Assessment of Tumor Hypoxia with DCE-MRI: A Preclinical Study on Human Melanoma Tumor Lines

T. A. Egeland[1], J-V. Gaustad[1], B. S. Mathiesen[1], and E. K. Rofstad[1]
[1]Department of Radiation Biology, The Norwegian Radium Hospital, Oslo, Oslo, Norway

Introduction: Human tumors have in general heterogeneous oxygenation, which may lead to the development of hypoxic regions. Tumor hypoxia constitute a challenge for curative treatment and may promote malignant progression, and patients with high fraction of hypoxic cells have been shown to have a poorer prognosis than patients with low fraction of hypoxic cells for several treatment modalities. A non-invasive assay for assessing the extent of hypoxia is therefore highly needed.

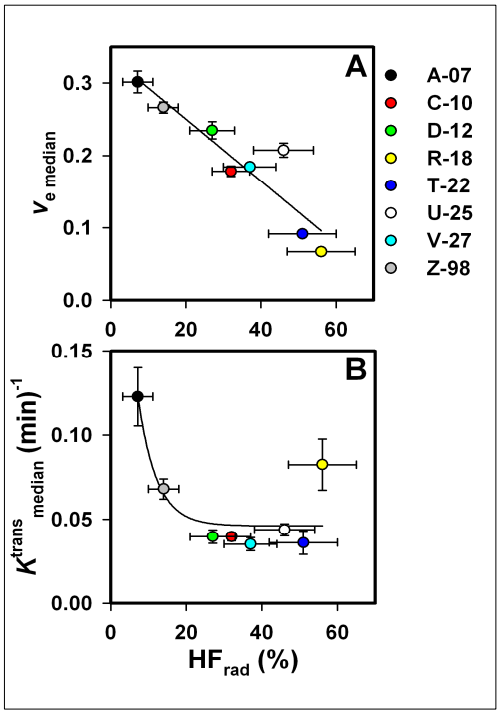
We are currently investigating the potential usefulness of Gd-DTPA–based DCE-MRI for assessing the extent of hypoxia in preclinical tumor models, and use the parameters K^{trans} (the volume transfer constant of Gd-DTPA, which is shown to be proportional to perfusion in our tumor models) and v_e (the extracellular volume fraction of the imaged tissue) from Tofts' model [1]. Hypoxia is a result of imbalance in oxygen supply and consumption, hence our hypothesis is that hypoxic areas would have low K^{trans} (i.e. low oxygen supply) and/or low v_e (i.e. areas with high cell density, hence high oxygen consumption).

In a previous study it was shown that several parameters derived from K^{trans} frequency distributions correlate strongly with the radiobiologically hypoxic fraction (HF_{rad}) for the tumor line A-07, but no positive correlations were found for parameters derived from v_e frequency distributions, possibly because the tumors were rather homogeneous with respect to v_e [2]. In this study we explore the hypothesis further. Tumors from 8 different tumor lines, differing significantly with respect to K^{trans}, v_e and hypoxic fractions, were subjected to DCE-MRI, and parameters derived from this imaging were compared to HF_{rad}.

Methods and Material: 12-17 A-07, C-10, D-12, R-18, T-22, U-25, V-27 and Z-98 human melanoma xenografts transplanted intradermally into BALB/c *nu/nu* mice were used as tumor models.

Tumor imaging was performed with a 1.5-T whole body clinical scanner (Signa, GE), using a cylindrical slotted tube resonator transceiver coil especially constructed for mice, and Gd-DTPA (Schering) diluted in saline to a final concentration of 0.06 M was used as contrast agent (5.0 mL/kg body weight). The tumors were imaged axially in a single section through the tumor center by using a scan thickness of 2 mm, a single excitation, an image matrix of 256×64, and a field of view of 6×3 cm^2. To types of SPGR images were recorded: PD-weighted images with repetition time TR = 900 ms, echo time TE = 3.2 ms and flip angel α = 20°; and T1-weighted images with TR = 200 ms, TE = 3.2 ms and α = 80°, resulting in a scan time of 64 and 14 s for the respective series. Two PD-weighted images and three T1-weighted images were recorded before contrast agent was administrated, and after the contrast agent was administrated T1-weighted images were recorded every 14 s for 15 minutes. Gd-DTPA concentrations were calculated from the signal intensities, and images of K^{trans} and v_e were made using Tofts' model [1], as described in more details elsewhere [2]. Images were analyzed on a voxel-by-voxel basis using software developed in IDL (Boulder).

HF_{rad} was measured for individual tumors using the paired survival curve method, as described in more details elsewhere [2].



Results: The numerical values for both HF_{rad}, median v_e and median K^{trans} varied substantially for the different tumor lines. Mean HF_{rad} differed among the 8 tumor lines by a factor ~ 7.5, while the corresponding factor for mean of median v_e and mean of median K^{trans} were ~ 4.5 and ~ 3.5, respectively. However, while the HF_{rad} and median v_e values for the different tumor lines were scattered over the whole range of values, 5 of the 8 tumor lines had mean of median K^{trans} within the lowest 10 % of the total range.

To investigate whether there was a correlation between v_e and HF_{rad}, and/or K^{trans} and HF_{rad}, different quartiles from v_e and K^{trans} were plotted against HF_{rad}. For all v_e quartiles, strong linear relationships were found between v_e and HF_{rad} ($p<0.002$ for all quartiles, median v_e vs. HF_{rad} shown in Fig. A). For all K^{trans} quartiles, most tumor lines with high HF_{rad} had lower K^{trans} than tumor lines with low HF_{rad}, and K^{trans} did not vary significantly for most tumor lines with high HF_{rad} (median K^{trans} vs. HF_{rad} shown in Fig. B). One tumor line, R-18, did however differ from these pattern as that tumor line had both high K^{trans} and high HF_{rad}. It was also found that the data was well described by an exponential decay function (R^2 = 0.5-0.9 for all quartiles), once more with R-18 as an outlier.

Discussion: These experiments were initiated to investigate the potential usefulness of Gd-DTPA-based DCE-MRI for assessing the extent of tumor hypoxia, and it was found that both v_e and K^{trans} contain information on the oxygenation status of the tumors in this study. This is consistent with the hypothesis that v_e and K^{trans} reflect respectively oxygen consumption and oxygen supply, and that these attributes are some of the factors determining the oxygenation status in tumors.

The tumor lines used in this study varied substantially in many physiologically and biologically characteristics such as cell density, vascular density, perfusion, hypoxic fraction, and necrotic fraction and pattern, while the tumor lines are rather homogeneous for some characteristics such as vascular permeability, interstitial conductivity and amount of connective tissue. One would hence expect that the tumor lines used in this study are excellent models for some human tumors, while not representative for other tumors, and that the relationships between hypoxic fraction and pharmacokinetic parameters found for these tumor lines will be present for human tumors similar to the tumor lines in this study, while it is not clear whether this will be the case for tumors with different characteristics. The results therefore suggest that parameters related to v_e and/or K^{trans} will be useful for assessing the amount of hypoxia in human tumors with similar characteristics as the tumor lines used in this study, and that similar parameters may be useful for human tumors with different characteristics, if similar relationships between hypoxic fraction and pharmacokinetic parameters are found. These possibilities warrant further clinical research, both in tumors similar to the tumors used in this study as well as tumors with different characteristics.

Conclusions: This preclinical study shows that it is possible to obtain information on oxygenation status of tumor tissue from Gd-DTPA-based DCE-MRI, and that both v_e and K^{trans} contain information relevant for the assessment of hypoxia for the tumor lines used in this study. The study also suggests that similar parameters may be utilized clinically to predict treatment response and/or to individualize treatment, and that these possibilities warrants further clinical investigations.

References: [1] Tofts, Brix, Buckley et al., JMRI, 1999 [2] Egeland, Gaustad, Vestvik et al., MRM, 2006