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LETTER TO THE EDITOR

Normal liver sparing by proton beam therapy for hepatocellular carcinoma: Comparison with helical intensity modulated radiotherapy and volumetric modulated arc therapy

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To the Editor,

Technical advances in radiotherapy (RT) planning systems using computed tomography (CT), such as three-dimensional conformal RT (3D-CRT), along with greater understanding of partial liver tolerance have increased the use of RT in the non-surgical management of patients with hepatocellular carcinoma (HCC) [1]. Radiation-induced liver disease (RILD) is one of the most common dose limiting toxicities in patients receiving RT for HCC. While most cases of RILD are self-limiting and manageable with supportive care, this complication may result in the deterioration of hepatic reserve, with severe injury resulting in liver failure and death. Therefore, when treating HCC patients with RT, it is important not only to maximize the effective dose delivered to the tumor but to minimize the dose delivered to the surrounding normal liver.

Intensity-modulated radiotherapy (IMRT), using intensity-modulated beams to deliver a high dose to the tumor while reducing the dose to the surrounding normal tissues, and image-guided RT (IGRT) have been available. Recently, the more sophisticated RT techniques, such as helical-IMRT (H-IMRT), a type of fusion technology that combines IMRT and IGRT, and volumetric modulated arc therapy (VMAT), which uses modulated treatment apertures [defined by dynamic multi-leaf collimator (MLC)] and dose rate, have been shown to provide equal or better tumor coverage and better sparing of normal tissues than 3D-CRT and/or IMRT in patients with HCC [2–7]. Proton beam therapy (PBT) is another promising treatment option that can deliver a high radiation dose to the tumor while minimizing the radiation dose delivered to the remaining normal liver due to the unique characteristics of proton beams, the Bragg peak, allowing deposition of high doses of radiation within the target, with much lower doses outside the target. However, despite the conceptual benefits and promising clinical outcomes of PBT [8–13], it is remained unclear whether PBT is beneficial in reducing the irradiated liver volume comparing with aforementioned more sophisticated RT techniques or not. Therefore, this study was designed to compare the effects of PBT, H-IMRT, and VMAT on irradiated liver volume in patients with HCC.

Materials and methods

The study cohort consisted of 30 patients with HCC who received PBT between April 2012 and June 2013. HCC was diagnosed by pathologic confirmation ($n = 7$) or based on radiologic findings plus serum alpha-fetoprotein concentrations ≥ 200 ng/ml ($n = 23$), in accordance with the guidelines of the

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Korean Liver Cancer Study Group and the National Cancer Center [1]. Patient characteristics were summarized in Supplementary Table I (available online at http://www.informahealthcare.com/doi/abs/10.3109/0284186X.2015.1009637.). The study was performed in accordance with the guidelines of our institutional review board, which waived the requirement for informed consent due to the nature of planning study.

The patients underwent CT simulation in a supine position with arms above the head and immobilized using an arm-up holder to improve setup reproducibility. Contrast-enhanced 4D CT images were acquired, with 2.5 mm slice thickness, under shallow respiration using a 4D CT simulator (LightSpeed RT; GE Healthcare, Waukesha, WI, USA). During the 4D CT scan, the respiration signals of the patients were monitored by a Real-Time Position Management (RPM) system (Varian Medical Systems, Palo Alto, CA, USA). The acquired CT images were reconstructed in 10 equally spaced respiratory phases, and in the post-processing stage, maximum intensity projection (MIP), minimum intensity projection (MinIP), and average intensity projection (AIP) CT images were reconstructed using exhalation (gated) phases (30% of total respiratory cycle) on an Advantage workstation (Version 4.3, GE Healthcare). All 4D CT images were transferred to the Eclipse treatment planning system (Version 8.1; Varian Medical Systems), and the contours for targets and organs at risk (OARs) were delineated in AIP-CT images during the exhalation (gated) phases. The gross tumor volume (GTV) included all detectable primary tumors as determined by contrast enhanced AIP-CT images during exhalation phase and the clinical target volume (CTV) was regarded as GTV. The gated internal target volume (ITV) was obtained by summing the GTVs in each CT images during exhalation phases. The planning target volume (PTV) included the ITV plus 5–10 mm margins in all directions and was identically used for PBT, H-IMRT, and VMAT in each patient.

For each patient, three sets of plans were performed, one each for PBT, H-IMRT, and VMAT, using the Eclipse (Version 8.1; Varian Medical Systems), TomoH (Version 2.0; Accuray Inc, Sunnyvale, CA, USA) and another Eclipse treatment planning system (Version 10.0; Varian Medical Systems) with 15 MV photon beam and 120 leaf MLC, respectively (Figure 1). A total of 60 Gy in 10 Gy fractions was prescribed to the PTV, with the intent to cover at least 95% of the PTV with 100% of the prescribed dose and with minimum and maximum doses $> 90\%$ and $< 110\%$, respectively. For PBT, three coplanar beams of 230 MeV protons were manually selected on morphological relationships of the PTVs and OARs. The beam energy and spread-out Bragg peak were fine-tuned so that the PTV was encompassed by the 90% isodose volume of prescribed dose, and the proximal, distal, border smoothing, smearing and aperture margins for proton beams using the double scattering mode (Proteus 235; Ion Beam Applications, S.A., Louvain-la-Neuve, Belgium) to PTV were set to 5 mm each. Plans for H-IMRT were performed using several optimization parameters, such as 1 cm field width for PTVs less than 5 cm in length and 2.5 cm field width for the other PTVs, a pitch of 0.25 or less, and a modulation factor of 2.0. Plans for VMAT were performed using two arcs rotating clockwise from 180.1 to 179.9 with 45° collimator angle and counterclockwise from 179.9 to 180.1 with 315° collimator angle using several parameters, such as 0° couch angle and the 5 mm margin of field size to PTV, and the dose rate varied between 0 MU/min and 600 MU/min (upper limit) [3]. The dose volume constraints for OARs were identical for PBT, H-IMRT and VMAT (Supplementary Table II, available online at http://www.informahealthcare.com/doi/abs/10.3109/0284186X.2015.1009637.) [3,12].

Dose volumetric analysis was performed using dose volume histograms (DVHs) of the treatment plans for individual patients. To compare PTV coverages, $V_{95\%}$, $V_{100\%}$, and $V_{105\%}$, defined as the percentages of the PTV receiving 95%, 100% and 105% of the prescribed dose, respectively, were calculated. Other calculated parameters included the conformity index (CI), defined as the volume within 95% of the prescribed dose divided by the PTV volume, and the homogeneity index (HI), defined as the minimum dose delivered to 5% of the PTV divided by the minimum dose delivered to 95% of the PTV [14]. CI and HI values closer to 1 indicated better conformity and homogeneity, respectively, of the PTV. The remaining normal liver volume was defined as the total liver volume minus the GTV. Parameters used to compare sparing of OARs included mean dose (D_{mean}) and sets of V_x, defined as the percentage of the irradiated volume receiving x Gy. Differences in the dose volume relationships among the three techniques were compared by one-way analysis of variance, with any significant differences ($p < 0.05$) further examined by Tukey's multiple comparison test. All statistical analyses were two-sided and were performed using STATA software (version 9.0; Stata Corp., College Station, TX, USA).

Results

The median age of the 30 patients was 62 years (range 40–82 years), and the median size of the primary tumor was 3.1 cm (range 1.3–9.1 cm). The median values of PTV, remaining normal liver and total liver

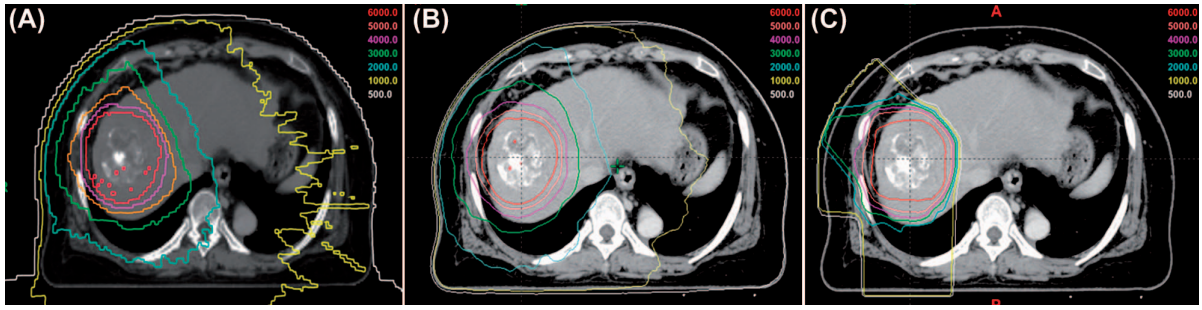

Figure 1. Axial isodose distributions of helical intensity modulated radiotherapy (A), volumetric modulated arc therapy (B), and proton beam therapy (C).

were 72.1 cm^3 (range 25.7–444.7 cm^3), 1086.7 cm^3 (range 583.3–1903.4 cm^3) and 1211.8 cm^3 (range 626.1–1944.4 cm^3), respectively (Supplementary Table I, available online at: http://informahealthcare.com/doi/abs/10.3109/0284186X.2015.1009637).

Comparisons of PTV coverages, conformity and homogeneity among the three plans are summarized in Table I. All PTV coverages ($V_{95\%}$, $V_{100\%}$ and $V_{105\%}$) and HI were similar for the three plans (Table I) (Figure 2A). The CI values for VMAT and H-IMRT differed significantly ($p < 0.05$), whereas neither differed significantly with the CI value for PBT ($p > 0.05$), indicating that the conformity of PBT was not significantly different from the conformities of VMAT and H-IMRT.

The dose volumetric parameters of the three plans are summarized in Table I and Figure 2B. The D_{mean} of remaining normal liver was significantly lower for PBT than for H-IMRT and VMAT ($p < 0.05$). These irradiated volumes of the remaining normal liver were significantly lower for PBT than for H-IMRT and VMAT at lower dose levels from V_5 to V_{45} and from V_5 to V_{35}, respectively ($p < 0.05$) (Table I) (Figure 2B). In contrast, the irradiated volumes of the remaining normal liver for PBT did not differ significantly with those of for VMAT at V_{55} and H-IMRT at V_{45} and V_{55} ($p > 0.05$) (Table I). The mean differences in relative (absolute) irradiated volumes of the remaining normal liver at higher dose levels from V_{45} to V_{55} differed between PBT and either H-IMRT or VMAT by less than about 3% (25 cm^3) (Supplementary Figure 1A and B, available online at http://www.informahealthcare.com/doi/abs/

Table I. Comparison of dose-volumetric parameters for helical intensity modulated radiotherapy (H-IMRT), volumetric modulated arc therapy (VMAT), and proton beam therapy (PBT).

		H-IMRT	VMAT	PBT	p-Value*
PTV	$V_{95\%}$ (%)	99.7 ± 0.5	100 ± 0.2	99.9 ± 0.4	NS
	$V_{100\%}$ (%)	93.5 ± 3.3	93.5 ± 3.3	93.5 ± 3.3	NS
	$V_{105\%}$ (%)	0.8 ± 3.7	5 ± 12.8	0.8 ± 1.9	NS
	CI	$1.52 \pm 0.15^{a\dagger}$	$1.38 \pm 0.20^{b\dagger}$	$1.45 \pm 0.12^{a,b\dagger}$	0.005
	HI	1.03 ± 0.01	1.03 ± 0.02	1.03 ± 0.01	NS
RNL	D_{mean} (Gy)	$17.6 \pm 4.0^{a\dagger}$	$15.0 \pm 4.0^{b\dagger}$	$6.7 \pm 2.4^{c\dagger}$	< 0.001
	V_5 (%)	$81.0 \pm 14.5^{a\dagger}$	$70.0 \pm 17.4^{b\dagger}$	$23.0 \pm 9.9^{c\dagger}$	< 0.001
	V_{15} (%)	$46.1 \pm 11.7^{a\dagger}$	$40.4 \pm 12.4^{a\dagger}$	$17.1 \pm 7.7^{b\dagger}$	< 0.001
	V_{25} (%)	$23.8 \pm 8.4^{a\dagger}$	$20.3 \pm 7.7^{a\dagger}$	$10.3 \pm 3.8^{b\dagger}$	< 0.001
	V_{35} (%)	$13.5 \pm 6.1^{a\dagger}$	$10.4 \pm 4.4^{b\dagger}$	$7.9 \pm 3.1^{c\dagger}$	< 0.001
	V_{45} (%)	$7.8 \pm 3.8^{a\dagger}$	$5.5 \pm 2.5^{b\dagger}$	$5.7 \pm 2.5^{b\dagger}$	0.007
	V_{55} (%)	$3.7 \pm 1.9^{a\dagger}$	$2.50 \pm 1.3^{b\dagger}$	$3.1 \pm 1.5^{a,b\dagger}$	0.023
Stomach	D_{2cm3} (Gy)	$15.1 \pm 6.5^{a\dagger}$	$13.3 \pm 7.2^{a\dagger}$	$1.8 \pm 3.1^{b\dagger}$	< 0.001
Intestine	$D_{2cm}{}^3$ (Gy)	13.3 ± 12.2	12.8 ± 12.7	7.1 ± 12.5	NS
Spinal cord	$D_{2cm}{}^3$ (Gy)	$14.7 \pm 5.0^{a\dagger}$	$14.0 \pm 6.1^{a\dagger}$	$2.8 \pm 5.2^{b\dagger}$	< 0.001
Right kidney	V_{20} (%)	5.2 ± 10.9	3.1 ± 8.3	1.8 ± 6.4	NS
Left kidney	V_{20} (%)	0.0 ± 0.2	0.1 ± 0.6	0.0 ± 0.0	NS

CI, conformity index; $D_{2cm}{}^3$, dose delivered dose to 2 cm^3 normal tissue; D_{mean}, mean dose delivered to normal tissues; HI, homogeneity index; NS, not significant; PTV, planning target volume; $V_{95\%}$, $V_{100\%}$, and $V_{105\%}$, percentage of the PTV receiving 95%, 100% and 105% of the prescribed dose; RNL, remaining normal liver; V_5, V_{15}, V_{25}, V_{35}, V_{45} and V_{55}, percentage of irradiated volume receiving ≥ 5, ≥ 15, ≥ 25, ≥ 35, ≥ 45 and ≥ 55 Gy, respectively.

*By one-way analysis of variance among three groups; †The same letters indicate non-significant difference among groups based on Tukey's multiple comparison tests.

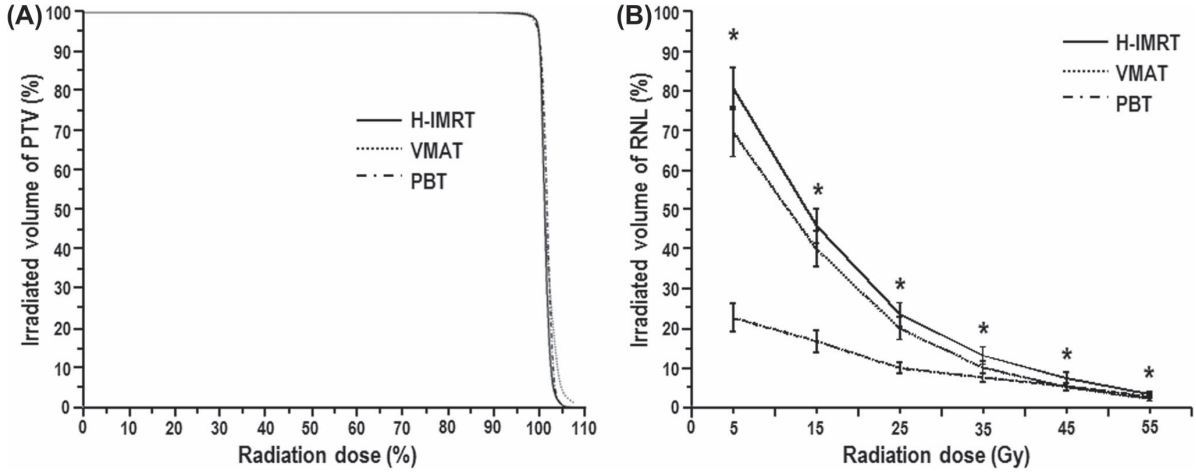

Figure 2. Dose-volume histograms for the planning target volume (PTV) (A) and remaining normal liver (RNL) (B) according to helical intensity modulated radiotherapy (H-IMRT), volumetric modulated arc therapy (VMAT), and proton beam therapy (PBT).

10.3109/0284186X.2015.1009637). D_{2cm^3} of the intestine and V_{20} for both kidneys did not differ significantly among the three plans ($p > 0.05$), whereas D_{2cm^3} values of the stomach and spinal cord were significantly lower for PBT than for H-IMRT and VMAT ($p < 0.05$) (Table I).

Discussion

The liver is one of the important dose limiting organs, with the risk of RILD associated with irradiated liver volume [15–18]. Thus, it is crucial during RT for HCC to minimize the radiation dose to the remaining normal liver. Conceptually, more sophisticated RT techniques, including H-IMRT, VMAT, and PBT, may improve tumor control in HCC patients by delivering a high radiation dose to the tumor, while minimizing the dose to the remaining normal liver, thereby minimizing impairment of the remaining hepatic reserve. In addition, several plan studies have shown dose volumetric benefits of H-IMRT, VMAT and PBT compared with 3D-CRT and/or IMRT for HCC [2–5,19]. A comparison of DVH data among 3D-CRT, IMRT and H-IMRT for HCC patients found that H-IMRT increased D_{mean} of remaining normal liver but decreased V_{40}, V_{50}, and V_{60} with 3D-CRT and IMRT [2]. Another comparison of DVH data among 3D-CRT, IMRT and VMAT for HCC found that VMAT resulted in better conformity of the PTV and V_{30} and V_{40} of remaining normal liver with similar homogeneity of PTV and sparing of non-liver OARs (stomach, duodenum, and spinal cord), than 3D-CRT or IMRT [4]. Similarly, VMAT resulted in a decreased V_{20} and V_{30} of remaining normal liver but an increased V_5 and V_{10} of remaining normal liver compared with 3D-CRT and IMRT [5]. Furthermore, PBT was found to reduce D_{mean}, V_{10}, V_{20}, and V_{30} of remaining normal liver and to better spare non-liver OARs (stomach and kidney) than 3D-CRT and IMRT [19]. Conceptually, although it is expected that the PBT has a potential to better spare the remaining normal liver than H-IMRT and VMAT, to our knowledge, the effects of PBT, H-IMRT and VMAT on irradiated liver volume had not previously been compared.

In the present study comparing DVH data among H-IMRT, VMAT and PBT for HCC, we found that PBT provided equal tumor coverage of PTV, CI, and HI and significantly better sparing of liver (D_{mean} and V_5 to V_{35} for remaining normal liver) and non-liver OARs (D_{2cm^3} of the stomach and spinal cord) compared with H-IMRT and VMAT. In addition, at higher dose levels from V_{45} to V_{55}, the relative (absolute) irradiated volumes of remaining normal liver showed mean differences between PBT and either H-IMRT or VMAT of less than about 3% (25 cm^3). The median PTV volume in this study was 72.1 cm^3, suggesting that differences at higher dose levels may be not clinically significant, whereas PBT could significantly reduce the irradiated liver volume at dose levels below V_{35} (about 50% of the prescribed dose). Several studies have reported that various dose volumetric parameters of remaining normal liver, such as D_{mean}, V_{20}, and V_{30} were associated with the risk of RILD [15,16,18]. Therefore, our finding that D_{mean}, V_{25} and V_{35} were lower for PBT than for H-IMRT and VMAT, suggests that PBT may be superior in reducing the risk of RILD. In addition, although the potential risk of RILD caused by low dose radiation from V_5 to V_{15} is unclear [20,21], the lower V_5 to V_{15} for PBT than for H-IMRT and VMAT suggests an advantage for PBT during dose escalation.

The present study had several limitations. First, this study did not analyze subgroups based on

tumor location and size due to small sample number of patients (n = 30), with relatively small tumors (median size, 3.1 cm), 21 (70%) of whom had tumors located in the right lobe. The liver is one of the largest organs of the body; its triangular shape renders different adjacent normal tissues, such as the stomach, small and large intestine, kidney, and spinal cord, vulnerable to radiation, depending on tumor location and size. Thus, further large scaled studies should be needed for subgroup analysis based on tumor location and size. Second, the interplay effect between MLC and tumor motion during respiration in H-IMRT and VMAT was not considered. However, several studies have noted that the interplay effect of H-IMRT and VMAT was not significantly affected by tumor motion [17,22]. Third, because this study was a comparative planning study using the same data sets to compare the effects of PBT, H-IMRT, and VMAT on irradiated liver volume, the differences of each technique's robustness against patient positioning, anatomical changes, and organ movement were not considered. In addition, the cost-effectiveness of PBT comparing with H-IMRT and VMAT was not compared in this study. However, the remaining normal liver sparing is one of important issues comparing the different treatment techniques, and thus further large scaled studies should be warranted.

In conclusion, our study evaluated the effects of PBT, H-IMRT and VMAT on irradiated liver volume in patients with HCC and showed that PBT resulted in consistently lower D_{mean} and V_5 to V_{35} than H-IMRT and VMAT. Although further larger and comprehensive studies should be needed, our data suggest that PBT may be superior to H-IMRT and VMAT in reducing the risk of RILD and also it may have a potential advantage during dose escalation.

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Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Supplementary material available online

Supplementary Figure 1 and Table 1.