

# Neoadjuvant Chemotherapy in Breast Cancer: Early Prediction of Response Using a Combination of DCE-MRI, ADC Mapping And Proton Spectroscopic Imaging

M. Lowry<sup>1</sup>, D. J. Manton<sup>1</sup>, D. Tozer<sup>2</sup>, A. Maraveyas<sup>1</sup>, A. Chaturvedi<sup>3</sup>, J. Greenman<sup>1</sup>, L. Cawkwell<sup>1</sup>, A. Hubbard<sup>3</sup>, A. Modi<sup>3</sup>, M. Lind<sup>1</sup>, L. W. Turnbull<sup>1</sup>

<sup>1</sup>University of Hull, Hull, East Yorkshire, United Kingdom, <sup>2</sup>University College London, London, England, United Kingdom, <sup>3</sup>Hull and East Yorkshire Hospitals NHS Trust, Hull, East Yorkshire, United Kingdom

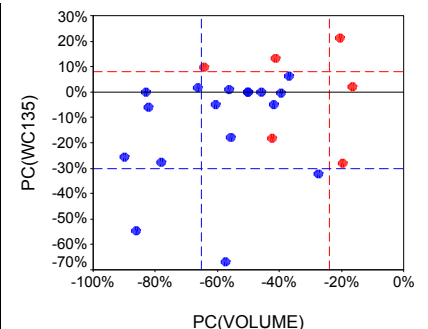
**Synopsis:** This study investigates the potential offered by quantitative MR imaging and spectroscopy for early prediction of ultimate tumour response to chemotherapy. Prediction of non-response would have great clinical benefit both in avoiding unnecessary toxicity and permitting early change to alternative treatments. Twenty-three breast cancer patients were imaged before, after their second and after their final courses of chemotherapy. Results suggest that a combination of parameters from spectroscopy (relative fat and water signal strength and water  $T_2$ ) and imaging (tumour volume and extracellular tissue volume fraction) can be used to achieve highly accurate prediction of ultimate tumour response.

**Introduction:** Change in tumour volume may be a relatively late manifestation of response to chemotherapy in patients with inoperable primary breast cancer. Studies have suggested that using MRI to quantify water apparent diffusion coefficient ( $ADC_w$ ) [1] or microvessel permeability [2], or alternatively using proton MR spectroscopy (MRS) to quantify the relative magnitudes of water and fat signals [3] may be able to provide an early indication of ultimate treatment response. Therefore a study was designed to compare the reliability of these three methods in women undergoing neoadjuvant chemotherapy for inoperable breast cancer.

**Methods:** Longitudinal MRI was carried out in 23 women; all of whom received a standard dosage chemotherapy regime involving intravenous administration of 5-Fluorouracil, Epirubicin and Cyclophosphamide. MRI and MRS were carried out prior to chemotherapy (TP0), between the second and third courses (TP2) and after the final course (TPF). ADC was measured using EPI with 8 diffusion gradient weightings up to 680 s/mm<sup>2</sup>. Microvasculature was assessed using  $T_1$ -weighted dynamic contrast-enhanced (DCE-) MRI: fast spoiled gradient echo (FSPGR) sequence, 13s temporal resolution, 7.5 minute duration. A 3 compartment pharmacokinetic model was used to calculate transfer constant ( $K^{trans}$ ), exchange rate ( $K_{ep}$ ), extracellular-extravascular tissue volume fraction ( $V_e$ ) and maximum percentage enhancement (MPE). The proportion of signal arising from water (i.e. water content, WC = water signal / sum of water and fat signals) was measured, at two echo times (30 and 135 ms), using a 1D STEAM spectroscopic imaging sequence with seven 0.25 ml voxels in a column through each tumour (water  $T_2$  was also estimated). Tumour volume was measured using manually traced regions-of-interest drawn on high resolution 3D, post-contrast, fat-suppressed FSPGR images. Changes in parameter values between TP0 and TP2 were calculated either as absolute differences,  $D(x)$ , or percentage change,  $PC(x)$ , as deemed most appropriate. A 65% or greater decrease in tumour volume at TPF ( $PCV_F$ ), was taken to indicate partial response (PR); this being equivalent to a decrease in cross-sectional area of 50%, itself broadly equivalent to the WHO criterion of a 50% decrease in the product of maximum orthogonal diameters. Correlation between  $D(x)$  and  $PC(x)$  data and  $PCV_F$  was assessed using the Spearman non-parametric test. Diagnostic efficacy was assessed using receiver-operator characteristic curves, with PR as the positive result, and the areas contained underneath them (AUC). Parameters were combined, in the hope of attaining a synergistic increase in diagnostic efficacy, using both 2D scatter plots and logistic regression analysis (LRA) modelling.

**Results:** All tumours showed reduced volume at TPF; 17 demonstrated PR and 6 remained clinically stable (NR). Parameters which demonstrated a significant correlation with  $PCV_F$  were:  $PC(vol)$ ,  $PC(WC_{135})$  &  $D(T_{2w})$ . Parameters which demonstrated an AUC significantly greater than 0.5 were:  $PC(vol)$ , AUC = 0.82,  $D(V_e)$ , 0.78 &  $D(T_{2w})$ , 0.77. For these four parameters, PR and NR data were often

| Parameter, combination or model | Spec. @ 100% NPV | Sens. @ 100% PPV |
|---------------------------------|------------------|------------------|
| $PC(volume)$                    | 3/6: 50%         | 6/17: 35%        |
| $D(V_e)$                        | 0%               | 53%              |
| $PC(WC_{135})$                  | 50%              | 18%              |
| $D(T_{2w})$                     | 0%               | 65%              |
| $PC(vol)$ & $PC(WC_{135})$      | 83%              | 47%              |
| $PC(vol)$ & $D(V_e)$            | 50%              | 71%              |
| $PC(vol)$ & $D(T_{2w})$         | 50%              | 76%              |
| $D(T_{2w})$ & $D(V_e)$          | 100%             | 100%             |
| LRA Model                       | 100%             | 100%             |



sufficiently well separated in order to permit an accurate prediction of ultimate response to be made in a substantial number of cases, as illustrated by the above graph. The proportions of cases where such accurate predictions could be made (i.e. with either 100% positive or negative predictive values, PPV and NPV respectively) are given in the above table. The figure and table also show how these four parameters contain complimentary information, leading to a gain in prognostic efficacy when used in combination. The LRA model developed using all four of the above parameters permitted complete separation of PR and NR data.

**Discussion:** Results would suggest that MRS, DCE-MRI and volume measurements provide complimentary information on tumour response which can be combined to give a highly accurate early prediction of ultimate volume response. Prediction of NR would be of great clinical benefit by sparing patients unnecessary toxicity and permitting an early switch to alternative therapy. Prediction of PR could have psychological benefits for patients. These findings are to be validated in a larger cohort of patients with the inclusion of imaging after the first course of chemotherapy, which might permit detection of short-term ADC changes.