DCE MRI for Quantitative Assessment of Therapy Response

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- Open positions for Post-Doctoral fellows
- Send CV to yuecao@umich.edu

Learning Objectives

- Understand the strengths and weaknesses of commonly used pharmacokinetic models
- Understand the influence of image acquisition parameters and image quality on derived quantitative metrics
- Provide examples of clinical applications in therapy assessment

Imaging For Assessment of Tx Response

- Rapid growth field
- Driven by the needs of fast development in therapeutic modalities
  - Targeted tx, concurrent or sequential multi-modality tx, organ-reserved tx,
  - aggressive, complex, risk vs benefit, individualized
- Challenging conventional paradigms for therapy assessment
  - Endpoints, e.g., TV reduction
  - Time, e.g., months after completion of Tx
- Changing in Tx assessment paradigms
  - Early, e.g., during the course of and early after therapy
  - Biomarkers as surrogate endpoints

DCE MRI for Tx Assessment

- Tumor response to anti-angiogensis and anti-vascular drugs in clinical trials (Galbraith 2002, Morgan 2003, Rugo 2005, Sorensen 2009)
- Early prediction of chemoradiation treatment response of GBM (Cao 2006a, 2006b)
- Early prediction of outcomes of chemo and radiation therapy in advanced HN cancers (Cao 2008, Dirix 2009)
- Early assessment of liver function during radiation therapy (Cao 2007, 2008)
- Early assessment and prediction for neurotoxicity after brain irradiation (Cao CCR, 2008)

Outline

- Typical protocols
- Physiological origins of DCE and DSC imaging
- Image processing and modeling
- limitations
- Clinical values of perfusion and vascular permeability imaging for therapy assessment

Overview

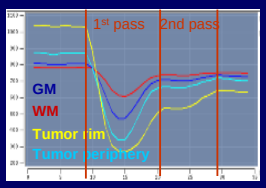
- Sequences
  - Dynamic susceptibility contrast (DSC) T2* (or T2)-weighted imaging
  - Dynamic contrast enhanced (DCE) T1-weighted imaging
- Vascular and perfusion parameters
  - Blood flow, blood volume, vascular permeability, extavascular extracellular space
- Trade-offs
  - Sequences, parameters, pharmacokinetic models
  - Complexity, robustness, accuracy, reliability, reproducibility,…, surrogacy (application)

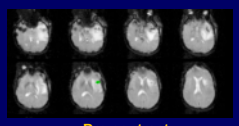
DSC Imaging

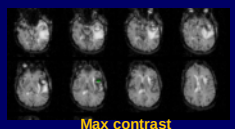
- Imaging Sequence
  - 2D GE or SE EPI sequence to acquire dynamic T2*- or T2-weighted images during a bolus of Gd-DTPA injection
  - TR/TE (ms): 1500/40-60 (GE) or 60-100(SE)
  - Flip angle: 30-60°, slice thickness: 4-6 mm
  - Dynamic repetition: 35-120
  - # slices: ~14-19
  - Single dose of Gd-DTPA (0.1 mMo/kg) w an injection rate 2-4 cc/s

Dynamic Contrast Uptake Curve

- Signal intensities decrease during the bolus arrival




Pre contrast


Max contrast

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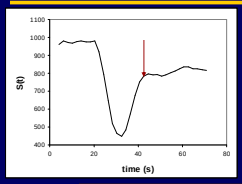
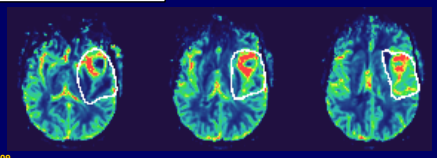
Estimation of Relative CBV



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

Rosen MRM 1991



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Tradeoffs of MRI parameters

- Gradient echo (GE) vs spin echo (SE)
  - SE:
    - sensitive to microvasculature
    - suitable for ischemic stroke, cognitive function, etc
    - Less sensitive to contrast, double doses
  - GE:
    - sensitive to both micro- and macro-vasculature
    - suitable for brain tumor due to neovascularization
    - More sensitive to contrast, single dose

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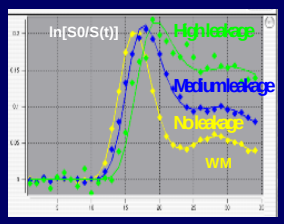
Tradeoffs of MRI parameters

- 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 mis-estimation
  - Reduce T1 effects
    - longer TR, smaller flip angle, and GE, single dose of contrast
  - Integrate only the area under the first pass of the Gd bolus
  - Correct the effect of vascular leakage numerically (Weisskoff 1994, Johnson 2003, Cao 2006b)



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Application Questions

- *In your setting, do you see any overshooting or undershooting in the tail of dynamic signal intensities?*
- *If yes, in what region(s), normal tissue, tumor, or ischemic stroke tissue, do you see overshooting or undershooting?*
- *Do you use the integral under the area of the first pass of contrast bolus to estimate relative CBV?*
- *If not, what are the tradeoffs of your method compared to the area under the first pass?*

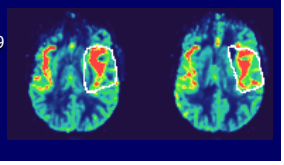
Estimation of Relative CBF

- Imaging sequence
  - Same as one for CBV
  - TR: 1500ms or shorter
- Estimation of relative CBF
  - Determine the artery input function (AIF), DR_2^*, usually from middle cerebral artery
  - Calculate DR_2^* in every voxel 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

$$\Delta R_{2\,AIF}^{*}(t) = \frac{1}{TE}\ln\left[\frac{S_{MCA0}}{S_{MCA}(t)}\right]$$

$$\Delta R_{2\,tiss}^{*}(t) = \frac{1}{TE}\ln\left[\frac{S_{tiss\,0}}{S_{tiss}(t)}\right]$$

$$\Delta R_{2\,tiss}^{*}(t) = \int_0^t \Delta R_{2\,AIF}^{*}(t')\,R(t-t')\,dt'$$



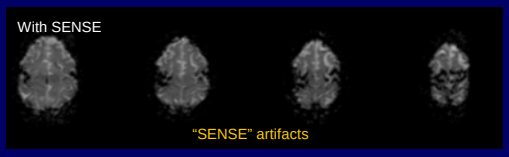
Concerns of Estimation of CBF

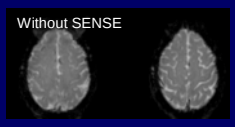
- Assumptions in the model
  - Intravascular contrast agent
  - Artery input function: a delta function or a short bolus
- Reality
  - Leaky vasculature in both brain tumor and ischemic stroke
  - Gd-DTPA is not an intravascular contrast agent with leaky vasculature
  - Artery input function is not a delta function
- Trade-offs in MRI parameters
  - Fast injection rate for a short bolus of contrast vs patient tolerance and safety
  - Shorter RT (<1.5 s) for more reliable estimation of CBF vs smaller number of slices (less spatial coverage)

Sources of Error

- Artery input function
  - Partial volume average in the middle cerebral artery → large uncertainty in the amplitude of AIF
  - Disperse and delay in AIF → distorted R
- Vascular leakage
- Susceptibility artifacts
- Sense artifacts
- Inadequate temporal resolution

SENSE Artifact During Dynamic Scans





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

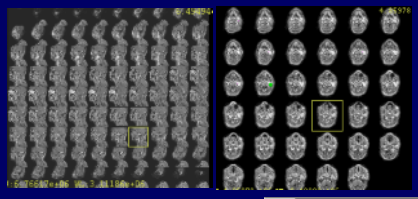
Application Questions

- *In your setting, do you think you can determine artery input function reliably and consistently?*
- *What percentage errors do you think the variation in artery input function will propagate into the variation in the estimation of CBF?*
- *Do you use SENSE in dynamic scans? If yes, what fraction of scans do you have "SENSE" artifacts?*
- *What are the limitations in your application due to the relative nature of CBF?*

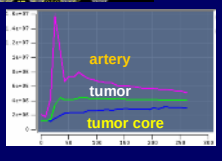
DCE Imaging

- Imaging sequence
  - 2D or 3D flash or SPGR sequence to acquire dynamic T1-weighted images during a bolus of Gd-DTPA injection
  - TR/TE (ms): min/min
  - Flip angle: 10-30°
  - plane: sagittal or axial
    - Sagittal plane to avoid the in-flow effect due to unsaturated blood spins
    - Iso-voxel size to permit reformatting images in the axial plane
  - Dynamic acquisition
    - Long enough to be sensitive to contrast uptake in tissue
    - Long enough to cover contrast wash-out in tissue

Example in HN DCE MRI



Imaging Acquisition:
Sagittal Plane
Isotropic voxel size; 2x2x2 mm^3
reformatted in axial
3D Volumetric coverage



Pharmacokinetic Models

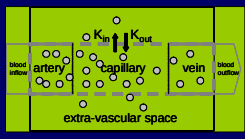
- Pharmacokinetic models
  - Parameters can be concerned in a PK model
    - Intravascular space (plasma plus blood cell)
    - Transfer constant from vasculature to tissue
    - Back-flux rate from tissue to vascular space
    - Extravascular extracellular space
    - Blood flow
  - Main differences among the models are what parameters have been considered for a particular physiological or pathological condition

Two compartmental model

- Two compartmental model – standard model (Kety or Toft model 1999 in JMRI)
  - Contrast concentration in a voxel due to intra (blood volume) and extra vascular (leakage or contrast uptake) contributions

$$C_t(t) = K^{trans}\int_0^t e^{-k_{ep}(t-t')}C_p(t')dt' + v_p C_p(t)$$

  - Inputs:
    - contrast concentrations in artery
    - contrast concentrations in tissue
  - Fitted parameters:
    - K^{trans}, plasma volume (v_p) and k_{ep}



DCE Data Modeling

- T1 weighted signal intensities

$$S = S_o \sin a \frac{1 - e^{-TR \cdot R_1}}{1 - \cos a \cdot e^{-TR \cdot R_1}}$$

- If TR x T1 << 1,

$$S = S_o \frac{\sin a}{1 - \cos a} TR \cdot R_1 [1 + O(10^{-2})]$$

- Signal intensity difference after and before contrast injection

$$\Delta S = S_a - S_b = S_o \frac{\sin a}{1 - \cos a} TR \cdot \Delta R_1 \Rightarrow \Delta R_1 \mu \Delta C \ ?$$

Concerns of K^{trans} and V_p (I)

- Interpretation of K^{trans} (Toft 1999)
  - Blood flow limited condition:
    - permeability surface area product (PS) >> perfusion (F) → K^{trans} =Fp(1-Hct) represents blood flow
  - Permeability limited condition:
    - F>>PS → K^{trans} =PSp depicts transfer constant of contrast from intravasculature to extravasculature space
  - mixed condition:
    - F~PS → K^{trans} =EFp(1-Hct) represents both blood flow and transfer constant

Concerns of K^{trans} and V_p (II)

- V_p
  - Vp is more reproducible than K^{trans}
  - What is a better method to estimate blood volume, DCE vs DSC, depends upon the organ
    - Brain → DSC
    - Other body sites → DCE
  - The DSC method may have high sensitivity than the DCE method but blood volume estimated from DSC is a relative measure

Application Questions

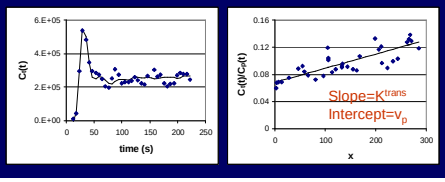
- *In your setting, do you use a TR that is short enough to satisfy the first order approximation of TR*R1 being negligible?*
- *Do you think you can use more complex models in a clinical trial setting given the quality of DCE data that you are getting? Why?*

Variation: Patlak Model

- Multiple time-graphic method (Patlak 1983)
  - The back flux of contrast from interstitial space to intravascular space is omitted if it is small enough

$$C_t(t) = K^{trans}\int_0^t C_p(t)dt + v_p C_p(t)$$

$$C_t(t)/C_p(t) = K^{trans}\left(\int_0^t C_p(t)dt / C_p(t)\right) + v_p \quad \Rightarrow \quad y = K^{trans}x + v_p$$



Variation: Toft model

- Toft models with and without the intravascular term

$$C_t(t) = K^{trans}\int_0^t e^{-k_{ep}(t-t')}C_p(t)dt + v_p C_p(t)$$

$$C_t(t) = K^{trans}\int_0^t e^{-k_{ep}(t-t')}C_p(t)dt$$

Values of the two K^{trans}s are not comparable! If the intravascular contribution is not small enough compared to the extravascular contribution, the second model results in a large error.

Application Questions

- *In your setting, do you include the intravascular contribution into your model?*
- *If not, do you estimate the percentage discrepancy in the estimation of K^{trans} with and without considering the intravascular contribution?*
- *How do they change over the longitudinal study of a clinical trial?*

Blood Flow from DCE Data

- Estimation of blood flow from DCE images (Mullani 1983, Hermans 1997, Cao 2008, Henderson 2000)
- Derivative form vs integral form

$$\left(\frac{dC_t(t)}{dt}\right)_{\max} = Fr\,C_p(t)_{\max}$$

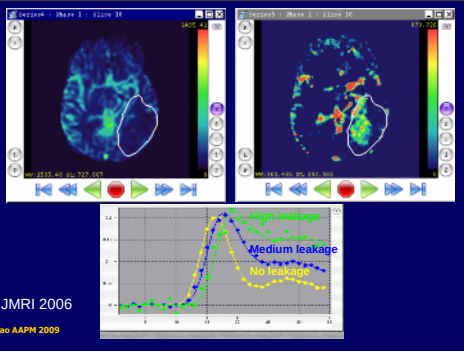
$$C_t(t) = Fr\int_0^t C_p(t)\,dt,\ t < T_c$$

The derivative form is easier to compute than the integral form!

Vascular Permeability from DSC Data

- Estimation of vascular permeability from DSC images (Weisskoff 1994, Johnson 2003, Cao 2006)

CBV and Vascular Leakage



Cao, JMRI 2006

Imaging for Therapy Assessment

- Longitudinal study
  - Repeated measures
  - Reproducibility of measures, robustness of the model → reliability of quantitative metrics
- Sensitive indicator (biomarker)
  - Sensitive to therapy-induced changes
- Predictive value
  - Early changes associated with Tx responses and outcomes
- surrogate endpoint

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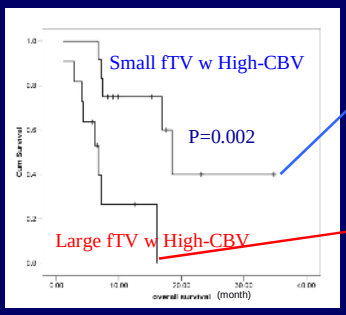
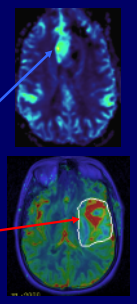
Pre-RT CBV in High-Grade Gliomas

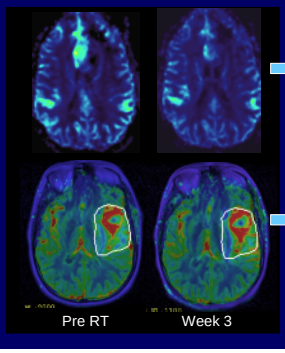




Cao, IJROPB, 2006

Cao AAPM 2009

Early CBV Changes During RT



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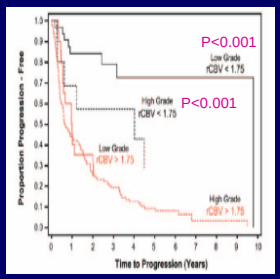
Prediction of PFS in Glioma

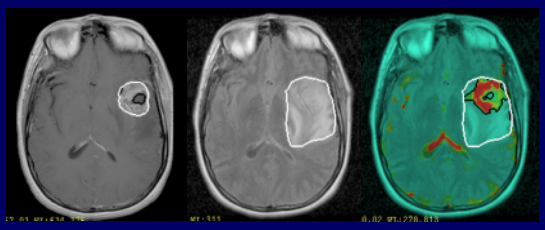
- 198 pts with low or high grade glioma
  - 136 pts w high-grade gliomas
- Mean relative CBV in gliomas
  - Predict median time for progression
  - Independent histological grade
- Age and mean relative CBV were independent predictors for clinical outcomes



Law, Radiology 2008

Cao AAPM 2009

Quantitative Vascular Leakage In High-Grade Gliomas

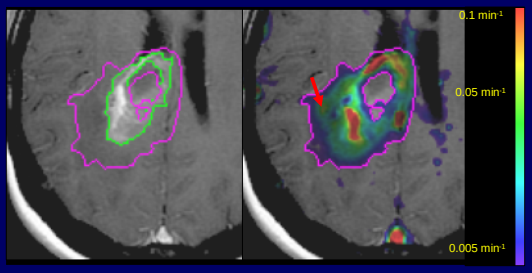


Post-Gd T1 Image | FLAIR Image | Vascular Leakage Volume Estimated from DSC MRI

Cao, et al, Cancer Research, 66(17):8912-8917 (2006)

Cao AAPM 2009

The extent of Vascular Leakage



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Predictors for OS

- Vascular leakage volume, reflecting angiogenesis, was a significant predictor for OS (Cox regression, p=0.02)
- Clinical prognostic factors: age, grade, resection, and concurrent chemo
  - Only age was a significant predictor for OS (p=0.03)
- The joint effect of age and vascular leakage volume was found stronger by multivariate Cox regression (p=0.009).
- The data provide supportive evidence for the potential benefit of anti-angiogenesis therapy in addition to chemo-RT
  - Multi-center trials, e.g., RTOG 0625 for recurrent GBM

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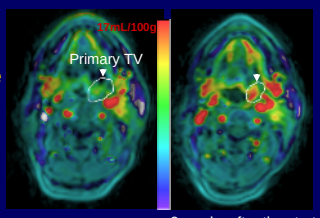
Early Assessment for Outcomes in Advanced HNC

- Prognostic values of Pre Tx tumor BV and perfusion
  - Outcome to RT (Hermans 1997 & 2003)
  - Response to induction chem therapy (Zima 2007)
  - Better perfused HNC → better response to CT & RT

Could changes in TBV during the early course of RT predict local control better?



Pre RT | 2 weeks after the start of FRT

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Early Assessment for Local Control in Advanced HNC

Primary Disease	TBV (mL/100g)	TBF (mL/100g min)	GTV
	Difference wk2-pre	Difference wk2-pre	%Difference wk2-pre
LC	5.1 (-0.6 – 13.2)	20.1 (-3.9 – 54.6)	-28%
LF	1.0 (-1.7 – 1.6)	15.0 (-22.1 – 41.1)	-21%
p	<0.03	n.s.	n.s.

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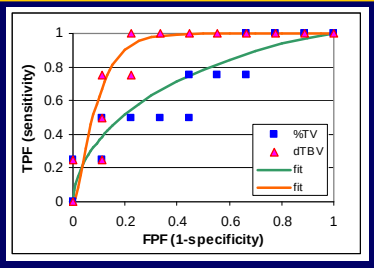
Cao Int J Rad Onc Biol Phys 2008

ROC Analysis

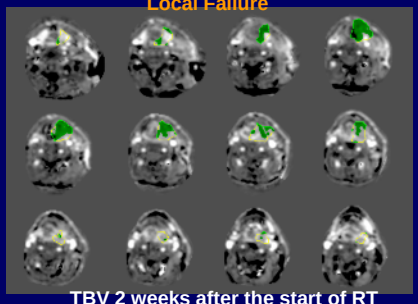


Changes in TBV after 2 weeks of FRT have better sensitivity and specificity than TV changes for prediction of local failure.

Cao AAPM 2009

Identify Poorly Perfused Sub-Tumor Volumes

Local Failure

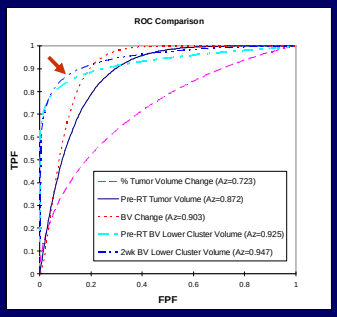


TBV 2 weeks after the start of RT

Cao AAPM 2009

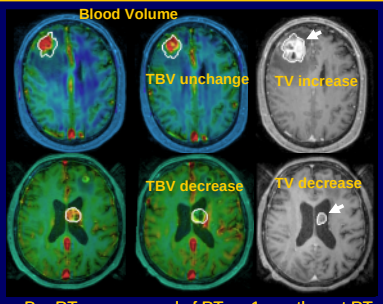
Wang, poster SU-DD-A3-2

ROC Analysis



Cao AAPM 2009

Brain Metastatic Tumors



Feng, ASTRO abstract

Summary

- Perfusion and vascular parameters estimated from DCE and DSC MRI have been demonstrated to have the potential to be biomarkers for therapy assessment, including targeted therapy (e.g., anti-angiogenesis drugs), multi-modality treatment (e.g., chemo and radiation therapy), and individualized therapy (risk vs benefit).
- It has been demonstrated that BV and BF could be more sensitive indicators of response/outcome to Tx than tumor volume reduction.
- They are generally available but standards for acquisition, and quantification are important for multi-center clinical trials .