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CLINICAL INVESTIGATION **Head and Neck**

MUCOSAL MALIGNANT MELANOMA OF THE HEAD AND NECK TREATED BY CARBON ION RADIOTHERAPY

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Purpose: To evaluate the efficacy of carbon ion radiotherapy for mucosal malignant melanoma of the head and neck.
Methods and Materials: Between 1994 and 2004, 72 patients with mucosal malignant melanoma of the head and neck were treated with carbon ion beams in three prospective studies. Total dose ranged from 52.8 GyE to 64 GyE given in 16 fixed fractions over 4 weeks. Clinical parameters including gender, age, Karnofsky index, tumor site, tumor volume, tumor status, total dose, fraction size, and treatment time were evaluated in relation to local control and overall survival.
Results: The median follow-up period was 49.2 months (range, 16.8–108.5 months). Treatment toxicity was within acceptable limits, and no patients showed Grade 3 or higher toxicity in the late phase. The 5-year local control rate was 84.1%. In relation to local control, there were no significant differences in any parameters evaluated. The 5-year overall and cause-specific survival rates were 27.0% and 39.6%, respectively. For overall survival, however, tumor volume (≥100 mL) was found to be the most significant prognostic parameter. Of the patients who developed distant metastasis, 85% were free from local recurrence.
Conclusion: Carbon ion radiotherapy is a safe and effective treatment for mucosal malignant melanoma of the head and neck in terms of high local control and acceptable toxicities. Overall survival rate was better than in those treated with conventional radiotherapy and was comparable to that with surgery. © 2009 Elsevier Inc.

Carbon ion radiotherapy, Mucosal malignant melanoma, Heavy ion beam, Linear energy transfer (LET), Head and neck.

INTRODUCTION

The worldwide incidence of malignant melanoma seems to be influenced by racial and/or geographical differences. For example, the rates are 16.2 per 100,000 in the United States and 0.383 per 100,000 in Japan (1–3). However, the incidence of malignant melanoma arising from mucosal membrane is relatively high in Japan compared with Western countries. Regarding the head-and-neck region, it constitutes approximately 30% of all malignant melanomas in Japan, whereas it represents only 1% in Western countries (4, 5). Thus, the rate of patients with mucosal malignant melanoma of the head and neck in both Japan and the United States comes to approximately 0.1 per 100,000, suggesting that this specific condition may generally be rare worldwide (6).

Because of this low incidence, the number of patients with mucosal malignant melanoma of the head and neck encountered by a single facility is also small, and it has as yet not been possible to establish an optimum treatment modality. Surgical resection has traditionally been the primary mode of treatment for this disease. Wide en-bloc excision is needed for the complete removal of the tumor, but in the case of a large tumor mass or involvement of adjacent critical structures, surgery is counter-indicated for cosmetic and functional reasons. Furthermore, even when total resection of the gross tumor has been performed, the outcome in terms of local tumor control and long-term survival has not been satisfactory. It is reported that the local recurrence rate is approximately 50%, and the overall postsurgery 5-year survival rate is 28–36% (7–13).

Malignant melanoma has long been regarded as radioresistant because it often demonstrated poor regression after photon radiotherapy, with recurrence developing within

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1 year (14, 15). It is reported, however, that the use of a high dose per fraction might improve the local response, with the 3-year local control rate being 30–60% (16, 17). This suggests that irradiation could be a definitive treatment modality for cure if administered appropriately.

In 1994, carbon ion radiotherapy was initiated at the National Institute of Radiological Sciences (NIRS) in Japan (18–20). Carbon ion beams provide superior physical dose distribution because of their finite range in the target tissue, and they possess a biological advantage due to their high relative biological effectiveness (RBE) in the Bragg peak (21, 22). It is therefore reasonable to assume that carbon ion beams might be superior to X-rays for the management of tumors characterized by poor radiosensitivity, such as malignant melanoma.

This report presents the results of a radiotherapy regimen for 72 patients with mucosal malignant melanoma of the head and neck treated with carbon ion beams at NIRS.

METHODS AND MATERIALS

Patients

From June 1994 through February 2004, a total of 156 patients with mucosal malignant melanoma were treated with carbon ion beams in three prospective trials: a Phase I/II study using an 18-fraction schedule ($n = 2$), a Phase I/II study using a 16-fraction schedule ($n = 9$), and a Phase II study ($n = 145$) with a 16-fraction schedule. The treatment techniques of the three protocols were the same except for the fractionation. The eligibility criteria were also the same. Of these patients, 72 treated with carbon ion radiotherapy on a 16-fraction schedule as primary treatment for the tumor were analyzed. Patient characteristics are shown in Table 1. All patients had gross tumors. Twenty-two patients had tumors with no previous treatment, and the remaining 50 patients had recurrent tumors after surgery or after chemotherapy. Diagnosis was histologically confirmed in all patients, and informed consent was obtained.

Carbon ion radiotherapy

The patient was positioned in a customized cradle, with the face immobilized with a low-temperature thermoplastic device. If the patient had metal prostheses that would be included in the radiation field, the prostheses were removed to avoid artifacts in the planning CT images.

A set of 2.5-mm-thick CT scans was taken for treatment planning, with the patient lying on an immobilization device. Three-dimensional treatment planning was performed using HIPLAN, a program developed at NIRS (23). This system permits the fusion of MRI images with CT images for precise delineation of the target volume. To create a clinical target volume, a margin of 5–10 mm was added to include both gross and potentially microscopic disease. Furthermore, a margin of 3–5 mm was added as an internal and setup margin around the clinical target volume to create a final planning target volume. When the tumor was located close to critical organs, such as the brain stem and spinal cord, those margins were reduced as necessary.

Dose was expressed in gray equivalent (GyE), which was calculated by multiplying the physical dose by the RBE. The clinical RBE of the carbon beam at our institute was determined according to the RBE for acute skin reaction, which was assessed to be 3.0 at the distal part of the spread-out Bragg peak (24).

Table 1. Patient characteristics

Gender (M/F)	35/37
Age (y), range (median)	38–83 (64)
Karnofsky index	
60	1 (1.4)
70	7 (9.7)
80	23 (32.0)
90	41 (56.9)
Tumor site	
Nasal cavity	44 (61.1)
Ethmoid sinus	9 (12.5)
Maxillary sinus	6 (8.3)
Sphenoid sinus	1 (1.4)
Oral cavity	7 (9.7)
Pharynx	5 (7.0)
Tumor volume (ml)	
<100	35 (48.6)
≥100, <200	25 (34.7)
≥200	12 (16.7)
Tumor status	
No previous treatment	22 (16.7)
Recurrence after surgery/CT	50 (83.3)

Abbreviations: M = male; F = female; CT = chemotherapy.
Values are number (percentage) unless otherwise noted.

At every treatment session, the patient's position was verified with a computer-aided on-line positioning system. The patient was positioned on the treatment couch with immobilization devices, and digital orthogonal X-ray images were taken and transferred to the positioning computer. The positioning images were compared with reference images that were digitally reconstructed from CT scans. If the difference in positioning was >1 mm, the treatment couch was moved until an acceptable position was attained.

Carbon ion radiotherapy was given in 16 fractions over 4 weeks, at 4 treatment days per week. The overall treatment time was 23–38 days (median, 28 days).

After radiotherapy, acute toxicity of skin, mucosa, and brain was scored according to the Radiation Therapy Oncology Group acute radiation morbidity scoring criteria, and late toxicity was scored according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer late radiation morbidity scoring scheme (25).

Local control and survival

Rates of local control, overall survival, and cause-specific survival were calculated using the Kaplan-Meier algorithm, and the potential prognostic factors (gender, age, Karnofsky index, tumor site, tumor volume, tumor status, total dose, fraction size, and treatment time) for local control and overall survival were evaluated using the log–rank test. Multivariate analysis was performed using the Cox proportional hazards model.

RESULTS

Treatment and tumor control

The median follow-up period was 49.2 months (range, 16.8–108.5 months). The cumulative 5-year local control rate for all 72 patients was 84.1% (Fig. 1). Tumor recurrence at the primary site was observed in 9 patients (12.5%) at 4.3–20.0 months (median, 13.9 months) after carbon ion radiotherapy, with 5 of the 9 subsequently receiving salvage