

# PREOPERATIVE THERAPY IN INVASIVE BREAST CANCER

Reviewing the State of the Science and Exploring New Research Directions

## Breast Imaging to Monitor the Response to Treatment

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# OVERVIEW

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- Conventional imaging methods for evaluating response (mammography and ultrasound)
- Emerging role of MRI for monitoring treatment response
- Functional imaging methods as in-vivo biomarkers (DCE-MRI, PET)

# Conventional imaging: agreement with pathological residual disease size

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- No large prospective studies evaluating conventional imaging
- Small studies have shown variable results for agreement between imaging and pathology
- Retrospective analysis of conventional imaging and physical exam in MD Anderson neoadjuvant chemotherapy trials (*Chagpar et al, Ann Surg, 2006*)
  - Included a comparison of published studies

# Conventional imaging for measuring treatment response

## MD Anderson study

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- 189 patients participating in 1 of 2 NACT trials
- Single direction tumor diameter measured by physical exam (PE), ultrasound (US) and/or mammography
- Residual disease size by imaging and physical exam compared to residual pathologic tumor size

# Correlation of Tumor Measurements

Comparison	Correlation Between Measurements*	
	Preneoadjuvant Chemotherapy	Postneoadjuvant Chemotherapy
PE vs. US	0.45	0.28
PE vs. M	0.40	0.26
US vs. M	0.58	0.35
PE vs. pathology	--	<b>0.42</b>
US vs. pathology	--	<b>0.42</b>
M vs. pathology	--	<b>0.41</b>

\*Spearman rank correlation coefficients.  
PE indicates physical examination; US, ultrasonography; M, mammography

Only moderate correlation of imaging with pathologic residual disease, similar among imaging methods.

Correlations between imaging measurements decreased from pre- to post-treatment.

# Agreement with pathology by size category (0, 0.1-1.0, 1.1-2.0, > 2.0 cm)

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Clinical measurement	Weighted Kappa
Physical Exam	0.24
Ultrasound	0.30
Mammography	0.35

Poor agreement between clinical measurements and pathologic measurements

# False negatives and false positives rates

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<b>Clinical measurement</b>	<b>False Positive Rate (%)</b>	<b>False Negative Rate (%)</b>
Physical Exam	20% (5/40)	57% (73/127)
Ultrasound	65% (26/40)	10% (14/137)
Mammography	46% (16/35)	20% (24/119)

Ultrasound had highest rate of false positives; physical exam had highest rate of false negatives.

# Correlation with pathologic tumor size among other published studies

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<b>Study</b>	<b>n</b>	<b>Physical Exam</b>	<b>Ultrasound</b>	<b>Mammography</b>
Fourouhi et al (1994)	35	0.88	0.96	0.94
Gawne-Caine et al (1995)	16	0.74	0.85	0.61
Herrada et al (1997)	100	0.73	0.60	0.65
Akashi-Tanaka et al (2001)	57	0.57	0.56	0.55
Fiorentino et al (2001)	141	0.68	0.29	0.33
Chagpar et al (2006)	189	0.42	0.42	0.41

Correlation is highly variable among studies; close correspondence within studies.



# Accuracy of conventional imaging for estimating residual disease:

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- Imaging correlation with pathology only fair ( $r^2 = .41-.42$ )
- **No strong evidence that mammography or US perform significantly better than physical exam for measuring estimating residual disease after chemotherapy**
  - Large prospective trials (NSABP B18, B27) have not incorporated imaging for measuring response, but have relied on physical exam

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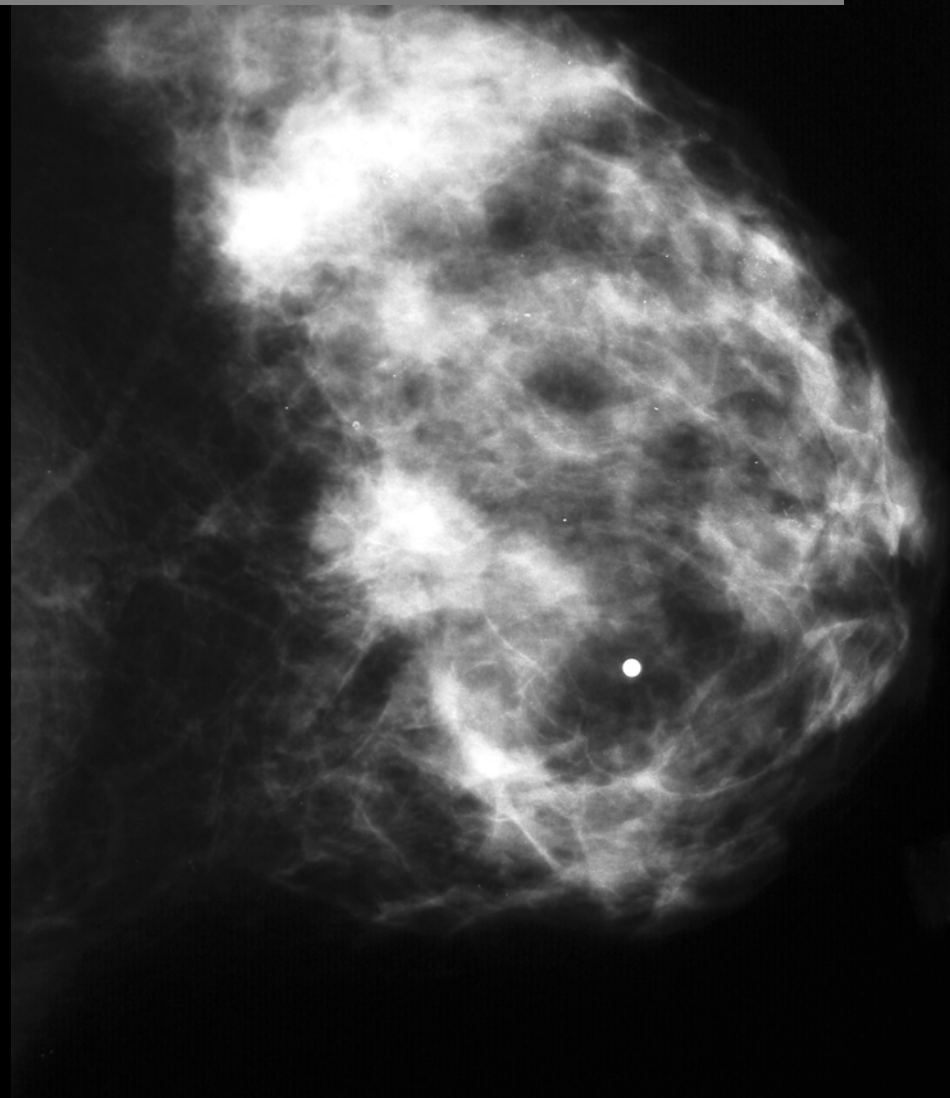
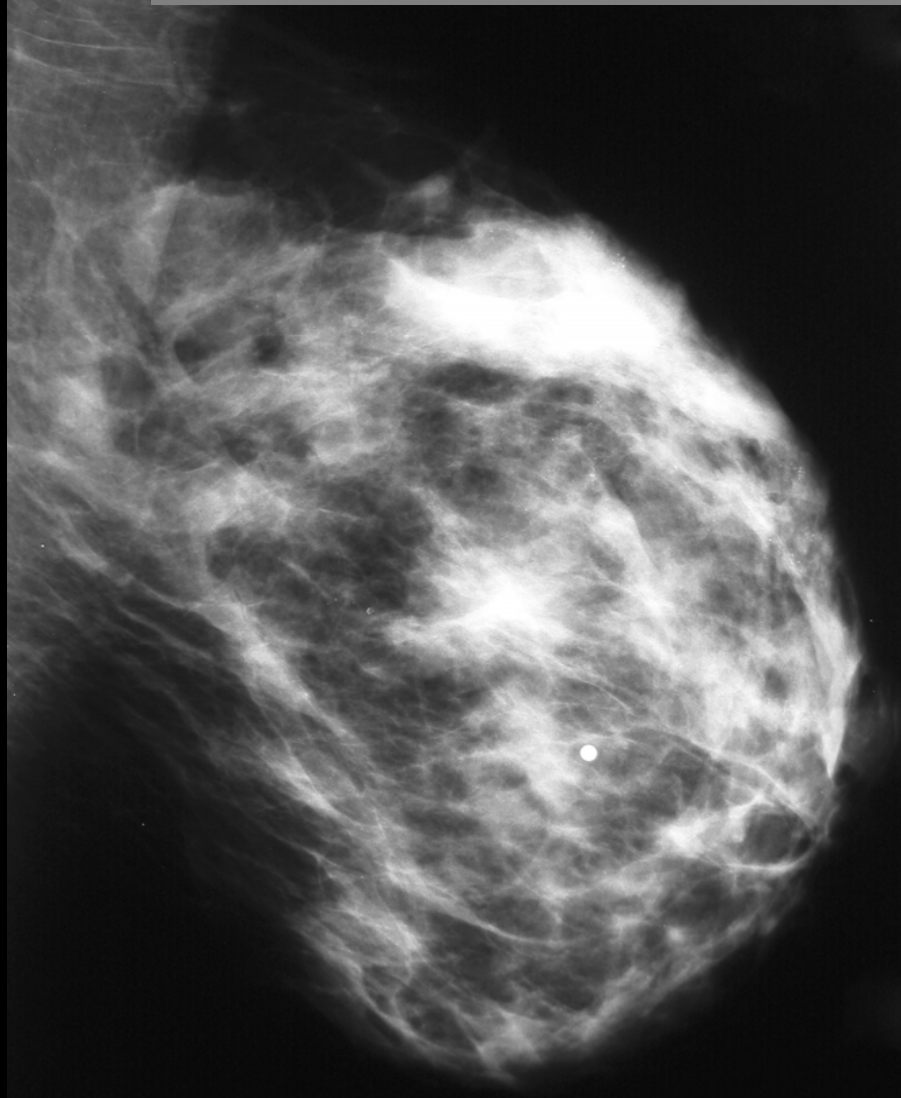
# Breast MRI for assessing residual disease and response to treatment

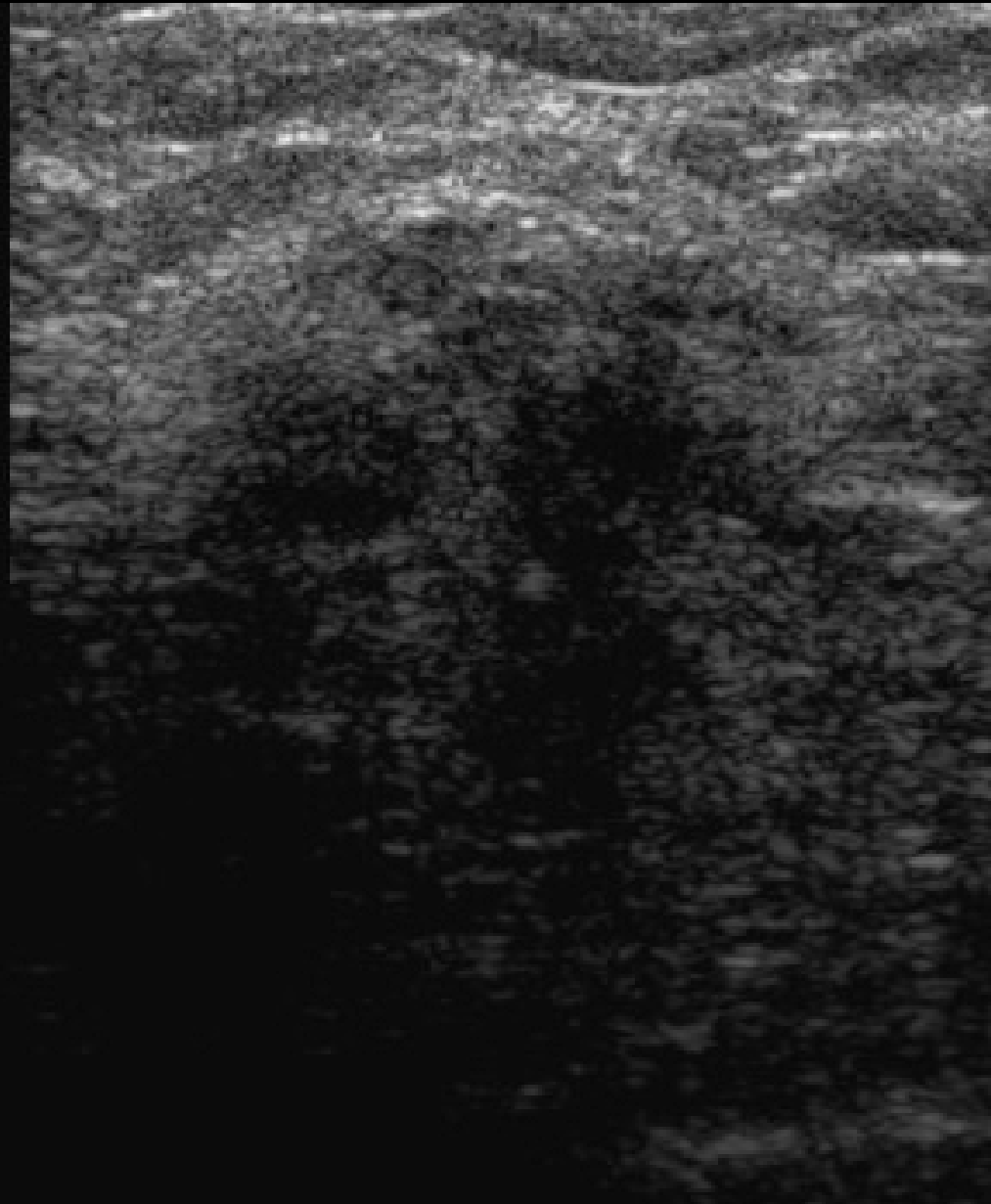
# Breast MRI for staging extent of disease pre-treatment

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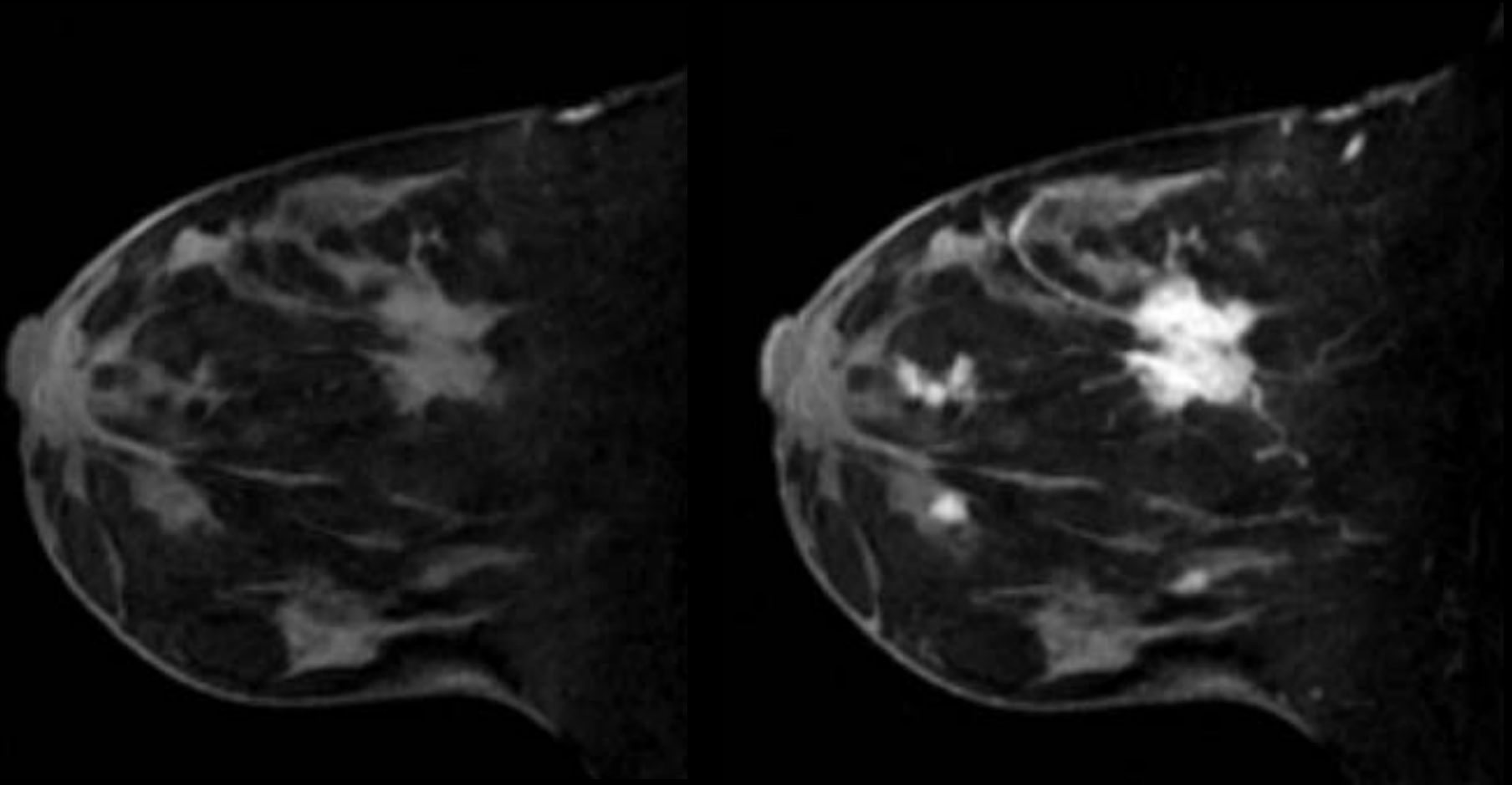
- MRI prior to chemotherapy has shown greater accuracy than mammography and ultrasound for estimating disease extent, particularly when multi-focal disease or DCIS is present

*Example: patient with a palpable mass; dense breast; mammography shows a spiculated mass and area of suspicious calcifications*

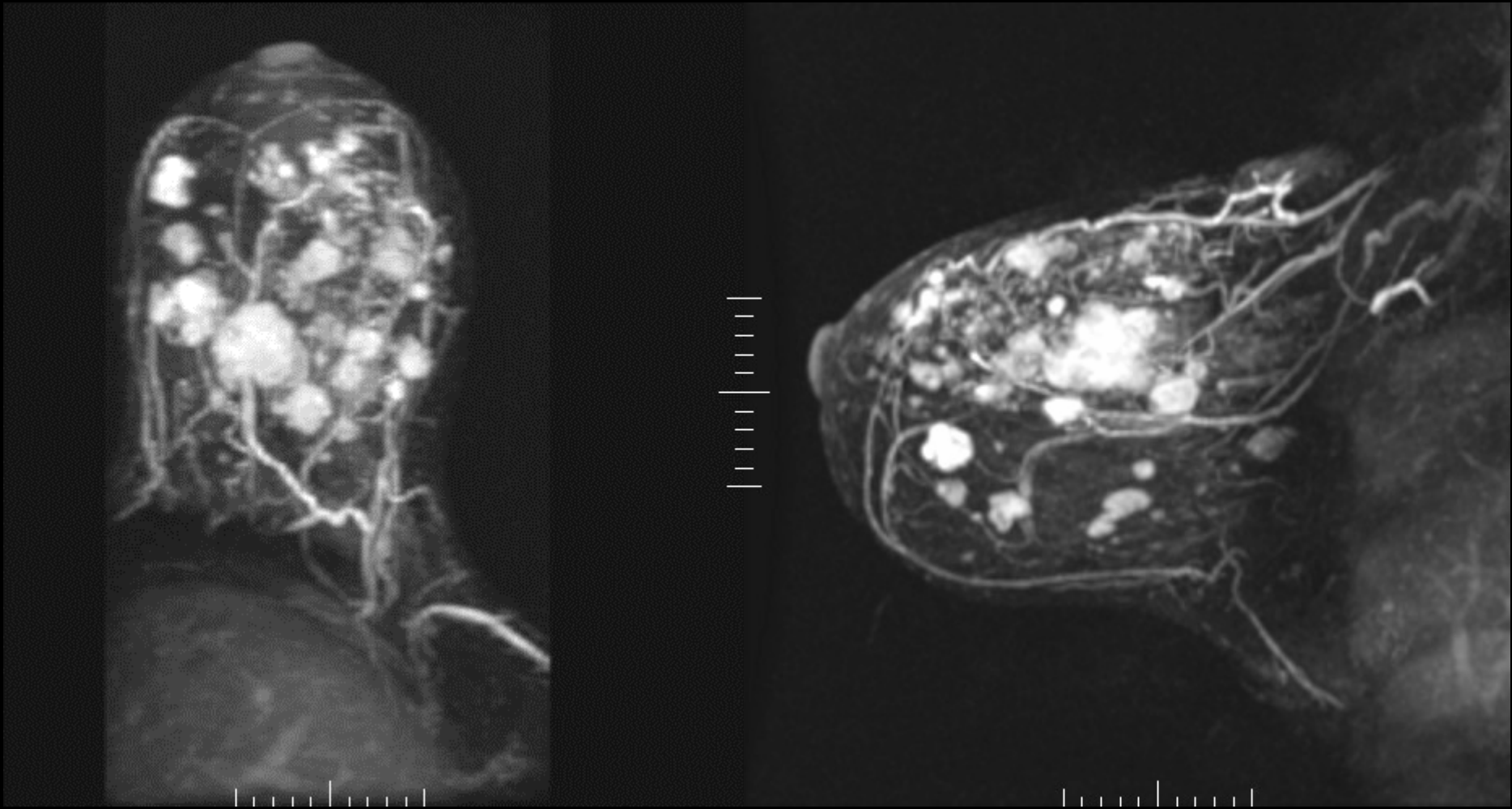




*Hypo-echoic, spiculated mass on ultrasound*



*Multiple enhancing masses on MRI*



*Extensive multi-focal and multi-centric disease*

# Breast MRI for staging residual disease post-treatment

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- MRI following chemotherapy is less effective, but still performs with greater accuracy than conventional imaging or clinical exam



# MRI versus conventional imaging for estimating residual disease

Study	n	MRI	Physical Exam	Mammo	US
Weatherall et al (2001)*	20	0.93	0.72	0.63	--
Rosen et al (2003)*	21	0.75	0.61	--	--
Akazawa et al (2006)*	38	0.89	--	--	0.48
Montemurro et al (2005)*	21	0.82	--	--	0.71
Balu-Maestro et al (2002)†	51	63%	52%	38%	43%
Yeh et al (2005)†	31	71%	19%	26%	35%

\*Comparison given by correlation coefficient.

†Comparison by concurrence criteria.

Consistent finding showing greater agreement of MRI with pathology compared to PE and conventional imaging.

# MRI false negatives post-treatment

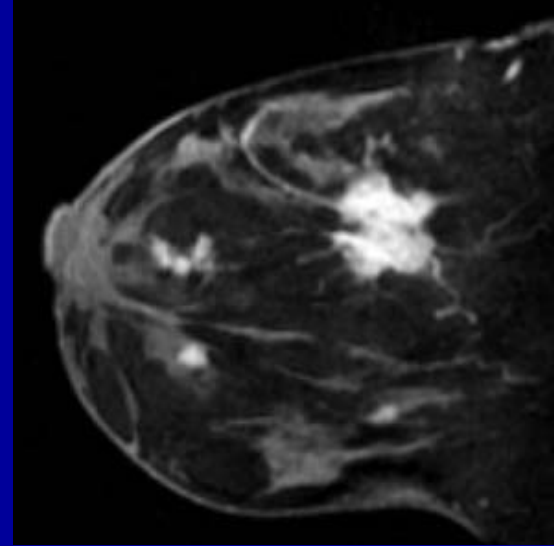
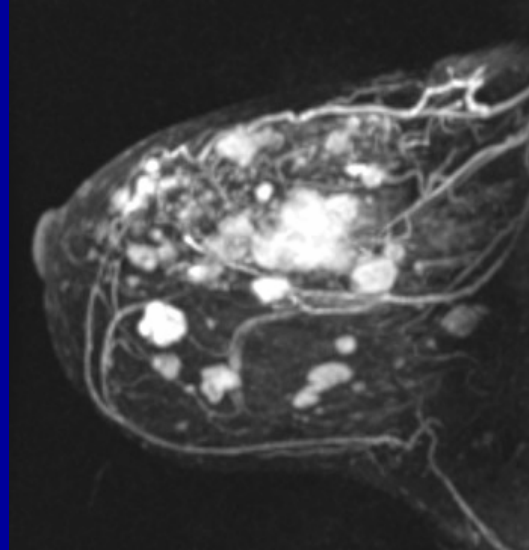
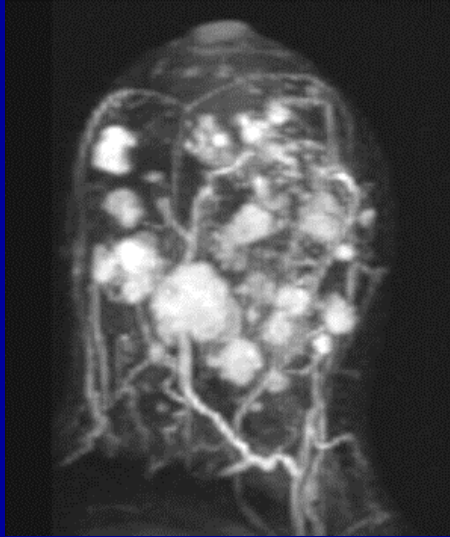
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- MRI is effective for measuring the degree of tumor response, but can miss residual disease, particularly for good responders
  - *Denis et al, EJSO 2004; Wasser et al, Eur Radiol 2003; Warren et al, Br J Cancer, 2004, Yeh et al, AJR 2005*
- Complete response on post-chemotherapy MRI cannot be used to rule out surgery

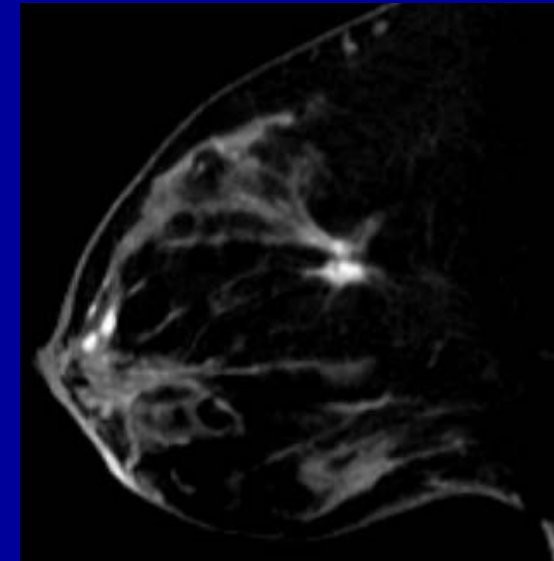
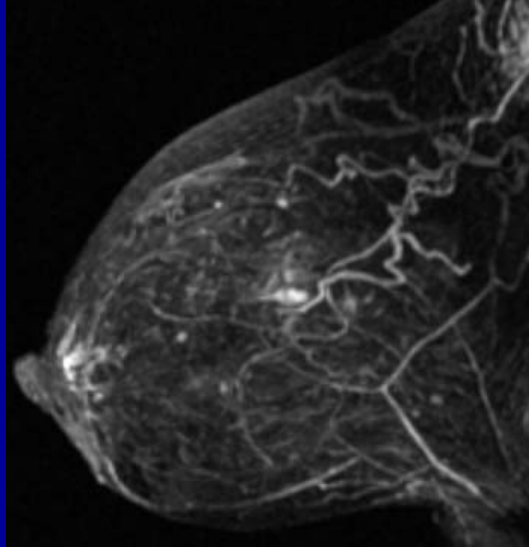
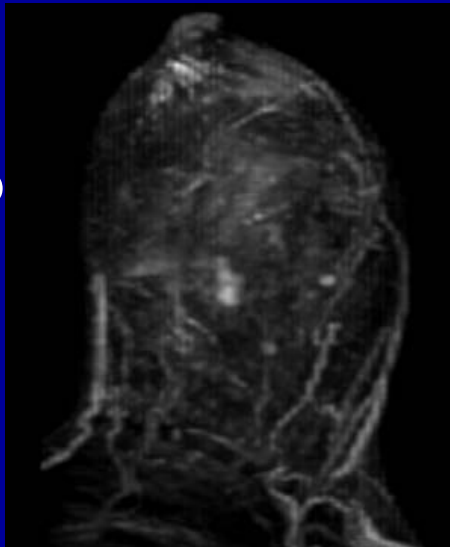
# Disease extent after chemotherapy by MRI

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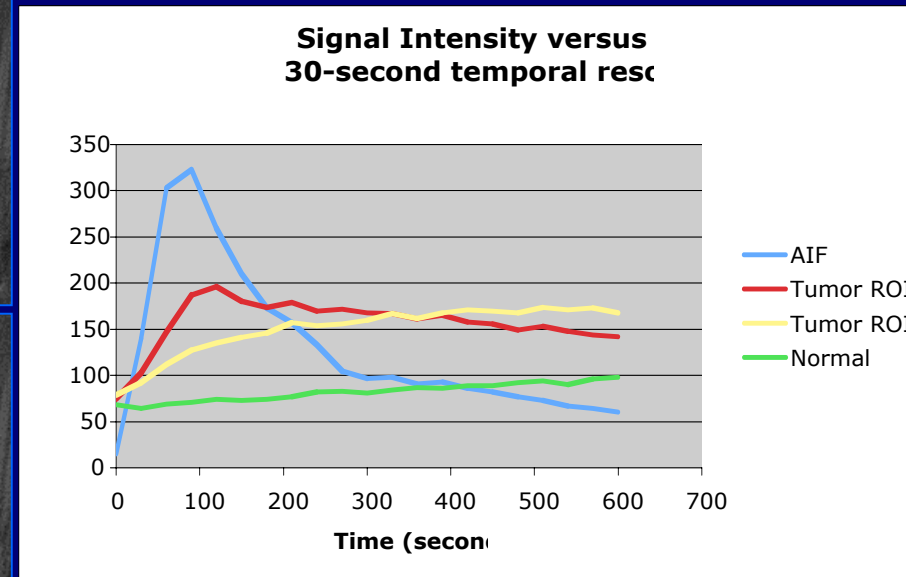
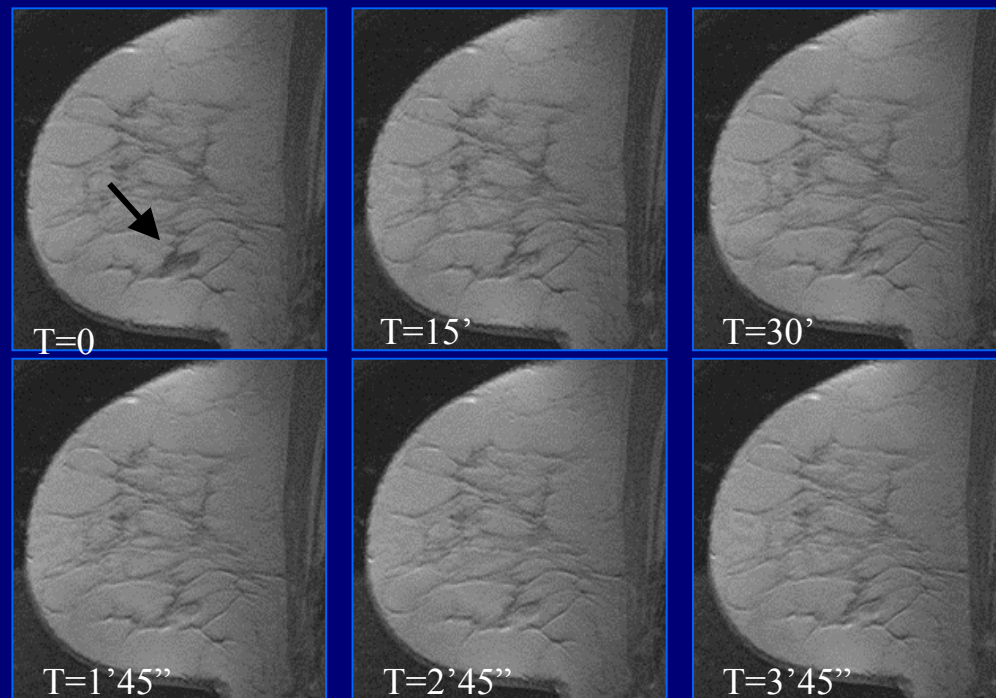
**Pre-chemo**



**Post-chemo**

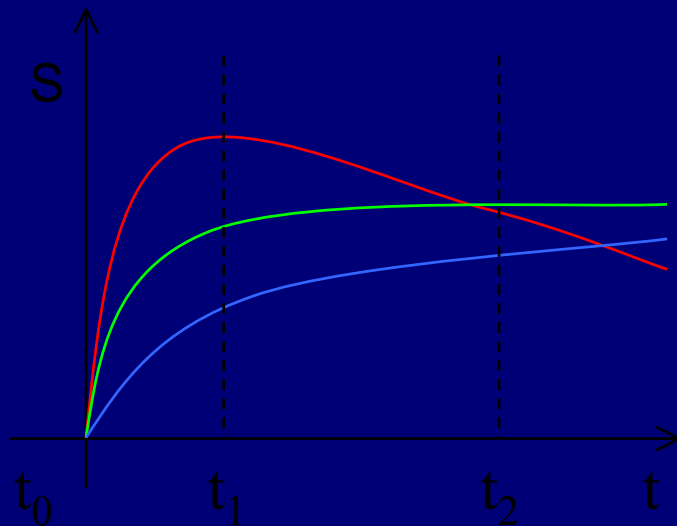
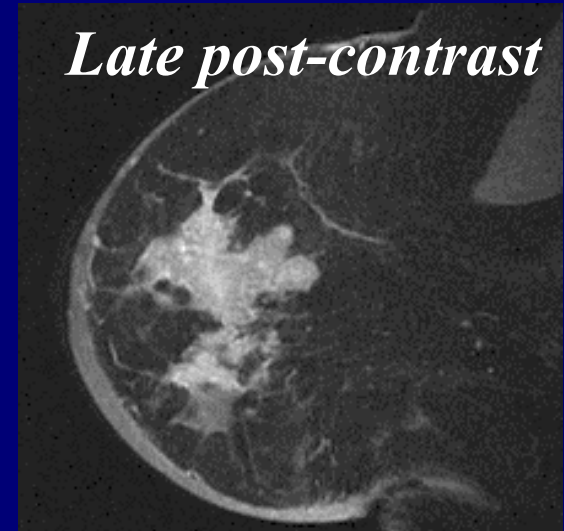
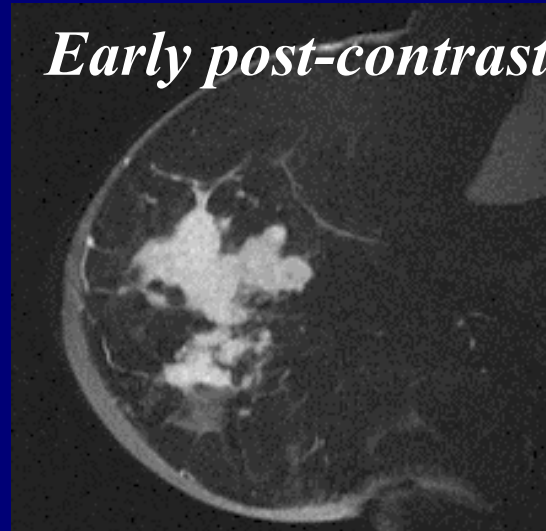
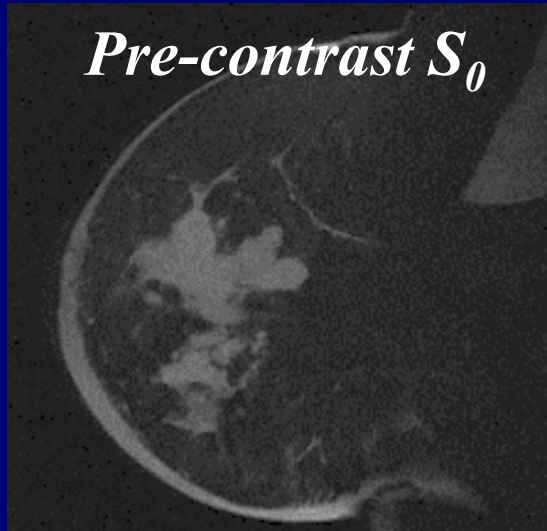


# Dynamic contrast-enhanced (DCE) MRI

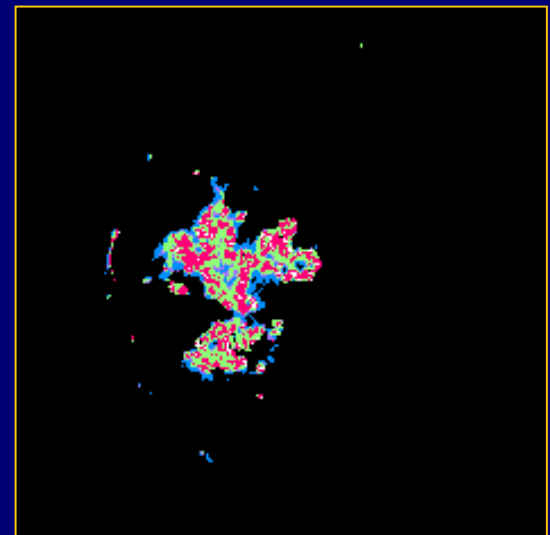
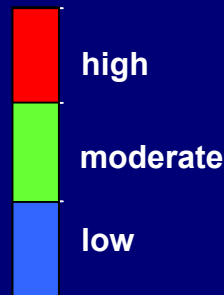


- T1-weighted imaging performed with injection of gadolinium-based contrast agent
- Time course of contrast enhancement analyzed to estimate pharmacokinetic parameters related to tumor permeability and blood volume ( $k_{trans}$ ,  $v_e$ )

# DCE-MRI combines anatomic staging with functional assessment



permeability



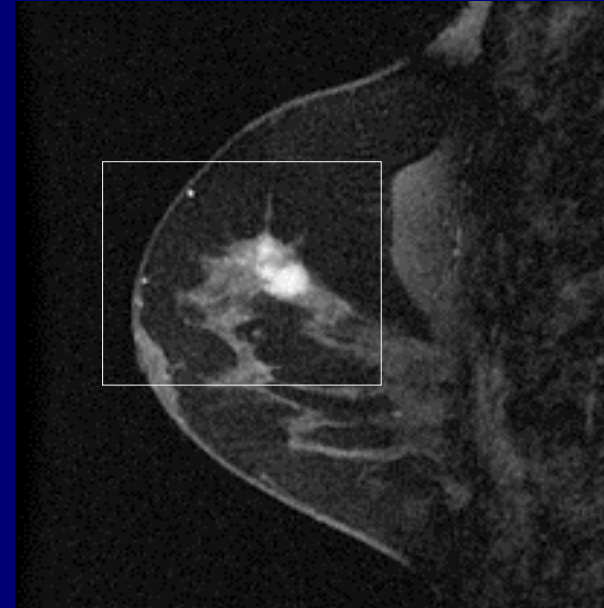
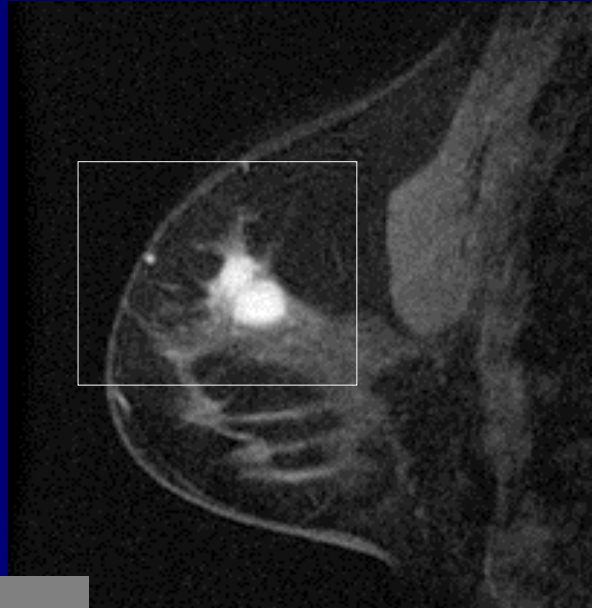
# MRI for Monitoring Response to Pre-operative Treatment

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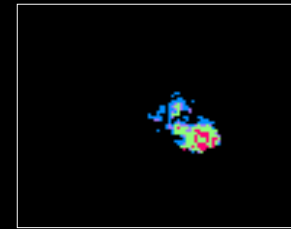
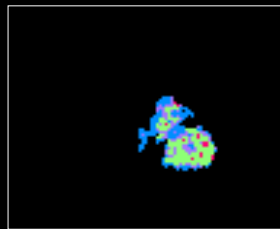
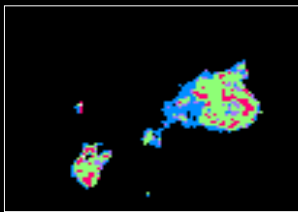
- MRI staging accuracy has led to increased interest in using MRI to assess response to treatment
  - ⇒ Conventional imaging has not been fully explored in this role
- Functional information can be obtained as part of the clinical exam
  - ⇒ No extra exams required

# Tracking tumor change during treatment

*Assess tumor size:*



*Assess tumor vascularity:*



**MRI before  
chemotherapy**

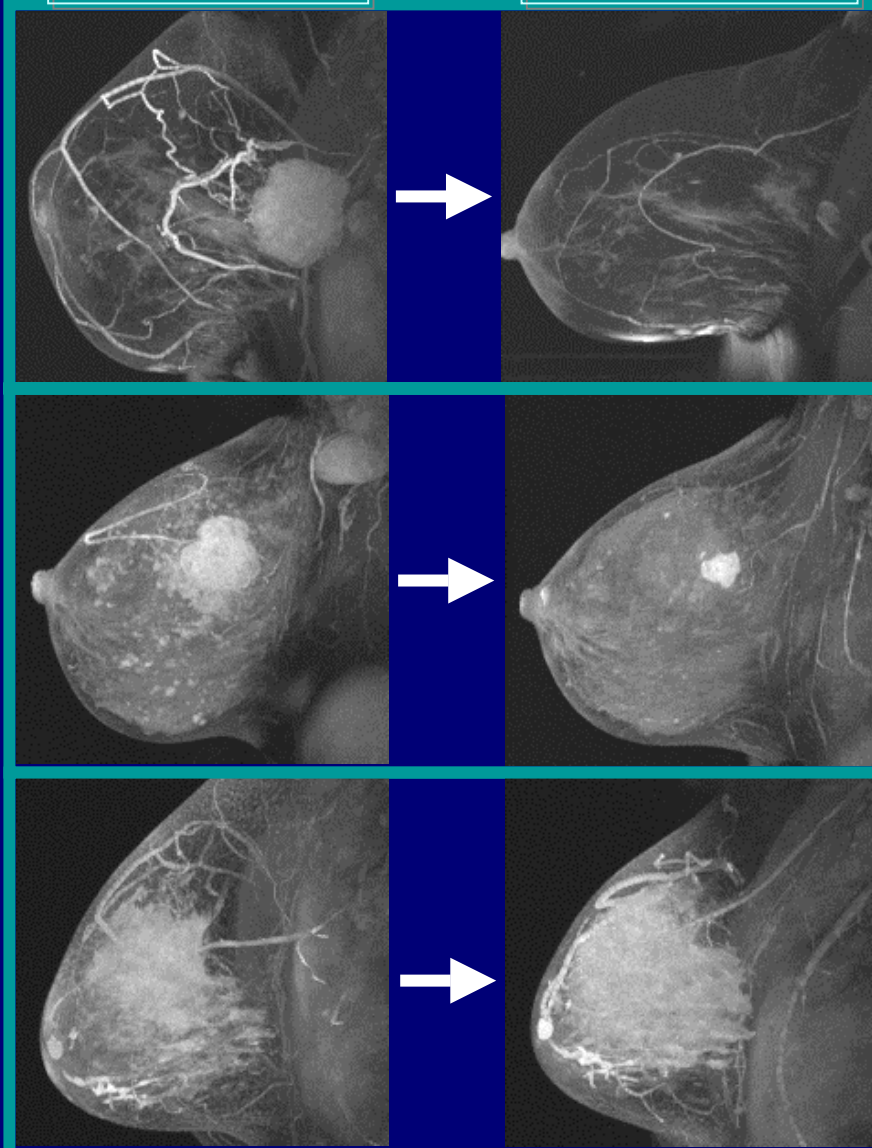
**MRI after 1 cycle of  
chemotherapy**

**MRI after full course of  
chemotherapy**

# Tumor response by MRI

*Pre-treatment*

*Post-treatment*



Complete response  
(Volume change = 100%)

Partial response  
(Volume change = 69%)

Progressive disease  
(Volume change = -178%)

**Can greater accuracy in capturing size change lead to better survival stratification?**



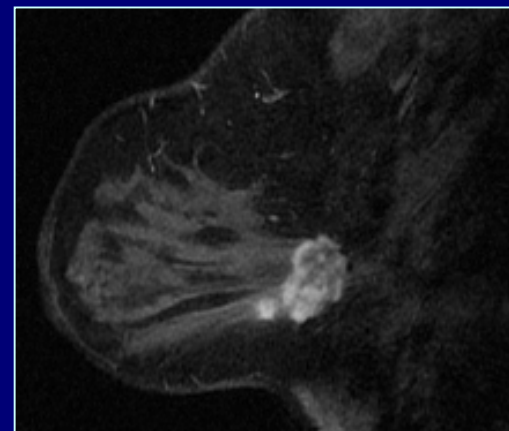
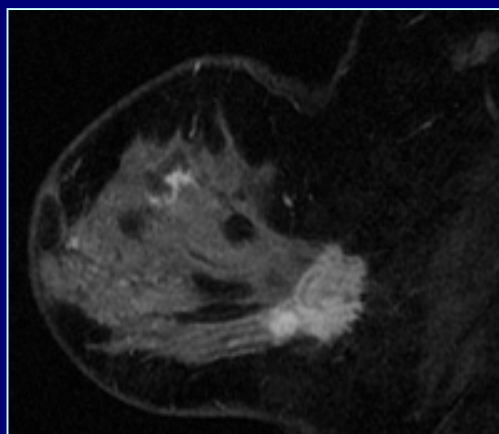
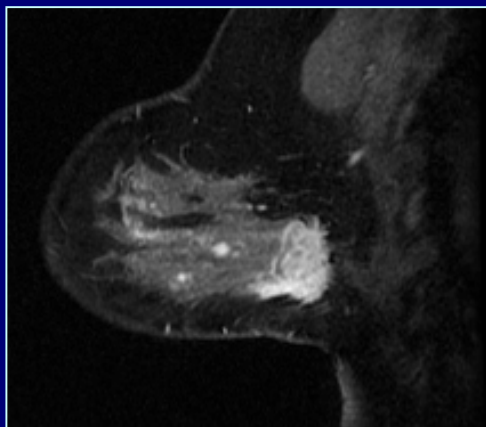
# Measurements other than longest diameter may also be informative

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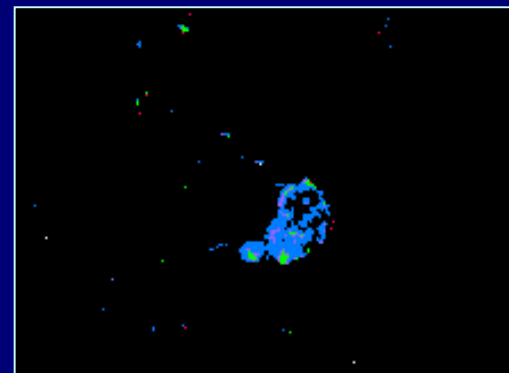
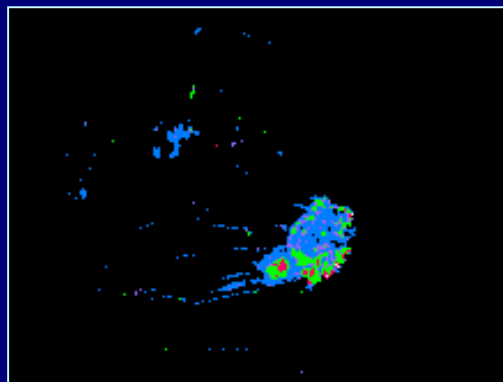
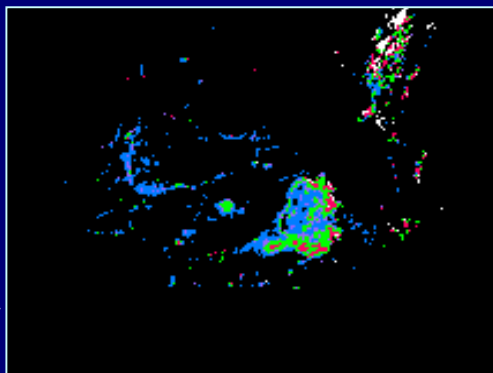
- Tumor volume
- Tumor morphology
- Vascular heterogeneity

# Volumetric Size Assessment

S1



SER



**BASELINE (pre-chemo):**

Longest diameter = 1.9 cm

Volume = 7.4 cc

**Change after 1 cycle AC:**

Longest diameter = 2.0 cm

Volume = 6.5 cc

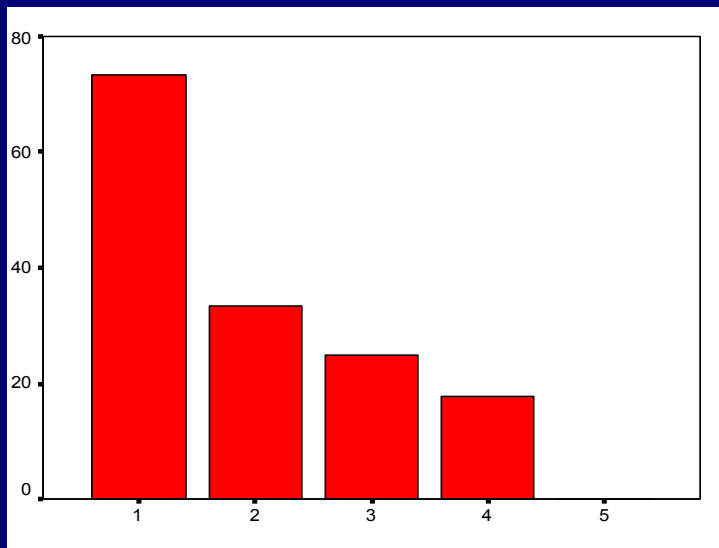
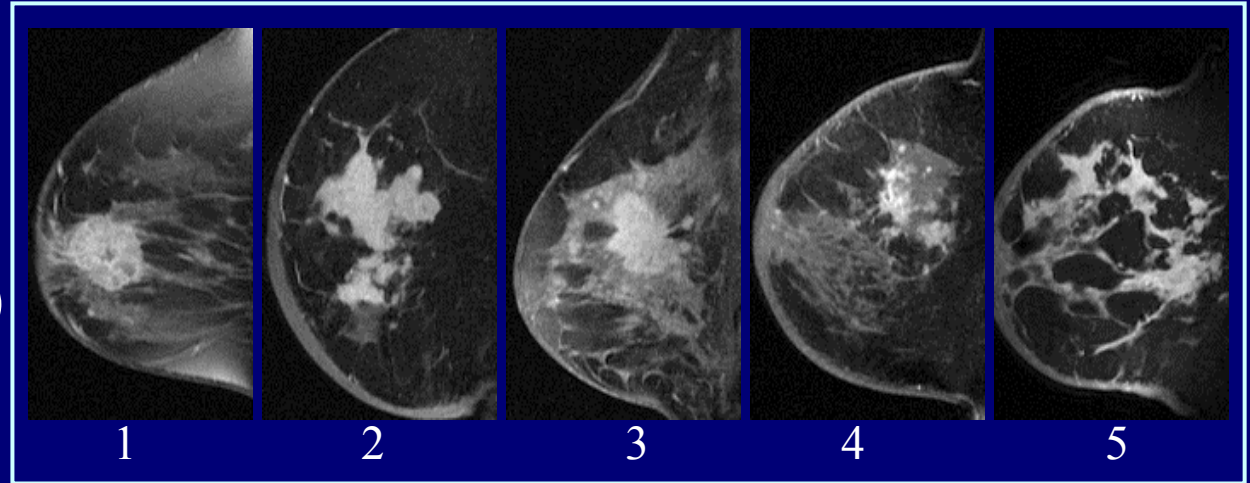
**Change after 4 cycles AC:**

Longest diameter = 1.4 cm

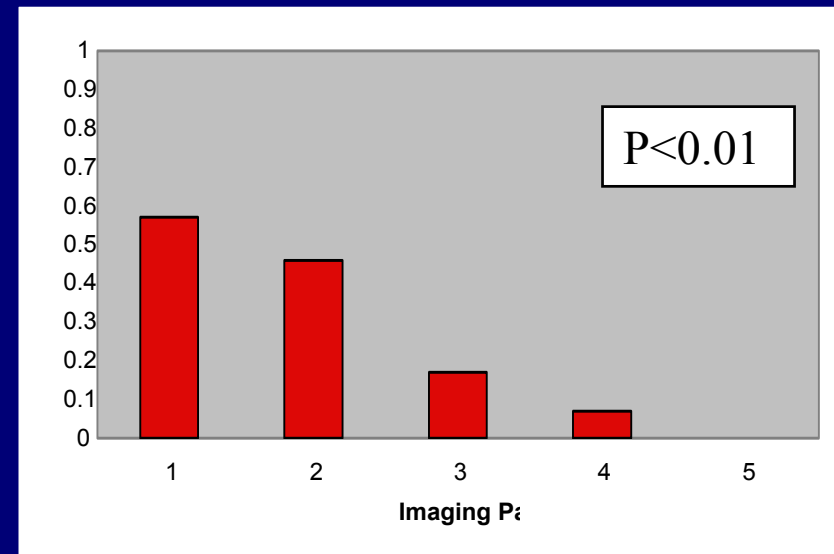
Volume = 3.9 cc

# Tumor Morphology

- *Baseline Imaging Patterns (IP) 1 - 5:*



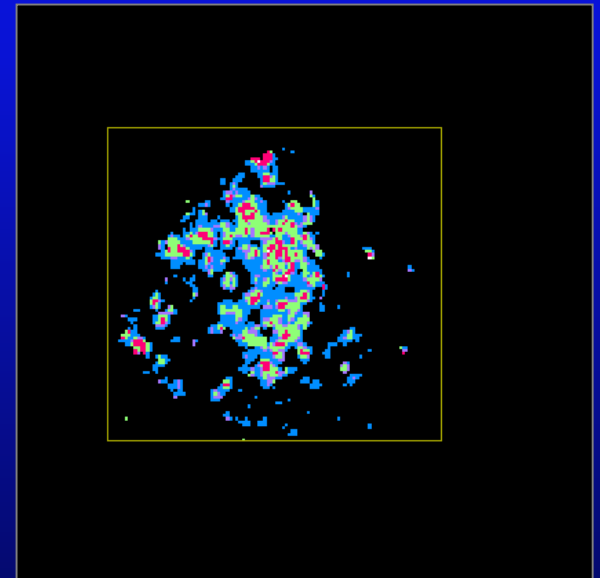
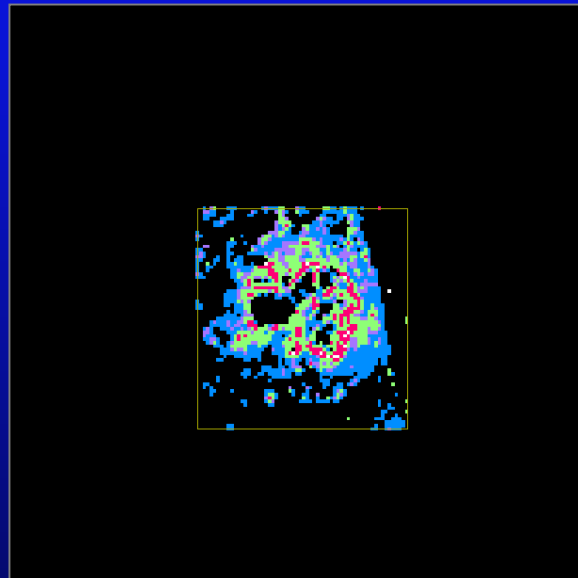
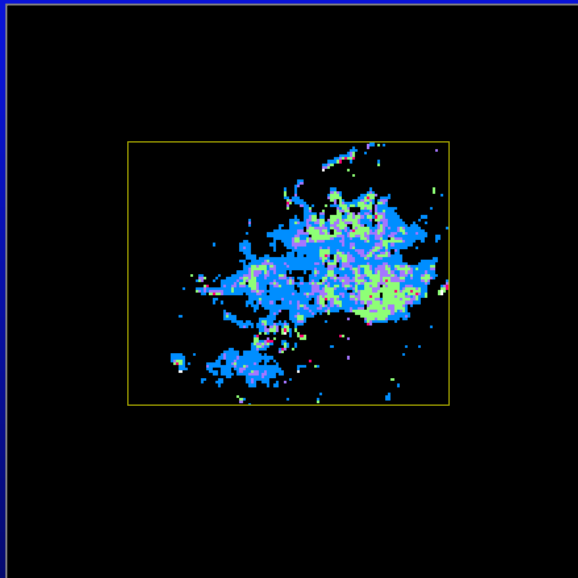
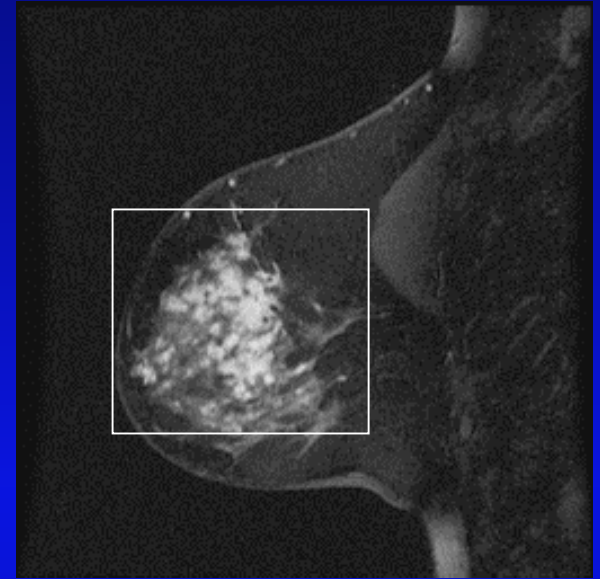
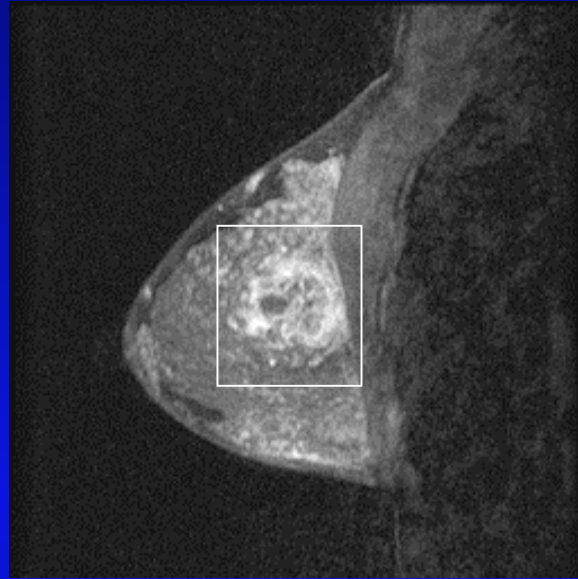
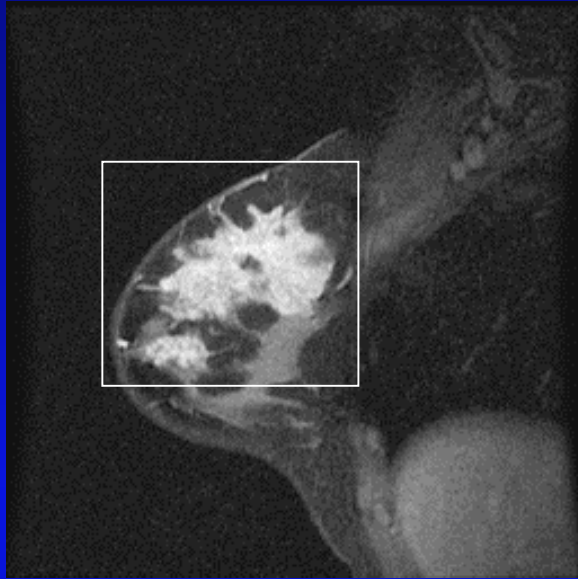
*% complete responders by IP*



*Breast conservation rates by IP*

# Heterogeneity of the microvasculature

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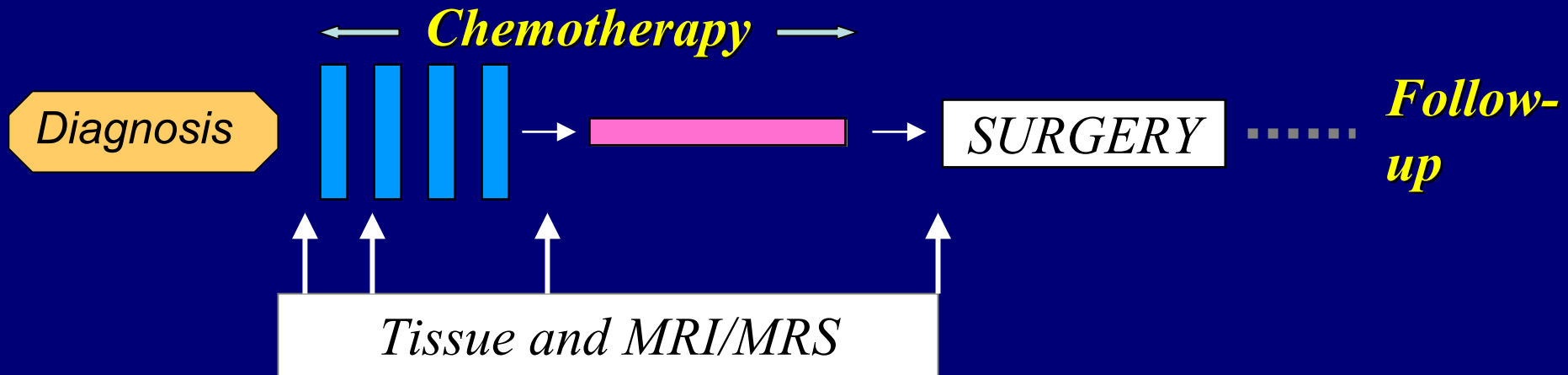
# ACRIN 6657

## Prospective Imaging Trial as part of the I-SPY Collaboration

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- The “I-SPY” trial combines serial imaging and tissue-based molecular markers for assessing response to pre-operative treatment
- ACRIN 6657 is testing MRI for measuring response to treatment
  - Compare to clinical response and path residual disease as a predictor of disease-free survival
  - Size is primary measurement; functional information about tumor vascularity also being explored

# I-SPY Trial Design



- Patients enroll on both CALGB 150007 (tissue markers) and ACRIN 6657 (imaging)
- Tissue acquisition and imaging performed at comparable times during treatment
  - Pre-treatment, post 1 cycle anthracycline, between anthracycline and taxane regimens, and post-chemo

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Functional imaging methods as in-  
vivo biomarkers (DCE-MRI, PET)

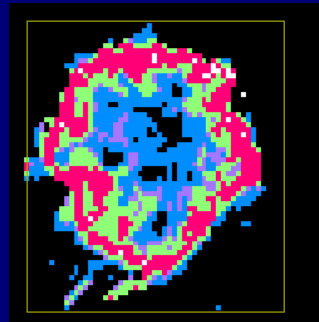
# Functional MRI as an Imaging Biomarker

- Functional measurements by MRI (DCE-MRI, diffusion-weighted MRI, MR spectroscopy) can be used to make quantitative measurements of tumor biology (microvascular permeability, water diffusion, choline concentration)

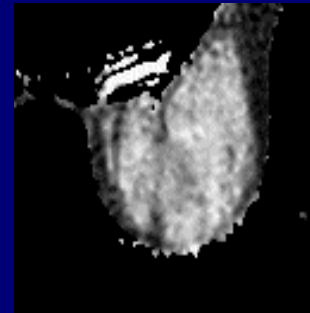
Contrast Enhanced T1-Weighted



$K^{trans}, v_e$



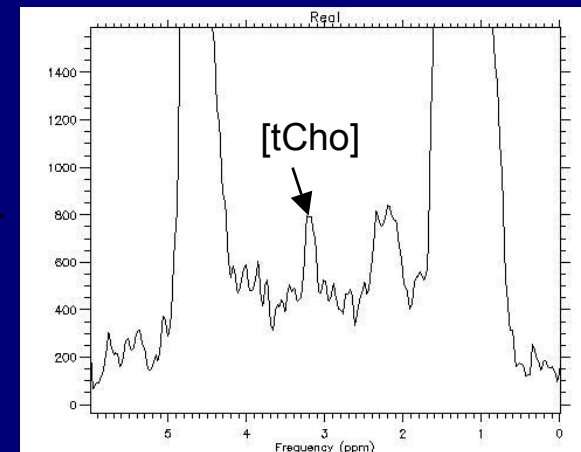
ADC Map



$^1\text{H}$  MRS



Choline





# DCE-MRI in Phase I trials

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- A number of recent Phase I clinical trials have added DCE-MRI to measure effects of anti-angiogenic agents (*Wedam et al, JCO 2006; O'Donnell et al, Br J Cancer 2005; Morgan et al, JCO 2003; Liu et al, JCO 2005*)
  - Most found correlations of  $k^{\text{trans}}$ ,  $v_e$  with treatment response endpoints
  - Some mixed results; several evaluated MRI in multiple metastatic solid tumors; correlative studies - not powered to answer imaging question
  - suggest potential for DCE-MRI as a biomarker of anti-tumor treatment

# FDG PET to Monitor Response to Neo-Adjuvant Chemotherapy

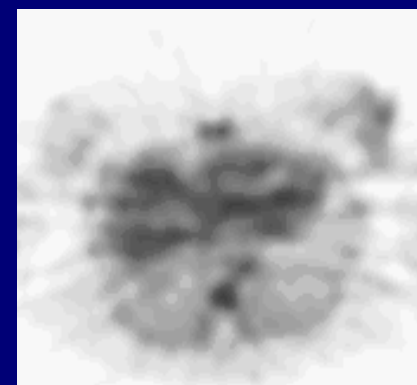
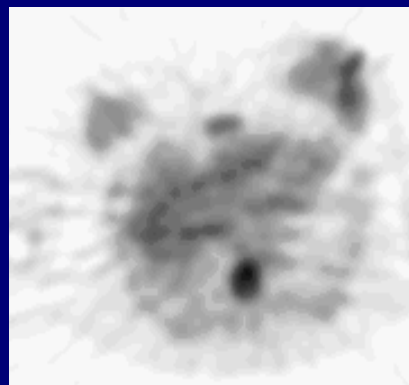
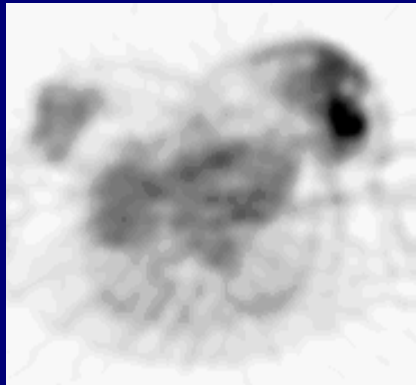
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**Pre-Rx**  
SUV = 5.7

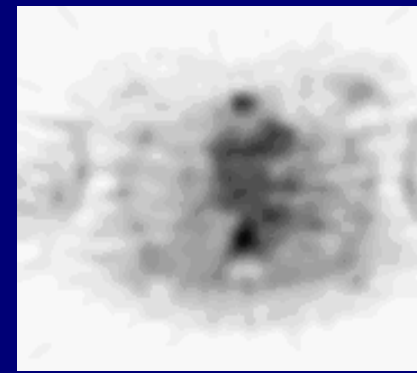
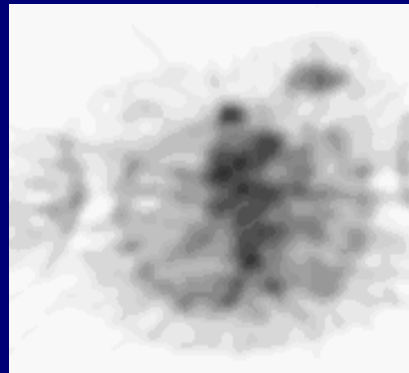
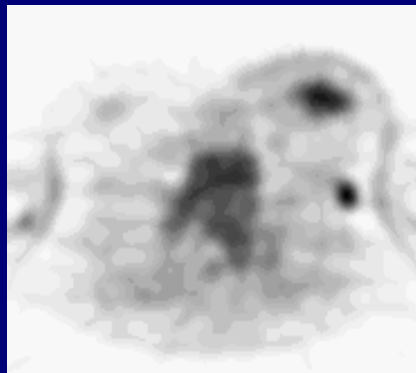
**2 months Rx**  
SUV = 4.1

**4 months Rx**  
SUV = 3.3

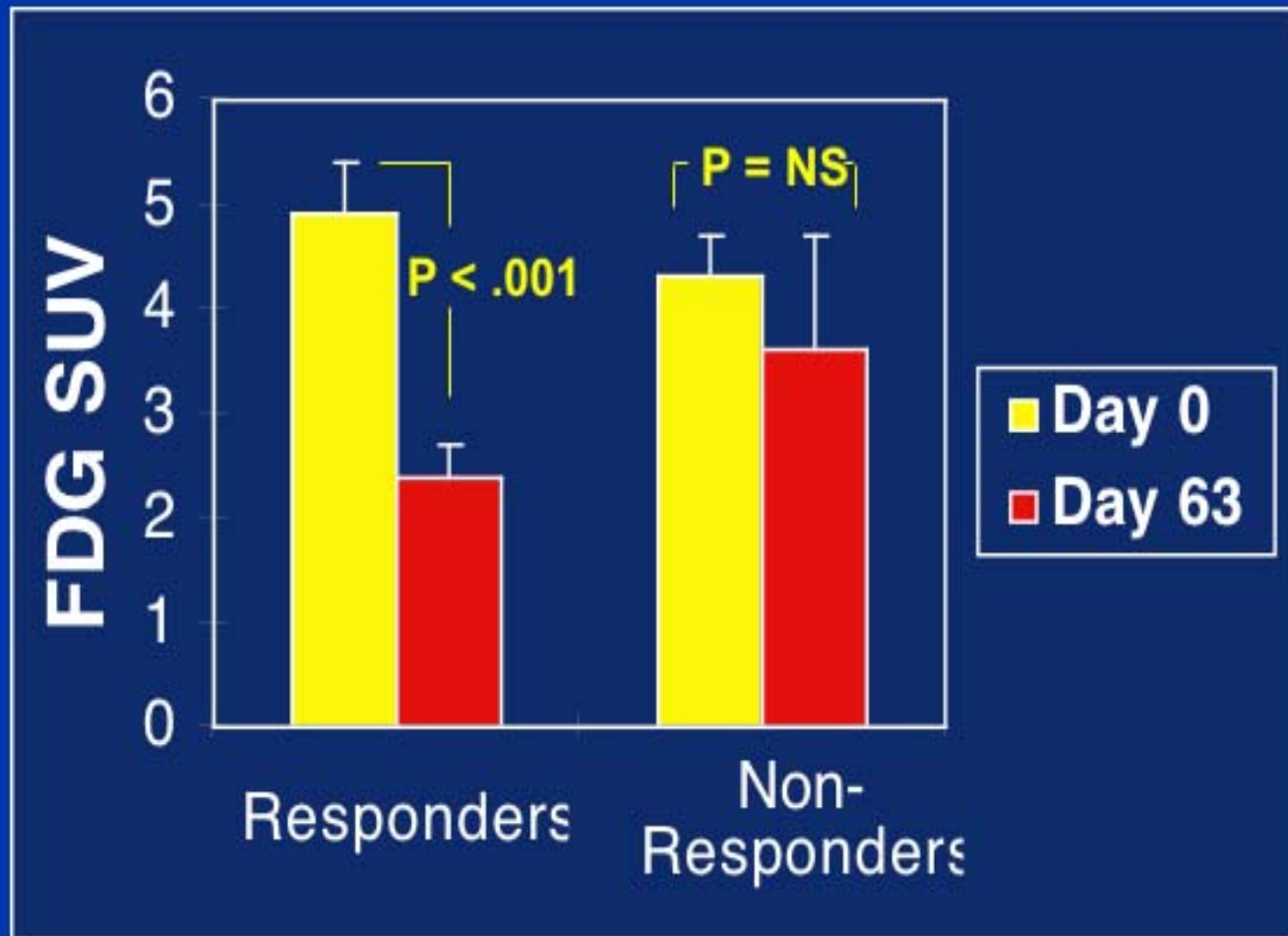
**breast  
lesion**



**axillary  
node**



# FDG PET to Monitor Breast Cancer Response to Therapy



(Wahl, J Clin Oncol 11:2101, 1993)

# Summary of Mid-Therapy Response Evaluation by PET

Reference	N	Rx	Results
Wahl, 1993	11	AC	R: -48% SUV NR: -19% SUV
Bassa, 1996	15	FAC	All: -51% SUV
Schelling, 2000	24	EC or ET	mCR: -46% SUV not mCR: -8% SUV
Smith, 2000	30	CVAP	mCR: -86% SUV not mCR: -40% SUV
Mankoff, 2003	35	FAC or AC (weekly)	mCR: -65% MRFDG PR: -49% MRFDG NR: -40% MRFDG

# In Summary

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- Conventional imaging has shown only fair accuracy for assessing response
  - Has not proven of greater accuracy than physical exam
- MRI establishing itself as a superior anatomic staging method, compared to mammography and ultrasound, for extent of primary tumor
  - Better agreement with pathology for residual disease assessment
  - Complete response by MRI cannot obviate surgery
- Functional imaging techniques (DCE-MRI, MRS, PET, Optical imaging) hold promise for in vivo assessment of tumor biology - but are still investigational