# Which DCE-MRI analysis method, pharmacokinetic or empirical, most accurately predicts eventual response during neoadjuvant chemotherapy?

**M. D. Pickles[1], D. J. Manton[1], M. Lowry[1], and L. W. Turnbull[1]**

[1]Centre for Magnetic Resonance Investigations, University of Hull, Hull, East Yorkshire, United Kingdom

**Introduction.** Traditionally response to treatment has been assessed via tumour size measurements. Unfortunately tumour size alterations during treatment are believed to be a relatively late event. Earlier biomarkers of response are urgently required, as these methods will enable early cessation of ineffective treatments. DCE-MRI data has been proposed as such a biomarker. However, both pharmacokinetic and empirical analysis methods can be employed to process DCE-MRI data. Pharmacokinetic modelling attempts to measure tissue contrast agent concentration during the DCE-MRI examination. By modelling the change in contrast agent concentration over time quantitative pharmacokinetic parameters are obtained. Empirical methods use a number of parameters such as upslope and area under the curve (AUC) to simply describe the signal intensity changes noted during the DCE-MRI examination. These two techniques have particular advantages and disadvantages. Pharmacokinetic modelling attempts to describe the underlining pathphysiology of the tissues under examination, however a number of assumptions are made that do not always fit the data. Whereas empirical methods are simpler to obtain the results do not attempt to describe the tissue pathophysiology. This work evaluates which technique, pharmacokinetic modelling or empirical analysis, best predicts response to neoadjuvant chemotherapy in a cohort of breast cancer patients.

**Methods.** 99 patients receiving neoadjuvant chemotherapy underwent breast MRI prior to and post 1$^{st}$, 2$^{nd}$ and final treatment cycles. Response classification was based upon overall tumour volume reduction in line with RECIST. DCE-MRI data were obtained with the following parameters: T1-W FSPGR TR/TE/flip 7.6ms/4.2ms/30$^{o}$ acquired over 35 phases with a temporal resolution of 11.6sec. To allow pharmacokinetic modelling a PD-W FSPGR sequence was utilised to correct for native T1 values. A two compartment pharmacokinetic model resulted in 3 parameters while empirical analysis resulted in 9. Hypothesis generation was undertaken to identify the most predictive time-points or differences (absolute Δ or relative %) between time-points, thereby streamlining the number of parameters analysed. ROC analysis provided the diagnostic accuracies, (represented by the AUC of the ROC curve) of the streamlined parameters. To identify which method provided the greatest prediction of treatment response the parameter with the greatest diagnostic accuracy from each group, pharmacokinetic and empirical, were compared utilising the methodology proposed by Hanley and McNeil. This affords a means of assessing whether the diagnostic accuracies of two tests significantly differ.

**Results.** 31 patients were classified as non-responders and 68 patients as responders following treatment. Hypothesis generation revealed the difference (Δ or %) between the pre and 2$^{nd}$ cycle time-points to be the most predictive of eventual response. As can be seen from Table I, the absolute differences in the transfer constant, $K^{trans}$, and percentage of maximum signal intensity recorded at 30sec, $PC_{30sec}$, demonstrated the greatest diagnostic accuracy for pharmacokinetic and empirical parameters respectively. However, the Hanley and McNeil test revealed no significant difference (p=0.769) between the diagnostic accuracies of $K^{trans}$ and $PC_{30sec}$; see Figure I.

| **Pharmacokinetic Parameters** | **Diagnostic Accuracy** | **95% C.I.** |
|---|---|---|
| *$K^{trans}$ (Δ)* | *0.695* | *0.580 – 0.810* |
| $v_e$ (Δ) | 0.693 | 0.587 – 0.799 |
| $k_{ep}$ (%) | 0.634 | 0.519 – 0.749 |
| **Empirical Parameters** | **Diagnostic Accuracy** | **95% C.I.** |
| *Percentage factor$_{30sec}$ (Δ)* | *0.676* | *0.569 – 0.782* |
| Rise time (%) | 0.662 | 0.549 – 0.774 |
| Initial slope$_{30sec}$ (%) | 0.658 | 0.549 – 0.768 |
| Enhancement factor$_{30sec}$ (%) | 0.658 | 0.548 – 0.767 |
| Area under curve (Δ) | 0.646 | 0.536 – 0.756 |
| MITR (%) | 0.635 | 0.519 – 0.752 |
| Tmax (Δ) | 0.628 | 0.518 – 0.738 |
| nMITR (%) | 0.618 | 0.507 – 0.729 |
| Final slope$_{120sec}$ (Δ) | 0.607 | 0.484 – 0.729 |

Table I. Diagnostic accuracy and 95% confidence intervals for various DCE-MRI parameters

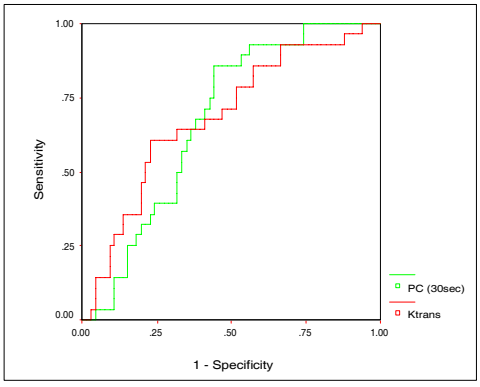


Figure I
ROC curve of absolute difference in $K^{trans}$ and $PC_{30sec}$ between the pre and 2$^{nd}$ cycle time-points

**Conclusion.** Caution is necessary when interpreting these results since many different pharmacokinetic models are available and only one was examined. Nevertheless these results indicate that the pharmacokinetic parameter $K^{trans}$ (Δ difference between pre and 2$^{nd}$ cycle time-points) achieved a higher diagnostic accuracy than the most accurate empirical parameter, $PC_{30sec}$ (Δ difference between pre and 2$^{nd}$ cycle time-points). However there was no significant difference in the diagnostic accuracy of the two DCE-MRI analysis methods. It is further concluded that the easier to implement empirical analysis technique could replace pharmacokinetic data without a diminished predictive power of eventual response.