Advances in whole brain sMRI to improve glioma imaging

https://brainimaging.emory.edu/
Glioblastoma (GBM)

- Most common malignant primary brain tumor in adults
  - Highly infiltrative
  - Treated w/max resection + RT/TMZ
  - Median survival is 14-16 months

Limitations of Anatomical MRI for Gliomas

- Overlap in appearance between neoplastic and non-neoplastic lesions
- Overlap in appearance between different grades
- Infiltration beyond regions of contrast enhancement
- Difficult to distinguish edema from infiltrating tumor
- Not reliable to determine tumor progression
- Qualitative → limitations for treatment monitoring.

CE-T1

T1 Enhancement ≈ Leaky BBB & neovasculature

T2/FLAIR

T2 Hyperintensity ≈ tumor, edema, ischemia, etc.
**1H MR Spectroscopy of the Brain**

- **N-Acetylaspartate (NAA):** Neuronal Integrity
- **Creatines (Cre):** Cellular Energetics
- **Cholines (Cho):** membrane synthesis & degradation
- **Glutamate/ Glutamine (Glu/Gln):** Neurotransmitters
- **Lactate (Lac):** hypoxia
- **Mobile lipids:** Necrosis
- **GABA, Alanine, Aspartate, 2HG, glycine**
- **myo-Inositol (ml):** Glial marker

**Non-invasive chemical analysis of tissue**

**Single Voxel Spectroscopy**

**2D Spectroscopic Imaging (MRSI)**
MR Spectroscopy of Brain Tumor

![Peak assignment for normal tissue and tumor tissue](image)

**Normal**

**Tumor**
**1H MR Spectroscopy of the Brain**

- **Non-invasive chemical analysis of tissue**

- **Current clinical implementations**
  - **N-Acetylaspartate (NAA):** Neuronal Integrity
  - **Creatines (Cre):** Cellular Energetics
  - **Cholines (Cho):** membrane synthesis & degradation
  - **Glutamate/ Glutamine (Glu/Gln):** Neurotransmitters
  - **Lactate (Lac):** hypoxia
  - **Mobile lipids:** Necrosis
  - **GABA, Alanine, Aspartate, 2HG, glycine**
  - **myo-Inositol (mI):** Glial marker

- **Single Voxel Spectroscopy**
- **2D Spectroscopic Imaging (MRSI)**
Whole Brain 3D MRSI @ 0.1cc (spectroscopic MRI, sMRI)
Echo-Planar SI (EPSI) with Interleaved Water Reference

Water suppression, and out-of-slice suppression

Spin-Echo Excitation
(simpler than standard MRS methods)

Metabolite Acquisition

Water Acquisition

$A I_{\text{linear}}^{\text{metab}} = \frac{S_{\text{voxel}}^{\text{metab}}}{mean^{\text{NAWM}}_{\text{metab}}}$

Cordova et al. 2016
sMRI: Tracerless Metabolic Imaging

T₁w-CE  Choline  NAA  Creatine  T₂w  Internal Water
Whole Brain sMRI

Contrast-enhanced T1w-MRI

T2w

Cho/NAA
Pilot Study for GBM surgery
(R21CA186169: sMRI to guide tumor resection)

Newly-diagnosed GBM pts (N=20)

Pre-surgical sMRI for target definition

Combining high resolution sMRI with 5-ALA to improve complete resection in GBM surgery

Stereotactic sampling matched to sMRI scan

Assess for feasibility, safety, neurocognition and outcomes (PFS/OS)
Fluorescence and Histological Validation of sMRI Tumor Infiltration

SOX2 Signal
HXN Signal
Stained Slide

Segment Nuclei and Tissue Area
Automated Nuclear Classification

White Light
405 nm Blue Light

SOX2
sMRI Identifies Infiltrating Tumor *in vivo*

sMRI biomarkers vs SOX2 Density

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>$\rho$</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAA</td>
<td>-0.50</td>
<td>0.01*</td>
</tr>
<tr>
<td>Cho</td>
<td>0.63</td>
<td>5E-4*</td>
</tr>
<tr>
<td>Cho/NAA</td>
<td>0.82</td>
<td>&lt;1E-4*</td>
</tr>
<tr>
<td>DWI-ADC</td>
<td>0.17</td>
<td>0.40</td>
</tr>
</tbody>
</table>

Cordova et al., Neuro Oncol 18:1180-9 (2016)
sMRI High-Risk Recurrence Regions

Before radiation therapy treatment @recurrence

Cordova et al., Neuro Oncol 18:1180-9 (2016)
Example of Dose Coverage w/sMRI Targets

Is 60 Gy enough?

2.0x Cho/NAA (pre-RT)

Recurrence

Current 60Gy

Cordova et al., Tomography 2:366-73 (2016)
Are current methods for defining RT targets good enough?
Pilot Study for GBM Dose Escalation
(R01CA214557: sMRI to guide dose escalation)

Newly-diagnosed GBM pts (N=30)

Pre-RT sMRI for target definition

Treat metabolically-defined Volume + any residual CE to 75Gy/30fxs

2 weeks sMRI for future assessment (plan adaptation)

Assess for feasibility, safety, neurocognition and outcomes (PFS/OS)

Enrollment at 3 institutions
Emory, Hopkins, Miami

Conventional MRI will be used to define 60 and 50 Gy volumes

1-year PFS (30-35% -> 55-60%)
Current Standard RT Target Volume

CTV2, Margin 5 mm – standard care

CTV1, Margin 5-7 mm – standard care

Resection cavity

GTV1: T2/FLAIR+ resection cavity+T1CE
GTV2: resection cavity+T1CE

PTV: adds additional 3 mm
PTV1: 46-54 Gy
PTV2: 60 Gy

Contrast-enhancing
RT Target Modification with sMRI

CTV1, Margin 5-7 mm – standard care

Resection cavity

GTV1: T2/FLAIR+ resection cavity+T1CE
GTV2: resection cavity+T1CE
GTV3: sMRI+T1CE

PTV: adds additional 3 mm
PTV1: 50 Gy
PTV2: 60 Gy
PTV3: 75 Gy

CTV2, Margin 5 mm – standard care

GTV2: resection cavity+T1CE

PTV1: 50 Gy

GTV3: sMRI+T1CE

CTV3 = GTV3

Contrast-enhancing

↑ Cho/NAA

PTV2: 60 Gy
PTV3: 75 Gy

60Gy

50Gy

75Gy
CTV3 Modification with sMRI (Emory #2)

CE-T1w

2.59cc

Cho/NAA=2x

23.82cc
Isodose Lines (75, 60, 50 Gy) of IMRT Plan
CTV3 Modification with sMRI (Miami #4)

T1w-CE  Cho/NAA=2x

2.3cc  34.8cc
sMRI Cloud App

- User-friendly, intuitive display
- Fit for busy clinicians, not for MR spectroscopists
- Web-based, no software installation needed
- Centralized Analysis for multisite trials
- Automated Quality control
- Auto-Segmentation for target volume definition
- Real-time collaborative editing capability
- Securely store anonymized sMRI data sets, including other clinical images, RT plans, and genomic/histological information
No Biopsy or RT targets on CE-T1w

T1w

FLAIR

Cho/NAA
(Sagittal)

Cho/NAA
3x volume
Acknowledgements

**Emory University**
Saumya Gurbani, MS (MD/PhD student)
Karthik Ramesh, MS (PhD student)
    J. Scott Cordova, MD, PhD
Costas G. Hadjipanayis, MD, PhD
    Jeffrey J. Olson, MD
    Ian Crocker, MD
    Jim Zhong, MD
Brent Weinberg, MD, PhD
Chad A. Holder, MD
    Lee Cooper, PhD
    Ying Guo, PhD
    Stewart Neill, MD
Daniel Brat, MD, PhD
Hui-Kuo Shu, MD, PhD
Hyunsuk Shim, PhD

**University of Miami**
Andrew Maudsley, PhD
Eric Mellon, MD, PhD
Sulaiman Sheriff, MS

**Johns Hopkins University**
Peter Barker, D Phil
Lawrence Kleinberg, MD
Michal Povazan, PhD

**Funding**
R21 CA 186169 (Holder, Hadjipanayis, & Shim)
U01 CA 172027 (Shu, Hu, Olson, & Shim)
R01CA214557 (Shu, Mellon, Kleinberg & Shim)
F31 CA 180319 (Cordova)
F30 CA206291 (Gurbani)
NCI Quantitative Imaging Network: Emory

Emory University: PIs: Hyunsuk Shim, Hui-Kuo Shu, Jeffrey Olson  
Co-Inv: Eduard Schreibmann, Ying Guo, Andrew Miller, Brent Weinberg, Alfredo Voloschin

Johns Hopkins University: PI: Peter Barker  
Co-Inv: Matthias Holdhoff, Doris Lin, Lawrence Kleinberg

University of Miami: Consultant: Andrew Maudsley
Thanks for your attention!

&

Questions?