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CLINICAL INVESTIGATION **Liver**

A PROSPECTIVE STUDY OF HYPOFRACTIONATED PROTON BEAM THERAPY FOR PATIENTS WITH HEPATOCELLULAR CARCINOMA

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Purpose: To evaluate the efficacy and safety of hypofractionated proton beam therapy for patients with hepatocellular carcinoma (HCC).

Methods and Materials: Between September 2001 and August 2004, 51 patients with HCC greater than 2 cm away from the porta hepatis or gastrointestinal tract were treated with proton beam therapy to 66 Gy-equivalents (GyE) in 10 fractions.

Results: Overall survival rates were 49.2 and 38.7% at 3 and 5 years after treatment. Local control rates were 94.5 and 87.8% at 3 and 5 years after treatment. Posttreatment serum α-fetoprotein values were significantly reduced when compared with pretreatment values ($p < 0.0001$). Patients experienced only minor acute reactions of Grade 1 or less, and 3 patients experienced late sequelae of Grade 2 or higher. However, there were no treatment-related deaths.

Conclusions: Hypofractionated proton beam therapy is safe and well-tolerated by patients with HCC located greater than 2 cm away from the porta hepatis or gastrointestinal tract and may be effective alternative to other modalities. © **2009 Elsevier Inc.**

Hepatocellular carcinoma, Proton beam therapy, Radiotherapy.

INTRODUCTION

Hepatocellular carcinoma (HCC) constitutes more than 80% of all cancer found in Asia and Africa and is a significant contributor to cancer mortality (1, 2). The prognosis of patients with HCC is generally poor because of rapid tumor progression and resulting hepatic impairment. The average survival for patients with HCC is on the order of months if left untreated (3–5).

Several treatment modalities are available for use in patients with HCC. According to the Liver Cancer Study Group of Japan, 19,920 patients were treated in Japan between January 2000 and December 2001 (6). Of these patients, 36.4% underwent transcatheter arterial chemoembolization (7–9), resulting in a 5-year survival rate of 23.5%; 31.3% were treated surgically (10, 11) with a 5-year survival rate of 54.6%; 26.8% chose local ablation therapy (12, 13) with a 5-year survival rate of 43.4%; and 4.6% received chemotherapy (14) with a 1-year survival rate of 39%. Surgery appears to be the most effective treatment of HCC; however, it is invasive and poorly tolerated by sicker patients. Local ablation therapy and transcatheter arterial chemoembolization, although less invasive than surgery, also carry significant limitations related to the variability of tumor volume, location, and feeding arteries.

In 1983, we initiated proton beam therapy for the treatment of various malignancies (15) and have since reported excellent local tumor control in patients with HCC (16–21). The purpose of this study is to evaluate the efficacy and safety of hypofractionated proton beam therapy for reducing the treatment time in patients with HCC.

PATIENTS AND METHODS

Patients

Patients who met the following conditions were eligible for hypofractionated proton beam therapy: (*1*) pathologically proven HCC or a clinical diagnosis of HCC as evidenced by arterial enhancement

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and venous washout on dynamic computed tomography (CT) and elevated tumor markers (serum α-fetoproteins [AFP] >20 ng/mL or protein induced by vitamin K absence or antagonist II >40 AU/mL in patients with documented hepatitis B or C viral infection; (*2*) solitary HCC or multiple tumor foci (totaling fewer than three in number), providing all lesions could be included in a single irradiation field with no other uncontrolled HCC; (*3*) a maximal tumor diameter of ≤10.0 cm; (*4*) tumor located ≥2 cm away from the porta hepatis or digestive tract; (*5*) Child-Pugh class A or B; and (*6*) European Organization for Research and Treatment of Cancer performance status of 0–2.

Between September 2001 and August 2004, 146 patients with HCC received proton beam therapy at the Proton Medical Research Center of the University of Tsukuba. Fifty-one of these patients were eligible for this study. Of these 51 patients, 13 carried a histologic diagnosis of HCC, whereas 38 were diagnosed based on hepatitis virus infection, elevated tumor markers, and CT findings. Tables 1 and 2 show patient and tumor characteristics. The median value of maximal tumor diameter was 2.8 cm (range, 0.8–9.3 cm). Twenty-nine patients presented with an elevated serum AFP value (>20 ng/mL). Thirty-three patients had a history of prior treatment for HCC (Table 3).

The present study was conducted according to the Helsinki Declaration and was approved by the Ethics Committee of the University of Tsukuba. Written informed consent was obtained from all patients before treatment onset.

Proton irradiation

Before the start of treatment, metallic fiducial markers were implanted percutaneously into the hepatic parenchyma adjacent to tumor. Custom-made body casts (ESFORM; Engineering System, Matsumoto, Japan) were created to ensure adequate immobilization of each patient during radiotherapy. Treatment planning was performed on respiratory-synchronized CT images taken at 5-mm intervals in the treatment position. Clinical target volume was defined as gross tumor volume plus a 5- to 10-mm margin in all directions. Planning target volume was defined as clinical target volume plus an 8- to 10-mm margin in all directions and an additional 5-mm margin in the caudal direction for respiratory movement. The clinical target volume was homogeneously covered with more than 90% of the prescribed dose using the spread-out Bragg peak of the proton beams. In patients with multiple tumors, all malignant lesions were included within a single target volume. The treatment planning system automatically derived the settings required for beam delivery including ridge filters, range shifter, collimator, and a bolus. Proton dosimetry was verified using a plastic phantom for each patient prior to initiation of treatment (22).

Proton beams of 155–250 MeV generated by an accelerator with a synchrotron were used for treatment. Beams were delivered using a rotation gantry under respiratory gating through one to three ports with coplanar angles (23). During each treatment session, the positional relationship between the center of the irradiated field and the implanted fiducial marker was examined using the orthogonal fluoroscopy unit attached to the treatment unit.

The total dose delivered was 66 GyE in fractions of 6.6 GyE. Equivalent doses based on 2 Gy per fraction regimens were calculated using a linear quadratic model with α/β ratios of 10 and 3 for early and late responding tissues, resulting in 91 GyE and 127 GyE, respectively, when conventional 2 Gy/fraction regimens were used (24). The relative biologic effectiveness value of our proton beams has been determined as 1.1.

Table 1. Patient characteristics

	Characteristics	No. patients (%)
Age (y)	<70	27 (52.9)
	≥70	24 (47.1)
Gender	Men	34 (66.7)
	Women	17 (33.3)
Child-Pugh class	A	41 (80.4)
	B	10 (19.6)
Hepatitis virus	B	8 (15.7)
	C	32 (62.7)
	Both B and C	2 (3.9)
	None	6 (11.8)
	Unknown	3 (5.9)
Prior treatment	Received	33 (64.7)
	None	18 (35.3)
Follow up treatment	Received	31 (60.8)
	None	20 (39.2)
Performance status	0 and 1	51 (100.0)

Table 2. Tumor characteristics

	Characteristics	No. patients (%)
Number of tumors	Solitary	31 (60.8)
	Multiple	20 (39.2)
Clinical stage	T1N0M0	31 (60.8)
	T2N0M0	19 (37.3)
	T3N0M0	1 (1.9)
Maximal tumor diameter (cm)	≤5.0	45 (88.2)
	>5.0	6 (11.8)
Serum AFP value (ng/ml)	≤20	22 (43.1)
	>20	29 (56.9)
V30 (%)	≤25	47 (92.2)
	>25	4 (7.8)

Abbreviations: AFP = α-fetoprotein: V30% = percentage of noncancerous portion of the liver receiving ≥30 G-equivalent.

Table 3. A list of treatments before proton beam therapy

	Prior treatment	No. patients
Present HCC	TAI/TAE	13
	TAI/TAE+PEIT	3
	TAI/TAE+RF+IA chemotherapy	1
	TAI/TAE+RF+PEIT	1
	TAI/TAE+PT	1
	systemic chemotherapy	1
	PEIT	1
Present HCC and other HCCs	TAI/TAE+(PT)	1
	TAI/TAE+(PEIT)	1
	TAI/TAE+(PT+PEIT)	1
	RF+(surgery+TAI/TAE)	1
Other HCCs	(TAI/TAE)	2
	(TAI/TAE+PT)	2
	(TAI/TAE+PEIT)	1
	(Surgery)	1
	(Surgery +PEIT)	1
	(PT)	1

Abbreviations: HCC = hepatocellular carcinoma; TAI = transcatheter arterial infusion; TAE = transcatheter arterial embolization; PEIT = percutaneous ethanol injection therapy; RF = radiofrequency ablation; IA = intra arterial; PT = proton beam therapy.

Parentheses indicate treatment to unirradiated HCCs.