Early prediction of nodal status following neoadjuvant chemotherapy treatment of breast cancer utilising MR parameters

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Introduction Malignant axillary lymph node (ALN) status following neoadjuvant chemotherapy (NAC) is the most significant predictor of a reduced survival interval for breast cancer patients. Given its prognostic value, a biomarker that could identity patients, prior to or early during NAC, that were likely to have malignant ALN present at surgery could aid patient management. In whose patients with a positive prediction for malignant ALN following NAC a switch to an alterative chemotherapy regime could be made early in the course of their treatment in the hope that the patient would be node negative at surgery, thereby increasing the likelihood of a prolonged survival period.

Methods Thirty-two biopsy proven breast cancer patients receiving NAC were scanned prior to and post 1st, 2nd and final treatment cycles. Patients underwent breast MR examinations at which data was collected regarding tumour volume, pharmacokinetic parameters (K^{trans}, k_{ep} and v_e), and apparent spin-spin relaxation rates (R_2*, R_2' and R_2). Tumour volume was determined from high spatial resolution post contrast fat suppressed T1W FSPGR images. Pharmacokinetic parameters were calculated via a two compartment model utilising DCE-MRI data 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 11.6 seconds. Additionally a PD-W FSPGR sequence was utilised to correct for native T1 values. To calculate R_2* values gradient echo images were acquired with four different TE values (9, 18, 27 and 36ms). The resulting gradient of a plot of the log of the signal intensity against the TE gave the R_2* value. R_2 was calculated in a similar manner to R_2* utilising a fast spin echo (TE 30, 60, 90, and 120ms TR 4000ms ETL 12). R_2' was simply calculated as $R_2'=R_2^*-R_2$. ALN status was determined histopathologically from surgical samples obtained post NAC.
Results at individual treatment cycles and paired results between the treatment points were analysed using independent and paired t-tests. Due to the multiple significance testing employed in this methodology p values underwent Bonferroni correction. Baseline parameter and percentage differences between treatment points were entered into a logistic regression analysis (LRA) with a ≥0.5 cut-off for ALN positive status.

Results 14 patients were ALN positive while 18 were negative following surgery. Prior to treatment only R_2 was significantly different between ALN groups (p=0.028). No significant results were noted post 1st or 2nd treatment cycles. Paired analysis revealed significantly increased $R2^*_{(pre\text{-}2nd)}$ and $R2'_{(pre\text{-}2nd)}$ (p=0.042 for both parameters) for ALN negative patients. The LRA output provided two models with step 2 been the final model which resulted in the following equation:

$$\ln(p/1-p)= 20.26 +(-1.51 \times \text{Baseline } R_2) + (-0.036 \times \text{Percentage Tumour Volume Change}_{\text{pre-2nd cycle}})$$

The model has the following characteristics: diagnostic accuracy 88%, sensitivity 80%, specificity 88%, positive predictive value 86%, and negative predictive value 83%. The LRA prediction results are presented in Table I. The results of a ROC analysis are demonstrated in Table II. This analysis was undertaken to determine which statistically method univariate t-tests or multivariate LRA model resulted in the highest diagnostic accuracy. For the purposes of this analysis paired changes in R_2* and R_2' where represented by percentage change in $R_2^*{}_{(pre\text{-}2nd)}$ and $R_2'{}_{(pre\text{-}2nd)}$.

Classification Table[a]

			Predicted		
			nodes		
	Observed		node positive	node neagative	Percentage Correct
Step 1	nodes	node positive	9	5	64.3
		node neagative	4	14	77.8
	Overall Percentage				71.9
Step 2	nodes	node positive	12	2	85.7
		node neagative	3	15	83.3
	Overall Percentage				84.4

a. The cut value is .500

Table I. LRA prediction results

Parameter	Diag. Accuracy	95% CI
LRA	0.877	0.750 – 1.000
Baseline R2	0.774	0.610 – 0.937
% Δ R2'	0.730	0.556 – 0.905
% Δ R2*	0.718	0.541 – 0.896

Table II. ROC analysis results

Conclusions These results demonstrate that prior to NAC R_2 may be an indicator of eventual ALN status. This probably reflects water content and in turn the accessible extracellular space available to chemotherapy agents. However, following the initiation of NAC it appears an increasing hypoxic environment (increased R_2* and R_2') predict negative ALN status at surgery. Nevertheless the results of the multivariate LRA model seem to indicate that the combination of baseline R_2 and tumour volume reduction achieved at the 2nd treatment cycle more accuracy predict ALN status at surgery as evident by the results of the ROC analysis.