Patient Management with Molecular Imaging:
A New Paradigm for Cancer Imaging

5th National Forum on
Biomedical Imaging in Oncology

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Patient Management with Molecular Imaging: Outline

- Clinical questions
- Biologic targets and radiopharmaceuticals for molecular imaging
- Examples of clinical applications
  - Assess the therapeutic targets
  - Identify resistance factors
  - Measure early response to treatment

A New Paradigm for Cancer Imaging:
Help Direct Cancer Treatment

- **Established role:**
  - Detect cancer
  - Find how far cancer has spread
- **New role for imaging:**
  - Guide cancer treatment selection
  - Evaluate early treatment response

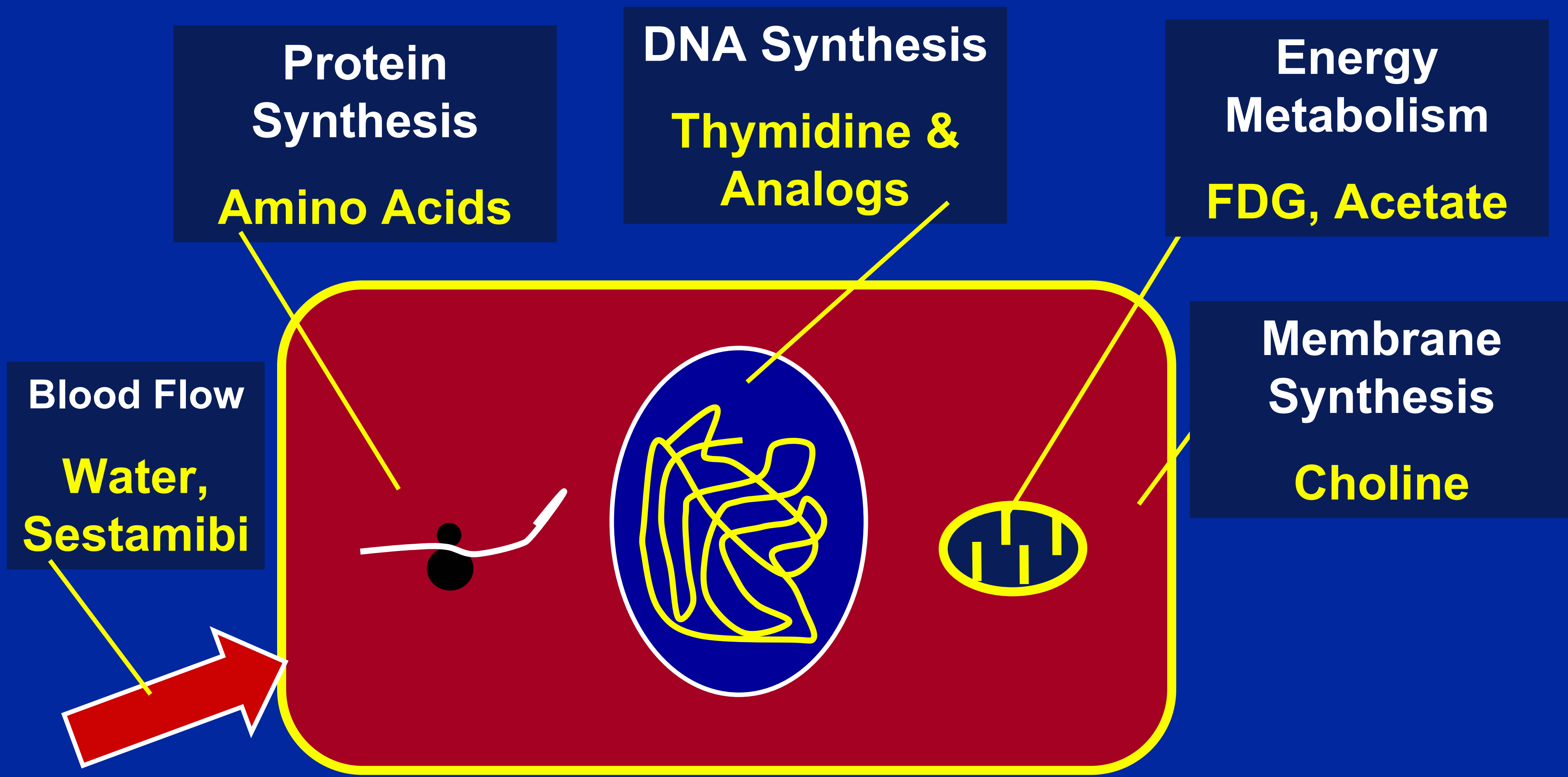
A New Paradigm for Cancer Imaging:
Help Match Therapy to Tumor Biology

- Emerging trends in cancer treatment
  - Characterize tumor biology pre-Rx
  - Individualized, specific therapy
  - Static response may be OK in some cases
- The implied needs for cancer imaging
  - Characterize in vivo tumor biology
  - Identify targets, predict response
  - Measure tumor response (early!)

Existing Cancer Imaging Paradigm:

Targets for Detecting Tumor Cells

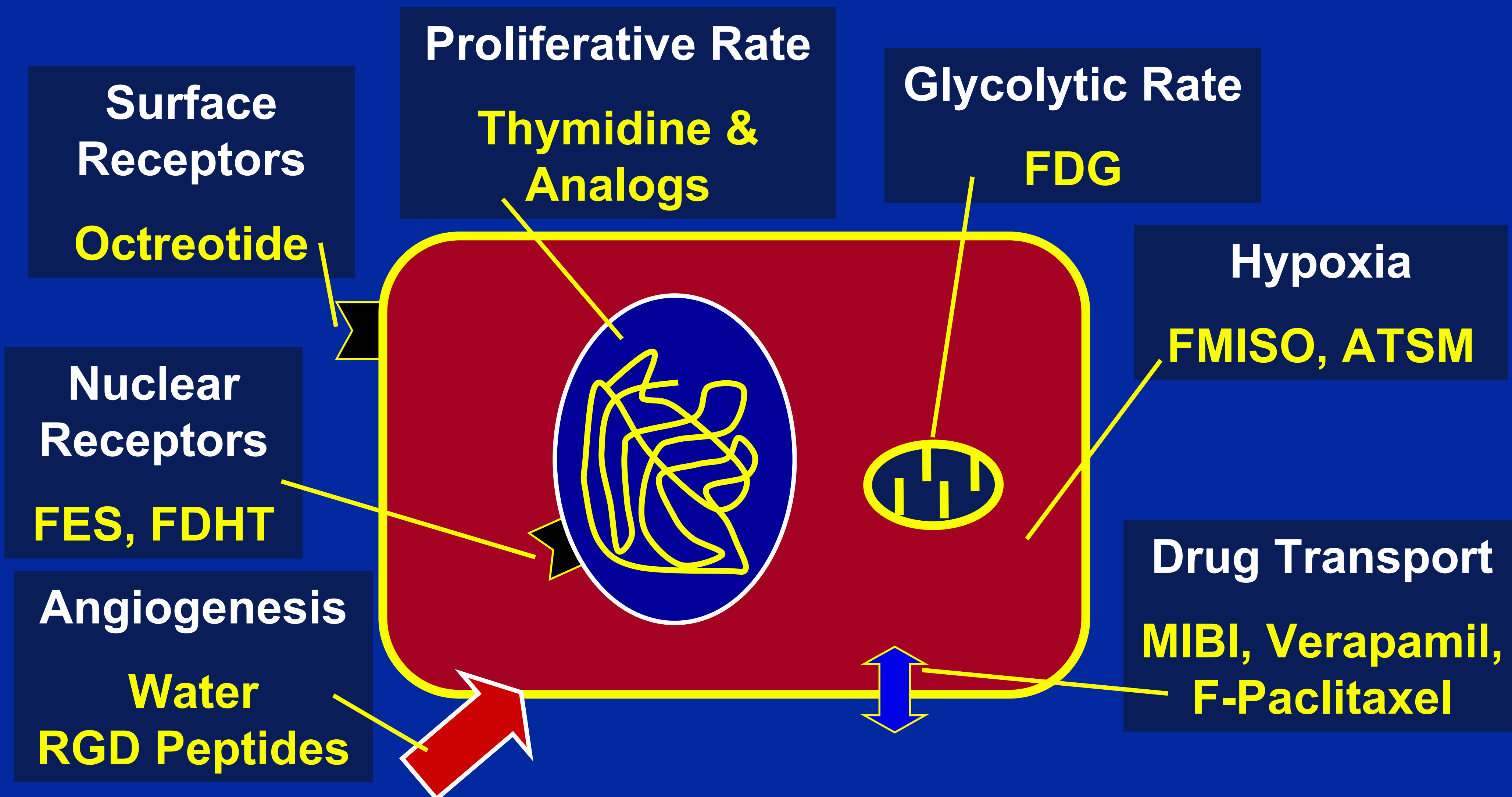
Higher in Tumor than Normal Tissue



Emerging Cancer Imaging Paradigm:

Measure Factors Affecting Response

Variable Levels in Tumor



New Cancer Imaging Agents: Desirable Properties for Clinical Use

- Fills a clinical need in cancer care
- Uptake based upon specific tumor biology
- Can be regionally distributed
- Clinically practical
  - Clinically-feasible imaging protocols
  - Qualitative and quantitative interpretation
    - Robust, automated image analysis

Why Radioisotope Imaging?

Answer: To achieve tracer conditions

- Example: Estrogen Receptor Imaging
  - Tracer specific activity: 1000 mCi/μmol
  - Injected activity dose: 5 mCi
  - Injected molar dose: 5 nmol
  - Peak blood concentration: 1 nM

  (Typical estradiol blood concentration is μM)
- Can image biochemical processes without disturbing them
- Radiographic, MR, or optical agents require ~mM

PET Imaging Agents: Isotope Choices

- ^{18}F (110 min) -model for clinical use from FDG
- ^{11}C (20 min) -important for science and development
  - $T_{1/2}$ too short for distribution
  - Clinical use at centers with cyclotrons
- Other choices:
  - ^{124}I (~4 days) - longer half life, high rad dose
  - Cu isotopes (^{60}Cu, ^{62}Cu) - ATSM, eg.
  - ^{94m}Tc (~50 min) - wealth of experience from SPECT
  - ^{68}Ga (68 min) - convenient generator

Specific Examples of Molecular Imaging to Direct Cancer Therapy

- Assess the therapeutic target
- Identify resistance factors
- Measure early response

Identifying Therapeutic Targets using Molecular Imaging:Why?

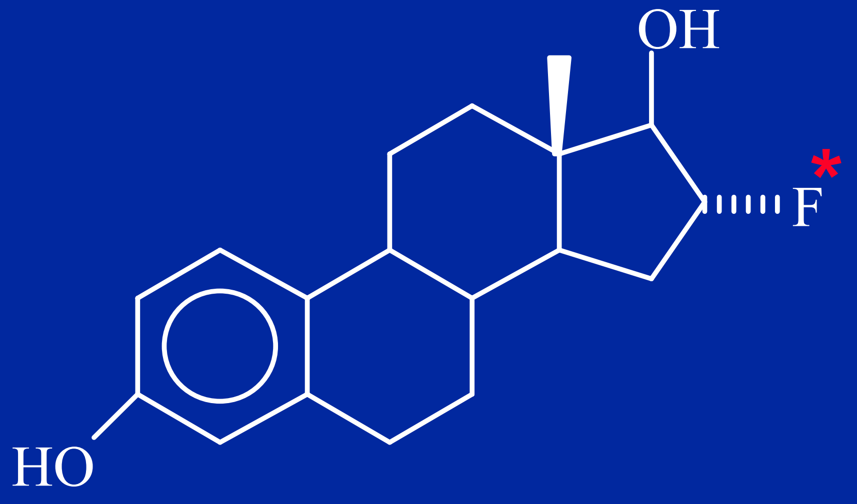
- Imaging can measure the level of expression
  - Heterogeneity of target expression
  - Especially for advanced disease
- Imaging can measure the *in vivo* effect of drug therapy on the target. Examples:
  - Receptor antagonism
  - Change in target expression

Agents for Measuring Therapeutic Targets

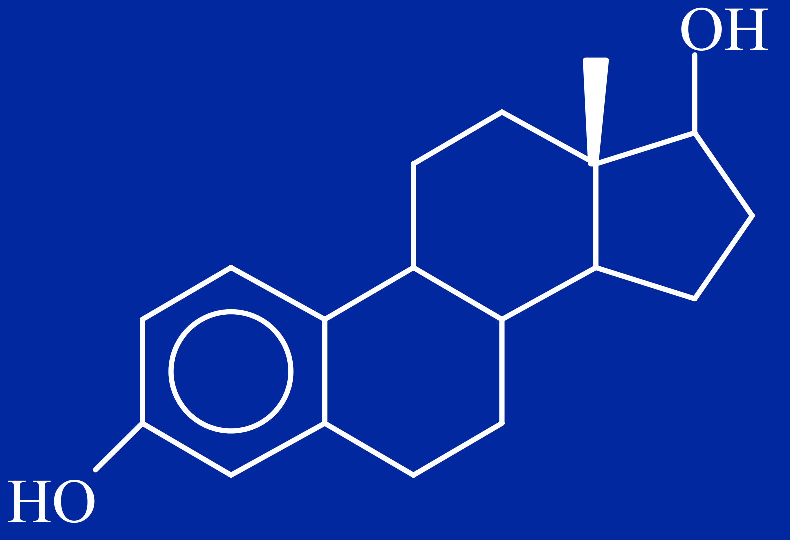
- Tumor Receptors
  - ER - ^{18}FES
  - AR - ^{18}FDHT
  - Others - SSR receptors, endocrine agents
- Oncogenes
  - MoAbs, Labeled tyrosine kinases
- Angiogenesis
  - Specific - ^{18}F-RGD peptides
  - Blood flow - $H_2{}^{15}O$

[F-18]-Fluoroestradiol (FES):
A Tracer for Estrogen Receptor Imaging

FES



Estradiol



(Kieswetter, J Nucl Med, 1984)

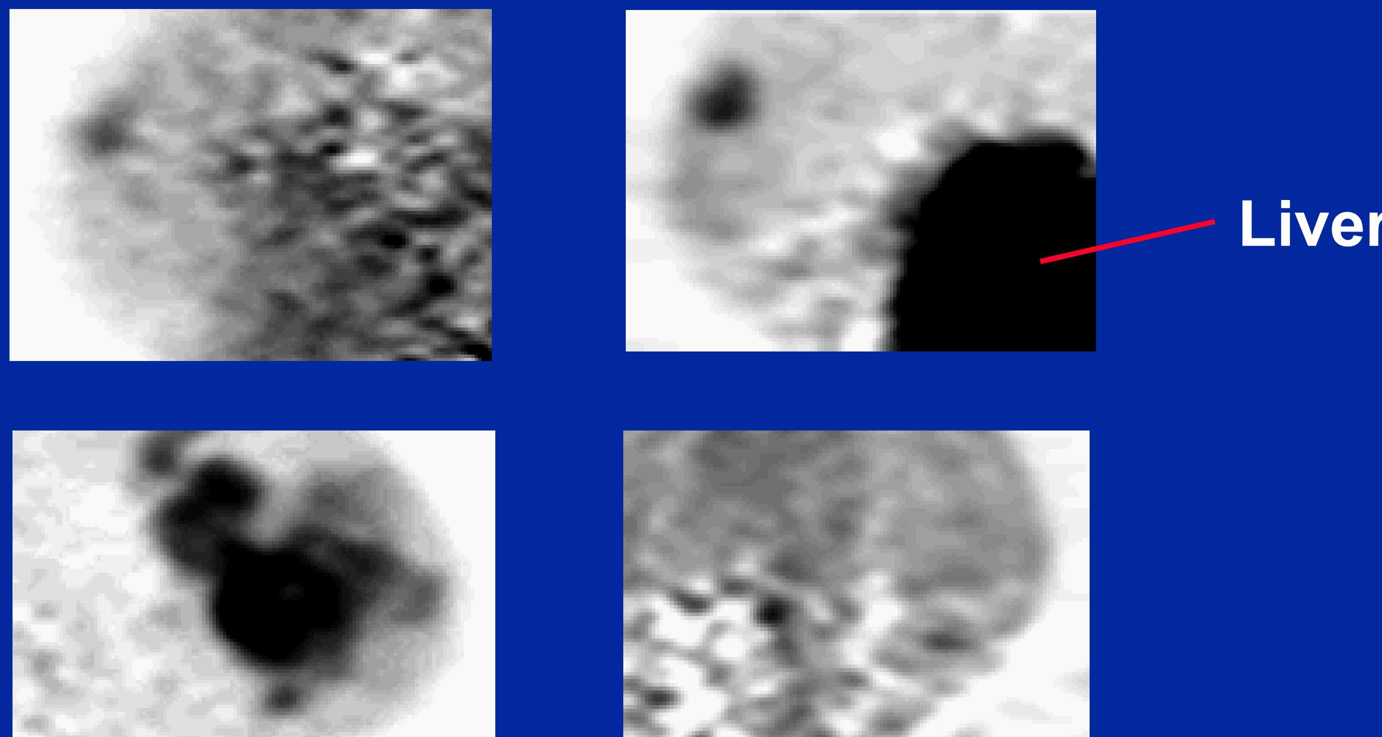
[F-18] FES Measures ER Expression in Breast Cancer

(thick sagittal planes)

FDG | FES

ER+

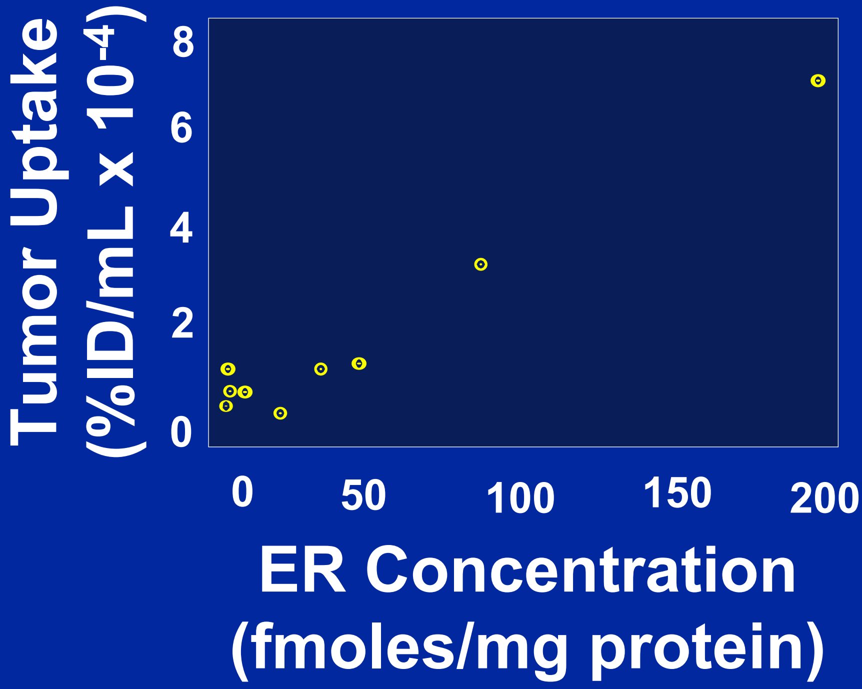
ER-



Glucose Metabolism | ER Expression

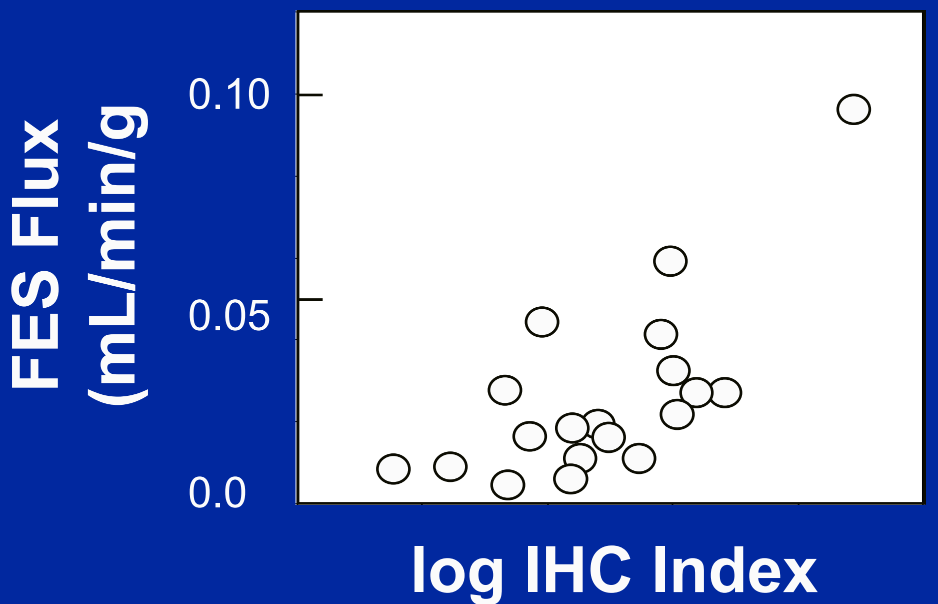
FES PET Provides a Quantitative Estimate of ER Expression

vs Radioligand Binding



(Mintun, Radiology 169:45, 1988)

vs Immunohistochemistry

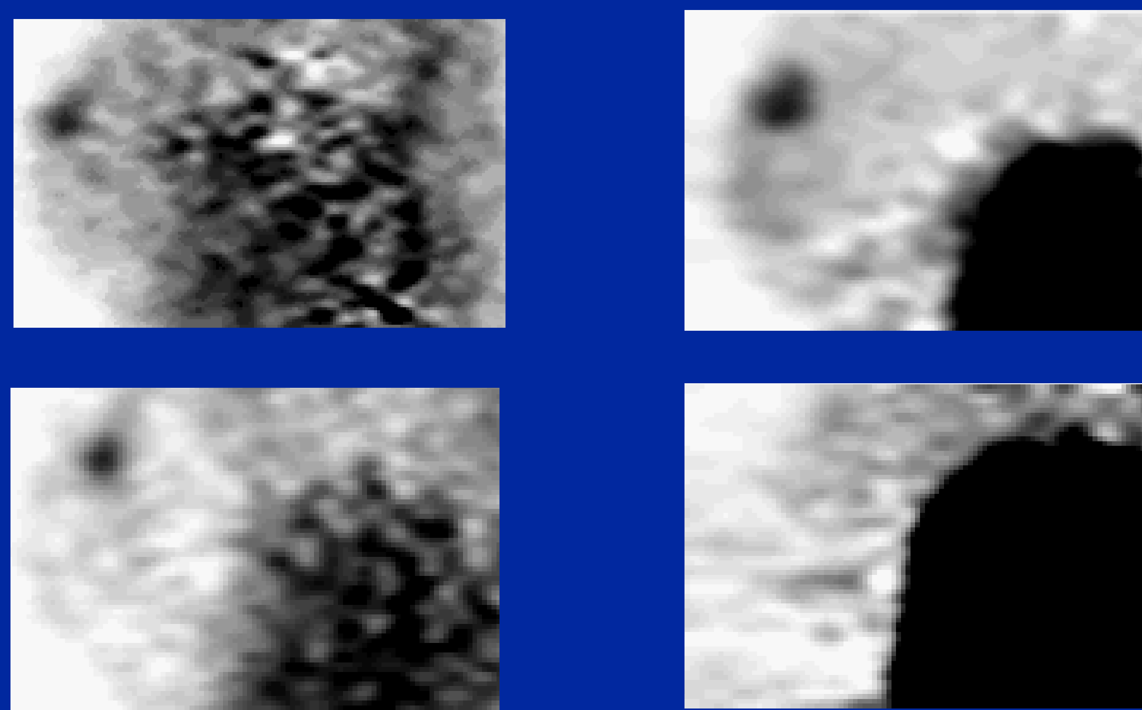


(Mankoff, J Nucl Med 43: 287P, 2002)

FES Imaging Measures Estrogen Binding Antagonism by Tamoxifen

(thick sagittal planes)

	FDG	FES
Baseline		
2 months Tamoxifen		



Glucose Metabolism | Estradiol Binding

How Can ER Imaging Help?

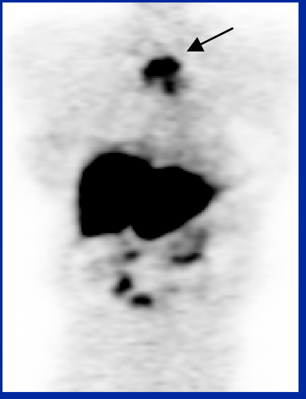
- Specific identification of breast cancer metastases
- Directly measure the effect of hormonal therapy
- Assess heterogeneity of ER
  - Spatial: Expression at each Dz site
  - Temporal: Changes in expression with Rx
  - Goal: Predict likelihood of response to hormonal Rx

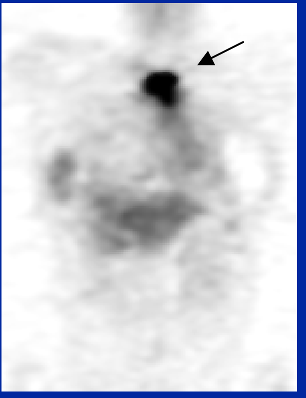
FES Uptake Predicts Breast Cancer Response to Hormonal Therapy

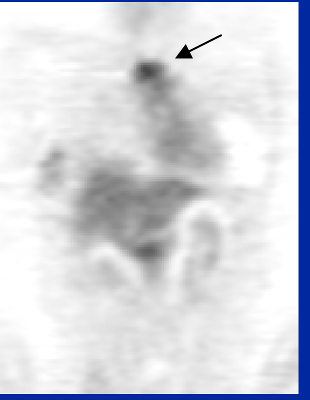
Example 1

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

Pre-Rx | Post-Rx





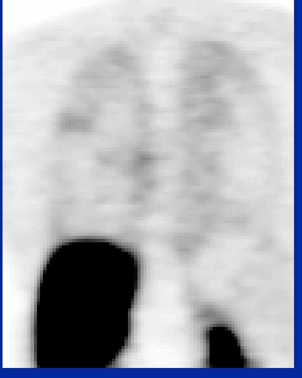


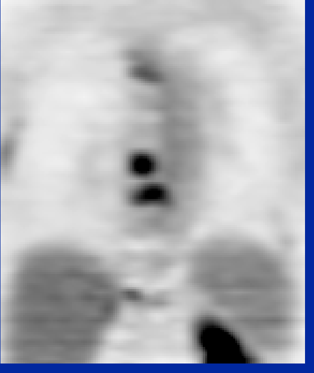
Excellent response
after 6 wks Letrozole

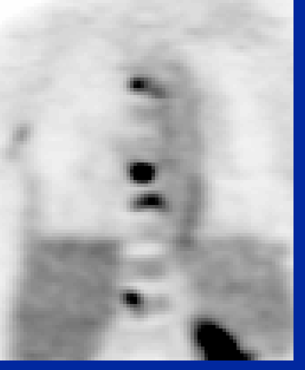
FES | FDG | FDG

Example 2

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







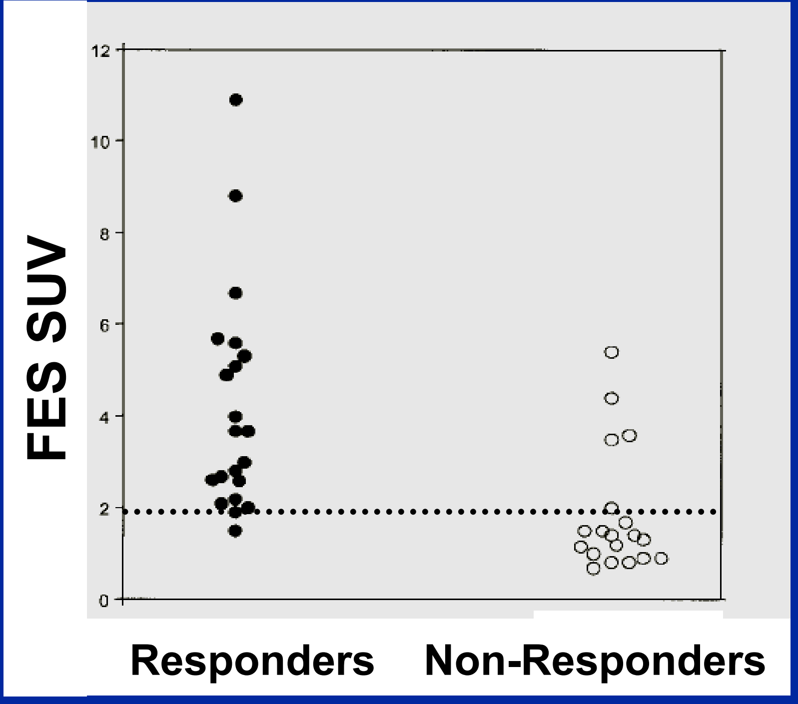
No response
to several different hormonal Rx's

University of Washington

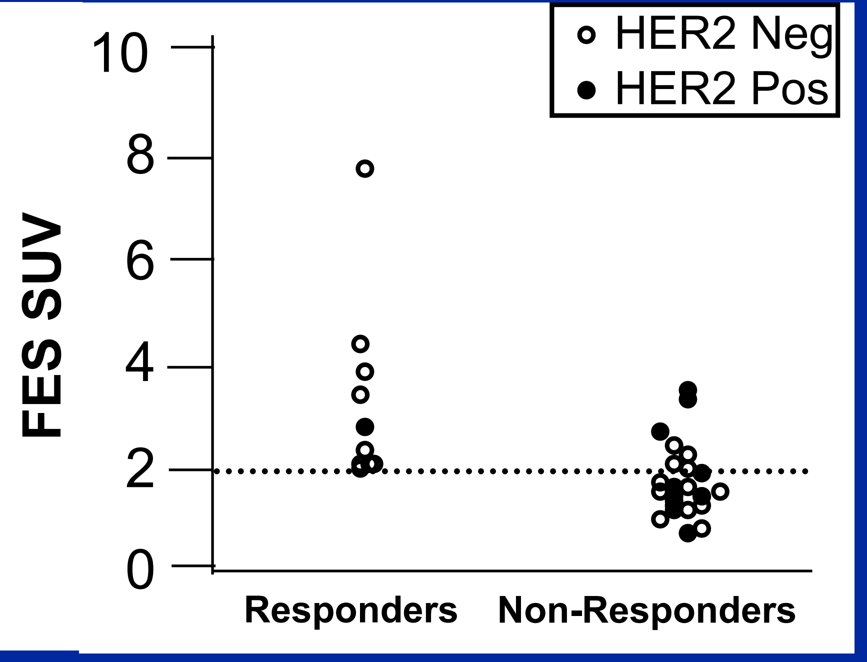
(Mankoff, J Nucl Med, 44: 126P, 2003)

FES Uptake Predicts Response of Advanced Breast Cancer to Hormonal Therapy

LABC or Metastatic Br CA
Primary Tamoxifen Rx



Recurrent or Metastatic Br CA
Aromatase Inhibitor Rx



(Mortimer, J Clin Onc, 19: 2797, 2001)

(P < .01 for both)

(Mankoff, J Nucl Med, 44: 126P, 2003)

Specific Examples of Molecular Imaging to Direct Cancer Therapy

- Assess the therapeutic target
- Identify resistance factors
- Measure early response

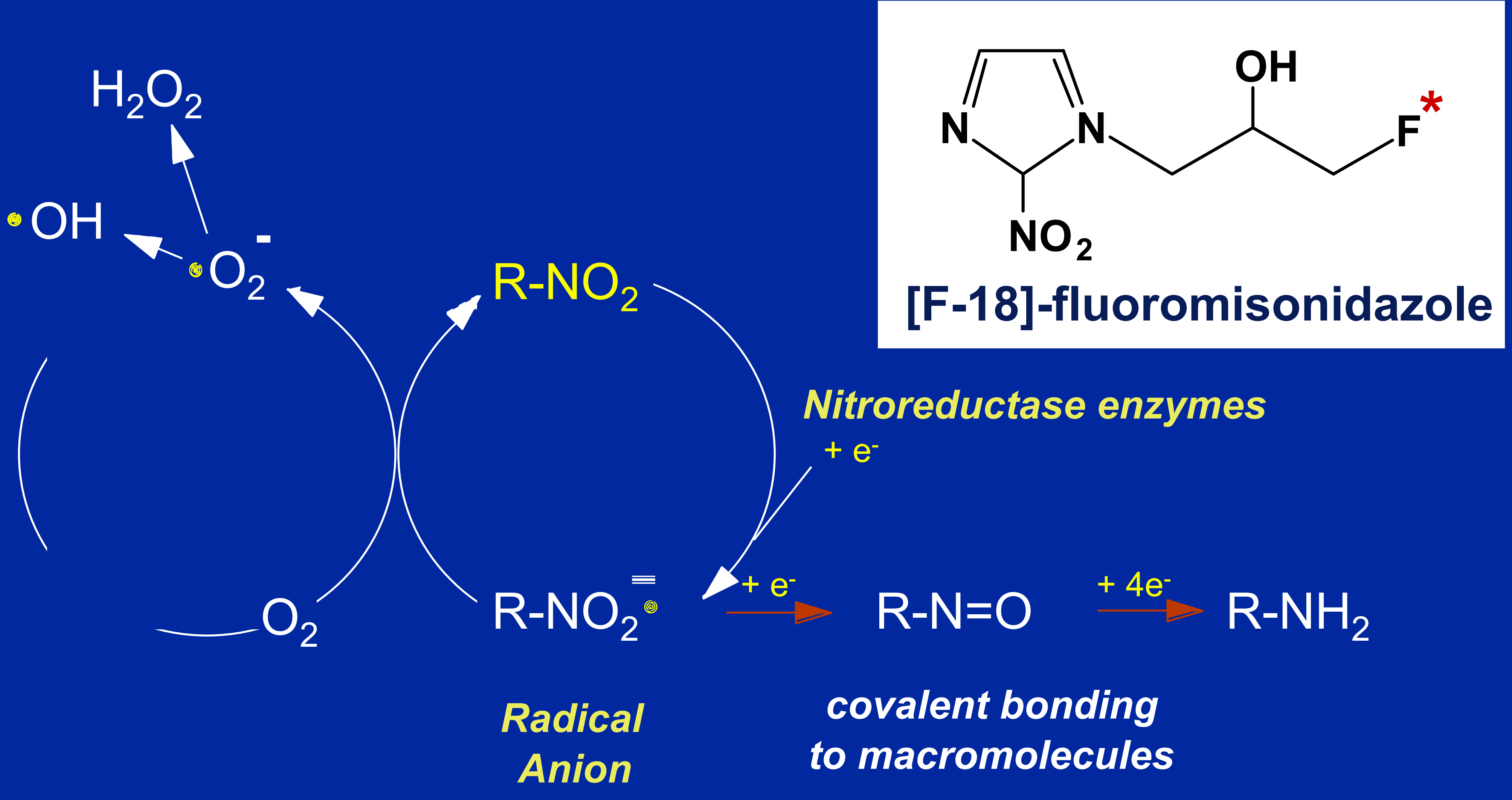
Agents for Identifying Tumor Resistance Factors

- Hypoxia
  - ^{18}FMISO, ^{60}Cu-ATSM, ^{18}FIAZA, ^{18}F-EF5
- Drug transport/efflux
  - ^{11}C-verapamil, ^{11}C -colchicine, ^{11}C - or ^{18}F -paclitaxel, ^{94m}Tc -sestamibi
- Resistance to Apoptosis
  - ?? ^{18}FDG

Biologic Consequences of Tumor Hypoxia

- Mediated through HIF-1 and other factors
- Associated with tumor aggressiveness:
  - Promotes angiogenesis
  - Increases transcription of glycolytic enzymes
- Leads to resistance
  - Alters cell cycle kinetics
  - May select cells resistant to apoptosis
  - Key factor in XRT, also in ChemoRx

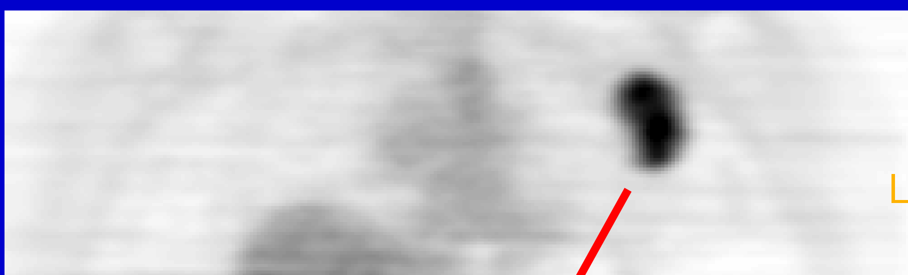
Imaging Hypoxia as the Accumulation of a Radiopharmaceutical



Tissue Hypoxia in Advanced Axillary Breast Cancer

[F-18]-FDG

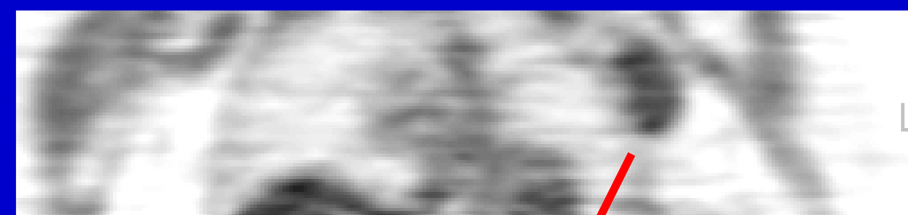
Glucose Metabolism



SUV max = 10.2

[F-18]-Fluoromisonidazole (FMISO)

Hypoxia

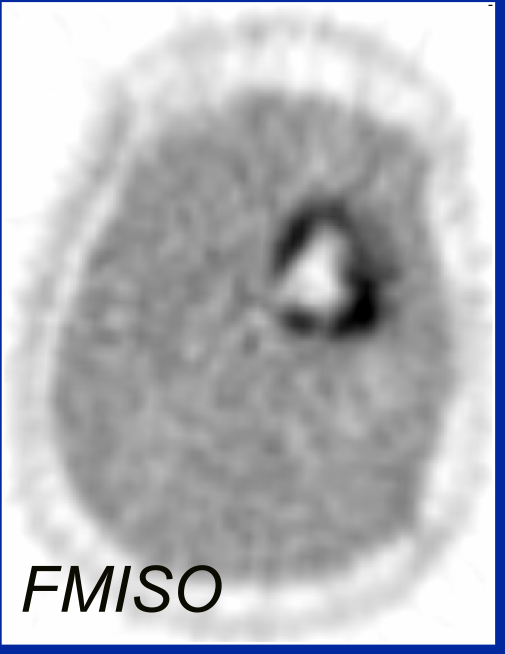


Tumor/Blood max = 1.8

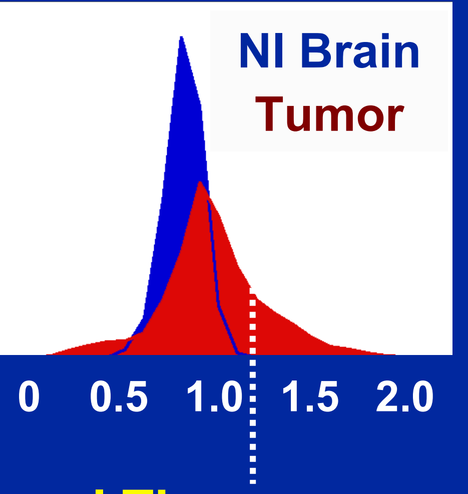
Significant FMISO uptake seen in ~ 30% of large breast cancers

(Rajendran, Clin CA Res, in press)

Tissue Hypoxia in Glioblastoma



Tissue:Blood Ratio Histogram

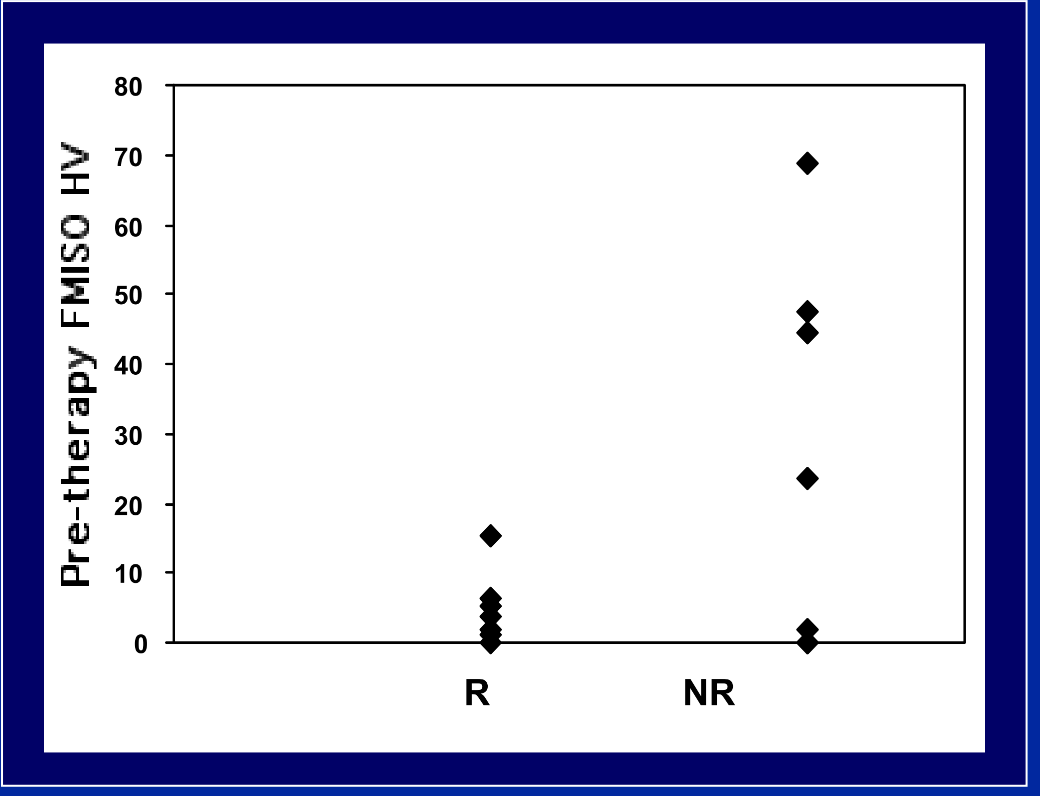


Normal Tissue:
95% < 1.12
99.9% < 1.2

(Spence, UW)

FMISO Uptake in Heand and Neck CA Predicts Response to XRT

Hypoxic volume (HV) from FMISO PET showed a significant correlation with response (p value = 0.05)



(Rajendran, SNM 2003, UW)

TROG 98.02

An International Trial Partnered by Academics and Industry

Stage III or IV H&N SCC

13 institutions

Stratify by Institution

Stratify by FMISO PET results

R A N D O M I S E

- Arm 1 – Radiotherapy 70 Gy/ 7 wks with "Chemo-boost" cisplat +5FU
- Arm 2 – Radiotherapy 70 Gy/ 7 wks with cisplat +tirapazamine

(Lester Peters, Peter MacCallum Cancer Centre,Melbourne, Australia)

Specific Examples of Molecular Imaging to Direct Cancer Therapy

- Assess the therapeutic target
- Identify resistance factors
- Measure early response

Biologic Events in Response to Successful Cancer Therapy

Rx

→

↓ Cellular Proliferation

or

↑ Cell Death

→

↓ Viable Cell Number

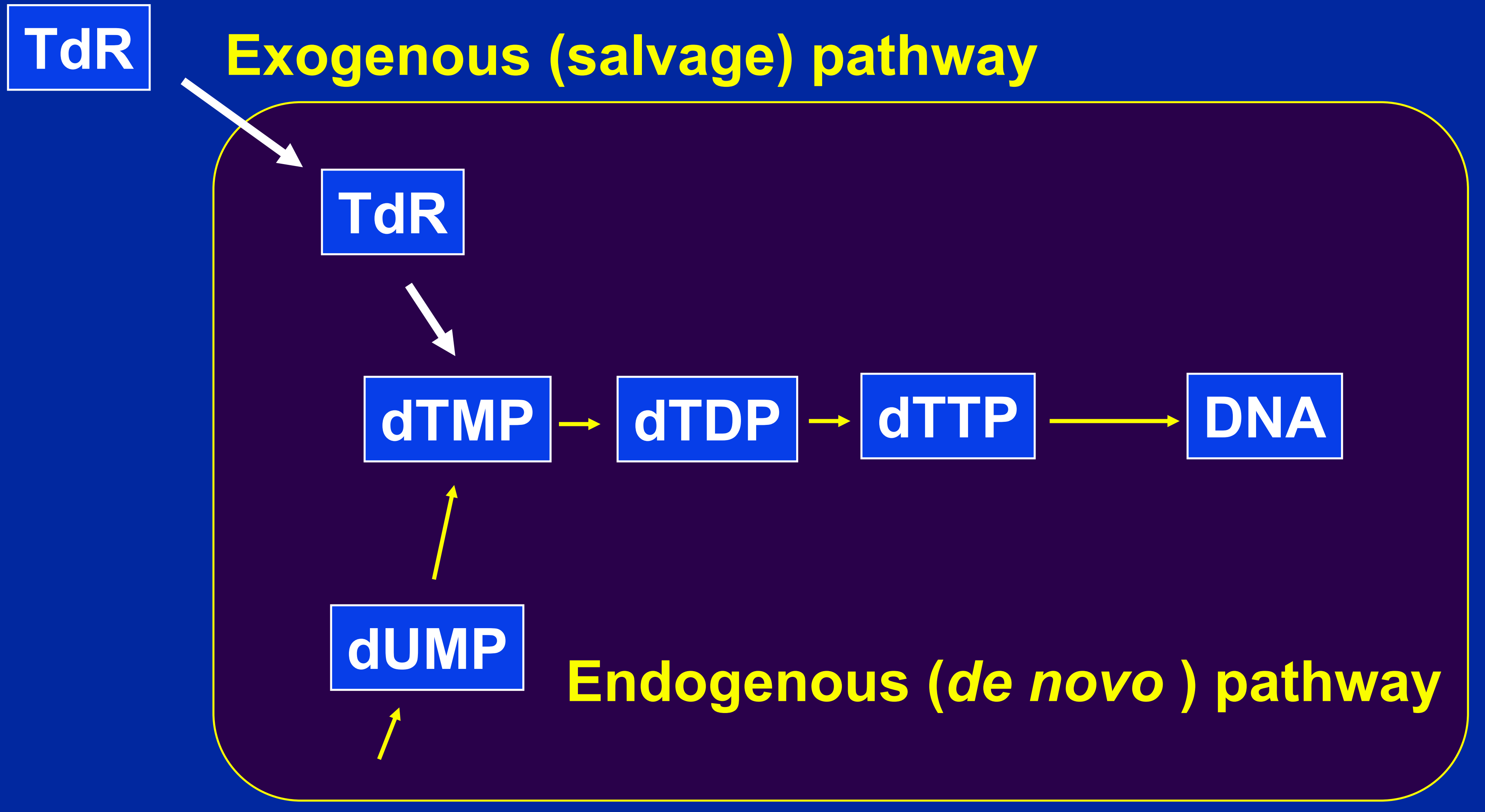
→

↓ Tumor size

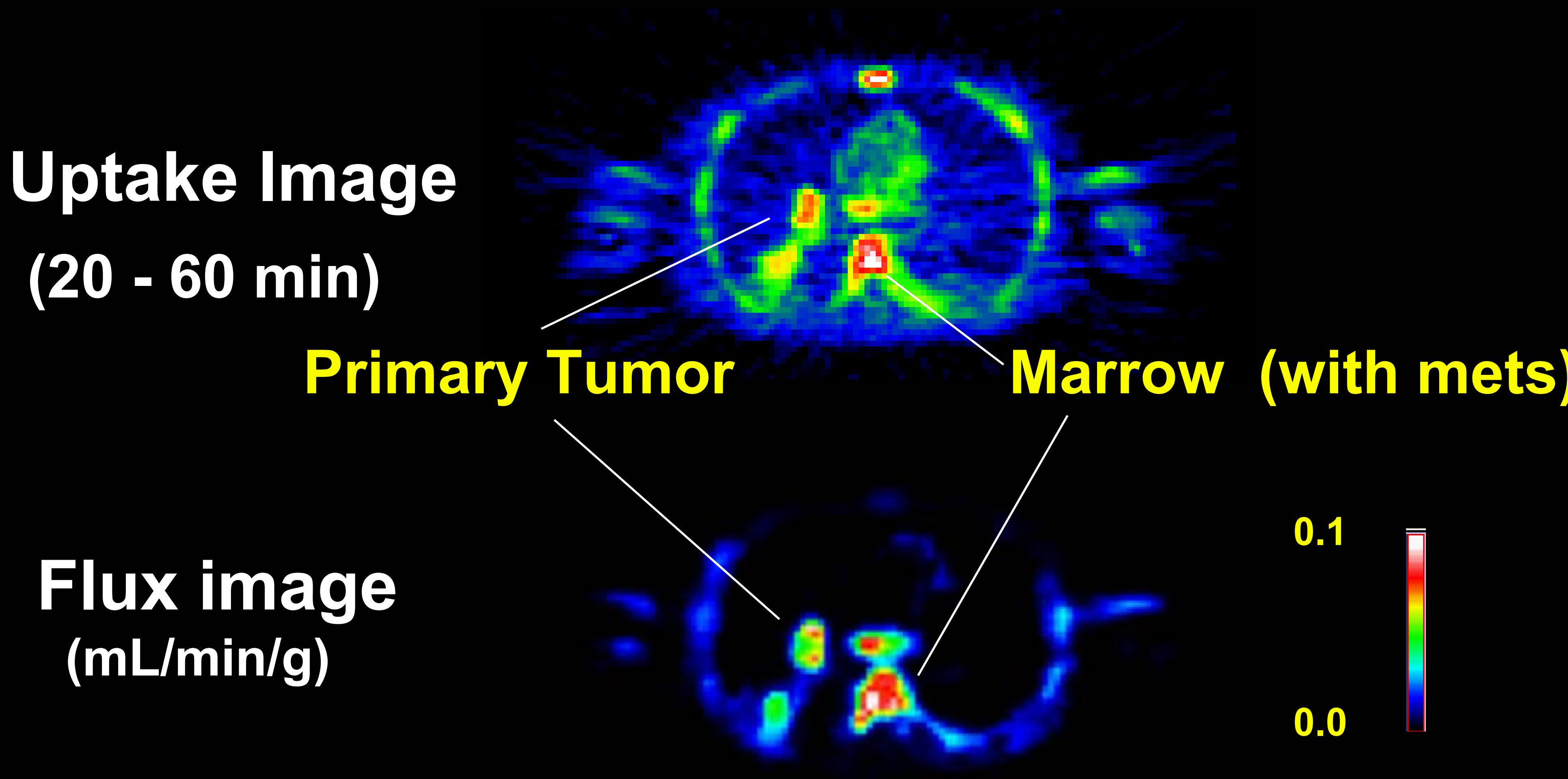
Cell Proliferation Imaging Agents

- Gold standard - thymidine
  - Methyl or 2-^{11}C-Thymidine
- Analogs with minimal metabolism
  - ^{18}FLT
  - ^{18}FMAU
- Analogs with longer half-life
  - ^{124}IUdR

Thymidine Incorporation Pathways

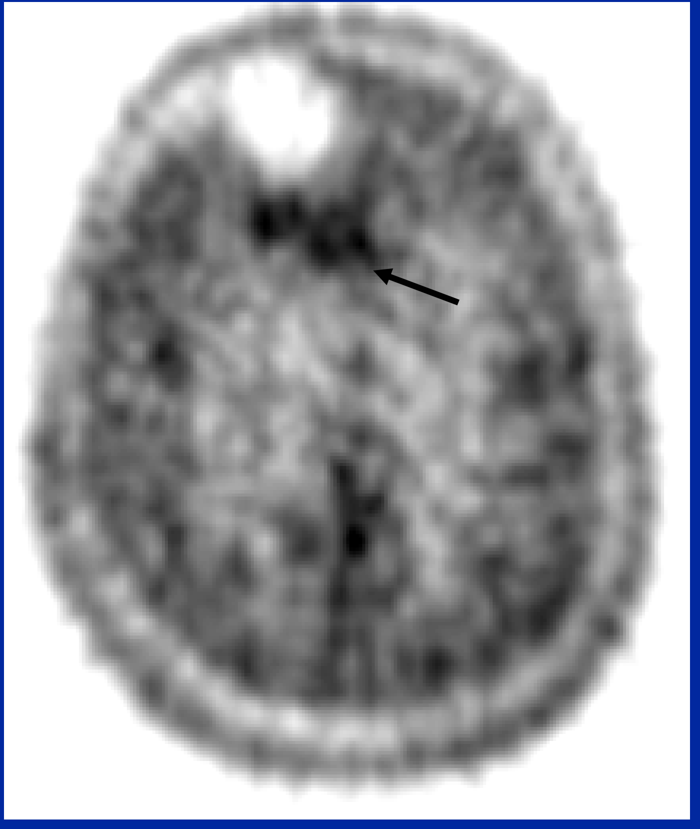


^{11}C-Thymidine Images of Small Cell Lung Cancer

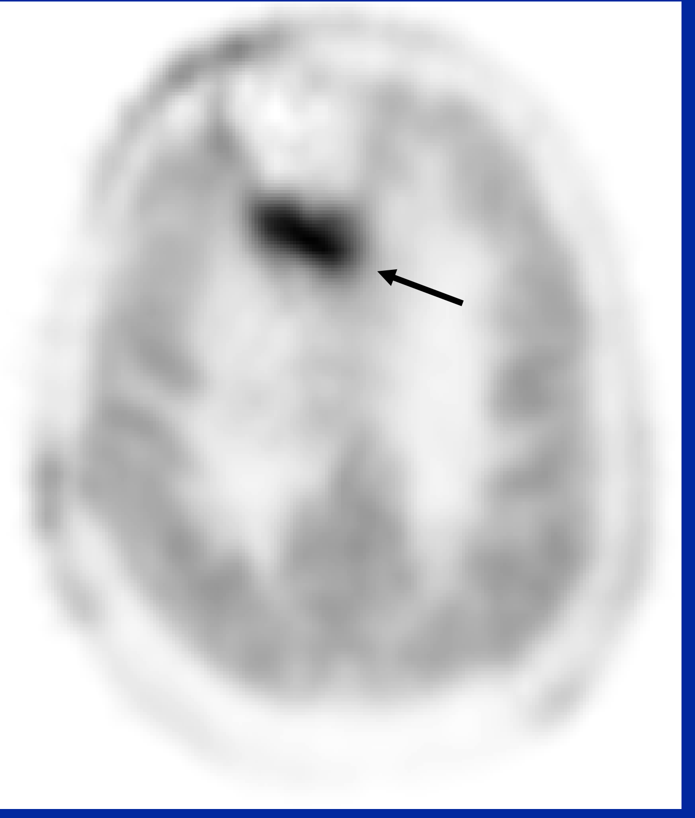


^{11}C-Thymidine Brain Tumor Images

Uptake Image



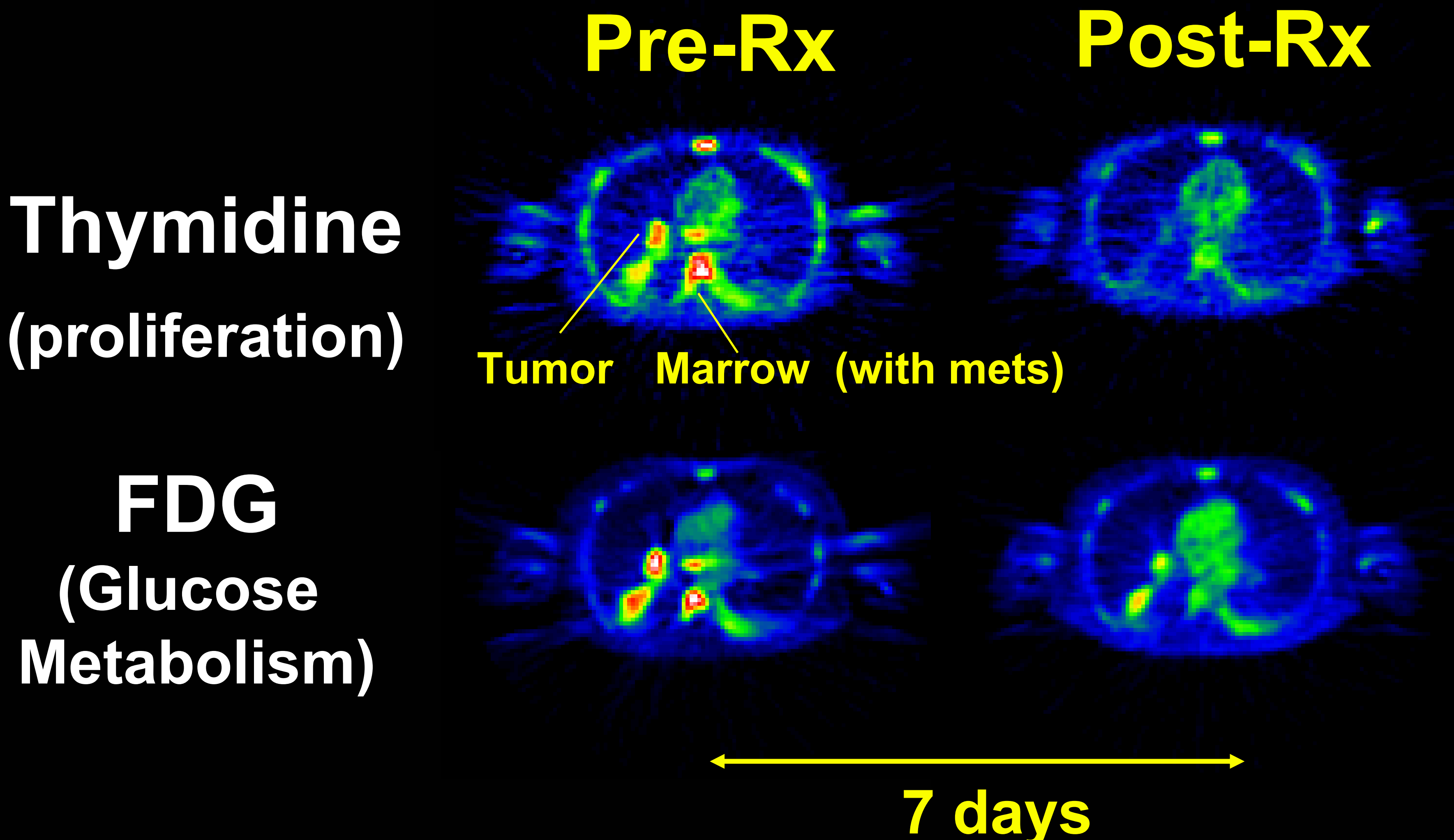
Flux Image



(Eary, Cancer Res, 1998)

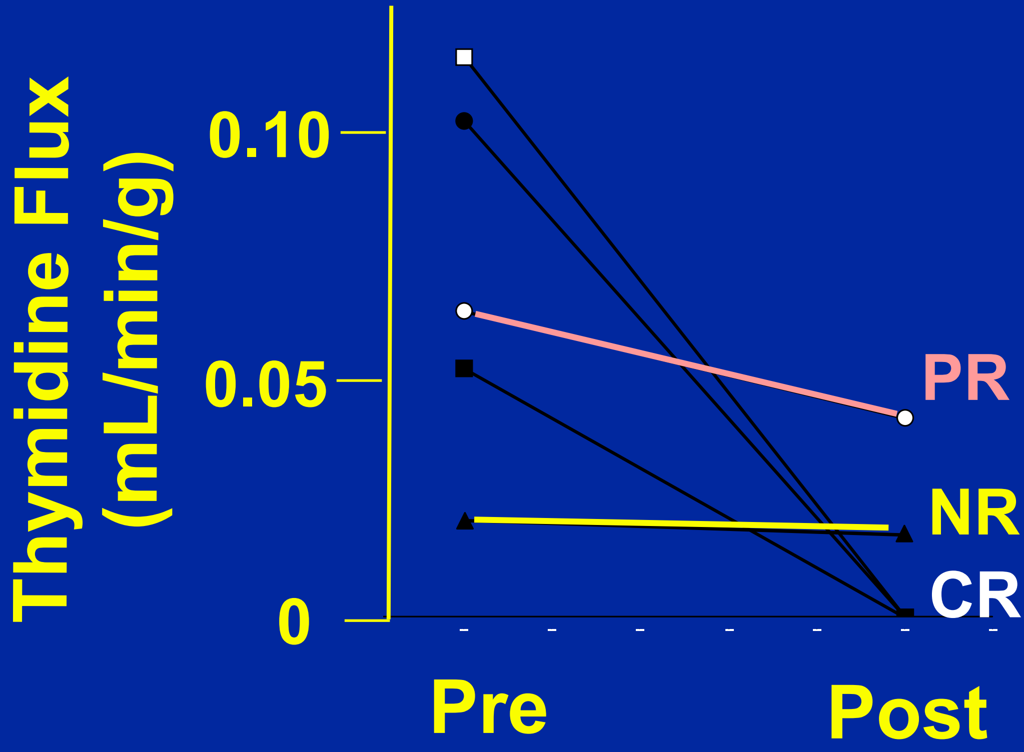
Small Cell Lung Cancer:

PET Imaging Pre-and Post One Cycle of Rx



^{11}C-Thymidine PET to Measure Response to Chemotherapy:

Thymidine Flux Pre-and Post One Cycle of Rx



(Shields, J Nucl Med, 1998)

Alternative to [^{11}C]-TdR: [^{18}F]-Fluoro-L-thymidine (FLT)

Thymidine

FLT

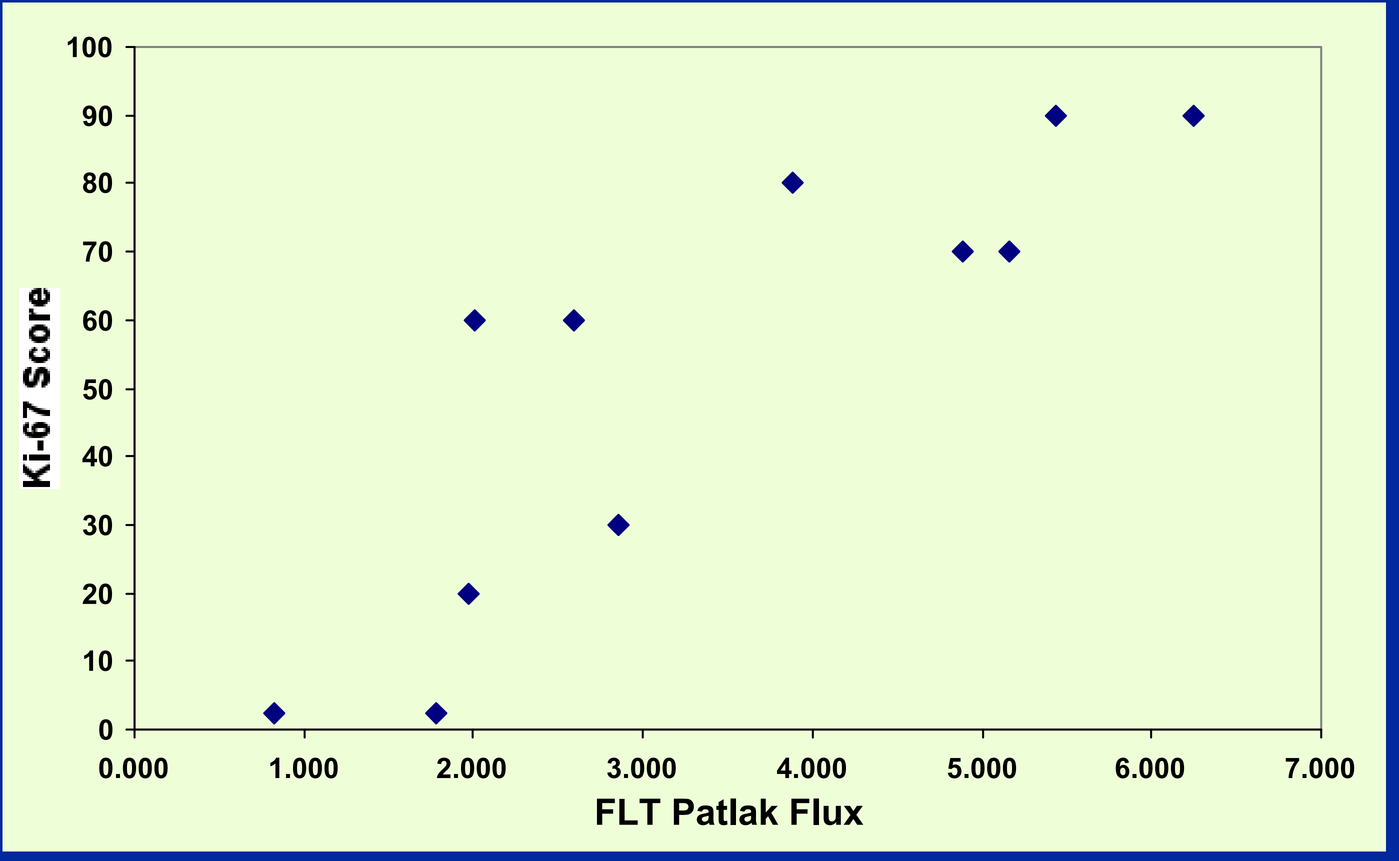
Not incorporated into DNA, but ...

minimal *in vivo* catabolism

(Grierson, Nucl Med Biol, 2000)

FLT as a Measure of Tumor Proliferation

FLT Flux versus Ki-67 Score



Spearman Rho = 0.94 , P < 0.0001; Pearson r = 0.86 , P = 0.0007

(Vesselle, Clin Ca Res, 2003)

Clinical Use of Molecular Imaging: Summary and Future Directions

- Driven by the goal of more individualized therapy
  - More specifically targeted
  - Less toxic
- Imaging will play a role in choosing therapy
  - Assess therapeutic targets
  - Identify resistance factors
- Better response monitoring will be key
  - Earlier measures of treatment efficacy
  - More specific measures of drug action
  - Quantitative surrogate endpoints for clinical trials
- The best is yet to come!

UW PET Cancer Imaging Research
Nuclear Medicine

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UW PET Cancer Imaging Research:
Key Collaborators

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- Thomas Lawton
- Jonathan Tait
- Allen Gown (Phenopath)

Biochemistry
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Cardiology/Bioengineering
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- James Caldwell

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- Gary Mann

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- Hannah Linden
- Robert Livingston
- Cheryl Pickett
- Ollie Press
- Scott Schuetze

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- David Schwartz
- Jeffrey Schwartz
- Mary Austin-Seymour