

Microsurgical resection of Spetzler–Martin grades 1 and 2 unruptured brain arteriovenous malformations results in lower long-term morbidity and loss of quality-adjusted life-years (QALY) than conservative management—results of a single group series

Hans-Jakob Steiger¹ · Igor Fischer² · Benjamin Rohn¹ · Bernd Turowski³ · Nima Etminan¹ · Daniel Hänggi¹

Received: 17 February 2015 / Accepted: 8 June 2015 / Published online: 7 July 2015
© Springer-Verlag Wien 2015

Abstract

Background The therapeutic benefits of microsurgery for unruptured brain AVM remain unclear.

Methods A series of 97 microsurgically resected unruptured brain AVM was analyzed in terms of postoperative morbidity and lifetime loss of quality-adjusted life-years (QALY). For comparison, the natural risk of becoming disabled was modeled on the basis of published data.

Results Discharge morbidity was recorded in 11 of the 69 of Spetzler–Martin (SM) grade 1 and 2 AVMs (16 %), eight of 22 (36 %) grade 3, and four of six grade 4 (67 %), permanent morbidity >mRS 1 in 3 (4.3 %) grade 1 and 2, four (18 %) grade 3, and three (50 %) grade 4. Treatment inflicted loss of QALY amounted to 0.5 years for SM grade 1–2, 2.5 years grade 3, 7.3 years for grade 4. For the SM grades 1 and 2, the treatment-related loss of 0.5 QALY was met by the natural course after 2.7–4.3 years. For the Spetzler–Martin grades 3 and 4, the treatment-induced loss QALY was not met by the natural risk within a foreseeable time. Permanent morbidity and treatment inflicted loss of QALY of patients younger than 39 years was lower than that of older patients (7 vs. 15 % and 1.0 vs. 2.1 QALY).

Conclusions Microsurgically managed SM grades 1 and 2 fared better than the modeled natural course but grades 3 and 4 AVM did not benefit from surgery. Younger patients appear to fare more favorably than older patients.

Keywords Unruptured brain arteriovenous malformation · Microsurgery · Morbidity · Quality of life

Introduction

Publication of the results of the ARUBA trial (A Randomized Trial for Unruptured Brain Arteriovenous Malformations) provoked a widespread echo from neurosurgeons, endovascular therapists, and also radiosurgeons [9, 23, 24]. Without any doubt, the study suffered of a number of weaknesses. The shortly after ARUBA published report of the *Scottish Audit Of Intracranial Vascular Malformations* encountered much less attention, mainly because these data did not come from a randomized trial but from cohort comparison [1]. Nonetheless, the Scottish Audit is as important as ARUBA and will probably affect together with ARUBA management strategy of unruptured brain arteriovenous malformations (AVM) profoundly. In this population-based inception cohort study, 204 residents of Scotland, aged 16 years or older, who were first diagnosed as having an unruptured AVM were followed up prospectively after intervention or under observation. There was no interference with treatment decisions. The results were comparable to the results of ARUBA in that at least during the first years conservative management was more favorable than intervention. Nonetheless, unruptured brain AVMs are not benign

✉ Hans-Jakob Steiger
steiger@uni-duesseldorf.de

¹ Department of Neurosurgery, Heinrich-Heine-Universität, Moorenstr. 5, Geb. 10.54, 40225 Düsseldorf, Germany

² Division of Informatics and Statistics, Department of Neurosurgery, Heinrich-Heine-Universität, Düsseldorf, Germany

³ Division of Neuroradiology, Institute of Radiology, Heinrich-Heine-Universität, Düsseldorf, Germany

hamartomas. The annual stroke rate in the conservative cohort of ARUBA and the Scottish Audit amounted to 2.3 and 2.7 %, respectively [1, 24]. Monocentric series provided annual hemorrhage rates of unruptured AVM between 1.3 and 42 %, with an average of 2.2 % [2, 3, 5, 8, 10, 11, 13, 15, 17, 18, 25, 26, 29, 30, 33]. Reported hemorrhage-related rates of death and disability vary from 16 to 88 %, with an average of some 50 % [5–8, 14, 25, 31, 32].

The purpose of the present study was to add a series of microsurgically removed unruptured AVM to the current body of data on the outcome of microsurgical resection and to define subgroups with particularly favorable or unfavorable treatment outcome compared to the natural course.

Methods

A series of 97 patients with unruptured brain AVM was included in the analysis that underwent complete microsurgical resection of an unruptured brain AVM by our group between July 1992 and June 2014.

Treatment protocol

Treatment of the unruptured AVM was generally recommended to all patients with Spetzler–Martin grades 1–3 AVMs unless age or comorbidities were considered a contraindication. The interdisciplinary management options offered to the patients during that period included endovascular embolization, microsurgery, and Gamma Knife radiosurgery. Individual treatment recommendations were discussed within a weekly interdisciplinary neurovascular conference. Microsurgical resection was recommended as the treatment of first choice except for deep-seated AVM. Presurgical embolization was used as an adjunct for larger AVM. Embolization was performed in one or several sessions between 1 day and 3 weeks prior to surgery. Surgery was performed on the day of the last embolization only in cases when embolization was complicated by hemorrhage. Complete resection of the AVM was angiographically verified prior to discharge from the hospital.

Follow-up

Initial follow-up was scheduled for 6–8 weeks following discharge. Instrumental diagnostics such as EEG, CT, or MRI were only used for specific indications, i.e., neurological deficit or epilepsy. A second angiography was performed in a few cases when the postoperative control angiography left some doubt regarding completeness of resection. One or two further follow-up visits were scheduled during the first postoperative years. Follow-up was terminated at that time in patients without symptoms. Follow-up was extended as needed in patients suffering of neurological deficits, epilepsy, or significant headache.

Data analysis

For the present analysis, demographic and clinical information and AVM characteristics were extracted from the medical records. Treatment-related morbidity was assessed at the time of postoperative discharge from the hospital at a median of 11 days after surgery (range, 6–66 days), and the last follow-up in terms of the modified Rankin scale (mRS). Discharge morbidity comprised total management morbidity, including complications due to presurgical embolization. Complications without an impact on discharge morbidity and/or late mRS, such as necessity for surgical site revision, were not included in the present analysis.

In order to define factors influencing postoperative outcome, patients, respectively AVM, were grouped according to age and Spetzler–Martin grade. Exploratory statistics correlated the postoperative outcome data to these potential influencing factors by univariate comparison. T-statistics were used to compare mean values of stratified groups; Fisher's exact test was used for proportions and Mann–Whitney–Wilcoxon for comparison of time lines.

The annual morbidity rates of untreated AVM as given in the literature and cited initially were used to decide whether and when the different groups of patients reached a point where the natural risk of the untreated AVM equaled the risk of microsurgical resection. In order to account for the fact that morbidity occurring immediately after treatment is a more severe loss than morbidity occurring in the distant future, the total functional restriction was recalculated in terms of expected lifetime loss of quality-adjusted life-years (QALYs) for a period up to the age of 70 years. QALYs were calculated by multiplying expected life-years with a corrective factor based on the modified Rankin scale (mRS). We adopted the utility factors that were assessed by Post and coworkers for stroke patients, 0 for death, 0.7 for mRS 2–3, and 0.4 for mRS 4–5 [16, 27].

Results

The total of 97 patients treated for unruptured brain AVM consisted of 55 male and 42 female patients with a median age of 38 years (see Table 1). Leading symptoms were epilepsy in 50 patients and headache in 23. Nine of these patients had both headache and epilepsy. Fourteen patients had some degree of mono- or hemiparesis at the time of admission. Six of these also had epilepsy.

Angiography defined a Spetzler–Martin grade 1 AVM in 25 patients, grade 2 in 44, grade 3 in 22, and grade 4 in six. Forty-seven (48 %) of the patients underwent preoperative endovascular embolization.

New morbidity at the time of discharge occurred in 23 of the 97 patients (24 %) (see Tables 1 and 2, Fig. 1). Average follow-up was 3.5 years. Up to the last follow-up, no secondary

Table 1 Key characteristics and outcome data

Age (mean, years±SD)	38±15
Female	42 (43 %)
Male	55 (57 %)
Spetzler–Martin grade	
-I	25 (26 %)
-II	44 (45 %)
-III	22 (23 %)
-IV	6 (6 %)
AVM location	
-lobar	89 (92 %)
-deep seated	2 (2 %)
-posterior fossa	6 (6 %)
Presurgical embolization	47 (48 %)
Overall discharge morbidity	23 (24 %)
Morbidity at last follow-up	
-mRS 0	72 (74 %)
-mRS 1	15 (15 %)
-mRS 2	2 (2 %)
-mRS 3	4 (4 %)
-mRS 4	3 (3 %)
-mRS 5	1 (1 %)

new hemorrhagic or ischemic stroke were recorded in 337 patient years of follow-up. At the time of the last follow-up, 72 patients (74 %) had no handicap, 15 (15 %) had deficits according to mRS 1, 2 (2 %) mRS 2, 4 (4 %) mRS 3, 3 (3 %) mRS 4, 1 (1 %) mRS 5. One patient with an incidental cerebellar AVM and an uneventful postoperative course died 8 years later of unrelated causes. Thus, permanent morbidity mRS>1 was recorded in ten patients (10.3 %). In five of these, some degree of hemiparesis had already been noticed prior to treatment but four of the five were classified as discharge morbidity since the deficit was more pronounced postoperatively.

Discharge morbidity was recorded in 11 of the 69 Spetzler–Martin grades 1 and 2 AVMs (16 %) and permanent morbidity >mRS 1 as recorded at the last follow-up in three (4.3 %). Regarding the 22 Spetzler–Martin grade 3 AVMs, discharge morbidity occurred in eight patients (36 %) and permanent

morbidity mRS>1 in four (18 %) patients. Discharge morbidity was noticed in four of the six Spetzler–Martin grade 4 AVM (67 %) and permanent morbidity mRS>1 in three (50 %) (Fig. 1).

When patients were stratified according to age, the following trend appeared although differences between age groups did not reach statistical significance (Fig. 2). While discharge morbidity of patients younger than 39 years and older patients was comparable, 21 and 25 %, respectively, permanent morbidity mRS>1 was recorded in only three (7 %) of the patients younger than 39 years and in six of the older patients (15 %).

QALY analysis

On average management associated loss of QALY amounted to 1.4 years. Stratified with regard to Spetzler–Martin grades, average loss of QALY amounted to 0.5 years with Spetzler–Martin grade 1–2 AVMs, to 2.5 years in grade 3, and to 7.3 years in grade 4. Stratified with regard to age, treatment was associated on average with a loss of 1.0 QALY up to the age of 70 years in patients younger than 39 years and a loss of 2.1 years in patients of 39 years or older.

Supplemental analyses

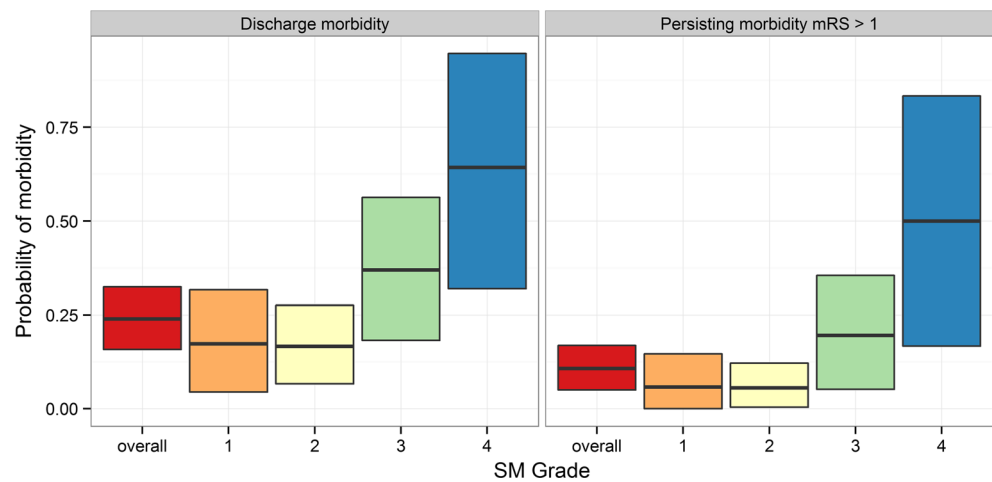
In order to compare the treatment-associated risk of the current series with the current best data on the natural course, the incidence rates of first hemorrhagic or ischemic stroke under conservative managements as given in the ARUBA as treated analysis were recalculated in terms of the occurrence of morbidity mRS>1 (Fig. 3), and the associated lifetime loss of QALYs was estimated as outlined above and assuming an initial age as the average of the respective subgroup. For a sensitivity analysis, due to the lack of exact data regarding hemorrhage-associated mortality and morbidity rates, calculations were performed for the average of reported death and disability rates, i.e., 15 % risk of death and 15 % risk of persisting disability mRS > 2–3 and 15 % risk of mRS 4–5 [2, 5, 14, 25], as well as for a lower risk boundary assuming 10 % risk of death and 10 % risk of persisting disability mRS > 2–3 and 10 % risk of mRS 4–5.

Table 2 Treatment morbidity of subgroups

Group	Discharge morbidity	Long-term morbidity >mRS1	Loss of QALY (years)
All patients	22 (23 %)	10 (10.3 %)	1.4
Spetzler–Martin 1 and 2	11 (16 %)	3 (4.3 %)	0.5
Spetzler–Martin 3	8 (36 %) * <i>p</i> =0.067	4 (18 %) * <i>p</i> =0.056	2.5 * <i>p</i> =0.034
Spetzler–Martin 4	4 (67 %) * <i>p</i> =0.013	3 (50 %) * <i>p</i> =0.005	7.3 * <i>p</i> <0.001
Younger than 39 years	9 (21 %)	3 (7 %)	1.0
39 years or older	10 (25 %) <i>p</i> =0.79	6 (15 %) <i>p</i> =0.30	2.1 <i>p</i> =0.26

*Compared to Spetzler–Martin 1 and 2

Fig. 1 Overall rate of additional neurological deficit at the time of discharge and late morbidity >mRS1 at the time of last follow-up



Our overall treatment risk resulting in a persistent deficit mRS>1 of 10 % was met by the cumulative natural course after 11.5 years assuming the higher natural risk boundary and after 18.7 years assuming a benign natural course (Table 3). For the Spetzler–Martin grades 1 and 2, the treatment risk of permanent morbidity >mRS1 of 4.3 % was met after 5.0 years, assuming the higher natural risk estimate and after 7.7 years on the premise of the lower natural risk. For the Spetzler–Martin grade 3, the risk of treatment morbidity >mRS 1 of 18 % was met by the natural risk only after 24.2 years, respectively, after 44.8 years. For the Spetzler–Martin grade 4, the risk of treatment morbidity >mRS 1 of 50 % was never met by the natural course.

Regarding the different age groups, the treatment risk of 7 % of patients younger than 39 years was met by the natural risk after 8.3 years or 13.0 years, respectively (Fig. 4). For older patients, the treatment risk of 15 % was met by the natural risk after 18.4 or 31.9 years, respectively.

Comparison of our treatment-associated lifetime loss of QALY with the calculation of loss of QALY during the natural

course showed that our overall treatment-associated loss of 1.4 QALY was met by the natural course after 8.6 years assuming the higher natural risk boundary and after 16 years assuming the benign natural course (Fig. 5). For the Spetzler–Martin grades 1 and 2, the treatment-associated loss of 0.5 QALY was met after 2.7 years assuming the higher natural risk estimate and after 4.3 years on the premise of the lower natural risk. For the Spetzler–Martin grade 3, the treatment loss of 2.5 QALY was met by the natural risk only after 25 years under the precondition of the higher natural risk and never under the assumption of a benign natural course. For the Spetzler–Martin grade 4, the treatment-induced loss of 7.3 QALY was never met by the natural risk.

Regarding the different age groups, the treatment loss of 1 QALY of patients younger than 39 years was met by the natural risk after 3.9 years or 6.1 years, respectively (Fig. 6). For older patients, the treatment-inflicted loss of 2.1 QALY was never met by the natural risk assuming either precondition.

Fig. 2 Rate of late morbidity >mRS1 at the time of the last follow-up stratified with regard to age. Patients younger than 39 years recovered better from initial postoperative deficits than older patients

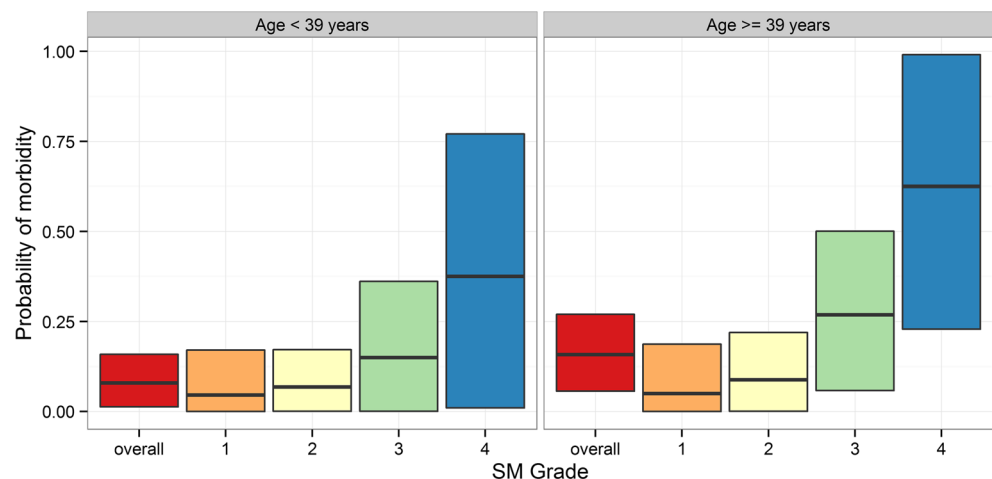
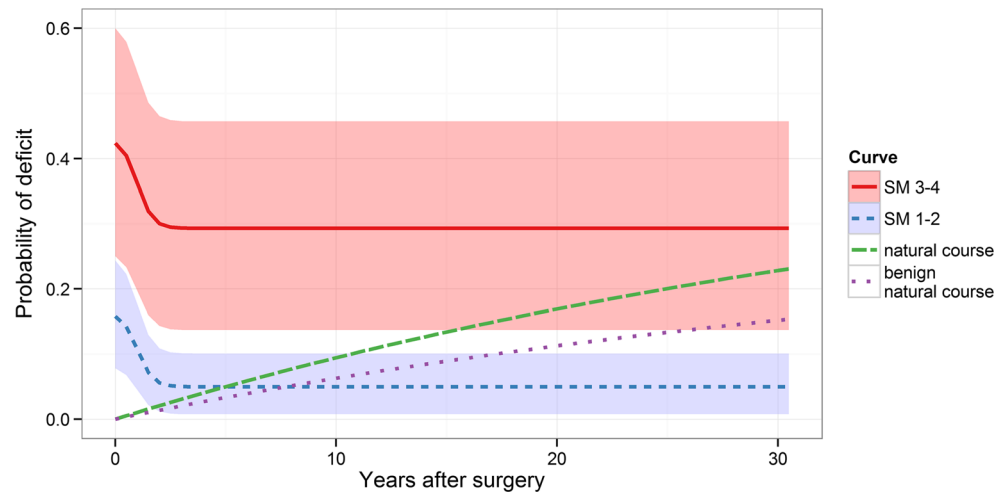


Fig. 3 Surgical morbidity >mRS 1 compared with the modeled natural course (proportion with 95% confidence bands). For the Spetzler–Martin grades 1 and 2, the treatment risk of permanent morbidity >mRS1 of 4.3 % was met after 5.0 years assuming the higher natural risk estimate and after 7.7 years on the premise of the lower natural risk



Discussion

The current attitude towards indication of treatment for unruptured AVM is heavily influenced by the published ARUBA results, despite the justified criticism. Less than 20 cases in the ARUBA study underwent surgery, so no conclusion regarding the value of surgery can be drawn from these data. The results of the Scottish Audit have so far gained much less public attention [1]. In essence, the results of the Scottish Audit are in line with the conclusion of ARUBA that conservative management of unruptured AVM is preferable. Although the weaknesses of ARUBA have been recognized and commented, i.e., the lack of affirmed AVM elimination and lumping together all treatment modalities and Spetzler–Martin grades [9, 23], the impact on management decisions must be assumed to be profound and long-lasting. Without correction of the perception by neurologists and general practitioners, referral of patients with unruptured AVM is expected to come to a halt, and it will be difficult to prove that AVM elimination can lead to a substantial benefit under certain preconditions. Harboring an unruptured AVM is no benign condition. Annual rupture rates amount to some 2.3 % with a

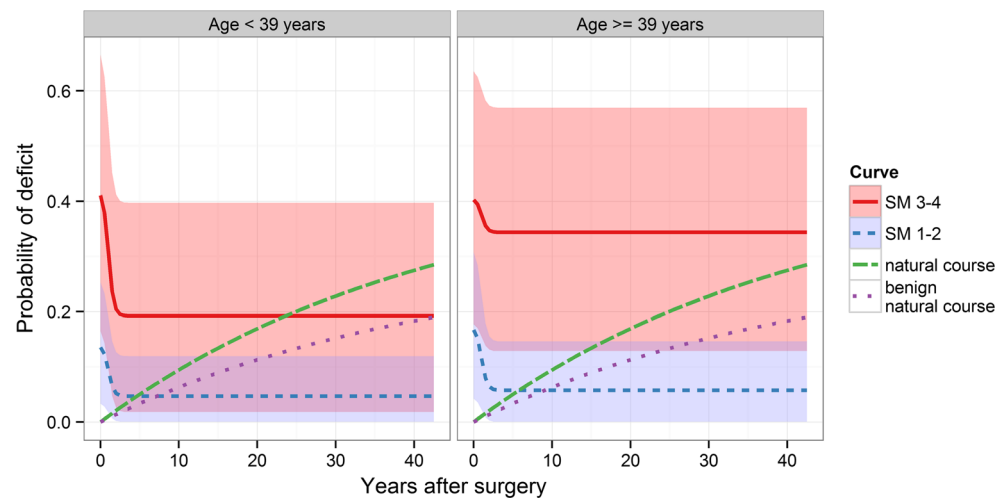
roughly 50 % chance of death or permanent morbidity [2, 11]. Extrapolated to only 10 years, the chance to die or become disabled amounts to some 10 % according to our extrapolation, assuming a risk of 45 % mortality or morbidity > mRS1. The longest follow-up on the natural history is available from the Finnish cohort. Laakso and coworkers published the results of the long-term follow-up of conservative and interventional treatment [20]. They followed their patients for an average of 11.9 years. Treatment was conservative in 155 patients. Total AVM occlusion was attained in 356 patients, and partial occlusion was obtained in 94 patients. Overall, 206 deaths were observed. Of these, 100 were related to AVMs. Diagnosis of AVM was associated with significant long-term excess mortality, with cumulative relative survival ratios of 0.85 and 0.69 at 10 and 30 years after admission, respectively. Men had higher excess mortality than women. The excess in mortality was highest in conservatively treated patients, intermediate in patients with partially occluded AVMs, and lowest in those with totally occluded AVMs. The subgroup with the best outcome consisted of those with totally occluded unruptured AVMs, which did not demonstrate excess mortality after the first year.

Table 3 Times of natural risk equaling surgical morbidity (years)

Group	Long-term morbidity >mRS1	Long-term morbidity >mRS1, benign natural course	Loss of QALY	Loss of QALY, benign natural course
All patients	11.5 (5–20)	18.7 (7.7–35.1)	8.6 (0–∞)	16 (0–∞)
Spetzler–Martin 1 and 2	5.0 (0.7–10.8)	7.7 (1.1–17.4)	2.7 (0–∞)	4.3 (0–∞)
Spetzler–Martin 3	24.2 (5.2–66)	44.8 (8–∞)	25 (0–∞)	∞ (0–∞)
Spetzler–Martin 4	∞ (19.6–∞)	∞ (34.4–∞)	∞ (0–∞)	∞ (0–∞)
Younger than 39 years	8.3 (1.2–18.5)	13 (1.8–32)	3.9 (0–∞)	6.1 (0–∞)
39 years or older	18.4 (5.7–38.9)	31.9 (8.9–∞)	∞ (0–∞)	∞ (0–∞)

All numbers are means (95 % confidence intervals)

Fig. 4 Effect of age on the comparison between treatment-inflicted morbidity and the natural course (proportions and 95 % confidence bands, overlapping). Both with the younger and the older cohort of Spetzler–Martin grade 1 and 2 AVMs, treatment risk was equaled within 3 to 10 years, even under the assumption of a benign natural course



These findings support the emerging concept that unruptured AVM should be completely eliminated if manageable with small risk. In this sense, there is little discussion based on the actual data that patients harboring an unruptured Spetzler–Martin grades 1 or 2 AVM should be recommended microsurgical resection. Possible strategies to correct the picture are conduction of a new randomized trial or collecting and analyzing existing differentiated data. Adding to the pool of information on the results of complete microsurgical resection was the incentive for publication of this monocentric data.

In our series, overall discharge morbidity was 24 %. In the long run, however, our discharge morbidity decreased to a permanent morbidity mRS>1 of 10 % and no new AVM-related morbidity occurred during the later course. This result is in line with the report by Bervini et al. who reported an overall persisting morbidity rate of 11 % [2, 3]. Lawton reported for unruptured AVM, less favorable overall results indicating persisting rates of morbidity >mRS1 in 38 % [22, 28]. Lawton also pointed out the critical effect of presenting symptoms on recovery after surgery [12, 22]. The impact of the

initial hemorrhage can masquerade negative consequences of treatment. Therefore, morbidity figures given in the many series focusing on the surgical results of unselected AVM cannot be uncritically adopted for unruptured AVM.

While the risk associated with microsurgical resection depends on size and location, i.e., the Spetzler–Martin grade, the natural risk does not increase for larger AVM [21]. Discharge morbidity and long-term morbidity mRS>1 of our Spetzler–Martin grades 1 and 2 was 16 and 4.3 %, respectively. The risk of mRS>1 was met by the natural history after 5 to 7.7 years. Bervini et al. reported recently a permanent morbidity >mRS1 of 1.6 % among 190 unruptured Spetzler–Martin grades 1 and 2 AVM [2]. These authors also concluded that complete microsurgical resection of Spetzler–Martin grades 1 and 2 AVM resulted in a better perspective than conservative management.

In the current series, discharge morbidity in the Spetzler–Martin group 3 was 36 % and the rate of long-term disability 18 %. Bervini et al. reported in their series permanent morbidity mRS>1 in 14 %. Based on the natural risk calculation, our

Fig. 5 Lifetime loss of QALY comparing microsurgical results and natural course. For Spetzler–Martin grades 1 and 2, the treatment-associated loss of 0.5 QALY was met after 2.7 years assuming the higher natural risk estimate and after 4.3 years on the premise of the lower natural risk. The treatment-inflicted loss with grades 3 and 4 AVM was never met by the natural course

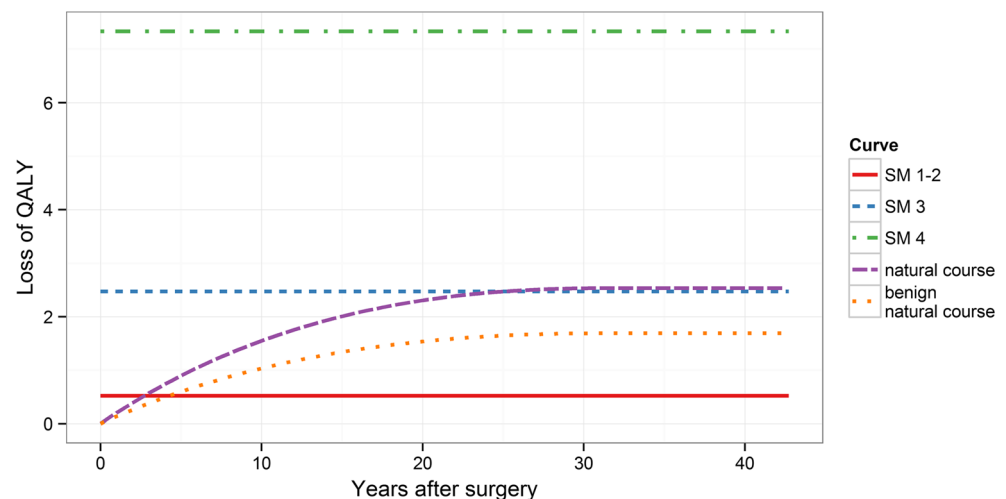
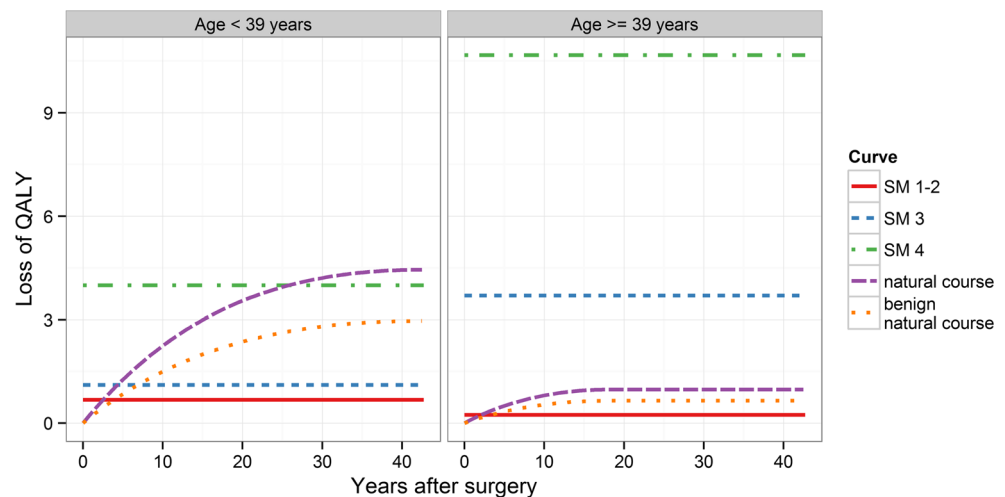


Fig. 6 Lifetime loss of QALY stratified with regard to age. The relation between natural risk and treatment-associated loss was comparable in both age groups for Spetzler–Martin grades 1 and 2. Furthermore, in the younger age group, surgically treated patients with Spetzler–Martin grade 3 AVM fared better than the modeled natural course



risk of treatment was counterbalanced by the risk of conservative management only after 24.2 years, and in the sensitivity analysis assuming a more benign natural course after 44.8 years, leading to the conclusion that treatment should not be recommended to patients for unruptured Spetzler–Martin grade 3 AVMs. This agrees with the conclusions of Bervini and coworkers that microsurgical resection for unruptured grade 3 AVM cannot be recommended at the present time, particularly in light of uncertainties regarding the natural risk of this subgroup.

Patient age was related to the risk of treatment-inflicted morbidity in our series. Although the discharge morbidity of 21 % of patients younger than 39 years was comparable to the 25 % of the older patients, morbidity mRS > 1 persisted in only 7 % of the patients younger than 39 years but in 15 % of the older patients. Although the small number of events in this series leave some statistical uncertainty, the better recovery of younger patients is not surprising since better recovery of younger patients is generally accepted after traumatic brain injury and stroke [4]. The significance of age has not found much attention so far in the discussion on management of unruptured AVM.

Disability occurring immediately after treatment differs from disability occurring later in the future because quality of life may be unaffected for many years. Therefore we converted the impact of morbidity in loss of quality-adjusted life-years. Quality of life is a subjective perception of patients and relatives and based on formalized instruments such as the Short-Form (SF) 36. Although the perceived quality of life decreases slightly with increasing age, we assumed for the present calculation that life is essentially equally worth living during the entire life time up to the age of 70. Uncertainties regarding quality of life of people beyond the age of 70 are multiple. In order to obtain the loss of quality-adjusted life-years due to morbidity we used the instrument developed by Post et al. for patients with ischemic stroke [16, 27]. They calculated QALYs by assigning a utility value to a specific

health state and multiplying this value by the number of years spent in that state. Death within 30 days was assigned a utility value of 0, while disabled survival was assigned a value of 0.7 or 0.4 depending on whether the mRS score at that point was 2–3 or 4–5, respectively. These values were generated by interviewing patients and relatives using various instruments. Calculating the expected lifetime loss of QALY, we also found that in Spetzler–Martin grades 1 and 2 AVM the treatment inflicted loss of QALY was balanced by the natural history within 5 years, even when assuming a benign natural course with only 30 % combined morbidity and mortality after hemorrhage. With Spetzler–Martin grades 3 and 4, the treatment-inflicted lifetime loss of QALY was never exceeded by the natural course. The effect of age on expected lifetime loss of QALY is interesting. While the benefit of treatment in terms of lost QALY was comparable for patients younger than 39 years and older patients with SM grade 1 and 2 AVMs, a benefit of surgical treatment was also seen in the younger patients also with grade 3 AVMs. The effect was due to the better recovery in the younger age group from postoperative deficits. However, statistical uncertainty due to the small number of events does not allow drawing a final conclusion regarding the potential benefit of microsurgical resection in younger patients with Spetzler–Martin grade 3 AVM.

The estimate of the lost QALY must be considered as a rough instrument to quantify the lifetime impact of treatment associated disability. Besides the lack of direct validation for AVM patients, it remains unclear whether the subjective estimate of the loss of life quality would be the same if reevaluated after some years. Furthermore, the long-term evolution of disability remains also uncertain to some degree. It appears possible that a postoperative deficit with good recovery still leads to premature disability at a higher age.

In the present analysis we used a linear model to calculate the natural risk of untreated unruptured AVM. The assumption that the risk remains the same from the time of diagnosis may

be simplified. Although the long-term data both of the ARUBA cohort and the Scottish Audit is too scarce for a final conclusion, it appears that the risk of an untreated AVM is somewhat higher during the early period than later. Cohort series indicate that the natural risk of untreated unruptured AVM is higher early after the diagnosis and then again increases with age [2, 3, 7, 15, 19]. It must be assumed that some instability of the AVM leading to diagnostic work-up may also represent a somewhat increased risk of rupture. The effect is minor and has therefore no direct implication, neither for the management of the individual patients nor for modeling the natural risk.

Whenever constructing complex models with some unknown variables, one must be aware that by slightly changing basic assumptions, the whole outcome of the calculations could be entirely different. Therefore, we used a sensitivity analysis assuming a lower proportion of death and disability resulting from AVM hemorrhage than the average of the reported numbers. The main result that patients harboring SM 1–2 AVM fared better after surgical treatment than under conservative management remained stable.

Limitations

The main limitation of the actual study is the retrospective nature of the analysis and the lack of a direct control group managed conservatively. A further limitation applies to the assumptions necessary for the predictive models. The loss of utility related to mRS scores was assessed for the first year after ischemic stroke and not for a lifetime perspective.

Conclusions

In this series, microsurgical removal of unruptured Spetzler–Martin grade 1 and 2 AVM produced more favorable long-term results than the modeled natural course while surgical treatment of grades 3 and 4 AVM did not. In addition, patients younger than 39 years tended to fare better after microsurgical treatment than older patients.

Disclosure All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Conflicts of interest None.

References

1. Al-Shahi Salman R, White PM, Counsell CE, du Plessis J, van Beijnum J, Josephson CB, Wilkinson T, Wedderburn CJ, Chandy Z, St George EJ, Sellar RJ, Warlow CP, Scottish Audit of Intracranial Vascular Malformations Collaborators (2014) Outcome after conservative management or intervention for unruptured brain arteriovenous malformations. *JAMA* 311(16): 1661–1669
2. Bervini D, Morgan MK, Ritson EA, Heller G (2014) Surgery for unruptured arteriovenous malformations of the brain is better than conservative management for selected cases: a prospective cohort study. *J Neurosurg* 121(4):878–890
3. Bervini D, Morgan MK, Ritson EA, Heller G (2014) Surgery for unruptured arteriovenous malformations of the brain is better than conservative management for selected cases: a prospective cohort study. *Neurochirurgie* 60(6):327
4. Blicher JU, Nielsen JF (2008) Does long-term outcome after intensive inpatient rehabilitation of acquired brain injury depend on etiology? *NeuroRehabilitation* 23(2):175–183
5. Brown RD Jr, Wiebers DO, Forbes G, O'Fallon WM, Piepgras DG, Marsh WR, Maciunas RJ (1988) The natural history of unruptured intracranial arteriovenous malformations. *J Neurosurg* 68(3): 352–357
6. Choi JH, Mast H, Sciacca RR, Hartmann A, Khaw AV, Mohr JP, Sacco RL, Stapf C (2006) Clinical outcome after first and recurrent hemorrhage in patients with untreated brain arteriovenous malformation. *Stroke* 37(5):1243–1247
7. Crawford PM, West CR, Chadwick DW, Shaw MD (1986) Arteriovenous malformations of the brain: natural history in unoperated patients. *J Neurol Neurosurg Psychiatry* 49(1):1–10
8. da Costa L, Wallace MC, Ter Brugge KG, O'Kelly C, Willinsky RA, Tymianski M (2009) The natural history and predictive features of hemorrhage from brain arteriovenous malformations. *Stroke* 40(1):100–105
9. Elhammady MS, Heros RC (2014) Editorial. Management of incidental cerebral AVMs in the post-ARUBA era. *J Neurosurg* 121(5): 1011–1014
10. Graf CJ, Perret GE, Torner JC (1983) Bleeding from cerebral arteriovenous malformations as part of their natural history. *J Neurosurg* 58(3):331–337
11. Gross BA, Du R (2013) Natural history of cerebral arteriovenous malformations: a meta-analysis. *J Neurosurg* 118(2):437–443
12. Guo Y, Saunders T, Su H, Kim H, Akkoc D, Saloner DA, Hetts SW, Hess C, Lawton MT, Bollen AW, Pourmohamad T, McCulloch CE, Tihan T, Young WL, University of California, San Francisco Brain Arteriovenous Malformation (UCSF bAVM) Study Project (2012) Silent intralesional microhemorrhage as a risk factor for brain arteriovenous malformation rupture. *Stroke* 43(5):1240–1246
13. Halim AX, Johnston SC, Singh V, McCulloch CE, Bennett JP, Achrol AS, Sidney S, Young WL (2004) Longitudinal risk of intracranial hemorrhage in patients with arteriovenous malformation of the brain within a defined population. *Stroke* 35(7):1697–1702
14. Hartmann A, Mast H, Mohr JP, Koennecke HC, Osipov A, Pile-Spellman J, Duong DH, Young WL (1998) Morbidity of intracranial hemorrhage in patients with cerebral arteriovenous malformation. *Stroke* 29(5):931–934
15. Hernesniemi JA, Dashti R, Juvola S, Väärt K, Niemelä M, Laakso A (2008) Natural history of brain arteriovenous malformations: a long-term follow-up study of risk of hemorrhage in 238 patients. *Neurosurgery* 63(5):823–829
16. Kelly AG, Holloway RG (2010) Health state preferences and decision-making after malignant middle cerebral artery infarctions. *Neurology* 75(8):682–687

17. Kim H, McCulloch CE, Johnston SC, Lawton MT, Sidney S, Young WL (2010) Comparison of 2 approaches for determining the natural history risk of brain arteriovenous malformation rupture. *Am J Epidemiol* 171(12):1317–1322
18. Kim H, Al-Shahi Salman R, McCulloch CE, Stapf C, Young WL, MARS Coinvestigators (2014) Untreated brain arteriovenous malformation: patient-level meta-analysis of hemorrhage predictors. *Neurology* 83(7):590–597
19. Korja M, Bervini D, Assaad N, Morgan MK (2014) Role of surgery in the management of brain arteriovenous malformations: prospective cohort study. *Stroke* 45(12):3549–3555
20. Laakso A, Dashti R, Seppänen J, Juvela S, Väärt K, Niemelä M, Sankila R, Hernesniemi JA (2008) Long-term excess mortality in 623 patients with brain arteriovenous malformations. *Neurosurgery* 63(2):244–253
21. Laakso A, Dashti R, Juvela S, Isarakul P, Niemelä M, Hernesniemi J (2011) Risk of hemorrhage in patients with untreated Spetzler–Martin grade IV and V arteriovenous malformations: a long-term follow-up study in 63 patients. *Neurosurgery* 68(2):372–377
22. Lawton MT, Du R, Tran MN, Achrol AS, McCulloch CE, Johnston SC, Quinnine NJ, Young WL (2005) Effect of presenting hemorrhage on outcome after microsurgical resection of brain arteriovenous malformations. *Neurosurgery* 56(3):485–493, discussion 485–93
23. Meling TR, Proust F, Gruber A, Niemela M, Regli L, Roche PH, Vajkoczy P (2014) On apples, oranges, and ARUBA. *Acta Neurochir (Wien)* 156(9):1775–1779
24. Mohr JP, Parides MK, Stapf C, Moquete E, Moy CS, Overbey JR, Al-Shahi Salman R, Vicaut E, Young WL, Houdart E, Cordonnier C, Stefani MA, Hartmann A, von Kummer R, Biondi A, Berkefeld J, Klijn CJ, Harkness K, Libman R, Barreau X, Moskowitz AJ, international ARUBA investigators (2014) Medical management with or without interventional therapy for unruptured brain arteriovenous malformations (ARUBA): a multicentre, non-blinded, randomised trial. *Lancet* 383(9917):614–621
25. Ondra SL, Troupp H, George ED, Schwab K (1990) The natural history of symptomatic arteriovenous malformations of the brain: a 24-year follow-up assessment. *J Neurosurg* 73(3):387–391
26. Pierot L, Cognard C, Spelle L (2004) Cerebral arteriovenous malformations: evaluation of the hemorrhagic risk and its morbidity. *J Neuroradiol* 31(5):369–375
27. Post PN, Stiggelbout AM, Wakker PP (2001) The utility of health states after stroke: a systematic review of the literature. *Stroke* 32:1425–1429
28. Rutledge WC, Abula AA, Nelson J, Halbach VV, Kim H, Lawton MT (2014) Treatment and outcomes of ARUBA-eligible patients with unruptured brain arteriovenous malformations at a single institution. *Neurosurg Focus* 37(3):E8
29. Sahlein DH, Mora P, Becske T, Huang P, Jafar JJ, Connolly ES, Nelson PK (2014) Features predictive of brain arteriovenous malformation hemorrhage: extrapolation to a physiologic model. *Stroke* 45(7):1964–1970
30. Stapf C, Mast H, Sciacca RR, Choi JH, Khaw AV, Connolly ES, Pile-Spellman J, Mohr JP (2006) Predictors of hemorrhage in patients with untreated brain arteriovenous malformation. *Neurology* 66(9):1350–1355
31. van Beijnum J, Lovelock CE, Cordonnier C, Rothwell PM, Klijn CJ, Al-Shahi Salman R, SIVMS Steering Committee and the Oxford Vascular Study (2009) Outcome after spontaneous and arteriovenous malformation-related intracerebral haemorrhage: population-based studies. *Brain* 132(Pt 2):537–543
32. van Beijnum J, van der Worp HB, Buis DR, Al-Shahi Salman R, Kappelle LJ, Rinkel GJ, van der Sprenkel JW, Vandertop WP, Algra A, Klijn CJ (2011) Treatment of brain arteriovenous malformations: a systematic review and meta-analysis. *JAMA* 306(18):2011–2019
33. Yamada S, Takagi Y, Nozaki K, Kikuta K, Hashimoto N (2007) Risk factors for subsequent hemorrhage in patients with cerebral arteriovenous malformations. *J Neurosurg* 107(5):965–972