Heterogeneity of Tumor Vasculature and Antiangiogenic Intervention by MR Angiography and DCE-MRI Investigation

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TARGET AUDIENCE: Cancer researchers and radiologists.

PURPOSE: Solid tumor vasculature is intrinsically heterogeneous, which presents challenges to antiangiogenic intervention as well as the evaluation of its therapeutic efficacy. Here we evaluated the spatially differential tumor vascular changes caused by combination bevacizumab/paclitaxel therapy using a combined analysis of MR angiography (MRA) and DCE-MRI data.

METHODS: Tumor vasculature of MCF-7 breast tumor mouse xenografts was studied by a combination of MRA and DCE-MRI with albumin-Gd-DTPA high-molecular weight contrast agent using a heavily T1-weighted short saturation recovery gradient echo sequence (1). Tumor macroscopic vasculature was extracted from the early enhanced images. Tumor microvascular parameters were obtained from the pharmacokinetic modeling of the DCE-MRI data. A spatial analysis of the microvascular parameters relative to the distance to the macroscopic vasculature was used to evaluate the vascular effects of a 12-day three cycles of bevacizumab and paclitaxel combination treatment by intraperitoneal injection, each at 10 mg/kg every four days, on MCF-7 breast tumor xenograft-bearing mice. Saline treated mice were used as controls.

RESULTS: Strongly enhanced macroscopic feeding vessels were detected extending from the body flank into the tumor periphery (Fig. 1). Tumor macrovasculature map (Fig. 2) was extracted from the early enhanced T1 weighted images. A 3D pixel-by-pixel map of distance (Fig. 3a, shown in 2D) to the nearest macroscopic vessel (Fig. 3b, shown in 2D) was subsequently generated. Tumor areas near these large vessels display higher average microvascular volume (*VV*) (Fig. 4) and permeability (*PS*) (Fig. 5) in general. Average *VV* decreased rapidly with increasing distance to these vessels and leveled off at around 250 µm (Fig. 4). The macroscopic vessels were not affected by the bevacizumab/paclitaxel combination therapy. A higher portion of the tumors was within close proximity of these large vessels after the treatment, concomitant with tumor growth retardation. There was a significant decrease in *VV* and *PS* in these tumor regions (Fig. 6 & 7), at distance to the vessel ≤ 1mm, $p < 2\times10^{-5}$.
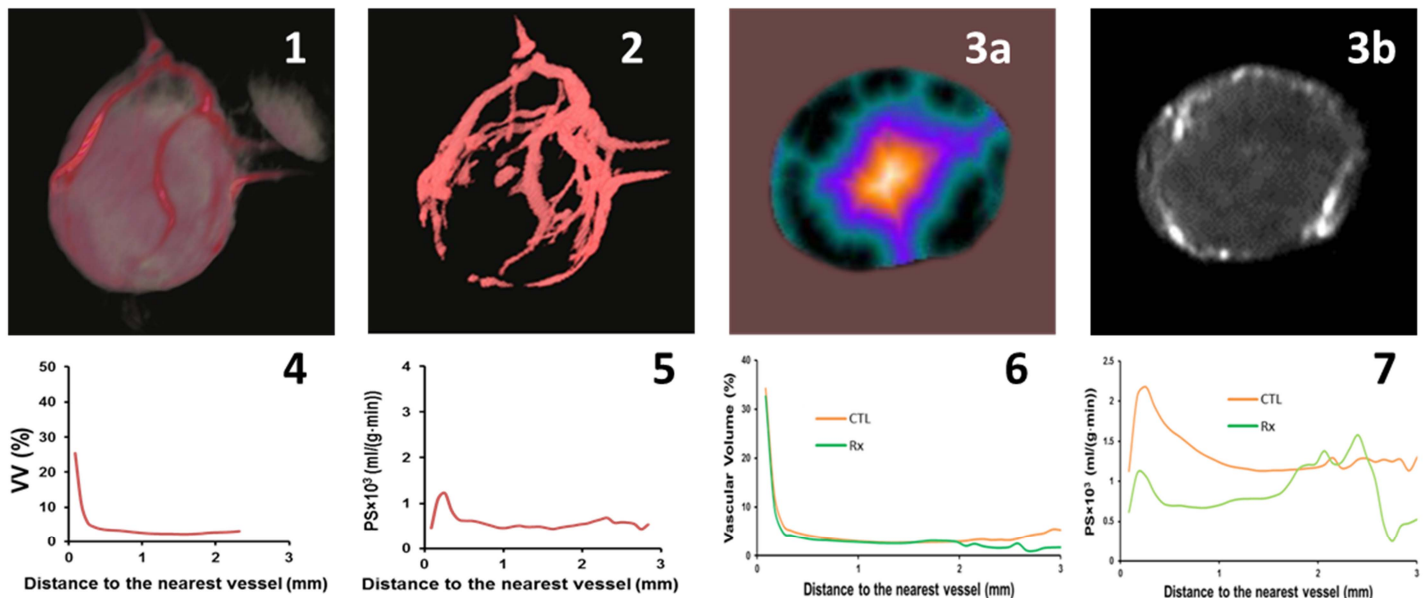
DISCUSSION and CONCLUSION: Despite a reduction of *VV* and *PS* in the tumor regions near the macroscopic vessels, bevacizumab/paclitaxel combination therapy did not significantly reduce the blood supply to the MCF-7 breast tumor due to the existence of the macroscopic tumor vessels. These vessels can survive antiangiogenic therapy, replenish the blood and nutrient supply to the remaining tumor cells, and maintain an avenue for tumor growth and expansion. Such finding is consistent with the modest survival benefits of adding bevacizumab to current treatment regimens for some types of cancers.

1. Zhu W, Kato Y, Artemov D. Water exchange-minimizing DCE-MRI protocol to detect changes in tumor vascular parameters: effect of bevacizumab/paclitaxel combination therapy. Magn Reson Mater Phy. 2013.