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FULL PAPER

Indicator for local recurrence of hepatocellular carcinoma after proton beam therapy: analysis of attenuation difference between the irradiated tumor and liver parenchyma on contrast enhancement CT

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Objectives: We aimed to identify dynamic CT features that can be used for prediction of local recurrence of hepatocellular carcinoma (HCC) after proton beam therapy (PBT).

Methods: We retrospectively retrieved CT scans of patients with PBT-treated HCC, taken between January 2004 and December 2016. 17 recurrent lesions and 34 non-recurrent lesions were retrieved. The attenuation difference between irradiated tumor and irradiated parenchyma (AD_{HCC-IP}) was compared in the two groups by using the Mann-Whitney U test. Cut-off value of AD_{HCC-IP} was estimated by using the Youden index.

Results: The follow-up time after PBT initiation ranged from 374 to 2402 days (median, 1069 days) in recurrent lesions, and 418 to 2923 days (median, 1091.5 days) in non-recurrent lesions ($p = 0.892$). The time

until appearance of local recurrence after PBT initiation ranged from 189 to 2270 days (median, 497 days). AD_{HCC-IP} of recurrent lesions [mean, -21.8 Hounsfield units (HU); from -95 to -31 HU] was significantly greater than that of non-recurrent lesions (mean, -51.7 HU; from -117 to -12 HU) at 1–2 years in portal venous phase ($p = 0.039$). 5-year local tumor control rates were 0.93 and 0.56 in lesions with AD_{HCC-IP} at 1–2 years in PVP < -55 and ≥ -55 HU, respectively.

Conclusion: The attenuation difference between irradiated HCC and irradiated liver parenchyma in portal venous phase at 1–2 years after PBT can predict long-term local recurrence of HCC after treatment.

Advances in knowledge: We identified a cut-off value for contrast enhancement of HCC after PBT that could predict future local recurrence.

INTRODUCTION

Proton beam therapy (PBT) has been shown to play an important role in the treatment of hepatocellular carcinoma (HCC).^{1–9} The 5 year overall survival rate for patients with PBT-treated HCC is 24–48%^{3,6} and the 5 year local tumor control (LTC) rate is approximately 80%.^{1,3} Favorable therapeutic effects have also been reported for HCCs larger than 10 cm,^{1,10} as well as for HCCs with portal vein tumor thrombosis (PVTT).^{1,11}

After PBT, treated HCC lesions are consistently surrounded by irregular-shaped irradiated parenchyma. Therefore, sufficient knowledge of the radiological features of the treated HCCs as well as the surrounding irradiated parenchyma is

necessary for the interpretation of LTC.^{4,12–16} PBT-induced hepatic injury is observed as low-attenuation areas on non-contrast CT and enhanced areas on dynamic CT with an early and prolonged enhancement pattern¹⁴ (Figure 1a). During angiography, the irradiated liver parenchyma shows early and prolonged staining.¹⁷ The irradiated parenchyma does not take up gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) and superparamagnetic iron oxide, which can cause difficulty in distinguishing PBT-treated HCCs from the surrounding irradiated parenchyma.^{18,19} Thus, dynamic CT or dynamic MRI scans using extracellular contrast agents are suitable for the assessment of tumor contrast enhancement, because they can more accurately distinguish treated HCC from irradiated parenchyma.

Figure 1. (a) CT image in PVP in an 82-year-old female who underwent PBT with 72.6 GyE, 22 fractions. CT images were obtained 8 months after the initiation of PBT. The irradiated liver parenchyma (black arrow) showed high attenuation compared with other normal liver parenchyma, due to radiation-induced hepatic injury. PBT-treated HCC (white arrow) was located in the center of the irradiated liver parenchyma. To assess local control of the PBT-treated HCC, we evaluated the attenuation of irradiated HCC against the surrounding irradiated parenchyma (AD_{HCC-IP}). (b) The attenuation of irradiated HCC (red circle) and irradiated liver parenchyma (yellow circle) was measured using the largest measurable ROI. HCC, hepatocellular carcinoma; PBT, proton beam therapy; PVP, portal venous phase; ROI, region of interest

Long-term imaging features of PBT-treated HCC and surrounding irradiated parenchyma in dynamic CT or dynamic MRI using extracellular contrast agents have been analyzed in a few previous articles.^{13–16} Onaya *et al* demonstrated that early enhancement followed by a wash-out could be a diagnostic clue for recurrent HCC after PBT in a MRI study using gadopentetate dimeglumine (Gd-DTPA).¹⁵ Conversely, Ahmadi *et al* showed preservation of arterial enhancement in dynamic CT studies in HCC without recurrence for a period of 9–36 months after PBT.¹³ Therefore, tumor contrast enhancement after PBT has remained a diagnostic dilemma for the assessment of local tumor recurrence.

Therefore, the purpose of this study was to investigate the association between LTC and tumor contrast enhancement on dynamic CT. We compared sequential changes in contrast enhancement between recurrent lesions and non-recurrent lesions, and sought to identify predictors for future local recurrence.

METHODS AND MATERIALS

The requirement for written informed consent was waived by the Institutional Review Board due to the retrospective nature of the study.

Patient acquisition

Among patients with HCC treated by PBT between January 2004 and December 2016, the data for patients who underwent CT scans at the same institution before and after PBT were retrieved. HCC was diagnosed on the basis of pathological or clinical characteristics.²⁰ The inclusion criteria were as follows: (i) followed up for more than 1 year after PBT; (ii) a baseline CT scan acquired within 3 months before PBT; and (iii) no other previous therapy performed on the PBT-treated lesion. We excluded patients with (i) HCC with baseline diameter >13 cm; (ii) HCC with PVTT in the baseline CT; and (iii) massive hepatic arterioportal (AP) shunts in the baseline CT. We chose a 1 year observation period as the selection criteria, because approximately 94% complete response could be achieved within 1 year after PBT.²¹

We classified recurrent and non-recurrent lesions according to the presence of local recurrence during the follow-up period. Local recurrence was defined as a lesion in the irradiated field that showed serial tumor growth on least three consecutive CT or MRI examinations. The diagnosis of local recurrence was confirmed on the basis of mutual agreement among three specialists: a radiation oncologist, a gastroenterologist, and a diagnostic radiologist. The requirement for lesion biopsy to confirm pathological recurrence was waived. The date of recurrence was defined as the day when the CT scan was taken in which the clinical diagnosis of local recurrence was made.

Irradiation procedure

We used the PROBEAT series (Hitachi, Ltd., Japan) for PBT, and the treatment plans were generated in a treatment planning system, VQA (Hitachi, Ltd.). Treatment planning was performed on respiratory phase-gated CT images acquired at 2.5- or 5 mm intervals during the end of the expiratory phase.²² Immobilization of each patient was ensured by using a custom-made body cast (ESFORM; Engineering System, Matsumoto, Japan). The clinical target volume was homogeneously covered with more than 95% of the prescribed dose using the passive scattering proton treatment technique. Proton dosimetry was verified using a plastic phantom before PBT treatment.²³ Irradiation protocols were classified into three regimens depending on the tumor location: (i) a total dose of 77.0 GyE in 35 fractions for tumors located within 2 cm of a gastrointestinal organ, (ii) a total dose of 72.6 GyE in 22 fractions for tumors located within 2 cm of the porta hepatis, and (iii) a total dose of 66.0 GyE in 10 fractions for peripheral tumors located >2 cm from both the GI tract and porta

hepatitis. The maximum cumulative dose was set below 50 GyE for the spinal cord, stomach, and duodenum; it was set below 60 GyE for the colon.²⁴

All patients received PBT for 5 days each week. Equivalent dose in 2 Gy fractions (EQD₂) was calculated using the following formula.

$$\text{EQD}_2 = nd \frac{d+\alpha/\beta}{2+\alpha/\beta}$$

(n: total fraction (fr), d: dose per fraction (Gy), $\alpha/\beta = 10$ (Gy))

CT scanning parameters and CM infusion protocols
CT examinations were performed in the supine position during inspiration breath-hold by using multirow detector CT scanners with 256, 64, or 16 detector rows (Brilliance iCT 256, 64, 16, or Mx8000 IDT 16, Philips Medical Systems, Best, the Netherlands). The collimation width was 0.625 or 1.5 mm. The beam pitch was 0.45–0.90. Contrast medium (CM) with 600 mg I/kg was delivered, followed by 30 ml of saline solution. Unenhanced image (native phase: NP) and three-phase contrast-enhanced images were acquired. A bolus-tracking technique was used to time the start of scanning. After attenuation of abdominal aortic blood reached 150 Hounsfield units (HU), the hepatic arterial phase (HAP), portal venous phase (PVP), and equilibrium phase (EP) were automatically initiated. The initiation timing of HAP varied depending on the CT scanner (ranging from 10 to 15 s); the initiation timings of PVP (50 s) and EP (160 s) were fixed.

Image analysis

The analysis was performed by mutual agreement between two radiologists (HT with 8 years of experience and KM with 25 years of experience). We used 5 mm axial slice images. The diameter of the lesion was measured, as were the attenuation values of the lesions and the irradiated liver parenchyma. The attenuation was measured using the largest measurable region of interest (ROI) (Figure 1b). The minimum diameter of the ROI was defined as 3 mm. The ROI of irradiated liver parenchyma was set in the area presumably covered by more than 90% of the prescribed dose. The ROI was placed based on agreement by the two radiologists to ensure reproducibility of the results. If the lesion could not be distinguished from the surrounding irradiated parenchyma in all four phases in a designated observation period, the lesion was defined as “disappeared” and excluded from analysis in that period. Follow-up CT scans performed after confirmation of local recurrence were excluded from measurement.

Indicators for predicting long-term local recurrence

The relative HCC size was defined as the ratio of the diameter in follow-up CT to that in baseline CT. The attenuation difference between the irradiated HCC and the irradiated parenchyma (AD_{HCC-IP}) was calculated by subtracting the attenuation of the irradiated liver parenchyma from that of the irradiated HCC (Figure 1a,b). Five indicators were used for analysis: relative HCC size, and AD_{HCC-IP} at NP, HAP, PVP, and EP. We evaluated whether each indicator demonstrated a significant difference between recurrent and non-recurrent lesions at 13–24 months.

Table 1. Lesion characteristics

	Recurrent lesions			Non-recurrent lesions			p value
Total number	17			34			
Numbers in each period ^a	Total	Measurable	Disappeared	Total	Measurable	Disappeared	
1–3 months	9	9 (100)	0 (0)	16	16 (100)	0 (0)	N/A
4–6 months	15	15 (100)	0 (0)	24	22 (91.7)	2 (8.3)	0.257
7–12 months	15	14 (93.3)	1 (6.7)	28	23 (82.1)	5 (17.9)	0.319
13–24 months	12	11 (91.7)	1 (8.3)	33	26 (78.8)	7 (21.2)	0.323
25–36 months	6	6 (100)	0 (0)	23	16 (69.6)	7 (30.4)	0.127
≥37 months	4	4 (100)	0 (0)	13	7 (53.8)	6 (46.2)	0.101
Male ^a	13 (76.5)			23 (67.6)			0.517
Age at PBT initiation, years ^{b, c}	71.9 ± 9.6 (55–90)			72.8 ± 7.6 (54–85)			0.752
Tumor diameter at PBT initiation, mm ^{b, c}	34.8 ± 19.2 (14–88)			29.9 ± 16.5 (6–73)			0.326
Median follow-up time after PBT initiation, days ^c	1069 (374–2402)			1091.5 (418–2923)			0.892
Median local recurrent time after PBT initiation, days ^c	497 (189–2270)						
Median Child-Pugh score at PBT initiation ^c	5 (5–8)			5.5 (5–10)			0.591
EQD ₂ ^{b, c}	82.1 ± 6.5 (74.0–91.3)			86.1 ± 6.4 (75.0–94.5)			0.046

EQD₂, equivalent dose in 2 Gy fractions; PBT, proton beam therapy; SD, standard deviation.

^aNumbers in parentheses are percentages.

^bMean ± SD.

^cNumbers in parentheses are ranges.

Figure 2. (a-d) The relative attenuation of the lesion to the irradiated parenchyma in the (a) NP, (b) HAP, (c) PVP, and (d) EP. Relative attenuation is the difference between the average CT value (HU) for the lesion and the average CT value (HU) for the irradiated parenchyma. (e) Relative HCC size change after PBT in recurrent lesions and non-recurrent lesions. Relative HCC size was the ratio of the size in the follow-up CT to that in the baseline CT. Disappeared lesions were excluded from the analysis. * $p < 0.05$. ** $p < 0.01$. Error bar indicates $\pm$ standard error. EP, equilibrium phase; HAP, hepatic arterial phase; HCC, hepatocellular carcinoma; HU, Hounsfield unit; NP, native phase; PBT, proton beam therapy

Figure 3. Kaplan–Meier plot for the LTC rate of the PBT-treated HCC. Two groups were classified according to the value of AD_{HCC-IP} at 13–24 months in PVP. Cut-off value calculated from the Youden index was -55 HU. Among lesions with AD_{HCC-IP} at 13–24 months in PVP ≥ -55 HU, 10 of 23 showed local recurrence; 3 year and 5 year LTC rates were 0.64 and 0.56. Among lesions with AD_{HCC-IP} at 13–24 months in PVP < -55 HU, 1 of 14 showed local recurrence; 3 year and 5 year LTC rates were 0.93 and 0.93. HCC, hepatocellular carcinoma; HU, Hounsfield unit; LTC, local tumor control; PBT, proton beamtherapy; PVP, portal venous phase.

For the significant indicators, LTC rates were calculated using the cut-off value estimated on the basis of the Youden index.

Statistical analysis

Paired *t*-tests were used to assess the age at PBT initiation, tumor diameter at PBT initiation, follow-up time after PBT initiation, and EQD₂ between recurrent and non-recurrent lesions. The Mann–Whitney *U* test was used to compare sex, the rates of disappeared lesions in each period, and Child–Pugh score at PBT initiation between recurrent and non-recurrent lesions. The Mann–Whitney *U* test was used to compare HCC size and AD_{HCC-IP} at NP, HAP, PVP, and EP in each period between recurrent and non-recurrent lesions. LTC rate was reported using the Kaplan–Meier method. All data were analyzed with the statistical software R (v. 3.3.2). Differences with $p < 0.05$ were considered to be statistically significant.

RESULTS

Among 1181 HCCs treated by PBT between January 2004 and December 2016, 96 lesions underwent CT scans at the same institution before and after PBT. Other lesions underwent baseline or follow-up examinations at other hospitals, or underwent MRI without CT scan as baseline or follow-up study. 83 of 96 lesions were followed up for more than 1 year after PBT. 81 of 83 lesions underwent baseline CT scan within 3 months before PBT. 68 of 81 lesions had no other previous therapy performed on the PBT-treated lesion. Among 68 lesions, 2 lesions with baseline diameter >13 cm, 8 lesions with PVT in the baseline CT, and 7 lesions with massive AP shunt in the baseline CT were excluded. Finally, 51 lesions in 48 patients were retrieved for this analysis, including 17 recurrent lesions and 34 non-recurrent lesions. 15 patients had 1 recurrent lesion, 30 had 1 non-recurrent lesion, 2

had 1 recurrent lesion and 1 non-recurrent lesion, and 1 had 2 non-recurrent lesions.

The characteristics of the two groups are summarized in Table 1. The lesion diameter on baseline CT examinations ranged from 14 to 88 mm with a mean $\pm$ standard deviation (SD) of 34.8 ± 19.2 mm in recurrent lesions, and 6 to 73 mm with a mean $\pm$ SD of 29.9 ± 16.5 mm in non-recurrent lesions ($p = 0.326$). The follow-up time after PBT initiation ranged from 374 to 2402 days (median, 1069 days) in recurrent lesions, and 418 to 2923 days (median, 1091.5 days) in non-recurrent lesions ($p = 0.892$). The time until appearance of local recurrence after PBT initiation ranged from 189 to 2270 days (median, 497 days). The Child–Pugh score at PBT initiation ranged from 5 to 8 (median, 5) in recurrent lesions, and 5 to 10 (median, 5.5) in non-recurrent lesions ($p = 0.591$). EQD₂ ranged from 74.0 to 91.3 GyE with a mean $\pm$ SD of 82.1 ± 6.5 GyE in recurrent lesions, and 75.0 to 94.5 GyE with a mean $\pm$ SD of 86.1 ± 6.4 GyE in non-recurrent lesions. The difference in EQD₂ between recurrent and non-recurrent lesions was statistically significant ($p = 0.046$).

The number of lesions during each period after PBT is summarized in Table 1. 11 of 17 recurrent lesions and 26 of 34 non-recurrent lesions were measurable at 13–24 months. Five recurrent lesions were diagnosed as recurrence before 1 year. One recurrent lesion temporarily disappeared at 13–24 months. Seven non-recurrent lesions temporarily disappeared at 13–24 months. One non-recurrent lesion was not assessed by follow-up CT during 13–24 months after PBT.

AD_{HCC-IP} in NP, HAP, PVP, and EP is plotted in Figure 2a–d. AD_{HCC-IP} of recurrent lesions demonstrated significantly greater

Figure 4. A recurrent case involving a 79-year female patient who underwent PBT with 66 GyE, 10 fractions. (a) A CT image of PBT planning. (b) Sequential CT images after PBT initiation. Note that the contrast enhancement remained in HAP, PVP, and EP at 13–24 months. AD_{HCC-IP} was -8.0 HU in NP, -21.0 HU in HAP, -21.0 HU in PVP, and -8.0 HU in EP at 13–24 months. Relative HCC size was 30.4% at 13–24 months. The recurrence was confirmed at 1080 days after PBT. The recurrent lesion showed confluent multinodular type with peripheral enhancement pattern. EP, equilibrium phase; HAP, hepatic arterial phase; HCC, hepatocellular carcinoma; HU, Hounsfield unit; NP, native phase; PBT, proton beam therapy.

attenuation than that of non-recurrent lesions at 25–36 months ($p = 0.001$) and ≥ 37 months ($p = 0.029$) in HAP; at 13–24 months ($p = 0.039$), 25–36 months ($p = 0.017$), and ≥ 37 months ($p = 0.012$) in PVP; and at 25–36 months in EP ($p = 0.027$). The relative HCC size is plotted in Figure 2e. Differences in relative HCC size between recurrent and non-recurrent lesions were not statistically significant during any period.

Among the five indicators (relative HCC size and AD_{HCC-IP} at NP, HAP, PVP, and EP), only AD_{HCC-IP} at PVP showed a significant difference between recurrent and non-recurrent lesions at 13–24 months. AD_{HCC-IP} of recurrent lesions [mean, -21.8 Hounsfield units (HUs); from -95 to -31 HU] was significantly greater than that of non-recurrent lesions (mean, -51.7 HU;

from -117 to -12 HU) at 1–2 years in PVP ($p = 0.039$). The cut-off value, estimated on the basis of Youden index, was -55 HU. A Kaplan–Meier plot for the LTC rate of two groups, classified according to the cut-off value, is shown in Figure 3. Among lesions with AD_{HCC-IP} at 13–24 months in PVP ≥ -55 HU, 10 of 23 showed local recurrence; 3 year and 5 year LTC rates were 0.64 and 0.56. Among lesions with AD_{HCC-IP} at 13–24 months in PVP < -55 HU, one of 14 showed local recurrence; 3 year and 5 year LTC rates were 0.93 and 0.93. Sensitivity, specificity and accuracy were 0.91, 0.50, and 0.62, respectively. Sequential CT images after PBT are shown in Figures 4 and 5. A case of a recurrent lesion and its PBT planning is shown in Figure 4a,b; a case of a non-recurrent lesion and its PBT planning is shown in Figure 5a,b.

Figure 5. A non-recurrent case involving a 68-year male patient who underwent PBT with 74 GyE, 37 fractions. (a) A CT image of PBT planning. (b) Sequential CT images after PBT initiation. Note that the contrast enhancement was reduced in the HAP, PVP, and EP at 13–24 months after PBT. AD_{HCC-IP} was -23.0 HU in NP, -53.0 HU in HAP, -110.0 HU in PVP, and -62.0 HU in EP at 13–24 months. Relative HCC size was 50.0% at 13–24 months. Recurrence was not observed throughout the observation period (904 days after PBT). EP, equilibrium phase; HAP, hepatic arterial phase; HCC, hepatocellular carcinoma; HU, Hounsfield unit; NP, native phase; PBT, proton beam therapy

AD_{HCC-IP} at 13–24 months of PVP was -21.0 HU in the recurrent case, whereas it was -110.0 HU in the non-recurrent case.

DISCUSSION

We investigated whether radiologic CT parameters, including the relative size change of the HCC from baseline CT and the attenuation difference between the irradiated HCC and irradiated parenchyma after PBT, could be useful for prediction of local recurrence of HCC after treatment with PBT. We demonstrated that AD_{HCC-IP} in PVP at 1–2 years after PBT initiation was a useful predictor of recurrence. The cut-off value of -55 HU showed high sensitivity (0.91) and medium specificity (0.50). Therefore, this cut-off value is especially useful for the screening of future local recurrence. The risk of future local recurrence

could be predicted to be low if the AD_{HCC-IP} of the lesion was < -55 HU in PVP at 1–2 years after PBT. In contrast, if the lesion showed preserved enhancement in PVP at 1–2 years after PBT, further attention was needed due to the ambivalent potential for future tumor growth.

Our study demonstrated the usefulness of PVP as an early predictor for recurrence, compared to HAP and EP. The difference of AD_{HCC-IP} between recurrent lesions and non-recurrent lesions in HAP and EP was not significant at 1–2 years, although it was significant at >2 years. Previous studies demonstrated that radiation-induced hepatic injury causes venous occlusion.^{14,25} As a result, the portal vein becomes the draining vein, and the irradiated liver parenchyma is supplied only by arterial

blood.^{14,25} We speculate that the timing of the peak enhancement of irradiated HCC might be delayed to PVP, rather than HAP, due to the delayed arterial supply to the tumor caused by the radiation-induced venous occlusion. Furthermore, coexistence of fibrotic change in HCC after PBT might result in the delayed peak enhancement of the irradiated tumor. We considered that these factors might overlap to cause the enhancement difference between viable and non-viable tumors in PVP in early period after PBT.

Tumor size is another important indicator for assessing PBT-treated HCC. Serial tumor regrowth strongly suggests local recurrence, and we adopted this as our definition of local recurrence. However, our study revealed that the relative change in HCC size from baseline CT did not significantly differ in any period between recurrent and non-recurrent lesions. Thus, the attenuation difference between irradiated HCC and irradiated parenchyma is a more useful indicator for predicting local recurrence than relative HCC size.

Disappearance of the lesion is also an important factor for assessing recurrence. Among recurrent lesions, only one showed temporary disappearance at 9–24 months. Among non-recurrent lesions, the number of disappeared lesions increased with elapsed time after PBT initiation: 0% at 1–3 months, 8.3% at 4–6 months, 17.9% at 7–12 months, 21.2% at 13–24 months, 30.4% at 25–36 months, and 46.2% at ≥ 37 months. Thus, disappearance of the lesion suggests that it is well-controlled, although significant differences were not observed in this study.

In our study, non-recurrent lesions showed significantly greater EQD₂ than recurrent lesions ($p = 0.046$). This result suggests an increased risk of recurrence in PBT-treated HCC located adjacent to gastrointestinal organs, because the EQD₂ of the irradiated protocol might be reduced. Therefore, radiologists should consider the tumor location when judging recurrence of PBT-treated HCC.

It has been reported that the CT appearances of irradiated liver parenchyma by stereotactic body radiotherapy (SBRT) are related to background liver function.²⁶ The complete response rate according to the modified Response Evaluation Criteria in Solid Tumors increased during a 2 year follow-up period in patients with hypervascular HCC treated by SBRT.²⁷ In our study, there were no significant differences in liver function

between the recurrent and non-recurrent groups, suggesting only a small influence of liver function in calculating the cut-off value of AD_{HCC-IP} in PVP. Furthermore, our study revealed that future local recurrence could be predicted by tumor contrast enhancement before the 2 year follow-up period. It is necessary to investigate whether our findings could also be applicable to the patients with HCC treated by SBRT.

This retrospective study had several limitations. First, the timing of the HAP was slightly variable, ranging from 10 to 15 s after bolus tracking reached the threshold. We retrieved patient data over a period of >10 years, and slight differences in the CM injection protocol were unavoidable. Second, we did not confirm the pathological diagnosis of local recurrence. In an actual clinical setting, the diagnosis of recurrence is not necessarily proven by biopsy; here, it was made according to imaging findings and clinical information. Third, the factors affecting LTC in our study showed some divergence from those of a previous study, in which the 5 year LTC was 94%, 87%, and 75% with CP grades A, B, and C, respectively,⁵ as well as a previous study in which three protocols with different irradiation doses showed no significant difference in LTC.³ This could be partly explained by the cohort inclusion criteria of our study, such that patients were observed in the same institution where PBT was performed. Finally, the specificity was not high for the prediction method using AD_{HCC-IP} in PVP at 1–2 years after treatment. Although a multi-parameter prediction model using AD_{HCC-IP} in other phases and adjusted for changes in size would be more helpful, multivariate analysis was not possible due to the small number of patients in this study. Further analysis is needed using a larger population.

CONCLUSION

The residual contrast enhancement of HCC in PVP at 1–2 years after PBT may be useful to assess the risk of recurrence. The risk of future local recurrence may be low if the AD_{HCC-IP} of the lesion was < -55 HU in PVP at 1–2 years after PBT. Disappearance of the lesion after PBT also suggests that the lesion is well-controlled.

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