Proton Beam Therapy for Hepatocellular Carcinoma: A Review of the University of Tsukuba Experience

Masashi Mizumoto, PhD; Yoshiko Oshiro, PhD; Toshiyuki Okumura, PhD; Nobuyoshi Fukumitsu, PhD; Haruko Numajiri, PhD; Kayoko Ohnishi, PhD; Teruhito Aihara, PhD; Hitoshi Ishikawa, PhD; Koji Tsuboi, PhD; Hideyuki Sakurai, PhD

Department of Radiation Oncology, University of Tsukuba, Tsukuba, Ibaraki, Japan

Abstract

Hepatocellular carcinoma (HCC) is the second most common cause of cancer-related death worldwide. Many treatment modalities were developed for HCC, including surgical resection, percutaneous ethanol injection, radiofrequency ablation, transarterial chemoembolization, liver transplantation, and sorafenib therapy. Our institution has shown that proton beam therapy (PBT) is also a safe, effective, and feasible treatment modality for HCC. The University of Tsukuba began to use PBT for HCC in 1983, and we have reported many findings during the past 3 decades. In this review, we will describe the history of PBT, our experience of using PBT for HCC, and its application based on tumor location, thrombosis, tumor size, and liver function.

Introduction

Hepatocellular carcinoma (HCC) is a common malignancy worldwide. Surgical resection or ablative treatment is the preferred choice. However, HCC is often unresectable, and ablative treatment may not be possible for patients with a tendency to bleed from portal vein tumor thrombosis (PVTT). In addition, the liver has a low radiation tolerance and is at risk of radiation-induced liver disease (RILD) when irradiated, even at a low dose. Therefore, only stereotactic body radiation therapy (SBRT) can be used as a curative photon radiation therapy for small tumors.

Proton beam therapy (PBT) is a particle radiation therapy with an excellent dose distribution because of its energy peak, commonly referred to as the Bragg peak. At the University of Tsukuba, we began to use PBT for HCC in 1983, a time during which time-surgical resection was the only curative treatment. Our initial use of HCC was experimental, but the results were favorable; we now use PBT in 30% of our cases. In this review, we will describe our experience with PBT for HCC.

History of Proton Beam Therapy for Hepatocellular Carcinoma

We started to use PBT at our former facility, the National Laboratory for High Energy Physics (KEK) in 1983. At that time, partial liver irradiation was rarely conducted worldwide, and PBT was commonly applied to relatively small tumors, such as orbital or intracranial tumors, because of the limited range of penetration from low-energy protons. We launched an investigation of PBT as a treatment modality for deep tumors in the trunk...
by using high-energy 250-MeV protons, and we explored PBT for HCC among truncal tumors. Our predecessors at KEK believed that the liver was favorable for PBT because it is a homogeneous parenchymal organ. At KEK, there were few patients, and dose fractionation was irregular because of a limited availability or shortage of machine time. However, many cases that were not suitable for standard treatment at that time were treated with PBT.

Our first clinical trial for PBT was conducted from 1983 to 1990 and is described in Tsujii et al [1]. The authors presented outcomes of a phase I/II trial conducted to determine the appropriate site and dose. Sixteen patients with HCC were included in that trial. Most of those patients could not undergo surgical resection because of poor liver function or because they had multiple HCCs. The maximum tumor diameter was 10.5 cm, and the delivered dose was 66 to 96.8 gray equivalents (GyE; average, 86.7 GyE). The Child-Pugh score was found to be a significant factor for survival based on 2-year survival rates of 68% and 18% for Child-Pugh A and B or C cases, respectively. No patients with a Child Pugh score of A died of liver failure, whereas 71% of Child-Pugh B/C patients died of liver failure within 2 years after PBT. No patients developed grade 3 or higher radiation toxicities. These results suggested that high-dose local liver irradiation was effective for patients with a single HCC tumor < 10 cm and with a Child-Pugh score of A or B [1].

Soon after this report, Matsuzaki et al [2] described an analysis of 24 patients with 32 HCCs. The tumor dose was 55 to 95.7 GyE in 17 to 69 days, and all tumors were controlled during a 2-year follow-up period. At that time, tumor biopsy was performed before, and 3 weeks after, PBT. In a subsequent analysis of those tissue samples, Saito et al [3] found that the mean ± SD MIB-1 labeling index significantly decreased from 13.0 ± 8.5% to 3.2 ± 2.4% after PBT and that cases with a decreased labeling index were recurrence-free, based on imaging 1 year after PBT. In the first large study of PBT for HCC, Chiba et al [4] reviewed 162 patients treated from 1985 to 1998 and found 5-year survival and local control rates of 23.5% and 87%, respectively.

Onaya et al [5, 6] found that a dynamic study was useful for differential diagnosis of RILD and HCC, which had previously been difficult. Ahmadi et al [7] reported 4 cases of hypervascular HCC, with good preservation of the arterial blood supply on dynamic computed tomography, in which the tumor size gradually decreased after PBT. Ohara et al [8] found that the normal liver volume in the treatment field decreased exponentially after PBT, whereas the nonirradiated liver showed a compensatory hypertrophic change that was correlated with the normal liver volume in the treatment field.

Respiratory movement of the tumor was a significant problem to be overcome for performance of precise liver PBT. Ohara et al [9] developed a respiratory gating technique for photon radiation therapy using a linear accelerator and a suggested possible clinical application of gated radiation therapy for tumors located close to the diaphragm. Tsujii et al [10] introduced respiratory-synchronized fluoroscopy in the treatment room that was used to monitor real-time organ motion and to verify the best timing for gating. Implanting of fiducial markers adjacent to the tumor was developed to facilitate tumor localization by fluoroscopy, and respiratory-gated irradiation was put into practical use in 1991. Four-dimensional radiation therapy is now common, but, at that time, it was still a developing technology.

Our current facility, the Proton Medical Research Center, was opened in 2001. This facility is exclusively used for daily clinical treatment and is equipped with a rotating gantry that allows for starting protocol treatments. Daily multiportal irradiation finally became possible, whereas machine time was strictly limited back at the KEK with treatment paused for 1 week after every delivery of 11 fractions over 3 weeks. Only single-port irradiation was possible at the old facility. At the new facility, we started protocol treatment and analyzed the outcomes of patients treated at the KEK, including results of PBT used for challenging cases where standard treatment was generally not possible. From these experiences, we have expanded the availability of PBT for HCC patients.

**Equipment for Proton Beam Therapy**

Design of our new facility started in 1997, and it was opened for operation in 2001. The treatment room includes a rotation gantry equipped with many devices to prepare the treatment field, including use of double scattering and the availability of 3 collimators: a patient collimator to form the treatment field, another to reduce scattering of the proton and neutron beams, and a coarse, multileaf collimator. A ridge filter is used to spread the proton beams from 10 to 120 mm in a distal direction. A range shifter controls the beam terminus, and a bolus is made for each patient to form a distal shape. Two dose monitors on the gantry are used to control the absolute dose.

We started using respiratory gating in 1993 by using a laser-displacement sensor (LDS; Keyence, Osaka, Japan). The detailed mechanism was described by Tsunashima et al [11]. The motion of abdominal wall respiration is converted into a respiratory waveform, and a gating signal is given to the accelerator for irradiation when the waveform drops below a certain threshold. Real-time tumor-tracking radiation therapy has become a major method in photon radiation therapy, but this is still
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difficult for proton beams because the distal dose distribution changes rapidly with the displacement of tissue density from respiration and with the need to control beam energy during targeting.

Fluoroscopy is used for verification using 2 imaging intensifiers in the frontal and lateral views. For tumors that cannot be imaged by fluoroscopy, such as HCC and prostate cancer, a fiducial marker is inserted adjacent to the tumor. For accurate irradiation, the center of the beam and the imaging intensifier should be matched. Therefore, quality confirmation is performed once each week by the Winston-Lutz test. If the gap between the centers of fluoroscopy and the proton beam is > 1 mm, an adjustment is made.

Protocol Study according to Tumor Location

The ability to perform daily treatment at our new facility permitted the start of prospective protocol studies. Protocols were decided based on the tumor location because doses were limited by critical organs adjacent to the tumor. Bile duct stenosis is a severe problem after high-dose radiation therapy for a tumor in the hepatic portal region, with Chiba et al [4] finding that 3 of 162 patients (1.9%) experienced PBT-related bile duct stenosis at a dose of 79.2 GyE in 16 fractions and 92.4 GyE in 24 fractions. Therefore, we use 72.6 GyE in 22 fractions for these tumors. In 55 patients with HCC in the portal region, Mizumoto et al [12] found 3-year local control and overall survival rates of 86% and 50.0%, respectively, without severe late toxicities, including bile duct stenosis.

Gastrointestinal hemorrhaging, ulceration, and perforation are significant problems associated with the irradiation of HCC adjacent to the gastrointestinal tract; therefore, doses per fraction should be reduced for this type of tumor. In a study that included 47 patients with HCC located within 2 cm of the gastrointestinal tract, Nakayama et al [13] used doses of 72.6 GyE in 22 fractions and 77 GyE in 35 fractions with shrinkage of the treatment margin to reduce radiation to the gastrointestinal tract to 33 to 39.6 and 50.6 to 55 GyE for total doses of 72.6 and 77 GyE, respectively. The 3-year local control and survival rates were 88.1% and 50.0%, respectively, and gastrointestinal hemorrhage of grade 2 or 3 occurred in 4 patients (8.5%). In this study, the fractional dose was reduced from 3.3 to 2.2 GyE after grade 3 colon hemorrhaging occurred. It has been suggested that the high-dose region should be reduced to an even smaller volume [13].

In contrast to tumors located close to the gastrointestinal tract, dose escalation seems to be possible for a tumor located peripherally in the liver parenchyma. We have used 66 GyE in 10 fractions for tumors > 2 cm from the portal region or gastrointestinal tract, with 3- and 5-year local-control rates of 94.5% and 87.3%, respectively, and 3- and 5-year overall survival rates of 49.2% and 38.7%, respectively [14]. No RILD occurred in 51 patients, but 3 developed rib fractures. A V60 of the rib ≥ 4.48 cm³ was indicated to be a predictor of rib fractures [15].

Survival and local control rates did not differ significantly among the above protocols used at the Proton Medical Research Center. The average 3- and 5-year overall survival rates were 61% (95% confidence interval [95% CI], 53% to 68%) and 48% (81% to 97%), respectively, and the 3- and 5-year local control rates were 87% (81% to 97%) and 81% (68% to 94%), respectively [16]. In a dose escalation study of 27 patients, Kim et al [17] found that the complete response rate was significantly greater in patients who received 72 GyE in 24 fractions compared with those treated with 60 Gy in 20 fractions or 66 GyE in 22 fractions, and the 3-year local progression-free rate was significantly higher in patients who achieved complete response than it was in those who did not (P = .003). In 30 patients treated with 76 GyE in 3.8 GyE daily fractions 4 times each week, Kawashima et al [18] found 2-year local progression free and overall survival rates of 96% (95% CI, 88% to 100%) and 66% (48% to 84%), respectively, with 4 deaths due to hepatic insufficiency without tumor recurrence 6 to 9 months after PBT. In a phase II study in 76 patients with HCC using a dose of 63 GyE in 4.2 GyE in 15 fractions over 3 weeks, the median survival time was 36 months (95% CI, 30 to 42 months), with local treatment failure in 15 patients (20%) and mild treatment toxicity of grade 2 gastrointestinal ulceration or inflammation in 5 patients [19]. In a study of proton and carbon ion therapy for HCC, Komatsu et al [20] showed that both treatments achieved 5-year local control rates of ≥ 90%, with no significant difference between the 2 methods. The results of these studies are shown in Table 1.

Portal Vein Tumor Thrombosis and Inferior Vena Cava Tumor Thrombus

The prognosis of advanced HCC with PVTT or inferior vena cava is extremely poor, with a median survival of only 2 to 3 months without treatment [21–24]. Photon radiation therapy in combination with transarterial chemoembolization (TACE) has been used for these patients [25–29]. Radiation therapy at a total dose of 45 to 50 Gy was administered to the PVTT in combination with TACE for intrahepatic tumors. However, the target volume is large for PVTT, and dose escalation is difficult with photon radiation therapy. The 1- and 2-year overall survival rates were 25% to 45% and 10% to 25%, respectively, and median survival ranged from 5.3 to 8.0 months, with 2% to 26% of the patients having severe treatment toxicities, including gastrointestinal ulcers and bleeding.
Treatment of PVTT may be possible using proton beams because normal liver tissue can be preserved because of the excellent dose distribution. In a study of PBT for 12 patients with PVTT at our institution, the total dose was escalated to 50 to 72 Gy (a relative biological effectiveness value of 1.0 was used at that time) [29]. The median doses of 2 Gy per fraction-equivalent, calculated using a linear quadratic model with $\alpha/\beta$ ratios of 10 and 3 Gy were 66 and 80 Gy, respectively. All treated tumor thrombi were found to be controlled in a follow-up period ranging from 0.3 to 7.3 years with no toxicities above grade 3.

In a study using a uniform dose of 72.6 GyE in 22 fractions, Sugahara et al [30] found that 29 of 35 patients showed an objective response. The 2- and 5-year overall survival rates were 48% and 21%, respectively, with median survival of 22 months (range, 2 to 88 months) and no severe toxicities (Table 2).

Outcomes of PBT for inferior vena cava tumor thrombus (IVCTT) were first reported in 2007 [31]. Only 3 patients were included in the study, but the inferior vena cava was recanalized after treatment without severe toxicities in all 3 cases. The treatment doses were 50 Gy in 13 fractions (15 Gy in 3 fractions plus 35 Gy in 10 fractions), 50 Gy in 10 fractions, and 70 Gy in

### Table 1. Proton beam therapy for hepatocellular carcinoma.

| Source, y | Treatment | Patients, No. | Patient condition | Dose, GyE | Fractions | Median survival, mo | 1-y OS, % | 2-y OS, % | 3-y LC, % | Toxicity grade $\geq$ 3, % |
|-----------|-----------|---------------|-------------------|----------|-----------|---------------------|----------|----------|-----------|--------------------------|
| Bush et al [19], 2004 | Proton | 76 | Cirrhosis | 63 | 15 | 36 | NA | NA | NA | 0 |
| Komatsu et al [20], 2011 | Proton | 242 | NA | 52.8–84.0 | 4–38 | NA | 90 | 38 | 90.2 | 3 |
| Mizumoto et al [16], 2011 | Proton | 266 | NA | 66.0–77.0 | 10–35 | 50.6 | 87 | 61 | 87 | 3 |
| Nakayama et al [13], 2011 | Proton | 47 | Adjacent to GI tract | 72.6–77.0 | 22–35 | 33.9 | 70.4 | 50.0 | 88.1 | 2 |
| Fukumitsu et al [14], 2009 | Proton | 51 | Away from GI tract, porta hepatis | 66.0 | 10 | NA | NA | 49.2 | 94.5 | 2 |
| Mizumoto et al [12], 2008 | Proton | 53 | Adjacent to porta hepatis | 72.6 | 22 | 34.0 | 57.0 | 45.1 | 86.0 | 0 |
| Kawashima et al [18], 2005 | Proton | 30 | NA | 76 | 20 | NA | 77 | 62 | 96 | 2 (y) |
| Chiba et al [4], 2005 | Proton | 162 | NA | 50–88 | 10–24 | NA | NA | 23.5 | 86.9 | 3.1 |

#### Abbreviations:
- OS, overall survival
- LC, local control
- NA, not applicable
- GI, gastrointestinal

### Table 2. Proton beam therapy for specific condition hepatocellular carcinoma.

| Source, y | Treatment | Patients, No. | Patient condition | Dose, GyE | Fractions | Median survival, mo | 1-y OS, % | 2-y OS, % | 1-y LC, % | Toxicity grade $\geq$ 3, % |
|-----------|-----------|---------------|-------------------|----------|-----------|---------------------|----------|----------|-----------|--------------------------|
| Lee et al [33], 2014 | Proton | 27 | PVTT | 50–66 | 20–22 | 13.2 | 55.6 | 33.3 | NA | 0 |
| Komatsu et al [32], 2011 | Proton | 16 | IVCTT | 52.8–76.0 | 8–38 | 25.4 | 61.1 | 36.7 | 100 | 0 |
| Sugahara et al [54], 2010 | Proton | 22 | Large ($\geq$ 10 cm) | 47.3–89.1 | 10–35 | NA | 64 | 36 | 87 | 2 (y) |
| Sugahara et al [30], 2009 | Proton | 35 | PVTT | 55–77 | 10–35 | 22 | NA | 48 | 91 | 9 (only hematologic) |
| Hata et al [47], 2007 | Proton | 21 | Old age ($\geq$ 80 y) | 66–77 | 10–35 | NA | 84 | 62 | 100 | 10 (only hematologic) |
| Hata et al [46], 2006 | Proton | 19 | Child-Pugh class C | 50–84 | 10–24 | 17 | 53 | 42 | 100 | 0 |

#### Abbreviations:
- OS, overall survival
- LC, local control
- PVTT, portal vein tumor thrombus
- IVCTT, inferior vena cava tumor thrombus
- NA, not applicable
- GI, gastrointestinal

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Tumor Size

There are many effective strategies for treatment of small tumors. These include percutaneous ethanol injection and radiofrequency ablation (RFA), which are generally applied for tumor of < 3 cm in size [34–37]. Photon radiation therapy is also suitable for small tumors and the efficacy of SBRT has been shown in this decade, with favorable 2- and 5-year local control rates of 92% to 100% and 66% to 100%, respectively [38–41]. However, this modality is limited for a large HCC, and surgery can only be used in < 20% of patients. In contrast, proton beams can be used to deliver an ideal dose to a larger HCC using a few ports and minimizing the dose to the normal liver. In a study of 22 patients with large HCC of > 10 cm using a median dose of 72.6 GyE in 22 fractions (range, 47.3 to 89.1 GyE in 10 to 35 fractions), Sugahara et al [30] reported 2-year local control and overall survival rates of 87% (95% CI, 65% to 100%) and 36% (15% to 56%), respectively, with no severe treatment toxicity.

A dosimetric comparison of spot-scanning proton therapy versus intensity-modulated photon radiation therapy for patients with HCC showed that the risks for RILD were 6.2% and 94.5%, respectively, for a tumor diameter > 6.8 cm, and that the risk of RILD after intensity-modulated photon radiation therapy was markedly increased for tumor diameters of 6.3 to 7.8 cm [42]. Also, Gandhi et al [43] showed that PBT significantly increased the volume of spared liver and decreased the mean liver dose compared with SBRT for patients with a dome or central tumor > 3 cm and that photons required a minor reduction in PTV coverage in delivery of 50 Gy in 5 fractions, whereas PBT allowed delivery of 80 Gy in 5 fractions. It was concluded that PBT should be considered for dome and central tumors > 3 cm and for any tumor > 5 cm if photon treatment fails to achieve adequate coverage and liver sparing [43].

Liver Function

In many cases, HCC develops from progression of liver cirrhosis, and treatment strategies become limited. Radiation therapy is also limited by liver function and it is well known that a poor Child-Pugh score is related to an increased risk of RILD. In a study of SBRT in 16 patients, Chan et al [44] found no treatment-related toxicity for Child-Pugh A cases, but severe liver failure in 2 Child-Pugh B cases. In a dose escalation study using SBRT, Cárdenes et al [45] planned to administer 48 Gy in 3 fractions and 42 Gy in 3 fractions for Child-Pugh A and B cases, respectively. However, the treatment doses were amended to 40 Gy in 5 fractions because of progressive liver failure in 1 patient. Nevertheless, RILD was observed in 3 patients with a Child-Pugh score ≥ 7, and the Child-Pugh score was concluded to be the only factor related to RILD within 6 months after SBRT.

Despite this difficult background, we have treated patients with poor liver function with PBT. Hata et al [46] found no treatment toxicities of grade 3 or higher in their report of 19 patients with Child-Pugh class C cirrhosis treated from 1990 to 2000 with total doses of 50 to 84 GyE in fractions of 3 to 5 GyE. There was no deterioration in Child-Pugh score; conversely, this score improved in 14 patients. The 2-year overall survival rate was 42%, and the objective response rate was 63%. These results suggest that PBT is less toxic for the normal liver and that amelioration of the tumor improves liver function. The same protocol was used in patients with limited treatment options because of old age, unfavorable conditions, and comorbidities [46, 47]. In patients older than 80 years, the 3-year cause-specific survival rate was 88% with no severe toxicity, and in patients who could not receive other treatment for HCC because of comorbidities, allergy, and severe cirrhosis, the 5-year local control rate was 83%.

Liver function is also an important prognostic factor in PBT. Prognosis differs significantly between Child-Pugh A and B/C cases [1, 4, 13, 16], and the indocyanine green retention rate at 15 minutes (ICG-15) is also related to survival after PBT [18, 48]. In an analysis of 250 patients, Mizumoto et al [48] found median survival times of 61 months (95% CI, 50 to 72 months) for all cases, and 64 and 20 months for Child-Pugh A and B cases, respectively (P < .001). The median survival times were 63 and 16 months for patients with ICG-15 < 39 and ≥ 40, respectively, and the 3-year survival rates were 72%, 72%, 75%, 63%, and 26% for patients with ICG-R15 of 0 to < 10, 10 to < 20, 20 to < 30, 30 to < 40, and ≥ 40, respectively (P < .001). Among Child-Pugh A cases, the 3-year survival rates were 70, 75, 77, 65, and 38% in the respective ICG groups, with significant differences in...
survival among these groups \( (P = 0.02) \). Multivariate analysis revealed that a low ICG-15 was associated with good survival in all patients and in Child-Pugh A cases. It was concluded that patients with a high ICG-15 should be monitored carefully, even if in the Child-Pugh A category because ICG-15 significantly affected prognosis in these patients [48].

Current major strategies for treatment of unresectable HCC include ablative therapy, percutaneous ethanol injection, and TACE/TAE. The RFA leads to a superior rate of complete necrosis in single HCCs < 3 cm, but the outcome is significantly poorer for large or multiple HCCs [49–51]. Otherwise, TACE is recommended when RFA is difficult because of tumor location or for a subcapsular tumor. The local control rate for TACE is comparable with that in RFA for a small tumor (< 3 cm) but is significantly decreased for large tumors. Riaz et al [52] found that complete tumor ablation was decreased in 89%, 65%, and 33% of HCCs of < 3, 3 to 5, and > 5 cm, respectively. For early stage HCC, the overall 1-, 3-, and 5-year survival rates are 85%, 60%, and 41% after RFA, and 86%, 55%, and 36% after TACE [53]. These results suggest that PBT is comparable with RFA and superior to TACE. We also consider that PBT aimed at local control is useful for HCC that is not suitable for RFA. Also, PBT covers a broad spectrum of indications, including large tumors, tumor thrombosis, and cases with poor liver function, as mentioned above.

**Conclusion**

Local control of HCC through radiation therapy has become possible with PBT because of its excellent dose distribution. In addition, PBT for HCC is safe and effective, and the 5-year local control rate has been > 80% since the 1980s. The best dose for HCC is unclear because there are no significant differences in outcomes among protocols using 66 GyE in 10 fractions, 72.6 GyE in 22 fraction, and 77 GyE in 35 fractions. However, these protocols reflect successful dose fractionation, and we recommend each of these fractionations depend upon the tumor location. Further strong evidence is required to establish the role of PBT for treatment of HCC.

**ADDITIONAL INFORMATION AND DECLARATIONS**

**Conflict of Interest:** The authors have no conflicts of interest to disclose.

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