

Introduction Patients who present with locally advanced breast cancer are commonly treated with neoadjuvant chemotherapy to down stage their disease. If sufficient down staging is achieved an appropriate surgical option, mastectomy or breast conserving surgery, can be performed followed by adjuvant therapies¹. Knowledge of a patient's response to their neoadjuvant therapy is essential not only to facilitate the correct post neoadjuvant treatment but also to detect whether a patient is responding to their neoadjuvant treatment. Monitoring response to neoadjuvant chemotherapy is usually based on tumour measurements undertaken by clinical examination and x-ray mammography yet both have been shown to be inferior to measurements obtained from MRI mammography (MRM)^{2,3}. Dynamic contrast enhanced MRI (DCE-MRI) is an essential part of MRM, which allows a non-invasive assessment of tumour vasculature. It is believed that changes in tumour physiology (e.g. vasculature) can be detected before tumour volume changes thereby allowing an early assessment of response to treatment⁴ and facilitating an earlier change in treatment if required. The purpose of this work was to determine if DCE-MRI derived pharmacokinetic parameters could differentiate between responders and non-responders at an early time point during their neoadjuvant treatment in a clinical setting.

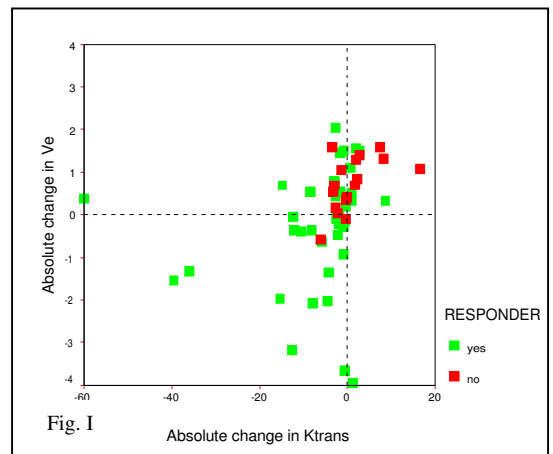
Methods Sixty patients with inoperable, biopsy proven breast cancer underwent MRM at three time points – pre treatment, early (2nd or 3rd cycle) and after their final cycle of chemotherapy. All MRM examinations were undertaken on a 1.5T scanner (GE Signa Advantage, GE Medical Systems, Milwaukee, USA) in combination with a dedicated bilateral breast coil. Sequences comprised of 3D T₁ weighted spoiled gradient echo (SPGR), proton density weighted SPGR, T₁ weighted SPGR acquired dynamically over 35 time points with a temporal resolution of 11.6sec and a post contrast fat suppressed (FS) 3D T₁ weighted SPGR. DCE-MRI images were analysed with in-house developed software on Sun workstations. A region of interest (ROI) was generated around the tumour on the slice which demonstrated the strongest contrast enhancement, a 3x3 pixel ROI was then generated from the original ROI, this is believed to represent the so called angiogenic hot spot of the lesion⁵. A two-compartment model (Brix)⁶ was then applied to both ROI's to generate pharmacokinetic parameters transfer constant (K^{trans}), rate constant (K_{ep}) and extracellular extravascular space (V_e) for each ROI to describe the tumour vasculature. To classify patients as responders or non-responders ROI's were drawn around any enhancing lesion noted on the post contrast FS 3D T₁ weighted SPGR images thereby providing a volume measurement. Patients were classified as responders based on a total tumour volume reduction of ≥65%, which equates to a 50% reduction in the product of a lesion's diameter, or non-responders based on a tumour reduction of <65%⁷.

Results K^{trans}, K_{ep}, V_e and tumour volume were analysed for significant differences between responders and non-responders for pre treatment values, early treatment values and the difference [percentage (%) and absolute (Δ)] between the two time points. No parameters were significant at the pre treatment time point, however V_e whole and hot spot ROI and K^{trans} hot spot were all borderline significant. Only the hot spot value for V_e was significant at the early time point, but whole ROI values for V_e and volume again had borderline significance. The difference between the two time points had the most dramatic results with significant values for K^{trans} hot spot, V_e hot spot, V_e whole ROI and tumour volume. Incorporating hot spot ROI figures made K^{trans} a significant parameter and increased the number of significant differences from two for whole ROI to five for hot spots.

	ROI	Pre	Early	% Diff.	Δ Diff.
K ^{trans}	Whole	NS	NS	NS	NS
	Hot spot	0.067	NS	0.023	0.019
K _{ep}	Whole	NS	NS	NS	NS
	Hot spot	NS	NS	NS	NS
V _e	Whole	0.067	0.061	0.012	0.012
	Hot spot	0.083	0.021	0.045	0.001
Volume	N/A	NS	0.063	0.001	0.054

P values for comparison of response and non-response

Discussion These results clearly demonstrate that pharmacokinetic parameters can differentiate responders from non-responders at an early time point and that hot spot analysis increases the number of significant differences between the two groups. However the percentage difference between pre and early tumour volume measurements are as significant as DCE-MRI pharmacokinetic hot spot analysis. It should be noted that the early time point did incorporate the second and third cycle of treatment; analysis after the first cycle of treatment may demonstrate a clear difference between DCE-MRI pharmacokinetic parameters and tumour volume parameters since volume changes are expected after vascular changes⁴. Interestingly the DCE-MRI pharmacokinetic parameter which constantly demonstrated a differences between responders and non-responders was V_e, which was lower for responders; this result supports our earlier work⁸ which noted a reduction in T₂ values for responders. As V_e reduces so will the amount of free water while the amount of bound water will remain static or even increase due to the increased ratio of cell membrane surface area to V_e, consequently T₂ will decrease. K^{trans} was also lower for responders therefore patients with a reduced V_e and K^{trans} are more likely to be responders than non-responders (see fig. I).



References ¹Booser DJ, et al., Semin Oncol. 1992; **19** 278-85. ²Cocquyt, V.F. et al., Breast. 2002; **11** 306-315 ³Gilles, R. et al., Radiology. 1994; **191** 633-638 ⁴Padhani, A.R., Eur J Cancer. 2002; **38** 2116-2127 ⁵Liney, P.G. et al., J Magn Reson Imaging. 1999; **10** 945-949 ⁶Brix, G. et al., J Comput Assist Tomo. 1991; **15** 621-628 ⁷Therasse, P. et al., J Nat Cancer Inst. 2000; **92** 205-216 ⁸Lowry, M. et al., Proc. ISMRM **11** 2003:601

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