Three cases of hepatocellular carcinoma treated 4 times with proton beams

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Abstract. HCC may recur following surgery or radiofrequency ablation. Proton beam therapy (PBT) is a type of radiotherapy that achieves excellent local control of HCC without severe toxicity. The present study reported the long-term outcome of 3 HCC patients who each received 4 repeat courses of PBT. All patients had a hepatitis B or C viral infection. A total of 14 lesions were treated using a curative PBT protocol and irradiated liver volumes in each treatment were 7-50% of the total liver volume. Liver function in all cases was considerably preserved until the last follow-up and patient survival was 51-107 months from the first PBT with no local recurrence observed in the 14 lesions. The presented cases indicated that repeated PBT is an effective treatment option for recurrent HCC due to reduced liver damage and superior local treatment compared with other treatment options such as transarterial chemoembolization.

Introduction

Worldwide, hepatocellular carcinoma (HCC) is the fifth most frequent cancer among men and the seventh among women. It frequently occurs in East Asia and Africa because of the high incidence of hepatitis infection in these regions (1). To address this disease, various treatment methods, curative and non-curative, have been developed based on factors such as liver function, tumor burden, and tumor size. For patients with single or up to three nodules of HCC, local treatment such as surgery or radiofrequency ablation (RFA) is the standard choice.

HCC is frequently comorbid in the cirrhotic liver with chronic hepatitis B or C virus (HBV or HCV) infections that cause HCC recurrence even after curative local treatment has been performed and local control have been achieved. A 2011 report indicated that the risk of HCC recurrence in the liver within five years after liver resection or RFA amounts to 70% (1). This recurrence pattern has two types, multicentric and intrahepatic (2), which force HCC patients to receive repeated treatments every few months or years.

Proton beam therapy (PBT) is a radiotherapy characterized by ultra-precise delivery of high dose radiation that limits off-target energy. HCC is one of the diseases to which PBT is often applied for treatment (3-5). PBT was started in our facility in 1983 and the current facility has been dedicated to clinical research and practice since 2002. We have since treated approximately 1400 HCC patients using proton beams and have demonstrated that PBT has the ability to achieve excellent local control of HCC without severe toxicity in several scientific reports (6-8). Among those patients, a total of 160 patients have subsequently received repeated PBT as of 2017 and the maximum number of treatment courses delivered has been 4 times in 3 of those patients. Although local treatment effect has been demonstrated in many reports, intrahepatic recurrence is as important an issue for PBT as other local treatments. In cases of single or few recurrent tumors, PBT is one of the local treatment options. However, as the number of treatments increase, cumulative dosages elevate and overlap of dose distribution in many organs would cause various clinical issues such as liver dysfunction, digestive tract/skin ulcers, and bile duct stenosis. However, in spite of the importance of this issue, it is poorly understood how repeated PBT affects the prognosis and treatment-derived side effects to the various organs from past studies of PBT. For this reason, we here describe the long-term treatment outcomes in patients who each received the maximum number of 4 courses of repeated PBT. The present study was approved by Institutional Research Committee of the University of Tsukuba (approval no. H28-101).

Case 1

A 60-year-old man with HCV infection had HCC with a maximum diameter of 1.2 cm in S4. PBT was performed using the respiratory-gating technique with an irradiation dose of 66 gray relative biological effectiveness [Gy (RBE)] in

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10 fractions over 22 days. A second PBT round for a new 2.2 cm diameter tumor in S7 was performed 12 months later [66 Gy (RBE)] in 10 fractions over 14 days). The third PBT course for a new 1.5 cm diameter tumor in S3 was performed 10 months after the second PBT round [72.6 Gy (RBE)] in 22 fractions over 31 days). A fourth and final PBT course for a new 1.6 cm diameter tumor in S5 was performed 21 months after the third PBT round [66 Gy (RBE)] in 10 fractions over 14 days) (Fig. 1A). Note that we took great care to minimize irradiation field overlap during all courses in all patients. The total liver volume was 1286 cm^3 at the first PBT while the irradiated liver volumes {an absolute volume of >1.0 Gy (RBE) delivery [$V_{1.0\ Gy\ (RBE)}$]} over the four treatments were 90, 176, 115 and 442 cm^3, respectively (Fig. 1B). Serum concentrations of aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin (Alb) and total bilirubin (T. Bil) showed no significant changes during follow up (Fig. 1C). The Child-Pugh classification remained class A and no acute or late treatment-related toxicity events of grade 2 or more (according to the Common Terminology Criteria for Adverse Events, version 4.03) were observed until the last follow-up 16 months after the fourth PBT (60 months from the first PBT). A multiple intrahepatic recurrence developed 22 months after the fourth PBT (66 months from the first PBT). Alpha-fetoprotein (AFP) and Des-gamma carboxyprothrombin (DCP) remained mainly below 100 mg/ml and 100 mAU/ml, respectively, during follow up (Fig. 1D). This patient died a total of 96 months after the first PBT.

Case 2

A 69-year-old man with HBV infection had an HCC of 3 cm in diameter in S8 and 4.5 cm in S6 and had already received transarterial chemoembolization (TACE) 5 times before consulting our hospital. PBT was performed simultaneously for the tumors in S8 [66 Gy (RBE) in 10 fractions over 15 days] and S6 [77 Gy (RBE) in 35 fractions over 57 days] and we confirmed that the two irradiation fields did not overlap. A second PBT course for a new 2.7 cm diameter tumor in S8 was performed 25 months later [77 Gy (RBE) in 35 fractions over 57 days]. A third PBT round for a new 1.8 cm diameter tumor in S8 was performed 14 months after the second PBT [72.6 Gy (RBE) in 22 fractions over 34 days]. In this treatment, beams were delivered from the back to avoid overlapping the first irradiation field, although a right lateral beam could have greatly reduced the irradiation dose of the right lung field. The fourth and final PBT for a recurrent tumor of 7 cm in diameter in S7/8 with inferior vena cava tumor thrombosis was performed 8 months after the third PBT course [66 Gy (RBE) in 10 fractions over 56 days] (Fig. 2A). The total liver volume was 1073 cm^3 at the first PBT while the irradiated liver volumes over the four treatments were 260, 221, 114 and 330 cm^3, respectively (Fig. 2B). Unirradiated volume in the liver throughout all treatment was 320 cm^3. Serum concentrations of ALT showed no significant changes but AST and T. Bil increased and Alb showed a reduced, albeit mild trend which was noticeable after the fourth treatment (Fig. 2C). The Child-Pugh classification remained class A and no acute or late treatment-related toxicity events of grade 2 or more were observed. A multiple intrahepatic recurrence appeared at 4 months after the fourth PBT (50 months from the first PBT). AFP was largely decreased after first PBT and rapidly increased after the second PBT. AFP once decreased from 2005 to 999 mg/ml during the fourth PBT but rebounded after that then reached 1789 mg/ml 5 months after the fourth PBT. DCP showed a similar pattern (Fig. 2D). This patient died 51 total months after the first PBT.

Case 3

A 51-year-old man with HCV infection had multiple HCC (1 cm in diameter in S5 and 1 cm in diameter in S6). PBT for both tumors were performed simultaneously [66 Gy (RBE) in 10 fractions over 15 days] and we confirmed that the two irradiation fields did not overlap. A second PBT round was then performed for a new 2 cm diameter tumor in S8 10 months later [66 Gy (RBE) in 10 fractions over 16 days]. In this treatment, beams were delivered from the front and right back to avoid overlapping the first irradiation field, although a right lateral beam could have greatly reduced the irradiation dose of the liver. A third PBT course for a new 3 cm diameter tumor in S4 was performed 4 months after the second PBT [66 Gy (RBE) in 10 fractions over 16 days]. The fourth and final PBT course for a new 4 cm diameter tumor in S8 was performed 27 months after the third PBT [72.6 Gy (RBE) in 22 fractions over 36 days] (Fig. 3A). The total liver volume was 1624 cm^3 at the first PBT while the irradiated liver volumes over the four treatments [$V_{1.0\ Gy\ (RBE)}$] were 225, 388, 177 and 295 cm^3, respectively (Fig. 3B). Total liver volume was dramatically altered by the repeated atrophy of the irradiation site and compensatory hypertrophy of the normal liver. AST and ALT showed a downward trend while Alb and T. Bil showed no significant changes (Fig. 3C). The Child-Pugh classification remained class A and no acute or late treatment-related toxicity events of grade 2 or more were observed until the last follow-up 60 months after the fourth PBT (101 months from the first PBT). A multiple intrahepatic recurrence appeared at 61 months after the fourth PBT (102 months from the first PBT). AFP and DCP showed no relatively big changes mainly at levels below 100 mg/ml and 100 mAU/ml, respectively, until the fourth PBT, but there was a rapid and large increase after that (Fig. 3D). This patient died 107 months after the first PBT.

Discussion

There are some reports which refer to outcomes multiple treatment courses for HCC patients. Nishikawa *et al* (9) reported that overall survival rates of 130 relapsed patients treated with repeated-RFA were not significantly different to those of 150 non-relapsed patients after RFA. Joliat *et al* (10) analyzed 67 patients with recurrent HCC after hepatectomy and found that the median survival time for patients receiving surgery, RFA or TACE was 77 months but it was 20 months for patients receiving chemotherapy or palliative care. Additionally, the survival period of those patients who received surgery/RFA/TACE was not significantly different from non-relapsed patients (10). These reports demonstrate that long-term survival can be obtained if sufficient local control is achieved in spite of HCC recurrence. However, patients were treated no more than twice in most of the published reports and there are very few reports on the survival period after multiple treatment courses for HCC.

While our facility commonly encounters HCC patients with multiple treatment histories, a lack of literature on this topic

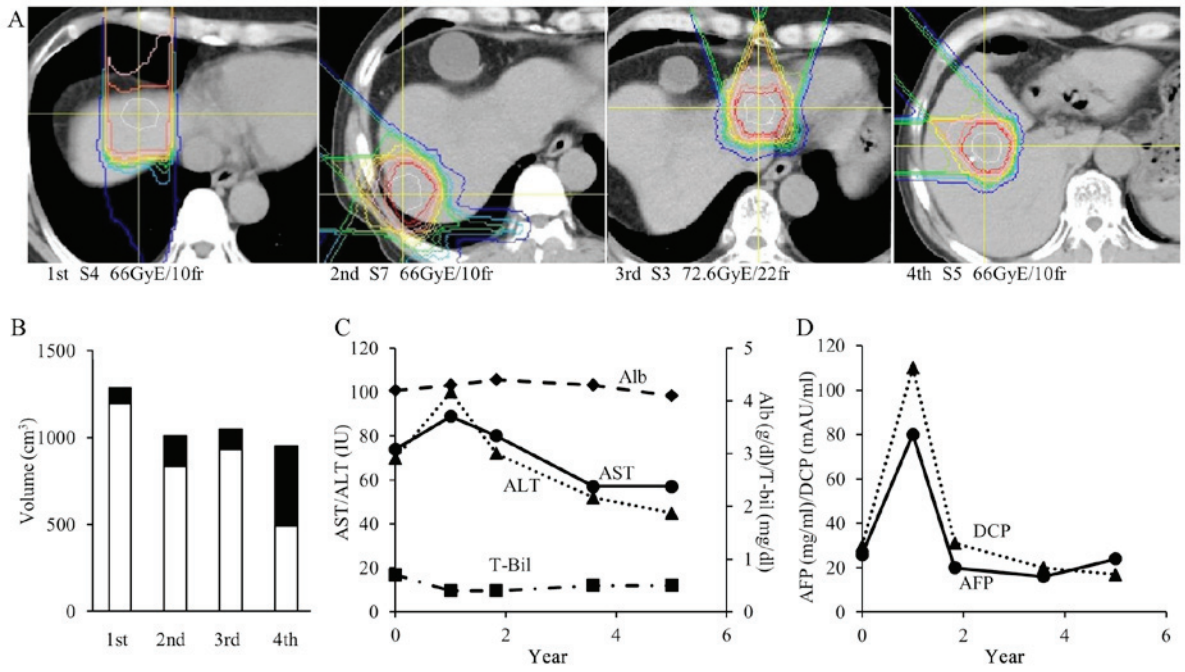

Figure 1. A 60-year-old male patient with hepatocellular carcinoma. (A) Dose distribution image of each treatment. Dose lines represent 95-10% of the isocenter dose from inside to outside. (B) Liver volume at each proton beam therapy. Irradiated volume represents an absolute volume of >1.0 Gy (RBE) delivery in the liver [$V_{1.0\ Gy\ (RBE)}$]. Unirradiated volume represents an absolute volume <1.0 Gy (RBE) delivery in the liver. (C) Change of liver function. AST, ALT, Alb and T. Bil values following each treatment session and the last follow-up are presented. (D) Change of tumor markers. AFP and DCP values at each treatment session and last follow-up are presented. GY, gray; RBE, relative biological effectiveness; AST, aminotransferase; ALT, alanine aminotransferase, Alb, albumin; T. Bil, total bilirubin; AFP, alpha-fetoprotein; DCP, Des-gamma carboxyprothrombin; S, couinaud liver segment.

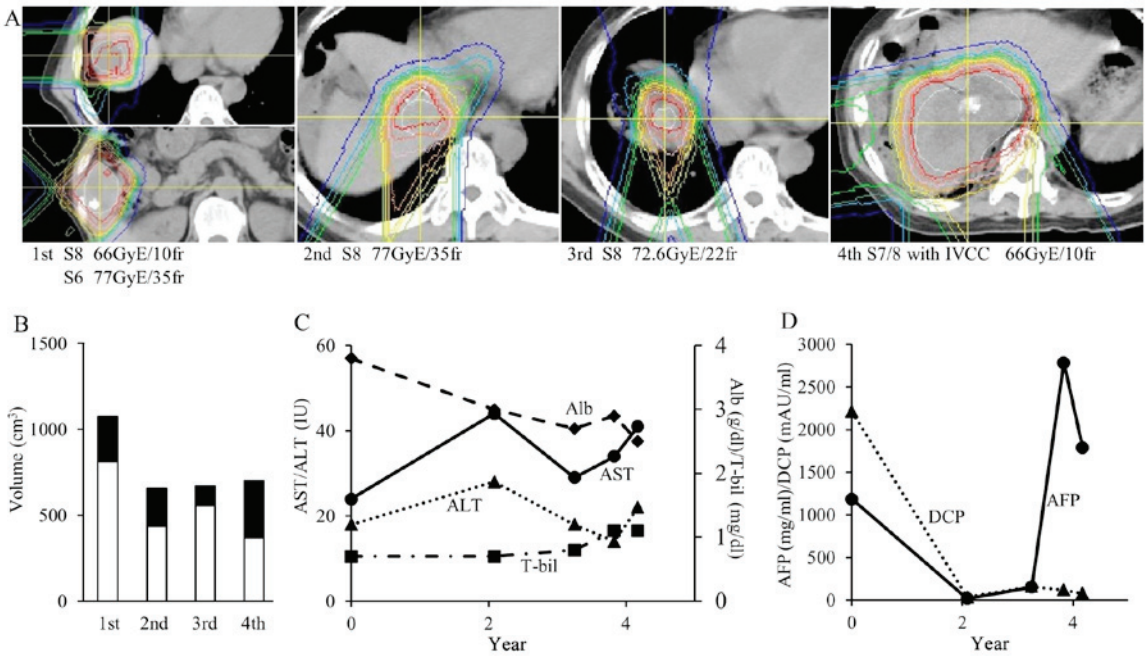

Figure 2. A 69-year-old male patient with hepatocellular carcinoma. (A) Dose distribution image of each treatment. Dose lines represent 95-10% of the isocenter dose from inside to outside. (B) Liver volume at each proton beam therapy. (C) AST, ALT, Alb and T. Bil values following each treatment session and the last follow-up are presented. (D) Change of tumor markers. AFP and DCP values at each treatment session and last follow-up are presented. AST, aminotransferase; ALT, alanine aminotransferase, Alb, albumin; T. Bil, total bilirubin; AFP, Alpha-fetoprotein; DCP, Des-gamma carboxyprothrombin; GY, gray; RBE, relative biological effectiveness; S, couinaud liver segment.

adds to the difficulty of accurately predicting patient outcomes. Although (to the best of our knowledge) there are no reports of repeated conventional photon radiotherapy treatments in HCC patients, Lo *et al* (11) reported the outcome of repeated stereotactic body radiotherapy (SBRT) in 14 HCC patients. The median first treatment dose was 41 Gy and second treatment dose was 40 Gy, leading to 1 and 2-year progression free survival rates of 68.6 and 42.9%, respectively, and 1 and 2-year overall

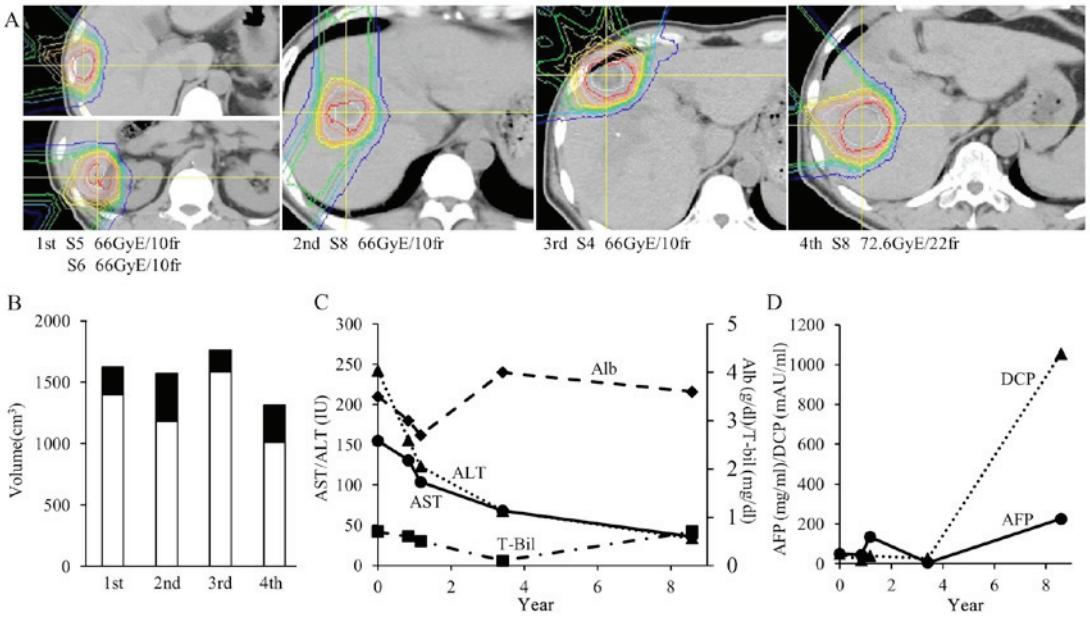

Figure 3. A 51-year-old male patient with hepatocellular carcinoma. (A) Dose distribution image of each treatment. Dose lines represent 95-10% of the isocenter dose from inside to outside. (B) Liver volume at each proton beam therapy. (C) AST, ALT, Alb and T. Bil values following each treatment session and the last follow-up are presented. (D) Change of tumor markers. AFP and DCP values at each treatment session and last follow-up are presented. AST, aminotransferase; ALT, alanine aminotransferase, Alb, albumin; T. Bil, total bilirubin; AFP, Alpha-fetoprotein; DCP, Des-gamma carboxyprothrombin; GY, gray; RBE, relative biological effectiveness; S, couinaud liver segment.

survival rates of 76 and 59.1%, respectively. As for treatment effect, in-field recurrence happened in only 1 of the 18 tumors (5.6%) but one patient developed radiation-induced liver disease and three showed progression in Child-Pugh classification after their second treatment. Sanuki *et al* (12) reported that 4% of patients who received SBRT suffered from fatal hepatic failure within 12 months after SBRT and liver function and platelet count can predict liver failure. Data such as these therefore indicate that, although local control may be established, preservation of liver function is not always guaranteed (12).

The criteria of repeated PBT in our facility is exactly the same as the first PBT, namely that PS is 0-2, Child-Pugh classification is A-B and tumor number must be single or a few with an upper size limit of 15 cm. However, tumor location and vessel invasion only have a small influence on treatment adaptation. The existence of ascites requires more careful treatment planning, especially if the ascites amount is unstable. Maintenance of liver function is clinically very important for repeated PBT but all three patients in our study were positive for HBV or HCV, potentially impacting liver dysfunction. The irradiated volume for the 12 total irradiation events was 7-50% of the total liver volume, the summation of which corresponded to 51-91% of the total liver volume at the first treatment. Most published liver dosage tolerances are based on whole liver irradiation data (13,14) and available data relating liver tolerance to PBT are scarce. It is thought that liver function or irradiation volume affects radiation-induced liver dysfunction (15,16); however, no definite consensus has been reached because of sparse data and reports. We therefore defined our own dose constraint as an unirradiated liver volume of > 500 cm^3 based on our previous studies and clinical experience (15). However, the unirradiated volume is occasionally forced to be <500 cm^3 by repeat irradiation. In such cases, liver dosage and treatment protocol are determined by multiple considerations, including age, PS, liver function, treatment strategy, patient wishes, etc. (example: Case 2). It is fortunate that no severe side effects occurred in these 3 cases. Clarification of the ability of these 3 patients to tolerate PBT for 4 courses is important. Our precise dose calculation for each organ and careful treatment strategy may be responsible. Alternately, these patients might have had some pathological condition or constitution conducive to enduring repeated treatment. One possible common point was the maintenance of liver function over several years after the first PBT in spite of the repetitive treatment. Next, as far as observing the transition of the biomarkers in these 3 cases, viral hepatitis and cumulative dosage to the liver did little to affect the prognosis. In summation, although we cannot conclude how liver dysfunction was avoided from such a small cohort, further studies with higher patient numbers could shed light upon this issue.

We have previously reported the results of repetitive PBT for HCC at our facility. At the initial treatment center (1989-2000), we analyzed 27 cases and revealed that re-irradiation is safe if liver function is Child-Pugh class A and the target is located in a peripheral tumor (17). At the current center (2002-2010), 83 cases were analyzed and it was revealed that liver function tended to gradually decline as the number of irradiation events increased (18). As the number of treatment courses piles on top of cumulative dose elevation, the treatment effect becomes difficult to be predicted and risk to normal organs becomes higher. In general, this analysis features long-term follow-ups and descriptions of side effects for selected HCC patients receiving many repetitions of PBT, which differs from past studies of PBT for HCC. Moreover, this data lends credence to our recommendation that repeated PBT can be safely selected for the curative treatment of HCC.

There are some limitations in the current study. Various reports for liver dose tolerance exist but they are mostly based on the outdated concept of total liver irradiation, which may

not always apply to modern, locally high dose treatment. Another subject is deformation of the liver, which dramatically and non-uniformly deforms after PBT in patients with chronic liver disease (18,19). This means that our method of summing irradiated volumes by simply adding them together may be overly simplistic. However, it is technically difficult to correctly calculate cumulative dose distribution in deformed livers, highlighting the necessity to improve dose distribution calculation techniques which can overcome this limitation and establish the safety of repeated PBT.

Here, we reported on three HCC patients who each received 4 courses of PBT. Liver function was considerably preserved until final follow-up and long-term survival (>48 months) was achieved. We consider that PBT has the potential to be applied to recurrent HCC due to less liver damage and a superior local treatment effect. Repeated PBT can therefore be an effective treatment option for persistently recurring HCC.

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Availability of data and materials

All data and materials included in the present study are included in this published article.

Authors' contributions

MMu, NF, HS and TO wrote this manuscript and analyzed all of the data. NF, TO, HN, KM, KO, HI, KT and MMi provided medical care for the patients and collected the data. TO and HS revised the article. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by institutional research committee of University of Tsukuba (approval no. H28-101).

Patient consent for publication

Patient consent was obtained for publication.

Competing interests

The authors declare that they have no competing interests.

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