

# **PET Biomarkers: Beyond FDG**

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CA90771, S10 RR17229**

# Cautions

- **Many of the imaging methods presented are considered investigational**
- **Discussion of results and possible applications is not a claim of clinical efficacy**

# Imaging to Direct Cancer Therapy: Outline

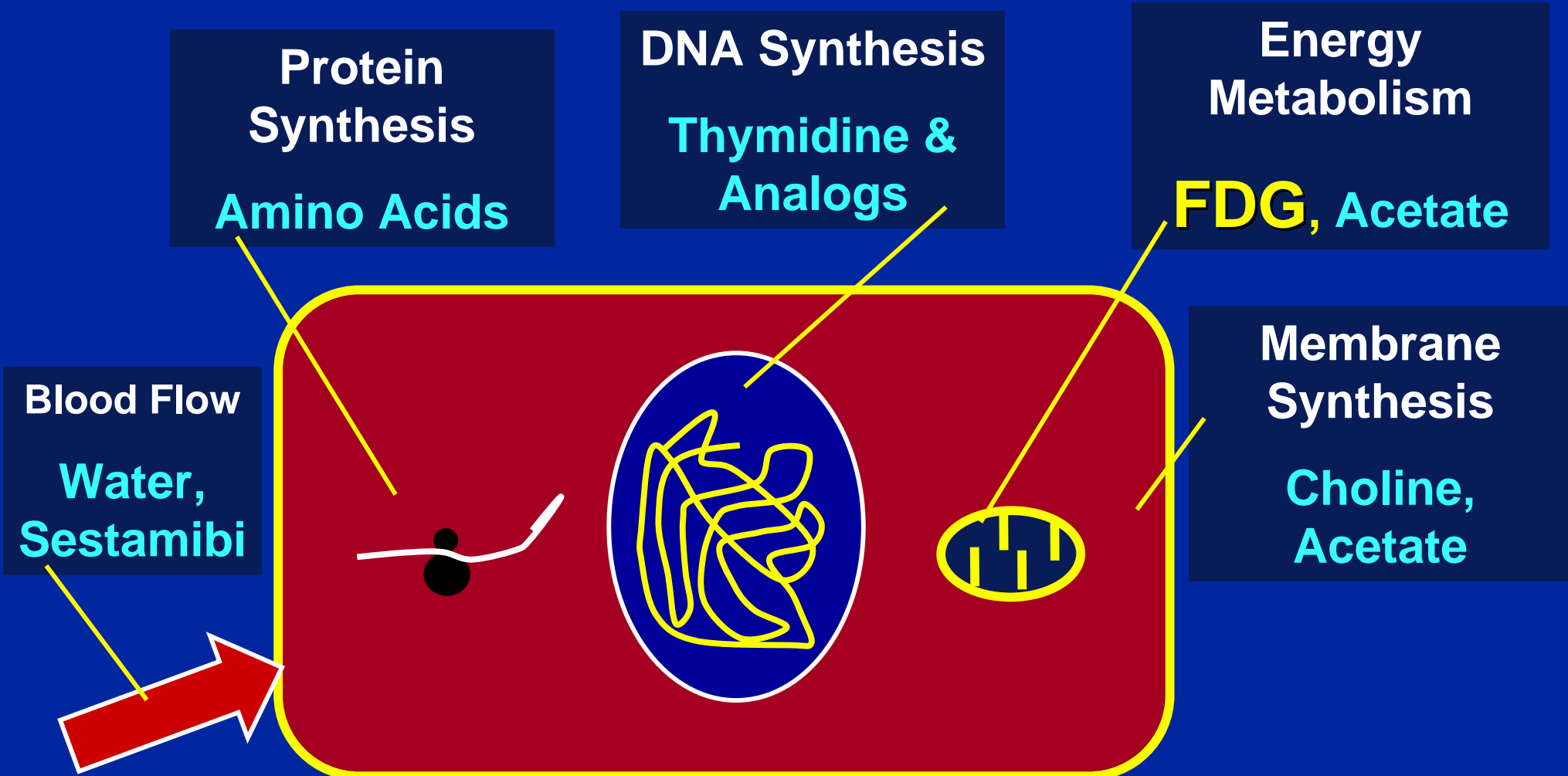
- **Clinical questions and biologic targets**
- **Examples of applications to cancer care**
  - **Assess the therapeutic targets**
  - **Identify resistance factors**
  - **Measure early response to treatment**
  - **Relate treatment response to patient outcome**

# Existing Paradigm for Cancer Imaging: Find the Cancer

- **Established role:**
  - Detect cancer
  - Find how far cancer has spread

# Existing Cancer Imaging Paradigm:

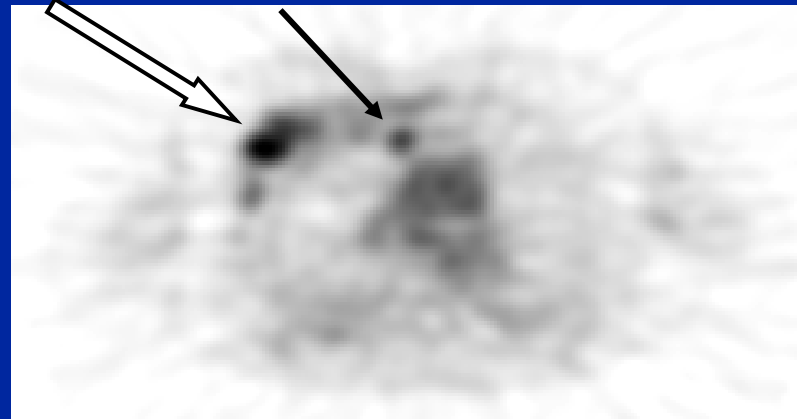
## Targets for Detecting Tumor Cells Higher in Tumor than Normal Tissue



# Internal Mammary Nodal Uptake on FDG PET: Locally Advanced Breast Cancer Pre-Therapy

**Breast Tumor**

**IM Node**



**Emission**



**Transmission**

# **A New Paradigm for Cancer Imaging:** **Help Direct Cancer Treatment**

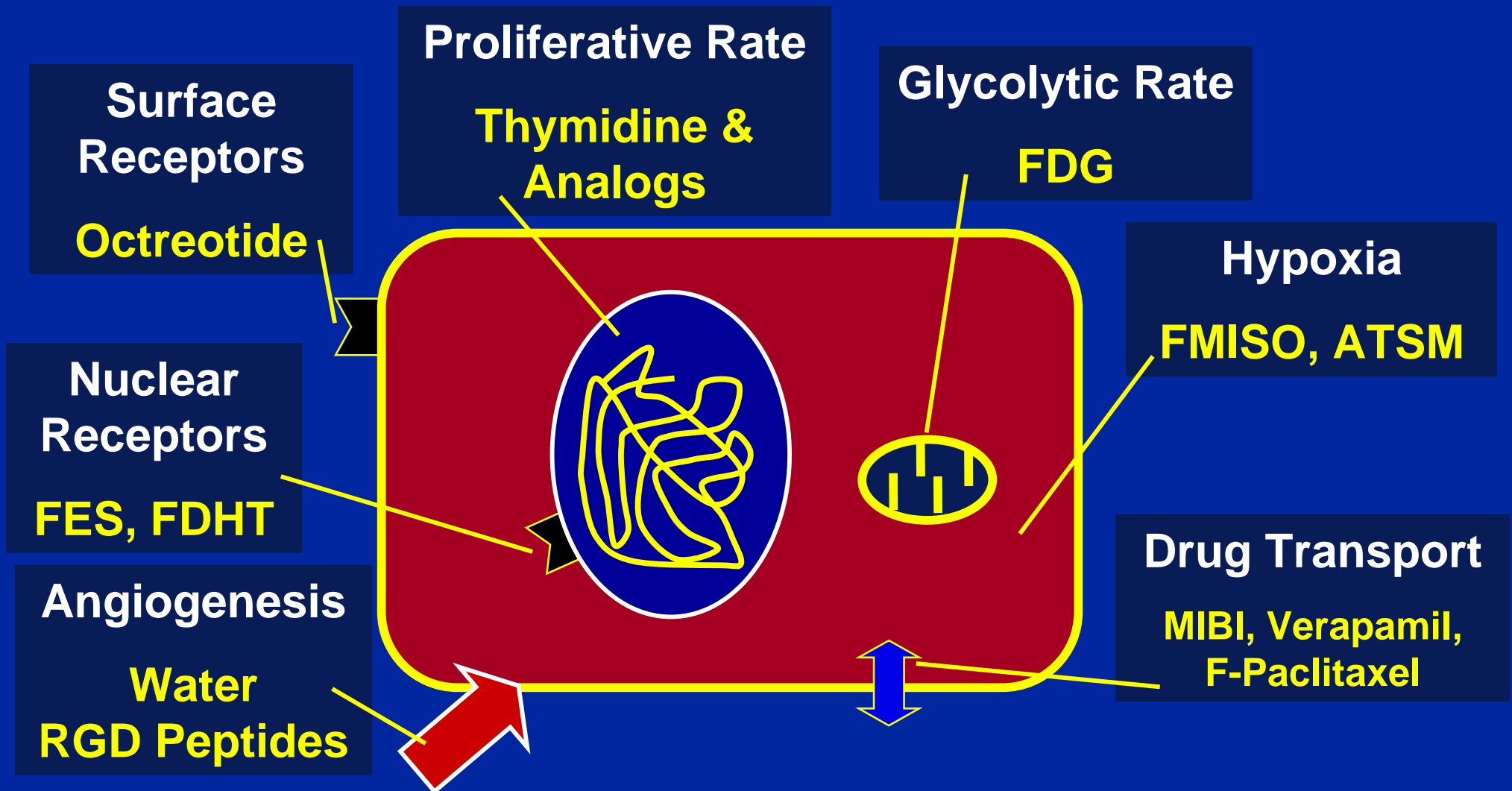
- **New role for imaging:**
  - **Guide cancer treatment selection**
  - **Evaluate early treatment response**

# Imaging and Targeted Therapy

## Help Match Therapy to Tumor Biology

- **Goals in cancer treatment**
  - Characterize tumor biology pre-Rx
  - Individualized, specific therapy
  - Static response may be acceptable
- **The implied needs for cancer imaging**
  - Characterize in vivo tumor biology
  - Identify targets, predict response
  - Measure tumor response (early!)
  - Pick treatments most likely to prolong survival

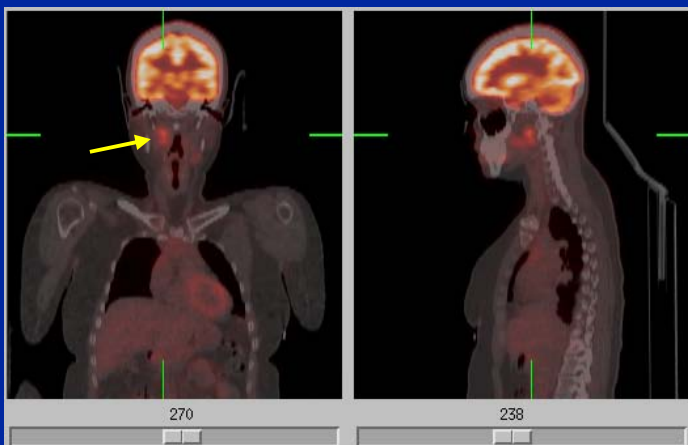
# Emerging Cancer Imaging Paradigm: Measure Factors Affecting Response Variable Levels in Tumor



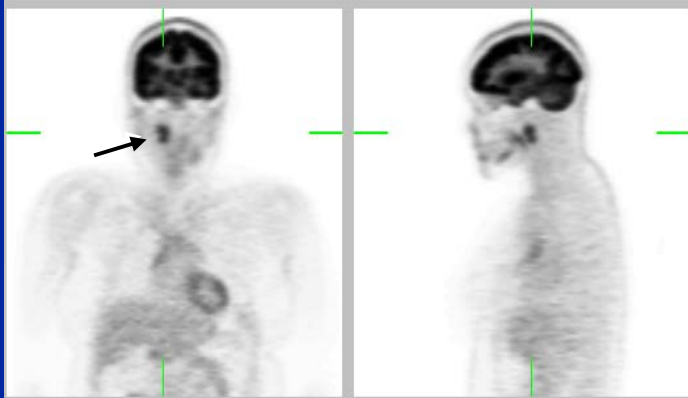
# Imaging Requirement for Biomarker Imaging: Simultaneously Localize and Characterize Disease Sites

## Functional/Anatomic Imaging

PET/CT  
Fusion

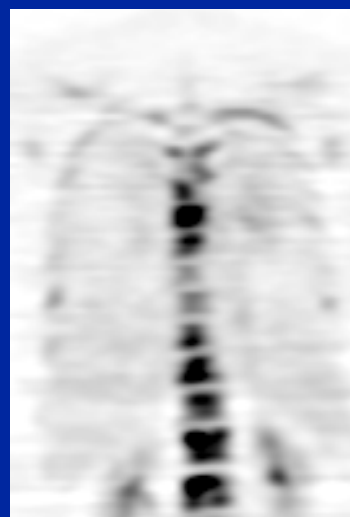


FDG  
PET



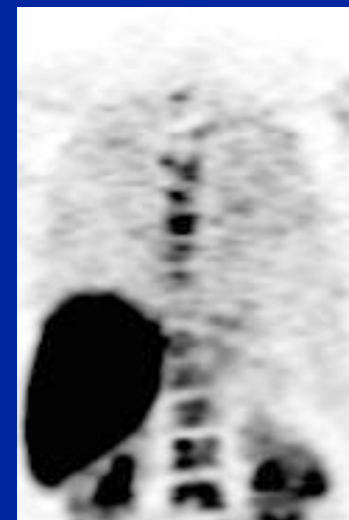
## Functional Imaging Combinations

FDG



Glucose  
Metabolism

FES

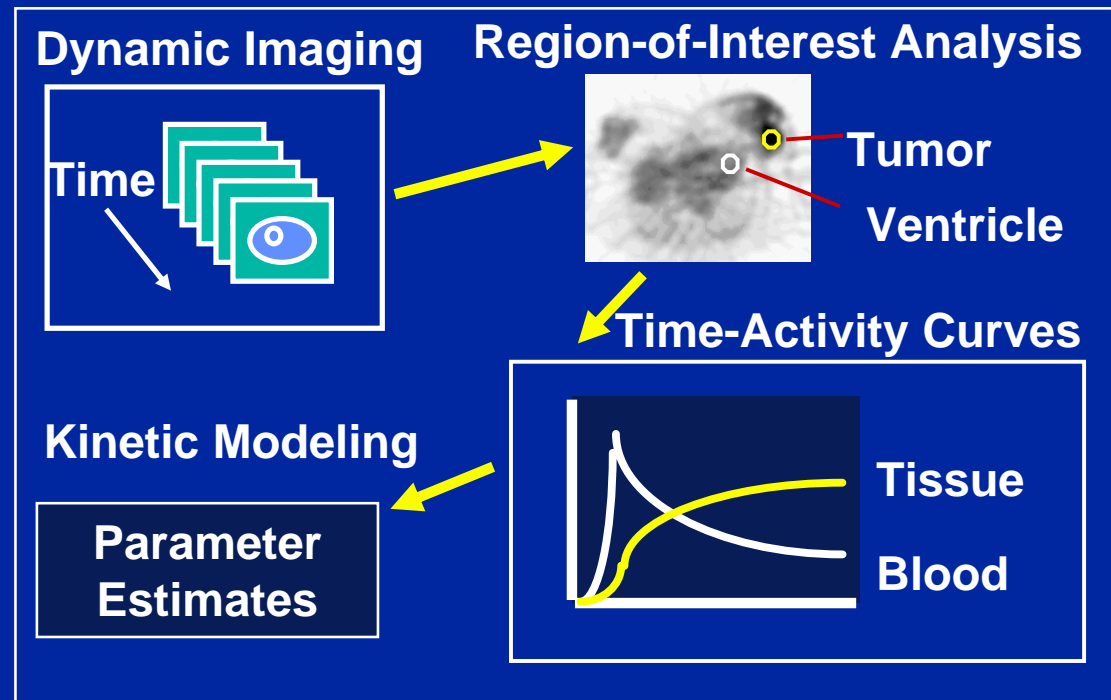


Estradiol  
Binding

# Imaging Requirement for Biomarker Imaging: Image Acquisition and Quantitative Analysis

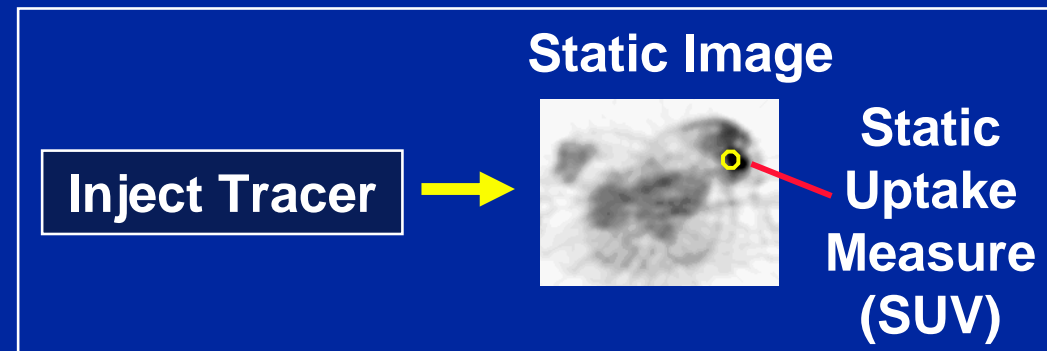
- **Dynamic protocols**

- Allows kinetic modeling
- Full range of analysis options
- But ... not for everyone



- **Static protocols**

- Clinically feasible, robust
- But ... only simple quantification possible



# Imaging and Clinical Trials

**Choices for Imaging Approaches**

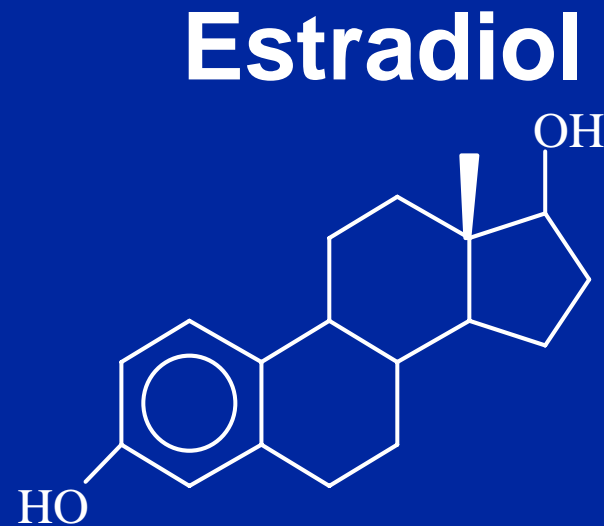
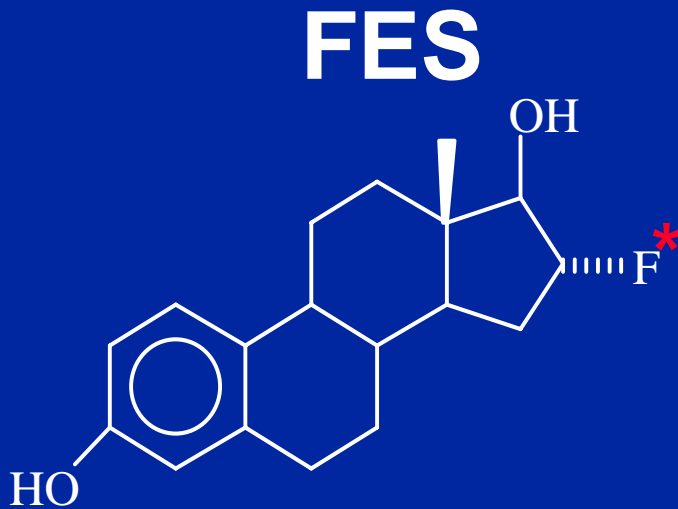
# Specific Examples of PET Imaging to Direct Cancer Therapy

- **Assess the therapeutic target**
- **Identify resistance factors**
- **Measure early response**
- **Relate response to outcome**

# Identifying Therapeutic Targets using Imaging: Why?

- Imaging can measure the level of expression
  - Heterogeneity - spatial and temporal
  - Especially for advanced disease
- Imaging can measure the *in vivo* effect of drug therapy on the target. Examples:
  - Target antagonism
  - Change in target expression
- Imaging is quantitative
- **Complementary to *in vitro* assay**

# [F-18]-Fluoroestradiol (FES): PET Estrogen Receptor (ER) Imaging



	<b>RBA</b> (FES vs Estradiol)
<b>ER</b>	<b>0.9</b>
<b>SHBG</b>	<b>0.8</b>

(Kieswetter, J Nucl Med, 1984)

# Validation: ER+ vs ER- Tumors

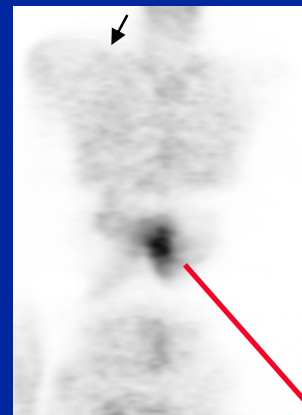
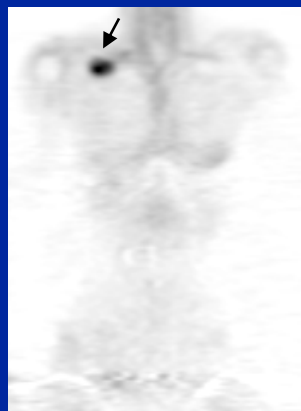
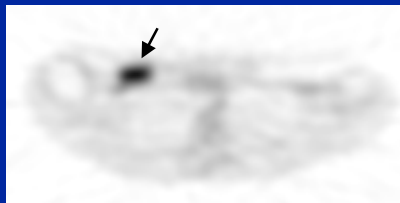
**FDG**

**FES**

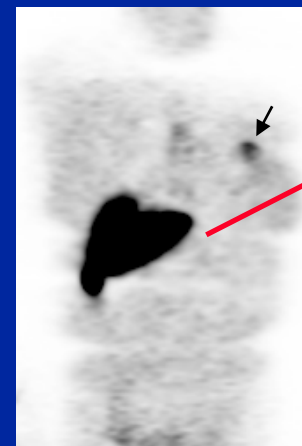
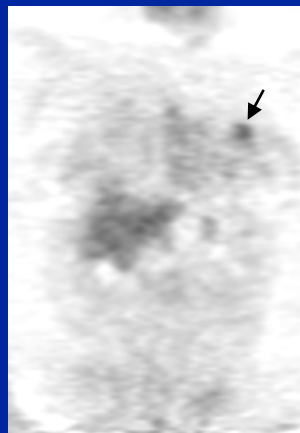
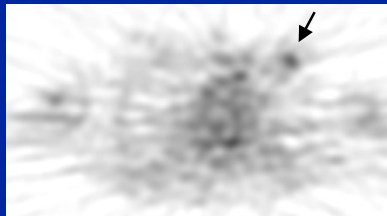
**ER-**

axial

coronal



**ER+**



**Liver**

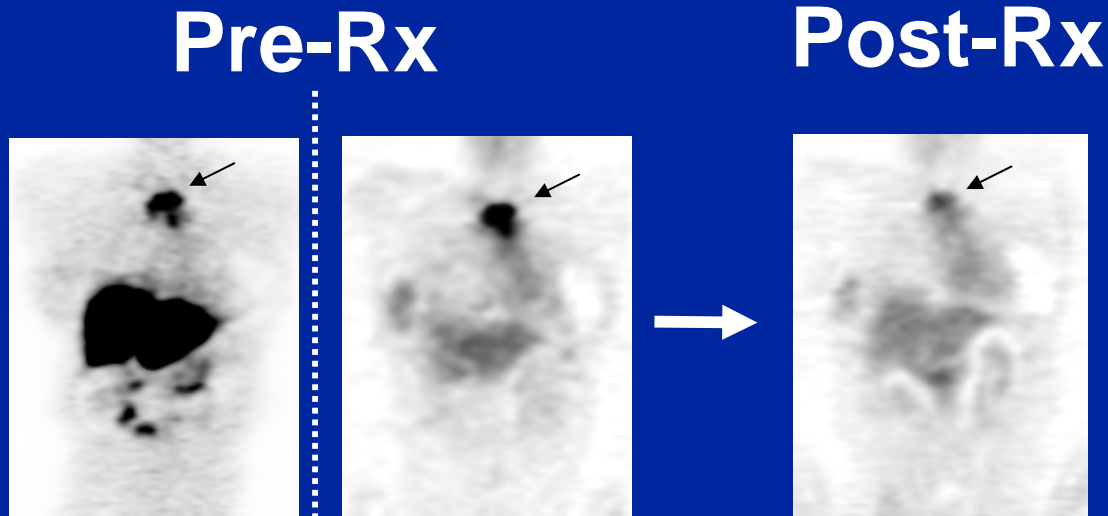
**Glucose Metabolism**

**ER Expression**

# FES Uptake Predicts Breast Cancer Response to Hormonal Therapy

## Example 1

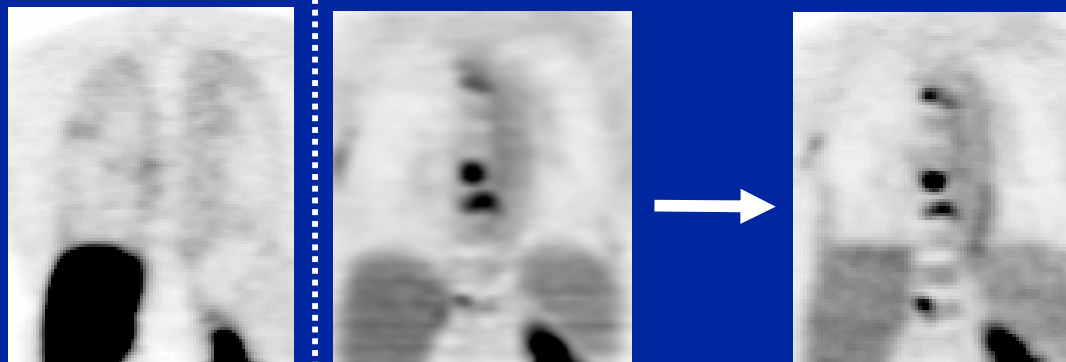
- Recurrent sternal lesion
- ER+ primary
- Recurrent Dz strongly FES+



Excellent response  
after 6 wks  
Letrozole

## Example 2

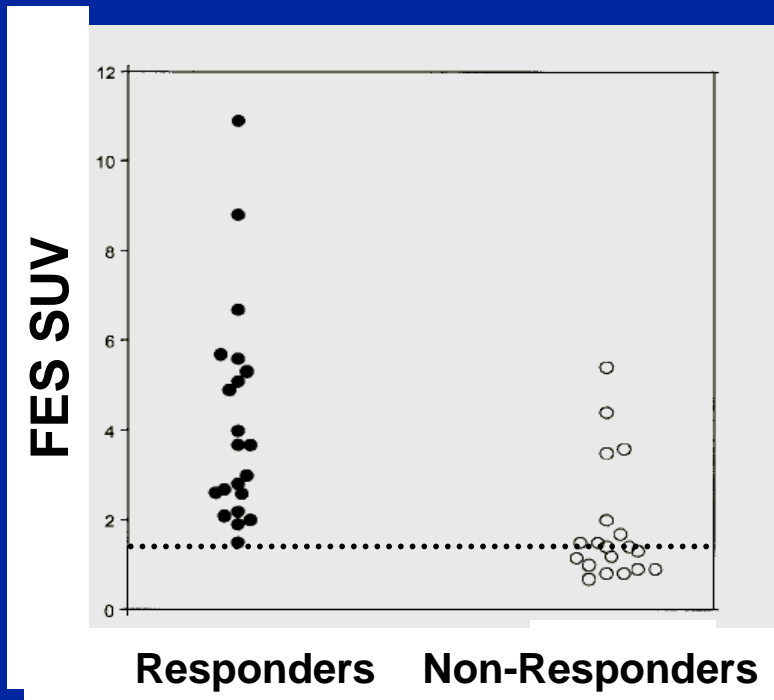
- Newly Dx'd met breast CA
- ER+ primary
- FES-negative bone mets



No response  
to several  
different  
hormonal Rx's

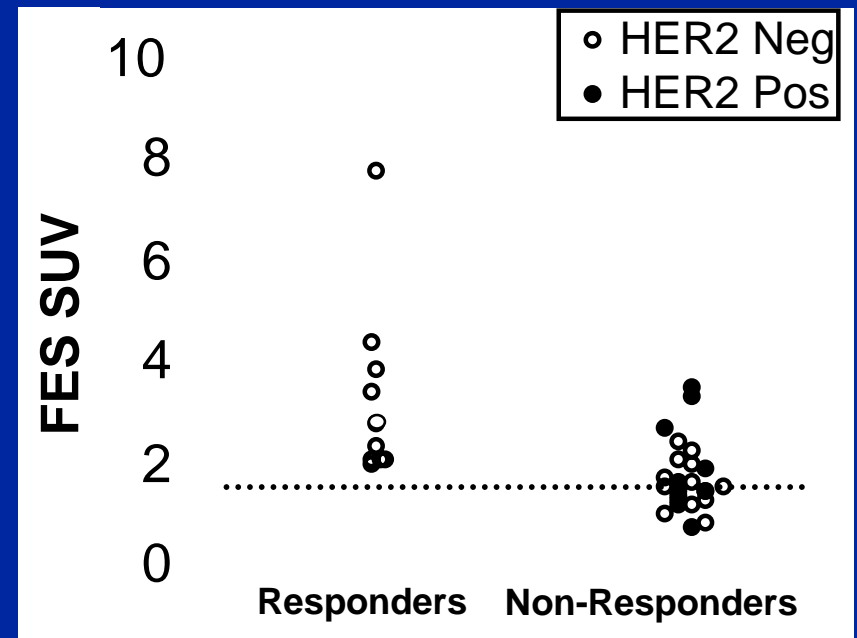
# FES Uptake Predicts Response of Advanced Breast Cancer to Hormonal Therapy

LABC or Metastatic Br CA  
Primary Tamoxifen Rx



(Mortimer, J Clin Onc, 2001)

Recurrent or Metastatic Br CA  
Aromatase Inhibitor Rx

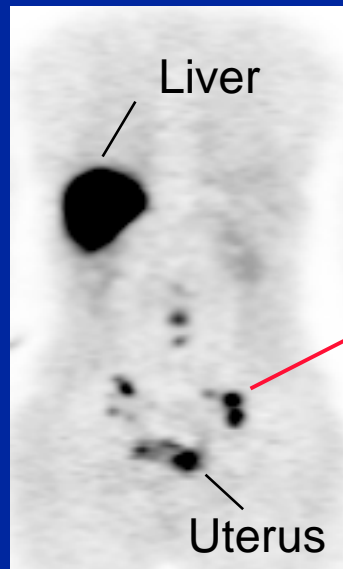


(Linden, J Clin Onc, 2006)

( $P < .01$  for both)

# FES PET Measures Fulvestrant ER Antagonism *In Vivo*

**Pre-Rx**

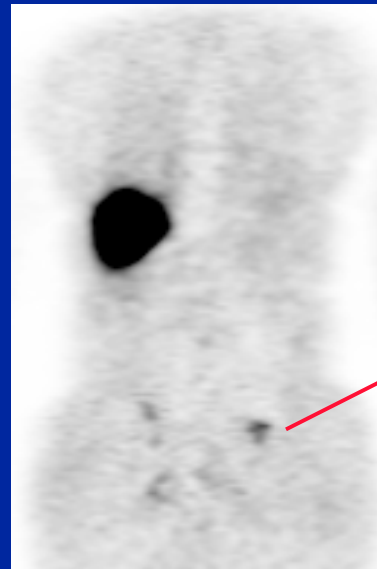


SUV=  
7.4

**Pre-Fulvestrant**

(FES PET,  
Coronal Slices)

**1 month**

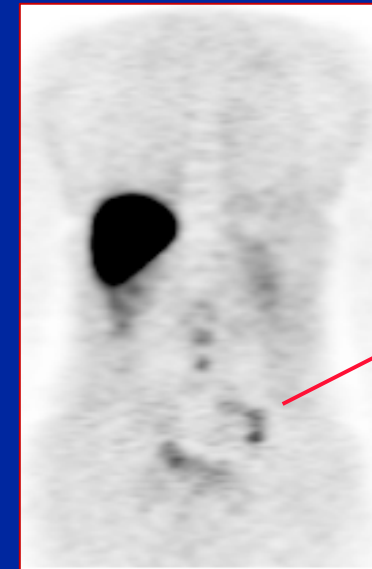


SUV=  
3.1

**Post-Fulvestrant  
250 mg qm**

**(Stable Dz, No  
Response)**

**5 Months**



SUV=  
3.2

**Post-Fulvestrant  
500 mg qm**

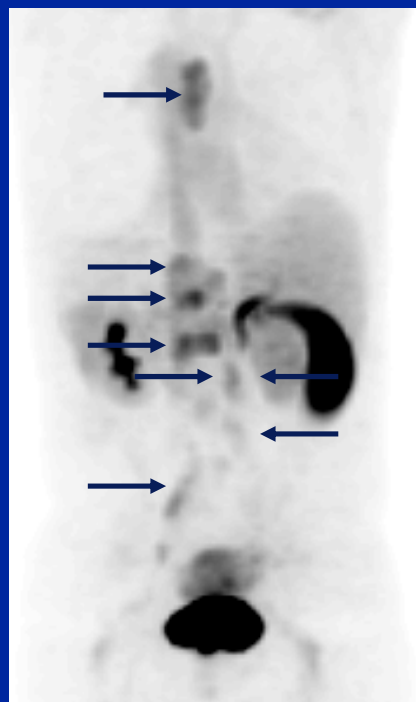
**(Dz Progression)**

# Imaging Androgen Receptor (AR) Blockade

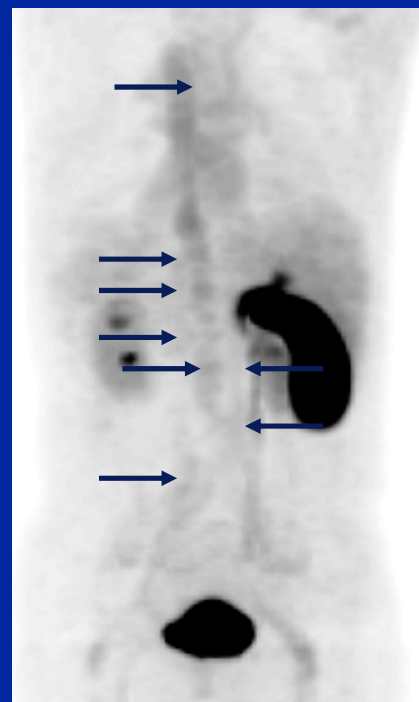
Dehdashti, EJNMMI 32:344, 2005

$^{18}\text{F}$ -fluorodihydrotestosterone (FDHT)

Pre-  
Flutamide



Post-  
Flutamide



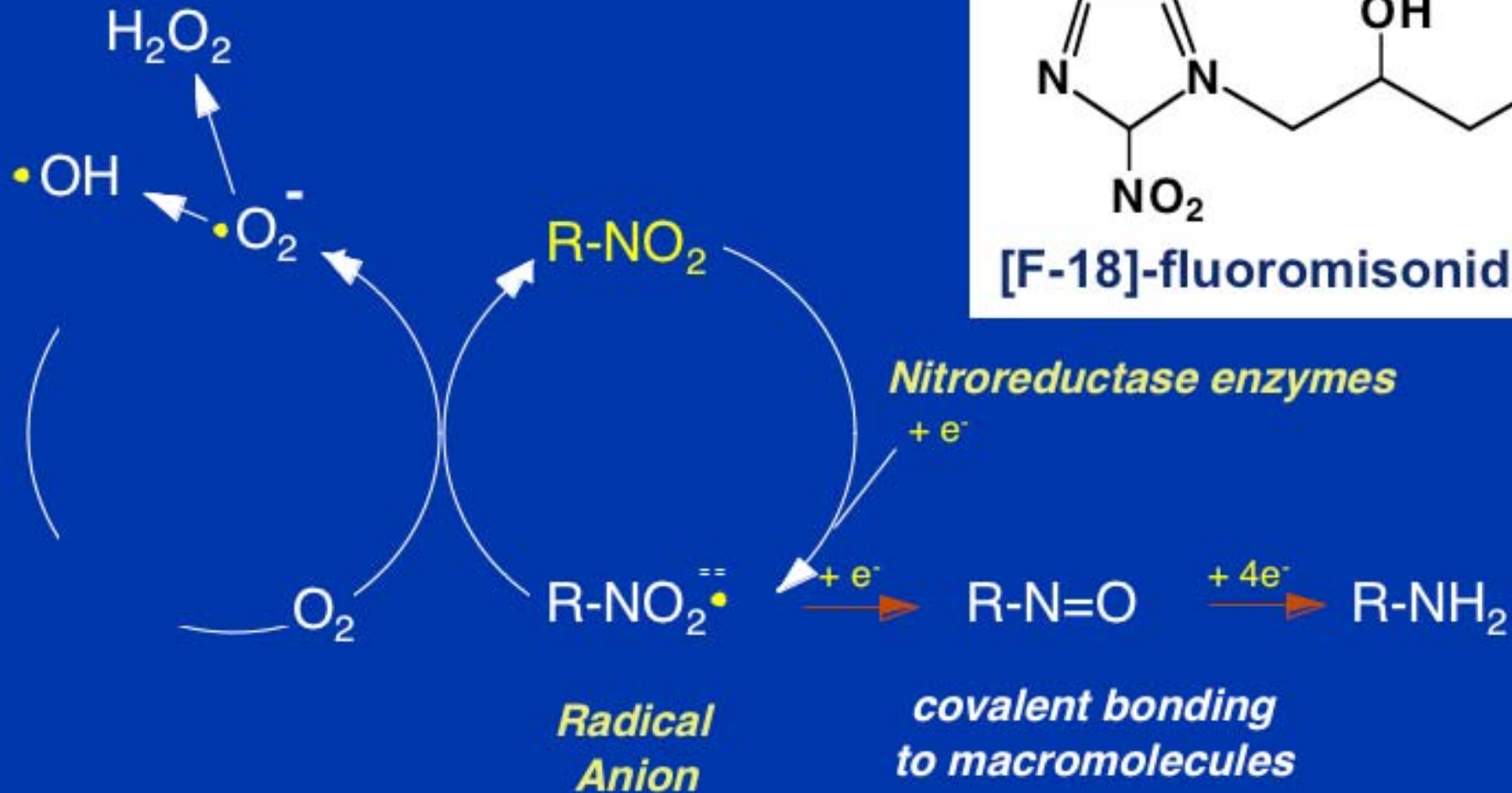
# Specific Examples of PET Imaging to Direct Cancer Therapy

- Assess the therapeutic target
- **Identify resistance factors**
- Measure early response
- Relate response to outcome

# Agents for Identifying Tumor Resistance Factors

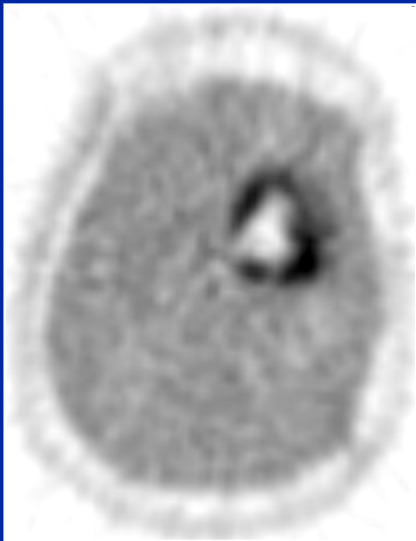
- Hypoxia
  - **$^{18}\text{F}$ FMISO**,  $^{60}\text{Cu}$ -ATSM,  $^{18}\text{F}$ FIAZA,  $^{18}\text{F}$ -EF5
- Drug transport/efflux ( p-gp)
  - **$^{11}\text{C}$ -verapamil**,  $^{11}\text{C}$  -colchicine,  
 $^{11}\text{C}$  - or  $^{18}\text{F}$  -paclitaxel,  $^{94\text{m}}\text{Tc}$  -sestamibi

# Imaging Hypoxia as the Accumulation of a Radiopharmaceutical



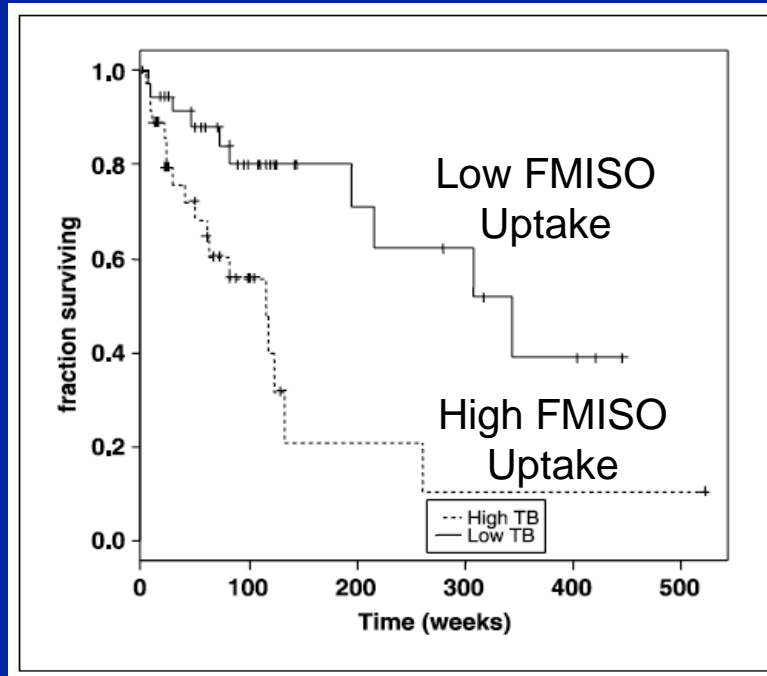
# Tumor Hypoxia Quantified by PET Predicts Survival

FMISO PET  
Brain Tumor



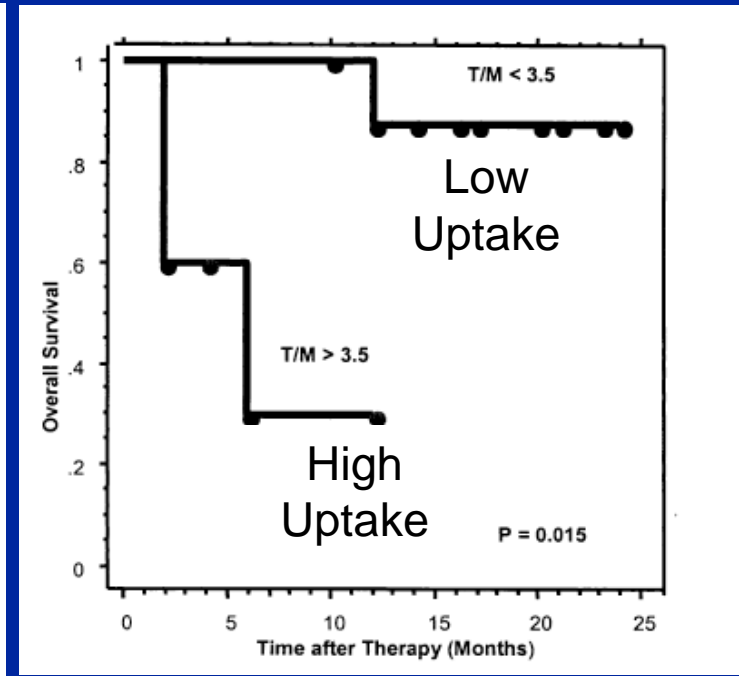
(Spence, UW)

FMISO PET H  
& N Cancer



(Rajendran, Clin Can  
Res, 2007)

Cu-ATSM PET  
Cervical Cancer



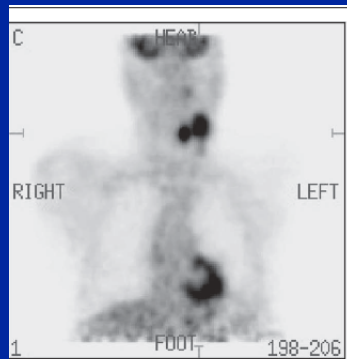
(Dehdashti, Int J Radiat  
Oncol Biol Phys, 2003)

# Imaging to Direct Hypoxia-Specific Treatment

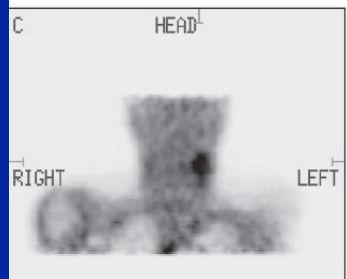
Rischin J Clin Oncol 24:298, 2006

- Advanced H & N Ca
- Randomized to
  - XRT + Cisplatin/5-FU
  - XRT + Cisplatin/Tirapazamine (TPZ)
- FMISO PET (observational only)

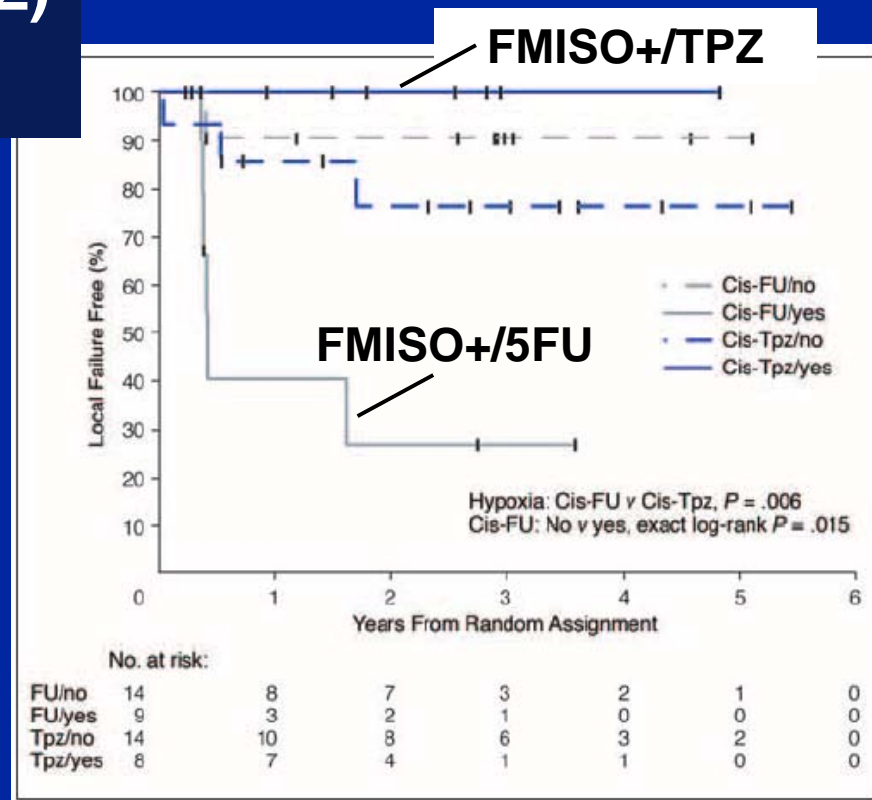
FDG PET



FMISO PET



## Time-to- Locoregional Failure



# Resistance Due to altered Drug Transport:

## PET to Measure P-gp Drug Transport

### Hypotheses:

- P-gp limits drug transport into the brain
- Inhibiting P-gp will increase brain transport

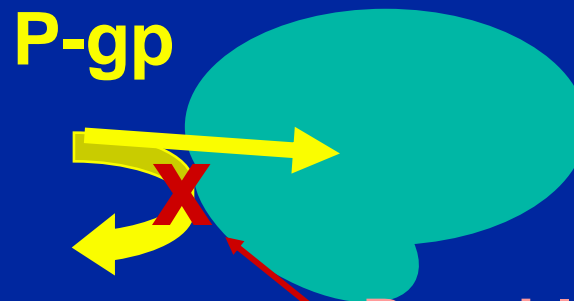
P-gp susceptible drug  
 $^{11}\text{C}$ -Verapamil



Other P-gp RPs:

- Sestamibi
- F-paclitaxel

P-gp susceptible drug  
 $^{11}\text{C}$ -Verapamil



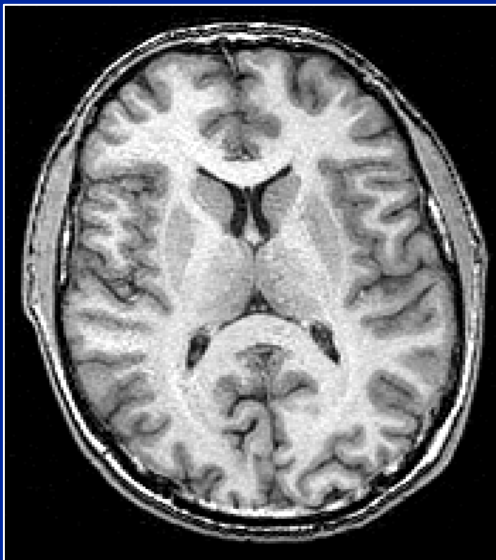
P-gp blockade  
e.g., cyclosporine

(Hendrickse, Br j Pharmacol, 1998)

# Imaging P-gp Activity *in vivo* in Humans

[<sup>11</sup>C]-Verapamil images pre- and post-cyclosporine (CSA)

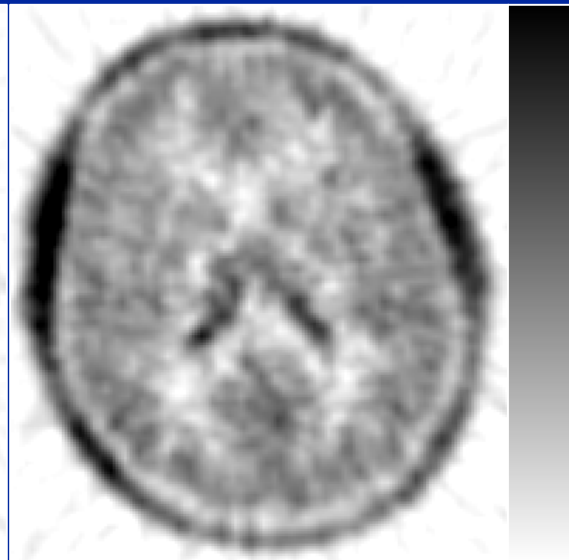
**MRI**



**Pre-CsA**



**Post-CsA**



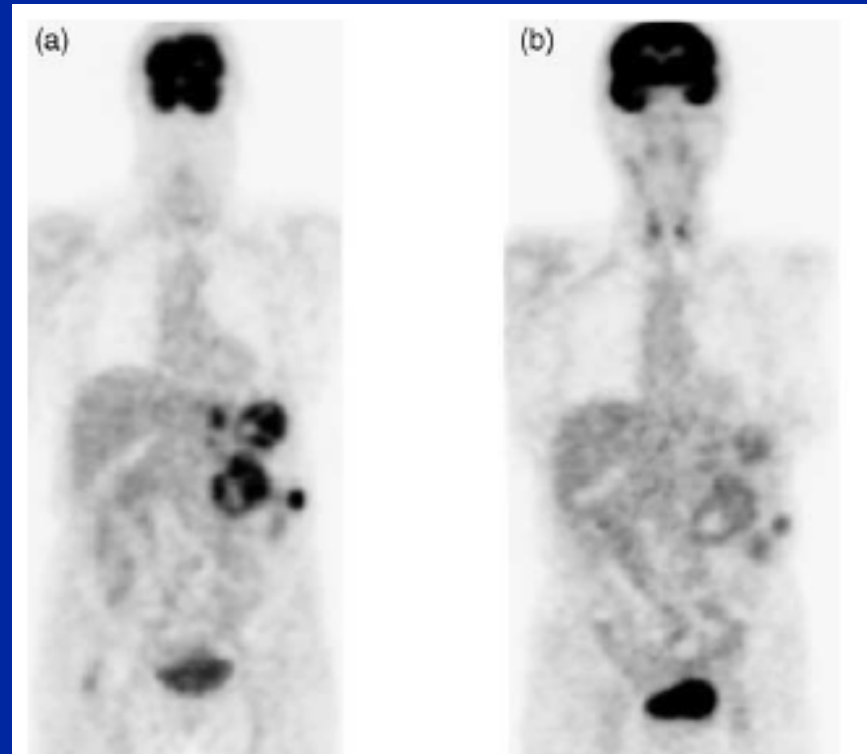
**88% +/- 12% increase in Verap. AUC post- vs pre-CSA  
(N= 12, P < .01)**

(Sosangko, Clin Pharm Ther, 2005)

# Specific Examples of PET Imaging to Direct Cancer Therapy

- Assess the therapeutic target
- Identify resistance factors
- **Measure early response**
- Relate response to outcome

# Response of GIST to Imatinib Measured by FDG PET

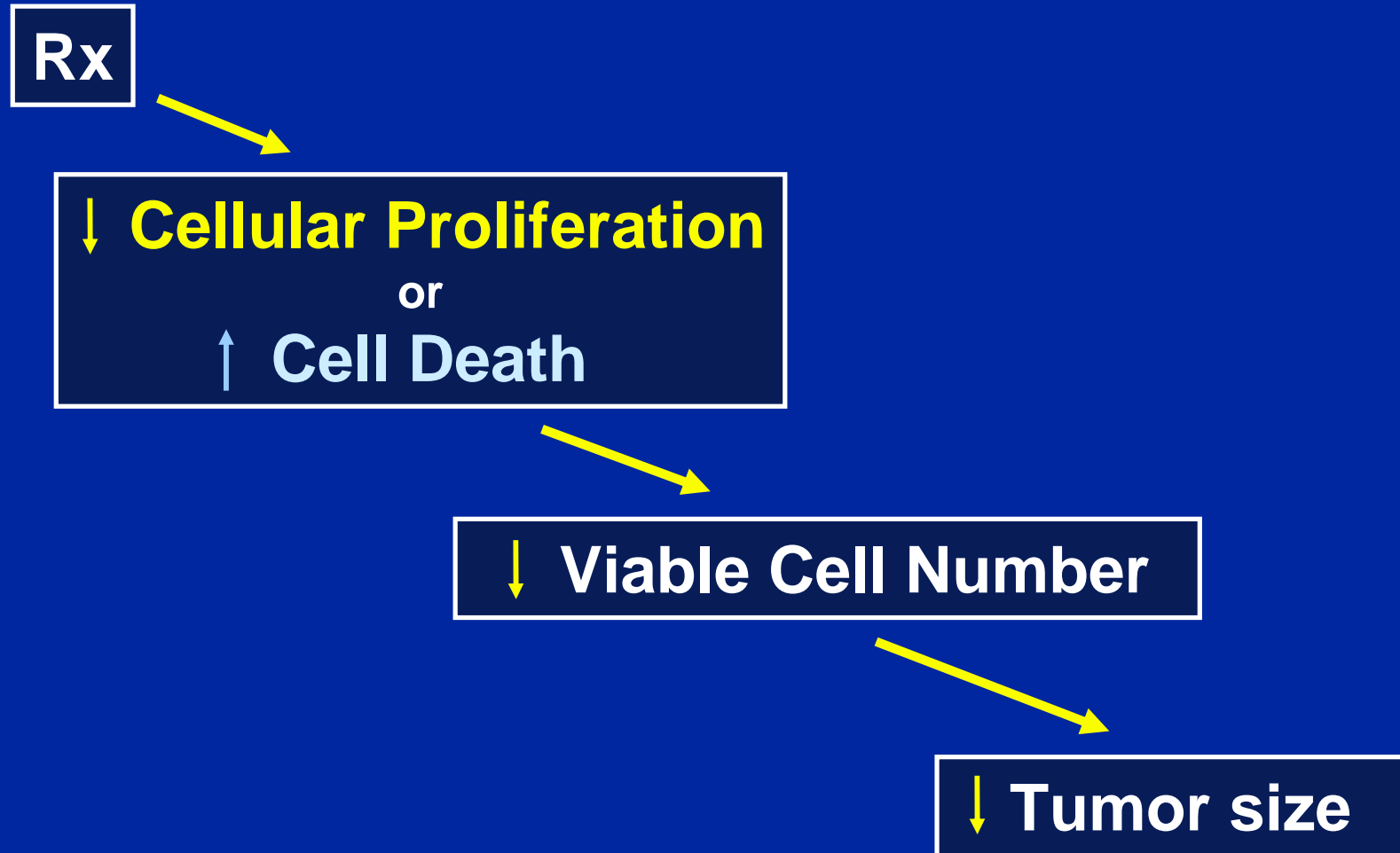


Pre-Rx

48 hrs

(Stroobants, Eur J Cancer 39:2012, 2003)

# Biologic Events in Response to Successful Cancer Therapy

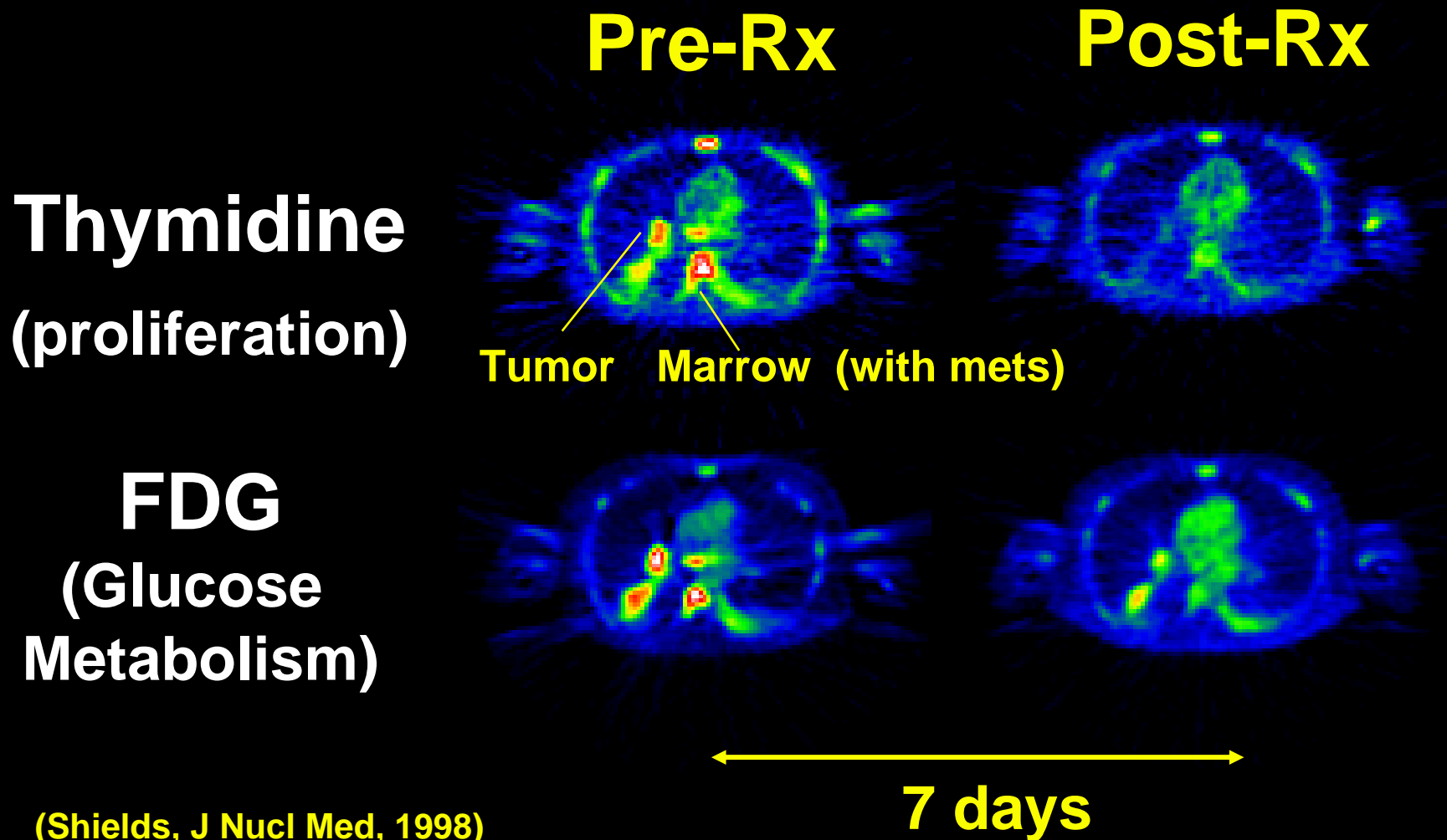


# Cell Proliferation Imaging Agents

- **Gold standard - thymidine**
  - **Methyl or 2-<sup>11</sup>C-Thymidine**
- **Analogs with minimal metabolism**
  - **<sup>18</sup>FLT**
  - **<sup>18</sup>FMAU**
- **Analogs with longer half-life**
  - **<sup>124</sup>IUdR**

# Small Cell Lung Cancer:

## PET Imaging Pre-and Post One Cycle of Rx



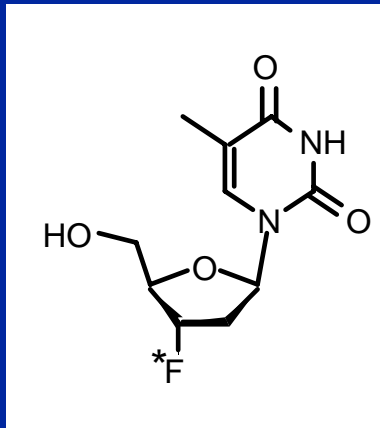
(Shields, J Nucl Med, 1998)

# Thymidine Analogs for PET Cell Proliferation Imaging

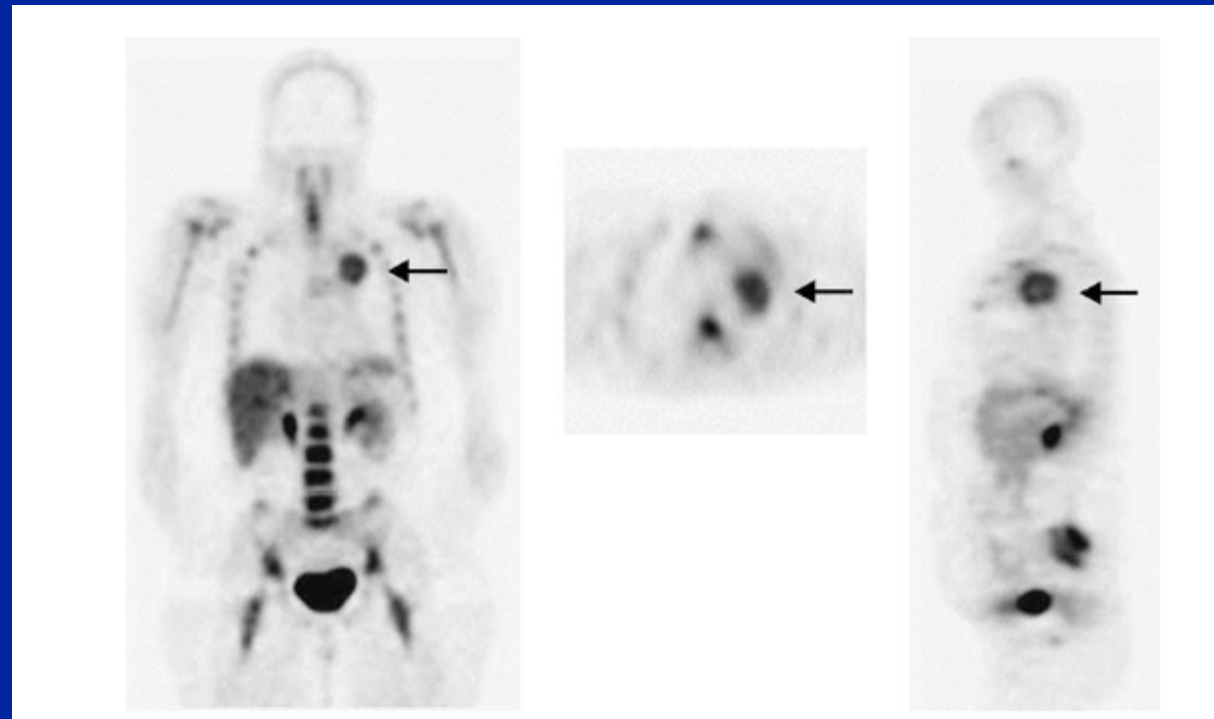
## Clinically Feasible Isotope and Imaging Protocol

### FLT PET Images of Lung Cancer

$^{18}\text{F}$ -Fluoro-L-thymidine  
(FLT)



(Grierson, Nucl Med Biol  
27:143, 2000)

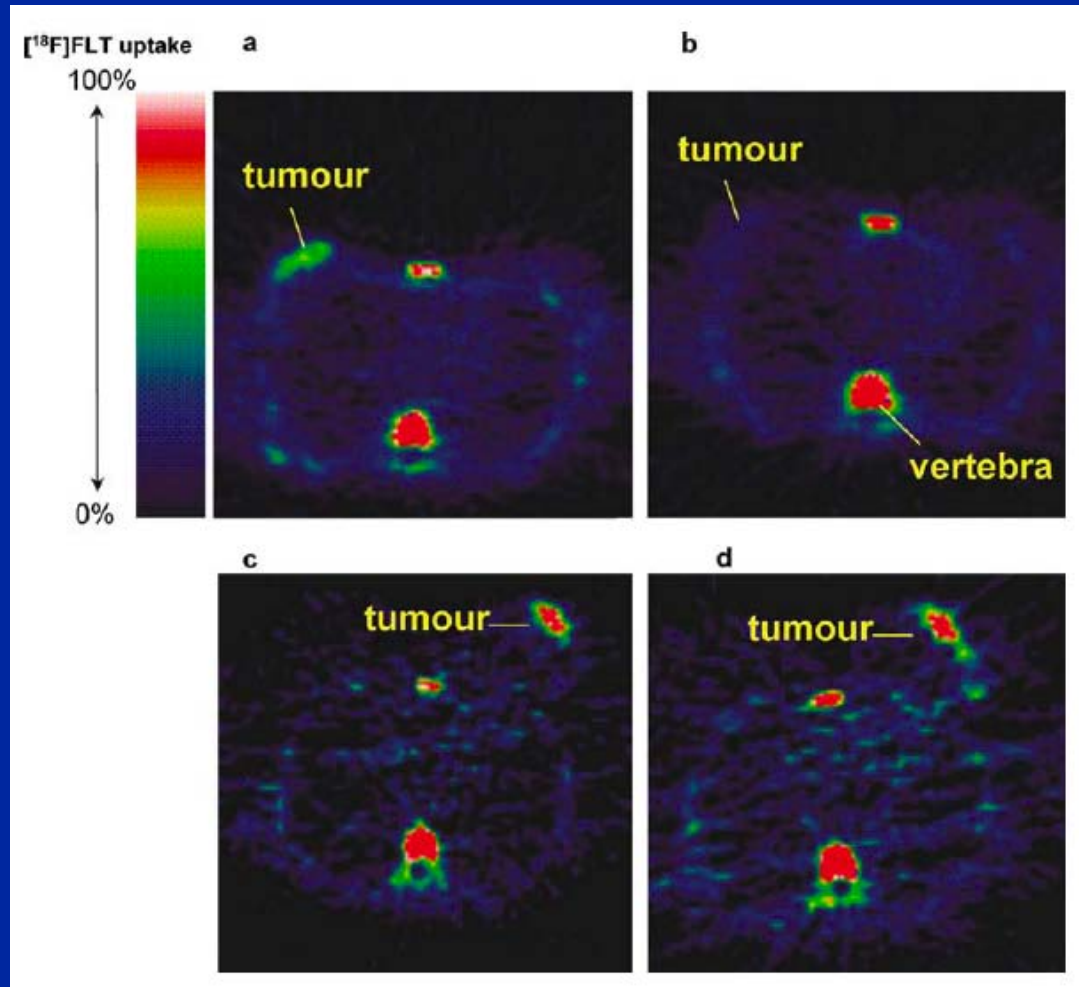


(Shields AF, from Mankoff, Shields, and Krohn,  
Rad Clin N Amer 43:153, 2005)

# Early Response of Breast Measured by FLT PET

Kenny, EJNMMI 34:1339, 2007

Pre-FEC    1 wk Post-FEC



**FLT Uptake  
Reproducibility:  
10% -15%**

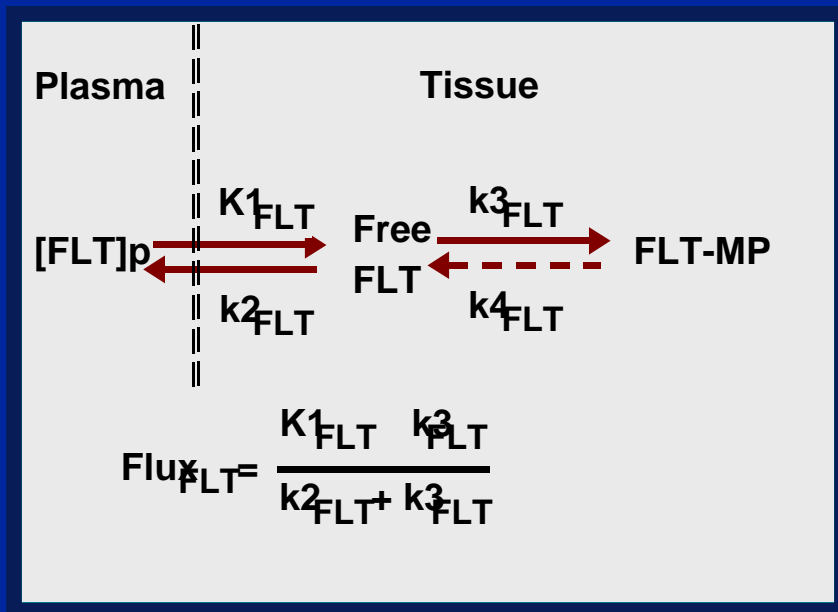
**Response**

**No-Response**

# FLT Brain Tumor Imaging to Measure Response: Proliferation or BBB Breakdown?

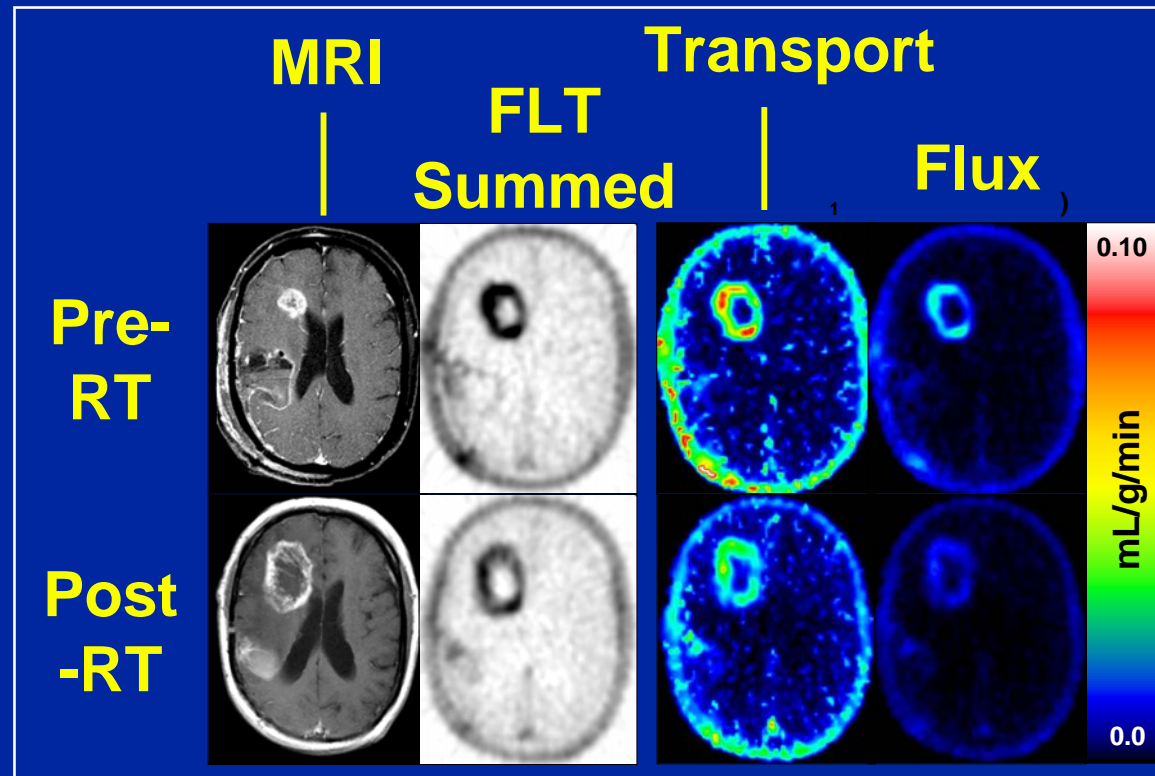
Muzi, J Nucl Med, 2006

Kinetic model:  $\longrightarrow$  Parametric Imaging:



(Visvikis, Eur J Nucl Med Mol Imag, 2003;

Muzi, J Nucl Med, 2005)



Parameter	Pre-RT	Post-RT
Flux	0.030	0.017
K1	0.066	0.059

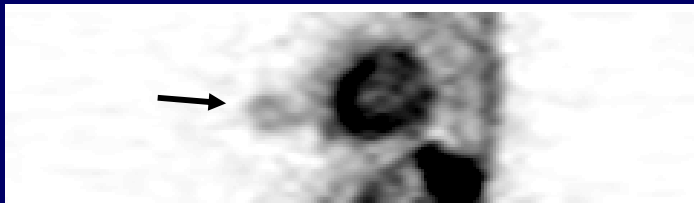
# Specific Examples of PET Imaging to Direct Cancer Therapy

- Assess the therapeutic target
- Identify resistance factors
- Measure early response
- **Relate response to outcome**

# A Mismatch Between Tumor Metabolism and Perfusion Predicts Poor Response

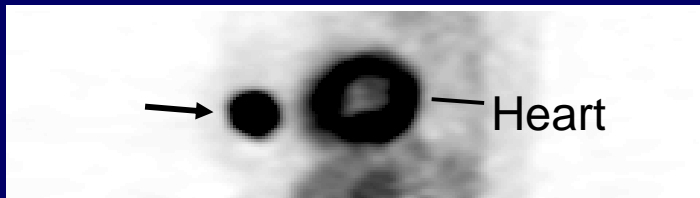
## $^{15}\text{O}$ -water and FDG PET

$^{15}\text{O}$ -Water (30 - 60 sec)



$F = 0.28 \text{ mL/min/g}$

FDG (30 - 60 minute)

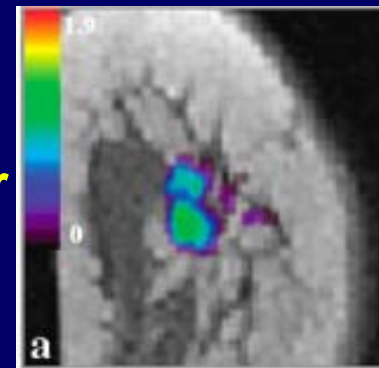


$\text{MRFDG} = 17 \text{ } \mu\text{mole/min/100g}$

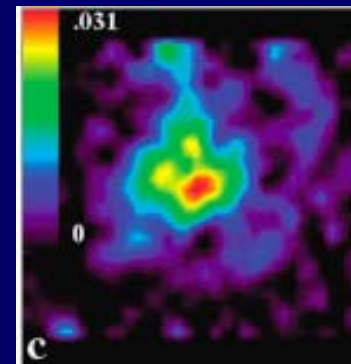
(Mankoff, J Nucl Med 43:  
500, 2002)

## DCE MRI and FDG PET

MRI Transfer  
Constant



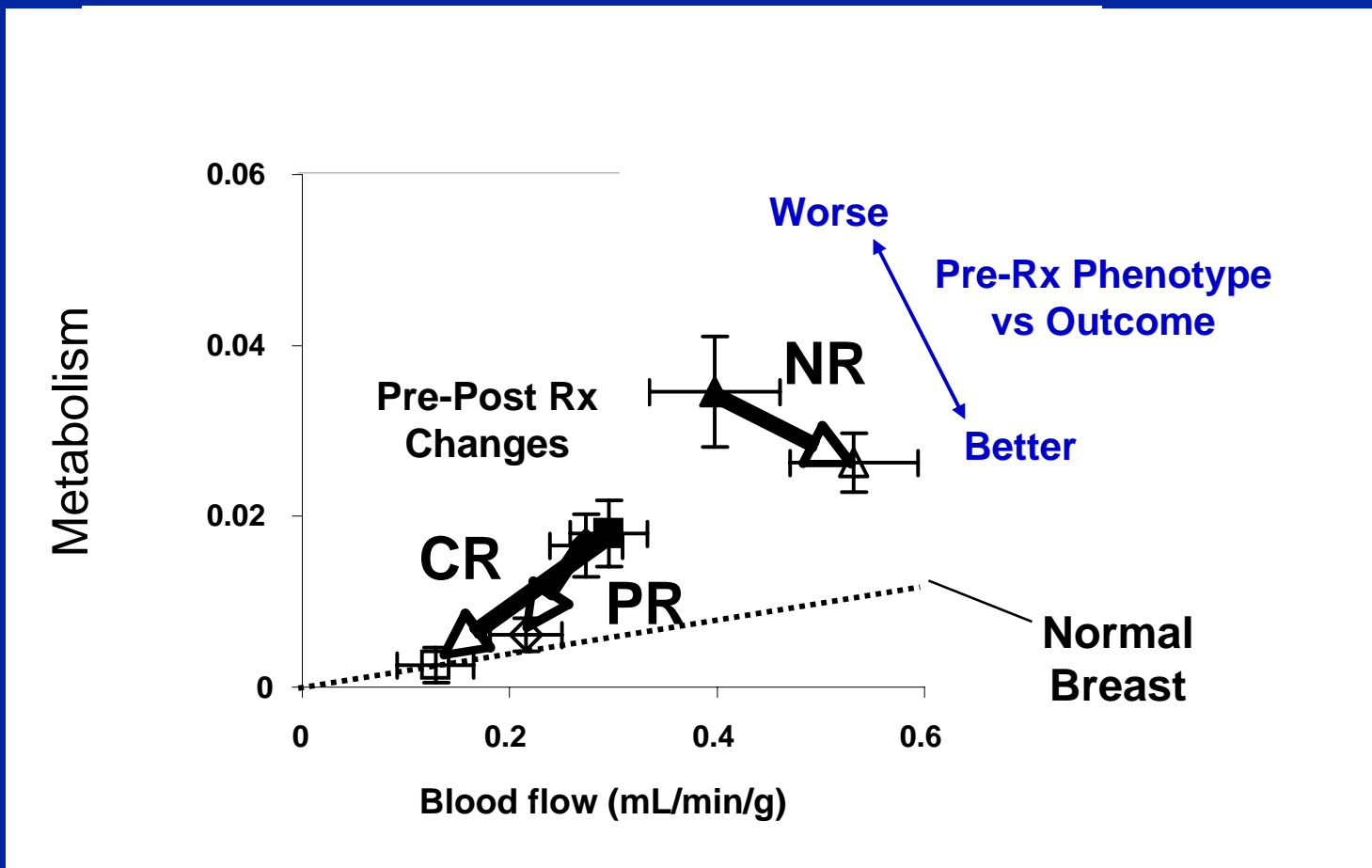
FDG PET  
SUV



(Semple, Annals Oncol,  
17: 1393, 2006)

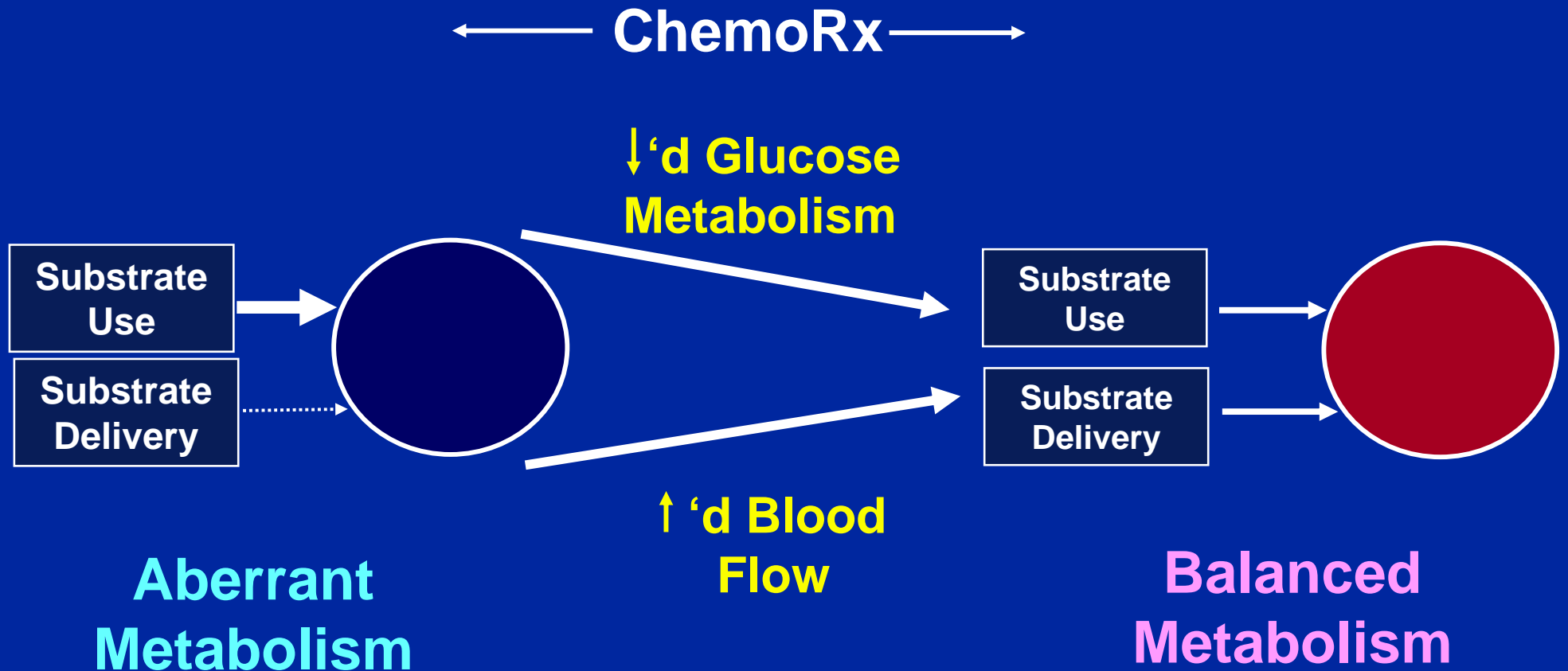
# Blood Flow and Metabolism Patterns of Change with Neo-Adjuvant Chemotherapy

## Altered Metabolic Phenotype with Rx



(Tseng, J Nucl Med, 45:1829, 2004)

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



# PET Biomarkers Beyond FDG: Summary

- Imaging ideally suited to testing new targeted drugs
- Imaging can help targeted drug testing and clinical practice by:
  - Better patient selection:
    - Identifying the therapeutic target
    - Identifying possible resistance factors
  - Better assessment of efficacy
    - Early measure of response
    - Relating response to patient outcome
- *In vivo* assessment by imaging is complementary to *in vitro* molecular assay of biopsy material

# **Acknowledgements: UW PET Cancer P01**

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  - Alex Spence
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  - Janet Eary, Ollie Press
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  - Joseph Rajendran
- **Project 4 - Breast Cancer**
  - David Mankoff, Hannah Linden
- **Project 5 - Sarcoma**
  - Chappie Conrad, Janet Eary
- **Project 6- Endocrine Tumors**
  - Jeanne Link, Gary Mann

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  - Jeanne Link
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  - Tom Lewellen, Paul Kinahan
- **Core C - Data analysis**
  - Mark Muzi, Finbarr O'Sullivan
- **Core D - Molecular Pathology**
  - Jonathan Tait, Kevin Yagle

# **UW PET Cancer Imaging Research:**

## **Key Collaborators**

### **Pharmaceutics**

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### **Radiology**

**William Eubank**

**Connie Lehman**

### **Pathology**

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**Jonathan Tait**

**Peggy Porter (FHCRC)**

**Allen Gown (Phenopath)**

### **Biochemistry**

**Philip Petra**

### **Cardiology/Bioengineering**

**James Bassingthwaite**

**James Caldwell**

### **Biostatistics**

**William Barlow (CRAB)**

**Brenda Kurland**

### **Neurology**

**Alex Spence**

### **Surgery/Orthopedics**

**David Byrd**

**Earnest Conrad**

**Gary Mann**

### **Oncology**

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**Julie Gralow**

**Hannah Linden**

**Robert Livingston**

**Ollie Press**

**Jennifer Specht**

**Lavanya Sundararajan**

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**Michelle Yao**