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Clinical Investigation: Central Nervous System Tumor

Challenges in Linear Accelerator Radiotherapy for Chordomas and Chondrosarcomas of the Skull Base: Focus on Complications

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Summary

Intracranial chordomas and chondrosarcomas are often difficult to treat due to their proximity to sensitive brain structures. This study reviewed a single institution's experience using linac-based stereotactic radiosurgery and radiotherapy to treat 15 patients. With an average follow-up of 4.5 years radiation-related complications were few. Photon therapy, judiciously given, represents a reasonable alternative to proton beam in those centers where proton technology is unavailable.

Purpose: Intracranial chordomas and chondrosarcomas are histologically low-grade, locally invasive tumors that infiltrate the skull base. Currently, consensus therapy includes surgical resection and adjuvant radiotherapy. Radiation delivery is typically limited by the proximity of these tumors to critical skull base structures.

Methods: This is a retrospective review of 13 cases of chordomas and 2 cases of chondroid chondrosarcomas of the skull based treated with linear accelerator stereotactic radiotherapy (SRT, $n = 10$) or stereotactic radiosurgery (SRS, $n = 5$). The average time to the most recent follow-up visit was 4.5 years. The tumor characteristics, treatment details, and outcomes were recorded. Each radiation plan was reviewed, and the dosage received by the brainstem, optic apparatus, and pituitary was calculated.

Results: Of the 10 patients treated with SRT, 6 were found to have unchanged or decreased tumor size as determined from radiographic follow-up. Of the 5 patients treated with SRS, 3 were found to have stable or unchanged tumors at follow-up. The complications included 1 SRT patient who developed endocrinopathy, 2 patients (1 treated with SRS and the other with SRT), who developed cranial neuropathy, and 1 SRS patient who developed visual deficits. Additionally, 1 patient who received both SRS and SRT within 2 years for recurrence experienced transient medial temporal lobe radiation changes that resolved.

Conclusions: Where proton beam therapy is unavailable, linear accelerator-based SRT or radiosurgery remains a safe option for adjuvant therapy of chordomas and chondrosarcomas of the skull base. The exposure of the optic apparatus, pituitary stalk, and brainstem must be considered during planning to minimize complications. If the optic apparatus is included in the 80% isodose line, it might be best to fractionate therapy. Exposure of the pituitary stalk should be kept to <30 Gy to minimize endocrine dysfunction. Brainstem exposure should be limited to <60 Gy in fractions. © 2012 Elsevier Inc.

Keywords: Linear accelerator, Stereotactic radiotherapy, Stereotactic radiosurgery, Chordoma, Skull base tumors

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Introduction

Chordomas are a rare group of slow-growing tumors arising from the notochord that can involve the cranial base, vertebrae, or sacrococcygeal regions (1). Chondrosarcomas are radiographically similar tumors derived from primitive mesenchymal cells within the cartilaginous matrix of the skull base (1, 2). Clinically, these tumors tend to present in a similar fashion (3). However, chordomas frequently arise from the clivus and tend to compress the brainstem, and chondrosarcomas commonly originate at the occipitotemporal bone synchondrosis and cause lower cranial nerve deficits (4). The definitive diagnosis can be made by histologic analysis. Although skull base chordomas and chondrosarcomas share similar radiographic features, clinical course, and locations, chondrosarcomas are associated with greater recurrence-free survival and responsiveness to therapy (3, 5). The therapeutic options for both chordomas and chondrosarcomas include surgical resection, fractionated radiotherapy, stereotactic radiosurgery (SRS), and proton beam radiotherapy. Complicating the treatment of these skull base tumors include the following: surgical therapy is rarely curative owing to their propensity to grow adjacent to and envelop critical structures and their propensity to recur (particularly chordomas); and radiation planning is frequently limited by their proximity to radiosensitive brain regions.

Surgical resection is considered the best first-line treatment, with greater degrees of resection associated with improved outcomes (2, 3, 6–8). Linear accelerator (LINAC) radiosurgery is widely available and has produced excellent tumor control rates, particularly when used as an adjuvant to surgical resection (9–12). LINAC radiosurgery has the inherent advantage of allowing a surgeon to target tumors with either single-dose radiosurgery or fractionated radiotherapy for a series of treatments. Gamma knife radiosurgery is another reasonable adjuvant therapy, with smaller tumors more likely candidates for SRS alone (13–16). More recently, proton beam radiotherapy has demonstrated tremendous promise, with excellent local tumor control and overall survival compared with conventional photon radiotherapy (17).

Given the location of these tumors and the difficulty in maintaining conformality because of the proximity of radiosensitive structures, any form of radiotherapy has met (at best) moderate success. A detailed analysis of treatment failures and complications is necessary to discern the limitations of LINAC radiotherapy and radiosurgery and additional future approaches to improve strategies for radiation delivery to these tumors. In the present series, we report 15 patients with cranial base chordomas and chondrosarcomas treated with LINAC radiosurgery, with particular regard to the potential reasons for failure or complications. To facilitate the present investigation, a detailed analysis of the radiotherapy treatment plans was conducted to provide the dosage received by critical brain structures.

Methods and Materials

Patient selection

The Institutional Review Board and Office for the Protection of Human Subjects at University of California, Los Angeles, approved the present retrospective review. The senior author (A.A.F.D.) performed 15 cases of postoperative adjuvant stereotactic radiotherapy (SRT, $n = 10$) and SRS ($n = 5$) for chordoma and chondrosarcoma between 1998 and 2006 using LINAC. All patients had undergone at least one surgical resection before receiving radiotherapy. The decision between performing SRS and SRT was reached through consensus of the neurosurgeon and radiation oncologist, mainly according to the tumor volume and the proximity to radiosensitive structures. In general, SRS was performed in patients with smaller volume tumors. In the SRT group, 6 patients were men and 4 were women. Two patients in this group were diagnosed with low-grade chondrosarcoma. The mean age at treatment was 48.9 ± 4.3 years. Six of these patients (60%) had tumors primarily located in the clivus, 3 (30%) had tumors growing out of the cavernous sinus, and 1 (10%) had a tumor predominantly located in the cerebellopontine angle. In the SRS group, 2 were men and 3 were women. One patient in this group received SRS 2 years after failing SRT. The mean age at treatment was 63.5 ± 3.6 years. Two patients (40%) had tumor predominantly involving the clivus, and three (60%) had tumor of the cavernous sinuses.

LINAC radiotherapy/radiosurgery

All radiosurgical procedures were targeted using 1.5T magnetic resonance imaging (MRI) scans fused to computed tomography scans of the brain, allowing for correction of magnetic resonance distortion. The magnetic resonance images were obtained using a Signa 1.5-Tesla MRI unit from General Electric Medical Systems (Milwaukee, WI). The computed tomography images were obtained using an MxTwin computed tomography scanner from Marconi Medical Systems (Mission Viejo, CA). The tumors were contoured using Brainlab iPlan software (Westchester, IL). During planning, three additional structures were contoured according to the magnetic resonance T_1-weighted and fluid-attenuated inversion recovery sequence images: the optic apparatus (nerves, chiasm, and tract), pituitary (gland and stalk), and brainstem (Fig.). This allowed for calculations of the dosage received by these structures at the 50%, 80%, and 90% isodose lines (IDLs). The neurosurgeon, radiation oncologist, and medical physicist formulated the final SRS plans. Radiation was delivered using the 6-MV Novalis LINAC equipped with multileaf collimator (Novalis, Heimstetten, Germany). SRT was delivered with the patient in a custom-fitted thermoplastic facemask. For SRS, patients received radiation while wearing the Brainlab stereotactic frame. The patients were discharged the same day as their radiation treatment.

Outcome and follow-up

All patients, except for 1, were followed up with sequential MRI and clinical visits. All patients were screened for new symptoms, including visual acuity or field deficits, cranial neuropathy, and endocrinopathy at scheduled postradiation visits. Endocrinopathy was defined as any evidence of new onset or worsening of existing endocrine dysfunction, including (but not limited to) diabetes insipidus, thyroid dysfunction, or panhypopituitarism after radiotherapy. The MRI scans were reviewed for evidence of radiation changes or tumor progression. Treatment failure was defined as evidence of tumor progression on neuroimaging after completion of SRT/SRS. This usually resulted in the patient being referred for further surgical resection or being considered for additional

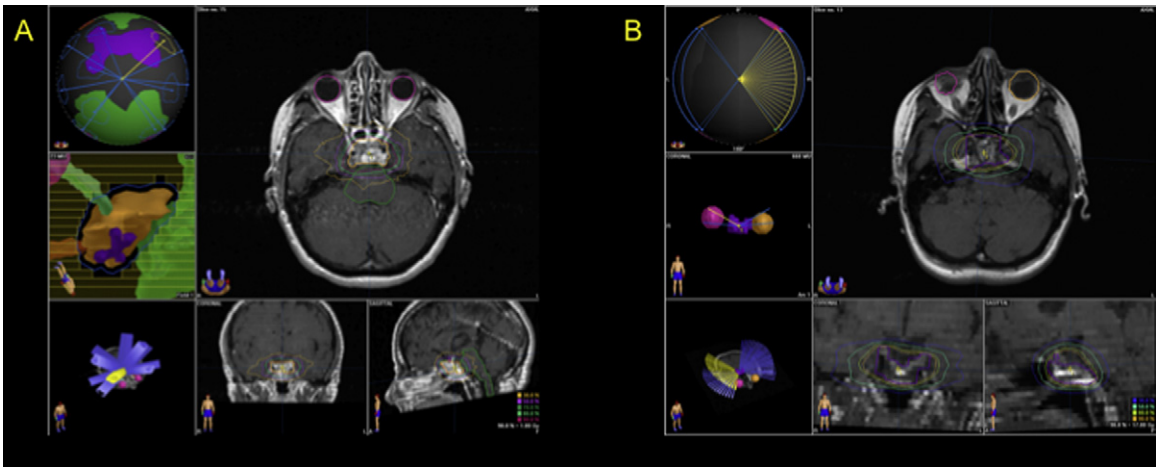

Fig. Postradiation imaging changes within the temporal lobe occurred in a patient who received both stereotactic radiotherapy and stereotactic radiosurgery for recurrent chordoma. (A) Treatment plan for stereotactic radiotherapy. (B) Treatment plan for stereotactic radiosurgery.

radiotherapy (1 patient was given SRS 2 years after SRT failed). The 1 patient lost to follow-up, who had received SRS, was considered to have treatment failure for statistical purposes.

Results

Tumor outcomes

The patient demographics, treatment parameters, and tumor outcomes are summarized in Table 1. Among the patients undergoing SRT, the average tumor size was 31.5 cm^3, and the average time to the initial radiologic follow-up examination was 44 months. Of those undergoing SRT, 6 (60%) were found to have reduced or stable tumor size on radiographic follow-up. Two of these patients had chondrosarcomas and four had chordomas. Four patients (40%), who had received SRT, developed tumor recurrence, all of whom had been diagnosed with chordoma. The average prescribed dose among patients with a reduced or stable tumor size was 57.7 Gy (95% confidence interval [CI], 52.6−62.8) with a maximal dose of 64.2 Gy (95% CI, 58.3−70.0). The average prescribed dose among patients with recurrence at radiographic follow-up was 65.1 Gy (95% CI, 54.2−75.9), with a maximal dose of 72.3 Gy (95% CI, 60.2−84.3). The prescribed dose between those with treatment success and those with treatment failure was not significantly different, nor was the tumor size. Among those with recurrent tumor after radiotherapy, the average time to progression was 66 months.

Five patients were treated with SRS. One patient was lost to follow-up. Of the remaining 4 patients, 3 were found to have reduced or stable tumor size at follow-up. One patient showed tumor recurrence on MRI 14 months after radiosurgery. Of the patients receiving SRS, the average tumor size was 13.3 cm^3, with an average prescribed dose of 15.5 Gy (95% CI, 13.2−17.9) to the 90% IDL and a maximal dose of 17.3 Gy (95% CI, 14.6−19.9) delivered to the tumor. No significant differences were noted in the radiation dosage in the patient with recurrence compared with the patients with tumor control. For the 3 patients with adequate tumor control, the average prescribed dose was 16.3 Gy (95% CI, 13.9−18.7), with a maximal dose of 18.1 Gy (95% CI, 15.5−20.8) compared with a prescribed dose of 16.0 Gy, with a maximal dose of 17.8 Gy for the patient with tumor recurrence. The patient who experienced recurrence did not have a significant difference in tumor volume compared with the 3 patients with tumor control.

Two patients in the SRT group were diagnosed with low-grade chondrosarcoma on histologic analysis. Neither patient developed tumor recurrence, endocrinopathy, or brainstem injury-related symptoms. The average prescribed dose in these patients was 62.1 Gy (95% CI, 60.3−63.9) to the 90% IDL with a maximal dose of 69 Gy (95% CI, 67−71). The average age at treatment was 39.3 years (95% CI, 38.3−40.3), with an average tumor volume of 24.0 cm^3 (95% CI, 19.8−28.1). Of the remaining 8 SRT patients with chordoma, 4 developed recurrence (50%). The average prescribed dose was 60.3 Gy (95% CI, 53.4−67.2) to the 90% IDL, with a maximal dose of 67.0 Gy (95% CI, 59.3−74.8). The average age at treatment was 51.3 years (95% CI, 41.1−61.4), with an average tumor volume of 33.4 cm^3 (95% CI, 9.9−56.9).

Treatment complications

In our series, 2 patients experienced permanent complications that could potentially be attributable to radiotherapy. The first, a 52-year-old white man, experienced endocrinopathy requiring replacement medications and post-treatment cranial neuropathy. He underwent SRT for recurrent chordoma involving the central and right clivus and extending dorsally into the prepontine cistern. The tumor also extended into the right medial petrous bone and partially involved the right internal carotid artery, right cavernous sinus, and right Meckels cave. He was prescribed 64 Gy in 32 fractions at the 90% IDL for a 41.84-cm^3 tumor. The maximal dose received by the tumor was 72 Gy. Although the treatment itself was well tolerated, in the months after treatment, the patient required several endocrine replacement medications. He also experienced persistent right facial weakness, although this was worsened by subsequent tumor recurrence and surgery. The patient experienced radiographic tumor recurrence 71 months after SRT that required additional surgical debulking. At the last follow-up, he was in hospice.

The second patient, a 74-year-old Asian woman, underwent SRS after two resections for a posterior and middle fossa chordoma in Japan. Before treatment, she described a 3-month history of increasing left facial numbness, intermittent double vision, and ptosis of the left eye. Imaging demonstrated an increased tumor

Table 1 Treatment specifics and outcomes for SRT and SRS cohorts

Pt. No.	Age (y)	Gender	Follow-up (d)	Pathologic finding	Tumor origin	Treatment	Tumor volume (cm^3)	Fractions *(n)*	Maximal dose (Gy)	Margins (mm)	Modality	Tumor outcome after RT
1	64.2	M	1,472	Chordoma	Cavernous sinus	SRT	81.52	36	72	0	Static beam	Stable
2	39.8	M	1,621	Chondroid chondrosarcoma	Clivus	SRT	26.3	35	70	2	Static beam	Stable
3	71.4	M	2,804	Chordoma	Clivus	SRT	23.78	42	84	0	Static beam	Recurrence
4	39.8	F	1,968	Chordoma	Cavernous sinus	SRT	13.32	39	78	1.5	Static beam	Recurrence
5	38.3	M	1,089	Chordoma	Cavernous sinus	SRT	71.75	30	60	3	Static beam	Stable
6	56.3	F	319	Chordoma	Clivus	SRT	9.95	28	56	0	Dynamic arcs	Recurrence
7	38.8	F	221	Chondroid chondrosarcoma	Clivus	SRT	11.31	34	68	0	Dynamic arcs	Stable
8	58.9	F	259	Chordoma	Clivus	SRT	13.42	28	53	2	Dynamic arcs	Stable
9	29.2	M	1,058	Chordoma	Cerebellopontine angle	SRT	0.9	31	62	0	Static beam	Stable
10	52.3	M	1,390	Chordoma	Clivus	SRT	41.84	32	72	0	Static beam	Recurrence
11	55.3	F	1,390	Chordoma	Cavernous sinus	SRS	13.1	1	15	3	Static beam	Recurrence
12	69.0	M	0	Chordoma	Clivus	SRS	10.3	1	18	3	Static beam	Unknown
13	60.8	M	148	Chordoma	Clivus	SRS	0.85	1	20	0	Static beam	Stable
14	58.1	F	821	Chordoma	Cavernous sinus	SRS	9.95	1	19	0	Dynamic arcs	Stable
15	74.4	F	221	Chordoma	Cavernous sinus	SRS	28.91	1	16	3	Static beam	Stable

Abbreviations: SRT = stereotactic radiotherapy; SRS = stereotactic radiosurgery; Pt. No. = patient number; M = male; F = female.

size at the petrous apex. On presentation at our institution, she first underwent subtotal resection and was followed up with serial imaging. Her chordoma then recurred in the clivus, petrous apex, cavernous sinus, and suprasellar space, with tumor extending to the left prepontine cistern. She received a single fraction of 14 Gy prescribed to the 90% IDL, with a maximal dose of 15.56 Gy. Five months after treatment, the patient presented with dysphagia, bilateral facial numbness, and dysarthria. Despite the absence of tumor growth on imaging, the patient also experienced a progressive decline in visual acuity of the left eye to blindness. At the last follow-up, she was in hospice.

One patient experienced a transient complication after radiotherapy. This patient, a 56-year-old white woman, had initially undergone SRT for her 9.95-cm^3 chordoma located primarily in the clivus with extension into the cavernous sinus. She was prescribed 50.4 Gy to the 90% IDL in 28 fractions (Fig.). This treatment was tolerated well. Approximately 2 years later, she experienced tumor recurrence and was treated with SRS. She was prescribed 17 Gy to the 90% IDL in a single fraction, with a maximal dose of 18.9 Gy received by the tumor. Approximately 2 years after treatment, she began to complain of déjà vu and anxiety. On MRI, she was noted to have diffuse T_2-weighted hyperintensity throughout her medial temporal lobe, thought to be radiation changes. Her symptoms and imaging findings completely resolved within 2 additional years, and at last follow-up, she was asymptomatic, with stable tumor.

Of the patients who received radiotherapy, 2 died. Neither death was apparently linked to radiosurgery or radiotherapy. One SRT patient died 9 years after treatment of complications related to a hip fracture. One SRS patient died 6 months after treatment of complications from pneumonia.

Endocrinopathy

The details of radiation to the pituitary gland and stalk and endocrine outcomes are summarized in Table 2. Endocrinopathy was defined as evidence of endocrine dysfunction, including diabetes insipidus, adrenal insufficiency, thyroid dysfunction, hypogonadism, or panhypopituitarism. One patient treated with SRT in the present series developed endocrinopathy as a result of treatment. Of the remaining SRT patients without endocrinopathy, the average percentage of the pituitary stalk volume at the 50% IDL was 71.7% (95% CI, 50.7−92.8), with an average dose of 33.5 Gy (95% CI, 30.1−36.9). The average percentage of the pituitary stalk at the 95% IDL was 6.5% (95% CI, −0.8 to 13.8), with an average dose of 63.7 Gy (95% CI, 57.2−70.1). In the patient who developed endocrinopathy, the entire pituitary stalk was exposed at the 50% IDL, with a dose of 35.6 Gy. At the 95% IDL, 27.1% of the pituitary stalk received 67.6 Gy.

In the SRS group, no patients reported endocrinopathy. The average percentage of the pituitary stalk at the 50% IDL was 54.6% (95% CI, 13.4−95.9), with an average dose of 9.6 Gy (95% CI, 8.2−11.0). The average percentage of the pituitary stalk at the 95% IDL was 1.5% (95% CI, −1.0 to 4.1), with an average dose of 18.2 Gy (95% CI, 15.6−20.8).

Brainstem exposure and cranial neuropathy

The brainstem exposure and cranial nerve outcomes are summarized in Table 3. Among the patients undergoing SRT, only 1 developed symptoms indicative of cranial neuropathy (facial nerve palsy) after treatment. Of the asymptomatic patients, the average percentage of the brainstem at the 50% IDL was 23.6% (95% CI, 4.6−42.6), with a dose of 33.5 Gy (95% CI, 30.1−36.9) compared with 27.3% of the brainstem, with a dose of 35.6 Gy, in the patient with right facial nerve palsy. One SRS patient developed dysphagia. In patients without new symptoms, the average percentage of the brainstem at the 50% IDL was 2.5% (95% CI, −0.4 to 5.3), with a dose of 10.2 Gy (95% CI, 9.2−11.2) compared with 21.1% of the brainstem at the 50% IDL, with a dose of 7.8 Gy in the symptomatic patient.

Optic neuropathy

The vision outcomes and optic apparatus exposure are summarized in Table 4. No SRT patients developed visual deficits after treatment. One patient receiving SRS developed a progressive decline in visual acuity after therapy. At the 50% IDL, 39.5% of the patients' optic apparatus received 7.8 Gy. At the 95% IDL, 0.93% of the optic apparatus received 14.8 Gy. In SRS patients without visual deficits, the average percentage of the optic apparatus at the 50% IDL was 0.61% (95% CI, −0.04 to 1.3). None of the optic apparatuses were exposed at the 95% IDL.

Discussion

Tumor control

In our series, the recurrence rate at radiographic follow-up among the SRT patients was 40% (4 of 10) and ≤40% (2 of 5) in the SRS patients (including the 1 patient lost to follow-up and assumed to have treatment failure). These rates are consistent with what others have reported using photon radiotherapy or radiosurgery (4, 5, 9, 10, 12−16, 18−22). Our mean follow-up time was approximately 44 months; previous reports have shown that the mean interval to progression after radiotherapy is approximately 40.8 months (23). Muthukumar *et al.* (22) reported that 73% of patients improved or remained stable after radiosurgery but that single-fraction radiosurgery is most effective for the treatment of either smaller tumors or tumors with a residual volume <20 cm^3 after surgical debulking. This is similar to another report from Chang *et al.* (10), which showed excellent control rates after radiosurgery for smaller tumors (<21.5 cm^3) using higher prescribed doses (18−24 Gy). For tumors for which fractionated SRT was thought to be preferable, Debus *et al.* (12) achieved 82% local control at 2 years and 50% local control at 5 years.

Regardless of modality, it seems apparent that major determinants of success after radiotherapy include the tumor volume and prescribed dose (24). Because of the reduced power of our small series, it is difficult to make statistical determinations about the failures of SRT and SRS.

Complications

Three patients had significant complications after radiotherapy, two with permanent and one with transient adverse events. To further characterize the radiation parameters that might have contributed to these adverse events, we identified the dosage to critical structures, including the optic apparatus, brain stem, and pituitary stalk.

Table 2 Radiation to pituitary stalk and gland and postradiotherapy endocrinopathy

Pt. No.	Treatment	Pituitary volume (cm^3)	Pituitary volume at 50% IDL (%)	Dose received at 50% IDL (Gy)	Pituitary volume at 80% IDL (%)	Dose received at 80% IDL (Gy)	Pituitary volume at 90% IDL (%)	Dose received at 90% IDL (Gy)	Pituitary volume at 95% IDL (%)	Dose received at 95% IDL (Gy)	Endocrinopathy after RT
1	SRT	0.03	100	36	69.75	57.6	8.13	64.8	0	68.4	No
2	SRT	0.07	63.24	35	4.64	56	0	63	0	66.5	No
3	SRT	0.14	81.62	42	39.58	67.2	26.11	75.6	10.92	79.8	No
4	SRT	0.13	80.19	39	24.04	62.4	0.67	70.2	0	74.1	No
5	SRT	0.07	100	30	100	48	100	54	32.71	57	No
6	SRT	0.05	100	28	59.6	44.8	32.05	50.4	12.19	53.2	No
7	SRT	0.03	0.77	34	0	54.4	0	61.2	0	64.6	No
8	SRT	0.73	63.89	26.53	26.09	42.44	12.5	47.75	2.48	50.4	No
9	SRT	0.07	55.95	31	5.81	49.6	0	55.8	0	58.9	No
10	SRT	0.12	100	35.56	97.74	56.89	55.27	64	27.1	67.56	Yes
11	SRS	0.13	61.49	11.11	22.88	17.78	11.15	20	0.76	21.11	No
12*	SRS	—	—	—	—	—	—	—	—	—	—
13	SRS	0.09	0	10	0	16	0	18	0	19	No
14	SRS	0.11	57.09	9.44	30.52	15.11	18.36	17	5.29	17.94	No
15	SRS	0.04	100	7.78	53.93	12.44	13.14	14	0	14.78	No

Abbreviations: IDL = isodose line; RT = radiotherapy; other abbreviations as in Table 1.

* Lost to follow-up.

Table 3 Radiation to brainstem and postradiotherapy brainstem injury

Pt. No.	Treatment	Brainstem volume (cm^3)	Brainstem volume at 50% IDL (%)	Dose received at 50% IDL (Gy)	Brainstem volume at 80% IDL (%)	Dose received at 80% IDL (Gy)	Brainstem volume at 90% IDL (%)	Dose received at 90% IDL (Gy)	Brainstem volume at 95% IDL (%)	Dose received at 95% IDL (Gy)	Brainstem injury symptoms after RT
1	SRT	30.18	82.85	36	34.81	57.6	23.22	64.8	7.29	68.4	No
2	SRT	30.95	22.43	35	5.51	56	2.35	63	0.05	66.5	No
3	SRT	27.25	0.88	42	0	67.2	0	75.6	0	79.8	No
4	SRT	24.56	18.84	39	4.52	62.4	1.23	70.2	0.01	74.1	No
5	SRT	32.04	59.03	30	22.96	48	14.19	54	4.33	57	No
6	SRT	20.85	11.5	28	2.85	44.8	1.43	50.4	0.37	53.2	No
7	SRT	26.48	11	34	1.02	54.4	0.08	61.2	0	64.6	No
8	SRT	30.07	5.17	26.53	0.4	42.44	0.06	47.75	0	50.4	No
9	SRT	29.43	0.36	31	0	49.6	0	55.8	0	58.9	No
10	SRT	27.27	27.28	35.56	11.91	56.89	3.88	64	0.01	67.56	Yes
11	SRS	23.23	0.46	11.11	0	17.78	0	20	0	21.11	No
12*	SRS	—	—	—	—	—	—	—	—	—	—
13	SRS	24.57	1.73	10	0.36	16	0.11	18	0.02	19	No
14	SRS	21.1	5.24	9.44	0.45	15.11	0.02	17	0	17.94	No
15	SRS	21.97	21.11	7.78	0.52	12.44	0	14	0	14.78	Yes

Abbreviations: IDL = isodose line; RT = radiotherapy; other abbreviations as in Table 1.

* Lost to follow-up.

Table 4 Radiation to optic apparatus and postradiotherapy visual deficit

Pt. No.	Treatment	Optic apparatus volume (cm^3)	Optic apparatus volume at 50% IDL (%)	Dose received at 50% IDL (Gy)	Optic apparatus volume at 80% IDL (%)	Dose received at 80% IDL (Gy)	Optic apparatus volume at 90% IDL (%)	Dose received at 90% IDL (Gy)	Optic apparatus volume at 95% IDL (%)	Dose received at 95% IDL (Gy)	Visual deficit after RT
1	SRT	3.63	36.9	36	3.42	57.6	0.17	64.8	0	68.4	No
2	SRT	0.83	1.68	35	0	56	0	63	0	66.5	No
3	SRT	1.86	25.3	42	0	67.2	0	75.6	0	79.8	No
4	SRT	0.98	14.1	39	2.96	62.4	0.61	70.2	0	74.1	No
5	SRT	1.16	73.07	30	56.02	48	41.65	54	18.35	57	No
6	SRT	1.23	31.84	28	15.03	44.8	7.72	50.4	1.87	53.2	No
7	SRT	1.7	13.9	34	0	54.4	0	61.2	0	64.6	No
8	SRT	1.62	0	26.53	0	42.44	0	47.75	0	50.4	No
9	SRT	1.08	31.91	31	8.74	49.6	2.23	55.8	0.37	58.9	No
10	SRT	0.97	45.83	35.56	8.75	56.89	2.27	64	0.72	67.56	No
11	SRS	1.45	1.11	11.11	0	17.778	0	20	0	21.111	NA
12*	SRS	—	—	—	—	—	—	—	—	—	—
13	SRS	1.79	1.79	10	0	16	0	18	0	19	No
14	SRS	1.69	0.71	9.45	0	15.11	0	17	0	17.94	No
15	SRS	0.86	39.51	7.78	9.73	12.44	2.78	14	0.93	14.78	Yes

Abbreviations: IDL = isodose line; RT = radiotherapy; other abbreviations as in Table 1.

* Lost to follow-up.

Pituitary endocrinopathy was seen in 1 patient who underwent SRT. It was not surprising that 100% of the pituitary stalk was in the 50% IDL (35.56 Gy) and 27.1% at the 95% IDL (67.56 Gy). Of all the patients treated with SRT, he received the most radiation to his pituitary stalk. Interestingly, 1 other patient also received high stalk exposure (57 Gy to 32% of the stalk at the 95% IDL and 54 Gy to 100% of the stalk at the 90% IDL) but did not experience post-treatment hypopituitarism. Exposure of the pituitary stalk to radiation must be considered when planning for chordoma patients. Recent work has shown that there is a high incidence of gonadotropin, thyroid-stimulating hormone, and adrenocorticotropic hormone deficiencies after exposure of the pituitary to >50 Gy of radiation (25). Deficiencies in growth hormone secretion are even more common, with the threshold for growth hormone dysfunction being about 30 Gy. Deficiencies of the anterior pituitary are irreversible and can have a significantly delayed presentation (*i.e.,* years) after radiation. Thus, we recommend considering pituitary stalk exposure similar to that for optic apparatus exposure in radiation planning. A reasonable goal would be to keep pituitary exposure <30 Gy when possible for SRT. Considering that not all the patients in our series who received >30 Gy experienced pituitary dysfunction, further work must be done to identify additional factors that increase the risk to the pituitary. In patients treated with single-fraction radiosurgery, the relationship between pituitary exposure and prescribed dose is not as clear (26, 27).

One patient treated with SRS developed visual deficits; however, this was likely attributable to the high radiation dose delivered to the optic apparatus. She had 39.51% of her optic apparatus at the 50% IDL (7.78 Gy) and <1% of her optic apparatus at the 95% IDL (14.78 Gy). These radiation doses delivered to the optic apparatus as hypofractionated therapy are significant and increase the risk of radiation-induced optic neuropathy (28). We therefore recommend avoiding SRS if the optic apparatus is included in the 80% IDL. Despite similar doses in the SRT group, the fractionation of radiation likely reduced the risk of injury.

One patient in each group developed brainstem symptoms after radiosurgery. Lower cranial nerve dysfunction subsequently arose in 1 patient receiving 7.78 Gy to 21.11% (4.64 cm^3) of the brainstem at the 50% IDL and 12.44 Gy to 0.52% (0.11 cm^3) of the brainstem at the 90% IDL. Compared with the other patients who received SRS, she experienced considerably greater brainstem radiation exposure. It has been suggested that exposure of the brainstem to ≥12 Gy even at small volumes can result in neurologic deficits after radiosurgery (29). In the SRT group, 1 patient experienced facial weakness after receiving 35.56 Gy to 27.28% (7.44 cm^3) of the brainstem at the 50% IDL and 64 Gy to 3.88% (1.05 cm^3) of the brainstem at the 90% IDL. As expected, cranial nerve and nuclei injury is strongly correlated with the radiation dose (30). The rates of injury are considered to be 1% at 60 Gy and 5% at 70 Gy. That this was not the only patient to receive high doses to the brainstem but was the only patient to have symptoms is not surprisingly in light of this fact. Although it is important to minimize the radiation dose to the brainstem, the reasonable radiation tolerance of the cranial nerves and nuclei allow for some flexibility in treating these and other challenging skull base tumors.

Finally, we had 1 patient who experienced temporal lobe radiation changes that appeared 24 months after a second radiation treatment for recurrent chordoma. These changes, which were accompanied by feelings of déjà vu and generalized anxiety, had completely resolved within an additional 24 months. The presentation of this radiation-induced adverse event has been well described in published studies, particularly in the setting of therapy for nasopharyngeal carcinoma (31). Usually this complication is managed with corticosteroids, and the symptoms are self-limiting. The risk factors for temporal lobe radiation necrosis are primarily linked to the prescribed dose, with patients receiving >200 cGy/fraction at greater risk. This patient had received two different radiation treatments within 2 years, putting her at greater risk of radiation changes. That these changes were transient, again suggests a degree of flexibility when aggressively treating recurrent chordomas with radiotherapy.

The very nature and location of chordomas has been, and will continue to be, the most challenging aspect of their treatment. It is clear that both surgery and radiotherapy are required to best address this pathology. Although proton (and potentially carbon) radiotherapy might have potential technical benefits, they are unavailable to many patients. Conventional photon radiotherapy is widely available and achieves reasonable tumor control rates. Clearly, the best chance of tumor control is provided by the maximal possible radiation dose and can be achieved with smaller tumor volumes. The particular challenges in planning radiotherapy for these tumors include their proximity to critical neural structures, including the optic apparatus, pituitary stalk, and brainstem cranial nuclei and cranial nerves. If the optic apparatus must be included in the 80% IDL, it is preferable to fractionate the radiation dosages to minimize the risk of injury. As for the pituitary stalk, it is best to keep exposure to <30 Gy to reduce pituitary dysfunction, a problem that can occur years after therapy. The brainstem and cranial nerves can be relatively more forgiving in radiation planning, with exposures best kept at <60 Gy to ensure preserved cranial nerve function. Even if this region receives 60 or 70 Gy, the risk of cranial nerve or nuclei impairment is still low (<5%). If radiosurgery is planned, however, brainstem exposure is best kept at <12 Gy.

References

1. Heffelfinger MJ, Dahlin DC, MacCarty CS, *et al*. Chordomas and cartilaginous tumors at the skull base. *Cancer* 1973;32:410–420.
2. Colli BO, Al-Mefty O. Chordomas of the skull base: follow-up review and prognostic factors. *Neurosurg Focus* 2001;10:E1.
3. Almefty K, Pravdenkova S, Colli BO, *et al*. Chordoma and chondrosarcoma: Similar, but quite different, skull base tumors. *Cancer* 2007;110:2457–2467.
4. Martin JJ, Niranjan A, Kondziolka D, *et al*. Radiosurgery for chordomas and chondrosarcomas of the skull base. *J Neurosurg* 2007;107:758–764.
5. Cho YH, Kim JH, Khang SK, *et al*. Chordomas and chondrosarcomas of the skull base: Comparative analysis of clinical results in 30 patients. *Neurosurg Rev* 2008;31:35–43.
6. Ammirati M, Bernardo A. Management of skull base chordoma. *Crit Rev Neurosurg* 1999;9:63–69.
7. Pallini R, Maira G, Pierconti F, *et al*. Chordoma of the skull base: Predictors of tumor recurrence. *J Neurosurg* 2003;98:812–822.
8. Yoneoka Y, Tsumanuma I, Fukuda M, *et al*. Cranial base chordoma—Long term outcome and review of the literature. *Acta Neurochir (Wien)* 2008;150:773–778.
9. Kocher M, Voges J, Staar S, *et al*. Linear accelerator radiosurgery for recurrent malignant tumors of the skull base. *Am J Clin Oncol* 1998;21:18–22.

10. Chang SD, Martin DP, Lee E, *et al*. Stereotactic radiosurgery and hypofractionated stereotactic radiotherapy for residual or recurrent cranial base and cervical chordomas. *Neurosurg Focus* 2001;10:E5.
11. Pedroso-Gorgulho A, De Salles A, Frighetto L, *et al*. Preliminary Novalis experience in the treatment of skull base chordomas with stereotactic radiosurgery and stereotactic radiotherapy. *Radiosurgery* 2004;5:82−90.
12. Debus J, Schulz-Ertner D, Schad L, *et al*. Stereotactic fractionated radiotherapy for chordomas and chondrosarcomas of the skull base. *Int J Radiat Oncol Biol Phys* 2000;47:591−596.
13. Ito E, Saito K, Okada T, *et al*. Long-term control of clival chordoma with initial aggressive surgical resection and gamma knife radiosurgery for recurrence. *Acta Neurochir (Wien)* 2010;152:57−67.
14. Kondziolka D, Lunsford LD, Flickinger JC. The role of radiosurgery in the management of chordoma and chondrosarcoma of the cranial base. *Neurosurgery* 1991;29:38−45. 36.
15. Liu AL, Wang ZC, Sun SB, *et al*. Gamma knife radiosurgery for residual skull base chordomas. *Neurol Res* 2008;30:557−561.
16. Hasegawa T, Ishii D, Kida Y, *et al*. Gamma knife surgery for skull base chordomas and chondrosarcomas. *J Neurosurg* 2007;107:752−757.
17. Amichetti M, Cianchetti M, Amelio D, *et al*. Proton therapy in chordoma of the base of the skull: A systematic review. *Neurosurg Rev* 2009;32:403−416.
18. Dassoulas K, Schlesinger D, Yen CP, *et al*. The role of gamma knife surgery in the treatment of skull base chordomas. *J Neurooncol* 2009; 94:243−248.
19. Gwak HS, Yoo HJ, Youn SM, *et al*. Hypofractionated stereotactic radiation therapy for skull base and upper cervical chordoma and chondrosarcoma: Preliminary results. *Stereotact Funct Neurosurg* 2005;83:233−243.
20. Henderson FC, McCool K, Seigle J, *et al*. Treatment of chordomas with CyberKnife: Georgetown University experience and treatment recommendations. *Neurosurgery* 2009;64:A44−A53.
21. Krishnan S, Foote RL, Brown PD, *et al*. Radiosurgery for cranial base chordomas and chondrosarcomas. *Neurosurgery* 2005;56:777−784.
22. Muthukumar N, Kondziolka D, Lunsford LD, *et al*. Stereotactic radiosurgery for chordoma and chondrosarcoma: Further experiences. *Int J Radiat Oncol Biol Phys* 1998;41:387−392.
23. Zorlu F, Gurkaynak M, Yildiz F, *et al*. Conventional external radiotherapy in the management of clivus chordomas with overt residual disease. *Neurol Sci* 2000;21:203−207.
24. Koga T, Shin M, Saito N. Treatment with high marginal dose is mandatory to achieve long-term control of skull base chordomas and chondrosarcomas by means of stereotactic radiosurgery. *J Neurooncol* 2010;98:233−238.
25. Darzy KH, Shalet SM. Hypopituitarism following radiotherapy. *Pituitary* 2009;12:40−50.
26. Castro DG, Cecilio SA, Canteras MM. Radiosurgery for pituitary adenomas: Evaluation of its efficacy and safety. *Radiat Oncol* 2010;5: 109.
27. Hayashi M, Chernov M, Tamura N, *et al*. Gamma knife robotic microradiosurgery of pituitary adenomas invading the cavernous sinus: treatment concept and results in 89 cases. *J Neurooncol* 2010; 98:185−194.
28. Mayo C, Martel MK, Marks LB, *et al*. Radiation dose−volume effects of optic nerves and chiasm. *Int J Radiat Oncol Biol Phys* 2010;76: S28−S35.
29. Sharma MS, Kondziolka D, Khan A, *et al*. Radiation tolerance limits of the brainstem. *Neurosurgery* 2008;63:728−732. 723.
30. Urie MM, Fullerton B, Tatsuzaki H, *et al*. A dose−response analysis of injury to cranial nerves and/or nuclei following proton beam radiation therapy. *Int J Radiat Oncol Biol Phys* 1992;23: 27−39.
31. Lee AW, Ng SH, Ho JH, *et al*. Clinical diagnosis of late temporal lobe necrosis following radiation therapy for nasopharyngeal carcinoma. *Cancer* 1988;61:1535−1542.