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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.
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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