# In Vivo Measurement of Brain Tumor Elasticity Using Intraoperative Shear Wave Elastography

## In-vivo-Messung der Elastizität von Hirntumoren mittels intraoperativer Scherwellen-Elastografie

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**Key words**
- brain
- ultrasound
- surgery

## Abstract

**Purpose:** Objective Shear wave elastography (SWE) enabled living tissue assessment of stiffness. This is routinely used for breast, thyroid and liver diseases, but there is currently no data for the brain. We aim to characterize elasticity of normal brain parenchyma and brain tumors using SWE.

**Materials and Methods:** Patients with scheduled brain tumor removal were included in this study. In addition to standard ultrasonography, intraoperative SWE using an ultrafast ultrasonic device was used to measure the elasticity of each tumor and its surrounding normal brain. Data were collected by an investigator blinded to the diagnosis. Descriptive statistics, box plot analysis as well as intraoperator and interoperator reproducibility analysis were also performed.

**Results:** 63 patients were included and classified into four main types of tumor: meningiomas, low-grade gliomas, high-grade gliomas and metastasis. Young's Modulus measured by SWE has given new insight to differentiate brain tumors: 33.1 ± 5.9 kPa, 23.7 ± 4.9 kPa, 11.4 ± 3.6 kPa and 16.7 ± 2.5 kPa, respectively, for the four subgroups. Normal brain tissue has been characterized by a reproducible mean stiffness of 7.3 ± 2.1 kPa. Moreover, low-grade glioma stiffness is different from high-grade glioma stiffness ($p = 0.01$) and normal brain stiffness is very different from low-grade gliomas stiffness ($p < 0.01$).

**Conclusion:** This study demonstrates that there are significant differences in elasticity among the most common types of brain tumors. With intraoperative SWE, neurosurgeons may have innovative information to predict diagnosis and guide their resection.

## Zusammenfassung

**Ziel:** Die Scherwellen-Elastografie (SWE) ermöglicht die Einschätzung der Steifigkeit von lebendem Gewebe. Sie wird routinemäßig bei Brust-, Schilddrüsen- und Lebererkrankungen angewandt, am Gehirn ist die Datenlage derzeit hingegen schlecht. Unser Ziel ist die Charakterisierung der Elastizität von normalem Hirnparenchym und von Hirntumoren mittels SWE.

**Material und Methoden:** Patienten mit geplanter Entfernung des Hirntumors wurden in die Studie eingeschlossen. Zusätzlich zum Routine-Ultraschall wurde die intraoperative SWE mittels Ultra-FAST-Ausstattung durchgeführt, um die Elastizität jedes Tumors und des umgebenden normalen Gewebes zu bestimmen. Vergleichende statistische Verfahren, Box-Plot-Analysen sowie die Auswertung der Intra- und Inter-Operator-Reproduzierbarkeit wurden ebenfalls durchgeführt.

**Ergebnis:** 63 Patienten wurden in die vier Haupttumortypen unterteilt: Meningeome, niedriggradige Gliome, hochgradige Gliome und Metastasen. Der mittels SWE gemessene Elastizitätskoeffizient lag für diese 4 Tumorgruppen bei 33,1 ± 5,9 kPa, 23,7 ± 4,9 kPa, 11,4 ± 3,6 kPa und 16,7 ± 2,5 kPa. Das normale Hirngewebe wurde durch eine reproduzierbare mittlere Steifigkeit von 7,3 ± 2,1 kPa charakterisiert. Darüber zeigt sich ein Unterschied in der Steifigkeit von niedriggradigen und hochgradigen Gliomen ($p = 0{,}01$), ebenso unterscheidet sich die Steifigkeit von normalem Hirngewebe sehr stark von der niedriggradiger Gliome ($p < 0{,}01$).

**Schlussfolgerung:** Es bestehen signifikante Unterschiede in der Elastizität der häufigsten Arten von Hirntumoren. Die intraoperative SWE kann dem Neurochirurgen neuartige Informationen für die Diagnosestellung und Unterstützung der Resektion bieten.

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## Introduction

Ultrasonography remains a major method for visualizing tumors in brain surgery. This imaging modality has been employed by neurosurgeons for several years [1, 2] as it offers real-time control of tumor resection. It has been proven that the use of intraoperative ultrasonography could have a benefit on the quality of life of patients with intracranial gliomas [3]. Ultrasonography will be a decisive issue in the next decade to improve brain tumor resection, regarding its portability, free-hand ability, real-time imaging acquisition, absence of brain shift and finally, to ensure cost efficiency. Three-dimensional ultrasonography-based navigation has also been developed to eradicate the intraoperative brain shift issue [4, 5]. Standard B-mode has been successfully used in intraoperative conditions to help tumor resection monitoring by delineation of tumor margins [6].

Tissue palpation has always been used by surgeons to differentiate normal brain tissue and lesions, but this remains a very subjective assessment. Ultrasonography now offers new modalities to assess living tissue stiffness, so-called elastography methods [7]. Dynamic elastography is based on the concept of shear wave propagation which allows one to quantify stiffness by measuring the local speed of shear waves generated directly within the tissue [8]. As shear waves propagate at a typical speed of 1 to 10 m.s-1, ultrafast ultrasound imaging [9] at frame rates higher than 1000 fps are mandatory for the real-time tracking of these transient mechanical vibrations [10, 11]. Preliminary approaches based on shear wave propagation have been evaluated in the framework of neurosurgery. Recently, the Supersonic Shear Imaging technique (SSI) was tested during intraoperative surgery through the shear wave elastography mode (SWE) to help physicians to detect a focal symptomatic epilepsy region [12]. In this study no obvious lesion was detected with B-mode ultrasound, but a focal area of increased stiffness was revealed by SWE approximately 1.5 cm under the brain surface.

Nowadays, ultrasound elastography and more specifically the SSI technique are routinely used in many specialties [13], such as in liver fibrosis assessment [14] and in breast imaging [15]. It also enables differentiation between benign and malignant lesions in multiple pathologies such as breast cancer [16] or thyroid nodules [17]. The aims of this study are to quantify the stiffness of normal brain tissue and brain tumors and to observe the ability of this biomarker to differentiate benign from malignant lesions in intraoperative conditions. The potential impact of these results for brain tumor characterization and resection is discussed as well as forthcoming applications.

## Materials and Methods

### Conventional Ultrasound and Shear Wave Elastography Acquisitions

Ultrasound images and stiffness maps were acquired with an ultrafast ultrasonic device (Aixplorer®, Supersonic Imagine, Aix-en-provence, France) driving a linear array (SL10 – 2, Supersonic Imagine, Aix-en-provence, France, 6 MHz central frequency, 192 elements). Conventional B-mode images were recorded during surgery in order to monitor brain tumor resection. The image size was typically 38.4 × 40.0 mm with 200 µm resolution. Stiffness maps were acquired with the same probe during surgery using the SSI technique as described in Bercoff *et al.* [10]. Briefly, shear waves were generated in the brain by focusing ultrasound during a short time (~100 µs). Then a movie of the shear wave propagation was captured in real time using an ultrafast ultrasonic scanner (up to 20,000 images/s). Stiffness maps were then extracted by analysis of the shear wave speed from recorded movies, since shear wave speed is directly linked to the stiffness in isotropic, locally homogeneous and quasi-incompressible media through the relationship: $E = 3\rho V_s^2$ (where $E$ is the Young's modulus (stiffness), $\rho$ the density (~1000 kg/m$^3$) and $V_s$ the shear wave speed in m/s). Finally, the stiffness was color-coded in kilopascals (kPa) and displayed over the classic B-mode image. The bluest coloration represented the softest elasticity, and the reddest represented the hardest. Stiffness quantification (and shear wave speed quantification) was then done by applying a region of interest (so-called Qbox®) in the desired anatomic region giving access to a mean value of stiffness and its standard deviation in kPa. The diameter of the Qbox was always chosen to be as big as possible regarding the tumor size, and at least 6 elastography maps targeting the tumor were recorded for each patient. Lesion and normal brain elasticity were quantified with full objectivity by the researcher blinded to the diagnosis.

### Population and Procedure

Between December 2012 and March 2014, all patients with a brain lesion requiring surgery were eligible for inclusion in the study. All types of tumor were recorded. Emergency surgeries were not taken into account. A total of 93 patients with a mean age of 53 years of age (with the total sample set ranging from 24 to 85 years of age), including 39 % male and 61 % female were recorded. All patients gave their informed consent. Ethical considerations had been previously validated by our institutional ethics committee, "Comité de Protection des Personnes – Ile-de-France VI – Pitié Salpêtrière".

At least one surgeon and one researcher were present at each session. In contrast to the surgeon, the researcher was always a blind observer, never aware of the diagnosis. In the operative room, the probe was disinfected according to our institution protocol and then inserted in a sterile plastic cap with sterile ultrasound gel on the top of the probe. During surgery, before or after dural opening, a standard B-mode acquisition was performed to detect the tumor and to assess its size, shape, boundaries, possible heterogeneities within the lesion and anatomical relationship to normal surrounding tissues. Normal brain structures, such as surrounding cortex, ventricles, etc., were also visualized. SWE was then performed at different locations by the surgeon: within the tumor, at the border of the tumor and within the normal brain when feasible. Special attention was paid when unusual structures were seen within the tumor, such as calcification or liquid cyst. Thus, elastographic windows were focused on these particularities to assess consistency changes within the tumor, with objective stiffness parameters.

At the end of the operation, final ultrasound imaging was performed with B-mode and SWE to confirm the quality of resection. Postoperative brain MRI assessed the final quality of removal. As the reference standard, the type and grade of each tumor were ascertained by anatomopathology analysis after surgery.

### Variability

Since the reproducibility of SWE has already been proved in organs like the breast [16] and the liver [14], the inter- and intraoperator variability was briefly studied. For five patients of the study, two surgeons were requested to assess the intraobserver and interobserver reproducibility regarding the probe positioning.

## Statistical Analysis

A boxplot test was used to study the stiffness distribution according to histological tumor types. The mean and standard deviation from the mean were calculated for each type of tumor for both tumorous and normal tissues. In addition, the Mann-Whitney U-test was used to delineate differences between the respective tumors types and between each type of tumor and normal brain. By conventional criteria, a two-tailed p-value under 0.05 was considered to be statistically significant. Receiver operating characteristic (ROC) analysis of stiffness was performed in order to evaluate the ability of stiffness to be a biomarker for benign and malignant tumor differentiation. The area under the ROC curve was estimated using the trapezoidal rule. Confidence intervals were stated at a 95 % confidence level.

The reliability of quantitative measurements was assessed by intra-class correlation coefficients (ICC). The relative standard deviation from the mean (%RSD) was also used to evaluate the inter-observer reproducibility and repeatability of SWE.

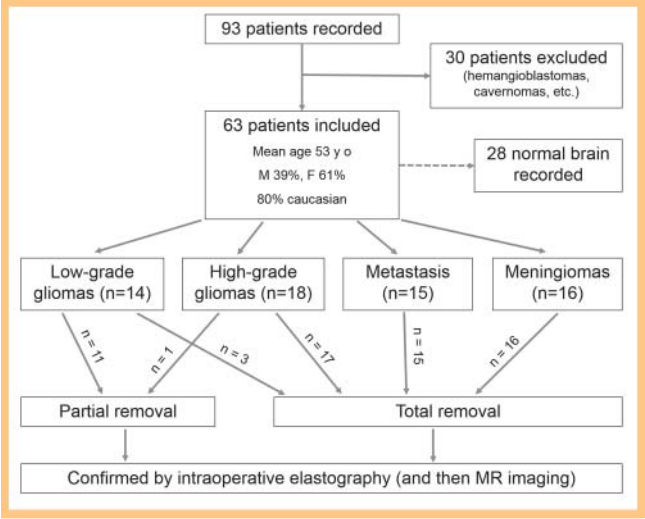


**Fig. 1** Distribution of all recorded patients.

## Results

### Population

Among the 93 patients recorded for the study, 63 patients were assigned to 4 categories that correspond to the main brain tumor types as follow: 16 meningiomas, 14 low-grade gliomas (WHO grade II), 18 high-grade gliomas (WHO grade III and IV) and 15 metastases. Therefore, the study included 30 benign tumors (meningiomas and low-grade gliomas) and 33 malignant tumors (high-grade gliomas and metastases) were studied. 25 patients with other lesion types (such as hemangioblastomas, cavernomas, *etc.*) were recorded but excluded from the present study because of their heterogeneity and rarity. Five patients had unusable results due to a very small surgical aperture. The patient distribution is summarized in **Fig. 1**.

Quantification of stiffness was feasible for all of the 63 patients included in the study and for 95 % of the total 93 imaged patients. The average time of the procedure was five minutes (min. 3, max. 10). Neither infection nor side effect was recorded.

### Ultrasonographic Imaging

During surgery, an elasticity map and stiffness values were acquired for every patient as shown for one patient in **Fig. 2**. Qbox diameters were always greater than 7 mm. Classification into four categories was then performed using histological results. All patients were pooled by subgroup with mean values and standard deviation from the mean of stiffness (Young's Modulus in kPa, shear wave speed in m/s) within the Qbox: 33.1 ± 5.9 kPa (3.3 ± 0.6 m/s), 23.7 ± 4.9 kPa (2.8 ± 0.6 m/s), 11.4 ± 3.6 kPa (1.9 ± 0.6 m/s) and 16.7 ± 2.5 kPa (2.4 ± 0.4 m/s), respectively, in meningiomas, low-grade gliomas, high-grade gliomas and metastases (**Fig. 3**).

Normal brain measurement was consistently tried and was successful in 44 % of the cases. The failures were due to a small surgical aperture, difficult access or loss of signal. The stiffness assessment of the normal brain was similar within the subgroups. A global mean elasticity of 7.3 ± 2.1 kPa (1.6 ± 0.5 m/s) was observed for normal brain tissue for all types of patient combined.

In **Fig. 4**, one patient of each studied tumor type is presented. MRI images were used to help during location determination

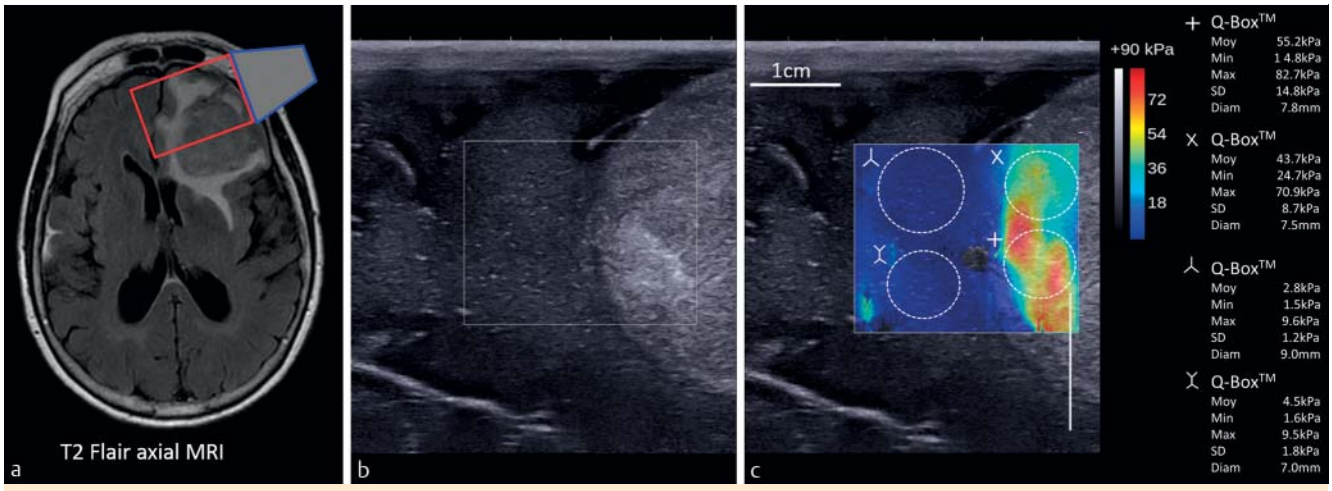


**Fig. 2** Imaging of the boundary between normal brain and tumor in a patient with meningioma. **a** T2 flair axial MRI, **b** standard ultrasound B-mode, **c** stiffness map and stiffness quantitative measurements in kPa (m/s) with Qbox®. Dimensions of ultrasound images: 38.4 mm wide, 45.0 mm depth. Blue trapezium: ultrasound probe. Red rectangle: imaging plan.

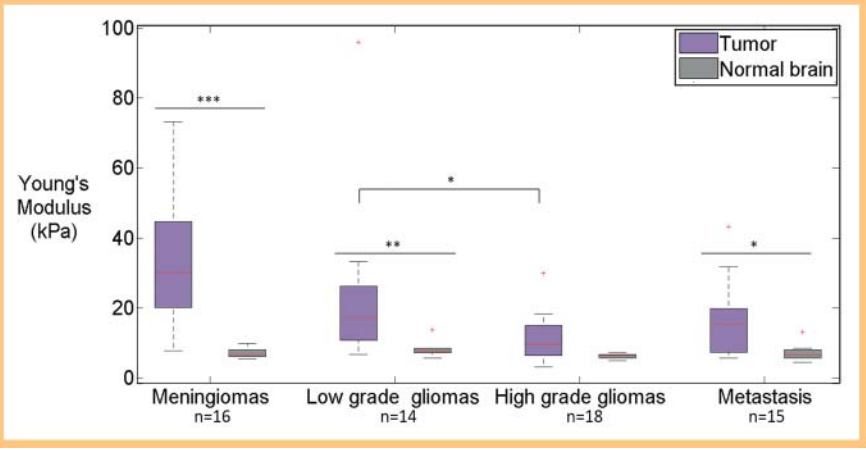


**Fig. 3** Young's Modulus in kPa of both tumor and normal brain for the four analyzed types of tumors: meningiomas, low-grade gliomas, high-grade gliomas and metastasis. The line through the middle of the box represents the median (50th percentile). The top and bottom of the boxes are the 75th and 25th percentiles. Between the upper and the lower adjacent lines are about 99 % of the values (Tukey Boxplot). All plus signs above these lines represent the outliers. For each category the n represents the number of patients. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ stand for each type of tumor for the p-value between normal brain and tumor. The star (*) between low-grade and high-grade gliomas stands for the p-value between these two tumorous tissues.

with ultrasound. Ultrasound images reveal echogenicity differences. Stiffness images reveal stiffness inside a region of interest (ROI). When shear wave propagation is not possible (obstacle, depth), there is no stiffness value (no colored pixel) on the stiffness image ROI (for example, in the top middle and left bottom of the ROI in the elastography image, **Fig. 4d**).

## Stiffness analysis by subgroup comparison

Regarding the mean stiffness values found for each subgroup, the Mann-Whitney U-test was used to observe how tissue stiffness could be a criterion to enable differentiation between the different types of tumor (**Table 1**).

First, the comparison between low-grade and high-grade gliomas was examined. With a mean elasticity of 23.7 ± 4.9 kPa, low-grade gliomas are significantly stiffer ($p = 0.01$) than high-grade gliomas, characterized by a mean elasticity of 11.4 ± 3.6 kPa (**Fig. 3**, **Table 1**). ROC curve analysis shows that SWE could enable differentiation between low-grade and high-grade gliomas (area under ROC curve = 0.76, $p = 0.002$, sensitivity: 77.8 %, specificity: 64.3 %). One example of the differentiation between low-grade and high-grade gliomas using intraoperative SWE is shown in **Fig. 5**.

More generally, statistical analysis using ROC curve analysis shows that SWE could enable differentiation between benign tumors (low-grade gliomas, meningiomas) and malignant tumors (high-grade gliomas, metastases). The area under the ROC curve which estimates the ability of elastography to differentiate benign from malignant tumors was 0.77 [0.64 – 0.87] (95 % confidence interval) ($p < 10^{-4}$, sensitivity: 87.9 % [71.8 – 96.6 %], specificity: 60.7 % [40.6 – 78.5 %]). The optimal cut-off for clinical use was 20 kPa. This differentiation between benign and malignant tumors can even be noticed by observing the color code in the SWE images (**Fig. 4**). All stiffness images have the same scale, from 1 kPa (dark blue) to 90 kPa (dark red). Colors like red, yellow and cyan can be observed for benign tumors, while almost only dark blue is present for malignant tumors.

Furthermore, intraoperative measurement of stiffness allows differentiation between low-grade gliomas and normal brain ($p = 7.10^{-3}$). With a mean elasticity of 23.7 ± 4.9 kPa, low-grade gliomas are significantly stiffer than normal brain characterized by a mean elasticity of 7.3 ± 2.1 kPa (**Fig. 3**).

## Variability analysis

Regarding the intra- and inter-variability during stiffness measurement using SWE, the best ICC was obtained for intra-operator repetition (ICC = 0.99) and reproduction (ICC = 0.99). Concerning inter-operator reliability, ICC was also good for both repetition (ICC = 0.96) and reproduction (ICC = 0.93). The mean and standard deviation were studied in every case (**Table 2**). The relative standard deviation was mostly below 30 %.

## Discussion

Improving the quality of brain tumor resection is an ultimate goal for neurosurgeons. Many technologies [18], such as intraoperative MRI control [19] or the use of 5-ALA fluorescence during surgery [20], are reported to be effective for improving brain tumor resection. Despite dissection under a microscope, surgeons cannot always differentiate normal tissue from brain tumor. This is the reason why tissue palpation is routinely used by surgeons, but this is a far from scientific guideline. In the present study, it has been attempted to define a stiffness atlas of brain tumors, divided into the four main types of lesion. This study is the first on ultrasonic elastography of brain tumors and demonstrates that the stiffness of the most frequent tumors differs significantly.

In practice, the main issue for surgeons was to distinguish the following in real time: high-grade and low-grade gliomas, low-grade gliomas and normal brain, metastases and high-grade gliomas. The comparison of these subgroups has therefore been studied. According to our intraoperative data, the SWE technique could be an important tool for the *in vivo* differentiation of malignant and benign lesions with good sensitivity (87.9 %) and relatively good specificity (60.7 %). More specifically, stiffness measurement could be invaluable in helping surgeons to quantitatively distinguish between high-grade and low-grade gliomas. This differentiation is very important because the tumor grade is significantly tied to prognosis and treatment strategies, whereas it is not always obvious to differentiate benign from malignant gliomas on the basis of MR imaging and intraoperative features. The use of SWE can therefore decrease the risk of error in intraoperative grading appraisal, help to adapt resection with respect to the grade and clarify the best intraoperative strategy.

On the other hand, stiffness measurement can improve differentiation between low-grade gliomas and normal brain ($p < 0.01$). In this case, SWE can help surgeons during resection by improving resection margin definition which is not trivial to the naked eye, reducing leftover resection or avoiding extra resection. In the case of glioma, invasive cerebral disease extending along white matter, surgery is an elaborate compromise between neu-

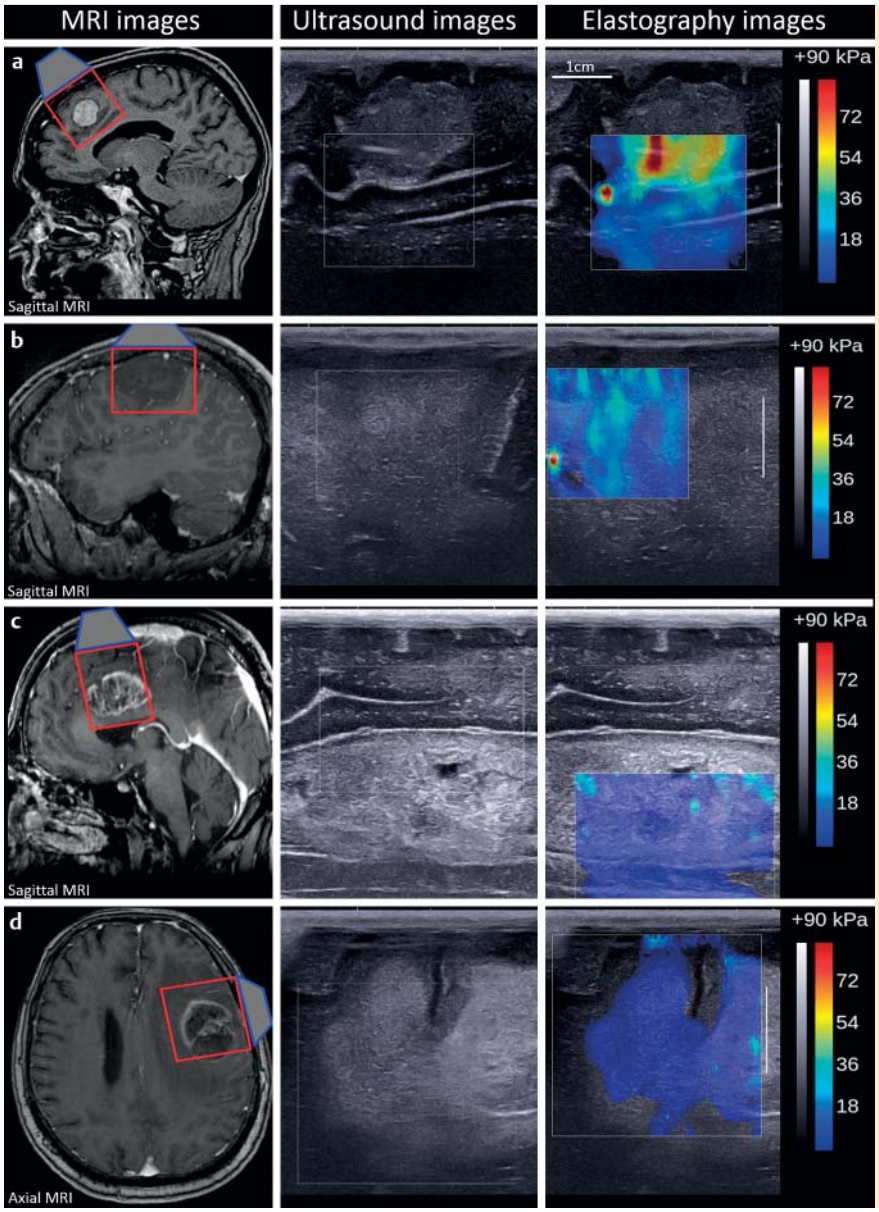


**Fig. 4** Example of MRI images (Gadolinium-enhanced T1), ultrasound images and elastography images for each of the different analyzed types of tumor: meningiomas **a**, low-grade gliomas, **b**, high-grade gliomas **c** and metastasis **d**. Dimensions of ultrasound images: 38.4 mm wide, 45.0 mm depth. Blue trapezium: ultrasound probe. Red rectangle: imaging plan.

**Table 1** P-value for the stiffness comparison between the different types of tumor.

| | Mann-Whitney test: p-value | Mann-Whitney U |
|---|---|---|
| high-grade gliomas vs. metastasis | $p = 0.17$ | 96 (80) |
| high-grade gliomas vs. meningiomas | $p = 10^{-4}$ | 29 (86) |
| high-grade gliomas vs. low-grade gliomas | $p = 0.01$ | 60 (74) |
| low-grade gliomas vs. metastasis | $p = 0.33$ | 82 (59) |
| low-grade gliomas vs. meningiomas | $p = 0.04$ | 54 (64) |
| metastasis vs. meningiomas | $p = 3.10^{-3}$ | 40 (70) |

By conventional criteria, two-tailed P-values under 0.05 are statistically significant. To be statistically significant, Mann-Whitney U has to be equal to or less than the critical value in brackets, according to the table of critical U values for the Mann-Whitney test for different group sizes, for a two-tailed test at the 0.05 significance level.

rology and oncology where tumor grade and boundaries are decisive information for neurosurgeons to maximize tumor resection while minimizing the risk of permanent neurological morbidity.

Concerning metastases and high-grade tumors, unfortunately the measurement of Young's modulus in intraoperative surgery does not allow differentiation between these two types of tumors. Both of these malignant tumors have low mean elasticity values – partially due to central necrosis. Nevertheless, the MRI features of both types of tumors are often precise enough to get a preoperative idea of their pathological nature.

Our study provides evidence to justify the use of intraoperative SWE in brain tumor surgery. Such imaging helps surgeons to quantitatively distinguish benign from malignant brain tumors (especially in gliomas) and thus to provide the optimum extent of resection. From this finding, it seems obvious that ultrasound elastography can provide complementary data for diagnosis, additionally to preoperative MR imaging. In 2005, Scholz et al. [21] described the first assessment of tumor stiffness by comparison with the normal brain, using a "vibrography" technique. This pio-

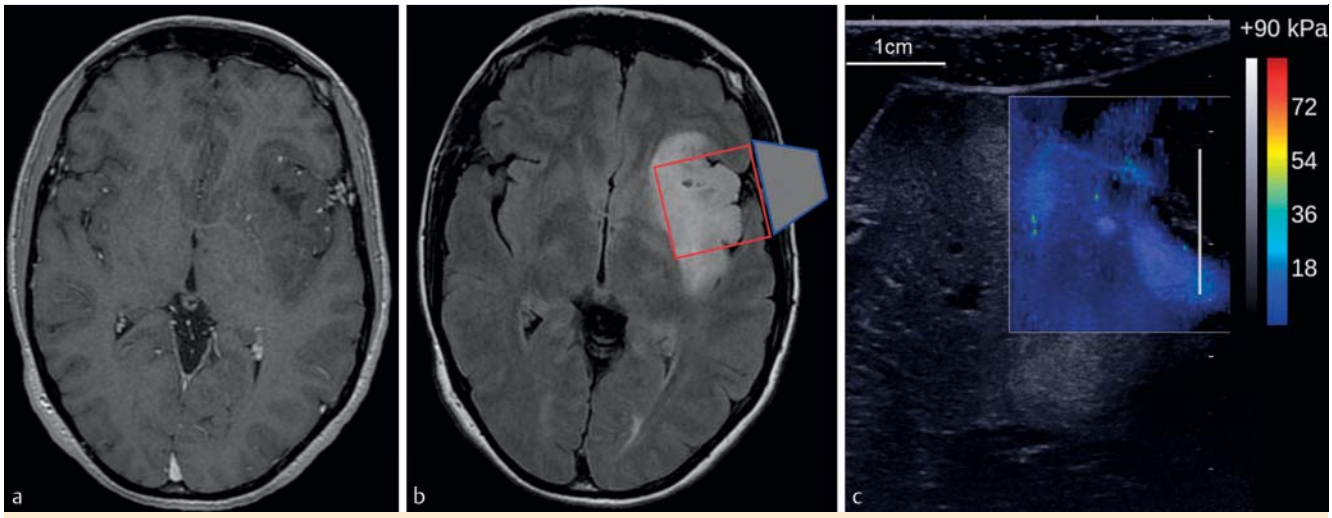


**Fig. 5** Imaging in a patient with glioma, ranked high grade with the elastography technique. **a** Gadolinium-enhanced T1 axial MRI that shows no enhancement of the glioma, **b** T2 Flair axial MRI of the corresponding tumor, **c** SWE image that shows a low elasticity value (global mean elasticity: 10kPa). Dimensions of ultrasound images: 38.4 mm wide, 45.0 mm depth. Brain MRI revealed a left insular glioma without gadolinium enhancement and MR spectroscopy was in favor of a low-grade tumor. Intraoperative SWE showed that the lesion was very soft (10 kPa) tending to demonstrate that the tumor was a rather high-grade one. Final pathology report confirmed that the glioma had high-grade features of an anaplastic glioma (classified WHO grade III).

**Table 2** Inter- and intra-operator analysis.

| repeatability | | | | | | reproducibility | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| (kPa) | surgeon 1 | | surgeon 2 | | | (kPa) | surgeon 1 | | surgeon 2 | | |
| | mean 1 | SD 1 | mean 2 | SD2 | %RSD | | mean 1 | SD 1 | mean 2 | SD2 | %RSD |
| patient 1 | 15.5 | 1.8 | 15.3 | 4.2 | 19.8 | patient 1 | 13.3 | 1.6 | 11.6 | 2.0 | 15.5 |
| patient 2 | 34.3 | 0.3 | 44.1 | 5.7 | 16.4 | patient 2 | 35.3 | 1.9 | 38.0 | 2.4 | 6.8 |
| patient 3 | 24.7 | 2.0 | 24.3 | 2.1 | 7.9 | patient 3 | 18.3 | 1.8 | 30.4 | 6.5 | 32.1 |
| patient 4 | 5.0 | 0.6 | 3.4 | 0.3 | 22.5 | patient 4 | 6.1 | 1.4 | 4.5 | 0.9 | 26.3 |
| patient 5 | 12.8 | 0.4 | 13.2 | 0.8 | 5.1 | patient 5 | 9.5 | 2.6 | 13.5 | 2.0 | 26.2 |

To assess inter-observer repeatability and reproducibility, the mean elasticity and standard deviation (SD) were calculated for surgeon 1 over five acquisitions, then for surgeon 2 over five other acquisitions. Finally the relative standard deviation from the mean (%RSD) was assessed inter-operatively for every patient.

neer study demonstrated that normal brain tissue and brain tumors have enough elastic properties to be detected and differentiated. With SWE it is now possible to quantitatively measure the elasticity of tissue, which offers an objective, precise and reproducible evaluation.

Since keeping operation time as short as possible is a major concern in neurosurgery, it is important to note that stiffness measurement is not time-consuming. Furthermore, this technology appears to be safe. Neither side effects nor postoperative infections have been observed. Compared to other intraoperative image-guided neuronavigation methods, SWE is not impacted in the same way by brain shift [22], which can make it difficult to locate the lesion within the brain. It seems obvious that future neuronavigation systems will come from the co-registration of preoperative MR imaging and 3 D intraoperative ultrasonography [23] and/or from intraoperative MRI improvement [24]. Because of the intuitive manageability of our ultrasonic device and the good reproducibility of our stiffness data, SWE could further reinforce surgical intraoperative guidance in a perspective of total resection. This has to be confirmed in larger series.

Despite our promising results, this study has some limitations. First, the probe has a defined maximal imaging field that cannot always include a whole tumor, depending on its size. However, this does not constitute a major issue as one can easily move the probe in the skull aperture to get a complete scan of the tumor. Concerning the depth of the field, there was no problem getting the whole lesion in the image, as the device allows acquisitions to a depth of 40 mm. However, images could not be acquired below this point, so that deep normal brain surrounding tissues and/or the controlateral cerebral hemisphere were/was not always seen. With the device used in this study, only 5 % of data (93 patients) was not usable due to a lack of signal in the tissues. This can be resolved by using a lower frequency probe. As an example, at 3 MHz, acquisitions can be obtained at a depth of 150 mm but with a loss in resolution.

Finally, recent studies in MR elastography have showed that in the case of a neuropathology, such as Alzheimer's disease [25] and Parkinson's disease [26], significant softening of the brain parenchyma and of the basal ganglia region occurs respectively. The use of SWE in such studies is currently limited by skull bones and requires a craniotomy. Nevertheless, classic low-frequency (usually 2 MHz) transcranial Doppler (TCD) [27] was developed to facilitate ultrasonic waves passing through skull natural windows (temporal or occipital window). The TCD technique could

be improved in order to solve this issue. As an example, the use of aberration correction techniques – such as the time-reversal concept in therapeutic high-intensity focused ultrasound [28 – 30] – could be implemented in the ultrasound elastography field. After further development, transcranial SWE could be used preoperatively through the skull windows.

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