Further Validation of MR Oximetry as a Useful Prognostic Indicator of Tumor Radiation Response

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Introduction: Tumor oxygenation may significantly modulate the efficacy of various therapeutic interventions, particularly radiation therapy. Hypoxic regions are characteristically more resistant to radiotherapy, and the ability to sample pretreatment oxygenation may prove to be a reliable predictor of outcome. We have recently developed a novel technique to sample tumor oxygen tension at multiple locations by FREDOM (Flurocarbon Relaxometery using Echo Planar imaging for Dynamic Oxygen Mapping) MRI, following direct intratumoral injection of the reporter molecule hexafluorobenzene (1). Previously, this technique was used to establish a correlation between baseline oxygenation and growth delay following radiation therapy in the slow growing HI subline of the R3327 Dunning prostate tumor (2). Here, we demonstrate similar results in the more hypoxic, rapidly dividing AT1 subline of Dunning R3327. Specifically, oxygen inhalation during radiation therapy resulted in enhanced growth delay for both large and small tumors, and large tumors exhibited significantly higher hypoxic fractions that did not respond well to oxygen inhalation.

Methods: Syngeneic Dunning prostate R3327-AT1 carcinomas were implanted in surgically prepared foreback pedicles of 28 adult male Copenhagen rats. The animals were randomized into three groups; Control animals (No treatment, n=5), large tumors (>3.0cc, n=10), and small tumors (<1.25cc, n=13). For all animals, tumor diameter was measured in three orthogonal axes every 3-7 days until the tumor burden (or condition) required sacrifice of the animal. In approximately half of the irradiated animals (Large, n=5; Small, n=6), MR measurements were obtained on a 4.7T Varian horizontal bore magnet system no more than 24 hours prior to irradiation. Each rat was maintained under general anesthesia (air+1% isoflurane). Hexafluorobenzene (50µl) was injected using a 32G needle into both central and peripheral regions to ensure representative sampling of the tumor's oxygen tension. Typically, HFB was deposited along three needle tracks to form a wedge shaped fan in a plane coronal to the rat's body. A tunable ($^{1}H/^{19}F$) single turn solenoid coil (either 2 or 3.5 cm, size matched to tumor diameter) was placed around the tumor bearing pedicle, and conventional three dimensional (3D) spin echo images were obtained for both ^{1}H (200.1 MHz) and ^{19}F (188.3 MHz) to reveal HFB distribution within the tumor (see Figure 1A). In four animals (Large, n=2; Small, n=2), tumor oxygenation was estimated using four consecutive 6 minute cycles (Δt=24min) of the previously described FREDOM sequence. Specifically, ^{19}F pulse burst saturation recovery echo planar imaging (EPI) relaxometry of the HFB (1). Post-processing of each FREDOM scan yields direct estimates of oxygen tension using the relationship pO_2 (torr)= [(R1- 0.0835)/ 0.001876]. Voxels were rejected when T1 error >2.5s and T1 error/T1 >50%. In another six animals (Large, n=3; Small, n=3) the initial four baseline sequences while breathing air were immediately followed by four consecutive 6 minute sequences during inhalation of 100% oxygen, for a total scan time of 48 minutes (see Figures 1B &1C). Within 24 hours of the initial MR scans, the animals were irradiated under general anesthesia, using a 4MV Varian Clinac 4/100 linear accelerator, to a total dose of 30 Gy. Six rats from the "small" group and five from the "large" group breathed oxygen during irradiation, while seven from the "small" group and five from the "large" group breathed air. Tumor size was followed until the animal's sacrifice, and treatment response was evaluated based upon the time (T_2) until doubling of the tumor's initial volume at irradiation.

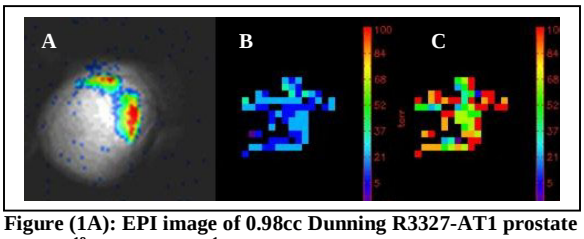
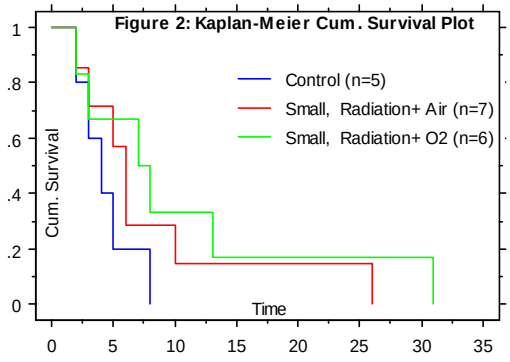


Figure (1A): EPI image of 0.98cc Dunning R3327-AT1 prostate tumor (^{19}F overlaid on ^{1}H). Figures (1B, 1C): pO_2 map obtained using the FREDOM approach in tumor 1A after (B) 24 min of air inhalation, and (C) 24 min of oxygen inhalation.

Results: In large tumors, there was a correlation between pre-irradiation pO_2 and tumor volume doubling time T_2 (R=0.9). No correlation could be established for the small tumors. The mean baseline oxygenation (air inhalation) of large tumors was 1.8 +/- 0.6 torr, whereas for small tumors it was 25.2+/- 0.8 torr. Oxygen inhalation caused the mean tumor oxygen tension to increase to 4.9 +/- 1.6 torr and 87.7 +/- 2.1 torr in large and small tumors, respectively. The initial hypoxic fraction (%<10 torr) was significantly (α=5%) higher in large tumors as compared to small. For large tumors, oxygen inhalation increased mean volume doubling time from 10.2 +/- 3.6 to 12.8 +/- 2.8 days. Similarly, oxygen inhalation in the small tumor group increased mean volume doubling time from 6.0+/- 1.2 to 7.7 +/- 2.0 days (See Figure 2).



Discussion: In this study, we are able to show that in the poorly differentiated, rapidly dividing AT1 subline of Dunning prostate R3327, for both the oxygen and air inhalation groups, small (<1.25cc) tumors are significantly (α=5%) better oxygenated than large (>3.0cc). Additionally, enhanced survival (as measured by an increase in volume doubling time) resulted for animals with small tumors that inhaled oxygen during radiation therapy. A growth delay resulting from oxygen inhalation during irradiation was also observed in large tumors, even though oxygen inhalation only modestly decreased the initial hypoxic fraction (%<10 torr) as compared to small tumors.

References:

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Acknowledgement: Supported by NIH Predoctoral Training Grant R01 CA79515-S