Relationship between VEGF receptor expression and DCE-MRI tracer kinetic parameters in advanced ovarian cancer

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Introduction Vascular endothelial growth factor (VEGF), and its receptors VEGFR-1 and VEGFR-2, are key angiogenic mediators in ovarian cancer[1] that greatly enhance tumor vascularity and are associated with poor prognosis[2]. Consequently, there has been an increase in the development of anti-VEGF therapies and integration of imaging strategies to help elucidate the underlying tumor physiology and assess drug efficacy[3]. Dynamic contrast-enhanced MRI (DCE-MRI) may be used to quantify tumor microvascular characteristics through the application of a tracer kinetic model to estimate parameters such as K^{trans} (contrast agent transfer coefficient, a composite of blood flow and capillary permeability) and v_p (blood plasma volume). In this study we explore the relationships between serological expression of soluble (s) VEGFR-1 and VEGFR-2 and ovarian cancer angiogenesis as quantified by DCE-MRI in order to gain an insight into the sensitivity of DCE-MRI to such processes.

Methods *Imaging:* The local ethics committee approved the study and 8 patients with histologically or cytologically confirmed ovarian or primary peritoneal carcinoma were recruited into the study. All patients had completed chemotherapy treatment at the time of entering the study and had measurable residual disease. Imaging was performed at 1.5 T using a Philips Intera (Philips Healthcare, Best, The Netherlands) MR scanner at baseline (study entry), 4, 8, 12, 18 and 26 weeks. Patients were withdrawn from the study if disease progression (RECIST criteria) was confirmed. 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 = 25, 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.

DCE-MRI analysis: Regions of interest (ROI) were defined for the whole tumor volume. Enhancing voxels were identified and the extended Kety model[4] was fitted to each voxel's time series using an automated arterial input function[5]. 3D maps of K^{trans}, v_e and v_p were generated and summarized using median (K^{trans}, v_e) and mean (v_p) summary statistics for each tumor.

Serological markers: Plasma samples were obtained immediately prior to the DCE-MRI scan. Following preparation procedures, samples were analyzed in duplicate using a validated, multiplex ELISA method (Searchlight multiplex ELISAs, Aushon Biosystems). Angiogenic markers,VEGFR-1 and VEGFR-2, were analyzed.

Statistical analysis: All paired DCE-MRI and serological markers were pooled on the basis that there was no therapeutic intervention. Scatter plots of K^{trans}, v_p, sVEGFR-1 and sVEGFR-2 were generated and a bivariate Spearman's correlation analysis was used to test for significance ($p < 0.05$).

Results Significant correlations between sVEGFR-1 and sVEGFR-2 with both v_p and K^{trans} were observed (Fig. 1). An inverse relationship was seen between sVEGFR-1, sVEGFR-2 and v_p ($p = 0.011$ and 0.001 respectively). A positive correlation between the serological markers and K^{trans} was observed ($p < 0.001$ and 0.026 respectively). K^{trans} and v_p were not co-related ($p = 0.225$), which suggests (but does not guarantee) that in these tumors K^{trans} reflects vessel permeability rather than blood flow[3].

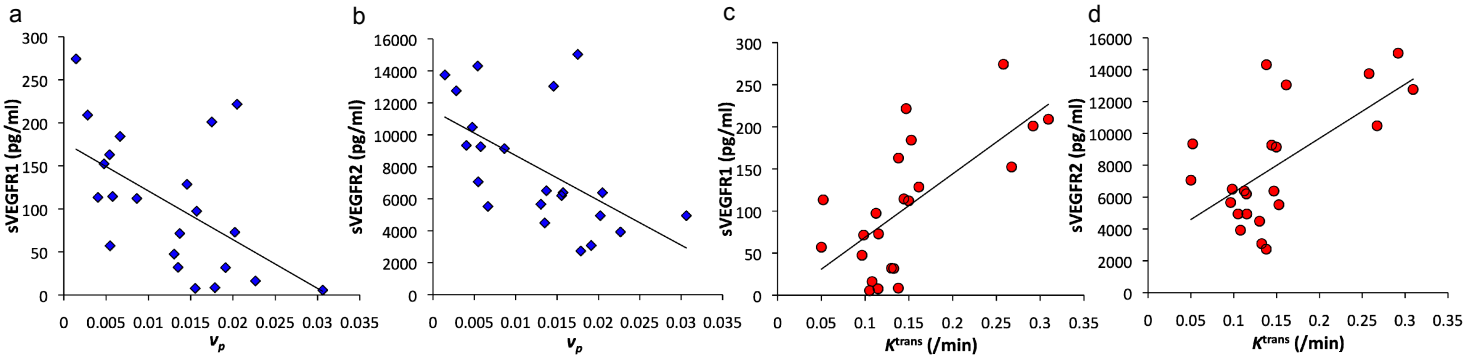

Figure 1: Scatter plots showing correlations between v_p (unitless) and sVEGFR-1 (a) sVEGFR-2 (b) (CC = -0.529 and -0.640 respectively) and between K^{trans} (units = min^{-1}) and sVEGFR-1 (c) and sVEGFR-2 (d) (CC = 0.702 and 0.474 respectively). The black line through the data shows the line of best fit.

Discsussion This study has demonstrated the differing relationships of tracer kinetic model parameters, K^{trans} (reflecting blood vessel permeability) and v_p (blood plasma volume), to the angiogenic mediators sVEGFR-1 and sVEGFR-2 in this group of tumors. One possible explanation for these observations is that in tumors where the blood supply is reduced, and that therefore have a reduced v_p, the resulting hypoxic stress leads to overexpression of VEGF and its receptors[6]. This relationship is clearly seen in Fig. 1a/b for both sVEGFR-1 and sVEGFR-2. In the same manner, the hypoxic stress and associated increase in VEGF production with upregulation of sVEGFR-1 and sVEGFR-2 leads to an increase in vessel permeability, measurable by K^{trans} (Fig. 1c/d). These findings suggest that the combination of low v_p, high K^{trans} and high sVEGFR-1/2 may infer local activation of the hypoxia-VEGF system in ovarian tumors. This study demonstrates that appropriate DCE-MRI modeling allows extraction of information specific to the angiogenic process and that these tumor level findings can be related to circulating biomarkers.

References **1.** Kumaran GC et al. Br J Cancer 2009;100(1):1-7. **2.** Raspollini MR et al. Int J Gynecol Cancer 2004;14(5):815-823. **3.** O'Connor JP et al. Clin Cancer Res 2009. **4.** Tofts, P. J Magn Reson Imaging 1997;7(1):91-101. **5.** Parker GJ et al. Magn Reson Med 2006;56(5):993-1000. **6.** North S et al. Cancer letters 2005;218(1):1-14.