Clinical Trials for Adult Brain Tumors - the Imaging Perspective

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Disclosure of Financial Relationships
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Has disclosed the following relationships with entities producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients.

**Disclosures:**

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- Advisory Board: Genentech, Amgen
Malignant Glioma Treatment: What is the Role of Imaging?

**Imaging:** Diagnosis, GTR?

- Surgery
- Concomitant TMZ + RT*
- Focal RT daily—30 x 200 cGy; total dose: 60 Gy

**Recurrence – Response – Progression**

- Adjuvant TMZ
- Salvage Tx

**Schedule:**
- Surgery
- TMZ 75 mg/m² PO QD for 6 weeks, then 150-200 mg/m² PO QD on Days 1-5 q 28 days for 6 cycles

Stupp et al, NEJM 2005 352:987-996
grade II oligoastrocytoma

grade II oligodendroglioma

grade III oligoastrocytoma

grade III astrocytoma
grade II oligoastrocytoma

grade II oligodendroglioma

grade III oligoastrocytoma

grade IV (glioblastoma)
Assessing for Gross Total Resection
Assessing for Gross Total Resection
Radiation Planning
Low Grade Glioma RT Volumes

Treatment plan with isodose distribution

54 Gy in 30 fractions using 2 cm field margin to block edge

Hauswald et al. Radiation Oncology 2012 7:189 doi:10.1186/1748-57...
Glioblastoma

- Rapidly progressive, contrasting enhancing lesions with extensive peritumoral edema
- Median OS approximately 16 months with concurrent chemo-radiotherapy
Clinical Trials for GBM – Response Assessment

Contrast enhancement is the benchmark for response assessment, even though it has never been validated for the FDA (just grandfathered in).
Measuring Target Lesions per Macdonald Criteria

- Bi-dimensional measurements

Response (-50%): 127.5 mm$^2$
17 mm x 15 mm = 255 mm$^2$

Progression (+25%): 318 mm$^2$

Or:
- Increasing steroids
- Declining neurological status
- New measurable lesion
Macdonald Criteria Limitations: Resection Cavity

- Macdonald criteria: stable disease
- Volumetric analysis: partial response

From Sorensen et al., Nature Clini Prac Onc, 2008
Volumetric Analysis
RESPONSE ASSESSMENT

• Pitfalls in the MRI diagnosis of recurrence
  – False negatives - pseudoresponse
  – False positives - pseudoprogression
MRI Shows Enhancing and Necrotic Tumor

Pre-tx, necrotic tumor, not infarct

S/P bevacizumab x 6 d
Enhancement resolved
Pseudoresponse: S/P Anti-angiogenic Therapy

Areas of low diffusion: tumor remains

T2  T1+ contrast
Areas of Low ADC Show Infiltrative Tumor

Red – within T1+C baseline ROI

Blue – within FLAIR baseline ROI

Amino Acid Tracers: fDOPA

Non-enhancing Tumor

Recruent Oligodendroglioma

fused image
Case - Possible Recurrence: Gliosis, Edema or Non-enhancing Tumor?

Hx of Anaplastic Astrocytoma

T2 Creep

9-28-10

10-25-11

5-4-12
## Response Assessment in Neuro-Oncology (RANO)

<table>
<thead>
<tr>
<th>Condition</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1-Gd +</td>
<td>None</td>
<td>≥ 50% ↓</td>
<td>&lt; 50% ↓ -</td>
<td>≥ 25% ↑*</td>
</tr>
<tr>
<td>T2/FLAIR</td>
<td>Stable or ↓</td>
<td>Stable or ↓</td>
<td>Stable or ↓</td>
<td>↑*</td>
</tr>
<tr>
<td>New Lesion</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Present*</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>None</td>
<td>Stable or ↓</td>
<td>Stable or ↓</td>
<td>NA</td>
</tr>
<tr>
<td>Clinical Status</td>
<td>Stable or ↑</td>
<td>Stable or ↑</td>
<td>Stable or ↑</td>
<td>↓*</td>
</tr>
<tr>
<td>Requirement for response</td>
<td>all</td>
<td>all</td>
<td>all</td>
<td>Any*</td>
</tr>
</tbody>
</table>

PD for patients < 12 weeks from completion of XRT/daily temozolomide requires:
- new lesion outside 80% isodose XRT line or
- unequivocal evidence of histopathologic tumor
Pseudoproggression

Since the introduction of chemoradiotherapy with temozolomide as the new standard of care for patients with glioblastoma, there has been an increasing awareness of post-therapeutic progressive and enhancing lesions on MRI, noted immediately after the end of treatment, which are not related to tumor progression, but which are a treatment effect.
Physiologic MRI: Differentiating True from Pseudoprogression with MR Perfusion

Dynamic Susceptibility Contrast (DSC) Perfusion

T1+C   Recurrence   CBV - elevated
Physiologic MRI: Differentiating True from Pseudoprogression with MR Perfusion
Pseudoprogression: FET-PET

Slide courtesy of Dr. J Tonn, Munich
Patient Selection - Predictive Biomarker for Bev Tx:
ADC Histogram Analysis:

1. Enhancing tumor segmented on post-contrast MRI
2. ROI’s mapped to corresponding ADC map
3. Histogram generated and fit with a 2-normal curve.
Pilot Study: ADC Histogram Analysis Predicts Survival in Recurrent GBM

Bevacizumab $P = 0.007$

Control Drug (no bev tx) $P = 0.106$

Creating a Radiogenomic Map

Radiogenomic map

Slide courtesy of Olivier Gevaert, PhD, Stanford
Target Therapy and Develop Targets for Therapy

Current: heterogeneity

Future: stratification of patients

- Nonselected therapeutics
- Dissect with microarrays

Imaging Correlates

- Leads for drug targets and markers
- Stratify patients

MRI

Survival (days)

Therapy 1

Therapy 2

Monitor Therapy
Image-Based Disease Assessment Paradigm

Measurement error -> Surrogate of Tumor Burden -> Response Bins -> Correlation with outcome

Measure the same thing over and over and determine the variability

- Contrast enhancement
  - Pseudoprog
  - Pseudoresponse

- Stable
- Partial Response
- Progression
- Comp Response

- Response rate
- Durability of Response
- PFS
- OS
Image Standardization for Multicenter Clinical Trials

Compliance Vs. Quality

Philosophical Questions Regarding Goals of MRI Standardization in Brain Tumor Clinical Trials

Maximizing Compliance
Parameters reflect the range of values that 100% of centers use

Maximizing Data Quality
Parameters reflect the range of values that >80% of centers use
T1 Subtraction Maps: Reduces Measurement Variation

Coefficient of Variation (COV)

Post-Treatment Undisclosed Drug X

T1+C
T1 Subt

44.7%
14.6%

Figure courtesy of Dr. Ben Ellingson, UCLA
Minimum Standard 1.5T & 3T MRI Protocol

<table>
<thead>
<tr>
<th>Sequence</th>
<th>3D T1w Pre^b</th>
<th>Ax FLAIR^c</th>
<th>Ax 2D DWI</th>
<th>Ax 2D T2w^h,l</th>
<th>3D T1w Post^b</th>
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</thead>
<tbody>
<tr>
<td>Plane</td>
<td>Sagittal/</td>
<td>Axial</td>
<td>Axial</td>
<td>Axial</td>
<td>Axial</td>
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<tr>
<td>Mode</td>
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<td>2D</td>
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<tr>
<td>TR [ms]</td>
<td>2100^m</td>
<td>&gt;6000</td>
<td>&gt;5000</td>
<td>&gt;2500</td>
<td>2100^m</td>
</tr>
<tr>
<td>TE [ms]</td>
<td>Min</td>
<td>100-140</td>
<td>Min</td>
<td>80-120</td>
<td>Min</td>
</tr>
<tr>
<td>TI [ms]</td>
<td>1100^a</td>
<td>2000-2500</td>
<td>1100^a</td>
<td>90-160</td>
<td>1100^a</td>
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<tr>
<td>Flip Angle</td>
<td>10-15</td>
<td>90/≥160</td>
<td>90/180</td>
<td>90/160</td>
<td>10-15</td>
</tr>
<tr>
<td>Frequency</td>
<td>≥172</td>
<td>≥256</td>
<td>≥128</td>
<td>≥256</td>
<td>≥172</td>
</tr>
<tr>
<td>Phase</td>
<td>≥172</td>
<td>≥256</td>
<td>≥128</td>
<td>≥256</td>
<td>≥172</td>
</tr>
<tr>
<td>NEX</td>
<td>≥1</td>
<td>≥1</td>
<td>≥1</td>
<td>≥1</td>
<td>≥1</td>
</tr>
<tr>
<td>Frequency</td>
<td>A/P</td>
<td>A/P</td>
<td>R/L</td>
<td>A/P</td>
<td>A/P</td>
</tr>
<tr>
<td>Direction</td>
<td>256mm</td>
<td>240mm</td>
<td>240mm</td>
<td>240mm</td>
<td>240mm</td>
</tr>
<tr>
<td>Slice Thickness</td>
<td>≤1.5mm</td>
<td>≤4mm^1</td>
<td>≤4mm^1</td>
<td>≤4mm^1</td>
<td>≤1.5mm</td>
</tr>
<tr>
<td>Gap/Spacing</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diffusion Options^p</td>
<td>Up to 2x</td>
<td>Up to 2x</td>
<td>Up to 2x</td>
<td>Up to 2x</td>
<td>Up to 2x</td>
</tr>
<tr>
<td>Parallel Imaging</td>
<td>5-10 min</td>
<td>4-8 min</td>
<td>2-4 min</td>
<td>4-8 min</td>
<td>5-10 min</td>
</tr>
<tr>
<td>Scan Time (Approx) [Benchmarked on 3T Skyra]</td>
<td>5:49 min for 1mm isotropic</td>
<td>3:22 for 2D FLAIR</td>
<td>1:22 for 3 direction DWI and 3 b-values</td>
<td>5:10 for dual echo</td>
<td>5:49 for 1mm isotropic</td>
</tr>
</tbody>
</table>

Volumetric Pre- and Post
1-1.5mm isotropic
Can be reformatted to 3mm slices (any plane)
Allows for T1 subtraction
Allows for longitudinal registration

T1+C   T1 Subt.
Summary

- **Pseudoprogression** (Stupp protocol) and **Pseudoresponse** (anti-angiogenic tx) remain important challenges in tumor imaging.

- **Diffusion, Perfusion** and **Non-FDG PET** show promise in overcoming these challenges, but require rigorous validation before they can be used clinically.

- We are moving towards semi-automated **quantitative** standardized imaging for multicenter clinical trials, and integrating “big data” from multiple information streams.