Advanced Imaging for Breast Cancer: Magnetic Resonance Imaging

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Motivation

How is treatment response currently monitored?

- RECIST = Response Evaluation Criteria in Solid Tumors
- First published in 2000
- Idea: develop a simple method to assess therapy response in tumors to

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- Applied only on patients with measurable disease at baseline
- Uses only anatomical CT and MRI for response assessment

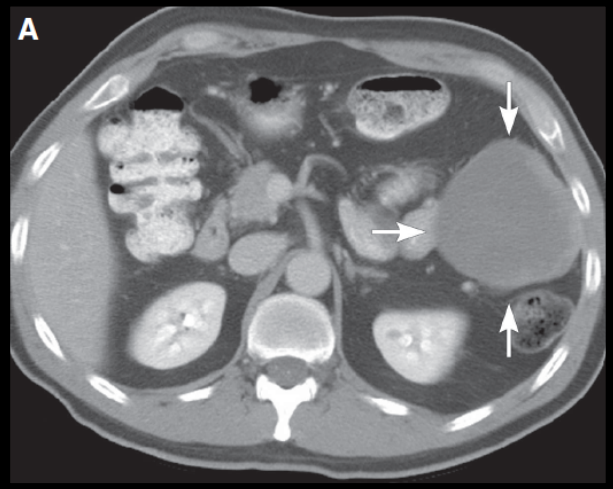
- Sum of longest diameter (LD) for all target lesions is calculated

  → *The change in baseline sum LD will be used to characterize response*

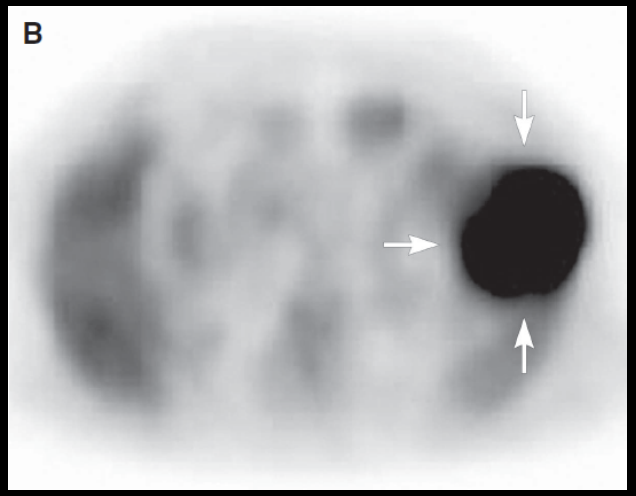
Therasse et al. J Natl Cancer Inst 2000;92:205–16

Motivation

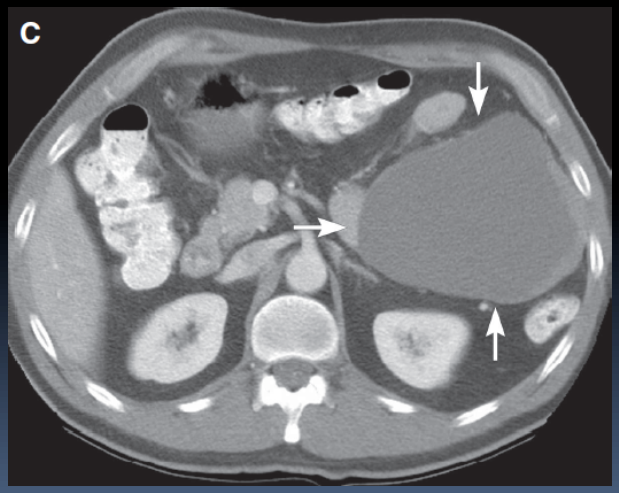
FDG-PET



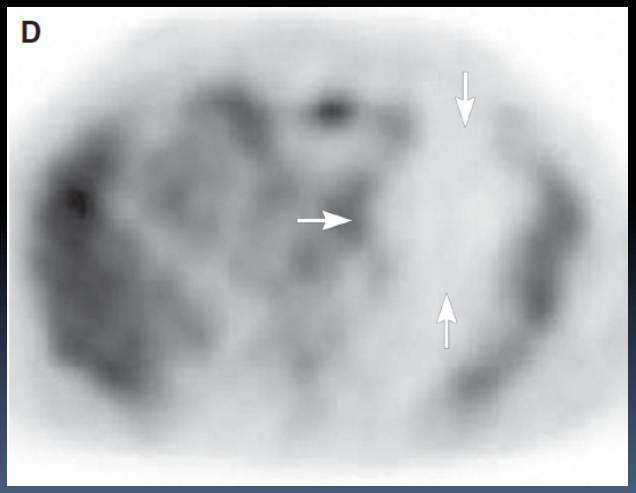
Pre-therapy



Pre-therapy



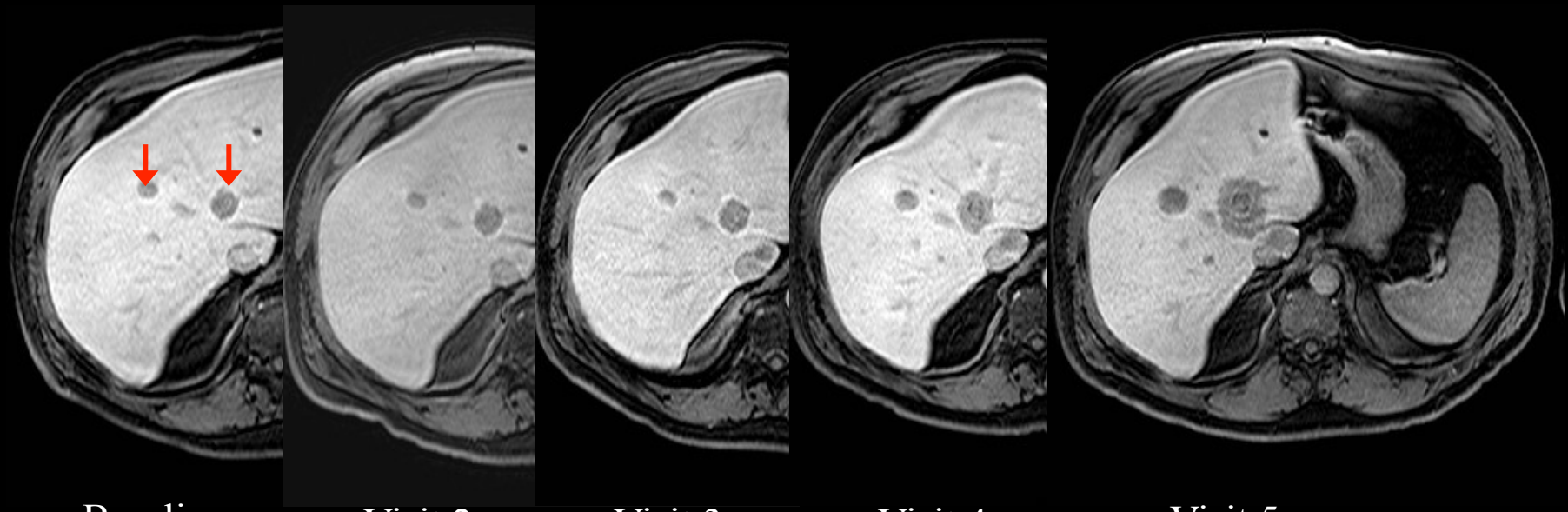
2 months post-therapy



2 months post-therapy

Choi et al. Am J Roentgenology 2004;183:1619-27.

Motivation



	Baseline	Visit 2	Visit 3	Visit 4	Visit 5
T1:	24	25	28	32	48
T2:	14	15	16	18	23
SLD:	38	40	44	50	71
(% ch)		+5%	+16%	+32%	+89%

- Anatomic imaging is limited; morphologic changes are nonspecific, often occur long after molecular changes are apparent
- Need methods to report on changes on the underlying pathophysiology

Rick Abramson, M.D.

Next ~20 minutes of Your Life

1. Imaging Biomarkers
2. MR-based methods

Imaging Biomarkers in Cancer

- Anatomical/physiological
  - Tumor size
  - Cellular density
  - Metabolism (glucose, choline, ATP, pH)
  - Oxygenation (hypoxia, pO_2)
  - Vascular properties (blood flow, angiogenesis)

Well-suited for MRI, CT, US

- Tumor-Host Interactions
  - Inflammation
  - Extracellular matrix changes + signaling
- Molecular
  - Cell surface receptor interactions
  - Intracellular signaling pathways (e.g. caspase)
  - Gene expression

Well-suited for Nuclear + Optical

- Things MRI cannot do especially well:

  1) Targeted agents not well suited to MRI

  → Optical (pre-clinical) and nuclear techniques have >> sensitivity

  2) Several questions regarding drug effects not addressable by MRI

- Why is this the case?

  - Tissue has a "background" relaxation rate, R_1 (= $1/T_1$)

  - To detect an R_1 contrast agent, R_1 must increase significantly compared to noise level and background variations; say, +10%

  - If native $R_1 \approx 1$ sec^{-1}, then minimum detectable $\Delta R_1 \approx 0.10$ sec^{-1}

  → ΔR_1 = relaxivity•[CA]

  → Relaxivity ≈ 4 $sec^{-1}mM^{-1}$ for Gd-DTPA

  → Minimum [CA] = 25 μM throughout ROI! (PET ~ 10^{-6} μm)

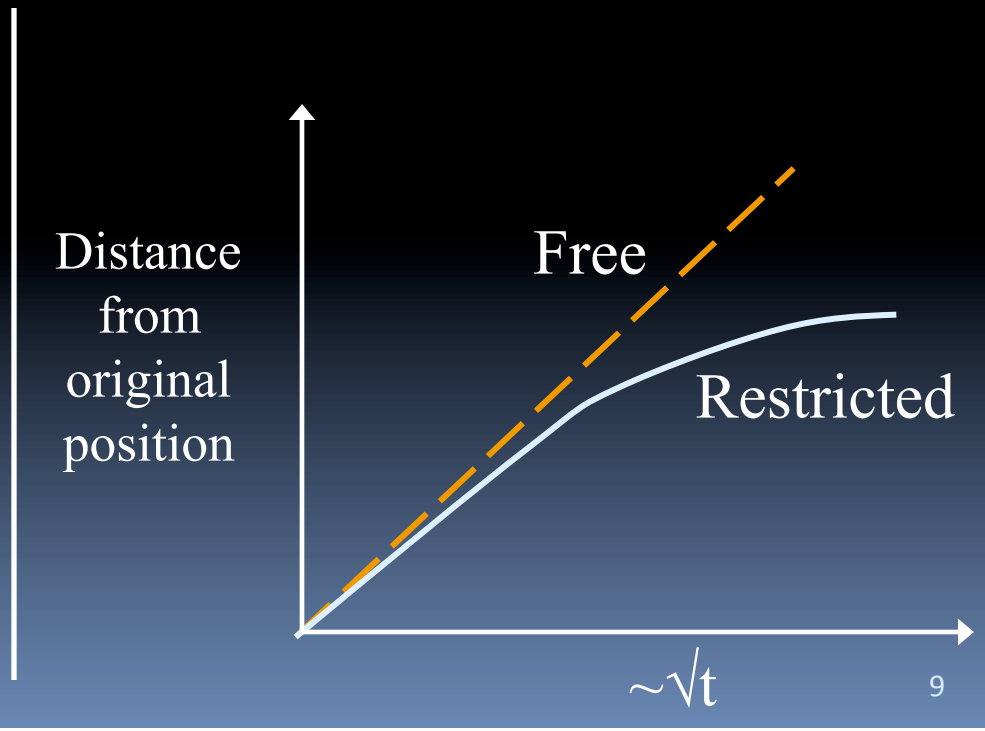
  (less if relaxivity higher, but still quite challenging)

Diffusion weighted MRI

Diffusion weighted MRI

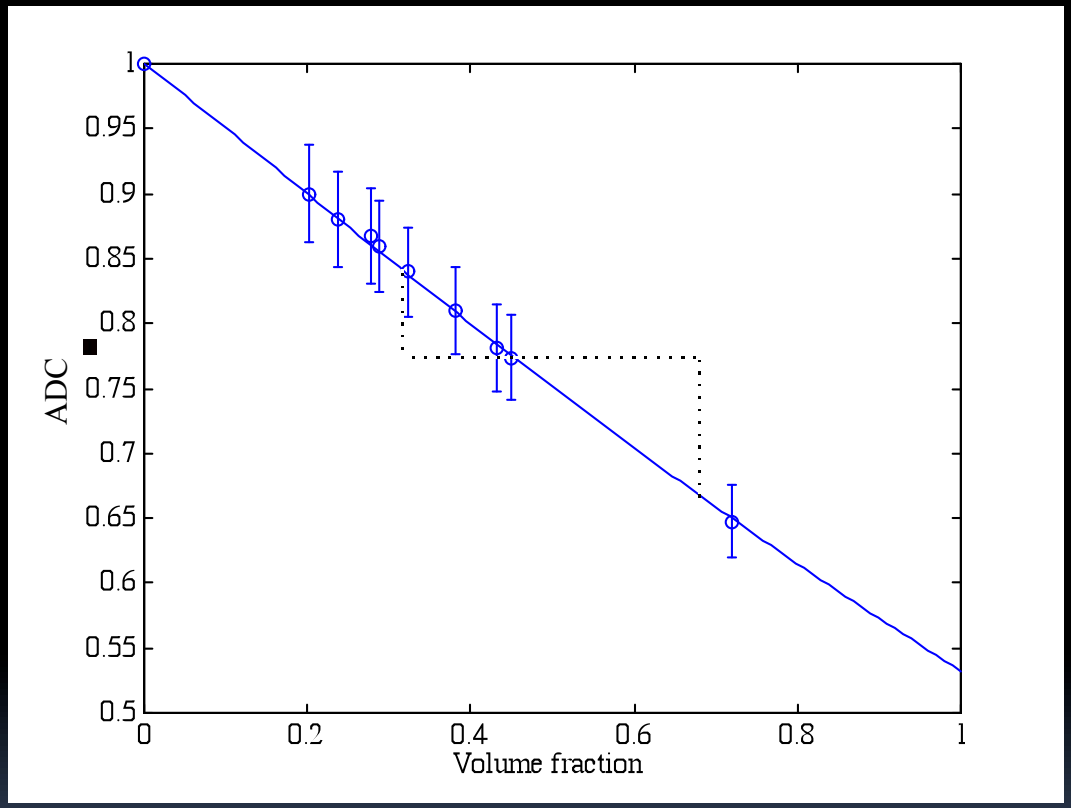
- Water molecules wander about randomly in tissue (Brownian Motion)
- In a free solution, after a time *t*, molecules travel (on average) a distance *L* from where they started
- But in tissue, compartment effects may hinder movement = restricted diffusion

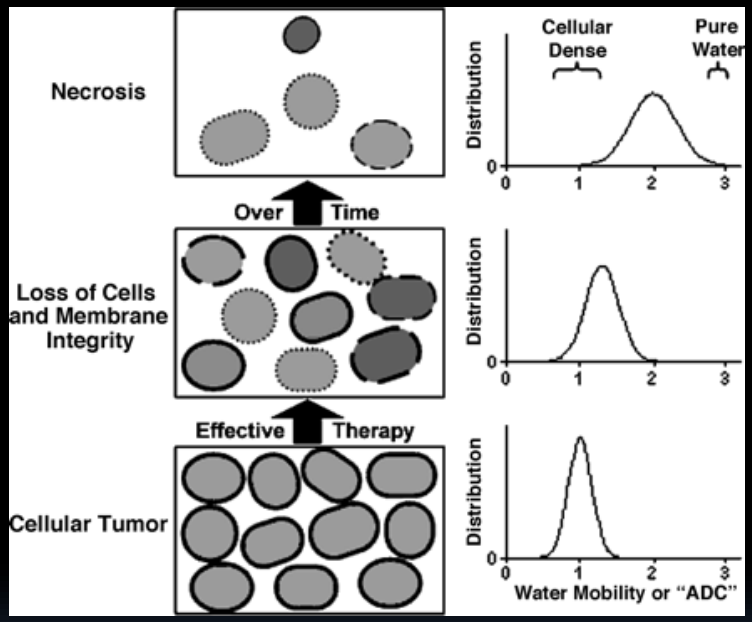
- Boundaries may reduce distance molecules travel when compared to free molecules
- Thus, the ***Apparent Diffusion Coefficient*** (ADC) is lowered



Diffusion weighted MRI

- ADC depends on cell volume fraction



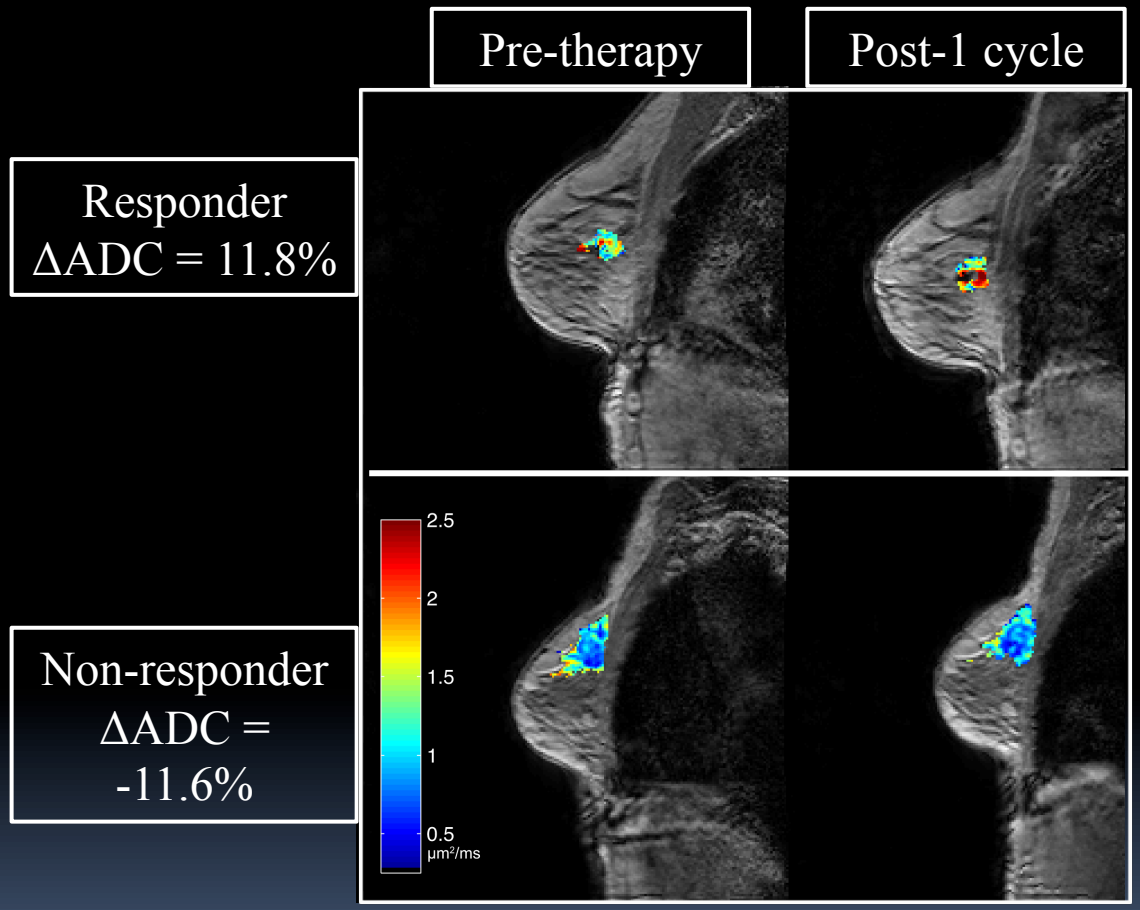


- Increasing cell density; more cell membranes per unit distance to hinder diffusion → lower ADC
- Tumor cellularity may be monitored by DWI

Anderson et al. Magn Reson Imaging. 2000;18:689-95.

Hall et al. Clin Canc Res 2004;10:7852

Diffusion weighted MRI



ROC Analysis
Sensitivity = 0.64
Specificity = 0.93
AUC = 0.70

→ Sensitivity = true positive rate = TP/(TP+FN)

→ Specificity = true negative rate = TN/(FP + TN)

Lori Arlinghaus et al., submitted

Dynamic Contrast Enhanced MRI

DCE-MRI

- Serial acquisition of images before, after an injection of contrast agent (CA)
- As CA perfuses into tissue, the T_1 and T_2 values of tissue water decrease
- Each voxel yields a signal intensity time course
- By fitting data to model, extract parameters that report tissue characteristics

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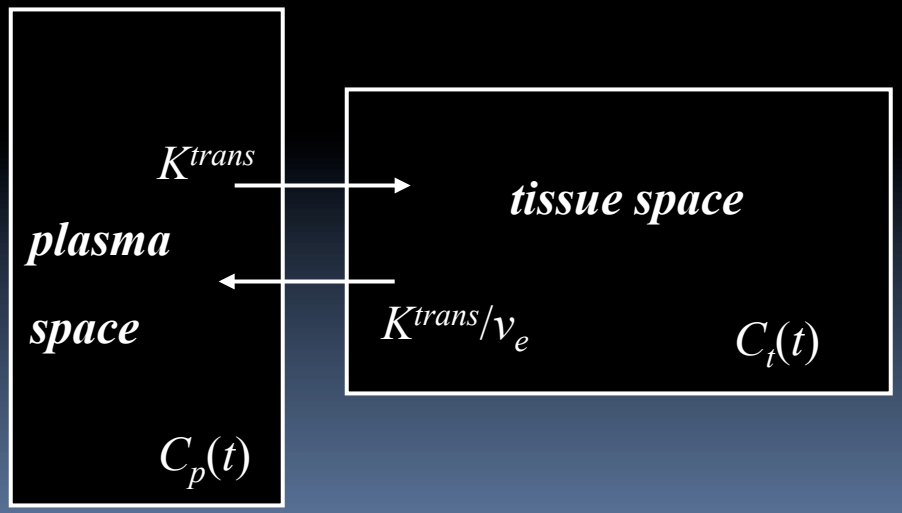


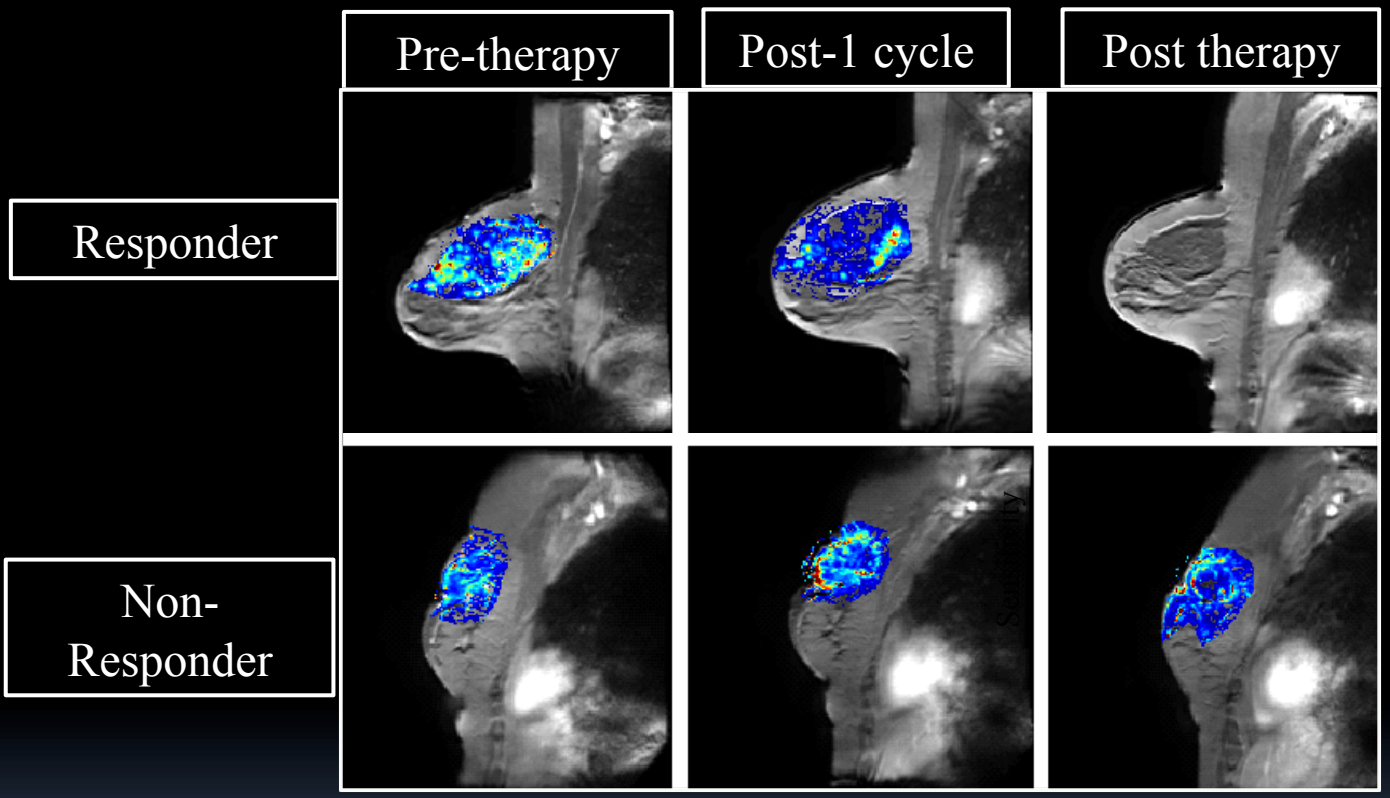
K^{trans} = transfer rate constant

v_e = extravascular extracellular volume fraction

v_b = blood volume fraction

Tofts, et al. J Magn Reson Imaging 1999;10:223-232.

DCE-MRI



ROC Analysis
Sensitivity = 0.81
Specificity = 0.75
AUC = 0.80

Combining DW-MRI & DCE-MRI data:
Sensitivity = 0.88
Specificity = 0.82
AUC = 0.86

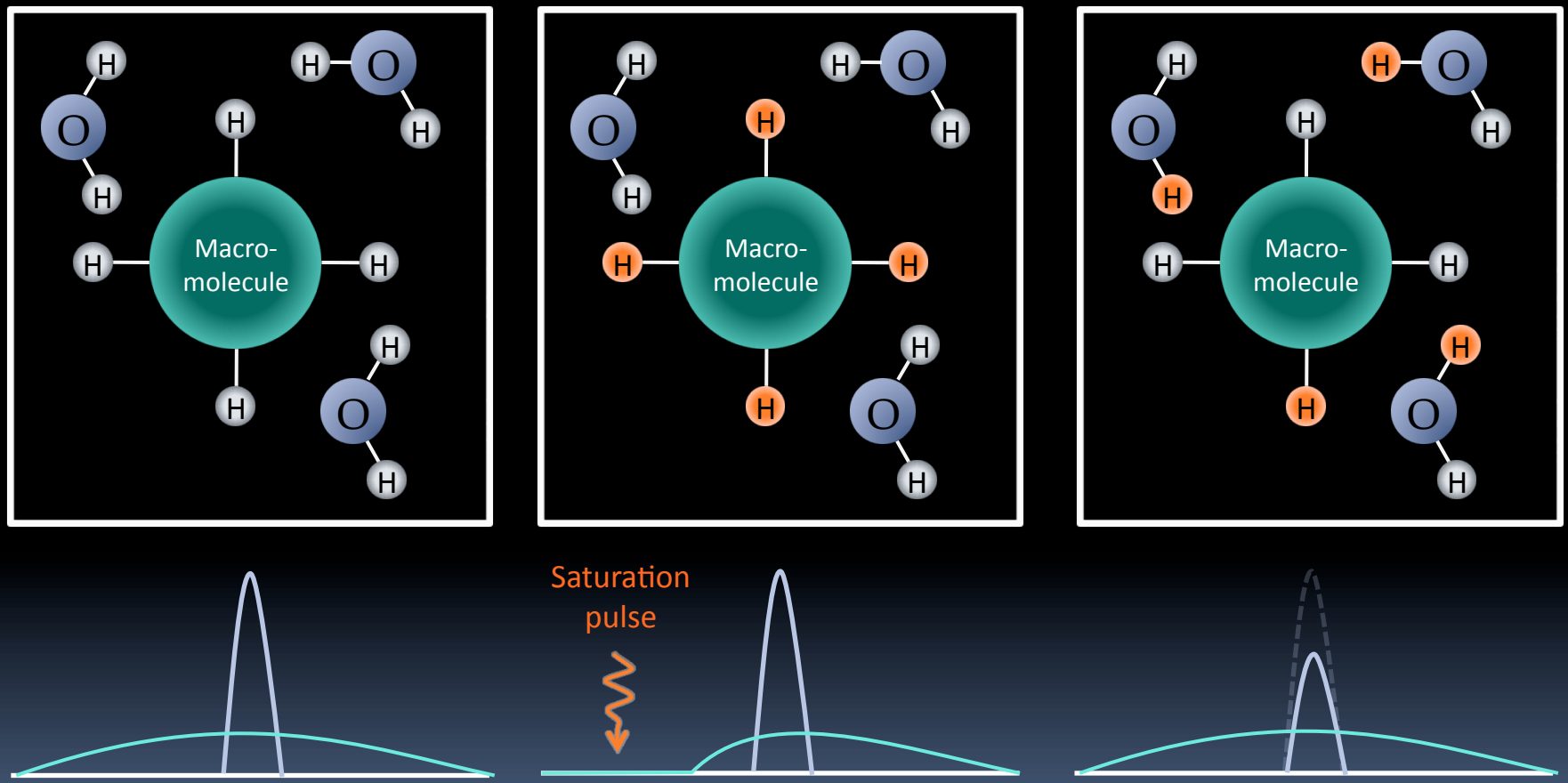
RECIST
Sensitivity = 0.33
Specificity = 0.95
AUC = 0.65

Lisa Li et al., submitted

Magnetization transfer MRI

Magnetization transfer MRI

• Exploits transfer of magnetization between protons bound in macromolecules and free water protons



• Image contrast depends upon:

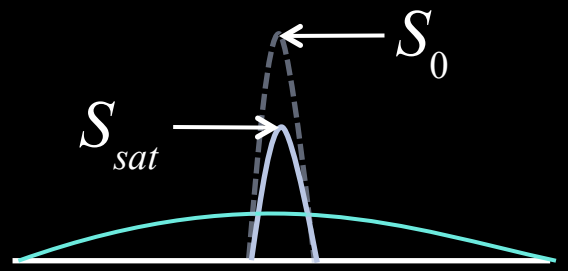
1) Concentration of macromolecules

2) Transfer rate between macromolecular and free water protons

Magnetization transfer MRI

- How do we quantify this measurement?
  Magnetization transfer ratio (MTR) maps

$$\mathrm{MTR} = 1 - \frac{S_{sat}}{S_0}$$



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No magnetization transfer

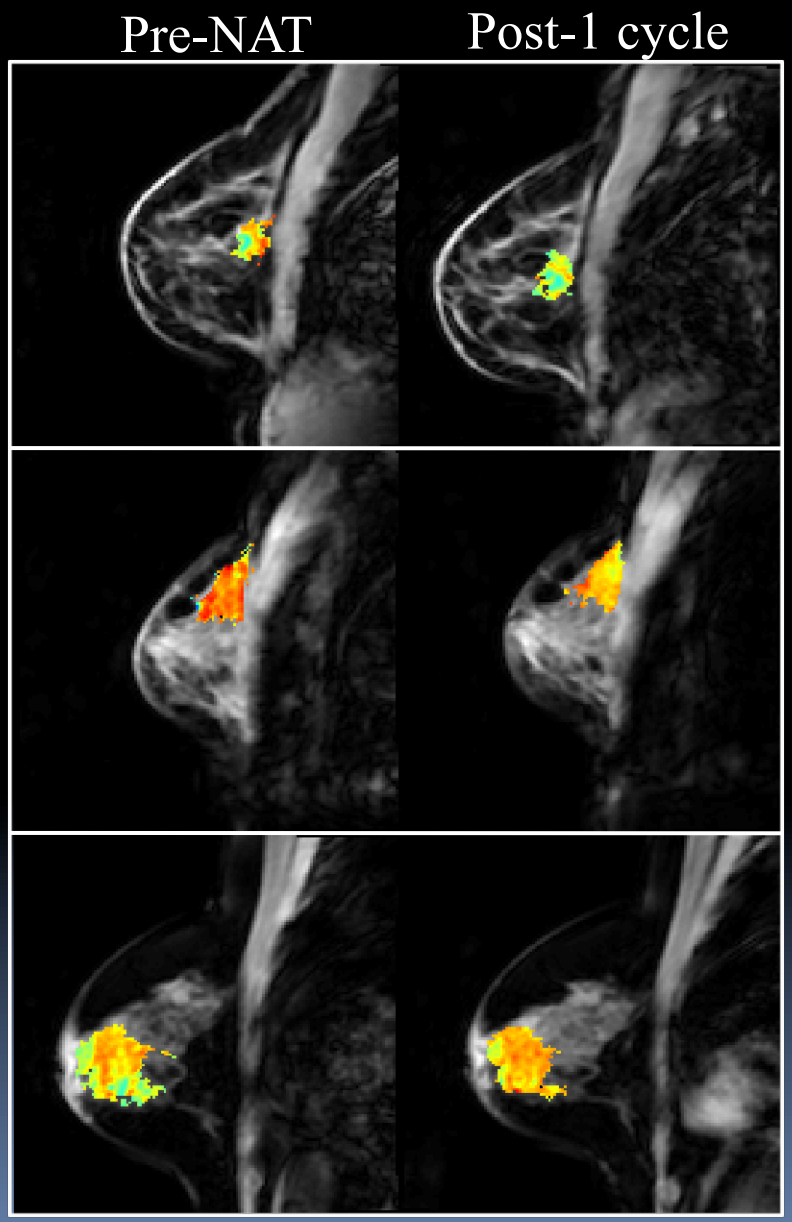
Complete magnetization transfer

Magnetization transfer MRI

pCR: ΔMTR = -14%

Partial responder: ΔMTR = -7%

Progressive disease: ΔMTR = +6%



Arlinghaus et al. ISMRM 2012

Magnetization transfer MRI

- Working hypotheses:

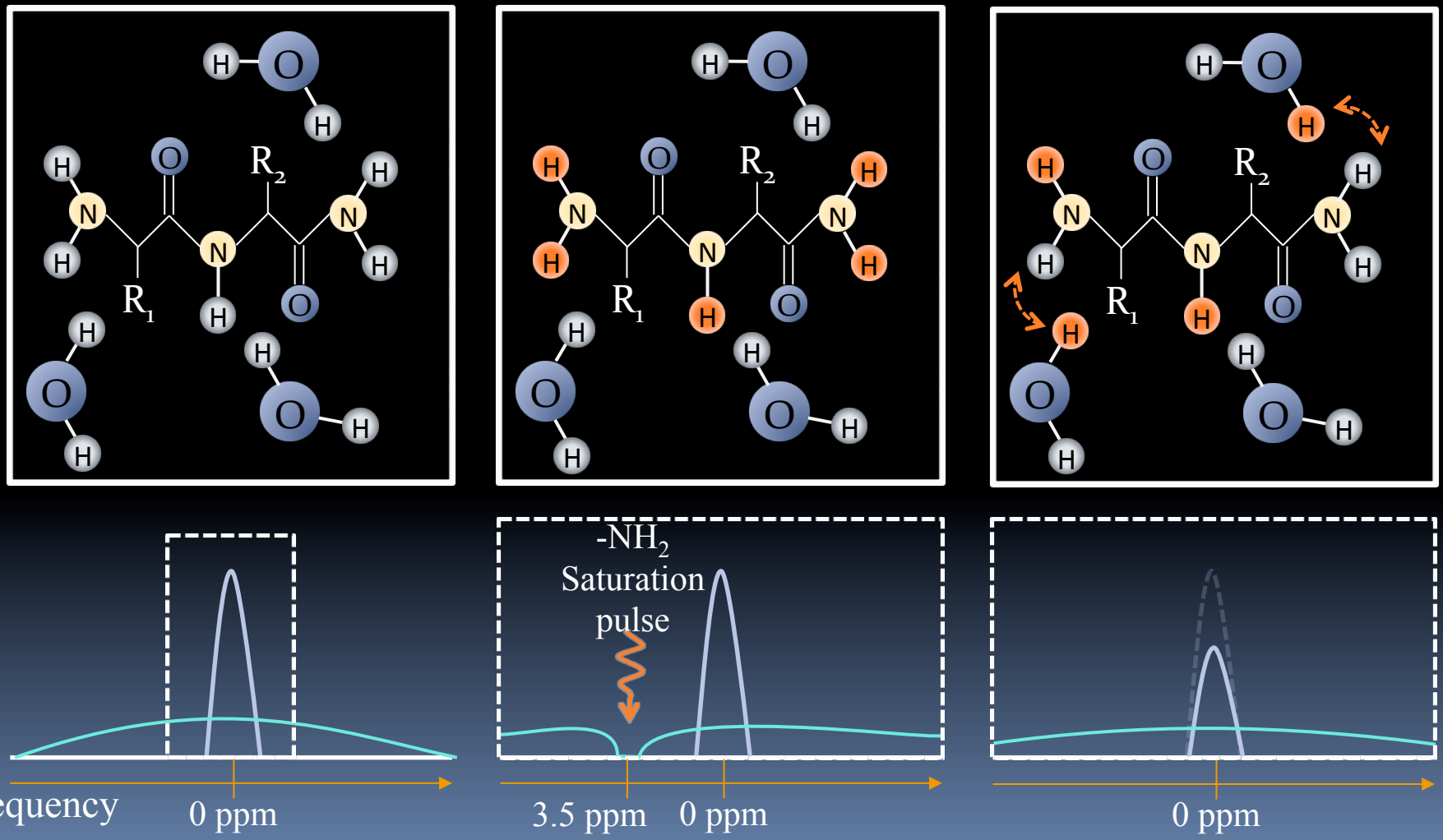
  1) Increased cellularity → Increased macromolecular pool → Increase in the MTR

  2) With successful treatment, MTR will return to values closer to healthy tissue

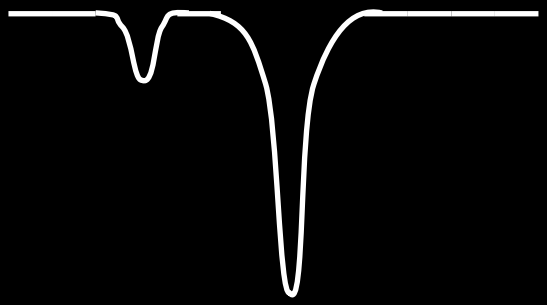
Chemical exchange saturation transfer MRI

Chemical exchange saturation transfer MRI

- Exploits magnetization transfer *and* chemical exchange of protons between amide protons and free water protons



Chemical exchange saturation transfer MRI



Quantification: $$APT_{asym} = \frac{S(-3.5\text{ppm}) - S(3.5\text{ppm})}{S_0}$$

- Image contrast depends upon:
  1) Concentration of amide protons
  2) Exchange rate between amide and free water protons

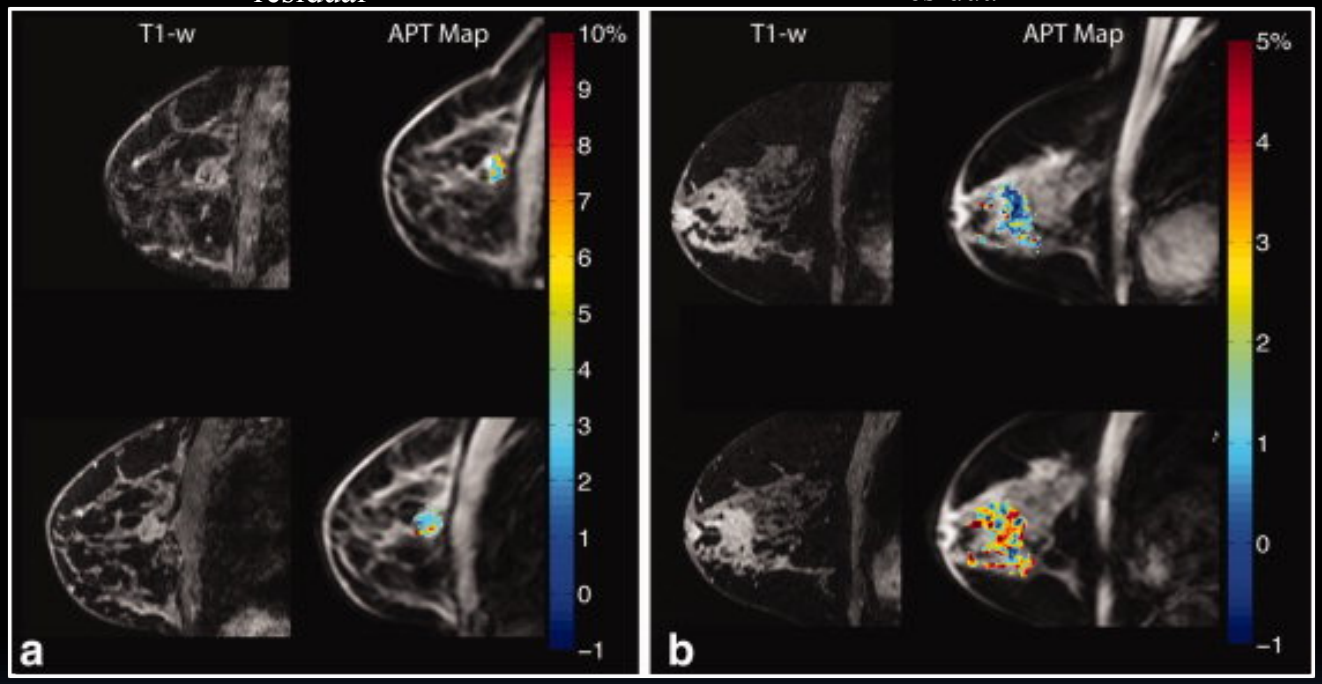
Chemical exchange saturation transfer MRI

Complete responder (pCR):
$\Delta APT_{residual}$ = -27%

Progressive disease:
$\Delta APT_{residual}$ = +78%

Pre-NAT

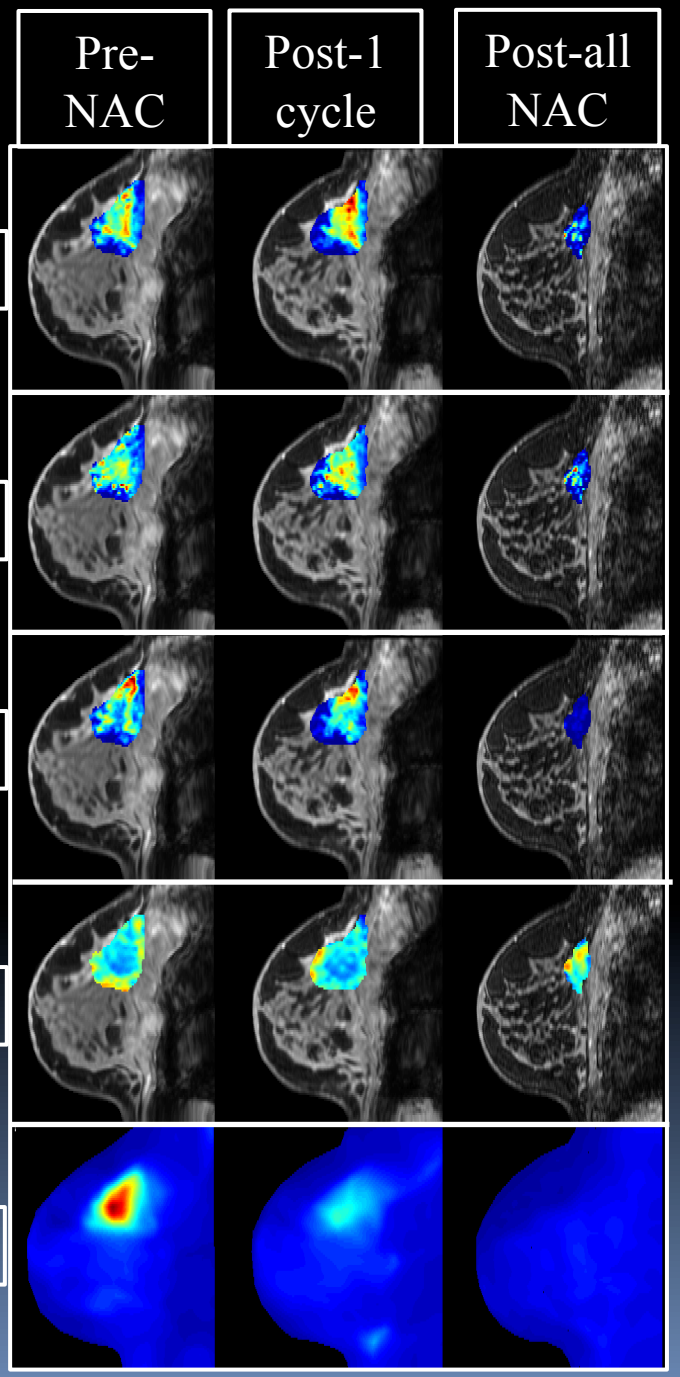
Post-1 cycle



- Working hypotheses:
  - → Backbones of proteins and peptides contain amides
  - → Proteins/peptides concentrations altered in the tumor environment
  - → Changes in APT_{asym} corresponding to molecular changes in tumor

Dula et al, MRM 2012

PET-MRI of breast cancer



blood perfusion and permeability

extravascular extracellular volume fraction

plasma volume fraction

cellularity

FDG-PET (glucose metabolism)

Atuegwu et al. ISMRM 2012

Summary

- RECIST criteria are fundamentally limited
- While MRI is not well-suited to molecular approaches, it can offer many clinical relevant measurements
  - → DW-MRI
  - → DCE-MRI
  - → MT-MRI
  - → CEST-MRI
  - → Hyperpolarized MRI/MRS (J. Kurhanewicz, K. Brindle)

Thank you very much for your time and attention.

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