Imaging as a Predictor of Therapeutic Response

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Imaging and Therapeutic Response

- Clinical scenarios and questions
- Cancer biomarker approaches for functional and molecular imaging
  - Prognosis
  - Prediction
  - Response
  - Biologic response
Guiding Cancer Therapy: Clinical Needs

Pre-Rx
- Aggressive Dz?
- Rx Targets

Therapy
- Early
- Mid-Rx
- Response? 
  - Yes/no
  - How much?

Post-Rx
- Residual Disease?

Relapse Survival
How Can Biomarkers Guide Cancer Therapy?

- **Goals in cancer treatment**
  - Characterize tumor biology pre-Rx
  - Individualized, specific therapy
  - Static response may be acceptable
- **The implied needs for cancer biomarkers**
  - Characterize tumor biology, predict behavior
  - Identify targets, predict response
  - Measure tumor response (early!)
  - Relate response to survival
Biomarkers and Cancer Therapy
What Can Imaging Do?

- **Goals in cancer treatment**
  - Characterize tumor biology pre-Rx
  - Individualized, specific therapy
  - Static response may be acceptable

- **The implied questions for cancer imaging**
  - Characterize in vivo tumor biology - prognosis
  - Identify targets, predict response - prediction
  - Measure tumor response (early!) - response
  - Relate response to survival - biologic response
Standards for Reporting Prognostic Tumor Marker Studies

Todd A. Alonzo, Division of Biostatistics, University of Southern California Keck School of Medicine, Los Angeles, CA
Imaging and Therapeutic Response

- Clinical scenarios and questions
- Cancer biomarker approaches for functional and molecular imaging
  - Prognosis
  - Prediction
  - Response
  - Biologic response
Study Design for: Prognosis

Kaplan-Meier Plot:

- In vitro assay examples:
  - Proliferation - Ki-67
  - Receptor expression - ER
  - Oncogene expression - HER2
# Brain Tumor FDG Uptake vs Survival: Tumor Volumes

- Tralins, J Nucl Med, 2002

## Table

<table>
<thead>
<tr>
<th>Variable</th>
<th>P value as prognostic marker</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>.25</td>
<td>.25</td>
<td>-</td>
</tr>
<tr>
<td>KPS</td>
<td>.27</td>
<td>.27</td>
<td>-</td>
</tr>
<tr>
<td>T2</td>
<td>.017</td>
<td>.017</td>
<td>-</td>
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<tr>
<td>T1 Gad</td>
<td>.0035</td>
<td>.0035</td>
<td>.91</td>
</tr>
<tr>
<td>T1 Gad + Cavity</td>
<td>.17</td>
<td>.17</td>
<td>-</td>
</tr>
<tr>
<td>FDG-PET</td>
<td>.0024</td>
<td>.0024</td>
<td>.0024</td>
</tr>
</tbody>
</table>
FDG Predicts Survival in Recurrent Thyroid Cancer - Robbins, JCEM, 2006

131I- FDG PET

High TG, Neg Scan L Cervical LN

B

Surviving Fraction

FDG-

p<0.001

FDG+

FDG - (n=180) FDG + (n=219)

At risk 314 186 94 40

Months from PET Scan
Imaging Hypoxia as the Accumulation of a Radiopharmaceutical

Nitroreductase enzymes

Radical Anion

covalent bonding to macromolecules

University of Washington
KA Krohn
Tumor Hypoxia Quantified by PET Predicts Survival

FMISO PET
Brain Tumor

FMISO PET
H & N Cancer

Cu-ATSM PET
Cervical Cancer

(Spence, Clin Cancer Res, 2008)

(Rajendran, Clin Can Res, 2007)

(Dehdashti, Int J Radiat Oncol Biol Phys, 2003)
ACRIN 6684
MULTICENTER, PHASE II ASSESSMENT OF TUMOR HYPOXIA IN GLIOBLASTOMA USING \(^{18}\)F-FLUOROMISONIDAZOLE (FMISO) WITH PET AND MRI
Elizabeth Gerstner, MD, PI

Outcomes:
Progression
Overall Survival (OS)

Diagnosis and Surgery
FMISO PET MRI
FMISO PET MRI

Radiotherapy and Temazolamide
ACIN 6684: Hypoxia PET and MRI Predict GBM PFS and OS

Table 3: Cox Regression Model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Overall Survival Time</th>
<th>Progression Free Survival</th>
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<tbody>
<tr>
<td></td>
<td>Hazard Ratio</td>
<td>95% CI</td>
</tr>
<tr>
<td>SUVpeak</td>
<td>1.54</td>
<td>1.00, 2.36</td>
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<tr>
<td>TBmax</td>
<td>1.16</td>
<td>0.75, 1.81</td>
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<tr>
<td>HV</td>
<td>1.00</td>
<td>0.97, 1.03</td>
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<tr>
<td>Mean k\text{\textsuperscript{trans}}</td>
<td>1.17</td>
<td>1.02, 1.34</td>
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<td>Median k\text{\textsuperscript{trans}}</td>
<td>1.32</td>
<td>1.01, 1.72</td>
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<tr>
<td>nRCBV</td>
<td>1.11</td>
<td>0.90, 1.37</td>
</tr>
<tr>
<td>nCBF</td>
<td>1.07</td>
<td>0.88, 1.29</td>
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</tbody>
</table>
Imaging and Therapeutic Response

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  - Prediction
  - Response
  - Biologic response
Outcomes for Cancer Imaging: Prediction

- Predictor of response to specific therapy
  - Positive - predicts who will respond
  - Negative - predicts who will not respond
Predictive Assays

- Examples of in vitro assay
  - ER - Endocrine therapy for breast cancer
  - TS - 5-FU for colon cancer
  - HER2 - Trastuzumab for breast cancer
Targeted Breast Cancer Therapy: The Estrogen Receptor (ER) and Endocrine Treatment

(Johnson and Dowsett, Nar Rev Cancer 3:821, 2002)
**18F-Fluoroestradiol (FES): PET Estrogen Receptor (ER) Imaging**

Provides a Quantitative Estimate of ER Expression

--

**vs Radioligand Binding**

![Graph showing Tumor Uptake vs ER Concentration](image)

- **ER Concentration (fmoles/mg protein)**
- **Tumor Uptake (% ID/mL x 10^-4)**

(Mintun, Radiology 169:45, 1988)

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**vs IHC**

![Graph showing PV SUV vs IHC index](image)

- **PV SUV**
- **IHC index**


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(FGFluoroestradiol (FES): PET Estrogen Receptor (ER) Imaging)

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 met breast CA
- ER+ primary
- FES-negative bone mets

Pre-Rx

Post-Rx

Excellent response after 6 wks Letrozole

No response to several different hormonal Rx’s

University of Washington

(Linden, J Clin Onc, 2006)
ECOG-ACRIN Biomarker Trial of FES PET: EAI142

Dehdashti & Linden

MBC from ER+ Primary

• First line therapy
• Stand-alone imaging trial:
  – Clinical indication for endocrine therapy
  – Standard Rx allowed (AI, FUL, TAM)
  – Allow measurable and non-measurable disease

Endocrine Therapy

Biopsy

Response
PFS
3, 6 month assessment

Primary Aim

Validation Aim

FES PET

FDG PET

Group Meeting • Nov 14-16, 2013 21
Cancer Markers: Prognostic, Predictive, or Both?

- ERG ER+
- PFS
- ER-directed therapy
- Non-targeted therapy
- No therapy
- ER- ER+
Imaging and Therapeutic Response

- Clinical scenarios and questions
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  - Prediction
  - Response
  - Biologic response
- Future directions
Outcomes for Cancer Imaging: Response

- Accuracy of response assessment
  - Response or not - R versus NR
  - Degree of response – residual dz versus CR
- Surrogate outcome measure
  - Predictor of DFS, OS
Study Design for:

Measuring Response

Pre-Rx Therapy Response

PreGRx PostGRx

Relapse & Survival

Difference

Outcomes:

Sens, Spec, ROC for Response

Predictor of TTP and Survival
Functional and Molecular Imaging Response
Neo-Adjuvant Therapy of Locally Advanced Breast Cancer (LABC)
FDG PET to Monitor Breast Cancer Response to Therapy
Wahl, J Clin Oncol 11:2101, 1993

Pre-Rx → Chemotherapy → Surgery (Path Response)

Baseline
Mid-Rx

P < .001  P = NS

(N=11)

FDG SUV

Responders  Non-Responders

Day 0  Day 63
Change in MIBI Uptake Predicts Response

Pathologic Complete Response

Uptake vs Response

Progressive Disease

ROC for CR versus PR

\[ A_z = 0.96 \]

\[ (A_z \text{ for size chng } = 0.77) \]

(Mankoff, Cancer, 1998)
Functional Imaging Predicts Outcome

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

Change in Uptake Predicts Response

Residual Uptake Predicts Outcome

\begin{itemize}
\item Disease-Free Survival
\item Overall Survival
\end{itemize}

\begin{itemize}
\item Low MIBI Uptake
\item High MIBI Uptake
\end{itemize}

\begin{itemize}
\item ($P < .001$)
\item ($P < .01$)
\end{itemize}

(Dunnwald, Cancer, 103: 680, 2005)
Biologic Events in Response to Successful Cancer Therapy

Rationale for Measuring Early Response by Cell Proliferation Imaging

Rx

↓ Cellular Proliferation or ↑ Cell Death

↓ DNA Synthesis

↓ Viable Cell Number

↓ Tumor size
Early Response Measured by $^{18}$F-fluorothymidine (FLT) PET

Breast CA, ChemoRx
(Kenny, EJNMMI 34:1339, 2007)

Lung CA, Genfitinib Rx
(Sohn, Clin Cancer Res 14: 7423, 2008)
ACRIN 6688 Study Outline

Establish Eligibility

- Baseline organ function
- Pathologically confirmed disease
- Determine primary systemic Rx

Obtain pre-treatment proliferative Indices

Ki-67, mitotic index on bx sample or re-biopsy (if available)

* Baseline Imaging

18FLT PET/CT (FLT-1)

Chemotherapy cycle 1

18FLT PET/CT (FLT-2)

* Early therapy Imaging

Chemotherapy last cycle

18FLT PET/CT (FLT-3)

Post-therapy Imaging

Surgical Resection

Obtain post-treatment proliferative Indices

- Pathologic response,
- Ki-67, mitotic index, surg. specimens
ACRIN 6688: FLT PET to Measure Early Breast Cancer Response (PI: Lale Kostakoglu)

Best $\Delta$SUV$_{\text{max}}$ cut-off for predicting pCR = -51% (sensitivity 56%; specificity 79%).

(Kostakoglu, J Nucl Med, 2015, epub)
Imaging and Therapeutic Response

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  - Prediction
  - Response
  - Biologic response
- Future directions
Outcomes for Cancer Imaging: Biologic Response

• Can functional/molecular response better predict outcome?
  • Predict DFS, OS, etc
  • And what are the biologic insights
• Surrogate outcome measure?
FDG PET Is Sensitive for HL and High-Grade NHL, and Its Response to Treatment

Hodgkin’s Lymphoma (HL)
Pre- and Post-ABVD
NHL, Partial Metabolic Response (Residual Tumor)

Pre- | Post-
Advanced Stage HL

- 260 HL patients, prospective
  - unfavorable stage IIA  26%
  - stage IIB  27%
  - stage III-IVB  47%
- End-point: 2yr PFS, med f/u 2.2 y
- 79% CR; 16% prog <6mo; 4% relapse
  - PPV  86%
  - NPV 95%
  - Sens and spec: 81% and 97%
- 2-yr PFS for PET2- vs PET2+
  95% vs 13%,
  Positive PET definition uptake > MBP

(courtesy of Lale Kostakoglu)

PET-2 was significant overshadowing the prognostic value of IPS

**TABLE I.**—Prognostic value of end-treatment 18F-FDG PET for Aggressive NHL and HL.

<table>
<thead>
<tr>
<th>AUTHOR</th>
<th>Patients (n°)</th>
<th>DISEASE</th>
<th>NOTES</th>
<th>FOLLOW-UP (months)</th>
<th>PFS PET+ vs PET−</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zinzani 1999</td>
<td>44</td>
<td>LH/LNH</td>
<td>Abdominal mass in all</td>
<td>20</td>
<td>1 yr: 15% vs 95%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 yr: 0% vs 95%</td>
</tr>
<tr>
<td>Jerusalem 1999</td>
<td>54</td>
<td>LH/LNH</td>
<td>RM in 24</td>
<td>21</td>
<td>1 yr: 0% vs 86%</td>
</tr>
<tr>
<td>Maisey 2000</td>
<td>24</td>
<td>LH/LNH</td>
<td>RM in 24</td>
<td>29</td>
<td>56% vs 73%</td>
</tr>
<tr>
<td>Mikhacel 2000</td>
<td>45</td>
<td>Aggressive LNH</td>
<td>RM in 17</td>
<td>30</td>
<td>1 yr: 0% vs 83%</td>
</tr>
<tr>
<td>Spaepen 2000</td>
<td>93</td>
<td>Aggressive LNH</td>
<td>RM in 24</td>
<td>22</td>
<td>2 yr: 4% vs 85%</td>
</tr>
<tr>
<td>Juweid 2002</td>
<td>38</td>
<td>Aggressive LNH</td>
<td>-</td>
<td>15.5</td>
<td>1 yr: 8% vs 88%</td>
</tr>
<tr>
<td>de Wit 2001</td>
<td>37</td>
<td>LH</td>
<td>RM in 37</td>
<td>25.6</td>
<td>54% vs 96%</td>
</tr>
<tr>
<td>Weihrauch 2001</td>
<td>28</td>
<td>LH</td>
<td>RM in 28</td>
<td>28</td>
<td>1 yr: 40% vs 95%</td>
</tr>
<tr>
<td>Spaepen 2001</td>
<td>60</td>
<td>LH</td>
<td>RM in 43</td>
<td>31</td>
<td>2 yr: 4% vs 85%</td>
</tr>
<tr>
<td>Mikhacel 2002</td>
<td>65</td>
<td>LH</td>
<td>-</td>
<td>36</td>
<td>1 yr: 0% vs 93%</td>
</tr>
</tbody>
</table>

Abbreviations: RM: residual mass; PET+: positive; PET−: negative
Early Interim FDG-PET and Prognosis

(a) FDG-PET after two cycles

- FDG-PET negative
  - 61 Patients, prog=3
  - 2-year PFS 96%

- FDG-PET positive
  - 16 Patients, prog=11
  - 2-year PFS 0%

P < 0.0001

(b) CT after two cycles

- Unsatisfactory remission
  - 2 Patients, prog=0
  - 2-year PFS 100%

- Satisfactory remission
  - 62 Patients, prog=11
  - 2-year PFS 82%

P = 0.554

(courtesy of A Shields, Karmanos Cancer Center)  M Hutchings, Blood, 2006
Lymphoma Guidelines 2014: The Lugano Criteria
Response Assessment
Cheson, J Clin Oncol 32: 3059, 2014

Table 1. Revised Criteria for Response Assessment

<table>
<thead>
<tr>
<th>Lesion Type</th>
<th>CR- and PR-Based Criteria</th>
</tr>
</thead>
</table>
| Complete lymph nodes and extranodal disease | Complete metabolic response
  Score: 4 or 5: complete response
  Score: 2 or 3: partial response
  Score: 0 or 1: no response

<table>
<thead>
<tr>
<th>Lesion Type</th>
<th>CR- and PR-Based Criteria</th>
</tr>
</thead>
</table>
| New lesions          | Absent
| Organ enlargement    | Regression to normal
| Bladder               | Yes
| Bone marrow           | No evidence of FDG and disease in marrow
| Lymph nodes and extranodal disease | Complete metabolic response
  Score: 4 or 5: complete response
  Score: 2 or 3: partial response
  Score: 0 or 1: no response

Table 3. Revised Criteria for Response Assessment (continued)

<table>
<thead>
<tr>
<th>Lesion Type</th>
<th>CR- and PR-Based Criteria</th>
</tr>
</thead>
</table>
| Progression disease  | Progressive disease requires at least of the following
  FDG progression
  New lesion(s) 4 or 5
  Increase in abnormal lesion
  Increase in metastasis

<table>
<thead>
<tr>
<th>Lesion Type</th>
<th>CR- and PR-Based Criteria</th>
</tr>
</thead>
</table>
| Stable disease       | Complete metabolic response
  Score: 4 or 5: complete response
  Score: 2 or 3: partial response
  Score: 0 or 1: no response

Oy!!
Imaging Biomarker in Cancer Trials: Integrated vs Integral Markers

ECOG 2410 Trial in bulky early stage HL (n=144)

FDG-PET after 2x ABVD

PET-

ABVD 4 more cycles (total of 6 cycles)

PET-

FDG-PET/CT

PET+

PET+

PET-

PET+

Follow up

Biopsy+ off

Biopsy-
Imaging as a Biomarker: Summary

• Imaging to guide treatment – imaging as a disease biomarker
  • Prognosis – How aggressive is the dz?
  • Prediction - Will the Rx work?
  • Response - Is the Rx working?
• Biologic Response
  • Can response predict survival?
  • Can we use insights from imaging to adapt therapy?