Vestibular Schwannoma

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Case

- 67 year old F presented with a ringing sensation in her ears for the past few years as well as progressive left sided hearing loss.
- For the past month she noted progressive vertigo causing her to be unable to drive.
- She also endorsed a posterior headache that felt like an earache.
Common presentations

- Symptoms are due to cranial nerve involvement and tumor progression:
  - Acoustic Nerve (VIII): 95% → hearing loss (only 2/3 realize it)
  - Vestibular nerve (VIII): 61% → unsteadiness
  - Facial nerve (VII): 6% → facial paresis and taste disturbances
  - Trigeminal nerve (V): 17% → facial numbness / pain.
  - Posterior fossa: rare → compression on cerebellum or brainstem, results in ataxia / hydrocephalus
Differential Diagnoses

- Vestibular schwannoma
- Meningioma (4-10%)
- Facial nerve schwannoma
- Glioma
- Cholesteatoma
- Epidermoid inclusion cyst
- Glomus jugulare
- Lymphoma
- Hemangioblastoma (VHL)
- Brain metastases
- Ependymoma
- Arachnoid cyst
- Lipoma

Non-oncologic: hemangioma, aneurysm, basilar artery ectasia
Workup

- **Physical exam:**
  - **Rinne test** (tuning fork on mastoid bone, *air conduction > bone conduction* is normal, with sensorineural both are depreciated)
    - In **conductive** hearing loss, *bone conduction > air conduction*
  - **Weber test** (assessed sensorineural hearing loss; vibratory sound louder on “good” side);
  - Cranial nerve test (facial weakness, facial numbness, corneal reflex)
  - Vestibular testing: May see decreased or absent caloric response on affected side.
  - Romberg, Dix Hall-Pike, and balance are typically normal
- **Audiometry:** Best initial screening test, since **only 5% will have normal initial test**.
  - Look for asymmetrical high frequency hearing loss.
  - Speech discrimination loss is often out of proportion to measured hearing loss
Imaging

MRI demonstrated a 14 x 7 mm left cerebellopontine angle cistern mass most likely representing an acoustic neuroma.
Typical imaging findings

- well circumscribed T1-gad enhancing lesions arising near porus acusticus. T2 isointense
  - “Ice cream on a cone” or “Dumbbell” in IAC
- CPA angle tumors: **80% are vestibular schwannomas.** Of remaining 20%, majority are meningiomas, cholesteatoma, etc.
- MRI sensitivity: 98% (miss some due to small size)
- MRI specificity – approaches 100%

<table>
<thead>
<tr>
<th></th>
<th>Vestibular Schwannoma</th>
<th>Meningioma</th>
<th>Cholesteatoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT scan</td>
<td>Usually iso intense and contrast enhancing</td>
<td>Greater contrast than VS</td>
<td>Hypodense with irregular, lobulated margins. No contrast enhancement</td>
</tr>
<tr>
<td>MRI T1</td>
<td>Isointense (compared to pons)</td>
<td>Iso- or minimally hyper-</td>
<td>Hypo, ~CSF-like</td>
</tr>
<tr>
<td>MRI T2</td>
<td>“filling defect” – heterogeneously hyperintense</td>
<td>Usually hypointense</td>
<td>hyperintense</td>
</tr>
<tr>
<td>MRI post contrast</td>
<td>Enhancing: may be homogeneous (50%), hetero (30%), or cystic (5-15%)</td>
<td>Strongly enhancing</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Obtuse angle with petrous ridge vs acute for VS</td>
<td>Keratinizing squamous epithelium, erosive (best seen on CT)</td>
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</tbody>
</table>
**Audiometry**

- Non-serviceable $\geq 50\text{dB}$ audiogram and $<50\%$ speech discrimination
- Gardner-Robertson scale used

<table>
<thead>
<tr>
<th>Gardner-Robertson scale</th>
<th>Grade</th>
<th>Description</th>
<th>Pure-tone Average (decibels)</th>
<th>Speech-discrimination Score (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>Good to excellent</td>
<td>0-30</td>
<td>70-100</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>Serviceable</td>
<td>31-50</td>
<td>50-69</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>Non-serviceable</td>
<td>51-90</td>
<td>5-49</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>Poor</td>
<td>91-100 (maximum)</td>
<td>1-4</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>None</td>
<td>Not testable</td>
<td>0</td>
</tr>
</tbody>
</table>
Epidemiology

- Overall incidence: 1-2/100,000 (increased over past the 30-40 years with improved non-invasive diagnostic studies)
- 3000 cases in US per year
- Size has decreased as incidence has increased
- Autopsy results have shown that subclinical acoustic neuromas are present in up to 1% of people
- Account for 8% of intracranial tumors and 80-90% of CPA tumors
- Age at presentation: 30 to 50
- Almost always unilateral, with exception of NF-2
Risk Factors

• **Acoustic trauma** - OR of 2.2 if 10 years exposure to extremely loud noise. OR 13.1 if 20 or more years of exposure but subject to RECALL BIAS (studies looking at occupational exposure negative)

• **Parathyroid adenoma** - OR of 3.4 for acoustic neuroma (cause/association is unknown)

• **Childhood radiation exposure** - 20x higher compared to normal population

• **NF-2 (bilateral)** - Accounts for 10% of patients with acoustic neuroma

• **Cell phone use (controversial)** - Ipsilateral use >1640 hr – OR 2.55 (1.5-4.4)
Neurofibromatosis (NF1 and NF2)

<table>
<thead>
<tr>
<th></th>
<th>NF1</th>
<th>NF2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inheritance</td>
<td>Autosomal dominant</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Incidence</td>
<td>1:3000</td>
<td>1:40,000</td>
</tr>
<tr>
<td>Chromosome</td>
<td>17q11.2</td>
<td>22q12.2</td>
</tr>
<tr>
<td>Gene product</td>
<td>Neurofibromin</td>
<td>Merin</td>
</tr>
<tr>
<td>Presentation</td>
<td>Café-au-lait macules, axillary/inguinal freckling, cutaneous neurofibromas, subcutaneous neurofibromas</td>
<td>Hearing loss or vestibular dysfunction at young age, cataracts, juvenile posterior subcapsular lenticular opacity cutaneous schwannomas</td>
</tr>
<tr>
<td>Intracranial tumors</td>
<td>Optic path gliomas, other astrocytomas/gliomas</td>
<td>Vestibular schwannomas, meningiomas</td>
</tr>
<tr>
<td>Cognitive</td>
<td>IQ mildly decreased</td>
<td>Normal</td>
</tr>
<tr>
<td>Other tumors</td>
<td>CML, pheochromocytoma</td>
<td>None</td>
</tr>
</tbody>
</table>

**Diagnosis of NF2:** 1. Bilateral eighth nerve masses with imaging OR 2. A first degree relative with NF2 with either a unilateral eighth nerve mass or 2 of the following: glioma, meningioma, schwannoma, neurofibroma, or juvenile posterior subcapsular lenticular opacity.

March 24, 2020
Pathology

• Arise from the **Schwann cell**: perineural elements of the affected nerve

• Occur with equal frequency on the superior and inferior branches of the vestibular nerve (rarely affect cochlear portion CN VIII)

• **Obersteiner-Redlich zone**: Arise at junction of central myelin produced by glial cells and peripheral myelin from Schwann cells
  – This zone is where the CNS meets the PNS so change from oligodendrocyte myelin to Schwann cell myelin

• **Antoni A and B areas**: Microscopically, zones of alternately **dense** (A) and **sparse** (B) cellularity are characteristic of AN’s.

• Stain positive for **S100**
Koos grading system

- Grade I: small intracanalicular tumor
- Grade II: small tumor with protrusion into the cerebellopontine angle
- Grade III: Tumor occupying the cerebellopontine cistern with no brainstem displacement
- Grade IV: Large tumor with brainstem and nerve displacement
Anatomy

- Common to have CN deficits in CN V, VII and VIII
House-Brackmann Score

- Scores the degree of facial nerve palsy
- Measurement determined by measuring the upwards (superior) movement of the mid-portion of the top of the eyebrow, and the outward (lateral) movement of the angle of the mount
- 1 point per 0.25 cm movement, up to a max. of 1 cm. Scores added together to give a number out of 8

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
<th>Measurement</th>
<th>Function %</th>
<th>Est. Function %</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Normal</td>
<td>8/8</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>II</td>
<td>Slight</td>
<td>7/8</td>
<td>76-99</td>
<td>80</td>
</tr>
<tr>
<td>III</td>
<td>Moderate</td>
<td>5/8-6/8</td>
<td>51-75</td>
<td>60</td>
</tr>
<tr>
<td>IV</td>
<td>Moderately Severe</td>
<td>3/8-4/8</td>
<td>26-50</td>
<td>40</td>
</tr>
<tr>
<td>V</td>
<td>Severe</td>
<td>1/8-2/8</td>
<td>1-25</td>
<td>20</td>
</tr>
<tr>
<td>VI</td>
<td>Total</td>
<td>0/8</td>
<td>0</td>
<td>0</td>
</tr>
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</table>
Treatment Options

• Observation
• Surgical resection
• Radiotherapy (EBRT, FSRT, SRS)
Observation

• MRI recommended every 6 to 12 months in patients without baseline hearing loss and stable or slow growth rates, especially elderly patients
  – Beware 15-30% are lost to follow-up.
• **Growth rate of 2.9 mm/year** per UCSF lit review (others say 1.2-1.9mm/yr)
• **30%-50% of tumors show no growth or regression** on serial imaging studies
• Growth rate is highest for those that grow in first year. Progressive decrease in rate of growth if growth starts later.
• No predictive relationship between growth rate and tumor size at presentation
Surgical Resection

• Typically performed by ENTs and neurosurgeons. Learning curve is steep → 20 to 60 cases.
• Often recommended for tumors > 3-4 cm or for salvage after RT.
• CN VII, VIII damage is significant
• French series also shows good CN VII function (preservation not correlated with surgical approach used), but 1/3 pts had disabling vestibular symptoms at 1 year.
Surgical Resection

Approaches (based on size, location, and consideration of hearing preservation):

- **Retromastoid suboccipital (retrosigmoid):** An incision is made behind the ear and mastoid bone and some inner ear structures are removed. **Often best hearing preservation**
  
  - Advantages: decreased risk of facial nerve damage, ability to attempt hearing preservation, any size tumors, good visualization of CPA
  
  - Disadvantage: If tumor extends distally into IAC, complete resection may not be possible; long term postop headaches; cerebellar retraction may increase rates of ataxia

- **Middle cranial fossa (transtemporal):** Incision anterior to the ear with removal of the underlying bone to expose the area of interest; used primarily for small tumors confined to IAC (allows for complete exposure of IAC)
  
  - Advantage: Hearing preservation attempted (preservation of inner ear structures), only approach for IAC fundus
  
  - Disadvantage: complete tumor removal may not be feasible due to poor visualization of CPA; risk of facial nerve palsies due to increased manipulation of nerve within the auditory canal (puts facial nerve between surgeon and tumor). Need to be less than 1.5 - 2 cm.

- **Translabyrinthine:** This approach goes directly through the inner ear and **invariably sacrifices hearing,** but preserves CN VII
  
  - Recommended for large vestibular schwannomas (> 3 cm) in young pts without serviceable hearing
  
  - Can be used for smaller tumors if hearing preservation is not important.
  
  - Associated with better post operate gait stability because there is minimal retraction of the cerebellum, lowest incidence of postoperative headaches

- **Retrolabyrinthine:**
  
  - Allows excision from both the CPA and the IAM, regardless of the histological nature of the tumor and size
SRS Data

• First used by Leksell at Karolinska institute in Sweden to treat vestibular schwannoma in 1969.
  – Tumor control 81% at 3.7y med f/u.
  – Transient CN V and VII in 18% and 14% of pts, respectively.
• Initially used for older patients, recurrence after surgery, bilateral tumors, and medically inoperable pts.
• Early Gamma Knife data (Pitt, Mayo) had significant CN toxicity (33-80% preservation). Prescribed to higher dose than given now.
• Initial Linac results (Florida, Cleveland Clinic) showed better toxicity profile. Likely because prescribing a lower dose (~12 Gy).

**Modern SRS series:**

- lower doses 12-13Gy, MRI-based planning, improved conformality in plans (multiple isocenters, improved planning systems)
- PFS: 92-100%
- CN V preservation: 92-100%
- CN VII preservation: 94-100%
- Hearing preservation: 60-68%
SRS Data

- **Flickinger Pittsburgh** (Gamma Knife)- 6 year follow-up after 12-13 Gy
  - Tumor control = 98.6%
  - Facial nerve function preservation = 100%
  - Normal trigeminal function = 95.6%
  - Unchanged hearing level = 70.3%
  - Useful hearing preservation = 78.6%

March 24, 2020
SRS vs. FSRT

- Jefferson (Andrews) (Gamma Knife) =
  - 12 Gy SRS vs. 50 Gy in 2 Gy fractions
  - Tumor control: 98% SRS vs 97% SRT
  - Hearing preservation was significantly higher in FSRT=81 % vs SRS=33%
  - Criticized for short follow-up time and worse patients in SRS group

- Heidelberg (Combs) (Linac) = both safe/effective
  - FSRT= 57.6 Gy/1.8 Gy fractions vs. median SRS of 13 Gy
  - SRS ≤ 13 Gy for smaller lesions (< 3cm), FSRT for larger lesions.
  - Local control: SRS=90% vs. FSRT=95% (NS)
  - Hearing at 5 years SRS=60% vs. FSRT 78% (p=0.02)

- BC (Chung) (Linac)= FSRT gives comparable tumor control, good rates of hearing preservation (all SRS patients were already had non-serviceable hearing)
  - 12 Gy SRS vs. 45 Gy/1.8 Gy fractions
  - Local control 100% in both groups

<table>
<thead>
<tr>
<th>Meijer Netherlands IJROBP 2003</th>
<th>Tumor Control</th>
<th>CN V Preservation</th>
<th>CN VII Preservation</th>
<th>Hearing Preservation</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRS</td>
<td>100%</td>
<td>92%</td>
<td>93%</td>
<td>75%</td>
</tr>
<tr>
<td>FSRT</td>
<td>94%</td>
<td>98%</td>
<td>97%</td>
<td>61%</td>
</tr>
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</table>
# Surgery vs. SRS

<table>
<thead>
<tr>
<th>Regis JNS France 2002</th>
<th>Facial motor disturbance</th>
<th>CN V disturbance</th>
<th>Preserved Hearing</th>
<th>Overall functional disturbance</th>
<th>Hospital Stay (Days)</th>
<th>Mean days missed from work</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surgery</strong></td>
<td>37%</td>
<td>29%</td>
<td>37.5%</td>
<td>39%</td>
<td>23</td>
<td>130</td>
</tr>
<tr>
<td><strong>Gamma Knife</strong></td>
<td>0%</td>
<td>4%</td>
<td>70%</td>
<td>9%</td>
<td>3</td>
<td>7</td>
</tr>
</tbody>
</table>
Observation vs. FSRS

- **Shirato Japan IJROBP**– Observation vs. FSRT as Initial Management for Vestibular Schwannoma
  - No permanent facial or trigeminal neuropathy observed in the SRT group
  - SRT: **Transient VII** in 5%, **Transient V** in 12%
  - Obs: 4% permanent facial palsy (after salvage surgery) and 4% w/transient V palsy (after salvage surgery)
  - **Hearing**: No SS difference in G & R class preservation rates for patients with measurable hearing
    - Hearing preservation: 60.9% (3yr) and 31% (5yr) observation vs 53% SRT (at 3yr and 5yr)
    - Analysis of Hearing preservation excludes/censors patients in observation group at time of salvage.
    - In reality 4/6 sx salvaged pts and 1/4 RT salvaged pts became DEAF but were NOT included in actuarial curve!
    - In **FSRT group**, 1 pt (3%) became deaf
Hearing Preservation after SRS
- Retrospective study of 307 patients with serviceable hearing at time of SRS
Dose and CN Toxicity

- **CN V and VII:** tumor size and prescription dose correlate with toxicity.
  - Friedman UF JNS 2006 (p.24) → CN VII tox: 1cc increase in tumor = 17% increase, 2.5Gy increase in dose = 8.1x increase
  - Boegle UF JNS 2007 → Dosimetric variables: Conformity and dose gradient: no effect on outcomes
  - Generally no SRS if >3cm tumors

- **CN VIII:** Fukuoka Japan Prog Neurol Surg 2009 17% transient dizziness/gait imbalance post SRS, 2% persistent dizziness post SRS

- **Hearing:** Range of hearing preservation 32-71%. Hearing can decline long-term (>10yrs) after SRS. Dose matters.
  - Prasad UVa JNS 2000 – no decline in first 2 years, then progressive decline
  - Chopra Pitt IJROBP 2007 – 3y 75% G-R I/II, 10y 44%
  - Combs Heidelberg RadOnc 2013 –@10yr, 72% if ≤13Gy (if >13Gy, 36%)
  - Yang UCSF J NSGY 2010 – Review: N=4234, Preservation of hearing about 50% overall, but can be increased to 60% if <13 Gy
Treatment

- **Sim**: Scan vertex to C2, 1mm thickness
- With IV contrast, upper alpha cradle, and stereotactic frame
- **Contour**: Contour GTV=PTV (in this case due to frame)
  - PTV expansion based on immobilization
    - Framed cases may use 0 mm expansion, while frameless SRS cases may use 2-3 mm expansion
Treatment

• Linac based framed SRS to L-sided vestibular schwannoma 12.5 Gy to 80% isodose line using 6 MV photons, FFF
Representative Isodose lines
OAR Constraints

- Brainstem: 12.5 Gy (<5% neuropathy or necrosis)
- Chiasm: 8 Gy (<10% optic neuropathy)
- Cochlea: 14 Gy (<25% sensory-neural hearing loss), Ideally keep cochlea/modiolus <5.3 Gy (possibly <4.2 Gy)
- Spinal cord: 13 Gy (1% myelopathy)
- Brain: V12 <5-10 cc (<20% symptomatic necrosis)

- **Conformality index:** (Rx isodose volume)/(tumor volume) should be <2
- **Homogeneity index:** (maximum dose)/(peripheral dose) should be <2

- **Gamma-knife:** Rx to 50% IDL
- **Linac:** Rx to 80% IDL
Follow-up

• ~ 30% vestibular schwannomas will show a transient increase in volume after SRS (mean time to max tumor is roughly 13 months)
• Hearing may continue to decline long term after SRS (even >10 years)
• 36% of tumors shrink, 58% remain unchanged after SRS
• Imaging can be performed at 3-6 months followed by yearly or if changes in symptoms
Summary

• SRS is a good treatment option for vestibular schwannoma with excellent control rates

• SRS has decreased rates of CN toxicities and increased rates of hearing preservation when compared to surgery

• Surgery may be a better option if there is brain stem compression, due to minimal change in size of tumor after SRS or transient increase in tumor size

• Observation with imaging every 6-12 months may be appropriate for some patients due to many vestibular schwannomas remaining stable or regressing without treatment
References


