Assessment of Treatment Efficacy in Preclinical Drug Testing Using Magnetic Resonance Imaging

Jonathan B. Moody, Patrick McConville, Richard J. Lister, Alicia R. Kreger, Erin Trachet, William L. Elliott, Bradford A. Moffat, Thomas L. Chenevert, Daniel L. Dexter, Alnawaz Rehemtulla, Brian D. Ross, W.R. Leopold.

Molecular Imaging Research, Inc., Ann Arbor, MI -- University of Michigan, Ann Arbor, MI

Molecular Imaging Research, Inc.
924 North Main Street Ann Arbor, MI 48104
734.222.9900 734.222.0500 fax
jonathan@molecularimaging.com email
www.molecularimaging.com

Motivation:

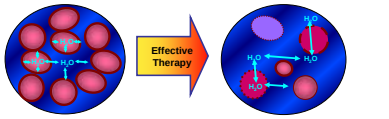
1. Diffusion MRI provides an early indicator of treatment response.
2. Diffusion MRI has been shown in a rat 9L glioma model to be a sensitive marker for treatment efficacy in response to BCNU chemotherapy.
3. In early clinical trials, diffusion MRI has demonstrated a positive correlation with clinical criteria for treatment response.

Aims:

1. Demonstrate the utility of diffusion MRI for *in vivo* assessment of treatment response in rodent subcutaneous tumor models.
2. Characterize the diffusion response in a range of human tumor types using a range of standard chemotherapeutics.
3. Expand the use of diffusion MR imaging methods to enhance the efficiency and cost-effectiveness of pre-clinical drug testing.

Background

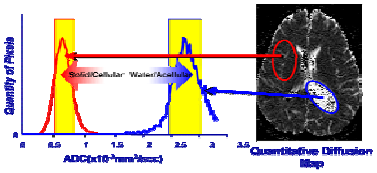
Apparent Diffusion Coefficient (ADC) ⇔ **Early Therapeutic Indicator**

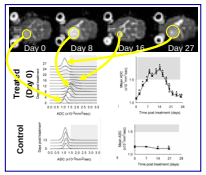


Intact Tumor
High Cellularity
Restricted diffusion of water
Low ADC

Tumor with dying cells
Decreased Cellularity
Increased diffusion of water
Increased ADC

MRI Diffusion Imaging ⇔ ADC Map





Diffusion MRI of Rat 9L Glioma after BCNU

- **Positive response to therapy indicated by right-shift of tumor ADC histogram**
- **Untreated control tumor ADC remains constant or decreases**

Chenevert, Stegman, Taylor, Robertson, Greenberg, Rehemtulla, Ross,
J. Natl. Cancer Inst. 90: 2029-2036 (2000)

Methods

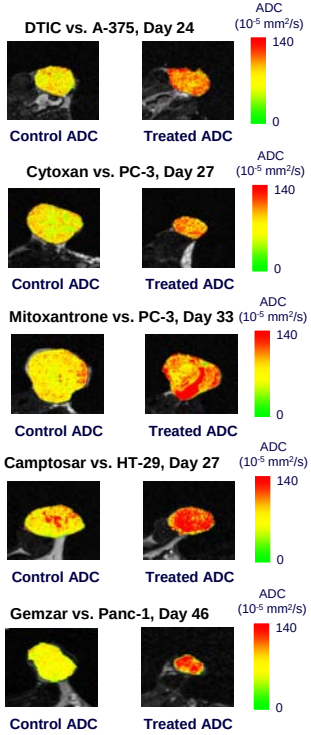
- Human tumor xenografts of four tumor cell types were implanted subcutaneously in athymic mice and grown to ~100 mg.
- Tumors were treated with six standard chemotherapeutics.
- Tumor growth was followed by conventional caliper measurements.
- Tumor ADC maps were acquired at 3-4 day intervals using motion-corrected, isotropic-weighted diffusion MRI sequence.

Tumor Cell Line Chemotherapeutics Dose Schedule

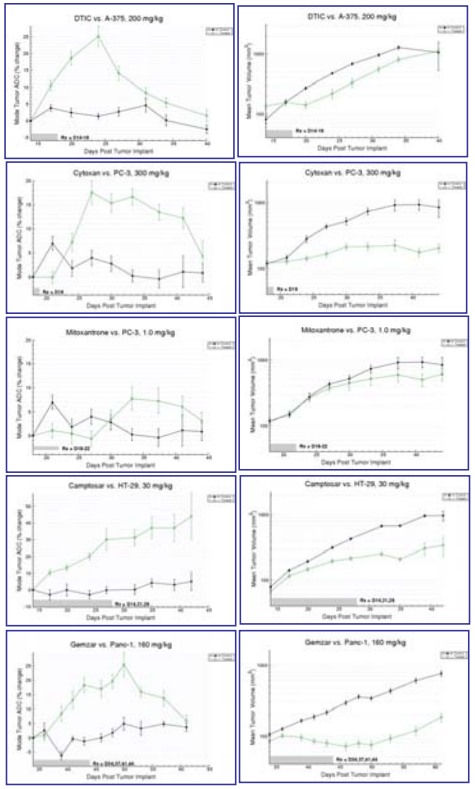
A-375	
Dacarbazine	Taxol
200 mg/kg I.P.	14 mg/kg I.P.
D14-18	D14,16,18, 20,22
PC-3	
Cytoxan	Mitoxantrone
300 mg/kg I.P.	1.0 mg/kg I.V.
D18	D18-22
HT-29	
Camptosar	
10 mg/kg I.P.	
D14,21,28	
Panc-1	
Gemzar	
160 mg/kg I.P.	
D34,37,41,44	

Results and Conclusions

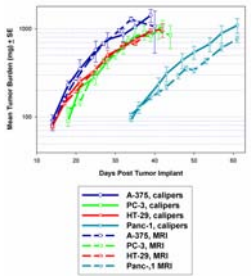
Tumor ADC Maps



Time-course of Tumor ADC and Tumor Burden



Tumor Burden: MRI vs. Calipers



CONCLUSIONS

Diffusion MRI was measured in four human tumor xenograft models tested against a total of six standard chemotherapeutic agents.

Diffusion MRI of these xenografts models provides:

- An early indicator of therapeutic response
- A reliable marker of treatment efficacy
- Accurate tumor volume measurements
- Highlights tumor heterogeneity