Management of CNS Malignancies

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Disclosure

• Abbott Oncology Consultant
• Varian Medical Systems Travel expenses
Learning Objectives

• Review the role of stereotactic radiosurgery and radiation therapy for brain metastases.
• Discuss the indications for radiation therapy and chemotherapy for malignant and low grade gliomas.
• Review the role of stereotactic radiosurgery and radiation therapy for benign brain tumors.
Pre-test Questions

Which of the following statements best describes the benefit of whole brain radiation therapy (WBRT) and stereotactic radiosurgery (SRS) compared to WBRT alone for patients with brain metastases based on the RTOG 9508 phase III trial?

A. The addition of WBRT to SRS improves survival for patients with 2-3 lesions compared to WBRT
B. The addition of WBRT to SRS decreases the development of extracranial metastases
C. WBRT and SRS decreases neurologic death compared to WBRT alone
D. The addition of WBRT to SRS significantly improves survival for patients with a single metastasis
E. WBRT and SRS improves neurocognitive outcomes compared to WBRT alone
Brain Metastases
## Brain Metastases: Epidemiology of Brain Metastases

### Primary Tumor

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Relative Prevalence of Brain Metastases*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon: 5%</td>
<td>Annual U.S. incidence: &gt; 170K</td>
</tr>
<tr>
<td>Melanoma: 9%</td>
<td>Ratio Mets/Primary: 10:1</td>
</tr>
<tr>
<td>Unknown primary: 11%</td>
<td>All Cancer Patients: 15 - 30%</td>
</tr>
<tr>
<td>Other known primary: 13%</td>
<td>Autopsy incidence: 10 - 30%</td>
</tr>
<tr>
<td>Breast: 15%</td>
<td>Mean age: 60 years</td>
</tr>
<tr>
<td>Lung: 48%</td>
<td>Median survival: 4-6 months</td>
</tr>
</tbody>
</table>

*Incidence increasing with better systemic Rx and improved survival*

Factors Used to Assess Therapy

- Number of metastases
- Size of lesion(s)
- Location
- Neurological deficits
- Age / KPS
- Primary tumor / stage
- Extracranial disease
- Patient’s input
Brain Metastases: Recursive Partitioning Analysis  

Class I

- **KPS ≥70**
- **Primary:** Controlled
- **Age:** <65
- **Extracranial metastases:** No

**MST 7.1 m**  
20%

Class II

- **KPS ≥70**
- **Primary:** Uncontrolled and / or  
- **Age:** ≥65 and / or  
- **Extracranial metastases:** Yes

**MST 4.2 m**  
65%

Class III

- **KPS <70**

**MST 2.3 m**  
15%
## Graded Prognostic Assessment (GPA) for brain metastases

Evaluated 1960 patients from five randomized RTOG studies

Develop a less subjective, more quantitative, easier to use

<table>
<thead>
<tr>
<th>Score</th>
<th>0</th>
<th>0.5</th>
<th>1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&gt;60</td>
<td>50-59</td>
<td>&lt;50</td>
</tr>
<tr>
<td>KPS</td>
<td>&lt;70</td>
<td>70-80</td>
<td>90-100</td>
</tr>
<tr>
<td>Number of CNS metastases</td>
<td>&gt;3</td>
<td>2-3</td>
<td>1</td>
</tr>
<tr>
<td>Extracranial metastases</td>
<td>Present</td>
<td>-</td>
<td>None</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.5-4</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>1.5-2.5</td>
</tr>
<tr>
<td>0-1</td>
</tr>
</tbody>
</table>

Treatment Strategies: Brain Metastases

• Corticosteroids
• Whole Brain Radiation Therapy (WBRT)
• Surgery +/- WBRT
• Surgery +/- localized radiation
• WBRT + radiation sensitizers
• WBRT + chemotherapy
• Stereotactic radiosurgery (SRS) +/- WBRT
• Chemotherapy
## WBRT-Alternative Fractionation Regimens

### Lack of Progress

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Randomization (Total Dose/# Fractions)</th>
<th>MST (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harwood et al. ('77)</td>
<td>101</td>
<td>30/10 vs. 10/1</td>
<td>4.0-4.3</td>
</tr>
<tr>
<td>Kurtz et al. ('81)</td>
<td>255</td>
<td>30/10 vs. 50/20</td>
<td>3.9-4.2</td>
</tr>
<tr>
<td>Borgelt et al. ('81)</td>
<td>138</td>
<td>10/1 vs. 30/10 vs. 40/20</td>
<td>4.2-4.8</td>
</tr>
<tr>
<td>Borgelt et al. ('81)</td>
<td>64</td>
<td>12/2 vs. 20/5</td>
<td>2.8-3.0</td>
</tr>
<tr>
<td>Chatani et al. ('85)</td>
<td>70</td>
<td>30/10 vs. 50/20</td>
<td>3.0-4.0</td>
</tr>
<tr>
<td>Haie-Meder et al. ('93)</td>
<td>216</td>
<td>18/3 vs. 36/6 vs. 43/13</td>
<td>4.2-5.3</td>
</tr>
<tr>
<td>Murray et al. ('97)</td>
<td>445</td>
<td>54.4/34 vs. 30/10</td>
<td>4.5</td>
</tr>
</tbody>
</table>
About 75% still had evidence of disease in the lung
About 70% still had evidence of disease elsewhere
PCI: 20-30 Gy in 5-12 fractions; mostly 5x4 Gy or 10x3 Gy
PCI is generally well tolerated; side effects may include headache, nausea/vomiting and fatigue

Symptomatic brain metastases

Overall survival

1 year: 14.6% vs. 40.4%
HR: 0.27 (0.16-0.44)
p<0.001

1 year: 27.1% vs. 13.3%
HR: 0.68 (0.52-0.88)
p=0.003

**RTOG 0214**

A PHASE III COMPARISON OF PROPHYLACTIC CRANIAL IRRADIATION VERSUS OBSERVATION IN PATIENTS WITH LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER

<table>
<thead>
<tr>
<th>STRATEGY</th>
<th>RANDOMIZE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage:</td>
<td>PCI: 2 Gy/fraction 15 daily fractions for total dose of 30 Gy</td>
</tr>
<tr>
<td>1. IIIA</td>
<td>ARM 1:</td>
</tr>
<tr>
<td>2. IIIB</td>
<td>ARM 2:</td>
</tr>
<tr>
<td>Histology:</td>
<td>Observation</td>
</tr>
<tr>
<td>1. Non-squamous cell</td>
<td></td>
</tr>
<tr>
<td>2. Squamous cell</td>
<td></td>
</tr>
<tr>
<td>Therapy:</td>
<td></td>
</tr>
<tr>
<td>1. No surgery</td>
<td></td>
</tr>
<tr>
<td>2. Surgery</td>
<td></td>
</tr>
</tbody>
</table>

Closed secondary to accrual issues in 2007
RTOG 0214 PCI for NSCLC

1-year rate for development of brain metastases
18% PCI vs. 7.7% OBS (p=0.004)

# RANDOMIZED SURGICAL TRIALS FOR BRAIN METASTASES

<table>
<thead>
<tr>
<th>Trial</th>
<th>Yr</th>
<th>Rx</th>
<th>N</th>
<th>MS</th>
<th>Fli</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patchell</td>
<td>90</td>
<td>S</td>
<td>25</td>
<td>40</td>
<td>38</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RT</td>
<td>23</td>
<td>15</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Noordijk</td>
<td>94</td>
<td>S</td>
<td>32</td>
<td>43</td>
<td>34</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RT</td>
<td>31</td>
<td>26</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Mintz</td>
<td>96</td>
<td>S</td>
<td>41</td>
<td>24</td>
<td>~</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RT</td>
<td>43</td>
<td>27</td>
<td>~</td>
<td></td>
</tr>
</tbody>
</table>
Randomized trial of surgery versus surgery + WBRT for single metastasis

<table>
<thead>
<tr>
<th></th>
<th>Observation</th>
<th>WBRT</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence anywhere in brain</td>
<td>70%</td>
<td>18%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Local failure</td>
<td>46%</td>
<td>10%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Distant failure</td>
<td>37%</td>
<td>14%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Neurologic death</td>
<td>44%</td>
<td>14%</td>
<td>&lt;0.003</td>
</tr>
<tr>
<td>Survival</td>
<td>43 wks</td>
<td>48 wks</td>
<td>0.39</td>
</tr>
<tr>
<td>KPS ≥70</td>
<td>35 wks</td>
<td>37 wks</td>
<td>0.61</td>
</tr>
</tbody>
</table>

Patchell R et al. JAMA 1998
<table>
<thead>
<tr>
<th>Test</th>
<th>Skill Tested</th>
<th>Real Life Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trailmaking Test A</td>
<td>Visual-motor scanning</td>
<td>Strongly related to everyday living skills: Visual-perceptual ability required for safe, independent ambulation, ability to dial a phone or manage money</td>
</tr>
<tr>
<td>Trailmaking Test B</td>
<td>Executive function, visual-motor sequencing</td>
<td>Executive functions involve judgment, ability to anticipate, set a goal, plan, implement a task, and self-correct mistakes. Self-awareness. Also assesses flexibility of response, ability to shift the course of an ongoing activity</td>
</tr>
<tr>
<td>Hopkins Verbal Learning Test (HVL T)</td>
<td>Verbal memory</td>
<td>Related to issues of safety, management of money and medication, etc.</td>
</tr>
<tr>
<td>Grooved Pegboard</td>
<td>Fine motor speed and dexterity</td>
<td>Strongly related to everyday living skills: writing, shaving, use of keys, etc.</td>
</tr>
<tr>
<td>Controlled Oral Word Association (COWA)</td>
<td>Executive function, verbal fluency</td>
<td>Executive functions as well as verbal communication</td>
</tr>
</tbody>
</table>
Patients Impaired at Presentation

Brain met patients have high rates of baseline deficits - 90%

Favorable Characteristics of Brain Metastases for SRS

- Radiographically distinct on MRI/CT
- Pseudospherical shape
- Displaces normal brain tissue
- Minimal invasion of normal brain
- Size at presentation ≤3 cm
Different linear accelerator/radiosurgery units
Radiosurgery Survival by Class

Retrospective 10-institution comparison to RTOG database

RTOG 95-08
333 RTOG RPA class I or II patients

**Stratify**

- Number of Metastases
  1. Single
  2. 2-3

- Extent of Extracranial Disease
  1. None
  2. Present

**Randomize**

- Arm 1: Whole brain RT to 37.5 Gy/15 fractions/2.5 Gy once daily, 5 days/week followed by radiosurgery to all (1-3) metastase(i)s
- Arm 2: Whole brain RT to 37.5 Gy/15 fractions/2.5 Gy once daily, 5 days/week

Primary endpoint: survival
RTOG 9508

Survival
Single Brain Met

- RT + SRS  MST = 6.5 mos
- RT Alone  MST = 4.9 mos
p=0.0470

## Rate of Regional Failure after RS Alone

### JROSG99-1

<table>
<thead>
<tr>
<th></th>
<th>RS</th>
<th>RS+RT</th>
<th>( P )-value</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>67</td>
<td>65</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MS (mos)</td>
<td>8.0</td>
<td>7.5</td>
<td>.42</td>
<td>-</td>
</tr>
<tr>
<td>LC (1 yr)</td>
<td>73%</td>
<td>89%</td>
<td>.002</td>
<td>1.22</td>
</tr>
<tr>
<td>DBF (6 m)</td>
<td>64%</td>
<td>42%</td>
<td>.003</td>
<td>1.52</td>
</tr>
</tbody>
</table>

**Note:** Deterioration in neurologic function was 59% in the RT group vs 86% in the RS-alone group \((P=0.05)\).

Withholding WBRT significantly increases the risk of brain tumor recurrence and associated risk of decline in neurologic function.

Aoyama H, et al. JAMA. 2006;295;2535-2536
Phase III randomized trial of SRS +/-WBRT

No prior surgery, SRS, or WBRT
No leukemias, lymphomas, germ-cell tumors, SCLC, leptomeningeal disease

RPA class I/II patients with 1-3 lesions from known primary
58 pts

SRS (15, 18 or 24 Gy)
SRS +WBRT (30 Gy/12 fx)

Stratification by
- RPA class (I or II)
- number of lesions (1 or 2 vs 3)
- “radioresistant” histologies (melanoma or RCC vs other)
- Baseline neurocognitive function and medications (opioids, sedatives)

Primary endpoint: neurocognitive function
- Defined as a decrease in HVLT-R total recall at 4 months by more than 5 points
- Trial was closed early by data monitoring committee

Chang EL et al. Lancet Oncol 2009:10:1037-1044
“A mean posterior probability of [neurocognitive] decline of 52% for the SRS plus WBRT group and 24% for the SRS only group.” (96% confidence)

Chang EL et al. Lancet Oncol 2009:10:1037-1044
Intracranial Progression
Higher local and distant brain tumor recurrence without WBRT

Chang EL et al. Lancet Oncol 2009:10:1037-1044
**Phase III randomized trial of surgery or SRS +/-WBRT**

**EORTC 22592-26001**

- **RPA class I/II patients** with 1-3 brain with stable systemic or asymptomatic primary WHO PS 0-2
- **Observation**
- **Surgery**
  - SRS
  - 359 pts
- **Rand**
- **WBRT 30 Gy/10 fx**

**Primary endpoint:** deterioration to WHO PS > 2

**Eligibility:** single ≤ 3.5 cm; 2-3 lesions ≤ 2.5 cm

**PTV = 1-2 mm margin**

**Dose 25 Gy to center with minimum dose of 20 Gy.**

# Phase III randomized trial of surgery or SRS +/- WBRT

**EORTC 22592-26001**

<table>
<thead>
<tr>
<th></th>
<th>Observation</th>
<th>WBRT</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time WHO PS &gt; 2</td>
<td>10 m</td>
<td>9.5 m</td>
<td>0.71</td>
</tr>
<tr>
<td>Median overall survival</td>
<td>10.9 m</td>
<td>10.7 m</td>
<td>0.89</td>
</tr>
<tr>
<td>2-year relapse at initial site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>59%</td>
<td>27%</td>
<td>0.001</td>
</tr>
<tr>
<td>SRS</td>
<td>31%</td>
<td>19%</td>
<td>0.04</td>
</tr>
<tr>
<td>2-year relapse at initial site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>42%</td>
<td>23%</td>
<td>0.008</td>
</tr>
<tr>
<td>SRS</td>
<td>48%</td>
<td>33%</td>
<td>0.023</td>
</tr>
</tbody>
</table>

Phase III trial of surgery or SRS +/-WBRT
EORTC 22592-26001

• Salvage therapies were more common in the observation arm (31%) versus the WBRT arm (3%).
• Intracranial progression caused death in
  – 70 (44%) of 179 patients in the observation arm
  – 50 (28%) of 180 patients in the WBRT arm (p<0.002)
• Progression free survival
  – 4.6 months (WBRT) versus 3.4 months (observation) (p=0.02)
• Intracranial failure
  – 78% (observation) versus 42% (WBRT) (p<0.001)
• Functional independence has bias and variability

**NCCTG N0574 (Intergroup)**

*Primary endpoint: neurocognitive status*

<table>
<thead>
<tr>
<th>Randomize</th>
<th>PE, QOL, &amp; Related Assessments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm 1: RS*</td>
<td>Arm 2: RS* + WBRT (30 Gy/12 fx)</td>
</tr>
</tbody>
</table>

- **Arm 1:**
  - **<2.0 cm:** 24 Gy
  - **2 - 2.9 cm:** 20 Gy
- **Arm 2:**
  - **<2.0 cm:** 22 Gy
  - **2 - 2.9 cm:** 18 Gy

Patients with histologically confirmed extra-cerebral primary tumor and 1 to 3 brain metastases detected by MRI

152 pts
SRS of the Post-Operative Cavity

- 72 patients treated at Stanford from 1998-2006
- PTV = GTV in 76%
- 1y LC: 79%

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GTR vs. STR</td>
<td>.52</td>
</tr>
<tr>
<td>Histology</td>
<td>.49</td>
</tr>
<tr>
<td>Number of Fractions</td>
<td>.92</td>
</tr>
<tr>
<td>Dose</td>
<td>.92</td>
</tr>
<tr>
<td>BED</td>
<td>.92</td>
</tr>
<tr>
<td>Conformity Index</td>
<td>.04</td>
</tr>
<tr>
<td>Volume</td>
<td>.29</td>
</tr>
</tbody>
</table>

Based on result, using 2 mm margin on GTV

## Post-Operative Cavity SRS

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Margin (mm)</th>
<th>1 year LC</th>
<th>LC (crude)</th>
<th>Distant Brain Failure (Crude)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soltys IJ ROBP 2008</td>
<td>67</td>
<td>0</td>
<td>79</td>
<td>86</td>
<td>51</td>
</tr>
<tr>
<td>Mathieu NSurg 2008</td>
<td>40</td>
<td>1</td>
<td>NR</td>
<td>73</td>
<td>54</td>
</tr>
<tr>
<td>Hwang J N Onc 2009</td>
<td>21</td>
<td>0</td>
<td>NR</td>
<td>100</td>
<td>33</td>
</tr>
<tr>
<td>Karlovits NS Focus 2009</td>
<td>52</td>
<td>2</td>
<td>82</td>
<td>82</td>
<td>44</td>
</tr>
<tr>
<td>Do IJ ROBP 2009</td>
<td>30</td>
<td>1-3</td>
<td>82</td>
<td>87</td>
<td>63</td>
</tr>
<tr>
<td>Jagannathan JNS 2009</td>
<td>47</td>
<td>2-3</td>
<td>NR</td>
<td>94</td>
<td>72</td>
</tr>
<tr>
<td>Iwai Surg Onc 2008</td>
<td>21</td>
<td>0</td>
<td>82</td>
<td>76</td>
<td>52</td>
</tr>
<tr>
<td>Stanford series</td>
<td>120</td>
<td>0</td>
<td>84</td>
<td>59</td>
<td></td>
</tr>
</tbody>
</table>

29 7. Slide courtesy of Dr. Scott Soltys
N107C

SRS vs. WBRT Resected Brain Mets

Determine if neurocog progression less at 6 months with SRS

Resected Brain Met

STRATIFY

Age <60 vs. >60

# Brain Mets 1 vs. 2-4

Extracranial Dz

Histology Lung vs. Radioresistant vs. Others

Surgical Cavity <3 vs. > 3 cm

RANDOMIZE

SRS Surgical Bed + SRS to unresected brain metastases

WBRT* + SRS to unresected metastases

*37.5 Gy/15 fx

192 patients
### N107C
#### Treatment

<table>
<thead>
<tr>
<th>SRS dosing guidelines:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesions &lt; 4.2 cc receive 20 Gy</td>
<td></td>
</tr>
<tr>
<td>Lesions ≥ 4.2 to &lt; 8.0 cc receive 18 Gy</td>
<td></td>
</tr>
<tr>
<td>Lesions ≥ 8.0 to &lt; 14.4 cc receive 17 Gy</td>
<td></td>
</tr>
<tr>
<td>Lesions ≥ 14.4 to &lt; 20 cc receive 15 Gy</td>
<td></td>
</tr>
<tr>
<td>Lesions ≥ 20 to &lt; 30 cc receive 14 Gy</td>
<td></td>
</tr>
<tr>
<td>Lesions ≥ 30 cc and ≤ 5 cm max 12 Gy</td>
<td></td>
</tr>
</tbody>
</table>

*2 mm margin. Soltys 2010*
Potential strategies to minimize risk for neurocognitive decline

- Pharmacologic
  - RTOG 0614 memantine
- Technologic
  - RTOG 0933 Hippocampal sparing
Summary

• Stereotactic radiosurgery represents a safe and effective strategy for managing patients with brain metastases.
• Class I data supports the use of SRS+WBRT and SRS alone in some patients.
• SRS alone lead to higher local and distant brain failures compared to SRS+WBRT.
• SRS to resection cavity requires further investigation but improves local control compared to observation.
Malignant Gliomas
Early randomized radiation trials

**BTCG 6901**
- Randomized trial that supported the use of radiation therapy in the treatment of malignant gliomas
  - Survival: 14 weeks with supportive care
  - 36 weeks with radiation therapy

**BTCG 7201**
- Radiation with or without chemotherapy was significantly better than MeCCNU alone

Walker et al. NEJM 303:1323-1329
Glioblastoma Multiforme - Dose

- Retrospective review of 3 BTSG protocols (1966 – 1975)
- 621 patients

<table>
<thead>
<tr>
<th></th>
<th>No RT</th>
<th>≤ 45 Gy</th>
<th>50 Gy</th>
<th>55 Gy</th>
<th>60 Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS (weeks)</td>
<td>18</td>
<td>13.5</td>
<td>28</td>
<td>36</td>
<td>42</td>
</tr>
<tr>
<td>p-value</td>
<td>0.346</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Glioblastoma Multiforme – Role of Hyperfractionation

- RTOG 90-06
  - Phase III study of hyperfractionated RT (72 Gy / 1.2 Gy BID) versus conventional RT (60 Gy / 2 Gy QD)
  - BCNU used as chemotherapy
- Analysis of multiple studies
  - No benefit to altered fractionation

Therapeutic Role of Surgery in Malignant Gliomas

- Analysis of 416 patients with GBM undergoing resection at MDACC
- Preoperative and postoperative tumor volumes measured
- Controlled for other prognostic variables such as age, performance status, tumor characteristics (necrosis, enhancement), and location
- Significant increase in survival with >98% resection: 13 vs 8.8 month median ($P <0.0001$)
- Other studies support this finding

Chemotherapy Wafers:
Local Chemotherapy Delivery
**Surgical Management**

**Overall Survival Intent-to-Treat Group**

**Note:** GBM patients (n=207) did not achieve survival benefit

Rationale behind stereotactic radiation techniques

• Majority of GBM fail locally
• “Boost” techniques focally escalate radiation dose to areas of greatest tumor density.
• Sharp dose fall-off spares normal brain tissue
• Techniques include brachytherapy (temporary or permanent) and stereotactic radiosurgery.
**BTCG 8701**

**Randomization**
- DX Surgery

**Temporary I-125 Seeds (60 Gy)**
- Dose rate 40 cGy/hr
- 5 - 7 days.
- Removal and Resection if Necessary

**WBRT**
- 172 cGy/day x 25 fx
- 4300 cGy

**plus**

**C/D**
- 172 cGy/ff x 10 fx
- 1720 cGy
- 6020 cGy total

**or**

**Partial fields**
- 172 cGy x 35 fx to tumor with 3 cm border
- 6020 cGy total

**Plus**
- BCNU IV 200 mg/m² every 8 weeks
Selker RG et al. Neurosurg 51:343-357, 2002
Randomized trial for malignant astrocytomas: PMH

- 140 pts randomized between 1986-1996
- Randomization was 50 Gy/25 fx vs 50 Gy/25 fx + temporary I-125 implant 60 Gy
- Did not stratify based on tumor type
- Median survival
  - 13.8 months (B) vs 13.2 months
  - 15.7 months for those who underwent implant
- Univariate
  - age $\leq 50$, KPS $> 90$, use of chemo at recurrence, reoperation

PMH Randomized Trial

Multi-institutional results of SRS boost as part of initial management for GBM patients

- Comparative study among 3 institutions (Univ. FL, Univ. Wisc., JCRT) using the RTOG recursive partitioning analysis.
  115 patients
  2 year survival 38%
  Median survival 24 months

RTOG 9305
A PHASE III STUDY COMPARING STEREOTACTIC EXTERNAL BEAM IRRADIATION FOLLOWED BY RT WITH BCNU TO RT WITH BCNU FOR SUPRATENTORIAL GLIOBLASTOMA MULTIFORME

Age
1. >=18 to <50
2. >=50

Performance Status
1. Karnofsky 90-100
2. Karnofsky 60-80

Arm 1: 60 Gy/30 fractions/2 Gy once daily, BCNU 80 mg/m² i.v. days 1-3 of RT then q 8 weeks for a total of 6 cycles.

Arm 2: Radiosurgery followed by 60 Gy/30 fractions/2 Gy once daily, BCNU 80 mg/m² i.v. days 1-3 of RT then q 8 weeks for a total of 6 cycles.
RTOG 9305
Phase III trial SRS+RT+BCNU vs. RT+BCNU

- Supratentorial tumor < 4 cm diameter
- RT 6000 cGy/30 fx with BCNU 80 mg per meter sq. days 1-3 of RT then q 8 weeks.

<table>
<thead>
<tr>
<th>Dose</th>
<th>Max diameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>2400 cGy</td>
<td>&lt;20 mm</td>
</tr>
<tr>
<td>1800 cGy</td>
<td>21-30 mm</td>
</tr>
<tr>
<td>1500 cGy</td>
<td>31-40 mm</td>
</tr>
</tbody>
</table>
9305 Overall Survival

Percent Alive

Months from Randomization

RT
RS + RT

p = 0.5328
## Survival: Pre-Op Tumor ≤ 4 cm

<table>
<thead>
<tr>
<th></th>
<th>RT</th>
<th>RS + RT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median Survival:</strong></td>
<td>14.1 mos</td>
<td>11.4 mos (p = 0.0925)</td>
</tr>
<tr>
<td><strong>2-yr Survival:</strong></td>
<td>18%</td>
<td>12%</td>
</tr>
<tr>
<td><strong>3-yr Survival:</strong></td>
<td>13%</td>
<td>5%</td>
</tr>
</tbody>
</table>
## Results for recurrent GBM

<table>
<thead>
<tr>
<th>TECHNIQUE</th>
<th>DOSE (Gy)</th>
<th>SURVIVAL</th>
<th>REOP. RATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>JCRT I-125</td>
<td>50.0</td>
<td>11.5 m</td>
<td>44%</td>
</tr>
<tr>
<td>UCSF I-125</td>
<td>64.4</td>
<td>12.0 m</td>
<td>38%</td>
</tr>
<tr>
<td>JCRT SRS</td>
<td>13.0</td>
<td>10.0 m</td>
<td>22%</td>
</tr>
<tr>
<td>CCF SRS</td>
<td>15.0</td>
<td>10.3 m</td>
<td>18%</td>
</tr>
</tbody>
</table>
EORTC 26981-22981 and NCIC CE.3: Schema

*PCP prophylaxis was required

![Diagram of treatment schema]

Concomitant TMZ/RT*  →  Adjuvant TMZ

RT Alone

Temozolomide 75 mg/m² po qd for 6 weeks, then 150–200 mg/m² po qd d1–5 every 28 days for 6 cycles

Focal RT daily — 30 x 200 cGy; Total dose 60 Gy

Stupp, NEJM 352, 2005
EORTC/NCIC study phase III study of GBM patients

- Randomized trial of 573 patients from 85 centers were randomized to RT vs. RT + TMZ followed by adjuvant TMZ
  - RT (60 Gy/30 fx)
  - TMZ 75 mg/m²/day for 42 days followed by 6 cycles of adjuvant TMZ (150-200 mg/m²/day, daily X5 days, q 28 days
- 18-70 years old with WHO grade IV
- Primary endpoint was survival

Stupp R et al. NEJM 352:987-996, 2005
EORTC/NCIC study: Phase III study of GBM patients

- Results
  - RT delivered as prescribed in 93%
  - Concomitant TMZ
    - Without interruption 76%
    - Temporarily interrupted 11%
    - Prematurely discontinued 12%
  - Adjuvant TMZ
    - All 6 cycles 36%
  - Grade 3/4 hematologic toxicities
    - Concomitant 6%
    - Adjuvant 16%

Stupp R et al. NEJM 352:987-996, 2005
EORTC Phase III Trial Overall Survival

Stupp, NEJM 2005

<table>
<thead>
<tr>
<th></th>
<th>RT</th>
<th>TMZ/RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, mo:</td>
<td>12.1</td>
<td>14.6</td>
</tr>
<tr>
<td>2-yr survival:</td>
<td>10%</td>
<td>26%</td>
</tr>
<tr>
<td>HR [95% C.I.]:</td>
<td>0.63</td>
<td>[0.52-0.75]</td>
</tr>
</tbody>
</table>

\[ p < 0.0001 \]
Impact of MGMT on outcomes

- Hegi et al. NEJM 2005
  - 206 samples (36% of all patients) successfully analyzed for promoter methylation status (inactivation) of MGMT, from 573 patients enrolled on EORTC 22981.
  - Analysis performed using methylation-specific PCR
Impact of MGMT on outcomes

• Kaplan–Meier Estimates of Overall Survival according to MGMT Promoter Methylation Status
Impact of MGMT on outcomes

**OS**

15.3 vs 21.7

**PFS**

5.9 vs 10.3
Placing things into perspective – the big picture.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>MGMT promoter?</th>
<th>2y OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT+TMZ</td>
<td>Methylated</td>
<td>46%</td>
</tr>
<tr>
<td>RT</td>
<td>Methylated</td>
<td>23%</td>
</tr>
<tr>
<td>RT+TMZ</td>
<td>Unmethylated</td>
<td>14%</td>
</tr>
<tr>
<td>RT</td>
<td>Unmethylated</td>
<td>2%</td>
</tr>
</tbody>
</table>
RTOG 0525/EORTC: Phase III GBM Trial; n = 1173 assessed for eligibility

Patients with
Newly diagnosed GBM
KPS ≥ 60
Age > 18 years
Tissue available

Radiation treatment
(60 Gy in 2 Gy Fractions)
Concurrent daily TMZ
(75 mg/m2 qday x 42)
Analysis for MGMT methylation

Arm A:
TMZ (200 mg/m²)
days 1-5 of 28 day cycle
12 cycle maximum

Arm B:
TMZ (100 mg/m²)
days 1-21, of a
28 day cycle
12 cycle maximum

"Stratify by:
Age (< 50 vs ≥ 50)
KPS (60-80 vs 90-100)
Extent of tumor resection
(Biopsy and subtotal vs gross total)
MGMT methylation status

Tumor tissue block > 1 cm²

Determine if increasing the “dose-density” of TMZ enhances efficacy (overall survival.)

Enrollment Jan 2006-Jun 2008
Primary Outcomes by Treatment

Overall survival sd TMZ vs dd TMZ

- Arm 1: 411 patients, 257 months
- Arm 2: 420 patients, 256 months

- Total: 831 patients, 513 months

p (1-sided) = 0.83
HR (95% CI) = 1.03 (0.88, 1.20)

Progression-free survival sd TMZ vs dd TMZ

- Arm 1: 374 patients, 187 months
- Arm 2: 379 patients, 184 months

- Total: 753 patients, 371 months

p (2-sided) = 0.08
HR (95% CI) = 0.87 (0.75, 1.00)

Slide courtesy of Dr. Mark Gilbert
Outcomes by MGMT Status

Slide courtesy of Dr. Mark Gilbert
<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall Survival</th>
<th>Progression Free Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p-value</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Treatment: Arm 2 vs 1</td>
<td>0.51</td>
<td>1.06 (0.90-1.24)</td>
</tr>
<tr>
<td>Methylation Status: Unmeth vs meth</td>
<td>&lt;0.0001</td>
<td>1.81 (1.51-2.17)</td>
</tr>
<tr>
<td>Radiation EORTC vs RTOG</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>RPA (IV vs III)</td>
<td>0.0001</td>
<td>1.63 (1.32-2.03)</td>
</tr>
<tr>
<td>RPA (V vs III)</td>
<td>&lt;0.0001</td>
<td>2.89 (2.22-3.75)</td>
</tr>
</tbody>
</table>

Slide courtesy of Dr. Mark Gilbert
<table>
<thead>
<tr>
<th>Patient Group</th>
<th>N</th>
<th>Overall Survival (Months)</th>
<th>Progression Free Survival (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All eligible</td>
<td>1120</td>
<td>16.0</td>
<td>7.5</td>
</tr>
<tr>
<td>All randomized</td>
<td>833</td>
<td>17.7</td>
<td>8.2</td>
</tr>
<tr>
<td>Arm 1</td>
<td>411</td>
<td>18.9</td>
<td>7.5</td>
</tr>
<tr>
<td>Arm 2</td>
<td>422</td>
<td>16.8</td>
<td>8.8</td>
</tr>
<tr>
<td>MGMT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm 1</td>
<td>245</td>
<td>23.2</td>
<td>10.5</td>
</tr>
<tr>
<td>Arm 2</td>
<td>517</td>
<td>16.0</td>
<td>7.8</td>
</tr>
<tr>
<td>Unmethylated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm 1</td>
<td>122</td>
<td>23.5</td>
<td>8.8</td>
</tr>
<tr>
<td>Arm 2</td>
<td>123</td>
<td>21.9</td>
<td>11.7</td>
</tr>
<tr>
<td>Methylated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm 1</td>
<td>254</td>
<td>16.6</td>
<td>7.1</td>
</tr>
<tr>
<td>Arm 2</td>
<td>263</td>
<td>15.4</td>
<td>8.2</td>
</tr>
</tbody>
</table>
RTOG 0825
Phase III trial of RT+TMZ ± bevacizumab

Central Pathology
- Central Pathology Confirmation
  - Histology
  - Adequacy of Tissue for Analysis

Concurrent Phase
- Stratify
  - MGMT Status
  - Molecular Profile
- RT (30 Gy)
- TMZ (75 mg/m²/d)

Adjuvant Phase
- Arm A
  - 30 Gy + Daily TMZ (75 mg/m² qd) + Placebo q 2 wks
  - TMZ (150-200 mg/m²) d 1-5 q28d X 12 cycles + placebo q 2 wks
- Arm B
  - 30 Gy + Daily TMZ (75 mg/m² qd) + Bev (10 mg/m² q 2 wks)
  - TMZ (150-200 mg/m²) d 1-5 q28d X 12 cycles + Bev (10 mg/m² q 2 wks)

GBM with supratentorial component
- Preop & Postop MRI
- Sample Size = 720
Adjuvant Chemotherapy for AA: PCV vs BCNU

- Patients enrolled before radiation, 60 Gy plus hydroxyurea
- Randomized to BCNU (200 mg/m² q 6-8 weeks x 1 year max) or PCV (CCNU 110 mg/m² day 1, PCB 60 mg/m² day 8-21, vincristine 1.4 mg/m² day 1 and 8 q 6-8 weeks x 1 year max)
  - Progression-free survival and survival compared

## PCV vs BCNU for AA

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median (m)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TTP</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT+HU+BCNU</td>
<td>62.7</td>
<td>.025</td>
</tr>
<tr>
<td>RT+HU+PCV</td>
<td>125.6</td>
<td></td>
</tr>
<tr>
<td><strong>Survival</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT+HU+BCNU</td>
<td>82.1</td>
<td>.021</td>
</tr>
<tr>
<td>RT+HU+PCV</td>
<td>157.1</td>
<td></td>
</tr>
</tbody>
</table>

Anaplastic Astrocytoma: PCV Does Not Improve Survival over BCNU

- 257 patients were treated with BCNU (RTOG protocols 7018, 8302, and 9006); 175 patients were treated with PCV (RTOG protocol 9404)
- The stratified analysis showed no improvement in survival by treatment group and there does not seem to be any survival benefit to PCV chemotherapy
- The Cox model identified only age, KPS, and extent of surgery as important variables influencing survival, not treatment group

AA: PCV vs BCNU: RTOG Database

Fig 1. Overall survival of all patients treated either with BCNU or PCV chemotherapy. There was no statistical difference in survival between the two groups ($P = .5460$).

RTOG 9404 phase III trial for Anaplastic Astrocytoma RT+PCV +/- BUdR

- 268 pts were randomized through NCOG, RTOG, SWOG, and NCCTG
- 190 were eligible for analysis
- BUdR (96 hour infusion) given each week of RT
- RT 5940 cGy/33 fx
- **Median survival**
  - 4.1 years versus 4.6 years (BUdR) \( p=0.61 \)
- Based on results, study was closed early

Intergroup 9813: Phase I/III AA Trial

**Phase I**

Arm 1: XRT + BCNU 200 mg/m² + TMZ 150 mg/m² x 5d q 8 wks
15 pts enrolled: 7/10 eligible pts needed dose modifications

Arm 5: XRT + TMZ 150 mg/m² x 5d + BCNU 150 mg/m² q 8 wks
15 pts enrolled. Combination produces unacceptable toxicity*

**Phase III n=480**

Arm 2: XRT + TMZ 150 mg/m² x 5d q 4 wks

Arm 3: XRT + BCNU 80 mg/m² q 8 wks

Over 200 patients enrolled: study closed in 2007 secondary to poor accrual

Anaplastic oligodendroglionma

Dense network of branching capillaries

Clear cytoplasm and well-defined plasma membrane
Molecular Diagnostics:
1p and 19q loss (FISH Assay)
Anaplastic Oligodendroglioma
Molecular Markers for Response

- Chromosome loss 1p + 19q predicts
  - 100% RR
  - 95% 5 years
  - Median survival >10 yrs
- Absence of both →
  - 25% response
  - Median survival 2 years
- Appears true for anaplastic oligoastrocytomatas (mixed anaplastic oligos)

RTOG 9402

**Stratify**
- Age <50 vs. ≥50
- KPS 60–70 vs. ≥80
- Moderate anaplasia vs. highly anaplastic

**Randomize**
- **Experimental Arm:** Intensive-PCV x 4 (q 6 wks), then RT 5940 cGy/33 fx
- **Standard Arm:** RT 5940 cGy/33 fx

Enrolled 289 patients

Endpoints: 1° overall survival, 2° TTP, toxicity and quality of life
EORTC 26951

**Experimental Arm:**
RT (5940 cGy/33 fx) followed by 6 cycles of PCV

**Standard Arm:**
RT 5940 cGy/33 fx

Enrolled 368 patients

Endpoints: 1º overall survival, 2º TTP, toxicity and quality of life
## Results

### RTOG 94-02
- 289 patients accrued
- 70% of patients with pure AO
- 68% age < 50 years
- ≥18 years old
- 148 on chemo+XRT, 143 on XRT alone
- groups were balanced for age, KPS
- tissue for 1p 19q available for 70%
- 50.4 Gy + 9 Gy boost

### EORTC 26951
- 368 patients accrued
- 72% of patients with pure AO
- Median age = 49
- 18-70 years old
- 185 on XRT+chemo, 183 on XRT alone
- groups were balanced for age, KPS
- tissue for 1p 19q available for 85%
- 45 Gy + 14.4 Gy boost
Results

**RTOG 94-02**
- Median f/u 5 years
- Toxicity:
  - 57% with grade III or IV heme toxicity with PCV, 1 death
- 1p 19q
  - 46% with 1p 19q LOH: median survival > 7 years
  - 1p 19q intact: median survival 2.8 years
(P < 0.001)

**EORTC 26951**
- Median f/u 5 years
- Toxicity
  - 46% with grade III or IV heme toxicity
- 1p 19q
  - 25% with 1p 19q LOH; median survival not reached
  - 1p 19q intact: median survival 23 months (P < .001)

Studies confirm importance of 1p 19q LOH in prospective trials
Kaplan-Meier estimates of overall survival by treatment group (RT vs. RT and PCV)

Overall survival in both treatment arms in the groups with and without combined 1p/19q loss
Updated results from RTOG 9402

• The use of PCV chemotherapy is **predictive** for survival for AO with 1p19q deletion.

• Median survival was 7 years RT group vs. 14 years for RT + PCV group
Anaplastic gliomas

RTOG t(1p;19q)

ON HOLD

NEWLY DIAGNOSED ANAPLASTIC GLIOMA t(1p;19q) → RANDOMIZE

- RT alone
- TMZ alone
- RT + TMZ

TMZ = temozolomide
Anaplastic gliomas (CATNON/RTOG 0834) *not* t(1p;19q)

- Newly diagnosed Anaplastic Glioma *not* t(1p;19q)

- Randomize

- Concurrent vs none

- Adjuvant vs none

- RT/TMZ

- TMZ 12 cycles

- No TMZ

RT/TMZ = Temozolomide
Conclusions

• Based on the results of the EORTC/NCI trial, RT+TMZ is the standard of care for newly diagnosed GBM patients.

• Based on the results of RTOG 9305, SRS is not recommended for patients with newly diagnosed GBM.

• For patients with an anaplastic or mixed oligoastrocytoma, patients whose tumors have 1p and 19q LOH live significantly longer than other patients.
Low grade gliomas

- Low grade represent about 10% of primary brain tumor cases
- Approximately 3,000 cases per year
- Genetic predisposition with NF-1, NF-2, tuberous sclerosis, and Li-Fraumeni
- Occur in younger patients (4th decade)
- Supratentorial location in adults (insula and supplementary motor areas)
NCCTG 86-72-51/RTOG 9110

• Patients (NCCTG/ECOG/RTOG)
  – 211 pts with low-grade gliomas from 1986-1994
  – Study Design
    50.4 Gy/1.8, n=101
    64.8 Gy/1.8, n=102

Results
5-year OS: 72% for 50.4 Gy arm vs. 65% for 64.8 Gy arm (p = 0.48)
No difference in time to progression
Age < 40, oligo predominance, tumor < 5 cm, GTR have better OS

Shaw et al. JCO 2002; 20:2267.
EORTC 22845

Karim et al. IJROBP 1996; 36:549

• Patients
  – 311 pts from 1986-1997
    • 303 pts assessable
  – Median follow-up: 7.8 yrs

• Study Design
  Resection or Biopsy
  Randomization
  Immediate RT 54 Gy/1.8, n=150
  Delayed RT 54 Gy/1.8, n=140

*No formal QOL, Neurocog/Neurologic studies performed
## EORTC 22845: Outcomes

<table>
<thead>
<tr>
<th>Endpoint/Finding</th>
<th>Immediate RT</th>
<th>Delayed RT</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Survival</td>
<td>7.4 yrs</td>
<td>7.2 yrs</td>
<td>NS</td>
</tr>
<tr>
<td>Progression-Free Survival</td>
<td>5.3 yrs</td>
<td>3.4 yrs</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Malignant Transformation*</td>
<td>72%</td>
<td>66%</td>
<td>NS</td>
</tr>
<tr>
<td>Seizures at 1-year**</td>
<td>25%</td>
<td>41%</td>
<td>.03</td>
</tr>
</tbody>
</table>

*Among histologically confirmed recurrences
**No difference between groups at baseline

Karim et al. IJROBP 1996; 36:549.
**RTOG 98-02 (RTOG, SWOG, ECOG)**

Phase I: Low risk LGG- Age <40 and GTR → observed (111 patients)

Phase III: High risk LGG- Age >40, subtotal resection or biopsy → randomized to RT (54 Gy/1.8) alone or RT + 6 cycles of PCV (Procarbazine, Lomustine, Vincristine) (251 patients)

Median f/u: 5.9 years

Observation arm patients (low risk): 5 yr OS 94% and PFS 50%

Treatment arm patients (RT vs. chemo-RT):
- 5-year OS RT 63% vs. RT + PCV 72% (NS)
- 5-year PFS RT 46% vs. RT + PCV 63% (p=0.06, NS)

Increased acute grade 3-4 toxicity with chemo-RT (67%) vs. RT (9%)

For 2 year survivors (n=211), OS for an additional 3 years RT 72% vs. RT + PCV 84% (SS); PFS RT 52% vs. RT + PCV 74% (SS).

Shaw EG et al. 2006 ASCO Meeting
Shaw EG et al. 2008 ASCO Meeting
Five unfavorable prognostic factors from two EORTC phase III trials

- Age ≥ 40 years
- Largest diameter ≥ 6 cm
- Tumor crossing midline
- Astrocytoma dominant histology
- Neurologic symptoms (Pignatti et al).

RTOG 0424
Phase II study of RT with TMZ for LGG

Eligibility (3 of 5 factors)
1. Age > 40
2. Tumor crossing midline
3. NFS > 1
4. Astrocytoma dominant
5. Preop tumor > 6 cm in diameter

RT (5040 cGy/28 fx) + TMZ 75 mg/m² daily

Cycles 1-12
Post-RT TMZ 150 mg/m² p.o. daily on days 1-5 q28 days. Cycles will be repeated every 28 days for up to 12 cycles
EORTC 22033-26033

- Eligibility: High risk LGGs (3/5 EORTC features) and biopsy only
- Stratified by 1p status
- Primary endpoint: PFS
- Secondary endpoint: QOL, toxicity, MMSE, NCF

Biopsy

Randomization

Temozolomide q28 days for up to 12 cycles

RT alone 50.4 Gy/28 fx

Closed March 2010
ECOG (E3F05)

Phase III study of RT with or without TMZ for symptomatic or progressive LGG

Stratification Factors

• Age < vs. ≥ 40 years

• 1p and 19q both deleted vs. either/both intact vs indeterminate

• Pre-op max. tumor diameter < vs. ≥ 6 cm (based on T2 or FLAIR)

• KPS 60-70 vs. 80-100

• Presence vs. absence of contrast enhancement on pretx MRI scan

STEP 0

STEP 1

ARM A

RT (5040 cGy/ 28 fx)

Follow-up

ARM B

Cycles 1-12

RT (5040 cGy/ 28 fx) + TMZ 75 mg/m² daily

Follow-up

Post-RT TMZ 150 mg/m² p.o.dail on days 1-5 q28 days. Cycles will be repeated every 28 days for up to 12 cycles
Benign Brain Tumors

- Meningiomas
- Pituitary adenomas
- Acoustic neuromas
Introduction: Meningiomas

- Most common primary intracranial neoplasm
- ~30% of all intracranial neoplasms
- Estimated prevalence is 97.5 per 100,000
- Most are identified on imaging alone
- F:M – 2:1 supratentorial

Klaus et al. Neurosurg 57:1088, 2005
Central Brain Tumor Registry 2007
Distribution of All Primary Brain and CNS Tumors by Histology (N=295,986)

CBTRUS Statistical Report: NPCR and SEER Data from 2004-2008

- Glioblastoma: 16.3%
- Meningioma: 34.7%
- Pituitary: 13.5%
- All Other: 6.7%
- Germ Cell Tumor: 0.5%
- Other Neuroepithelial: 5.0%
- Lymphoma: 2.3%
- Nerve Sheath: 8.5%
- Craniopharyngioma: 0.9%
- Astrocytoma: 6.8%
- Ependymoma: 1.8%
- Oligodendroglioma: 1.9%
- Embryonal, including Medulloblastoma: 1.1%

Gliomas (ICD-O-3: 9380-9384, 9391-9460, 9480) account for 30% of all tumors and 80% of malignant tumors.
### Meningioma

#### EPIDEMIOLOGY

**Most Common Brain and CNS Tumors by Age**

**CBTRUS Statistical Report: NPCR and SEER Data 2004-2006**

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Most Common Histology</th>
<th>2nd Most Common Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>Embryonal / Medulloblastoma</td>
<td>Pilocytic Astrocytoma</td>
</tr>
<tr>
<td>5-9</td>
<td>Pilocytic Astrocytoma</td>
<td>Malignant Glioma , NOS</td>
</tr>
<tr>
<td>10-14</td>
<td>Pilocytic Astrocytoma</td>
<td>Neuronal / Glial</td>
</tr>
<tr>
<td>15-19</td>
<td>Pituitary</td>
<td>Pilocytic Astrocytoma</td>
</tr>
<tr>
<td>20-34</td>
<td>Pituitary</td>
<td><strong>Meningioma</strong></td>
</tr>
<tr>
<td>35-44</td>
<td>Meningioma</td>
<td>Pituitary</td>
</tr>
<tr>
<td>45-54</td>
<td>Meningioma</td>
<td>Glioblastoma</td>
</tr>
<tr>
<td>55-64</td>
<td>Meningioma</td>
<td>Glioblastoma</td>
</tr>
<tr>
<td>65-74</td>
<td>Meningioma</td>
<td>Glioblastoma</td>
</tr>
<tr>
<td>75-84</td>
<td>Meningioma</td>
<td>Glioblastoma</td>
</tr>
<tr>
<td>85+</td>
<td>Meningioma</td>
<td>Neoplasm, unspecified</td>
</tr>
</tbody>
</table>

Treatment Options

Observation
Surgery
Radiotherapy
Radiosurgery
Chemotherapy
Limitations of Surgery

- Recur despite “complete resection”
- Even with gross total resection, tumor recurrence rates can range from 18-25% at 10 years
- Surgically inaccessible
- Invasion of normal neural or vascular structures
- Higher grade lesion have a more aggressive clinical course
### Simpson Criteria

<table>
<thead>
<tr>
<th>Degree of Resection</th>
<th>Recurrence rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete resection with dural margin</td>
<td>9%</td>
</tr>
<tr>
<td>Complete resection with coagulation of dura</td>
<td>19%</td>
</tr>
<tr>
<td>Complete resection (no treatment of dura)</td>
<td>29%</td>
</tr>
<tr>
<td>Partial removal leaving tumor <em>in situ</em></td>
<td>40%</td>
</tr>
<tr>
<td>Decompression</td>
<td>NA</td>
</tr>
</tbody>
</table>
# Meningioma

## Likelihood of total excision

### Historical MGH experience

<table>
<thead>
<tr>
<th>Tumor Location</th>
<th>n</th>
<th>% Total Excision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Convexity</td>
<td>47</td>
<td>96 %</td>
</tr>
<tr>
<td>Orbit</td>
<td>5</td>
<td>80 %</td>
</tr>
<tr>
<td>Spine</td>
<td>18</td>
<td>78 %</td>
</tr>
<tr>
<td>Olfactory Groove</td>
<td>22</td>
<td>77 %</td>
</tr>
<tr>
<td>Parasagittal Area/Falx</td>
<td>38</td>
<td>76 %</td>
</tr>
<tr>
<td>Parasellar Region</td>
<td>28</td>
<td>57 %</td>
</tr>
<tr>
<td>Posterior Fossa</td>
<td>31</td>
<td>32 %</td>
</tr>
<tr>
<td>Sphenoid Ridge</td>
<td>36</td>
<td>28 %</td>
</tr>
<tr>
<td><strong>TOTAL:</strong></td>
<td>225</td>
<td><strong>64%</strong></td>
</tr>
</tbody>
</table>

## Pathologic subtypes of Intracranial Meningioma

<table>
<thead>
<tr>
<th>Grade</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>90</td>
</tr>
<tr>
<td>Atypical</td>
<td>5</td>
</tr>
<tr>
<td>Malignant</td>
<td>3-5</td>
</tr>
</tbody>
</table>

## Meningioma Grade (WHO 2000 & 2007)

<table>
<thead>
<tr>
<th>Benign WHO Grade I</th>
<th>Atypical WHO Grade II</th>
<th>Malignant/Anaplastic WHO Grade III</th>
</tr>
</thead>
<tbody>
<tr>
<td>No mitoses</td>
<td>Frequent mitoses (≥ 4/10 hpf)</td>
<td>High mitotic index (≥20/10 hpf)</td>
</tr>
<tr>
<td>No necrosis</td>
<td>3 or more of the following:</td>
<td>Focal or diffuse loss of meningothelial differentiation resembling sarcoma, carcinoma, or melanoma</td>
</tr>
<tr>
<td>No brain invasion</td>
<td>• Sheeting architecture with loss of the whorling pattern</td>
<td>Frankly malignant features</td>
</tr>
<tr>
<td></td>
<td>• Hypercellularity (focal or diffuse)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Prominent nucleoli</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Small cells with high nucleus: cytoplasm ratio</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Foci of spontaneous necrosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Brain invasion: finger-like projections that breach the pia mater, engulf individual islands of brain tissue, and evoke reactive astrocytosis</td>
<td></td>
</tr>
</tbody>
</table>

Meningioma

Recurrence-Free Survival by Grade (643 pts)

- **Benign, n=464 (72.1%)**: 88% 5-yr RFS
- **Atypical, n=156 (24.3%)**: 59% 5-yr RFS
- **Anaplastic, n=23 (3.6%)**: 28% 5-yr RFS

*p < 0.001

Meningioma

PFS by Treatment Era
STR + p-op EBRT
UCSF

1980: “when CT or MRI was used for planning therapy.”

98%: Tx After 1980 *
(n= 77)
p=0.002

77%: Tx Before 1980 *
(n= 40)

Atypical Meningioma

108 patients with Simpson grade 1 resection with radiographic recurrence after resection

- 48 men, 60 women,
- Mean age 55
- Mean serial imaging f/u 39 month

Atypical Meningioma

% of Simpson grade 1 resected AMs with radiographic recurrence after resection with and without post-op RT (mean 60.2 Gy)

Atypical Meningioma

Disease-specific survival after 1st recurrence of AM, initial GTR alone (n = 30)

30 pts with recurrence
16 (53%) were symptomatic
Re-do craniotomy in 22 of 30
21/22 were still AM, 1 anapl
Several tumors required mult, avg 2.7 per recurrent tumor

All 30 received RT
14 fractionated FSRT (55 Gy)
16 SRS (~ dose 18 Gy)

Some received systemic therapy.

Aghi MK, Carter BS, Cosgrove GR, Ojemann RG, Amin-Hanjani S, Martuza RL, Curry WT, Barker FG. Long-term recurrence rates of atypical meningiomas after GTR with or without postoperative adjuvant radiation. 2009;64(1):56-60
Anaplastic Meningioma

Initial vs Recurrent Disease + EBRT

Methodist Hospital (Baylor), Houston, Texas

Phase II Study of IMRT for Intermediate and High Risk Meningiomas, and Observation for Low Risk Meningiomas

**Group 1 (Low Risk):** New Grade 1, GTR or STR

**Group 2 (Interm Risk):** Recurrent Grade 1, GTR or STR
New Grade 2, GTR

**Group 3 (High Risk):** Any Grade 3
Recurrent Grade 2
New Grade 2, STR

Primary endpoint: 3 yr PFS

- **Group 1** → Observation
- **Group 2** → 3D-CRT/IMRT 54 Gy / 30 fxs
- **Group 3** → IMRT 60 Gy / 30 fxs
Current EORTC 22042-26042 Trial

Adjuvant postoperative high-dose radiotherapy for atypical and malignant meningioma: a Phase II and observation study
Vast majority of meningiomas are durally based.
The linear trailing enhancement is referred to as the “dural tail,” and is typically composed entirely or almost entirely of hypervascular dura.
Microscopic clusters of meningioma are occasionally observed.
No evidence to suggest that recurrences are more likely to occur within the dural tail than any other portion of dura next to the main tumor mass.

Meningioma as a radiosurgery target

- Well circumscribed targets without infiltration
- Easily visualized with sharp delineation
- Slow growth rate makes high dose single fraction treatment potentially desirable over fractionation
- Late complications have time to occur
Indications for radiosurgery

• Newly diagnosed patients
  – Skull base
  – Convexity
  – Parasagittal
  – Not used for optic nerve sheath tumors

• Recurrent tumors

• Residual tumor after resection
Conclusions

- Radiation therapy provides excellent local control for patients with benign meningiomas.
- Radiation therapy should be offered to all patients with atypical and malignant meningiomas.
- Modern radiation techniques provide more conformal, safe and accurate delivery of radiation.
- Enrollment of patients on RTOG 0539 is strongly encouraged.
Introduction

- Pituitary adenomas are very common
  - ~10% of all intracranial tumors
  - ~20% incidence in autopsy series
- Clinically evident cases can have severe morbidity
  - 70% are secretory: PRL, GH, FSH, LH, TSH
  - Mass effect can cause: visual deficits, CN deficits, headaches, PRL secretion
Multidisciplinary approach is important

- Endocrinologist
- Neurosurgeon
- Neuroradiologist
- Neuropathologist
- Neuro-opthalmologist
- Otorhinolaryngologist
- Radiation oncologist
Treatment options for sellar and parasellar tumors

- Observation
- Microsurgery
- Medical
- Radiosurgery
- Radiation therapy
- Multimodality approach

Depends on symptoms, tumor size at presentation, involvement of adjacent structures, and vicinity to optic apparatus
Indications for radiation therapy and radiosurgery

- Primary therapy
- Adjunctive therapy
- Salvage therapy
Ideal sellar and parasellar SRS target

• Well circumscribed target without infiltration
• Easily visualized with sharp delineation on MRI
• Target is away from radiosensitive structures
Gamma Knife treatment plan for pituitary tumor
## TABLE 27-1  Summary of Recently Published Studies of SRS for Nonfunctioning Pituitary Adenomas

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Number of Patients</th>
<th>Follow-up (mo)</th>
<th>Peripheral Dose (Gy)</th>
<th>Local Control Rate (%)</th>
<th>Visual Complication Rate (%)</th>
<th>Hypopituitarism Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sheehan</td>
<td>2002</td>
<td>42</td>
<td>31.2*</td>
<td>16</td>
<td>97</td>
<td>2.3</td>
<td>NA</td>
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<tr>
<td>Petrovich</td>
<td>2003</td>
<td>56</td>
<td>36</td>
<td>15</td>
<td>94</td>
<td>4</td>
<td>NA</td>
</tr>
<tr>
<td>Losa</td>
<td>2004</td>
<td>56</td>
<td>41*</td>
<td>16.6</td>
<td>96</td>
<td>0</td>
<td>24</td>
</tr>
<tr>
<td>Iwai</td>
<td>2004</td>
<td>34</td>
<td>59.8</td>
<td>14</td>
<td>93</td>
<td>0</td>
<td>6</td>
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<tr>
<td>Mingione</td>
<td>2006</td>
<td>90</td>
<td>44.9*</td>
<td>18.5</td>
<td>92</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>Liscak</td>
<td>2007</td>
<td>140</td>
<td>60</td>
<td>20</td>
<td>100</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Pollock</td>
<td>2008</td>
<td>62</td>
<td>44.9</td>
<td>16</td>
<td>95</td>
<td>0</td>
<td>32</td>
</tr>
</tbody>
</table>

*Gy, Gray; mo, months; NA, not available.

*Mean follow-up.

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Suh JH, Chao ST, Weil RJ. Chapter 27 in Clin Rad Oncol, 3rd Ed
Gunderson, Tepper Ed 2011
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Number of Patients</th>
<th>Follow-up (mo)</th>
<th>Peripheral Dose (Gy)</th>
<th>Hormone Remission Rate (%)</th>
<th>Local Control Rate (%)</th>
<th>Visual Complication Rate (%)</th>
<th>Hypopituitarism Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Landolt</td>
<td>2000</td>
<td>20</td>
<td>29</td>
<td>25</td>
<td>25</td>
<td>NA</td>
<td>5</td>
<td>NA</td>
</tr>
<tr>
<td>Pan</td>
<td>2000</td>
<td>128</td>
<td>33</td>
<td>31.5</td>
<td>52</td>
<td>98.4</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Choi</td>
<td>2003</td>
<td>21</td>
<td>42.5</td>
<td>28.5</td>
<td>24</td>
<td>100</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Pouratian</td>
<td>2006</td>
<td>23</td>
<td>58</td>
<td>18.6</td>
<td>26</td>
<td>89</td>
<td>7</td>
<td>29</td>
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<tr>
<td>Jezkova</td>
<td>2008</td>
<td>35</td>
<td>75</td>
<td>34</td>
<td>37.1</td>
<td>97.1</td>
<td>0</td>
<td>14.3</td>
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<tr>
<td>Pollock</td>
<td>2008</td>
<td>11</td>
<td>54</td>
<td>25</td>
<td>18</td>
<td>100</td>
<td>9%*</td>
<td>36</td>
</tr>
<tr>
<td>Castinetti</td>
<td>2009</td>
<td>15</td>
<td>86</td>
<td>26</td>
<td>43</td>
<td>100</td>
<td>0</td>
<td>13.3</td>
</tr>
</tbody>
</table>

Gy, Gray; mo, months; NA, not available.

*One patient with multiple sclerosis had bilateral vision loss that began at 3 months. This improved with high-dose corticosteroids.
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Number of Patients</th>
<th>Follow-up (mo)</th>
<th>Peripheral Dose (Gy)</th>
<th>24-Hour Urinary Free Cortisol Normalization Rate (%)</th>
<th>Local Control Rate (%)</th>
<th>Visual Complication Rate (%)</th>
<th>Hypopituitarism Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoybye\textsuperscript{134}</td>
<td>2001</td>
<td>18</td>
<td>204</td>
<td>NA</td>
<td>83</td>
<td>NA</td>
<td>0</td>
<td>69</td>
</tr>
<tr>
<td>Kobayashi\textsuperscript{135}</td>
<td>2002</td>
<td>20</td>
<td>60</td>
<td>40</td>
<td>35</td>
<td>100</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Jagannathan\textsuperscript{48}</td>
<td>2007</td>
<td>90</td>
<td>42</td>
<td>23</td>
<td>53</td>
<td>95</td>
<td>5.6</td>
<td>22</td>
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<tr>
<td>Castinetti\textsuperscript{35}</td>
<td>2009</td>
<td>18</td>
<td>96</td>
<td>28.5</td>
<td>46</td>
<td>NA</td>
<td>0</td>
<td>82.8</td>
</tr>
</tbody>
</table>

Gy, Gray; mo, months; NA, not available.

Suh JH, Chao ST, Weil RJ. Chapter 27 in Clin Rad Oncol, 3rd Ed Gunderson, Tepper Ed 2011
Generalized Treatment Algorithm for a GH-secreting pituitary adenoma

Suh JH, Chao ST, Weil RJ. Chapter 27 in Clin Rad Oncol, 3rd Ed Gunderson, Tepper Ed 2011
### TABLE 27-3
Summary of Recently Published Studies of Radiation Therapy for Acromegaly

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Number of Patients</th>
<th>Follow-up (yr)</th>
<th>Hormone Remission Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barrande</td>
<td>2000</td>
<td>128</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5</td>
<td>35</td>
</tr>
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<td></td>
<td></td>
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<td>15</td>
<td>66</td>
</tr>
<tr>
<td>Minniti</td>
<td>2005</td>
<td>74</td>
<td>2</td>
<td>9</td>
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<tr>
<td></td>
<td></td>
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<td>5</td>
<td>29</td>
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<td>77</td>
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<td>Jenkins</td>
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<td>2</td>
<td>22</td>
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<td></td>
<td></td>
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<td>10</td>
<td>60</td>
</tr>
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<td></td>
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<td>20</td>
<td>77</td>
</tr>
<tr>
<td>Jallad</td>
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<td>89</td>
<td>5.9</td>
<td>54</td>
</tr>
</tbody>
</table>

Suh JH, Chao ST, Weil RJ. Chapter 27 in Clin Rad Oncol, 3rd Ed Gunderson, Tepper Ed 2011
### TABLE 27-4
Summary of Recently Published Studies of Stereotactic Radiosurgery for Acromegaly

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Number of Patients</th>
<th>Follow-up (mo)</th>
<th>Peripheral Dose (Gy)</th>
<th>IGF-1 Normalization Rate (%)</th>
<th>Local Control Rate (%)</th>
<th>Visual Complication Rate (%)</th>
<th>Hypopituitarism Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jezkova</td>
<td>2006</td>
<td>96</td>
<td>54</td>
<td>32</td>
<td>50</td>
<td>100</td>
<td>0</td>
<td>27.1</td>
</tr>
<tr>
<td>Pollock</td>
<td>2007</td>
<td>46</td>
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<tr>
<td>Vik-Mo</td>
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<td>53</td>
<td>66</td>
<td>26.5</td>
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<td>100</td>
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<td>18</td>
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<td>Losa</td>
<td>2008</td>
<td>83</td>
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<td>21.5</td>
<td>60.2</td>
<td>97.6</td>
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<tr>
<td>Jagannathan</td>
<td>2008</td>
<td>95</td>
<td>57</td>
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<td>Ronchi</td>
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<td>35</td>
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<td>Castinetti</td>
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<td>43</td>
<td>96</td>
<td>26</td>
<td>42</td>
<td>NA</td>
<td>NA</td>
<td>21</td>
</tr>
</tbody>
</table>

Gy, Gray; mo, months; NA, not available.

*Thirteen patients underwent a second course of SRS.

*6 patients did not have measurement on follow-up scans.
Use of medicines during radiation

- Since it may take some time for normalization of hormonal levels, the use of medicine may be required.
- Based on the worse outcomes reported by Landolt for patients receiving dopamine agonists at time of radiosurgery, a 2-month break between medical therapy and radiosurgery is suggested.
- Series from Pouratian also reported worse outcomes in patients receiving anti-secretory medication at time of SRS.

Radiosurgery for secretory pituitary tumors

- Need higher margin doses than other benign skull base lesions
- Endocrine hypersecretion is difficult to control
- Optic nerves and chiasm are near target, limiting the dose of radiation that can be prescribed
- Pts are younger (fertility and prolonged survival)
- Anti-secretory drugs can interfere with radiation effect
- Target can be difficult to define
Cranial nerve complications secondary to SRS

- Special sensory nerves (optic and vestibulocochlear) are the most sensitive to radiation.
- No relationship of dose to cavernous sinus and neuropathy in CN III-VI (range 10-40 Gy)
- Significant increase in complications to optic apparatus with dose
Radiation Optic Neuropathy (RON)

- Austrian study of 50 patients with skull base tumors
- Risk for radiation optic neuropathy
  - 0% for pts receiving < 10 Gy
  - 26.7% for pts receiving 10 to < 15 Gy
  - 77.8% for pts receiving ≥ 15 Gy

Radiation Optic Neuropathy (RON)

- Retrospective review of 215 patients treated at Mayo Clinic
- Tumors of the sella and parasellar region
- 157/215 (73%) received > 8 Gy to optic apparatus
- Median dose to optic nerve = 10 Gy; max dose = 16 Gy
- 4/215 (1.9%) developed RON at a median of 48 months
  - All had prior surgery
  - 3 of 4 had EBRT
- 1.1% developed clinically significant RON at ≤ 12 Gy

Complications of radiosurgery for pituitary tumors

- Endocrine dysfunction (72% @ 17 years)
- Vascular injury (4/1621)
- Vision loss (16/1621)
- Radiation necrosis (13/1621)
- Second malignancies (0/1621)
- Injury to cranial nerves (21/1567)

Summary

- Radiosurgery and radiation therapy are safe and effective treatment option for patients with sellar and parasellar tumors.
- Radiosurgery and radiation therapy can be used as primary, adjunctive or salvage therapy.
- Treatment complications are low for properly selected patients.
- Long-term follow-up is needed for these patients.
- Given lack of prospective trials, these are needed to better understand role of SRS for sellar and parasellar tumors.
Epidemiology of Acoustic Neuromas

- 2000-3000 new cases of VS diagnosed per year in the U.S., an incidence of 1/100,000 per year
- 8-10% of all primary intracranial tumors
- 80-90% of all cerebellopontine angle tumors
- Commonly present between 30-50 year of age
- Can be associated with NF-2
- Incidence of occult VS in human temporal bones: 0.57-0.87%
Presentation

- Hearing Loss (95%)
- Tinnitus (63%)
- Vestibular Nerve (61%)
- Trigeminal Nerve (17%)
- Facial Nerve (6%)

Natural History

Retrospective study of unilateral acoustic neuromas managed with conservative management

- 80 patients followed by serial imaging
- 49 patients with subtotal resection

Growth rate for nonsurgical patients: 0.91 mm/year
Growth rate for surgical patients: 0.35 mm/year

Observed 6 different growth patterns

## Gardener-Robertson Classification

<table>
<thead>
<tr>
<th>Auditory Grade</th>
<th>Pure Tone Loss (dB)</th>
<th>% Speech Discrimination</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Good</td>
<td>0-30</td>
<td>70-100</td>
</tr>
<tr>
<td>2. Serviceable</td>
<td>31-50</td>
<td>50-69</td>
</tr>
<tr>
<td>3. Nonserviceable</td>
<td>50-90</td>
<td>5-49</td>
</tr>
<tr>
<td>4. Poor</td>
<td>91 maximum</td>
<td>1-4</td>
</tr>
<tr>
<td>5. None</td>
<td>Nontestable</td>
<td>0</td>
</tr>
</tbody>
</table>

Adapted from Kaplan, DM et al., *Otolaryngology* 32:23-32, 2003
Treatment options for vestibular schwannomas

- Expectant observation
- Microsurgery
- Radiosurgery
- Fractionated radiation therapy

Goals of treatment:
- Long-term tumor control
- Preservation of CN function
- Maintenance of QOL
Observation

• An acceptable option for certain patients
  – Elderly
  – Contraindications for surgery
  – No CNS deficits
  – Evidence of slow tumor growth

• Growth
  – Less than 30% of untreated acoustic neuromas have growth greater than 2.0 mm/year on MR imaging
  – Tumors > 2.0 cm are more likely to grow
  – Rate of growth is usually constant, but may have sudden increase in size

Fucci et al., Am J Otol 1999; 20:495-499
Surgery

1000 acoustic neuroma tumors (1978-1993)

• 979 complete tumor removal via suboccipital approach/ 21 subtotal resections

• 0.7% (6/880 pts without NF2) had tumor recurrence

Complications:

- CSF fistulas 9.2%
- Hematomas 2.2%
- Hydrocephalus 2.3%
- Bacterial meningitis 1.2%
- Wound revisions 1.0%
- Death- within 2-69 days postoperatively 1.1%

Samii M et al., Neurosurg 2001; 40: 684-695
Gamma Knife radiosurgery plan
Gamma Knife radiosurgery
University of Pittsburgh experience

- A retrospective study of 162 patients who had radiosurgery between 1987 and 1992 for acoustic neuromas
- 16 Gy average marginal dose
- Mean tumor diameter was 22 mm
- 42 patients had prior resection

Kondziolka D, et al., N Eng J Med 1998; 339(20); 1426-1472
Gamma Knife radiosurgery
University of Pittsburgh experience

- Tumor Control: 98%
  94% by neuroimaging
- Preservation of VIIth nerve function: 79%
- Preservation of Vth nerve function: 73%
- Preservation of serviceable hearing: 51%

Kondziolka, D et al., *NEJM* 1998; 339(20); 1426-1472
Longer term follow-up for VS: Komaki City Hospital

- Retrospective review of 346 patients treated between 5/91 and 12/98 on Gamma Knife.
- Excluded 29 patients with NF2 and 29 patients lost to f/u
- Median f/u 7.8 years
- Imaging response
  - 1% complete response/61% partial response/31% stable
  - 7% treatment failure
- Actuarial PFS at 5- and 10-years was 93% and 92%, respectively.
- For tumors < 15 cc, 10-year PFS was 96% (p<0.001)
- Using 13 Gy or less, hearing preservation rate was 68%, transient facial palsy was 1%, facial numbness was 2%

Prospective comparison of microsurgery vs. SRS for small- to medium-sized VS: Mayo Clinic

- Cohort of unilateral, unoperated VS < 3 cm
  - Surgery (n=36) or SRS with Gamma Knife (n=46)
- Groups were similar with regard to hearing loss, associated symptoms, and tumor size. Surgery group was younger 48.2 yr versus 53.9 yr, p=0.03
- Median f/u 42 months
- No difference in tumor control
- Outcomes such as hearing preservation, normal facial movement, Health status questionnaire, and Dizziness Handicap Inventory scores were better for the SRS group.

Enlargement of VS after SRS

- Retrospective review of 208 consecutive patients at Mayo Clinic between 3/90 to 12/01.
- 30 patients (14%) had tumor enlargement of 2 mm or more after SRS (median f/u 56 months)
- Median time to enlargement was 9 months (5-60 months)
- Median volume increase was 75%
- Loss of central enhancement noted in 28 patients (93%)
- Six patients had new symptoms associated with tumor enlargement. Three patients underwent additional therapy at time of initial enlargement
  - 16 of 28 had tumor regression
  - 8 of 28 remained larger without progressive growth
  - 4 of 28 underwent additional treatment

SRS vs FSRT
Which one is better?

• AN have a very low proliferative index
• The doses of SRS are high enough to affect even benign neoplastic cells regardless of their current stage within the cell cycle
• Three roles for fractionated radiotherapy
  1. Malignant schwannomas
  2. Tumors larger than 3.5 cm
  3. NF2 acoustic neuromas (higher proliferative indices)

Linskey M et al. *J Neurosurg* (Suppl 3) 2000;93:90-95
SRS vs FSR: Jefferson Results

• Retrospective study of 125 patients with AN
  • 69 treated with Gamma Knife (12 Gy to the 50% IDL)
  • 56 treated with Linac (50 Gy/25 fx)

<table>
<thead>
<tr>
<th></th>
<th>Tumor Control</th>
<th>Preserv Trigem</th>
<th>Preserv Facial</th>
<th>Preserv Hearing</th>
<th>Tumor Control NF2</th>
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</thead>
<tbody>
<tr>
<td>SRS</td>
<td>98%</td>
<td>95%</td>
<td>98%</td>
<td>33%</td>
<td>80%</td>
</tr>
<tr>
<td>FSR</td>
<td>97%</td>
<td>93%</td>
<td>98%</td>
<td>81%</td>
<td>67%</td>
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<tr>
<td>P value</td>
<td>0.6777</td>
<td>0.5893</td>
<td>0.8202</td>
<td>0.0228</td>
<td>0.6615</td>
</tr>
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</table>

Dosing recommendation: 46.8 Gy/26 fx

SRS vs FSR from Netherlands

• All treatments were linac-based from 1992 to 1999

• 129 patients prospectively randomized to SRS vs. FSR
  – Dentate: FSR (20 Gy/5 fx and 25 Gy/5 fx)
  – Edentate: SRS (10 Gy and 12.5 Gy)

• Mean Tumor Diameter (FSR: 2.5 cm vs. SRS: 2.6 cm)

<table>
<thead>
<tr>
<th></th>
<th>Local Control</th>
<th>Preserved Hearing</th>
<th>Preserved VII Function</th>
<th>Preserved Vth Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSR</td>
<td>94%</td>
<td>61%</td>
<td>97%</td>
<td>98%</td>
</tr>
<tr>
<td>SRS</td>
<td>100%</td>
<td>75%</td>
<td>93%</td>
<td>92%</td>
</tr>
</tbody>
</table>

Meijer et al. Neurosurg 2003; 56(5): 1390-1396
SRS versus FSRT for vestibular schwannomas

200 patients treated at Heidelberg and DFKZ
Hearing preservation SRS $\leq 13$ Gy and FSRT $57.6$ Gy/32 fx

SRS versus FSRT for vestibular schwannomas

200 patients treated at Heidelberg and DFKZ
SRS 13 Gy and FSRT 57.6 Gy/32 fx

Conclusions

• Number of treatment options exist for patients with vestibular schwannomas.
• Tumor control is similar among the various treatment options (surgery, SRS, and FSRT)
• Facial nerve preservation is greater for patients undergoing SRS and FSRT compared to surgery.
• Hearing preservation with surgery, SRS and FSRT varies depending on tumor size.
• Prospective trials are needed to optimize treatment for patients with vestibular schwannomas
Post-test Questions

Which of the following statements best describes the benefit of whole brain radiation therapy (WBRT) and stereotactic radiosurgery (SRS) compared to WBRT alone for patients with brain metastases based on the RTOG 9508 phase III trial?

The addition of WBRT to SRS improves survival for patients with 2-3 lesions compared to WBRT
B. The addition of WBRT to SRS decreases the development of extracranial metastases
C. WBRT and SRS decreases neurologic death compared to WBRT alone
D. The addition of WBRT to SRS significantly improves survival for patients with a single metastasis
E. WBRT and SRS improves neurocognitive outcomes compared to WBRT alone