CLINICAL DEBATE: Optimal Treatment of Hemangioblastomas

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Disclosures

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• Asymptomatic growth
• Peritumoral edema
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• Hypervascularity
• Large & complex tumors
• Tumor associated cyst in brain
• Hydrocephalus
• Extra-parenchymal
• Radiosurgery
• Complications
• Medical Therapy

CNS correlations

*25-33% of patients presenting with a hemangioblastoma will have VHL

*60-90% of patients with VHL will have multiple hemangioblastoma

von Hippel-Lindau disease
Genetic testing

<table>
<thead>
<tr>
<th>Simplex case is sufficient</th>
<th>&gt;1 tumor is suggested for referral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinal/CNS HB</td>
<td>Pancreatic cyst adenoma</td>
</tr>
<tr>
<td>PCC/PGL</td>
<td>PNET</td>
</tr>
<tr>
<td>ELST</td>
<td>Epididymal/adnexal cyst adenoma</td>
</tr>
<tr>
<td>Clear Cell RCC (&lt;50 yo OR family history)</td>
<td>Clear Cell RCC</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>VHL Subtype</th>
<th>VHL Mutation Type</th>
<th>High Risk</th>
<th>Low Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1:</td>
<td>Genes, insertions, truncations, missense</td>
<td>CNS/glial HB, RCC</td>
<td>PCC</td>
</tr>
<tr>
<td>Type 1B:</td>
<td>Germline gene deletions encompassing VHL</td>
<td>CNS/glial HB</td>
<td>PCC, RCC (risk may increase if CR or FL remains increased)</td>
</tr>
<tr>
<td>Type 1C:</td>
<td>Mosaic loss, p.1160V, p.1144L, p.1170L</td>
<td>CNS/glial HB, PCC, RCC</td>
<td>RCC</td>
</tr>
<tr>
<td>Type 1D:</td>
<td>Mosaic loss, p.1160V, p.1144L, p.1170L</td>
<td>CNS/glial HB, RCC, PCC, RCC</td>
<td>RCC, CNS/glial HB, RCC absent</td>
</tr>
<tr>
<td>Type 1E:</td>
<td>Mosaic loss, p.1160V, p.1144L, p.1170L</td>
<td>CNS/glial HB, RCC, PCC, RCC</td>
<td>RCC, CNS/glial HB, RCC absent</td>
</tr>
</tbody>
</table>

ELST

- 13% of VHL patients
- up to 30% are bilateral
- Mean age at symptom onset - 22 years (12-50 years)
- First symptom (audiovestibular) in 63% of patients

Question #1

When is the ideal time to treat an endolymphatic sac tumor when diagnosed in a patient with VHL?

- hearing preservation is a likely outcome (>95%) and is durable
- reversal of SNHL is unlikely (<10%)
- risk of sudden SNHL due to hemorrhage (50%)
- consider cochlear implantation possibility (preserve otic capsule)
**Question #1**

When is the ideal time to treat an endolymphatic sac tumor when diagnosed in a patient with VHL?

- early resection of ELSTs is preferred to prevent SNHL/vestibulopathy
- SNHL without vestibular symptoms - resect with growth (facial nerve, otic capsule invasion)
- always ask about audiovestibular symptoms

**Question #2**

When should a CNS hemangioblastoma be addressed?

- 1/16
- 1/17
- 1/18
- 7/18

**hemangioblastoma**

- Brainstem (7%)
- Cerebellum (45%)
- Spinal cord (36%)
- Cauda equina (11%)
- Supratentorial (1%)

**natural history**

- New tumors: 162 Patients (72%) 584 HB
- 225 Patients 1921 HB 8.5 ± 7.0 HB/pt median 7 HB/pt
- Symptomatic: 75 Patients 159 HB (14 new tumors*)
- 225 Patients 16 Died 2505 HB 6.9 ± 1.6 years (range 2.1–9.0 years) median 8 HB/pt

growth patterns

- Tumors grew faster in males
- Thresholds for location-dependent tumor size can predict the likelihood of symptom development

1278 demonstrated no growth (51%)
1227 demonstrated growth (49%)
- stuttering (886 tumors [72%])
- linear (76 [6%])
- exponential (264 [22%])

3.1 mm³/year
1.2 mm³/year
0.3 mm³/year

Question #3

When should a CNS hemangioblastoma be addressed?

Edema to cyst formation 36±23 months (range, 8 to 72 months)

Edema Is a Precursor to Central Nervous System Peritumoral Cyst Formation
**cyst development**

T1-weighted FLAIR precontrast FLAIR postcontrast

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**natural history**

New tumors
- Patients
- Median

Symptomatic
- Patients
- Median

**pregnancy & VHL**

Pregnancy cohort: 9 patients, 32 tumors

No-Pregnancy cohort: 27 patients, 145 tumors

**Question #4**

When should a CNS hemangioblastoma be addressed? What if this patient wants to become pregnant?

Is the plural of anecdote data?
Is surgery the best option? What about radiosurgery?

**The Role of Stereotactic Radiosurgery for Intracranial Hemangioblastomas**

- Overall control
  - 3 years – 85%
  - 5 years – 82%
  - 8 tumors, 5 patients with radiation toxicity (10%, 16%)
- Spinal hemangioblastoma
  - 13 tumors, 9 VHL patients
  - 2 tumors, 2 patients with radiation toxicity (15%, 22%)
  - No radiation necrosis
  - Control 12/13 tumors at median f/u – 37 months

- 20 VHL patients
- 44 CNS hemangioblastomas
  - 39 (88.6%) cerebellar and 5 (11.4%) Obex
  - 5 post surgical recurrence
- Age: 37.5 ± 12.0 years (range: 13 – 67 years)
  - f/u: 8.5 ± 3.2 years (median: 8 years; range: 3 – 17.6 years)
- Treated volume - .5 cm³
- Mean prescribed dose – 18.9 Gy

Prospective evaluation of radiosurgery for hemangioblastomas in von Hippel–Lindau disease
• 7/11 patients with symptoms improved
• 4/11 patients required surgical resection due to worsening symptoms and tumor growth

Question #5

What about radiosurgery?

• The value of SRS in prophylactically treating asymptomatic tumors is questionable
• Previous studies agree that presence of a cyst may be a contraindication to treatment
• The role in treating surgically inaccessible tumors remains a
Question #6

What does surgically accessible mean?

- 44 patients
- 51 operations
  - 31 with peritumoral cyst
  - 2 with intratumoral cyst
  - remainder all with edema
- 71 brainstem HB
  - 35.7 ± 10.8 years (range 12.7–58.0 years)
  - 5.9 ± 5.0 years (range 1.0–20.8 years)

brainstem HB

- 21 operations (41%) required myelotomy
- 8/9 patients with worse immediate outcomes at baseline by 6 months

spinal HB

- 108 patients
- 156 operations, 218 HB
  - 93% with edema or cyst
- Cord location
  - 6% ventral
  - 21% completely intramedullary
  - 51% DREZ associated
- Age: 33.8 ± 11.1 years (range 13–61 years)
- f/u: 7.0 ± 5.0 years (range 0.5–20.9 years)
- 61% immediate neurologic findings (15% McCormick grade changes)
spinal HB

<table>
<thead>
<tr>
<th>Preop McCormick Grade</th>
<th>6-Month McCormick Grade</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>62*</td>
<td>3</td>
<td></td>
<td></td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>6</td>
<td>40*</td>
<td>4</td>
<td>50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>2</td>
<td>11*</td>
<td>13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>5*</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>88</td>
<td>46</td>
<td>16</td>
<td>5</td>
<td>156</td>
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</tr>
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</table>

<table>
<thead>
<tr>
<th>Factor</th>
<th>p Value</th>
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<tbody>
<tr>
<td>age*</td>
<td>0.55</td>
</tr>
<tr>
<td>largest tumor volume*†</td>
<td>0.91</td>
</tr>
<tr>
<td>combined tumor volume†</td>
<td>0.98</td>
</tr>
<tr>
<td>no. of tumors resected</td>
<td>0.59</td>
</tr>
<tr>
<td>edema w/o syrinx</td>
<td>0.78</td>
</tr>
<tr>
<td>syrinx present</td>
<td>0.91</td>
</tr>
<tr>
<td>RCC†</td>
<td>0.17</td>
</tr>
</tbody>
</table>

natural history

<table>
<thead>
<tr>
<th>Years</th>
<th>Stable McCormick Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>92%</td>
</tr>
<tr>
<td>5</td>
<td>85%</td>
</tr>
<tr>
<td>10</td>
<td>77%</td>
</tr>
<tr>
<td>15</td>
<td>77%</td>
</tr>
</tbody>
</table>

VHL specific issues

- Development of new tumors and syringes
- Multiple operations
  - Cervical spinal cord
  - Immediately adjacent segments
- Fixed neurologic deficits

Question 7

When is cervical spinal fusion necessary in the setting of VHL?
Radiographic deformity (54%) (↑ age) (p = .05) and instability (36%) may develop following multilevel cervical laminectomy.

- ↑ Operations (Suboccipital - T4) (p = .01) associated with disability
- Clinical instability is less frequent (12%)
- At risk populations
  - C2 laminectomy
  - Multiple surgeries including adjacent regions
  - Older patients

Clinical instability

- 25 patients
- 34 operations
- Mean = 3.0 ± 1.3 laminae
- Age = 33.9 ± 11.9 years (18 to 61 years)
- f/u: 9.1 ± 5.6 years (median, 7.75 years)
- 15 patients underwent 32 additional surgeries at (Suboccipital, T1-T4)

Question #8

When should a CNS hemangioblastoma be addressed? Can there be “too much of a good thing” (surgery)?
Variable response of hemangioblastoma to Pazopanib

(Journal of Clinical Neuroradiology (2018))

**conclusions**

- Signs and symptoms of VHL-HB are dependent on location; associated edema and eventual cyst formation/progression are key factors
- Absolute size does not predict symptom onset and subsequent possible quiescent phases mandate close observation
- The mainstay of treatment remains surgical resection
- Early resection of ELST can preserve hearing
- Pregnancy does not appear to affect tumor or cyst formation/progression
- The exact role and utility of radiosurgery for VHL-HB remains controversial
- Multilevel laminectomy can be performed without predetermined need for fusion

**Difficult issue #1:**

Locations of these tumors are quite sensitive

(Brainstem image)
Brainstem

Access tricky and risk significant!

For spinal hemangioblastomas...

<table>
<thead>
<tr>
<th>Symptom or Sign</th>
<th>Number of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensory disturbance of posterior columns and spinthalamic pathway</td>
<td>17 (94.4)</td>
</tr>
<tr>
<td>Motor weakness</td>
<td>15 (83.3)</td>
</tr>
<tr>
<td>Abnormality of reflexes</td>
<td>15 (83.3)</td>
</tr>
<tr>
<td>Muscle atrophy</td>
<td>5 (27.8)</td>
</tr>
<tr>
<td>Localized pain</td>
<td>9 (50)</td>
</tr>
<tr>
<td>Sphincter disturbance</td>
<td>6 (33.3)</td>
</tr>
<tr>
<td>Impotence</td>
<td>1 (5.6)</td>
</tr>
<tr>
<td>Cranial nerve signs</td>
<td>1 (5.6)</td>
</tr>
</tbody>
</table>
Difficult issue #2: Patient selection

Smaller tumors managed conservatively show unpredictable patterns of progression

Untreated tumors show step-wise growth

What happens if you watch and wait?

Treatment is needed within 5 years in tumors of...

- Cord: 20%
- Cerebellum: 38%
- Brainstem: 60%

Difficult issue #3:

What is the best management of a tumor-associated syrinx?
The syrinx can be large

- Tumor is at T11
- Syrinx extends through entire cord
- *Myelopathy is from syrinx > tumor*

The syrinx is reversible

- Removing tumor clears syrinx
- Takes 4-12 weeks
- Mechanism unknown
- If syrinx does not clear, suspect residual tumor!

Even small tumors can make a syrinx

<table>
<thead>
<tr>
<th>Maximum Tumor Size</th>
<th>Presence of Syringomyelia</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 250 mm$^2$</td>
<td>No</td>
</tr>
<tr>
<td>&lt; 250 mm$^2$</td>
<td>Yes</td>
</tr>
</tbody>
</table>


Which tumors sustain the syrinx?
Pick your battles

- Multiple small tumors
- Too many to remove at once
- Syrinx makes the symptoms
- One tumor is primarily responsible for syrinx
- Treat that tumor first

When tumors are multiple, which should be removed?

Upper 3 tumors were removed
Not the lower one(s)

Syrinx persisted, so lower tumors had to be removed

16 months after first operation

Difficult issue #4
The hypervascularity of hemangioblastomas
Angiography is diagnostic.
Embolization?

- Series are small
- ?Danger of spinal stroke
- Risk of bleeding with particulate emboli
- Not curative
- Requires high level of expertise

The bleeding gets worse when the patient has one of these too

... a pheochromocytoma
Difficult issue #5

Large, complex tumors in tricky places

This patient did not have tumor removal

The cervicomedullary junction

The spinal cord...not too difficult?

Cervicomedullary tumor + Cervical spinal stenosis
Looks accessible on MRI …but…

It comes to the surface laterally

86 tumors
All operated
7% are ventral


Difficult issue #6
Dealing with a tumor-associated cyst in the brain
What to do about a tumor cyst

- 55% of tumors in large series have a peritumoral cyst
- If you remove the tumor nodule, the cyst will always resolve itself
- Stripping out cyst lining:
  - is unnecessary
  - can cause brain injury
  - will not prevent the cyst from coming back

Sometimes a cyst is helpful!

Sometimes the tumor nodule is subtle

- 40 yo M with ataxia and difficulty swallowing
- 32 yo F with headache, vomiting, and intermittent leg weakness

Peritumoral cysts

- 132/225 patients (59%) had cysts
- 72% of cysts progress within 3 yrs
- 59% of cysts observed for > 2 yrs became symptomatic, needing surgery
- Cyst grow 6x faster than tumors
  - Tumors: 50% grow in 5.6-8.9 yrs
  - Cysts: 50% grow in 1.5 yrs

Huntoon et al, J Neurosurg epub 30 Oct 2015
Difficult issue #7
When hemangioblastomas cause hydrocephalus, do we shunt?

Difficult issue #8
The optimal management of tumors outside the cord or brain

Hydrocephalus and shunts
- N = 126 operations for cerebellar Hgb
- 28% had hydrocephalus
- After surgery:
  - 94% showed resolution
  - PREOP SHUNT NOT NEEDED!

Jagannathan et al., J Neurosurg 2008

Some patients have tumors on nerve roots
~ 25 cases have been reported
In surgery, they look like this

Tumor on nerve root going into chest

Difficult issue #9
Can radiosurgery replace surgery?

In many, radiosurgery does not work well

From J Neurosurg 2006
University of Virginia series
Radiosurgery for hemangioblastoma

Note:
89% of patients with VHL have multiple hemangioblastomas

Local tumor control rates were:
- 1 yr 89%
- 5 yr 74%
- 10 yr 50%


Difficult issue #10
The neurological complications of surgery

Recovery depends on *which symptom* and on *degree of preop deficit*

Weakness  Intractable nausea

Immediate neurological decline after surgery is seen, usually as new sensory dysfunction, but it is not inevitable. Most maintain their function.
Neurological status before and after surgery in hemangioblastoma patients

1. Open circles = ventral tumor

1. No or minimal clinical deficit
2. Independent ambulation
3. Ambulation with cane or brace
4. Wheelchair dependent

The better the neurological condition of the patient is before surgery, the better the condition will be after surgery.... and the more rapid and complete the recovery.

Therefore, waiting for profound clinical decline is unwise.

Difficult issue #11

Too many tumors to remove safely...
Is there a medical

67 yo woman after 3 operations
Posterior fossa 1985
Posterior fossa 2005
C6-7 laminectomy 2012

Post laminectomy she spent 45 days in hospital for rehab, still uses walker
Drugs tried for hemangioblastoma

- Antiangiogenic agents
- EGFR tyrosine kinase inhibitors (erlotinib)
- Interferon-α-2a
- VEGFR2 inhibitors (SU5146)
- Sunitinib (Sutent)....study done by us at MDACC, published 2011

- Often work for RCC, but not for HB

Sunitinib
Oral multi-receptor tyrosine kinase inhibitor incl PDGF-R + VEGF-R

Pazopanib (aka Votrient): approved by FDA for Rx of metastatic RCC
- Oral multi-tyrosine kinase receptor blocker, antagonizing:
  - VEGFR-1, -2, -3
  - PDGFR-α, -β
  - FGFR-1, -3

Only RCC showed partial response (33%)
NO tumor showed complete response

For RCC
A 47 yo M with VHL found at age 18
Multiple HB of post. fossa and spinal cord + RCC bilat. + ocular hemangiomas
6 prior craniotomies + 1 gamma knife SRS
C/o progressive gait ataxia, dysarthria, dysphagia
Tried Sutent but stopped due to severe neutropenia
Pazopanib (800 mg/d): global neuro improvement after 4 wks
Side effects: hypertension, moderate neutropenia, transient diarrhea

Baseline

After Rx for 15 m (pazopanib)

Each tumor got smaller
(25-60% by volume)

4 yrs 4 m later (still on pazopanib) he returned with this…
Which was magically converted to this….
By the miracle of….. Surgery!

Targeted therapy is imperfect

Adverse events
Lab abnormalities

Sanford and Keating: Biodrugs 24:279, 2010
### Overall response rate

<table>
<thead>
<tr>
<th>Overall response rate</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total evaluable</td>
<td>31 (100)</td>
</tr>
<tr>
<td>CR</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>13 (42)</td>
</tr>
<tr>
<td>SD</td>
<td>18 (58)</td>
</tr>
<tr>
<td>PD</td>
<td>0</td>
</tr>
<tr>
<td>Inevaluable</td>
<td>1</td>
</tr>
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</table>

### Response by organ site

<table>
<thead>
<tr>
<th>Response by organ site</th>
<th>No. of sites (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal</td>
<td>CNS</td>
</tr>
<tr>
<td># Target Lesions</td>
<td></td>
</tr>
<tr>
<td>59 (100)</td>
<td>49 (100)</td>
</tr>
<tr>
<td>CR (%)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>PR (%)</td>
<td>29 (49)</td>
</tr>
<tr>
<td>SD (%)</td>
<td>28 (47)</td>
</tr>
<tr>
<td>PD (%)</td>
<td>0</td>
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</table>

Jonasch et al: Lancet Oncol 2018