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DESCRIPTION OF A TAILORED FUNCTIONAL APPROACH IN THE SURGICAL TREATMENT OF ARTERIOVENOUS MALFORMATIONS IN ELOQUENT AREAS

FINAL DEGREE PROJECT

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1. ABREVIATION

AVMs: Arteriovenous malformations

BA: Broadman areas

CT: Computed Tomography

CTA: Computed Tomography Angiography

MRI: Magnetic Resonance Imaging

fMRI: functional Magnetic Resonance Imaging

MRA: Magnetic Resonance Angiography

DTI: Diffusion Tensor Imaging

DSA: Digital subtraction Angiography

HHT: Hereditary hemorrhagic telangiectasia

SM: Spetzler-Martin

TMS: Transcranial Magnetic Stimulation

VEGF: Vascular Endothelial Growth Factor

NRP1: Receptor Neuropilin 1

SHH: Sonic Hedgehog

COUP-TF2: Chicken Ovalbumin Upstream Promoter-Transcription Factor

EPH B4: EPH receptor B4

S: Size

V: Drainage venous pattern

E: Eloquent

SM-Supp: Supplemented Spetzler-Martin

NBCA: N-butyl cyanoacrylate

SRS: Stereotactic radiosurgery

RDS: Radiosurgery

IONM: Intraoperative Neurophysiological Monitoring

MEP: Motor Evoked Potentials

SSEP: Somatosensory Evoked Potentials

TES: Transcranial Electrical Stimulation

DCS: Direct Cortical Stimulation

SD: Standard deviation

AEDs: Antiepileptic drugs

UCSF: University of California San Francisco

2. ABSTRACT

BACKGROUND:

Brain arteriovenous malformations (AVMs) are congenital abnormalities of cerebral blood vessels due to inadequate development of capillary network and characterized by a collection of abnormal dilated and entangled vessels denominated nidus fed by arteries and drained by veins without capillary involvement. AVMs have a low prevalence in the general population but are an important cause of spontaneous intracranial bleeding in young adults.

The treatment of AVMs in eloquent areas is controversial due to the high risk of post-surgical neurological deficits, and there is a debate between conservative management and invasive treatments (microsurgery, embolization or radiosurgery). With a tailored pre- and intraoperative functional study, good results can be obtained, reducing the risk of post-operative neurological deficits to preserve an adequate neurological function.

HYPOTHESIS AND OBJECTIVE:

We hypothesize that a tailored functional approach for the management and treatment of AVMs in eloquent supratentorial areas (individualized pre- and intraoperative functional assessment) allows complete surgical resection in most cases (> 70 %) and a cure rate > 90% (reached in combination with embolization and/or radiosurgery), while obtaining a good clinical result (mRS ≤ 2) and a correct preservation of neurological function (< 25% patients with neurological deficit) at 6 months. The aim is to describe the outcomes of the Bellvitge University Hospital Neurosurgery Department functional protocol for the treatment of eloquent sited AVMs, and to examine the usefulness of functional assessment (pre- and intraoperative) and multidisciplinary approach for these particular AVMs.

METHODS AND MATERIALS:

It was designed a case series study with a total sample of 25 patients harboring AVM located in supratentorial eloquent areas. Individualized intraoperative functional monitoring was performed focus on the function at risk demonstrated by presurgical function assessment. 22 patients (88%) underwent asleep surgery, whereas 3 patients (12%) underwent an awake procedure.

RESULTS:

Patients were 13 male (52%) and 12 female (48%). Complete AVM obliteration was achieved in 24 patients (96%), of which 19 cases (76%) by complete surgical resection and 5 cases (20%) after postoperative stereotactic radiosurgery. In one patient, total obliteration was not possible, corresponding to the highest Spetzler-Martin (SM) grade (SM V). Six cases presented minor complications (24%) and there were no intraoperative seizures. Twelve patients (48%) had no neurological deficits and 13 patients (52%) presented neurological deficits in the immediate postoperative period, 8 of them (61.5%) transient. Eighteen patients (78.2%) had no neurological deficits at 6 months, although 2 patients had not been evaluated at 6 months yet. Among the patients with presurgical seizures (16 patients), 56.2% were seizure free during follow-up. As for the mRS, in the immediate postsurgical period, 19 patients (76%) showed a good clinical outcome (mRS ≤ 2) and only 6 cases (24%) presented moderate or severe deficits (mRS ≥ 3). During follow-up 11 cases improved in the mRS score at 6 months and 3 cases at 12 months. Thus, in total, 22 patients presented a mRS ≤ 2 at 6 and 12 month post-surgery, although 2 patients had not been evaluated at 6 months follow-up yet.

CONCLUSION:

Our results suggest that a tailored functional approach using intraoperative brain mapping and/or neuromonitoring is feasible, useful and safe allowing to achieve the highest degree of AVM resection while preventing permanent neurological damage.

KEYWORDS: brain arteriovenous malformations, eloquent areas, tailored functional approach, brain mapping, modified ranking scale.

3. INTRODUCTION

3.1-BRAIN ARTERIOVENOUS MALFORMATIONS (AVMs)

3.1.1-DEFINITION, NEUROPATHOLOGY, EPIDEMIOLOGY, ETIOLOGY AND PATHOPHYSIOLOGY

3.1.1.1-DEFINITION

Brain arteriovenous malformations (AVMs) are congenital abnormalities of cerebral blood vessels due to inadequate development of capillary network. Are characterized by a collection of abnormal dilated and entangled vessels denominated nidus fed by arteries and drained by veins without capillary involvement. Arterial blood flows is shunted directly into the draining veins resulting in the formation of high-flow, low-resistance conduit. Brain AVMs have a low prevalence but are an important entity that may led to spontaneous intracranial hemorrhage, due to rupture of nidal vessels, associated aneurysms or venous outflow obstruction, and others neurological symptoms, usually in young adults. (1–3).

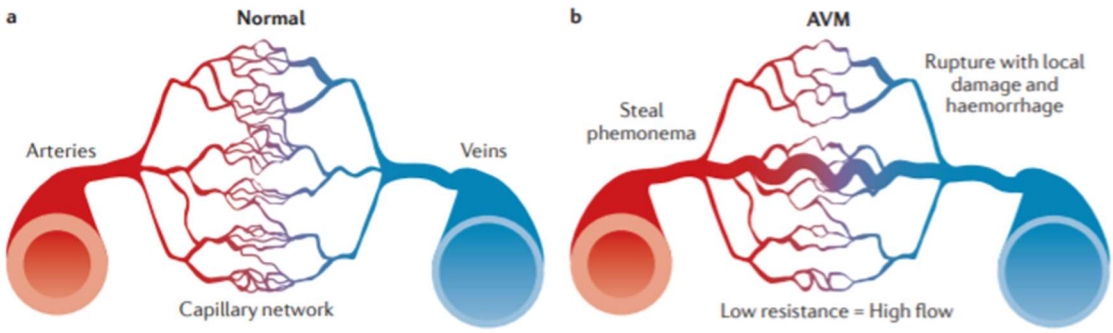

Figure 1. Schematic representation of normal vasculature and an arteriovenous malformation (AVM) extracted from (1). **(a)** Normal circumstances and **(b)** Arteriovenous malformation

3.1.1.2-NEUROPATHOLOGY

Macroscopically, AVMs vary in size from several millimeters to several centimeters in diameter. The AVM nidus, which does not contain brain parenchyma, is composed of a complex network of dilated dysplastic vessels where arteries and veins connect directly without the intervention of a capillary bed. This hemodynamic shunt may favor the formation of aneurysms in the draining venous system, due to the high flow it receives directly from the arterial system, and also within the nidus and the afferent arteries (4).

At the microscopic level the vascular tissue components of AVMs present several alterations: thickened walls with elastin and smooth muscle (hypertrophic arteries and arterialized veins), areas of unspecific fibrosis, excess of collagen type II and III, disruption of the media or interruption of the internal elastic membrane. Other alterations are intense expression of type IV collagen in the basal lamina and laminin in the internal elastic membrane, decreased expression of fibronectin and lysanin (3,4).

AVM types differ within age groups providing differences in phenotypical characteristics:

- In neonates and infants: the AVM are rare. Present as large high-flow arteriovenous fistulas that characteristically have no nidus or abnormal vascular network. The flow is very high which gives a high hemorrhagic risk (1).
- In children and young adults: different to the previous group, these have true nidal AVMs as they present abnormal vascular network (nidus) between the arterial and venous connection in addition to the arteriovenous fistula (1).
- In adults: nidal arteriovenous malformations are observed almost exclusively (1).

3.1.1.3-EPIDEMIOLOGY

Most studies report a low prevalence of AVMs in the general population, all of them agreeing that are a pathology to be taken into account because it presents an important cause of spontaneous intracranial bleeding usually in young adults.

The estimated prevalence of the AVMs has been reported to be approximately 50 cases per 100,000 persons (1). The crude annual detection rate of the AVM reported by several studies was close to is estimated at 1.31 cases per 100,000 person-year, varying between 1,12-1,42 (5–7). The detection rate for unruptured AVMs was 0,70 per 100,000 and for ruptured AVMs was 0,72 per 100,000 (5).

In recent years, improvement in neuroimaging resolution techniques to detect smaller lesions and the increasing rates of Computed Tomography (CT), Magnetic Resonance Imaging (MRI) and angiography (DSA) utilization, have led to an increase in the incidence of unruptured AVMs, while the incidence of ruptured AVMs has remained stable over time (1).

AVMs are usually found in young adults between the ages of 20 and 40 years with a mean age at diagnosis of 31.2 years. These can present in different forms: the most frequent is AVM hemorrhage which occurs in half of the patients, followed by generalized and focal seizures described in approximately 20% (30% and 10% respectively), chronic headaches in 14%, focal neurological deficits or asymptomatic in 15%. Some studies suggested that this presentation forms varies between different AVM centers (8).

The overall AVM annual hemorrhage rates range from 2-4% (9). The risk of hemorrhage in the natural history of AVMs varies according to the characteristics of the patient (age, sex, ethnicity) and of the AVM itself (nidus size, venous drainage, location, associated aneurysm, venous dilatation) and the form of initial presentation of the AVM (intracranial hemorrhage or no intracranial hemorrhage), being initial hemorrhagic presentation the strongest predictor for future hemorrhage in untreated AVM patients (10,11). For unruptured AVM, the rate of hemorrhage is low (approximately 1% per year) however, once ruptured the risk increases fivefold (1,9). Additional independent predictor factors for future bleeding in untreated AVM patients include increasing patient age (approximately 30% increase for every 10 years increase in age (9)), exclusively deep draining vein, deep localization and brain stem (1,9,11). In contrast, other factors have not been confirmed by studies as independent factors of increased risk of hemorrhage: female sex, ethnicity, infratentorial localization, associated unruptured aneurysm, venous dilatation, and nidus size (although some do).

Although there is controversy in the literature, it is considered that women do not present a higher risk of hemorrhage during pregnancy and puerperium (12).

3.1.1.4-ETIOLOGY AND PHATOGENESIS

The pathogenesis of AVMs currently remains unclear and controversial. AVMs have long been considered congenital lesions due to errors in vascular morphogenesis secondary to dysfunction of the embryonic process of capillary maturation. Another possibility is that AVMs are not congenital, but are acquired secondary to vascular lesions during the late fetal or immediate postpartum period (1,3).

During the embryological period the primitive vascular bed is converted into arteries, capillaries, and veins through the processes of vasculogenesis and angiogenesis. This process allows the formation of three types of vessels with a differentiated anatomical structure and function: on the one hand, arteries are formed by thick walls to support the high pressure flow necessary to irrigate the tissues, and on the other hand, veins are formed by thin walls and some with valves to return the low pressure blood flow to the heart. These two elements are not normally directly connected, instead are separated by a capillary network located in the tissues. An important regulator of these processes is vascular endothelial growth factor (VEGF), which is an angiogenic factor that regulates the proliferation, migration and organization of endothelial cells and the maturation of blood vessels. Its activity is mediated by VEGF receptors (VEGF1 and VEGF2) and modulated by a number of additional coreceptors that are differentially expressed in arterial and venous endothelial cells allowing their differentiation (or specialization). Arterial endothelium expresses VEGF co-receptor neuropilin 1 (NRP1) and Ephrin B2 and Notch family members, which is activated by sonic hedgehog (SHH) through VEGF stimulation, allowing arterial development. In contrast, venous endothelial development is primarily determined by chicken ovalbumin upstream promoter-transcription factor (COUP-TF2), which inhibits the expression of the arterial-specific genes NRP1 and Notch and promotes the expression of the venous marker EPH receptor

B4 (EPHB4). It is postulated that an error in this control system could lead to the formation of AVMs (13).

Most AVMs present as solitary, single or sporadic lesions, with no clear genetic basis. Because they are sporadic lesions and have a very low prevalence in relatives with AVM, screening of first-degree relatives is not recommended. Occasionally we can find individuals with multiple lesions, in these cases we should suspect the presence of a genetic syndrome of arteriovenous malformations. These include Hereditary Hemorrhagic Telangiectasias (HHT), also known as Osler-Weber-Rendu syndrome, and other syndromes such as capillary malformation-arteriovenous malformation syndrome and Sturge-Weber syndrome (1,3).

3.1.1.5-PATHOPHYSIOLOGY

The clinical consequences of AVMs are due to the direct and indirect effects of flow disturbances and rupture-associated hemorrhage. AVMs are dynamic lesions that can change over time as hemodynamic forces cause various effects: dilation of afferent arteries and sometimes development of aneurysms, dilation and thickening of the draining veins due to high flow and recruitment of additional collateral afferent vessels, resulting in dilation of the nidus dysplastic vessels (3,14).

The interaction between normal brain parenchyma and AVMs is not static, but changes over time. The surrounding brain tissue can be affected by different mechanisms:

- Cerebral gliosis: gliosis is a local response of the central nervous system in response to insult. This reaction affects the brain tissue within the cerebral interstitium of the AVM causing the formation of an irregular pseudocapsule surrounding the AVM (3).
- Vascular steal phenomenon: occurs when the blood flow around the AVM instead of being conducted to the surrounding capillary network is conducted to the low resistance short circuit of the AVM, causing 'theft' of blood flow from the adjacent brain parenchyma (1).

- Normal perfusion pressure breakthrough: this phenomenon was described by Spetzler and Wilson in 1978. They postulated that the maintained high flow of the AVM induces a chronic reactive hypotension in the adjacent cerebral parenchyma causing changes in the vascular tissue such as chronic arteriolar dilatation and loss of normal autoregulation and recruitment of leptomeningeal collateral. During the AVM resection or afferent occlusion these changes induce an increase blood flow to these altered areas, which are unable to regulate flow, causing edema and/or hemorrhage of the surgical bed and adjacent tissue. This phenomenon may occur in the late phases of resection or in the immediate postoperative period of a large volume AVM (3).

The development of aneurysms associated with AVMs (18% of patients) (15) is secondary to increased flow through the arteriovenous communication and pathological changes in the afferent arteries. These can be single or multiple and can be differentiated into two main types: flow-related aneurysms and non-flow-related aneurysms. Flow-related aneurysms represent 40-70% of cases, originate in the arteries that supplied the AVMs and are found more frequently in older patients. Their angiographic demonstration worsens the prognosis of patients with AVMs. Depending on their topography and the nidus are classified into proximal and distal, the latter may be located in the distal segments of the afferent arteries (extranidal) or within the nidus (intranidal). Flow-related aneurysms may involute after resection or obliteration of the AVM (3,14).

3.1.2-DIAGNOSIS:

3.1.2.1-CLINICAL PRESENTATION

From a clinical point of view, AVMs can present in different forms: intracranial hemorrhage (the most frequent presentation), seizures, chronic headache or focal neurological deficits (8). In a small percentage of individuals AVMs are asymptomatic lesions and therefore found incidentally (9).

3.1.2.1.1-Intracranial hemorrhage (AVM rupture):

Is the most severe and common initial presentation of AVMs, occurring in half of all cases and accounting for one-third of hemorrhagic strokes in young adults. The annual risk of hemorrhage is 2-4%, which varies according to the various risk factors previously discussed. The most important risk factor is previous AVM rupture history, which increases the risk of bleeding fivefold. AVM bleeding may be due to rupture of structures inside the nidus, aneurysms of the draining veins or saccular aneurysms of the afferent arteries. This generates intraparenchymal bleeding (more frequent), subarachnoid hemorrhage (due rupture of a saccular aneurysm on or near the Circle of Willis) and/or intraventricular hemorrhage. In general, hemorrhage due to rupture of the AVM is considered less serious than intracranial hemorrhage due to rupture of a cerebral aneurysm or spontaneous hypertensive intracranial hemorrhage (16). However, these lesions are not trivial because they can cause significant neurologic deficit, which is linked to the location of the bleeding (4,17).

3.1.2.1.2-Seizures:

Is the second most common form of presentation, with the generalized form appearing in 30% and the partial or focal form in 10%. AVMs can act as epileptogenic areas inducing epileptic seizures, which can be generalized as well as simple or complex partial seizures with or without secondary generalization. Most patients with seizures as initial presentation have the AVM at the cortical level and present superficial venous drainage. Other associated factors have been described: male sex, AVM size, location at the arterial borderline and frontal lobe AVM (18).

3.1.2.1.3-Chronical headaches:

Is a fairly common symptom appearing in some series up to 14% of cases (9), although there is controversy about the relationship between AVM and headache. They usually present in two forms: atypical migraine and cluster headache. Migraine associated with AVMs has atypical characteristics, being very localized, always affecting the same side ipsilateral to the AVM (16).

3.1.2.1.4-Focal neurological deficit

Are rare symptoms with a not well established prevalence. These deficits have been attributed to vascular steal phenomenon, which causes a reduction of blood flow in the perilesional area, or epileptic episodes. These deficits may be transient, persistent or, infrequently, progressive (16).

3.1.2.2-RADIOLOGICAL FINDINGS

Different imaging tests are used in the diagnosis of AVMs in order to perform a detailed analysis of the AVM structures (nidus, feeder artery, venous drainage) and the adjacent brain parenchyma. Generally, basic noninvasive imaging tests such as Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) are used in the initial evaluation of AVMs, followed by Computed Tomography Angiography (CTA) or Magnetic Resonance Angiography (MRA), the latter allowing differentiation of AVM from other vascular lesions. However, currently, Digital Subtraction Angiography (DSA) remains as the Gold Standard test to confirm the diagnosis and obtain the hemodynamic characteristics of AVMs (1,19).

For an adequate diagnosis and subsequent classification and grading of AVMs, radiological reports should provide the following elements:

- Size: dimensions (height x width x depth in mm) and estimation of volume in mm3 of the nidus.
- Location: infra or supratentorial, lobar (frontal, temporal, parietal or occipital), cortical (superficial) and/or deep, site of the shunt and eloquent or no eloquent area.
- Type of venous drainage: single or multiple, superficial or deep and anomaly associated with dural sinus (thrombosis, stenosis, agenesis).
- Afferent arterial system (feeder arteries): anterior, middle or posterior cerebral artery or branches of the external carotid.
- Morphologic features associated with an increased risk of future hemorrhage: initial hemorrhage presentation, associated arterial aneurysms, deep venous drainage(4).

3.1.2.2.1-Computed Tomography (CT):

CT Scan is a non-invasive, non-contrast imaging technique used in the acute evaluation of patients with symptoms suggestive of cerebral hemorrhage. This technique allows demonstration of intracranial hemorrhage and/or subarachnoid hemorrhage (SAH) with a sensitivity > 90% (2,20). One of the main limitations regarding AVM diagnosis is its poor differentiation between blood vessels and brain parenchyma (21). However, it allows the suspicion of a possible AVM in the presence of calcified or dilated vessels specially when associated with hemorrhage (2,22).

3.1.2.2.2-Magnetic Resonance Imaging (MRI):

MRI is mainly used, in contrast to CT, for the detection of AVM and not for the detection of acute hemorrhage. T1/T2 weighted MRI allows to identify the anatomical location, size and edema around the AVM (2).

In turn, this technique can detect signs of previous bleeding, such as the presence of hemosiderin deposits, using sequences blood-sensitive sequences including gradient-recalled echo, T2 weighted and susceptibility-weighted (1,2).

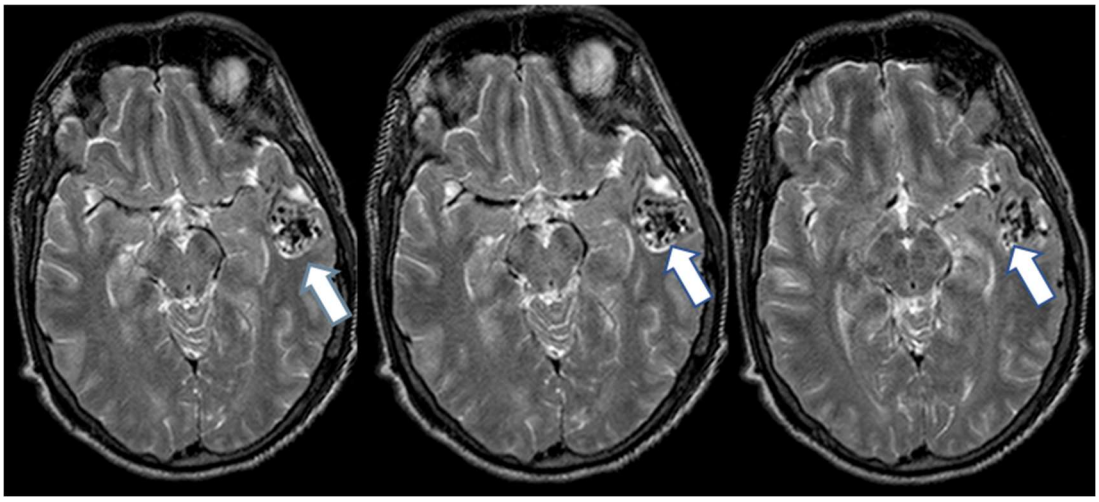

Figure 2. Axial T2-weighted Magnetic Resonance Imaging (MRI) image showing a left temporal AVM (Spetzler-martin grade III)

3.1.2.2.3-Computed Tomography Angiography (CTA) and Whole-Brain CTA and Perfusion Imaging.

CTA is performed using a timed CT acquisition after IV bolus of iodinated contrast material. It is a noninvasive technique with good spatial resolution and fast inspection speed. It is used for the initial differential diagnosis of acute spontaneous cerebral hemorrhage, allowing detection of the causative vascular malformation, with high sensitivity (83.6%-100%) and specificity (77.2-100%) (2). This technique can also identify the bleeding point of feeding artery aneurysms, intranidal aneurysms or venous drainage (1). Its limitations are due to the use of ionizing radiation and lacks temporal resolution due images are acquired in a single pass (22).

Currently, a new modality can be used for the evaluation of patients with suspected AVM, Whole-Brain CTA and Perfusion Imaging, which combines dynamic three-dimensional time-resolved CTA (4-dimensional CTA) of the brain with CT perfusion imaging of the whole brain. This technique provides excellent spatial resolution and

allows recognition of AVM properties, such as identification and differentiation between feeding arteries and normal arteries, and showing arteriovenous shunting and early venous filling (19). This technique allows us to detect altered perfusion patterns in the brain parenchyma adjacent to the AVM. There are two patterns: the arterial steal phenomenon (which can lead to focal ischemia) and venous congestion (which can lead to hemorrhage). Their detection is very important to avoid ischemic or hemorrhagic complications during AVM treatment (19). Although this technique is one of the best for the evaluation of AVMs, it is still inferior to angiographic catheterization (DSA), especially in complex lesions (22).

3.1.2.2.4-Magnetic Resonance Angiography (MRA):

MRA is a noninvasive technique that is based on separation of the arterial, capillary and venous phases of contrast passage. This technique can identify the nidus, size, localization, diffuseness, hemorrhage, feeding arteries and draining veins of the AVM during the arterial phase. Advantage over CTA are avoidance of radiation exposure and use of iodinated contrast material. Some limitations are incompatibility with some devices, as pacemakers, and not being able to be used in acute situations (2,19).

3.1.2.2.5-Digital Subtraction Angiography (DSA)

DSA remains the gold standard for diagnosis AVMs and provides detailed information of the angio-architectures and hemodynamics features. Once an AVMs is identified or suspected by CT or MRI, DSA is generally pursued to further characterize the lesion if treatment is being considered (23). This invasive technique consists in the insertion of a catheter into the femoral or radial artery and guiding it back through the arterial circulation to the cerebral arteries. Precontrast x-ray image are taken and then contrast dye is injected from the catheter into the cerebral artery in which it is positioned taken more image (21).

This technique is specifically designed for the detailed analysis of feeding arteries, necessary for the consideration of endovascular treatment, and to identify the presence of flow-related aneurysms. In addition, angiography provides detailed information of the arterial supply, nidus and venous drainage of an AVMs and the hemodynamic factors, such as the degree of arteriovenous shunt. All of this element are best assessed by DSA compared with noninvasive techniques (1,19).

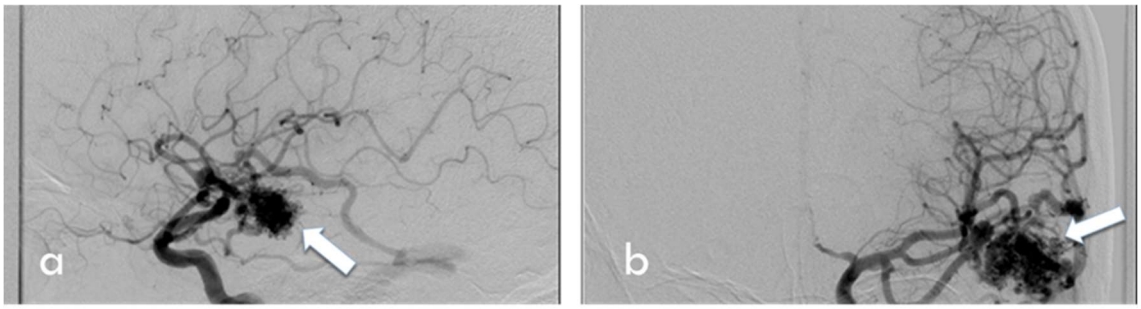

Figure 3. Digital Subtraction Angiography (DSA) shows diagnosis of an AVM (arrow) in left temporal lobe, seen in anterior-posterior **(a)** and lateral **(b)** views

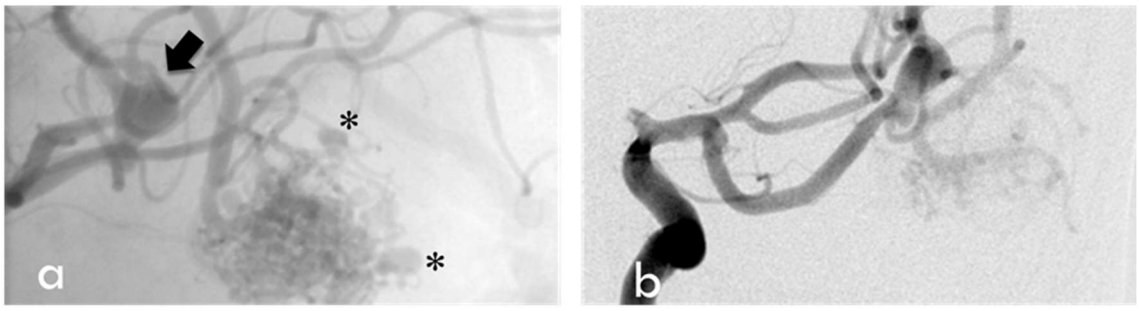

Figure 4. Detailed Digital Subtraction Angiography (DSA) image shows diagnosis of flow-related aneurysm prenidal (arrow) and intranidals aneurysm (asterisks), seen in anterior-posterior **(a)** and lateral **(b)** views

3.1.3-GRADING AND CLASSIFICATION

In order to avoid surgical complications and worse neurological outcomes after AVM microsurgery, and to assess the surgical prognosis, different AVM grading systems have been developed.

The grading systems are important tools used to stratify the surgical risk of the patient (morbidity and mortality) allowing the correct selection of the treatment in each case (1,3,24).

3.1.3.1-SPETZLER-MARTIN (SM) GRADING SCALE

Proposed by Robert F. Spetzler and Neil Martin in 1986, originally designed to predict the outcome of microsurgical treatment of AVMs. It is the most widely used grading scale at present due to its simplicity and high reproducibility. This scale is based on three anatomical factors: size of the nidus (cm), location of the nidus (whether or not it affects the eloquent area) and type of venous drainage. These three factors are determined by angiography, CT and/or MRI (1,24,25).

The size (S) of the AVM is determined by calculating the largest diameter of the nidus on angiography. This can be small (less than 3 cm), medium (3 to 6 cm) or large (more than 6 cm). This is related to the technical difficulty of resecting the AVM, the larger the more complicated. The venous drainage pattern (V), also determined by angiography, is considered superficial if all AVM drains are through the cortical venous system and deep if any or all drains are through deep veins (such as internal cerebral veins, basal veins, or precentral cerebellar veins). The drainage pattern is related to surgical accessibility to the AVM, being more complicated in deep drainage. The following areas are considered eloquent (E) on the scale: sensorimotor cortex, visual cortex, internal capsule, thalamus and hypothalamus, brain stem, cerebellar nuclei. During resection of AVMs adjacent to eloquent areas there is a high risk of neurological dysfunction not present in those located in non-eloquent areas (24).

The AVM score varies from 1 to 5 points with the following scoring system: nidus size (< 3 cm = 1 point, 3-6 cm =2 points; and > 6 cm = 3 points), nidus location (no eloquent = 0 points, eloquent = 1 point) and venous drainage pattern (superficial only = 0 points, deep = 1 point). As a result of the sum of the different categories (S + E + V) the AVM grade is obtained. There are 5 grades of AVM which are directly related to the incidence of complications and postoperative mortality.

Low grades (grade I-III) have acceptable low morbidity rates and high grades (grade IV-V) have unacceptably high morbidity and mortality rates, in which surgery should not be considered (23,24). Spetzler recommended dividing AVMs into 3 categories for individualized diagnosis and treatment. Type A (grade I-II) recommends microsurgery, type B (grade III) recommends multimodal treatment and type C (grade IV-V) recommends conservative treatment with follow-up angiography, reserving surgical treatment for special cases such as recurrent bleeding or worsening neurological deficits (2).

Table 1. Spetzler-martin (SM) Grading Scale extracted from (24)

Spetzler-martin (SM) Grading Scale*		
Variable	**Parameter**	**Points**
Size (S)	<3 cm	1
	3-6 cm	2
	>6 cm	3
Eloquence (E)	No	0
	Yes (located in sensorimotor cortex, language areas, visual cortex, hypothalamus, internal capsule, brain stem, cerebellar peduncle or deep cerebellar nuclei)	1
Venous drainage (V)	Superficial drainage	0
	Deep drainage	1
SM Total grade = S + E + V (Total score = 5) *SM grade, Spetzler-Martin grade		

3.1.3.2-SUPPLEMENTED SPETZLER-MARTIN (SM-SUPP.) OR LAWTON-YOUNG GRADING SYSTEM

This grading scale was proposed to improve the predictive ability of the SM grading scale in microsurgical outcomes.

It is based on other important factors for surgical patient selection not found in the SM scale, which are patient age (< 20 years old = 1 point; 20-40 years old = 2 points, > 40 years old = 3 points), hemorrhagic presentation (yes = 0 point, no = 1 point) and compactness (yes = 0 point, no =1 point) (2,25).

The hemorrhagic presentation implies on the one hand an increased risk of AVM rebleeding and on the other hand facilitates surgery. The latter because the hematoma separates the AVM from the brain tissue creating a working space when it is evacuated. Compact AVMs with tightly woven arteries and veins have distinct borders clearly separated from normal brain tissue. In contrast, diffuse AVMs have ragged borders and intermixed brain tissue, which makes surgical resection difficult. Diffuseness is qualitatively determined by angiography. Patients are grouped into 3 age categories. The group < 20 years, which includes pediatric patients, presented better surgical tolerance, better recovery and neuronal plasticity than the adult groups. The adults were divided into 2 groups: < 40 years, those without comorbidities, and > 40 years, those with comorbidities (25).

This grading system supplements rather than replaces the traditional SM grading scale. The sum of SM grading scale and Lawton-Young grading scale is a better predictor of neurological outcomes (1,25).

Table 2. Lawton-Young grading system extracted from (1,25)

SM-SUPP OR LAWTON-YOUNG GRADING SYSTEM*		
Variable	**Parameter**	**Points**
Age	< 20 years	1
	20-40 years	2
	> 40 years	3
Hemorrhage presentation	Yes	0
	No	1
Compactness	Yes	0
	No	1
SM-Supp Total Grade = Age + Hemorrhage presentation + Compactness (Total Score = 5) *SM-Supp, Supplemented Spetzler-Martin		

3.1.4-TREATMENT MODALITIES

The goal of AVM treatment is to eliminate the risk of hemorrhage by complete obliteration of the nidus and arteriovenous shunt. When located in eloquent areas, a second goal is added, protection of neurological functions (preservation of function). Patients with AVMs can be managed in two ways: conservative treatment and invasive treatment (2,23).

3.1.4.1-CONSERVATIVE TREATMENT:

This type of management is reserved for special situations in which there is a high surgical risk due to the characteristics of the AVM (large size, location in critical places) and the patient (advanced age, unruptured AVM) (2).

At present we do not have any drug capable of obliterating AVMs or reducing the risk of bleeding, but we do have medication to control some of the clinical presentations of AVMs, such as epilepsy and headaches. In patients with epilepsy associated with AVMs, antiepileptic drugs are used as the first option for seizure treatment, with invasive treatment being used in the case of epilepsies refractory to anticonvulsant treatment. In patients with headache, preventive or acute symptomatic treatment can be used (1,2).

3.1.4.2-INVASIVE TREATMENT:

Invasive treatment includes three therapeutic tools, microsurgical resection, endovascular embolization and stereotactic radiosurgery, which can be used alone or combined. Microsurgical resection can be performed primarily or after endovascular embolization to reduce the risk of hemorrhage and facilitate complete resection.

Endovascular embolization is frequently used as a precursor to other treatments, such as surgery or radiosurgery. This is because complete obliteration is rarely obtained when used alone. Stereotactic radiosurgery, like microsurgery, can be performed primarily or after embolization. It is usually reserved for small lesions and those located in deep or eloquent regions of the brain. Finally, there is multimodal treatment, which combines several types of strategies for the treatment of complex AVMs (2,23).

3.1.4.2.1-Microsurgery

Microsurgical resection is the most common approach to achieve the complete obliteration of AVMs. Compared to the other therapeutic techniques, it has the highest rate of complete obliteration of AVMs, which means immediate elimination of morbidity and mortality associated with bleeding risk.

From a surgical point of view, AVMs can be resected following steps (1):

- Exposure: the intervention begins with the performance of a craniotomy to obtain adequate exposure to the AVM.
- Subarachnoid dissection: includes the study of the AVM under the microscope, the opening and deconstruction of the arachnoid membranes and the trabecular interlobular disconnection and the intercommunicating cisternal compartments.
- Defining the draining vein: the efferent veins must be preserved until the end of the intervention to avoid the hemorrhage of the AVM.
- Defining the feeding arteries: This phase consists of occlusion of the feeding arteries, which should be as close to the AVM as possible to avoid occlusion of normal arterial branches, which would lead to ischemia and subsequent infarction of adjacent brain areas.
- Parenchymal dissection: This phase corresponds two thirds of the circumdissection. In this phase the AVM is separated from the normal brain tissue. In compact AVMs this separation phase is simpler as they have distinct borders, however, in diffuse AVMs that, have indistinct margins with the brain parenchyma, this phase is very complicated.

- Resection

As previously mentioned, it is recommended to use the SM grading scales and the supplementary scale for preoperative assessment of surgical risk and possible neurological outcomes.

There are a number of tools that allow adequate patient selection and improve the safety and efficacy of AVM surgery. Functional MRI (fMRI) and Diffusion Tensor Imaging (DTI) allow to determine the proximity of the AVM to eloquent areas and white matter tracts, information used to minimize the risk of post-surgical neurological defects. Neuronavigation uses special quantitative images fused from the patient's pre-operative CT and MRI with a coordinated fiducial system, used as a real-time guide to localize the AVM and adjacent tissue. Preoperative endovascular embolization used to occlude feeder arteries, reduce nidus volume and treat high-risk angiographic features, such as an associated aneurysm, diminishes the surgical risk and operation time and facilitates surgical resection. Intra-operative imaging, such as DSA, indocyanine green videoangiography, and fluorescein videoangiography, used to verify complete obliteration of the AVM, i.e. to rule out the presence of residues, prevent from leaving AVM remnants and therefore avoid further procedures or surgical reinterventions (23).

3.1.4.2.2-Endovascular embolization

Endovascular treatment consists in the occlusion of the blood flow of the nidus and/or feeder arteries by means of embolic agents introduced through a microcatheter. The embolic agents can be divided into two types: solid agents (consisting of polyvinyl alcohol (PVA) particles, fibers, coils and balloons) and liquid agents (consisting of cyanoacrylate monomers such as N-butyl cyanoacrylate (NBCA) and polymeric precipitates in solution, such as ethylene co-vinyl alcohol). The main agents currently used for the treatment of AVMs are NBCA and Onyx. Endovascular treatment can be employed for three possible purposes: preoperative, palliative and curative (2,26).

Preoperative embolization is the main form of application of endovascular treatment of AVMs. This strategy is used to facilitate surgical resection by: reducing the risk of bleeding, occluding the main artery and decreasing the volume of the nidus, eliminating deep perforators that are inaccessible for surgeries, and embolizing associated aneurysms (2,23). Palliative embolization can be used in cases in which the AVM produces focal neurological defects or seizures through the steal phenomena or local venous hypertension, although there is no evidence that supports this indication (23). Curative embolization is only obtained in a very small group of individuals. Complete obliteration is very difficult when used in monotherapy, occurring in 20% of patients (1). It may be useful in small AVMs (< 3 cm) and superficial location with a single feeding artery (1,2).

The two most frequent complications of embolization are intracranial hemorrhage and ischemic stroke. Cerebral hemorrhage may be due to vessel injury or AVM rupture secondary to closure of the venous vein prior to complete removal of the nidus (23).

3.1.4.2.3-Stereotactic Radiosurgery (SRS)

SRS involve the precise image guided delivery of a radiation dose to a defined target. In SRS the objective remains the same, the complete obliteration of the AVM. SRS leads to endothelial cell proliferation, progressive, concentric vessel wall thickening, and eventually luminal closure. The main disadvantage of this tool is the latency period between intervention and obliteration, which differs from 6 months to several years. During this latency period, patients remained the risk of hemorrhage similar to the natural history risk of AVM (annual risk of post-SRS hemorrhage is 1-3%) (1,2,23). Most series demonstrate obliteration in 70% to 80% of AVM post-SRS (23).

SRS would be indicated in those patients who present with small size (< 3 cm) AVM in deep eloquent areas, including those located in critical areas such as the basal ganglia, thalamus, corpus callosum, cerebellum and brainstem (2).

The main drawbacks of SRS are latency period, previously commented, and adjacent tissue damage. Injury to adjacent brain tissue can cause new neurological deficits.

This is caused by the adverse effect of radiation that induces inflammation of the parenchyma and hemodynamic changes (1).

3.1.4.2.4-Multimodality treatment

Multimodality treatment included different combination of monotherapy tools (microsurgery, embolization and radiosurgery). Most of the time they are used in cases of high-grade AVM, which cure is difficult to obtain through monotherapy or is not indicated. It can also be indicated in low-grade AVM with the aim of minimizing surgical risks and protecting neurological functions (2).

3.1.4.3-FOLLOW-UP AFTER TREATMENT

The follow-up after treatment depends on the approach taken. In all cases it should include clinical evaluation and neuroimaging tests, such as subjective and objective neurological evaluation. In microsurgery cases, intra- or postoperative angiography should be performed to evaluate and confirm complete obliteration of the AVM nidus. In case of finding residues of the nidus, it is possible to reoperate or use other strategies (2).

In cases of radiosurgery and embolization, follow-up neuroimaging should be performed. In SRS an MRI/MRA is usually performed every 6 months during the latency period. If MRI is contraindicated, CT/CTA can be performed. When obliteration is suspected after the latency period, confirmation with DSA is mandatory. In cases of embolization, follow-up is performed by MRI/MRA (23).

3.2-ANATOMY OF ELOQUENT AREAS

Eloquent areas are brain regions that have a specific neurological function attributed to them and that are essential in people's daily life activities. The most common areas of eloquent cortex are in the left temporal lobe and frontal lobes for speech and language, bilateral occipital lobes for vision, bilateral parietal lobes for sensation, and bilateral motor cortex for movement. Therefore, if damaged the result will be a permanent neurological deficit (loss of sensory processing or linguistic ability, visual field impairment or motor paralysis).

Currently neuroradiological imaging techniques allow the functional and anatomical localization of the eloquent areas through the use of: preoperative functional tests, such as functional Magnetic Resonance Imaging (fMRI), Diffusion Tensor Imaging (DTI), transcranial magnetic stimulation (TMS), magnetic resonance imaging (MRI), magnetoencephalography (MEG) and positron emission tomography (PET), and intraoperative functional tests (intraoperative brain mapping), such as electrocortical stimulation (ECS). To localize these areas with functional tests, different mechanisms are used to activate a specific eloquent area by directly stimulating the area, as in the case of the visual, auditory and sensory areas, or the area is stimulated by asking the patient to perform specific tasks during the test, such as motor tasks (mobilization of a part of the body), expressive tasks (language) and cognitive tasks (memory, calculation) (27).

These tests allow a specific and personalized evaluation of the eloquent functions in the study of lesions located in these areas, performing a specific evaluation depending on where the lesion is located.

3.2.1-SENSORIMOTOR BRAIN AREAS

- Primary motor cortex (Brodmann's Area (BA) 4): is in the precentral gyrus of the frontal lobe. Its function is to stimulate the muscles to produce the motor action.

- Supplementary motor cortex (medial part of BA 6): is in the medial aspect of the frontal lobe. Its main function is motor planning or programming and bimanual coordination.
- Premotor cortex: located on the lateral side of the frontal lobe. It is related to executive functions associated with cognitive processes, such as the use of memory, decision making, planning and selection of objectives and problem solving.
- Primary somatosensory cortex (BA 1-3): located in the postcentral gyrus of parietal lobe, where their cortical areas reflect specific regions of the body organized in the form of the somatosensory homunculus (homunculus Penfield).
- Corticospinal tract (CST) is the most important fiber tract related to motor function that allows the control of voluntary muscle movements, which consist of axons of pyramidal neurons (Betz cells) of the motor cortex and other cortical regions that connects with the lower motor neurons of the anterior horn of the spinal cord (2).

3.2.2-LANGUAGE RELATED BRAIN AREAS

- Broca area: It is in the frontal lobe in the pars opercularis and triangularis (BA 44 and 45, respectively) in the posterior inferior frontal gyrus of the dominant hemisphere. It is responsible for programming and executing motor activity related to the expression of words and short sentences and is involved in speech production and comprehension. It is linked to the center of language comprehension, Wernicke's area (28).
- Wernicke area: is traditionally located in the posterior third of the superior temporal gyrus (STG) of the dominant hemisphere (correspond to BA 22 while there is no uniform definition of the specific range). It is primarily responsible for the identification and understanding of language. In recent years functional neuroimaging converge on the conclusion that Wernicke’s area is also involved in speech production (29).

- Geschwind area: is located in the supramarginal gyrus and angular gyrus (BA 39 and 40) of the inferior parietal lobe of the dominant hemisphere. It is involved in multiple speech functions such as phonetic judgement, speech understanding and reading (2).
- Cerebellum: is involved in executive control of world generation.
- The subcortical fiber bundle language-related can be divided in two: Dorsal pathway and ventral pathway. Dorsal pathways: consist of arcuate fasciculus and the superior longitudinal fasciculus connecting the superior temporal lobe and the premotor cortices in the frontal lobe. Ventral pathway: includes the inferior fronto-occipital fasciculus, inferior longitudinal fasciculus and the uncinate fasciculus connecting middle temporal lobe and the ventrolateral prefrontal cortex. Is suggested that the dorsal pathway is involved in the processing of phonetic functions and the ventral pathway in the linguistic processing of sound (30).

3.2.3-COGNITION RELATED BRAIN AREA

The main brain structure related to cognition is the so-called "hippocampal region" which is part of the limbic system. It is responsible for cognition, short-term and long-term memory, spatial positioning and is also involved in decision-making. Besides this structure, other brain structures are also involved in cognitive functions: the ventromedial prefrontal cortex, the amygdala, the right somatosensory cortex and the insula (2).

3.2.4-VISION RELATED BRAIN AREA

They are formed by different brain structures including cortical areas and cerebral pathways located around the calcarine fissure of the occipital lobe. The visual cortex consists of the primary visual cortex (striate cortex) and extrastriate cortex, which correspond respectively to BA 17 and 18-19.

The primary visual cortex is the first cortical area that receives visual information and performs the first processing of visual information. Within the optic pathways stand out the Optic radiation, that connects lateral geniculate body and the striate cortex (2).

3.2.5-OTHER ELOQUENT RELATED BRAIN AREAS

3.2.5.1-BASAL GANGLIA

They are located at the base of the cerebral hemispheres and consist of the striatum (caudate and putamen), globus pallidus, subthalamic nucleus and substantia nigra. Their function consists, together with other areas (thalamus, cerebellum and cortex), the voluntary control of movements, cognition and emotion learning.

3.2.5.2-THALAMUS

It is located in the middle of the brain, within the diencephalon. Together with the cerebral cortex, it is responsible for the analysis and integration of motor and sensory information (except smell), and it is also involved in higher functions (attention, language, memory and executive function) (31).

3.2.5.3-HYPOTHALAMUS

It is located below the thalamus in the diencephalon and is composed of several nuclei (the supraoptic, the paraventricular, and the tuberal nuclei). These nuclei release different hormones that act as regulators of the endocrine system through the hypothalamic-pituitary axis. Its function is to regulate different functions: body temperature, heart rate, thirst, hunger, sleep cycles and blood pressure.

3.2.5.4-BRAIN STEM

It is a very important structure within the nervous system located in an area limited posteriorly by the cerebellum, superiorly by the brain and in its lower part by the spinal cord. It is an information passage zone that conducts information between the body and brain and cerebellum and vice versa, and has functions related to the control of the cardiorespiratory system, pain sensibility control and the state of consciousness and attention (2).

3.2.5.5-CEREBELLAR PEDUNCLES

These structures communicate the midbrain, cerebellum, and brain. They act as mediators of visual and auditory reflexes.

3.2.5.6-INTERNAL CAPSULE (IC)

IC is a white matter structure located in the inferomedial portion of each cerebral hemisphere which run between the caudate nucleus, thalamus and the lenticular nucleus. IC is composed of ascending and descending fibers tracts that connect the cerebral hemispheres with subcortical structures, the brainstem, and the spinal cord. The internal capsule can subdivide into the anterior limb, genu, posterior limb, retrolenticular segment, and sublenticular segment.

Two very important nerve fiber tracts converge in it: the corticospinal tract and the corticobulbar tract, which are responsible for controlling the voluntary movement of the body. Through the corticospinal tract run the nerve bundles that control fine movements. The corticobulbar tract carries the fibers responsible for mobilizing the muscles of the head and neck and is responsible for facial expression or mouth movements and swallowing.

3.2.5.7-DEEP CEREBELLAR NUCLEI

It consists of 4 pairs of nuclei, the fastigial, globose, emboliform, and dentate nuclei, located within the deep white matter of each cerebellar hemisphere. They are involved in the coordination and precision of limb movements (2).

3.2.6-BRAIN CONNECTOME

In recent years, new imaging techniques have been developed to map the different intraneuronal connections in the brain. The brain connectome is formed by complex brain networks that allow the interaction of several functional areas to perform specific functions. For the reconstruction of these neural networks are used: Diffusion Tensor Imaging (DTI), which allows the examination of the axonal connections of the white matter throughout the brain, and Diffusion Spectrum Imaging (DSI), which allows to define the direction of the connections (32).

3.3-AVMs IN ELOQUENT AREAS

In 1986 Robert F. Spetzler and Neil A. Martin proposed a grading system designed to predict the risk of surgical morbidity and mortality depending on three characteristics of the AVM: size, venous drainage pattern, and location in eloquent or non-eloquent area. They defined eloquent areas as those regions that are attributed to a neurological function and, if injured, resulting in neurological disability. AVMs in these areas have a higher surgical risk than non-eloquent AVMs, due to the risk of injury with subsequent neurological deficit and have classically been approached with less-invasive treatment options, either conservatively or with radiosurgery (24).

In the AVM grading system, they considered as neurological eloquent areas (*see in FIGURE 5*):

- Deep eloquent areas: hypothalamus, thalamus, internal capsule, brain stem, cerebellar peduncles and deep cerebellar nuclei.
- Cortical eloquent areas: cortical sensorimotor areas, language areas and primary visual areas.

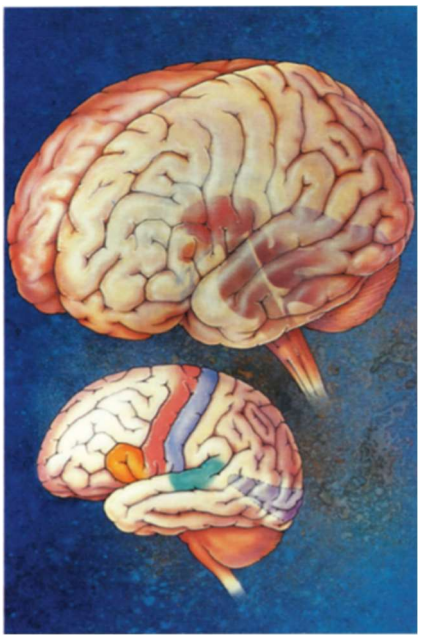

Figure 5. The anatomical areas considered neurological eloquent extracted from (24). The deep eloquent areas are highlighted in the upper image. The cortical eloquent areas are identified on the lower image.

4. JUSTIFICATION

Brain arteriovenous malformations (AVMs) are congenital vascular lesions characterized by an alteration in the communication between cerebral arteries and veins in which the intervening capillary bed disappears. It is an entity with low prevalence in the general population that mainly affects young adults, generally presenting as an intracranial hemorrhage, being responsible for 38% of cerebral hemorrhages in patients between 15 and 45 years of age (33). The annual risk of bleeding is 2-4% in unruptured AVMs (9) with a mortality secondary to rupture of 1%, which increases to 6-10% in the first year, increasing with repeat bleeds to 20% (34).

Currently there are different strategies regarding the possibilities of treating this type of malformation: microsurgical resection, embolization and radiosurgery, or merely its observation (conservative treatment). These treatments can be carried out individually or in combination. All of them are subject to some controversy, because the treatment, regardless of its modality, is not without risk (33). The therapeutic decision in a patient with an AVM must take into account both its natural history (whether or not it ruptures) and the risk/benefit ratio of the intervention itself, highlighting whether or not it affects the eloquent areas, due to the potential risk of severe neurological deficits. Hence, the surgical treatment of AVMs located in eloquent areas, such as language and the motor cortex, is controversial and they are frequently considered as unresectable lesions.

Surgery in these regions is therefore challenging and carries a significant risk of new neurological deficits in the postoperative period, which is more noticeable in patients who present before the operation with unruptured AVMs and minimal neurological deficits or nonexistent (27). In general, AVMs located in these areas have classically been approached with less invasive treatment options, either conservatively (follow-up) or with radiosurgery (27). When actively treating these lesions, both surgically and with radiosurgery, the preservation of neurological function has to be a primary goal.

The surgical approach to lesions in eloquent areas, both intrinsic (gliomas) and extrinsic (metastases, cavernomas), despite the controversy that it entails due to the risk posed by surgery in these locations, is widely described and the Bellvitge Hospital

Neurosurgery Department has extensive experience in the management of these lesions through an individualized approach focused on the identification and preservation of neurological function at risk. Through techniques such as intraoperative neurophysiological monitoring (IONM), neuronavigation or brain mapping, the treatment of lesions in eloquent areas has become possible and increasingly safe. However, in the case of AVMs, the usefulness of intraoperative brain electrical stimulation techniques and functional intraoperative navigation applied to surgical management and treatment in eloquent areas is not as well defined and their use is not widespread. Only neurosurgical teams that master both functional approaches and vascular microsurgery in AVMs perform this type of treatment.

In order to evaluate the therapeutic outcomes and postsurgical sequelae of patients with AVMs located in eloquent areas, we have reviewed the location, drainage type and size of the AVM, the type of treatment and the clinical evolution in a consecutive series of 25 patients undergoing surgery for an eloquent AVM at the Neurosurgery Department of the Bellvitge University Hospital.

This study aims to describe the clinical and therapeutic outcomes after the application of an individualized functional approach in patients operated at Bellvitge Hospital with AVMs located in eloquent supratentorial areas of the brain. We argue that the preoperative functional evaluation and tailored functional approach for each AVMs sited in eloquent area can increase the possibility of treatment while obtaining a good clinical and neurological outcome (preservation of eloquence).

5. HYPOTHESIS

We hypothesize that the use of a tailored functional approach for the management and treatment of AVMs in supratentorial eloquent areas (individualized pre-surgical functional assessment and intraoperative functional monitoring appropriate to the neurological function at risk), allows complete surgical resection in most cases (> 70 %) and a cure rate > 90%, including cases in which surgery does not achieve complete resection but is reached in combination with other techniques (embolization and/or radiosurgery), while obtaining a good clinical result (mRS ≤ 2) and a correct preservation of neurological function (< 25% patients with neurological deficit) at 6 months follow-up.

6. OBJECTIVES

The aim of the study is to describe the outcomes of the application of the functional and individualized protocol of the Bellvitge University Hospital Neurosurgery Department for the treatment of arteriovenous malformations located in eloquent areas of the brain, and to examine the usefulness of functional assessment (pre- and intraoperative) and the multidisciplinary approach in AVMs located in these areas.

7. METHODOLOGY

7.1-STUDY DESIGN

To describe the collected data a case series study has been designed.

7.2-STUDY SUBJECTS

The clinical records of the Bellvitge University Hospital (SAP) from 2005 to 2021 were retrospectively reviewed for eloquent AVMs treated surgically, with or without a combination of other treatment modalities. AVMs were considered eloquent when located ≤ 10 mm from an eloquent area on functional Magnetic Resonance Imaging (fMRI).

7.2.1-INCLUSION CRITERIA

This study includes all data from the mentioned registry, but not all patients were included in the registry. The inclusion criteria were:

- Patients harboring supratentorial AVMs ≤ 10 mm to a functional area:
    - Evaluated by fMRI and/or TMS and DTI
    - Concordance with anatomical areas shown in MRI and angiography
- In case of AVMs in language areas (requiring language mapping) patients only included if in each spoken language they obtain:
    - Pre-surgical neuropsychological language testing with > 90% language proficiency

7.2.2-EXCLUSION CRITERIA

Patients with AVMs not located in the eloquent areas, > 10 mm of any eloquent area or infratentorial location.

In case of AVMs in language areas, patients with < 90% language proficiency in the pre-surgical evaluation will be excluded.

7.3-SAMPLE

A consecutive sampling method was performed for our study population resulting in a total of 25 patients with AVM in eloquent areas meeting the inclusion criteria who were managed in the Neurosurgery Department of Bellvitge University Hospital during 2005 and 2021.

The study is limited to AVM cases in eloquent areas that meet the inclusion criteria. A total of 25 patient were included in our series. All data used in our study was retrospectively collected from patient medical records, surgical reports, and review of available imaging studies. Patient's data was appropriately anonymized at the early stage of study for further analysis.

7.4-STUDY VARIABLES

All the data used in our study was retrospectively collected from patient's medical records, surgical reports, and review of available imaging studies. Patient's data was appropriately anonymized at the early stage of study for further analysis. The fundamental variables that were included in the created database, area gathered in this table below (*see in TABLE 3*).

Table 3. Variables included in database

VARIABLES INCLUDED IN DATABASE*			
Name of the variable	**Definition**	**Level of measurement**	**Operating level**
Gender (Sex)	Phenotypic sexual characteristics of the patient, recorded in the medical record	Qualitative nominal	-M: Male -F: Female
Age at surgery	Age in years at the time of surgery	Quantitative continuous	
Toxic habits	Whether they consumed alcohol and/or tobacco prior to surgery, recorded in the medical record	Qualitative nominal	-Yes: Alcohol and/or tabaco consume -No: No alcohol and tabaco consume
Preop antiepileptic drugs (AEDs)	Pharmacological treatment received for the control of epileptic seizures prior to surgery, recorded in the medical record	Qualitative nominal	-Yes: 1 or more AEDs -No: No AEDs
Presentation	Main clinical presentation at AVM debut, recorded in the medical record	Qualitative nominal	-Cerebral hemorrhage: Rupture of AVM -Seizures: Simple or complex partial or generalized epileptic seizures -Headache: Headache of atypical characteristics -Progressive Neurological deficits: Due to the phenomenon of arterial theft
Modified Ranking Scale (mRS) Preop	The degree of disability or dependence in the activities of daily living	Qualitative Ordinal	-0: No symptoms at all -1: No significant disability despite

	measured by the modified Ranking Scale (mRS) assessed prior to surgery, recorded in the medical record.		symptoms, able to carry out all usual duties and activities -2: Slight disability: unable to perform all previous activities but able to look after own affairs without assistance -3: Moderate disability: requiring some help but able to walk without assistance -4: Moderately severe disability: unable to walk without assistance and unable to attend to own bodily needs without assistance -5: Severe disability: bedridden, incontinent and requiring constant nursing care and attention -6: Death
Location	Location of bAVMs performed by angiography (DSA), CT or/and MRI.	Qualitative Nominal	-L: Left Hemisphere -R: Right Hemisphere -Frontal -Parietal -Temporal -Occipital -Basal ganglia -Fronto-parietal -Parieto-temporal
Largest size (mm)	Nidus largest size obtained by DSA in mm	Quantitative Continuous	Numeric with decimals
Spetzler-Martin (SM) grade	Grading system that predicts the risk of surgical morbidity and mortality depending on three anatomical	Quantitative Continuous	-S1 (1 point): < 3cm -S2 (2 points): 3-6cm -S3 (3 points): >6 cm -V0 (0 points): Superficial drainage

	characteristics of the AVM: -Size (S): largest diameter of the nidus by DSA in cm -Venous drainage pattern (V): determined by DSA, is considered superficial if all AVM drains are through the cortical venous system and deep if any or all drains are through deep veins -Eloquent (E): if the nidus is located in the eloquent areas: sensorimotor cortex, language areas, visual cortex, hypothalamus, internal capsule, brain stem, cerebellar peduncle or deep cerebellar nuclei		-V1 (1 point): Deep drainage -E0 (0 points): No eloquent area -E1(1 point): Eloquent area SM grade is result of the sum of these factors (S+V+E)
Preop functional test	Type of functional tests perform in the presurgical evaluation	Qualitative Nominal	-fMRI: Functional Magnetic Resonance Imaging -DTI: Diffusion tensor imaging -TMS: Transcranial Magnetic Stimulation -NPE: Neuropsychological Evaluation -Navegator: Neuronavigation
Functional Approach	Type of function assessed during surgery using intraoperative functional brain mapping techniques, reported in the medical report	Qualitative Nominal	-Motor: Motor function -Sensitive: Sensory function -Language: Language function -Visual: Visual function
Function Identified	Brain function detected during intraoperative	Qualitative Nominal	-Yes: Function identified -No: Function non identified

	brain mapping, recorded in the medical record		
Awake/Asleep Monitoring	Type of intraoperative brain mapping technique performed during surgery, recorded in the medical record	Qualitative Nominal	-Awake: Awake monitoring with partial anesthesia -Asleep: Asleep monitoring with general anesthesia
AVM resection	Result of surgery confirmed by postoperative DSA	Qualitative Nominal	-Complete resection: Disconnected afferents arteries and complete resection of the AVM -Partial resection: Disconnected afferent arteries and resection of part of the AVM -Circumdissection: Disconnected afferent arteries without AVM resection
Combined treatment	Type of treatment performed: unimodal treatment or combined treatment. -Unimodal treatment with surgery only. -Combined treatment includes the following options: -Preop embolization + surgery -Preop embolization + surgery + radiosurgery -Surgery + radiosurgery	Qualitative Nominal	-Yes: Combined treatment performed -No: Only surgery
Number of embolization	Total number of endovascular embolization that had been performed during treatment, reported in the medical report	Quantitative Continuous	

Complication	Postoperative complications secondary to surgery	Qualitative Nominal	-No: No complication -Surgical wound infection: Caused by the same bacteria (Enterobacter cloacae) due to an epidemic outbreak of this pathogen in hospital surgical area -Hematoma -Perilesional bleeding
Neurological Symptoms (Postop and 6 months)	Presence of neurological deficit assessed in the immediate postoperative period and at 6 months follow-up, reported in the medical report	Qualitative Nominal	-NNS: No neurological symptoms -NA: No available -Language disorders -Motor deficit -Sensitive deficit
Modified Ranking Scale (mRS) Postop, 6 months and 12 months	The degree of disability or dependence in the activities of daily living measured by the modified Ranking Scale (mRS) assessed in immediate postoperative period, at 6 months and 12 months follow-up, reported in the medical report	Qualitative Ordinal	-NA: No available -0: No symptoms at all -1: No significant disability despite symptoms, able to carry out all usual duties and activities -2: Slight disability: unable to perform all previous activities but able to look after own affairs without assistance -3: Moderate disability: requiring some help but able to walk without assistance -4: Moderately severe disability: unable to walk without assistance and unable to attend to own bodily needs without assistance -5: Severe disability: bedridden, incontinent and requiring constant

			nursing care and attention -6: Death
Seizures Intraop, Postop and 6 months	Presence of epileptic seizures during surgery (Intraoperative), in the immediate postoperative period and at 6 months follow-up, reported in the medical report	Qualitative nominal	-NA: No available -Yes: Presence of epileptic seizures -No: No presence of epileptic seizures
Cured	If the AVM was completely resected after surgery in case of complete resection or in case of incomplete resection (partial resection or circumdissection) total obliteration at the end of the combined treatment, confirmed by DSA	Qualitative nominal	-Yes: Final total obliteration (Cured) -No: No final total obliteration (No cured)
Antiepileptic drugs (AEDs) removal	If antiepileptic drugs were withdrawn after surgery during follow-up, reported in the medical report.	Qualitative nominal	-Yes: Drugs removal -No: Required AEDs -NP: No previous AEDs
*AVM, Arteriovenous Malformation; DSA, Digital Subtraction Angiography; CT, Computed Tomography; MRI, Magnetic Resonance Imaging; fMRI, functional Magnetic Resonance Imaging; DTI, Diffusion Tensor Imaging; mRS, modified Ranking Scale; Preop, preoperative; Intraop, Intraoperative; Postop, postoperative; SM grade, Spetzler-Martin grade; AEDs, Antiepileptic drugs			

7.6-DATA COLLECTION

All the data used in our study was retrospectively collected from patient's medical records, surgical reports, and review of available imaging studies. Patient's data was appropriately anonymized (no-identifying numeric codes) at the early stage of study for further analysis. Before being able to access the above mentioned data and perform its subsequent analysis and description we required the authorization of the CEIC (Comité Ètic d'Investigació Clínica) of the Bellvitge University Hospital, in l'Hospitalet de Llobregat (Barcelona) (*see in ANNEX II*). The method to acquire the data was done by all the Neurosurgery Department registering all the information needed in an excel document for the study.

Figure 6. Chronogram representation of data collection. CEIC: Comité Ètic d'Investigació Clínica

7.5-TAILORED FUNCTIONAL APPROACH BELLVITGE UNIVERSITY HOSPITAL PROTOCOL

7.5.1-ALGORITHM OF MANAGEMENT PROPOSED AND APPLIED AT BELLVITGE UNIVERSITY HOSPITAL FOR PATIENTS HARBORING ARTERIOVENOUS MALFORMATIONS (AVMS)

The management of patients with brain AVMs depends on several factors: clinical presentation (hemorrhage, seizures, incidental finding…), patient characteristics (age, comorbidities, neurological status…) and AVM features (size, number of feeders, venous outflow, aneurysms, location, SM grading).

Regarding the clinical presentation patients presenting with acute intracranial hemorrhage with elevated intracranial pressure or with progressive deterioration of the level of consciousness and/or neurological deficits might be candidates for urgent surgical treatment. The goal of the surgery is the release of intracranial pressure and not the AVM resection, although in some cases AVM complete obliteration is also achieved.

If acute bleeding occurs but urgent surgery is not required, AVM treatment is postponed and reconsidered after patient discharged home and fully recovered. In case of risk factors for early rebleeding such as flow related or intranidal aneurysms, these could be secured by endovascular means during the acute period after AVM rupture.

In patients harboring unruptured AVMs treatment is considered, after completing all the imaging studies, in a multidisciplinary committee formed by neurosurgeons, neurointerventionalists and neuroanesthesiologists. Based on patient and AVM characteristics, treatment decision and treatment modality is decided, including conservative management with follow-up (clinical observation with periodic neuroimaging studies). When presenting with symptoms, such as seizures or chronic headache, symptomatic treatment is prescribed.

In patients with pharmacoresistant epilepsy, untreatable chronic headache or focal neurological defects secondary to steal phenomenon elective surgical treatment is usually recommended.

Overall, in the event of a surgical decision and based on the SM classification: grade I and II patients are considered surgical, grade III require a combined approach, and grades IV and V are considered for conservative management or partial endovascular treatment (palliative) in some specific cases.

All cases of AVM amenable to surgical resection undergo a complete neurological examination (including modified Rankin Scale (mRS)), MRI/MRA and angiographic examination with Digital Subtraction Angiography (DSA). In case of AVMs in an eloquent location functional studies are added (see in *FIGURE 7*).

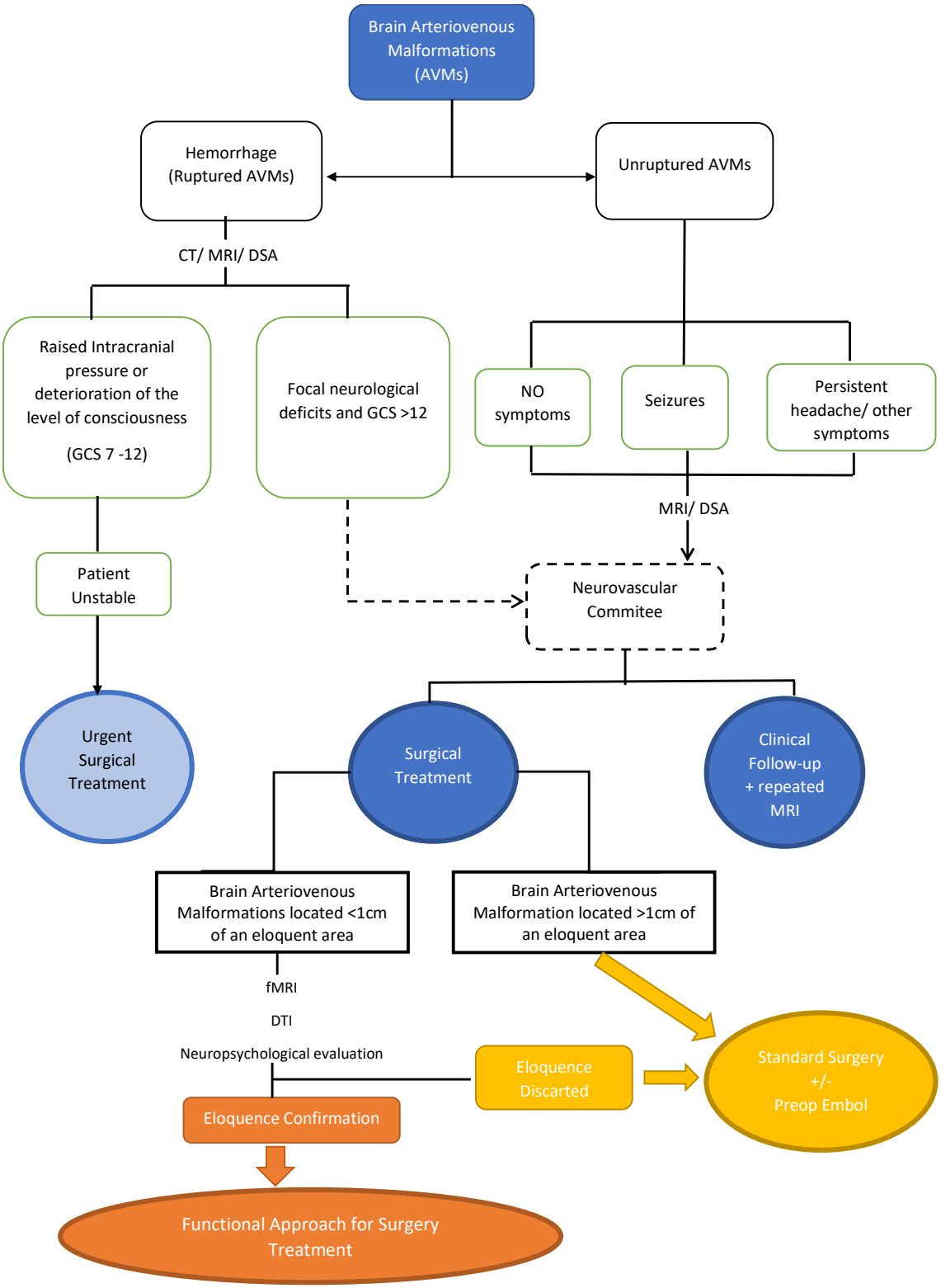

Figure 7. Algorithm of management proposed and applied for patients harboring supratentorial arteriovenous malformation. *AVM, Arteriovenous Malformation; Preop Embol, Preoperative embolization; CT, Computed Tomography; MRI, Magnetic Resonance Imaging; fMRI, functional Magnetic Resonance; DTI, Diffusion Tensor Imaging; DSA, Digital Subtraction Angiography; GSC, Glasgow Coma Scale

7.5.2-FUNCTIONAL APPROACH PROTOCOL FOR SUPRATENTORIAL ELOQUENT AVMS

A specific approach is done in supratentorial AVMs located ≤ 10 mm or within eloquent areas. This is an individualized tailored approach based on the function at risk. First of all, a preoperative functional evaluation in order to confirm the eloquence surrounding the AVM is performed. The techniques used for the functional assessment are: functional Magnetic Resonance Imaging (fMRI), Diffusion Tensor Imaging (DTI), Transcranial Magnetic Stimulation (TMS) and neuropsychological assessment, as language test, if language areas involvement is suspected. The functional information obtained and its concordance with anatomical areas shown on MRI and angiography will guide the intraoperative strategy.

During the fMRI acquisition, patients are asked to perform hand movements alternating and coordinating both sides, as well as bilateral finger-tapping movements. For those patients in whom perisylvian language functional areas is affected and/or in whom language is slightly impaired during clinical evaluation (e.g., impaired verbal fluency, impaired sentence repetition, or impaired object naming), number counting, noun generation, verb generation, and picture-naming tasks are included. Same language tests are performed during neuropsychological evaluation and repeated intraoperatively in case awake surgery is to be performed.

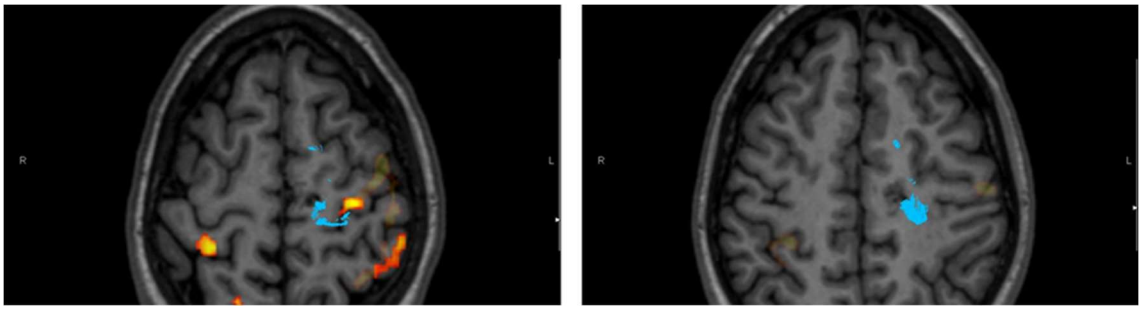

Figure 8. Functional MRI (fMRI) demonstrating activation of functional eloquent area (yellow) during motor task in close relation to the AVM (blue)

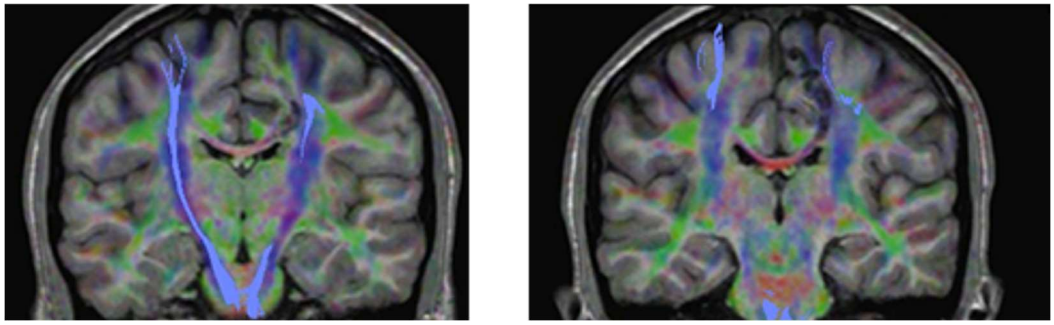

Figure 9. Diffusion Tensor Imaging (DTI) image showing functional activation of the cortico-spinal tracts (blue)

The subsequent tailored functional approach performed using intraoperative mapping techniques therefore depends on the neurological function potentially risk during surgery as demonstrated by those preoperative functional assessments.

There are two types of intraoperative mapping depending on the results of functional techniques: asleep surgery monitoring and awake surgery mapping. In cases where the AVM is closely related to motor and/or sensory function, surgery is performed under general anesthesia (Asleep surgery) with the aid of multimodal Intraoperative Neurophysiological Monitoring (IONM). Both the motor and somatosensory pathways are controlled with continuous Transcranial Electrical Stimulation (TES), using scalp corkscrew electrodes, of Motor Evoked Potentials (MEP) and Somatosensory Evoked Potentials (SSEP). Furthermore, MEP are also monitored via Direct Cortical Stimulation (DCS) with a subdural electrode grid (8 contacts) placed over the motor cortex, in order to be more focal and avoid deeper stimulus than the cortical-subcortical level (more selective stimulus). Therefore, the lowest threshold intensity for MEPs monitoring is selected trying to guarantee such focal stimulation. In addition, monopolar cortical and subcortical direct stimulation is also carried out during the surgery according to the surgeon's assessment at each step of the surgery.

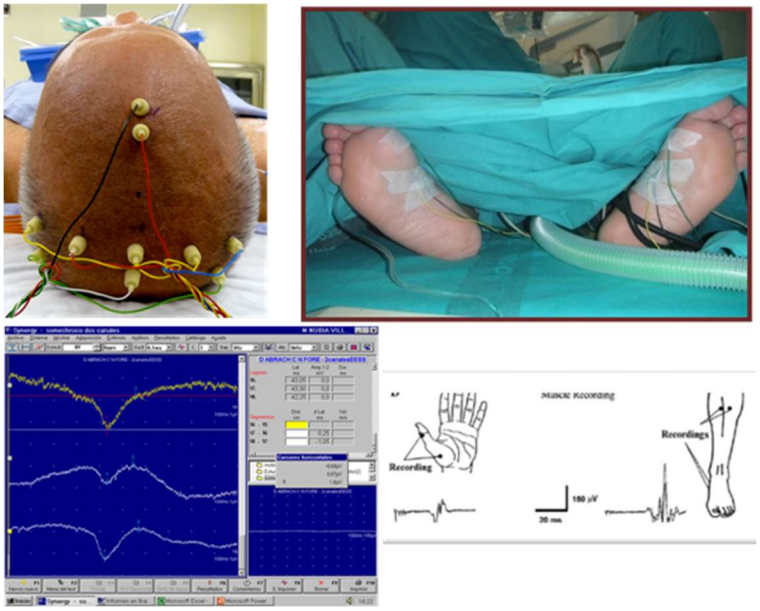

Figure 10. Asleep surgery: somatosensory and motor pathways controlled by continuous transcranial electrical stimulation (TES) of somatosensory evoked potentials (SSEP) and motor evoked potentials (MEP) using scalp corkscrew electrodes

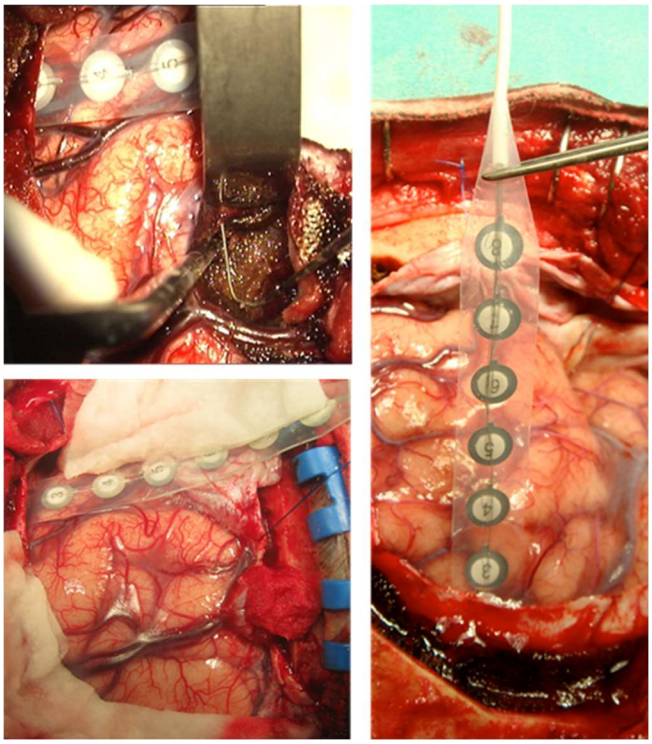

Figure 11. Asleep surgery: motor pathway monitored by direct cortical stimulation (DCS) with a subdural electrode grid placed over the motor cortex

On the other hand, in cases where AVM is closely related to language, vision, bimanual coordination and/or other functions (cognitive functions such as calculation, learned skills…), surgery is performed under awake conditions (awake surgery). Language tests performed during surgery (adapted Boston Naming Test, verb generation task, noun generation, number counting...) are selected based on the exact functional structures affected by the lesion, and also patient's performance same tests during pre-operative evaluation. Stimulation is performed with bipolar Ojemann stimulator at both cortical and subcortical levels, starting by mapping the cortical eloquent surface. In the case that the patient is bilingual or multilingual, all languages spoken by the patient are assessed. In order to perform a reliable language mapping >90% language proficiency in pre-surgical language testing is needed (27).

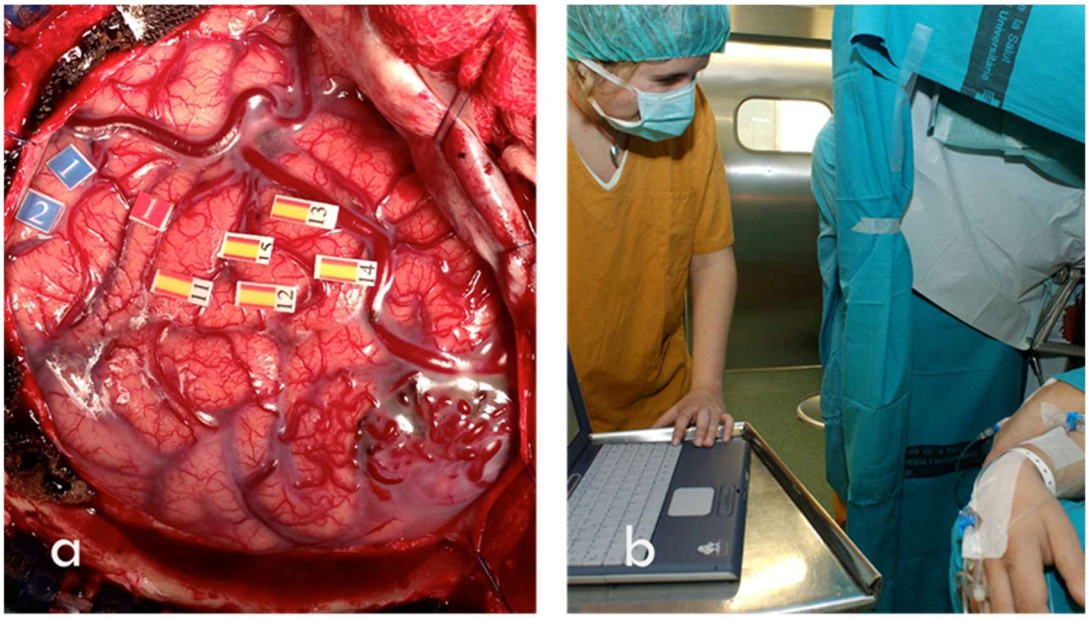

Figure 12. Awake language mapping. **(a)** Intraoperative picture. Numbered blue labels were used for areas where sensory response was elicited after stimulation, numbered red labels were placed in the areas where motor response was elicit and "flag" labels were used to demarcate areas in which language disturbance was elicit after stimulation in different language (Spanish). **(b)** Neuropsychologist performing language test during awake surgery

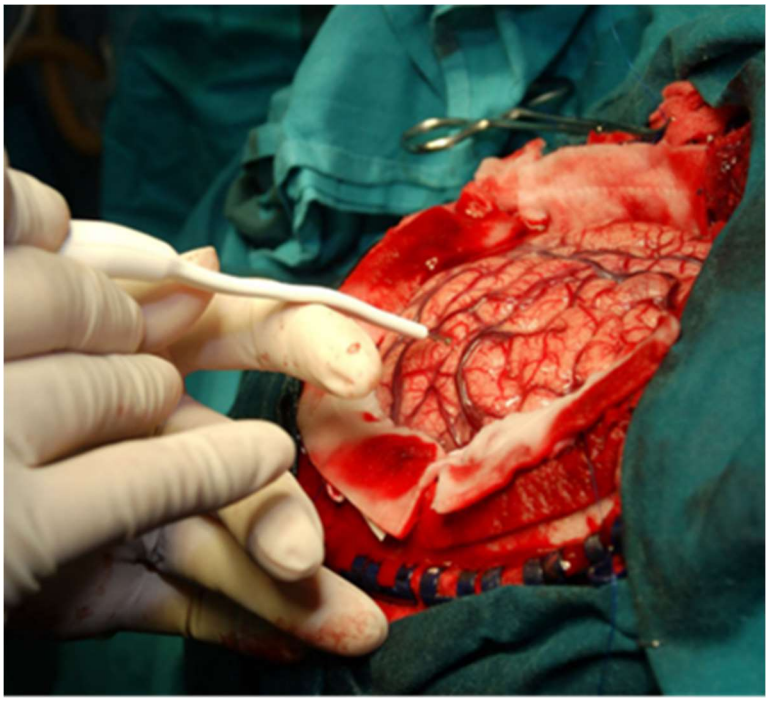

Figure 13. Awake language mapping: cortical stimulation with bipolar Ojemann stimulator

After intraoperative function identification is performed, the surgery continues with the microsurgical removal of the AVM but always maintaining permanent monitoring of the areas at risk as it's been described.

7.5.3-MANAGEMENT ALGORITHM

The type of AVM treatment performed depended on the preoperative SM classification and whether the AVM was ruptured or unruptured. This is detailed in *TABLE 4*.

Table 4. Management algorithm of Eloquent AVM

MANAGEMENT ALGORITHM OF ELOQUENT AVM*		
Spetzler-Martin (SM) Grade	**Ruptured**	**Unruptured**
SM 2	1.Preop Embolization + surgery 2.Radiosurgery	1.Radiosurgery 2.Preop Embolization + surgery
SM 3	1.Preop Embolization + surgery 2.Radiosurgery	1.Radiosurgery 2.Preop Embolization + surgery
SM 4	1.Preop Embolization + surgery 2.Embolization	1.No treatment 2.Embolization
SM 5	1.Preop Embolization + surgery 2 Embolization	1.No treatment 2.Embolization
*AVM, Arteriovenous Malformation; SM, Spetzler-Martin grade; Preop, preoperative		

7.5.4-POSTOPERATIVE FOLLOW-UP

All patients underwent postoperative DSA prior to discharge to confirm the complete resection of the AVM. In case of complete surgical resection clinical follow-up was performed 1, 3, 6 and 12 months after surgery and yearly after the first year. Imaging follow-up was performed at 3 months with MRI. In the event of incomplete resection, followed by radiosurgery, a new DSA assessment was performed at 2-3 years of the radiosurgical treatment or earlier in case of suspected obliteration on follow-up MRI.

The clinical follow-up consisted in the evaluation of neurological symptoms, presence or absence of epileptic seizures and the degree of disability or dependence in the activities of daily living measured by the modified Ranking Scale (mRS) (*see in TABLE 5 in ANNEX III*), assessed during the immediate postoperative period, at 6 months and 12 months after surgery.

8. LEGAL AND ETHICAL CONSIDERATIONS

This study respects the four basic bioethical principles described by Beauchamp and Childress in 1979 and has not any commercial bias or interest.

In first place, this study obeys with the ethical doctrines of the Declaration of Helsinki determined by the World Medical Association for medical research involving human subjects, including research on identifiable human material and information. The author did not have access to any confidential information of the patients, as they were registered anonymously under non-identifying numeric codes, following the Organic Law 15/1999 of 13 of December about Protecting Personal Data. Before the start of this study to have access to the data obtained from anonymized patients, the project was evaluated and accepted by the CEIC (Comité Ètic d'Investigació Clínica) of the Hospital Universitari de Bellvitge, l'Hospitalet de Llobregat (Barcelona) (*see in ANNEX II*).

Secondary, this study has been carried out considering the regulations established by Law 41/2002, of November 14, regulating patient autonomy and rights and obligations regarding clinical information and documentation.

In order to respect the legal framework of human rights and confidentiality and protection of personal data, specified in the Organic Law 3/2018, of December 5, about the Protection of Personal Data and Guarantee of Digital Rights, all data collected were recorded and analyzed anonymously and under non-identifying numeric codes. Moreover, the information about patients was only used for the research purpose and the author did not have access to any confidential information of the patient.

9. STATISTICAL ANALYSIS

A descriptive analysis of the study variables was carried out using absolute and relative frequencies for qualitative variables, and central tendency and dispersion measures for quantitative variables. All the statistical analyses were conducted using Jamovi software (The jamovi project (2021). jamovi (Version 1.6) [Computer Software]. Retrieved from https://www.jamovi.org).

10. RESULTS

10.1-PATIENTS DEMOGRAPHICS AND AVM CHARACTERISTICS

Our results were obtained from a total sample of 25 patients with BAVM in eloquent areas of which 13 were male (13/25, 52%) and 12 were female (12/25, 48%). The mean age during surgery was 36.7 years with a standard deviation (SD) of 13.4 years, with the extremes being 20 years and 68 years. There were no relevant past medical history although 28% (7 cases) of the patients smoke or consumed alcohol regularly and 64% (16 cases) used 1 or more antiepileptic drugs prior to surgery. A total of 11 patients (11/25, 44%) presented with bleeding (ruptured AVM), associating debut seizures in 4 of them. Thus, including these 4 cases, up to 15 patients (15/25, 60%) presented with epileptic seizures, the majority in unruptured AVM. Therefore, being seizures the most common presenting symptom. Three patients (3/25, 12%) presented with headache and another 2 (2/25, 8%) presented with a progressive focal neurological deficit.

At presentation the degree of disability or dependence on preoperative activities of daily living, assessed using the modified Ranking Scale (mRS), ranged from 0 to 3 with a mean mRS of 0,96 (SD of 0,79). 13 patients (13/25, 52%) presented symptoms without significant disabilities, corresponding to mRS 1. Only 7 cases (7/25, 28%) did not present symptoms or deficits (mRS = 0). 4 cases (4/25, 16%) presented symptoms with slightly disability (mRS = 2). A single case presented a preoperative mRS of 3, which corresponded to the lesion classified with the highest grade in the study (SM V) and the only case where the lesion could not be totally obliterated.

The malformations mainly corresponded to superficial lesions (cortical lesions), 18 (18/25, 72%) of the cases in total. AVMs were sited in the left dominant hemisphere in 16 patients (16/25, 64%) and the remaining 9 patients (9/25, 36%) in the right hemisphere. The most common location was the frontal region in both hemispheres followed by the temporal region.

Regarding the Spetzler-Martin (SM) scale, the mean SM was 2.96 (SD of 0.889), with the extremes being grade II and V. The majority of the cases were Grade II and III (9/25, 36% and 9/25, 36%) and 7 patients had high-grade AVMs (6 grade IV, 1 grade V). Venous drainage (V) was superficial in 16 cases (16/25, 64%) and deep in the remaining 9 cases (9/25, 36%). The size of the malformation (S) was variable with a mean size of 31.87 mm (SD of 13.32 mm), ranging between 10 mm and 62 mm in maximum diameter with only 2 cases measuring ≥ 60mm. Eleven cases (11/25, 44%) corresponded to S1 (< 3 cm), 12 cases (12/25, 48%) to S2 (3—6 cm) and the 2 cases left (2/25, 8%) to S3 (> 6 cm). All AVMs were located in an eloquent area (E1) (see detailed data in *TABLE 6 in ANNEX IV*).

10.2-FUNCTIONAL APPROACH

In all cases, a pre-surgical functional evaluation was performed, including fMRI, DTI and TMS. In 4 cases, language tests were included in the preoperative study due to the relationship between the lesion and the language areas.

The modalities to approach the AVM included surgical treatment, embolization (pre and/or postsurgical) and radiosurgery, which could be used in different combinations between them depending on the score on the SM scale and whether or not there was a rupture of the AVM. In only 6 cases (6/25, 24%) a single treatment was performed, which consisted of a microsurgical resection. These patients characteristically presented lesions smaller than 3 cm (S1) of which 5 cases (5/6, 83.3%) were located in the frontal lobe, as well as, 5 of the cases presented superficial drainage and a grade II on the SM scale. In the remaining 19 cases (19/25, 76%) a combined treatment was performed. Embolization was performed in 18 cases (18/25, 72%) mostly preoperatively, and 5 of these patients were embolized twice or more. Almost all cases were SM grade III or higher (14/18, 77.7%). 6 patients (6/25, 24%) underwent postsurgical radiosurgery, all of them due to incompletely obliterated AVM during the surgery (partial resection or circumdissection), in order to preserve the neurological function, as see in *TABLE 8* (see in *ANNEX VI*).

10.3-UTILITY OF BRAIN MAPPING (INTRAOPERATIVE FUNCTIONAL ASSESSMENT)

Intraoperative identification of the eloquent areas was performed using intraoperative electric brain stimulation (EBS) aided by neuronavigation tools (fMRI + DTI) and neuropsychological language tests when needed. The functional approach carried out during the surgical intervention was adapted according to the function potentially at risk. In the majority of the patients, 21 (21/25, 84%), the motor and sensory modalities were both evaluated.

Language was evaluated in 2 patients (2/25, 8%), in one case together with motor activity, in another case with both motor and sensory activity. Visual function was assessed in a total of 2 patients (2/25, 8%).

In most of the patients (22/25, 88%) the functional approach was performed using general anesthesia (Asleep surgery), coinciding with the evaluation of motor and sensory function by neurophysiological monitoring and stimulation. Three patients (3/25, 12%) underwent awake surgery and mapping to assess language or visual function, therefore requiring patient participation during the intervention (see in *TABLE 7* in *ANNEX V*).

There were two patients with preoperative language function evaluation in which the awake approach was not performed. In one of them, the poor tolerance of the laryngeal mask forced orotracheal intubation preventing the awake surgery. In the other case, the relationship of the AVM with the arcuate fasciculus was considered doubtful by fMRI due to artifacts and the patient was reluctant to undergo awake surgery.

During the surgical procedure, cortical and/or subcortical functional areas were localized in 96% (24/25) of cases. However, cortical mapping was considered useful in all 25 patients since the inability to identify the motor cortex in one patient was still considered useful because it allowed confident and safe dissection in the parenchymal planes around the nidus. In six cases (6/25, 24%), intraoperative electric brain stimulation (EBS) techniques forced the surgeon to change the surgical strategy and

affected the attitude toward the extent of AVM resection. These changes consisted in: (1) resection stopped due to inability to approach the lesion while sparing the motor function (continuous decline in amplitude of motor-evoked potentials with surgical manipulation) in 3 cases. (2) Change of the location and size of the previously planned corticotomy due to the presence of functional cortical language areas during cortical stimulation in 2 cases. (3) Identification of deep perforating artery supply from lenticulostriate arteries and significant branches of the middle cerebral artery involved in the nidus and the surrounding brain parenchyma in 1 case. Further dissection and disconnection of these branches was aborted.

In these cases of incomplete resection, the nidus was circumferentially dissected in all planes except those associated with functional sites, disconnecting most arterial feeders while preserving the major draining vein (circumdissection), or a small AVM remnant was left in the most compromised region due to its intimate relationship with the functional area (partial resection). Dearterialized AVMs and AVM remnants were left in situ with the intent to treat with radiosurgery.

10.4-SURGICAL COMPLICATIONS

Complications occurred in the immediate postoperative period and during follow-up in a total of 6 cases (6/25, 24%). Most of the complications, 5 patients (5/6, 83.3%), were infections of the surgical wound that required surgical debridement and subsequent cranioplasty. One of them, associated small petequial perilesional hemorrhage. All infections were caused by the same bacteria (*Enterobacter Cloacae*) and occurred during the same period of time due to an epidemic outbreak of this pathogen in hospital surgical area. The infection was not related to the size of the lesion, awake surgery or duration of the intervention. There was one hemorrhagic complication (postsurgical epidural hematoma) that did not require evacuation surgery neither represent a neurological deficit. No intraoperative seizures were reported. There was no mortality (see in *TABLE 8* in *ANNEX VI*).

10.5-PATIENTS OUTCOMES AFTER AVM SURGERY

As shown in *TABLE 8* (in *ANNEX VI*) and *TABLE 10* (in *ANNEX VIII*), in 19 cases (19/25, 76%) a complete resection of the AVM was obtained, confirmed with postoperative angiography images, of which 13 cases received endovascular embolization prior to surgery. In 6 cases (6/25, 24%) the resection was incomplete, with a partial resection in 3 cases (3/25, 12%) and a circumdissection in the other 3 cases (3/25, 12%). In 24 patients (24/25, 96%) the lesion was cured after completing all the combined therapies, meaning total AVM resection after surgical treatment (19 cases) and completed AVM obliteration after stereotactic radiosurgery in cases where total resection was not obtained (5 cases). There was only one case (1/25, 4%) where total obliteration of the lesion was not achieved, which corresponded to the patient with highest SM grade (SM V) and 60 mm nidus size. This patient underwent a total of 16 endovascular embolization procedures, surgical circumdissection and postsurgical radiosurgery.

As shown in *TABLE 9* (in *ANNEX VII*), we assessed 3 clinical items postsurgically and during follow-up at 6 and 12 months: neurological symptoms, mRS and the presence of seizures. In two cases it was not possible to obtain these 3 parameters at 6 months and 12 months because the surgery was performed at the end of 2021 and follow-up has not been yet performed.

In the immediate postoperative period, 12 patients (12/25, 48%) had no neurological deficits while 13 patients (13/25, 52%) presented symptomatic deficits, of which 8 cases (8/13, 61.5%) were transient. Seven of them presented a complete recovery of impaired functions at 6 months and the other case recovered the sensitive and language function while keeping the motor function impairment. The postoperative neurological deficits were as follows: 10 cases (10/25, 40%) presented motor deficits, 7 cases (7/25, 28%) language disorders, 3 cases (3/25,12%) sensory disturbance and 1 case (1/25, 4%) visual impairment. Language and motor disorders were presented jointly in 4 cases and in 2 cases language, motor and sensory function were all affected.

One case (1/25, 4%) who had no neurological alterations in the immediate postoperative period developed neurological symptoms at 6 months. A total of 11 patients (11/25,

44%) with no immediate postoperative neurological deficits remained asymptomatic during follow-up at 6 and 12 months. Overall, 18 patients (18/23, 78.2%) had no neurological deficits at 6 months follow-up, although 2 patients had not been evaluated at 6 month follow-up yet.

Regarding postsurgical seizures, 6 cases (6/25, 24%) presented immediate postoperative epileptic seizures, 5 of which had already seizures as the main clinical presentation prior to surgery. Two of these cases were seizures free at 6 months follow-up after the intervention. There was also one case without preoperative seizures who presented new-onset seizures but 6 months after the intervention. Of the 16 patients with preoperative epileptic seizures, 9 cases (9/16, 56.2%) did not present seizures in the clinical control at 6 months. 16 patients were taking 1 or more antiepileptic drugs preoperatively, and in 3 cases it was possible to completely withdraw the medication remaining seizure-free. Of the 9 patients with no preoperative seizures, 3 cases (3/9, 33.3%) required postsurgical antiepileptic treatment for seizure control.

As for the mRS, 9 patients (9/25, 36%) present no disability in the immediate postoperative period (mRS = 0). A total of 16 patients (16/25, 64%) presented any degree of symptoms or deterioration in the immediate postoperative period (mRS ≥ 1), the majority, 10 cases (10/16, 62.5%) presented symptoms without deficits or with slight deficits (mRS 1 or 2), and only 6 cases (6/16, 37.5%) presented moderate or severe deficits (mRS ≥ 3). Overall, 76% of the patients (19/25) showed a good clinical outcome (mRS ≤ 2) at the immediate postoperative period. The mean postoperative mRS was 1.4 (SD 1.35), compared to the mean preoperative mRS of 0,96 (SD 0.79).

Clinical follow-up performed at 6 and 12 months after surgery, showed that a large part of this initial deterioration was transient with a mean mRS at 6 and 12 months of 0.52 (SD 1.04) and 0.39 (SD 0.78), respectively. As shown in *TABLE 9* (in *ANNEX VII*), 11 cases improved in the mRS score at 6 months and 3 cases at 12 months. Curiously, 1 patient showed a progressive deterioration and worsening at 6 months follow-up and improved later on, returning to its initial function at 12 months. Thus, in total, 22 patients presented a mRS ≤ 2 at 6 and 12 months post-surgery, although 2 patients had not been evaluated at 6 months follow-up yet.

11. DISCUSSION

The management of AVM located in eloquent areas generates a great controversy among different authors, because the treatment, regardless of its modality, is not without significant risk (33). Lesions located in eloquent areas represent a higher surgical risk than those located in non-eloquent areas. This is due to the fact that the eloquent areas are brain regions that have a specific neurological function and that in the case of being injured, either by the lesion itself or iatrogenically during treatment, the result is catastrophic, resulting in a permanent neurological defect of the specific neurological function. Most AVMs overpass the subarachnoid space and the pial surface, therefore becoming somehow intraparenchymal lesion, and a significant number of AVMs have diffuse limits, leading the neurosurgeon into the brain parenchyma while surrounding all the nidus.

Surgery in these regions is therefore challenging and carries a significant risk of new neurological deficits in the postoperative period, which is more noticeable in patients who present before the operation with unruptured AVMs and nonexistent or minimal neurological deficits (27). In general, AVMs located in these areas have classically been approached with less invasive treatment options, either conservatively (follow-up) or with radiosurgery (27).

We advocate to manage the AVM located in a supratentorial eloquent area with the same modality that would have been chosen if it was located in a non-eloquent area, but applying an individualized functional approach, performed using intraoperative mapping techniques, focused on the identification and preservation of neurological function at risk demonstrated by preoperative functional techniques (fMRI, DTI, TMS and neuropsychological assessment). There are two types of intraoperative mapping depending on the results of functional techniques: asleep surgery monitoring and awake surgery mapping. In cases where the AVM is closely related to motor and/or sensory function, surgery is performed under general anesthesia (Asleep surgery) with the aid of multimodal IONM (MEP and SSEP). And in cases where AVM is closely related to

language, vision, bimanual coordination and/or other functions, surgery is performed under awake conditions (awake surgery).

Currently, brain mapping techniques have been proven to be a safe and useful technique to maximize the extent of surgical resection and reduce the late severe neurological deficits in patients with intrinsic brain tumors (such as gliomas) (35,36) and extrinsic brain lesions (such as metastases, meningiomas and cavernomas) (37,38) located in eloquent areas. However, the use and safety of brain mapping techniques remains unclear in the literature regarding surgery for AVM located in eloquent areas.

A previous article (27) had already pointed out the safety of electrocortical stimulation mapping during the intervention of cerebral AVMs, which had previously been reported by other authors (39–44), and supports the systematic use of this techniques when dealing with this kind of lesions.

Different authors have shown that the use of brain mapping during surgery of supratentorial AVMs located in eloquent areas helps to prevent brain damage during surgery with good functional results after resection, without an increased risk of major intraoperative complications (27,39,45,46). However, Brain mapping implies the need of fulfill some requirements in order to be implemented, such as adequate equipment and an experienced neurovascular and brain mapping team. It also involves some infrequent risks that the neurosurgical team must consider, which are an increased intraoperative risk of epileptic seizures, high risk of bleeding and a longer duration of surgery. This implies that the neurosurgeon should have a treatment protocol to control intraoperative seizures (27). In fact, although there were no intraoperative seizures in this study, with intraoperative electric brain stimulation techniques intraoperative seizures could appear in up to 16% (3-16.6%) (27,37,38) of the cases. The accumulated experience of the team in the treatment of other lesions in eloquent areas and with these monitoring techniques, helped to define and refine a specific protocol. If stimulation-evoked seizures occurs during the procedure, iced Ringer's lactate is applied directly onto the brain cortex (37,38) and anticonvulsant therapy is initiated immediately (loading dose) and maintained during at least the postoperative period.

The evaluation of the same tailored functional approach described in this study but adapted for cavernous malformations in supratentorial eloquent area was previously published by the Bellvitge's Neurosurgery team. In that work, cortical and/or subcortical functional areas were located in 100% of the cases during surgery through brain mapping techniques (38). In our study, with the designed functional approach customized for AVM in eloquent areas, it was possible to identify the function of eloquent areas in 96% of cases (24/25 cases). These results were similar to the largest series to date of surgically treated eloquent AVMs where the usefulness of intraoperative mapping with language/motor AVMs was also evaluated (27). They were able to identify cortical function in 92% of patients (11/12 cases) (see in *TABLE 11* in *ANNEX IX*). These shows that, when correctly performed, intraoperative mapping techniques are very useful and sensitive for the detection of a specific neurological function. Moreover, although in one patient it was not possible to identify the motor cortex, cortical mapping was considered still useful since allowed confident and safe dissection in the parenchymal planes around the nidus.

In our study, the motor and sensory modalities were both evaluated in most of the patients (84%). Language was evaluated only in 2 patients (8%) and visual function in another 2 patients (8%). The numbers obtained differ from other studies, due mainly to differences in either the type of malformation or the location and extent of the lesion (2,47,48).

With our particular functional approach total obliteration (cure) of the AVM was achieved in 24 patients (96%), 19 of them (76%) by complete resection after surgery and 5 cases (20%) after postsurgical radiosurgery. In one patient (4%), total resection was not achieved. This was related to the AVM size (60 mm) and SM grade (SM V, highest grade). These results differ from other more general AVM studies, in which the number of patients treated only with surgery tends to be higher. This is due to the fact that in our study we evaluated treatment of AVMs in eloquent areas, which, considering the extra risk involved in these locations, implies the use of combined treatment on many occasions to minimize surgical risk (49,50). It is clear that for an adequate approach to these lesions with curative intention a multidisciplinary perspective is mandatory.

When comparing to eloquent AVMs surgical series in the literature our results go in line with their results, especially in the comparison with the UCSF study (27). This work uses a very similar functional approach both pre- and intraoperatively and mainly differs in number of AVMs involving language areas and treated under awake conditions (12% vs 41.6%). In our study complete surgical resection is higher (76% vs 66%), but this is probably influenced by the eloquence itself and its intimate idiosyncratic relationship with the AVM rather than related to surgical skills or aggressiveness. That being said, our monitoring protocol includes a multimodal stimulation with continuous Direct Critical Stimulation (DCS) unlike the aforementioned study and has been refined and optimized over the years with other surgeries for eloquent lesions. However, if this plays a major role in the difference of resection extent between the 2 series it is difficult to establish (see in detail in *TABLE 11 in ANNEX IX* and in *TABLE 12* in *ANNEX X*).

As for the postoperative complications, minor complications appeared in our series in only 6 cases (24%). The majority (5 cases) were surgical wound infection, which occurred during the same period due to an epidemic outbreak of Enterobacter Cloacae that affected the surgical area of the hospital. These cases were not related to surgical maneuvers over the AVM or AVM eloquent location. There was no association to the size of the AVM, the awake surgery or duration of the intervention. This unfortunate situation, already addressed, affects the rate of complications of the study, that its higher than expected and when comparing to the pre-existing literature (16% in UCSF study) where mostly are hemorrhagic complications (27). If we could avoid such postsurgical infections, complications would have suffered a significant drop (from 24% to 4%), being lower than anticipated based on previous studies. Nevertheless, all of these complications were solved and did not affect the AVM cure rate or the neurological deficits.

In our series, seizures were the most common presenting symptom of AVM, occurring in up to 64% of patients (16 patients), an incidence somewhat higher than in the literature, since several studies have reported that between 12% and 57% of AVM patients experience seizures, and epilepsy could appear or persist after surgical resection (51).

Postoperative seizures, as reported by other authors, are one of the main immediate postoperative findings. Despite the high presence of presurgical seizures in our series, postoperative seizures were only observed in 6 patients (24%), 5 of whom had already seizures preoperatively. Therefore, 9 of the 16 patients with preoperative epilepsy were seizures-free status during follow-up. Our postsurgical seizures rate was slightly lower than those reported by other authors, in which postoperative epileptic seizures occurred in 29 to 37.7% of cases (18,52). The differences observed with regard to other series are attributed to the fact that the studies show differences in the brain area where the lesion is located and in its extension, which in some series correlate with the location of the lesion, being more frequent the presence of seizures in those located in the temporal and frontal lobe, and with other factors, such as peri-MAV edema, long draining vein, and larger size based on Spetzler-Martin grade categorization (53). The fact that we also have a higher rate of complete surgical resection could have also affected the seizure outcomes since without complete AVM excision the seizure focus (epileptogenic zone) could more easily persist (51). Nevertheless, we did not perform any specific workup to define the extension of the epileptogenic zone because surgery in eloquent areas could not go beyond the limits of the lesion itself

A total of 28% of patients presented epileptic seizures 6 months after the intervention and of the 16 patients who were taking 1 or more antiepileptic drugs preoperatively, the medication was withdrawn in 3 cases. Those results were lower than the one observed in other studies with a longer follow-up period, in which it was observed that of those who were seizure-free, 48% withdrew anticonvulsant therapy (54). However, although we marked the follow-up period at 12 months, most of the cases have been followed for several years and with a longer follow-up period we'll be probably closer to these rates of antiepileptic drug withdrawal found in the literature.

In our results 9 patients (36%) were asymptomatic in the follow-up and 13 patients (52%) presented neurological symptoms in the immediate postoperative period, 8 of which (8/25, 32%) were transient neurological symptoms, achieving total neurological recovery in 7 cases and partial neurological recovery in 1 case. On the other hand, 5 patients (20%) remained with neurological symptoms during follow-up (permanent symptoms) and 1 patient (4%) who did not present symptoms postoperatively,

worsened neurologically 6 months after surgery recovering afterwards. These outcomes correlate fairly well with the UCSF series (27), with not negligible better results in our series (66% vs 32% transient deficits; 33% vs 20% permanent deficits) since in both series the percentage of patients with immediate transient neurological defects was higher than the percentage of patients with permanent defects (see in *TABLE 12* in *ANNEX X*). Such results could be expected taking into account the manipulation in the vicinity of eloquent areas and also the fact that direct electric brain stimulation is performed throughout the surgery with subsequent postoperative focal edema and some stunning of the repeatedly stimulated areas.

Finally, regarding the evaluation of the degree of disability and dependence assessed by the modified Ranking Scale (mRS), in our series 64% of patients presented with some degree of clinical symptoms in the immediate postoperative period (mRS ≥ 1), 10 of which (62.5%) corresponded to mRS ≤ 2, considered in the study as a good clinical outcome, and only 6 cases (43%) presented moderate or severe deficits (mRS ≥ 3). Similar to other studies (27,38,55), during the follow-up at 6 and 12 months after surgery there was an improvement in the mRS, which went from 76% of patients with mRS ≤ 2 in the immediate postoperative period to 88% of patients at 6 and 12 months. Therefore, showing that good clinical and long term result can be achieved with our particular approach to these eloquent sited lesions.

12. LIMITATION OF STUDY

Our study has several limitations:

- One of the main limitations of the study is the small number of patients in the sample size and the high number of staging variables that made it difficult to draw statistically significant conclusions and impeded hypothesis testing. This is due to the fact that AVMs in eloquent areas are a particular type of brain malformation with low prevalence in the general population and the surgical treatment aided by functional assessment is rarely used for these lesions.
- Another important limitation of the study is that study data was obtained from a retrospective observational cohort that is not yet closed, in which there are two cases where follow-up has not been evaluated and in which future patients who meet the study inclusion criteria will be added over time.
- Due to the inherent nature of the study design (case series), several methodological limitations can be found. The lack of a control group makes it impossible to make causal inferences about the relationship between the personalized functional approach and the resection and clinical results obtained, which makes it impossible to determine whether the results are attributable to the effect of the treatment or to patient characteristics.
- Due to the retrospective nature, the data collected may not be fully complete and led recordkeeping biases.
- There are selection biases inherent to the observational design of this study. In two of the patients included in the study, clinical follow-up was not evaluated at 6 months or 12 months after surgery due to the fact that less than 6 months had passed since surgery. It should be considered that the results of these patients could modify our final results; one way to solve this problem would be to eliminate these two cases or repeat the study more than one year after surgery.
- There is a possibility of information bias during the measurement of lesion size and when classifying the AVM according to SM grade using the data obtained from the imaging tests. To minimize this error in the study, the two variables were measured

in all patients with the same diagnostic test, using angiography (DSA), which is currently the Gold Standard test for the diagnosis of AVMs.

- There is a possibility of observer (interviewer) bias while making an erroneous assessment of the degree of disability or dependence on activities of daily living assessed by the modified ranking Scale (mRS) in the preoperative, postoperative and follow-up periods. To minimize this error, the assessment of all patients should be carried out by a single professional experienced in the use of the mRS or prior education of the investigators.
- Among the strengths of the study is that being a case series is a relatively efficient and cost-saving design.
- On the other hand, since it did not interfere in the neurosurgeon's therapeutic decision, the results obtained in the study were similar to those obtained in routine clinical practice (higher external validity) and allowed performing the operations in which they had more experience. The presence of confounding bias was minimal due to the lack of a control group.
- To minimize the methodological limitations due to the design, new studies should be performed to prove this hypothesis by means of including a control group of patients with (non-eloquent) AVMs treated surgically for comparison. A multicentric design could also help to improve statistical power by increasing the number of patients (n). A randomized controlled trial in which the results of a group receiving a personalized functional approach for the management of AVM in eloquent areas are compared with the results of a control group in which AVM treatment is performed without including the personalized functional approach would be, theoretically the optimal study in order to establish a relationship between the functional approach and the results obtained. However due to the highly sensitive areas with increased risk of neurological injury such a design would inappropriate and unethical.

13. CONCLUSION

As stated in the hypothesis, the use of the tailored functional approach for these lesions allowed us to obtain a complete resection in 76% of the cases, and a cure rate of 96%, after postsurgical radiosurgery, achieving a good clinical outcome (mRS ≤ 2) at 6 and 12 months follow-up in 88% of the cases.

Although the methodological limitations of our case series study, our results suggest that tailored functional approach for the treatment of supratentorial eloquent AVMs could help neurovascular surgeons in adapting surgical strategies to prevent patients permanent neurological damage while obtaining good surgical results.

Further studies with a higher level of evidence are necessary to demonstrate the efficacy and usefulness of such functional approach for the management of AVMs located in supratentorial eloquent areas. In turn new prospective multicentric studies with higher statistical power and with comparison groups should be performed to prove this hypothesis.

14. BIBLIOGRAPHY

1. Lawton MT, Rutledge WC, Kim H, Stapf C, Whitehead KJ, Li DY, et al. Brain arteriovenous malformations. Nat Rev Dis Prim [Internet]. 2015;1:1–21. Available from: http://dx.doi.org/10.1038/nrdp.2015.8

2. Wang M, Jiao Y, Zeng C, Zhang C, He Q, Yang Y, et al. Chinese Cerebrovascular Neurosurgery Society and Chinese Interventional & Hybrid Operation Society, of Chinese Stroke Association Clinical Practice Guidelines for Management of Brain Arteriovenous Malformations in Eloquent Areas. Front Neurol. 2021;12:651663.

3. López FG, Gil A, López-Ibor L, Boto GR, Serna CC. Malformaciones arteriovenosas cerebrales: Desde el diagnóstico, sus clasificaciones y patofisiología, hasta la genética. Rev Mex Neurocienc. 2010;11(6):470–9.

4. Barreau X, Marnat G, Gariel F, Dousset V. Intracranial arteriovenous malformations. Diagn Interv Imaging. 2014;95(12):1175–86.

5. Gabriel RA, Kim H, Sidney S, McCulloch CE, Singh V, Johnston SC, et al. Ten-year detection rate of brain arteriovenous malformations in a large, multiethnic, defined population. Stroke. 2010;41(1):21–6.

6. Al-Shahi R, Bhattacharya JJ, Currie DG, Papanastassiou V, Ritchie V, Roberts RC, et al. Prospective, population-based detection of intracranial vascular malformations in adults: The Scottish Intracranial Vascular Malformation Study (SIVMS). Stroke. 2003;34(5):1163–9.

7. Stapf C, Mast H, Sciacca RR, Berenstein A, Nelson PK, Gobin YP, et al. The New York Islands AVM Study: design, study progress, and initial results. Stroke. 2003;34(5).

8. Hofmeister C, Stapf C, Hartmann A, Sciacca RR, Mansmann U, Terbrugge K, et al. 1289 Patients With Brain Arteriovenous Malformation. Stroke. 2000;1307–10.

9. Kim H, Al-Shahi Salman R, McCulloch CE, Stapf C, Young WL. Untreated brain arteriovenous malformation: Patient-level meta-analysis of hemorrhage

predictors. Neurology. 2014;83(7):590–7.

10. Halim AX, Johnston SC, Singh V, McCulloch CE, Bennett JP, Achrol AS, et al. Longitudinal risk of intracranial hemorrhage in patients with arteriovenous malformation of the brain within a defined population. Stroke. 2004;35(7):1697–702.

11. Stapf C, Mast H, Sciacca RR, Choi JH, Khaw A V., Connolly ES, et al. Predictors of hemorrhage in patients with untreated brain arteriovenous malformation. Neurology. 2006;66(9):1350–5.

12. Liu XJ, Wang S, Zhao YL, Teo M, Guo P, Zhang D, et al. Risk of cerebral arteriovenous malformation rupture during pregnancy and puerperium. Neurology. 2014;82(20):1798–803.

13. Kume T. Specification of arterial, venous, and lymphatic endothelial cells during embryonic development. Histol Histopathol [Internet]. 2010;25(5):637–46. Available from: https://neuro.unboundmedicine.com/medline/citation/20238301/Specification_of_arterial_venous_and_lymphatic_endothelial_cells_during_embryonic_development_

14. Redekop G, TerBrugge K, Montanera W, Willinsky R. Arterial aneurysms associated with cerebral arteriovenous malformations: Classification, incidence, and risk of hemorrhage. J Neurosurg. 1998;89(4):539–46.

15. Gross BA, Du R. Natural history of cerebral arteriovenous malformations: A meta-analysis ; Clinical article. J Neurosurg. 2013;118(2):437–43.

16. Al-Shahi R, Warlow C. A systematic review of the frequency and prognosis of arteriovenous malformations of the brain in adults. Brain. 2001;124(10):1900–26.

17. Laakso A, Hernesniemi J. Arteriovenous Malformations: Epidemiology and Clinical Presentation. Neurosurg Clin N Am. 2012;23(1):1–6.

18. Garcin B, Houdart E, Porcher R, Manchon E, Saint-Maurice JP, Bresson D, et al.

Epileptic seizures at initial presentation in patients with brain arteriovenous malformation. Neurology. 2012;78(9):626–31.

19. Mokin M, Dumont TM, Levy EI. Novel Multimodality Imaging Techniques for Diagnosis and Evaluation of Arteriovenous Malformations. 2014;32:225–36.

20. Byyny RL, Mower WR, Shum N, Gabayan GZ, Fang S, Baraff LJ. Sensitivity of Noncontrast Cranial Computed Tomography for the Emergency Department Diagnosis of Subarachnoid Hemorrhage. Ann Emerg Med. 2008;51(6):697–703.

21. Josephson CB, White PM, Krishan A, Al-Shahi Salman R. Computed tomography angiography or magnetic resonance angiography for detection of intracranial vascular malformations in patients with intracerebral haemorrhage. Cochrane Database Syst Rev. 2014;(9).

22. Tranvinh E, Heit JJ, Hacein-Bey L, Provenzale J, Wintermark M. Contemporary imaging of cerebral arteriovenous malformations. Am J Roentgenol. 2017;208(6):1320–30.

23. Derdeyn CP, Zipfel GJ, Albuquerque FC, Cooke DL, Feldmann E, Sheehan JP, et al. Management of Brain Arteriovenous Malformations: A Scientific Statement for Healthcare Professionals from the American Heart Association/American Stroke Association. Stroke. 2017;48(8):e200–24.

24. Spetzler RF, Martin NA. A proposed grading system for arteriovenous malformations. J Neurosurg. 1986;65(4):476–83.

25. Lawton MT, Kim H, McCulloch CE, Mikhak B, Young WL. A supplementary grading scale for selecting patients with brain arteriovenous malformations for surgery. Neurosurgery. 2010;66(4):702–13.

26. Bruno CA, Meyers PM. Endovascular Management of Arteriovenous Malformations of the Brain. Interv Neurol. 2013;1(3–4):109–23.

27. Gabarrós A, Young WL, McDermott MW, Lawton MT. Language and motor mapping during resection of brain arteriovenous malformations: Indications, feasibility, and utility. Neurosurgery. 2011;68(3):744–52.

28. Ferpozzi V, Fornia L, Montagna M, Siodambro C, Castellano A, Borroni P, et al. Broca's area as a pre-articulatory phonetic encoder: Gating the motor program. Front Hum Neurosci. 2018;12:1–17.

29. Binder JR. The Wernicke area: Modern evidence and a reinterpretation. Neurology. 2015;85(24):2170–5.

30. Saura D, Kreher BW, Schnell S, Kümmerera D, Kellmeyera P, Vrya MS, et al. Ventral and dorsal pathways for language. Proc Natl Acad Sci U S A. 2008;105(46):18035–40.

31. Perea Bartolomé M V, Ladera Fernández V. [Neurofunctional aspects of the thalamus]. Rev Neurol. 2004;38(7):687–93.

32. Takahashi E, Dai G, Wang R, Ohki K, Rosen GD, Galaburda AM, et al. Development of cerebral fiber pathways in cats revealed by diffusion spectrum imaging. Neuroimage. 2010;49(2):1231–40.

33. Starke RM, Komotar RJ, Hwang BY, Fischer LE, Garrett MC, Otten ML, et al. Treatment guidelines for cerebral arteriovenous malformation microsurgery. Br J Neurosurg. 2009;23(4):376–86.

34. Sahlein DH, Mora P, Becske T, Huang P, Jafar JJ, Connolly ES, et al. Features predictive of brain arteriovenous malformation hemorrhage: extrapolation to a physiologic model. Stroke [Internet]. 2014;45(7):1964–70. Available from: https://cancerres.unboundmedicine.com/medline/citation/24923721/Features_predictive_of_brain_arteriovenous_malformation_hemorrhage:_extrapolation_to_a_physiologic_model_

35. Hervey-Jumper SL, Berger MS. Maximizing safe resection of low- and high-grade glioma. J Neurooncol. 2016;130(2):269–82.

36. De Witt Hamer PC, Robles SG, Zwinderman AH, Duffau H, Berger MS. Impact of intraoperative stimulation brain mapping on glioma surgery outcome: a meta-analysis. J Clin Oncol. 2012;30(20):2559–65.

37. Sanmillan JL, Fernández-Coello A, Fernández-Conejero I, Plans G, Gabarrós A.

Functional approach using intraoperative brain mapping and neurophysiological monitoring for the surgical treatment of brain metastases in the central region. J Neurosurg [Internet]. 2017;126(3):698—707. Available from: https://doi.org/10.3171/2016.2.JNS152855

38. Sanmillan JL, Lopez-Ojeda P, Fernández-Conejero I, Fernández-Coello A, Plans G, Ali-Ciurana Y, et al. Treatment of cavernous malformations in supratentorial eloquent areas: experience after 10 years of patient-tailored surgical protocol. Acta Neurochir (Wien). 2018;160(10):1963–74.

39. Burchiel KJ, Clarke H, Ojemann GA, Dacey RG, Winn HR. Use of stimulation mapping and corticography in the excision of arteriovenous malformations in sensorimotor and language-related neocortex. Neurosurgery. 1989;24(3):322–7.

40. Cannestra AF, Pouratian N, Forage J, Bookheimer SY, Martin NA, Toga AW. Functional Magnetic Resonance Imaging and Optical Imaging for Dominant-hemisphere Perisylvian Arteriovenous Malformations. Neurosurgery [Internet]. 2004;55(4):804–14. Available from: https://doi.org/10.1227/01.NEU.0000137654.27826.71

41. Duffau H, Lopes M, Arthuis F, Bitar A, Sichez J-P, Van Effenterre R, et al. Contribution of intraoperative electrical stimulations in surgery of low grade gliomas: a comparative study between two series without (1985–96) and with (1996–2003) functional mapping in the same institution. J Neurol Neurosurg & Psychiatry [Internet]. 2005;76(6):845–51. Available from: http://jnnp.bmj.com/content/76/6/845.abstract

42. Ebeling U, Schmid UD, Ying H, Reulen HJ. Safe surgery of lesions near the motor cortex using intra-operative mapping techniques: a report on 50 patients. Acta Neurochir (Wien). 2005;119:23–8.

43. Kombos T, Suess O, Funk T, Kern BC, Brock M. Intra-Operative Mapping of the Motor Cortex During Surgery in and Around the Motor Cortex. Acta Neurochir (Wien) [Internet]. 2000;142(3):263–8. Available from: https://doi.org/10.1007/s007010050034

44. Zamorano L, Matter A, Saenz A, Portillo G, Diaz F. Interactive image-guided surgical resection of intracranial arteriovenous malformations. Comput aided Surg Off J Int Soc Comput Aided Surg. 1998;3(2):57–63.

45. Stapleton CJ, Walcott BP, Fusco MR, Thomas AJ, Ogilvy CS. Brain Mapping for Safe Microsurgical Resection of Arteriovenous Malformations in Eloquent Cortex. World Neurosurg [Internet]. 2015;83(6):1148–56. Available from: https://www.sciencedirect.com/science/article/pii/S1878875015000625

46. Gamble AJ, Schaffer SG, Nardi DJ, Chalif DJ, Katz J, Dehdashti AR. Awake Craniotomy in Arteriovenous Malformation Surgery: The Usefulness of Cortical and Subcortical Mapping of Language Function in Selected Patients. World Neurosurg. 2015;84(5):1394–401.

47. Lepski G, Honegger J, Liebsch M, Sória MG, Narischat P, Ramina KF, et al. Safe resection of arteriovenous malformations in eloquent motor areas aided by functional imaging and intraoperative monitoring. Neurosurgery. 2012;70(2 Suppl Operative):276–9.

48. Akers A, Al-Shahi Salman R, A Awad I, Dahlem K, Flemming K, Hart B, et al. Synopsis of Guidelines for the Clinical Management of Cerebral Cavernous Malformations: Consensus Recommendations Based on Systematic Literature Review by the Angioma Alliance Scientific Advisory Board Clinical Experts Panel. Neurosurgery. 2017;80(5):665–80.

49. Rutledge C, Nelson J, Lu A, Nisson P, Jonzzon S, Winkler EA, et al. Cost determinants in management of brain arteriovenous malformations. Acta Neurochir (Wien) [Internet]. 2020;162(1):169–73. Available from: https://doi.org/10.1007/s00701-019-04134-6

50. Castaño C, de teresa S, Solivera J, Quintana C, Tresserras P, Rodríguez R, et al. Manejo actual de las malformaciones arteriovenosas: Estudio retrospectivo de 31 casos y revisión de la literatura. Neurocir Organo Of la Soc Española Neurocir. 2007;18(5):394–405.

51. Lopez-Ojeda P, Labib M, Burneo J, Lownie SP. Temporal lobe arteriovenous

malformations: Surgical outcomes with a focus on visual field defects and epilepsy. Neurosurgery. 2013;73(5):854–62.

52. Galletti F, Costa C, Cupini LM, Eusebi P, Hamam M, Caputo N, et al. Brain arteriovenous malformations and seizures: an Italian study. J Neurol Neurosurg Psychiatry. 2014;85(3):284–8.

53. Benson JC, Chiu S, Flemming K, Nasr DM, Lanzino G, Brinjikji W. MR characteristics of unruptured intracranial arteriovenous malformations associated with seizure as initial clinical presentation. J Neurointerv Surg. 2020;12(2):186–91.

54. Piepgras DG, Sundt TM, Ragoowansi AT, Stevens L. Seizure outcome in patients with surgically treated cerebral arteriovenous malformations. J Neurosurg [Internet]. 1993;78(1):5—11. Available from: https://doi.org/10.3171/jns.1993.78.1.0005

55. Liu R, Zhan Y, Piao J, Yang Z, Wei Y, Liu P, et al. Treatments of unruptured brain arteriovenous malformations: A systematic review and meta-analysis. Medicine (Baltimore). 2021;100(25):e26352.

56. Banks JL, Marotta CA. Outcomes validity and reliability of the modified Rankin scale: implications for stroke clinical trials: a literature review and synthesis. Stroke. 2007;38(3):1091–6.

15. ANNEXES

ANNEX I: CONVENI DE COOPERACIÓ EDUCATIVA PER A LA REALIZACIÓ DE PRACTIQUES ACADÈMIQUES EXTERNES EN ENTITATS COL·LABORADORES

CONVENI DE COOPERACIÓ EDUCATIVA PER A LA REALITZACIÓ DE PRÀCTIQUES ACADÈMIQUES EXTERNES EN ENTITATS COL·LABORADORES

REUNITS:

D'una part, Joan San Molina, degà de la Facultat de Medicina de la Universitat de Girona, domiciliada a Girona, C/ Emili Grahit, 77, 17071, amb NIF Q-6750002 E.

D'una altra part, Marta Ferrer Garcia com a Vicerectora d'Estudiants i Participació en nom i representació de l'entitat col·laboradora Universitat de Barcelona, domiciliada a Gran Via de les Corts Catalanes, 585 (08007) Barcelona, amb CIF Q0818001J.

I, d'una altra part, Oscar López Lombardia, amb DNI 40369985V, estudiant del GRAU EN MEDICINA a la Facultat de Medicina de la Universitat de Girona.

Les parts es reconeixen la capacitat legal necessària per formalitzar aquest conveni i

MANIFESTEN

Que, en el marc de la normativa vigent per la qual es regulen les pràctiques acadèmiques externes dels estudiants universitaris, les parts subscriuen aquest document i

Per la Universitat de Girona	L'estudiant	Per l'entitat col·laboradora
Juan San Molina - DNI 37660157A (TCAT) Firmado digitalmente por Juan San Molina - DNI 37660157A (TCAT) Fecha: 2021.12.02 08:50:35 +01'00'	LOPEZ LOMBARDIA OSCAR - 40369985V Signat digitalment per LOPEZ LOMBARDIA OSCAR - 40369985V Data: 2021.11.23 11:33:43 +01'00'	GABARROS CANALS ANDREU - 77301410C
Joan San Molina Degà	Oscar López Lombardia	Andreu Gabarros Canals Tutor UB

ANNEX II: CEIC'S AUTHORIZATION

Salut/ Bellvitge Hospital Universitari

INFORME DEL COMITÉ DE ÉTICA DE LA INVESTIGACIÓN SOBRE PROYECTOS DE INVESTIGACIÓN BIOMÉDICA

El Comité de Ética de la Investigación, mediante el procedimiento de evaluación rápida de la documentación contemplado en los Procedimientos Normalizados de Trabajo del Comité (esta aprobación se hará constar en el Acta 02/22 de fecha 27/01/22), tras examinar toda la documentación presentada sobre el proyecto de investigación con nuestra Ref. **PR440/21**, titulado:

"EVALUACIÓN DEL ABORDAJE FUNCIONAL INDIVIDUALIZADO EN EL TRATAMIENTO QUIRÚRGICO DE LAS MALFORMACIONES EN ÁREAS ELOCUENTES"

Presentado por el Dr. Pablo López Ojeda, del servicio de Neurocirugía del Hospital Universitari de Bellvitge, como promotor e investigador principal, ha acordado emitir INFORME FAVORABLE al mencionado proyecto.

Que la composición actual del Comité de Ética de la Investigación es la siguiente:

Presidente	Dr. Francesc Esteve Urbano	Médico - Medicina Intensiva
Vicepresidenta	Dra. Pilar Hereu Boher	Médico - Farmacología Clínica
Secretario	Dr. Enric Sospedra Martínez	Farmacéutico - Farmacia Hospitalaria
Vocales:	Dr. Jordi Adamuz Tomás	Enfermero – Enfermería
	Sra. Anna Boix Traserra	Derecho - DPD
	Dra. Concepción Cañete Ramos	Médico - Neumología
	Dr. José Luis Ferreiro Gutiérrez	Médico - Cardiología
	Dra. Ana María Ferrer Artola	Farmacéutica - Miembro sanitario
	Dr. Xavier Fulladosa Oliveras	Médico - Nefrología
	Dra. Margarita García Martín	Médico - Oncología Médica
	Dr. Carles Lladó i Carbonell	Médico - Urología
	Dr. Josep Manel Llop Talaveron	Farmacéutico – Farmacia Hospitalaria
	Dra. Sara Larriba Bartolomé	Farmacia - Sanitario
	Sra. Sonia López Ortega	Graduado Social - Atención a la Ciudadanía
	Dr. Sergio Morchón Ramos	Médico - Medicina Preventiva
	Dr. Miguel Ángel Pavón Ribas	Biólogo- Miembro no sanitario
	Dr. Joan Josep Queralt Jiménez	Jurista
	Dra. Gemma Rodríguez Palomar	Farmacéutica – Atención Primaria
	Dr. Petru Cristian Simon	Médico - Farmacología Clínica

Que este Comité cumple la legislación española vigente para este tipo de proyectos, así como las normas ICH y las Normas de Buena Práctica Clínica.

Que en dicha reunión del Comité de Ética de la Investigación se cumplió el quórum preceptivo legalmente.

Generalitat de Catalunya

Salut/ Bellvitge Hospital Universitari

Lo que firmo en L'Hospitalet de Llobregat, a 19 de enero de 2022

SOSPEDRA MARTINEZ ENRIQUE - 36986426B

Signat digitalment per SOSPEDRA MARTINEZ ENRIQUE - 36986426B
DN: c=ES, serialNumber=IDCES-36986426B, givenName=ENRIQUE, sn=SOSPEDRA MARTINEZ, cn=SOSPEDRA MARTINEZ ENRIQUE - 36986426B
Data: 2022.01.19 15:35:34 +01'00'

Dr. Enric Sospedra Martínez

ANNEX III: MODIFIED RANKING SCALE (MRS) EXTRACTED FROM (56)

Table 5. Modified Ranking Scale (mRS) extracted from (56)

Modified Ranking Scale (mRS)	
Rankin Grade	**Description**
0	No symptoms at all
1	No significant disability: despite symptoms, able to carry out all usual duties and activities
2	Slight disability: unable to perform all previous activities but able to look after own affairs without assistance
3	Moderate disability: requiring some help but able to walk without assistance
4	Moderately severe disability: unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability: bedridden, incontinent and requiring constant nursing care and attention
6	Death

ANNEX IV: TABLE 6. PATIENTS DEMOGRAPHICS AND AVM CHARACTERISTICS

Table 6. Patients Demographics and AVM Characteristics

PATIENT DEMOGRAPHICS AND AVM CHARACTERISTICS*									
Number	**Sex**	**Age**	**Toxic Habits**	**Preop AEDs**	**Presentation**	**mRS Preop**	**Location**	**Largest Size (mm)**	**SM grade**
1	F	35	No	No	Cerebral hemorrhage	1	L Frontal	30	3 (S1 E1 V1)
2	F	22	No	Yes	Seizures	2	L Frontal	35	3 (S2 E1 V0)
3	F	25	No	Yes	Seizures	1	R Frontal	50	3 (S2 E1 V0)
4	F	52	No	Yes	Seizures	1	R Frontal	26	2 (S1 E1 V0)
5	M	35	No	Yes	Seizures	1	R Frontal	40	3 (S2 E1 V0)
6	F	27	No	Yes	Cerebral hemorrhage, Seizures, Headache	3	L Fronto-parietal	60	5 (S3 E1 V1)
7	M	60	Yes	No	Cerebral hemorrhage	0	L parietal	26	2 (S1 E1 V0)
8	M	27	No	Yes	Seizures	1	R Frontal	30	3 (S1 E1 V1)
9	M	37	Yes	Yes	Seizures	1	L Frontal	10	2 (S1 E1 V0)
10	M	68	Yes	No	Seizures	1	L Occipital	15	2 (S1 E1 V0)
11	F	49	No	Yes	Cerebral hemorrhage, Seizures	1	R Frontal	18	2 (S1 E1 V0)
12	F	30	Yes	Yes	Seizures	2	L Frontal	33	3 (S2 E1 V0)
13	F	38	No	No	Cerebral hemorrhage	0	R Frontal	11,5	2 (S1 E1 V0)
14	F	46	No	Yes	Seizures	1	R Temporal	62	4 (S3 E0 V1)
15	F	23	Yes	No	Cerebral hemorrhage	0	R Basal ganglia	34	4 (S2 E1 V1)
16	F	54	No	No	Headache	1	L Frontal	36	3 (S2 E1 V0)
17	M	26	No	Yes	Cerebral hemorrhage, Seizures	0	L Frontal	18	2 (S1 E1 V0)
18	M	52	No	No	Progressive Focal Neurological deficits	2	L Temporal	32	4 (S2 E1 V1)

19	M	21	No	No	Cerebral hemorrhage	0	L Frontal	41	4 (S2 E1 V1)
20	F	39	Yes	Yes	Seizures, Progressive Focal Neurological deficits	1	L Parietal	38	4(S2 E1 V1)
21	M	20	No	Yes	Seizures	0	L Parieto-temporal	33,25	3(S2 E1 V0)
22	M	21	No	Yes	Cerebral hemorrhage	1	L Parietal	20	2(S1 E1 V 0)
23	M	37	No	yes	Cerebral hemorrhage, Seizures	2	L Frontal	35	3 (S2 E1 V0)
24	M	29	Yes	Yes	Seizures	1	R Frontal	42	4 (S2 E1 V1)
25	M	45	No	No	Cerebral hemorrhage, Headache	0	L Temporal	21	2 (S1 E1 V0)

*AVM, arteriovenous malformation; F, female; M, male; AEDs, Antiepileptic drugs; mRS, modified Ranking Score; Preop, preoperative; R, right; L, left; mm, millimeters; SM grade, Spetzler-Martin grade

ANNEX V: TABLE 7. Preop and Intraoperative Functional Approach

Table 7. Preop and Intraoperative Functional Approach

PREOP AND INTRAOPERATIVE FUNCTIONAL APPROACH*				
Number	**Preop functional test**	**Functional approach (Mapping)**	**Function identified**	**Awake/Asleep Monitoring**
1	fMRI, DTI, TMS, NPE, navegator	Motor, Sensitive, Language	Yes	Awake
2	fMRI, DTI, TMS, NPE, navegator	Motor, Sensitive	Yes	Asleep
3	fMRI, DTI, TMS, NPE, navegator	Motor, Sensitive	Yes	Asleep
4	fMRI, DTI, TMS, NPE, navegator	Motor, Sensitive	Yes	Asleep
5	fMRI, DTI, TMS, NPE, navegator	Motor, Sensitive	Yes	Asleep
6	fMRI, DTI, TMS, NPE, navegator	Motor, Sensitive	Yes	Asleep
7	fMRI, DTI, TMS, NPE, navegator	Motor, Sensitive	Yes	Asleep
8	fMRI, DTI, TMS, NPE, navegator	Motor, Sensitive	Yes	Asleep
9	fMRI, DTI, TMS, NPE, navegator	Motor, Sensitive	No	Asleep
10	fMRI, DTI, TMS, NPE, navegator	Visual	Yes	Awake
11	fMRI, DTI, TMS, NPE, navegator	Motor, Sensitive	Yes	Asleep
12	fMRI, DTI, TMS, NPE, navegator	Motor, Language	Yes	Awake
13	fMRI, DTI, TMS, NPE, navegator	Motor, Sensitive	Yes	Asleep
14	fMRI, DTI, TMS, NPE, navegator	Motor, Sensitive	Yes	Asleep
15	fMRI, DTI, TMS, NPE, navegator	Motor, Sensitive	Yes	Asleep
16	fMRI, DTI, TMS, NPE, navegator	Motor, Sensitive	Yes	Asleep

17	fMRI, DTI, TMS, NPE, navegator	Motor, Sensitive	Yes	Asleep
18	fMRI, DTI, TMS, NPE, navegator	Motor, Sensitive	Yes	Asleep
19	fMRI, DTI, TMS, NPE, navegator	Motor, Sensitive	Yes	Asleep
20	fMRI, DTI, TMS, NPE, navegator	Motor, Sensitive	Yes	Asleep
21	fMRI, DTI, TMS, NPE, navegator	Visual	Yes	Asleep
22	fMRI, DTI, TMS, NPE, navegator	Motor, Sensitive	Yes	Asleep
23	fMRI, DTI, TMS, NPE, navegator	Motor, Sensitive	Yes	Asleep
24	fMRI, DTI, TMS, NPE, navegator	Motor, Sensitive	Yes	Asleep
25	fMRI, DTI, TMS, NPE, navegator	Motor, Sensitive	Yes	Asleep
*fMRI, functional Magnetic Resonance Imaging; DTI, Diffusion Tensor Imaging; TMS, Transcranial Magnetic Stimulation; NPE, Neuropsychological Evaluation; Preop, preoperative				

ANNEX VI: TABLE 8. SURGICAL RESULTS AFTER AVM SURGERY

Table 8. Surgical Results After AVM Surgery

SURGICAL RESULTS AFTER AVM SURGERY*					
Number	**AVM Resection**	**Combined treatment**	**Number embolization**	**Complications**	**Cured**
1	Complete	No	0	No	Yes
2	Complete	Yes	2	No	Yes
3	Complete	Yes	2	Surgical wound infection	yes
4	Complete	No	0	No	Yes
5	Complete	Yes	3	No	Yes
6	Circumdissection	Yes	16	Surgical wound infection	No
7	Complete	Yes	1	No	Yes
8	Partial	Yes	0	Hematoma	Yes
9	Complete	No	0	No	Yes
10	Complete	No	0	No	Yes
11	Complete	Yes	1	No	Yes
12	Partial	Yes	1	Surgical wound infection	Yes
13	Complete	No	0	No	Yes
14	Complete	Yes	1	No	Yes
15	Circumdissection	Yes	5	No	Yes
16	Complete	Yes	1	Surgical wound infection	Yes
17	Complete	No	0	No	Yes
18	Complete	Yes	1	No	Yes
19	Partial	Yes	1	Surgical wound infection, Perilesional bleeding	Yes
20	Circumdissection	Yes	1	No	Yes
21	Complete	Yes	1	No	Yes
22	Complete	Yes	1	No	Yes
23	Complete	Yes	1	No	Yes
24	Complete	Yes	1	No	Yes
25	Complete	Yes	1	No	Yes
*AVM, arteriovenous malformation; Cured, Total obliteration of AVM					

ANNEX VII: TABLE 9. PATIENTS OUTCOMES AFTER AVM SURGERY

Table 9. Patients Outcomes After AVM Surgery

PATIENTS OUTCOMES AFTER AVM SURGERY*									
Number	**Neurological Symptoms**		**mRS**			**Seizures**			**AEDs removed**
	Postop	**6 months**	**Postop**	**6 months**	**12 months**	**Intraop**	**Postop**	**6 months**	
1	Language disorders	NNS	0	0	0	No	No	No	NP
2	NNS	NNS	0	0	0	No	No	No	Yes
3	Motor Deficit	NNS	1	2	1	No	No	Yes	No
4	NNS	NNS	2	0	0	No	Yes	No	Yes
5	NNS	NNS	2	0	0	No	Yes	Yes	No
6	Language disorders, Motor Deficit	Language disorders, Motor Deficit	3	2	2	No	No	Yes	No
7	Sensitive deficit	NNS	1	0	0	No	No	No	NP
8	Motor Deficit	NNS	3	0	0	No	No	No	No
9	NNS	NNS	1	0	0	No	Yes	Yes	No
10	NNS	NNS	0	0	0	No	No	No	NP
11	NNS	NNS	1	1	1	No	Yes	No	No
12	NNS	NNS	0	0	0	No	No	No	No
13	NNS	NNS	0	0	0	No	No	No	NP
14	Language disorders, Motor Deficit	NNS	2	0	0	No	No	No	No
15	Visual Deficit	NNS	2	0	0	No	No	No	NP
16	Language disorders, Motor Deficit	Language disorders, Motor Deficit	3	2	1	No	No	No	No
17	NNS	NNS	0	0	0	No	No	No	No

18	Language disorders, Motor Deficit	Language disorders, Motor Deficit	3	1	1	No	No	No	No
19	Motor Deficit	NNS	4	0	0	No	Yes	Yes	No
20	Language disorders, Motor Deficit, Sensitive deficit	Motor deficits	4	4	3	No	Yes	Yes	No
21	NNS	NNS	0	0	0	No	No	No	No
22	NNS	NNS	0	0	0	No	No	Yes	No
23	Language disorders, Motor Deficit, Sensitive deficit	NA	2	NA	NA	No	No	NA	No
24	Motor Deficit	NA	1	NA	NA	No	No	NA	No
25	NNS	Language disorders	0	0	0	No	No	No	NP

*AVM, arteriovenous malformation; mRS, modified Ranking Scale; AEDs, Antiepileptic drugs; Postop, postoperative; Intraop, intraoperative; NNS, No Neurological Symptoms; NA, No available; NP, No previous AEDs

ANNEX VIII: TABLE 10. AVM FINAL TOTAL OBLITERATION

Table 10. AVM Final Total Obliteration

AVM FINAL TOTAL OBLITERATION*	**24/25**
Complete Resection	**19/25**
-Preop embol + surgery	**13/19**
-Surgery	**6/19**
Incomplete Resection	**6/25**
-Preop embol +Partial Resection + RDS	**3/6**
-AVM cured	3/3
-Preop embol + Circumdissection + RDS	**3/6**
-AVM cured	2/3
*AVM, arteriovenous malformation; Preop, preoperative; embol, endovascular embolization; RDS, radiosurgery	

ANNEX IX: TABLE 11. COMPARISION WITH UCSF: UTILITY OF BRAIN MAPPING ADAPTED FROM (27)

Table 11. Comparison with UCSF: Utility of brain mapping adapted from (27)

UTILITY OF BRAIN MAPPING*		
Variables	**UCSF**	**HUB**
Function identified	11/12	24/25
Increasing attention during dissection	8	18
Change of surgical strategy	2	3
Stop surgery	1	3
*UCSF, University of California San Francisco; HUB, hospital Universitari Bellvitge		

ANNEX X: TABLE 12. COMPARISION WITH UCSF: SURGICAL RESULTS AND PATIENTS OUTCOMES AFTER AVM SURGERY ADAPTED FROM (27)

Table 12. Comparison with UCSF Surgical Results and Patients Outcomes After AVM surgery adapted from (27)

SURGICAL RESULTS AND PATIENTS OUTCOMES AFTER AVM SURGERY*		
Variables	**UCSF**	**HUB**
Number of patients	12	25
Asleep Mapping	7/12 (58.3%)	22/25 (88%)
Awake Mapping	5/12 (41.6%)	3/25 (12%)
Preop seizures	5/12 (41.6%)	16/25 (64%)
Intraop seizures	2/12 (16.6%)	0 (0%)
Postop seizures	3/12 (25%)	6/25 (24%)
New deficit transient	8 /12(66.6%)	8/25 (32%)
New deficit permanent	4/12 (33.3%)	5/25** (20%)
mRS ≤ 2 (6 months)	10/12 (83.3%)	22/25**(88%)
Mortality	0 (0%)	0 (0%)
Complications	2/12 (16.6%)	6/25 (24%)
Total resection (complete)	8/12 (66.6%)	19/25 (76%)

*UCSF, University of California San Francisco; HUB, hospital Universitari Bellvitge; mRS, modified Ranking Scale; Preop, preoperative; Intraop, intraoperative; Postop, postoperative

**No 6 months follow-up in two cases