Intrinsic susceptibility contrast (R_2*) in the evaluation of tumour oxygenation at baseline and in response to neoadjuvant chemotherapy in breast cancer

S. P. Li[1], N. J. Taylor[2], J. J. Stirling[2], M-L. W. Ah-See[1], M. J. Beresford[1], D. J. Collins[3], J. A. d'Arcy[3], A. Makris[1], and A. R. Padhani[2]
[1]Mount Vernon Hospital, Northwood, Middlesex HA6 2RN, United Kingdom, [2]Paul Strickland Scanner Centre, Mount Vernon Hospital, Northwood, Middlesex HA6 2RN, United Kingdom, [3]CR-UK Clinical MR Research Group, Royal Marsden Hospital, Sutton, Surrey, SM2 5PT, United Kingdom

Introduction: The ability to image tumour hypoxia and evaluate oxygenation changes in response to treatment using R_2* is a powerful yet underexplored tool in breast cancer in humans [1]. This study evaluates the relationship between baseline histology and dynamic contrast enhanced (DCE) and dynamic susceptibility enhanced (DSC) MRI parameters with R_2* in breast cancer. The role of R_2* as an imaging biomarker of response to neoadjuvant chemotherapy (NAC) is also explored.
Methods: 37 patients with solid, well defined, primary invasive ductal breast adenocarcinomas were imaged with a spoiled multi-gradient echo T_2*-weighted MRI sequence (TE 5-75ms, TR100s, flip angle (α) 40˚, 8mm slice thickness, FOV 260mm, 256^2 matrix). T_1-weighted DCE-MRI sequences (TE 4.7ms, TR 11ms, α 35˚, 256^2 matrix) and DSC-MRI sequences (TE 20ms, TR 30ms, α 40˚, 128^2 matrix) were also performed using 0.1mmol/kg and 0.2 mmol/kg body weight of Gd-DTPA respectively. R_2* values were calculated using a least-squares fitting routine on *ln*[signal] plotted against TE. DCE-MRI images were analysed with Tofts' pharmacokinetic model [2] and a modified Fritz-Hansen assumed arterial input function [3] using specialist MRIW software (Institute of Cancer Research, London) [4]. DSC parameters were calculated from a fitted Γ–variate function using MRIW [4]. Whole tumour ROI parametric values were acquired: R_2*, K^{trans}, v_e, k_{ep}, $IAUGC_{60}$, rBV, rBF and the MTT of the fitted curve. Relationships between baseline R_2* and tumour characteristics (size, grade, ER/PR/HER2 status) and DCE and DSC-MRI parameters were explored using Spearman's rank correlation for continuous variables and the Mann-Whitney U test for discrete variables. Baseline R_2* and changes in R_2* with treatment were also correlated with final pathological response using paired t-testing. R_2* was compared with DCE and DSC kinetic parameters as a predictor of response using ROC (receiver operating characteristic curve) analyses.

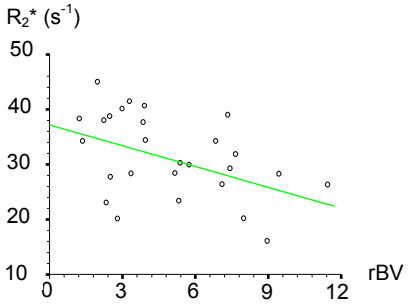

Figure 1 Relationship between R_2* and rBV

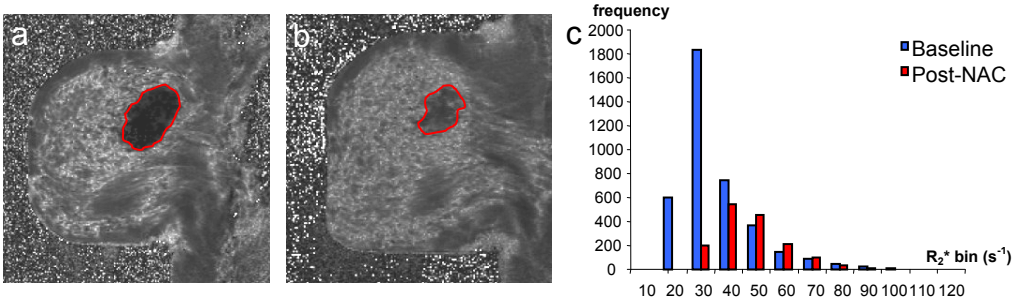

Figure 2 R_2* maps of a malignant breast tumour in a responder (a) at baseline (R_2* 16.2 s^{-1}, K^{trans} 0.27 min^{-1}, rBV 431) and (b) after 2 cycles of NAC (R_2* 30.5 s^{-1}, K^{trans} 0.15 min^{-1}, rBV 256) with (c) corresponding histogram depiction of R_2* values

Results: Patients were imaged both prior to (n=31) and after 2 cycles of NAC (n=27). Significant negative correlations were observed between baseline R_2*, and rBV & rBF (r=0.51, p=0.006; r=-0.46, p=0.015) (Fig.1). This relationship disappeared after NAC. There were no correlations observed between baseline R_2* and other imaging or tumour characteristics, or pathological response. Increases in R_2* values were seen with NAC in pathological responders ($36.5s^{-1}$ vs $31.7s^{-1}$, mean of differences -4.9, p=0.025) (Fig.2). ROC analysis showed that R_2* was a relatively poor predictor of response compared to other kinetic imaging parameters (Table 1).

Parameter	Responders (n=16)			Non-responders (n=11)			ROC
	Baseline	Post 2 cycles NAC	t-test	Baseline	Post 2 cycles NAC	t-test	
R_2* (s^{-1})	31.7 (16.2-45.1)	36.5 (28.0-50.4)	p=0.025	30.4 (20.2-40.2)	32.4 (26.1-41.5)	p=0.066	0.62
K^{trans}(min^{-1})	0.28 (0.13-0.47)	0.12 (0.00-0.25)	p<0.001	0.22 (0.18-0.26)	0.21 (0.04-0.32)	p=0.570	0.84
k_{ep} (min^{-1})	0.72 (0.41-1.44)	0.31 (0.00-0.66)	p<0.001	0.57 (0.41-0.98)	0.53 (0.26-0.93)	p=0.330	0.90
v_e (%)	39.9 (27.4-59.2)	34.7 (0.0-69.6)	p=0.097	41.6 (23.0-58.5)	39.5 (6.9-54.5)	p=0.572	0.59
$IAUGC_{60}$ (mM.s)	16.72 (9.53-26.05)	8.58 (4.01-16.25)	p<0.001	14.10 (12.24-17.60)	13.14 (4.65-18.41)	p=0.479	0.83
rBV (AU)	285.8 (58.8-503.6)	141.3 (4.4-382.7)	p=0.005	156.3 (66.8-257.4)	174.7 (60.9-488.8)	p=0.548	0.83
rBF (AU)	6.2 (1.2-11.4)	2.9 (0.2-7.7)	p=0.005	3.2 (1.3-5.4)	3.6 (1.2-10.0)	p=0.569	0.84
MTT of fit curve (s)	46.9 (40.5-50.1)	46.5 (26.7-54.1)	p=0.694	48.8 (44.3-55.9)	49.1 (44.6-53.9)	p=0.842	0.53
Size (mm)	38 (17-61)	20 (0-35)	p<0.001	37 (22-85)	34 (16-85)	p=0.011	0.86

Table 1 MRI kinetic parameters at baseline and according to pathological response

Discussion: The strong pre-treatment inverse correlations between R_2* and rBV & rBF suggest that R_2* is dominated by the oxygenation status of blood in treatment-naïve breast cancers. The uncoupling of R_2* from blood volume/flow and increases observed in R_2* after 2 cycles of NAC may indicate that human breast cancers become more hypoxic in those that successfully respond to chemotherapy, an assertion that is supported by preclinical data [5]. R_2* after treatment may more accurately reflect tumour oxygenation. However, changes in R_2* are a poor predictor of chemotherapy response in breast cancer compared with DCE and DSC-MRI kinetic parameters [6].

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