Abnormal Tumor and Peritumor Vasculature and Metabolism Differentiate Primary from Metastatic Brain Tumors

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TARGET AUDIENCE: Clinicians, biologists and researchers involved in imaging studies of human brain tumors.

PURPOSE: The mechanisms behind tumor angiogenesis and growth are not fully understood. Malignant neovascularisation includes, among others, arteriogenesis and co-option of peritumor vessels by expression of vascular endothelial growth factors (VEGF) [1]. Microvascular proliferation from VEGF expression is a key factor for growth of glial neoplasms and VEGF concentrations in the cystic fluids of human glioblastomas (GBMs) are also known to be hundredfold higher than in serum [2]. Here, we use *Vessel Architectural Imaging* (VAI) [3] to reveal mechanisms of malignant neovascularization in GBMs and in regions of peritumoral edema. We compare our results to metastatic brain tumors (METs) which have a different phenotype to that of GBMs and typically displace surrounding brain parenchyma during growth rather than invading it [4].

METHODS: Voxel-wise estimations of vessel calibers and relative oxygen saturation levels (ΔSO_2) were acquired by VAI using combined gradient-echo and spin-echo dynamic susceptibility contrast MRI at 3T (Philips Ingenia or Siemens TimTrio/Skyra) on 13 pre-surgical adult patients with GBMs and 8 patients with METs (3 from malignant melanomas and 5 from non-small cell lung cancer) [3, 5, 6]. Regions of enhancing tumor (ROI_{tumor}) and edema (ROI_{edema}) were identified on contrast-enhanced T_1-weighted and FLAIR images, respectively. In addition, peri-edematous ROIs containing a +1 and +5 voxel wide dilation of the region with FLAIR signal abnormality ($ROI_{edema+1}$, $ROI_{edema+5}$) were created. VAI parameters were slice-wise normalized to the corresponding mean value in normal-appearing tissue and compared using Mann-Whitney tests with Holm-Bonferroni corrections for multiple comparisons.

RESULTS: Example images of ΔSO_2 from ROI_{edema} overlaid on contrast-enhanced T_1 MRIs are shown in **Fig. 1A** for a GBM patient and in **Fig. 1C** for a MET patient. Levels of ΔSO_2 were found to be higher in GBMs than METs from ROI_{tumor} to $ROI_{edema+1}$ ($P < 0.05$) (**Fig. 1B**). Compared to normal tissue, ΔSO_2 levels in GBMs were higher in ROI_{tumor} ($P < 0.05$) while lower in edematous regions of METs ($P < 0.05$). The corresponding vessel calibers in ROI_{tumor} of GBMs ($P < 0.01$) and METs ($P < 0.05$) were approximately 100% and 50% bigger than reference tissue, respectively. Vessel calibers of GBMs were also larger than those of METs ($P < 0.01$) (**Fig. 1D**).

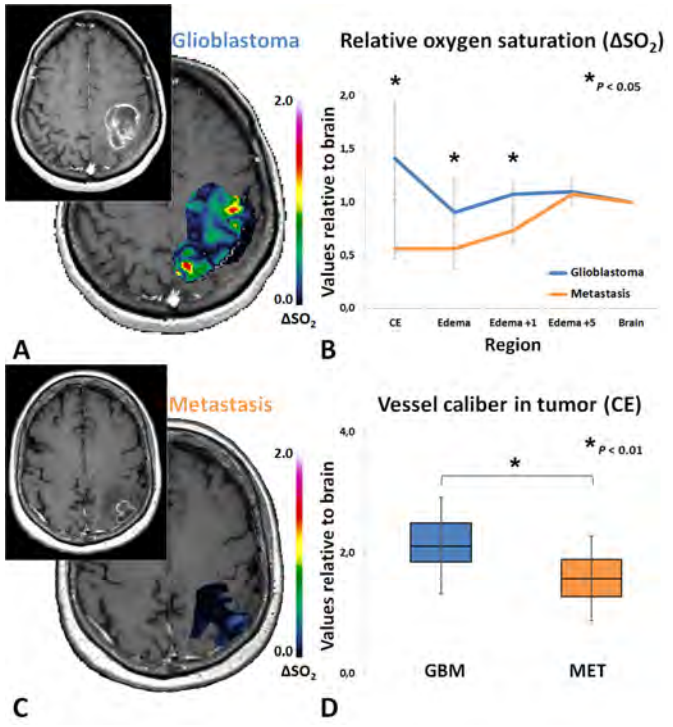

Figure 1 - Vessel Architectural Imaging: Example images of contrast-enhanced (CE) T_1-weighted MRIs of a patient with a glioblastoma (**A**) and a patient with a metastatic brain tumor from non-small cell lung cancer (**C**). The images also show corresponding ΔSO_2 levels representative of the CE and edema regions. The ΔSO_2 levels of GBMs are markedly higher than METs for both CE and regions of peritumoral edema (**B**). The vessel calibers of GBMs are larger than those of METs and normal-appearing tissue ($P < 0.01$) (**D**).

DISCUSSION: Our data shows that the vascular signature of GBMs is markedly different from that of METs in both tumor and peritumoral regions. Upregulated levels of ΔSO_2 and vessel calibers in infiltrative GBMs suggest an active crosstalk between early cancer angiogenesis and metabolism reaching well beyond contrast-enhanced tumor regions [1, 4, 7]. This is in stark contrast to that of METs, where low levels of ΔSO_2 indicate a dramatically different vascular phenotype with vasogenic edema consisting mostly of increased extracellular water. Therefore, we believe VAI can also help discriminate between tumor-infiltrative and vasogenic edema. Collectively, our findings suggest different microvascular environments involved in the growth and dissemination of GBMs compared to METs, which may be explored for differential diagnosis as well as to help guide conventional and targeted treatment options.

CONCLUSION: Our study suggests that there are marked differences in tumoral and peritumoral vascular microenvironments in primary and metastatic malignant brain tumors and that advanced MRI techniques may give valuable insights into the mechanisms of angiogenesis and growth in brain tumor patients *in vivo*.

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