Dynamic MRI assays of endothelial permeability for the non-invasive differentiation of tumors with high from tumors with low VEGF-activity

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Purpose: To evaluate dynamic MRI assays of endothelial permeability for their potential to differentiate tumors with high intrinsic vascular endothelial growth factor (VEGF) activity from tumors with low VEGF-activity by correlating dynamic MRI assays of endothelial permeability with immunohistochemical measurements of VEGF on a tumor-by-tumor basis.

Methods and Material: Subcutaneous tumor xenografts were grown in athymic rats (n=13) from two poorly differentiated, estrogen-receptor-negative human breast cancer cell lines; MDA-MB-231 (n=5) with a high level of intrinsic VEGF-activity and MDA-MB-435 (n=8) with a low level of intrinsic VEGF-activity. Dynamic contrast-enhanced MRI was performed at 2.0T using the macromolecular contrast agent albumin-$(Gd\text{-}DTPA)_{27}$ (1). Quantitative estimates of tumor microvessel permeability (K^{PS}; µl/min·100cm^3), based on a two-compartment kinetic model (2), were correlated with area-density (%) measurements of VEGF-immunoreactivity on tumor sections.

Results: Tumor endothelial permeability, assayed as the endothelial transfer coefficient K^{PS}, was significantly higher ($p<0.03$) in MDA-MB-231 tumors (K^{PS}=58±30.9 µl/min·100cm^3) than in MDA-MB-435 tumors (K^{PS}=24±8.4 µl/min·100cm^3, $p<0.05$). Correspondingly, VEGF area-density in MDA-MB-231 tumors was significantly higher (27.3±2.2%) than in MDA-MB-435 human breast cancer xenografts (10.5±0.5%, $p<0.05$). Individual measurements for the two groups did not overlap. The correlation between K^{PS} values and measurements of VEGF area-density was significant ($r=0.73$, $p<0.01$).

Conclusion: Dynamic MRI assays of endothelial permeability have the potential to non-invasively assess VEGF-activity in tumors and could be clinically applicable to define the suitability of patients for VEGF-inhibiting anti-angiogenic drug therapy.

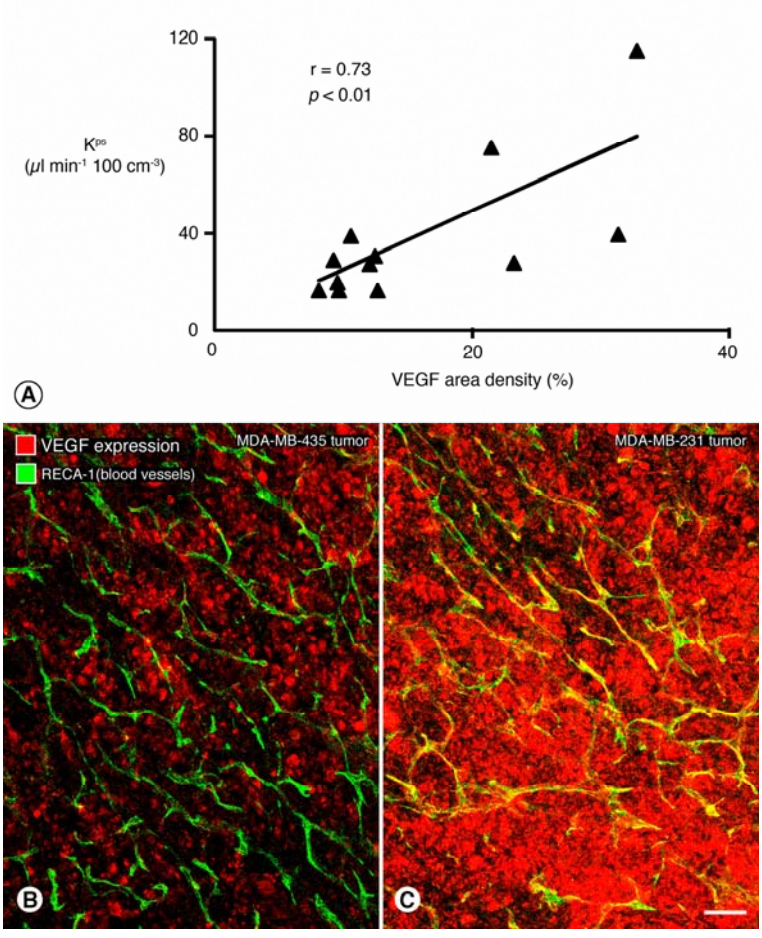

Figure (A). Graph showing the correlation, r = 0.73, p < 0.01, for each examined MDA-MB-435 and MDA-MB-231 tumor, between the MRI-assayed endothelial transfer coefficient K^{PS} (µL · min^{-1} · 100 cm^{-3}) and the immunohistochemically-assessed VEGF-area density (%). All values of VEGF area density greater than 20% are from MDA-231 tumors. Solid line denotes the best fit.

Figure (B, C) Confocal microscopic images of MDA-MB-435 and MDA-MB-231 tumors, stained for VEGF (red) and blood vessels (green), showing the relatively low expression of VEGF in MDA-MB-435 tumor (**B**) and the high expression of VEGF in MDA-MB-231 tumor (**C**). Scale bar: 120 µm in (**B**, **C**).

References:

1. Van Dijke CF et al Acad Radiol 9 (Suppl 1) 2002; 257–260.
2. Cyran CC et al J Magn Reson Imaging. 2008; 27(3):581-9.