Chapter

Oncological, Vascular, and Spinal Uses of Contrast-Enhanced Ultrasound in Neurosurgery

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Abstract

Contrast-enhanced ultrasound (CEUS) is a real-time, feasible technique. Both intraoperatively and bedside, it satisfies the need for serial assessment and easy performability. Initially employed in neuro-oncology, it has recently overcome this first application. The chapter aims to give a comprehensive view of its use in oncological, vascular, and spinal neurosurgery. CEUS versatility across the aforementioned areas is analyzed, underlining its complementarity to other well-settled imaging techniques. Its major oncological (both cerebral and spinal) and vascular (including aneurysms, AVMs, dAVFs, carotid plaques, and stroke) application and state of the art are discussed. The chapter is focused on reporting CEUS advantages and disadvantages, giving an insight to future perspectives and applications.

Keywords: contrast-enhanced ultrasound, CEUS, ultrasonography, brain tumors, spinal tumors, intraoperative imaging, neuro-oncology

1. Introduction

Neurosurgery is experiencing the rediscovery of intraoperative ultrasound (ioUS). In particular, growing enthusiasm was shown after the introduction of contrast-enhanced ultrasound (CEUS) in the field of neuro-oncology, following the leads of other surgeries such as thyroid and hepatic surgery. Besides this pioneering use in brain and spinal oncology, other applications including stroke, brain traumatology, vascular neurosurgery, and peripheral nerve surgery [1–9] were reported.

Those experiences in literature proved the integration of ioUS and CEUS to be a valuable tool in different neurosurgical scenarios: it provides a truly real-time, feasible, and modern intraoperative imaging technique, allowing the assessment of unexposed, hidden, anatomical, and pathological structures [10] in both traditional and emerging settings.

2. CEUS in neurosurgery: where do we stand?

Standard B-mode ultrasound has been presented since several years in many neurosurgical operating rooms: it represented de facto one of the first tools to study anatomy through unexposed, hidden, parenchymal tissues. For this reason, it is incorrect to classify ioUS/CEUS use as an innovation, being it more a rediscovery:

ioUS has been employed in neurosurgery since the 1960s [11], and it granted intraoperative imaging and navigation well before more evolved technologies, such as intraoperative CT (iCT), intraoperative MRI (iMRI), indocyanine green video angiography (ICG-VA), and navigation, were broadly available [12–15]

Nonetheless, significant limitations of ioUS as a reliable and feasible application in neurosurgery were represented by both imaging interpretation, unfamiliar to neurosurgeons, and artifacts related to manipulation. A good evidence of this is that as surgical resection advances, the ioUS image quality decreases: due to surgically induced artifacts and edema, imaging interpretation becomes challenging [1]. Moreover, all information provided by ultrasound (US) relies on echogenicity of insonated structures: no dynamic information, such as overall vascularization, is given through standard B-mode ultrasonography.

Even though the aforementioned limitations could have prevented further research, major technological advancements in the US field, such as image fusion for navigation, CEUS, and elastosonography, have been developed; new applications in their usage in neurosurgery, although on a small scale, have constantly been achieved and reported in recent years [16–20].

Being capable of highlighting tumor tissue not relying on its echogenicity but on its vascularization, CEUS has been specifically found to be a versatile innovation. Introduced in other medical branches, such as hepatic oncological surgery, the technique is feasible in both diagnostic and intraoperative settings: it allows practitioners to differentiate between benign and malignant lesions, helps in localizing the target, and controls treatment efficacies [10, 19].

On the heel of these observations, CEUS intraoperative experiences have been borrowed to neurosurgery to overcome the strains of standard B-mode US imaging.

CEUS is a harmonic imaging modality that depicts the distribution of microbubble contrast agent in tissues. Thanks to their structure, sulfur hexafluoride-filled lipidic microbubbles cannot diffuse to the interstitial space, giving a representation of the vascular district only. The degree of contrast enhancement (CE) is a consequence of the density of the capillaries, which in turn is proportional to tissue activity [19, 21].

Microbubbles are visible through a contrast-specific algorithm that permits a real-time assessment of contrast enhancement, measurement of vascularity of focal lesions during different dynamic phases, and analysis of tissue perfusion; CEUS algorithm suppresses the linear US echo, thus producing a specific representation only of the microbubbles. In other words, images are a direct representation of vascularization and become independent from tissue echogenicity. Furthermore, microbubbles, being micron-sized, are not able to extravasate from vessels and behave as a purely intravascular contrast agent, allowing to study all vascular tree districts: arterial, venous, and capillary [19, 22]. On these bases, CEUS has been introduced in neurosurgery for the intraoperative visualization of brain tumors: it is a dynamic modality which permits to visualize them according to their degree of vascularization [1, 23].

This first application has led to the following use in a variety of neurosurgical fields. As shown in the herein presented review, a consistent literature has been published describing CEUS use in settings other than cerebral neuro-oncology, including spinal oncology, vascular neurosurgery (cerebral and spinal), TBI, and pediatric and peripheral nerve surgery.

Besides their undisputed value, traditional intraoperative imaging techniques (CT scan and MRI) have several limitations, including costs, temporary stop of surgical procedure, and time wasting. These important strains make iCT and iMRI hardly repeatable during surgery [12, 24].

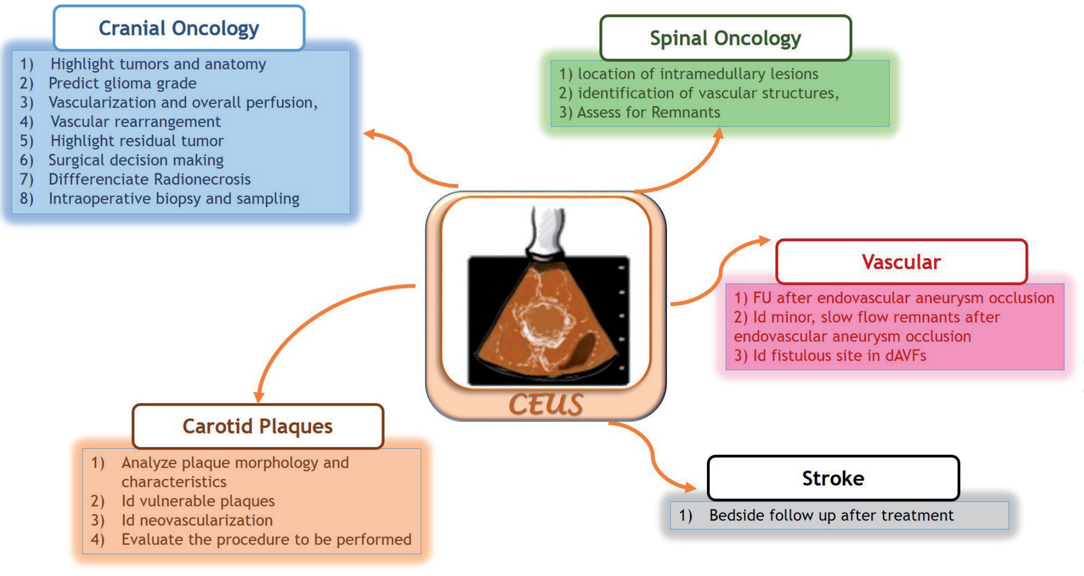

Figure 1.
Diagrammatic representation of the fields of application of CEUS in neurosurgery.

Conversely, as demonstrated by several experiences, CEUS/ioUS is a feasible intraoperative imaging technique, as it is readily repeatable, dynamic, and inexpensive and provides a truly real-time dynamic visualization of anatomical characteristics and vascular patterns in several neurosurgical settings. Assessment is rapid, can be performed any time during surgery, and is independent of brain shift [4, 8–10, 20].

Besides, microbubbles do not only allow the visualization of high-definition intraoperative images after craniotomy but, as reported later, can enhance the resolution of intracranial arteries also in transcranial studies at bedside [25–27].

Figure 1 summarizes the major fields of application of CEUS in neurosurgery.

3. Cerebral neuro-oncology

The use of CEUS during neuro-oncological procedures has been recently included in the guidelines from the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB), representing a paradigm shift for the use of US in neurosurgery [28] (**Figure 2**).

In comparison with other imaging modes, CEUS showed itself as a rapid, practical, and cost-effective technique, suggesting additional and alternative information about brain tumor vasculature and perfusion, being B-mode limited in providing only morphological information regarding the lesion. In their seminal study, Prada et al. [29] demonstrated how, once enhanced, the tumor is highlighted and reveals other specific characteristics of both low-grade gliomas (LGGs) and high-grade gliomas (HGGs).

LGGs show a mild, dotted CE with diffuse appearance and blurred margins. Arterial feeders are usually not identifiable, microbubble transit is regular and organized, and venous drainage is diffuse through numerous capillaries and consequently not discernible. Relying not on its echogenicity but upon vascularization, CEUS proved to be particularly valuable in differentiating oncological tissue from surrounding edema, thus helping in depicting the true limits of infiltration [30, 31].

HGGs have a high CE with a more nodular, nonhomogeneous appearance and fast perfusion patterns, with a rapid CE, marked by rapid arterial phase, very fast CE peak, and chaotic transit of microbubbles within the lesion. The arterial supply

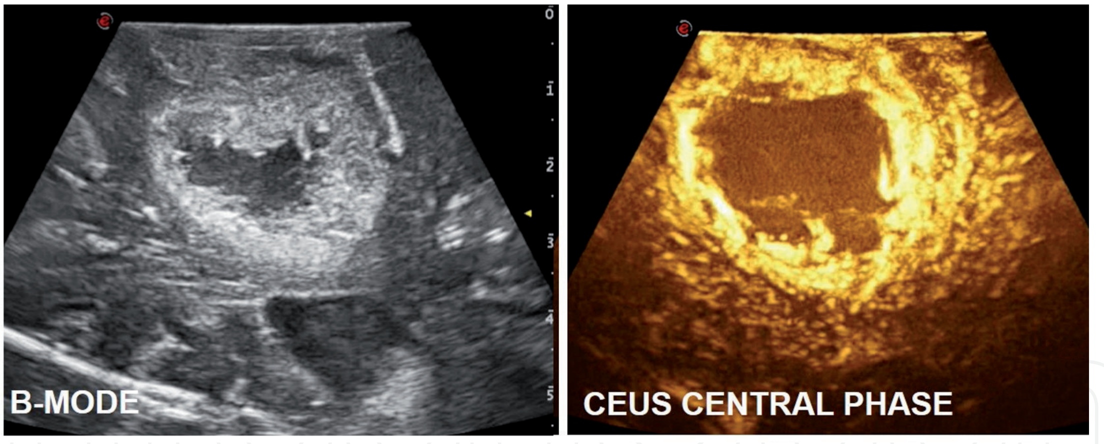

Figure 2.
B-mode CEUS evaluation of a high-grade glioma. The microbubble contrast medium allows to visualize the tumor parenchyma with its necrotic non-enhancing component. In advanced phases of resection, CEUS can be repeated to identify inadvertent residuals.

was clearly visible, showing many macrovessels within the lesion and a typical peripheral enhancement that moved toward the inner areas of the lesion. The venous phase was rapid (5–10 seconds), and the venous drainage system was diffuse, with multiple medullary veins aiming toward the periventricular zone. CEUS in HGGs is useful in differentiating solid from cystic components. In the specific case of glioblastomas (GBMs), CEUS CE is consistent in proliferating areas, and, on the contrary, no CE at all is seen in necrotic zones and surrounding brain parenchyma. Two CE patterns are identifiable in GBM: (1) heterogeneous with nodular high CE spots interspersed by low CE areas of necrosis and (2) peripheral rim CE surrounding a central core of necrosis without CE. In all cases, GBM shows a clearly demarcated border after UCA administration due to the different vascularization of the tumor and healthy brain parenchyma [29] (**Figure 3**).

Highlighting the residual tumor tissue with great accuracy and overcoming the difficulties of ultrasound interpretation caused by artifacts, edema, and surgical manipulation [10, 23, 32], CEUS has been demonstrated valuable in guiding tumor resection. In conclusion, the introduction of CEUS embodies one of the most recent innovations in HGG surgery.

Furthermore, in a series of publications, CEUS showed its capability in identifying tumor remnants after HGG surgery [10, 23, 30]. These are generally defined as nodular tissue at the edges of the surgical cavity, depicting an early and persistent enhancement, compared to the surrounding brain parenchyma. Because of artifacts due to surgical manipulation, B-mode evaluation alone can show unclear results if performed after neurosurgical resection. In the advanced phase of surgery, CEUS can fill the gap left by ioUS, guiding the surgeon also in the final survey at the end of the procedure [33]. Moreover, US is independent of brain shift, and this grants useful information to surgeons throughout the procedure also in advanced phases of resection, such as final survey at the end of the procedure.

CEUS potential in detecting inadvertent residuals proved particularly effective in a 5-ALA-guided setting [10], where the resection is built with the 5-ALA assistance, and CEUS supplementary supports the surgeon by providing information before and after resection. Incomplete resections also in a 5-ALA setting can indeed result from residual tumor covered by blood, cottonoid, or overlapping normal brain: in these scenarios it does not light up under blue light conditions and can be missed [34–37]. Moreover, in deep fields or conditions of non-orthogonal working corridors, microscope light might fail to thoroughly illuminate the surgical field, resulting in blind corners facilitating a partial removal. Thus, CEUS final survey

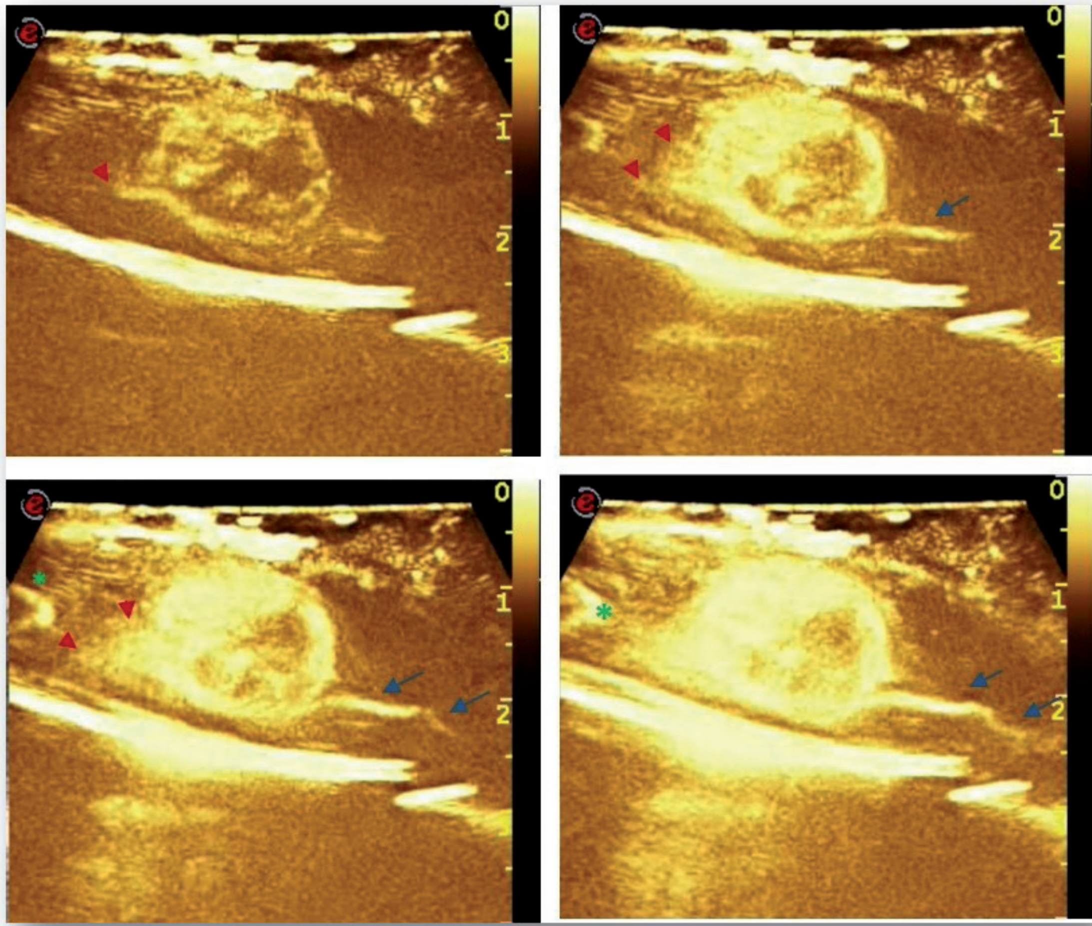

Figure 3.
CEUS visualization of lesion's vascular characteristics of a hemangiopericytoma of the cauda equina after CEUS—The exams depict the main feeders afferent to the lesion (red arrowheads) and the main venous drainage outgoing the lesion (blue arrows). The tumor is highly and rapidly enhancing after intraoperative contrast administration confirming its highly vascularized characteristics. Vessels not directly related to the tumor and belonging to conus medullaris can be identified (green asterisk).

has a role of refinement of the 5-ALA procedure by identifying sub-centimetric remnants. The two techniques approach the surgical field from a different point of view: 5-ALA fluorescence is a result of direct microscope illumination, whereas ultrasounds investigate through brain tissue, depicting also distant, unexposed, hidden cerebral or neoplastic anatomy. Indeed, they observe two different phenomena: 5-ALA is an expression of glial cell metabolism, whereas CEUS is a consequence of pathological tumor vascularization. When integrated, these complementary techniques increase the chance of identifying neoplastic residual tissue.

CEUS-assisted intraoperative imaging does not modify the overall surgical procedure, as it does not interrupt the central phase of surgery and the overall surgical strategy, is not time demanding, and does not require expensive equipment; these considerations are surely important, especially when compared with other intraoperative imaging techniques.

Also, CEUS provides other valuable information to identify vascular supply, giving further insight into the surgical strategy, facilitating vascular deafferentation and removal, and thus maximizing resection voiding neurological sequelae resulting from damaged healthy brain tissues or vessels [38].

Serious weaknesses of CEUS in vascularization assessment are angle of insonation susceptibility, low-flow veins not always visible, and small vessel overestimation due to blooming artifacts that scatter color signals nearby the vessel margins [17]. Possible limitations in the assessment of resection margin are evaluating the tumor removal degree of patients with recurrent gliomas or patients with gliomas after radiotherapy [39].

CEUS can also be compared with perfusion MRI in both preoperative and post-operative settings: US offers a morphologic representation of GBM similar to the one provided by preoperative gadolinium-enhanced T1-weighted MRI [40]. Several experiences in literature compared, instead, CEUS with pMRI in a postoperative setting [41, 42] and suggested it as a cost-effective method in evaluating changes in tumor vascularity during the follow-up period in patients with brain tumors who are undergoing radiotherapy, chemotherapy, or antiangiogenic therapy.

When combined with fusion imaging including US with MRI, CEUS has several advantages over B-mode alone [43, 44]:

1. Detection of poor sonographic visibility tumor.

2. Better recognition of the tumor and edema tissue compared with reconstructive preoperative coplanar-enhanced MRI in real time and multiplane from different angles.

3. Application by neurosurgeons who lack the expertise in US technology as an easier way to discern the structure of the brain.

4. Improved orientation and compensation for the brain shift.

Recent reports highlighted other potential applications of CEUS in cranial oncological surgery, although these experiences are still anecdotal with few cases reported. Apart from the evaluation of intraoperative resection control, CEUS has been used as biopsy guidance to correctly localize the needle and target the most representative samples for pathology [5, 45] or to guide and assess hemodynamic effects after intraoperative embolization of highly vascularized tumors such as hemangioblastomas [20, 38]. In addition, CEUS use can space from a bedside technique adding helpful information not only in noninvasive staging of tumors but also in differentiating tumor recurrence from radionecrosis as postulated by Vicenzini et al. [46] and Mattei et al. [47]; relying on microbubble diffusion through vascularization radionecrosis shows a completely different, poorer, enhancement pattern compared to HGGs.

CEUS has thus proven its utility in:

1. Highlighting tumors and their phases compared to brain parenchyma [42].

2. Characterizing glioma grade [29, 30, 48].

3. Assessing vascularization and degree of overall perfusion [29, 30].

4. Showing vascular rearrangement that takes place with tumor removal [17].

5. Highlighting residual tumor (especially feasible in a 5-ALA setting) [10, 30, 39].

6. Aiding surgical decision-making through serial imaging assessment of surgical anatomy [5, 7, 41, 42].

7. Helping in differential diagnosis of radionecrosis with neoplastic tissue due to its lack of contrast enhancement [46, 47].

8. Guiding to intraoperative biopsy and tissue sampling [5, 45]

4. Spinal tumors

Primary spinal tumors are relatively rare lesions, for which MRI represents the gold standard for diagnosis. Nevertheless, MRI may not always differentiate accurately between different types of intramedullary tumors: even if not well defined nor standardized, the role of CEUS in this surgical field appears as a problem solver. Even though a small number of cases were reported, it has proven to be a simple and relatively inexpensive technique representing a real-time dynamic procedure that can be performed during a spinal tumor surgery. Its benefits include:

1. Better characterization of the location of the intramedullary lesions [49, 50].

2. Easier identification of vascular structures, giving further insight in vascular deafferentation and then surgical removal [8, 9, 49, 50].

3. Possible combination with color Doppler to better identify the main arterial feeders and draining vessels [8, 9].

4. As for HGG surgery, CEUS helps in the identification of inadvertent remnants [8].

The important drawbacks in this setting are:

1. Possibility to analyze one portion of the lesion at the time.

2. Reduced visibility of low-flow veins and possible overestimation of small vessels due to blooming artifacts.

3. Less defined imaging due to a reduced depth of the explored surgical field compared to brain surgery [4, 8, 9]

5. Vascular applications

Providing an angiogram-like display of the parent and downstream vessel segments in high spatial resolution, CEUS might be a feasible tool for both aneurysm and arteriovenous malformation (AVM) treatment. Indeed, it could implement their intraoperative management by providing real-time imaging: this is true both in the visualization of the vascular supply before the intervention and in flow assessment at the end of the procedure [51]. Furthermore, since it allows the identification of target vessels even when covered by brain parenchyma, it could be synergistically used with ICG-VA, which relies on direct vessel visualization, in situations in which a complex approach is required [13, 52].

Focusing on aneurysms, CEUS was found particularly useful in occlusion follow-up after endovascular treatment. As opposed to a neuro-oncological setting, in which CEUS examination can be performed only after craniotomy, in the vascular setting, it can amplify vessel resolution also during transcranial examination. CEUS can selectively monitor intracranial aneurysms and detect refilling rate in aneurysms with a minor neck remnant. In the end, they suggested to perform transcranial color-coded duplex sonography (TCCS) examination with contrast enhancement at the time of initial surveillance with digital subtraction angiography (DSA) and, if findings were similar, to undertake an additional follow-up by TCCS alone until changes in aneurysm status. Transcranial examination is cost-effective, rapid, easily repeatable, and feasible compared to standard digital subtraction angiogram or angio-MRI monitoring.

To summarize, CEUS in the setting of intracranial aneurysms has the following advantages:

1. Accurate display of flow direction and velocity.

2. Increased focus and resolution, allowing detection of very low flow as often presented in coiled aneurysms.

3. Gives the possibility to be performed immediately as a control examination in the intensive care unit (ICU).

4. Produces less severe metal artifacts compared to other imaging modalities.

The main drawback underlined in both papers was the limited acoustic window in aneurysms located outside the circle of Willis, despite the introduction of contrast agent [25, 26].

In dural arteriovenous fistula (dAVF) surgery, both cranial and spinal, one of the most important steps is the correct identification of the fistulous site [53–55]. In the two reported cases [4, 56], CEUS allowed both pre- and post-ligation real-time visualization of site of the fistula and blood flow changes occurring in the spinal cord and perimedullary plexus. Not only it does encompass the limitations of Doppler imaging, which can be used simultaneously to confirm the type of flow and flow dynamics, but, as already in the case of aneurysms, it might be integrated with other imaging modalities such as fluorescence [11, 51]. However, larger series are needed to determine the significance of this tool in the obliteration of intradural spinal dAVFs [51] (**Figure 4**).

Pioneer experiences have recently been reported also in AVM surgery. Providing an angiogram-like display of the parent and downstream vessel segments in high spatial resolution, CEUS is a feasible tool for both aneurysms and AVM treatments. Indeed, it could implement their intraoperative management by providing real-time imaging: this is true both in visualization of the vascular supply before the intervention and in flow assessment at the end of the procedure. Furthermore, since it allows the identification of target vessels even when covered by the brain parenchyma, it has been proposed as a complement to standard ICG-VA.

The integration of color Doppler sonography and CEUS allows to:

1. Accurately display flow direction and velocity within the nidus and in surrounding vessels

2. Identify AVM feeders from non-AVM-related vessels

3. Evaluate the flow modifications produced into the nidus after temporary occlusion of feeders

4. Assess completeness of devascularization and eventual residual flow to the AVM

5. Assess restored venous flow into surrounding veins before dissection and isolation of the venous compartments of the malformation

Knowledge of the vascular characteristics of the AVM and the relationships of the nidus with the brain parenchyma is mandatory during these complex surgical

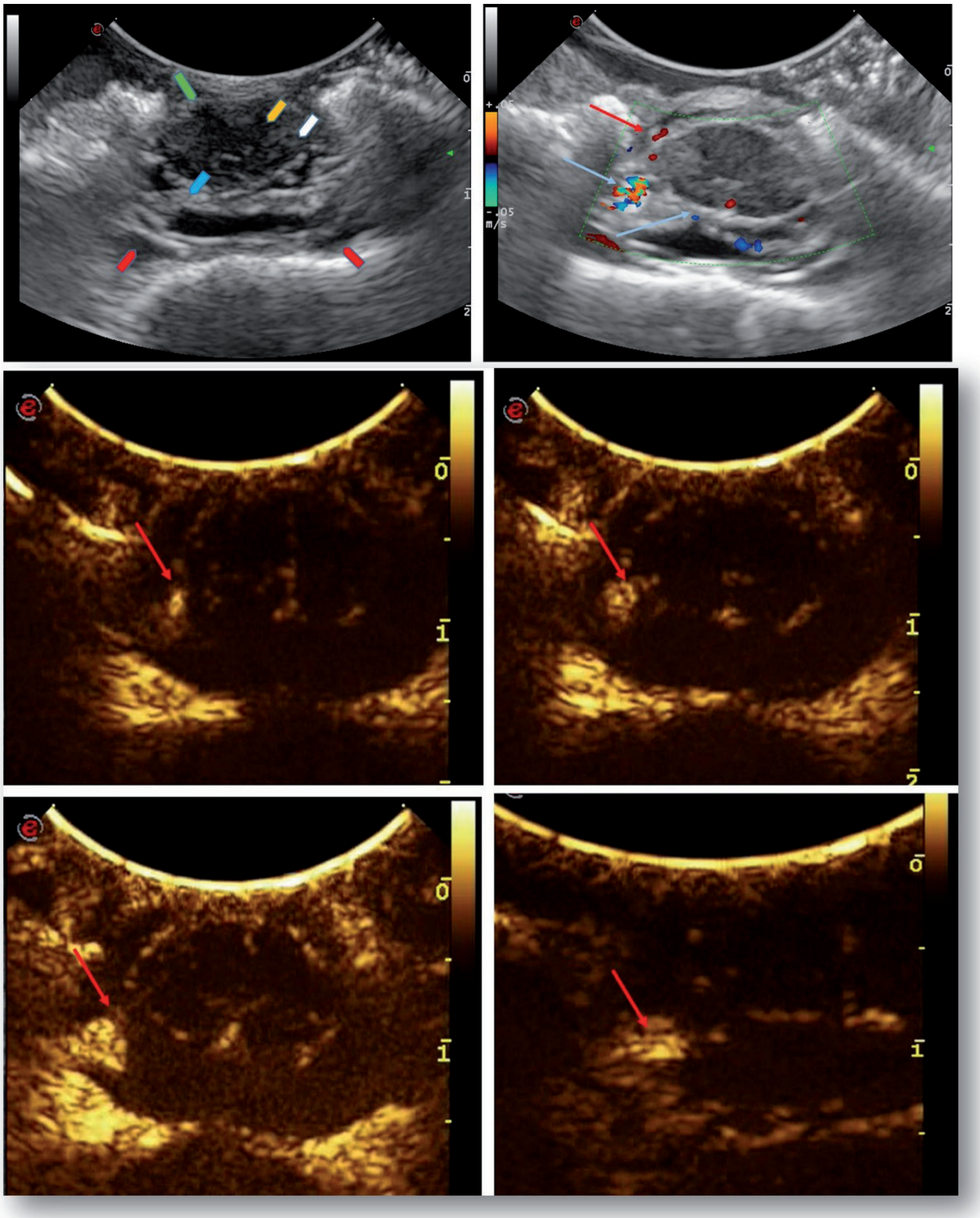

Figure 4.
B-mode and color Doppler visualization of a spinal dAVF characteristic. Epidural standard B-mode imaging showing the spinal cord anatomical proportional plan features: Green arrow, dura mater; blue arrow, peridural venous plexus; yellow arrow, spinal cord gray matter; white arrow, spinal cord white matter; red arrows, vertebral arteries. Color Doppler sonography displaying radicular artery (red arrow) and engorged peridural veins (blue arrows) with a turbulent flow. Doppler US confirms the arterialized nature of peridural plexus veins. After CEUS administration the main feeders afferent to the lesion can be observed and the main venous arterialized drainage outgoing the lesion (red arrows), thus identifying fistulous point. Peridural venous vessels not directly related to the dAVF are not visualized at this early arterial stage (arterial stage).

procedures; hence, the real-time identification of the feeding arteries and draining veins is surely valuable during surgery. Basically, the operative strategy is guided throughout the procedure by several CEUS assessments with temporary clipping of the feeding vessel, and real-time confirmation of the hemodynamic modification inside the nidus is semiquantitatively evaluated both by means of color Doppler US and CEUS. This reduces the risk of inadvertently sacrificing parenchymal non-AVM-related arterial vessels (**Figure 5**).

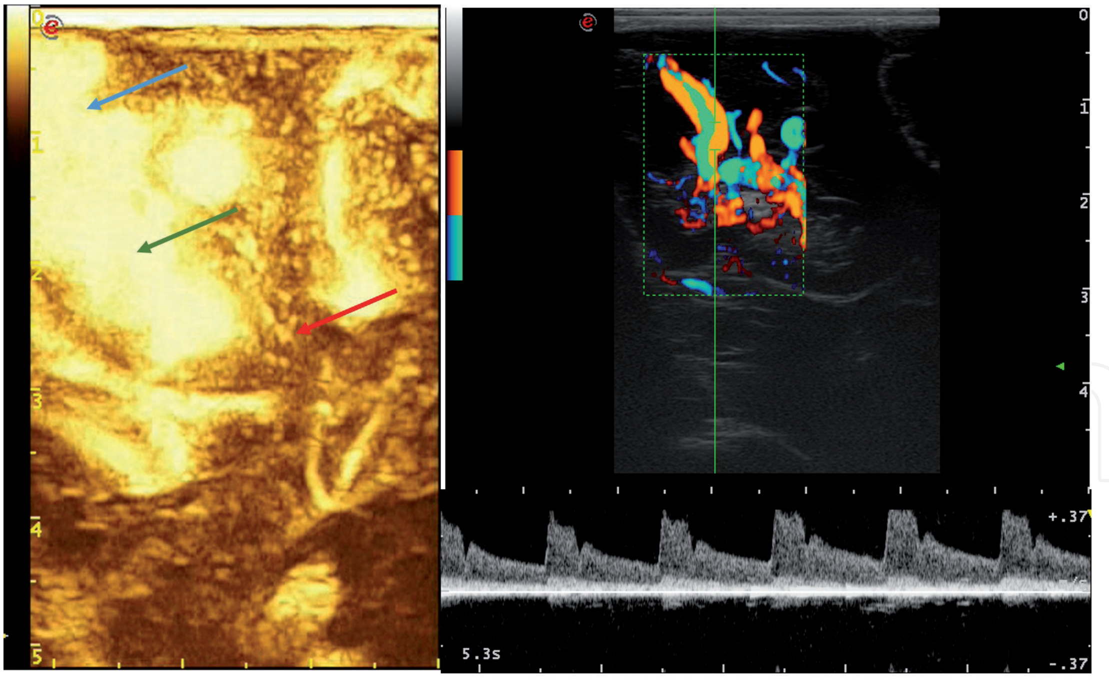

Figure 5.
CEUS and color Doppler US evaluation of an AVM, in which main arterial feeders (red arrows) can be identified, as well as the nidus (green arrow) and venous drains (green arrow). Color Doppler shows the flow direction, arterial vs. venous flow, and confirms turbulent flow within the malformation.

In advanced phases of dissection, CEUS allows the surgeon to:

a. Spatially identify in which area of the nidus residual flow is present.

b. Establish a gross estimation of the overall residual flow within the malformation (as CEUS enhancement is directly proportional to flow).

Furthermore, the restored venous flow into AVM draining veins can be reliably identified providing a final confirmation of completeness of nidal deafferentation, before the procedure is completed.

6. Stroke

An adequate supply of blood containing oxygen and nutrients is crucial for the recovery and survival of brain tissue. Monitoring of cerebral perfusion is essential in the prevention of secondary brain damage in patients with acute brain injury. CEUS has been suggested as a new method to measure cerebral perfusion in patients both with acute brain injury at the ICU and in the acute state of cerebral ischemia. The technique has a high temporal resolution which can be used at the bedside; moreover, the contrast enhancement can be used for visualization of the cerebral vasculature to overcome the restricted level of acoustic intensity. However, in this context the accuracy of CEUS for the detection of hyperperfusion has not yet been assessed.

This aligns with the idea that for patients after ischemic stroke, CEUS may serve as an additional clinical tool for the bedside evaluation of brain tissue perfusion and response to recanalization therapy, with more efforts to be made to improve its reliability [57–59]. However, when it comes to this clinical application, two key problems arise:

1. Different protocols were used by the involved research groups, and, more crucial, patients presenting with acute stroke were examined at different time windows.

2. Patients with insufficient insonation conditions were excluded in advance, and the percentage of stroke patients for which the technique could represent a consistent improvement remains questionable. Indeed, in cited studies [57–59], one of the inclusion criteria was a sufficient temporal acoustic window for conventional transcranial color-coded sonography.

As a last note, CEUS can be used as a follow-up strategy in stroke patients: it is a fast and repeatable bedside technique [3]. However, these potential advantages are undermined by (1) a small sample of studies; (2) non-validated comparison with the other imaging technique already in use in this particular area; and (3) the need for specific ecographic equipment.

7. Carotid plaques

Carotid atherosclerotic disease represents a major current health problem accounting for approximately 20% of all cases of cerebral ischemia. Risk stratification and patient management are traditionally based on the presence or absence of symptoms and the degree of stenosis, both of which have been found to correlate with the occurrence of stroke. US is the cornerstone of both screening and diagnostic approach of carotid disease, and introduction of CE has been providing promising results, leading to the publication of recommendation of use [28, 60]. An impressive number of works demonstrated CEUS is a feasible and effective tool to:

1. Analyze plaque morphology and characteristics [61]

2. Identify vulnerable plaques and detect neovascularization [62–65]

3. Perioperatively assess the procedure to be performed [66–68]

Moreover, a comparison and a proof of the relationship between CEUS and 3DT1-WI MRI plaque imaging were recently published [69]. However, on board with the purpose of this review, we decided to focus only on those works in which a prospective relationship between CEUS on carotid intraplaque neovascularization and ischemic stroke was analyzed. The grade of contrast enhancement was an independent risk factor for ischemic stroke or recurrent transitory ischemic attack. Therefore, the grade of CEUS contrast enhancement could become a predictive index of ischemic stroke, identifying those patients in need of an effective treatment. A potential source of bias coming from the exclusive selection of large plaques, a semiquantitative grading system, and a relatively small sample size are however important limitations associated with this finding.

8. Conclusions

CEUS has reached in recent years a wide utilization in various neurosurgical fields, mainly in neuro-oncological surgery. Despite its main limitations in being an operator-dependent technique and its shared drawbacks with US technology, it revealed itself as a promising tool: CEUS is comparable and complementary to traditional imaging techniques, allows for a serial assessment, is easily performable in different settings, and has a wide range of future applications yet to be explored.

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