An Integrated MRI Protocol for Radiation Therapy

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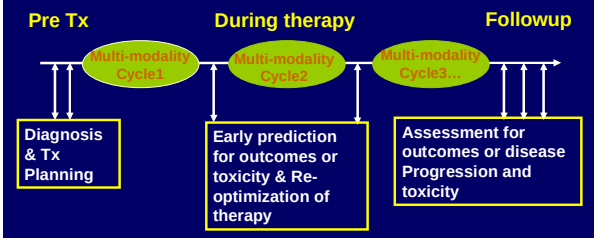
Treatment Paradigm



Functional and molecular Imaging could provide early prediction for both Tx outcome and toxicity prior to conventional followup and symptomatic injury.

Clinical Value of Imaging for Treatment Assessment

- Tumor local/regional control/failure
  - Tumor failure pattern
  - Most aggressive or resistant subvolume
  - Radiation boost volume
- Early assessment and prediction of tumor response to therapy
- Early assessment and indication of normal tissue injury due to treatment

- **Metabolic, functional, and molecular imaging can provide additional information to anatomic imaging**

Imaging Techniques

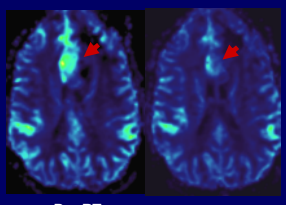
- New molecular imaging techniques
  - Image molecular processes
  - High specificity and sensitivity
  - Under evaluation and development
  - Limited availability
- Functional and Physiological Imaging
  - Demonstrate their clinical values for treatment assessment
  - Provide additional information compared to anatomic images

Early Assessment for GBM Response to CRT

- Max TBV (high neovascularization) in glioma pre therapy

→ tumor grade & a prognostic factor of OS

- Does reduction in high TBV of glioma during early treatment of CRT predict clinical outcomes?
- A decrease in the fractional tumor volume of high BV is associated with better survival (Cao 2006a)



Pre RT | Week 3 during RT

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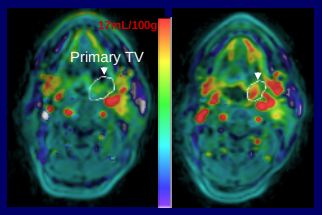
Early Assessment for Outcomes in Advanced HNC

•Prognostic Values of Pre RT TBV
- •Response to RT
- •Response to induction chem therapy
- •Better perfused HNC → better response to CT & RT

•Changes in TBV during the early course of RT → better prediction for outcomes?

•An increase in BV of primary HNC → better local control (ASTRO 2008)



Pre RT | 2 weeks after the start of FRT

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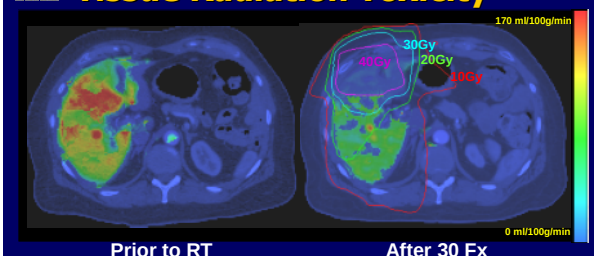
Early Prediction for Normal Tissue Radiation Toxicity



Prior to RT | After 30 Fx

1. Reduction in regional portal venous perfusion after 30Fx of radiation and local dose predict the decrease of venous perfusion after RT. (Cao, 2007a)
2. The measure of portal venous perfusion predict overall liver function.
3. Portal venous perfusion can be used to assess individual sensitivity to radiation. (Cao, 2007b)

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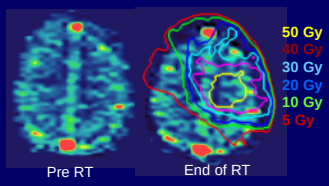
Early Changes in Normal Tissue Vasculature

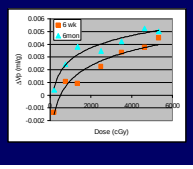
▪Changes in vasculature in response to irradiation
- ➢Early
- ➢Related to tissue injury

▪Early changes in vasculature During the course of FRT
- ➢Detectable using imaging?
- ➢Dose dependent?
- ➢Predicable for late neurocognitive dysfunction?

▪Early increase in BV
- ➢Week 3 & week 6 of FRT
- ➢Dose dependent
- ➢Predict for late changes in Neurocognotove function (ASTRO 2008)



Pre RT | End of RT



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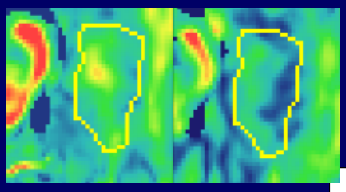
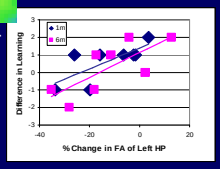
Critical Brain Structure Injury



Prior to RT 6 months after RT



Courtesy of Nagesh

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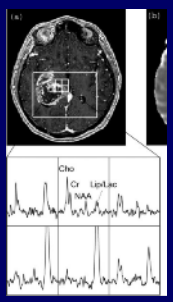
Tumor Target Definition

- Abnormal Cho signals in GBM
  - Abnormal cho signals beyond the contrast enhanced abnormality
  - Volume of CNI > 2 predicts survival (Oh 2004)
- Cho/NAA is associated with the degree of tumor cell infiltration but not tumor cell density (Croteau 2001)



Oh et al. JMRI, 2004

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Learning Objectives

- Understand the physiological origins of perfusion, diffusion and diffusion tensor imaging;
- Understand typical imaging acquisition protocols and basic image processing methods;
- Understand clinical applications and limitations.

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Outline

- Clinical values of perfusion, diffusion, and diffusion tensor imaging for therapy assessment
- Physiological origins of perfusion, diffusion, and diffusion tensor imaging
- Typical protocols
- Image processing
- Applications and limitations

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Typical Brain MRI Protocol

- 3-plane localizer
- 3D (2D) high-resolution T1W images
- 2D T2W images
- 2D FLAIR images
- DTI images
- Series of Saturation recovery T1W images
- DCE dry run
- DCE images
- DSE dry run
- DSE images
- Post-Gd 3D (2D) high-resolution T1W images
- 3D (2D) chemical shift images

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Typical Protocol: CBV and CBF (brain)

MR parameters for DSE images

Sequence type	2D SE or GE EPI
Plane	axial (AC-PC)
TR/TE (ms)	1300-1500/30-60(GE), 60-105(SE)
FOV (mm)	220-240
Temporal repetition	35-120
Flip angle (degree)	60-90
Phase FOV (%)	75-100
Slice thickness (mm)	4-6
Spacing (gap) (mm)	0-2.5
Number of slices	10-15
Acquisition matrix	128
Number of average	1
Dosage of Gd-DTPA (mmol/kg)	0.1-0.2
Injection rate (cc/s)	2-5 cc/s
SENSE	

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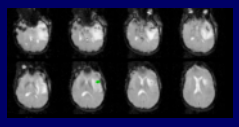
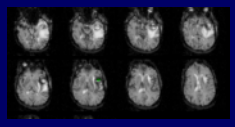
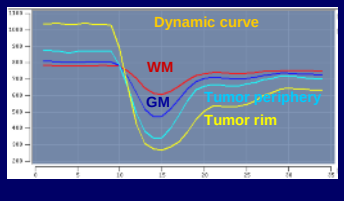
Typical DSE MR Images of High Grade Glioma



Pre contrast



Max contrast



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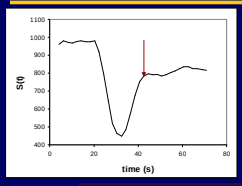
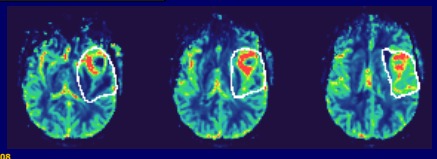
Estimation of Relative CBV



$$CBV \propto \int_{\text{Over the first pass}} \ln\left[\frac{S_0}{S(t)}\right] dt$$

Rosen MRM 1991



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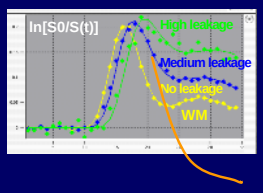
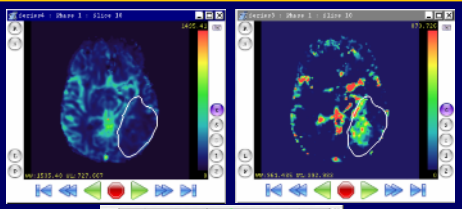
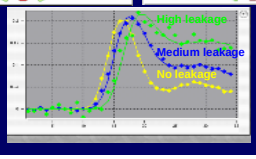
Tradeoff of MRI parameters for Estimation of Relative CBV

- Gradient echo (GE) vs spin echo (SE)
  - Spin echo: sensitive to microvasculature
  - Gradient echo: sensitive to both micro- and macro-vasculature
    - Spin echo for stroke, cognitive function, etc..
    - GE for brain tumor due to tumor vascularization
- Mis-estimation of CBV
  - Vascular leakage, contrast effects on T1, or both
  - T1 effect is more problematic for SE than GE
    - Underestimation for SE and overestimation for GE
  - Minimize misestimation
    - Reduce T1 effects by using longer TR, smaller flip angle, and GE
    - The integration for CBV only upto the first pass of the Gd bolus
    - Correct the effect of vascular leakage numerically (Weisskoff 1994, Cao 2006b)



CBV and Vascular Leakage





Cao, JMRI 2006

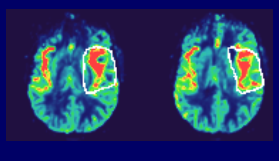
Estimation of Relative CBF

- Determine the artery input function, ΔR_2^*, usually from middle cerebral artery
- Calculate ΔR_2^* in every volxe of tissue
- The residual function R is determined by deconvolution computation, which can be done by SVD (Ostergaard 1999 MRM)
- The amplitude of the residual function R is proportional to blood flow

$$AIF(t) = \frac{1}{TE} \ln\left[\frac{S_{MCA0}}{S_{MCA}(t)}\right]$$

$$Tiss(t) = \frac{1}{TE} \ln\left[\frac{S_{tiss\,0}}{S_{tiss}(t)}\right]$$

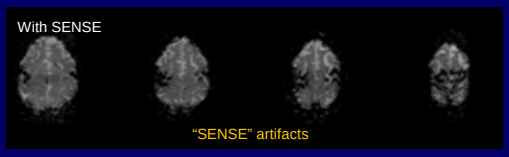
$$Tiss(t) = \int_0^t AIF(\tau)\, R(t-\tau)\, d\tau$$

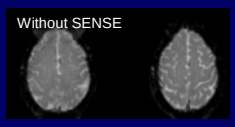


Concerns of Estimation of CBF

- Assumption in the model
  - Intravascular contrast
  - Artery input function: a delta function or a short bolus
- Reality
  - Leaky vasculature in both brain tumor and ischemic stroke
  - Gd-DTPA is not an intravascular contrast
  - Artery input function is not a delta function and compromised by the partial volume effect
- MRI parameters
  - Short bolus of the contrast and temporal resolution better than 1.5 s

Artifacts in SENSE During Dynamic Scans





All other parameters were the same!
SENSE: 19 slices within 1.5 s
No SENSE: 14 slices within 1.5 s

Only testing the protocol on the Phantom is not enough!!

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Typical Protocol for DCE MRI

Sequence Type	3D flash or SPGR
Plane	saggital or axial
TR/TE (ms)	min/min (scanner & body part)
Flip angle	10-20
FOV (mm)	240-360
Phase FOV (%)	75-100
Repetition	50-120
Slice thickness (mm)	2-5
Spacing (gap) (mm)	0
Number of slices	16-32
Acquisition matrix	128 or 256
Phase encoding direction	S/I or A/P
Number of average	1
SENSE	

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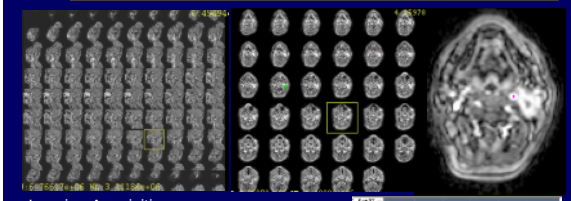
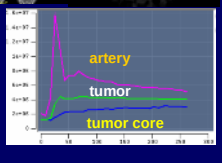
Typical HN DCE MRI



Imaging Acquisition:
Saggital Plane → avoiding in-flow effect
Isovoxel size:
2x2x2 mm → reformatted in axial
3D Volumetric coverage



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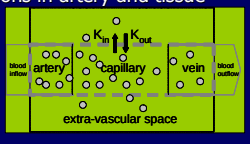
Modeling of DCE Images

- Modified Toft model (2 compartmental model)
  - Contrast concentration in a voxel due to intra (blood volume) and extra vascular contribution (leakage or contrast uptake)

$$C_t(t) = K_{in}\int_0^t e^{-k_{ep}(t-\tau)}C_p(\tau)d\tau + v_p C_p(t)$$

  - If TR*R1 ~ 0.01, $\Delta S \sim \Delta R1$ (after – before the injection of contrast)
    $\Delta R1$ is assumed to be proportional to C_t
  - Inputs: contrast concentrations in artery and tissue
  - Fitted parameters:
    transfer constant K_{in}
    blood volume (v_p)



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Concerns of Kin and Vp

- Interpretation of K_{in} (Toft 1999)
  - Blood flow limited condition: K_{in} most likely represents blood flow
  - Permeability limited condition: K_{in} depicts transfer constant of contrast from intravasculature to extravasculature space
  - Between the two conditions: K_{in} represents both blood flow and transfer constant
- Relationship between $\Delta R1$ and C_t
- Acquisition
  - Saggital plane acquisition → avoid the effect from in-flow fresh blood spins

Applications

- DCE and DSE Imaging
  - Early assessment for tumor response to anti-angiogenesis drugs
  - Early assessment for tumor treatment response to chemo and RT
  - Evaluation of radiation-induced BBB opening
  - Possibly provide information on tissue oxygenation delivery

Typical Protocol for Diffusion and DTI

Sequence Type	2D SE EPI
Plane	axial (AC-PC)
TR/TE (ms)	2000-10000/40-70
B-value (s/mm^2)	0, 700-1000
Number of directions	≥6
FOV (mm)	220-240
Phase FOV (%)	75
Slice thickness (mm)	3-5
Spacing (gap) (mm)	0-1.5
Number of slices	25-50
Acquisition matrix	128
Phase encoding direction	L/R
Number of average	1
SENSE	

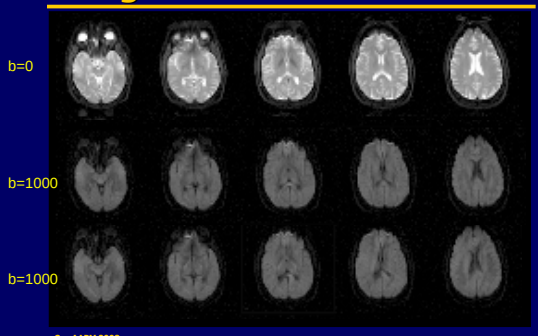
Diffusion and Diffusion Tensor Imaging

- DWI and DTI are sensitive to the random motion of the water protons by using motion-sensitive magnetic gradient fields, which cause de-phasing of spins
- DTI is sensitive to the anisotropic water diffusion in a tissue fiber or the orientation of the fiber, e.g. white matter and mussel fibers
- The diffusional signal loss by the gradient application is given

$$S = S_0 \exp(-b\vec{q}\overline{D}\vec{q})$$

  - Where q is a unit vector of the magnetic gradient, D is the diffusion tensor, and b is the b-value that is proportional to the square of the amplitude of the gradient
  - To obtained DT, 6 (or greater) non-colinear gradients have to be applied

Typical Diffusion-Weighted Images



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Diffusion coefficient and DT Indices

- DT can be calculated by using 6 or greater DW images and a null (b=0) image (Basser 1996) and LS fitting

$$D = \begin{pmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{xy} & D_{yy} & D_{yz} \\ D_{xz} & D_{yz} & D_{zz} \end{pmatrix}$$

- DT indices
  - Mean diffusivity <D> or trace of the DT Dtr
    - Dtr=Dxx+Dyy+Dzz
    - Or <D>=Dtr/3
- Eigenvalues of the DT

$$D = U \begin{pmatrix} \lambda_1 & 0 & 0 \\ 0 & \lambda_2 & 0 \\ 0 & 0 & \lambda_3 \end{pmatrix} U^{-1}$$

- Fractional anisotropy (FA)

$$FA = \sqrt{\frac{3}{2}} \frac{\sqrt{(\lambda_1 - \langle D \rangle)^2 + (\lambda_2 - \langle D \rangle)^2 + (\lambda_3 - \langle D \rangle)^2}}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}$$

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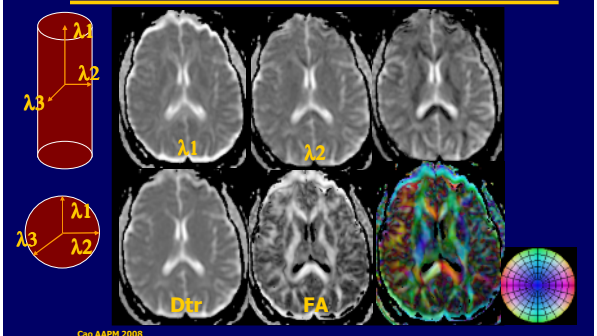
Example of DT Indices



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Applications

- DTI
  - Assess radiation-induced white matter injury
    - Demyelination → increase in perpendicular diffusivities (2nd & 3rd eigen values)
    - axonal injury → increase in parallel diffusivity (1st eigen value)
  - possible for evaluation of tumor cell infiltration to white matter

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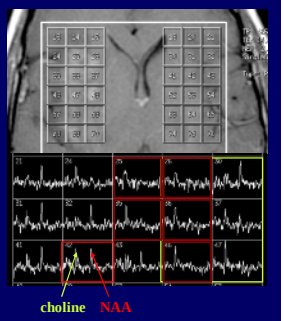
Typical Protocols of Proton Spectroscopy Imaging

Sequence Type	2D CSI PRESS
Plane	Axial
TR/TE (ms)	1500-2500/144
FOV (mm)	220-240
Phase FOV (%)	100
Slice Thickness (mm)	10-15
Number of slices	1-4
Acquisition matrix	12x12, 16x16
Phase encoding direction	A/P
Number of averages	1

Example of Proton SI

- Chemical compounds and metabolites commonly detected in brain tissue
  - choline-containing compounds, creatine, lactate, lipid, and N-acetylaspartate (NAA)
  - Useful ratios
    - Cho/NAA, Cho/Cr, Cr/NAA or NAA/Cr
    - Using contralateral values as control



Possible Applications

- Tumor target definition
  - Glioma, breast and prostate cancer
- Prediction of tumor treatment outcomes
- Assessment of brain injury
  - NAA decrease → neuronal injury
  - Assessment of recovery from ischemic stroke
- Limitations
  - Low spatial resolution,
  - Difficulty for absolute quantification
  - Quality of data

Summary

- Therapy assessment is a longitudinal study
- Protocol design
  - Quality control
  - Image processing and modeling
  - Addressing clinical questions vs validating imaging techniques
  - Consistency

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