ARROCase

Meningioma

*SRS post Subtotal Resection*

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Jacksonville, FL
Case: Presentation

• 39-year-old female presents with recent seizure, transient left sided weakness, and syncopal episode.

• **PMH/PSH**: Endometriosis, morbid obesity, asthma, HTN, myomectomy

• **FH**: None relevant

• **Meds**: OCP

• **SH**: Widowed. Former smoker. Social alcohol consumption. Limited exercise.
Case: Physical Exam

• **General:** No acute distress. Tearful.
• **CV:** RRR. No m/r/g.
• **Lung:** CTAB. No increased WOB.
• **Abdomen:** Soft, non-tender, non-distended. NABS.
• **Neurologic Exam:**
  – **Mental status:** Awake, alert, and oriented to person, place, time, and situation. Speech is fluent. No aphasia or dysarthria. Able to provide historical detail. Can follow all commands.
  – **CRANIAL NERVES:** Pupils are equally round and reactive to light. Extraocular movements intact without nystagmus. Visual fields are full to finger counting. Facial sensation intact to light touch. Facial activation is normal and symmetric. Tongue and palate move in the midline. Hearing is grossly symmetric. Shoulder shrug symmetrical.
  – **STRENGTH:** No drift with eyes closed. Segmental strength testing revealed 5/5 strength throughout the bilateral upper and lower extremities. Tone is normal throughout.
  – **SENSATION:** Normal and symmetric to light touch throughout.
  – **REFLEXES:** Normal and symmetric with downgoing toes to plantar stimulation.
  – **COORDINATION:** No ataxia/dysmetria with finger to nose with eyes opened and closed.
  – **GAIT:** Normal casual and tandem gait with no Romberg. Normal heel walk and toe walk. Normal arm swing.
Case: Diagnostic Workup

• **Head CT without contrast**
  - Revealed right parietal mass. Borders difficult to distinguish without contrast.

• **Brain MRI with contrast (T1 and Venogram)**
  - Large right parafalcine parietal meningioma with localized mass effect, extensive underlying vasogenic edema
  - MRV suggestive of sagittal sinus invasion and localized occlusion.
    - If venous flow present, surgeon must avoid further sinus injury to prevent venous stroke
Case: Surgical Intervention

- Evaluated by neurosurgery and subsequently underwent maximal safe resection given active symptoms and radiographic appearance of meningioma.
- Postoperative MRI demonstrated complete resection of the right side of the parietal mass. Small left parafalcine component still present.
- Pathology revealed diagnosis of WHO grade I meningioma. No brain invasion. Mitotic figures not elevated.
Case: Adjuvant Radiation

- Repeat Brain MRI 1 year post resection demonstrated slight interval increase in the residual parasagittal meningioma, measuring 2.6 cm. Sinus partially patent.
- Radiation Oncology consulted:
  - Patient reported markedly improved left sided paresthesias and weakness. Denied recent seizures.
  - Discussed further management options including continued observation, stereotactic radiosurgery, fractionated external beam radiation therapy, and repeat surgery.
  - Reviewed potential radiotherapy side effects: Radiation necrosis, worsened edema, additional neurologic deficits
- Consensus decision made to proceed with single fraction frame-based SRS based off size (< 3 cm) and location. Total dose: 12 Gy.
  - Observation possible, but further growth would limit SRS as an option and increase risk of radiation necrosis
  - Difficult to surgically remove residual tumor given proximity to sinus
Case: SRS Treatment Delivery

• Leksell Gamma Knife® Icon™
  – 192 60Co sources divided into 8 moveable sectors
    • Each can be collimated to 4mm, 8 mm, 16 mm, or blocked
    • All 192 beams intersect as single point → high dose to conformal target
    • Accommodates both frame and mask-based immobilization with onboard cone-beam CT and intrafraction motion management system
Case: GammaPlan® Treatment Planning

- **Forward Planning:**
  - Position shots → Adjust collimation (4, 8, 16mm) and weighting manually
  - Must balance coverage, selectivity, and beam time

- **Interactive Inverse Planning Functions:**
  - **Auto-Fill:** Geometrically packs TV with shots
    - Can customize collimation, composites, etc.
    - Drawback: May use more shots than necessary
  - **Optimize:** Uses annealing algorithm to optimize shots per user specified:
    - Collimation
    - Weights
    - Coverage vs. Selectivity
eContour
Fractionated RT Example (per RTOG 0539)

Link: https://econtour.org/cases/102

Treatment paradigm per RTOG 0539:

GROUP I: Newly diagnosed WHO grade I s/p gross total resection (GTR) or subtotal resection (STR)
- No radiation

GROUP II: Recurrent WHO grade I or newly diagnosed grade II s/p GTR
- 54Gy to GTV+1cm

GROUP III: Recurrent WHO grade II or newly diagnosed WHO grade II s/p STR or WHO grade III of any resection extent
- 54Gy to GTV+2cm with cone down to 60Gy to GTV+1cm using SIB (all in 30 fractions)
# Dosimetric Guidelines

<table>
<thead>
<tr>
<th>Target/OAR</th>
<th>Fractionated</th>
<th>SRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>GTV</td>
<td>D100% ≥ 95%</td>
<td>D100% ≥ 95%</td>
</tr>
<tr>
<td>Brain</td>
<td>50 Gy (whole brain)</td>
<td>12 Gy (5-10cc)</td>
</tr>
<tr>
<td>Brainstem</td>
<td>54-60 Gy</td>
<td>15 Gy</td>
</tr>
<tr>
<td>Cord</td>
<td>45-50 Gy</td>
<td>14 Gy</td>
</tr>
<tr>
<td>OC/ON</td>
<td>55 Gy</td>
<td>10 Gy</td>
</tr>
<tr>
<td>Cochlea</td>
<td>45 Gy (Mean)</td>
<td>4 Gy (Mean)</td>
</tr>
<tr>
<td>Lens</td>
<td>7 Gy</td>
<td>1.5 Gy</td>
</tr>
<tr>
<td>Orbit</td>
<td>55 Gy</td>
<td>8 Gy</td>
</tr>
</tbody>
</table>

****Max point dose unless otherwise specified
Case: DVH Evaluation

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Planned Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>GTV</td>
<td>98.6% ≥ 12 Gy</td>
</tr>
<tr>
<td>Brain</td>
<td>12 Gy (9.8 cc)</td>
</tr>
<tr>
<td>Brainstem</td>
<td>Max: ≤0.5</td>
</tr>
<tr>
<td>ON_L</td>
<td>Max: ≤0.5</td>
</tr>
<tr>
<td>ON_R</td>
<td>Max: ≤0.5</td>
</tr>
<tr>
<td>OC</td>
<td>Max: ≤0.5</td>
</tr>
<tr>
<td>Orbit_L</td>
<td>Max: ≤0.1</td>
</tr>
<tr>
<td>Orbit_R</td>
<td>Max: ≤0.1</td>
</tr>
<tr>
<td>Lens_L</td>
<td>Max: ≤0.1</td>
</tr>
<tr>
<td>Lens_R</td>
<td>Max: ≤0.1</td>
</tr>
</tbody>
</table>
Meningioma Overview
Epidemiology

- > 26,000 new cases per year
- Roughly 1/3 of all primary brain tumors
- Increased incidence with age
Risk Factors

• Intrinsic
  – Female (2:1), African American, breast and thyroid cancer, uterine fibroids, genetic polymorphisms (GLTSCR1, BRCA1, NF2, etc.), BMI

• Extrinsic
  – Ionizing radiation (pediatric radiotherapy, tinea capitis treatment)
    • No known association with low energy electromagnetic fields (cell phones, power lines)
  – Exogenous hormones? Controversial
    • ~ 80% of meningiomas have progesterone receptors, 40% estrogen receptors
    • No definitive association with oral contraceptives, HRT, etc.
Anatomic Sites

- Originate from arachnoid cap cells
- Common sites: parasagittal, falcine, cerebral convexity, sphenoid wing
- < 10% found in spinal meninges
WHO Classification

• Grade 1 (> 80%), benign
  – Features: Calcifications, psammoma bodies

• Grade 2 (5-15%), atypical, still benign
  – Brain invasion OR
  – 4-19 mitoses/10 HPF OR
  – ≥ 3 atypical features:
    • Small cell + high N/C ratio, increased cellularity, large nucleoli, patternless or sheet like growth, focal of necrosis

• Grade 3 (1-2%), malignant/anaplastic
  – ≥ 20 mitoses/10 HPF OR
  – Sarcomatous/Carcinomatous/Melanomatous features
## WHO Classification Subtypes

<table>
<thead>
<tr>
<th>Grade 1 (Benign)</th>
<th>Grade II (Atypical)</th>
<th>Grade III (Malignant)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psammomatous</td>
<td>Atypical (criteria)</td>
<td>Anaplastic (criteria)</td>
</tr>
<tr>
<td>Fibroblastic</td>
<td>Clear Cell</td>
<td>Papillary</td>
</tr>
<tr>
<td>Meningothelial</td>
<td>Choroid</td>
<td>Rhabdoid</td>
</tr>
<tr>
<td>Transitional</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiomatous</td>
<td></td>
<td></td>
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<tr>
<td>Secretory</td>
<td></td>
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</tr>
<tr>
<td>Metaplastic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microcystic</td>
<td></td>
<td></td>
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<tr>
<td>Lymphoplasmacyte rich</td>
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</tr>
</tbody>
</table>
Simpson Grade


- Evaluated recurrence rates after resection alone, 265 pts

<table>
<thead>
<tr>
<th>Grade</th>
<th>Resection Extent</th>
<th>Recurrence Rate (10 year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Complete removal including resection of underlying bone and associated dura</td>
<td>9%</td>
</tr>
<tr>
<td>2</td>
<td>Complete removal and coagulation of dural attachment</td>
<td>19%</td>
</tr>
<tr>
<td>3</td>
<td>Complete removal without resection of dura or coagulation (e.g., invaded sinus)</td>
<td>29%</td>
</tr>
<tr>
<td>4</td>
<td>Subtotal resection</td>
<td>44%</td>
</tr>
<tr>
<td>5</td>
<td>Simple decompression with or without biopsy</td>
<td>100%</td>
</tr>
</tbody>
</table>
Standard Workup

- H&P with full neurological exam
  - Presentation: Headache or asymptomatic most common. May present with various focal deficits based on anatomic location
- CT Head (with contrast)
  - Homogenously contrast enhances and isodense without contrast
  - Hyperostosis (5%), differs from skull invasion
- MRI Brain/Skull Base (T1 with contrast)
  - Homogenously contrast enhances and isotense without contrast
  - Broad dural base “tail” common
  - > 50% with vasogenic edema, positively correlated with aggressiveness
  - T2 hyperintensity seen in hypervascular tumors (choroid, angiomatous)
General Treatment Paradigm

1. Observation
   - Preferred for small asymptomatic tumors (≤ 3cm)
   - Consider potential for future symptoms (E.g., proximity to optic nerve)
   - Annual MRI for surveillance; 1-2 mm growth per year is typical

2. Maximal Safe Resection
   - Preferred intervention if accessible
   - Consider patient’s age, ECOG/KS, preference, comorbidities
   - Consider likelihood of complete resection, potential for neurologic consequence
   - Post operative RT dependent on WHO grade and resection extent

3. Definitive Radiotherapy
   - Typically reserved for unresectable disease
   - Fractional RT or stereotactic radiosurgery
   - Dose dependent on WHO grade and size
Treatment Approach: WHO Grade I

- Preferred primary treatment is resection
  - GTR → Observation
  - STR → Observation OR Adjuvant RT
  - Unresectable → Definitive RT

- Fractionated RT Dose
  - 50.4-54 Gy/28-30fx for all Grade I
  - Suggested PFS advantage over 52 Gy

Goldsmith et al. Postoperative irradiation for subtotally resected meningiomas. Columns above include only 'benign' meningiomas (n = 117)
Treatment Approach: WHO Grade II

- Preferred primary treatment is still resection
  - GTR or STR → Adjuvant RT
  - Unresectable → Definitive RT
- Fractionated RT Dose
  - GTR: 54 Gy/30fx
  - STR/Unresectable: 59.4-60 Gy/30-33fx

The role of adjuvant RT in atypical meningioma (2013)

PFS advantage in Others + ART vs. Others (Others = STR + unknown)
Treatment Approach: WHO Grade III

- Resection if accessible
  - GTR or STR → Adjuvant RT
  - Unresectable → Definitive RT
- Fractionated RT Dose
  - 59.4-66 Gy/30-33fx for all grade III

Anaplastic Meningioma OS (1999)

When To Consider SRS

• Suitability Criteria:
  1. Small tumor volume (≤ 3cm)
  2. Well defined margins (no CTV/PTV)
  3. Maintains dose constraints for proximal OARs
  4. WHO Grade I

• Consider FSRT (2-5 fractions) if:
  1. Tumor volume 2-5cm
  2. Very close proximity to OARs
  3. Reirradiation
Treatment Approach: SRS

Kondziolka et al. Radiosurgery as Definitive Management of Intracranial Meningiomas (2008)

- > 900 pts, prospective review, 18-year interval
- Mean dose: 14 Gy/1fx
- Adjuvant SRS Rationale
  - Small volume (< 3.5cm, residual/recurrent tumor post resection
- Definitive SRS Rationale
  - Small volume (< 3.5cm)
  - Symptomatic and unresectable
  - Significant comorbidities
  - Patient preference

SRS Tumor Control Rates

- Grade 1 (n = 384)
- Grade 2 (n = 54)
- Grade 3 (n = 29)
- Primary (n=488)
Treatment Approach: SRS


- Dose analysis of WHO Grade I-III meningiomas post GKSRS
  - $n = 101$, 1998-2001
- Median Dose (single fraction)
  - Grade I: 14 Gy ($r$, 10-18 Gy)
  - Grade II/III: 16 Gy ($r$, 12-20 Gy)
    - Mostly recurrent post resection
- Local failure association:
  - Lower GKSRS dose
  - Higher grade
Multi-institutional retrospective review of 233 pts

All pts with WHO grade II meningioma treated with SRS
- All with recurrent or persistent disease
- Prior surgery: GTR (48.3 %), STR (51.7%)

RPA prognostic group model, 1 point for each of the following:
- Age > 50
- Treatment volume > 11.5 cc
- Prior radiation or multiple surgeries

“Good” = 0-1 points; “Poor” = 2-3 points

“Good” prognostic group: 3-year PFS = 63.1%
- Authors suggest this group should be considered for SRS specifically
# Prospective Trials: RTOG 0539

## RISK GROUPS

<table>
<thead>
<tr>
<th>LOW (n=65)</th>
<th>INTERMEDIATE (n=56)</th>
<th>HIGH (n =57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO Grade I → GTR or STR</td>
<td>Recurrent WHO Grade I OR WHO Grade II → GTR</td>
<td>WHO Grade II → STR OR WHO Grade III</td>
</tr>
<tr>
<td>Observation</td>
<td>54 Gy/30 fx</td>
<td>60Gy/30 fx (HD PTV) 54 Gy/30 fx (LD PTV)</td>
</tr>
</tbody>
</table>

### HD PTV = Gross tumor + resection bed + 1 cm
### LD PTV = Gross tumor + resection bed + 2 cm
Prospective Trials: RTOG 0539

**Primary Endpoint = Three Year PFS**

<table>
<thead>
<tr>
<th>LOW</th>
<th>INTERMEDIATE</th>
<th>HIGH</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-year PFS: 91.8%</td>
<td>3-year PFS: 93.8%</td>
<td>3-year PFS: 58.8%</td>
</tr>
<tr>
<td>3-year LC: 93.5%</td>
<td>3-year LC: 95.9%</td>
<td>3-year LC: 68.9%</td>
</tr>
<tr>
<td>3-year OS: 98.4%</td>
<td>3-year OS: 96.0%</td>
<td>3-year OS: 78.6%</td>
</tr>
</tbody>
</table>

40% 5-year LF post STR

92.9% of recurrences within the RT PTV
Prospective Trials: EORTC 22042-26042

- WHO Grade II post GTR (n=56)
  - Observation Cohorts: WHO GII post STR and WHO GIII
- Escalated dose: 60 Gy
  - 50% IMRT, 46 % 3DCRT, 4% FSRT
- Primary Endpoint: 3-year PFS > 70%
- Results:
  - 3-year PFS: 88.7%
  - 3-year OS: 98.2%
  - Late Toxicity ≥ G3: 14.3%
Ongoing Phase III Trials

WHO Grade II post GTR

• NRG BN-003 Oncology
  – 59.4 Gy/33fx vs. Observation
  – Primary endpoint: PFS

• ROAM/EORTC-1308
  – 60 Gy/30fx vs. Observation
  – Primary endpoint: DFS
Role of Heavy Ions
Proton Therapy

- 2005-2013, 22 pts WHO Grade II Meningioma
  - 12 adjuvant
  - 10 recurrence/progression of residual
- Median dose 63 Gy (RBE) proton
- Local Control 71.1% Overall
  - 87.5% if >60 Gy (RBE)
  - 50.0% if <60 Gy (RBE)
## Role of Heavy Ions

Systemic Review of Heavy Ions

### Table 1. Summary of the Studies Using Ion Radiotherapy in Treatment of Atypical and Anaplastic Meningiomas

<table>
<thead>
<tr>
<th>Study</th>
<th>Experimental Design</th>
<th>Country</th>
<th>Meningioma World Health Organization Grade, n*</th>
<th>Type of Ion Therapy</th>
<th>Median Time of Follow-Up (months)</th>
<th>Reported Local Control (Grade, %, months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boskos et al., 2009</td>
<td>Retrospective cohort</td>
<td>France</td>
<td>II, 19, III, 5</td>
<td>Proton</td>
<td>48</td>
<td>II/III, 46.7, 60</td>
</tr>
<tr>
<td>Slater et al., 2012</td>
<td>Retrospective cohort</td>
<td>United States</td>
<td>II, 4</td>
<td>Proton</td>
<td>74</td>
<td>II, 50, 60</td>
</tr>
<tr>
<td>Rieken et al., 2012</td>
<td>Retrospective cohort</td>
<td>Germany</td>
<td>II, 3, 3, 1</td>
<td>Carbon</td>
<td>4.5</td>
<td>II/III, 100.3</td>
</tr>
<tr>
<td>Chan et al., 2012</td>
<td>Prospective case series</td>
<td>United States</td>
<td>II, 4, III, 2</td>
<td>Proton</td>
<td>145</td>
<td>II/III, 83, 145</td>
</tr>
<tr>
<td>Weber et al., 2012</td>
<td>Retrospective case series</td>
<td>Switzerland</td>
<td>II, 9, III, 2</td>
<td>Proton</td>
<td>54.8</td>
<td>II/III, 491, 60</td>
</tr>
<tr>
<td>Adeberg et al., 2012</td>
<td>Prospective cohort</td>
<td>Germany</td>
<td>II, 62, III, 2</td>
<td>Carbon</td>
<td>73</td>
<td>II, 95, 24, III, 63, 24</td>
</tr>
<tr>
<td>Combs et al., 2013</td>
<td>Retrospective cohort</td>
<td>Germany</td>
<td>II/III, 36</td>
<td>Carbon</td>
<td>12</td>
<td>II/III, 54, 12, 33, 24</td>
</tr>
<tr>
<td>Combs et al., 2013</td>
<td>Prospective cohort</td>
<td>Germany</td>
<td>II, 23, III, 4</td>
<td>Carbon</td>
<td>6</td>
<td>II/III, 67, 5</td>
</tr>
<tr>
<td>Mozes et al., 2017</td>
<td>Retrospective cohort</td>
<td>Germany</td>
<td>II, 17, III, 5</td>
<td>Carbon</td>
<td>49.5</td>
<td>II/III, 100, 48</td>
</tr>
<tr>
<td>Murray et al., 2017</td>
<td>Retrospective cohort</td>
<td>Switzerland</td>
<td>II, 33, III, 2</td>
<td>Proton</td>
<td>56.9</td>
<td>II/III, 680, 60</td>
</tr>
<tr>
<td>El Shafie et al., 2019</td>
<td>Retrospective cohort</td>
<td>Germany</td>
<td>II, 251, 4/25 proton, III, 6, 0/6 proton</td>
<td>Proton Carbon</td>
<td>49.7</td>
<td>II, 50, 34.3, III, 50, 10.2</td>
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<tr>
<td>El Shafie et al., 2018</td>
<td>Retrospective cohort</td>
<td>Germany</td>
<td>II, 7, III, 1</td>
<td>Proton Carbon</td>
<td>46.8</td>
<td>II/III, 75, 60</td>
</tr>
</tbody>
</table>
## RT Dose Summary

<table>
<thead>
<tr>
<th></th>
<th>WHO Grade I</th>
<th>WHO Grade II</th>
<th>WHO Grade III</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GTR</strong></td>
<td>Observation</td>
<td>54-60 Gy/30fx OR Observation</td>
<td>59.4-66 Gy/30-33 fx</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>STR</strong></td>
<td>Observation OR 50.4-54 Gy/28-30fx OR SRS 12-14 Gy</td>
<td>59.4-60 Gy/30-33 fx SRS controversial, consider prognostic group</td>
<td>59.4-66 Gy/30-33 fx SRS controversial</td>
</tr>
<tr>
<td></td>
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<td></td>
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</tr>
<tr>
<td><strong>Unresectable OR Recurrence</strong></td>
<td>50.4-54 Gy/28-30fx OR SRS 12-14 Gy</td>
<td>59.4-60 Gy/30-33 fx OR SRS 14-18 Gy</td>
<td>59.4-66 Gy/30-33 fx OR SRS 18-24 Gy</td>
</tr>
</tbody>
</table>

**Note:**
- OR = Observation

**SRS controversial,** consider prognostic group

---

**Association of Residents in Radiation Oncology**

**ARRO**
References


2. Winnie Li, Angela Cashell, Ivy Lee, Messeret Tamerou, Catherine Coolens, Mark Bernstein, Paul Kongkham, Normand Laperruque, David Shultz. Patient perspectives on frame versus mask immobilization for gamma knife stereotactic radiosurgery. VOLUME 51, ISSUE 4 PS67-573, DECEMBER 01, 2020


4. https://econtour.org/cases/102


References

• Please provide feedback regarding this case or other ARRO cases to arrocase@gmail.com