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Optimization of DCE-MRI protocol for the assessment of patients with brain tumors

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ABSTRACT

The interstitium-to-plasma rate constant (k_{ep}), extracted from dynamic contrast enhancement (DCE-MRI) MRI data, seems to have an important role in the assessment of patients with brain tumors. This parameter is affected by the slow behavior of the system, and thus is expected to be highly dependent on acquisition duration. The aim of this study was to optimize the scan duration and protocol of DCE-MRI for accurate estimation of the k_{ep} parameter in patients with high grade brain tumors. The effects of DCE-MRI scan duration and protocol design (continuous vs integrated scanning) on the estimated pharmacokinetic (PK) parameters and on model selection, were studied using both simulated and patient data. Scan duration varied, up to 60 min for simulated data, and up to 25 min in 25 MRI scans obtained from patients with high grade brain tumors, with continuous and integrated scanning protocols.
Converging results were obtained from simulated and real data. Significant effect of scan duration was detected on k_{ep}. Scan duration of 9 min, with integrated protocol in which the data are acquired continuously for 5 min, and additional volumes at 7 and 9 min, was sufficient for accurate estimation of even low k_{ep} values, with an average error of 3%. Over-estimation of the PK parameters was detected for scan duration <12 min, being more pronounced at low k_{ep} values (<0.1 min^{-1}). For the model selection maps, significantly lower percentage of the full extended-Tofts-model (ETM) was selected in patients at scan duration of 5 min compared to >12 min. An integrated protocol of 9 min is suggested as optimal for clinical use in patients with high grade brain tumors. Lower acquisition time may result in over-estimation of k_{ep} when using ETM, and therefore care should be taken using model selection.

1. Introduction

Dynamic contrast enhanced T_1 weighted magnetic resonance imaging (DCE-MRI) is increasingly being used for the characterization of tumor microvasculature and therapy response assessment in patients with high grade brain tumors [1,2]. DCE-MRI is acquired using dynamic T_1 weighted images, during bolus injection of a contrast agent. When applying a pharmacokinetic (PK) model, such as the commonly used extended-Tofts-model (ETM), several pharmacokinetic parameters can be extracted, including the volume transfer constant (k^{trans}), extravascular extracellular space (v_e), interstitium to plasma rate constant (k_{ep}; $k_{ep}=k^{trans}/v_e$) and plasma volume (v_p) [3,4]. In recent years there has been an effort to establish the use of DCE-MRI as a quantitative endpoint biomarker for patient assessment, and in particular for the assessment of antiangiogenic therapies, targeting the tumor blood supply [5].

k_{ep} represents the wash-out phase, i.e., the re-entrance of the contrast agent into the blood vessel. This parameter was shown to have a clinically important role in patient assessment and prognosis. Several studies in patients with high grade brain tumors [6,7], rectal [8] and breast [9] cancer have reported significant high correlations between k_{ep} and several markers of tumor angiogenesis and aggressiveness (such as microvessel density), demonstrating the role of k_{ep} in differentiating between radiation necrosis and recurrent tumor. These studies suggest k_{ep} as a potential imaging biomarker for patient evaluation and prognosis [6,7].

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The estimation of DCE PK parameters is highly dependent on acquisition parameters and particularly temporal resolution and scan duration [10–12]. A systematic review performed on the existing literature on DCE-MRI up to February 2014 concluded that scan duration varied widely in pathologies of intracranial neoplasms, with median scan duration of 5.5 min and median temporal resolution of 5.3 s [13]. Higher temporal resolution (<2 s) is recommended in order to extract the perfusion parameters (including cerebral blood flow) and to increase the estimation accuracy of the parameters [11,14–16], however this requirement is less applicable in current clinical practice due to the demand for sufficient brain coverage and high signal to noise ratio.

Regarding scan duration, the total scan time should be long enough to capture PK parameters with slow rate such as k_{ep} [11,12,17]. This implies a long scan duration in the order of $1/k_{ep}$ that may reach dozens of minutes, which is not practical in clinical settings. Several works have previously studied the effect of scan duration on the accuracy and precision of the estimated DCE-MRI PK parameters. Aerts et al. [12] studied the effect of scan duration on the precision of PK parameters in a simulation study, concluding that for accurate estimation of k^{trans} and v_e scan duration should be above 2 min, whereas durations of more than 7 min do not further improve parameter estimation. Cramer and Larsson [11], studied simulated data, healthy volunteers and patients with multiple sclerosis, and reported that long acquisition duration (15 min) improved accuracy of tissue permeability assessment (compared to 5 min) with over-estimation detected at 5 min using the extended Tofts method. Larsson et al. [16], investigating the effect of scan duration (up to 15 min) on the estimations of k^{trans}, k_{ep}, v_e and v_p in patients with high grade brain tumors, found that scan duration should be at least 5 min for this patient group and that scan duration <5 min results in over-estimation of k^{trans} and k_{ep} and under-estimation of v_p and v_e.

The choice of the pharmacokinetic model was also shown to affect the accuracy of the PK parameter estimation. Nested models, in which a model is selected based on voxels, which better represent the system behavior in order to avoid over fitting, have been previously shown to improve the accuracy of DCE-MRI PK parameter estimation in animal models and in patients with glioblastoma [18,19]. However, the effect of scan duration on the model selected has not been fully investigated.

In this work we further optimized the DCE-MRI protocol in relation to scan duration and acquisition design taking into account clinical constraints, focusing mainly on k_{ep} estimation, using both simulated data and real data obtained from patients with high grade brain tumors.

2. Materials and methods

2.1. Simulated data

Simulated data were generated based on the ETM with three free parameters: k^{trans}, k_{ep} and v_p; population-averaged arterial input function (AIF) was simulated using Ref. [20] and convolved with 1000 impulse response functions (IRFs). The IRFs were built using ETM and the convolution results were set to be the concentration time curves (CTCs). The simulated AIF and CTCs were generated with high temporal resolution, 1 ms intervals, to accurately simulate the continuous process, and then down-sampled to a temporal resolution of 6 s, to reflect the temporal resolution usually performed in clinical settings. A Gaussian noise with a realistic contrast to noise ratio (CNR) of 15, was added to both AIF and CTC. A broad range of clinically relevant PK values from patients with brain tumors, previously used in other simulation studies [12,21], was used, with varying values of: $k^{trans} = 0.05–0.5\ min^{-1}$, $v_p = 0.01–0.3$ and $k_{ep} = 0.01–0.30\ min^{-1}$; PK parameters were extracted from different scan durations, 5, 12, 20, 30 and 60 min. The effect of the scan duration on different values of k_{ep} (0.03, 0.08, 0.12, 0.18, 0.23, 0.27 min^{-1}) was studied.

2.2. Real data

2.2.1. Subjects

Twenty-five MRI scans obtained from nineteen patients with high grade brain tumors (17 patients with glioblastoma and two patients with anaplastic astrocytoma grade 3) were included in this study (thirteen males, age range 19–71 years old). Inclusion criteria were as follows: (1) patients with biopsy-proven high grade glioma, (2) patients with enhanced region on conventional contrast enhancement T_1 weighted images, and (3) normal glomerular filtration rate, and no contraindication to MRI scan. The study was approved by the hospital review board, and written informed consent was obtained from all subjects.

2.2.2. MRI protocol

Scans were performed on a 3.0 Tesla MRI scanner. 13 scans were performed on a GE system (Signa EXCITE, Milwaukee, WI) using an eight channel head coil, and 12 scans were performed on a Siemens system (MAGNETOM Prisma, Germany) using a twenty channel head coil. The protocol included conventional imaging: high-resolution T_1 weighted imaging performed before and after contrast agent injection (Gadolinium Dotarem); and fluid attenuated inversion recovery (FLAIR) images. The DCE data were acquired using multi-phase 3D T_1 weighted SPGR/FLASH imaging before and during contrast agent injection, field of view FOV = 250 mm; matrix 256 × 256/256 × 184, slice thickness of 5 mm, repetition time (TR)/echo time (TE) ≈ 5/2.2 millisecond, and flip angle (FA) = 20°. For the T_1 maps, variable flip angle (VFA) SPGR/FLASH data was acquired with nominal FAs = 3/5/10/15/20/30°. All data were acquired with temporal resolution of 6 s. 20 data sets were acquired with a continues protocol of 6 min (with 50 s of baseline before contrast agent injection), and additional volumes acquired at 13 and 24 min following injection, maintaining the same parameters and calibrations throughout the entire scan, with anatomical scans acquired in between. Five data sets were acquired with continuous protocol of at least 9 min (following the simulation results). A power injector (MEDRAD, Solaris) was used to infuse single dose—0.2 cm^3/kg of contrast agent, followed by a flush of 20 cm^3 saline, both at a constant rate of 5 cm^3/s. 14–20 slices were centered on the tumor area as identified in the conventional images, providing brain coverage of 70–100 mm;

2.2.3. Estimation of the DCE-MRI PK parameters

k^{trans}, v_e, k_{ep} and v_p were calculated using DUSTER, an in-house code written in MATLAB for DCE Up Sampled Temporal Resolution based on the ETM [3,4], incorporating correction for bolus arrival time (BAT) [22,23]. The analysis pipeline included baseline T_1 maps calculated from the variable flip angle SPGR (VFA-SPGR) using $DESPOT_1$ [24] analyzed with correction for FA deviations [22]; motion correction on the 4D data using SPM8b′ rigid-body co-registration; brain extraction using FMRIB Software Library (FSL) [25]; identification and compensation for noisy time-points; raw-signal-to-T_1-to-concentration time curves (CTC) conversion; B_1 inhomogeneity correction; semi-automatic artery localization; AIF extraction at temporal super-resolution. Fitting of the contrast agent CTCs to the PK model was done using Murase's method [26].

Model selection was performed in a manner similar to [18], by analyzing each voxel's CTC with four nested models, with the BAT parameter added to three of the four following models, enabling extraction of v_p, k^{trans}, v_e and k_{ep}; where model #1 = empty model; model #2 = no leakage (BAT and v_p only); model #3 = leakage

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