Molecular Imaging and Targeted Cancer Therapy

Novel Molecular Imaging Techniques to Personalize Cancer Treatment
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Current Clinical Use of Molecular Imaging:
Cancer Detection and Staging

\[ ^{18} \text{F} \]FDG PET/CT Breast Cancer Staging
(Eubank, J Clin Oncol. 9:3618, 2001)

\[ ^{18} \text{F} \]Fluciclovine PET/CT Prostate Cancer Re-Staging
(Schneider, Radiology 261: 838, 2011)
Beyond Detection:
Molecular Imaging is a Cancer Biomarker that can Guide Targeted Therapy

- Measuring therapeutic target expression
- Assessing target engagement by drug therapy
- Measuring early therapeutic response
- Predicting therapeutic outcomes: DFS, PFS, OS

Molecular Imaging Biomarkers
Biologic Factors Affecting Tumor Behavior

Surface Receptors
SSR, HER2

Nuclear Receptors
FES, FDHT, FFNP

Angiogenesis
Water, RGD

Proliferative Rate
Thymidine & Analogs, Sigma-2

Cancer Metabolism
FDG, Glutamine

Hypoxia
FMISO, EF-5

DNA Repair
PARP (FTT)

Drug Transport
MIBI, Verapamil

Molecular Imaging to Guide Therapy:
Outline

- Clinical/biological questions and methods to address them
- Molecular imaging and targeted cancer therapy
  - Measuring the target
    - Assessing target engagement
    - Early response assessment
    - Predicting therapeutic outcomes
  - Future Directions
Targeted Breast Cancer Therapy: The Estrogen Receptor (ER) and Endocrine Treatment

Endocrine Therapy Response Rate:

<table>
<thead>
<tr>
<th>ER</th>
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<tbody>
<tr>
<td>-</td>
<td>&lt; 5%</td>
</tr>
<tr>
<td>+</td>
<td>50% - 75%</td>
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(Mintun, Radiology 169:45, 1988)

ER Concentration (fmoles/mg protein)

Tumor Uptake (%ID/mL x 10^-4)


18F-Fluoroestradiol (FES): PET Estrogen Receptor (ER) Imaging Provides a Quantitative Estimate of ER Expression

Kieswetter, J Nucl Med, 1984

Peterson, Mol Imag Biol 16:431, 2014

18F-Fluoroestradiol (FES) PET Images ER Expression in Breast Cancer

Patient A
Biopsy = ER+

Patient B
Biopsy = ER-

Patient A
Patient B
Is the Target Present?
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

Excellent response after 6 wks Letrozole
No response to several different hormonal Rx’s

University of Washington
(Linden, J Clin Onc, 24:2793, 2006)

ECOG-ACRIN Biomarker Trial of FES PET: EAI142
Dehdashti & Linden

MBC from ER+ Primary

Endocrine Therapy

Validation Aim
Response PFS 3, 6 month assessment

Primary Aim

- First line therapy
- Stand-alone imaging trial:
  – Clinical indication for endocrine therapy
  – Standard Rx allowed (AI, FUL, TAM)

FES PET

Heterogeneity of Target Expression
FES PET Imaging of ER Expression

Circulating Tumor Cells (CTCs) & ER Assay
Erica Carpenter, U Penn
Imaging Other Steroid Receptors

Progesterone Receptor: ¹⁸F-FFNP PET/CT
Breast Cancer Primary and Nodal Sites

Androgen Receptor: ¹⁸F-FDHT PET/CT
Metastatic Prostate Cancer

HER2 and HER2/HER3 Expression

HER2:
⁹⁹Zr-Trastuzumab

HER2/HER3:
⁹⁹Zr-pertuzumab

Fluorthanatrace ([¹⁸F]FTT): PARP-1 in Ovarian Cancer

(Makvandi...Lin, J Clin Invest, 128:1727, 2018)
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Serial FES PET Measures Endocrine Therapy Impact on Tumor Estrogen Binding
Incomplete ER Blockade by Fulvestrant Compared to Tamoxifen
(Linden, Clinical Cancer Res, 17:4799, 2011)

FES Applied to Dose Determination for New ER-Targeted Agent: GDC-810 (SERD)
Wang, Clinical Cancer Res 23:3053, 2017

[^F]FT: PARP1 Occupancy Study in Ovarian Cancer
Study PI: F Simpkins
Imaging PgR as a Marker of ER Activation

Pre-Estradiol FFNP-PET/CT

\[ \text{SUV}_{\text{max}}: 3.0 \]

Post-Estradiol FFNP-PET/CT

\[ \text{SUV}_{\text{max}}: 8.6 \]

(Farrokh Dehdashti, Washington University)

Adaptive Radiotherapy Targeting: RTOG 1106/ACRIN 6697
Sprang Kong, Dan Pryma

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Early Changes in FDG Uptake in Response to HER2-Targeted Therapy Predict Response

Metabolic Responder: Achieved pCR

Metabolic Non-Responder: No pCR


TBCRC 008, Connolly, J Nucl Med 56:201, 2015

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

Thymidine Incorporation Pathways
Imaging Tumor Proliferation

(Moskoff and Eary, Clin Cancer Res 14: 7139, 2008)
ACRIN 6688: FLT PET Measures Breast Cancer Response 1 Week After Chemotherapy

Best ΔSUVmax cut-off for predicting pCR = -51% (sensitivity 56%; specificity 79%).

(Kastaloglu, J Nucl Med, 2015)

FDG and Thymidine PET Response to NSCLC Chemoradiation

FLT PET Monitors Response of NSCLC to Chemoradiotherapy
Everitt, IJROBP 75: 1098, 2009
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Breast Cancer Bone Metastases
Response to Therapy? ???!!

Pre-Rx  Post-Rx

Bone Metastasis Response Monitoring
FDG PET: Response? - Yes!

Pre-Rx  Post-Rx
Prospective Trial of FDG PET to Predict Outcomes in Bone-Dominant Breast Cancer, PERCIST Criteria
(Peterson...Specht, J Nucl Med, epub, 2018)

FDG PET/CT Measures Bone Metastasis Response to Endocrine Therapy at 4 wks
Korhonen...Clark, RSNA, 2017

Pre-Rx 4 wks Rx

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Molecular Imaging and Targeted Therapy: Summary

- Molecular imaging, beyond staging, is a powerful tool for directing cancer therapy
- Molecular imaging can:
  - Measure target expression
  - Measure drug delivery and target engagement
  - Measure response, early
  - Predict outcome
- Success requires a framework for clinical trials to test and validate these tools
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- Farrokh Dehdashti, Amy Fowler, Geraldine Gebhart, Lale Kostakoglu, Ken Krohn, Lillie Lin, Hannah Linden, Robert Nordstrom, Lanell Peterson, Joseph Rajendran, Jennifer Specht, Gary Ulaner