Is There a Role for Imaging as a Predictive Biomarker?

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Questions for speakers:

- What is needed to improve these technologies and make them useful for developing better and more efficient trials?
- How would the use of predictive markers affect trial design and implementation? Can you provide a case study or specific example of cost-effectiveness or cost saving of using predictive markers in cancer clinical trials?
- Would use of such markers increase the number of patients willing to participate in cancer clinical trials?
- Would the use of predictive markers limit the number of sites available to recruit patients for clinical trials, and would it add significantly to the variability across multiple sites?
- Will selection of patient subpopulations be an incentive or disincentive to drug development by pharmaceutical companies?
- What does it mean to "qualify" a biomarker, and what are the steps in this process?
- What would be the practical results if this approach succeeds?
Can Imaging be used to select patients who have an appropriate molecular phenotype for a targeted therapeutic?

- Imaging methods typically provide less molecular information than in vitro methods.
- However, imaging methods usually provide more context for spatial and/or temporal localization and distribution of molecular or physiological processes.
- Imaging methods may preserve physiological information that is lost in sample preparation.
- Imaging methods may be non-invasive or minimally invasive compared with in vitro methods.
Possible Predictors:

- Imaging of drug localization
- Imaging of ligand localization
- Imaging of some physiological state, e.g., hypoxia, hemodynamic status, diffusivity
- Multi-parametric imaging
Examples of labeled drugs (Microdosing)

- $^{18}$F-5-FU
- $^{11}$C-DACA
- $^{11}$C-BCNU
- $^{11}$C-temozolomide
- $^{13}$N-cisplatin
- $^{13}$N-gemcitabine
- $^{11}$C-verapamil
- $^{11}$C-daunorubicin
- $^{11}$C-colchicine
- $^{18}$F-paclitaxel
- $^{111}$In-britumomab Tiuxetan (Zevalin)
- $^{131}$I-tositumomab (Bexxar)
F-Paxlitaxel in Breast Cancer

Kurdziel, VCU, 2006
Imaging of tumor uptake of $^{18}$F-gefitinib

Gefitinib

$[^{18}F]$Gefitinib

A431 Tumor xenograft SCID mouse 90 min p.i.

VD: 2.8 ml/ml

UCLA
Issues: Radiolabeled drugs

- **Pro**
  - Localization mechanism is identical
  - Take advantage of preclinical drug studies

- **Con**
  - Need rapid synthetic pathway
  - Drug kinetics may not be optimal for imaging (irreversible binding better for imaging)
  - Could take years to get into patients
Possible Predictors:

- Imaging of drug localization
- **Imaging of ligand localization**
- Imaging of some physiological state, e.g., hypoxia, hemodynamic status, diffusivity
- Multi-parametric imaging
PET: $\alpha_v\beta_3$ positive lymph node metastasis (melanoma)

$^{18}$F-Galacto-RGD PET (5 mCi, 50 min p.i.)

“Fusion image”
FES Uptake Predicts Breast Cancer Response to Hormonal Therapy

**Example 1**
- Recurrent sternal lesion
- ER+ primary
- Recurrent Dz strongly FES+

**Example 2**
- Newly Dx’d breast cancer
- ER+ primary
- FES-neg bone mets

**Pre-Rx**

**Post-Rx**

Univ of Washington

Excellent response after 6 wks Letrozole

No response to several different hormonal Rx’s
$^{18}$F-Fluoroestradiol (FES) PET: Heterogeneous ER Expression in Bone Mets

FDG

Glucose Metabolism

FES

ER Expression

Liver

Bowel

Bladder

Uterus

Univ of Washington
Quantitative Fluoroestradiol Positron Emission Tomography Imaging Predicts Response to Endocrine Treatment in Breast Cancer

FES Uptake Predicts Response of Advanced Breast Ca to Hormonal Therapy

**LABC or Metastatic Br CA**
- Primary Tamoxifen Rx

**Recurrent or Metastatic Br CA**
- Aromatase Inhibitor Rx

(P < .01 for both)

*(Mortimer, J Clin Onc, 2001)*

*(Linden, J Clin Onc, 2006)*
Combining Imaging and Other Assays
Linden, ASCO, 2006

Lack of FES uptake predicts NR:

<table>
<thead>
<tr>
<th></th>
<th>FES SUV &lt; 1.5</th>
<th>FES SUV &gt; 1.5</th>
<th>Total</th>
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<tbody>
<tr>
<td>R</td>
<td>0</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>NR</td>
<td>23</td>
<td>29</td>
<td>52</td>
</tr>
<tr>
<td>Total</td>
<td>23</td>
<td>47</td>
<td>70</td>
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</table>

Response rate: 26% --> 38%  
(P < .001)

Incomplete estradiol suppression predicts NR:

<table>
<thead>
<tr>
<th></th>
<th>Estradiol &lt; 30</th>
<th>Estradiol &gt; 30</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>17</td>
<td>1</td>
<td>18</td>
</tr>
<tr>
<td>NR</td>
<td>20</td>
<td>8</td>
<td>28</td>
</tr>
<tr>
<td>Total</td>
<td>37</td>
<td>9</td>
<td>46</td>
</tr>
</tbody>
</table>

Response rate: 38% --> 46%  
(P = .05)
Issues: Labeled ligands

- **Pros**
  - Labeling synthesis may be easier (than for drug)
- **Cons**
  - Localization mechanism may be different (need more validation than for labeled drug).
  - Time course for development may be very long – out of synch with corresponding drug development.
- **Other issues are similar to labeled drugs.**
- **FDA Regulatory issue.**
Possible Predictors:

- Imaging of drug localization
- Imaging of ligand localization
- Imaging of some physiological state, e.g., hypoxia, hemodynamic status, diffusivity
- Multi-parametric imaging
Normoxic Responder

FDG-PET

Pre-therapy CT

Cu ATSM-PET

Post-therapy CT

T/M = 1.26

Hypoxic Non-Responder

FDG-PET

Pre-therapy CT

Cu ATSM-PET

Post-therapy CT

T/M = 3.6

Prognostic Significance of 18F-Misonnidazole Positron Emission Tomography-Detected Tumor hypoxia in Patients with Advanced Head and Neck Cancer Randomly Assigned to Chemoradiation With or Without Tirapazamine: A Substudy of Trans-Tasman Radiation Oncology Group Study 98.02

- Rischin et.al., JCO 2006
- For hypoxic patients:
  - 8/13 chemoboost patients LRF
  - 1/19 TPZ patients LRF
DCE-MRI as a Predictive Biomarker

Reddick et al, Cancer 2001; osteosarcoma, surgery + chemotherapy, N=31, $k_{21}$

Flaherty, K. T. Clin Cancer Res 2007; RCC, sorafenib, N=17, $k_{\text{trans}}$
ADC as Predictor of Glioma Response

Ross, et.al. U Mich, PNAS 2005
Predicting Treatment Response by \textit{in vivo} $^{31}$P MR spectroscopy in Non-Hodgkin’s Lymphoma

Brown, Arias-Mendoza, Columbia University

[Duke University, Fox Chase Cancer Center, Memorial Sloan-Kettering Cancer Center, The Royal Marsden Hospital, St. George’s Hospital Medical School, University of California at San Francisco, University Hospital Nijmegen, University of Pennsylvania, Wayne State University]
Localized NHL P31 MR Spectrum

Axial

Coronal

Inguinal Nodes

δ (ppm)

PCr

PC

NTP

PE

Pi

PDE

α

β

γ
Pretreatment $P_E P_C / NTP$ correlation with long-term response to treatment

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean ± Standard Error</th>
<th>n</th>
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</thead>
<tbody>
<tr>
<td>Whole Group</td>
<td>1.8 ± 0.2</td>
<td>14</td>
</tr>
<tr>
<td>Naïve Group</td>
<td>2.0 ± 0.2</td>
<td>29</td>
</tr>
<tr>
<td>Naïve Aggressive Group</td>
<td>2.2 ± 0.2</td>
<td>7</td>
</tr>
<tr>
<td>Naïve Indolent Group</td>
<td>1.9 ± 0.2</td>
<td>17</td>
</tr>
<tr>
<td>Recurrent Group</td>
<td>1.6 ± 0.2</td>
<td>6</td>
</tr>
<tr>
<td>Recurrent Aggressive Group</td>
<td>1.8 ± 0.2</td>
<td>9</td>
</tr>
<tr>
<td>Recurrent Indolent Group</td>
<td>1.5 ± 0.2</td>
<td>1</td>
</tr>
</tbody>
</table>

p-values: p = 0.0006, p = 0.009, p = 0.02, NA, p = 0.04, NS, NA

mean ± standard error (n under the bar)
Pretreatment $P_{EP/C}/NTP$ and NHL segregation by IPI-dependent $P_{EP/C}/NTP$
Issues: Physiologic measures

- **Pros**
  - Imaging well-suited for this.

- **Cons**
  - Measurement may be strongly influenced by systemic conditions (resulting in a misleading tumor measurement).
Possible Predictors:

- Imaging of drug localization
- Imaging of ligand localization
- Imaging of some physiological state, e.g., hypoxia, hemodynamic status, diffusivity
- **Multi-parametric imaging**
High Field (3T) Multi-parametric Approach - MRI/\(^1\)H MRSI/DTI/DCE

**T2 MR Image**

**<D> map**

**DTI-EPI Parallel imaging sequence**

**DCE - Uptake Curves**

3D FSPGR w/ 3.4sec temporal resolution, 480 FOV, 5 mm thick slices, TR/TE/flip = 5ms / 2.1ms / 6°

**DCE - Peak Enhancement**

**3-D \(^1\)H MRSI**

0.16 cc
Combining MRI/MRSI and Clinical Data
Prediction of Indolent Disease

- N = 220 pt; MR-RRP
- Indolent disease at surgery - localized disease, < 0.5 cc of cancer, no Gleason pattern 4 or 5.
- Clinical parameters without MRI/MRSI (AUC = 0.726)
  - PSA
  - Gleason
  - Clinical Stage
  - % Ca in specimen
  - % positive cores
  - Prostate volume

- Clinical parameters + MRI/MRSI
  - AUC= 0.854

Shukla-Dave, MSKCC BJU Int 2007
Key question for Predictive Biomarkers:

- What level of accuracy is required for oncologists to change their practice, i.e., their decision-making?
Issues in Validation of Imaging Methods:

- Physical sources of variability:
  - Scanner calibration
  - Different machines
  - Different image acquisition parameters
  - Different algorithms for data processing
- Physiological sources of variability
  - Intra- and inter-patient variation
  - Reader variability
- Performing repeatability tests for imaging methods is difficult and costly (because performed on people, not specimens).
If Imaging is to become a reliable in vivo assay – there must be:

- Uniformity of instrumentation
- Uniformity of protocol-specified acquisition
- Independent quality control
- Reliability/independence of reader interpretation
- Provenance, auditability and storage accessibility
Thank you.