Comparison of Hemorrhagic Risk in Intracranial Arteriovenous Malformations Between Conservative Management and Embolization as the Single Treatment Modality

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BACKGROUND: Embolization has been discussed as a feasible single modality treatment for intracranial arteriovenous malformations (AVMs).

OBJECTIVE: To compare hemorrhagic risk between embolization and conservative management in a multivariate survival analysis.

METHODS: We retrospectively reviewed records of patients with intracranial AVMs evaluated at our institution from 1990 to 2013. We included patients recommended to undergo embolization without other treatment modalities and patients managed conservatively. Multivariate Cox regression analysis of hemorrhage-free survival was performed, with the survival interval right-censored to date of either last follow-up or salvage treatment.

RESULTS: We identified 205 patients matching our inclusion criteria, with 160 patients in the noninterventional group and 45 in the embolization group. The average age of all patients was 40.2 ± 19.5 yr, with younger patients undergoing embolization more often ($P = .026$). Fifty-one (31.9%) conservatively managed patients and 13 (28.9%) patients treated by embolization ($P = .703$) presented with hemorrhage. Other baseline characteristics were similar between the 2 management groups. During an average follow-up period of 7.7 yr, 30 patients (14.6%) experienced hemorrhage recurrence. Multivariate Cox regression revealed older age ($P = .031$) and hemorrhagic presentation ($P < .001$) to be statistically associated with follow-up hemorrhage. In a subset analysis of unruptured AVMs, embolization was associated with a 4-fold hazard ratio of hemorrhage compared to conservative management ($P = .044$).

CONCLUSION: Older age and initial presentation with hemorrhage were associated with increased risk of hemorrhage during follow-up. Treatment of AVMs with embolization as the sole modality may increase hemorrhagic risk compared with conservative management, especially in unruptured AVMs.

KEY WORDS: Arteriovenous malformations, Conservative management, Embolization, Hemorrhage

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Embolization is conventionally considered an adjuvant therapy to microsurgery or radiosurgery for treatment of brain arteriovenous malformations (AVMs).[1-4] However, improvement in endovascular approaches has made embolization of cerebral AVMs with the intent to cure an increasingly discussed treatment option.[5-17] Despite these advances, the obliteration rate of small, superficial AVMs with a favorable embolization risk profile is still significantly lower than that achieved by microsurgery or radiosurgery.[7] While findings from endovascular series suggest that obliteration rates are improving, there remain specific concerns regarding the interpretations of these studies. Wide variation in reported obliteration rates (2.3%-100.0%) and morbidity rates (0.0%-22.2%) strongly suggests reporting bias. Furthermore, most studies report a short

ABBREVIATIONS: AVM, arteriovenous malformation; **CI,** confidence interval; **HR,** hazard ratio; **mRS,** modified Rankin Scale follow-up period, which may reflect inadequate surveillance of long-term AVM hemorrhage risk.[18] Conservative management has been recommended over embolization for AVM management by the ARUBA (A Randomized Trial of Unruptured Brain Arteriovenous Malformations) trial, but these findings are contentious owing to concerns regarding the trial's design and implementation. In this study, we aim to elucidate the relative risks and benefits of embolization and conservative management by comparing the long-term risk of hemorrhage and functional outcomes.

METHODS

Study Cohort Selection

We performed a retrospective cohort study of 2 groups—those who received conservative management and those who underwent endovascular embolization, identified with an AVM, either ruptured or found by other means. This study was approved by the institutional review boards of our institution; patient consent was not required for retrospective analysis. Patients with missing data or those lost to follow-up were also excluded from our study. Differences in population characteristics were appreciated by comparing baseline characteristics between the 2 groups. Outcomes of interest included functional status as determined by the last follow-up modified Rankin Scale (mRS) and the hemorrhage-free follow-up survival interval. Multivariate survival analysis was used to adjust for confounding variables.

Selection of Treatment

In our institution, patients who were deemed having an unfavorable treatment risk profile were recommended for conservative management. For hemorrhaged patients, definitive treatment is rigorously considered; however, for those with AVMs seated in deep or extremely eloquent locations, or with high-grade lesions, conservative management may also be recommended based on individualized clinical judgment. Embolization for high-risk pedicles may be attempted for patients with hemorrhage but considered unfavorable for surgery (high-grade AVMs) or radiosurgery (AVMs with high risk of hemorrhage, larger AVMs, or AVMs with prior embolization).[19-22] Patients managed conservatively throughout their disease course were assigned to the conservative group. Patients initially recommended for conservative management without intention to treat, but who eventually underwent procedural intervention owing to disease progression were also included in the conservative group. Similarly, patients treated with embolization only, or those recommended to receive other treatment modalities but who were instead managed initially with embolization were assigned to the embolization group. For patients intended for treatment, an evaluation for surgery or radiosurgery is always prioritized before embolization, and for the majority of patients with embolization as the initial and only modality, embolization was initiated with the intent for symptom control or hemorrhage prevention.

Variable Definition

Patient demographics, clinical characteristics, and AVM angiographic features were collected. Age was defined as age at AVM diagnosis. Associated aneurysms were referred to intranidal aneurysms or aneurysms on the feeding artery. Management cross-over refers to the patient receiving a treatment modality treatment distinct from that which was initially assigned.

Follow-up period was defined as the interval between initial presentation and last follow-up or treatment cross-over for the conservative group; whereas for the embolization group, the follow-up period was defined as the interval between initial embolization and last follow-up. Functional prognosis was evaluated by comparing the difference between baseline and last follow-up mRS and was classified as unchanged, improved, or worsened. The mRS of patients was assessed before the cross-over phase. The survival time, defined as the time in which the patient was free of subsequent hemorrhage, was measured from baseline presentation or initial embolization, and right-censored to either the date of first hemorrhage, first cross-over treatment, or last follow-up or first cross-over treatment. AVM obliteration before and after treatment cross-over was also included in the descriptive analysis.

Statistical Methods

Baseline and clinical characteristics were compared between the 2 assigned groups. Student's *t*-test was used for continuous variables, and Chi-square or Fisher's exact test was used accordingly for categorical variables. The primary outcome of interest was the hemorrhage-free survival compared between the 2 treatment groups. Univariate Cox regression analysis was used to test the impact of baseline characteristics on the hemorrhage-free survival time. Kaplan–Meier curve with Log-rank test was also used for descriptive analysis. All variables were included in a multivariate Cox regression analysis to adjust for confounding effects. Baseline characteristics differing significantly between the 2 groups were also included in the multivariate analysis. The proportional hazard assumption was tested to assure no violation of the model and scaled Schoenfeld residuals were plotted. Subset analysis using the same methodology was also performed in patients with unruptured AVMs. All P values were reported as 2-sided, and statistical significance was defined as $P < .05$. All statistical analysis was performed using R Statistical Software (Version 3.2.1, 2015, Vienna, Austria).

RESULTS

Patient Selection and Treatment Group Assignment

As shown in Figure 1, a total of 205 AVM patients were included in this study, with 160 patients assigned to the conservative management group and 45 patients assigned to the embolization group. Patients with missing data regarding Spetzler–Martin grading, size of AVM, pretreatment mRS, and follow-up were excluded from the cohort. Among the 160 patients in the conservative group, 117 were managed conservatively through the duration of treatment, while 43 were initially managed conservatively but underwent treatment cross-over. Among the 45 patients in the embolization group, 29 were treated by embolization only, and 16 patients crossed over to another treatment. Five patients were treated before 1990 (1977-1988) and subsequently seen in our institution after 1990, and 3 of these patients underwent subsequent radiotherapy. Forty patients (88.9%) in the embolization group were first treated between 1995 and 2013, with 28 (70.0%) treated after 2005, and 14 (35.0%) after 2010. Common reasons for deviation from the initial treatment recommendation included

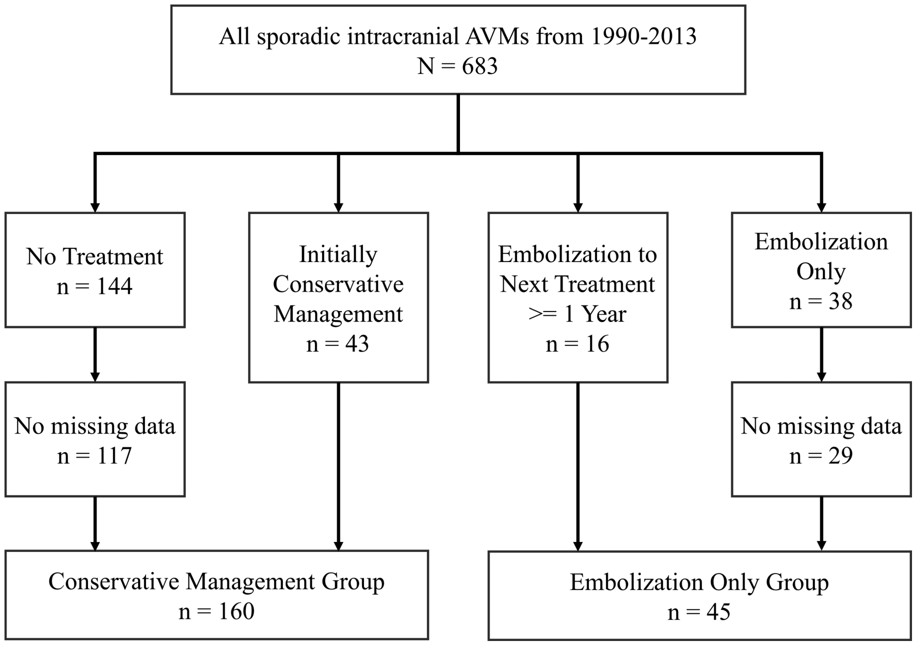

FIGURE 1. *Flow diagram of patient selection.*

delay in patient decision to pursue treatment, significant comorbidities delaying treatment, refusal of treatment, pregnancy, and treatment abortion amongst other reasons. The specific reasons for treatment abortions (n = 8) are as follows: 3 patients in embolization group that were initially planned for embolization followed by immediate radiosurgery or surgery had plan revision with abortion of subsequent definitive treatment, and was observed for a long period (>1 yr) before eventually crossing-over to radiosurgery; 1 patient had a plan revision and only underwent embolization despite initial recommendation of embolization and radiosurgery; 1 patient was planned for serial embolization and aborted due to personal preference; for 3 other patients, the treatment was aborted due to high risk of further embolization. We compiled the reasons for deviation from initial treatment recommendation and subsequent treatment cross-over into surgery or radiosurgery in a Sankey plot (Figure 2).

Study Population Characteristics

The average age of all patients was 40.2 ± 19.5 yr, with 41.6 ± 20.1 and 35.0 ± 16.1 yr in conservative group and embolization group, respectively ($P = .026$). Male patients comprised 50.7% of all AVM patients, and the gender distribution across the 2 groups was similar ($P = .196$). There were slightly more Black patients in the embolization group, but the difference was not significant ($P = .083$). There were no significant differences in angiographic features (size, location, deep venous drainage, and Spetzler–Martin grading) between the 2 treatment groups. A total of 64 patients presented with hemorrhage attributable to AVM rupture (31.2%), with 51 (31.9%) in the conservative and 13 (28.9%) in the embolization group, and the difference was not significant ($P = .703$). For comparison of likelihood of eventual cross-over to surgery, the conservative group (n = 10, 6.3%) is similar to the embolization group (n = 2, 4.4%); whereas for likelihood of crossing-over to radiosurgery, there were slightly more patients (n = 14, 31.1%) in the embolization group compared to the conservative group (n = 33, 20.6%), but the difference was not significant ($P = .329$).

During an average follow-up period of 7.7 yr, subsequent hemorrhage occurred in 30 (14.6%) patients, with 21 (13.1%) in the conservative and 9 (20.0%) in the embolization group ($P = .249$). Functional outcomes in the embolization group were less stable, with more patients experiencing improvement or deterioration of last follow-up mRS, but the difference between the 2 treatment groups was not significant ($P = .107$). Prior to definitive treatment cross-over, 6 conservative group patients (3.8%) experienced spontaneous AVM obliteration, whereas 2 (4.4%) embolization group patients experienced AVM obliteration. Among the 29 patients with embolization as the only modality, 10 were attempted for curative treatment, with 1 being obliterated (10.0%). At last follow-up after treatment cross-over, the obliteration rate was 13.1% and 13.3% in the conservative group and embolization group, respectively ($P = .971$). A comparison of patient demographics, clinical and angiographic characteristics, and follow-up outcomes is shown in Table 1.

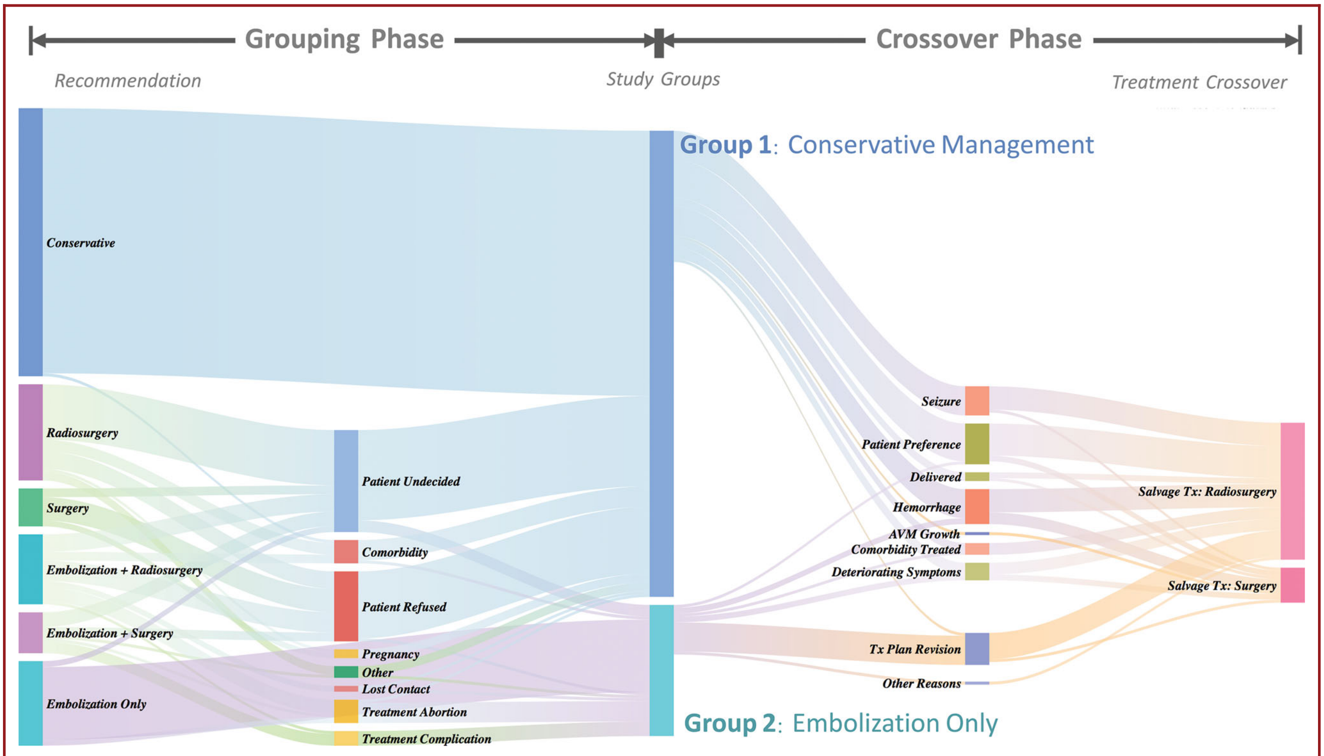

FIGURE 2. *Sankey plot of treatment group assignment and patient cross-over through the disease course. Reasons for non-compliance of initial treatment recommendation and cross-over after treatment group assignment were separately listed in the graph. The width of the band is proportionate to the number of patients.*

Hemorrhagic Risk Control in All Patients

Characteristics distributed differently between the 2 groups (age and race) in univariate analysis as determined by a statistical significance level threshold ($P < .1$) were included in the multivariate analysis to adjust for selection bias on treatment effectiveness. Hemorrhagic presentation, size, and location were also included in the analysis as they were clinically determined to be associated with hemorrhagic risk. As shown in Figure 3A, there was no significant difference between conservative management and embolization for hemorrhagic risk ($P = .83$); however, an earlier decline of survival was noted in the embolization group. Results from multivariate Cox proportional hazard regression analysis (Table 2) show that increasing age (hazard ratio [HR]: 1.02, confidence interval [CI]: [1.00, 1.04], $P = .044$), hemorrhagic presentation (HR: 4.20, CI: [1.98, 8.90], $P < .001$), and nonlobar location (HR: 2.17, CI: [1.04, 4.56], $P = .040$) were independently associated with higher follow-up risk of hemorrhage. The unadjusted annual risk of hemorrhage in a 10-yr period was 2.74% for the conservative group, 2.48% for the embolization group, and 2.67% for both groups as a collective whole. However, in patients with nonlobar AVMs with a ruptured presentation, the overall risk increased to 6.82%.

Hemorrhagic Risk Control in Unruptured AVMs

We also performed a subset analysis of patients with unruptured AVMs. A total of 141 patients were identified as having a nonhemorrhagic presentation, with 109 in conservative group and 32 in embolization group. For patients in the conservative group, 60 were initially recommended for conservative management, and 49 were recommended for treatment but no treatment was received for a variety of reasons including patient refusal. Among 60 patients recommended for conservative management, only 18 were grade 1 or 2, with 6 being 60 yr or older, and the remaining 12 are highly functional individuals currently working or studying. Figure 3B compares the association of follow-up hemorrhage between conservative management and embolization. Conservative management trended toward being superior in association with less likelihood of hemorrhage at last follow-up ($P < .10$). Results from a multivariate analysis (Table 3) showed that embolization bears a significantly greater risk of follow-up hemorrhage compared to conservative management (HR: 3.74, CI: [1.03, 13.50], $P = .044$), whereas age (HR: 1.04, CI: [1.00, 1.08], $P = .060$) and nonlobar location (HR: 2.88, CI: [0.85, 9.76], $P = .089$) only demonstrated borderline significance. The unadjusted annual hemorrhagic risk in a 10-yr period was 1.09% for the conservative group,

TABLE 1. Comparison of Patient Characteristics between Conservative Management and Embolization

Parameters	Total (n = *205*)	Conservative management (n = *160*)	Embolization (n = *45*)	*P* value
Demographics				
Age at diagnosis, year, mean (SD)	40.2 (19.5)	41.6 (*20.1*)	35.0 (*16.1*)	*.026*[a]
Gender, male, n (%)	104 (50.7)	85 (*53.1*)	19 (*42.2*)	*.196*
Race, n (%)				*.083*
White	136 (66.3)	110 (*68.8*)	26 (*57.8*)	
Black	40 (19.5)	26 (*16.3*)	14 (*31.1*)	
Others	29 (14.1)	24 (*15.0*)	5 (*11.1*)	
AVM characteristics				
AVM location, n (%)[b]				*.190*
Lobar	154 (75.1)	119 (*74.4*)	35 (*77.8*)	
Deep	33 (16.1)	29 (*18.1*)	4 (*8.9*)	
Cerebellar	18 (8.8)	12 (*7.5*)	6 (*13.3*)	
Associated aneurysm, n (%)	33 (16.1)	24 (*15.0*)	9 (*20.0*)	*.420*
Venous stenosis, n (%)	22 (10.7)	16 (*10.0*)	6 (*13.3*)	*.523*
Deep venous drainage, n (%)	107 (52.2)	82 (*51.2*)	25 (*55.6*)	*.609*
Eloquence, n (%)	146 (71.2)	116 (*72.5*)	30 (*66.7*)	*.445*
AVM size, cm, mean (SD)	3.6 (2.4)	3.5 (*2.3*)	4.0 (*2.5*)	*.245*
Spetzler–Martin Grading, n (%)[b]				*.144*
Grade 1	19 (9.3)	16 (*10.0*)	3 (*6.7*)	
Grade 2	62 (30.2)	48 (*30.0*)	14 (*31.1*)	
Grade 3	64 (31.2)	48 (*30.0*)	16 (*35.6*)	
Grade 4	29 (14.1)	27 (*16.9*)	2 (*4.4*)	
Grade 5	31 (15.1)	21 (*13.1*)	10 (*22.2*)	
Clinical presentation/treatment				
Baseline mRS, n (%)[b]				*.202*
0	31 (15.1)	26 (*16.3*)	5 (*11.1*)	
1	63 (30.7)	49 (*30.6*)	14 (*31.1*)	
2	76 (37.1)	63 (*39.4*)	13 (*28.9*)	
3	26 (12.7)	16 (*10.0*)	10 (*22.2*)	
4	6 (2.9)	4 (*2.5*)	2 (*4.4*)	
5	3 (1.5)	2 (*1.3*)	1 (*2.2*)	
Hemorrhagic presentation, n (%)	64 (31.2)	51 (*31.9*)	13 (*28.9*)	*.703*
Seizures, n (%)	73 (35.6)	55 (*34.4*)	18 (*40.0*)	*.486*
Headaches, n (%)	104 (50.7)	83 (*51.9*)	21 (*46.7*)	*.537*
Management cross-over, n (%)[b]				*.329*
No cross-over	146 (71.2)	117 (*73.1*)	29 (*64.4*)	
to surgery	12 (5.9)	10 (*6.3*)	2 (*4.4*)	
to radiosurgery	47 (22.9)	33 (*20.6*)	14 (*31.1*)	
Follow-up				
Interval, years, mean (SD)	7.7 (10.8)	8.0 (*11.4*)	6.5 (*8.1*)	*.310*
mRS at last follow-up, n (%)[b]				*.241*
0	39 (19.2)	35 (*21.3*)	4 (*10.3*)	
1	69 (34.0)	58 (*35.4*)	11 (*28.2*)	
2	61 (30.0)	46 (*28.0*)	15 (*38.5*)	
3	20 (9.9)	14 (*8.5*)	6 (*15.4*)	
4	8 (3.9)	7 (*4.3*)	1 (*2.6*)	
6	6 (3.0)	4 (*2.4*)	2 (*5.1*)	
mRS change				*.107*
Unchanged, n (%)	96 (46.8)	81 (*50.6*)	15 (*33.3*)	
Improved, n (%)	62 (30.2)	46 (*28.7*)	16 (*35.6*)	
Worsened, n (%)	47 (22.9)	33 (*20.6*)	14 (*31.1*)	
Subsequent hemorrhage, n (%)	30 (14.6)	21 (*13.1*)	9 (*20.0*)	*.249*
Obliteration before cross-over, n (%)[b]	8 (3.9)	6 (*3.8*)	2 (*4.4*)	>*.999*
Obliteration at last follow-up, n (%)	27 (13.2)	21 (*13.1*)	6 (*13.3*)	*.971*

[a] Significant variables ($P < .050$).
[b] Comparison using Fisher's exact test, nonlabeled were tested using chi-square.

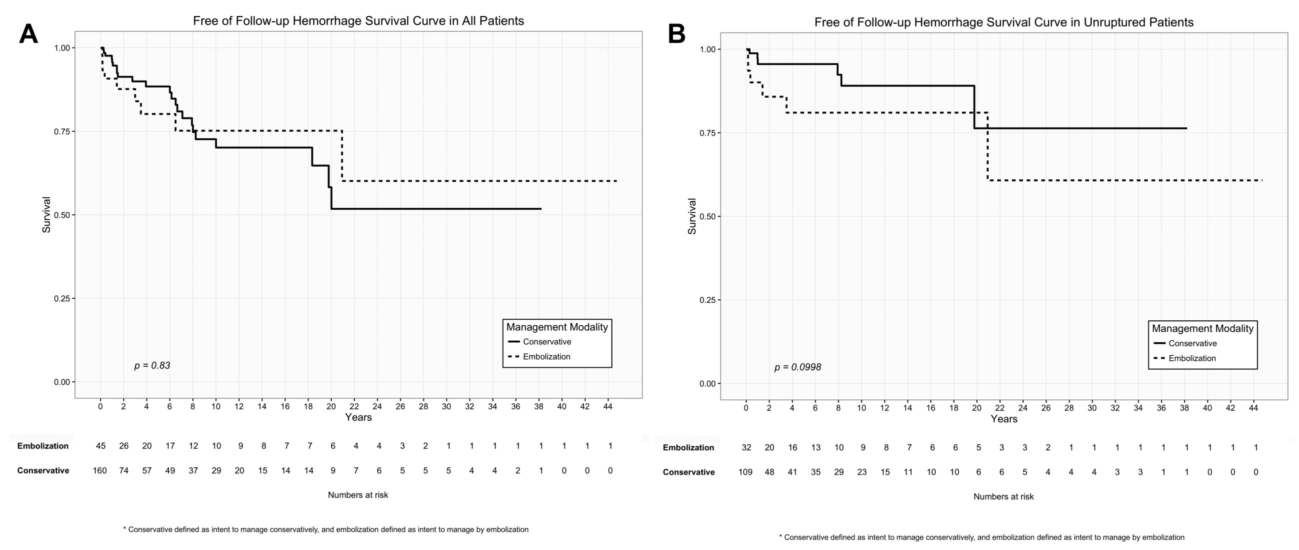

FIGURE 3. *Kaplan–Meier curve depicting survival of free of follow-up hemorrhage.* **A**, *Unadjusted Kaplan–Meier curve of free of follow-up hemorrhage by treatment modalities in all patients.* **B**, *Unadjusted Kaplan–Meier curve of free of follow-up hemorrhage by treatment modalities in patients with unruptured presentation.*

TABLE 2. Univariate and Multivariate Cox Proportional Hazard Regression on Follow-up Hemorrhage in All Patients

	Univariate analysis			Multivariate analysis		
Parameters	**HR**	**95% CI**	***P value***	**HR**	**95% CI**	***P value***
Age, per 1 yr increase	1.03	[1.01, 1.05]	*.011*[a]	1.02	[1.00, 1.04]	*.044*[a]
Race						
White	*ref*	–	–	*ref*	–	–
Non-White	0.96	[0.44, 2.08]	*.908*	0.72	[0.31, 1.68]	*.447*
Hemorrhagic presentation						
No	*ref*	–	–	*ref*	–	–
Yes	4.30	[2.09, 8.85]	*<.001*[a]	4.20	[1.98, 8.90]	*<.001*[a]
Size						
<3cm	*ref*	–	–	*ref*	–	–
≥3cm	0.62	[0.30, 1.29]	*.197*	0.89	[0.46, 1.97]	*.782*
Location						
Lobar	*ref*	–	–	*ref*	–	–
Non-lobar	2.01	[0.97, 4.18]	*.061*[b]	2.17	[1.04, 4.56]	*.040*[a]
Management modality						
Conservative management	*ref*	–	–	*ref*	–	–
Embolization only	1.09	[0.50, 2.36]	*.829*	1.67	[0.70, 4.00]	*.248*

[a]Statistical significance ($P < .05$).
[b]Trend towards significance ($P < .1$).

1.9% in the embolization group, and 1.31% for both groups as a whole.

Hemorrhagic Risk Control in Ruptured AVMs

An identical analysis to the unruptured patients was performed in ruptured patients (n = 64), with 51 in conservative group and 13 in embolization group. Conservative management was recommended in 31 patients based on clinical judgment of treatment risk. Of note, 17 patients in the conservative group eventually crossed over to surgery or radiosurgery. No variables including treatment modality was found to have a significant impact on subsequent hemorrhagic risk in these patients in univariate analysis, therefore a multivariate survival analysis was not performed. Unadjusted annual hemorrhagic risk in a

TABLE 3. Univariate and Multivariate Cox Proportional Hazard Regression on Follow-up Hemorrhage in Unruptured Patients

	Univariate analysis			Multivariate analysis		
Parameters	HR	95% CI	*P* value	HR	95% CI	*P* value
Age, per 1 yr increase	1.03	[1.00, 1.07]	*.060*[a]	1.04	[1.00, 1.08]	*.060*[a]
Race						
White	*ref*	–	–	*ref*	–	–
Non-White	1.51	[0.43, 5.23]	*.519*	1.10	[0.30, 4.02]	*.882*
Size						
<3 cm	*ref*	–	–	*ref*	–	–
≥3 cm	0.53	[0.16, 1.78]	*.303*	0.72	[0.15, 3.48]	*.684*
Location						
Lobar	*ref*	–	–	*ref*	–	–
Nonlobar	2.60	[0.82, 8.26]	*.106*	2.88	[0.85, 9.76]	*.089*[a]
Management modality						
Conservative management	*ref*	–	–	*ref*	–	–
Embolization only	2.53	[0.81, 7.90]	*.112*	3.74	[1.03, 13.50]	*.044*[b]

[a]Trend towards significance ($P < .1$).
[b]Statistical significance ($P < .05$).

10-yr period was 5.78% for the conservative group, 4.23% in the embolization group, and 5.52% for both groups as a whole.

DISCUSSION

Summary of Key Results

The present study describes our institutional series of 205 AVMs managed either via conservative management or by embolization alone. According to the Spetzler-Ponce classification system, approximately 40% of our patients were class A, 30% were class B, and 30% were class C,[23] with no significant difference in classification distribution between the 2 treatment groups. The obliteration rate of our embolization series before crossing over to definitive treatment was 4.4%, which is on the lower end of findings from reported series,[18] but is reasonable provided that the majority (77.8%) of patients in the embolization group were treated with a noncurative approach.

When comparing outcomes between conservative management vs embolization, we noticed a trend of survival benefit in an initial period of 8 yr in conservative group compared to embolization group in the Kaplan–Meier survival curve, and the survival benefit for embolization was not realized until 8 yr of treatment. However, when calculating overall survival in the entire study cohort or in the unruptured patients, embolization alone did not achieve significant benefit of hemorrhage control compared to the former, nor did it significantly improve functional outcomes. This result suggests that for patients deemed unsuitable for surgery or radiosurgery, hemorrhage control may not be improved when initiating embolization in the absence of an additional definitive treatment plan for cure. In addition, for unruptured, nonoperable AVMs, embolization as a sole treatment strategy is problematic since it conferred a nearly 4-fold increase in the HR for subsequent hemorrhage risk compared to conservative management.

Embolization in Management of AVM

As suggested by Potts et al[18] and Başkaya et al,[24] the role of embolization in the management of AVMs can be categorized into 4 major categories: (1) presurgical flow reduction, (2) preradiosurgery volume reduction, (3) palliative flow reduction or partial treatment, and (4) curative. Amongst these, the role of embolization as an adjuvant modality for microsurgery is well established; in contrast, preradiosurgery embolization has been viewed as less advantageous owing to its reported negative impact on radiosurgical AVM obliteration.[20,25] Literature reports of palliative embolization for symptomatic, inoperable AVMs are mixed. While embolization may be palliative for medically refractory symptoms as suggested by sporadic case reports,[9,26-28] its ability to achieve hemorrhagic control remains less clear.

Embolization has been traditionally considered as a noncurative modality in AVM treatment, and therefore the curative role of embolization is perhaps the most controversial among the 4 categories. Recently, however, more studies are suggestive of the curative potential of embolization in AVM management. Potts et al[18] summarized recent findings from several AVM embolization series and found 3 studies describing curative embolization with reported obliteration rates of approximately 31% to 100% and a combined curative rate of approximately 45%.[18] In a more recent study by Saatci et al[29] examining a consecutive cohort of 350 patients treated by embolization, obliteration was achieved in 51.0% of patients with 1.4% mortality, 7.1% permanent morbidity, and a recanalization rate of 1.1% during 1–8 yr of follow-up.

Despite reported improvements in the use of embolization as a curative means for AVM treatment,[5,7,8,10-12,14-16,18,29-32] whether an aggressive embolization strategy should be pursued—especially for low-grade AVMs where risk of both surgery and radiosurgery are minimal—remains debatable.[33,34] Nevertheless, in rare cases of small AVMs with high risk for hemorrhage and where surgery is not possible, embolization may be potentially used where endovascular access is favorable, and may, in fact, be recommended over radiosurgery for immediate angiographic obliteration. Conversely, for high-grade AVMs or those with complex angiographic architecture, "curative" embolization is less likely to be planned at the beginning of the treatment course since the decision-making process must account for angiographic changes arising after early embolization sessions. For embolization in these AVMs, a relatively high rate of treatment plan revision, aborted treatment, and incompleteness may be observed.[29] While some patients from our cohort may have achieved eventual endovascular obliteration with further, more aggressive embolization, this may have also exposed them to increased hemorrhage risk attributable to immediate hemodynamic changes or the prolonged interval before obliteration by definitive treatment.[24] From our study's perspective, the risk of initiating endovascular treatment may exceed its benefit when compared to conservative management, and further evidence to refine patient selection criteria is critically needed before an aggressive embolization regimen can be recommended for most patients.

Relation to the ARUBA Trial

Despite being designed as a randomized controlled trial, the ARUBA trial was criticized for its poor design, biased execution, and clinical irrelevancy of the proposed study question.[35,36] Supported by the fact that approximately 20% of our AVM patients were initially conservatively managed, it is evident that conservative management remains one of the most common treatment modalities for certain AVM subtypes, especially those that are high grade and with unruptured presentation; however, for other unruptured AVMs, the decision of whether to manage conservatively should always be considered alongside surgery, radiosurgery, embolization, or combined modalities. Moreover, as evidenced by the significant treatment cross-over in our study (Figure 2), the perplexing decision process is hardly captured by defining initial treatment recommendation as the treatment group, but rather must reflect the dynamics of disease progression or de novo circumstances such as comorbidities or evolving patient preferences. The complexity of noncompliance with initial treatment recommendations in our study may also partly explain the significant dropout of patients from the ARUBA trial during randomization.

As previously mentioned, selecting harder-to-treat patients with lower risk of hemorrhage into conservative management or palliative/curative embolization is reasonable, since those that were clinically determined optimal for surgery or radiosurgery may achieve better angiographic and functional outcome. The fact that only 37% of our unruptured patients were Spetzler-Ponce class A—which were best treated with surgery—supports this consensual algorithm. Conversely, it is worrisome to note that this proven assertion was fundamentally challenged in ARUBA, which included approximately 70% of Spetzler-Ponce class A patients in the intervention arm, with 30 out of 114 patients (26.3%) who underwent embolization alone.[35,37] In conjunction with our findings that in unruptured patients, embolization alone with or without curative intent may confer worse hemorrhagic control than conservative management without improved functional status, it is likely that a significant proportion of suboptimal outcomes observed in the intervention arm of ARUBA were attributable to the unconventional management strategy. Nevertheless, despite its shortcomings, the ARUBA trial has raised awareness of the underreporting of outcomes of conservative management in the AVM literature; as a consequence, more studies are now focusing on the comparative effectiveness of a specific treatment modality over conservative management.[38-42]

Limitations

There are limitations to our study that require elaboration to ensure accurate interpretation of our findings. Selection bias to treatment arms exists in this study, and we have rigorously addressed it by comparing patient and lesion characteristics that might influence treatment decision between the 2 groups, and included those that were unevenly distributed into a multivariate model for adjustments. Like all retrospective designs, our study suffers from attrition bias as demonstrated in the patient selection flow diagram (Figure 1). However, we attempted to minimize this risk through rigorous chart review and data retrieval, and in turn managed to retain 85% of the original cohort in our study. At our institution, only a small portion of patients were treated with palliative or curative embolization, resulting in a small number of patients in the embolization group. This uneven distribution of patients between treatment arms may limit statistical power and therefore, our ability to address subtle confounding variables in the multivariate analysis. The small sample size, especially for the embolization cohort, also limited our capability to stratify the cohort by different grades or classifications. Future studies employing data from multi-institutional registries may confirm and further explore decision algorithms in a more refined subcohort of patients

Another limitation of our study is related to the long time-span of the study period. One of the primary reasons that a long time-span is needed is that complications of treatment decisions require a long follow-up time to appreciate. Additionally, the progressive advancement of endovascular techniques and its impact on AVM patient outcome is implied but has yet to be confirmed. Paradoxically, in a recent meta-analysis of AVM embolization series, despite an increase in curative rate compared to earlier studies, more recent reports demonstrate a higher complication rate,[9] which indicates that the impact of endovascular technique advancements on patient outcome may be overshadowed by a stronger emphasis on optimal patient selection and management strategy. The embolization group included a heterogeneous cohort of patients treated with n-butyl cyanoacrylate as well as ethylene vinyl alcohol copolymer. These materials have been reported to have slight differences in curative rates, and post-treatment mortality and morbidity rates; however, recent literature suggests that the clinical significance of these differences might be doubtful.[5,9]

CONCLUSION

While the potential of embolization in the management of AVMs is known, its utility as a standalone treatment modality requires further investigation. Our study shows that embolization alone does not confer a functional gain over conservative management, and may lead to higher hemorrhage risk for patients with unruptured AVMs. This elevated hemorrhage risk was found to be independently associated with increasing age and nonlobar AVM location. For AVM patients unamenable to conventional definitive treatment, the choice of embolization as a treatment modality requires rigorous optimization of patient selection algorithms to ensure safety and the effectiveness of AVM treatment. The decision of how to treat AVMs is a complex and dynamic process that requires simultaneous comparison of multiple treatment arms. Further studies employing a comparative effectiveness approach are warranted to determine the superiority of each treatment modality for specific patient subgroups.

Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

REFERENCES

1. Nataraj A, Mohamed MB, Gholkar A, et al. Multimodality treatment of cerebral arteriovenous malformations. *World Neurosurg*. 2014;82(1-2):149-159.
2. Natarajan SK, Ghodke B, Britz GW, Born DE, Sekhar LN. Multimodality treatment of brain arteriovenous malformations with microsurgery after embolization with onyx: single-center experience and technical nuances. *Neurosurgery*. 2008;62(6):1213-1225; discussion1225-6.
3. Heros RC. Multimodality treatment of cerebral arteriovenous malformations: modern treatment of cerebral arteriovenous malformations. *World Neurosurg*. 2014;82(1-2):46-48.
4. Hoh BL, Chapman PH, Loeffler JS, Carter BS, Ogilvy CS. Results of multimodality treatment for 141 patients with brain arteriovenous malformations and seizures: factors associated with seizure incidence and seizure outcomes. *Neurosurgery*. 2002;51(2):303-309; discussion 309-11.
5. Elsenousi A, Aletich VA, Alaraj A. Neurological outcomes and cure rates of embolization of brain arteriovenous malformations with n-butyl cyanoacrylate or Onyx: a meta-analysis. *J Neurointerv Surg*. 2016;8(3):265-272.
6. de Castro-Afonso LH, Nakiri GS, Oliveira RS, et al. Curative embolization of pediatric intracranial arteriovenous malformations using Onyx: the role of new embolization techniques on patient outcomes. *Neuroradiology*. 2016:1-10. doi:10.1007/s00234-016-1666-1.
7. Robert T, Blanc R, Ciccio G, et al. Angiographic factors influencing the success of endovascular treatment of arteriovenous malformations involving the corpus callosum. *J Neurointerv Surg*. 2015;7(10):715-720.
8. Lopes DK, Moftakhar R, Straus D, Munich SA, Chaus F, Kaszuba MC. Arteriovenous malformation embocure score: AVMES. *J Neurointerv Surg*. 2015. doi:10.1136/neurintsurg-2015-011779.
9. Crowley RW, Ducruet AF, Kalani MYS, Kim LJ, Albuquerque FC, McDougall CG. Neurological morbidity and mortality associated with the endovascular treatment of cerebral arteriovenous malformations before and during the Onyx era. *J Neurosurg*. 2015;122(6):1492-1497.
10. Consoli A, Scarpini G, Rosi A, et al. Endovascular treatment of unruptured and ruptured brain arteriovenous malformations with Onyx18: a monocentric series of 84 patients. *J Neurointerv Surg*. 2014;6(8):600-606.
11. Strauss I, Frolov V, Buchbut D, Gonen L, Maimon S. Critical appraisal of endovascular treatment of brain arteriovenous malformation using Onyx in a series of 92 consecutive patients. *Acta Neurochir (Wien)*. 2013;155(4):611-617.
12. van Rooij WJ, Jacobs S, Sluzewski M, van der Pol B, Beute GN, Sprengers ME. Curative embolization of brain arteriovenous malformations with onyx: patient selection, embolization technique, and results. *AJNR Am J Neuroradiol*. 2012;33(7):1299-1304.
13. Andreou A, Ioannidis I, Lalloo S, Nickolaos N, Byrne JV. Endovascular treatment of intracranial microarteriovenous malformations. *J Neurosurg*. 2008;109(6):1091-1097.
14. Katsaridis V, Papagiannaki C, Aimar E. Curative embolization of cerebral arteriovenous malformations (AVMs) with Onyx in 101 patients. *Neuroradiology*. 2008;50(7):589-597.
15. Raymond J, Iancu D, Weill A, et al. Embolization as one modality in a combined strategy for the management of cerebral arteriovenous malformations. *Interv Neuroradiol*. 2005;11(suppl 1):57-62.
16. Campos J, Biscoito L, Sequeira P, Batista A. Intra-arterial Embolization in the treatment of brain arteriovenous malformations. *Interv Neuroradiol*. 2005;11(suppl 1):81-94.
17. Davies JM, Yanamadala V, Lawton MT. Comparative effectiveness of treatments for cerebral arteriovenous malformations: trends in nationwide outcomes from 2000 to 2009. *Neurosurg Focus*. 2012;33(1):E11. doi:10.3171/2012.5.FOCUS12107.
18. Potts MB, Zumofen DW, Raz E, Nelson PK, Riina HA. Curing arteriovenous malformations using embolization. *Neurosurg Focus*. 2014;37(3):E19. doi:10.3171/2014.6.FOCUS14228.
19. Nagy G, Rowe JG, Radatz MWR, Hodgson TJ, Coley SC, Kemeny AA. A historical analysis of single-stage γ knife radiosurgical treatment for large arteriovenous malformations: evolution and outcomes. *Acta Neurochir (Wien)*. 2012;154(3):383-394.
20. Sun DQ, Carson KA, Raza SM, et al. The radiosurgical treatment of arteriovenous malformations: obliteration, morbidities, and performance status. *Int J Radiat Oncol Biol Phys*. 2011;80(2):354-361.
21. Spetzler RF, Martin NA. A proposed grading system for arteriovenous malformations. *J Neurosurg*. 1986;65(4):476-483.
22. Lv X, Wu Z, Jiang C, et al. Angioarchitectural characteristics of brain arteriovenous malformations with and without hemorrhage. *World Neurosurg*. 2011;76(1-2):95-99.
23. Spetzler RF, Ponce FA. A 3-tier classification of cerebral arteriovenous malformations. Clinical article. *J Neurosurg*. 2011;114(3):842-849.
24. Başkaya MK, Heros RC. Indications for and complications of embolization of cerebral arteriovenous malformations. *J Neurosurg*. 2006;104(2):183-186; discussion186-187. doi:10.3171/jns.2006.104.2.183.
25. Andrade-Souza YM, Ramani M, Scora D, Tsao MN, terBrugge K, Schwartz ML. Embolization before radiosurgery reduces the obliteration rate of arteriovenous malformations. *Neurosurgery*. 2007;60(3):443-451; discussion451-452. doi:10.1227/01.NEU.0000255347.25959.D0.
26. Levitt MR, Ramanathan D, Vaidya SS, Hallam DK, Ghodke BV. Endovascular palliation of AVM-associated intractable trigeminal neuralgia via embolization of the artery of the foramen rotundum. *Pain Med*. 2011;12(12):1824-1830.
27. Sugita M, Takahashi A, Ogawa A, Yoshimoto T. Improvement of cerebral blood flow and clinical symptoms associated with embolization of a large arteriovenous malformation: case report. *Neurosurgery*. 1993;33(4):748-751; discussion752.
28. Reitz M, Schmidt NO, Vukovic Z, et al. How to deal with incompletely treated AVMs: experience of 67 cases and review of the literature. *Acta Neurochir Suppl*. 2011;112(Chapter 22):123-129.

29. Saatci I, Geyik S, Yavuz K, Cekirge HS. Endovascular treatment of brain arteriovenous malformations with prolonged intranidal Onyx injection technique: long-term results in 350 consecutive patients with completed endovascular treatment course. *J Neurosurg*. 2011;115(1):78-88.
30. Ivanov AA, Alaraj A, Charbel FT, Aletich V, Amin-Hanjani S. Recurrence of cerebral arteriovenous malformations following resection in adults: Does preoperative embolization increase the risk? *Neurosurgery*. 2016;78(4):562-571.
31. Frizzel RT, Fisher WS. Cure, morbidity, and mortality associated with embolization of brain arteriovenous malformations: a review of 1246 patients in 32 series over a 35-year period. *Neurosurgery*. 1995;37(6):1031-1039; discussion 1039-1040.
32. Fournier D, terBrugge KG, Willinsky R, Lasjaunias P, Montanera W. Endovascular treatment of intracerebral arteriovenous malformations: experience in 49 cases. *J Neurosurg*. 1991;75(2):228-233.
33. Ding D, Yen CP, Xu Z, Starke RM, Sheehan JP. Radiosurgery for low-grade intracranial arteriovenous malformations. *J Neurosurg*. 2014;121(2):457-467.
34. Potts MB, Lau D, Abla AA, et al. Current surgical results with low-grade brain arteriovenous malformations. *J Neurosurg*. 2015;122(4):912-920.
35. Cockroft KM, Jayaraman MV, Amin-Hanjani S, Derdeyn CP, McDougall CG, Wilson JA. A perfect storm: how a randomized trial of unruptured brain arteriovenous malformations' (ARUBA's) trial design challenges notions of external validity. *Stroke*. 2012;43(7):1979-1981.
36. Russin J, Spetzler R. Commentary: the ARUBA trial. *Neurosurgery*. 2014;75(1):E96-E97.
37. Mohr JP, Parides MK, Stapf C, et al. Medical management with or without interventional therapy for unruptured brain arteriovenous malformations (ARUBA): a multicentre, non-blinded, randomised trial. *Lancet*. 2014;383(9917):614-621.
38. Ding D, Starke RM, Kano H, et al. Radiosurgery for cerebral arteriovenous malformations in a randomized trial of unruptured brain arteriovenous malformations (ARUBA)-eligible patients: a multicenter study. *Stroke*. 2016;47(2):342-349.
39. Bervini D, Morgan MK, Ritson EA, Heller G. Surgery for unruptured arteriovenous malformations of the brain is better than conservative management for selected cases: a prospective cohort study. *J Neurosurg*. 2014;121(4):878-890.
40. Darsaut TE, Magro E, Gentric J-C, et al. Treatment of brain AVMs (TOBAS): study protocol for a pragmatic randomized controlled trial. *Trials*. 2015;16(1):497. doi:10.1186/s13063-015-1019-0.
41. Rutledge WC, Abla AA, Nelson J, Halbach VV, Kim H, Lawton MT. Treatment and outcomes of ARUBA-eligible patients with unruptured brain arteriovenous malformations at a single institution. *Neurosurg Focus*. 2014;37(3):E8. doi:10.3171/2014.7.FOCUS14242.
42. Nerva JD, Mantovani A, Barber J, et al. Treatment outcomes of unruptured arteriovenous malformations with a subgroup analysis of ARUBA (A Randomized Trial of Unruptured Brain Arteriovenous Malformations)-eligible patients. *Neurosurgery*. 2015;76(5):563-70; discussion 570-quiz 570.

COMMENT

Endovascular embolization of intracranial arteriovenous malformations (AVMs) is commonly employed as adjunctive therapy prior to definitive microsurgical resection or stereotactic radiosurgery. However, curative embolization is used at some centers, often with higher rates of complication and lower rates of obliteration compared to surgery or radiosurgery.

The authors describe their experience with AVM embolization comparing embolization alone to medical management. The major findings of this study were that embolization was associated with an increased risk of hemorrhage during follow-up in unruptured patients and that embolization provided no protection against future hemorrhage in ruptured AVMs. The goal of embolization was not necessarily curative and thus may not necessarily serve as a direct comparison to studies that promote "curative" embolization; however, it does demonstrate the potential risks of embolization alone. Ideally, the study would have included a subgroup analysis based on Spetzler-Martin or Spetzler-Ponce grading systems given the differences in outcome among different grades of AVMs.

At our institution, endovascular embolization alone, either curative or palliative, is rarely used, but it is part of the AVM treatment armamentarium and may be employed in select situations. Far more commonly, embolization is performed prior to definitive microsurgical resection or radiosurgery, especially for ruptured AVMs. The controversy of AVM embolization requires larger, multi-center studies to elucidate the potential risks and benefits.

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