Heterogeneity of angiogenesis on DCE-MRI in human tumours: Implications for antiangiogenic therapies

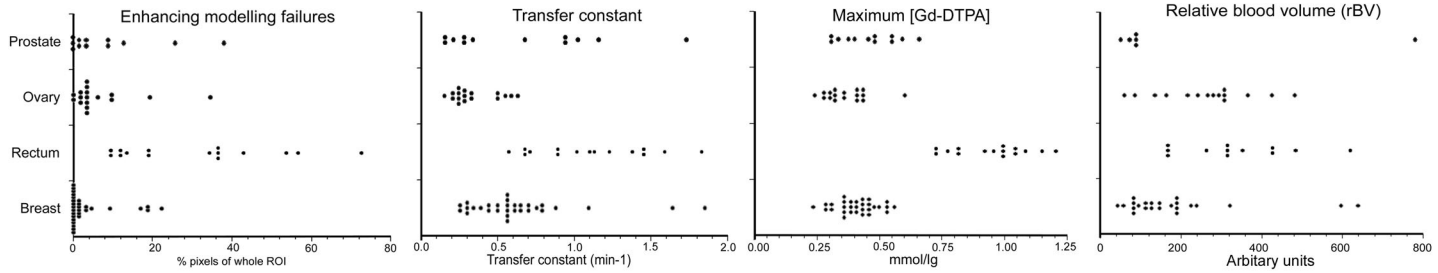
A. R. Padhani[1], N. J. Taylor[1], K. J. Lankester[2], M-L. W. Ah-See[2], G. Atkin[2], D. M. Carnell[3], J. J. Stirling[1], R. Glynne-Jones[2], A. Makris[2], P. J. Hoskin[3], J. A. D'Arcy[4], M. O. Leach[4], G. J. Rustin[2]

[1]Paul Strickland Scanner Centre, Mount Vernon Hospital, Northwood, Middlesex HA6 2RN, United Kingdom, [2]Mount Vernon Hospital, Northwood, Middlesex HA6 2RN, United Kingdom, [3]Marie Curie Research Wing, Mount Vernon Hospital, Northwood, Middlesex HA6 2RN, United Kingdom, [4]CRUK Clinical MR Research Group, Institute of Cancer Research, Sutton, Surrey SM2 5PT, United Kingdom

Introduction: New therapeutic drugs that target tumour blood vessels hold out the promise of improved efficacy and tolerability in anti-cancer treatment. Early clinical data indicate that efficacy of treatment appears to vary between tumours types (greater efficacy for colorectal and renal cancers[1, 2]). Non-invasive characterization of the angiogenic state of tumours may allow rational selection of such treatments. Here we report distinct differences in the functional vascular status of four malignant human adenocarcinomas examined by multi-parametric quantitative dynamic contrast enhanced MRI (DCE-MRI). Such head-to-head comparisons using the same DCE-MRI techniques have not been previously reported.

Methods: All patients had adenocarcinomas; 30 patients with primary breast cancer, 12 with primary prostate cancer, 15 with primary rectal cancer and 17 had recurrent ovarian tumours (6 previously treated with chemotherapy). All patients underwent an identical examination protocol as follows: Spoiled gradient-echo (GRE) [FLASH] sequences with 8 different TE [5-75ms], TR=100ms, $\alpha=40^o$, 1 slice were used for R_2* measurement with the parametric R2* image calculated using a standalone IDL® least-squares fitting routine. Following this, T1W DCE-MRI images were acquired using another spoiled GRE sequence (TE=4.7ms, TR=11ms, $\alpha=35^o$, 4 slices). 40 images were acquired every 12 seconds for 8 min 5s. An injection of 0.1mmol/kg Gd-DTPA was given using a power injector at 4ml/s during the 5th data acquisition point. The data were fitted to the Tofts and Kermode model[3] using methods previously described[4] and quantitative (K^{trans}, v_e, k_{ep}, and maximum Gd-DTPA concentration) kinetic parameters were calculated. The proportions of pixels failing the modelling process were also recorded. Following this, a T_2*-weighted Spoiled GRE sequence was used to acquire data every 2 seconds over 2 minutes (TE=20ms, TR=30ms, $\alpha=40^o$, 1 slice) with 0.2mmol/kg Gd-DTPA injected at 4ml/s after 20s. These data were used to calculate relative blood volume (rBV), relative blood flow (rBF) and mean transit time (MTT) using the central volume theorem by applying a gamma variate fit function[5]. All calculations were performed using in-house software (Magnetic Resonance Imaging Workbench – Institute of Cancer Research, London). Regions of interest (ROI) were drawn around the tumour edge by a single experienced observer. Histograms of pixel data were obtained and median values were analyzed using the Kruskal-Wallis test using the StatsDirect™ analysis package with the level of significance set at p=0.01.

Results: Differences between tumour types were found for DCE-MRI parameters (K^{trans}, v_e, k_{ep}, [Gd-DTPA], rBF) but not for rBV, MTT or R_2* (figure). Rectal cancers were noticeably different (P=0.001) in the proportion of enhancing modelling failures (34%) and K^{trans} and maximum [Gd-DTPA] for rectal cancer were higher than other tumours (p=0.001). Ovarian cancer had the lowest K^{trans} and v_e (p=0.01) but had rBV and rBF values that were not statistically different to rectal and breast cancer.
There were no correlation between T1 and T2* weighted DCE-MRI kinetic parameters in rectal cancers. However, K^{trans} correlated significantly with rBF and rBV in both breast and ovarian cancer (r_s =0.60, p<0.01 and r_s = 0.55, p<0.05) and (r=0.76, p=0.001 and r= 0.75, p=0.002).



Discussion: Primary rectal adenocarcinoma has a distinct functional signature on DCE-MRI that is likely to be related to the underlying state of perfusion, angiogenesis and degree of vessel maturation[6]. Greater modelling failures and higher estimates of K^{trans} and maximum [Gd-DTPA] in rectal cancer may be related to greater blood flow/volume; however we did not detect a correlation between these parameters and independent T_2* DCE-MRI estimates of rBV and rBF. Interestingly, positive correlations between T_1- and T_2*-weighted kinetic parameters were seen for both breast and ovarian cancers. The lower K^{trans} and v_e in recurrent ovarian cancer may be due to previous chemotherapy which has the effect of maturing vasculature. It is unlikely that our findings are due to technical factors, as imaging protocols and analysis methods for all tumours were similar. These results may be of importance when evaluating the efficacy of antiangiogenic/vascular targeting drugs.

References:

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