Risk Reduction of Cerebral Stroke After Stereotactic Radiosurgery for Small Unruptured Brain Arteriovenous Malformations

Shunya Hanakita, MD, PhD; Masahiro Shin, MD, PhD; Tomoyuki Koga, MD, PhD; Hiroshi Igaki, MD, PhD; Nobuhito Saito, MD, PhD

Background and Purpose—A Randomized Trial of Unruptured Brain Arteriovenous Malformations (ARUBA) indicated the superiority of medical management in reducing the risks for strokes and other neurological deficits over observation alone. The aim of our study was to verify the rationale for stereotactic radiosurgery (SRS) for small unruptured arteriovenous malformation.

Methods—A retrospective review was performed for 292 patients with unruptured arteriovenous malformations referred for SRS. The risks for cerebral hemorrhages were statistically compared before and after SRS.

Results—Of the 292 patients in whom arteriovenous malformation was found unruptured at initial diagnosis, 17 sustained hemorrhages in the period between the diagnosis and the initial therapeutic intervention (annual bleeding rate, 2.1%; 95% confidence interval [CI], 1.2%–3.4%). Of the remaining 275 patients, 240 were initially treated with SRS, and 16 sustained a hemorrhage after SRS (annual bleeding rate, 1.1%; 95% CI, 0.6%–1.8%), but only 2 sustained a hemorrhage after angiographic obliteration (annual bleeding rate, 0.3%; 95% CI, 0.04%–1.2%). Comparing the risk of hemorrhage between the periods before and after SRS, a 53% risk reduction was achieved after SRS (hazard ratio, 0.47; 95% CI, 0.24–0.94; \( P=0.03 \)), and 85% reduction was achieved after angiographic obliteration (hazard ratio, 0.15; 95% CI, 0.02–0.53; \( P=0.002 \)).

Conclusions—SRS can significantly reduce the risk of stroke in the patients with small unruptured arteriovenous malformations. To definitively determine the clinical benefits of SRS, a longer follow-up will be necessary. However, based on our results, we can recommend SRS for patients who face a latent risk for stroke from this intractable vascular disease. (Stroke. 2016;47:1247-1252. DOI: 10.1161/STROKEAHA.116.013132.)

Key Words: arteriovenous malformation ■ hemorrhage ■ radiosurgery ■ stroke ■ vascular disease

An arteriovenous malformation (AVM) of the brain is a congenital vascular malformation that increases the risk for cerebral strokes in young individuals, with the potential for serious neurological complications or death.1–3 In patients with ruptured AVMs, the annual risk of rebleeding has been estimated to be between 3.7% and 7.5%.4–10 Radical treatment, including surgical excision, radiosurgery, endovascular treatment, and combinations of these procedures, is considered when the risks associated to a therapeutic intervention are estimated to be lower than the accumulated risks of the outcomes of AVM-related cerebral hemorrhage.2 In contrast, for patients with an unruptured AVM, therapeutic intervention remains uncertain because the expected risk for cerebral hemorrhage with the natural history of AVMs largely depends on the characteristics of the patients selected for observation and on the definition of the starting point of observation. The annual bleeding risk of observed AVMs has been reported to be relatively low, ranging between 1.3% and 4.0%, even when the period of observation has been limited to the time from diagnosis to the last follow-up.4–10 Therefore, there is a significant clinical controversy around recommendation of invasive interventions of AVMs, considering their relatively benign natural course.

To evaluate the clinical benefits, or nonbenefits, of an invasive management of AVMs, a randomized trial of unruptured brain AVMs, A Randomized Trial of Unruptured Brain Arteriovenous Malformations (ARUBA) study, was started to prospectively determine the risk of death and symptomatic stroke in patients who were followed-up by observation only compared with patients who were allocated to either a medical management of unruptured AVM or a medical management combined with an interventional procedure.11 At its first, short-term point of analysis of 33 months, the ARUBA study provided evidence of the benefits of medical management in

Received February 17, 2016; final revision received February 17, 2016; accepted March 17, 2016.
From the Departments of Neurosurgery (S.H., M.S., T.K., N.S.), and Radiology (H.I.), The University of Tokyo Hospital, Tokyo, Japan.
The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.116.013132/-/DC1.
Correspondence to Masahiro Shin, MD, PhD, Department of Neurosurgery, The University of Tokyo Hospital, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. E-mail SHIN-NSU@h.u-tokyo.ac.jp
© 2016 American Heart Association, Inc.
Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.116.013132
lowering the risks for strokes and for neurological deficits unrelated to stroke. Although follow-up from the ARUBA study is ongoing for another 5 years to establish longer-term results, we used the short-term outcomes of the study to justify our aim of evaluating the rational for stereotactic radiosurgery (SRS), one of the least invasive therapeutic interventions for small, unruptured brain AVMs. Our previous study on the clinical indications for SRS indicated that SRS could significantly reduce the risk of hemorrhage from brain AVM, regardless of evidence of angiographic obliteration. However, in this study, the subgroup analysis failed to prove the risk reduction in patients with an unruptured AVM, and the clinical benefits of SRS in this clinical group remained controversial at that time. Ten years have passed since these results were published, and we have accumulated >100 cases of unruptured brain AVMs with longer follow-up periods. Therefore, the aim of this study was to reevaluate the clinical benefits of SRS for small unruptured AVMs.

Methods

Patients
The methods for our retrospective study were approved by the institutional review board of the University of Tokyo Hospital (IRB No. 2231). Between July 1990 and December 2010, 730 patients underwent SRS for an intracranial AVM using the Leksell Gamma Knife (Elekta Instruments, Norcross, GA). The diagnosis of AVM was confirmed by the combination of cerebral angiography and either computed tomography or magnetic resonance imaging (MRI).

The selection of patients included in our retrospective analysis is shown in Figure. Prospective subjects were 298 patients who were referred to our hospital for radiosurgery before rupture of their AVM. All patients were informed of the expected outcomes of the natural history of unruptured AVMs, SRS, and other therapeutic alternatives previously reported. All patients provided informed consent to proceed with SRS. In 6 patients, the AVM nidi was estimated to be too large for safe treatment using a single-session SRS; these patients were treated using volume-staged SRS, with their data excluded from the analysis. Therefore, the medical information of 292 patients was included in the final analysis. Initial clinical presentations of patients forming our study group included seizures (117 patients, 40%) and headaches (54 patients, 18%). The remaining 88 patients (30%) did not report any AVM-related symptoms, with the malformation being identified incidentally during other procedures (Table 1).

Radiosurgical Procedures
After the Leksell stereotactic frame was fixed to the head, the patient underwent stereotactic imaging, using a combination of angiography with either computed tomography or MRI, to obtain precise information on the shape, volume, and 3-dimensional (3D) coordinates of the AVM nidus. Surgical planning was collaboratively determined by neurosurgeons and radiation oncologists, using commercially available software (KULA from 1990 to 1998, Leksell GammaPlan thereafter; Elekta Instruments, Norcross, GA). In principle, the ideal dose applied to the margin of each AVM nidus was 20 Gy, with the use of 50% isodose lines. Prescribed doses were occasionally modified after; Elekta Instruments, Norcross, GA). In principle, the ideal dose applied to the margin of each AVM nidus was 20 Gy, with the use of 50% isodose lines. Prescribed doses were occasionally modified.

Follow-Up Evaluation and Statistical Analysis
After SRS, follow-up clinical examinations were performed at our hospital or by referring physicians, with images obtained independently evaluated by neurosurgeons and radiologists at our hospital. Until the end of 1992, patients underwent serial cerebral angiography every year after SRS. After 1992, patients underwent less invasive imaging for assessment every 6 months, either by enhanced MRI or computed tomography; cerebral angiography was recommended when image-based assessment indicated probable obliteration of the nidus. Obliteration of the nidus was identified by angiography as a disappearance of both abnormal vessels related to the AVM and early venous drainage. For patients who declined angiography, obliteration was defined as the disappearance of flow voids for the AVM on T2-weighted images and on 3D contrast-enhanced time-of-flight MR angiography.

Statistical analyses were performed using JMP 11 software (SAS Institute, Cary, NC). The actuarial obliteration rate was calculated using the Kaplan–Meier method. A time-dependent Cox proportional hazards model was used, in univariate and multivariate analyses, to evaluate factors potentially affecting nidus obliteration and hemorrhage post SRS. Factors associated with adverse events were also evaluated using univariate and multivariate logistic regression analysis to control for duration of observation. To evaluate the contribution of SRS in reducing the risk of AVM-related stroke, our previously reported methods were applied. Specifically, the follow-up period for each patient was separated into 3 different time periods: duration from time of diagnosis to SRS, duration from SRS to angiographic confirmation of obliteration, and duration from time of angiographic confirmation of obliteration to cerebral hemorrhage or neurological deficits. The risks of cerebral hemorrhages and neurological deficits unrelated to stroke were statistically compared. The reduction in the incidence of hemorrhage in the periods after radiosurgery was calculated as

\[
\text{Reduction in the incidence} = 100 \times (1 - \text{hazard ratio}) \tag{1}
\]

A two-sided P value of <0.05 was considered to be statistically significant. The annual hemorrhage rate was calculated as the number of hemorrhages divided by the sum of the observation periods. To adjust for potential biases, a secondary analysis for hemorrhage risk assessment was performed, including the 12 patients who had
sustained a hemorrhage before SRS and were treated solely with SRS, as, in reality, these patients cannot be considered to have had an unruptured AVM at the time of SRS. In addition, as obliteration of the nidus was identified at the time of angiographic investigation, actual obliteration of nidi likely would have occurred before imaging.

Therefore, we recalculated our risk analysis with the assumption that obliteration occurred 6 months before angiographic confirmation, as previously described. In addition, in this analysis, 6 patients had confirmed obliteration on MRI but not on angiography (further angiography is scheduled). We principally categorized these 6 patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total</th>
<th>Unruptured AVM</th>
<th>Subsequent Rupture of AVM</th>
<th>Unruptured AVM Initially Treated With SRS</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>292</td>
<td>275</td>
<td>17</td>
<td>240</td>
<td></td>
</tr>
<tr>
<td>Male/female</td>
<td>187/105</td>
<td>175/100</td>
<td>12/5</td>
<td>151/89</td>
<td>0.37</td>
</tr>
<tr>
<td>Median age at SRS (IQR)</td>
<td>38 (29–50)</td>
<td>38 (29–50)</td>
<td>33 (30–44)</td>
<td>39 (30–50)</td>
<td>0.61</td>
</tr>
<tr>
<td>Median f/u period, mo (IQR)</td>
<td>62 (36–106)</td>
<td>62 (36–102)</td>
<td>42 (25–86)</td>
<td>62 (36–102)</td>
<td>0.19</td>
</tr>
</tbody>
</table>

### Clinical presentation

- **Seizure**: 117 (40) 107 (37) 10 (3.4) 89 (30) 0.12
- **Incidental**: 88 (30) 86 (29) 2 (0.7) 78 (27) 0.10
- **Headache**: 54 (18) 53 (18) 1 (0.3) 49 (17) 0.21
- **Others**: 32 (11) 29 (10) 3 (1.0) 24 (8)

### Treatment with other modalities

- **No. of patients**: 35† 0‡

### Location of nidi

- **Basal ganglia/thalamus**: 17 (5.8) 13 (4.4) 4 (1.7) 12 (4.1) 0.01*
- **CP angle/brain stem**: 8 (2.7) 6 (2.0) 2 (0.7) 5 (1.7) 0.07
- **Cerebellum**: 11 (3.8) 11 (3.8) 0 10 (3.4) 0.39
- **Corpus callosum**: 11 (3.8) 9 (3.1) 2 (0.7) 8 (2.7) 0.14
- **Frontal lobe**: 79 (27) 75 (26) 4 (1.7) 62 (21) 0.83
- **Temporal lobe**: 70 (24) 68 (23) 2 (0.7) 58 (20) 0.37
- **Occipital lobe**: 39 (13) 37 (13) 2 (0.7) 34 (12) 0.78
- **Parietal lobe**: 57 (20) 56 (19) 1 (0.3) 52 (18) 0.21

### Radiosurgical dosimetry

- **Median nidus, volume, cm³ (IQR)**: 4.4 (2.1–8.4) 4.3 (2.1–8.0) 5.6 (1.9–11.4) 4.3 (2.3–8.3) 0.48
- **Median AVM score (IQR)**: 1.32 (0.99–1.75) 1.31 (0.99–1.73) 1.66 (1.26–1.93) 1.32 (1.00–1.75) 0.09

### AVM score

- **<1**: 73 (25) 71 (24) 2 (0.7) 59 (20) 0.22
- **1.0–1.5**: 108 (37) 102 (35) 6 (2.1) 89 (30) 0.47
- **1.5–2.0**: 69 (24) 63 (23) 6 (2.1) 57 (20) 0.55
- **>2**: 42 (14) 39 (14) 3 (1.0) 35 (12) 0.72

### Spetzler–Martin grade

- **I**: 84 (29) 82 (30) 2 (0.7) 76 (26) 0.10
- **II**: 115 (39) 110 (40) 5 (1.7) 95 (33) 0.45
- **III**: 69 (24) 64 (23) 5 (1.7) 53 (18) 0.54
- **IV**: 15 (5) 13 (5) 3 (1.0) 11 (3.8) 0.06
- **VI**: 8 (3) 6 (2) 2 (0.7) 5 (1.7) 0.07

Data are expressed as n (%) unless otherwise indicated. AVM indicates arteriovenous malformation; CP angle, cerebellar-pontine angle; f/u, follow-up; IQR, interquartile range; and SRS, stereotactic radiosurgery.

*Statistical analysis of the 17 patients who had subsequent rupture of AVM and the 240 patients who had unruptured AVM initially treated with SRS was performed to compare the patient characteristics.

†Thirty-five patients underwent combination therapy with other modalities (endovascular treatment+SRS in 29, surgery+SRS in 3, endovascular treatment+surgery+SRS in 3).

‡None underwent treatment before subsequent hemorrhage, but 5 of 17 patients underwent endovascular treatment after subsequent hemorrhages.
as unobliterated nidus. However, in assumption of best scenario, we secondly analyzed at the assumption that these patients would be obliterated (Table 2).

Results

Patients, Characteristics of Lesions, and Treatment

The clinical characteristics of all patients are summarized in Table 1. Among the 292 patients, the median age at the time of SRS was 38 years (interquartile range [IQR], 29–50 years). The median maximum nidus diameter was 25 mm (IQR, 20–32 mm) and median nidus volume was 4.4 cm³ (IQR, 2.1–8.4 cm³). Using the Spetzler–Martin grading system of AVMs, 84 (29%) of AVMs were classified as grade I, 115 (39%) as grade II, 69 (24%) as grade III, and 15 (5%) as grade IV. Eight lesions (3%), which were partially or entirely located in the brain stem, were classified as grade V lesions (3%), which were partially or entirely located in the brain stem. The median post SRS follow-up period was 62 months (IQR, 36–106 months), with 266 patients (91%) followed for >2 years.

Risk of Hemorrhage Before SRS

Of the 292 patients with an unruptured AVM at initial diagnosis, 17 patients sustained a single hemorrhage before the time of diagnosis and the initial therapeutic intervention, including surgery, endovascular treatment, or SRS. The period of observation from diagnosis to initial intervention ranged between 0.5 and 410 months (mean ± SD, 33 ± 63 months; median, 6 months; IQR, 3–32 months). AVM-related hemorrhages occurred 4 to 192 months after diagnosis (mean, 51 months; median, 36 months), with 17 hemorrhages observed in 796 patient-years. Therefore, the annual bleeding rate before intervention was 2.1% (95% confidence interval [CI], 1.2%–3.4%; Table 3). The initial clinical presentation for the 17 patients who sustained a hemorrhage included seizures in 10 patients (59%) and headache in 1 patient (56%), with 2 patients (12%) being asymptomatic. The clinical characteristics of these 17 patients were comparable with those of 240 patients who did not sustain a hemorrhage during the observation period (Fisher exact test, Table 1).

Obliteration Rate After SRS

Of the 275 patients who underwent SRS for their unruptured AVM, 240 patients (87.3%) were initially treated with SRS at our institution, with the other 35 patients (12.7%) initially treated with other modalities, including endovascular surgery (n=29), surgical resection (n=3), and surgical resection with endovascular treatment (n=3), and they were referred to our institution for SRS of the residual nidi. For the 240 patients who were treated only with SRS, after SRS, nidus obliteration was identified by angiography in 133 patients and on MRI in 32, at a median of 35 months (IQR, 25–44 months) postintervention. Of the 32 patients in whom nidus obliteration was confirmed on MRI, 6 patients were scheduled for further angiographic evaluation at the last follow-up, with the remaining 26 patients declining further angiographic investigation. The overall actuarial angiographic obliteration rates

<table>
<thead>
<tr>
<th>Type of Analysis</th>
<th>No. of Points</th>
<th>No. of Hemorrhage Before Treatment</th>
<th>No. of Hemorrhage After SRS</th>
<th>After Treatment vs Before Treatment</th>
<th>Latency Period vs Before Treatment</th>
<th>After Obliteration vs Before Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>292</td>
<td>17/292</td>
<td>14/240*</td>
<td>2/128</td>
<td>0.47 (0.24–0.94)</td>
<td>0.03</td>
</tr>
<tr>
<td>Secondary analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Including patients with subsequent hemorrhage†</td>
<td>252</td>
<td>15/252†</td>
<td>2/133</td>
<td>0.49 (0.25–0.96)</td>
<td>0.04 (0.29–1.20)</td>
<td>0.14 (0.02–0.52)</td>
</tr>
<tr>
<td>Assumption of earlier occlusion‡</td>
<td>240</td>
<td>12/240</td>
<td>4/126</td>
<td>1.03 (0.47–2.34)</td>
<td>0.94 (0.02–0.53)</td>
<td>0.002</td>
</tr>
<tr>
<td>Including patients with subsequent hemorrhage with the assumption of earlier occlusion</td>
<td>252</td>
<td>13/252</td>
<td>4/131</td>
<td>0.53 (0.25–1.11)</td>
<td>0.09 (0.08–0.72)</td>
<td>0.008</td>
</tr>
<tr>
<td>Assumption of MRI occlusions as AVM occlusion§</td>
<td>240</td>
<td>14/240</td>
<td>2/134</td>
<td>0.56 (0.26–1.16)</td>
<td>0.12 (0.02–0.53)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

AVM indicates arteriovenous malformation; CI, confidence interval; HR, hazard ratio; MRI, magnetic resonance imaging; and SRS, stereotactic radiosurgery.

†The time of obliteration was assumed to be 6 months before evidence of obliteration on angiography. For 6 patients who are confirmed obliteration on MRI and further angiography is scheduled are assumed as occlusion.

‡Including 12 patients who sustained hemorrhage between initial diagnosis and initial SRS who were treated only by SRS.

§In the assumption that 6 patients in whom nidus obliteration was confirmed on MRI but not on angiography was classified as obliterated, and the time of obliteration was occurred 6 months earlier before the date of angiographic confirmation.
were 46%, 69%, and 73% at 3, 5, and 6 years, respectively. Factors associated with obliteration of AVM were analyzed, with higher marginal dose being the only significant factor identified on univariate (P=0.007, Table I in the online-only Data Supplement) and multivariate analyses (P=0.01, Table II in the online-only Data Supplement).

**Risk of Hemorrhages After SRS**

Of the 240 patients who underwent only SRS, 16 sustained a hemorrhage. The annual risk of hemorrhage was estimated at 1.1% (16 hemorrhages over 1406 patient-years; 95% CI, 0.6%–1.8%). The median time from SRS to hemorrhage was 15 months (range, 5–92 months; mean±SD, 30±30 months; IQR, 9–56 months), with 14 hemorrhages occurring before angiographic confirmation of nidus obliteration, of which 12 patients sustained their hemorrhage within 3 years of SRS treatment (Table 3). Two patients sustained a hemorrhage after confirmation of nidus obliteration at 50 and 75 months post SRS and at 16 and 27 months after obliteration. Therefore, the annual risk of hemorrhage in the latency period post SRS was estimated at 1.7% (14 hemorrhages over 807 patient-years; 95% CI, 1.0%–2.9%) before confirmation of obliteration by imaging, and 0.3% (2 hemorrhages over 599 patient-years; 95% CI, 0.04%–1.2%) after obliteration. The overall annual rates of hemorrhage post SRS were 2.1% at 1 year, 2.3% at 2 years, 1.0% at 3 years, and 0.5% thereafter (Table 3).

**Risk Reduction and Clinical Benefits of SRS**

The accumulated risks of hemorrhages before SRS were 5.7% at 2 years, 11% at 5 years, and 23% at 10 years, with risks and post SRS of 4.3% at 2 years, 5.9% at 5 years, and 9.5% at 10 years. Comparing the risk for hemorrhage between the periods before SRS to those after SRS, a 53% risk reduction was achieved after SRS (hazard ratio, 0.47; 95% CI, 0.24–0.94; P=0.03; Table 2). However, when comparing the risk for hemorrhage between the period before SRS and the latency period from SRS to confirmation of angiographic obliteration, a risk reduction was not apparent (hazard ratio, 0.56; 95% CI, 0.27–1.15; P=0.11). After confirmation of AVM obliteration by imaging, the risk for hemorrhage was further reduced, with an 85% reduction in risk for hemorrhaging achieved after angiographic obliteration (hazard ratio, 0.15; 95% CI, 0.02–0.53; P=0.002). Of the factors associated with AVM-related hemorrhaging post SRS analyzed, existence of deep venous drainage was the only significant factor in univariate (P=0.006, Table I in the online-only Data Supplement) and in multivariate analyses (P=0.002, Table II in the online-only Data Supplement).

**Neurological Deficits Unrelated to Stroke**

Radiation-induced adverse events were observed in 27 patients (10%) at a median 12 months post SRS (range, 2–37 months). The symptoms for 23 of these patients were mild and transient, with 4 patients (1.7%) experiencing persistent neurological deficit. In 8 patients, preexisting symptoms further deteriorated, and in 18 patients, new neurological symptoms developed: seizures in 4, hemiparesis in 6, dysesthesis in 5, hemianopia in 4, and aphasia in 1. By univariate analysis, factors associated with transient and persistent neurological events included younger age (P=0.05), headache as an initial symptom (P=0.02), and lesion localization in eloquent areas (P=0.03). None of these remained as significant factors on multivariate analyses (Table II in the online-only Data Supplement). Ten patients had delayed complications (cyst formation 6, chronic expanding hematoma 3, and 1 radiation necrosis, ranging 72–240 months after SRS, at median 120 months), in whom 7 required surgical resection of the obliterated nidi. The accumulated risks of delayed complications events unrelated to stroke were 0% at 5 years, 4.3% at 7 years, and 8.9% at 10 years.

**Discussion**

In our study, we evaluated the clinical benefits of SRS for patients with small unruptured AVMs by comparing the risk for stroke before and after SRS. Radical treatment of AVM inevitably carries certain risks of affecting surrounding brain tissues because of direct impact or hemodynamic stress caused by rapid obliteration of prominent arteriovenous shunts.17,18 The recent ARUBA study provided evidence that the overall risks associated to radical treatment surpass the risks for stroke in conservative observation during a short-term period, making the role of therapeutic intervention controversial.14 On the basis of these results, 2 contrasting alternatives can be proposed to patients with an unruptured AVM, a curative option that increases the risk for harm and a conservative option that carries these potential risks continuously for the rest of a patient’s life. For small AVMs, we propose that SRS may provide a justified balance between these 2 alternative, achieving nidus obliteration in a relatively slow fashion with minimum impact on surrounding brain tissues.19 In this way, SRS could provide a curative solution with equal or less risks during the latency period.

AVM is predominantly found in younger individuals who have a life expectancy of more than half century. Although the risks associated with surgical resection of an AVM are usually considered to be immediate and single phase, from the
long-term perspective of the life expectancy of young adults, there might be a time at which point the risks of natural history surpass the risks associated with surgical excision. Although the short-term risks of SRS are known to be generally less frequent than those associated to other treatment modalities, the longer, continuous risks of radiation, which may occur even >10 years after treatment, remain unclarified, with its accumulated risks, based on follow-up periods of >20 years, still largely unknown. To definitively determine the clinical benefits of SRS for small unruptured AVMs, prospective studies with such long follow-up periods are needed. However, based on our results, we consider SRS to be a reasonable option for patients facing a latent menace of stroke because of a small unruptured AVM, providing new hope.

Conclusions
SRS can significantly reduce the risk for stroke in patients with small brain AVMs. On the basis of the results of our study, we recommend SRS for patients at latent risk for AVM-related stroke. To definitively determine the clinical benefits of SRS, outcomes based on longer follow-up time are necessary.

Disclosures
None.

References
Risk Reduction of Cerebral Stroke After Stereotactic Radiosurgery for Small Unruptured Brain Arteriovenous Malformations

Shunya Hanakita, Masahiro Shin, Tomoyuki Koga, Hiroshi Igaki and Nobuhito Saito

Stroke. 2016;47:1247-1252; originally published online April 12, 2016; doi: 10.1161/STROKEAHA.116.013132

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2016 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/47/5/1247

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2016/04/22/STROKEAHA.116.013132.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/
Table I: Univariate analysis for higher obliteration, adverse events, and hemorrhage after SRS.

<table>
<thead>
<tr>
<th>Factors</th>
<th>Higher Obliteration</th>
<th>Adverse events</th>
<th>Hemorrhage after SRS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95%CI)</td>
<td>OR (95% CI)</td>
<td>HR (95%CI)</td>
</tr>
<tr>
<td>Younger Age</td>
<td>1.01 (0.99-1.02)</td>
<td>1.03 (1.00-1.06)</td>
<td>1.0 (0.97-1.04)</td>
</tr>
<tr>
<td>Male / Female</td>
<td>1.04 (0.74-1.50)</td>
<td>0.93 (0.41-2.23)</td>
<td>1.32 (0.48-4.19)</td>
</tr>
<tr>
<td>Initial symptoms /Seizure</td>
<td>1.51 (0.89-2.60)</td>
<td>0.73 (0.29-1.70)</td>
<td>1.54 (0.57-4.20)</td>
</tr>
<tr>
<td>/Headache</td>
<td>1.05 (0.69-1.55)</td>
<td>2.80 (1.15-6.58)</td>
<td>0.9 (0.22-2.92)</td>
</tr>
<tr>
<td>Larger volume</td>
<td>1.00 (0.97-1.03)</td>
<td>1.07 (0.99-1.14)</td>
<td>1.03 (0.93-1.12)</td>
</tr>
<tr>
<td>Max nidus diameter &lt;3 cm</td>
<td>1.06 (0.65-1.39)</td>
<td>0.54 (0.23-1.30)</td>
<td>0.99 (0.34-3.56)</td>
</tr>
<tr>
<td>Deep venous drainage</td>
<td>0.84 (0.57-1.21)</td>
<td>1.09 (0.43-2.56)</td>
<td>4.00 (1.48-11.8)</td>
</tr>
<tr>
<td>Lesions in eloquent areas</td>
<td>0.92 (0.65-1.29)</td>
<td>2.50 (1.09-6.11)</td>
<td>1.69 (0.63-4.73)</td>
</tr>
<tr>
<td>Higher marginal dose</td>
<td>1.17 (1.04-1.30)</td>
<td>0.98 (0.76-1.29)</td>
<td>0.91 (0.73-1.23)</td>
</tr>
<tr>
<td>Increased AVM score</td>
<td>0.90 (0.65-1.23)</td>
<td>1.25 (0.60-2.48)</td>
<td>1.41 (0.59-3.09)</td>
</tr>
<tr>
<td>AVM score &gt; 1</td>
<td>0.98 (0.66-1.49)</td>
<td>1.42 (0.55-4.41)</td>
<td>1.59 (0.51-6.95)</td>
</tr>
<tr>
<td>AVM score &gt; 1.5</td>
<td>0.89 (0.62-1.27)</td>
<td>1.20 (0.52-2.93)</td>
<td>2.17 (0.81-6.04)</td>
</tr>
<tr>
<td>AVM score &gt; 2</td>
<td>0.84 (0.55-1.37)</td>
<td>0.74 (0.17-2.30)</td>
<td>0.91 (0.14-3.26)</td>
</tr>
</tbody>
</table>

Notes: *, P<0.05 are significant; HR, hazard risk; CI, confidence interval; AVM, arteriovenous malformation
Table II: Multivariate analyses for higher obliteration, adverse events, and hemorrhage after SRS.

<table>
<thead>
<tr>
<th>Factors</th>
<th>Higher Obliteration</th>
<th>Adverse events</th>
<th>Hemorrhage after SRS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95%CI)</td>
<td>p value</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Younger Age</td>
<td>0.99 (0.98-1.01)</td>
<td>0.74</td>
<td>1.02 (0.95-1.01)</td>
</tr>
<tr>
<td>Male / Female</td>
<td>1.10 (0.77-1.58)</td>
<td>0.61</td>
<td>1.16 (0.48-2.91)</td>
</tr>
<tr>
<td>Initial symptom /Seizure</td>
<td>1.64 (0.81-3.43)</td>
<td>0.10</td>
<td>1.00 (0.33-3.00)</td>
</tr>
<tr>
<td>/Headache</td>
<td>1.11 (0.70-1.73)</td>
<td>0.31</td>
<td>2.65 (0.94-7.74)</td>
</tr>
<tr>
<td>Larger volume</td>
<td>1.02 (0.96-1.08)</td>
<td>0.46</td>
<td>1.08 (0.95-1.22)</td>
</tr>
<tr>
<td>Max nidus diameter &lt;3 cm</td>
<td>1.06 (0.58-1.88)</td>
<td>0.84</td>
<td>0.92 (0.23-3.32)</td>
</tr>
<tr>
<td>Deep venous drainage</td>
<td>0.90 (0.61-1.32)</td>
<td>0.60</td>
<td>1.08 (0.41-2.70)</td>
</tr>
<tr>
<td>Lesions at eloquent area</td>
<td>0.91 (0.64-1.28)</td>
<td>0.58</td>
<td>2.24 (0.94-5.67)</td>
</tr>
<tr>
<td>Higher marginal dose</td>
<td>1.23 (1.04-1.35)</td>
<td>0.01*</td>
<td>1.17 (0.84-1.59)</td>
</tr>
</tbody>
</table>

Notes: * p <0.05 are significant: HR, hazard risk; OR, odds ratio; CI, confidence interval; AVM, arteriovenous malformation