Temporal requirements in dynamic contrast-enhanced MRI of glioblastoma multiforme

Magne Mørk Kleppestø[1], Christopher Larsson[1], Raimo Aleksi Salo[1], Jonas Vardal[1], Kine Mari Bakke[2], Knut Lote[3], Petter Brandal[3], I. Andre Rasmussen[1], and Atle Bjørnerud[1,2]

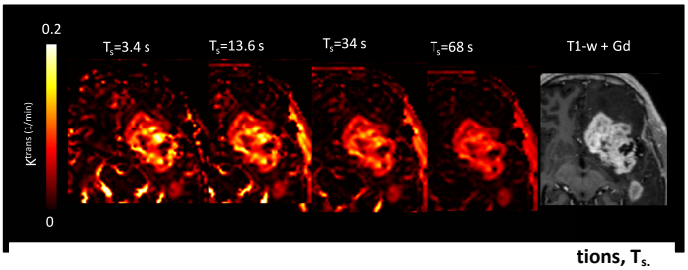
[1]The Intervention Centre, Oslo University Hospital, Rikshospitalet, Oslo, Norway, [2]Department of Physics, University of Oslo, Oslo, Norway, [3]Departement of Neuro-oncology, Oslo University Hospital, Rikshospitalet, Oslo, Norway

Introduction

Dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI) is used to assess brain hemodynamics and blood-brain barrier integrity in brain tumors. Dynamic changes in signal intensity (SI) following an intravenous bolus of a paramagnetic contrast agent (CA) are measured, and established tracer kinetic models used to estimate the volume CA transfer constant across the capillaries, CA distribution volume fractions in the extravascular extracellular space and plasma. Clinical interpretation and utility of DCE is limited by a lack of standardization of acquisition protocols and analysis approach. Theoretic studies have addressed factors affecting the accuracy and reproducibility of DCE derived metrics but results are typically not linked to clinical relevance in a defined patient population. The main objective of the current study was to systematically investigate the effect of varying temporal resolution and total sampling duration on the ability to estimate standard kinetic parameters through simulations and in clinical DCE data from a patient population suffering from glioblastoma multiforme.

Materials and Methods

Patients: A total of 101 DCE-MRI measurements from 15 patients with histologically confirmed glioblastoma multiforme were included in the study. Individual patients were imaged between 4 and 9 times before-, during-, and up to 15 months after radio-chemotherapy.
MRI*:* DCE data was acquired using a 3D saturation recovery (SR) based gradient echo (GRE) sequence [1] at 3T (Philips Achieva) with high temporal resolution (2.2 s – 3.4 s).
DCE analysis in patient data: The DCE time series were analyzed using the extended Tofts model [2] and the arterial input function (AIF) was estimated using an automated AIF detection algorithm [3].
Temporal resolution analysis: The effect of reduced time resolution was simulated by successive averaging of images, thereby providing directly comparable DCE time series with a range of different temporal resolutions. The image series was temporally down-sampled between two and 20 times resulting in an effective temporal resolution (T_s) of 3.4 s to 68 s (patients 1-7) and 2.2 s to 44 s (patients 8-15). Down-sampling by a factor of n was performed by averaging the dynamic images from n consecutive time-points, and AIFs were subject to the same down-sampling scheme.
Total measurement time analysis*:* The effect of variations in total measurement time (T_{acq}) was investigated by truncating the tail of the time-series for both the pixel-wise tissue response and the AIF, giving dynamic time series with T_{acq} = 1, 2, 3, 4 and 5.2 minutes.
Region-of-interest(ROI) analysis*:* FLAIR and post contrast T1-weighted images were pre-processed to remove B1-effects before automatically defining tumor masks from the high intensity clusters common to both the images, followed by manual editing by an experienced neuroscientist. Masks were co-registered to the DCE images, and ROI values extracted from the parametric images representing K^{trans}, v_e, v_p and k_{ep}, for the original and for the down-sampled and truncated series. ROI statistics was performed in terms of whole tumor median values and as pixel-wise correlation as function of down-sampling-, and truncation factor. Finally, the number of tumor pixels under-sampled (i.e. pixels with $k_{ep} \geq 1/2T_s$) was estimated across all examinations as a function of T_s.
Simulations*:* A reference AIF was generated by applying a dispersion model and reference tissue response curves were generated using a range of kinetic parameters randomly chosen from intervals representing clinically observed values. Gaussian noise was added, Both the synthetic tissue response curves and the AIF were then down-sampled or truncated as described above for the clinical data. For each temporal resolution or truncation level, the kinetic parameters were estimated using the same methodology as for the clinical data analysis.
Statistical analysis*:*Mean, standard deviation (SD) and upper 10 percentile values were calculated for all kinetic parameters from all ROIs. One-way ANOVA was used to investigate dependence of K^{trans}, k_{ep}, v_e and v_p on T_s and T_{acq}. Differences between reference kinetic values (obtained at T_s^{min} and T_{acq}^{max}) and the values obtained at each T_s and T_{acq} was tested using Wilcoxon signed rank test. Difference in parameter values from two different DCE sequences was tested with Mann-Whitney test. The response to variations in T_s and T_{acq} was analyzed separately and combined for the two different DCE sequence parameter groups to detect possible sequence dependent response differences. Probability values of $p < .01$ were considered significant for all tests.



tions, T_s.
15 s

Summarized results

Temporal resolution requirements: Figure 1 shows the effect of reducing temporal resolution from 3.4 s to 68 s in a sample patient. Insufficient temporal resolution resulted in under-estimation of k_{ep} and K^{trans} and over-estimation of v_p and also a general increase in uncertainty of the parameter estimates. Sampling time had little effect on the estimated parameters for $T_s \leq 10$ s. Using T_s =10 s, the highest value of k_{ep} that can be reliably measured is $k_{ep}^{max}=1/2T_s= 3$ min^{-1}. Using T_s= 30 s only resulted in under-sampling (in terms of pixels with $k_{ep}>1/2T_s$) of approximately 7% of tumor pixels across all 101 DCE-MRI acquisitions.
Total acquisition time requirements: Short total sampling time resulted in an over-estimation of K^{trans} and k_{ep}, and increased uncertainly in their estimates. From simulations, T_{acq} was not found to have significant effect on v_p but a significant reduction in v_p with T_{acq} below 5 minutes was observed in the clinical data.

Conclusions

Based on systematic simulations and clinical data it is recommend to use a temporal resolution of the order of 10 seconds for glioblastoma patients in order minimize uncertainties due to sampling errors and to ensure that tumor "hot-spots" are not missed. Total DCE sampling time should be at least 5 minutes.

[1]. Larsson H et al. JMRI 2008; [2]. Tofts, PS et al. J.Magn Reson.Imaging; 1999;[3]. Bjørnerud A and Emblem KE. JCBFM 2010