Use of An Individually Measured Hematocrit in DCE-MRI studies

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Introduction

Dynamic contrast-enhanced MRI (DCE-MRI) is commonly applied in early-phase drug development to quantify tumor microvascular characteristics through the application of a tracer kinetic model to estimate parameters such as K^{trans} (contrast agent transfer coefficient, a composite of blood flow and capillary permeability) and v_p (blood plasma volume). An important influence on DCE-MRI parameters that is commonly overlooked is the hematocrit (Hct), which relates the measured whole blood contrast agent concentration to the blood plasma contrast agent concentration, thereby influencing the arterial input function (C_p), K^{trans} and v_p. In most DCE-MRI a fixed global value for Hct is assumed (Hct_a). However, in cancer patients where the Hct level may be reduced [1], for example as a result of pathophysiological processes or drug induced effects, using an assumed value for Hct will lead to error in estimates of K^{trans} and v_p. In this study we investigate the magnitude of errors caused by assuming Hct when the true measured Hct (Hct_m) is known.

Methods

Imaging: 13 patients with advanced prostate cancer and bone metastases were imaged at 1.5 T using a Philips Achieva (Philips Healthcare, Best, The Netherlands) MR scanner on up to 5 separate occasions (2 baseline visits and 3 post-treatment) as part of a clinical trial. The DCE-MRI protocol used an axial 3-D spoiled gradient echo (FFE/SPGR) sequence with baseline T_1 measured using the variable flip angle method [2] with the following parameters: 2°, 10° and 20° flip angles, TR/TE = 3.0/0.82 ms, FOV = 375 x 375 mm^2, matrix = 160 x 160, slices = 25, thickness = 4 mm. The dynamic image acquisition used the same parameters with a flip angle of 20°, 130 dynamic timepoints and a temporal resolution of 4.6 s. On the sixth dynamic timepoint, 0.1 mmol/kg of body weight of 0.5 mmol/ml Dotarem (Guerbet, France) was administered through a Spectris power injector (Medrad Inc.) at a rate of 3 ml/s followed by an equal volume of saline flush also at 3 ml/s.

Initial DCE-MRI analysis: Regions of interest (ROI) were defined for the whole tumor volume within the bone. Enhancing voxels were identified and the extended Kety model [3] was fitted to each voxel's time series using an automated arterial input function measurement [4]. Hct_a was set as 0.42 in the initial analyses. 3D maps of K^{trans}, v_e and v_p were generated and summarized using median (K^{trans}, v_e) and mean (v_p) summary statistics for each tumor.

Hct measurement: Whole blood was collected in standard EDTA tubes immediately prior to each DCE-MRI scan. Samples were processed using an automated analyzer (Advia 2120, Siemens, Germany) and the Hct was calculated as [red cell count (/L) *x* mean cell volume (fL)].

Correction using Hct_m: K^{trans} and v_p parameters derived using Hct_a in the initial analyses were corrected by scaling by $(1\text{-}Hct_m)/(1\text{-}Hct_a)$.

Results

Hct_m values for all patients and timepoints throughout the study were sytematically lower than the Hct_a of 0.42. The Hct_m show inter-visit variation in each patient and also between patients (Fig. 1), with Hct_m values ranging from 0.213 to 0.401. The errors in K^{trans} and v_p parameters as a result of using the Hct_a value in the analysis range from -3% to -27% (Fig. 1).

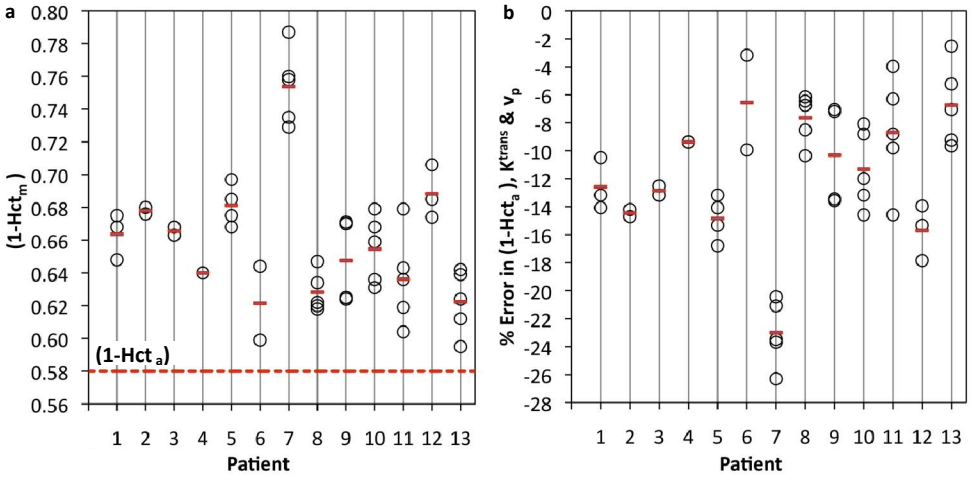

Figure 1: (a) Plot showing $(1\text{-}Hct_m)$ for each individual patient/visit (open circles) and the mean $(1\text{-}Hct_m)$ across all visits for each patient (small red horizontal bars). Dashed red line represents $(1\text{-}Hct_a)$, which was used in the initial DCE-MRI analysis. **(b)** Plot showing the % error in $(1\text{-}Hct_a)$, K^{trans} and v_p for each patient/visit (open circles) and the average % error across all visits (small red horizontal bars). The % error represents the error by using Hct_a of 0.42, rather than the measured patient/visit specific Hct_m, in the DCE-MRI analysis.

Discsussion

This study has demonstrated the magnitude of potential errors in tracer kinetic parameters when using an assumed value for Hct, rather than an individually measured Hct. These findings have implications for clinical trials where a treatment effect may be masked due to the fluctuations in patients' Hct throughout a course of therapy not being accounted for. Large fluctuations in Hct_m were observed not only within each patient in this intervention study but also between the patients – the mean $(1\text{-}Hct_m)$ shows this in Fig.1a. This is of importance if DCE-MRI parameters are used to understand inter-patient differences (for example when predicting response to therapy). In recent years, much work has been done to minimise AIF-related errors in DCE-MRI studies, such as correcting for blood inflow, B_1 inhomogeneity [5] and optimising temporal resolution. Our results demonstrate that the errors that can be caused by neglecting Hct measurements in patient studies are of a similar magnitude to or greater than other sources of error, indicating that Hct measurement should be included as standard for all patient visits.

References **1.** Caro et al. Cancer 2001;91(12):2214-2221 **2.** Fram E.K. et al. Magn Reson Imaging 1987;5(3):201-208. **3.** Tofts, P. J. Magn Reson Imaging 1997;7(1):91-101. **4.** Parker G.J. et al. Magn Reson Med 2006;56(5):993-1000. **5.** Roberts C. et al Magn Reson Med 2010;Oct Early View.