

Quantitative MRI Assays of Angiogenesis with Microscopic Correlation in a Bevacizumab-Treated Human Breast Cancer Model

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Purpose: To compare and correlate two fundamentally different techniques for measuring tumor vascular richness: in vivo contrast-enhanced MRI and perfusion-dependent fluorescent microscopy

Materials and Methods: 13 female nude rats with implanted MDA-MB 435 breast cancers received angiogenesis-inhibiting treatment, bevacizumab, at dose levels of 0.1 mg (n = 5) and 1.0 mg (n = 3) or saline (n = 5) every third day for a total of four doses. The treatment was initiated when tumors reached a diameter of 1 cm. 24 hours after completion of treatment, dynamic MRI enhanced with a macromolecular blood-pool contrast agent was performed using a 2T system with regions of interests measured over the tumor and in the IVC. Estimates of tumor fractional blood volume were calculated based on the dynamic MRI data. Immediately after each MRI experiment, 100 µg of FITC-labeled *Lycopersicon esculentum* lectin in 1 ml saline was administered intravenously to the living animal distributing to the perfused microvessels. Two minutes later, the vasculature was perfused and flushed for 2 minutes with fixative (PFA). Tumors were then removed and further processed for microscopic analysis to determine the percentage of lectin area density, a microscopic parameter of vascular richness.

Results: MRI-based estimates of fractional plasma volume (fPV) were significantly higher in control tumors ($5.1 \pm 0.59\%$ [mean \pm S.E.]) when compared to the 0.1 mg ($2.9 \pm 0.48\%$) and 1.0 mg ($2.2 \pm 0.75\%$) bevacizumab-treated breast cancers, $p < 0.05$. Microscopic immunohistochemical assays of the same tumors demonstrated lectin area densities of $15.5 \pm 1.5\%$ in control tumors, $10.9 \pm 0.3\%$ in the 0.1 mg bevacizumab group and $5.8 \pm 0.3\%$ in the 1.0 mg bevacizumab group. Comparison of the two bevacizumab treatment groups with the control group yielded significant differences, $p < 0.01$. Correlation of MRI-derived estimates of fPV and microscopic measurements of lectin-area densities was strong and significant: $r^2 = 0.74$, $p < 0.001$.

Discussion: The richness of vascularity, shown microscopically by the percentage of lectin area density is in good proportional agreement with MRI estimates of fractional plasma volume in control and angiogenically inhibited tumors. Results from both methods serve to confirm and validate each other.

Conclusion: Fractional plasma volume (fPV), a quantitative MRI measurement of vascular richness, can be estimated reliably in cancers by non-invasive dynamic MRI using a prototype macromolecular blood-pool contrast agent.