NON-RIGID REGISTRATION OF SEQUENTIAL DCE-MRI IN THE ASSESSMENT OF RESPONSE TO NEOADJUVANT CHEMOTHERAPY IN BREAST CANCER

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Target Audience: Physicists and radiologists with an interest in measuring DCE-MRI treatment response in oncology trials.

Purpose: Tumor heterogeneity is well recognized in breast cancer and is associated with differential responses to chemotherapy. DCE-MRI is an established biomarker for predicting treatment response and has previously been exploited to measure tumor vasculature following anti-angiogenic therapies[1]. Quantitative and semi-quantitative perfusion metrics are well established in breast radiology[2]. Typically perfusion parameters are summarized and reported over a region of interest (ROI), a highly data reductive process. ROI-based definitions are subjective, fail to capture tissue heterogeneity and discard spatial information. Methods that retain spatial information typically require that sequential images are co-registered into a common image space. Registration algorithms have previously been reported for breast DCE-MRI[3]. Li *et al.* validated registration of 3D breast MR images acquired at different time points to allow for analysis of corresponding low-resolution parameter maps[4]. The purpose of this work is to improve the quality of diagnostic information obtained over sequential DCE-MRI examinations, retaining its inherent high-dimensional data characteristics, by performing intra- and inter-visit non-rigid registration on DCE-MRI data and extracting semi-quantitative perfusion metrics to monitor voxel-wise heterogeneity and tumor response to neoadjuvant chemotherapy (NACT).

Methods: Breast cancer patients were imaged on a 3T whole body MRI scanner (MR750 GE Healthcare, Waukesha, WI) over a course of NACT, as part of an ongoing randomized double-blinded oncology trial (www.clinicaltrials.gov/NCT01093235). Patients received six cycles of taxane and anthracycline-based NACT with randomization to additional bevacizumab (a monoclonal antibody which inhibits vascular endothelial growth factor). Patients were scanned at four time points (Visits A-D): at baseline and after completion of chemotherapy cycles one, three and six. To date, two patients have been analyzed following the completion of their treatment regime; upon study completion both patients underwent biopsy and were characterized as partial responders.
3D Registration. Image registration code was developed in C++ by extending functionality within the Insight Toolkit (www.itk.org). *(Visit A)* Mattes' mutual information-based B-spline non-rigid registration was used to register each temporal phase to the pre-contrast image to correct for intra-visit motion occurring due to respiratory, cardiac and involuntary patient movement. (*Visits B-D*) A 3D rigid translation was used to initialize a non-rigid B-spline transform to align the inter-visit pre-contrast images. This initial 'bulk transform' accounted for global motion due to patient repositioning on the scanner table. Subsequent temporal phases were registered to the transformed pre-contrast phase using known transform parameters established from the initial inter-visit registration step to correct any motion artifacts. In all cases a low-resolution B-spline mesh (35 mm spacing) was used to account for gross local distortion while reducing the potential to distort treatment effects.
Image Analysis. In-house software was developed in Matlab (version 7.14) to allow the user to import and navigate through unaligned and aligned 5-dimensional datasets (x, y, slice, phase, visit), render the selected image, plot voxel-wise and ROI based pharmacokinetic response to Gadolinium and compute semi-quantitative perfusion metrics.

Results: Spatially registered parameter maps showing area under the SI-time curve (AUC) were generated for both patients (Fig 1). Our approach demonstrates that spatially registered parameter maps allow for subsequent voxel-wise assessment of treatment response. Spatially registered regions of interest were then defined to summarize treatment response (Fig 2). Mean AUC decreased in both partial responders in response to treatment.

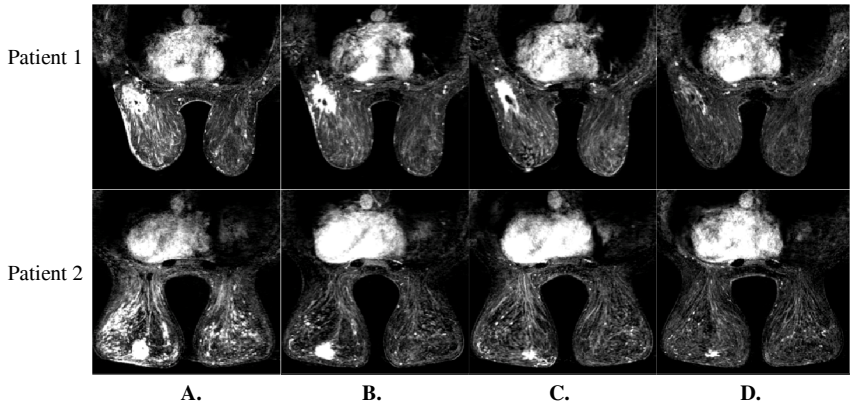

Figure 1. Spatially registered AUC parameter maps at (**A**) baseline and following (**B**) one (**C**), three and (**D**) six cycles of NACT

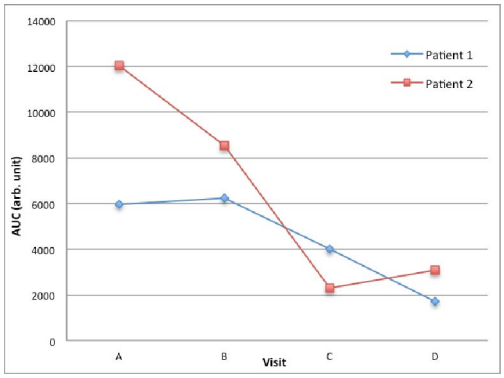

Figure 2. AUC averaged over spatially registered ROI at baseline and following up cycles

Discussion: The ability to register dynamic and sequential DCE-MRI data volumetrically and to visualize raw data and parameter maps in a common image space allows spatial changes in perfusion metrics to be explored. A major challenge in sequential registration of breast DCE-MRI data is to maximally register normal tissue whilst simultaneously preventing distortion of the tumor, which will typically change shape and volume significantly during treatment. We are currently optimizing registration for this purpose. Development of these techniques will ideally increase the statistical sensitivity in differentiating responders and non-responders. At the conclusion of this study, following unblinding of the anti-angiogenic randomization, our techniques will be applied to investigate differences in the treatment regimes.

Conclusions: Dynamic and sequential DCE-MRI data were registered into a common image space to account for intra-session motion artifacts as well as patient repositioning and large deformations of the breast tissue between sessions. We have introduced the ability to perform voxel-wise comparisons of physiological parameters obtained from sequential DCE-MRI examinations, which provides an insight into tumor microstructure and physiology in response to therapy.

References:

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