



Review Article

Synergistic Use of Intraoperative Ultrasound and Contrast-enhanced Ultrasound for Image-guided Brain Tumor Surgery: A Narrative Review



Ying He*, Danni Zhu, Yuwei Zeng, Jienv Lou and Dan Mao

Department of Ultrasound Medicine, The Affiliated People's Hospital of Ningbo University, Ningbo, Zhejiang, China

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Abstract

Brain tumors represent a common class of life-threatening neoplastic conditions. The core objective of neurosurgery is to achieve maximal safe resection of tumors while preserving the patient's neurological function. Intraoperative ultrasound (IOUS) assists surgeons in achieving complete lesion removal, helping to avoid insufficient resection or excessive excision of normal tissue, thereby reducing surgical morbidity. Contrast-enhanced ultrasound (CEUS), through harmonic imaging, enables more precise localization of lesions and intracranial structures. This review focuses on the synergistic value of IOUS and CEUS in brain tumor surgery. It traces the technological evolution from two-dimensional ultrasound to elastography, color Doppler flow imaging, microvascular flow imaging, artificial intelligence, and beyond, with an emphasis on CEUS for cranial tumors. It also examines the clinical applications of IOUS and CEUS in precise resection, residual tumor identification, vascular protection, boundary differentiation from peritumoral edema, and prognostic assessment. The review concludes by summarizing diagnostic performance, current limitations, and future directions, offering neurosurgeons a theoretical and practical framework for optimizing intraoperative guidance.

Introduction

Brain tumors are prevalent and life-threatening, with approximately 308,000 new cases and 251,000 deaths worldwide in 2020. Their infiltrative growth and indistinct boundaries pose significant surgical challenges.^{1,2} The paramount objective of neurosurgery is to achieve maximal safe resection while preserving neurological function.

Intraoperative ultrasound (IOUS) has played a pivotal role in real-time, precise localization of intracranial lesions since its introduction to neurosurgery in the 1980s, facilitated by rapid advancements in ultrasonography. It helps surgeons maximize lesion resection while minimizing unnecessary removal of normal tissue, thereby reducing iatrogenic injury.² Recent advances in multimodal IOUS, including color/power Doppler imaging, contrast-en-

hanced ultrasound (CEUS), and elastosonography, have expanded IOUS from real-time anatomical localization to the assessment of vascular/perfusion characteristics and tissue stiffness in brain tumor surgery.³

Despite advantages such as procedural simplicity, cost-effectiveness, and radiation-free operation, conventional IOUS exhibits limitations in residual tumor detection (particularly for isoechoic lesions), vascular structure discrimination, and demarcation of tumor boundaries from surrounding edema.² Additionally, brain shift caused by intracranial pressure changes or focal resection compromises anatomical landmark identification and lesion localization during surgery.⁴

CEUS significantly enhances the sensitivity of ultrasound in detecting low-velocity blood flow through harmonic imaging, enabling more precise localization of lesions and intracranial structures. It provides comprehensive visualization of the entire vascular network, offering anatomical information, tumor perfusion characteristics, and adjacent vessel details, thereby assisting surgeons in intraoperative tumor boundary assessment and tumor grading.^{5–7} The application of ultrasound in neurosurgery continues to advance, and currently, multiple ultrasound imaging techniques, including two-dimensional grayscale ultrasound, ultrasound elastography, color Doppler flow imaging (CDFI), microvascular flow imaging (MFI), CEUS, artificial intelligence (AI), and navigated ultrasound, can be used in real time during surgery,

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*Correspondence to: Ying He, Department of Ultrasound Medicine, Ningbo University Affiliated People's Hospital, 251 Baizhang East Road, Yinzhou District, Ningbo, Zhejiang 315000, China. ORCID: <https://orcid.org/0009-0009-8123-3749>. Tel: +86-18888663982, E-mail: hy13028997602@163.com

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making the resection of brain tumors more precise, thorough, safe, and effective.^{7,8}

In summary, despite significant advances in IOUS and CEUS for brain tumor surgery, most existing studies focus on validating single techniques, with limited systematic synthesis of multimodal synergies. This narrative review aims to present the principles and clinical applications of IOUS and CEUS in brain tumor surgery, with particular emphasis on their complementary and synergistic roles; summarize the diagnostic performance of related IOUS modalities in tumor boundary delineation, residual tumor detection, vascular preservation, and tumor–edema differentiation; and identify current limitations and future directions to provide practical insights for image-guided precision neurosurgery.

Evolving ultrasound technology in brain tumor surgery: Synergistic complementarity of IOUS and CEUS

IOUS

Since its introduction into neurosurgery in the 1980s, IOUS has undergone a developmental trajectory from low-frequency, low-resolution imaging toward high-frequency, high-resolution imaging. In the early stages of ultrasound technology development, two-dimensional grayscale ultrasound predominated; during this period, image quality was suboptimal, resolution was relatively low, and artifacts were prominent.^{4,5} This technology was primarily employed for deep lesion localization and puncture guidance; however, limited image quality restricted its ability to delineate detailed tumor characteristics.

With continuous advancements in probe technology, the application of high-frequency linear array probes (e.g., 7–15 MHz) significantly enhanced spatial resolution, facilitating more precise observation of brain tissue architecture, tumor boundaries, morphology, internal echogenicity patterns, and their relationships with surrounding structures.² This proved particularly valuable for intraoperative localization of infiltrative tumors such as gliomas.⁶ During IOUS procedures, two-dimensional ultrasound is first utilized, followed by the integration of other ultrasound techniques to acquire more comprehensive multimodal information encompassing anatomical and functional imaging characteristics.⁵

In recent years, the integration of technologies such as elastography and Doppler flow imaging has further expanded the capabilities of IOUS, enabling it to provide not only anatomical information but also insights into tissue stiffness and hemodynamic status.^{3,9} Ultrasound elastography, as an emerging non-invasive imaging technique, facilitates tumor identification through quantitative or semi-quantitative assessment of tissue stiffness differences.^{10–12} Currently, elastography techniques commonly employed in brain tumor surgery include strain elastography and shear wave elastography (SWE).^{13,14} The former, a quasi-static strain imaging modality, generates tissue strain by applying stress to the region of interest, allowing assessment of tissue softness or hardness based on ultrasound echo signals; the latter, a dynamic elastography technique, utilizes color-coded mapping for differentiation and offers superior reproducibility and contrast compared with strain elastography.

Chauvet *et al.*¹⁵ demonstrated in their 2016 study that differences in stiffness exist between low-grade and high-grade gliomas (HGGs), as well as between low-grade gliomas (LGGs) and normal brain tissue. In the study by Wang *et al.*,¹⁶ SWE was employed alone during brain tumor surgery, with postoperative magnetic resonance imaging (MRI) serving as the gold standard for assess-

ing residual tumor detection accuracy. The study found that SWE yielded a Kappa value of 0.714 with MRI, comparable to the 0.717 achieved by two-dimensional ultrasound, suggesting comparable performance in identifying residual tumor. Cepeda *et al.*¹⁷ applied strain elastography to 102 patients with brain tumors, calculating mean tissue elasticity values through semi-quantitative analysis. They identified significant differences in elasticity values among tumors of different pathological types ($P < 0.001$). A substantial body of research indicates that elastography provides valuable supplementary information for surgeons during cranial tumor procedures.^{14,15,17,18}

CDFI utilizes Doppler technology to visualize blood flow direction and measure flow velocity. In the context of brain tumor surgery, it primarily encompasses color Doppler ultrasound and power Doppler ultrasound.^{19,20} In imaging results, red typically indicates blood flow moving toward the transducer, whereas blue denotes flow moving away from the transducer.⁵ The optimal timing for this technique is after craniotomy but before dural incision. This technology provides comprehensive information regarding tumor vascularity,³ including the relationship between major vessels and the tumor, tumor vessel caliber, tumor feeding arteries, and tumor-draining veins. Such information assists surgeons in more precisely determining surgical location and depth while avoiding injury to critical vessels. However, color Doppler is notably susceptible to scanning angle effects,^{4,19} and image quality degrades with deeper target locations. Large sampling windows may introduce artifacts; while it demonstrates advantages in visualizing larger vessels, its capacity for microvascular visualization is limited.²¹ In contrast, power Doppler is unaffected by flow angle and direction,² offering greater sensitivity in detecting small-caliber and deep-seated vessels. Nevertheless, power Doppler does not provide information on flow direction. Previous studies have demonstrated that Doppler ultrasound assessment of critical tumor and peritumoral vessels reduces intraoperative vascular injury and decreases postoperative complications.^{3,19}

MFI and superb microvascular imaging (SMI), as emerging Doppler imaging techniques,^{21–25} effectively suppress tissue motion artifacts, offer high resolution, and preserve microvascular blood flow signals. Their capability in displaying low-velocity blood flow surpasses that of conventional color and power Doppler. The terminological distinction primarily reflects vendor-specific nomenclature rather than fundamental technical differences.^{3,26} However, reports on their application in cranial surgery remain relatively scarce.

In 2017, Ishikawa *et al.*²¹ first applied MFI in cranial surgery, describing the MFI characteristics of various brain tumors and proposing that MFI could be used to differentiate tumors from peritumoral tissues. In 2023, the same team²⁶ applied MFI in 20 patients diagnosed with brain tumors. Their findings revealed that when MFI was performed alone, it was difficult to clearly visualize blood flow in numerous small vessels; however, after the administration of a contrast agent, repeated MFI examinations achieved clear visualization. Consequently, they concluded that contrast agent injection enhances the imaging performance of MFI, enabling clear depiction of tumor microvascular architecture, and that analysis of vessel density and contrast agent arrival time allows assessment of tumor blood supply characteristics.

In 2024, Cai *et al.*²² demonstrated that SMI significantly outperformed grayscale ultrasound in improving the delineation of HGG boundaries ($P = 0.033$). This study directly compared the clinical value of CDFI and SMI, confirming the advantages of SMI as an advanced technology over CDFI. In 2025, Dixon *et al.*²⁷ employed

SMI to acquire tumor microvascular images and conducted both qualitative and quantitative analyses, concluding that HGG exhibits greater vascular complexity and disorganization, thereby establishing SMI as a novel intraoperative real-time tool for glioma grading.

Currently, MFI still presents several limitations, including restricted visualization of deep-seated lesions and a lack of standardized quantitative parameters.⁴ Future applications in cranial surgery are expected to involve its combination with functional techniques such as CEUS to provide surgeons with more comprehensive information.

Navigated IOUS integrates ultrasound probes with neuronavigation systems to achieve real-time imaging during surgery, which can be compared with preoperative MRI. This approach effectively addresses the localization challenges posed by brain shift that affect conventional ultrasound. This technology combines the real-time convenience of ultrasound with the spatial localization advantages of navigation.^{28,29} In 2025, a study by Cepeda *et al.*³⁰ validated a deep-learning model for glioma segmentation on 2D IOUS images from 197 patients. Concurrently, the team employed the YOLO11 architecture on 1,732 IOUS images,³¹ achieving outstanding performance, where the mean average precision at an IoU threshold of 0.50 (mAP@50) was 0.95, and the mAP averaged across IoU thresholds from 0.50 to 0.95 (mAP@50-95) was 0.65 at a processing speed of 34 frames per second. Neurosurgeons confirmed that the system integrated seamlessly into the surgical workflow, providing real-time, accurate prediction and delineation of tumor regions. These findings validate the clinical feasibility of AI-assisted IOUS. Vahdani *et al.*³² proposed a novel deep learning architecture named U-ConvNext, specifically designed for IOUS segmentation of LGGs. This study was the first to introduce uncertainty quantification into IOUS segmentation, providing a reliability assessment for AI-assisted decision-making and holding significant clinical translational value. Zeineldin *et al.*³³ developed NeuroIGN, an open-source, multimodal, explainable AI neuronavigation system that seamlessly fuses preoperative MRI with real-time IOUS, offering intuitive decision support for intraoperative navigation. The advancement of navigated IOUS and AI signifies the transition of IOUS from an auxiliary localization tool to a multifunctional intraoperative navigation platform. It is anticipated that soon this technology will become a cost-effective and precise intraoperative guidance tool in precision neurosurgery.

Despite the promising performance of YOLO11,³¹ U-ConvNext,³² and NeuroIGN in IOUS image analysis,³³ several barriers hinder their clinical adoption, namely the scarcity of large-scale, standardized, multicenter annotated datasets, limited cross-device and cross-scenario generalizability, and high computational requirements for real-time processing.^{4,31}

CEUS

CEUS involves intravenous administration of ultrasound contrast agents (primarily gas-filled phospholipid microbubbles, such as those containing sulfur hexafluoride and perflutren lipid microspheres), which significantly enhances blood contrast and enables dynamic visualization of tumor microvascular kinetics.^{7,34} These microbubbles exhibit excellent biocompatibility, remain confined to the vascular space without extravasation, undergo no metabolism *in vivo*, and are eliminated via the pulmonary circulation, offering a high safety profile with no nephrotoxicity or hepatotoxicity.³⁵ Absolute contraindications include known hypersensitivity to sulfur hexafluoride or perflutren components. Caution is advised in patients with severe cardiopulmonary disease or the presence of

right-to-left shunts, as microbubbles may enter the systemic circulation.³⁵ The underlying principle is that microbubbles undergo nonlinear oscillation under ultrasound exposure, generating harmonic signals that facilitate high-contrast, high-resolution imaging under low mechanical index conditions.³⁴ Consequently, CEUS provides clear visualization of intravascular blood flow distribution, unaffected by scanning angle, and enables real-time dynamic display of comprehensive vascular information within brain tumor tissues, including anatomical details, tumor perfusion characteristics, and adjacent vessel information, thereby assisting surgeons in intraoperative tumor boundary assessment and tumor grading.^{5,35}

In clinical practice, administration and dosage typically consist of an intravenous bolus injection of 1.2–2.4 mL of contrast agent, followed by a 5–10 mL saline flush. Repeat administrations (usually 2–3 times) are safe.³⁵ For perfusion analysis, continuous infusion is recommended.³⁵ CEUS imaging should be performed at three key time points: (1) after dural opening (baseline), (2) during resection (residual tumor detection), and (3) after resection (final check). Each acquisition should last 60–120 seconds to capture the arterial phase (10–30 s), parenchymal phase (30–60 s), and venous phase (60–120 s).^{4,35} A low mechanical index (<0.2) should be used to preserve microbubble integrity.³⁵ Figure 1 provides a schematic overview of the intraoperative CEUS operational steps and key parameters.^{4,35}

The application of CEUS in cranial settings dates to 1993, when Bogdahn first utilized it for cerebral vascular examination.³⁶ To date, CEUS has achieved significant advancements in cranial surgery, diagnostics, and therapeutics,³⁷ with applications including glioma grading,³⁸ brain tumor surgery,³ diagnosis and evaluation of cerebrovascular diseases,^{39,40} and even microbubble-mediated enhancement of targeted therapeutic efficacy.^{41,42} In brain tumor surgery, CEUS has been employed to differentiate residual lesions, protect vascular structures, and distinguish tumor boundaries from peritumoral edema.²

The study by Wang *et al.*¹⁶ demonstrated that CEUS exhibited the highest diagnostic concordance with MRI, outperforming B-mode ultrasound, MFI, and SWE, strongly supporting CEUS as the preferred technique for intraoperative assessment of residual lesions. CEUS enhancement patterns correlate with tumor pathology and angiogenic characteristics. Cheng *et al.*³⁸ confirmed that HGGs typically display rapid, heterogeneous “ring-like” enhancement with non-enhancing central necrotic areas and highly enhancing peripheral viable tumor tissue, reflecting pathological features of dense microvasculature at the tumor periphery and central ischemia-necrosis. LGGs manifest as slow, homogeneous, or mild enhancement, with some tumors exhibiting no enhancement due to low microvascular density, suggesting that CEUS may have limitations in LGG identification and that multimodal imaging approaches are necessary. Meningiomas, as highly vascular tumors, commonly exhibit homogeneous, marked enhancement on CEUS, with sharp tumor–brain interfaces.⁵ CEUS features of metastatic tumors are influenced by the vascular characteristics of their primaries, with most hypervascular metastases demonstrating rapid, marked enhancement and relatively well-defined margins.⁴³

Notably, ultrasound contrast microbubbles remain intravascular and do not ordinarily extravasate into brain parenchyma; therefore, CEUS enhancement in brain tumors mainly reflects abnormal tumor microvasculature and perfusion rather than direct microbubble entry into the parenchyma.^{35,38} Furthermore, microbubbles can serve as therapeutic vehicles; upon ultrasound triggering, they can transiently open the BBB, facilitating targeted delivery of chemotherapeutic agents, antibodies, and immunomodulators, thereby

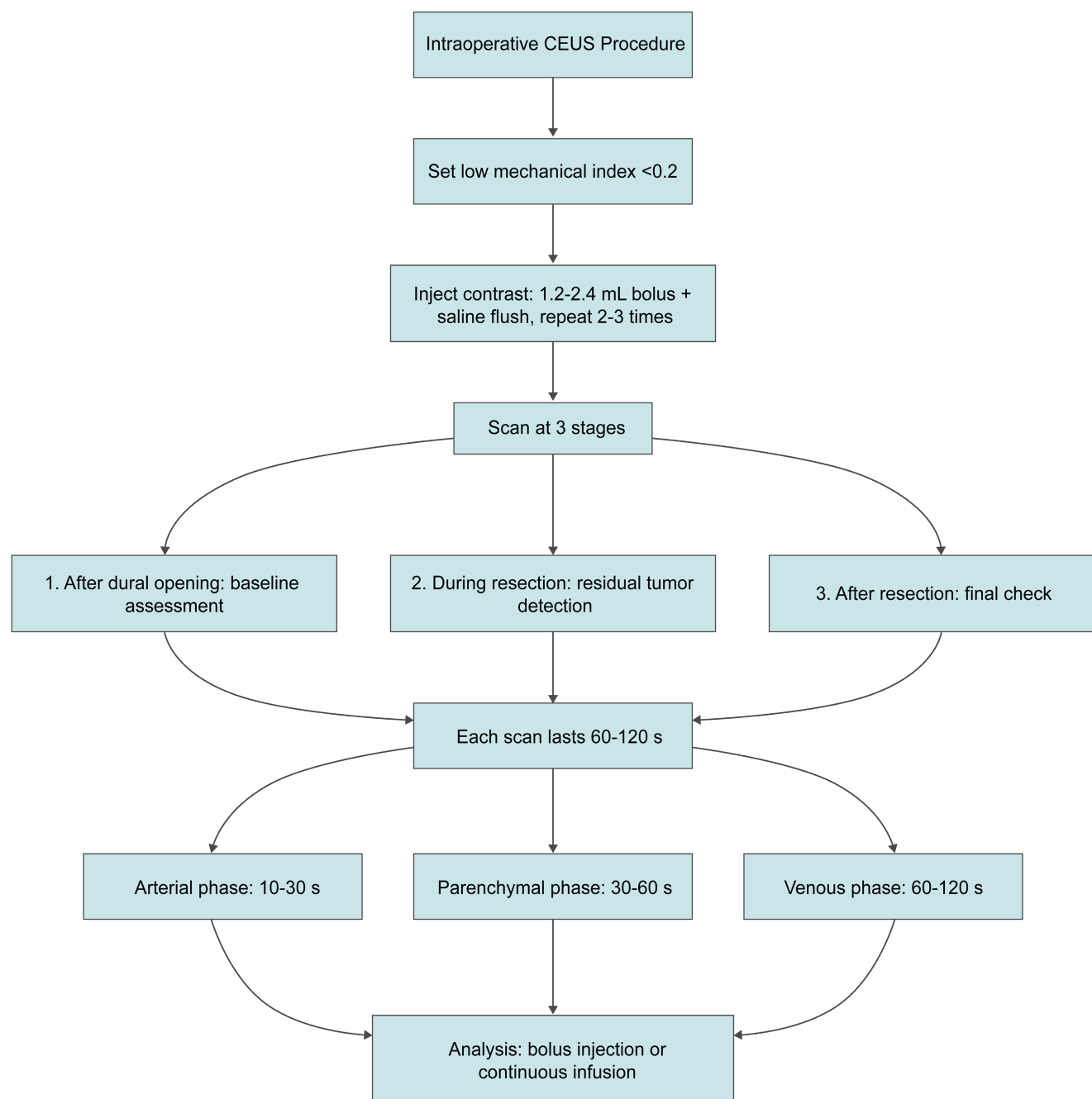


Fig. 1. Intraoperative CEUS protocol for brain tumor surgery. Standard intraoperative CEUS workflow for brain tumor resection. A mechanical index below 0.2 is applied to protect microbubbles. Contrast medium is injected intravenously as a 1.2–2.4 mL bolus, followed by 5–10 mL saline flushing; 2–3 repeated injections are clinically safe. Imaging is acquired at three critical surgical stages: baseline scanning after dural opening, residual tumor identification during resection, and final verification after lesion removal. Each 60–120 s scan covers arterial (10–30 s), parenchymal (30–60 s), and venous (60–120 s) perfusion phases. Continuous infusion is preferred for quantitative perfusion evaluation. Data are derived from published literature.^{4,35} CEUS, contrast-enhanced ultrasound.

enabling theranostic integration.^{35,41,42} Thus, CEUS not only addresses the limitations of conventional IOUS in perfusion quantification and boundary identification but also expands its potential for precision therapeutic applications. From a clinical workflow perspective, CEUS requires no additional hardware beyond standard ultrasound equipment, apart from the intravenous administra-

tion of a contrast agent. This low-barrier adoption, combined with its real-time imaging capability, positions CEUS for widespread integration into neurosurgical practice. In summary, conventional ultrasound offers multiple advantages in brain tumor surgery, including ease of operation, low cost, and excellent repeatability. However, it exhibits significant limi-

Table 1. Comparison of advantages and limitations of different intraoperative ultrasound modalities in brain tumor surgery

Modality	Imaging principle	Key advantages	Major limitations	Refs
Conventional IOUS	Structural imaging based on differences in acoustic impedance between tissues	Real-time, convenient, low-cost; Accurate localization and puncture guidance	Boundary interpretation is subjective and echo-dependent; Unable to assess microcirculatory perfusion	2,4
CEUS	Pure blood pool imaging utilizing nonlinear harmonic signals of microbubbles under low acoustic pressure	Functional imaging: visualizes tumor microcirculatory perfusion; Accurately delineates viable tumor boundaries and residual lesions	Requires intravenous contrast agent injection; LGG may show iso-enhancement	2,16, 35,38
SMI	Adaptive algorithm suppresses tissue motion artifacts to visualize slow blood flow	Contrast-agent-free visualization of microvascular architecture; Improves HGG boundary delineation	Reduced resolution for deep-seated lesions; Unable to provide perfusion information	3,4,21
SWE	Quantitatively calculates tissue stiffness (Young's modulus) by measuring shear wave velocity	Provides objective quantitative stiffness values; Assists in tumor grading and infiltrative zone assessment	Susceptible to intraoperative interference (e.g., electrocautery); Lacks standardized universal cutoff values	4,13, 15,17

IOUS, intraoperative ultrasound; CEUS, contrast-enhanced ultrasound; LGG, low-grade glioma; SMI, superb microvascular imaging; HGG, high-grade glioma; SWE, shear wave elastography.

tations in identifying residual tumors, delineating vascular structures, distinguishing tumor boundaries from peritumoral edema, and assessing the completeness of postoperative resection, particularly when tumor echogenicity differences are subtle, which may lead to missed residual lesions.⁶ Furthermore, conventional gray-scale ultrasound cannot accurately assess tumor microcirculatory perfusion status, creating an information gap for IOUS-guided precise resection.^{4,7} CEUS precisely fills this gap. By intravenously administering pure blood-pool microbubble contrast agents, CEUS enables dynamic visualization of tumor microvascular perfusion patterns.^{7,35} Compared with surrounding normal brain tissue and peritumoral edema, glioma tissue generally shows stronger enhancement on intraoperative CEUS, with HGGs demonstrating earlier enhancement than adjacent edema and normal brain tissue.³⁸ This functional contrast makes CEUS a valuable tool for identifying viable tumor boundaries and residual lesions, thereby complementing the structural imaging provided by conventional IOUS (Table 1).^{2-4,13,15-17,21,35,38}

Clinical synergy of IOUS and CEUS

Applications of IOUS and CEUS in different brain tumor subgroups

Brain tumor subgroups, including pediatric brain tumors, brain metastases, and skull base lesions, demonstrate divergent pathological and anatomical characteristics, necessitating tailored IOUS and CEUS strategies to optimize resection accuracy and functional preservation.

Pediatric LGGs represent the most common brain tumors in children. However, their echogenicity differences from normal brain tissue are often indistinct, posing challenges for intraoperative boundary identification. Mattei *et al.*⁴⁴ demonstrated that both B-mode ultrasound and CEUS facilitate delineation of LGG boundaries and characterization of tumor vascularity, thereby enhancing the safety of radical resection. A study encompassing 45 pediatric supratentorial lesions reported that IOUS ensures reliable real-time imaging during surgery for space-occupying brain lesions.⁴⁵ Preoperative IOUS enabled accurate lesion localiza-

tion; in deeply seated lesions, the addition of CEUS improved visualization of tumor vascular patterns and assisted in surgical route planning. Notably, approximately 30% of cases prompted a change in surgical strategy due to the intraoperative detection of residual tumor. A further study in 2024 confirmed that navigated IOUS achieves a sensitivity of 100% and a specificity of 84.6% for detecting residual tumor, demonstrating reliable accuracy compared with intraoperative magnetic resonance imaging (Table 2).^{2-5,7,16,19,21,29,35,38,44,46}

Brain metastases represent the most common intracranial tumors in adults, and the surgical goal is to achieve gross total resection (GTR) to improve survival outcomes. Cheng *et al.*⁴³ observed that on conventional ultrasound, metastatic tumors frequently presented with well-defined margins (32/46, 69.6%), hypervascularity (35/46, 76.1%), and severe peritumoral edema (33/46, 71.7%). During CEUS, brain metastases typically exhibit a “rapid, heterogeneous, high-enhancement” pattern with delayed washout, and CEUS can assist in delineating tumor boundaries. A 2025 study further quantified the value of IOUS.⁴⁷ In this study, 80% of IOUS-guided cases achieved a GTR rate of >96%, which was significantly higher than that of the conventional neuronavigation group (42.86%, $P = 0.008$). IOUS significantly increased the odds of achieving GTR (odds ratio [OR] = 5.33, $P = 0.011$). Larger tumor volume reduced the likelihood of GTR (OR = 0.469, $P = 0.025$).

Skull base tumors pose a major surgical challenge due to their proximity to critical vessels and nerves, making intraoperative identification and preservation of vascular structures paramount. Prada *et al.*⁵ applied navigated CEUS in 18 patients with skull base tumors (including 10 meningiomas, 3 craniopharyngiomas, 2 giant pituitary adenomas, 1 posterior fossa epidermoid cyst, and 2 dermoid cysts).

This technique enables comprehensive visualization of both high- and low-flow vessels, clearly delineating the three-dimensional spatial relationship between tumors and major neurovascular structures. Such detailed vascular depiction facilitates avoidance of perforating arteries and effectively reduces the risk of intraoperative vascular injury. This subtype-specific multimodal imaging strategy compensates for the inherent diagnostic limitations of single-modality ultrasound, greatly improving the individualized

Table 2. Intraoperative ultrasound blind spots, CEUS advantages, and synergistic value in brain tumor surgery

Clinical challenge	IOUS blind spots	CEUS core advantages	Synergistic value	Refs
Tumor boundary delineation	Dependent on tissue echogenicity differences; Poor delineation in isoechoic lesions or peritumoral edema; Unable to distinguish infiltrative tumor from peritumoral edema	Pure blood pool imaging: rapid tumor enhancement vs. no/delayed enhancement in edema; Highest concordance with MRI (Kappa = 0.892)	IOUS identifies suspicious areas; CEUS confirms true boundaries	2,4,5,16,44
Residual tumor detection	Low sensitivity for small residuals; Postoperative artifacts may mimic residual tumor	Abnormal enhancement at resection cavity margins suggesting abnormal microvascular perfusion; Sensitivity 77.78%, specificity 100%	CEUS provides real-time confirmation of residuals, guiding further resection (GTR: 82% vs. 48%)	2,16
Vascular structure identification	CDFI is angle-dependent; Low sensitivity to slow blood flow; Unable to visualize microvasculature	Angle-independent; Clearly depicts feeding arteries, draining veins, and perforating vessels (SMI visualizes microvessels)	IOUS plans surgical approach; CEUS identifies critical vessels, avoiding injury	3,4,19,21
Tumor vs. edema differentiation	Both tumor and edema appear hyperechoic; Infiltrative margin indistinguishable from edema	Tumor: early rapid enhancement, late rapid washout; Edema: no enhancement (intact BBB, low MVD)	CEUS clearly distinguishes tumor (enhanced) from edema (non-enhanced), defining safe boundaries	2,4,7,35,38
Functional area perfusion	No real-time perfusion information; Unable to assess microcirculatory status	TIC parameters such as PI, TTP, and AUC reflect tumor perfusion characteristics	CEUS provides supplementary perfusion information for surgical planning	2,35,46

AUC, area under the curve; BBB, blood–brain barrier; CDFI, color Doppler flow imaging; CEUS, contrast-enhanced ultrasound; GTR, gross total resection; IOUS, intraoperative ultrasound; MRI, magnetic resonance imaging; MVD, microvessel density; PI, peak intensity; SMI, superb microvascular imaging; TIC, time–intensity curve; TTP, time to peak.

precision of neurosurgical resection. It provides robust real-time intraoperative guidance for maximizing the extent of tumor resection while preserving critical neurological functions across diverse brain tumor populations.

Real-time image-guided precise resection: Complementarity of conventional IOUS and CEUS

Achieving maximal safe resection is a critical goal for improving patient outcomes in brain tumor surgery. IOUS, as a real-time, radiation-free, and cost-effective imaging modality, has been widely employed to assist intraoperative localization and boundary delineation of brain tumors.² CEUS not only enhances contrast between tumors and normal brain tissue but also provides information on tumor angiogenesis, thereby supporting more precise resection decisions.² On CEUS, tumors typically exhibit early rapid enhancement and rapid washout, whereas surrounding edematous brain tissue, characterized by an intact BBB and low microvascular density, often shows no enhancement or delayed low enhancement.¹⁶ This difference in perfusion enables CEUS to accurately delineate tumor boundaries, with its accuracy in assessing residual lesions demonstrating high concordance with postoperative MRI (Kappa = 0.892).¹⁶

In clinical practice, conventional IOUS and CEUS form a strong complementary relationship: IOUS provides real-time anatomical localization and surgical pathway planning, while CEUS provides information on tumor blood supply and perfusion boundaries. Their combined application enables multidimensional tumor assessment. The study by Wang *et al*.¹⁶ demonstrated that the GTR rate under CEUS guidance reached 82%, significantly higher than

that of the conventional IOUS group (48%). Furthermore, CEUS allows intraoperative real-time assessment of tumor angiogenic activity and pathological grading through quantitative parameters (peak intensity, time to peak) and their correlation with microvessel density ($r = 0.78$, $P < 0.001$).^{38,46} For HGGs, the ring-enhancing region visualized by CEUS accurately delineates the boundary of viable tumor tissue, guiding surgeons to achieve maximal resection while preserving critical functional areas.^{5,46}

Moreover, the complementary application of conventional IOUS and CEUS enables real-time navigation during intracranial tumor resection and can be further integrated with AI. Combined with preoperative MRI data, this approach helps mitigate intraoperative brain shift and enhances surgical precision.^{28,29} Artificial intelligence-assisted image interpretation, capable of automatically delineating tumor boundaries,^{32,33} is advancing neurosurgical procedures toward greater precision and safety.

Identification of residual tumor tissue

Timely identification of residual lesions during tumor resection is crucial for improving the GTR rate. Studies have shown that in newly diagnosed isocitrate dehydrogenase (IDH)-wildtype glioblastoma, extensive resection of non-enhancing tumor is associated with better survival outcomes, with smaller postoperative residual volumes correlating with reduced mortality risk.⁴⁸ Although conventional grayscale ultrasound provides real-time structural information, its ability to detect small residual lesions is limited, particularly when echogenicity differences are subtle, which may lead to missed residual tumors.²

Leveraging its high sensitivity to microcirculatory perfusion,

Table 3. Diagnostic performance of different intraoperative ultrasound modalities for residual tumor detection and boundary delineation in brain tumor surgery

Modality	Primary application	Key finding	Quantitative metric	Ref
CEUS	Residual tumor detection	Highest diagnostic concordance with MRI among all ultrasound techniques	Kappa = 0.892; Sensitivity: 77.8%; Specificity: 100.0%	Wang <i>et al.</i> , 2025 ¹⁶
Conventional IOUS	Residual tumor detection	Comparable diagnostic accuracy to SWE, inferior to CEUS	Kappa = 0.717	Wang <i>et al.</i> , 2025 ¹⁶
SMI	HGG boundary delineation	Significantly superior to grayscale ultrasound in delineating HGG boundaries	$P = 0.033$	Cai <i>et al.</i> , 2024 ²²
SWE	Tumor grading / boundary assessment	Provides objective stiffness parameters to differentiate LGG from HGG	AUC = 0.855; Sensitivity: 88.9%; Specificity: 86.7%	Cai <i>et al.</i> , 2025 ⁴⁹

CEUS, contrast-enhanced ultrasound; MRI, magnetic resonance imaging; IOUS, intraoperative ultrasound; SMI, superb microvascular imaging; HGG, high-grade glioma; SWE, shear wave elastography; LGG, low-grade glioma; AUC, area under the curve.

CEUS enables immediate postoperative assessment of whether abnormal enhancement areas exist at the resection cavity margins; such areas often indicate the presence of residual tumor tissue. Because ultrasound contrast agent microbubbles remain confined to the vascular lumen without extravasating into normal brain parenchyma, abnormal enhancement at the resection cavity margin may indicate residual viable tumor tissue with abnormal microvascular perfusion, but it should be interpreted together with tumor morphology and the surgical context.^{2,16,35} In contrast, necrotic or cystic areas and surrounding edematous brain tissue usually show absent, lower, or delayed enhancement compared with viable tumor tissue; CEUS can also help distinguish residual tumor from surgically induced artifacts.^{7,38} This unique characteristic gives CEUS a distinct advantage in distinguishing postoperative reactive changes from true residual tumors.

The study by Wang *et al.*¹⁶ directly compared the efficacy of two-dimensional ultrasound, MFI, CEUS, and SWE in assessing the extent of brain tumor resection. The results showed that CEUS exhibited the highest diagnostic concordance with MRI (Kappa = 0.892) and outperformed other ultrasound techniques in detecting residual lesions. The study concluded that CEUS is the preferred technique for intraoperative assessment of residual tumors.

SMI also plays a role in residual tumor identification. The study by Ishikawa *et al.*²⁶ combined contrast-enhanced SMI with CEUS and found that analyzing vessel density and contrast agent arrival time enabled a more comprehensive assessment of tumor blood supply status, aiding in the identification of residual lesions (Table 3).^{16,22,49}

Vascular structure identification and hemodynamic monitoring of functional areas: From structural preservation to functional conservation

In brain tumor surgery, real-time intraoperative assessment of the anatomical relationships among tumor feeding arteries, draining veins, and adjacent perforating vessels, as well as the planning of safe resection pathways and intraoperative bleeding control, significantly impacts surgical prognosis. CDFI, as a fundamental blood flow imaging technique, can visualize the direction and velocity of blood flow in larger vessels, assisting surgeons in identifying major feeding arteries and draining veins.¹⁹ However, CDFI has low sensitivity to low-velocity blood flow and exhibits strong angle dependence, limiting its ability to visualize microvascular structures and thereby restricting its application in fine vascular identification.⁴ The advent of SMI has addressed the limitations of CDFI, enabling clear visualization of microvessels as small as

0.1–0.2 mm in diameter, and has been effectively applied in HGG surgery.²² Intraoperative CEUS further enhances vascular identification. By dynamically displaying tumor blood perfusion through microbubble contrast agents, CEUS can clearly differentiate feeding arteries, draining veins, and normal perforating vessels, playing a crucial role in intraoperative vascular localization for hypervascular tumors such as meningiomas.^{5,46}

Future synergistic use of CDFI, SMI, and CEUS may provide complementary vascular information from macrovascular to microvascular levels.³ Together with AI-assisted tumor or tissue boundary delineation and ultrasound-based vascular identification,^{5,31} this strategy may provide dual support for achieving maximal safe resection.

Differential diagnosis of tumor boundaries and peritumoral edema zones

Accurate differentiation between tumor parenchyma and surrounding vasogenic edema represents a key challenge in brain tumor surgery. Tumor cells often infiltrate surrounding brain tissue along white matter tracts, forming transitional zones mixed with edema. Conventional grayscale ultrasound struggles to distinguish these regions, as both tumor tissue and edematous brain tissue may appear hyperechoic. In addition, surgical manipulation and bleeding can further increase the echogenicity of peritumoral tissue, making it difficult to differentiate tumor invasion using conventional ultrasound.^{2,4} This can lead neurosurgeons to either under-resect (leaving residual infiltrating tumor) or over-resect (removing normal functional brain tissue), thereby affecting patient prognosis.⁴⁸

CEUS facilitates the identification of tumor boundaries and peritumoral edema zones by visualizing microvessel density and perfusion patterns.³⁵ The key differentiating features are as follows: tumor tissue exhibits early rapid enhancement and late rapid washout, whereas edematous zones, due to an intact BBB and low microvascular density, show no enhancement or delayed low enhancement.^{16,35} Therefore, combining IOUS with CEUS aids in delineating tumor margins.^{7,38} Studies have shown that the intraoperative application of CEUS in glioma surgery enables delineation of tumor boundaries and further differentiation between tumor tissue and brain edema.⁷ The study by Cheng *et al.*³⁸ also demonstrated that cranial CEUS could distinguish between tumor and edema and effectively detect postoperative residual tumor. The 2017 EFSUMB CEUS guidelines detail the clinical standards for non-hepatic applications, including urological, vascular, and intracranial intraoperative use indications. Thanks to its superior blood-pool imaging and safety profile, CEUS has

also been adopted in neurosurgery to support intraoperative decision-making.^{35,50}

SMI also holds significant value in differential diagnosis. The study by Cai *et al.*²² showed that SMI significantly outperformed grayscale ultrasound in improving the delineation of HGG boundaries, and the microvascular architecture visualized by SMI can help distinguish the tumor core from surrounding edematous areas. For LGGs, SMI can reveal sparse microvascular structures within the tumor, whereas edematous zones typically show no distinct blood flow signals.²⁶

Ultrasound elastography provides complementary information from the perspective of tissue stiffness. Tumor tissue, characterized by high cellular density and fibrosis, typically exhibits significantly higher stiffness than edematous brain tissue.^{13,15} Cepeda *et al.*¹⁷ demonstrated that strain elastography can clearly visualize the stiffness transition zone between tumor and edematous tissue, with significant differences in mean tissue elasticity values among different pathological types ($P < 0.001$). SWE enables further quantitative analysis, providing Young's modulus values and thereby enhancing the objectivity of differential diagnosis.^{13,15}

Collectively, the synergistic combination of IOUS and CEUS serves as a core pillar for accurate differentiation of tumor infiltration and peritumoral edema, with auxiliary support from SMI and ultrasound elastography. By complementing the limitations of conventional single-modality IOUS, this dual-modality synergistic strategy integrates vascular perfusion characteristics and morphological details to eliminate diagnostic ambiguity in boundary identification. It thus provides a robust and practical intraoperative imaging solution for precisely distinguishing tumor lesions from edematous tissue.

Long-term outcomes: From GTR to survival benefit

Although GTR is the core metric of intraoperative efficacy, its ultimate value lies in translating into long-term patient survival. Chen *et al.*⁵¹ demonstrated in a survival analysis of 64 malignant gliomas that the intraoperative CEUS group achieved significantly superior overall survival (OS) and progression-free survival (PFS), with multivariate analysis confirming intraoperative CEUS-guided surgery as an independent prognostic factor for both OS and PFS ($P < 0.05$). A 2026 meta-analysis reported that the GTR rate under CEUS guidance was significantly higher than that of the non-CEUS group (OR = 5.37).⁵² Given that GTR has been consistently confirmed as an important predictor of survival, the survival benefit of CEUS follows a clear mechanistic logic: precise delineation of infiltrative margins enables complete tumor burden removal, which in turn delays recurrence and ultimately prolongs survival. These findings suggest that CEUS-guided surgery may improve tumor visualization, resection outcomes, and survival, although its effects on postoperative neurological function and quality of life require further validation.^{51,52}

Collectively, these findings support the translational potential of IOUS–CEUS synergy and suggest that improved intraoperative visualization may contribute to better long-term outcomes, although further prospective validation is needed.

Future perspectives

Despite the proven value of IOUS and CEUS in brain tumor surgery, current studies lack sufficient solutions to address specific clinical challenges. Future research should therefore focus on the following priority directions.

Targeted design of miniaturized high-resolution probes for

deep-seated lesions

Benson *et al.*⁵³ developed a miniaturized, high-resolution, trackable ultrasound imaging endoscope as a novel intraoperative imaging adjunct. This probe achieves axial and lateral resolutions of 38 μm and 113 μm , respectively. During tumor resection, it can differentiate neoplastic tissue from healthy parenchyma and detect residual tumors that would otherwise be missed under conventional surgical guidance. When the integrated system was tested in a brain phantom, the tumor boundaries identified by navigated MRI and ultrasound imaging demonstrated excellent concordance.

In LGGs, due to the relatively intact BBB, CEUS often demonstrates iso-enhancement or weak enhancement, making it difficult to delineate tumor infiltrative boundaries using a single modality.³⁸ SWE can provide complementary information through tissue stiffness parameters. Using a Young's modulus threshold of 13.90 kPa, the sensitivity and specificity for differentiating HGGs were 88.9% and 86.7%, respectively, with an area under the curve of 0.855 (95% confidence interval: 0.741–0.968, $P = 0.001$). In this study, the Young's modulus values of LGGs and HGGs were 23.4 ± 11.6 kPa and 12.1 ± 13.7 kPa, respectively, demonstrating a statistically significant difference ($P = 0.005$).⁴⁹ Future efforts may be directed toward establishing a fusion scoring model integrating CEUS perfusion parameters and SWE stiffness parameters to predict the added value of this multimodal approach in delineating LGG boundaries.⁷

Furthermore, multicenter prospective registry studies should establish standardized data acquisition protocols, unify ultrasound parameters, contrast agent regimens, and outcome measures, and conduct large-scale prospective cohort studies to validate the clinical value of CEUS/IOUS across different tumor subgroups. Long-term outcome studies should use OS, PFS, and neurological function preservation as primary endpoints to clarify the independent impact of CEUS-guided surgery on patients' long-term prognosis. Artificial intelligence assistance should focus on developing explainable deep learning models capable of real-time intraoperative tumor boundary delineation, residual tumor detection, and perfusion parameter quantification, thereby reducing operator dependency.^{31,32}

These future directions directly address the current limitations of IOUS–CEUS imaging. By advancing equipment, multimodal data fusion, and AI, the synergistic potential of this dual-modality strategy will be fully realized, paving the way for its standardized and intelligent application in precision neurosurgery.

Limitations

Several limitations of this narrative review should be acknowledged. First, unlike a systematic review, this work did not implement exhaustive literature retrieval, which may introduce selection bias. Second, most available evidence summarized herein originates from single-center studies with limited sample sizes, thereby restricting the generalizability of our conclusions. Third, marked heterogeneity exists across included studies with respect to ultrasound devices, contrast administration protocols, and outcome assessment metrics, making quantitative comparative analysis infeasible. Fourth, given the rapid iterative advancement of AI-assisted ultrasound techniques, several newly developed applications were not comprehensively covered in this review. Lastly, although we described the synergistic advantages of combined IOUS and CEUS, the supporting evidence to date remains preliminary, and large-scale prospective randomized controlled trials are still lacking for further validation.

Conclusions

Conventional IOUS offers real-time, low-cost imaging for brain tumor surgery but has limitations in boundary delineation, perfusion assessment, and residual tumor detection. The integration of CEUS addresses these gaps by visualizing tumor vascularization and infiltrative margins. The synergistic use of IOUS and CEUS provides surgeons with precise, real-time decision support for tumor resection, residual tumor identification, vascular preservation, and boundary differentiation from peritumoral edema.

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Conflict of interest

The authors declare that they have no conflicts of interest.

Author contributions

Literature search and summarization (YZ, JL, DM), writing and preparation of the original draft (YH, DZ), review and editing of the manuscript (YH, YZ, JL). All authors made significant contributions to this study and have read and approved the final manuscript.

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