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Protons for olfactory neuroblastoma

Proton beam therapy for olfactory neuroblastoma

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ABSTRACT

Purpose: To clarify the efficacy and feasibility of proton beam therapy (PBT) for olfactory neuroblastoma (ONB).

Methods and materials: We retrospectively reviewed 42 consecutive patients who received PBT with curative intent for ONB at National Cancer Center Hospital East from November 1999 to March 2012.

Results: Five patients (12%) had Kadish A disease, nine (21%) had Kadish B, and twenty-eight (67%) had Kadish C. All patients except one received a total dose of 65 Gy (relative biological effectiveness: RBE) in 26 fractions. Twenty-four patients (57%) received induction and/or concurrent chemotherapy. The median follow-up for all eligible patients was 69 months (7–186). The 5-year overall survival (OS) and progression-free survival (PFS) rates were 100% and 80% for Kadish A, 86 and 65% for Kadish B, and 76% and 39% for Kadish C, respectively. The sites of the first progression were local in six patients (30%), regional in eight (40%), distant in two (10%), local and regional in two (10%), and local and distant in two (10%). Late adverse events of grade 3–4 were seen in six patients (ipsilateral visual impairment, 3; bilateral visual impairment, 1; liquorrhea, 1; cataract, 1).

Conclusion: PBT was a safe and effective modality for ONB.

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Olfactory neuroblastoma (ONB) is a rare malignant neoplasm of the nasal cavity, believed to arise from the olfactory epithelium [1]. Because of its rarity, a standard treatment strategy has not been established. Radiotherapeutic management for ONB is challenging because of its proximity to organs at risk (OAR), such as the anterior visual pathway or brain stem [2–8]. Proton beam therapy (PBT) can provide a better dose distribution compared with conventional X-ray treatment because of its physical characteristics [9]. Therefore, PBT may facilitate curative high-dose irradiation of the tumor, without increasing normal tissue toxicity [10,11]. In our institution, we recommended the treatment modality according to the stage classification based on Kadish et al. [12]. For patients with Kadish A, which is limited to the nasal cavity, single modality treatment by surgery or PBT is recommended. For those with Kadish B, which extends to the paranasal sinus, concurrent therapy of PBT and chemotherapy is recommended. For those with Kadish C, which extends beyond the paranasal sinus, induction chemotherapy followed by concurrent therapy of PBT and chemotherapy is recommended. There are multiple reasons why we recommend induction chemotherapy for Kadish C: (1) to reduce the intracranial irradiated volume and risk of radiation brain injury, (2) expecting the reduction of distant metastases, and (3) to quickly start treatment. For those with Kadish D, which is accompanied by cervical lymph node or distant metastases, curative treatment is not usually recommended. We previously reported clinical outcomes following PBT for ONB in our institution in 2007 [13]. To further examine the efficacy and feasibility of PBT for ONB, we provide an update of our experience.

Methods and materials

Patient identification

We identified 42 consecutive patients who received PBT with curative intent for ONB at National Cancer Center Hospital East from November 1999 to March 2012. With the approval of our Institutional Review Board, we performed a retrospective chart review of patient characteristics, treatments, and clinical outcomes.

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Treatments

All patients received passive PBT. The clinical target volume (CTV) typically included the gross tumor volume and adjacent sinus. The planning target volume (PTV) was set by isotropically expanding the CTV by 2 mm. To avoid late toxicity, we determined the dose constraints for OAR as follows: <64 Gy (relative biological effectiveness: RBE) for the surface of the brainstem, <53 Gy (RBE) for the center of the brainstem, <60 Gy (RBE) for the optic nerves and optic chiasm, and <13 Gy (RBE) for the optic lenses. The dose was prescribed at the isocenter. A dose distribution and dose–volume histogram for typical treatment planning is shown in Figs. 1 and 2.

Endpoints and statistical analysis

As clinical outcomes, overall survival (OS), progression-free survival (PFS), the site of the first progression, and adverse effects were evaluated. The response to induction chemotherapy was assessed using the Response Evaluation Criteria in Solid Tumors (RECIST). Adverse effects were evaluated by the chart review and graded based on the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Non-hematological adverse effects of grade 3 or higher were collected. Adverse effects that occurred within 3 months from the start of PBT were regarded as acute adverse effects, while those that occurred after 3 months were regarded as late adverse effects.

We used EZR [14] version 1.27 for statistical analysis. Time analysis was calculated from the day when induction chemotherapy began for patients who received induction chemotherapy, and from the day when PBT began for the others. Fisher's exact test was used to determine the significance of intergroup differences in discontinuous variables, and the independent *t*-test was used for continuous variables. Survival probabilities were estimated using the Kaplan–Meyer method, and comparisons of survival according to clinical parameters were performed using the log-rank test. Differences were deemed significant when two-tailed *p*-values were less than 0.05.

Results

Patient characteristics

The median follow-up for all eligible patients was 69 months (7–186). Patient characteristics are shown in Table 1. For induction chemotherapy, a regimen comprising three agents (cisplatin, S-1, and docetaxel) [15,16] was used for twelve patients. A nonplatinum-based regimen with irinotecan and docetaxel was used for six patients [17]. Other regimens used were cisplatin and etoposide for one patient, cisplatin, etoposide, and adriamycin for one patient, cisplatin, docetaxel, and adriamycin for one patient, and cisplatin, etoposide, Adriamycin, and vincristine for one patient. For concurrent chemotherapy, a single cisplatin regimen was used except for one patient who received a regimen with irinotecan and docetaxel.

Survival

The 5-year OS and PFS rates were 100% and 80% for Kadish A, 86% and 65% for Kadish B, and 76% and 39% for Kadish C, respectively (Fig. 2). OS and PFS according to the age are shown in Figs. 3 and 4.

Patients who were younger than 50 years showed significantly better OS than those who were 50 years or older ($p = 0.01$) (Supplementary Fig. 1). However, PFS was not significantly different between the two groups ($p = 0.34$) (Supplementary Fig. 2). Patient characteristics according to age are summarized in Supplementary Table 1.

Among 28 Kadish C patients, eight did not receive chemotherapy because of comorbidities, old age, or patient's refusal. Among twenty patients who received induction chemotherapy, nine patients received concurrent chemotherapy, while eleven patients did not receive it because of a poor response to induction chemotherapy, severe adverse effects, or patient's refusal. The response to induction chemotherapy was a complete response in one patient (5%), partial response in five (25%), stable disease in eleven (55%), and progressive disease in three patients (15%). OS and PFS according to the usage of chemotherapy in Kadish C

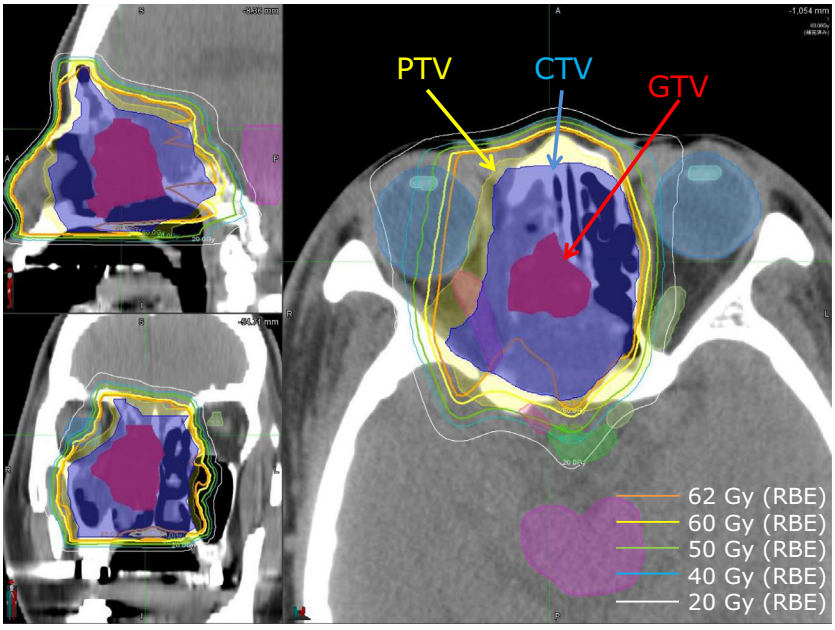

Fig. 1. Dose distribution for typical treatment planning. *Abbreviations:* GTV = gross tumor volume; CTV = clinical target volume; PTV = planning target volume; RBE = relative biological effectiveness.