

Univerzita Karlova v Praze

1. lékařská fakulta

Autoreferát disertační práce



Treatment for Brain Arteriovenous Malformations

Léčba arteriovenózních malformací mozku

Ondřej Bradáč

2015

Doktorské studijní programy v biomedicině

Univerzita Karlova v Praze a Akademie věd České republiky

Obor: Neurovědy

Předseda oborové rady: Prof. MUDr. Karel Šonka, DrSc.

Školící pracoviště: NCH klinika 1. LF UK a ÚVN-VFN

Školitel: Prof. MUDr. Vladimír Beneš, DrSc.

Disertační práce bude nejméně pět pracovních dnů před konáním obhajoby zveřejněna k nahlížení veřejnosti v tištěné podobě na Oddělení pro vědeckou činnost a zahraniční styky Děkanátu 1. lékařské fakulty.

Table of content

| | |
|-----------------------------|----|
| Abstrakt - Český | 4 |
| Abstract - English | 5 |
| Introduction..... | 6 |
| Aims | 6 |
| Materials and methods | 6 |
| Results..... | 8 |
| Discussion..... | 11 |
| Conclusions..... | 14 |
| References..... | 15 |
| Authors publications | 18 |

Abstrakt - Český

Úvod: V této práci jsou prezentovány neurologické výsledky chirurgické a endovaskulární léčby mozkových arteriovenózních 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 podskupina sestává z 85 pacientů, endovaskulárně bylo léčeno 55 pacientů. Dalších 34 pacientů bylo odesláno přímo k radiochirurgické léčbě. Zbýlých 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 míra závažných komplikací 3.5% s úspěšností totální okluze 96.5%. V čistě endovaskulárně léčené podskupině byla míra závažných komplikací 5.5% s úspěšností totální okluze 36.4%. Jeden z observovaných pacientů zemřel následkem intracerebrálního krvácení. Ke srovnání s literárními daty byla provedena literární rešerše. Na jejím základě byla pro jednotlivé léčebné modalitty 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 pacientů dělených dle léčebné modalitty 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 používány pouze v případě předoperační embolizace, i tehdy jen u přísně vybraných patologií. Jako léčebná modalita by měla být užívána pouze u pacientů s AVM nízkého SM stupně, pokud jsou chirurgicky riziková. 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 obsírně 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.

Abstract - English

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 in 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

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. From surgical point of view Spetzler-Martin grading system appropriately inform our patients about the possible surgical risks ². This doesn't hold true for the possible neuropsychological sequelae, which has only been studied by a few authors to date ³⁻⁶.

Aims

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 endovascular results achieved at our institution and based on these comparisons treatment recommendation for AVM is articulated. Furthermore, 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. Finally, the efficacy of different treatment methods in the long-term perspective is studied.

Materials 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, 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 showed 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 were comparable. 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 Spearman correlation coefficient with 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 December 2013 were included in this literature review.

Altogether 66 patients were enrolled in the neuropsychological 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.

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.

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 ⁷.
- Frontal / Execution functions were tested by FAS test in Czech version and Trail Making Test, part B ⁸.
- Attention and processing speed was measured by Trail Making Test, part A ⁸.
- Nonverbal intelligence was measured by Test of intellect potential - TIP ⁹.
- Visuospatial functions by Cubes analysis, subtest of VOSP battery ¹⁰.
- Verbal memory was measured by Auditory-verbal learning test - AVL T ⁸.

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 occurred after the procedure. The patient was surgically treated after 6 months after his deficit improved markedly. A serious complication during surgery occurred 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 ¹¹. 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 Spearman's coefficient $r = 0.32$.

At the one year follow 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. 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 inadvertent 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 follow 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 significant. Forty-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. 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. 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 haemorrhage after 10 years of observation.

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 1. Furthermore on the acceptance of 30% probability of poor recovery after AVM –related bleeding, thirty-year prospective period is plotted in Graph 2 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.

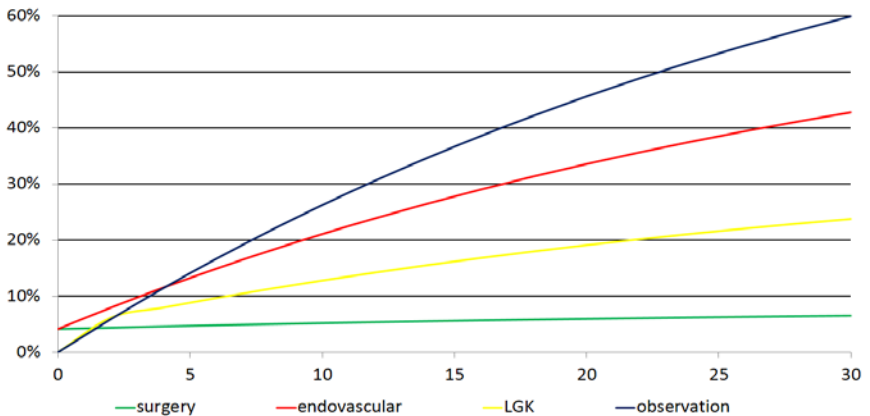
However the values given for radiosurgical treatment and for observation are derived from literary sources since our LGK group is quite small and atypical. Literature review showed 23 surgical studies, analysing altogether 2721 patients with a mean age of 36 years. Average efficacy within published microsurgical series was 95.9%, whereas mean complication rate of 7.2%. Mean efficacy within 29 endovascular series comprising of 4021 patients with mean age of 35 years was 22.4%, whereas mean complication rate of 7.0%. Literature review of radiosurgical series was based on 41 studies comprising of 8683 patients with mean age of 31 years showing mean complication rate of 5.3%, but mean occlusion rate of 66.1%.

In neuropsychological study, no significant differences between the groups were found when the presentation was hemorrhage; 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.

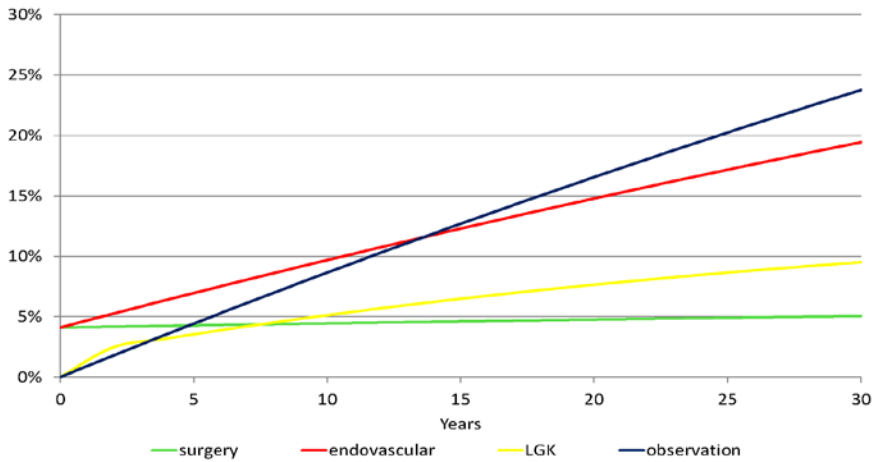
When we analysed patients according to the presence or absence of complete obliteration after treatment and compared these to the control group, we found no significant differences.

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.

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.



Graph 1: Probability of bleeding in 30 years perspective.



Graph 2: Probability of poor outcome after bleeding in 30 years perspective.

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. 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. Our results are comparable with the published ones¹²⁻¹⁴. 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.

The efficacy and rate of complications of independent endovascular embolization 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 Graphs 1 and 2 will show that only after years post-embolisation is the patient's prognosis slightly more favourable than the natural course of the disease with regard to potential risk of bleeding due to a ruptured AVM. On the whole then, the benefit of independent curative embolisation is negligible. It is yet to be established the role of endovascular treatment in the management of AVMs. Recently, some groups report much higher success rate^{15, 16} 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^{15, 17}.

The position of radiosurgery remains unshakeable in the treatment of AVM. On the other hand, surgical treatment of grade I and II AVM is associated with 0% probability of permanent deficit¹⁸ 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%¹⁹. 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%²⁰. In the case of larger-size AVM a similarly very high efficacy is reported after single or multiple irradiation. One study²¹ mentions an efficacy of 62% for a group of AVMs larger than 9 cm³; Sirin et al.²² attained an efficacy of 50% for AVMs of more than 15cm³ in size. Conversely, there have been cases of bleeding from an AVM even after radiosurgical treatment and angiographic evidence of its obliteration^{23, 24}. 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 therapy²⁵. What is still missing, however, is clear evidence of this logical conclusion as some authors question the effect of pre-radiosurgical embolisation²⁶. 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 angioarchitecture, 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.

In our neuropsychological study 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 study²⁷ 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 previously²⁸. 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.²⁹ 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.³⁰ 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 deficits³¹⁻³⁴.

Conclusions

1. Active treatment policy for brain AVMs is justified.
2. Active AVM treatment doesn't cause deterioration in neuropsychological performance.
3. AVM location regarding hemispherical 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.

References

1. Ajiboye N, Chalouhi N, Starke RM, Zanaty M, Bell R. Cerebral arteriovenous malformations: Evaluation and management. *TheScientificWorldJournal*. 2014;2014:649036
2. Spetzler RF, Martin NA. A proposed grading system for arteriovenous malformations. *J Neurosurg*. 1986;65:476-483
3. Andersen EB, Petersen J, Mortensen EL, Udesen H. Conservatively treated patients with cerebral arteriovenous malformation: Mental and physical outcome. *J Neurol Neurosurg Psychiatry*. 1988;51:1208-1212
4. Mahalick DM, Ruff RM, Heary RF, U HS. Preoperative versus postoperative neuropsychological sequelae of arteriovenous malformations. *Neurosurgery*. 1993;33:563-570; discussion 570-561
5. Stabell KE, Normes H. Prospective neuropsychological investigation of patients with supratentorial arteriovenous malformations. *Acta Neurochir (Wien)*. 1994;131:32-44
6. Marshall GA, Jonker BP, Morgan MK, Taylor AJ. Prospective study of neuropsychological and psychosocial outcome following surgical excision of intracerebral arteriovenous malformations. *J Clin Neurosci*. 2003;10:42-47
7. Váňa J, Hrabal V. *Vit (vážňuv inteligenční test)*. Bratislava: Psychodiagnostické a didaktické testy 1975.
8. Preiss M, Rodriguez M, Kawaciuková R, Laing H. *Neuropsychologická baterie psychiatrického centra praha*. Praha: Psychiatrické centrum Praha; 2007.
9. Řičan P. *Test intelektového potenciálu (tip)*. Bratislava: Psychodiagnostické a didaktické testy; 1971.
10. Warrington EV, James M. *The visual object and space perception battery* Praha Testcentrum; 2002.
11. Spetzler RF, Wilson CB, Weinstein P, Mehdorn M, Townsend J, Telles D. Normal perfusion pressure breakthrough theory. *Clin Neurosurg*. 1978;25:651-672
12. Sisti MB, Kader A, Stein BM. Microsurgery for 67 intracranial arteriovenous malformations less than 3 cm in diameter. *J Neurosurg*. 1993;79:653-660
13. Schaller C, Schramm J. Microsurgical results for small arteriovenous malformations accessible for radiosurgical or embolization treatment. *Neurosurgery*. 1997;40:664-672
14. Morgan MK, Rochford AM, Tsachtsarlis A, Little N, Faulder KC. Surgical risks associated with the management of grade i and ii brain arteriovenous malformations. *Neurosurgery*. 2004;54:832-839

15. Mounayer C, Hammami N, Piotin M, Spelle L, Benndorf G, Kessler I, et al. Nidal embolization of brain arteriovenous malformations using onyx in 94 patients. *AJNR Am J Neuroradiol.* 2007;28:518-523
16. Saatci I, Geyik S, Yavuz K, Cekirge HS. Endovascular treatment of brain arteriovenous malformations with prolonged intranidal onyx injection technique: Long-term results in 350 consecutive patients with completed endovascular treatment course. *J Neurosurg.* 2011
17. Pierot L, Januel AC, Herbreteau D, Barreau X, Drouineau J, Berge J, et al. Endovascular treatment of brain arteriovenous malformations using onyx: Results of a prospective, multicenter study. *J Neuroradiol.* 2009;36:147-152
18. Greenberg MS. *Handbook of neurosurgery.* New York: Thieme Medical Publishers; 2006.
19. Pollock BE, Lunsford LD, Kondziolka D, Maitz A, Flickinger JC. Patient outcomes after stereotactic radiosurgery for "operable" arteriovenous malformations. *Neurosurgery.* 1994;35:1-8
20. Kurita H, Kawamoto S, Sasaki T, Shin M, Tago M, Terahara A, et al. Results of radiosurgery for brain stem arteriovenous malformations. *J Neurol Neurosurg Psychiatry.* 2000;68:563-570
21. Karlsson B, Jokura H, Yamamoto M, Soderman M, Lax I. Is repeated radiosurgery an alternative to staged radiosurgery for very large brain arteriovenous malformations? *J Neurosurg.* 2007;107:740-744
22. Sirin S, Kondziolka D, Niranjan A, Flickinger JC, Maitz A, Lunsford LD. Large arteriovenous malformations: Indications and outcomes in otherwise untreatable patients. *Neurosurgery.* 2006;58:17-27
23. Bradac O, Mayerova K, Hrabal P, Benes V. Haemorrhage from a radiosurgically treated arteriovenous malformation after its angiographically proven obliteration: A case report. *Cen Eur Neurosurg.* 2010;71:92-95
24. Shin M, Kawahara N, Maruyama K, Tago M, Ueki K, Kirino T. Risk of hemorrhage from an arteriovenous malformation confirmed to have been obliterated on angiography after stereotactic radiosurgery. *J Neurosurg.* 2005;102:842-846
25. Ogilvy CS, Stieg PE, Awad I, Brown RD, Jr., Kondziolka D, Rosenwasser R, et al. Recommendations for the management of intracranial arteriovenous malformations : A statement for healthcare professionals from a special writing group of the stroke council, american stroke association. *Stroke.* 2001;32:1458-1471
26. Andrade-Souza YM, Ramani M, Scora D, Tsao MN, TerBrugge K, Schwartz ML. Embolization before radiosurgery reduces the obliteration rate of arteriovenous malformations. *Neurosurgery.* 2007;60:443-452
27. Mohr JP, Parides MK, Stapf C, Moquete E, Moy CS, Overbey JR, et al. Medical management with or without interventional therapy for unruptured brain arteriovenous malformations (aruba): A multicentre, non-blinded, randomised trial. *Lancet.* 2014;383:614-621

28. Bradac O, Charvat F, Benes V. Treatment for brain arteriovenous malformation in the 1998-2011 period and review of the literature. *Acta Neurochir (Wien)*. 2013;155:199-209
29. Baker RP, McCarter RJ, Porter DG. Improvement in cognitive function after right temporal arteriovenous malformation excision. *Br J Neurosurg*. 2004;18:541-544
30. La Piana R, Bourassa-Blanchette S, Klein D, Mok K, Del Pilar Cortes Nino M, Tampieri D. Brain reorganization after endovascular treatment in a patient with a large arteriovenous malformation: The role of diagnostic and functional neuroimaging techniques. *Interv Neuroradiol*. 2013;19:329-338
31. Madl C, Grimm G, Kramer L, Koppensteiner R, Hirschl M, Yeganehfar W, et al. Cognitive brain function in non-demented patients with low-grade and high-grade carotid artery stenosis. *European journal of clinical investigation*. 1994;24:559-564
32. King GD, Gideon DA, Haynes CD, Dempsey RL, Jenkins CW. Intellectual and personality changes associated with carotid endarterectomy. *Journal of clinical psychology*. 1977;33:215-220
33. De Leo D, Serraiotto L, Pellegrini C, Magni G, Franceschi L, Deriu GP. Outcome from carotid endarterectomy. Neuropsychological performances, depressive symptoms and quality of life: 8-month follow-up. *International journal of psychiatry in medicine*. 1987;17:317-325
34. Ucles P, Almarcegui C, Lorente S, Romero F, Marco M. Evaluation of cerebral function after carotid endarterectomy. *Journal of clinical neurophysiology : official publication of the American Electroencephalographic Society*. 1997;14:242-249

Authors publications

1. publikace *in extenso*, které jsou podkladem disertace

a) s IF:

BRADÁČ, Ondřej - CHARVÁT, František - BENEŠ, Vladimír. Treatment for brain arteriovenous malformation in the 1998-2011 period and review of the literature.. *Acta Neurochirurgica*, 2013, 155(2), 199-209. ISSN 0001-6268. DOI 10.1007/s00701-012-1572-1. IF – **1.788** (2013), 2 Times Cited

BRADÁČ, Ondřej - MAYEROVÁ, K. - HRABAL, P.. Haemorrhage from a radiosurgically treated arteriovenous malformation after its angiographically proven obliteration: a case report. *Central European Neurosurgery*, 2010, 71(2), 92-5. ISSN 0044-4251. DOI 10.1055/s-0029-1220937. 2 Times Cited

b) bez IF – v recenzním řízení

BRADAC, O., PULKRABKOVA, A., De LACY, P., BENES, V., Neuropsychological outcome of AVM treatment. Revision submitted to *British Journal of Neurosurgery*, 2015

2. publikace *in extenso* bez vztahu k tématu disertace

a) s IF:

Články

BRADÁČ, Ondřej; VRANA, Jiri; JIRU, Filip; et al. Recognition of anaplastic foci within low-grade gliomas using MR spectroscopy , *BRITISH JOURNAL OF NEUROSURGERY* Volume: 28 Issue: 5 Pages: 631-636, ISSN: 0268-8697, DOI: 10.3109/02688697.2013.872229 Published: OCT 2014, IF – 0.960, 0 Times Cited

BRADÁČ, Ondřej - MOHAPL, Milan - KRAMÁŘ, Filip. Carotid endarterectomy and carotid artery stenting: changing paradigm during 10 years in a high-volume centre. *Acta Neurochirurgica*, 2014, 156(9), 1705-1712. ISSN 0001-6268. DOI 10.1007/s00701-014-2166-x. IF – 1.766 (2014), 0 Times Cited

MASOPUST, Václav - NETUKA, David - BENEŠ, Vladimír. Endonasal Endoscopic Pituitary Adenoma Resection: Preservation of Neurohypophyseal Function. *Journal of neurological surgery. Part A, Central European neurosurgery*, 2014, 75(5), 336-342. ISSN 2193-6315. DOI 10.1055/s-0034-1368687., IF – 0.608 (2014), 0 Times Cited

AMLEROVÁ, Jana - CAVANNA, Andrea E. - BRADÁČ, Ondřej. Emotion recognition and social cognition in temporal lobe epilepsy and the effect of epilepsy surgery. *Epilepsy and Behavior*, 2014, 36, 86-89. ISSN 1525-5050. DOI 10.1016/j.yebeh.2014.05.001. IF – 2.257 (2014), 1 Times Cited

VANĚK, Petr - BRADÁČ, Ondřej. Burst fractures Response. *Journal of Neurosurgery: Spine*, 2014, 20(2), 149-149. ISSN 1547-5654. IF – 2.383 (2014), 0 Times Cited

VANĚK, Petr - BRADÁČ, Ondřej - KONOPKOVA, Renata. Treatment of thoracolumbar trauma by short-segment percutaneous transpedicular screw instrumentation: prospective comparative study with a minimum 2-year follow-up. *Journal of Neurosurgery: Spine*, 2014, 20(2), 150-156. ISSN 1547-5654. DOI 10.3171/2013.11.SPINE13479, IF – 2.383 (2014), 2 Times Cited

ŠTEKLÁČOVÁ, Anna - BRADÁČ, Ondřej - BENEŠ, Vladimír. WHO Grade II ependymomy IV. komory u dospělých - zkušenosti s léčbou. *Česká a slovenská neurologie a neurochirurgie*, 2014, 77(6), 753-759. ISSN 1210-7859., IF – 0.165 (2014), 0 Times Cited

MÁJOVSKÝ, Martin - NETUKA, David - BRADÁČ, Ondřej. Chirurgická léčba supratentoriálních kortiko-subkortikálních kavernomů. *Surgical Treatment of Supratentorial Cortico-subcortical Cavernous Malformation. Česká a slovenská neurologie a neurochirurgie*, 2014, 77/110(5), 631-637. ISSN 1210-7859. IF – 0.165 (2014), 0 Times Cited

BRADAC, O.; MAJOVSKY, M.; de LACY, P.; et al. Surgery of brainstem cavernous malformations *ACTA NEUROCHIRURGICA* Volume: 155 Issue: 11 Pages: 2079-2083 Published: NOV 2013, ISSN: 0001-6268 , DOI: 10.1007/s00701-013-1842-6 , IF – 1.788, 3 Times Cited

VANĚK, Petr - BRADÁČ, Ondřej - DELACY, Patricia. Anterior interbody fusion of the cervical spine with Zero-P spacer. *Spine*, 2013, 38(13), E792-E797. ISSN 0362-2436. DOI 10.1097/BRS.0b013e3182913400, IF – 2.447 (2013), 4 Times Cited

ŠPATENKOVÁ, Věra - BRADÁČ, Ondřej - SKRABALEK, Pavel. Outcome and frequency of sodium disturbances in neurocritically ill patients. *Acta Neurologica Belgica*, 2013, 113(2), 139-145. ISSN 0300-9009. DOI 10.1007/s13760-012-0137-7. IF 0.598 (2013), 3 Times Cited

JURÁK, Lubomír - BRADÁČ, Ondřej - KAISER, Miroslav. Hydrocefalus jako komplikace subarachnoidálního krvácení. Hydrocephalus as a Complication of Subarachnoid Hemorrhage. Česká a slovenská neurologie a neurochirurgie, 2013, 76(1), 70-75. ISSN 1210-7859. ISSN: 1210-7859 , IF – 0.159 (2013), 0 Times Cited

VARJASSYOVA, Alexandra; HORINEK, Daniel; ANDEL, Ross; et al. Recognition of Facial Emotional Expression in Amnesic Mild Cognitive Impairment , JOURNAL OF ALZHEIMERS DISEASE Volume: 33 Issue: 1 Pages: 273-280 Published: 2013, ISSN: 1387-2877 , DOI: 10.3233/JAD-2012-120148 , IF – 3.612 (2013), 3 Times Cited

VANĚK, Petr - BRADÁČ, Ondřej - DELACY, P.. Comparison of 3 Fusion Techniques in the Treatment of the Degenerative Cervical Spine Disease. Is Stand-Alone Autograft Really the "Gold Standard?" Prospective Study With 2-Year Follow-up. Spine, 2012, 37(19), 1645-1651. ISSN 0362-2436. DOI 10.1097/BRS.0b013e31825413fe. IF – 2.159 (2012), 9 Times Cited

AMLEROVA, J - CAVANNA, AE - BRADÁČ, Ondřej. Hyperfamiliarity in patients with temporal lobe epilepsy. Epilepsy and Behavior, 2012, 24(3), 332-335. ISSN 1525-5050. DOI 10.1016/j.yebeh.2012.04.116. IF - 1,844 (2012), 0 Times Cited

BRADÁČ, Ondřej - HIDE, S - MENDELOW, DA. Aneurysm treatment in Europe 2010: an internet survey. Acta Neurochirurgica, 2012, 154(6), 971-978. ISSN 0001-6268. DOI 10.1007/s00701-012-1340-2. IF – 1.546 (2012), 7 Times Cited

SPATENKOVA, Vera; BRADAC, Ondrej; KAZDA, Antonin; et al. N-terminal pro-B-type Natriuretic Peptide with fractional excretion and clearance of sodium in relation to cardiovascular events after elective cervical spine surgery NEUROENDOCRINOLOGY LETTERS Volume: 32 Issue: 6 Pages: 874-878 Published: 2011, ISSN: 0172-780X , IF – 1.296 (2011), 2 Times Cited

SPATENKOVA, Vera; BRADAC, Ondrej; KAZDA, Antonin; et al. Central diabetes insipidus is not a common and prognostically worse type of hypernatremia in neurointensive care , NEUROENDOCRINOLOGY LETTERS Volume: 32 Issue: 6 Pages: 879-884 Published: 2011 , ISSN: 0172-780X , IF – 1.296 (2011), 2 Times Cited

NETUKA, David - OSTRÝ, Svatopluk - BELSAN, T. Magnetic resonance angiography, digital subtraction angiography and Doppler ultrasonography in

detection of carotid artery stenosis: a comparison with findings from histological specimens. *Acta neurochirurgica*, 2010, 152(7), 1215-1221. ISSN 0001-6268. DOI: 10.1007/s00701-010-0645-2 , IF – 1.329 (2010), 4 Times Cited

SUCHOMEL, P - JURAK, L - BENEŠ, Vladimír. Clinical results and development of heterotopic ossification in total cervical disc replacement during a 4-year follow-up. *European Spine Journal*, 2010, 19(2), 307-315. ISSN 0940-6719. DOI: 10.1007/s00586-009-1259-3 , IF – 1.994 (2010), 39 Times Cited

VANĚK, Petr - BRADÁČ, Ondřej - SAUR, Karel. Faktory ovlivňující výsledek chirurgické léčby herniace bederní disku. Factors Influencing the Outcome of Surgical Treatment of Lumbar Disc Herniation. *Česká a slovenská neurologie a neurochirurgie*, 2010, 73/106(2), 157-163. ISSN 1210-7859. IF – 0.393, 0 Times Cited

BENEŠ, Vladimír - BRADÁČ, Ondřej - OSTRÝ, Svatopluk. Intramedulární astrocytom - série 15 pacientů a přehled literatury. Intramedullary Astrocytoma - a Series of 15 Patients and Literature Overview . *Česká a slovenská neurologie a neurochirurgie*, 2010, 73/106(2), 169-177. ISSN 1210-7859. IF - 0,393 (2010), 0 Times Cited

MOHAPL, Milan - VANĚK, Petr - BRADÁČ, Ondřej. Srovnání přínosu lumbálního infuzního testu a lumbální drenáže v indikaci léčby hydrocefalu. Comparison of the Benefits of the Lumbar Infusion Test and Lumbar Drainage in the Treatment of Hydrocephalus *Česká a slovenská neurologie a neurochirurgie*, 2010, 73/106(6), 685-688. ISSN 1210-7859., IF – 0.393, 0 Times Cited

MASOPUST, Vaclav; HÄCKEL, Martin; NETUKA, David; et al Postoperative Epidural Fibrosis *CLINICAL JOURNAL OF PAIN* Volume: 25 Issue: 7 Pages: 600-606 Published: SEP 2009, ISSN: 0749-8047 , IF – 3.005 (2009), 4 Times Cited

Nemedicínské články

BRADAC, Ondrej; ZIMMERMANN, Tomas; BURDA, Jaroslav V. Can Satraplatin be hydrated before the reduction process occurs? The DFT computational study *JOURNAL OF MOLECULAR MODELING* Volume: 19 Issue: 11 Pages: 4669-4680 Published: NOV 2013 , IF – 1.067 (2013), 1 Times Cited

BRADÁČ, Ondrej; ZIMMERMANN, Tomas; BURDA, Jaroslav
V. Comparison of the electronic properties, and thermodynamic and kinetic parameters of the aquation of selected platinum(II) derivatives with their anticancer IC(50) indexes . JOURNAL OF MOLECULAR MODELING Volume: 14 Issue: 8 Pages: 705-716 Published: AUG 2008 , IF – 2.018 (2008), Times Cited: 6

b) bez IF

Kapitola v knize

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.

Články

BIČÍKOVÁ, V - SOSVOROVÁ, L - BRADÁČ, Ondřej. Fytoestrogeny v menopauze: pracovní mechanismy a klinické výsledky u 28 pacientů. Česká gynekologie, 2012, 77(1), 10-14. ISSN 1210-7832. Cited by 1 document – SCOPUS

NETUKA, David - KRAMÁŘ, Filip - BELŠÁN, T. Význam biologického chování nitrolebních meningiomů pro jejich dlouhodobý management. Rozhledy v chirurgii, 2012, 91(6), 322-326. ISSN 0035-9351, Cited by 0 documents – SCOPUS

VANEK, P.; BRADAC, O.; SAUR, K Anterior Interbody Fusion of the Cervical Spine with a Zero-P Spacer. Radiographic Results with a Minimum Follow-up of One Year in a Prospective Study ACTA CHIRURGIAE ORTHOPAEDICAE ET TRAUMATOLOGIAE CECOSLOVACA Volume: 78 Issue: 6 Pages: 562-567 Published: DEC 2011 , ISSN: 0001-5415 , 2 Times Cited