in a Rat Model of Cerebral Tumor, Exudate Flux is Controlled by Peritumoral Compression

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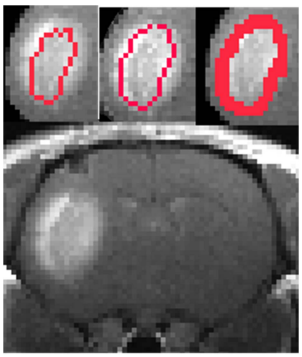

Fig 1: Three ROIs. Left – the boundary of the Model 3 region (inner edge). Middle – the voxels immediately outside the inner rim of the tumor (outer rim). Right – a wider ROI that includes the outer rim.

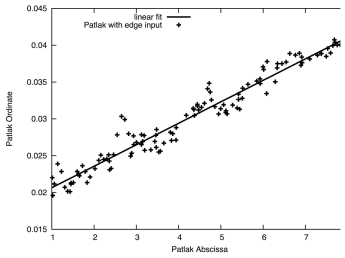

Fig 2: A Patlak Plot (Model 2) of the concentration-time data in the enlarged outer rim of the tumor (top right ROI in Figure 1), using as an input function the data of the innermost adjacent ring. The slope of the line yields an estimate of interstitial flow of tumor exudate.

Target Audience: Oncologists, radiologists, physiologists, medical physicists and others who are interested in MRI measures of tumor physiology.

Purpose: To relate the compression of the mostly normal tissue in the periphery of an embedded tumor to the flux of exudate from the tumor to the surrounding tissue.

Methods: A method for using DCE-MRI in the rim of a model tumor to estimate distribution volume (V_D), which is approximately equal to the extracellular volume fraction, has been previously presented (1). In addition, the flux of tumor exudate from the tumor to its surrounding tissue was estimated.

In a U251 rat model of cerebral tumor, a model selection paradigm was employed to describe the rim region of interest (ROI), and the ROI of the tumor itself. See Fig 1 for an example of the three regions. V_D was estimated in the mostly normal outer rim by fitting the linear portion of a Logan plot (2, 3), generated by using the inner rim concentration as a forcing function. Flux between the inner rim and the outer rim was estimated by integrating the accumulation of contrast in a thickened outer rim (rightmost ROI in Fig 1) and again using the inner rim concentration as a forcing function. This data, when plotted as a Patlak plot (Fig 2), yields a straight line whose slope is the volumetric flow. Normalized to the volume of the thick outer rim and the area of the interface between the inner and outer rims, this yields the flux across the outer surface of the inner rim.

Results and Conclusion: In 18 animals, 16 with repeated studies, the sample mean of V_D in the inner ring ROI was ~ 15%; in the outer ring, it was ~ 10%. These estimates are smaller than the measured distribution volume of normal brain, which is about 18% across a wide variety of mammalian species (4). A GLM analysis found the outer ring ROI v_D to be highly predictive of the inner ring's V_D ($p < 1X10^{-5}$). A regression slope of 0.528 demonstrated that the outer ring V_D was usually about half that of the inner ring V_D, presenting a picture of a relatively porous inner ring of tissue that was mainly tumor, and a compressed outer ring of mainly normal tissue.

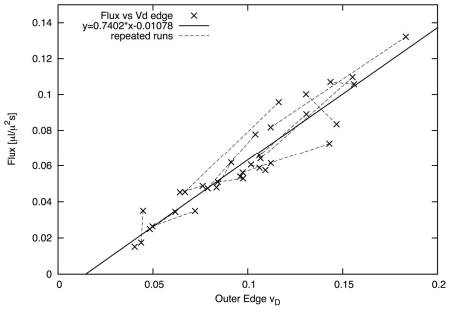

Fig 3: Contrast agent (Magnevist) flux from the inner rim of the tumor to the outer ring in 18 animals. Sixteen repeated studies are connected with dashed lines. R^2=0.9. This very significant co-variance implies that a knowledge of V_D in the rim of the will yield a remarkably precise prediction of Contrast Agent flux, regardless of other parameters such as TIFP and tumor porosity, which might otherwise be thought necessary for a prediction of the exudate flow rate.

The V_D of the outer ring was significantly correlated (R^2 = 0.9, $p < 10^{-5}$) with tumor exudate flow from the inner rim (Fig 3). Peritumoral extracellular volume, thus, was a reliable predictor of the rate of the outward flux of CA from the tumor. Although tumor interstitial fluid pressure and porosity can vary in this tumor model by factors of three or more, only a knowledge of tissue distribution volume in the normal brain bordering the rim of the tumor was necessary to explain the great majority of systematic variation in tumor exudate flow. This data appears to imply that perfusion, i.e., the *delivery* of blood to the tumor, was regulated by the compression of the tumor rim, and that the total contrast agent flux was limited by total perfusion. This has generated a unique insight into the control of perfusion in an embedded tumor and suggested the tumor surround as a participant in the pathological physiology of embedded tumors.

References: 1. Ewing JR, et al. Toward an MRI Estimate of Tumor Interstitial Pressure: Annual Meeting ISMRM-ESMRMB; 2014; Milan, Italy: 2. Aryal MP et al.. Magn Reson Med. 2013. 3. Logan J, et al. J Cereb Blood Flow Metab. 1990;10(5):740-7. 4. Levin VA et al. Am J Physiol. 1970;219(5):1528-33. PubMed PMID: 4990676.