Skull Base and Upper Cervical Spine Tumors

18

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Abstract

Major types of skull base and upper cervical spine tumors include chordoma, chondrosarcoma, and olfactory neuroblastoma, for which complete resection is rarely achieved because of the vicinity to the critical organ structure. Radiotherapy is the second treatment option; however, the limiting factor for photon radiotherapy conventionally applied to skull base and upper cervical spine tumors is damage to adjacent normal tissues, owing to poor local control. On the other hand, proton radiotherapy with its superior physical spatial distribution has provided a major improvement in local control in view of possible dose escalations. However, in certain patient groups, local control with proton radiotherapy is difficult to achieve even at elevated doses. For example, the reported 5-year local control rates for skull base chordoma after proton therapy ranged from 46 to 81 %. Therefore, the high linear energy transfer of carbon ion radiotherapy (C-ion RT) has a promising potential for the treatment of skull base tumors, especially chordoma. The 5-year local control and overall survival rates for 44 chordoma patients treated with carbon ion radiotherapy were 88 and 87 %, respectively. The 5-year actuarial local control and overall survival rates for 12 chondrosarcoma patients were 86 and 63 %, respectively. Acute and late normal tissue reactions were within acceptable limit. Thus, C-ion RT can be a promising treatment option for skull base and upper cervical spine tumors.

Keywords

Carbon ion radiotherapy • Chordoma • Skull base tumor

18.1 Introduction

The management of skull base and upper cervical spine tumors is most challenging because they lie in close vicinity of critical structures such as the brain stem, spinal cord, and anterior optic pathways. These anatomic structures often limit surgical access and resectability, as well as the delivery of high-dose radiations. In addition, some tumors that originate from the skull base region are dose dependent. For example, more than 70 Gy of radiation is needed for achieving local control of chordoma, and more than 60 Gy is needed for chondrosarcoma [1]. New treatment techniques such as intensity-modulated radiotherapy and stereotactic radiotherapy have improved dose distribution and are being used for skull base tumors. However, the clinical results are still unclear.

On the other hand, proton therapy with its superior physical spatial distribution has provided a major improvement in local control with regard to possible dose escalations. Several studies reported promising results of using proton therapy for skull base tumors. Munzenrider et al. reported that the 10-year local control rate for chondrosarcoma treated with proton therapy was 94 % [2]. Wenkel et al. reported that the 10-year local control rate for meningioma

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treated with combined proton and photon radiotherapy was 88 % [3]. However, the reported 5-year local control rates for chordoma treated with proton therapy ranged from 46 to 81 % [2, 4–6].

18.2 Significance of C-Ion RT

In chordoma patients, local control with proton radiotherapy, even at elevated doses, is difficult to achieve. Therefore, the high linear energy transfer of C-ion RT has a promising potential in the treatment of skull base chordoma. Thus, C-ion RT should be able to achieve excellent local control in other skull base tumors such as chondrosarcoma and meningioma.

18.3 Clinical Features and Diagnostic Work-Up

The clinical symptoms of skull base tumors vary according to the location and extent of the tumor. Volpe et al. [7] reviewed the clinical features of 48 patients with chordoma and 49 patients with chondrosarcoma of the skull base. Half of these patients had ocular symptoms such as diplopia and visual impairment at initial manifestation of the disease.

In C-ion RT, it is important to define the distance between the tumor and the organs at risk, such as the brain stem, spinal cord, or cranial nerves including optic nerves, because it may be difficult to spare nerve functions when the tumor is located close to the organ at risk. Computed tomography (CT) with contrast enhancement and magnetic resonance imaging (MRI) with gadolinium are useful in evaluating tumor extension. However, specific staging for chordoma and chondrosarcoma of the skull base is not standardized.

18.4 General Management of Radiation Technique

18.4.1 Target Delineation

Determination of the gross tumor volume (GTV) was based on T1-weighted, T2-weighted, and contrast-enhanced T1-weighted MRI. The clinical target volume (CTV) had minimum margins of 5 mm added to the GTV. In case of carbon ion radiotherapy for residual tumor after surgery, the tumor bed region before surgery was included in the CTV. Furthermore, a margin of 3–5 mm was added as an internal and setup margin around the CTV to create a final planning target volume (PTV). When the tumor was located close to critical organs, such as the brain stem, spinal cord, optic nerves, or brain, the margins were reduced as necessary.

18.4.2 Dose Constraints for the Organs at Risk

The limiting doses for critical normal tissues were decided as 30 Gy equivalent (GyE) for the spinal cord and brain stem and 40 GyE for the optic chiasm and optic nerves. When the ipsilateral optic nerve was located very close to the tumor, the dose limitation for the optic nerve was ignored. The limiting dose for the brain was not provided. However, it was recommended that brain volumes receiving more than 50 GyE should be less than 5 cc to reduce the risk of developing brain necrosis.

18.4.3 Beam Direction

More than two portals were used in principle to improve dose distributions. Because two fixed beams (horizontal and vertical directions) were available, the head of the patient was occasionally immobilized with the patient in oblique or prone position to spare the critical organs.

In the case that a tumor surrounded the critical organ, patch field technique [8] was used to spare critical organs and maintain the minimum coverage dose of the tumor.

18.4.4 Treatment Schedule and Dose

A phase I/II dose escalation study for skull base and upper cervical spine tumors was initiated in April 1997. The patients were treated with a total dose of 48.0, 52.8, 57.6, or 60.8 GyE administered in 16 fractions for 4 weeks. At the level of 60.8 GyE, no dose-limiting toxicity was observed; however, tumors were well controlled. Finally, a dose of 60.8 GyE in 16 fractions was recommended for treatment of skull base tumors [9].

18.5 Results of Therapy

18.5.1 Chordoma

Previously, we reported the effects of C-ion RT on 33 patients with skull base or cervical spine chordoma [10]. Our report included the results of patients treated using the following three protocols: (1) a pilot study with a total dose of 48.0 GyE; (2) a phase I/II study with a total dose of 48.0, 52.8, 57.6, and 60.8 GyE; and (3) a phase II study with a total dose of 60.8 GyE. All the patients had a macroscopic lesion and were treated with 16 fractions over 4 weeks. The CTV ranged from 2 to 328 cc, with a median value of 32 cc. Median follow-up was 53 months (range, 8–129 months). The 5-year actuarial local control rate and overall survival rate of the 33 patients were 85.1 and 87.7 %, respectively.

Table 18.1 Clinical characteristics of reported cases of skull base chordoma

	Authors	*N*	Median dose	Median f/u (year)	Local control rate (%)		
					3-year	5-year	10-year
Photon	Catton et al. [12]	24	50	5.2		23	15
	Romero et al. [13]	18	50	3.1		17	
	Forsyth et al. [14]	39	50	8.3		39	31
	Magrini et al. [15]	12	58	6		25	25
Proton (± photon)	Munzenrider et al. [2]	169	66–83	3.4		73	54
	Noel et al. [4]	100	67	2.6	86 (2 year)	54 (4 year)	
	Igaki et al. [5]	13	72	5.8	67	46	
	Ares et al. [6]	42	73.5	3.2 (mean)		81	
Helium	Castro et al. [16]	53	65	4.3		63	
Carbon	Shults-Ertner et al. [11]	96	60	2.6 (mean)	81	70	
	NIRS	47	60.8	4.5		91	82

The 5-year actuarial local control rate and overall survival rate of the 19 patients treated with 60.8 GyE were 100 and 94.4 %, respectively. Acute reactions were classified according to the Radiation Therapy and Oncology Group (RTOG) scoring system, with a maximum reaction occurring within 3 months after initiation of C-ion RT. Late reactions were classified according to the RTOG/European Organisation for Research and Treatment of Cancer (EORTC) scoring system. One patient had grade 2 acute skin reaction and six had grade 2 acute mucosal reaction. Acute reactions of grade 3 or greater were not observed in the skin or mucosa. No acute reactions were observed in the brain or spinal cord. Regarding late reactions, no severe reactions of the skin or mucosa were noted. Only one patient developed grade 2 brain toxicity.

Schulz-Ertner et al. reported their experience of treating 96 skull base chordoma patients with C-ion RT at the Gesellschaft für Schwerionenforschung institute in Germany [11]. The median total dose was 60 cobalt Gy equivalent (CGE) (range, 60–70 CGE) delivered in 20 fractions over 3 weeks. The mean follow-up was 31 months. The mean 5-year actuarial local control rate and overall survival rate were 70.0 and 88.5 %, respectively. Optic nerve neuropathy (RTOG/EORTC grade 3) was observed in 4.1 % of patients and minor temporal lobe injury (RTOG/EORTC grade 1/2) occurred in 7.2 % of patients.

The local control rates of various radiotherapies for skull base chordoma are summarized in Table 18.1 [2–6, 11–16]. We have presented the updated data regarding the effects of C-ion RT for chordoma. The median follow-up was 54 months. The 5-year actuarial local control rate and overall survival rate of 47 chordoma patients were 91 and 92 %, respectively.

18.5.2 Chondrosarcoma

Twelve patients with chondrosarcoma were treated with C-ion RT at our institute. The 5-year actuarial local control rate and overall survival rate were 86 and 63 %, respectively. In Germany, Schulz-Ertner et al. employed C-ion RT for the treatment of 54 patients with low- and intermediate-grade chondrosarcoma of the skull base [17]. The median total dose administered was 60 CGE in 20 fractions over 3 weeks. The median follow-up was 33 months. The 4-year actuarial local control rate and 5-year overall survival rate were 89.8 and 98.2 %, respectively. Grade 3 late toxicity occurred in one patient only.

18.5.3 Other Tumors

Nine patients with olfactory neuroblastoma were treated with C-ion RT, and their 5-year actuarial local control rate and overall survival rate were 100 and 56 %, respectively. In 7 patients with skull base meningioma, the 5-year actuarial local control rate and overall survival rate were 80 and 86 %, respectively.

18.6 Case Study

18.6.1 Case 1 (Chordoma of the Skull Base)

A 61-year-old woman presented with nasal septum tumor and bilateral nasal obstructions. An incisional biopsy revealed chordoma of the skull base. MRI examination revealed a lesion in the clivus invading the nasal septum, sphenoid sinus, and anterior vertebral muscle (Fig. 18.1a). C-ion RT was delivered at 60.8 GyE/16 fractions. Determination of the GTV was based on T1-weighted and contrast-enhanced T1-weighted and T2-weighted MRI obtained using image fusion technique. The CTV had minimum margins of 8 mm added to the GTV. The margin to the brain stem was reduced to meet the dose constraint for the brain stem. Three portals, one vertical and two horizontal, were used to spare the temporal lobes. The vertical beam

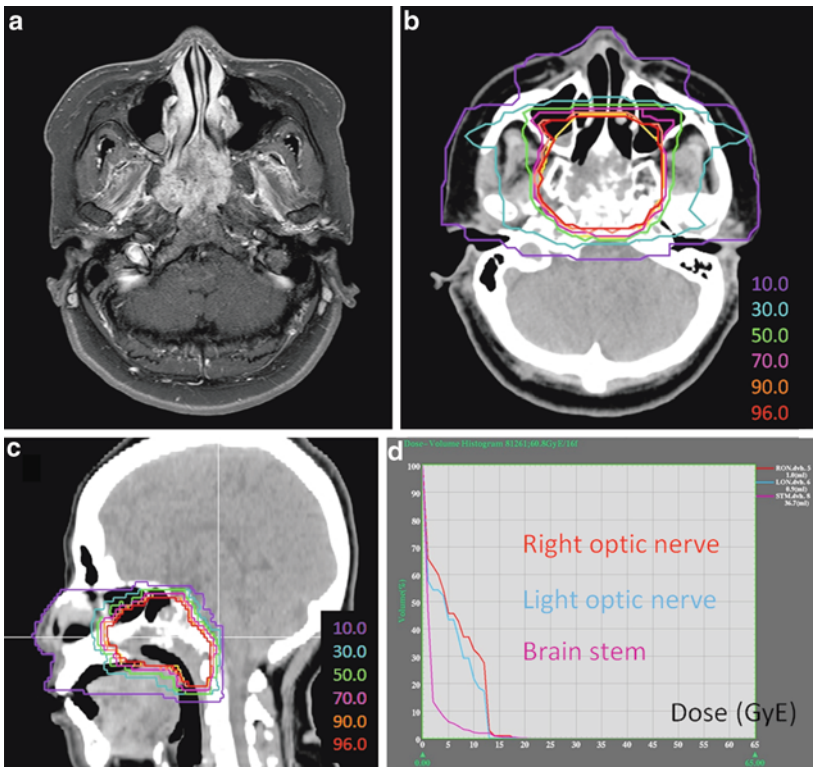

Fig. 18.1 (**a**) Contrast-enhanced T1-weighted magnetic resonance axial image obtained before carbon ion radiotherapy. (**b**) and (**c**) Representative axial and coronal isodose distributions in the clivus tumor. (**d**) Dose-volume histogram of risk organs such as the brain stem and both optic nerves

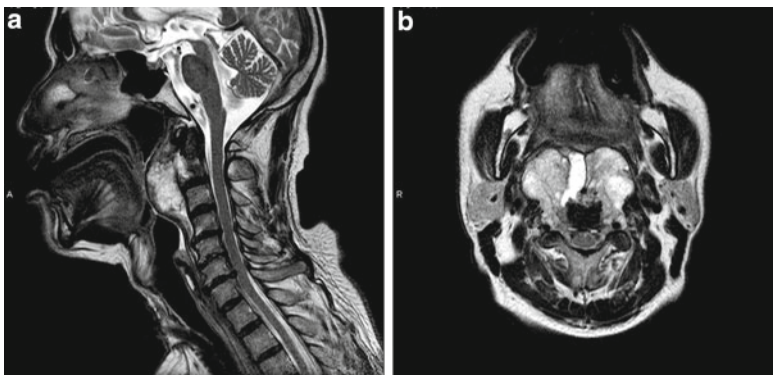

Fig. 18.2 (**a**) Axial and (**b**) sagittal T2-weighted magnetic resonance images obtained before carbon ion radiotherapy

direction should not be parallel to the nasal septum, because the beam targeted at the nasal septum may reach the brain stem, even if there is a small setup error. This patient was rotated 10° from the supine position when the vertical beam was used (Fig. 18.1b, c). The dose constraint of the optic nerves and brain stem were accomplished (Fig. 18.1d). The patient recovered well and is without any disease 2 years later.

18.6.2 Case 2 (Chordoma of the Cervical Region)

A 74-year-old man presented with neck pain and dysphagia. An incisional biopsy revealed chordoma. MRI revealed a lesion in the second cervical spine, invading the spinal canal (Fig. 18.2a, b). C-ion RT was delivered at 60.8 GyE/16 fractions. Determination of the GTV was based on T1-weighted and contrast-enhanced T1-weighted and T2-weighted MRI obtained using image fusion technique. The CTV had minimum margins of 5–10 mm added to the GTV, except for in the direction of the critical organs. The margin to the spinal cord was reduced to meet the dose constraint for the spinal cord. To optimize dose distribution within an irregular volume in close proximity to the spinal cord, the patch combination technique was used. The target volume was divided into three segments, each treated by a separate radiation field. Utilizing the sharp dose fall-off after Bragg peak, the distal edges of the vertical fields were matched with the lateral field edge of the horizontal field

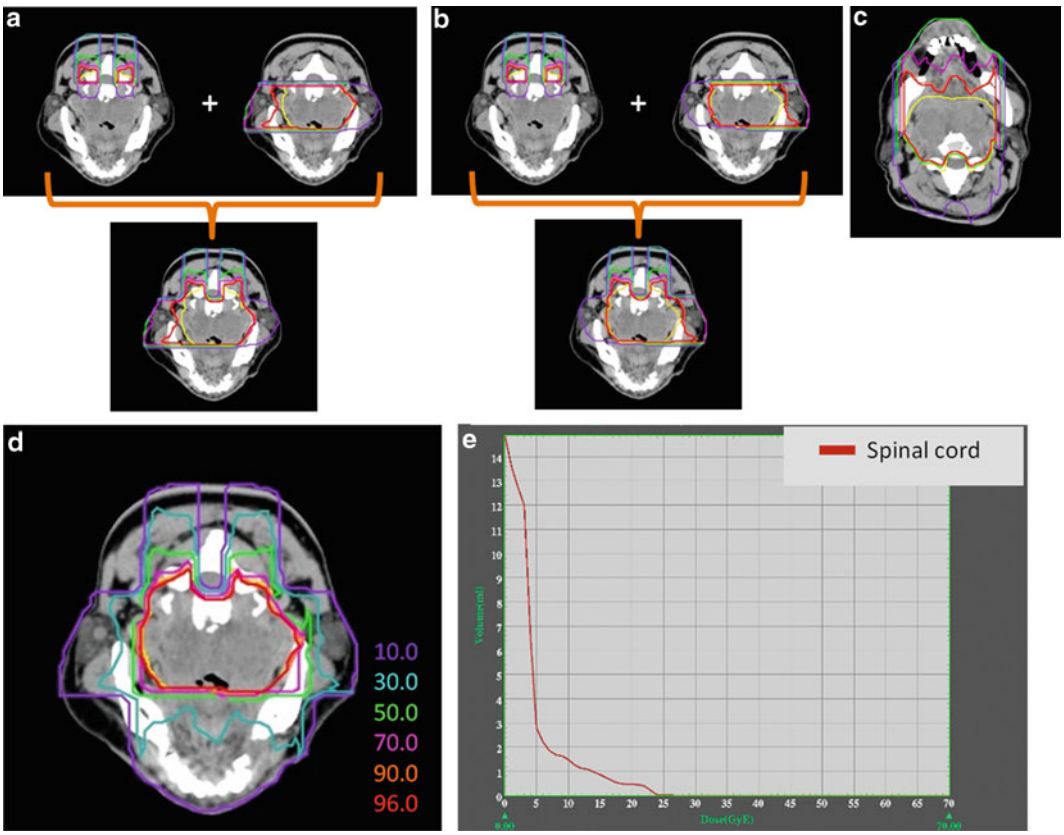

Fig. 18.3 (**a**) Port 1 consisted of two vertical beams and one horizontal beam from the right side of the patient. The patient was immobilized in the prone position. (**b**) Port 2 consisted of two vertical beams and one horizontal beam from the left side of the patient. The patient was immobilized in the prone position. (**c**) Port 3 consisted of a horizontal beam. The patient was immobilized in the supine position. (**d**) Combined dose distribution. (**e**) Dose-volume histogram of the spinal cord

(Fig. 18.3a–d). Dose constraint of the brain stem was accomplished (Fig. 18.3e). The patient recovered well and is without any disease 2 years later.

18.6.3 Case 3 (Brain Injury)

A 33-year-old woman presented with right ptosis, decreased visual acuity, and trigeminal neuralgia. She underwent partial tumor resection, and her condition was diagnosed as skull base chordoma. Four years later, tumor recurrence was detected by MRI examination. She was referred to our hospital for C-ion RT. The tumor was located in the right middle cranial fossa through right cavernous sinus and was in contact with the right temporal lobe and pons (Fig. 18.4a, b). C-ion RT was delivered at 57.6 GyE/16 fractions. Determination of the GTV was based on T1-weighted and contrast-enhanced T1-weighted and T2-weighted MRI obtained using image fusion technique. The CTV had minimum margins of 5–10 mm added to the GTV, except for in the direction of the critical organs. The margin to the brain stem was reduced to clear the dose constraint of the brain stem. The PTV margin toward the right temporal lobe was reduced as much as possible to avoid severe brain injury. The brain volume receiving more than 50 GyE radiation was 10 cc. It was difficult to abide by the dose constraints of the right optic nerve. Four portals were used (Fig. 18.4c, d). Twenty-six months after the treatment, a small enhanced lesion appeared in the right temporal lobe (Fig. 18.5a). However, the patient did not show any clinical symptom regarding brain injury. Forty-two months after the treatment, brain necrosis developed at the bottom of right temporal lobe (Fig. 18.5b). The patient experienced mild headache; however, she did not require any medication. The tumor was slightly reduced. Eleven years after the treatment, the patient is alive without any tumor recurrence. The enhanced brain lesion almost disappeared and cyst formation occurred (Fig. 18.5c). No clinical symptom of brain injury was observed.

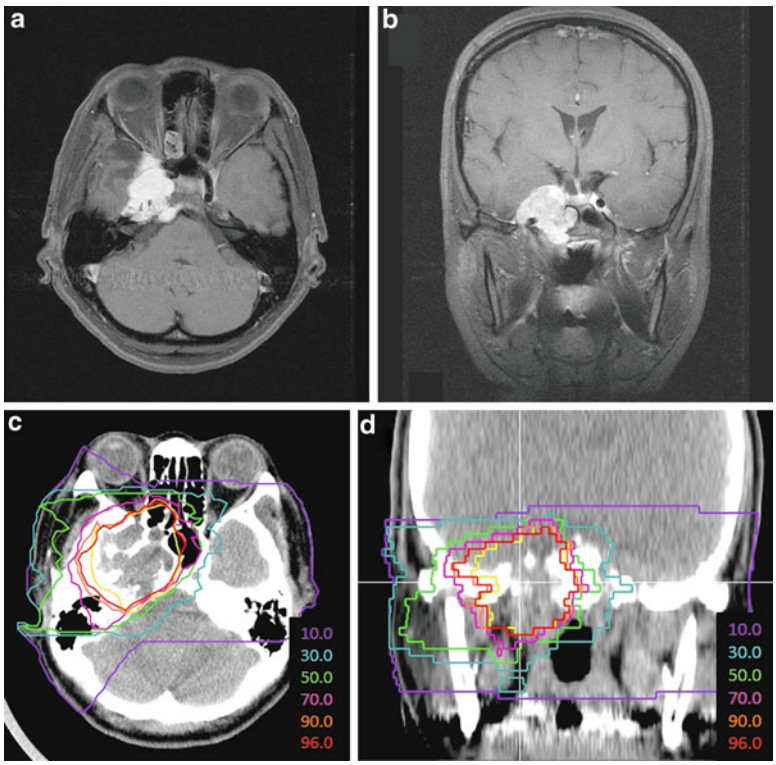

Fig. 18.4 (**a**) Axial and (**b**) sagittal contrast-enhanced T1-weighted magnetic resonance images obtained before carbon ion radiotherapy. Representative (**c**) axial and (**d**) coronal isodose distributions

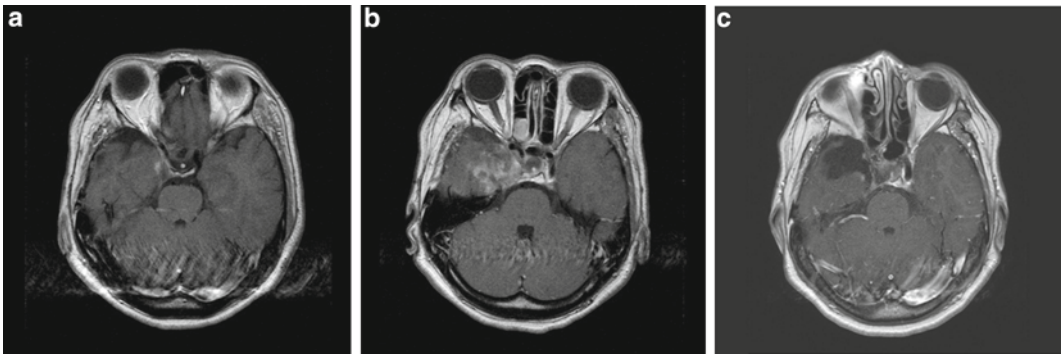

Fig. 18.5 (**a**) Axial contrast-enhanced T1-weighted magnetic resonance image at the level of temporal lobe obtained 26 months after carbon ion radiotherapy. (**b**) Axial contrast-enhanced T1-weighted magnetic resonance image obtained 42 months after carbon ion radiotherapy. (**c**) Axial contrast-enhanced T1-weighted magnetic resonance image obtained 11 years after the treatment

References

1. Debus J, Schulz-Ertner D, Schad L, Essig M, Rhein B, Thillmann CO, Wannenmacher M. Stereotactic fractionated radiotherapy for chordomas and chondrosarcomas of the skull base. Int J Radiat Oncol Biol Phys. 2000;47:591–6.
2. Munzenrider JE, Liebsch NJ. Proton therapy for tumors of the skull base. Strahlenther Onkol. 1999;175:57–63.
3. Wenkel E, Thornton AF, Finkelstein D, Adams J, Lyons S, De La Monte S, Ojeman RG, Munzenrider JE. Benign meningioma: partially resected, biopsied, and recurrent intracranial tumors treated with combined proton and photon radiotherapy. Int J Radiat Oncol Biol Phys. 2000;48:1363–70.
4. Noël G, Habrand JL, Jauffret E, de Crevoisier R, Dederke S, Mammar H, Haie-Méder C, Pontvert D, Hasboun D, Ferrand R, Boisserie G, Beaudré A, Gaboriaud G, Guedea F, Petriz L, Mazeron JJ. Radiation therapy for chordoma and chondrosarcoma of the skull base and the cervical spine. Prognostic factors and patterns of failure. Strahlenther Onkol. 2003;179:241–8.
5. Igaki H, Tokuuye K, Okumura T, Sugahara S, Kagei K, Hata M, Ohara K, Hashimoto T, Tsuboi K, Takano S, Matsumura A, Akine Y. Clinical results of proton beam therapy for skull base chordoma. Int J Radiat Oncol Biol Phys. 2004;60:1120–6.
6. Ares C, Hug EB, Lomax AJ, Bolsi A, Timmermann B, Rutz HP, Schuller JC, Pedroni E, Goitein G. Effectiveness and safety of spot scanning proton radiation therapy for chordomas and chondrosarcomas of the skull base: first long-term report. Int J Radiat

Oncol Biol Phys. 2009;75:1111–8. doi:10.1016/j.ijrobp.2008.12.055.
7. Volpe NJ, Liebsch NJ, Munzenrider JE, Lessell S. Neuro-ophthalmologic findings in chordoma and chondrosarcoma of the skull base. Am J Ophthalmol. 1993;115:97–104.
8. Hug EB, Adams J, Fitzek M, De Vries A, Munzenrider JE. Fractionated, three-dimensional, planning-assisted proton-radiation therapy for orbital rhabdomyosarcoma: a novel technique. Int J Radiat Oncol Biol Phys. 2000;47:979–84.
9. Koto M, Hasegawa A, Takagi R, Fujikawa A, Morikawa T, Tsujii H, Kamada T. Carbon ion radiotherapy for skull base and paracervical tumors. In: Proceedings of NIRS-ETOILE 2nd joint symposium on carbon ion radiotherapy. Lyon: Centre ETOILE; 2011. NIRS-M-243:12–7.
10. Mizoe JE, Hasegawa A, Takagi R, Bessho H, Onda T, Tsujii H. Carbon ion radiotherapy for skull base chordoma. Skull Base. 2009;19:219–24.
11. Schulz-Ertner D, Karger CP, Feuerhake A, Nikoghosyan A, Combs SE, Jäkel O, Edler L, Scholz M, Debus J. Effectiveness of carbon ion radiotherapy in the treatment of skull-base chordomas. Int J Radiat Oncol Biol Phys. 2007;68:449–57.
12. Catton C, O'Sullivan B, Bell R, Laperriere N, Cummings B, Fornasier V, Wunder J. Chordoma: long-term follow-up after radical photon irradiation. Radiother Oncol. 1996;41:67–72.
13. Romero J, Cardenes H, la Torre A, Valcarcel F, Magallon R, Regueiro C, Aragon G. Chordoma: results of radiation therapy in eighteen patients. Radiother Oncol. 1993;29:27–32.
14. Forsyth PA, Cascino TL, Shaw EG, Scheithauer BW, O'Fallon JR, Dozier JC, Piepgras DG. Intracranial chordomas: a clinicopathological and prognostic study of 51 cases. J Neurosurg. 1993;78:741–7.
15. Magrini SM, Papi MG, Marletta F, Tomaselli S, Cellai E, Mungai V, Biti G. Chordoma-natural history, treatment and prognosis. The Florence Radiotherapy Department experience (1956–1990) and a critical review of the literature. Acta Oncol. 1992;31:847–51.
16. Castro JR, Linstadt DE, Bahary JP, Petti PL, Daftari I, Collier JM, Gutin PH, Gauger G, Phillips TL. Experience in charged particle irradiation of tumors of the skull base: 1977–1992. Int J Radiat Oncol Biol Phys. 1994;29:647–55.
17. Schulz-Ertner D, Nikoghosyan A, Hof H, Didinger B, Combs SE, Jäkel O, Karger CP, Edler L, Debus J. Carbon ion radiotherapy of skull base chondrosarcomas. Int J Radiat Oncol Biol Phys. 2007;67:171–7.