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On the relationship between the apparent diffusion coefficient and extravascular extracellular volume fraction in human breast cancer☆

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Abstract

MRI techniques have been developed that can noninvasively probe the apparent diffusion coefficient (ADC) of water via diffusion-weighted MRI (DW-MRI). These methods have found much application in cancer where it is often found that the ADC within tumors is inversely correlated with tumor cell density, so that an increase in ADC in response to therapy can be interpreted as an imaging biomarker of positive treatment response. Dynamic contrast enhanced MRI (DCE-MRI) methods have also been developed and can noninvasively report on the extravascular extracellular volume fraction of tissues (denoted by v_e). By conventional reasoning, the ADC should therefore also be directly proportional to v_e. Here we report measurements of both ADC and v_e obtained from breast cancer patients at both 1.5 and 3.0 T. The 1.5-T data were acquired as part of normal standard of care, while the 3.0-T data were obtained from a dedicated research protocol. We found no statistically significant correlation between ADC and v_e for the 1.5- or 3.0-T patient sets on either a voxel-by-voxel or a region-of-interest (ROI) basis. These data, combined with similar results from other disease sites in the literature, may indicate that the conventional interpretation of either ADC, v_e or their relationship is not sufficient to explain experimental findings.

Keywords: Apparent diffusion coefficient; Extravascular extracellular volume fraction; Human breast cancer

1. Introduction

The microscopic thermally induced behavior of molecules moving in a random pattern is referred to as self-diffusion or Brownian motion. The rate of diffusion in cellular tissues is described by means of an apparent diffusion coefficient (ADC), which largely depends on the number and separation of barriers that a diffusing water molecule encounters in a specified time interval [1]. Diffusion-weighted magnetic resonance imaging (DW-MRI) methods sensitive to water diffusion have been developed to map the ADC, and in well-controlled situations the variations in ADC have been shown to correlate inversely with tissue cellularity [2]. More specifically, as the number and density of barriers increase, the ADC will decrease because water molecules are not able to diffuse as far per unit time as they would in a free solution. This interpretation has been of particular (recent) interest to the cancer imaging community where changes in the ADC have been interpreted to report on the ability of various anti-cancer therapies to kill tumor cells. There are mounting preclinical and clinical data indicating that exposure of tumors to both

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chemotherapy and radiotherapy consistently leads to measurable increases in conventional measurements of ADC in cases of favorable treatment response [3–6]. Studies in humans have shown that ADCs in both normal tissues and benign lesions have significantly higher ADCs compared to those of malignant breast lesions [7,8]. Furthermore, recent results indicate that the ADC is a promising quantitative biomarker for assessing the response of breast tumors to neoadjuvant chemotherapy [9,10].

In parallel with developments of DW-MRI, there have been advances in tissue characterization based on the quantification of the kinetics of injectable MRI contrast agents. The most common MRI contrast agents are gadolinium-based chelates which are pharmaceuticals administered intravenously to patients and are designed to change the contrast between different tissues by decreasing a tissue's native T_1 and/or T_2 relaxation times. Except in the healthy brain, these agents pass from the circulation into the extravascular extracellular interstitial volume of normal tissues. Studies designed to exploit the change in T_1 are referred to as dynamic contrast enhanced MRI (DCE-MRI; reviewed in Ref. [11]). In a typical DCE-MRI procedure, MR images are collected before, during and after a contrast agent (CA) is injected into an appropriate peripheral vein of a patient. Each image corresponds to one time point, and each pixel in each image set gives rise to its own signal time course which can be analyzed with a mathematical model. The parameters that are typically returned from such analysis are the volume transfer constant (K^{trans}), the extravascular extracellular volume fraction (v_e) into which the agent distributes, and the blood plasma volume fraction (v_p).

In this contribution, we compare and correlate the DW-MRI measure of cellularity (ADC) with the DCE-MRI derived measure of extravascular volume fraction (v_e) for multiple voxels in a series of patients. Conventional models of ADC and DCE parameters would suggest that these two parameters should be directly related; that is, as the volume of extracellular space increases (as v_e increases) water diffusion should be less restricted and therefore the ADC should also increase. However, in the one article studying this relationship in the literature (to the best of our knowledge) there was no relationship found between these two parameters [12]. Moreover, our own previous study of treatment effects in breast tumors found the converse relationship [13]. Using two different DCE protocols, we were able to explore the relationship between ADC and v_e using a number of pharmacokinetic models to return estimates of v_e. Our overall goal is to establish whether ADC and v_e are related in the case of invasive ductal carcinomas in human breast cancer patients.

2. Methods

Patient data were acquired at 1.5 T as part of a clinical standard-of-care exam and at 3.0 T as part of a research study, so we have divided the following sections along those lines.

2.1. Data acquisition at 1.5 T

Data were acquired from 13 patients as part of the clinical, standard-of-care, breast MRI for diagnostic and staging purposes. DW-MRI and DCE-MRI were performed using a Philips 1.5-T Achieva MR scanner (Philips Healthcare, Best, The Netherlands) prior to neoadjuvant chemotherapy and following completion of the first cycle of chemotherapy. A four-channel receive double-breast coil covering both breasts was used for all imaging (In-vivo, Inc., Gainesville, FL, USA).

DW-MRIs were acquired with a single-shot spin-echo (SE) echo planar imaging (EPI) sequence in three orthogonal diffusion encoding directions (x, y and z), with two b values (0 and 500 s/mm^2), FOV=320×320 (bilateral) and an acquisition matrix of 100×97 reconstructed to 160×160. SENSE parallel imaging (acceleration factor=2) and spectral presaturation with inversion recovery fat saturation were implemented to reduce image artifacts. Subjects were breathing freely, with no gating applied. The patient DWIs consisted of 20 transverse slices with slice thickness=5 mm (no slice gap) and TR/TE=4280/43 ms, Δ=20.6 ms and δ=10.9 ms, respectively, number of signal averages (NSA)=6, for a total scan time of 5 min and 43 s.

Data for a T_1 map were acquired with a 3D RF-spoiled gradient echo multi-flip angle approach with TR=7.9 ms, TE=1.3 ms and 10 flip angles from 2° to 20° in 2° increments. The acquisition matrix was 240×240×30 over the same FOV as above. There were one signal acquisition and a SENSE factor of 2 for an acquisition time of 5 min and 37 s. The dynamic scans used a TR/TE=5.3/2.6 ms with a flip angle of 10° and an acquisition matrix of 448×448×150 over the same FOV as above. Each 150-slice set was collected in 90 s at eight time points for approximately 12 min of scanning. A catheter placed within an antecubital vein delivered 0.1 mmol/kg of the contrast agent gadopentetate dimeglumine (Magnevist, Wayne, NJ, USA) over 20 s (followed by a saline flush) after the acquisition of one baseline dynamic scan.

2.2. Data acquisition at 3.0 T

Data were acquired from nine patients with locally advanced breast cancer who were enrolled in an ongoing clinical trial. The patients provided informed consent and the study was approved by the ethics committee of our cancer center. DW-MRI and DCE-MRI were performed using a Philips 3-T Achieva MR scanner (Philips Healthcare) prior to neoadjuvant chemotherapy, and four patients were also scanned following completion of the first cycle of chemotherapy; thus, we had 13 total data sets. A four-channel receive double-breast coil covering both breasts was used for all imaging (In-vivo Inc.).