Advanced MR Spectroscopy and Perfusion to Detect *Metabolism* and *Response* to Therapy in Gliomas

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Disclosures

- Consultant, ACR Imaging Network (ACRIN) & ACR Image Metrix
  - Glioblastoma multi-institutional trial ABTC 0901
  - RANO Reader (ACR Image Metrix) Eisai TM610-002 Study
  - Phase III Trial RTOG 0825(4508)/ACRIN 6686

- PI: High Resolution MRI/ MRS to Evaluate Therapeutic Response to Optune in Recurrent Glioblastomas
  - NovoCure Advisory board

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  - Adaptive Radiology Interpretation Education System (ARIES)
1. **MR Spectroscopy**
   1. 2D Localized Correlated Spectroscopy (L-COSY) at 7.0 T
   2. Chemical Shift Imaging (CSI) at 3.0 T
      IDH1 mutation & 2HG

2. **Whole brain Spectroscopic Imaging**
   1. CSI at 3.0 T for disease monitoring in IDH-mutant gliomas
   2. 3-D Echo-Planar Spectroscopic Imaging (EPSI) at 3.0 T
      TP versus PsP

3. **MR perfusion**
   1. TP versus PsP
   2. Response Assessment (CAR-T, TTFields), Survival

4. **Multi-modal Approach (DTI/EPSI/Perfusion)**
IDH mutations & 2-HG

- Enzyme catalyzes the oxidative decarboxylation of isocitrate to α-KG
- Mutant IDH1/2 causes accumulation of 2-HG (5-35 mM)
- Reported in ~70% LGG/ sec GBM
2-HG: 'Ideal' biomarker

1. Virtually no normal 2-HG background

2. 99% of tumors with IDH mutations have increased levels of 2-HG

3. Only other known cause of elevated 2HG is hydroxyglutaric aciduria,
   1. Rare inborn error of metabolism with a different clinical phenotype

✓ Hence, tumors with ▲ levels of 2-HG are unlikely to represent false +ve cases for IDH mutations
In vivo detection of 2-HG

- Unambiguous detection of 2-HG with MRS, in vivo, is challenging because its coupled five-spin system yields a complex spectral pattern.

- Five resonance peaks:
  - 4.02, 2.27, 2.22, 1.98, 1.83 ppm

- 2-HG signals from $H\beta$ (1.91 ppm) and $H\gamma$ (2.24 ppm) protons are superimposed by glutamate, glutamine, & GABA, while $H\alpha$ (4.02 ppm) signals are obscured by mI, phosphocreatine, & lactate.
Why 2D Spectroscopy?

2HG

[Chemical structure and 2D spectroscopy graph]
Increased Spectral Separation

- **Uniquely resolve 2HG**

  - **1D MRS**
    - N-acetylaspartate
    - Creatine
    - Choline
    - Myo-Inositol
    - Overlap Lactate/Lipids
    - Overlap Glx

  - **2D L-COSY MRS**
    - NAA
    - Myo-Inositol
    - Creatine
    - Choline
      - PC, GPC, PE, GPE
    - Resolve Lac/Lipids
    - Resolve Glu/Gln/GSH
    - Amino Acids
      - Ile, Leu, Lys
Clinical examples Case # 1
18 Y/M after a grand mal seizure
Case # 1

7T 2D L-COSY Spectrum
L frontal astrocytoma (WHO grade II)

Mutant IDH 1 positive

Slides courtesy: McLean Nasrallah MD, PhD
Case # 2
36 Y/M vision changes & seizure
Case # 2

7T 2D L-COSY Spectrum
R temporal anaplastic oligoastrocytoma (WHO grade III)

Mutant IDH 1 positive

Slides courtesy: McLean Nasrallah MD, PhD
Case # 3 – IDH1 Wild-Type

- No detectable 2HG
- WHO Grade I
  - Ganglioglioma
- 8.8 ml VOI
Chemical Shift Imaging (CSI) at 3.0 T

- 2D CSI (3T Tim-Trio clinical MRI scanner)
  - TE/TR = 97/1700 ms, 3 averages, 16x16 Array
  - 1.5 ml voxels, 6:53 min scan time
  - Optimized for detection of 2HG

- LC Model Fitting
  - 40% CRLB, neighboring voxels

- Nine patients assessed
  - 4 female, 5 male
  - Ages 31 to 83, mean = 48 years
  - 4 IDH1 mutants

- Compare to immunohistochemical staining
Case # 1 CSI at 3.0 T
Case # 2 CSI at 3.0 T

Voxel [10,5]
2HG
5.215 Conc.
0.354 /Cr
30% CRLB

2HG

Grade III AOA
Grade II Oligodendroglioma with some Grade III features
Case # 4 CSI at 3.0 T

No detectable 2HG

Path Result: Wild-Type Glioblastoma
Outline

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4. Multi-modal Approach (DTI/EPSI/Perfusion)
Chemical Shift Imaging (CSI) at 3.0 T

Integration of 2-hydroxyglutarate-proton magnetic resonance spectroscopy into clinical practice for disease monitoring in isocitrate dehydrogenase-mutant glioma

RESULTS:
- Detection of 2HG in IDH-mutant gliomas was closely linked to tumor volume
  - Sensitivity: 8% for small tumors (<3.4 mL) to 91% for larger tumors (>8 mL)
- 2HG-MRS prior to surgery corresponded with tumor cellularity
- Cytoreduction results in gradual decrease in 2HG levels

CONCLUSIONS:
- 2HG-MRS can be linked with routine MRI to provide quantitative measurements of 2HG
- Useful imaging biomarker to non-invasively monitor the abundance of IDH-mutant tumor cells during therapy & disease monitoring
Potential to detect IDH1 mutation in vivo
- To date, in vivo MRS is the only imaging method that is specific to IDH mutations
  - Existing PET or SPECT radiotracers are not!

Significant translational implications
- HGG – better prognosis
- LGG – early intervention before it transforms to a higher grade
- Potential use as an early biomarker of malignant progression
- Disease monitoring
- Endpoint for targeted therapy (AGIOS 121 drug)
Multi-Slice EPSI: Cho/Cr Maps

- Whole-Brain
- High Resolution
- Single Scan

Cho/Cr Map
True Progression
Enhancing
n = 20

Immediate Peritumoral
n = 27

Distant Peritumoral
n = 132
EPSI Metabolite Maps

Cho/NAA

Cho/Cr

NAA

Cr
Median Cho/Cr Ratio vs. Normal

True Progression (N=7)

- Enhancing: 1.782
- Immediate: 1.603
- Distal: 1.419

P = .008

Pseudoprogession (N=7)

- Enhancing: 1.266
- Immediate: 1.024
- Distal: 0.956

P = .045

P = .040

Verma G. et al. ISMRM 2016
Cho/Cr in TP vs. PsP Enhancing Region

Verma G. et al. ISMRM 2016
EPSI: Response Assessment

- EPSI Detects Tumor Heterogeneity
  - ▲ Cho/Cr in True Progression
    - Enhancing Lesion
    - Immediate Peritumoral

- Histogram analysis of the enhancing lesions better separates PsP from TP
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MR Perfusion: PsP versus TP

Pseudoprogression

True Progression

T1 gad  CBV

H&E

rCBVmax = 2.71

rCBVmax = 4.26
Response Assessment: CAR-T therapy

Quantitative Perfusion analysis - provides a better estimation of treatment response

Baseline rC BVmax 5.29
1 month rC BVmax 2.88
2 month rC BVmax 2.17
3 month rC BVmax 2.00
CAR-T Multimodal (DTI/ PWI/ EPSI)

Wang S. et al. ISMRM 2016
Response Assessment: TTFields

Baseline (before TTFields)  3 month follow up

Post contrast T1 of 51 Y/F with left thalamic GBM
PC-T1  MD  FA  CBV  Cho/Cr

Baseline

2 month follow-up


- Early response to TTFields showed trends toward:
  - Increasing MD
  - Decreasing tumor volume, FA, rCBV and Cho/Cr

- Potential for physiologic and metabolic MRI to assess early treatment response to TTFields
Prognostic Value of Dynamic Susceptibility Contrast-Enhanced and Diffusion-Weighted MR Imaging in Patients with Glioblastomas

G. Çoban, S. Mohan, F. Kural, S. Wang, D.M. O'Rourke, and H. Poptani

Long Survivor (n=28)
Short survivor (n=30)

rCBV cutoff: 5.79
P<0.01

Conclusion

- Advanced techniques are establishing new paradigms in brain tumor research & therapy
- Immense translational potential
- Can be used for more sensitive assessment of tumor metabolism and response to therapy
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