Exploring the Biomechanical Properties of Brain Malignancies and Their Pathologic Determinants

In Vivo with Magnetic Resonance Elastography

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Abstract

Malignant tumors are typically associated with altered rigidity relative to normal host tissue. Magnetic resonance elastography (MRE) enables the noninvasive quantitation of the mechanical properties of deep-seated tissue following application of an external vibrational mechanical stress to that tissue. In this preclinical study, we used MRE to quantify (kPa) the elasticity modulus $G_0$ and viscosity modulus $G_1$ of three intra-cranially implanted glioma and breast metastatic tumor models. In all these brain tumors, we found a notable softness characterized by lower elasticity and viscosity than normal brain parenchyma, enabling their detection on $G_0$ and $G_1$ parametric maps. The most circumscribed tumor (U-87 MG glioma) was the stiffest, whereas the most infiltrative tumor (MDA-MB-231 metastatic breast carcinoma) was the softest. Tumor cell density and microvessel density correlated significantly and positively with elasticity and viscosity, whereas there was no association with the extent of collagen deposition or myelin fiber entrapment. In conclusion, although malignant tumors tend to exhibit increased rigidity, intracranial tumors presented as remarkably softer than normal brain parenchyma. Our findings reinforce the case for MRE use in diagnosing and staging brain malignancies, based on the association of different tumor phenotypes with different mechanical properties.

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Introduction

Altered tissue stiffness through loss of tensional homeostasis is a hallmark of cancer. The changes that occur at a cellular level during oncogenesis and tumor progression cause dramatic changes in the architecture and mechanical properties of both the tumor and surrounding host tissue. Malignant tumors have been typically associated with increased tissue rigidity relative to the normal host tissue, which may influence therapeutic response and promote metastasis and invasiveness (1–3). There is also growing evidence that an increase in local stiffness may promote the malignant transformation of normal cells (4, 5).

The morphology of both tumor cells and each component of their microenvironment [vasculature, fibroblast/immune cell infiltration, and extracellular matrix, (ECM)] manifestly shape the macroscopic mechanical properties of each tumor type, and may also define aggressive, invasive, metastatic, and resistant phenotypes (6, 7). Physical palpation exploits the differences in compliance between tumor and host tissue, and has provided an invaluable, yet limited, diagnostic tool for the detection of malignancies since before the origin of modern medicine. Diagnostic imaging is an essential tool in the management of patients with brain cancer. MRI has become the methodology of choice due to its exquisite soft tissue image contrast, which enables the visualization of detailed anatomical features with high resolution. Advanced functional MRI methodologies have improved radiological-based diagnosis of brain tumors, but still demonstrate low specificity. The final diagnosis still relies on pathologic examination of the resected tumor or biopsy samples, both obtained at high risk of morbidity. Patients with grade 4 malignant glioma only have a median survival of 12 to 15 months. Although low-grade gliomas have a better prognosis, there is, as yet, no assured cure. Patients with brain metastases, which affect up to 40% of patients with metastatic cancer, have a similarly poor prognosis. With promising new targeted strategies for the treatment of patients with brain malignancies has come the unmet need for refined noninvasive imaging strategies that could provide more specific diagnostic, predictive (enabling the stratification of patients who would benefit from the treatment), and prognostic (to determine the potential to achieve favorable clinical outcome) biomarkers.
Elastography is the imaging of the mechanical properties of tissue, which may be accomplished with any conventional anatomical imaging modality such as MRI, ultrasound, X-ray, and optical imaging. Magnetic resonance elastography (MRE) is an emerging MRI methodology, which enables the quantitative and noninvasive assessment of tissue mechanical properties in vivo. MRE relies on the ability of MRI to visualize the propagation of low-frequency shear waves, in which characteristics are directly determined by the local viscoelastic properties of the tissue of interest (8). Because low-frequency waves can be mechanically applied through the skull, MRE is uniquely positioned to assess the viscoelastic properties of brain tissue in situ. MRE has already been successfully implemented in the clinic, in both healthy volunteers and patients with brain tumors (9–12).

In this study, we used MRE to investigate the viscoelastic properties of three intracranially implanted tumors with different infiltrative patterns of growth. Using histopathologic correlates, we investigated the physiologic and structural determinants of the different viscoelastic properties measured between brain parenchyma and tumors, as well as between different tumor types, and discuss the potential of MRE for the diagnosis and stratification of patients presenting with brain malignancies.

Materials and Methods

Cell Lines

U-87 MG human glioblastoma cells (ATCC; LGC Standards) engineered to stably express pCDEF1–MC52–EFl-Puro-luc, RG2 rat glioma cells (ATCC) that stably express pGL4.50[luc2/CMV/hygro] (kind gift from Dr. D. Crichton, Cancer Research Technology, The Beatson Institute for Cancer Research, Glasgow, Scotland) and luciferase-expressing MDA-MB-231 LM2-4 human glioma cells (ATCC) that stably express pGL4.50[luc2/CMV/hygro] (kind gift from Dr. D. Crichton, Cancer Research Technology, The Beatson Institute for Cancer Research, Glasgow, Scotland) and luciferase-expressing MDA-MB-231 LM2-4 human triple-negative breast carcinoma cells (provided by Dr. R. Kerbel, University of Toronto, Canada; ref. 13) were maintained in DMEM supplemented with 10% (v/v) FBS (Invitrogen, Life Technologies, The Beatson Institute for Cancer Research, Glasgow, Scotland) and luciferase-expressing MDA-MB-231 LM2-4 human triple-negative breast carcinoma cells (provided by Dr. R. Kerbel, University of Toronto, Canada; ref. 13) were maintained in DMEM supplemented with 10% (v/v) FBS (Invitrogen, Life Technologies). All cells were tested for mycoplasma at the time of tumor propagation and were found to be negative.

Animals

Six-week-old female athymic (Ncr Foxn1n mice were obtained from Charles River Ltd. All experiments were performed in accordance with the local ethical review panel, the UK Home Office Animals (Scientific Procedures) Act 1986, the United Kingdom National Cancer Research Institute guidelines for the welfare of animals in cancer research (14), and the ARRIVE (animal research: reporting in vivo experiments) guidelines (15).

Intracranial injections and bioluminescence imaging

U-87 MG (5 × 10⁶), RG2 or MDA-MB-231 cells (5 × 10⁵) were implanted supratentorially in the brains of mice. Animals were anesthetized using 1% to 2% isoflurane in oxygen (1 L/min). An approximately 1-cm incision was made in the skin on the top of the head, and a 1-mm hole drilled 2-mm posterior to the junction of sagittal and coronal sutures of the skull (bregma) and 1-mm lateral to the midline using a surgical bone microdrill (Harvard Apparatus). Cell suspension (5 μL) was then injected at a depth of 3 mm from the dura, at a rate of 2 μL/min, using a 10 μL syringe (VWR International), and a nanomite syringe pump (Harvard Apparatus). The needle was removed 3 minutes after completion of the injection, and the skin repaired with Vetbond Tissue Adhesive (3M Animal Care Products). Tumor establishment and growth were monitored with bioluminescence imaging using a Xenogen IVIS 200 system coupled with LivingImage software (Caliper Life Sciences). Luciferin (150 mg/kg; Caliper Life Sciences) was administered i.p. 10 minutes before imaging. Total photon flux was established for automatically drawn regions of interest (ROI) at a constant threshold. MRE was performed when the photon flux reached a threshold value previously determined to represent a tumor of approximately 30 to 40 mm³, a volume considered of sufficient size to acquire MRE data, but not large enough to cause neurological effects in the mice. The average time from implantation to imaging was 18 days for the U-87 MG and MDA-MB-231 tumors and 22 days for the RG2 tumors.

Magnetic resonance elastography

All MRI studies were performed on a 7T Bruker horizontal bore MicroImaging system (Bruker Instruments) using a 3-cm birdcage volume coil. Anesthesia was induced by an i.p. 10 mL/kg injection of a combination of fentanyl citrate (0.315 mg/mL) plus fluanisone (10 mg/mL; Hypnorm, Janssen Pharmaceutical), and midazolam (5 mg/mL; Roche) and water (1:1:2). Core body temperature was maintained at approximately 37 °C with warm air blown through the magnet bore.

MRE was performed as recently described (16). The mechanical vibrations were generated by an electromagnetic shaker (Bruel & Kjaer), and were transmitted through a flexible nylon rod to a square semicurved piston positioned on the mouse head within the volume coil at the isocenter of the magnetic field (Supplementary Fig. S1). Anatomical T2-weighted images [using a rapid acquisition with refocused echoes (RARE) sequence, with TE = 36 ms, TR = 4.5 s, RARE factor = 8, 40 contiguous 1-mm thick transverse slices, 1 average, matrix size 128 × 128 over a 3 × 3 cm² field of view] covering the whole brain were used for determining tumor volumes, planning of the MRE acquisition, and optimization of the local field homogeneity over the ROI using the FASTMAP algorithm. MRE was performed using mechanical excitations at a vibration frequency of 1,000 Hz, which generates mechanical waves inside the tumor with amplitude greater than 0.5 μm. A two-dimensional spin–echo sequence was modified with sinusoidal motion-sensitizing gradients synchronized to the mechanical excitation. Data were acquired in three orthogonal directions, from ten contiguous transverse slices (300-μm thick), using two averages of 64 phase-encoding steps over a 1.92 × 1.92 cm² FOV, with TE = 27 ms, TR = 1,001 ms, and 8 time sampling steps, giving an isotropic spatial sampling of 300 × 300 × 300 μm³ of the mechanical wave propagation displacement inside the tumor. The total acquisition time was approximately 51 minutes. High-resolution anatomical T2-weighted images were subsequently acquired from the same 10 contiguous transverse slices (using a RARE sequence, with TE = 36 ms, TR = 4.5 s, RARE factor = 8, 300-μm thick, 10 averages, matrix size 128 × 128 over a 1.92 × 1.92 cm² field of view).

Image reconstruction and analysis

Parametric maps of the absolute value of the complex shear modulus (|G|), elasticity G and viscosity G (where G = G + iG), were reconstructed using in-house software from the three-dimensional displacement vector measured as described above, and using the following equation (17):

\[-\rho \omega^2 \ddot{q} = G' \nabla \cdot \ddot{q} + G \nabla \times \dot{u} \in \mathbb{C}^3,\]
where $\vec{\omega}$ is the complex-valued curl of the measured displacement field $\vec{u}$, $\rho$ is the density of the material, and $\omega$ is the angular frequency. For each slice, $G_G$ and $G_v$ (kPa) were determined pixel wise from an ROI covering the whole tumor identified from T2-weighted images.

**Histological analysis**

Tissue sections (5 µm) were cut from tumor-bearing brains that had been formalin-fixed and paraffin-embedded (FFPE). FFPE sections were stained with hematoxylin and eosin (H&E), visualized by light microscopy, then blind reviewed and scored by an experienced pathologist (S. Popov) for invasive growth, the presence of necrosis, edema, and hemorrhage. Cellular density was also assessed on sections from two levels through each tumor, by counting the number of nuclei in four square ROIs from a total area of 0.01 mm² per section. Collagen I and III were stained on adjacent FFPE tissue sections using picrosirius red staining (Supplementary Materials and Methods). In addition, collagen IV deposition was detected by immunohistochemistry (rabbit polyclonal antibodies, ab6586; Abcam). Microvessel density was assessed on FFPE sections stained for the murine vascular endothelial marker CD31 (rabbit EP3095; Millipore). CD31-positive vessels were counted in four or five random fields at ×200 magnification (area per field = 0.15 mm²) and the number converted to vessels/mm². Luxol fast blue staining was also used to assess myelin fibers in adjacent sections (Supplementary Materials and Methods).

**Statistical analysis**

Statistical analysis was performed with GraphPad Prism 6 (GraphPad Software Inc.). The mean of median values for all the quantitative MRE parameters, the mean values for tumor volume, cellular density, and microvessel density were used for statistical analysis. Any significant differences in quantitative MRE parameters were identified using the nonparametric Mann–Whitney $U$ test, with a 5% level of significance. Any significant differences in tumor volume and quantitative histopathological parameters were identified using the Student two-tailed unpaired $t$ test, with a 5% level of significance. Significant correlations between the mean values for all the quantitative MRE parameters and cellular and microvessel density were determined using linear regression analysis, confirmed by using the robust regression and outlier removal approach (19).

**Results**

Intracranially implanted U-87 MG, RG2, and MDA-MB-231 tumors are softer and less viscous than healthy brain parenchyma

Parametric maps of elasticity ($G_E$) and viscosity ($G_v$) revealed the symmetrical and characteristic anatomical structures of the healthy mouse brain, including the relatively stiffer corpus callosum and the softer thalamus (Fig. 1). In mouse brains bearing tumors derived from U-87 MG, RG2, or MDA-MB-231 cells, both elasticity and viscosity maps showed pronounced contrast between the established tumor (mean tumor volume 35 ± 3 mm³) and the surrounding brain, based on viscoelastic image appearances and on analyses within regions of interest drawn using boundaries defined on the T2-weighted MR images (Fig. 2 and Supplementary Fig. S2). The presence and location of the tumors were confirmed by H&E staining of FFPE tissue sections. Quantitative analysis of the elastic modulus $G_E$ and the viscosity modulus $G_v$ revealed that the three tumor types were significantly less elastic ($G_E$ U-87 MG: 4.80 ± 0.21 kPa > RG2: 4.22 ± 0.14 kPa > MDA-MB-231: 3.74 ± 0.14 kPa) and viscous ($G_v$ U-87 MG: 2.94 ± 0.19 > RG2: 2.41 ± 0.09 kPa > MDA-MB-231: 2.21 ± 0.07 kPa) than healthy brain parenchyma ($G_E$: 5.89 ± 0.17 kPa and $G_v$: 4.36 ± 0.17 kPa; Fig. 3A and B). Histogram analysis demonstrated a clear shift in the distribution of $G_E$ and $G_v$ values in the tumor compared with healthy brain tissue (Fig. 3C and D). In the majority of mice with tumors, the lateral ventricles were markedly dilated and demonstrated low elasticity and viscosity (Fig. 1).
Intracranially implanted U-87 MG, RG2, and MDA-MB-231 tumors have different viscoelastic properties

Significantly different values of $G_d$ were determined across the three tumor models, with tumors derived from U-87 MG cells being the stiffest and tumors derived from MDA-MB-231 the softest (Fig. 3A and C). A similarly significant trend was also found for $G_l$, with tumors derived from U-87 MG cells significantly more viscous than tumors derived from either RG2 or MDA-MB-231 cells (Fig. 3B and D).

Figure 2.
Frequency histograms showing the distribution of elasticity ($G_d$) and viscosity ($G_l$) in tumors and their periphery, in representative mice bearing intracranially implanted U-87 MG, RG2, or MDA-MB-231 tumors. Tumor ROIs were defined on T2-weighted images. Histogram analysis was also performed in the brain of a control healthy mouse.
Cellular and microvessel density contribute to the relative stiffness of intracranially implanted brain tumors

Table 1 summarizes the histopathological features of each tumor model. Markedly different growth patterns were apparent, with tumors derived from U-87 MG cells being well circumscribed with sparse foci of infiltrative cells, whereas tumors derived from MDA-MB-231 cells were substantially more invasive (Fig. 4). Tumors derived from U-87 MG and RG2 cells had a homogeneous density in tumors derived from MDA-MB-231 cells presented with regions of sparse cell density and edema. Quantitative analysis confirmed a significantly lower cellular density in tumors derived from MDA-MB-231 cells compared with tumors derived from U-87 MG or RG2 cells (Fig. 5A). At the time of imaging or excision, no areas of gross necrosis were detected in any of the tumor models.

Myelin was only detected as sparse and very fine fibers within tumors derived from U-87 MG cells. Myelin fibers were also detected at the invasive margin of all tumors in the myelinated structures of the brain that were being invaded (Supplementary Fig. S3). Type I, III, and IV collagen were more abundant in tumor compared with brain parenchyma, but were mainly localized to the basement membrane of the vasculature in all tumor types. There was no difference in collagen content between the tumor types. The three models demonstrated significantly different microvessel density (MVD) as measured on CD31-stained FFPE tissue sections of the MRE-imaged mice, with the highest vessel density in U-87 MG tumors and the lowest score in MDA-MB-231 tumors (Figs. 4 and 5B). Microvessel density was significantly lower in normal brain parenchyma compared with U-87 MG and RG2 tumors (P < 0.05).

The functional vascular phenotype of the three tumor models was also investigated in separate cohorts using the perfusion marker Hoechst 33342 (see Supplementary Materials and Methods). Fluorescence microscopy of Hoechst 33342 uptake revealed no significant difference in the degree of functionally perfused vasculature (Supplementary Fig. S4A and S4B). However, subsequent processing and quantitative analysis of CD31 immunofluorescence on the same frozen tissue sections corroborated the CD31 MVD data acquired on FFPE sections of the imaged tumors (Supplementary Fig. S4A and S4C).

Linear regression analysis revealed significant positive correlations between tumor cellular density and MVD with both elasticity $G_d$ ($r = 0.61, P = 0.01$ and $r = 0.54, P = 0.03$, respectively) and viscosity $G_v$ ($r = 0.57, P = 0.02$ and $r = 0.48, P = 0.07$, respectively; Fig. 5C and D).

Discussion

It is well established that increased tissue rigidity in extracranial tumors is associated with an invasive phenotype, and can influence therapeutic response (3). Reciprocally, therapeutic prevention of tissue stiffening is predicted to impede cancer progression and metastasis, and drugs targeting the mechanical properties of the ECM are being developed (4, 20–22). In this setting, the ability of MRE to noninvasively quantify tumor mechanical properties is being actively exploited and should prove beneficial for cancer
diagnosis, prognosis, and for monitoring response to these novel therapeutics (23, 24).

Using MRE, we have shown that three intracranially implanted tumors derived from U-87 MG human glioma, RG2 rat glioma, or MDA-MB-231 metastatic human breast carcinoma cells, which present with different growth patterns, were all significantly softer than the surrounding brain tissue in vivo. Given the well-described association of increased stiffness with malignancy in, for example, breast or liver cancer (23), the relative softness of these intracranially implanted tumor models compared with normal brain was initially unexpected. However, this observation is consistent with the reported soft consistency of brain malignancies, based on pathological examination or intraoperative assessment (25–27). In a recent clinical prospective study, preliminary evidence of the relative softness of malignant primary brain tumors and metastases with a range of differentiation status and grade was provided by MRE (12).

In interrogating the pathological determinants underpinning our MRE data, we have demonstrated that both cellular density and MVD contribute to the relative stiffness of these soft brain tumor models. More generally, cellular architecture (cellular arrangement, size, shape, and density), the vascular network and its collagen-supported scaffold are major structural components of the tumor microenvironment, and as such represent important determinants of the intrinsic stiffness of tumors. This is corroborated by recent MRE studies showing a decrease in the magnitude of the shear modulus ($G'$) upon therapy-induced necrosis or a decrease in MVD, and the correlation between increased $G'$ and MVD upon progression in in vivo models of colon cancer and lymphoma (28, 29).

These pathological correlates, however, do not explain the softness of brain tumors. The ECM is another major contributor to the viscoelastic properties of tumors. Breast cancer cells have been shown to be more compliant (softer) than their nonmalignant counterparts (30), yet malignant breast tumors are stiff due to their ECM, being rich in cross-linked collagen fibers (31). In contrast, the ECM of brain tumors has been shown to share the unique composition of that of the healthy brain, characterized by high concentrations of hyaluronic acid and the absence of fibrillar networks such as collagen, fibronectin and vitronectin, or basement membrane proteins such as laminin, which are only found in the vascular or perivascular space (32).

The unique composition of the ECM contributes to making the brain the softest tissue in the human body (33). The lower viscoelastic properties of brain tumors relative to the brain parenchyma itself may be attributed to the absence of structural anisotropy due to the rapid and chaotic tumor cell growth, which contrasts with the highly networked and organized microstructure of brain tissue. The heterogeneous and symmetrical distribution of mechanical properties in the healthy brain, observed in our study, correlates with the regional differences in the microstructure and organization of the brain parenchyma (34). For example, the elevated viscoelasticity associated with the corpus callosum, a compact bundle of myelin-sheathed axonal projections connecting the two brain hemispheres, is a prime example of the direct relationship between increased organization and increased stiffness in the brain. In contrast, the lower stiffness observed in the dilated ventricles in tumor-bearing mice is a consequence of the inability of cerebrospinal fluid to withstand a shear stress (35).
Our histopathologically correlated MRE data provide further in vivo evidence of the sensitivity of MRE-measured viscoelastic properties for changes in tissue microstructure at scales that are far below the resolution of the MR images (36, 37), demonstrated here for the first time in brain tumors. This is consistent with the predictions of models for the mechanical properties of networked microstructures that have been shown to scale into unique macroscopic mechanical signatures (38), making MRE a very promising methodology for the detection and differential diagnosis of malignancies (36), as illustrated herein by the discrimination of the three intracranial tumor models based on their differential mechanical phenotypes.

MRE is already in use clinically for the staging of liver fibrosis and the differential diagnosis of malignant nodules in breast, liver, and prostate cancer (23, 39–41). Having overcome the challenges of transmitting waves through the human cranium, MRE has also been successfully implemented for the routine examination of neurology patients, including those with brain malignancies (9, 11, 12), and shown to detect changes in brain tissue integrity associated with several neurological disorders, including multiple sclerosis (42, 43). The potential use of MRE in preoperative planning in patients with meningioma, in which the complexity of surgical resection increases with tumor stiffness, has been recently highlighted (44).

The ability of MRE to assist in the delineation of brain tumors for preoperative management is also being actively investigated. The provision of strong conclusions on the accuracy of tumor delineation on our viscoelastic maps is challenging, as nonlinear deformations occurring during tissue processing preclude the use of H&E-stained sections as a gold standard to define tumor boundaries. Further in vivo studies coregistering MRE-acquired viscoelastic maps with images acquired with techniques such as stimulated Raman scattering microscopy, shown to accurately delineate tumors in orthotopic models of human gliomas both
In Vivo MR Elastography of Brain Malignancies

Figure 5. Quantitative histological assessment of cell density (A) and microvessel density (B), determined from intracranially implanted U-87 MG \( (n = 6) \), RG2 \( (n = 5) \), and MDA-MB-231 \( (n = 5) \) tumors. Microvessel density was also quantified in healthy brain parenchyma in control mice \( (n = 6) \). Data are presented as the median values for each tumor and as the mean \( \pm 1 \) SEM across each cohort. Significance testing used Student two-tailed paired \( t \) tests with a 5% level of significance. The relationship of MR elastography-derived elasticity \( G_\alpha \) and viscosity \( \eta \) with cell density \( r = 0.61, P = 0.01 \) and \( r = 0.57, P = 0.02 \), respectively; C), and microvessel density \( r = 0.54, P = 0.03 \) and \( r = 0.48, P = 0.07 \), respectively; D) across all the intracranially implanted tumors is shown ( □, △, U-87 MG; □, △, RG2; □, △, MDA-MB-231).

in situ and ex vivo using fresh tissue slices (45), would provide definitive conclusions on the utility of MRE to delineate brain tumors.

In conclusion, our preclinical study provides definitive evidence for the relative softness of intracranial tumors in vivo. In addition to measuring stiffness, we demonstrate that MRE is sensitive to changes in intracranially implanted tumor microstructure, including those within the vascular and cellular networks, allowing the discrimination of three phenotypically different tumor models based on their different mechanical properties. Our study, thus, supports further evaluation of clinical MRE for the detection and differential diagnosis of brain tumors (or metastases) and reinforces MRE as a promising and attractive addition to the multiparametric diagnostic neuroimaging methodologies, which already play a crucial role in the management of patients with brain malignancies (46).

Disclosure of Potential Conflicts of Interest
J.L. Ulloa was a senior research scientist at AstraZeneca. J.C. Bamber is a consultant/advisory board member of SuperSonic Imagine. No potential conflicts of interest were disclosed by the other authors.

Authors’ Contributions
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): Y. Jamin, J.K.R. Boult, J. Li, G. Box, C. Jones, R. Sinkus
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): Y. Jamin, J.K.R. Boult, J. Li, S. Popov, J.C. Bamber, R. Sinkus
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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J.C. Bamber

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