The Risk of Stroke or Clinical Impairment After Stereotactic Radiosurgery for ARUBA-Eligible Patients

Bruce E. Pollock, MD; Michael J. Link, MD; Robert D. Brown, MD

Background and Purpose—The best management of patients with unruptured brain arteriovenous malformations (BA VM) is controversial. In this study, we analyzed the stroke rate and functional outcomes of patients having stereotactic radiosurgery (SRS) for unruptured BA VM using the same eligibility criteria and primary end points as the ARUBA trial.


Results—The median follow-up after SRS was 64 months. Fifteen patients (8.7%) had a hemorrhagic stroke at a median of 21 months after SRS. Six patients (3.5%) had a focal neurological deficit and 4 patients died (2.3%). The risk of stroke or death was 10.3% at 5 years and 11.5% at 10 years. Twelve additional patients (6.9%) had a focal neurological deficit from either radiation-related complications (7) or subsequent resection (5). The risk of patients’ having clinical impairment (modified Rankin Score ≥2) was 8.4% at 5 years and 12.0% at 10 years. Increasing BA VM volume was associated with both stroke or death (hazard ratio=1.06; 95% confidence interval, 1.0–1.11; P=0.04) and clinical impairment (hazard ratio=1.06; 95% confidence interval, 1.01–1.09; P=0.01). The 10-year risk of stroke or death and clinical impairment for patients with BA VM ≤5.6 cm³ was 5% and 4%, respectively.

Conclusions—The observed risk of stroke or death after SRS was approximately 2% per year for the first 5 years after SRS, declining to 0.2% annually for years 6 to 10. Patients with small volume BA VM may benefit from SRS compared with the natural history of unruptured BA VM over the planned follow-up interval of the ARUBA trial (5–10 years). (Stroke. 2013;44:437-441.)

Key Words: arteriovenous malformation • hemorrhage • stereotactic radiosurgery • stroke

Brain arteriovenous malformations (BA VM) are abnormal blood vessel collections with an incidence of 1.12 to 1.34 per 100,000 person-years.1,2 Most BA VM are discovered after an intracranial hemorrhage (ICH) with seizures and headaches being less frequent presentations. Whereas the treatment of patients with ruptured BA VM is typically directed at eliminating the nidus to reduce the chance of rebleeding, the best management of patients with unruptured BA VM is controversial.3,4 The argument against treatment of patients with unruptured BA VM is based on 3 factors. First, some older studies may have overestimated the annual risk of ICH for patients with unruptured BA VM.5 Second, the morbidity associated with arteriovenous malformations (AVM) bleeding may be less than previously thought.6,7 Third, the risk of neurological injury after treatment of unruptured BA VM may be greater than previously described.8-10 A randomized trial of unruptured brain arteriovenous malformations (ARUBA) was designed to compare the risk of observation versus prophylactic intervention for patients diagnosed with unruptured BA VM. The primary end points of the ARUBA trial are the composite risk of death or stroke and risk of death or clinical impairment, defined as a modified Rankin Score (MRS) ≥2. Although the design of ARUBA has been criticized for a number of reasons, including the intended follow-up period after randomization (planned, 5–10 years),11,12 it was funded by the National Institute of Neurological Disorders (U01 NS051483) and began enrolling patients in April 2007 at cerebrovascular centers around the world. In this study, we analyzed the risk of stroke or death and clinical impairment of patients having stereotactic radiosurgery (SRS) for unruptured BA VM using the same eligibility criteria and primary end points as the ongoing ARUBA trial.

Methods

Patients

All aspects of this retrospective study were approved by the Mayo Clinic Institutional Review Board, Rochester, MN. To be eligible for inclusion in the ARUBA trial and the current study, patients must have an unruptured BA VM and be aged at least 18 years. Exclusion criteria include: (1) evidence of recent or prior hemorrhage, (2) prior BA VM treatment, (3) BA VM that are deemed untreatable, (4) MRS ≥2, (5) life expectancy <10 years, (6) pregnancy, (7) thrombocytopenia, (8) uncorrectable coagulopathy, (9) multiple BA VM, (10) previous diagnosis of other intracranial vascular malformations, and (11) any neurocutaneous syndromes.

Information on all patients having SRS at our center was entered into a prospectively maintained database. BA VM morphology was defined by size (largest dimension), volume, anatomic location, and venous drainage. Location was defined as superficial (cerebral hemisphere, cerebellum, corpus callosum) or deep (basal ganglia,
thalamus, or brain stem). BAVM were further classified based on the Spetzler-Martin grading scale\textsuperscript{13} and the radiosurgery-based AVM score (RBAS=0.1[volume, cm\textsuperscript{3}]+0.02[age, years]+0.5[location, hemispheric/corpus callosum/cerebellar=0; basal ganglia/thalamus/brain stem=1]).

**Stereotactic Radiosurgery and Additional Procedures**

Radiosurgery was performed using the Leksell Gamma Knife (Elekta Instruments, Norcross, GA). Dose planning was based off a combination of either contrast-enhanced computed tomography or magnetic resonance imaging (MRI) and stereotactic biplanar angiography. One hundred sixty-two patients (93.1\%) underwent single-session SRS, whereas 12 patients (6.9\%) underwent staged-volume AVM procedures.\textsuperscript{14} The median treatment volume was 3.6 cm\textsuperscript{3} (interquartile range, 2.9–10.0). The median AVM margin dose was 18.0 Gy (interquartile range, 18–20). Follow-up after radiosurgery consisted of clinical examination and MRI at 1, 2, and 3 years after radiosurgery. Follow-up angiography was performed 3 to 5 years after SRS to determine the status of the AVM. Patients with residual BAVM on follow-up angiography were reevaluated for repeat radiosurgery or surgical resection. Twenty-four patients (13.8\%) underwent repeat SRS and 7 patients (4.0\%) underwent surgical resection. One patient required placement of a ventriculoperitoneal shunt after an intraventricular hemorrhage caused hydrocephalus.

**Follow-Up and Statistical Analysis**

Follow-up after SRS was performed at either our institution or by local physicians with imaging sent for independent review. A stroke after SRS was defined as a new focal neurological deficit (FND), seizure, or headache that was associated with an ICH or infarction identified on computed tomography or MRI. Clinical impairment was defined as a MRS ≥2 at the last follow-up examination. The risk of stroke or death and clinical impairment were determined using the Kaplan–Meier method. Univariate testing (log rank test) was performed on the following variables: sex, patient age, location (superficial versus deep), location (eloquent versus noneloquent), size (<3 cm versus ≥3 cm), volume, venous drainage (superficial versus any deep), Spetzler–Martin grade, and RBAS. Multivariate testing was performed on the patient and BAVM variables using a Cox proportional hazards model. We excluded the Spetzler–Martin grade and RBAS from multivariate testing because of the redundant variables (size, volume) and high concordance between these classification systems. Statistical significance was determined by a \(P<0.05\).

**Results**

Review of our prospectively maintained database found 185 ARUBA-eligible patients having SRS from 1990 to 2005. In accordance with Minnesota state statutes, living patients were required to consent to review of their medical records; 4 patients (2.3\%) refused research authorization. Eight patients (4.3\%) had no clinical or radiological follow-up. The characteristics of the remaining 174 patients are shown in Table 1. The median follow-up after SRS was 64 months (interquartile range, 36–120). Forty-four patients (25.3\%) had ≥10 years of follow-up after SRS.

One hundred fifteen of 165 patients (69.7\%) with ≥2 years of follow-up had BAVM obliteration confirmed after initial SRS by angiography (n=86) or MRI (n=29). Fifteen patients had BAVM obliteration confirmed (angiography, n=8; MRI, n=7) after additional BAVM treatment for an overall obliteration rate of 78.9\%. The median time to obliteration after patients' first procedure was 40 months (range, 12–90). Fifteen patients (8.6\%) had a hemorrhagic stroke at a median of 21 months (range, 7–70) after SRS. No patient had an ischemic stroke after SRS. Six patients (3.5\%) had FND and 4 patients died (2.3\%). The risk of stroke or death was 10.3\% at 5 years and 11.5\% at 10 years after SRS (Figure 1). Univariate analysis found BAVM size >3 cm \((P=0.02)\), increasing BAVM volume \((P=0.001)\) and higher RBAS \((P<0.001)\) were associated with stroke or death after SRS (Table 2). Multivariate testing found increasing BAVM volume predictive of stroke or death after SRS (hazard ratio=1.06; 95% confidence interval, 1.0–1.11; \(P=0.04\); Figure 2).

Twelve additional patients (6.9\%) had a FND from either radiation-related complications (n=7) or subsequent resection (n=5). Combined with the morbidity of post-SRS bleeding, 16 patients (9.2\%) progressed to an MRS ≥2 at last follow-up. Specifically, 11 of 86 patients (12.8\%) with a pre-SRS MRS of...
0 had a decline in their MRS (MRS 1=6; MRS 2=3; MRS 5=1; MRS 6=1), and 11 of 88 patients (12.5%) with a pre-SRS MRS of 1 had a decline in their MRS (MRS 2=4; MRS 3=2; MRS 4=1; MRS 6=4). Of note, 16 patients (18.2%) who presented with seizures and had a pre-SRS MRS of 1 became seizure-free off medications after SRS, thereby improving to a MRS of 0. The risk of progression to MRS ≥2 at last follow-up was 8.4% at 5 years and 12.0% at 10 years (Figure 3). Univariate analysis found BAVM size >3 cm (P=0.02), increasing BAVM volume (P=0.003), and higher RBAS (P=0.002) were associated with an increased risk of clinical impairment (Table 2). Multivariate testing found increasing BAVM volume predictive of progression to MRS ≥2 after SRS (hazard ratio=1.06; 95% confidence interval, 1.01–1.09; P=0.01; Figure 4).

Discussion

Although interventional therapy for patients with unruptured BAVM may provide benefit with regard to headache or epilepsy, the primary rationale for treatment is to reduce the future risk of ICH. A number of BAVM natural history studies were published from 1980 to 1990 that showed an annual future risk of ICH. As stated by Heros and Tu, “since the natural history of AVMs, whether ruptured or unruptured, is relatively poor, and since with careful selection many of these lesions can presently be excised with acceptable morbidity, surgical consideration should be given individually to every patient with an AVM.”19 In general, this has been standard neurosurgical teaching for the past 25 years,20 although the indications for resection of unruptured BAVMs has been questioned because of the chance of functional decline when outcomes are assessed using more sensitive measures, such as the MRS.3 Moreover, some recent natural history data suggest that the annual risk of ICH may be as low as 1% for patients with unruptured BAVM.21,22 Applying a 1% annual hemorrhage rate to our hypothetical patient aged 45 years, the lifetime risk of BAVM rupture decreases to 30%. If the chance of serious morbidity or mortality after a BAVM hemorrhage is in the range of 27% to 40%,6,7 then the lifetime risk of death or significant clinical impairment would be approximately 10%. Therefore, to provide clinical benefit for patients with unruptured BAVM, if such low long-term hemorrhage rates are correct, the risk of BAVM treatment must be less than the natural history of these lesions to justify intervention.

Stereotactic radiosurgery is an accepted treatment option for patients with BAVM. Similar to microsurgery, the primary goal of SRS is BAVM elimination to reduce the chance of future hemorrhage. However, unlike BAVM resection that eliminates the risk of bleeding at the time of surgery, SRS results in nidus obliteration typically between 1 and 5 years after the procedure. Initially, it was believed that there was an increased risk of ICH after SRS prior to obliteration, but more detailed analysis of this question has suggested that the risk of bleeding is either unchanged or decreased after BAVM SRS.23–26 Maruyama et al25 reviewed 500 BAVM patients having SRS based arteriovenous malformation score.

Table 2. Analysis of Factors Associated With Stroke/Death or Progression to MRS ≥2 After SRS

<table>
<thead>
<tr>
<th>Factor</th>
<th>Stroke or Death</th>
<th>Progression to MRS ≥2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate HR (95% CI, P-Value)</td>
<td>Multivariate HR (95% CI, P-Value)</td>
</tr>
<tr>
<td>Sex</td>
<td>1.7 (0.6–5.0, 0.33)</td>
<td>2.3 (0.7–7.3, 0.16)</td>
</tr>
<tr>
<td>Age</td>
<td>1.03 (0.99–1.07, 0.12)</td>
<td>1.03 (0.99–1.07, 0.19)</td>
</tr>
<tr>
<td>Presentation (Seizure vs other)</td>
<td>1.3 (0.5–3.8, 0.62)</td>
<td>1.4 (0.5–4.3, 0.54)</td>
</tr>
<tr>
<td>Size (≤3 cm vs &gt;3 cm)</td>
<td>3.8 (1.2–12.0, 0.02)</td>
<td>1.9 (0.5–7.6, 0.34)</td>
</tr>
<tr>
<td>BAVM location (superficial vs deep)</td>
<td>2.7 (0.6–11.9, 0.19)</td>
<td>3.3 (0.6–17.0, 0.16)</td>
</tr>
<tr>
<td>BAVM location (eloquent vs noneloquent)</td>
<td>1.6 (0.5–5.6, 0.47)</td>
<td>1.08 (0.3–4.6, 0.92)</td>
</tr>
<tr>
<td>BAVM volume</td>
<td>1.08 (0.14–1.02, 0.001)</td>
<td>1.06 (1.01–1.11, 0.04)</td>
</tr>
<tr>
<td>Venous drainage (superficial vs any deep)</td>
<td>1.2 (0.4–3.3, 0.76)</td>
<td>1.2 (0.4–3.7, 0.70)</td>
</tr>
<tr>
<td>Spetzler-Martin grade</td>
<td>1.6 (0.9–2.8, 0.10)</td>
<td>NT</td>
</tr>
<tr>
<td>RBAS</td>
<td>2.1 (1.5–2.9, &lt;0.001)</td>
<td>NT</td>
</tr>
</tbody>
</table>

BAVM indicates brain arteriovenous malformation; CI, confidence interval; HR, hazard ratio; MRS, modified Rankin Score; NT, not tested; and RBAS, radiosurgery-based arteriovenous malformation score.
and reported an overall 54% reduction in the bleeding risk during the latency interval before nidus obliteration. Of note, the risk reduction was greater for the 310 patients who presented with ICH compared with the 190 patients without prior ICH. Karlsson et al. found some degree of protection against ICH occurred as early as 6 months after SRS for patients receiving a BAVM margin dose of 25 Gy. Included in all of these studies were patients with both ruptured and unruptured BAVM. One of the primary objections to the ARUBA trial is that the follow-up period is insufficient and, consequently, the complication rate of interventional therapy will surpass the natural history bleeding rate. In the current series of unruptured BAVM, we noted an annual ICH risk of approximately 2% for the first 5 years after SRS, which declined to 0.2% per year for years 6 to 10 after the procedure. Thus, the hemorrhage risk in the first several years after SRS is comparable with the annual bleed rate noted in natural history BAVM studies on patients with unruptured BAVM (1.6%–2.2%), and then appears to decrease below the risk for untreated BAVM as more patients achieve nidus obliteration and are protected against the future risk of bleeding.

In addition to the morbidity associated with BAVM bleeding, patients having SRS are also at risk for radiation-related complications. Significant improvements in neuroimaging, dose-planning software, and SRS devices over the past 30 years have all contributed to improved patient outcomes after BAVM SRS. Nonetheless, the parenchyma adjacent to the BAVM receives a dose of ionizing radiation that can result in tissue damage. The primary factors associated with the amount of radiation delivered to nearby structures are the BAVM volume and the prescribed radiation dose. Treatment of larger BAVMs and higher prescribed doses both increase the radiation exposure of the nearby tissues. Areas of increased signal on long-repetition time MRI are noted in 30% to 50% of patients after BAVM SRS. The imaging changes generally occur in the first year after SRS, most are asymptomatic and typically resolve on later MRI studies. Patients with BAVMs involving the thalamus, basal ganglia, and brain stem are more likely to develop FND secondary to the imaging changes noted on MRI. Only 7 patients (4.0%) developed a permanent radiation-related FND after SRS, likely relating to both the size of the treated BAVM (median, 5.6 cm³) and small number (5.8%) of patients with BAVM in deep locations.

Patient selection is a critical component of successful BAVM SRS. The Spetzler–Martin grading scale is an accepted method to predict outcomes after the surgical resection of BAVM, but is less reliable in predicting obliteration and radiation-related complications after SRS. To that end, we developed a RBAS based on 3 patient factors (patient age, BAVM volume, BAVM location) associated with not only nidus obliteration, but also radiation-related complications. The RBAS has been validated by centers performing Gamma Knife SRS, linear accelerator-based SRS, and the CyberKnife SRS. In the current series, patients with larger volume BAVM, and thus higher RBAS, were at greater risk of stroke or clinical impairment after SRS. For example, the 10-year risk of MRS ≥2 for patients with a RBAS ≤1.50 was 2%, compared with 13% at 5 years and 18% at 10 years for patients with a RBAS >1.50. This means that younger patients with small-volume unruptured BAVM had a very low risk of clinical impairment or death after SRS, whereas older patients with larger BAVM are more likely to suffer either a hemorrhagic stroke or radiation-related complication after SRS. Consequently, this data suggests that select patients with unruptured BAVM may benefit from SRS compared with medical management, even at the follow-up period planned for the ARUBA trial.

A number of factors must be considered that limit the results of this study. First, the study is a retrospective review of patients selected to have SRS at our center, and therefore it does not provide the quality of evidence derived from prospectively acquired population-based studies or randomized controlled trials.
clinical trials. Second, there is no control group so comparing our results with previously published studies may not accurately reflect the outcomes between randomized BAVM patients having medical management or SRS. Third, although BAVM obliteration after SRS was not the focus of this report, the ARUBA trial requires angiography to confirm cure after intervention, whereas we calculated our post-SRS obliteration rate using both angiography and MRI. Fourth, our follow-up period (median, 61.5 months) is similar to what is planned for the ARUBA trial, but is not sufficient to evaluate the risk of late radiation-related complications after BAVM SRS.23,23 Fifth, patients in our study underwent SRS from 1990 through 2005, and the ARUBA trial did not begin enrolling patients until 2007. Although the patients in the present study were not treated concurrently with the ARUBA trial, no significant changes to our SRS technique or dose-prescription guidelines have occurred in recent years. The characteristics of 60 ARUBA-eligible patients having SRS at our center from 2007, until the present were comparable with the patients in this study with regard to age, BAVM location, BAVM volume, and radiation doses (data not shown). The crude annual risk of ICH in 48 of these patients with follow-up after SRS (median, 22 months) was 2.9% (3 ICH/103.1 patient-years), which is similar to the bleeding risk noted in our study group.

Disclosures

The authors have no financial or commercial disclosures. Bruce E. Pollock is an adjudicator (Radiosurgery) for the ARUBA trial.

References

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