## *Treatment Assessment of Radiation Therapy using MR Functional Imaging*

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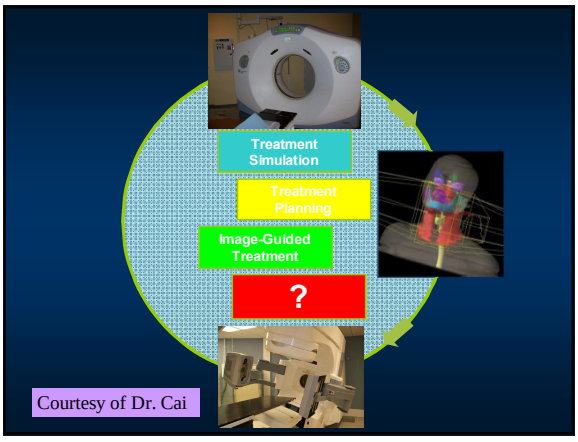
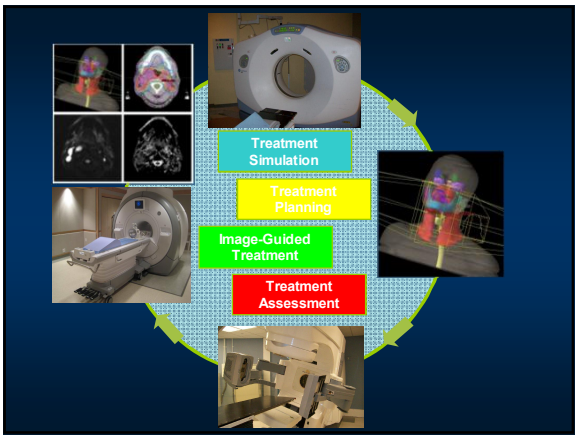
## *Symposium Objectives*

Å Understand MR functional imaging techniques
DWI, DTI, MRS, DCE-MRI é
Å Understand Issues of MR functional imaging
technical, clinical é
Å Understand Clinical applications
CNS, Liver, Prostate, GYN é

## *Outline*

- Introduction to MR functional imaging for treatment assessment
- Review of diffusion imaging (DWI & DTI)
- Review of MR spectroscopy (MRS)
- Review of dynamic contrast enhanced (DCE) or susceptibility change (DSC) imaging
- Review of functional MRI (fMRI)
- Application to Intracranial Stereotactic Radiosurgery
- Summary




## *Introduction*

Recent developments in MRI have substantially improved its performance, making it a potentially powerful tool for not only diagnosis but also therapy.

Treatment assessment using MR functional imaging is the process of using MR functional imaging before and/or during and/or after a course of radiation therapy (RT) to assess treatment responses and as such to optimize therapeutic outcome.

# *Introduction*

Various MR functional techniques including, but not limited to, DWI, DTI, MRS and DCE or DSC imaging, have been investigated to assess therapeutic outcome in radiotherapy.

- DCE or DSC-MRI uses fast imaging and contrast material to assess changes in the micro-vascular environment.
- MRS can be used to assess non-invasively biochemical changes caused by RT.
- Diffusion imaging techniques are used to assess the changes of cellular density and neural fibers caused by RT.

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# *Diffusion*

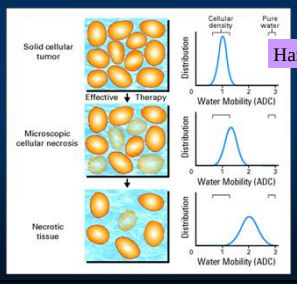
- Diffusion is known as random molecular translational motion
- Diffusion can be characterized by D (diffusion coefficient)

$$\square^{2} = 2\square\square\square$$

where R is the mean distance traveled by a water molecule in time Ű in N dimension

# Diffusion Imaging

Diffusion imaging techniques are used to determine the rate and principle direction of thermal (Brownian) motion of protons

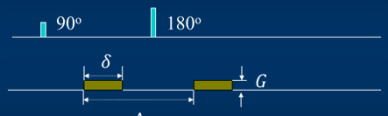



Hamstra,et al, JCO 2007

Diffusion affected by intra-cellular and extra-cellular architecture

# Diffusion-Weighting Gradients

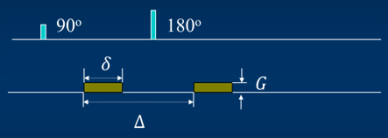
Diffusion-weighting gradient is often referred to as bipolar gradient (or Stejskal-Tanner gradient)




Stejskal, Tanner. *J Chem Physics*, 1965

Spin Echo: 90° RF, first gradient lobe, 180° RF, second gradient lobe

# Diffusion-Weighting Gradients




b-factor for rectangular pulse of spin echo

$$b = \gamma^2 G^2 \delta^2 (\Delta - \delta/3)$$

$$\rightarrow \frac{S}{S_0} = \exp(-bD)$$

## *Diffusion-Weighting Gradients*

When diffusion-weighting gradient is included in sequence, water diffusion can cause signal attenuation, depending the product of diffusion coefficient and b-factor.

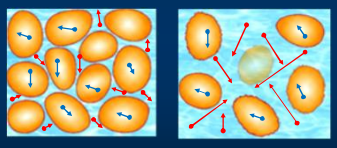
The b-factor is determined by the diffusion-weighting gradient waveform. The increase in gradient amplitude, pulse width and pulse separation can cause greater b-factor, more attenuation.

The b-factor is analogous to TE in T2-weighted imaging: greater b-factor, greater diffusion effect; greater TE, greater T2-weighting.

## *Diffusion-Weighting Gradients*

Tissue A

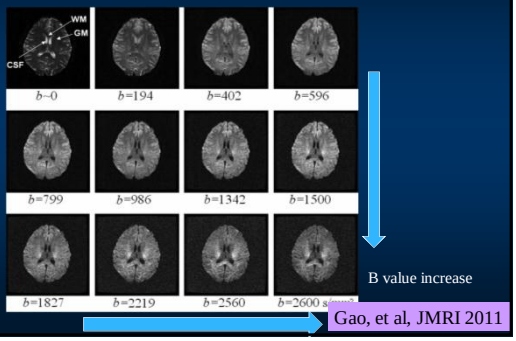
Tissue B



Restricted Diffusion
Bright Contrast

Freely Diffusion
Dark Contrast

## *Diffusion Weighted Imaging*




Gao, et al, JMRI 2011

## *Diffusion Imaging Acquisition*

Three categories of methods for obtaining diffusion imaging:

- The most popular diffusion imaging methods are ultra-fast sequences, such as the diffusion sensitized EPI
- Methods employing navigator echoes
- Methods that are insensitive to phase errors between excitations. For example, LSDI (line scan diffusion imaging) and PR (projection reconstruction)

## *Diffusion Imaging Acquisition*

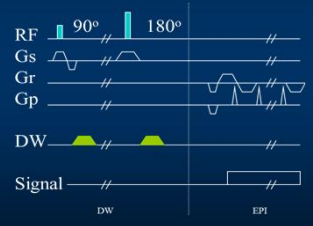
The ultrafast imaging methods include:

- Single or multi-shot EPI
- Other single-shot techniques, such as those based on the RARE and GRASE

Among the ultrafast imaging modalities, EPI is the most commonly used.

## *Diffusion Imaging Acquisition*

A standard DW-SE-EPI pulse sequence :



## *Diffusion Imaging Acquisition*

In order to keep the balance between the scan time and image quality, segmented sequences are introduced.

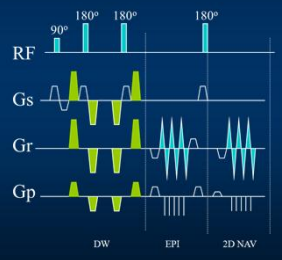
Examples are FSE(RARE) and segmented EPI.

In a segmented sequence, motion of a patient during each diffusion sensitization causes different phase errors, which cause severe image artifacts.

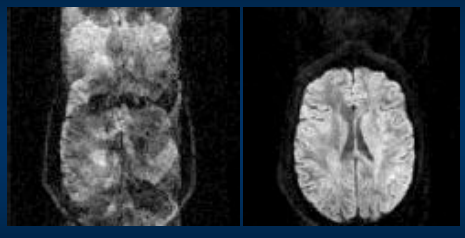
Correction can be applied through the use of navigator echoes.

## *Diffusion Imaging Acquisition*

The sequence of segmented EPI with navigator echoes




## *Diffusion Imaging Acquisition*



(left) one measure, no correction; (right) four measures, with correction

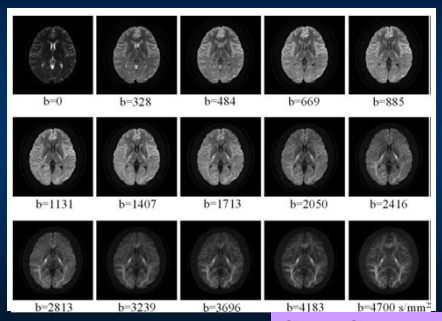
Atkinson, et al. MRM, 2000

## *Diffusion Imaging Acquisition*

Methods that are insensitive to phase errors include

- Line scan diffusion imaging (LSDI)
  lower SNR
  not rely on spatial phase encoding. This is why LSI is inherently insensitive to phase variation
- Methods based on projection reconstruction (PR)
  acquire data along radial lines of Fourier space
  no significant artifacts due to motion

## *High b-Value Diffusion*




Zhou, et al. MRM, 2010

## *High b-Value Diffusion*

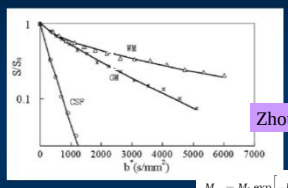
- In many biologic tissues, the diffusion-induced MR signal loss deviates from mono-exponential decay, exp(-bD) (where D is the diffusion coefficient and b is the b factor), particularly at high b values (e.g., >1500 sec/mm² for human brain tissues).
- has been modeled extensively using a bi-exponential function:

$$S/S_0 = (1-f)\exp(-bD_{fast}) + f\exp(-bD_{slow})$$

- The ǿbiexponentialõ behavior has been attributed intra- and extracellular spaces; however, biexponential behavior has been observed from the intracellular compartment alone. The division of water molecules between the two compartments is somewhat arbitrary.

Zhou, et al. MRM, 2010

## *High b-Value Diffusion and Fractional Calculus*



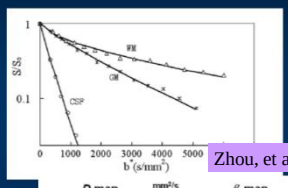

Zhou, et al. MRM, 2010

$$M_{stj} = M_0 \exp\left[-D\mu^{2(\beta-1)}(\gamma G_d \delta)^{2\beta}\left(\Delta - \frac{2\beta-1}{2\beta+1}\delta\right)\right]$$

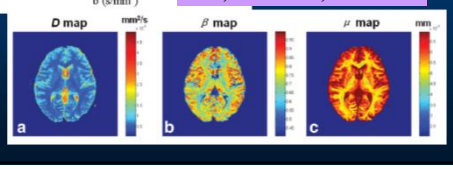
Eq. reduces to the classic mono-exponential expression when β = 1

$$M_{stj} = M_0 \exp\left[-D(\gamma G_d \delta)^2\left(\Delta - \frac{1}{3}\delta\right)\right]$$

## *High b-Value Diffusion and Fractional Calculus*



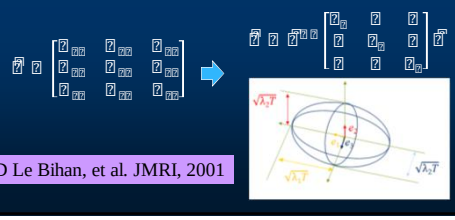

Zhou, et al. MRM, 2010




## *Diffusion Tensor Imaging*

Diffusion is truly a three-dimensional process. Hence, molecular mobility in tissues may not be the same in all directions.

- Diffusion can be described by a tensor, with min. 7 acquisitions.
- The diffusion tensor can be an ellipsoidal approximation

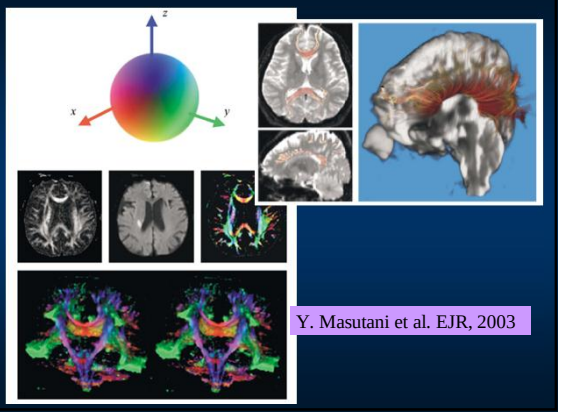


D Le Bihan, et al. JMRI, 2001

## *Diffusion Tensor Imaging*

Three diffusion indexes: apparent diffusion coefficient (<D>), fractional anisotropy (FA), and the number of fibers (NF) can be derived from the diffusion tensors.

- <D> is the quantitative measure of magnitude of diffusion, which is generally calculated as the mean of the diffusivities in the three orthogonal directions.
- FA is the quantitative measure of direction or anisotropy of diffusion. the greater the FA value, the more restricted water molecular diffusion.
- The structure of neural fibers were tracked along axonal projections.



Y. Masutani et al. EJR, 2003

## A standard DTI needs at least

| | | |
|---|---|---|
| 20% | 1. | 4 acquisitions |
| 20% | 2. | 6 acquisitions |
| 21% | 3. | 7 acquisitions |
| 19% | 4. | 8 acquisitions |
| 19% | 5. | 9 acquisitions |

Answer: 3 ï 7 acquisitions

Ref: D. Le Bihan, et al., Diffusion Tensor Imaging: Concepts and Applications, JMRI, 13:534ï 546 (2001)

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# Introduction to Spectroscopy

- Larmor Equation: resonant frequency dependent on magnetic field strength

$$\nu = \gamma B_{nucleus}$$

where ν is the resonant frequency (MHz), γ is the gyromagnetic ratio (γ/(2π)=42.57 MHz/T for protons), and B is the applied magnetic field strength (T) at a given nucleus

# Introduction to Spectroscopy

$$\nu = \gamma B_{nucleus} = \gamma B_0(1 - \sigma)$$

- value of $B_{nucleus}$ depends on the local electronic environment
- value of the applied field, $B_0$, is modified due to the chemical environment
- Nuclei in different chemical environments have slightly different resonance frequencies depending on the amount of local nuclear shielding, σ,
- Results in spectra with multiple peaks for a given nuclear species

## *Introduction to Spectroscopy*

- The position of a given spectral peak is usually given in terms of *chemical shift* with respect to some reference.
- Chemical shift characterizes the variation in the Larmor frequency of a given nucleus in different chemical environments.

$$\delta = [(\nu - \nu_{ref})/\nu_{ref}] \times 10^6$$

- The amount of the shift is proportional to magnetic field strength and is usually specified in parts per million (ppm) of the resonance frequency relative to a reference

## *Introduction to Spectroscopy*

The success of MRS depends upon the following:

- Efficient water suppression (1H MRS)
- High quality localization
- Highly homogeneous magnetic field
- Spectral quantitation

## *MRS: Water Suppression*

- The metabolites of interest are usually much less in concentration than water.
- Suppress the water resonance to detect the metabolite resonances


- multiple (often 3), narrow bandwidth (~50 Hz) pulses are applied at the water resonance frequency

# *MRS: Localization*

In MRS, the region must be accurately known. The most commonly used localization techniques are:

- Single voxel volume localization (SVL):
  VOI is the intersection of three slice selective gradient/RF
- Spectroscopic imaging (MRSI):
  Uses phase-encoding for localization.

# *MRS: Localization*

The most common SVL techniques are:

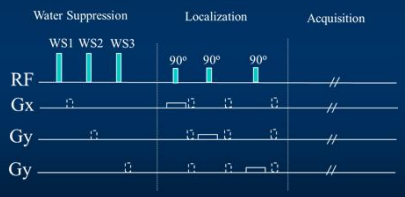
- STEAM: 90º-90º-90º-Data Acquisition
- PRESS: 90º-180º-180º-Data Acquisition

ÅAdvantage of STEAM: shorter minimum echo times

ÅAdvantage of PRESS: 2x SNR increase vs. STEAM

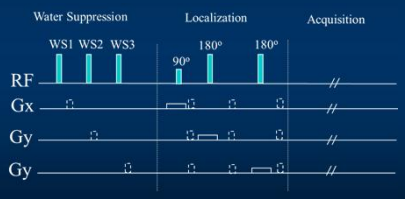
# *MRS: Localization*

STEAM: 90º-90º-90º-Data Acquisition

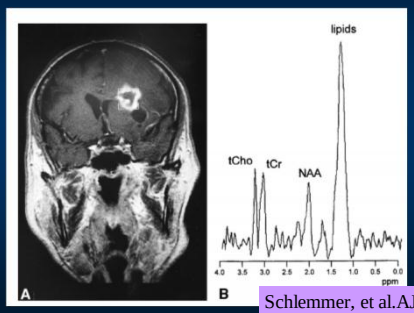


# *MRS: Localization*

PRESS: 90º-180º-180º-Data Acquisition




# *MRS: Localization (SVL)*



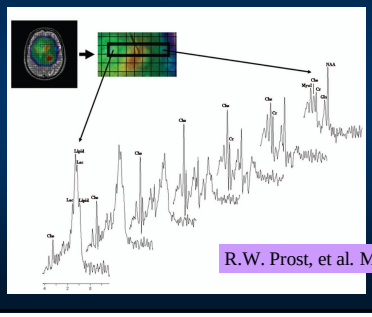

Schlemmer, et al.AJNR, 2001

# *MRS: Localization*

Compared with SVL, MRSI techniques use phase-encoding for part or all of the localization to yield multiple VOIs.

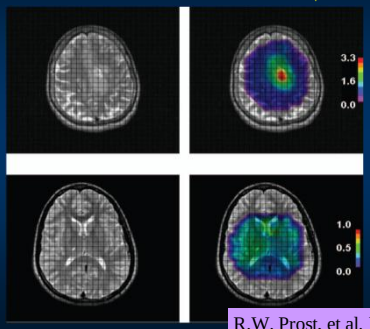
- 2D MRSI: Uses one slice selection gradient/RF pair to define a slice, and then phase-encodes the remaining two dimensions.
- 3D MRSI: Uses three phase-encoding gradients to define a 3D VOIs

## MRS: Localization (MRSI)



R.W. Prost, et al. MedPhys, 2008

## MRS: Localization (MRSI)

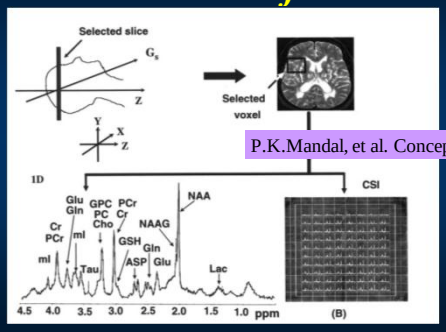



R.W. Prost, et al. MedPhys, 2008

## MRS: Localization (MRSI)

- Advantages of MRSI:
  - ï Spectra from multiple VOIs obtained for comparison.
  - ï Spectra from smaller VOIs can be obtained.
  - ï ñMetabolite mapsò
- Disadvantages of MRSI:
  - ï long acquisition times
  - ï spatially-dependent water suppression
  - ï ñspectral-bleedò from one voxel to another

## MRS: Workflow




P.K.Mandal, et al. Concept, 2007

## MR Spectrocopy

Practical Considerations:

The choice of TE in MRS is critical. As TE increases, the signal from metabolites decreases due to spin dephasing.

Each metabolite has its inherent T1 and T2 relaxation times. Therefore, change of TE and/or TR results into the changes of relative peak areas and heights.

Corrections are required when comparing data acquired at different TE and TR values

## Which is to obtain metabolite maps?

| | | |
|---|---|---|
| 22% | 1. | Diffusing tensor imaging |
| 20% | 2. | Dynamic susceptibility-change imaging |
| 23% | 3. | Dynamic contrast-enhanced imaging |
| 17% | 4. | Single voxel MR spectroscopy |
| 18% | 5. | Multi-voxel MR spectroscopic imaging |

Answer: 5 ï Multi-voxel MR spectroscopic imaging

Ref: R.W. Prost, et al. Magnetic resonance spectroscopy, MedPhys, 35:4530-4544, (2008)

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# Angiogenesis

- Angiogenesis is a complex process critical to the growth and metastasis of malignant tumors.
- Tumor growth beyond 1ï 2 mm in solid tissues cannot occur without vascular support.
- Early detection of such changes would allow assessment of the therapeutic outcome of anti-vascular agents and aid in diagnosis.

J. Folkman Eur J Cancer 1996

# Detection of Angiogenesis

Current methods of assessing angiogenesis can be considered as either direct or indirect.

- direct method: microvascular density counting with immunostaining (most frequently used)
  - invasive and no functional information
- indirect method: indirect biomarkers of angiogenesis detected by imaging such as MRI
  - Non-invasive and provide functional information

J.A. dôArcy RadioGraphics 2006

## *Detection of Angiogenesis*

- MR techniques require the infusion of exogenous contrast agents to assess microvascular changes
- Gadolinium is the most common paramagnetic atom used in MR agents
  - ï Gd is toxic - must be tightly chelated
  - ï Three common Gd agents:
    - ÅMagnevist (gadopentetate dimeglumine)
    - ÅOmniscan (gadodiamide)
    - ÅProhance (gadoteridol)
  - ï low molecular weight contrast media

## *Contrast Agent Kinetics*

- When a bolus of contrast agent passes through a capillary bed, it is transiently confined within the vascular space. Blood volume (BV) and blood flow (BF) can be derived from the ñfirst passò of the contrast medium.
  - The ñfirst passò describes the initial passage of the bolus of contrast medium and lasts for a few cardiac cycles
- Mostly, the contrast agent rapidly passes into the extravascular-extracellular space (EES) (also called the leakage space [$v_e$]) at a rate determined by the permeability of the microvessels (described by transfer constant $K^{trans}$) and their surface area and by blood flow.

## *Contrast Agent Kinetics*

- As low molecular weight contrast media do not cross cell membranes, the volume of distribution is effectively the EES.
- Over a period typically lasting several minutes to an hour, the contrast agent diffuses back into the vasculature (described by the rate constant or $k_{ep}$).
- When capillary permeability is very high, the return of contrast medium is typically rapid, resulting in faster washout.
- Finally, contrast medium is excreted (usually by the kidneys)

# DCE and DSC MRI

MR imaging sequences can be designed to be sensitive to two different phases:

- Vascular phase of contrast medium delivery

  Dynamic susceptibility-change (DSC) MR imaging
  Reflects blood perfusion and blood volume

- presence of contrast medium in the EES

  Dynamic contrast-enhanced (DCE) MR imaging

  Reflect microvascular perfusion, permeability, and extracellular leakage space

# DCE and DSC MRI

**Table 1**
**Comparison of the T2*- and T1-weighted Dynamic Contrast-enhanced MR Imaging Techniques**

| Parameter | T2*-weighted Imaging | T1-weighted Imaging |
|---|---|---|
| Change in tissue signal intensity | Darkening | Enhancement |
| Duration of effect | Seconds | Minutes |
| Period of optimal data acquisition | Subsecond | 2–25 sec |
| Magnitude of effect | Small | Larger |
| Optimal dose of contrast medium | ≥0.2 mmol/kg | 0.1–0.2 mmol/kg |
| Quantification methods used | Relative more than absolute | Relative and absolute |
| Physiologic properties measured | Perfusion, blood volume | Transendothelial permeability, capillary surface area, lesion leakage space |
| Kinetic parameters derived | Blood volume and flow, transit time | Transfer and rate constants, leakage space |
| Pathologic correlates | Tumor grade, microvessel density | Microvessel density, vascular endothelial growth factor |
| Clinical MR imaging applications | Characterization of breast, liver, and brain lesions; noninvasive grading of brain tumors; directing biopsy of brain tumors; determination of prognosis for brain tumors; monitoring treatment (eg, radiation | Lesion detection and characterization; improving accuracy of tumor staging; prediction of response to treatment; monitoring response to treatment; allowing novel therapies, including antiangiogenic drugs; detection of tumor relapse |

J.A. dôArcy RadioGraphics 2006

# DSC-MRI

Contrast agent concentration in vascular phase in perfusion measurement:

- Change in *R2** (æ*R2**) with time caused by the presence of contrast agent
- Change in *R2** can be quantified from a single-echo T2*-weighted dynamic series

$$\Delta R2^{*}(t) = -\frac{1}{TE}\ln\left(\frac{S(t)}{S_0}\right)$$

- where $S_0$ is the mean pre-enhancement signal intensity, S(t) is the signal intensity as a function of time, and TE is the echo time

# DSC-MRI

Contrast agent concentration in vascular phase in perfusion measurement:

- Change in *R2** can be quantified from a single-echo T2*-weighted dynamic series

$$\Delta R2^*(t) = -\frac{1}{TE}\ln\left(\frac{S(t)}{S_0}\right)$$

- Contrast agent concentration, C(t), can be calculated

$$C(t) = \frac{1}{r2}\Delta R2^*(t)$$

# DSC-MRI: Perfusion Model

- The decrease in signal intensity corresponding to the passage of a bolus of contrast agent is manifested as a peak
- Fitting a model function (i.e. gamma variate) to the first peak:

$$\gamma(t) = S(t) = S(0)(1 - A\,C(t))^{\alpha}e^{-(t-t_0)/\beta}$$

- Relative blood volume (rBV):

$$rBV = \frac{\int_{\tau} C(t)\,dt}{\int_{0} C_a(t)\,dt}$$

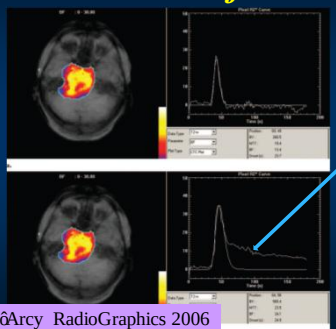
- Relative mean transit time (MTT):

$$rMTT = \frac{\int_{\tau} t\,C(t)\,dt}{\int_{\tau} C(t)\,dt}$$

- Relative blood flow (rBF)

$$rBF = rBV/rMTT$$

# DSC-MRI: Perfusion Model




J.A. dôArcy RadioGraphics 2006

## *Quantitative Perfusion*

- All the previous formula assume an idealized instantaneous arterial input function (AIF)!!!
- AIF has to be known for quantification of the BV and BF

$$C(t) = C_a(t) \otimes \text{[illegible]}(t)$$

K.A. Rempp, et al. Radiology 1994

## *Quantitative Perfusion*

- BV represents the amount of blood in a given tissue.

$$\text{r[illegible]} = \int_{\text{[illegible]}} \text{[illegible]}(t)\,dt$$

$$\text{[illegible]} = \frac{1}{\text{[illegible]}} \frac{(1 - \text{[illegible]})}{(1 - \text{[illegible]})} \frac{\text{[illegible]}(t)\,dt}{\text{[illegible]}(t)\,dt}$$

K.A. Rempp, et al. Radiology 1994

## *DCE-MRI*

Contrast concentration during measurement of contrast agent uptake:

- Change in R1 with time caused by the presence of contrast agent
- R1 or T1 relaxation rate at a given time during the dynamic imaging period is calculated from the ratio of the T1-weighted signal intensity.

Spoiled gradient echo (SPGR) signal intensity (S) is

$$S = S_0 \frac{\sin\alpha\,(1 - E1)E2}{(1 - E1\cos\alpha)}$$

where Ü is flip angle, E1 = $e^{-TR/T1}$ and E2 = $e^{-TR/T2}$

# DCE-MRI

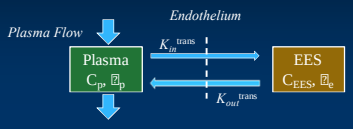
Contrast concentration during measurement of contrast agent uptake:

- The concentration, C, of contrast agent in the voxel is calculated from the observed changes in T1 relaxation rate from the pre-contrast value $T1_0$.

$$C = (R1 - R10)/r1 = \left(\frac{1}{T1} - \frac{1}{T10}\right)/r1$$

where $r1$ is the longitudinal relaxivity of the contrast agent at the field strength of the MR imaging unit

# Pharmacokinetic Model

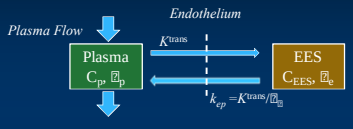



$C(t) = v_p C_p(t) + K^{trans} \int_0^t C_p(u)\, e^{-k_{ep}(t-u)}\, du$ C(t) = [Gd] in tissue measured

$C(t) = K^{trans} \int_0^t C_p(u)\, e^{-(K^{trans}/v_e)(t-u)}\, du + v_p C_p(t)$

P.S. Tufts, et al. JMRI, 1997

# Pharmacokinetic Model




$C(t) = K^{trans} \int_0^t C_p(u)\, e^{-(K^{trans}/v_e)(t-u)}\, du + v_p C_p(t)$

Assume small plasma volume $v_p = 0$ and $K^{trans} = k_{ep} v_e$

$\Rightarrow C(t) = K^{trans} \int_0^t C_p(u)\, e^{-k_{ep}(t-u)}\, du$

## *Pharmacokinetic Model*

$$C_t(t) = K^{trans} \int_0^t C_p(\tau) e^{-k_{ep}(t-\tau)} d\tau$$

In this case, *Cp* is measured arterial input function (AIF)

Alternatively, the concentration of contrast agent in the plasma, *Cp*, can be derived theoretically to be a bi-exponential decay

$$C_p(t) = D[k_1 e^{-m_1 t} + k_2 e^{-m_2 t}]$$

The two terms in plasma washout curve correspond to the equilibration of contrast agent between the plasma and extracellular space (fast) and the removal of contrast agent from the plasma by the kidneys (slow).

## *Pharmacokinetic Model*

$$C_t(t) = K^{trans} \int_0^t C_p(\tau) e^{-k_{ep}(t-\tau)} d\tau$$

$$C_p(t) = D[k_1 e^{-m_1 t} + k_2 e^{-m_2 t}]$$

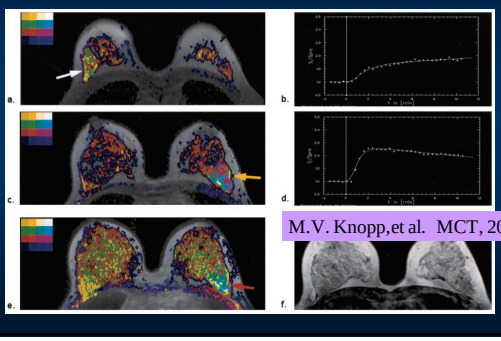
$$\Rightarrow C_t(t) = K^{trans} \frac{D[k_1(e^{-m_1 t} - e^{-k_{ep} t}) + k_2(e^{-m_2 t} - e^{-k_{ep} t})]}{k_{ep} - m_1} \quad m_2$$

P.S. Tufts, et al. JMRI, 1997

## *DCE-MRI Analysis*

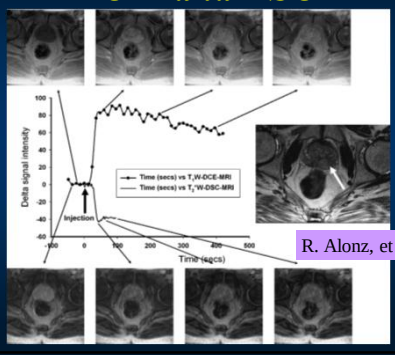
- Qualitative
  - Visual examination of uptake curves
- Semi-quantitative
  - Time to peak enhancement
  - Maximum uptake (maximum signal difference)
  - Maximum rate of uptake (maximum slope)
  - Area under the curve (AUC) and initial AUC
- Quantitative
  - Pharmacokinetic modeling

## DCE-MRI



M.V. Knopp,et al. MCT, 2003

## DCE- and DSC-MRI




R. Alonz, et al. EJR 2007

## Which sequence used in DSC?

17% 1. Proton-density sequence

20% 2. T1-weighted sequence

20% 3. T2*-weighted sequence

21% 4. Inversion recovery sequence

23% 5. Diffusing weighted sequence

Answer: 3 ï T2*-weighted sequence

Ref: d'Arcy JA, et al., Informatics in Radiology (infoRAD): Magnetic Resonance Imaging Workbench: analysis and visualization of dynamic contrast-enhanced MR imaging data, RadioGraphics, 26:621-632, (2006)

# Outline

- Introduction to MR functional imaging for treatment assessment
- Review of diffusion imaging (DWI & DTI)
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- Review of functional MRI (fMRI)
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- Summary

# Functional MRI

- In 1990, a series of breakthroughs: transformed MRI into a non-invasive means of revealing physiological activity in the brain.
- Later, it has been reported that task-related changes in the BOLD contrast can be detected in the human brain, which provides image contrast based on difference of oxyhemoglobin (diamagnetic) and deoxyhemoglobin (paramagnetic)
- Blood-oxygenation-level-dependent (BOLD) contrast imaging is now commonly known : functional MRI (fMRI)

Ogawa et al., MRM, 1990

Kwong et al., Proc Natl Acad Sci, 1992.

# Functional MRI

- During activation of the brain, the oxygen consumption of the local tissue increase by approximately 5%.
- With that, the oxygen tension will decrease. As a consequence, after a short period of time vasodilatation occurs, resulting in a local increase of blood volume and flow by 20 - 40%.
- The change in local blood flow and oxygen extraction increases the local oxygen level.
- As a consequence, susceptibility effect decreases, leading to increase in signal intensity.

Ogawa et al., MRM, 1990

Kwong et al., Proc Natl Acad Sci, 1992.

# Functional MRI

*Blood Flow*

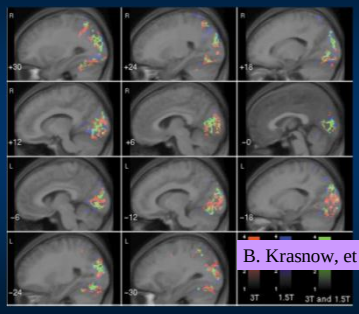
| Normal State | Neuronal Activated State |
|---|---|
| Baseline oxyHb (diamagnetic) | ↑ increased oxyHb by 20ł 40% |
| Normal oxygen extraction rate | ↑ oxygen extraction rate by 5% |
| Baseline oxyHb/deoxyHb | ↑ oxyHb/deoxyHb |
| Relatively large susceptibility effect | ↓ Decreased susceptibility effect |
| Baseline MR signal intensity | ↑ Increased MR signal intensity |

# Functional MRI

- T2 weighted gradient echo EPI sequences are commonly used, which are highly susceptibility sensitive and fast enough to capture the three-dimensional nature of activated brain areas.
- As the effects are subtle and of the order of 2% in 1.5 T MR imaging, sophisticated methodology, paradigms and data analysis techniques have to be used to consistently demonstrate the effect.
- Various tasks to be studied, such as visual perception task, working memory task, affect-processing task é

B. Krasnow, et al., NeuroImage, 2003

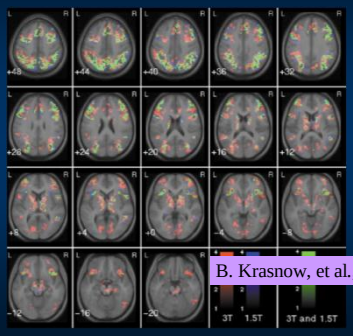
# Functional MRI



visual perception task

B. Krasnow, et al., NeuroImage, 200

## *Functional MRI*




working memory task

B. Krasnow, et al., NeuroImage, 2003

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## *Stereotactic Radiosurgery*

- Stereotactic radiosurgery (SRS) has been an effective treatment for the management of brain metastases, acoustic neuromas and other brain diseases
- SRS often delivers high radiation dose in a single fraction. SRS differs from conventional fractionated radiotherapy in its much greater fractional dose and its hypofractionation scheme.

Leksell, L. Acta Chir Scand, 1951

Breneman, et al., Int J Radiat Oncol Biol Phys, 2009.

## SRS Study of Giloma

- In this study, fifteen patients were enrolled in this study. All the patients have recurrent, unifocal malignant gliomas, each up to 5 cm in maximum dimension.
- The patients were treated with DACT, IMRT or VMAT. The prescription dose received by the patients ranged from 18Gy to 25Gy.
- Patients were also scanned with MRI 1-4 days prior to SRS and 7 days and two months following the SRS treatment.
- The study was approved by institutional review board.

## SRS Study of Giloma

All MRI scans including DTI were acquired on a 1.5T clinical scanner (GE Healthcare, Milwaukee, WI) using a standard quadrature birdcage head coil.

- The imaging protocol included T1- and T2-weighted imaging, FLAIR, DTI, DCE-MRI, and 3D high-resolution post-contrast T1-weighted imaging.
- DTI scans were acquired in the axial plane using a spin-echo echo-planar imaging sequence.
- DCE-MRI scans were acquired in the axial plane using a 3D spoiled gradient recalled echo imaging sequence.

## MR Functional Imaging

- DCE-MRI data were analyzed to derive parameters:
  - Transport constant $K^{trans}$
  - *f*ractional EES volume $f_e$
  - Area under curve AUC
- Diffusion tensors were calculated and fiber tracking was performed:
  - Apparent diffusion coefficient <D>
  - Fractional anisotropy FA
  - Number of fibers (NF)
- Volume of interest: PTV
  Normal-appearing white matter dose Ó5Gy

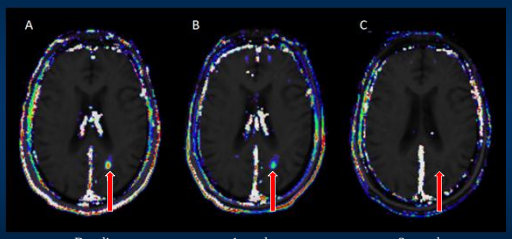
# Patient Characteristics

| Patient No. | Age(y) | Gender | Diagnosis | Tumor location | Dose (Gy) |
|---|---|---|---|---|---|
| 1 | 35 | M | astrocytoma | left parietal | 25 |
| 2 | 53 | M | glioblastoma | right parietal | 18 |
| 3 | 41 | M | anaplastic oligodendroglioma | right frontal | 18 |
| 4 | 38 | M | glioblastoma | inferior parietal | 25 |
| 5 | 48 | M | glioblastoma | right frontal | 18 |
| 6 | 66 | M | glioblastoma | left parietal | 24 |
| 7 | 64 | M | glioblastoma | left frontal | 25 |
| 8 | 50 | M | glioblastoma | left frontal | 24 |
| 9 | 55 | M | anaplastic oligodendroglioma | left parietal | 24 |
| 10 | 58 | F | anaplastic oligodendroglioma | left frontal | 25 |
| 11 | 58 | M | glioblastoma | right temporal | 18 |
| 12 | 65 | M | glioblastoma | left frontal | 18 |
| 13 | 55 | F | glioblastoma | right temporal | 18 |
| 14 | 27 | M | glioblastoma | right temporal | 18 |
| 15 | 56 | F | glioblastoma | right frontal | 25 |

# DCE-MRI Analysis

- DCE-MRI to interrogate tumor biology and treatment-related changes in tumor vasculature caused by SRS:
  - Transport constant $K^{trans}$
  - Fractional EES volume $v_e$
  - Area under curve AUC
- Volume of interest: PTV

# DCE-MRI Analysis

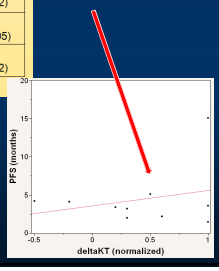



Baseline 1 week 2 months

# DCE-MRI Analysis

| | Baseline | 1 Week | 2 Months |
|---|---|---|---|
| **Median $K^{trans}$** ($min^{-1}$) | 6.7 | 4.1 ($p$=0.04)* | 0 ($p$=0.002) |
| **Median AUC** (mmol/kg s) | 2.1 | 1.4 ($p$=0.02) | 0.1 ($p$=0.0005) |
| **Median EVF** | 0.58 | 0.48 ($p$=0.53) | 0 ($p$=0.002) |

*p-values reflect comparisons with baseline imaging



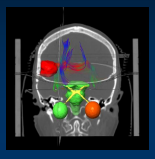

*deltaKT = ($KT_{baseline} - KT_{1\ week}$) / KTbaseline*
*deltaKT =1: KT decreased to zero by Week 1*
*deltaKT <0: KT had increased by Week 1*

Courtesy of Dr. Cabrera

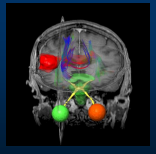
# DTI Analysis

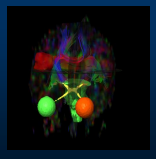
- DTI was used in this work to investigate the structural changes in the white matter fiber tracts caused by SRS:
  - Apparent diffusion coefficient <D>
  - Fractional anisotropy FA
  - Number of fibers (NF)
- Volume of interest: Normal-appearing white matter dose Ó5Gy

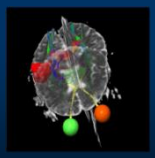
# Results: DTI Analysis



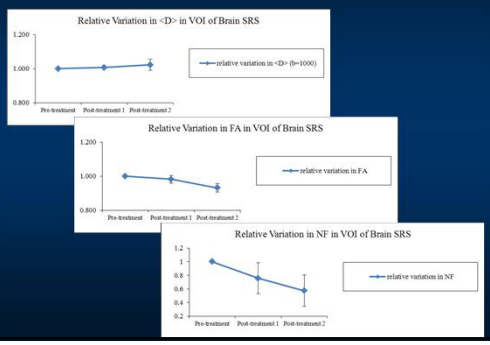
Representative Patient



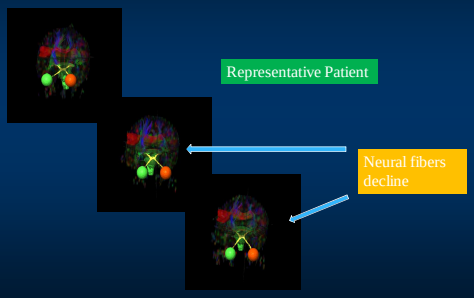




## Results: DTI Analysis




## Results: DTI Analysis




## DTI Analysis

- After 7 days of SRS, <D> increased by 0.7% ($p$= 0.53), and FA decreased by 1.8% ($p$ = 0.17) with 24% decline of NF ($p$ = 0.12).
- After two months, <D> increased by 2.3% ($p$= 0.36), and FA decreased significantly by 6.8% ($p$<0.01) with 40% decline of NF ($p$ = 0.02).
- These preliminary results suggest that dose sparing to white matter should be considered in SRS, particularly when the target is close to white matter fiber bundles such as genu and splenium.

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## Summary

- MR functional imaging has various applications:
  DWI, DTI, MRS, DCE-MRI, DSC-MRI, fMRIé
- MRI functional imaging has shown both challenges and great potentials.
- MRI functional imaging is valuable in guiding and assessing RT.
- Pave the road to future development of RTé


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