Mechanical characterization of a mouse GL261 glioma model using MR elastography

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Target audience: Physicians and biologists interested in the mechanical properties of glioblastoma (GB).

Purpose: Glioblastoma (GB) is the most aggressive type of glioma and it is recognized by its infiltrative growth and overall poor prognosis[1]. Magnetic resonance elastography (MRE)[2] is capable of measuring in vivo the mechanical properties of the mouse brain[3]. A recent MRE study of GB in patients revealed that on average GB is softer than healthy tissue, however, the representation of tumor tissue is highly heterogeneous including necrotic areas, vasculature and different solid types of tissue inside the lesion[4]. To better understand the mechanical properties of GB in vivo, we applied MRE to GB in a mouse model.

Methods: 9 2-month-old C57BL/6 mice were implanted with 5×10^4 GL261 cells in 1 µL at 1 mm anterior and 2 mm lateral to the bregma, at a depth of 3 mm below the dura. MRE measurements were performed at five time-points: day0 prior to cell implantation, day0, day7, day14 and day21 post implantation. MRE was performed on a 7 T scanner (Bruker, Germany). An air-cooled Lorentz coil in the fringe field of the scanner produced 900 Hz vibrations which were recorded by a FLASH sequence equipped with a sinusoidal motion sensitizing gradient (MSG) along the through-plane direction. Four axial slices with slice thickness of 1mm were acquired. Further imaging parameters were: 128x128 matrix, 25 mm FoV, 14.3 ms TE, 116.2 ms TR, 285 mT/m MSG strength, 8 time steps over a vibration period. The pre-processed 2D scalar wave fields were analyzed for the complex shear modulus G^* by algebraic Helmholtz inversion [3]. $G^*$is represented as the magnitude $|G^*|$= abs(G^*) and the loss tangent given by φ = arctan(G''/G'). In materials with dominating elastic behavior, the $|G^*|$ reflects the tissue stiffness and phase angle φ relates to geometrical changes in the mechanical network [5]. For tumor morphology, T2w and T1w Gd-enhanced images with 0.5mm slice thickness were acquired.

Results: We monitored the tumor growth longitudinally and the tumor size (24.7 mm^3 based on T1 post-Gd-DTPA) was suitable for MRE measurement on day21. T1 (post Gd-DTPA)**,** T2, MRE wave images and elastograms are shown for two slices in **Fig.1**. MRE parameters were spatially averaged over two ROI's, the tumor and the rest of brain parenchyma which is considered as reference region. Individual $|G^*|$ and φ values were plotted in **Fig.2**. The comparison of $|G^*|$ and φ prior (d0) and after (d0_IP) cell implantation suggested that no significant tissue damage occurred due to tumor implantation. On day21, the tumor-$|G^*|$ (d21_tumor) was significantly lower than baseline values (d0_IP:7.7±0.8 kPa vs. d21_tumor:5.2±1.1 kPa, $P < 0.005$ [Wilcoxon signed-rank test]; d21_ref: 6.8±1.3 kPa vs. d21_tumor:5.2±1.1 kPa, $P < 0.005$ [Wilcoxon signed-rank test]). The phase angel φ was not significantly altered in the tumor. However, a higher heterogeneity of values was observed (0.49±0.11) with 20% standard deviation.

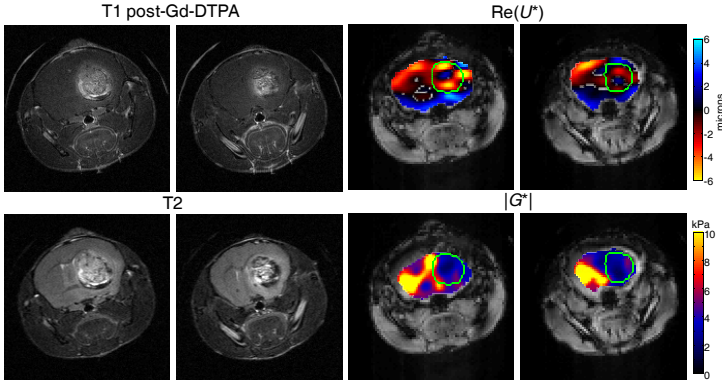

Fig.1: Post Gd-DTPA T1**,** T2, MRE wave images Re(U*) and elastograms |G*| in two slices on day21. The tumor region is demarcated in the wave images and elastograms.

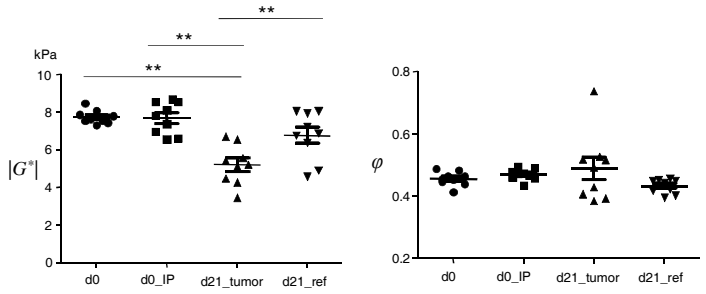

Fig.2: Individual MRE parameters $|G^*|$ and φ of the entire brain on day0 prior and after cell implantation, tumor and reference tissue on day21, denoted by 'd0', 'd0_IP', 'd21_tumor' and 'd21_ref', respectively.

Discussion: Our results showed that in the mouse GL261 tumor model, GB tissue is softer compared to healthy brain tissue as indicated by reduced $|G^*|$ values. The results agree to recent findings in humans where in GB was found to be softer than healthy brain parenchyma (4). Phase angle φ which is closely linked to the mechanical network didn't change in our study; however, the large variability of does not allow further conclusions. As reported in (6), GL261 tumors altered the vascularization within the glioma region, which may have strong influence to the viscoelastic properties of the tissue. Furthermore, differences in the mechanisms of implantation, tumor cell migration and diffusive tumor infiltration might cause variations of the averaged viscosity of the tumor region in our group which needs to be validated by the on-going histological assessment.

Conclusion: MRE was performed to study the viscoelasticity of GB in a mouse model. We found that GL261 tumor is significantly softer compared to healthy brain tissue.

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