High Resolution Magnetic Resonance Elastography of Orthotopic Murine Glioma In Vivo

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Introduction

Multiple pathologies have been characterised through loss of tensional homeostasis, including liver fibrosis, atherosclerosis and cancer. The changes that occur at a cellular level during oncogenesis, tumour progression and following treatment cause dramatic changes in the architecture and mechanical properties of both the tumour and host tissue (1,2). Noninvasive imaging biomarkers of mechanical properties of tumours will help improve the diagnosis and staging of malignancies, and both facilitate and accelerate the development of novel anti-cancer therapeutics. Innovative techniques such as magnetic resonance elastography (MRE) afford noninvasive biomarkers of the mechanical or visco-elasticity properties of tissue *in vivo*, and have been shown to afford accurate biomarkers of disease progression (3). The aim of this study was to assess the ability of MRE to noninvasively assess the visco-elastic properties of orthotopically propagated RG2 gliomas in mouse brain, shown to display an infiltrative pattern of growth and which are a faithful representation of the most common primary brain tumour, astrocytoma (4).

Materials and Methods

RG2 rat glioma cells engineered to stably express firefly luciferase ($5x10^3$) were implanted orthotopically in the brains of female NCr nude mice. The establishment of tumours was monitored by bioluminescence imaging using a Xenogen IVIS® 200. Two mice underwent MRE, performed on a 7T Bruker Microimaging system using a 3cm birdcage coil. High resolution axial T_2-weighted RARE images (150μmx150μm in plane resolution) were first acquired to localise the tumour. Subsequently, 3D steady-state MRE data was acquired, as previously described (5), using a vibration frequency of 1000Hz. Reconstructed maps of G* (complex shear modulus), Gd (elasticity) and Gl (viscosity) were reconstructed with an isotropic pixel resolution of 300μm. Tumour extent was histologically confirmed by haematoxylin and eosin (H&E) staining of tissue sections.

Results and Discussion

RG2 tumours were identified on T_2 weighted images (Figure 1a). Maps of the complex shear modulus, the sum of elasticity and viscosity, were calculated from tumour bearing slices (Figure 1b), and revealed that RG2 gliomas were softer and less viscous than the surrounding brain tissue. Such soft consistency has been previously reported for the RG2 glioma model (4), and for astrocytomas in the clinic (6). The visco-elastic properties and anatomical characteristics of the brain tissue are in good agreement with previous measurements of healthy mouse brain (5). Histology revealed relatively well-encapsulated tumours, with some areas of localised tumour invasion into the brain parenchyma (Figure 1c).

Conclusion

This proof-of-principle study demonstrates that MRE affords noninvasive measurements of the visco-elastic properties of orthotopic murine gliomas. MRE provides a powerful platform to interrogate the utility of elasticity and viscosity as emerging non-invasive imaging biomarkers of the mechanical properties of tumors, and for monitoring treatment response. Furthermore, as MRE has been successfully implemented and performed in man, these biomarkers should readily translate into the clinic (7).

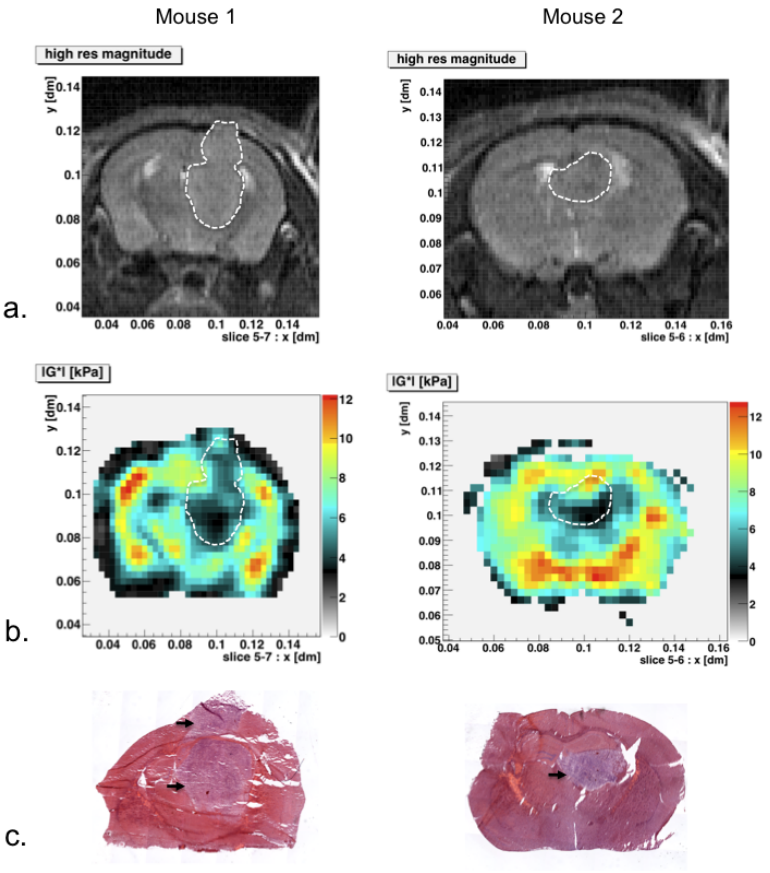

Figure 1. a. High resolution T_2-weighted images from two mice bearing orthotopic RG2 gliomas (---), **b.** their associated maps of the absolute value of the complex shear modulus G*, and **c.** composite images of whole brain H&E stained sections, with the tumour location indicated.

References. (1) Butcher *et al., Nat. Rev. Cancer* **9**:108-122 (2009), **(2)** Paszek *et al.*, *Cancer Cell* **9**:108-122 (2005), **(3)** Huwart *et al.*, *Gastroenterol.* **1**:32-40 (2005), **(4)** Aas *et al.*, *J.Neurooncol* **23**:175-183 (2005), **(5)** Diguet *et al.*, *Proc. ISMRM* 714 (2009), **(6)** Hedges, "Tumors of Neuroectodermal Origin" *in* Clinical Neuro-Opthalmology, p1413-1483, 2004, **(7)** Green *et al.*, *NMR Biomed.* **21**:755-764 (2008).

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