Molecular Imaging:
Can we predict residual disease?

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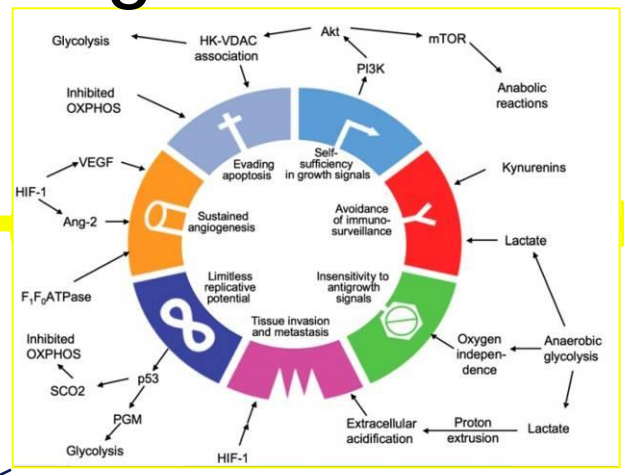
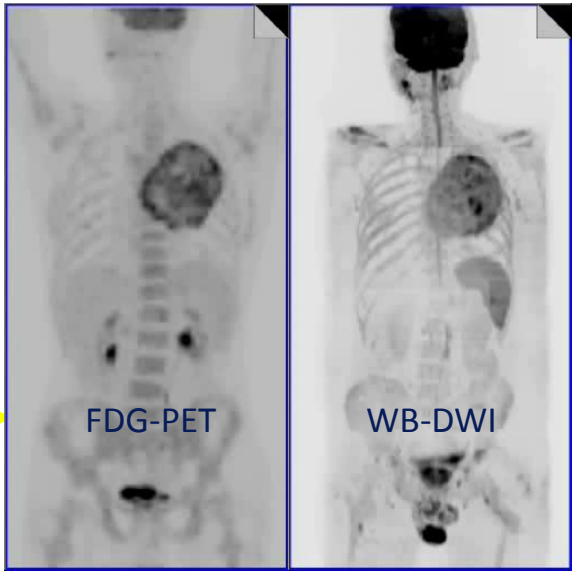
Cancer hallmarks & metabolic derangements

Normal — **Atypia**





- Limitless proliferation
- Evading apoptosis
- Self sufficiency in growth signals
- Insensitivity to anti-growth signals
- Abnormal glucose uptake & metabolism
- Extra-cellular acidosis and resistance to acid-mediated toxicity
- Tissue invasion and metastasis
- Sustained angiogenesis
- Avoidance of immune surveillance
- Hypoxia
- Raised interstitial pressures

Altered metabolism & hypoxia

^{18}FDG-PET
^{1}H and ^{13}C MRS
BOLD-MRI
^{18}F-MISO PET

Angiogenesis

DCE-MRI
DSC-MRI
DCE-CT
DCE-US
$H_2{}^{15}O$-PET

Proliferation

^{18}FLT-PET
^{1}H-MRS
DW-MRI

Apoptosis

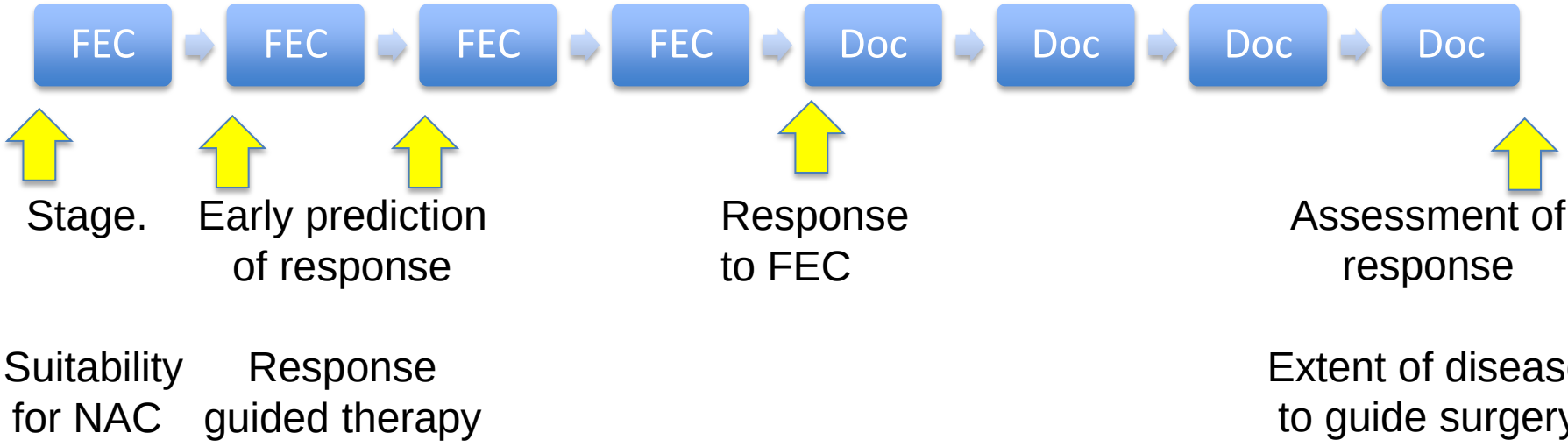
^{99m}Tc-Annexin V
DW-MRI

Metastasis

Lymphography
WB-DWI
Bone scan
CT etc

Gatenbury RA & Gillies RJ. Nature Cancer Reviews 2008; 8: 56-61

Imaging during Neoadjuvant Chemotherapy



Options for Imaging during Neoadjuvant Therapy

- Magnetic Resonance Imaging:
  - DCE
  - DWI
  - Spectroscopy
- Radionuclide Imaging:
  - FDG-PET
  - FLT-PET

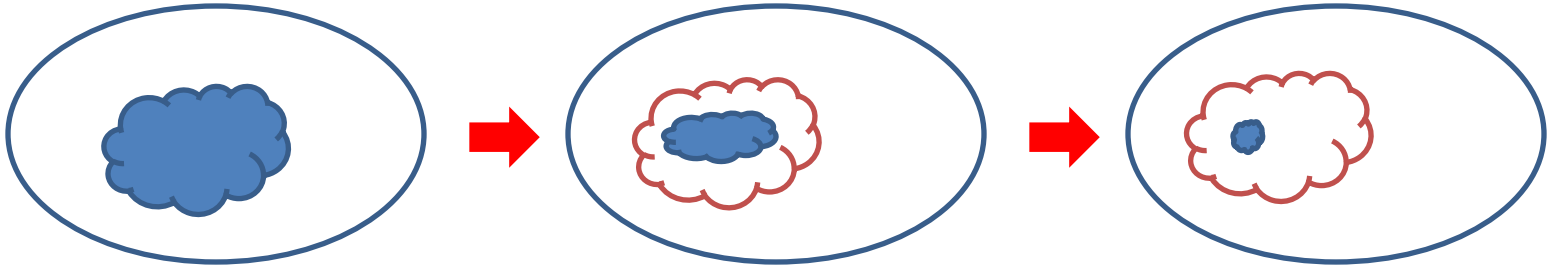
MRI: role in Neoadjuvant Therapy

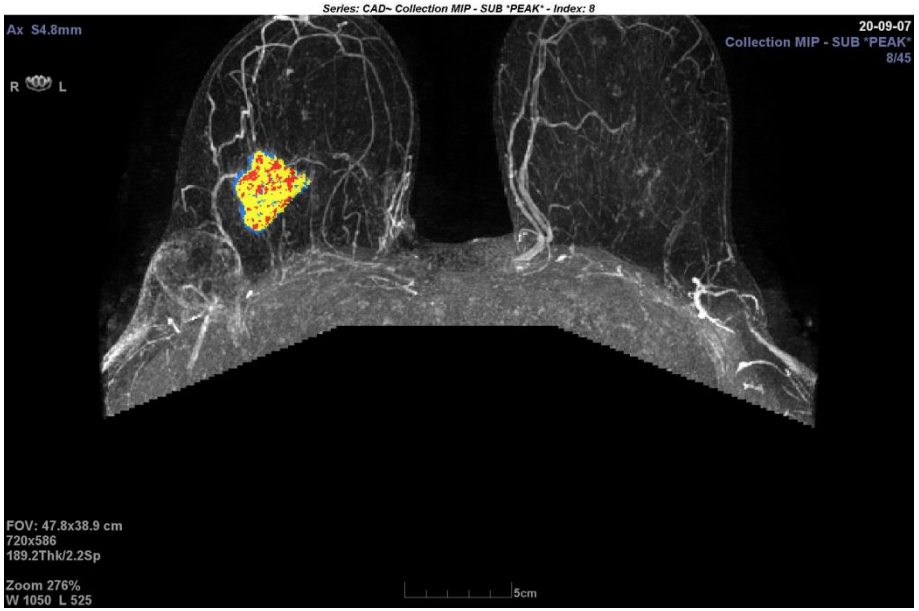
- Pretreatment staging to determine extent of disease
  - tumour size, multifocal/multicentric disease, chest wall/pectoralis muscle invasion
- Post-chemotherapy assessment
  - Good correlation with residual invasive cancer
- Early assessment of response

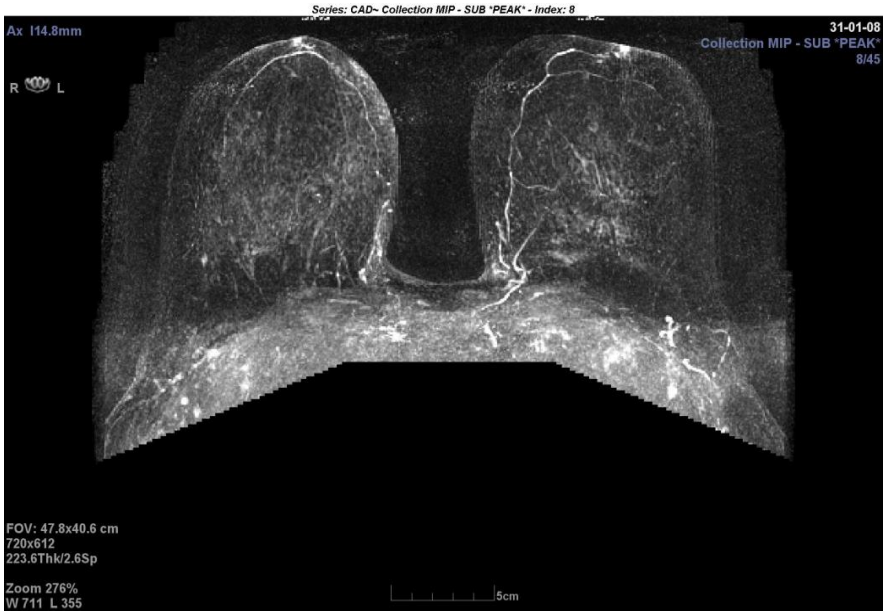
AR Padhani, MW Ah-See, A Makris. Expert Review of Anticancer Therapy 2005; 5(2):239-252

Patterns of response to Neoadjuvant Chemotherapy

A. Concentric shrinking



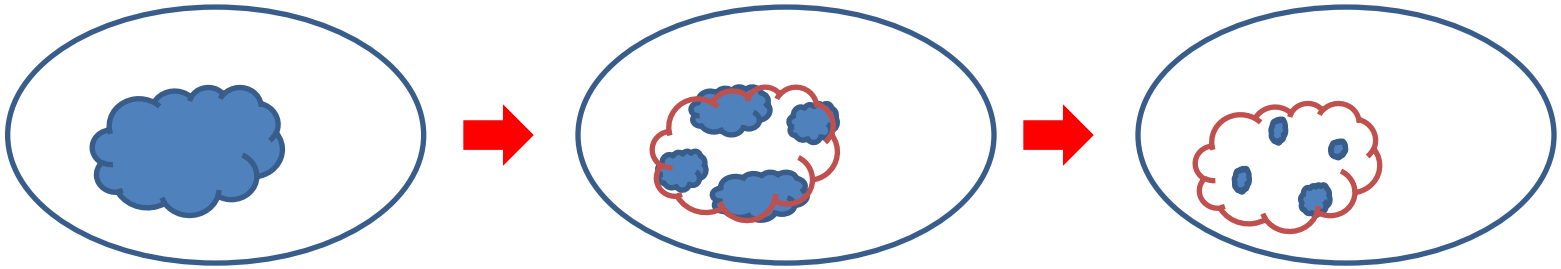


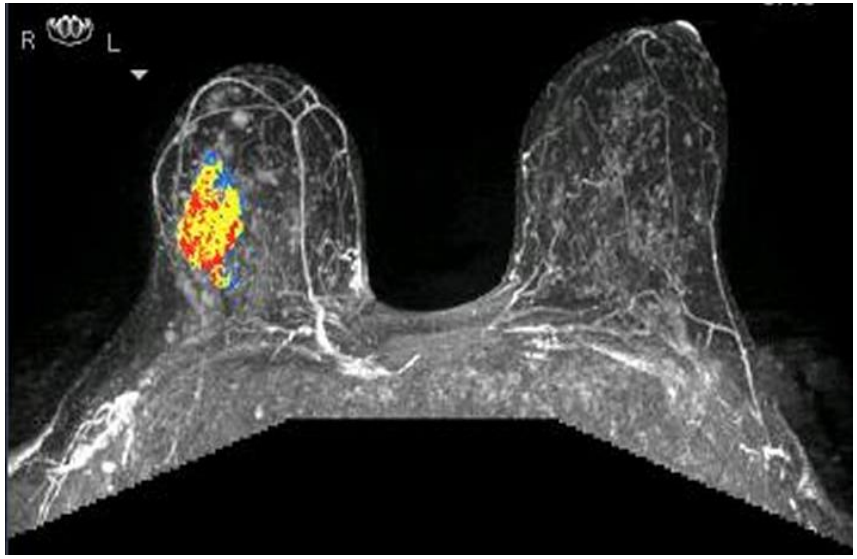


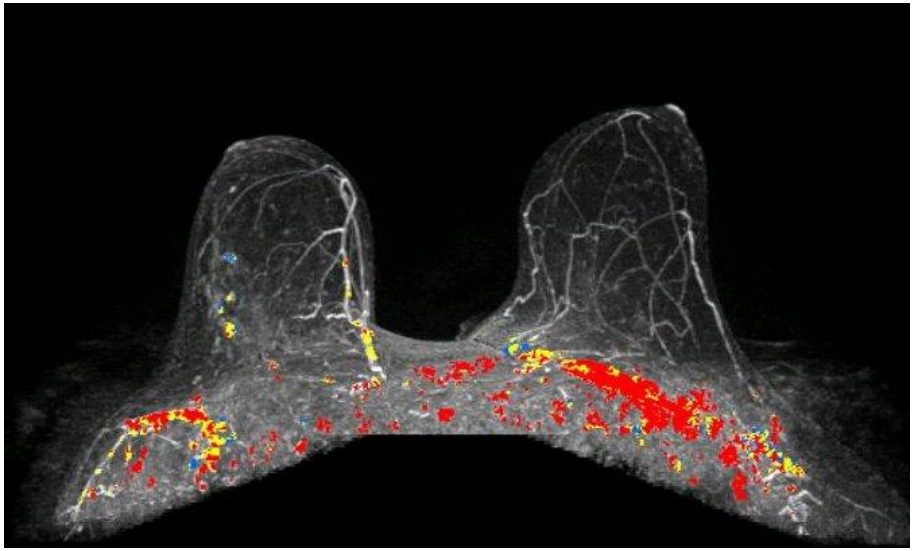
Courtesy of: E Provenzano and P Britton

Patterns of response to Neoadjuvant Chemotherapy

B. Scatter pattern







Courtesy of: E Provenzano and P Britton

Accuracy of Clinical Exam, Mammography, US and MRI in determining post-neoadjuvant pathological response to NAC

Characteristic	Clinical Examination	Digital Mammography	Ultrasound	MRI
Accuracy	57%	74%	79%	84%
Positive Predictive Value	91%	85%	85%	93%
Negative Predictive Value	31%	41%	44%	65%
Sensitivity	50%	81%	90%	86%
Specificity	82%	48%	33%	79%

- Image-guided biopsy needed to confirm pCR
- Imaging could play a role in identifying patients without pCR who may benefit from longer and/or modified NAC

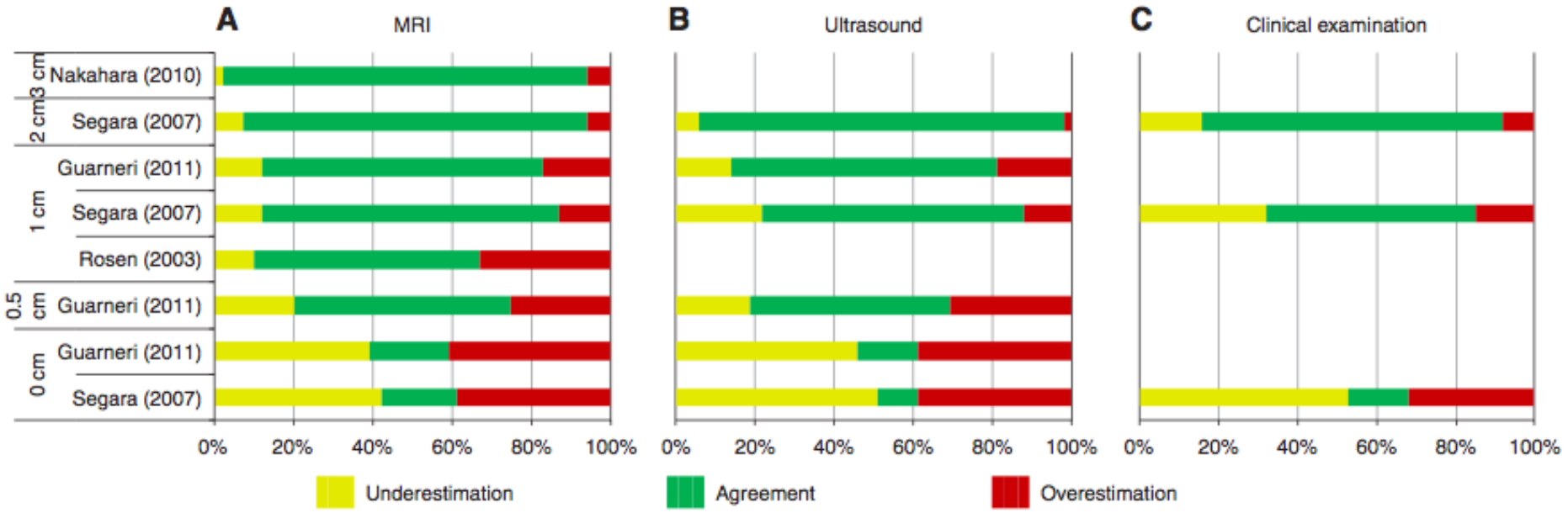
Croshaw R et al. Ann Surg Oncol 2011; 18: 3160-3163

Meta-analysis of agreement between MRI and pathologic tumor size post-NAC

- Data from 19 studies (958 patients)
- Mean differences and limits of agreement reported
- MRI better than mammography and US
- MRI overestimates pathologic size
- Studies comparing imaging and pathologic size have inherent limitations:
  - errors in pathologic measurement: re-excisions, orientation, fixation, residual DCIS, scatter shrinkage
- But these studies largely preceeded taxanes, herceptin, and tumour subtyping

Marinovich ML et al BJC 2013; 109: 1528-1536

Percentage agreement, underestimation and overestimation for MRI, US, and clinical examination

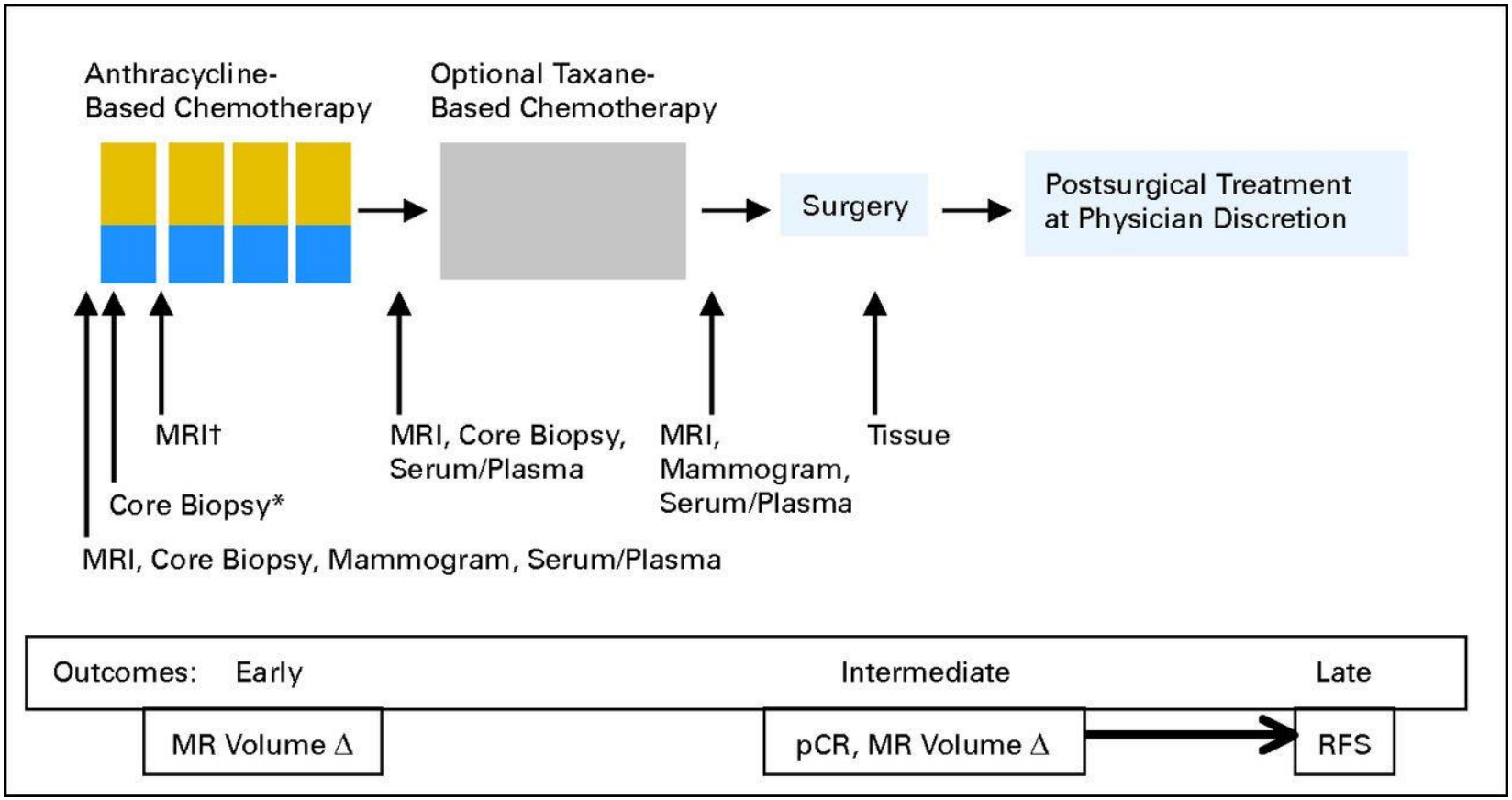


Marinovich ML et al BJC 2013; 109: 1528-1536

Functional MRI Imaging Techniques

- DCE-MRI
  - Vascular Parameters: Perfusion/Permeability
- DW-MRI
  - Diffusivity of water
  - Cell density/necrosis
- MR-Spectroscopy
  - Cell membrane turnover
- BOLD-MRI
  - Oxygenation/Hypoxia

I-SPY 1 TRIAL (Investigation of Serial Studies to Predict Your Therapeutic Response With Imaging and Molecular Analysis) schema.



Esserman L J et al. JCO 2012;30:3242-3249

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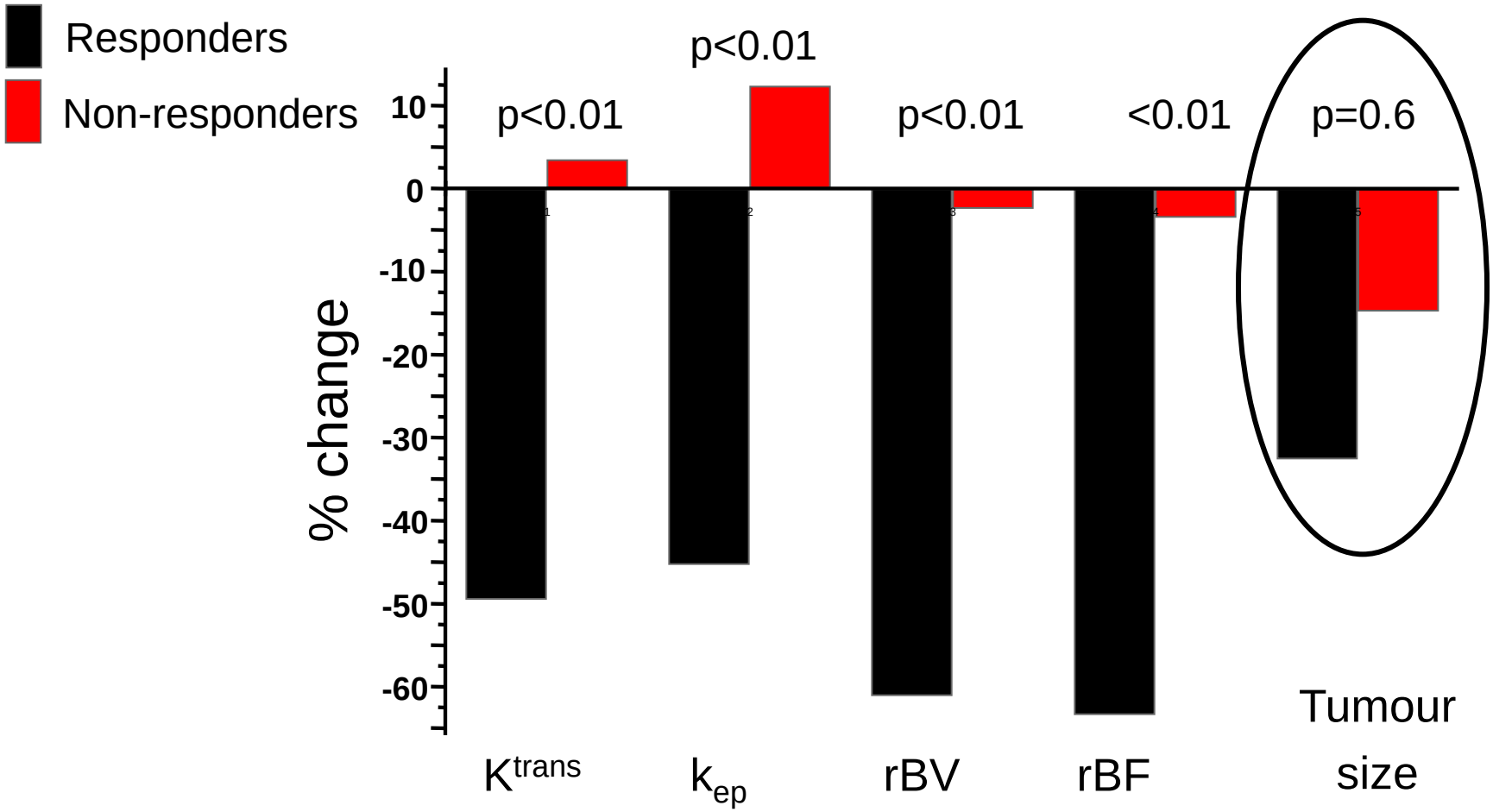
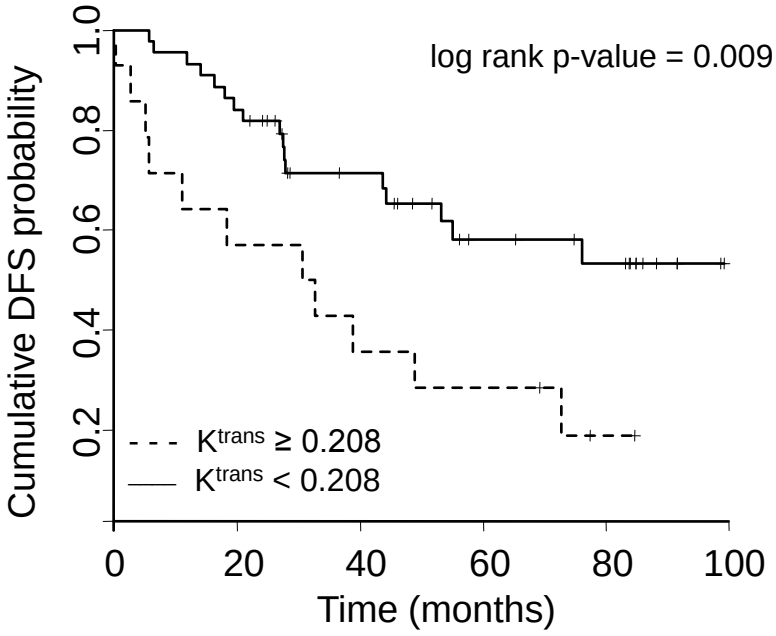
Changes in DCE-MRI kinetic parameters classified by pathological response post NAC

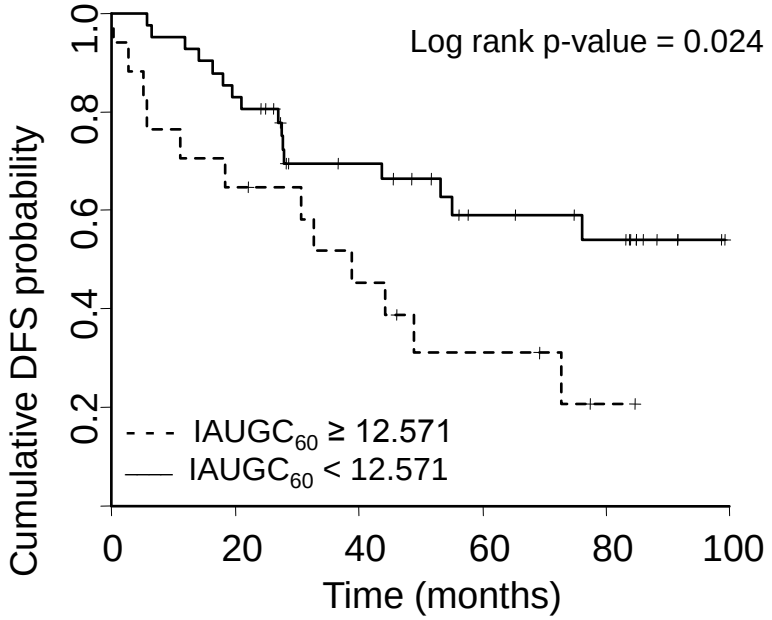


Ah-See ML et al Clin Cancer Res 2008; 14: 6580-89

DCE-MRI as prognostic biomarker

- High K^{trans} and $IAUGC_{60}$ values after two cycles of neoadjuvant chemotherapy are associated with a worse DFS (K^{trans} p=0.009; $IAUGC_{60}$ p=0.024) and OS (K^{trans} p=0.07, $IAUGC_{60}$ p=0.06) on Kaplan Meier analysis

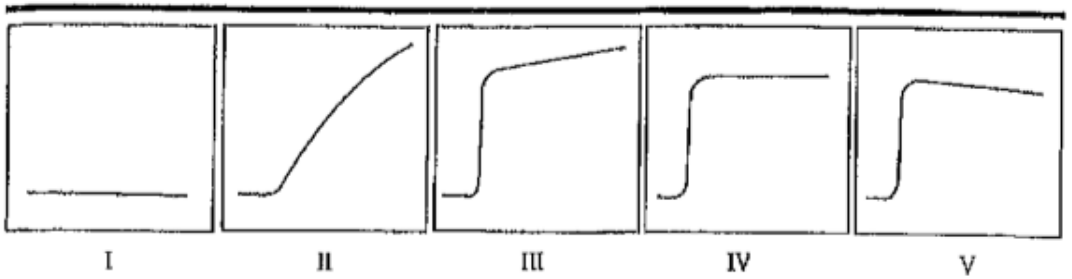




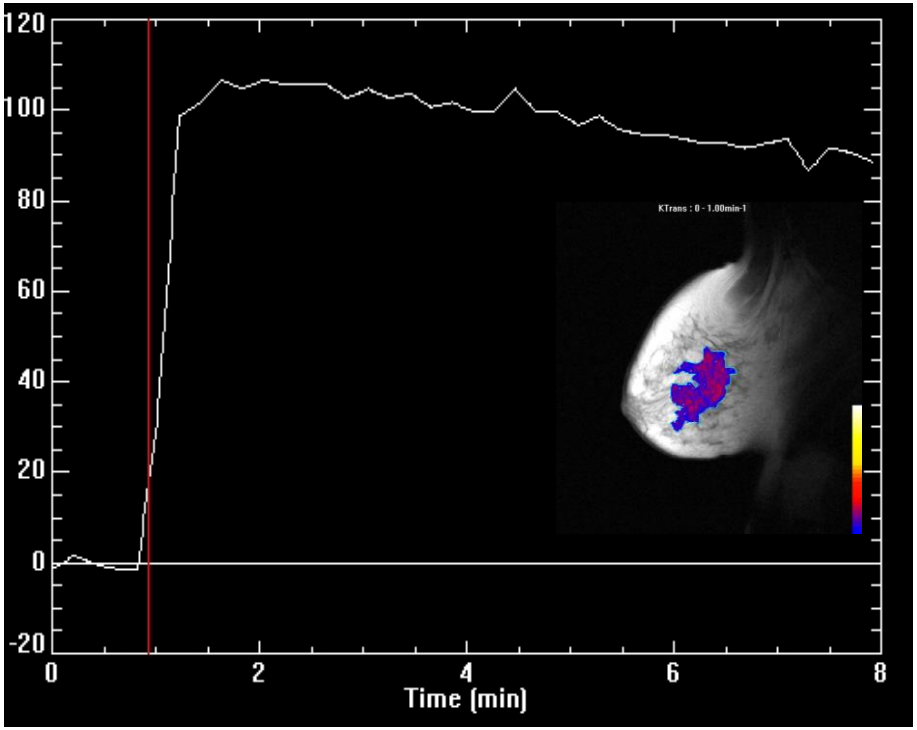
Li SP, Makris A, Padhani AR. Radiology 2011; 260: 68-78

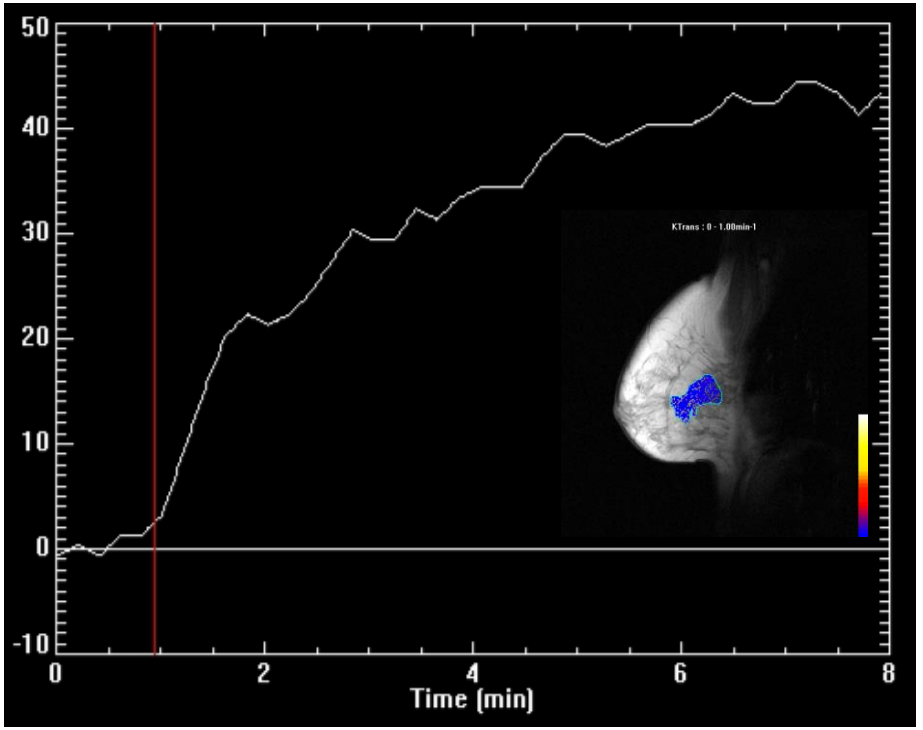
Signal Intensity Time Curves (SITCs)

- Allows visual classification taking into account the steepness of SI change in early phase of contrast enhancement (wash-in) and intermediate / late phase (wash-out)
- Already used to help distinguish benign and malignant disease
- Easier to use than quantitative parameters e.g K^{trans}



Classification scheme for SITCs reproduced with permission from: Daniel et al. Radiology; 1998; 209: 499-509

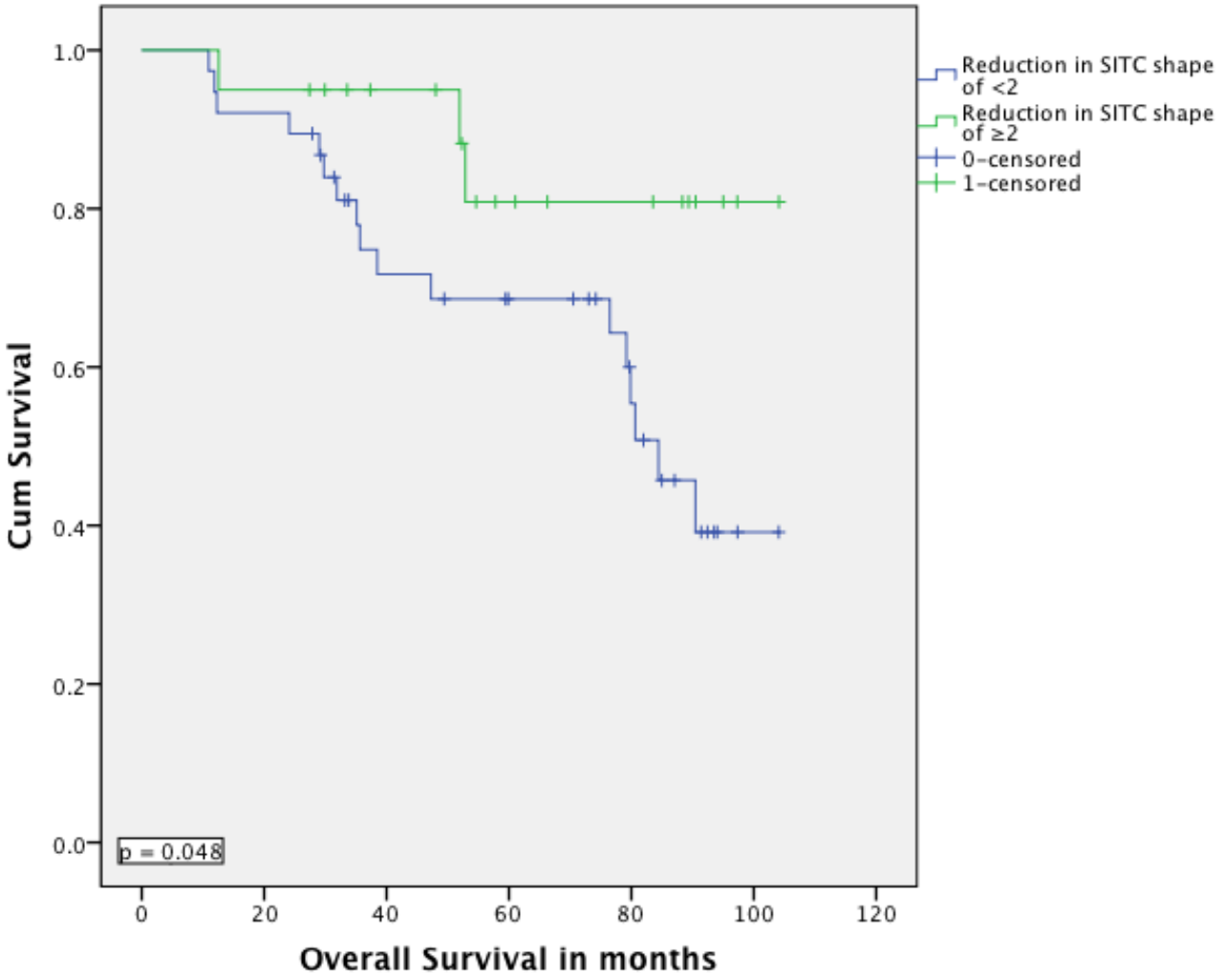




SITC for 42 year old woman with a 72mm G2 IDC of the breast ER and HER 2 positive, who had a complete pathological response and remains alive and disease free at 5 years. K^{trans} map (colour scale 0-1.0 min-1) is superimposed upon SITC at baseline and after 2 cycles of docetaxel chemotherapy. The y-axis is the % signal intensity enhancement about baseline.

(a) pre chemotherapy image shows a curve shape of 5 with the corresponding K^{trans} value of 0.239 min^{-1}.
(b) post 2 cycles of chemotherapy shows a curve shape of 2 (reduction of 3 points) and K^{trans} of 0.045 min^{-1} (reduction of 81%).

Reduction in SITC of ≥2 predicts for OS



Woolf DK at al BCRT 2014; 147: 335-343

MRI response monitoring during NAC Relevance of Breast Cancer Subtype

- N=188 primary breast ca
- MRI pre and 6w post NAC
- Correlation of MRI changes with breast cancer subtype by IHC and residual disease post-NAC
  - TN, HER2+, ER+/HER2-
  - pCR: TN 34%, HER2+ 40%, ER+ 7%
- Correlations between change in largest diameter of late enhancement seen during NAC and residual disease seen in TN and HER2+ but not ER+/HER2-

Loo CE et al JCO 2011; 29: 660-666

MRI response monitoring during NAC Relevance of Breast Cancer Subtype

- Unifocal mass seen in
  - 57% TN, 18% HER2+, 33% ER+/HER2-
- Multifocal masses
  - 32% TN, 53% HER2+, 30% ER+/HER2-
  - (diffuse disease in the rest)

- TN regressed significantly more often as a shrinking mass than other two subtypes ($p<0.001$)

Loo CE et al JCO 2011; 29: 660-666

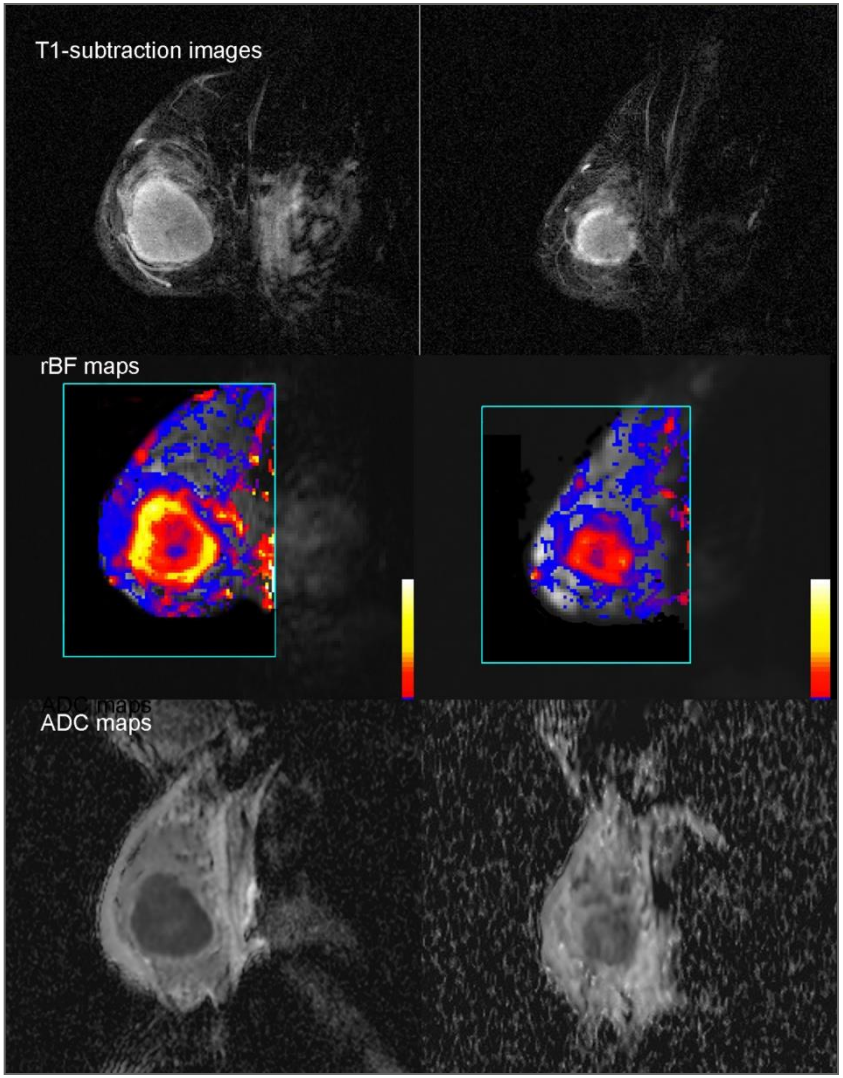
DCE-MRI characterisation of triple negative breast carcinomas

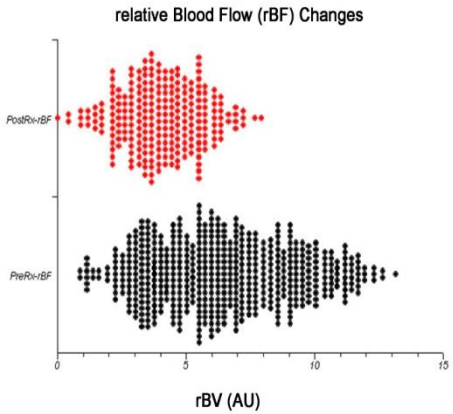
MRI parameter	ER-/PR-/HER2-	ER+/PR+/HER2-	p values
K^{trans}	0.19	0.23	p=0.575
v_e	0.33	0.39	p=0.001
k_{ep}	0.70	0.56	p=0.044
$IAUGC_{60}$	12.59	14.17	p=0.596
rBV	215.51	132.96	p=0.533
rBF	5.68	2.98	p=0.252
MTT	44.27	47.69	p=0.007

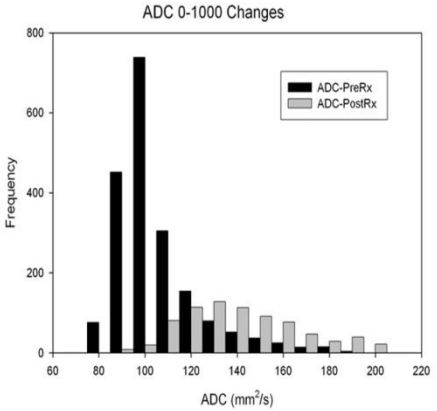
- DCE-MRI vascular parameters correlate well with histological features in TNBC
- Lower v_e values in TNBC reflect a more cellular, less stromal environment
- Higher k_{ep} values reflect the rapid return of contrast into vasculature consistent with higher capillary permeability

Li SP et al Eur Radiol 2011; 21: 1364-73

DW-MRI: Response to NAC







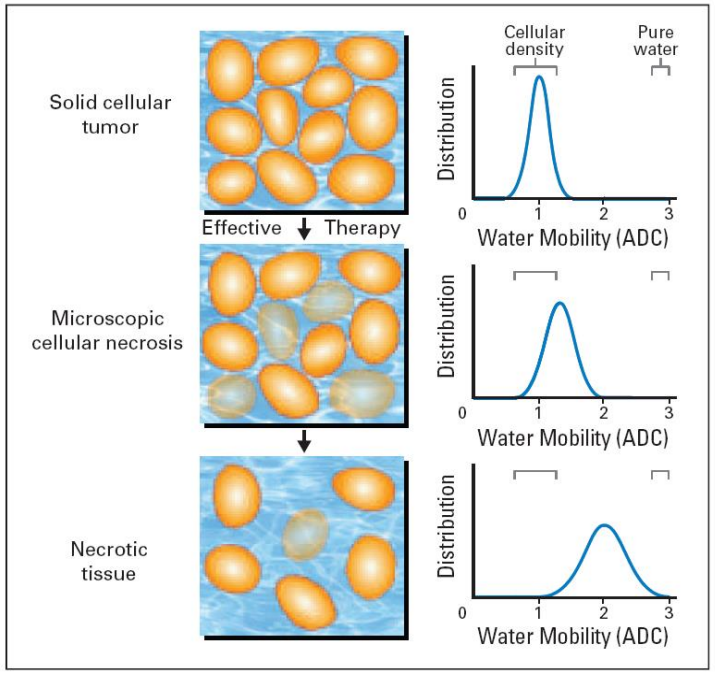


Fig 1. A schematic of the change in cellularity (left) and increased molecular water mobility measured as an apparent diffusion coefficient (ADC; right) as a tumor responds to treatment (top to bottom). For a tumor responding to therapy, an increase in extracellular space/membrane permeability allows greater water mobility and an increase in the ADC.

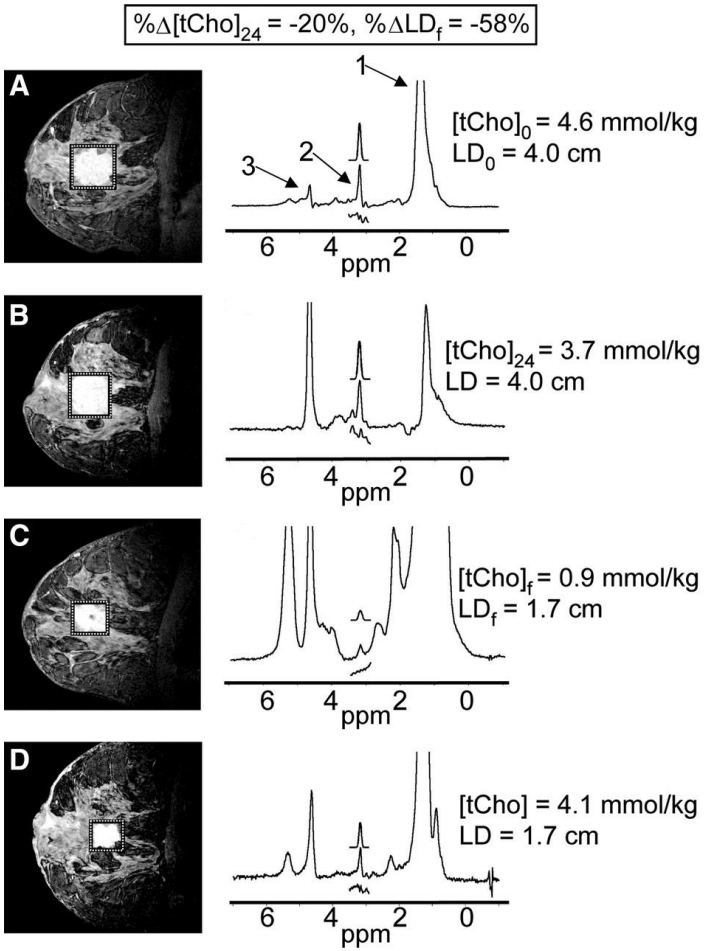
Hamstra DA, et al, J Clin Oncol 2007: 25:4104-4109

MR Spectroscopy

- Can be performed alongside MRI
- Initial studies with ^{31}P-MRS more recently with ^{1}H-MRS because of increased sensitivity
- Provides information on changes in phospholipid metabolism
  - choline containing-compounds (tchol) elevated in malignant lesions
- Precise mechanisms unknown but tchol may reflect cellular proliferation. Precursor of membranes and may reflect increased membrane turnover by replicating cells
- Clinical applications
  - Diagnosis
  - Monitoring response to treatment

Bolan PJ et al Breast Ca Res 2005; 7: 149-152

MR Spectroscopy
Monitoring response to treatment



- 13/16 patients
- AC x4 PST
- MRS 4T
  - Pre
  - Post: 24 hr, x4 cycles
- Clin Resp after AC x4
  - 8/13 R, 5/13 NR

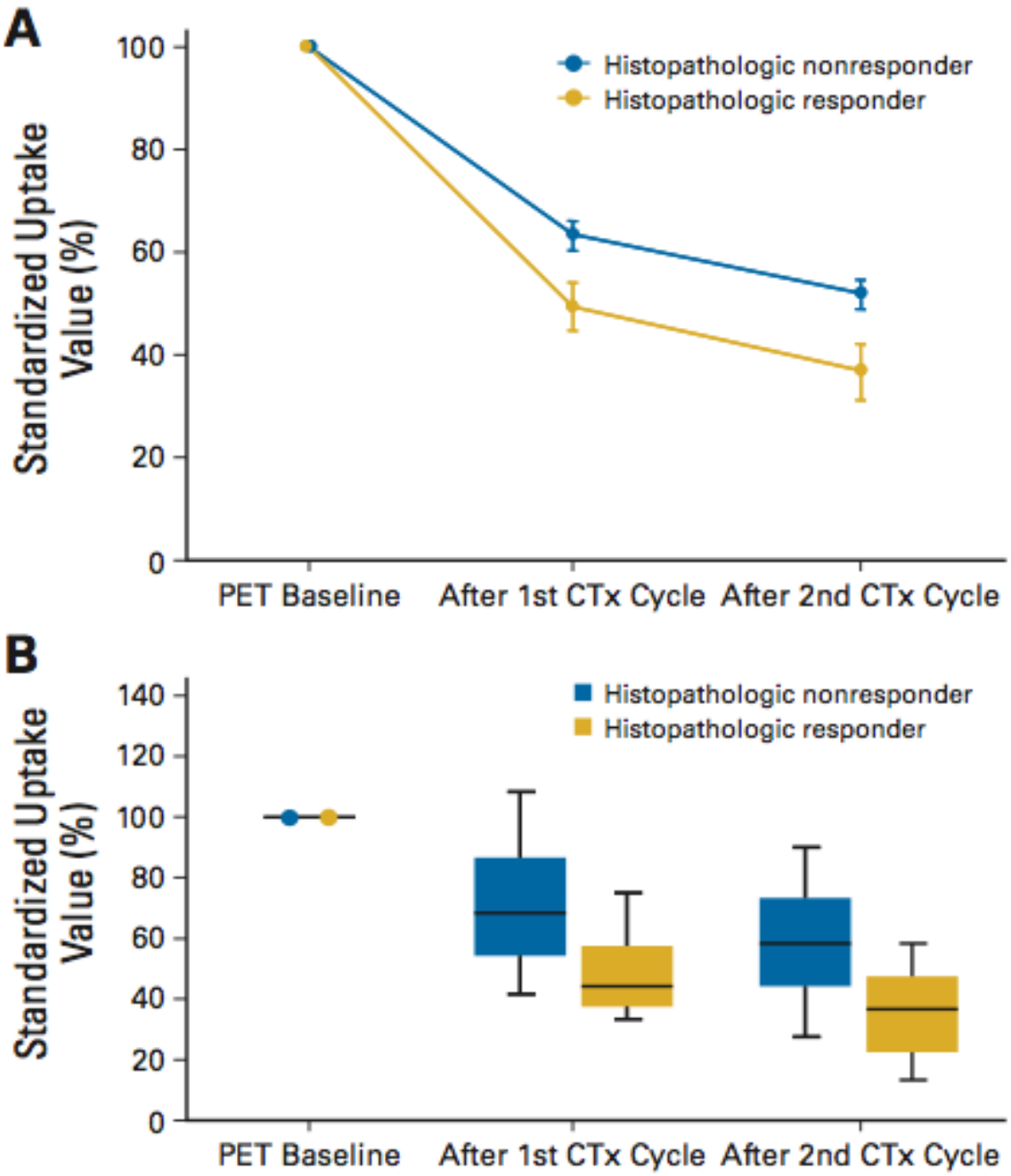
Change in tCho at 24 hrs predictive of response

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

FDG PET to assess response in NAC

Study	No. of breast cancers	No. of cycles of NAC	Timing of PET scans	Definition of pathological response	Optimal SUV threshold
Schelling; JCO, 2000	24	3-4	After 1st or 2nd cycle	pCR or residual small foci of tumour cells	55%
Smith; JCO, 2000	30	8	After 1st, 4th, 7th cycles	Complete microscopic and Complete macroscopic response	Not determined
Rousseau; JCO, 2006	64	6	After 1st, 2nd, 3rd, 6th cycles	>50% therapeutic effect	60%
Berriolo-Riedinger; Eur J Nucl Med Mol Imaging, 2007	47	4-6	After 1st cycle	pCR	60%
McDermott; Breast cancer Res Treat, 2007	96	6-8	After 1st, 3rd or 4th, final cycle	>90% reduction in cellularity	Various
Duch; Eur J Nucl Med Mol Imaging, 2009	50	4	After 2nd cycle	pCR	40%
Kumar; Eur Radiol, 2009	23	6	After 2nd cycle	pCR	50%
Schwarz-Dose; JCO, 2009	104	4-6	After 1st and 2nd cycles	pCR or residual small foci of tumour cells	45% after 1st cycle, 55% after 2nd cycle
Martoni; Cancer, 2010	34	6-8	After 2nd, 4th, final cycles	>90% reduction in cellularity	50%
Hatt; Journal Nucl Med, 2013	51	8	After 2nd cycle	pCR or >50% therapeutic response	48%
Zucchini; European Journal Cancer, 2013	60	6-8	After 2 cycles	Uncertain	50%

- No established definition of pathological response
- No established optimal SUV threshold



Schwarz-Dose; JCO 2009

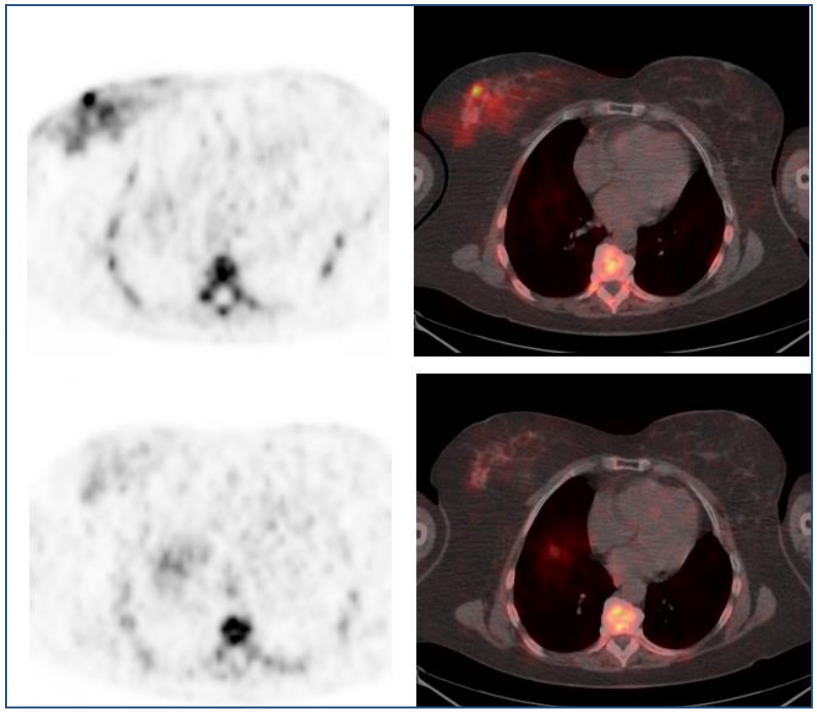
FLT-PET as an early biomarker of response to NAC

Thymidine analogue

Uptake is related to activity of thymidine kinase 1 enzyme (high in proliferating cells)

Neoadjuvant study at MVCC (n=20)

-baseline FLT-PET scan
-repeat 2 weeks post-NAC

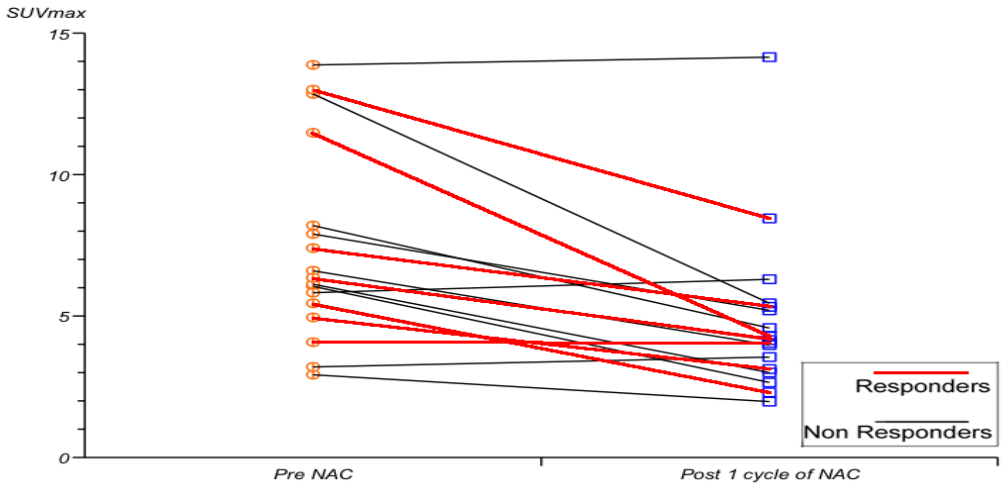


At the 2-week scan, there is an early reduction in FLT uptake with little morphological change.

Woolf DK et al BJC 2014; 110: 2847-2854

FLT PET-CT as a biomarker of proliferation

- Ki-67 measured at baseline
- Ki-67 was correlated with baseline SUV_{max} (p=0.006)
- $Mean_{SUV}$ 7.3 pre, 4.6 post chemo
- 3/20 did not have a drop in SUV
- Δ SUV did not predict path response



Woolf DK et al BJC 2014; 110: 2847-2854

FDG PET does not identify residual disease post NAC

- N=10 with ‘good clinical response’ (after FEC x 6)
- FDG PET post-NAC/pre-surgery and compared to histology

- No patient had uptake in the primary breast ca
- 9/10 patients had residual invasive carcinoma ranging from 2 – 20mm

Burcombe RJ et al EJC 2002; 38: 375-379

Challenges of imaging in assessing response to NAC

- Most studies tend to be non-randomised, single institution with <100 patients
- Expensive and evolving technology
  - Not widely available
  - Techniques not standardised
  - timing of repeat scanning unknown

    may be different for different modalities, treatments, sub-types
- Neoadjuvant therapy not standardized
- Endpoints used may (e.g., pCR, clinical response) may be surrogates for DFS/OS

Conclusions

- Multi-modality imaging in an MDT setting is an essential part of neoadjuvant therapy
- MRI is a good predictor of residual disease but less so for predicting pCR
- Functional/Molecular Imaging techniques yield data that reflect
  - biochemical, molecular, cellular processes
  - can be co-registered onto anatomical images
- Changes in tumour metabolism, proliferation and vascularity precede changes in tumour size
- Standardised imaging should be incorporated into future neo-adjuvant trials