Toxicity considerations and Re-Irradiation in Brain Tumor

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Topics

• Introduction to Re-Irradiation
• Rationale
• Indication
• Timing
• Dose and Fractionation
• RT Techniques
• Clinical outcomes and evidences
• Toxicity consideration
Introduction

• Delivery of a clinically significant RT dose post initial RT ± Chemotherapy, post proven recurrence.

• Points under consideration
  ➢ What is a clinically significant dose!!
  ➢ How long after initial treatment!!
  ➢ How to define recurrence !!!
Rationale

• Radiobiological consideration - Key to any hypothesis in RT response.

*Preclinical study (monkey and rabbit) and some clinical data*

Model of target cell responses in the CNS cells
Radiobiological consideration

• Earliest sign of damage – In the white matter

  Nodal widening and segmental demyelination

• As early as 2 weeks after doses of 60 Gy

• Remyelination - By 2 months

• Latent period of 4-6 months, areas of white matter necrosis - critical depopulation of oligodendrocytes and vascular damage.

• The probability of occurrence of necrosis and the latent period is a function of dose
Figure 1  A schematic representation of the major cell types in the CNS, and their assumed participation in the development of different types of radiation-induced lesions. Schwann cells (on the left) are not part of the CNS, but are the primary parenchymal cells in the spinal nerve roots.
Indication

• Glioma: Oligodendroglioma and Astrocytoma

• Brain metastasis: Post WBRT, post SRS/FSR
Defining a Recurrence in Gliomas

• Warning sign
  - Post treatment after initial improvement developing new neurological deficit
  - Stable clinical scenario but radiological progression

• Major confounding factor
  - Recurrence/progression
  - Pseudo-progression
  - Radio-necrosis
MRI

- Gadolinium-enhanced T1-weighted MRI – Was Investigation of choice for long time
  - High False positive
  - Only detects the disruption of the blood-brain barrier and not the tumor activity specifically.

- To overcome the limitations multimodal MRI has been proposed, including
  - Magnetic resonance spectroscopy (MRS),
  - Diffusion-weighted imaging (DWI)
  - Perfusion-weighted imaging (PWI)

- High diagnostic accuracy of MRS and PWI but low accuracy of DWI

PET-CT

- FDG-PET can demonstrate differences in the analysis of areas of radiation injury and residual/recurrent brain tumors.

- Low sensitivity and good specificity.

- High background activity - High glucose use in the brain

- RANO (Response Assessment in Neuro-Oncology) group proposed other PET CT scan
  - 18F-FET PET
  - 11C-MET PET
  - 18F-DOPA PET
Overall sensitivity and specificity of FDG PET-CT were 70% and 97% respectively.

Contrast enhanced MRI was 95% and 23%.

FDG PET-CT - higher accuracy (80%) compared to MRI (70%).
33 studies
1,734 patients
1,811 lesions suspected of glioma recurrence.

High Sensitivity of amino acid PET and high Specificity of FDG-PET
Combination of commonly used FET-PET and FDG-PET may be more accurate especially for low-grade glioma.
Radio-necrosis

- Typically occurs 18–24 months post-treatment.

- **Difficult** to distinguish from recurrence

- Gold standard: Biopsy

- Limiting factor for biopsy: Surgical morbidity
Radio-Necrosis

MRI

- **T2/FLAIR**: white matter high signal
  - Edema and mass effect early
  - Loss of volume later
- **T1 C+ (Gd)**
  - White (more common) or grey matter
  - Single or multiple
  - Nodular or curvilinear
  - “Soap-bubble”, “cut green pepper” or "Swiss-cheese" enhancement
  - Occasionally can be ring-enhancing
- **MR spectroscopy**: Low choline, creatine, and NAA
- **MR perfusion**: Areas of enhancement and high T2/FLAIR don't show increased rCBV in radiation necrosis or pseudoprogression and could be helpful in distinguishing them from residual lesion or recurrence
- **FDG-PET**
  - Radiation necrosis is hypometabolic whereas tumor is hypermetabolic
PSEUDO-PROGRESSION

- Increase of lesion size related to treatment, which simulates progressive disease.

- Especially for high grade gliomas (GBM)

- More common with CTRT (30%) less with RT alone (15%)

- Disruption of BBB, Endothelial damage and consequent tissue hypoxia post CTRT

- ~60% - First 3 months

- May occur from 1st weeks to 6 months post treatment
Fig 1. Representative patient with glioblastoma multiforme treated with concurrent temozolomide and radiation. T1 postgadolinium magnetic resonance imaging at (A) baseline and (B) 3 months after treatment showed a significant increase in contrast-enhancing lesion. At resection, pathology was notable for (C) fibrinoid radiation necrosis involving blood vessel wall and (D) predominantly gliotic brain parenchyma with no viable neoplasm, consistent with pseudoprogression.
Approach to Re-Irradiation

- Rule out pseudo progression and post RT necrosis.
- Use of contrast enhanced MRI and functional imaging to characterize progression
- Patient performance status
- Feasibility of resection
- Interval from last RT or CTRT
- Previous volume, dose, fractionation, technique
- OAR doses
- Feasibility of further prolonging gap by chemotherapeutic agent.
The factors associated with poor postoperative survival were:

- Tumor involvement of prespecified eloquent/critical brain regions (P= .021)
- Karnofsky performance status (KPS) <80 (P= .030)
- Tumor volume 50 cm3 (P= .048)

- Non of the factors - best survival (median 9.2 months)
- All 3 factors : worst survival (median 1.9 months)

- Whenever feasible resurgery should be attempted.
Re-irradiation after Gross Total Resection of Recurrent Tumor

- Controversial

- Some evidence supporting RE-RT in both paediatric and adult ependymoma.


- Straube et al: Spatial recurrence patterns after GTR of recurrent GBM
  - 70% of cases, second recurrence in the region of the first recurrence

- Recommended: PORT resection cavity + contrast enhancing lesion and a 5-10 mm CTV margin.
Prognostic factor for Re-irradiation

Heidelberg prognostic score for re-irradiation of recurrent glioma

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>Subgroups</th>
<th>Value for prognostic score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histology</td>
<td>WHO grade IV</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>WHO grade III</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>WHO grade II</td>
<td>0</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;50 years</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>≥50 years</td>
<td>1</td>
</tr>
<tr>
<td>Time between primary radiotherapy and re-irradiation</td>
<td>≤12 months</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&gt;12 months</td>
<td>0</td>
</tr>
</tbody>
</table>

- Scoring 0-2 best survival
- Scoring 3-4 had lower survival after re-irradiation.

Modified Combs’ group scoring: Yet to be validated

- PTV volume (>47/47 ml)
- Karnofsky performance status (<80%/80%)
- Whether or not re-resection had been carried out

Prognostic factors for Re-irradiation

• MGMT promoter methylation status was significant on both univariate and multivariate analyses.


• On 18F-FET PET significant prognostic factors:
  ➢ Uptake kinetics of the radioisotope
  ➢ Biological tumour volume at baseline imaging

RT Technique for RE-RT

- CONVENTIONAL
- FSR
- SRS
- BRACHYTHERAPY
- TTF
Target Volume Delineation

• Review the plan and dose details for the primary treatment.

• Specifically: Serial organ

• 11C-methionine-PET (MET-PET) imaging can be beneficial.

• NOA 10 study is looking at whether target volume definition with amino acid PET is beneficial.

• Contour the GTV using T1Gd-MRI + FET-PET.

• PTV margin as per immobilization and institutional protocol.
Dose Limitation

- Cumulative EQD2 around 100 Gy with conventional technique and slightly higher with conformal and SRT.


- SRS and interstitial brachytherapy are not favored
  - Higher toxicity (20-30%)
  - Suitability only for very small tumours (<30 cc)

Dose Limitation

• Normalised tissue dose (NTD) cumulative of > 100Gy for conventional fractionation was associated with radiation induced white matter necrosis.

• Smaller volumes and FSR –
  – NTD cumulative doses (90–133.9 Gy for FSRT, 111.6–137.2 Gy for SRS).

• No correlation between time interval of the radiotherapy courses and incidence of complications

Dose & Fractionation

• No large phase III randomized data.

• Evidence base for fractionated radiotherapy comes almost exclusively from single institutional retrospective case series.
<table>
<thead>
<tr>
<th>Year</th>
<th>Cases</th>
<th>Technique</th>
<th>Dose</th>
<th>Equivalent dose (2 Gy/fraction)</th>
<th>Median PTV (cm³)</th>
<th>Median overall survival after re-irradiation</th>
<th>Neurological toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>2017</td>
<td>5 GBM</td>
<td>HFSRT</td>
<td>36–39 Gy in 3 Gy/fraction</td>
<td>45–48.75 Gy</td>
<td>30.2 cm³</td>
<td>9 months</td>
<td>No RN clinically or radiologically</td>
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<tr>
<td>1993</td>
<td>12 GBM</td>
<td>HFSRT</td>
<td>30–50 Gy in 5 Gy/fraction</td>
<td>52.5–87.5 Gy</td>
<td>Range 61–180 cm³</td>
<td>9.8 months</td>
<td>22.7% steroid-responsive late toxicity</td>
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<tr>
<td>1997</td>
<td>36 HGG</td>
<td>HFSRT</td>
<td>20–50 Gy in 5 Gy/fraction</td>
<td>35–87.5 Gy</td>
<td>NR TV 24 cm³</td>
<td>11 months</td>
<td>36% late radiation-induced damage (clinical) No RN</td>
</tr>
<tr>
<td>1999</td>
<td>19 GBM</td>
<td>HFSRT</td>
<td>24–35 Gy in 5 Gy/fraction</td>
<td>30–48.13 Gy</td>
<td>NR TV 12.7 cm³</td>
<td>10.5 months</td>
<td>No RN</td>
</tr>
<tr>
<td>2000</td>
<td>15 GBM</td>
<td>HFSRT</td>
<td>Median 25 Gy in 4–6 Gy/fraction</td>
<td>12.7 cm³</td>
<td>12.7 cm³</td>
<td>6.7 months</td>
<td>No RN</td>
</tr>
<tr>
<td>2001</td>
<td>42 HGG/LGG</td>
<td>2D fields</td>
<td>Median 46 Gy in 2 Gy/fraction</td>
<td>46 Gy</td>
<td>NR</td>
<td>10.9 months</td>
<td>4.8% RN</td>
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<tr>
<td>2005</td>
<td>20 GBM</td>
<td>FSRT (63.6%)</td>
<td>45–54 Gy in 2–3 Gy/fraction</td>
<td>54–56.25 Gy</td>
<td>154.4 cm³</td>
<td>7 months</td>
<td>No RN</td>
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<tr>
<td>2005</td>
<td>59 GBM</td>
<td>FSRT (36.4% HFSRT)</td>
<td>Median 36 Gy in 2 Gy/fraction</td>
<td>52.5 Gy</td>
<td>41.7 cm³</td>
<td>NR</td>
<td>No RN</td>
</tr>
<tr>
<td>2005</td>
<td>14 GBM</td>
<td>HFSRT</td>
<td>Median 30 Gy in 4–10 Gy/fraction</td>
<td>36 Gy</td>
<td>49.3 cm³</td>
<td>8 months (GBM)</td>
<td>0.6% RN (histologically confirmed)</td>
</tr>
<tr>
<td>2007</td>
<td>11 GBM</td>
<td>HFSRT</td>
<td>Median 30 Gy in 2 Gy/fraction</td>
<td>30–60 Gy</td>
<td>15 cm³</td>
<td>12 months (est)</td>
<td>NR</td>
</tr>
<tr>
<td>2009</td>
<td>53 GBM</td>
<td>HFSRT</td>
<td>Median 30 Gy in 2–5 Gy/fraction</td>
<td>30–60 Gy</td>
<td>35.01 cm³</td>
<td>9 months</td>
<td>No radiological evidence of RN</td>
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<tr>
<td>2009</td>
<td>29 GBM</td>
<td>3D CRT</td>
<td>Median 20 Gy in 5 Gy/fraction</td>
<td>35 Gy</td>
<td>52.7 cm³</td>
<td>10.2 months</td>
<td>No clinically detected RN</td>
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<tr>
<td>2010</td>
<td>105 GBM</td>
<td>HFSRT</td>
<td>Median 35 Gy in 5 Gy/fraction</td>
<td>48.13 Gy</td>
<td>22 cm³</td>
<td>10 months</td>
<td>0.7% late neurological toxicity</td>
</tr>
<tr>
<td>2011</td>
<td>5 GBM</td>
<td>HFSRT</td>
<td>Median 25 Gy in 5 Gy/fraction</td>
<td>43.75 Gy</td>
<td>69.5 cm³</td>
<td>7.6 months</td>
<td>12.5% RN</td>
</tr>
<tr>
<td>2012</td>
<td>89 GBM</td>
<td>FSRT</td>
<td>Median 36 Gy in 2 Gy/fraction</td>
<td>36 Gy</td>
<td>47 cm³</td>
<td>8 months (GBM)</td>
<td>0.4% RN (histologically confirmed)</td>
</tr>
<tr>
<td>2013</td>
<td>15 GBM</td>
<td>HFSRT</td>
<td>Median 25 Gy in 5 Gy/fraction</td>
<td>43.75 Gy</td>
<td>NR</td>
<td>9.5 months</td>
<td>13.3% had neurological deterioration managed with steroids</td>
</tr>
</tbody>
</table>
Dose Escalation

• Dose-escalation with FSR

• Re-irradiation dose of >40 Gy (5 Gy/fraction, EQD2 70 Gy)

  ➢ Significant predictor of radiation damage

  ➢ Having 6.4 times the risk compared with those receiving 40 Gy.

Shepherd et al. Hypofractionated stereotactic radiotherapy in the management of recurrent glioma. IJROBP: 1997;37:393e398
Dose Escalation

Hudes RS et al. 1999;43:293-298

• Dose-escalation with salvage SRT was delivered using daily 3.0–3.5 Gy/#

• 24.0 Gy/8 # vs 30.0 Gy/10 # vs 35.0 Gy/10 #

• Median tumor volume 12.66 cc (0.89–47.5 cc).

• Dose response relationship, with increasing dose being associated with a response.

  ➢ Clinical neurology
  ➢ Reduction in steroid requirement
  ➢ Imaging response.

• The cut-off for improving overall survival was about 30-35 Gy @ 3-3.5 Gy/#
<table>
<thead>
<tr>
<th>Year</th>
<th>Cases</th>
<th>SRS platform</th>
<th>Dose</th>
<th>Median treatment volumes</th>
<th>Median overall survival after re-irradiation</th>
<th>Neurological toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>26 GBM</td>
<td>Linac</td>
<td>Median 20 Gy to 50% isodose</td>
<td>28 cm³</td>
<td>8 months</td>
<td>14% RN</td>
</tr>
<tr>
<td>1999</td>
<td>46 HGG</td>
<td>Linac</td>
<td>Median 17 Gy to 50% isodose</td>
<td>30 cm³</td>
<td>11 months</td>
<td>13% clinical RN</td>
</tr>
<tr>
<td>2000</td>
<td>23 GBM</td>
<td>Linac (56.5%) Gamma knife (43.5%)</td>
<td>Median 15 Gy to 60% isodose</td>
<td>9.9 cm³</td>
<td>10.3 months</td>
<td>4.3% RN</td>
</tr>
<tr>
<td>2005</td>
<td>32 GBM</td>
<td>Linac</td>
<td>Median 15 Gy to 80% isodose</td>
<td>10 cm³</td>
<td>10 months</td>
<td>No RN</td>
</tr>
<tr>
<td>2005</td>
<td>41 GBM</td>
<td>Linac</td>
<td>NR</td>
<td>4.7 cm³</td>
<td>11 months</td>
<td>14.6% RN</td>
</tr>
<tr>
<td>2008</td>
<td>65 GBM</td>
<td>Gamma knife</td>
<td>Median 16 Gy to 50% isodose</td>
<td>10.6 cm³</td>
<td>13 months (GBM)</td>
<td>24.4% RN on imaging, mostly asymptomatic 7.7% RN</td>
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<tr>
<td>2009</td>
<td>26 GBM</td>
<td>CyberKnife</td>
<td>Median 18 Gy to 90% isodose</td>
<td>10.4 cm³</td>
<td>8.5 months</td>
<td>7.7% RN</td>
</tr>
<tr>
<td>2011</td>
<td>16 GBM</td>
<td>Gamma knife</td>
<td>Median 15 Gy to 50% isodose</td>
<td>7.0 cm³</td>
<td>7 months</td>
<td>NR</td>
</tr>
<tr>
<td>2011</td>
<td>13 GBM</td>
<td>NR</td>
<td>Median 17 Gy to 50% isodose</td>
<td>5.3 cm³</td>
<td>11 months</td>
<td>23% asymptomatic RN</td>
</tr>
<tr>
<td>2011</td>
<td>19 GBM</td>
<td>Linac</td>
<td>Median 16 Gy to 80–95% isodose</td>
<td>13 cm³</td>
<td>9.3 months</td>
<td>No acute toxicity</td>
</tr>
<tr>
<td>2012</td>
<td>18 GBM</td>
<td>Gamma knife</td>
<td>20 Gy</td>
<td>C: 15 cm³ E: 13 cm³</td>
<td>C: 10.5 months E: 9 months</td>
<td>C: 6.5% asymptomatic RN E: 29% RN requiring steroids</td>
</tr>
<tr>
<td>2012</td>
<td>51 GBM</td>
<td>Gamma knife</td>
<td>Median margin dose 12.2 Gy to 50% isodose</td>
<td>4.8 cm³</td>
<td>12 months</td>
<td>9.8%</td>
</tr>
<tr>
<td>2013</td>
<td>22 GBM</td>
<td>Gamma knife</td>
<td>Median margin dose 17.5 Gy to 50% isodose</td>
<td>5.20 cm³</td>
<td>15.8 months (GBM) 34.8 months (G3)</td>
<td>13.8% RN</td>
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<tr>
<td>2014</td>
<td>35 GBM</td>
<td>Gamma knife</td>
<td>Median 20 Gy to 44% isodose</td>
<td>6 cm³</td>
<td>11.3 months (GBM) 24.2 months (G3)</td>
<td>25% symptomatic</td>
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<tr>
<td>2014</td>
<td>46 GBM</td>
<td>Linac</td>
<td>Median 18 Gy to 50% isodose</td>
<td>6 cm³</td>
<td>10 months</td>
<td>No RN</td>
</tr>
<tr>
<td>2015</td>
<td>29 GBM</td>
<td>Gamma knife</td>
<td>Median 14 Gy to 49% isodose</td>
<td>11.4 cm³</td>
<td>7.9 months</td>
<td>5.6% RN</td>
</tr>
<tr>
<td>2015</td>
<td>24 GBM</td>
<td>Gamma knife</td>
<td>Median 16 Gy to 50% isodose</td>
<td>6.05 cm³</td>
<td>22.8 months</td>
<td>NR</td>
</tr>
<tr>
<td>2015</td>
<td>88 GBM</td>
<td>CyberKnife</td>
<td>Median 15 Gy to 80% isodose Some received median 23 Gy/3 fractions</td>
<td>5.2 cm³</td>
<td>11.5 months</td>
<td>6% RN</td>
</tr>
<tr>
<td>First author, year</td>
<td>Patients, n</td>
<td>WHO grade (n)</td>
<td>Treatment type</td>
<td>Source activity*, mCi</td>
<td>Total dose*, Gy</td>
<td>Dose rate*, cGy/h</td>
</tr>
<tr>
<td>-------------------</td>
<td>-------------</td>
<td>---------------</td>
<td>----------------</td>
<td>----------------------</td>
<td>----------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Simon et al., 2002</td>
<td>42</td>
<td>IV (42)</td>
<td>Temp + LDR + 192Ir implant</td>
<td>NR</td>
<td>50 (15-60)</td>
<td>37 (16-73)</td>
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<tr>
<td>Tatter et al., 2003</td>
<td>21</td>
<td>IV (15)</td>
<td>Temp + LDR + 192Ir GlaSite</td>
<td>73.459</td>
<td>40-60</td>
<td>41.61</td>
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<tr>
<td>Larson et al., 2004</td>
<td>38</td>
<td>IV (38)</td>
<td>Perm + LDR + 192Ir implant</td>
<td>0.67 (0.40-0.93)</td>
<td>300</td>
<td>15</td>
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<tr>
<td>Chan et al., 2005</td>
<td>24</td>
<td>IV (24)</td>
<td>Perm + LDR + 192Ir GlaSite</td>
<td>53.1 (29.9-80)</td>
<td>52.7</td>
<td>9.1 months (1.3-23.6 months)</td>
</tr>
<tr>
<td>Gabayan et al., 2006</td>
<td>95</td>
<td>GBM (80)</td>
<td>Temp + LDR + GlaSite</td>
<td>369 (90-950)</td>
<td>60</td>
<td>52.3</td>
</tr>
<tr>
<td>Tselis et al., 2007</td>
<td>84</td>
<td>IV (84)</td>
<td>Temp + HDR + 192Ir implant</td>
<td>NR</td>
<td>40 (30-50)</td>
<td>5.0 Gy twice a day</td>
</tr>
<tr>
<td>Darakchiev et al., 2008</td>
<td>34</td>
<td>IV (34)</td>
<td>Perm + LDR + 192Ir implant + BCNU wafers</td>
<td>0.67/seed</td>
<td>120</td>
<td>NR</td>
</tr>
<tr>
<td>Fabrini et al., 2009</td>
<td>21</td>
<td>III (3)</td>
<td>Temp + HDR + 192Ir balloon-shaped applicator</td>
<td>219 GBq (106-325)</td>
<td>18</td>
<td>6171.4 (750-4720)</td>
</tr>
<tr>
<td>Archavisi et al., 2013</td>
<td>50</td>
<td>IV (50)</td>
<td>Temp + HDR + 192Ir implant</td>
<td>NR</td>
<td>40 (30-50)</td>
<td>5.0 Gy twice a day</td>
</tr>
<tr>
<td>Kickingrecker et al., 2014</td>
<td>98</td>
<td>IV (98)</td>
<td>LDR + 192Ir implant</td>
<td>16.1 (2.1-63.3)</td>
<td>60</td>
<td>7.53</td>
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<tr>
<td>Archavisi et al., 2014</td>
<td>17</td>
<td>IV (17)</td>
<td>Temp + HDR + 192Ir implant</td>
<td>NR</td>
<td>40</td>
<td>5.0 Gy twice a day</td>
</tr>
</tbody>
</table>

*Data presented as the median (range); †calculated from information provided. KPS, Karnofsky performance status; WHO, World Health Organization; OS, overall survival; PFS, progression-free survival; post-OS, median OS after re-irradiation; post-PFS, median PFS after re-irradiation; OS-6, 6-month OS rates; OS-12, 12-month OS rate; OS-24, 24-month OS rate; PFS-6, 6-month PFS rate; PFS-12, 12-month PFS rate; PFS-24, 24-month PFS rate; TTP1, time to progression after initial irradiation; TTP2, time to progression after re-irradiation; RPA, recursive partitioning analysis; NR, data not reported; BCNU, Carmustine; GBM, glioblastoma multiforme; PTV, permanent; temp, temporary; LDR, low-dose rate; HDR, high-dose rate; I, Iodine; Ir, Iridium.
Combinations with Systemic Therapy and Re-irradiation

• Bevacizumab has been most studied.

• Several series have suggested an improvement in OS and PFS with bevacizumab + radiotherapy

• Combination with gamma knife SRS, bevacizumab also results in a lower risk of adverse radiation effect.  

• Anecdotal evidence for concurrent temozolamide.

• More recent work has involved combining RT with panobinostat (a histone deacetylase inhibitor).  
Novocure (TTF):

- Uses **electric fields** within the human body that disrupt the rapid cell division exhibited by cancer cells.

- Disrupt **mitotic spindle microtubule** assembly and to lead to dielectrophoretic dislocation of intracellular macromolecules and organelles during cytokinesis.

- Affect only **one cell type** at a time; The frequency used for a particular treatment is specific to the cell type being treated.

- TTF therapy has not been shown to affect cells that are not undergoing division.
• Overall response rate across was 15%

• Responses to TTF Therapy
  – Slow: (median time to response, 5.2 months)
  – Durable (median duration, 12.9 months)

➢ Response duration was highly correlated with OS ($P<.0001$)
Thank You