Functional and Physiological MR Imaging for Therapy Assessment

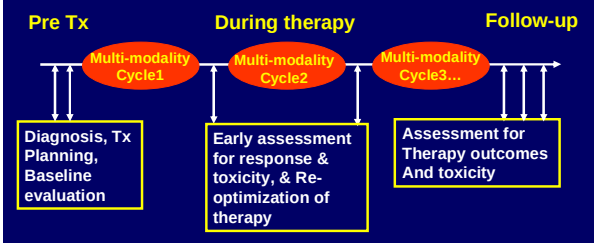
Yue Cao, Ph.D.

Departments of Radiation Oncology and Radiology, University of Michigan

Related Symposia in AAPM 2007

- President's symposium: Imaging as a biomarker for therapy (Monday)
- Molecular Imaging: as biomarkers (Tuesday)
- Imaging for Therapy Assessment
  - Wednesday, 1:30-3:20 pm, Room M100F

Paradigm Changes in Tx and Assessment



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

Clinical Value of Functional Imaging for Therapy Assessment

- Tx target definition and baseline evaluation
- Early assessment and prediction of tumor response to therapy prior to morphological changes
- Early assessment of normal tissue injury or toxicity
- Determination of most aggressive tumor subvolumes for radiation boost
- For molecular targeted therapy, conventional endpoints are no longer adequate to determine Tx responses

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

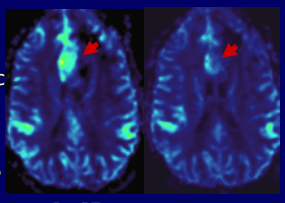
Imaging Techniques

- New molecular imaging techniques
  - Image molecular and biological processes, and monitor specific processes or pathways
  - High specificity
  - Under evaluation and development
  - Limited availability
- Functional and Physiological Imaging
  - Measure downstream products or processes
  - Demonstrate their clinical values for treatment assessment in phase I and/or II clinical trials
  - Provide additional information compared to anatomic images

Cao AAPM 2007

Early Assessment for Tumor Response to CRT

- Several studies have shown that max CBV in high-grade gliomas is associated with tumor grade, and is a prognostic factor of OS.
- Does reduction in high CBV in glioma during early treatment of CRT predict clinical outcomes?
- A decrease in the fractional tumor volume of high CBV 3 wks of RT is associated with better survival (Cao 2006a).



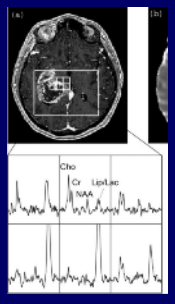
Pre RT Week 3 during RT

An increased high CBV in the tumor volume at 3 wks of RT could be a target for dose escalation.

Cao AAPM 2007

PSI: Tumor Target Definition

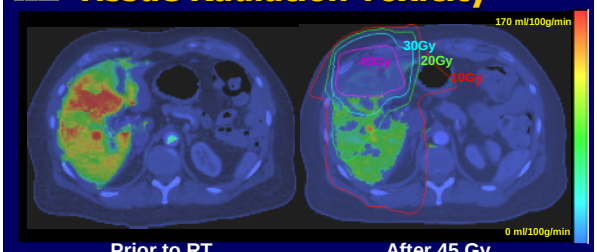
- **Elevated Cho signals in GBM and prostate tumors**
- **Abnormal Cho signals**
  - **beyond the contrast enhanced abnormality**
  - **Volume of CNI > 2 in GBM predicts survival (Oh 2004)**
- **Comparison of abnormal cho signals with histology in GBM**
  - **Elevated Cho signals are associated with the degree of tumor cell infiltration but not tumor cell density (Croteau 2001)**



Oh et al. JMRI, 2004

Cao AAPM 2007

Early Prediction for Normal Tissue Radiation Toxicity

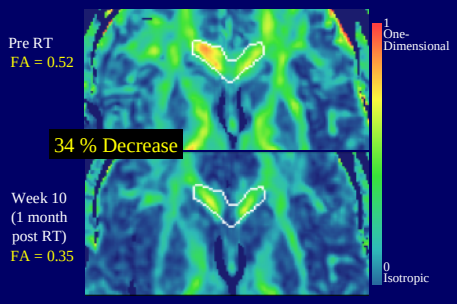


Prior to RT **After 45 Gy**

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)**

Cao AAPM 2007

White Matter Injury after Cranial Irradiation



Courtesy of Nagesh

Learning Objectives

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

Outline

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

Perfusion

- "Perfusion"
  - Definition: microscopic blood flow, and in brain blood flow in the capillary
  - blood volume (BV), blood flow (BF), and vascular permeability
  - Cerebral BV and cerebral BF in brain
- Imaging methodologies
  - Dynamic contrast enhanced (DCE) or dynamic susceptibility enhanced (DSE) MRI
  - DCE CT
  - 15O-PET
  - SPECT
- Advantages and disadvantages
  - MRI and CT
    - Generally available, high spatial and temporal resolutions, short scan time, cheaper, no need for an onsite radiochemist
    - Relative measure, semiquantitative or quantitative
    - CT: high radiation dose
  - PET and SPECT
    - Limited availability, low spatial and temporal resolution, long scan time, costly, onsite radiochemist (e.g. for 15O for cerebral perfusion)
    - Semi quantitative, quantitative

Typical Protocol: DSC MRI CBV and CBF (brain)

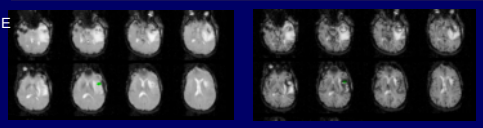
MR parameters for DSE images

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

Cao AAPM 2007

Typical DSC MR Images of High Grade Glioma

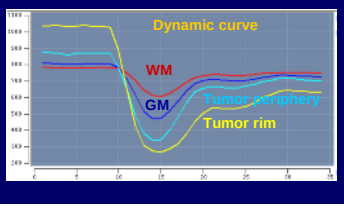
GE



Pre contrast

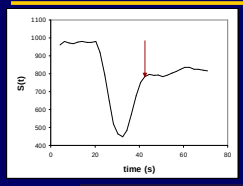
Max contrast enhancement

Tumor:
Increased enhancement at the peak
Elevated tail
Broadened peak



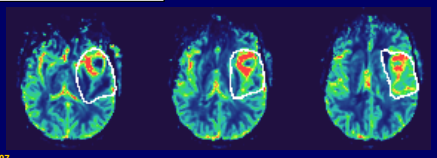
Cao AAPM 2007

Estimation of Relative CBV



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

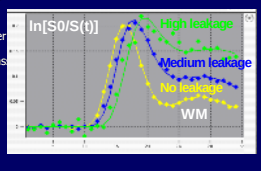
Rosen MRM 1991



Cao AAPM 2007

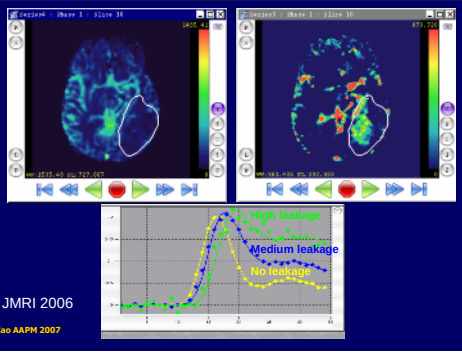
Tradeoff of MRI parameters for Estimation of Relative CBV

- 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)



Cao AAPM 2007

CBV and Vascular Leakage



Cao, JMRI 2006

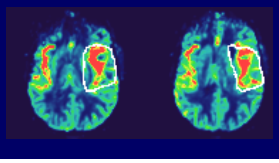
Estimation of Relative CBF

- 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 at t=0 is proportional to blood flow

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

$$Tiss(t) \quad \frac{1}{TE}\ln\left[\frac{S_{tiss0}}{S_{tiss}(t)}\right]$$

$$Tiss(t) \quad \int_0^t AIF(\ )\,R(t\quad)\,d$$

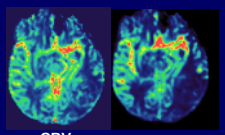


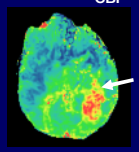
Concerns of Estimation of CBF

- 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 –> extravascular contrast agent
  - Artery input function is not a delta function
  - Artery input function is easily corrupted
- MRI parameters
  - Short bolus of the contrast injection and high temporal resolution < 1.5 s

Estimation of Mean Transition Time (MTT)

- MTT is the mean time for a bolus traveling via the capillary system (a physiological definition)
  - MTT=CBV/CBF
  - MTT is not the first moment of the contrast uptake curve
  - Prolonged MTT observed in ischemic stroke and brain tumor, suggesting reduced blood flow, or increased tortuous configuration of micro-vasculature



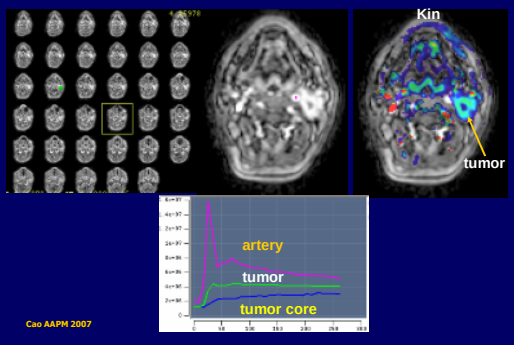


Typical Protocol for DCE MRI

Sequence Type	3D flash or SPGR
Plane	saggital or axial
TR/TE (ms)	min/min (scanner, FOV)
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	L/R or A/P
Number of average	1

Cao AAPM 2007

Typical HN DCE MRI



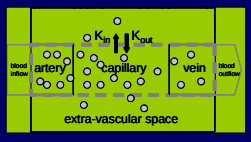
Cao AAPM 2007

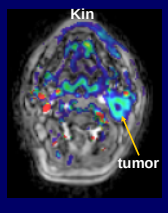
Modeling of DCE Images

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

$$C_t(t) \quad K_{in}\int_0^t e^{k_{ep}(t\quad)}C_p(\quad)d \quad v_pC_p(t)$$

  - ⇑ R1 is proportional to Ct
  - Inputs: contrast concentrations in artery and tissue
  - Fitted parameters: K_{in}, blood volume (v_p) and kep=K_{in}/V_{eec}





Cao AAPM 2007

Concerns in Kin and Vp

- Interpretation of K_{in} (Toft 1999)
  - Blood flow limited condition (slow BF but high leakage): K_{in} most likely represents blood flow
  - Permeability limited condition (high BF but slow leakage): K_{in} depicts the transfer constant of the contrast from intravasculature to extravasculature space (vascular permeability to the contrast)
  - Between the two conditions: K_{in} represents both blood flow and transfer constant
- Concern in v_p
  - Estimation of blood volume Vp may not be accurate as from DSC images
- Parameters Kin and Vp might not be the physiological parameters as we thought!
- Consistency is more important!

Cao AAPM 2007

Applications

- DCE and DSE Imaging
  - Early assessment for tumor response to anti-angiogenesis drugs
  - Early assessment for tumor treatment response to chemo and RT
    - Tumors: brain, HN, cervical, breast, liver…
  - Evaluation of radiation-induced BBB opening
  - Possibly provide information on tissue oxygenation

Typical Protocol for Diffusion and DTI

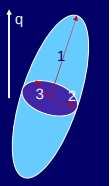
Sequence Type	2D SE EPI
Plane	axial (AC-PC)
TR/TE (ms)	2000-10000/40-70
B-value (s/mm^2)	0, 700-1000
Number of gradient directions	≥6
FOV (mm)	220-240
Phase FOV (%)	75
Slice thickness (mm)	3-5
Spacing (gap) (mm)	0-1.5
Number of slices	25-50
Acquisition matrix	128
Phase encoding direction	L/R
Number of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

Diffusion and Diffusion Tensor Imaging

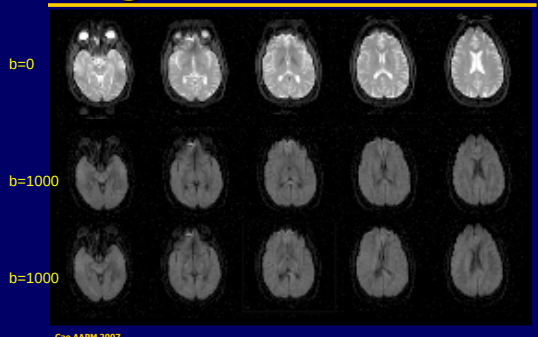
- DWI maps the random motion of the water protons by using motion-sensitive magnetic gradient fields, which cause de-phasing of proton spins
- DTI is sensitive to the anisotropic water diffusion in tissue fibers or the orientation of the fiber, e.g. white matter and mussel fibers, by applying motion-sensitive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

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

  - 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 obtain DT, 6 (or greater) non-collinear gradients have to be applied



Typical Diffusion-Weighted Images



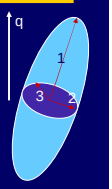
Diffusion coefficient and DT Indices

- DT can be calculated by using 6 or greater DW images and a null (b=0) image (Basser 1996)
  - D is a 3x3 symmetric matrix
- DT indices
  - Mean diffusivity <D> or trace of the DT Dtr
    - Dtr=Dxx+Dyy+Dzz
    - Or <D>=Dtr/3
- Eigenvalues of the DT
- Fractional anisotropy (FA)

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

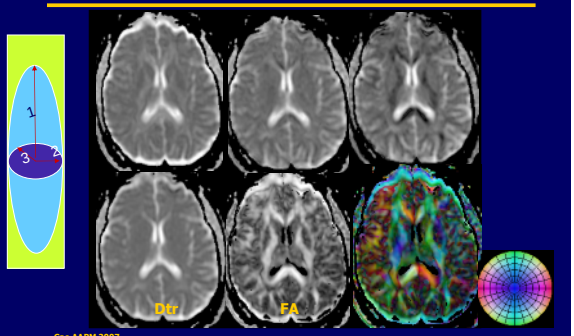
$$D \quad U \begin{pmatrix} {}_1 & 0 & 0 \\ 0 & {}_2 & 0 \\ 0 & 0 & {}_3 \end{pmatrix} U^{\ 1}$$

$$FA \quad \sqrt{\frac{3}{2}} \frac{\sqrt{({}_1 \ \langle D \rangle)^2 \ ({}_2 \ \langle D \rangle)^2 \ ({}_3 \ \langle D \rangle)^2}}{\sqrt{{}_1^2 \ {}_2^2 \ {}_3^2}}$$



Cao AAPM 2007

Example of DT Indices



Cao AAPM 2007

Applications

- DTI
  - Assess white matter diseases
    - MS, stroke, close head injury, demyelination, axonal injury
  - Assess white matter injury, e.g., radiation injury to normal white matter due to cranial irradiation
  - possible for evaluation of tumor cell infiltration to white matter

Cao AAPM 2007

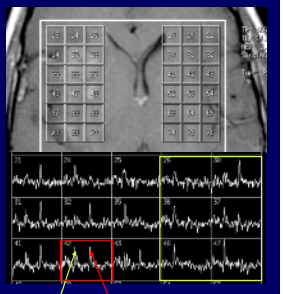
Typical Protocols of Proton Spectroscopy Imaging

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

Cao AAPM 2007

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, and prostate cancer
- Prediction of tumor treatment outcomes
- Assessment of brain injury
  - NAA decrease → neuron injury
  - Assessment of recovery from ischemic stroke
- Limitations
  - Low spatial resolution
  - Quality of data

Summary

- DCE and DSE MRI, DTI and proton PSI have been playing very important roles in diagnosis, and treatment evaluation.
- They provide complimentary information to anatomic imaging.
- They are more generally available.

References

- Basser, JMR B, 1996
- Cao, JMRI, 2006
- Cao, Int J Rad Onc phys Bio, 2006
- Cao, Cancer Research 2006
- Cao, JCO 2006 (review paper)
- Cao, Med Phys, 2007
- Cao, Int J Rad Onc Phys Bio, 2007
- Croteau, Neurosurgery 2001
- Nagesh, Int J Rad Onc Phys Bio 2007
- Nelson, Mol Cancer Therapy 2003
- Oh, JMRI 2004
- Ostergaard, MRM 1999
- Rosen, MRM 1991
- Toft, JMRI 1999