Towards Optimization of DCE-MRI Analysis for Early Prediction of the Response of Breast Cancer Patients to Neoadjuvant Chemotherapy

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INTRODUCTION Tumor response to neoadjuvant chemotherapy is currently monitored by changes in tumor size as measured by physical exam, ultrasound, or conventional MRI. However, these methods often do not correlate with pathologic findings at surgery. Dynamic contrast enhanced MRI (DCE-MRI) offers information related to tumor perfusion and permeability (K^{trans}), vascular volume (v_p), extravascular extracellular volume fraction (v_e), and the intracellular water lifetime of a water molecule (τ_i). In this study, we attempted to determine the optimal analysis method for assessing if changes in these parameters after one cycle of therapy could separate pathologic complete responders (pCR) from non-responders (NR; i.e., patients with residual disease).

METHODS 22 patients with Stage II/III breast cancer were enrolled in an IRB-approved clinical trial where serial breast MRI scans were acquired pre-therapy (t_1) and after one cycle of therapy (t_2). Imaging was performed on a 3.0 T Achieva MR scanner (Philips Healthcare, Best, The Netherlands). The DCE-MRI acquisition employed a 3D spoiled gradient echo sequence with TR\TE\α =7.9ms\1.3ms\20°. The acquisition matrix was 192×192×20 over a sagittal (22 cm)^2 FOV with a slice thickness of 5 mm. Each 20-slice set was collected in 16.5 seconds at 25 time points and 0.1 mmol/kg of Magnevist was injected at 2 ml s^{-1} after three baseline dynamic scans. Eleven patients were pCR and the other 11 patients were NR.

Three pharmacokinetic models were used to estimate physiological parameters: the Tofts-Kety (TK), the Extended Tofts-Kety (ETK), and the fast exchange regime (FXR). For each model, eight DCE-MRI parameters were estimated to predict treatment response: the change in mean, median, mean of top 15%, and standard deviation (STD) from t_1 to t_2, the mean at t_1 and t_2, respectively, and the STD at t_1 and t_2, respectively. A Wilcoxon rank sum test was then used to determine if there was a significant difference between the pCR and NR groups.

RESULTS The table displays the ability of K^{trans} and v_p to statistically separate pCR from NR patients. K^{trans} (as estimated by the TK and ETK models) and v_p (as estimated by the ETK model) lead to the most significant results. In particular, the TK estimates of the change of mean, change of the mean of the top 15%, the change in the STD, and the STD at t_2 of K^{trans} are the most sensitive variables, achieving significance at the $p<0.01$ level. Nearly all p values of v_e and τ_i are not significant. It is very important to note that there was not a significant difference in enhancing tumor volume between the two groups (p=0.24), indicating that K^{trans} and v_p outperform tumor volume changes.

Parameter	K^{trans}			v_p
Model	TK	ETK	FXR	ETK
Δmean	**0.01**	**0.03**	0.12	**0.04**
Δmedian	**0.02**	**0.02**	**0.02**	0.09
Δmean of top15%	**0.01**	0.08	0.15	**0.03**
ΔSTD	**0.01**	0.13	0.15	**0.02**
Mean at t_1	0.69	0.39	0.36	0.39
Mean at t_2	**0.02**	**0.04**	0.07	0.08
STD at t_1	0.69	0.26	0.29	0.51
STD at t_2	**0.01**	**0.02**	0.15	**0.03**

The Table lists the p values of eight ways of summarizing K^{trans} and v_p as estimated by the different models. While the TK model presents the most parameters displaying significant differences between the patient group, the ETK model shows several as well. It is important to note that changes in tumor volume from t_1 to t_2 were not significant (p=0.24) between groups.

CONCLUSIONS K^{trans} as estimated by the TK and ETK models, as well as v_p, can separate complete responders from non-responders after a single cycle of neoadjuvant chemotherapy. These data contribute to a developing literature on quantitative DCE-MRI in the neoadjuvant setting. For example, Padhani *et al.* [1] showed that both tumor size and change in K^{trans} range (similar to our STD measurement) were equally able to predict response, and Ah-See *et al.* [2] reported that changes in K^{trans} were the best predictor of non-response. Our study, combined with those data, may ultimately allow clinicians to tailor therapy on an individual basis for this patient population.

ACKNOWLEDGMENTS NCI 1R01CA129961, NCI 1U01CA142565, NCI 1P50 098131, NCI P30 CA68485, NCRR/NIH UL1 RR024975-01.

REFERENCES 1.Padhani AR et al., Radiology 2006. 2.Ah-See ML et al., Clin Cancer Res. 2008.