Noninvasive Investigation of the Viscoelastic Properties of Intracranial Tumours with Magnetic Resonance Elastography

Yann Jamin[1], Jessica K.R. Boult[1], Jin Li[1], Craig Cummings[1], Jeffrey C. Bamber[1], Ralph Sinkus[2], and Simon P Robinson[1]

[1]*Division of Radiotherapy and Imaging, The Institute of Cancer Research, Sutton, Surrey, United Kingdom,* [2]*INSERM U773, CRB3, Centre de Recherche Biomédicale Bichat-Beaujon, Paris, France*

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). Increased tissue rigidity is typically associated with a more invasive tumour phenotype, can influence therapeutic response and may also promote metastasis. Non-invasive imaging biomarkers of mechanical properties of tumours will help improve the diagnosis and staging of malignancies, and facilitate and accelerate the development of novel anti-cancer therapeutics. Innovative techniques such as magnetic resonance elastography (MRE) afford non-invasive biomarkers of the mechanical or visco-elastic properties of tissue *in vivo*, and have been shown to afford accurate biomarkers of disease progression (3). The aim of this study was to interrogate non-invasively the visco-elastic properties of three intracranially propagated tumours in mouse brain, shown to display differential infiltrative patterns of growth.

Materials and Methods

U87-MG (human adult glioblastoma, $5x10^4$, n=6), RG2 (rat ENU-induced glioma, $5x10^3$, n=5) or MDA-MB-231 (human triple negative breast adenocarcinoma, $5x10^3$, n=4) cells engineered to stably express firefly luciferase were implanted supratentorially in the brains of female NCr nude mice. The establishment of tumours was monitored by bioluminescence imaging using a Xenogen IVIS® 200. MRE was 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 localize the tumour within the mouse brain. Subsequently, 3D steady-state MRE data was acquired, as previously described (5), using a vibration frequency of 1000Hz. Maps of |G*| (complex shear modulus), G_d (elasticity) and G_l (viscosity) were reconstructed with an isotropic pixel resolution of 300µm. Tumour extent was histologically confirmed by haematoxylin and eosin (H&E) staining of formalin-fixed paraffin-embedded tissue sections.

Results and Discussion

U87, RG2 and MDA-MB-231 tumours were identified on T_2 weighted images. There was no significant difference in tumour volume between the different models (mean $35 \pm 3mm^3$). Both RG2 and MDA-MB-231, but not U87 tumours, were identifiable in maps of elasticity, G_d (Fig. 1), a consequence of their being significantly less elastic than the residual brain (Table 1). Maps of viscosity, G_l, afforded a more pronounced contrast between tumour and brain, and good delineation of the tumour boundaries in all three tumour models. Quantitative data showed that U87, RG2 and MDA-MB-231 tumours were significantly less viscous than the residual brain. The visco-elastic properties and anatomical characteristics of the brain tissue are in good agreement with previous measurements determined in healthy mouse brain (5), indicating that, at the time of acquisition, the tumour burden did not directly affect the visco-elastic properties of the residual brain. The relatively soft consistency of these intracranial tumours has also been previously reported for the RG2 glioma model (4), and for astrocytomas in the clinic (6).

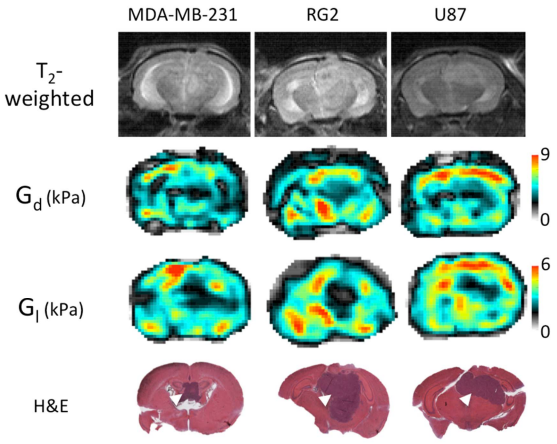

Fig. 1. High resolution T_2-weighted images from representative mice bearing orthotopic MDA-MB_231, RG2 and U87 tumours, their associated maps of elasticity G_d and viscosity G_l, and composite images of whole brain H&E stained sections, with the tumour location indicated (white arrow).

Table 1. Quantitation of tumour and residual brain |**G***|, G_d and G_l (data are mean ± 1 s.e.m, p values in parenthesis, unpaired Student's t-test.)

	Tumour			Residual Brain		
	G_d	G_l	|G*|	G_d	G_l	|G*|
MDA-MB-231	3.9 ± 0.1	2.3 ± 0.1	4.7 ± 0.2	4.4 ± 0.2 **(0.03)**	3.2 ± 0.1 **(0.005)**	5.9 ± 0.2 **(0.006)**
RG2	4.4 ± 0.2	2.6 ± 0.1	5.4 ± 0.2	4.9 ± 0.1 **(0.02)**	3.7 ± 0.2 **(<0.001)**	6.6 ± 0.2 **(<0.001)**
U87	4.5 ± 0.2	2.6 ± 0.1	5.5 ± 0.2	4.6 ± 0.2 (0.76)	3.3 ± 0.2 **(0.004)**	6.1 ± 0.2 **(0.06)**

Interestingly MDA-MB-231 tumours, previously shown to have a more diffuse infiltrative phenotype (7), were significantly softer and less viscous than the relatively well-circumscribed RG2 and U87 gliomas (Fig. 2). Histological correlates are currently being investigated to understand the pathological and phenotypic differences in these models that affect tumour stiffness, in order to identify if viscosity and elasticity can afford non-invasive biomarkers of the diffuse infiltrative phenotype in brain tumours.

MRE has been successfully implemented and performed in man (8). Given that invasion within the brain remains the biggest challenge facing oncologists treating brain tumours, MRE may provide a more accurate method to ensure the accurate delineation of tumour margins in diffuse disease, essential for surgery or radiotherapy planning, and for assessing response to chemotherapy.

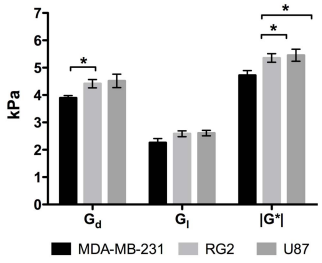

Fig. 2. Comparison of the viscoelastic properties of MDA-MB-231, RG2 and U87 tumours measured with MRE. (*, p<0.05, unpaired Student's test).

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