PRESENTED AT

RSNA 2010

PERSONALIZED MEDICINE:
In Pursuit of Excellence

MRI/MRS Biomarkers

Robert E. Lenkinski, Ph.D.

Disclosure

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GE Healthcare-Research Grant
Aspect MR-Scientific Advisor
Aposense-Scientific Advisor
Brainwatch-Scientific Advisor

I will be discussing “off-label” use of Gadolinium based Contrast agents

The major focus will be on non-neuro applications

Issues-quantitation, relationship to physiology, metabolism

Examples-DCEMRI, ASL, DWI, MRS

Issues

- Quantitation-accuracy, precision, detection limits
- Standardization-acquisition, processing/analysis
- Validation

ADNI, NIHPD, OAI, RSNA-QIBA, ACRIN

Ashton, JMRI 31:279-288 (2010)

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Table 1
Examples of Differences in Basic Terminology Among MRI System Vendors

Sequence or term	Siemens	GE	Philips
Spoiled gradient echo	FLASH	SPGR	T1FFE
Steady state free procession	TrueFISP	FIESTA	Balanced-FFE
Parallel imaging	IPAT	ASSET	SENSE
Repeated measurements	Acquisitions, no. of averages	NEX	NSA
Oversampling in phase	Phase oversampling	No Phase Wrap	Fold over suppression
Half Fourier imaging	Half Fourier	½ NEX, Fractional NEX	Half scan, HS
Partial echo	Asymmetric echo	Fractional echo	Partial echo

Inter-vendor and intra-vendor variability
Software and hardware upgrades

ACR MRI Phantom

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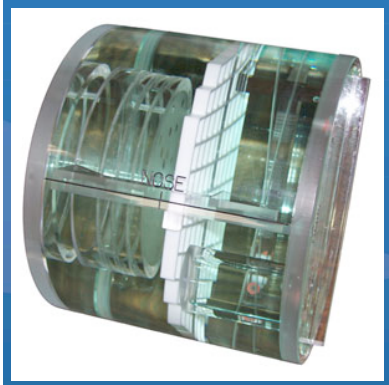
http://www.acr.org/SecondaryMainMenuCategories/ACRStore/FeaturedCategories/QualityandSafety/MagneticResonanceImaging/phantom_test_guidance.aspx



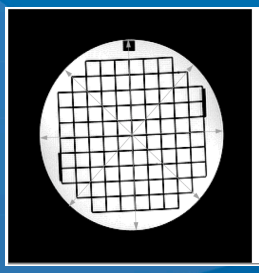


Figure 3.

Image of Slice #5 with array of squares. Grey arrows indicate the positions of the measurements for determinig percent geometric distortion.

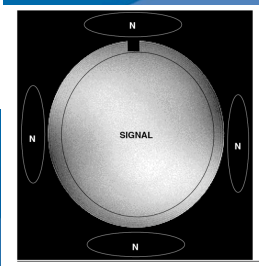


Figure 4.

Image of Slice #7 used for signal-to-noise measurements. Signal is obtained from mean value of large circular ROI. Maximum and minimum signal values should also be obtained from within this ROI. Noise is obtained from the standard deviation of the signal in the background ROI's, depicted by the ellipses marked "N". Noise ROI's should be placed above, below, to the right and to the left of the phantom image.

https://nihpd.crbs.ucsd.edu/nihpd/info/data_access.html

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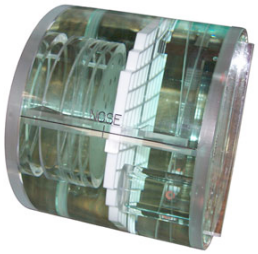

Automated Analysis of Multi Site MRI Phantom Data for the NIHPD Project

Luke Fu, Vladimir Fonov, Bruce Pike, Alan C. Evans, and D. Louis Collins

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Quebec, Canada
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www.bic.mni.mcgill.ca/nihpd/

https://nihpd.crbs.ucsd.edu/nihpd/info/data_access.html

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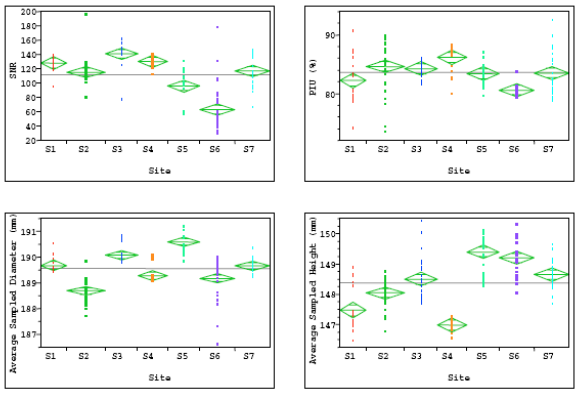

Fig. 1. Plot of SNR, PIU, phantom diameter and height vs. site for the T1 modality. The horizontal line represent the grand mean of all sites, while the diamond represent 95% normal confidence interval centered at the sample mean.

https://nihpd.crbs.ucsd.edu/nihpd/info/data_access.html

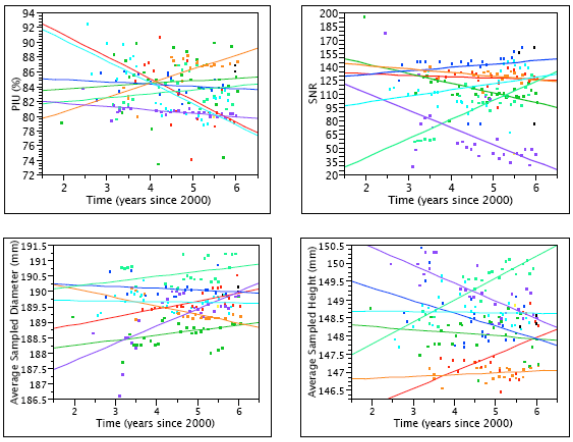

Fig. 2. Longitudinal T1 plots of PIU, SNR, diameter and height for all sites. The legend is as follows: Red = Site 1, Green = Site 2, Blue = Site 3, Orange = Site 4, Lime = Site 5, Purple = Site 6, Aqua = Site 7.

http://www.adni-info.org/

NeuroImage 52 (2010) 508–514

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Whole brain quantitative T2 MRI across multiple scanners with dual echo FSE: Applications to AD, MCI, and normal aging☆

Corinna M. Bauer [a], Hernán Jara [b,c], Ron Killiany [a,d,e,*] and Alzheimer's Disease Neuroimaging Initiative

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[b] Department of Radiology, Boston Medical Center, Boston University School of Medicine, 820 Harrison Avenue, Boston, MA 02118, USA
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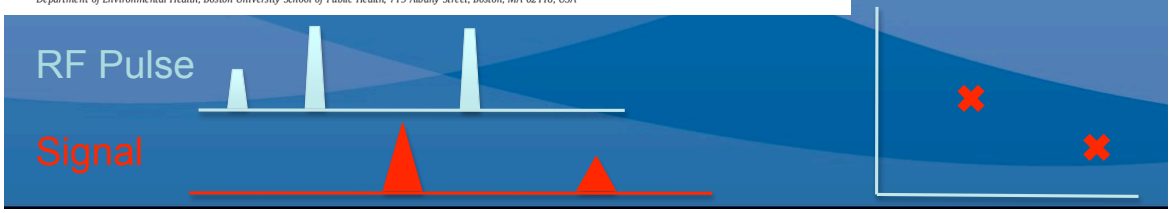

http://www.adni-info.org/

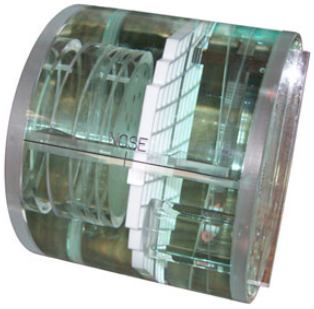

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Table 2
ACR phantom results from 4 scanners. Siemens shows approximately 30 ms prolonged peak T2 compared to GE and Philips. GE showed 10 ms variance between scanners.

ACR phantom peak T2 and histogram width				
	GE HDx	GE Signa Excite	Philips Intera	Siemens Avanto
Peak T2 (ms)	145	135	140	170
T2 histogram width	50	50	50	55

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Table 1
Subject gender breakdown by vendor and diagnostic group (female/male).

Subject enrollment table				
	Philips	GE	Siemens	Total
Normal	6/3	5/13	4/4	15/20
MCI	2/5	7/6	7/4	16/15
AD	4/7	6/4	6/4	16/15
Total	12/15	18/23	17/12	47/50

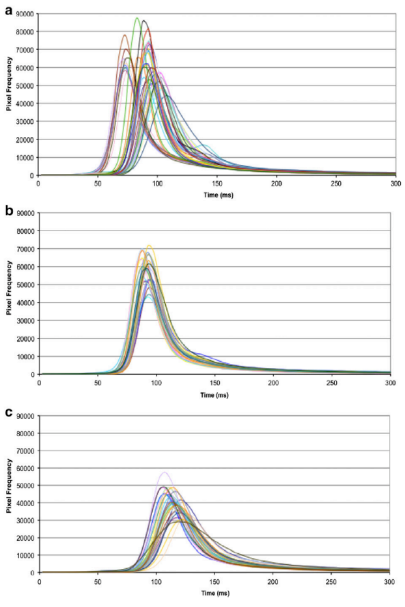

Fig. 4. ICM T2 histograms from all subjects and scanner platforms, a) Philips b) GE and c) Siemens.

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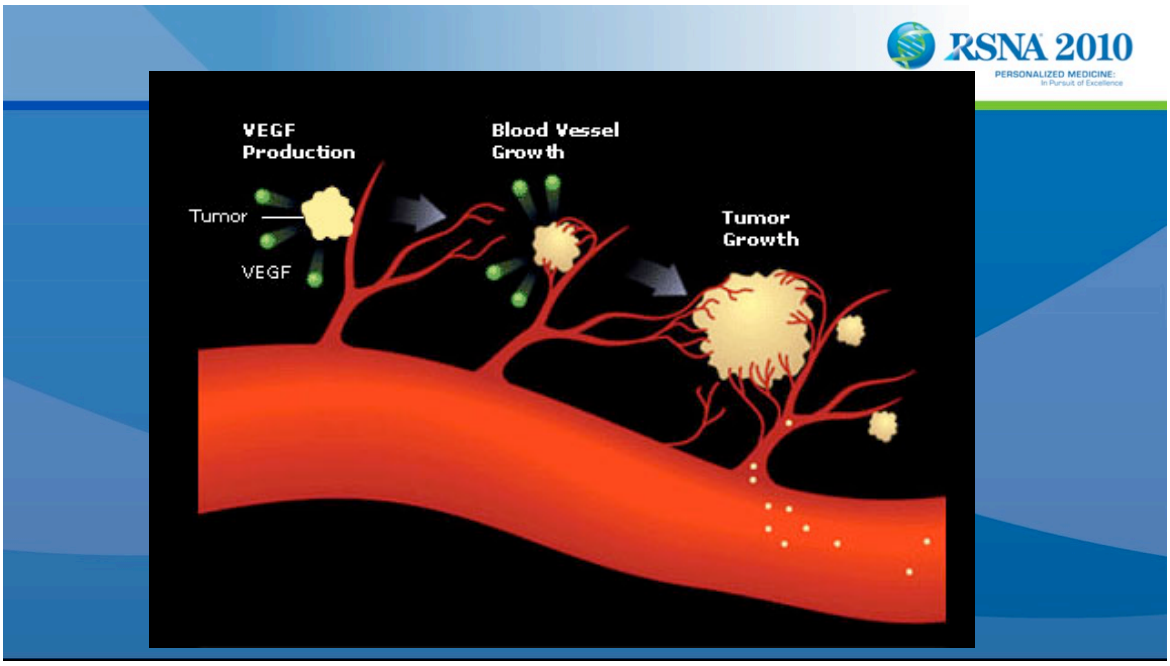
Contrast Enhanced MRI Has Diagnostic Value in Oncology
Breast, Lung, Prostate, etc.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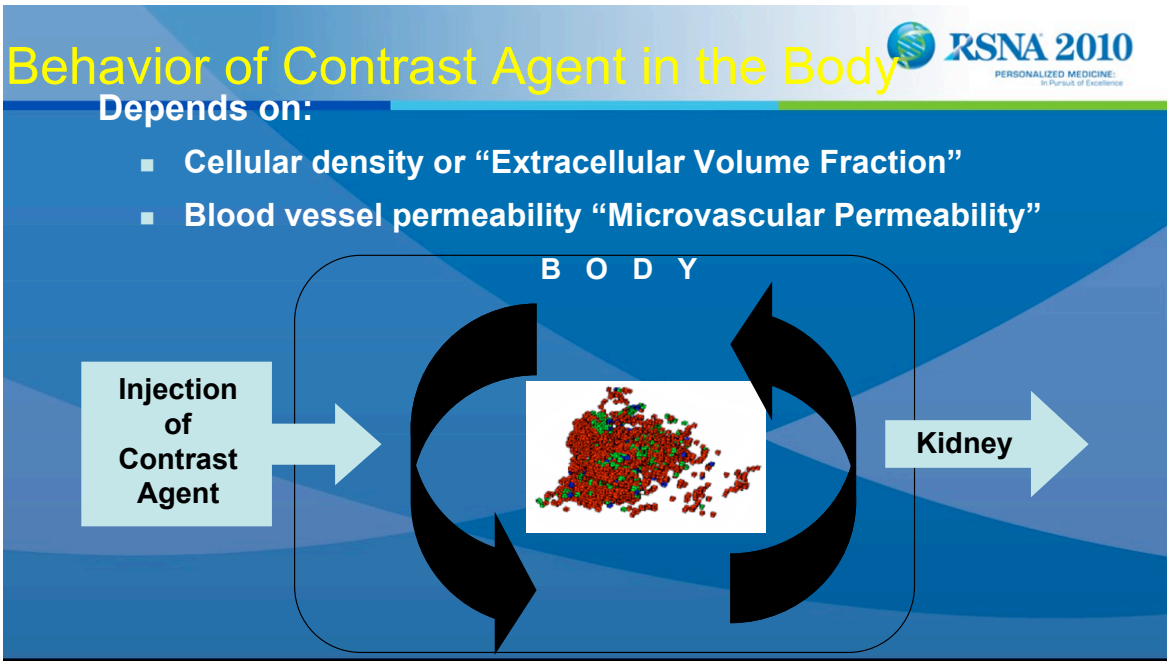
VEGF Production
Blood Vessel Growth
Tumor
VEGF
Tumor Growth


Behavior of Contrast Agent in the Body
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Depends on:
Cellular density or "Extracellular Volume Fraction"
Blood vessel permeability "Microvascular Permeability"
B O D Y
Injection of Contrast Agent
Kidney

Dynamic Contrast Enhanced MRI (DCEMRI)

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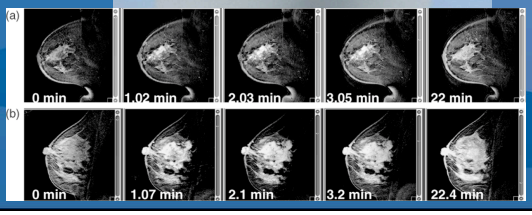
Components

- "High-field" MRI machine (1.0 tesla or greater)
- Phased array coil
- Gadolinium contrast agent (GdDTPA)
- Images taken at several time points (spatial vs temporal resolution
- Software algorithm processes data for either parametric maps or semi-quantitative plots



Christiane Katharina Kuhl, MD
Peter Mielcareck, MD
Sven Klaschik, MD
Claudia Leutner, MD
Eva Wardelmann, MD
Jürgen Gieseke, PhD
Hans H. Schild, MD

Dynamic Breast MR Imaging: Are Signal Intensity Time Course Data Useful for Differential Diagnosis of Enhancing Lesions?[1]

Radiology 1999; 211:101–110

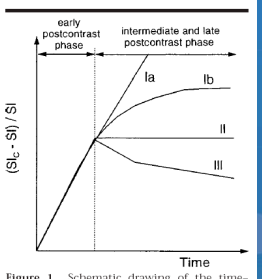


Figure 1. Schematic drawing of the time–signal intensity curve types. Type I corresponds to a straight (*Ia*) or curved (*Ib*) line; enhancement continues over the entire dynamic study. Type II is a plateau curve with a sharp bend after the initial upstroke. Type III is a washout time course ($(SI_c - SI)/SI$).

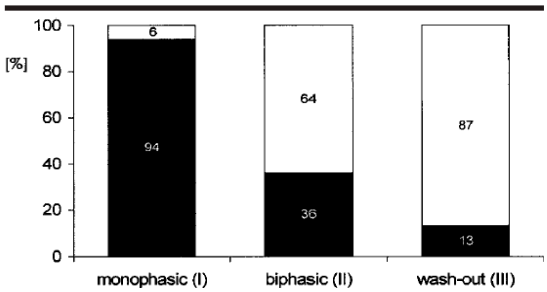
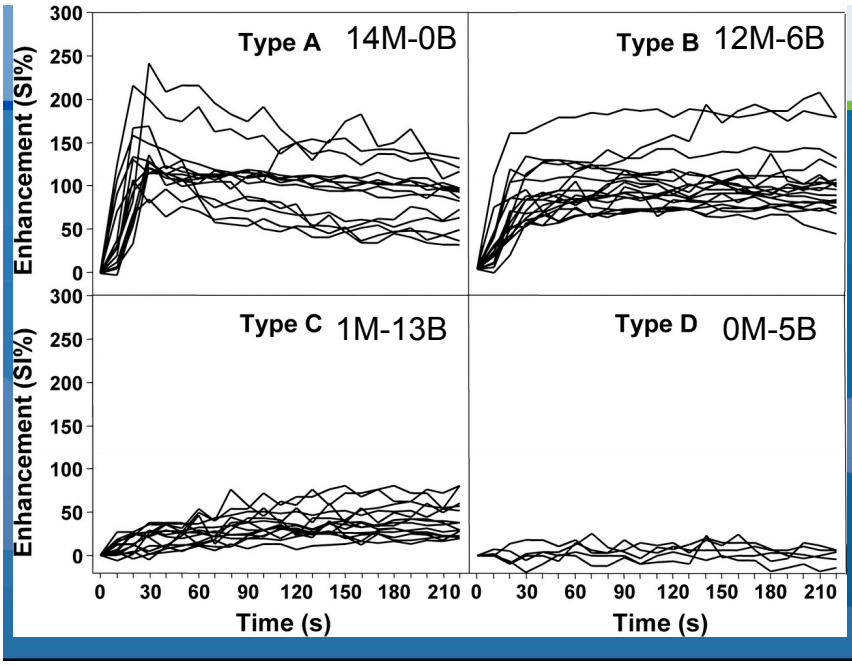


Figure 4. Bar graph shows the prevalence of benign (black bars) and malignant (white bars) lesions for the three different signal intensity time courses.

Juergen F. Schaefer, Joachim Vollmar, Fritz Schick, Reinhard Vonthein, Marcus D. Seemann, Herrmann Aebert, Rainer Dierkesmann, Godehard Friedel, and Claus D. Claussen

Solitary Pulmonary Nodules: Dynamic Contrast-enhanced MR Imaging—Perfusion Differences in Malignant and Benign Lesions

Radiology August 2004 232:544-553;



Tofts Model Equation

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$$SI = [a_1*(e^{(-ktrans*t/ve)} - e^{(-m1*t))/(m1-ktrans/ve)} + a_2*(e^{(-ktrans*t/ve)} - e^{(-m2*t))/(m2-ktrans/ve)} + a_1*e^{(-m1*t)} + a_2*e^{(-m2*t)}]*d*k_{trans}$$

Two Compartment Model

Negligble vascular space

Idealized arterial input function

(SI linear with Gd Agent Concentration)

Challenges/Issues

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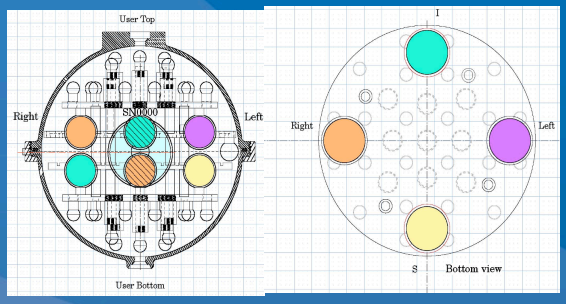
- How accurate is the model?
- How precise are the values of Ktrans and Ve?
- What is the influence of SNR and temporal resolution?

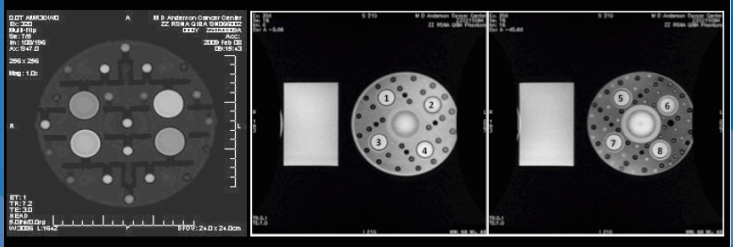
RSNA QIBA DCE-MRI Technical Committee



- Modified ADNI/IRAT phantom for DCE-MRI
- Defined generic DCE-MRI acquisition protocols
- Conduct multi-center phantom reproducibility study
- Define procedure for routine phantom use
- Develop simulated data set for algorithm testing

http://www.rsna.org/research/qiba.cfm

RSNA QIBA DCE-MRI Phantom v1 Studies



Axial Coronal

Typical images showing the eight T1 contrast spheres

RSNA QIBA DCE-MRI Phantom v1 Studies

- Phantom measurements (overview):
  - Phased array acquisition
  - Body coil acquisition
  - SNR acquisition
  - Variable flip angle T1 measurement acquisition
  - DCE acquisition

  } Ratio map correction for RF coil sensitivity characteristics

- Each of the above acquisitions repeated with phantom rotated by 90, 180, 270, and 360°
- All acquisitions repeated one week later
- Sites / vendors

– MDACC	GE (new)	Site 1 / Vendor A
– UPenn	Siemens (2)	Site 2 / Vendor B
– Univ Chicago	Philips	Site 3 / Vendor C
– Duke Univ	Philips	Site 4 / Vendor C
– Univ CA Davis	GE (older)	Site 5 / Vendor A

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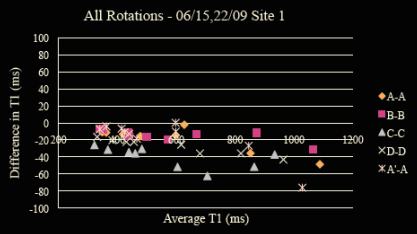
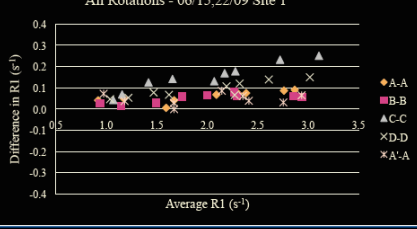
RSNA QIBA – Multiple Vendors / Three Time Points



Difference in T1 from each contrast sphere, week 1 minus week 0.



Difference in R1 from each contrast sphere, week 1 minus week 0.

Requirements for validating imaging biomarkers

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- Standardized acquisition, processing, and analysis
- Implementation in prospective multicenter clinical trials
- Comparison with gold standards such as pathology or other imaging techniques
- Validation with clinical outcome (e.g. survival, quality of life)

Anatomic T2W and T1W early subtraction images and parametric maps for rBV and Ktrans at baseline and following 2 cycles of neoadjuvant chemotherapy in a clinically and pathologically (A) responding patient and (B) nonresponding patient.

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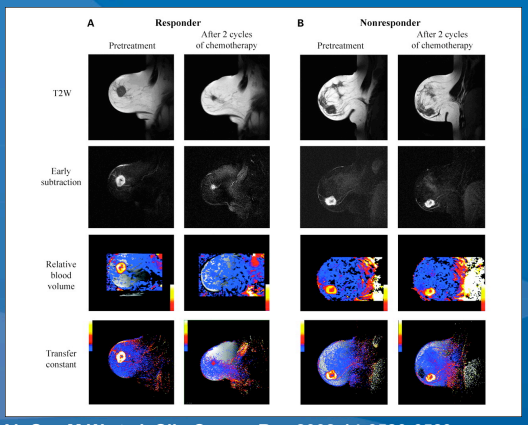

Ah-See M W et al. Clin Cancer Res 2008;14:6580-6589

Clinical Cancer Research

Change in MRI-derived tumor size and DCE-MRI kinetic parameters according to (A) clinical tumor response and (B) pathologic tumor response.

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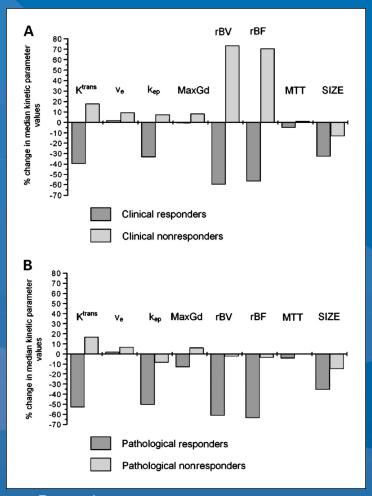

Clinical Cancer Research

ASL Subtraction Experiment

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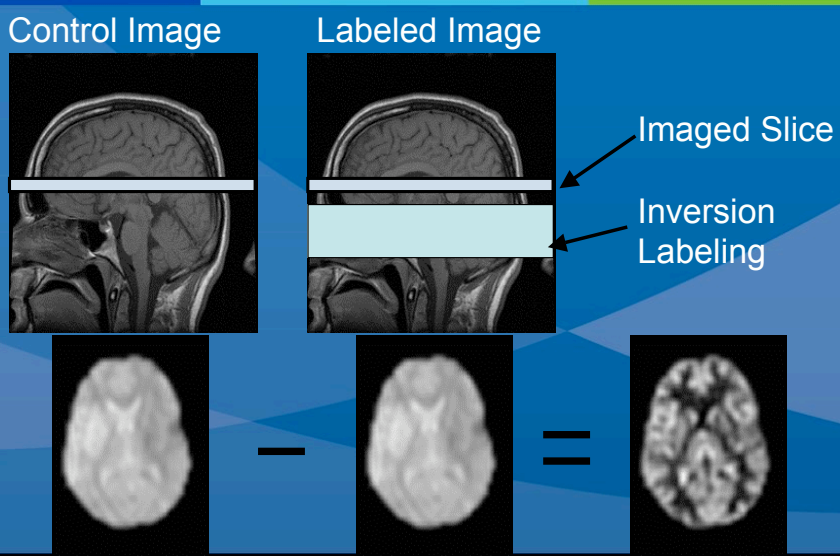
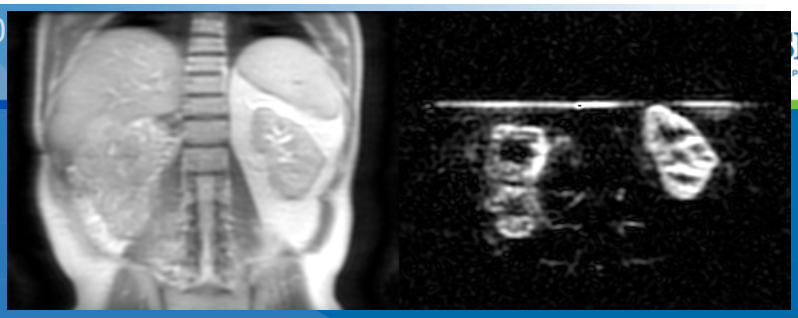
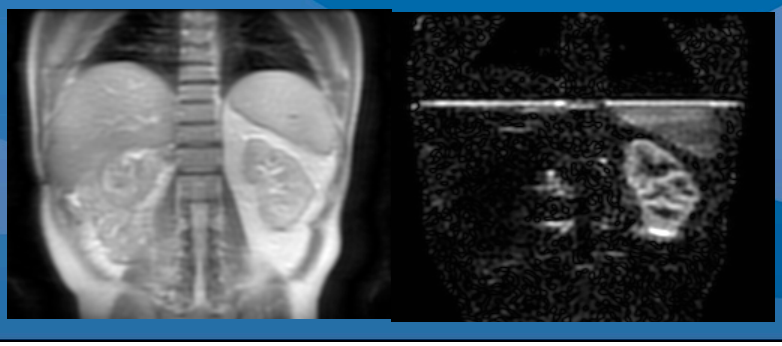


DAY 0



DAY 8

sorafenib + bevacizumab



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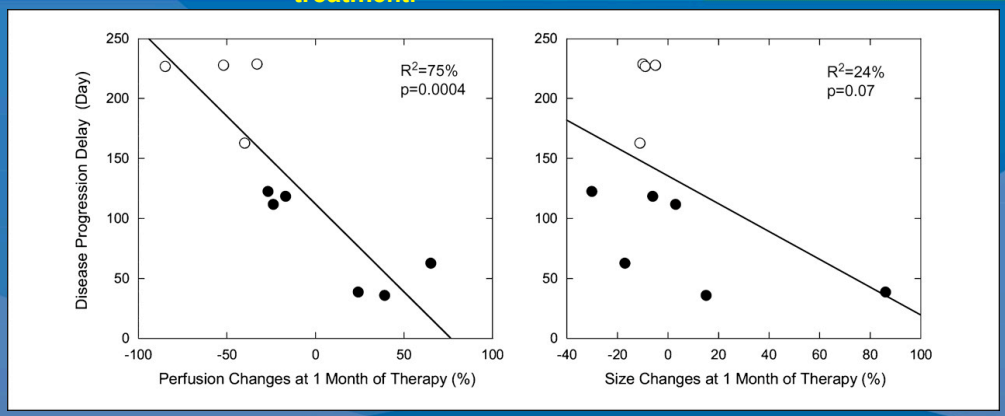
Early changes at 1 mo in blood flow and tumor size compared with delay of progression of the disease after initiation of the treatment.



de Bazelaire C et al. Clin Cancer Res 2008;14:5548-5554

Clinical Cancer Research

JOURNAL OF MAGNETIC RESONANCE IMAGING 32:2–16 (2010)

Review

Predicting and Monitoring Cancer Treatment Response with Diffusion-Weighted MRI

CME

Harriet C. Thoeny, MD[1*] and Brian D. Ross, PhD[2]

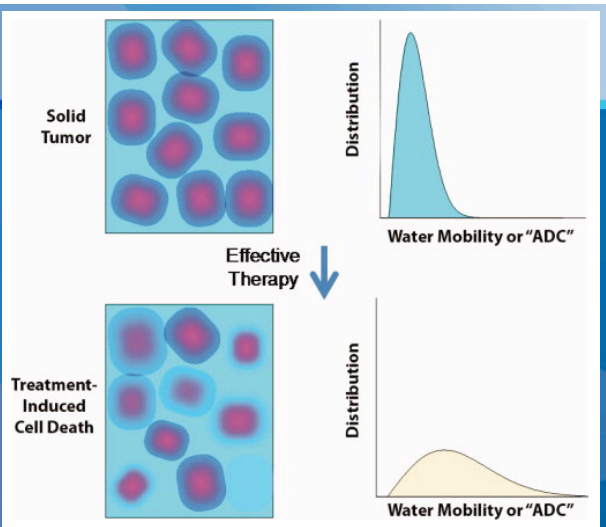
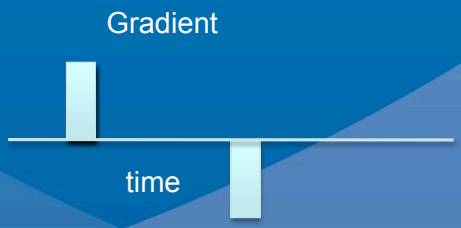


Figure 1. Schematic representation of the relationship between change in cellular density following an effective therapy and the corresponding distribution of water diffusion values within the tumor. Note that the mean diffusion value of a tumor increases early following the loss of cellular density. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]



Radiol med (2008) 113:199–213
DOI 10.1007/s11547-008-0246-9

URO-GENITAL RADIOLOGY
RADIOLOGIA URO-GENITALE

Malignant renal neoplasms: correlation between ADC values and cellularity in diffusion weighted magnetic resonance imaging at 3 T

Neoplasie renali maligne: correlazione tra valori di ADC e cellularità nelle sequenze pesate in diffusione con risonanza magnetica a 3 T

G. Manenti[1] • M. Di Roma[1] • S. Mancino[1] • D.A. Bartolucci[1] • G. Palmieri[2] • R. Mastrangeli[1]
R. Miano[3] • E. Squillaci[1] • G. Simonetti[1]

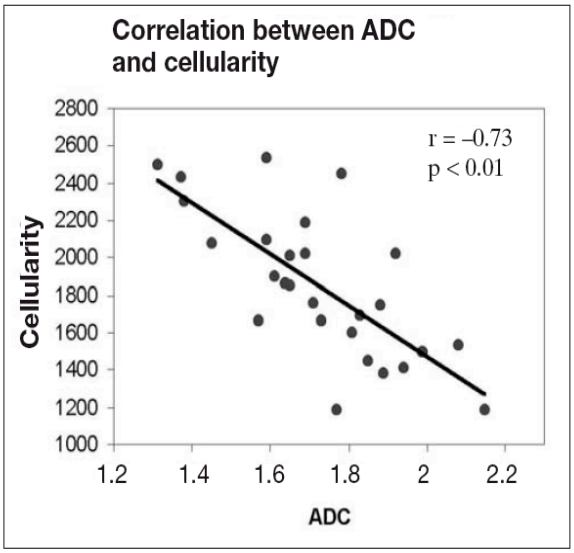


Fig. 7 Correlation between apparent diffusion coefficient and cellularity.

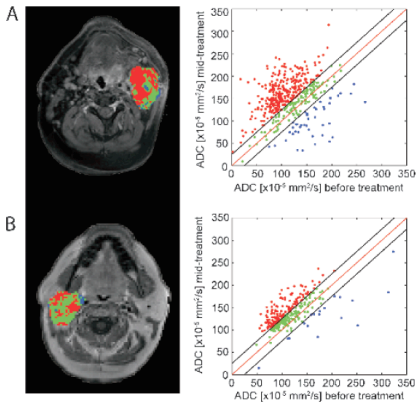


Figure 3. Representative slices of PRM_{ADC} for patients whose conditions were diagnosed as (A) CR and (B) PR; color-coded VOIs are overlaid on contrast-enhanced T_1-weighted MR images before therapy and corresponding scatter plots for quantification and distribution of ADC before and 3 weeks after treatment initiation for the entire tumor volume. Unity and threshold designating significant change in ADC within the scatter plot are presented by red and black lines, respectively. Voxels with significant increased, decreased, or unchanged ADC values were assigned as red, blue, and green, respectively.

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Computational Radiology Laboratory
Harvard Medical School
www.crl.med.harvard.edu

Children's Hospital
Department of Radiology
Boston Massachusetts

NdH/dT: A new quantitative measure for Diffusion Weighted Imaging based evaluation of abdominal tumor response to therapy

Moti Freiman[1], Stephan Voss[2], Simon K. Warfield[1].

[1]Computational Radiology Laboratory, Children's Hospital, Harvard Medical School, Boston MA USA

[2]Dept. Of Radiology, Children's Hospital, Harvard Medical School, Boston MA USA

Submitted to: ISMRM'2011

Children's Hospital Boston
The Hospital for Children

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Our approach

- NdH/dT: Normalized cumulative histogram difference over time
  - Difference between the Cumulative histograms of the tumor ADC values
  - Area Under the Curve (AUC) represent the overall change in tumor diffusivity
  - Normalization by the AUC of healthy tissue sample produce absolute global measure

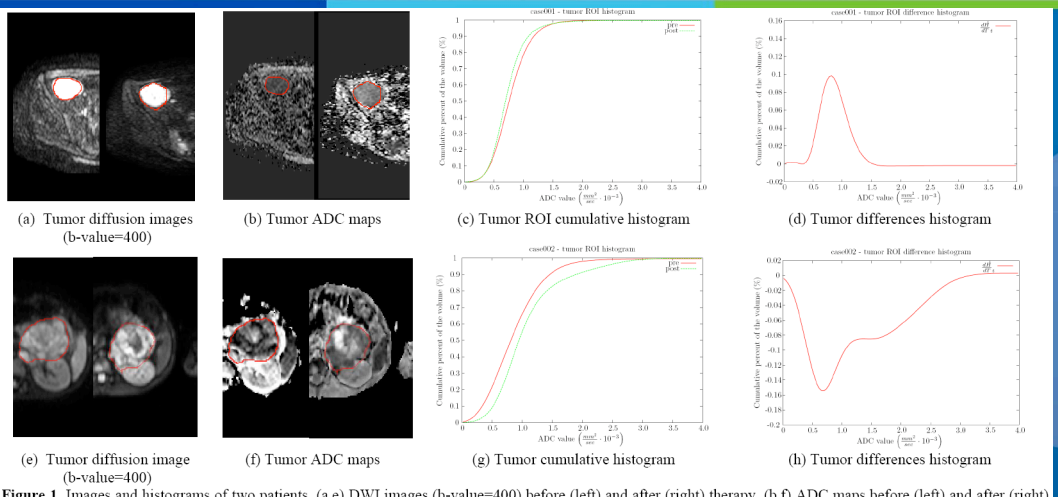
✓ Single number

✓ Intuitive to interpret

✓ No non-rigid registration is required

✓ Capture tumor heterogeneity

NdH/dT: Representative examples



(a) Tumor diffusion images (b-value=400) (b) Tumor ADC maps (c) Tumor ROI cumulative histogram (d) Tumor differences histogram

(e) Tumor diffusion image (b-value=400) (f) Tumor ADC maps (g) Tumor cumulative histogram (h) Tumor differences histogram

Figure 1. Images and histograms of two patients. (a,e) DWI images (b-value=400) before (left) and after (right) therapy, (b,f) ADC maps before (left) and after (right) therapy. The tumors are encircled in red. (c,g) Cumulative histograms of the ADC values, before (red) and after (green) therapy. (d,h) The differences between time-points histograms.

^{1}H-MRS of Breast Carcinoma

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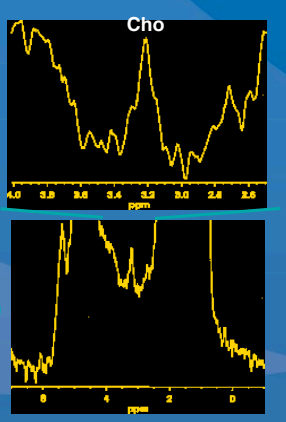

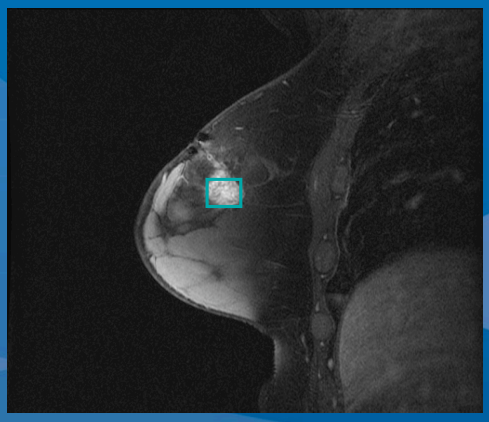

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Journal of the National Cancer Institute, Vol. 94, No. 16, 1197-1203, August 21, 2002

REVIEW

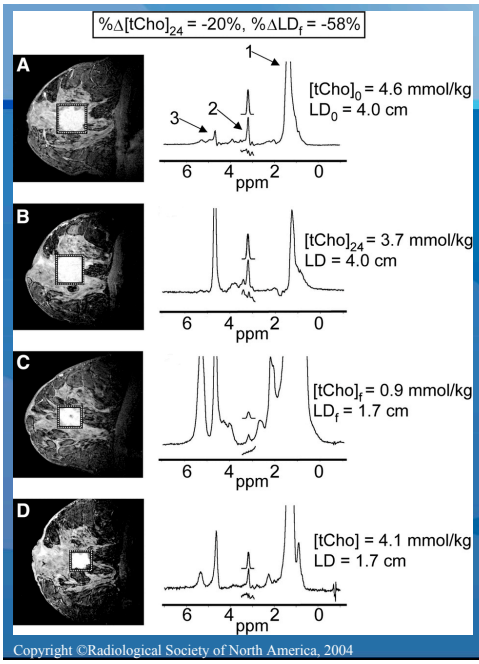
Clinical Utility of Proton Magnetic Resonance Spectroscopy in Characterizing Breast Lesions

Rachel Katz-Brull, Philip T. Lavin, Robert E. Lenkinski

Table 2. Breast proton magnetic resonance spectroscopy (^{1}H MRS) studies and results*

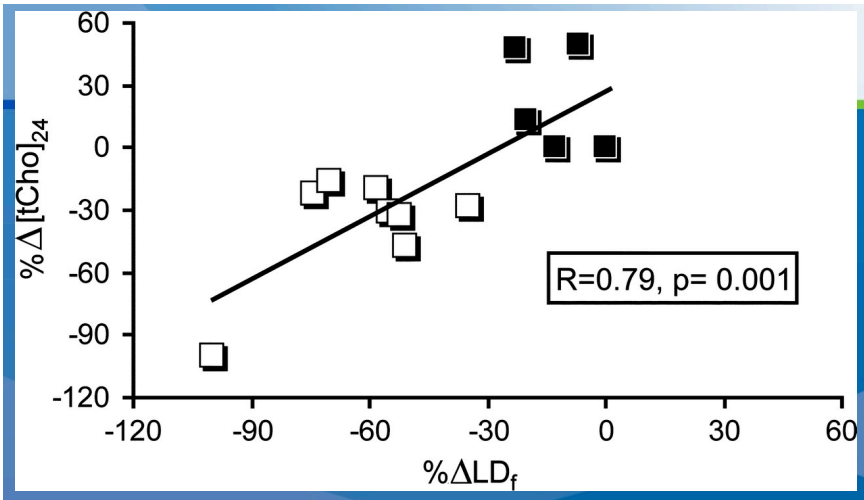
Study	No. of malignant tumors	No. of benign tumors	Sensitivity, %	Specificity, %	No. of true positives	No. of true negatives	No. of false negatives	No. of false positives
Cecil et al. *(16)*	19	14	100	93	19	13	0	1
Yeung et al. *(19)*	23	6	96	83	22	5	1	1
Roebuck et al. *(18)*	10	6	70	100	7	6	3	0
Total	52	26	92	92	48	24	4	2

*Cases in which hardware failed, the patient moved during examination, MRS was done after fine-needle aspiration procedure, and cases of tubular adenoma (in studies where these cases were reported in detail) were excluded. Data were reproduced from studies cited or calculated from data presented therein.



Meisamy, S. et al. Radiology 2004;233:424-431

Radiology



Meisamy, S. et al. Radiology 2004;233:424-431

Radiology

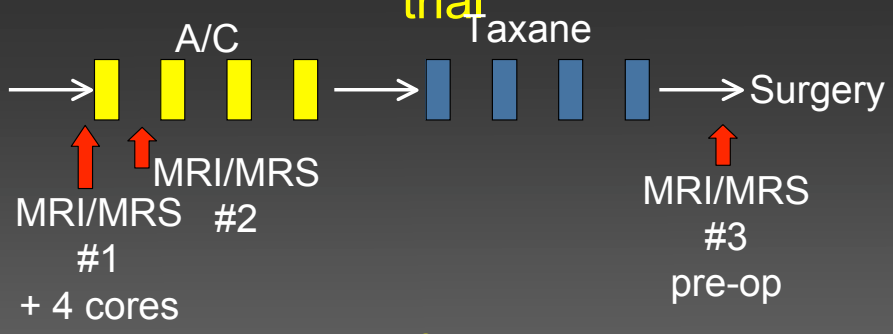
http://www.acrin.org/

ACRIN protocol 6657 (open)

ACRIN Principal Investigator
Nola M. Hylton, PhD
University of California, San Francisco
San Francisco, CA

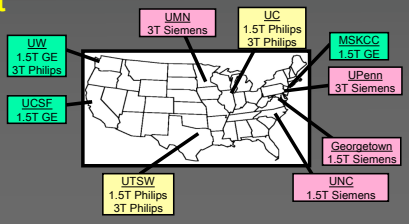
Treatment Monitoring of Breast Cancer with MRI and MRSI

I-SPY 1 / ACRIN 6657 ext: Multi-site breast MRS trial



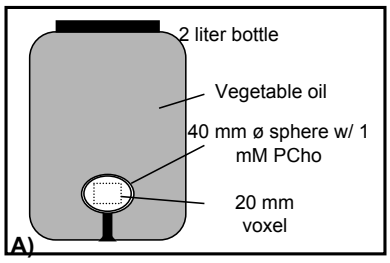
Can immediate (1-3 days) change in [tCho] predict response?

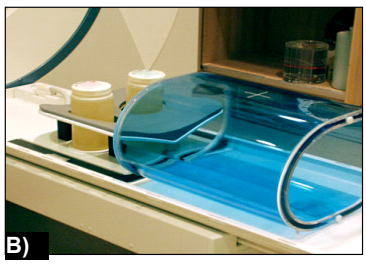
- PI: Nola Hylton & Laura Esserman, UCSF
- Single voxel MRS, T2-corrected water as internal reference
- 1.5T and 3T, GE/Siemens/Philips
- Central MRS analysis (UMN – Bolan)
- Fall 2010: 114/144 subjects completed

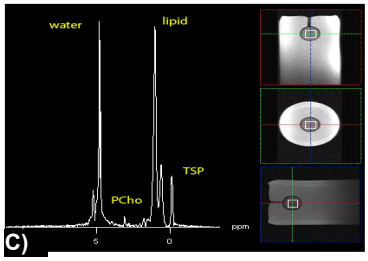


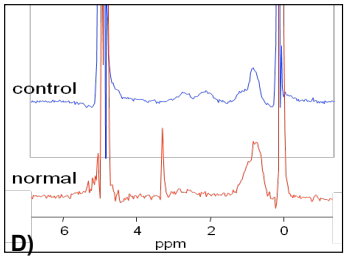
QC Protocol

- Standard phantoms
- Qualifying and weekly QC scanning
- Choline + and control phantoms

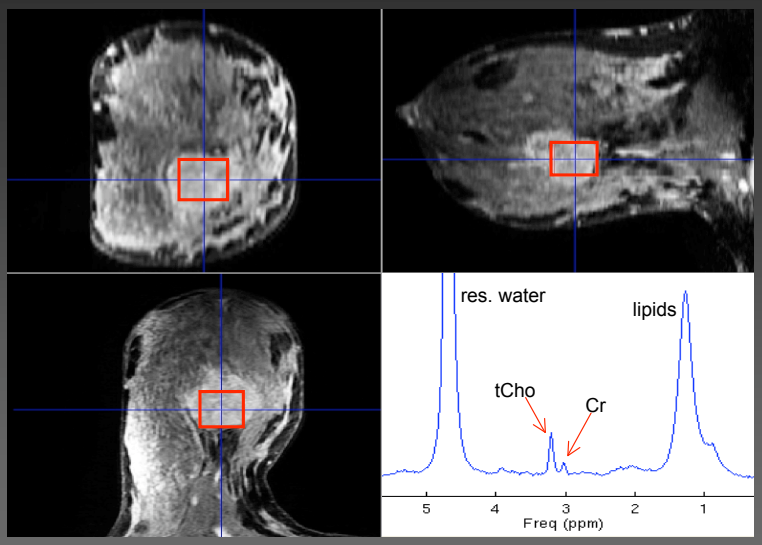








Bolan et al., ISMRM 2008



Example Case
1.5 T MRI
7 mL voxel
Water T_2 = 103 ms

[tCho] = 6.2 mmol/kg

MRI Biomarkers

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DCEMRI-Vascular permeability
ASL-tissue perfusion
DWI-cellularity
MRS-metabolism (choline)

MRI/MRS is Complicated
Navigating through the maze to reach quantitation requires a systematic approach