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Phase II trial

Phase II study of proton beam therapy as a nonsurgical approach for mucosal melanoma of the nasal cavity or para-nasal sinuses

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ABSTRACT

Purpose: The aim of this phase II study was to assess the clinical benefit of proton beam therapy for mucosal melanoma of the nasal cavity and para-nasal sinuses.

Materials and methods: N0M0 mucosal melanoma of the nasal cavity and para-nasal sinuses were enrolled. Proton therapy was delivered three times per week with a planned total dose of 60 GyE in 15 fractions. Primary endpoint was local control rate at 1 year after treatment. Based on the results of a pilot study, the local control rate was estimated at 75%.

Results: Thirty-two patients were enrolled from June 2008 through October 2012. Patient characteristics were as follows: median age 73 years (range, 36–89 years); male/female ratio, 12/20; and T stage 3/4, 11/21. Local control rate at 1 year was 75.8% (95% CI: 63.8–92.4%). With a median follow-up period of 36.4 months, 3-year overall survival rate was 46.1%. The most frequent pattern of first failure was distant metastasis. The main cause of death was cancer death due to distant metastases (93.3%).

Conclusions: Proton beam therapy showed sufficient local control benefits for mucosal melanoma as an alternative treatment of surgery.

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Mucosal melanoma of the head and neck is a rare oncological entity which accounts for approximately 10% of melanomas arising in the head and neck and only 1% of all malignant melanomas [1]. Several reports have described the use of radiotherapy alone for mucosal melanoma of the head and neck, with 5-year survival rates slightly less than those of the surgical approach [2–4]. In Japan, Wada et al. [4] reported a series of 66 cases of mucosal melanoma of the head and neck, of which 21 were treated with radiotherapy as the main modality. The rate of complete response in these 21 cases was 29%, and the 3-year disease-specific survival rate was 33%. However, X-ray irradiation of these tumors is limited by dose distribution to nearby organs at risk, such as the optic nerve and brain stem, and the delivery of sufficient dosage to the planned target volume is often difficult.

Proton beam therapy (PBT) is characterized by rapid fall-off at the distal end of the Bragg peak and a sharp lateral penumbra, depending on the energy, depth, and delivery [5]. Because of its physical characteristics, PBT provides better dose distribution than X-ray irradiation. In a pilot clinical trial [6], 14 patients with mucosal melanoma underwent a hypofractionated course of PBT as the definitive modality. A total dose of 60 Gray equivalent (GyE) was delivered in 15 fractions, with a dose per fraction of 4 GyE. The local control rate of 86% and 3-year overall survival rate of 58% were comparable to the outcomes observed with photon RT.

Here, we conducted a prospective phase II study to examine the efficacy and safety of PBT as an alternative treatment to surgery.

Patients and methods

Eligibility

Eligibility at the National Cancer Center Hospital East and Tsukuba University Hospital. Entry criteria were (1) pathologically proven mucosal melanoma of the head and neck; (2) clinical TNM status of N0M0; (3) Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less; (4) adequate organ function; and (5) no active concomitant malignancy. The study protocol was approved by the institutional review boards of the National Cancer Center Hospital and Tsukuba University Hospital and written informed consent to treatment was obtained from all patients before trial entry. This trial was registered with the UMIN-clinical trials registry (UMIN-CTR: UMIN000001505).

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Diagnosis and pretreatment evaluation

Pretreatment clinical evaluation was performed using magnetic resonance imaging (MRI); cervical, chest, and abdominal computed tomography (CT); and/or positron emission tomography-CT (PETCT).

Radiological evaluations for staging were jointly reviewed by radiologists, surgeons, and oncologists at our institution. In the present study, all diseases were staged based on the 7th TNM classification.

Treatment

Treatment methods and procedures in this phase II study followed those of a previous pilot study [6]. PBT was delivered three times per week for a planned total dose of 60 GyE in 15 fractions using a 150- to 190-MeV proton beam. Treatment planning was performed with a three-dimensional CT planning system. Relative biologic effectiveness was defined as 1.1, based on our preclinical experiments. Gross tumor volume (GTV) was determined with pretreatment CT, MRI and/or PET-CT. CTV was defined as the region of the gross tumor lesion and adjacent sinuses. When intracranial invasion was seen, the area of T2-weighted prolongation on MRI was also included in the CTV.

The planning target volume (PTV) was defined as the CTV plus a 1–3 mm margin but could be finely adjusted where necessary in consideration of organs at risk. Beam energy and the spread-out Bragg peak were fine-tuned such that the PTV encompassed a 90% isodose volume of the prescribed dosage (Fig. 1). Irradiation dose and volume for organs at risk was usually minimized using a two- or three-field technique. Dose constraints for organs at risk at 4 GyE per fraction were (1) surface of the brainstem, 45 GyE; (2) center of the brainstem, 33 GyE; (3) optic nerves on the healthy side/chiasm, 42 GyE; and (4) optic lens, 13 GyE. To evaluate the risk of radiation-induced complications in normal tissue, dose–volume histograms were calculated for all patients. Patients were immobilized with custom-made immobilization devices that provided high reproducibility at every treatment fraction. Patient setup was verified before the delivery of each fraction, using a digital radiography subtraction system.

Toxicity

Toxicities were graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Weekly follow-up was continued until acute toxicity was easily manageable, and post-treatment MRI was performed at 3 months after the end of PBT to rule out treatment-induced empyema and brain necrosis.

Response evaluation

To confirm local control, MRI and/or PET-CT was performed every 3–6 months after the end of treatment, and distant metastases were assessed by CT/PET-CT. In our previous research, we demonstrated that radiological response evaluation within 6 months after radiation therapy with or without chemotherapy in patients with malignancies of the nasal cavity or paranasal sinuses did not have a significant impact on prognosis [7]. The achievement of initial local control was confirmed when all of the following criteria were fulfilled: (1) patients were alive at 1 year after the initiation of treatment; (2) no progressive disease was detected at the primary site for 1 year; and (3) no recurrence was detected at the primary site for 1 year.

Statistical analysis

The primary endpoint was local control rate at 1 year, which was estimated from the pilot study to be 75%. When a local control rate is below 50%, the study treatment is regarded as having no advantage over other alternatives, and thus the local control rate and its threshold are set at 75% and 50%, respectively. On the assumption of $\alpha = 0.05$ and $\beta = 0.9$, the study required 32 patients. Overall survival time was calculated from the start of treatment to the date of death or last confirmed date of survival. Survival time was censored at the last confirmed date of survival if the patient was alive. Progression-free survival (PFS) time was defined from

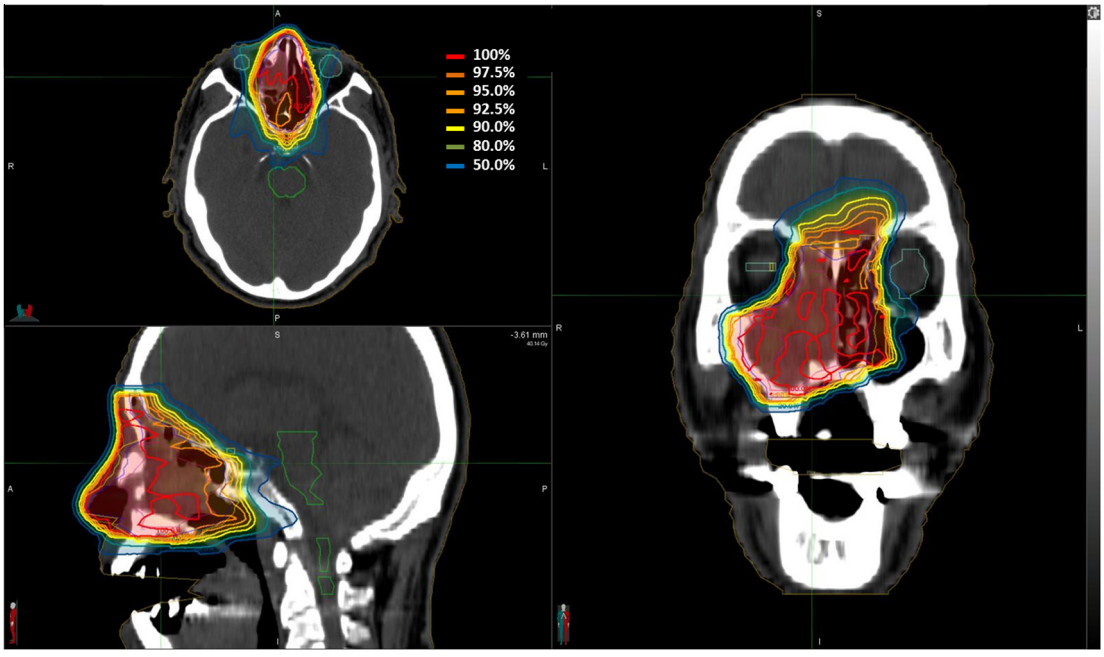

Fig. 1. Case: Mucosal melanoma T4N0M0. The primary tumor was located in the maxillary sinus. CTV included not only the maxillary sinus but also the nasal cavity. PBT can provide curative high-dose irradiation to the tumor volume without increasing toxicity to normal tissue.