Scientific Research Publishing

Journal of Cancer Therapy, 2017, 8, 327-332
http://www.scirp.org/journal/jct
ISSN Online: 2151-1942
ISSN Print: 2151-1934

Preliminary Result of Hyperfractionated High-Dose Proton Beam Radiotherapy for Pediatric Skull Base Chordomas

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How to cite this paper: Mizumoto, M., Akutsu, H., Yamamoto, T., Fukushima, T., Oshiro, Y., Takizawa, D., Tanaka, K., Goto, M., Okumura, T., Matsumura, A., Tsuboi, K. and Sakurai, H. (2017) Preliminary Result of Hyperfractionated High-Dose Proton Beam Radiotherapy for Pediatric Skull Base Chordomas. *Journal of Cancer Therapy*, **8**, 327-332.
https://doi.org/10.4236/jct.2017.84028

Received: February 17, 2017
Accepted: April 12, 2017
Published: April 14, 2017

Abstract

Objective: Proton beam therapy (PBT) may provide good local control for skull base chordoma and reduced toxicities, especially for pediatric patients. **Methods**: We evaluated the efficacy and safety of hyperfractionated high-dose PBT in6 pediatric patients with newly-diagnosed skull basechordoma who were treated with PBT at our institute from 2011 to 2015. The patients were 5 males and one female, and the median age was 9 years old (range: 5 - 13). All patients received surgery before PBT. The median period between surgery and PBT was 57 days (range: 34 - 129 days). The treatment dose was 78.4 GyE in 56 fractions (twice per day). **Results**: All patients received PBT without severe acute toxicity. The median follow-up period was 27 months (range: 21 - 71 months). At the last follow-up, all patients were alive and all tumors were well controlled. Acute and late toxicities were generally acceptable, with only grade 1 and 2 events. Late toxicities included growth hormone abnormality and cortical hormone abnormality. One patient needed growth hormone and cortical hormone replacement therapy. **Conclusion**: Although the number of pediatric patients was small, our overall findings in the 6 cases indicate that hyperfractionated high-dose PBT is safe and effective for pediatric patients with skull base chordoma.

Keywords

Chordoma, Radiotherapy, Proton Beam Therapy, Proton Radiotherapy, Pediatrics

1. Introduction

Chordomas are rare primary bone tumors that originate from remnants of the notochord. Chordomas are low grade histologically, but their aggressive behavior means that few patients can be cured by surgery alone [1] [2]. Postoperative radiotherapy is standard therapy, but the radiation dose for a skull base chordomais limited by normal tissue around the tumor, such as the brainstem, optic chiasm and temporal lobe. This limits of conventional radiotherapy considered about 50 Gy in 25 fractions, which is insufficient and results in a poor local control rate of 50% or less [3].

Proton beam therapy (PBT) can deliver a high dose to a tumor without critical late toxicity for surrounding normal tissue [4] [5] [6]. We have reported early clinical results in 13 cases of clivalchordomas treated by PBT, in which >70 GyE was delivered and the 5-year local control rate exceeded 50% [7]. Other studies have also shown good local control after high dose PBT [8] [9]. We found that hyperfractionated high-dose PBT (78.4 GyE in 56 fractions, 2 fractions per day) for skull base chordoma gave a 5-year local control rate of 70% to 80% in adults [10]. But the information of safety and effectiveness of PBT for pediatric skull base chordoma is still insufficient.

Here, we describe treatment of pediatric skull base chordoma using the same PBT protocol as that used for adult patients.

2. Material and Methods

2.1. Patients

From January 2011 to December 2015, a total of 6 patients with newly-diagnosed chordoma received postoperative PBT at our institute. The patients comprised 5 males and 1 female, and had a median age of 9 years old (range: 5 to 13 years old). One had received partial resection, 4 had undergone subtotal, and one had undergone gross total resection (This patient had multiple relapse) before PBT. None had metastasis at the time of PBT. The characteristics of the patients are shown in **Table 1**. Institutional Review Boards approved the study at our hospital.

2.2. Treatment Methods

We have been treating patients with a hyperfractionation scheme (2 fractions per day). The fractional and total doses were escalated to 1.40 CGE (56 fractions) and 78.40 CGE, respectively. For treatment planning, computed tomography (CT) was performed in slices of 5 mm or less in the treatment position. Proton beam therapy was basically performed for partial resection or subtotal resection cases. At first, 39.2 GyE in 28 fractions was irradiated to tumor bed and surgical pathway as possible. From 40.6 to 58.8 GyE, tumor bed and surgical pathway close tumor bed was irradiated. At this timing, the dose of optic chiasm (50% or less) and brain stem (90% or less at the surface) was reduced. From 60.2 to 78.4 GyE, only tumor bed was irradiated. At this timing, the dose of optic chiasm

(almost zero) and brain stem (50% or less at the surface) was additionally reduced.

2.3. Follow-Up Procedures and Evaluation Criteria

Acute treatment-related toxicities were assessed weekly during treatment. After completion of PBT, the patients were evaluated by physical examinations, MRI, and blood tests every 6 months for the first 5 years and every 12 months the reafter. Acute and late treatment-related toxicities were assessed using the National Cancer Institute Common Criteria ver.3.0 and the RTOG/EORTC late radiation morbidity scoring scheme.

3. Results

The period between surgery and PBT was 34 to 129 days (median 56 days), and PBT was completed in 41 to 46 days (median 43 days). At the time of analysis, all patients were alive and median follow-up period was 27 months (range: 21 - 71 months). All tumors were well controlled.

Acute toxicity was generally acceptable, with only grade 1 and 2 events. 3 patients had growth hormone abnormalityas late toxicities. 2 of 3 patients were checked by only blood test. And one of three patients needed growth hormone and cortical hormone replacement therapy one year after PBT. This patient received surgery several times before PBT and growth hormone and cortical hormone also began to decrease before PBT.

Acute and late toxicities are summarized in Table 2.

Table 1. Patients and PBT characteristics (n = 6).

Item	Value
Age at treatment (median)	5 - 13 years (9)
Sex (male/female)	5/1
Pathology	
Chordoma	6
Surgery	
Subtotal resection	5
Partial resection	1

Table 2. Acute and Late toxicities of proton beam therapy.

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Dermatitis	5	1	0	0
Radiation sickness	1	0	0	0
Acute otitis	1	1	0	0
Pharyngitis	2	0	0	0
Growth hormone abnormal	2	1	0	0
Cortical hormone abnormal	0	1	0	0

As an illustrative case, an 11-year-old female was diagnosed with a skull base chordoma. Before surgery, the tumor was widely compressing the brain stem (**Figure 1(a)**). Subtotal resection was performed by a transnasal approach (**Figure 1(b)**). Postoperative PBT was started 103 days after surgery. A dose of 39.2 GyE in 28 fractions (2 fractions per day) was initially administered to the tumor bed and surgical pathway (**Figure 1(c)**). The dose was then reduced for irradiation of the optic nerve and brainstem. After reaching 58.8 GyE, the target volume was limited to the tumor bed and a dose up to 78.4 GyE was administered in 56 fractions (**Figure 1(d)**, **Figure 1(e)**).

4. Discussion

Conventional radiotherapy for skull base chordomais limited by the critical organs around the tumor bed [3]. In contrast, PBT allows irradiation at a high dose of >70 GyE without critical late toxicities [8] [9] and achieves a good 5-year local control rate of 60% - 100% for pediatric skull base chordoma at a dose of 65 - 74 GyE at 1.8 - 2.0 GyE/Fr [11] [12] [13]. We have also obtained good local control for adult chordoma using PBT at 78.4 GyE in 56 fractions (2 fractions per day). Pituitary insufficiency is the most common late toxicity in PBT, but the risk of high grade late toxicity is low [14] [15] [16]. Our patients showed the same tendency, with most late toxicities being of low grade (grade 1 or 2).

Our results and previous reports indicate that PBT for pediatric chordoma is effective and that the risk of severe late toxicity is low. However, this conclusion is based on follow-up periods of only 5 to 10 years. A recent large study showed that the main cause of death after pediatric cancer treatment changes from cancer-related death to treatment-related death (late toxicity, secondary cancer, etc) 30 years after treatment [17]. Additionally, the risk of subsequent malignancy

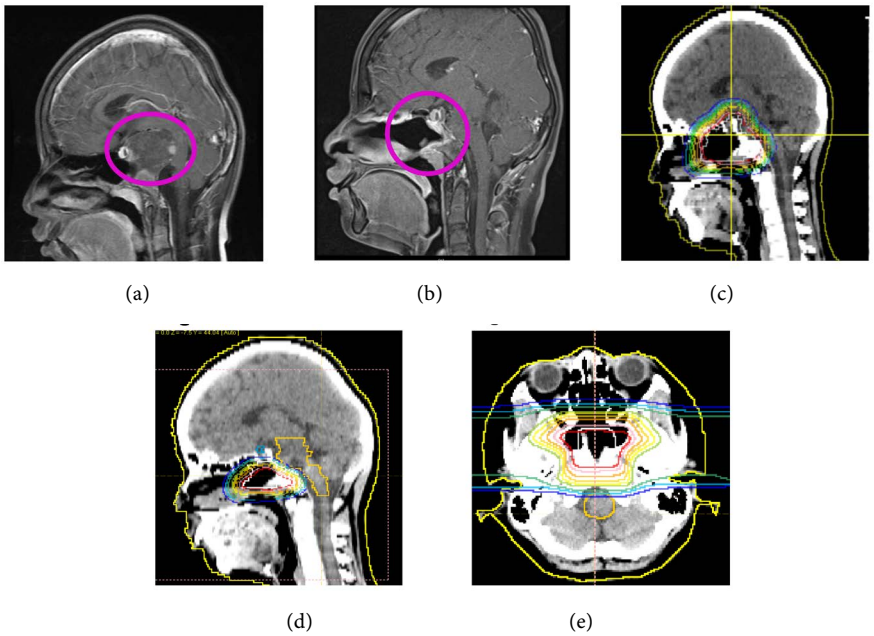

Figure 1. Treatment course of PBT for skull base chordomain an11-year-old female.

also continues to increase after 40 years old [18] and at age 55 the cumulative incidence of new malignancy reaches 16.3%. These data indicate that longer follow-up is needed to evaluate the late toxicity of PBT.

PBT for a pediatric tumor is mainly used to reduce late toxicity and secondary cancer [19] [20]. For pediatric chordoma, the dose of PBT is high and longer survival is likely, which further emphasizes the need for longer follow-up. Although the number of pediatric patients was small, we consider that PBT is safe and effective for pediatric chordoma. Further follow-up is needed to evaluate late toxicities and the risk of secondary cancer.

Acknowledgements

This research was supported by a grant for Practical Research for Innovative Cancer Control (15ck0106186h0001) from the Japan Agency for Medical Research and Development (AMED), and in part by Grants-in-Aid for Scientific Research (B) (15H04901) and Young Scientists (B) (25861064) from the Ministry of Education, Science, Sports and Culture of Japan.

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