Reducing measurement error of DCE-MRI by altering arterial input functions does not improve the prediction of outcomes for breast cancers patients treated with chemotherapy

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Background: Neoadjuvant chemotherapy (NAC) is used for the treatment of locally advanced breast cancers, resulting in fewer mastectomies compared to primary surgery while providing an equivalent survival outcome. 2-30% of patients receiving NAC will fail to respond to treatment and the ability to identify non-responders early during treatment would enable the use of alternative therapies. Many clinical studies have documented that DCE-MRI performed after 1-2 cycles of chemotherapy can predict eventual clinical and pathological outcomes of patient with breast cancer, with changes in transfer constant (K^{trans}) having the highest accuracy in making this determination[1-3]. When making individual patient decisions regarding discontinuance of potentially ineffective therapy, it is important to know whether "real" changes in K^{trans} have occurred (i.e., measurement error must be known). Measurement error can be dramatically improved by changing the arterial input function for model derived K^{trans} estimates[4,5] but it is unknown whether there is an improved sensitivity to treatment-related change. This study evaluates whether improving measurement error of DCE-MRI by using "more physiological" input functions improves the prediction of pathological response for breast cancer patients.

Methods: Patients were studied using a 1.5T Siemens Symphony scanner. Two cohorts were evaluated: (1) 11 patients studied twice within 1 week to determine measurement error – reproducibility cohort. (2) Response cohort (7 pathological non-responders and 13 responders) before and after 2 cycles of chemotherapy (FEC - 5-fluorouracil, epirubicin and cyclophosphamide) (n=16) or taxanes (n=4). T_1 weighted DCE-MRI studies were obtained using methods previously described[6]. Briefly, spoiled GRE [FLASH] sequences (TE 4.7ms, TR 11ms, α=35°, 4 slices) were acquired before and after the bolus administration of 0.1 mmol/kg bw of Gd-DTPA with 40 time points over 8 min, through the centre of their breast cancers. Whole tumour ROIs were outlined by a radiologist on all slices and pixel-by-pixel values of K^{trans} were calculated using Tofts' methods and MRIW software (MRI Workbench, Institute of Cancer Research, London)[6,7]. The pharmacokinetic analysis was performed by specifying 4 pooled input plasma clearance coefficients in accordance with data reported by Weinmann[8], Fritz-Hansen[9], by combining Weinmann and Fritz-Hansen data[10] (modified Fritz-Hansen) and Just[11] (femoral artery – internal data obtained from 20 men using a dual gradient echo sequence for bolus tracking studies). The Bland-Altman approach[12] was used to assess the measurement error of K^{trans} for the 4 AIFs for the reproducibility cohort. The following statistics were generated: mean for averaged data, repeatability coefficient (r) in % which represents the range beyond which differences are considered statistically significant and within patient coefficient of variability (wCV). The ability of K^{trans} to predict pathological response was assessed using ROC analysis with cut-offs chosen by the repeatability coefficient (–r%) to calculate corresponding sensitivity and specificity.

Results: The table shows reductions in K^{trans} values (noted in individual tumours and for the cohorts) with improvements in measurement error when non-Weinmann input functions are used. However, no improvements in test performance assessed by ROC methodology are seen (overlapping confidence intervals of area under ROC curves – data not shown). The ability to predict pathological response in individual patients (using –r% as the lower cut-off limit for responding patients) was also not improved.

Plasma input function coefficients	Reproducibility cohort (n=11)			Response assessment cohort (20)				
	K^{trans} mean (min^{-1})	r% mean	wCV (%)	Responders correctly predicted	Non-responders correctly predicted	Area under ROC curve	Sensitivity (%)	Specificity (%)
Weinmann[8]	0.683	-53.7 to 116.2	32.1	8/13	7/7	0.82	61.5	100
Modified Fritz-Hansen[10]	0.220	-36.0 to 56.3	17.5	9/13	7/7	0.85	69.2	100
Fritz-Hansen[9]	0.303	-35.8 to 55.8	17.4	9/13	7/7	0.88	69.2	100
Femoral artery[11]	0.163	-31.5 to 46.0	14.6	9/13	7/7	0.87	69.2	100

Conclusions: Our analyses indicate that improvements in reproducibility by using "more physiological" (non-Weinmann) arterial input functions do not result in improved test performance. That is, we were not able to more correctly predict pathological outcomes using DCE-MRI after 2 cycles of chemotherapy in patients with advanced breast cancers. Our data show that this occurs because of concomitant reductions in the mean K^{trans} values, which has the effect of reducing the dynamic range of the test. Other methodological improvements that improve measurement error (e.g. by whole tumour analysis and by minimizing observer variability) but without affecting kinetic parameter estimates may be preferable when trying to improve test performance.

References: [1]Hayes C, NMR in Biomed 2002; 15:154; [2]Padhani AR, Radiology 2006; 239:361; [3]Ah-See M-L, ISMRM 2004; 1992; [4]Taylor NJ, ISMRM 2006; 776; [5]Sharoyan V, ISMRM 2006; 2936; [6]Tofts, PS and Kermode, AG. JMRI 1997; 7:91; [7]d'Arcy JA, RadioGraphics 2006; 26:621; [8]Weinmann HJ, Physiol Chem Phys Med NMR 1984; 16:16, [9]Fritz-Hansen T, Magn Reson Med 1996; 36:225, [10]Walker-Samuel S, Phys. Med. Biol. 2006; 51**: 3593** [11] Just, N, Proc. I.S.M.R.M. 2002**; 2128***;* [12]Bland JM,BMJ 1996;312:1654.