MR-Elastography differentiates intracranial tumors in presurgical patients-a prospective histology controlled study

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Background: In daily clinical routine, the physical examination of a patient including manual palpation provides a traditional, but - even today - most important key to medical diagnosis. While palpation is a routine technique for soft tissue medical examination, e.g. searching for breast or abdominal pathology, it is hardly practical to investigate the brain, which is protected from palpation by the skull - and thus remains an experience exclusive to pathologists and neurosurgeons. However, the recent development of cerebral Magnetic Resonance Elastography (MRE) [1] may bring clinical diagnoses of central nervous system diseases into the workscope of physicists: Gentle shear vibrations of the brain combined with motion-sensitive MRI provide a probe for intracranial viscoelasticity measurements. This principle was recently proven sensitive to the consistency of meningeoma [2], the maturation of the brain [3] as well as to the disseminated disruption of brain parenchymal tissue integrity related to Alzheimer's disease [4], multiple sclerosis [5], or hydrocephalus [6]. Recent single cell experiments suggested that biomechanical cell properties might be very sensitive also in detecting cellular malignancy [7].

Problem: The presurgical non-invasive differentiation of brain tumors has remained unsatisfying even for specialized academic hospitals, despite major advances in clinical and neuroradiological diagnostic techniques – the vast majority of neurooncology patients still need to undergo brain biopsy in order to make a diagnosis.

Objective: We applied magnetic resonance elastography as diagnostic tool for the clinical routine diagnostic work-up of intracranial neoplasm.

Methods: MRE was added to a routine diagnostic or presurgical neuroradiological MRI work-up in 16 patients, and was well tolerated in all cases. In order to yield sufficient spatial resolution for the biomechanical characterization of intracranial tumors, we modified a recently introduced least-squares solution of the stationary wave equation, facilitating stable solutions of the magnitude $|G^*|$ and the phase angel ϕ of the complex shear modulus G^*.

Results and Discussion: Our preliminary tumor MRE data revealed alterations in viscoelastic constants, e.g. a loss in stiffness in all malignancies in comparison to healthy reference tissue or benign variants. In some examples (Fig.1), conventional MRI techniques such as T2w or contrast enhanced T1w MRI could not differentiate benign (e.g. meningeoma) from intermediate (e.g. astrocytoma) or highly aggressive devastating tumor entities (e.g. multiform glioblastoma). In terms of viscoelastic properties, these tumors showed a large discrepancy (Tab.1) and were easily distinguishable, even by naked eye on the according viscoelasticity maps (Fig. 1).

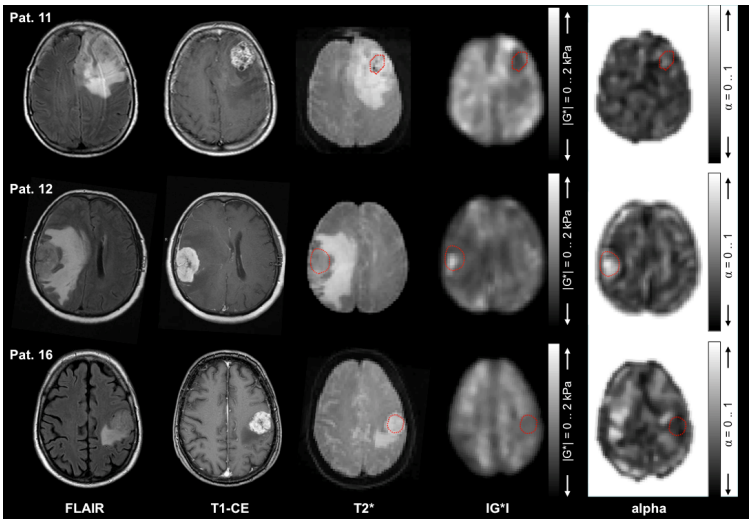

Fig. 1: Anatomical scans and parameter maps of three cases with high similarity on conventional MRI: Patient 11 presented with an anaplastic oligoastrocytoma (WHO III); patient 12 with a benign meningeoma (WHO I); and patient 16 with a high grade glioblastoma (WHO IV). In contrast to the similarity on the anatomical conventional MRI, the biomechanical properties distinctly differentiate the tumor entities as visible on the parameter maps already by the naked eye. The regions-of-interest (ROI) are demarcated as red dotted lines.

No.	Entity (histologically confirmed)	ratio $\|G^*\|$ (t/wm)	ratio α (t/wm)
1	primary b cell lymphoma	0.926	0.568
2	Oligodendroglioma WHO II	0.635	0.719
3	Multiform glioblastoma WHO IV	0.480	0.591
4	Malignant Glioma WHO III	0.729	1.448
5	Astrocytoma WHO II	0.488	0.776
6	Malignant anaplastic Meningeoma	1.302	2.282
7	Solitary metastasis of low-grade bronchial adenocarcinoma	0.757	0.857
8	Oligoastrocytoma WHO II	0.854	1.372
9	Multiform glioblastoma WHO IV	0.611	0.952
10	Anaplastic astrocytoma WHO III	0.891	1.072
11	Malignant glioma WHO III (anaplastic oligoastrocytoma)	0.689	1.454
12	Meningeoma	1.390	3.250
13	Oligodendroglioma WHO II	0.577	0.705
14	Metastasis of adenocarcimona (colon)	1.065	0.627
15	Metastasis of neuroendocrine carcinoma	0.604	0.734
16	Glioblastoma WHO IV	0.664	0.680

Table 1: MRE parameters $|G^*|$ and α, presented as the ratio between tumor and reference tissue (NAWM) of all 16 patients. $|G^*|$ values are taken as the magnitude of the complex modulus; t = tumor; wm = white matter; ratio $|G^*|$(t/wm) = $|G^*|t/|G^*|wm$; ratio α (t/wm) = $\alpha t/\alpha wm$;

Conclusion: MRE may provide a predictive marker for tumor malignancy and therewith contribute to an early noninvasive clinical assessment of suspicious cerebral lesions. Our motivation to further investigate intracranial malignancies by cerebral MRE is additionally triggered by current reports on the sensitivity of biomechanical parameters in tumor cells. Here, the mechanical interaction between tissue matrix and tumor cells was shown to be highly influential to tumor progression, migration and metastatic transformation [7]. MRE is potentially capable to scale such - transient and permanent - biomechanical qualities of tumor cells into the image contrast of *in vivo* MRI given the scaling properties of multi-hierarchic viscoelastic networks in biological tissue, and thus contribute to presurgical clinical diagnosis.

Literature: [1] Muthupillai et al. Magnetic resonance elastography. Nature Med 1996;2(5):601-603. [2] Murphy et al. Preoperative assessment of meningioma stiffness using magnetic resonance elastography. Journal of neurosurgery 2012. [3] Sack et al. Non-invasive measurement of brain viscoelasticity using magnetic resonance elastography. NMR Biomed 2008;21(3):265-271. [4] Murphy et al. Decreased brain stiffness in Alzheimer's disease determined by magnetic resonance elastography. J Magn Reson Imaging 2011;34(3):494-498. [5] Wuerfel et al. MR-elastography reveals degradation of tissue integrity in multiple sclerosis. Neuroimage 2010;49(3):2520-2525. [6] Streitberger et al. In vivo viscoelastic properties of the brain in normal pressure hydrocephalus. NMR Biomed 2011;24(4):385–392. [7] Are biomechanical changes necessary for tumour progression? Nature Physics 2010;6(10):730-732.