

## Original Article

# Image-guided linear accelerator-based spinal radiosurgery for hemangioblastoma

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## Abstract

**Purpose:** To retrospectively review the efficacy and safety of image-guided linear accelerator-based radiosurgery for spinal hemangioblastomas.

**Methods:** Between August 2004 and September 2010, nine patients with 20 hemangioblastomas underwent spinal radiosurgery. Five patients had von Hippel–Lindau disease. Four patients had multiple tumors. Ten tumors were located in the thoracic spine, eight in the cervical spine, and two in the lumbar spine. Tumor volume varied from 0.08 to 14.4 cc (median 0.72 cc). Maximum tumor dimension varied from 2.5 to 24 mm (median 10.5 mm). Radiosurgery was performed with a dedicated 6 MV linear accelerator equipped with a micro-multileaf collimator. Median peripheral tumor dose and prescription isodose were 12 Gy and 90%, respectively. Image guidance was performed by optical tracking of infrared reflectors, fusion of oblique radiographs with dynamically reconstructed digital radiographs, and automatic patient positioning. Follow-up varied from 14 to 86 months (median 51 months).

**Results:** Kaplan–Meier estimated 4-year overall and solid tumor local control rates were 90% and 95%, respectively. One tumor progressed 12 months after treatment and a new cyst developed 10 months after treatment in another tumor. There has been no clinical or imaging evidence for spinal cord injury.

**Conclusions:** Results of this limited experience indicate linear accelerator-based radiosurgery is safe and effective for spinal cord hemangioblastomas. Longer follow-up is necessary to confirm the durability of tumor control, but these initial results imply linear accelerator-based radiosurgery may represent a therapeutic alternative to surgery for selected patients with spinal hemangioblastomas.

**Key Words:** Hemangioblastoma, image-guided radiosurgery, spine

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## INTRODUCTION

Hemangioblastomas are rare, benign vascular tumors

of the central nervous system and account for approximately 3% of primary spinal cord neoplasms.<sup>[9]</sup> The tumor may manifest as a solitary, sporadic lesion

or in a multifocal pattern associated with the autosomal dominant genetic disorder von Hippel–Lindau disease.<sup>[10]</sup> Spinal cord hemangioblastomas may present as an asymptomatic finding on imaging studies or produce pain, sensory disturbance, and/or weakness. Complete microsurgical removal is the standard of care for spinal cord hemangioblastomas.<sup>[4,21]</sup> Resection, however, may exacerbate underlying neurological symptoms or cause new deficits.<sup>[12]</sup> Furthermore, some patients, particularly those with co-morbid illnesses or multiple tumors, may be unsuitable for a surgical approach. Several investigators have reported encouraging local control rates and absence of serious morbidity following gamma knife or linear accelerator-based stereotactic radiosurgery (SRS) for intracranial hemangioblastomas.<sup>[8,11,17,25]</sup> By extension, a similar radiotherapeutic strategy should be equally efficacious for spinal cord hemangioblastomas. Stanford University investigators recently reported favorable results following CyberKnife SRS treatment of spinal cord hemangioblastomas.<sup>[13]</sup> We report the results of image-guided SRS for the treatment of spinal cord hemangioblastomas using a dedicated linear accelerator.

## MATERIALS AND METHODS

Between August, 2004 and September, 2010, nine patients with 20 hemangioblastomas underwent spinal radiosurgery. Table 1 provides a summary of the clinical and anatomic characteristics of the tumors. Patients were eligible for spinal radiosurgery if they refused surgical intervention, had residual or recurrent disease after surgery, or were judged inoperable due to co-morbid conditions after evaluation by a neurosurgeon. There were seven females and two males. Patient age ranged from 26 to 71 years (median 51 years). Ten tumors were located in the thoracic spine, eight in the cervical spine, and two in the lumbar spine. Two lesions were exclusively intramedullary and one of these had an associated cyst. The remaining lesions were solid and intradural/extramedullary. Four patients presented with sporadic isolated tumors. Two of these patients underwent radiosurgery for progressive tumor growth 12–24 months after prior subtotal tumor removal. One of these patients had received 30 Gy conventional radiotherapy after initial subtotal removal. Tumor in these two patients was associated with pain and hypesthesia. One patient with a sporadic isolated tumor had spinal magnetic resonance imaging (MRI) and angiography consistent with hemangioblastoma and was treated due to progressive growth over 24 months associated with pain. The final patient with sporadic hemangioblastoma was treated for a non-progressive lesion causing pain. Five patients presented with spinal cord lesions in association with von Hippel–Lindau disease. None of these patients had histopathologic confirmation of spinal hemangioblastoma. All of these patients, however, had undergone at least

one prior neurosurgical procedure for histopathologically confirmed intracranial hemangioblastoma and had new spinal cord lesions detected on routine surveillance imaging. One patient with von Hippel–Lindau disease presented with an isolated spinal tumor causing arm numbness and underwent radiosurgery after documented tumor growth. Four patients with von Hippel–Lindau disease presented with multiple spinal lesions (total 15). Three of these lesions were asymptomatic and were treated due to documented progressive enlargement. Two of these lesions were symptomatic (pain or sensory disturbance) and were treated without documented tumor growth. The remaining 10 lesions in this group were treated electively. Eight occurred in patients scheduled to undergo spinal radiosurgery for at least one other progressive or symptomatic lesion.

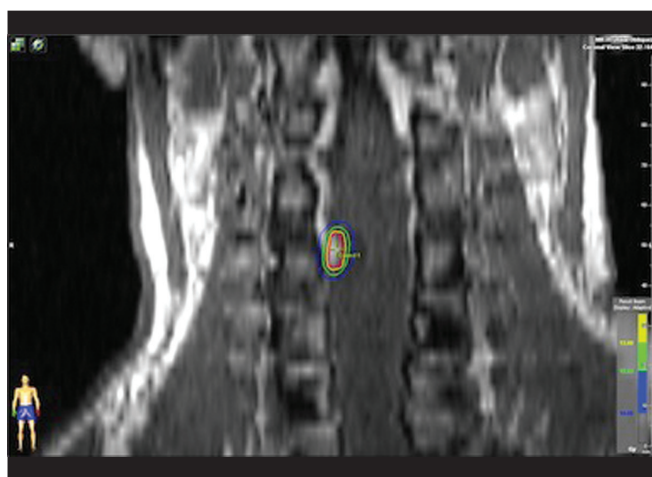
The technique of image-guided linear accelerator-based spinal radiosurgery has been described elsewhere.<sup>[1]</sup> Patient immobilization was achieved with a vacuum-set custom-fitted cushion (BodyFix, Medical Intelligence, Schwabmünchen, Germany) for lesions of the thoracic or lumbar spine. Additional immobilization with a U-Frame face mask (CIVCO, Orange City, IA, USA) was utilized for cervical lesions. Patient positioning on the accelerator couch was performed using Novalis Body (Novalis®, BrainLAB AG, Feldkirchen, Germany). Initial patient positioning was achieved through an infrared localization system consisting of a pair of treatment room cameras that generate and detect infrared radiation reflected from markers placed on the patient's skin both at the time of planning computed tomography (CT) and patient treatment. The treatment couch was driven to a position near the isocenter of the linear accelerator, based on information from the infrared system. Final patient positioning was achieved using radiographic image guidance based upon internal vertebral anatomy. The radiographic system consisted of a pair of ceiling-mounted amorphous silicon detectors and two floor-mounted kV X-ray sources. A pair of oblique kV radiographs was obtained following infrared positioning to determine the current position of the spine relative to the planned position. The kV radiographs were fused with dynamically generated digitally reconstructed radiographs generated from the treatment planning CT scan to establish final couch motion to correct patient position to match the planned position. In order to monitor patient intrafraction motion, the radiographic image guidance process was repeated prior to each treatment arc or field. The precision of this approach has been documented.<sup>[1]</sup> Out-patient spinal radiosurgery was delivered in a single fraction using a dedicated linear accelerator (Clinac® 600SR, Varian Associates, Palo Alto, CA, USA). The accelerator is equipped with a micro-multileaf collimator (m<sub>3</sub>™ BrainLAB, AG, Feldkirchen, Germany).

Treatment planning was carried out with a commercially

available system (iPlan 3.0 and BrainSCAN® 5.3×, BrainLAB AG, Feldkirchen, Germany). All patients underwent supine CT and MRI which were fused by the mutual information technique and verified visually. Maximum tumor dimension was calculated using the formula  $a \pm b \pm c/3$ , where a, b, and c represent the largest anterior-posterior, medial-lateral, and superior-inferior dimensions displayed on contrast-enhanced axial, sagittal, and coronal MRI scans. Maximum tumor dimension varied from 2.5 to 24 mm (median 10.5 mm). The gross tumor volume (GTV) was contoured slice by slice on T<sub>1</sub>-weighted contrast-enhanced axial, coronal, and sagittal treatment planning MRI scans. Tumor volume varied from 0.08 to 14.4 cc (median 0.72 cc). All tumors demonstrated homogeneous contrast enhancement and one had a cystic component. The GTV did not include the cystic component in this lesion. A margin of normal tissue (range 1–3 mm, median 2 mm) was added to the GTV to create the clinical target volume (CTV). The prescription isodose encompassed the CTV. Nineteen targets received 12 Gy and one received 14 Gy. Dose was consistently prescribed at the 90% isodose line. In all cases,  $\geq 95\%$  of the target volume was included within the prescription isodose line [Figure 1].

Spinal cord was considered a critical object at risk (OAR) and was contoured slice by slice along the pial surface of the cord as displayed on the axial T<sub>2</sub>-weighted MRI. The length of spinal cord contoured in this series varied from 2 to 6 mm (median 6 mm) above and below the GTV in accordance with the recommendations of Ryu *et al.*<sup>[19]</sup> In all cases, the spinal cord D<sub>Max</sub> was  $\leq 12$  Gy and the V<sub>10Gy</sub> (volume of the cord receiving 10 Gy) was 10%.

Forward treatment planning was used for 17 targets and inverse planning methods for 3 lesions. Forward planned targets were irradiated with 2–5 (median 3) dynamic arcs



**Figure 1: Representative spinal radiosurgery treatment plan. A 0.15-cc lateral C4 hemangioblastoma (red contour) received 12 Gy prescribed at the 90% isodose line (green contour). Also displayed are the 13 Gy (yellow) and 10 Gy (blue) isodose lines**

and inverse planned targets with 5 modulated beams. All targets were treated with a single isocenter. Patients with multiple tumors were treated in a single session. The treatment process typically required 20 minutes per target.

Follow-up ranged from 14 to 86 months (median 51 months). Sixteen lesions were followed for more than 36 months. Follow-up included contrast-enhanced MRI every 6 months for 24 months and yearly thereafter plus clinical examination or telephonic interview. Computer-generated tumor volumes were not available on follow-up MRI examinations. Tumor progression was defined as a  $>25\%$  increase in maximum tumor dimension persisting on two or more consecutive studies. Expansion of a known cyst or development of a new cyst was included in the definition of progression for the purpose of analyzing overall local control. Tumor response was defined as a  $>25\%$  decrease in maximum tumor dimension persisting on two or more consecutive studies. Stable tumor was defined as no change in size or change  $<25\%$ . Control rates were calculated by the Kaplan–Meier method. Adverse treatment effects were graded according to the common terminology criteria for adverse events (CTCAE v 3.0).<sup>[22]</sup>

## RESULTS

All patients were alive at the time of this report. Kaplan–Meier estimated overall local control and solid tumor control rates at 48 months were 90% and 95%, respectively [Figures 2 and 3]. Imaging progression occurred in two patients with symptomatic, sporadic hemangioblastomas [Table 1]. A new cyst was documented 10 months after treatment in the patient with non-progressive sporadic tumor associated with pain. The solid component of tumor in this patient was unchanged in size compared to pretreatment measurement. Pain worsened with appearance of the cyst and the patient underwent microsurgical removal of the tumor/cyst. This patient was followed for potential radiosurgery morbidity. Solid tumor in the patient who had received prior external beam radiotherapy after subtotal removal progressed 12 months after salvage radiosurgery. This patient also underwent neurosurgical intervention due to worsening of underlying sensory disturbance and remains under follow-up for potential morbidity. One tumor in this series (5%) responded in size and 17 other tumors (85%) remained stable. Among the stable tumors, none enlarged by 25% or less. Of the seven tumors presenting with symptoms, improvement was noted in only one instance.

Patients tolerated immobilization, automatic couch adjustments, and delivery of spinal radiosurgery without incident. No patient developed acute or delayed skin, tracheal, esophageal, or gastrointestinal morbidity. No patient experienced exacerbation of preexisting

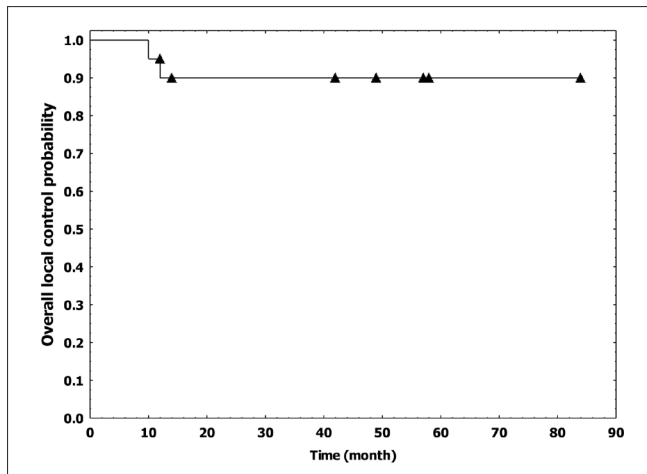


Figure 2: Kaplan–Meier estimate of overall local control

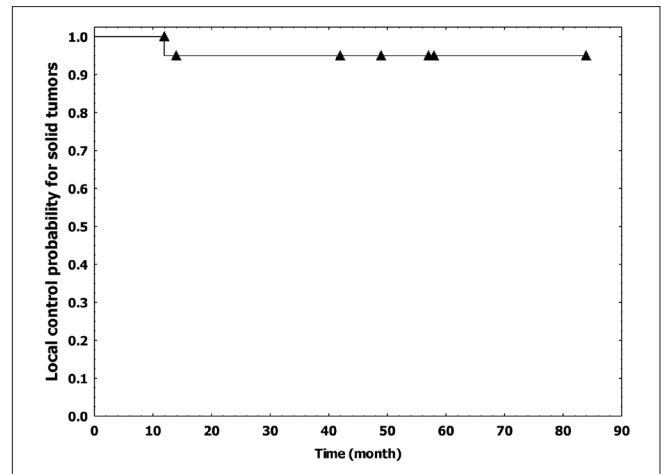


Figure 3: Kaplan–Meier estimate of solid tumor control

Table 1: Summary of spinal hemangioblastoma patients

Pt #	Gender	Age	VHL	Tumor #	Site	MTD (mm)	Volume (cc)	Growth pre-SRS	Symptoms	Follow-up (months)	Outcome
1	M	41	±	1	C1	7.6	0.31	N	-	86	Stable tumor
				2	C1	10	0.54	N	-		Stable tumor
				3	C4	6.6	0.17	N	-		Stable tumor
				4	T1	13.3	1.1	N	-		Stable tumor
				5	T6	9	0.92	N	-		Stable tumor
				6	T12	5.2	0.33	N	Sensory		Stable tumor, no change in symptom
2	F	71	-	7	T9	12.4	0.77	Y	Pain	60	Tumor response, decreased pain
3	F	53	-	8	C3	9.9	0.53	Y	Pain	59	Stable tumor, no change in pain
4	F	55	-	9	T9	11.3	0.67	Y*	Sensory	58	Tumor growth 12 months, worse symptom
5	F	28	±	10	C1	12.1	1.1	Y	-	51	Stable tumor
				11	T5	11	0.6	Y	-		Stable tumor
6	M	52	±	12	C5	8.1	0.5	Y	-	44	Stable tumor
				13	T7	17.1	2.05	N	-		Stable tumor
				14	T10	10.9	0.78	N	-		Stable tumor
				15	L1	24	14.4	N	Pain		Stable tumor, no change in pain
				16	L5	22	8.3	N	-		Stable tumor
7	F	50	±	17	C2	4	0.11	Y	Sensory	16	Stable tumor, no change in symptom
8	F	26	-	18	C4	4	0.12	N	Pain	14	New cyst 10 months, stable tumor, pain worse
9	F	43	±	19	T6	2.5	0.06	N	-	14	Stable tumor
				20	T8	10.5	1.3	N	-		Stable tumor

\*Prior 30 Gy external beam radiotherapy, MTD: Mean tumor dimension

neurologic symptoms due to treatment without concomitant imaging evidence of progression. There was no imaging evidence for loss of central tumor contrast

enhancement or perilesional edema suggestive of tumor necrosis. No patient manifested clinical or imaging findings compatible with spinal cord injury/myelopathy.

## DISCUSSION

The results of this retrospective review demonstrate that image-guided linear accelerator-based radiosurgery safely controls growth of spinal cord hemangioblastomas. After a median follow-up of 51 months, the overall and solid tumor 4-year actuarial local control rates were 90% and 95%, respectively. The results of our series are similar to those reported elsewhere. Moss *et al.* reported a 5-year actuarial local control rate of 92% in a series of 16 spinal cord hemangioblastomas followed up for a median of 33.5 months after CyberKnife treatment.<sup>[13]</sup> Five-year control rates of 71–95% have been reported following either linear accelerator-based or gamma knife radiosurgery for intracranial hemangioblastomas.<sup>[8,11,17,25]</sup>

Statistically significant predictors of local progression could not be identified due to the rareness of relapse. The only solid tumor progression in this series occurred in a sporadic lesion treated after unsuccessful external beam radiotherapy. It is unclear if spinal hemangioblastomas that recur after prior exposure to ionizing irradiation are resistant to subsequent radiosurgery. Patrice and associates reported more frequent tumor relapse following radiosurgery for intracranial hemangioblastomas previously exposed to conventionally fractionated radiotherapy compared to unexposed tumors.<sup>[17]</sup>

A symptomatic cyst developed in 1 of 19 solid hemangioblastomas in this series. Following radiosurgery for intracranial hemangioblastoma, new cyst formation in the setting of controlled solid tumor has been reported by several authors.<sup>[11,15,16]</sup> Although frequently included as a component of relapse after radiosurgery, new cyst formation is a recognized feature of the natural history of solid hemangioblastomas. In a series of 160 von Hippel–Lindau patients with central nervous system hemangioblastomas followed with sequential MRI, investigators at the National Institutes of Health reported new cyst development in 10%.<sup>[24]</sup> Although new cyst development in our series occurred 10 months after treatment, the onset of new cysts in the literature varies from 3 to 80 months after cranial radiosurgery. Asthagiri and associates reported a 6-year mean latency to new cyst formation after cranial radiosurgery.<sup>[3]</sup>

Both tumor response and clinical improvement were less frequent in our series than reported elsewhere. On follow-up MRI, one lesion responded according to the definition used in our study. Moss *et al.* reported tumor regression in 6 of 16 spinal tumors, but did not define the criteria for imaging response.<sup>[13]</sup> In a series of 74 intracranial hemangioblastomas undergoing gamma knife radiosurgery at the University of Pittsburgh, >50% reduction in the volume of enhancing solid tumor was reported in 38 tumors by Kano *et al.*<sup>[8]</sup> In a series of 67 tumors from the Yokohama City University

gamma knife center, Matsunaga and colleagues reported complete disappearance of 10 intracranial tumors and partial response (>25% reduction in maximum tumor dimension) in 40 other tumors.<sup>[11]</sup> Symptoms improved in one of seven symptomatic tumors in our series. Following cranial radiosurgery, by contrast, symptomatic improvement was reported in 55% by Chang *et al.* and in 64% by Asthagiri *et al.* Neither of those series, however, employed objective scales of symptom severity.<sup>[3,5]</sup>

The infrequent imaging and clinical response rates noted in our series may be a result of the low homogeneous dose used for spinal radiosurgery. The median prescribed dose and tumor maximum dose in our series were 12 Gy and 13.3 Gy, respectively. In the cranial gamma knife experience, Kano *et al.* delivered median prescribed and tumor maximum doses of 16 Gy and 32 Gy, respectively.<sup>[8]</sup> Matsunaga and associates administered a median prescribed dose of 14 Gy and a median tumor maximum of 22 Gy.<sup>[11]</sup> The symptomatic improvement noted by Asthagiri *et al.* followed gamma knife SRS with mean prescribed/tumor maximum doses of 18.9 Gy/34.6 Gy or linear accelerator-based mean prescribed/maximum doses of 20 Gy/25.1 Gy.<sup>[3]</sup> Several authors report a statistically significant effect of dose on tumor response rate following intracranial radiosurgery for hemangioblastomas.<sup>[5,8]</sup> Administration of a prescribed radiosurgery dose in excess of 12 Gy, however, was not possible given the intradural/extramedullary location of tumor and the partial volume spinal cord dose constraints applied in our series. The aim of spinal radiosurgery treatment planning in our institution, furthermore, was homogeneous dose deposition since dose inhomogeneity has been shown to correlate significantly with the incidence of morbidity following cranial radiosurgery.<sup>[14]</sup> The homogeneous dose deposition that accompanies prescription at the 90% isodose lines invariably results in a relatively small incremental difference between tumor marginal and maximum doses.

Linear accelerator-based spinal radiosurgery for hemangioblastomas was free of acute and long-term morbidity. Investigators at Stanford University reported a 3-year actuarial rate of Grade  $\geq 2$  myelopathy of 4% despite delivery of doses considerably higher than used in our series.<sup>[6]</sup> The low incidence of spinal cord injury hinders elucidation of clinical or treatment parameters that might preclude safe delivery of radiosurgery for hemangioblastoma. In the literature, predictors of myelopathy due to radiosurgery remain uncertain. Ryu *et al.*, utilizing image-guided radiosurgery techniques identical to our approach, reported 177 patients with spinal metastases.<sup>[19]</sup> In a subgroup of 86 patients with more than 1 year follow-up, the average dose to 10% of the contoured spinal cord OAR was 8.6 Gy and the average spinal cord maximum dose was 12.2 Gy. The authors reported a single case of radiation-induced

myelopathy in this subgroup. In this case, the dose to 10% of the cord volume was 9.6 Gy and the cord maximum dose was 14.6 Gy. The authors concluded that the partial volume tolerance of the spinal cord to single-fraction radiosurgery was 10 Gy to  $\leq 10\%$  cord volume, a guideline adhered to in our series. Saghal *et al.* performed a dosimetric comparison of 5 patients with myelopathy following radiosurgery and 19 control patients without cord injury.<sup>[20]</sup> The patients with myelopathy were drawn from the Stanford University and University of Pittsburgh experiences with CyberKnife treatment for benign and metastatic tumors, as well as the case of Ryu *et al.* cited above. Three patients with myelopathy received single-fraction treatment and the remainder received radiosurgery in 2–3 fractions. The control group was extracted from the authors' CyberKnife experience at the University of California, San Francisco. Statistically significant differences were found between the mean and median maximum cord doses of the myelopathy patients compared to those patients without this complication. The authors suggested limiting the single-fraction cord maximum to 10 Gy. Finally, Gibbs *et al.* analyzed the combined Stanford University/University of Pittsburgh experience with single-fraction or hypofractionated spinal radiosurgery for 1075 patients with benign and metastatic tumors.<sup>[7]</sup> Single-fraction treatment was used for 915 patients with metastatic disease. Six patients developed radiation-induced myelopathy at a median of 6 months (range 2–10 months) post-treatment. Three of these cases occurred after single-fraction treatment. The authors found no patient/treatment factors significantly predictive of cord injury, although analysis of potential risk factors was hampered by the low incidence of injury. The authors advocated limiting the volume of spinal cord receiving  $\geq 8$  Gy to  $< 1$  cc. The median follow-up duration of our series should be sufficient to detect radiation-induced myelopathy according to the findings of Gibbs *et al.* The absence of spinal cord injury lends support to the definition of partial volume cord tolerance used during treatment planning in our series.

There are several shortcomings of this study. Hemangioblastomas are benign neoplasms and encouraging short-term local control rates do not necessarily ensure durable remission. In a series of 44 hemangioblastomas followed for a median of 8.5 years after cranial radiosurgery, Asthagiri and associates reported 2- and 10-year local control rates of 91% and 51%, respectively.<sup>[3]</sup> Among 14 progressing tumors in that series, the median time to progression was 5.9 years and the authors cautioned that early volumetric response was not always predictive of final outcome. It is likely that patients with spinal hemangioblastomas must be followed for an equally long period before concluding that image-guided radiosurgery is as efficacious as microsurgery. While the median follow-up period in our

series is 51 months, only six lesions have been followed for a length of time in excess of the median progression interval documented by Asthagiri *et al.* Furthermore, hemangioblastomas are notorious for a saltatory growth pattern characterized by periods of quiescence alternating with periods of active growth. Ammerman *et al.* reported the natural history of 19 von Hippel–Lindau patients with 143 central nervous system hemangioblastomas followed for at least 10 years.<sup>[2]</sup> Overall, 138 tumors demonstrated imaging progression over the duration of the study and growth was saltatory in 134 instances. Progressing tumors demonstrated a mean of 1.85 growth arrest phases prior to symptom development. The average duration of the growth arrest phase was  $25 \pm 19$  months. In our series, 13 tumors underwent radiosurgery without documented growth prior to treatment. All of these tumors remain stable, but four of these have been followed for less than 3 years after treatment. It may be inappropriate to conclude that failure of these tumors to progress after radiosurgery is a beneficial effect of irradiation rather than merely a feature of the natural history of hemangioblastoma in a quiescent phase. Lastly, 13 asymptomatic lesions underwent radiosurgery in our series. According to Ammerman *et al.*, imaging progression alone is not a sufficient criterion for elective treatment of hemangioblastoma.<sup>[2]</sup> In their longitudinal follow-up series, among the 138 progressing tumors, only 58 developed symptoms requiring therapeutic intervention. Upon multivariate analysis, the authors found total tumor volume (solid  $\pm$  cyst components) to be the only significant predictor of eventual symptom development requiring treatment. Among tumors  $< 8$  mm<sup>3</sup>, 8–51 mm<sup>3</sup>, and  $> 51$  mm<sup>3</sup>, symptoms developed within 5 years in 10%, 37%, and 90%, respectively. In our series, four of the asymptomatic tumors receiving spinal SRS were  $< 51$  mm<sup>3</sup>.

The decision to irradiate asymptomatic spinal hemangioblastoma remains controversial. Several authors have reported that neurological function following microsurgery is significantly correlated with preoperative performance status in patients with spinal hemangioblastoma.<sup>[18,23]</sup> Given the modest symptom resolution rates following spinal radiosurgery and the lack of radiation myelopathy, early intervention may be rational for asymptomatic, non-progressing hemangioblastomas, particularly in those patients already undergoing radiosurgery for other progressive and/or symptomatic lesions.

## CONCLUSION

The results of this limited experience indicate that linear accelerator-based radiosurgery is safe and effective for patients with spinal cord hemangioblastomas. Longer follow-up is required to document the durability of

local control. Microsurgical tumor resection remains the treatment of choice for spinal cord hemangioblastomas. Our initial results imply that linear accelerator-based radiosurgery may represent a therapeutic alternative to surgery for selected patients with spinal hemangioblastomas.

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