

DETECTION OF PRIMARY AND SECONDARY BRAIN TUMOURS USING MOLECULARLY-TARGETED MAGNETIC RESONANCE IMAGING

Imaging Pre-Clinical

S. Serres¹, M. Kirkman¹, N. de Pennington¹, C. Bristow¹ and N.R. Sibson¹

¹CRUK and MRC Oxford Institute for Radiation Oncology Department of Oncology, University of Oxford, Oxford, United Kingdom

Abstract

Objectives: Currently, both primary and secondary brain tumours are diagnosed and monitored clinically using passive contrast-enhanced magnetic resonance imaging (MRI). Although these methods provide reasonable information on tumour size and spatial extent, they often fail to accurately delineate tumour margins; an essential criterion for effective surgical resection and/or radiotherapy. Recent advances in molecularly-targeted MRI offer a number of advantages over conventional methodologies, including identification of specific molecular processes, such as upregulation of endothelial cell adhesion molecules (e.g. vascular cell adhesion molecule 1 [VCAM-1]), that may be particularly active in the invasive margins of the tumour. The aim of this study, therefore, was to determine whether VCAM-1-targeted MRI could facilitate improved spatial delineation of tumour margins and more accurate assessment of tumour activity.

Methods: Three cohorts of nude rats were injected intracerebrally. Cohorts 1 and 2 were injected in the left striatum with either a metastatic human breast carcinoma cell line (MDA231BR-GFP; 10,000 cells in 1µl) or a multiform glioblastoma cell line (U87-MG; 10,000 cells in 1µl), and used 4 weeks after injection. For the third cohort, animals were injected in the cerebellum with a desmoplastic medulloblastoma cell line (DAOY; 10,000 cells in 1µl) and used 8 weeks after injection. All animals underwent T1- and T2-weighted MRI to follow macroscopic structural changes, and post-gadolinium T1-weighted gradient echo 3D MRI to assess blood-brain barrier (BBB) integrity. For VCAM-1-targeted MRI, animals underwent T2* gradient echo 3D MRI after injection of microparticles of iron oxide (MPIO) functionalised with either an anti-VCAM-1 antibody (VCAM-

MPIO) or a control IgG antibody (IgG-MPIO). Immunohistochemical assessment was performed post-mortem to detect tumour cells (GFP or human Vimentin), blood vessels (CD31), vascular cell adhesion molecule-1 (VCAM-1) and a proliferative marker (Ki67).

Results: In all cases, brain tumours were detected using T1- and T2-weighted imaging and exhibited a compromised BBB using post-gadolinium T1-weighted imaging. In all cases, marked hypointensities were evident on T2*-weighted MRI following intravenous injection of VCAM-MPIO, but not IgG-MPIO, and this was particularly evident at the margins of the tumours. VCAM-1 upregulation detected immunohistochemically was significantly greater on blood vessels associated with the tumour margins than the tumour core, and co-localised with proliferative regions of the tumour, as confirmed by Ki67 immunohistochemistry. Spatial comparison of VCAM-MPIO binding and gadolinium-enhanced signal, using a 3D composite analysis method, indicated clearer delineation of tumour margins with the molecularly-targeted approach.

Conclusion: The results of this study indicate that upregulation of VCAM-1 is closely associated with the proliferative tumour margin, and that this can be detected with high sensitivity using molecularly-targeted MRI. These findings suggest that VCAM-1-targeted MRI may enable improved detection of tumour margins, as compared to the current clinical gold standard of gadolinium-enhanced MRI, for both primary and secondary tumours in the brain. Clinical application of this approach may, thus, provide a sensitive biomarker for effective surgical resection and/or radiotherapy and improved outcomes in brain tumour patients.

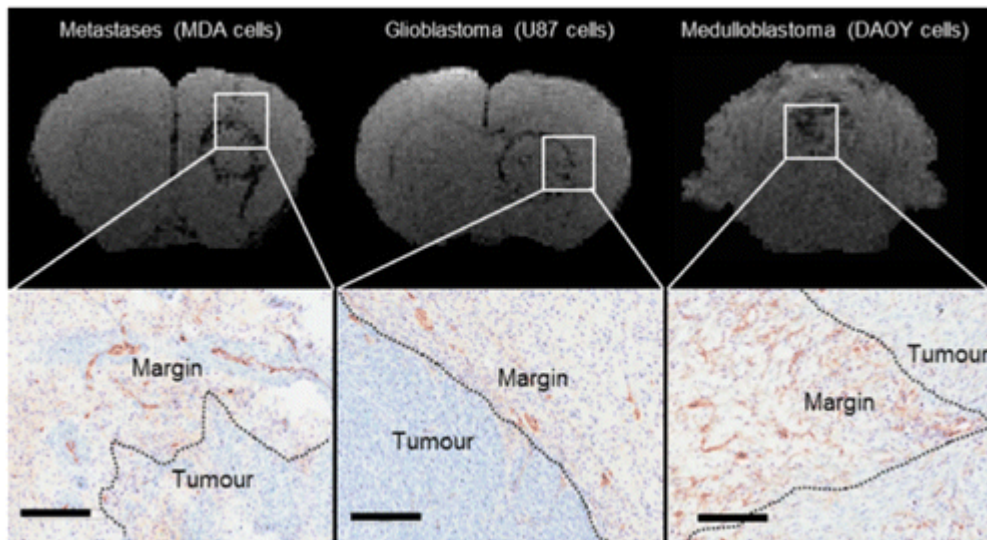


Figure 1- T_2^* -weighted MRI following intravenous injection of VCAM-MPIO reveals VCAM-MPIO binding at the margins of the tumours and correlates with immunohistochemical detection of VCAM-1 (brown).