Imaging modulation of tumor hypoxia in vivo using a nitroimidazole based T_1 MR contrast agent

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Introduction:

Hypoxic regions in tumors are known to affect radiation sensitivity and promote development of metastases [1]. Noninvasive imaging based methods such as MRI are particularly suitable for longitudinal measurements and generation of three-dimensional spatial maps of tumor hypoxia [2]. An MRI method that could differentiate hypoxic *versus* normoxic tissues without relying on washout modeling would be clinically useful. Previous research demonstrated *in vitro* and *in vivo* evidence for selective accumulation of a T_1 shortening agent, a GdDOTA monoamide conjugate of 2-nitroimidazole (abbreviated as GdDO3NI), under hypoxia. With "patient stratification" in mind, we chose two tumor lines (Dunning R3327-AT1 and HI) with known responses of tumor pO_2 to oxygen breathing to investigate the utility of GdDO3NI in detecting changes in the hypoxic fraction of tumors. In this work, we report ^{1}H MR imaging of differential response to oxygen breathing in these two prostate cancer sublines using GdDO3NI.

Materials and Methods:

MR experiments were performed on a Varian 4.7T MR scanner. *In vivo* imaging studies were performed on Copenhagen rats bearing subcutaneous syngeneic R3327 - AT1 (n=4) or HI (n=4) prostate tumors (volume ~3cc). Following baseline T_1 mapping (TR: 0.1-6 s and TE: 12 ms), T_1-weighted images (TR/TE = 200/10 ms, FOV = 5 cm X 5 cm, matrix = 128 X 128, slice thk = 1 mm) were obtained pre and post injection of 0.1 mmole/kg body wt GdDO3NI for 150 min. On day 1, imaging was performed with animals breathing air while on the subsequent day, the study was repeated with the animals breathing oxygen during the entire duration. Data analysis was performed by segmenting the voxels in the tumor region into periphery and center, based on a criterion of 50% enhancement at 90 s post injection. Gd concentration in the tumor slices was calculated using the relation $[CA] = (R_{1,post} - R_{1,pre}) / r_1$, with r_1=5.45 ± 0.294 $mM^{-1}s^{-1}$ as determined in vitro.

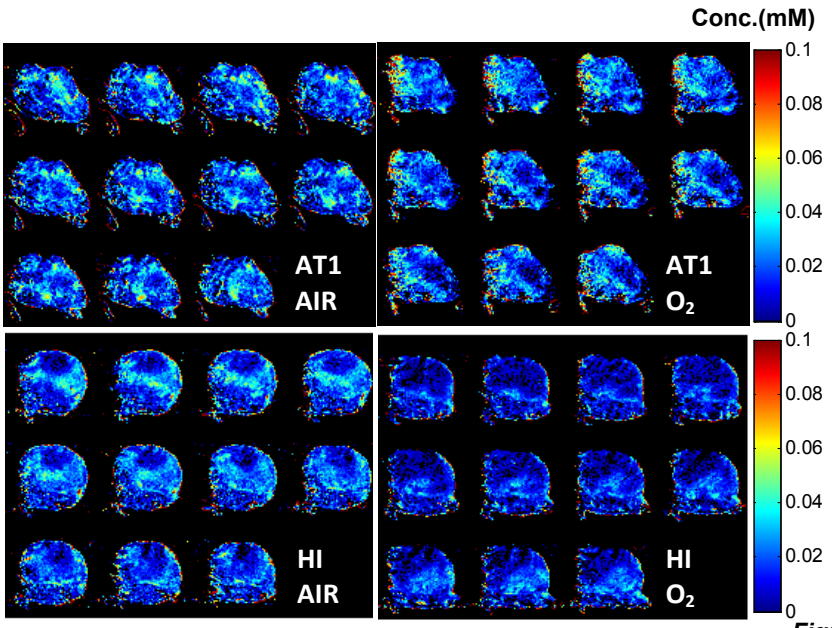

Figure 1: *Gd concentration maps of multiple slices of representative AT1 (top row) and HI (bottom row) tumors at 150 minutes after the injection of GdDO3NI following air (left column) and oxygen (right column) breathing.*

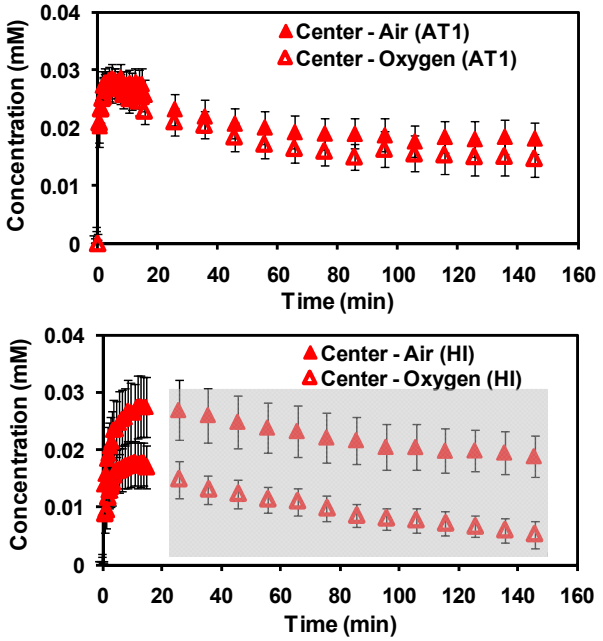

Figure 2: *Kinetics of mean Gd concentration (n=4) for central regions of AT1 tumors (top) and HI tumors (bottom) in animals injected with GdDO3NI following air and oxygen breathing. Region shaded in gray represents p<0.0001.*

Results and Discussion:

In AT1 tumors, we did not observe statistically significant differences in GdDO3NI concentration at late time points between air and oxygen breathing. The contrast kinetic profiles of periphery, center (Fig 2, top) and thigh regions were very similar. In the HI tumors, no significant difference of GdDO3NI uptake in peripheral and thigh regions was observed at late time points between air and oxygen breathing, but we observed a significant decrease in GdDO3NI uptake in the central regions of the tumor when the animals breathed oxygen as compared to air (Fig 2 bottom). These observations are in accordance with the previously published data using ^{19}F MR oximetry, which have shown that large AT1 and HI tumors (> 3 cc) are hypoxic while breathing air with mean (± SE) pO_2 values of 3.5 ± 1.5 torr and 12.7 ± 1.1 torr respectively and while HI tumors had shown a rapid response to oxygen breathing (mean pO_2 = 102 torr), AT1 tumors resisted modulation [3, 4]. Thus, GdDO3NI not only allows imaging of hypoxic regions but can also aid in stratifying tumor response to hypoxia altering interventions.

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References: 1) Tatum *et al*., *Int J Radiat Biol* 2006;82(10):699-757. 2) Cho *et al*., *Neoplasia* 2009; 11(3): 247-259. 3) Zhao *et al*., *Neoplasia* 2003; 5(4): 308 -318. 4) Zhao *et al*., Int J Radiat Oncol Biol Phys 2002;53(3):744-756.