

Long-term natural history of hemangioblastomas in patients with von Hippel–Lindau disease: implications for treatment

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Object. In the course of their lives most patients with von Hippel–Lindau (VHL) disease require treatment for 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 lesions that will later produce symptoms and ultimately require treatment would allow for earlier excision of hemangioblastomas of the spinal cord, brainstem, or cerebellum, and may identify cerebellar hemangioblastomas that can be treated with radiosurgery at a stage before treatment is contraindicated because of tumor size or the presence of an associated cyst.

Methods. To identify features predictive of symptom development that might allow for earlier treatment of smaller, presymptomatic hemangioblastomas in patients with VHL disease, the authors reviewed and analyzed the serial clinical and imaging findings in all patients with VHL disease who were followed up at the National Institutes of Health for more than 10 years. Features predictive of symptom formation were determined by recursive partition and regression analyses.

Nineteen patients (10 men and nine women; mean age 32.6 ± 11.6 years) harboring a total of 143 hemangioblastomas were identified (mean follow-up duration 12.4 ± 1.4 years). Hemangioblastomas were located in the cerebellum (68 hemangioblastomas, 48% of patients), brainstem (17 hemangioblastomas, 12% of patients), and spinal cord (58 hemangioblastomas, 40% of patients). Despite measurable growth in almost all hemangioblastomas (138 lesions, 97% of patients), only 58 (41% of patients) became symptomatic. Hemangioblastomas grew in a stuttering pattern. (mean growth period 13 ± 15 months, mean quiescent period 25 ± 19 months). Twenty-six (45%) of the hemangioblastomas that eventually produced symptoms were not among the tumors that were apparent on the initial MR imaging study. Depending on location, the hemangioblastoma size and/or tumor and cyst growth rates predicted symptom development and the need for treatment ($p < 0.05$). Cerebellar hemangioblastomas growing faster than $112 \text{ mm}^3/\text{month}$ or larger than 69 mm^3 with associated tumor and cyst growth rates greater than $14 \text{ mm}^3/\text{month}$ became symptomatic (100% sensitivity, 72% specificity). Brainstem hemangioblastomas larger than 245 mm^3 with growth rates greater than $0.1 \text{ mm}^3/\text{month}$ became symptomatic (75% sensitivity, 89% specificity). Spinal hemangioblastomas larger than 22 mm^3 became symptomatic (79% sensitivity, 94% specificity).

Conclusions. Because hemangioblastomas exhibit a stuttering growth pattern, frequently remain asymptomatic, and do not require treatment for long intervals, unqualified radiographic progression is not an indication for treatment. Basing the decision to intervene in individual tumors solely on radiographic progression would have resulted in approximately four additional procedures per patient during the 10-year study period. Threshold values are presented for tumor size and/or tumor and cyst growth rates that can be used to predict symptom formation and future need for treatment.

KEY WORDS • hemangioblastoma • natural history • treatment planning • von Hippel–Lindau disease

VON Hippel–Lindau disease is an inherited multisystem cancer syndrome with visceral and CNS manifestations.⁹ It is transmitted in an autosomal dominant fashion (chromosome 3p25) with greater than 90% penetrance by 60 years of age.¹² Visceral lesions include renal cell carcinomas and cysts, pancreatic islet cell tumors

and cysts, pheochromocytomas, and papillary cystadenomas of the epididymis and broad ligament. The CNS manifestations of VHL disease include hemangioblastomas of the retina, brainstem, cerebellum, spinal cord, and nerve roots as well as endolymphatic sac tumors.

In the course of their lives, most patients with VHL disease 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

Abbreviations used in this paper: CNS = central nervous system; MR = magnetic resonance; NIH = National Institutes of Health; VHL = von Hippel–Lindau.

Hemangioblastoma natural history

treatment might allow for earlier excision of hemangioblastomas of the spinal cord, brainstem, or cerebellum and for identification of cerebellar hemangioblastomas in 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 that might be used to predict tumor behavior during the course of several years requires an extended interval of observation. To define the long-term natural history of VHL disease and identify predictive tumor features for surgical intervention for CNS hemangioblastomas, we reviewed the serial clinical and MR imaging findings in all patients with VHL disease who were followed up at the NIH for more than 10 years.

Clinical Material and Methods

Clinical Data

Clinical charts and MR images were reviewed for all patients with VHL disease who received a minimum of 10 years of follow-up care at the NIH. Patients were seen at approximately 6- to 12-month intervals for clinical and neuroimaging assessment. Changes in functional status during the study interval were assessed using the McCormick Scale (Table 1).¹⁴

Radiographic Data

Craniospinal MR imaging was used to determine the presence of and to quantify the size of each hemangioblastoma. Postcontrast T₁-weighted, spoiled gradient-recalled acquisition, and T₂-weighted sequences were reviewed. Tumor volumes were calculated in cubic millimeters by using a modified ellipsoid formula: (length × width × height) × 0.5.¹⁰ Intracranial peritumoral edema and cysts were measured in a similar manner. Spinal cord edema and cysts were quantified based on 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 (cerebellum, brainstem, and spinal cord). The time period of tumor observation up to the point of intervention (prompted by symptom formation) was evaluated using 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 constraints imposed by the anatomy, categorization of tumor volume was accomplished by terciles of volume separately for each location. Growth rates were computed for the follow-up period and annualized. Recursive partitioning was used separately for each of the three regions to find a classification tree for treatment, based on factors available at the initial evaluation or observed during the course of follow up.

Results

Patient Demographics

Nineteen patients (10 men and nine women) with VHL disease were identified and followed up for a minimum of 10 years. All patients had one or more hemangioblastomas. Their mean age at the time they entered the study was 32 ± 11.6 years (median 31.5 years), and the mean follow-up period was 12.2 ± 1.6 years (median 12.5 years). Imaging was obtained on average every 10.3 ± 3.2 months (median 10.5 months). The mean interval between clinical evaluations was 10.1 ± 4.1 months (median 11 months).

Other VHL Disease-Related Lesions

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

Hemangioblastomas in the CNS

In the 19 patients in this study, 143 hemangioblastomas were identified (mean 7.5 ± 6.1 tumors per patient; median 7 tumors). Seventeen (89%) of 19 patients had multiple hemangioblastomas (range one–25 tumors). In five patients (26%) all of the tumors were confined to a single CNS region (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, with 56 (82%) of those tumors located in the cerebellar hemispheres and 12 (18%) in the vermis. Seventeen hemangioblastomas (12%) were located in the brainstem, with 12 (71%) of those tumors located precisely at the obex. An additional 58 tumors (40%) were confined to the spinal cord as follows: 29 (50%) cervical, 19 (33%) thoracic, and 10 (17%) lumbar (Fig. 1). No supratentorial hemangioblastomas were identified.

Hemangioblastoma Growth

Of 143 hemangioblastomas, 138 (97%) demonstrated evidence of growth on neuroimaging obtained during the study period. Of these 138 lesions, 134 (97%) displayed a stuttering growth pattern (Fig. 2), and four (3%) exhibited a progressive growth pattern. The hemangioblastomas had an average of 1.85 growth arrests before becoming symptomatic. Fifty-eight tumors (41%) became symptomatic and required intervention. Twenty-six (45%) of these symptomatic hemangioblastomas were not among the tumors that were apparent on the initial MR images. Tumor growth periods averaged 13 ± 15 months, and growth arrest intervals averaged 25 ± 19 months.

Functional Outcomes

Patients generally remained at their neurological baseline during the study period. The maximum reduction in functional status during the study period was 1 point (mean 0.26 ± 0.46 points) and was observed in five patients (26%). These reductions in functional status were not relat-

TABLE 1
McCormick Scale*

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; still functions and ambulates independently
III	more severe neurological deficit; requires cane/brace for ambulation or significant bilat upper extremity impairment; may or may not function independently
IV	severe deficit; requires wheelchair or cane/brace with bilat upper extremity impairment; usually not independent

* This scale is an objective measure of ambulation, gait, and the ability to perform activities of daily living. Reprinted from McCormick PC, Torres R, Post KD, Stein BM: Intramedullary ependymoma of the spinal cord. *J Neurosurg* 72:523-532, 1990.



FIG. 1. Drawing demonstrating the distribution of 143 hemangioblastomas (black dots) in the cerebellum, brainstem, and spinal cord of 19 patients.

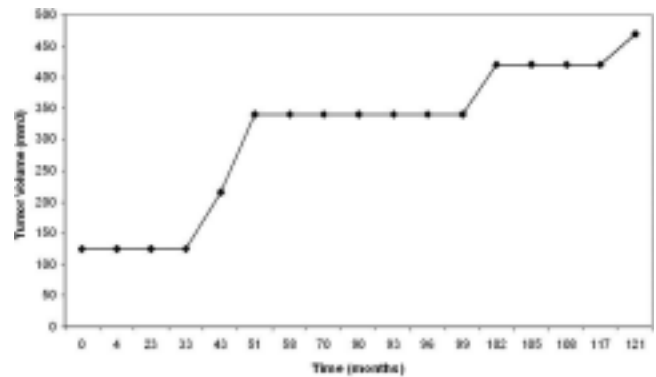


FIG. 2. Graph showing a representative growth curve for hemangioblastomas of the CNS. This cerebellar hemangioblastoma in a 36-year-old woman demonstrates a stuttering or stepwise growth pattern. It eventually required treatment because of the development of symptoms.

ed to surgery but were the result of increasing tumor burden and/or growth. These five patients had a large tumor burden (12 ± 7.5 tumors per patient) compared with those who did not experience a drop in functional status (6.6 ± 4.6 tumors per patient) during the period of observation. Nevertheless, this difference was not statistically significant. There were no deaths related to CNS disease. One death occurred as the result of metastatic renal cell carcinoma.

Radiation Therapy

In three patients, four cerebellar hemangioblastomas (all without associated cysts) were treated with stereotactic radiosurgery (all were < 3 cm in maximum diameter). The radiosurgery did not eliminate any of these tumors. Three of the four tumors continued to grow and eventually required resection; the other tumor demonstrated a 33% reduction in volume at 12 months posttreatment (Fig. 3).

One patient received conventional fractionated craniospinal radiation for multifocal, progressive disease. Five hemangioblastomas were present: three continued to grow, one stabilized, and one became smaller. A new tumor developed in this patient's brainstem following radiation treatment.

Need for Resection

Only tumors that produced symptoms were resected. Ten (59%) of the 17 brainstem tumors required resection by 60 months of observation. Of the 68 cerebellar tumors, 34 (50%) required intervention by 80 months. Only 12 (20%) of the 58 spinal cord tumors required intervention by 170 months (the end of the study interval) (Fig. 4). Within all three regions, tumor size was a significant factor ($p < 0.05$, Cox regression) in determining the need for resection. In each region and at any point in time, there was an indirect relationship between tumor size and the number of untreated tumors.

Predictive Markers for Symptom Formation

Several characteristics of tumors and cysts were examined using Cox regression and recursive partitioning analysis with cross-validation (see *Clinical Material and Methods*) in an attempt to identify features predictive of symptom development and eventual need for therapy. The

Hemangioblastoma natural history

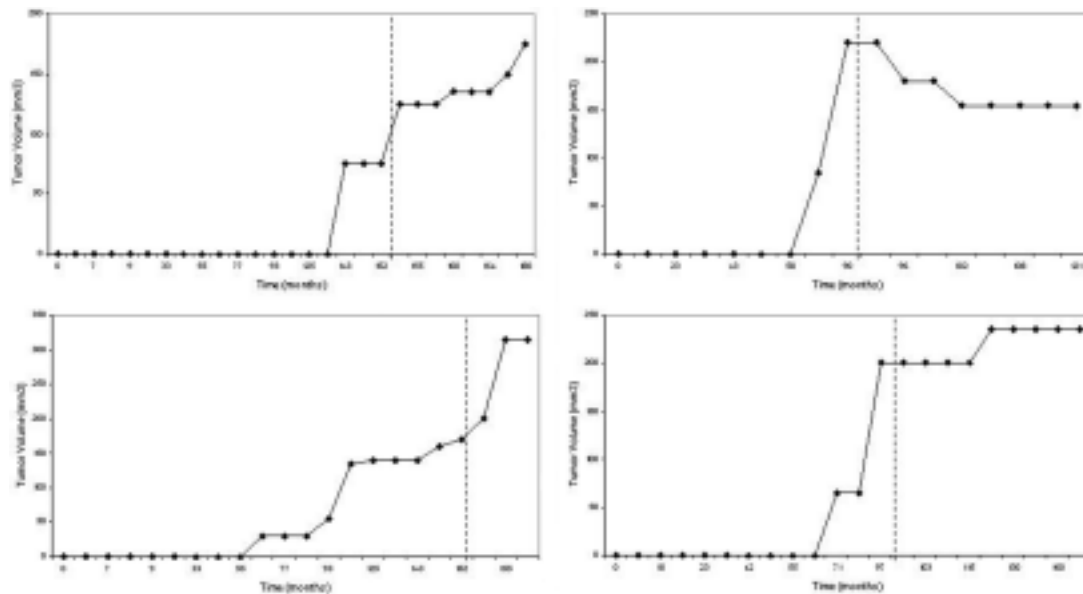


FIG. 3. Graphs showing growth curves for four cerebellar hemangioblastomas that were treated with stereotactic radio-surgery (*broken line*). Three of the four treated tumors displayed continued growth and required resection.

variables assessed were tumor size, tumor growth rate, tumor and cyst sizes and growth rates combined, presence of a peritumoral cyst, presence of peritumoral edema, patient age, patient sex, tumor region, and total number of preexisting tumors.

Overall tumor size and combined tumor and cyst growth rates ($p < 0.05$) were significant predictors of the eventual need for therapy. Spinal cord tumors demonstrated longer symptom-free intervals than did cerebellar tumors, which remained symptom free longer than brainstem lesions. At 5 years from 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 compared with 70% of cerebellar hemangioblastomas (Fig. 5).

Cerebellum. The combined tumor and cyst growth rates (the sum of the volume of the tumor and the volume of the cyst) and the combined tumor and cyst sizes are the strongest predictors of symptom development for hemangioblastomas in the cerebellum. All hemangioblastomas with combined tumor and cyst growth rates greater than $112 \text{ mm}^3/\text{month}$ eventually produced symptoms that required intervention. All tumors with combined tumor and cyst volumes larger than 69 mm^3 (equivalent to the volume of a sphere 5.2 mm in diameter) and with combined growth rates in excess of $14 \text{ mm}^3/\text{month}$ also went on to produce symptoms and require therapy. Overall, the decision tree shown in Fig. 6 yielded a sensitivity of 100% (that is, 100% of the tumors that required surgery because of symptoms were predicted to require surgery) and a specificity of 72% (that is, 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 cerebellar hemangioblastoma size alone, at 5 years 20% of tumors smaller than 14 mm^3 (3 mm in diam-

eter) at initial observation had been treated after producing symptoms, and 60% of tumors between 14 and 63 mm^3 (3–5 mm in diameter) had been treated, as had nearly 100% of tumors whose initial volume exceeded 63 mm^3 (5 mm diameter). At 10 years, a similar trend occurred: 50% of the initial small ($< 14 \text{ mm}^3$) tumors required treatment compared with 92% of the medium-sized (14 – 63 mm^3) tumors (Fig. 5A).

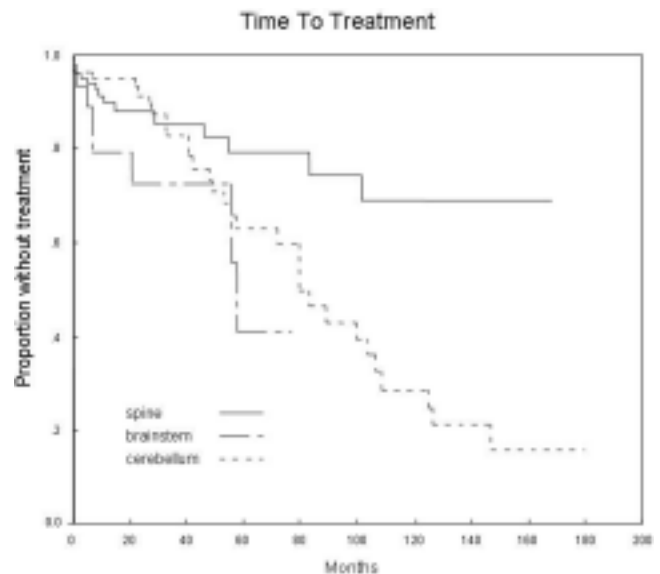


FIG. 4. Actuarial graph illustrating the proportion of hemangioblastomas that remained asymptomatic, by location, from the time of initial observation. At 5 years from initial observation, 20% of spinal cord tumors, 38% of cerebellar hemangioblastomas, and 60% of brainstem lesions had required treatment. At 10 years, 30% of spinal cord tumors produced symptoms compared with 70% of cerebellar hemangioblastomas.

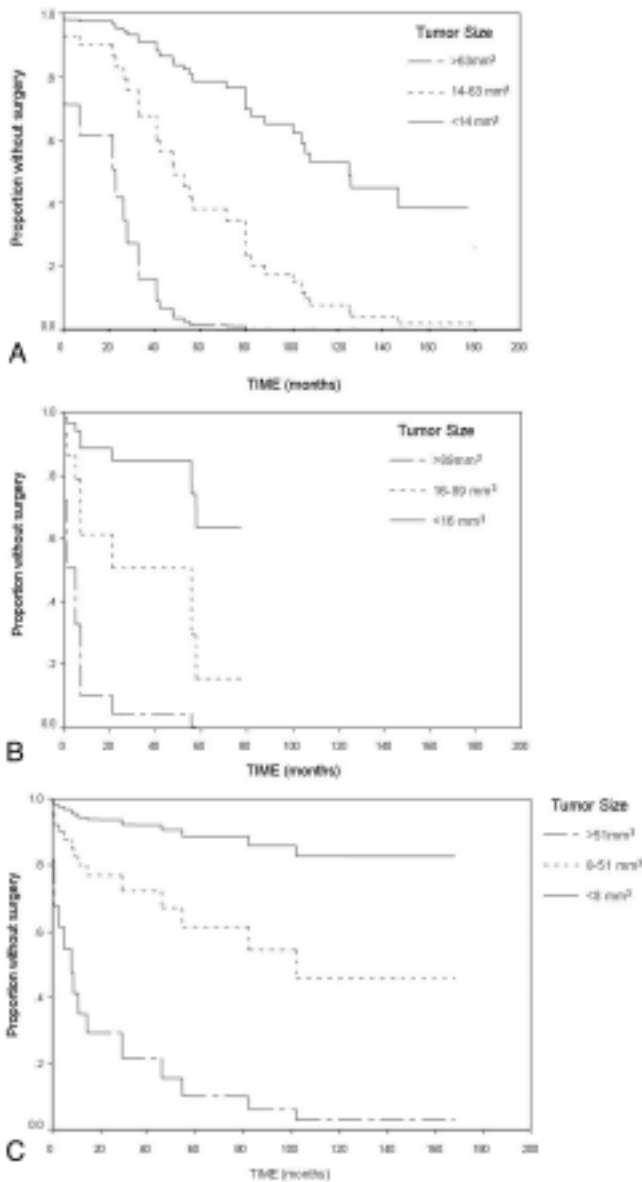


FIG. 5. Actuarial graphs showing the proportion of hemangioblastomas that did not require surgery stratified by size within the cerebellum (A), brainstem (B), and spinal cord (C). At 5 and 10 years, smaller tumors were substantially less likely to have required therapy ($p < 0.05$).

When we examined cerebellar hemangioblastomas based solely on combined tumor and cyst growth rates, we found that only 15% of tumors and their associated cysts that were growing at less than $112 \text{ mm}^3/\text{month}$ required treatment after 5 years, compared with 40% of those growing in excess of $112 \text{ mm}^3/\text{month}$. Similarly, at 10 years 50% of slower-growing tumors and cysts ($< 112 \text{ mm}^3/\text{month}$) had required treatment, compared with 95% of faster-growing tumors ($> 112 \text{ mm}^3/\text{month}$; $p < 0.05$; Fig. 7).

Brainstem. Rapid tumor growth and initial tumor size were predictors of symptom development for hemangioblastomas in the brainstem. Tumor size greater than 245 mm^3 (7.9 mm in diameter) and tumors that were growing

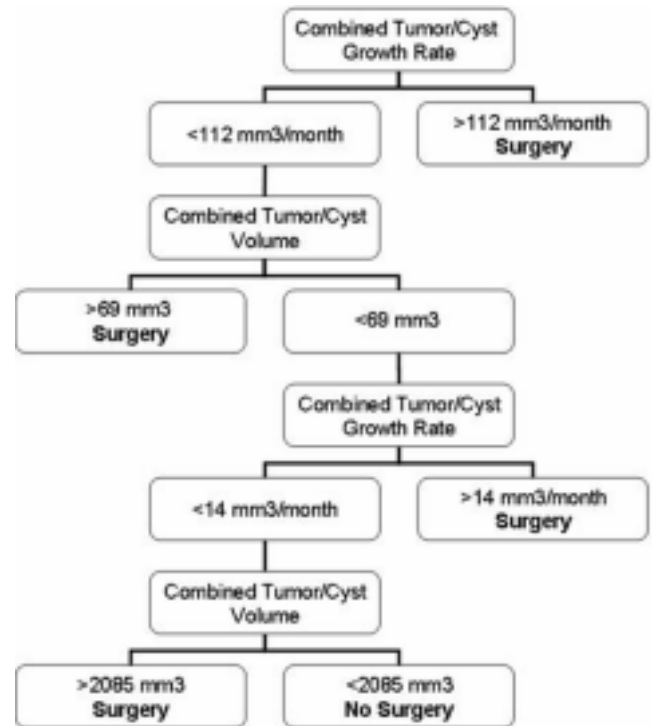


FIG. 6. Chart demonstrating recursive partitioning analysis for hemangioblastomas of the cerebellum. Combined tumor and cyst growth rates and combined tumor and cyst sizes were the primary predictors of eventual need for therapy (sensitivity 100%, specificity 72%). Recursive partitioning analysis involves the selection of a primary variable (for example, therapy or no therapy) and the subsequent segregation of the values for all other variables (for example, age, size, and so on) so that they 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. Decision trees generated by recursive partitioning analysis are easily interpreted and lend themselves to use in clinical decision making.

more than $0.07 \text{ mm}^3/\text{month}$ were predictors of symptom development and need for treatment, with a sensitivity of 75% and a specificity of 89% (Fig. 8).

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

Spinal Cord. Within the spinal cord, tumor size was the only variable that served as a predictor of the development of symptoms and eventual need for therapy. Tumor volume greater than 22 mm^3 (3.5 mm in diameter) yielded a sensitivity of 79% and a specificity of 94% as a predictor of the need for intervention (Fig. 9).

At 5 years, 10% of spinal cord tumors smaller than 8 mm^3

Hemangioblastoma natural history

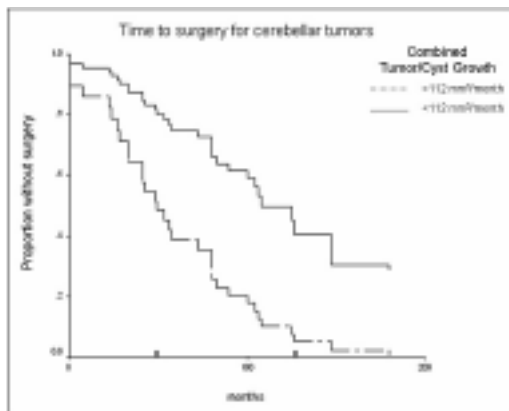


FIG. 7. Actuarial graph showing the proportion of cerebellar hemangioblastomas that did not require surgery stratified by combined tumor and cyst growth rates. At 5 and 10 years, slower-growing tumors were substantially less likely to have required therapy, and by 10 years nearly all rapidly growing tumors had received treatment ($p < 0.05$).

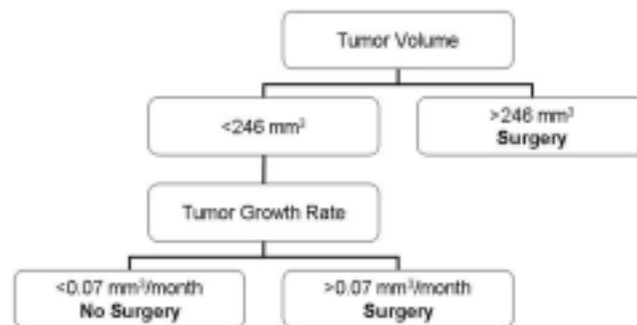


FIG. 8. Chart demonstrating recursive partitioning analysis for hemangioblastomas of the brainstem. Tumor volume and growth rate were the primary predictors of the eventual need for therapy (sensitivity 75%, specificity 89%).

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 demonstrated improvement in visual function after administration of SU5416, a vascular endothelial growth factor receptor inhibitor.^{1,5} Although Madhusudan, et al.,¹¹ reported a 33% response rate of CNS hemangioblastomas in six patients who were treated with systemic SU5416, response was defined as radiographic and clinical stabilization, which are not valid indicators of therapeutic effect, for the reasons described earlier with regard to radiation therapy, because most tumors have periods of stable size that can last for months or years.

Previous Studies of Treatment of Hemangioblastomas

In 2001, Conway, et al.,⁴ examined 40 patients with hemangioblastomas, 63% of whom had VHL disease. They concluded that spinal cord hemangioblastomas were particularly associated with a diagnosis of VHL disease and that surgical outcomes in patients with VHL disease were worse than in those treated for sporadic hemangioblastomas. In 2003, Van Velthoven, et al.,¹⁸ reviewed the cases of 28 patients with spinal cord hemangioblastomas (64% with VHL disease) and concluded that tumor resection should be undertaken based on radiographic progression.

Wanebo, et al.,¹⁹ recently published an NIH study of 160

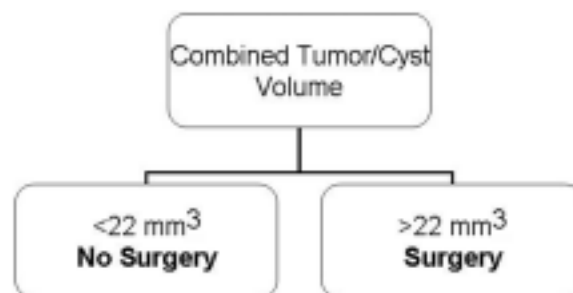


FIG. 9. Chart showing recursive partitioning analysis for hemangioblastomas of the spinal cord. Combined tumor and cyst volume was the primary predictor of the eventual need for therapy (sensitivity 79%, specificity 94%).

(2.5 mm in diameter) at initial observation had produced symptoms requiring treatment, but 37% of tumors between 8 and 51 mm³ (2.5–4.7 mm in diameter) and 90% of tumors whose initial volume exceeded 51 mm³ (4.7 mm in diameter) had required treatment. Once again, at 10 years a similar trend occurred, in that 15% of the initial small (< 8 mm³ in diameter) tumors, 52% of the medium-sized (8–51 mm³ in diameter) tumors, and 98% of the large (> 51 mm³ in diameter) hemangioblastomas had required treatment (Fig. 5C).

Discussion

Association With VHL Disease

Hemangioblastomas are histologically benign, vascular neoplasms composed of endothelial and stromal cells, with a tendency toward the formation of peritumoral edema and cysts. They enhance brightly on contrast-enhanced MR images and have well-defined borders. Hemangioblastomas occur both sporadically and in association with VHL disease. Up to 72% of patients with VHL disease will harbor at least one cerebellar hemangioblastoma, and spinal cord hemangioblastomas will develop in more than 40% of patients with this disease. Between 5 and 31% of cerebellar hemangioblastomas occur in association with VHL disease, and 80% of spinal cord hemangioblastomas are associated with this disease.^{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} Nevertheless, it is important to recognize that in these reports the term “control” refers to tumors that did not show enlargement on follow-up MR imaging studies. This investigation and a previous report¹⁸ clearly demonstrate that untreated hemangioblastomas frequently have intervals of stable size (as demonstrated on serial MR imaging studies) and frequently do so for longer than the follow-up intervals used

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 months) that study did not address some of the long-term features of VHL disease-associated hemangioblastomas or 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 genetic aspects of VHL disease and its associated tumors have been studied by several groups around the world. Extensive work has been performed regarding genetic transmission of VHL disease, CNS manifestations of the disease, and its relationship to renal cell carcinoma and pheochromocytoma. The distribution of visceral lesions observed in the current study is consistent with other large, published series.^{6,9}

Growth Pattern. Wanebo and colleagues¹⁹ suggested, and this report confirms, a number of features of hemangioblastomas associated with VHL disease. For instance, phases of rapid growth that are interspersed with quiescent intervals are consistently observed in hemangioblastomas. This feature, along with the fact that a significant number of the tumors that eventually required intervention were not present on the initial images (45% of the hemangioblastomas in the current series that eventually required treatment were not even apparent in the initial MR imaging study) underscores the need for ongoing neuroimaging and clinical assessment and the difficulty in 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 in these tumors solely on radiographic progression would have resulted in approximately four additional procedures per patient during the 10-year study period. This suggests that radiographic progression alone is not an optimal predictor of the need for therapy.

Functional Outcomes. Excellent functional status can be maintained in patients with VHL disease by using careful clinical and radiographic 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 over the course of the study.

Radiation Therapy. Stereotactic radiosurgery for the treatment of hemangioblastomas has been advocated by a number of groups.^{3,7,16} However, large tumors (> 3 cm) and those with peritumoral cysts have been shown to respond poorly.^{8,15} Although the four tumors in our study population that were treated with radiosurgery were all smaller than 3 cm and without peritumoral cysts, three of them demonstrated radiographic and clinical progression despite the treatment. Because these tumors display a stuttering growth pattern, the follow-up intervals in previous studies have been inadequate to discover resumption of growth in the treated lesions. Craniospinal radiation, which was used

in one of our patients who had 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 the presence of edema or peritumoral cysts. This approach has been influenced by the large number of tumors that patients with VHL disease 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, like hemangioblastomas, presumes that the long-term natural history of the lesions is known. Until now this had not been the case for hemangioblastomas in patients with VHL disease. 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 in different regions that require treatment and the different thresholds of size and growth rates that serve as predictors of the need for treatment is probably a reflection of the physiological constraints imposed by local anatomy. Use of these predictive markers permits the 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. Treatment of these tumors when they are smaller and before they produce any neurological deficits in patients might be associated with less risk and improved neurological outcomes.

Conclusions

Hemangioblastomas exhibit a stuttering growth pattern and frequently remain asymptomatic, not requiring treatment. Therefore, neither the mere presence of a tumor nor isolated radiographic progression is an indication for therapy. Depending on the location of a hemangioblastoma, threshold values for tumor size and/or tumor and cyst growth rates can be used to predict symptom formation and the need for treatment with reasonable clinical accuracy. Asymptomatic tumors should be followed with serial imaging at regular intervals (6–12 months, depending on tumor size, presence of associated cysts, volume and number of associated hemangioblastomas in the same anatomical region, and so on) to detect changes that predict future symptom formation.

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Manuscript received June 9, 2005.

Accepted in final form February 15, 2006.

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