COMPARISON OF LOGAN PLOT ANALYSIS AND NESTED MODEL SELECTION TECHNIQUE FOR MR ESTIMATION OF DISTRIBUTION VOLUME IN HUMAN BRAIN TUMOR AT 3TESLA

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Target Audience: Neuroradiologists, neurologists, and medical physicists who are interested in compartmental modeling and brain tumor permeability.

Introduction: Reasoning that assessment of the pathological physiology of solid tumors can aid in treatment planning and assessing drug therapy [1], researchers and clinicians are increasingly employing Dynamic Contrast Enhanced (DCE) magnetic resonance imaging (MRI) to study high-risk breast cancers and different types of brain tumors [1, 2]. Graphical Analysis techniques such as Gjedde-Patlak and Logan plots [2, 3] are widely used for estimating physiological parameters in Positron Emission Tomography (PET) studies. In DCE-PET studies, Logan Plot has become a standard calculation method for receptor-ligand studies. Logan Plots are used to estimate the distribution volume (V_D: plasma volume + interstitial volume) and binding potential of ligand tracers that have reversible binding kinetics. If a receptor-free region exists, a distribution volume ratio can be calculated [3, 4]. Our group has recently investigated the correlation of distribution volume (V_D) estimated by the Logan plot with tumor cellularity in rat brain model [5]. However, to the best of our knowledge, application of Logan Plot in DCE-MRI for estimation of V_D in the human brain has not been reported. The V_D parameter is a key factor for the assessment of pathological physiology of solid tumors. In this study, the Logan Plot analysis and Nested Model Selection (NMS) technique [6] as an alternative and standard method of DCE-MRI data analysis were used to estimate V_D for 15 patients with Glioblastoma Multiforme (GBM) tumors (grade 4 and higher) and results were compared.

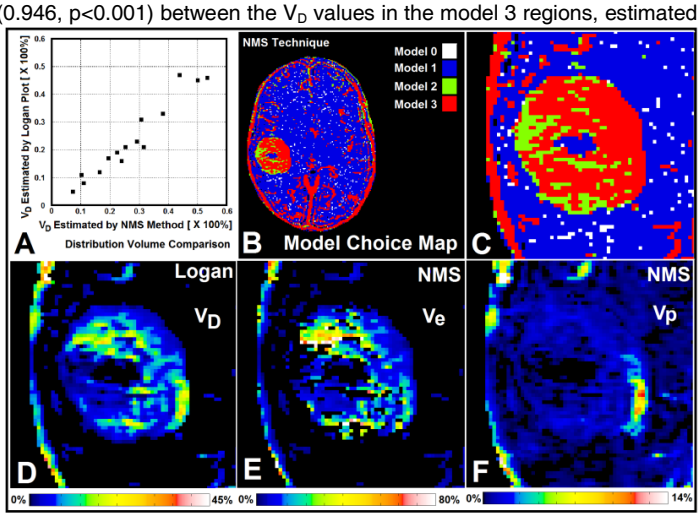
Theory: Graphical analysis technique is a simplified method that converts the pharmacokinetic [1,2] model equations into a linear equation evaluated at different time points and provides fewer parameters (*i.e.,* slope and intercept). For any reversible receptor system, in the Logan plot analysis, the integrated measured time trace of the Contrast Agent (CA) concentration of tissue, $C_T(t)$ and the integrated plasma $C_p(t)$, are plotted according to Equation (1). The observation equation can be written as Equation (2) where $\Delta R_{1P}(t)$ and $\Delta R_{1T}(t)$ refer to the subtraction of the pre-contrast relaxation rate ($R_1=1/T_1$) from its post-contrast value in the feeding artery and underlying tissue respectively at different times, and H_{CT} is the hematocrit ratio. After sufficient equilibration time, this plot will approach a straight line. The slope and the intercept of the line are interpreted according to the underlying compartment model; the slope of the fitted straight line gives the V_D.

$$\frac{\int_0^t C_T(\tau)d\tau}{C_T(t)} = V_D \frac{\int_0^t C_P(\tau)d\tau}{C_T(t)} + Int \quad (1)$$

$$(1 - Hct)\frac{\int_0^t \Delta R_{1T}(\tau)d\tau}{\Delta R_{1T}(t)} = V_D \frac{\int_0^t \Delta R_{1P}(\tau)d\tau}{\Delta R_{1T}(t)} + Int \quad (2)$$

Material and Methods: The Logan plot and the NMS techniques both were applied to 107 slices (all containing lesions) of the 3D-Spoiled Gradient Echo MR experiments of 15 patients with GBMs. The MR experiments were performed on a 3 Tesla clinical system (Signa Excite, GE) with the following MR specifications: fast 3D-SPGRE pulse sequence, matrix size: 256×256, 70 time points, 5.7 sec time interval, FOV: 240×240 mm^2 with 5 mm slice thickness, 16 slices, T_R/T_E: 5.88/0.98 ms, and multiple flip angle set of 2, 5, 10, 15, 20, and 25 for T_1 mapping. Bolus injection of CA (Magnevist, 0.1 mmol/kg) was performed by a power injector at time 30 sec. Arterial input functions were manually selected and normalized so that the white matter areas in the normal hemisphere yielded a plasma volume of ~1%. In Logan analysis, to exclude the nonlinear portion of the profile, equilibrium cut off time for each voxel was determined using BDS (after the initials of W. A. Brock, W. Dechert and J. Scheinkman) statistics [7]. The NSM technique was used to select an appropriate pharmacokinetic model [6, 8] for estimating the following physiological parameters: vascular volume (v_p), or v_p and forward vascular transfer constant for the CA Gd-DTPA (K^{trans}), or v_p, K^{trans}, and the reverse vascular transfer constant (k_{ep}). These constitute Models 1, 2, and 3, respectively. Model 0 presents areas with no evidence of CA filling.

Results and Conclusion: As shown in Figure A, there is a strong correlation (0.946, p<0.001) between the V_D values in the model 3 regions, estimated by the NMS technique and Logan Plot analysis for all 15 patients. Figure B and C illustrate the regular and magnified versions of the model choice map generated by the NMS technique for an exemplary slice. Figure D presents the V_D map estimated by the Logan Plot and BDS statistics for the same slice. Figures E and F illustrate interstitial space (v_e) and plasma volume (v_p) maps of the same slice estimated by the NMS technique. V_D estimated in the NMS technique is defined as v_e+v_p for Model 3. This study confirms that the V_D values estimated by the two techniques are quite in agreement within a subject (see Figures D and E), while there is considerable variation between subjects in both methods (V_D varies from 5% to 46% in Logan plot and 7% to 53% in NMS). The mean and standard deviation of the V_D estimated by the two methods are comparable (Logan Plot: V_D=0.23% ±0.13% and NMS: V_D=0.27% ±0.14%). Despite V_D being based on a compartmental model, one advantage of the Logan method is that it doesn't require prior knowledge of the tracer's kinetics. Parametric images derived by the Logan plot give rise to direct quantitative intra and inter-subject comparisons. Logan plot allows estimation of distribution volume from a linear plot using linear regression analysis. This method is computationally efficient and its estimates not only are not limited to Model 3 areas and also are usually highly reliable compared to other methods. Thus, this pilot study suggests that the Logan plot analysis can be used as a practical approach in DCE-MRI data analysis for estimating the distribution volume (V_D), which is a key component in grading and accessing tumors and their therapeutic responses.



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