Multi-parametric MRI in evaluating pre-and post-menopausal ER positive breast cancer

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TARGET AUDIENCE: Radiologists and physicists with an interest in breast MRI in assessing response to therapy.

PURPOSE: The vast majority of breast cancers (up to 75%) are estrogen receptor (ER) positive and this luminal subtype has the best overall prognosis. In premenopausal women large locally invasive ER positive tumours are treated with neo-adjuvant chemotherapy while in post-menopausal women endocrine therapy using an aromatase inhibitor such as letrozole is preferred to avoid chemotherapy related co-morbidity. Response rates to chemotherapy are 70-98% (3,4) compared to 40-60% to letrozole in randomised clinical trials (1,2). Pathological complete response (pCR) is expected in 3-16% of premenopausal women (5), but in only 3.5% taking letrozole (6). The purpose of this study was to compare multiparametric MRI parameters of ER positive tumours in pre- and postmenopausal women to assess any differences in tumour functional characteristics and to establish which parameter correlated significantly with response as defined by tumor volume reduction.

METHODS: Research ethics committee approval and patient written informed consent were obtained. 22 women with histologically proven invasive ductal carcinoma (including 13 pre-menopausal (median age 48 years, range 38-63 years) and 9 post-menopausal (median age 74 years (range 60-82 years) underwent breast MRI prior to and after two cycles of neoadjuvant chemotherapy (epirubicin (90 mg/m^2), and cyclophosphamide (600 mg/m^2) for the premenopausal women or 6 weeks of letrozole on a 3.0T Philips Achieva MRI scanner (Best, Netherlands). Diffusion weighted (sagittal single shot EPI, SPAIR fat suppression with 4 b values (0, 100, 700, 1150mm^2/s) (TR/TE=3771/66 ms, flip angle 90°, 180 mm FOV, one excitation and a 1.96x2.02x3mm acquisition voxel)), T2* (sagittal gradient echo (FFE) with 12 echoes (TR/TE=1400/4.6ms, echo spacing 6.9ms, FA 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 voxel)) following intravenous injection of 0.2ml/kg of gadolinium chelate were performed. Regions of interest (ROI) were drawn manually slice-by-slice on an early subtracted DCE image using in-house software (MRIW, ICR, London) and a modified Tofts pharmacokinetic model estimated kinetic parameters (Ktrans, ve and kep). 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. 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 multiplied by the reconstructed voxel size determined tumor volume. The enhancement fraction (EF) was calculated as total number of pixels achieving >20% enhancement/total number of pixels. One patient declined intravenous contrast and so had a non-contrast study with ADC and R2*values recorded only.

RESULTS: Baseline tumor volumes were significantly greater in premenopausal compared to postmenopausal women, kep was significantly higher and v_e significantly lower (table 1). In premenopausal women following 2 cycles of chemotherapy, tumor volume fell by a mean of 63.7% +/-27.4%, in postmenopausal women following 6 weeks of letrozole tumour volume fell by a mean of 30.6% +/-26.8%. In premenopausal women a rise in v_e correlated best with volume reduction, while in postmenopausal women, no paramete correlated with volume reduction (table 2).

Table 1:

Baseline Parameter	Pre-menopausal (n=13)	Post-menopausal (n=9)	P value
Ktrans (min^{-1})	0.124 +/- 0.066	0.104 +/- 0.035	0.371
V_e (%)	0.348 +/- 0.083	0.441 +/- 0.092	**0.034**
Kep (min^{-1})	0.350 +/- 0.107	0.248 +/- 0.078	**0.021**
IAUGC (mM s)	14.0 +/- 6.1	11.7 +/- 2.4	0.240
ADC (mm^2/s)	963.1 +/- 226	878.0 +/- 170	0.326
R2*(sec^{-1})	46.2 +/- 8.4	48.6 +/- 8.46	0.505
Volume (mm^3)	30707 +/- 34354	7676 +/- 5401	**0.034**
EF (%)	88.7 +/- 9.1	76.9 +/- 27.4	0.268

% Change in Parameter	Pre-menopausal (n=13)	r^2	P value	Post-menopausal (n=9)	r^2	P value
Ktrans	↓33.9 +/- 24.3	0.20	0.121	↓19.0 +/- 28.9	0.27	0.186
Ve	↑12.4 +/- 26.8	0.43	**0.015**	↓1.6 +/- 20.4	0.37	0.109
Kep	↓36.0 +/- 26.6	0.005	0.819	↓16.7 +/- 20.9	0.09	0.476
IAUGC	↓40.9 +/- 19.2	0.15	0.199	↓19.0 +/- 31.2	0.29	0.173
ADC	↑7.6 +/- 31.6	0.26	0.076	↑4.3 +/- 8.7	0.13	0.333
R2*	↑13.7 +/- 11.3	0.18	0.24	↓0.99 +/-12.8	0.06	0.517
EF (%)	↓10.0 +/- 20.1	0.17	0.165	↓7.2 +/- 12.4	0.01	0.785

DISCUSSION AND CONCLUSION: In premenopausal women with ER positive breast cancer, tumors were larger and more vascular than in postmenopausal women. A rise in the ve correlated significantly with volume reduction in premenopausal women; no specific parameter correlated with response in postmenopausal women.

REFERENCES:

[1] Eiermann et al Ann Oncol 2001, [2] Smith et al. JCO 2005, [3] Powles et al JCO 1995, [4] Fisher et al JCO 1998, [5] Swain et al Can Res 1987, [6] Bottini et al. JCO 2006.