Advantages and Limitations of Intraoperative Ultrasound Strain Elastography Applied in Brain Tumor Surgery: A Single-Center Experience

BACKGROUND: Strain elastography is an intraoperative ultrasound (ioUS) modality currently under development with various potential applications in neurosurgery.

OBJECTIVE: To describe the main technical aspects, usefulness, and limitations of ioUS strain elastography applied in a large case series of brain tumors.

METHODS: We retrospectively analyzed patients who underwent craniotomy for a brain tumor between March 2018 and March 2021. Cases with an ioUS strain elastography study were included. The elastograms were processed semiquantitatively, and the mean tissue elasticity (MTE) values were calculated from the histogram of intensities. An analysis was performed to correlate the histopathological groups and the tumor and peritumoral MTE values using the Kruskal–Wallis test and a decision tree classifier. Furthermore, elastogram quality was assessed to discuss possible artifacts and weaknesses of the ultrasound technique.

RESULTS: One hundred two patients with the following histopathological diagnoses were analyzed: 43 high-grade gliomas, 11 low-grade gliomas, 28 meningiomas, and 20 metastases. The tumor MTE values were significantly different between the histopathological groups (P < .001). The decision tree classifier showed an area under the curve of 0.73 and a classification accuracy of 72%. The main technical limitations found in our series were the presence of artifacts after dural opening, the variability of the frequency and amplitude of the mechanical pulsations, and the challenge in evaluating deep lesions.

CONCLUSION: Tumor stiffness revealed by ioUS strain elastography has a plausible histopathological correlation. Thus, this fast and versatile technique has enormous potential to be exploited in the coming years.

KEY WORDS: Brain tumor, Ultrasound, Elastography, Machine learning

Intraoperative ultrasound (ioUS) has recently proven to be a valuable tool within the neurosurgical armamentarium.1-3 Its versatility and low cost make it an optimal intraoperative imaging technique that can be used in almost any center.

Improvements in image quality, the incorporation of new ultrasound modalities such as contrast-enhanced ultrasound and elastography, and the possibility of integrating MRI through navigated ultrasound have fostered a resurgence of this technique, gaining followers in recent years.4-9

Tissue stiffness assessed by palpation for the diagnosis of neoplasms has been used for several years. Ultrasound elastography has been recently developed to display information about tissue stiffness through images.10-12 Its use is widespread in other surgical specialties and shows incremental application in neurosurgery.13-17 In brain tumors, elasticity/stiffness contributes to surgical planning, but this physical property may also be related to the histology and aggressiveness of the tumors.18,19 If we add advanced image processing techniques and algorithms based on

ABBREVIATIONS: CA, classification accuracy; HGG, high-grade glioma; LGG, low-grade glioma; ioUS, intraoperative ultrasound; IQR, interquartile range; METs, metastases; MTE, mean tissue elasticity; PR, partial resection; STR, subtotal resection; SWE, shear wave elastography.

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artificial intelligence, the capacity of this modality opens a new line of research yet to be developed.

This study aims to share our experience in the performance, interpretation, and analysis of ioUS strain elastography in brain tumors. Furthermore, we highlight the most relevant technical aspects, the technique’s main limitations, and future perspectives.

METHODS

Patient Selection

A retrospective analysis was performed on patients diagnosed with brain tumors consecutively operated on in our center between March 2018 and March 2021. Patients with an ioUS study, including the strain elastography modality, were selected. Cases with poor-quality ioUS images because of artifacts were discarded. Written informed consent was obtained from all patients, in addition to the approval of the ethics committee of our center and following the strengthening the reporting of observational studies in epidemiology guidelines.

ioUS Image Acquisition Technique

All cases underwent craniotomy, ensuring that its dimensions were sufficient for the placement and maneuverability of the ultrasound probe. The first ultrasound image acquisition was performed after craniotomy and before dural opening. Our ultrasound equipment was a Hitachi Noblus model with a C42 microconvex probe in a frequency range of 4 to 8 MHz, a scan width of 20 mm radius, and a field of view scan angle of 80°. The probe was protected with double sterile sheets, and a minimum amount of conductive gel was used inside the sheet.

To perform the strain elastography, the probe was kept in a perpendicular position to the dura in orthogonal planes in which the largest tumor diameter could be seen. Because biological tissue deforms in a nonlinear manner, precompression should be minimal with the probe held lightly in contact with the dura. Strain images are produced by using the probe to apply constant gentle pressure toward the brain. The consequent tissue displacement is tracked between pairs of echo frames, and strain is computed from the axial gradient of the displacements. As a guide for constant pulses, the ultrasound scanner gives a scale indicating the optimal stress and providing real-time feedback to the examiner on the degree and uniformity of the compression technique. The most valuable frames for evaluating strain images with an excellent signal-noise ratio are those with a steady rate of displacement, that is, during the time of downward or upward movement of the transducer. The ultrasound screen simultaneously displays the B-mode image and a color map translucently superimposed on the conventional B-mode image, called an elastogram. The color scale ranges from red (soft) to blue (hard). A regular color pattern obtained in several consecutive frames indicates a reliable technique. Quantitative elasticity measurements cannot be achieved because the local amount of stress is unknown. Thus, strain elastography is a qualitative method in which relative stiffness differences are displayed. Table 1 shows a quick guide to perform an elastosonographic study and summarizes the main technique’s features.

| TABLE 1. A Quick Guide to Perform Strain Ultrasound Elastography for Brain Tumors and a Summary of Its Advantages and Limitations |
|---------------------------------------------------------------|
| **Step-by-step guide** | **Advantages** | **Pitfalls** |
| • Select a suitable probe for cranial application. If it is not sterilizable, use sterile covers and place a minimum amount of conductive gel | Ultrasound strain imaging provides a sharper contrast of tumor boundaries compared with B-mode | It is an operator-dependent ultrasound technique |
| • Perform a craniotomy wide enough to allow maneuverability of the probe | Elastography allows a real-time assessment of tumor consistency. For meningiomas, it permits the identification of the separation plane from adjacent noble structures. This information is used for adapting the surgical strategy | Depending on the manufacturer of the ultrasound scanner, interobserver variability may occur if mechanical pulses are required to generate the elastograms |
| • Try to maintain the integrity of the dura after craniotomy | Ultrasound strain images can be used to perform a semiquantitative analysis based on the intensity histogram. Thus, subjectivity in the evaluation of the elastograms is reduced | The quality of the elastograms is susceptible to being affected by dural tears, tumors with extensive calcified areas, large cystic components, and deeply located tumors |
| • First, acquire images in B-mode and explore anatomic landmarks. Use navigated ultrasound if available | The analysis of radiomic features and deep learning–based models give elastograms a diagnostic and prognostic capacity to be exploited in future studies | The deformation of the parenchyma and the interposition of fluids within the surgical cavity seriously limit ultrasound strain elastography performance after surgical resection |
| • Place the probe perpendicular to the dura. Perform gentle mechanical compressions of constant amplitude and frequency. The pulse wave graph can help to standardize the acquisition | | |
| • Save Images in various orthogonal planes to obtain a qualitative assessment of tumor heterogeneity. Acquiring multiple images in the same plane will help to reduce intraobserver variability | | |
Elastogram Processing

A semiquantitative analysis was performed to transform the colorimetric scale into a dimensionless scale of values called mean tissue elasticity (MTE). The MTE is calculated from the histogram of intensities of the pixels and expressed in arbitrary units. To perform this analysis, the elastograms were converted to hue–saturation–brightness format using ImageJ software version 1.8.0 (National Institutes of Health). The new scale uses hue images with values ranging from 0 (hard) to 256 (soft).

Three images were selected for each patient on which tumor segmentation and elasticity measurements were performed. The tumor was manually segmented using the free-hand tool of ImageJ to create the regions of interest (ROIs). Three circular ROIs with a diameter of 20 pixels were also created for the peritumor, placed in the areas of alteration of echogenicity surrounding the tumor area as shown in Figure 1.

Statistical Analysis

The distribution of the quantitative variables was evaluated using the Kolmogorov–Smirnov test. The comparison between the histopathological groups and their MTE values in the tumor and peritumoral regions was performed using the Kruskal–Wallis test. Then, post hoc comparisons were made using Dunn’s test with Holm’s correction.

A classification model based on the tumor and peritumoral MTE values was developed using 3 categories: glioma, meningioma, and metastases (METs). A decision tree was used as a classification algorithm. Then, a 10-fold cross-validation process was performed. Basic statistics were performed using R version 4.0.5 (R Foundation for Statistical Computing), and the decision tree was elaborated using Orange version 3.28.0 (University of Ljubljana).24

RESULTS

During the study period, 150 patients with a diagnosis of brain tumor underwent surgery. Of these, 40 patients were excluded because they did not have an ioUS study. Furthermore, 8 patients were not included because they had poor-quality ioUS images, making their interpretation and analysis impossible. The sources of artifacts in these cases were extensive dural tears (4), deep-located tumors (3), and, in 1 case, an extensively calcified meningioma.
Thus, 102 patients met the selection criteria. Histopathological diagnoses were 43 high-grade gliomas (HGGs), 11 low-grade gliomas (LGGs), 28 meningiomas, and 20 METs. The characteristics of each group and other clinical and demographic variables are shown in Table 2.

The tumor MTE values were significantly different between histopathological groups, \( P < .001, \chi^2 = 46.34, \) and \( \varepsilon^2 = .45 \). Thus, HGGs were characterized by a softer pattern with MTE values of 79.3 (19.3), followed by LGGs with 88.7 (13.7) and METs with 114 (29.2). Finally, meningiomas exhibited a significantly higher stiffness than the abovementioned tumor groups, with a MTE value of 120 (30.9).

There were also significant differences in the MTE values regarding the peritumor, \( P < .001, \chi^2 = 25.47, \) and \( \varepsilon^2 = .25 \). Thus, in HGGs (93.2 [25.5]) and LGGs (91.6 [19.6]), the peritumoral region shows lower stiffness values than meningiomas (126 [31.9]) and METs (122 [37.3]) (Figure 2 and Table 3).

Among the histological types of gliomas, tumor MTE values had the following distribution: astrocytoma grade II = 94.2 (20.8), anaplastic astrocytoma grade III = 73.7 (6.5), oligodendroglioma grade II = 80.2 (3.3), anaplastic oligodendroglioma grade III = 73.7 (6.5), and glioblastoma = 84 (18.4). The following peritumoral MTE values were obtained: astrocytoma grade II = 94.8 (11.1), anaplastic astrocytoma grade III = 101 (25.9), oligodendroglioma grade II = 83.7 (17.6), anaplastic oligodendroglioma grade III = 121 (16.70), and glioblastoma = 89.3 (18.5). No significant differences were found between these groups.

The classifier decision tree was applied with a pruning technique of at least 2 instances in leaves and at least 5 instances in each node with a maximum depth of 5. It is a binary tree with stop splitting when reaching 95% of the instances. In the total sample, the area under the curve of the average over classes was 0.97 and the classification accuracy (CA) was 86%. After 10-fold cross-validation, the area under the curve of the average over classes was 0.73 and the CA was 72%. However, it should be mentioned that...
for the glioblastoma multiforme class, the model reaches a CA of 85% and a sensitivity of 91%. However, for meningiomas and METs, the CA falls to 76% and 81% and the sensitivity to 68% and 25%, respectively. A summary of the results is shown in Table 4 and Figure 3 (see Figure, Supplemental Digital Content 1, http://links.lww.com/ONS/A131, which illustrates the model’s classification performance by confusion matrices, and Figure, Supplemental Digital Content 2, http://links.lww.com/ONS/A132, which shows the decision tree classifier).

### DISCUSSION

In this study, we demonstrate that ioUS strain elastography is a safe and easy-to-apply technique. Furthermore, through the semiquantitative analysis of the elastograms, it is possible to characterize the different tumor types based on the calculated values of MTE.

Among the strengths of our study, we can mention that this is the largest published series on the application of ioUS strain elastography in brain tumor surgery. In addition, we are pioneers in applying this type of semiquantitative analysis of elastograms in brain tumors.

### Elastogram Quality

The image quality of ultrasound images and elastograms is susceptible to multiple factors. The ultrasound equipment used in our series requires gentle mechanical compressions to acquire strain images. However, other ultrasound scanners are capable of generating elastograms using spontaneous brain pulsations. The dura mater offers resistance, and thanks to its elastic capacity, it is possible to perform more homogeneous pulsations, which translates into more uniform elastograms and fewer signal voids (Figure 4). In the cases in which small dural tears occurred, the quality of the elastogram did not vary significantly, at least in a qualitative way (Figures 5A and 5B).

Regarding the ROI size, strain elastography demonstrates the relative stiffness of tissue, so it is crucial to include enough normal tissue surrounding the tumor. The most suitable image quality was registered in phantom experiments when the lesion of interest covered 25% to 50% of the ROI. Caution must be taken when using a convex probe because the region immediately in the middle of the transducer could apply more stress than the lateral portions of the probe, producing a “lateral stiffness artifact.”

Another factor that influences the quality of the image is the presence of cystic areas, as shown in Figure 5C and 5D. The interposition of liquid content can seriously influence the transmission of mechanical pulsations. In these cases, the penetration of mechanical waves does not occur homogeneously throughout the tissue to be explored. A commonly described artifact is the blue–green–red sign encountered in small cystic tumors. Large cystic lesions are more likely to be seen as “black holes.”

### TABLE 3. Analysis of MTE Values of Tumor Types in Their Different Regions

| Region                  | Pathology | n  | Median | IQR | χ² | df | P    | 95% CI | Comparison P (Holm) | Comparison P (Holm) |
|-------------------------|-----------|----|--------|-----|----|----|------|--------|---------------------|---------------------|
| Tumor (MTE)             | HGG       | 43 | 79.3   | 19.3| 46.34 | 3  | <.001| 0.46   | 0.31-0.60            | HGG-LGG .366         |
|                         | LGG       | 11 | 88.7   | 13.7| 53.26 | 3  | <.001| 0.64   | 0.46-0.82            | HGG-meningioma <.001 |
|                         | Meningioma| 28 | 120    | 30.9| 41.20 | 3  | <.001| 0.64   | 0.46-0.82            | LGG-meningioma .009  |
|                         | Meningioma| 20 | 114    | 29.2| 25.47 | 3  | <.001| 0.12   | 0.04-0.25            |
| Peritumoral region (MTE)| HGG       | 43 | 93.2   | 25.5| 25.47 | 3  | <.001| 0.25   | 0.12-0.44            | HGG-LGG .86          |
|                         | LGG       | 11 | 91.9   | 19.6| 25.47 | 3  | <.001| 0.25   | 0.12-0.44            | HGG-meningioma <.001 |
|                         | Meningioma| 28 | 126    | 31.9| 25.47 | 3  | <.001| 0.25   | 0.12-0.44            | LGG-meningioma .011  |
|                         | Meningioma| 20 | 122    | 37.2| 25.47 | 3  | <.001| 0.25   | 0.12-0.44            | Meningioma-METs .905 |

df, degrees of freedom; HGG, high-grade glioma; IQR, interquartile range; LGG, low-grade glioma; METs, metastases; MTE, mean tissue elasticity.

### TABLE 4. Performance Evaluation of the Classification Model by the Decision Tree Algorithm

| Model                      | AUC  | CA   | Precision | Recall |
|----------------------------|------|------|-----------|--------|
| **Training**               |      |      |           |        |
| Average over classes       | 0.968| 0.863| 0.860     | 0.863  |
| Glioma                     | 0.983| 0.933| 0.883     | 0.981  |
| Meningioma                 | 0.978| 0.922| 0.833     | 0.893  |
| METs                       | 0.932| 0.882| 0.833     | 0.500  |
| **10-fold cross-validation**|      |      |           |        |
| Average over classes       | 0.734| 0.716| 0.702     | 0.716  |
| Glioma                     | 0.859| 0.833| 0.831     | 0.907  |
| Meningioma                 | 0.725| 0.765| 0.559     | 0.679  |
| METs                       | 0.573| 0.814| 0.566     | 0.250  |

AUC, area under the curve; CA, classification accuracy; METs, metastases.
Elastograms can also vary depending on the tumor’s location and, therefore, on how the mechanical impulse spreads. For example, in deep-located tumors, the distance from the probe to the tumor can produce artifactual images and overestimate its stiffness (Figure 5E).

**Meningiomas**

In meningioma surgery, strain elastography permits addressing the resection of the tumor with reliable information about its stiffness. The presence of a cleavage plane and the relationships with surrounding neurovascular structures allow the surgeon to adapt the surgical technique and anticipate the extent of the resection. This utility is well described in the work of Della Pepa et al.28 The authors apply ioUS strain elastography in 36 meningiomas and conclude that this technique has a better predictive capacity for tumor consistency and the slip-brain interface than MRI.

**Gliomas**

Gliomas are usually tumors softer than the surrounding brain parenchyma, with extensive involvement of the peritumoral white matter, which also shows less stiffness. Peritumoral infiltration may explain a change in elasticity in these regions, as has been postulated.15,32 Ultrasound strain images provide better discrimination between normal brain tissue and glial tumor tissue than conventional ultrasound B-mode imaging, as reported by Selbekk et al.33 through a quantitative analysis of 45 measurements in 15 patients (8 LGGs and 7 HGGs) of the contrast curves of B-mode intensities and strain magnitudes.

**METs**

METs also tend to be softer than the normal parenchyma. However, the stiffness of the white matter does not seem to be significantly different compared with that found in primary tumors. Possibly, the presence of pure vasogenic edema in METs and meningiomas could explain this difference in peritumoral elasticity.

**Histological Classification Based on Elastography and Glioma Grading**

Our results show significant differences in tumor and peritumoral stiffness expressed through MTE between gliomas and the rest of the tumor groups (METs and meningiomas). These results are validated by applying the classification algorithm based on a
FIGURE 4. Examples of modifications in the elastograms by different types of compressions. In the right lower corner of each image, the ultrasound scanner shows a graph on a unitless scale from −5 to +5 representing the frequency and amplitude of manual compressions. 

A. High-frequency pulses affect the quality of deeper zones, producing heterogeneous images. 

B. Slower compression with less amplitude can produce elastograms with black zones (white asterisk). 

C. Regular compressions with a constant amplitude generate the best quality elastograms.
decision tree, which reaches a precision of 70%. However, the model shows a better performance in the classification of glioblastoma multiforme compared with the other types of tumors. In addition, we highlight that the results of our classification model are based on ultrasound strain images being inferior to other studies that apply MRI and deep learning–based algorithms with accuracy values close to 98%.34-36 Nevertheless, the simplicity and cost-effectiveness of ultrasounds contrast with the excessive complexity required for the elaboration and interpretation of this type of model.

Regarding glioma grading by ioUS elastography, we found previous descriptions in the literature in which a lower elasticity was observed in HGG than in LGG.18,19,27,37 However, in our study, although tumor MTE values were indeed lower in high-grade glioma than in low-grade glioma (79.3 vs 88.7), these differences were not statistically significant.

### Strain Elastography vs Shear Wave Elastography

Shear wave elastography (SWE) is a quantitative method that offers an estimated value of the tissue stiffness that can be...
expressed in either the shear wave speed through the tissues in meters per second or converted to Young’s modulus and expressed in kilopascals. Using strain elastography, it is not feasible to perform compressions on the deformed parenchyma and the interposition of fluid that fills the surgical cavity. In this sense, SWE stands as the best option to assess residual tumors. Recently, Chan et al. analyzed 34 cases of brain tumors of different histologies and used SWE to assess residual tumors. The authors report that SWE has greater sensitivity to detect residual tumor than the surgeon’s perception, and they did not find significant differences compared with MRI.

Limitations

We are aware of the limitations of our work, such as the lack of an assessment of intra- and interobserver variability. We emphasize that a single surgeon (S.C.) acquired all the intraoperative images in our case series. In addition, because of the technical limitations of the ultrasound scanner, we cannot perform a correlation analysis with the MRI findings because of the absence of navigated ultrasound.

Brain Elastography and Future Perspectives

The usefulness of intraoperative cerebral elastography goes beyond the characterization of the histopathological types and serves as a support for surgical resection. Knowledge of the elasticity and stiffness of tissues is biologically based and is related to the cytoarchitecture of tumors and their ability to infiltrate gliomas.

Advanced image processing techniques, such as texture analysis, also known as radiomics, can increase the diagnostic potential of this imaging technique and even contribute to predicting the survival and progression of primary brain neoplasms.

Nevertheless, image processing automation and the combination of recognition techniques based on artificial intelligence are yet to be explored in depth.

CONCLUSION

Our experience with brain tumor ioUS transmitted through this series of cases allows us to confirm the applicability of strain elastography in brain tumor surgery. In addition, this technique provides relevant information for surgical planning and differentiation of the different tumor types. Its potential is still under development, but it is already emerging as a valuable neurosurgical tool for the near future.

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Supplemental Digital Content 1. Figure. Confusion matrices show the distribution of predicted cases by the decision tree A, in the training cohort and B, after cross-validation.

Supplemental Digital Content 2. Figure. The tree viewer tool allows visualization of the results of the decision tree. For the first division of the sample into 2 parts, the feature with the most significant relevance is used (tumoral [tum] MTE). Then, each node contains a decision criterion based on a single feature (tumor [tum] or peritumour [peritum] MTE). This procedure is repeated until no more divisions are possible. Glio, glioma; Menin, meningioma; METs, metastases; MTE, mean tissue elasticity.

COMMENT

Despite the fact that elastography is not a new technique, it has not yet reached the status of routine application during brain tumor surgery. The authors present their experience gained in a variety of tumors. They could demonstrate the clinical applicability of the technology as an adjunct of intraoperative imaging. Tumor stiffness quantified by strain elastography was plausible with tumor histology. The authors see elastography as an emerging valuable tool; however, an actual clinical benefit of elastography is not yet within reach because the differentiation between a meningioma and a glioma during surgery does not really add clinical value. Potentially, elastography will provide interesting scientific data on the texture of a tumor. It will be interesting to see whether elastography might provide some additional information during surgery on tumor borders and on the heterogeneity of tumors to focus the histological and molecular evaluation of the removed tissue samples on special areas. To facilitate such investigations, the integration of elastography in 3-dimensional navigated ultrasound would be mandatory, which also would allow us to better compare the elastography findings with other multimodal imaging data.

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