Neurosurgical Treatments for Adult Patients with VHL

James C. Miller MD
Assistant Professor of Neurological Surgery
IU School of Medicine
Von Hippel-Lindau Disease (VHL)

- Autosomal dominant inherited disorder of the VHL gene on chromosome 3.
- Characteristic lesions:
  - Hemangioblastomas of the brain (cerebellum and brainstem) and spinal cord
  - Retinal angiomatosis
  - Pancreatic cysts
  - Renal cell carcinoma
  - Pheochromocytoma
  - Epididymal cysts
Hemangioblastoma

- Comprises 1-2% of all intracranial tumors.
- Comprises 2-11% of intramedullary spinal cord tumors.
- Grade I (benign) by the World Health Organization (WHO).
- Hemangioblastomas are present in roughly 75% of patients with VHL.
- Whereas 30% of patients with sporadic hemangioblastomas will have VHL.
- Mixture of two cell types
  - Stromal cells
  - Vascular cells
- Stromal cells contain the VHL gene mutation and are the true tumor cells. Vascular cells are reactive.
- The mutation of the VHL protein disrupts the cell’s ability to sense hypoxia and then attempts to increase vascular supply. This leads to the highly vascular network seen in hemangioblastomas.
Loss of *VHL* promotes increased production of angiogenesis producing peptides: vascular endothelial growth factor (VEGF), vascular permeability factor (VPF) and erythropoietin to stimulate RBC production.

Vascular endothelial cell propagation leading to angiogenesis

Plasma exudate between cells
Figure 1 Histological features of cerebellar capillary haemangioblastoma. The tumour is composed of a juxtaposition of variable sized vascular spaces (capillaries with variable sized, closely packed, thin walled vessels), large neoplastic stromal cells (arrowhead) with pink to clear foamy cytoplasm with fine vacuoles, hyperchromatic nuclei and numerous mast cells (arrow) (a–d: H&E stain, ×100, ×100, ×400 and ×1000 respectively). No atypia; no fibrillar cells, no necrosis, and no mitotic figures.
Symptoms related to Hemangioblastoma

- In general it is related to location, caused by enlargement of tumor, cyst, or edema:
  - Headache
  - Vomiting
  - Balance or gait dysfunction
  - Discoordination
  - Double vision
  - Weakness
  - Numbness
  - Back pain
Natural history of hemangioblastomas

The natural history of hemangioblastomas of the central nervous system in patients with von Hippel–Lindau disease

JOHN E. WANEBO, M.D., RUSSELL R. LONSER, M.D., GLADYS M. GLENN, M.D., PH.D., AND EDWARD H. OLDFIELD, M.D.

Surgical Neurology Branch, National Institute of Neurological Disorders and Stroke; Genetic Epidemiology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland; and Department of Neurosurgery, Naval Medical Center, San Diego, California

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

JOSHUA M. AMMERMAN, M.D., RUSSELL R. LONSER, M.D., JAMES DAMBROSIA, PH.D., JOHN A. BUTMAN, M.D., PH.D., AND EDWARD H. OLDFIELD, M.D.

Surgical Neurology Branch and Biostatistics Branch, National Institute of Neurological Disorders and Stroke, and Diagnostic Radiology Department, Warren G. Magnuson Clinical Center, National Institutes of Health, Bethesda, Maryland; and Department of Neurological Surgery, George Washington University Medical Center, Washington, DC
Natural History of Hemangioblastomas

- 650 tumors in 160 patients with long term follow up provides critical information about natural history.
- Most symptoms are related to mass effect from cyst enlargement.
- All tumors and cysts will continue to enlarge over time, none regressed during the study.
- De novo hemangioblastomas often arise in patients with VHL. Over 51 month follow up: 34/160 patients developed 115 new tumors. 15/160 developed new tumor associated cysts.
- In 2006 study, 19 patients with 143 hemangioblastomas were followed for greater than 10 years.
- 97% (138) of the tumors demonstrated measurable growth, only 41% (58) of tumors became symptomatic.
- Growth pattern was in a stuttering pattern: average 13 months of growth and 25 months quiescent.
- Importantly, 26 of the 58 tumors that caused symptoms were not apparent on initial MRI.
- Risk of spontaneous hemorrhage is very low 0.0024 per person per year. This increases in larger tumors typically around 3 cm or larger. (Glasker et al. Neurosurgery 2005).
Recommendations for treatment based on volume

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 98%).

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%).

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%).
Hemangioblastoma treatment options

• Surgical resection
• Gamma knife radiosurgery
• When standard treatments fail: Immunotherapies to angiogenesis are being evaluated in clinical investigations
  • Bevicizamab (Avastin)
  • Panzopanib
Surgical management of brainstem hemangioblastomas in patients with von Hippel–Lindau disease

Robert J. Weil, M.D., Russell R. Lonser, M.D., Hetty L. DeVroom, R.N., John E. Wanebo, M.D., and Edward H. Oldfield, M.D.

Surgical Neurology Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland
MRI images of hemangioblastomas of brainstem

R. J. Weil, et al.
Surgical management of cerebellar hemangioblastomas in patients with von Hippel–Lindau disease

JAY JAGANNATHAN, M.D.,¹,² RUSSELL R. LONSER, M.D.,¹ RENE SMITH, R.N.,¹
HETTY L. DEVROOM, R.N.,¹ AND EDWARD H. OLDFIELD, M.D.¹

¹Surgical Neurology Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland; and ²Department of Neurological Surgery, University of Virginia Health System, Charlottesville, Virginia
Fig. 4. Enhanced MR images demonstrating 4 types of cerebellar hemangioblastomas that were identified based on the presence or absence of associated cysts. Radiographic tumor types included hemangioblastomas without associated cysts (A), hemangioblastomas with intratumoral cysts (B, asterisk), hemangioblastomas with associated peritumoral cysts (C), and hemangioblastomas associated with both peri- and intratumoral cysts (D, asterisk).
Incise pia at tumor-cerebellar junction

Tumor dissection

Deeper tumor dissection

J. Jagannathan et al.
Gamma Knife Treatment

• Alternative option to surgery in the treatment hemangioblastomas.
• Utilizes focused beam high energy radiation.
Gamma Knife Radiosurgery

- Multidisciplinary team effort
  - Neurosurgeon
  - Radiation Oncologist
  - Medical Physicist
- Provides focused beams of radiation to the tumor with a sharp drop-off to the surrounding brain. Delivered in a single fraction.
- Designed by Lars Leksell in Sweden in 1951 using a stereotactic head frame and focused radiation tube and coined the name “Gamma Knife”.
- Later radiation source changed to radioactive cobalt (Cobalt-60).
Hallmarks of Stereotactic Radiosurgery

• High Precision
  – High degree of reproducible spatial correlation of target to radiation source

• High Accuracy (< 1 mm)
  – Dose delivery within 1 mm of the intended position
  – Gamma Knife is accurate to 0.3 mm per Elekta

• Rapid fall off of radiation dose at the periphery of the target (marginal dose)
  – Will minimize the dose to tissues adjacent to the target

• High Dose conformity
  – Helps to minimize the normal tissue dosage
Gamma Knife

4 mm collimator

Gamma Knife helmet and frame
Gamma Knife Perfexion Unit
Ionizing Radiation Effects

DNA damage

Vascular occlusion
Gamma knife radiosurgery in 11 hemangioblastomas

MIKA NIEMELÄ, M.D., YOUNG JIN LIM, M.D., PH.D., MICHAEL SÖDERMAN, M.D.,
JUHA JÄÄSKELÄINEN, M.D., PH.D., AND CHRISTER LINDQUIST, M.D., PH.D.

Department of Neurosurgery, Helsinki University Hospital, Helsinki, Finland; Department of
Neurosurgery, Kyung Hee University Hospital, Seoul, Korea; and Department of Neuroradiology and
The Gamma Knife Center, Department of Neurosurgery, Karolinska Hospital, Stockholm, Sweden

One suprasellar, one mesencephalic, and nine cerebellar hemangioblastomas were treated with the gamma knife in
10 patients (median age 48 years) in Stockholm between 1978 and 1993. Four patients had von Hippel–Lindau dis-
Gamma knife surgery for hemangioblastomas

MASAO TAGO, M.D., ATSURO TERAHARA, M.D., MASAHIRO SHIN, M.D.,
KEISUKE MARUYAMA, M.D., HIROKI KURITA, M.D., KEEICHI NAKAGAWA, M.D.,
AND KUNI OHTOMO, M.D.

Departments of Radiology and Neurosurgery, University of Tokyo Hospital; Department of Radiology,
Toho University, Omori Hospital; and Department of Neurosurgery, Kyorin University Hospital,
Tokyo, Japan
Gamma knife surgery for multiple hemangioblastomas

Yong Sook Park, M.D, Jong Hee Chang, M.D., Ph.D, Jin Woo Chang, M.D., Ph.D., Sang Sup Chung, M.D., Ph.D, and Yong Gou Park, M.D., Ph.D.

Department of Neurosurgery, Yonsei University College of Medicine, Seoul, Korea
The long-term results of gamma knife radiosurgery for hemangioblastomas of the brain

En-Min Wang, M.D., Ph.D., Li Pan, M.D., Ph.D., Bing-Jiang Wang, M.D., Nan Zhang, M.D., Liang-Fu Zhou, M.D., Ya-Fei Dong, M.D., Jia-Zhong Dai, M.D., Ph.D., Pei-Wu Cai, M.D., and Hong Chen, M.D.

Departments of Neurosurgery and Radiology, Huashan Hospital and Shanghai Gamma Knife Hospital Fudan University, Shanghai Neurosurgical Center, Department of Neuropathology, Hua Shan Hospital, Fudan University Shanghai, China

Object. The authors assessed the long-term result of gamma knife surgery (GKS) for hemangioblastomas of the brain (HABs) and show histopathological findings after GKS.
Combined surgery and radiosurgery

A planned combined stereotactic approach for cystic intracranial tumors

Report of two cases

Wael Abdel Halim Reda, M.D., Ph.D., Alla Abdel Hay, M.D., Ph.D., and Jeremy C. Ganz, M.A., Ph.D., F.R.C.S.
The Gamma Knife Center Cairo, Nasser Institute, Department of Neurosurgery, Ain Shams University, Cairo, Egypt

Same-day stereotactic aspiration and Gamma Knife surgery for cystic intracranial tumors

Clinical article

*Xiomin Liu, M.D., Ph.D.,1 Qi Yu, M.D.,2 Zhiyuan Zhang, M.D.,1 Yippei Zhang, M.D.,1 Yanhe Li, M.D.,1 Dong Liu, M.D.,1 Qiang Jia, M.D., Ph.D.,1 Ligao Zheng, M.D.,1 and Desheng Xu, M.D.1

1Gamma Knife Center, Department of Neurosurgery, Second Hospital of Tianjin Medical University; 2Graduate School of Tianjin Medical University; and 3Huanhu Hospital, Tianjin, People’s Republic of China
Stereotactic radiosurgery for intracranial hemangioblastomas: a retrospective international outcome study

Hideyuki Kano, MD, PhD,1 Takashi Shuto, MD,2 Yoshiyasu Iwai, MD, PhD,3 Jason Sheehan, MD, PhD,4 Masaaki Yamamoto, MD,5 Heyyoung L. McBride, MD,6 Mitsuya Sato, MD, PhD,7 Toru Serizawa, MD, PhD,8 Shoji Yomo, MD, PhD,9 Akihito Moriki, MD, PhD,10 Yukihiko Kohda, MD, PhD,11 Byron Young, MD,12 Satoshi Suzuki, MD, PhD,13 Hiroyuki Kenai, MD, PhD,14 Christopher Duma, MD,15 Yasuhiro Kikuchi, MD, PhD,16 David Mathieu, MD,17 Atsuya Akabane, MD, PhD,18 Osamu Nagano, MD,19 Douglas Kondziolka, MD,20 and L. Dade Lunsford, MD1

1Departments of Neurological Surgery, University of Pittsburgh, Pennsylvania; 2Yokohama Rosai Hospital, Yokohama; 3Osaka City General Hospital, Osaka; 4Katsuta Hospital Mito GammaHouse, Hitachinaka; 5Kitanihon Hospital, Gosen; 6Tsukiji Neurological Clinic, Tokyo; 7Saitama Gamma Knife Center, Saitama; 8Mominoki Hospital, Kochi; 9Asanogawa General Hospital, Kanazawa; 10Steel Memorial Yawata Hospital, Kitakyushu; 11Nagatomi Neurosurgical Hospital, Oita; 12Southern Tohoku Hospital, Koriyama; 13NTT Kanto Hospital, Tokyo; 14Chiba Cardiovascular Center, Ichihara, Japan; 15University of Virginia, Charlottesville, Virginia; 16Barrow Neurological Institute, Phoenix, Arizona; 17University of Kentucky, Lexington, Kentucky; 18Hoag Hospital, Newport Beach, California; 19Université de Sherbrooke, Centre de Recherche Clinique Étienne-LeBel, Sherbrooke, Quebec, Canada; and 20New York University Langone Medical Center, New York, New York
Multicenter trial of SRS and hemangioblastoma

- Prospective trial involving six North American and 13 Japanese Gamma Knife centers.
- 186 patients with 517 hemangioblastomas were treated.
- 80/186 patients had VHL with 335 hemangioblastomas.
- 106/186 patients had 182 sporadic hemangioblastomas.
- Median target volume was 0.2 cm$^3$ (7 mm diameter) in patients with VHL. Marginal dose 18Gy.
- Median target volume was 0.7 cm$^3$ (11 mm diameter) in patients with sporadic tumors. Marginal dose 15 Gy.
- Survival rates: 94% at 3 years, 90% at 5 years, 74% at 10 years.
- 33/80 (43%) patients with VHL developed new tumors at five years.
- 17/106 (16%) patients with sporadic hemangioblastomas developed recurrence of original tumor.
- Gamma Knife was not effective in cystic and larger tumors. These tended to be factors for poorer tumor control.
FIG. 1. A: Kaplan-Meier curves comparing the overall survival after SRS for patients with sporadic hemangioblastomas versus patients with VHL-associated hemangioblastomas. B: Kaplan-Meier curves comparing the probability of new tumor (VHL) or recurrences of residual tumor from the original tumor (sporadic) development after SRS for sporadic hemangioblastomas versus VHL-associated hemangioblastomas. C: Kaplan-Meier curves comparing the local tumor control rate after SRS for sporadic hemangioblastomas versus VHL-associated hemangioblastomas.
Solid vs Cystic Tumor Control Rates

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<th>Option</th>
<th>Sporadic</th>
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<th>VHL</th>
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<tbody>
<tr>
<td></td>
<td>No. of</td>
<td>Time btwn SRS &amp;</td>
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<td>Time btwn SRS &amp;</td>
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<td></td>
<td>Patients</td>
<td>Additional Treatment (mos)</td>
<td>Patients</td>
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<tr>
<td>Repeat SRS for treated tumor progression</td>
<td>4 (4%)</td>
<td>Median, 68; range, 38–131</td>
<td>2 (3%)</td>
<td>13, 102</td>
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<td>Resection for treated tumor progression</td>
<td>14 (13%)</td>
<td>Median, 14; range, 3–60</td>
<td>8 (10%)</td>
<td>Median, 44; range, 12–121</td>
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<td>Cyst aspiration for treated tumor progression</td>
<td>5 (5%)</td>
<td>Median, 43; range, 15–73</td>
<td>5 (6%)</td>
<td>Median, 60; range, 4–86</td>
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<td>SRS for new (VHL) or recurrent (sporadic) tumors</td>
<td>10 (9%)</td>
<td>Median, 34; range, 8–103</td>
<td>13 (16%)</td>
<td>Median, 55; range, 8–153</td>
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<tr>
<td>Resection for (VHL) or recurrent (sporadic) tumors</td>
<td>2 (2%)</td>
<td>8, 49</td>
<td>10 (13%)</td>
<td>Median, 44; range, 8–144</td>
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<tr>
<td>Cyst aspiration for (VHL) or recurrent (sporadic) tumors</td>
<td>1 (1%)</td>
<td>51</td>
<td>1 (1%)</td>
<td>109</td>
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Conclusion

• Hemangioblastoma of the brain and spinal cord is a tumor commonly seen in patients with VHL.

• These are benign tumors that gradually increase in size or create cysts causing mass effect and ultimately neurological symptoms.

• Treatment is most commonly with surgery.

• An alternative treatment option is gamma knife radiosurgery.
Thank you!