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Original article

Proton beam therapy for metastatic liver tumors

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ABSTRACT

Purpose: The purpose of this study was to investigate the safety and efficacy of proton beam therapy (PBT) for the treatment of metastatic liver tumors.
Material and methods: A total of 140 patients with liver metastasis who received PBT were retrospectively investigated. The main primary tumor sites were the colorectum (60) and the pancreas (19).
Results: One hundred thirty-three patients (95%) completed treatment. Two patients experienced late adverse effects (rib fracture and cholangitis). The 5-year overall survival (OS) rate was 24%. In the 85 patients with lesions confined to the liver, the 5-year OS rate of was 28%, and in the 55 patients with lesions both inside and outside the liver, it was 16% ($P = 0.007$). Among the patients with lesions confined to the liver, the 5-year OS rate of the 62 patients who received curative treatment was 30%, and that of the 23 patients who received palliative treatment, 23% ($P = 0.016$). Multivariate analysis showed that the treatment strategy (curative and palliative) alone was associated with the OS rate ($P = 0.02$).
Conclusion: PBT is a potentially safe and effective treatment for metastatic liver tumors.
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The liver is the second most common site of metastasis [1,2]. Surgical resection is an option for only a limited number of patients with metastatic liver tumors and depends on the tumor size, number, and location. Most patients receive treatment largely composed of chemotherapy [3–5]. Chemotherapy, however, is associated with its own potentially severe toxicities and complications, and these are frequent causes of treatment interruption or discontinuation. Moreover, a growing number of patients now search for alternative treatments to chemotherapy, either because they are refractory to chemotherapy or because they have declined chemotherapy over concerns about its complications. In fact, every year we see an increase in the number of patients who approach our institute to consult us about the appropriateness of proton beam therapy (PBT) for treating liver metastasis (less than 10 patients per year in the early 2000s, but more than 20 per year in the 2010s).

Although radiotherapy (RT) has been used to treat metastatic liver tumors for over 3 decades, its application has been restricted by the risk of radiation-induced liver damage (RILD) [6]. PBT has the physical characteristic of precisely delivering a high dose of radiation to the target tumor, while greatly limiting the exposure to the regions beyond the target. It is well known that PBT for primary liver cancer enables excellent local control rates with few adverse effects [7–11]. The aim of the present study, therefore, was to assess the safety and efficacy of PBT for metastatic liver tumors.

Methods and materials

Patients

We retrospectively investigated 140 liver metastasis patients who received PBT at the University of Tsukuba between 2001 and 2013. They comprised 83 men and 57 women and had a median age of 63 years (range, 24–87 years). The patients' tumors could be categorized as follows: (1) solitary lesion; (2) multiple lesions that could be included within a few irradiation fields; (3) multiple lesions, with 1 large tumor clinically expected to influence survival; and (4) tumor thrombosis in either the portal or hepatic vein or the bile duct, where control of the tumor growth was predicted to cause a sudden decline in the patients' status.

The primary tumor sites were the colorectum (60 patients), followed by the pancreas (19 patients), the breast (12 patients), the stomach (12 patients), and others (37 patients). Duration from onset to PBT was 0.2–16.8 years (median, 2.9 years). All 7 patients with duration of longer than 10 years had previously received curative surgery for the primary lesions. Of the 140 patients, 85 had tumors confined to the liver, and 49 of those had solitary

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tumors. The remaining 55 patients had tumors both inside and outside the liver. The maximal diameter of the lesions was 1–18 cm (median, 4 cm). Of the 140 patients, 87 had received another form of treatment before PBT, such as chemotherapy, radiofrequency ablation, transcatheter arterial chemoembolization, and surgery. Thirty-one patients received other therapies concurrently, such as chemotherapy and hormone therapy. According to the Eastern Cooperative Oncology Group Performance Status (PS) scale, 127 patients had a PS of 0–1; 9, a PS of 2; 2, a PS of 3; and 2, a PS of 4. Using the Child-Pugh classification for the degree of impairment of liver function, 121 patients were categorized as having class A impairment (scores 5–6); 9, as having class B impairment (scores 7–9); 1, as having class C impairment (scores 10–12); and 9, as unknown. The only patient with class C impairment had drug-induced liver injury. The longest follow-up period after PBT was 11.5 years, and the median follow-up, 1.2 years. Data from the follow-up of 2 patients could not be obtained. Written informed consent was obtained from all patients before PBT. The characteristics of the patients and tumors are shown in Table 1.

Proton beam therapy

CT images were taken at 5-mm intervals during the expiratory phase under a respiratory gating system [12]. At the treatment planning stage, an aperture margin of 5–10 mm, a depth margin of 5–10 mm, and a 5-mm margin on the caudal axes were added to cover the entire clinical target volume to compensate for uncertainty resulting from respiration-induced hepatic movements. These margins included the field margins. A bolus was fabricated for the smearing process. Proton beams from 155 to 250 MeV, generated through a linear accelerator and synchrotron, were spread out and shaped with ridge filters, double-scattering sheets, multicollimators, and custom-made boluses to ensure that the beams conformed to the treatment planning data. The patient's position was registered using an implanted fiducial marker and orthogonal fluoroscopy unit attached to the treatment unit. PBT was performed using a respiratory gating system [7].

The proton beam schedule was selected dependent on the tumor location and treatment strategy. The total irradiation dose was 9–77 Gray equivalent (GY[RBE]) (median, 72.6 GY[RBE]). The most frequent dosage was 72.6 GY(RBE) in 22 fractions, used in 72 lesions, followed by 66 GY(RBE) in 10 fractions, used in 34 lesions. We defined the treatment as curative when the same irradiation doses that are used for primary liver cancers in our institute (66 GY[RBE] in 10 fractions, 72.6 GY[RBE] in 22 fractions, and 70–77 GY[RBE] in 35–37 fractions to the isocenter) [8] could be delivered to all lesions; we defined all other treatments as palliative, that is to say, these doses were not delivered to at least 1 lesion. In the curative treatment group, the total irradiation dose was 66–77 GY(RBE) (median, 72.6 GY[RBE]): 15 cases, 66 GY (RBE); 14 cases, 72.6 GY(RBE); and so forth. In the palliative treatment group, the total irradiation dose was 9–77 GY(RBE) (median, 66 GY[RBE]): 23 cases, 72.6 GY(RBE); 14 cases, 60 GY(RBE); and so forth. The maximum cumulative dose was set for the spinal cord, stomach, and duodenum below 50 GY(RBE), and for the colon, below 60 GY(RBE). The relative biologic effectiveness of the PBT was assumed to be 1.1 [13].

Table 1
Characteristics of the patients.

Sex	M/F (83/57)
Primary site	Colorectum 60 (43%)
	Pancreas 19 (14%)
	Stomach 12 (9%)
	Breast 12 (9%)
	Gall bladder 6 (4%)
	Uterus 6 (4%)
	Lung 5 (4%)
	Adrenal gland 3 (2%)
	Bile duct 3 (2%)
	Esophagus 3 (2%)
	Others 11 (8%)
Duration from onset to PBT	0.2–16.8 (M: 2.9) years
Neoadjuvant therapy for liver lesions	Systemic chemotherapy 72
	Surgery 4
	TACE (TAE) 3
	RFA 2
	PEIT 2
	Hormone therapy 1
	Combined therapy 5
	None 51
PS	0–1/2/3/4 (127/9/2/2)
Child-Pugh classification	A/B/C/unknown (121/9/1/9)
Maximal lesion diameter	1–18 (median: 4) cm
Lesions location	Confined to/inside and outside the liver (85/55)
Number of the lesions	Solitary/multiple (49/36)
Treatment strategy	Curative/palliative (62/23)
Concurrent therapy	Systemic chemotherapy 26
	Hormone therapy 2
	Hyperthermia 1
	Systemic chemotherapy + hyperthermia 1
	Immunotherapy 1
	None 109

Abbreviations: PBT: proton beam therapy, TACE: transcatheter arterial chemoembolization, RFA: radiofrequent ablation PEIT: percutaneous ethanol injection therapy.

Treatment after PBT

A total of 53 patients received adjuvant therapy after PBT: chemotherapy, 42 patients; immunotherapy, 5 patients; hormone therapy, 4 patients; others, 2. Moreover, a total of 35 patients received additional treatment to the new lesions or recurrent tumors: PBT, 11 patients; chemotherapy, 9 patients; chemotherapy and PBT, 5 patients; PBT and RT, 3 patients; RT, 2 patients; surgery and chemotherapy, 2 patients; and others, 3.

Follow-up procedures and evaluation criteria

During the treatment sessions, acute treatment-related toxicities were assessed weekly in all patients. After completion of PBT, the patients were evaluated by means of physical examinations, blood tests, and CT or MRI scans. Assessment of response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1) [14]. We defined local failure as an increase in the maximal diameter of the treated target lesions of more than 20% or 5 mm. Adverse events were assessed after every procedure according to the Common Terminology Criteria for Adverse Effects (CTCAE; version 4.0) [15]. The patients treated before 2010 were also retrospectively reviewed using the CTCAE, version 4.0.

For examination of safety, the treatment completion rate was calculated and late adverse effects were examined. To examine the treatment effect, the overall survival (OS) rate and local control (LC) rate were calculated using the Kaplan–Meier method. The OS rate was analyzed according to the location and number of lesions, treatment strategy, primary site, and concurrent therapy.

Statistical analysis

The OS rate was examined using the log-rank test. Univariate and multivariate analyses were performed using a Cox proportional hazards model. Probability values below 0.05 were considered significant.

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