ARROCase

Meningioma

SRS post Subtotal Resection

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Jacksonville, FL
Case: Presentation

• 39-year-old female presented to emergency department 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. CRANIAL NERVES: Pupils are equally round and reactive to light. CN II-XII grossly intact.
  - STRENGTH: Segmental strength testing revealed 5/5 strength throughout the bilateral upper and lower extremities.
  - REFLEXES: Normal and symmetric with downgoing toes to plantar stimulation.
  - COORDINATION: No ataxia/dysmetria with finger to nose.
  - GAIT: Normal casual and tandem gait with no Romberg.
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.
  - Patient not referred to radiation oncology at this time.

- 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 (from 2.2 cm). Sinus partially patent, stable.

• 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 GTV 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
## 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>Region of Interest</th>
<th>Max Dose (Gy)</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>

 ASSOCIATION OF RESIDENTS IN RADIATION ONCOLOGY
Meningioma Overview
Epidemiology

- > 26,000 new cases per year
- Roughly 1/3 of all primary brain tumors
- Increased incidence with age
- 50% diagnosed incidentally
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 nucleus to cytoplasm 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>
</tr>
<tr>
<td>Secretory</td>
<td></td>
<td></td>
</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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</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)
• Radiographic findings sufficient for final diagnosis
Initial Management Options
Following radiographic diagnosis

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, especially if acutely symptomatic
   - 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)

Atypical meningioma post GTR alone (2009)

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

When To Consider SRS

• Suitability Criteria:
  1. Small tumor volume (≤ 3cm)
  2. Well defined GTV margins (no CTV/PTV needed)
  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
• Consider conventional fractionation if GTV < 3mm from optic chiasm/nerves or parasagittal (edema risk)25
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)

Post Resection
Definitive
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
Treatment Approach: SRS

Treatment of WHO Grade II Meningiomas with SRS: Identification of an Optimal Group for SRS Using RPA (2021)

- 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>
</table>
| WHO Grade I $\rightarrow$ GTR or STR | Recurrent WHO Grade I  
*OR*  
WHO Grade II $\rightarrow$ GTR | WHO Grade II $\rightarrow$ STR  
*OR*  
Recurrent WHO Grade II  
*OR*  
WHO Grade III |
| Observation | 54 Gy/30 fx | 60Gy/30 fx (HD PTV)  
54 Gy/30 fx (LD PTV) |

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

|        | 40% 5-year LF post STR   |                               | 92.9% of recurrences within the RT PTV |

**Graphs:**

- **Graph A:** Progression-Free Survival (%)

- **Graph B:** Progression-Free Survival (%)

**ASSOCIATION OF RESIDENTS IN RADIATION ONCOLOGY (AKKO)**
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 III, 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, 49.1, 60</td>
</tr>
<tr>
<td>Adeberg et al., 2012</td>
<td>Prospective cohort</td>
<td>Germany</td>
<td>II, 62 III, 23</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>
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<td>Mazes 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>
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<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, 68.0, 60</td>
</tr>
<tr>
<td>El Shafie et al., 2019</td>
<td>Retrospective cohort</td>
<td>Germany</td>
<td>II, 25 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><strong>STR</strong></td>
<td>Observation <strong>OR</strong></td>
<td>59.4-60 Gy/30-33 fx</td>
<td>59.4-66 Gy/30-33 fx</td>
</tr>
<tr>
<td></td>
<td>50.4-54 Gy/28-30fx</td>
<td>SRS controversial, consider prognostic group</td>
<td>SRS controversial</td>
</tr>
<tr>
<td></td>
<td>SRS 12-14/1fx Gy</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Unresectable</strong></td>
<td>50.4-54 Gy/28-30fx</td>
<td>59.4-60 Gy/30-33 fx</td>
<td>59.4-66 Gy/30-33 fx</td>
</tr>
<tr>
<td><strong>OR Recurrence</strong></td>
<td>SRS 12-14/1fx Gy</td>
<td>SRS 14-18/1fx Gy</td>
<td>SRS 18-24/1fx Gy</td>
</tr>
</tbody>
</table>
References

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