Int. J. Radiation Oncology Biol. Phys., Vol. 81, No. 5, pp. 1473–1478, 2011

0360-3016/$ - see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2010.08.009

CLINICAL INVESTIGATION **Head and Neck**

PROTON BEAM THERAPY FOR UNRESECTABLE MALIGNANCIES OF THE NASAL CAVITY AND PARANASAL SINUSES

Sadamoto Zenda, M.D.,* Ryosuke Kohno, Ph.D.,* Mitsuhiko Kawashima, M.D.,* Satoko Arahira, M.D.,* Teiji Nishio, Ph.D.,* Makoto Tahara, M.D., PhD.,† Ryuichi Hayashi, M.D.,‡ Seiji Kishimoto, M.D., Ph.D.,§ and Takashi Ogino, M.D.*

Division of *Radiation Oncology, †Gastrointestinal Oncology and Endoscopy, and ‡Head and Neck Surgery, National Cancer Center Hospital East, Chiba, Japan; and §Department of Head and Neck Surgery, Tokyo Medical and Dental University, Tokyo, Japan

Purpose: The cure rate for unresectable malignancies of the nasal cavity and paranasal sinuses is low. Because irradiation with proton beams, which are characterized by their rapid fall-off at the distal end of the Bragg peak and sharp lateral penumbra, depending on energy, depth, and delivery, provide better dose distribution than X-ray irradiation, proton beam therapy (PBT) might improve treatment outcomes for conditions located in proximity to risk organs. We retrospectively analyzed the clinical profile of PBT for unresectable malignancies of the nasal cavity and paranasal sinuses.

Methods and Materials: We reviewed 39 patients in our database fulfilling the following criteria: unresectable malignant tumors of the nasal cavity, paranasal sinuses or skull base; N0M0 disease; and treatment with PBT (>60 GyE) from January 1999 to December 2006.

Results: Median patient age was 57 years (range, 22–84 years); 22 of the patients were men and 17 were women. The most frequent primary site was the nasal cavity (n = 26, 67%). The local control rates at 6 months and 1 year were 84.6% and 77.0%, respectively. With a median active follow-up of 45.4 months, 3-year progression-free and overall survival were 49.1% and 59.3%, respectively. The most common acute toxicities were mild dermatitis (Grade 2, 33.3%), but no severe toxicity was observed (Grade 3 or greater, 0%). Five patients (12.8%) experienced Grade 3 to 5 late toxicities, and one treatment-related death was reported, caused by cerebrospinal fluid leakage Grade 5 (2.6%).

Conclusion: These findings suggest that the clinical profile of PBT for unresectable malignancies of the nasal cavity and paranasal sinuses make it is a promising treatment option.

Proton beam therapy, nasal cavity, paranasal sinus, radiotherapy, craniofacial surgery, organ preservation.

INTRODUCTION

Malignant tumors that arise in the nasal or paranasal sinuses and that otherwise involve the base of the skull usually present a difficult clinical problem. Most cases are curatively treated by craniofacial surgery and postoperative radiotherapy, either alone or in combination (1–5). However, several problems with this strategy remain. In cases in which the disease has spread deeply to the intracranial region, surgical approaches are often complicated by serious functional deformity, and satisfactory surgical clearance is often markedly difficult to obtain (6 ,7). For theses cases, definitive radiotherapy is often performed as an alternative treatment, but aggressive irradiation of the intracranial region increases the risk of severe late toxicity (8–10).

Proton beams are characterized by their rapid fall-off at the distal end of the Bragg peak and sharp lateral penumbra, depending on energy, depth, and delivery (11). These physical characteristics give proton beam therapy (PBT) better dose distribution than X-ray irradiation, and PBT is now deemed a feasible and effective treatment modality that provides curative high-dose irradiation to the tumor volume without increasing normal tissue toxicity. However, few papers have described the use of PBT in unresectable malignancies of the nasal cavity and paranasal sinuses.

Here, we conducted a retrospective analysis to clarify the clinical profile of PBT for unresectable malignancies of the nasal cavity and paranasal sinuses.

METHODS AND MATERIALS

Patients

A total of 39 patients in our database fulfilling the following criteria were reviewed: unresectable malignant tumors of the nasal

Reprint requests to: Sadamoto Zenda, M.D., Division of Radiation Oncology, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa, Chiba 277-8577, Japan. Tel: +81-4-7133-1111; Fax: +81-4-7131-9960; E-mail: szenda@east.ncc.go.jp

Conflict of interest: none.

Received Feb 17, 2010, and in revised form July 23, 2010. Accepted for publication Aug 5, 2010.

cavity, paranasal sinuses, or skull base; no lymph node metastases or distant metastases; and treatment with definitive PBT (>60 GyE) from January 1999 to December 2006. Unresectable disease was defined as the inability of a surgeon to perform complete resection because of functional or technical limitations. Patients recruited for other clinical trials were excluded from this analysis.

Pretreatment evaluation

Pretreatment clinical evaluation was performed using magnetic resonance imaging (MRI), cervical, chest, and abdominal computed tomography (CT), or positron emission tomography (PET)–CT. Tumor staging in the present study was based on the sections on the nasal cavity and paranasal sinuses in the TNM classification of the International Union Against Cancer (UICC 6th), regardless of histology type. Radiological evaluations for staging were jointly reviewed by radiologists, head-and-neck surgeons, and medical oncologists at our institution.

Efficacy and toxicity evaluation

Overall survival was calculated from the start of treatment to the date of death or last confirmed date of survival. Progression-free survival (PFS) was defined as from the day of initiation of treatment to the first day of confirmation of progressive disease or death by any cause. Local control was defined as the lack of progressive disease at the primary site.

The pattern of treatment failure was defined as the first site of failure, with local failure indicating recurrence or persistent disease after PBT at the primary site, regional failure indicating neck lymph node metastases after PBT, and distant failure indicating recurrence at any site beyond the primary site and neck lymph nodes.

Acute and late toxicities were graded according to the Common Terminology Criteria for Adverse Events v3.0 (CTCAE v3.0). Time to onset of toxicity Grade 2 or greater was defined as from the day of initiation of treatment to the first day of confirmation of late toxicity of Grade 2 or greater.

Proton beam therapy

Treatment planning was performed on a three-dimensional CT planning system. In this system, the proton beam was generated with a Cyclotron C235 with an energy of 235 MeV at the exit. Relative biologic effectiveness was defined as 1.1, based on our preclinical experiments (12). Proton beam therapy at our institution is conducted using passive irradiation with dual-ring double-scatter methods. Dose distribution is optimized using the spread-out Bragg peak method and obtained using a broad-beam algorithm.

Gross tumor volume (GTV) was determined by pretreatment with CT, MRI, and PET-CT, either alone or in combination. Clinical target volume (CTV) was defined as the GTV plus a 5-mm margin and the sinuses adjacent to the GTV. In cases with brain invasion, the area of T2 prolongation on MRI was also included in the CTV. Planning target volume (PTV) was basically defined as the CTV plus a 3-mm margin but could be finely adjusted where necessary in consideration of organs at risk. Beam energy and spread-out Bragg peak were fine-tuned such that the PTV was at least covered in a 90% isodose volume of the prescribed dosage. The irradiated dose was minimized by delivery of the proton beam with two or three beam arrangements (Fig. 1). The biologically equivalent dose (BED) using a linear-quadratic model was defined as follows: BED = $nd\ (1+ d/\ 1/(\alpha/\beta))$, where n is the fractionation number, d is the daily dose, and α/β ratio was 3.0 Gy for normal tissue (12).

Dose constraints for organs at risk at 2.5 GyE per fraction were as follows: (*1*) surface of brainstem, 51 GyE; (*2*) center of brainstem, 46 GyE; (*3*) optic nerves of the healthy side/chiasm, 46 GyE; and (*4*) optic lens, 9 GyE.

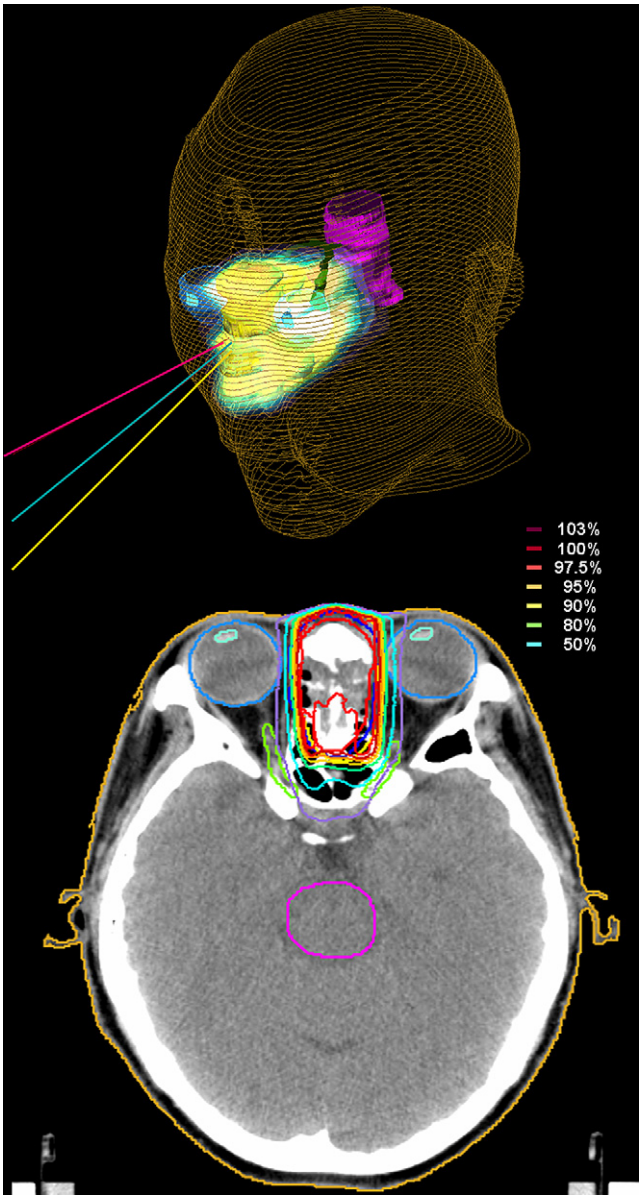

Fig. 1. Beam arrangement. Irradiation dose and volume for organs at risk was usually minimized using a noncoplanar three-field technique. In this case, curative high-dose irradiation to the tumor volume was provided, whereas overdose irradiation to the optic nerve was avoided.

Statistical analysis

Overall and progression-free survival time were estimated by the Kaplan–Meier product–limits method using commercially available statistical software (StatView version 5.0, SAS Institute, Cary, NC).

Univariate analysis was conducted using the log-rank test and multivariate analysis using the Cox proportional hazard model.

RESULTS

Patient characteristics

All patients had T4 disease and an Eastern Cooperative Oncology Group performance status of 0 or 1. Median age