

Diffusion mri in preclinical drug testing

An early surrogate marker for efficacy in subcutaneous human tumor xenografts



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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.

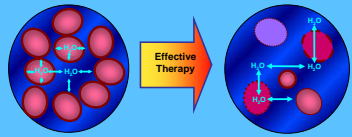
Aims:

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.

Concepts

Previous Results

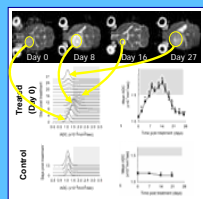
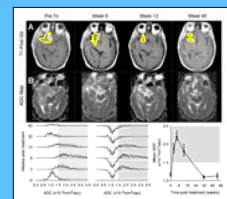
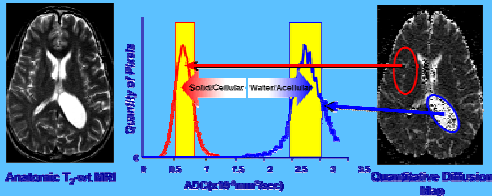
Apparent Diffusion Coefficient (ADC) ↔ Early Therapeutic Indicator



Intact Tumor
High Cellularity
Restricted diffusion of water
Low ADC

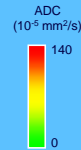
Tumor with dying cells
Decreased Cellularity
Increased diffusion of water
Increased ADC

MRI Diffusion Imaging ↔ ADC Map



Methodology

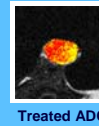
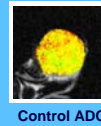
- Human tumor xenografts of four tumor cell types were implanted subcutaneously in athymic mice and grown to ~100 mg.
- Tumor growth was followed by conventional caliper measurements.
- Tumor ADC maps were acquired at 3-4 day intervals using motion-corrected, isotropic-weighted diffusion MRI sequence.



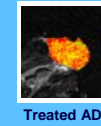
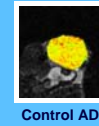
Tumor Cell Line Chemotherapeutics Dose Schedule

A-375	
Dacarbazine	Taxol
200 mg/kg I.P.	14 mg/kg I.P.
D14-18	D14,16,18, 20,22
PC-3	
Cytosan	Mitoxantrone
300 mg/kg I.P.	1.0 mg/kg I.V.
D18	D18-22
HT-29	
Camptosar	Fluorouracil
10 mg/kg I.P.	100 mg/kg I.P.
D14,21,28	D14,21,28
Panc-1	
Gemzar	
160 mg/kg I.P.	
D34,37,41,44	

Taxol vs. A-375, Day 27



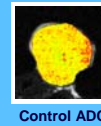
DTIC vs. A-375, Day 24



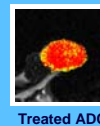
Cytosan vs. PC-3, Day 27



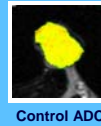
Mitoxantrone vs. PC-3, Day 33



Camptosar vs. HT-29, Day 27

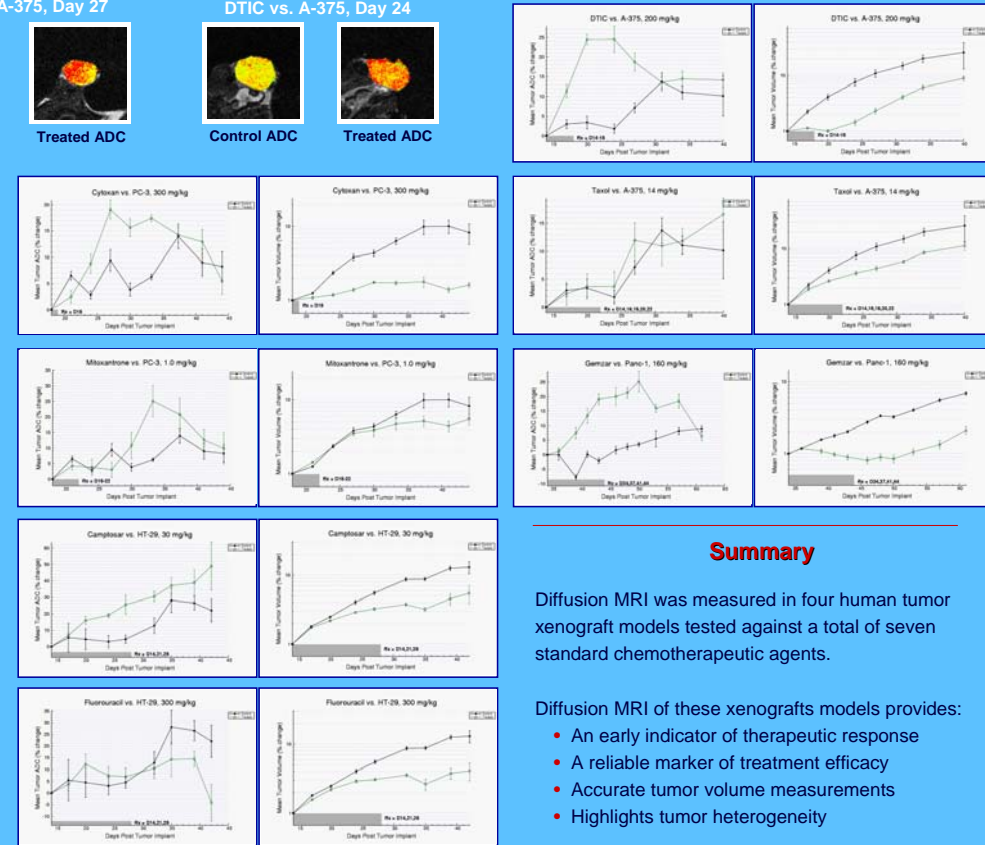


Gemzar vs. Panc-1, Day 46



Results

Summary



Summary

Diffusion MRI was measured in four human tumor xenograft models tested against a total of seven 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