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ARTICLE

Mechanical properties of human glioma

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ABSTRACT

Brain gliomas represent some of the most aggressive tumors encountered by modern medicine and, despite major efforts to optimize early diagnosis and treatment, the prognosis remains poor. Due to the complex structure of the brain and the unique mechanical properties of the extracellular matrix, gliomas invade and expand into the brain parenchyma, along white matter tracts and within perivascular spaces, usually sparing normal vessels. Different methods have been developed to study the mechanical properties of gliomas in a wide range of scales, from cells and the microscale to tissues and the macroscale. In this review, the current view on glioma mechanics is presented and the methods used to determine glioma mechanical properties are outlined. Their principles and current state of affairs are discussed.

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Introduction

Brain gliomas are primary intrinsic neuroepithelial tumors [1]. They compose a heterogeneous group of neoplasms, including astrocytomas (WHO grade I–IV), oligodendrogliomas, and ependymomas (WHO grade II–III) [2]. Gliomas represent 28% of all central nervous system (CNS) neoplasms and 80% of CNS malignancies in the USA [3]. Despite their relatively low incidence (5.4 cases/100,000 person years in Europe [4]), the prognosis is poor with related burdens on patient functionality and the society [5]. This certainly justifies the use of multidisciplinary methods and approaches to clarify their pathogenesis and develop novel diagnostic and therapeutic modalities.

There is an abundance of clinical data supporting that the extent of resection is a key prognostic factor for patient outcome for brain gliomas [6,7]. Maximal resection within functional boundaries is the primary treatment goal of modern neurosurgical oncology [8]. Intraoperatively, the macroscopic distinction between tumor and adjacent brain is based on vision and touch, as the consistency of the neoplastic tissue is different from the brain, reflecting differences in histology [9–11]. Nevertheless, the surgical assessment regarding the macroscopic limit of the tumor and the completeness of resection is not as reliable as magnetic resonance imaging (MRI) [12,13]. Therefore, total resection of the depicted neoplasm is not commonly achieved, when the surgeon depends only on subjective perception [14–16].

Different techniques have been developed to improve the intraoperative visualization of brain gliomas such as neuronavigation [17], the administration of 5-aminolevulinic acid [18], and intraoperative imaging methods, namely MRI [19] and ultrasonography [20]. All these techniques for visual improvement present inherent disadvantages and, thus, much room is available for the development of new intraoperative tumor identification methods. The quantitative characterization and measurement of the mechanical properties of tissues are necessary, in order to reliably utilize the differences between glioma and brain 'texture', which at present remain empirical, subjective, and suboptimal. The aim of this review is to explicate the current view on glioma mechanics and its connection with tumor aggression. Moreover, various quantitative approaches for the determination of glioma mechanical properties are further analyzed and the respective methods used are discussed in terms of the principles that they are based upon and their potential.

Mechanical interactions in the pathophysiology of gliomas

Mechanomics, i.e. the study of the interplay between biomechanical and biological processes [21], has attracted considerable research attention with regards to cancer [22], as the mechanical interactions between cancer cells and the extracellular matrix (ECM) are

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related to cell proliferation and aggressiveness [23], cytoskeleton reorganization [24], and ECM remodeling [25] to advance disease progression. Gliomas readily infiltrate the CNS but rarely invade blood vessels. They exhibit a radically different invasion pattern than most other malignant tumors, partly dictated by the distinctive structure of the central nervous system ECM [26]. In fact, proteoglycans, hyaluronic acid, and tenascins are the prominent constituents of normal brain ECM, while collagen, fibronectin, vitronectin, and laminin are nearly absent, except for the blood vessel basement membrane [27].

The influence of ECM stiffness on glioma cell invasion has been investigated using cell cultures on brain ECM biomimetic scaffolds, providing clues about the influence of glioma cell motility by ECM mechanical properties. For example, on 2D substrates, stiffer scaffolds were found to be associated with more aggressive glioma cells [28,29], a fact indicative of the role of a rigid substrate to adhere and expedite cell motility. However, on 3D substrates, stiffer scaffolds were found to be associated with less aggressive glioma cells [30], indicating that the dense space-filling ECM represents an obstacle for cell migration [31]. To overcome such obstacles, glioma cells overexpress metalloproteinases [32,33] that cleave normal ECM and they secrete fibronectin, collagen, vitronectin, tenascin-C [34], laminin [35], and hyaluronic acid [36]. This leads to structural degradation, thus affecting the mechanical properties of their microenvironment and disrupting the mechanical homeostasis of the tissue.

Elasticity and related investigation methods

It has become evident that the investigation of the mechanical behavior of tissues and their elements, cells and ECM, under the influence of internally developed stress is necessary at both microscale and macroscale levels. The simplest theory to consider the response of materials under stress is linear elasticity. During elastic deformation, energy is temporarily stored in the material, to be released during the recovery to the initial state. Conversely, the deformed material may follow a dissipative process, whereby energy is lost. Such is the case with viscous materials, in which the rate of deformation is proportional to the applied stress [37,38].

For nano/microstructured materials such as cells and tissues, more complex theories for structured linear and nonlinear continuum media should be used, but this is outside the scope of the present review. Thus, although cells and tissues are complex inhomogeneous materials, their behavior under low stresses and strains is usually assumed to be homogeneous and linear elastic, in order to facilitate the interpretation of the experimental measurements. The two principal

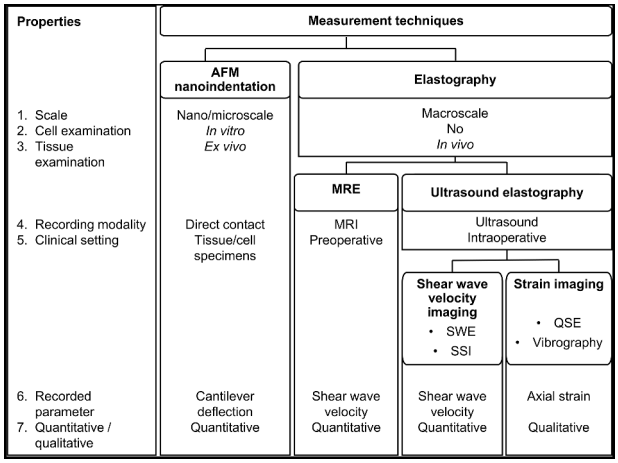

Figure 1. Comparison between techniques used to determine the mechanical properties of gliomas. AFM: atomic force microscopy; MRE: magnetic resonance elastography; SWE: shear wave elasticity imaging; SSI: supersonic shear imaging; QSE: quasistatic strain elastography.

parameters that characterize linear elastic materials are the tension/compression elastic modulus E and the shear modulus G. The modulus E measures the extension/contraction of an elementary square drawn on the material when this is subjected to tensile/compressive forces. The modulus G measures the change of the angle when two antiparallel forces are exerted on the two opposite sides of the elementary square. More precisely, both moduli are defined as the ratio of the stress (applied force/unit surface) to the strain (length change/initial length) along the deformation axis, for stress values within the linear elasticity range [37,38]. These elastic properties can be experimentally measured with static, dynamic, elastographic, comprising ultrasound elastography and magnetic resonance elastography (MRE), and (nano)indentation methods, such as nanoindenter and atomic force microscope (AFM) [39,40]. In particularly soft and sensitive materials, like neoplastic tissues and cells, elasticity is commonly investigated using nanoindentation, for *in vitro* and *ex vivo* measurements, or elastographic methods, for *in vivo* measurements (Figure 1).

AFM nanoindentation

AFM [41] is a scanning probe microscope, that 'feels' surface topology at the micro/nanoscale by 'touching' it. In principle, the sample is displaced under the tip of a microcantilever (Figure 2a). The cantilever deflection, due to the contact of the tip with the sample, is recorded along with the sample displacement. Accordingly, both the depiction of the sample surface at the nanoscale and the measurement of the corresponding mechanical properties are feasible. The AFM can function in air or a liquid environment. Thus, biological samples are usually studied in an

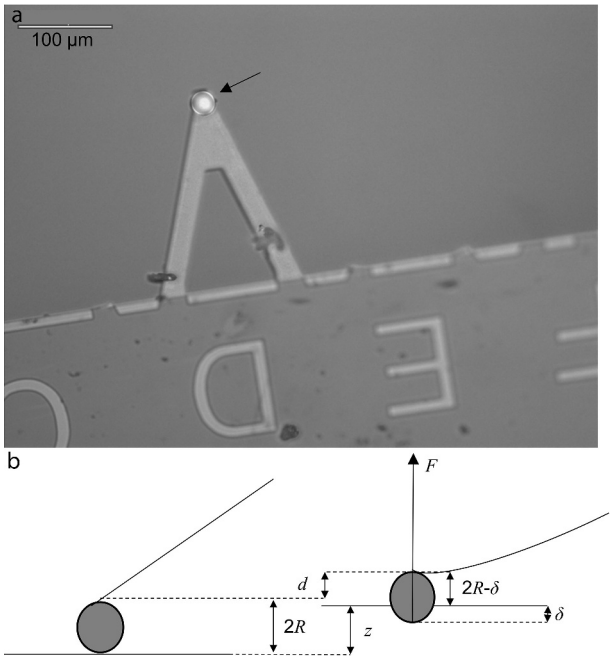

Figure 2. An AFM cantilever with a spherical tip (arrow) from below (a). General principles of AFM nanoindentation with a tip of radius *R* (b). The deflection *d* and the displacement *z* are recorded, to estimate the force *F*, the indentation *δ*, and the elastic modulus.

appropriate buffer that is supposed to approximate their natural environment. Due to its nanoscale resolution concerning both forces and displacements, AFM has become a widely accepted and powerful instrument for the study of biological objects ranging from tissues to macromolecules [42].

AFM nanoindentation, in particular, is an established technique for the determination of elasticity of particularly soft materials, like fresh unfixed tissues and living cells [43–48]. It is performed under controlled stress, deformation, indentation depth, and deformation rate conditions. Typically, the recorded deflection versus displacement curves are transformed to force versus indentation depth curves. The latter are fitted to a mechanical model, in order to estimate the elastic modulus (Figure 2b) [49].

A disadvantage of AFM nanoindentation, due to its versatility, is that the estimated elastic modulus may differ between experimental setups. Therefore, the conditions imposed on every study have produced an assortment of conflicting results. As an example, very thin samples or large indentation depth may result in overestimation of the elastic modulus, due to the substrate effect, i.e. the influence of the typically hard substrate [50]. Additionally, very low indentation speeds (<1 μm/s) may lead to viscous dissipation, while indenting at very high speed (>10 μm/s) may lead to increased forces due to hydrodynamic drag. Moreover, tip shape plays a pivotal role in the determination of elastic modulus. Spherical probes tend to apply forces in a uniform way and they are less prone to cause sample damage, strain hardening, or substrate effect [51]. As a consequence, results of AFM nanoindentation using spherical tips agree with other sensitive at low applied forces techniques, like optical and magnetic tweezers [52]. Conversely, sharp tips, although better for mapping surfaces, may cause nonlinear elastic or inelastic behavior [53] with more prominent viscous effects [54]. In addition, because of the higher pressures involved, strain hardening and substrate effects cannot be excluded. As a result, the elastic modulus tends to be overestimated [52]. Furthermore, buffer composition [55], osmolarity, and pH [56] also affect the measurements, often leading to an overestimation of the elastic modulus [57].

Glioma cells and nanoindentation

The elasticity of cancer cells seems to depend, at least in part, on their origin. Using AFM nanoindentation, it has been noted that breast [58,59], prostate [58], and urinary bladder cancer cells [60] were softer than normal ones, as they showed lower elastic modulus. In contrast, HL60 leukemic cells [61] were stiffer than the respective normal ones.

For gliomas, in particular, SNB-19 glioma cells were found stiffer than the respective normal cells [62]. In contrast, SNB-19 cells that lost a considerable portion of their ability to migrate [63] were softer than wild-type ones [64].

Glioma tissue and nanoindentation

Upscaling from the cellular to the tissue level, using AFM nanoindentation, it has been observed that endometrial cancer tissues were softer than the respective normal ones [58]. However, in breast cancer [58,65] and hepatocellular cancer [66] the elastic modulus followed a bimodal distribution along the tissue surface. The lower peak was attributed to cancer cells and the higher to the ECM, as elements with different morphology and composition differentiate between the behavior of neoplastic and normal tissue [58,66,67].

Ciasca et al. [68] compared the elasticity of fresh necrotic glioblastoma tissues to that of non-necrotic ones using sharp tips in a hyperosmotic buffer [65]. Necrotic tissues showed homogeneously low values of the elastic modulus, attributed to the action of matrix-metalloproteinases and hyaluronidases on the ECM. In contrast, the elasticity of non-necrotic tissues was found to be highly inhomogeneous with its range being rather wide, also exhibiting negative skewness. In particular, apart from regions with low values of the elastic modulus, much stiffer regions were also found, attributed to the overproduction of hyaluronic acid and microvascular proliferation. White matter from one patient has also been shown to exhibit inhomogeneous elasticity, without the very high values of the

elastic modulus observed on non-necrotic tissues. Even though the sample size was small, the white matter was generally observed to be stiffer than necrotic tissues and softer than non-necrotic ones.

Miroshnikova et al. [69] studied the relation of brain glioma elasticity with IDH1 mutation status using spherical tips on fresh frozen tissues. IDH1 R132 H mutations were associated with softer tissues, while increased tumor grade was associated with stiffer ones.

Elastography

While AFM nanoindentation determines elasticity at the nano/microscale, elastography determines elasticity at the macroscale. The latter encompasses various imaging techniques, namely MRE and ultrasound elastography, that map tissue elasticity *in vivo*. In principle, the examined tissue undergoes a mechanical disturbance and the elastic properties are estimated from the recorded tissue response [70].

Ultrasound elastography of gliomas

Ultrasound elastography records the tissue response using an ultrasound system. Its application in neurosurgery is limited by the impermeability of the skull to ultrasound. However, it shows the advantage of easy integration with intraoperative B-mode ultrasound during glioma surgery. An assortment of techniques has been developed in this direction, both qualitative, measuring relative differences in elasticity between the examined tissues, and quantitative, measuring absolute elastic or shear modulus values. The recorded parameter is either the axial strain induced by the mechanical disturbance or the propagation velocity of an induced shear wave [71].

Quasistatic strain elastography (QSE) [72], a strain imaging technique, has been extensively studied for the diagnosis of neoplastic [73,74] and non-neoplastic diseases [75–77]. In principle, manual compression causes different strains on the examined tissues, with stiffer tissues undergoing smaller strains. When applied to the brain, tissue pulsations under the static ultrasound probe can also serve as a source of mechanical distortion without the need of external compression [78]. Using this technique on 16 gliomas, tumor tissue was found stiffer than the brain on average [79], while glioma tissue and brain could be distinguished more efficiently than using B-mode [80]. Moreover, Chakraborty et al. [81] verified the ability of QSE to recognize tumor heterogeneity, in agreement with surgical opinion on tissue rigidity. Recently, Prada et al. [82] observed that low-grade glioma tissue was stiffer than the brain in six of the seven (86%) cases examined, while high-grade glioma tissue was softer than the brain in 35 of the 38 (92%) cases studied. Tumor margin was sharper using QSE rather than B-mode in six of the seven (86%) low-grade gliomas and 28 of the 38 (74%) high-grade gliomas. Even though QSE is qualitative, as the stress is non-uniform and unknown, efforts to achieve semi-quantitative results based on the pixel intensities of the recorded images have been made [83]. Using such semi-quantitative analyses, Cepeda et al. [84] found that high-grade glioma tissue is softer than low-grade glioma tissue, although not significantly, whereas glioma tissue is softer than brain tissue on average. Both low and high-grade glioma groups showed substantial differences in elasticity across patients. In another strain imaging technique, i.e. vibrography [85], low-frequency axial vibrations are induced by the ultrasound transducer, while the quasistatic tissue strain is recorded. Although qualitative, it achieves low computational costs and improved image quality. Vibrography suggested that the elasticity of gliomas may show substantial variation across tumor grades and types [86], while the technique has also been used at several stages of the operation to control tumor resection [87].

Shear wave velocity measurement and/or imaging techniques are inherently quantitative. In shear wave elasticity (SWE) imaging [88], the ultrasound transducer applies an acoustic radiation force; i.e. a focused ultrasound beam onto the tissue to induce shear waves. Shear wave propagation parameters are recorded to estimate the elastic or shear modulus. Supersonic shear imaging (SSI) [89] is an improvement of SWE, whereby successive pulses of acoustic radiation force cause the motion of a shear wave source perpendicularly to the tissue surface at a supersonic speed. The propagation velocity of the induced shear waves is recorded using ultrafast plane wave imaging and used for the estimation of the proportional to the squared velocity elastic/shear modulus. Chan et al. [90] using SSI on 11 brain tumors, including 2 astrocytomas, concluded that good agreement exists between the results of elastography and surgeon's assessment on tissue elasticity. In particular, the contrast in elastic modulus between tumor and brain tissue was sharper in tumors stiffer than the brain. In tumors softer than the brain, the contrast was better at the macroscopic margin of the tumor, while average tumor and brain tissue elasticity overlapped substantially. On extending this study to 34 cases, including 12 gliomas, they clearly showed the superiority of SSI to surgeon's opinion, as the former was comparable to MRI and B-mode for the delineation of residual tumor [91]. Finally, Chauvet et al. [92] using SSI found a significantly different elastic modulus between low-grade gliomas and brain tissue, as well as between low and high-grade gliomas, but not between high-grade gliomas and brain tissue.

Magnetic resonance elastography of gliomas

Similar to ultrasound elastography, MRE [93] utilizes MRI to record the physical response of the examined tissue to shear waves induced by an actuator, in order to estimate the elasticity of the examined tissue. In contrast to ultrasound elastography and AFM nanoindentation, it can be used preoperatively, thus allowing for an early determination of the tumor elasticity.

Four studies have investigated glioma elasticity using MRE on patients so far. Simon et al. [94] and Reiss-Zimmermann et al. [95] studied gliomas along with other brain tumors, Pepin et al. [96] studied only gliomas, and Streitberger et al. [97] studied only glioblastomas. Tumor on average was found softer than the brain, either significantly [96,97] or non-significantly [95]. Moreover, tumor was softer than the brain in all (10/10 cases [94]) or the majority of gliomas (17/22 [97], 10/14 [95], and 16/18 cases [96]). Similarly, MRE on animals transplanted with glioma cells found that neoplastic tissue was also softer than brain tissue [98]. However, in a minority of patients with glioma (5/22 [97], 4/14 [95], and 2/18 cases [96]) tumor was stiffer than the brain. Considerable intra-tumor heterogeneity was found in glioblastoma patients [97].

Increased grade was associated with decreased stiffness, significantly [94,96] or non-significantly [95]. Pepin et al. [96] further found that IDH1 mutant tumors were stiffer than IDH1 wild-type ones. These results are in contrast to those of Miroshnikova et al. [69], who found that increased tumor grade was associated with increased stiffness and IDH1 mutant tumors were softer than IDH1 wild-type tumors. However, it should be pointed out that MRE studies explore brain glioma elasticity at the macroscopic scale, while Miroshnikova et al. investigated it at the micro/nanoscale [96]. Moreover, MRE averages over the entire region of interest, inevitably taking into account necrotic tissues as well, which are in general softer than non-necrotic tumor or even normal appearing white matter [68]. Conversely, AFM nanoindentation can be performed on preselected regions, so as to avoid necroses. In this connection, it should also be noted that the status of the rarer IDH1/2 mutations, similar in their biochemical, oncologic, and histopathologic consequences to IDH1 R132 C, was not investigated by either study [69,96], thus resulting in an increase of error margins.

Perspectives

Study of glioma elasticity is an emerging research field with new possibilities of further elucidating gliomagenesis and guiding clinical practice. Among others, it is expected to contribute to the development of models for the oncogenesis and the behavior of gliomas [99,100], the evolution of cancer cells population [101], the role of the mechanical properties at the tissue and the cellular level, and the interpretation of the *in vivo* (MRE, intraoperative ultrasonography) and *ex vivo* measurements of the mechanical properties (indentation, shear, tensile test, compression). Clinically, it could contribute to the simulation and the design of neurosurgical operations, the production of experimental data to feed new models for real-time imaging [102] necessary for the neuronavigation, and the development of haptic devices for the implementation of robotics in neuro-oncologic surgery [103–105]. Challenges, like *in situ* measurement of the mechanical properties with nanoindentation, although not currently lying within the capabilities of the present technology, could further shed light on the bio-chemo-mechanical properties of gliomas and their role in disease progression or therapeutic treatments.

Conclusions

The ever-expanding field of neuro-oncology has come to encompass a plethora of interdisciplinary research approaches in the study of gliomas. Mechanomics and biomechanics offer a novel view on the pathophysiology of gliomas. Along with genomics, epigenomics, transcriptomics, proteomics, and metabolomics, they seem to have the potential to further advance our knowledge on the underlying mechanisms of oncogenesis, tumor invasion, and disease progression. Although there are still many open questions, research techniques are continuously optimized, giving initial promising results. Concurrently, clinical methods, like elastography, become gradually available to the practitioner, thus proving another useful tool for the treatment of gliomas.

Contributors

AT and NF conceived and designed the study, obtained funded and ethics approval and wrote the initial draft. ECA guided the investigation on mechanical aspects, edited, and made revisions to the manuscript. AK, AST, AC, and PS made revisions to the manuscript. All authors agreed on the final version.

Disclosure statement

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