Comparing Functional Tumor Volume and Pharmacokinetic Parameter in DCE-MRI Prediction of Breast Cancer Therapy Response: A Preliminary Study

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Introduction: As a noninvasive imaging method capable of 3D characterization of *in vivo* tissue microvasculature, dynamic contrast-enhanced MRI (DCE-MRI) is increasingly being used in research settings and early phase clinical trials to assess tumor therapeutic response (1). Both quantitative pharmacokinetic (PK) (2) and empirical (3,4) analysis of DCE-MRI time-course data have been shown useful for assessment of breast cancer response to neoadjuvant chemotherapy (NACT). Both data analysis approaches have advantages and disadvantages. Though PK analysis produces biological parameters (such as K^{trans} and v_e) that are, in principle, independent of data acquisition details, the accuracy and precision of these parameters are often affected by not only errors in several measurements that are integral steps of PK analysis, such as quantifications of arterial input function (AIF) and pre-contrast T_1, but also the selection of PK analysis algorithm/software tool (5). Empirical analysis is simple and straightforward. However, since it deals with signal intensity directly, acquisition parameters and scanner platform and settings can influence results (6), making it difficult to compare studies at different sites. It is an open question which analysis approach is better suited for DCE-MRI evaluation of therapy response. In this study, by analyzing high-temporal-resolution breast DCE-MRI data quantitatively and empirically, we sought to examine whether one approach is superior to the other in early prediction of breast cancer response to NACT.

Methods: Fourteen consecutive women with locally advanced breast cancer (one patient had two independent primary tumors) who underwent NACT consented to research DCE-MRI studies performed at Visit 1 (V1) - before NACT, V2 - after first NACT cycle, V3 – midpoint of NACT, and V4 - after NACT completion before surgery. Axial bilateral DCE-MRI images with full breast coverage were acquired with a 3D gradient echo-based TWIST sequence (7) using a 3T Siemens scanner. DCE-MRI acquisition parameters included 10° flip angle, 2.9/6.2 ms TE/TR, a parallel imaging acceleration factor of two, 30-34 cm FOV, 320x320 matrix size, and 1.4 mm slice thickness. The total acquisition time was ~ 10 min for 32-34 image volume sets with 17-20 s temporal resolution. Gd contrast agent (Prohance®) IV injection (0.1 mmol/kg at 2 mL/s) was timed to start at the beginning of the third image volume acquisition, followed by 20 mL saline flush.

For PK data analysis, tumor ROIs were drawn on post-contrast DCE images by experienced radiologists who also measured one dimensional tumor size based on the RECIST guidelines (8). The ROI-averaged DCE time-course data were subjected to the Shutter-Speed model (SSM) (9) PK analyses to estimate K^{trans}, v_e, k_{ep} (= K^{trans}/v_e), and τ_i (mean intracellular water lifetime) parameters. The SSM-unique τ_i parameter was used to account for the transcytolemmal water exchange kinetics. The whole tumor mean parameter value was calculated as the weighted (by ROI pixel number) average of the single-slice ROI values from the image slices covering the entire tumor.

For empirical analysis, one baseline and six post-contrast image volumes were selected from the original DCE-MRI data to form a new DCE-MRI data set that simulates the timing of the DCE-MRI protocol used in the ISPY 2 TRIAL (http://ispy2.org) (80-100s temporal resolution and > 8 min post-contrast acquisition time). The new data set was then used to quantify functional tumor volumes (FTV) based on voxel thresholds for early percent enhancement [$PE=100*(S_E-S_0)/S_0$] and signal enhancement ratio [$SER=(S_E-S_0)/(S_L-S_0)$] using a Hologic CAD system (10). S_0 was the baseline (pre-contrast) signal intensity, while S_E and S_L were the early and late signal intensities at time points that were closest to 150 s and 450 s post-contrast injection, respectively; PE threshold was 70%; SER thresholds were as shown in **Table 1**. SER > 1.1 represented washout curve pattern which was further stratified into three sub-classes; while 0.9 < SER < 1.1 and SER < 0.9 characterized plateau and gradual patterns, respectively. FTV was calculated as the volume of voxels conforming to PE and SER thresholds, within a user defined 3D tumor bounding ROI. The total FTV, which included voxels of all three curve patterns, was represented by SER > 0.0.

Table 1. ULR c Value for Early Prediction of Therapy Response

		V1	V2	V21%
Functional Tumor Volume (PE > 70%)	SER > 0.0	0.750	0.886	0.955
	SER > 1.1	0.682	0.977	0.977
	SER > 1.75	0.545	0.920	0.807
	1.3 < SER < 1.75	0.682	0.932	0.955
	1.1 < SER < 1.3	0.750	1.00	0.909
	0.9 < SER < 1.1	0.705	1.00	0.955
	SER < 0.9	0.705	0.784	0.648
PK Parameters	K^{trans}	0.682	0.977	1.00
	v_e	0.648	0.909	0.909
	k_{ep}	0.625	0.977	0.955
	τ_i	0.784	0.750	1.00
RECIST		0.648	0.682	0.600

This study compares early prediction capability between PK and FTV analyses of DCE-MRI data. Thus, only the MRI metrics at V1 and V2, and their percent changes (V21%, V2 relative to V1) were correlated with pathologic response end points using univariate logistic regression (ULR) analysis.

Results: Pathology analyses of post-NACT resection specimens revealed that four patients had pathologic complete response (pCR), while the other 10 patients (11 tumors) were non-pCRs. Table 1 lists the ULR c statistics values [equivalent to area-under-the-curve (AUC) of ROC analysis] for early prediction of breast cancer response to NACT with c = 1 representing complete separation of pCRs from non-pCRs. The metrics with c values in red were good ($0.8 \le c < 0.9$) to excellent ($0.9 \le c \le 1$) early predictors of response. At baseline (V1), neither PK parameters nor various FTVs were good predictors of pathologic response. However, except for the tumor volume with gradual kinetics (SER < 0.9), all other FTV measures at V2 and V21% provided good to excellent early prediction of response: V2 total tumor volume and V21% FTV with SER > 1.75 had c values of 0.886 and 0.807, respectively, while the rest had c values ranging from 0.909 to 1.00. Except for τ_i at V2 with c < 0.8, all the PK parameters at V2 and V21% were excellent early markers of response with a c value range of 0.909 – 1.00. For early prediction of response, DCE-MRI data analysis with either the volumetric SER or the quantitative PK method substantially outperformed anatomic image based RECIST tumor size measurement, which had ULR c values of 0.648, 0.682, and 0.600 for V1, V2, and V21%, respectively.

Discussion and Conclusion: The results from this preliminary study of a limited cohort size show that FTV metrics computed based on empirical SER analysis of DCE-MRI data performed comparably in early prediction of breast cancer response to NACT in comparison with quantitative PK parameters. Similar to PK analysis which generated several predictive markers, multiple FTV metrics, including tumor volume with plateau kinetics at V2 and V21%, were highly predictive of therapy response, potentially allowing multivariate analysis to further improve accuracy in prediction of response. These findings should be validated with data from a larger cohort. The predictive accuracies of FTV metrics in this study are much higher than that of FTV change (ULR c = 0.70) reported in a previous prospective study (11). The difference is most likely due to the much larger sample size (N = 173) and a considerably different breast DCE-MRI protocol [4.5-5.0 min temporal resolution and three-time-point acquisition (one pre- and two post-contrast)] used in the earlier study (11). A recent study (12) of empirical analysis of high-temporal-resolution breast DCE-MRI data reports that only one metric, the percent change in washout volume, was a fair (ROC AUC = 0.77) early predictor of response. However, the full high-temporal-resolution data were used for empirical analyses in that study and the calculation of signal intensity change for curve pattern classification was based on an equation different from the SER equation employed in this study. These differences discussed above underscore the dependence of empirical results on data acquisition and analysis details, and the necessity of uniform protocol for data acquisition and analysis if empirical data analysis is to be used in a multicenter trial of DCE-MRI evaluation of therapy response.

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