National Cancer Institute

Preoperative Therapy in Invasive Breast Cancer

Reviewing the State of the Science and Exploring New Research Directions

Research Issues: Imaging

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

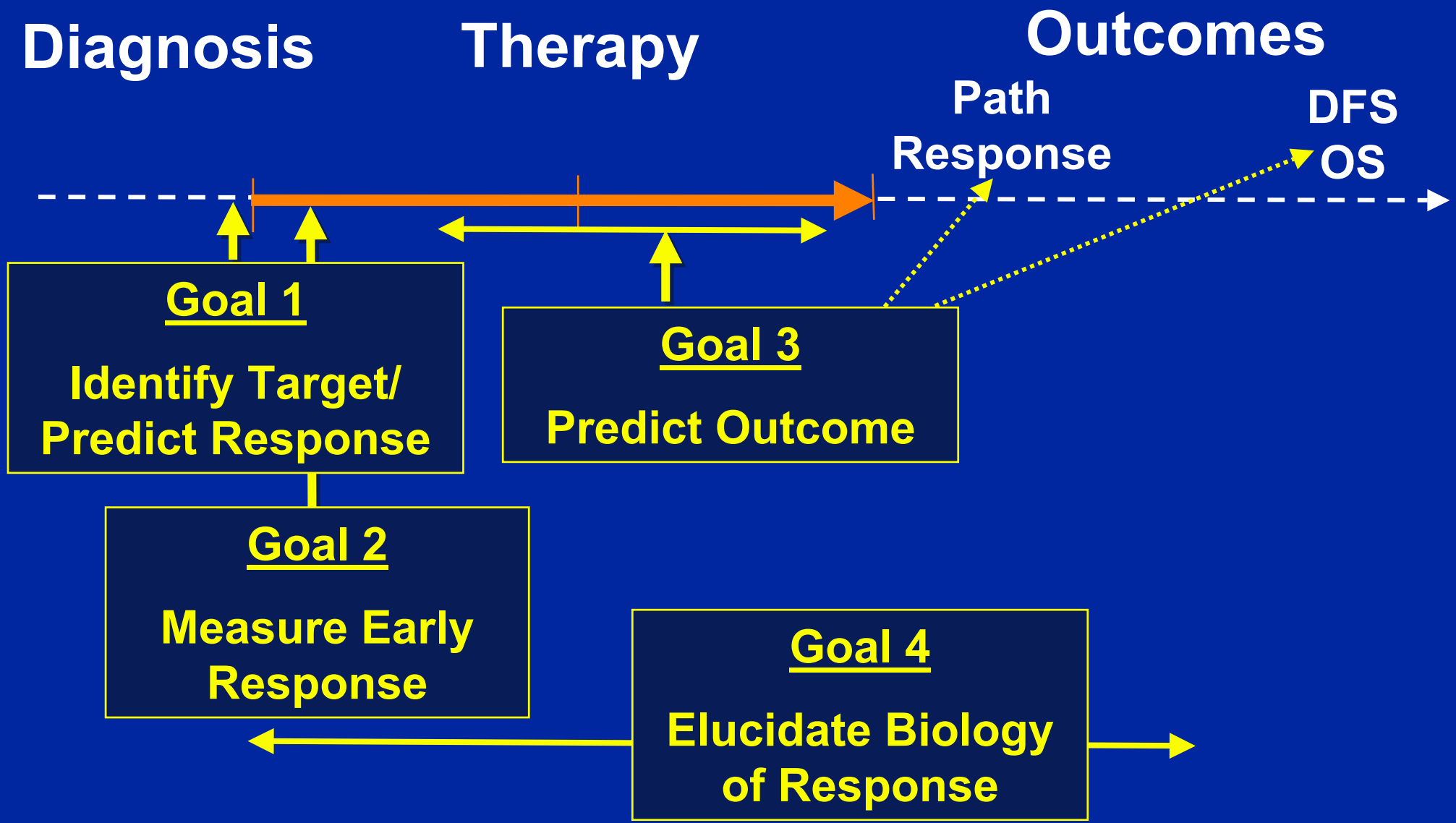
Imaging Research in Pre-Operative Therapy: Outline

- Research Goals
- What imaging tests are available?
- Examples of research imaging results
  - Target identification
  - Early response
  - Predicting cancer outcomes
  - Insights into biology of pre-op Rx
- Future Directions

Cautions

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

Pre-Op Therapy: Imaging Research Goals

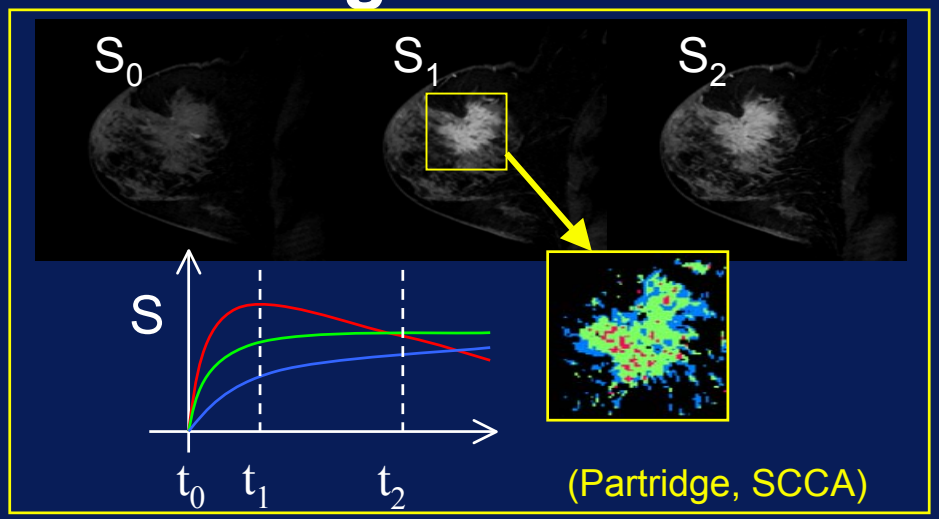


Imaging Modalities

- X-ray transmission - Computed Tomography (CT)
- Magnetic Resonance (MR)
  - Magnetic Resonance Imaging (MRI)
  - Magnetic Resonance Spectroscopy (MRS)
- Radionuclide imaging
  - Positron Emission Tomography (PET)
  - Single-Photon Emission Computed Tomography (SPECT)
- Ultrasound (U/S)
- Optical imaging

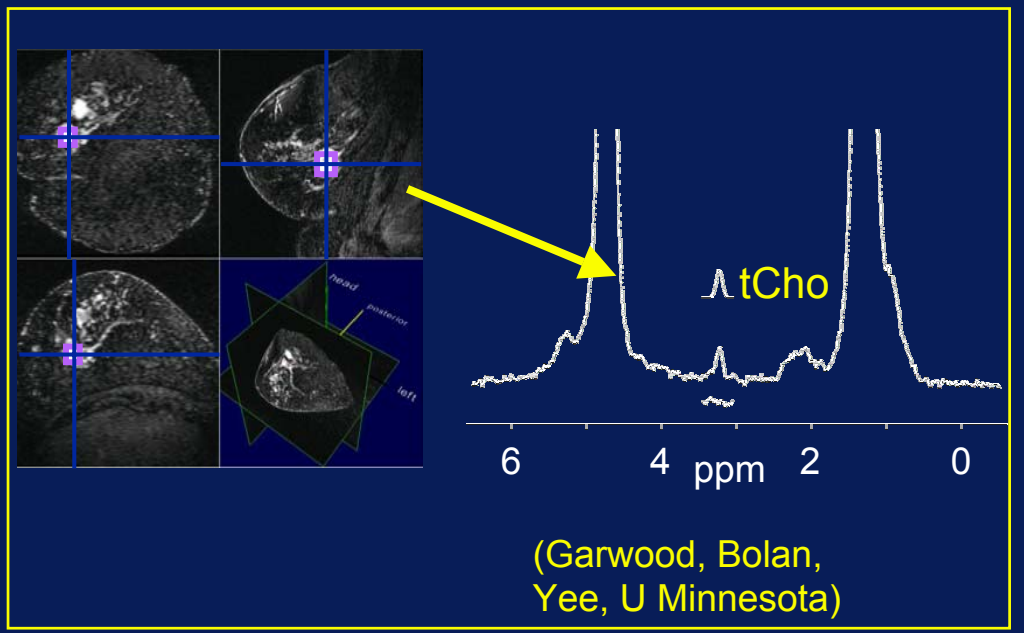
Imaging Modalities: MRI

- Creates 3D image related to proton environment
- Contrast can be made using atoms like Gd and Fe
- Novel measures possible - e.g., diffusion imaging
- Capability influenced by field strength - current clinical maximum 3T
- **Advantages**
  - High spatial resolution
  - No radiation dose
- **Disadvantages**
  - Confined environment, high magnetic field
  - Contrast possibilities limited by concentration needs and need for elements like Gd or Fe



Imaging Modalities: MRS

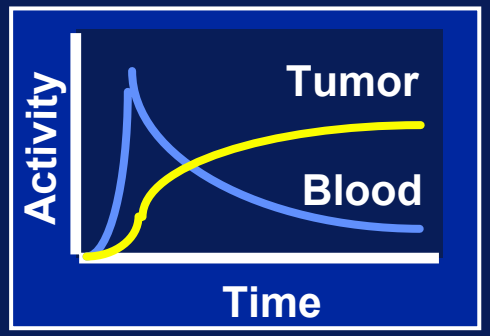
- Collects spatially localized MR spectra
- Calculates regional concentrations - e.g., choline
- With higher field strength, 3D voxel sets (i.e., images) possible
- **Advantages**
  - No contrast needed
  - Wide range of mols.
  - Many mols. at same time
- **Disadvantages**
  - Limited spatial resolution
  - Challenging data analysis



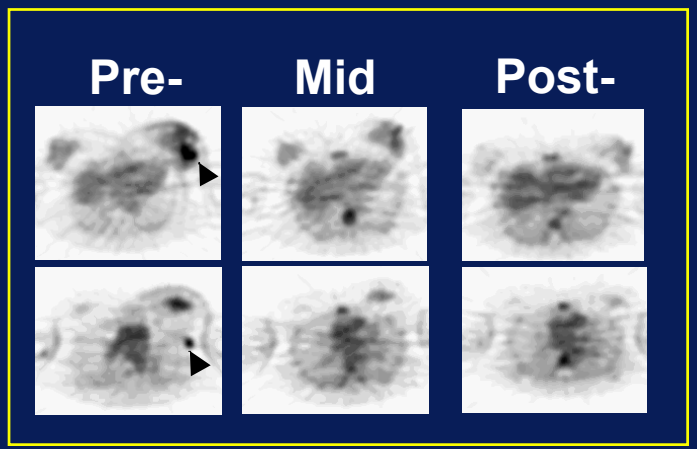
(Garwood, Bolan, Yee, U Minnesota)

Imaging Modalities: PET and SPECT

- Detects emission of administered radionuclides
  - SPECT: ^{99m}Tc, ^{123}I
  - PET: ^{11}C, ^{18}F
- 3D image of radionuclide concentration
- Dynamic imaging possible



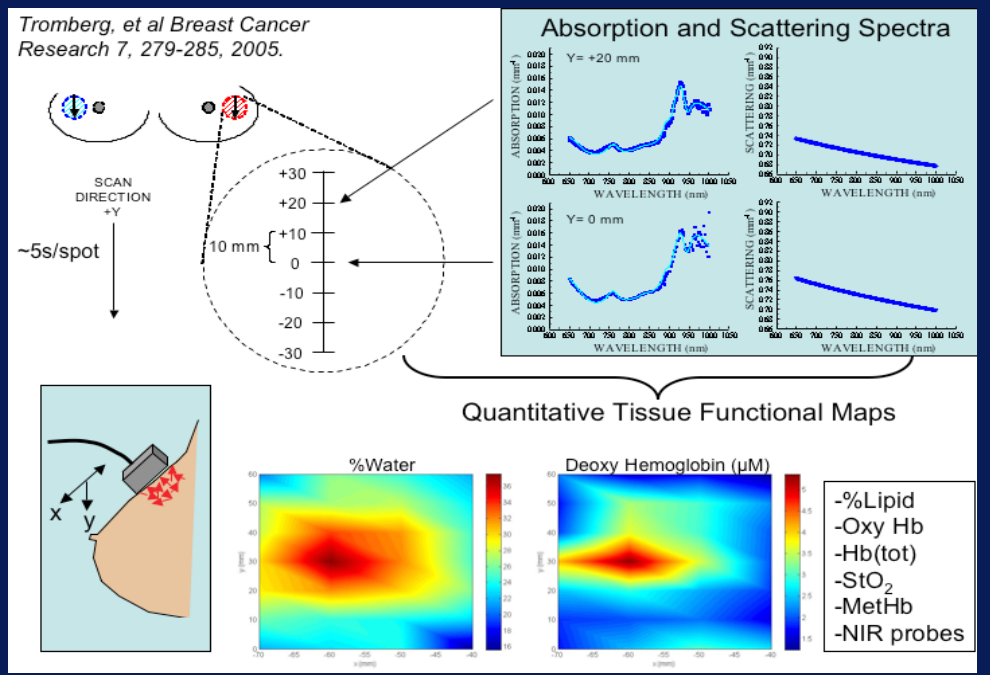
- **Advantages**
  - Sensitive - tracer conditions
  - Quantification - esp. PET
  - Wide range of mols. - esp PET



- **Disadvantages**
  - Limited spatial resolution/anatomy (PET/CT helps)
  - Some radiation dose (< diagnostic CT)

Imaging Modalities: Optical

- Imaging based upon visible light
- Can use transmitted or reflected light
- Can use light emitted by contrast agent or embedded molecule - bioluminescence, near-infrared spectroscopy
- **Advantages**
  - Highly portable
  - Inexpensive
  - Minimally invasive
  - Molecular contrast agents
- **Disadvantages**
  - Limited penetration

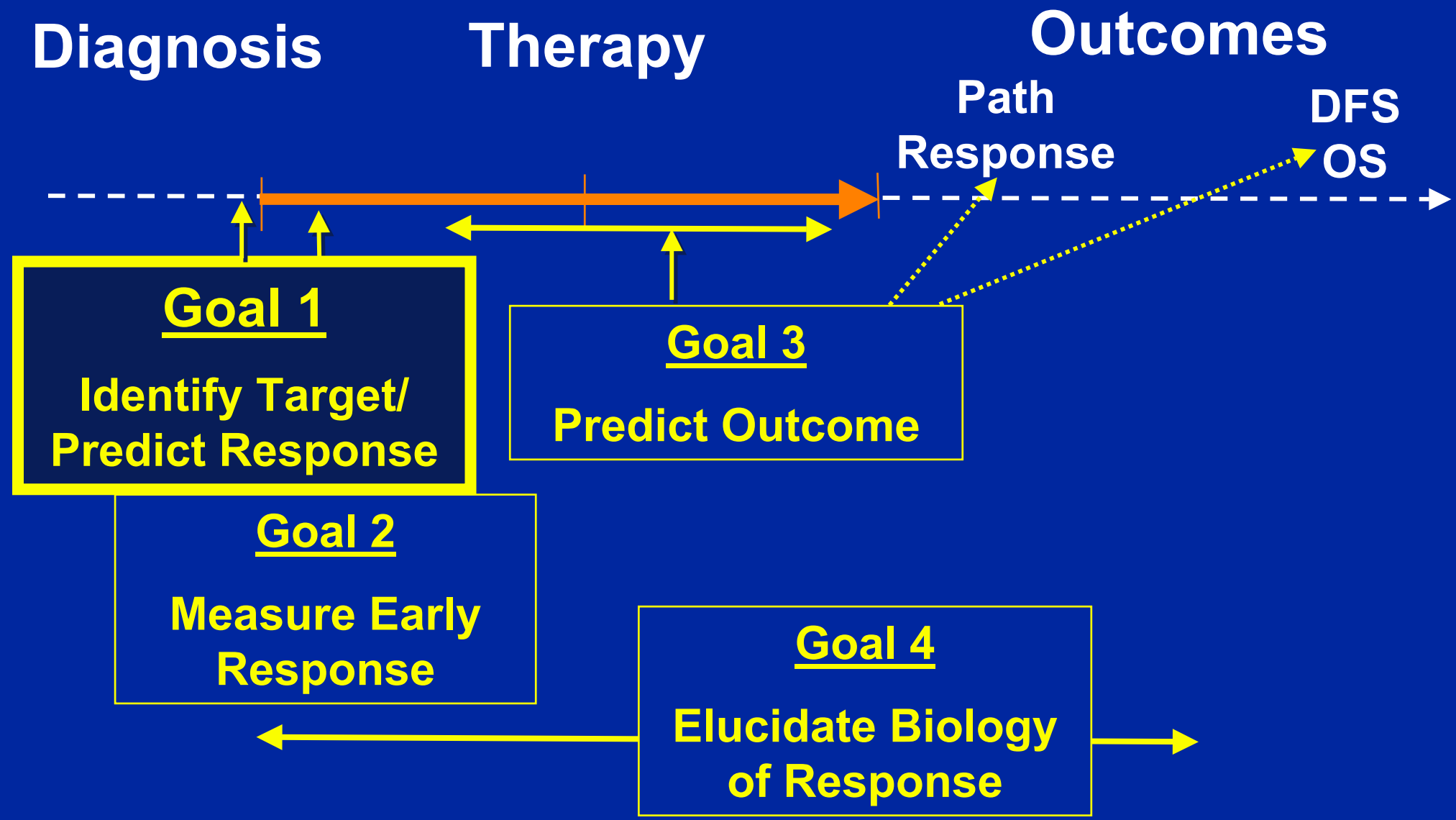


(Tromberg, UCI)

Imaging Studies: Burden to Patient

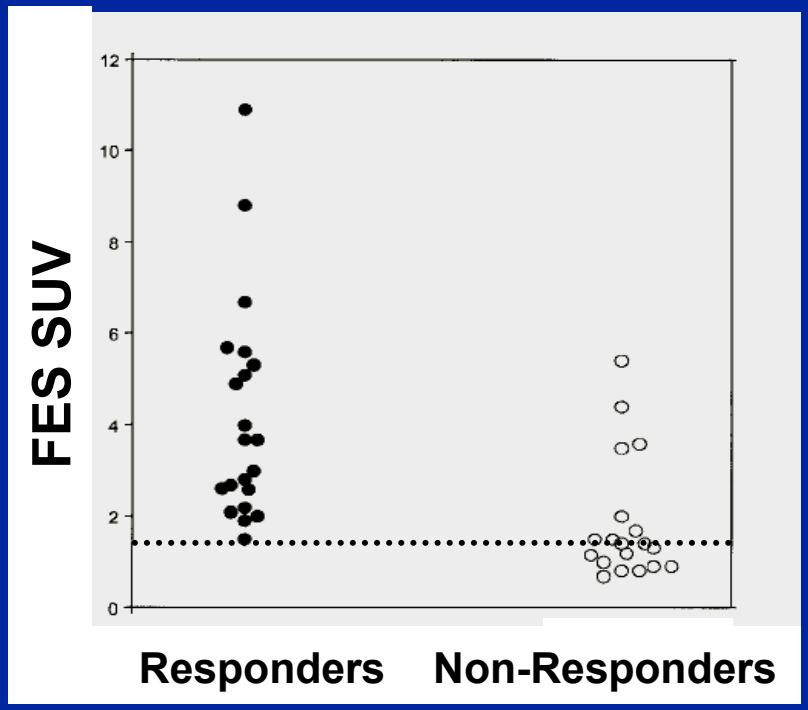
Study	Time	Other
MRI	30 - 60 min	IV, closed space
MRS	15 - 30 min	closed space
PET/SPECT	30 - 90 min	IV, radiation
Ultrasound	15- 30 min	
Optical	5 - 30 min	

Pre-Op Therapy: Imaging Research Goals

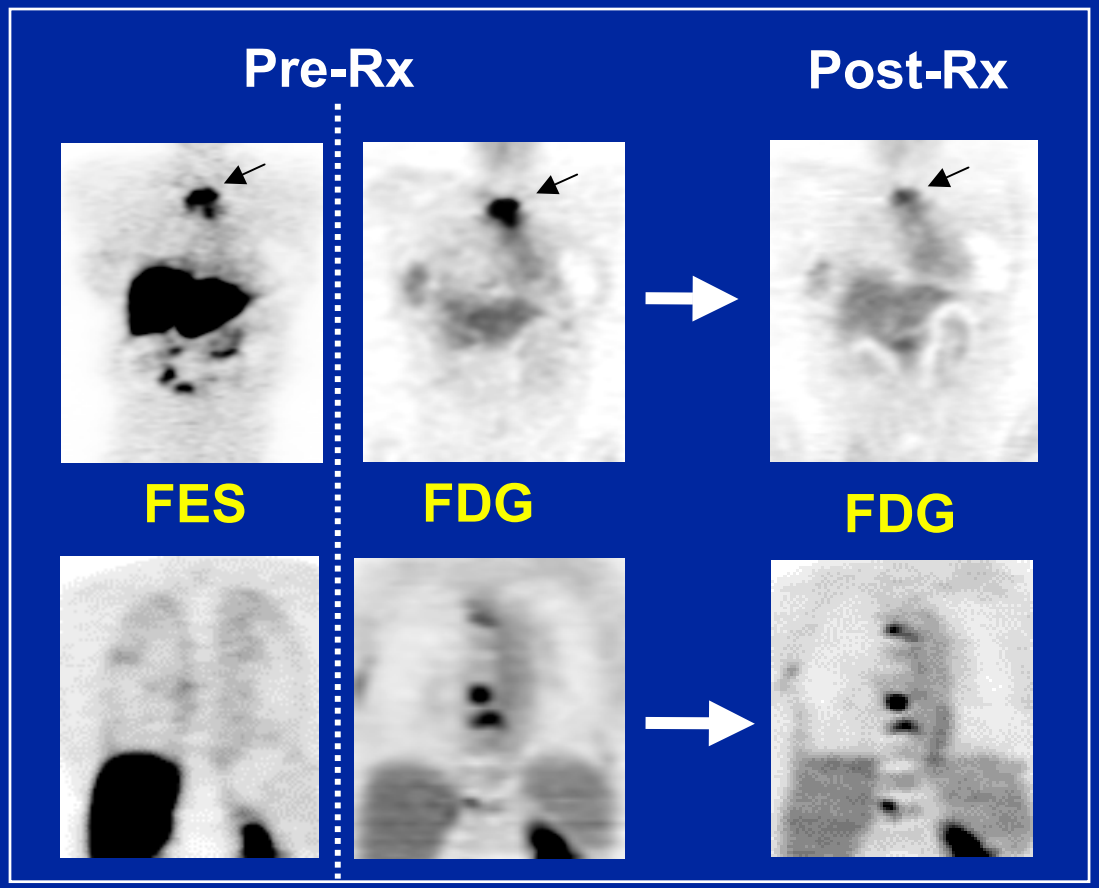


^{18}F-Fluorestradiol (FES) PET

Measures Target for Endocrine Therapy



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



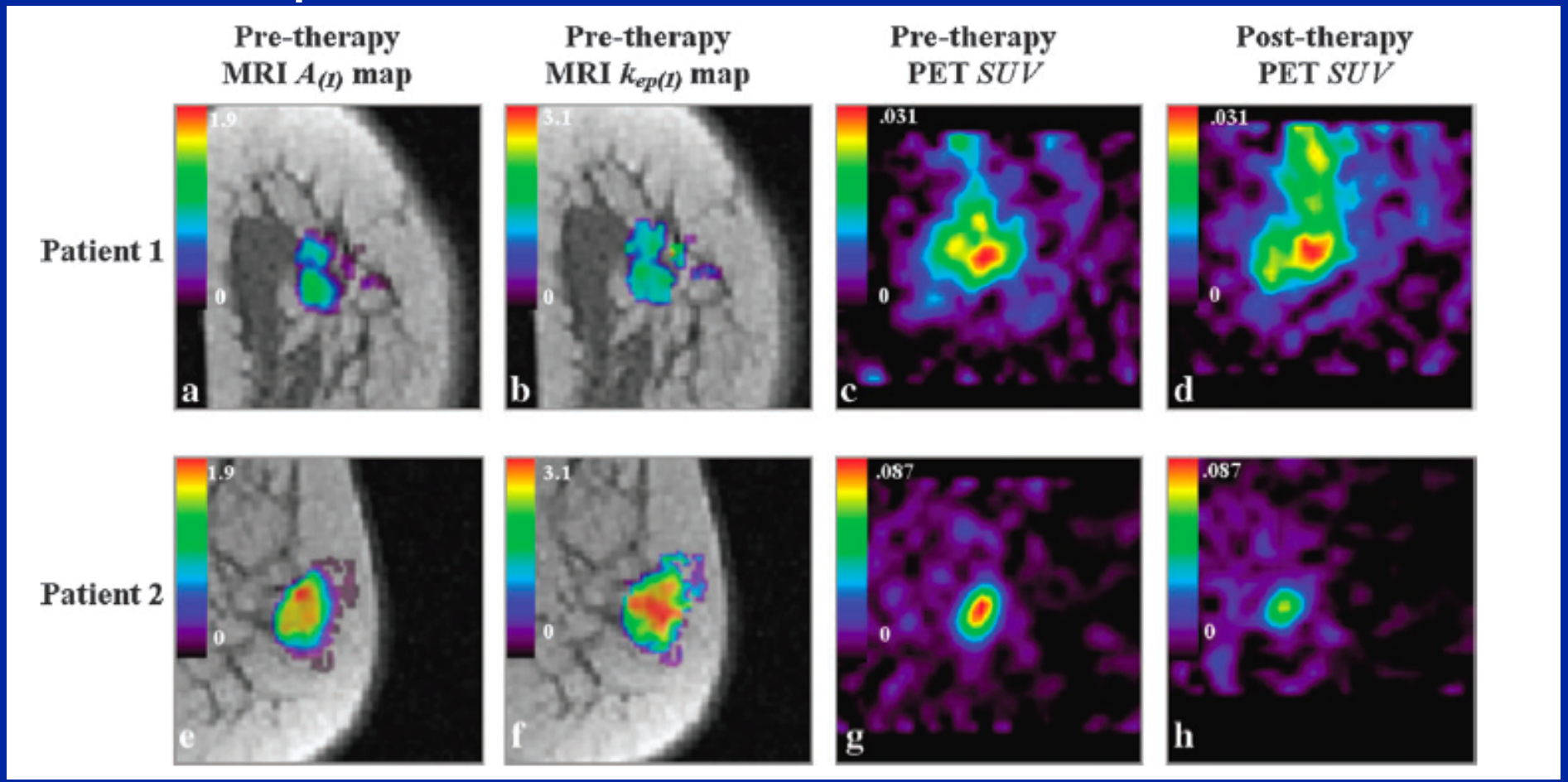
(Linden, J Clin Onc, 24: 2793, 2006)

Vascular Parameters from DCE-MRI MRI Predict Response to Pre-Operative Chemotherapy

Enhancement Amplitude

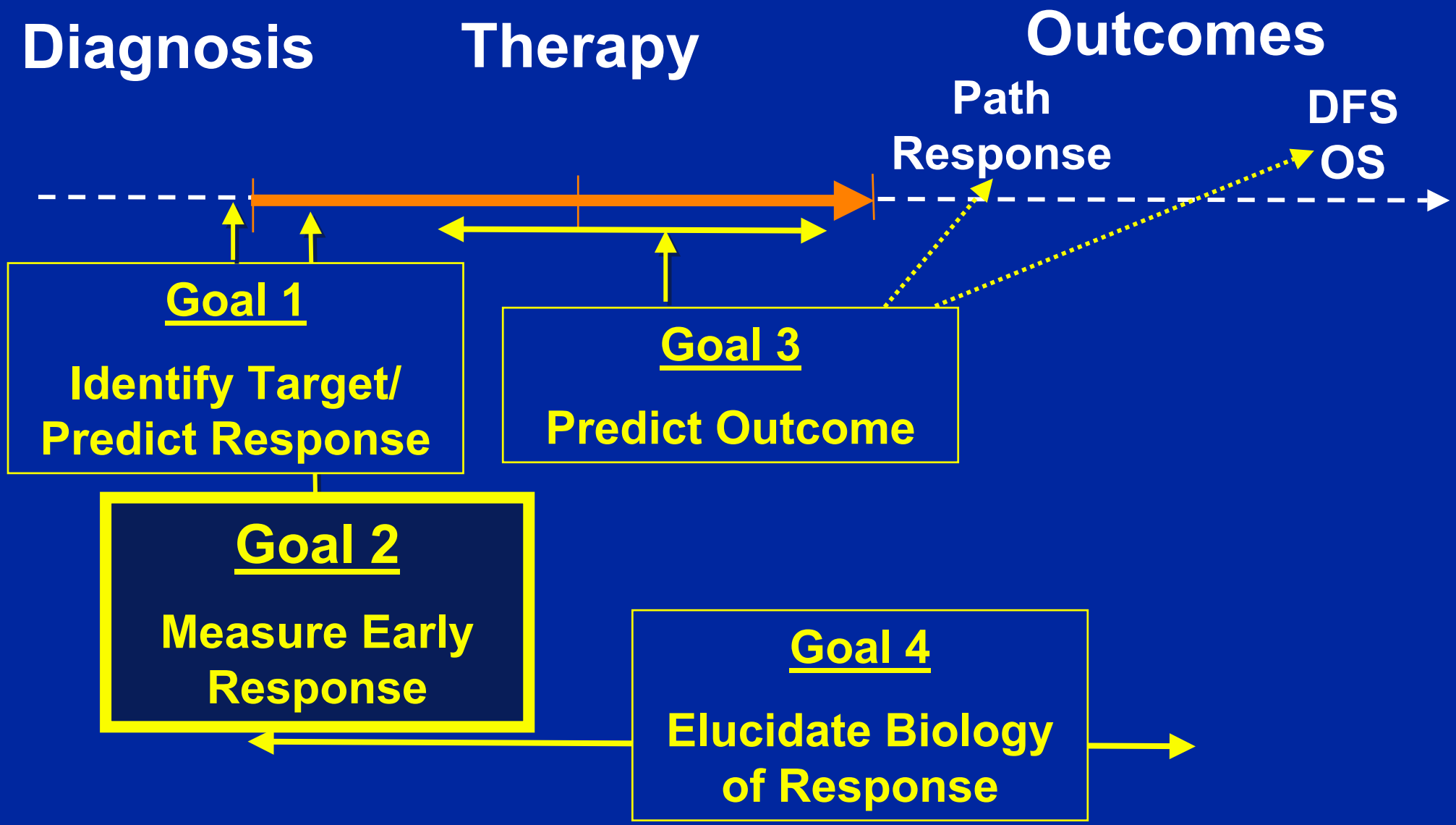
Transfer Constant

← FDG SUV Change →

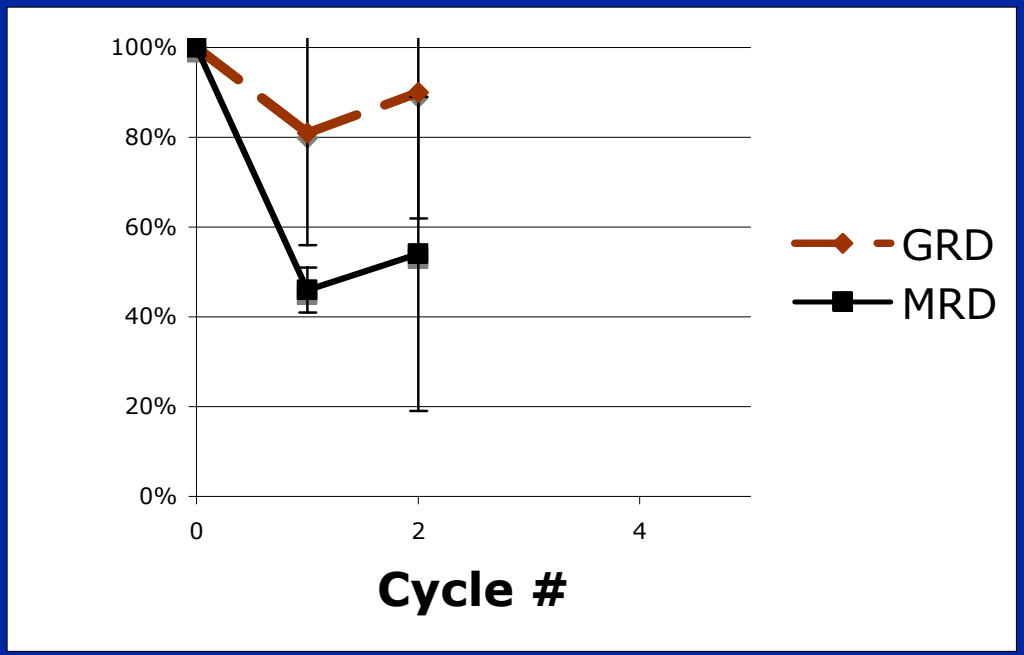


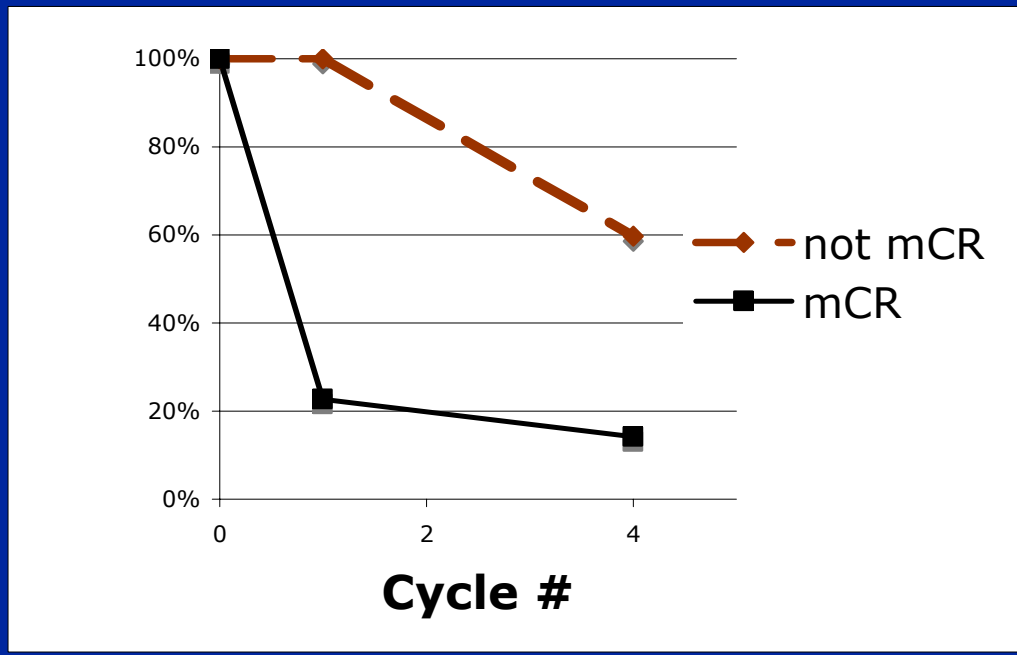
(Semple, Annals Oncol, 17: 1393, 2006)

Pre-Op Therapy: Imaging Research Goals



Early Response to Neo-Adjuvant Chemotherapy of Breast Cancer
FDG PET





Schelling, J Clin Oncol 2000; 18:1689

EC or ET q ??

17 - GRD; 7 - MRD

Smith, J Clin Oncol 2000; 18:1676

CVAP q 21 days

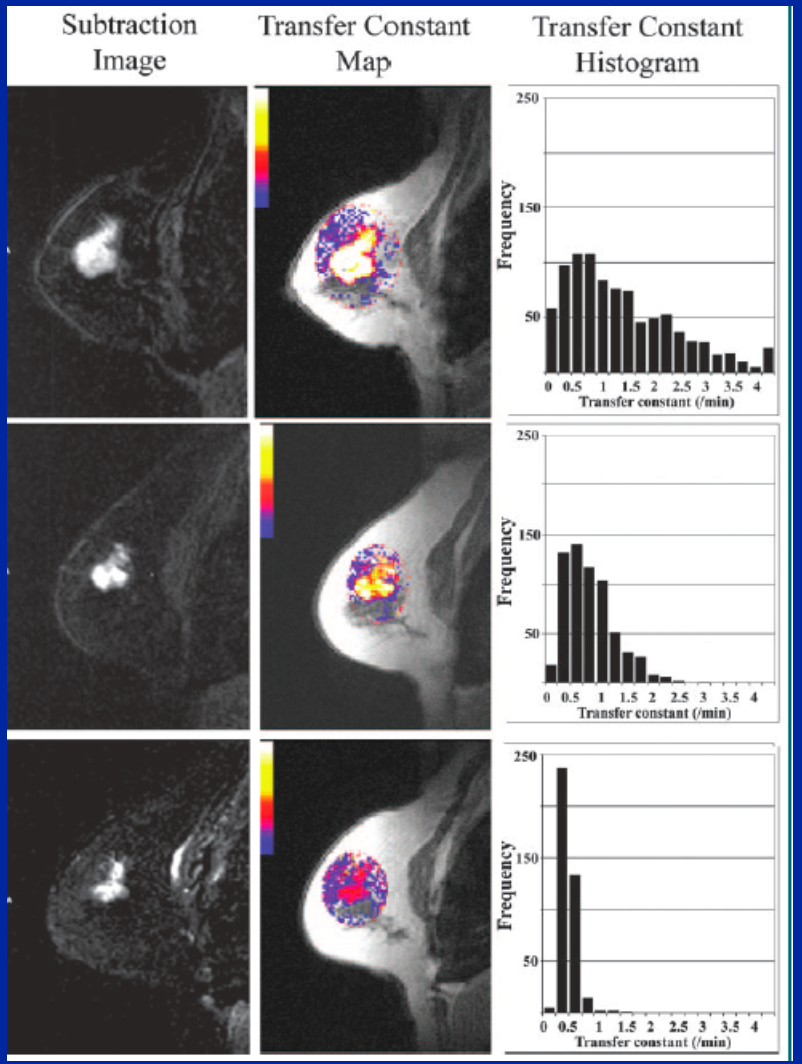
Not mCR - 20; mCR - 11

Changes in DECE-MRI Enhancement Kinetics Predict Response

Pre-Rx

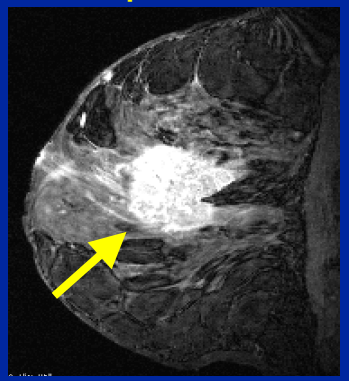
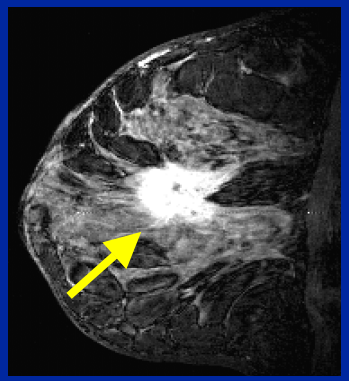
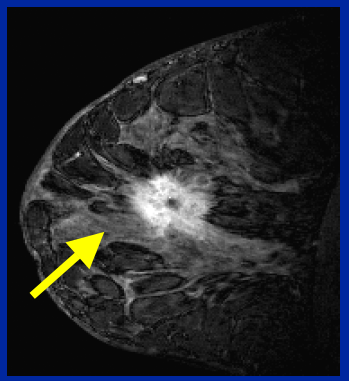
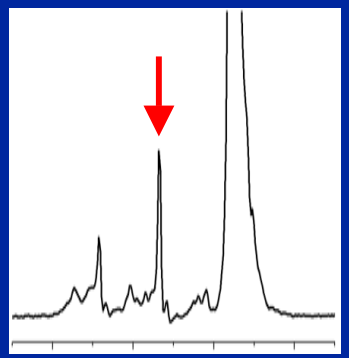
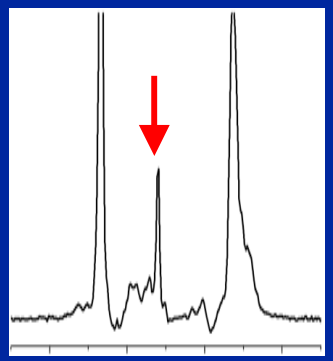
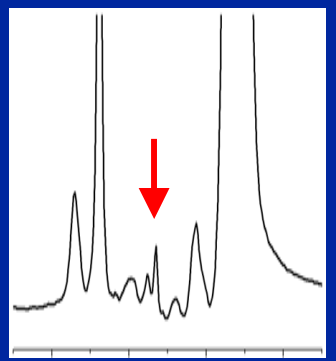
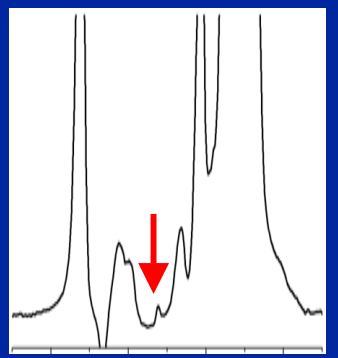
1 Cycle

2 Cycles



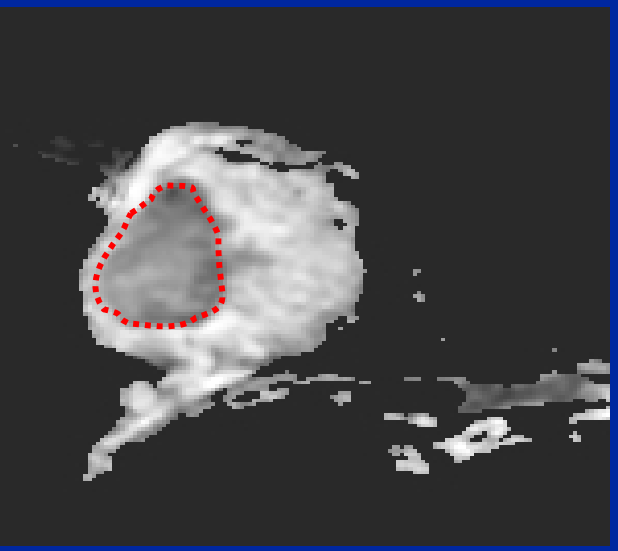
(Padhani, Radiology, 239: 361, 2006)

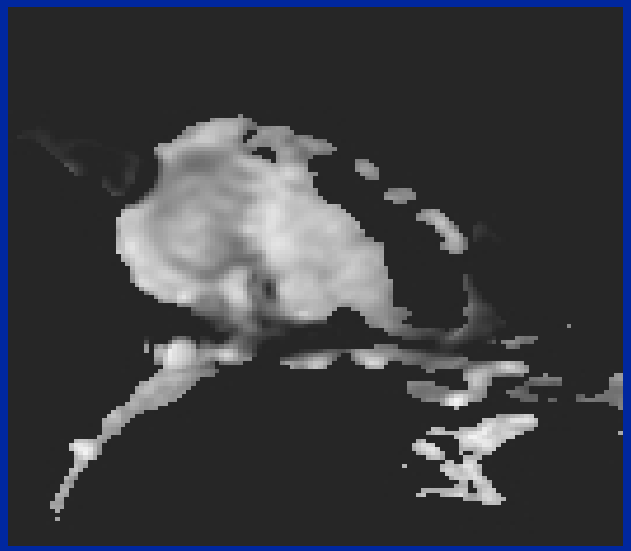
Chemotherapy Response by MRI & MRS
University of Minnesota

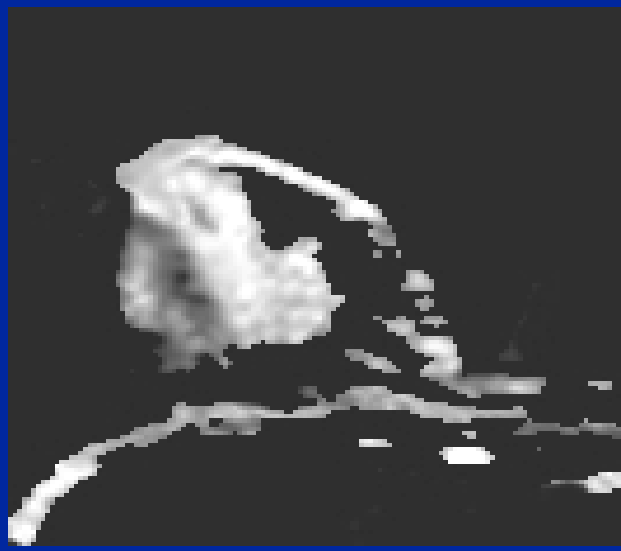
1 wk pre-Tx	Day 1 AC x1	Day 42 AC x3	Day 70 AC x4
			
			
Cho: (μmol/g) **4.6**	**3.7**	**1.6**	**0.9**
LD: (cm) **4.0**	**4.0**		**1.7**

Meisamy S et al. Radiology 233:424-431 2004

Diffusion MRI: ADC Map of Breast Cancer Therapy







Pre-therapy **II NACT** **III NACT**

	ADC	Water mobility
Normal	↑	↑
Pre therapy	↓	↓
Post therapy	↑	↑

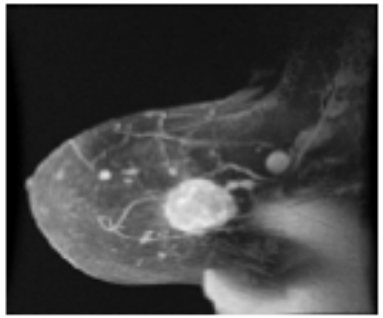
NR Jagannathan AIIMS,
New Delhi

Monitoring Chemotherapy: MRI/Optics

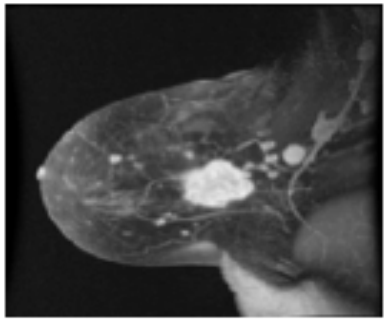
B. Tromberg, N. Hylton *et al.* J. Biomed. Opt. 10, 051503 (2005)

DCE- MRI

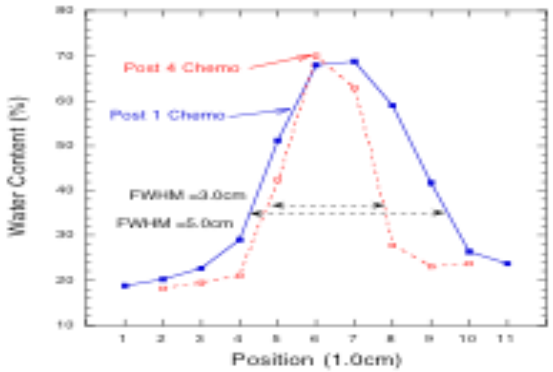
Post 1 cycle

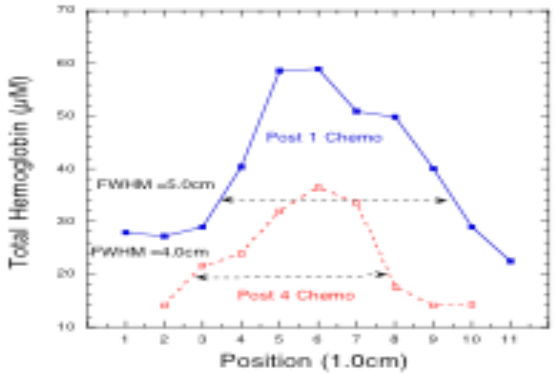


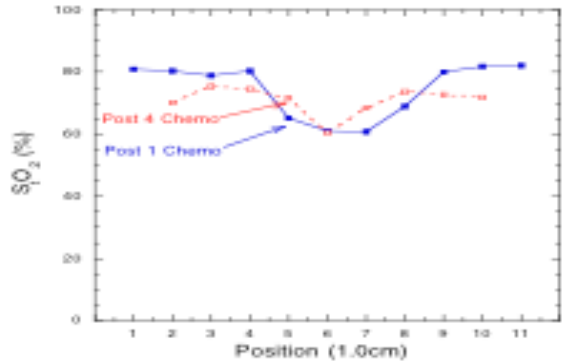
Post 4 cycles

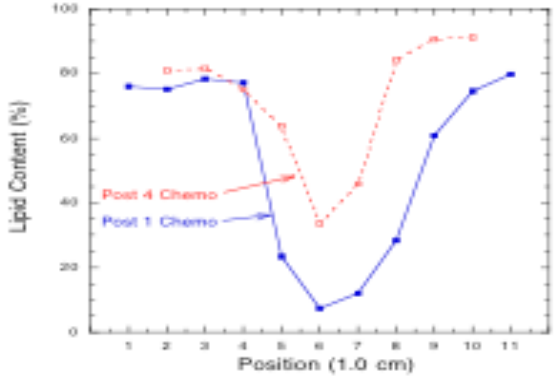


Optical Line Scan

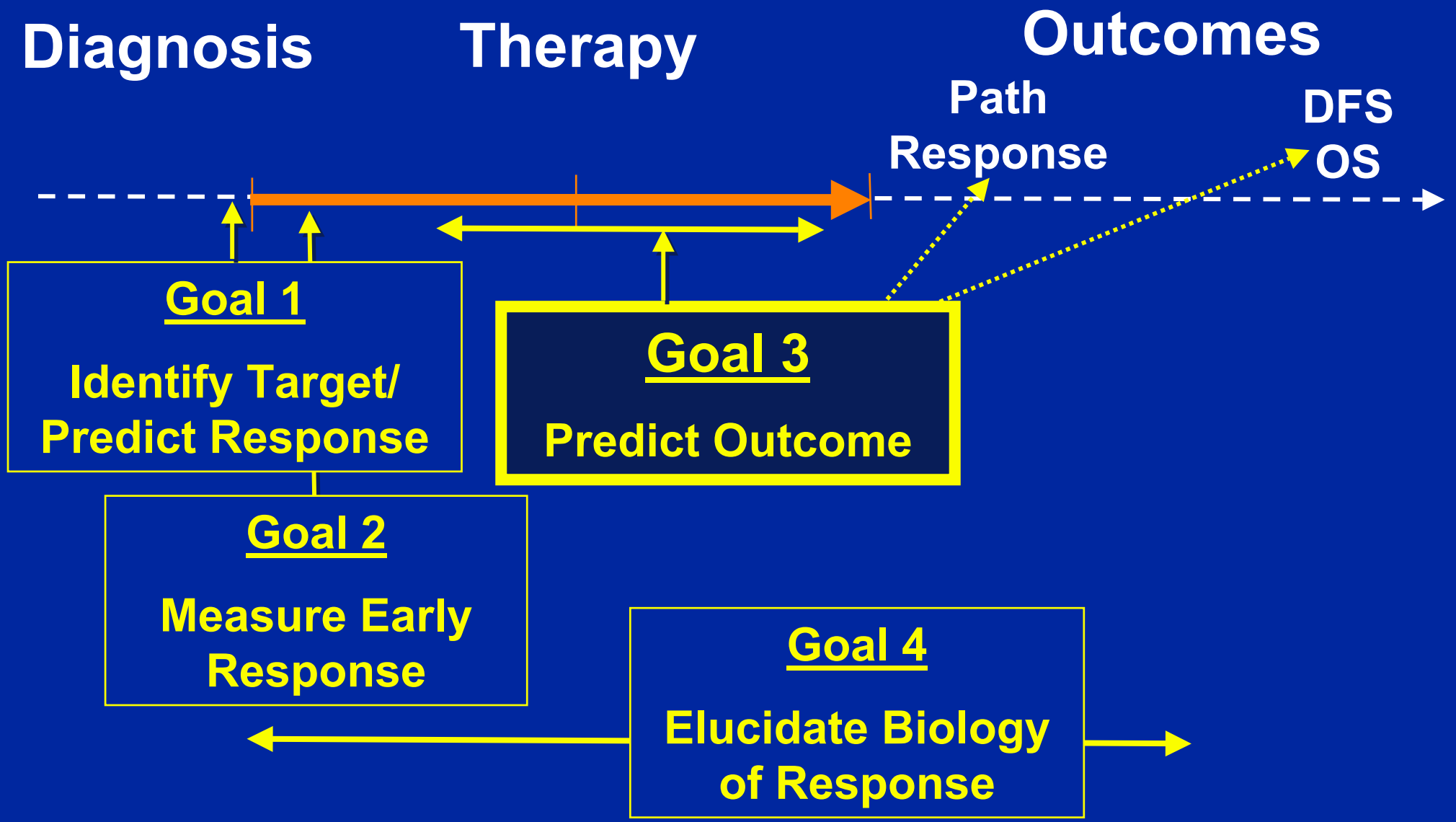








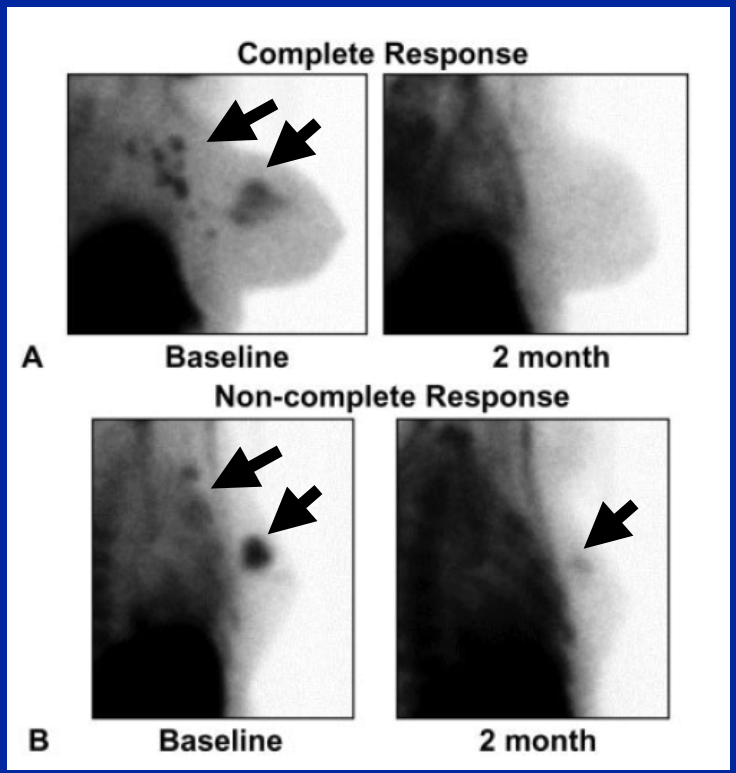
Pre-Op Therapy: Imaging Research Goals



Functional Imaging Predicts Outcome

^{99m}Tc-MIBI Serial Imaging

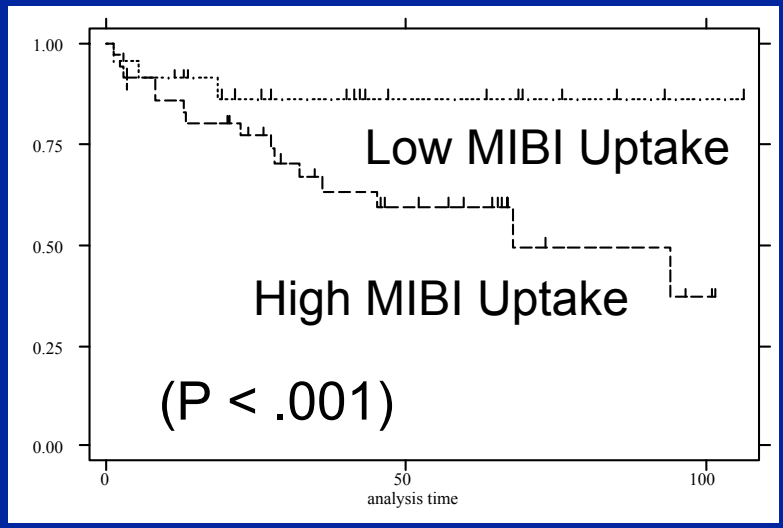
Change in Uptake Predicts Response



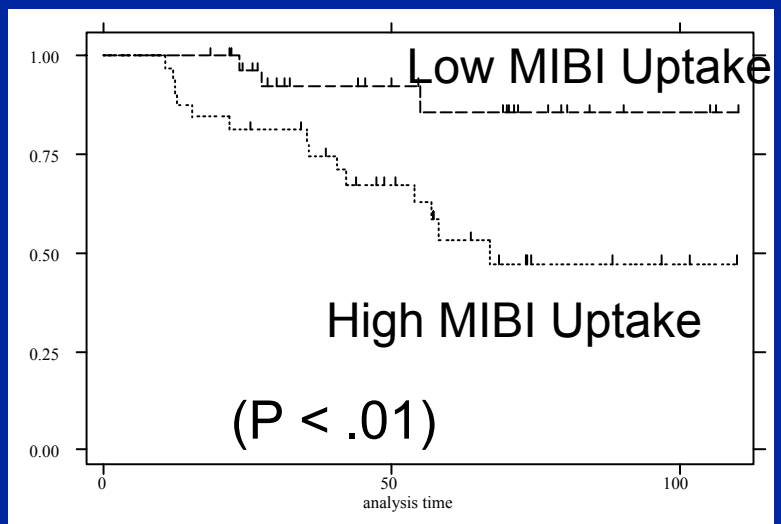
(Dunnwald, Cancer, 103: 680, 2005)

Residual Uptake Predicts Outcome

Disease-Free Survival



Overall Survival



Residual MIBI Uptake Versus DFS

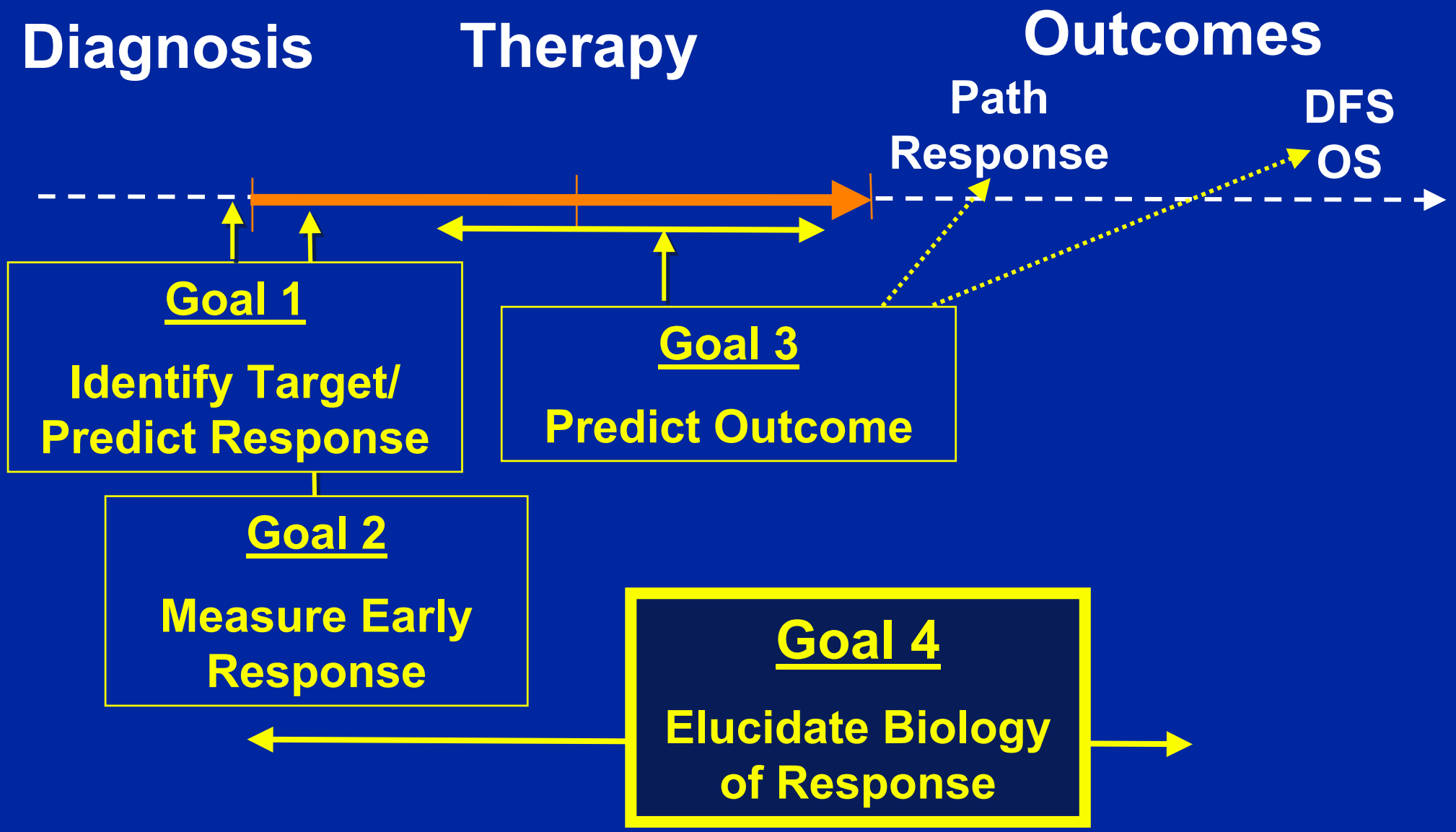
Comparison to Established Markers (Dunnwald, Cancer, 103:680, 2006)

Characteristic	Log-rank P-value	HR
ER Status	0.12	2.0
HER2 Overexpression	0.66	1.2
Ki-67	0.02	3.0
Primary Tumor Path CR	0.05	3.1
Axillary nodes (> 3)	0.19	1.8
Two month MIBI ratio	0.05	1.2**
Final MIBI ratio	0.001*	1.3**

* Multi-variate model P-value = 0.01

**Continuous variable, HR per unit change

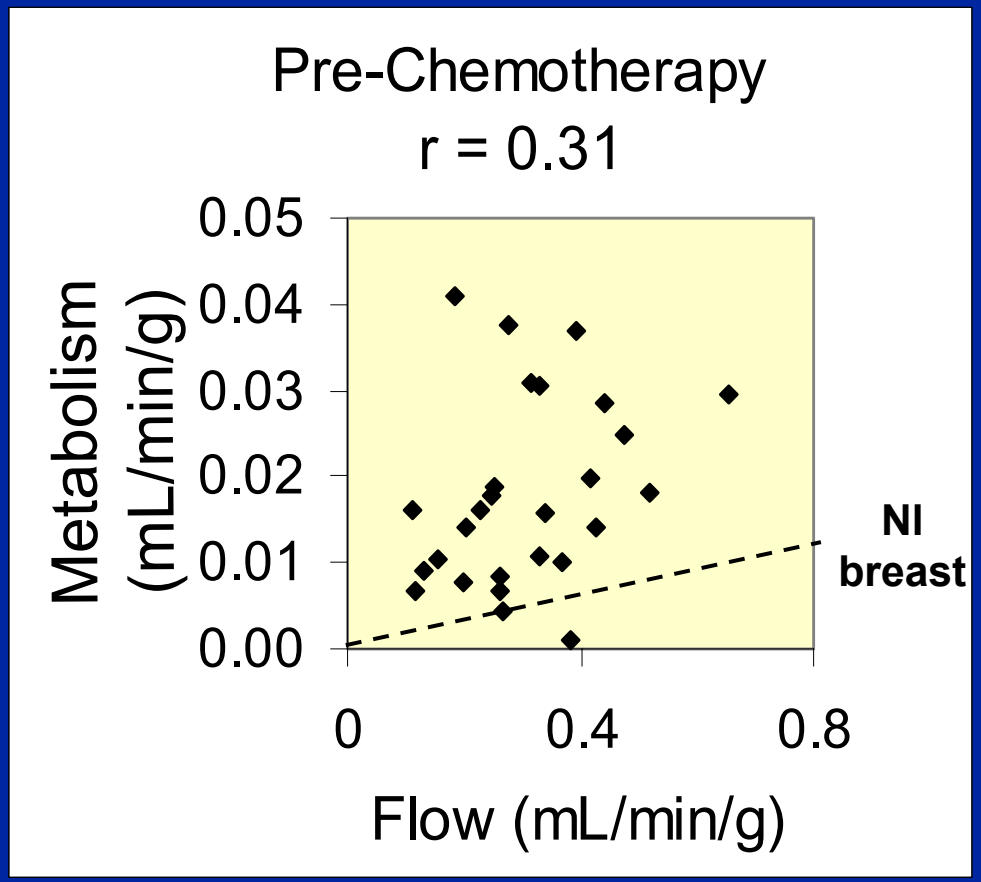
Pre-Op Therapy: Imaging Research Goals

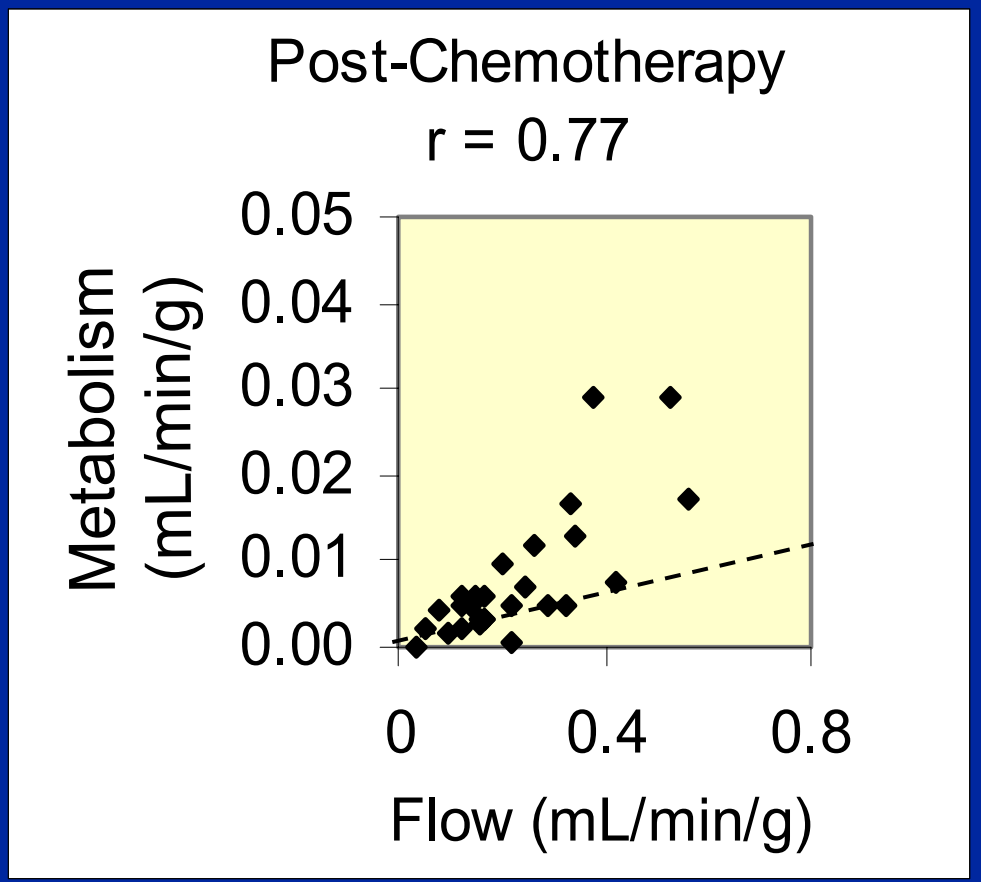


Metabolic Phenotype: Change with Therapy?

Shift Towards More Balanced Substrate Delivery and Utilization

Glucose Metabolism (FDG K_i) vs Blood Flow

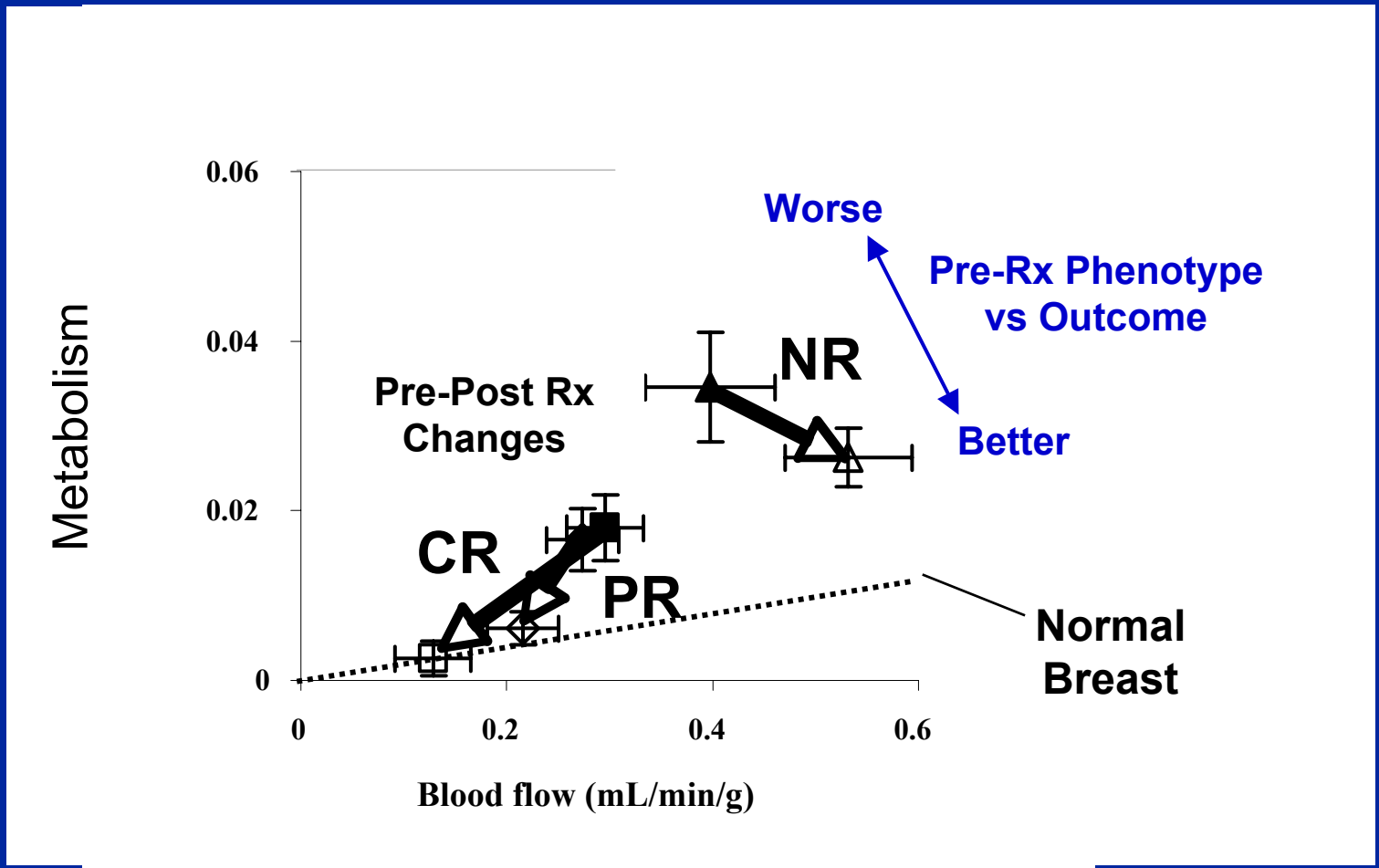




(Tseng, J Nucl Med, 45:1829, 2004)

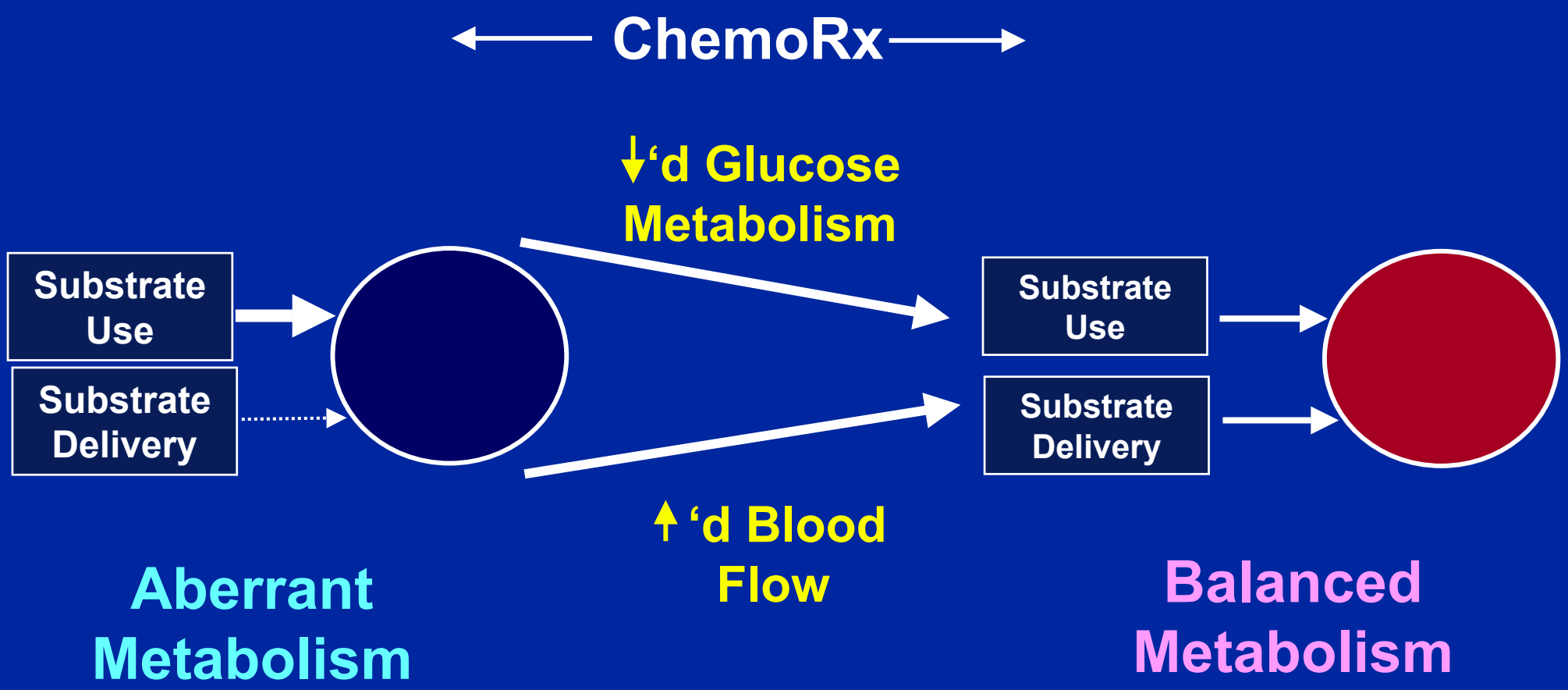
Blood Flow and Metabolism Patterns of Change with Neo-Adjuvant Chemotherapy

Altered Metabolic Phenotype with Rx



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

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



Imaging Research: Summary

- Variety of modalities
  - Increasing ability to measure biochemical, molecular, and cellular process
- Goals - clinical endpoints
  - Predict response/guide therapy selection
  - Measure response early
  - Predict outcome - surrogate endpoint
- Goals - biologic insights
  - Measure in vivo tumor biology of cancer Rx
  - Translational: Laboratory findings <--> clinical framework