Stereotactic Radiosurgery for Gliomas

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Disclosures

• None
Learning points

• SRS – Basics & Radiobiology
• Glioma classification -2021
• SRS in circumscribed gliomas
• SRS in Low grade gliomas
• SRS in high grade gliomas
• SRS in recurrent gliomas
• Conclusion
SRS – Basics & Radiobiology
Radiosurgery – As defined by Leksell

A single high dose fraction of radiation, stereotactically directed to an intracranial region of interest through intact skull

One versus > 1 fraction

2007 – AANS, CNS, ASTRO – suggested that SRS be used for up to 5 fractions
Radiosurgery Machines

- Gamma Knife
- Proton Therapy
- Cyberknife
- Tomotherapy
- Brainlab Vero
- Varian-Truebeam
Definition - Elaborated

Technical Principles
- Focussed radiation
- Steep Dose Fall off
- Non coplanar Setup

SRS

Radiobiological Principles
- Single session treatment
- Not O2 dependent
- Radioresistant tumours
Hallmarks of Radiosurgery

- Precision
- Accuracy
- Dose Conformity
- Rapid Dose Fall off
- Small / Sharply defined target

SRS

Minimizes dose to normal tissues

Maximum Dose to Target
Radiobiology -- SRS

Radiobiological Effect of Single Fraction (> 10 Gy):

1. Endothelial cell Damage $\rightarrow$ Cytotoxicity & Apoptosis. (Ceramide Pathway)

2. Vascular Damage at High Doses $\rightarrow$ ++ 2$^{nd}$ Cell Killing.

3. Enhanced Anti-Tumor Immunity after Tumor Irradiation.

4. Tumor Hypoxia is of Less Importance.

Radiobiological Complexity of Cranial Targets

**Late Responding Targets**
- AVM (Embedded)
- Schwannomas (Surrounded)
- Brain -- Late responding tissue - $\alpha/\beta = 2$

**Early Responding Targets**
- GBM, Metastases (Embedded)
- Low Grade Glioma (Surrounded)

**Treatment Options**
- Radiosurgery
- Fractionated RT
# SRS – Typical Indications

<table>
<thead>
<tr>
<th>Benign</th>
<th>Malignant</th>
<th>Functional</th>
</tr>
</thead>
<tbody>
<tr>
<td>AV malformations</td>
<td>Brain Metastases</td>
<td>Trigeminal neuralgia</td>
</tr>
<tr>
<td>Schwannomas</td>
<td>Recurrent Glioma</td>
<td>Temporal lobe epilepsy</td>
</tr>
<tr>
<td>Meningioma (&lt;3cm)</td>
<td>Small residual LGG</td>
<td></td>
</tr>
<tr>
<td>Pituitary Adenoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Craniopharyngioma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glomus tumor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paraganglioma</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Radiosurgery and BED

BED 2 – Response of normal tissue to RT Greater
Greater BED2 → Greater Toxicity Risk

BED 10 – Response of tumor tissue to RT
Greater BED10 → Higher tumor control probability

For SRS D=d

BED for SRS rises rapidly with increasing dose
Steps of Radiosurgery

1. Create Stereotactic Space
2. Identify Target in Stereotactic Space
3. Place target at isocentre of radiation delivery system
4. Treat with non coplanar beams
5. Quality Assurance

SRS
## Pros of Radiosurgery in Gliomas

<table>
<thead>
<tr>
<th>Technology</th>
<th>Radiobiology</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>- High Precision techniques</td>
<td>- High dose rate to target and low dose rate to surrounding normal tissues</td>
<td>- Gliomas fail within 1-2 cm of tumor margins</td>
</tr>
<tr>
<td>- Allows Dose escalation</td>
<td>- Threshold dose rates of 1Gy/min intensify this effect</td>
<td>- Shorter overall Treatment time</td>
</tr>
<tr>
<td>- Minimal collateral normal tissue damage</td>
<td>- Rapid dose fall off</td>
<td>- Well suited for children under anaesthesia</td>
</tr>
<tr>
<td>- Short treatment time can allow access to specialized centres</td>
<td>- Neuromodulation</td>
<td>- Short course minimize lymphopenia and the immunosuppressive effect of prolonged treatment courses</td>
</tr>
</tbody>
</table>
Cons of Radiosurgery in Gliomas

Infiltrative pattern
- Gliomas are infiltrative in nature
- Ill defined margins
- Unsuitable for radiosurgery

Alpha/Beta Ratio
- LGG have low a/b ratio and are more focal – attractive targets
- HGG have high a/b ratio and are ill defined – poor targets

Toxicity
- Narrow therapeutic window between tumor control and toxicity
- SRS for gliomas associated with high rates of radiation necrosis

No Level 1 Evidence showing SRS has superior outcome in Gliomas
Glioma – Classification 2021
Gliomas according to WHO 2021 classification

**Adult type diffuse gliomas**
- Astrocytoma IDH mutant
- Oligodendroglioma, IDH mutant and 1p19q codeleted
- Glioblastoma, IDH wild type

**Paediatric type diffuse low grade gliomas**

**Paediatric type diffuse high grade gliomas**

**Circumscribed gliomas**
- Pilocytic astrocytoma
- High grade Astro with piloid
- Pleomorphic xanthoastrocytoma
- SEGA
- Choroid glioma

**Ependymal tumors**

**Table 1. Gliomas according to WHO 2021 classification of CNS tumours**

<table>
<thead>
<tr>
<th>Category</th>
<th>Tumours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult type diffuse gliomas</td>
<td>Astrocytoma, IDH-mutant</td>
</tr>
<tr>
<td>Oligodendroglioma, IDH-mutant and 1p19q codeleted</td>
<td></td>
</tr>
<tr>
<td>Glioblastoma, IDH-wildtype</td>
<td></td>
</tr>
<tr>
<td>Paediatric type diffuse low grade gliomas</td>
<td>Diffuse astrocytoma, MYB or MYBL1 altered</td>
</tr>
<tr>
<td>Angiomyxoma glioma</td>
<td></td>
</tr>
<tr>
<td>Polymorphous low-grade neuronal-ependymal tumour of the young</td>
<td></td>
</tr>
<tr>
<td>Diffuse low-grade glioma, MAPK pathway altered</td>
<td></td>
</tr>
<tr>
<td>Paediatric type diffuse high-grade gliomas</td>
<td>Diffuse midline glioma, H3 K27-mutant</td>
</tr>
<tr>
<td>Diffuse hemispheric glioma, H3 G34-mutant</td>
<td></td>
</tr>
<tr>
<td>Diffuse paediatric type high-grade glioma, H3-wildtype and EPH-wildtype</td>
<td></td>
</tr>
<tr>
<td>Infant type hemispheric glioma</td>
<td></td>
</tr>
<tr>
<td>Circumscribed astrocyte gliomas</td>
<td>Pilocytic astrocytoma</td>
</tr>
<tr>
<td>High-grade astrocytoma with piloid features</td>
<td></td>
</tr>
<tr>
<td>Metastatic xanthoastrocytoma</td>
<td></td>
</tr>
<tr>
<td>Subependymal giant cell astrocytoma</td>
<td></td>
</tr>
<tr>
<td>Craniopharyngioma</td>
<td></td>
</tr>
<tr>
<td>Acute oligodendroglioma, MIB1-altered</td>
<td></td>
</tr>
<tr>
<td>Ependymal tumours</td>
<td>Supratentorial ependymoma</td>
</tr>
<tr>
<td>Supratentorial ependymoma, 2F1A fusion-positive</td>
<td></td>
</tr>
<tr>
<td>Supratentorial ependymoma, 1P1F1 fusion-positive</td>
<td></td>
</tr>
<tr>
<td>Posterior fossa ependymoma</td>
<td></td>
</tr>
<tr>
<td>Posterior fossa group A (PFA) ependymoma</td>
<td></td>
</tr>
<tr>
<td>Posterior fossa group B (PFB) ependymoma</td>
<td></td>
</tr>
<tr>
<td>Spinal ependymoma</td>
<td></td>
</tr>
<tr>
<td>Spinal ependymoma, MYC-N-myc amplification</td>
<td></td>
</tr>
<tr>
<td>Myxopapillary ependymoma</td>
<td></td>
</tr>
<tr>
<td>Subependymoma</td>
<td></td>
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</table>
### 2021 – WHO classification of gliomas

<table>
<thead>
<tr>
<th>Type</th>
<th>WHO grade 1</th>
<th>WHO grade 2</th>
<th>WHO grade 3</th>
<th>WHO grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astrocytoma</td>
<td>Pilocytic astrocytoma</td>
<td>Grade 2 Astrocytoma</td>
<td>Grade 3 Astrocytoma</td>
<td>Grade 4 Astrocytoma</td>
</tr>
<tr>
<td></td>
<td>Circumscribed type</td>
<td></td>
<td></td>
<td>Glioblastoma</td>
</tr>
<tr>
<td>Oligodendroglioma</td>
<td></td>
<td>Grade 2 Oligodendroglioma</td>
<td>Grade 3 Oligodendroglioma</td>
<td></td>
</tr>
</tbody>
</table>
Diffuse Gliomas

- Accumulation of tumour cells around neurons (perineuronal satellitosis, arrowhead)
- Around blood vessels (arrow)
- Under the pia (asterisk)
- Tumour cells migrating along white matter tracts (intrafascicular growth; + in a)
GBM is a highly angiogenic and infiltrative tumor.
Cells invade along blood vessels to support tumor growth (co-option).
GBM displaces astrocytes end-feet and alters pericyte stability, leading to perivascular niches and cell evasion.
# SRS in circumscribed gliomas

<table>
<thead>
<tr>
<th>Type</th>
<th>WHO grade 1</th>
<th>WHO grade 2</th>
<th>WHO grade 3</th>
<th>WHO grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Astrocytoma</strong></td>
<td>Pilocytic astrocytoma</td>
<td>Grade 2 Astrocytoma</td>
<td>Grade 3 Astrocytoma</td>
<td>Grade 4 Astrocytoma</td>
</tr>
<tr>
<td><strong>Oligodendroglioma</strong></td>
<td>Grade 2 Oligodendroglioma</td>
<td>Grade 3 Oligodendroglioma</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
SRS for PA in recurrent or unresectable pts

37 patients
GTV : 4.7 cc
Margin dose : median 15 Gy (9.6 – 22.5 Gy)
Tumor control : 93 %
Overall survival : 89 %

Grade 1 Glioma
Solid, cystic or mixed
Well circumscribed
1st option : Radical resection when feasible
RT avoided due to young age

Poor prognostic factors:
Age > 18 yrs
Marginal dose < 15 Gy
Multifocal disease
Prior RT
SRS for Pilocytics in paediatric population

50 patients
GTV : 2.1 cc
Margin dose : 14.5 Gy (11-22.4 Gy)

Tumor control (5yr PFS) : 71 %
Overall survival (10yr) : 98 %
ARE : 10 %

89% @ 10 yrs
45% @ 10 yrs
SRS for PA in recurrent or unresectable pts

18 patients
GTV : 9.1 cc
Margin dose : 15 Gy (12-20 Gy)

Tumor control (5yr PFS) : 41 %
10 yr PFS : 17 %
Overall survival (5 yr) : 71 %
10 yr OS : 71 %
ARE : 10 %
Poor prognostic factors : Prior EBRT

Clinical Investigation: Central Nervous System Tumor
Stereotactic Radiosurgery for Recurrent or Unresectable Pilocytic Astrocytoma
Christopher L. Hallameier, M.D.,* Bruce E. Pollock, M.D.,*† Paula J. Schomberg, M.D.,* Michael J. Link, M.D.,† Paul D. Brown, M.D.,† and Scott L. Stafford, M.D.*
Departments of *Radiation Oncology and †Neurological Surgery, Mayo Clinic, Rochester, MN and ‡Department of Radiation Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, TX

2012
SRS for small PA

28 patients
GTV : 1.84 cc (0.19 – 15.9cc)
Margin dose : 16 Gy (4 – 20 Gy)
Tumor control : 93 %
Overall survival : 100 %

6 yr PFS 96 %,
12 yr PFS 80 %
ARE - None
Pooled Data Analysis for SRS in PAs.

141 patients
GTV : 3.45 cc
Margin dose : 14.0 Gy (11-22.4 Gy)
Primary SRS : 39 %
Secondary SRS : 61 %

10 yr OS 92.5 %,
10 yr PFS 70 %
ARE - 10 %
## SRS for Pilocytic Astrocytoma's

<table>
<thead>
<tr>
<th>First author</th>
<th>Patients, n</th>
<th>Pediatric, %</th>
<th>Median age, years</th>
<th>Local tumor control, %</th>
<th>5-year PFS, %</th>
<th>Tumor volume, cc</th>
<th>Median margin dose, Gy</th>
<th>Median follow-up, years</th>
<th>Complications, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somaza, 1996</td>
<td>9</td>
<td>100</td>
<td>–</td>
<td>100</td>
<td>–</td>
<td>–</td>
<td>15 (mean)</td>
<td>1.6 (mean)</td>
<td>0</td>
</tr>
<tr>
<td>Kano, 2009</td>
<td>50</td>
<td>100</td>
<td>10.5</td>
<td>76</td>
<td>70.8</td>
<td>2.1</td>
<td>14.5</td>
<td>4.6</td>
<td>10</td>
</tr>
<tr>
<td>Kano, 2009</td>
<td>14</td>
<td>0</td>
<td>32.3</td>
<td>50</td>
<td>31.5</td>
<td>4.7</td>
<td>13.3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Hallemeier, 2012</td>
<td>18</td>
<td>33</td>
<td>23</td>
<td>75</td>
<td>41</td>
<td>9.1</td>
<td>15</td>
<td>8</td>
<td>44</td>
</tr>
<tr>
<td>Simonova, 2016</td>
<td>25</td>
<td>100</td>
<td>13</td>
<td>84</td>
<td>–</td>
<td>2.7</td>
<td>16(^a)</td>
<td>–</td>
<td>16</td>
</tr>
<tr>
<td>Trifiletti, 2017</td>
<td>28</td>
<td>50</td>
<td>17.4</td>
<td>93</td>
<td>96</td>
<td>1.84</td>
<td>16</td>
<td>5.4</td>
<td>0</td>
</tr>
</tbody>
</table>

2.1 cm Diameter sphere has 5 cc volume
Conclusion- SRS in Pilocytic astrocytoma's

• SRS can minimise potential long term ARE by targeting tumor with sharp borders and can achieve radiobiological effect by accurate focused RT.

• SRS should be considered
  • When re-resection is not feasible or there is an early recurrence
  • Prior to EBRT or chemotherapy
  • Solitary, small solid residual tumors ( < 5 cc)
  • Age < 18 yrs

• SRS is less effective for cystic tumors
## SRS in Low Grade gliomas

<table>
<thead>
<tr>
<th>Type</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astrocytoma</td>
<td>Circumscribed type</td>
<td>Low Grade</td>
<td>Diffuse type</td>
<td>High Grade</td>
</tr>
<tr>
<td></td>
<td>Pilocytic astrocytoma</td>
<td>Grade 4 Astrocytoma</td>
<td>Grade 3 Astrocytoma</td>
<td>Grade 4 Astrocytoma Glioblastoma</td>
</tr>
<tr>
<td></td>
<td>Grade 2 Astrocytoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oligodendroglioma</td>
<td>Grade 2 Oligodendroglioma</td>
<td></td>
<td>Grade 3 Oligodendroglioma</td>
<td></td>
</tr>
</tbody>
</table>
Early Vs Delayed SRS
Grade 2 Astrocytomatas

25 patients - Median age 30 yrs
GTV : 3.7 cc
Margin dose : 14 Gy
Followup : 65 months

Tumor control : 52 %
5 yr PFS : 54 %
10 yr PFS : 37 %

Good prognostic factors
Tumor volume < 6cc
SRS Dose ≥ 15 Gy
Non contrast enhancing tumor

Early SRS : 16
Delayed SRS : 9

2.26 cm Diameter sphere has 6 cc volume
Primary Vs Adjuvant SRS Oligodendrogliomas

30 patients - Median age 41 yrs
GTV : 15.4 cc
Margin dose : 14.5 Gy
Followup : 65 months

Median OS : 33 months
5 yr OS : 91 %
10 yr OS : 68 %

Good prognostic factors
Tumor volume < 15 cc
Better PFS for Grade 2 tumors
Better PFS for 1p19q LOH

Primary SRS
5 (Biopsy)
Adjuvant SRS
25

3.1 cm Diameter sphere has 15 cc volume
# SRS for Grade 2 or Fibrillary Astrocytomas

<table>
<thead>
<tr>
<th>First author</th>
<th>Patients, n</th>
<th>Median age, years</th>
<th>Local tumor control %</th>
<th>5-year PFS %</th>
<th>Tumor Volume in CC</th>
<th>Median margin dose, Gy</th>
<th>Median Follow up, years</th>
<th>Complications, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Kida, 2000</strong></td>
<td>39</td>
<td>30.9 (mean)</td>
<td>87.2</td>
<td>–</td>
<td>2.37 (diameter)</td>
<td>15.7 (mean)</td>
<td>2.2 (mean)</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>25</td>
<td>67</td>
<td>–</td>
<td>4.6</td>
<td>16</td>
<td>4.3</td>
<td>–</td>
</tr>
<tr>
<td><strong>Hadjipanayis, 2002</strong></td>
<td>12</td>
<td>25</td>
<td>67</td>
<td>–</td>
<td>2.4</td>
<td>16.5</td>
<td>4.1</td>
<td>40</td>
</tr>
<tr>
<td><strong>Wang, 2006</strong></td>
<td>17 Grade 1: 8</td>
<td>20</td>
<td>67</td>
<td>–</td>
<td>3.4</td>
<td>13.4 (mean)</td>
<td>2.8 (mean)</td>
<td>23.5</td>
</tr>
<tr>
<td></td>
<td>Grade 2: 13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Szeifert, 2007</strong></td>
<td>17</td>
<td>29.4 (mean)</td>
<td>71</td>
<td>–</td>
<td>3.7</td>
<td>14</td>
<td>5.4</td>
<td>4</td>
</tr>
<tr>
<td><strong>Park, 2011</strong></td>
<td>25</td>
<td>30</td>
<td>52</td>
<td>54</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## SRS for Grade 1 and 2 Gliomas

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Year</th>
<th>No. of Patients</th>
<th>Tumor Grade</th>
<th>No. of Patients w/ Prior RT</th>
<th>Tumor Size*</th>
<th>Marginal Dose (Gy)</th>
<th>FU (mos)</th>
<th>% Patients w/ Tumor Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barcia et al.</td>
<td>1994</td>
<td>16</td>
<td>I, II, UK</td>
<td>12</td>
<td>NA</td>
<td>21.7</td>
<td>NA</td>
<td>81</td>
</tr>
<tr>
<td>Somaza et al.</td>
<td>1996</td>
<td>9</td>
<td>I</td>
<td>2</td>
<td>1.6 cc</td>
<td>15</td>
<td>19</td>
<td>100</td>
</tr>
<tr>
<td>Kida et al.</td>
<td>2000</td>
<td>12</td>
<td>I</td>
<td>null</td>
<td>2.5 cm</td>
<td>12.5</td>
<td>27.6</td>
<td>91.7</td>
</tr>
<tr>
<td>Boëthius et al</td>
<td>2002</td>
<td>16</td>
<td>I</td>
<td>2</td>
<td>3.3 cc</td>
<td>11.3</td>
<td>102</td>
<td>100</td>
</tr>
<tr>
<td>Hadjipanayis et al</td>
<td>2002</td>
<td>37</td>
<td>I</td>
<td>10</td>
<td>3.4 cc</td>
<td>15</td>
<td>28</td>
<td>92</td>
</tr>
<tr>
<td>Kano et al</td>
<td>2009</td>
<td>50</td>
<td>I</td>
<td>5</td>
<td>2.1 cc</td>
<td>14.5</td>
<td>55.5</td>
<td>70</td>
</tr>
<tr>
<td>Henderson et al</td>
<td>2009</td>
<td>8</td>
<td>I</td>
<td>NA</td>
<td>4.4 cc</td>
<td>13</td>
<td>48.2</td>
<td>75</td>
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<tr>
<td>Mansur et al</td>
<td>2011</td>
<td>6</td>
<td>I</td>
<td>1</td>
<td>NA</td>
<td>15.5</td>
<td>60</td>
<td>80</td>
</tr>
<tr>
<td>Weintraub et al</td>
<td>2012</td>
<td>24</td>
<td>I, II, III</td>
<td>NA</td>
<td>2.4 cc</td>
<td>15</td>
<td>144</td>
<td>96</td>
</tr>
<tr>
<td>Simonova et al</td>
<td>2016</td>
<td>25</td>
<td>I</td>
<td>6</td>
<td>2.7 cc</td>
<td>16 Gy/1 fx, 25 Gy/5 fxs</td>
<td>181</td>
<td>80</td>
</tr>
<tr>
<td>Trifiletti et al</td>
<td>2017</td>
<td>28</td>
<td>I</td>
<td>4</td>
<td>1.8 cc</td>
<td>16</td>
<td>62.4</td>
<td>93</td>
</tr>
</tbody>
</table>
Conclusion- SRS in LGGs

• Why SRS for LGG:
  • EBRT is not shown to improve Survival
  • Young patients could avoid chemotherapy
  • Tumor near critical organs.

Early SRS for poor prognosis LGG
Age > 40
Tumor > 5cm
Not a candidate for Near total excision

Delayed SRS for good prognosis LGG
(At recurrence)
Age < 40
Tumor < 5cm
Near total excision
### SRS in high grade gliomas

<table>
<thead>
<tr>
<th>Grade Type</th>
<th>WHO grade 1</th>
<th>WHO grade 2</th>
<th>WHO grade 3</th>
<th>WHO grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Astrocytoma</strong></td>
<td>Pilocytic astrocytoma</td>
<td>Grade 2 Astrocytoma</td>
<td>Grade 3 Astrocytoma</td>
<td>Grade 4 Astrocytoma</td>
</tr>
<tr>
<td><strong>Oligodendroglioma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Levels:**
- **Circumscribed type**
- **Low Grade**
- **Diffuse type**
- **High Grade**
SRS in high grade gliomas

• As a Boost to chemoRT
• As a primary treatment
• In recurrent scenario
RTOG 9305 – Newly diagnosed glioblastoma
SRS Boost → Standard RT

Median survival
14.1 mths vs 13.7 mths +/- SRS

>90% failures in each arm accounted for local failures

Arm 1
RT – 60Gy / 30 #
BCNU 80mg/m2 D1-3 of RT then Q8weeks for 6 cycles

Arm 2
SRS followed by RT – 60Gy / 30 #
BCNU 80mg/m2 D1-3 of RT then Q8weeks for 6 cycles

SRS Dose
24Gy – Lesion < 2cm
18 Gy- Lesion 2.1 -3 cm
15 Gy – Lesion 3.1-4 cm
RTOG 0023
Weekly SRS Boost

**EBRT – 50 Gy in 25 fractions**

**Week 3-56 → 4 fractions of 5-7 Gy**

---

Fig. 1. Treatment schema. I = external beam radiation therapy (EBXRT; preoperative tumor volume plus edema), 2 Gy × 25 fractions. * = Stereotactic radiotherapy (SRT) boost, 5-7 Gy × 4 fractions.

Fig. 2. Overall survival for Radiation Therapy Oncology Group (RTOG) 0023 patient group vs. historical controls from the RTOG database (p = 0.24).
• For patients with malignant glioma, there is Level I-III evidence that the use of radiosurgery boost followed by external beam radiotherapy and BCNU does not confer benefit in terms of overall survival, local brain control, or quality of life as compared with external beam radiotherapy and BCNU.

• The use of radiosurgery boost is associated with increased toxicity.

• For patients with malignant glioma, there is insufficient evidence regarding benefits / harm of using
  – radiosurgery at the time progression or recurrence.
  – stereotactic fractionated radiation therapy in patients with newly diagnosed or progressive/recurrent malignant glioma
SRS vs fSRS

Demographic & Radiosurgical

OS: PFS

Outcome

54.9 years
WHO grade 4 (82.9%)
Target volume 5.9 cc
Dose 16 Gy

55.1 years
WHO grade 4 (76.3%)
Target volume 19.3 cc
Dose 28 Gy

Overall survival 12.7 months
Radiation necrosis 20.5%

Overall survival 12.6 months
Radiation necrosis 18.8%

Variable

<table>
<thead>
<tr>
<th></th>
<th>sSRS (n=41)</th>
<th>fSRS (n=17)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>41</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Age (years) (mean±SD)</td>
<td>54.9±13.1</td>
<td>55.1±12.9</td>
<td>0.95*</td>
</tr>
<tr>
<td>Sex (Female:Male)</td>
<td>23:18</td>
<td>6:11</td>
<td>0.25*</td>
</tr>
<tr>
<td>Pathologic diagnosis (% (no. of case))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO grade 4</td>
<td>41 (98.8%)</td>
<td>16 (94.1%)</td>
<td></td>
</tr>
<tr>
<td>AA 9.4% (2/41)</td>
<td>AA 11.8% (2/17)</td>
<td>0.55**</td>
<td></td>
</tr>
<tr>
<td>AOA 2.4% (1/41)</td>
<td>AODG 11.8% (2/17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AODG 9.8% (4/41)</td>
<td>DMG 5.9% (1/17)</td>
<td></td>
<td></td>
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<tr>
<td>GBM 78.0% (32/41)</td>
<td>GBM 70.6% (12/17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glosarcoma 4.9% (2/41)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior therapy (%) (no. of case)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTx 85.4% (35/41)</td>
<td>76.5% (13/17)</td>
<td>0.46**</td>
<td></td>
</tr>
<tr>
<td>RTx 100% (41/41)</td>
<td>88.2% (15/17)</td>
<td>0.08**</td>
<td></td>
</tr>
<tr>
<td>None 41.5% (17/41)</td>
<td>29.4% (9/31)</td>
<td>0.56**</td>
<td></td>
</tr>
<tr>
<td>Concomitant therapy (%) (no. of case)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMZ 48.8% (20/41)</td>
<td>47.1% (8/17)</td>
<td>1.1**</td>
<td></td>
</tr>
<tr>
<td>BEZ 0% (0/41)</td>
<td>5.9% (1/17)</td>
<td>0.29**</td>
<td></td>
</tr>
<tr>
<td>others 9.8% (4/41)</td>
<td>17.6% (3/17)</td>
<td>0.34**</td>
<td></td>
</tr>
<tr>
<td>Target volume (mm³) (mean±SD)</td>
<td>5.9±6.67</td>
<td>19.3±13.0</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Dose (Gy) (median) (range)</td>
<td>18 (11–25)</td>
<td>28 (24–35)</td>
<td></td>
</tr>
<tr>
<td>Isodose (%) (median) (range)</td>
<td>50% (50–50)</td>
<td>50% (50–65)</td>
<td></td>
</tr>
</tbody>
</table>

2.26 cm Diameter sphere has 6 cc volume
3.3 cm Diameter sphere has 19 cc volume

Fractionated stereotactic radiosurgery for malignant gliomas: comparison with single session stereotactic radiosurgery

Seung Won Choi¹ - Kyung Rae Cho¹ - Jung Won Choi¹ - Doo-Sik Kong¹ - Ho Jun Seol¹ - Do-Hyun Nam¹ - Jung-Il Lee¹

https://doi.org/10.1007/s11060-019-03328-3
<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Treatment Schema</th>
<th>Survival Rate</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarkaria</td>
<td>115</td>
<td>54-60 Gy RT + 6-20 Gy SRS</td>
<td>2-yr OS: 45%, 2-yr OS for KPS ≥ 70: 60%, 2-yr OS for KPS &lt; 70: 15%</td>
<td>NR</td>
</tr>
<tr>
<td>Gannett</td>
<td>30</td>
<td>44-62 Gy RT + 0.5-18 Gy SRS</td>
<td>1-yr DSS: 57%, 2-yr DSS: 25%, 3-yr survival: 13.9</td>
<td>13.9</td>
</tr>
<tr>
<td>Masciopinto</td>
<td>31</td>
<td>RT + 15-35 Gy SRS</td>
<td></td>
<td>9.5</td>
</tr>
<tr>
<td>Mehta</td>
<td>31</td>
<td>54 Gy RT + 15-30 Gy SRS</td>
<td></td>
<td>2 yr OS: 37%</td>
</tr>
<tr>
<td>Nwokedi</td>
<td>33</td>
<td>28-80 (median 50 Gy) RT + 19 Gy SRS</td>
<td>1-yr OS: 40%, 2-yr OS: 63%</td>
<td>1 yr OS: 26%</td>
</tr>
<tr>
<td>Balducci</td>
<td>41</td>
<td>59.4 Gy or 50.4 Gy RT + 10 or 19 Gy SRS (total dose of 69.4 Gy) + temozolomide</td>
<td>2-yr OS: 63%</td>
<td>All pts: 30 GBM: 28</td>
</tr>
<tr>
<td>Cardinale</td>
<td>30</td>
<td>RT + 15-35 Gy SRS</td>
<td>NR</td>
<td>GBM: 16 AA: 33</td>
</tr>
<tr>
<td>Shrieve</td>
<td></td>
<td>RT + SRS</td>
<td>1-yr OS: 88.5%, 2-yr OS: 35.9%</td>
<td>19.9</td>
</tr>
<tr>
<td>Floyd</td>
<td></td>
<td>40 Gy RT + 24 Gy SRS, temozolomide</td>
<td>NR</td>
<td>13</td>
</tr>
<tr>
<td>Landis</td>
<td>23</td>
<td>Estramustine + SRS</td>
<td>2-yr OS: 38%</td>
<td>16</td>
</tr>
<tr>
<td>Omuro</td>
<td>40</td>
<td>6 x 6 Gy or 6 x 4 Gy SRS + temozolomide + bevacizumab</td>
<td>1-yr OS: 93%</td>
<td>19</td>
</tr>
</tbody>
</table>

**CAUTION --- These patients were not classified on basis of IDH mutations - Wildtype vs mutant**

SRS treatment of newly diagnosed glioblastoma
Leading Edge Radiosurgery
Glioblastoma

Microscopic infiltrative growth up to 4 cm from visible tumor location along white matter tracts in normal brain tissue

• “leading-edge” is defined by FLAIR MRI

• LERS a median of 18 days from diagnosis

• Median target volume of 48.5 cm³ (range 2.5-222.0 cm³)
• Median dose of 8 Gy (range, 6-14 Gy) at 50% isodose line

• As a boost to standard therapy

Glial cells express genes that produce membrane type 1 MMP2
Enables breakdown of the extracellular matrix of white matter
Leads to migration along white matter tracts.
Contralateral spread via corpus callosum and corona radiata
Lead to diffuse incurable disease.
FIG. A: T1-weighted Gd-enhanced MRI image obtained the day of Gamma Knife LERS, showing postoperative 95% resor- tion of the tumor bed. B: An LERS FLAIR sequence from the same day, showing “invisible” dramatic migration of tumor across midline and posteriorly down the corpus callosum. The LERS plan is overlaid. The patient received 12 Gy at the 50% isodose line (yellow). C: The same LERS plan is overlaid on the T1-weighted post-Gd MRI image, showing “invisible” tumor spread apparently treating normal brain. D: T1-weighted contrast-enhanced MRI images, from the day of LERS and at 5 years later, respectively, showing residual scar tissue. This patient lived 8 years after treatment and ultimately died as a result of GBM progression.
The median overall survival from diagnosis was 23 months (standard error 0.78 months, mean 43 months).

At the time of analysis, 149 patients (86%) were dead.

The 2-, 3-, 5-, 7-, and 10-year actual overall survival rates using LERS were 39%, 26%, 16%, 10%, and 4%, respectively.
Leading Edge Radiosurgery
Glioblastoma

Day -1 - To do 1.5- or 3.0-T MRI 2-mm-thick FLAIR

Contour the The FLAIR abnormality

Check the volume - Exclude those with TV > 80 cc

Doses will be administered to this target volume as follows:
0–20 cm³, 10 Gy;
21–40 cm³, 9 Gy;
41–60 cm³, 8 Gy; and
61–80 cm³, 7 Gy

After this proceed with Concurrent ChemoRT and Adj Temozolomide as per stupps protocol.
IAEA Trial

Frail → Age > 50 years and KPS 50 - 70
Elderly and frail → age > 65 years and KPS 50 - 70
Elderly Age→ > 65 years and KPS 80 - 100

- Arm 1 – Short-course radiotherapy
  (25 Gy in five daily fractions over 1 week)
- Arm 2 – HFRT
  40 Gy in 15 daily fractions over 3 weeks

<table>
<thead>
<tr>
<th></th>
<th>Arm 1</th>
<th>Arm 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS</td>
<td>7.9m</td>
<td>6.4m</td>
</tr>
<tr>
<td>Median PFS</td>
<td>4.2 m</td>
<td>4.2 m</td>
</tr>
</tbody>
</table>

QOL at median follow up of 6.3 months was similar with both arms

Gross tumor volume was defined as the entire postoperative enhancing tumor and surgical cavity.

The clinical target volume added a 2.0-cm margin to the gross tumor volume with no expansion beyond anatomic boundaries (e.g., skull).

The planning target volume (PTV) equaled the clinical target volume plus 0.5 cm in all directions.

International Atomic Energy Agency Randomized Phase III Study of Radiation Therapy in Elderly and/or Frail Patients With Newly Diagnosed Glioblastoma Multiforme

5Fr SRS for Glioblastoma

- N = 30, From 2010 to 2015
- The 5-fraction SRS dose was escalated in a standard 3 + 3 design at 4 dose levels: 25 Gy, 30 Gy, 35 Gy, and 40 Gy.
- The median PTV 60 cm³ (range, 14.7–137.3 cm³)
- Contouring
  - CTV - GTV + 5mm (not extending beyond anatomic borders of tumor spread such as the calvarium, falx, and tentorium)
  - Edema was excluded
  - PTV – Same as CTV 0 mm margin.
- Coverage
  - 95 % PTV to be covered by prescription isodose line
  - Optic pathway - 98% of the optic pathways received less than 27.5 Gy
  - Brainstem maximum dose of 30 Gy in 5 fractions
- Treatment Schema:
  - RT - Delivered on 5 consecutive days over 7 elapsed days
  - Concurrent Chemo - TMZ at a dose of 75 mg/m²
  - Standard adjuvant - TMZ at 150–200 mg/m² daily, 5/28 days x 6 months
5Fr SRS for Glioblastoma

- Toxicity
  - 2 deaths – while on treatment
  - Late grades 1–2 ARE occurred in 8 patients at a median of 7.6 months (range 3.2–12.6 mo).
  - No grades 3–5 ARE occurred.

- Efficay
  - Follow up period - 13.8 months (range 1.7–64.4 mo)
  - PFS - 8.2 months (95% CI: 4.6–10.5)
  - OS - 14.8 months (95% CI: 10.9–19.9)

- O6-methylguanine-DNA methyltransferase hypermethylated, 19.9 months (95% CI: 10.5–33.5) versus 11.3 months (95% CI: 8.9–17.6) for no/unknown hypermethylation (P = 0.03), and 27.2 months (95% CI: 11.2–48.3) if late ARE occurred versus 11.7 months (95% CI: 8.9–17.6) for no ARE (P = 0.08).
Early GK SRS to Residual Tumor After Surgery of Newly Diagnosed Glioblastoma (Gamma-GBM) (NCT03055208)

To start in October 2022
Will end recruitment in 2024
Results in 2025

Primary EP:
- Median PFS

Secondary EPs:
- Median OS
- Radiation-related (acute / early delayed / late) neurotoxicity
- Incidence of symptomatic radionecrosis
Preoperative SRS Rationale

1. Smaller RT target volumes and more precise target delineation
   • Decreasing dose delivery to nearby NT
   • Lowers treatment-related toxicities (e.g., RN)

2. Intact tissues - high O2 concentrations - more effective RT-induced DNA DSBs

3. Post-irradiation tissue available for analysis – future research

4. Risk of nodular LMD is low

• Ionizing radiation alters the tumor microenvironment and enhances anti-tumor immunity in gliomas
• RT may enhance cytotoxic T-cell activity against GBM
• RT enhances anti-tumor immunity against glioma cells, which may be further amplified by ICI
Preoperative SRS

Preoperative Radiosurgery for the Treatment of High Grade Glioma, The NeoGlioma Study

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

Sponsor:
Mayo Clinic

Collaborator:
National Cancer Institute (NCI)

Information provided by (Responsible Party):
Mayo Clinic

Tracking Information
First Submitted Date: August 23, 2021
First Posted Date: September 1, 2021
Last Update Posted Date: August 4, 2022
Estimated Study Start Date: October 1, 2022
Estimated Primary Completion Date: September 15, 2024 (Final data collection date for primary outcome measure)

ClinicalTrials.gov Identifier: NCT05030298

Recruitment Status: Not yet recruiting
First Posted: September 1, 2021
Last Update Posted: August 4, 2022
See Contacts and Locations

https://clinicaltrials.gov/ct2/show/record/NCT05030298
SRS in recurrent gliomas
<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Treatment Schema</th>
<th>Median Time to 1st Recurrence (Range) Months</th>
<th>OS Rate After SRS Salvage</th>
<th>Median OS (Range) Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shrieve</td>
<td>86 - SRS alone; 32 - Brachytherapy alone</td>
<td>13 Gy (median) SRS</td>
<td>NR</td>
<td>1-yr (SRS pts): 45%; 2-yr (SRS pts): 19%</td>
<td>10.2 for SRS pts</td>
</tr>
<tr>
<td>Vordermark</td>
<td>19</td>
<td>20-30 Gy SRS</td>
<td>19 (3-116)</td>
<td>1-yr: 26%; 2-yr: 16%</td>
<td>9.3 (1.9-77.6+)</td>
</tr>
<tr>
<td>Lederman</td>
<td>9 SRS alone; 14 SRS + Taxol</td>
<td>SRS alone: Mean dose 19.2 Gy in 1# SRS + Taxol: Mean dose of 24 Gy in 4#</td>
<td>11</td>
<td>1-yr SRS alone: 11%; 1-yr SRS + Taxol: 50%</td>
<td>SRS alone: 6.3 SRS + Taxol: 14.2</td>
</tr>
<tr>
<td>Combs</td>
<td>32</td>
<td>10-20 Gy (median 15 Gy)</td>
<td>10 (1-77)</td>
<td>6 months: 72%; 1-yr: 38%</td>
<td>10</td>
</tr>
<tr>
<td>Fogh</td>
<td>147</td>
<td>28-80 Gy (median dose 35 Gy in 3.5 Gy fractions)</td>
<td>8 (4-205)</td>
<td>NR</td>
<td>11</td>
</tr>
<tr>
<td>Maranzano</td>
<td>22</td>
<td>17 Gy (median) SRS or 30 Gy (median) fractionated SRS</td>
<td>9</td>
<td></td>
<td>11</td>
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<tr>
<td>Greenspoon</td>
<td>31</td>
<td>25 – 30 Gy + temozolomide</td>
<td>NR</td>
<td>NR</td>
<td>9</td>
</tr>
<tr>
<td>Hudes</td>
<td>20</td>
<td>24 Gy/3 fx or 30 Gy/3 fx or 35 Gy/3.5 fx after Paclitaxel</td>
<td>3.1 (0.7-45.5)</td>
<td>1-yr OS: 20%</td>
<td>20</td>
</tr>
<tr>
<td>Lederman</td>
<td>88</td>
<td>4 weekly irradiation (median 6 Gy) after Paclitaxel</td>
<td>6.5</td>
<td>1-yr: 17%; 2-yr: 3.4%</td>
<td>7</td>
</tr>
<tr>
<td>Cuneo</td>
<td>WHO Grade 3: 16; WHO Grade 4: 33</td>
<td>12.5-25 (median 15) Gy SRS; 12.5 – 25 Gy SRS + bevacizumab</td>
<td>All pts: 20</td>
<td>Gr3 gliomas: 1-yr: 22%; Gr4 gliomas: 1-yr: 50%</td>
<td>Gr 3 glioma: 3.9 Gr 4 glioma: 11.2</td>
</tr>
<tr>
<td>Minniti</td>
<td>54</td>
<td>30 Gy/6 fx SRS + temozolomide</td>
<td>Median time between primary RT and reirradiation: 15.5</td>
<td>1-yr: 53%; 2-yr: 10%</td>
<td>12.4</td>
</tr>
</tbody>
</table>

**SRS for recurrent glioblastoma**

1 yr OS ~10 – 50%
## Extended Field SRS Vs Conventional SRS
For recurrent Glioblastoma

<table>
<thead>
<tr>
<th>Extended Field SRS</th>
<th>Conventional SRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Leksell head frame</td>
<td>• Leksell head frame</td>
</tr>
<tr>
<td>• MRI for fusion</td>
<td>• MRI for fusion</td>
</tr>
<tr>
<td>• CTV – Gado enhanced lesion with no margin + 1 cm</td>
<td>• CTV – Gado enhanced lesion with no margin.</td>
</tr>
<tr>
<td>• Marginal dose – 20 Gy</td>
<td>• Marginal dose – 20 Gy</td>
</tr>
<tr>
<td>• Median CTV - 15 cc</td>
<td>• Median CTV - 15 cc</td>
</tr>
<tr>
<td>• Vol receiving &gt;20 Gy to limit to &lt;15 cc.</td>
<td>• Vol receiving &gt;20 Gy to limit to &lt;15 cc.</td>
</tr>
</tbody>
</table>

Extended field SRS Vs Conventional SRS
For recurrent Glioblastoma

93% local control vs 47%
28.6% adverse radiation effects

Table 3. Comparison of Characteristics and Outcomes of the Patients Who Received Conventional SRS and Extended Field SRS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Conventional SRS</th>
<th>Extended Field SRS</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>9</td>
<td>9</td>
<td>—</td>
</tr>
<tr>
<td>Primary glioblastoma</td>
<td>8</td>
<td>7</td>
<td>1.0</td>
</tr>
<tr>
<td>Patient age, median y, range</td>
<td>43, 17-64</td>
<td>53, 27-79</td>
<td>.36</td>
</tr>
<tr>
<td>KPS at onset, median, range</td>
<td>90, 80-90</td>
<td>90, 80-90</td>
<td>.62</td>
</tr>
<tr>
<td>Time from Dx to 1st SRS, median mo, range</td>
<td>14.5, 1-51</td>
<td>12, 6-39</td>
<td>.66</td>
</tr>
<tr>
<td>KPS at 1st SRS, median, range</td>
<td>90, 40-90</td>
<td>70, 40-90</td>
<td>.21</td>
</tr>
<tr>
<td>Local control</td>
<td>16/34</td>
<td>13/14</td>
<td>.0035</td>
</tr>
<tr>
<td>Radiation necrosis</td>
<td>2/34</td>
<td>4/14</td>
<td>.052</td>
</tr>
<tr>
<td>Median OS after Dx, mo</td>
<td>24</td>
<td>21</td>
<td>.71</td>
</tr>
<tr>
<td>Median OS after 1st SRS, mo</td>
<td>10.5</td>
<td>9</td>
<td>.83</td>
</tr>
<tr>
<td>6-month OS after 1st SRS, %</td>
<td>63</td>
<td>89</td>
<td>.83</td>
</tr>
</tbody>
</table>

Abbreviations: Dx, diagnosis of glioblastoma; KPS, Karnofsky Performance Scale; OS, overall survival; SRS, stereotactic radiosurgery.

• Gamma-Tile cesium-131 (\(^{131}\)Cs)
• Permanent brain implant
• FDA approved for Recurrent Gliomas
• It is a form of brachytherapy where seeds are placed inside a mesh, called a tile
Conclusion - SRS in Recurrent Gliomas

• Reasonable outcome post SRS in many studies
• SRS – GTV based on T1 Contrast enhanced images
  • Any role of functional imaging to delineate target
  • PET imaging to delineate target
• SRS Margins – Studies use 0-2 mm
• Effect of total dose / fractionation / combination with BVZ not understood clearly
• SRS alone unlikely to offer durable control
SRS Treatment related Toxicities - Gliomas

1. Acute
   - Is usually self limiting
   - Exacerbations of existing symptoms occur

2. Late
   - Serious Neurological deficits
   - Hemiparesis
   - Headache, Somnolence
   - Vision loss
   - Radiation necrosis (20%)
   - Re surgery (50%)
   - Prolonged steroid requirement
<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Dose</th>
<th>Toxicity</th>
<th>Radiation Necrosis</th>
<th>Defecits</th>
<th>Re-Sur</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarkaria</td>
<td>115</td>
<td>54 – 60 Gy RT + 10 – 20 Gy SRS</td>
<td>17 patients with radiation necrosis, 1 patient with hemiparesis. 47% required prolonged steroid use. One patient with double vision and hydrocephalus requiring ventricular shunt.</td>
<td>14.80%</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Schrieve</td>
<td>78</td>
<td></td>
<td>50% had reoperation for symptomatic necrosis or recurrent tumor. Rate of reoperation at 24 months after SRS was 54.8%.</td>
<td></td>
<td></td>
<td>54.80%</td>
</tr>
<tr>
<td>Fogh</td>
<td>147</td>
<td>Median 35 Gy/3.5 Gy fx</td>
<td>One late Grade 3 CNS toxicity 4 months after hypofractionated SRS.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cuneo</td>
<td>21 SRS</td>
<td>12.5 to 25 Gy</td>
<td>14% Grade 3, 5% Grade 4, 19% radionecrosis, 29% worsening of neurologic symptoms, 19% increase seizures 10% Grade 3, 5% radionecrosis, 24% worsening of neurologic symptoms, 21% increase seizures</td>
<td>19%</td>
<td>29%</td>
<td>24%</td>
</tr>
<tr>
<td></td>
<td>42 SRS +</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>bevacizum</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minniti</td>
<td>54</td>
<td>30 Gy/5 fx + temozolomide</td>
<td>7% Grade 3 neurologic deterioration with radiation-induced necrosis; 7 patients with Grade 3 lymphopenia, 3 patients with Grade 4 lymphocytopenia, 2 patients with Grade 3 thrombocytopenia,</td>
<td></td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>Park</td>
<td>11</td>
<td>13-18 Gy + bevacizum</td>
<td>One Grade 3 toxicity and 1 major adverse radiation effect.</td>
<td></td>
<td></td>
<td>9%</td>
</tr>
<tr>
<td>Gutin</td>
<td>25 (20 GBM and 5 AA)</td>
<td>30 Gy/5 fx + bevacizum</td>
<td>8% Grade 3 leukopenia, 8% Grade 3 neutropenia, 28% Grade 3 lymphopenia, 8% Grade 3 thrombocytopenia, 12% Grade 3 anemia, 4% Grade 3 fatigue, 4% Grade 3 hypertension, 4% Grade 3 CNS hemorrhage, 8% Grade 4 lymphopenia, 4% Grade 4 thrombocytopenia, 4% Grade 4 bowel perforation, 4% Grade 4 wound healing complication, 4% Grade 4 gastrointestinal bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Niyazi</td>
<td>20 SRS alone 10 SRS + bevacizum</td>
<td>36 Gy/18 fx +/ - bevacizum</td>
<td>1 Grade 2 fatigue, 1 Grade 2 hypertension, 1 Grade 3 deep vein thrombosis, 1 Grade 4 wound healing complication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ogura</td>
<td>30</td>
<td>22.5 – 35 Gy/5 fx</td>
<td>2 patients with Grade 3 radionecrosis</td>
<td></td>
<td></td>
<td>6%</td>
</tr>
<tr>
<td>Cabrera</td>
<td>15</td>
<td>18 or 24 Gy/1 fx or 25/5 fx + bevacizum</td>
<td>1 Grade 3 severe headache, 2 Grade 2 CNS toxicities. No Grade 4 or 5 events.</td>
<td></td>
<td></td>
<td>0%</td>
</tr>
</tbody>
</table>

**SRS Toxicities**
# OAR Dose Constraints in SRS

## Table 8.2 Optic pathway dose constraints for avoidance of ≥ grade 3 optic neuritis

<table>
<thead>
<tr>
<th></th>
<th>1 FRACTION</th>
<th>3 FRACTIONS</th>
<th>4 FRACTIONS</th>
<th>5 FRACTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume (cc)</td>
<td>&lt;0.2 cc</td>
<td>&lt;0.2 cc</td>
<td>&lt;0.2 cc</td>
<td>&lt;0.2 cc</td>
</tr>
<tr>
<td>Volume max (Gy)</td>
<td>8 Gy</td>
<td>15.3 Gy (5.1 Gy/fx)</td>
<td>19.2 Gy (4.8 Gy/fx)</td>
<td>23 Gy (4.6 Gy/fx)</td>
</tr>
<tr>
<td>Max point dose (Gy)</td>
<td>10 Gy</td>
<td>17.4 Gy (5.8 Gy/fx)</td>
<td>21.2 Gy (5.3 Gy/fx)</td>
<td>25 Gy (5 Gy/fx)</td>
</tr>
</tbody>
</table>

## Table 8.3 Cochlear dose constraints to avoid ≥ grade 3 hearing loss

<table>
<thead>
<tr>
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<th>3 FRACTIONS</th>
<th>4 FRACTIONS</th>
<th>5 FRACTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max point dose (Gy)</td>
<td>9 Gy</td>
<td>17.1 Gy (5.7 Gy/fx)</td>
<td>21.2 Gy (5.3 Gy/fx)</td>
<td>25 Gy (5 Gy/fx)</td>
</tr>
</tbody>
</table>

## Table 8.4 Brain stem (not medulla) dose constraints to avoid ≥ grade 3 cranial neuropathy

<table>
<thead>
<tr>
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<th>1 FRACTION</th>
<th>3 FRACTIONS</th>
<th>4 FRACTIONS</th>
<th>5 FRACTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume (cc)</td>
<td>&lt;0.5 cc</td>
<td>&lt;0.5 cc</td>
<td>&lt;0.5 cc</td>
<td>&lt;0.5 cc</td>
</tr>
<tr>
<td>Volume max (Gy)</td>
<td>10 Gy</td>
<td>18 Gy (6 Gy/fx)</td>
<td>20.8 Gy (5.2 Gy/fx)</td>
<td>23 Gy (4.6 Gy/fx)</td>
</tr>
<tr>
<td>Max point dose (Gy)</td>
<td>15 Gy</td>
<td>23.1 Gy (7.7 Gy/fx)</td>
<td>27.2 Gy (6.8 Gy/fx)</td>
<td>31 Gy (6.2 Gy/fx)</td>
</tr>
</tbody>
</table>

Ideal Candidate for SRS
Ideal Candidate for SRS in gliomas

1. **Pilocytic Astrocytoma**
   - Age < 18 yrs
   - Tumor Volume < 5 cc
   - No prior EBRT / Chemo
   - Non contrast enhancing tumor
   - SRS Dose > 15 Gy
   - Oligo histology

2. **LGG**
   - Good KPS
   - Good response to initial ChemoRT

3. **New HGG**
   - Long Interval to recurrence
   - Limited volume
   - Circumscribed recurrence
   - SRS Dose > 15 Gy
   - Oligo histology

4. **Recurrent HGG**
   - Good KPS
   - Small Volume
   - < 4cm in diameter
   - Atleast 5 mm away from BS / Optic pathway
   - Oligo histology

**Fractionated SRS**