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Variations of Dynamic Contrast-Enhanced Magnetic Resonance Imaging in Evaluation of Breast Cancer Therapy Response: A Multicenter Data Analysis Challenge[1]

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Abstract

Pharmacokinetic analysis of dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) time-course data allows estimation of quantitative parameters such as K^{trans} (rate constant for plasma/interstitium contrast agent transfer), v_e (extravascular extracellular volume fraction), and v_p (plasma volume fraction). A plethora of factors in DCE-MRI data acquisition and analysis can affect accuracy and precision of these parameters and, consequently, the utility of quantitative DCE-MRI for assessing therapy response. In this multicenter data analysis challenge, DCE-MRI data acquired at one center from 10 patients with breast cancer before and after the first cycle of neoadjuvant chemotherapy were shared and processed with 12 software tools based on the Tofts model (TM), extended TM, and Shutter-Speed model. Inputs of tumor region of interest definition, pre-contrast T_1, and arterial input function were controlled to focus on the variations in parameter value and response prediction capability caused by differences in models and associated algorithms. Considerable parameter variations were observed with the within-subject coefficient of variation (wCV) values for K^{trans} and v_p being as high as 0.59 and 0.82, respectively. Parameter agreement improved when only algorithms based on the same model were compared, e.g., the K^{trans} intraclass correlation coefficient increased to as high as 0.84. Agreement in parameter percentage change was much better than that in absolute parameter value, e.g., the pairwise concordance correlation coefficient improved from 0.047 (for K^{trans}) to 0.92 (for K^{trans} percentage change) in comparing two TM algorithms.

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Nearly all algorithms provided good to excellent (univariate logistic regression c-statistic value ranging from 0.8 to 1.0) early prediction of therapy response using the metrics of mean tumor K^{trans} and k_{ep} ($=K^{trans}/v_e$, intravasation rate constant) after the first therapy cycle and the corresponding percentage changes. The results suggest that the interalgorithm parameter variations are largely systematic, which are not likely to significantly affect the utility of DCE-MRI for assessment of therapy response.

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Introduction

With advances in targeted molecular therapy for cancer treatment, change in tumor size in response to therapy, which is routinely used in standard care for therapeutic monitoring, is often found to manifest later than changes in underlying tumor characteristics [1–8], such as vascularization and vascular permeability, cellularity, metabolism, and biochemistry. Thus, imaging modalities that can quantify tumor functions are becoming increasingly important for evaluation and prediction of therapy response. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is a minimally invasive imaging method that measures changes in tissue microvascular properties and has been widely used in research or early phase clinical trial settings to provide assessment of tumor therapeutic response [1–8], as many cancer drugs affect tumor vasculature directly or indirectly [9]. The quantitative approach for DCE-MRI data analysis using pharmacokinetic models allows extraction and mapping of quantitative parameters of tumor biology *in vivo*. These parameters are usually variants of K^{trans}, a rate constant for contrast agent (CA) molecule plasma/interstitium transfer, v_e, the volume fraction of interstitial space (extracellular and extravascular, the putative CA distribution volume), and v_p, the plasma volume fraction. The CA intravasation rate constant, k_{ep}, can be calculated as K^{trans}/v_e. Recent workshops on both sides of the Atlantic have generated guidelines and recommendations on acquisition and analysis of DCE-MRI data for the purpose of assessing tumor therapy response [9–11].

Unlike qualitative (such as description of curve shape) or semiquantitative (such as calculation of maximum signal change) analysis, the parameters derived from pharmacokinetic modeling of DCE-MRI time-course data should, in principle, be independent of MRI scanner platform (vendor and field strength), data acquisition details (pulse sequence and parameters), CA dose and/or injection rate, personnel skills, and so on, which makes them desirable imaging end points in multicenter clinical trial studies. However, the accuracy and precision of these parameters can be affected by a plethora of factors, including errors in quantification of pre-contrast T_1 [12–15] and determination of arterial input function (AIF) [4,9,16,17], inadequate temporal resolution [9,18,19] or signal-to-noise ratio [15], as well as selection of models to fit the data [9,20,21]. A recent study [22] comparing four commercial software packages for quantitative DCE-MRI data analysis has revealed considerable variability in pharmacokinetic parameter quantification from data sets of 15 subjects, with up to 74% within-subject coefficient of variation (wCV) among the tools, even though all four software packages were presumably based on the same Tofts model (TM) [23]. Commercialization of software tools for kinetic modeling of DCE-MRI data represents a necessary step for wide dissemination of DCE-MRI as a quantitative imaging biomarker in clinical trials and general practice. However, the poor reproducibility shown by this study among the available commercial solutions is one of the major obstacles in integration of quantitative DCE-MRI into standard care. Thorough comparison and validation of algorithms/software tools for DCE-MRI data analysis are necessary within the context of monitoring tumor response to therapy.

Recognizing the importance of quantitative imaging for assessment of cancer response to therapy and rapid evaluation of the efficacy of new anticancer drugs, the National Cancer Institute has recently established the Quantitative Imaging Network (QIN) to provide resources for developing and validating quantitative imaging tools. The main mission of the QIN Image Analysis and Performance Metrics Working Group is to provide guidance and reach consensus on quantitative image analysis methods through comparison and validation of analysis algorithms. The available QIN infrastructure facilitates collaborative challenge projects involving multiple QIN centers. Here, we report the results from a DCE-MRI data analysis challenge project, in which several QIN centers performed analyses of DCE-MRI data from a digital reference object (DRO) [24] and human breast tumors using site-specific employment of algorithms/software tools. The overall goal of the project was to compare and validate DCE-MRI data analysis tools available within the QIN. Because ultimately the utility of a quantitative imaging method for assessing cancer therapy response is judged by its robustness in evaluation/prediction of clinical and/or pathologic end points of response, the DCE-MRI pharmacokinetic parameters and their changes following therapy were correlated with pathologic response status of the patients with breast cancer to compare the capabilities of the algorithms/tools in predicting complete response *versus* noncomplete response.

Materials and Methods

DCE-MRI Challenge Participating QIN Centers

The QIN centers that participated in this DCE-MRI data analysis challenge project are Oregon Health and Science University (OHSU), Vanderbilt University (VU), University of Pittsburgh (UP), Brigham and Women's Hospital (BWH) and in collaboration with General Electric Research and Development (BWH-GE), University of Michigan (UM), University of Washington (UW), and Icahn School of Medicine at Mount Sinai (ISM).

Simulated DRO DCE-MRI Data Sharing and Analysis

A software phantom or DRO with known pharmacokinetic parameter values can be an effective means to compare and validate different