A role for DCE MRI in predicting tumor radiation response

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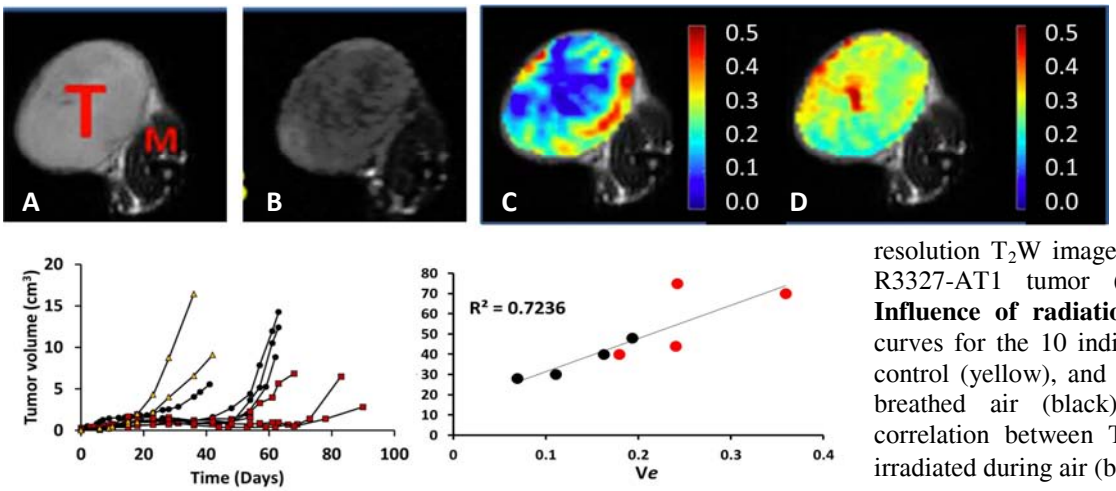
Audience: Researchers and clinicians interested in noninvasive biomarkers for predicting tumor response to radiation

Introduction: It has been long appreciated that hypoxic tumors are more resistant to radiotherapy (*Int. J. Radiat. Biol.* 2006;82:699). Various methods have been described to assess tumor oxygenation including electrodes, ^{19}F MRI and oxygen enhanced MRI (BOLD and TOLD). There have also been various reports that parameters associated with Dynamic Contrast Enhanced (DCE) MRI are related to radiation response (*Int. J. Radiat. Oncol. Biol. Phys.* 2002;54:759; *Radiother. Oncol.* 2012;102:429). Several reports have compared DCE parameters with surviving fraction in culture following irradiation of tumors *in vivo*. We have now evaluated correlations between DCE MRI and tumor growth delay following radiation of the well characterized syngeneic Dunning prostate rat tumor R3327-AT1.

Methods: Ten male Copenhagen rats were implanted subcutaneously in the thigh with Dunning R3327-AT1 tumors and MRI studies conducted on a horizontal bore 4.7 T magnet two to five weeks later. Rats were anesthetized (isoflurane/oxygen) and T_1 maps were acquired using a spin echo sequence (SEMS). Time course DCE data were then acquired using a spin echo sequence with a TR/TE of 200/15 ms pre and up to 30 mins following injection Gd-DTPA (Magnevist®; 0.1 mmol/kg body weight *IV*). DCE data were analyzed using the approach of Faranesh and Yankeelov (*Phys. Med. Biol.* 2008;53:2617) to calculate K_{trans} and Ve, whereby muscle provides a reference tissue, thus avoiding the need for the arterial input function (AIF). The following day, eight tumors were irradiated with a single high dose of 30 Gy (half the reported $TCD_{50;}$ *Int. J. Radiat. Oncol. Biol. Phys*. 2011;79:239), while animals breathed air (n=4) or oxygen (n=4) using a dedicated small animal x-ray irradiator (XRAD 225Cx), while two served as non-irradiated controls. Tumor growth was monitored and compared with pre-irradiation DCE assessments.



Upper Figure: MRI of R3327-AT1 tumor A) High resolution T_2W image showing the tumor (T) and muscle (M). B) Post-contrast (Gd-DTPA) T_1W image. C) K_{trans} map. D) Ve map overlaid on high resolution T_2W image of a small Dunning prostate R3327-AT1 tumor (0.8 cm^3). **Lower Figure**: **Influence of radiation on growth.** Left: growth curves for the 10 individual tumors: non-irradiated control (yellow), and single dose 30 Gy while rats breathed air (black) or oxygen (red). Right: correlation between T4 and V_e for those tumors irradiated during air (black) or oxygen (red).

Results: Both K_{trans} and Ve maps showed considerable heterogeneity. Irradiation caused significant tumor growth delay and T4 (the time for tumor volume to quadruple) ranged from 28 to 75 days, as compared to non-irradiated tumors (T4 ~8 days). The rats breathing oxygen during tumor irradiation generally exhibited a greater tumor growth delay, but there was overlap between the groups and it was not significant ($p<0.081$) emphasizing the importance of individual measurements. No obvious correlation was observed between tumor growth delay and vessel permeability (K_{trans}). However, strong correlation between extravascular-extracellular volume fraction (v_e) and T4 was observed in both air and oxygen breathing groups ($R^2>0.7$).

Conclusion: A strong correlation was observed between V_e and tumor growth delay, irrespective of the inhaled gas during irradiation. It was not possible to dichotomize the sub-populations as reported recently with respect to oxygen enhance MRI (DOI 10.1002/mrm.24846), but the trend was quite remarkable. Since contrast is part of most radiological examinations, it would appear that high temporal resolution DCE MRI could provide predictive insight into response to radiation. It should be noted that this study used a single high dose irradiation and this is becoming increasingly relevant as radiation oncology practice moves towards hypofractionated (SBRT) regimens.

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