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Utility of preoperative meningioma consistency measurement with magnetic resonance elastography (MRE): a review

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Abstract Meningioma consistency is a critical factor that influences preoperative planning for surgical resection. Recent studies have investigated the utility of preoperative magnetic resonance elastography (MRE) in predicting meningioma consistency. However, it is unclear whether existing methods are optimal for application to clinical practice. The results and conclusions of these studies are limited by their imaging acquisition methods, such as the use of a single MRE frequency and the use of shear modulus as the final measurement variable, rather than its storage and loss modulus components. In addition, existing studies do not account for the effects of cranial anatomy, which have been shown to significantly distort the MRE signal. Given the interaction of meningiomas with these anatomic structures and the lack of supporting evidence with more accurate imaging parameters, MRE may not yet be reliable for use in clinical practice.

Keywords Magnetic resonance elastography · Meningioma · Tumor consistency

Alexander G. Chartrain and Mehmet Kurt contributed equally to this work.

Highlights - MRE is a promising tool for preoperative meningioma consistency determinations.
- Previous studies have only used a single frequency for measurement acquisition, which may limit the applicability of the results.
- Previous studies have measured the storage modulus, which may not yield clinical results as reliable as the storage and loss moduli do, separately.
- Improved understanding of MRE measurements may be needed prior to clinical application.

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Abbreviations

MRE	Magnetic resonance elastography
FLAIR	Fluid-attenuated inversion recovery
FA	Fractional anisotropy
DWI	Diffusion-weighted imaging
DTI	Diffusion tensor imaging
CT	Computed tomography
ICP	Intracranial pressure

Introduction

The consistency and mechanical properties of tissue appreciated through physical examination is an important diagnostic tool, but is only convenient for pathologies that present superficially. Because palpation can only detect superficial pathology, ultrasound is often used to assess the consistency of deeper tissues. However, palpation and ultrasound have limited applicability to neurosurgery. While ultrasonography has shown promise in identifying the consistency of intracranial pathology intraoperatively, it is ineffective in the preoperative setting due to the limited acoustic window related to presence of the skull [4].

Magnetic resonance elastography (MRE) was developed to respond to this clinical need [25]. MRE is a magnetic resonance imaging (MRI) technique that measures the propagation of vibration-induced displacement and the viscoelastic mechanical properties in the tissue of interest [12, 17, 19]. This

method of imaging measures the storage and loss moduli, which are viscoelastic properties of tissue that are analogous to palpation by physical examination [21]. MRE therefore allows for the examiner to determine the mechanical quality of a tissue that is otherwise inaccessible to physical or ultrasound examination [25].

Recent investigations have employed MRE to assess the consistency of meningiomas preoperatively [11, 24, 37]. Meningiomas are of particular interest, as those with stiff and fibrous consistency may require special considerations during preoperative planning. While soft meningiomas are readily resected and lend themselves well to minimally invasive techniques, such as endoscopy and keyhole surgery, firm meningioma resections are typically more challenging and require a conventional craniotomy and open strategy. Meningioma consistency also has bearing on the choice of surgical approach and can provide valuable information in the context of additional challenges, including its proximity to critical neural and vascular structures [41]. Knowledge of preoperative consistency may help guide operative decisions for planned staged resections or expected subtotal resections [41]. An imaging modality capable of identifying preoperative meningioma consistency may also help guide decisions regarding whether preoperative embolization might be beneficial [12, 15, 24, 35, 38]. In this review, we investigate the clinical utility of meningioma consistency measurements with MRE, review its current limitations, and discuss the research efforts to overcome these limitations.

Non-MRE meningioma consistency imaging methods

Prediction of preoperative meningioma consistency has been a focus of research interest and, as a result, various imaging modalities have been investigated. Comprehensive reviews of non-MRE investigations have been outlined previously [32, 39]. These various imaging techniques have been tested for correlation with qualitative surgeon assessment at the time of surgical resection, which remains the reference standard. A five-point grading scale that incorporates the surgeon's ability to internally debulk the tumor, the types of instruments used during the resection, and the capsule characteristics has been proposed and improves upon previous binary "hard/soft" classifications [41]. Ex vivo testing of surgical specimen consistency with various instruments, including the Shore durometer (Rex Guage Co, Buffalo Grove, IL) and the Warner-Bratzler shear force cell (MTS, Eden Prarie, MN), has also been attempted, though the lack of consistency in instrument type and measurement output limits the comparability across studies [11, 27].

Among the non-MRE imaging techniques that have been investigated, T1- and T2-weighted imaging patterns, fluid-attenuated inversion recovery (FLAIR) signal intensity, and fractional anisotropy (FA) values have shown the most promise in differentiating very hard and very soft meningiomas [39]. T2 hypointensity tends to predict firm meningiomas while T2 hyperintensity, combined with T1 hypointensity, correlates with soft meningiomas [10]. FLAIR signal intensity tends to parallel T2 findings, with high-intensity signal correlating with softer meningiomas and lower intensity with firmer meningiomas, though its significance remains debated in the literature [30, 33, 34, 36, 40]. High FA values have been shown to predict firm meningiomas, though this also remains debated in the literature [16, 27]. The existing literature varies considerably on the efficacy of other non-MRE-based imaging techniques, such as MR diffusion-weighted imaging (DWI), diffusion tensor imaging (DTI), MR spectroscopy, and computed tomography (CT) for characterizing meningioma consistency. Regardless, non-MRE imaging techniques are an indirect measure of consistency, and each of these modalities lacks the ability to differentiate meningiomas with intermediate consistency [10, 16, 27, 39]. As a result, there is currently no well-established preoperative imaging technique that can reliably predict meningioma consistency at the time of surgical resection [32, 34, 39]. However, MRE, an imaging modality that directly, objectively, and quantitatively measures tissue consistency, has been frequently cited as a possible solution [12, 21, 32, 39]. With its ability to quantitatively measure consistency across the entire continuum of consistency, as opposed to indirect imaging techniques that merely detect consistency at the extremes of the continuum, MRE has the promising potential to assist in preoperative decision-making and surgical planning.

Scientific basis of MRE

MRE is an established technology, particularly in the field of liver consistency imaging, and has recently been adapted for diagnostic use in intracranial pathology, including meningiomas [19]. MRE is an MRI technique that is able to quantitatively measure propagating acoustic strain waves in tissues subjected to harmonic mechanical excitation [20, 25]. A motion-sensing gradient set to image tissue at the desired frequency is added to a conventional MRI scanner and is coupled with a mechanical oscillator that stimulates the tissue of interest in synchrony and at the same frequency [20]. Any cyclic motion of the tissue causes a phase shift that is measured and recorded in the MRI sequence. From this phase shift, the displacement at each voxel can be calculated to yield a direct image of the acoustic wave in the tissue. From the images constructed by measuring the phase shifts, the local wavelengths of the propagating acoustic waves can be determined, as can the storage and loss moduli at each voxel.

These images can then be assigned a color gradient to represent the viscoelastic properties of the tissue. MRE has the ability to measure tissue consistency over five orders of magnitude, providing improved resolution over that of conventional MRI and ultrasound [21]. This improved resolution allows for a finer differentiation, especially for lesions of intermediate consistency, and, for this reason, it has potential to overcome the shortfalls of consistency imaging with conventional MRI modalities.

MRE: clinical investigations and limitations

Literature search strategy

We conducted a literature search of the PubMed, SCOPUS, and Cochrane databases for relevant clinical studies. We queried the databases using the search term "magnetic resonance elastography" and "meningioma." The inclusion criteria were case series and clinical studies describing attempts to correlate preoperative MRE findings with tumor consistency. Titles and abstracts were reviewed for the following exclusion criteria: (1) does not use MRE, (2) does not study meningiomas, (3) non-human studies, (4) studies not written in English, (5) studies that do not correlate MRE findings with consistency at time of surgery, and (6) review articles that offer no new information. After redundant articles were removed, full text review was performed for publications that met these criteria. Reference lists of relevant articles were searched

to identify additional studies. The date of the last search was April 6, 2017. All studies that described correlation between preoperative MRE findings and meningioma consistency were reviewed. The studies were abstracted for sample size, field strength, frequency parameters, variable used for measurement, and intraoperative assessment of consistency. In studies involving different types of brain tumors, only meningioma cases were included in the review.

Literature search results

The PubMed search yielded five abstracts and the SCOPUS database returned eight (Fig. 1). The search of the Cochrane database did not retrieve any additional abstracts. After removal of duplicates, eight studies were screened for inclusion and exclusion criteria, as outlined above, and three were eligible for inclusion in this review.

Three studies have investigated the ability for MRE to measure meningioma consistency and compared it with intraoperative stiffness upon surgical resection (Table 1). In a case series of six patients, four with meningioma, Xu et al. found that MRE imaging perfectly correlated with intraoperative consistency [37]. In a subsequent study for 13 patients with meningioma, Murphy et al. also found that MRE measurements correlated well with intraoperatively determined tumor stiffness [24]. MRE measurements for one tumor in this series did not correlate with the surgical consistency (predicted to be firm on MRE, but soft at surgery), and it was postulated that the elevated
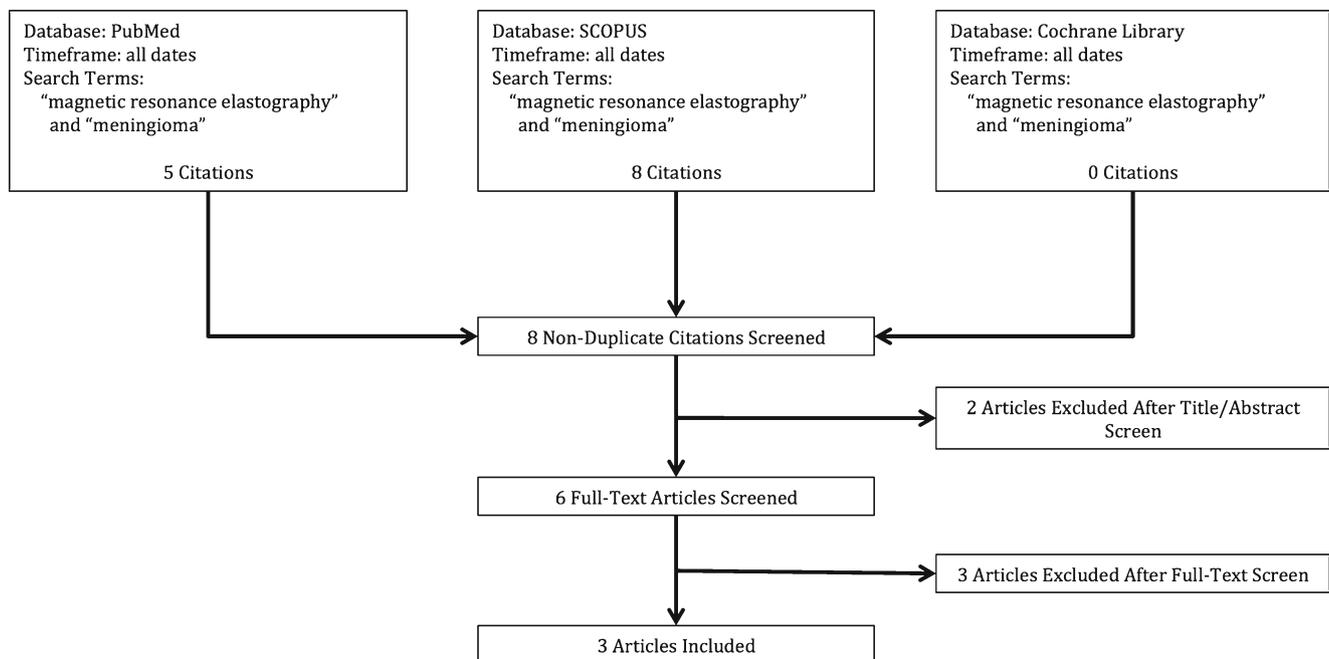

Fig. 1 Flow chart outlining the selection of relevant studies

Table 1 Current literature studying magnetic resonance elastography in meningiomas

Author	Year	Number	Field strength (T)	MRE frequency (Hz)	Measurement variable	Intraoperative correlation
Xu	2007	4	3	150	Shear stiffness	4/4 (100%)
Murphy	2013	13	3	60	Shear stiffness	11/12[a] (92%)
Hughes	2015	15[b]	3	60	Shear stiffness	10/15 (67%)

[a] One patient in this study was excluded due to small meningioma size

[b] This study included 15 tumors in 14 patients

stiffness in the surrounding tissue and an elevated intra-cranial pressure (ICP) might have contributed to this in-accuracy. The same group performed a second study of 15 meningiomas in 14 patients and, similarly, found that MRE imaging characteristics significantly correlated with intraoperative consistency grading [11]. They concluded that MRE performed well at predicting hard tumor con-sistency, but demonstrated limitations in positive predic-tive value for soft tumors and sensitivity for hard consis-tency [11]. Although the results from these studies appear to support MRE as a clinically useful tool, such a conclu-sion may be limited by the imaging methods and interpre-tations that were used.

The primary limitation to be noted in these studies is the use of a single frequency for image acquisition. It is well established that tissues display frequency-dependent stiffness behavior, meaning that tissues will display higher stiffness on MRE when higher frequencies are used [20]. This property is variable and depends on the tissue type (e.g., white matter, gray matter) and anatomical surroundings (e.g., skull base, dural folds) [5]. The use of a single frequency, while able to capture the shear modulus of certain tissue types correctly, inaccurately displays the shear modulus of other tissues with different properties.

A second concern in these studies is the use of the shear modulus (sometimes referred to as shear stiffness) measure rather than individually analyzing the storage and loss modulus values. The storage and loss modulus in a viscoelastic material are measures of the stored energy (elastic component) and the dissipated energy (viscous component), respectively. These two moduli can be uti-lized to interpret the relative solid-liquid behavior of the tissue (i.e., if the storage modulus is higher than loss modulus, the material is more solid-like than fluid-like, and vice versa). Shear stiffness is the root sum square of these two modulus values (i.e., magnitude). Using only the stiffness parameter potentially may restrict the preop-erative assessment capability of the surgeon by neglecting the relative elastic and viscous behavior of the tissue [26]. Based on these limitations in the available clinical studies, more thorough consideration of the mechanism of MRE and its current limitations is warranted for future investigations.

MRE considerations

Shear wave frequency

Since the initial description of MRE, it has been recognized that there is no single best mechanical frequency for MRE imaging in the brain. Much like the sound waves imaged with ultrasound, the shear waves imaged with MRE can be applied over a wide range of frequencies. Low frequencies are optimal for tissue penetration and minimize the amount of signal at-tenuation that is seen as the frequency increases [20]. Very low frequencies can decrease signal-to-noise ratios, but prolong the scan substantially with increased time to echo. Higher frequencies (i.e., shorter wavelengths) improve the resolution of the MRE image but are accompanied by a proportional increase in attenuation, which decreases the signal strength [20]. Furthermore, it has been clearly established that almost all of the biological tissues are viscoelastic and display frequency-dependent stiffness behavior. In the case of the brain, it has been demonstrated that brain tissue displays higher stiffness on MRE when higher frequencies are used (Fig. 2). Higher frequencies, therefore, are prone to inaccuracy due to the smaller displacement values. Similarly, the struc-tures that are in close proximity to anatomical areas that are not predisposed to large amplitude motion (e.g., skull base, dural folds) are weighted towards low frequencies and can
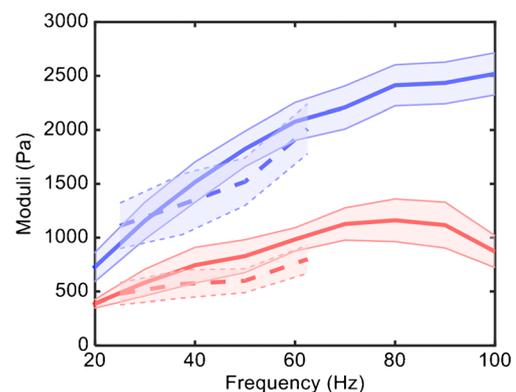

Fig. 2 Shear modulus measurements during MRE as a function of frequency. Two multi-frequency MRE studies, namely, Sack et al., 2009 (*dashed line*) and Kurt et al., 2016 (*solid line*), found a substantial variation of storage (*blue*) and loss (*red*) moduli for the average brain between 20 and 100 Hz

therefore appear falsely soft [5, 14]. This poses a significant obstacle to consistency measurements of meningiomas, which arise from dura-associated cells and that often interact with the skull. A clinical example of this is shown in Fig. 3.

Furthermore, MRE imaging measurements at a single frequency are tied to the experimental conditions in which they were produced, and therefore cannot be applied generally. In light of this, there has been a concerted effort to describe the optimal imaging methods for the brain and its subregions by performing MRE measurements at multiple frequencies. Sack et al. studied the impact of aging and gender on the brain's viscoelasticity by following a multi-frequency MRE protocol and chose 25, 37.5, 50, and 62.5 Hz as actuation frequencies [31]. They observed a monotonic increase in the shear stiffness, storage modulus, and loss modulus values for the brain average within this frequency range. Subsequently, Papazoglou et al. introduced a multi-frequency inversion scheme for obtaining viscoelastic parameters from MRE [28]. This proposed inversion scheme was utilized by Guo et al. to study the frequency-dependent shear moduli of white matter, gray matter, corpus callosum, and the head of the caudate nucleus between 30 and 60 Hz and with it were able to produce a frequency-averaged elastographic atlas of these brain structures [8]. Reiss-Zimmermann et al. used this same algorithm to image brain tumors, including seven meningiomas, though did not correlate these with intraoperative consistency [29]. More recently, Kurt et al. studied a larger range of frequencies, between 20 and 100 Hz and determined that the highest variation in storage, loss, and stiffness parameters for

brain average occurred between 40 and 80 Hz [18]. MRE imaging at multiple frequencies removes the bias associated with single-frequency measurements and has the potential to improve MRE's clinical applicability [2, 28, 31].

Effects of cranial anatomy

Recent work has identified the presence of significant MRE measurement distortions in relation to the cranial anatomy, particularly in the areas of the skull base and dural folds [5, 23]. Clayton et al. first focused on this possibility in a study of six healthy human subjects. They found that MRE mechanical oscillations applied during MRE generally propagate perpendicular to the surface of the skull [5]. However, their analysis revealed that anomalies in signal propagation arise at the midline, with the posterior midline region showing greater signal distortion than anterior [5]. This distortion corresponds to the falx cerebri, which is larger posteriorly and correlates with the signal abnormalities that are seen. They postulated that the tentorium cerebelli also contributes to the increased signal anomaly in the posterior midline [5].

McGrath et al. studied these effects of cranial anatomy on the accuracy of MRE in greater detail using a computational model of the human brain [23]. The authors specifically focused on the refractive and deflective effects of the meninges. They found that the MRE signals at the brain-falx interface and the brain-CSF boundary produce MRE wave reflections and distortions, which become more pronounced at higher frequencies [23]. Reflections and signal artifacts at the edges
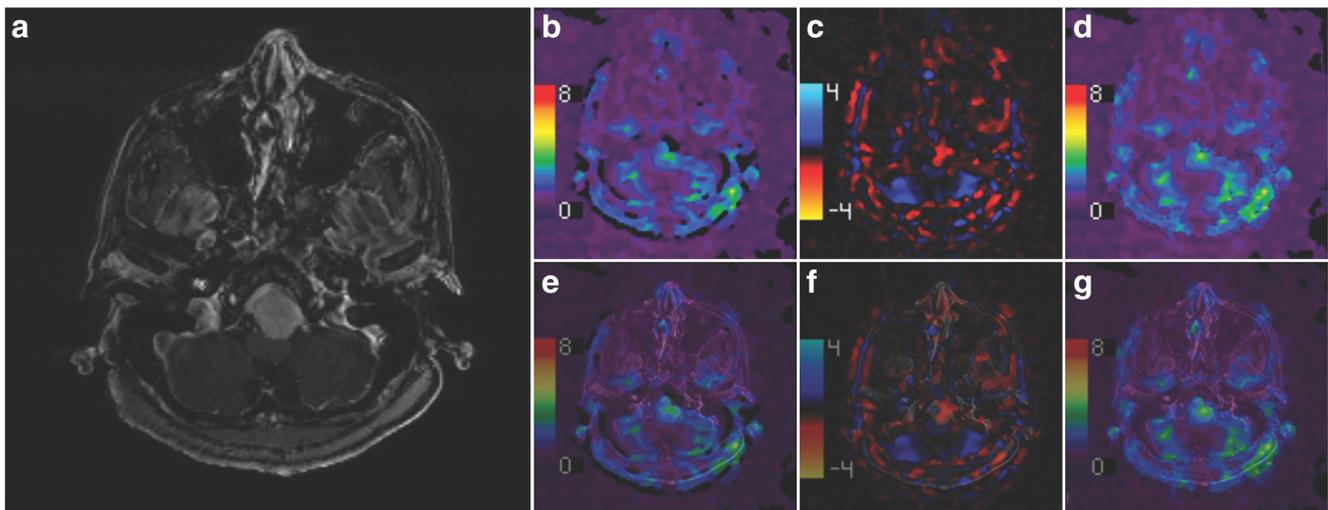

Fig. 3 A 55-year-old woman presented with neck pain of several years duration that had recently progressed to include cough, loss of balance, left hand numbness, and weakness of the left fifth digit. On imaging workup, she was found to have an anterior foramen magnum/medullary meningioma. MRE suggested a soft meningioma based on a combination of loss modulus, storage modulus, and shear stiffness measurements. Prior to planned surgery, she underwent embolization of the bilateral feeding vessels from the external carotid artery. Despite MRE imaging indications of a soft tumor, at the time of surgery, the meningioma had a stiff consistency that resulted in a challenging surgical resection. **a** Volumetric T1-weighted MRI demonstrating an anterior foramen magnum/medullary meningioma. **b** MRE storage modulus measurement indicating a low elastic component to the tumor. **c** MRE loss modulus measurement demonstrating a low viscosity component to the tumor. **d** MRE shear stiffness measurement suggesting a soft consistency of the tumor. **e** MRE storage modulus superimposed on T1 MRI. **f** MRE loss modulus superimposed on T1 MRI. **g** MRE shear stiffness superimposed on T1 MRI

of their model (representing the skull) and at the brain-falx interface were noted on three-dimensional simulations [23]. The dural folds (falx cerebri, tentorium cerebelli, falx cerebelli) acted as sources of wave reflection, echoing the experimental findings of Clayton et al. [5, 23]. McGrath et al. estimated that a 10–20% MRE distortion artifact might be present in regions associated with the dural folds and other elements of the cranial anatomy. This is compounded by the widely established skull-base distortions related to B_0 inhomogeneities that result from echo planar imaging (EPI) acquisition schemes, which are commonly used in MRE [6, 9]. These MRE distortions were noted by the authors in clinical investigations, who postulated, based on their results, that consistency discrepancies might arise when tumors are located near the skull base or the dural folds [11, 24]. Coupled with the supporting evidence from human and computational models, these findings exhibit the challenges of reliably correlating MRE meningioma consistency measurements in clinical practice, where these distortions could result in the inappropriate selection of surgical candidates.

Current and future research

Current efforts to improve MRE measurements are concentrated on accounting for the dural folds and skull base in MRE measurements. The efforts are still at the stage of understanding the underlying physics of if and how the skull-brain interface affects motion transmission during measurements. Recent in silico studies have focused on the effect of dural folds and dynamical characteristics of the skull [22, 23]. Experimental efforts have been made to decouple the skull motion from MRE brain tissue motion by using MRI-safe accelerometers, which would provide novel insights into how skull-brain interface influences shear wave transmission [1]. Along with the efforts that address the unknown physical phenomena, development of higher-resolution MRE methods and novel MRE actuation devices will likely improve the meningioma viscoelasticity measurements in the near future [3, 7, 13, 29].

Conclusions

The existing literature on meningioma consistency measurement with MRE is sparse and employs suboptimal imaging frequency parameters, limiting the applicability to clinical practice. The diagnostic accuracy of MRE is potentially further limited by the artifact introduced by the dural origins of meningiomas and the regional signal interference of surrounding cranial anatomy. Improved understanding and ability to account for the inaccuracies these structures pose are needed before MRE can be considered a clinically reliable diagnostic

tool. Clinical MRE studies in patients with meningiomas are the subject of our ongoing research.

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