Feasibility of Proton Beam Therapy for Chordoma and Chondrosarcoma of the Skull Base

Hiroshi Fuji, M.D., Ph.D.,¹ Yoko Nakasu, M.D., Ph.D.,² Yuji Ishida, M.D., Ph.D.,³ Satoshi Horiguchi, M.D., Ph.D.,⁵ Koichi Mitsuya, M.D., Ph.D.,² Hiroya Kashiwagi, M.D., Ph.D.,⁴ and Shigeyuki Murayama, M.D., Ph.D.¹

ABSTRACT

We explored the general feasibility of proton beam therapy for chordoma and chondrosarcoma of the skull base. Clinical records and treatment-planning data of patients with the pathological diagnosis of chordoma or chondrosarcoma were examined. Proton beam therapy was administered for gross tumor mass as well as microscopic residual disease after surgery. The prescribed dose was determined to maximize the coverage of the target and to not exceed predefined constraints for the organs at risk. Eight cases of chordoma and eight cases of chondrosarcoma were enrolled. The median tumor volume was 40 cm³ (range, 7 to 546 cm³). The prescribed dose ranged from 50 to 70 Gy (relative biological effectiveness [RBE]), with a median of 63 Gy RBE. The median follow-up duration was 42 months (range 9 to 80 months). The overall survival rate was 100%, and the local control rate at 3 years of chordoma and chondrosarcoma were 100% and 86%. None of the patients developed radiation-induced optic neuropathy, brain stem injury, or other severe toxicity. Proton beam therapy is generally feasible for both chordoma and chondrosarcoma of the skull base, with excellent local control and survival rates.

KEYWORDS: Proton beam, radiotherapy, skull base, chordoma, chondrosarcoma

Chordoma and chondrosarcoma of the skull base are rare tumors. The combined incidence of these tumors of the skull base in the United States is reported to be 0.03 per 100,000 population. Chordoma is a tumor arising from the remnants of the notochord. About half of these tumors occur at the sacrococcygeal synchondrosis, and ~30 to 40% occur at the sphenoid-occipital synchondrosis.¹ Chondrosarcomas originate from primitive mesenchymal cells or from the embryonic rests of the cartilaginous matrix. This neoplasm may arise in any

bone, and the most common sites of origin are the pelvis and extremities. About 5% of all chondrosarcomas occur at the skull base.² Although chordomas and chondrosarcomas have distinct histological features, the clinical presentation and treatment strategies for these tumors occurring at the skull base are similar, and the treatments remain challenging, in contrast to those for these tumors arising at other sites.^{3,4}

Similar to the case for such tumors arising at other sites, surgical removal is the primary curative option.⁵

Divisions of ¹Proton Therapy, ²Neurosurgery, ³Pediatrics and ⁴Ophthalmology, Shizuoka Cancer Center, Nagaizumi, Shizuoka; ⁵Division of Neurosurgery, Ako-City Hospital, Ako, Japan.

Address for correspondence and reprint requests: Hiroshi Fuji, M.D., Ph.D., Proton Therapy Division, Shizuoka Cancer Center, 1007 Shimonagakubo, Nagaizumi, Shizuoka 411-8777, Japan (e-mail: h.fuji@scchr.jp).

Skull Base 2011;21:201–206. Copyright © 2011 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA. Tel: +1(212) 584-4662.

Received: November 28, 2010. Accepted: January 10, 2011. Published online: March 25, 2011.

DOI: <http://dx.doi.org/10.1055/s-0031-1275636>.

ISSN 1531-5010.

However, the complex bony structures of the skull base and the surrounding critical organs may not allow complete resection of these tumors.⁶ Therefore, adjuvant treatments need to be considered both for the remaining gross tumor mass and for microscopic tumor cells around the primary tumor as adjuvant treatment; about half of the patients receive postoperative radiotherapy according to reports from several institutes.⁷

Proton beam therapy has been reported to be useful for adjuvant treatment of tumors of the skull base, reportedly yielding excellent outcomes.⁸ The main advantageous effect of a proton beam are the protons' physical feature of the Bragg peak, which provides excellent conformity of the irradiation field. The physical rationale of the treatment was tested at select institutes between the 1970s and 1990s.^{9,10} At the same time, more reliable dose constraints for normal tissues at the skull base for protons rather than the doses known to be acceptable for photon treatment were explored.¹⁰⁻¹³ These dose constraints for organs at risk surrounding a tumor were then used at individual institutes. Apparently, the developed dose constraints enabled escalation of the target dose in proton beam therapy, whereas the target dose in photon treatment is usually compromised with historically accepted dose constraints for the surrounding organs.

After these revisions of the prescription method of proton beam therapy, few data have been published on the outcomes of this treatment for skull base tumors. Furthermore, the reproducibility of the results among institutes has also not been assessed. Therefore, it was considered that reproducible or better outcomes of treatment planning with objectively established parameters should be tested before general application of the treatment. Furthermore, preferential selection of proton beam therapy over other newly developed techniques of radiotherapy needs to be assessed more clearly with appropriate selection of subjects suitable for the treatment, because comparable clinical outcomes of other advanced radiotherapeutic techniques are emerging for certain types of skull base tumors.^{14,15}

METHODS

The data of consecutive patients who underwent proton beam therapy for chordoma or chondrosarcoma of the skull base from July 2003 through November 2008 were retrospectively reviewed. All patients had a histopathologically confirmed diagnosis of chordoma or chondrosarcoma based on previous surgery or biopsy. The eligibility for surgical resection of the patients referred to our institute was estimated by experienced neurosurgeons or head and neck surgeons. In patients eligible for surgery, the tumor was removed to the maximum extent possible before proton beam therapy.

The gross tumor volume (GTV) was defined as the gross extent of the tumor observed on computed tomography (CT) or magnetic resonance imaging (MRI). The clinical target volume (CTV) was defined as the GTV plus a margin of 5 to 8 mm. The planning target volume (PTV) was determined to be the same as the CTV. Critical organs around the target were also delineated on the planning CT images. Taking into account the relative biological effect of a proton beam, the dose was reported in Gy (relative biological effectiveness [RBE]), which was equivalent to the physical dose in Gy multiplied by 1.1. We adopted unique constraints for critical organs in the proton beam therapy, according to a previous report from the proton beam therapy institute. The dose to the optic nerves and chiasma were constrained to 60 Gy RBE. The maximum doses covering 0.9 cm³ of the brain stem (D_{0.9}) and the center of the brain stem were limited to less than 67 Gy RBE and 60 Gy RBE, respectively.¹⁰ The prescribed dose was defined as the dose that covered 90% of the GTV. An attempt was made to deliver more than 50 Gy RBE to the PTV. According to the dose constraints and predefined homogeneity value for PTV, the maximum dose to the PTV was within 105% of the prescribed dose and was 70 Gy RBE. Every patient was treated by the conventional fractionated schedule, at 1.8 Gy RBE/fraction. The treatment was not combined with photon beam therapy in any of the patients. During the treatment session, the head and neck were immobilized by thermoplastic shells. Orthogonal fluoroscopy was performed before every treatment session to verify the localization.

Patients were seen at our institute or by the local physician after the treatment and were monitored for survival, disease progression, and development of adverse events. The patterns of failure and response of the irradiated tumors were examined by MRI, CT, and positron emission tomography performed every 3 to 6 months. The images were compared with the baseline images obtained before the treatment planning. Local progression was defined as increase of the tumor volume as compared with the pretreatment volume or the appearance of new lesions in the CTV. Toxicities were scored according to the Common Toxicity Criteria, version 3.0, of the National Cancer Institute.

The end points analyzed were the overall survival rate and the local control rate. All events were measured from the first day of the proton beam therapy to the last day of follow-up. The overall survival rates and the actual local progression-free rates were calculated using the Kaplan-Meier approach. All the statistical analyses were performed using the PASW 17 (IBM, Chicago, IL).

RESULTS

The characteristics of the patients and the tumors are shown in Table 1. Nine patients presented with diplopia

Table 1 Characteristics of the Patients and Tumors

Characteristics	Value
Age, median (range)	38 (9–78)
Gender (n): male/female	10/6
Histological type: chordoma/chondrosarcoma/mesenchymal chondrosarcoma	8/5/3
Previous treatment (n): surgery/chemotherapy/none	13/2/2
Pretreatment symptom (n): diplopia/pain/diminished visual acuity/facial nerve palsy	9/3/2/2
Gross tumor volume (cm ³), median (range)	40 (7–546)
Clinical target volume (cm ³), median (range)	113 (39–667)

Table 2 Characteristics of Tumor Extension

Tumor Location	Number of Patients (%)
Clival invasion	11 (61%)
Parasellar extension	8 (44%)
Sphenoid sinus invasion	10 (55%)
Suprasellar extension	7 (38%)
Petrous bone invasion	10 (55%)
Occipital bone invasion	7 (38%)
Frontal bone invasion	3 (18%)
Cervical spine	5 (27%)

before treatment and two with decreased visual acuity. The tumor extents are illustrated in Table 2. The tumors mainly involved the clivus, sphenoid sinuses, and petrous bone. Except for the tumors arising from the cervical spine, the tumors presented with extension to more than seven sites.

The delivered radiation doses are shown in Figs. 1 and 2. The mean dose to the GTV and mean dose to the CTV were 63 Gy RBE (range, 50 to 70 Gy RBE) and 60 Gy RBE (range, 48 to 69 Gy RBE). The D₉₅ was lower than the mean dose to the GTV (median, 57 Gy RBE, range 41 to 70 Gy RBE) and to the CTV (median, 47 Gy RBE, range 28 to 62 Gy RBE). There were two

patients with a lower prescribed dose (50 Gy RBE). The doses in these patients were selected taking into account the risk of radiation-induced optic neuropathy. One patient had a mesenchymal chondrosarcoma arising from the frontal bone. The posterior margin abutted on the optic nerves and optic chiasma. Considering his age and the scant information on the potential response of the tumor to radiotherapy, the dose to the tumor was limited to the dose constraint for the optic nerve as accepted for ordinary photon beam therapy. The other patient with the lower dose to the target also had mesenchymal chondrosarcoma. In an attempt to preserve the visual acuity on both sides, 50 Gy RBE was also selected as a constraint for the optic nerves by the patient. The mean and D_{0.9} dose to the brain stem were 27 Gy RBE (range, 0 to 48 Gy RBE) and 45 Gy RBE (range, 0 to 63 Gy RBE). The median dose to the optic nerve was 43 Gy RBE (range, 0 to 67 Gy RBE). The median dose to the cochlea was 27 Gy RBE (range, 0 to 69 Gy RBE).

The median follow-up period for the study patients was 42 months (range, 9 to 80 months). At the time of the analysis, all the patients were alive. One mesenchymal chondrosarcoma recurred at 23 months after the proton beam therapy in the CTV, which was delivered at a dose of 50 Gy RBE. Another two cases

Figure 1 Delivered dose to target volumes and organs at risk. CTV, clinical target volume; GTV, gross tumor volume.

Figure 2 Dose distribution in a case of chondrosarcoma. The gross tumor volume (GTV) and clinical target volume (CTV) were irradiated with a mean dose of 56 Gy and 50 Gy, respectively. High-dose area in brain stem was limited at the surface.

recurred in the CTV at 55 months and 71 months after the treatment. One patient underwent reconstruction surgery for the vertebrae immediately after the proton beam therapy with 60 Gy RBE to the GTV. The tumor was found in the CTV, but not within the GTV. Another patient presented with a recurrent lesion at the center of the GTV, which was delivered 60 Gy RBE. The patient underwent stereotactic radiosurgery for the tumor, which measured 5 mm in diameter.

No patient developed radiation-induced optic neuropathy. There was a patient with variations in the visual acuity during the follow-up period. Because of the frequent intervention for cataract and the normal optic nerve findings throughout the observation period, the perturbations of the visual acuity were not regarded as being attributable to the radiation neuropathy.

There were no patients with symptoms of brain stem radiation necrosis, such as ataxia, weakness, and dysarthria. Deterioration of ocular motion was not observed in any of the patients at the time of the analysis. In the eight patients who presented with diplopia, the symptom improved after the treatment. Grade 2 serous otitis was observed in six patients. Among these, three patients showed persistent disease for more than 3 months. Five patients showed petrous bone destruction by the tumor, and in three of these patients, more than 60 Gy RBE had been delivered to the cochlear systems.

DISCUSSION

Proton beam therapy for chordoma and chondrosarcoma is known to be one of the best options to decrease the

probability of recurrence after surgical removal. Excellent local control and survival rates have been reported from the United States and Europe from 1989 to 2001 (Table 3). The treatment targets in these reports consisted of the clinical target volume with addition of a significant margin to the remnant tumor. Because microscopic tumor cells around the tumor need to be treated in the postoperative setting, this expanded treatment target volume is large and irregular in shape and frequently involves the critical organs at the skull base (i.e., central nervous system, sensory organs, and cranial nerves). Nevertheless, the prescribed doses are markedly higher than the dose constraints for the critical organs. Proton beam therapy is considered the ideal method for dose-gradient irradiation to irregular-shaped targets among critical organs. Even though the number of subjects was small, the inclusion of larger tumors in the present study, as compared with that in previous reports of proton beam therapy, with adequate 3-year disease control rates lends support to the concept of use of proton beam therapy for the disease.

There are several reports of excellent long-term control rates of chordomas and chondrosarcomas with stereotactic radiotherapy and radiosurgery. These reports indicate identical outcomes with stereotactic treatment as with proton beam therapy in selected cases. However, the tumor volumes in these reported cases were smaller than those in patients treated by proton beam therapy, and unfavorable control rates were noted for larger tumors. The irradiated targets in these cases were the gross tumors alone. In this limited-volume irradiation, microscopic residual tumor cells around the primary nests were not irradiated. On the other hand, repeated treatment may be possible in the event of the tumor arising in different parts of the skull base. The differences in the target volume and size of the tumors treated may cause difficulties in comparison of the treatment outcomes between the modalities. However, at least the eligibility of large

tumors for treatment may be an advantage in proton beam therapy.

The present series included subjects with extensive invasions to skull base structures. Except for the lesion arising from the cervical vertebrae, all the lesions caused destruction of the petrous bone or suprasellar part of the sphenoid. Additionally, most patients presented with ocular symptoms or visual disturbances, suggestive of encasement or involvement of the cranial nerves by the tumor. Even proton beams could not provide the dose gradient needed at the microscopic border between the tumor and the surrounding organs. Consequently, most patients needed to be given comparable or equivalent doses to the dose constraints for critical organs. Except for two cases of chondrosarcoma, we introduced experimental dose constraints for the optic nerves and brain stem. These were almost identical to the dose constraints reported from experienced high-volume proton beam therapy institutes, but higher than the doses generally accepted for photon beam treatment.¹⁶ Among 32 optic nerves, 10 were delivered a dose identical to the constraint dose, 50 to 60 Gy RBE. Absence of radiation-induced optic neuropathy in our case series with a median follow-up duration of 36 months suggests that the experimental constraint dose is feasible. Our results also suggested the feasibility of using the dose constraint for the brain stem. Terahara et al. reported that the incidence of brain stem injury was associated with the volume irradiated with a certain dose.¹¹ The constraint dose for D_{0.9} implemented in our study according to their report allowed us to deliver a higher dose to the target than that to the whole brain stem.

Although the treatment-related morbidity rate in the present study was acceptable, there were six patients who developed grade 2 otitis after proton beam therapy. There have been few reports of otitis following proton beam therapy, although the adverse effect has been reported following radiotherapy for nasopharyngeal

Table 3 Reported Outcomes of Skull Base Chordoma and Chondrosarcoma

Study	Munzenrider et al 1999 ¹⁰	Austin-Seymour et al 1989 ¹¹	Hug et al 1999 ¹²	Noël et al 2001 ⁹	Present Study
Number of patients	621	68	58	67	16
Mean volume (range), mL	NA	45 (2–282)	*	28 (1–125)	40 (7–546)
Mean dose (range)	(66–83)	69 (57–76)	71 (65–79)	67 (60–70)	63 (50–70)
Follow-up (range)	41 (1–254)	34 (17–152)	33.2 (7–75)	29 (4–71)	42 (9–80)
Histology: Ch/Cn	375/246	40/28	33/25	49/18	8/8
Local control	Ch: 5 y 98% Cn: 5 y 73%	5 y 82%	Ch: 3 y 67% Cn: 3 y 94%	Ch: 3 y 85% Cn: 3 y 71%	Ch: 3 y 100% Cn: 3 y 86%
Overall survival	Ch: 5 y 80% Cn: 5 y 48%	5 y 80%	Ch: 3 y 87% Cn: 3 y 100%	Ch: 3 y 75% Cn: 3 y 88%	Ch: 3 y 100% Cn: 3 y 100%

*, cases more than 25 mL. Ch, chordoma; Cn, chondrosarcoma; NA, not applicable.

tumors. One reason it has not been reported as an adverse effect of proton beam therapy is that the disease has not yet been recorded as a severe event according to the toxicity criteria. Another reason is the anatomic site of the tumors in previously reported series. Chondrosarcomas in a half of the present subjects tended to arise from the off-axis part of the skull base as compared with chordomas.² Therefore, they are likely to occupy the eustachian tube and the auric media. The dose-effect relationship with otitis in the patients with nasopharyngeal tumors suggested an increase risk of the symptom with a dose of 70 Gy delivered to the auric media. In the present study, the otitis media developed in patients who had more than 60 Gy delivered to the auric media. Establishment of a method to predict the risk of otitis after proton beam therapy will be necessary for improving the quality of life.

In the current study, we demonstrated the features of tumors and the prescription and outcomes of treatment. The present report including subjects with tumors showing local extension and adequate local control rates indicates the advantages of proton beam in the treatment of skull base tumors. We observed a few local recurrences in cases treated with lower doses, but no case of severe toxicity. It could be interpreted that further improvement of the treatment may be expected with dose escalation to the target and with establishment of more predictive dose constraints for organs at risk in the skull base region.

REFERENCES

1. Erdem E, Angtuaco EC, Van Hemert R, Park JS, Al-Mefty O. Comprehensive review of intracranial chordoma. *RadioGraphics* 2003;23:995–1009
2. Rapis AD, Archondakis G, Anteriotis D, Skouteris CA. Chondrosarcomas of the skull base: review of the literature and report of two cases. *J Craniomaxillofac Surg* 1997;25:322–327
3. Korten AG, ter Berg HJ, Spincemaille GH, van der Laan RT, Van de Wel AM. Intracranial chondrosarcoma: review of the literature and report of 15 cases. *J Neurol Neurosurg Psychiatry* 1998;65:88–92
4. Fuller DB, Bloom JG. Radiotherapy for chordoma. *Int J Radiat Oncol Biol Phys* 1988;15:331–339
5. Maira G. *Surgical Management of Lesions of the Clivus*. Philadelphia: W. B. Saunders; 2000
6. Tamaki M, Aoyagi M, Kuroiwa T, Yamamoto M, Kishimoto S, Ohno K. Clinical course and autopsy findings of a patient with clival chordoma who underwent multiple surgeries and radiation during a 10-year period. *Skull Base* 2007;17:331–340
7. Mendenhall WM, Mendenhall CM, Lewis SB, Villaret DB, Mendenhall NP. Skull base chordoma. *Head Neck* 2005;27:159–165
8. Amichetti M, Cianchetti M, Amelio D, Enrici RM, Minniti G. Proton therapy in chordoma of the base of the skull: a systematic review. *Neurosurg Rev* 2009;32:403–416
9. Noël G, Habrand JL, Mammar H, et al. Combination of photon and proton radiation therapy for chordomas and chondrosarcomas of the skull base: the Centre de Protonthérapie D'Orsay experience. *Int J Radiat Oncol Biol Phys* 2001;51:392–398
10. Munzenrider JE, Liebsch NJ. Proton therapy for tumors of the skull base. *Strahlenther Onkol* 1999;175(Suppl 2):57–63
11. Austin-Seymour M, Munzenrider J, Goitein M, et al. Fractionated proton radiation therapy of chordoma and low-grade chondrosarcoma of the base of the skull. *J Neurosurg* 1989;70:13–17
12. Hug EB, Loredó LN, Slater JD, et al. Proton radiation therapy for chordomas and chondrosarcomas of the skull base. *J Neurosurg* 1999;91:432–439
13. Terahara A, Niemierko A, Goitein M, et al. Analysis of the relationship between tumor dose inhomogeneity and local control in patients with skull base chordoma. *Int J Radiat Oncol Biol Phys* 1999;45:351–358
14. Debus J, Hug EB, Liebsch NJ, et al. Brainstem tolerance to conformal radiotherapy of skull base tumors. *Int J Radiat Oncol Biol Phys* 1997;39:967–975
15. Habrand IL, Austin-Seymour M, Birnbaum S, et al. Neurovisual outcome following proton radiation therapy. *Int J Radiat Oncol Biol Phys* 1989;16:1601–1606
16. Hasegawa T, Ishii D, Kida Y, Yoshimoto M, Koike J, Iizuka H. Gamma knife surgery for skull base chordomas and chondrosarcomas. *J Neurosurg* 2007;107:752–757
17. Miller RC, Foote RL, Coffey RJ, et al. The role of stereotactic radiosurgery in the treatment of malignant skull base tumors. *Int J Radiat Oncol Biol Phys* 1997;39:977–981
18. Emami B, Lyman J, Brown A, et al. Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys* 1991;21:109–122