Image-guided linear accelerator-based spinal radiosurgery for hemangioblastoma

Michael T. Selch, Steve Tenn, Nzhde Agazaryan, Steve P. Lee, Alessandra Gorgulho, Antonio A. F. De Salles

Departments of Radiation Oncology and Neurosurgery, David Geffen School of Medicine at UCLA, Los Angeles, California, USA

E-mail: *Michael T. Selch - mselch@mednet.ucla.edu; Steve Tenn - stenn@mednet.ucla.edu; Nzhde Agazaryan - nagazaryan@mednet.ucla.edu; Steve P. Lee - splee@mednet.ucla.edu; Alessandra Gorgulho - agorgulho@mednet.ucla.edu; Antonio A. F. De Salles - adesalles@mednet.ucla.edu

*Corresponding author

Received: 30 January 12 Accepted: 19 June 12 Published: 14 July 12

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

INTRODUCTION

Hemangioblastomas are rare, benign vascular tumors of the central nervous system and account for approximately 3% of primary spinal cord neoplasms. The tumor may manifest as a solitary, sporadic lesion...
Spinal cord hemangioblastomas may present as an asymptomatic finding on imaging studies or produce new deficits. 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. 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. 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/extradural. 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. Patient immobilization was achieved with a vacuum-set custom-fitted cushion (BodyFix, Medical Intelligence, Schwabmunchen, 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.

Out-patient spinal radiosurgery was delivered in a single fraction using a dedicated linear accelerator (Clinac® 600SR, Varian Associates, Palo Alto, GA, USA). The accelerator is equipped with a micro-multileaf collimator (m™ 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 \( T_1 \)-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 \( T_2 \)-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.\(^{[19]} \). In all cases, the spinal cord \( D_{\text{max}} \) was \( \leq 12 \) Gy and the \( V_{10\text{Gy}} \) (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 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).\(^{[22]} \)

**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...
Table 1: Summary of spinal hemangioblastoma patients

| Pt # | Gender | Age (y) | 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       | -    | 86       | Stable tumor |              |          |                   |         |
| 3   | C4     | 6.6     | 0.17| N       | -    | 86       | Stable tumor |              |          |                   |         |
| 4   | T1     | 13.3    | 1.1 | N       | -    | 86       | Stable tumor |              |          |                   |         |
| 5   | T6     | 9       | 0.92| N       | -    | 86       | Stable tumor |              |          |                   |         |
| 6   | T12    | 5.2     | 0.33| N       | Sensory | 86       | 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 | 12  | T12     |      | 51       | Stable tumor |              |          |                   |         |
| 6   | M      | 52      | +   | 12      | C5   | 8.1      | 0.5 Y       | -            | 44       | Stable tumor      |         |
| 13  | T7     | 17.1    | 2.05| N       | -    | 44       | Stable tumor |              |          |                   |         |
| 14  | T10    | 10.9    | 0.78| N       | -    | 44       | Stable tumor |              |          |                   |         |
| 15  | L1     | 24      | 14.4| N       | Pain | 44       | Stable tumor, no change in pain | |          |                   |         |
| 16  | L5     | 22      | 8.3 | N       | -    | 44       | Stable tumor |              |          |                   |         |
| 7   | F      | 50 ± 19 | 17  | C2      |      | 4.11 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 ± 4  | 19  | T6      |      | 2.5      | 0.06 N      | -            | 14       | Stable tumor      |         |
| 20  | T8     | 10.5    | 1.3 | N       | -    | 14       | 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. Five-year control rates of 71–95% have been reported following either linear accelerator-based or gamma knife radiosurgery for intracranial hemangioblastomas. 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.

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. 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%. 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.

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. 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. 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. 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.

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. Matsunaga and associates administered a median prescribed dose of 14 Gy and a median tumor maximum of 22 Gy. The symptomatic improvement noted by Asthagiri et al. followed gamma knife SRS with mean prescribed/tumor maximum doses of 18.9 Gy/54.6 Gy or linear accelerator-based mean prescribed/maximum doses of 20 Gy/25.1 Gy. Several authors report a statistically significant effect of dose on tumor response rate following intracranial radiosurgery for hemangioblastomas. Administration of a prescribed radiosurgery dose in excess of 12 Gy, however, was not possible given the intradural/extradural 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. The homogeneous dose deposition that accompanies prescription at the 90% isodose line 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 ≥2 myelopathy of 4% despite delivery of doses considerably higher than used in our series. 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. 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 ≤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.[20] 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 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.[7] 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 ≥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.[10] 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.[1] 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 ± 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.[8] 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 ± cyst components) to be the only significant predictor of eventual symptom development requiring treatment. Among tumors <8 mm³, 8–51 mm³, and >51 mm³, symptoms developed within 5 years in 10%, 37%, and 90%, respectively. In our series, four of the asymptomatic tumors receiving spinal SRS were <51 mm³.

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.[18,23] 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.

REFERENCES

1. Agazaryan N, Tenn SE, Desalles AA, Selch MT. Image-guided radiosurgery for spinal tumors: Methods, accuracy and patient intrafraction motion. Phys Med Biol 2008;53:1715-27.
2. Ammerman JM, Lonser RR, Dambrosia J, Butman JA, Oldfield EH. Long-term natural history of hemangioblastomas in patients with von Hippel-Lindau disease: Implications for treatment. J Neurosurg 2006;105:248-55.
3. Asthagiri AR, Mehta GU, Zach L, Li X, Butman JA, Camphausen KA, et al. Prospective evaluation of radiosurgery for hemangioblastomas in von Hippel-Lindau disease. Neuro Oncol 2009;11:80-6.
4. Bostrom A, Hans Fj, Reinacher PC, Krings T, Bürgel U, Gilsbach JM, et al. Intramedullary hemangioblastomas: Timing of surgery, microsurgical technique and follow-up in 23 patients. Eur Spine J 2008;17:882-6.
5. Chang SD, Meisel JA, Hancock SL, Martin DP, McManus M, Adler JR. Treatment of hemangioblastomas in von Hippel-Lindau disease with linear accelerator-based radiosurgery. Neurosurgery 1998;43:28-34.
6. Daly ME, Choi CY, Gibbs IC, Adler JR, Chang SD, Lieberson RE, et al. Tolerance of the spinal cord to stereotactic radiosurgery: Insights from hemangioblastomas. Int J Radiat Oncol Biol Phys 2011;80:213-20.
7. Gibbs IC, Pacl C, Gersten PC, Adler JR Jr, Burton SA. Delayed radiation-induced myelopathy after spinal radiosurgery. Neurosurgery 2009;64 Suppl 2:A67-72.
8. Kano H, Niranjan A, Mongia S, Kondziolka D, Flickinger JC, Lunsford LD. The role of stereotactic radiosurgery for intracranial hemangioblastomas. Neurosurgery 2008;63:443-50.
9. Lonser RR, Oldfield EH. Spinal cord hemangioblastomas. Neurosurg Clin N Am 2006;17:37-44.
10. Lonser RR, Weil RJ, Wanebo JE, DeVrooom HL, Oldfield EH. Management of spinal cord hemangioblastomas in patients with von Hippel-Lindau disease. J Neurosurg 2003;98:106-16.
11. Matsunaga S, Shuto T, Inomori S, Fujino H, Yamamoto I. Gamma knife radiosurgery for intracranial hemangioblastoma. Acta Neurochir (Wein) 2007;149:1007-13. Discussion 1013.
12. Mehta GU, Asthagiri AR, Bakhtian KD, Auh S, Oldfield EH, Lonser RR. Functional outcome after resection of spinal cord hemangioblastomas associated with von Hippel-Lindau disease. J Neurosurg Spine 2010;12:233-42.
13. Moss JM, Choi CY, Adler JR Jr, Soltys SG, Gibbs IC, Chang SD. Stereotactic radiosurgical treatment of cranial and spinal hemangioblastomas. Neurosurgery 2009;65:79-85.
14. Nedzi LA, Kooy H, Alexander E 3rd, Gelman RS, Loeffler JS. Variables associated with the development of complications from radiosurgery of intracranial tumors. Int J Radiat Oncol Biol Phys 1991;21:591-9.
15. Niemelä M, Lim YJ, Söderman M, Jääskeläinen J, Lindquist C. Gamma knife radiosurgery in 11 hemangioblastomas. J Neurosurg 1996;85:591-6.
16. Pan L, Wang EM, Wang BJ, Zhou LF, Zhang N, Cai PW, et al. Gamma knife radiosurgery for hemangioblastomas. Stereotact Funct Neurosurg 1998;70 Suppl 1:S179-86.
17. Patrice SJ, Sneed PK, Flickinger JC, Shrieve DC, Pollock BE, Alexander E 3rd, et al. Radiosurgery for hemangioblastoma: Results of a mutinstitutional experience. Int J Radiat Oncol Biol Phys 1996;35:493-9.
18. Pavesi G, Feleti A, Berlucchi S, Opocher G, Martella M, Murgia A, et al. Neurosurgical treatment of von Hippel-Lindau-associated hemangioblastomas: Benefits, risks and outcome. J Neurosurg Sci 2008;52:29-36.
19. Ryu S, Jin YJ, Jin R, Rock J, Ajlouni M, Movsas B, et al. Partial volume tolerance of the spinal cord and complications of single dose radiosurgery. Cancer 2007;109:628-36.
20. Saghal A, Ma L, Gibbs IB, Gersten PC, Ryu S, Soltys S, et al. Spinal cord tolerance for stereotactic body radiotherapy. Int J Radiat Oncol Biol Phys 2010;77:548-53.
21. Sandalcioglu IE, Gasser T, Agari S, Lazorissak A, Engelhorn T, Egelhof T, et al. Functional outcome after surgical treatment of intramedullary spinal cord tumors: Experience with 78 patients. Spinal Cord 2005;43:34-41.
22. Trotti A, Colevas AD, Sester A, Rusch VJ, Jaques D, Budach V, et al. CTCAE v3.0: Development of a comprehensive grading system for the adverse effects of cancer treatment. Semin Radiat Oncol 2003;13:176-81.
23. Van Velthoven V, Reinacher PC, Klijsh J, Neumann HF, Gläsker S. Treatment of intramedullary hemangioblastomas, with special attention to von Hippel-Lindau disease. Neurosurgery 2003;53:1306-13; discussion 1313-4.
24. Wanebo JE, Lonser RR, Glenn GM, Oldfield EH. The natural history of hemangioblastomas of the central nervous system in patients with von Hippel-Lindau disease. J Neurosurg 2003;98:82-94.
25. Wang EM, Pan L, Wang BJ, Zhang N, Zhou LF, Dong YF, et al. The long-term results of gamma knife radiosurgery for hemangioblastomas of the brain. J Neurosurg 2005;102 Suppl:5225-9.