Multiparametric MRI detection and prediction of response to neoadjuvant chemotherapy in breast cancer.

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TARGET AUDIENCE: Radiologists and physicists with an interest in breast MR and assessing response to neoadjuvant chemotherapy.

PURPOSE: Neoadjuvant chemotherapy (NAC) is increasingly being offered to women diagnosed with large and locally advanced breast cancer to down-stage the tumour and facilitate successful breast conserving surgery. Clinical response rates are excellent ranging from 70-98%[1,2] with pathological complete response (pCR) seen in 3-16% of patients[3]. Achieving pCR is desirable as it is associated with improved overall and disease-free survival[4]. Evaluation of response to NAC with MRI has shown volumetric assessment of response early in treatment and diffusion-weighted imaging (DWI) to hold the most promise for incorporation into clinical practice[5,6]. Multiparametric MRI is now being increasingly incorporated into oncological imaging and could further improve the diagnostic performance and accuracy of breast MRI. We investigate the role of mMRI in the detection and prediction of response to NAC in breast cancer.

METHODS: Research ethics committee approval and patient written informed consent were obtained. 27 women with histologically proven invasive ductal carcinoma, median age 50 Years (range 32-81 years) underwent breast MRI prior to and after two cycles of neoadjuvant chemotherapy (epirubicin (90 mg/m^2), and cyclophosphamide (600 mg/m^2) on a 3.0T Philips Achieva MRI scanner (Best, Netherlands). A diffusion weighted sequence (sagittal single shot echoplanar sequence, with SPAIR and a slice-selection gradient reversal (SSGR) method for fat suppression with 4 b values (0, 100, 700, 1150mm^2/s) (TR/TE=3771/66 ms, flip angle 90°, 180 mm FOV, 3 mm slice thickness with 0 slice gap, one excitation and a 1.96x2.02x3mm acquisition voxel)), T2* sequence (sagittal gradient echo (FFE) with 12 echoes (TR/TE=1400/4.6ms, echo spacing 6.9ms, flip angle 18°, slice thickness 3mm, 180mm FOV, a 1.22x1.2x3mm acquisition voxel reconstructed to 0.94x0.94x3mm) and a dynamic contrast enhanced (DCE) sequence (sagittal 3D gradient echo sequence with a temporal resolution of 2.5seconds (TR/TE=4.5/2.3 ms, flip angle 16°, 180mm FOV, 3mm slice thickness with 0 slice gap, one excitation and a 2.37x2.4x6mm acquisition voxel reconstructed to 0.94x0.94x3mm)) following intravenous injection of 0.2ml/kg of gadoterate meglumine (n=22) or gadopentate dimeglumine (n=5) were performed covering the tumour-containing breast. Regions of interest (ROI) were drawn manually slice-by-slice on an early subtracted DCE image using in-house software (MRIW, Institute of Cancer Research, London). A modified Tofts pharmacokinetic model was used to estimate kinetic parameters Ktrans, ve and kep. The ROI's were aligned to the corresponding ADC and R2*maps using in-house software (Adept Institute of Cancer Research, London). The ADC maps were computed from mono-exponential fitting of signal intensity for all 4 b values. R2* was computed using echo times (4.6–59.81ms). Values for ADC, R2*, Ktrans, ve, kep and IAUGC were recorded pixel-by-pixel for each patient and the median documented. Non-enhancing pixels were excluded in this part of the analysis, to prevent bias of results towards 0. The number of enhancing pixels per slice was recorded and multiplied by the reconstructed voxel size (0.94x0.94x3mm) to determine tumour volume for each time point. The enhancement fraction (EF) was calculated as total number of enhancing pixels/total number of pixels for each patient. 11 patient achieved pCR or near-pCR defined on final surgical histology and 16 patients were partial or non-responders. An independent t-test was used to determine any difference in the mean of each parameter at baseline and percentage change after 2 cycles. The area under the receiver operating characteristic (ROC) curve each parameter was calculated. Linear discriminant analysis was performed using % change in kep, tumour volume, EF, ADC and R2 to determine the most important predictive parameter.

RESULTS: There was no significant difference in mean baseline parameters between complete and partial/non-responders (table 1). Following 2 cycles of chemotherapy there were significant differences in mean Ktrans (p=0.015), kep (p=0.004), tumour volume (p=0.017) and enhancement fraction (p=0.007) between complete and partial/non-responders (table 2). ROC curve analysis on the percentage change in mean parameters is shown in table 3. Using a percentage decrease in EF of 21% yielded a sensitivity of 81.8% and specificity of 81.1%. The change in enhancement fraction after 2 cycles of NAC was the best discriminant parameter of complete response with a correlation coefficient of 0.66 in the structure matrix (p=0.005). The fitted discriminant function had 70.4% overall ability to discriminate correctly.

Table 1:

Baseline Parameter	Complete responder (n=11)	Partial/Non-responder (n=16)	P value
Ktrans (min^{-1})	0.140 +/- 0.074	0.109 +/- 0.022	0.210
Ve (%)	0.391 =/- 0.107	0.346 +/- 0.018	0.247
Kep (min^{-1})	0.364 =/- 0.158	0.332 +/- 0.085	0.538
IAUGC (mM s)	15.4 +/- 7.42	13.38 +/- 2.77	0.467
ADC (mm^2/s)	1006.51 +/- 318.5	999.49 +/- 1889	0.949
R2*(sec^{-1})	43.21 +/- 10.67	46.99 +/- 8.01	0.331
Volume (mm^3)	22349 +/- 28359	27314 +/- 25864	0.648
EF (%)	78.4 +/- 17.4	79.6 +/- 17.4	0.865

Table 2:

% Change in Parameter	Complete responder (n=11)	Partial/Non-responder (n=16)	P value
Ktrans	↓54.7 +/- 33.9	↓20.3 +/- 32.2	**0.015**
Ve	↓12.0 +/- 61.9	↑18.2 +/- 24.7	0.150
Kep	↓67.7 +/- 34.4	↓25.9 +/- 29.9	**0.004**
IAUGC	↓54.3 +/- 35.5	↓27.4 +/- 31.6	0.057
ADC	↓18.5 +/- 54.9	↑8.9 +/- 20.6	0.140
R2*	↑23.0 +/- 63.5	↑10.2 +/-17.7	0.528
Volume	↓73.4 +/- 22.4	↓46.8 +/- 31.8	**0.017**
EF (%)	↓50.3 +/- 39.2	↓8.79 +/- 23.7	**0.007**

Table 3:

Parameter (% change in)	Cut-off	AUC	Sensitivity (%)	Specificity (%)
Ktrans	↓33%	0.750	72.7	63
ve	↑11%	0.625	63.6	62.5
kep	↓33%	0.818	90.9	68.7
IAUGC	↓32%	0.722	81.8	68.7
ADC	↑8%	0.722	81.8	50
R2*	↑11%	0.651	72.7	62.5
volume	↓54%	0.764	81.8	56.2
EF	**↓21%**	**0.818**	**81.8**	**81.1**

DISCUSSION AND CONCLUSION:

In a multiparametric breast MR model, percentage decrease in enhancement fraction after 2 cycles of NAC was the best predictor of complete response. EF should be considered as a potential biomarker for predicting response to NAC. The contribution of vascular pharmacokinetic parameters and tumour volume in the assessment of early breast cancer response should also be emphasised.

REFERENCES:

[1] Powles et al JCO 1995, [2] Fisher et al JCO 1998, [3]Swain et al Can Res 1987, [4]Scholl et al EJC 1995, [5] Hylton et al, Radiology 2012, [6] Prevos et al Eur Rad, 2012.