Typifying Pseudoprogression in Glioblastoma Multiforme using MR Cerebral Blood Flow Measurements

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Objectives

- Review the MR characteristics of GBMs
- Define pseudoprogression and the challenges it presents in evaluating GBM treatment response
- Discuss arterial spin-labeling measured cerebral blood flow to differentiate true progressive disease from pseudoprogression
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Glioblastoma Multiforme

- Most common primary brain neoplasm in adults
  - 17,000 new cases of primary CNS tumors yearly
    - 60-70% are malignant gliomas
- Epidemiology
  - 40% more common in men
  - More common in Caucasians
  - Median age at diagnosis: 64
- Associated risk factors: ionizing radiation
- Overall survival (18-70 yo)
  - 2 years: 26.5%
  - 5 years: 9.8%
GBM

• Presentation varies by location
  – Headache
  – Seizure
  – Focal neurologic deficit
  – Confusion or memory loss
  – Personality changes
Magnetic Resonance in GBM

- **T1 without contrast**
  - Hypo- to isointense white matter mass
  - Heterogeneous signal from necrosis and hemorrhage
  - Often crosses white matter commisural tracts
- **T1 with contrast**
  - Heterogeneous enhancement
- **T2 and FLAIR**
  - Hyperintense
  - Extensive vasogenic edema
Magnetic Resonance in GBM

- **GRE**
  - Susceptibility from blood or calcification
- **DWI**
  - Mild restriction from increased cellularity
- **Perfusion**
  - Increased
- **MRS**
  - ↑ Choline (membrane turnover)
  - ↓ N-acetyl-aspartate (decreased neuronal cellularity)
49 yo Man with HA and L-sided Weakness

A: R-temporal hypointense mass (arrow) with leftward subfalcine herniation
B: T1 with gadolinium demonstrates thick irregular enhancing rim (arrow)
49 yo Man with HA and L-sided Weakness

A: Hyperintense mass on T2 FLAIR (arrow) with extensive vasogenic edema (yellow star)
B: Foci of increased susceptibility likely represent blood products (yellow arrow)
49 yo Man with HA and L-sided Weakness

A: Slight diffusion restriction (arrow)
B: Area of diffusion restriction correlates with hypointensity in ADC (arrow)
Post-Operative Imaging

A: Unenhanced image shows hemorrhage in resection cavity (box)
B: No contrast enhancing lesion noted in resection cavity, exam limited by hemorrhage seen in A
Pathology

A: Pseudopalisades (arrow)
B: Pseudopalisading necrosis (arrow)
C: Microvascular hyperplasia (arrow) induced by hypoxic pseudopallisading cells (arrowhead)
D: Pseudopalisading necrosis (arrowhead) with microvascular hyperplasia (arrow)
Current Management

• Standard of care:
  – Maximal resection
  – Radiotherapy (RT) + temozolomide (TMZ)
  – Adjuvant TMZ

• Symptom management
  – Antiepileptic drugs
  – Steroids

• Follow-up imaging

• Recurrence
  – Anti-angiogenic drugs
    • bevacizumab
  – Clinical trials
Response Assessment: MacDonald Criteria

<table>
<thead>
<tr>
<th>Response</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>Complete response</td>
<td>Requires all of the following: complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks; no new lesions; no corticosteroids; and stable or improved clinically</td>
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<tr>
<td>Partial response</td>
<td>Requires all of the following: $\geq 50%$ decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks; no new lesions; stable or reduced corticosteroid dose; and stable or improved clinically</td>
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<tr>
<td>Stable disease</td>
<td>Requires all of the following: does not qualify for complete response, partial response, or progression; and stable clinically</td>
</tr>
<tr>
<td>Progression</td>
<td>Defined by any of the following: $\geq 25%$ increase in sum of the products of perpendicular diameters of enhancing lesions; any new lesion; or clinical deterioration</td>
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Wen, 2010
Imaging Pitfalls

• Enhancement reflects blood-brain barrier (BBB) impairment
  – Steroids $\rightarrow \downarrow$
  – Post-surgical $\rightarrow \uparrow$
  – Post-ictal $\rightarrow \uparrow$

• T2 changes can represent:
  – Edema
  – Post-radiation
  – Non-enhancing tumor

• Post-radiation changes
  – Late (after standard 60 Gy)
    • 1.3% (RT alone), 9.3% (RT+adjuvant chemotherapy) at median 11.6 mos
  – ?Early changes $\rightarrow$ pseudoprogression
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Pseudoprogression

• RT+TMZ leads to disruption of BBB, allowing passage of TMZ and thus enhancing its activity → better disease control

• However, months after completing RT, BBB may still be altered from concomitant TMZ, allowing passage of gadolinium → ↑enhancement = pseudoprogression
### Current Literature

<table>
<thead>
<tr>
<th>Study</th>
<th>Total</th>
<th>Tx</th>
<th>Frequency of f/u</th>
<th>Progression</th>
<th>Time to progression</th>
<th>Progressed</th>
<th>Pseudo-progression</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chamberlain (2007)</td>
<td>51 GBM</td>
<td>RT + TMZ</td>
<td>2-3 wks s/p tx, then q2mos</td>
<td>↑ neuro s/sx and MRI progression</td>
<td>6 mos</td>
<td>26/51 (51%)</td>
<td>Pathology proven necrosis; 15 were re-operated or re-biopsied</td>
<td>7/15 (47%)</td>
</tr>
<tr>
<td>Taal (2007)</td>
<td>68 GBM</td>
<td>RT + TMZ</td>
<td>4 wks s/p tx, then q3mos</td>
<td>≥25% ↑ CE +/- neuro s/sx and stable or ↑ steroid dose</td>
<td>1 mo</td>
<td>36/85 (45%)</td>
<td>≥50% ↓ CE with stable/↓ steroid OR clinically + MRI stable with stable/↓ steroid @ 6 mo</td>
<td>18/36 (50%)</td>
</tr>
<tr>
<td>Brandes (2008)</td>
<td>103 GBM</td>
<td>RT + TMZ</td>
<td>4 wks s/p tx, then in 3 mos</td>
<td>Lesion growth on MRI</td>
<td>3 mos</td>
<td>50/103 (48.5%)</td>
<td>↓/stable lesion on f/u MRI s/p 2 cyles of TMZ after initial f/u MRI @ 1 mo</td>
<td>32/50 (64%)</td>
</tr>
</tbody>
</table>

~54% of progressive malignant glioma is pseudoprogressive disease
Clinical Impact

• If pseudoprogression is thought to be progressive disease, then:
  – Lose treatment that was working well
  – False attribution of success to experimental drug
  – May abandon treatment altogether
The Problem

• To differentiate true progression from pseudoprogression we need better response assessment than MacDonald Criteria

• Proposed solution: use advanced MR imaging techniques that demonstrate perfusion to distinguish progressive disease from radiation necrosis (pseudoprogression)
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Cerebral Perfusion

- Traditionally, dynamic susceptibility contrast (DSC) perfusion used to differentiate recurrent tumor from radiation necrosis
- Requires contrast to measure cerebral blood flow (CBF)
Arterial Spin-Labeling

- MR perfusion technique that quantitatively measures CBF
- Concept: arterial water used as freely diffusible tracer
  - Inversion pulse tags inflowing spins proximal to imaging plane
  - Transit delay to allow tagged spins to enter plane, then control and label images are obtained
  - Pair-wise subtraction of these two images yields perfusion map
ASL Quantified CBF

- Post-processed CBF map
  - displayed in mL/100 g tissue/min

Deibler, 2008
ASL Advantages & Disadvantages

• Advantages:
  – No need for large-bore IV access
  – No gadolinium
    • No risk of nephrogenic systemic fibrosis
  – Validated in various disease states

• Disadvantages
  – Post-processing
  – Low signal-to-noise ratio
  – Impact of heart rate, cardiac output, anemia
ASL in Tumor Imaging

• Correlation between tumor grade and CBF
• Monitoring of tumor response to therapy
• Distinguish areas of recurrence from radiation necrosis
ASL in Tumor Imaging Example 1

- **A**: T1 post-contrast image shows avidly enhancing high-grade neoplasm in genu of corpus callosum (arrow)

- **B**: ASL map demonstrates high signal intensity corresponding to increased flow within tumor (arrow)
ASL in Tumor Imaging Example 2

- **A**: T2 hyperintense lesion (arrowhead)
- **B**: T1 post-contrast shows no enhancement (arrowhead)
- **C**: MRS shows ↑Cho:Cr (yellow arrow)
- **D**: ASL demonstrates high signal intensity (white arrow)
One month s/p RT+TMZ

A: Two new regions of increased enhancement (arrows) extending into medial temporal lobe
B: T2 FLAIR abnormality could represent vasogenic edema (arrow)
CBF one month s/p RT+TMZ

- ASL:
  - ↓ perfusion in L temporal lobe laterally (white arrow)
  - Questionable focus of ↑ perfusion in area of medial enhancement (yellow arrow)

- Pt neurologically stable, off steroids; continue adjuvant TMZ with f/u imaging in 1 mo
Two months s/p RT+TMZ

A: Persistent regions of increased enhancement (arrows) extending into medial temporal lobe
B: Unchanged T2 FLAIR abnormality (arrow)
CBF two months s/p RT+TMZ

- ASL:
  - ↓ perfusion throughout areas of enhancement (white arrow)
- Pt remains neurologically stable, off steroids; on adjuvant TMZ
Nine months s/p RT+TMZ

A: Decreased enhancement in medial temporal lobe (arrow), lateral area of enhancement not seen
B: Persistent T2 FLAIR abnormality (arrow)
CBF nine months s/p RT+TMZ

• ASL:
  – Area of persistent hypoperfusion (white arrow)
• Pt neurologically stable, off steroids
• Previous areas of enhancement attributed to pseudoprogression
Follow-up 21 months s/p RT+TMZ

A: No areas of abnormal enhancement seen
B: Persistent T2 FLAIR abnormality (arrow) stable
ASL in Progressive Disease

Companion Patient
49 yo Man with HA and Syncope

A: Frontal lobe mass with heterogenous enhancement (arrow)
B: Large hyperintense lesion (arrow) with peritumoral vasogenic edema (yellow star)
3 mos s/p Resection and RT+TMZ

A: Frontal lobe resection cavity with thick enhancement along cavity margins (arrow)
B: T2 FLAIR abnormality adjacent to resection cavity (yellow star)
CBF three months s/p RT+TMZ

- ASL:
  - Questionable area of ↑ perfusion in medial R frontal lobe (white arrow)

- Pt neurologically stable, off steroids; decision made to follow-up MR in 1 mo
F/u four months s/p RT+TMZ

A: Resection cavity with increased thick enhancement extending posterolaterally (arrow) into rostrum of corpus callosum
B: Increased T2 FLAIR signal surrounding enhancing region consistent with peritumoral edema (yellow star)
CBF four months s/p RT+TMZ

- **ASL:**
  - Marked hyperperfusion consistent with tumor recurrence in R frontal lobe (arrow)
- Pt neurologically stable, off steroids
- Recurrent disease
- Neurosurgery deemed lesion operable
Pre-operative Imaging

- R frontal enhancing mass extending into corpus callosum and into contralateral side (arrow)
- Pathology
  - Recurrent GBM
Looking Forward

• New Response Assessment in Neuro-Oncology Working Group (RANO)
  – Within 12 wks s/p RT+TMZ progression is defined as majority of new enhancement outside of radiation field or pathology-proven
  – No enrollment into clinical trials for recurrent gliomas if progression vs pseudoprogression cannot be determined

• Can arterial spin-labeling be used to differentiate between true tumor progression and pseudoprogression in GBMs?
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References

Acknowledgements

• Rafael Rojas, MD
• Rivka Colen, MD
• David Alsop, PhD
• Gillian Lieberman, MD
• Larry Barbaras