Correlating Tumor Viscosity with Hypoxia

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Target Audience: Members of the MR community and physicians involved in tumor diagnostics, detection, radiation therapy and targeted drug delivery.

Purpose: The purpose of this work is to establish a relationship between tumor viscosity and partial oxygen pressure (pO_2), the two important physiologic parameters that can be channelized to provide targeted radiation therapy. Tumors have a highly heterogeneous environment frequented with areas of low oxygen concentration (hypoxic regions). These hypoxic areas are resistant to radiation and thus, require higher radiation dosage for the destruction of tumor cells. Current practice of ignoring oxygen distribution while applying homogeneous radiation treatment leads to excessive damage of the neighboring healthy tissues, and thereby reduced quality of patient life. Solid tumors have abnormal organization of blood vessels that results in heterogeneous perfusion and extravasation, and a hostile microenvironment with increased interstitial pressure (1). The higher cellularity, tissue disorganization, and increased extracellular space all result in lower apparent diffusion coefficients, equivalent to higher viscosities, for malignant tumors as compared to normal tissue (2). The knowledge of pO_2, in conjunction with viscosity and tissue anisotropy, can predict tissue health and may eventually be used in combination with Intensity-Modulated Radiation Therapy (IMRT) for targeted destruction of radiation-resistant areas, while sparing healthy tissues. In this study, we aim to correlate tumor viscosity acquired using diffusion weighted magnetic resonance imaging (DWI) with pO_2 obtained by electron paramagnetic resonance oxygen imaging (EPROI). This is first such study correlating these two physiologic parameters at the tissue microstructure level.

Materials and Methods: $5x10^5$Human MCa4 tumor cells were injected intramuscularly in the hind leg of a 6 to 8 week old C3H mouse. The tumor grew to 0.5 - 1 cm^3 within 1-2 weeks. The tumor was immobilized using a vinyl polysiloxane dental mold to encompass around half of the tumor bearing leg. MRI and EPROI experiments were performed sequentially under isoflurane anesthesia.

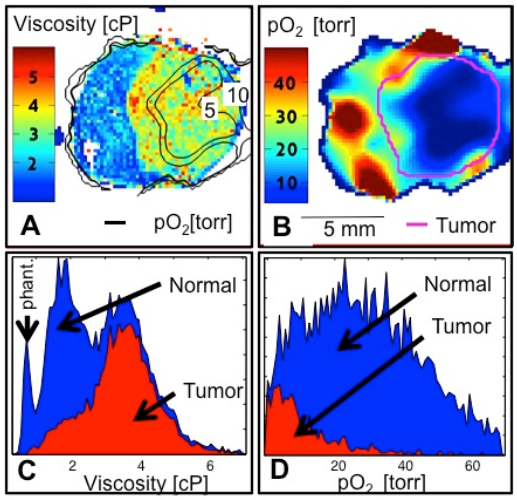

Figure 1: (A) Viscosity and (B) oxygen images from an axial slice of a murine leg with MC4a tumor. Color bar shows viscosity scale in the range of 0 – 6 cP and pO_2 scale in the range of 0-50 torr. (C) and (D) shows histogram for viscosity and pO_2 values from the whole image (blue) and from the tumor volume only (red). Note that only 7 slices were acquired for DWI experiments thus showing smaller amount of normal tissue volume in the histogram.

MRI Experiments: All MRI measurements were performed using a 9.4 T preclinical MRI scanner with a custom-built 30 mm rf coil. Apparent diffusion coefficient (ADC) maps were acquired using diffusion weighted spin echo MRI sequence. The experimental parameters were: TE/TR = 26 ms /3500ms, slice thickness = 0.75 mm, number of slices = 7, δ = 7 ms, Δ = 14 ms, FOV = 2.56 cm x 2.56 cm, matrix size = 128 x 128, and b values = 0, 50, 250, 500, 750, 1000, and 1500 s/mm^2, total experimental time ~ 44 min. The ADC maps were calculated by fitting the signal intensity to single exponential curve. The viscosity maps were calculated using ADC maps by applying Stoke-Einstein equation $D= kT/6\pi a\eta$, where D = ADC/λ. The constant λ is a coefficient dependent on diffusion gradient pulses and was calculated to be 1.39 using water phantoms.

EPR Oxygen Imaging Experiments: Electron Paramagnetic Resonance Oxygen Imaging (EPROI) derives absolute oxygen partial pressure *in vivo*, and hence is a promising tool for providing targeted radiation therapy to patients. For soluble spin probes, the Smoluchowski diffusion equation, $R_1 = A*[pO_2] + Rx$ predicts a linear relationship between pO_2 and relaxation rates (in this case spin-lattice relaxation, R_1) of the paramagnetic spin probe injected into an animal (3). Here pO_2 is partial oxygen pressure and Rx is oxygen independent contribution to relaxation time. We used pulse EPR inversion recovery methodology for pO_2 image acquisition (3). 208 equal solid angle projections were acquired with maximum gradient of 15 mT/m and a isotropic field of view of 4.24 cm. Images were reconstructed using filtered back projection algorithm. OX063 spin probe was injected IV into animal 0.56 mmol/kg followed by infusion at 0.78 mmol/kg/hr during imaging time. Image was acquired in 10 minutes and had 1.5 mm spatial and 1 torr pO_2 resolution. Viscosity images were registered with oxygen images using a custom built Matlab program.

Results and Discussion: Figure 1 shows registered viscosity and pO_2 images for an axial slice of murine leg with MCa4 tumor. It is clear from the histogram that within the tumor volume the distribution of viscosity is two fold, with a more ordered region (low viscosity) and a more chaotic region (high viscosity) even though hypoxia is common to both regions. It is possible that sparing the more structurally integrated region from high dose will improve the overall effective radiation therapy. The knowledge of spatial distribution of viscosity in combination with the spatial distribution of pO_2 may eventually lead to efficient targeted drug delivery and efficient radiation dose treatment. In future, we plan to derive statistically significant correlation between viscosity and pO_2, two important physiological parameters.

Conclusions: This study aims at establishing a correlation between viscosity and pO_2 based on DTI and EPR oxygen imaging. We have found that in solid tumors, in general the hypoxic regions have higher viscosity.

References: 1. Jain RK, Stylianopoulos T. Delivering nanomedicine to solid tumors. Nature reviews Clinical oncology. 2010;7(11):653-64. **2.** Padhani AR, Liu G, Koh DM, et al. Diffusion-weighted magnetic resonance imaging as a cancer biomarker: consensus and recommendations. Neoplasia. 2009;11(2):102-25. **3.** Epel B, Bowman MK, Mailer C, Halpern HJ. Absolute oxygen R imaging in vivo with pulse electron paramagnetic resonance. Magnetic resonance in medicine, 2013, in press.