Neuro-Oncology 14(8):1097–1104, 2012.
doi:10.1093/neuonc/nos133
Advance Access publication June 21, 2012

Supratentorial hemangioblastoma: clinical features, prognosis, and predictive value of location for von Hippel–Lindau disease

Steven A. Mills, Michael C. Oh, Martin J. Rutkowski, Michael E. Sughrue, Igor J. Barani, and Andrew T. Parsa

Department of Neurological Surgery (S.A.M., M.C.O., M.J.R., M.E.S., A.T.P.), and Department of Radiation Oncology, University of California, San Francisco, California (I.J.B.)

Supratentorial hemangioblastoma is a rare form of hemangioblastoma; little information is available regarding prognosis, treatment, and clinical characteristics, because the available literature is primarily composed of case reports and small case series. Therefore, we performed a systematic review of the literature to analyze clinical characteristics, disease progression, and surgical outcomes with respect to survival for supratentorial hemangioblastomas. The rate of progression-free survival (PFS) was determined using Kaplan-Meier analysis. Differences in categorical factors, including location of tumor and diagnosis of von Hippel-Lindau (VHL) disease, were analyzed using the Pearson χ^2 test. A total of 106 articles met the search criteria, which combined for a total of 132 patients. Of the patients with supratentorial tumors, 60% had VHL disease, and 31 (84%) of 37 patients with tumors in the sellar/suprasellar region had associated VHL (χ^2, $P < .001$). Five-year PFS for gross-total resection and subtotal resection were 100% and 53%, respectively (Log rank, $P < .01$). On the basis of our analysis of the literature on published cases of supratentorial hemangioblastoma, gross-total resection appears to be superior to other treatment modalities in extending PFS. Von Hippel–Lindau disease is positively correlated with supratentorial hemangioblastoma when compared with non-supratentorial CNS hemangioblastomas, particularly when present in the sellar/suprasellar region.

Keywords: hemangioblastoma, supratentorial, von Hippel-Lindau.

Hemangioblastomas are uncommon tumors of the central nervous system (CNS) that were first described by von Hippel in 1895.[1] They are benign, vascular tumors of uncertain origin principally composed of stromal and endothelial cell components and comprise 1.1%–2.4% of all intracranial space-occupying lesions.[2–4] Hemangioblastomas typically occur in the cerebellum, brainstem, and spinal cord and are often associated with von Hippel-Lindau (VHL) disease.[5,6] Approximately one-third of hemangioblastomas are associated with VHL, whereas remaining cases occur sporadically.[5,7–9]

Supratentorial hemangioblastomas are exceedingly rare. Because of the rarity of hemangioblastomas in this location, the literature is primarily composed of case reports and small series. Little information is available regarding the clinical features of these tumors, particularly in comparison with lesions found in other locations. No consensus is currently available regarding appropriate management approaches for supratentorial hemangioblastomas or whether supratentorial hemangioblastoma is part of the stigmata of VHL.

To supplement the current understanding of the clinical significance and management of supratentorial hemangioblastoma, we systematically reviewed the published literature to determine what is known about the presentation and clinical course in patients with this disease. Where possible, we performed statistical analysis to determine the efficacy of various treatment approaches using the existing body of published patient data.

Materials and Methods

Article Selection

A comprehensive systematic review of the English-language literature was performed. Articles were

Received March 6, 2012; accepted May 2, 2012.

Corresponding Author: Andrew T. Parsa, MD, PhD, Department of Neurological Surgery, University of California at San Francisco, 505 Parnassus Ave., San Francisco, CA 94117 (parsaa@neurosurg.ucsf.edu).

identified via PubMed search using the key words "hemangioblastoma" and "haemangioblastoma" alone and in combination with the key words "capillary" and "supratentorial." All references of these articles were then searched to extract data on patients who underwent surgery for supratentorial hemangioblastoma. A total of 1052 articles was identified, of which 106 had patient data regarding supratentorial hemangioblastomas.

All references that contained individual patient data or purely supratentorial aggregated data sets of either histologically confirmed tumors or tumors presenting in the context of confirmed diagnosis of VHL disease were included in our analysis. Patients with tumors unrelated to hemangioblastoma or VHL disease were excluded from all analyses.

Data Extraction

Data from individual and aggregated case series were extracted from each article. The median largest tumor dimension and median tumor volume were not reportable or analyzable in our analysis, because studies did not consistently report either value. Patients were considered to have VHL disease if the study reported that they met clinical diagnostic criteria or genetic testing requirements. A clinical diagnosis was made if patients met either of the following 2 criteria: (1) a family history of VHL disease in conjunction with a CNS hemangioblastoma, pheochromocytoma, or clear cell renal carcinoma or (2) $\geq$2 CNS hemangioblastomas or 1 CNS hemangioblastoma and a visceral tumor, excluding epididymal and renal cysts.[10]

Statistical Analysis

Pearson' χ^2 test was used to analyze differences in preoperative categorical factors. Fisher's exact test was used if there were $<$five values per cell. Kaplan-Meier analysis was used to generate time to progression curves. Differences in time to progression were analyzed using the log-rank test. Analyses were performed using the statistical software package PASW Statistics 18 (IBM).

Results

Clinical Characteristics

The literature search yielded a total of 106 references[2,4,6,11–112] meeting the inclusion criteria, containing data on 132 patients with supratentorial hemangioblastomas (Table 1). There was a slight male preponderance (53%), and the median age was 35 years. The most common presenting symptom was headache (39%), followed by visual changes (28%) and paresis (21%). Most patients with supratentorial hemangioblastoma reported in the literature (60%) received a diagnosis of VHL disease.

Table 1. Patient, tumor, and treatment characteristics

Characteristic	*n*/total (%)
Sex	
Male	69/129 (53)
Female	60/129 (47)
Median age in years (range)	35 (0.1–85)
Symptom	
Headache	48/122 (39)
Nausea	34/122 (28)
Visual	26/122 (21)
Gait	22/122 (18)
Mental status	22/122 (18)
Seizures	22/122 (18)
Abnormal Gait	15/122 (12)
Cystic	35/105 (33)
Solid	67/105 (67)
VHL disease	59/99 (35)
Solitary tumor	88/125 (70)
Surgery	
Biopsy	3/79 (4)
Subtotal	15/79 (19)
Gross total	61/79 (77)
Radiation therapy	
Yes	11/133 (8)
No	116/133 (87)
Radiosurgery/Gamma knife	6/133 (5)

Table 2. Tumor locations

Location	*n*/total (%)
Cerebral	85/147 (58)
Sellar/suprasellar	38/147 (26)
Intraventricular	15/147 (10)
All other locations	9/147 (6)

Of the 131 patients with available tumor location data, 147 supratentorial tumors were identified (Table 2). Eighty-five tumors (58%) were found in the cerebrum, 38 (26%) were found in the sellar/suprasellar region, 15 (10%) were intraventricular, and 9 (6%) were in other locations. One-third of the tumors (33%) were found to be cystic, whereas the majority were solid (67%).

Of the 79 patients with data describing extent of resection, 3 (4%) underwent a biopsy procedure, 15 (19%) underwent subtotal resection (STR), and 61 (77%) underwent gross-total resection (GTR). Five percent of patients underwent postsurgical treatment with fractionated radiotherapy. Follow-up ranged from 0 to 276 months in these studies.

GTR Provides Optimal Progression-Free Survival

Of the 79 cases that reported extent of resection, 61 (77%) achieved GTR. Of the 15 tumors that had STR,

only 2 (13%) were in noneloquent locations and 1 (7%) in an unknown location. All other tumors were in eloquent or hazardous locations (Table 3). Analysis suggested that patients undergoing GTR experienced a significant improvement in progression-free survival (PFS), compared with those receiving STR (5-year PFS: GTR 100% vs STR 53%; log rank, $P < .01$) (Fig. 1). Further analysis suggested that patients undergoing GTR experienced a significant improvement in PFS, compared with those receiving fractionated radiotherapy (RT) alone (5-year PFS: GTR 100% vs RT 33%; log rank, $P < .001$) (Fig. 2). All patients receiving fractionated RT as the only treatment modality had presumed hemangioblastoma based on diagnosis of VHL disease.

Because of limitations of the available data on survival, survival analysis provided no significant results for specific treatment modalities. Overall 5-year survival was 88%, with all 8 total deaths occurring within the first 2 years after diagnosis.

Table 3. Location of subtotally resected tumors

Location	*n*/total (%)
Sub-total resection	
Eloquent cerebral	5/15 (33)
Non-eloquent cerebral	2/15 (13)
Suprasellar	3/15 (20)
Intrasellar	2/15 (13)
Intraventricular	2/15 (13)
Unknown	1/15 (7)

Solid Tumors Are Associated with Earlier Recurrence

Of the 105 cases that reported tumor composition, 35 tumors (33%) were reported to have a cystic component. There was a trend toward significance in the association between presence of cysts and PFS; patients with cystic tumors were less likely to present with progression than were those with solid tumors (5-year PFS: cystic 100% vs solid 76%; Log rank, $P = .110$) (Fig. 3). Analysis revealed no significance in the

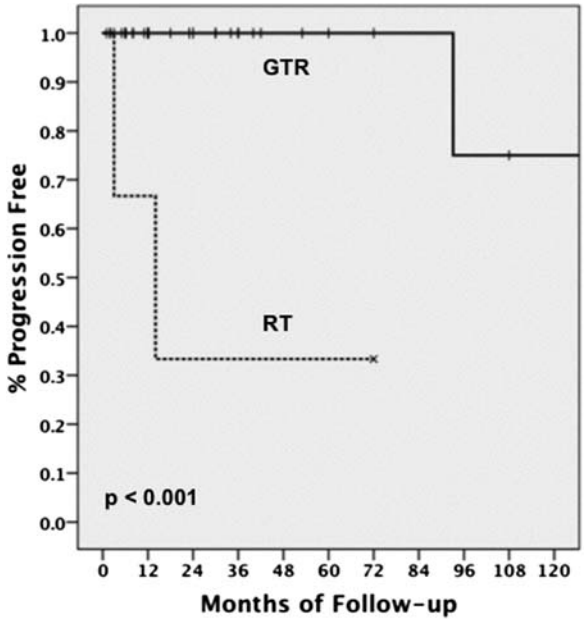

Fig. 2. Rate of progression-free survival among patients with gross-total resection (GTR) and radiation therapy (RT) of tumors.

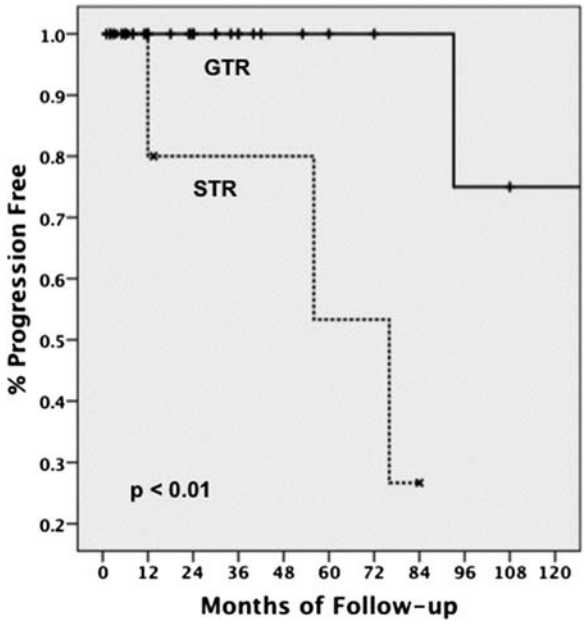

Fig. 1. Rate of progression-free survival among patients with gross-total resection (GTR) and subtotal resection (STR) of tumors.

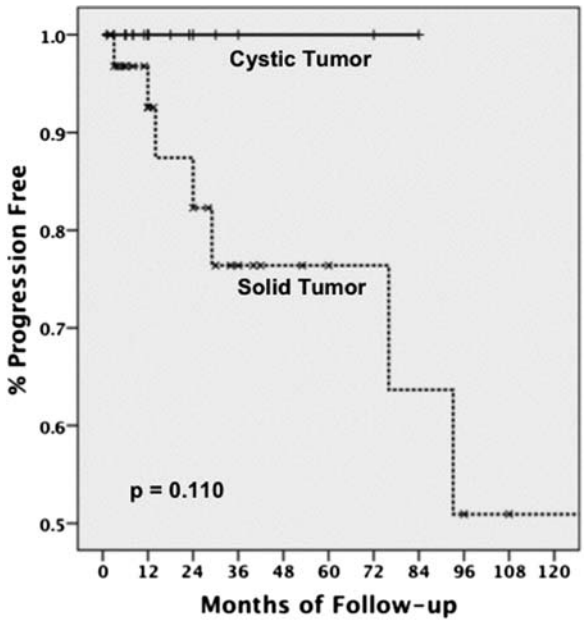

Fig. 3. Rate of progression-free survival among patients with cystic tumors and solid tumors.

association between cystic tumors and extent of resection (χ^2, $P = .973$).

Supraselllar Hemangioblastomas Are Associated with VHL Disease

To determine whether location was an indicator of VHL disease, we compared tumor location with VHL status. A significant association was found between tumors found in the sellar/suprasellar location and diagnosis of VHL disease (χ^2, $P < .001$). When stratified by age, sex, and cystic composition, the association remained significant. No other significant association was found between tumor location and VHL disease.

Discussion

CNS hemangioblastomas, especially multiple hemangioblastomas, are the most common manifestation of VHL disease. Approximately 80% of all patients with VHL develop CNS hemangioblastomas.[10] Although most VHL-associated hemangioblastomas are found in the cerebellum, brainstem, or spinal cord,[113–115] supratentorial hemangioblastomas are rare,[6,8,67,115] with little information in the literature to guide management. Our principle goal was to identify features of these tumors that would not be immediately obvious by reading isolated case reports.

Supratentorial hemangioblastomas are rare and have been reported to comprise only 1%–6% of all hemangioblastomas associated with VHL disease.[8,10,116] Peyre et al. screened 409 patients with VHL disease in the French-speaking VHL Study Group database from 1981 through 2008 and only found 13 patients (3.2%) harboring 18 supratentorial tumors, where 4 patients had multiple tumors.[8] Six (33.3%) of 18 patients presented with symptoms, with the main symptom being increased intracranial pressure. Of more importance, among 14 tumors with documented serial imaging, 13 tumors showed growth, suggesting that these tumors show high propensity for growth.[8] By comparison, a large series reported by Wanebo et al. consisting of 373 hemangioblastomas located primarily in the cerebellum, brainstem, and spinal cord (nonsupratentorial locations) reported only 44% tumor growth.[115] Thus, a higher percentage of supratentorial hemangioblastomas (92.9%) seems to grow during follow-up, compared with infratentorial and spinal cord hemangioblastomas (44%), based on the small number of supratentorial hemangioblastomas reported by Peyre et al.[8]

Hemangioblastoma is currently considered to be a grade I meningeal neoplasm of uncertain origin according to the latest World Health Organization classification of CNS tumors.[117] Despite its benign histology, hemangioblastomas can cause symptoms because of mass effect on the surrounding structures by tumor growth, cyst formation/growth, and peritumoral edema. Thus, surgery has been the mainstay treatment for CNS hemangioblastomas with good outcomes. In series by Jagannathan et al., 98% of patients with VHL disease who underwent resection of cerebellar hemangioblastomas had improved or stabilized symptoms 3 months after surgery.[5] Consistent with this finding, our analysis of the available data suggests that GTR alone provides excellent tumor control rates, particularly if the tumor lacks a cystic component. Solid tumors seem to have a higher rate of recurrence. Because of insufficient data, we were unable to statistically analyze the efficacy of STR plus adjuvant RT in extending PFS, especially when GTR cannot be achieved safely.

In our analysis of PFS for fractionated RT as the sole treatment modality for supratentorial hemangioblastomas, RT was found to be inferior to GTR. Reported rates of 5-year PFS for fractionated RT for all CNS hemangioblastomas (combined primary treatment modality and adjuvant therapy) range from 33% to 90.5%.[118–120] Evidence suggests that high-dose RT provides greater PFS; Smalley et al. reported 57% 5-year PFS for patients receiving $\geq$50 Gy external beam RT, compared with 33% for patients receiving $<$50 Gy, whereas Sung et al. reported 90.5% 5-year PFS for patients receiving 40–55 Gy, compared with 54.5% for those receiving 20–36 Gy.

Although not enough data were available to analyze the effectiveness of stereotactic radiosurgery on supratentorial hemangioblastomas, reported rates of 5-year PFS for all CNS hemangioblastomas for both VHL and sporadic cases ranges from 63% to 85%.[118,121–125] Evidence suggests that GTR should be the primary goal for the treatment of supratentorial hemangioblastomas; however, in cases in which lesions occur in eloquent, inoperable locations or only STR can be achieved, stereotactic radiosurgery or high-dose adjuvant RT should be considered as alternate treatment modalities.

Among all patients with CNS hemangioblastomas, 33%–38% concurrently receive a diagnosis of VHL disease.[5,7–9] Patients with VHL tend to form CNS hemangioblastomas at a younger age, have multiple tumors, and develop new tumors throughout their lifetime, compared with those with sporadic hemangioblastomas.[7,75] One study by Conway et al. reported that 53% of patients with VHL harbor multiple hemangioblastomas and have more prevalent spinal hemangioblastomas.[7] Moreover, 67% of VHL patients developed new CNS hemangioblastomas during the follow-up at a rate of new tumor every 2.1 years.[7] Surgical outcomes were similarly favorable in both groups, with a low complication rate of 15%, which was similar for the VHL-associated supratentorial hemangioblastomas.[8] Because patients with VHL are at a high risk for new tumor formation and surgery provides good outcomes at a relatively low risk, a close follow-up with serial imaging is recommended in patients with VHL with CNS hemangioblastomas. Moreover, hemangioblastomas in patients with VHL have high propensity for tumor growth (92.9%),[8] compared with sporadic cases (44%).[115] Thus, those patients with supratentorial hemangioblastomas should be followed up closely, because our results indicate high incidence of VHL disease in patients harboring tumors at this location.

Asymptomatic lesions should be carefully followed up with a low threshold for surgical resection with development of new symptoms given low risks involved with surgery.[7,8] For example, Peyre et al. reported postoperative focal neurological deficits in 15% of patients after supratentorial hemangioblastoma resection, all of which ultimately improved.[8] Although the primary objective of surgery is to resect the symptomatic tumor, other lesions can be considered for resection if they are easily accessible with the same approach. In one study by Jagannathan et al., a total of 164 cerebellar hemangioblastomas were resected during 126 operations, in which 136 tumors were symptomatic (83%) and 28 tumors were asymptomatic (17%) tumors that were easily accessible during the same surgery.[5] Because of the high propensity for tumor growth for VHL-associated hemangioblastomas,[8] careful preoperative planning should be conducted, especially in patients with VHL with multiple tumors.

In our study, we found that the rate of occurrence of VHL disease is significantly greater in patients with supratentorial hemangioblastoma, with 60% of patients receiving a diagnosis of VHL disease. Tumors located in the sellar/suprasellar region are even more likely to be associated with VHL disease, with 84% of patients with tumors in this location having associated VHL disease. Considering the high rate of occurrence of VHL disease in association with hemangioblastomas in the sellar/suprasellar region, we suggest that sellar/suprasellar hemangioblastomas be considered part of the stigmata of VHL disease, and the clinical suspicion of VHL disease should be raised in patients with supratentorial hemangioblastomas in the sellar/suprasellar region.

Study Limitations

As a retrospective study, this review is limited by the data available and may reflect source study biases. The diverse range of available data limits the number of variables that can be analyzed and controlled. Variables of possible interest, such as tumor volume and histological variants, were reported inconsistently and could not be analyzed.

Conclusion

In conclusion, we report patient, tumor, and treatment characteristics for previously published cases of supratentorial hemangioblastomas. GTR appears to be superior, compared with other treatment modalities, in extending PFS. VHL disease is positively correlated with supratentorial hemangioblastoma, compared with nonsupratentorial CNS hemangioblastomas, particularly when present in the sellar/suprasellar region. Because of the relative rarity of this tumor, this study aims to accurately describe outcome and tumor location characteristics using a data set that would be difficult to accumulate at a single center treating this tumor.

Acknowledgments

Conflict of interest statement. None declared.

Funding

This work was supported by the National Institutes of Health (National Research Service Award to F32NS073326-01 to M.O., F32NS066719-01 to M.S.), the Doris Duke Charitable Foundation (to M.R.), and the Reza and Georgianna Khatib Endowed Chair in Skull Base Tumor Surgery (A.T.P.).

References

1. Toyoda H, Seki M, Nakamura H, Inoue Y, Yamano Y, Takaoka K. Intradural extramedullary hemangioblastoma differentiated by MR images in the cervical spine: a case report and review of the literature. *J Spinal Disord Tech*. 2004;17(4):343–347.
2. Acikalin MF, Oner U, Tel N, Pasaoglu O, Altinel F. Supratentorial hemangioblastoma: a case report and review of the literature. *Arch Pathol Lab Med*. 2003;127(9):e382–e384.
3. Hussein MR. Central nervous system capillary haemangioblastoma: the pathologist's viewpoint. *Int J Exp Pathol*. 2007;88(5):311–324.
4. Wasenko JJ, Rodziewicz GS. Suprasellar hemangioblastoma in Von Hippel-Lindau disease: a case report. *Clin Imaging*. 2003;27(1):18–22.
5. Jagannathan J, Lonser RR, Smith R, DeVroom HL, Oldfield EH. Surgical management of cerebellar hemangioblastomas in patients with von Hippel-Lindau disease. *J Neurosurg*. 2008;108(2):210–222.
6. Lonser RR, Butman JA, Kiringoda R, Song D, Oldfield EH. Pituitary stalk hemangioblastomas in von Hippel-Lindau disease. *J Neurosurg*. 2009;110(2):350–353.
7. Conway JE, Chou D, Clatterbuck RE, Brem H, Long DM, Rigamonti D. Hemangioblastomas of the central nervous system in von Hippel-Lindau syndrome and sporadic disease. *Neurosurgery*. 2001;48(1):55–62; discussion -3.
8. Peyre M, David P, Van Effenterre R, et al. Natural history of supratentorial hemangioblastomas in von Hippel-Lindau disease. *Neurosurgery*. 2010;67(3):577–587; discussion 87.
9. Richard S, Graff J, Lindau J, Resche F. Von Hippel-Lindau disease. *Lancet*. 2004;363(9416):1231–1234.
10. Lonser RR, Glenn GM, Walther M, et al. von Hippel-Lindau disease. *Lancet*. 2003;361(9374):2059–2067.
11. Adegbite AB, Rozdilsky B, Varughese G. Supratentorial capillary hemangioblastoma presenting with fatal spontaneous intracerebral hemorrhage. *Neurosurgery*. 1983;12(3):327–330.
12. Agostinelli C, Roncaroli F, Galassi E, Bernardi B, Acciarri N, Tani G. Leptomeningeal hemangioblastoma. Case illustration. *J Neurosurg*. 2004;101(suppl 1):122.

13. Albrechtsen R. Supratentorial haemangioblastoma. *Dan Med Bull*. 1971;18(4):73–75.
14. Bachmann K, Markwalder R, Seiler RW. Supratentorial haemangioblastoma. Case report. *Acta Neurochir (Wien)*. 1978;44(3–4):173–177.
15. Baggenstos M, Chew E, Butman JA, Oldfield EH, Lonser RR. Progressive peritumoral edema defining the optic fibers and resulting in reversible visual loss. *J Neurosurg*. 2008;109(2):313–317.
16. Balcer LJ, Galetta SL, Curtis M, Maguire A, Judy K. von Hippel-Lindau disease manifesting as a chiasmal syndrome. *Surv Ophthalmol*. 1995;39(4):302–306.
17. Black ML, Tien RD, Hesselink JR. Third ventricular hemangioblastoma: MR appearance. *AJNR Am J Neuroradiol*. 1991;12(3):553.
18. Boughey AM, Fletcher NA, Harding AE. Central nervous system haemangioblastoma: a clinical and genetic study of 52 cases. *J Neurol Neurosurg Psychiatry*. 1990;53(8):644–648.
19. Chakraborti PR, Chakrabarti KB, Doughty D, Plowman PN. Stereotactic multiple are radiotherapy. IV–Haemangioblastoma. *Br J Neurosurg*. 1997;11(2):110–115.
20. Cosar M, Hatiboglu MA, Iplikcioglu AC, Ozcan D. Parasagittal leptomeningeal hemangioblastoma–case report. *Neurol Med Chir (Tokyo)*. 2006;46(6):294–297.
21. Courcoutsakis NA, Prassopoulos PK, Patronas NJ. Aggressive leptomeningeal hemangioblastomatosis of the central nervous system in a patient with von Hippel-Lindau disease. *AJNR Am J Neuroradiol*. 2009;30(4):758–760.
22. Crivelli G, Dario A, Cerati M, Dorizzi A. Solid supratentorial haemangioblastoma. Case report. *J Neurosurg Sci*. 1992;36(3):161–166.
23. D'Aliberti G, Mancuso P, Chiaramonte I, Giuffrida S, Lombardo M, Tropea R. Supratentorial haemangioblastomas. Report of two cases. *Acta Neurol (Napoli)*. 1986;8(6):639–647.
24. Dan NG, Smith DE. Pituitary hemangioblastoma in a patient with von Hippel-Lindau disease. Case report. *J Neurosurg*. 1975;42(2):232–235.
25. Deck JH, Rubinstein LJ. Glial fibrillary acidic protein in stromal cells of some capillary hemangioblastomas: significance and possible implications of an immunoperoxidase study. *Acta Neuropathol*. 1981;54(3):173–181.
26. Di Lorenzo N, Spallone A, Morselli E. Cerebral and cerebellar haemangioblastoma occurring in the same patient. *Ital J Neurol Sci*. 1983;4(1):99–102.
27. Diehl PR, Symon L. Supratentorial intraventricular hemangioblastoma: case report and review of literature. *Surg Neurol*. 1981;15(6):435–443.
28. Elster AD, Arthur DW. Intracranial hemangioblastomas: CT and MR findings. *J Comput Assist Tomogr*. 1988;12(5):736–739.
29. Ferrante L, Acqui M, Mastronardi L, Fortuna A. Supratentorial hemangioblastoma. Report of a case and review of the literature. *Zentralbl Neurochir*. 1988;49(3):151–161.
30. Ferrante L, Celli P, Fraioli B. Supratentorial haemangioblastomas in children. Case report. *Acta Neurochir (Wien)*. 1982;62(3–4):241–246.
31. Fomekong E, Hernalsteen D, Godfraind C, D'Haens J, Raftopoulos C. Pituitary stalk hemangioblastoma: the fourth case report and review of the literature. *Clin Neurol Neurosurg*. 2007;109(3):292–298.
32. Fu Y, Ward J, Young HF. Unusual, rod-shaped cytoplasmic inclusions (Hirano bodies) in a cerebellar hemangioblastoma. *Acta Neuropathol*. 1975;31(2):129–135.
33. Ginzburg BM, Montanera WJ, Tyndel FJ, et al. Diagnosis of von Hippel-Lindau disease in a patient with blindness resulting from bilateral optic nerve hemangioblastomas. *AJR Am J Roentgenol*. 1992;159(2):403–405.
34. Goto T, Nishi T, Kunitoku N, et al. Suprasellar hemangioblastoma in a patient with von Hippel-Lindau disease confirmed by germline mutation study: case report and review of the literature. *Surg Neurol*. 2001;56(1):22–26.
35. Grisoli F, Gambarelli D, Raybaud C, Guibout M, Leclercq T. Suprasellar hemangioblastoma. *Surg Neurol*. 1984;22(3):257–262.
36. Hande AM, Nagpal RD. Cerebellar haemangioblastoma with extensive dissemination. *Br J Neurosurg*. 1996;10(5):507–511.
37. Hankey GJ, Davies L, Gubbay SS. Long term survival with early childhood intracerebral tumours. *J Neurol Neurosurg Psychiatry*. 1989;52(6):778–781.
38. Ho YS, Plets C, Goffin J, Dom R. Hemangioblastoma of the lateral ventricle. *Surg Neurol*. 1990;33(6):407–412.
39. Hoang MP, Amirkhan RH. Inhibin alpha distinguishes hemangioblastoma from clear cell renal cell carcinoma. *Am J Surg Pathol*. 2003;27(8):1152–1156.
40. Hoff JT, Ray BS. Cerebral hemangioblastoma occurring in a patient with von Hippel-Lindau disease. Case report. *J Neurosurg*. 1968;28(4):365–368.
41. Ikeda M, Asada M, Yamashita H, Ishikawa A, Tamaki N. [A case of suprasellar hemangioblastoma with thoracic meningioma]. *No Shinkei Geka*. 2001;29(7):679–683.
42. Iplikcioglu AC, Yaradanakul V, Trakya U. Supratentorial haemangioblastoma: appearances on MR imaging. *Br J Neurosurg*. 1997;11(6):576–578.
43. Isaka T, Horibe K, Nakatani S, Maruno M, Yoshimine T. Hemangioblastoma of the third ventricle. *Neurosurg Rev*. 1999;22(2–3):140–144.
44. Ishwar S, Taniguchi RM, Vogel FS. Multiple supratentorial hemangioblastomas. Case study and ultrastructural characteristics. *J Neurosurg*. 1971;35(4):396–405.
45. Isolan GR, Krayenbuhl N, Mahmoud M, Al-Mefty O. A hemangioblastoma in the pineal region: case report. *Neurosurgery*. 2007;61(2):E423; discussion E.
46. Jang H. Supratentorial leptomeningeal hemangioblastoma: case report. *Yeungnam University J of Med. [Case Report]*. 2007;24(suppl 2):S770–S774.
47. Jeffreys RV. Supratentorial haemangioblastoma. *Acta Neurochirurgica*. 1974;31(1–2):55–65.
48. Johnson MD, Mitchell AR, Troup EC, et al. Congenital cystic hemangioblastomas of the cerebral hemisphere in a neonate without alteration in the VHL gene. *Pediatr Neurosurg*. 2004;40(3):124–127.
49. Jung SM, Kuo TT. Immunoreactivity of CD10 and inhibin alpha in differentiating hemangioblastoma of central nervous system from metastatic clear cell renal cell carcinoma. *Mod Pathol*. 2005;18(6):788–794.
50. Jyotsna VP, Singh SK, Chaturvedi R, et al. Cranial irradiation–an unusual cause for diabetes insipidus. *J Assoc Physicians India*. 2000;48(11):1107–1108.
51. Kachhara R, Nair S, Radhakrishnan VV. Sellar-sphenoid sinus hemangioblastoma: case report. *Surg Neurol*. 1998;50(5):461–463; discussion 3–4.
52. Karabagli H, Karabagli P, Alpman A, Durmaz B. Congenital supratentorial cystic hemangioblastoma. Case report and review of the literature. *J Neurosurg*. 2007;107(suppl 6):515–518.
53. Katayama Y, Tsubokawa T, Miyagi A, Goto T, Miyagami M, Suzuki K. Solitary hemangioblastoma within the third ventricle. *Surg Neurol*. 1987;27(2):157–162.
54. Keith J, Ang LC, Megyesi J. Cytodiagnosis of supratentorial hemangioblastoma. *Acta Cytol*. 2008;52(2):260–263.

55. Kepes JJ, Rengachary SS, Lee SH. Astrocytes in hemangioblastomas of the central nervous system and their relationship to stromal cells. *Acta Neuropathol*. 1979;47(2):99–104.
56. Kerr DJ, Scheithauer BW, Miller GM, Ebersold MJ, McPhee TJ. Hemangioblastoma of the optic nerve: case report. *Neurosurgery*. 1995;36(3):573–580; discussion 80–81.
57. Kim JM, Cheong JH, Bak KH, Kim CH, Park DW, Oh YH. Congenital supratentorial hemangioblastoma as an unusual cause of simultaneous supra- and infratentorial intracranial hemorrhage: case report. *J Neurooncol*. 2006;77(1):59–63.
58. Kouri JG, Chen MY, Watson JC, Oldfield EH. Resection of suprasellar tumors by using a modified transsphenoidal approach. Report of four cases. *J Neurosurg*. 2000;92(6):1028–1035.
59. Lee KR, Kishore PR, Wulfsberg E, Kepes JJ. Supratentorial leptomeningeal hemangioblastoma. *Neurology*. 1978;28(7):727–730.
60. Leibner IW. Brain tumors in infancy; a report of seven cases. *Pediatrics*. 1948;1(3):346–363.
61. Leung SY, Chan AS, Wong MP, Yuen ST, Fan YW, Chung LP. Expression of vascular endothelial growth factor in von Hippel-Lindau syndrome-associated papillary cystadenoma of the epididymis. *Hum Pathol*. 1998;29(11):1322–1324.
62. Liang L, Korogi Y, Sugahara T, et al. Dynamic MR imaging of neurohypophyseal germ cell tumors for differential diagnosis of infundibular diseases. *Acta Radiol*. 2000;41(6):562–566.
63. Lindvall P, Brannstrom T. Spontaneous regression of two putative supratentorial haemangioblastomas in one patient. *Acta Neurochir (Wien)*. 2008;150(1):73–76; discussion 6.
64. Loftus CM, Marquardt MD, Stein BM. Hemangioblastoma of the third ventricle. *Neurosurgery*. 1984;15(1):67–72.
65. Maiuri F. Cysts with mural tumor nodules in the cerebral hemispheres. *Neurosurgery*. 1988;22(4):703–706.
66. McDonnell DE, Pollock P. Cerebral cystic hemangioblastoma. *Surg Neurol*. 1978;10(3):195–199.
67. Meyerle CB, Dahr SS, Wetjen NM, et al. Clinical course of retrobulbar hemangioblastomas in von Hippel-Lindau disease. *Ophthalmology*. 2008;115(8):1382–1389.
68. Miller MH, Tucker WS, Bilbao JM. Supratentorial hemangioblastoma associated with Von Hippel Lindau disease: case report and review of the literature. *Can Assoc Radiol J*. 1986;37(1):35–37.
69. Miyagami M, Katayama Y. Long-term prognosis of hemangioblastomas of the central nervous system: clinical and immunohistochemical study in relation to recurrence. *Brain Tumor Pathol*. 2004;21(2):75–82.
70. Miyata S, Mikami T, Minamida Y, Akiyama Y, Houkin K. Suprasellar hemangioblastoma. *J Neuroophthalmol*. 2008;28(4):325–326.
71. Mizuno J, Iwata K, Takei Y. Immunohistochemical study of hemangioblastoma with special reference to its cytogenesis. *Neurol Med Chir (Tokyo)*. 1993;33(7):420–424.
72. Morello G, Bianchi M. Cerebral Hemangioblastomas: Review of Literature and Report of Two Personal Cases. *J Neurosurg*. 1963;20:254–264.
73. Moss JM, Choi CY, Adler JR, Jr, Soltys SG, Gibbs IC, Chang SD. Stereotactic radiosurgical treatment of cranial and spinal hemangioblastomas. *Neurosurgery*. 2009;65(1):79–85; discussion.
74. Murali R, Jones WI, Ma Wyatt J. A 57-year-old man with a dural-based parietal lobe tumor. *Brain Pathol*. 2007;17(4):460–463, 74.
75. Neumann HP, Eggert HR, Weigel K, Friedburg H, Wiestler OD, Schollmeyer P. Hemangioblastomas of the central nervous system. A 10-year study with special reference to von Hippel-Lindau syndrome. *J Neurosurg*. 1989;70(1):24–30.
76. Niemela M, Lim YJ, Soderman M, Jaaskelainen J, Lindquist C. Gamma knife radiosurgery in 11 hemangioblastomas. *J Neurosurg*. 1996;85(4):591–596.
77. O'Reilly GV, Rumbaugh CL, Bowens M, Kido DK, Naheedy MH. Supratentorial haemangioblastoma: the diagnostic roles of computed tomography and angiography. *Clin Radiol*. 1981;32(4):389–392.
78. Ohata K, Takami T, Tsuyuguchi N, Hara M, Haque M. Hemangioblastoma of hippocampus without von Hippel-Lindau disease: case report and review of literature. *Neurol India*. 2006;54(1):89–90.
79. Orakcioglu B, Sakowitz OW, Perren A, Heppner FL, Yonekawa Y. An unusual case of a highly progressive supratentorial capillary haemangioblastoma - histopathological considerations. *Acta Neurochir (Wien)*. 2007;149(4):419–423.
80. Ozveren MF, Topsakal C, Erol FS, Kaplan M, Uchida K, Tanik C. Tentorial vascularization in solid hemangioblastoma–case report. *Neurol Med Chir (Tokyo)*. 2001;41(4):201–205.
81. Pan L, Wang EM, Wang BJ, et al. Gamma knife radiosurgery for hemangioblastomas. *Stereotact Funct Neurosurg*. 1998;70(suppl 1): 179–186.
82. Peker S, Kurtkaya-Yapicier O, Sun I, Sav A, Pamir MN. Suprasellar haemangioblastoma. Report of two cases and review of the literature. *J Clin Neurosci*. 2005;12(1):85–89.
83. Perks WH, Cross JN, Sivapragasam S, Johnson P. Supratentorial haemangioblastoma with polycythaemia. *J Neurol Neurosurg Psychiatry*. 1976;39(3):218–220.
84. Peyre M, Di Rocco F, Varlet P, et al. Supratentorial hemangioblastoma in the neonatal period. *Pediatr Neurosurg*. 2009;45(2):155–156.
85. Pinto JA, Pereira JR, Guimaraes A, Veiga-Pires JA. The value of CT-scanning in supratentorial haemangioblastomas. *Neuroradiology*. 1987;29(6):573–575.
86. Prieto R, Roda JM. Hemangioblastoma of the lateral ventricle: case report and review of the literature. *Neurocirugia (Astur)*. 2005;16(1):58–62.
87. Rachinger J, Buslei R, Prell J, Strauss C. Solid haemangioblastomas of the CNS: a review of 17 consecutive cases. *Neurosurg Rev*. 2009;32(1):37–47; discussion -8.
88. Raila FA, Zimmerman J, Azordegan P, Fratkin J, Parent AD. Successful surgical removal of an asymptomatic optic nerve hemangioblastoma in von Hippel-Lindau disease. *J Neuroimaging*. 1997;7(1):48–50.
89. Rho YM. Von Hippel-Lindau's disease: a report of five cases. *Can Med Assoc J*. 1969;101(3):135–142.
90. Richmond BK, Schmidt JH, 3rd. Congenital cystic supratentorial hemangioblastoma. Case report. *J Neurosurg*. 1995;82(1):113–115.
91. Rickert CH, Hasselblatt M, Jeibmann A, Paulus W. Cellular and reticular variants of hemangioblastoma differ in their cytogenetic profiles. *Hum Pathol*. 2006;37(11):1452–1457.
92. Rivera E, Chason JL. Cerebral hemangioblastoma. Case report. *J Neurosurg*. 1966;25(4):452–454.
93. Roberti F, Jones RV, Wright DC. Cranial nerve hemangioblastomas. Report of a rare case and review of literature. *Surg Neurol*. 2007;67(6):640–646; discussion 6.
94. Romero FJ, Rovira M, Ortega A, Ibarra B. Computed tomography in supratentorial hemangioblastoma. *Comput Radiol*. 1984; 8(5):319–323.
95. Rumboldt Z, Gnjidic Z, Talan-Hranilovic J, Vrkljan M. Intrasellar hemangioblastoma: characteristic prominent vessels on MR imaging. *AJR Am J Roentgenol*. 2003;180(5):1480–1481.

96. Sajadi A, de Tribolet N. Unusual locations of hemangioblastomas. Case illustration. *J Neurosurg*. 2002;97(3):727.
97. Sawin PD, Follett KA, Wen BC, Laws ER, Jr. Symptomatic intrasellar hemangioblastoma in a child treated with subtotal resection and adjuvant radiosurgery. Case report. *J Neurosurg*. 1996; 84(6):1046–1050.
98. Sharma RR, Cast IP, O'Brien C. Supratentorial haemangioblastoma not associated with Von Hippel Lindau complex or polycythaemia: case report and literature review. *Br J Neurosurg*. 1995; 9(1):81–84.
99. Sherman JH, Le BH, Okonkwo DO, Jane JA. Supratentorial dural-based hemangioblastoma not associated with von Hippel Lindau complex. *Acta Neurochir (Wien)*. 2007;149(9):969–972; discussion 72.
100. Sobottka SB, Frank S, Hampl M, Schackert HK, Schackert G. Multiple intracerebral haemangioblastomas in identical twins with von Hippel-Lindau disease–a clinical and molecular study. *Acta Neurochir (Wien)*. 1998;140(3):281–285.
101. Stefani FH, Rothemund E. Intracranial optic nerve angioblastoma. *Br J Ophthalmol*. 1974;58(9):823–827.
102. Stein AA, Schilp AO, Whitfield RD. The histogenesis of hemangioblastoma of the brain. A review of twenty-one cases. *J Neurosurg*. 1960;17:751–761.
103. Takeuchi H, Hashimoto N, Kitai R, Kubota T. A report of supratentorial leptomeningeal hemangioblastoma and a literature review. *Neuropathology*. 2008;28(1):98–102.
104. Tan DS, Evanson J, Plowman PN, Chew SL. Post-radiation inflammatory reaction controlled with thalidomide and rofecoxib. *Clin Oncol (R Coll Radiol)*. 2004;16(8):585–586.
105. Tekkok IH, Sav A. Supratentorial cystic hemangioblastoma with infratentorial extension–a unique location and a rare infant case. *Childs Nerv Syst*. 2006;22(9):1177–1181.
106. Tomaccini D, Cordelli F, Luzi P, Scarfo GB. Supratentorial hemangioblastoma in childhood. *Childs Brain*. 1980;6(6):313–317.
107. Tomasello F, Albanese V, Iannotti F, Di Iorio G. Supratentorial hemangioblastoma in a child. Case report. *J Neurosurg*. 1980; 52(4):578–583.
108. Vuia O. Malignant haemangioblastoma (haemangiosarcoma) of the meninges. *Neurochirurgia (Stuttg)*. 1978;21(5):164–172.
109. Wakai S, Inoh S, Ueda Y, Nagai M. Hemangioblastoma presenting with intraparenchymatous hemorrhage. *J Neurosurg*. 1984;61(5):956–960.
110. Wylie IG, Jeffreys RV, Maclaine GN. Cerebral haemangioblastoma. *Br J Radiol*. 1973;46(546):472–476.
111. Yamakawa N, Noda M, Ohyama T, Furuno M, Tsutsumi A, Taki W. A cellular variant of supratentorial hemangioblastoma. *Brain Tumor Pathol*. 2000;17(1):15–19.
112. Zamzuri I, Ghazali MM, Zainuddin N, et al. Molecular genetic analysis of a supratentorial haemangioblastoma in a non-Von Hippel Lindau patient. *Med J Malaysia*. 2005;60(3):360–363.
113. 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(2):248–255.
114. Slater A, Moore NR, Huson SM. The natural history of cerebellar hemangioblastomas in von Hippel-Lindau disease. *AJNR Am J Neuroradiol*. 2003;24(8):1570–1574.
115. 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(1):82–94.
116. Neumann HP, Eggert HR, Scheremet R, et al. Central nervous system lesions in von Hippel-Lindau syndrome. *J Neurol Neurosurg Psychiatry*. 1992;55(10):898–901.
117. Louis DN, Ohgaki H, Wiestler OD, et al. The 2007 WHO classification of tumours of the central nervous system. *Acta Neuropathol*. 2007;114(2):97–109.
118. Koh ES, Nichol A, Millar BA, Menard C, Pond G, Laperriere NJ. Role of fractionated external beam radiotherapy in hemangioblastoma of the central nervous system. *Int J Radiat Oncol Biol Phys*. 2007;69(5):1521–1526.
119. Smalley SR, Schomberg PJ, Earle JD, Laws ER, Jr, Scheithauer BW, O'Fallon JR. Radiotherapeutic considerations in the treatment of hemangioblastomas of the central nervous system. *Int J Radiat Oncol Biol Phys*. 1990;18(5):1165–1171.
120. Sung DI, Chang CH, Harisiadis L. Cerebellar hemangioblastomas. *Cancer*. 1982;49(3):553–555.
121. Asthagiri AR, Mehta GU, Zach L, et al. Prospective evaluation of radiosurgery for hemangioblastomas in von Hippel-Lindau disease. *Neuro Oncol*. 2010;12(1):80–86.
122. Wang EM, Pan L, Wang BJ, et al. The long-term results of gamma knife radiosurgery for hemangioblastomas of the brain. *J Neurosurg*. 2005;102(suppl):225–229.
123. Rajaraman C, Rowe JG, Walton L, Malik I, Radatz M, Kemeny AA. Treatment options for von Hippel-Lindau's haemangioblastomatosis: the role of gamma knife stereotactic radiosurgery. *Br J Neurosurg*. 2004;18(4):338–342.
124. Jawahar A, Kondziolka D, Garces YI, Flickinger JC, Pollock BE, Lunsford LD. Stereotactic radiosurgery for hemangioblastomas of the brain. *Acta Neurochir (Wien)*. 2000;142(6):641–644; discussion 4–5.
125. Patrice SJ, Sneed PK, Flickinger JC, et al. Radiosurgery for hemangioblastoma: results of a multiinstitutional experience. *Int J Radiat Oncol Biol Phys*. 1996;35(3):493–499.