Collection of Recorded Radiotherapy Seminars

http://humanhealth.iaea.org
The Role of Radiosurgery in the Treatment of Gliomas

Luis Souhami, MD
Professor
Department of Radiation Oncology
McGill University, Montreal, Canada
Stereotactic Radiosurgery

- Radiotherapy technique characterized by accurate delivery of high doses of radiation, in a single session, to small, stereotactically defined, intracranial targets in such way that the dose fall-off outside the targeted volume is very sharp.
Focal Irradiation Boost in Gliomas

Is it Worth?
Early Trials for Malignant Gliomas

• RT Improves Survival

BTSG Trials
RT vs SX: 8.3 vs 3.2 mos
RT vs BCNU: 8.3 vs 5.5 mos

A – Surgery
B – BCNU
C – RT
D – RT + BCNU

McGill

Walker et al J Neurosurg 1978
GBM - FACTS

- Poor prognosis
- Recurrences near the tumor margin
  - Hochberg, Pruitt Neurology 1980
- Unifocal in more than 90% of cases
- Metastatic disease rare
- Dose-response effect
  - Walker et al Int J Radiat Oncol Biol Phys 1979
  - Bleeheen, Stenning Br J Cancer 1991

McGill
GBM - How to improve results?

Hypothesis

- Higher RT doses will lead to better tumor control

McGill
Dose Escalation

- Conventional Fractionation (> 60 Gy)
- Hyperfractionation
- Hypofractionation
- Focal “Boost”

McGill
Stereotactic Brachytherapy


• Initial studies (UCSF)
  • 29 Non-GBM
  • 34 GBM
• No changes in anaplastic astrocytomas
• Increased survival in GBM
Stereotactic Radiosurgery
Loeffler et al J Clin Oncol 1992

- 37 patients malignant gliomas
  - Non GBM 14
  - GBM 23
- SRS post EBRT
RPA Radiosurgery RTOG

<table>
<thead>
<tr>
<th>RPA</th>
<th>Med S</th>
<th>2 yr S</th>
<th>Med S</th>
<th>2 yr S</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>38.1</td>
<td>75%</td>
<td>17.9</td>
<td>35%</td>
</tr>
<tr>
<td>4</td>
<td>19.6</td>
<td>34%</td>
<td>11.1</td>
<td>15%</td>
</tr>
<tr>
<td>5</td>
<td>13.1</td>
<td>21%</td>
<td>8.9</td>
<td>6%</td>
</tr>
</tbody>
</table>

• Sarkaria et al 1995 (Int J Radiat Oncol Biol Phys)
• 115 patients - 3 institutions
• Median Survival 22.5 months
SRS Publications - Malignant Gliomas

McGill
# Patient Selection?

Florell et al J Neurosurg 1992

Brachytherapy eligible vs non-eligible patients

<table>
<thead>
<tr>
<th>Status</th>
<th># Pts</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligible</td>
<td>43</td>
<td>16.57 mos</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p = 0.004</td>
</tr>
<tr>
<td>Non- Eligible</td>
<td>58</td>
<td>9.30 mos</td>
</tr>
</tbody>
</table>

McGill
Radiosurgery-Eligible Patients
Curran et al J Clin Oncol 1993

RTOG treated patients
778 pts malignant glioma
Selection based on: KPS
tumor size
tumor location
12% eligible

Median Survival
RS: 14.4 mos
Non-RS: 11.7 mos
p = 0.047
Brachytherapy

- 2 randomized trials

Toronto and BTCG
No difference in survival
Similar local control

Laperriere IJROBP 1998
Selker Neurosurgery 2002
RTOG 93-05

Study Design
Prospective Randomized Trial

Arm 1 - RT + BCNU

Arm 2 - RS + RT + BCNU

Objectives

- To determine if the use of radiosurgery prior to conventional RT + BCNU improves survival
- To determine and compare toxicities
- To compare the effect of treatments on neurological function and quality of life

Eligibility Criteria

- Supratentorial GBM, ≤ 4 cm
- Age ≥ 18 years
- KPS ≥ 60
- Neurological Function Status 0, 1, 2, or 3
- Adequate blood work
- Signed informed consent form

Statistical Design

- Phase III Trial
  - Stratification: Age (18 -<50 vs ≥50)
  - KPS (90 - 100 vs 60 - 80)
- Seeking 50% improvement in MS
  - (12.5 mos to 18.75 mos)
- 200 patients

Standard Radiation Therapy

- **Plan 1** - Dose: 46 Gy/ 23 Fxs
  - Volume: enhancing lesion + edema + 2 cm margin

- **Plan 2** - Dose: 14 Gy/ 7 Fxs
  - Volume: enhancing lesion + 2.5 cm margin

Stereotactic Radiosurgery

- **Dose:** Size dependent (RTOG 90-05)

<table>
<thead>
<tr>
<th>Maximum Tumor Diameter</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 20 mm</td>
<td>24 Gy</td>
</tr>
<tr>
<td>21-30 mm</td>
<td>18 Gy</td>
</tr>
<tr>
<td>31-40 mm</td>
<td>15 Gy</td>
</tr>
</tbody>
</table>

- **Volume:** enhancing lesion, without margin

BCNU

- 80 mg/m² days 1, 2 and 3 of RT then q 8 weeks for a total of 6 cycles
- Maximum Dose: 1440 mg/m²
Accrual

- 203 patients (Feb 94 to June 2000)
- Arms well balanced for age, KPS, gender, neurological function, pre and post-op tumor size, RPA stage, mini mental status and Spitzer quality of life index
- Median follow-up time: 44 months

9305 Overall Survival

% Alive vs Months from Randomization

- RT
- RS + RT

p = 0.5328
Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>RT</th>
<th>RS + RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Survival:</td>
<td>14.1 mos</td>
<td>13.7 mos</td>
</tr>
<tr>
<td></td>
<td>(p = 0.5328)</td>
<td></td>
</tr>
<tr>
<td>2-yr Survival:</td>
<td>22%</td>
<td>18%</td>
</tr>
<tr>
<td>3-yr Survival:</td>
<td>16%</td>
<td>8%</td>
</tr>
</tbody>
</table>
9305 Survival
RPA III, IV

Percent Alive

RT
SRS + RT

p = 0.4777
Survival RPA III or IV

<table>
<thead>
<tr>
<th></th>
<th>RT</th>
<th>RS + RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Survival</td>
<td>14.7 mos</td>
<td>14.2 mos</td>
</tr>
<tr>
<td></td>
<td>(p = 0.4777)</td>
<td></td>
</tr>
<tr>
<td>2-yr Survival</td>
<td>27%</td>
<td>20%</td>
</tr>
<tr>
<td>3-yr Survival</td>
<td>16%</td>
<td>9%</td>
</tr>
</tbody>
</table>
### Survival: Treatment Delivery

<table>
<thead>
<tr>
<th></th>
<th>γ Knife</th>
<th>Linac</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Survival</td>
<td>14.9 mos</td>
<td>14.0 mos</td>
</tr>
<tr>
<td>(p = 0.4528)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-yr Survival</td>
<td>14%</td>
<td>20%</td>
</tr>
<tr>
<td>3-yr Survival</td>
<td>0%</td>
<td>11%</td>
</tr>
</tbody>
</table>
Survival: Pre-Op Tumor ≤ 4 cm

- Median Survival: 14.1 mos 11.4 mos (p = 0.0925)
- 2-yr Survival: 18% 12%
- 3-yr Survival: 13% 5%

## Toxicity (Grade 3 or 4)

<table>
<thead>
<tr>
<th></th>
<th>Arm 1</th>
<th>Arm 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>5%</td>
<td>10%</td>
</tr>
<tr>
<td>Late</td>
<td>0%</td>
<td>4.5%</td>
</tr>
<tr>
<td>Pattern</td>
<td>Arm 1</td>
<td>Arm 2</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-----------</td>
<td>-----------</td>
</tr>
<tr>
<td>Local only</td>
<td>47 (69%)</td>
<td>36 (56%)</td>
</tr>
<tr>
<td>Adjacent only</td>
<td>4 (6%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Local + Adjacent</td>
<td>14 (21%)</td>
<td>17 (27%)</td>
</tr>
<tr>
<td>Local + Non-Adjacent</td>
<td>2 (3%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Local + Adjacent + NonAdjacent</td>
<td>1 (1%)</td>
<td>4 (6%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>4 (6%)</td>
</tr>
<tr>
<td>No Failure</td>
<td>28</td>
<td>20</td>
</tr>
</tbody>
</table>
## Salvage Therapy

<table>
<thead>
<tr>
<th></th>
<th>RT</th>
<th>RS+RT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surgery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial resection</td>
<td>13 (13%)</td>
<td>6 (6%)</td>
</tr>
<tr>
<td>Total resection</td>
<td>12 (12%)</td>
<td>14 (14%)</td>
</tr>
<tr>
<td>Others</td>
<td>10 (10%)</td>
<td>9 (9%)</td>
</tr>
<tr>
<td><strong>Non-Protocol RT</strong></td>
<td>6 (6%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td><strong>Non-Protocol RS</strong></td>
<td>18 (18%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td><strong>Non-Protocol CT</strong></td>
<td>48 (48%)</td>
<td>42 (42%)</td>
</tr>
<tr>
<td>Status</td>
<td>RT</td>
<td>RS + RT</td>
</tr>
<tr>
<td>---------------</td>
<td>----------</td>
<td>----------</td>
</tr>
<tr>
<td>Decline</td>
<td>23 (40%)</td>
<td>22 (50%)</td>
</tr>
<tr>
<td>Stable</td>
<td>14 (24%)</td>
<td>7 (16%)</td>
</tr>
<tr>
<td>Improve</td>
<td>21 (36%)</td>
<td>15 (34%)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.4606</td>
<td></td>
</tr>
</tbody>
</table>
## Cognitive Functioning (Mini Mental)

<table>
<thead>
<tr>
<th></th>
<th>End of RT</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RT</td>
<td>RS + RT</td>
<td>p-value</td>
</tr>
<tr>
<td>Decline</td>
<td>17 (31%)</td>
<td>13 (29%)</td>
<td>0.5531</td>
</tr>
<tr>
<td>Stable</td>
<td>19 (35%)</td>
<td>13 (29%)</td>
<td></td>
</tr>
<tr>
<td>Improve</td>
<td>19 (35%)</td>
<td>19 (42%)</td>
<td></td>
</tr>
</tbody>
</table>
Unlike radiosurgery/brachytherapy trials:

- Patients with gross total resection allowed
- Entire resection cavity is included in boost volume
- Strict dose homogeneity requirement
- Technique uses shaped conformal fields
- Large target sizes (post-op diameter up to 60 mm allowed)
Methods

Eligibility Criteria

- Histologically confirmed GBM (gross total resection allowed)
- Boost GTV \( \leq 60 \) mm
- Performance status 0-1, Neurologic function status 0-3
- Adequate bone marrow reserve

Ineligibility Criteria

- Multifocal disease
- Tumors of the brainstem or within 10 mm of the optic chiasm
### Treatment Schedule

<table>
<thead>
<tr>
<th>Week #</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
<td>III</td>
<td>III</td>
<td>III</td>
<td>III</td>
<td>III</td>
</tr>
</tbody>
</table>

*I = standard EBXRT (pre-op tumor volume plus edema), 2 Gy x 25 fractions*

*SRT boost, 5-7 Gy x 4 fractions*

**BCNU** - 80 mg/m² i.v. for 3 days, beginning within one month after the completion of RT then q 8 weeks for a total of 6 cycles

Cardinale et al. IJROBP 2006
4 SRT Boosts: weeks 3-6

**GTV**: Postoperative residual enhancing lesion plus entire resection cavity

**PTV**: GTV + 5 mm

**Dose**: Maximum PTV Diameter

<table>
<thead>
<tr>
<th>Diameter</th>
<th>Dose/fx</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤40 mm</td>
<td>7 Gy</td>
</tr>
<tr>
<td>&gt;40 mm</td>
<td>5 Gy</td>
</tr>
</tbody>
</table>

**SRT planning**: sites pre-certified, MRI, conformal fields, strict homogeneity requirement
Results

80 pts enrolled from June, 2001 - June, 2004
4 patients ineligible, 76 analyzed

Patient Characteristics:

- **Age (median)**: 58
- **Gender (male, female)**: 63%, 37%
- **Performance Status (0, 1)**: 64%, 36%
- **Surgery Type**
  - Biopsy: 24%
  - Subtotal resection: 35%
  - Gross total resection: 41%
- **RPA Class**
  - III: 25%
  - IV: 50%
  - V: 25%
Overall Survival: 12.5 mos. RTOG 0023(____) vs. Historical control(---) (Same RPA distribution)

\[ p = 0.5 \]

Cardinale et al. IJROBP 2006
Overall Survival – Gross Total Resection
RTOG 0023 (___) vs. Historical control (---)

17 vs. 12 mos.
p=0.1

Cardinale et al. IJROBP 2006
## Toxicity

Significant toxicity included: one grade 4 acute (lethargy) and one grade 3 late (necrosis).

10 pts experienced grade 4 hematologic toxicity.

<table>
<thead>
<tr>
<th>Grade (RT late)</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>3</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Skin (within the field)</td>
<td>6</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Eye</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Subcutaneous Tissue</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>9</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Worst toxicity per patient</strong></td>
<td><strong>9</strong></td>
<td><strong>3</strong></td>
<td><strong>1</strong></td>
</tr>
</tbody>
</table>

(13%) (4%) (1%)
Pattern of First Failure

*in relation to boost volume*

65 patients

- Within target volume: 64%
- Within target volume plus adjacent: 25%
- Adjacent: 6%
- Beyond adjacent: 4%

Re-operation in 28 patients: 43%
Is there a role for SRS/FSRT in recurrent disease?

ASTRO REPORT

THE AMERICAN SOCIETY FOR THERAPEUTIC RADIOLOGY AND ONCOLOGY (ASTRO) EVIDENCE-BASED REVIEW OF THE ROLE OF RADIOSURGERY FOR MALIGNANT GLIOMA

May N. Tsao, M.D., Minesh P. Mehta, M.D., Timothy J. Whelan, M.D., David E. Morris, M.D., James A. Hayman, M.D., John C. Flickinger, M.D., Michael Mills, Ph.D., C. Leland Rogers, M.D., and Luis Souhami, M.D.

The American Society for Therapeutic Radiology and Oncology, Fairfax, VA

Purpose: To systematically review the evidence for the use of stereotactic radiosurgery or stereotactic fractionated radiation therapy in adult patients with malignant glioma.

Methods: Key clinical questions to be addressed in this evidence-based review were identified. Outcomes considered were overall survival, quality of life or symptom control, brain tumor control or response and toxicity. MEDLINE (1990–2004 June Week 2), CANCERLIT (1990–2003), CINAHL (1990–2004 June Week 2), EMBASE (1990–2004 Week 25), and the Cochrane library (2004 issue 2) databases were searched using OVID. In addition, the Physician Data Query clinical trials database, the proceedings of the American Society of Clinical Oncology (1997–2004), ASTRO (1997–2004), and the European Society of Therapeutic Radiology and Oncology (ESTRO) (1997–2003) were searched. Data from the literature search were reviewed and tabulated. This process included an assessment of the level of evidence.
Does SRS as salvage for recurrent or progressive malignant glioma improve survival?

**ASTRO REPORT**

THE AMERICAN SOCIETY FOR THERAPEUTIC RADIOLOGY AND ONCOLOGY (ASTRO) EVIDENCE-BASED REVIEW OF THE ROLE OF RADIOSURGERY FOR MALIGNANT GLIOMA

May N. Tsao, M.D., Minesh P. Mehta, M.D., Timothy J. Whelan, M.D., David E. Morris, M.D., James A. Hayman, M.D., John C. Flickinger, M.D., Michael Mills, Ph.D., C. Leland Rogers, M.D., and Luis Souhami, M.D.

The American Society for Therapeutic Radiology and Oncology, Fairfax, VA

Thus there is insufficient evidence to support a survival benefit in the use of radiosurgery at the time of progressive or recurrent malignant glioma as compared with competing strategies of management such as debulking surgery, chemotherapy, or best supportive care.

SRS Publications - Malignant Gliomas

McGill
How About Low Grade Gliomas?

- May make better SRS targets
  - Less infiltrative
  - Favorable outcome after gross total resection
  - Lower $\alpha/\beta$ ratio

McGill
LGG - Prognostic Factors

**RPA Analysis**

- **EORTC analysis:**
  - Age >40 years
  - Astrocytoma subtype
  - Tumor ≥6 cm
  - Crossing midline
  - Neurological deficit

**Graphs:**

- Bauman G et al. *IJROBP* 1999
- Pignatti et al. *J Clin Oncol* 2002
Is RT of any benefit in LGG?
EORTC 22845

van den Bent et al. Lancet 2005
Low Grade Glioma: McGill

- July 1987 to November 1992
- 21 patients, median age 23 (9-74)
- Median size 20 mm
- Gr I (29%) or Gr II (71%) astrocytoma
- Treated with 42 Gy in 6 fractions over 2 weeks with frame-based linac SRS technique
- Median f/u for living patients 160 months

Roberge et al. Brain Cancer Therapy and Surgical Interventions 2006
FSRT in LGG

11 y.o, Astro II

4 months post FSRT

10 years post FSRT
FSRT in LGG

27 y.o., Astro II

6 months post FSRT
LGG - McGill experience

Overall survival for the 21 patients

76% at 5 years
71% at 10 years
63% at 15 years
<table>
<thead>
<tr>
<th>Institution</th>
<th>Date</th>
<th>Nº patients</th>
<th>Median Size</th>
<th>Dose/ fractions</th>
<th>F/U (mos)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vincenza</td>
<td>1989</td>
<td>14 Gr I/II Astro</td>
<td>20 mm</td>
<td>16-50/1-2</td>
<td>27.5</td>
<td>85% RR 14% toxicity</td>
</tr>
<tr>
<td>Valencia</td>
<td>1994</td>
<td>20 (7 confirmed Gr I/II)</td>
<td>33 mm</td>
<td>EBRT + 21.7/1</td>
<td>50</td>
<td>50% CR 81% OS at 10 yrs</td>
</tr>
<tr>
<td>Komaki</td>
<td>2000</td>
<td>12 Gr I Astro 39 Gr II Astro</td>
<td>25.4 mm 23.7 mm</td>
<td>12.5/1 15.7/1</td>
<td>27.6</td>
<td>58-63% RR</td>
</tr>
<tr>
<td>Pittsburgh</td>
<td>2002</td>
<td>37 Gr I Astro 12 Gr II Astro</td>
<td>3 cm³ 4.6 cm³</td>
<td>15/1 16/1</td>
<td>28 52</td>
<td>42-48% RR GrII 100% OS 10yr</td>
</tr>
<tr>
<td>Karolinska</td>
<td>2002</td>
<td>19 Gr I Astro</td>
<td>2.2 cm³</td>
<td>10/1</td>
<td>84</td>
<td>85% RR 100% OS at 5 yr</td>
</tr>
<tr>
<td>Prague</td>
<td>2005</td>
<td>34 Gr I Astro 34 GrI/II Astro</td>
<td>4.2 cm²</td>
<td>25/5</td>
<td>≥48</td>
<td>83% RR 77 mo median OS</td>
</tr>
<tr>
<td>McGill</td>
<td>2006</td>
<td>4 Gr I/Astro 17 Gr II/Astro</td>
<td>14 mm</td>
<td>42/6</td>
<td>160</td>
<td>71% OS at 10 yr 63% OS at 15 yr</td>
</tr>
</tbody>
</table>
High-Grade Gliomas

Conclusions

• No improvement in survival (level 1)
• No change in pattern of failure
• Toxicity acceptable
• No difference in general QOL and cognitive functioning

McGill
Low-Grade Gliomas
Conclusions

- Very limited data on highly selected patients
- Patients technically eligible for SRS rare
- Insufficient to data to recommend SRS or FSRT over conventional 3DCRT or FSRT with conventional fractionation