Magnetic Resonance Spectroscopy of Breast and Prostrate Cancer

Michael A. Jacobs[1,2], Peter B. Barker[1], Katarzyna J. Macura[1]

[1]The Russell H. Morgan Department of Radiology and Radiological Science and [2]Sidney Kimmel Oncology Department,
The Johns Hopkins University School of Medicine, Baltimore, MD

Objectives

- Brief outline of Magnetic Resonance Imaging (MRI)
- Difference between MRI and Magnetic Resonance Spectroscopy
- Magnetic Resonance Spectroscopy (MRS) Sequences
- MRS in Breast
- MRS in Prostrate
- Future Directions

Background MRI

- **Recall that the magnetization vector M is described by the Bloch equation:**

$$\frac{dM}{dt} = M \times \gamma B - \frac{M_x i + M_y}{T_2} - \frac{(M_z - M_0)k}{T_1} + fM_a - \frac{f}{\lambda} M_b$$

M_a = longitudinal magnetization per gram of brain tissue; M_b = longitudinal magnetization per ml of arterial blood
T_{1app} = relaxation of brain magnetization; f = brain blood flow (ml/g/sec); λ = brain blood partition coefficient (0.9 ml/g)

Larmor Frequency

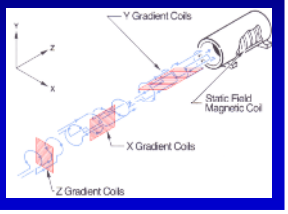
- **The Larmor frequency is defined as:**

$$\omega_0 = \gamma B_0 / 2\pi$$

Where ω = Larmor frequency, γ=gyromagnetic constant (42.6Mhz/T), and B is the Magnetic Field

Background MRI

- **Localization of MR signal**
  - **Fields**
    - **B_0 Main Magnetic Field**
    - **B_1 Radiofrequency Field**
  - **Gradients**
    - **x,y,z**



Background MRI

- **Gradient Vector Definition：**

$$\vec{G} = \frac{\partial B_z}{\partial x}\vec{X} + \frac{\partial B_z}{\partial y}\vec{Y} = \frac{\partial B_z}{\partial z}\vec{Z} \equiv \vec{G} = G_x\vec{x} + G_y\vec{y} + G_z\vec{z}$$

- Gx, Gy, and Gz are generated by three different coils.
- Gradients are measured in Tesla per meter (T/m) or Gauss per cm (G/cm), where 0.01mT/m=1G/cm
- Typical values range from 20 up to 80mT/m

Background MRI

- The magnetic field is linearly dependent on the location within the magnet

$$\vec{B}_i = B_0 + \vec{G} \otimes \vec{r}_i$$

•Where B_i = magnetic field at r_i and G is the total gradient vector

- For example, in the x-direction

$$\vec{B}_x = B_0 + \vec{G} \otimes \vec{r}_x$$

Larmor Frequency

- **The Larmor frequency is defined as:**

$$\omega_0 = \gamma B_0 / 2\pi$$

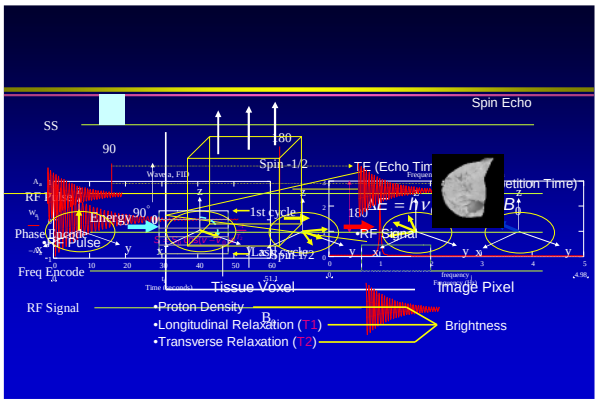
- **The variation in Larmor frequency is defined as:**

$$\omega_i = \omega_0 + \gamma \vec{G} \otimes r_i$$

Where ω = Larmor frequency, γ=gyromagnetic constant (42.6Mhz/T), and G is the total gradient vector

- **For example, in the x-direction**

$$\omega_x = \omega_0 + \gamma \vec{G} \otimes \vec{r}_x$$



Proton Spectroscopy

- Chemical Shift
  - » Nuclei are "shielded" from the magnetic field the electrons. This shielding is called chemical shift and defined as

$$\vec{B}_i = B_0(1-\sigma_i)$$

•Where B_i = magnetic field, σ_i = shielding (depends on the chemical environment)

- Thus, resonance condition is

$$\omega = \frac{\gamma}{2\pi} B_0(1-\sigma)$$

Proton Spectroscopy

- Chemical shift measurements
  - » Parts per Million (ppm)

$$\delta_i = (\omega_i - \omega_{ref}) / \omega_{ref}$$

  - » Independent of magnetic field strength
  - » (Increases when measured in Hz)

Proton Spectroscopy

- Example:
  - » Water is 4.7ppm and Lipids (Fat) is 1.3ppm
  - » At 1.5T, what is the chemical shift?
  - » (4.7-1.3) =3.4

$$\delta_i = (\omega_i - \omega_{ref}) / \omega_{ref}$$

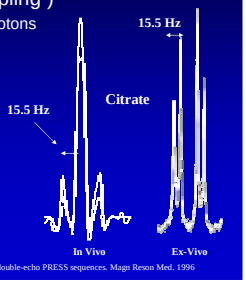
$$3.4\,ppm * \omega_{ref} = 3.4\,ppm(63.8\,Mhz) = (\omega_i - \omega_{ref})$$

$$(\omega_i - \omega_{ref}) = 217\ hz \approx 220\ hz$$

  - » At 3T, ~440 hz
  - » Implies greater spectral resolution

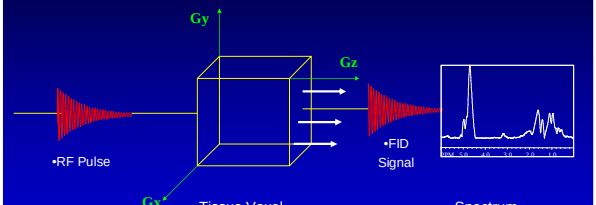
Proton Spectroscopy

- Spin-Spin Coupling (J or scalar coupling)
  - » Molecular interaction between adjacent protons
  - » Causes additional splitting of the spectra
  - » Need high magnetic field
- J constant
  - » Measured in Hz
  - » Independent of magnetic field strength



Mulkern RV, et al, Citrate signal enhancement with a homonuclear J-refocusing modification to double-echo PRESS sequences. Magn Reson Med. 1996

Overview



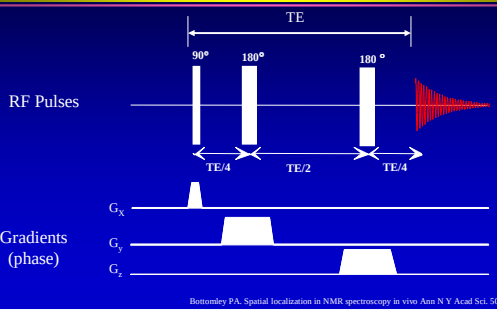
Tissue Voxel
- •Metabolites
- •Longitudinal Relaxation (T1/TR)
- •Transverse Relaxation (T2-TE)

Spectrum
Spectral Resolution

Spectroscopy Sequences

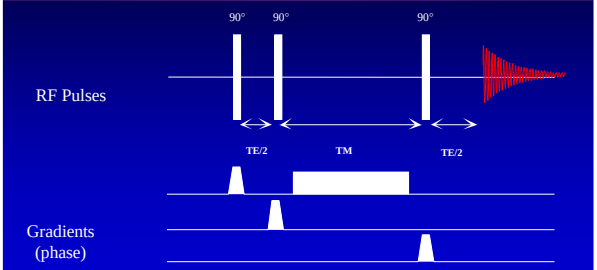
- PRESS
  - » Bottomley PA. Spatial localization in NMR spectroscopy in vivo Ann N Y Acad Sci. 508:333-348 (1987)
- STEAM
  - » Frahm J, Merboldt KD, Hänicke W. Localized proton spectroscopy using stimulated echos J Magn Reson. 72:502-508 (1987)
- ISIS
  - » Ordidge RJ, Connelly A, Lohman JA. Image-selected in0vivo spectroscopy (ISIS) A new technique for spatially selective NMR spectroscopy. Spin echo imaging of multiple chemical shifts. J Magn Reson. 66:283-294 (1986)
- LASER
  - » Garwood M, DelaBarre L. The return of the frequency sweep: designing adiabatic pulses for contemporary NMR. J Magn Reson. 153:155-177 (2001)
  - » Slotboom J, Mehlkopf AF, Bovée WM. A single shot localization pulse sequene sutied for coils with inhomogeneous RF fields using adiabatic pulses. J Magn Reson. 95:396-404 (1991)

Spectroscopy Sequence
PRESS (Point Resolved Spectroscopy)



Bottomley PA. Spatial localization in NMR spectroscopy in vivo Ann N Y Acad Sci. 508:333-348 (1987)

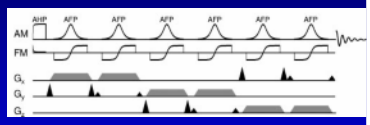
Spectroscopy Sequences
STEAM (Stimulated Echo Acquisition Mode)



Frahm J, Merboldt KD, Hänicke W. Localized proton spectroscopy using stimulated echos J Magn Reson. 72:502-508 (1987)

Localization by Adiabatic Selective Refocusing (LASER) Spectroscopy Sequence

- AFP =
  - » Adiabatic Full Passage pulses
  - » B_1 insensitive
- AM =amplitude modulation
- FM= frequency modulation



Garwood M, DelaBarre L. The return of the frequency sweep: designing adiabatic pulses for contemporary NMR. J Magn Reson. 153:155-177 (2001)

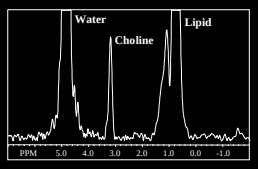
What are the differences in the RF pulses in PRESS and STEAM spectroscopy sequences?

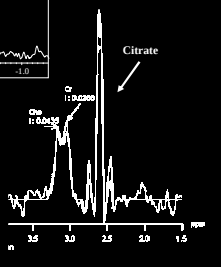
25%	a. The number and type of RF pulses and duration of pulses
25%	b. 90-90-180
25%	c. 90-90-90
25%	d. 90-180-180

10

Spectroscopy Metabolites

- Water
  - » 4.7 ppm
- Lipids
  - » 1.3 ppm
- Choline (Cho)
  - » 3.2 ppm
- Creatine (Cr)
  - » 3.0 ppm
- Citrate (Ci)
  - » 2.6 ppm





Spectroscopy Metabolites

- Choline (Cho)
  - 3.2 ppm
  - Membrane turn over and breakdown
  - Increased in cancer
  - Decreased in Stroke
- Creatine (Cr and PCr)
  - 3.0 ppm
  - 3.94 ppm (if >3T and good water suppression)
  - Energy buffer
- Citrate (Ci)
  - 2.6 ppm
  - Intermediate compound of the citrate acid cycle
  - It produced by a unique testosterone-induced pathway

Gillies RJ and Morse D Annu. Rev. Biomed. Eng. 2005. 7:287–326

Background-Breast Cancer

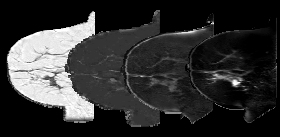
- Breast cancer is the most frequently diagnosed cancer in women
  - Breast cancer is the second leading cause of death
- Current detection methods include:
  - Clinical breast exam
  - Mammography
  - Ultrasound
- Magnetic Resonance Imaging (MRI) provides additional information in patients with occult breast cancer or equivocal findings on the other common detection methods.

Lehman CD, et al, ACRIN Trial 6667 Investigators Group MRI evaluation of the contralateral breast in women with recently diagnosed breast cancer N Engl J Med. 2007 Mar 29;356(13):1295-303.

- By using MRS as an adjunct, the chemical and molecular environment of a breast tumor can be examined.

Data Acquisition: MRS

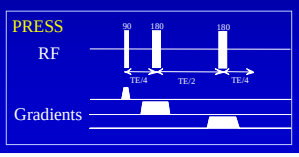
- **T1 FSPGR (TR/TE = 250/4.2)**
- **Fat Suppressed T2 FSE (TR/TE =5700/102)**
- **3D FSPGR, pre/post 0.1mM/kg Gd**
  - **3.5 min, (TR/TE =20/4) (2 x 0.4 x 1.1mm^3)**

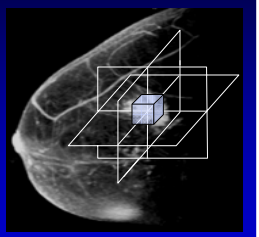


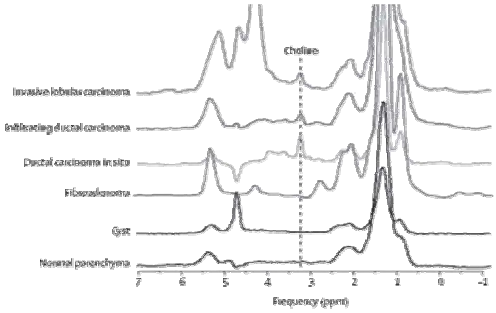
- **Spectroscopy**
  - **PRESS CSI; single slice 10mm, TR/TE =2000/272 ms**
  - **Manual Shimming on lesion**
  - **Lipid Suppression using STIR pulses (TI = 171 ms)**

Single Voxel Applications

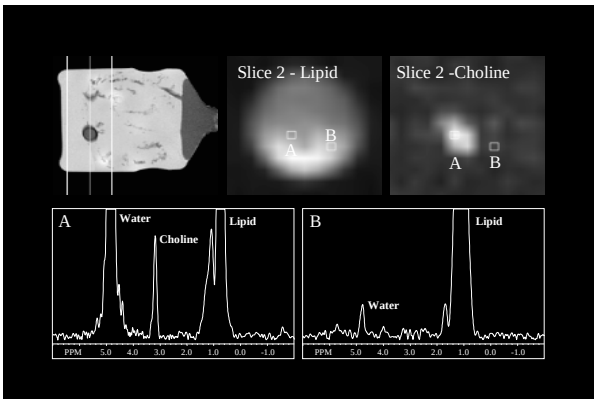
- **Spectroscopy (1.5T)**
  - **PRESS, TR/TE =2000/272 ms, 256-512 points,**
  - **Auto or Manual Shimming on lesion**
  - **Lipid Suppression using STIR pulses (TI = 171 ms)**
  - **After lesion localization**

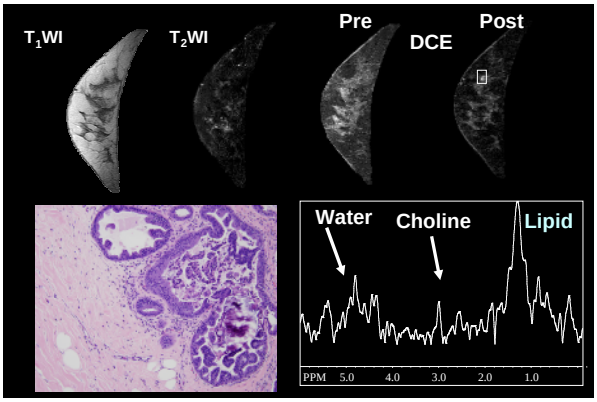


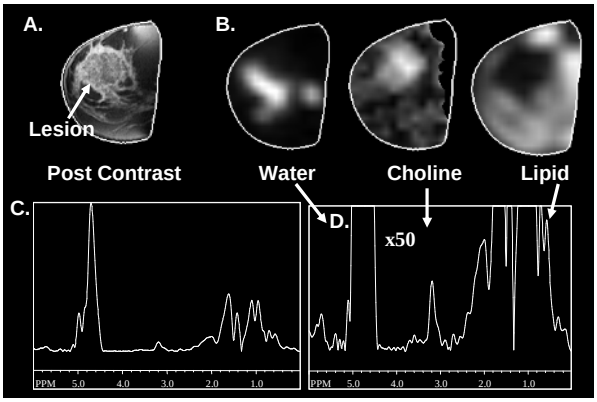


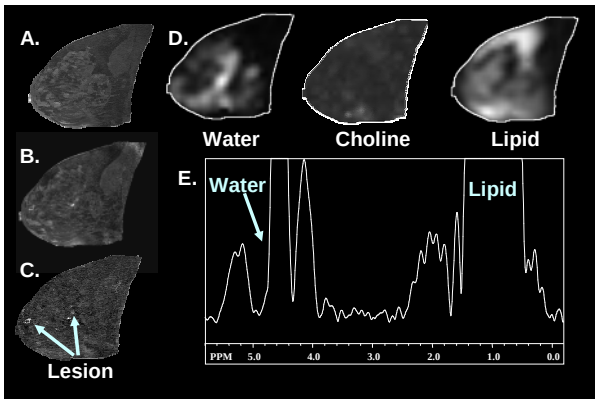


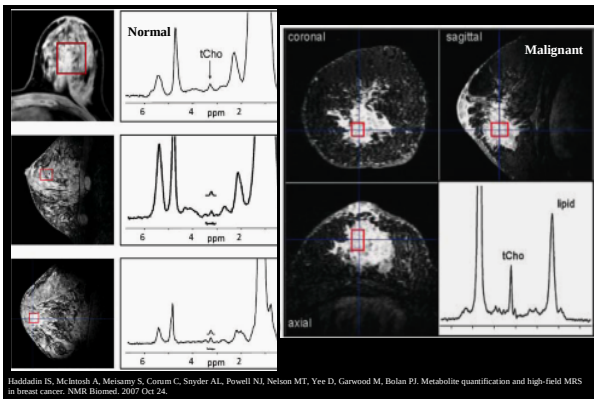
Courtesy of M. Garwood and P. Bolan, University of Minnesota











What are the major metabolites and parts per million (ppm) in cancerous breast tissue at 1.5T or 3T and long echo times

33% a. Taurine (3.4ppm)

33% b. Water (4.7ppm), lipid (1.2ppm) and choline (3.2ppm)

33% c. Water (4.7ppm), lipid (1.2ppm) and myo-inositol 3.6ppm

10

What are the possible lesions/conditions that might lead to increased metabolites (ie, choline, etc) in benign conditions.

25% a. Fibrocystic changes

25% b. Lactating women, fibroadenoma, BPH, and high membrane turnover

25% c. Invasive ductal carcinoma

25% d. d. BPH

10

Why Prostrate MRS

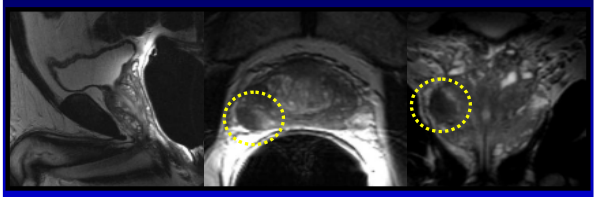
- Current detection methods include:
  - Digital Rectal Exam and/or clinical symptoms
  - Prostate-specific antigen (PSA),
  - Transrectal ultrasonography (TRUS) with biopsy
  - MRI/MRSI
- Magnetic Resonance Imaging (MRI) and Spectroscopy (MRSI) is being used more frequently for diagnosing and monitoring prostate cancer in men
- Prostate MRSI provides additional information in patients with occult prostate cancer or equivocal findings on the other common detection methods.

Kurhanewicz J, Vigneron DB, Hricak H, Carroll P, Narayan P, Nelson S. Three-dimensional H-1 MR spectroscopic imaging of the in situ human prostate with high resolution (0.24-0.7-cm3) spatial resolution. *Radiology* 1996;198:795-805.

Background: MRI/MRS Data Acquisition

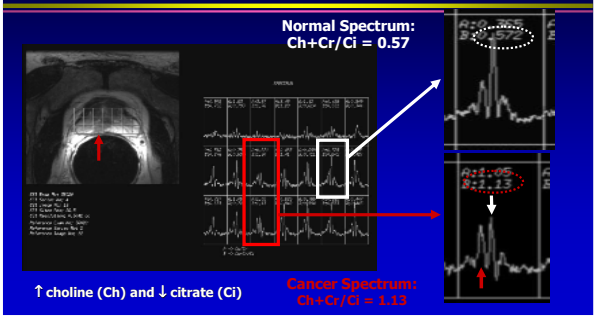
- Pelvic Coil:
  - Axial T1-weighted images (TR/TE = 600-700/-12 ms)
  - Axial T2-weighted (TR/TE = 4000-6000/90-120 ms)
  - Diffusion weighted EPI (TR/TE = 10,000/99 msec, b=0,500,1000)
  - T1-weighted fast low angle contrast-enhanced GRE (TR/TE = 50/4.4 ms).
- Endorectal coil
  - T2 FSE; Axial and Coronal (TR/TE = 4000-6000/90-120 ms)
  - 3D MRSI (TR/TE = 1000 ms; 144 ms; phase encoding steps = 16 x 8 x 8; FOV = 110 x 55 x 55 mm3)

T_2WI Criteria for Prostrate Cancer

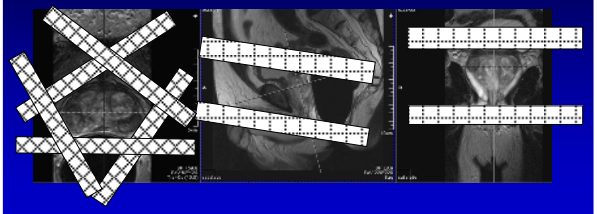


On T2-weighted image a discrete, focal nodule-like dark signal.

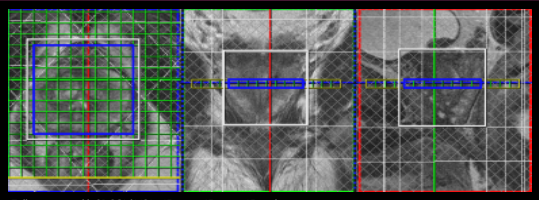
MRSI Criteria



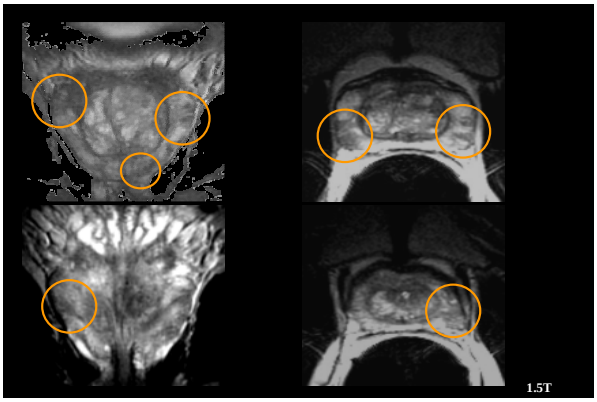
Localizers

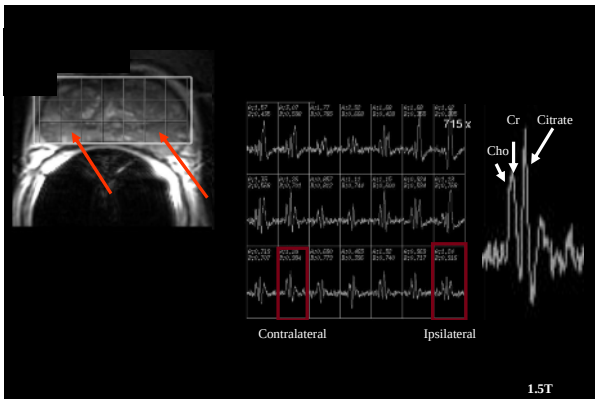


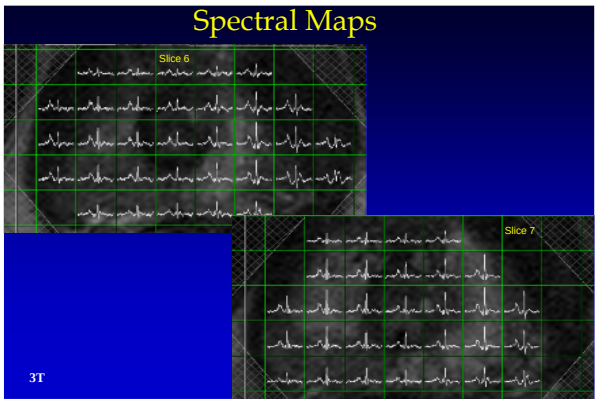
MRSI localizers and protocol

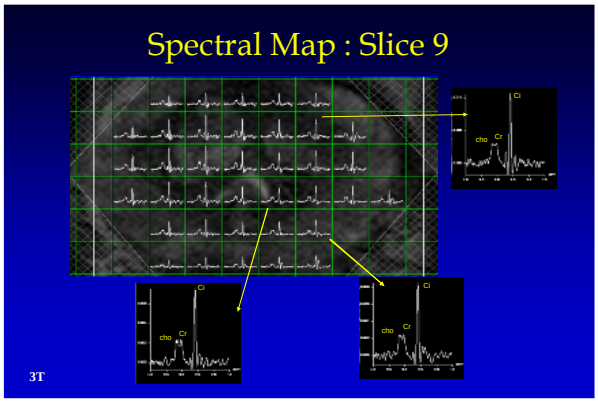


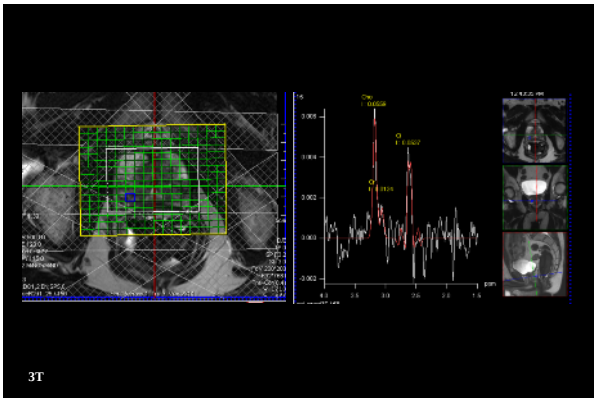
- Full coverage with 3DCSI (VOI : 45 mm x 45 mm x 45 mm)
- TR = 750 ms
- TE = 145 ms
- 8 averages
- 8 saturation slabs
- Spectral water and fat suppression within VOI
- Spatial resolution 5 mm x 5 mm x 5 mm
- TA = 12 minutes

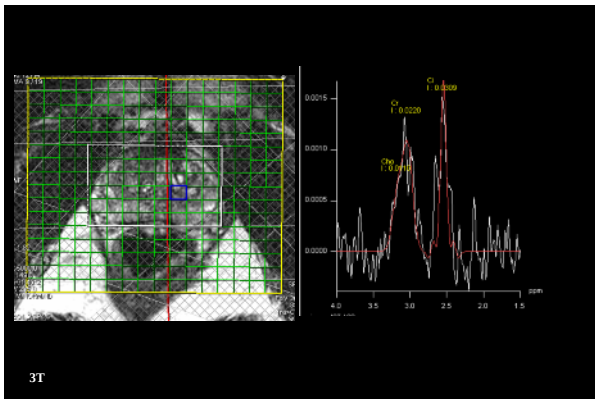



715 x
Cr
Citrate
Cho
Contralateral
Ipsilateral
1.5T


Spectral Maps
Slice 6
Slice 7
3T


Spectral Map : Slice 9
Cho
Cr
Cho
Cr
Cho
Cr
3T


3T



What are the major metabolites in cancerous prostrate tissue at 1.5T or 3T and long echo times

33% a. Taurine

33% b. Water (4.7ppm), lipid (1.2ppm) , choline (3.2ppm) and NAA (2.2ppm)

33% c. Water (4.7ppm), lipid (1.2ppm) , choline (3.2ppm) creatine (3.0ppm) , and citrate (2.6ppm)

10

Why is spectroscopy used in breast or prostrate imaging?

25% a. Diagnosis of the lesion

25% b. Classification of the lesion

25% c. Adjunct for diagnosis and research for detecting abnormal metabolites

25% d. Detection of hypertrophy

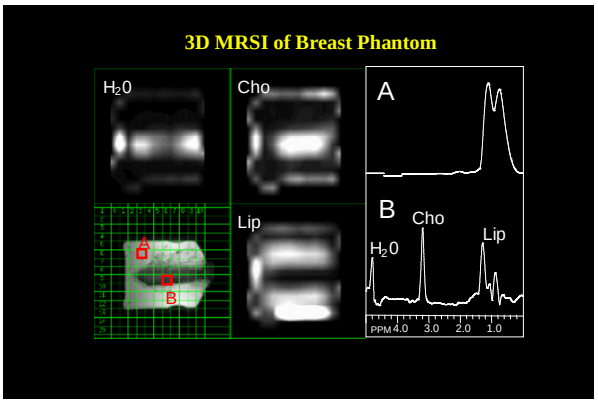
10

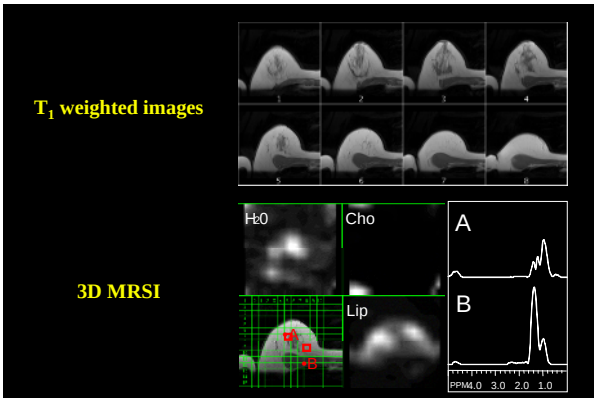
Future Directions

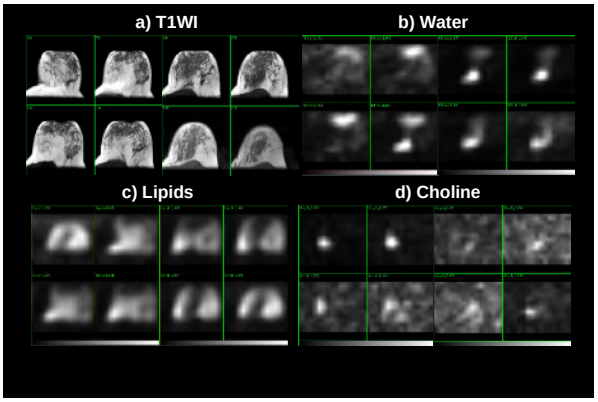
- 3D MRS
- SENSE MRS
- High Field (7T)
  - Brain
  - Breast

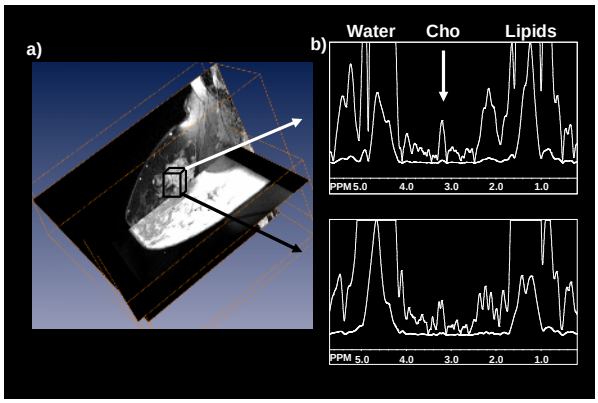
3D Spectroscopy

- **3D Spectroscopy**
  - » 3D PRESS CSI; 8 slices, 10mm, TR/TE =1010/280 ms
  - » 1500 Hz bandwidth, 1024 data points, acquisition window 682 msec (echo position 20%),
  - » CHESS water and lipid suppression (3 pulses, flip angles 161°, 83°, 89°),
  - » one signal average(NEX 1), scan time = 12 min 6 secs.









SENSE MRSI

Phase and Sensitivity data best obtained by B_1 field mapping using MRI

Body Coil + Phased Array Images

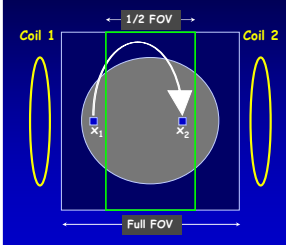
Raw MRSI Data, N Channels

B_1 Sensitivity Profiles Degrade to MRSI Resolution (i.e. 32x24 or 32x16)

Spatial Filter, 2D FFT (X,Y)

$$s(t,x,y) = \frac{\sum_{n=1}^{N} \exp(-i\arg(a_n(x,y))) \times b_n(t,x,y)}{\sum_{n=1}^{N} a_n(x,y)}$$

SENSE MRSI



MRSI signal coil 1

$b_1 = a_{11}x_1 + a_{12}x_2$

MRSI signal coil 2

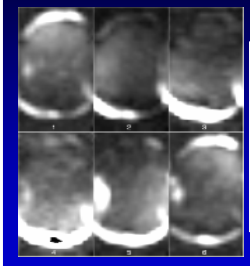
$b_2 = a_{21}x_1 + a_{22}x_2$

[a_{nm} - sensitivity of nth coil at point m]

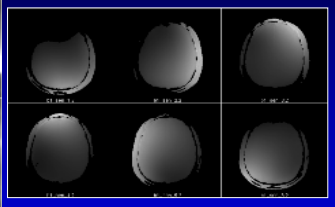
$b = A.x$

$x = A^{-1}.b$

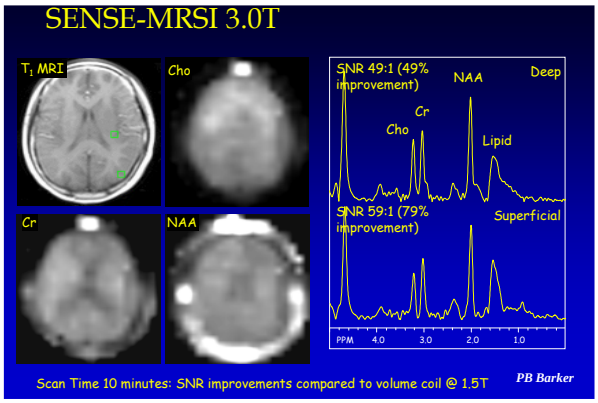
SENSE MRSI

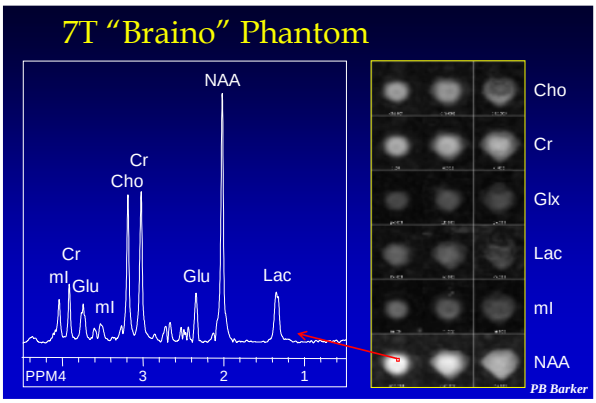


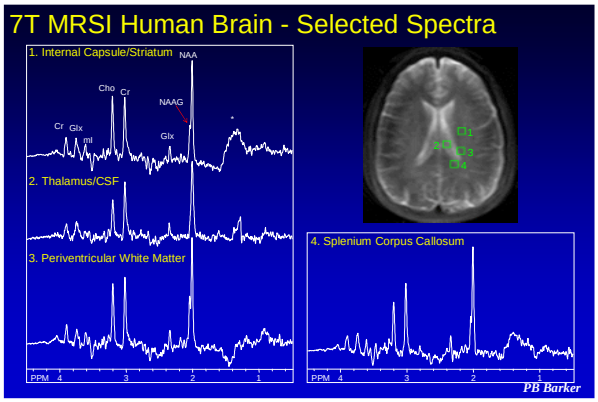
RF coil sensitivity

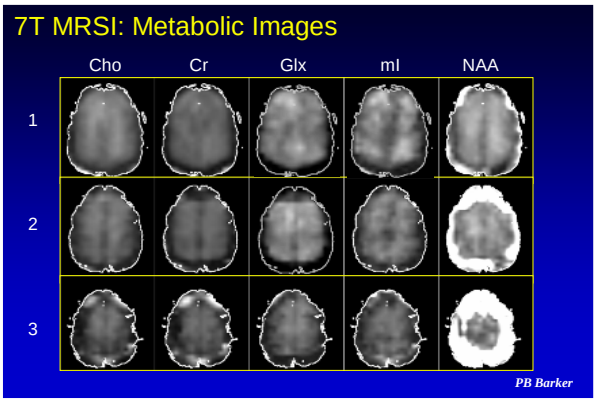


B_1 Maps

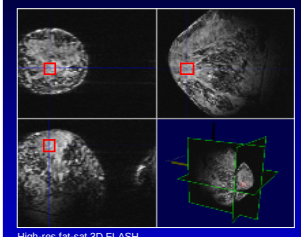

SENSE-MRSI 3.0T
T1 MRI
Cho
Cr
NAA
SNR 49:1 (49% improvement)
Deep
NAA
Cr
Cho
Lipid
SNR 59:1 (79% improvement)
Superficial
PPM 4.0 3.0 2.0 1.0
Scan Time 10 minutes: SNR improvements compared to volume coil @ 1.5T
PB Barker

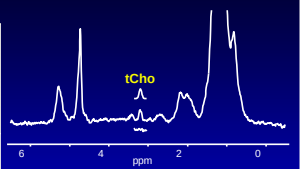

7T "Braino" Phantom
NAA
Cr
Cho
Cr
mI
Glu
mI
Glu
Lac
PPM4 3 2 1
Cho
Cr
Glx
Lac
mI
NAA
PB Barker


7T MRSI Human Brain - Selected Spectra
1. Internal Capsule/Striatum
NAA
Cho
Cr
NAAG
Cr
Glx
mI
Glx
2. Thalamus/CSF
3. Periventricular White Matter
4. Splenium Corpus Callosum
PPM 4 3 2 1
PB Barker


7T MRSI: Metabolic Images
Cho
Cr
Glx
mI
NAA
1
2
3
PB Barker

7T Breast Normal subjects





[tCho] = 0.30 ± 0.14 mmol/kg
1.65 mL voxel
TE Ave 40-193ms, 128 incr.
water LW ~20Hz

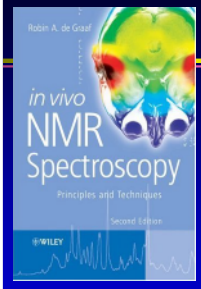
High-res fat-sat 3D FLASH
0.5 x 0.5 x 2.2 mm resolution

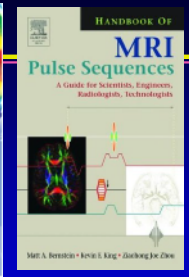
Overall
- 6 voxels measured in 5 normal subjects
- tCho in 5/6 normal voxels; taurine in 2/6
- mean [tCho] = 0.29 mmol/kg

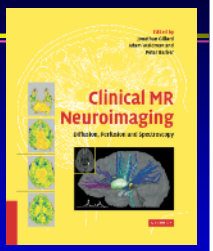
Courtesy of P. Bolan and M. Garwood, University of Minnesota

Conclusions

- MRS of breast and prostate has tremendous potential
- Imaging at high spatial resolution and high magnetic field strength ex-vivo improves detail of morphology and MRS results
- These MRS methods will be useful for therapeutic monitoring
- Future trends will lead to faster imaging time and improved spectral resolution







Acknowledgments

Peter Barker
Zaver Bhujwalla
David Bluemke
Paul Bottomley
Ihab Kamel
Jonathan S. Lewin
Kasia Macura
Ronald Ouwerkerk
Donald Peck
Vered Stearns
Richard Wahl
Antonio Wolff
Nouha Salibi
Patrick Bolan
Michael Garwood
Nathan Yanasak

NCI Grant support:1R01CA100184 ,P50 CA103175, ARRS Scholarship