



Comparison of different new ultrasonic technologies in resection assessment of neurosurgery

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Background: New ultrasound (US) techniques, such as contrast-enhanced ultrasound (CEUS) and shear wave elastography (SWE), are being used to identify artifacts, guide the interventions and evaluate the extent of resection, as it is difficult for gray-scale ultrasound to distinguish the artifacts in intraoperative ultrasound (IOUS). However, to date, no comparative study has been conducted on the role of several new US technologies in guiding brain tumor resection. Thus, this study sought to compare the roles of various new US technologies in guiding brain tumor resection to find a convenient and useful guiding technology for brain tumor resection.

Methods: From July 2022 to July 2023, 64 brain tumor patients (33 men and 31 women), with ages ranging from 26 to 78 years (53.2 ± 11.6 years), were included in the study. Before surgery, a planned resection (pRS) was determined for all of the included patients by a multidisciplinary neuro-oncology team. All patients underwent microsurgical resection of the lesion. After the craniotomy and before the dural opening, ultrasonic techniques, including B-mode, micro-flow imaging (MFI), CEUS, and SWE, were used to evaluate the features of the brain tumor and its surrounding structure. Then, those ultrasonic techniques were applied to each patient to confirm the microsurgical margin achieving the pRS at the end of the resection. Next, 3 days after surgery, a magnetic resonance imaging (MRI) scan was performed on each patient as the reference standard. The agreement between B-mode, color Doppler flow imaging (CDFI), MFI, CEUS, SWE, and MRI was measured by Fleiss' kappa agreement.

Results: In the evaluation of the surgical resection edges, all the included US technologies showed substantial agreement compared to the MRI results. The Kappa values were 0.717, 0.751, 0.714, and 0.892 for B-mode, MFI, SWE, and CEUS, respectively. CEUS and MRI showed the best diagnostic consistency. CEUS had the highest sensitivity, specificity, positive predictive value, and negative predictive value under the receiver operating characteristic (ROC) curve analysis (77.78%, 100%, 100%, and 86.05%, respectively), followed by MFI. B-mode and SWE showed similar accuracy in detecting tumor residue.

Conclusions: US is a convenient and cost-effective method for guiding the procedure and evaluating the

extent of resection in neurosurgery. CEUS has the highest diagnostic accuracy for residual lesions among the new US technologies. Thus, MFI can be recommended as a technique for guiding and evaluating residues in neurosurgery in addition to CEUS.

Keywords: Comparison; different new ultrasound technologies (different new US technologies); neurosurgery; resection assessment

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Introduction

Brain and central nervous system (CNS) tumors consist of neoplasms originating from the brain and adjacent structures (e.g., cranial nerves, the meninx, and the medulla spinalis). Such tumors are comparatively rare worldwide, constituting only approximately 1.6% of all cancers in adults; however, their incidence has increased in some regions following improvements in diagnostic techniques and the standardization of tumor registration (1). The epidemiology of such tumors differs significantly. Notably, East Asia, and China more specifically, has the highest incidence of brain and CNS tumors. Primary malignant brain and CNS cancers often have an unfavorable prognosis, directly impair neurological functions, and cause symptoms such as headaches, vision deterioration, seizures, speech difficulties, and paralysis. Due to their location in the brain, even benign tumors can be life-threatening, resulting in high mortality and disability rates, and significantly affecting patients' ability to function independently. Thus, the treatment of brain and CNS tumors is crucial. Currently, surgery is the main treatment method for brain and CNS tumors (2,3).

The main goals of neurosurgery are to maximize the extent of resection, minimize normal tissue damage, and most importantly, reduce postoperative recurrence rates. Due to the unique location of the CNS tumors and their structures, neurosurgery relies heavily on continuous, real-time imaging guidance.

Previous studies have shown that the extent of resection is a key prognostic factor in neurosurgery oncology (4-6). Intraoperative assistive imaging techniques include intraoperative magnetic resonance imaging (iMRI), computed tomography (CT), neuronavigation, frameless stereotaxy, fluorescence staining, and ultrasound (US). Although iMRI is the best available technique, it is not widely used due to its prolonged operative times, complex

operations, and high costs (7). Intraoperative CT imaging is less accurate, costly, and not widely available. Navigation and frameless stereotaxy is based on the magnetic resonance imaging (MRI) scans acquired preoperatively and acts like a global positioning system for the surgery (8-10); however, its accuracy is compromised due to the brain shift during surgery. Conversely, intraoperative ultrasound (IOUS) has been widely used in neurosurgery due to its ease of use, real-time capability, portability, and affordability (7,8,11-22).

Currently, gray-scale US is the major type of IOUS used to guide the procedure and evaluate the extent of resection in neurosurgery. However, it is difficult for gray-scale IOUS to identify artifacts, such as acoustic shadowing from surgical, post-surgical, and post-radiation artifacts, post-resection hyperechoic rim, peritumoural-oedema hyperechogenicity, and hyperechoic blood. Thus, new ultrasonic techniques, such as contrast-enhanced ultrasound (CEUS) and shear wave elastography (SWE), are used to identify such artifacts, guide the procedure, and evaluate the extent of resection (23-34).

To date, no comparative study has been conducted on the role of several new US technologies in guiding brain tumor resection. This study sought to compare the roles of various new US technologies in guiding brain tumor resection to find a convenient and useful guiding technology for brain tumor resection. We present this article in accordance with the STARD reporting checklist (available at <https://qims.amegroups.com/article/view/10.21037/qims-24-2271/rc>).

Methods

This prospective study is part of a clinical trial on the application of multimodal US in the intraoperative evaluation of brain tumors. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Institutional Ethics Board

of Sichuan Cancer Hospital (No. SCCHEC-02-2023-071), and informed consent was obtained from all individual participants.

From July 2022 to July 2023, 64 brain tumor patients (33 men and 31 women), with ages ranging from 28 to 78 years (mean age: 53.2 ± 11.6 years), were included in our study. To be eligible for inclusion in the study, the patients had to meet the following inclusion criteria: (I) have been diagnosed with a brain tumor by CT and enhanced MRI at Sichuan Cancer Hospital and be eligible for brain tumor surgery; (II) be aged from 18 to 80 years; and (III) voluntarily choose to undergo an IOUS examination and sign an informed consent form. Patients were excluded from the study if they met any of the following exclusion criteria: (I) had previously received other treatments, such as radiotherapy, chemotherapy, or brain tumor surgery; (II) could not undergo brain tumor surgery due to severe coagulation dysfunction, heart failure, etc.; and/or (III) were allergic to ultrasonic contrast agents.

Before surgery, the resections were planned for all included patients by a multidisciplinary neuro-oncology team. All patients underwent microsurgical resection of the lesion. IOUS (Philips EPIQ7, the Netherlands) equipped with a 5–7- and 3–10-MHZ transducer was used during the surgery. After the craniotomy and before the dural opening, the US techniques, including B-mode, color Doppler flow imaging (CDFI), micro-flow imaging (MFI), CEUS, and SWE, were used to evaluate the features of the brain tumor and its surrounding structure. Those US techniques were then performed on the patient to confirm the microsurgical margin achieving the planned resection (pRS) at the end of the resection.

We developed a grade standard for each evaluation method based on previous literature (*Table 1*) (18). The US evaluation before and at the end of the resection was performed by two sonographers with at least 3 years of experience in US. Two radiologists defined the grade of resection for each US technique based on the grade standard (*Table 1*). If a disagreement arose, the two US physicians discussed the issue and made a unified decision. Next, 3 days after surgery, an MRI scan was performed on each patient as the reference standard. All scans were reviewed by two experienced radiologists blinded to the IOUS scan. If a disagreement arose, the two radiologists discussed the issue and made a unified decision.

Statistical analysis

Fleiss' kappa agreement was used to measure the agreement

between the multiple US evaluations and MRI. The intra-operator agreement for the US techniques and MRI was also measured by Fleiss' kappa agreement. The correlation between the categorical variables was analyzed using the Pearson correlation coefficient. The categorical variables are expressed as the absolute number and percentage. The statistical analyses were performed using SPSS 22.0 (SPSS Inc., USA).

Results

In total, 68 brain tumor patients were included in the study. Most of the tumors had supratentorial locations (55 supratentorial, 8 infratentorial, and 1 both supratentorial and infratentorial). The most frequent histology was glioma ($n=31$), followed by meningioma ($n=13$), metastases ($n=14$), schwannoma ($n=2$), lymphoma ($n=2$), and other ($n=2$) (*Table 2*).

Complete resection was the most commonly planned procedure (pRS0 in 47 cases), followed by “near total” resection (pRS1 in 4 cases), partial resection (pRS2 in 11 cases), and biopsy (pRS3 in 2 cases) (*Table 1*).

During the surgery, microscopy and US techniques were integrated to estimate the extent of resection. The US techniques were used in all cases (*Figures 1,2*). Once the information is provided by integrating the microscopy and US techniques accorded with the pRS, the surgery could be completed.

Two sonographers and two MRI radiologists randomly selected 10 lesions in each group to independently evaluate the grade. There was a good correlation between the observers' evaluations of the grade for each US technique and MRI ($r_b=0.855$, $P<0.0001$; $r_s=0.811$, $P<0.0001$; $r_e=0.811$, $P<0.0001$; $r_m=0.841$, $P<0.0001$; $r_c=0.855$, $P<0.0001$; $r_M=0.845$, $P<0.0001$).

Compared to the MRI results, all the included US technologies showed substantial agreement. The Kappa values were 0.717, 0.751, 0.714, and 0.892 for B-mode, MFI, SWE, and CEUS, respectively. CEUS and MRI had the best diagnostic consistency (*Table 3*). In general, CEUS underestimated the tumor residual. B-mode, MFI, and SWE can both underestimate and overestimate the tumor residual. CEUS had the highest sensitivity, specificity, positive predictive value, and negative predictive value under the receiver operating characteristic (ROC) curve analysis (77.78%, 100%, 100%, and 86.05%, respectively) (*Table 4*).

To analyze the factors affecting the evaluation accuracy

Table 1 Evaluation of resection range grading by multimode ultrasound and MRI (18)

Grade	Explanation
pRS0	Total resection, no tumor residue
pRS1	Near total resection, allowing for a residual edge of the postoperative site ≤ 3 mm
pRS2	Partial resection
pRS3	Tumor volume unchanged, biopsy
MR0	No visible tumor
MR1	Rim enhancement or signal abnormality (matching the tumor) at the operation site only ("Rim"), ≤ 3 mm in any of the dimensions and enhancement or signal abnormality was equivocal for tumor residue
MR2	Residual tumor measuring >3 mm in all three dimensions (greater than MR1, less than MR3)
MR3	No significant change to the preoperative tumor size ("minimal change")
bRS0	No visible tumor
bRS1	Residual tumor (matching the tumor) at the operation site only ("Rim"), ≤ 3 mm in any of the dimensions and the image of the B-mode ultrasound was equivocal for tumor residue
bRS2	Residual tumor measuring >3 mm in all three dimensions (greater than bSR1, less than bSR3)
bRS3	No significant change to the preoperative tumor size ("minimal change")
cRS0	No visible tumor
cRS1	Residual tumor with blood flow signal (matching the tumor) at the operation site only ("Rim"), ≤ 3 mm in any of the dimensions and the image of the blood flow signal was equivocal for tumor residue
cRS2	Residual tumor measuring >3 mm in all three dimensions (greater than cSR1, less than cSR3)
cRS3	No significant change to the preoperative tumor size ("minimal change")
mRS0	No visible tumor
mRS1	Residual tumor with micro-blood flow signal (matching the tumor) at the operation site only ("Rim"), ≤ 3 mm in any of the dimensions and the image of the micro-blood flow signal was equivocal for tumor residue
mRS2	Residual tumor measuring >3 mm in all three dimensions (greater than mSR1, less than mSR3)
mRS3	No significant change to the preoperative tumor size ("minimal change")
ceRS0	No visible tumor
ceRS1	Rim enhancement or signal abnormality (matching the tumor) at the operation site only ("Rim"), ≤ 3 mm in any of the dimensions and the enhancement or signal abnormality was equivocal for tumor residue

Table 1 (continued)**Table 1** (continued)

Grade	Explanation
ceRS2	Residual tumor measuring >3 mm in all three dimensions (greater than ceSR1, less than ceSR3)
ceRS3	No significant change to the preoperative tumor size ("minimal change")
sRS0	No visible tumor
sRS1	Rim stiffness increasing or abnormality (matching the tumor) at the operation site only ("Rim"), ≤ 3 mm in any of the dimensions and the stiffness increasing or abnormality was equivocal for tumor residue
sRS2	Residual tumor measuring >3 mm in all three dimensions (greater than MR1, less than MR3)
sRS3	No significant change to the preoperative tumor size ("minimal change")

pRS0–3: the planned resection (pRS) grade standard determined by a multidisciplinary neuro-oncology team. MR0–3: the grade standard for MRI. bRS0–3: the grade standard for B-mode. cRS0–3: the grade standard for color Doppler. mRS0–3: the grade standard for MFI. ceRS0–3: the grade standard for CEUS. sRS0–3: the grade standard for SWE. CEUS, contrast-enhanced ultrasound; MRI, magnetic resonance imaging; MFI, micro-flow imaging; SWE, shear wave elastography.

Table 2 Patient characteristics

Variable	Value
Gender (male:female)	33:31
Age (years)	
Range	26–78
Mean \pm SD	53.2 \pm 11.6
Tumor size (cm), n	
≤ 5	39
> 5	25
Pathology, n	
Glioma	31
Meningioma	13
Metastases	14
Schwannoma	2
Lymphoma	2
Other	2
Location, n	
Supratentorial	55
Subtentorial	8
Both	1

SD, standard deviation.

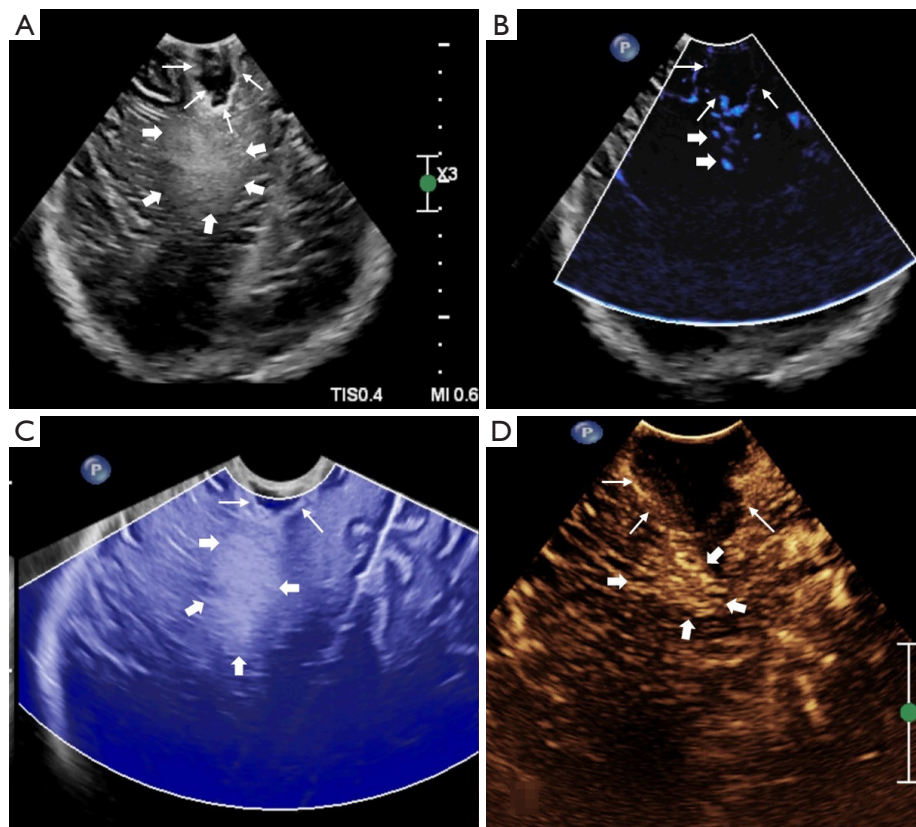


Figure 1 Images of a 68-year-old male with diffuse large b-cell lymphoma who had tumor residue after neurosurgery. (A) The tumor residue was clear on the B-mode image; (B) the tumor residue showed intralesional vascularization on micro-flow imaging; (C) young's modulus value of the tumor residue and normal brain tissue showed no difference on the SWE image. Thus, the tumor residue was not clear on the SWE image; (D) the tumor residue showed high enhancement on the CEUS image. Thick arrows indicate the tumor residue and thin arrows indicate the surgical cavity. CEUS, contrast-enhanced ultrasound; SWE, shear wave elastography.

of the US techniques, a Pearson correlation analysis was conducted. The results showed that only the number of lesions was associated with discordance in the two imaging tests for B-mode, MFI, and SWE ($P=0.011$, 0.020 , and 0.015 , respectively). In relation to those three techniques, no correlations were found in relation to the other clinical variables, including age, gender, histology, tumor size, lesion location, boundaries, shape, and edema zone around the tumor. In relation to CEUS, only tumor size was found to be correlated with evaluation accuracy ($P=0.021$) (Table 5).

Discussion

IOUS is widely used in neurosurgery, but new US techniques are also being employed (7,8,11-22). Several studies have evaluated the role of these new US techniques in assessing tumor residual in the procedure. He *et al.* used

B-mode, CDFI, and CEUS to evaluate tumor residual in brain surgery, and found that CEUS was better able to distinguish between the border of the tumor and the remaining tumor tissue, and the healthy brain tissue than conventional US during the operation (24). Cepeda *et al.* reported that tumor stiffness measured by IOUS strain elastography was correlated with histopathology (25). Tao *et al.* explored the use of CEUS in the removal of remnants surrounding the resection cavity in 51 patients, and found that the total removal rate of the CEUS group (23/28, 82%) was significantly higher than that of the US group (11/23, 48%) ($P<0.05$) and the recurrence rate was lower [18% (5/23) in the CEUS group *vs.* 22% (5/28) in the US group, $P>0.05$] (26). Yu *et al.* evaluated the diagnostic significance of CEUS in estimating the resection degree of brain glioma, and found that IOUS contrast has high sensitivity (62.2%) and specificity (92.8%) in evaluating the excision degree

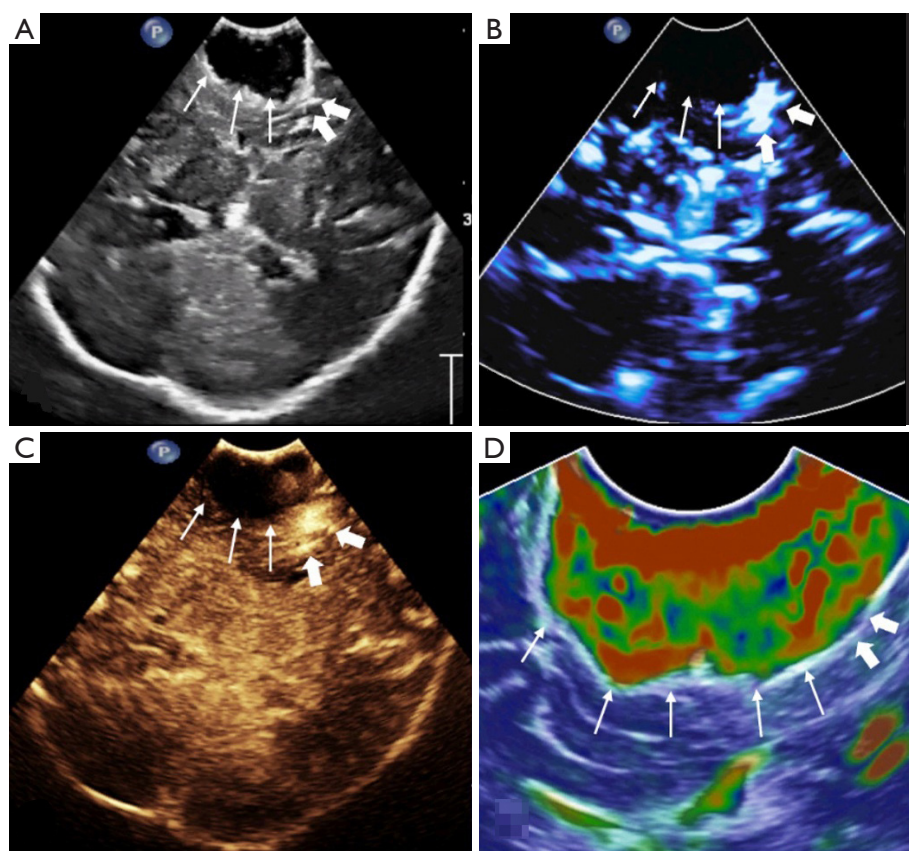


Figure 2 Images of a 68-year-old male with meningioma who had tumor residue after neurosurgery. (A) Unclear tumor residue on the B-mode image; (B) the tumor residue showed rich intralesional vascularization on micro-flow imaging; (C) no tumor residue was shown on the SWE image; (D) the tumor residue showed high enhancement on the CEUS image. Thick arrows indicate the tumor residue; thin arrows indicate the surgical cavity. CEUS, contrast-enhanced ultrasound; SWE, shear wave elastography.

Table 3 Consistency of multimodal ultrasound and MRI evaluation of resection range

Technic	RS0	RS1	RS2	RS3	Kappa
MRI	37	13	12	2	–
B-mode	36	15	11	2	0.717
MFI	38	13	11	2	0.751
SWE	40	11	11	2	0.714
CEUS	42	9	11	2	0.892

CEUS, contrast-enhanced ultrasound; MRI, magnetic resonance imaging; MFI, micro-flow imaging; SWE, shear wave elastography.

of tumors (32). Chan *et al.* studied the clinical application of SWE in assisting brain tumor resection, and found that the sensitivities of residual tumor detection by the

surgeon, US B-mode, and SWE were 36%, 73% and 94%, respectively, while their specificities were 100%, 63%, and 77%, respectively (34). However, no comparative study had previously been conducted on the role of different new US technologies in guiding brain tumor resection.

The present study compared the roles of different US technologies in guiding brain tumor resection. We found that compared to the MRI results, all the included US technologies showed substantial agreement. The Kappa values were 0.717, 0.751, and 0.714, and 0.892 for B-mode, MFI, SWE, and CEUS, respectively. CEUS and MRI had the best diagnostic consistency. CEUS had the highest sensitivity, specificity, positive predictive value, and negative predictive value under the ROC curve analysis (77.78%, 100%, 100%, and 86.05%, respectively), followed by MFI. B-mode and SWE had similar accuracy in detecting tumor residue. Thus, the use of CEUS in IOUS may be beneficial

Table 4 Diagnostic efficacy of multimodal ultrasound compared with MRI

Technic	Sensitivity	Specificity	Positive predictive value	Negative predictive value
B-mode	70.37%	78.38.5%	78.38%	70.37%
MFI	70.37%	83.78%	76%	79.49%
SWE	62.96%	83.78%	73.91%	75.61%
CEUS	77.78%	100%	100%	86.05%

CEUS, contrast-enhanced ultrasound; MRI, magnetic resonance imaging; MFI, micro-flow imaging; SWE, shear wave elastography.

Table 5 Factors affecting the accuracy of ultrasound technology diagnosis

Factor	P value			
	B-mode	MFI	SWE	CEUS
Age	0.162	0.086	0.061	0.584
Gender	0.887	0.469	0.313	0.937
Histology	0.127	0.307	0.201	0.056
Lesion location	>0.999	0.823	0.913	0.339
Numbers of lesions	0.011*	0.020*	0.015*	0.162
Tumor size	0.238	0.359	0.167	0.021*
Boundaries	>0.999	0.823	0.913	0.339
Shape	0.302	0.445	0.368	0.751
Edema zone around the tumor	0.867	0.844	0.725	0.687

*, statistically significant. CEUS, contrast-enhanced ultrasound; MFI, micro-flow imaging; SWE, shear wave elastography.

in reducing tumor residue and recurrence rates, and improving the quality of life of patients. Further research on CEUS in IOUS could provide insights into the advantages and disadvantages of CEUS in practical applications and improve its related parameters.

MFI is a novel US technique that enables the detection of slow-velocity flow, providing the visualization of the blood flow in small vessels without the need of intravenous contrast agent administration (35,36). The applications of MFI in the clinic have increased in recent years due to the quality of this non-invasive, swift, and user-friendly technique. Moreover, it has been shown to be useful in tumor diagnosis and the treatment of related conditions, including cervical cancer, head and neck malignancies, and thyroid tumors (37-40). However, no study on the use of MFI in neurosurgery had previously been conducted. Our team used MFI to evaluate tumor residual in neurosurgery. The concordance analysis between MFI and MRI showed substantial agreement (kappa =0.751). The diagnostic efficiency of MFI was the second best

after CEUS (sensitivity, specificity, positive predictive value, and negative predictive value under the ROC curve analysis: 70.37%, 83.78%, 76%, and 79.49%, respectively). Compared to CEUS, MFI is non-invasive, swift, and user-friendly. Thus, MFI can be recommended as a technique for guiding and evaluating tumor residual in neurosurgery in addition to CEUS. CEUS can be used when the MFI is unable to distinguish tumor residue.

There are several artifacts related to surgery, including acoustic shadowing from surgical, post-surgical, and post-radiation artifacts, post-resection hyperechoic rim, and hyperechoic blood. CEUS can overcome the limitations of B-mode, MFI, and SWE in identifying these artifacts. This may be the reason for the high diagnostic efficiency of CEUS. In our study, B-mode overestimated resection in 8 cases and underestimated resection in 8 cases, SWE overestimated resection in 6 cases and underestimated resection in 9 cases, and MFI, overestimated resection in 6 cases and underestimated resection in 8 cases. Conversely, CEUS only underestimated resection in 6 cases.

We evaluated the relevant factors of residual misdiagnosis caused by these US techniques. The results showed that only the number of lesions was associated with discordance in the two imaging tests for B-mode, MFI, and SWE. In relation to CEUS, only tumor size was correlated with evaluation accuracy. Frassanito *et al.* reported similar results (16). This may be due to the collapsed surgical cavity, especially when the ventricular system is opened, and by artifacts that may simulate or hide residual tumors. Based on our analysis, all cases with residual tumors misdiagnosed by CEUS had peripheral edema zones. However, no statistically significant results were found in relation to the relationship between the misdiagnosis of CEUS and the surrounding edema zone. However, this might have been related to the small sample size of the study.

No major complications related to US arose in our study. US is more convenient and cost-effective than MRI and CT. In addition, US has no radiation.

This study had some limitations. The sample size was relatively small. Thus, our findings and conclusions must be considered preliminary. Further studies need to be conducted with a larger variety and number of cases. Additionally, the relevant factors of residual misdiagnosis caused by the US techniques need to be studied, and the accuracy of residual diagnosis by US should be improved.

Conclusions

US is a convenient and cost-effective method for guiding the procedure and evaluating the extent of resection in neurosurgery. CEUS has the highest diagnostic accuracy for residual lesions among the new US technologies. MFI can be recommended as a technique for guiding and evaluating residuals in neurosurgery in addition to CEUS.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at <https://qims.amegroups.com/article/view/10.21037/qims-24-2271/rc>

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://qims.amegroups.com/article/view/10.21037/qims-24-2271/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Ethics Board of Sichuan Cancer Hospital (No. SCCHEC-02-2023-071), and informed consent was obtained from all individual participants.

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