

MEASUREMENT OF RAT BRAIN TUMOR KINETICS USING AN INTRAVASCULAR MR CONTRAST AGENT AND DCE-T1 NESTED MODEL SELECTION

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Target audience: Neuroradiologists, neurologists, and medical physicists interested in Perfusion Studies.

Purpose: The purpose of this study was to investigate parameters of vascular physiology such as plasma volume (v_p), forward vascular transfer constant (K^{trans}), and (extracellular-extravascular space volume) v_e in a rat glioma model using two different contrast agents, an intravascular or blood pool agent (gadofosveset) and an extravascular agent (gadolinium-diethylenetriaminepentaacetic acid, Gd-DTPA). These parameters were estimated using dynamic contrast-enhanced (DCE) T1 nested model selection (NMS)¹.

Methods: DCE T1 MRI studies were done in 9 Fisher 344 rats inoculated intracerebrally with 9L gliosarcoma cells. Animals were scanned using both gadofosveset and Gd-DTPA in the same animal 24 hours apart. T1-weighted multislice sequence (TR/TE=500/12 ms, 256 x 256 matrix, 13-15 slices, 1 mm thick, 40 x 30 mm field of view (FOV), 1 mm slice thickness, NEX=4). T2-weighted images were obtained using standard two-dimensional Fourier transformation (2DFT) multislice (13-15) multiecho (4 echoes) MRI. A series of 4 sets of images (13-15 slices for each set) were obtained using TEs of 15, 30, 45 and 60 msec and a TR of 1500 msec. The images were produced using 40 x 30 mm FOV, 1 mm slice thickness, 256 x 256 matrix, and NEX = 2-4. For DCE MRI, multi flip angle (2 to 35) fast SPGR 3D images were obtained to create T1 maps. Then dynamic images were obtained for 15 minutes using a fixed 30-degree flip angle. v_p , K^{trans} , and v_e were estimated using nested model selection from the DCE data¹, using a standardized arterial input function (AIF). Descriptive statistics were computed for the two contrast agents, as well as for the whole lesion and central core. Nonparametric Wilcoxon signed rank tests were done, and intra-class correlation coefficients (ICC) were computed to assess the agreement or reliability between the two contrast agents.

Results: For the whole lesion, K^{trans} measures were significantly lower ($p=0.0039$) using gadofosveset compared to Gd-DTPA, and there was almost perfect agreement between the two contrast agents. Both v_e and v_p measurements were not statistically different, and there was almost perfect agreement for v_e and substantial agreement for v_p . For the central core, K^{trans} was significantly lower ($p=0.0039$) using gadofosveset compared to Gd-DTPA, with substantial agreement. No difference was observed between the contrast agents for v_e and v_p . Substantial agreement was observed for v_p , but not for v_e which showed poor agreement.

Discussion: Currently used low molecular weight extravascular contrast agents leak rapidly through the leaky tumor vasculature, whereas albumin-bound intravascular contrast agents may provide a better assessment of the leakiness of vasculature due to their larger size and hence, more controlled leakage across the deficient BBB. DCE-MRI non-invasively measures tumor vascular kinetics; however, a robust post-processing pharmacokinetic model is needed to obtain stable and accurate estimates of various vascular parameters (v_p , K^{trans} and v_e), whether using extravascular or intravascular contrast agents^{2,3}. In this study, we have demonstrated that using DCE-MRI and NMS, K^{trans} measures were significantly higher with Gd-DTPA due to its smaller size and rapid extravasation from the intravascular compartment compared to gadofosveset. This is consistent with previous literature showing that K^{trans} values decreased with increasing molecular weight of the contrast agent⁴. K^{trans} measures were also highly correlated using both contrast agents suggesting stability of the NMS DCE technique.

Conclusion: In conclusion, both volume of extravascular extracellular space and blood plasma volume can be measured accurately whether we use an extravascular or intravascular contrast agent in an animal glioma model. K^{trans} measurements were significantly lower using a blood pool contrast agent due to the much larger size of the albumin-bound contrast agent, and these were measured with very good accuracy using NMS in DCE-MRI. The goal of this research is to demonstrate the stability of NMS in DCE-MRI for measurement of these important vascular physiology markers which can provide important information about the tumor microenvironment, and hence, could potentially expand their role into prognostic or predictive imaging biomarkers, an area of very active clinical interest.

References: 1. Bagher-Ebadian H, Jain R, Nejad-Davarani SP, et al. Model selection for DCE-T1 studies in glioblastoma. Magn Reson Med. 2012 Jul;68(1):241-51. 2. Wu X, Feng Y, Jeong EK, et al. Tumor characterization with dynamic contrast enhanced magnetic resonance imaging and biodegradable macromolecular contrast agents in mice. Pharm Res. 2009 Sep;26(9):2202-8. 3. Roberts C, Issa B, Stone A, et al. Comparative study into the robustness of compartmental modeling and model-free analysis in DCE-MRI studies. J Magn Reson Imaging. 2006 Apr;23(4):554-63. 4. Ewing JR, Brown SL, Nagaraja TN, et al. MRI measurement of change in vascular parameters in the 9L rat cerebral tumor after dexamethasone administration. J Magn Reson Imaging. 2008 Jun;27(6):1430-8.

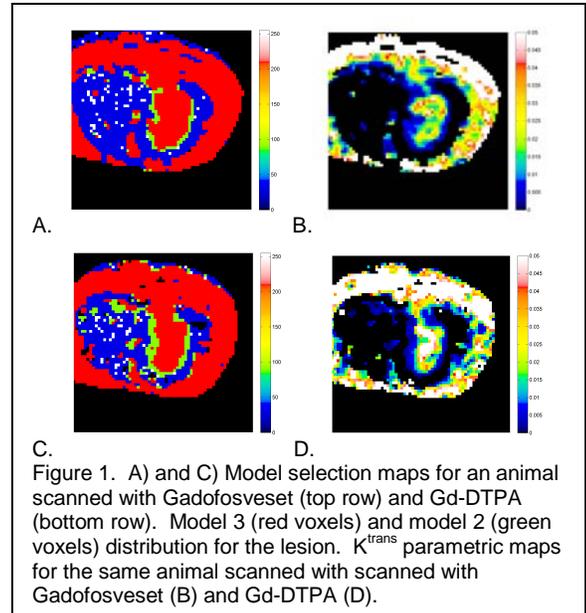


Figure 1. A) and C) Model selection maps for an animal scanned with Gadofosveset (top row) and Gd-DTPA (bottom row). Model 3 (red voxels) and model 2 (green voxels) distribution for the lesion. K^{trans} parametric maps for the same animal scanned with Gadofosveset (B) and Gd-DTPA (D).

	Contrast agent	Mean (SD)	p-value	ICC	Agreement
K^{trans} (min^{-1})	Gadofosveset	0.025 (0.008)	0.0039	0.848	Almost perfect
	Gd-DTPA	0.046 (0.011)			
v_e (%)	Gadofosveset	22.7 (4.7)	0.425	0.880	Almost perfect
	Gd-DTPA	23.6 (5.6)			
v_p (% or ml/100g)	Gadofosveset	1.5 (0.5)	0.25	0.798	Substantial
	Gd-DTPA	1.6 (0.4)			

Table 1. Results for the whole lesion analysis in 9 animals scanned with Gadofosveset as well as Gd-DTPA.