The relationships between ADC, T_1 and DCE-MRI tracer kinetic parameters in solid ovarian tumors

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Introduction An understanding of the tumor microenvironment may be provided through the use of imaging techniques such as dynamic contrast-enhanced MRI (DCE-MRI), relaxation time measurement, and diffusion weighted imaging (DWI), which provide quantitative estimates of parameters such as the endothelial transfer constant (K^{trans}), fractional extracellular extravascular space (EES, v_e), blood plasma volume (v_p), the longitudinal relaxation time (T_1) and the apparent water diffusion coefficient (*ADC*). While there is a good understanding of DCE-MRI parameters in the context of physiological processes, the interpretation of *ADC* is less clear. In general, the increased cellularity of the tumor environment is expected to lead to a greater restriction of water diffusion and therefore reduced *ADC*. This was observed, for example, by Zelhof *et al* who found a negative correlation between *ADC* and histological measures of cell density[1]. However, since *ADC* depends not only on cell density but also on factors such as cell size distribution, membrane permeability and extracellular space tortuosity the relationship is not always so clear. Yankeelov *et al* observed a negative correlation of *ADC* with v_e in breast tumors suggesting that in this setting the geometrical factors affecting *ADC* are important[2]. Besides *ADC* and v_e, the parameter that is most sensitive to water distribution is often T_1. In this study, we explore the relationships between *ADC*, v_e, and T_1 in ovarian tumors.

Method *Imaging:* Eleven patients with confirmed ovarian cancer (stages IIc to IV) were recruited into the study. Each patient underwent two imaging sessions, which were separated by chemotherapy. DCE-MRI and DWI images were acquired using a Philips 1.5 T Intera (Philips Healthcare, Best, The Netherlands). The DCE-MRI protocol used an axial 3-D spoiled gradient echo (FFE/SPGR) sequence with baseline T_1 measured using the variable flip angle method with the following parameters: 2°, 10° and 20° flip angles, TR/TE = 4.0/0.92 ms, FOV = 375 x 375 mm, matrix = 128 x 128, slices = 26, thickness = 4 mm. The dynamic image acquisition used the same parameters with a flip angle of 20°, 75 dynamic timepoints and a temporal resolution of 5 s. On the sixth dynamic timepoint, 0.1 mmol/kg of body weight of 0.5 mmol/ml Omniscan (GE Healthcare) was administered through a Spectris power injector (Medrad Inc.) at a rate of 3 ml/s followed by an equal volume of saline flush also at 3 ml/s. DW images were acquired using a non-breath hold fat-supressed spin-echo EPI sequence with FOV = 375 x 375 mm, matrix = 142 x 142, slices = 26, thickness = 4 mm with b = 50, 400, 800, TR/TE = 3900/76 ms with 5 signal averages.

DCE-MRI and DWI analysis: Regions of interest (ROI) were defined for the whole tumor volume. For the DCE-MRI data, enhancing voxels were identified and the extended Kety model[3] was fitted to each voxel's time series using an automated arterial input function[4]. 3D maps of DCE-MRI parameters and baseline T_1 were generated. Parameter medians were computed to summarize each tumor. *ADC* values were calculated voxel-by-voxel by fitting to $S(b)=S_0e^{-b*ADC}$. The same ROIs were used to calculate the median *ADC* for each tumor. Scatter plots of T_1, *ADC* and v_e were generated and a bivariate two-tailed Spearman's correlation analysis was used to test for significance ($p < 0.05$). Tumors that were predominantly cystic (as determined on high resolution T_2-weighted images) were excluded from the statistical analysis.

Results There were no significant post-treatment changes in any of the parameters. Our analysis showed a significant positive correlation between tumor median *ADC* and v_e (CC = 0.7290, $p = 0.002$) (Fig. 1a). The relationships between T_1 and both *ADC* and v_e were negatively correlated (CC = -0.818, $p < 0.001$ and CC = -0.668, $p = 0.007$ respectively) (Fig. 1b/c). Significant correlations were not seen between *ADC* and K^{trans} or v_p. Median parameters derived from the cystic tumors are also shown in each plot.

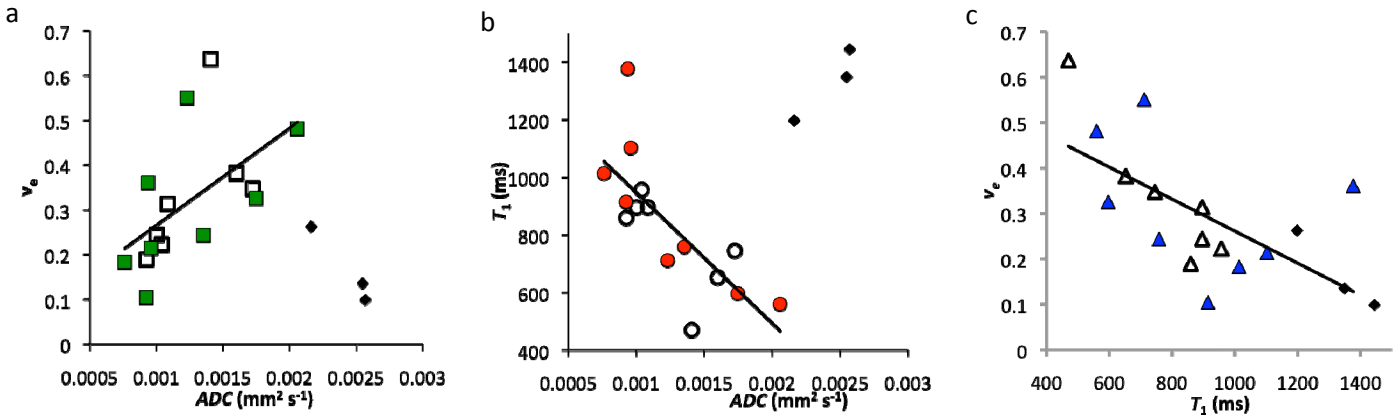

Figure 1: Correlations between *ADC* and v_e (a), T_1 (b), and for T_1 and v_e (c). Closed and open symbols represent visit 1 and visit 2 respectively. Solid line represents the line of best fit through the non-cystic tumors. Solid diamond symbols represent the cystic tumors in the group.

Discsussion The positive relationship seen between *ADC* and v_e is likely to reflect the tumor EES geometry, and suggests that in this tumor type *ADC* is inversely related to cell density. The observed low v_e values in the cystic tumors are likely to be caused by low contrast agent uptake in these tumors. The inverse relationship between *ADC* and T_1 is unexpected, since tumor tissue with an elevated *ADC* and v_e would also be expected to have a long T_1 but this is observed in the predominantly cystic tumors only (Fig 1b). This relationship could be due to increased levels of mucin glycoproteins[5] and collagen typically seen in this tumor type, but other sources of T_1-shortening such as products of haemoglobin breakdown may be responsible. These observations offer insight into the interpretation of *ADC* in this tumor type, highlight the variable nature of the relationship of ADC with cell density across tumor types (when compared with previous results in breast tumours[2]) and demonstrate that T_1 measurements should not be overlooked in tumor assessment.

References **1.** Zelhof B, et al. BJU Int 2009;103(7):883-888. **2.** Yankeelov TE et al. Magn Reson Imaging 2007;25(1):1-13. **3.** Tofts PS. J Magn Reson Imaging 1997;7(1):91-101. **4.** Parker GJ et al. Magn Reson Med 2006;56(5):993-1000. **5.** Giuntoli RL, 2nd, et al. Cancer Res 1998;58(23):5546-5550.