Effects of Acquisition Time Variation on DCE-MRI Prediction of Breast Cancer Therapy Response

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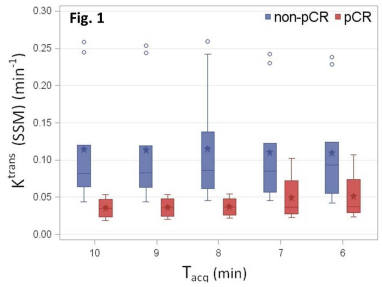
Introduction: Quantitative dynamic contrast-enhanced (DCE) MRI has been shown to be an important imaging biomarker for early prediction of breast cancer response to neoadjuvant chemotherapy (NACT) (1,2). The accuracy and precision of pharmacokinetic (PK) parameters estimated by PK modeling of DCE-MRI data can be affected by many steps in data acquisition and analysis - such as quantifications of arterial input function (AIF) and pre-contrast T_1, causing significant parameter variations. Within the context of therapy response assessment, however, it is important to find acceptable range of parameter variations under which DCE-MRI still plays an effective role in monitoring therapy response. In this study, we sought to investigate the effects of another factor, the DCE-MRI acquisition time (T_{acq}), on DCE-MRI prediction of breast cancer response to NACT. Breast cancer patients receiving NACT can be quite debilitated and fatigued secondary to treatment. Consequently, a relatively long T_{acq} causes significant patient discomfort in the scanner magnet, often resulting in motion artifacts in the acquired images and low-quality data. Therefore, without sacrificing the ability of DCE-MRI for assessment of therapy response, shorter T_{acq} is more desirable.



Methods: Fourteen women with locally advanced breast cancer (one patient had two independent primary tumors) underwent NACT before definitive surgeries. They consented to research DCE-MRI studies that were performed at visit 1 (V1) - before NACT, at V2 - after first NACT cycle, at V3 – midpoint of NACT (usually after 3-4 NACT cycles), and at V4 - after NACT completion. Axial bilateral DCE-MRI images with fat-saturation and full breast coverage were acquired using a 3T Siemens scanner, with a 3D gradient echo-based TWIST sequence (3), 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 DCE-MRI T_{acq} was ~10 min (slightly longer than 10 min for all studies) for 32-34 image volume sets with 18-20 s temporal resolution. Gadolinium contrast agent (ProHance®) IV injection (0.1 mmol/kg at 2 mL/s) was timed to start following acquisitions of two baseline image volumes. Tumor ROIs were drawn by experienced radiologists on post-contrast DCE images. The ROI and pixel-by-pixel (within the ROI) DCE time-course data were then subjected to both the Standard (Tofts) Model (SM) (4) and the Shutter-Speed Model (SSM) (5) analyses as previously described (6) to estimate PK parameters. The SSM accounts for the effects of finite intercompartmental water exchange kinetics (5). The whole tumor mean parameter value was calculated as the weighted (by ROI pixel number) average of the ROI values from each of the image slices covering the entire tumor.

To simulate DCE-MRI data with shorter T_{acq}, data points from the originally acquired DCE-MRI time-course data were incrementally dropped from the far end of the time course, resulting in T_{acq} values of ~9, ~8, ~7, and ~6 min. These new time-courses were then subjected to the same SM and SSM analyses. This study evaluates only the effects of T_{acq} on DCE-MRI early prediction of therapy response. We have shown in a previous study of the same cohort (7) that K^{trans} and k_{ep} of either PK model at V2 and their percent changes (V21%, V2 relative to V1), estimated from the originally acquired ~10 min T_{acq} data, are good to excellent early predictors of breast cancer response to NACT. Therefore, only the effects of T_{acq} on these PK metrics as early markers of response were assess through univariate logistic regression analysis and correlation with pathologic response endpoints.

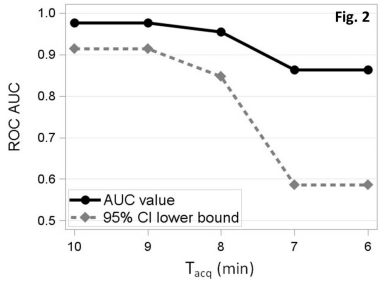
Table 1. ROC AUC of PK Metrics at Different T_{acq} for Early Prediction of Therapy Response

PK Metrics	T_{acq} = ~10 min	~9 min	~8 min	~7 min	~6 min
V2 K^{trans}(SM)	0.886 (0.690)*	0.909 (0.749)	0.886 (0.690)	0.796 (0.440)	0.796 (0.440)
V2 K^{trans}(SSM)	0.977 (0.914)	0.977 (0.914)	0.955 (0.847)	0.864 (0.586)	0.864 (0.586)
V2 k_{ep}(SM)	0.977 (0.914)	0.955 (0.852)	0.955 (0.852)	0.705 (0.325)	0.705 (0.275)
V2 k_{ep}(SSM)	0.977 (0.914)	1.00 (1.00)	1.00 (1.00)	0.796 (0.440)	0.750 (0.312)
V21% K^{trans}(SM)	0.977 (0.914)	0.977 (0.914)	0.932 (0.804)	0.841 (0.599)	0.818 (0.562)
V21% K^{trans}(SSM)	0.977 (0.914)	0.955 (0.847)	0.932 (0.804)	0.818 (0.562)	0.796 (0.509)
V21% k_{ep}(SM)	0.977 (0.914)	0.841 (0.566)	0.955 (0.852)	0.523 (0.166)	0.568 (0.109)
V21% k_{ep}(SSM)	0.955 (0.852)	0.955 (0.847)	0.932 (0.804)	0.568 (0.110)	0.591 (0.154)

*: value in () is the 95% confidence interval lower bound.

The predictive accuracy of each metric at each T_{acq} was quantified with point and interval estimates of AUC (area-under-the-curve) of Receiver Operating Characteristic (ROC) analysis.

Results: Pathology analyses of the surgical specimens revealed that four tumors had pathologic complete response (pCR) while the other 11 were non-pCRs. **Fig. 1** shows the box plots of V2 K^{trans}(SSM) for the two response groups, estimated by SSM fitting of DCE time-course with T_{acq} = ~10, ~9, ~8, ~7, ~6 min. It is quite clear that there was more overlap of the K^{trans} value between the two groups when T_{acq} was reduced to ~7 and ~6 min. Similar patterns were observed for the other parameters of either PK model at V2 and V21%. **Table 1** lists the ROC AUC values and the corresponding 95% confidence interval (CI) lower bounds (LB) for the V2 and V21% metrics of the SM and SSM K^{trans} and k_{ep} parameters at different T_{acq}. The values in red indicate AUC 95% CI LB < 0.8. When T_{acq} is ~ 8 min or longer, with the exception of V2 K^{trans}(SM) at all three T_{acq} values and V21% k_{ep}(SM) at T_{acq} = ~9 min, which are still good (0.8 ≤ AUC < 0.9) to excellent (AUC ≥ 0.9) markers for early prediction albeit with 95% CI LB < 0.8, all the other listed metrics are excellent and reliable early predictors of response with AUC > 0.9 and 95% CI LB > 0.8. However, when T_{acq} is reduced to ~7 min or shorter, none of the metrics is a reasonable early predictor of response with all 95% CI LB values substantially below 0.8 and most AUCs < 0.8. **Fig. 2** shows an example scatter plot for the V2 K^{trans}(SSM) metric. Though the ROC AUC values remain above 0.8 for T_{acq} = ~7 and ~6 min, the 95% CI LB values drop below 0.6, rendering V2 K^{trans}(SSM) an unreliable marker for early prediction at 7 min or shorter T_{acq}.



Discussion and Conclusion: The results from this study suggest that, if quantitative PK data analysis is used in DCE-MRI assessment of breast cancer therapy response, a T_{acq} of 8 min may be sufficient for DCE-MRI data collection. A relatively short T_{acq} speeds-up DCE-MRI protocol, reduces patient discomfort, and minimizes the possibility of motion artifacts. However, any T_{acq} shorter than 8 min could significantly reduce the capability of DCE-MRI for early prediction of therapy response. Compared to a previous study on DCE-MRI T_{acq} variation using simulated noiseless data (8), this study utilized real data with noise and presumably produced results more relevant to actual experimental conditions. The findings from this study are based on a limited cohort, and need to be validated with a larger cohort. Furthermore, it should be investigated whether the conclusion on T_{acq} of breast DCE-MRI is applicable to tumors of other organs, which may have different ranges of PK parameter values compared to breast tumors and thus different, tumor type-specific optimal T_{acq}.

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References: **1.** Marinovich *et al. The Breast* 2012;21:669-677. **2.** Li *et al. Magn Reson Med* 2014;71:1592-602. **3.** Tudorica *et al. Magn Reson Imaging* 2012;30:1257-67. **4.** Tofts *et al. JMRI* 1999;10:223-32. **5.** Li *et al. Magn Reson Med* 2005;54:1351-9. **6.** Huang *et al. Radiology* 2011;261: 394-403. **7.** Tudorica *et al. Proc Intl Soc Magn Reson Med* 2014;22:920. **8.** Wang *et al. Proc Intl Soc Magn Reson Med* 2010;18:4811.