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CLINICAL INVESTIGATION **Normal Tissue**

TOLERANCE OF THE SPINAL CORD TO STEREOTACTIC RADIOSURGERY: INSIGHTS FROM HEMANGIOBLASTOMAS

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Purpose: To evaluate spinal cord dose–volume effects, we present a retrospective review of stereotactic radiosurgery (SRS) treatments for spinal cord hemangioblastomas.

Methods and Materials: From November 2001 to July 2008, 27 spinal hemangioblastomas were treated in 19 patients with SRS. Seventeen tumors received a single fraction with a median dose of 20 Gy (range, 18–30 Gy). Ten lesions were treated using 18–25 Gy in two to three sessions. Cord volumes receiving 8, 10, 12, 14, 16, 18, 20, 22, and 24 Gy and dose to 10, 100, 250, 500, 1000, and 2000 mm^3 of cord were determined. Multisession treatments were converted to single-fraction biologically effective dose (SFBED).

Results: Single-fraction median cord D_{max} was 22.7 Gy (range, 17.8–30.9 Gy). Median V10 was 454 mm^3 (range, 226–3543 mm^3). Median dose to 500 mm^3 cord was 9.5 Gy (range, 5.3–22.5 Gy). Fractionated median $SFBED_3$ cord D_{max} was 14.1 Gy_3 (range, 12.3–19.4 Gy_3). Potential toxicities included a Grade 2 unilateral foot drop 5 months after SRS and 2 cases of Grade 1 sensory deficits. The actuarial 3-year local tumor control estimate was 86%.

Conclusions: Despite exceeding commonly cited spinal cord dose constraints, SRS for spinal hemangioblastomas is safe and effective. Consistent with animal experiments, these data support a partial-volume tolerance model for the human spinal cord. Because irradiated cord volumes were generally small, application of these data to other clinical scenarios should be made cautiously. Further prospective studies of spinal radiosurgery are needed.

Hemangioblastoma, Spinal, SBRT, Radiosurgery, Spinal cord tolerance.

INTRODUCTION

Stereotactic radiosurgery (SRS) has gained increasing acceptance as a treatment modality for tumors of the spine. The majority of spinal SRS treatments, herein defined as stereotactic treatment in 1 to 5 fractions, are directed at metastatic lesions of the vertebral body. Multiple studies describe excellent clinical efficacy and few side effects in this setting (1–9). However, appropriate dose constraints for the spinal cord with single-fraction or high-dose-per-fraction radiosurgery are poorly defined, with significant discordance among the major SRS groups. In part, this situation stems from the limited survival of many spinal metastasis patients previously treated with SRS. Human cord tolerance to conventionally fractionated radiotherapy to full-thickness cord is relatively well understood. The risk of myelopathy after 50–55 Gy in 2-Gy daily fractions is approximated at <1%, with sharply increasing risk at doses exceeding 60 Gy (10–13). However, for SRS, published cord limits range from a maximum cord dose (cord D_{max}) of 10 Gy to 14 Gy (3, 4, 7) or a partial-volume tolerance of 10 Gy (V10) to 10% of the contoured cord (9), with cord toxicity infrequently reported using these parameters (8, 9). Given a paucity of reported cord myelopathy among SRS series, the tolerance of the spinal cord to the dosimetry encountered in SRS remains unclear.

Human clinical data are particularly lacking for radiosurgery treatments targeting small volumes of cord with relatively high doses. Data from animal models suggest that the rat cord tolerance to single-fraction SRS increases significantly with partial-cord-thickness irradiation as compared with full-thickness irradiation (14). Additional animal studies have suggested that a strong length effect exists with SRS, with a dramatic increase in cord tolerance as the length of irradiated cords drops below 8 mm in a rat model (15). The applicability of these findings to the human spinal cord remains unknown.

Hemangioblastomas are benign, vascular, pial-based tumors most commonly located in the cerebellum, brainstem, and spinal cord. Approximately one third are associated

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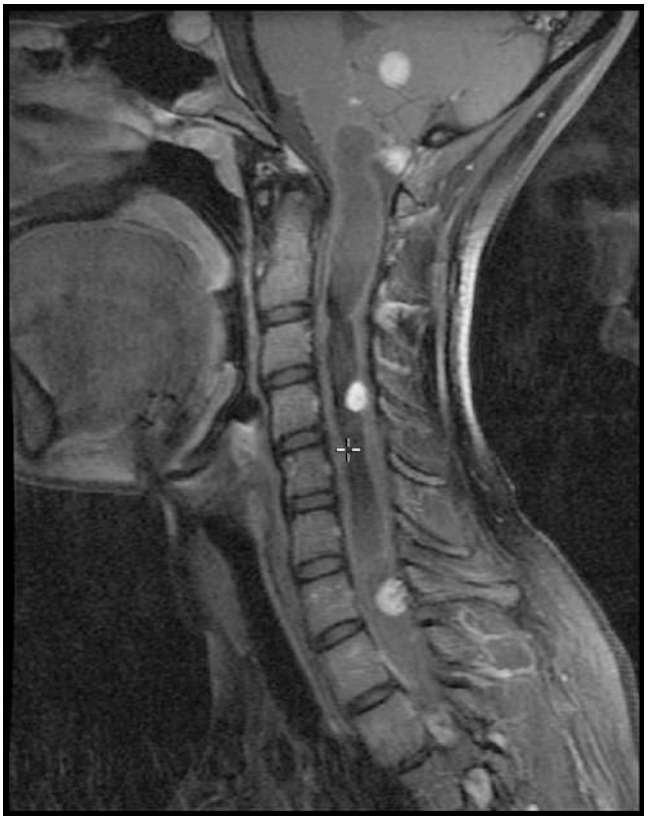

Fig. 1. A patient with von Hippel-Lindau disease with disseminated posterior fossa and spinal hemangioblastomas. She was diagnosed in 2000 with von Hippel-Lindau disease and subsequently underwent stereotactic radiosurgery in 2001 to five intracranial lesions. In 2002, she underwent additional stereotactic radiosurgery to three separate spinal hemangioblastomas. Pre-existing syringomyelia is apparent.

with the autosomal dominant genetic disorder von Hippel-Lindau disease (VHL), in which widespread lesions throughout the central nervous system are observed (Fig. 1). Although the mainstay of management for hemangioblastomas has historically been surgical resection, prior studies suggest that local control of intracranial hemangioblastomas may be achieved with SRS (16–19).

At our institution, we have developed an aggressive radiosurgical approach to these relatively radioresistant tumors in both the brain and spine, with cord doses often exceeding published guidelines. Typical SRS plans for these lesions provide a relatively high dose to a small volume of partial-thickness spinal cord with a steep dose gradient. These patients constitute an optimal cohort in which to examine the tolerance of the human cord to high-dose, low-volume SRS. In this report, we retrospectively evaluate a series of radiosurgical patients by performing a detailed dose–volume analysis of each treated spinal cord.

METHODS AND MATERIALS

Patients

Between July 1995 and June 2008, 31 pial-based spinal cord hemangioblastomas in 19 patients were treated with robotic SRS at Stanford University Medical Center. Treatment plans for 4 lesions generated on an older planning system (before 2001) were not retrievable; the remaining 27 lesions form the population for this analysis. Median patient age at treatment was 30 years (range, 20–62 years). Nine women and 10 men were included. Fourteen patients had a confirmed diagnosis of VHL; tumors were sporadic in 5 cases. Tumors were located within the cervical (12), thoracic (14), or lumbar/conus (1) spinal cord. Eight tumors (30%) had undergone a previous attempt at surgical resection and received SRS for residual or recurrent disease. Among the VHL patients in this series, the median number of prior spinal surgeries was 1 (range, 0–2). Patient and tumor characteristics are outlined in Table 1.

Table 1. Patient and treatment characteristics

Gender	
Male	10
Female	9
Age (y)	30.2 (19.6–61.9)
Genetic status	
VHL	14
Sporadic	5
Spinal level	
Cervical	12
Thoracic	14
Lumbar	1
Tumor site	
Intramedullary	20
Extramedullary	7
Tumor volume (cm^3)	0.16 (0.06–9.80)
Prescribed dose (Gy)	
Single session	20 (18–30)
Two sessions	22 (20–25)
Three sessions	21 (18–21)
Prescription isodose line (%)	77 (68–86)
Modified conformity index	1.47 (1.08–2.60)

Abbreviation: VHL = von Hippel-Lindau disease.
Values are number or median (range).

Before SRS, all patients underwent a comprehensive history and physical examination by both a radiation oncologist and neurosurgeon, and magnetic resonance imaging (MRI) of the tumor was reviewed.

Stereotactic radiosurgery

The CyberKnife image-guided robotic radiosurgery system (Accuray, Sunnyvale, CA) was used for all treatments. Patient immobilization was achieved with an Aquaplast face mask (WFR/Aquaplast, Wyckoff, NJ) for cervical spine lesions or a vacuum-set moldable styrofoam immobilization cushion (Vac Bag; Med-Tech, South Plainsfield, NJ) for lesions of the thoracic or lumbar spine. Supine contrast-enhanced 1.25-mm-thick computed tomography (CT) scans were obtained through the spinal region of interest. Contiguous axial 2.0-mm-thick stereotactic MR images were similarly acquired with the patient in the supine position. Both the CT and MR image sets were then fused on the treatment-planning workstation as part of the process of tumor delineation. The target volume and critical structures were contoured slice by slice on the treatment-planning CT. Spinal cord was contoured at least one vertebral level above and below each target lesion. Treatment plans were generated with iterative inverse treatment-planning software.

As a prelude to radiosurgical imaging, patients with tumors caudal to C2 and who were treated before September 2004 underwent surgical insertion (minimally invasively) of three to five small

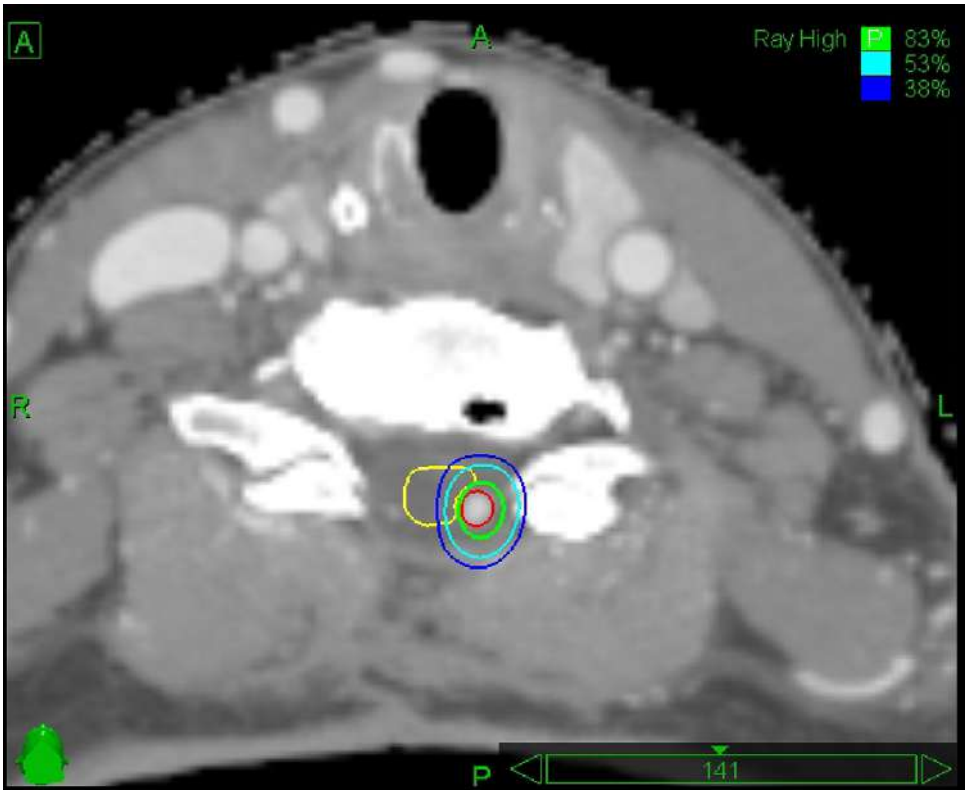

Fig. 2. A representative spinal stereotactic radiosurgery treatment plan. A 0.73-cm^3 lateral C6 spinal hemangioblastoma (red contour) was treated with 22 Gy in a single fraction prescribed to the 83% isodose line (green contour). The 53% (cyan) and 38% (blue) isodose lines corresponding to 14 Gy and 10 Gy, respectively, are displayed. The spinal cord D_{max} was 22.8 Gy, with a V14 of 130 mm^3 and V10 of 241 mm^3. Note that this lesion lies over the lateral corticospinal tract.

stainless steel fiducial markers into the posterior elements of adjacent vertebral bodies. After September 2004, bony anatomy alone has been used for target localization with the Xsight skeletal structure tracking system (Accuray). The process of real-time image acquisition and dynamic targeting has previously been described in detail (4).

Seventeen tumors were treated with single-fraction SRS, with a median target dose of 20 Gy (range, 18–30 Gy). Three tumors received a 2-fraction regimen, with a median dose of 22 Gy (range, 20–25 Gy). Seven tumors received 3 fractions, with a median target dose of 21 Gy (range, 18–21 Gy). A typical treatment plan is shown in Fig. 2. Although the dose and fractionation determinations were made according to the preference of the treating physicians, fractionated regimens tended to be used with larger target volumes. The median tumor volume among single- and multisession treatments was 97 mm^3 (range, 60–2490 mm^3) and 392 mm^3 (range, 97–9080 mm^3), respectively.

Dose–volume analysis and multifraction dose conversion

For each treated lesion, a spinal cord dose–volume histogram (DVH) was retrieved from the electronic archives and reviewed. The pial margin of the spinal cord was contoured on consecutive axial slices without additional margin. In some cases, the contoured volume included an adjacent intramedullary cyst and/or syrinx. Spinal cord contours were re-reviewed. The maximum cord dose (D_{max}) and dose to 10, 100, 250, 500, 1000, and 2000 mm^3 were calculated, as was the volume of cord receiving 8, 10, 12, 14, 16, 18, 20, 22, and 24 Gy (V8 through V24, respectively). Prescription dose, maximum target dose, prescription isodose line, PIV/TIV (prescribed isodose volume/tumor volume encompassed by the prescription isodose line), and modified conformity index (4) were also recorded. Tumor volume in cubic millimeters and tumor location within the cord (midline vs. lateral; laterality, anterior vs. posterior; and estimated spinal neural tracts at risk) were determined and recorded.

Multifraction treatments were converted to a single-fraction biologically effective dose (SFBED) using the linear-quadratic (LQ) model (20): BED = nd[1 + d/(α/β)], where n = number of fractions, d = dose per fraction, and α/β is estimated as 3 for purposes of late cord toxicity. Given the potential inherent inaccuracies of the LQ model in describing high-dose-per-fraction radiation (21), an alternate set of calculations for each multifraction treatment was also performed with the linear-quadratic–linear (LQ-L) model/universal survival curve hybridizing the LQ model with the multitarget model, as described by Park *et al.* (22). A transition dose between the LQ model and multitarget model of 6.2 Gy was assumed, and α/β of 3 was used. The LQ-L calculations were performed with TDFPlan software (Eye Physics, Los Alamitos, CA). The SFBED values for spinal cord D_{max} using both the LQ model and LQ-L model were calculated.

Patient follow-up

Patients were evaluated every 6–12 months with MRI and clinical examination to monitor for treatment side effects and disease progression. Disease progression was defined as clear evidence of tumor or cyst progression by imaging. Actuarial estimates of local control were calculated using the Kaplan-Meier method (23).

Table 2. Volume of spinal cord receiving 8–20 Gy of radiation

Parameter	No. of lesions	V8*	V10*	V12*	V14*	V16*	V18*	V20*
No. of sessions								
1†	17	695 (323–3919)	454 (226–3543)	286 (150–3104)	172 (88–2544)	103 (34–2016)	50 (5–1496)	17.2 (0–1026)
2	3	905 (165–1558)	711 (114–1216)	557 (77–920)	424 (49–629)	313 (28–380)	169 (13–208)	17 (3–111)
3	7	1152 (485–3829)	788 (335–3426)	579 (218–3022)	409 (122–2442)	203 (56–1544)	64 (11–468)	7 (3–102)
Patient with toxicity (1 session)		543	340	204	99	34	0	0

* Volume of spinal cord receiving 8, 10, 12, 14, 16, 18, or 20 Gy. Values shown in cubic millimeters as median (range).
† Including the patient with Grade 2 spinal cord neurotoxicity.

Toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0 (24).

RESULTS

DVH and tumor location analyses

Median tumor volume was 160 mm^3 (range, 60–9800 mm^3). Seventeen tumors were treated in a single session, with a median target dose of 20 Gy (range, 18–30 Gy). Median prescription isodose line was 77% (range, 68–86%). Median modified conformity index and PIV/TIV were 1.46 (range, 1.08–2.60) and 1.60 (range, 1.20–2.94), respectively. In the single-fraction group, the median spinal cord D_{max} was 22.7 Gy (range, 17.8–30.9 Gy), and the median dose received by 100 mm^3 was 15.9 Gy (range, 13.6–25.1 Gy). The V8 was 695 mm^3 (range, 323–3919 mm^3), and the V10 was 454 mm^3 (range, 226–3543 mm^3). Tables 2 and 3 show the detailed spinal cord DVH analysis. Of note, 10 of 17 single-fraction treatments (59%) had spinal cord DVHs that exceeded the spinal radiosurgery protocol Radiation Therapy Oncology Group (RTOG) 0631 parameter of a V10 of <350 mm^3. All 17 single-fraction treatments exceeded the RTOG 0631 cord D_{max} constraint of 14 Gy. Of the 7 of 17 treatments in which a V10 of <350 mm^3 was achieved, the median D_{max} was 22.8 Gy (range, 17.8–25.0 Gy).

Ten tumors were treated in multiple fractions, with 18–25 Gy delivered in 2 to 3 fractions. The median SFBED spinal cord D_{max}, as calculated using the LQ model, was 14.1 Gy_3 (range, 12.3–19.4 Gy_3). Converted median SFBED to 500 mm^3 was 8.5 Gy_3 (range, 2.4–11.3 Gy_3). The LQ-L model suggested a median D_{max} of 17.7 Gy_3 (range, 15.2–24.1 Gy_3). Examination of the anatomic region within the cord treated revealed 7 anterior lesions, 19 posterior cord lesions, and 1 lesion overlapping both the anterior and posterior regions of cord, with 6 right-sided, 13 left-sided, and 8 midline lesions. To estimate the spinal neural tracts potentially at risk should radiation injury occur immediately adjacent to the radiosurgically treated tumor, the lateral corticospinal tract was considered the primary motor tract (posterolateral spinal cord location); meanwhile, the spinothalamic tracts, located in the anterior cord, and the dorsal columns, in the posterior cord, were designated as the sensory tracts. Using this simplification, the sensory tracts were most at risk in 11 lesions, motor tracts in 11, and both motor and sensory tracts were equally at risk for 5 lesions. Figure 3 illustrates this simplified anatomic classification system.

Patient outcomes

Local control. One patient with two treated lesions was lost to follow-up after radiosurgery and is excluded from the outcomes analysis. Among the remaining 18 patients with 25 tumors, median follow-up was 33.7 months (range, 6.6–84.0 months). Three patients developed cyst progression surrounding the tumor, 2 of whom ultimately required surgical resection at 2.4 and 11.2 months, and the third of whom was unfortunately lost to follow-up shortly after experiencing cyst enlargement. The 3-year actuarial estimate of local control was 86% (Fig. 4).

Toxicity. Acute sequelae were rare and typically mild. Grade 2 vomiting was noticed in 1 patient after treatment of a C2 lesion; he was managed conservatively, with

Table 3. Dose of radiation to 10-mm^3 to 2000-mm^3 volume of the spinal cord

Parameter	No. of lesions	D_{max}	D10*	D100*	D250*	D500*	D1000*	D2000 *
No. of sessions								
1†	17	22.7 (17.8–30.9)	20.0 (17.4–28.1)	15.9 (13.6–25.1)	12.7 (9.5–23.8)	9.5 (5.3–22.5)	5.9 (1.6–20.1)	2.2 (0.6–16.0)
2	3	22.0 (21.3–26.6)	20.2 (18.2–23.6)	19.6 (10.7–20.3)	17.1 (5.8–17.1)	12.8 (2.9–15.0)	7.3 (1.1–11.5)	2.9 (0.3–5.7)
3	7	21.9 (19.7–25.4)	19.3 (17.9–21.4)	17.3 (14.6–19.2)	15.5 (11.4–18.7)	12.9 (7.8–17.9)	8.8 (3.9–17.0)	5.1 (1.2–15.1)
Patient with toxicity (1 session)			17.4	14.0	11.2	8.6	3.6	1.0

* Dose to 10, 100, 250, 500, 1000, and 2000 mm^3 of the spinal cord. Values shown in gray as median (range).
† Including the patient with Grade 2 spinal cord neurotoxicity.

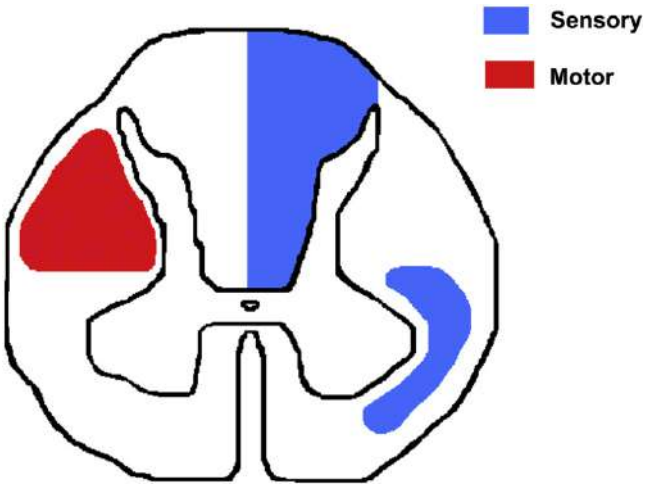

Fig. 3. Location of spinal stereotactic radiosurgery targets in relation to the spinal cord neuronal tract potentially at risk of injury. For simplification, the lateral corticospinal tract (located in the posterolateral cord) constituted the motor tract, whereas the spinothalamic tracts, located in the anterior cord, and the dorsal columns, in the posterior cord, were designated as the sensory tracts. With this classification, the sensory tracts were most at risk in 11 lesions, motor tracts in 11, and both motor and sensory tracts were equally at risk for 5 lesions.

complete resolution of symptoms. One Grade 2 toxicity occurred (1 of 18 patients [6%] or 1 of 25 treatments [4%]), for a 3-year rate of Grade ≥2 toxicity of 4% (Fig. 5). One patient with a history of VHL and multiple prior treatments (microsurgical resection of a T8–9 spine hemangioblastoma and SRS for a T2 hemangioblastoma 48 and 44 months earlier, respectively) developed a Grade 2 left-sided foot drop with associated decreased sensation in the left second and third toes 5 months after treatment with 20 Gy in a single fraction to a T10 hemangioblastoma (tumor volume of 157 mm^3 with a maximum cord dose of 17.8 Gy and a V10 of 340 mm^3). Of note, this patient's cord D_{max} was the lowest among all single-fraction treatments in this series. Follow-up MRI of the spinal cord revealed diffuse myelomalacia of the thoracic cord with interval increase in high T2 signal without evidence of necrosis (contrast enhancement). On examination, left leg spasticity was noted. At last follow-up, plantar flexion was assessed as $4^+/5$ strength by the Medical Research Council Scale, and the patient reported no significant limitation of his mobility. No other motor sequelae were observed in other patients.

Two patients described new Grade 1 sensory deficits that developed after treatment. A patient with VHL treated with 18 Gy in a single fraction to an anterior/midline 74-mm^3 lesion at T7 developed a Grade 1 sensory neuropathy involving the bilateral toes approximately 3 years after treatment; no changes to explain her symptoms were observed by MRI. A second patient with pre-existing lower extremity numbness and weakness was treated with 20 Gy in 2 fractions to a 221-mm^3 left lateral/posterior T11 sporadic hemangioblastoma. He gradually developed subjective loss of coordination in both legs approximately 18 months after treatment. On examination, gait was steady, with 5/5 strength in the lower extremities. No new MRI findings were identified to explain his symptoms either. Given his history of prior open spine surgery and long interval from treatment to onset of symptoms, a causative link between the SRS course and symptoms was unclear.

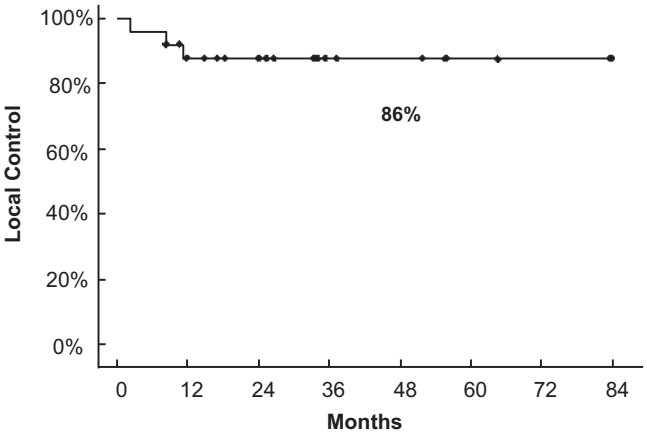

Fig. 4. Kaplan-Meier estimate of local control.

DISCUSSION

In this retrospective review of patients treated with radiosurgery for spinal cord hemangioblastomas, we provide further evidence for a partial-volume effect for the human spinal cord; namely, the delivery of high doses of radiation to a small volume of spinal cord can be performed safely. To our knowledge, this series represents the highest reported maximum radiosurgical doses to the human spinal cord yet reported; those treated in a single fraction received a median spinal cord D_{max} of 22.7 Gy (range, 17.8–30.9 Gy), albeit to a small volume (median tumor volume of 97 mm^3 [range, 58–2494 mm^3]).

Several recent studies reporting outcomes for spinal SRS have delineated dose constraints for the spinal cord, with significant variation among the major spinal SRS groups (Table 4). Chang *et al.* (1) report the results of a prospective

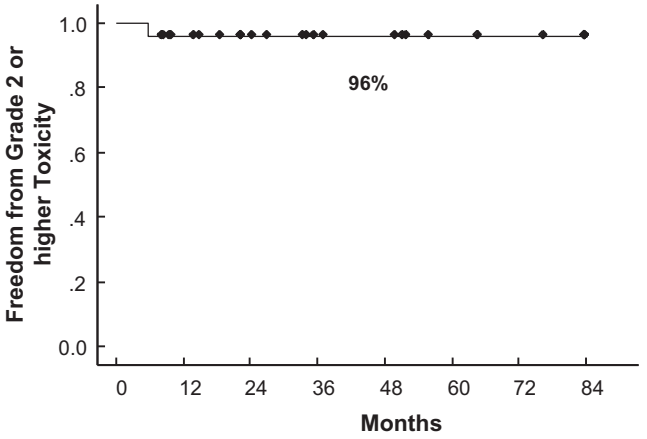

Fig. 5. Kaplan-Meier estimate of freedom from Grade ≥2 neurologic sequelae.

Phase I/II trial evaluating 74 spinal lesions treated with SRS. No cord toxicity was observed when a spinal cord D_{max} was restricted to <10 Gy. Yamada *et al.* (7), treating 93 patients with 103 spinal lesions with a spinal cord D_{max} limit of 14 Gy, observed no neurologic sequelae. Ryu *et al.* (9) retrospectively evaluated 230 metastatic tumors to the spine treated with SRS, limiting the volume of spinal cord receiving 10 Gy (V10) to 10% of the cord as contoured 6 mm above and below the target volume, with an average spinal cord volume of 5.9 cm^3 (range, 2.4–14.7 cm^3). The investigators describe 1 case of radiation-induced spinal cord injury 13 months after treatment. These data form the basis for the RTOG 0631 spinal SRS trial (25), which limits the cord V10 to 10% or 350 mm^3, with a D_{max} of 14 Gy. Gibbs *et al.* (4) reported a series of 74 patients with 102 metastatic lesions treated with spinal SRS, citing a D_{max} of 10 Gy and 3 cases of cord injury, 2 of which occurred in patients who had received prior external-beam radiation.

Because of the rare observation of spinal cord toxicity with radiosurgery (0.6% in a series of 1075 patients [8]), scant data exist to develop dosing guidelines for the human spinal cord. In contrast, excellent data from rat models provide some insight into the potential upper limits of partial cord tolerance. Bijl *et al.* (14, 15) describe a series of experiments performed with high-precision single-fraction proton irradiation in a rat model. The investigators established a length effect for high-dose-per-fraction radiation with varying lengths of full-thickness cord treated. They demonstrated a dramatic increase in the ED_{50} (dose at which 50% of the treated animals developed limb paralysis) to single-fraction treatment with decreasing lengths of cord irradiated. For a 20-mm cord length, the ED_{50} was 20.4 Gy, whereas for 4-mm and 2-mm cord lengths, the ED_{50} was 53.7 Gy and 87.8 Gy, respectively. A second set of experiments demonstrated an increase in the partial cord tolerance to high-precision proton irradiation as compared with full-thickness cord irradiation (14). Treatment of the lateral cord with a tight beam penumbra yielded an ED_{50} of 33.4 Gy, as compared with 20.4 Gy ED_{50} for full-thickness cord. When the central cord was treated with relative sparing of the lateral portions, the ED_{50} increased dramatically to 71.9 Gy. Given the diameter of the rat spinal cord, these animal data may not be directly applicable to the human cord. A series of ongoing experiments using a porcine model (26), an animal with similar spinal anatomy to that of a human, may provide additional insight. Although there are potential limitations of applying animal model results to clinical practice, given these highly convincing animal studies it may be reasonable to postulate that length and partial thickness effects may also exist for the human spinal cord.

The present series demonstrates that maximum cord doses far exceeding the current guidelines for SRS may be achieved safely in select patients. The median cord dose of 22.7 Gy in a single fraction is more than twice the frequently cited limit of 10 Gy, and patients were treated to point doses as high as 30.9 Gy without cord toxicity greater than Grade 2. On the basis of the animal data, the high tolerance of the human spinal cord observed in our series may in part be due to the relatively steep gradient, short length, and small partial thickness of cord irradiated.

In the present series, late toxicity included 1 patient with a Grade 2 unilateral foot drop and 2 patients with Grade 1 sensory deficits. In this patient population it is difficult to assign causation of worsening neurologic status to either a radiation-associated or disease-related etiology. Given that there were spinal cord MRI signal changes in the patient with a Grade 2 motor deficit, this case is likely radiation associated (8, 27). Causation is difficult to definitively establish for the 2 patients (11% of evaluable patients) with Grade 1 sensory deficits, given the absence of imaging changes attributable to radiation effect as well as the finding that 26% of patients with hemangioblastomas that are observed without treatment develop a worsening of neurologic status (28). This rate in untreated patients is similar to the 22% actuarial rate at 4 years of Grade 1 or higher neurologic decline in the present series. In comparison, surgical series note mild Grade

Table 4. Spinal radiosurgery series

First author (reference)	Lesions (*n*)	Median follow-up (mo)	Spinal cord constraints	Neurologic toxicity
Chang (1)	74	21.3	$D_{max} \leq 10$ Gy	None
Yamada (7)	103	15	$D_{max} \leq 14$ Gy	None
Ryu (9)	230	6.4	V10 ≤10% of cord contoured 6 mm above and below target	One Grade 4 cord injury 13 mo after SRS
Nelson (5)	33	7	$D_{max} \leq 12$ Gy or $D_{max} \leq 83.3$ Gy_3-BED_{prior}	None
Gibbs (4)	102	9 (mean)	$D_{max} \leq 10$ Gy	3 cases of Grade 4 spinal myelopathy
Gagnon (2)	274	12	Not available	None
Gerszten (3)	500	NA	$D_{max} \leq 9$–10 Gy	None
Present series	27	33.7	Single-fraction median D_{max} 22.7 Gy (range, 17.8-30.9 Gy); Multifraction median $SFBED_3$ D_{max} 14.1Gy_3 (range, 12.3–19.4 Gy_3)	Grade 2 unilateral foot drop (n = 1)

Abbreviations: D_{max} = maximum dose; V10 = volume of cord receiving ≥10 Gy; SRS = stereotactic radiosurgery; BED = biologic effective dose; SFBED = single-fraction biologic effective dose.

1 sensory changes in 50–80% of patients (29). Given that it is not possible to conclusively differentiate radiosurgical complications from non–treatment-related causes, we have been descriptive of each neurologic decline, even for minor Grade 1 toxicity not affecting function.

The present series has a 4% actuarial estimate of potential Grade 2 toxicity. These risks must be considered in the context of potential surgical morbidity for each patient when selecting a treatment modality. Although surgical case series are relatively small, as reviewed recently (29), up to 18% of patients have a worse clinical grade after microsurgical resection. The largest reported surgical series ($n = 44$) from the National Institutes of Health reported 18% immediate and 9% long-term Grade ≥ 2 neurologic toxicity. A recent series noted that 17% of patients had worsened neurologic status in 34 surgically treated spinal hemangioblastomas (30). The potential toxicity in the present radiosurgical series compares favorably to that in the published surgical series.

An analysis of the tumor cross-sectional location for each case showed that lesions were distributed both centrally and laterally, suggesting that the high radiation tolerance of the central cord white matter found in animal models is not a primary consideration. As highlighted by Ryu *et al*. (9), a majority of the spinal radiosurgical data are for spinal metastases, which most commonly affect the vertebral body (31, 32) and less commonly the posterior elements. As such, studies reporting a lack of toxicity with spinal SRS for metastatic disease may mainly represent the tolerance of the anterior cord, primarily composed of the sensory tracts, to which an injury may be less clinically apparent compared with overt motor weakness or paralysis. This observation is assuming that the mechanism of spinal cord injury is via localized demyelination of the affected tract. However, the potential exists that local injury to the vascular supply of the cord can affect neural tracts distant from the site of irradiation. For example, should irradiation to the anterior cord, distant from the posterior motor tracts, compromise the cord perfusion from the anterior spinal artery, paralysis due to ischemia of the lateral corticospinal tract may ensue, as is seen in occlusive anterior spinal artery syndrome (33). The radiation doses delivered in this series are similar to those causing endothelial injury and intimal proliferation leading to obliteration of vascular malformations, but no severe vascular injury was seen. This serves to highlight the complex dosimetric and anatomic variables potentially involved in evaluating the partial-volume tolerance of the spinal cord to the dosimetry encountered with radiosurgery.

The applicability of the data in this series to other clinical situations, such as the more commonly treated vertebral body metastases, is somewhat limited. No patients in our series received systemic chemotherapy or targeted cancer therapies, agents that could potentially increase the susceptibility of the cord to radiation-induced injury. Additionally, the volume of cord treated with metastatic lesions often dramatically exceeds the volumes treated in this series, given our rather modest median tumor volume of 0.16 cm^3. Potential toxicities noted in this series were relatively mild and difficult to discern from complications arising from the natural history of VHL. Additionally, although no clinical data have suggested that VHL patients have an enhanced or diminished sensitivity to radiation, it is possible that this rather unique population may not be entirely representative of the population at large. Nonetheless, the present series suggests that small volumes of the human spinal cord may be treated with SRS to doses higher than the commonly cited dose limits. Further analysis with normal tissue complication probability modeling of these and other spinal radiosurgical patients from our institution is ongoing.

CONCLUSIONS

The partial-volume tolerance of the human spinal cord to the dosimetry encountered in spinal radiosurgery remains unknown. The present series provides further insight that a partial-volume effect exists in humans: a small volume of spinal cord can tolerate doses that are markedly higher than the commonly cited dose constraints. It must be emphasized that the general application of these data to other clinical scenarios should be made with caution. Larger patient numbers and collaborative, prospective collection of spinal cord dose–volume parameters are needed to draw further conclusions about appropriate spinal cord dose constraints for spinal radiosurgery.

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