Research Issues: Imaging

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Imaging Research in Pre-Operative Therapy: Outline

- Research Goals
- What imaging tests are available?
- Examples of research imaging results
  - Target identification
  - Early response
  - Predicting cancer outcomes
  - Insights into biology of pre-op Rx
- Future Directions
Cautions

• Most of the imaging methods presented are considered investigational
• Discussion of results and possible applications is not a claim of clinical efficacy
Pre-Op Therapy: Imaging Research Goals

Diagnosis

Goal 1
Identify Target/Predict Response

Goal 2
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Therapy

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Goal 4
Elucidate Biology of Response

Outcomes

Path Response

DFS

OS
Imaging Modalities

- X-ray transmission - Computed Tomography (CT)
- Magnetic Resonance (MR)
  - Magnetic Resonance Imaging (MRI)
  - Magnetic Resonance Spectroscopy (MRS)
- Radionuclide imaging
  - Positron Emission Tomography (PET)
  - Single-Photon Emission Computed Tomography (SPECT)
- Ultrasound (U/S)
- Optical imaging
Imaging Modalities: MRI

- Creates 3D image related to proton environment
- Contrast can be made using atoms like Gd and Fe
- Novel measures possible - e.g., diffusion imaging
- Capability influenced by field strength - current clinical maximum 3T

Advantages
- High spatial resolution
- No radiation dose

Disadvantages
- Confined environment, high magnetic field
- Contrast possibilities limited by concentration needs and need for elements like Gd or Fe

(Partridge, SCCA)
Imaging Modalities: MRS

- Collects spatially localized MR spectra
- Calculates regional concentrations - e.g., choline
- With higher field strength, 3D voxel sets (i.e., images) possible

**Advantages**
- No contrast needed
- Wide range of mols.
- Many mols. at same time

**Disadvantages**
- Limited spatial resolution
- Challenging data analysis

(Garwood, Bolan, Yee, U Minnesota)
Imaging Modalities: PET and SPECT

- Detects emission of administered radionuclides
  - SPECT: $^{99m}Tc, ^{123}I$
  - PET: $^{11}C, ^{18}F$
- 3D image of radionuclide concentration
- Dynamic imaging possible

**Advantages**
- Sensitive - tracer conditions
- Quantification - esp. PET
- Wide range of mols. - esp PET

**Disadvantages**
- Limited spatial resolution/anatomy (PET/CT helps)
- Some radiation dose (< diagnostic CT)
Imaging Modalities: Optical

- Imaging based upon visible light
- Can use transmitted or reflected light
- Can use light emitted by contrast agent or embedded molecule - bioluminescence, near-infrared spectroscopy

**Advantages**
- Highly portable
- Inexpensive
- Minimally invasive
- Molecular contrast agents

**Disadvantages**
- Limited penetration

(Tromberg, UCI)
# Imaging Studies: Burden to Patient

<table>
<thead>
<tr>
<th>Study</th>
<th>Time</th>
<th>Other</th>
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</thead>
<tbody>
<tr>
<td>MRI</td>
<td>30 - 60 min</td>
<td>IV, closed space</td>
</tr>
<tr>
<td>MRS</td>
<td>15 - 30 min</td>
<td>closed space</td>
</tr>
<tr>
<td>PET/SPECT</td>
<td>30 - 90 min</td>
<td>IV, radiation</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>15 - 30 min</td>
<td></td>
</tr>
<tr>
<td>Optical</td>
<td>5 - 30 min</td>
<td></td>
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</tbody>
</table>
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$^{18}$F-Fluorestradiol (FES) PET Measures Target for Endocrine Therapy

Vascular Parameters from DCE-MRI MRI Predict Response to Pre-Operative Chemotherapy

(Semple, Annals Oncol, 17: 1393, 2006)
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DFS
OS
Early Response to Neo-Adjuvant Chemotherapy of Breast Cancer

FDG PET

Schelling, J Clin Oncol 2000; 18:1689
EC or ET q ??
17 - GRD; 7 - MRD

Smith, J Clin Oncol 2000; 18:1676
CVAP q 21 days
Not mCR - 20; mCR - 11
Changes in DECE-MRI Enhancement Kinetics Predict Response

(Padhani, Radiology, 239: 361, 2006)
Chemotherapy Response by MRI & MRS
University of Minnesota

1 wk pre-Tx

Day 1
AC x1

Day 42
AC x3

Day 70
AC x4

Cho: 4.6 (µmol/g)
LD: 4.0 (cm)

3.7
4.0
1.6
1.7

0.9

Diffusion MRI: ADC Map of Breast Cancer Therapy

Pre-therapy | II NACT | III NACT
---|---|---
| ADC | Water mobility |
| Normal | ↑ | ↑ |
| Pre therapy | ↓ | ↓ |
| Post therapy | ↑ | ↑ |

NR Jagannathan AIIMS, New Delhi
Monitoring Chemotherapy: MRI/Optics

DCE- MRI

Optical Line Scan
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Functional Imaging Predicts Outcome

$^{99m}$Tc-MIBI Serial Imaging

Change in Uptake Predicts Response

Residual Uptake Predicts Outcome

(Dunnwald, Cancer, 103: 680, 2005)
Residual MIBI Uptake Versus DFS
Comparison to Established Markers \( (Dunnwald, \text{Cancer, 103:680, 2006}) \)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Log-rank P-value</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER Status</td>
<td>0.12</td>
<td>2.0</td>
</tr>
<tr>
<td>HER2 Overexpression</td>
<td>0.66</td>
<td>1.2</td>
</tr>
<tr>
<td>Ki-67</td>
<td>0.02</td>
<td>3.0</td>
</tr>
<tr>
<td>Primary Tumor Path CR</td>
<td>0.05</td>
<td>3.1</td>
</tr>
<tr>
<td>Axillary nodes (&gt; 3)</td>
<td>0.19</td>
<td>1.8</td>
</tr>
<tr>
<td>Two month MIBI ratio</td>
<td>0.05</td>
<td>1.2**</td>
</tr>
<tr>
<td>Final MIBI ratio</td>
<td>0.001*</td>
<td>1.3**</td>
</tr>
</tbody>
</table>

* Multi-variate model P-value = 0.01

**Continuous variable, HR per unit change
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Metabolic Phenotype: Change with Therapy?
Shift Towards More Balanced Substrate Delivery and Utilization

Glucose Metabolism (FDG $K_i$) vs Blood Flow

Pre-Chemotherapy
$r = 0.31$

Post-Chemotherapy
$r = 0.77$

Blood Flow and Metabolism Patterns of Change with Neo-Adjuvant Chemotherapy

Altered Metabolic Phenotype with Rx

Changing Metabolic Phenotype in Resistant Br CA Treated with Neo-Adjuvant Chemotherapy

ChemoRx

Substrate Use
Substrate Delivery

Aberrant Metabolism

↓‘d Glucose Metabolism

↑‘d Blood Flow

Substrate Use
Substrate Delivery

Balanced Metabolism
Imaging Research: Summary

- Variety of modalities
  - Increasing ability to measure biochemical, molecular, and cellular process
- Goals - clinical endpoints
  - Predict response/guide therapy selection
  - Measure response early
  - Predict outcome - surrogate endpoint
- Goals - biologic insights
  - Measure in vivo tumor biology of cancer Rx
  - Translational: Laboratory findings <--> clinical framework