In vivo high resolution multifrequency MR elastography of neuro tumors compared to single cell mechanical properties

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Target audience: Physicians and physicists interested in the physical properties of cancer.

Background: Multifrequency MRE (MMRE) can image the viscoelastic properties of in vivo tumorous tissue in vivo with high spatial fidelity and full 3D coverage (1). On the micro scale, micro mechanical test methods such as the optical stretcher (OS) can stage the malignancy of tumorous cells in vitro with high sensitivity and specificity (2). From these laboratory studies we learned that malignant transformation is often associated with marked softening of tumor cells providing prospect of a mechanics-based staging of the aggressiveness of cancer by in vivo elastography. It is important therefore to bridge the gap from laboratory studies to clinical investigations.

Purpose: To measure for the first time viscoelastic constants of cells and in vivo cerebral tumors from the same tissue by applying in vivo MMRE within clinical routine exams and OS after surgery.

Methods: 7 tumors were investigated (3 glioblastoma multiforme [GBM], 1 metastasis [MET], 1 astrocytoma WHO II [AC2], 2 meningioma [MEN]). MMRE was applied on a 3T Scanner (Siemens Trio) using the method described in (1). MRE parameter maps were reconstructed for |G*| and φ, the magnitude and the phase angle of the complex shear modulus. Regions of interest were defined by FLAIR or T2-weighted as well as contrast-enhanced T1-weighted images. The regions were confirmed by the neurosurgeon who performed the resection and provided parts of the tumorous tissue from the prescribed regions for further use in the optical stretcher. Core piece of an optical stretcher is a microfluidic chip containing a flow channel and two counter-propagating divergent laser beams emitted from opposing fibers perpendicular to the channel (2). Single suspended cells, which were isolated from the tumorous tissue are optically deformed by the laser light. In a step stress experiment (for 2s with 0.8W laser power), the surface stress increases and deforms a cell along the laser axis. In an automated procedure hundreds of single cell experiments are carried out for the cell population of each patient sample. The relative deformation of the cells is detected by video microscopy, which can be further quantified using biomechanical models. Using a Kelvin-Voigt model we derived the elastic modulus μ for each cell population.

Results: Fig.1 demonstrates the representation of two tumors, (soft GBM and stiff meningioma, MEN) by MMRE parameter maps. Their |G*|- and φ-values averaged in the demarcated regions were 1123 ± 236 Pa and 0.797 ± 0.268 rad (GBM) and 2395 ± 425 Pa and 0.981 ± 0.146 rad (MEN). Mean OS-derived cellular shear moduli according to the Kelvin-Voigt model were μ = 25.8 and 45.7 Pa for GBM and MEN, respectively. Fig.2 displays |G*| of all cases measured by MMRE vs. μ from OS revealing a high linear correlation of both methods (R = 0.924, P = 0.003). φ was neither correlated with μ nor with the corresponding cell viscosity η. Separation of the contribution of elasticity and viscosity to G* revealed that both the storage modulus, Re(G*), and the loss modulus, Im(G*), were significantly correlated with μ (Re(G*): R = 0.790, P = 0.034; Im(G*): R = 0.897, P = 0.006) but not with η. |G*| significantly decreased with WHO grade (R = -0.807, P = 0.028).

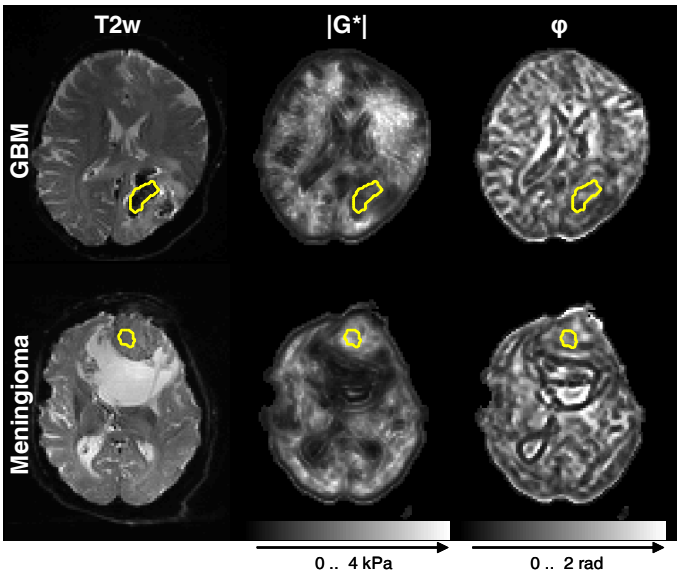

Fig.1: Representation of two tumors by MMRE parameter maps (|G*| and φ) and conventional MRI contrast (T2w) acquired by the same MRE scan.

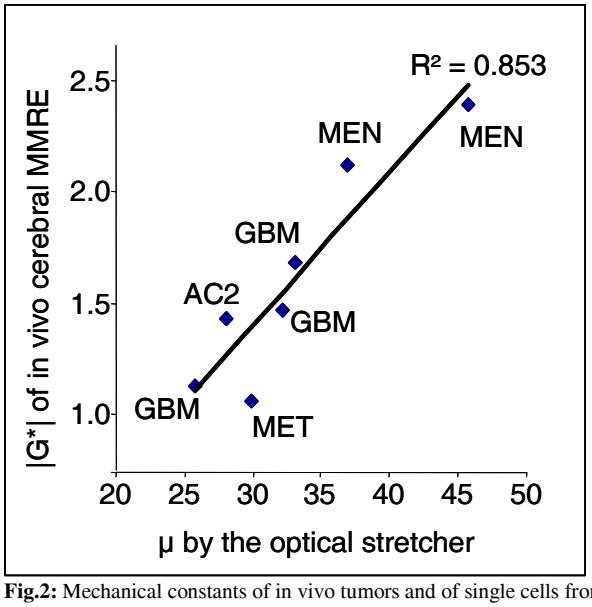

Fig.2: Mechanical constants of in vivo tumors and of single cells from the same tissue.

Discussion and Conclusion: Our study provides first evidence that single cell mechanical properties contribute to the macroscopic mechanical response of tumorous tissue as can be measured by in vivo MMRE. The observed decrease of |G*| and μ with degree of malignancy corroborates previous findings (1). The observed correlation between micromechanical tests and noninvasive examinations opens many avenues for basic research on the biophysical properties of cancer and its translation to clinical diagnosis. Further research should include micro-mechanical tests on tissue compounds (4) as well as investigations of different regions within the tumor masses. Further validation is needed by more cases and entities including other organs.

Literature: (1) Reiss-Zimmermann et al. Clin. Neurorad. 2014, DOI 10.1007/s00062-014-0311-9, (2) Guck et al. Biophysical Journal. 2005;88:3689–98, (3) Plodinec et al. Nat Nanotechnol, 2012, 7, 757-65.