

# Long-term clinical outcomes of patients receiving proton beam therapy for caudate lobe hepatocellular carcinoma

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## ABSTRACT

Hepatocellular carcinoma (HCC) located in the caudate lobe (caudate HCC) is rare; however, patients with this type of tumour have poorer prognoses than those with HCC in other segments. Despite many published reports on the clinical usefulness of proton beam therapy (PBT) for HCC, data on the clinical outcomes of patients undergoing PBT for caudate HCC remain scarce. Therefore, the present study aimed to investigate the outcomes of this group of patients. Thirty patients with caudate HCC who underwent definitive PBT between February 2002 and February 2014 were retrospectively analysed. The total irradiation doses ranged from 55 to 77 (median 72.6) Gy relative biological dose. The median follow-up period was 37.5 (range, 3.0–152.0) months. The overall survival (OS) rates at one, three and five years were 86.6%, 62.8% and 46.1%, respectively. According to univariate and multivariate analyses, Child-Pugh A ( $P < 0.01$ ), having a single tumour ( $P = 0.02$ ) and a low serum alpha-fetoprotein level (AFP;  $P < 0.01$ ) were significant factors predicting longer survival. The local control (LC) rates at one, three and five years were 100%, 85.9% and 85.9%, respectively, while the corresponding progression-free survival (PFS) rates were 65%, 27.5% and 22%, respectively. No grade 3 or worse adverse events were observed. PBT is effective and safe for the treatment of caudate HCC, and should therefore be considered a feasible option for intervention in patients with this disease.

**Keywords:** hepatocellular carcinoma (HCC); caudate lobe; proton beam therapy (PBT); radiotherapy

## INTRODUCTION

Liver cancer, which most often presents as hepatocellular carcinoma (HCC), constitutes the sixth most common type of malignancy and the fourth leading cause of cancer-related deaths worldwide [1]. Despite recent developments in surveillance programmes for patients with risk factors for HCC, many individuals are still diagnosed at more advanced stages [2]. HCC located in the caudate lobe (caudate HCC) is relatively rare and has a poorer prognosis than HCC in other lobes owing to the involvement of the portal vein and/or inferior vena cava

(IVC); this facilitates tumour spread both intra- and extra-hepatically early in the course of the disease [3].

Surgical resection is considered a first-line curative treatment for caudate HCC given its efficacy [4–13]. However, hepatic resection of caudate HCC is technically challenging and maintains high complication and tumour recurrence rates given that the lesion is embedded between the hepatic hilum and IVC [4,14]. Moreover, cirrhotic liver and poor functional reserve, which are commonly observed among patients with HCC, also render the surgery difficult [10]. Non-surgical

treatments, including percutaneous ablation therapies such as radiofrequency ablation (RFA), are also challenging because of the narrow percutaneous puncture window and adjacent major vessels [14]. The existence of several branches of feeding arteries also complicate the treatment of caudate HCC using transcatheter hepatic arterial chemoembolization (TACE) [15–17]. The caudate lobe is also considered the most dangerous hepatic zone for targeting with stereotactic body radiation therapy (SBRT), especially when main portal vein tumour thrombosis (PVTT) occurs [18].

Proton beam therapy (PBT) has the ability to deposit high amounts of energy over a very short distance with no exit dose [19,20], and is widely used for the treatment of various kinds of cancers owing to this unique advantage. Patients with HCC can benefit from PBT given that it spares a large volume of the unaffected liver from low to moderate doses of radiation, which would elevate the risk of radiation-induced liver disease [2,21]. Previous studies have shown PBT to be useful for achieving good local control (LC) with tolerable adverse events for the treatment of HCC [22–26]. Several studies have also reported that PBT is beneficial for the treatment of HCC with PVTT [27,28] or IVC tumour thrombosis (IVCTT) [29,30]. However, to date, information on the clinical outcomes of patients who receive PBT for caudate HCC is limited; there has only been a case report discussing radiation therapy for the treatment of this type of HCC [31]. The purpose of this study was to evaluate the clinical outcomes of patients who received PBT for caudate HCC.

## MATERIALS AND METHODS

### Study population

Between February 2002 and February 2014, a total of 973 patients with HCC underwent PBT at our hospital. Fifty-two patients with inoperable caudate HCC were consecutively treated, among whom 30 received definitive treatment and were included in this study. Treatment was considered definitive if all visible tumours were included in the clinical target volume. All study procedures involving human participants were conducted according to the ethical standards of the institutional research committee under the principles of the Declaration of Helsinki or its equivalent. This retrospective analysis was approved by the Institutional Review Board of our hospital (IRB; R01–167). The IRB waived informed consent and approved the retrospective review, which was compliant with the Health Insurance Portability and Accountability Act.

### Proton beam therapy

Metallic fiducial markers were implanted into the liver parenchyma beside the tumour under ultrasound guidance. Surgical clips and/or lipiodol accumulation were substituted for fluoroscopically detectable fiducial markers that were present in patients who were previously treated for HCC. All patients underwent simulation computed tomography (CT) with respiratory synchronization during the expiratory phase at 2.5 or 5 mm intervals in the treatment position [32], and these data were directly transferred to a treatment planning system (Hitachi Co., Ltd., Japan). The clinical target volume was delineated by including visible tumours with a 5–10 mm margin. An aperture margin of 5.5–14 mm and an additional 0–5 mm margin in the caudal axis direction were added to encompass the entire clinical target volume.

**Table 1. Treatment doses received by the patients (n = 30)**

Total dose Gy (RBE)/fraction	
55 Gy (RBE)/10 fraction	1 (3.3%)
60 Gy (RBE)/15 fraction	1 (3.3%)
72.6 Gy (RBE)/22 fraction	21 (70.0%)
74 Gy (RBE)/37 fraction	5 (16.7%)
77 Gy (RBE)/35 fraction	2 (6.7%)

Abbreviations: Gy, gray; RBE, relative biological effectiveness

Proton beams ranging from 155 to 250 MeV, generated through a linear accelerator and synchrotron, were spread out and shaped with ridge filters, double-scattering sheets, multi-leaf collimators and a custom-made bolus to conform to the treatment planning data [33]. The proton beam was synchronized to the end-expiratory phase by a respiratory gating system, which is a laser range finder that monitors the movement of the patient's body surface caused by respiratory motion. The irradiation dose was calculated by multiplying the physical dose (Gy) by the relative biological effectiveness (RBE) and was expressed as Gy (RBE), under the assumption that a proton RBE value relative to high-energy photons was 1.1.

### Treatment

The PBT treatment doses are summarized in Table 1. A total dose of 72.6 Gy (RBE) in 22 fractions was delivered in most cases (70%). While the majority of patients had received other treatments prior to undergoing PBT, 11 newly diagnosed patients were also included (36.7%). The dose constraints to spinal cord, stomach and duodenum was set below a cumulative maximum dose of 50 GyE and to colon below 60 GyE.

### Follow-up and toxicity evaluation

Serum alpha-fetoprotein (AFP) and/or des-gamma-carboxy prothrombin (DCP) measurements were obtained for all patients every two to four months after completion of PBT. Patients also underwent abdominal CT or magnetic resonance imaging as long as they remained in good condition. Toxicity was evaluated using the Common Terminology Criteria for Adverse Events version 4.0.

### Statistical analysis

Continuous data are expressed as medians. Overall survival (OS), LC and progression-free survival (PFS) curves were constructed using the Kaplan–Meier method. OS, LC and PFS were calculated as the intervals between the first day of PBT and death, local recurrence and disease progression, respectively, or else were censored at the time of the last follow-up. Univariate and multivariate Cox regression analysis were used to identify clinical factors that were of independent prognostic significance. In this prognostic analysis, the median was used as the cut-off level for stratification of patients into two groups for continuous variables. All statistical analyses were performed using the R software, version 4.0.0 (R Foundation for Statistical Computing, Vienna, Austria, <https://R-project.org>). Differences were considered significant when the *P*-value was <0.05.

**Table 2. The basic characteristics of the patients (n = 30)**

Age (years), median (range)	67 (50–83)
Sex	
Male	26 (86.7%)
Female	4 (13.3%)
Performance status score	
0	12 (40.0%)
1	17 (56.7%)
2	1 (3.3%)
Child-Pugh classification	
A (5)	17 (56.7%)
A (6)	7 (23.3%)
B (7)	3 (10.0%)
B (8)	1 (3.3%)
C (11)	1 (3.3%)
NA	1 (3.3%)
Underlying cause	
HBV	8 (26.7%)
HCV	16 (53.3%)
HBV and HCV	1 (3.3%)
Non-HBV/HCV	5 (16.7%)

Abbreviations: NA, not applicable; HBV, hepatitis B virus; HCV, hepatitis C virus.

## RESULTS

### Baseline patient characteristics

The median follow-up period was 37.5 (range, 3–152) months, and the median patient age was 67 (range, 50–83) years. The patients were predominantly male (86.7%). Twenty-four patients (80%) were classified as Child-Pugh A (i.e. scores of 5 and 6). Four patients (13.3%) were classified as Child-Pugh B, and one (3.3%) as Child-Pugh C; the Child-Pugh score of one patient with atrial fibrillation could not be assessed owing to the use of warfarin. The median tumour size was 2.3 cm; the majority of patients (76.7%) had a solitary tumour, although seven (23.3%) had multiple tumours. Five patients had vascular invasion. The median AFP level was 26.5 ng/mL and that of DCP was 59.0 mAU/mL. The baseline patient and tumour characteristics are summarized in Tables 2 and 3.

### Survival, local control and progression-free survival

The patients' clinical outcomes are shown in Fig. 1. The OS rates at one, three and five years were 86.6%, 62.8% and 46.1%, respectively. According to univariate and multivariate analyses, Child-Pugh A status (hazard ratio (HR) = 4.83; 95% CI, 1.52–15.4;  $P < 0.01$ ), having a single tumour (HR = 3.73; 95% CI, 1.28–10.31;  $P = 0.02$ ) and serum AFP levels below the median of 26.5 ng/mL (HR = 4.07; 95% CI, 1.52–10.92;  $P < 0.01$ ) were significant predictors of longer survival (Table 4). The LC rates at one, three and five years were 100%, 85.9% and 85.9%, respectively, while the corresponding PFS rates were 65%, 27.5% and 22%, respectively.

### Toxicity

Acute grade 1–2 dermatitis was observed in most patients ( $n = 17$ , 56.7%). Grade 1 nausea and grade 2 abdominal bloating were observed

**Table 3. Characteristics of the tumours of the patients**

Size (cm), median (range)	2.3 (1.0–9.0)
Number	
Single	23 (76.7%)
Multiple	7 (23.3%)
Number of previous treatments	
None	11 (36.7%)
One	7 (23.3%)
Two	3 (10.0%)
Three or more	9 (30.0%)
Vascular invasion	
None	25 (83.3%)
Vp3	2 (6.7%)
Vp4	1 (3.3%)
IVCTT	2 (6.7%)
Tumour marker	
AFP, median (range), ng/mL	26.5 (1–16861.3)
DCP, median (range), mAU/mL	59 (11–168 890)

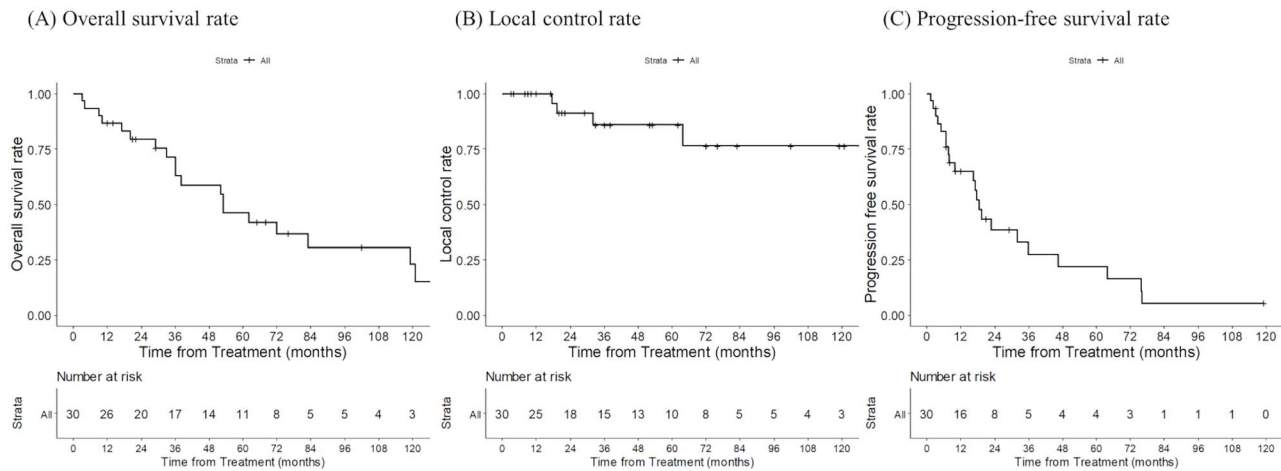
Abbreviations: Vp3, right or left portal vein; Vp4, main trunk; IVCTT, inferior vena cava tumour thrombosis; AFP, alpha-fetoprotein; DCP, des-gamma-carboxy prothrombin

in one patient (3.3%). In terms of late toxicities, grade 2 ascites were observed in one patient (3.3%) and grade 1 pneumonitis and hyperpigmentation were observed in one (3.3%) and three (10.0%) of the patients, respectively. No grade 3 or worse acute or late toxicities were observed (Table 5).

## DISCUSSION

Treatment of caudate HCC is technically challenging regardless of whether surgical resection or non-surgical interventions (including percutaneous ablation therapy, TACE and SBRT) are used. Moreover, clear evidence has not been established for the treatment of caudate HCC because of its rarity. While previous studies demonstrated that PBT is a promising treatment option for HCC, those that specifically focus on PBT for caudate HCC are scarce. To the best of our knowledge, there is only a single case report describing the treatment of caudate HCC; this intervention included SBRT [31]. In the present study, we investigated the survival, tumour control and adverse events in patients with caudate HCC who were treated with PBT; as such, this was the first study of its kind.

Our observed one-, three- and five-year OS rates were 86.6%, 62.8% and 46.1%, respectively. In Mizumoto *et al.*'s investigation of the clinical outcomes of 266 patients with HCC who received PBT between 2001 and 2007 [24], the one-, three- and five-year OS rates were 87%, 61% and 48%, respectively, while the corresponding PFS rates were 56%, 21% and 12%, respectively. They also reported that the one-, three- and five-year LC rates were 98%, 87% and 81%, respectively. Although the background factors of that study (which was performed at our institution) may be different from those in the current study (rendering exact comparisons impossible), the clinical outcomes in patients of both studies were comparable even though the previous investigation included patients with HCCs located in other segments of the liver parenchyma.



**Fig. 1. Clinical outcomes of patients receiving proton beam therapy for hepatocellular carcinoma located in the caudate lobe. (A) Overall survival rates, (B) local control rates and (C) progression-free survival rates.**

**Table 4. Univariate and multivariate analyses of overall survival**

Variables	Univariate			Multivariate		
	HR	95% CI	P-value	HR	95% CI	P-value
Performance status score (0 vs 1–2)	1.53	0.58–4.00	0.39			
Child-Pugh (A vs B/C)	4.83	1.52–15.4	<0.01	13.79	3.35–56.8	<0.01
Vascular invasion (absent vs present)	1.64	0.53–5.07	0.39			
Age ( $\geq 67$ vs $< 67$ years, the median)	2.15	0.85–5.42	0.11			
Sex (male vs female)	1.41	0.46–4.30	0.55			
Maximum tumour diameter ( $\geq 2.3$ vs $< 2.3$ cm, the median)	1.37	0.56–3.40	0.49			
Number of tumours (solitary vs multiple)	3.73	1.28–10.91	0.02	4.49	1.31–15.35	0.02
Serum AFP level ( $\geq 26.5$ vs $< 26.5$ ng/mL, the median)	4.07	1.52–10.92	<0.01	4.92	1.66–14.56	<0.01
Serum DCP level ( $\geq 59$ vs $< 59$ mAU/mL, the median)	0.82	0.34–1.99	0.66			
Previous treatment status (naïve vs recurrent)	0.70	0.27–1.79	0.45			

Abbreviations: Vp3–4, main, right, or left portal vein; IVCTT, inferior vena cava tumour thrombosis; AFP, alpha-fetoprotein; DCP, des-gamma-carboxy prothrombin; HR, hazard ratio; CI, confidence interval

**Table 5. Toxicities experienced by the patients (n = 30)**

Acute	Grade		
	1	2	3 or higher
Dermatitis	15	2	0
Abdominal bloating	0	1	0
Nausea	1	0	0
Late	Grade		
	1	2	3 or higher
Hyperpigmentation	3	0	0
Ascites	0	1	0
Pneumonitis	1	0	0

The mainstay of treatment for caudate HCC is surgical resection. However, owing to the anatomical complexity of the caudate lobe, the procedure is challenging and carries a higher risk of complications than conventional hepatectomy. This is particularly true if tumour

invasion into the surrounding vessels (causing PVTT and IVCTT) occurs. Additionally, resection of the caudate lobe is not indicated for patients with poor liver function reserves. The reported three- and five-year OS rates for patients who underwent surgical treatment for caudate HCC were 34–90% and 25.9–76%, respectively [4,5,7,10–13,34–36]. In our study, the corresponding OS rates were 62.8% and 46.1%, respectively. Our cohort included five patients with major vascular invasion (three with PVTT [two Vp3 and the other Vp4] and two with IVCTT). Among five patients, the cause of death was tumor progression for one patient, cirrhosis complication for two patients and advanced oesophageal cancer for one patient. No treatment-related complication was observed as the cause of death. Moreover, the long-term, 128 months, survival and LC were obtained for one patient with IVCTT. Given that the prognosis of patients who undergo surgical resection for caudate HCC is generally worse than that of patients who undergo surgery for lesions in other segments, our results suggest that the effectiveness of PBT for the former group may be comparable to that of surgery. Complications such as blood loss and liver decompensation are major risks when opting for surgical treatment in patients

with caudate HCC; however, we observed manageable acute and late toxicities, none of which were grade 3 or higher. As such, PBT appears to be a suitable modality for the treatment of caudate HCC given its acceptable survival rates and tolerable adverse events.

Despite their low complication rates, the main setback of performing percutaneous ablation therapy for caudate HCC is the high rates of tumour recurrence compared with HCCs in other segments [37–40]. A higher local tumour progression rate after RFA for caudate HCC is presumably associated with the difficulty of positioning the needle electrode owing to the narrow percutaneous puncture and the surrounding major vessels [14,36,37]. The cooling effect from the major vessels adjacent to the caudate lobe, known as the heat sink effect, has the potential to weaken the coagulation produced by RFA and result in tumour recurrence [36,37]. The OS rates for patients who underwent percutaneous ablation therapies for caudate HCC at three and five years were reported to be 31.3–74% and 11.2–21.9%, respectively [14,15,39,41–43], which are worse than those reported in patients whose lesions are in other hepatic segments [44]. Effective TACE for caudate HCC is also technically challenging owing to the presence of multiple feeding arteries, and the tumour recurrence rate is high [15,16,45]. Previous studies found a high LC rate (>80%) following PBT for HCC performed in patients since 1980 [21]. In the current study, we confirmed that the caudate HCC LC rate at five years remained high (85.9%), indicating that PBT ought to be considered for the treatment of caudate HCC.

This study had several limitations. First, it included a mix of patients with naive and recurrent HCC, and most (63.3%) had undergone several rounds of previous treatments. Second, this was a retrospective study conducted at a single institution. Third, the number of patients was relatively small owing to the rarity of the studied condition. As such, selection bias may have occurred. However, given that caudate HCC is rare, data from retrospective studies with small sample sizes can be used to establish treatment data. Although our research indicated that PBT might be a promising option for the definitive treatment of caudate HCC, further studies with a larger number of patients from multiple institutions are required.

Our results indicate that PBT is effective and tolerable for patients with caudate HCC. Child-Pugh A, the presence of a single tumour and low serum AFP levels are favourable prognostic factors. Therefore, PBT may be a promising treatment option for patients with caudate HCC.

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#### CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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