

## Quantification of Tumor Vascular Heterogeneity and Efficacy of Antiangiogenic Therapy

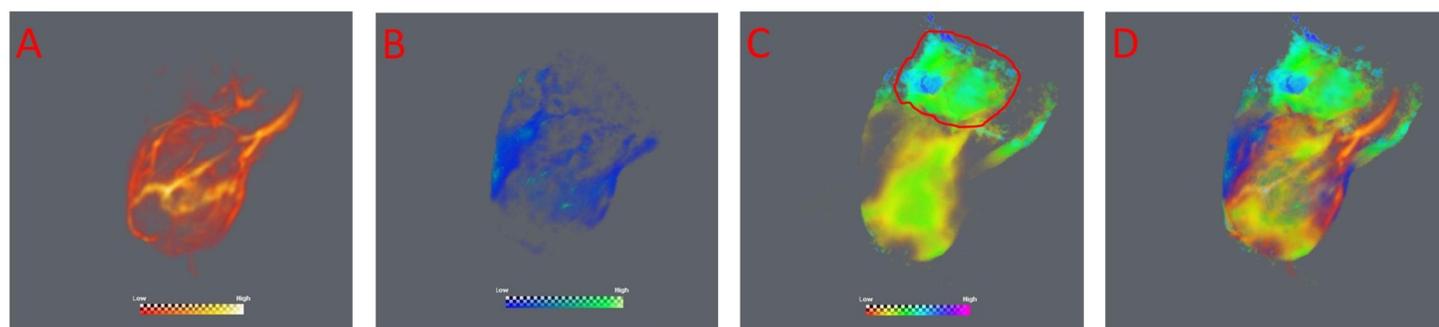
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**Introduction:** Tumor vasculature heterogeneity is highly conspicuous on DCE-MRI scans. Typically tumor peripheral area is more angiogenically active and has abundant blood supply while vasculature in the center area is less developed. However, this wealth of spatial information is under-utilized when DCE-MRI quantitative parameters are simply presented as averages over the entire tumor. The clinical application of quantitative DCE-MRI biomarkers in oncology remains limited due to poor correlation. It is proposed here that new DCE-MRI quantitative analysis based on tumor macroscopic vascular structure may produce more biologically relevant biomarkers that reflect the vascular heterogeneity. Preliminary results of the vascular changes induced by a bevacizumab/paclitaxel combination therapy are presented.

**Material and Methods:** MCF-7 breast tumor xenograft-bearing mice were treated with three doses of bevacizumab and paclitaxel by intraperitoneal injection, each at a dose of 10 mg/kg every five days. DCE-MRI images were acquired before and at the conclusion of the treatment with a heavily T<sub>1</sub> weighted 3D saturation recovery gradient echo sequence using a recovery delay of 20 ms, enhanced by albumin-Gd-DTPA. Pixel-by-pixel vascular permeability surface area product (PSP) parameters were obtained through a linear regression of the albumin-Gd-DTPA concentration vs time. Enhancing tumor vessels were selected by a semi-automated segmentation method from the early enhanced images. Pixel-by-pixel vessel distance maps were generated by calculating the distance between each voxel with non-zero PSP to the nearest vessel.

**Results and Discussions:** Three-dimensional volume rendering of the tumor vasculature map, PSP map, vessel distance map, and an overlay of all three maps are shown in Figures A, B, C, and D, respectively. Figure A shows that MCF-7 tumor is indeed very



heterogeneous and only the peripheral area is highly vascularized. Figure B shows that vascular permeability in the tumor is closely associated with its enhanced vasculature. Permeability is mainly observed at the peripheral area near the blood vessels. Tumor core is avascular and almost non-permeable. Figure C confirms these observations: permeable area in the tumor rim is in the close vicinity to the vessels while the tumor core is characterized by both low permeability and long distance from the blood vessels. The hyper-intense area within the outline shows that blood vessels that feed to the tumor are not permeable.

Average distance of all permeable voxel to the nearest blood vessels over the entire field of view ( $D_{ave}$ ) of the mice before and after treatment is shown at the table below. All voxels in the tumor area were segmented by the distance between the voxel and the nearest blood vessel. Average of PSP of the voxels with a distance above and below  $D_{ave}$  were calculated and shown. Area close to the blood vessels is defined as having a distance to the nearest vessel below  $D_{ave}$  while area away from vessels as having a distance above  $D_{ave}$ . Averages of the pixel-by-pixel PSP values over the entire tumor are also shown in this table. There were three mice in each group.

	Average distance of permeable pixels to the nearest vessel ( $\mu\text{m}$ )	Average PSP of areas close to the blood vessels ( $\text{min}^{-1}$ )	Average PSP of areas away from the blood vessel ( $\text{min}^{-1}$ )	Average PSP of entire tumor ( $\text{min}^{-1}$ )
Before treatment	6.8	0.0046	0.0041	0.0037
After treatment	8.1	0.0021	0.0023	0.0016

Results in this table show that bevacizumab/paclitaxel combination therapy reduced tumor permeability. An increase in the distance between the permeable voxels to their nearest blood vessels was also observed, suggesting the pruning of the tumor microvasculature by the combination therapy.

**Conclusion:** DCE-MRI analysis based on tumor vascular structure can provide quantitative tumor vascular heterogeneity information. Average PSP value over the tumor as well as average PSP value segmented by the distance to the blood vessels show that bevacizumab/paclitaxel combination therapy reduced tumor permeability.

**Acknowledgement:** We thank Mr. Gary Cromwell for mouse tumor inoculation, Dr. Noriko Mori for the preparation of the albumin-Gd-DTPA used in this study, Eugene Kim for help in figure preparation, and Meiyappan Solaiyaappan and Dr. Arvind Pathak for stimulating discussions.