Breast cancer

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Breast Cancer: towards personalised screening and treatment?

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Breast Cancer: Issues

- Screening: overdiagnosis, overall accuracy

  Personalised, risk-adapted
- Diagnosis: non-specific conventional imaging

  Better characterisation required
- Treatment planning: often inaccurate

  Multimodal pre-operative imaging
- Systemic therapy: early prediction of response

  Multimodal, multiparametric assessment
- Overtreatment:

  Commensurate with risk

Better Screening

- Better techniques
  - Full field digital mammography (FFDM)[1,2]
  - Digital breast tomosynthesis (DBT)[3]
  - (supplemental whole breast US, ABUS)
  - Breast MRI? (high risk patients)

- Better risk assessment

[1]*Pisano et al NEJM 2005*

[2]*Vinnicombe et al Radiology 2009*

[3]*Houssami Breast 2013*

Better Risk Assessment

- Risk factors for breast cancer:
  - Age
  - Family history (+/- previous XRT)

  - Mammographic breast density
  - Mammographic texture
  - Reproductive factors (menarche, menopause, parity)
  - Lifestyle factors (BMI, alcohol)
  - Genetic (low risk single nucleotide polymorphisms)

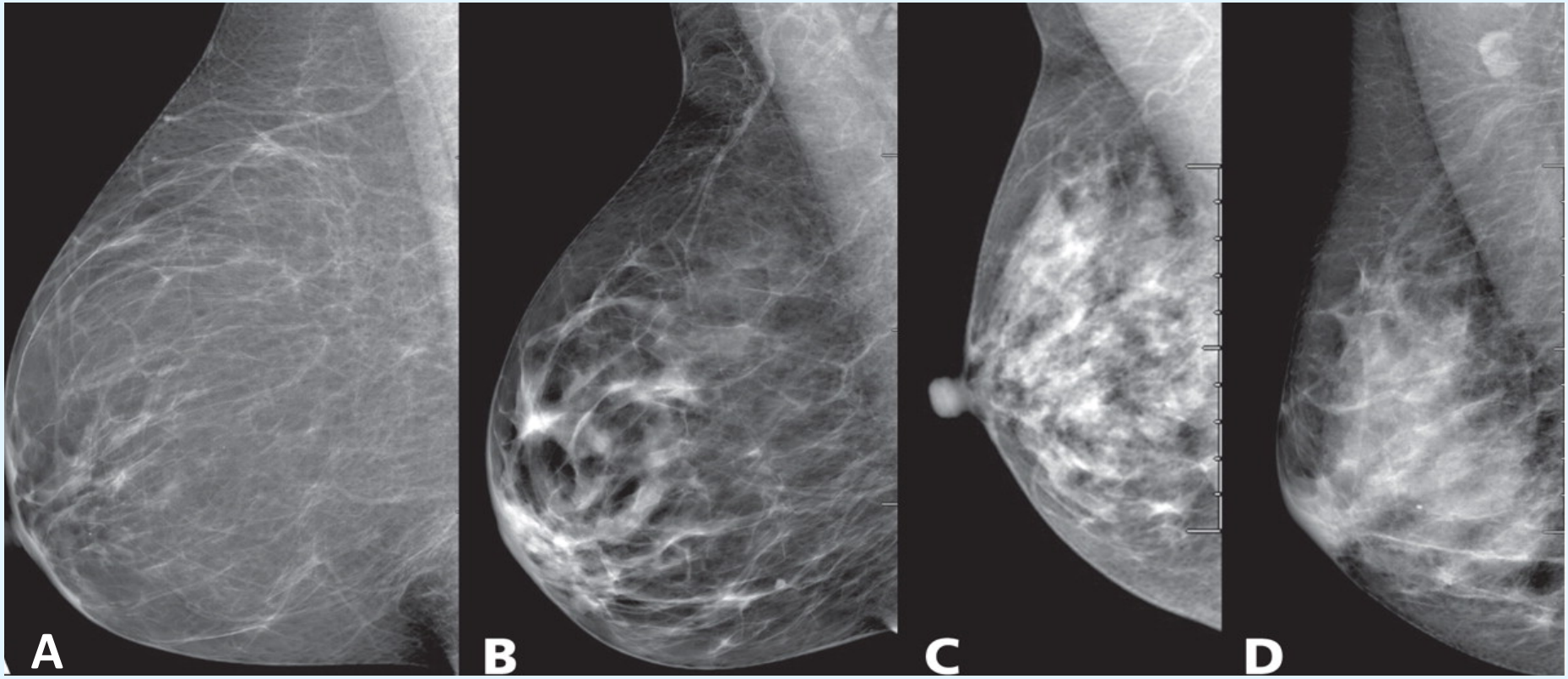
Risk Assessment: Density (MD)

- Women with 76-100% MD have 4-6x relative risk compared to women with 1-25% MD[1,2]
- Breast density is highly heritable[1]
- Explains 14% of FH risk[3]

Only factor with higher relative risk at extremes is age

[1]*Boyd Methods Mol Biol 2009*
[2]*Dos Santos Silva Cancer Epidem Biom Prev 2006*
[3]*Martin et al. Cancer Epidem Biom Prev 2010*

Breast Density



50% all ca's detected 1y after normal screen attributable to having > 50% density

Risk Assessment: Density

- Can we measure it accurately & reliably enough?
- Is its effect independent of other risk factors?
- Does incorporation of density into established risk models improve their predictive ability?

Density: Measurement

- Visual: poor reproducibility & agreement
- Computer assisted thresholding: research tool
- FFDM: automated volumetric measurements
  - Volpara ® (Matakina)
  - Quantra ® (Hologic)
    - Breast volume
    - Dense volume
    - % volumetric density

Density: Measurement

Digital mammographic density and breast cancer risk: a case-control study of six alternative density assessment methods

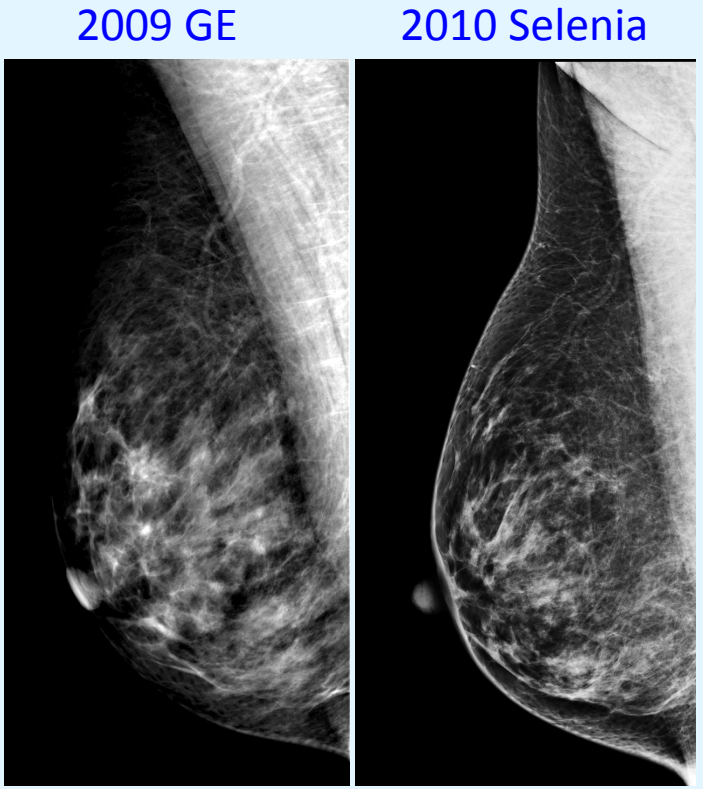
Breast Cancer Res. 2014 Sep 20;16:439

Eng A, Gallant Z, Shepherd J, McCormack V, Li J, Dowsett M, Vinnicombe S, Allen S, dos-Santos-Silva I

- PD (volumetric) positively associated with breast cancer
- Increase in risk per standard deviation increment in PD highest for Volpara (1.83; 95% CI: 1.51 to 2.21)
- Same technique needed for longitudinal measurements

Does the FFDM unit matter?

- Retrospective analysis,
  100 paired FFDM, Selenia & GE units, 1 y apart
- NSD in Volpara readings (ICC >0.9)
- Mean absolute difference for pairs 0.67% (8% of median, 8%)
- Visual assessment: 10% paired scores disagreed
  - GE FFDM perceived as denser



Vinnicombe, Hart, Whelehan ECR 2014

Risk Assessment: Density

- Is its effect independent of other risk factors?
- HAMAM (EU FP7 funded, 2008)
  - Case-control study
  - 18 SNP genotype score (predictive of risk)
  - NO correlation between BOADICEA risk
    - SNP score
    - Volumetric MD (Volpara)

Merrick, Mallin, Berg, Vinnicombe (submitted)

Can addition of MD improve risk assessment models?

- Most risk models (Gail, BOADICEA) poor for individual women
- Studies to date:
  - Visual assessment of MD or computerised thresholding
  - Only slight increases in predictive accuracy
- Results of studies with volumetric MD & better calibrated models awaited

Other measures

- MRI measurement of fibroglandular volume
  - Inherently 3D, therefore gold standard?
  - Anonymous Trust Grant
  - Analyze® segmentation software
  - Reproducibility varies with MR sequence (T1, T2)
  - Good absolute agreement with volumetric MD (ICC 0.742)
  - Systematic bias (Volpara PD > MRI FGV)[1]

[1]*Vinnicombe, Wood, Waugh, Cui UKRC 2015*

Personalised screening

Risk-adapted screening: challenges

- How to incorporate MD, texture, SNP score into risk model?
- Logistics of data collection and integration
- Presentation to patient and clinician
- Personalised screening programme
- Effect of lifestyle interventions

"I am worried about my risk of breast cancer"

WP 1
Recruitment
Getting correct imaging,
DNA and clinical data

WP 2
Image processing 7 output
DNA analysis
Integration of data

"I understand and can manage my risk of breast cancer"

WP 3
How patient and clinician receive and use information

WP 4
Delivering tailored management
"Individual management pathway"

Vinnicombe, Anderson, Berg, Whelehan, Ozakinci
Under review at CSO

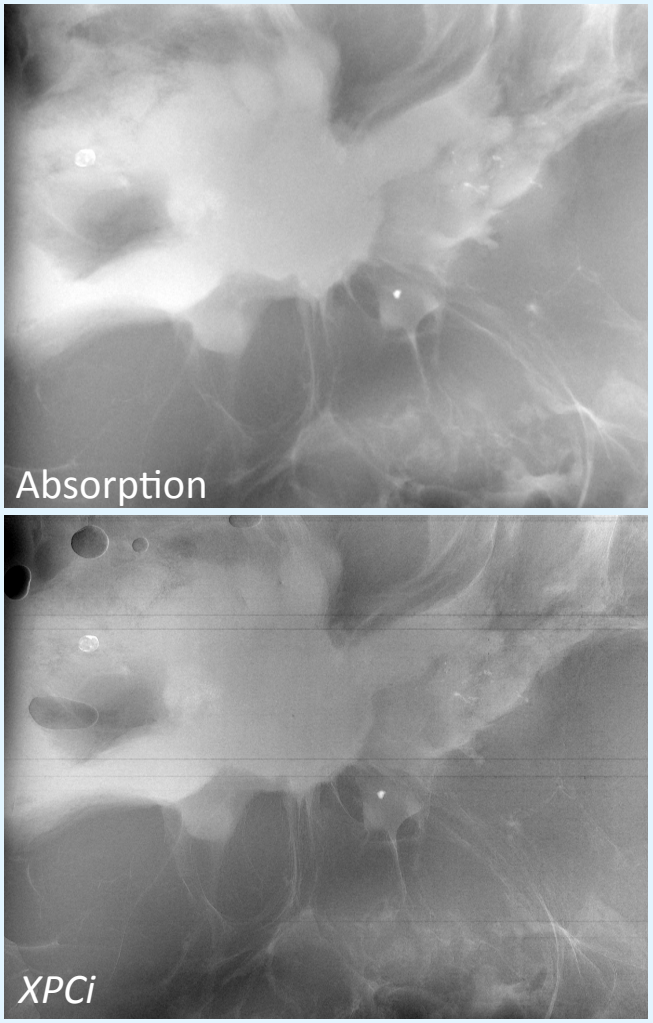
Better Lesion characterisation

- Phase contrast mammography (XPCi)
- X-ray diffraction mammography
- Digital breast tomosynthesis (DBT)
- US shear wave elastography (SWE)

Phase Contrast Mammography

XPCi:

- Wellcome Trust Translational Award, £461k
- Medical Physics, UCL (Prof Rob Speller)
- Low dose phase contrast mammography c. conventional x-ray sources
- Better visualisation high contrast detail (trabeculae, Ca^{2+})
- Submitted to *Radiology*



Olivo A, Vinnicombe SJ, Speller RD. Med Phys. 2013 Sep;40(9):090701

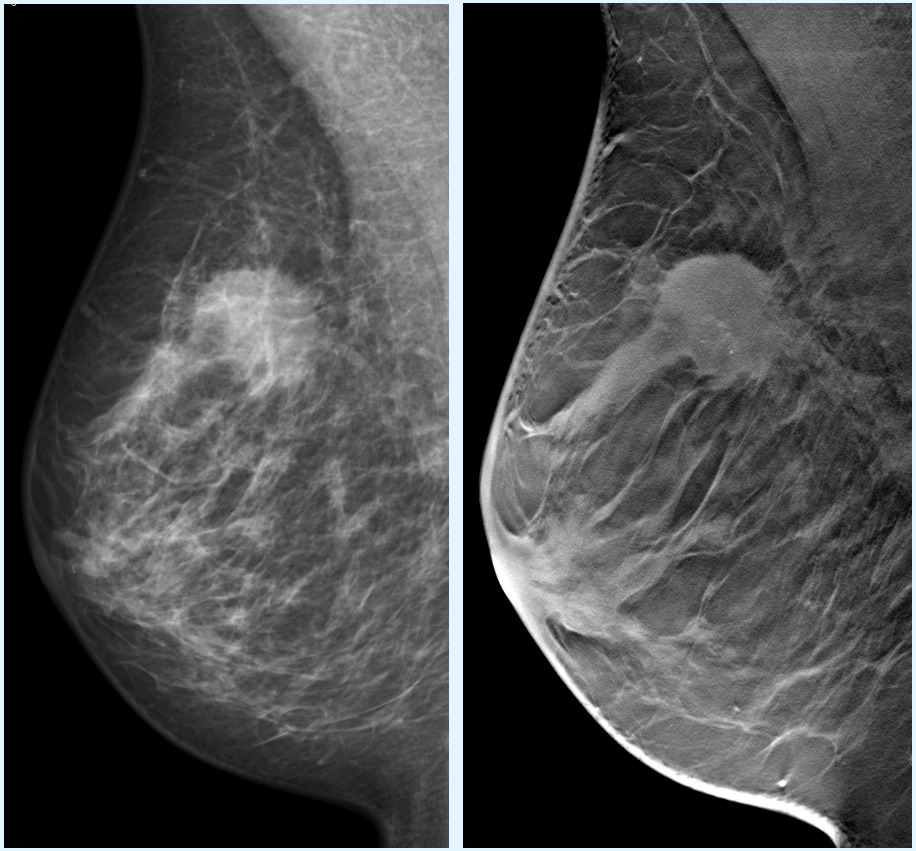
X-ray Diffraction Imaging

- Collaboration with Prof Rob Speller, Med Physics, UCL
- Pilot study funded by BCC, December 2014
- Can we identify abnormal collagen in & around cancers?
  - 20 excised breast cancers
  - Diffraction signatures (from tumour, peritumoural & normal tissues)
- Correlation with high res. mammography & pathology
- Potential impact:
  - 'high risk' phenotype; targeted screening
  - better surgical planning
  - i.d. of likely non-responders to adjuvant R_x

breast cancer campaign
Research that saves lives

Digital Breast Tomosynthesis (DBT)

- Screening: increased sensitivity cf. FFDM (generally low grade, spiculate ca's)
- Higher specificity (reduced recall rates)
- Better characterisation of mammographic lesions
- Better lesion sizing for surgical planning



DBT

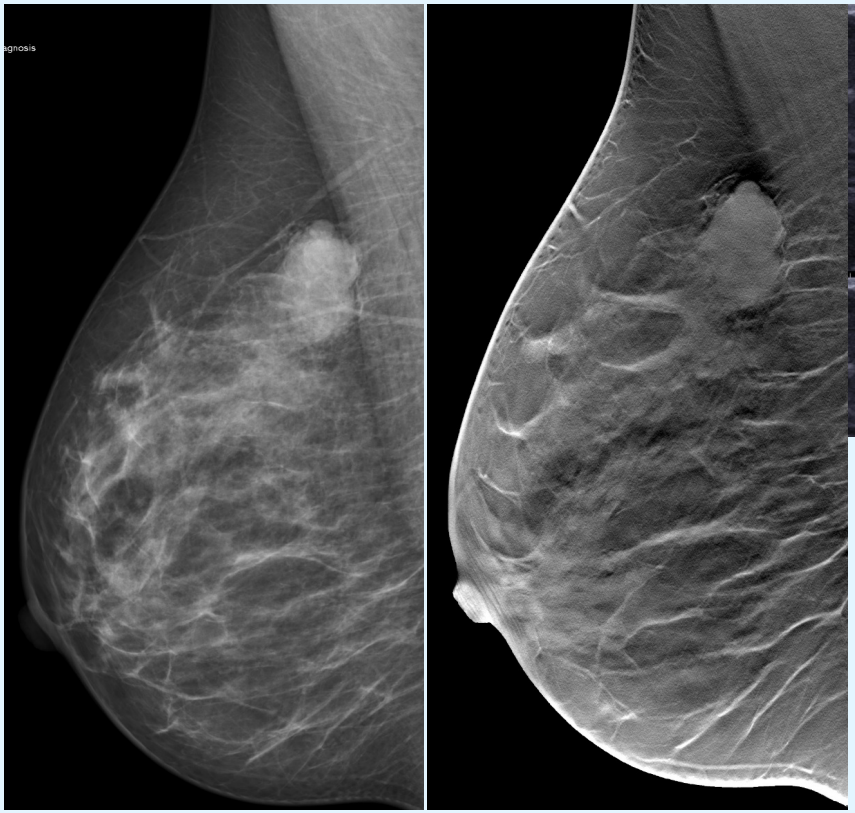
- Not all DBT units are the same!
- Only Selenia Dimensions recognised by NHS BSP
- Breast Imaging Research Group UoD coordinating multi-reader study of Siemens DBT in screening assessment (Munich, Germany)
  - Funded by Siemens
  - Whelehan, Vinnicombe, Evans

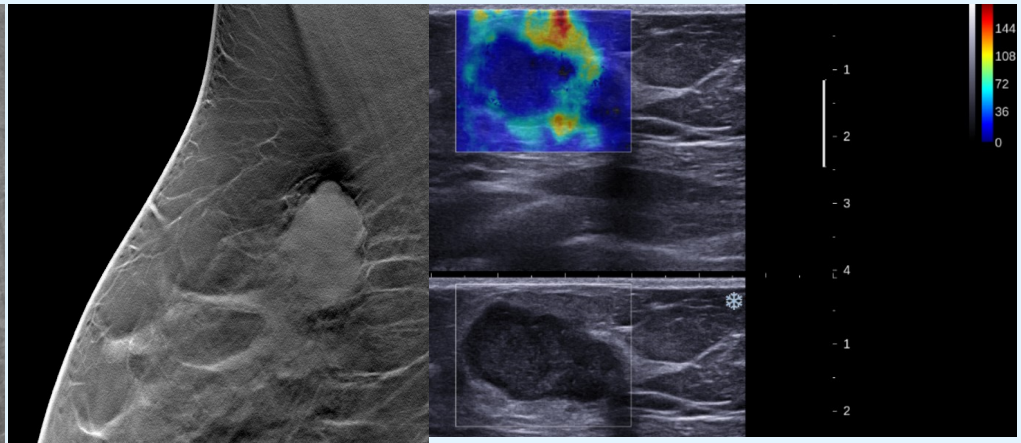
Shear Wave Elastography (SWE)

- Combination of grey scale US and SWE v. sensitive for cancer detection (NPV 100%)[1]
- False negatives very rare (small, low grade ca's, DCIS)[2]
- Obviates need for biopsy of benign appearing masses in women < 40 yrs
- Research has formed basis for breast US elastography practice guidelines in:
  - Japanese Society of US in Medicine
  - Korean Society of US in Medicine

[1]*Evans et al Br J Cancer 2012*
[2]*Vinnicombe et al Eur Radiol 2014*

SWE: Lesion Characterisation





- 42 y.o
- P3 lump
- 2D M3, 3D M4

- U/S U3
- SWE: U5
- Grade 3 triple negative ca

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- Overtreatment:

  – Commensurate with risk

VPH-PRISM

- Virtual Physiological Human: Personalized Predictive Breast Cancer Therapy through Integrated Tissue Micro-Structure Modelling

- EU FP7 funded
  265,000 Eu to UoD (2013-16)

EUROPEAN INSTITUTE FOR BIOMEDICAL IMAGING RESEARCH

VPHPRISM

VPH-PRISM

Collaborating Partner Centres

1) EIBIR (Vienna)
2) Fraunhofer-Mevis (Bremen)
3) Stichting Katholieke Universitat (Nijmegen) - RUNMC
4) University College London (UCL)
5) Phillips Technologie GMBH (Hamburg)
6) University of Dundee – UDUN
7) University of Chicago - UCHI
8) Medizinische Universitaet Wien - MUW
9) Boca Raton Hospital (USA)

VPH-PRISM: Aims

- Optimisation of breast cancer imaging by integrated forward modelling of the image formation process
- Predict personal risks for cancer progression *and sensitivity to NAC*
- Proof of concept study

VPH-PRISM

Study Overview:

- 4 core clinical sites (RUNMC, UDUN, UCHI, MUW)
  - data from at least 50 patients each, collected prospectively, all have DBT, 3T MRI then 2D & 3D SWE prior to surgery
- Cases collected at each site will include:-
  - 10-15 cases of pure DCIS > 20 mm in extent
  - 10-15 surgically treated T1 tumours
  - 10-15 surgically treated T2+ tumours
  - 10-15 T2+ tumours treated with neoadjuvant chemotherapy, with at least 3 MRI examinations: prior, halfway and after NAC

Medical imaging markers of cancer initiation, progression and therapeutic response in the breast based on tissue microstructure

Grant Reference: EP/K020439/1
April 2013 to March 2016
£340k for UoD

Partners:

- UCL CMIC
  - Prof D Hawkes (PI)
  - Prof D Alexander (co-I)
  - Dr P Taylor (co-I)
  - Dr J Hipwell
  - Dr L Panagiotaki
  - Dr T Mertzanidou
  - Dr C Bailey
  - Dr P Wijeratne
- Uni. of Dundee
  - Prof A Evans (co-I)
  - Dr S Vinnicombe (co-I)
  - Prof L Bidaut (co-I)
  - Ms P Whelehan (co-I)
  - Dr K Kitching
  - Dr R Morin
- KCL
  - Prof S Pinder

MIMIC: Aims

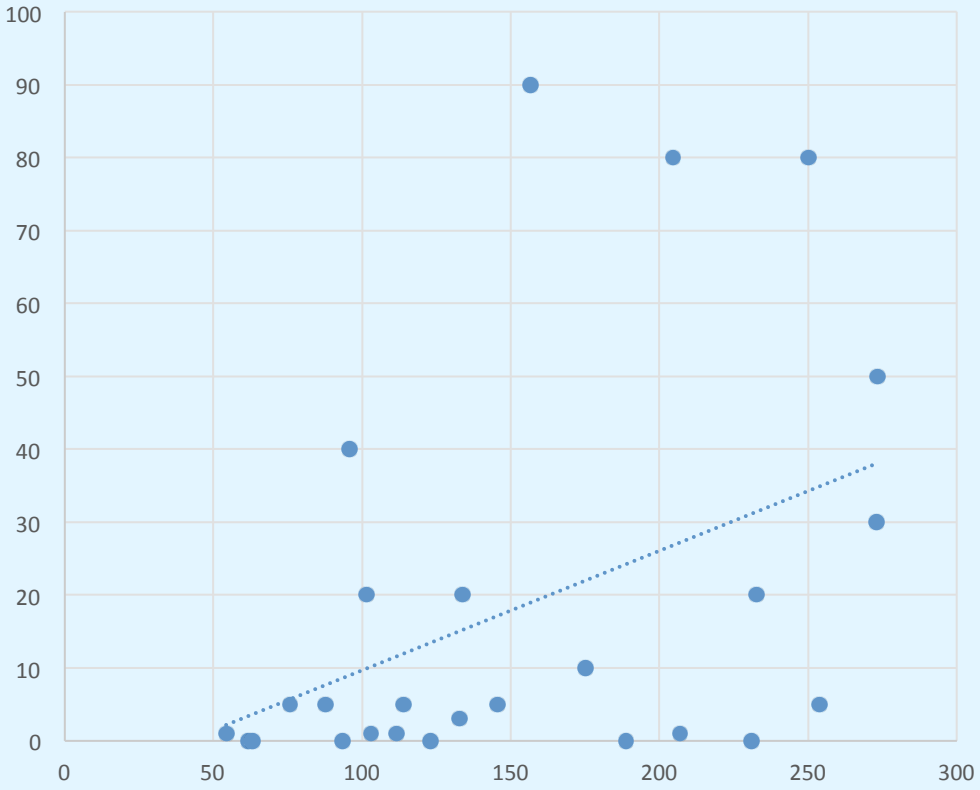
- Development of computational and imaging tools to stratify tumours & peri-tumoural stroma regarding risk of metastatic progression and response to NAC
- Imaging peri-tumoural stroma
  - may provide prognostic and predictive information
  - stromal enhancement on MRI correlates with response to NAC[1]
  - boundary can be defined by diffusion weighted MRI[2]
  - SWE: stromal stiffness predicts aggressive histological characteristics and chemoresistance[3]

[1] *Hattangadi et al, Am J Roentgenol 2008*
[2] *McLaughlin et al, JMRI 2014*
[3] *Evans et al, Br J Cancer 2013*

Baseline stiffness vs. NAC response

HER2 +ve tumours

% residual cellularity



R=0.42

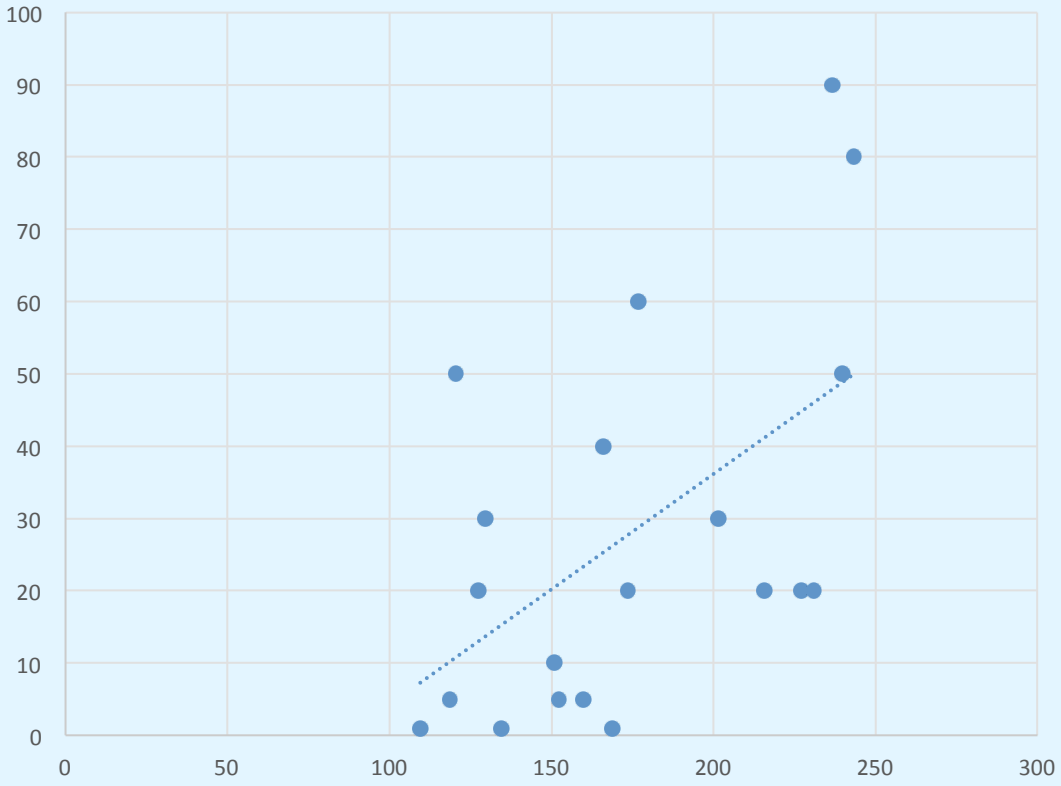
Mean stiffness kPa

Evans A, Armstrong S, Whelehan P, Thomson K, Rauchhaus P, Purdie C, Jordan L, Jones L, Thompson A, Vinnicombe S. Br J Cancer 2013;109:2798-02

Baseline stiffness vs. NAC response

Luminal tumours

% residual cellularity



R=0.55

Mean stiffness kPa

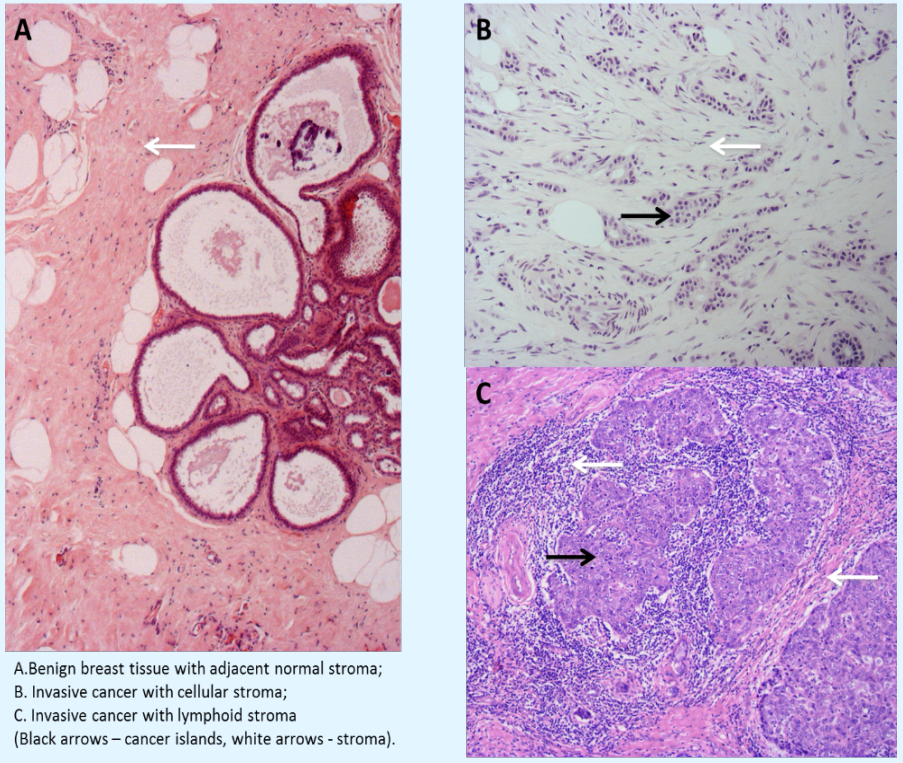
Evans A, Armstrong S, Whelehan P, Thomson K, Rauchhaus P, Purdie C, Jordan L, Jones L, Thompson A, Vinnicombe S. Br J Cancer 2013;109:2798-02

SPECIALS

- Breakthrough Breast Cancer Programme Grant 2013-17, £900k
- Predicting response to NAC
  - Stromal protocol evaluating Chemotherapy: Imaging and Laboratory studies
  - Co-PIs AE, SV, FFP
  - DBT, 2D & 3D US & SWE of stroma, high res multiparametric MRI (MP-MRI) - DCE, DWI, DTI

Background

- Stroma in breast cancer differs from normal breast stroma
- Stroma-related gene signatures predict resistance to neoadjuvant chemotherapy (NAC)[2]
- Breast cancer stroma thus determines prognosis of breast ca & likelihood of response to NAC



A.Benign breast tissue with adjacent normal stroma;
B. Invasive cancer with cellular stroma;
C. Invasive cancer with lymphoid stroma
(Black arrows – cancer islands, white arrows - stroma).

[1]*Farmer et al. A stroma-related gene signature predicts resistance to neoadjuvant chemotherapy in breast cancer. Nature Medicine 2009;15(1):68-74*

Key Research Questions

1. Can peritumoural imaging distinguish subtypes of breast cancer?
2. Which imaging features of peritumoural tissues change during NAC and predict response?
3. What are the pathophysiological features of peritumoural tissue in subtypes of breast cancer?
4. Are the pathophysiological changes in peritumoural tissues with NAC predictive or prognostic?
5. What are the features of peritumoural stromal tissues compared with intra-tumoural stroma?
6. Can these imaging and laboratory data be used to populate developing mathematical modelling techniques at the cellular, intercellular and whole tissue levels?

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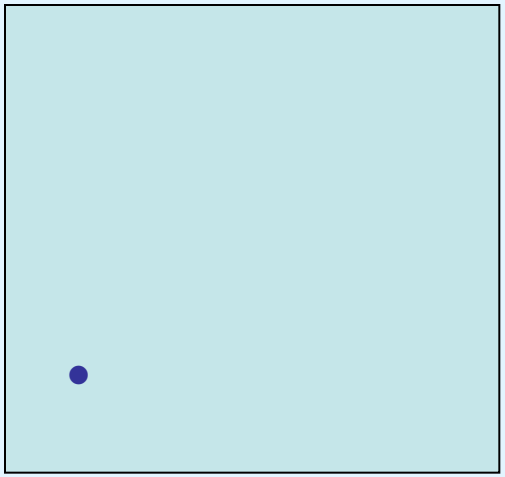
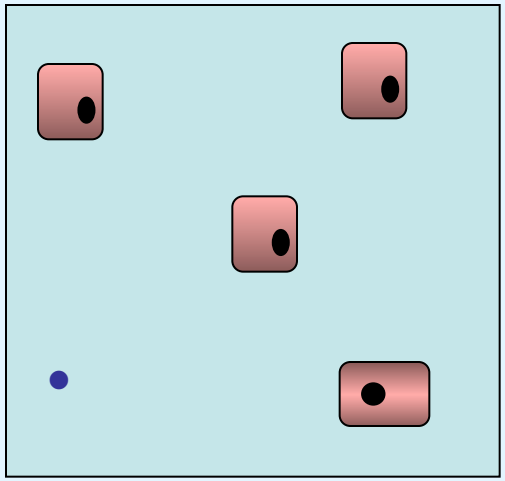
Diffusion Weighted MR Imaging

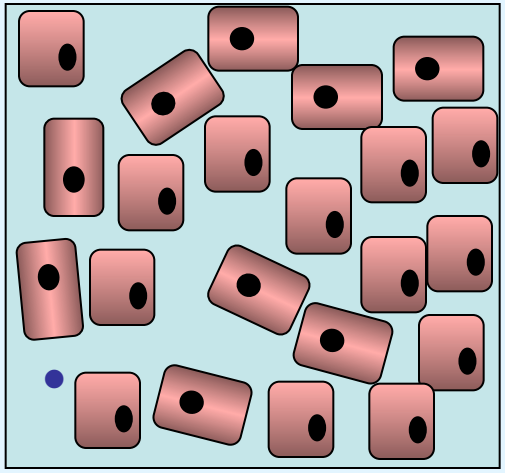
Sensitive to factors affecting microscopic motion of water



Random Brownian Motion



Free diffusion
Low signal intensity DWI
High signal ADC



Restricted diffusion
High signal intensity DWI
Low signal ADC

cell • water molecule

ADC = Apparent diffusion coefficient

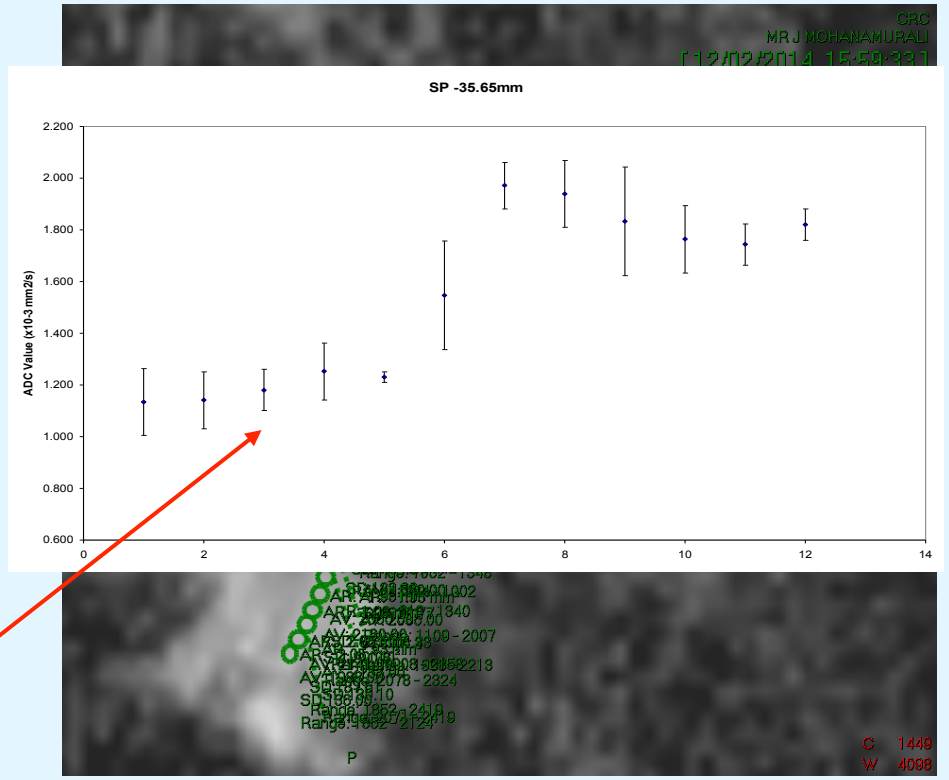
Peri-tumoural Diffusion

- Analysis currently performed manually

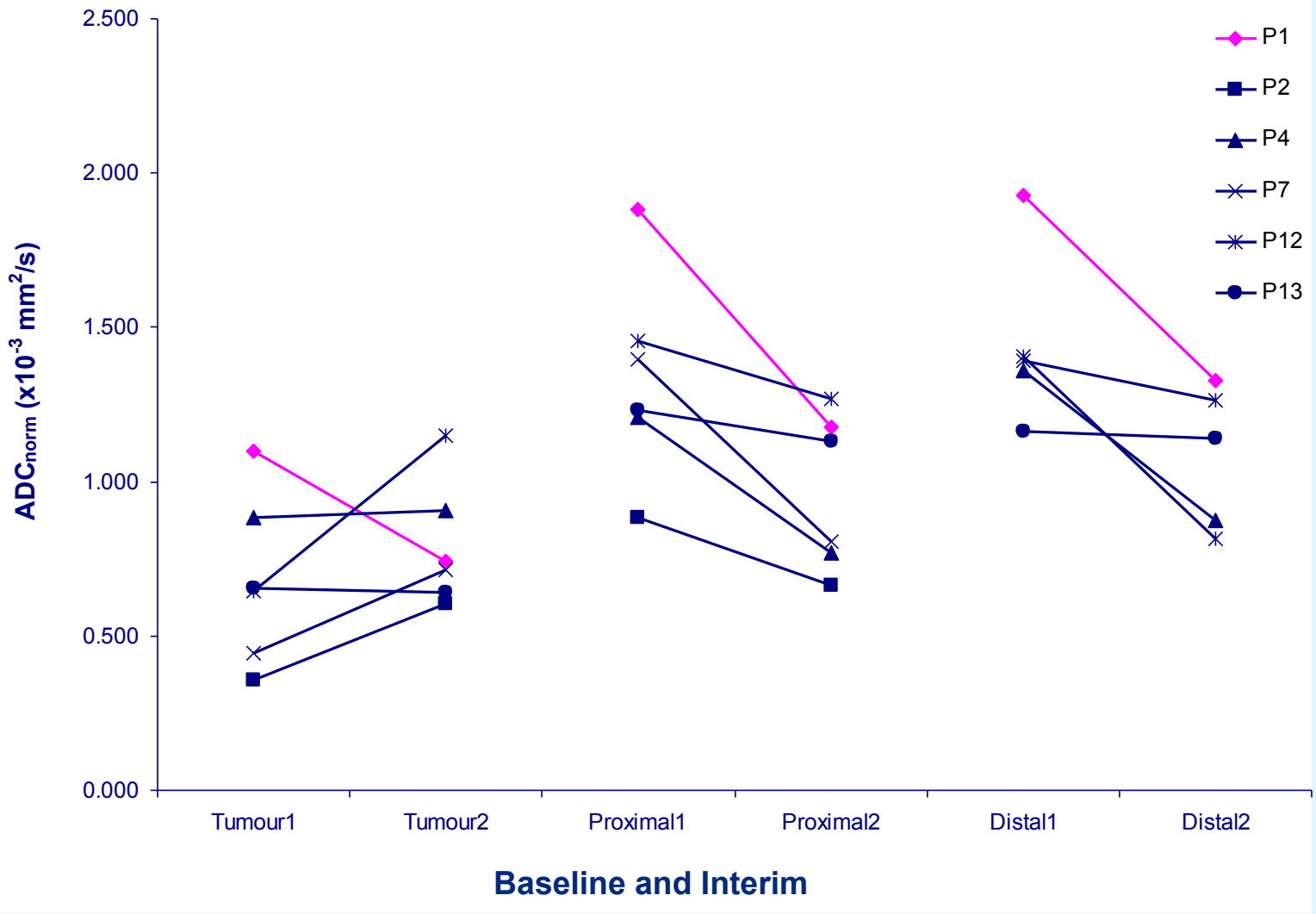
- Within the tumour:
  2-5mm within perceived boundary

- Proximal to the tumour:
  2-5mm from perceived boundary

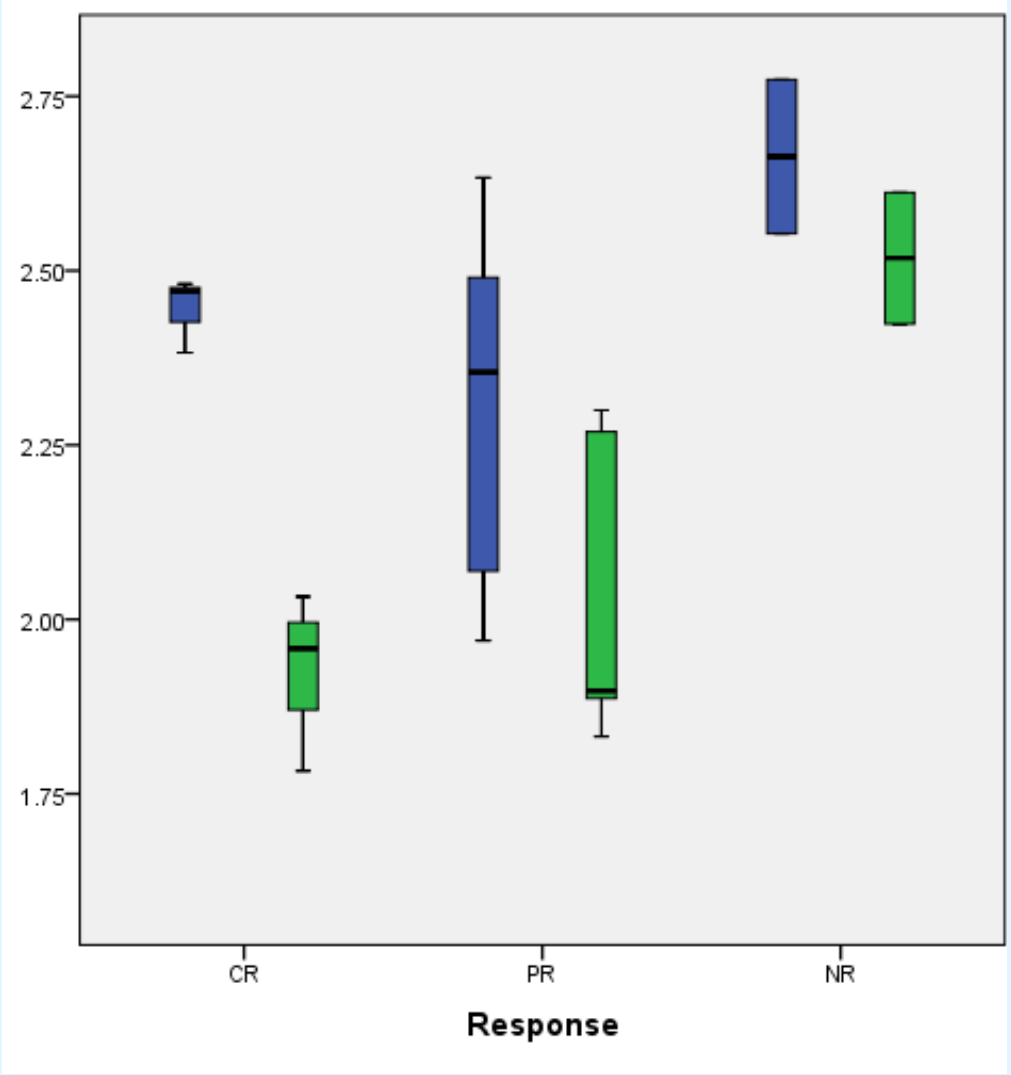
- Distal to the tumour:
  9-13mm from perceived boundary



ADC_{norm}

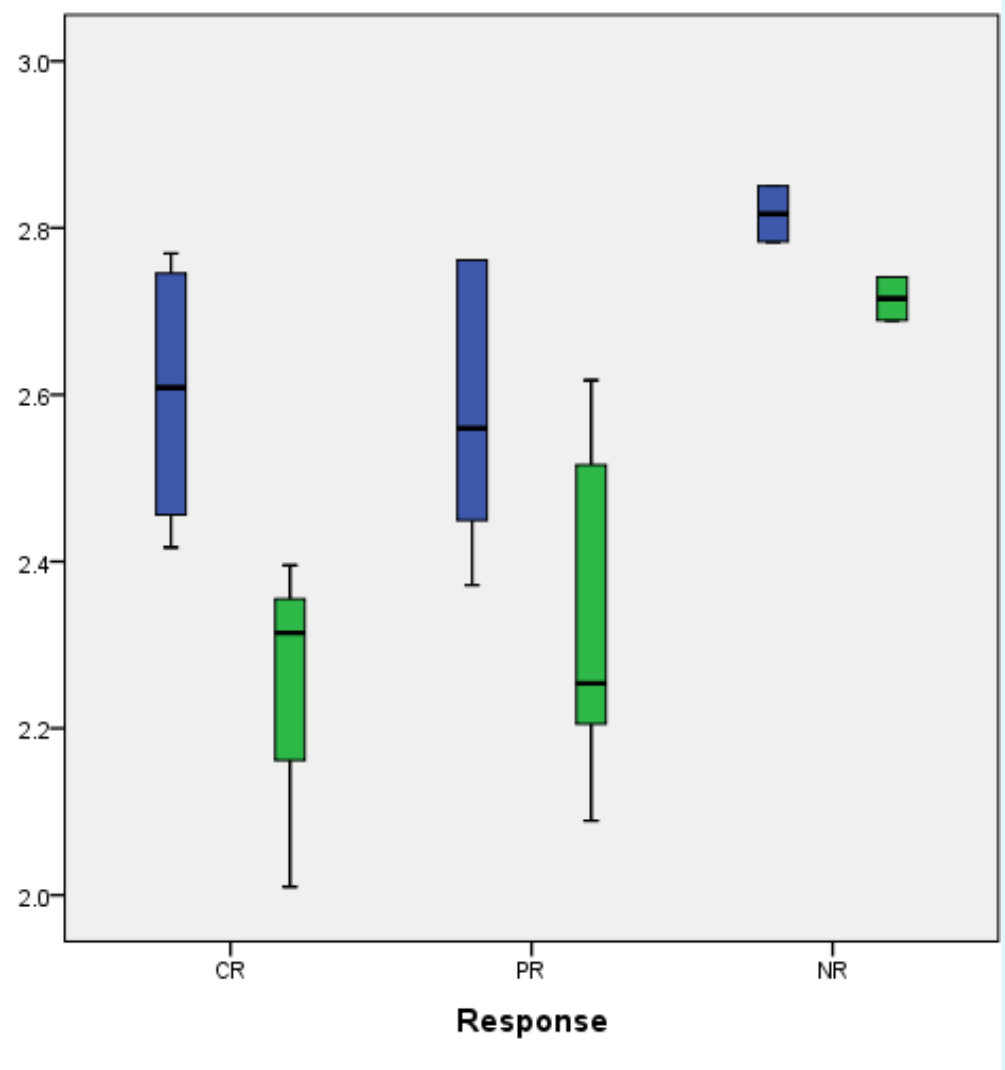

2.500
2.000
1.500
1.000
0.500
0.000
ADCnorm (x10-3 mm2/s)
P1
P2
P4
P7
P12
P13
Tumour1
Tumour2
Proximal1
Proximal2
Distal1
Distal2
Baseline and Interim

Textural Analysis: ADC Entropy



p=0.021

Textural Analysis: T2 Entropy



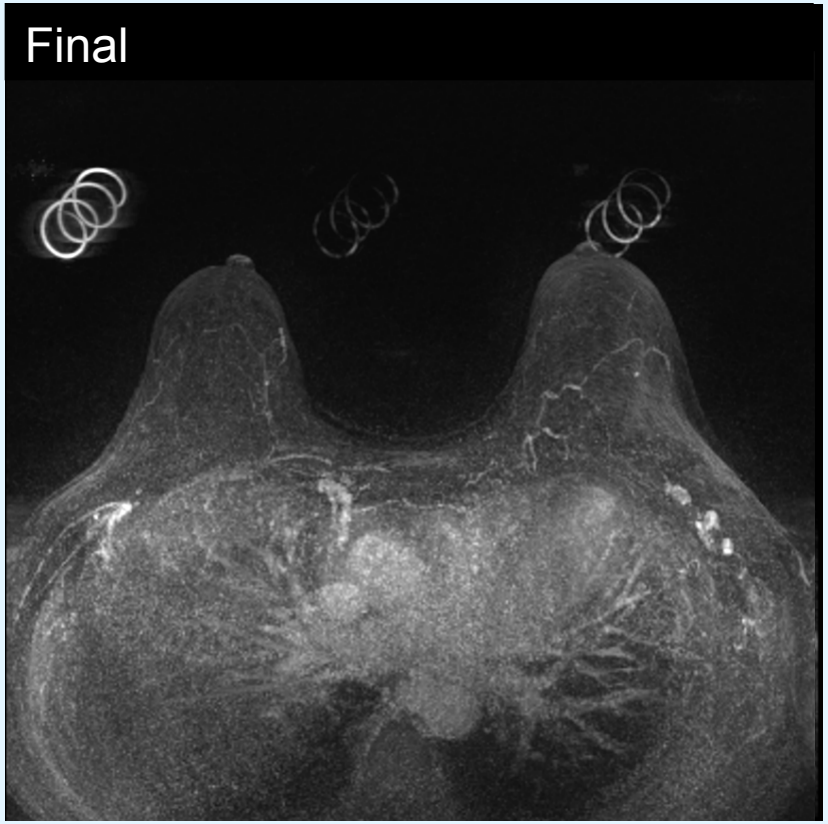
Visit 1

Visit 2

p= 0.008

Patient 4

- Grade 3 invasive ductal carcinoma
- Triple negative basal phenotype



Volumes:

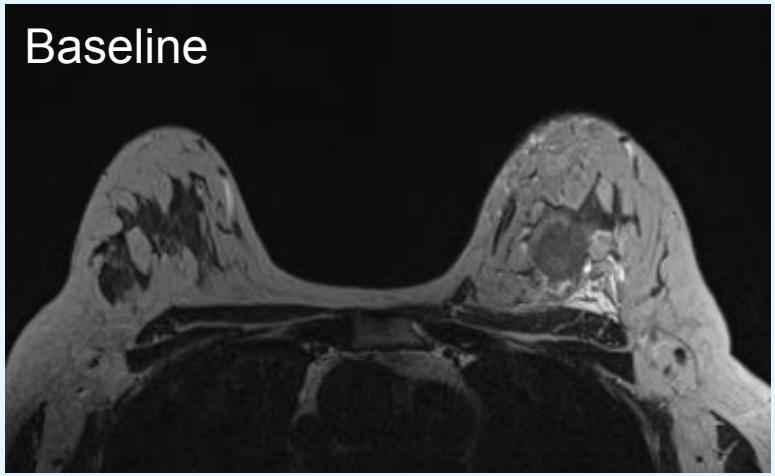
Baseline: 36.3 cc

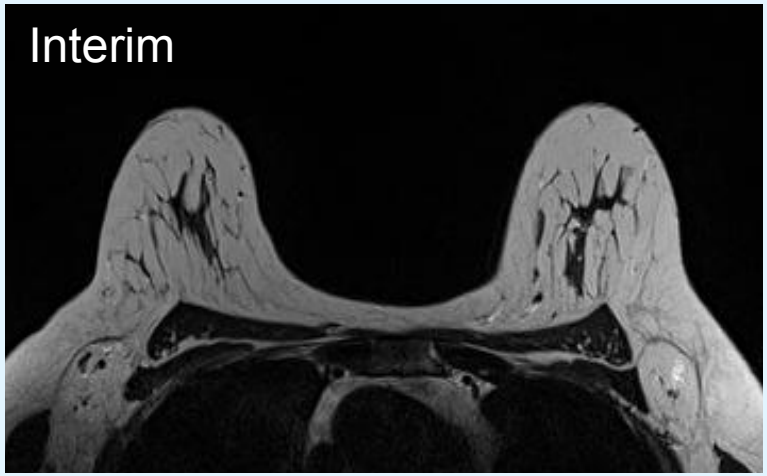
Interim: 3.7 cc

Final: 0.0 cc

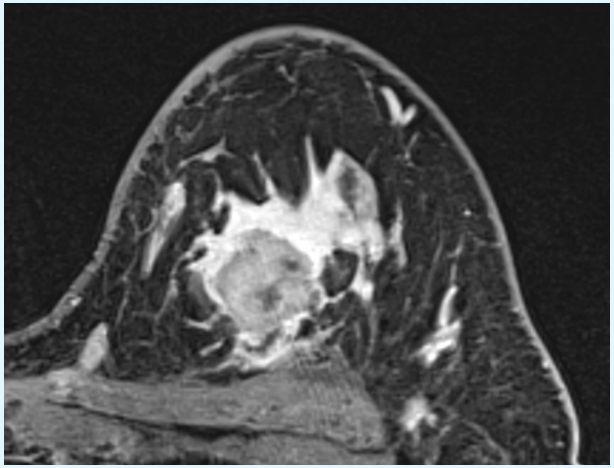
Multiparametric MR Imaging

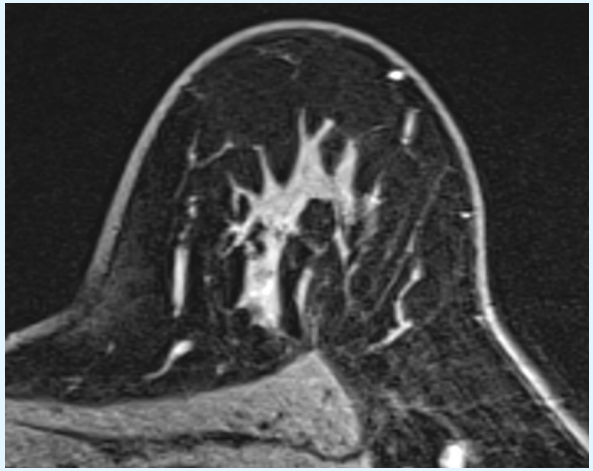
T2W





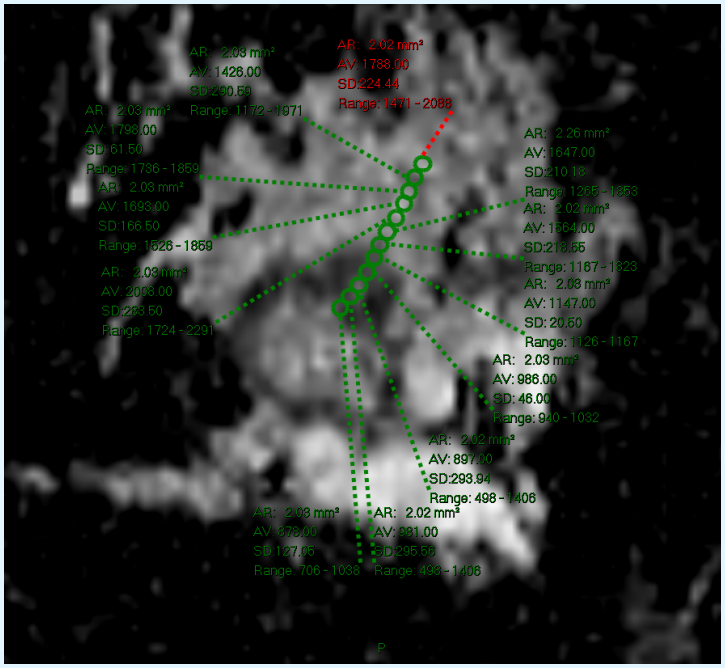
Stromal enhancement

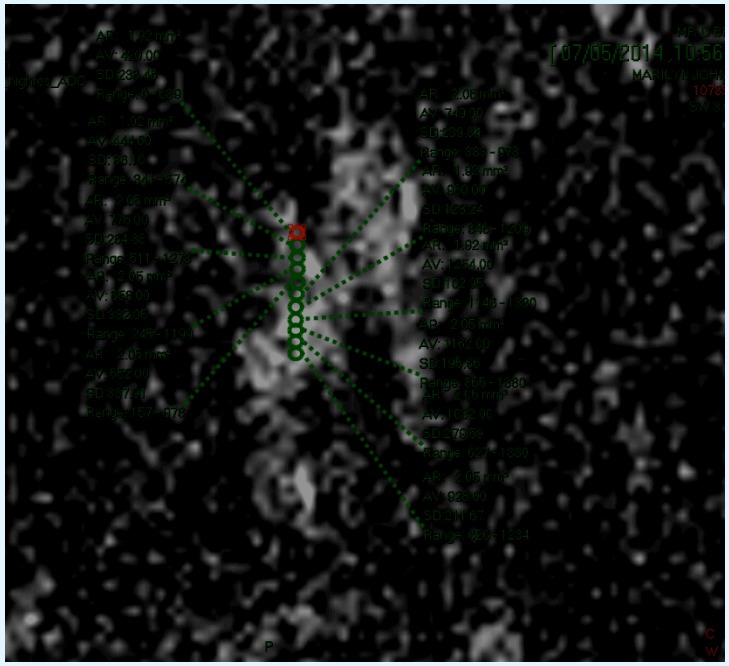




Multiparametric MR Imaging: ADC

	Within tumour (2-5mm)	Proximal to tumour (2-5mm)	Distal to tumour (9-13mm)
Visit 1	1.276 ± 0.167	1.748 ± 0.230	1.967 ± 0.190
Visit 2	1.169 ± 0.178	0.990 ± 0.230	1.128 ± 0.200
Visit 3	-	-	-





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Overtreatment

- Treatment should be commensurate with risk
- Less axillary surgery
  - can imaging predict likelihood of nodal disease?[1]
- Noninvasive Rx for low risk cancers
  - MR guided focused ultrasound surgery (MRgFUS)
  - Current systems slow, suboptimal for breast
  - Can Thiel cadavers be used as a model for research?

[1]*Evans A, Rauchhaus P, Whelehan P, Thomson K, Purdie CA, Jordan LB, Michie CO, Thompson A, Vinnicombe S. Breast Cancer Res Treat 2014*

MRgFUS

- DCC funded feasibility study 2014
  - Thiel and fresh breast tissue for sonication in lab, 1.5T MR unit, 3T CRC unit
  - MR compatible chamber built for sonication of samples[1]
  - MR compatible thermocouple
- Results:
  - No visible lesions in Thiel tissue post sonication[2]
  - Dampened temperature rises cf. fresh tissue samples
  - First samples sonicated in CRC 3T magnet successfully[3]

[1]Joy, Purdie, Melzer, Cochran, Vinnicombe 2014 ISTU

[2]Joy, Yang, Karakitsios, Eisma, Purdie, Melzer, Cochran, Vinnicombe 2014 FUS Symposium

[3]Joy, Yang, Cavin, Vinnicombe

Conclusions:

- Journey of the patient at risk of or with breast cancer highlights challenges of risk-adapted personalised screening and treatment
- Multimodal, multiparametric imaging has the potential to advance progress towards this goal

Acknowledgments

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Frances Fuller-Pace
Celine Pourreyron
Andy Evans
The Tayside patients

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