Toward an MRI Estimate of Tumor Interstitial Pressure: Porosity in the Tumor Rim

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Target Audience: Oncologists, radiologists and medical physicists who are interested in tumor interstitial fluid pressure as a signature as a signature of tumor aggressiveness and response to treatment.

Purpose: To use dynamic contrast enhanced MRI (DCE-MRI) to estimate porosity, φ, in the rim of an animal model of cerebral tumor.

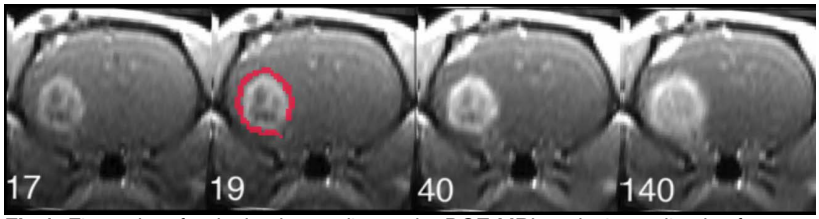

Fig 1: First echo of a dual-echo gradient-echo DCE-MRI study, immediately after injection of CA, and at subsequent intervals: 8, 92, and 492 s post-injection. The movement of the contrast agent wave front in normal tissue is evident. An ROI drawn in red around the leaky area refers to a region in which microvascular leakage of CA is minimal, but convective transport of CA is evident.

Methods: Darcy's law relates the fluid velocity **u** to the local gradient of interstitial pressure, p_i: $\mathbf{u} = -k\nabla p_i$, where k is the hydraulic conductivity of the tissue. In essence, Darcy's law relates fluid velocity at the tumor boundary to the pressure gradient at the boundary, scaled by the fluid conductivity *k*. The fluid conductivity is, to first-order, inversely proportional to φ. Velocity at the tumor rim can be estimated using the analysis of DCE-MRI data suggested by Hompland et al (1). This leaves the parameter k to be determined, requiring an estimate of φ. An example of the method for estimating φ follows.

Consider Fig. 1, showing the first echo at selected times in a dual-echo DCE-MRI study in the brain of a U251 rat model of cerebral tumor, imaging parameters as in Aryal et al. (2). A region of interest (ROI) forms a horseshoe shape around the body of the tumor. Using the first and second echoes of this study, maps of T_1 before and after the DCE-MRI study, a trace of $\Delta R_1(t)$ was constructed across the 10 min duration of the experiment, with image sets at 4 s intervals (3). In the early points of the sequence, a Model 2 Patlak plot is *convex*, and then linear. This is a clear case of model failure that also presents an interesting picture in which the most likely explanation is that CA leaks into the ROI from the highly permeable regions interior to it (explains the convexity of the data), and, since the CA cannot re-enter the microvasculature *via* the tight junctions of the intact BBB surrounding the tumor, it accumulates in the tumor surround, thus fulfilling the Patlak criterion (hence the late linearity). where an equilibrium between the plasma and tissue has been established.

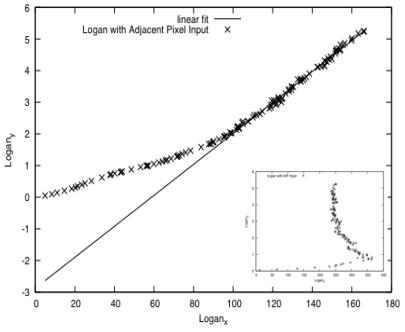

Fig 2: A Logan plot formed by using the 'horseshoe' of Fig 1 to estimate the concentration-time curve of the response region, and the adjacent inner band of pixels to form the input function. Insert: the Logan plot of the same data using an AIF The interstitial volume estimate of ~4.9% is consistent with a compressed parenchyma in the tumor surround.

See Fig 2. If the arterial input function (AIF) used to construct the standard maps of DCE-MRI parameters (2,3) is employed as an input function, and the response function consists of the concentration-time data summed in the ROI with negative values in v_p and presented as a Logan plot, the results are nonsensical and nonphysical (negative final slope). However, if the inner adjacent pixel to the region of negative values is used as an input function, a smooth Logan plot with an estimate of v_D of 4.9% is the result. This is significant because a straight-line on the Logan plot signals a secular equilibrium – in this case, and equilibrium in the amount of contrast agent entering and exiting the ROI. The slope of this line is the 'distribution volume,' V_D, which by definition is equal to the porosity, φ.

Results: Using the techniques outlined in the previous paragraphs, we analyzed a set of 16 DCE-MRI control studies for v_D in the tumor boundary. Estimates of v_D ranged from 1.8% to 8.3%. Test-retest values, with a 24 hr interval separating the measures, were remarkably stable, with a mean difference of (0.29% ± 0.27%). This demonstrated that a stable estimate of distribution space in the normal tissue adjacent to the tumor can be produced. In a 6-study subset of animals, a preliminary comparison of direct estimates of TIFP by the wick-in-needle technique (4) with MRI-derived measures using exudate velocity and Logan estimates of V_D, yielded a correlation of 0.7 ($p < 0.01$).

Discussion: In many solid tumors TIFP is a critically important measure of tumor aggressiveness, metastatic potential, and response to treatment. A noninvasive measure of TIFP, using the data of aDCE-MRI study, would add a clinically significant parameter to those measures of vascular permeability, interstitial volume, and plasma volume already on hand in the body of the tumor itself.

References: 1) Hompland T, et al.. Cancer Res 2012;72(19):4899-4908, PMCID: 2) Aryal MP et al.. Magn Reson Med 2013, PMCID: 3) Ewing JR, Bagher-Ebadian H. NMR Biomed 2013;26(8):1028-1041, PMCID: 3752406. 4) Nathanson SD, Nelson L.. Ann Surg Oncol 1994;1(4):333-338, PMCID: