See the corresponding editorial in this issue, pp 875–877.

J Neurosurg 121:878–890, 2014

Surgery for unruptured arteriovenous malformations of the brain is better than conservative management for selected cases: a prospective cohort study

Clinical article

David Bervini, M.Adv.Surg.,[1] Michael Kerin Morgan, M.D.,[1] Elizabeth Anne Ritson, M.B.B.S.,[2] and Gillian Heller, Ph.D.[3]

[1]Australian School of Advanced Medicine, [2]Macquarie University Hospital, and [3]Statistics Department, Macquarie University, Sydney, New South Wales, Australia

Object. The aim of this study was to identify patients who are likely to benefit from surgery for unruptured brain arteriovenous malformations (ubAVMs).

Methods. The authors' database was interrogated for the risk and outcome of hemorrhage after referral and the outcome from surgery. Furthermore, the outcome from surgery incorporated those cases excluded from surgery because of perceived greater risk (sensitivity analysis). Finally, a comparison was made for the authors' patients between the natural history and surgery. Data were collected for 427 consecutively enrolled patients with ubAVMs in a database that included patients who were conservatively managed. Kaplan-Meier analysis was performed on patients observed for more than 1 day to determine the risk of hemorrhage. Variables that may influence the risk of first hemorrhage were assessed using Cox proportional hazard regression models and Kaplan-Meier life table analyses from referral until the first occurrence of the following: hemorrhage, treatment, or last review. The outcome from surgery (leading to a new permanent neurological deficit with last review modified Rankin Scale [mRS] score > 1) was determined. Further sensitivity analysis was made to predict risk from surgery for the total ubAVM cohort by incorporating outcomes of surgical cases as well as cases excluded from surgery because of perceived risk, and assuming an adverse outcome for these excluded cases.

Results. A total of 377 patients with a ubAVM were included in the analysis of the risk of hemorrhage. The 5-year risk of hemorrhage for ubAVM was 11.5%. Hemorrhage resulted in an mRS score > 1 in 14 cases (88% [95% CI 63%–98%]). Patients with Spetzler-Ponce Class A ubAVMs treated by surgery (n = 190) had a risk from surgery of 1.6% (95% CI 0.3%–4.8%) for a permanent neurological deficit leading to an mRS score > 1 and 0.5% (95% CI < 0.1%–3.2%) for a permanent neurological deficit leading to an mRS score > 2. Patients with Spetzler-Ponce Class B ubAVMs treated by surgery (n = 107) had a risk from surgery of 14.0% (95% CI 8.6%–22.0%) for a permanent neurological deficit leading to an mRS score > 1. Sensitivity analysis of Spetzler-Ponce Class B ubAVMs, including those in patients excluded from surgery, showed that the true risk for surgically eligible patients may have been as high as 15.6% (95% CI 9.9%–23.7%) for mRS score > 1, had all patients who were perceived to have a greater risk experienced an adverse outcome. Patients with Spetzler-Ponce Class C ubAVMs treated by surgery (n = 44) had a risk from surgery of 38.6% (95% CI 25.7%–53.4%) for a permanent neurological deficit leading to an mRS score > 1. Sensitivity analysis of Class C ubAVMs, including those harbored by patients excluded from surgery, showed that the true risk for surgically eligible patients may have been as high as 60.9% (95% CI 49.2%–71.5%) for mRS score > 1, had all patients who were perceived to have a greater risk experienced an adverse outcome.

Conclusions. Surgical outcomes for Spetzler-Ponce Class A ubAVMs are better than those for conservative management.

(http://thejns.org/doi/abs/10.3171/2014.7.JNS132691)

Key Words • **brain** • **arteriovenous malformation** • **natural history** • **Cox regression** • **Kaplan-Meier** • **surgery** • **prospective cohort** • **vascular disorders**

The risk of hemorrhage from unruptured brain arteriovenous malformations (ubAVMs) is approximately 2.2% per year.[9] Even though a number of risk factors have been proposed that may modify this overall rate,[2–4,8,10–12,21,22,27–30,33] an analysis of the literature shows that recent diagnosis, deep location, and associated aneurysms may be associated with an increased risk of future hemorrhage.[9] Presentation with hemorrhage is also a reported risk factor[3,4,7,8,10–12,21,28,31,33] but does not relate to our study looking at only ubAVMs. The cumulative risk of first hemorrhage over 20 years has been reported to be 29%.[11]

The consequence of a hemorrhage occurring in a diagnosed ubAVM while under surveillance is significant. Mortality of 6%–29%, permanent morbidity of 16%–35%, and combined morbidity and mortality of 41%–85% have been reported.[2–4,20]

Abbreviations used in this paper: ARUBA = A Randomized Trial of Unruptured Brain Arteriovenous Malformations; AVM = arteriovenous malformation; bAVM = brain AVM; DSA = digital subtraction angiography; mRS = modified Rankin Scale; RCT = randomized controlled trial; ubAVM = unruptured brain AVM.

The risk from surgery for brain AVMs has been stratified by the Spetzler-Martin grading system using 3 components of the AVM: size, deep venous drainage, and eloquent location.[5,13,23,25,26] The importance of this grading system is to assist in selection of cases with a low risk of permanent adverse outcomes from surgery. It has been recommended by Spetzler and Ponce that the grading system can best be reduced to 3 tiers: Spetzler-Martin Grades I and II (Spetzler-Ponce Class A), Spetzler-Martin Grade III (Spetzler-Ponce Class B), and Spetzler-Martin Grades IV and V (Spetzler-Ponce Class C).[26] This risk has been reported to be 8% in a combined series for Spetzler-Ponce Class A ubAVMs and no greater than 1% in 3 series.[26] Some series reported the lack of impact of size or eloquent location of AVMs on surgical outcome.[14,24] This may be explained by cohort surgical series that do not take into consideration patients at high risk because they have been excluded from surgical treatment. Davidson and Morgan attempted to account for the patients who had been excluded from surgical treatment and concluded that all the variables of the Spetzler-Martin grading system were of importance and that the Spetzler-Martin grading system was a reliable way of stratifying risks from surgery.[5] The principle for this 3-tier grading is based upon series incorporating both ruptured and unruptured brain AVMs (bAVMs). The application of the Spetzler-Martin grading system for risk from surgery is likely reasonable. However, no large series of ubAVMs report on the application of the Spetzler-Martin grading system in predicting surgical outcome to date. We showed that the risks reported for outcome for surgery for Spetzler-Ponce Class A ubAVMs could be generalized to all patients suitable for surgery with Spetzler-Ponce Class A ubAVMs (both operated and unoperated) due to the very high proportion of patients treated by surgery, whereas the surgical series results for Spetzler-Ponce Class B and Spetzler-Ponce Class C ubAVMs could not be generalized due to selection bias (that is, exclusion of high-risk cases in surgical series). This bias relates to patients excluded from surgery because of perceived surgical risk.[5] If this number is a large percentage of the group as a whole, the surgical risk reported will underestimate the risks for all patients with similar Spetzler-Ponce class ubAVMs.

Because of the complexity of potential risks of first hemorrhage, the variability in outcomes of management, and the perceived absence of compelling data from case series, A Randomized Trial of Unruptured Brain Arteriovenous Malformations (ARUBA) was undertaken. Within ARUBA, 7.9% (10 patients) of the medical management arm experienced death or stroke compared with 35% (34 patients) of the interventional therapy arm over 33 months with a relative risk of 0.35 (95% CI 0.19–0.65).[1] This study was performed to "compare the risk of death and symptomatic stroke in patients with an unruptured brain arteriovenous malformation who are allocated to either medical management alone or medical management with planned efforts at eradication of the brain arteriovenous malformation with interventional therapy."[17] This interventional therapy included some surgery for 16% (the sole modality in 4% of cases), radiotherapy (presumably focused irradiation) in 26%, and some contribution by embolization in 40% (the sole modality in 26% of cases).[17]

Although ARUBA was initially aimed and powered to recruit 800 patients, the study was ultimately analyzed for a total of 223 patients from 39 centers. The difficulty of recruitment encountered with ARUBA is unlikely to be overcome with future randomized controlled trials (RCTs) due to the need for "ethical equipoise" and the increasing knowledge of the natural history of ubAVMs, the low surgical risks for Spetzler-Ponce Class A ubAVMs, and the high surgical risks for Spetzler-Ponce Class C ubAVMs. Therefore, a role remains for large cohort series from prospectively collected databases (with enough information for the selection bias available to the reader) to provide evidence to answer the question, "Can treatment be superior to nontreatment for ubAVM?"

We performed an analysis of a prospectively collected database of ubAVMs for both the natural history of hemorrhage and the risk from surgery. The database included patients who underwent surgery and those who were conservatively managed. We performed a sensitivity analysis to include how the patients who did not undergo surgery might have influenced the predicted outcome from surgery for all cases of similar Spetzler-Ponce class ubAVMs had they undergone surgery and had an adverse outcome from surgery. The initial recommendation of the surgeon and the decision made by the patient were recorded. The risk from surgery for those patients recommended for surgery but who were treated elsewhere or refused recommended management is unlikely to have changed the risk occurring in our analyzed series of patients undergoing surgery. However, for those patients recommended by the surgeon for conservative treatment because of the perceived risk from surgery, predicted outcomes (if surgery had been performed) could be expected to be worse than for those with similar Spetzler-Ponce class ubAVMs undergoing surgery. Although age and some comorbidity are not necessarily a barrier for surgical treatment, for the purpose of the sensitivity analysis in this report, we considered patients younger than 65 years and without significant comorbidity as eligible for surgery. These eligible patients were incorporated into the sensitivity analysis to improve the external validity (generalizability) of the reported risk from surgery.

A limitation of our study is that this is a prospective cohort study and patients were not randomly chosen for surgery versus conservative management. However, we have attempted to provide sufficient information to understand how this may have impacted outcome, analysis, and conclusions.

Methods

Patient Population

This study was approved by the Macquarie University Human Ethics Committee and was performed in accordance with institutional ethics committee guidelines. A prospectively collected database of the senior author (M.K.M.) of consecutive patients who harbored bAVMs was retrospectively analyzed for the years 1989 to September 2013. The responsibility for entry into the database was that of the senior author. However, the database

was accessible to residents, fellows, and occupational therapists at the time of assessment and follow-up. The database contained demographic, clinical, radiological, and treatment-related information. Patients were included if they were confirmed to have a ubAVM on MRI, CT angiography, or digital subtraction angiography (DSA), and if they had at least 1 follow-up review after the initial referral. The Spetzler-Ponce class was allocated when sufficient radiological detail had been obtained to grade the ubAVM and was allocated prior to surgery. Hemorrhage, in those followed to establish the natural history, was considered a new neurological deficit if there was a radiological confirmation of hemorrhage and it could be related to the ubAVM. The adverse events from surgery were considered to be new permanent neurological deficits (assigned within the first 6 weeks of surgery) with a modified Rankin Scale (mRS) score > 1 (assigned at last follow-up consultation) due to preoperative embolization or surgery. The mRS score assigned to each patient was subject to open access to fellows, occupational therapists, and other neurosurgeons on follow-up consultations.

Risk of Hemorrhage for Untreated ubAVMs

For the study of the risk of hemorrhage, all patients with a ubAVM irrespective of management plan were analyzed. Patients were excluded if they had only 1 contact date, if they were treated on the same day of referral, if they did not have a parenchymal bAVM, if they had a history of hemorrhage from the bAVM, or if they presented with hemorrhage from the bAVM. For the Kaplan-Meier analysis of the risk of hemorrhage for this study group, the initial date was taken as the first of either the available date of referral or first consultation. The event was hemorrhage caused by the bAVM (confirmed by CT scan or MRI). In the absence of an event, the cases were censored at the first of either the first date of treatment (by embolization, focused irradiation, or surgery) or last follow-up. Analyzed ubAVM characteristics were 1) presentation with and without seizure; 2) presentation with and without neurological deficits (unrelated to seizure or hemorrhage); 3) presence or absence of aneurysm (intranidal or located on feeding arteries) on initial DSA; 4) age (as a continuous variable); 5) supratentorial versus infratentorial location; 6) deep (either brainstem or bAVM with no pial surface) versus superficial location; 7) presence or absence of exclusive deep venous drainage; 8) maximum size (as a continuous variable); and 9) sex.

Risk From Surgery for ubAVMs

The outcomes from surgery leading to a new neurological deficit with last review mRS score > 1 (as well as mRS score > 2) was determined for ubAVMs using the Spetzler-Ponce grading system. Analysis was first made for patients undergoing surgery. In addition, a sensitivity analysis was performed incorporating patients undergoing surgery with the addition of eligible patients (< 65 years and without significant comorbidity) who were not surgically treated because of perceived risk from surgery (as recorded at the time of the initial management decision). These added patients who did not undergo surgery were assumed to have an adverse outcome for the purpose of the sensitivity analysis. The surgery group included patients who had preoperative embolization. Adverse outcomes attributed to embolization were included as surgical adverse events.

Statistical Analysis

Statistical analysis was performed using Prism software (version 6, GraphPad Software Inc.) and IBM SPSS Statistics (version 21, IBM Corp.). For the risk of hemorrhage from untreated ubAVMs, univariate Cox regression was performed for each variable to calculate the hazard ratios and 95% confidence intervals. For the risk from surgery analysis, comparison by Spetzler-Ponce groups was performed using the Pearson chi-square test for categorical variables and ANOVA for continuous variables. A statistical significance level of $p < 0.05$ was used throughout.

Results

From 760 consecutive patients with bAVMs, 427 patients with ubAVMs were identified. The other 333 patients had a history of hemorrhage. The flowchart of analysis is provided in Fig. 1.

Risk of Hemorrhage for ubAVMs

Of the 427 patients with a ubAVM, 377 were analyzed for the risk of hemorrhage. Fifty patients were excluded as they were either treated on the day of referral or were reviewed on only 1 occasion. The mean time interval between initial referral and censoring (that is, the first of either the 1st day of treatment or last day of follow-up) or event (hemorrhage) was 270 days (range 1–5840 days), for a total of 279 case-years of follow-up.

Hemorrhage after referral, unrelated to treatment, occurred in 16 patients (Table 1). The overall outcomes from hemorrhage were a permanent downgrade in function to an mRS score > 1 in 88% (95% CI 63%–98%; 14 of 16 patients) and an mRS score > 2 in 69% (95% CI 44%–86%; 11 of 16 patients), including death in 31% (95% CI 14%–56%; 5 of 16 patients). The baseline characteristics for the patients with a ubAVM and the variables examined are reported in Table 2. For the entire group, the number of patients at risk had declined to 20 by 5 years. The cumulative rate of ubAVM hemorrhage was 8.1% at 1 year using the Kaplan-Meier product-limit method and 5.7% if calculated as the number of patients with new hemorrhage during follow-up divided by case-years of follow-up. At 5 years, the cumulative rate of ubAVM hemorrhage was 11.5% using the Kaplan-Meier product-limit method. This gives an annualized risk of first hemorrhage of 2.3% over the first 5 years. The cumulative risk of hemorrhage for different times and the number of cases at risk from the study cohort can be seen in Table 3 along with a literature review. The risk for the first 17 years from referral can be seen in Fig. 2.

Influence of Variables in Predicting Hemorrhage of ubAVMs

Of the 9 variables examined by univariate Cox regression, deeply located (brainstem or not presenting on

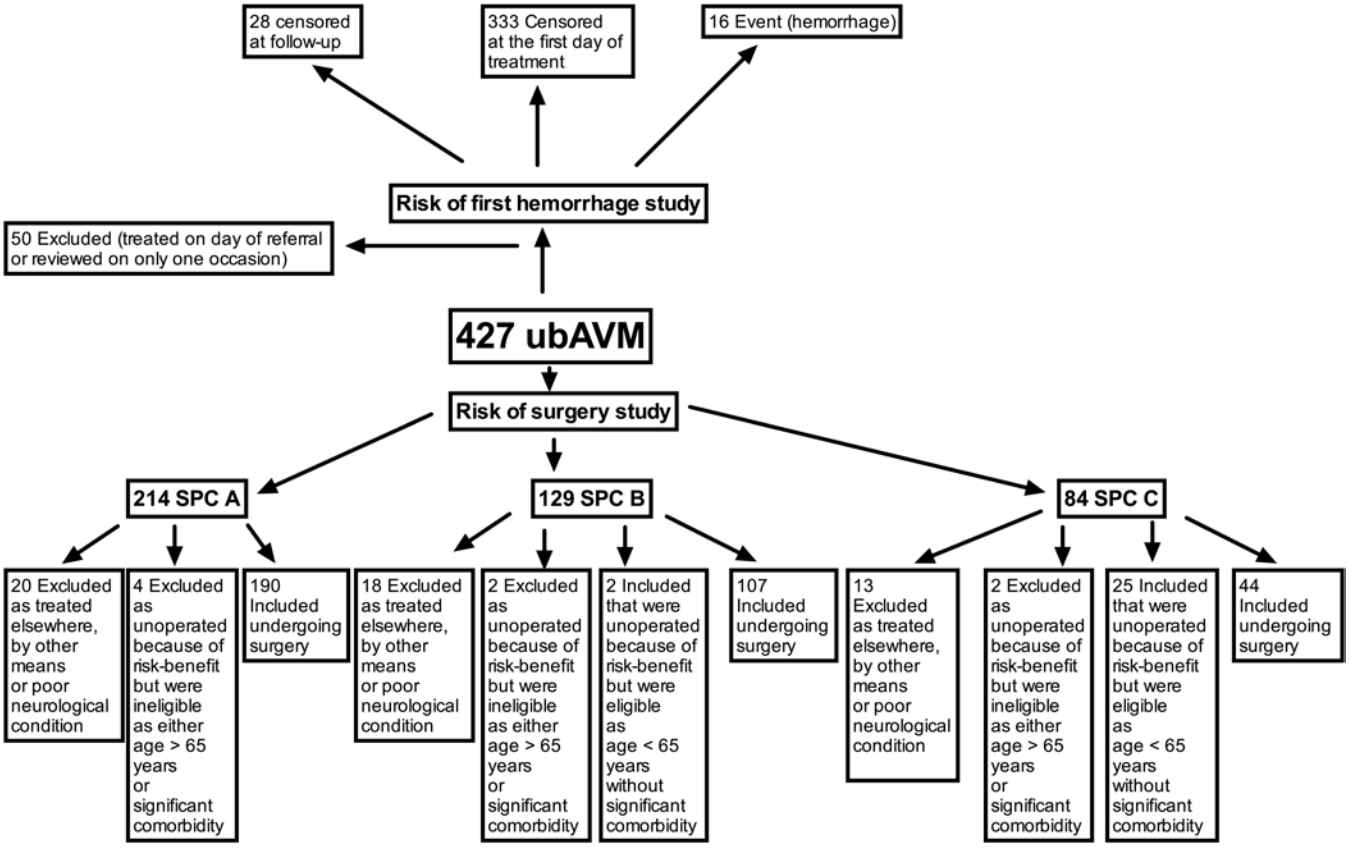


Fig. 1. Flowchart analysis. SPC = Spetzler-Ponce Class.

any pial surface) ubAVMs had a significantly shorter time to hemorrhage (p = 0.032, HR 3.78 [95% CI 1.12–12.72]) (Table 2). However, the significance of this result needs to be treated with caution due to the number of variables examined (9) and the low number of events (4) occurring in the deep ubAVM group. Aneurysms were known to be present in 32% (119 of 377) of cases. This was not significant in predicting subsequent hemorrhage (p = 0.98). None of the 3 variables contributing to the Spetzler-Ponce class was significant in predicting the time to hemorrhage.

Sensitivity Analysis of the Risk From Surgery (With or Without Preoperative Embolization)

Of the 427 patients with a ubAVM, 368 were included in this analysis. Fifty-nine patients were excluded because they were treated by embolization only or were treated elsewhere (including those treated by focused irradiation). There was no case in which surgery was planned but not performed due to subsequent major adverse events from diagnostic DSA or embolization. Of these 368 patients, 27 eligible patients (< 65 years and no significant comorbidity) did not undergo surgery because of perceived risk of operative complications. There were no eligible patients excluded from surgery for a Spetzler-Ponce Class A ubAVM. For Spetzler-Ponce Class B ubAVMs, 2 eligible patients did not undergo surgery because of perceived risk of operative complications. For Spetzler-Ponce Class C ubAVMs, 25 eligible patients did not undergo surgery because of perceived risk of operative complications. The comparison between the results from surgery and that for the sensitivity analysis is shown in Fig. 3.

For patients with Spetzler-Ponce Class A ubAVMs treated by surgery, 1.6% (95% CI 0.3%–4.8%; 3 of 190 patients) experienced a new permanent neurological deficit from surgery with an mRS score > 1 at last follow-up. For Spetzler-Ponce Class A ubAVMs, new permanent neurological deficits with an mRS score > 2 at last follow-up were caused by surgery in 0.5% (1 of 190 [95% CI < 0.1%–3.2%]). Five patients with Spetzler-Ponce Class A ubAVMs were recommended for conservative management. These patients were either elderly (4 patients, 69–78 years) or had a significant comorbidity (1 patient with terminal liver failure). There were no eligible patients excluded from surgery because of perceived risk for Spetzler-Ponce Class A ubAVMs. The breakdown of the characteristics of cases as analyzed is presented in Table 4. The median time between referral and surgery for Spetzler-Ponce Class A ubAVMs was 27 days (25th percentile and 75th percentile of 10 and 60 days, respectively).

For patients with Spetzler-Ponce Class B ubAVMs treated by surgery, 14.0% (95% CI 8.6%–22.0%; 15 of 107 patients) experienced a new permanent neurological deficit with an mRS score > 1 at last follow-up from either embolization (2 cases) or surgery (14 cases; 13.1% [95% CI 7.8%–20.9%], including 1 patient who experienced 2 adverse events related to both preoperative embolization and surgery). For Spetzler-Ponce Class B ubAVMs treated by surgery, 2.8% (95% CI 0.6%–8.3%; 3 of 107

TABLE 1: Patients experiencing their first bAVM hemorrhage after referral*

Case No.	Age (yrs), Sex	Spetzler-Martin Grade, Side & Location	Neurological Presentation	Days Btwn Referral & 1st Hemorrhage	Outcome mRS Score	Complication Due to Surgery Leading to mRS Score >1
1	76, M	I, rt temporal	normal	6	0	none
2	13, M	II, lt cerebellum	normal, seizure	8	2	none
3	45, M	III, lt fronto-parietal	normal, seizure	14	6	NA
4	53, M	IV, lt basal ganglia	normal	56	3	none
5	30, M	II, rt parietal	normal, seizure	137	6	NA
6	17, M	II, rt temporal	normal, seizure	194	3	none
7	42, F	III, rt frontal	normal, seizure	218	6	NA
8	36, F	III, rt frontal	normal	330	6	NA
9	43, F	IV, lt parietal	mild hemiparesis & dysphasia	1057	3	none
10	13, F	IV, lt thalamic	normal	2195	2	NA
11	56, F	III, lt frontal	mild dysphasia	2436	1	NA
12	35, M	V, pons	hemiparesis & hemiparesthesia	2607	2	NA
13	63, F	III, lt fronto-parietal	hemiparesis	2917	4	NA
14	54, M	III, lt parietal	normal	3065	3	NA
15	44, M	III, rt frontal	normal	3086	3	NA
16	44, M	II, lt cerebellum	normal	3263	6	NA

* NA = not applicable because surgery was not performed.

patients) experienced a new permanent neurological deficits with an mRS > 2 at last follow-up from either embolization (1 case) or surgery (3 cases; 2.8% [95% CI 0.6%–8.3%], including 1 patient who experienced 2 adverse events related to both preoperative embolization and surgery). Twenty-two patients with Spetzler-Ponce Class B ubAVMs were recommended for conservative management or were treated elsewhere. Of these, 2 (1.8% of 109 combined patients at increased risk and patients undergoing surgery) who were eligible for surgery were excluded because of perceived increased risk from surgery. The breakdown of the characteristics of patients as analyzed is presented in Table 4. Had patients who were excluded because of perceived risk from surgery undergone surgery and experienced an adverse outcome, the risk of a new permanent neurological deficit with an mRS score > 1 would have been 15.6% (95% CI 9.9%–23.7%; 17 of 109 patients) and for an mRS score > 2 it would have been 4.6% (95% CI 1.7–10.6%; 5 of 109 patients). The median time between referral and surgery for Spetzler-Ponce Class B was 38 days (25th percentile and 75th percentile of 9 and 94 days, respectively).

For patients with Spetzler-Ponce Class C ubAVMs treated by surgery, 38.6% (17 of 44 [95% CI 25.7–53.4%]) experienced a new permanent neurological deficit with an mRS score > 1 at last follow-up from either embolization (2 patients) or surgery (15 patients; 34.1% [95% CI 21.8%–48.9%]).

For patients with Spetzler-Ponce Class C ubAVMs treated by surgery, 15.9% (7 of 44 [95% CI 7.6%–29.7%]) experienced new permanent neurological deficits with an mRS score > 2 at last follow-up from either embolization (2 patients) or surgery (5 patients; 11.4% [95% CI 4.5%–24.4%]). Forty patients with Spetzler-Ponce Class C ubAVMs were recommended for conservative management or were treated elsewhere. Of these, 25 patients who were eligible for surgery (36.2% of 69 combined patients with increased risk and patients undergoing surgery) were excluded because of perceived increased risk from surgery. The breakdown of the characteristics of cases as analyzed is presented in Table 4. Had patients excluded because of perceived risk from surgery undergone surgery and experienced an adverse outcome, the risk of a new permanent neurological deficit with an mRS score > 1 would have been 60.9% (95% CI 49.2%–71.5%; 42 of 69 patients) and for mRS score > 2 would have been 46.4% (95% CI 36.5%–59.4%; 32 of 69 patients). The median time between referral and surgery for Spetzler-Ponce Class C was 67 days (25th percentile and 75th percentile of 36 and 176 days, respectively).

Complete bAVM resection was confirmed by postoperative DSA in 333 of 341 patients (97.7% [95% CI 95.4%–98.9%]). Three patients who had a persisting bAVM underwent further treatment to achieve DSA-confirmed complete resection by focused irradiation in 2 patients and endovascular treatment in 1 patient. Five patients died and did not undergo postoperative DSA. All patients with Spetzler-Ponce Class A ubAVMs (except for the patient who died of myocardial infarction during surgery) had confirmed complete resection of the bAVM by postoperative DSA.

Risk of Hemorrhage for Untreated ubAVMs Compared With the Sensitivity Analysis of the Risk From Surgery

Superimposing upon the Kaplan-Meier curve (of the risk of hemorrhage) the risk from surgery, the crossover occurred within 5 months for Spetzler-Ponce Class A

TABLE 2: Characteristics of 377 patients with ubAVMs with a recorded referral date and subsequent date of hemorrhage or censoring (the earliest of last clinical review or treatment)*

Variable	No. of Patients w/ Variable (%)	% of Group Developing Hemorrhage After Referral (actual no.)	p Value†	HR (95% CI)‡
sex				0.83 (0.31–2.25)
M	198 (52.5)	4.5 (9 of 198)	0.711	
F	179 (47.5)	3.9 (7 of 179)		
age in yrs (mean 37.4 ± 15.6 yrs)			0.264 (continuous variable)	1.02 (0.99–1.05)
0–19	49 (13.0)	6.1 (3 of 49)		
20–39	172 (45.6)	1.7 (3 of 172)		
40–59	120 (31.8)	6.7 (8 of 120)		
60–79	35 (9.3)	5.7 (2 of 35)		
>79	1 (0.3)	0 (0 of 1)		
location			0.159	2.50 (0.70–8.94)
infratentorial	23 (6.1)	13 (3 of 23)		
supratentorial	354 (93.9)	3.7 (13 of 354)		
location			0.032	3.78 (1.12–12.72)
deep§	32 (8.5)	12.5 (4 of 32)		
superficial	345 (91.5)	3.5 (12 of 345)		
maximum size			0.282 (continuous variable)	0.85 (0.63–1.14)
<3 cm	126 (33.4)	1.6 (2 of 126)		
3–6 cm	217 (57.6)	6.0 (13 of 217)		
>6 cm	34 (9.0)	2.9 (1 of 34)		
deep venous drainage (exclusive)			0.455	1.62 (0.46–5.72)
yes	42 (11.1)	7.1 (3 of 42)		
no	335 (88.9)	3.9 (13 of 335)		
presentation w/ seizures			0.479	0.70 (0.26–1.89)
seizures	196 (52.0)	3.6 (7 of 196)		
no seizures	181 (48.0)	5.0 (9 of 181)		
presentation w/ neurological deficit			0.161	2.05 (0.75–5.57)
neurological deficit	63 (16.7)	11.1 (7 of 64)		
no neurological deficit	314 (83.3)	2.9 (9 of 314)		
aneurysms (on initial DSA)			0.983	1.01 (0.35–2.93)
present	119 (31.6)	4.2 (5 of 119)		
absent	258 (68.4)	4.3 (11 of 258)		

* NA = not applicable.
† Univariate Cox regression.
‡ Univariate analysis.
§ Deep = brainstem or not located on a pial surface.

ubAVMs, between 8 and 9 years for Spetzler-Ponce Class B ubAVMs, and did not occur for Spetzler-Ponce Class C ubAVMs for outcomes with mRS score > 1 (Fig. 4). However, little reliance should be placed on the point of crossover if this is predicted to occur beyond 5 years because of the small number of patients remaining at risk at this time.

Superimposing upon the Kaplan-Meier curve (of the risk of hemorrhage) the risk from surgery, the crossover occurred before 5 months for Spetzler-Ponce Class A ubAVMs, between 6 and 8 months for Spetzler-Ponce Class B ubAVMs, and beyond 8 years for Spetzler-Ponce Class C ubAVMs for outcomes with mRS score > 2 (Fig. 4).

We further examined the relationship between the 95% confidence intervals for both the natural history and sensitivity analysis of surgery (Fig. 4). That is, for this analysis, we included both those patients who underwent surgery as well as those who were excluded from surgery because of risk although eligible (< 65 years and with no comorbidity). We wanted to know whether the upper 95% risk from surgery (that is, the lower 95% confidence interval of being free of adverse outcomes) crossed the lowest 95% risk of a hemorrhage causing a deficit (that is, the upper 95% confidence interval of being free of adverse outcomes). This was specifically performed for outcomes with mRS score > 1 and mRS score > 2. The upper 95%

TABLE 3: Risk of hemorrhage reported in the literature (case series reporting more than 25 ubAVM cases) as well as present series*

Authors & Year	Initial No. of ubAVM Cases at Risk	% 12-Mo Risk of 1st Hemorrhage	% 5-Yr Risk of 1st Hemorrhage	% Averaged Annualized Risk of 1st Hemorrhage From ubAVM	Yrs of Follow-Up to Which the Annual Risk Applies	Method of Calculation
Graf et al., 1983	66	2	14	2–3	20	Kaplan-Meier
Brown et al., 1988	168	1.3	8.5	2.3	15	Kaplan-Meier
Pollock et al., 1996	119	1.9†	9.5†	1.9	NA	patient-yr method
Halim et al., 2004	423	3	9	2	10	Kaplan-Meier
Stapf et al., 2006	340	1.3†	5‡	1.3	NA	Kaplan-Meier
Yamada et al., 2007	146	3.1†	15.5†	3.1	5	patient-yr method
Kim et al., 2007	781§	1.4†	7†	1.4	5	Kaplan-Meier
da Costa et al., 2009	420	3.6¶	18‡	3.6	5	patient-yr method
Hernesniemi et al., 2008	99	2.3†	10	2.3	5	patient-yr method
ARUBA, 2013[17]	125	2.2	12‡	2.3	5	Kaplan-Meier
present series	377	8.1	11.5	2.3	5	Kaplan-Meier

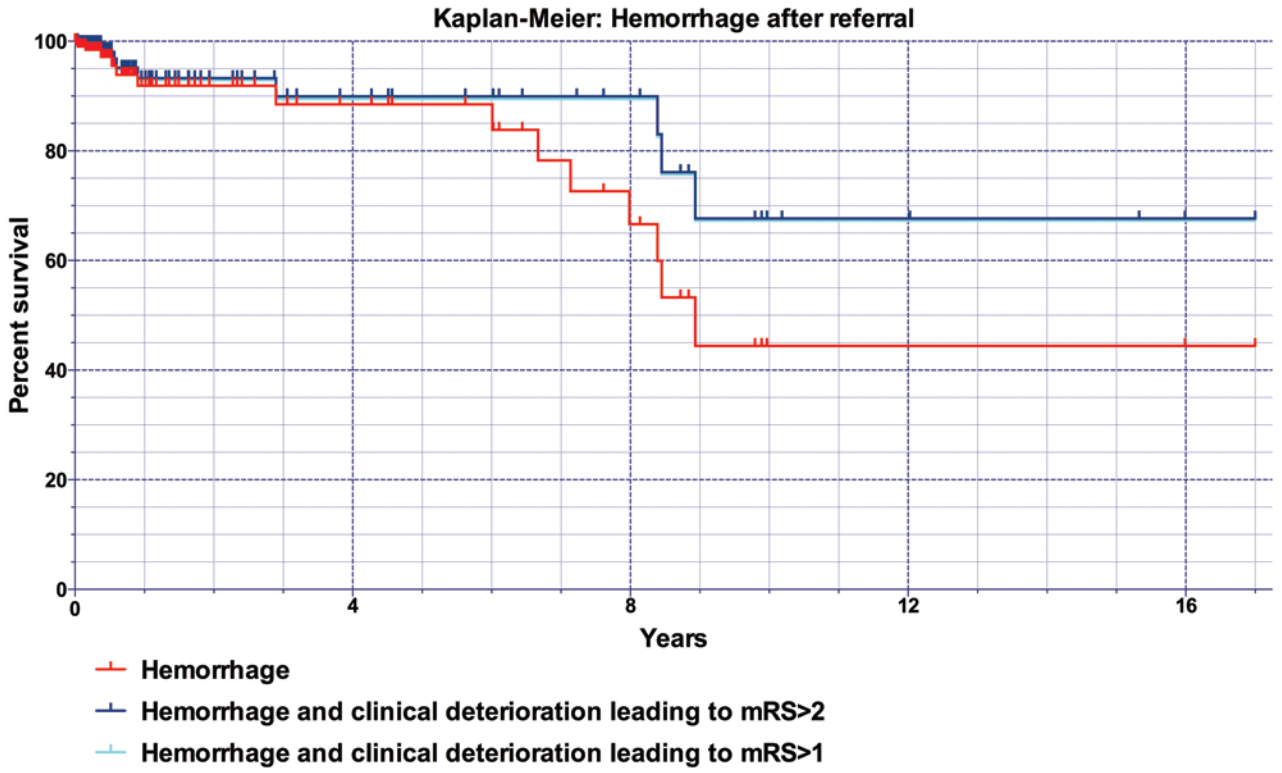
* NA = not available.
† Derived from the averaged annualized risk of first hemorrhage from ubAVM.
‡ Approximated from Kaplan-Meier figure provided in publication.
§ Some cases are likely to have been included in earlier report (Halim et al.).
¶ Seizure presentation.

confidence interval for the natural history (of hemorrhage leading to a permanent neurological deficit) and the lower 95% confidence interval of surgery (being free of adverse outcomes leading to a permanent neurological deficit) were superimposed to identify when the upper 90% confidence (combining the two 95% confidence intervals) of surgery risk crossed the natural history risk. The mRS score > 1 upper 95% confidence interval was crossed by the lower outcome Spetzler-Ponce Class A at 3065 days. Such crossing did not occur for either Spetzler-Ponce Class B or Spetzler-Ponce Class C ubAVMs. The mRS score > 2 upper 95% confidence interval was crossed by the lower outcome Spetzler-Ponce Class A ubAVMs at 1057 days. The mRS score > 2 upper 95% confidence interval was crossed by the lower outcome Spetzler-Ponce Class B at 3065 days. Such crossing did not occur for Spetzler-Ponce Class C ubAVMs.

Discussion

Our results showed that Spetzler-Ponce Class A ubAVMs treated by surgery had a better outcome than conservatively managed ubAVMs within a short period of time with a high rate of cure. Where the outcome is considered mRS score > 2, both surgically treated Spetzler-Ponce Class A and Spetzler-Ponce Class B ubAVMs had a better outcome than conservatively managed ubAVMs within a short period of time. Therefore, in this cohort study, it is reasonable to conclude that surgery can be superior to conservative management for a defined group of patients.

These findings are in stark contrast to the results of ARUBA, where treatment was reported to be significantly worse than conservative management for ubAVMs.[17] Although considered a high standard of evidence, for a multicentered RCT to be generalizable (that is, have external validity), the application of ethical equipoise must result in a sum of subjects reflective of the real world. The large number of centers agreeing to participate but failing to enroll patients either reflects these centers' inability to recruit patients (despite the selection of these centers for this capability) or an inability to apply ethical equipoise. A major difference in how ubAVMs were managed between our study and ARUBA was that our interventions analyzed were 100% surgery, with surgery alone as the sole interventional treatment in 84% of patients (285 of 341 patients; 56 patients underwent preoperative embolization); compared with ARUBA where surgery was performed in 16% (18 of 114) of interventions and surgery alone was the sole interventional treatment in 4% (5 of 114) of interventional cases. As such, ARUBA cannot be considered a study assessing the role of surgery for ubAVMs.[17] Furthermore, the claim from ARUBA that the "baseline characteristics of trial participants are much the same as those representative of population-based cohorts" is true for sex, age, and presentation (factors that are unlikely to impact upon treatment bias) but is not necessarily true for those characteristics that influence the risk of surgery. Comparing characteristics of ARUBA-enrolled patients with our patients reveals the following: Deep venous drainage was absent in 66% of ARUBA patients (95% CI, 59–72%), whereas it was absent in 89% of our patients (95% CI 85%–92%); Spetzler-Ponce Class C classification was present in 10% of ARUBA patients (95% CI 7%–15%), whereas it was present in 22% of our patients (95% CI 18%–27%); and AVM < 3 cm was present in 62% of ARUBA patients (95% CI 55%–68%), whereas it was present in 33% of our patients (95% CI 29%–38%). Although referral bias for complex ubAVMs may have occurred in our case series, the differences may also be explained by distortion of patients considered to



Years		Initial	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Number at risk	H	377	46	31	26	23	20	19	14	11	5	2	2	2	2	2	2	2	1
	H and mRS >2	377	48	33	26	23	20	19	16	14	8	5	4	4	3	3	3	2	1
	H and mRS>1	377	47	32	26	23	20	19	16	14	8	5	4	4	3	3	3	2	1

Fig. 2. Kaplan-Meier curves and numbers at risk for the 377 patients with bAVMs enrolled in the risk of hemorrhage study. H = hemorrhage.

meet clinical equipoise enrolled in ARUBA. Given that selection bias may have occurred in ARUBA, the generalizability of conclusions needs to be questioned. This justifies the continued examination of case series at this time.

Natural History

Because of the lower risk of hemorrhage from ubAVMs compared with those presenting with hemorrhage, concern has been raised as to whether treatment of ubAVMs is justified.[17] A meta-analysis found an annual ubAVM hemorrhage rate of 2.2% (95% CI 1.7%–2.7%).[9] Of interest for ubAVMs, the rate of hemorrhage has been found to be considerably higher during the 1st year after diagnosis.[11,12,33] In a prospective study from Japan, the rate of first hemorrhage was greater during the first 12 months after presentation (4.8%).[12] As there may be a nonlinear relationship between time from presentation and hemorrhage, the time from diagnosis to enrollment in prospective studies is important. As there was often a delay between referral and treatment, we used all our potential 377 patients with a ubAVM in the analysis of the risk of hemorrhage. Although our method using Kaplan-Meier product-limit method found an 8.1% 1st year risk of hemorrhage, when utilizing the method of these studies (calculated as the number of patients with hemorrhage during follow-up divided by case-years of follow-up) the risk of hemorrhage in our series is 5.7%. This is marginally greater than previously published series for the 1st year risk of hemorrhage. The 11.5% 5-year risk of first hemorrhage is similar to that reported in the literature (Table 3). The cumulative hemorrhage rate found in ARUBA at 5 years was estimated to be approximately 12% from the Kaplan-Meier figure provided. Considering the number at risk in our study at each stage of follow-up, we believe our

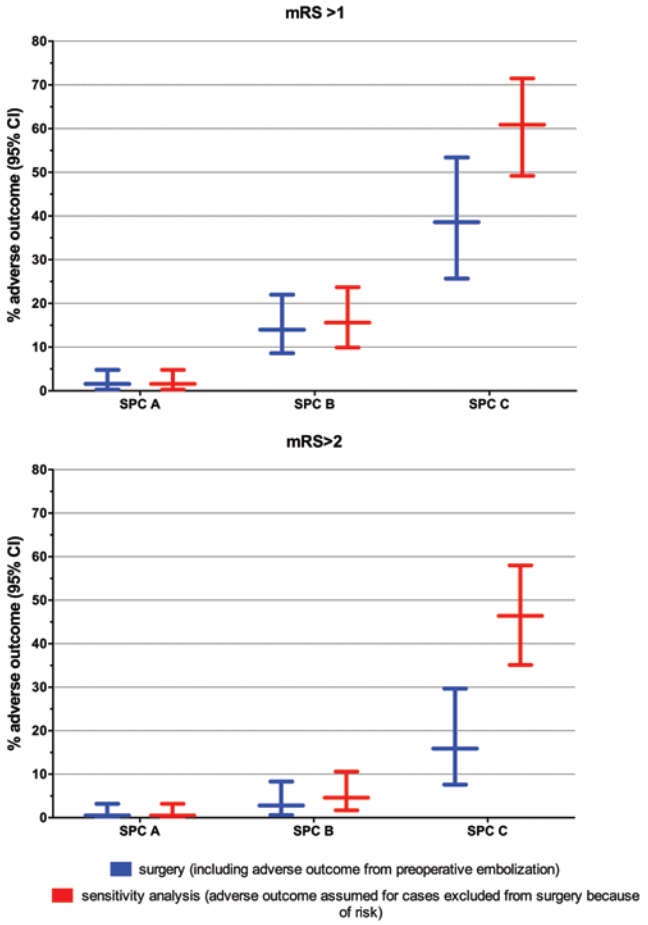


Fig. 3. Sensitivity analysis and comparison between the adverse outcomes from surgery for 341 ubAVMs and that projected if 27 cases excluded from surgery underwent surgery and experienced an adverse outcome.

results are reliable for the first 5 years from initial referral. However, Hernesniemi and colleagues, who provide the longest long-term analysis (with a mean of 13.5 years) of 99 ubAVMs, found a cumulative first hemorrhage risk of 10% and 29% at 5 and 20 years, respectively.[11] They excluded patients with less than 1 month of follow-up (which differs from our own analysis). On an annualized basis, our results suggest a risk of first hemorrhage of 2.3% per year over 5 years. This is within the range of literature estimates (Table 3) and is similar to 2.2% calculated by Gross and Du in their meta-analysis.[9]

Our finding that ubAVMs had a slightly greater risk of rupture in the first 12 months after diagnosis (Table 3) than previously reported may be explained by the inclusion of patients from the time of referral, capturing patients who otherwise would have been excluded if the commencement of the database had coincided with admission to hospital. That a higher rate of hemorrhage occurs early in some series may be explained by a small number of patients presenting with clinical symptoms due to changes within the ubAVM that alter the hemodynamics (for example, venous outflow stenosis or occlusion) that might predispose to hemorrhage.[6,15,16,32] Such changing hemodynamics would not be captured in most database interrogations. The importance of knowing the time from diagnosis in estimating the future risk needs to be considered.

The clinical consequence of hemorrhage for ubAVMs in our experience was significant, resulting in a permanent adverse outcome with mRS score > 2 in more than two-thirds (of these, nearly half resulted in death). This is in the range of outcomes reported in the literature. Of 77 patients who suffered hemorrhage, Crawford et al. reported a 25% mortality and 19% incidence of hemiparesis.[3] Brown and colleagues reported a similar 29% mortality and 16% morbidity from hemorrhage in follow-up.[2] Ondra and colleagues reported that 85% of 64 patients died or sustained major permanent morbidity.[20] Da Costa and colleagues reported 89 hemorrhages after enrollment to their bAVM database (both unruptured and ruptured bAVMs) for a 6% mortality and 35% significant permanent disability.[4] It is reasonable to assume that approximately half of those experiencing hemorrhage from a ubAVM will have a significant permanent deficit or fatal outcome.

Arranging a classification for ubAVMs according to characteristics that impact upon risk of hemorrhage is an appealing strategy. Stapf and colleagues identified a combination of a number of factors that may predict a high rate of hemorrhage, and the corollary was also proposed that in the absence of these factors the risk of hemorrhage is very low.[28] Our results suggest that such classification would have limited utility in predicting the risk of ubAVM hemorrhage during the first years after diagnosis for our cohort. In our cases, deep location had a weak predictive value and no other variable was significant.

Surgical Outcomes

We have previously reported the lower risk for surgery for Spetzler-Ponce Class A bAVMs compared with Spetzler-Ponce Class B and Spetzler-Ponce Class C bAVMs. Also, we previously reported that very few Spetzler-Ponce Class A bAVMs were not recommended for surgery due to perceived risks,[5] which differed from the higher grades where a number of cases were selected for conservative management because of the perceived risk from surgery. Therefore, to assess the generalizable risk from surgery for all Spetzler-Ponce Class B and Spetzler-Ponce Class C bAVMs, consideration needs to be made of those eligible patients who do not undergo surgery because of perceived risk from surgery. The 5 patients with Spetzler-Ponce Class A bAVMs recommended for conservative management were either elderly or had comorbidity suggesting an unlikelihood of benefit from surgery and were considered not eligible for surgery. Our findings that Spetzler-Ponce Class A ubAVMs treated by surgery had a new permanent neurological deficit (mRS score > 1 outcome) of 1.6% due to surgery can be generalized to all eligible cases (treated by surgery or not). With regard to Spetzler-Ponce Class B ubAVMs, 2 of 109 eligible patients (< 65 years and without significant comorbidity) were excluded due to a perceived higher risk from surgery. Had both of these cases been incorporated in the surgical outcomes and had an adverse outcome, 15.6% of these cases would have had an adverse outcome and in

TABLE 4: Characteristics of cases included in the surgical and in the sensitivity analysis groups*

Variable	Analyzed Groups	SPC A	SPC B	SPC C	p Value†
no. of cases	total operated & unoperated	214	129	84	
	total cases undergoing surgery w/ or w/o preop embolization	190	107	44	
features of surgical cases	mean pt age in yrs	39.5 ± 15.7	33.3 ± 13.4	37.0 ± 14.7	0.004
	mean ubAVM diameter in cm	2.7 ± 1.2	4.3 ± 1.5	5.9 ± 1.6	<0.001
	female	45.8% (87 of 190)	52.3% (56 of 107)	47.7% (21 of 44)	0.555
presentation of surgical cases	seizure	47.9% (91 of 190)	57.9% (62 of 107)	56.8% (25 of 44)	0.202
	neurological symptoms (other than seizure)	12.1% (23 of 190)	17.8% (19 of 107)	20.5% (9 of 44)	0.232
AVM features of surgical cases	eloquent	17.9% (34 of 190)	64.5% (69 of 107)	81.8% (36 of 44)	<0.001
	deep location	5.8% (11 of 190)	6.5% (7 of 107)	11.4% (5 of 44)	0.412
	exclusive deep venous drainage	7.4% (14 of 190)	10.3% (11 of 107)	18.2% (8 of 44)	0.089
	aneurysm	26.3% (50 of 190)	38.3% (41 of 107)	45.5% (20 of 44)	0.016
	infratentorial	5.8% (11 of 190)	6.5% (7 of 107)	4.5% (2 of 44)	0.892
SMG of surgical cases	I: % of SPC A	34.7% (66 of 190)	—	—	
	II: % of SPC A	65.3% (124 of 190)	—	—	
	III: % of SPC B	—	100% (107 of 107)	—	
	IV: % of SPC C	—	—	77.3% (34 of 44)	
	V: % of SPC C	—	—	22.7% (10 of 44)	
follow-up of surgical cases	mean mos following surgery	31.0 ± 36.3	34.9 ± 37.7	36.3 ± 36.1	0.566
adverse outcomes of treatment	mRS score 2	1.1% (2 of 190)	11.2% (12 of 107)	22.7% (10 of 44)	
	mRS score 3–5	—	1.9% (2 of 107)‡	9.1% (4 of 44)	
	dead	0.5% (1 of 190)	0.9% (1 of 107)	6.8% (3 of 44)	
	mRS score >1 w/in SMG subgroup (95% CI)	1.6% (0.3–4.8%)	14.0% (8.6–22.0%)	38.6% (25.7–53.4%)	
	mRS score >2 w/in SMG subgroup (95% CI)	0.5% (<0.1–3.2%)	2.8% (0.6–8.3%)	15.9% (7.6–29.7%)	
cause of adverse outcomes	preop embolization w/in SPC group	0% (0 of 11)	9.1% (2 of 22)‡	8.7% (2 of 23)	
	surgery	1.6% (3 of 190)	13.1% (14 of 107)‡	34.1% (15 of 44)	
excluded from surgery & sensitivity analysis	treated elsewhere or by other means or poor neurological condition	9.3% (20 of 214)	14.0% (18 of 129)	15.5% (13 of 84)	0.262
	ineligible because of age >65 yrs or comorbidities	1.9% (4 of 214)	1.6% (2 of 129)	2.4% (2 of 84)	
included in sensitivity analysis	unoperated cases due to surgical risk added to cases undergoing surgery	190	109	69	
assumption that all eligible cases would have adverse outcome for the purpose of sensitivity analysis	mRS score >1 including all eligible cases w/in SPC subgroup (95% CI)	1.6% (0.3–4.8%)	15.6% (9.9–23.7%)	60.9% (49.2–71.5%)	
	mRS score >2 including all eligible cases w/in SPC subgroup (95% CI)	0.5% (<0.1–3.2%)	4.6% (1.7–10.6%)	46.4% (35.1–58.0%)	
time from referral to surgery	median no. of days (25th–75th percentile)	27 (10–60)	38 (9–94)	67 (36–176)	

* Values in parentheses are number of cases (%) unless noted otherwise. Mean values are presented as the mean ± SD. pt = patient; SMG = Spetzler-Martin grade; SPC = Spetzler-Ponce class.

† Chi-square test for categorical variable and 1-way ANOVA test for continuous variables.

‡ One patient experienced 2 adverse events, related to both preoperative embolization and surgery.

4.6% of cases would this have led to an mRS score > 2. The results for Spetzler-Ponce Class C ubAVMs cannot be generalized due to the large number of potentially eligible patients (< 65 years and without significant comorbidity) excluded because of perceived higher risk from surgery. Had these patients been incorporated in the surgical outcomes and had an adverse outcome, the adverse outcome rate would be closer to 61%, which is greater than the 39% seen for those cases that were selected for surgery.

Despite the demonstration that the Spetzler-Martin grading system[25] is a good way of stratifying the risks from surgery, this has not been reported for ubAVMs be-

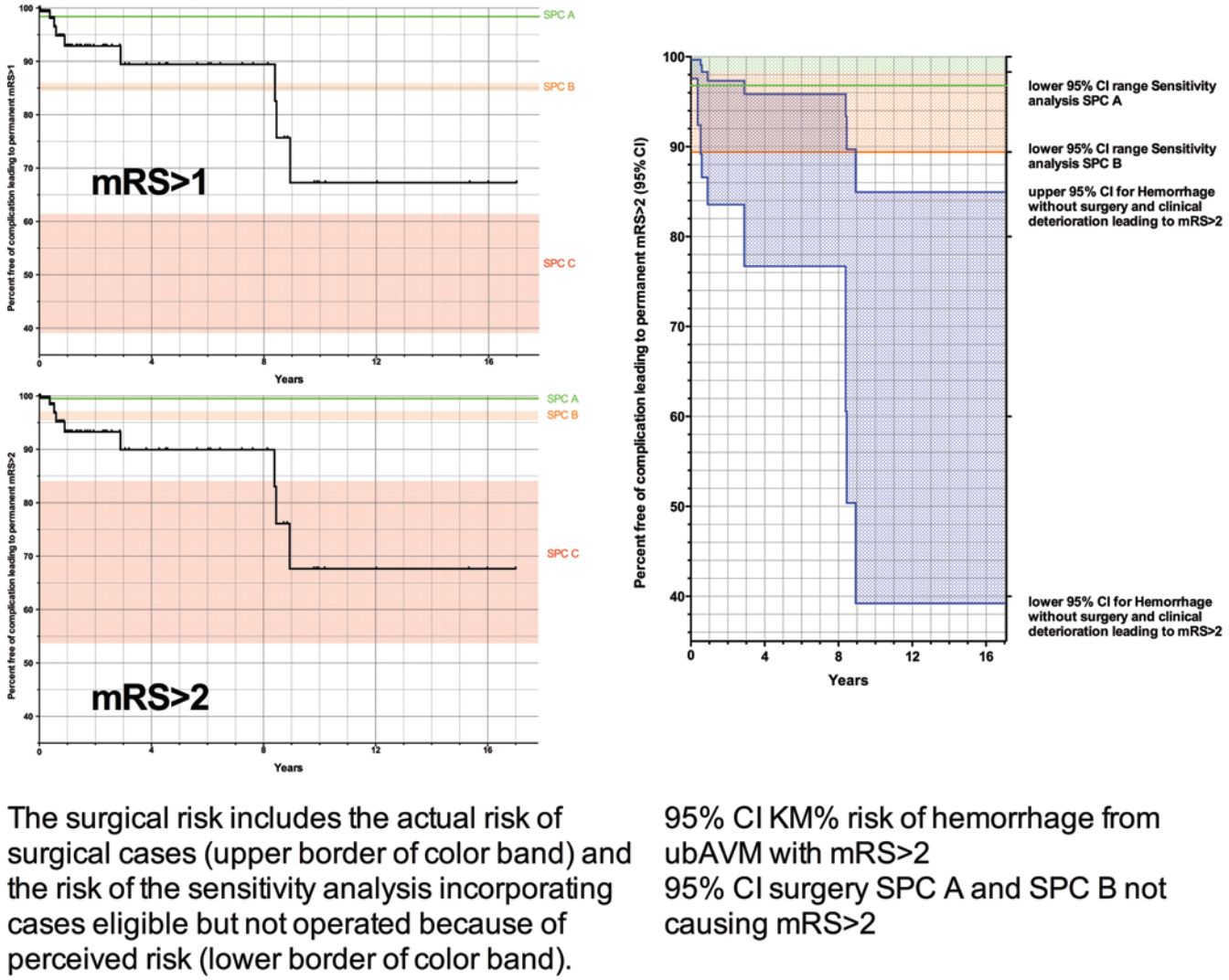


Fig. 4. Modified Rankin Scale score outcomes for surgery, sensitivity analysis of surgery, and hemorrhage from ubAVM. The mRS outcome of Kaplan-Meier percentage of natural history (377 patients) is superimposed on sensitivity analysis of surgery. A total of 190 patients had Spetzler-Ponce Class A ubAVMs, 109 had Spetzler-Ponce Class B ubAVMs, and 69 had Spetzler-Ponce Class C ubAVMs. KM = Kaplan-Meier.

fore. Our finding that the Spetzler-Martin grading system applied to ubAVM surgery was useful in stratifying the incidence of adverse outcomes.

A proportion of the morbidity and mortality arose as a consequence of preoperative embolization. We have previously published our results of embolization and the lack of evidence of benefit from preoperative embolization for cases of Spetzler-Ponce Class A ubAVMs.[18,19] Consideration should be given to early surgery, elimination of the use of embolization, and perhaps reduction in the use of preoperative diagnostic DSA for Spetzler-Ponce Class A ubAVMs to reduce adverse outcomes from all causes in this group.

For Spetzler-Ponce Class B and Spetzler-Ponce Class C ubAVMs, the risk of an adverse outcome from surgery is high. Therefore, recommending management for these patients remains a highly nuanced process and may not be made for several years after first referral. Despite the high morbidity for this group, the 1% and 7% mortality for Spetzler-Ponce Class B and Spetzler-Ponce Class C ubAVMs, respectively, are likely lower than the long-term mortality if untreated. This mortality may come into consideration in the decision making for some patients (particularly younger patients).

Comparing Surgery and Conservative Management

We believe that we can generalize the conclusion that our results confirm that Spetzler-Ponce Class A ubAVMs treated by surgery have a better outcome than conservatively managed ubAVMs. This was investigated by looking at the most optimistic boundary of our results of natural history (the upper 95% confidence interval for not experiencing an adverse outcome) with the most pessimistic boundary of surgery (the lower 95% confidence interval for not experiencing an adverse outcome). Superimposing these 95% boundaries, for mRS score >

1 there was crossover within 9 years and for mRS > 2 crossover was within 3 years of surgery. Therefore, our results suggest a 90% likelihood (combining the two 95% confidence intervals) that there is a benefit for surgery over conservative treatment within 3 years of treatment for our cases. The superimposition of sensitivity analysis upon the natural history curve suggests a tendency to an advantage for Spetzler-Ponce Class B ubAVMs; however, using the higher level of confidence by superimposing the 95% boundaries, the outcome for surgery for Spetzler-Ponce Class B and Spetzler-Ponce Class C ubAVMs may not be better than conservative management of ubAVMs. However, there are a number of complex factors that may come into play for individual patients (such as the likely lower mortality rate from surgery) that result in the recommendation for surgery despite the daunting morbidity. Although we have shown that for selected cases surgery can be better than medical management, a weakness of our results relates to the generalizability to other surgeons and institutions. An avenue for future research is to explore results from larger administrative areas to see whether results for the population of patients being treated by surgery are better than medical management.

Conclusions

Our study suggests that surgical outcomes for Spetzler-Ponce Class A ubAVMs can be better than those for conservative management. The difficulty in performing RCTs is clear from ARUBA. The prospect of mounting a future RCT becomes increasingly difficult as the window of ethical equipoise continues to close because there is increasing evidence for a specific management pathway (even if this evidence is from cohort series). Future research in this area should concentrate on the selection process for management pathways that provide enough context to inform consensus and identify those that can best be managed by surgery.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper. Dr. Bervini was supported by a scholarship funded by Johnson and Johnson Medical, Pty Limited.

Author contributions to the study and manuscript preparation include the following. Conception and design: Morgan. Acquisition of data: Morgan, Bervini. Analysis and interpretation of data: Morgan, Bervini, Heller. Drafting the article: Morgan, Bervini, Ritson. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Morgan. Statistical analysis: Morgan, Bervini, Heller. Administrative/technical/material support: Morgan. Study supervision: Morgan.

References

1. Bambakidis NC, Cockroft K, Connolly ES, Amin-Hanjani S, Morcos J, Meyers PM, et al: Preliminary results of the ARUBA study. **Neurosurgery 73:**E379–E381, 2013
2. Brown RD Jr, Wiebers DO, Forbes G, O'Fallon WM, Piepgras DG, Marsh WR, et al: The natural history of unruptured intracranial arteriovenous malformations. **J Neurosurg 68:**352–357, 1988
3. Crawford PM, West CR, Chadwick DW, Shaw MD: Arteriovenous malformations of the brain: natural history in unoperated patients. **J Neurol Neurosurg Psychiatry 49:**1–10, 1986
4. da Costa L, Wallace MC, Ter Brugge KG, O'Kelly C, Willinsky RA, Tymianski M: The natural history and predictive features of hemorrhage from brain arteriovenous malformations. **Stroke 40:**100–105, 2009
5. Davidson AS, Morgan MK: How safe is arteriovenous malformation surgery? A prospective, observational study of surgery as first-line treatment for brain arteriovenous malformations. **Neurosurgery 66:**498–505, 2010
6. Dobbelaere P, Jomin M, Clarrisse J, Laine E: [Prognostic importance of the study of venous drainage in cerebral arteriovenous aneurysms.] **Neurochirurgie 25:**178–184, 1979 (Fr)
7. Fullerton HJ, Achrol AS, Johnston SC, McCulloch CE, Higashida RT, Lawton MT, et al: Long-term hemorrhage risk in children versus adults with brain arteriovenous malformations. **Stroke 36:**2099–2104, 2005
8. Graf CJ, Perret GE, Torner JC: Bleeding from cerebral arteriovenous malformations as part of their natural history. **J Neurosurg 58:**331–337, 1983
9. Gross BA, Du R: Natural history of cerebral arteriovenous malformations: a meta-analysis. Clinical article. **J Neurosurg 118:**437–443, 2013
10. Halim AX, Johnston SC, Singh V, McCulloch CE, Bennett JP, Achrol AS, et al: Longitudinal risk of intracranial hemorrhage in patients with arteriovenous malformation of the brain within a defined population. **Stroke 35:**1697–1702, 2004
11. Hernesniemi JA, Dashti R, Juvela S, Väärt K, Niemelä M, Laakso A: Natural history of brain arteriovenous malformations: a long-term follow-up study of risk of hemorrhage in 238 patients. **Neurosurgery 63:**823–831, 2008
12. Itoyama Y, Uemura S, Ushio Y, Kuratsu J, Nonaka N, Wada H, et al: Natural course of unoperated intracranial arteriovenous malformations: study of 50 cases. **J Neurosurg 71:**805–809, 1989
13. Kim H, Sidney S, McCulloch CE, Poon KY, Singh V, Johnston SC, et al: Racial/ethnic differences in longitudinal risk of intracranial hemorrhage in brain arteriovenous malformation patients. **Stroke 38:**2430–2437, 2007
14. Lawton MT, Kim H, McCulloch CE, Mikhak B, Young WL: A supplementary grading scale for selecting patients with brain arteriovenous malformations for surgery. **Neurosurgery 66:**702–713, 2010
15. Marks MP, Lane B, Steinberg GK, Chang PJ: Hemorrhage in intracerebral arteriovenous malformations: angiographic determinants. **Radiology 176:**807–813, 1990
16. Miyasaka Y, Yada K, Ohwada T, Kitahara T, Kurata A, Irikura K: An analysis of the venous drainage system as a factor in hemorrhage from arteriovenous malformations. **J Neurosurg 76:**239–243, 1992
17. 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 383:**614–621, 2014
18. Morgan MK, Davidson AS, Koustais S, Simons M, Ritson EA: The failure of preoperative ethylene-vinyl alcohol copolymer embolization to improve outcomes in arteriovenous malformation management: case series. Clinical article. **J Neurosurg 118:**969–977, 2013
19. Morgan MK, Zurin AA, Harrington T, Little N: Changing role for preoperative embolisation in the management of arteriovenous malformations of the brain. **J Clin Neurosci 7:**527–530, 2000
20. Ondra SL, Troupp H, George ED, Schwab K: The natural history of symptomatic arteriovenous malformations of the brain: a 24-year follow-up assessment. **J Neurosurg 73:**387–391, 1990

21. Pollock BE, Flickinger JC, Lunsford LD, Bissonette DJ, Kondziolka D: Hemorrhage risk after stereotactic radiosurgery of cerebral arteriovenous malformations. **Neurosurgery 38:**652–661, 1996
22. Redekop G, TerBrugge K, Montanera W, Willinsky R: Arterial aneurysms associated with cerebral arteriovenous malformations: classification, incidence, and risk of hemorrhage. **J Neurosurg 89:**539–546, 1998
23. Schaller C, Schramm J, Haun D: Significance of factors contributing to surgical complications and to late outcome after elective surgery of cerebral arteriovenous malformations. **J Neurol Neurosurg Psychiatry 65:**547–554, 1998
24. Spears J, Terbrugge KG, Moosavian M, Montanera W, Willinsky RA, Wallace MC, et al: A discriminative prediction model of neurological outcome for patients undergoing surgery of brain arteriovenous malformations. **Stroke 37:**1457–1464, 2006
25. Spetzler RF, Martin NA: A proposed grading system for arteriovenous malformations. **J Neurosurg 65:**476–483, 1986
26. Spetzler RF, Ponce FA: A 3-tier classification of cerebral arteriovenous malformations. Clinical article. **J Neurosurg 114:** 842–849, 2011
27. Stapf C, Khaw AV, Sciacca RR, Hofmeister C, Schumacher HC, Pile-Spellman J, et al: Effect of age on clinical and morphological characteristics in patients with brain arteriovenous malformation. **Stroke 34:**2664–2669, 2003
28. Stapf C, Mast H, Sciacca RR, Choi JH, Khaw AV, Connolly ES, et al: Predictors of hemorrhage in patients with untreated brain arteriovenous malformation. **Neurology 66:**1350–1355, 2006
29. Stapf C, Mohr JP, Pile-Spellman J, Sciacca RR, Hartmann A, Schumacher HC, et al: Concurrent arterial aneurysms in brain arteriovenous malformations with haemorrhagic presentation. **J Neurol Neurosurg Psychiatry 73:**294–298, 2002
30. Stapf C, Mohr JP, Sciacca RR, Hartmann A, Aagaard BD, Pile-Spellman J, et al: Incident hemorrhage risk of brain arteriovenous malformations located in the arterial borderzones. **Stroke 31:**2365–2368, 2000
31. Svien HJ, McRae JA: Arteriovenous anomalies of the brain. Fate of patients not having definitive surgery. **J Neurosurg 23:**23–28, 1965
32. Viñuela F, Nombela L, Roach MR, Fox AJ, Pelz DM: Stenotic and occlusive disease of the venous drainage system of deep brain AVM's. **J Neurosurg 63:**180–184, 1985
33. Yamada S, Takagi Y, Nozaki K, Kikuta K, Hashimoto N: Risk factors for subsequent hemorrhage in patients with cerebral arteriovenous malformations. **J Neurosurg 107:**965–972, 2007

Manuscript submitted December 5, 2013.
Accepted July 10, 2014.
Please include this information when citing this paper: published online August 8, 2014; DOI: 10.3171/2014.7.JNS132691.

Address correspondence to: Michael Kerin Morgan, M.D., Health and Medical Development, Macquarie University, 2 Technology Pl., Macquarie University, Sydney, NSW 2109, Australia. email: michael.morgan@mq.edu.au.