Logan Plot Estimates of Tracer Distribution Volume from Dynamic Contrast Enhanced MRI Data and Tumor Cellularity in a Rat Model of Cerebral Glioma at 7T

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Introduction: Logan plot graphical approach for estimating tracer distribution volume(V_D) is widely used in positron emission tomography (PET) data to assess tumor vasculature. However, its application in dynamic contrast enhanced MRI (DCE-MRI) for the estimation of V_D (plasma volume plus interstitial volume), an important parameter for assessing tumor physiology, has not been reported. In this study, we performed T_1-weighted DCE-MRI using a dual-echo gradient-echo (2GE) sequence to generate a pure time trace of the change in R_1 ($R_1=1/T_1$), which in turn was used to estimate V_D. Since tumor cellularity, i.e., the number of cells in a given volume of tumor tissue, is an important factor for tumor grading, its comparison to noninvasive DCE-MRI measure is a significant test for validation of the clinical utility of DCE-MRI derived parameter. Thus, the objectives of this study were; 1) to apply Logan plot graphical approach on DCE-MRI data to estimate V_D, 2) to test the hypothesis that the tumor cellularity and the DCE-MRI-derived V_D, were correlated.

Theory: Logan Plot: Logan graphical analysis model (1) for tissue and plasma concentration of the contrast agent(CA) is given by the equation;

$$\frac{\int_0^t C_t(\tau)d\tau}{C_t(t)} = V_D \frac{\int_0^t C_p(\tau)d\tau}{C_t(t)} + Const. \quad (1)$$

where $C_p(t)$ and $C_t(t)$ are the plasma and tissue concentrations of CA, respectively, V_D is the distribution volume. Since the change in longitudinal relaxation rate is approximately proportional to tissue concentration of the contrast agent, the observation equation for the Logan plot becomes;

$$(1-Hct)\frac{\int_0^t \Delta R_{1t}(\tau)d\tau}{\Delta R_{1t}(t)} = V_D \frac{\int_0^t \Delta R_{1a}(\tau)d\tau}{\Delta R_{1t}(t)} + Const. \quad (2)$$

where $\Delta R_{1a}(t)$ and $\Delta R_{1t}(t)$ refers to the subtraction of the pre-contrast relaxation rate from its post-contrast value at artery and tumor region respectively as a function of time, and Hct is the hematocrit. If there is a time after which the plot of $\frac{(1-Hct)\int_0^t \Delta R_{1t}(\tau)d\tau}{\Delta R_{1t}(t)}$ vs. $\frac{\int_0^t \Delta R_{1a}(\tau)d\tau}{\Delta R_{1t}(t)}$ yields a straight line, the slope of the fitted straight line gives the distribution volume.

Material and Methods: MRI: DCE- MRI studies were performed on 7T in 18 nude rats implanted with a U251 model of cerebral glioma. The image sets were acquired by means of a dual-echo gradient-echo (2GE) sequence on a Varian, 20 cm bore system with a 32x32 mm FOV. The 2GE sequence acquired 150 image sets at 4.0 sec intervals: (matrix = 128x64, three 2.0 mm slices, NE= 2, NA=1, TE/TE/TR = 2.0/4.0/60 ms). Bolus injection of the CA (Magnevist, 0.25 mmol/kg) was performed by hand push at image 15. In order to establish test-retest variation in this animal model, two MRI studies were conducted for each animal, twenty-four hours apart. A radiological arterial input function(AIF) (3)), normalized so that the caudate putamen of the normal hemisphere yielded a plasma volume of 1%, was employed to estimate V_D.**Histology:** After 2nd MRI study rats were transcardially perfused with paraformaldehyde, and post-fixed prior to paraffin embedding. Brain tissues were sectioned and stained with Hematoxylin and Eosin. Cell count were measured in several regions of interest (ROIs) spanning the tumor, including in the core, periphery and body of the tumor.

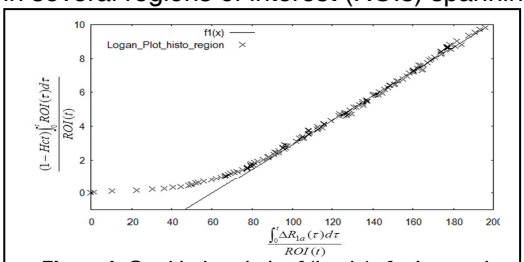

Figure 1. Graphical analysis of the data for Logan plo estimate of distribution volume. The solid line shows the linear fit of the data in the range 100:190, the slope o the line gives distribution volume.

Results and Conclusion: Eighteen animal studies having DCE-MRI and histological findings were available. Figure 1 shows the Logan plot graphical analysis of the data, the straight line fitting was made in the range 100:190 time points where the graph was linear, to obtain the slope 0.0725 equivalent to the distribution volume of 7.25%. Test-retest values were quite stable within an animal, although there was considerable variation between animals. The test group mean V_D (7.94%) moved downward to the retest group mean (7.21%), but not significantly (p=0.2). The combined (2 studies) sample mean of V_D was (7.58±2.33)%. Also, the Logan estimated V_D showed a strong correlation to the corresponding Patlak plot estimates (r=0.93, p<0.01). The cell count values in adjacent to the tumor core region ranged from a low of 751 to a high 3776 (2441±850). Tumor cellularity and distribution volume(V_D) were highly correlated (r = 0.76, p< 0.01). Thus, the Logan plot graphical approach can be a useful tool in DCE-MRI for assessing tumor cellularity and its therapeutic response.

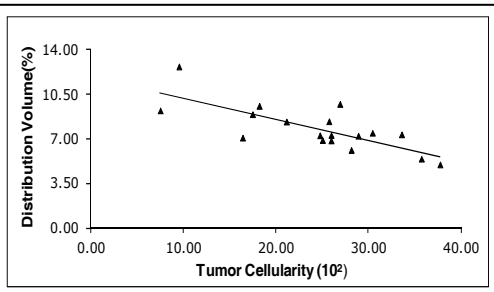

Figure 2: Scatter plot of Logan plot estimates of distribution volume versus tumor cellularity measured in the ROI(r = 0.76, p < 0.01).

References: 1) Logan J et al. J Cereb Blood Flow Metab, 1990;10: 740-7.
2) Nagaraja TN et al. Magn Reson Med 2010; 63:1502-09.
3) Ewing JR et al. ISMRM, 11 May 2012. Melbourne, Australia.