MRI, Digital Mammography and Sonography: tumor characteristics and tumor biology in the primary setting

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Primary Systemic Therapy

- Options for PST
  - Chemotherapy
  - Endocrine therapy
  - Trastuzumab, Lapatinib
- Improved surgical options
  - LABC > Mastectomy
  - Large operable > BCS
- In vivo assessment of response
- Evaluation of new agents
- pCR is a surrogate for improved long-term outcome
Role of Imaging in Primary Systemic Therapy

• Pre-treatment
  – Evaluate suitability for PST

• During treatment
  – Early assessment of response
  – In sequential schedules to determine response to initial treatment

• Post-treatment
  – Evaluate response
  – Determine extent of disease to aid surgery
Mammography

- Widely used in screening / diagnostics
- Screen film mammography now being replaced with digital mammography
- Allows better rates of cancer detection in younger women, dense breasts, pre / perimenopausal
Mammography in response assessment (1)

• Most studies are >15 years old due to changes in imaging and multi-modality approach

• Study of 49 pts receiving NA CMF showed examination predicted response better than mammography (65.7% vs 54.3%)\(^1\)

• Retrospective study of 95 pts showed 5/8 pts with imaging CR had residual tumour and only 3/8 who had pCR were correctly identified\(^2\)

• Retrospective review of 56 pts comparing mammogram to clinical examination showed mammography was more sensitive for residual disease (79% vs 49%) but less specific (77% vs 92%)\(^3\)

\(^1\) Cocconi G et al. Breast Cancer Res Treat 1984
\(^2\) Vinnicombe SJ et al. Radiology 1996
\(^3\) Helvie MA et al. Radiology 1996
Mammography in response assessment (2)

- No studies evaluating the routine use of mammography during NAC.
- Only used at the end therefore reducing utility in early identification of non responders
Ultrasonography

- Widely used for imaging of primary lesions and nodes as well as image guided biopsies and interventions

- Use of ultrasound in addition to that of mammography has been shown to increase sensitivity (97% vs 74%) in the detection of primary breast cancer, with a false positive rate of 2.4%\(^1\)

\(^1\) Kolb TM et al. Radiology 2002
Ultrasound in response assessment

• Most studies have compared US to mammography or added the two together
• Retrospective study of 100 patients found that ultrasound had a worse correlation with pathological outcome than examination or mammography but better correlated with lymph node response\(^1\)
• Smaller study of 42 patients compared physical examination alone, a combination of mammography and ultrasound, and a combination of all three. The most accurate combination was found to be mammography and ultrasound (67%) \(^2\)
• The German Breast studied 285 patients and demonstrated after two cycles of NAC, US assessment was more accurate than clinical examination in predicting non-responding patients as well as patients who went on to have a pCR\(^3\)

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\(^1\) Herrada J et al. Clin Cancer Res 1997
\(^2\) Peintinger F et al. Ann surg Oncol 2006
\(^3\) Minckwitz von G Annals of oncology 2005
Newer US techniques

- 3D power doppler US
- Microbubble US
- Automated whole breast US
- 3D US
- Sonoelastography

3D power doppler ultrasound of tumour neovascularisation
MRI: role in primary systemic 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

Meta-analysis of accuracy in prediction of tumour response

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Clinical Examination</th>
<th>Digital Mammography</th>
<th>Ultrasound</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accuracy</td>
<td>57%</td>
<td>74%</td>
<td>79%</td>
<td>84%</td>
</tr>
<tr>
<td>Positive Predictive Value</td>
<td>91%</td>
<td>85%</td>
<td>85%</td>
<td>93%</td>
</tr>
<tr>
<td>Negative Predictive Value</td>
<td>31%</td>
<td>41%</td>
<td>44%</td>
<td>65%</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>50%</td>
<td>81%</td>
<td>90%</td>
<td>86%</td>
</tr>
<tr>
<td>Specificity</td>
<td>82%</td>
<td>48%</td>
<td>33%</td>
<td>79%</td>
</tr>
</tbody>
</table>

Patterns of response to Neoadjuvant Chemotherapy

A. Concentric shrinking
MRI showing complete response
Pathology: complete response also

Pre-Chemo

Mid-Chemo

Post-Chemo
B. Scatter pattern
Pre Rx
Final pathology: 50mm of disease including DCIS
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
Cancer hallmarks & metabolic derangements

Kroemer, G & Pouyssegur J. Cancer Cell 2008; 13: 472-482

- 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

Apoptosis
- $^{99m}$Tc-Annexin V

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

Metastasis
- Lymphography
- WB-DWI
- Bone scan
- CT etc

Gatenbury RA & Gillies RJ. Nature Cancer Reviews 2008; 8: 56-61
Contrast medium in different tissue compartments are the cause for these appearances.
Physiology based quantification of T₁W DCE-MRI

- Transfer constant \((K^{\text{trans}})\)
- Extracellular leakage space \((v_e)\)
- Rate constant \((k_{ep})\)

\[
K_{ep} = \frac{K^{\text{trans}}}{V_e}
\]

Modified from Tofts 1995
Changes in perfusion parameters after 2 cycles according to clinical response

**Antracyclines (FEC)**
Responders n=19; Non-responders n=9

- **Ktrans** (p<0.01)
  - Responders: -29.5
  - Non-responders: -34.2

- **kep** (p<0.01)
  - Responders: 19.5
  - Non-responders: 5.7

- **rBV** (p<0.01)
  - Responders: 56.8
  - Non-responders: -32.6

**Taxanes (docetaxel)**
Responders n=21; Non-responders n=4

- **Ktrans** (p=0.01)
  - Responders: -58.1
  - Non-responders: -52.2

- **kep** (p=0.09)
  - Responders: -8.9
  - Non-responders: -41.3

- **rBV** (p=0.63)
  - Responders: -48.4
  - Non-responders: -33.2
DCE-MRI as prognostic biomarker

- High $K_{\text{trans}}$ and IAUGC$_{60}$ values after two cycles of neoadjuvant chemotherapy are associated with a worse DFS ($K_{\text{trans}}$ $p=0.009$; IAUGC$_{60}$ $p=0.024$) and OS ($K_{\text{trans}}$ $p=0.07$, 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 $K_{\text{trans}}$

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

- 73 patients with locally advanced breast cancer planned for NAC
- 58 completed baseline MRI and after 2 cycles of NAC
- SITCs evaluated by 2 senior oncological radiologists
- $K_{\text{trans}}$ measured
- Pathological response, DFS and OS recorded

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<thead>
<tr>
<th>Age at diagnosis (yrs)</th>
<th>&lt;50</th>
<th>≥50</th>
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<td>36 (62%)</td>
<td>22 (38%)</td>
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<table>
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<tr>
<th>Menopausal Status</th>
<th>Premenopausal</th>
<th>Postmenopausal</th>
<th>Perimenopausal</th>
<th>Unevaluable</th>
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<tr>
<td></td>
<td>36 (62%)</td>
<td>20 (34%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
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<table>
<thead>
<tr>
<th>Histological characteristic</th>
<th>Invasive Ductal Carcinoma</th>
<th>Invasive Lobular Carcinoma</th>
<th>Other or not otherwise specified</th>
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<tr>
<td></td>
<td>46 (79%)</td>
<td>9 (16%)</td>
<td>3 (5%)</td>
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<table>
<thead>
<tr>
<th>Grade</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>Unknown or unevaluable</th>
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<tbody>
<tr>
<td></td>
<td>3 (5%)</td>
<td>30 (52%)</td>
<td>21 (36%)</td>
<td>5 (9%)</td>
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<table>
<thead>
<tr>
<th>Clinical Tumour Stage</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
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<tbody>
<tr>
<td></td>
<td>31 (53%)</td>
<td>18 (31%)</td>
<td>9 (16%)</td>
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<thead>
<tr>
<th>Clinical nodal stage</th>
<th>Positive</th>
<th>Negative</th>
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<tr>
<td></td>
<td>27 (47%)</td>
<td>31 (53%)</td>
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<table>
<thead>
<tr>
<th>Estrogen receptor status</th>
<th>Positive</th>
<th>Negative</th>
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<tbody>
<tr>
<td></td>
<td>39 (67%)</td>
<td>19 (33%)</td>
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<table>
<thead>
<tr>
<th>Progesterone receptor status</th>
<th>Positive</th>
<th>Negative</th>
<th>Unknown or unevaluable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>31 (53%)</td>
<td>24 (41%)</td>
<td>3 (5%)</td>
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<table>
<thead>
<tr>
<th>HER 2 Status</th>
<th>Positive</th>
<th>Negative</th>
<th>Unknown or unevaluable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12 (21%)</td>
<td>41 (71%)</td>
<td>5 (9%)</td>
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</table>
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. $K_{\text{trans}}$ 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 $K_{\text{trans}}$ value of 0.239 min$^{-1}$.
(b) post 2 cycles of chemotherapy shows a curve shape of 2 (reduction of 3 points) and $K_{\text{trans}}$ of 0.045 min$^{-1}$ (reduction of 81%).
Box and whisker plot showing SITC shape against $K_{\text{trans}}$ pre and post NAC
Whiskers show range of data; box shows upper and lower quartile and central line shows median.
Kaplan-Meier survival curve showing overall survival on the basis of reduction in SITC of >1 point
DCE-MRI in the characterisation of triple negative breast carcinomas

Distinct biological entity with relatively underexplored imaging features

- To compare DCE-MRI kinetic parameters between TNBC & ER+/PR+/HER2- BC
- n=37 (TNBC 16 patients, ER+/PR+/HER2- 21 patients) who were all imaged with MRI before commencing NAC
- Kinetic parameters for permeability and EES ($K^{\text{trans}}$, $k_{\text{ep}}$, $v_e$, IAUGC$_{60}$) and perfusion (relative blood flow & volume, Mean Transit Time) analysed
<table>
<thead>
<tr>
<th>MRI parameter</th>
<th>ER-/PR-/HER2-</th>
<th>ER+/PR+/HER2-</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td>$K^{\text{trans}}$</td>
<td>0.19</td>
<td>0.23</td>
<td>p=0.575</td>
</tr>
<tr>
<td>$v_e$</td>
<td>0.33</td>
<td>0.39</td>
<td>p=0.001</td>
</tr>
<tr>
<td>$k_{ep}$</td>
<td>0.70</td>
<td>0.56</td>
<td>p=0.044</td>
</tr>
<tr>
<td>IAUGC$_{60}$</td>
<td>12.59</td>
<td>14.17</td>
<td>p=0.596</td>
</tr>
<tr>
<td>rBV</td>
<td>215.51</td>
<td>132.96</td>
<td>p=0.533</td>
</tr>
<tr>
<td>rBF</td>
<td>5.68</td>
<td>2.98</td>
<td>p=0.252</td>
</tr>
<tr>
<td>MTT</td>
<td>44.27</td>
<td>47.69</td>
<td>p=0.007</td>
</tr>
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</table>

- 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
- DCE-MRI is an effective non-invasive method of characterising TNBC in-vivo and confirms its distinct biological phenotype
Diffusion-weighted MRI

- Provides information about the cellularity and perfusion within tumours through the measurement of the random Brownian motion of water molecules in tissues
- Any process that causes lysis or necrosis will lead to increased water diffusion, measured as the apparent diffusion coefficient (ADC)
- ADC correlates with apoptosis in animal models
Breast cancer response to neoadjuvant chemotherapy (2 cycles of taxanes)

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.

Window of opportunity studies

- Peri-operative
  - POETIC
  - FLT-PET validation
- Pre-chemotherapy
  - Bevacizumab Trial
- Post-chemotherapy/Pre-surgery
  - In development
Investigation of pathways regulating early anti-angiogenic response to single agent bevacizumab given prior to neoadjuvant breast cancer chemotherapy

• This is a two-centre, Phase II, non-randomised, open label investigator-led study sponsored by the Oxford Radcliffe Hospitals NHS Trust

• Participating Centres:
  1) Medical Oncology Unit, Oxford Radcliffe Hospitals NHS Trust, Oxford.
  2) Breast Unit, Mount Vernon Hospital
Trial Schema

Primary Breast Cancer Patient (pre-NAC) → MRI scan Core biopsies Bloods → Bevacizumab (15mg/kg) → MRI scan Core biopsies Bloods

MRI scans (DWI, BOLD, DCE-MRI)

RNA extraction from Fresh frozen samples → Gene expression profiling using Affymetrix Exon 1.0 ST array Platform

Patient

Core biopsy

Imaging

FFPE blocks → IHC analysis
Response to Bevacizumab
Plots showing significant reduction in DCE-MRI parameters after bevacizumab.
Waterfall plot showing percentage change in Median $K^{\text{trans}}$ across all the patients in response to bevacizumab.
No Surgery Trial
Can early breast cancer patients safely avoid surgery following a pCR (pathological Complete Response) resulting from neo-adjuvant anti-HER2 therapy with chemotherapy, confirmed by multiple ultrasound directed biopsies?
Pre-NOSTRA Schema

A Feasibility Study for the planned Phase III NOSTRA Trial to assess both the accuracy of tumour-bed biopsies in combination with clinical and radiological assessment in identifying those patients with Residual Cancer Burden (RCB) following an effective targeted to dual anti-HER2 chemotherapy combination and the acceptability.

ER-neg, HER2-pos early invasive breast cancer, suitable for neo-adjuvant chemotherapy

Neo-adjuvant taxane +/- epirubicin +/- carboplatin chemotherapy with dual anti-HER2 therapy

Clinical and radiological assessment of response

Clinical response

No clinical Response

Multiple USS guided tumour-bed biopsies

Local reporting of tumour-bed biopsies confirms absence of RCB?

No

Assessment of patients likely willingness to participate in the planned NOSTRA trial (via telephone interview)

Yes

Surgery

Central pathology review of surgical excisions
WB DW-MRI: differential response

Feb 2013
Baseline WB DW-MRI
ER +ve Her-2 –ve IDC

April 2013
Post 4 X FEC

July 2013
Post 8 X FEC

Sept 2013
On Tamoxifen
Conclusions

- Multi-modality imaging in an MDT setting is an essential part of primary systemic therapy.
- Functional MRI techniques yield data that reflect on specific aspects of the underlying tumour and tissue biology.
- Quantitative biomarker data can be mapped and co-registered onto anatomical images.
- The multi-parametric approach goes beyond any single functional technique and allows improved understanding of biological processes and responses to therapeutic interventions.
- Important clinical roles and useful for assessing novel drugs and for predicting therapeutic efficacy.