**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. 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 \( v_p \) in breast tumors suggesting that in this setting the geometrical factors affecting \( ADC \) are important. 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: \( 2^\circ, 10^\circ \) and \( 20^\circ \) 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 \( 20^\circ \), 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-suppressed 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\(^6\) was fitted to each voxel’s time series using an automated arterial input function\(^7\). 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 \( S(b) = S_0 e^{-bADC} \). 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.

**Discussion** 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 \( T_1 \) and \( ADC \) 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 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 tumors\(^1\)) and demonstrate that \( T_1 \) measurements should not be overlooked in tumor assessment.

**References**