Radiosurgery for Cerebral Arteriovenous Malformations in A Randomized Trial of Unruptured Brain Arteriovenous Malformations (ARUBA)-Eligible Patients

A Multicenter Study

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Background and Purpose—The benefit of intervention for patients with unruptured cerebral arteriovenous malformations (AVMs) was challenged by results demonstrating superior clinical outcomes with conservative management from A Randomized Trial of Unruptured Brain AVMs (ARUBA). The aim of this multicenter, retrospective cohort study is to analyze the outcomes of stereotactic radiosurgery for ARUBA-eligible patients.

Methods—We combined AVM radiosurgery outcome data from 7 institutions participating in the International Gamma Knife Research Foundation. Patients with ≥12 months of follow-up were screened for ARUBA eligibility criteria. Favorable outcome was defined as AVM obliteration, no postradiosurgery hemorrhage, and no permanently symptomatic radiation-induced changes. Adverse neurological outcome was defined as any new or worsening neurological symptoms or death.

Results—The ARUBA-eligible cohort comprised 509 patients (mean age, 40 years). The Spetzler–Martin grade was I to II in 46% and III to IV in 54%. The mean radiosurgical margin dose was 22 Gy and follow-up was 86 months. AVM obliteration was achieved in 75%. The postradiosurgery hemorrhage rate during the latency period was 0.9% per year. Symptomatic and permanent radiation-induced changes occurred in 11% and 3%, respectively. The rates of favorable outcome, adverse neurological outcome, permanent neurological morbidity, and mortality were 70%, 13%, 5%, and 4%, respectively.

Conclusions—Radiosurgery may provide durable clinical benefit in some ARUBA-eligible patients. On the basis of the natural history of untreated, unruptured AVMs in the medical arm of ARUBA, we estimate that a follow-up duration of 15 to 20 years is necessary to realize a potential benefit of radiosurgical intervention for conservative management in unruptured patients with AVM.

Key Words: intracranial arteriovenous malformation ■ intracranial hemorrhages ■ radiosurgery ■ stroke ■ vascular malformations
the short follow-up duration (mean, 33.3 months), probable selection bias among participants, the considerable heterogeneity of the modalities used to treat AVMs in the intervention arm, and an unexpectedly excessive rate of AVM hemorrhage in the interventional arm (25% of treated patients). Despite these criticisms, the ARUBA trial was interpreted to indicate that patients with unruptured AVMs should be observed. The aims of this retrospective, multicenter cohort study are to determine the outcomes of ARUBA-eligible patients, who uniformly received treatment with radiosurgery and define the predictors of AVM radiosurgery outcomes in ARUBA-eligible patients.

Methods

Patient Selection for the ARUBA-Eligible Cohort

Institutional Review Board approved retrospective evaluations of Gamma Knife radiosurgery databases from 7 institutions that participate in the International Gamma Knife Research Foundation, including the University of Virginia, the University of Pittsburgh, the University of Sherbrooke, New York University, the University of Puerto Rico, Beaumont Health System, and the Cleveland Clinic, were performed to identify patients who underwent AVM radiosurgery between 1977 and 2014. The data from each individual center were deidentified and pooled by an independent third party. Ambiguities in the data were addressed by the contributing institution. The pooled data were then sent to the institution of the first, second, and senior authors for statistical analysis.

The inclusion criteria were AVM patients with sufficient baseline data to assess demographic information, nidus angiarchitectural, and radiosurgery parameters, ≥12 months of neuroimaging and clinical follow-up, and radiosurgery performed in a single stage. Patients with <12 months follow-up who developed complications were also included. To select patients for the ARUBA-eligible cohort, the following exclusion criteria were applied: Previous AVM hemorrhage, any previous AVM intervention including embolization or microsurgery, age <18 years, life expectancy <10 years (age >66 years for men or >71 years for women), and Spetzler–Martin grade V AVMs.

Baseline Data and Variables

The baseline data included patient, AVM, and radiosurgery variables. Patient attributes were sex, age, and time interval from clinical presentation to treatment with radiosurgery. AVM variables were maximum diameter, volume, eloquent location, deep venous drainage, and presence of associated intranidal or prenidal arterial aneurysms. Eloquent locations were defined as sensorimotor, language, and visual cortex, hypothalamus and thalamus, internal capsule, brain stem, cerebellar peduncles, and deep cerebellar nuclei. The Spetzler–Martin grade, modified radiosurgery-based AVM score, and Virginia Radiosurgery AVM Scale (VRAS) were determined for each AVM.

The radiosurgery technique used at each institution has been previously described. Briefly, a Leksell Model G stereotactic frame (Elekta AB, Stockholm, Sweden) was affixed to the calvarium after administration of local anesthesia. Thin-slice (typically a slice width of 1–2 mm) magnetic resonance imaging (MRI) or computed tomographic angiography, when MRI was not feasible, with intravenous contrast and digital subtraction angiography were performed to define the angiarchitectural and spatial anatomy of the AVM nidus. Radiosurgery treatment and dose planning were performed by an institutional team comprised a neurosurgeon, radiation oncologist, and medical physicist. Radiosurgery variables included year of treatment, margin dose, maximum dose, isodose line, and number of isocenters.

Follow-Up

Patients were followed with routine neuroimaging (MRI or computed tomographic angiography when MRI was not feasible) at 6-month intervals for the first 2 years after radiosurgery, and then annually thereafter. Additional neuroimaging was performed for neurological deterioration after radiosurgery.

Obliteration was defined by a lack of flow voids on MRI or anomalous arteriovenous shunting on angiography. Angiography was typically performed to confirm MRI-defined obliteration or to reevaluate a residual nidus for further intervention(s). Radiologically evident radiation-induced changes (RIC) were defined, by MRI, as perinidal T2-weighted hyperintensities. Symptomatic RIC were radiological changes associated with worsened neurological status, and they were defined as permanent when neurological deterioration persisted. Postradiosurgery hemorrhage was defined as any AVM-related intracranial hemorrhage in the latency period after radiosurgery. Clinical follow-up was obtained concurrently with neuroimaging follow-up whenever feasible. Follow-up data from outside institutions or physicians were transmitted to the treating institution for review. The patients’ neurological statuses at the most recent follow-up were compared with their baseline neurological examinations at the time of radiosurgery. Permanent neurological morbidity was defined as any sustained deterioration, at the most recent clinical follow-up, from the patient’s baseline neurological status. Adverse neurological outcome was defined as any symptomatic RIC (either transient or permanent), postradiosurgery hemorrhage, permanent neurological morbidity, increased seizure frequency in a patient with previous seizures, de novo seizures in a patient without previous seizures, or death. Favorable outcome was defined as AVM obliteration, no postradiosurgery hemorrhage, and no permanent RIC.

Statistical Analysis

Data are presented as mean and SD for continuous variables, and as frequency and percentage for categorical variables. Kaplan–Meier analysis was used to calculate actuarial obliteration rates. Patient, AVM, and radiosurgery variables were assessed as covariates in a Cox proportional hazards regression analysis for predictors of obliteration, and a logistic regression analysis for predictors of favorable outcome. Covariates with P<0.15 in the univariate analysis were entered into a multivariate model. Spetzler–Martin grade, radiosurgery-based AVM score, and VRAS were not included in the multivariate models because components of these scales were analyzed. All statistical tests were 2 sided. Statistical significance was defined as P<0.05.

Results

ARUBA-Eligible Cohort

From a total of 2361 patients with ≥12 months follow-up, 509 met the inclusion criteria for the ARUBA-eligible cohort, and these patients were derived from 7 institutions (Figure 1). Table 1 details the patient characteristics, AVM angiarchitectural features, and radiosurgery parameters. The mean age was 39.7 years, and the most common presenting symptoms were seizures (20.2%), headache (16.9%), and focal neurological deficit (7.1%). The mean AVM maximum diameter and nidus volume were 2.0 cm and 3.0 cm³, respectively. AVMs were localized to eloquent brain areas in 69.2% and had a component of deep venous drainage in 68.8%. The Spetzler–Martin grade was I or II in 45.6% and III or IV in 54.4%. The VRAS was 0 or 1 in 62.5% and 2 or 3 in 37.5%. The mean radiosurgery-based AVM score was 1.30. The mean radiosurgical margin dose was 21.7 Gy, and the mean follow-up duration after radiosurgery was 86.2 months.
A VM Obliteration

A VM obliteration was confirmed in 382 patients (75.0%), including 76 determined by MRI alone (14.9%) and 306 verified by angiography (60.1%). The actuarial obliteration rate after radiosurgery was 44.1% at 3 years, 70.3% at 5 years, 76.8% at 7 years, and 85.2% at 10 years (Figure 2A).

Table 1 details the univariate and multivariate Cox proportional regression analyses for predictors of A VM obliteration after radiosurgery. In the multivariate analysis, smaller A VM maximum diameter ($P=0.012$) and higher margin dose ($P=0.001$) were found to be independent predictors of obliteration.

AVM Hemorrhage, Complications, and Clinical Outcomes

A total of 34 AVM hemorrhages occurred in 32 patients (6.3%), including a single hemorrhage in each of 30 patients, and 2 hemorrhages in each of 2 patients, during the latency interval after radiosurgery. The cumulative latency period of the study was 3657 risk years, which yielded an annual postradiosurgery hemorrhage rate of 0.9%. RIC was radiologically evident in 138 patients (27.1%), symptomatic in 57 (11.2%), and permanent in 13 (2.6%).

Permanent neurological morbidity occurred in 23 patients after radiosurgery (4.5%) and 22 patients died (4.3%), yielding a combined permanent neurological morbidity and mortality rate of 8.8%. Of the 22 patients who died after radiosurgery, the cause of death was AVM hemorrhage in 5 (22.7%), unrelated to the patient’s AVM in 7 (31.8%), and unknown in 10 (45.5%). There were no mortalities associated directly with the radiosurgery procedure. Therefore, the range of AVM-related mortality was 1.0% (ie, assuming none of the unknown causes of death were related to the patient’s AVM) to 2.9% (ie, assuming all of the unknown causes of death were related to the patient’s AVM). Similarly, the...
mortality rate from AVM hemorrhage was as low as 15.6% (5/32 patients) and as high as 46.9% (15/32 patients). The rates of increased seizure frequency and de novo seizures were 1.9% (2/103 patients) and 0.5% (2/406 patients), respectively. Adverse neurological outcome occurred in 68 patients after radiosurgery (13.4%).

**Favorable Outcome**

Favorable outcome was achieved in 354 patients (69.5%, Figure 2B). Table 3 details the univariate and multivariate logistic regression analyses for predictors of favorable outcome after radiosurgery. In the multivariate analysis, smaller AVM maximum diameter \((P=0.035)\) and noneloquent AVM location \((P=0.023)\) were found to be independent predictors of favorable outcome. Patients with a nidus volume <4 cm\(^3\) and treated with a margin dose of \(\geq 18\) Gy were significantly more likely to have a favorable outcome (76.3%, 284/372 patients) compared with those with a nidus volume \(\geq 4\) cm\(^3\) or who were treated with a margin dose of \(<18\) Gy (51.1%, 70/137 patients; \(P<0.001\)).

**Discussion**

The primary treatment goal in the management of AVMs is elimination of hemorrhage risk. Presently, the only manner in which this can be achieved is through complete extirpation,
Table 3. Univariate and Multivariate Regression Analyses for Predictors of Favorable Outcome After AVM Radiosurgery

<table>
<thead>
<tr>
<th>Factors</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio</td>
<td>95% CI</td>
</tr>
<tr>
<td>Smaller AVM maximum diameter</td>
<td>1.92</td>
<td>1.54–2.39</td>
</tr>
<tr>
<td>Smaller AVM volume</td>
<td>1.15</td>
<td>1.09–1.22</td>
</tr>
<tr>
<td>Noneloquent AVM location</td>
<td>1.80</td>
<td>1.17–2.79</td>
</tr>
<tr>
<td>Absence of associated aneurysms</td>
<td>1.60</td>
<td>0.88–2.92</td>
</tr>
<tr>
<td>Lower Spetzler–Martin grade</td>
<td>1.83</td>
<td>1.40–2.41</td>
</tr>
<tr>
<td>Lower RBAS</td>
<td>3.02</td>
<td>1.97–4.63</td>
</tr>
<tr>
<td>Lower VRAS</td>
<td>1.81</td>
<td>1.47–2.23</td>
</tr>
<tr>
<td>Higher margin dose</td>
<td>1.24</td>
<td>1.16–1.31</td>
</tr>
<tr>
<td>Higher maximum dose</td>
<td>1.05</td>
<td>1.02–1.08</td>
</tr>
<tr>
<td>Higher isodose line</td>
<td>1.02</td>
<td>1.00–1.04</td>
</tr>
<tr>
<td>Fewer isocenters</td>
<td>1.09</td>
<td>1.01–1.18</td>
</tr>
</tbody>
</table>

Only factors with P<0.15 in the univariate analysis were listed. AVM indicates arteriovenous malformation; CI, confidence interval; NS, not significant in the multivariate analysis. *Statistically significant in the univariate analysis (P<0.05). †Grading scales were not included in the multivariate analysis.

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endothalvascular closure, or obliteration of the AVM nidus. AVM intervention risks upfront neurological morbidity, which is the tradeoff for permanent freedom from AVM hemorrhage. At the other end of the management spectrum, a conservative approach does not expose a patient to the upfront risk of treatment-related morbidity, but leaves the long-term residual risk of intracranial hemorrhage and death.18 The merits of intervention must be balanced by the estimated risk of an AVM’s natural history in patients who are managed conservatively. The benefit of intervention for patients with unruptured AVMs is a subject of considerable debate, primarily based on 2 factors interpreted to favor conservative management: (1) the hemorrhage risk of unruptured AVMs is lower than that of ruptured AVMs4 and (2) the treatment morbidity for unruptured AVMs may be higher than that of ruptured AVMs.4,5,19

The notion that patients with unruptured AVMs can be harmed by intervention more than conservative management was suggested by the early analysis of ARUBA, as well as by the prospective, observational AVM cohort study from the Scottish Audit of Intracranial Vascular Malformations.15,20 ARUBA has been appropriately scrutinized for its numerous methodological weaknesses.19 By analyzing a multicenter cohort of ARUBA-eligible patients treated with radiosurgery alone, we endeavor to address some of these weaknesses. First, the follow-up duration of ARUBA was too brief, given the young age at which many AVMs are diagnosed and the lifelong nature of the disease. The clinical follow-up duration of our study (86±62 months) was appreciably longer than that of ARUBA (33±20 months). In addition, this study included patients with AVMs in all brain locations, not just ones considered eligible for endovascular or microsurgical intervention (Table I in the online-only Data Supplement). Compared with ARUBA, in this study, fewer AVMs were supratentorial and lobar (44% in the current cohort versus 91% in the ARUBA cohort), more AVMs were found in critical brain locations (69% versus 47%), deep venous drainage was more common (69% versus 34%), and the Spetzler–Martin grade was higher (46% versus 61% grade I or II).

Patients in ARUBA had significant heterogeneity in the treatment approaches. A sizeable proportion of patients were treated with embolization alone (26%), despite the fact that embolization typically has the lowest obliteration rates as well as an estimated morbidity of 10% and mortality rate of 1% per embolization procedure.3,21 Furthermore, 66% of the treated patients in ARUBA had Spetzler–Martin grade I or II AVMs, for which resection can be strongly considered at experienced centers, and radiosurgery provides an excellent risk to benefit profile.22–25 Radiosurgery is a minimally invasive modality for the treatment of AVMs, and it is especially favorable, relative to microsurgery, for small- to moderate-sized AVMs in eloquent or deep brain areas.26–42 The results of many previous radiosurgery series are confounded by the inclusion of patients who were previously treated with surgical resection, embolization, and fractionated radiation therapy. Thus, comparing the outcomes of these unfiltered studies to those of the interventional arm of ARUBA cannot lead to generalizable conclusions. Because we applied the same inclusion and exclusion criteria as ARUBA, we are able to demonstrate the merits of radiosurgery for patients with unruptured AVMs in a large patient cohort.

The obliteration rates of the interventional arm of ARUBA were not reported. The majority of the patients who reached the primary end point of ARUBA experienced intracranial hemorrhage (67%). The early difference in the hemorrhage rates is presumably because of treatment-related hemorrhage. Either complete and incomplete surgical resection or embolization can result in postoperative hemorrhage because of cerebral vasomotor dysregulation or bleeding from a residual AVM.43–46 However, if treatment-related hemorrhage was the sole contributor, one would expect the Kaplan–Meier plot for the interventional arm to flatten over time. Because this does not occur, one can assume that any delayed hemorrhage is because of incomplete AVM occlusion. Patients with
obliterated nidi are afforded complete protection from AVM hemorrhage, except in unusual cases of recanalization after curative embolization, which occurs in ~1% of cases. In fact, at the time of ARUBA’s analysis, 46% of patients had not completed treatment and 18% of patients had not even initiated therapy. Therefore, at least half of the ARUBA patients randomized to intervention had patent AVMs at the time of analysis. The high rate of hemorrhage in the interventional arm of ARUBA further suggests that partial AVM treatment could have a destabilizing effect on the residual nidus, resulting in an increased hemorrhage rate compared with the expected natural history. Compared with the 24.5% of ARUBA patients who underwent intervention and experienced hemorrhage, only 8.3% of patients in our study had a hemorrhage after radiosurgery. One should also consider that the longer follow-up duration of our study translates to an even greater disparity in the annual post-treatment hemorrhage rates.

Overall, the most important finding of this multicenter study is that, for ARUBA-eligible patients, treatment with radiosurgery alone yields complete obliteration in the majority of cases with an acceptable long-term safety profile. Previous studies have also reported reasonably good outcomes after AVM resection and radiosurgery in ARUBA-eligible patients, although these analyses were performed in single-center cohorts. A crude comparison of our rates of unfavorable treatment outcome and adverse neurological outcome to the rates of the primary end point (death or symptomatic stroke) in the interventional and medical arms of ARUBA does not definitively support the use of radiosurgery for unruptured patients with AVM (Table II in the online-only Data Supplement). However, one should note that persistent AVM patency after radiosurgery was a significant contributor to the designation of unfavorable outcome in our analysis. In contrast, failure to achieve AVM obliteration was not factored into the analysis of adverse events in ARUBA. Using our definition of a favorable outcome, those who achieved AVM obliteration without postradiosurgery hemorrhage and permanent RIC have been provided a durable benefit from radiosurgery. We note that 70% of patients in this study had no new or worsening intervention-related neurological deficit and gained lifelong protection from AVM hemorrhage. Patients with small AVMs ($P=0.035$) located in noneloquent brain regions ($P=0.023$) were more likely to have a favorable outcome, which is consistent with previous AVM radiosurgery series.

With radiosurgery, the vast majority of complications associated with the treatment of ARUBA-eligible patients occurred within the first 2 years. Thereafter, the benefits of radiosurgery became more apparent over time, especially after the typical 3-year latency period after radiosurgery (Figure 2B).

Any interpretation of this study’s findings must occur in the context of its limitations. First and foremost, the retrospective design of this study subjects it to selection bias and treatment preferences of the participating institutions and physicians. Pooling data from multiple centers may mitigate the biases of any individual center or physician. However, only 7 of the 27 institutions that currently comprise the International Gamma Knife Research Foundation contributed data to this study. At its inception, a proposal for this study was sent to all member institutions of the International Gamma Knife Research Foundation, and only centers that provided data were included. This voluntary self-selection of contributing centers represents another potential source of bias. Although the primary goal of this study is to challenge the findings of ARUBA, the differences in study design do not allow an unequivocal comparison between our cohort of radiosurgically treated patients and the interventional and medical arms of ARUBA. Although we acknowledge that our classification of adverse neurological outcome is not the same as the primary end point of ARUBA, we think that it represents a similar clinically relevant end point, which can be reasonably used to compare the outcomes of patients enrolled in ARUBA to that of ARUBA-eligible patients treated with radiosurgery in our study cohort. Notably, complication rates reported in retrospective analyses are typically lower than those reported in prospective studies. Thus, any comparison of our results to those of ARUBA is probably being favorably biased toward better outcomes in our retrospective cohort. Also, the participating centers and their respective clinicians performing radiosurgery had significant experience in this procedure. The results achieved herein probably reflect the treatment biases of the physicians at these tertiary care facilities, but also the clinical experience afforded by a highly proficient multidisciplinary team.

Because of the nature of being tertiary referral centers, detailed clinical follow-up was not fully available for some patients whose data were contributed to this analysis. As such, we were unable to report the functional outcomes (ie, modified Rankin Scale scores) for the study cohort. In addition, the rigor of clinical follow-up was not uniform across the various participating institutions. This further complicates the comparison of our outcomes to those of ARUBA. Furthermore, obliteration was determined in 15% of patients by MRI only. Although angiography is the gold standard, MRI has been shown to be an accurate substitute for evaluating AVM obliteration without postradiosurgery hemorrhage and permanent RIC have been provided a durable benefit from radiosurgery. We note that 70% of patients in this study had no new or worsening intervention-related neurological deficit and gained lifelong protection from AVM hemorrhage. Patients with small AVMs ($P=0.035$) located in noneloquent brain regions ($P=0.023$) were more likely to have a favorable outcome, which is consistent with previous AVM radiosurgery series.

Despite the limitations of this study, we think that our analysis might stimulate the design of future prospective studies that compare radiosurgery to conservative management for patients with unruptured AVMs. The annual hemorrhage risk of the conservatively managed patients in ARUBA was 2.2%, which is consistent with previous natural history studies but higher than the 0.9% annual hemorrhage rate observed during the latency period of our cohort. Because 30% of the patients with in this study were determined to have an unfavorable outcome (incomplete AVM obliteration, hemorrhage during the latency period, or permanent treatment–related complication), we estimate that patients who undergo radiosurgery would have superior outcomes to observation after 17 years of follow-up. This estimate does not account for other neurological sequelae originating from a patent AVM, such as seizures and focal deficits secondary to chronic vascular steal.

Conclusions

Radiosurgery seems to decrease the hemorrhage risk of unruptured AVMs compared with their natural history. For unruptured AVMs that are deemed appropriate for either intervention or conservative management, treatment with radiosurgery...
may provide a benefit for some patients. However, considering only AVM rupture, an extended follow-up duration of \( \geq 15 \) to 20 years may be necessary to fully realize the benefit of intervention in unruptured patients with AVM who undergo radiosurgery. Prospective comparisons between radiosurgery and conservative management are necessary to more convincingly demonstrate the superiority, inferiority, or equivalency of this therapeutic modality for unruptured patients with AVM.

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**Disclosures**

Dr. Grills is a stockholder and serves on the Board of Directors of Greater Michigan Gamma Knife. Dr. Lunsford is a consultant and stockholder in Elekta. The other authors report no conflicts.

**References**


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SUPPLEMENTAL MATERIAL

Table I. Comparison of the baseline characteristics of the ARUBA-eligible patients treated with radiosurgery and patients enrolled in ARUBA.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ARUBA-eligible Patients Treated with Radiosurgery (N=509)</th>
<th>Patients Enrolled in ARUBA (N=223)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean±SD years)</td>
<td>40±14</td>
<td>44±12</td>
</tr>
<tr>
<td>Female Gender</td>
<td>238 (47%)</td>
<td>93 (41%)</td>
</tr>
<tr>
<td>Asymptomatic at Presentation</td>
<td>252 (50%)</td>
<td>94 (42%)</td>
</tr>
<tr>
<td>Seizure at Presentation</td>
<td>103 (20%)</td>
<td>95 (43%)</td>
</tr>
<tr>
<td>AVM Maximum Diameter &lt;3 cm</td>
<td>446 (88%)</td>
<td>138 (62%)</td>
</tr>
<tr>
<td>Lobar AVM Location</td>
<td>226 (44%)</td>
<td>203 (91%)</td>
</tr>
<tr>
<td>Infratentorial AVM Location</td>
<td>108 (21%)</td>
<td>12 (5%)</td>
</tr>
<tr>
<td>Eloquent AVM Location</td>
<td>352 (69%)</td>
<td>105 (47%)</td>
</tr>
<tr>
<td>Any Deep Venous Drainage</td>
<td>350 (69%)</td>
<td>75 (34%)</td>
</tr>
<tr>
<td>Associated Arterial Aneurysm</td>
<td>50 (10%)</td>
<td>36 (16%)</td>
</tr>
<tr>
<td>Spetzler-Martin Grade I</td>
<td>49 (10%)</td>
<td>65 (29%)</td>
</tr>
<tr>
<td>Spetzler-Martin Grade II</td>
<td>183 (36%)</td>
<td>71 (32%)</td>
</tr>
<tr>
<td>Spetzler-Martin Grade III</td>
<td>245 (48%)</td>
<td>63 (28%)</td>
</tr>
<tr>
<td>Spetzler-Martin Grade IV</td>
<td>32 (6%)</td>
<td>23 (10%)</td>
</tr>
<tr>
<td>Follow-up (mean±SD months)</td>
<td>86±62</td>
<td>33±20</td>
</tr>
</tbody>
</table>

ARUBA=A Randomized Trial of Unruptured Brain AVMs.
Table II. Comparison of the rates of unfavorable outcome and adverse neurological outcome in the ARUBA-eligible cohort after treatment with radiosurgery to rates of the primary endpoint for the interventional and medical arms of ARUBA (as treated), stratified by Spetzler-Martin grade.

<table>
<thead>
<tr>
<th>Spetzler-Martin Grade</th>
<th>Unfavorable Outcome(^1) in ARUBA-eligible Cohort Treated with Radiosurgery (N=509)</th>
<th>ANO(^2) in ARUBA-eligible Cohort Treated with Radiosurgery (N=509)</th>
<th>Primary Endpoint(^3) in ARUBA Interventional Arm as Treated (N=98)</th>
<th>Primary Endpoint(^3) in ARUBA Medical Arm as Treated(^4) (N=125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>12.2% (6/49)</td>
<td>8.2% (4/49)</td>
<td>14.3% (4/28)</td>
<td>5.4% (2/37)</td>
</tr>
<tr>
<td>II</td>
<td>27.3% (50/183)</td>
<td>12.0% (22/183)</td>
<td>43.3% (16/37)</td>
<td>2.9% (1/34)</td>
</tr>
<tr>
<td>III</td>
<td>31.8% (78/245)</td>
<td>15.9% (39/245)</td>
<td>57.1% (16/28)</td>
<td>8.8% (3/34)</td>
</tr>
<tr>
<td>IV</td>
<td>65.5% (21/32)</td>
<td>9.4% (3/32)</td>
<td>0% (0/5)</td>
<td>22.2% (4/18)</td>
</tr>
</tbody>
</table>

ARUBA=A Randomized Trial of Unruptured Brain AVMs.
\(^1\)Unfavorable outcome = incomplete AVM obliteration, post-radiosurgery hemorrhage, or permanently symptomatic radiation-induced changes.
\(^2\)Adverse neurological outcome (ANO) = Symptomatic radiation-induced changes (transient or permanent), post-radiosurgery hemorrhage, deterioration from baseline neurological status at last clinical follow-up (permanent neurological morbidity), worsening of baseline seizure status (i.e. increased seizure frequency in a patient with prior seizures or de novo seizures in a patient without prior seizures), or death (any cause).
\(^3\)Primary endpoint = death or symptomatic stroke (any clinically symptomatic event, including new focal neurological deficit, seizure, or new-onset headache, associated with hemorrhage or infarction on neuroimaging).
\(^4\)Baseline Spetzler-Martin grade not available for two patients in the medical arm due to lack of diagnostic angiography at enrollment.