

Hybrid functional diffusion and perfusion maps for evaluation of gliomas

B. M. Ellingson^{1,2}, D. P. Bedekar^{1,2}, M. G. Malkin^{1,3}, S. D. Rand^{1,2}, A. Hoyt⁴, J. Connelly³, S. N. Kurpad^{1,4}, and K. M. Schmainda^{1,2}

¹Translational Brain Tumor Program, Medical College of Wisconsin, Milwaukee, WI, United States, ²Department of Radiology, Medical College of Wisconsin, Milwaukee, WI, United States, ³Department of Neurology, Medical College of Wisconsin, Milwaukee, WI, United States, ⁴Department of Neurosurgery, Medical College of Wisconsin, Milwaukee, WI, United States

Introduction

In vivo identification of tumor cell density and vascularity are critical parameters in the assessment and treatment of human gliomas.¹ Diffusion and perfusion MRI are non-invasive techniques that can be applied in vivo to elicit insight into the cellular and vascular microenvironments. Functional diffusion maps (fDMs)² and functional perfusion maps (fPMs)³ were developed to examine voxel-wise changes in apparent diffusion coefficient (ADC) and relative cerebral blood volume (rCBV) during serial MRI comparisons, thus providing spatial localization of changes in cellularity and vascularity within brain tumors. In the current study we have merged these two techniques into a Hybrid Functional Diffusion and Perfusion Map in order to localize and quantify regions with both increasing cellularity and increasing vascularity during treatment with the anti-angiogenic agent bevacizumab.

Methods

Eight patients with recurrent intracranial tumors were enrolled in the current study. Baseline MRI sessions were performed prior to treatment with bevacizumab (10mg/kg) and irinotecan (125mg/m²), and multiple MRI sessions were performed during treatment. MRI sessions consisted of clinical MRI (SPGR, FLAIR, and pre/post-contrast T1-weighted images), perfusion MRI (dynamic susceptibility contrast, or DSC-MRI), and diffusion MRI (DWI). DSC-MRI estimates of rCBV were corrected for any confounding leakage effects and standardized as previously described.⁴ Estimates of ADC were calculated from the DWI obtained at $b = 0$ and $b = 1000$ s/mm². Registered sequential diffusion weighted images were used to calculate fDMs, within the FLAIR abnormalities, using ADC thresholds of 0.55×10^{-3} mm²/s, as per the fDM protocol.² Voxels were classified as decreasing (hypercellular, blue), increasing (hypocellular, red), or not changing (green) according to this threshold. Similarly, fPMs were calculated from registered sequential rCBV maps. With the FLAIR abnormality, the fPM voxels were classified as decreasing (hypovascular, blue), increasing (hypervascular, red), or no change (green) using a threshold of change of 100%. Hybrid fDM+fPMs were created by spatially determining regions of hypercellularity (blue regions from fDMs), hypervascularity (red regions from fPMs), and regions containing both hypercellularity and hypervascularity (yellow voxels in hybrid fDM+fPMs, in mL) were calculated after each MRI scan session.

Results

Hybrid fDM+fPMs were useful in spatially localizing high-risk lesions in all patients observed in this study. Fig. 1 illustrates one example of clinical MRI (FLAIR), fDM, fPM, and hybrid fDM+fPM localization. The average spatial separation between hypercellular and hypervascular clusters was 2.02 ± 0.33 cm. Surprisingly, the volume of hypercellularity and hypervascularity resulted in distinctively different temporal profiles easily categorized into either vascular-independent (Pearson's Correlation Coefficient of $R^2 < 0.5$) or vascular-coupled tumor growth ($R^2 > 0.5$; Fig. 2).

Discussion

Hybrid fDM+fPMs represent a new method of combining multimodal MRI datasets to both spatially localize and temporally monitor high-risk regions of recurrent brain tumors. This technique may be useful in pre-surgical planning and/or image-guided biopsy of lesions having a high probability of recurrence. Trends in the volumes of hypercellularity, hypervascularity, and hypercellularity+hypervascularity from hybrid maps suggest two different tumor types may be prevalent in recurrence during treatment with the anti-angiogenic agent bevacizumab: vascular-independent and vascular-coupled tumor growth. These two tumor types likely represent two distinct populations (or phenotypes) of tumor cells: infiltrative tumor cells that thrive in ischemic/hypoxic conditions (such as "stem-like" tumor cells) and tumor cells that proliferate largely in the presence of high blood volume.

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References

1. Zonari P, Baraldi P, Crisi G. Multimodal MRI in the characterization of glial neoplasms: the combined role of single-voxel MR spectroscopy, diffusion imaging, and echo-planar perfusion imaging. *Neuroradiology* 2007;49(10):795-803.
2. Moffat BA, Chenevert TL, Lawrence TS, et al. Functional diffusion map: A noninvasive MRI biomarker for early stratification of clinical brain tumor response. *Proc Natl Acad Sci* 2005;102(15):5524-5529.
3. Galbán CJ, Hamstra DA, Meyer CR, et al. The functional perfusion map: A novel imaging biomarker for early prediction of tumor patient response. *Proc Intl Soc Mag Reson Med* 2008;16:2194.
4. Madabhushi A, Udupa JK. New methods of MR image intensity standardization via generalized scale. *Med Phys* 2006;33(9):3426-3434.

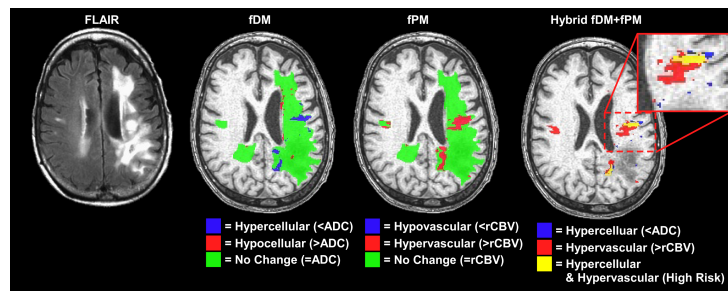


Figure 1: Clinical MRI (FLAIR), functional diffusion map (fDM), functional perfusion map (fPM), and hybrid fDM+fPM for a single patient on a single scan day showing regions of hypercellularity (blue in hybrid maps), hypervascularity (red in hybrid maps), and both hypercellularity and hypervascularity (yellow in hybrid maps). Spatial localization of high-risk regions may be useful in pre-surgical planning and image-guided biopsy.

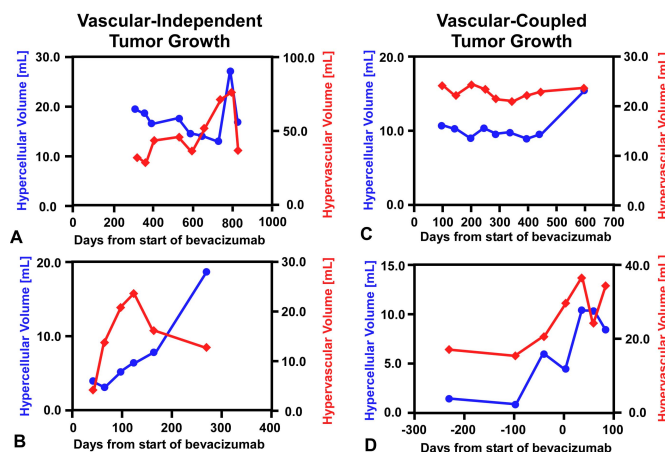


Figure 2: Trends in hypercellular volume and hypervascular volume for four of the eight patients in this study. These trends suggest two distinct tumor populations may flourish during treatment with the anti-angiogenic agent bevacizumab: vascular-independent (A-B) and vascular-coupled (C-D) tumor growth. These tumor cell populations may likely represent differing tumor cell phenotypes, where vascular-independent tumor regions may represent CD133 positive or "stem-like" tumor cells.