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Treatment for Brain Arteriovenous Malformations

PhD thesis

Léčba arteriovenózních malformací mozku

Disertační práce

Školitel:

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Abstract

Introduction: The surgical and endovascular results of the treatment of pial AVM provided at our Neurosurgical centre are presented. These results are supported by neuropsychological outcomes of subgroup of treated patients. Going by these results and by an overview of literary data on the efficacy and complications of each therapeutic modality, the optimal algorithm of indications is presented

Cohort of patients: The main series comprises 222 patients aged 9 to 87 years treated in the years 1998 - 2013. The surgical group consists of 85 patients, 55 patients received solely endovascular treatment. Thirty-four patients were consulted and referred directly to the Radiosurgical unit. The remaining 48 were recommended to abide by the strategy of „watch and wait". A subgroup of 66 patients, who underwent treatment of AVM was neuro-psychologically tested at least two years after treatment using a battery of tests constructed specifically for this study. A control group consisted of 10 subjects without any neurological disease.

Results: In the surgical group, serious complications were 3.5% at a 96.5% therapeutic efficacy. As for AVM treated with purely endovascular methods, serious procedural complications were seen in 5.5% of patients, with efficacy totalling 36.4%. One observed patient suffered bleeding resulting in death. For comparison with literary data for each modality, a survival analysis without haemorrhage following monotherapy for AVM with each particular modality was carried out.

Within neuro-psychology study the subgroup of patients with an obliterated AVM after treatment was compared to the control group showed no significant differences, similarly as divided according to treatment modality and in comparison of the SM groups.

Conclusions: Those patients in whom complete obliteration was achieved with treatment, scored in neuropsychological test similarly to the background population, implying active AVM treatment doesn't cause deterioration in neuropsychological performance.

1. We regard surgical treatment as the treatment of choice for AVM of Spetzler-Martin (S-M) grades I and II. As for grade III cases - only for those which are surgically accessible.

2. Endovascular intervention should be used mainly for preoperative embolization ion strictly selected cases, as a curative procedure solely for lower-grade AVM in patients with co-morbidities; for higher-grade cases as a palliation only.

3. Stereotactic irradiation with LGK is advisable mainly for poorly accessible, deep-seated grade-III AV malformations. In the case of lower grades, the final decision is left to the properly informed patient him/herself.

4. Observation should be used as the method of choice in AVM of grades IV and V where active therapy carries greater risk than the natural course of the disease

Keywords: Brain arteriovenous malformation, AVM, Microsurgery, Resection, Endovascular treatment, Radiosurgery, Literature review, Neuropsychology, Outcome, Cognitive deficit

Abstrakt

Úvod: V této práci jsou prezentovány neurologické výsledky chirurgické a endovaskulární léčby mozkových arteriovenozních malformací. Tyto neurologické výsledky jsou podpořeny studií výsledků neuropsychologických na podskupině pacientů. Na základě těchto výsledků a extenzivní literární rešerše doporučujeme optimální léčebný algoritmus.

Sestava: Hlavní sestava čítá 222 pacientů ve věku 9 až 87 let, léčených mezi léty 1998 a 2013. Chirurgická poodskupina sestává z 85 pacientů, endovaskulárně bylo léčeno 55 pacientů. Dalších 34 pacientů bylo odesláno přímo k radiochirurgické léčbě. Zbylých 48 pacientů bylo léčeno konzervativně. Podskupina 66 pacientů byla podrobena neuropsychologickému testování minimálně 2 roky po léčbě za použití testové baterie konstruované speciálně pro tuto studii. Kontrolní skupina sestávala z 10 zdravých dobrovolníků.

Výsledky: V chirurgicky léčené podskupině pacientů byla mírá závažných komplikací 3.5% s úspěšností totální okluze 96.5%. V čistě endovaskulárně léčené podskupině byla mírá závažných komplikací 5.5% s úspěšností totální okluze 36.4%. Jeden z observovaných pacienů zemřel následkem intracerebrálního krvácení. Ke srovnání s literárními daty byla provedena literární rešerše. Na jejím základě byla pro jednotlivé léčebné modality předpovězena pravděpodobnost krvácení v dlouhodobém horizontu.

V rámci neuropsychologické studie byli srovnáni pacienti s kompletně okludovanou AVM s kontrolní skupinou. Toto srovnání neukázalo významné rozdíly v neuropsychologickém výkonu, stejně jako srovnání pacienů dělených dle léčebné modality a SM stupně.

Závěry: Pacienti, u kterých bylo dosaženo kompletní okluze AVM, skórovali v neuropsychologických testech stejně, jako kontrolní skupina, aktivní léčba AVM tedy nezpůsobuje zhoršení neuropsychologického výkonu.

1. Chirurgická léčba je metodou volby pro pacienty s AVM SM stupně I a II. Pro pacienty s AVM SM stupně III je vhodná, pokud je léze chirurgicky přístupná.

2. Endovaskulární intervence by měly být používany pouze v případě předoperační embolizace, i tehdy jen u přísně vybraných patologií. Jako léčebná modalita by měla být užívana pouze u pacientů s AVM nízkého SM stupně, pokud jsou chirurgicky rizikoví. U pacientů s AVM vyššího stupně pouze jako paliativní metoda.

3. Stereotaktická radiochirurgie je zejména vhodná k léčbě obtížně přístupných, hluboko uložených lézí SM stupně III. V případě lézí nižšího stupně je rozhodnutí ponecháno na obšírně informovaném pacientovi.

4. Observace by měla být použita u pacientů s AVM stupně IV a V, u kterých je jakákoli aktivní terapie spojena s vyššími riziky, než přirozený průběh.

Klíčová slova: Mozková arteriovenozní malformace, AVM, Mikrochirurgie, Resekce, Endovaskulární intervence, Radiochirurgie, Literární rešerše, Neuropsychologie, Léčebný výsledek, Kognitivní deficit

Poděkování

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Many thanks to Patricia de Lacy, MD, who helped me a lot with translation into English.

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List of abbreviations

AVM / bAVM – brain arteriovenous malformation

CBF – cerebral blood flow

CT – computed tomography

CT – computed tomography angiogram

DSA – digital subtracton angiography

DTI – diffusion tensor imaging

fMRI – functional magnetic resonance imaging

FND – focal neurological deficit

GCS – Glasgow coma scale

GOS – Glasgow outcome scale

HHT – hereditary hemorrhagic teleangiectasia

ICH – intracerebral hemorrhage

IL-1, 6 – interleukins 1, 6

LGK – Leksell gamma knife

MM – morbidity and mortality

MMP – matrix metlloproteinases

MRI – magnetic resonance imaging

mRS – modified Rankin scale

NPPB – normal perfussion pressure breakthrough

SAH – subarachnoid hemorrhage

S-M grade – Spetzler-Martin AVM grade

TGF-β – transforming growth factor beta

TNF-α – tumor necrosis factor alpha

VEGF – vascular endothelial growth factor

1. Introduction

Brain Arteriovenous malformations (AVM) have been described more than a century ago by Steinheil. Since the introduction of cerebral angiography and the large development of non-invasive imaging techniques in the latter half of 20th century, the number of AVMs being diagnosed is rapidly increasing [1]. Although there has been significant developments in the active treatment techniques such as surgical resection, endovascular embolization and stereotactic radiosurgery, observation alone is still a useful treatment technique that is adopted for some AVMs. The decision regarding which treatment modality should be adopted in a particular case depends on many features of a particular AVM, the patient affected, the possible morbidity and mortality of the proposed treatment procedures and their efficacy in a particular institution. Moreover, the natural history of the disease must be taken into account and compared to the possible benefits of active treatment. All these factors must be meticulously studied before the decision to undertake active treatment is made.

1.1. Motivation to this study

In this study we present a literature review of the natural course of AVM disease and the active treatment modalities. These are compared with surgical and neuropsychological results achieved at our institution and based on these comparisons, treatment recommendation for AVM is articulated. Furthermore, the efficacy of different treatment methods in the long-term perspective is studied.

2. AVM definition and angioarchitecture

Arteriovenous malformation of brain (pial AVM) is complex tangle of abnormal vessels. AVM has three main morphological components:

1. Arterial feeders
2. Racemose centre comprising of dysplastic vessels called “nidus”
3. Draining veins

2.1. Feeding arteries

These can be single or multiple. They are not always exclusively devoted to AVM. Arterial feeders of a particular AVM could have their origin from more than one main cerebral artery. Besides typical feeding arteries there could be normal brain arteries around the AVM, which are just stuck to the AVM nidus and these should be preserved during surgery.

2.2. Associated aneurysms

AVMs are often associated with aneurysms. These could be divided according to its relation to AVM to:

1. Distal flow-related aneurysm – on feeding artery
2. Proximal flow-related aneurysm – on main trunk from which feeding artery sprouts
3. Nidal aneurysm – within an AVM nidus
4. Remote / Not flow-related aneurysm – on different cerebral artery

AVM–associated aneurysms could be single or multiple – Křupka et al. [2] reported seven AVM-associated aneurysms in mid-age woman presenting with SAH. Platz et al. [3] found at least one AVM-associated aneurysm in 59 out of 216 patients, most often feeding artery aneurysm. Hemorrhagic presentation was more frequent in these patients than in patients without aneurysm, similarly as was presence of aneurysm associated with poor outcome. Stapf et al. [4] found concurrent aneurysms in 117 (25%) of 463 consecutive patients. Out of these 117 aneurysms only 18 were remote. Presence of intranidal aneurysm raised relative risk of haemorrhage to 2.28, whereas feeding artery aneurysm to 1.88.

2.3. Nidus component

There could be single- or multiple-compartmental nidus according to the number of feeding arteries and microscopic development of the nidus. Vessels within the nidus are dysplastic, with thin walls due to deficient lamina muscularis. Furthermore, the nidus could be compact, without intervening brain tissue, or diffuse, where brain tissue could be found in between vascular channels.

2.4. Draining veins

Could be single or multiple. Similarly as feeders not exclusively devoted to AVM. Surrounding brain tissue could be drained into AVM draining veins. This fact is of great importance during surgery and possible post-operative complications such as occlusive hyperemia. From a surgical point of view, draining veins are divided into two groups:

1. Deep draining veins – Great cerebral vein of Galen, Basal vein of Rosenthal, Internal cerebral vein, Straight sinus and Inferior saggital sinus
2. Superficial draining veins – the rest of cerebral veins and sinuses

3. Genetics of arteriovenous malformations

AVMs are usually sporadic lesions, except in some hereditary diseases such as Osler-Weber-Rendu syndrome (Hereditary Haemorrhagic Teleangiectasia, HHT), Wyburn-Mason syndrome (Encephaloretinofacial angiomatosis), Sturge-Weber syndrome (Encephalotrigeminal angiomatosis) or Louis-Barr syndrome (ataxia-teleangiectasia). Two main subtypes of HHT were identified (HHT1 and HHT2), both showing autosomal dominant Mendelian hereditary pattern. In both subtypes, the genes involved in the TGF-β signalling pathways are impaired [5]. In patients harbouring HHT1, the prevalence of brain AVM is 1000 times higher than in the normal population and in patients harbouring HHT2, the prevalence is 100 times higher than in the normal population [6].

Historically, AVMs were regarded as congenital lesions developing during embryonic and the early fetal stages [7-11]. This hypothesis has been challenged in recent studies. In sporadic cases of brain AVMs, candidate genes have been identified and possessing single nucleotide polymorphism connected with AVM incidence or haemorrhagic presentation of AVMs [12, 13]. According to recent studies, inflammatory genes (TNF-α, IL-1) are connected with those AVMs at higher risk of haemorrhagic presentation during the natural course of disease [14, 15]

It has been shown that in the AVMs there is overexpresseion of the vascular endothelial growth factor (VEGF) and this has been shown to correlate with the haemorrhagic tendency of an AVM [16]. Furthermore, overexpression of angiopoietins (ANG) has also been shown [17]. Overexpression of these signalling molecules leads to overexpression of matrix metalloproteinases (MMPs), particularly MMP-9 expression which is significantly higher in

AVM tissue compared to normal brain [18, 19]. MMP-9 is strongly correlated with inflammatory molecules such as interleukin 6 (IL-6) and myeloperoxidase [18, 20].

All these facts led to the recent view that AVMs are dynamic lesions which are growing, regressing and even could form de novo, especially as a response to minor brain injury, infection or irradiation [21, 22].

4. Epidemiology of AVM

The incidence of AVM is 1 per 100,000 according to a paper published by Stapf in 2002 [23]. These findings were based on a cohort of 207 patients identified in a prospective database NOMASS (Northern Manhattan Stroke Study). The incidence rate of first-ever haemorrhage was found to be 0.55/100 000 in the same study. They also found similar results in a larger population in 'The New York AVM study' [24]. This study was conducted on roughly 9.5 million residents of New York between years 2000 and 2002, altogether on more than 21 million patient-years. The incidence of AVM was found to be 1.34 per 100,000, (95% CI, 1.18 to 1.49). The incidence of a first-ever AVM haemorrhage was 0.51 per 100,000, (95% CI, 0.41 to 0.61). The prevalence of AVM haemorrhage was 0.68 per 100,000 (95% CI, 0.57 to 0.79).

According to another prospective population-based study; the Scottish Intracranial Vascular Malformations Study (SIVMS) published in 2003 [25], the incidence of AVM was 1.12 (95% CI, 0.90 to 1.37). The results were based on a 2 year follow-up of the Scottish population of 4.1 million people.

The Mayo Clinic study was published in 1996 [26]. The population of Olmsted County, Minnesota, was followed between 1965 and 1992 and the incidence of symptomatic intracranial vascular malformations was 1.22 per 100,000 of which the prevalence of AVMs was found in 26 out of the 48 symptomatic cases.

5. Physiology of arteriovenous malformations

5.1. Arterial side

It has been shown in many studies that smaller AVMs are more prone to rupture [27-31]. Spetzler et al. [31] presented a study of 24 patients in whom intra-arterial pressure in the feeder vessels was recorded during surgery. The difference between mean arterial pressure and feeding artery pressure was significantly higher in unruptured AVMs than in ruptured ones. Furthermore, smaller AVMs were associated with significantly higher feeding artery pressures. Similar results were achieved by Henkes [32, 33], who measured arterial pressure within AVM feeders on 139 patients, showing higher pressures in previously ruptured and smaller AVMs. Furthermore, direct relationship between AVM feeder pressure and the degree of endovascular embolization was clearly demonstrated.

5.2. Steal phenomenon

This phenomenon may be responsible for clinical presentation in patients who suffer from neurological deficit. This deficit could be temporary depending on the actual hemodynamic status of a particular patient. SPECT and perfusion CT studies [34, 35] showed decreased blood flow in cortical areas surrounding AVMs. This blood flow restored after AVM resection.

Chronic hypoperfusion of adjacent cortex leads to overexpression of VEGF and other vascular growth factors producing capillary neovascularization with many fenestrations, with increase water diffusibilty. Thus, after AVM resection, increased blood flow could cause cerebral

oedema and even haemorrhagic transformation. Upregulation of VEGF in chronic hypo-perfused cortex could be understood as the molecular explanation for normal perfusion pressure breakthrough phenomenon. A similar mechanism is probably causing AVM remodelling and neovascularization after partial endovascular embolization [36].

The concept of local and distant steal phenomenon is supported by neuropsychological studies showing a deficit in cognitive tests (especially verbal processing and memory) regardless of whether an AVM is located in a dominant or non-dominant hemisphere [37, 38].

5.3. Normal perfusion pressure breakthrough

First described by Spetzler in 1978 [39]. This theory suggests that CO_2 reactivity and autoregulation of vessels in AVM surrounding brain tissue is impaired. The malformation is understood to be a channel without resistance, thus surrounding vessels remain maximally dilated to ensure adequate cerebral perfusion. This chronic dilatation leads to loss of autoregulation. After AVM resection, the pressure in these surrounding low-resistance vessels increase steeply and oedema and/or haemorrhage could occur. Animal models were constructed by Beneš in 1997 [40] to prove this concept. Although this concept was supported in several studies [41-44], the others are contradictory. Young [45] showed an increase in cerebral blood flow in regions adjacent to an AVM after resection in 25 patients . However no further increase of cerebral blood flow was noted after the increase of mean arterial pressure after resection. To date, normal perfusion pressure breakthrough theory seems to be related and complementary in explanation of haemodynamic changes after AVM resection as recently discussed by Rangel-Castila and Spetzler [46].

5.4. Venous side

Disturbances on the venous side of an AVM undoubtedly contribute to the pathogenesis of this disease. According to some authors [47-49] developmental venous anomalies could be predecessors of AVMs. During further development, venous hypertension promotes cerebral hypoperfusion which starts an angiogenic cascade and AVM formation. A similar mechanism could be responsible for the AVM formation in case of venous outflow obstruction due to developmental stenosis or venous thrombosis [50]. Venous architecture is, according to some studies, associated with the risk of haemorrhage. Exclusively deep venous drainage and venous stenosis increase the risk of AVM rupture [51-53].

5.5. Occlusive hyperemia

Suggested by al-Rodhan in 1993 [54] showing decrease of venous intraluminal pressure after AVM resection, which could lead to thrombus formation and subsequent obliteration [55]. Furthermore, AVM draining veins could drain brain tissue adjacent to an AVM, which is under influence of angiogenesis factors forming so called „perinidal vessels“ or „red veins“. These vessels could be incorporated into AVM nidus during AVM development. After venous thrombosis haemorrhage from perinidal vessels can occur [36].

5.6. Compartmental model of AVM nidus

In the most simple case, AVM nidus is monocompartmental, compact, with one feeder and one draining vein (Figure 8.2). In case of multicompartmental nidus, several feeders and several draining veins are present. These compartments could be confluent or separated by brain tissue and could be visualized separately using catheter angiography (Figures 8.13 – 8.15). Subsequently, surgical plan could be adequately prepared [56]. Concept of multicompartmental model brought attention to so-called "hidden compartments" [57], which are not filled on catheter angiography and could be responsible for AVM pseudo-growth – enlargement of AVM nidus on serial angiograms. When left behind during surgery could be responsible for post-op bleeding after abrupt filling of previously collapsed channels. Similarly, filling of previously hidden compartments after surgery or radiosurgery could be explanation of AVM recurrence after treatment [58-60]. On the other hand, transnidal pressure gradients are lower in multicompartmental AVMs. The more compartments AVM has, the lesser are transnidal pressures, as was shown by Litao [61]. This fact is in accordance with known fact that larger AVMs are less prone to rupture than smaller ones.

6. AVM presentation

Clinical presentation of AVM is usually interpreted as first event, which is attributable to subsequently diagnosed AVM. Classical types of presentation are understood as the following possible situations:

1. Intracranial bleeding, especially intra-cerebral hematoma
2. Epilepsy
3. Focal neurologic deficit

Other types of presentations would be headaches, dizziness, cognitive deficit (which is attributable to steal phenomenon). These are not unanimously understood as typical AVM presentations and data regarding these are scarcely reported in the literature.

6.1. Hemorrhagic presentation

According to Olmsted county study published by Brown [62], haemorrhagic presentation occurred in 69% of symptomatic patients. The most common type of haemorrhage was intracerebral bleeding, the second most common subtype was subarachnoid haemorrhage. The age and gender adjusted annual occurrence rate of intracranial haemorrhage was 0.82% per 100.000 person-years. In Columbia databank analysis from 2004 [63], 45% of AVMs presented with intracranial haemorrhage. Furthermore, authors found independent association of infratentorial region AVMs with haemorrhagic presentation. In 2009 da Costa et al. [64] presented Toronto experience with 678 AVM patients, followed for 1932 patient-years. Haemorrhagic presentation was found in 258 (38%) patients.

6.2. Morbidity and mortality of AVM related intracranial haemorrhage

In the Olmsted county study 30-days AVM related haemorrhage mortality accounted to 17.6% [62]. In a recent paper by van Beijnum [65] the outcome after AVM-related haemorrhage was found to be significantly better than in spontaneous ICH. Death or dependence was found after two years follow-up in 83% of patients after spontaneous ICH, whereas only in 40% of patients after AVM-related haemorrhage.

6.3. Epilepsy presentation

Garcin et al. [66] found 29% of 155 patients harbouring newly diagnosed AVM presenting with epilepsy. Independent risk factors for epilepsy presentation were male sex, increasing AVM size, frontal lobe and arterial borderzone location. Al-Shahi, based on Scottish population-based study, reported 8% five-year risk of first seizure in patients with AVM. For patients presented with haemorrhage, this risk raised to 23% [67]. In recently published Italian study [68], initial clinical manifestation of AVM was seizure in 30.7% (31 out of 101) patients. The main associated factors with epilepsy presentation were temporal or frontal lobe location and superficial topography. Angioarchitecture of AVM was studied by Sturiale [69] on 168 patients. Out of these patients 47% presented with haemorrhage and 29% presented with seizure. Seizure presentation was associated with nidus size above 4cm in diameter, AVM fed by middle and posterior cerebral arteries and cortical location without lobe predisposition. Shankar et al. [70] studied angioarchitecture of AVM and based on his observation proposed grading system for prediction of seizure occurrence. Grading system takes into account AVM

location, fistulous component within AVM nidus, venous outflow stenosis and a presence of long pial course of draining vein.

6.4. Focal neurologic deficit (FND)

FND is a rare type of AVM presentation. According to Choi et al. [71], only 7% of patients presented with a FND, predominantly females. Other independently associated conditions were increasing age, deep brain location, brainstem location and venous ectasias. No association was found between AVM nidus size, lobar location, arterial supply and venous drainage pattern. Lv [72] analysed 302 consecutive AVM patients. Non-haemorrhagic neurological deficit was found in 24 (7.9%) of them. An association with female sex, deep location, more than three feeders, more than three draining veins, venous ectasias and Spetzler-Martin grade III-V was found.

7. Natural course

The annual rupture rate of AVM was estimated as 4% in a classical study by Ondra in 1990 [73]. These esults were based on the follow-up of 160 patients with a mean follow-up period of 23.7 years. The majority (114) of patients in this study presented with intracranial haemorrhage and the mean time to re-bleeding was 7.7 years.

Stapf et al. [74] in 2006 analysed Columbia database showing annual rupture rate of 0.9% for patients without haemorrhagic AVM presentation. This number increased up to 34.4% according to the presence of identified risk factors - exclusively deep venous drainage, increasing age, initial haemorrhagic presentation and deep brain location. Relatively low rupture rate of most favourable patients led to the initiation of the ARUBA study [75].

In Toronto, an AVM databank [64] da Costa found the annual bleeding rates of 4.61% for a whole cohort of 678 patients. In patients presenting with AVM haemorrhage, the rupture rate increased to 7.48%. In patients presenting with seizures, the annual rupture rate was 4.16%. The presence of associated aneurysm increased annual ruptue rate to 6.93%.

Hernesniemi et al. [76] followed 238 patients with a mean follow-up period of 13.5 years. The annual rupture rate was 2.4%. The risk was highest during first 5 years and decreasing thereafter. Risk factors connected with haemorrhage were previous rupture, large size and infratentorial and deep locations.

8. AVM grading

8.1. Surgical AVM grading

There are several proposed grading systems for pial arteriovenous malformations. These classifications are based on a sole nidus diameter, angioarchitecture and/or location. The first classification system was suggested by Luessenhop and Genarelli in 1977 [77]. Nowadays, the most commonly used grading system is that proposed by Spetzler and Martin in 1986 [78]. (S-M grading) This grading system evaluates the diameter of the AVM nidus, the eloquence of adjacent brain tissue and the presence (or absence) of deep venous drainage. The complete system is described in Table 8.1 and examples are depicted in Figures 8.1. – 8.15. This grading system was validated on a surgical series of 100 AVMs showing excellent correlation with surgical results. Later S-M grade VI was added to distinguish essentially inoperable AVMs. Dr Spetzler recently published his new 3-tier classification system [79], in which S-M grades I and II are combined just like S-M grades IV and V. Modifications of the Spetzler-Martin grading system were suggested by de Oliveira [80] and Lawton [81]. Both modifications are concerning S-M grade III AVMs due to the heterogeneity of this subgroup, in which small and deep AVMs are pooled together with larger superficial AVMs. The reported surgical results of this subgroup were heterogenous as well [80, 82]. De Oliveira suggested to divide S-M group III into two groups – IIIa and IIIb, where IIIa AVMs are larger size AVMs and IIIb are smaller sized AVMs in eloquent areas. Due to the poor definition of IIIa and IIIb grades, Lawton suggested a 4-tier classification of S-M grade III AVMs according to the points obtained in each S-M category. Lawton's III- (S1V1E1) grade AVMs were found to carry a surgical risk comparable with AVMs in S-M grades I and II. On the other hand, Lawton's grade III+ (S2V0E1) AVMs carry a higher

surgical risk comparable with S-M grade IV AVMs. Lawton's grade III (S2V1E0) were found to possess intermediate surgical risks. Grade III*AVM's (S3V0E0) are very rare types of AVMs and therefore the surgical risks could not be properly established [81].

		points
Nidus diameter		
	< 3 cm	1
	3 - 6 cm	2
	> 6 cm	3
Deep venous drainage		
	No	0
	Yes	1
Eloquence of adjacent brain		
	No	0
	Yes	1

Table 8.1. Spetzler-Martin AVM grading system

8.2. Radiosurgical AVM grading

Radiosurgical AVM grading could be understood from 2 different points of view. The 'K' index suggested by Karlsson [83] or the 'Obliteration Prediction Index' (OPI) suggested by Schwartz [84] are using a ratio of radiation dose to AVM diameter for the likelihood of AVM obliteration. On the other hand, the grading system suggested by Pollock in 2002 [85] emphasizes the patients' age, AVM location and volume and is strongly correlated with patient outcome. This grading system was further modified by the same group in 2008 [86].

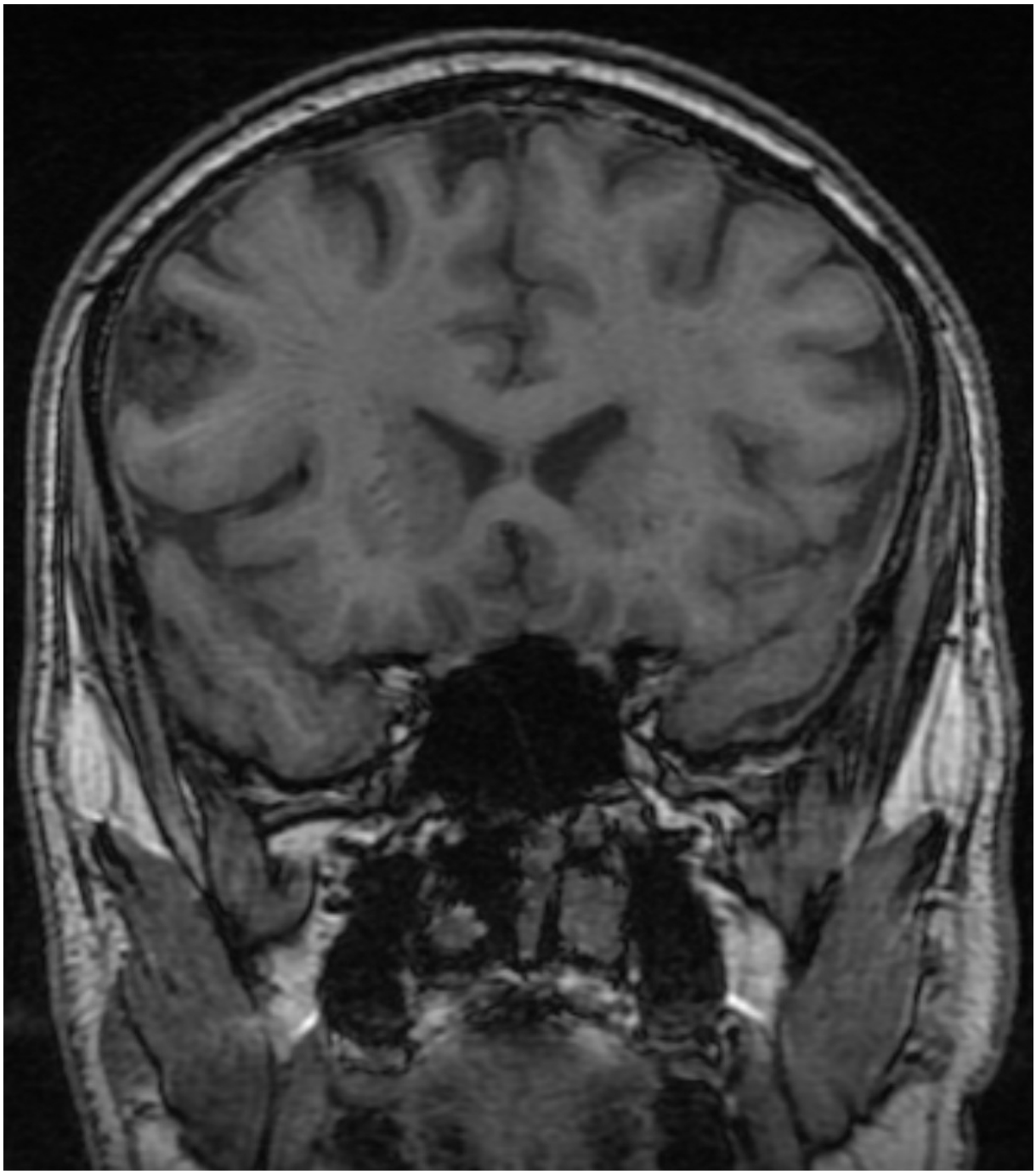


Figure 8.1. Coronal MR scan of right frontal AVM SM I

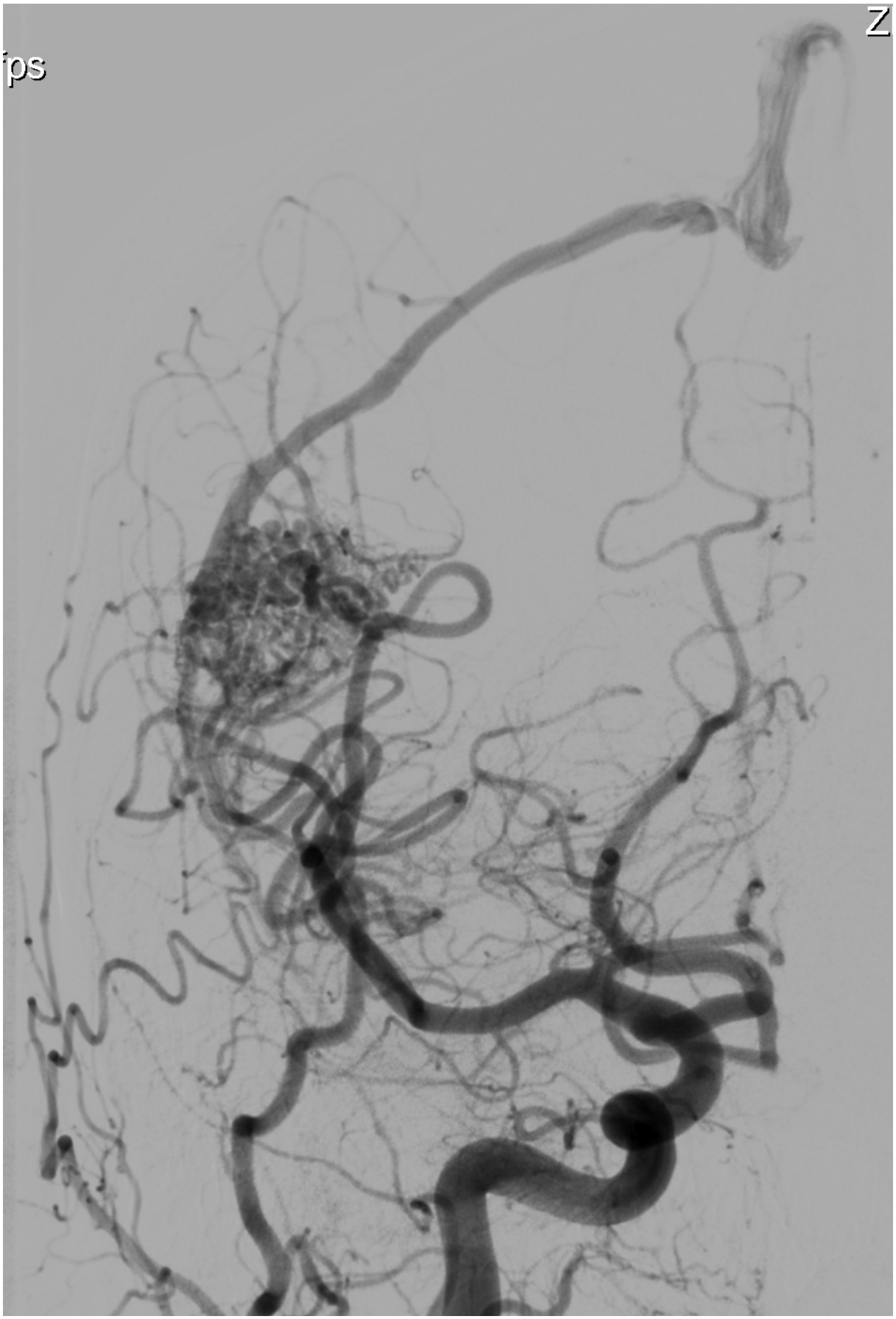


Figure 8.2. Cathether angiogram (A-P view) of right frontal AVM SM I with superficial draining vein.

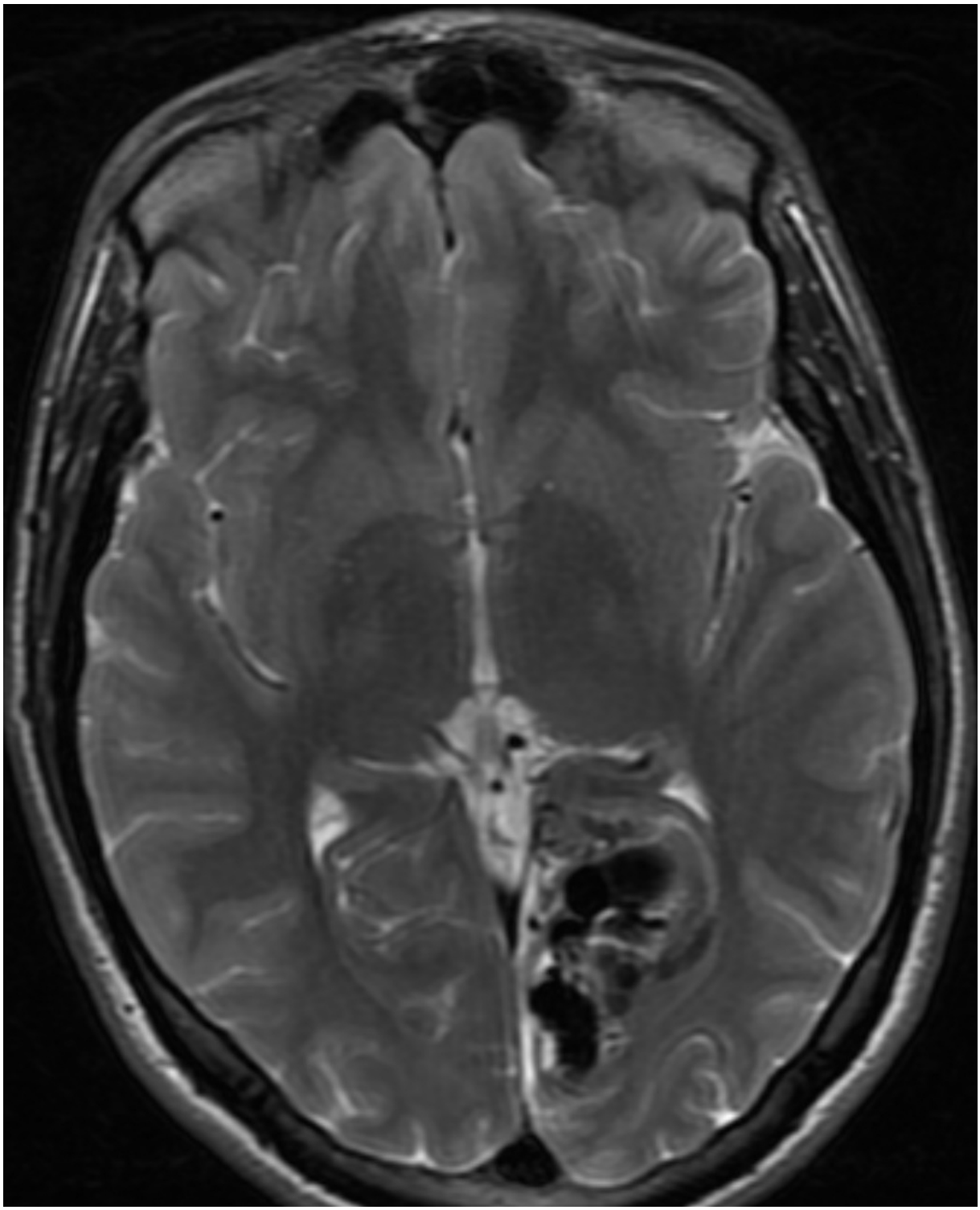


Figure 8.3. T2-weighted axial MR scan of left occipital AVM SM II

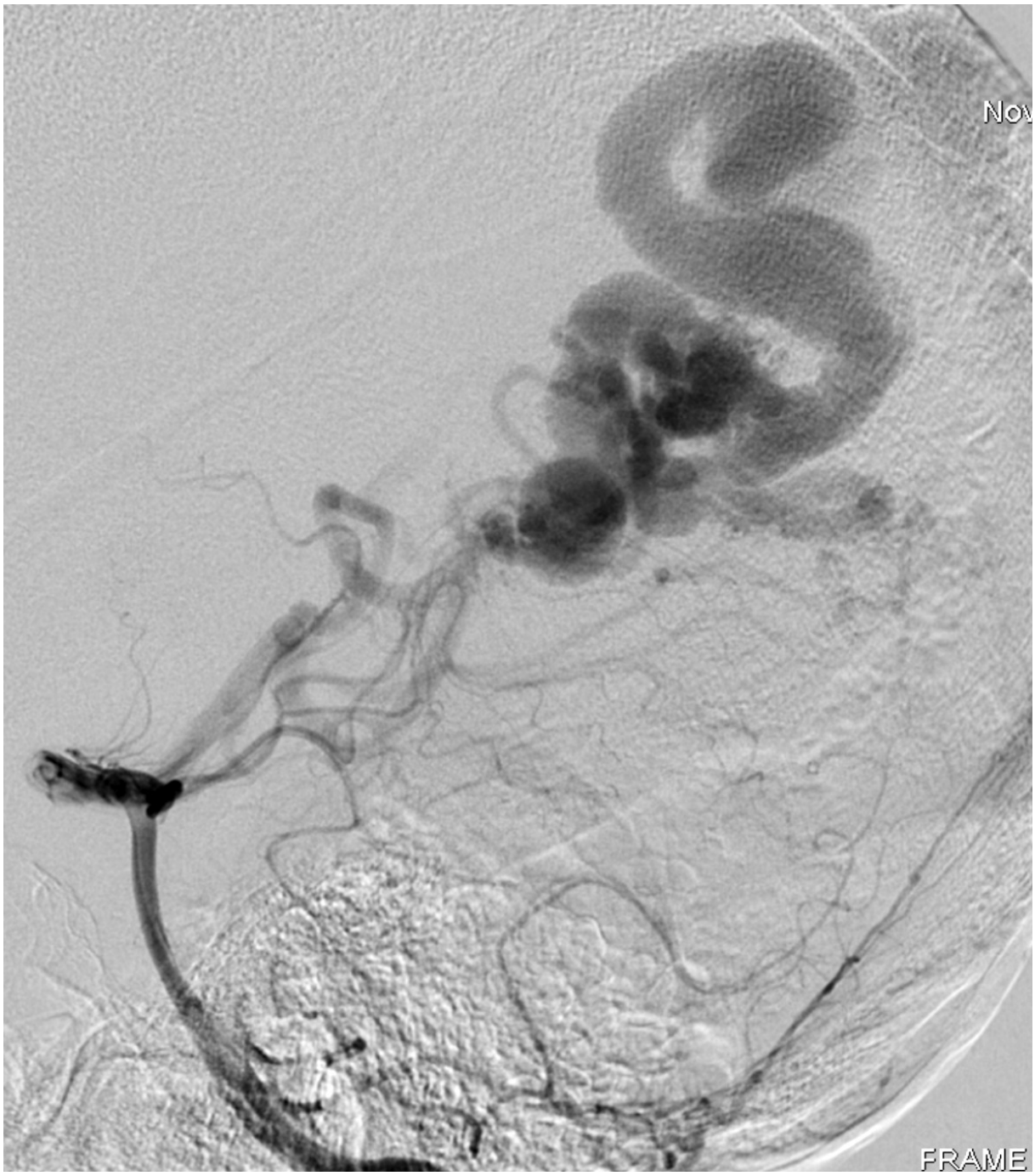


Figure 8.4. Catehteher angiogram (lateral view) of left occipital AVM SM II – feeders from posterior circulation

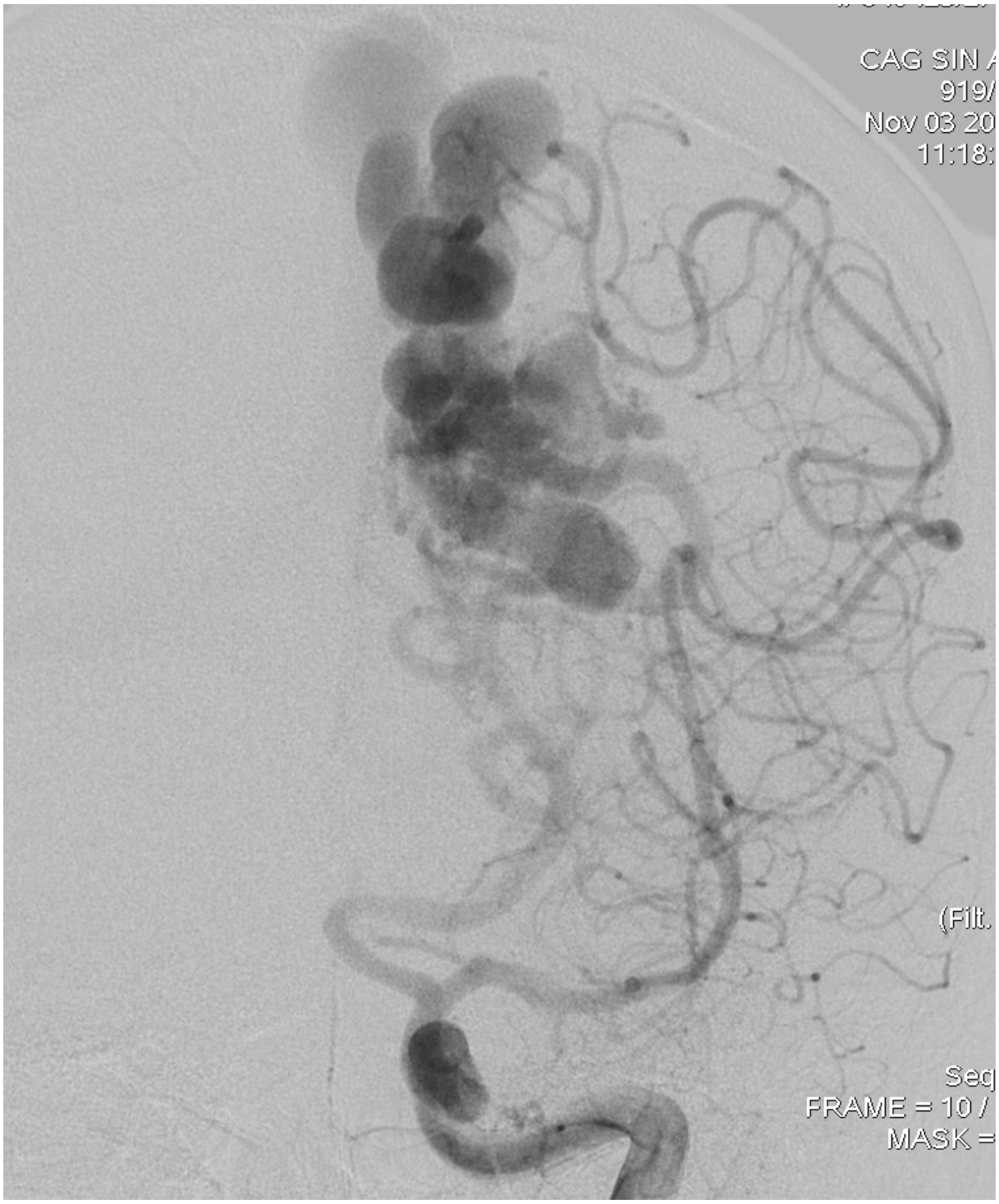


Figure 8.5. Catehteher angiogram (A-P view) of left occipital AVM SM II – feeders from anterior circulation.

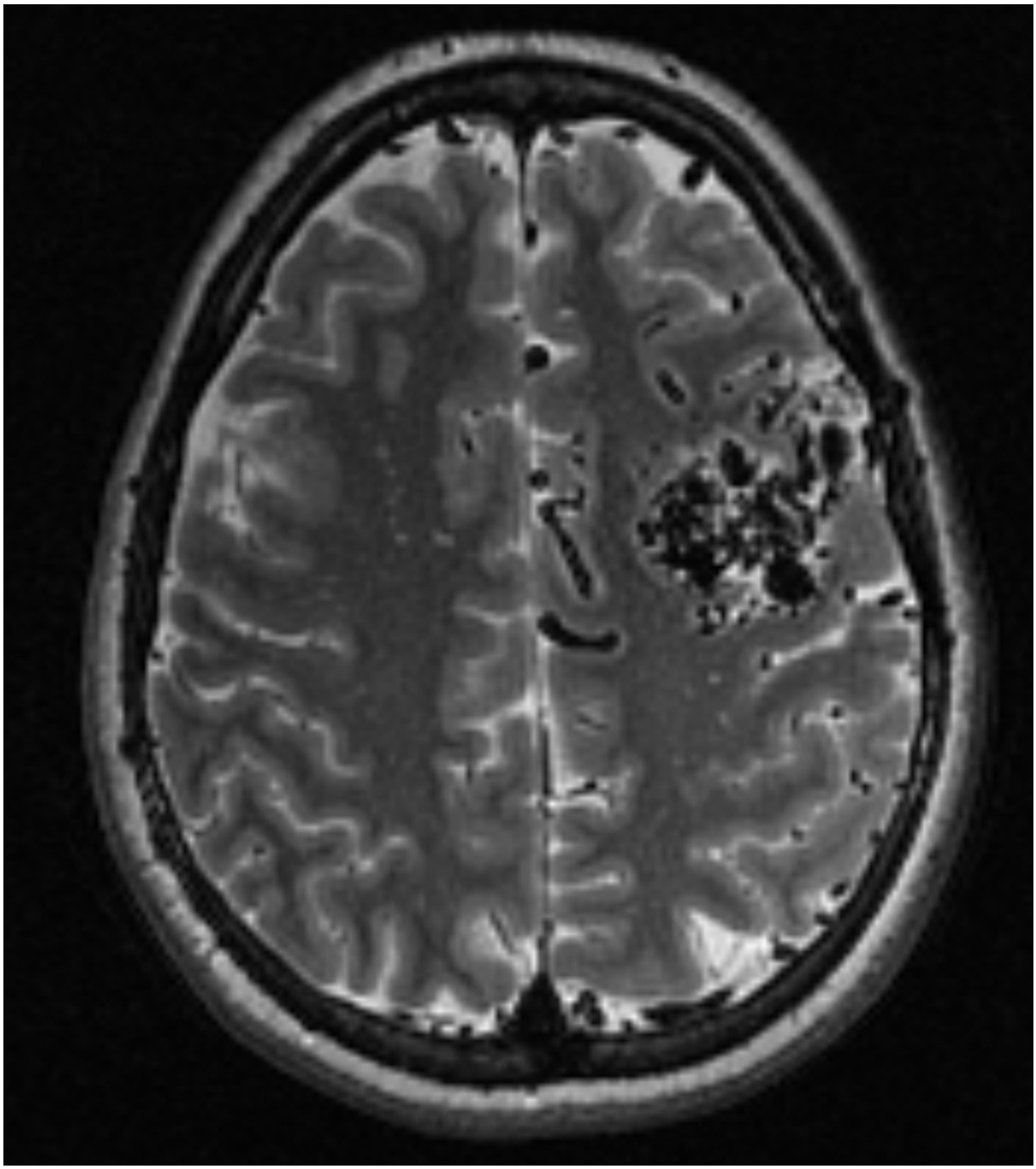


Figure 8.6. T2-weighted axial MR scan of left frontal AVM SM III.

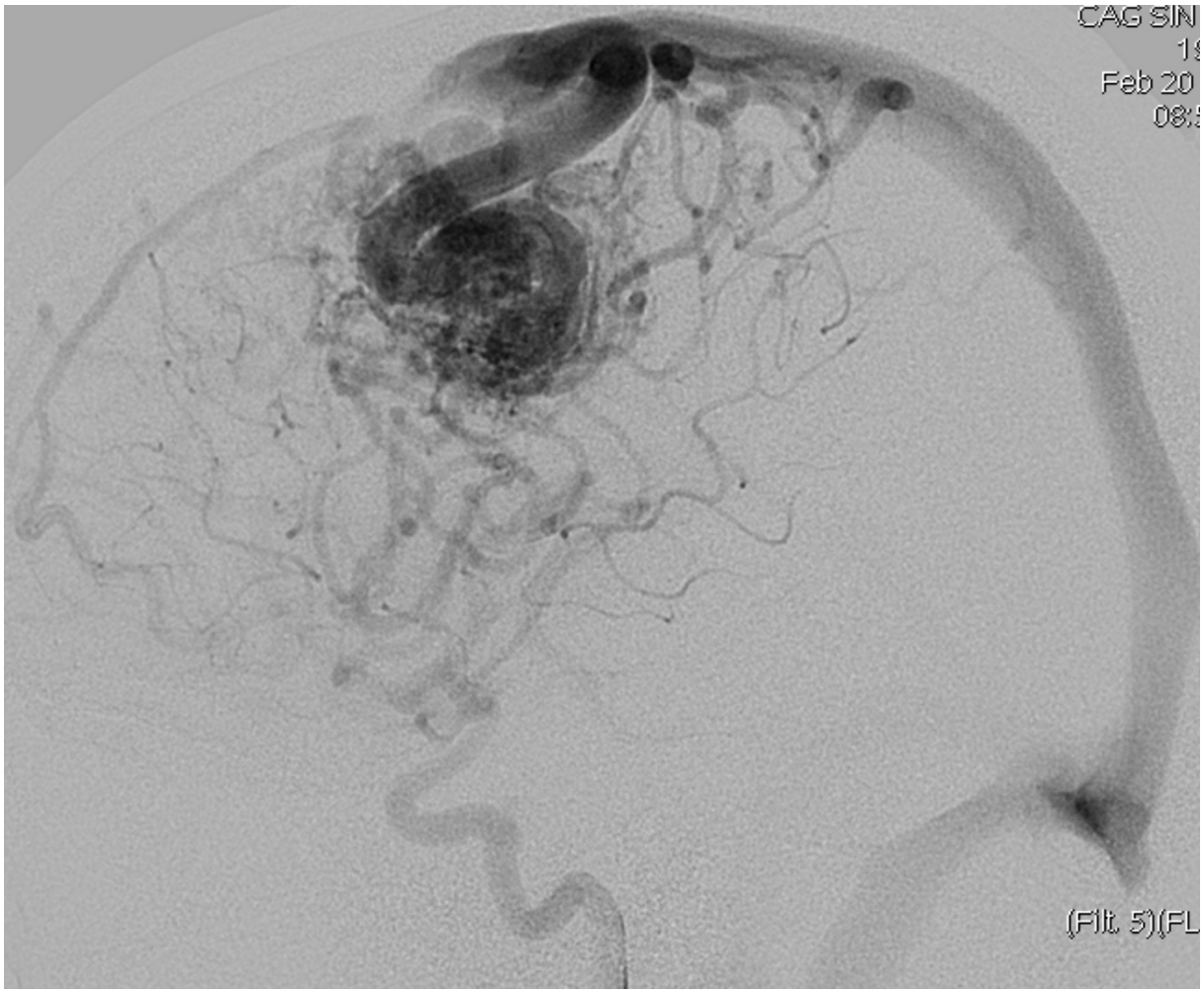


Figure 8.7. Catheter angiogram (lateral view) of left frontal AVM SM III – feeders from anterior circulation, superficial venous drainage.

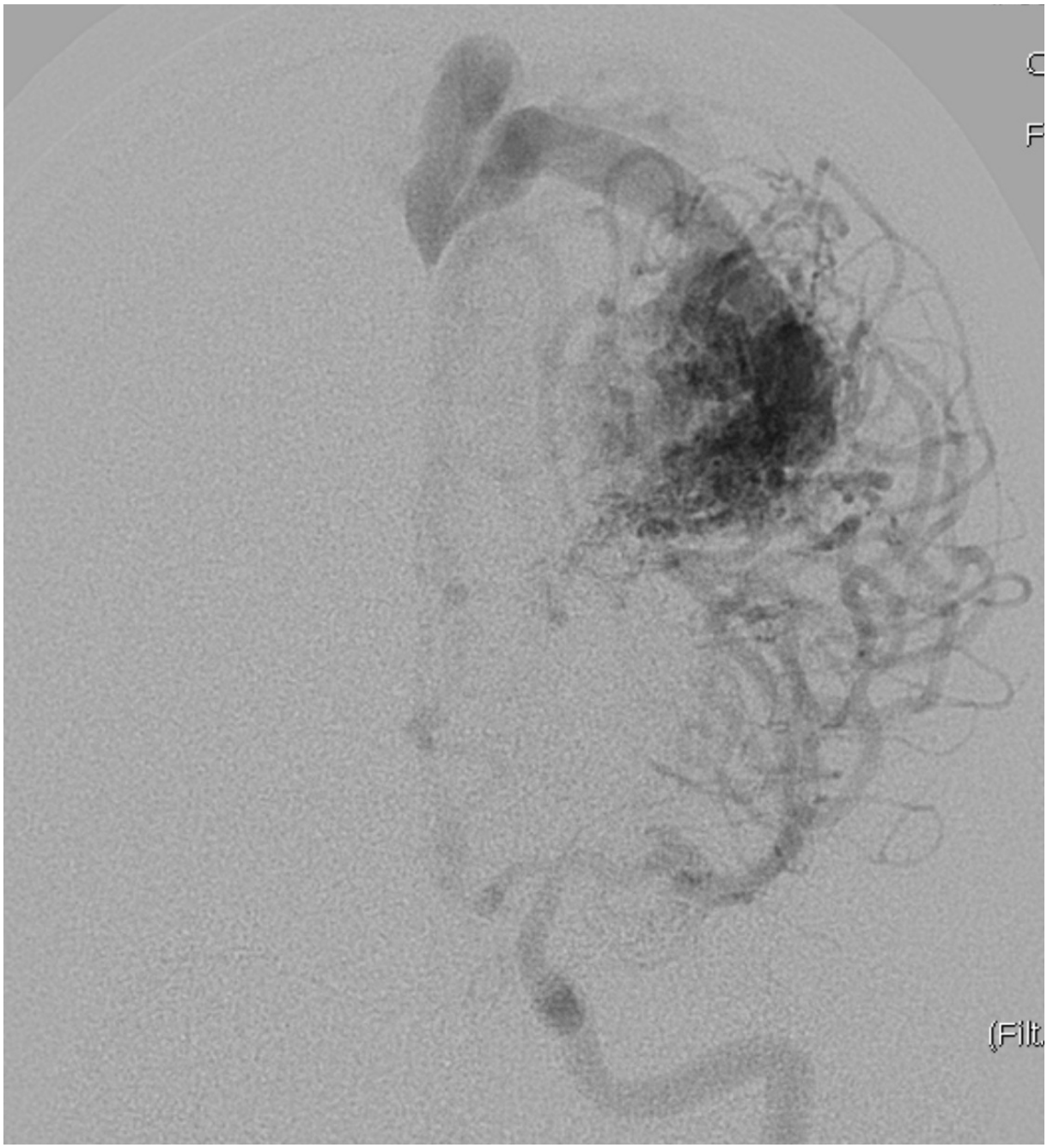


Figure 8.8. Catheter angiogram (A-P view) of left frontal AVM SM III – feeders from anterior circulation, superficial venous drainage, typical conical shape of AVM nidus with base superficially on cerebral cortex.

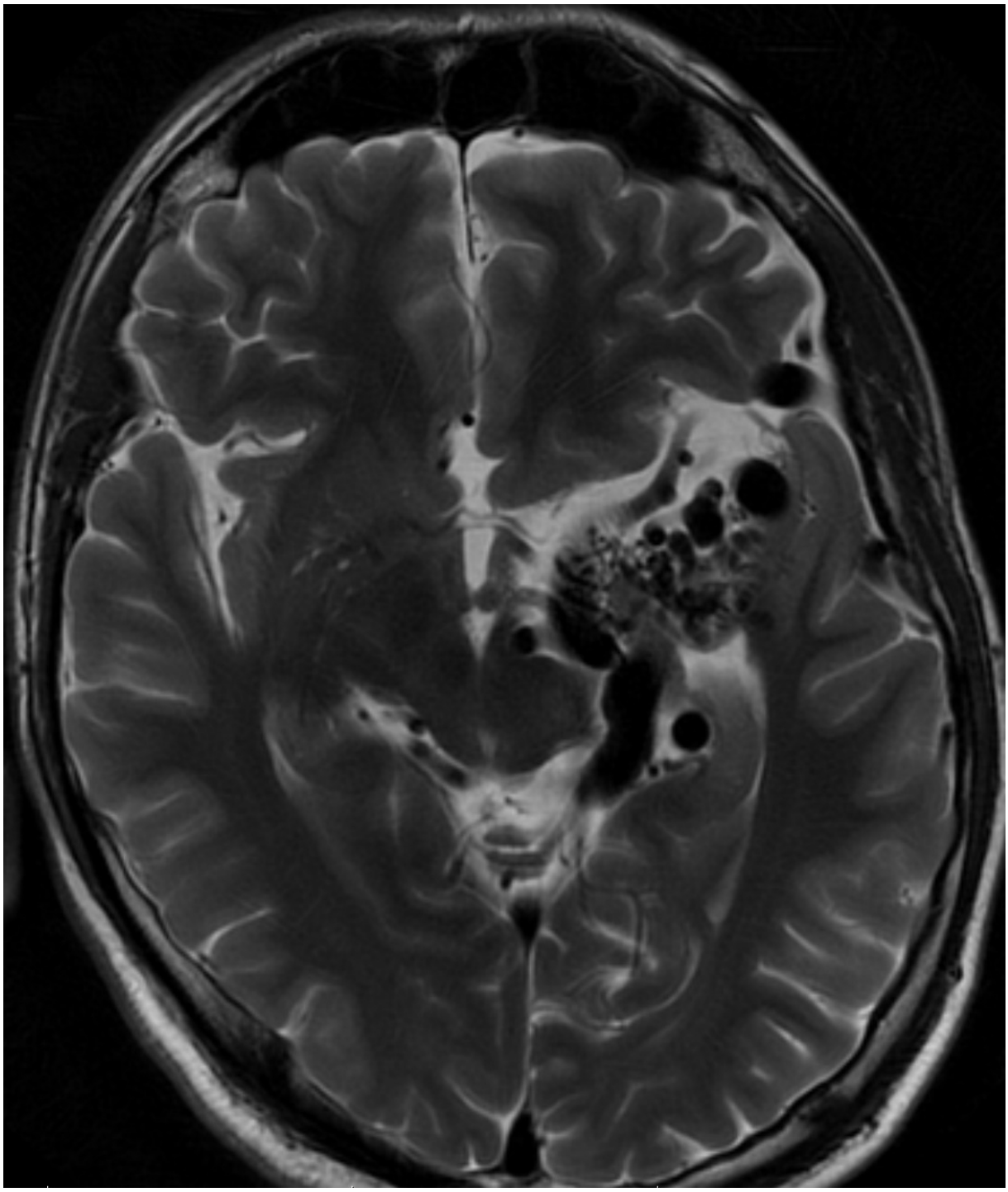


Figure 8.9. T2-weighted axial MR scan of left temporal AVM SM IV, involvement of deep eloquent areas.

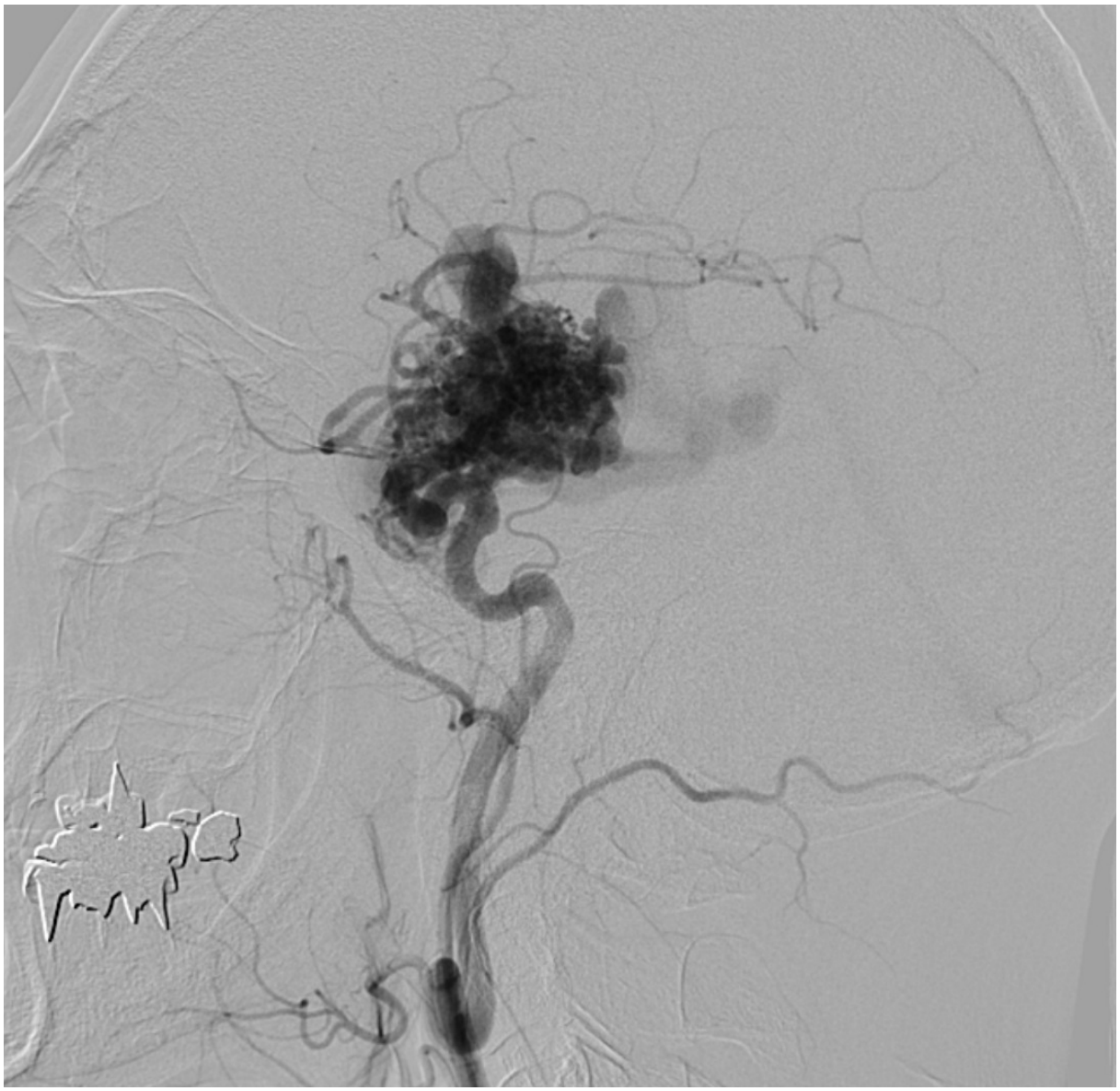


Figure 8.10. Catheter angiogram (lateral view) of left temporal AVM SM IV – feeders from anterior circulation, deep venous drainage.

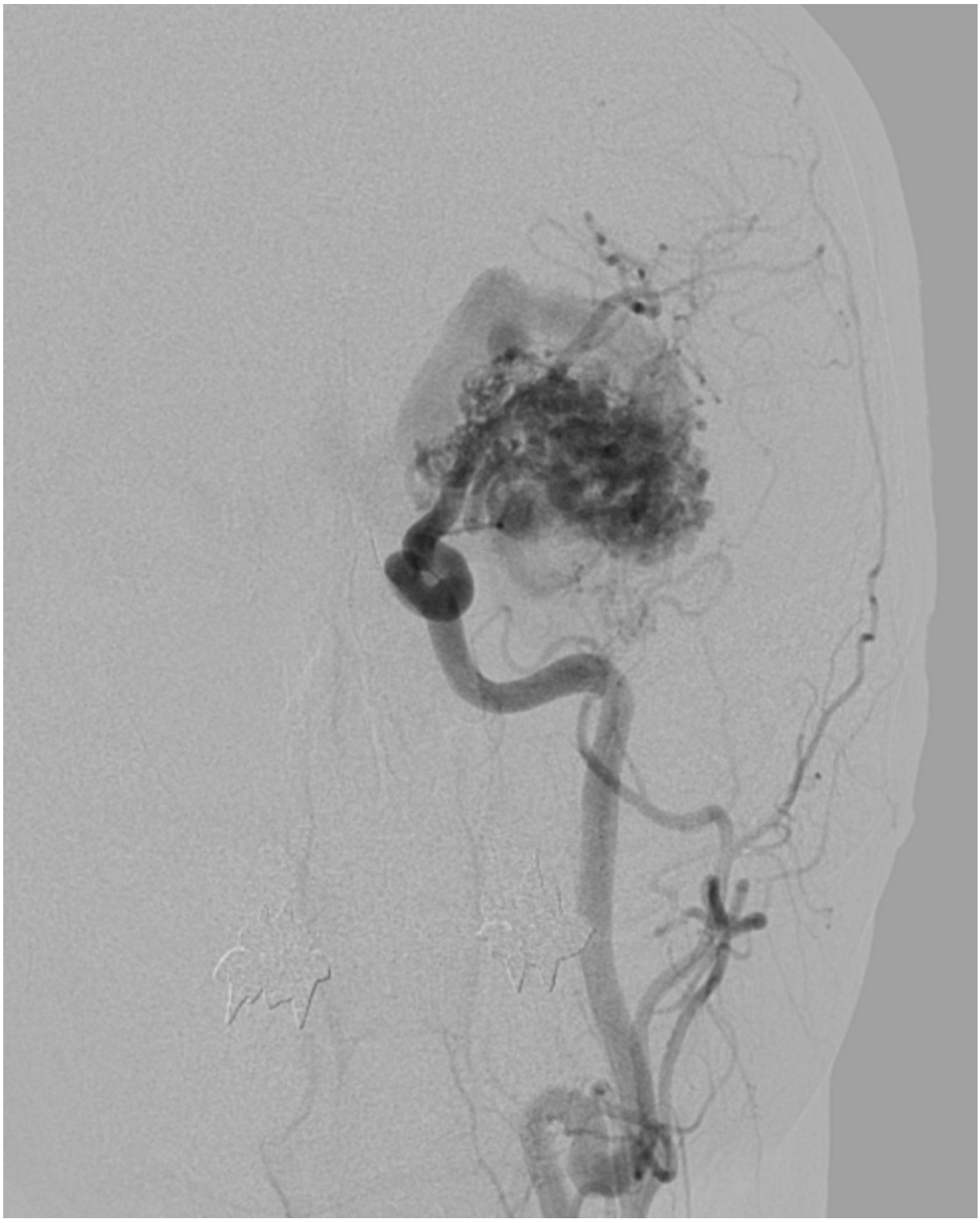


Figure 8.11. Catheter angiogram (A-P view) of left temporal AVM SM IV – feeders from anterior circulation, deep venous drainage, involvement of deep eloquent areas.

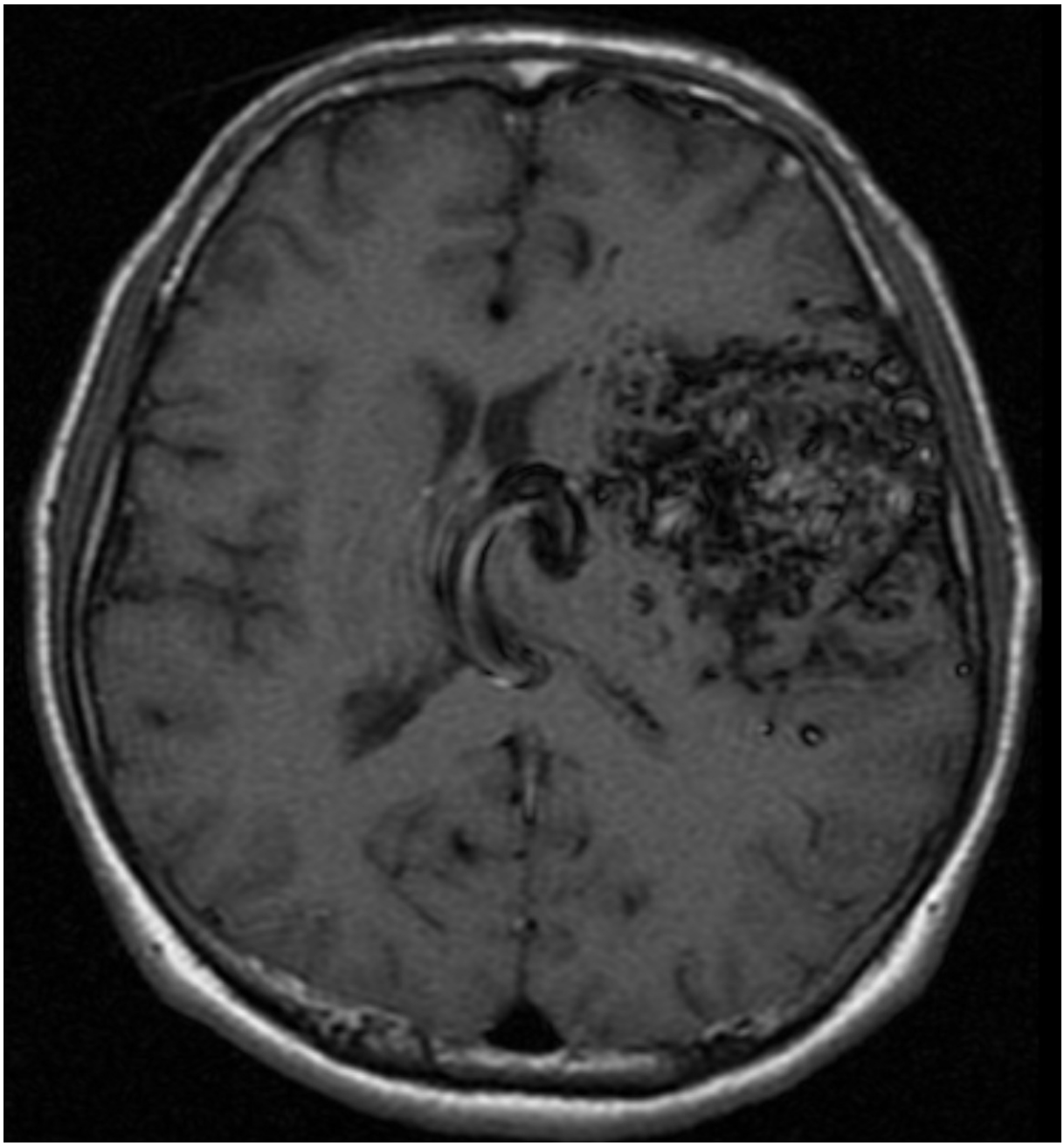


Figure 8.12. T1-weighted axial MR scan of left hemisphere AVM SM V, involvement of eloquent areas.

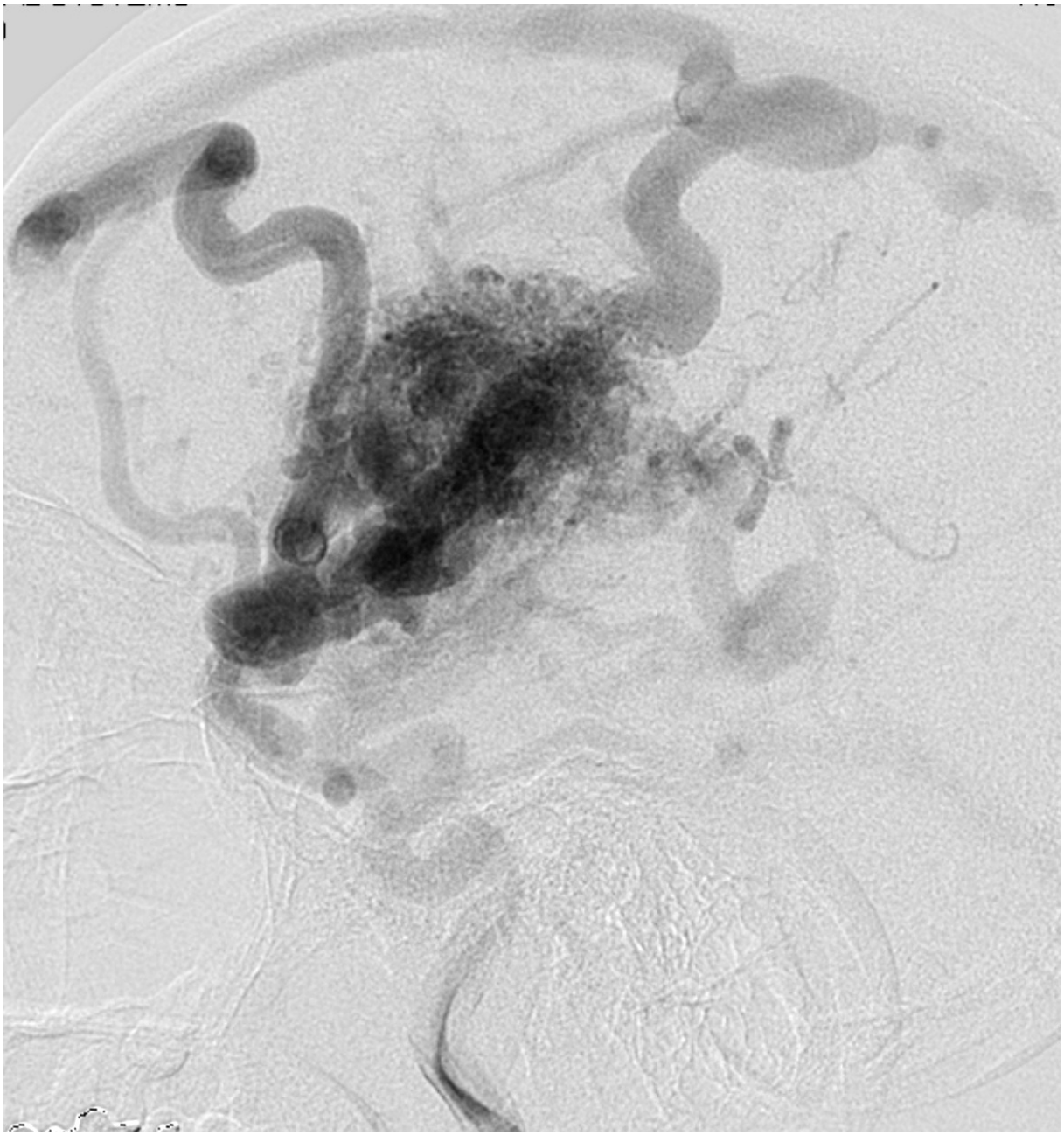


Figure 8.13. Catheter angiogram (lateral view) of left hemisphere AVM SM V – feeders from anterior circulation, deep and superficial venous drainage.

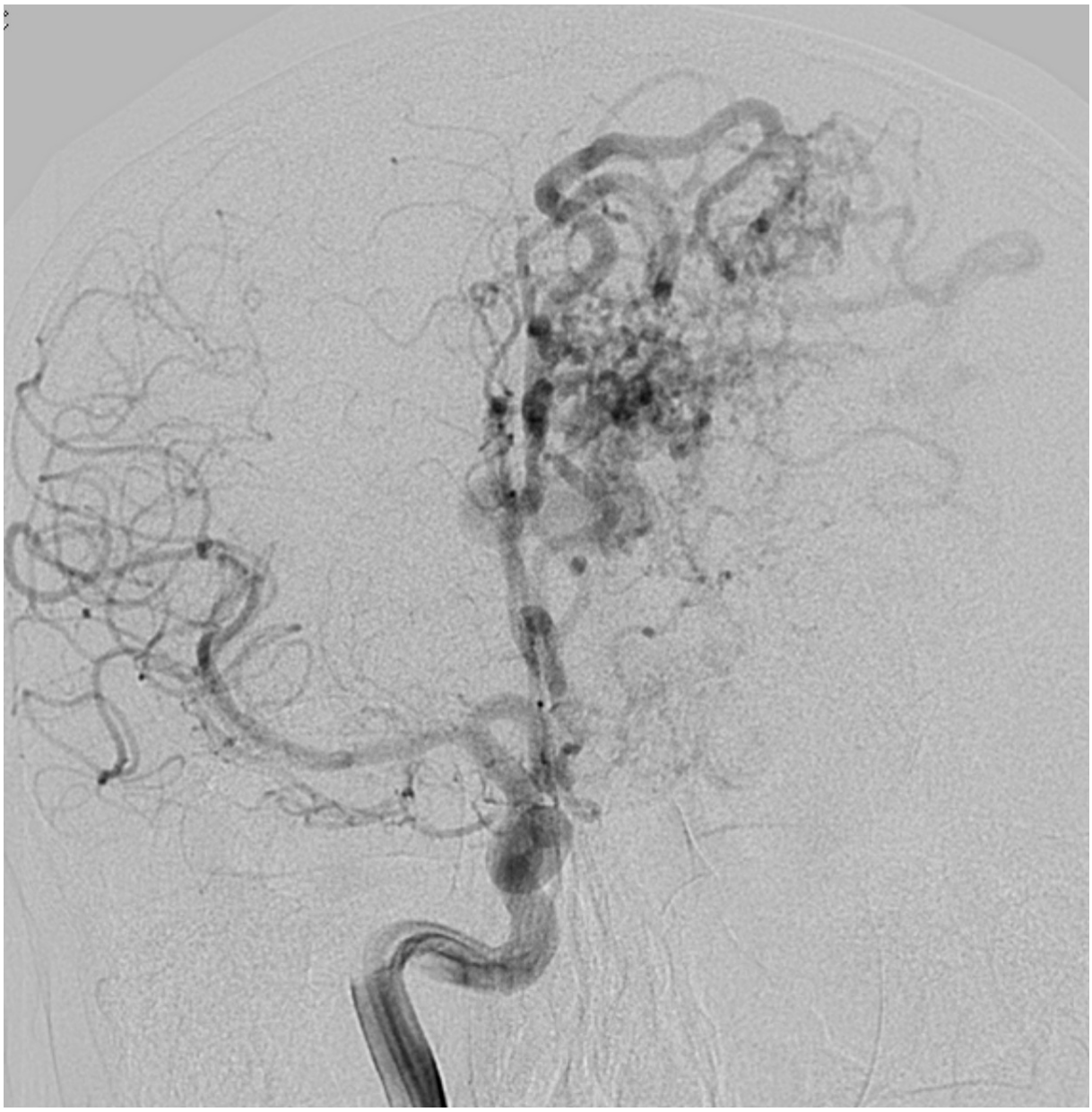


Figure 8.14. Catheter angiogram (A-P view) of left hemisphere AVM SM V – feeders from anterior circulation, deep venous drainage, second compartment of AVM nidus.

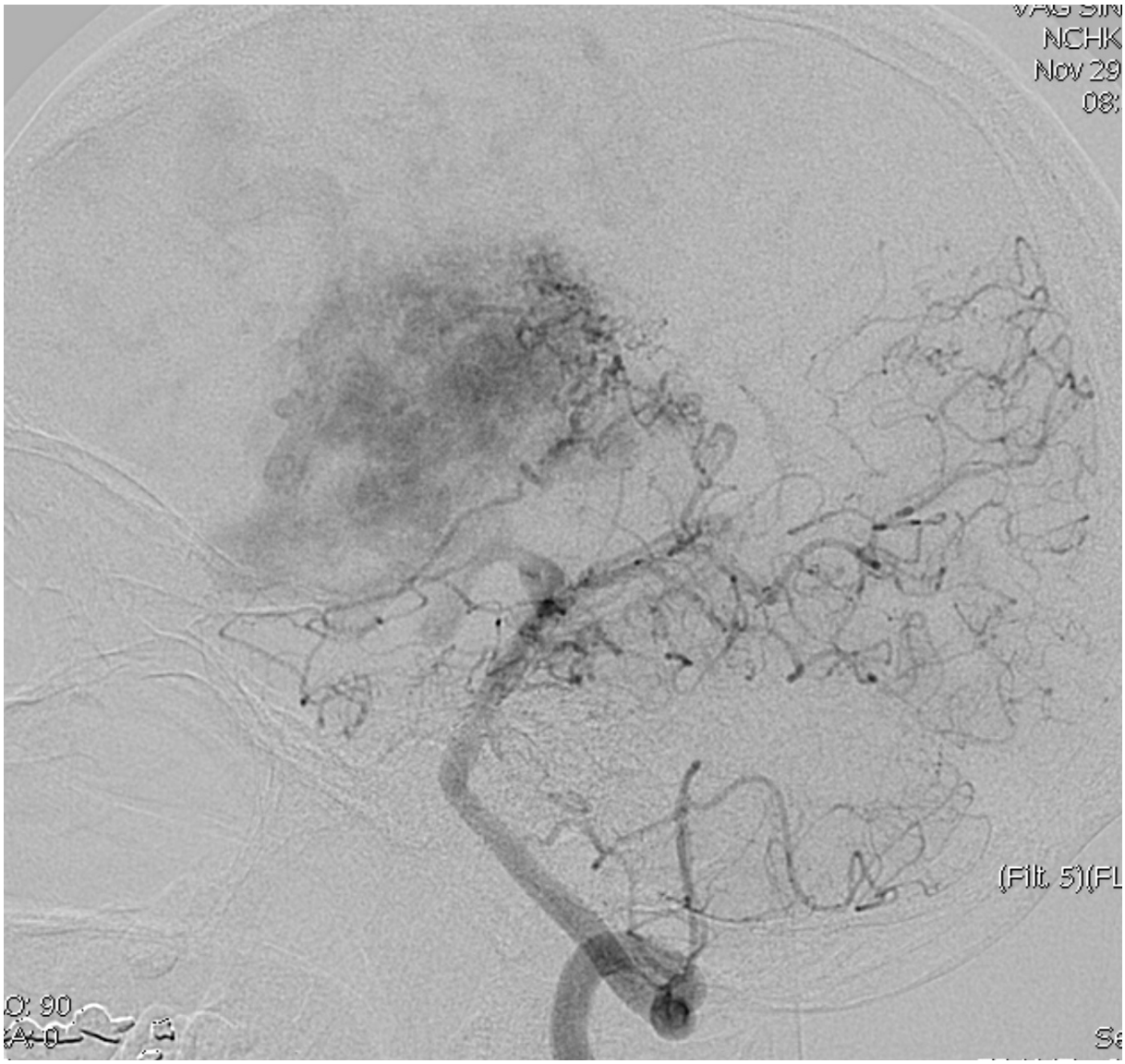


Figure 8.15. Catheter angiogram (lateral view) of left hemisphere AVM SM V – feeders from posterior circulation.

9. Imaging

9.1. Catheter angiography

Catheter angiography is the golden standard investigation for imaging an AVM [1, 87], allowing exact assessment of angioarchitectural parameters such a feeding arteries anatomy, nidus location and size, pattern of venous drainage. Furthermore, associated aneurysms, venous ectasias and other vasculopathies such as arterial stenosis, dysplastic segments or venous ectasias could be diagnosed. Another main advantage of angiography is its time resolution, which is very helpful in the diagnosis of early draining veins, and possibility of 3D model construction to better anatomical understanding of angioarchitecture [88]. However, in case of thrombosis in parts of an AVM, angiography is not able to visualize this well.

9.2. Magnetic resonance imaging

Magnetic resonance imaging is still a developing modality, which is very useful for surgical planning. The exact relation of AVM parts to surrounding brain tissue could be assessed well on MRI. Furthermore, thrombosed components and signs of previous haemorrhage could be visualized in T2-weighted and GRE sequences. However, for exact definition of the nidus, a catheter angiogram is still a crucial tool, which should be combined with MRI as shown in various studies [89-92]. MRI is routinely used to follow-up patients after radiosurgery [93-95] before final angiogram is performed after the latency period.

MRI has great potential in its applications such as DTI or fMRI. Using fMRI hemispheral dominance and eloquent areas could be assessed [96], similarly as potential shift of eloquent brain areas due to brain plasticity. This phenomenon has been studied in various imaging studies [97-101]. Functional MR imaging together with MR tractography based on DTI sequences [102] became routine in clinical practice for surgical treatment planning. MR perfusion imaging is used to demonstrate perfusion changes in surrounding brain tissue after AVM resection or during latent period after radiosurgery [103]. However, its clinical importance for treatment decision is rather low.

9.3. Computed tomography

CT is the most important diagnostic tool in the acute phase to investigate for intracranial haemorrhage. The type and location of haemorrhage and mass effect can be assessed on CT imaging; combined with CTA is an excellent diagnostic tool for identifying the presence of an AVM during the acute phase. However, only native CT scan could lead to misdiagnosis, as pointed out by Zvěřina [104], who reported a case of AVM operated under picture of high-grade glioma. Furthermore, even CTA resolution is not as good as catheter angiography and thus is not the method of choice for surgical planning [87].

10. Treatment for brain AVMs

The goal of any treatment for AVM is to aim for complete occlusion. This must be confirmed by catheter angiography. Incompletely occluded AVM still poses a risk of haemorrhage. Although a paper published by Laakso from Helsinki group [105] proved on historical series of patients effect of partial treatment in the sense of decreasing morbidity from intracranial hemorrhage over time, partial occlusion of AVM should not be the goal of treatment.

10.1. Literature series

We have performed a literature search in PubMed database using keywords “brain avm” up to end of 2013. All series, where the method of treatment was clearly defined, the series of patients was larger than 30 and the major morbidity and mortality was clearly stated were included. Altogether, we identified 93 studies comprising of 15 425 treated patients. The mean values of age, complication rates and efficacy were computed as weighted means, where the weighing factor was the number of patients in particular study.

10.2. Surgery

The first successful surgical treatment of an AVM was reported in 1936 by Olivecrona and Tonnis [106]. Nowadays surgical treatment of AVMs is well established treatment method with well described indications, complication and efficacy rate.

10.2.1. Efficacy of surgical treatment

In the literature review, we identified 23 surgical studies, analysing altogether 2721 patients with a mean age of 36 years. Average efficacy within published microsurgical series was 95.9%, Table 12.3. It is necessary to bear in mind, that majority of surgical series, although consecutive, were based on patients amenable to surgery, thus the distribution of AVM S-M grades were skewed towards the lower grades. The same fact could be demonstrated on our surgical series, discussed in chapter 12.

10.2.2. Complication rate of surgical series

The complication rate ranged from 2% to 20% with mean of 7.2% according to our literature review as can be seen in Table 12.3. The exact rate of complications is strongly dependent on S-M grades of resected AVMs. In his initial paper from 1986, where S-M grading system was introduced, Spetzler [78] showed on 100 AVM patients 0% major morbidity and mortality in S-M grade I and II lesions, 4% for grade III, 7% for grade IV and 12% for grade V lesions. Similar results were subsequently obtained by other authors [107-115].

10.2.3. Indications for surgical treatment of AVM

Based on these results, stable over a 30 year period, indication scheme was suggested by Spetzler in 2011 (31). Spetzler-Martin grades I and II should be predominantly operated, grade III AVMs should be considered for multidisciplinary combined treatment according to

particular AVM anatomy, location and patient characteristics. AVM S-M grades IV and V should not be treated surgically, in fact the risks of active treatment are higher than the natural course of the disease. Surgical treatment of an AVM should be performed on an elective basis, even in the case of a haemorrhagic presentation. If an ICH is causing substantial mass effect, only those ICH should be gently removed to alleviate intracranial pressure, leaving the AVM to be treated in a delayed fashion, usually after a couple of weeks. The only exception could be a small AVM in a non-eloquent area operated on by experienced hands, then the AVM could be resected in an acute fashion. However, even under these circumstances, surgery is usually not straightforward (32).

10.2.4. Rules of AVM resection

- We do not have any specific preparations for AVM surgery, the only requirement being intrarterial blood pressure monitoring focused on keeping normotension
- We routinely use neuronavigation to place craniotomy properly
- Craniotomy is done large enough, well beyond the nidus margins
- Expose the nidus, if possible in a way that the nidus long axis is vertical (e.g.transfalcine approach for deeper midline parasagittal AVMs)
- Open dura carefully (there are freqeunt adhesions between the nidus and inner layer of the dura)
- Inspect the brain surface to get a good correlation of angio and surgical view
- Dissect the nidus margins circumferentially first with respect to sulci

- Dissect the en passage arteries (untill proven otherwise, all arteries are treated as en passage)
- Patient and thorough coagulation of dissected vessels, not within the brain
- Use miniclips to enhance coagulation, especially in deep feeders
- Use non-stick higher power coagulation if necessary and in brain tissue only
- Cut the coagulated vessels stepwise
- Identify the bleeding source properly and control bleeding before further resection
- Take extreme care with deep feeders
- Last step is cut of the draining vein
- Use ICG during and at the end of resection
- After surgery, the patient is left intubated and blood pressure is aggressively controlled to maintain hypotension and patient is woken up slowly.
- The day after surgery cathether angiogram is performed to confirm completeness of resection

10.3. Endovascular embolization

Endovascular treatment of AVM's was introduced in 1960 by Luessenhop and Spence [116]. Since its introduction, endovascular methods have made great progress and its efficacy increased substantially over the years as can be seen in Table 12.4. Mean efficacy within 29 series comprising of 4021 patients with mean age of 35 years was 22.4%, with numbers ranging from 0% to approx. 50% in some series.

10.3.1. Complication rate of endovascular series

The mean complication rate in the literature review was 7.0%, ranging from 0% to 17%. The actual rate of complication depended on the aggressiveness of treatment. In the cases of pre-surgical embolization, when complete obliteration of AVM is not the ultimate goal, the rate of complication is lower, than in the cases of intended curative endovascular procedures (34, 35).

10.3.2. Indications for endovascular treatment

Based on the results of our literature review and prediction models, which will be discussed thoroughly in chapter 12, the indications for curative embolization are rather narrow. A curative procedure could be safely and effectively performed in patients harbouring small AVM s with low number of feeder vessels (35). An example of a successful AVM embolization is depicted in Figures 10.1. and 10.2. However, these patients are usually treatable via microsurgery with higher efficacy. Although some centres prefer endovascular treatment of AVMs (36, 37), according to majority of authors endovascular methods are reserved for palliative treatment such as embolization of flow-related aneurysms (38-42). On the other hand, endovascular treatment is one of the most progressively developing modalities in vascular neurosurgery. Crowley et al. (43) reviewed the advances in the field of endovascular treatment, discussing improvement in liquid embolic agents and new types of catheters such as flow-directed catheters, balloon-tipped catheters, detachable-tipped catheters, and distal access catheters, thus improvement in embolization results especially in the sense of increasing efficacy is probable.

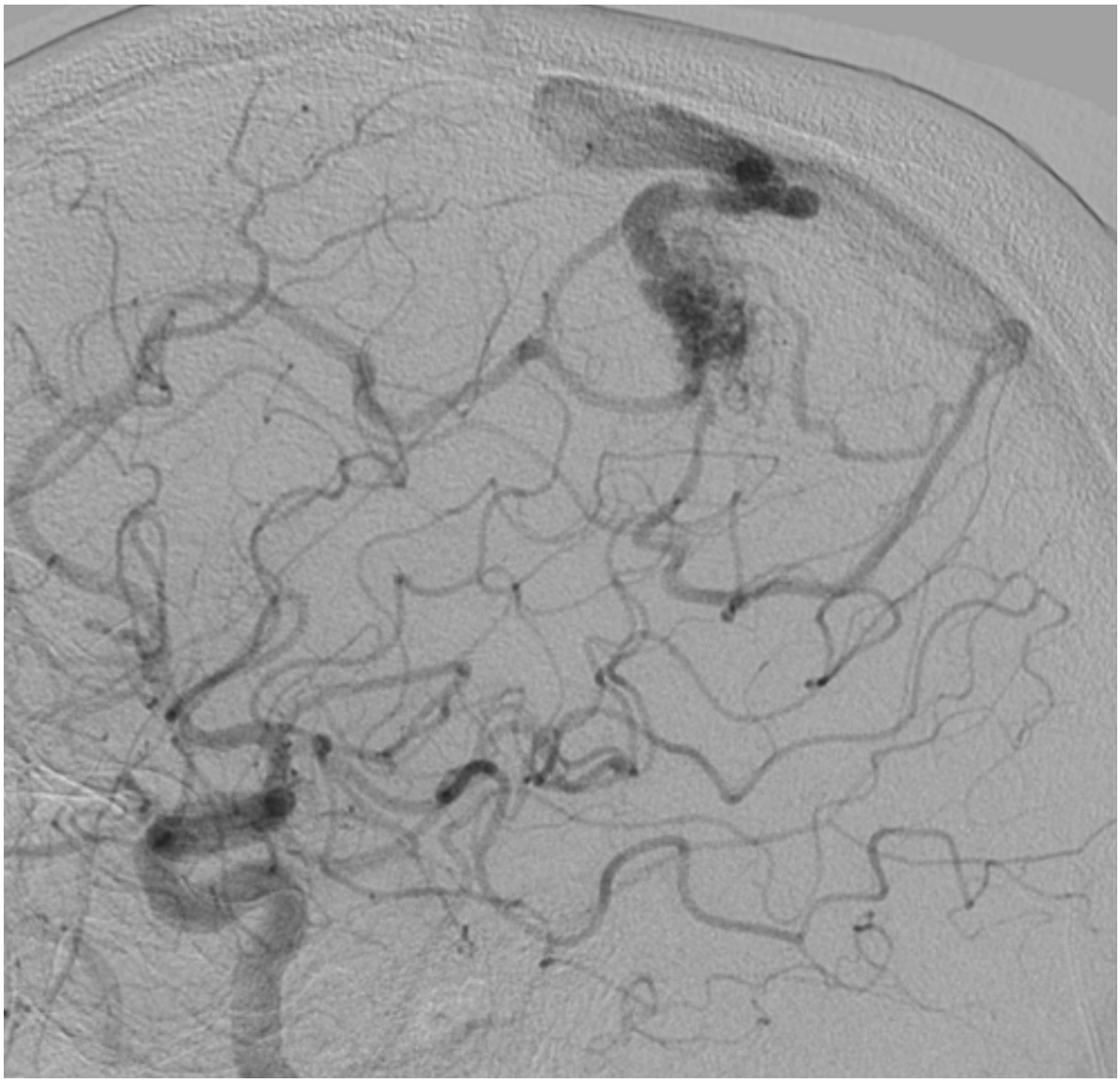


Figure 10.1. Catheter angiogram (lateral view) of SM II AVM, status before embolization.

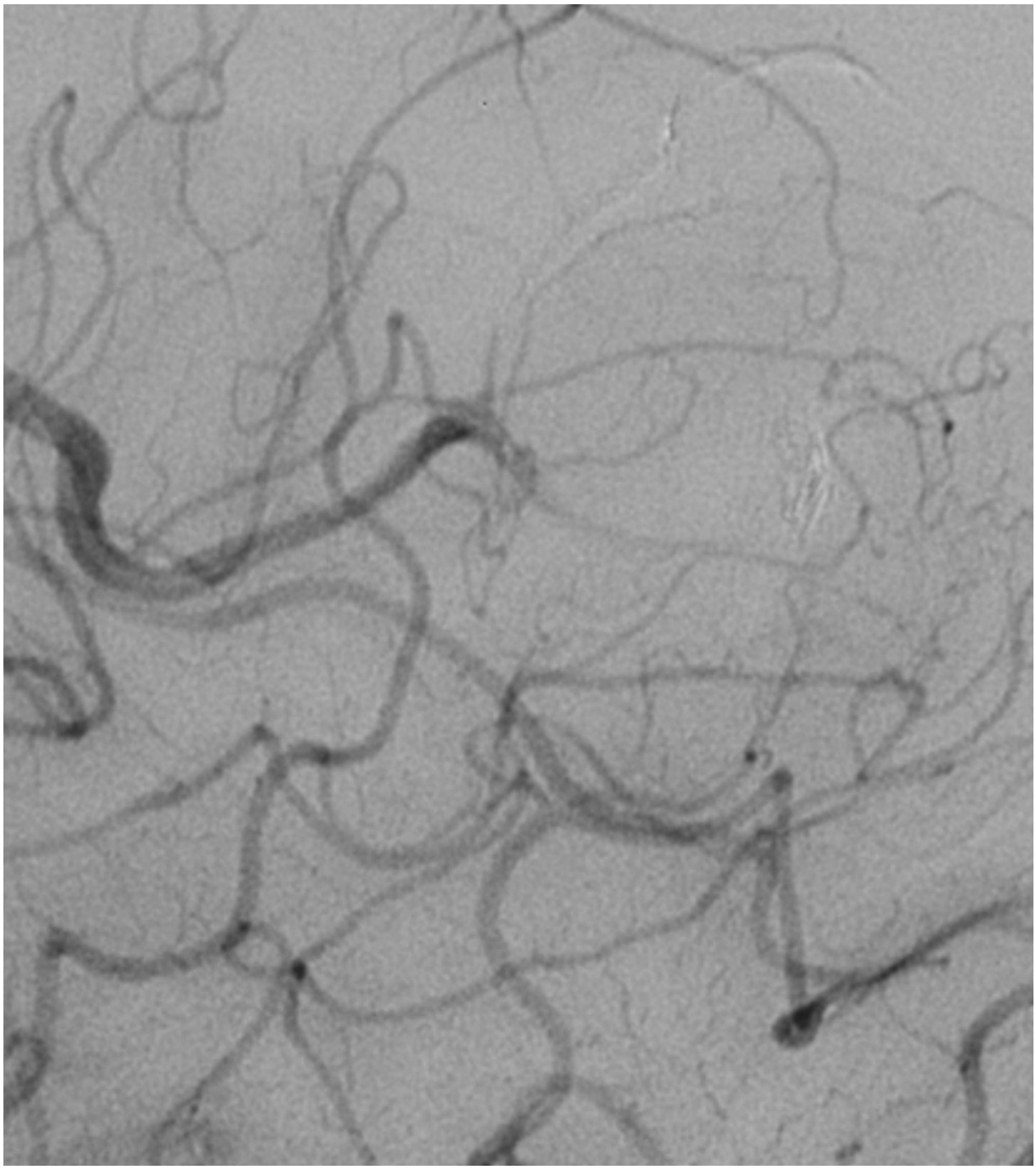


Figure 10.2. Catheter angiogram (lateral view) of SM II AVM, complete occlusion by embolization.

10.4. Stereotactic radiosurgery

Stereotactic radiosurgery is well established treatment method for brain AVMs. Variety of radiosurgical instruments (LGK, LINAC, Cybeknife…) and techniques (multisession, volume-staged, intensity modulated…) are deployed nowadays. Mechanism of action is still not completely understood, but microscopic and immunohistochemical studies showed endothelial destruction and proliferation of modified myofibroblasts in subendothelial layer having contractile capacity and presumably contribute to vessel occlusion after SRS [117, 118]. Literature review was based on 41 studies comprising of 8683 patients with mean age of 31 years, Table 12.5.

10.4.1. Complications of radiosurgery

The mean morbidity and mortality within studied series was 5.3%, ranging between 0% and 14%. However, although severe morbidity and mortality appears to be relatively low, significant amount of patients after radiosurgery suffer from radiation injuries – blood-brain barrier breakdown, necroses, edema and cyst formation [119]. According to Herbert [120] 17% of patients with AVM below 28 ccm volume and more than 50% of patients with larger AVMs suffered from some degree of radiation injury. Parkhutik [121] referred that only 42% out of 102 patients were free of radiation injury and major injury was found in 20 patients. Furthermore, obliteration occurs only after 2 to 3 years latency period, during which probability of haemorrhage is not significantly reduced. Risk of haemorrhage within first year could be as high as 8% as referred by Zabel-du Bois [122]. On the other hand, Parkhutik referred bleeding

risk to be 2.2% per annum for hemorrhagic AVMs and only 1.4% for non-hemorrhagic AVMs during latency period of 3 years. However, possible bleeding during this period is necessary to count together with adverse effects of radiosurgery and in fact is responsible for majority of unfavourable outcomes after SRS [123, 124]. Rare complications of AVM radiosurgery such as radiosurgery-induced brain tumor [125], development of intractable epilepsy [126] or delayed neural degeneration [127] were described as well.

10.4.2. Efficacy of radiosurgical treatment

The mean efficacy within studied series was 66.1%, ranging from 40% to 90%. Efficacy decreases with AVM size and S-M grade [124, 128], where multi-staged treatment is necessary [129-131].

10.4.3. Indications for radiosurgical treatment of AVMs

Radiosurgery from its minimally invasive nature is the method of choice for patients possessing high surgical risks due to age or, more often, comorbidities. Another great advantage of radiosurgery is its ability to treat deep or eloquent-located lesions, which carries unacceptable high surgical risks [132, 133]. Kano et al. [129, 134-138] presented a comprehensive review of indications and results of SRS treatment of various types of AVMs from Pittsburgh database. As in case of surgical treatment, results of treatment for low S-M grade lesions is very good – obliteration rate referred to be around 90% [122] with minimal morbidity and mortality. However, efficacy decreases and complication rate increases with AVM grade as was shown

in many studies [128, 138, 139]. From this point of view SRS compete with other modalities in lower grade AVMs. Case presented in Figures 10.3 – 10.6. represents a typical AVM indicated for radiosurgery – deep seated, S-M III lesion.

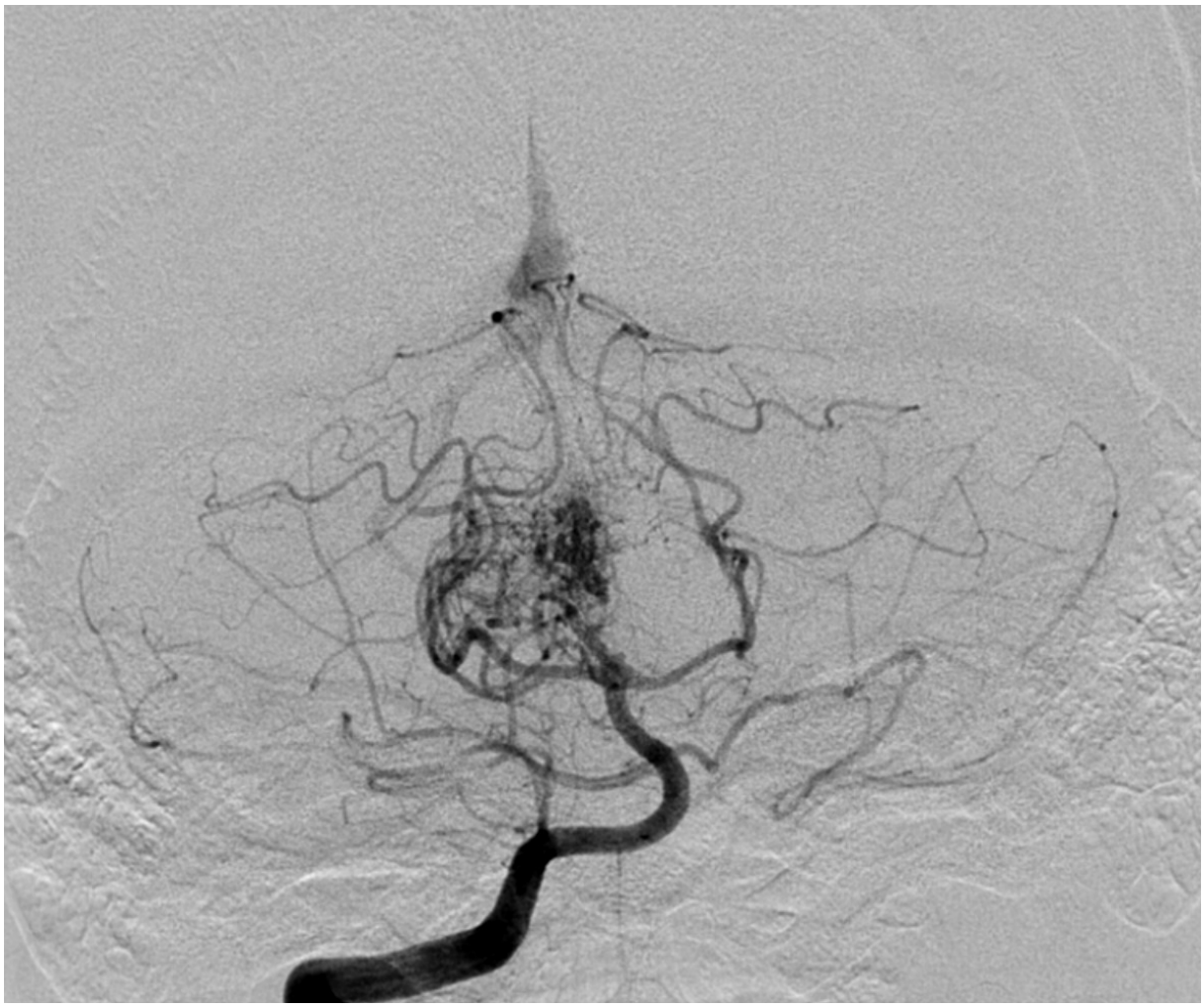


Figure 10.3. Catheter angiogram (A-P view) of deep seated S-M III AVM.

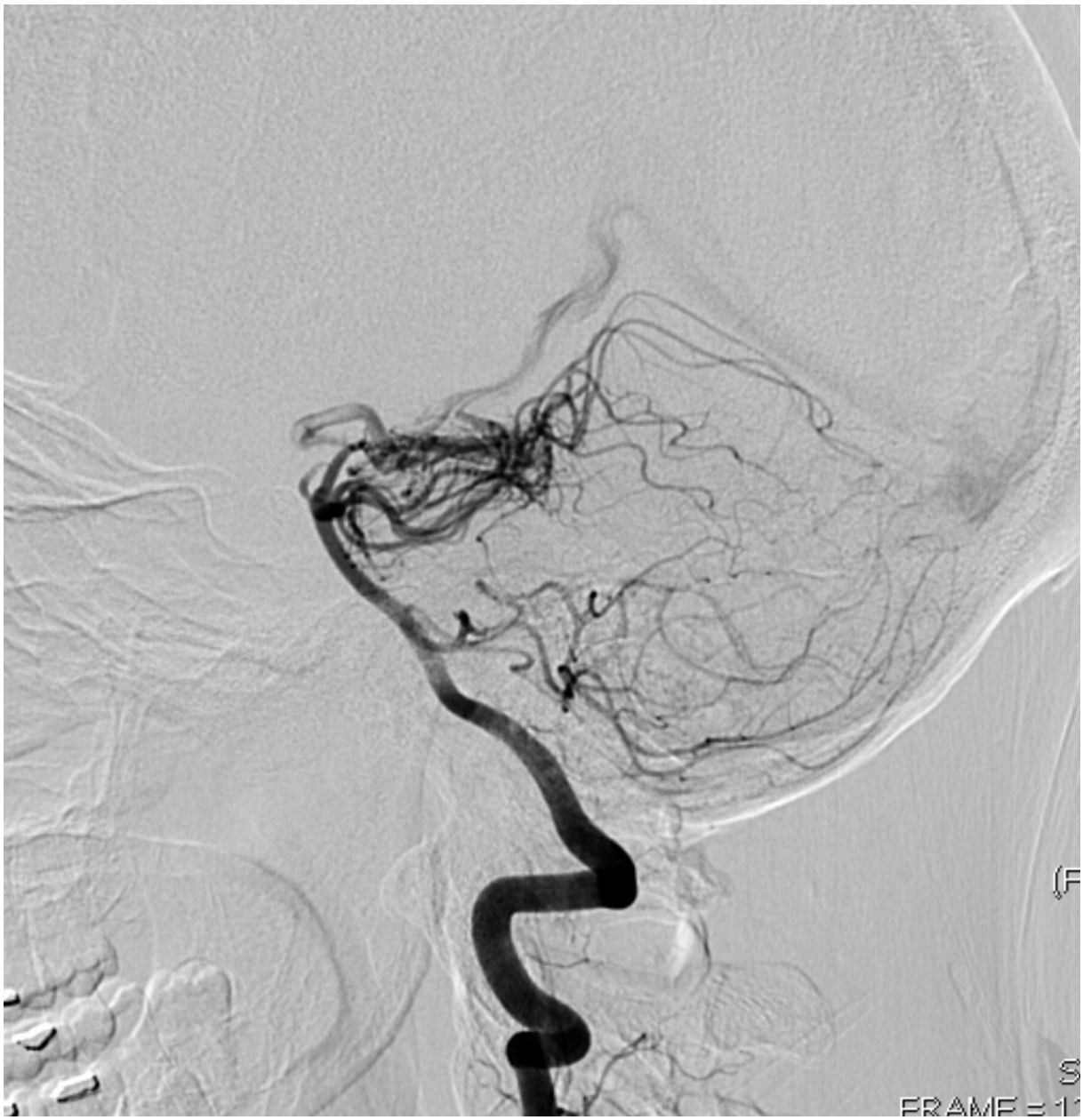


Figure 10.4. Catheter angiogram (lateral view) of deep seated S-M III AVM. Deep venous drainage.

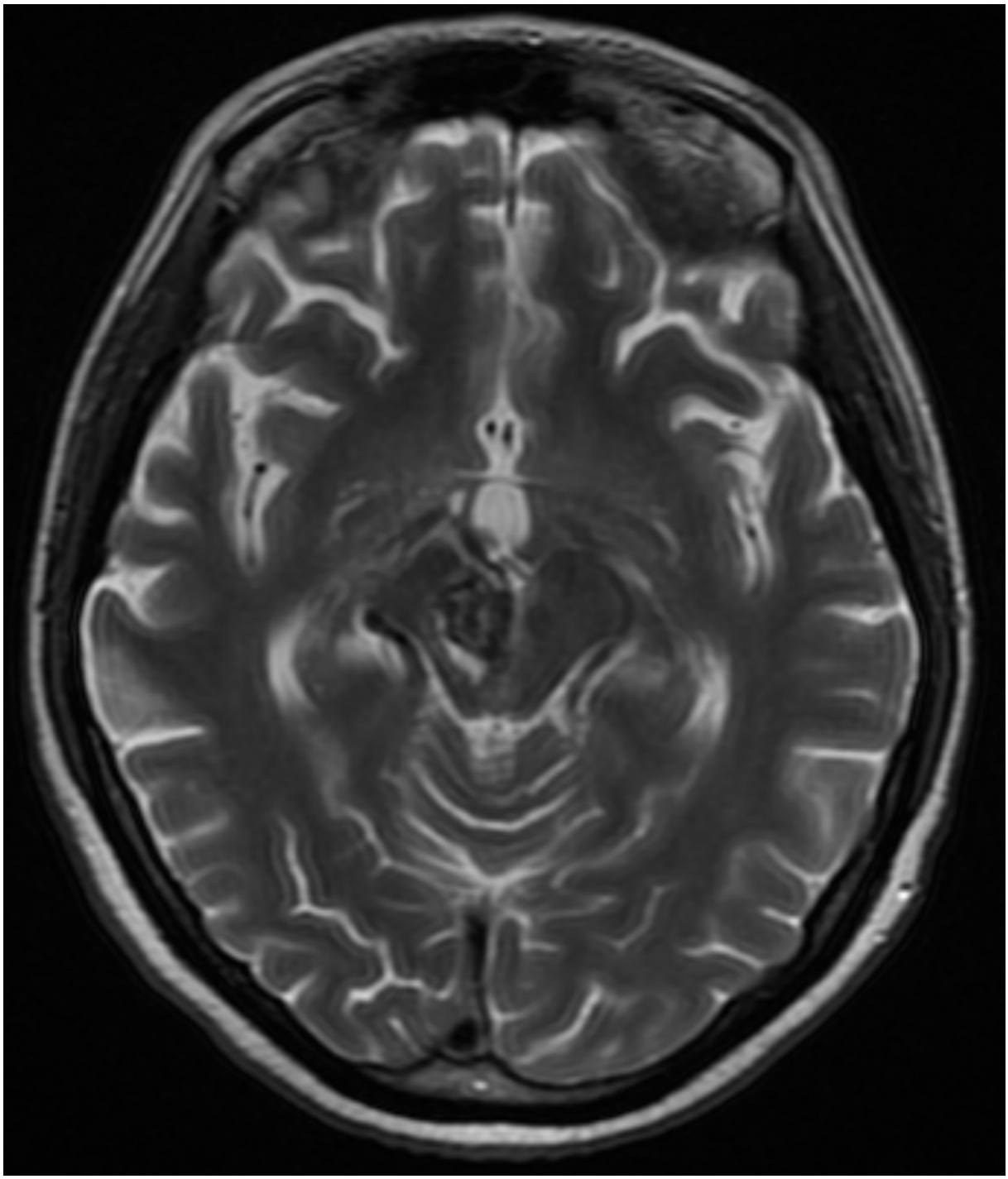


Figure 10.5. Axial MR scan (T2 weighted) of deep seated S-M III AVM before radiosurgical treatment.

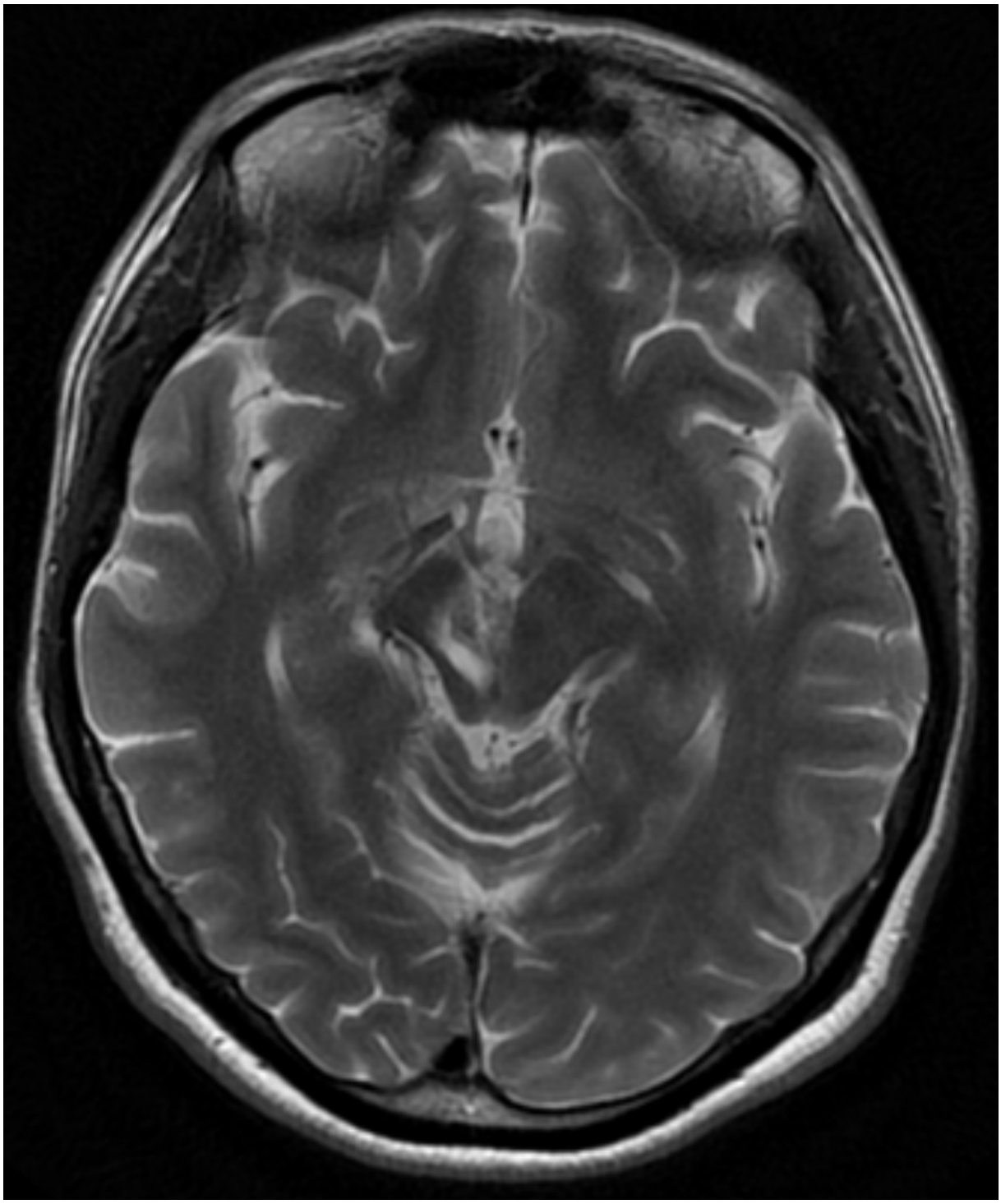


Figure 10.6. Axial MR scan (T2 weighted) of deep seated S-M III AVM after occlusion.

10.5. Combined treatment

Various combinations of treatment modalities could be used for AVM treatment. The most common is pre-surgical embolization [140-142]. However, this method was recently challenged. Morgan et al. [143] pointed out some serious complications of ethylene-vinyl copolymer embolization agent usage together with no improvement in surgical morbidity and mortality. Similar position advocate Heros et al. [144]. The question surrounding the use of pre-surgical embolization is when and how aggressively it should be used?

Embolization is often used in large AVMs before radiosurgery. The rationale of this method is to shrink AVMs and make them more amenable for radiosurgery. Even this technique was challenged recently by Kano [145] showing a decrease in the obliteration rate, but no change in risk of haemorrhage during latency period. Schaler described a case of an irradiated, previously embolized AVM, who developed massive perifocal edema several months after radiosurgery, which needed to be treated surgically. Furthermore, parts of the AVM, which seems to be completely occluded immediately after embolization are in fact still patent and could be responsible for the post-radiosurgical hemorrhage [146]. The effect of embolization after radiosurgery remains to be studied. However, embolization of a residual fistula after SRS as was reported by Hodgson [147] seems to be a viable option.

Surgical resection after previous stereotactic radiosurgery has not been intensively studied yet. Sanchez-Mejia [148] studied 21 patients who underwent resection of irradiated AVM and compare them to resected controls. Radiosurgery achieved decrease in S-M grade of AVM in

52% of patients and mean AVM volume by 78%. Subsequent surgical excision was significantly shorter, blood loss lesser and most importantly, outcomes measured by mRS were significantly better. Similar observation was done by our group [149] in case of a patient who underwent repeated radiosurgery with angiographical proof of occlusion. Subsequently they suffered bleeding from AVM recurrence, which was surgically excised. Surgery was straightforward and easy. Matsumoto described similar case of delayed bleeding after radiosurgical AVM obliteration.[150] Abla et al. [151] recommended volume-staged radiosurgery for treatment of large AVMs and turning them into resectable lesions. Using this strategy 16 patients were treated and mean S-M grade decreased by 1.5 before resection. Surgical risks were then adequately lowered.

11. ARUBA study comments

The only randomized study comparing active treatment with best medical treatment of unruptured AVMs is the ARUBA study (A Randomised trial of Unruptured Brain Arteriovenous malformations) [152], published in 2013. This study was performed on 232 patients in 39 centres across 9 countries and was stopped prematurely due to the superiority of medical management over interventional treatment.The mean follow-up time was 33.3 months and the hazard ratio of stroke or death for patients randomized to medical treatment compared to patients randomized to interventional treatment was 0.27 (95% CI 0.14-0.54). On the other hand, ARUBA study results are based on 98 actively treated patients and out of these 98 patients, only 18 patients underwent surgical excision alone, or in combination, with other treatment modalities. The vast majority of patients were treated using embolisation alone (30), radiotherapy alone (31), or a combination of these two modalities (15).

As the authors stated in their discussion, the ARUBA study was not powered to distinguish among the different treatment modalities. From a neurosurgeon's point of view, the number of events (strokes and deaths) in the interventional branch of ARUBA study was extremely high (30.7% as intention-to-treat analysis, 36.7% as treated analysis). Out of these events, the majority were haemorrhagic strokes (22% and 25%), followed by ischaemic strokes (8% and 11%). These numbers could not be confirmed by analysis of our data and literature search, which was published previously [153]. On the other hand, it is necessary to bear in mind, that the vast majority of these events happened during the first two years after treatment and thus on partially treated AVMs(either by radiosurgery or embolization). This puts in doubt the role of these modalities in active AVM treatment. Embolisation alone is not usually used as the

first choice treatment for unruptured brain AVMs in many high-volume neuroradiology centres (prof. Emmanuel Houdart, personal communication).

Another very important point is the relatively short follow-up in the ARUBA study (mean 33 months). The mean age of the patients randomized to this study was 44.5 years, which is slightly higher than in recently published studies [74, 154]. However, it is necessary to think about the prognosis and risk of haemorrhage in decades, not only in months or five to ten years, which is time during which the observational part of ARUBA study is planned. The risk of haemorrhage of unruptured medically treated AVMs in the ARUBA study was 2.2% per year. Even if we accept the extreme number of events in the treated patients (37%) it follows, under 2.2% annual haemorrhage risk, that after 21 years or more then 37% of medically treated patients will suffer from haemorrhage.

The proportion of randomized patients was quite low (13%), although according to the authors in 'actively randomising centres' the proportion of enrolled patients was unusually high (63%). The key issue is that none of the centres reflected the possibility of referring outcome data for patients outside the study. This suggests the possibility that 'easy and straightforward' cases were treated actively outside the study and only 'complicated' cases from any point of view (not only SM grade, but also age, comorbidities or possible technical difficulties) were randomized. This could explain excessively high number of events in the interventional branch of ARUBA study.

12. Treatment for brain AVM in the 1998 – 2013 period and review of the literature

Ondrej Bradac, M.D., M.Sc., Frantisek Charvat, M.D., Ph.D., Vladimir Benes, M.D., Ph.D.

12.1. List of Figures and Tables:

12.2. Abstract:

Introduction

The results of the treatment of pial AVM provided at our Neurosurgical centre are presented. Going by these results and by an overview of literary data on the efficacy and complications of each therapeutic modality, the algorithm of indications as used at our institution is presented

Cohort of patients

The series comprises 222 patients aged 9 to 87 years treated in the years 1998 - 2013. The surgical group consists of 85 patients, 55 patients received solely endovascular treatment. Thirty-four patients were consulted and referred directly to the Radiosurgical unit. The remaining 48 were recommended to abide by the strategy of „watch and wait".

Results

In the surgical group, serious complications were 3.5% at a 96.5% therapeutic efficacy. As for AVM treated with purely endovascular methods, serious procedural complications were seen in 5.5% of patients, with efficacy totalling 36.4%. One observed patient suffered bleeding resulting in death. For comparison with literary data for each modality, a survival analysis without haemorrhage following monotherapy for AVM with each particular modality was carried out. On the basis of this analysis were drawn the following.

Conclusions:

1. We regard surgical treatment as the treatment of choice for AVM of Spetzler-Martin (S-M) grades I and II. As for grade III cases - only for those which are surgically accessible.

2. Endovascular intervention should be used mainly for preoperative embolisation, as a curative procedure solely for lower-grade AVM in patients with co-morbidities; for higher-grade cases as palliation only.

3. Stereotactic irradiation with LGK is advisable mainly for poorly accessible, deep-seated grade-III AV malformations. In the case of lower grades, the final decision is left to the properly informed patient him/herself.

4. Observation should be used as the method of choice in AVM of grades IV and V where active therapy carries greater risk than the natural course of the disease

12.3. Introduction

Pial arteriovenous malformation (AVM) is a benign cerebrovascular disease, in which pathological direct communications between cerebral arteries and veins (bypassing capillary system) form the morphological lesion. The malformation is surrounded by a layer of reactive gliosis. Presenting signs are mostly: haemorrhage (50% of all cases), seizures (25%), headache (25%), less often neurological deficit caused by ischaemia due to the steal phenomenon [106]. The annual likelihood of AVM rupture was estimated at 2-4% in a Ondra's study [73] based on a 24-year follow-up of a cohort of 166 patients with symptomatic AVM; this value is regarded as constant throughout the follow-up period [76]. While AVM-related intraparenchymal

haemorrhage is associated with a more favourable prognosis compared to intraparenchymal bleeding from other causes; the intraperenchymal component of bleeding from an AVM carries with itself a worse recovery [155]. The probability of poor post-haemorrhage recovery (Rankin score greater than or equal to 2, neurological deficit) is reported at about 5 to 60% [154-157].

According to the commonly used Spetzler and Martin scheme, AVMs are classified into 5 or 6 groups relative to their size, localisation in eloquent areas and the presence or absence of deep venous drainage [78] or recently published 3-tier classification based on the same parameters [79]. Certain principles of treatment are also based on this AVM grading system. We currently have the choice of surgical resection, endovascular therapy and stereotactic radiosurgical treatment. Indeed, the methods can be combined – with observation being an additional, though not insignificant, modality.

We opted for an analysis of our own data and for a review of literature of published series. Using figures and graphs thus acquired, we were able to confirm the globally acknowledged principles of AVM management. In our view, the published data provide a suitable basis for discussions with our patients as, in principle, they are the ones to choose the procedure and type of treatment.

12.4. Patients and methods

Our cohort is made up of 222 patients (129 men, 93 women) treated at the Department of Neurosurgery, Charles University and Central Military Hospital, Prague. The patients received treatment between 1st January 1998 and 31st December 2013. The database was developed

prospectively, the patients´ data were assessed retrospectively. The patient´s age span was between 9 and 87 years of life, mean age was 42.5 years. Enrolled were all those patients, for whom we acted as the primarily consulted centre. Not included were cases where we merely provided a second opinion on documents from the Czech Republic and from abroad. Consequently, our institution performed angiography served as the basic parameter for enrollment in the cohort. Malformations were classified according the Spetzler-Martin system. Then, following detailed discussion with each patient and his/her family, we jointly chose the therapeutical modality: surgical resection, endovascular treatment with embolisation, stereotactic radiosurgery referral to Prague Leksell Gama Knife (LGK) centre, or observation.

The surgical group consisted of 85 patients, all operated by senior author; 28 of whom had undergone preoperative embolisation of their AVM. Endovascular treatment alone was used for 55 patients, 34 patients were directly referred to the centre of radiosurgery, the remaining 48 were advised to undergo a policy of „watch and wait“. However, there were also patients enrolled whose clinical condition was too serious to permit any therapeutic intervention. The distribution of AVMs according to the Spetzler-Martin grades in each group is given in Graph 12.1 showing preponderance of lower-grade AVM in the surgical group compared to endovascular and other groups ($p = 0.003$, chi-square test). The basic characteristics of the patients in surgical and endovascular groups are given in Table 12.1. None of the parameters under study: age distribution in each group, or presentation – haemorrhage or epileptic seizure – revealed any significant inter-group differences at the 5% level (t-test, chi square test). The surgical and endovascular groups were studied for the rate of serious procedural complications (GOS lesser than or equal to 3 after 30 days). Correlation between AVM grade and outcome measured by GOS was assessed using Spearmann correlation coefficient with

ommiting patients admitted in poor clinical state in whom poor outcome was due to severity of initial bleeding. The efficacy of each therapeutic modality was assessed after complete obliteration of the AVM. The same parameters for the surgical, endovascular and radiosurgical groups were set on the basis of literary search. All larger series obtained by searching PubMed database with key words „brain avm“ up to December 2013 were included in this literature review.

12.5. Results

Fourteen out of the 85 surgical patients were admitted in a serious condition marked by severe neurological deficit or a GCS of less than 9. Three patients in this group were admitted after bleeding from previously irradiated AVM. Preoperative embolisation was used in 28 cases; a total of 51 interventions were made. As an embolisation agent was used Onyx in 10 cases and NBCA in 18. In one patient severe deficit due to intracerebral hemorrhage occured after the procedure. The patient was surgically trated after 6 months after his deficit improved markedly. A serious complication during surgery occured in 3 patients; 2 patients (S-M grade 3 and 4) died. First one after one week, the other one after eight months in a vegetative state. The cause of unfavourable result was probably Normal perfusion pressure breakthrough (NPPB) phenomena [39] (in both cases we experienced uncontrollable peroperative bleeding resulting in intracerebral hematoma in the AVM bed and severe surrounding brain edema). A third patient (SM grade 3) suffered severe hemiparesis and aphasia. Surgical morbidity and mortality was 3.5%. Correlation between AVM grade and outcome was significant ($p<0.05$) with Spearmann’s coefficient $r = 0.32$.

At the one year follw up visit, six patients suffered from serious consequences of the initial haemorrhage. Three AVMs (3.5%) had not been removed completely. In one patient postoperative angiography was not done due to severe postoperative condition and ensuing death. The second unresolved case was a S-M grade-IV AVM in a 16-year old girl. Her malformation was localised in the basal ganglia and dominant frontal lobe. Embolisation attempt failed after the Brietal testing (feeders were from A1 and M1 segments. The AVM was planned only for partial resection and after this patient was twice irradiated with LGK. The AVM disappeared but the patient vision severely and permanently deteriorated after the second radiosurgical procedure. In the third case S-M grade IV AVM was partially resected and subsequently the residual AVM was successfully embolized. The overall rate of surgical effectiveness was 96.5%.

In the endovascular group, 55 patients had total of 96 endovascular procedures. One patient was admitted after bleeding from previously irradiated AVM. As an embolisation agent was used Onyx in 30 cases and NBCA in 25. In addition coils were used in 9 cases, mainly for treatment of flow-related aneurysms. There were two cases of unmanageable haemorrhage during embolisation; in another case embolisation caused severe neurological deficit due to inadverent occlusion of major cerebral artery. All these patients died. Consequently, the endovascular group morbidity and mortality amounts to 5.5% (patient-related) and 3.1% (procedure-related). Complete occlusion was achieved in 20 AVMs, which is success rate of 36.4% per patient and 20.8% per procedure. Five patients died within the one year follw up: three after procedural complications, and the other two due to primary haemorrhage. At the annual check-up, two patients had a GOS 3 as a result of primary bleeding. Correlation between AVM grade and GOS was not significiant. Table 12.2 sums up the results of surgical

and endovascular therapy for AVM – procedural mortality and morbidity and effectiveness of obliteration – attained at our neurosurgical centre.

Fourty-eight patients were shared with the LGK unit; 34 patients were referred there for treatment primarily and 13 patients were referred to the LGK unit after previous partial embolisation of AVM and one after surgery. Prior to radiotherapy, one patient had coiling performed for an incidental aneurysm on the basilar artery. The only procedural complication of LGK (severe vusual impairment) has already been mentioned. Up to the present day out of these 48 patients 16 have their AVM already obliterated, the rest is still in latency period without angiographical proof of AVM obliteration.

The observation group consists of 48 patients whose AVM was deemed either intractable with any of the available therapeutic techniques, or those who declined active treatment, or to whom active treatment was not recommended (advanced age, incidental lesion, serious comorbidity). This group included five patients whose initial haemorrhage was too serious to permit the consideration of any beneficial therapy, and four of them subsequently died. Seven others underwent active treatment for some other neurosurgical pathology, in all these cases the AVM was an incidental finding. Four patients were examined for ACI stenosis and three of them had carotid endarterectomy performed, and the last patient underwent carotid stenting. One patient was admitted for acute subarachnoid haemorrhage following rupture of one of two aneurysms of the circle of Willis, coiling was performed on both. One patient suffered SAH from PICA aneurysm, which was subsequently coiled. One patient had carotido-cavernous fistula successfully coiled.

In one case AVM thrombosed spontaneously after minor bleeding. We encountered only one bleeding in group of patients under observation. 56 years old patient with parieto-occipital grade IV AVM suffered fatal devastating heamorrhage after 10 years of observation.

Tables 12.3, 12.4 and 12.5, show the studies which helped to set the values for comparisons with our own results [7, 78, 83, 108, 111, 112, 115, 120, 124, 130, 133, 158-239].

The method of weighted mean was used for this purpose, the number of patients in each given study being the weight. The probability of procedural complications in radiosurgery is equal to the likelihood of bleeding during the three-year period of latency and severe adverse events of irradiation.

Due to the fact that AVM is disease of young and mid-age we have to make inferences at least thirty years ahead. On the acceptance of 3% annual bleeding rate a comparison of a thirty-year outlook of bleeding in patients treated with the particular techniques is given in Graph 12.2. Furthermore on the acceptance of 30% probability of poor recovery after AVM –related bleeding, thirty-year prospective period is plotted in Graph 12.3 as a determinant of the likelihood of serious mortality and morbidity. For the Graph 12.4, discussing ARUBA study was used probability of bleeding 1% per annum. The values of mortality and morbidity, just as those of the efficacy of treatment for the surgical and endovascular groups were used for constructing the graphs based on our centre´s data. However the values given for radiosurgical treatment and for observation are derived from literary sources since our LGK group is quite small and atypical. As for radiosurgery, an 8% probability of bleeding was used for the first three post-operative years – the period of latency. Exposed to the yearly probability of bleeding are all patients treated with the given method where some AVM remnants are detectable.

12.6. Discussion

Results of surgical treatment for pial AVM at our Neurosurgical department as well as those in the rest of the studies referred to the results from a meticulous selection of patients. Graph 12.1 makes it quite obvious that most of the higher-grade malformations were dealt with by methods other than surgical. The preponderance of lower-grade AVM in the surgical group compared to endovascular group ($p = 0.003$, chi-square test) is attributable to the surgical centre´s preferences. Patients a priori refusing surgical intervention often look for some other therapeutic option themselves. In contrast, patients with operable AVM who seek advice at the surgical centre are mostly well disposed to resection from the outset. Our results are comparable with the published ones [108, 163, 240]. Most of the patients with S-M Grade I and II AVMs are now indicated for surgical treatment as all other modalities fall far short of offering such an efficacy with such a low rate of complications. Thus the only decisive factor is the surgeon´s ability to weigh his/her own skills as not even an operation for a small AVM is an easy task.

The efficacy and rate of complications of independent endovascular embolisation attained at our centre is fully comparable with the average quoted in the rest of the published results. However, assessed over a 30-year span of time, the position of embolisation as an independent method is debatable. An analysis of Graph 12.2 will show that only after five to ten years post-embolisation is the patient´s prognosis more favourable than the natural course of the disease with regard to potential risk of bleeding due to a ruptured AVM. Analysing Graph 12.3 we can see the point of intersection shifting as far as 15 to 20 years from the treatment. On the whole then, owing to its low efficacy and relatively higher rate of procedural complications in comparison with the other modalities, the benefit of independent

curative embolisation is negligible as it can never reach a significant difference assessed against the natural course of the disease. It is yet to be establish the role of endovascular treatment in the management of AVMs. In our view, endovascular intervention is an essential part of AVM obliteration, though solely for selective embolisation of deep branches. As for the superficial branches, embolisation is a counterproductive approach hampering subsequent AVM resection. The superficial branches are easy to deal with after the dura is opened, there is no need for obstructive surgical glue, and in addition anatomical orientation is better. Embolisation of those branches will distend the deep feeders; their treatment is already the hardest part of AVM surgery even without embolisation. As we have seen repeatedly, even an embolised vessel can bleed readily after being cut as a whole. Arresting such hemorrhage is no easy task as the glue cannnot be coagulated easily nor the vessel clipped. Recently, some goups report much higher success rate [191, 201] but it is questionable whether these results are repeatable on a much broader scale. Another important finding of this study is absence of correlation between AVM grade and clinical outcome meaning similar risk of endovascular procedure to all AVM grades. This result strongly favours surgery with very low morbidity as a method of choice for lower grade AVMs. The new procedures, mainly the introduction of Onyx into endovascular practice, did not change efficacy of endovascular methods significantly and only few groups of authors presents markedly better results [191, 196].

In contrast, the position of radiosurgery remains unshakeable in the treatment of AVM; objections can only be raised against its unidirectional and liberal limits of indications. Surgical treament of grade I and II AVM is associated with 0% probability of permanent deficit [157] at a well nigh 100% rate of efficacy. In view of this, a solid medical substantiation is called for if the patient is to be exposed to the hazards of AVM-related haemorrhage during the period of latency at a markedly lower probability of obliteration – 84% [241]. Conversely, for deep-seated,

poorly accessible small-sized malformations radiosurgery is the method of choice. In such malformations, suitable for radiotherapy, the rate of obliteration is reported at up to some 70% [210]. In the case of larger-size AVM a similarly very high efficacy is reported after single or multiple irradiation. One study [130] mentions an efficacy of 62% for a group of AVMs larger than 9 cm^3; Sirin et al. [242] attained an efficacy of 50% for AVMs of more than 15cm^3 in size. On the other hand, there have been cases of bleeding from an AVM even after radiosurgical treatment and angiographic evidence of its obliteration [149, 243]. In our view, the greatest problem of radiosurgery lies in the variously high percentage of patients (reported at 10 up to 50%), in whom the AVM is discernible even after repeated irradiation. Admittedly, ours is a limited body of experience (3 patients) of surgery on AVM after LGK treatment. Nevertheless, it is a very optimistic experience; the operations were not more difficult, on the contrary. This prompts ideas of converting higher-grade AVM radiosurgically into AVMs of grades I and II to make them suitable for neurosurgery. In irradiated patients, the definitive therapy is in fact postponed by more than 6 years. As follows from the above facts, the therapeutical modalities are competitive as regards low-grade malformations. This applies mainly to surgical resection relative to stereotactic irradiation. True inter-modality cooperation has been reached in grade-III AVM where pre-operative or pre-radiosurgical embolisation can facilitate obliteration and reduce the risks of subsequent therapy [244]. What is still missing, however, is clear evidence of this logical conclusion as some authors question the effect of pre-radiosurgical embolisation [245]. It should be noted that grade-III AVMs are a very heterogeneous group. Therefore any decision must take into account the individual characteristics of each AVM.

Grade IV and V AVMs are complex and large malformations; straightforward surgery is too risky and radiosurgery is inefficacious. This is why we usually opt for the watch and wait

strategy. In some cases endovascular active approach can be used, depending on angioarchtecture, risk factors such as intranidal aneurysm, etc). As a rule, complete occlusion can hardly be achieved, though it is possible to treat e.g. an intranidal aneurysm or to reduce the malformation blood flow. Today, most neurosurgical teams regard AVM of grades IV and V as lesions suitable for observation. Some of those lesions, however, could be managed by cooperation of all three treatment modalities. Such and option and a well thought through management plan is to be considered especially in young patients with high rupture risk AVMs. In patients treated by multimodal approach each new step should be established anew according to the results of the previous one. The team must not dogmatically follow the management plan devised at the beginning of treatment.

During the construction of the probability graphs, the constant probability of AVM rupture was estimated at 3% per annum, leaving aside the opinion that during a few post-rupture years the likelihood of AVM rerupture is prominently higher; 6 to 18 % in the first year and gradually approaching the initial value [154, 246]. For the graph discussing ARUBA study was used probability of bleeding 1% per annum.

The previous paragraphs discussed the decisive **AVM-related factors**. The most important point here is the AVM classification according to Spetzler and Martin. The decision-making process invariably involves the need to estimate the risks and efficacy of the therapy against the hazards of the natural course. Apart from assessing the AVM as such, it is necessary to weigh up a number of other variables unrelated to the AVM. These are, firstly, **patient-related factors**. The presenting symptoms of the AVM. A patient whose AVM triggered only a single epileptic paroxysm needs an approach that is different from another patient with recurrent AVM haemorrhage. The patient´s age is important; some statistics show that any active

therapy in patients over 45 years of age can no longer counteract the risks of the natural course. Another factors are concomitant diseases and subsequent ASA grade. A patient with a congenital heart defect where anaesthesia would already be dangerous should be recommended for radiosurgical treatment. **Institution-related factors.** Is the clinical centre sufficiently experienced and equipped? Are the results comparable with those reported in literature? Have they been published? **Factors pertaining to the attending physician/surgeon** are the most difficult to evaluate. As a rule, self-assessment is the least objective. However, honesty is the most important quality of any physisian. Ultimately it is the patient, correctly and fairly informed, who should have the main say in deciding on the therapy.

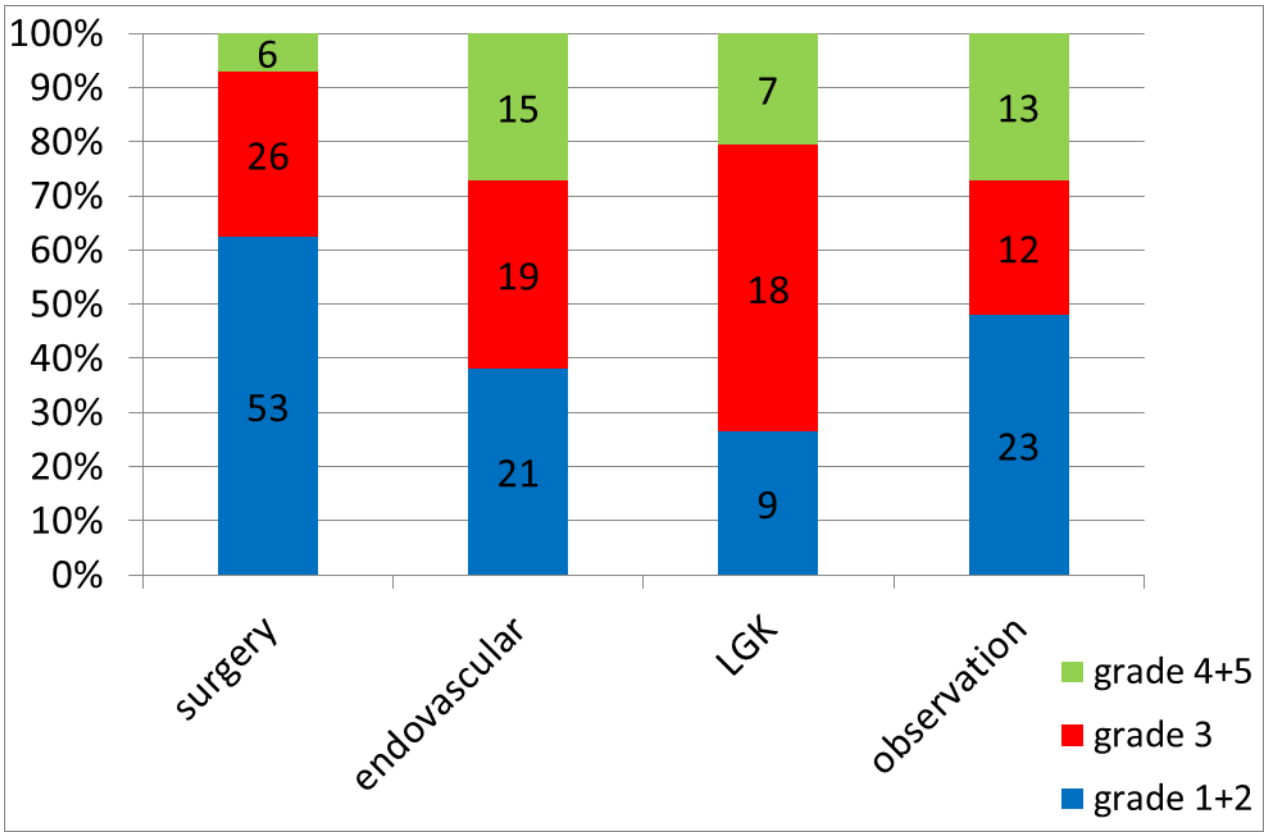
12.7. Conclusions

Backed by our experience of AVM treatment and by our assessment of the likelihood of post-treatment haemorrhage we have devised the following algorithm of treatment:

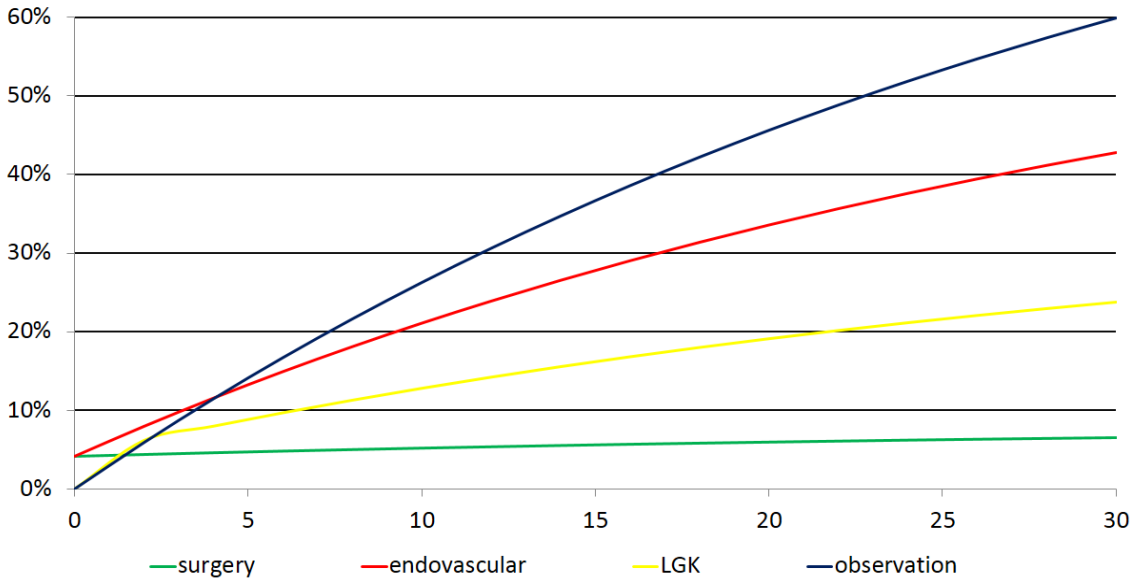
1. Surgery is to be seen as the method of choice for AVM of S-M grades I and II; as for grade III cases – only for superficially localised lesions. Higher-grade AVMs are only suitable surgery in exceptional cases, palliatively or in cases of recurrent haemorrhage.
2. Endovascular intervention should be used mainly for preoperative embolisation (that in itself is questionable), or as a curative procedure solely for lower-grade AVM in polymorbid patients, and for higher grades again only palliatively – the steal phenomenon, intranidal aneurysm.

3. Stereotactic radiotherapy with LGK is advisable mainly for poorly accessible, deep-seated grade-III AVM. In the case of lower grades, the final decision is left to the thoroughly informed patient himself/ herself.
4. Observation is to be taken as the method of choice for AVM of grades IV and V where active therapy represents a greater risk that the natural course of the disease.

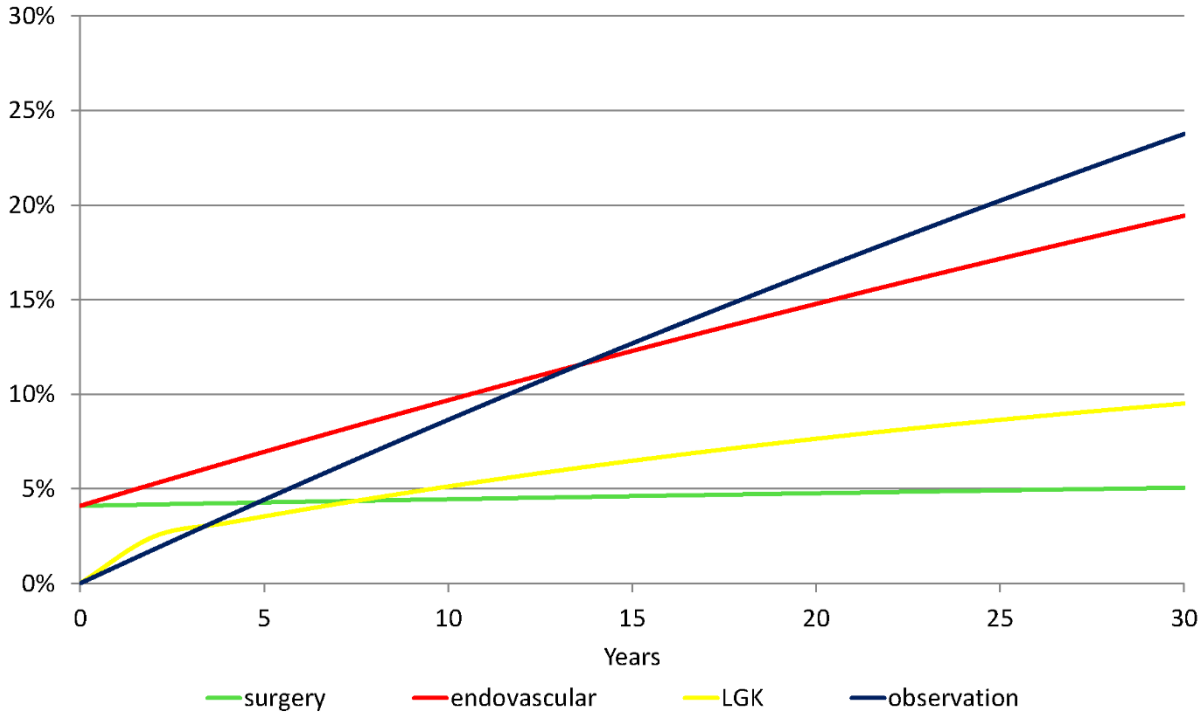
12.8. Graphs and tables



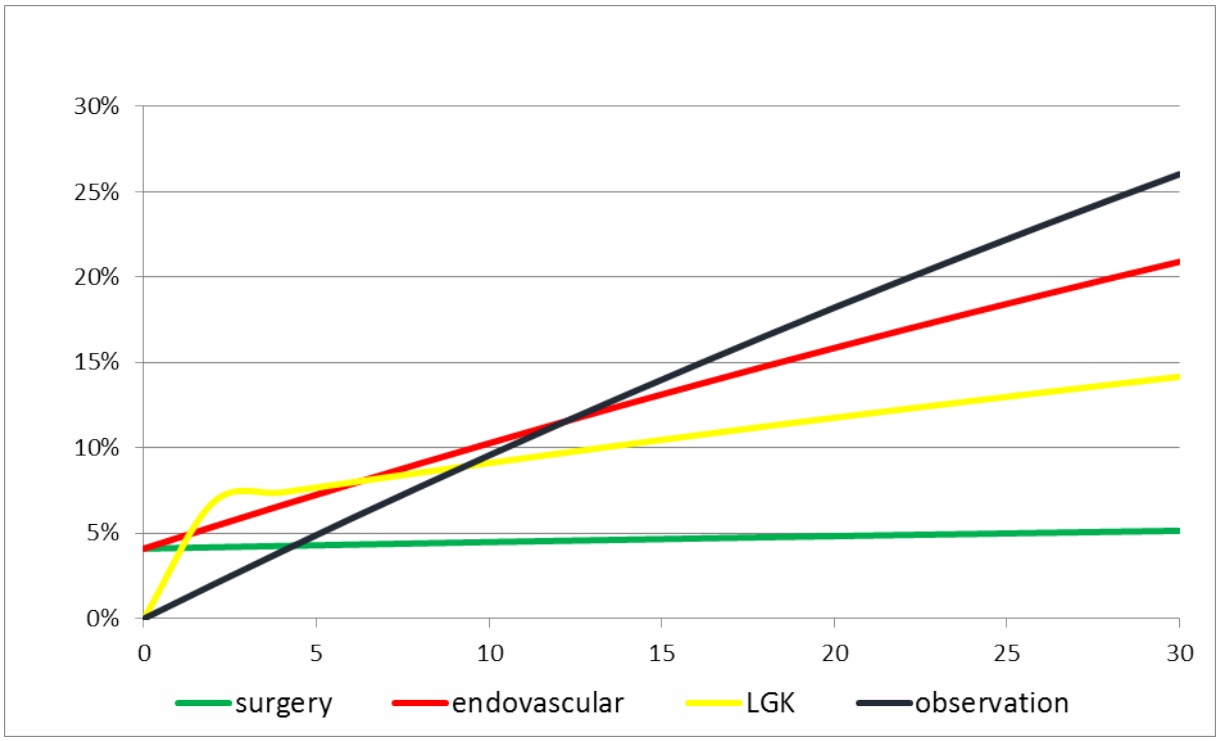
Graph 12.1: AVM grade distribution across groups.



Graph 12.2: Probability of bleeding in 30 years perspective.



Graph 12.3: Probability of poor outcome after bleeding in 30 years perspective.



Graph 12.4: Probability of bleeding in 30 years perspective for unruptured AVMs using ARUBA 1% annual bleeding probability.

	N	Age ± SD	ICH	IVH	SAH	Seizures
Surgery	85	38.3 ± 15.6	34	16	27	14
Endovascular	55	40.9 ± 16.4	26	8	14	14
p value		N.S.	N.S.	N.S.	N.S.	N.S.

Table 12.1: Basic demographic characteristics and AVM presntation of patients in surgical and endovascular groups. No significant difference was found.

Modality	Efficacy [%]	M/M [%]
Surgery overall	**96.5**	**3.5**
Surgery SM 1-2	100	0
Surgery SM 3	96.2	8.3
Surgery SM 4-5	83.3	16.7
Endovascular	**36.4 / 20.8**	**5.5 / 3.1**

Table 12.2: Achieved efficacy and morbidity and mortality of surgical and endovascular treatment of AVM. Values in endovascular treatment corresponds to per patient/per session efficacy and M/M.

Author	year	n	age	comp. [%]	eff. [%]	S-M grade
Abad	1983	70		11.0	81.4	
Jomin	1985	128		21.0	92.9	
Spetzler	1986	100		4.0	100.0	I - V
Andrews	1987	28	34	10.7	67.9	
Heros	1990	153		8.4	100.0	I - V
Deruty	1993	64		18.8	93.7	I - V
Sisti	1993	67		1.5	94.0	I - III
Hamilton	1994	120	36	8.3	100.0	I - V
O'Laorie	1995	56	36	5.3	92.9	I - V
Tew	1995	39	30	15.4	97.4	III - V
Malik	1996	156	33	14.7	95.8	
Schaller	1998	150	35	13.3		I - V
Pikus	1998	72		8.3	98.6	I - III
Hassler	1998	191		11.0		I - V
Pik	2000	110	38	2.7	98.8	I - III
Hartmann	2000	124	33	6.0		I - II
Solomon	2000	86		1.2	90.7	
Stapf	2002	240	34	1.7	93.8	
Morgan	2004	220		1.4	98.6	I - II
Lawton	2005	224	38	7.1	98.0	I - V
Spears	2006	175	40	13.5		I - IV
Rodriguez-Hernandez	2012	60	41	5.0	100.0	I - IV
Gabarros Canals	2013	88		5.0	93.0	
Total		**2721**	**36**	**7.2**	**95.9**	**I - V**

Table 12.3: Overview of published surgical series.

Author	year	n	age	comp. [%]	eff. [%]	S-M grade
Merland	1986	67		10.0	9.0	
Vinuela	1986	30			5.5	III - V
Huang	1995	72		4.0	40.3	
Lundqvist	1996	150	36	13.3	13.3	
Debrun	1997	54		5.6	5.6	
Sorimachi	1999	36	31	16.7	13.9	I - V
Valavanis	1998	387		2.6	40.0	
Song	2000	70	42			
Liu	2000	103		8.7	10.7	I - V
Hartmann	2002	233	36	3.0	34.0	I - V
Meisel	2002	450	30	8.0	16.0	I - V
Taylor	2004	201	36	11.0	0.0	I - V
Kim	2006	139	38	5.1	7.9	I - V
Ledezma	2006	168	41	9.2	2.5	I - V
Haw	2006	306	34	7.5	9.5	I - V
van Rooij	2007	44	42	6.8	15.9	I - V
Mounayer	2007	94	32	8.5	49.0	I - V
Weber	2007	93	38	12.0	20.0	I - V
Jayaraman	2008	192		6.3	9.9	I - V
Katsaridis	2008	101		11.0	27.7	
Panagiotopoulos	2009	82	44	6.2	24.4	I - V
Pierot	2009	50	35	10.0	8.3	I - V
Gao	2009	88	29	3.5	26.1	I - V
Xu	2010	86	30	4.7	18.6	I - V
Maimon	2010	43	31	2.3	37.0	I - V

Lv	2010	147	28	4.8	19.7	I - V
Saatci	2011	350	34	7.1	51.1	I - V
Pierot BRAVO	2013	117	43	5.1	23.5	I - V
Strauss	2013	68		8.7	37.0	
Total		**4021**	**35**	**7.0**	**22.4**	**I - V**

Table 12.4: Overview of published endovascular series.

Author	year	n	age	comp. [%]	eff. [%]	S-M grade
Colombo	1989	97		7.1	52.0	
Lunsford	1991	227		1.7	80.4	I - IV
Coffey	1995	121		8.0	35.5	
Kobayashi	1996	324		2.7	79.3	
Aoki	1996	236		4.4	86.6	I - III
Karlsson	1997	945	31		56.0	I - V
Yamamoto	1998	53		11.3	60.4	
Miyawaki	1999	73	30	13.7	38.4	I - V
Pan	2000	240		8.0	47.9	I - V
Kurita	2000	30		5.0	52.5	
Massager	2000	87	37	8.4	73.0	II - III
Schlienger	2000	169	33	7.7	64.0	I - IV
Zhou	2000	132		3.8	73.7	
Hadjipanayis	2001	33	32	9.1	70.0	
Smyth	2002	40		10.3	40.0	II - V
Pollock	2003	144		7.7	76.0	I - V
Friedman	2003	269		11.0	53.0	I - IV
Zipfel	2004	268		10.0	57.8	I - V
Shin	2004	408	31	6.8	88.1	I - V
Izawa	2005	237		9.3	54.9	I - V
Maruyama	2005	500	32	7.2	91.0	I - V
Zabel	2005	110	40	11.8	52.7	I - V
Andrade-Soussa	2006	38	40	8.0	60.5	II - III
Cohen-Gadol	2006	38	15	0.0	68.4	I - V

Veznedaroglu	2004	30	41	10.0	37.5	I - V
Andrade-Soussa	2007	45		12.0	61.9	II - IV
Reyns	2007	100	12	5.0	70.0	I - V
Kiran	2007	103	14	6.7	87.0	
Karlsson	2007	133		14.0	62.0	
Liščák	2007	330		3.4	92.0	I - V
Javalkar	2009	37		2.7	46.5	II - V
Sun	2010	127	37	11.0	64.0	
Kim	2010	44	27	4.6	34.1	II - V
Yen	2010	186	13	1.1	58.6	I - V
Blamek	2011	62	40	0.0	35.5	I - V
Cetin	2012	70			80.0	I - V
Herbert	2012	52	39	4.1	78.8	I - IV
Parkhutik	2012	108	36	5.6	75.9	I - IV
Teashineetanakul	2012	139	36		66.0	
Starke	2013	1012		2.1	69.0	I - V
Yen	2013	1286	34	1.8	55.6	I - V
Total		**8683**	**31**	**5.3**	**66.1**	**I - V**

Table 12.5: Overview of published radiosurgical series.

13. Neuropsychological performance after brain arteriovenous malformations treatment

Bradac O. MD, MSc, Pulkrabkova A. Mgr, de Lacy P. MD and Benes V MD, PhD

13.1. List of Figures and Tables:

13.2. Abstract

Background

Neurological sequel from the treatment of bAVMs was extensively studied. The Spetzler-Martin grading is used to estimate possible surgical risks. However, possible neuropsychological sequel has not been studied in detail by many authors to date. We decided to evaluate the neuropsychological outcome of our patients whom underwent treatment for brain AVMs.

Methods

A total of 66 underwent treatment of bAVM and neuropsychological testing for at least two years post-operatively using a battery of tests constructed specifically for this study. A control group consisted of 10 subjects without any neurological disease.

Results

No significant differences were found between the follwing groups; presenting feature being haemorrhage, gender and hemisphere dominance, when the whole cohort was analysed. Patients harboring SM IV-V scored significantly worse than patients harboring SM I-III. Patients who presented with epilepsy scored lower than patients presenting with other symptomatology, but the difference had only borderline significance.

When we analysed patients according to the presence or absence of obliteration after treatment and compare these to the control group, we found no significant differences.

The subgroups of patients with an obliterated bAVM after treatment divided according to treatment modality was compared to the control group which showed no significant differences, similarly as in comparison of the SM groups.

The subgroups of patients with non-obliterated AVMs analyzed according to SM grade, showed a borderline significant difference with SM IV-V being worse in their neuropsychological outcome compared to the other groups.

Conclusions

This study lends support to an active treatment policy for bAVMs. Those patients in whom complete obliteration was achieved with treatment, scored similarly to the background population, implying active AVM treatment doesn't cause deterioration in neuropsychological performance. This, together with a near 100% bAVM obliteration rate favors microsurgery as the treatment modality of choice, whenever the bAVM could be safely resected.

13.3. Introduction

Brain arterio-venous malformations (AVMs) consist of a complex tangle of pathological vessels causing shunting between arteries and veins within the surrounding brain tissue [36]. Brain AVMs are a relatively rare entity with a prevalence of 1/100 000 [25]. On the other hand, the incidence rate of non-ruptured AVM's is increasing due to an increase in the availability, easy accessibility and an improvement in imaging techniques [246]. We studied the neurological sequale of patients treated in our unit for brain AVMs' treatment. We used the Spetzler-Martin grading system to appropriately inform our patients about the possible surgical risks [78]. This doesn't hold true for the possible neuropsychological sequale, which has only been studied by a few authors to date [37, 247-249]. We decided to evaluate the neuropsychological outcome of our patients treated for brain AVM's using standardized neuropsychological tests and compare these results with a control group chosen from our background population. Furthermore, we have compared neuropsychological functions across treatment modalities.

13.4. Materials and methods

Altogether 66 patients were enrolled in the study. All patients underwent treatment of their brain AVM at our institution and expressed willingness to participate in the study after their treatment. If the patient was treated actively with microsurgical resection or endovascular embolization, they were enrolled into our study within 2 years of their treatment date. Those patients with moderate or severe neurologic deficit (modified Rankin scale > 2) after their initial presentation with haemorrhage from their AVM or due to procedural morbidity and

mortality were excluded from this study. We also excluded patients from other countries, who could have artificially worse results due to a language barrier.

Altogether 113 patients were treated for brain AVM in our institution between years 2001 and 2009. Out of these 113 patients, 4 patients died, 8 patients were in poor clinical status and 2 patients were from other countries. The remaining 99 patients were asked to participate in our study. Out of these 99 patients, 33 refused to participate or did not respond to their invitation to attend the out-patient clinic (Figure 13.1.).

Our final patient cohort consisted of 39 males and 27 females; mean age was 38 ± 16 years. Microsurgical resection was performed in 35 patients, endovascular embolisation in 17 and 14 patients were observed. Thirty-six malformations were localized in the dominant hemisphere and thirty in the non-dominant hemisphere. Complete obliteration was achieved in 40 cases: 33 with resection, 5 with embolisation, and in 2 patients there was evidence of spontaneous obliteration during the follow up period. Five patients from those in the observed group were sent for stereotactic radiosurgery, similarly as 3 patients after partial embolization. Thirty-two AVMs were Spetzler-Martin grades I&II, 18 were grade III and 16 were grades IV&V. The presentation was with haemorrhage in 31 cases (intracerebral haemorrhage in 25, intraventricular haemorrhage in 10 and subarachnoid haemorrhage in 17). 21 cases presented with seizures.

The control group consisted of 10 subjects (age 44 ± 10 years) without any neurological disease willing to undergo neuropsychological testing.

Neuropsychological testing was performed using a battery of tests constructed specifically for this study consisting of the following standard tests:

- Verbal / Language intelligence was tested by Vana's intelligence test - VIT [250].

- Frontal / Execution functions were tested by FAS test in Czech version and Trail Making Test, part B [251].
- Attention and processing speed was measured by Trail Making Test, part A [251].
- Nonverbal intelligence was measured by Test of intellect potential - TIP [252].
- Visuospatial functions by Cubes analysis, subtest of VOSP battery [253].
- Verbal memory was measured by Auditory-verbal learning test - AVLT [251].

The study was approved by local ethical committee of Military University Hospital, Prague.

13.5. Statistical evaluation

All results were evaluated using Czech normal values standardized for age and education. As a measure of the overall neuropsychological performance, composite z scores for each patient were computed as a mean of the standardized scores in each test. Univariate statistical analysis was used to determine the studied factors' influence on outcomes. Comparisons of continuous variables were made using one-way ANOVA or t-tests. Comparisons of categorical variables were done using chi-square test. In all cases a p-value of less than 0.05 was considered significant. All computations were performed using STATISTICA 10.0 software (StatSoft Inc., Tulsa, USA, distributed by StatSoft CR sro, Czech Republic).

13.6. Results

No significant differences between the groups were found when the presentation was haemorrhage; gender and hemispheric dominance when the whole cohort was analysed. Patients harboring SM grade IV-V lesions scored significantly worse than patients harboring SM grade I-III lesions. Patients who presented with epilepsy scored lower than patients presenting with other symptomatology, but the difference had only borderline significance, Table 13.1.

When we analysed patients according to the presence or absence of complete obliteration after treatment and compared these to the control group, we found no significant differences, Table 13.2. Distributions of S-M grade in obliterated and non-obliterated subgroups are in Table 13.3.

When we analysed the subgroup of patients with completely obliterated AVM after treatment according to their treatment modality, we found no significant differences compared to the control group, similarly as in comparison of S-M grade groups, Table 13.4.

When the subgroup of non-obliterated AVMs is analysed according to S-M grade, we find borderline significance with S-M grade IV-V who scored worse than the other groups, Table 13.5.

13.7. Discussion

In this study, we evaluated the cognitive outcomes of AVM patients after various types of treatment. Although there are some case reports showing improvement in neuropsychological functions after AVM resection [254-256], the main issue for the responsible neurosurgeon is to choose the most appropriate treatment modality which is able to obliterate the AVM, but in so doing, having the lowest risk of harm to the patient. From this point of view, comparison of post-treatment results in patients in whom obliteration was achieved, across various treatment strategies, makes sense. In our results, we found no differences between patients treated with surgical resection and endovascular embolization and their performance was not different from the background population. This finding supports an idea of active treatment being the treatment of choice, whenever treatment can be performed safely. The recently published ARUBA study [152] showed that in cases where an AVM has not bled, observation is the treatment choice. Organization of this study was one of initial moments for evaluation of neuropsychological outcomes of our patients. Although final results of ARUBA study supports an idea of watch and wait strategy, these results are based on 98 actively treated patients and out of these 116 patients only 18 patients underwent surgical excision alone or in combination with other treatment modalities. As the authors stated in their discussion, the ARUBA study was not powered to distinguish amongst the different treatment modalities. From our point of view, the number of events (strokes and deaths) in the interventional branch of the ARUBA study was extremely high (37%) – a number which could not be confirmed by analysis of our unit's data and also a literature search, which was published previously [153]. On the other hand, it is necessary to bear in mind that the vast majority of post-treatment events occurred during the first two years after treatment on

partially treated AVMs (either by radiosurgery or embolization). This puts doubt on the usage of these modalities in active AVM treatment. Surgery with its known low morbidity and mortality (in our hands 1.4%) and high efficacy (in our hands above 97%) in well selected patients is not comparable to the ARUBA findings.

According to our results, patients harbouring non-obliterated high grade AVMS (S-M IV-V) scored worse than those patients harbouring AVM S-M grade I-III. This finding implies a possible role of the 'steal phenomenon', which has been suggested by other authors as the most likely reason for a neuropsychological and a neurological improvement after AVM obliteration. Baker et al. [254] reported a case of a patient with a right temporal AVM, who showed improvement in IQ and visual memory after AVM excision. La Piana et al. [257] reported a case of patients harbouring right temporal S-M grade V AVM, presenting with progressive hemiparesis, who showed improvement in neurological status after partial embolization and motor cortex reorganization, which was documented on CT perfusion scans. The fact that especially high-grade lesions scored lower in composite score imply that possible steal phenomenon caused by AVM is in fact a 'whole brain' problem. This is similar to improvements seen in cognitive functions after carotid endarterectomy, where severe internal carotid stenosis before treatment can cause cerebral hypoperfusion with subsequent cognitive deficits [258-261].

Altogether 8 patients (observed or after embolization) received Leksell Gamma Knife treatment. This was not emphasized in the results as various reports show minimal sequale of stereotactic radiosurgery treatment on cognitive function [262-264].

Patients in a poor clinical state after initial haemorrhage of their AVM or as a result of active treatment were not evaluated. In our opinion, neuropsychological testing is a fine tool used

to measure and compare outcomes. Rates of procedural complications and morbidities and mortalities together with efficacy of all treatment modalities are well known [153]. Therefore, the decision on treatment modality must be made by the responsible neurosurgeon based on the AVM architecture, location, patient clinical state, institutional experience, patient wish and other individual factors. Only in case of equipoise about a preferred treatment modality, knowledge of neuropsychological outcomes of either treatment modality could be used as a factor in influencing the treatment decision.

Although the mean age of the subjects in the control group was slightly higher than in the patient study group, this difference did not reach statistical significance. Furthermore, all neuropsychological results are age and level of education adjusted. Therefore comparison of these groups is perfectly feasible.

The major weakness of this study is its retrospective manner with absence of pre-op evaluation of neuropsychological functions. On the other hand, comparison to control group showed that patients after AVM treatment has neuropsychological performance fully comparable to background population. Comparisons of pre-treatment and post-treatment neuropsychological performances to evaluate role of steal phenomenon are part of ongoing study of our group.

13.8. Conclusions

This study lends support to an active treatment policy for cerebral AVMs. Those patients in whom treatment achieved complete obliteration scored similarly to the background population showing that active AVM treatment doesn't cause deterioration in

neuropsychological performance. Also there was no difference between the various treatment modalities. A near 100% AVM obliteration rate favors microsurgery as the treatment of choice whenever the AVM could be safely resected.

13.9. Graphs and tables

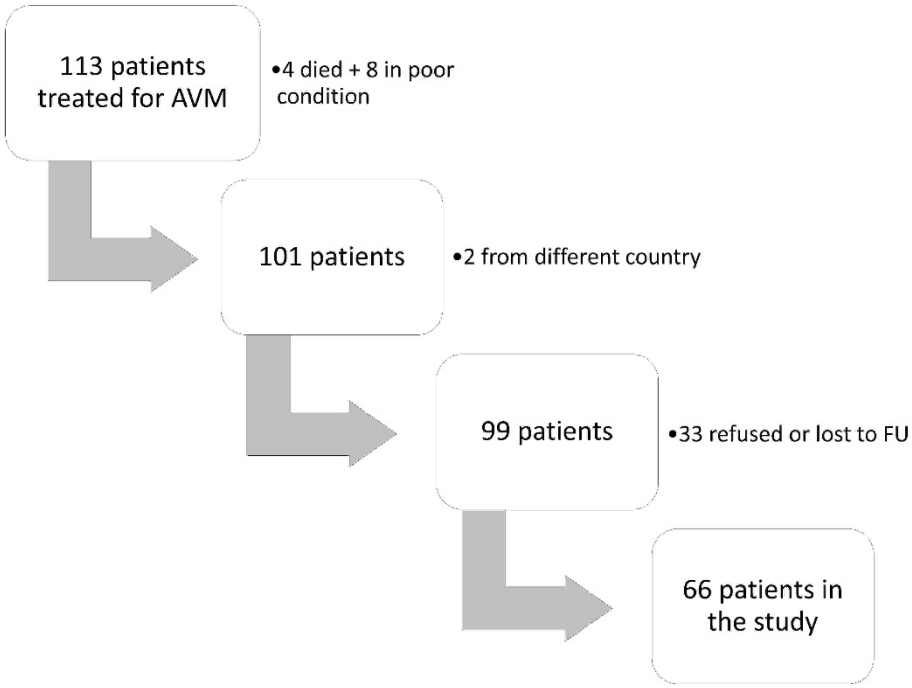


Figure 13.1. Study flowchart

	Standardized composite scores		p-value
	Yes (N=21)	**No (N=45)**	
Epilepsy presentation	-0.30 ± 0.80	0.08 ± 0.73	**0.064**
	Yes (N=31)	**No (N=35)**	
Bleeding presentation	-0.02 ± 0.76	-0.06 ± 0.78	**0.828**
	Yes (N=16)	**No (N=50)**	
SM grade IV-V	-0.38 ± 0.83	0.06 ± 0.72	**0.041**
	Yes (N=39)	**No (N=27)**	
Male gender	-0.11 ± 0.68	0.05 ± 0.89	**0.426**
	Yes (N=36)	**No (N=30)**	
Dominant hemisphere	-0.08 ± 0.82	0.02 ± 0.66	**0.597**

Table 13.1. Differences in neuropsychological outcome according to presentation, grade, gender and hemisphere dominance.

	Obliterated (N=41)	Non-obliterated (N=25)	Control group (N=10)	p-value
Standardized Composite Score	-0.05 ± 0.67	-0.03 ± 0.92	0.13 ± 0.58	**0.793**

Table 13.2. Neuropsychological outcome according to status after treatment.

	Grade I-II	Grade III	Grade IV-V
Non-obliterated	6	7	12
Obliterated	26	11	4
p-value	**0.001**		

Table 13.3. Spetzler-Martin grade distribution according to status after treatment.

	Surgery (N=33)	Endovascular (N=5)	Control group (N=10)	p-value
Standardized Composite Score	-0.06 ± 0.65	-0.06 ± 1.00	0.13 ± 0.58	**0.743**

	Grade I-II (N=26)	Grade III (N=11)	Grade IV-V (N=4)	p-value
Standardized Composite Score	0.07 ± 0.62	-0.32 ± 0.83	-0.07 ± 0.33	**0.286**

Table 13.4. Patients with AVM obliterated after treatment divided according to treatment modality and Spetzler-Martin grade.

	Grade I-II (N=6)	Grade III (N=7)	Grade IV-V (N=12)	p-value
Standardized Composite Score	0.45 ± 0.61	0.33 ± 0.84	-0.49 ± 0.93	**0.053**

Table 13.5. Patients with AVM not obliterated after treatment divided according to Spetzler-Martin grade.

14. Haemorrhage from a radiosurgically treated arteriovenous malformation after its angiographically proven obliteration: a case report

Bradáč O., M.D., M.Sc., Mayerová K., M.D., Hrabal P., M.D., Beneš V., M.D., Ph.D.

14.1. List of Figures:

14.2. Introduction

Treatment for pial arteriovenous malformations (AVMs) currently rests on three pillars: surgical resection, stereotactic Gamma knife radiosurgery and the use of LINAC and endovascular embolisation. The pros and cons of each of the modalities are sufficiently well known [244]. Surgical intervention offers a high degree of effectiveness at a low rate of complications, both transient and chronic, though admittedly not suitable for all types of lesion. Endovascular embolisation is rather a complementary method, particularly because of its low effectiveness. At our place of work, independent embolisation is an exceptional option likely to be put to use in combination therapy. Although radiosurgery for AVM is a viable option, the problem is that it requires regular monitoring of the course of the condition and angiographic proof of AVM removal. Moreover, concerning the relatively uneventful course, it is necessary in high-grade AVMs (Spetzler-Martin grades IV-V) to weigh meticulously the indication for any active therapy [265, 266].

In our report we present the case of a patient with an AVM repeatedly treated at our Leksell Gamma knife centre yet marred by rebleeding despite angiographically proven obliteration.

14.3. Case report

Our 42-year-old patient, a man treated for hypertension, was, at the age of 35 years, examined for intensive migraine-type cephalea, for phosphenes in the left-hand half of his field of vision and for a transient left temporal deficit of visual field. Magnetic resonance imaging (MRI) raised the suspicion of a pial AVM in the right-hand occipital region. On its verification in

August 1995 (Spetzler-Martin grade III), the AVM was irradiated with a Leksell Gamma knife; at the first session, its volume was 7.9 cm^3 (Figure 14.1). Irradiation helped to improve the clinical condition (i.e. the symptoms subsided), but because the AVM failed to be completely obliterated during the latency period, a second session was arranged in August 1998 to complete the irradiation of the residual nidus. By then, the volume had been reduced by 80% to 1.5 cm^3. At either time, the minimal marginal irradiation dose applied was 16 Gy at the 50% isodose line. MRI, which was repeatedly performed during the subsequent follow-up, showed a gradual abatement of a reactive oedema. Following angiography in August 2002, complete elimination of the AVM was diagnosed, whereupon the patient's dispensary care could be discontinued (Figure 14.2). In May 2007, however, his clinical condition changed suddenly with the development of diplopia, meningism and spatial disorientation. Ophthalmological examination revealed congestion in the papillae of optic nerves +3D and +4D and a sector deficit of the field of vision on the left side. The patient was acutely admitted at a neurological department for the management of intracranial hypertension. In June and July 2007, MRI scans revealed cystic foci, haematomas of diverse age and suspected bleeding from the residual AVM at the site of the original AVM (Figure 14.3). Multiple cavernomas were thought of in differential diagnostic terms. Diagnostic angiography revealed no AVM. Despite this finding, a surgical revision was decided on and eventually performed in October 2007. The peroperative finding indicated a pial AVM, which was completely resected. Because of the histologically discovered presence of thick-walled vessels with elastics and muscle tissue in the walls (Figure 14.4), an AVM was considered the most likely variant in agreement with the peroperative findings (Figure 14.5). Immunostaining with VEGF and Ki-67 antibodies showed only minimal endothelial proliferation activity (Figure 14.6). At the time of discharge, the patient was free from extremity lateralisation, meningeal, with a minor deficit persisting in

the left side of his visual field. Follow-up MRI demonstrated a perfect resection of the focus and discernible abatement of the preoperative oedema.

14.4. Discussion

Tiny, deep-seated, surgically inoperable AVMs are a typical indication for radiosurgical intervention. When considering superficially localised AVMs of lower Spetzler-Martin grades, the choice of therapeutic modality depends on the preference and line of specialisation of the indicating surgical centre [267]: outstanding results are achieved with both methods [83, 229, 240, 268]. Active therapy is almost invariably appropriate [241].

Radiosurgical treatment for malformations is exposed to a number of sources of risk. There are complications associated with the operation proper: disorders of cranial nerve functions, onset or worsening of attacks or late formation of cysts. The most serious of such events is the threat of the patient's bleeding from an AVM, which is likely to appear at a rate of 3-4% annually [244, 269] throughout the approximately three-year period of latency. What is more, as our case shows, there is still the risk of rupture and haemorrhage from the residual nidus, even after verified complete obliteration of the AVM.

Nowadays, it is proven, that AVM and cavernous angioma are dynamic lesions. Immunoreactivity of both was studied extensively and many publications concerned on various proliferation markers were published [270-273]

In paediatric recurrent AVMs was shown significantly higher degree of VEGF expression than in non-recurrent paediatric and adult groups [271]. In series of 25 AVM published by Sure et al. VEGF expression was found in 60% of cases, antibodies against Ki-67 in 12% [270].

By histological examination of our specimen the presence of AVM was proven, but immunostaining with VEGF and Ki-67 antibodies shown absence of endothelial proliferation. This is in good agreement with recent experimental work of Kilic et al. [274]. In this work is studied dose-dependent inhibition of neoangiogenesis in rat corneas by gamma knife irradiation. Absence of proliferation markers in our specimen supports conception of rebleeding from residual nidus of irradiated AVM.

The de novo development of a cavernous malformation, which was our second differential diagnostic option, has repeatedly been reported as a complication of radiation therapy for other intracranial lesions [275-277]. There is also multiple proof of a relation between a pre-existent venous malformation and de novo development of a cavernoma-like lesion [278, 279]. Maeder et al. [280] reported the case of a 14-year-old boy treated with irradiation for a posterior fossa medulloblastoma. Three years after the therapy he suffered from haemorrhage adjacent to a previously diagnosed venous malformation in the left hemisphere. A discussion is presented there of the process of cavernoma development: radiation-induced changes in the venular endothelium led to capillary teleangiectasy with continual petechial haemorrhage in the immediate neighbourhood. This is how a typical cavernoma is formed. In the case of an irradiated AVM such a mechanism is a plausible explanation of recurrent sub-clinical haemorrhage. On the other hand, histological examination didn't show any signs of neovascularization and endothelial proliferation activity. Thus de novo development of cavernous angioma, similar as AVM, is quite improbable.

Cases of bleeding from an obliterated AVM have been described in a number of reports [150, 243, 281, 282]. For instance, Shin et al. estimated the probability of rupture of a residual AVM with angiographically verified obliteration at 0.3% annually. Consequently, although the risk of rupture is about ten to fifteen times lower than that in the natural course or in the latency period, it is obviously necessary to follow-up the patients even after angiographically verified obliteration of the AVM. Magnetic resonance with contrast medium appears to be an adequate method as it not only exposes late developing cysts [281] but also exploits the statistically proven interdependence between haemorrhage from the "obliterated" AVM and from a persistent enhancing area revealed by contrast medium MR imaging [243].

14.5. Conclusions

In the case of primary radiosurgical treatment the patient should be followed up not only during the period of latency before angiographically confirmed obliteration but also during the following years, though certainly at longer intervals.

14.6. Figures

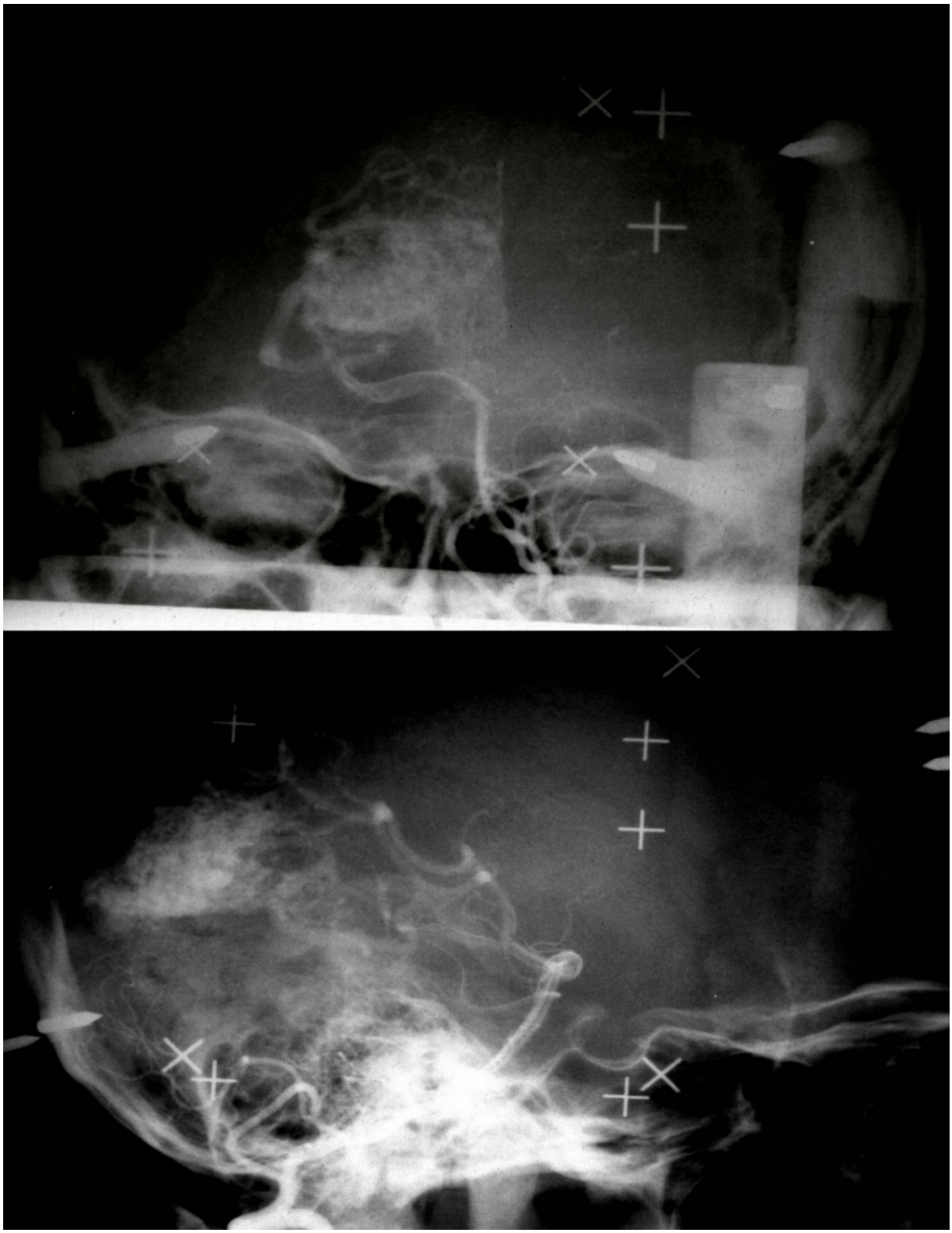


Figure 14.1: Angiographic scan before first irradiation showing a Spetzler-Martin grade III AVM. Scans provided by courtesy of Na Homolce Hospital.

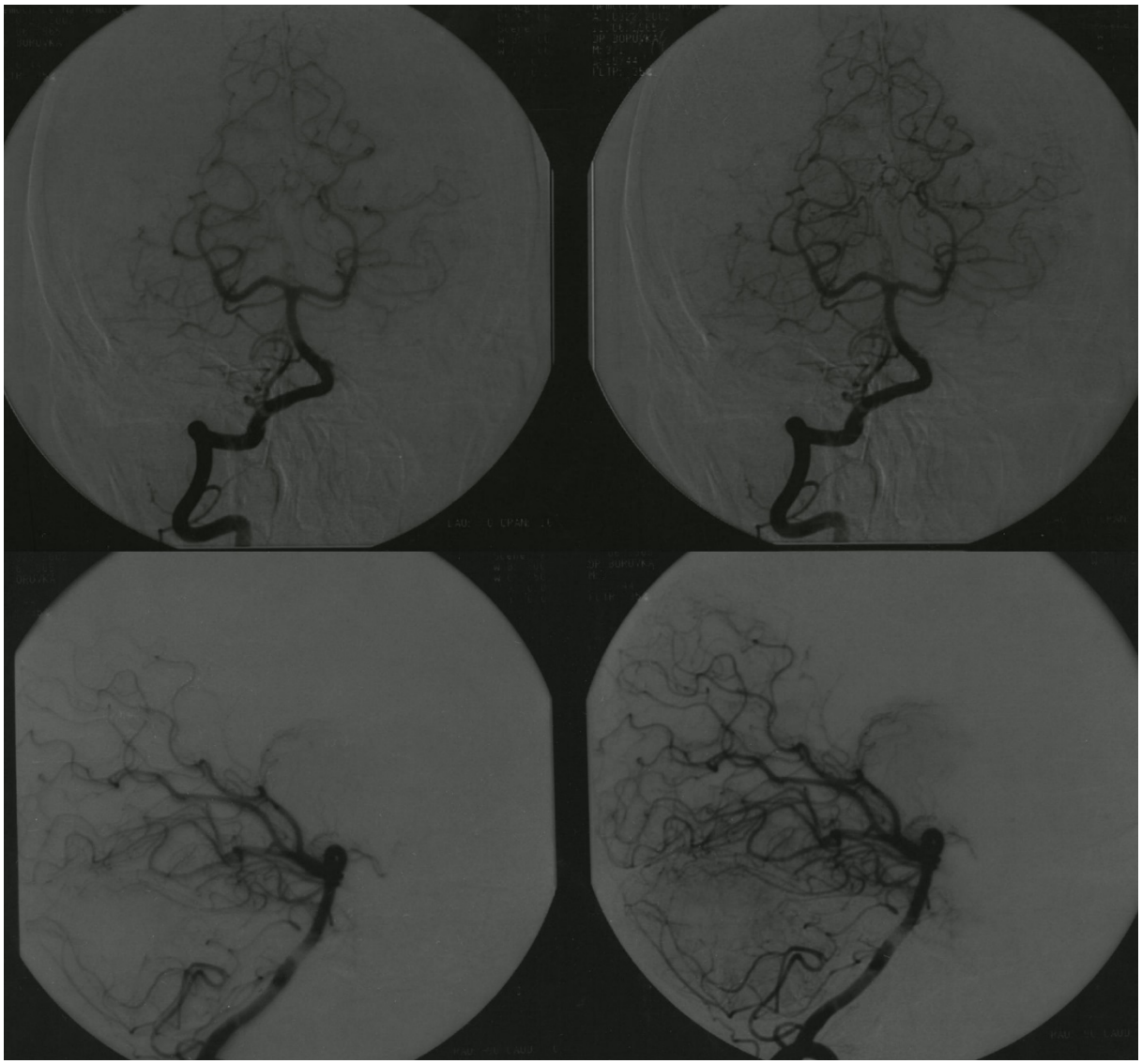


Figure 14.2: Angiographic scan showing obliteration of irradiated AVM. Scans provided by courtesy of Na Homolce Hospital.

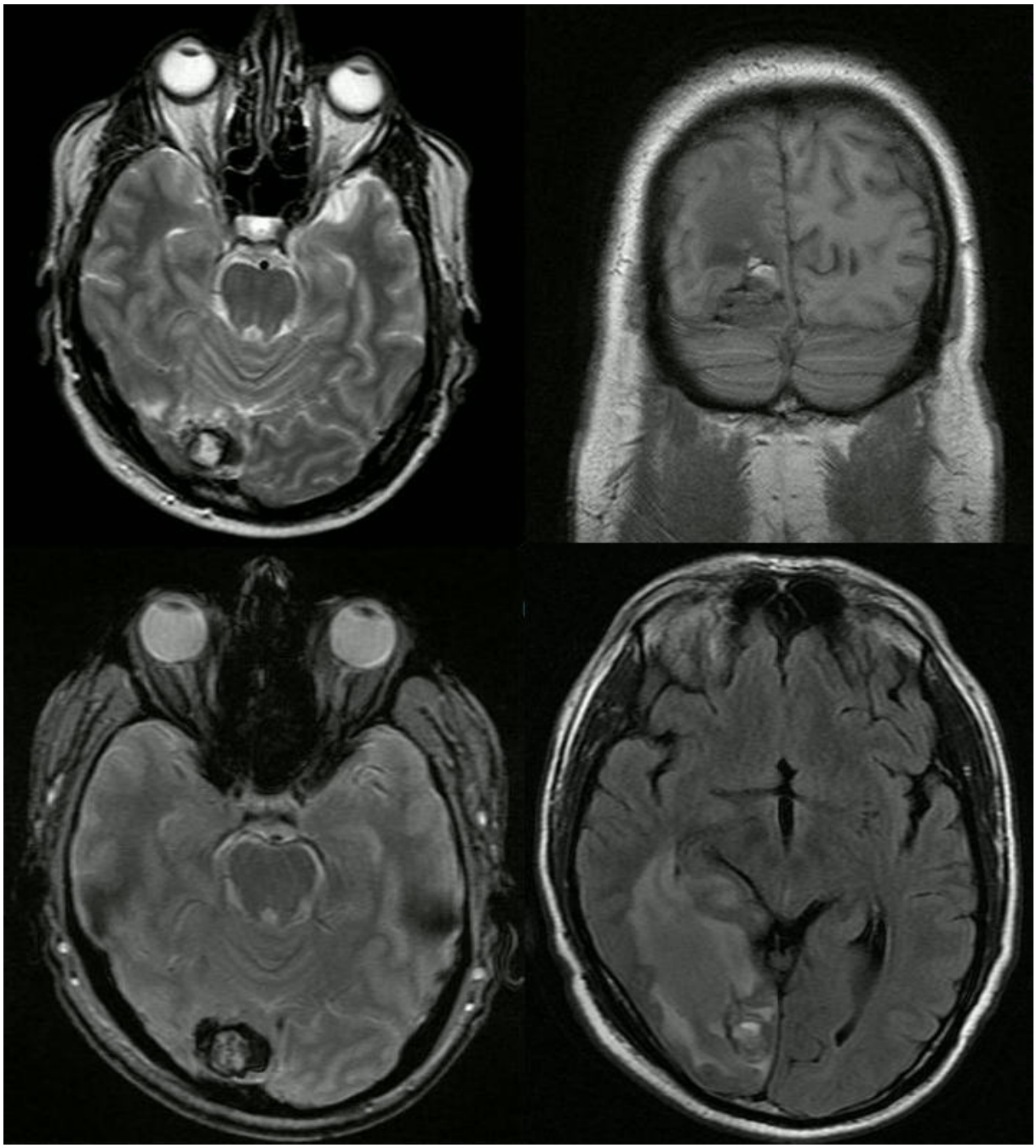


Figure 14.3: Preoperative MR scans. *Top left:* T2-weighted axial section. *Bottom left:* Axial section in gradient echo sequence. *Top right:* T1-weighted coronary section. *Bottom right:* Axial section in FLAIR sequence. A major oedema is discernible throughout the occipital lobe.

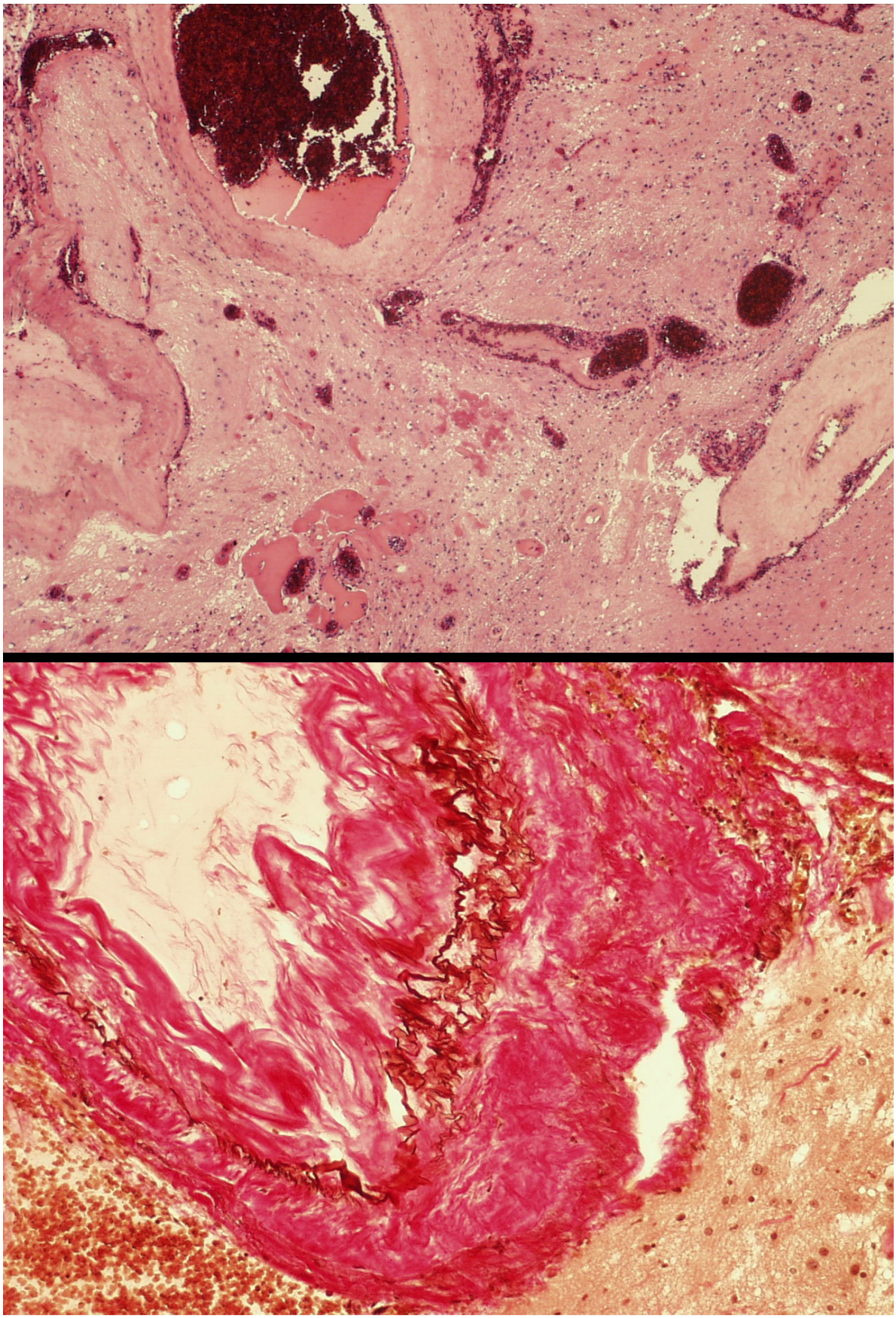


Figure 14.4. *Top:* AVM, Hematoxilin-eosin staining, 40x; *Bottom:* Elastics in vessel walls, Van Gieson + Orcein stainig, 100x

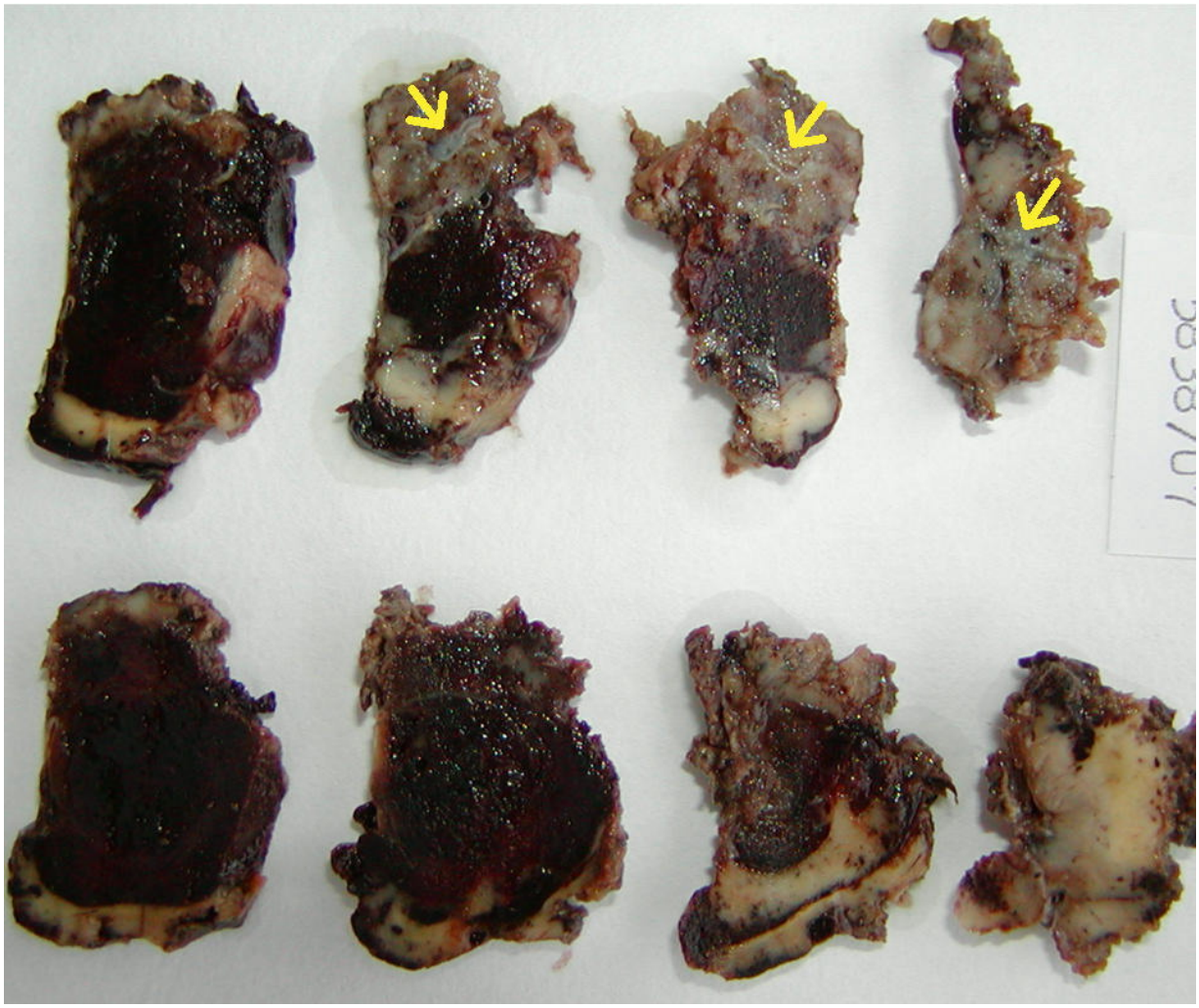


Figure 14.5. Section finding, haematomas of different age: the arrow-marked transected vessels forming the residual nidus.

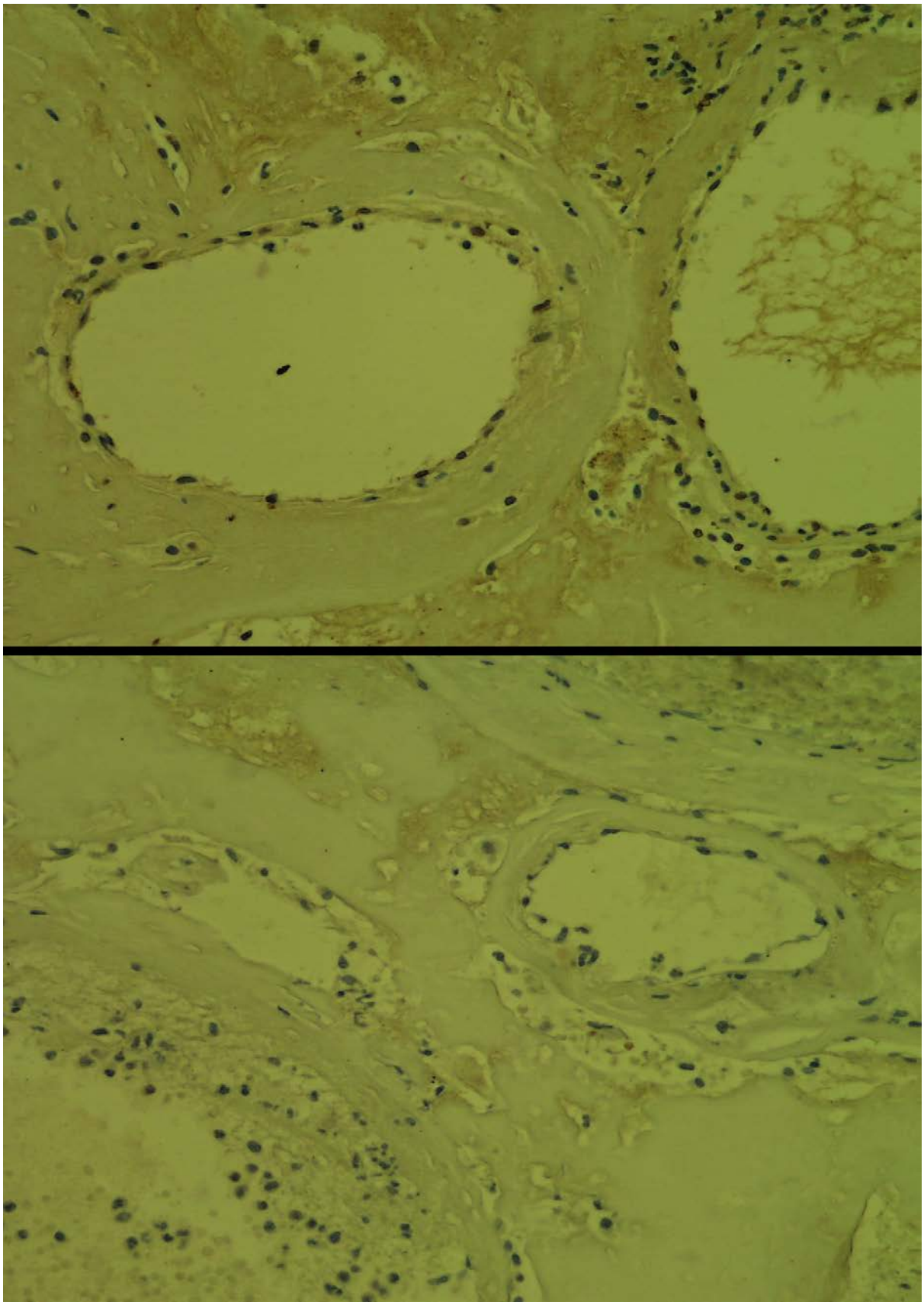


Figure 14.6. *Top:* Immunostaining with VEGF antibodies; *Bottom:* Immunostaining with Ki-67 antibodies.

15. Conclusions summary

1. **Active treatment policy for brain AVMs is justified.**
2. **Active AVM treatment doesn't cause deterioration in neuropsychological performance.**
3. **AVM location regarding hemispheral dominance does not play major role in neuropsychological outcome.**
4. **Surgery is able to achieve near 100% AVM obliteration rate in selected cases.**
5. **Complications related to surgical treatment is low in selected cases.**
6. **Surgical treatment is the treatment of choice for AVM of Spetzler-Martin grades I and II.**
7. **AVM grade III cases should be treated surgically only when lesion is accessible.**
8. **Endovascular intervention should be used mainly for preoperative embolization, as a curative procedure solely for lower-grade AVM in patients with co-morbidities.**
9. **Endovascular intervention should be used in patients with higher-grade AVMs only as a palliative treatment for associated aneurysms and other vascular pathologies.**
10. **Stereotactic radiosurgery is method of choice for poorly accessible, deep-seated grade-III AVMs.**
11. **Observation is the method of choice in AVM of grades IV and V where active therapy carries greater risk than the natural course of the disease and frequently fails.**
12. **In the case of primary radiosurgical treatment the patient should be followed up not only during the period of latency before angiographically confirmed obliteration but also during the following years, though certainly at longer intervals.**

16. References

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17. Authors literature

17.1. Book chapter

ŠEVČÍK, Pavel - MATĚJOVIČ, Martin - ČERNÝ, Vladimír. Intenzivní medicína. Kapitola Multimodální monitoring. Kapitola v monografii. 3 vyd. Praha: Galén, 2014. 1195 s. ISBN 978-80-7492-066-0.

17.2. Articles

Articles in bold are connected with studied topic

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18. Appendix 1

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CLINICAL ARTICLE - VASCULAR

Treatment for brain arteriovenous malformation in the 1998–2011 period and review of the literature

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Abstract
Purpose The results of the treatment of pial AVM provided at our neurosurgical centre are presented. Based on these results and on an overview of literary data on the efficacy and complications of each therapeutic modality, the algorithm of indications, as used at our institution, is presented.
Cohort of patients The series comprises 195 patients, aged 9 to 87 years and treated in the years 1998–2011. The surgical group consists of 76 patients; of these, 49 patients solely received endovascular treatment, 25 were consulted and referred directly to the radiosurgical unit, and the remaining 45 were recommended to abide by the strategy of "watch and wait".
Results In the surgical group, serious complications were 3.9 %, at a 96.1 % therapeutic efficacy. As for AVM treated with purely endovascular methods, serious procedural complications were seen in 4.1 % of patients, with efficacy totalling 32.7 %. One observed patient suffered bleeding, resulting in death. For comparison with literary data for each modality, a survival analysis without haemorrhage following monotherapy for AVM with each particular modality was carried out.
Conclusions Based on our analysis, we have devised the following algorithm of treatment:

1. We regard surgical treatment as the treatment of choice for AVM of Spetzler-Martin (S-M) grades I and II, and only for those grade III cases that are surgically accessible.
2. Endovascular intervention should mainly be used for preoperative embolisation, as a curative procedure for lower-grade AVM in patients with comorbidities, and as palliation only for higher-grade cases.
3. Stereotactic irradiation with Leksell Gamma Knife (LGK) is advisable, mainly for poorly accessible, deep-seated grade-III AV malformations. In the case of lower grades, the final decision is left to the properly informed patient.
4. Observation should be used as the method of choice in AVM of grades IV and V, where active therapy carries greater risk than the natural course of the disease.

Keywords Brain arteriovenous malformation · AVM · Microsurgery · Resection · Endovascular treatment · Radiosurgery · Literature review

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Introduction

Pial arteriovenous malformation (AVM) is a benign cerebrovascular disease, in which direct pathological communications between cerebral arteries and veins (bypassing the capillary system) form the morphological lesion. The malformation is surrounded by a layer of reactive gliosis. Presenting signs include haemorrhage (50 % of all cases), seizures (25 %), headache (25 %), and less often, neurological deficit caused by ischaemia due to the steal phenomenon [10]. The annual likelihood of AVM rupture was estimated at 2–4 % in Ondra's study [61], based on a 24-year follow-up of a cohort of 166 patients with symptomatic AVM; this value is regarded as constant throughout the follow-up period [28]. While AVM-related intraparenchymal haemorrhage is associated with a more favourable prognosis compared to intraparenchymal bleeding from other causes, the intraparenchymal component of bleeding from

an AVM carries with itself a worse recovery [11]. The probability of poor post-haemorrhage recovery (Rankin score greater than or equal to 2, neurological deficit) is reported at about 5–60 % [11, 19, 21, 23].

According to the commonly used Spetzler and Martin scheme, AVMs are classified into five or six groups relative to their size, localisation in eloquent areas, and the presence or absence of deep venous drainage [83] or recently published three-tier classification based on the same parameters [84]. Certain principles of treatment are also based on this AVM grading system. We currently have the choice of surgical resection, endovascular therapy and stereotactic radiosurgical treatment. Indeed, the methods can be combined—with observation being an additional, though not insignificant, modality.

We opted for an analysis of our own data and for a review of literature of published series. Using figures and graphs thus acquired, we were able to confirm the globally acknowledged principles of AVM management. In our view, the published data provide a suitable basis for discussions with our patients as, in principle, they are the ones to choose the procedure and type of treatment.

Patients and methods

Our cohort is made up of 195 patients (113 men, 82 women) treated at the Department of Neurosurgery, Charles University and Central Military Hospital, Prague. The patients received treatment between 1 January 1998 and 31 August 2011. The database was developed prospectively; the patients' data were assessed retrospectively. The patients' age span was between 9 and 87 years, mean age was 42 years. Enrolled were all those patients for whom we acted as the primarily consulted centre. Not included were cases where we merely provided a second opinion on documents from the Czech Republic and from abroad. Consequently, our institution-performed angiography served as the basic parameter for enrolment in the cohort. Malformations were classified according the Spetzler–Martin system. Then, following detailed discussion with each patient and his/her family, we jointly chose the therapeutical modality: surgical resection, endovascular treatment with embolisation, stereotactic radiosurgery, referral to Prague Leksell Gamma Knife (LGK) centre, or observation.

The surgical group consisted of 76 patients, all operated by the senior author; 27 of who had undergone preoperative embolisation of their AVM. Endovascular treatment alone was used for 49 patients, 25 patients were directly referred to the centre of radiosurgery, and the remaining 45 were advised to undergo a policy of "watch and wait". However, there were also patients enrolled whose clinical condition was too serious to permit any therapeutic intervention. The distribution of AVMs according to the Spetzler–Martin grades in each group is given in Fig. 1, showing preponderance of lower-grade AVM in the surgical group compared to the endovascular group (p=0.003, chi-square test). The basic characteristics of the patients in the surgical and endovascular groups are given in Table 1. None of the parameters under study (age distribution in each group, or presentation – haemorrhage or epileptic seizure) revealed any significant intergroup differences at the 5 % level (t-test, chi square test). The surgical and endovascular groups were studied for the rate of serious procedural complications (GOS lesser than or equal to 3 after 30 days). Correlation between AVM grade and outcome measured by GOS was assessed using Spearmann correlation coefficient, omitting patients admitted in poor clinical state, in whom poor outcome was due to severity of initial bleeding The efficacy of each therapeutic modality was assessed after complete obliteration of the AVM. The same parameters for the surgical, endovascular and radiosurgical groups were set on the basis of literary search. All larger series obtained by searching PubMed database with key words "brain avm" up to mid 2011 were included in this literature review.

Results

Fourteen out of the 76 surgical patients were admitted in a serious condition, marked by severe neurological deficit or a GCS of less than 9. Three patients in this group were admitted after bleeding from previously irradiated AVM. Preoperative embolisation was used in 27 cases; a total of 50 interventions were made. As an embolisation agent, Onyx was used in nine cases and NBCA in 18. In one patient, severe deficit due to intracerebral haemorrhage occurred after the procedure. The patient was surgically treated and improved markedly 6 months after his deficit. A serious complication during surgery occurred in three patients; two patients (S-M grade 3 and 4) died. One died after 1 week, the other after 8 months in a vegetative state. The cause of unfavourable results was probably normal perfusion pressure breakthrough (NPPB) phenomena [85] (in both cases we experienced uncontrollable perioperative bleeding, resulting in intracerebral hematoma in the AVM bed and severe surrounding brain edema). A third patient (SM grade 3) suffered severe hemiparesis and aphasia. Surgical morbidity and mortality was 3.9 %. Correlation between AVM grade and outcome was significant (p<0.05) with Spearmann's coefficient r=0.32.

At the 1-year follow-up visit, six patients suffered from serious consequences of the initial haemorrhage. Three AVMs (3.9 %) had not been removed completely. In one patient, postoperative angiography was not done due to severe postoperative condition and ensuing death. The

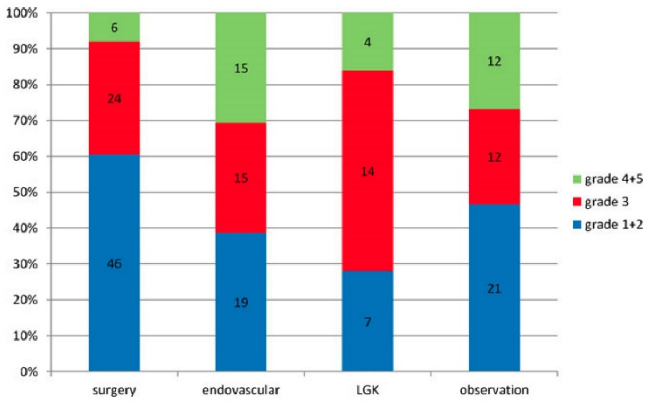

Fig. 1 AVM grade distribution across groups

second unresolved case was a S-M grade-IV AVM in a 16-year old girl. Her malformation was localised in the basal ganglia and dominant frontal lobe. Embolisation attempt failed after the Brietal testing feeders were from A1 and M1 segments. The AVM was planned for only partial resection, and after this patient was twice irradiated with LGK. The AVM disappeared, but patient vision severely and permanently deteriorated after the second radiosurgical procedure. In the third case, S-M grade IV AVM was partially resected and subsequently the residual AVM was successfully embolised. The overall rate of surgical effectiveness was 96.1 %.

In the endovascular group, 49 patients had total of 87 endovascular procedures. One patient was admitted after bleeding from previously irradiated AVM. As an embolisation agent, Onyx was used in 24 cases and NBCA in 25. In addition, coils were used in nine cases, mainly for treatment of flow-related aneurysms. There was one case of unmanageable haemorrhage during embolisation; in another case, embolisation caused severe neurological deficit due to inadvertent occlusion of the major cerebral artery. Both these patients died. Consequently, the endovascular group morbidity and mortality amounted to 4.1 % (patient-related) and 2.3 % (procedure-related). Complete occlusion was achieved in 16 AVMs, which is success rate of 32.7 % per patient and 18.4 % per procedure. Four patients died within the 1-year follow-up: two after procedural complications, and the other two due to primary haemorrhage. At the annual check-up, one patient had a GOS 3 as a result of primary bleeding. Correlation between AVM grade and GOS was not significant. Table 2 sums up the results of surgical and endovascular therapy for AVM—procedural mortality and morbidity and effectiveness of obliteration—attained at our neurosurgical centre.

Thirty-nine patients were shared with the LGK unit; 25 patients were referred there primarily for treatment; 13 patients were referred after previous partial embolisation of AVM; and one after surgery. Prior to radiotherapy, one patient had coiling performed for an incidental aneurysm on the basilar artery. The only procedural complication of LGK (severe visual impairment) has already been mentioned. At the time of publication, 11 of these 39 patients had their AVM obliterated, the rest were still in latency period without angiographical proof of AVM obliteration.

The observation group consisted of 45 patients whose AVM was deemed either intractable with any of the available therapeutic techniques, or those who declined active treatment or to whom active treatment was recommended (advanced age, incidental lesion, serious comorbidity). This group included five patients whose initial haemorrhage was too serious to permit the consideration of any beneficial therapy, and four of these patients subsequently died. Six

Table 1 Basic demographic characteristics and AVM presentation of patients in surgical and endovascular groups. No significant difference was found

	N	Age ± SD	ICH	IVH	SAH	Seizures
Surgery	76	38.3±15.6	31	14	25	12
Endovascular	49	40.9±16.4	23	7	12	13
p value		0.378	0.498	0.546	0.315	0.143

ICH intracerebral haemorrhage, IVH intraventricular haemorrhage, SAH subarachnoid haemorrhage

Table 2 Achieved efficacy and morbidity and mortality of surgical and endovascular treatment of AVM. Values in endovascular treatment correspond to per patient/per session efficacy and M/M

Modality	Efficacy [%]	M/M [%]
Surgery overall	96.1	3.9
Surgery SM 1-2	100	0
Surgery SM 3	95.8	8.3
Surgery SM 4-5	83.3	16.7
Endovascular	32.7 / 18.4	4.1 / 2.3

M/M morbidity and mortality

others underwent active treatment for another neurosurgical pathology; in all these cases, the AVM was an incidental finding. Three patients were examined for ACI stenosis; two of them had carotid endarterectomy performed, and the third patient underwent carotid stenting. One patient was admitted for acute subarachnoid haemorrhage following rupture of one of two aneurysms of the circle of Willis, coiling was performed on both. One patient suffered subarachnoid haemorrhage (SAH) from posterior inferior cerebellar artery (PICA) aneurysm, which was subsequently coiled. One patient had carotido-cavernous fistula successfully coiled.

In one case, AVM thrombosed spontaneously after minor bleeding. We encountered only one bleeding in the group of patients under observation: a 56-year-old patient with parieto-occipital grade IV AVM suffered fatal devastating heamorrhage after 10 years of observation.

Tables 3, 4 and 5 show the studies that helped to set the values for comparisons with our own results [1, 3, 5–8, 12–18, 20, 22, 24–27, 29–59, 62–67, 69, 70, 72, 73, 75, 77–83, 86–100].

The method of weighted mean was used for this purpose, the number of patients in each given study being the weight. The probability of procedural complications in radiosurgery is equal to the likelihood of bleeding during the three-year period of latency and severe adverse events of irradiation.

Due to the fact that AVM is disease of young and mid age, we have to make inferences at least 30 years ahead. On the acceptance of 3 % annual bleeding rate, a comparison of a thirty-year outlook of bleeding in patients treated with the particular techniques is given in Fig. 2. Furthermore, on the acceptance of 30 % probability of poor recovery after AVM-related bleeding, thirty-year prospective period is plotted in Fig. 3, as a determinant of the likelihood of serious mortality and morbidity. The values of mortality and morbidity, just as those of the efficacy of treatment for the surgical and endovascular groups, were used for constructing the graphs based on our centre's data. However, the values given for radiosurgical treatment and for observation are derived from

Table 3 Overview of published surgical series

Author	Year	N	Age (mean)	M/M [%]	Efficacy [%]	S-M grade
Abad	1983	70		11.0	81.4	
Jomin	1985	128		21.0	92.9	
Spetzler	1986	100		4.0	100.0	I–V
Andrews	1987	28	34	10.7	67.9	
Heros	1990	153		8.4	100.0	I–V
Deruty	1993	64		18.8	93.7	I–V
Sisti	1993	67		1.5	94.0	I–III
Hamilton	1994	120	36	8.3	100.0	I–V
O'Laorie	1995	56	36	5.3	92.9	I–V
Tew	1995	39	30	15.4	97.4	III–V
Malik	1996	156	33	14.7	95.8	
Schaller	1998	150	35	13.3		I–V
Pikus	1998	72		8.3	98.6	I–III
Hassler	1998	191		11.0		I–V
Pik	2000	110	38	2.7	98.8	I–III
Hartmann	2000	124	33	6.0		I, II
Solomon	2000	86		1.2	90.7	
Stapf	2002	240	34	1.7	93.8	
Morgan	2004	220		1.4	98.6	I, II
Lawton	2005	224	38	7.1	98.0	I–V
Spears	2006	175	40	13.5		I–IV
Our series		74	40	1.4	97.3	I–IV
Total		2573	36	7.3	95.9	I–V

M/M morbidity and mortality

Table 4 Overview of published endovascular series

Author	Year	N	Age (mean)	M/M [%]	Efficacy [%]	S-M grade
Merland	1986	67		10.0	9.0	
Vinuela	1986	30			5.5	III–V
Huang	1995	72		4.0	40.3	
Lundqvist	1996	150	36	13.3	13.3	
Debrun	1997	54		5.6	5.6	
Sorimachi	1999	36	31	16.7	13.9	I–V
Valavanis	1998	387		2.6	40.0	
Song	2000	70	42			
Liu	2000	103		8.7	10.7	I–V
Hartmann	2002	233	36	3.0	34.0	I–V
Meisel	2002	450	30	8.0	16.0	I–V
Taylor	2004	201	36	11.0	0.0	I–V
Kim	2006	139	38	5.1	7.9	I–V
Ledezma	2006	168	41	9.2	2.5	I V
Haw	2006	306	34	7.5	9.5	I–V
van Rooij	2007	44	42	6.8	15.9	I–V
Mounayer	2007	94	32	8.5	49.0	I–V
Weber	2007	93	38	12.0	20.0	I–V
Jayaraman	2008	192		6.3	9.9	I V
Katsaridis	2008	101		11.0	27.7	
Panagiotopoulos	2009	82	44	6.2	24.4	I–V
Pierot	2009	50	35	10.0	8.3	I–V
Gao	2009	88	29	3.5	26.1	I–V
Maimon	2010	43	31	2.3	37.0	I V
Lv	2010	147	28	4.8	19.7	I–V
Xu	2011	86	30	4.7	18.6	I–V
Saatci	2011	350	34	7.1	51.1	
Our series		49	41	4.1	32.7	I–V
Total		3836	34	7.1	22.1	I V

M/M morbidity and mortality

literary sources, since our LGK group is quite small and atypical.

As for radiosurgery, an 8 % probability of bleeding was used for the first three postoperative years—the period of latency. All patients treated with the given method where some AVM remnants are detectable are exposed to the yearly probability of bleeding.

Discussion

Results of surgical treatment for pial AVM at our neurosurgical department, as well as results in the rest of the studies, refer to a meticulous selection of patients. Figure 1 makes it quite obvious that most of the higher-grade malformations were dealt with by those methods other than surgical. The preponderance of lower-grade AVM in the surgical group compared to endovascular group (p=0.003, chi-square test) is attributable to the surgical centre's preferences. Patients a priori refusing surgical intervention often look for some other therapeutic option themselves. In contrast, patients with operable AVM who seek advice at the surgical centre are mostly well disposed to resection from the outset. Our results are comparable with the published ones [57, 71, 77]. Most of the patients with S-M Grade I and II AVMs are now indicated for surgical treatment, as all other modalities fall far short of offering such an efficacy with such a low rate of complications. Thus, the only decisive factor is the surgeon's ability to weigh his/her own skills, as not even an operation for a small AVM is an easy task.

The efficacy and rate of complications of independent endovascular embolisation attained at our centre is fully comparable with the average quoted in the rest of the published results. However, assessed over a 30-year span of time, the position of embolisation as an independent method is debatable. An analysis of Fig. 2 will show that only after 10 years post-embolisation is the patient's prognosis more favourable than the natural course of the disease, with

Table 5 Overview of published radiosurgical series

Author	Year	N	Age (mean)	M/M [%]	Efficacy [%]	S-M grade
Colombo	1989	97		7.1	52.0	
Lunsford	1991	227		1.7	80.4	I–IV
Coffey	1995	121		8.0	35.5	
Kobayashi	1996	324		2.7	79.3	
Aoki	1996	236		4.4	86.6	I–III
Karlsson	1997	945	31		56.0	I–V
Yamamoto	1998	53		11.3	60.4	
Miyawaki	1999	73	30	13.7	38.4	I–V
Pan	2000	240		8.0	47.9	I–V
Kurita	2000	30		5.0	52.5	
Massager	2000	87	37	8.4	73.0	II–III
Schlienger	2000	169	33	7.7	64.0	I–IV
Zhou	2000	132		3.8	73.7	
Hadjipanayis	2001	33	32	9.1	70.0	
Smyth	2002	40		10.3	40.0	II–V
Pollock	2003	144		7.7	76.0	I–V
Friedman	2003	269		11.0	53.0	I–IV
Zipfel	2004	268		10.0	57.8	I–V
Shin	2004	408	31	6.8	88.1	I V
Veznedaroglu	2004	30	41	10.0	37.5	
Izawa	2005	237		9.3	54.9	I–V
Maruyama	2005	500	32	7.2	91.0	I–V
Zabel	2005	110	40	11.8	52.7	I–V
Andrade-Soussa	2005	45		12.0	61.9	
Andrade-Soussa	2006	38	40	8.0	60.5	II–III
Cohen-Gadol	2006	38	15	0.0	68.4	I–V
Reyns	2007	100	12	5.0	70.0	I–V
Kiran	2007	103	14	6.7	87.0	II–IV
Karlsson	2007	133		14.0	62.0	I V
Liščák	2007	330		3.4	92.0	
Javalkar	2009	37		2.7	46.5	
Kim	2010	44	27	4.6	34.1	I–V
Yen	2010	186	13	1.1	58.6	II–V
Sun	2011	127	37	11.0	64.0	
Blamek	2011	62	40	0.0	35.5	
Total		6016	33	6.8	67.4	I–V

M/M morbidity and mortality

regard to potential risk of bleeding due to a ruptured AVM. Analysing Fig. 3, we can see the point of intersection shifting as far as 25 years from the treatment. On the whole then, owing to its low efficacy and relatively higher rate of procedural complications in comparison with the other modalities, the benefit of independent curative embolisation is negligible, as it can never reach a significant difference assessed against the natural course of the disease. The role of endovascular treatment in the management of AVMs is yet to be established. In our view, endovascular intervention is an essential part of AVM obliteration, though solely for selective embolisation of deep branches. As for the superficial branches, embolisation is a counterproductive approach, hampering subsequent AVM resection. The superficial branches are easy to deal with after the dura is opened, there is no need for obstructive surgical glue, and in addition, anatomical orientation is better. Embolisation of those branches will distend the deep feeders; their treatment is already the hardest part of AVM surgery even without embolisation. As we have seen repeatedly, even an embolised vessel can bleed readily after being cut as a whole. Arresting such haemorrhage is no easy task, as the glue cannot be coagulated easily, nor the vessel clipped. Recently, some goups report much higher success rates [58, 70],

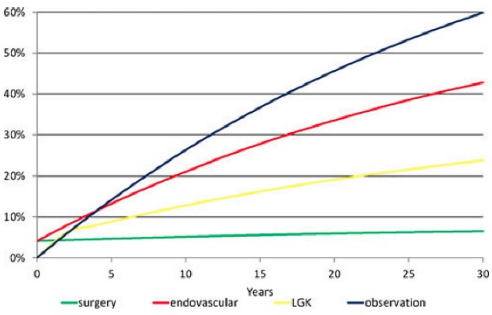

Fig. 2 Probability of bleeding in 30 year perspective

but it is questionable whether these results are repeatable on a much broader scale. Another important finding of this study is the absence of correlation between AVM grade and clinical outcome, meaning risk of endovascular procedure is similar for all AVM grades. This result strongly favours surgery with very low morbidity as a method of choice for lower grade AVMs. New procedures, mainly the introduction of Onyx into endovascular practice, did not change efficacy of endovascular methods significantly, and only few groups of authors presents markedly better results [58, 64].

In contrast, the position of radiosurgery remains unshakeable in the treatment of AVM; objections can only be raised against its unidirectional and liberal limits of indications. What comes as a surprise in our milieu are the 20 % better results than those commonly reported [45] (Table 5). Surgical treament of grade I and II AVM is associated with 0 % probability of permanent deficit [19], at a well nigh 100 % rate of efficacy. In view of this, a solid medical substantiation is called for if the patient is to be exposed to the hazards of AVM-related haemorrhage during the period of latency at a markedly lower probability of obliteration—84 % [68].

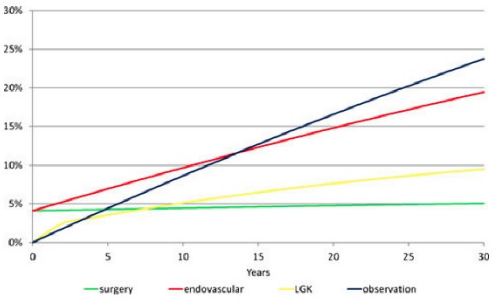

Fig. 3 Probability of poor outcome after bleeding in 30 year perspective

Conversely, for deep-seated, poorly accessible small-sized malformations, radiosurgery is the method of choice. In such malformations suitable for radiotherapy, the rate of obliteration is reported at up to 70 % [42]. In the case of larger-size AVM, a similarly very high efficacy is reported after single or multiple irradiations. One study [35] mentions an efficacy of 62 % for a group of AVMs larger than 9 cm^3; Sirin et al. [76] attained an efficacy of 50 % for AVMs of more than 15 cm^3 in size. On the other hand, there have been cases of bleeding from an AVM, even after radiosurgical treatment and angiographic evidence of its obliteration [9, 74]. In our view, the greatest problem of radiosurgery lies in the variously high percentage of patients (reported at 10 up to 50 %) in whom the AVM is discernible even after repeated irradiation. Admittedly, ours is a limited body of experience (three patients) of surgery on AVM after LGK treatment. Nevertheless, it is a very optimistic experience; the operations were not more difficult. This prompts ideas of converting higher-grade AVM radiosurgically into AVMs of grades I and II, to make them suitable for neurosurgery. In irradiated patients, the definitive therapy is in fact postponed by more than 6 years. As follows from the above facts, the therapeutical modalities are competitive with regard to low-grade malformations. This applies mainly to surgical resection relative to stereotactic irradiation. True inter-modality cooperation has been reached in grade III AVM, where preoperative or pre-radiosurgical embolisation can facilitate obliteration and reduce the risks of subsequent therapy [60]. What is still missing, however, is clear evidence of this logical conclusion, as some authors question the effect of pre-radiosurgical embolisation [4]. It should be noted that grade III AVMs are a very heterogeneous group. Therefore, any decision must take into account the individual characteristics of each AVM.

Grade IV and V AVMs are complex and large malformations; straightforward surgery is too risky and radiosurgery is inefficacious. This is why we usually opt for the watch and wait strategy. In some cases, endovascular active approach can be used, depending on angioarchtecture, risk factors such as intranidal aneurysm, etc.. As a rule, complete occlusion can hardly be achieved, though it is possible to treat, e.g. an intranidal aneurysm, or to reduce the malformation blood flow. Today, most neurosurgical teams regard AVM of grades IV and V as lesions suitable for observation. Some of those lesions, however, could be managed by cooperation of all three treatment modalities. Such an option and a well thought through management plan is to be considered, especially in young patients with high rupture-risk AVMs. In patients treated by multimodal approach, each new step should be established anew, according to the results of the previous one. The team must not dogmatically follow the management plan devised at the beginning of treatment.

During the construction of the two graphs, the constant probability of AVM rupture was estimated at 3 % per

annum, leaving aside the opinion that during a few post-rupture years the likelihood of AVM rerupture is prominently higher; 6 to 18 % in the first year and gradually approaching the initial value [2, 21].

The previous paragraphs discussed the decisive **AVM-related factors**. The most important point here is the AVM classification according to Spetzler and Martin. The decision-making process invariably involves the need to estimate the risks and efficacy of the therapy against the hazards of the natural course. Apart from assessing the AVM as such, it is necessary to weigh up a number of other variables unrelated to the AVM. These are: 1) **patient-related factors**—the presenting symptoms of the AVM. A patient whose AVM triggered only a single epileptic paroxysm needs an approach that is different from another patient with recurrent AVM haemorrhage. The patient's age is important; some statistics show that any active therapy in patients over 45 years of age can no longer counteract the risks of the natural course. Other patient-related factors include concomitant diseases and ASA grade. A patient with a congenital heart defect where anaesthesia would already be dangerous should be recommended for radiosurgical treatment. 2) **Institution-related factors.** Is the clinical centre sufficiently experienced and equipped? Are the results comparable with those reported in literature? Have they been published? 3)**Factors pertaining to the attending physician/surgeon.** These are the most difficult to evaluate. As a rule, self-assessment is the least objective. However, honesty is the most important quality of any physician. Ultimately it is the patient, correctly and fairly informed, who should have the main say in deciding on the therapy.

Conclusion

Backed by our experience of AVM treatment and by our assessment of the likelihood of post-treatment haemorrhage, we have devised the following algorithm of treatment:

1. Surgery is to be seen as the method of choice for AVM of S-M grades I and II; as for grade III cases—only for superficially localised lesions. Higher-grade AVMs are only suitable for surgery in exceptional cases, palliatively or in cases of recurrent haemorrhage.
2. Endovascular intervention should mainly be used for preoperative embolisation (that in itself is questionable), or as a curative procedure for lower-grade AVM in polymorbid patients, and again only palliatively for higher grades—the steal phenomenon, intranidal aneurysm.
3. Stereotactic radiotherapy with LGK is advisable mainly for poorly accessible, deep-seated grade-III AVM. In the case of lower grades, the final decision is left to the thoroughly informed patient.
4. Observation is to be taken as the method of choice for AVM of grades IV and V, where active therapy represents a greater risk that the natural course of the disease.

Conflicts of interest None.

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19. Appendix 2

Haemorrhage from a Radiosurgically Treated Arteriovenous Malformation after its Angiographically Proven Obliteration: a Case Report

Blutung aus einer radiochirurgisch therapierten arteriovenösen Malformation trotz angiographisch bewiesener Obliteration: ein Fallbericht

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Key words
- pial AVM
- stereotactic radiosurgery
- nidus obliteration
- rupture

Abstract

Small lower-grade Spetzler-Martin AVMs are mainly treated by microsurgical resection or stereotactic radiosurgery. The choice of treatment largely depends on the referring centre's preference and the patient's decision. We present here a patient with an AVM repeatedly treated at our Leksell Gamma Knife unit with radiographically confirmed obliteration of the AVM which subsequently began bleeding from the residual nidus. This case demonstrates the possibility of late complications in radiosurgically treated AVMs even after their demonstrable obliteration. Meticulous histological examination was performed, proving patency of the AVM nidus. The risk of haemorrhagic complications of radiosurgically removed AVMs despite angiographic proof of their obliteration is, in our view, a cogent argument for preferring surgical resection if the AVM is accessible and for prolonged follow-up after radiosurgical treatment of an AVM.

Zusammenfassung

Kleine arteriovenöse Malformationen (AVM) niedrigen Spetzler-Martin-Grades werden hauptsächlich mittels mikrochirurgischer Resektion oder Radiochirurgie behandelt. Diese beiden Methoden stehen in gewisser Konkurrenz zueinander. Die Entscheidung über die Therapiemodalität hängt in starkem Maße von der Präferenz der Klinik und des mittlerweile meist gut informierten Patienten ab. Wir präsentieren einen Fall eines Patienten, der wiederholt radiochirurgisch mit dem Gamma Knife behandelt wurde. Trotz angiographisch dokumentiertem Verschluss der AVM kam es zu einer Blutung. Histologische Untersuchungen nach neurochirurgischer Entfernung belegten einen noch patenten AVM-Nidus. Das nicht eliminierte Blutungsrisiko radiochirurgisch behandelter, angiographisch anscheinend komplett obliterierter AVMs ist unserer Meinung nach ein Argument für die primäre mikrochirurgische Resektion gut zugänglicher AVMs. Eine prolongierte Nachbeobachtungszeit ist auch bei dokumentierter Obliteration radiochirurgisch therapierten AVMs anzuraten.

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Introduction

Currently, the treatment for pial arteriovenous malformations (AVMs) consists of three options: surgical resection, stereotactic gamma-knife radiosurgery and the use of LINAC, and endovascular embolisation. The advantages and disadvantages associated with each of these modalities are well known (Ogilvy, Stieg et al., 2001). Surgical intervention offers a high degree of effectiveness with a low rate of complications but is not suitable for all lesion types. Because of its low effectiveness, endovascular embolisation is used more as a complementary modality. In our department, independent embolisation is rarely used, and then usually only in combination therapy. Although radiosurgery is a viable option, this requires regular monitoring of the patient together with angiographic proof of AVM removal. Moreover, to ensure a relatively uneventful course in high-grade AVMs (Spetzler-Martin grades IV-V) the indications for active therapy should be carefully weighed (Hartmann, Mast et al., 2007; Jayaraman, Marcellus et al., 2007).

We present the case of a patient with an AVM who underwent repeated treatment at our Leksell Gamma Knife centre but suffered rebleeding episodes despite angiographically proven obliteration.

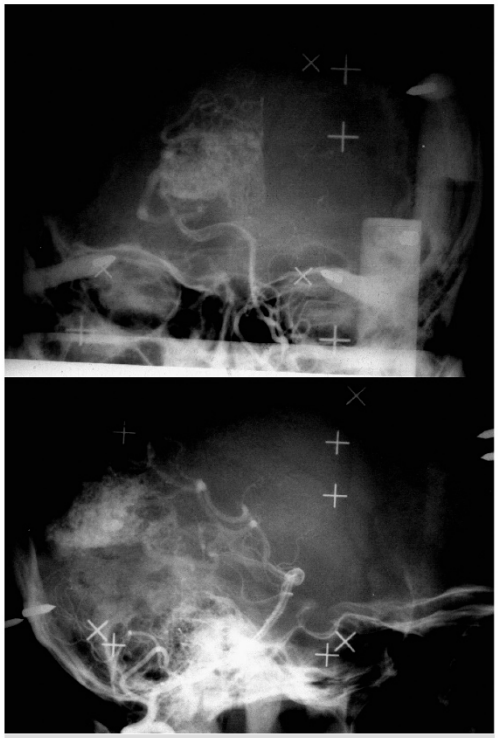

Fig. 1 Angiographic scan prior to first irradiation showing a Spetzler-Martin grade III AVM.

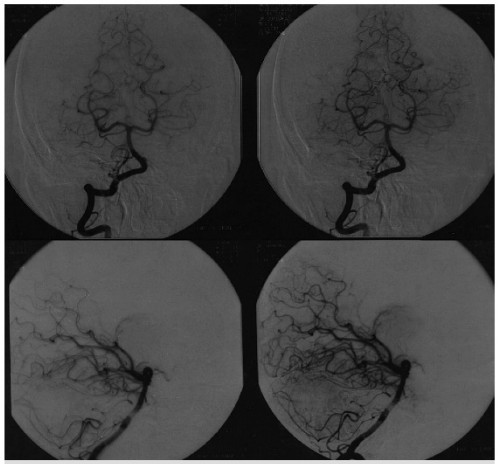

Fig. 2 Angiographic scan showing obliteration of irradiated AVM.

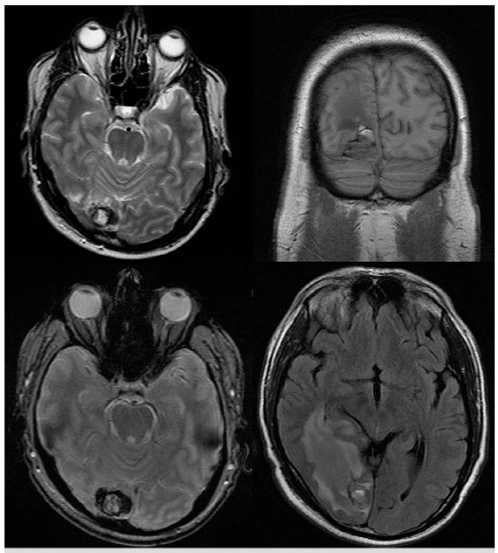

Fig. 3 Preoperative MR scans. *Top left:* T2-weighted axial section. *Bottom left:* Axial section in gradient echo sequence. *Top right:* T1-weighted coronary section. *Bottom right:* Axial section in FLAIR sequence. A major oedema is discernible throughout the occipital lobe.

Case report

Our 42-year-old patient had a history of hypertension. At the age of 35 years, he underwent examination for intensive migraine-type cephalea, phosphenes in the left half of his field of vision and transient left temporal visual field deficits. Magnetic resonance imaging (MRI) raised the suspicion of a pial AVM in the right occipital region. After verification in August 1995 (Spetzler-Martin grade III), the AVM was irradiated using a Leksell Gamma Knife; the volume at the first session was 7.9 cm^3 (**Fig. 1**). The patient's clinical condition improved after radiation with subsidence of the symptoms, but because the AVM was not completely obliterated during the latency period, a second session was arranged in August 1998 to complete irradiation of the residual nidus. At that time, the volume had been reduced by 80% to 1.5 cm^3. Both times, the minimal marginal radiation dose applied was 16 Gy at the 50% isodose line. MRI, which was repeatedly performed during follow-up, showed a gradual abatement of a reactive oedema. Following angiography in August 2002, complete elimination of the AVM was diagnosed, after which the patient's dispensary care was discontinued (**Fig. 2**). In May 2007, however, his clinical condition changed abruptly, with the development of diplopia, meningism and spatial disorientation. Ophthalmological examination revealed congestion in the papillae of the optic nerves +3D and +4D and a sector deficit in the field of vision on the left side. The patient was acutely admitted to a neurological department for the management of intracranial hypertension. In June and July 2007, MRI scans revealed cystic foci, haematomas of varying ages and suspected bleeding from the residual AVM at the site of the original AVM (**Fig. 3**). A diagnosis of multiple cavernomas was considered. Diagnostic angiography revealed no AVM. Despite this finding, surgical revision was decided on and performed in October 2007. The perioperative finding indicated a pial AVM, which was completely resected. Because of the histologically verified presence of muscular elastic thick-walled vessels

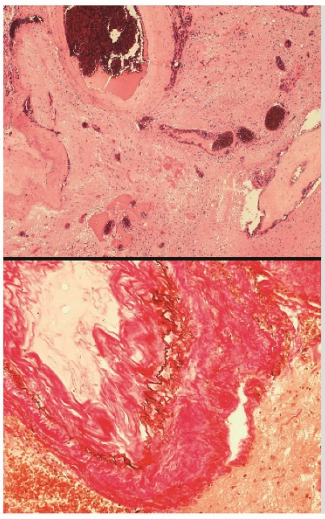

Fig. 4 *Top:* AVM, haematoxylin-eosin staining, 40x; *Bottom:* Elastic vessel walls, van Gieson + Orcein staining, 100x.

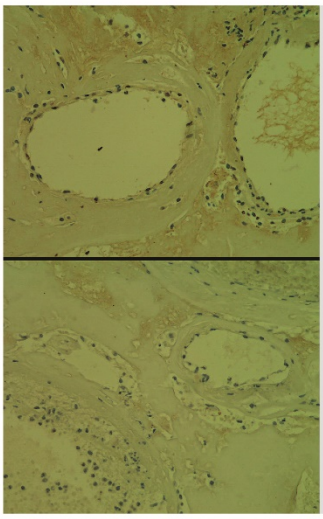

Fig. 6 *Top:* Immunostaining with VEGF antibodies; *Bottom:* Immunostaining with Ki-67 antibodies.

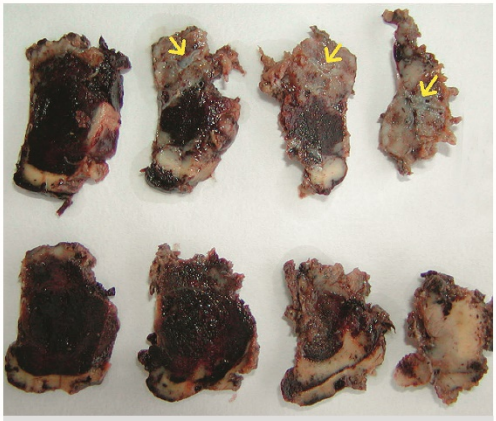

Fig. 5 Section finding, haematomas of different ages. Arrows show the transected vessels forming the residual nidus.

(● **Fig. 4**), an AVM was considered the most likely variant in agreement with the perioperative findings (● **Fig. 5**). Immunostaining with VEGF and Ki-67 antibodies showed only minimal endothelial proliferation activity (● **Fig. 6**). At discharge, the patient was free from extremity lateralisation, with only a minor deficit persisting on the left side of his visual field. Follow-up MRI demonstrated perfect resection of the focus and a discernible abatement of the preoperative oedema.

Discussion

Tiny, deep-seated, surgically inoperable AVMs are a typical indication for radiosurgical intervention. When considering superficially localised AVMs with lower Spetzler-Martin grades, the choice of the therapeutic modality depends on the preference and line of specialisation of the indicating surgical centre (Richling, Killer et al., 2006): outstanding results have been achieved with both methods (Karlsson, Lindquist et al., 1997; Schaller and Schramm 1997; Beneš and Mohapl 1998; Liščák, Vladyka et al., 2007). Active therapy is almost invariably appropriate (Pollock, Lunsford et al., 1994).

Radiosurgical treatment for malformations involves a number risks. Complications of surgery include disorders of the cranial nerve functions, onset or worsening of attacks or late formation of cysts. The most serious potential event is bleeding from an AVM, which has an annual incidence of 3–4% (Ogilvy, Stieg et al., 2001; Nataf, Ghossoub et al., 2004) over an approximately three-year period of latency. Furthermore, as our case demonstrates, there is still the risk of rupture and haemorrhage from the residual nidus, even after verified complete obliteration of the AVM.

It has been demonstrated that AVM and cavernous angiomas are dynamic lesions. The immunoreactivity of both was studied extensively and many reports on various proliferation markers have been published (Sonstein, Kader et al., 1996; Kilic, Pamir et al., 2000; Sure, Butz et al., 2001; Sure, Freman et al., 2005).

In recurrent AVMs occurring in the paediatric population, a significantly higher VEGF expression was found than in paediatric and adult groups with non-recurrent AVMs (Sonstein, Kader et al., 1996). In series of 25 AVMs published by Sure et al., VEGF expression was found in 60% of cases and Ki-67 antibodies in 12% (Sure, Butz et al., 2001).

The presence of an AVM was proven by histological examination, but immunostaining with VEGF and Ki-67 antibodies showed an absence of endothelial proliferation. This is in accordance with a recent experimental study by Kilic et al., (Kilic, Konya et al., 2007) on the dose-dependent inhibition of neoangiogenesis in rat corneas using gamma-knife irradiation. The absence of proliferation markers in our specimen supports the idea of rebleeding from the residual nidus of the irradiated AVM.

The de novo development of a cavernous malformation, which was our second differential diagnostic option, has repeatedly been reported as a complication of radiation therapy for other intracranial lesions (Larson, Ball et al., 1998; Nimjee, Powers et al., 2006; Iwai, Yamanaka et al., 2007). Several reports have

also indicated a relation between a pre-existent venous malformation and the de novo development of a cavernoma-like lesion (Cakirer 2003; Campeau and Lane 2005). Maeder et al., (Maeder, Gudinchet et al., 1998) reported the case of a 14-year-old boy treated with irradiation for a posterior fossa medulloblastoma. Three years after therapy he suffered a haemorrhage adjacent to a previously diagnosed venous malformation in the left hemisphere. The process of cavernoma development in this case was typically considered to be due to radiation-induced changes in the venular endothelium leading to capillary teleangiectasia with continual petechial haemorrhage in the immediate neighbourhood. This mechanism is a plausible explanation for recurrent sub-clinical haemorrhage in the case of an irradiated AVM. Moreover, histological examination showed no signs of neovascularisation and endothelial proliferation activity. Thus, the de novo development of a cavernous angioma similar to an AVM is quite improbable.

Cases of bleeding from an obliterated AVM have been described previously (Yamamoto, Jimbo et al., 1996; Lindqvist, Karlsson et al., 2000; Shin, Kawahara et al., 2005; Matsumoto, Takeda et al., 2006). Shin et al., estimated the probability of rupture of a residual AVM with angiographically verified obliteration as 0.3% annually. Consequently, although the risk of rupture is ten to fifteen times lower than with the natural course or in the latency period, it is necessary to follow-up patients even after angiographically verified obliteration of the AVM. Magnetic resonance imaging with contrast medium appears to be an adequate method as it not only demonstrates late developing cysts (Yamamoto, Jimbo et al., 1996) but also exploits the statistically proven interdependence between haemorrhage from the "obliterated" AVM and from a persistent enhancing area revealed by contrast medium MR imaging (Shin, Kawahara et al., 2005).

Conclusion

In cases with AVM undergoing primary radiosurgical treatment, the patient should be followed up not merely during the period of latency before angiographically confirmed obliteration but also subsequently at longer intervals.

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Conflict of Interest: None

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