Original Paper

Effectiveness of Particle Radiotherapy in Various Stages of Hepatocellular Carcinoma: A Pilot Study

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Keywords

Carbon ion · Hepatocellular carcinoma · Local control · Particle radiotherapy · Proton beam

Abstract

Aim: We analyzed the effectiveness of external particle radiotherapy (PRT) as an alternative therapy for various stages of hepatocellular carcinoma (HCC). **Methods:** Eighty-three patients with HCC underwent PRT in our hospital from 2007 to 2015 (proton beam radiation in 58 patients and carbon ion radiation in 25 patients), including patients with early-stage HCC (single HCC measuring ≤ 3 cm, Barcelona Clinic Liver Cancer [BCLC] stage 0 or A) (group A, $n = 30$), those with intermediate-stage HCC (HCCs measuring ≥ 3 cm but inoperable or multinodular and transcatheter arterial embolization [TACE]-refractory, BCLC stage B) (group B, $n = 31$), and those with advanced-stage HCC (HCC with portal invasion or extrahepatic metastasis) (group C, $n = 22$). The median radiation dose was 72.6 GyE (range 50–74) for proton beam radiation and 45.0 GyE (range 45–52.8) for carbon beam radiation. Local control ability was defined as continuous shrinkage of the tumor size without development of new lesions for ≥ 6 months after PRT. **Results:** The rates of local control of the target tumor at 6 months, 1 year, and 2 years were 91.9, 86.3, and 84.8%, respectively. The overall survival rates at 1, 2, and 3 years were 83.0, 65.6, and 55.1%, respectively. Patients in group A showed the best survival rates (100.0% at 1 year and 85.9% at 2 years). The 1-year survival rate was poor in group C (63.6%) despite a good local tumor control rate of 74.7%. The overall survival rates were significantly better in groups A and B than in group C. **Conclusions:** The local control rates after PRT were sufficiently high compared to TACE or sorafenib. Thus, PRT should be adopted for patients with difficult-to-treat HCC in the early and intermediate stages.

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Introduction

Hepatocellular carcinoma (HCC) is currently one of the most common neoplasms worldwide [1, 2]. Generally, HCC tends to initially stay within the liver, and distant metastasis usually occurs in its late stage; thus, intrahepatic local therapy can be repeatedly performed surgically and medically when 3 or fewer tumor nodules are present. However, for patients with difficult-to-treat HCC (multiple HCC nodules, poor liver function with advanced cirrhosis, or various comorbidities making local ablative therapy difficult), less curative modalities of therapy, such as transcatheter arterial chemoembolization (TACE) or systemic chemotherapy, are usually adopted. Although HCC can be treated in a variety of ways, it often recurs as intrahepatic metastasis, multi-centric carcinogenesis, or both and gradually progresses to more advanced stages [3–6].

External radiotherapy is an effective type of local therapy for the treatment of various neoplasms [7]. However, it has been considered to have less potent antitumor activity against HCC than other local ablative therapies, including surgery and radiofrequency ablation (RFA). Particle radiotherapy (PRT) has been used for the treatment of HCC, and high effectiveness has been reported in recent decades [8–12].

PRT requires large-scale, expensive equipment for accelerating proton or carbon ion beams. Compared to conventional photon beam radiation therapy, this modality enables higher-dose delivery to the target by a physical feature called the Bragg peak [13, 14]. PRT can cover a large radiation area of ≥ 10 cm in diameter, allowing radiation therapy for large tumors (≥ 5 cm) that are difficult to treat with 3-dimensional conformal radiotherapy or stereotactic body radiotherapy. Although patients with HCC usually have chronic liver disease with impaired liver function, Hata et al. [15] reported that patients with HCC and severe cirrhosis could be successfully treated with proton beam therapy.

The HCC treatment method is usually chosen based on a treatment algorithm that includes the tumor location, size and number of HCC nodules, and certain biological malignant behaviors that often affect clinical decisions in the management of HCC. However, many patients with early- and intermediate-stage HCC have various obstacles to the performance of radical HCC therapy, such as significant systemic diseases, chronic heart failure, chronic kidney disease, dementia, bleeding tendencies, allergies to contrast medium, and other conditions. TACE-refractory tumors and advanced HCCs with portal invasion or extrahepatic metastasis are also difficult to manage with ordinary medical and surgical procedures.

Considering these tumor factors and patients' associated diseases, substantial numbers of patients with HCC cannot undergo the radical treatment recommended by the Barcelona Clinic Liver Cancer (BCLC) staging algorithm [16] or the Japanese algorithm for HCC therapy [17, 18]. Therefore, we analyzed the effectiveness and adverse effects of PRT and explored optimal candidates for PRT in the treatment of various conditions of HCC.

Materials and Methods

Patients

Eighty-three patients in Toranomon Hospital underwent PRT for treatment of HCC from 2007 to 2015. They comprised 65 men and 18 women aged 39–90 years. Twenty patients were positive for hepatitis B surface antigen, 47 had anti-hepatitis C virus antibodies, and 17 were negative for both hepatitis B surface antigen and anti-hepatitis C virus antibodies. Sixty-two patients had Child-Pugh class A liver disease, and the remaining 21 had Child-Pugh class B disease. The median HCC diameter was 30 mm (range 10–141), and 34 patients (40.9%) had multiple tumors. Twenty-seven patients underwent PRT as the initial therapy for HCC, and 56 had a history of prior treatment for HCC before PRT (Table 1).

Table 1. Patient characteristics
(*n* = 83)

<i>Basic characteristics</i>	
Age, years	79 (39–90)
Sex	
Male	65 (78.3)
Female	18 (21.7)
Child-Pugh classification	
A	62 (74.7)
B	21 (25.3)
C	0 (0)
Underlying cause	
HBV	19 (22.9)
HCV	46 (55.4)
Both	1 (1.2)
Neither	17 (20.5)
<i>Laboratory data</i>	
Albumin, g/dL	3.6 (2.1–4.6)
Total bilirubin, mg/dL	0.9 (0.3–3.9)
Platelet count, $\times 10^3/\mu\text{L}$	12.2 (4.0–34.1)
PT, %	79.6 (57.9–104.2)
AFP, ng/mL	18.7 (2.0–308,800)
PIVKA-II, AU/L	41.0 (4.0–209,590)
<i>Tumor characteristics</i>	
Size of largest tumor, mm ^a	30 (10–141)
Tumors	
Single	49 (59.0)
Multiple	34 (41.0)
Prior treatment history	
None	27 (32.5)
One	17 (20.5)
Two	7 (8.4)
More than 3 times	32 (38.6)
BCLC stage	
0	8 (9.6)
A	38 (45.8)
B	13 (15.7)
C	24 (28.9)

Values are medians (ranges) or *n* (%) unless otherwise indicated. AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; HBV, hepatitis B virus; HCV, hepatitis C virus; PIVKA-II, protein induced by vitamin K absence or antagonist II; PT, prothrombin time. ^a Values are mean (range).

All HCCs were diagnosed by clinical history, abdominal imaging (computed tomography [CT] or magnetic resonance imaging [MRI]), and tumor markers within 3 months before radiotherapy. Hepatologists, surgeons, and radiologists assessed the tumor characteristics and discussed the indications for conventional treatment and PRT in all patients.

PRT was performed as a curative therapy in patients with all stages of HCC who met one or both of the following inclusion criteria: (a) unresectable HCC with medical contraindications to hepatectomy and HCC that was considered difficult to control with conventional nonsurgical treatments (RFA, ethanol injection, TACE, or systemic chemotherapy including sorafenib) or (b) refusal of any conventional treatment.

The indications for PRT were classified into 3 categories: (a) early-stage HCC (a single HCC measuring ≤ 3 cm, BCLC stage 0 or A) (group A, *n* = 30), (b) intermediate-stage HCC (large HCCs measuring ≥ 3 cm but inoperable or multinodular and TACE-refractory, BCLC stage B) (group B, *n* = 31), and (c) advanced-stage HCC (HCCs with portal invasion or extrahepatic metastasis) (group C, *n* = 22) (Fig. 1). The concomitant asso-

<p>Group A (<i>N</i> = 30)</p> <p>Single or small</p> <p>Early stage</p>
<p>Group B (<i>N</i> = 31)</p> <p>Large with complications (<i>n</i> = 17)</p>
<p>Intermediate stage</p> <p>TACE-refractory (<i>n</i> = 14)</p>
<p>Group C (<i>N</i> = 22)</p> <p>Vascular invasion (<i>n</i> = 19)</p>
<p>Advanced stage</p> <p>Extrahepatic metastasis (<i>n</i> = 3)</p>

Fig. 1. Classification of hepatocellular carcinoma (HCC) stages used in this study. Early-stage HCC: single small HCC (≤ 3 cm) that is difficult to resect or ablate because of its location (*n* = 30) (group A). Intermediate-stage HCC: large HCC (> 3 cm) that is unsuitable for surgical resection because of comorbidities (*n* = 17) and transcatheter arterial embolization (TACE)-refractory HCC (*n* = 14) (group B). Advanced-stage HCC: accompanied by vascular invasion with tumor thrombosis (*n* = 19) and extrahepatic metastasis (*n* = 3) (group C).

Fig. 2. Contrast-enhanced computed tomography images showing representative responses to particle radiotherapy. **a** Local control: this tumor shrunk progressively during 22 months of follow-up. **b** Recurrence: this tumor was not detected 4 months after treatment; however, at 10 months after treatment, a new lesion had appeared on the border of the previous tumor.

ciated diseases in groups A and B included chronic renal failure ($n = 9$), chronic heart failure ($n = 7$), bleeding tendencies ($n = 5$), dementia ($n = 5$), biliary tract complications ($n = 3$), and other miscellaneous comorbidities ($n = 10$).

Radiotherapy

Proton beam radiotherapy was performed in 58 of the 83 patients; the remaining 25 patients underwent carbon ion radiotherapy. Proton therapy was performed in 10–37 fractions with a median dose of 72.6 GyE (range 50–74), and carbon ion therapy was performed in 2–4 fractions with a median dose of 45.0 GyE (range 45.0–52.8).

The radiation protocols were based on the size and location of the tumor nodules as assessed by CT scans performed immediately prior to therapy. To ensure accurate radiation procedures, metallic fiducial markers for PRT were usually percutaneously implanted into the hepatic parenchyma adjacent to the tumors before the therapy. PRT was performed in external and domestic medical facilities. Patients were required to visit other facilities for PRT. Therefore, we allowed them to undergo treatment at an easy-to-visit facility. In Child-Pugh class C liver disease patients, PRT was contraindicated.

Effect of Treatment

The effectiveness of therapy was assessed at 3, 6, and 12 months after the end of radiotherapy. Local control was defined as progressive tumor shrinkage without development of new lesions for ≥ 6 months after radiotherapy (Fig. 2a, b). Local control should normally be diagnosed according to the RECIST or modified RECIST criteria, but post-PRT image findings differ from those of other treatments. For example, post-PRT

tumors sometimes shrink while maintaining their enhancement in the arterial phase of contrast-enhanced CT (Fig. 2a). Local control is defined by the necrotic part of the tumor according to the RECIST criteria, potentially leading to misinterpretation of irradiated lesions that do not necrotize. In this study, 15 of 68 (22%) lesions that achieved local control were judged as viable lesions according to the RECIST criteria. Thus, we established original criteria. Additionally, because a tumor decreases very slowly in size, it may not seem to change. Even when a tumor does not seem to necrotize on imaging or the tumor size does not decrease in the short term (e.g., 3 months), the tumor sometimes slowly decreases in size 6 months later.

Follow-Up

The patients' physical status and relevant hematologic and biochemical variables were assessed on a monthly basis during and after therapy. Alpha-fetoprotein and des-gamma carboxy prothrombin were also assessed as tumor markers. Additionally, abdominal imaging studies (contrast-enhanced CT or MRI) were performed every 1–3 months during follow-up. Child-Pugh scores were assessed at 3 months.

The patients were followed up for a median of 26.8 months (range 2.3–99.5). Six patients (7.2%) were lost to follow-up.

Statistical Analysis

Cumulative local control and survival rates were calculated, and differences between subgroups were compared by Kaplan-Meier analysis and the log-rank test [19]. A *p* value of <0.05 was considered to denote statistical significance. The Fisher exact test or the Pearson χ^2 test was used to compare categorical variables (adverse events). Statistical analyses were performed using IBM-SPSS Statistical Software version 18 (IBM Corp., Armonk, NY, USA).

Results

Cumulative Local Control Rates

The response rate to PRT was assessed in 74 patients who were evaluated with CT or MRI 6 months after treatment cessation. The response rate could not be evaluated in the other 9 patients because of death within 6 months (*n* = 6) and a lack of imaging diagnosis after 6 months (*n* = 3).

The local control rate was 91.9% (68/74 patients) at 6 months (47/52 [90.4%] in the proton beam radiation group and 21/22 [95.5%] in the carbon ion radiation group). The local control rates were not different between the 2 modalities of PRT (χ^2 test, *p* = 0.358). Six patients (6/74, 8.1%) developed local tumor progression or recurrence, and new intrahepatic metastatic lesions appeared in 4 of these patients (4/74, 5.4%). Patients with recurrent tumors usually received additional treatment, including surgical resection, RFA, TACE, and further radiotherapy.

The cumulative local control rates at 1, 2, and 3 years were 86.3, 84.8, and 84.8%, respectively, in all patients. The local control rates did not decrease after the second year. The median time to recurrence was 4.3 months (range 1.0–12.3) in the 11 patients who developed local tumor recurrence.

The cumulative local control rates at the end of 1, 2, and 3 years after PRT according to patient group were as follows: 89.3, 85.7, and 85.7%, respectively, in group A; 92.3% at all time points in group B; and 74.7% at all time points in group C. The local control rates tended to be lower in group C, but the difference was not statistically significant between the 3 groups (χ^2 test, *p* = 0.203) (Table 2).

The cumulative local control rates at the end of 1, 2, 3, and 4 years according to tumor size were 88.0% at all time points for small tumors (<3 cm) and 83.3% at all time points for large tumors (≥ 3 cm) (Fig. 3a). The local control rates did not differ significantly between the 2 groups (*p* = 0.535). When the treated tumors were divided into 2 groups according to a diameter of 4 cm, the cumulative local control rates at the end of 1, 2, 3, and 4 years were

Fig. 3. Local control rate according to initial tumor size. **a** <3 and ≥3 cm. **b** <4 and ≥4 cm. The difference was not statistically significant.

Table 2. Local control rates according to group ($n = 74$)

Group	Patients, n	6 months, %	1 year, %	2 years, %	3 years, %	4 years, %
A	28	96.4	89.3	85.7	85.7	85.7
B	26	92.3	92.3	92.3	92.3	92.3
C	20	85.0	74.7	74.7	74.7	74.7

86.2% at all time points for small tumors (<4 cm) and 85.7% at all time points for large tumors (≥4 cm) (Fig. 3b). These rates also did not differ significantly between the 2 groups ($p = 0.811$).

Adverse Events

Dermatitis is a common adverse event after PRT. Various degrees of dermatitis occurred at the radiation site in 34 patients. Dermatitis was graded based on the Common Terminology Criteria of Adverse Effects (CTCAE) version 4.0 [20]. Three (8.8%) patients had CTCAE grade 2 dermatitis, and 31 (91.2%) had CTCAE grade 1 dermatitis. No patients developed irreversible or significant skin damage, except for pigmentation.

Within 12 months after the end of radiotherapy, ascites newly developed in 19 patients (22.9%), worsening of pre-existing ascites in 6 patients, and encephalopathy in 5 patients (Table 3). Transient ascites or pleural effusion developed in 25 patients, and temporary encephalopathy developed in 5 patients during the first 12 months. Slight increases in Child-Pugh scores also indicated radiation-induced liver damage to the surrounding irradiated liver. Hepatic encephalopathy occurred in 2/62 patients (3.2%) with Child-Pugh class A disease and in 3/21 patients (14.3%) with Child-Pugh class B disease. The incidence of hepatic encephalopathy was not significantly different between patients with Child-Pugh class A and B disease (Fisher exact test, $p = 0.100$). Ascites occurred in 11/62 patients (17.7%) with Child-Pugh class A disease and in 14/21 patients (66.7%) with Child-Pugh class B disease. The incidence of ascites after therapy was significantly higher in patients with less liver reserve (χ^2 test, $p = 0.0001$).

Table 3. Adverse effects in the first 12 months

Adverse effect	Patients, <i>n</i>	Child-Pugh grade	
		class A (<i>n</i> = 62)	class B (<i>n</i> = 21)
Dermatitis	34	28 (82.4%)	6 (17.6%)
Ascites or pleural effusion	25	11 (44.0%)	14 (56.0%)
Encephalopathy	5	2 (3.2%)	3 (14.3%)
Increase in Child-Pugh score	35	21 (60.0%)	14 (40.0%)

Table 4. Survival rates according to group (*n* = 83)

Group	Patients, <i>n</i>	1 year, %	2 years, %	3 years, %	4 years, %
A	30	100.0	85.9	80.8	61.1
B	31	80.4	58.3	52.5	43.7
C	22	63.6	49.0	27.2	0.0

The Child-Pugh scores did not change during the first 6 months after therapy in 53 patients (63.9%), worsened by 1 point in 16 patients (19.3%), and worsened by 2 points in 14 patients (16.9%). The score did not increase by ≥ 3 points during the study period (Table 3). Gastrointestinal bleeding did not occur during the study period.

Survival Rates

During the median observation period of 23.8 months, 40 patients (48.2%) died. The causes of death were liver failure (*n* = 15, 18.1%), intrahepatic tumor progression (*n* = 7, 8.4%), extrahepatic tumor progression (*n* = 3, 3.6%), and miscellaneous conditions other than liver disease (*n* = 14, 16.9%).

The overall cumulative survival rates at the end of 1, 2, 3, 4, and 5 years were 83.0, 65.6, 55.1, 38.9, and 38.9%, respectively. We also calculated the cumulative survival rates according to the patient groups: the 1-, 2-, 3-, and 4-year survival rates in group A were 100.0, 85.9, 80.8, and 61.1%, respectively; those in group B were 80.4, 58.3, 52.5, and 43.7%, respectively; and those in group C were 63.6, 49.0, 27.2, and 0.0%, respectively (Table 4; Fig. 4). The tumor stages and background characteristics differed significantly between the 3 groups, and the survival rates were significantly better in groups A and B than in group C. Thus, patients with early- and intermediate-stage HCC (groups A and B) lived longer than those with advanced-stage disease (group C) ($p = 0.001$) (Fig. 4).

Discussion

Locoregional therapy for HCC has gradually developed with refinement of surgical techniques and radiofrequency or microwave ablation as well as with improvements in sophisticated imaging techniques and 3-dimensional simulation of diagnostic procedures. The number of patients with difficult-to-treat HCC has recently been increasing because of patients' longer lifespans and increased complications associated with older age. Conventional radiotherapy has limitations as a curative treatment for HCC. Therefore, we investigated the effectiveness of PRT for HCC. Because conventional external radiotherapy is

Fig. 4. Overall survival (OS) rates after treatment according to Barcelona Clinic Liver Cancer (BCLC) stages. OS was significantly better for early- and intermediate-stage hepatocellular carcinoma (HCC) (groups A and B) than for advanced-stage HCC (group C) ($p = 0.001$). The BCLC guidelines recommend treating the latter group with sorafenib [16].

generally considered less effective in patients with HCC than in patients with certain other malignancies, we assessed the usefulness of PRT in the treatment of HCC.

Komatsu et al. [9] reported no significant differences between proton beam therapy and carbon ion therapy with respect to local control ability or survival. Therefore, we assessed the effectiveness of proton beam radiotherapy together with carbon ion radiotherapy for HCC. We also analyzed the effectiveness of proton beam radiotherapy together with carbon ion radiotherapy for HCC in clinical practice.

The overall local control rate for all patients was 91.9% at 6 months in this study, although the tumor eradication rate was similar or equivalent to that of surgical resection or conventional therapy with percutaneous radiofrequency. In 2 studies comparing resection or RFA in patients with Child-Pugh class A disease with a solitary HCC of <5 cm, the 1-year overall survival rates after percutaneous RFA and surgery were 96 and 93%, respectively [21, 22]. All 83 patients in the present study had difficult-to-treat HCC because of severe extrahepatic comorbidities, portal vein invasion, bleeding diatheses, allergies to contrast medium, advanced cirrhosis with decompensation, and other conditions. Such patients cannot undergo percutaneous ablation or TACE as standard and conventional manners of treatment. Lu et al. [23] reported that pathologically confirmed HCC became completely necrotic after RFA in 83% of tumors measuring <3 cm, and similar rates were obtained for HCC with a median volume of 40.5 mL after stereotactic body radiotherapy [24]. Sophisticated stereotactic radiation is also believed to be effective for difficult-to-treat HCC. PRT can be used to manage rather large tumors of ≥ 10 cm, and our data show that larger tumors of ≥ 4 cm were also successfully treated with extracorporeal PRT (Fig. 3a, b).

Jeong et al. [25] reported that 28.2% of patients with various stages of HCC who underwent TACE showed a complete response after treatment. Another study showed that 6 months after treatment for BCLC stage B/C HCCs, the overall response rate was 12.50% in the sorafenib monotherapy group and 18.75% in the TACE + sorafenib group [26]. When patients with early-stage HCC (groups A and B) could not undergo radical therapies because of comorbidities, they usually underwent a less curative therapy, such as TACE or possibly sorafenib-based chemotherapy. Our data indicate that PRT is superior to TACE or chemotherapy with respect to the local control ability of small HCCs.

For inoperable HCC in patients who are not transplant candidates, the National Comprehensive Cancer Network (NCCN) guidelines recommend locoregional therapy (preferred) (e.g., ablation, arterially directed therapies, or external beam radiotherapy), systemic therapy (e.g., sorafenib or chemotherapy), clinical trial, or best supportive care [27]. PRT is worth considering as a useful treatment for compromised patients with solitary or small HCCs.

In the present study, PRT often achieved complete necrosis of TACE-resistant nodules in some patients (group B). We also performed PRT for only several nodules among multiple HCCs. We do not usually perform PRT for multiple HCCs, but the particular nodules in this study were resistant to repeated TACE and regarded as prognosis-determining nodules based on their size, location, or vascular invasion. However, the actual effectiveness of PRT remained uncertain in the treatment of those “prognosis-determining tumors” among multiple nodules.

Sorafenib or another chemotherapeutic was usually chosen for advanced-stage HCC (group C) with or without extrahepatic progression, but the local control rate was very low [26]. Regarding the effect of PRT on portal tumor thrombi and extrahepatic metastasis, the local tumor control rates were unexpectedly high in group C (Table 2). However, intrahepatic recurrence often occurred in peripheral parts of the liver in patients with portal thrombi, and extrahepatic metastasis occurred in the bone and lung. As a result, these patients’ survival rates were the worst (Fig. 4). This study shows that PRT effectively ablates portal thrombi and metastatic foci, although other authors have stated that its effect is limited for these lesions [28–30]. Thus, patients with advanced-stage HCC, such as those with a medium-sized tumor with portal vein invasion and possibly a single extrahepatic metastasis including the bone and lung, are not appropriate candidates for PRT.

Further studies are needed to evaluate the usefulness of PRT. Sorafenib and other chemotherapeutics are contraindicated in some patients, including those with impaired liver function (Child-Pugh class B and C), bleeding diathesis, brain metastasis, and other conditions. PRT can be a valid alternative to chemotherapy, even in patients with advanced-stage HCC. Although we did not compare PRT to other treatment modalities, such as RFA, surgical resection, or stereotactic body radiotherapy, we should consider PRT as an alternative treatment for patients with difficult-to-treat HCCs.

With respect to adverse events associated with PRT, treatment-related gastrointestinal bleeding was not found in any patients. Transient hepatotoxicity occurred in some patients with HCC nodules located deep in the liver. A previous study revealed the safety of PRT for patients with severe cirrhosis, and another study showed no deterioration in the post-treatment Child-Pugh scores after radiotherapy [15, 31]. In the present study, however, multiple factors including a large tumor size, deep tumor location, large radiation volume, and poor liver function seemed to be associated with deterioration of liver function. We consider that the increased amount of irradiation to important organs, such as the normal liver and portal vein, as well as irradiation in patients with less liver reserve are likely to further decrease the liver’s reserve capacity.

PRT showed a high ability of local control with few complications in patients with HCC with various clinicopathological states. The overall survival rates were significantly better in groups A and B than in group C. Higher rates of radical cure were achieved in the former groups, whereas many recurrences, including in nonirradiated areas, occurred in the latter group. Some studies have revealed the effectiveness and safety of PRT for HCC, but no reports have described both the survival rate and local control rate according to patient backgrounds [8, 9, 32]. This pilot study is the first to classify various groups of patients who could be candidates for PRT and analyze the intermediate-term survival rates together with the local control ability in these groups.

The BCLC staging system [16] and Japanese guidelines [17, 18] do not address external radiotherapy as a standard treatment for HCC. The way in which PRT should be used for

various stages of HCC and various patients has not yet been standardized. Although this was a single-center retrospective pilot study, we again emphasize the usefulness of PRT in terms of its local control ability and relatively low rate of adverse events. Future studies should compare the survival rates of patients who received PRT to those with the same stage of HCC who received only conservative or less radical therapy.

In conclusion, PRT achieves a high local control rate in patients with various stages of difficult-to-treat HCCs. Further studies are required to analyze and evaluate the ability of PRT to achieve local control, prevent recurrence, and impact survival rates, while also evaluating the risk of causing deterioration in liver function.

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Statement of Ethics

This retrospective study was approved by the ethics committees of our institution and was performed in accordance with the Helsinki Declaration. All participants provided written informed consent.

Disclosure Statement

The authors declare no conflicts of interest.

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