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Original research article

Validation of the liver mean dose in terms of the biological effective dose for the prevention of radiation-induced liver damage

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ABSTRACT

Aim: The purpose of this study was to determine the optimal mean liver biologically effective dose (BED) to prevent radiation-induced liver disease (RILD) in stereotactic body radiation therapy (SBRT).

Background: The actual mean doses appropriate for liver irradiation in modern radiotherapy techniques have not been adequately investigated, although SBRT is sometimes alternatively performed using fractionated regimens.

Materials and methods: SBRT treatment plans for liver tumors in 50 patients were analyzed. All distributions of the physical doses were transformed to BED_2 using the linear-quadratic model. The relationship between physical doses and the BED_2 for the liver were then analyzed, as was the relationship between the mean BED_2 for the liver and the planning target volume (PTV).

Results: A significantly positive correlation was observed between the mean physical dose for the background liver and the mean BED_2 for the whole liver ($P < 0.0001$, $r = 0.9558$). Using the LQ model, a mean BED_2 of 73 and 16 Gy for the whole liver corresponded to the hepatic tolerable mean physical dose of 21 and 6 Gy for Child–Pugh A- and B-classified patients, respectively. Additionally, the PTV values were positively correlated with the BEDs for the whole liver ($P < 0.0001$, $r = 0.8600$), and the background liver ($P < 0.0001$, $r = 0.7854$).

Conclusion: A mean BED_2 of 73 and 16 Gy for the whole liver appeared appropriate to prevent RILD in patients with Child–Pugh classes A and B, respectively. The mean BED_2 for the liver correlated well with the PTV.

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1. Background

Surgical resection is the first choice treatment for hepatocellular carcinoma (HCC).[1,2] Transarterial chemoembolization, percutaneous ethanol injection, radiofrequency ablation, and radiotherapy have been used in cases of unresectable HCC. Additionally, conformal radiotherapy is a palliative option for HCC. However, recent advances in modern radiotherapy, including intensity modulated radiation therapy (IMRT) and stereotactic body radiation therapy (SBRT), have made them suitable for curative treatments.[3–10]

Radiation-induced liver disease (RILD) has traditionally been recognized as an almost fatal complication.[11–21] Several dosimetric models that make use of dose–volume histograms have been generated to quantitatively predict RILD in patients who receive three-dimensional conformal radiotherapy (3D-CRT). The mean liver dose has been thoroughly debated, and approximately 30 Gy was deemed to be the dose–volume limit of the liver.[20] However, the actual mean doses appropriate for liver irradiation in modern radiotherapy techniques have not been adequately investigated.

Xu et al. reported a prediction model for RILD after 3D-CRT where the hepatic tolerable doses (TD5; the mean dose that produce a 5% incidence of RILD) for a normal liver were 21 Gy and 6 Gy for Child–Pugh A- and B-classified patients, respectively.[19] In their study, the incidence and mortality rate of RILD were 16% and 76%, respectively. Currently, modern radiotherapeutic techniques can significantly reduce the doses to organs at risk (OARs) and provide effective doses to the target with high precision. RILD after SBRT has not been well described or understood compared to that after 3D-CRT.[21–26] Therefore, it is important to establish the probability of RILD due to radiotherapy. In addition, IMRT can be used in various regimens based on the biologically effective dose (BED) using a linear-quadratic (LQ) model.[27,28] Previously described mean physical doses may be insufficient for predicting RILD in modern radiotherapy. Based on this information, we chose to conduct a planning study to assess the mean liver BED in an SBRT plan to prevent RILD.

The purpose of this study was to assess the BED in SBRT using radiotherapy planning data for liver tumors, and to establish an SBRT protocol that does not cause RILD in treatment of such tumors.

2. Materials and methods

Our study was conducted according to the principles of the Declaration of Helsinki. The institutional review board of our clinic approved this retrospective study (Approval No. 9). We analyzed SBRT treatment plans for liver tumors in 50 patients at our institution between January 2010 and February 2014. We excluded patients who received re-irradiation in the same area. Patients' characteristics are shown in Table 1. Radiotherapy of the liver tumors was performed as described previously.[28] Computed tomography (CT) images and magnetic resonance imaging (MRI) for treatment planning were obtained using the 4-slice BrightSpeed Excel™ (GE Healthcare, Waukesha, WI, USA) and the SIGNA EXCITE HDx 1.5T™ (GE Healthcare), respectively. Planning contrast-enhanced four-dimensional CT scans and gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid-enhanced MRI images were used to determine gross tumor volume. To account for respiratory tumor motion, an internal target volume (ITV) was generated by contouring the imaging data of the four-dimensional CT. The planning target volume (PTV) was typically created by adding a 4- to 8-mm margin to the ITV in all directions. PTV margins of 4, 5, 6, and 8 mm were applied in 11, 2, 9, and 28 patients, respectively. Moreover, additional 2- and 3-mm margins were added in the longitudinal direction in 4 and 2 patients based on their respiratory status, respectively. The prescription radiation doses were documented at the reference point using conformal beams in 6 patients or were designed to deliver 100% of the prescription dose to 95% of the PTV using IMRT in 44 patients. Among 6 patients who received conformal beam radiotherapy, the treatment plans incorporated 7, 8, 9, and 10 beams in 1, 1, 3, and 1 patients, respectively. Among 44 patients who received IMRT, the treatment plan was devised using 5, 6, 7, 8, and 9 beams in 5, 25, 10, 2, and 2 patients, respectively. Additionally, Pencil-beam and Monte Carlo dose calculation algorithms were used in 30 and 20 patients, respectively, including one who received conformal beam radiotherapy for planning calculations. Treatment planning was performed by using iPlan RT Image™ version 4.1.0 and iPlan RT Dose™ version 4.1.2 (BrainLAB AG, Germany) units.

Table 1 – Patients' characteristics and summary of the radiotherapy.

Characteristics		Number of patients
Number of patients		50
Age (years)		73.5 (48–89)
Tumor background		
Hepatocellular carcinoma		36
Metastatic liver tumor		13
Cholangiocellular carcinoma		1
Background liver		
Normal liver (metastatic liver tumor)		13
Child–Pugh classification	A	29
	B	8
Summary of radiotherapy		
Total prescription dose (Gy)		50.0 (40.0–65)
Number of fractions		9 (4–25)
Fraction size (Gy)		5.7 (2.6–11)
BED_{10} (Gy)		80.0 (56.0–115.5)
PTV (cm^3)		80.2 (17.1–1242.7)
Volume of the whole liver (cm^3)		1048.5 (683–1701)
Volume of the background liver (cm^3)		929.4 (574.2–1574.7)
Mean physical dose for the whole liver (Gy)		14.8 (5.34–35.93)
Mean physical dose for the background liver (Gy)		11.1 (3.91–24.96)
Mean BED_2 for the whole liver (Gy)		36.8 (9.26–99.91)
Mean BED_2 for the background liver (Gy)		22.5 (7.49–58.88)

HCC = hepatocellular carcinoma; PTV = planning target volume; BED = biologically effective dose.
The background liver was defined as the whole liver minus the PTV.