Stereotactic Radiosurgery and Stereotactic Radiotherapy for Gliomas

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Frontiers of Radiosurgery
Centro Diagnostico Italiano - the Radiosurgery Society
Milan, Italy October 2019
Disclosures

• Stanford University: Employer
• Inovio Pharmaceuticals, Inc.: Consultant
• IJROBP: Senior Editor - CNS
Objectives

• Review the data that support stereotactic radiosurgery (SRS) and hypofractionated stereotactic radiotherapy (fSRT) for primary and recurrent gliomas
Outline – SRS/fSRT for Gliomas

Stereotactic radiosurgery and stereotactic radiotherapy for:

- **Recurrent Gliomas**
- **Primary Gliomas**
  - Newly diagnosed lower grade gliomas
  - Newly diagnosed glioblastoma
Objectives:

• Given the lack of high level evidence for guidance, I will share example cases of how I manage repeat irradiation for recurrent gliomas...
Recurrent GBM: No Standard of Care...

- Clinical Trial
- Repeat surgery
- Chemotherapy
- Bevacizumab
- Tumor Treating Fields (TTF)
- Repeat Irradiation:
  - Conventionally fractionated
  - Hypofractionated
  - Stereotactic radiosurgery
- Supportive Care
Outline: Repeat Radiotherapy for Recurrent Glioma

• Background:
  – Recurrence, Patterns of Progression

• Repeat Radiotherapy
  – Conventionally fractionated radiotherapy
  – Hypofractionated radiotherapy
  – Stereotactic Radiosurgery (SRS)
Recurrence?

Prior to RT/TMZ  1 month
At the MRI at 1 month after chemoRT:

- If tumor was larger: 64% were psPD
- If psPD: 66% had methylated MGMT
- If early progression: 90% unmethylated MGMT

Brandes JCO 26, 2008
Pseudoprogression

Prior to RT/TMZ  1 month  3 months  5 months
Response Assessment in Neuro-Oncology (RANO)

- Can call progression <3 months after chemoradiotherapy ONLY if:
  - New enhancement beyond 80% isodose line
  - Unequivocal pathologic evidence of viable tumor

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Table 2. Criteria for Determining First Progression Depending on Time From Initial Chemoradiotherapy

<table>
<thead>
<tr>
<th>First Progression</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progressive disease &lt; 12 weeks after completion of chemoradiotherapy</td>
<td>Progression can only be defined using diagnostic imaging if there is new enhancement outside of the radiation field (beyond the high-dose region or 80% isodose line) or if there is unequivocal evidence of viable tumor on histopathologic sampling (e.g., solid tumor areas [i.e., &gt; 70% tumor cell nuclei in areas], high or progressive increase in MIB-1 proliferation index compared with prior biopsy, or evidence for histologic progression or increased anaplasia in tumor). Note: Given the difficulty of differentiating true progression from pseudoprogression, clinical decline alone, in the absence of radiographic or histologic confirmation of progression, will not be sufficient for definition of progressive disease in the first 12 weeks after completion of concurrent chemoradiotherapy.</td>
</tr>
</tbody>
</table>

Progressive disease ≥ 12 weeks after chemoradiotherapy completion

1. New contrast-enhancing lesion outside of radiation field on decreasing, stable, or increasing doses of corticosteroids.
2. Increase by ≥ 25% in the sum of the products of perpendicular diameters between the first postradiotherapy scan, or a subsequent scan with smaller tumor size, and the scan at 12 weeks or later on stable or increasing doses of corticosteroids.
3. Clinical deterioration not attributable to concurrent medication or comorbid conditions is sufficient to declare progression on current treatment but not for entry onto a clinical trial for recurrence.
4. For patients receiving antiangiogenic therapy, significant increase in T2/FLAIR nonenhancing lesion may also be considered progressive disease. The increased T2/FLAIR must have occurred with the patient on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy and not be a result of comorbid events (e.g., effects of radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects).

Abbreviation: FLAIR, fluid-attenuated inversion recovery.

Wen JCO 28, 2010
Pseudoprogression in Lower Grade Glioma

- n=199
- IDH mt or grade 2
- Pseudoprogression in 44%
- Higher risk with RT + TMZ than RT alone (HR 2.2)
- Better OS in those with pseudoprogression

Dworkin, Shih JNeuroOnc 142, 2019
Outline: Repeat Radiotherapy for Recurrent Glioma

• Background:
  – Recurrence, Patterns of Progression

• Repeat Radiotherapy
  – Conventionally fractionated radiotherapy
  – Hypofractionated radiotherapy
  – Stereotactic Radiosurgery (SRS)
Repeat RT Example: 60 Gy in 30 fractions

51 yo woman with GBM:
60 Gy in 30 + TMZ
↓
Recurred 8 years later (MGMT hypermethylated)
Mainly out of prior RT field
↓
Repeat 60 Gy in 30 + TMZ

Initial Diagnosis:
60 Gy in 30
(note: pre-resection MRI shown)

8 years later:
60 Gy in 30
Outline: Repeat Radiotherapy for Recurrent Glioma

• Background:
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• Repeat Radiotherapy
  – Conventionally fractionated radiotherapy
    – Hypofractionated radiotherapy
  – Stereotactic Radiosurgery (SRS)
Repeat RT Example: 35 Gy in 10 fractions

50 yo man with GBM:
60 Gy in 30 + TMZ
↓
Recurred in 5 months
(MGMT not hypermethylated)
↓
Resection #2
↓
Clinical Trial
↓
Still localized, so repeated RT

Initial Diagnosis:
60 Gy in 30

1 year later:
35 Gy in 10
GBM Re-Irradiation: Hypofractionated RT

- n=147
- Median 35 Gy in 10 fractions to T1 post-contrast GTV
- Median OS – 11 m

Fogh JCO 28, 2010
RTOG 1205: BEV +/- 35 Gy in 10 for Recurrent GBM

• n=182 with recurrent GBM

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab alone</td>
<td>9.7 months</td>
</tr>
<tr>
<td>Bevacizumab + 35 Gy in 10</td>
<td>10.1 months</td>
</tr>
</tbody>
</table>

p=0.5

Conclusion:

• In all patients enrolled, no benefit to re-irradiation
• Await patterns of progression data

PI: Christina Tsien – ASTRO 2019
Outline: Repeat Radiotherapy for Recurrent Glioma

• Background:
  – Recurrence, Patterns of Progression

• Repeat Radiotherapy
  – Conventionally fractionated radiotherapy
  – Hypofractionated radiotherapy
  – Stereotactic Radiosurgery (SRS)
Repeat RT Example: SRS

44 yo man grade III astro
59.4 Gy + TMZ
↓
3 years later:
1 cm recurrence
↓
Offered Surgery vs. SRS*
↓
Stable 1.4 years later

*Generally, I only offer SRS as an option if surgery is an option. Otherwise I do hypofractionation over 1-2 weeks.
SRS for Recurrent GBM

• No randomized data (phase III or phase II)
• Most all data are retrospective case series
  – Many reviews exist...
## SRS/HFRT for Recurrent GBM

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Type of Study</th>
<th>Number of patients</th>
<th>HFRT or SRS</th>
<th>Re-RT Dose</th>
<th>Median OS from SRS (months)</th>
<th>Adverse Radiation Effect (ARE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laing [42]</td>
<td>1993</td>
<td>phase 1/2</td>
<td>22</td>
<td>HFRT</td>
<td>5 Gy x 4-10</td>
<td>9.8</td>
<td>23%</td>
</tr>
<tr>
<td>Shepherd [41]</td>
<td>1997</td>
<td>retrospective</td>
<td>33</td>
<td>HFRT</td>
<td>5 Gy x 4-10</td>
<td>10.7</td>
<td>36%</td>
</tr>
<tr>
<td>Hudes [45]</td>
<td>1999</td>
<td>phase 1</td>
<td>20</td>
<td>HFRT</td>
<td>3 – 3.5 x 7-10</td>
<td>10.5</td>
<td>0%</td>
</tr>
<tr>
<td>Schwer [54]</td>
<td>2008</td>
<td>phase 1</td>
<td>15</td>
<td>HFRT</td>
<td>6-12 Gy x 3</td>
<td>10</td>
<td>13%</td>
</tr>
<tr>
<td>Park [17]</td>
<td>2012</td>
<td>case-control</td>
<td>11</td>
<td>SRS</td>
<td>16 Gy x 1</td>
<td>18</td>
<td>9% with BEV vs 43%</td>
</tr>
<tr>
<td>Cuneo [43]</td>
<td>2012</td>
<td>retrospective</td>
<td>63</td>
<td>SRS</td>
<td>15 Gy x 1</td>
<td>11.2 with BEV, 3.9 no BEV</td>
<td>19% no BEV, 5% with BEV</td>
</tr>
<tr>
<td>Koga [18]</td>
<td>2012</td>
<td>retrospective</td>
<td>18</td>
<td>SRS</td>
<td>20 Gy x 1</td>
<td>9-10.5</td>
<td>22% for C-SRS, 44% for EF-SRS</td>
</tr>
</tbody>
</table>

Shah, Soltys NSurg 2017
Redmond, Cureus Dec 2015
Brainstem Toxicity: Repeat Irradiation with SRS

- n=38 Pediatric recurrent Ependymoma
- Median time between RT courses: 16 months
  - n=32 Conventionally fractionated re-irradiation:
    - Median combined dose 111.6 Gy (typically 55.8Gy + 55.8Gy again)
  - n=6 had SRS → ‘significant brainstem toxicity and one death’

Merchant IJROBP 71, 2008
Updated: Tseng IJROBP 100, 2018
Without randomized data to guide us, multiple reasonable re-irradiation strategies exist...
Re-irradiation for GBM: Systematic Review

- n=29 re-irradiation studies
- Re-irradiation Proposal:

Table 6
Strategy proposed in the present analysis (to be confirmed in prospective further studies): patients should be stratified according to different disease volume and then, treated with differentiated total dose and fractionation. RS: radiosurgery; HFSRT: hypofractionated stereotactic radiotherapy; CFRT: conventionally fractionated radiotherapy.

<table>
<thead>
<tr>
<th>Tumor Volume</th>
<th>Technique</th>
<th>EQD2</th>
<th>Example of total dose and number of fractions</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 12.5 ml</td>
<td>RS</td>
<td>&lt; 65 Gy</td>
<td>12-15 Gy in a single fraction</td>
</tr>
<tr>
<td>&gt; 12.5 ml and &lt; 35 ml</td>
<td>HFSRT</td>
<td>&lt; 50 Gy</td>
<td>25 Gy in 5 fractions</td>
</tr>
<tr>
<td>&gt; 35 ml up to 50 ml</td>
<td>CFRT</td>
<td>36 Gy</td>
<td>36 Gy in 20 fractions</td>
</tr>
</tbody>
</table>

Scoccianti Crit Review Onc 126, 2018
Re-irradiation for GBM: Critical Review

- Re-irradiation Proposal:

Table II. Examples of re-irradiation techniques and regimens for patients with recurrent supratentorial gliomas.

<table>
<thead>
<tr>
<th>Recurrence Type</th>
<th>Treatment Recommendations</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-volume recurrence</td>
<td>Consider SRS, brachytherapy or FSRT, e.g. 35 Gy in 5 fractions</td>
<td>Proximity to critical structures might require reduced EQD2, e.g. by reducing fraction size (35 Gy in 10 fractions)</td>
</tr>
<tr>
<td>Intermediate volume recurrence</td>
<td>Consider FSRT, e.g. 30 Gy in 5 fractions</td>
<td></td>
</tr>
<tr>
<td>Large-volume recurrence</td>
<td>Consider FSRT, e.g. 25 Gy in 5 fractions</td>
<td></td>
</tr>
</tbody>
</table>

Nieder Anticancer Research 36, 2016
Conclusion: My Approach to Repeat RT for Glioma

- No high level data to guide dose/fractionation
- Conventional Fractionation: 54-60 Gy in 30
  - Lower Grade Glioma with long time to progression
  - GBM if out of prior RT field (and therefore long time to progression)
- Hypofractionation: 25-30 Gy in 5, 35 Gy in 10
  - Lower Grade Glioma if early recurrence or transformation to GBM
  - GBM if within prior RT field
- SRS: 16-22 Gy x 1
  - As a replacement for surgical resection
Conclusion: Prospective Data are Needed..

Ongoing clinical trials:

- NCT02709226: NCI – Dose escalation: 3.5 Gy x 10, x12, x 14
- NCT01925573: U Maryland – BEV + 35 Gy in 10 or 30 in 5 + TTF
- NCT01252459: U Freiburg – 39 Gy in 13 + PET
- NCT01464177: Brazil – 25 Gy in 5 vs. 35 Gy in 5
- NCT01666600: NOA-12 – 36 Gy in 18 + BIBF 1120
- NCT02149459: Sheba – 30-35 Gy in 10 + SMC 0712-13
Outline – SRS/fSRT for Gliomas

Stereotactic radiosurgery and stereotactic radiotherapy for:

• Recurrent Gliomas

• Primary Gliomas
  – Newly diagnosed lower grade gliomas
  – Newly diagnosed glioblastoma
SRS for Pilocytic Astrocytomas

• SRS (maybe) makes sense:
  – Grade I
  – Usually well demarcated

• But, concerns with toxicity → IMRT is standard

• Overall, little data:

Table 1  Articles reporting results following GKS of JPA

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Dose</th>
<th>Mean follow-up</th>
<th>Tumor control (%)</th>
<th>Cyst progression (%)</th>
<th>Complications (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boethius (1)</td>
<td>17</td>
<td>10–20 Gy</td>
<td>6 years</td>
<td>100</td>
<td>12</td>
<td>30</td>
</tr>
<tr>
<td>Hafez (6)</td>
<td>1</td>
<td>12 Gy</td>
<td>3 years</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Kano (7)</td>
<td>50</td>
<td>11–22 Gy</td>
<td>4.5 years</td>
<td>96</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Kida (10)</td>
<td>12</td>
<td>Mean 12 Gy</td>
<td>2 years</td>
<td>92</td>
<td>8</td>
<td>17</td>
</tr>
<tr>
<td>Trifiletti (23)</td>
<td>28</td>
<td>Median 16 Gy</td>
<td>Median 5.2 years</td>
<td>93</td>
<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>

Liu Child’s Nervous System 35, 2019
SRS for Newly Diagnosed GBM

• If ~80% of GBMs recur within the 60 Gy radiotherapy field, why not give more dose with SRS?
RTOG 9305: ChemoRT +/- SRS Boost

• n=203  GBM (<40cc)

• 60 Gy + BCNU

• Upfront SRS → 60 Gy + BCNU
  – SRS dosing per RTOG 9005
    • 0-2cm 24Gy, 2-3cm 18Gy, 3-4cm 15Gy

Souhami IJROBP 60, 2004
RTOG 9305: CRT +/- SRS Boost

Results:
- No difference in OS
- No difference in patterns of progression

Conclusion:
No role of SRS boost in newly diagnosed GBM

Fig. 1. Survival by treatment arm. RT = radiation therapy; SRS = stereotactic radiosurgery; MST = median survival time.

Souhami IJROBP 60, 2004
Dose escalation with SRS boost added to 6 weeks of radiotherapy was a negative trial

What about other trials of dose escalation through hypofractionation in 1 to 2 weeks?
• n=16  Phase I  Tumor <6cm
• With TMZ
• Dose escalation trial of:
  – 60 Gy in 20 fractions
  – 60 Gy in 15 fractions
  – 60 Gy in 12 fractions
  – 60 Gy in 10 fractions
• No Dose limiting toxicity \( \rightarrow \) 60 Gy in 10 is safe
  – Confirmed in another phase II trial of 24 patients

<table>
<thead>
<tr>
<th>Level</th>
<th>Fractions (n)</th>
<th>Total dose (Gy)</th>
<th>Fraction size (Gy)</th>
<th>Total dose (Gy)</th>
<th>Fraction size (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>60</td>
<td>3</td>
<td>45</td>
<td>2.25</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>60</td>
<td>4</td>
<td>40.5</td>
<td>2.7</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>60</td>
<td>5</td>
<td>36</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>60</td>
<td>6</td>
<td>30</td>
<td>3</td>
</tr>
</tbody>
</table>

*Abbreviation: PTV = planning target volume.*

Chen IJROBP 81, 2011
Reddy, Chen IJROBP 84, 2012
Phase II: 60 Gy in 10 + TMZ + BEV

- n=30  phase II
- 60 Gy in 10 fractions with TMZ + Bevacizumab
- Median OS: 16.3 months
- 50% with symptomatic radiation necrosis → Trial stopped

- Conclusion: Large tumor volumes (rather than BEV) likely led to necrosis at doses of 60 Gy in 2 weeks
  – Abandoned further trials at this high dose

Ney, Chen JNOnc 2015
SRS for Newly Diagnosed GBM

• Problems with 60 Gy in 2 weeks:
  – Perhaps dose too high for volumes of that size (up to 6 cm)
  – 2 weeks of treatment is still too long for some patients

• What about 1 week (5 days) of SRS for GBM → Stanford Trial
Shortened Treatment for Glioblastoma

- Rationale for Hypofractionated RT (shorter than 6 weeks):
  - 6 weeks of radiotherapy may be 5-10% of remaining life
  - Shorter course → better access to specialized care
  - Less cost than 6 weeks
  - Possibly a different radiobiology (combine with immunotherapy)
Stanford 5-Fraction Trial Design

- Standard 3 + 3 Dose Escalation Schema
- 2 Arms Based on PTV Size
- PTV = GTV + 5 mm margin (Stupp was 20 mm margin)
- Standard Concurrent TMZ (8 days) → Adjuvant TMZ

<table>
<thead>
<tr>
<th>PTV Size</th>
<th>Diameter</th>
<th>Dose Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm 1: &lt;60 cm³</td>
<td>~5 cm</td>
<td>25 → 30 → 35 → 40 Gy</td>
</tr>
<tr>
<td>Arm 2: 60-150 cm³</td>
<td>~6.6 cm</td>
<td>25 → 30 → 35 → 40 Gy</td>
</tr>
</tbody>
</table>

Azoulay, Soltys – under review Oct 2019
SRS Treatment

• GTV = Cavity/Residual Tumor
• CTV = 5 mm margin
  – shaved at anatomic boundaries
• PTV = 0 mm

• Non-enhancing tumor included, but no intent to cover edema
### Results: Acute and Late SRS-Related Toxicity

<table>
<thead>
<tr>
<th>Treatment Arm:</th>
<th>Dose 25 Gy</th>
<th>Dose 30 Gy</th>
<th>Dose 35 Gy</th>
<th>Dose 40 Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number per Arm</td>
<td>n = 6</td>
<td>n = 6</td>
<td>n = 6</td>
<td>n = 12</td>
</tr>
<tr>
<td>Grade 3-5 SRS Related Toxicity</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>17%</td>
</tr>
<tr>
<td>Grade 1-5 SRS Related Toxicity</td>
<td>17%</td>
<td>17%</td>
<td>67%</td>
<td>33%</td>
</tr>
</tbody>
</table>

**Conclusion:**
- Per protocol maximum tolerated dose is 40 Gy in 5 fractions

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Azoulay, Soltys – under review Oct 2019
Results: Overall Survival

Median OS:
- All: 14.8 months
- MGMT:
  - Methylated: 19.9 months
  - Unmethylated: 11.3 months
  \( p = 0.03 \)
Results: Survival Improved in Those with Necrosis

- Median OS:
  - Necrosis: 27.2 months
  - None: 11.7 months
  - $p=0.08$

Time to Necrosis:
- Median 8 months (3-12)
Results: Adverse Radiation Effect Did NOT impact HRQOL

139 total questionnaires: EORTC QLQ-30, BN20, MDASI-BT

Time 0 = date of ARE

Conclusion:

• Tumor progression leads to communication deficit
• Radiation Necrosis did not impact any scale

Pollom IJROBP 98, 2017
Conclusions: 5-Fraction SRS with 5mm Margin with TMZ

• The per-protocol Maximum Tolerated Dose is 40 Gy in 5 fractions
• Although 27% got G1-2 Adverse Radiation Effect
  – ARE did not impact Quality of Life
  – Patients with ARE had improved OS (27 vs. 12 months)
• Asymptomatic ARE, especially in the era of bevacizumab, may be clinically desirable, rather than considered a dose limiting ‘toxicity’
Future Directions in Treatment of GBM: SRS/Hypofractionation and Immunotherapy

Hypofractionation may be:

• More immunostimulatory (larger dose per day)
  – Perhaps better to combine with immunotherapy (NCT02383212)

• Less immunosuppressive (less normal brain irradiated)
  – Lymphopenia is independently associated with worse OS\(^1\)
  – 6 weeks of cranial IMRT $\rightarrow$ irradiates the entire circulating lymphocyte pool, akin to TBI (total body irradiation)\(^2\)

2. Yovino Cancer Inv 31, 2013
Lymphopenia: 1 week vs. 6 weeks ChemoRT

- Analyzed 1 week SRS (n=30) vs. 6 weeks IMRT (n=79)
- Treatment-related lymphopenia much higher with 6 weeks of treatment (p<0.0001)
- Grade 2-4 lymphopenia:
  - 9% (1 week) vs 56% (6 weeks) at 90 days

Fujimoto, Soltys ASTRO 2018
Conclusions: SRS for Glioma

- SRS/Hypofractionated RT for recurrent glioma:
  - Lower grade gliomas: reirradiation is an option
    - Fractionation based on histology, time to recurrence, location, size
  - GBM: reirradiation is an option
    - SRS – Data largely limited to retrospective case series
    - Hypofractionated RT: await patterns of progression analysis on RTOG 1205

- SRS for Newly Diagnosed Glioma:
  - Pilocytic gliomas: limited data exist
  - GBM:
    - RTOG 9305 → SRS boost no benefit when added to conventional 60 Gy
    - Single arm prospective data:
      - 10-fraction Colorado studies → high rates of necrosis in later trials
      - 5-fraction Stanford study → SRS perhaps less immunosuppressive