BJR

https://doi.org/10.1259/bjr.20220720

Received: 22 July 2022 | Revised: 29 November 2022 | Accepted: 12 December 2022 | Published online: 19 January 2023

Cite this article as:
Uchinami Y, Katoh N, Abo D, Morita R, Taguchi H, Fujita Y, et al. Study of hepatic toxicity in small liver tumors after photon or proton therapy based on factors predicting the benefits of proton. *Br J Radiol* (2023) 10.1259/bjr.20220720.

FULL PAPER

Study of hepatic toxicity in small liver tumors after photon or proton therapy based on factors predicting the benefits of proton

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Objectives: In a previous study of hepatic toxicity, the following three factors were identified to predict the benefits of proton beam therapy (PBT) for hepatocellular carcinomas (HCCs) with a maximum diameter of ≤5 cm and Child-pugh grade A (CP-A): number of tumors (1 vs ≥2), the location of tumors (hepatic hilum or others), and the sum of the diameters of lesions. The aim of this study is to analyze the association between these three factors and hepatic toxicity.

Methods: We retrospectively reviewed patients of CP-A treated with PBT or photon stereotactic body radiotherapy (X-ray radiotherapy, XRT) for HCC ≤5 cm. For normal liver dose, the V5, V10, V20 (volumes receiving 5, 10, and 20 Gy at least), and the mean dose was evaluated. The albumin-bilirubin (ALBI) and CP score changes from the baseline were evaluated at 3 and 6 months after treatment.

Results: In 89 patients (XRT: 48, PBT: 41), those with two or three (2–3) predictive factors were higher normal liver doses than with zero or one (0–1) factor. In the PBT group, the ALBI score worsened more in patients with 2–3 factors than those with 0–1 factor, at 3 months (median: 0.26 *vs* 0.02, p = 0.032) and at 6 months (median: 0.35 *vs* 0.10, p = 0.009). The ALBI score change in the XRT group and CP score change in either modality were not significantly different in the number of predictive factors.

Conclusion: The predictive factor numbers predicted the ALBI score change in PBT but not in XRT.

Advances in knowledge: This study suggest that the number of predictive factors previously identified (0–1 vs 2–3) were significantly associated with dosimetric parameters of the normal liver in both modalities. In the proton group, the number of predictive factors was associated with a worsening ALBI score at 3 and 6 months, but these associations were not found in the photon SBRT group.

INTRODUCTION

In hepatocellular carcinomas (HCCs), X-ray radiotherapy (XRT) with stereotactic body radiotherapy (SBRT) has been widely used and favorable results have been reported.[1–5] Compared to XRT, proton beam therapy (PBT) is expected to further reduce adverse events and improve treatment outcomes,[6–8] but a difficult issue remains for how to select the more advantageous treatment: XRT or PBT. As a method of selecting cases that would benefit from PBT, a model-based approach has been proposed.[9,10] This strategy is conducted by generating the treatment plan for photon and proton therapy, then comparing normal tissue complication probability (NTCP) values to predict the risk of adverse events. If the difference in NTCP values (ΔNTCP) is greater than a predetermined criterion, PBT is judged to be more

beneficial than photons and can be suggested for use. In several studies comparing treatment plans for liver tumors, the advantages of PBT are clear when the tumor diameter is large (6.3–7.9 cm).[11–13] However, for small tumors, there is still discussion as to which cases would be beneficial with PBT.

To establish the advantages of PBT in small liver tumors, we have conducted a simulation study using five NTCP models to predict radiation-related hepatic toxicity in patients with the maximum tumor diameter ≤5 cm and Child-pugh grade A (CP-A).[14] In this study, we have shown that the benefits of PBT were predicted by the following three factors: total tumor diameter (sum of the diameters of each lesion), number of tumors (1 *vs* 2), and tumor location (hepatic hilum or other location). That is, if a single, small tumor is located in the periphery of the liver, the benefit of PBT is small. However, the opposite is true when large, multiple tumors are in the porta hepatis. Our previous study showed that not only tumor size, but also the location and number of tumors should be considered important factors.

Although this previous study is promising in that it provided suggestions for how to select photon or proton treatment in patients with small liver tumors, clinical data have not been analyzed. To resolve this issue, we thought it necessary to evaluate the associations between the predictive factors and hepatic toxicity using clinical data. The aim of this study is to investigate how the predictive factors influence the post-treatment liver function in patients treated with XRT or PBT.

METHODS AND MATERIALS.

Patients

This study was approved by the Ethical Review Committee of our institution (IRB number: 021–111). Eligible patients were those who received radical PBT or XRT for HCC with a maximum diameter ≤5 cm and CP-A. In Hokkaido University Hospital, we have conducted PBT for primary HCC since 2015. To compare cases treated during the same period, patients who received either PBT or XRT from January 2015 to September 2021 were included in the analysis. In principle, PBT was selected based on patient medical situations, preferences, and financial background.

Proton beam therapy

All patients were treated by a spot-scanning proton therapy system incorporating respiratory-gating by a fiducial marker (PROBEAT-RT, Hitachi, Ltd., Tokyo, Japan). The treatment planning CT was scanned at the natural expiratory phase of the respiration cycle without contrast agents. Unless medically compromised, contrast-enhanced CT and MRI was performed at the same respiratory phase and registered into the treatment planning CT. The gross tumor volume (GTV) was defined as the tumor, and the clinical target volume (CTV) was generated as the GTV with a 3–5 mm margin. The CTV margin was reduced in cases with concerns about deterioration of liver function after treatment. The CTV area outside the liver was modified.

The dose prescriptions was the following regimen: 66 GyE (gray equivalent) in 10 fractions, 72.6 GyE in 22 fractions, or 76 GyE in 20 fractions, which are suggested by the Japanese Society for Radiation Oncology (JASTRO) depending on the tumor location. The fraction regimen of 20 or 22 were chosen for tumors in the hepatic hilum or near to the gastrointestinal tract (GI-tract). In PBT planning, the dose was generally prescribed for 99% of the CTV volume (CTV D99). In some cases, doses were prescribed for CTV D50 or adjusted due to its proximity to the GI-tract or other critical organs. The general dose constraints are shown in Table 1. The PBT plan was optimized with single-field uniform dose optimization with two or three beams with a VQA v. 3.077 (Hitachi Ltd., Tokyo). The intensity-modulated proton therapy (IMPT) by multifield optimization was also used for cases where the tumor is close to critical organs such as the gastrointestinal tract. A 5 mm margin was adapted lateral to the beam direction considering internal and setup margins. Distal and proximal margins were calculated as 3.5% of the range plus 1 mm and they were added as range uncertainties. For the dose calculations, the relative biological effectiveness (RBE) of 1.1 was used.

X-ray radiotherapy

XRT was performed with photon SBRT using a fiducial marker.[5] Contouring of targets other than the planning target volume (PTV) is the same as the procedure for PBT described above. The PTV was defined as the CTV plus a 5 mm margin considering

Table 1. General dose constraints

	XRT			PBT		
		Fraction			Fraction	
Organs at risk	values	4	8	values	20–22	10
Normal liver (Liver—GTV)	≥700 cm^3	<15 Gy	<17.5 Gy	Mean	<30 GyE	<25 GyE
Stomach	D_{1cc}	<26.7 Gy	<35 Gy	$D_{0.5cc}$	<60 GyE	<47 GyE
Duodenum	D_{1cc}	<26.7 Gy	<35 Gy	$D_{0.5cc}$	<50 GyE	<40 GyE
Intestine	D_{1cc}	<26.7 Gy	<35 Gy	$D_{0.5cc}$	<50 GyE	<40 GyE
Spinal cord (For PBT, + 8 mm margin)[a]	Max	<25 Gy	<35 Gy	Max	<45 GyE	<36 GyE

GTV, gross tumor volume; PBT, proton beam therapy; RBE, relative biological effectiveness; XRT, X-ray radiotherapy.
Doses were normalized to 2 Gy equivalent doses, using linear quadric model with an α/β ratio of 3.
D_{Xcc} indicates the maximum dose to X_{cc} volume.
[a]In PBT, the spinal cord as an organ at risk was assigned as the spinal cord +8 mm considering robustness evaluations.

setup margin and gating window. A general dose prescription was 48 Gy in 8 fractions or 40 Gy in 4 fractions as a dose to cover 95% of the PTV (PTV D95) according to the dose constraints shown in Table 1. Overall, PTV D95 were enclosed by 65–85% isodose line of the dose at the reference point. XRT in eight fractions were adapted in tumors located in hepatic hilum or close to the GI-tract. In other cases, four fractions were adapted. Final dose prescriptions were determined according to patient's liver function and tumor size in each case.

The doses were delivered by a six mega-voltage (MV) X-ray generated with multiple (7–10) static beams or step and shoot IMRT planned by XiO (Elekta AB, Stockholm, Sweden) or Pinnacle^3 (Philips, Amsterdam, Netherlands). All patients were treated with respiratory gating using an implanted fiducial marker by a Varian CLINAC iX (Varian Medical Systems, Palo Alto, CA) with SyncTraX (Shimadzu Co., Kyoto, Japan) or a TrueBeam (Varian Medical Systems) with a SyncTraX FX4 version (Shimadzu Co).

Toxicity evaluation

Follow-up was performed every 3 months for about 1 or 2 years after treatment and every 6 months thereafter. Acute adverse events were evaluated at 3 and 6 months from the last day of treatment. Patients were excluded if they met the following criteria at a time point: had received treatment for HCC, local recurrence, and in cases where data were not available. To evaluate the changes in the liver function, the albumin-bilirubin (ALBI) and Child-Pugh (CP) score were evaluated at baseline, at 3, and at 6 months after the treatment. In the evaluation of the international normalized ratio (INR) score, this was estimated as one for patients taking anticoagulant medication and estimated as the most recent INR score for patients with missing data in the follow-up period, as previously used.[5,15] Classic and non-classic radiation-induced liver diseases (RILD) were also evaluated without progressive HCC within 3 months after treatment. Classic RILD was an elevation of alkaline phosphatase (to twice the higher normal or baseline level), or anicteric hepatomegaly and non-malignant ascites.[16] Non-classic RILD was at elevated transaminases of more than five times the upper normal level, or Common Terminology Criteria for Adverse Events (CTCAE) Grade 4 levels in patients with pre-treatment values more than five times the upper normal level, or a worsening of two or more in the CP score, without classic RILD.[16]

Data analysis

In this study, the XRT and PBT cohort were stratified by the following three factors: the total tumor diameter, tumor location (hepatic hilum or other location), and number of tumors (1 *vs* ≥2). The hepatic hilum was defined as within 20 mm of the main stem or first branch of the portal vein, in at least one of the lesions. For the total tumor diameter, the median total diameter was 23 mm (interquartile range, IQR: 17.5–34.0) for the entire cohort, and the factor of total tumor diameter was divided into two groups based on 23 mm, and cases of ≥23 mm were considered predictors of benefit from PBT. Similarly, when two or more tumors were targeted or tumors were in the porta hepatis, this was a factor for predicting benefits of the proton therapy. To investigate the association between the number of predictive factors and clinical outcomes, patients were divided into a cohort with one or zero factors (0–1 factors) and those with two or three factors (2–3 factors). To compare the dose between the two modalities, PTV were also prepared in the PBT plan as well as in XRT. For dosimetric comparisons, doses were normalized to 2 Gy equivalent doses (EQD2), using a linear quadric model with an α/β ratio of 3 for normal livers and α/β ratio of 10 for tumors.

To compare the two groups, Pearson χ^2 test or Fisher's exact test was used for categorical variables and the Mann-Whitney test for continuous variables, with p-values < 0.05 considered significant. The statistical analysis was performed using JMP v. 16 (SAS, Cary, NC).

RESULTS

Patient backgrounds

A total of 89 patients were eligible, with 48 patients receiving XRT and 41 PBT. Table 2 shows the details of the patient backgrounds. Compared to the XRT group, the patients in the PBT group had larger median tumor sizes (20 mm [IQR: 11–25] *vs* 26 mm, [19 – 36], p = 0.008) and GTV volume (6.7 cm^3 [IQR: 2.6–15.0] *vs* 8.0 cm^3 [4.6–33.0], p = 0.014). In addition, the EQD2 to the 95% volume of PTV (PTV D95) was significantly higher in the PBT group (64.0 [IQR: 50.0–64.0] in XRT *vs* 83.4 [76.4–86.0] in PBT, p < 0.001). Since the total tumor diameter was the median 23 mm (IQR: 17.5–34.0), we based our factor for size on 23 mm (<23 mm or ≥23 mm). Table 3 shows patient details by the number of predictive factors. In the XRT group, the EQD2 at PTV D95 was higher in patients with 0–1 predictive factors than with 2–3 factors (64.0 Gy [IQR: 50.0–64.0] *vs* 50.0 Gy [50.0–64.0], p = 0.010). Figure 1 shows the V5, V10, V20, and mean doses of normal livers by the number of factors (0–1 *vs* 2–3). For all dose indicators, each value was higher in patients with a larger number of factors (p < 0.001).

ALBI and CP score changes

Figure 2 shows the changes in the ALBI and CP score at 3 and 6 months after the treatment, except for patients with other treatments, local recurrence, and where data was not available at the respective time point. Finally, 77 patients (XRT: 39, PBT: 38) were included in the analysis at 3 months and 64 (XRT: 32, PBT: 32) at 6 months (Supplementary Material A) At 3 months, the ALBI score changes by predictive factors, 0–1 *vs* 2–3 were 0.09 (IQR: −0.03 to 0.23) *vs* 0.23 (0 to 0.46, p = 0.253) in XRT and 0.02 (−0.22 to 0.32) *vs* 0.26 (0.16 to 0.34, p = 0.032) in PBT, respectively. At 6 months, ALBI score changes were 0.22 (IQR: −0.09 to 0.32) *vs* 0.18 (0.12 to 0.40, p = 0.930) in XRT and 0.10 (IQR: −0.13 to 0.24) *vs* 0.35 (0.18 to 0.40, p = 0.009) in PBT, respectively. A significant difference was found in the PBT group at 3 and at 6 months. In ALBI grade changes, one patient in the XRT group worsened from Grade 2 to Grade 3 at 3 months after the treatment (Supplementary Material B). For CP score changes, there was no significant difference in the results of the number of factors or the changes in CP scores (≥2 vs <2). Although a direct comparison of XRT and PBT is difficult due to significant differences in patient backgrounds, it did not find significant differences in ALBI or CP score changes for both modalities (Supplementary Material C)

Table 2. Patient backgrounds of XRT *vs* PBT

		XRT (n = 48)	PBT (n = 41)	p-value
Gender				0.844
Male		36 (75.0%)	30 (73.1%)	
Female		12 (25.0%)	11 (26.8%)	
Age (median, years)		76 (range: 58–89)	69 (range: 44–88)	0.026
Baseline liver disease				
Virus	HBV	9 (18.7%)	9 (21.9%)	0.707
	HCV	21 (43.7%)	11 (26.8%)	0.097
Baseline Child-Pugh grade/ score				0.204
A	5	29 (60.4%)	30 (73.1%)	
	6	19 (39.5%)	11 (26.8%)	
Baseline ALBI score		−2.46 (IQR: −2.80 to −2.16)	−2.70 (IQR: −2.87 to −2.31)	0.097
Baseline ALBI grade				0.112
	1	20 (41.6%)	24 (58.5%)	
	2	28 (58.3%)	17 (35.4%)	
Tumor size (median, mm)		20 (IQR: 11–25)	26 (IQR: 19–36)	0.008
Total tumor size (median, mm)		22 (IQR: 12–29)	29 (IQR: 20–38)	0.004
Prescribed dose				
48 Gy in 8 fractions		24 (50.0%)		
40 Gy in 8 fractions		21 (43.7%)		
40 Gy in 4 fractions		3 (6.2%)		
72.6 GyE in 20 fractions			11 (26.8%)	
76 GyE in 22 fractions			18 (43.9%)	
66 GyE in 10 fractions			12 (29.2%)	
EQD2 at reference point[a] (median, Gy[E])		87.5 (IQR: 87.5–87.5)	87.4 (IQR: 80.4–91.3)	0.011
EQD2 at PTV D95[a] (median, Gy[E])		64.0 (IQR: 50.0–64.0)	83.4 (IQR: 79.7–85.9)	<0.001
Normal liver (Liver—GTV) volume, cm^3 (median)		1126 (IQR: 960–1313)	1241 (IQR: 1074–1512)	0.021
GTV volume, cm^3 (median)		6.7 (IQR: 2.6–15.0)	8.0 (IQR: 4.6–33.0)	0.014
Number of patients by factors				
	Single lesion (*vs* ≥2 lesions)	42 (87.5%)	30 (73.1%)	0.086
	Peripheral of liver (*vs* hepatic hilum)	24 (50.0%)	20 (48.7%)	0.908
	Total tumor diameter of <23 mm (*vs* ≥23 mm)	28 (58.3%)	15 (36.5%)	0.040
Number of predictive factors				0.087 [b]
0–1	0	15 (31.2%)	5 (12.1%)	(0–1 *vs* 2–3)
	1	17 (35.4%)	15 (31.2%)	
2–3	2	15 (31.2%)	20 (41.6%)	
	3	1 (2.0%)	1 (2.0%)	

ALBI grade, albumin-bilirubin grade; BCLC, Barcelona Clinic Liver Cancer; EQD2, 2 Gy equivalent doses; GTV, gross tumor volume; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, Hepatitis C virus; IQR, interquartile ratio; NASH, non-alcoholic steatohepatitis; PBT, proton beam therapy; PTV, planning target volume; XRT, X-ray radiotherapy.

[a]Calculated using $\alpha/\beta = 10$

[b]Patients were categorized into two groups based on the number of factors (with zero or one factors *vs* two or three factors) and statistical analysis was performed.

Table 3. Risk based details for photon XRT *vs* PBT

		XRT			PBT		
Number of predictive factors[a]		**0–1 (*n* = 32)**	**2–3 (*n* = 16)**	***p*-value**	**0 –1(*n* = 20)**	**2–3 (*n* = 21)**	***p*-value**
Baseline Child-Pugh grade/ score				0.296			0.654
A	5	21	8		14	16	
	6	11	8		6	5	
Baseline ALBI score (median)		−2.57 (IQR: −2.84 to −2.18)	−2.34 (-2.62 to -1.85)	0.034	−2.64 (IQR: −2.81 to −2.36)	−2.78 (-2.88 to -2.25)	0.539
Baseline ALBI grade				0.097			0.653
	1	16	4		11	13	
	2	16	12		9	8	
Tumor size (median, mm)		18 (IQR: 10–22)	25 (18–32)	0.011	20 (IQR: 13–32)	32 (25–43)	0.002
Total tumor size (median, mm)		19 (IQR: 10–22)	29 (24–33)	<0.001	20 (IQR: 14–32)	37 (25–44)	<0.001
GTV volume (median, cm^3)		4.2 (IQR: 1.6–10.9)	14.6 (6.1–22.2)	0.005	5.7 (IQR: 3.9–17.0)	22.5 (7.4–47.1)	0.002
EQD2 at reference point[b] (median, Gy[E])		87.5 (IQR: 87.5–87.5)	87.5 (87.5–87.5)	0.318	87.4 (IQR: 87.4–91.3)	87.4 (80.4–87.4)	0.022
EQD2 at PTV D95[b] (median, Gy[E])		64.0 (IQR: 50.0–64.0)	50.0 (50.0–64.0)	0.010	83.8 (IQR: 80.7–87.1)	83.3 (77.1–84.7)	0.256

ALBI grade, albumin-bilirubin grade; EQD2, 2 Gy equivalent doses; GTV, gross tumor volume; IQR, interquartile ratio; PBT, proton beam therapy; PTV, planning target volume; XRT, X-ray radiotherapy.
[a]Patients were divided into a cohort with one or zero factors (0–1 factors) and one with two or three factors (2–3 factors)
[b]Calculated as EQD2 using $\alpha/\beta = 10$

RILD

Classic RILD was not observed and non-classic RILD was found in 2 of 38 patients (5.2%) who had undergone PBT, but none in the XRT group ($p = 0.151$).

DISCUSSION

In this study, we have shown that the previously identified three factors can predict liver dose parameters in both XRT and PBT groups, in cases where the tumor diameter is ≤5 cm and CP grade A. Furthermore, the PBT group showed an association between the number of factors and the changes in ALBI scores after treatment. In the model-based approach, the risk of adverse events is predicted at the treatment planning using NTCP models.[17] These may be useful when the prescribed doses are the same for photons and protons.[10]

One of the difficulties in comparing photon and proton therapy in liver tumors is the differences in dose prescription. We found a significantly higher dose at PTV D95 in the PBT group compared with the XRT treatment. In our institutional protocol for XRT, we have commonly used the dose prescription of 48 Gy in 8 fractions (EQD2 64.0 Gy) or 40 Gy in 4 fractions (EQD2 66.7 Gy) to the PTV D95, mainly depending on the tumor location. In proton therapy for HCC in Japan, the three dose prescriptions suggested by JASTRO are generally used (66 Gy in 10 fractions, 72.6 Gy in 22 or 76 Gy in 20). The lowest prescribed dose in the PBT group is 72.6 GyE in 22 fractions, which is equivalent to 80.5 Gy in EQD2. As a result, the dose administered to the PTV D95 in the PBT group was a median of 83.4 Gy (IQR: 79.7–85.9), which was significantly higher than that in the XRT group ($p < 0.001$). Cheng et al reported a similar trend from a total of 110 HCC patients who received photon or proton therapy. They reported that the prescribed dose was significantly higher in the proton cohort than with photons (median biologically effective dose 96.56 *vs* 62.6 Gy, using α/β ratio of 10).[7] In our study, no classic RILD was determined and the incidence of non-classic RILD was not significantly different for the XRT and PBT groups (0% *vs* 5.2%, $p = 0.151$). Considering these results, it may be suggested that protons could be able to deliver higher doses to the tumor without significantly increasing the RILD.

Our previous simulation study compared photon and proton therapies for liver tumors assuming the same dose prescription, then proposed the three factors predicting the benefits of proton therapy.[14] However, the present study showed higher doses for the PBT group compared to XRT. In actual clinical practice with HCC, the dose prescription is often determined in consideration of the liver dose and other factors, which lead

Figure 1. Dosimetric parameters of the normal liver (Liver-GTV) by the number of predive factors between one or zero factors (0–1 factors) and two or three factors (2–3 factors). V5, V10, V20 shows volumes receiving 5, 10, and 20 Gy (E) at least, respectively. Boxes indicate the interquartile range from the 25 to 75‰. Median values are shown as horizonal lines within the box and outliers are filled circles. GTV, gross tumor volume; XRT, X-ray radiotherapy.

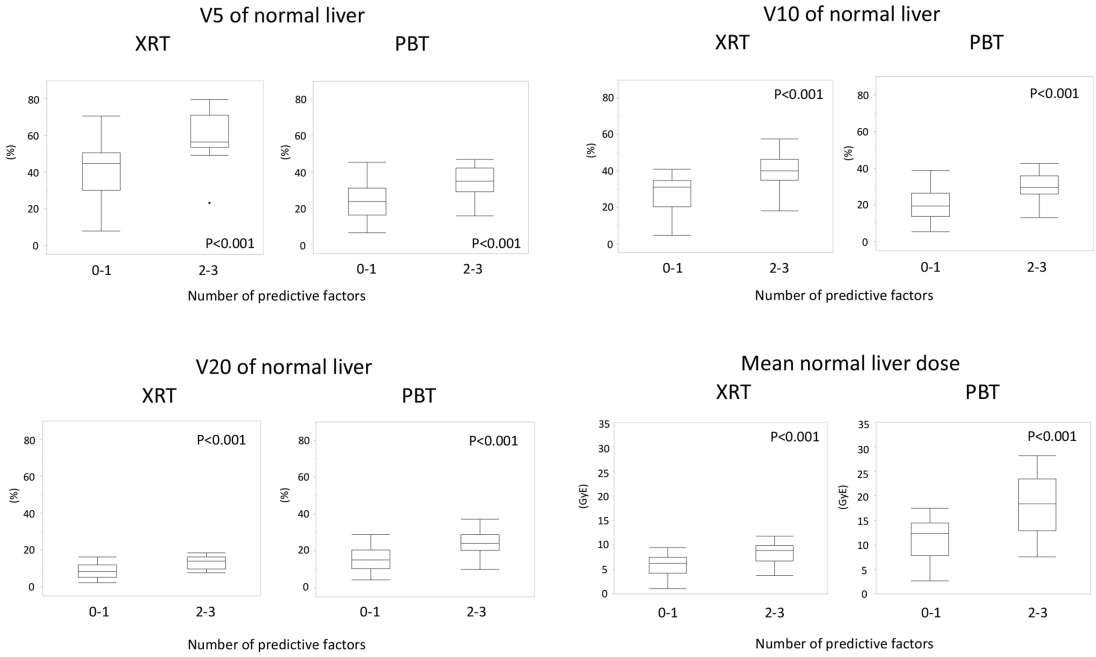
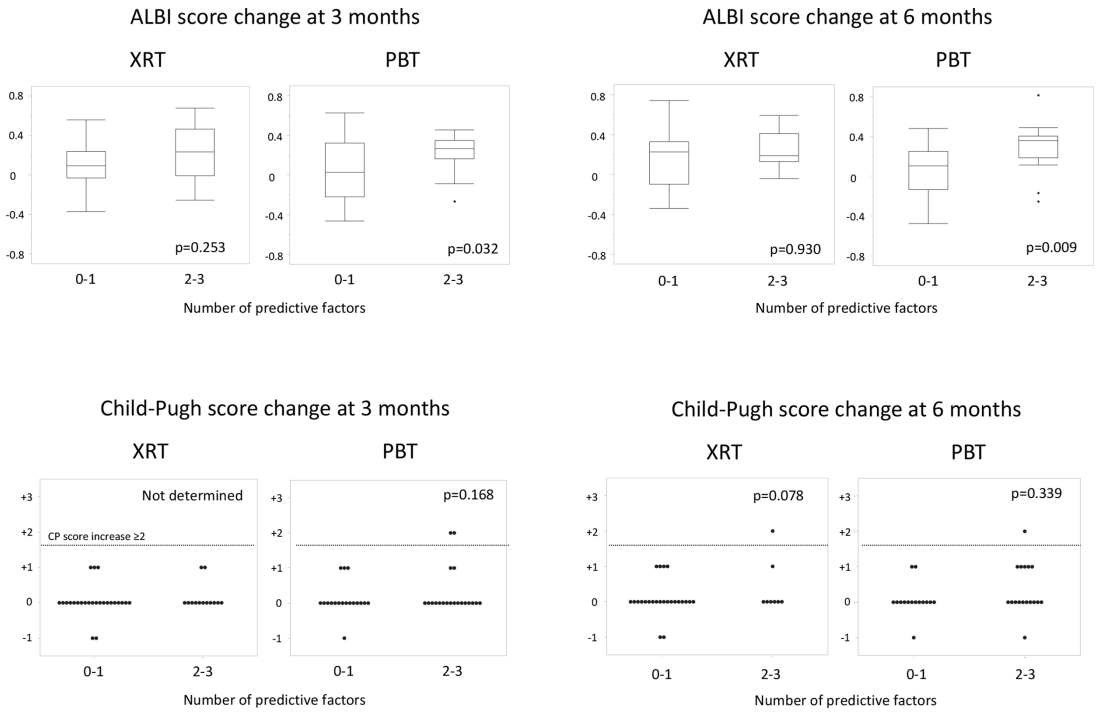


Figure 2. Changes in ALBI and Child-Pugh score at 3 and 6 months after the treatment by number of predictive factors between one or zero factors (0–1 factors) and two or three factors (2–3 factors). In ALBI score changes (upper panel), boxes indicate the interquartile range from the 25 to 75‰. Median values are shown as horizonal lines within the box and outliers are filled circles. In Child-Pugh score changes (lower panel), each dot represents a score change of one case. Statistical analysis was performed for Child-Pugh score increases ≥2 vs <2. ALBI, albumin-bilirubin; PBT, proton beam therapy; XRT, X-ray radiotherapy.



to different prescribed doses for proton and photon therapies.[6,7] From 989 patients who had undergone photon SBRT or PBT, Hasan et al also reported that the median number of fractions was different (photon SBRT: 5 *vs* PBT: 15 fractions), although there was no significant difference in biologically effective dose.[8] In a model-based approach, the benefit of protons over photons is determined based on the NTCP models, assuming that the dose prescriptions are the same.[10] For the radiation-related liver toxicity, most NTCP models depend on the irradiated normal liver dose.[18–20] This suggests that if the same modality is used, lower prescription doses are advantageous in terms of liver toxicity. The treatment selection of HCC with protons or photons may be considered both in terms of adverse events, as well as of the increased therapeutic efficacy with higher prescribed doses of protons.

For hepatic toxicity, there was a significant association in the ALBI score change of the PBT group at 3 and 6 months. This result is consistent with the results in Figure 1 that each index of the liver dose was higher in patients with 2–3 predictive factors. Differently, the ALBI and CP score changes were not associated with the number of predictive factors in the XRT group, although the liver dose was higher in patients with 2–3 predictive factors than 0–1 factor. An interpretation of this result is difficult, but one possible explanation is that it is due to the low number of patients. As the number of patients increases, the correlation between the number of predictive factors and hepatic toxicity may become clearer. Another possibility is that the dose prescription was adjusted appropriately for each case in the XRT group. The CTV margin or the prescribed dose may have been reduced in cases where the risk of liver damage was expected to be high at the treatment planning. The EQD2 at PTV D95 was higher in patients with ≤1 predicting factors (median 64.0 Gy) than with ≥2 factors (median 50.0 Gy, $p = 0.010$).

The limitations of this study are as follows: this study does not support a direct comparison between XRT and PBT regarding changes in the ALBI or CP scores, because patient backgrounds vary greatly between the two modalities. The methods of dose optimization are also different, and a rigorous comparison using retrospective data has not been performed. Another limitation is the differences in the dose prescription between the XRT and PBT groups, where the former had 4–8 fractions, whereas the latter had 10–22 fractions. Although this difference was converted to equivalent doses using the EQD2 formula, but high-dose hypofractionated radiotherapy may differ from the typical LQ model.[21] Moreover, the survival rate could not be analyzed due to the short observation period. Sanford et al analyzed 133 patients treated with either photons or protons for non-resectable HCC with the median GTV of 118 ml in the photon and 106 ml in the proton group. They reported that PBT was associated with improved overall survival, possibly due to decreased incidence of non-classic RILD as compared with photon radiation therapy.[6] In the present study of patients with smaller GTV volume, classic RILD was not observed and non-classic RILD was identified in two patients in the PBT group (5.2%). Therefore, further studies are needed to clearly identify which cases of small HCC would benefit from PBT.

In conclusion, the previously identified three factors (the number of tumors, the location of tumors, and the sum of diameters in each lesion) were significantly associated with the normal liver dose in both modalities. Because these factors allowed predicting a worsening of the ALBI score in the PBT group, future studies comparing outcomes in XRT *vs* PBT should reduce the bias of patient backgrounds based on three factors in each group. In addition, differences in the prescribed doses as well as the probability of adverse events should also be considered in determining the appropriate treatment selecting XRT or PBT.

DISCLOSURE STATEMENT.

K.K. is an employee of the research institute of Hitachi, Ltd., currently working for Hokkaido University under a secondment agreement. K.K. declares that this research has no relationship to Hitachi, Ltd. All other authors declare that they have no conflicts of interest to declare.

FUNDING

This research was supported by the Akiyama memorial foundation and Grant-in-aid for research on radiation oncology of JASTRO 2022-2023

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