Whole Brain MRSI predicts early response to therapy and enables adaptation

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Glioblastoma (GBM)
- Most common malignant primary brain tumor in adults
- Highly infiltrative
- Treated with 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.

Problems Monitoring Response in GBM
Pseudoprogression & Pseudoresponse
- Std Care (RT+TMZ)
- Anti-angiogenic Therapy
H MR Spectroscopy of the Brain

Non-invasive chemical analysis of tissue

- 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

Current clinical implementations
Whole Brain 3D MRSI @ 0.1cc (spectroscopic MRI, sMRI)

sMRI: Tracerless Metabolic Imaging

Whole Brain sMRI
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

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

Fluorescence and Histological Validation of sMRI Tumor Infiltration

Fluorescence vs SOX2/sMRI

sMRI Identifies Infiltrating Tumor in vivo

sMRI biomarkers vs SOX2 Density

<table>
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<th>Biomarker</th>
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<tr>
<td>NAA</td>
<td>-0.50</td>
<td>0.01*</td>
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<tr>
<td>Cho</td>
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<td>DWI-ADC</td>
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Centola et al., Neuro Oncol 18:1180-9 (2016)
Reprograms tumor genes to carry out normal activity.
Blocks abnormal HDAC and makes tumor DNA receptive to attack by temozolomide (TMZ).

HDAC opens up tumor DNA, providing better access to TMZ.

HDACi opens up tumor DNA, providing better access to TMZ.

Stop tumor growth & encourages tumor cells to behave more like normal brain cells.

TMZ tumor cell killing is increased with SAHA.

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**BBB Penetration (LC-MS-MS)**

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**QIN U01: HDAC Inhibitor Response**

Total 30 patients (Johns Hopkins and Emory)
sMRI for Radiation Treatment Planning

Evaluate how sMRI can modify target volumes for RT planning
- 11 patients treated with std-of-care RT/TMZ
- Obtained sMRI pre-RT
- Generated target volumes based on conventional imaging and sMRI
- Compared std vs sMRI-defined targets

RT Target Volume Modification with sMRI

Dose coverage of target

Dose coverage of std and sMRI targets

Cordova et al., Tomography 2:366-73 (2016)
Improved recurrence coverage with sMRI target

Example of Dose Coverage with sMRI Targets

Current trial for GBM Dose Escalation
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)
- Enrollment at 3 institutions: Emory, Hopkins, Miami
- 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)
- 1-year PFS (30-35% = 55-60%

Current Standard RT Target Volume

GTV1: T2/FLAIR+ resection cavity+ T1CE
CTV1: Margin 5.7 mm – standard care
PTV1: 46-54 Gy

GTV2: T1CE
CTV2: Margin 5 mm – standard care
PTV2: 60 Gy
RT Target Modification with sMRI

- CTV1: T2/FLAIR + resection cavity + T1CE
- CTV2: resection cavity + T1CE
- GTV1: sMRI + T1CE
- PTV: adds additional 3 mm
- PTV1: 50 Gy
- PTV2: 60 Gy
- PTV3: 75 Gy

CTV3 Modification with sMRI (Emory #2)

- CE-T1w
- Cho/NAA = 2x

- 2.59cc
- 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
- Automated 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
New molecular pathology of lower grade gliomas

Oligodendrogliomas

Astrocytomas


Grade III Anaplastic Astrocytoma
(IDH mutant/1p19q intact/TP53 mutant)

Grade II Astrocytoma
(IDH WT)
Grade II Oligodendroglioma
(IDH mutation, 1p/19q co-deletion, and ATRX wild-type)

No Biopsy or RT targets on CE-T1w

Summary

- Technical advances with sMRI has improved clinical utility
- Biopsy/resection location may be guided by sMRI
- Infiltrating GBM not seen on standard MRI may be detectable
- RT treatment plans for GBMs may be significantly altered/improved if sMRI data is considered
- Ongoing directions
  - sMRI defined targets for RT dose escalation
  - Improve sMRI clinical interface to enhance adoption
  - Expand use to lower grade glioma histologies
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Thanks for your attention!
& Questions?