Application of Intraoperative Contrast-Enhanced Ultrasound in the Resection of Brain Tumors*

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[Abstract] Objective: To investigate the value of routine intraoperative ultrasound (IU) and intraoperative contrast-enhanced ultrasound (ICEUS) in the surgical treatment of brain tumors, and to explore the utilization of ICEUS for the removal of the remnants surrounding the resection cavity. **Methods:** In total, 51 patients who underwent operations from 2012 to 2018 due to different tumors in the brain were included in this study. The clinical data were evaluated retrospectively. IU was performed in all patients, among which 28 patients underwent ICEUS. The effects of IU and ICEUS on tumor resection and recurrence were evaluated. Semiquantitative analysis was performed to compare ICEUS parameters of the brain tumor with those of the surrounding tissue. **Results:** In total, 36 male and 15 female patients were included in this study. The average age was 43 years (range: 14–68 years). The follow-up period was from 7 to 74 months (mean follow-up 32 months). IU was used in all patients, and no lesion was missed. Among them, 28 patients underwent ICEUS. The rate of total removal of the ICEUS group (23/28, 82%) was significantly higher than that of the IU group (11/23, 48%) (P<0.05). The recurrence rate of ICEUS and IU was 18% (5/23), and 22% (5/28), respectively, and the difference did not reach statistical significance (P>0.05). The semiquantitative analysis showed that the intensity and the transit time of microbubbles reaching the lesions were significantly different from the intensity and the transit time of microbubbles reaching the surrounding tissue (P<0.05) and reflected indirectly the volume and the speed of blood perfusion in the lesions was higher than those in the surrounding tissue. **Conclusion:** ICEUS is a useful tool in localizing and outlining brain lesions, especially for the resection of the hypervascular lesions in the brain. ICEUS could be more beneficial for identifying the remnants and improving the rate of total removal of these lesions than routine intraoperative ultrasound.
Key words: intraoperative ultrasound; intraoperative contrast-enhanced ultrasound; brain tumor; hypervascular; glioma

Total removal of subcortical lesions in the brain is always challenging, especially gliomas which often have no clear or definite boundary. Not only the localization of lesions but also the range of resection must be taken fully into account. Although neuronavigation has been used generally in neurosurgical operations and offers an accurate localization of the lesion which is deeply or subcortically located, it cannot exclude the influence of intraoperative brain shift, which can be caused by the loss of cerebrospinal fluid, tumor debulking or brain deformation due to positioning of the head[1]. Intraoperative MRI is also regarded as an effective and useful means for the total removal of the lesion; however, the expensiveness of intraoperative MRI limits its application and is often not available in many neurosurgical centers. Moreover, interpretation of the intraoperative MRI after removal of the lesion can also be affected by the resulting brain shift and thus sometimes become difficult[2].

Intraoperative ultrasound (IU) has been proved as a very valuable real-time tool that helps to localize subcortical lesions under a normal appearance of the brain cortex and to define the border of the resection of lesions in the brain in real time[2–4]. However, the extent of resection cannot be defined exclusively by routine IU, especially during the resection of gliomas, since the resolution power of the ultrasound cannot differentiate the normal brain from surrounding remnants due to a hyperechoic rim, which is an important unsolved problem and may be caused by some substances attached to the resection margin such as blood,

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cerebrospinal fluid with proteic contaminants and micro air bubbles. This phenomenon often interferes with the sonographic assessment of the wall of the cavity and sometimes means that a reliable sonographic examination is impossible[5].

Recently, intraoperative contrast-enhanced ultrasound (ICEUS) has become increasingly common and has been reported to have more advantages in highlighting different brain lesions than routine IU[6]. Unlike routine IU, contrast agents containing microbubbles are intravenously injected for ICEUS, which can offer dynamic imaging and real-time perfusion data, and therefore help to distinguish the tumor tissue from the normal brain[6, 7]. In the present study, we investigate the value of routine IU and ICEUS in the surgical treatment of subcortical lesions and focused on the utilization of ICEUS for the resection of the hypervascular lesions in the brain.

1 MATERIALS AND METHODS

1.1 Clinical Data

In total, 51 patients who underwent operations from 2012 to 2018 due to different tumors in the brain were included in this study. The clinical data were evaluated retrospectively, including the medical history, surgical reports, preoperative neuroimaging, recordings of IU and ICEUS as well as postoperative pathology and outcome. Neuronavigation was performed to localize the tumor and to design the surgical approach in the cases with small subcortical or deeply located lesions. IU was performed in all patients, among which 28 patients were chosen randomly and underwent ICEUS. Patients were classified into two groups: the IU group (patients with IU only); and the ICEUS group (patients with IU and ICEUS). IU and ICEUS data were evaluated by an experienced sonologist with 9 years in performing IU and 7 years in ICEUS.

1.2 Intraoperative Ultrasound

The ultrasound device used was the GE LOGIC-E9 (GE, USA), and the probe was 9L-D, which was 4.5 cm long, with a frequency of 6–9 MHz. The linear probe was used with low-power insonation and low-mechanical index (0.14). During the standard IU process, the ultrasound probe, which can switch between the abdomen model and small part model according to the depth of the lesions. The probe was covered with a surgical sterile transparent sheath, along with saline gel used as an acoustic coupling agent, was placed gently on the dura mater or the brain surface if the dura was opened. The surgical field was rinsed with sterile saline before sonography. The lesion was identified in the two-dimensional images, and the intra- and peri-lesional vessels were shown at the same time with color Doppler imaging.

The sulfur hexafluoride-filled lipidic microbubbles (SonoVue®, Bracco, Italy) were used intravenously as an ultrasound contrast agent (UCA). ICEUS was performed with the same probe, and the collected signals were transduced with the Contrast Tuned Imaging algorithm. Before the UCA was injected, the lesion was shown with standard IU, along with the adjacent healthy brain tissue as well as the blood vessels. The focus of the US was positioned at the bottom of the lesion at the level with maximum diameter. Then, the patients received a peripheral venous bolus injection of 2.0 mL UCA, followed by a flush of 10 mL saline. The timer was started after UCA injection and perfusion dynamics analysis began when UCA arrived in the lesion. The research window included the baseline US recording and after UCA bolus injection for 300 seconds. Time-intensity curves (TIC) were calculated on 2 regions of interest (ROIs) and then considered for statistical analysis: one is in the lesion, and the other is in the surrounding region outside the lesion (the region surrounding the enhanced area). To minimize the deviation due to inhomogeneity of the tumor, the data from three different points were collected for each region of ROI and the average was adopted for further analysis. The following parameters were investigated for each ROI: peak intensity (A, the difference between baseline and peak), baseline intensity (B), the indicator for the gradient of the curve (κ), the time to peak intensity (TtoPk, from the first frame to the last frame), curve gradient (Grad, the gradient between the first frame data and the peak intensity frame data), and area under the curve (AUC).

1.3 Resection Guided by ICEUS

Before resection, initial ICEUS was carried out to highlight the lesion, following routine IU. When the lesion was removed, the second ICEUS was performed, and the sonographic findings were assessed by the sonologist together with the neurosurgeon. If the second ICEUS still showed enhancement in the resection field, a further resection was carried out, until the enhancement disappeared. Usually, ICEUS was carried out twice; however, it could be more if required.

1.4 Statistical Analysis

Statistical analysis was performed using a *t*-test for comparison of ICEUS parameters and χ^2 test for the evaluation of tumor resection and recurrence, using the software SPSS 22.0 with significance at $P<0.05$.

2 RESULTS

2.1 Clinical Features of Patients

In total, 36 male and 15 female patients were included in this study. The average age was 43 years (range: 14–68 years). The follow-up was carried out at the outpatient clinic or by telephone. The period was from 7 to 74 months (mean follow-up 32 months). In total, 21 patients underwent resection of the lesion on the left side and 30 on the right side. Overall, 17 lesions (17/51, 33.33%) were located in the frontal lobe, and 15 (15/51, 29.41%) were temporal, with 12 (12/51, 23.53%) parietal, 3 (3/51, 5.88%) occipital, 1 ventricular, 2 (2/51, 3.92%) in the cerebellum, and 1 (1/51, 1.96%) in the insula respectively (table 1).

Postoperative pathological examinations showed 25 gliomas (WHO Ⅱ 9, Ⅲ 6, Ⅳ 10), 13 cavernomas, 7 metastases (of 4 lung adenocarcinomas, 1 small cell lung cancer, 1 liver cancer, 1 clear-cell renal cell carcinoma and 1 lymphoma, respectively), 2 meningiomas, 2 abscesses, and 2 gliosis (table 1).

2.2 Rate of Total Removal in ICEUS Group

In all 51 patients, IU was used to localize the lesion and no target was missed. ICEUS analysis was performed in 28 patients including those with low or high-grade gliomas, metastases, abscesses and cavernomas. Most of them were contrast-enhanced on preoperative MRI imaging. No adverse event or side effect caused by the administration of UCA was observed. The postoperative MRI was carried out 1 month and 6 months after the operation, and then once per year or 2 years. The neuroimaging was assessed by one neuroradiologist who was blinded to the study. No residue on the first postoperative MRI was referred to as total removal. The rate of total removal of the ICEUS group (23/28, 82%) was significantly higher than that of the IU group (11/23, 48%) (P<0.05, table 1).

Table 1 Clinical features of patients

Parameters	Values
Sex, n (%)	
Female	15 (29.41%)
Male	36 (70.59%)
Age, years	
Range	14–68
Average	43
Side, n (%)	
Left	21 (41.18%)
Right	30 (58.82%)
Locations, n (%)	
Frontal	17 (33.33%)
Temporal	15 (29.41%)
Parietal	12 (23.53%)
Occipital	3 (5.88%)
Cerebellar	2 (3.92%)
Ventricle	1 (1.96%)
Insular	1 (1.96%)
Follow-up (months)	
Range	7–74
Average	32
Groups (n)	
IU	23
ICEUS	28
Pathology (n)	
Glioma Ⅱ	9
Glioma Ⅲ	6
Glioma Ⅳ	10
Cavernoma	13
Metastasis	7
Meningioma	2
Abscess	2
Gliosis	2
Extent of resection (n)	
Total	34
Subtotal	17
Recurrence (n)	
Yes	10
No	41

IU: intraoperative ultrasound; ICEUS: intraoperative contrast-enhanced ultrasound

2.3 Recurrence Rate in ICEUS Group

Compared with the first postoperative MRI, any progress or reemergence of the lesion on the following postoperative MRI during the follow-up, excluding pseudo-progression on MRI[8], was referred to as a recurrence. The recurrence rate of ICEUS was 18% (5/28) and lower than that of IU (5/23, 22%), however, the difference did not reach statistical significance (P>0.05) (table 2, fig. 1–5).

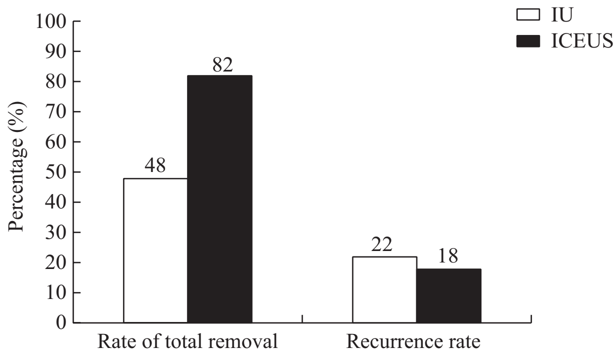

Fig. 1 The rate of total removal of ICEUS group (82%) was significantly higher than that of IU group (48%) (P<0.05). The recurrence rate of ICEUS was 18% and lower than that of IU (22%); however, the difference did not reach statistical significance.

Table 2 Comparison of rate of total removal and recurrence rate between two groups

Groups	Rate of total removal	Recurrence rate
IU	11/23 (48%)	5/23 (22%)
ICEUS	23/28 (82%)	5/28 (18%)
	P<0.05	P>0.05

IU: intraoperative ultrasound; ICEUS: intraoperative contrast-enhanced ultrasound

2.4 Quantitative Analysis of ICEUS

The results of ICEUS quantitative analysis are shown in table 3. The values of A, Grad, AUC in the lesion was significantly higher than those in the surrounding tissue (P<0.05, table 3), while TtoPk in the lesion was significantly less than that in the surrounding tissue (P<0.05, table 3). These parameters showed that the intensity and the transit time of microbubbles getting to the lesions were significantly different from the intensity and the transit time of microbubbles getting to the surrounding tissue and reflected indirectly the volume and the speed of blood perfusion in the lesions was higher than that in the surrounding tissue. The difference of the baseline intensity (B) and *κ* between both groups was not statistically significant (P>0.05, table 3).

3 DISCUSSION

IU is usually used to localize the deeply located lesion, as real-time intraoperative imaging. Although intraoperative neuronavigation can do the same work, it is affected by the brain shift that takes place after the dura mate is opened and turns more during removal, and therefore makes often the neuronavigation unreliable. Recently, Petridis *et al* reported that IU could overcome brain shift and was an excellent tool in localizing low-grade gliomas intraoperatively. However, they highlighted that IU was unreliable for the identification of the extent of resection of low-grade gliomas[2]. In our study, we found that IU could identify the lesion very well before starting resection in all cases. However, it was difficult to distinguish the remnants and peritumor tissues after the lesion was removed. Several studies have reported this in the literature. Van Velthoven *et al*[9, 10] compared the intraoperative US images with the preoperative CT and MRI images in a study of 374 cases with different pathologies. The results showed that IU was an excellent tool for localization of cerebral and medullar lesions and detailed description of their

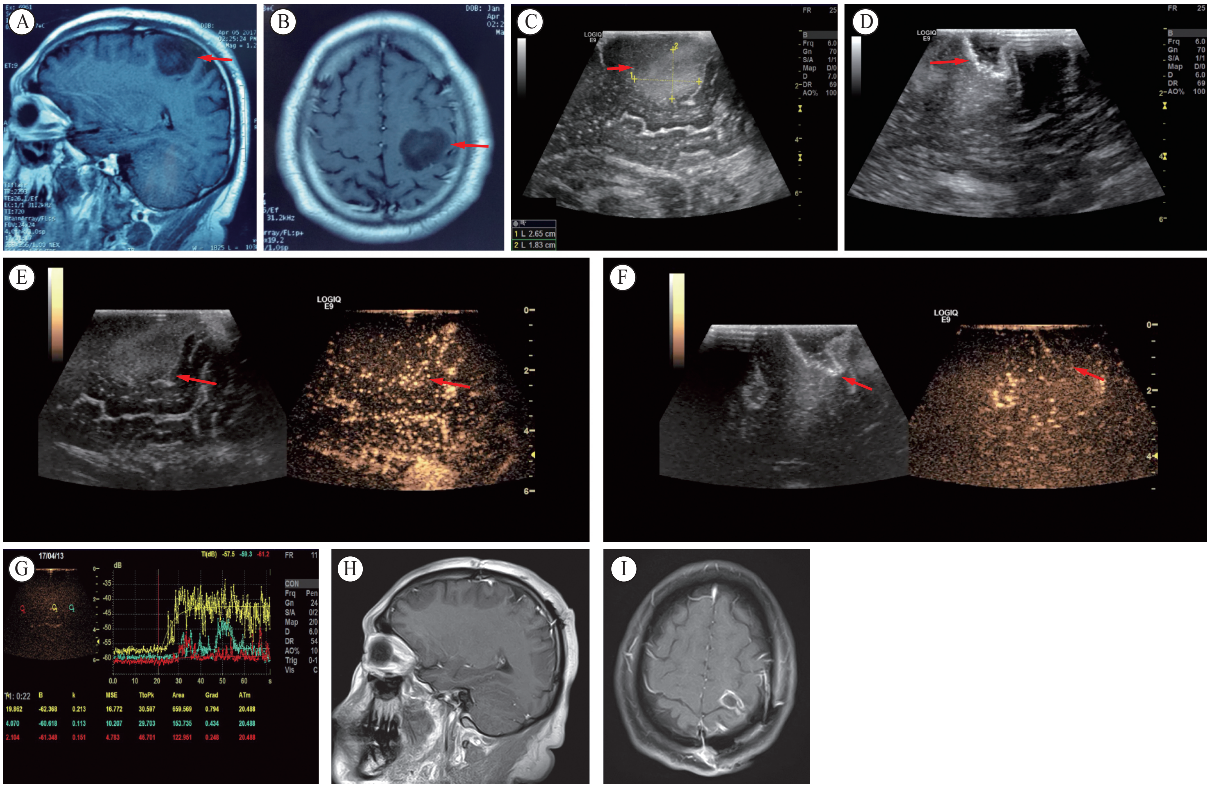

Fig. 2 A 42-year–old male patient, suffering from tumor-related epilepsy, with presurgical contrast-enhanced MRI images showing a left parietal lesion without enhancement (A and B, red arrow). Intraoperative ultrasound (IU) was used to localize the lesion in real-time and to guide the resection. After craniotomy, the probe was used, and the lesion was identified in the two-dimensional images (C). IU showed the tumor was completely removed despite acoustic enhancement artifacts appearing at the bottom of the tumor cavity (D, red arrow). Intraoperative contrast-enhanced ultrasound (ICEUS) showed the tumor was completely removed and no contrast-enhancement was detected, compared with routine IU. E: the intraoperative sonographic images before resectioning of the lesion (red arrow) (left: IU, right: ICEUS). F: the intraoperative sonographic images after resection of the lesion (red arrow) (left: IU, right: ICEUS). G: the result of quantitative analysis of ICEUS in this patient, comparing the brain tumor (yellow) and the surrounding tissue (blue). Postoperative MRI confirmed the complete removal of the lesion (H and I). Postoperative pathology showed glioma (WHO Ⅱ).

Table 3 Quantitative analysis of ICEUS parameters

Parameters	A	B	κ	TtoPk	Grad	AUC
Lesion	22.620±10.820	63.714±3.516	0.678±0.939	15.299±9.552	2.072±1.432	632.966±259.958
Surrounding tissue	7.228±5.288	62.767±3.185	0.335±0.321	21.994±11.662	0.905±0.794	184.581±108.153
P	<0.05	>0.05	>0.05	<0.05	<0.05	<0.05

A: the difference between baseline and peak; B: baseline intensity; κ: the indicator for the gradient of curve; TtoPk: the time to peak intensity; Grad: curve gradient; Area: area under the curve

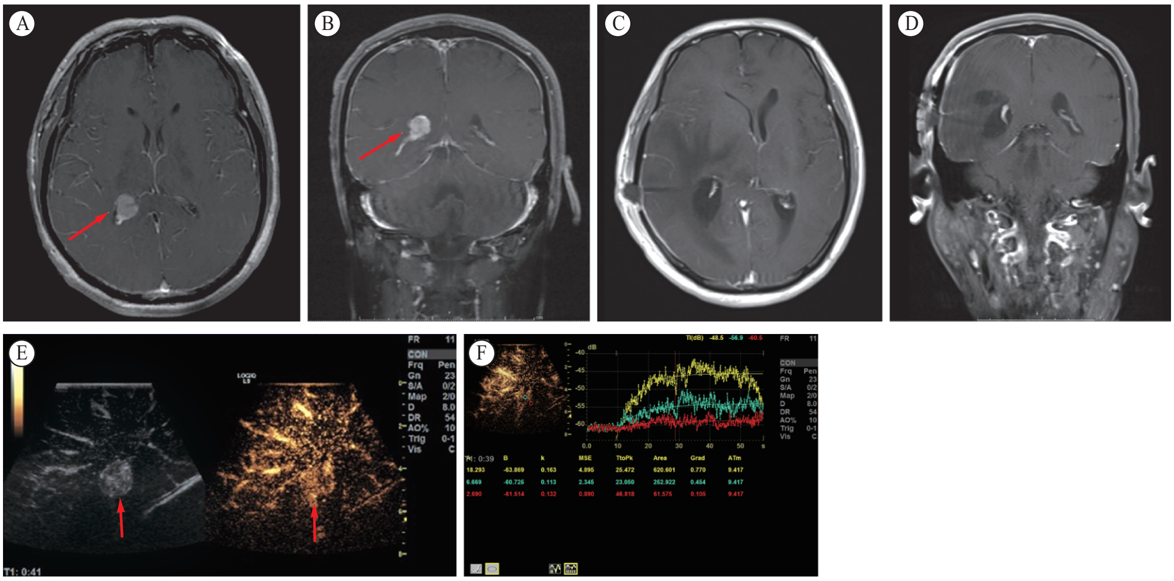

Fig. 3 Presurgical MRI showed right intraventricular meningioma in a 51-year-old male patient (A and B, red arrow). Postoperative MRI showed that the lesion was completely removed (C and D). The lesion, which was contrast-enhanced on MRI, presented as hyperechoic with a distinct difference compared with the surrounding brain tissue, when the intraoperative contrast-enhanced ultrasound was performed (E, red arrow). F: the quantitative analysis of intraoperative contrast-enhanced ultrasound of this patient, comparing the brain tumor (yellow) and the surrounding tissue (red)

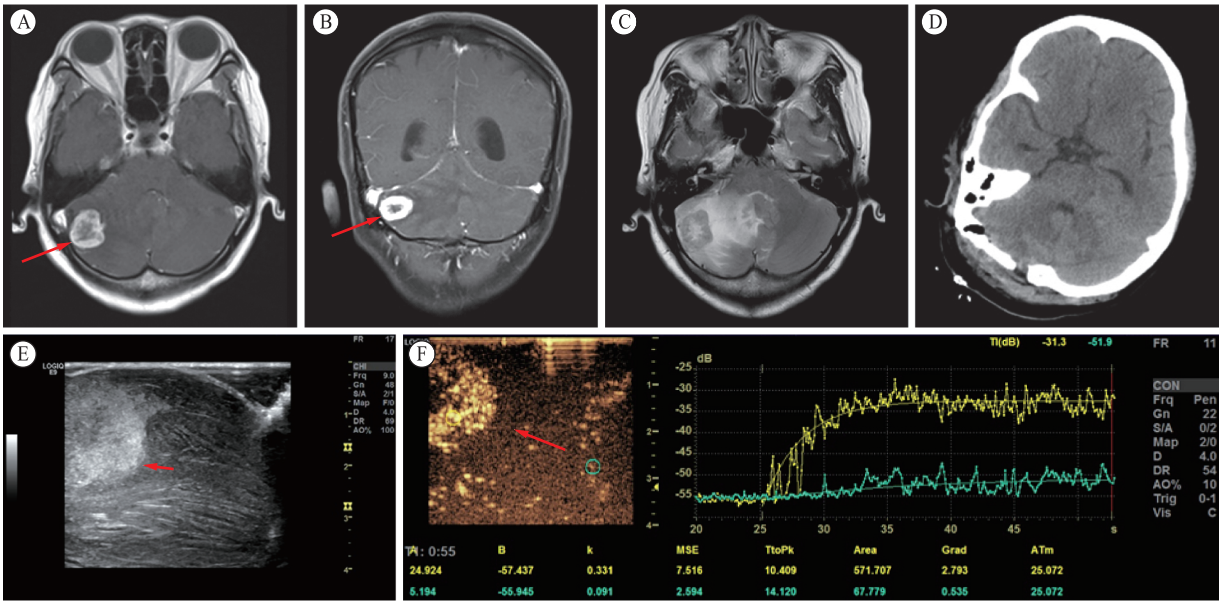

Fig. 4 A cerebellar lesion presented ring-enhancement with peritumoral edema on MRI (A, B and C, red arrow), which was completely removed (D) and was confirmed as clear cell renal cell carcinoma by postoperative pathology. Routine intraoperative ultrasound identified the lesion as hyperechoic with cystic area, and well-circumscribed (E, red arrow). The contrast-enhancement of the lesion was very strong and intense, comprising hypoperfused necrotic area, and tumor borders were clear when intraoperative contrast-enhanced ultrasound (ICEUS) was used (F, red arrow). The semiquantitative analysis of ICEUS parameters was also shown in it (F), comparing the brain tumor (yellow) and the surrounding tissue (blue).

interior, however, they also described the difficulty in identifying the exact lesion margin zones in gliomas. In particular, they could not find reliable criteria for differentiation between the tumor margin zone, the tumour-infiltrating zone and the edematous brain tissue. Woydt *et al*[5] found the IU imaging at the tumor margin zones was correlated with histopathologic findings. Biopsies taken from the thin hyperechoic rim surrounding the resection cavity showed a non-specific finding, and the histopathologic results varied between the solid tumor, the infiltrating zone and the normal brain tissue.

A possible reason could be that some substances in the resection cavity, such as blood, cerebrospinal

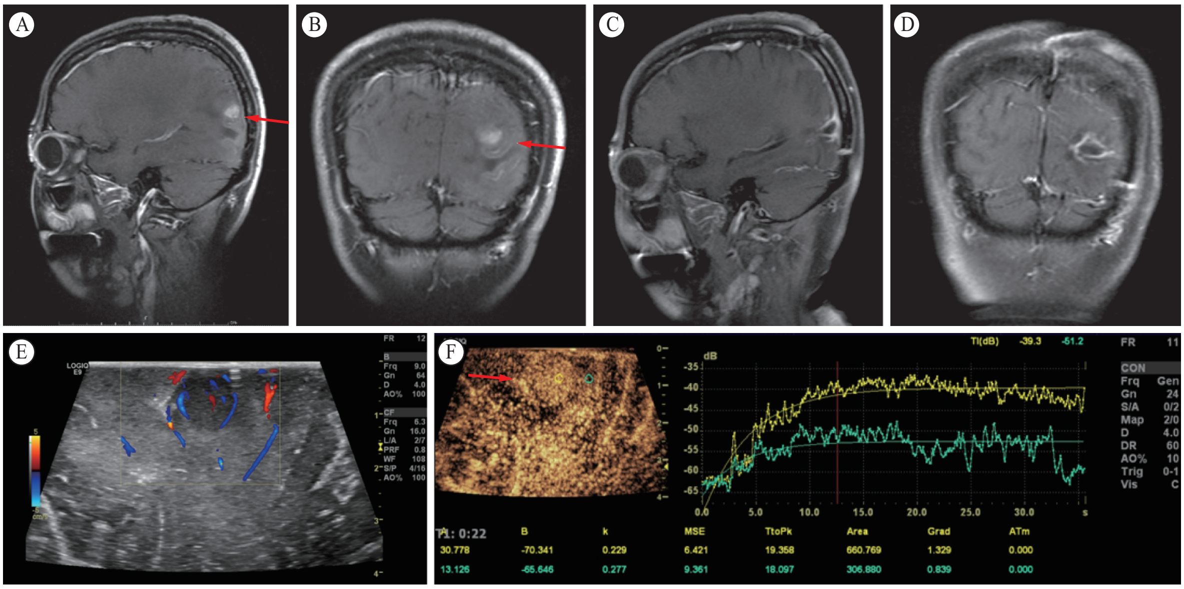

Fig. 5 A lesion located in the left occipital was shown on MRI (A and B, red arrow), appearing as heterogeneous enhancement with obscure boundary, and was removed (C and D). Postoperative pathology confirmed the lesion as anaplastic astrocytoma (high-grade glioma). Routine intraoperative ultrasound display the lesion as hyperechoic with a heterogeneous appearance and the tumor boundary was unclear (E). The contrast-enhancement of the lesion was intense, with a relatively longer parenchyma phase compared with normal brain parenchyma. Tumor border was better defined than routine intraoperative ultrasound when intraoperative contrast-enhanced ultrasound was used (F, red arrow). The semiquantitative analysis of ICEUS parameters was also shown in it (F), comparing the brain tumor (yellow) and the surrounding tissue (blue).

fluid with proteic contaminants, and micro air bubbles attached to the resection margin could produce ultrasound artifacts and disturb the ultrasound imaging, which rendered IU unreliable[2, 5, 11]. Steno *et al* pointed out that acoustic enhancement artifacts (AEAs) appearing at the bottom of the tumor cavity, due to a large difference between a very low attenuation of acoustic waves in saline and high attenuation of acoustic waves in brain tissue, might also hamper the quality of IU about the guidance for resection of tumor remnants[12]. Moreover, we found that excessive coagulation by bipolar forceps on the wall of the tumor cavity could generate overheat and burn the tissues including both the tumor and normal tissues, which might also disturb the final identification of the tumor remnants. For these reasons, some measures have been reported in the literature to improve differentiation. Lindseth *et al* fused intraoperative 3D-ultrasound and preoperative MRI to provide a real-time and extended overview of the surgical field during surgery, and to facilitate the assessment of the degree of anatomical changes, based on which, it was possible to indirectly differentiate tumor remnants[13]. Steno *et al* used a 3D-ultrasound device equipped with a miniature probe to reduce AEAs, during which, a miniature probe was inserted into the resection cavity for a close-up view of the areas with suspected tumor remnants[14]. Another study about a new acoustic coupling fluid was reported by Selbekk *et al*[15], which had attenuation of ultrasound energy similar to brain tissue, and was expected to minimize the artifacts. Although these attempts are promising, it is still difficult to differentiate between the tumor margin zone and “not tumor” including the edematous tissue, gliosis and normal brain tissue by routine ultrasound.

ICEUS is a relatively novel technique, which can distinguish brain lesions from normal brain tissue by comparison with baseline ultrasound. Our study demonstrated that ICEUS is more beneficial for defining the resection range than routine IU. Some studies have been reported in the literature, concerning the ability of CEUS to distinguish some brain lesions from the brain parenchyma[6, 16]. Prada *et al* studied the dynamic morphological and vascular pattern of brain tumor, showing that ICEUS can highlight vascular structures in different kinds of lesions[6], which is inspirational for the identification of the hypervascular lesions. After intravenous injection, contrast agents containing microbubbles rapidly reach the surgical field through the circulation, and give the highest contrast, especially when the lesions are rich in blood supply. In our study, several parameters calculated on time-intensive curves, such as peak intensity, the time to peak intensity, curve gradient and the area under the curve, presented a significant difference between the tumor and the surrounding brain tissue, and such difference remained after gross tumor removal in some cases, as ICEUS was performed once again to highlight the tumor remnants in realtime. Under the circumstances, ICEUS was used to guide the resection. The results of this study also demonstrated that ICEUS was beneficial to improve the rate of total removal, although the rate of recurrence was not improved in this study. A relatively short period of follow-up might be a reason for this. There has been agreement that the extent of resection is one of the most important predictive factors for prognosis and maximal safe resection is usually associated with improved survival[17–19]. Further studies with large cohorts and longer follow-up are needed to evaluate the association between ICEUS and the prognosis of gliomas.

The hypervascular lesions in our series included high-grade gliomas (WHO Ⅲ and Ⅴ), metastasis, meningiomas, and abscess (the walls of abscess), presenting contrast-enhancement on preoperative MRI and confirmed by pathological examination postoperatively. A former study has demonstrated that intratumoral vascularity and cell proliferation are associated with radiologic enhancement on MRI. It has been known that contrast enhancement is a mark of a leaking blood-brain barrier (BBB) and is related to the neovascularity of the tumor[20]. Especially in high-grade tumors, the endothelium is fenestrated, and BBB is discontinuous. Tumor enhancement is presumed to be due to the formation of capillaries with an incomplete BBB rather than active destruction of the existing BBB[21, 22]. Such concordance between tumor enhancement and intratumoral vascularity makes it possible to identify the tumor intraoperatively with a real-time assessment of vascularity. Since the contrast agent of CEUS is microbubbles, which are usually 5 μm in diameter and can go through the smallest capillaries, ICEUS can be used as a real-time measurement of vascularity of focal lesions[23, 24]. Moreover, the contrast-enhanced ultrasound with TIC analysis has been shown helpful in the diagnosis of different kinds of tumors[25–27]. The results of our semiquantitative study also suggest that ICEUS can not only be used to highlight the vascularity of the lesions but also to identify the hypervascular lesions and their remnants, which will facilitate to guide the resection of high-grade gliomas and other hypervascular lesions. In this sense, ICEUS is a useful tool in localizing brain lesions, especially for the resection of the hypervascular lesions in the brain. ICEUS could be more beneficial for improving the rate of total removal of these lesions than conventional intraoperative ultrasound.

About the clinical practice, however, some limitations remain. For example, both IU and ICEUS are restricted to a limit and fixed bone window. For this reason, precise preoperative localization is indispensable. Another limit is that only one portion of the lesion is analyzed at a time. Therefore, it is important to perform IU carefully and to scan the lesion fully, to choose the most significant portion for ICEUS. However, we noted that ICEUS could show more contrast in lesions with an abundant blood supply than those with less blood supply (data not shown). This is interesting because it seems that ICEUS might be more beneficial for malignant tumors, which often present contrast enhancement on preoperative MRI. However, there is one thing to be noted that contrast enhancement or the lack of enhancement is not accurate in differentiating between low- and high-grade gliomas, although generally, high-grade tumors are more likely to enhance than low-grade tumors[28]. According to literature reports, 32%–40% of nonenhancing glial tumors contain histologically anaplastic components (i.e., are at least grade Ⅲ lesions). Therefore, further studies remain needed to explore the application of ICEUS in the resection of hypovascular lesions and to improve the rate of complete resection of these lesions.

ICEUS is a useful tool in localizing and outlining brain lesions, especially for the resection of the hypervascular lesions in the brain. ICEUS could be more beneficial to identify the remnants and improve the rate of total removal of these lesions than IU.

Conflict of Interest Statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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