# *Integra Foundation Award:* Long-term Natural History of Hemangioblastomas in von Hippel-Lindau Disease: Implications for Treatment

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## INTRODUCTION

Von Hippel-Lindau disease (VHL) (OMIM193300) is an inherited multisystem cancer syndrome with visceral and central nervous system (CNS) manifestations.[9] It is transmitted in an autosomal dominant fashion (chromosome 3p25) with greater than 90% penetrance by age 60 years.[12] Visceral lesions consist of renal cell carcinomas and cysts, pancreatic islet cell tumors and cysts, pheochromocytomas, and papillary cystadenomas of the epididymis and broad ligament.[9] The CNS manifestations of VHL include hemangioblastomas of the retina, brainstem, cerebellum, spinal cord, and nerve roots, as well as endolymphatic sac tumors (ELST).[9]

During the course of their lives, most patients with VHL require treatment of several symptom-producing hemangioblastomas of the cerebellum, brainstem, or spinal cord. However, many tumors never produce symptoms and do not require treatment. Detection at an early stage of the lesions that will produce symptoms and, ultimately, require treatment, would permit earlier excision of hemangioblastomas of the spinal cord, brainstem, or cerebellum, and may identify cerebellar hemangioblastomas for which treatment with radiosurgery can be justified at a stage before treatment is contraindicated because of tumor size or the presence of an associated cyst. Identification of variables predicting tumor behavior over several years requires an extended interval of observation. To define the long-term natural history of VHL and identify predictive tumor features for surgical intervention for CNS hemangioblastomas, we reviewed the serial clinical and magnetic resonance imaging (MRI) findings in all VHL patients followed at the National Institutes of Health (NIH) for longer than 10 years.


0148-703/06/5301-0324

## PATIENTS AND METHODS

### Clinical Data

Clinic charts and MRI scans were reviewed for all patients with VHL disease and a minimum of 10 years of follow-up at the NIH. Patients were seen at approximately 6 to 12 month intervals for clinical and radiographic assessment. Changes in functional status during the study interval were assessed using the McCormick scale (*Table 38.1*).[14]

### Radiographic Data

Craniospinal MRI scanning was used to determine the presence and to quantify the size of each hemangioblastoma. Postcontrast T1, spoiled gradient recall, and T2-weighted sequences were reviewed. Tumor volumes were calculated in cubic millimeters using a modified ellipsoid formula (length $\times$ width $\times$ height $\times$ 0.5).[10] Intracranial peritumoral edema and cysts were measured in a similar manner. Spinal cord edema and cysts were quantified on the basis of the number of involved spinal levels. To avoid confusing blood vessels imaged in cross-section with hemangioblastomas, contrast-enhancing lesions smaller than 3 mm in diameter were excluded.

### Statistical Analysis

Descriptive statistics were obtained using exact methods for categorical factors and general linear models analysis of variance for continuous measures with comparison of the three tumor locations (i.e., cerebellar, brainstem, and spinal cord). Time for tumor observation to intervention (i.e., symptom formation) was evaluated in a Cox proportional hazards model with tumor location, tumor volume at initial examination categorized at three levels with respect to location, and annual growth rate as covariates. Because of differences associated with spatial constraint imposed by the anatomy, categorization of tumor volume was accomplished by tiercels of volume separately for each location. Growth rates were computed over follow-up time and annualized. Separately for each of the three regions, recursive partitioning was used to

**TABLE 38.1. McCormick scale[a]**

| Grade | Definition |
|---|---|
| I | Neurologically normal; mild focal deficit not significantly affecting function of involved limb; mild spasticity or reflex abnormality; normal gait |
| II | Presence of sensorimotor deficit affecting function of involved limb; mild-to-moderate gait difficulty; severe pain or dysesthetic syndrome impairing patient's quality of life; functions and ambulated independently |
| III | More severe neurological deficit; require cane/brace for ambulation or significant bilateral upper extremity impairment; may or may not function independently |
| IV | Severe deficit; requires wheelchair or cane/brace with bilateral upper extremity impairment; usually not independent |

[a]This scale is an objective measure of ambulation, gait, and the ability to perform activities of daily living (from, McCormick P, Torres R, Post K, et al.: Intramedullary ependymoma of the spinal cord. J Neurosurg 72:523–532, 1990 [14]).

find a classification tree for treatment, on the basis of factors available at the initial evaluation or observed during the course of follow-up.[18]

## RESULTS

### Patient Demographics

Nineteen patients with VHL (10 male and 9 female patients) were identified with a minimum of 10 years of follow-up. All patients had one or more hemangioblastomas. Mean age at study entry was 32.0 ± 11.6 years (median, 31.5 years). Mean follow-up time was 12.2 ± 1.6 years (median, 12.5 years). Imaging was obtained on average every 10.3 ± 3.2 months (median, 10.5 mo). Mean interval between clinical evaluations was 10.1 ± 4.1 months (median, 11.0 mo).

### Other VHL-related Lesions

Seventeen patients (89%) had renal cysts. Pancreatic cysts were detected in six (32%) patients. Four patients (21%) had renal cell carcinomas, six (32%) had pheochromocytomas, two (11%) had pancreatic islet cell tumors, and five (26%) had ELSTs.

### CNS Hemangioblastomas

One hundred forty-three hemangioblastomas were identified in the 19 patients (mean, 7.5 ± 6.1 per patient; median, 7.0). Seventeen (89%) of 19 patients had multiple hemangioblastomas (range, 1–25). Five patients (26%) had all of their tumors confined to a single CNS region (i.e., cerebellum, brainstem, or spinal cord), seven patients (37%) had tumors isolated to two regions, and the remaining seven patients (37%) had hemangioblastomas in all three regions. Ninety-two tumors (65%) were followed for a minimum of 2 years, and 57 tumors (40%) were followed for at least 5 years.

Sixty-eight tumors (48%) were located in the cerebellum, 56 (82%) of which were in the cerebellar hemispheres and 12 (18%) of which were in the vermis. Seventeen hemangioblastomas (12%) were located in the brainstem, of which 12 (71%) were precisely at the obex. An additional 58 tumors (40%) were confined to the spinal cord: 29 cervical (50%), 19 thoracic (33%), and 11 lumbar (17%) (*Fig. 38.1*). No supratentorial hemangioblastomas were identified.

### Hemangioblastoma Growth

One hundred thirty-eight (97%) of 143 hemangioblastomas demonstrated radiographic evidence of growth during the study period. One hundred thirty-four tumors (94%) displayed a stuttering growth pattern (*Fig. 38.2*), and 4 (6%) had a progressive growth pattern. Hemangioblastomas had an average of 1.85 growth arrests before becoming symptomatic. Fifty-eight (41%) tumors became symptomatic, requiring intervention. Twenty-six (45%) of the hemangioblastomas that eventually produced symptoms were not among the tumors that were apparent on the initial MRI scan. Tumor growth periods averaged 13 ± 15 months and growth arrests intervals of 25 ± 19 months.

### Functional Outcomes

Patients generally remained at their neurological baseline during the study period. The maximal reduction in functional status during the study period was one point (mean, 0.26 ± 0.46) and was observed in five patients (26%). These reductions in functional status were not related to surgery, but were a result of increasing tumor burden and/or growth. All five patients had a large tumor burden (12 ± 7.5 tumors per patient) as opposed to those who did not experience a drop in function status (6.6 ± 4.6 tumors per patient) during the period of observation. However, this difference was not statistically significant. There were no mortalities related to CNS disease. One mortality occurred, a result of metastatic renal cell carcinoma.

### Radiation Therapy

Four cerebellar hemangioblastomas, all without associated cysts, in three patients, were treated with stereotactic

**FIGURE 38.1.** Distribution of 143 hemangioblastomas in the cerebellum, brainstem, and spinal cord affecting the 19 patients.

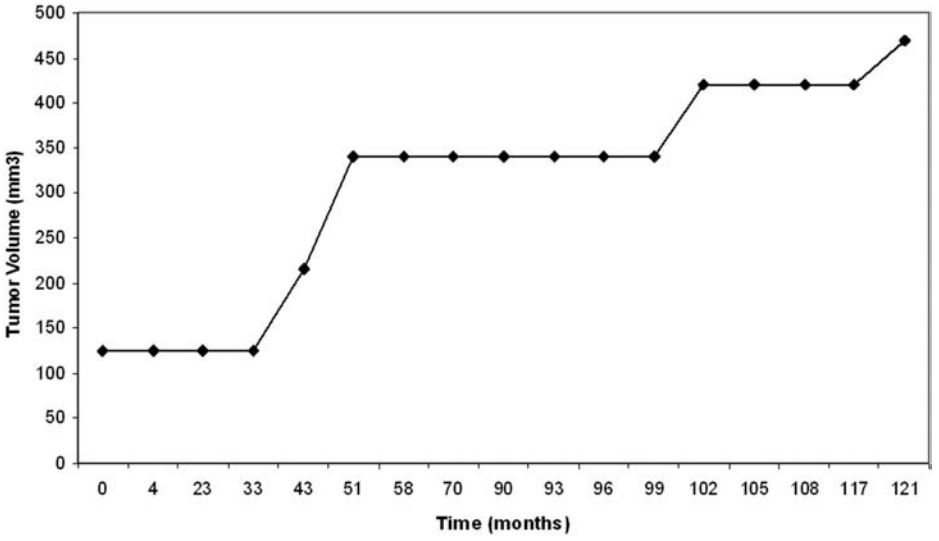


**FIGURE 38.2.** Representative growth curve for CNS hemangioblastomas. This cerebellar hemangioblastoma in a 36-year-old woman demonstrates a stuttering or stepwise growth pattern. It eventually required treatment because of the development of symptoms.

radiosurgery (all were less than 3 cm in maximum diameter). None of the tumors were eliminated by radiosurgery. Three of the four tumors continued to grow, and eventually required resection. The other tumor demonstrated a 33% reduction in volume at 12 months after treatment (*Fig. 38.3*).

One patient received conventional fractionated craniospinal irradiation for multifocal, progressive disease. Five hemangioblastomas were present; three continued to grow, one stabilized, and one became smaller. The patient also developed a new tumor in the brainstem after radiation.

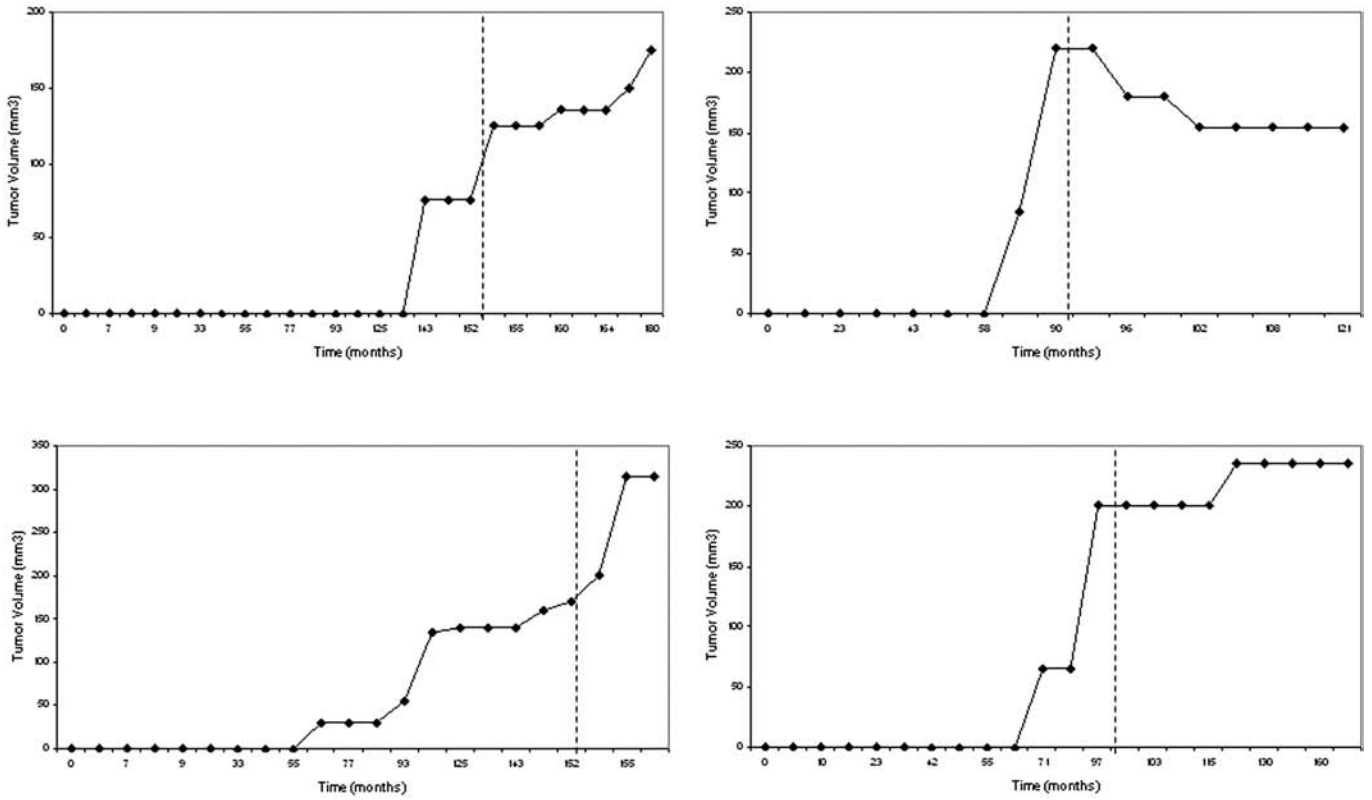


**FIGURE 38.3.** Growth curves for cerebellar hemangioblastomas treated with stereotactic radiosurgery (broken line). Three of four treated tumors displayed continued growth and required resection.

## Need for Resection

Only tumors producing symptoms were resected. Ten brainstem tumors (60%) required resection by 60 months of observation. For cerebellar tumors, 34 (50%) required intervention by 80 months. Only 12 spinal cord tumors (20%) required intervention by 170 months (end of study interval) (*Fig. 38.4*). Within all three regions, tumor size was a significant factor ($P < 0.05$; Cox regression) in determining need for resection. In each region, there was an indirect relationship between tumor size and the number of untreated tumors at any point in time.

## Predictive Markers for Symptom Formation

Several characteristics of tumor and cyst were examined by Cox regression and recursive partitioning analysis with cross validation (see Patients and Methods) in an attempt to identify features predictive of symptom development and eventual need for therapy. The variables assessed were tumor size, tumor growth rate, tumor and cyst size and growth rate combined, presence of a peritumoral cyst, presence of peritumoral edema, patient age, gender, tumor region, and total number of preexisting tumors.

Overall tumor size and combined tumor and cyst growth rate ($P < 0.05$) were significant predictors of eventual need for therapy. Spinal cord tumors demonstrated longer treatment-free intervals than cerebellar tumors, which remained symptom-free longer than brainstem lesions. At 5 years after initial observation, 20% of spinal cord tumors, 38% of cerebellar hemangioblastomas, and 60% of brainstem lesions had required treatment because of symptoms. At 10 years, 30% of spinal cord tumors had been treated versus 70% of cerebellar hemangioblastomas (*Fig. 38.5*).

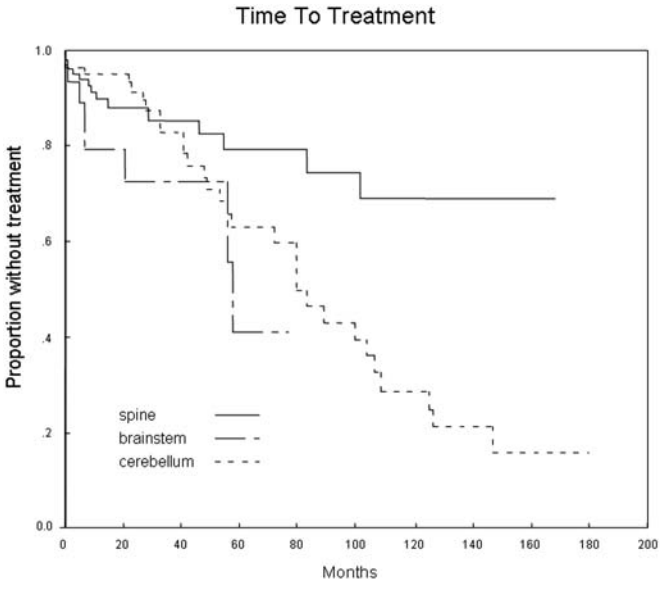


**FIGURE 38.4.** Actuarial graph showing proportion of hemangioblastomas that remained asymptomatic, by location. At 5 years from initial observation, 20% of spinal cord tumors, 38% of cerebellar hemangioblastomas, and 60% of brainstem lesions had required treatment. At 10 years, 30% of spinal cord tumors produced symptoms compared with 70% of cerebellar hemangioblastomas.

### Cerebellum

The combined tumor and cyst (the sum of the volume of the tumor and the volume of the cyst) growth rate, followed by combined tumor and cyst size are the strongest predictors of symptom development for hemangioblastomas in the cerebellum. All hemangioblastomas with combined growth rates (tumor and cyst) greater than 112 $mm^3$/mo eventually produced symptoms requiring intervention. All tumors with combined tumor and cyst volumes larger than 69 $mm^3$ (equivalent to the volume of a sphere of 5.2-mm diameter) and with combined growth rates in excess of 14 $mm^3$/mo also went on to produce symptoms and require therapy. Overall, the decision tree shown in *Fig. 38.6* yielded a sensitivity of 100% (i.e., 100% of the tumors that required surgery because of symptoms were predicted to require surgery) and a specificity of 72% (i.e., 72% of tumors that did not require surgery during the observation interval were predicted not to require surgery) in predicting symptom formation and eventual need for intervention.

Considering only the cerebellar hemangioblastoma size alone, at 5 years, 20% of tumors smaller than 14 $mm^3$ (3.0-mm diameter) at initial observation had received therapy after producing symptoms, whereas 60% of tumors between 14 $mm^3$ and 63 $mm^3$ (3.0- to 5.0-mm diameter) had been treated, and nearly 100% of those tumors whose initial volume exceeded 63 $mm^3$ (5.0-mm diameter) received therapy. At 10 years, a similar trend occurred, 50% of the initial small ($<14$ $mm^3$) tumors required treatment versus 8% of the medium-sized ($14-63$ $mm^3$) tumors (*Fig. 38.5A*).

When examining cerebellar hemangioblastomas solely on the basis of combined tumor/cyst growth rate, only 15% of tumors and their associated cysts growing at less than 112 $mm^3$/mo underwent treatment by 5 years versus 40% of those growing in excess of 112 $mm^3$/mo. Once again, at 10 years, 50% of slower growing tumor/cysts ($<112$ $mm^3$/mo) had undergone treatment as opposed to 95% of fast-growing tumors (112 $mm^3$/mo) ($P < 0.05$) (*Fig. 38.7*).

### Brainstem

Rapid tumor growth and initial tumor size predict symptom development for hemangioblastomas in the brainstem. Tumor size greater than 245 $mm^3$ (7.9 mm diameter) and growing more than 0.07 $mm^3$/mo predicted symptom development and need for treatment with a sensitivity of 75% and a specificity of 89% (*Fig. 38.8*).

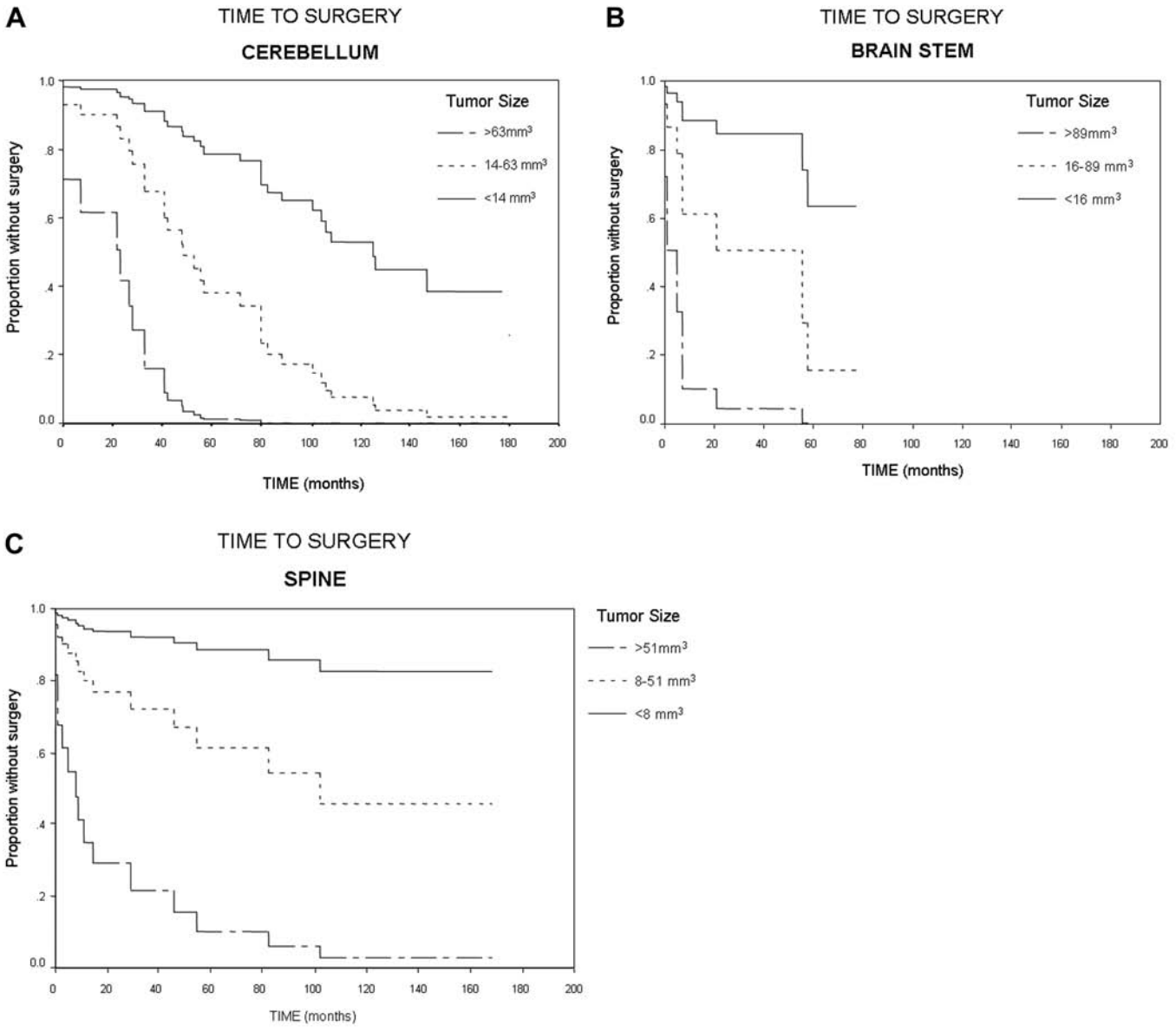


**FIGURE 38.5.** Actuarial graphs showing proportion of hemangioblastomas without surgery stratified by size within the cerebellum (*A*), brainstem (*B*), and spinal cord (*C*). At 5 and 10 years, smaller tumors were substantially less likely to have required therapy ($P < 0.05$).

Tumor volume dictated the time to treatment for brainstem hemangioblastomas. At 5 years, 15% of tumors smaller than 16 $mm^3$ (3.2 mm diameter) at initial observation had received therapy, whereas 50% of tumors between 16 $mm^3$ and 89 $mm^3$ (3.2–5.6 mm diameter) had been treated, and 100% of tumors with an initial volume exceeding 89 $mm^3$ (5.6 mm diameter) received therapy (*Fig. 38.5B*).

**Spinal Cord**

Within the spinal cord, tumor size was the only variable that predicted the development of symptoms and eventual need for therapy. Tumor volume greater than 22 $mm^3$ (3.5-mm diameter) yielded a sensitivity of 79% and a specificity of 94% as a predictor of need for intervention (Fig. 38.9).

At 5 years, 10% of spinal cord tumors smaller than 8 $mm^3$ (2.5-mm diameter) at initial observation had produced symptoms requiring treatment, whereas 37% of tumors between 8 $mm^3$ and 51 $mm^3$ (2.5–4.7 mm diameter) had been treated, and 90% of tumors whose initial volume exceeded 51 $mm^3$ (4.7 mm diameter) received therapy. Once again, at 10 years, a similar trend occurred, in that 15% of the initial small

 

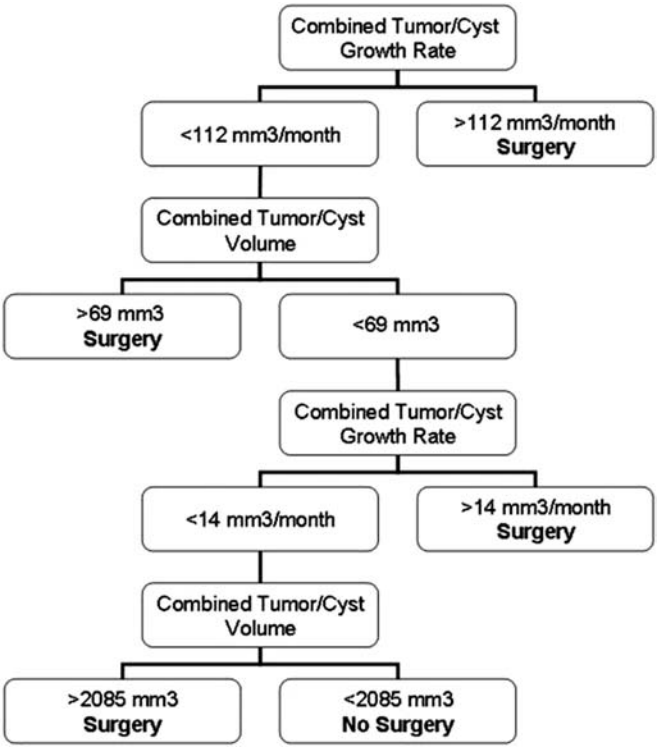


**FIGURE 38.6.** Recursive partitioning analysis for hemangioblastomas of the cerebellum. Combined tumor/cyst growth rate and combined tumor/cyst size were the primary predictors of eventual need for therapy (sensitivity, 100%; specificity, 72%). Recursive partitioning analysis involves the selection of a primary variable (i.e., therapy or no therapy) and subsequent segregation of the values for all other variables (i.e., age, size, etc.) to most accurately divide subjects with respect to the primary variable. This is accomplished by generating a decision tree composed of progressive binary splits or nodes based on the predictor variable that makes the best separation. Each parent node in the decision tree produces two child nodes, which subsequently become parent nodes producing additional child nodes. This process is repeated until statistical analysis indicates that the optimal or most homogeneous tree has been generated for the data set analyzed. The decision trees generated by recursive partitioning analysis are easily interpreted and lend themselves to clinical decision making.

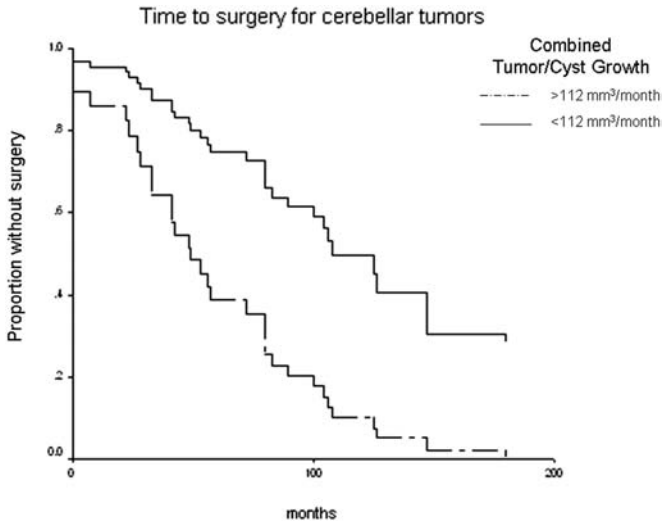


**FIGURE 38.7.** Actuarial graphs showing proportion of cerebellar hemangioblastomas without surgery stratified by combined tumor/cyst growth rate. At 5 and 10 years, slow-growing tumors were substantially less likely to have required therapy and by 10 years nearly all rapidly growing tumors had received treatment ($P < 0.05$).

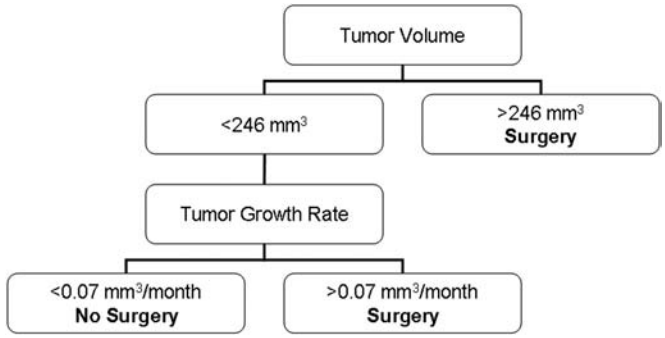


**FIGURE 38.8.** Recursive partitioning analysis for hemangioblastomas of the brainstem. Tumor volume and growth rate were the primary predictors of eventual need for therapy (sensitivity, 75%; specificity, 89%).

(<8 $mm^3$) tumors, 52% of the medium-sized (8–51 $mm^3$) tumors, and 98% of the large (51 $mm^3$) hemangioblastomas had required treatment (*Fig. 38.5C*).

## DISCUSSION

### VHL

Hemangioblastomas are histologically benign, vascular neoplasms composed of endothelial and stromal cells with a tendency toward peritumoral edema and cyst formation. They enhance brightly with contrast on MRI scans and have well-defined borders. Hemangioblastomas occur sporadically and in association with VHL. Up to 72% of VHL patients will harbor at least one cerebellar hemangioblastoma and greater than 40% of VHL patients will develop spinal cord hemangioblastomas. Five to 31% of cerebellar hemangioblastomas occur in association with VHL, whereas 80% of spinal cord hemangioblastomas are VHL associated.[13,17]

Nonsurgical modalities, such as radiation and pharmacotherapy have been investigated in the treatment of hemangioblastomas. Stereotactic radiosurgery has been used with reported tumor control rates of 26 to 80%.[2,3,15,16] However, it is important to recognize that, in these reports, "control" includes tumors that did not enlarge on follow-up MRI scan. This study and a previous report[19]

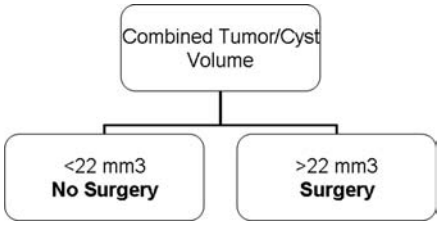


**FIGURE 38.9.** Recursive partitioning analysis for hemangioblastomas of the spinal cord. Combined tumor/cyst volume was the primary predictor of eventual need for therapy (sensitivity, 79%; specificity, 94%).

clearly demonstrate that untreated hemangioblastomas frequently have intervals of stable size on serial MRI and frequently do so for longer intervals than the intervals of follow-up used to define "tumor control" in response to radiosurgical treatment. Medical management for hemangioblastomas has centered on drugs with antiangiogenic properties. Two patients with retinal disease showed improvement in visual function after administration of SU5416, a vascular endothelial growth factor receptor inhibitor.[1,5] Although Madhusudan et al., reported a 33% response rate of CNS hemangioblastomas in six patients with CNS disease treated with systemic SU5416, response was defined as radiographic and clinical stabilization, which, for the reasons described above with regard to radiation therapy, are not valid indicators of therapeutic affect, because most tumors have periods of stable size that can last for months or years.[11]

## Previous Studies of Treatment of Hemangioblastomas

In 2001, Conway et al.[4] examined 40 patients with hemangioblastomas, 63% of whom had VHL. They concluded that spinal cord hemangioblastomas were particularly associated with a diagnosis of VHL and that surgical outcomes for VHL patients were poorer than those treated for sporadic hemangioblastomas. In 2003, Van Velthoven et al.[19] reviewed 28 patients (64% with VHL) with spinal cord hemangioblastomas and concluded that tumor resection should be undertaken based on radiographic progression.

Wanebo et al.[20] recently published the NIH experience of 160 consecutive patients with 655 hemangioblastomas. Among the conclusions reached in that study were that peritumoral cysts occur frequently in symptom-producing hemangioblastomas, the rate of cyst growth is typically much greater than the rate of tumor growth, and hemangioblastomas follow multiple growth patterns. However, given its relatively short follow-up interval (mean, 21 mo) that study did not address some of the long-term features of VHL-associated hemangioblastomas, or address the issue of predicting the need for treatment of individual lesions based on tumor size, cyst presence, or tumor growth rates.

## Current Study

### Visceral Lesions

The genetics of the VHL syndrome and its associated tumors has been studied by several groups around the world. Extensive work on genetic transmission, renal cell carcinoma, and pheochromocytoma, in addition to the examination of the CNS manifestations has been performed. The distribution of visceral lesions observed in this study are consistent with other large published series.[6,9]

### Growth Pattern

Wanebo et al.[20] suggested, and this report confirms, a number of features of hemangioblastomas in VHL. Stepwise, stuttering growth is a consistent observation in hemangioblastomas. Phases of rapid growth are interspersed with quiescent intervals. This feature, along with the fact that a significant number of the tumors that eventually required intervention were not present on the initial imaging (45% of the hemangioblastomas in the current series that eventually required treatment were not even apparent on the initial MRI scan), underscores the need for ongoing radiographic and clinical assessment and the difficulty determining which lesion is likely to require treatment next.

Nearly all of the tumors studied demonstrated some evidence of radiographic progression, but only half went on to require therapy. Basing the decision to intervene on these tumors solely on radiographic progression would have resulted in approximately four additional procedures per patient during a 10-year period. This suggests that using radiographic progression alone is not an optimal predictor of need for therapy.

### Functional Outcomes

Excellent functional status can be maintained in VHL patients with careful surveillance and the use of microsurgery in symptomatic patients or those who meet the new criteria outlined in this report. This is illustrated by the relatively small declines in functional status seen in our patient population during the course of the study.

### Radiation

Regarding radiation, stereotactic radiosurgery for the treatment of hemangioblastomas has been advocated by a number of groups.[3,7,16] However, large tumors (greater than 3 cm) and those with peritumoral cysts have been shown to respond poorly.[8,15] Although the tumors treated in our study population were all less than 3 cm and without peritumoral cysts, most (three of four) demonstrated radiographic and clinical progression despite the treatment. Because these tumors display a stuttering growth pattern, the follow-up intervals of previous work have been inadequate to discover resumption of growth in the treated tumors. Craniospinal radiation, which was used in one of our patients with severe, diffuse disease, provided incomplete tumor control.

### Predictive Markers

We and most other groups have waited for hemangioblastomas to become symptomatic before recommending treatment, regardless of tumor size and/or presence of edema or peritumoral cyst. This approach has been influenced the large number of tumors that VHL patients harbor and the inability to predict the future of individual tumors. However, some tumors attain significant size and some patients may develop potentially irreversible neurological deficits during the interval of observation. Treatment of small, asymptomatic, benign lesions, similar to hemangioblastomas, presumes that the long-term natural history of the lesion is known. Until now, this had not been the case for hemangioblastomas in VHL. Using the data obtained in this study, we can now predict with reasonable accuracy, based on size and growth rate, which tumors will go on to become symptomatic. The differences in the proportion of tumors needing treatment between regions and the different thresholds of size and growth rates predicting requirement for treatment is likely a reflection of the physiological constrains imposed by local anatomy. Use of these predictive markers permit removal of certain tumors when they are small, but have met criteria indicating that they will produce symptoms and require treatment within the next few years, and treatment of these tumors when they are smaller and before they produce a neurological deficit may be associated with less risk and improved neurological outcomes.

## CONCLUSIONS

Hemangioblastomas exhibit a stuttering growth pattern and frequently remain asymptomatic and do not require treatment. Therefore, neither the mere presence of a tumor nor undefined radiographic progression is an indication for treatment. Depending on hemangioblastoma location, threshold values for tumor size and/or tumor/cyst growth rate can be used to predict symptom formation and need for treatment with reasonable clinical accuracy.

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