Advanced Imaging for Breast Cancer: Magnetic Resonance Imaging

Tom Yankeelov

Ingram Associate Professor of Cancer Research
Departments of Radiology, Physics, Biomedical Engineering, Cancer Biology
Vanderbilt University Institute of Imaging Science

Vanderbilt University

7 August 2013
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
  
  • 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

Motivation

Pre-therapy

2 months post-therapy

FDG-PET

Pre-therapy

2 months post-therapy

Motivation

- 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)

• Tumor-Host Interactions
  • Inflammation
  • Extracellular matrix changes + signaling

• Molecular
  • Cell surface receptor interactions
  • Intracellular signaling pathways (e.g. caspase)
  • Gene expression

Well-suited for MRI, CT, US

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$^{-1}$
  \[ \Delta R_1 = \text{relaxivity} \cdot [\text{CA}] \]
  \[ \text{Relaxivity} \approx 4 \text{ sec}^{-1}\text{mM}^{-1} \text{ for Gd-DTPA} \]
  \[ \text{Minimum } [\text{CA}] = 25 \text{ } \mu\text{M throughout ROI! (PET } \sim 10^{-6} \text{ } \mu\text{m)} \]
  (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

![Graph showing the relationship between ADC and volume fraction](image)

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

**Diffusion weighted MRI**

Responder
\[ \Delta \text{ADC} = 11.8\% \]

Non-responder
\[ \Delta \text{ADC} = -11.6\% \]

ROC Analysis
- Sensitivity = 0.64
- Specificity = 0.93
- AUC = 0.70

\[ \text{Sensitivity} = \frac{\text{true positive rate}}{\text{TP} + \text{FN}} \]

\[ \text{Specificity} = \frac{\text{true negative rate}}{\text{FP} + \text{TN}} \]

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

\[
K^{\text{trans}} = \text{transfer rate constant}
\]

\[
\nu_e = \text{extravascular extracellular volume fraction}
\]

\[
\nu_b = \text{blood volume fraction}
\]

### DCE-MRI

<table>
<thead>
<tr>
<th></th>
<th>Pre-therapy</th>
<th>Post-1 cycle</th>
<th>Post therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responder</td>
<td>![Image]</td>
<td>![Image]</td>
<td>![Image]</td>
</tr>
<tr>
<td>Non-Responder</td>
<td>![Image]</td>
<td>![Image]</td>
<td>![Image]</td>
</tr>
</tbody>
</table>

**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

\[ \text{MTR} = 1 - \frac{S_{sat}}{S_0} \]

\( S_0 \)

\( S_{sat} \)

0

1

No magnetization transfer

Complete magnetization transfer
**Magnetization transfer MRI**

pCR: $\Delta$MTR = -14%

Partial responder: $\Delta$MTR = -7%

Progressive disease: $\Delta$MTR = +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
Quantification: \[ APT_{\text{asym}} = \frac{S(-3.5\text{ppm}) - S(3.5\text{ppm})}{S_0} \]

- 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):
\[ \Delta \text{APT}_{\text{residual}} = -27\% \]

Progressive disease:
\[ \Delta \text{APT}_{\text{residual}} = +78\% \]

**Pre-NAT**

**Post-1 cycle**

- **Working hypotheses:**
  - Backbones of proteins and peptides contain amides
  - Proteins/peptides concentrations altered in the tumor environment
  - Changes in \( \text{APT}_{\text{asym}} \) 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.

thomas.yankeelov@vanderbilt.edu