Early DCE-MRI Changes after Longitudinal Registration May Predict Breast Cancer Response to Neoadjuvant Chemotherapy

Xia Li, Lori R. Arlinghaus, A. Bapsi Chakravarthy, Jaime Farley, Ingrid A. Mayer, Vandana G. Abramson, Mark C. Kelley, Ingrid M. Meszoely, Julie Means-Powell, and Thomas E. Yankeelov

Institute of Imaging Science, Vanderbilt University, Nashville, Tennessee, USA
{xia.li.1,lori.Arlinghaus,Bapsi.chak,Jaime.farley,ingrid.mayer, vandana.abramson,mark.kelley,ingrid.meszoely,Julie.means, tom.yankeelov}@vanderbilt.edu

Abstract. To monitor tumor response to neoadjuvant chemotherapy, investigators have begun to employ quantitative physiological parameters available from dynamic contrast enhanced MRI (DCE-MRI). However, most studies track the changes in these parameters obtained from the tumor region of interest (ROI) or histograms, thereby discarding all spatial information on tumor heterogeneity. In this study, we applied a nonrigid registration to longitudinal DCE-MRI data and performed a voxel-by-voxel analysis to examine the ability of early changes in parameters at the voxel level to separate pathologic complete responders (pCR) from non-responders (NR). Twenty-two patients were examined using DCE-MRI pre-, post one cycle, and at the conclusion of all neoadjuvant chemotherapy. The fast exchange regime model (FXR) was applied to both the original and registered DCE-MRI data to estimate tumor-related parameters. The results indicate that compared with the ROI analysis, the voxel-based analysis after longitudinal registration may improve the ability of DCE-MRI to separate complete responders from non-responders after one cycle of therapy when using the FXR model ($p = 0.02$).

Keywords: Longitudinal registration, DCE-MRI, breast cancer.

1 Introduction

Early investigations in monitoring tumor response to neoadjuvant chemotherapy focused on semi-quantitative analyses based on changes in morphology and/or anatomical measures [1-7]. More recently, investigators have begun to employ the quantitative physiological parameters available from dynamic contrast enhanced MRI (DCE-MRI). For example, Ah-See *et al* [8] acquired DCE-MRI data on thirty-seven patients with primary breast cancer. Through calculating the changes in seven kinetic parameters, they reported the that change in the volume transfer constant (K^{trans}) was the best predictor of pathologic nonresponse. In performing their analysis, the

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investigators tracked the changes in parameters obtained from tumor ROI or histogram data. While this approach is the current standard, it does discard all spatial information on tumor heterogeneity. Li *et al* presented [9] and validated [10] a method for the registration of breast MR images obtained at different time points throughout the course of neoadjuvant chemotherapy. In this study, we applied the approach to longitudinal pharmacokinetic parameters estimated by the fast exchange regime model (FXR) and performed a voxel-by-voxel analysis to examine the ability of early changes in parameters at the voxel level to separate pathologic complete responders (pCR) from non-responders (NR). The FXR model assumes that tissue is not homogeneous and water exchange between the vascular, extravascular intracellular space, and the extravascular extracellular spaces are not sufficiently fast. To the best of our knowledge, it is the first work to report the ability of the FXR model to predict breast cancer response and demonstrate the influence of tumor heterogeneity on the analysis of treatment response.

2 Patients and Methods

2.1 MRI Data Acquisition

Twenty-two 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 (t_2), and at the completion of neoadjuvant chemotherapy (t_3). 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 $(22\ \text{cm})^2$ field of view 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 the third dynamic scan. Responders (n=11) were defined as those patients who had a pathologic complete response at time of surgery. Non responders (n=11) were defined as patients with residual invasive cancer at the primary tumor site.

2.2 Data Registration

The purpose of the registration in this study is to align DCE-MRI data acquired at three time points: pre-, post-one cycle, post-all cycles of neoadjuvant chemotherapy. Since the DCE-MRI data at each imaging session consists of 25 dynamic scans, we apply the registration to the average of the post-contrast DCE-MRI data (i.e., the average of the 4th – 25th scans; this is done to increase the SNR of the data to yield a more accurate registration). First, the average DCE data pre- and post-one cycle of therapy are aligned to the data at the conclusion of all therapy by a rigid body registration algorithm [11], which searches the optimal rotation and translation parameters through maximizing the normalized mutual information (NMI). A nonrigid registration method [9] is then applied to refine the registration. This method extends the

adaptive bases algorithm (ABA) [12] through incorporating an additional term designed to preserve the tumor volume during the registration process. The reason the tumor volume must be preserved is that compressing or expanding the tumor during the registration process could provide results that are misleading in regard to assessing biological changes in the tumor (e.g., disease progression or response) that occur between imaging sessions.

Both the ABA and the extended ABA algorithm with a tumor volume conserving constraint employ NMI as the similarity measure, and the deformation field is modeled by a linear combination of radial basis functions. To constrain the tumor volume, we compute the Jacobian determinant over the tumor regions in the MR images:

$$f_{con} = \alpha \int_T \left| log\left(J_T(x)\right) \right| dx , \tag{1}$$

where $J_T(x)$ is the Jacobian determinant on the tumor area and α is the parameter to control the weight of this constraint term, which is set to 0.15 – 0.3 based on empirical evidence. Hence the cost function is composed of the negative NMI term and the tumor volume constraint term:

$$f_{cost} = -NMI + \alpha \int_T \left| log\left(J_T(x)\right) \right| dx , \tag{2}$$

Through minimizing Eq. (2), the algorithm can optimally register the normal tissues while simultaneously minimizing tumor distortion. The generated transformation is applied to each dynamic scan to obtain the registered DCE-MRI data.

2.3 Data Analysis

The fast exchange regime model (FXR) is applied to both the original and serially registered DCE-MRI data to estimate the volume transfer constant (K^{trans}, related to tumor perfusion and permeability), efflux rate constant (k_{ep}), extravascular extracellular volume fraction (v_e), and the average intracellular water lifetime of a water molecule (τ_i).

In order to perform quantitative DCE-MRI, the arterial input function (AIF) must be measured. Individual AIFs are detected by a semi-automatic AIF tracking algorithm, the details of which can be found in reference [13]. Here we use a population-averaged AIF which is calculated through averaging fifty individual AIFs.

For each patient at each time point, a conservative ROI is manually drawn around the contrast enhanced tumor region; that is, the ROI encompasses the entire tumor as well as surrounding healthy appearing tissue. Given this set of voxels, eleven subsets of enhancing tumor voxels are constructed on the basis of their averaged post-contrast signal intensity increase over the average of the three pre-contrast time points. Each subset is defined for different percent enhancement thresholds ranging from 10% to 110% in 10% increments. This allows us to establish an optimal "cut-off" point for selecting enhancing voxels to include in the analysis.

To evaluate the effectiveness of the longitudinal registration algorithm, both ROI and voxel-based analyses are performed. The ROI analysis is based on the unregistered DCE-MRI data and three parameters are computed: the change of mean, median, and mean of the top 15% parameters. The voxel analysis is performed on the registered data and the same parameters are calculated on voxels showing an increase in the parameter from t_1 to t_2. A Wilcoxon rank sum test is then used to determine if there is a significant difference between the pCR and NR groups.

3 Results

Figure 1 shows the registered DCE-MRI data at three time points with the corresponding K^{trans} maps superimposed; the top row shows a representative patient achieving a pCR, while the bottom row is a NR.

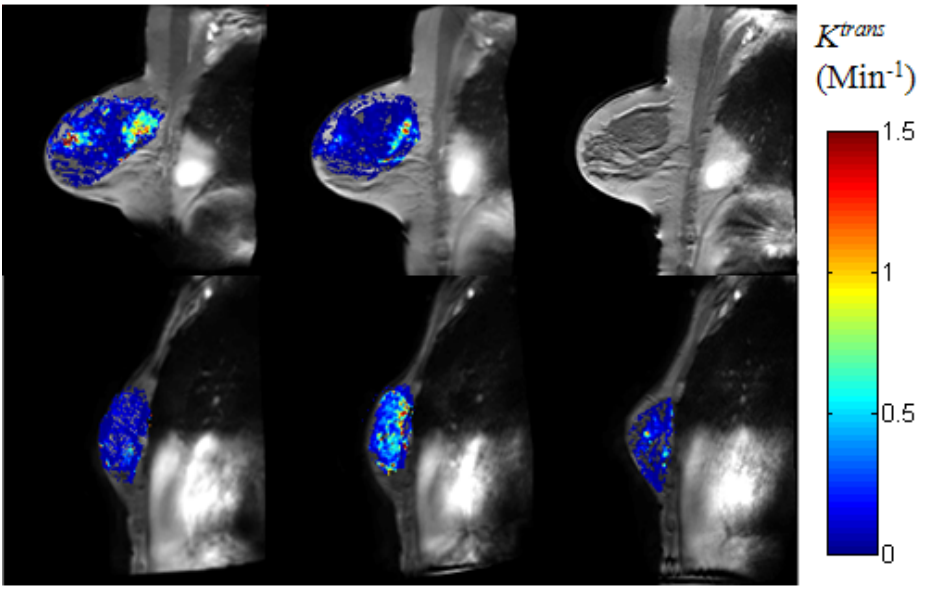

Fig. 1. The registered DCE-MRI data at three time points (columns) with the corresponding K^{trans} superimposed; the top row shows a patient with pCR, while the bottom row is a NR.

Figure 2 shows the p values obtained by both the ROI and voxel-based analyses at different enhancement thresholds. Before registration, only two ROI analyses are significant (the median K^{trans} when the 20% and 30% enhancement rates used as the cut-off) at the $p < 0.05$ level (indicated by the solid black line in the figure). However, after the longitudinal registration, p values are significant when the enhancement rates ranging from the 20% to 70% are used, indicating the parameters estimated by the FXR model with registration can distinguish the differences between two groups.

Table 1 lists the p values of three ways of summarizing different pharmacokinetic parameters by the ROI and voxel-based analyses. The results indicate that the registration makes the change in mean K^{trans} move from a not significant (p = 0.12 in the ROI analysis) to a significant difference (p = 0.02 in the voxel analysis). Similar conclusions can be made for the change in mean of the top 15% of K^{trans} and k_{ep}. The other parameters studied in this effort, v_e and τ_i, do not yield significant results in either analysis.

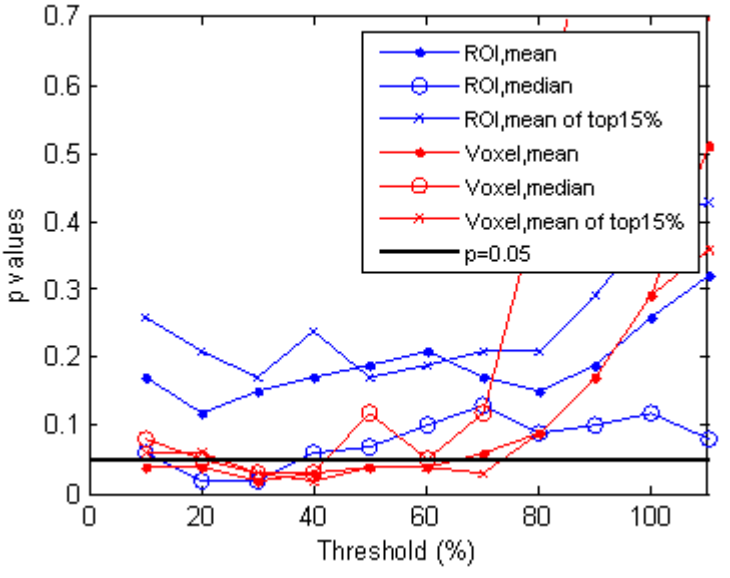

Fig. 2. The p values of k^{trans} obtained by both the ROI and voxel-based analyses at different enhancement thresholds. Most p values in the voxel-based analysis are significant (< 0.05) when the enhancement rates ranging from the 20% to 70% are used, compared with two significant p values in the ROI analysis, indicating the longitudinal registration may improve the ability of DCE-MRI data to predict treatment response.

Table 1. The table lists the p values of three ways of summarizing different pharmacokinetic parameters by the ROI and voxel-based analyses. The results after the voxel-based analysis, in general, lead to smaller p values, indicating the longitudinal registration may improve the ability of DCE-MRI data to separate pCR from NR patients.

	K^{trans}		k_{ep}		v_e		τ_i	
Analysis	ROI	Voxel	ROI	Voxel	ROI	Voxel	ROI	Voxel
Δmean	0.12	**0.02**	**0.04**	**0.04**	0.12	0.39	0.69	0.26
Δmedian	**0.02**	**0.03**	0.08	0.06	0.17	0.15	0.51	0.13
Δmean of top15%	0.15	**0.02**	0.07	**0.04**	0.74	0.13	0.51	0.13

4 Conclusions

A nonrigid registration algorithm has been employed to retain the spatial information in DCE-MRI parameter maps obtained before and after neoadjuvant chemotherapy, thereby enabling a voxel-based analysis to be performed to predict response. The quantitative analysis demonstrates that K^{trans} and k_{ep} can separate pCR from non-responding patients after the parameters are aligned by this algorithm. Although v_e and τ_i cannot lead to any significant results, the p values trend to smaller values after registration. The results indicate that the voxel-based analysis after longitudinal registration may improve the ability of DCE-MRI to separate pCR from non-responders after one cycle of therapy when using the FXR model.

There are a number of limitations in the study. First, the population AIF was used to estimate the physiological parameters from DCE-MRI data. In practice, it is difficult to obtain a reliable AIF from each patient at each time point. Li *et al.*'s study [13] indicates that K^{trans} and v_p show a good agreement between the population AIF and individual AIF. Thus, the population AIF in this study may not be the main concern, although future work should investigate the role of individual AIFs in predicting treatment response. The temporal resolution of 16 s used in this study is also an important limitation. It is not optimal for AIF characterization; rather it represents a balance between temporal and spatial resolution and field of view coverage so we can perform longitudinal registration. A final limitation is that the number of patients is modest and we are currently working to expand the data set to explore the ability of the voxel-based analysis to predict treatment response.

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