Molecular Imaging and Targeted Cancer Therapy

Novel Molecular Imaging Techniques to Personalize Cancer Treatment

AAPM Annual Meeting, August, 2018

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Amy Clark, Farrokh Dehdashti, Amy Fowler, Geraldine Gebhardt, Ken Krohn, Lillie Lin, Hannah Linden, Bob Mach, Mehran Makvandi, Bob Nordstrom, Austin Pantel, Lanell Peterson Dan Pryma, Joseph Rajendran, Mitch Schnall, Fiona Simpkins, Jennifer Specht, Gary Ulaner

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Disclosures

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  - Reflexion
  - Blue Earth Diagnostics
  - Zionexa
- Research Funding
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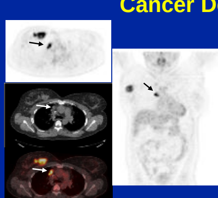
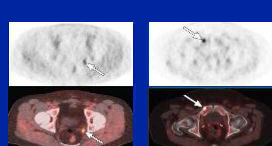
Current Clinical Use of Molecular Imaging: Cancer Detection and Staging



[18F]FDG PET/CT Breast Cancer Staging
(Eubank, J Clin Oncol 19:3516, 2001)



[18F]Flucciclovine PET/CT Prostate Cancer Re-Staging
(Schuster, Radiology 259: 852, 2011)

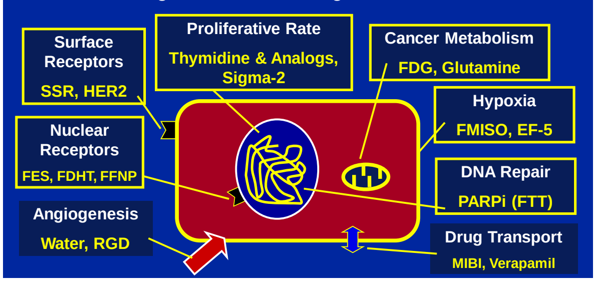
Beyond Detection:

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



Molecular Imaging to Guide Therapy: Outline

- Clinical/biological questions and methods to address them
- Molecular imaging and targeted cancer therapy
  - Measuring the target
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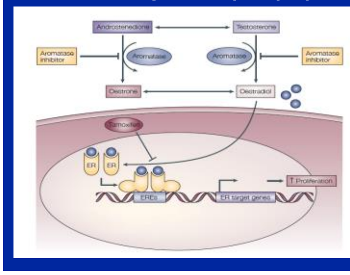
  - Predicting therapeutic outcomes
- Future Directions

Targeted Breast Cancer Therapy:
The Estrogen Receptor (ER) and Endocrine Treatment

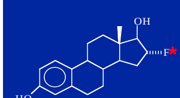


Endocrine Therapy Response Rate:

ER -	< 5%
ER +	50% - 75%

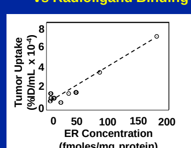
(Johnson and Dowsett, Nar Rev Cancer 3:821, 2002)

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



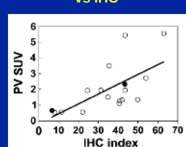
(Kieswetter, J Nucl Med, 1984)

vs Radioligand Binding



(Mintun, Radiology 169:45, 1988)

vs IHC



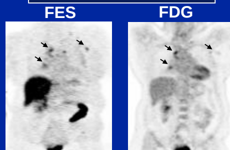
(Peterson, J Nucl Med 49: 367, 2008)

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

Peterson, Mol Imag Biol 16:431, 2014

Patient A
Biopsy = ER+

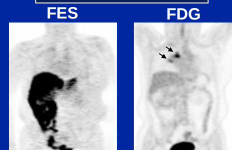
FES FDG



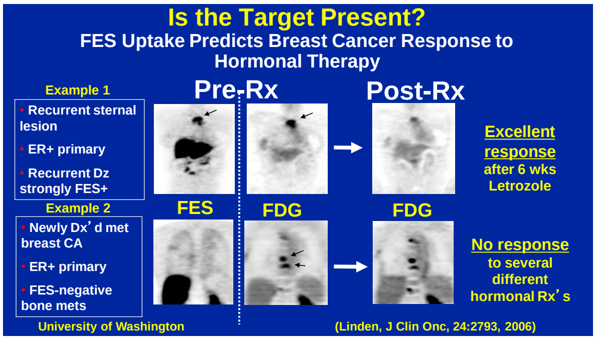
Estradiol Binding Glucose Metabolism

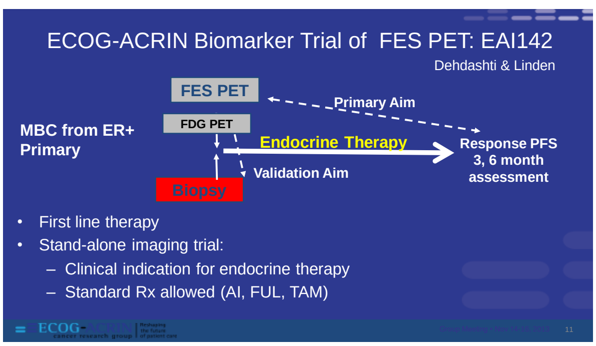
Patient B
Biopsy = ER-

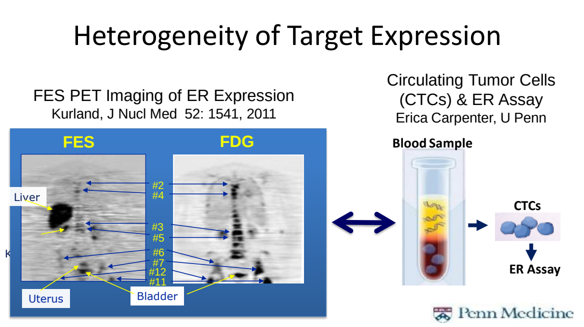
FES FDG



Estradiol Binding Glucose Metabolism

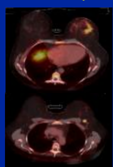

Is the Target Present?
FES Uptake Predicts Breast Cancer Response to Hormonal Therapy
Example 1
Recurrent sternal lesion
ER+ primary
Recurrent Dz strongly FES+
Pre-Rx
Post-Rx
FES
FDG
FDG
Excellent response
after 6 wks Letrozole
Example 2
Newly Dx'd met breast CA
ER+ primary
FES-negative bone mets
No 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
FES PET
Primary Aim
MBC from ER+ Primary
FDG PET
Endocrine Therapy
Response PFS
3, 6 month assessment
Validation Aim
Biopsy
First line therapy
Stand-alone imaging trial:
Clinical indication for endocrine therapy
Standard Rx allowed (AI, FUL, TAM)
ECOG


Heterogeneity of Target Expression
FES PET Imaging of ER Expression
Kurland, J Nucl Med 52: 1541, 2011
Circulating Tumor Cells (CTCs) & ER Assay
Erica Carpenter, U Penn
FES
FDG
Liver
#2
#4
#3
#5
#6
#7
#12
#11
Uterus
Bladder
Blood Sample
CTCs
ER Assay
Penn Medicine

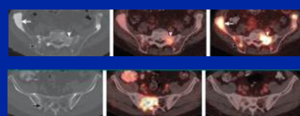
Imaging Other Steroid Receptors

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



Fowler, Strigel
(University of Wisconsin-Madison)

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



Vargas, Radiology 271:220, 2014 (MSKCC)

HER2 and HER2/HER3 Expression

HER2:
^{89}Zr-Trastuzumab

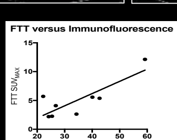
(Ulaner et al, J Nucl Med 2016 Oct 57(10):1523-15128)

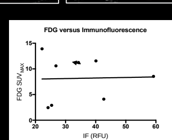
HER2/HER3:
^{89}Zr-pertuzumab

(Ulaner, J Nucl Med, e-pub)

Memorial Sloan Kettering Cancer Center

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





(Makvandi...Lin, J Clin Invest, 128:1727, 2018)

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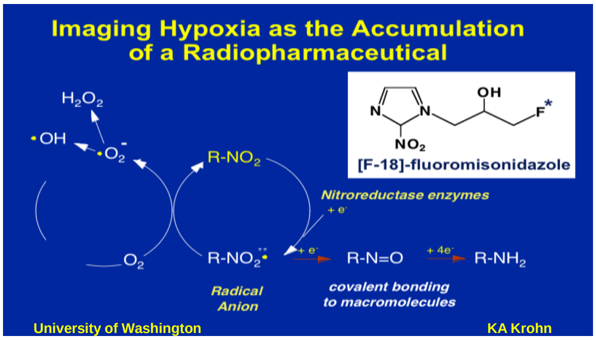

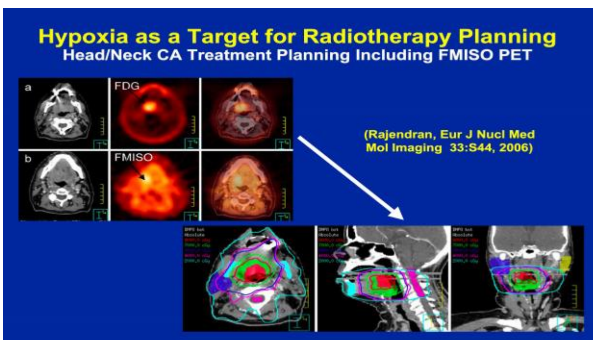

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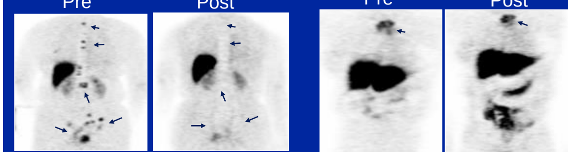
Serial FES PET Measures Endocrine Therapy Impact on Tumor Estrogen Binding

Incomplete ER Blockade by Fulvestrant Compared to Tamoxifen

(Linden, Clinical Cancer Res, 17:4799, 2011)

Tamoxifen — Pre / Post

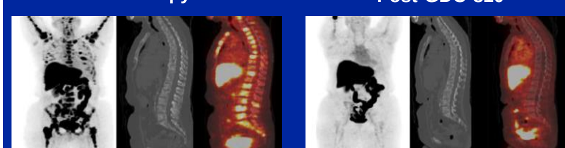
Fulvestrant — Pre / Post



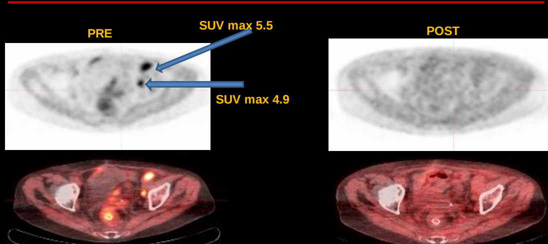
FES Applied to Dose Determination for New ER-Targeted Agent: GDC-810 (SERD)

Wang, Clinical Cancer Res 23:3053, 2017

Pre-therapy — **Post-GDC-810**



[18F]FTT: PARPi Occupancy Study in Ovarian Cancer



Study PI: F Simpkins

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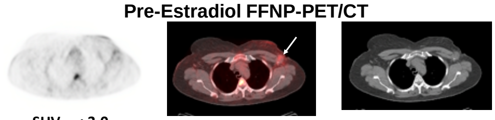
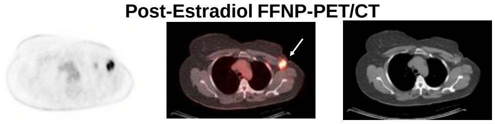
Imaging PgR as a Marker of ER Activation

Pre-Estradiol FFNP-PET/CT



SUV_{max}: 3.0

Post-Estradiol FFNP-PET/CT

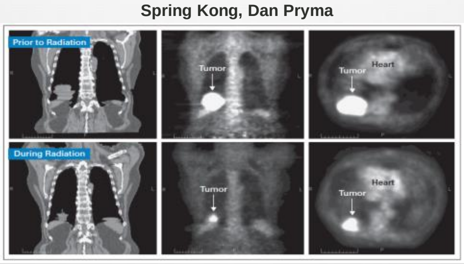


SUV_{max}: 8.6

(Farrokh Dehdashti, Washington University)

Adaptive Radiotherapy Targeting: RTOG 1106/ACRIN 6697

Spring Kong, Dan Pryma



Kong et al. JCO 2007

Penn
University of Pennsylvania

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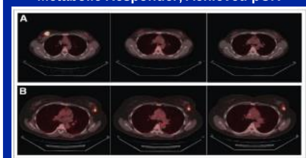
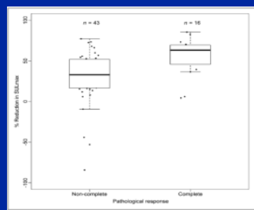
Early Changes in FDG Uptake in Response to HER2-Targeted Therapy Predict Response

Metabolic Responder; Achieved pCR



Metabolic Non-Responder; No pCR

NeoAlTTO Study, Gebhart, J Nucl Med 54:1862, 2013



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 →

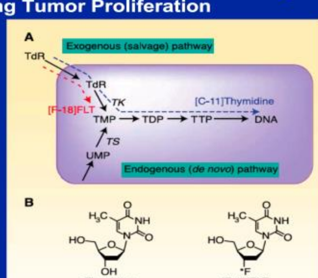
↓ Cellular Proliferation or ↑ Cell Death ← ↓ DNA Synthesis

→ ↓ Viable Cell Number

→ ↓ Tumor size

Thymidine Incorporation Pathways

Imaging Tumor Proliferation

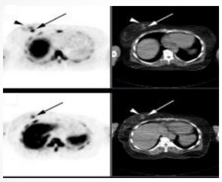


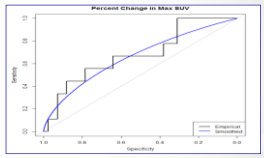
(Mankoff and Eary, Clin Cancer Res 14: 7159, 2008)

ACRIN 6688: FLT PET Measures Breast Cancer Response 1 Week After Chemotherapy

Pre-Therapy

7 d Post



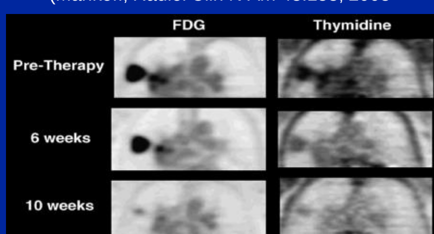


Best ΔSUV_{max} cut-off for predicting pCR = -51% (sensitivity 56%;specificity 79%).

(Kostakoglu, J Nucl Med, 2015)

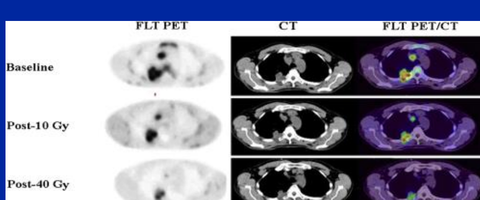
FDG and Thymidine PET Response to NSCLC Chemoradiation

(Mankoff, Radiol Clin N Am 43:153, 2005



FLT PET Monitors Response of NSCLC to Chemoradiotherapy

Everitt, IJROBP 75: 1098, 2009



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Breast Cancer Bone Metastases

Response to Therapy? ???!!

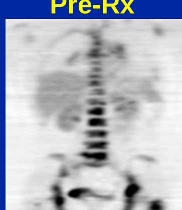
Pre-Rx

Post-Rx

Bone Metastasis Response Monitoring

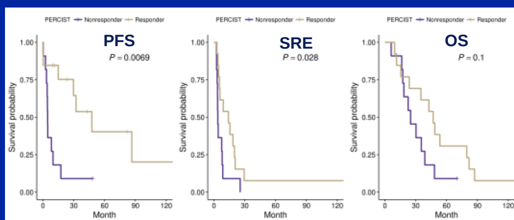
FDG PET: Response? - Yes!

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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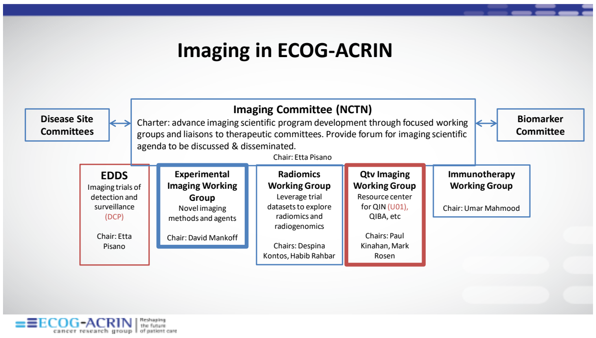
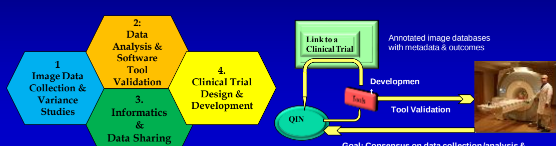


NCI Quantitative Imaging Network (QIN)

- Develop quantitative imaging (QI) methods that are automated, platform independent and reproducible to use in therapy trials
- Share, test, refine, validate, and finally evaluate these methods in therapy trials using four working groups organized across all sites



(courtesy of Bob Nordstrom, NCI)

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

Acknowledgements

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  - P01CA42045, CA12457, S10 RR17229, U01CA148131, U01CA190254, P50CA138293, Komen SAC140060, DOE DE-DE-SE0012476, Penn Basser Center
- Organizations
  - ACRIN/ECOG-ACRIN, NCI CIP, NCI QIN
- University of Pennsylvania
  - Amy Clark, Joel Karp, Katrina Korhonen, Bob Mach, Mehran Makvandi, Elizabeth McDonald, Austin Pantel, Dan Pryma, Mitch Schnall, Fiona Simpkins
- Others
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