Usefulness of Ultrasound-Guided Microsurgery in Cavernous Angioma Removal

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■ BACKGROUND: **Primary elements of surgical treatment of cavernous angiomas (CAs) are precise lesion identification and optimal trajectory determination. Navigation techniques allow for better results compared to microsurgery alone. In this study, we examined the benefits of intraoperative ultrasound (IOUS) use as an adjunct to standard localization systems.**

■ METHODS: **We retrospectively analyzed 59 CAs, comparing outcomes in 2 groups of patients: 34 who underwent frame-based or frameless navigation-assisted microsurgery (no-IOUS group) and 25 who underwent IOUS-guided microsurgery associated with these techniques (IOUS group).**

■ RESULTS: **The use of IOUS did not significantly increase the surgery time (mean, 172 ± 1.7 minutes in the IOUS group and 192.6 ± 11.5 in no-IOUS group; *P* = 0.08). In all 25 patients in the IOUS group, IOUS allowed for ready identification of CA as a hyperechoic mass. At the last follow-up (mean, 41.7 ± 3.5 months postsurgery), 95.2% of the IOUS group and 80.8% of the no-IOUS group had a modified Rankin Scale score of 0—1 and an Extended Glasgow Outcome Scale score of 7—8 (*P* = 0.2), with 100% and 64%, respectively, included in Engel outcome scale class IA (*P* = 0.006). Complete removal, as confirmed on postoperative magnetic resonance imaging, was achieved in all patients in the IOUS group and in almost all (97.1%; *P* = 0.4) patients in the no-IOUS group.**

■ CONCLUSIONS: **IOUS is a valid tool for the intraoperative identification of CAs. Implementation of standard localization methods with IOUS guidance was associated with complete resection in all cases, without increasing surgical time. Compared with microsurgery without IOUS guidance, long-term functional outcomes showed better trends, and the epilepsy-free rate was significantly higher.**

INTRODUCTION

Cerebral cavernous malformations, or cavernous angiomas (CAs), are proliferative hemorrhagic lesions consisting of sinusoidal caverns lined by a single layer of endothelial cells, filled with thrombus at various stages of organization.[1] Their prevalence is unknown, although it is estimated at around 0.5%.[2] Patients usually present with seizures and focal neurologic deficits (FNDs) due to mass effect or hemorrhage, but asymptomatic CAs may be discovered incidentally.

CA-related epilepsy (CRE) is defined as seizure in patients with at least 1 lesion and evidence of seizure onset referable to the anatomic location of the CA.[3] In 2011, Josephson et al.[4] reported a 5-year risk of first-ever seizures of 6% in symptomatic CAs and 4% in asymptomatic CAs. Among adults presenting with epilepsy, the rate of 2-year freedom from seizure over 5 years was 47%.[4]

The definition of intracranial hemorrhage related to CA was standardized in 2008 as "acute or subacute onset symptoms (any of headache, epileptic seizure, impaired consciousness, or new/worsened FND) accompanied by radiological, pathological, or surgical evidence of recent extralesional or intralesional hemorrhage."[5] The annual hemorrhagic risk is estimated as 0.7%—6.7%.[6] Previous hemorrhage and brainstem location

Key words
- Cavernous angioma
- Cavernomas
- Frame-based surgery
- Frameless-navigation surgery
- Intraoperative ultrasound
- Ultrasound-guided surgery

Abbreviations and Acronyms
CA: Cavernous angioma
CRE: Cavernous angioma-related epilepsy
FND: Focal neurologic deficit
GOSE: Extended Global Outcome Scale
IOUS: Intraoperative ultrasound
MRI: Magnetic resonance imaging
mRS: modified Rankin Scale
US: Ultrasound

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increase this risk up to 29.5% and 60%, respectively, whereas for first intracranial hemorrhage it ranges from 0.4% to 2.4%.[6,7]

Surgical resection is generally performed for symptomatic, readily accessible CAs, but only after previous hemorrhage in deep or eloquent areas. Recently published guidelines suggest that surgical removal should be considered in patients with CRE, given the rate of seizure control of 70%–90% in patients with sporadic seizures or those with a seizure duration <1 year.[6,8] Surgery finally may be proposed for asymptomatic CAs as well, when easily removable and in noneloquent areas, to prevent future hemorrhage, avoid expensive and time-consuming follow-up, or facilitate lifestyle or career decisions.[6]

The aim of surgery is the complete removal of CA without any significant morbidity. Most CAs are subcortical or more deeply located lesions not emerging on the brain surface; therefore, proper location of the craniotomy, precise identification of the CA, and optimal planning of the trajectory to avoid eloquent areas and fibers are crucial. The path should be the shortest available, through the closest sulcus if possible. Frame-based stereotaxy and frameless navigation systems are usually used to plan the surgical strategy; the former system is the most precise,[9] but it is uncomfortable and not suitable for all locations, whereas the latter is slightly less accurate but more adaptable. Neither allows a real-time examination, however.

In recent years, intraoperative ultrasound (IOUS) has been introduced in neurosurgery, allowing for both lesion identification and final surgical cavity inspection.[10] To understand and establish the limitations and advantages of IOUS in the removal of CAs, we compared our results adopting the best-known methods, frame-based stereotactic microsurgery or frameless navigation, alone and in association with IOUS-guided microsurgery.

METHODS

Patient Selection and Data Collection

In 2010, our department adopted the use of IOUS in addition to stereotactic frame-based or navigation-assisted procedures for microsurgical removal of CAs. A prospective database of all IOUS-guided microsurgeries was created. We carried out a retrospective review of all frame-based or navigation-assisted microsurgeries for CA performed between January 2010 and April 2017, and compared the IOUS and no-IOUS groups. Clinical data of 65 patients were analyzed, including preoperative information, intraoperative reports, complications, postoperative magnetic resonance imaging (MRI) findings, and condition at discharge. We reexamined all MRIs performed before surgery to define the brain area involved and the greatest CA diameter (in mm), excluding 6 cases located in the brain stem, because these CAs have a particularly high morbidity and mortality and thus represent a different and specific surgical subpopulation.[11] All 59 included cases were classified as eloquent or noneloquent, deep (white periventricular matter, insula, thalamus, basal ganglia, cerebellar peduncles) or superficial (cortical–subcortical <2 cm from the brain surface), infratentorial or supratentorial, and finally large (>15 mm) or small (≤15 mm) in diameter. The study cohort was divided into 2 groups according to surgical technique: frame-based or navigation-assisted microsurgery with IOUS guidance (IOUS group) or without IOUS guidance (no-IOUS group). We compared the surgical time (from skin incision to skin closure), complications, outcomes at the last follow-up, and total removal.

Follow-Up

The duration of clinical and MRI follow-up was at least 3 months in all 59 patients. Permanent FNDs were evaluated at the last follow-up in 50 patients as worse or no worse, a category that includes normal patients, preexisting FNDs, and recovered FNDs.

Functional outcomes were obtained in 47 patients using the modified Rankin Scale (mRS) and the Extended Global Outcome Scale (GOSE), both at the last follow-up. Furthermore, in 44 patients, we recorded the Lawton Instrumental Activities of Daily Living Scale score before surgery and at the last follow-up. Long-term CRE improvement was evaluated at the last follow-up in 43 of the 55 patients with supratentorial CAs using the Engel Outcome Scale.

Complete CA removal was defined as the absence of any residual, visible on postoperative MRI, and in 47 cases a long-term MRI was also available.

Surgical Techniques

The surgical strategy was planned on preoperative MRI and functional studies or tractography when useful, according to the neurosurgeon experience and preference. All patients performed a volumetric MRI (axial T2-weighted and T1-weighted with contrast) the day before or the day of surgery.

Frame-based craniotomy was adopted in small, deep, and sovratentorial CAs. After general anesthesia induction, a Leksell G frame (Elekta AB, Stockholm, Sweden) was fixed to the patient's skull, and MRI was performed. The patient was transported to the operating room, and the trajectory from the dural surface (entry point) to the CA (target) was planned using SurgiPlan (Elekta AB). The frame was fixed to the headrest with a Leksell Stereotactic System Clamp (Elekta AB), and the target coordinates were set with the Leksell Stereotactic System (Elekta AB). A craniotomy around the entry point was performed. On dural opening, a silicon catheter was inserted using a Backlund Catheter Insertion Needle Kit (Elekta AB). The operative microscope was positioned, and the corticectomy was continued along the catheter until the CA was reached at the tip. The dissection between the gliosis and the lesion was performed, the CA was removed, and the resection of hemosiderin-stained tissue was completed. Once hemostasis was achieved, the dura was closed, and flat bone was repositioned with micro screws and titanium plaques.

The Stealth Station S7 navigation system (Medtronic, Minneapolis, Minnesota, USA) was used. MRI data were transferred to the computer workstation, and registration was performed using skin markers with the head fixed in the 3-pin head holder. A sterile pointer was used to pinpoint the craniotomy centered on the lesion, and its projection was used to trace the trajectory. The microsurgical procedure was as described previously.

Table 1. Epidemiologic, Morphologic, and Anatomic Characteristics of 59 Cases of Cavernous Angiomas

Characteristic	No-IOUS Group	IOUS Group	*P* Value	Total
Number of patients	34	25		59
Age (years), mean ± SE (range)	44.3 ± 2.7 (15–72)	40.2 ± 2.9 (16–71)	0.3	42.6 ± 2 (15–72)
Males, number (%)	13 (38.2)	12 (48)	0.4	25 (42.4)
Females, number (%)	21 (61.8)	13 (52)		34 (57.6)
Greatest diameter (mm), mean ± SE (range)	14.7 ± 1 (5–27)	16.4 ± 1.7 (6–43)	0.4	15.4 ± 0.9 (5–43)
Large (>15 mm), number (%)	15 (44.1)	10 (40)	0.8	34 (42.4)
Small (<15 mm), number (%)	19 (55.9)	15 (60)		25 (57.6)
Deep, number (%)	16 (47.1)	10 (40)	0.6	26 (44.1)
Superficial, number (%)	18 (52.9)	15 (60)		33 (55.9)
Infratentorial, number (%)	1 (2.9)	3 (12)	0.3	4 (6.8)
Supratentorial, number (%)	33 (97.1)	22 (88)		55 (93.2)
Eloquent area, number (%)	20 (58.8)	16 (64)	0.8	36 (61)
Noneloquent area, number (%)	14 (41.2)	9 (36)		23 (39)
Surgery time (minutes), mean ± SE (range)	192.6 ± 11.5 (100–404)	172 ± 8.7 (109–261)	0.08	183.6 ± 7.6 (100–404)

IOUS, intraoperative ultrasound; SE, standard error.

Ultrasound (US) examinations were performed with an Aloka ProSound Alfa 7 US system with a UST-9120 convex sterile probe (Hitachi, Tokyo, Japan). The frequency ranged from 5.0 to 10.0 MHz. To increase the acoustic interface, continuous irrigation of the operative field with sterile saline was necessary. After the craniotomy, with the aid of the stereotactic frame or the navigation system, the lesion was identified and characterized by IOUS. The corticectomy site was carefully delineated, and the navigation pointer was used only to control the trajectory defined by IOUS. A small dissector (or a stereotactic catheter in 2 cases) was used to indicate the path and, under real-time US guidance, advanced to the target. We then positioned the operating microscope and removed the CA.

Finally, another US scan was performed, after the surgical cavity was filled with sterile saline, to check the completeness of CA removal. In 2 cases, we used navigation with integrated coupled US (MyLab UltraNeuroNav; Esaote, Genoa, Italy) with a linear array probe and an operating frequency of 3–11 MHz. The probe was placed in a transparent plastic surgical sterile sheath and secured with a sterile rubber band, with gel between the transducer and sterile drape to improve the acoustic coupling.

All procedures were in performed in accordance with the standards of the institutional Research and Ethics Committee and with the 1964 Declaration of Helsinki. Informed consent was obtained from all patients.

Statistical Analysis

All calculations were performed using SPSS version 20.0 for Macintosh (IBM, Armonk, New York, USA). Continuous data are expressed as mean ± SE and compared using the paired or unpaired Student *t* test and analysis of variance for more than 2 group samples. Categorical variables are reported as number and/or percentage and compared using the Pearson χ^2 and Fisher exact test as appropriate. A *P* value <0.05 was considered to indicate statistical significance.

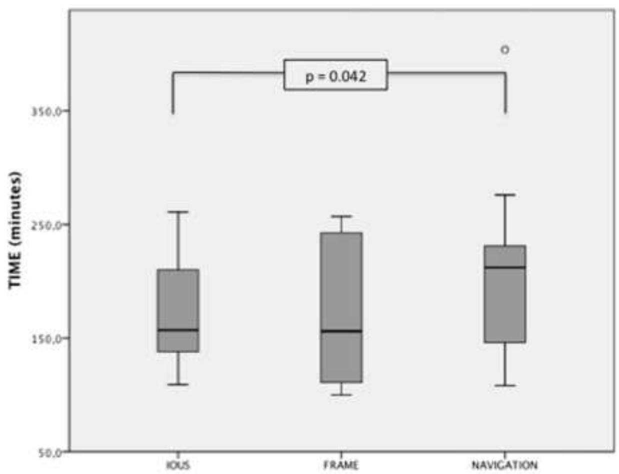
RESULTS

General Results

CA was discovered incidentally in 8 of 59 cases (13.6%), whereas epilepsy appeared as the initial clinical manifestation in 40 patients (67.8% of the total cohort and 72.7% of the 55 patients with supratentorial CA) either associated or not associated with FND, which occurred in 19 of 59 cases (32.2%).

The microsurgical resection of CAs was frame-based in 8 patients and navigation-assisted in 26, for a total of 34 procedures performed without IOUS guidance. In 25 patients, IOUS guided the surgery in addition to the standard localization techniques. When comparing the 2 groups, IOUS and no-IOUS, with similar epidemiologic, morphologic, and anatomic characteristics, the application of IOUS did not increase the duration of surgery (Table 1). IOUS-guided microsurgery took significantly less time than non-IOUS navigation-assisted microsurgery and a similar time as frame-based non-IOUS navigation-assisted microsurgery ($P = 0.042$; Figure 1).

In all cases, the use of IOUS allowed for ready and clear identification of CAs that appeared as a well-circumscribed and hyperechoic masses with respect to the brain parenchyma. In many cases (18 of 25; 72%), calcifications were present, producing reverberation artifacts such as comet tails and shadowing phenomena (Table 2 and Figure 2). CAs were polyconcamerated or multicystic in the majority of cases (16 of 25; 64%), but some were regular and uniform, typically those that never bled (Table 2). The echo texture was generally finely inhomogenous



	n	mean	SE	median	SD	minimum	maximum
IOUS	25	172	8.7	157	43.4	109	261
FRAME	8	172	23.4	156	67.8	100	257
NAVIGATION	26	199.5	13.1	212.7	64.3	108	404

Figure 1. Operative time (minutes) according to surgical technique. The mean time is significantly shorter for intraoperative ultrasound (IOUS)-guided microsurgery compared with navigation-assisted (NAVIGATION)-microsurgery ($P = 0.042$, unpaired t test). The mean time of frame-based (FRAME) microsurgery is similar to that of IOUS-guided surgery.

(15 of 25; 60%), and in some cases CA was circumscribed by a hypoechoic/anechoic ring: the halo sign (7 of 25; 28%).

Complications and Long-Term Outcomes

Worsening or new-onset FNDs occurred in 14 of the 34 patients in the no-IOUS group (32.8%) and in 7 of the 25 in the IOUS-guided group (28%; P = 0.4); they were usually transient. In 1 patient in the IOUS group (1.7%), a symptomatic fluid collection into the surgical bed occurred 2 weeks after surgery, and open drainage was performed; the culture was negative, and the outcome was excellent. In this case, an abnormal reaction to hemostatic material was the likely cause of the sterile cyst formation.

Permanent FND, after a mean clinical follow-up of 41.7 ± 3.5 months (range, 3–88 months), was present in 4 of the 29 patients in the no-IOUS group (13.8%) but in 0 of the 21 patients in the IOUS group (P = 0.12). No major morbidity, severe disability, or mortality occurred, as demonstrated by the lack of significant change in the Lawton Instrumental Activities of Daily Living Scale between before and after surgery in either group (Figures 3 and 4) and by the final GOSE score, corresponding to good outcome in 41 of the 47 tested patients (87.2%); the other 6 patients (12.8%) had slight to moderate disability (GOSE score of 6). At the last follow-up, 31 of 47 patients were normal (66%), 10 (21.3%) showed no disability despite symptoms (mRS score of 1), and 6 (12.8%) had a slight disability, able to live without assistance but unable to perform all previous activities

Table 2. Ultrasound Appearance of 25 Cavernous Angiomas

Characteristic	Appearance, number (%)
Mass	Well defined, 25 (100); not defined, 0
Signal	Hyperechoic, 25 (100); hypoechoic, 0
Calcifications	Yes, 18 (72); no, 7 (28)
Halo sign	No, 18 (72); yes, 7 (28)
Echo texture	Finely inhomogeneous, 15 (60); grossly inhomogeneous, 9 (36); uniform, 1 (4)
Shape	Polyconcamerated/multicystic, 16 (64%); regular, 8 (32%); spongiform, 1 (4)
Artifact	Yes, 15 (60); no, 10 (40)

(mRS score of 2). The mRS and GOSE scores were better in the IOUS group compared with the no-IOUS group, although the difference was not statistically significant (Figure 5).

CRE was improved in 34 of 43 tested patients (79.1%), corresponding to Engel Outcome Scale class IA (completely seizure-free since surgery), and 22 of 45 patients (51.2%) were without anticonvulsant therapy at the last follow-up (mean, 41.6 ± 3.7 months; range, 3–88 months). All the patients in the IOUS-guided microsurgery group were in Engel class IA at last follow-up (Figure 5), so the long-term epilepsy outcome was significantly better in the IOUS group (100% vs. 64%; P = 0.006).

Complete Removal

Complete removal, evaluated by postoperative MRI (1–3 months), was achieved in all patients in the IOUS group (25 of 25; 100%) and in almost all patients in the no-IOUS group (33 of 34; 97.1%; P = 0.4). The MRI follow-up, at a mean of 22.1 ± 2.9 months (range, 3–78 months), was continued in 47 patients, confirming the early results.

DISCUSSION

Key Data

IOUS was introduced in CA surgery only relatively recently.[12-14] In 2013, Mair et al.,[15] reporting on a grading system for the US visibility of brain lesions, described 3 cases of CA as clearly identifiable masses with variably defined borders. Our experience, presented in this paper, established that in all cases, the recognition of CA was easy and extremely fast, on condition that the US physical principle was well known and the setting was finely adjusted. Indeed, a recent hemorrhage could affect interpretation of the US signal, because incident US waves are strongly reflected by a discrete amount of acute blood that is highly hyperechoic; therefore, a fine setting of frequency, time gain compensation, probe focus and "gain" should be best managed to recognize CA (Figure 2). A massive hemorrhage could mask it, but this is relatively uncommon, and in our experience, no CA required emergent surgery for a large bleeding.

We observed that CAs were almost always recognizable, because their unique echogenity, which is usually lower than in recent blood (highly hyperechogenic) and higher than in brain

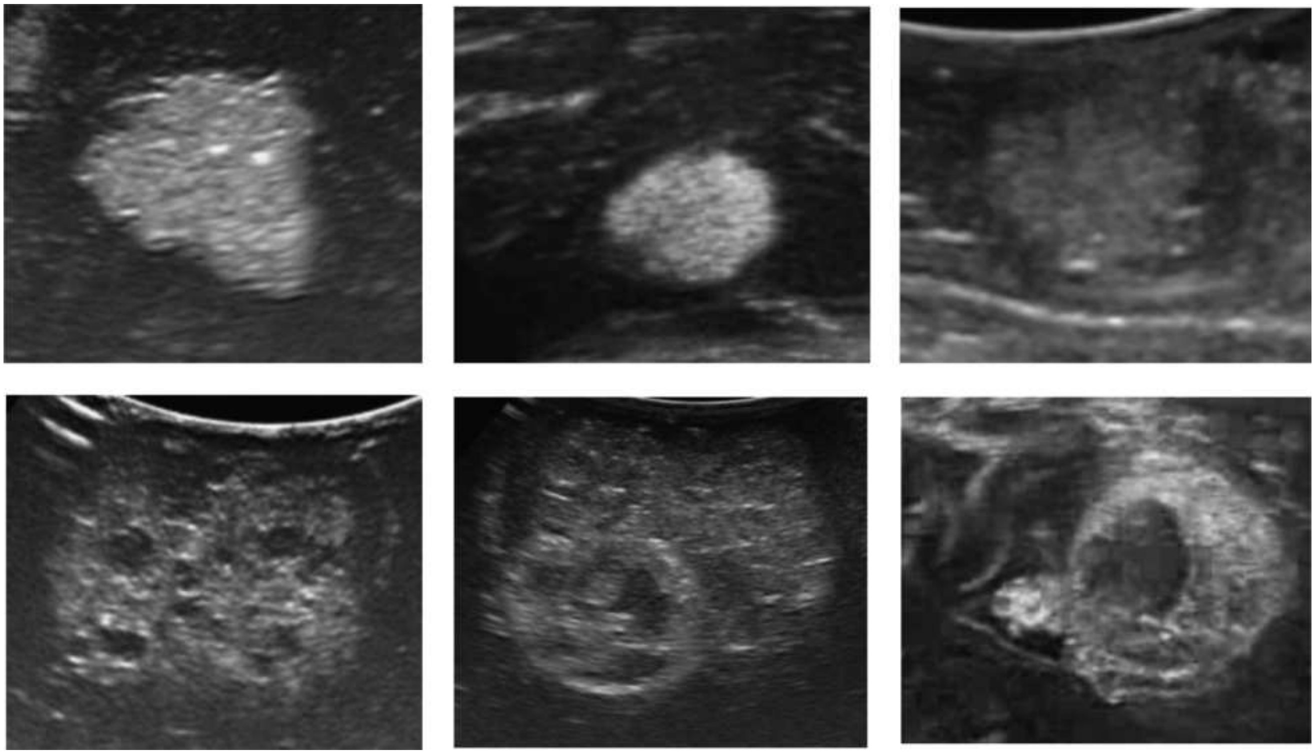


Figure 2. Intraoperative ultrasound appearance of cerebral cavernous angiomas (CAs), viewed with an Aloka Pro-Sound alfa 7 with convex probe UST-9120 (Hitachi). (*Top*) Hyperechoic CAs with a finely nonhomogenous echo texture; the halo sign is present in the image on the right. (*Bottom*) Heterogenous variably shaped CAs, policoncamerated and cystic.

parenchyma (reference to determine mean exam echogenicity). CAs appeared as well-circumscribed masses, frequently calcified and sometimes circumscribed by a hypoechoic/anechoic ring (halo sign). They were uniform and regular or polyconcamerated, multicystic, and even spongiform. The echo texture generally was finely inhomogeneous but sometimes grossly inhomogeneous, and rarely uniform. These conditions are due to blood sedimentation and degradation, with consequent deposition of hemosiderin and calcifications. These typical intrinsic characteristics, usually maintained even if hemorrhage occurs, help identify a CA.

Although CAs are silent lesions on angiography and arterial vessels are not usually present, Doppler imaging can be used to assess the presence of the typically deep venous anomalies. Power Doppler is more sensitive than color Doppler for detecting flow in small vessels, is relatively independent of the probe angle, and causes less noise interference than color Doppler.

Patient positioning must be carefully considered. The prone and park bench positions permit instillation and maintenance of saline solution in the surgical cavity. Inversely, during supine surgical procedures, constant irrigation was provided to reduce air impedance and permit valuable visualization of the lesion. The recently adopted nonsterile probe required a drape to make it possible to fill the scan head with sterile gel, partially resolving the air interposition.

Given the consistent ability to recognize and locate brain CAs, we suggest performing IOUS-guided microsurgery in all cases, particularly with small and deeply located CAs. Likewise, in our experience, as has been reported previously,[16] IOUS use did not increase surgical time. In our data, especially in the comparison of IOUS-guided and navigation-assisted microsurgery, the operative time was significantly reduced by the US use. The ready identification of CA, the ability to visualize the surrounding structures associated with the real-time features of IOUS that permit following any introduced instrument, and, finally, the ability to immediately check the total excision are responsible for the significantly decreased surgical time. Similar times were obtained in the few cases of frame-based stereotactic craniotomy, the most accurate and precise technique described in the literature,[17] although this did not encompass the time required for frame fixation, MRI acquisition, and patient transfer to the surgical theater.

The main complications of CA surgery are FNDs, especially in eloquent or deep areas. A recent review documented an overall risk of death or nonfatal stroke of 6% after CA removal.[18] In most cases, morbidity is transient and related to the CA location, ranging from 75% for CAs in the occipital lobe, with 40% recovery after several months, to 35% for deep paraventricular CAs.[19,20] Reported postsurgical morbidity for insular or basal

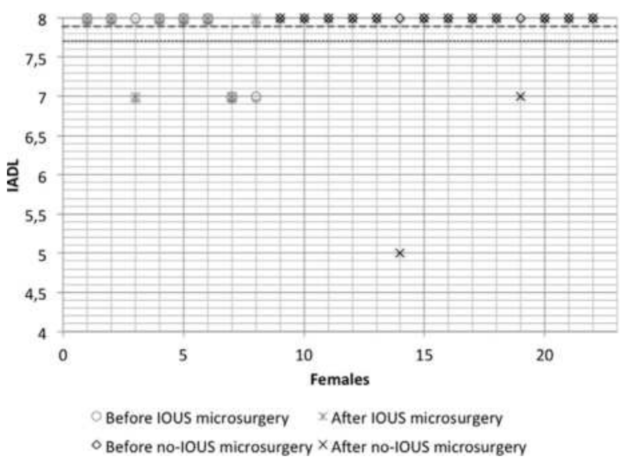


Figure 3. Instrumental activities of daily living scale before and after microsurgical removal of cavernous angiomas in female patients. The dashed line represents the mean values before (7.9 ± 0.6) and after surgery (7.7 ± 0.13). A paired *t* test applied before and after surgery shows no significant difference ($P = 0.26$).

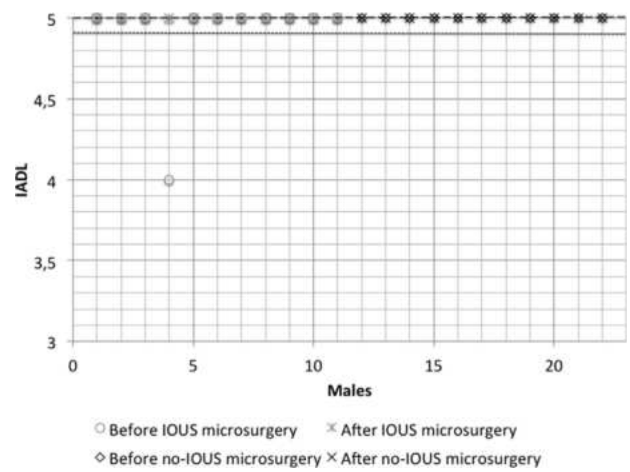


Figure 4. Instrumental activities of daily living scale before and after microsurgical removal of cavernous angioma in male patients. The dashed line represents mean values before (4.9 ± 0.5) and after surgery (5 ± 0). A paired *t* test applied before and after surgery shows no significant difference ($P = 0.34$).

ganglia CAs is 11%–18%, and mortality is approximately 2%.[21,22] In our cohort, no mortality was observed; the overall permanent FND rate was 8%, and in all cases, the defect was slight. Indeed, the final mRS and GOSE scores corresponded to slight to moderate disability in 6 patients (12.8%), and no patient had a severe disability. These results were similar comparing the stereotactic frame-based or frameless techniques to IOUS-guided microsurgery in addition to conventional localization methods, even if the data seemed to be slightly better in the IOUS group. The only significant difference was in the long-term epilepsy outcome; all patients (100%) in the IOUS group were completely seizure-free (Engel class IA) at the last follow-up, compared with only 64% of the no-IOUS group.

Finally, IOUS does not seem to be associated with a greater risk of infection even if the probe is not sterile and merely covered by a sterile drape.[13] Our experience confirms this finding, although we methodically sterilized the US probes in all but 2 cases; therefore, we observed a shortening of probe half-life with a consequent increase in frequency of its replacement and higher costs.

Stereotactic and navigation methods improve the results in terms of total removal compared with conventional microsurgery alone, as reported previously.[16,23,24] In our experience, all CAs were completely removed with the aid of IOUS; therefore, we believe that this procedure might add some advantages to the most common techniques, but more data are needed to demonstrate statistical significance. Moreover, IOUS is the only way to directly check the surgical cavity at the end of resection and is extremely useful in cases of residual CA, as well as in cases of hemorrhagic complication.

Study Limitations and Interpretation

A drawback of our study is its retrospective, not randomized nature, which limits the final value of our results, although epidemiologic and anatomic characteristics of the 2 comparison groups were similar. The selection of surgical technique, based on neurosurgeon preference and experience, may constitute a bias, but it is probable that more difficult cases were included in IOUS

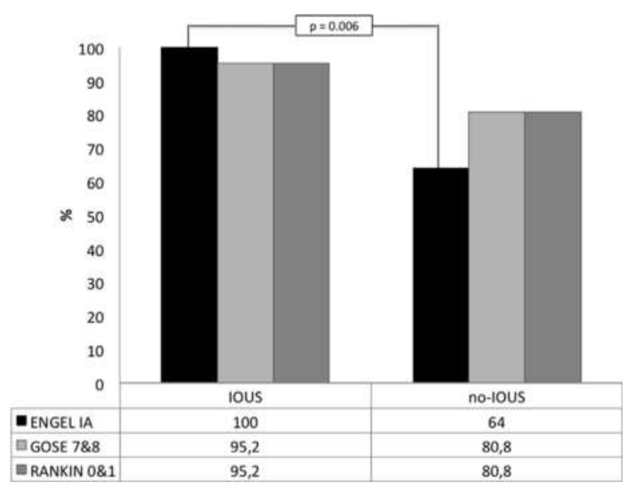


Figure 5. Outcomes at last follow-up after cavernous angioma removal in the intraoperative ultrasound (IOUS)-guided and no-IOUS microsurgery groups. Frequency of patients included in Engel class IA are in black (18 of 18, 100% vs. 16 of 25, 64%; $P = 0.006$, Pearson χ^2 with Fisher exact test), Extended Glasgow Outcome Scale (GOSE) score 7–8 in light gray (20 of 21, 95.2% vs. 21 of 26, 80.8%; $P = 0.2$, Pearson χ^2 with Fisher exact test), and modified Rankin Scale (mRS) score 0–1 in gray (12 of 21, 95.2% vs. 21 of 26, 80.8%; $P = 0.2$, Pearson χ^2 with Fisher exact test).

group; thus, outcomes of this group could be overestimated, but not underestimated.

Our findings obviously must be judged with caution, but nonetheless demonstrate that IUOS, in addition to a frame or navigation system, does not increase operative time and morbidity while improving long-term outcomes, at least for epilepsy. It must be kept in mind that IOUS is a completely operator-dependent technique that requires discrete training. However, technological advances, such as the possibility of pairing US with preoperative navigated MRI, will further facilitate more widespread application of this technology.

CONCLUSIONS

In our experience, IOUS allowed an easy identification of CAs without increasing operative time and morbidity compared with frame-based and navigation-assisted microsurgery without IOUS guidance. Moreover, it was extremely valuable to immediately ascertain the total excision of CA. Significantly better long-term outcomes of epilepsy (Engel outcome scale class IA 100%), lack of permanent FND, and good functional outcomes in the majority of patients (95.2%) are convincing data to support the utility of this technique.

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