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Original Article

Radiation-induced Liver Injury after 3D-conformal Radiotherapy for Hepatocellular Carcinoma: Quantitative Assessment Using Gd-EOB-DTPA-enhanced MRI

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Focal liver reaction (FLR) appears in the hepatobiliary-phase images of gadolinium-ethoxybenzyl-diethylene-triamine pentaacetic acid-enhanced magnetic resonance imaging (Gd-EOB-DTPA-enhanced MRI) following radiotherapy (RT). We investigated the threshold dose (TD) for FLR development in 13 patients with hepatocellular carcinoma (HCC) who underwent three-dimensional conformal radiotherapy (3D-CRT) with 45 Gy in 15 fractions. FLR volumes (FLRVs) were calculated based on planning CT images by referring to fused hepatobiliary-phase images. We also calculated the TD and the irradiated volumes (IVs) of the liver parenchyma at a given dose of every 5 Gy (IV_{dose}) based on a dose-volume histogram (DVH). The median TD was 35.2 Gy. The median IV_{20}, IV_{25}, IV_{30}, IV_{35}, IV_{40}, and IV_{45} values were 371.1, 274.8, 233.4, 188.6, 145.8, and 31.0 ml, respectively. The median FLRV was 144.9 ml. There was a significant difference between the FLRV and IV_{20}, IV_{25}, and IV_{45} ($p < 0.05$), but no significant differences between the FLRV and IV_{30}, IV_{35}, or IV_{40}. These results suggest that the threshold dose of the FLR is approx. 35 Gy in HCC patients who undergo 3D-CRT in 15 fractions. The percentage of the whole liver volume receiving a dose of more than 30-40 Gy (V_{30-40}) is a potential candidate optimal DVH parameter for this fractionation schedule.

Key words: Gd-EOB-DTPA, hepatocellular carcinoma, magnetic resonance imaging, radiation-induced liver disease, radiotherapy

Hepatocellular carcinoma (HCC) is one of the most common causes of death due to cancer worldwide [1]. Surgical resection, radiofrequency ablation, and transarterial chemoembolization are commonly performed as standard treatment modalities for HCC. Advanced radiotherapy (RT) techniques such as three-dimensional conformal radiotherapy (3D-CRT) and stereotactic body RT (SBRT), which provide dose escalation to the tumor while minimizing dose exposure to organs at risk, have been introduced as alternatives to standard treatment modalities [2-4].

SBRT in 1 to 5 fractions with a fraction size of generally not less than 6 Gy is performed for small HCCs that are < 3 cm in diameter and distant from the gastrointestinal tract and kidney, whereas 3D-CRT is more commonly performed for patients who are not candidates for SBRT [5]. These treatment techniques are widely regarded to be valuable for HCC treatment, but radiation-induced liver injury remains a problematic adverse effect because of pre-existing liver dysfunctions that occur secondary to comorbid conditions such as

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hepatitis B/C infection and cirrhosis. These conditions can increase the vulnerability of the surrounding liver parenchyma to radiation-induced injury [2,6]. Many groups have evaluated the relationship between the absorbed RT dose and radiation-induced liver injury based on a dose-volume histogram (DVH) of RT planning, but an optimal parameter has not yet been identified [6].

Contrast-enhanced magnetic resonance imaging (MRI) has an important role in HCC diagnosis [7]. Among the commercially available liver contrast agents, the recently introduced contrast agent gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) has theoretical advantages over extracellular agents. Similar to extracellular contrast agents, Gd-EOB-DTPA allows for dynamic perfusion imaging to evaluate tumor vascularity. Additionally, its absorption by hepatocytes facilitates liver-specific imaging (i.e., hepatobiliary-phase images) [7,8]. Recent reports have suggested that Gd-EOB-DTPA-enhanced MRI allows for the direct evaluation of the degree of liver damage following irradiation [9-11].

Several reports on Gd-EOB-DTPA-enhanced MRI following RT suggested that focally decreased enhancement appears in the liver parenchyma of hepatobiliary-phase images, which is often described as a 'focal liver reaction (FLR)' to radiation [9,10,12]. The identification of the threshold dose (TD) that induces FLR may facilitate the determination of an optimal DVH parameter in RT planning for HCC treatment. Sanuki *et al.* [9] recently reviewed patients with HCC who underwent SBRT treatment with a total RT dose of 35-40 Gy in 5 fractions. They found that for 5 fractions, the TD for FLR was 25-30 Gy. Jung *et al.* [13] reviewed HCC patients who underwent SBRT treatment with a total RT dose of 45 Gy in 3 fractions. They found that for 3 fractions, the TD for FLR was approx. 20 Gy. However, the TD for other fractionation schedules was not fully evaluated. At our institution, we usually perform moderately hypofractionated 3D-CRT with a total dose of 45 Gy administered in 15 fractions to HCC patients who are not candidates for SBRT [3]. This fractionation schedule has been performed at many institutions [14,15]. In the present study, we investigated the TD for FLR in patients with HCC who underwent 3D-CRT in 15 fractions.

Materials and Methods

Patients. This retrospective study was approved by the ethics committee at our institution (No. 864). Prior informed consent for treatment and the use of data for the study was obtained from all patients. From September 2007 to August 2014, 73 consecutive patients underwent 3D-CRT for HCC at our institution. Among these patients, there were 14 who were subjected to Gd-EOB-DTPA-enhanced MRI within 12 months after the completion of RT. One patient was excluded from this evaluation because we performed RT replanning during the treatment period, leaving a final study population of 13 patients.

The patient characteristics are summarized in Table 1. All patients were Child-Pugh class A or B with a tumor size < 5 cm and had no previous RT.

Radiotherapy. The details of 3D-CRT have been reported [3]. The dose distribution was calculated using a 3D-radiotherapy planning system (RTPS, Pinnacle^3 version 8.0-9.2; Philips Medical Systems, Fitchburg, WI, USA). For all patients, a daily fraction of 3 Gy was administered at the isocenter to deliver a total dose of 45 Gy in 15 fractions over 3 weeks. Three-dimensional CRT was performed with a 10-MV linear accelerator (Clinac iX; Varian Medical Systems, Palo Alto, CA, USA) using 3-6 ports.

MRI. We used images of the first MRI study after the completion of RT. The median interval between the completion of RT and MRI was 131 days (range 27-279 days). MRI was performed using a 3-T MRI system (Achieva; Philips Medical Systems, Best, The Netherlands). The baseline MRI examination consisted of a breath-hold, fat-suppressed, T2-weighted sequence; a double-echo T1-weighted gradient-echo sequence, with in-phase and opposed-phase images; a diffusion-weighted sequence; and a contrast-enhanced dynamic sequence. Fat-suppressed, T1-weighted gradient-echo images with a 3D acquisition sequence (THRIVE) were obtained precontrast and 5,10,15, and 20 min after the intravenous administration of 0.025 mmol/kg of Gd-EOB-DTPA (Primovist, Bayer Schering Pharma, Berlin, Germany). The images were acquired in the transverse plane with a 4-mm section thickness and a 4-mm interval. The repetition time was 3.1 msec. The echo time was 1.2 msec. The flip angle was 10°; the number of excitations was 1. The field of view was 40 × 40 cm. The matrix was 256 × 204, and the

Table 1 Patient characteristics

Patient No.	Age (yrs)	Gender	Viral infection	Child-Pugh		Largest tumor dia. (mm)
				Class	Score	
1	68	M	HCV	A	5	24
2	74	M	HCV	A	6	40
3	79	F	HCV	A	6	40
4	78	F	HCV	A	5	26
5	72	F	HCV	B	7	43
6	62	M	–	B	8	49
7	45	M	HBV	A	6	36
8	54	F	HCV	B	7	33
9	78	M	HCV	B	7	36
10	51	F	HBV	A	6	33
11	77	F	HCV	A	6	27
12	71	M	HCV	A	5	27
13	79	M	HCV	A	5	42

HCV, hepatitis C virus; HBV, hepatitis B virus.

acquisition time was 15.2 sec.

Image analysis. FLR was evaluated on hepatobiliary-phase images that were obtained 20 min after Gd-EOB-DTPA administration. Images were transferred to the RTPS, and registration between images of hepatobiliary-phase and planning CT was performed. Two experienced investigators (a radiologist with 9 years of experience in abdominal MRI and a radiation oncologist with 10 years of experience with HCC treatment) confirmed the geometric accuracy of the registered images and manually delineated the border of the focally decreased enhancement area on the planning CT images by referring to the hepatobiliary-phase images after reaching a consensus.

The FLR volumes (FLRVs) were calculated as the delineated volume. The TD and the irradiated volumes (IVs) of the liver parenchyma at a given dose of every 5 Gy (IV_{dose}) were also calculated based on the DVH of the RT planning.

Statistical analysis. We used the Wilcoxon-signed rank test to compare each IV_{dose} to the FLRV. All statistical analyses were performed using SPSS software (ver. 22.0, Chicago, IL, USA). Differences at $p < 0.05$ were considered significant.

Results

The median TD was 35.2 Gy (range 22.8-44.6 Gy). The median IV_{20}, IV_{25}, IV_{30}, IV_{35}, IV_{40}, and IV_{45} values were 371.1, 274.8, 233.4, 188.6, 145.8, and 31.0 ml, respectively (Table 2). The median FLRV was 144.9 ml. The FLRV was significantly different from IV_{20}, IV_{25}, and IV_{45}, but there were no significant differences between IV_{30}, IV_{35}, and IV_{40} and the FLRV. An example of the dose distribution chart used for RT planning and the corresponding hepatobiliary-phase images are presented in Fig. 1.

Table 2 Comparison between irradiated volume of the liver parenchyma and focal liver reaction volume

Parameter	Median (range)	*p*-value*
IV_{20}	371.1 (158.1–807.9)	0.001
IV_{25}	274.8 (107.6–619.6)	0.013
IV_{30}	233.4 (89.1–538.0)	0.087
IV_{35}	188.6 (70.2–466.1)	0.507
IV_{40}	145.8 (54.4–387.5)	0.279
IV_{45}	31.0 (7.7–130.4)	0.001
FLRV	144.9 (26.7–443.3)	

IV_{dose}, Irradiated volume of the liver parenchyma at a given radiation dose; FLRV, focal liver reaction volume.
*By Wilcoxon signed-rank test between IV_{dose} and FLRV.

Discussion

A dose-response relationship exists for the HCC response to RT [3,16], but there is a fine balance between the delivery of a sufficient RT dose to control the HCC and avoiding RT-induced liver toxicity. Tse *et al.* [17] recommended the prescription of individualized dosing with a fixed fraction number to improve the

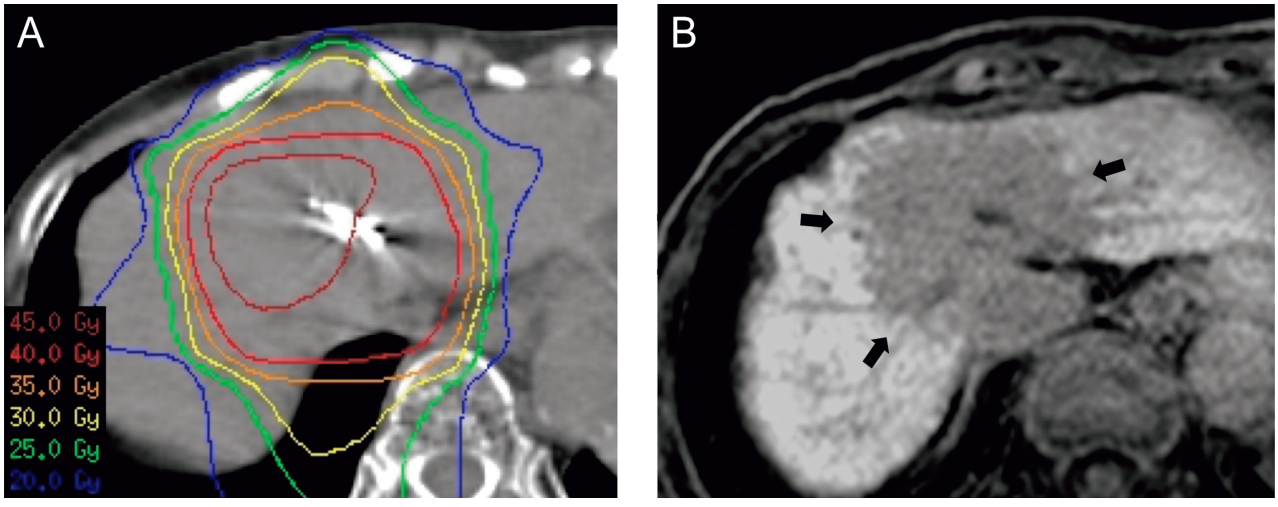

Fig. 1 A dose-distribution chart (A) and hepatobiliary-phase images captured 192 days after the completion of 3D conformal radiotherapy (B) for Patient 3. The 35-Gy isodose line (orange line) is almost equal to the focally decreased enhancement area (arrows). The threshold dose (TD) of this patient was 35.2 Gy.

outcomes of patients with HCC. Finding the dose tolerated by the non-tumorous liver tissue based on a fixed fraction number may be critical to tailored RT. The results of the present study suggest that the threshold dose of FLR is approx. 35 Gy for patients with HCC who undergo 3D-CRT in 15 fractions for tumor sizes < 5 cm. Our results, which were obtained from HCC patients treated with moderately hypofractionated RT, are consistent with those reported by Sanuki *et al.* [9] and Jung *et al.* [13]. A dose evaluation for recent advanced RT techniques was performed based on DVH. The previously recommended DVH parameters for HCC treatment varied; the percentage of the whole liver volume receiving a dose ranged from more than 5 Gy (V_5) to 40 Gy (V_{40}) [6]. Our present findings also suggest that V_{30}-V_{40} is a potential candidate parameter for predicting liver damage in patients with HCC who undergo 3D-CRT in 15 fractions for a tumor size < 5 cm.

Some studies have evaluated RT liver toxicity based on an equivalent dose calculation according to the linear-quadratic model. Although an α/β ratio of 10 can be used to calculate the biologically effective dose (BED) delivered to a tumor, it is difficult to calculate the BED delivered to a non-tumorous liver because the α/β ratio for non-tumorous liver tissue is unknown. In fact, α/β ratios ranging from 2 to 10 have been used in previous analyses of hepatic toxicity [18-20]. Okamoto *et al.* [10] evaluated 11 patients with various cancers treated with total RT doses of 30-65.4 Gy in 10-35 fractions using Gd-EOB-DTPA-enhanced MRI. Using an α/β ratio of 10, they found that the TD was equivalent to the dose of 24-29 Gy in 2-Gy fractions. Their TD results were lower than ours, although we treated patients with the larger fraction size of 3 Gy. Similarly, their TD results were very similar to those reported by Sanuki *et al.* [9], who evaluated HCC patients who received treatment with 7- to 8-Gy fractions. Their use of an α/β ratio of 10 might have resulted in an underestimation of the TD.

Our study has some limitations, including the retrospective design and the variability in the interval between the RT completion and MRI. Okamoto *et al.* [10] reported a patient who underwent Gd-EOB-DTPA-enhanced MRI studies on the 40th and 123rd day from the initiation of RT. The irradiated area in the liver of this patient showed a slightly decreased enhancement on the 40th day and a clearly decreased enhancement on the 123rd day. The difference in the interval between the RT completion and MRI may influence the TD and FLRV results. We also did not directly evaluate the potential correlation between the TD and the incidence of radiation-induced liver disease (RILD); therefore, we cannot comment on the optimal dose constraint of V_{30}-V_{40} for predicting RILD. The liver tolerance dose might also be influenced by the existence or severity of cirrhosis [11,21]; however, we were not able to evaluate the potential influence of cirrhosis due to the small number of patients evaluated. Further investigations are underway to address this issue.

In conclusion, in HCC patients who undergo 3D-CRT in 15 fractions, the threshold dose for focal liver reaction is approx. 35 Gy. V_{30}-V_{40} is a potential candidate for an optimal DVH parameter for this fractionation schedule.

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