MRI Basic for Clinical Trial

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Imaging based clinical trials

- Determine the value of imaging procedures for detecting, diagnosing, guiding, or monitoring the treatment of disease
- Important factors:
  - Patient positioning
  - Imaging acquisition protocol (including consistencies in acquisition slice location!)
  - Imaging analysis hardware and software
  - Interpretation guidelines are much more important to imaging trials compared to therapeutic trials (more critical when quantitative imaging analysis is involved)
- Standardization of the various components in an imaging clinical trial is key and optimization every step of the imaging chain is critical!
- There are efforts to create imaging standards and guidelines by the Cancer Imaging Program of the NIH, RSNA, ACR, ISMRM and many other organizations

Therapeutic trials using imaging

- More on the overall consistency and accuracy among multiple institutions, less focus on the various components in the imaging chain
- Using imaging as biomarkers (or surrogate biomarkers): both anatomical and functional imaging
- Consistency in imaging acquisition protocol, patient positioning, imaging analysis hardware and software, analysis and measurement guidelines are also important, especially when quantitative imaging analysis is involved.
- The promotion in the effort to create imaging biomarker standards is one of the goals of the QIBA, a joint effort by the Cancer Imaging Program of the NIH, RSNA, ACR, ISMRM and many other organizations

To ensure the quality of imaging biomarker

- Define well-established imaging biomarkers (DWI? T1,T2,T2*)
- Ensure consistency and equality at all sites
- Identical data acquisition for all sites, at all time
  - Including patient prep, positioning, protocol, reconstruction, QA
- Standardizes data analysis
- Ensure imaging data harmonization (data acquired on different imaging systems are comparable)

Utilization of MRI in Clinical Trial

- How are MRI used in clinical trials
  - Anatomical MRI
  - Functional MRI (Quantitative vs. qualitative)
- MRI QA in Clinical Trials
  - Prospectively planned
  - Scanner System QA (monitoring hardware changes)
  - Scanning Sequence QA/QC (acquisition sequence and patient positioning consistency)
  - QA of the Image Analysis Tools
  - Quantitative MRI initiatives (QIBA etc.)

Physicist's role in Clinical Trial

Must ensure MRI anatomical and quantitative imaging accuracy

- Consistency and standardization are critical
- MRI scanner system check (routine QA)
- Geometric Fidelity (distortion/Linearity)
- Signal Intensity Stability
- Quantitative Imaging QA
- AAPM, ACR QA guidelines for MRI system QA
- QIBA guidelines for quantitative MRI

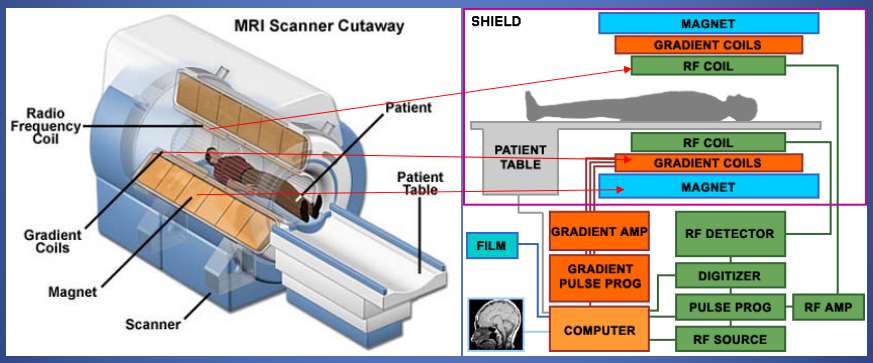
Key Factors Affects the Characteristics of MR Images

- MRI System
  - B0 (uniformity, stability)
  - B1 (gradients linearity, stability)
  - Coils (sensitivity, stability)
  - Artifacts (due to environment)
- Pulse Sequences
  - Various types of sequences (also affected by hardware)
- Analysis Tools
  - Models, algorithms, software bugs etc.

Reviews of MRI Basics Relevant to Clinical Trials

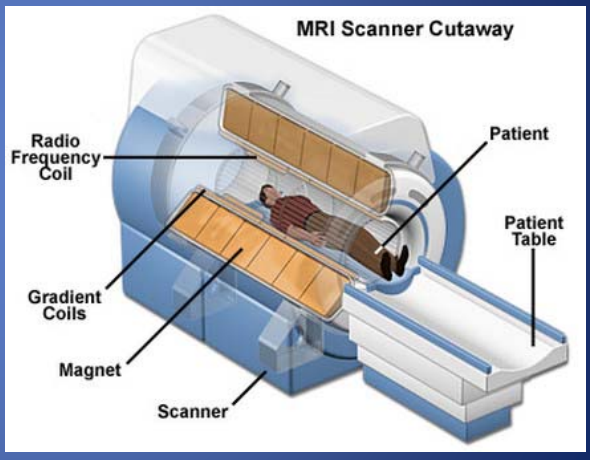
1. MRI hardware/system components
2. MRI sequences
3. QA procedures

MRI System Diagram



Key Elements of MR Image Formation

1. Place nuclear spins in a strong magnetic field (Magnet Bore)
2. Deposit energy to these spins (by means of a "resonant" RF pulses)
3. Measure the relaxation of these spins (or record the "echo" signal) in combination of gradients
   - Steps 2 and 3 are obtained using one or more RF emit and receiving coils
   - Steps 2 and 3 are done in the presence of magnetic field gradients
4. Reconstruct the images using Fourier transforms (using computer)



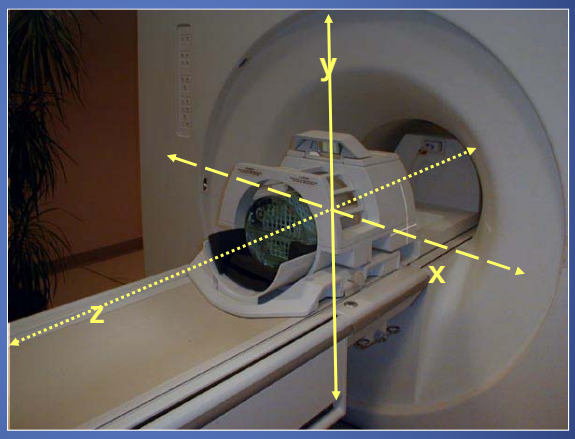
Spatial Axis Definition in MRI

Z - slice selection

X - frequency-encoded

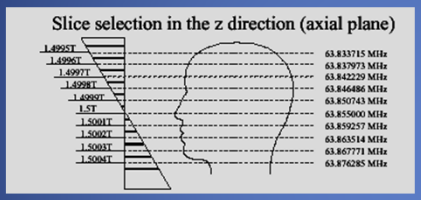
Y - phase-encoded

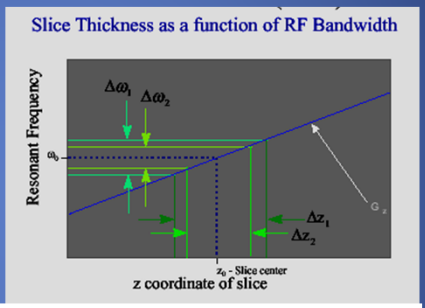
Unlike CT, MR Images can be acquired at any oblique direction!!!



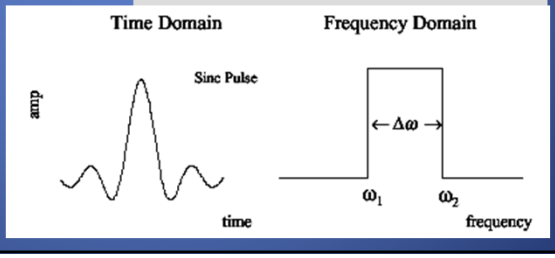
Note: The slice, frequency and phase encoding may be on any axis!!!

Slice Selection: Z axis-encoding

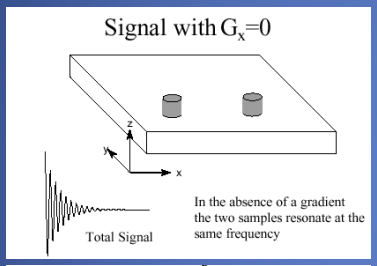


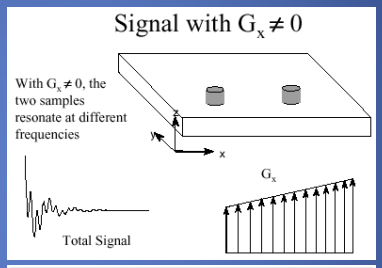


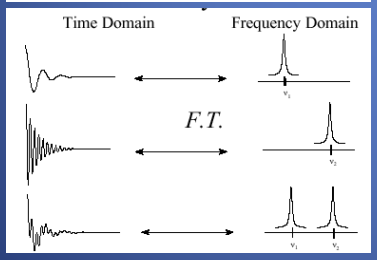
Band-limited Radiofrequency pulse



Frequency encoding: How does it work?







MRI Signal Intensity is Dependent On Both

Intrinsic Parameters:

- Proton Density
- Longitudinal Relaxation (T_1)
- Transverse Relaxation (T_2)
- Motion (flow)
- Susceptibility

Pulse Sequence Parameters

- Flip Angle
- TR (TI)
- TE
- Gradient Moment
- K-space Trajectory

Relative Contrast/Signal Intensities Depends on Pulse Sequence Parameters too!

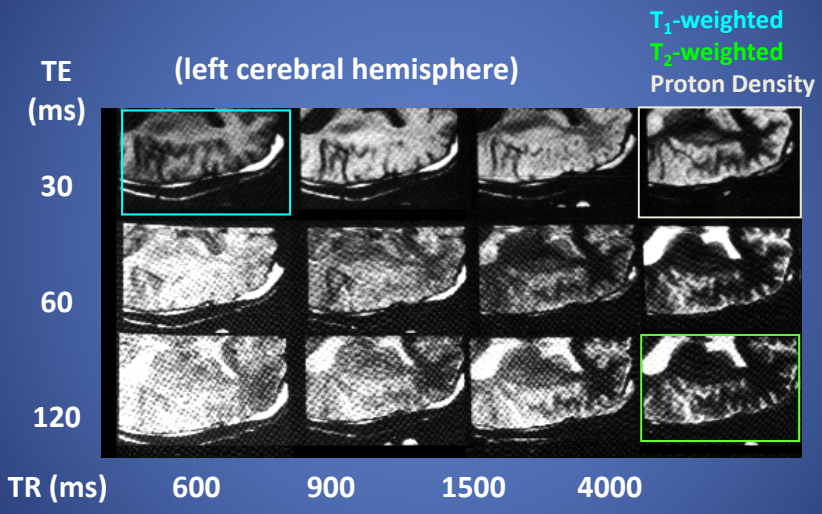
TE = 30
TR = 315

TE = 30
TR = 2000

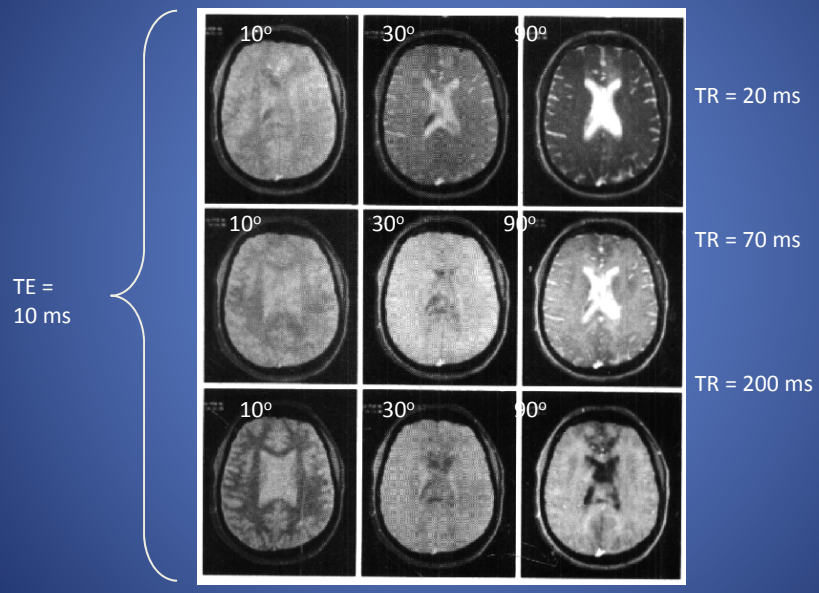
TE = 90
TR = 2000

TE = 240
TR = 2000

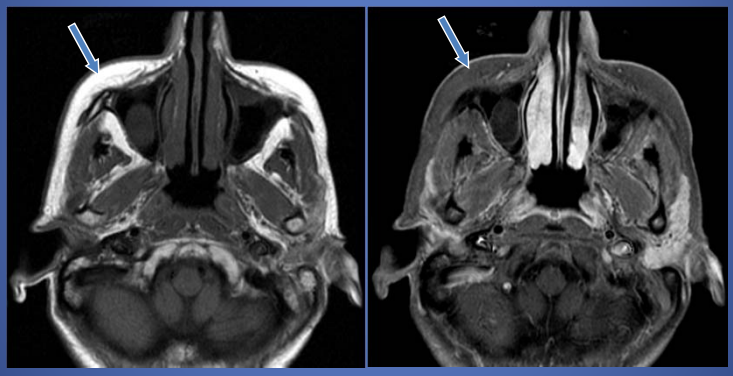
Relaxation and Relative Tissue Contrast



Partial Flip Angle Images of the Brain

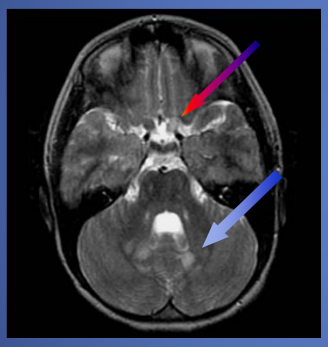


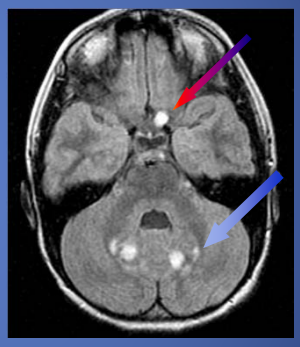
Fat Suppression



T1W images without (left) and with (right) fat suppression.

FLAIR Imaging

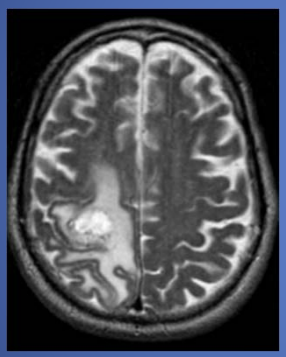




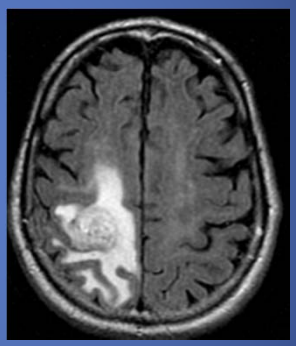
- **T2W-FSE**
- TE/TR = 98/3500ms, 5/1.5mm, ET:8 (split)
- 256x224, 1 NEX, 20x20 cm FOV, 3:23

FLAIR
TI/TE/TR = 2200/147/10000ms, 5/1.5mm
256x160, 1 NEX, 20x20cm FOV, 3:40

FLAIR Imaging



T2 FSE

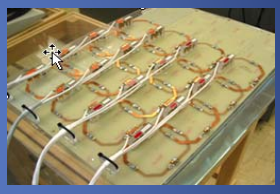


T2 FLAIR

Notice the suppression of CSF & the enhancement of contrast

Coils (RF Signal Antenna/Detector)

- Classification based on function: Transmit, Receive, Transmit-Receive
- Coil Classification based on geometry & specialty: Volume coil, Surface coil, Phased-array coil, Parallel-Imaging-Optimized PA coil
- Sensitivity and coverage are the key specs



GP Coil

Knee Coil

12 element Torso Array

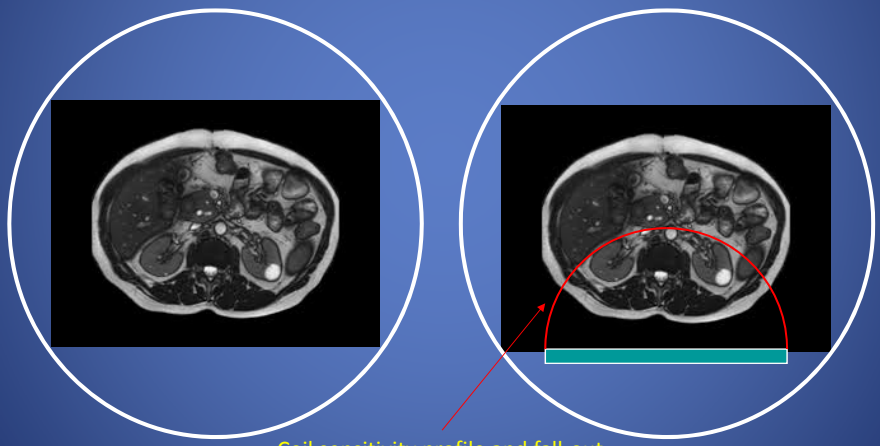
8 ch HR Brain

32 element PV Array

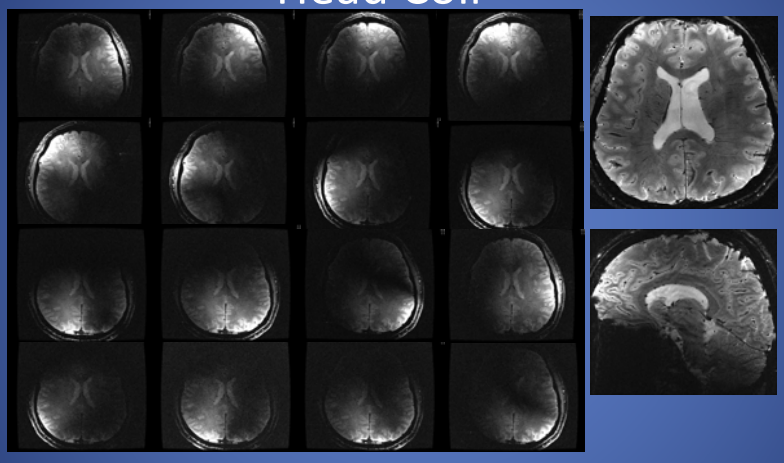
Spatial-Dependence of MRI Signal: Volume vs. Surface Coils

- ***Volume coils***
  - provide homogeneous transmission of B_1 fields
  - yield excellent image uniformity
  - BUT, receive patient noise from entire volume of tissue in the active region of the coil and signal from a small volume
- ***Surface coils***
  - provide very poor homogeneity of transmitted B_1 fields
  - yield highly variable image intensity
  - BUT, have very high SNR for superficial tissues since the volume of tissue from which noise is acquired is much smaller than in volume coils

Volume vs Surface Coils

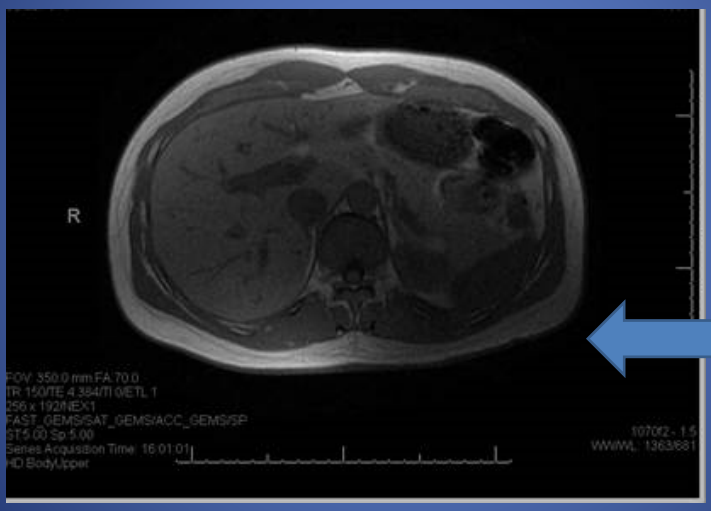


Effect of Coils on Images: Images from 7T 16-ch Head Coil



Notice the un-even signals due to elements of surface coils, even though the composite image intensities are relatively uniform!

Coils Check


R
FOV 350.0 mm FA 70.0
TR 150/TE 4.384/TI 0/ETL 1
256 x 192/NEX1
FAST_GEMS/SAT_GEMS/ACC_GEMS/SP
ST 5.00 Sp 5.00
Series Acquisition Time: 16:01:01
HD BodyUpper
1070f2 - 1.5
WW/WL: 1363/681

Basic Anatomical Imaging Sequences Types

- Spin Echo
- Gradient Echo
- Inversion Recovery

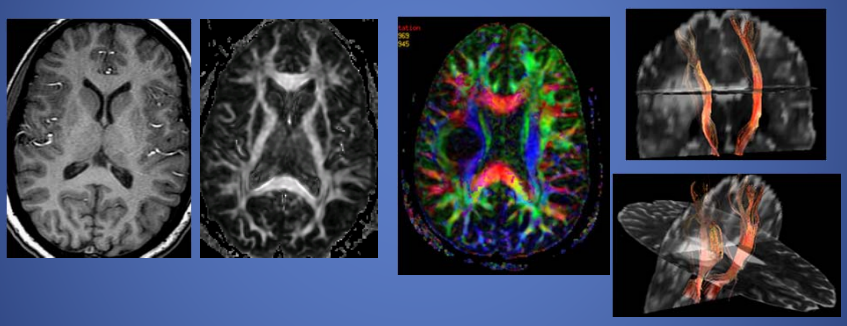
- Pre-sequence

- Functional Imaging Sequences

List of Functional MRI Techniques

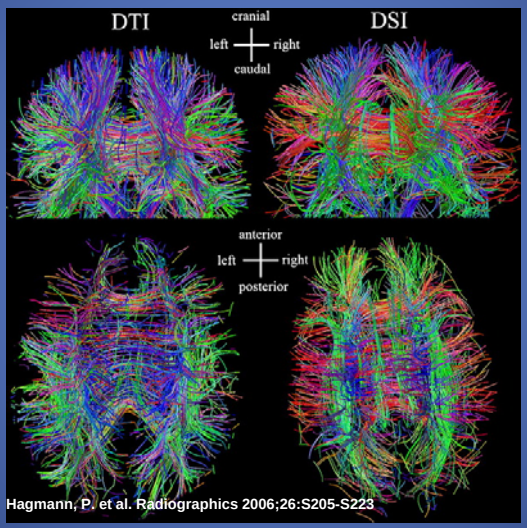
- Diffusion MRI
  - DWI
  - DTI
- BOLD fMRI
- Perfusion
  - DSC
  - DCE
  - ASL
- MR Spectroscopy
- CEST:

Diffusion Tensor Imaging (DTI)



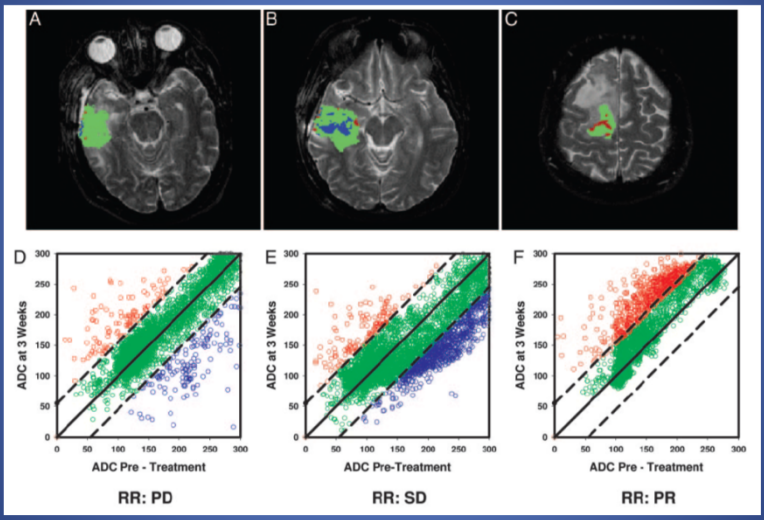
For Human Brain…..

Comparison of fiber tractography based on diffusion tensor imaging (DTI) versus fiber tractography based on diffusion spectrum imaging (DSI) in two healthy volunteers



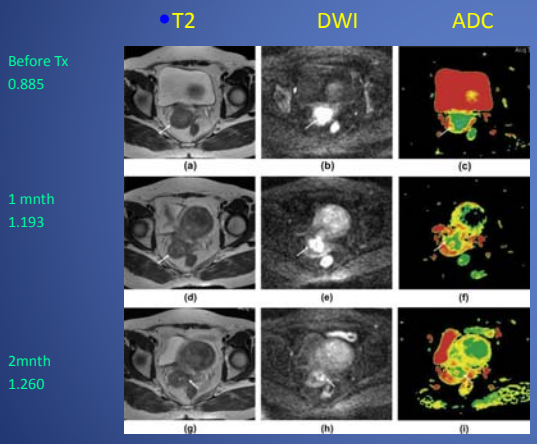
Hagmann, P. et al. Radiographics 2006;26:S205-S223

Using ADC Temporal Changes as a Early Imaging Biomarker

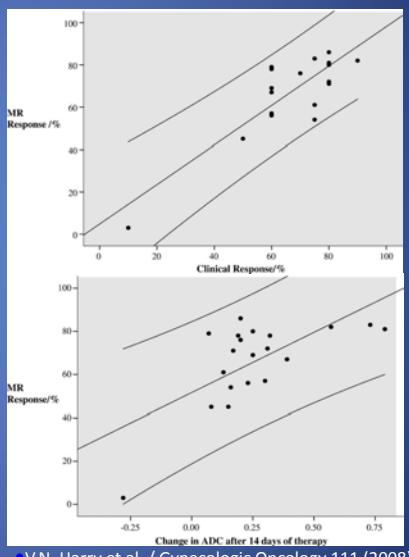


Diffusion map is an earlier predictor (at 3 weeks) than the conventional McDonald radiological response criteria.
D Hamstra J Clin Oncology 26:3387, 2008

DWI in Response Assessment

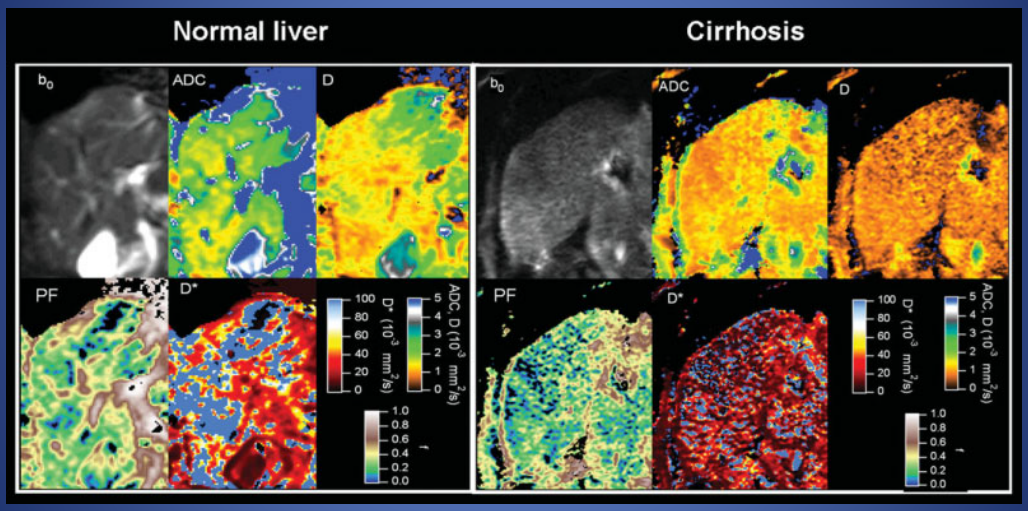


Y Liu et al Clinical Radiology (2009) 64



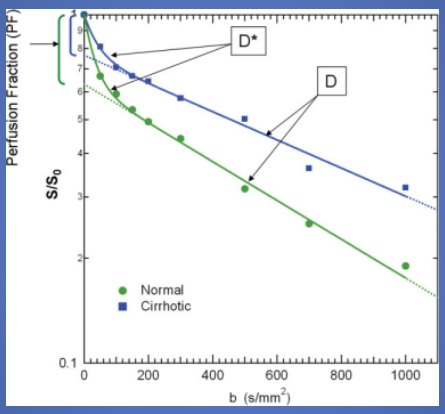
V.N. Harry et al. / Gynecologic Oncology 111 (2008)

IVIM DWI of Normal and Cirrhotic Liver



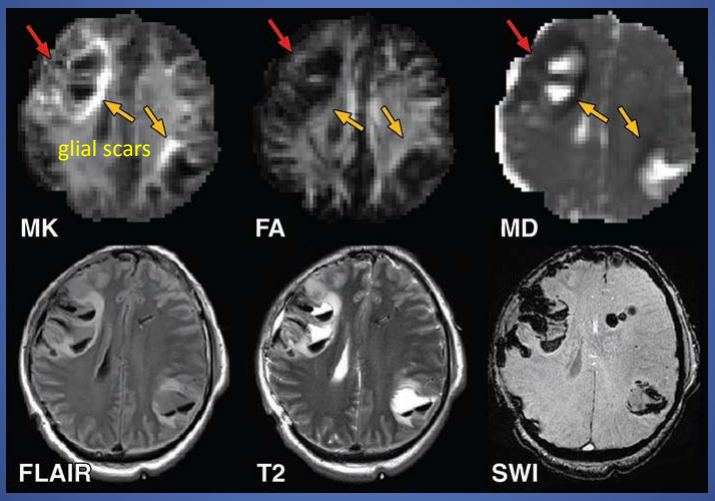
J. Magn. Reson. Imaging 2010;31:589–600

Perfusion Fraction (PF)



$$S/S_{b=0} = (1-PF)*\exp(-b*D) + PF*\exp(-b*(D+D_{PF}))$$

DKI of Traumatic Brain Injury

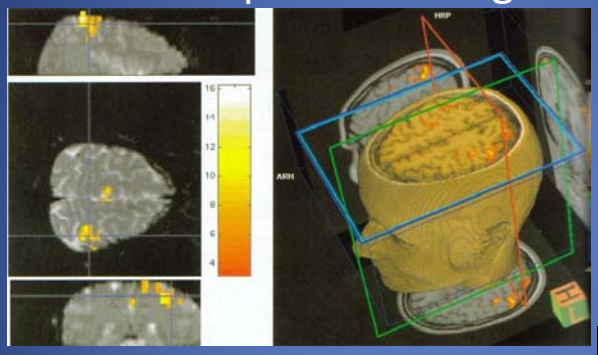


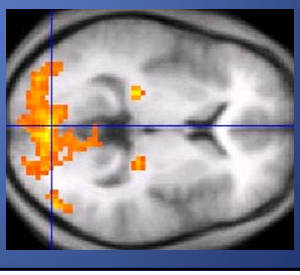
Steven et al *AJR* 2014; 202:W26–W33

Courtesy of Chen Lin, PhD DABR 3/15

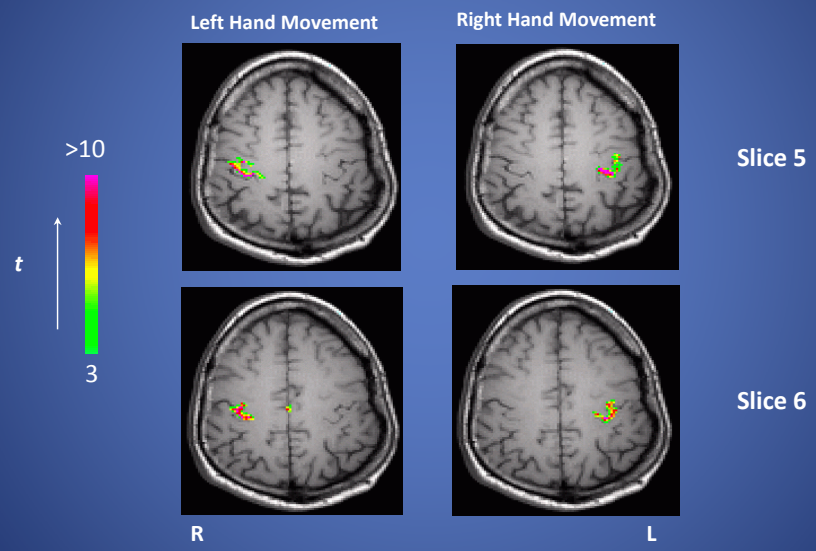
BOLD based functional MRI

Sample fMRI Images



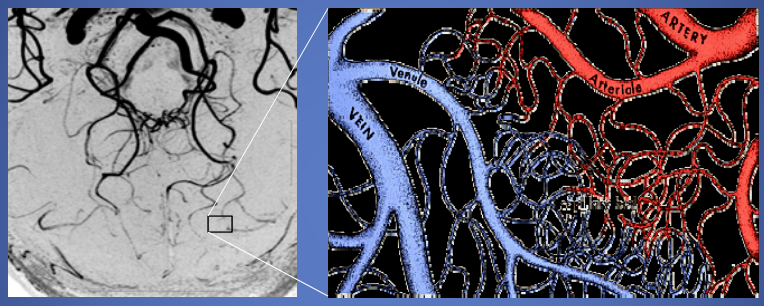


BOLD-fMRI in human



Perfusion based functional MRI

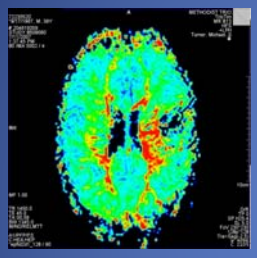
Perfusion



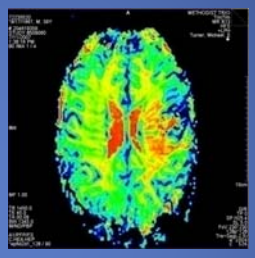
- Blood via perfusion delivers oxygen and nutrients to the cells
- Perfusion affected by pathological and physiological conditions, such as tumor angio-genesis, stroke and infarct, vascular wall changes.

Courtesy of Chen Lin, PhD

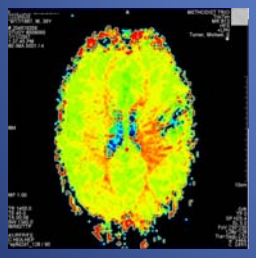
DSC Perfusion Maps



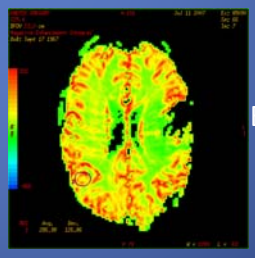
Relative Mean Transit Time (relMTT)



Percent Baseline at Peak (PBP)

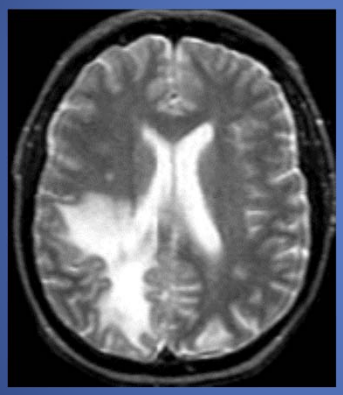


Time to Peak (TTP)

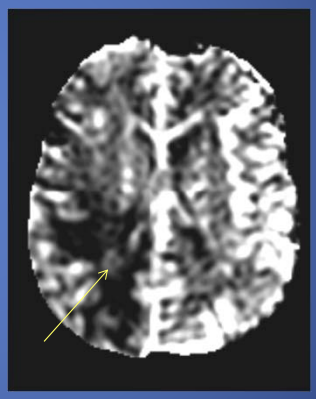


Negative Enhancement Integral (NEI)

Tumor versus Radiation Necrosis



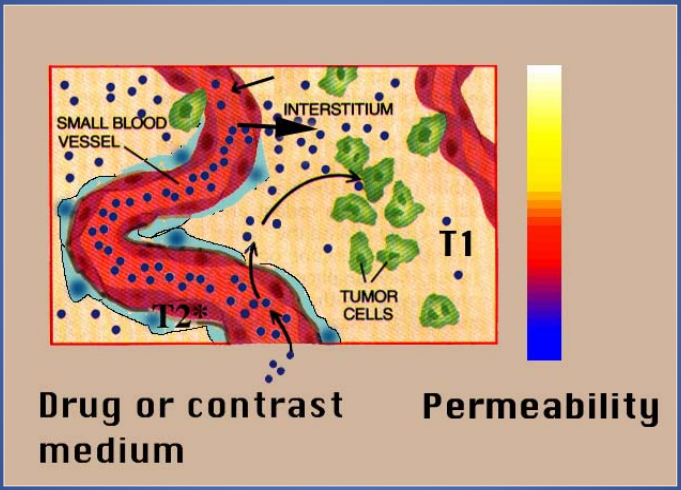
T2w



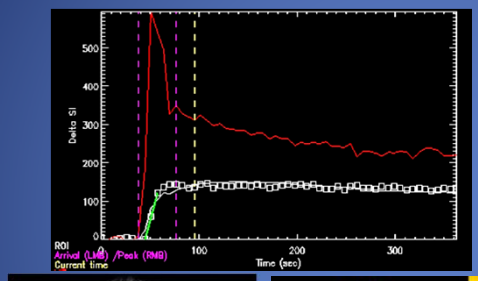
rCBV

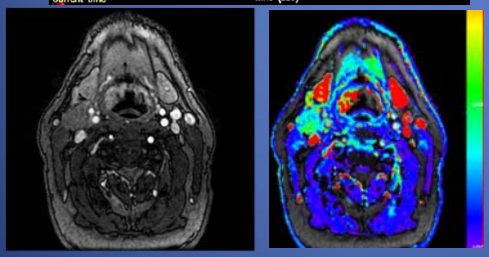
DCE (Dynamic Contrast Enhancement)

Leakage and Permeability



Dynamic Contrast Enhanced in H&N Cancer





- 3.0 T 3D FSPGR
- 20 3.5-mm sections every 4.5 s
- 0.86-mm in-plane resolution

- K^{trans} Parametric Map

10/22/2007

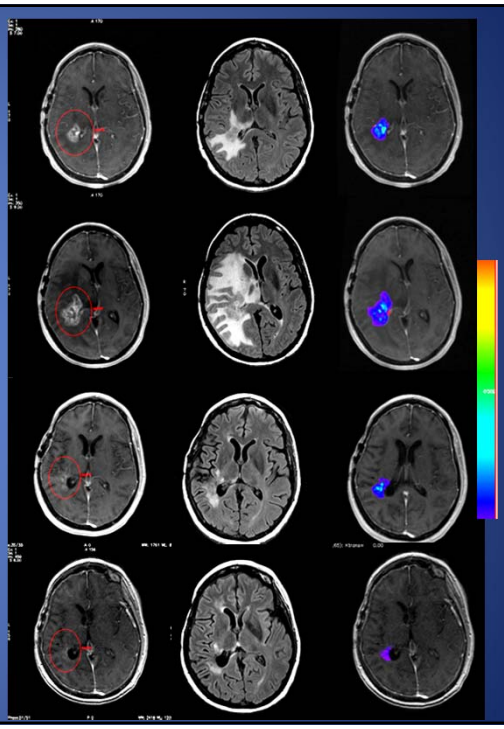
11/30/2007

Treatment :TMZ + XRT ± Bevacizumab

Images: T1+Gd & T_2FLAIR & K^{trans}

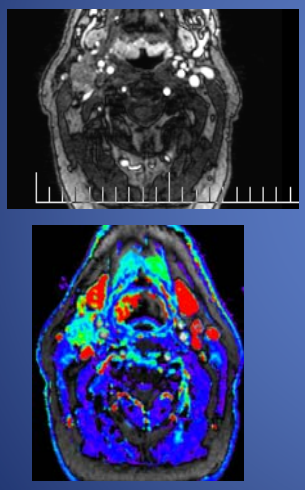
1/11/2008

2/20/2008



3T DCE-MRI – H&N

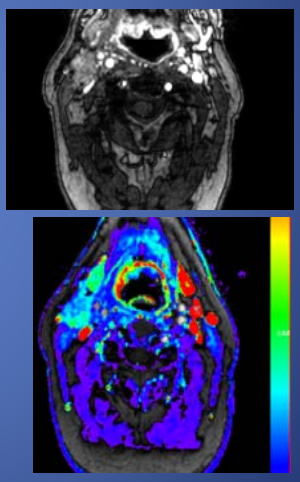
8/02/07



T1 N2 SCC Tongue Base

IMRT Treatment

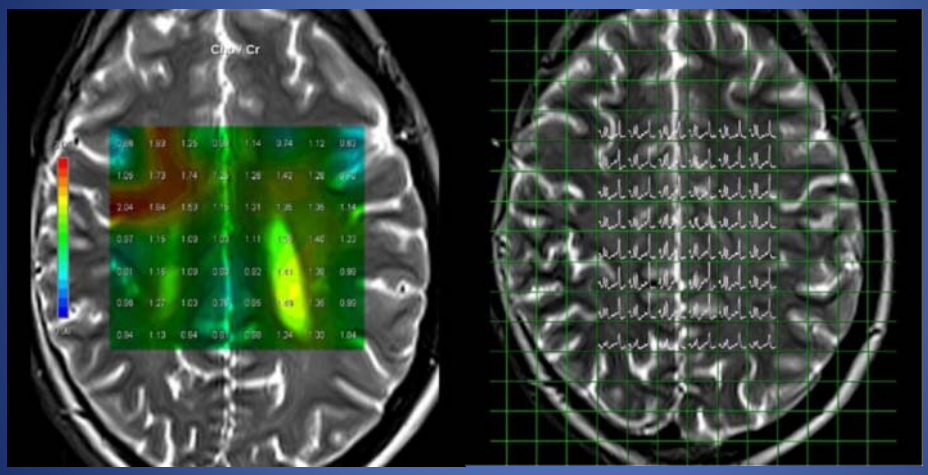
8/27/07



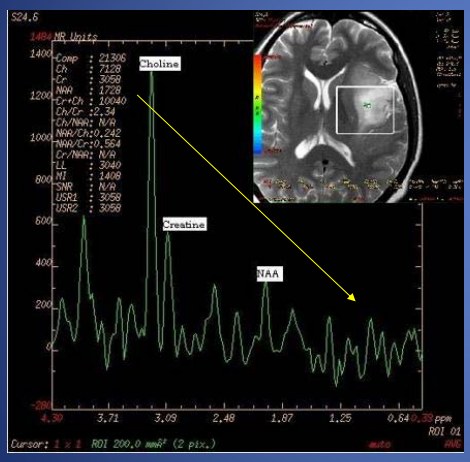
Courtesy of Dave Fuller

MR Spectroscopy

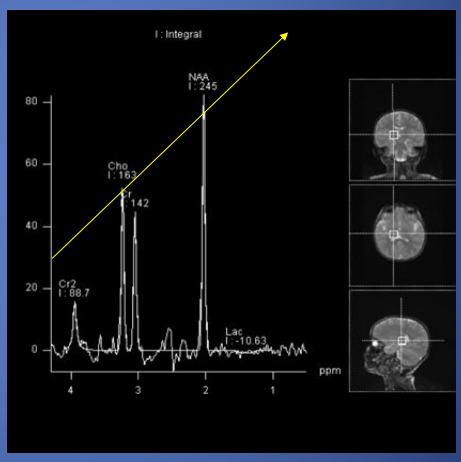
MR Spectroscopy (Chemical Shift Imaging)



MRS of Brain

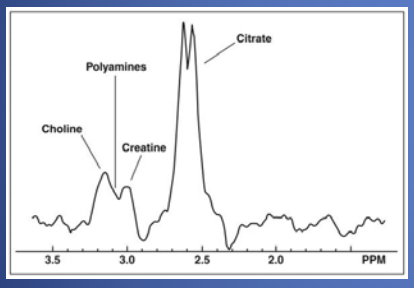


Glioma



Normal 2 yr old

MRS Prostate



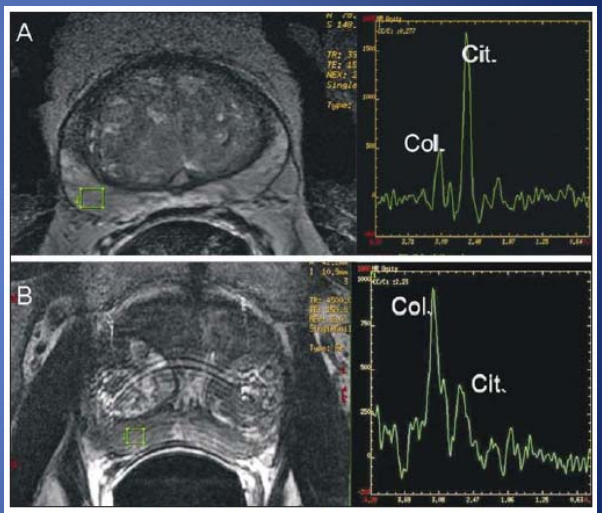


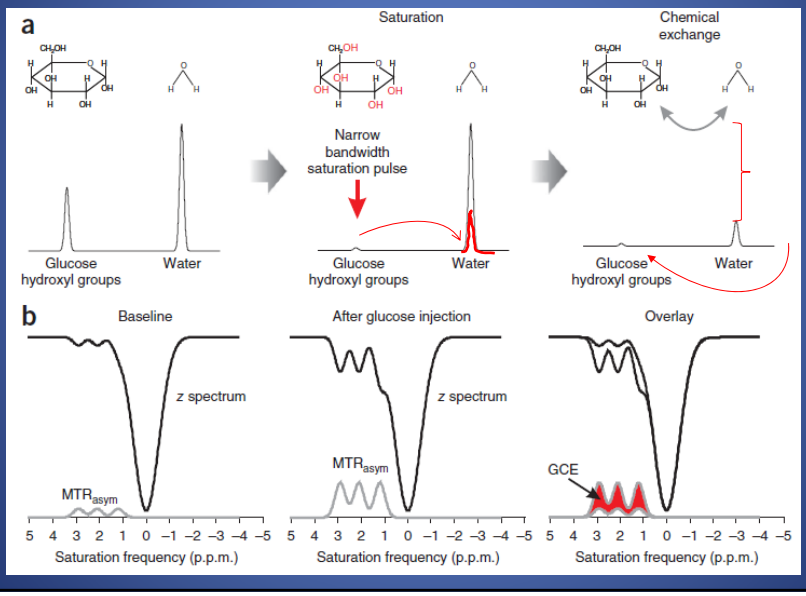
Figure 7. A: Normal peripheral zone, with high signal-intensity on MR axial T2-weighted image, and with a spectral graph demonstrating low choline and high citrate levels **B:** PCa in the peripheral region, with low signal-intensity on MR axial T2-weighted image, and spectral graph showing high choline and low citrate levels.

CEST MRI

(Chemical Exchange Saturation Transfer)

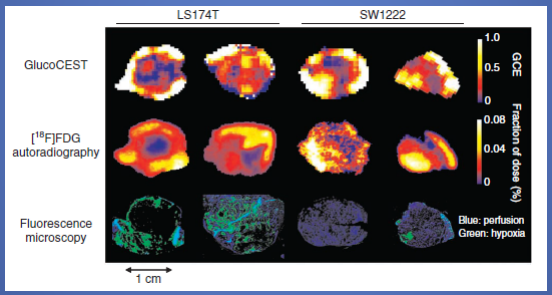
An MR based Imaging Tool of Metabolism

CEST: How?

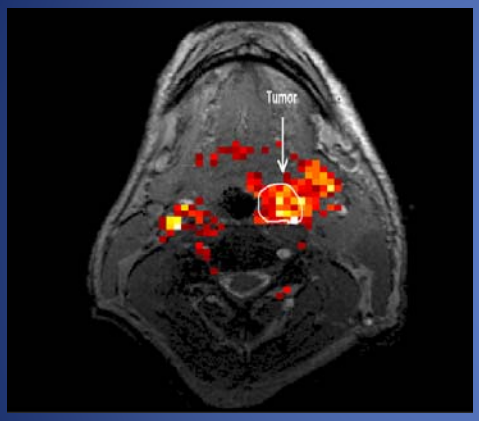


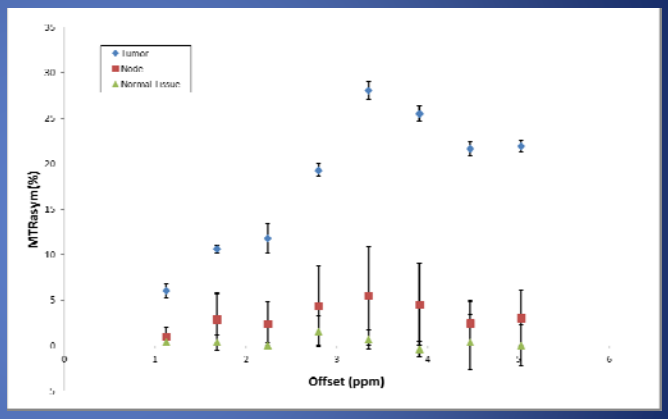
Measurable! Thus indirectly measure the glucose in tissue

CEST Imaging of Glucose Uptake



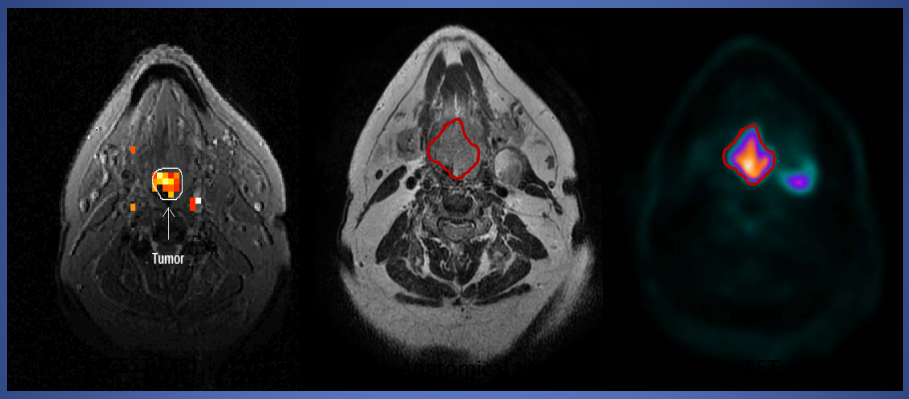
Results: CEST Signal in Tumor Different from Normal Tissue





The color map of MTR overlaid over one of the CEST images (left) and the measured MTR of the tumor, involved node and normal tissue (right). MTR in tumor region is clearly higher than that of the surrounding normal area, consistent with previous findings in brain tumor patients.

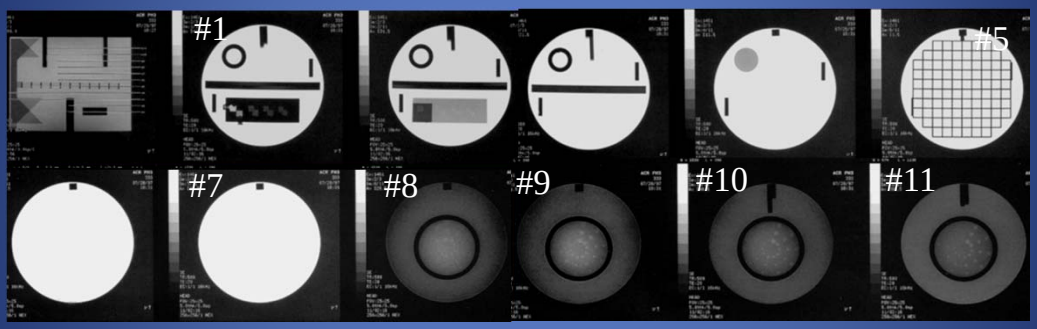
Comparison of glucoCEST with PET



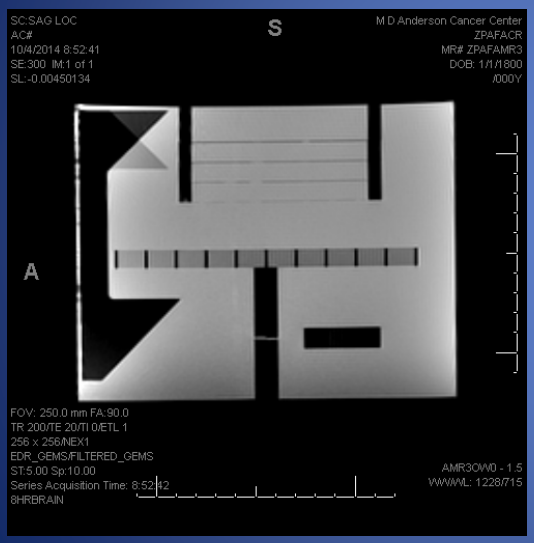
Color map of the CEST signal change after injection of unlabeled glucose overlaid over a CEST image(left) and the corresponding anatomical image (middle) as well as the PET image (right). Similar to PET, glucoCEST imaging detected higher uptake of glucose in tumor. This shows the potential of ***CEST imaging as a possible alternative metabolic imaging tool to PET***, without the use of the expensive and radioactive isotope.

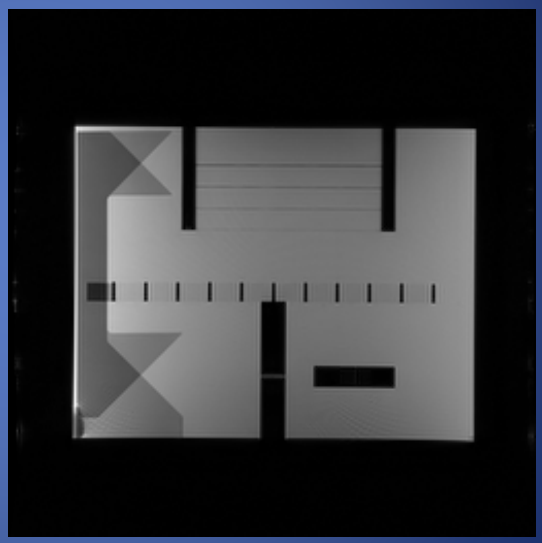
MRI QA for Clinical Trials

ACR Phantom Imaging

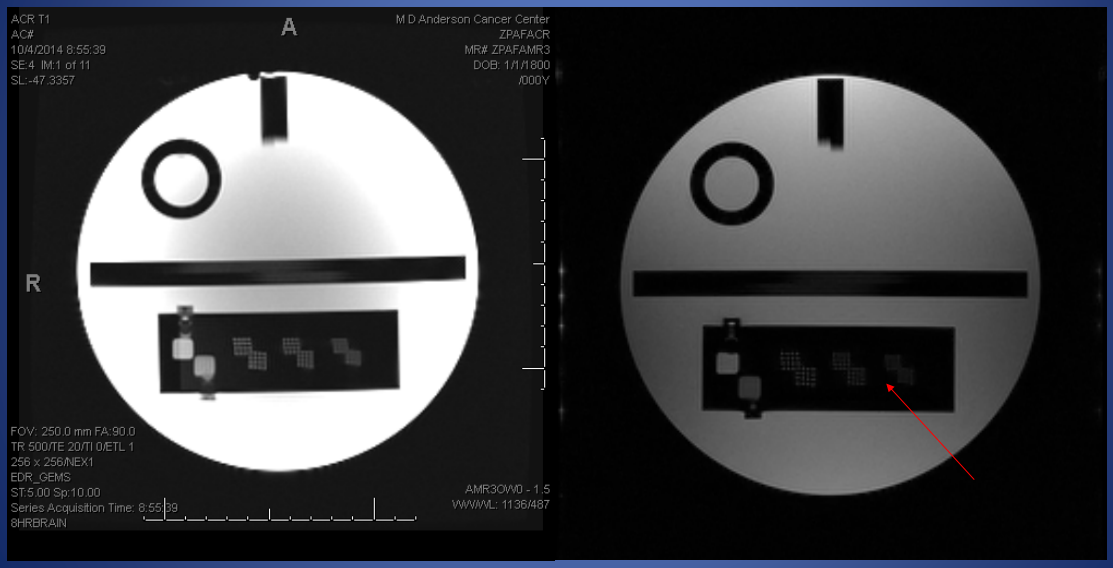


Saggital View

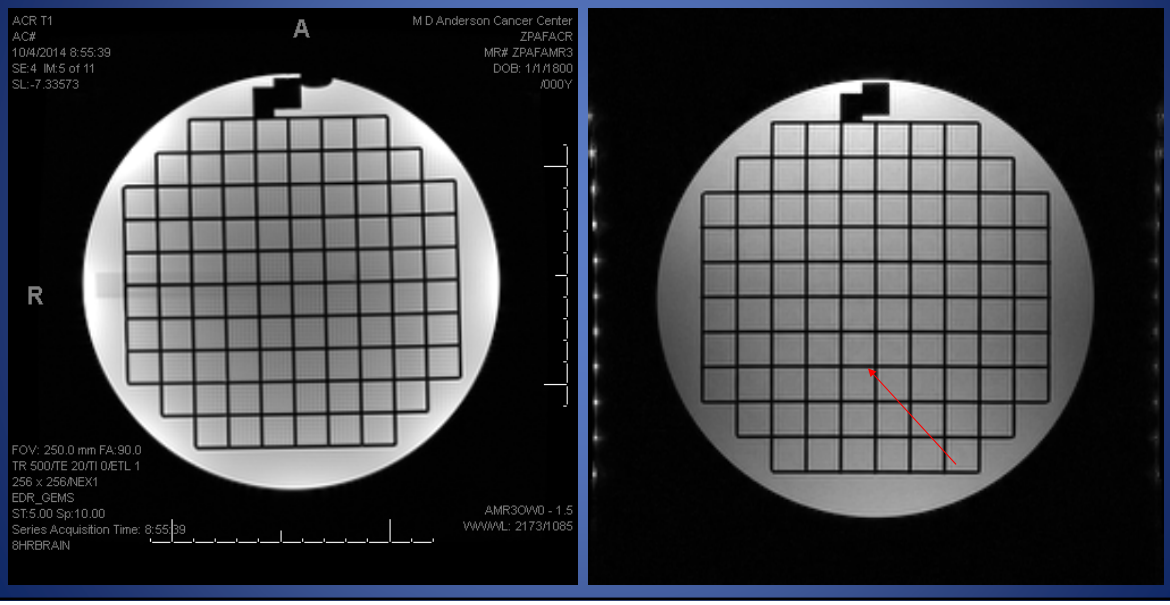




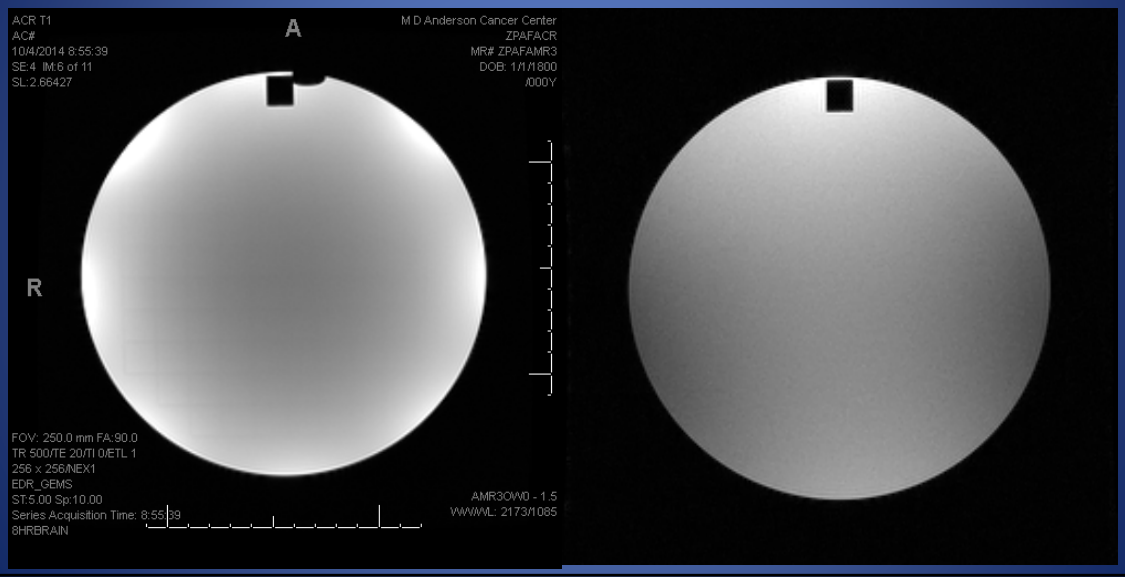
Axial T1 slice #1



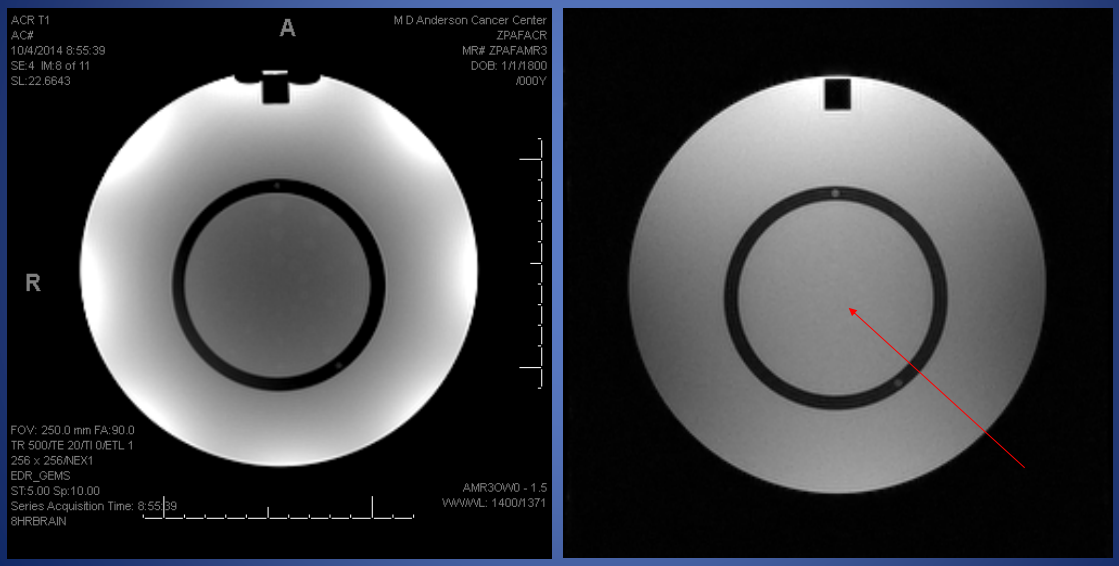
Axial T1 slice #5



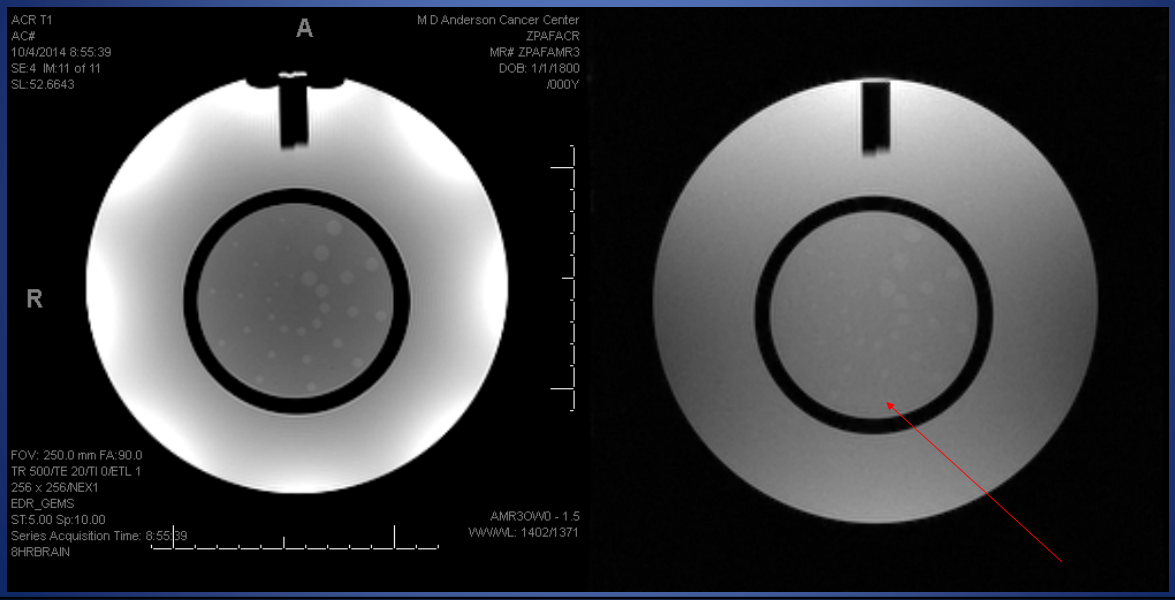
Axial T1 slice #6



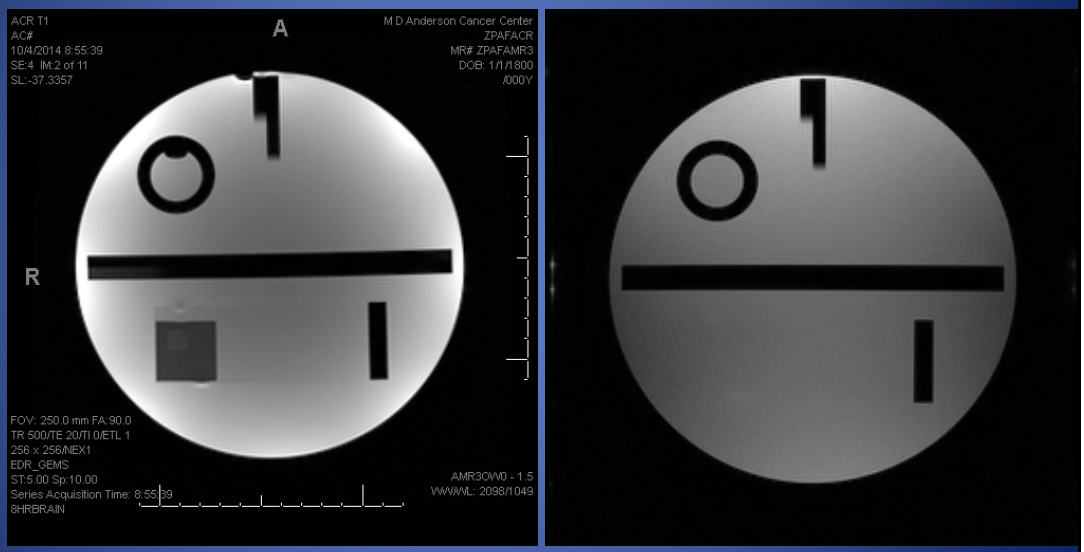
Axial T1-slice #8 Fewer Low-contrast objects



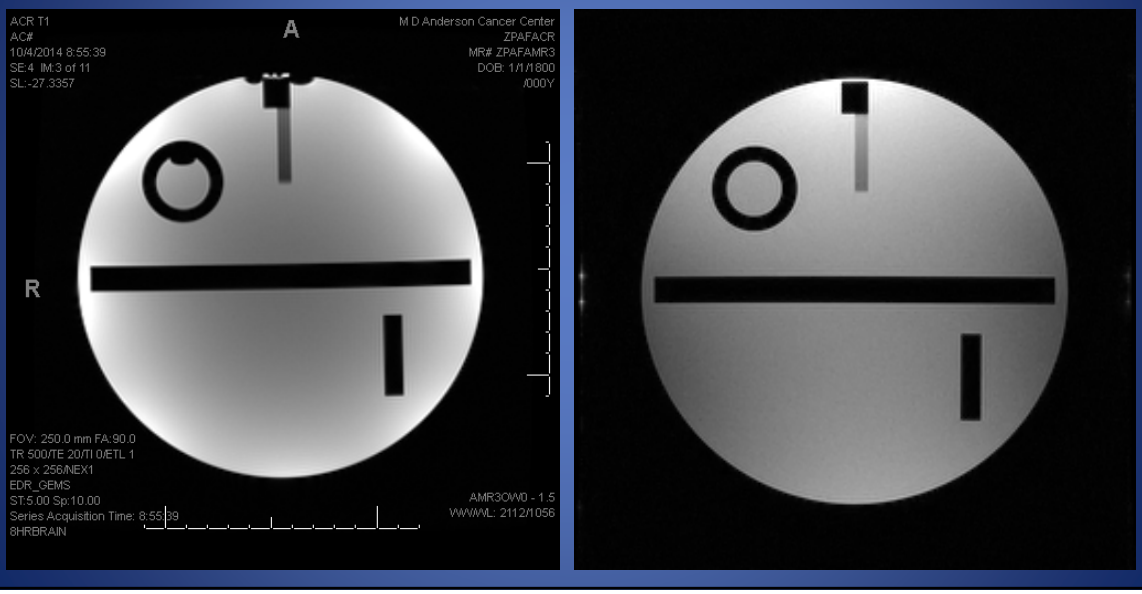
Axial T1-slice #11



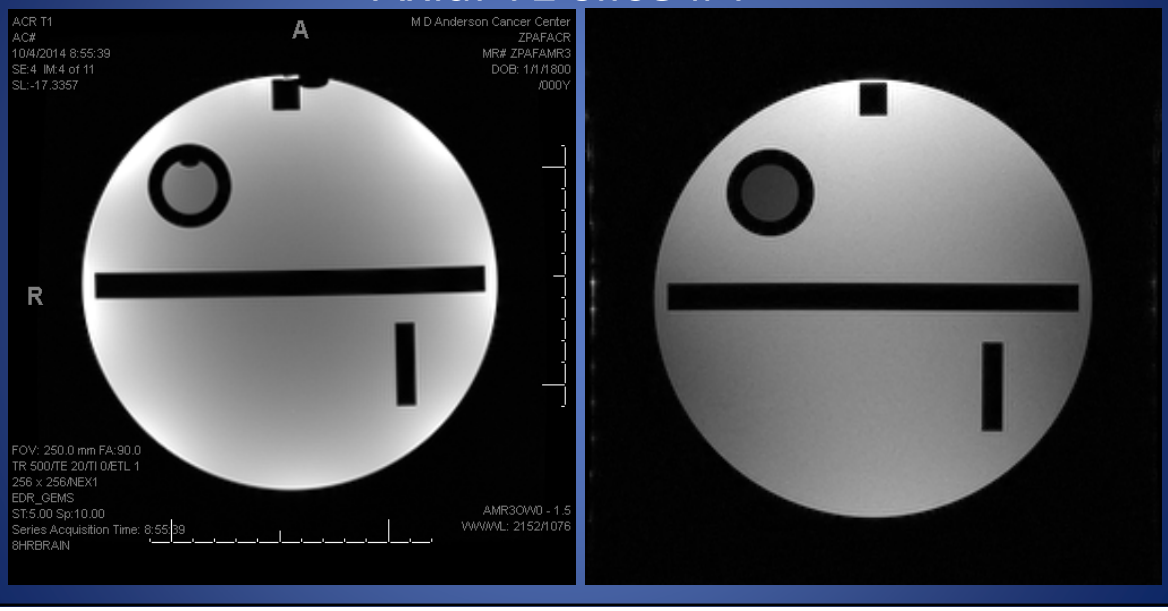
Axial T1 Slice #2



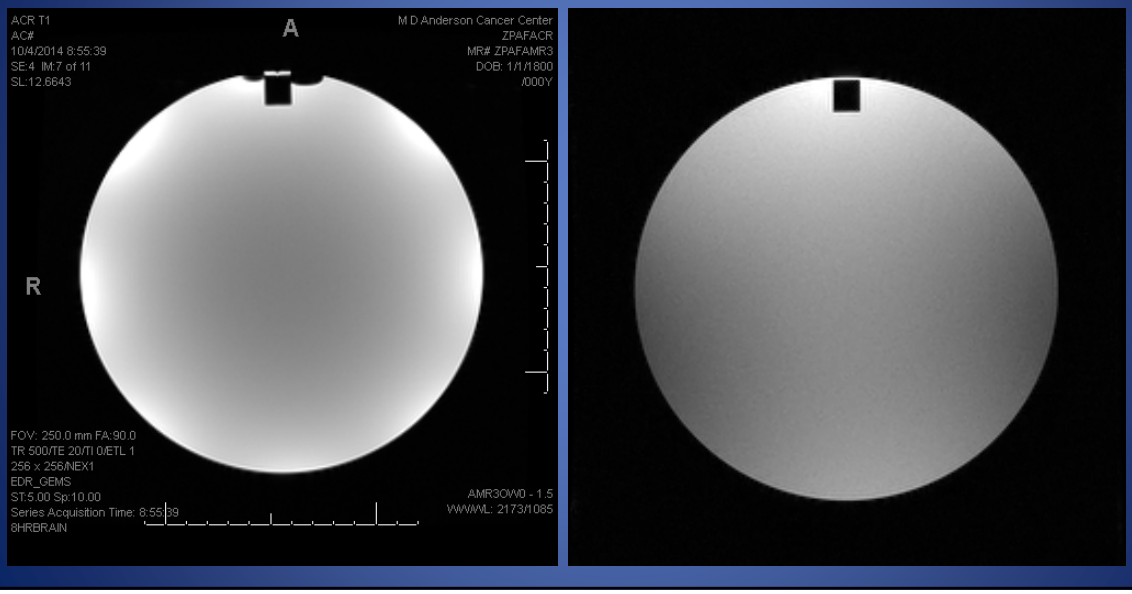
Axial T1 slice #3



Axial T1 slice #4

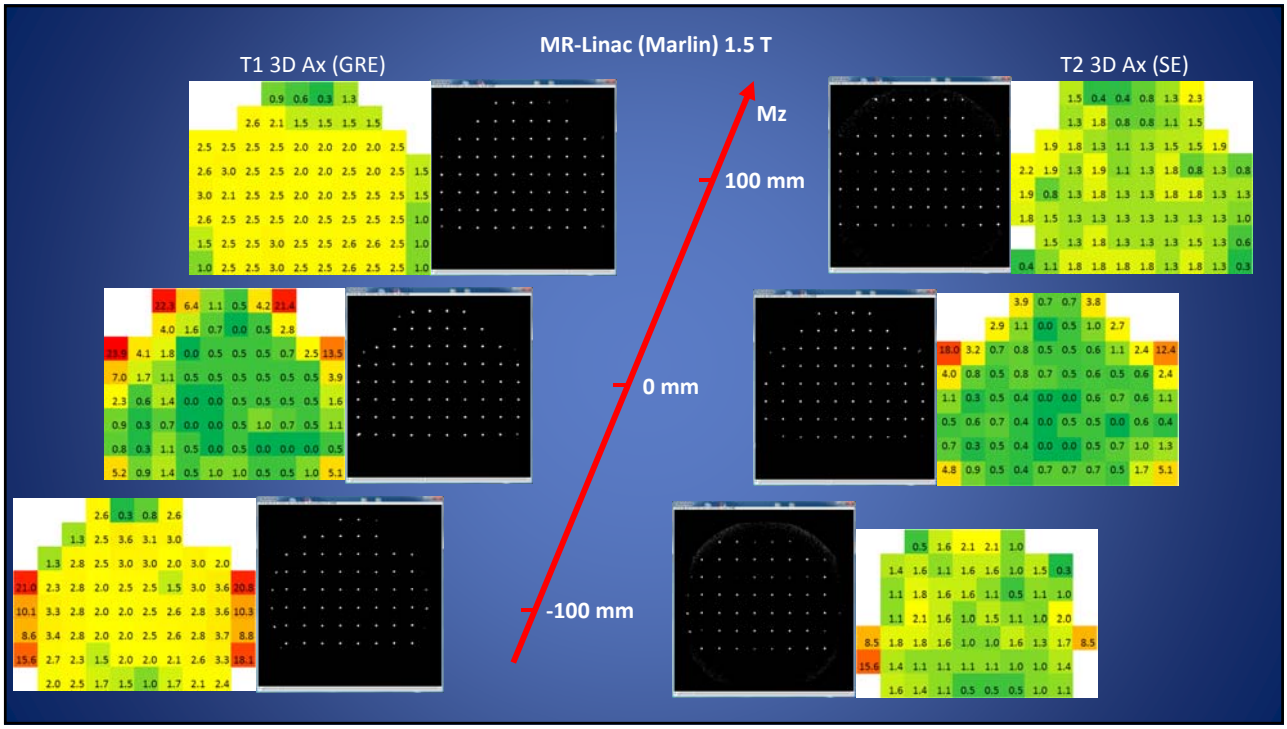


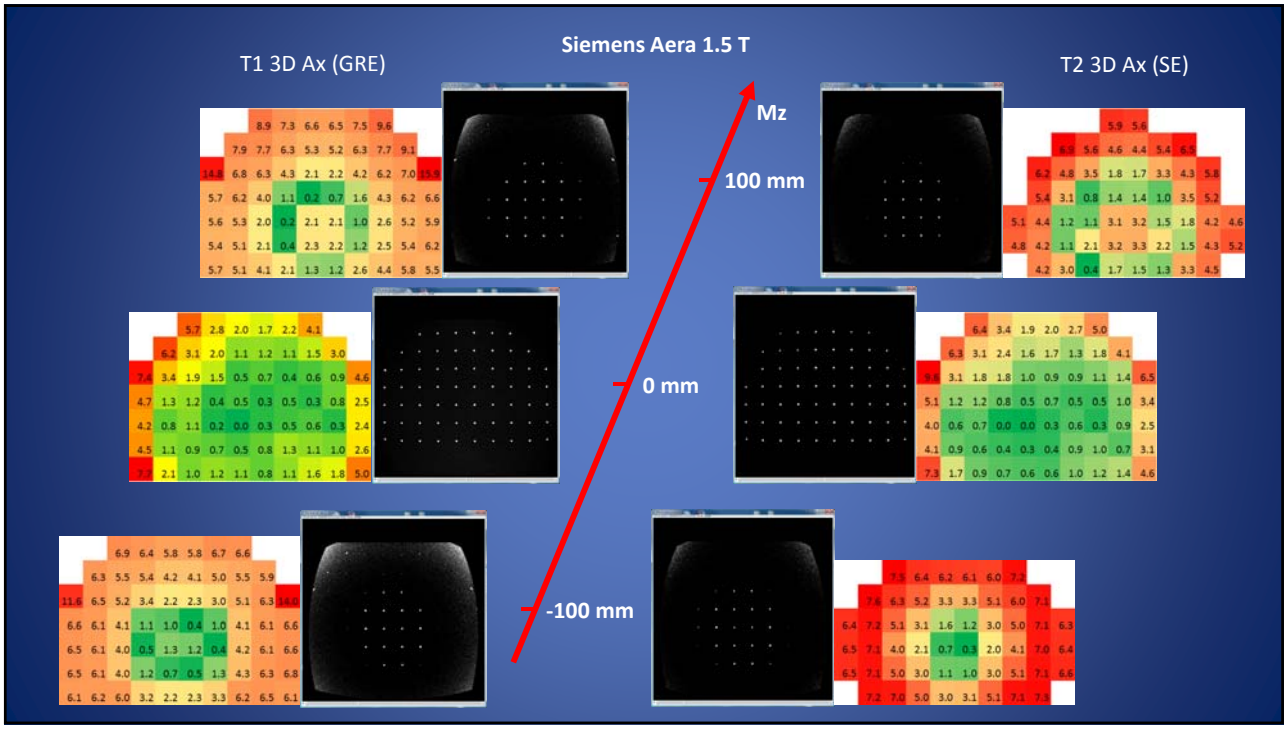
Axial T1 slice #7



MR Simulation Parameters

Philips Marlin 1.5 T		Siemens Aera 1.5 T	
T1 3D Ax (GRE)	T2 3D Ax (SE)	T1 3D Ax (GRE)	T2 3D Ax(SE)
FOV=500mm; Thk=2mm; Acq matrix=512*512; Rec matrix=1024*1024			
TR/TE=11/4.6ms	TR/TE=1535/172ms	TR/TE=7.4/3.6ms	TR/TE=1600/94ms
FA=30 deg	FA=90 deg	FA=10 deg	FA=170 deg
rBW= 191 Hz/Pixel	rBW= 394 Hz/Pixel	rBW=250 Hz/Pixel	rBW=575 Hz/Pixel
	ETL=61		ETL=61


MR-Linac (Marlin) 1.5 T
T1 3D Ax (GRE)
T2 3D Ax (SE)
Mz
100 mm
0 mm
-100 mm


Siemens Aera 1.5 T
T1 3D Ax (GRE)
T2 3D Ax (SE)
Mz
100 mm
0 mm
-100 mm

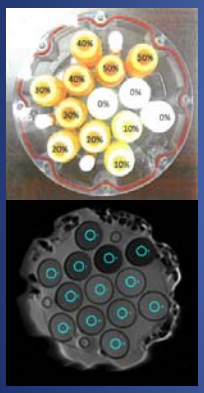
Phantom for Quantitative Imaging

Quantitative MRI – Diffusion Phantom (QIBA DWI)

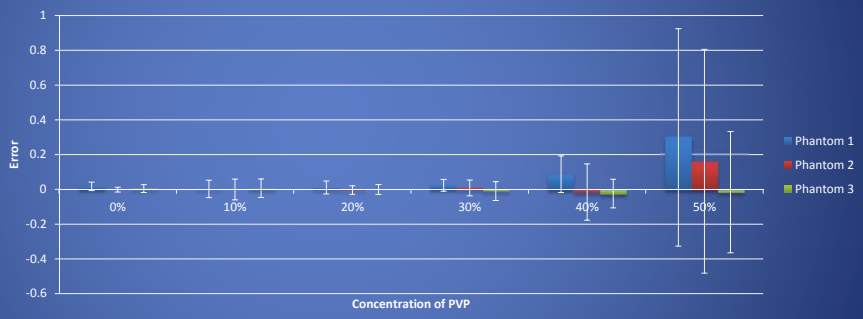
- High *Precision* Devices, Inc, Boulder, CO
- Diameter: 194 mm
- 13 vials filled with aqueous solutions of polymer polyvinylpyrrolidone (PVP) from 0 to 50 % w/w
- Measurements taken with vials in ice bath at 0°C

http://hpd-online.com/diffusion-phantom.php

QIBA DWI Phantom – Multiple Phantom Comparison

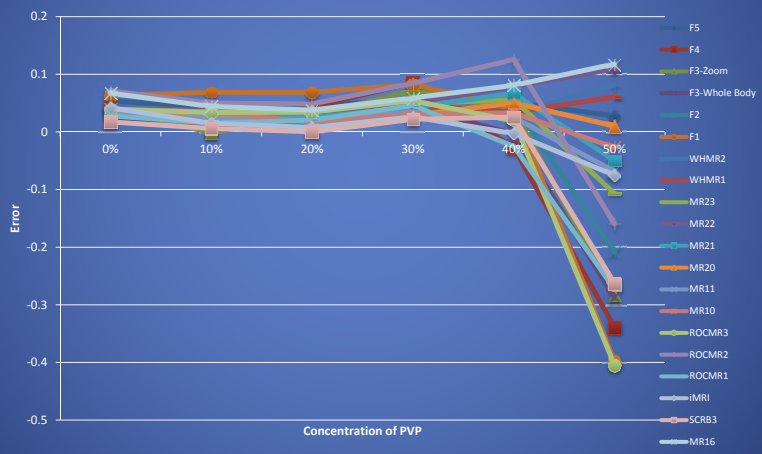


ROI placement



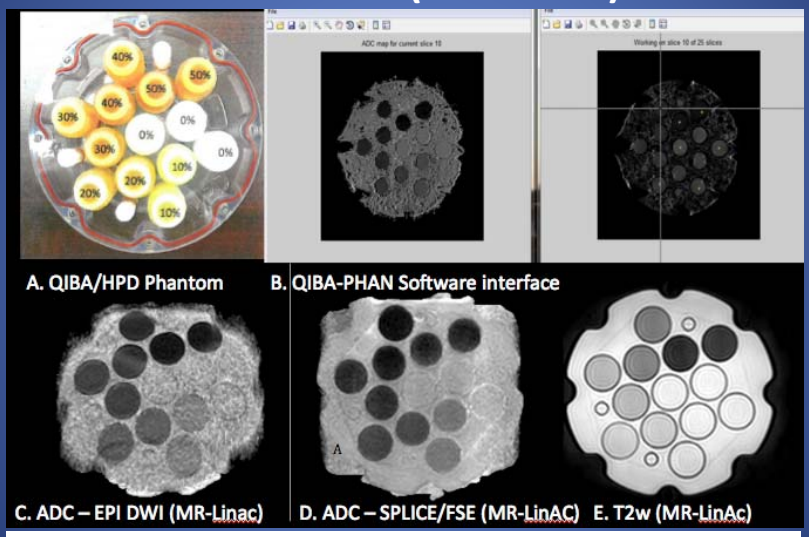
Error in measured ADC values in three different diffusion phantoms across the PVP concentrations in the phantom

QIBA DWI Phantom – Multiple MRI System QA

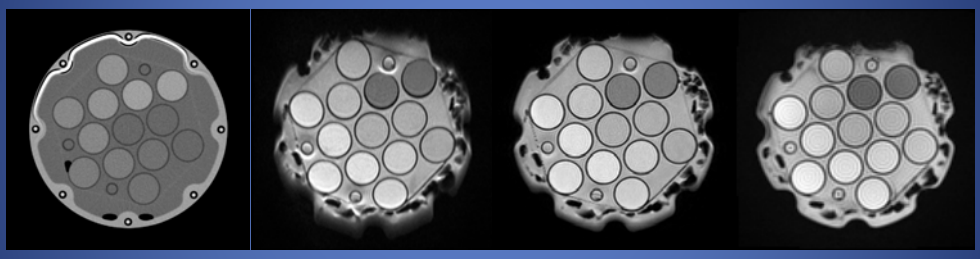


Error in measured ADC values in 20 different MR systems across the PVP concentration in the phantom

QIBA DWI Phantom – MRI System and Sequence Evaluation (MR-Linac)

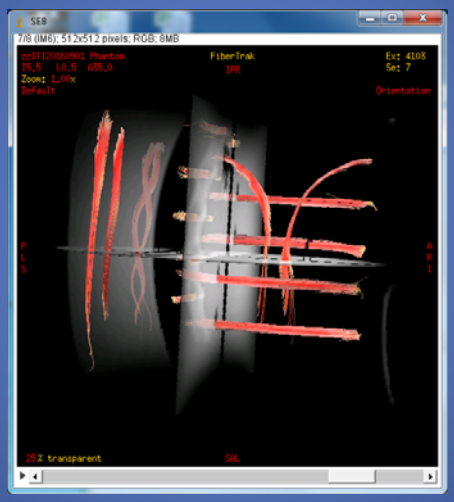


QIBA DWI Phantom – MRI System and Sequence Evaluation (Siemens Aera 1.5 T)



CT | SS-DWI | Resolve-DWI | Blade-DWI

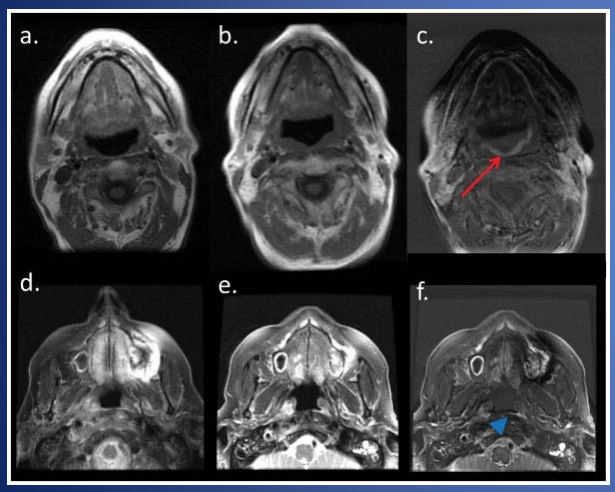
DTI phantom

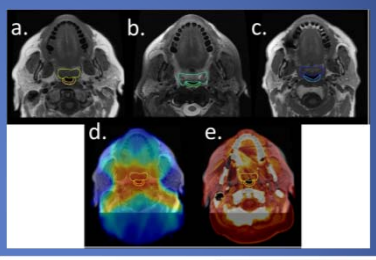


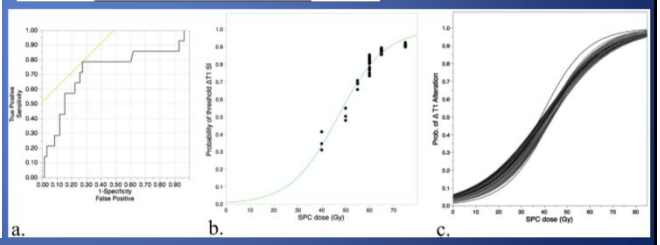
Courtesy of Synaptive Medical Inc., D. Yao, C Chung, D Fuller, et al

Let's not forget the basics: T1/R1, T2/R2 and PD images

T1 and T2 Imaging Useful to Assess Pharyngeal Constrictor Toxicity After Radiation



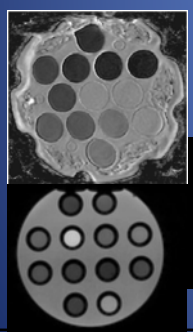


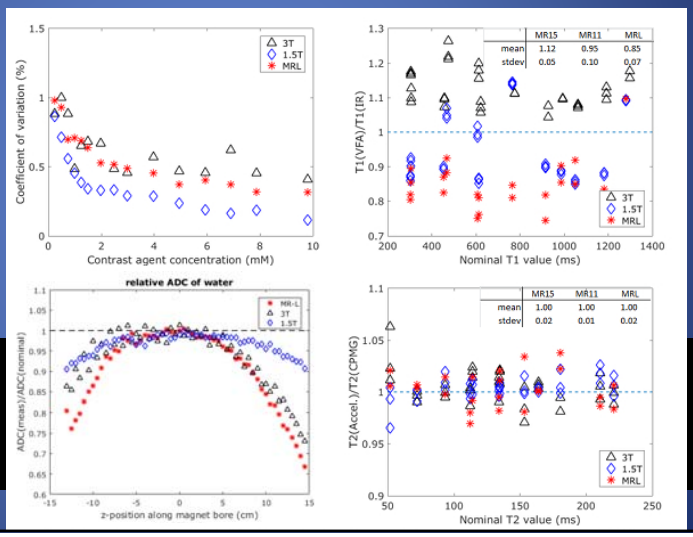


Messer J et al Radiotherapy and Onc. 2016

Imaging marker discovery in the MR-linac

- T1 mapping
- T2 mapping
- ADC (diffusion)
- DCE stability (perfusion)





Summary

- Physicists' role in clinical trials are critical
- MRI in clinical trial should be carefully considered prospectively and holistically as a system, not as a single or multiple isolated components
- Do know forget patient positioning!!!