

# MOLECULAR DIAGNOSTIC AND IMAGING CAPABILITIES OF INTRAOPERATIVE ULTRASOUND NAVIGATION

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## ABSTRACT

Intraoperative ultrasound navigation (ioUS) is one of the most promising areas of modern neurosurgery, providing the surgeon with the opportunity to obtain images in real time and adapt intervention tactics taking into account dynamic changes in brain structures. ioUS technology is based on the use of ultrasound waves to visualize the anatomical and functional characteristics of brain tissue during surgery, which makes it an effective tool for navigation and control of the radicality of resection. Unlike traditional methods such as intraoperative MRI and CT, ioUS has a high data acquisition rate, economic accessibility, and no radiation exposure. The review is devoted to the analysis of modern intraoperative ultrasound technologies, including 3D imaging, contrast enhancement (CEUS), Dopplerography and elastosonography, as well as the assessment of their clinical effectiveness in the surgical treatment of brain tumors. The advantages of ioUS in eliminating the "brain shift" effect, integrating with neural navigation systems, and providing an individualized surgical approach are considered. Special attention is paid to the role of ioUS in increasing the radicality of resection, reducing the residual volume of the tumor and preserving functionally significant areas. Based on the analysis of domestic and foreign publications, key areas for further development of the technology have been identified, including standardization of protocols for its application, development of training systems for specialists, and integration of artificial intelligence for automated image interpretation. The conclusion is made about the high clinical and practical significance of ioUS as a universal visual monitoring tool capable of improving the safety and effectiveness of neurosurgical operations.

**KEYWORDS:** intraoperative ultrasound navigation, neurosurgery, brain tumors, contrast ultrasound, elastosonography, neuronavigation, clinical efficacy.

## INTRODUCTION

Modern neurosurgery requires high precision and safety, which makes the choice of effective intraoperative navigation methods a key area of clinical practice development. Historically, the first neural navigation systems were based on static preoperative images obtained using computer and magnetic resonance imaging, but their limited flexibility in a dynamically changing operating field reduced the accuracy of manipulations [21, 30].

In the last two decades, intraoperative CT and MRI have been considered as the "gold standard" of navigation, providing high spatial resolution and the possibility of three-dimensional mapping of brain structures [12, 33]. Nevertheless, even these technologies have significant limitations, including the high cost of equipment, duration of procedures, and dependence on preoperative data, which is especially critical in conditions of "brain shift" during manipulation of tumors [14, 29]. According to world reports, over 300,000 cases of brain tumors are diagnosed annually in the world, and about 10,000—12,000 in Russia, while up to 60% of operations require navigation support to minimize neurological complications [3, 4].

In response to these challenges, the field of intraoperative ultrasound navigation (iUS) is developing, combining high information content, safety and economic accessibility [8, 21]. Ultrasound imaging provides real-time imaging without exposing the patient to radiation, and allows for prompt correction of the surgeon's actions at all stages of the intervention [10, 20]. Modern 2D and 3D ultrasound systems demonstrate comparable accuracy to intraoperative MRI, but they

significantly exceed it in terms of data acquisition speed and ease of use [12, 26]. An important advantage of iUS is the ability to compensate for the effect of brain displacement, since images are updated directly during surgery, which makes the method especially useful for resection of deep-seated or infiltrative tumors [33, 38].

The experience of international clinics shows that the use of intraoperative ultrasound helps to increase the radicality of neoplasm removal and reduce the risk of postoperative complications [8, 38]. According to reviews, the introduction of ultrasound navigation makes it possible to increase the accuracy of tumor localization to 92-95% and reduce the duration of operations by 15-20% [29, 36]. Thus, intraoperative ultrasound navigation today is not just an auxiliary technology, but an independent diagnostic and navigation tool capable of providing an individualized approach to treatment [26, 40]. The purpose of this review is to identify current trends, technological advances, and clinical effectiveness of the use of intraoperative ultrasound navigation (ioUS) in neurosurgery, analyze its advantages and limitations compared to traditional imaging techniques (MRI and CT), and justify the need for standardization of protocols and specialist training to integrate ioUS into routine clinical practice.

## MATERIALS AND METHODS

The research materials are scientific publications and clinical data on modern aspects of the use of intraoperative ultrasound navigation (iUS) in neurosurgery. The search and selection of sources were carried out in leading international and Russian databases — PubMed, Scopus, Web of Science, eLIBRARY.ru, CyberLeninka — using keywords: intraoperative ultrasound, neuronavigation, brain tumor surgery, intraoperative imaging, glioma resection. The analysis included original clinical studies, systematic reviews, and meta-analyses published between 2015 and 2025, providing information on the diagnostic accuracy, advantages, and limitations of iUS compared to CT and MRI.

The methods of content analysis, comparative descriptive and analytical synthesis were used to structure the collected data, which made it possible to determine the main directions of development of intraoperative navigation technologies and their effectiveness in clinical practice. Special attention was paid to the characteristics of ultrasound systems used in neurosurgery, imaging parameters, integration with neural navigation platforms, and the impact on surgical outcomes.

A summary of the database and the stages of literature selection is presented in Table 1, which ensures transparency, reproducibility and reliability of the analysis.

**Table 1: Clinical and experimental studies on the use of intraoperative ultrasound navigation in neurosurgery**

The authors of the study	Year	A country	Navigation method /	Key results / benefits	Number of patients/observations	Control / comparison
Simfukwe K. et al. [8]	2022	Russia / Italy	iUS technology (intraoperative ultrasound)	Improving the accuracy of brain tumor resection, reducing surgery time	30 patients	Intraoperative MRI
Prada F. et al. [10]	2020	Italy	3D iUS	Accurate visualization of focal boundaries in focal cortical dysplasia	25 patients	MRI
Bø H.K. et al. [12]	2019	Norway	3D Ultrasound navigation	Increased radicality of low-grade glioma resection	40 patients	MRI
Bastos D.C.A. et al. [14]	2021	USA	3D ultrasound + neural navigation	Comparison of accuracy with intraoperative MRI, comparable effectiveness has been proven	32 patients	iMRI
Yeole U. et al. [16]	2020	India	Navigated ultrasound	Improving the efficiency of tumor removal, improving the visualization of borders	27 patients	Without navigation
Shetty P. et al. [19]	2021	India	Ultrasound navigation for gliomas	Improved decision-making during surgery, reduced relapses	45 patients	Traditional methods
Tao A-Y. et al. [25]	2022	China	Contrast Ultrasound (CEUS)	Improving the accuracy of identification of the residual tumor	38 patients	MRI scan
Hu X. et al. [29]	2021	China	US–MRI Fusion	Increased percentage of total glioma resections	50 patients	MRI scan
Trevisi G. et al. [31]	2020	Italy	Real-time ultrasound of	High sensitivity in detecting a residual tumor was confirmed	732 patients (meta-analysis)	Not applicable
Pichardo-Rojas P.S. et al. [38]	2024	Mexico	iUS for high-grade gliomas	Clinical efficacy and reduction of	732 patients (meta-analysis)	Without ultrasound navigation

				complications have been confirmed.		
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**The stages of introducing ultrasound navigation into neurosurgical practice**

Ultrasound navigation has become one of the most dynamically developing areas of modern neurosurgery, having gone from an auxiliary diagnostic tool to a key element of intraoperative imaging. The first mentions of the use of intraoperative ultrasound (ioUS) in brain surgery date back to the late 1970s, when the method was used primarily for rough assessment of tumor boundaries and localization of the pathological focus [8, 9]. At that time, the resolution of ultrasound devices was low, and the lack of standardized protocols limited their use. However, further development of technologies, primarily digital signal processing and sensor miniaturization, has significantly improved the accuracy and stability of images, which has led to the gradual introduction of ioUS into elective and oncological brain surgeries [10, 15, 16].

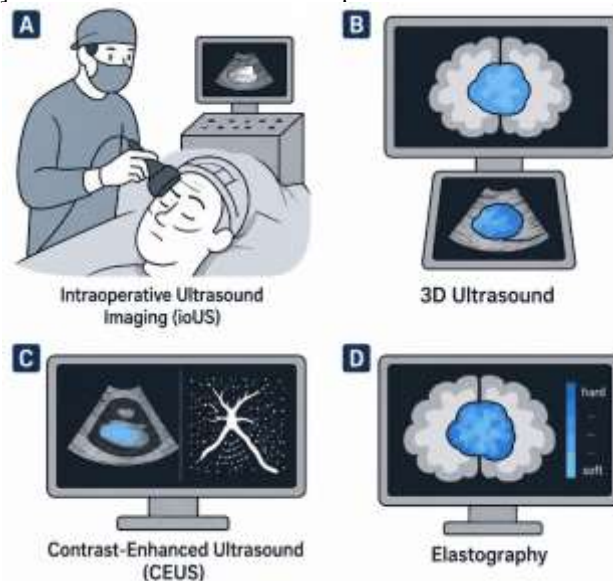
An important stage was the creation of three-dimensional and Doppler visualization systems that provide real-time structural and functional data acquisition. Such solutions, as shown by the research of F. Prada and colleagues [20, 26], allowed surgeons to compensate for the effect of "brain shift" and improve navigation accuracy when removing deep and low-grade gliomas. Russian researchers, including R. S. Talybov and V. V. Mochalova [1], noted that the use of intraoperative ultrasound technologies in combination with fluorescence and MR navigation ensures more complete removal of the tumor and reduces the incidence of complications.

Modern modifications of ioUS are based on the principles of multispectral analysis and contrast enhancement, which makes it possible to detail the vascular architecture of the tumor and the infiltration zone [25, 28]. Studies by Bastos et al. [14] and Yeole et al. [16] have shown that ultrasound navigation is comparable in information content to intraoperative MRI, while it has significantly lower costs and does not require interruption of the surgical process. Additionally, it is noted that the integration of ioUS with neural navigation systems and machine learning forms the basis for the creation of intelligent algorithms capable of automatically correcting tissue displacement and clarifying anatomical landmarks [33].

Thus, the evolution of ultrasound neuronavigation has gone through several key stages: from simple echographic observations to the introduction of hybrid 3D systems with contrast and elastographic modules. This is confirmed by the works of both foreign and domestic authors, from the studies of Konovalov A.N. [2] and Samokhvalov I.M. [6] to multicenter reviews of Prada F., Dixon L. and Gerard I.J. [21, 33]. As a result, ioUS has taken a strong place among modern neurosurgical instruments, while remaining the most accessible, versatile and safe method of intraoperative navigation.

**Modern technologies and technical solutions for intraoperative ultrasound**

Modern neurosurgery is based on the principles of visual inspection, where intraoperative ultrasound (ioUS) becomes a key tool for accurate guidance and assessment of dynamic changes in the brain during surgery. After cranial trepanation, the unique mechanical properties of the brain tissue provide optimal conditions for the propagation of ultrasonic waves, which allows high-definition images to be obtained in real time. In recent years, there has been a significant technological breakthrough — modern ultrasound systems integrate 3D capabilities, Doppler modes, contrast enhancement and elastosonography, providing the surgeon with not only morphological but also functional information about the structure and perfusion of tissues [8, 9, 21]. These improvements have taken ioUS beyond the auxiliary technology, turning it into a full-fledged navigation platform comparable in diagnostic value to intraoperative MRI and CT systems, but much more accessible and mobile [14, 20]. The main directions of development and varieties of ioUS are shown in Figure 1.



**Figure 1: Modern technologies of intraoperative ultrasound (ioUS)**

One of the most promising areas has become multiparametric ultrasound imaging (MPUs), which combines B-mode, Dopplerography, contrast ultrasound (CEUS) and elastosonography, which provides a comprehensive view of the structure, vascularization and density of tissues. This approach provides the neurosurgeon with the opportunity to assess the tumor in real time, differentiate between healthy and affected areas, and control the degree of resection, minimizing the risk of damage to functionally significant areas [10, 26]. The use of CEUS proved to be particularly valuable, which, thanks to microbubble contrasts, visualizes the vascular bed and the dynamics of tumor perfusion, allowing the identification of residual neoplastic areas inaccessible to the standard B-mode [25, 28].

An equally significant achievement is the introduction of elastosonography (SE and SWE), which has opened up the possibility of quantifying the mechanical properties of tumor tissue and the surrounding brain. These data make it possible to differentiate the type of tumor, assess its degree of malignancy, and plan safe surgical access trajectories [30, 31]. Due to the combination of high information content, compact equipment and the absence of radiation exposure, ioUS is now considered as a universal navigation tool capable of significantly improving the accuracy and safety of neurosurgical interventions, especially in conditions of limited resources. [8, 13, 19, 46].

Despite significant progress in the development of intraoperative ultrasound, its use is still limited by a number of technical factors, including the dependence of image quality on operator experience, the difficulty of interpreting the data obtained, and artifacts that occur during surgical procedures [8, 9].

To overcome these limitations, advanced imaging modes have been developed - 3D ultrasound, elastosonography, contrast-enhanced ultrasound (CEUS) and hybrid technologies with the integration of MRI data, which can compensate for the effect of brain shift and improve the accuracy of spatial orientation [14, 20, 26]. In addition, the introduction of machine learning and automated image processing systems opens up new opportunities for standardizing the interpretation of ultrasound data, reducing dependence on the human factor and improving the reproducibility of results [19, 31].

### **Clinical application and results**

The expansion of the functionality of intraoperative ultrasound (ioUS) is directly reflected in its clinical effectiveness. Current data confirm that IOUS provides not only high-precision guidance, but also a comprehensive assessment of the condition of brain tissue, allowing the surgeon to adapt an intervention strategy in real time [8, 9]. The use of multilevel ultrasound modes - from the standard B-mode to contrast and elastographic - makes it possible to visually distinguish between the tumor and unaffected parenchyma, assess vascularization and determine the residual volume of the tumor (RTV), which is directly related to survival rates and a reduced risk of recurrence [19, 30].

In practical neuro-oncology, ioUS is used primarily in the removal of glial tumors, meningiomas, and metastatic lesions, where navigation accuracy plays a crucial role in preserving functional areas of the brain. According to the research results of Simfukwe et al. (2022) [8], the use of ioUS increases the probability of achieving complete resection (GTR) by more than 25% compared with traditional microsurgery. At the same time, the integration of the method with fluorescent navigation (5-ALA) and CEUS provides maximum information content, combining morphological and functional monitoring of the state of the tumor bed [48-50].

Russian neurosurgeons have also made a significant contribution to the development of the clinical application of ioUS. So, Talibov R.S. et al. [1] showed that the use of navigation ultrasound in combination with neural navigation systems and fluorescent control allowed to increase the frequency of total glioblastoma resection to 88.2%, while the level of postoperative complications remained minimal. These results confirm that IOUS is able not only to increase the radicality of tumor removal, but also to ensure the functional safety of the patient.

Additional studies by Bastos et al. (2021) and Gerard et al. [14, 33] emphasized that IOUS is an effective means of compensating for brain shift, one of the key limitations of preoperative MR navigation. In conditions of altered anatomy, ultrasound navigation retains spatial accuracy, providing the surgeon with up-to-date visual data and reducing intervention time.

Special attention is paid to the capabilities of ioUS in multidisciplinary neurosurgical complexes. Samokhvalov I.M. et al. (2019) [6] consider IOUS as a natural extension of stereotactic and optical navigation, where the combination of various visual technologies forms an integrated intraoperative control system. This approach makes it possible to reduce the proportion of residual tumor tissue and increase the safety of intervention even when working in functionally significant areas of the brain.

In general, the accumulated data of domestic and foreign authors convincingly demonstrate that the clinical use of ioUS increases the accuracy and safety of neurosurgical operations, increases the duration of the disease-free period and improves the quality of life of patients. The technological evolution of ultrasound navigation has transformed it from an auxiliary tool into a strategically important element of personalized neurosurgery, providing a real advantage in complex intracranial operations. [8, 9, 14, 19, 33].

At the same time, the rapid development of technologies exposes new challenges related to the need to standardize approaches to using ioUS and ensure high reproducibility of the results obtained. Modern practice shows that the effectiveness of the method is largely determined by the qualifications of the surgeon and the uniformity of the protocols used.

### **Further research and development directions**

Of course, the further development of intraoperative ultrasound in neurosurgery requires not only technical improvement, but also unification of approaches to its clinical application. The lack of uniform standards for interpreting ultrasound

data and the significant dependence of imaging quality on operator experience remain key limiting factors [52, 53]. In this regard, the development of national and international protocols for the use of ioUS, including standardized methods, training systems and accreditation of specialists, becomes an urgent task [40-45].

In this context, the creation of interdisciplinary training programs that bring together neurosurgeons, radiologists, and medical engineers to improve their skills in interpreting ultrasound data and working with hybrid navigation systems plays a special role. The development of specialized competence centers will allow the formation of expert databases and algorithms for machine image analysis, which will increase the objectivity and reproducibility of the results [47, 49]. In the future, the widespread introduction of artificial intelligence and automated systems for recognizing brain structures will become the basis for personalized ultrasound navigation in real time. Thus, the standardization of techniques and the development of human resources are key conditions for integrating ioUS into modern neurosurgical protocols and improving the effectiveness of surgical treatment of brain tumors [41-43].

## CONCLUSION

The analysis of modern research shows that intraoperative ultrasound navigation (ioUS) has become an integral element of modern neurosurgery, providing the surgeon with the opportunity to obtain high-precision images in real time and promptly adjust intervention tactics. The multilevel use of ioUS - from the standard B-mode to contrast and elastographic technologies - has proven effective in increasing the radicality of tumor resection, reducing residual volume and minimizing neurological complications. The data on the high informative value of the method for resection of glial neoplasms are particularly significant, which confirms its value as an alternative to expensive MRI navigation systems and highlights its advantages in conditions of limited resources [8, 19, 29].

Thus, the practical significance of the study lies in the fact that the introduction of standardized protocols for the use of ioUS and the development of specialist training systems can ensure the widespread introduction of the method into clinical practice, improving the quality of neurosurgical care and improving treatment outcomes for patients with brain tumors.

## REFERENCES

1. Talybov RS, Mochalov VV, Akulov MM, Kleshchevnikova TM, Loginova NV. Modern intraoperative neuroassistance in surgery of diffuse high-grade gliomas. *National Bulletin of Medical Associations*. 2025;2(1):65-75. doi:10.24412/3034-509X-2025-1-65-75.
2. Kononov AN, Pilipenko YuV, Okishev DN, Artemyev AA, Mamedbekova GSh, Ivanov VM, et al. The use of augmented reality as a method of neuronavigation during extracranial-intracranial microanastomosis. *Operative Surgery and Clinical Anatomy*. 2024;8(3):28-34. doi:10.17116/operhirurg2024803128.
3. Likhterman LB, Okhlopov VA, Ryzhova MV, Snigireva GP, Shishkina LV, Pronin IN, et al. Brain tumors: methodology and innovations in comprehensive recognition of histobiological characteristics. *Neurosurgery and Neurology of Kazakhstan*. 2023;(3):56-70. doi:10.53498/24094498\_2023\_3\_56.
4. Arias Parra SL, Noumeh NM. Fighting brain tumors: modern methods of diagnosis and treatment. *Bulletin of Science*. 2025;4(3):449-456.
5. Potapov AA, Goryainov SA, Okhlopov VA, Pitskhelauri DI, Kobayakov GL, Zhukov VYu, et al. Clinical guidelines for the use of intraoperative fluorescence diagnostics in brain tumor surgery. *Burdenko Journal of Neurosurgery*. 2015;79(5):91-101.
6. Samokhvalov IM, Badalov VI, Korostelev KE, Spitsyn MI, Tyulikov KV, Shevelev PYu, et al. Neuronavigation as an evolution of stereotaxis. *Bulletin of the Russian Military Medical Academy*. 2019;21(4):186-194. doi:10.17816/brmma630096.
7. Makhkamov KE, Tukhtabekov ZL. Application of neuronavigation in modern surgery of brain masses. *Bulletin of Emergency Medicine*. 2009;(1):91-94.
8. Simfukwe K, Iakimov I, Sufianov R, Borba L, Mastronardi L, Shumadalova A. Application of Intraoperative Ultrasound Navigation in Neurosurgery. *Front Surg*. 2022 May 10;9:900986. doi: 10.3389/fsurg.2022.900986. PMID: 35620193; PMCID: PMC9127208.
9. Sastry R, Bi WL, Pieper S, Frisken S, Kapur T, Wells W, 3rd, et al. Applications of ultrasound in the resection of brain tumors. *J Neuroimaging*. (2017) 27:5–15. 10.1111/jon.12382
10. Prada F, Gennari AG, Quaia E, D'Incerti L, de Curtis M, DiMeco F, et al. Advanced intraoperative ultrasound (ioUS) techniques in focal cortical dysplasia (FCD) surgery: a preliminary experience on a case series. *Clin Neurol Neurosurg*. (2020) 198:106188. 10.1016/j.clineuro.2020.106188
11. Tringali G, Bono B, Dones I, Cordella R, Didato G, Villani F, et al. Multimodal approach for radical excision of focal cortical dysplasia by combining advanced magnetic resonance imaging data to intraoperative ultrasound, electrocorticography, and cortical stimulation: a preliminary experience. *World Neurosurg*. (2018) 113:e738–46. 10.1016/j.wneu.2018.02.141
12. Bø HK, Solheim O, Kvistad KA, Berntsen EM, Torp SH, Skjulsvik AJ, et al. Intraoperative 3D ultrasound-guided resection of diffuse low-grade gliomas: radiological and clinical results. *J Neurosurg*. (2019) 132:518–29. 10.3171/2018.10.JNS181290 [DOI] [PubMed] [Google Scholar]
13. Kaale AJ, Rutabasibwa N, McHome LL, Lillehei KO, Honce JM, Kahamba J, et al. The use of intraoperative neurosurgical ultrasound for surgical navigation in low- and middle-income countries: the initial experience in Tanzania. *J Neurosurg*. (2020) 134:1–8. 10.3171/2019.12.JNS192851

14. Bastos DCA, Juvekar P, Tie Y, Jowkar N, Pieper S, Wells WM, Bi WL, Golby A, Frisken S, Kapur T. Challenges and Opportunities of Intraoperative 3D Ultrasound With Neuronavigation in Relation to Intraoperative MRI. *Front Oncol.* 2021 May 3;11:656519. doi: 10.3389/fonc.2021.656519.
15. Unsrud G, Lindseth F. 3D Ultrasound-Guided Resection of Low-Grade Gliomas: Principles and Clinical Examples. *Neurosurg Focus* (2019) 47(6):E9. 10.3171/2019.9.FOCUS19605
16. Yeole U, Singh V, Mishra A, Shaikh S, Shetty P, Moiyadi A. Navigated Intraoperative Ultrasonography for Brain Tumors: A Pictorial Essay on the Technique, its Utility, and its Benefits in Neuro-Oncology. *Ultrason* (2020) 39(4):394–406. doi: 10.14366/usg.20044
17. Ellison DW, Aldape KD, Capper D, Fouladi M, Gilbert MR, Gilbertson RJ, et al. cIMPACT-NOW Update 7: Advancing the Molecular Classification of Ependymal Tumors. *Brain Pathol* (2020) 30(5):8636. doi: 10.1111/bpa.12866
18. Louis DN, Wesseling P, Aldape K, Brat DJ, Capper D, Cree IA, et al. cIMPACT-NOW Update 6: New Entity and Diagnostic Principle Recommendations of the cIMPACT-Utrecht Meeting on Future CNS Tumor Classification and Grading. *Brain Pathol* (2020) 30(4):84456. doi: 10.1111/bpa.12832
19. Shetty P, Yeole U, Singh V, Moiyadi A. Navigated Ultrasound-Based Image Guidance During Resection of Gliomas: Practical Utility in Intraoperative Decision-Making and Outcomes. *Neurosurg Focus* (2021) 50(1):E14. doi: 10.3171/2020.10.FOCUS20550
20. Prada F, Del Bene M, Mattei L, Casali C, Filippini A, Legnani F, Mangraviti A, Saladino A, Perin A, Richetta C, Vetrano I, Moiraghi A, Saini M, DiMeco F. Fusion imaging for intra-operative ultrasound-based navigation in neurosurgery. *J Ultrasound.* 2014 Jun 24;17(3):243–51. doi: 10.1007/s40477-014-0111-8.
21. Dixon L, Lim A, Grech-Sollars M, Nandi D, Camp S. Intraoperative ultrasound in brain tumor surgery: A review and implementation guide. *Neurosurg Rev.* 2022 Aug;45(4):2503–2515. doi: 10.1007/s10143-022-01778-4.
22. del Bene M, Perin A, Casali C, et al. Advanced ultrasound imaging in glioma surgery: Beyond Gray-Scale B-mode. *Front Oncol.* 2018 doi: 10.3389/fonc.2018.00576.
23. Sidhu P, Cantisani V, Dietrich C, et al. The EFSUMB Guidelines and Recommendations for the Clinical Practice of Contrast-Enhanced Ultrasound (CEUS) in Non-Hepatic Applications: Update 2017 (Long Version) *Ultraschall Med Eur J Ultrasound.* 2018;39(02):e2–e44. doi: 10.1055/a-0586-1107.
24. Prada F, Vitale V, del Bene M, et al. Contrast-enhanced MR Imaging versus Contrast-enhanced US: A Comparison in Glioblastoma Surgery by Using Intraoperative Fusion Imaging. *Radiology.* 2017;285(1):242–249. doi: 10.1148/radiol.2017161206.
25. Tao A-Y, Chen X, Zhang LY, et al. Application of Intraoperative Contrast-Enhanced Ultrasound in the Resection of Brain Tumors. *Curr Med Sci.* 2022;42(1):169–176. doi: 10.1007/s11596-022-2538-z.
26. Prada F, Vetrano IG, Gennari AG, et al. How to Perform Intra-Operative Contrast-Enhanced Ultrasound of the Brain—A WFUMB Position Paper. *Ultrasound Med Biol.* 2021;47(8):2006–2016. doi: 10.1016/j.ultrasmedbio.2021.04.016.
27. de Pepa GM, Sabatino G, la Rocca G. “Enhancing Vision” in High Grade Glioma Surgery: A Feasible Integrated 5-ALA + CEUS Protocol to Improve Radicality. *World Neurosurg.* 2019;129:401–403. doi: 10.1016/j.wneu.2019.06.127.
28. della Pepa GM, Ius T, la Rocca G, et al. 5-Aminolevulinic Acid and Contrast-Enhanced Ultrasound: The Combination of the Two Techniques to Optimize the Extent of Resection in Glioblastoma Surgery. *Neurosurgery.* 2020;86(6):E529–E540. doi: 10.1093/neuros/nyaa037.
29. Hu X, Xu R, Ding H, et al. The total resection rate of glioma can be improved by the application of US-MRI fusion combined with contrast-enhanced ultrasound. *Clin Neurol Neurosurg.* 2021;208:106892. doi: 10.1016/j.clineuro.2021.106892.
30. Prada F, del Bene M, Rampini A, et al. Intraoperative Strain Elastasonography in Brain Tumor Surgery. *Oper Neurosurg.* 2019;17(2):227–236. doi: 10.1093/ons/opy323.
31. Trevisi G, Barbone P, Treglia G, Mattoli MV, Mangiola A. Reliability of intraoperative ultrasound in detecting tumor residual after brain diffuse glioma surgery: a systematic review and meta-analysis. *Neurosurg Rev.* 2020;43(5):1221–33.
32. Unsgaard G, Ommedal S, Muller T, Gronningsaeter A, Nagelhus Hernes TA. Neuronavigation by intraoperative three-dimensional ultrasound: initial experience during brain tumor resection. *Neurosurgery.* 2002;50(4):804–12.
33. Gerard IJ, Kersten-Oertel M, Hall JA, Sirhan D, Collins DL. Brain shift in Neuronavigation of Brain tumors: an updated review of Intra-operative Ultrasound Applications. *Front Oncol.* 2021;10:618837.
34. Naik A, Smith EJ, Barreau A, Nyaeme M, Cramer SW, Najafali D, et al. Comparison of fluorescein sodium, 5-ALA, and intraoperative MRI for resection of high-grade gliomas: a systematic review and network meta-analysis. *J Clin Neurosci.* 2022;98:240–7.
35. Hosmann A, Millesi M, Wadiura LI, Kiesel B, Mercea PA, Mischkulnig M, et al. 5-ALA fluorescence is a powerful prognostic marker during surgery of low-Grade Gliomas (WHO Grade II)-Experience at two Specialized centers. *Cancers (Basel).* 2021;13(11):2540.
36. Sweeney JF, Rosoklija G, Sheldon BL, Bondoc M, Bandlamuri S, Adamo MA. Comparison of sodium fluorescein and intraoperative ultrasonography in brain tumor resection. *J Clin Neurosci.* 2022;106:141–4.
37. abeghi P, Zarand P, Zargham S, Golestany B, Shariat A, Chang M, et al. Advances in Neuro-Oncological imaging: an update on Diagnostic Approach to Brain tumors. *Cancers (Basel).* 2024;16(3):576.
38. Pichardo-Rojas PS, Zarate C, Arguelles-Hernández J, Barrón-Lomelí A, Sanchez-Velez R, Hjeala-Varas A, et al. Intraoperative ultrasound for surgical resection of high-grade glioma and glioblastoma: a meta-analysis of 732 patients. *Neurosurg Rev.* 2024;47(1):120.

39. Xiong Z, Luo C, Wang P, Hameed NUF, Song S, Zhang X, Wu S, Wu J, Mao Y. The intraoperative utilization of Multimodalities could improve the prognosis of adult glioblastoma: a single-Center Observational Study. *World Neurosurg.* 2022;165:e532–45.
40. Moiraghi A, Prada F, Delaidelli A, Guatta R, May A, Bartoli A, et al. Navigated Intraoperative 2-Dimensional Ultrasound in High-Grade Glioma Surgery: Impact on Extent of Resection and Patient Outcome. *Oper Neurosurg* (2020) 18(4):363–73. doi: 10.1093/ons/opz203
41. Sacino MF, Ho CY, Murnick J, Tsuchida T, Magge SN, Keating RF, et al. Intraoperative MRI-guided resection of focal cortical dysplasia in pediatric patients: technique and outcomes. *J Neurosurg Pediatr.* (2016) 17:672–8. doi: 10.3171/2015.10.PEDS15512
42. Goren O, Monteith SJ, Hadani M, Bakon M, Harnof S. Modern intraoperative imaging modalities for the vascular neurosurgeon treating intracerebral hemorrhage. *Neurosurg Focus.* (2013) 34:E2. doi: 10.3171/2013.2.FOCUS1324
43. Ghinda D, Zhang N, Lu J, Yao CJ, Yuan S, Wu JS. Contribution of combined intraoperative electrophysiological investigation with 3-T intraoperative MRI for awake cerebral glioma surgery: comprehensive review of the clinical implications and radiological outcomes. *Neurosurg Focus.* (2016) 40:E14. doi: 10.3171/2015.12.FOCUS15572
44. Braun V, Dempf S, Tomczak R, Wunderlich A, Weller R, Richter HP. Multimodal cranial neuronavigation: direct integration of functional magnetic resonance imaging and positron emission tomography data: technical note. *Neurosurgery* 2001;48:1178-81.
45. Dakson A, Hong M, Clarke DB. Virtual Reality Surgical Simulation: Implications for Resection of Intracranial Gliomas. *Prog Neurol Surg* 2018;30:106-16.
46. Gerard IJ, Kersten-Oertel M, Petrecca K, Sirhan D, Hall JA, Collins DL. Brain shift in neuronavigation of brain tumors: A review. *Med Image Anal* 2017;35:403-20.
47. Lindseth F, Langø T, Bang J, Nagelhus, Hernes TA. Accuracy evaluation of a 3D ultrasound-based neuronavigation system. *Comput Aided Surg* 2002;7:197-222.
48. Unsgaard G, Rygh OM, Selbekk T, Müller TB, Kolstad F, Lindseth F, Hernes TA. Intra-operative 3D ultrasound in neurosurgery. *Acta Neurochir (Wien)* 2006;148:235-53.
49. Yu H, Shen G, Wang X, Zhang S. Navigation-guided reduction and orbital floor reconstruction in the treatment of zygomatic-orbital maxillary complex fractures. *Journal of Oral and Maxillofacial Surgery.* 2010;68(1):28-34. <https://doi.org/10.1016/j.joms.2009.07.058>
50. Selbekk T, Jakola AS, Solheim O, Johansen TF, Lindseth F, Reinertsen I, Unsgård G. Ultrasound imaging in neurosurgery: approaches to minimize surgically induced image artefacts for improved resection control. *Acta Neurochir (Wien)* 2013;155:973-80.
51. Alomari A, Jaspers C, Reinbold WD, Feldkamp J, Knappe UJ. Use of intraoperative intracavitary (direct-contact) ultrasound for resection control in transsphenoidal surgery for pituitary tumors: evaluation of a microsurgical series. *Acta Neurochir (Wien)* 2019;161:109-17.
52. Morin F, Courtecuisse H, Reinertsen I, Le Lann F, Palombi O, Payan Y, Chabanas M. Brain-shift compensation using intraoperative ultrasound and constraint-based biomechanical simulation. *Med Image Anal* 2017;40:133-53.
53. Chan, H. W., Uff, C., Chakraborty, A., Dorward, N., and Bamber, J. C. (2021). Clinical application of shear wave elastography for assisting brain tumor resection. *Front. Oncol.* 11:619286. doi: 10.3389/fonc.2021.619286
54. Chauvet, D., Imbault, M., Capelle, L., Demene, C., Mossad, M., Karachi, C., et al. (2016). In vivo measurement of brain tumor elasticity using intraoperative shear wave elastography. *Ultraschall Med.* 37, 584–590. doi: 10.1055/s-0034-1399152
55. Cheng, L. G., He, W., Zhang, H. X., Song, Q., Ning, B., Li, H. Z., et al. (2016). Intraoperative contrast enhanced ultrasound evaluates the grade of glioma. *BioMed Res. Int.* 2016:2643862. doi: 10.1155/2016/2643862
56. D'Amico, R. S., Englander, Z. K., Canoll, P., and Bruce, J. N. (2017). Extent of resection in glioma—a review of the cutting edge. *World Neurosurg.* 103, 538–549. doi: 10.1016/j.wneu.2017.04.041
57. del Bene, M., Raspagliesi, L., Carone, G., Gaviani, P., Silvani, A., Solbiati, L., et al. (2022). Cranial sonolucent prosthesis: a window of opportunity for neuro-oncology (and neuro-surgery). *J. Neuro Oncol.* 156, 529–540. doi: 10.1007/s11060-021-03929-x
58. della Pepa, G. M., Menna, G., Stifano, V., Pezzullo, A. M., Auricchio, A. M., Rapisarda, A., et al. (2020). Predicting meningioma consistency and brain-meningioma interface with intraoperative strain ultrasound elastography: a novel application to guide surgical strategy. *Neurosurg. Focus* 50, 1–11. doi: 10.3171/2020.10.FOCUS20797
59. Fountain, D. M., Bryant, A., Barone, D. G., Waqar, M., Hart, M. G., Bulbeck, H., et al. (2021). Intraoperative imaging technology to maximise extent of resection for glioma: a network meta-analysis. *Cochrane Database Syst. Rev.* 2021:CD013630. doi: 10.1002/14651858.CD013630.pub2
60. Grgurevic, I., Tjesic Drinkovic, I., and Pinzani, M. (2019). Multiparametric ultrasound in liver diseases: an overview for the practising clinician. *Postgrad. Med. J.* 95, 425–432. doi: 10.1136/postgradmedj-2018-136111
61. Incekara, F., Smits, M., Dirven, L., Bos, E. M., Balvers, R. K., Haitsma, I. K., et al. (2021). Intraoperative B-mode ultrasound guided surgery and the extent of glioblastoma resection: a randomized controlled trial. *Front. Oncol.* 11:649797. doi: 10.3389/fonc.2021.649797
62. Kim, H. J., Kim, S. M., Kim, B., la Yun, B., Jang, M., Ko, Y., et al. (2018). Comparison of strain and shear wave elastography for qualitative and quantitative assessment of breast masses in the same population. *Sci. Rep.* 8:6197. doi: 10.1038/s41598-018-24377-0

63. Kloth, C., Kratzer, W., Schmidberger, J., Beer, M., Clevert, D. A., and Graeter, T. (2021). Ultrasound 2020 – diagnostics & therapy: on the way to multimodal ultrasound: contrast-enhanced ultrasound (ceus), microvascular doppler techniques, fusion imaging, sonoelastography, interventional sonography. *RoFo* 193, 23–32. doi: 10.1055/a-1217-7400
64. Louis, D. N., Perry, A., Wesseling, P., Brat, D. J., Cree, I. A., Figarella-Branger, D., et al. (2021). The 2021 WHO classification of tumors of the central nervous system: a summary. *Neuro-Oncology* 23, 1231–1251. doi: 10.1093/neuonc/noab106
65. Mannaerts, C. K., Wildeboer, R. R., Postema, A. W., Hagemann, J., Budäus, L., Tilki, D., et al. (2018). Multiparametric ultrasound: evaluation of greyscale, shear wave elastography and contrast-enhanced ultrasound for prostate cancer detection and localization in correlation to radical prostatectomy specimens. *BMC Urol.* 18:98. doi: 10.1186/s12894-018-0409-5
66. Mazzucchi, E., la Rocca, G., Ius, T., Sabatino, G., and della Pepa, G. M. (2020). Multimodality imaging techniques to assist surgery in low-grade gliomas. *World Neurosurg.* 133, 423–425. doi: 10.1016/j.wneu.2019.10.120
67. Menna, G., Olivi, A., and della Pepa, G. M. (2021). Integration of different intraoperative ultrasound modalities in meningioma surgery: a 4-step approach. *World Neurosurg.* 146, 376–378. doi: 10.1016/j.wneu.2020.12.005
68. Moiyadi, A. V. (2016). Intraoperative ultrasound technology in neuro-oncology practice—current role and future applications. *World Neurosurg.* 93, 81–93. doi: 10.1016/j.wneu.2016.05.083
69. Munkvold, B. K. R., Jakola, A. S., Reinertsen, I., Sagberg, L. M., Unsgård, G., and Solheim, O. (2018). The diagnostic properties of intraoperative ultrasound in glioma surgery and factors associated with gross total tumor resection. *World Neurosurg.* 115, e129–e136. doi: 10.1016/j.wneu.2018.03.208
70. Newman, P. G., and Rozycki, G. S. (1998). The history of ultrasound. *Surg. Clin. North Am.* 78, 179–195. doi: 10.1016/S0039-6109(05)70308-X
71. Newsome, I. G., and Dayton, P. A. (2020). Visualization of microvascular angiogenesis using dual-frequency contrast-enhanced acoustic angiography: a review. *Ultrasound Med. Biol.* 46, 2625–2635. doi: 10.1016/j.ultrasmedbio.2020.06.009
72. Ng, A., and Swanevelder, J. (2011). Resolution in ultrasound imaging. *Contin. Educ. Anaesth. Crit. Care Pain* 11, 186–192. doi: 10.1093/bjaceaccp/mkr030
73. Pang, T., Huang, L., Deng, Y., Wang, T., Chen, S., Gong, X., et al. (2017). Logistic regression analysis of conventional ultrasonography, strain elastosonography, and contrast-enhanced ultrasound characteristics for the differentiation of benign and malignant thyroid nodules. *PLoS One* 12:e0188987. doi: 10.1371/journal.pone.0188987
74. Prada, F., del Bene, M., Fornaro, R., Vetrano, I. G., Martegani, A., Aiani, L., et al. (2016a). Identification of residual tumor with intraoperative contrast-enhanced ultrasound during glioblastoma resection. *Neurosurg. Focus* 40:E7. doi: 10.3171/2015.11.FOCUS15573
75. Prada, F., del Bene, M., Mauri, G., Lamperti, M., Vailati, D., Richetta, C., et al. (2018). Dynamic assessment of venous anatomy and function in neurosurgery with real-time intraoperative multimodal ultrasound: technical note. *Neurosurg. Focus* 45:E6. doi: 10.3171/2018.4.FOCUS18101
76. Prada, F., del Bene, M., Moiraghi, A., Casali, C., Legnani, F. G., Saladino, A., et al. (2015). From grey scale b-mode to elastosonography: multimodal ultrasound imaging in meningioma surgery – pictorial essay and literature review. *BioMed Res. Int.* 2015:925729. doi: 10.1155/2015/925729
77. Prada, F., Gennari, A. G., Linville, I. M., Mutersbaugh, M. E., Chen, Z., Sheybani, N., et al. (2021). Quantitative analysis of in-vivo microbubble distribution in the human brain. *Sci. Rep.* 11:11797. doi: 10.1038/s41598-021-91252-w
78. Prada, F., Mattei, L., del Bene, M., Aiani, L., Saini, M., Casali, C., et al. (2014a). Intraoperative cerebral glioma characterization with contrast enhanced ultrasound. *BioMed Res. Int.* 2014:484261. doi: 10.1155/2014/484261
79. Solheim, O., Selbekk, T., Jakola, A. S., and Unsgård, G. (2010). Ultrasound-guided operations in unselected high-grade gliomas—overall results, impact of image quality and patient selection. *Acta Neurochir.* 152, 1873–1886. doi: 10.1007/s00701-010-0731-5
80. Solheim, O., Selbekk, T., Lindseth, F., and Unsgård, G. (2009). Navigated resection of giant intracranial meningiomas based on intraoperative 3D ultrasound. *Acta Neurochir.* 151, 1143–1151. doi: 10.1007/s00701-009-0395-1
81. Šteňo, A., Buvala, J., Babková, V., Kiss, A., Toma, D., and Lysak, A. (2021). Current limitations of intraoperative ultrasound in brain tumor surgery. *Front. Oncol.* 11:659048. doi: 10.3389/fonc.2021.659048
82. Šteňo, A., Jezberová, M., Holli, V., Timárová, G., and Šteňo, J. (2016). Visualization of lenticulostriate arteries during insular low-grade glioma surgeries by navigated 3D ultrasound power doppler: technical note. *J. Neurosurg.* 125, 1016–1023. doi: 10.3171/2015.10.JNS151907
83. Unsgård, G., Sagberg, L. M., Müller, S., and Selbekk, T. (2019). A new acoustic coupling fluid with ability to reduce ultrasound imaging artefacts in brain tumour surgery—a phase I study. *Acta Neurochir.* 161, 1475–1486. doi: 10.1007/s00701-019-03945-x
84. Wang, J., Yang, Y., Liu, X., and Duan, Y. (2019). Intraoperative contrast-enhanced ultrasound for cerebral glioma resection and the relationship between microvascular perfusion and microvessel density. *Clin. Neurol. Neurosurg.* 186:105512. doi: 10.1016/j.clineuro.2019.105512
85. Wu, D. F., He, W., Lin, S., Han, B., and Zee, C. S. (2019). Using real-time fusion imaging constructed from contrast-enhanced ultrasonography and magnetic resonance imaging for high-grade glioma in neurosurgery. *World Neurosurg.* 125, e98–e109. doi: 10.1016/j.wneu.2018.12.215

86. Yin, L., Cheng, L., Wang, F., Zhu, X., Hua, Y., and He, W. (2021). Application of intraoperative B-mode ultrasound and shear wave elastography for glioma grading. *Quant. Imaging Med. Surg.* 11, 2733–2743. doi: 10.21037/qims-20-1368
87. Yoo, J., Je, B. K., and Choo, J. Y. (2020). Ultrasonographic demonstration of the tissue microvasculature in children: microvascular ultrasonography versus conventional color doppler ultrasonography. *Korean J. Radiol.* 21, 146–158. doi: 10.3348/kjr.2019.0500
88. Zhang, G., Li, Z., Si, D., and Shen, L. (2017). Diagnostic ability of intraoperative ultrasound for identifying tumor residual in glioma surgery operation. *Oncotarget* 8, 73105–73114. doi: 10.18632/oncotarget.20394
89. Renovanz M, Hickmann AK, Henkel C, Nadji-Ohl M, Hopf NJ. Navigated versus non-navigated intraoperative ultrasound: Is there any impact on the extent of resection of high-grade gliomas? A retrospective clinical analysis. *J Neurol Surg A, Cent Eur Neurosurg.* 2014 doi: 10.1055/s-0033-1356486.
90. Bal J, Camp SJ, Nandi D. The use of ultrasound in intracranial tumor surgery. *Acta Neurochir.* 2016 doi: 10.1007/s00701-016-2803-7.
91. Halliwell M. Diagnostic ultrasound: Physics and equipment, 2nd edition. *Ultrasound.* 2010;18:209. doi: 10.1258/ult.2010.100018.
92. Lindseth F, Kaspersen JH, Ommedal S, et al. Multimodal image fusion in ultrasound-based neuronavigation: Improving overview and interpretation by integrating preoperative MRI with intraoperative 3D ultrasound. *Comput Aided Surg.* 2003 doi: 10.3109/10929080309146040.
93. Moiyadi AV, Shetty P. Direct navigated 3D ultrasound for resection of brain tumors: A useful tool for intraoperative image guidance. *Neurosurg Focus.* 2016 doi: 10.3171/2015.12.FOCUS15529.
94. Rohde V, Coenen VA. Intraoperative 3-dimensional ultrasound for resection control during brain tumour removal: preliminary results of a prospective randomized study. *Acta Neurochir Suppl.* 2011 doi: 10.1007/978-3-211-99651-5\_29.
95. Rasmussen IA, Lindseth F, Rygh OM, et al. Functional neuronavigation combined with intra-operative 3D ultrasound: Initial experiences during surgical resections close to eloquent brain areas and future directions in automatic brain shift compensation of preoperative data. *Acta Neurochir.* 2007;149(4):365–678. doi: 10.1007/s00701-006-1110-0.
96. Nimsky C, Ganslandt O, Cerny S, Hastreiter P, Greiner G, Fahlbusch R. Quantification of, Visualization of, and Compensation for Brain Shift Using Intraoperative Magnetic Resonance Imaging. *Neurosurgery.* 2000;47(5):1070–1080. doi: 10.1097/00006123-200011000-00008.
97. D’Agostino E, Maes F, Vandermeulen D, Suetens P. A viscous fluid model for multimodal non-rigid image registration using mutual information. *Medic Imag Anal.* 2003;7(4):565–575. doi: 10.1016/S1361-8415(03)00039-2.
98. Ferrant M, Nabavi A, Macq B, Jolesz FA, Kikinis R, Warfield SK. Registration of 3-d intraoperative MR images of the brain using a finite-element biomechanical model. *IEEE Trans Medic Imag.* 2001;20(12):1384–1397. doi: 10.1109/42.974933.
99. Mercier L, Araujo D, Haegelen C, del Maestro RF, Petrecca K, Collins DL. Registering Pre- and Postresection 3-Dimensional Ultrasound for Improved Visualization of Residual Brain Tumor. *Ultrasound Med Biol.* 2013;39(1):16–29. doi: 10.1016/j.ultrasmedbio.2012.08.004.
100. Shin HS, Kim SY, Cha HG, Han BL, Nam SM. Real Time Navigation-Assisted Orbital Wall Reconstruction in Blowout Fractures. *Journal of Craniofacial Surgery.* 2016;27(2):370-373. <https://doi.org/10.1097/SCS.0000000000002410>
101. Bell RB, Markiewicz MR. Computer-assisted planning, stereolithographic modeling, and intraoperative navigation for complex orbital reconstruction: a descriptive study in a preliminary cohort. *Journal of Oral and Maxillofacial Surgery.* 2009;67(12):2559-2570. <https://doi.org/10.1016/j.joms.2009.07.098>
102. Novelli G, Tonellini G, Mazzoleni F, Bozzetti A, Sozzi D. Virtual surgery simulation in orbital wall reconstruction: integration of surgical navigation and stereolithographic models. *Journal of Cranio-Maxillofacial Surgery.* 2014;42(8):2025-2034. <https://doi.org/10.1016/j.jcms.2014.09.009>