. Nowadays, patients with unresectable HCC who are not suitable for local ablative therapies may be offered radiotherapy. In the past, the use of radiotherapy for HCC was limited because of the high risk of liver toxicity.[8] With the advances in radiotherapy techniques,[9] stereotactic body radiotherapy (SBRT) has been shown to be a safe and effective treatment for unresectable HCC.[10,11] However, HCC patients who were HBV carriers have a significantly greater susceptibility to radiation-induced liver disease (RILD).[12] Evidence for this inference was based on clinical data derived from conventional dose fractionation treatment for relatively small unresectable HCCs. To our knowledge, the impact on liver function after SBRT to patients with large HBV-related HCCs in a palliative setting was rarely reported in the literature. In the present study, we set out to investigate the rate of HBV reactivation, chronic hepatitis B (CHB) reactivation, RILD, and decline of Child-Pugh class in patients with relatively large unresectable HBV-related HCCs treated with palliative fractionated SBRT. In addition, we analysed clinical and dosimetric parameters that might predict deterioration of liver function.

METHODS

Patients

Patients with unresectable HCC were assessed in a multidisciplinary meeting involving radiation oncologists, hepatobiliary surgeons, and interventional radiologists. Palliative SBRT was considered for patients who were not suitable for or had failed local ablative therapies. Other eligibility criteria included Karnofsky performance status of ≥60, life expectancy of >3 months, well-circumscribed tumour visualised by computed tomography (CT), and with an uninvolved liver volume (defined as total liver volume minus gross tumour volume [GTV]) of >700 ml. Even the presence of multiple satellite nodules in both lobes of liver were considered acceptable. Moreover, if extra-hepatic disease was present, most of the tumour burden had to be in the liver. The study patients had to have: no gross ascites, no more than Child-Pugh grades A or early B cirrhosis, adequate major organ function (platelet count >60 x 10^9/l, absolute neutrophil count >1.5 x 10^9/l, aspartate aminotransferase [AST] or alanine aminotransferase [ALT] <5 x upper limit normal, creatinine <150 μmol/L), and with HBV-related HCC. Patients were excluded if they received additional local treatment to the liver and / or early progression of liver disease (in the first 3 months post-radiotherapy).

RADIOTHERAPY TREATMENT

Treatment Planning and Setup

During CT simulation with four-dimensional (4D) scans, patients were positioned supine on an evacuated foam bag (Vac-LokTM; MEDTEC, Iowa, USA) with both arms abducted. The extent of tumour motion during respiration determined whether treatment was delivered with free breathing or gating. Various target volumes were delineated according to the following definitions. The GTV was defined by tumour visualised in the CT image. The clinical target volume (CTV) was defined as GTV plus a margin of 0 to 5 mm. The internal target volume (ITV) was defined as the composite CTV of all the respiratory phases to account for tumour motion.

Planned target volume (PTV) was defined with a margin ranging from 3 to 5 mm extending from the CTV or ITV. Radiation was delivered mostly in a coplanar manner, but sometimes non-coplanar with multiple static beams or dynamic conformal arcs. The treatment setup was performed with the ExacTrac stereotactic body setup system (BrainLab Ltd, Feldkirchen, Germany).

Treatment Dose and Constraints of Organ at Risk

4 Gy per fraction was prescribed to the periphery of the PTV for 5 to 10 fractions daily. The number of fractions was largely determined by keeping the uninvolved liver V30 to below 40%. The uninvolved liver volume was defined as total liver volume minus GTV. Other normal tissue dose constraints were as follows: mean dose to uninvolved liver <28 Gy; ipsilateral kidneys,[13,14] V20 <75% , total V20 <40%; spinal cord <45 Gy; heart, 60 Gy to <1/3, 45 Gy to <2/3, and 40 Gy to <100 %; stomach, maximum <50 Gy; small bowel, maximum <50 Gy; large bowel, maximum <55 Gy. These dose constraints were calculated in 2 Gy per fraction using the linear-quadratic model (alpha/beta ratio of 3) for conversion of equivalent biological effects. Toxicity was graded according to National Cancer Institute (NCI) Common Toxicity Criteria version 3.0. The prescribed dose to the PTV was capped at 40 Gy in 10 fractions. The final doses prescribed were determined by the treating physician who also took into account other clinical factors such as performance status, liver function, CT appearance of the liver and disease extent.

Monitoring and Therapy for Hepatitis B Virus

Prior to SBRT, all patients had baseline blood tests. These included routine liver function tests (LFTs), international normalised ratio, hepatitis B surface antigen, anti-hepatitis B surface antibody, hepatitis e antigen (HBeAg), HBV DNA level, complete blood count, routine renal function tests, and alpha-fetoprotein. The HBV DNA levels were measured by quantitative real-time polymerase chain reaction. An antiviral agent (e.g. lamivudine) was prescribed 1 week before and continued for at least 3 months after the SBRT.

During treatment, patients were assessed weekly for acute toxicity such as fatigue, anorexia, nausea, vomiting, pain, and diarrhoea. Baseline blood tests were repeated weekly. After treatment, patients were assessed for acute toxicity every 2 to 4 weeks in the first 3 months. At 3 months post-radiotherapy, blood tests for liver function, HBV DNA level, HBeAg level, and CT abdomen were performed. In accordance with our local practice guidelines, antiviral therapy was discontinued if HBV DNA, HBeAg, and LFTs were all normal.

HBV reactivation was defined as a rebound of serum HBV DNA to a level of >2 $\log_{10}$ copies/ml from baseline level after the initiation of radiotherapy.[12] A CHB exacerbation was defined as an ALT elevation of ≥2.5-fold the upper limit of normal in association with HBV reactivation and in the absence of (i) obvious tumour progression, (ii) a history of herbal or toxic medication intake, or (iii) interruption by other therapy, such as TACE, during the follow-up period.[12] RILD was sub-typed into classic and non-classic. Classic type was defined as anicteric elevation of alkaline phosphatase levels of ≥2-fold the upper limit of normal, and non-malignant new ascites.[15] Non-classic type was defined as elevated AST/ALT of ≥5-fold the upper limit of normal,[16] which amounts to grade 3 or 4 hepatic toxicity according to the NCI Common Toxicity Criteria Adverse Event (CTCAE version 2.0).[17] The latter change in LFT results had to ensue in the absence of obvious tumour progression, a history of herbal medication or toxic hepatitis, or interruption by other therapy (such as TACE) during the follow-up period.

Statistical Analysis

The data were analysed using the JMP IN version 5.1 software (SAS Institute Inc., Carey [NC], USA). Fisher's exact test and the independent *t*-test were used for univariate analysis of patients, disease, and treatment factors associated with liver toxicity. The binary logistic regression analysis was used for the univariate analysis of dose-volumetric parameters associated with liver toxicity.

RESULTS

Between January 2008 and December 2010, 36 eligible patients (median age, 62 years) with HBV-related HCC who were treated with fractionated SBRT were analysed. All data were collected prospectively. Patient characteristics are shown in Table 1. The majority of patients had a Karnofsky performance status score of >80 (77%). 50% of patient had stage IV disease. Radiotherapy details are summarised in Table 2. All patients received 4 Gy per fraction with a median total prescription dose of 32 Gy (range, 20-40 Gy). Twenty-three patients underwent TACE before radiotherapy. Nine patients had had previous hepatic resections or radiotherapy frequency ablation. Eleven patients

Table 1. Patient characteristics.

Characteristic	No. (%) of patients*
Sex	
Male	30 (83%)
Female	6 (17%)
Age (years)	
Median	62
Range	36-90
KPS	
100	3 (8%)
80-90	25 (69%)
60-70	8 (22%)
Pre-radiotherapy status	
HBeAg +ve	8 (22%)
Child-Pugh classification	
Pre-radiotherapy	
A	31 (86%)
B	5 (14%)
Post-radiotherapy	
A	27 (75%)
B	7 (19%)
C	2 (6%)
Pre-radiotherapy HBV DNA level†	
Negative	13 (36%)
Positive	23 (64%)
Post-radiotherapy HBV DNA level†	
Negative	25 (69%)
Positive	11 (31%)
Invasion of portal vein or bile duct	
Yes	13 (36%)
No	23 (64%)
Size of tumour	
≤5 cm	12 (33%)
>5 to 10 cm	8 (22%)
>10 to 15 cm	11 (31%)
>15 cm	5 (14%)
AJCC staging 7th edition	
Stage II	4 (11%)
Stage III	14 (39%)
Stage IV	18 (50%)
Previous treatment	
Previous hepatic resection/RFA	
Yes	9 (25%)
No	27 (75%)
Sorafenib before RT	6 (17%)
Sorafenib after RT	5 (14%)
TACE	23 (64%)
Steroid	0 (0%)

Abbreviations: KPS = Karnofsky performance status; HBeAg = hepatitis B virus e antigen; HBV = hepatitis B virus; AJCC = American Joint Committee on Cancer; RFA = radiofrequency ablation; RT = radiotherapy; TACE = transarterial chemoembolisation.

* Unless otherwise indicated

† HBV DNA level definition: negative <1.0 x 10^5 copies/ml; positive >1.0 x 10^5 copies/ml.

received sorafenib (6 before and 5 after SBRT). No patient received corticosteroids.

The percentage of pre-SBRT HBeAg positivity and HBV DNA level elevation were 22% (8/36) and 64% (23/36), respectively. At pre-SBRT, these patients had Child-Pugh class A and B cirrhosis in 86% and 14%, respectively; while at post-SBRT, Child-Pugh class A, B and C was present in 75%, 19% and 6%, respectively. No HBV reactivation, CHB exacerbation, or RILD was encountered in the 3 months post-SBRT. Very likely due to the use of antiviral therapy, HBV DNA positivity decreased from 64% to 31% (33% absolute reduction). Four patients (11%) manifested a deterioration in their Child-Pugh cirrhosis class within 3 months of having SBRT (1 from B to C, 2 from A to B, and 1 from A to C). Findings pertaining to RILD, HBV reactivation, and CHB exacerbation are summarised in Table 3. Among the clinical and dosimetric factors in Tables 1 and 2, no parameter was significantly associated with a decline of Child-Pugh class in the univariate analysis. We also tried to investigate the relationship between the percentage of normal liver that received various radiation doses and the decline of Child-Pugh class, but no significant cut-off Vx value (V was defined as a range of % of normal liver volume received more than x Gy which was ranged from 4-40 Gy) was predictive. At 3 months after completion of SBRT, CT showed that the

Table 2. Radiotherapy details.

Radiotherapy	Median	Range
Total dose (Gy)	32	20-40
Dose per fraction (Gy)	4	4
Mean dose of uninvolved liver (Gy)	18	3-30
V30 of uninvolved liver (%)	23	3-45
GTV (cm^3)	509	2-3088
Volume of liver (cm^3)	1621	583-4348
Uninvolved liver volume (cm^3)	1104	567-1858

Abbreviations: V30 = % of normal liver volume which received ≥30 Gy in normal liver (total liver volume – gross tumour volume); GTV = gross tumour volume.

Table 3. Results of RILD, HBV reactivation, CHB exacerbation, and shift of CP class.

Characteristic	No. of patients
Cumulative rate of RILD	
Yes	0 (0%)
No	36 (100%)
HBV reactivation	
Yes	0 (0%)
No	36 (100%)
CHB exacerbation	
Yes	0 (0%)
No	36 (100%)
Shift of CP class	
Yes	4 (11%)
No	32 (89%)

Abbreviations: RILD = radiotherapy-induced liver disease; HBV = hepatitis B virus; CHB = chronic hepatitis B; CP class = Child-Pugh class.

rates of stable disease, partial response, and complete response were 42%, 50%, and 8%, respectively.

DISCUSSION

SBRT is derived from the techniques of stereotactic radiosurgery used to treat lesions in the brain and spine. It delivers high-dose radiation to an extracranial target in the body in a single dose or a few fractions.

SBRT allows us to treat tumours close to critical organs with less damage to surrounding healthy tissues. We apply this technique for palliative treatment of HCC using conventional dose fractionation with an aim to achieve good palliation while minimising toxicities to diseased liver. There are a few reports in the literature supporting the safety and efficacy of this approach. However, most involved relatively small tumours. For example, Tse et al[10] reported a series with a median tumour size of 173 cm^3 (9-1913 cm^3 and the median dose was 36 Gy in 6 fractions, ranged from 24-54 Gy). Likewise, the GTV was 18.3 ± 15.9 cm^3 (range, 3.0-81.3 cm^3) in Son et al's report,[18] and the total dose administered was 30-39 Gy in 3 fractions. In our daily practice, we are seeing many HCC patients with large tumours. Among patients in the current study cohort, 48% of the tumours were >10 cm in diameter with a median GTV of 508 cm^3. They were treated with a total dose of 20-40 Gy in 5-10 fractions over 1-2 weeks. The total dose used in our patients was generally less than that used in Tse et al's study,[10] because our treatment aimed at palliation and the large tumour rendered high-dose RT prohibitive.

Table 4[10,12,19] summarises similar studies with respect to liver toxicities of HCC treated by SBRT in the literature. Kim et al[12] recommended antiviral therapy in HBV-related HCC to prevent liver function deterioration after 3D conformal radiotherapy (CRT). Cheng et al[19] reported that HCC patients who were HBV carriers or had Child-Pugh class B cirrhosis had a statistically significant greater susceptibility to RILD after 3D CRT. In the present study, the cumulative rate of RILD was zero, compared with 12.5% reported by Kim et al.[12] In their study, two out of 16 patients experienced RILD after 3D CRT,[12] whereas the doses used in our patients were relatively low. The biological equivalent dose of 4 Gy x 5 is 60 Gy_2 (equal to a conventional dose of 30 Gy in 15 Fr with alpha-beta ratio = 2) while 4 Gy x 10 is 120 Gy_2 (equal to a conventional dose of 60 Gy in 30 Fr assuming alpha-beta ratio = 2). In Kim et al's series,[12] doses were 45-57.5 Gy in 2-3 Gy/fraction. Similar to the present study, no patients in Kim et al's series who received an antiviral agent suffered from HBV reactivation. This implies that antiviral agent is mandatory for patients receiving SBRT to the liver.

Several studies reported the risk factors and parameters indicated an increased risk of RILD after radiotherapy.[8,14,18] RILD corresponds to grade 2 or worse hepatic toxicity according to the CTCAE.

Lawrence et al[8] reported that the mortality rate of RILD was 10 to 20%. Son et al[18] reported that 33% of the patients developed grade 2 or higher hepatic toxicity and suggested that the total liver volume should receive a dose of less than 18 Gy (rV18 Gy) by Cyberknife SBRT. Normal liver volume should be >800 ml in order to reduce the risk of hepatic function deterioration. Most patients recovered from hepatic toxicity after a median of 2 months.[18]

Table 4. Summary of recent liver toxicity studies after stereotactic body radiotherapy of hepatocellular carcinoma.

	Present study	Kim et al, 2007[12]	Tse et al, 2008[10]	Son et al, 2010[18]
No. of patients	36	48	41	36
HBV reactivation	0% (0/36)	0% (0/48)	Not available	Not available
CHB reactivation	0% (0/36)	0% (0/48)	Not available	Not available
RILD	0% (0/36)	12.5% (2/16)	Not available	Not available
Grade of liver enzyme	Not available	Not available	24% (10/41) Grade 3	33% (12/36) Grade 2
Shift of CP class	11% (4/36) [2 from A to B; 1 from A to C; 1 from B to C]	Not available	17% (7/41) from A to B	11% (4/36) from A to B
Dose per fraction (Gy)	4	2-3	4-9	10-13
Total dose range (Gy)	20-40	45-57.5	24-54	30-39
Median GTV (cm^3)	509	Not available	173	18.3
TACE (%)	64	Not available	15	75
Hepatic resection/RFA (%)	25	Not available	24	14
RR (%)	CR 8%; PR 50%; SD 42%	Not available	PR 49%; SD 42%	Not available

Abbreviations: HBV = hepatitis B virus; CHB = chronic hepatitis B; RILD = radiation-induced liver disease; CP = Child-Pugh; GTV = gross total volume; TACE = transarterial chemoembolisation; RFA = radiofrequency ablation; RR = response rate; CR = complete response; PR = partial response; SD = static disease.

In the present study, we showed SBRT was safe for treating relatively large (>15 cm diameter) HBV-related HCCs. Of the 36 patients analysed, none developed HBV reactivation, CHB exacerbation, or RILD within the first 3 months, though four (11%) experienced Child-Pugh class deterioration of their cirrhosis, which was comparable to the 11% and 16% rates reported in two recently published SBRT studies.[10,18] Among our four patients with deterioration in cirrhosis class, one presented with a ruptured 12-cm diameter vascular HCC in the left lobe of the liver with multiple satellite nodules in both lobes. Though the main tumour was controlled with radiation, there was outfield progression of disease. Subsequently, the tumour progressed locally despite further TACE, and could explain the cirrhosis deterioration. In both the univariate and multivariate analysis of our study patients, there was no significant predictor for deterioration in the Child-Pugh class, which could have been due to the small sample size.

Nevertheless, individualised dose prescription was safe up to a ceiling dose of 40 Gy in 10 fractions according to dose constraints to uninvolved liver (V30 <40% and mean dose <28 Gy) and uninvolved liver volume of >700 cm^3, even for relatively large liver tumours (median GTV 508 cm^3, 70% >200 cm^3).

CONCLUSION

Palliative SBRT with individualised doses of up to 40 Gy in 10 fractions can be safely delivered to large HCCs in hepatitis B carriers without development of complications like HBV reactivation, CHB exacerbation, and RILD. However, Child-Pugh class progression occurred in 11% of our patients. Pre-emptive antiviral therapy appears mandatory for the prevention of HBV-related complications after such radiotherapy.

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