This article is one of a series published in the *Journal of Neurosurgery* and the *Journal of Neurosurgery: Pediatrics*. See *Appendix* for a complete series listing.

J Neurosurg 116:21–32, 2012

Stereotactic radiosurgery for arteriovenous malformations, Part 3: outcome predictors and risks after repeat radiosurgery

Clinical article

Hideyuki Kano, M.D., Ph.D.,[1,3] Douglas Kondziolka, M.D.,[1,3] John C. Flickinger, M.D.,[1–3] Huai-che Yang, M.D.,[1,3,4] Thomas J. Flannery, M.D., Ph.D.,[1,3] Nasir R. Awan, F.C.P.S.,[1,3] Ajay Niranjan, M.Ch., M.B.A.,[1,3] Josef Novotny Jr., Ph.D.,[2,3] and L. Dade Lunsford, M.D.[1–3]

Departments of [1]Neurological Surgery and [2]Radiation Oncology, and [3]Center for Image-Guided Neurosurgery, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; and [4]Department of Neurosurgery, Taipei Veterans General Hospital, Taipei, Taiwan

Object. The object of this study was to evaluate the outcomes and risks of repeat stereotactic radiosurgery (SRS) for incompletely obliterated cerebral arteriovenous malformations (AVMs).

Methods. Between 1987 and 2006, Gamma Knife surgery was performed in 996 patients with AVMs. During this period, repeat SRS was performed in 105 patients who had incompletely obliterated AVMs at a median of 40.9 months after initial SRS (range 27.5–139 months). The median AVM target volume was 6.4 cm^3 (range 0.2–26.3 cm^3) at initial SRS but was reduced to 2.3 cm^3 (range 0.1–18.2 cm^3) at the time of the second procedure. The median margin dose at both initial SRS and repeat SRS was 18 Gy.

Results. The actuarial rate of total obliteration by angiography or MR imaging after repeat SRS was 35%, 68%, 77%, and 80% at 3, 4, 5, and 10 years, respectively. The median time to complete angiographic or MR imaging obliteration after repeat SRS was 39 months. Factors associated with a higher rate of AVM obliteration were smaller residual AVM target volume ($p = 0.038$) and a volume reduction of 50% or more after the initial procedure ($p = 0.014$). Seven patients (7%) had a hemorrhage in the interval between initial SRS and repeat SRS. Seventeen patients (16%) had hemorrhage after repeat SRS and 6 patients died. The cumulative actuarial rates of new AVM hemorrhage after repeat SRS were 1.9%, 8.1%, 10.1%, 10.1%, and 22.4% at 1, 2, 3, 5, and 10 years, respectively, which translate to annual hemorrhage rates of 4.05% and 1.79% of patients developing new post–repeat-SRS hemorrhages per year for Years 0–2 and 2–10 following repeat SRS. Factors associated with a higher risk of hemorrhage after repeat SRS were a greater number of prior hemorrhages ($p = 0.008$), larger AVM target volume at initial SRS ($p = 0.010$), larger target volume at repeat SRS ($p = 0.002$), initial AVM volume reduction less than 50% ($p = 0.019$), and a higher Pollock-Flickinger score ($p = 0.010$). Symptomatic adverse radiation effects developed in 5 patients (4.8%) after initial SRS and in 10 patients (9.5%) after repeat SRS. Prior embolization ($p = 0.022$) and a higher Spetzler-Martin grade ($p = 0.004$) were significantly associated with higher rates of adverse radiation effects after repeat SRS. Delayed cyst formation occurred in 5 patients (4.8%) at a median of 108 months after repeat SRS (range 47–184 months).

Conclusions. Repeat SRS for incompletely obliterated AVMs increases the eventual obliteration rate. Hemorrhage after obliteration did not occur in this series. The best results for patients with incompletely obliterated AVMs were seen in patients with a smaller residual nidus volume and no prior hemorrhages. *(DOI: 10.3171/2011.9.JNS101741)*

Key Words • **arteriovenous malformation** • **Gamma Knife surgery** • **stereotactic radiosurgery** • **repeat treatment** • **embolization** • **complications**

Stereotactic radiosurgery has been widely used to treat patients with intracranial AVMs.[5,8,14,19,21] Management options for AVMs include resection, embolization, or SRS, alone or in combination. The generally accepted goal of SRS for AVMs is complete obliteration without associated AREs. Total obliteration rates vary from 70% to 80% within 5 years of an initial SRS procedure.[5,8,14,17,19,21] Total obliteration that is confirmed by angiography appears to reduce the cumulative lifetime risk of hemorrhage to approximately 1%, in comparison with an annual hemorrhage risk that varies from 1% to 4%.[20] Whether partial obliteration of AVMs after SRS affects the delayed risk of bleeding remains unclear.[15,19,20,27] Approximately 3 years after SRS, patients with residual AVMs are

Abbreviations used in this paper: ARE = adverse radiation effect; AVM = arteriovenous malformation; HR = hazard ratio; SRS = stereotactic radiosurgery.

This article contains some figures that are displayed in color online but in black and white in the print edition.

reevaluated to assess whether additional salvage management options (for example, resection, embolization, and/or repeat SRS) are warranted.[10,22,24,33] Several studies have shown that in approximately 60%–70% of patients with incomplete obliteration of AVMs after initial SRS, total obliteration is achieved after repeat SRS.[14,18,39]

We reviewed factors associated with total obliteration, risks of bleeding, AREs, and delayed cyst formation in patients with incomplete obliteration of AVMs treated by repeat SRS.

Methods

This retrospective study was approved by the University of Pittsburgh institutional review board.

Patient Population

Between August 1987 and December 2006, 996 AVM patients underwent single-stage SRS with the Leksell Gamma Knife (Elekta AB) at our center. During this same interval, 131 patients with residual AVMs underwent repeat SRS between 27 and 139 months after their initial procedure. Eighteen patients who underwent repeat SRS after prospective volume-staged SRS for a large nidus and 8 patients who were lost to follow-up were excluded, leaving 105 patients for evaluation. The series includes 53 males and 52 females. The median patient age was 31 years (range 2–66 years) at the initial SRS and 35 years (range 6–68 years) at repeat SRS. Eleven patients (10%) had undergone resection before their initial SRS. Thirty-four patients (32%) had undergone prior embolization before SRS. Sixty-five patients (62%) had SRS as their initial AVM management. Symptoms leading to the diagnosis of AVMs were hemorrhages in 43 patients (41%), seizures in 37 (35%), headaches in 20 (19%), limb weakness in 1 (1%), and tinnitus in 2 (2%). In 2 patients, the AVMs were diagnosed incidentally. The median interval between the initial and repeat SRS was 40.9 months.

The AVMs were located in the cerebral hemispheres in 73 patients, corpus callosum in 1, thalamus in 14, basal ganglia in 6, pineal region in 1, cerebellum in 6, and brainstem in 4 (Table 1). The Spetzler-Martin grades at the time of initial and repeat SRS are shown in Table 2.[34] The modified Pollock-Flickinger AVM grading system has been previously described.[26,36] The equation used to calculate the modified Pollock-Flickinger AVM grading score is as follows: Score = (0.1) (volume in cm^3) + (0.02) (age in years) + (0.5) (location: basal ganglia, thalamus, or brainstem = 1, others = 0). The modified Pollock-Flickinger AVM scores at the time of initial and repeat SRS also are shown in Table 2. The data were collected by 4 neurosurgeons (H.K., H.Y., T.J.F., and N.R.A.) who had not participated in patient management. The Spetzler-Martin grades were decided by 2 experienced neurosurgeons (L.D.L. and D.K.) who had participated in patient management. The modified Pollock-Flickinger AVM scores were calculated retrospectively by the first author (H.K.).

TABLE 1: Clinical and demographic characteristics of 105 patients*

Characteristic	Value
sex	
male	53
female	52
age at initial SRS (yrs)	
median	31
range	2–66
age at repeat SRS (yrs)	
median	35
range	6–68
interval btwn initial & repeat SRS (mos)	
median	40.9
range	27.5–139
AVM location	
frontal	18
parietal	22
temporal	19
occipital	14
corpus callosum	1
thalamus	14
basal ganglia	6
pineal region	1
cerebellum	6
brainstem	4
prior hemorrhage	43
prior embolization	34

* Values represent numbers of patients unless otherwise indicated.

Radiosurgery Technique

Our radiosurgical technique has been described in detail in previous reports.[17,18,28] In brief, adult patients underwent application of an imaging-compatible stereotactic head frame, with local anesthesia supplemented by intravenous sedation. Children underwent the procedure after induction of general endotracheal anesthesia. High-resolution axial-plane imaging (MR imaging after 1991) coupled with biplane stereotactic angiography was performed for dose planning. The margin SRS dose included the entire AVM nidus volume, defined as the shunt between the afferent arteries and the draining veins. Stereotactic radiosurgery was performed with a Model U, B, C, or 4-C Leksell Gamma Knife (Elekta AB). Eight patients had MR imaging planning only, 39 had angiography planning only, and 58 had MR imaging plus angiography planning during the second SRS procedure. All patients received an intravenous dose of 20–40 mg methylprednisolone after radiosurgery, and all were discharged from the hospital 2–24 hours after the procedure.

Dose Prescription at the Time of Initial and Repeat SRS

The target of both initial and repeat SRS was the AVM nidus, defined as the vasculature that lies between feeding arteries and draining veins. At the time of repeat SRS, only the residual nidus was treated; any volume eliminated

TABLE 2: Grading of AVMs in 105 patients*

Measure	Initial SRS	Repeat SRS
Spetzler-Martin Grade		
I	2	5
II	14	20
III	57	53
IV	20	15
V	0	1
VI	12	11
Pollock-Flickinger score		
≤1.00	23	45
1.01–1.50	44	36
1.51–2.00	24	18
>2.00	14	6

* Values for initial and repeat SRS represent numbers of patients.

by prior embolization or initial SRS was excluded. The median maximum diameter of the AVM nidus was 29.0 mm (range 7.8–48.0 mm) at the time of the initial SRS and 20.0 mm (range 7.4–45 mm) at repeat SRS. The median target volume was 6.4 cm^3 (range 0.2–26.3 cm^3) at initial SRS and 2.3 cm^3 (range 0.1–18.2 cm^3) at repeat SRS. The prescription dose guidelines remained similar for both the initial and the subsequent SRS procedures. As a general guideline we increased the margin dose by 1–2 Gy if the AVM volume was significantly smaller than the original volume. A margin dose reduction of 1–2 Gy was used if the retreatment AVM volume was larger than the initial volume, as was occasionally seen when embolized components recanalized. A similar dose reduction was used in patients who had sustained symptomatic ARE after the first procedure. The median prescription dose delivered to the nidus margin was 18.0 Gy (range 13.5–25 Gy) at initial SRS and 18.0 Gy (range 12.5–23 Gy) at repeat SRS. The median maximum dose was 35.0 Gy (range 18–50 Gy) at initial SRS and 36.0 Gy (range 22.2–46 Gy) at repeat SRS. The median number of isocenters was 3 at both the initial and repeat SRS (range 1–12 at initial SRS, 1–11 at repeat SRS) (Table 3).

Patient Follow-Up

After repeat SRS, patients were requested to have clinical and imaging assessments at intervals of 6–12 months. If at the end of 3 years, MR imaging suggested complete obliteration, we requested that repeat angiography be performed. If MR imaging clearly defined a residual nidus, the patient was reevaluated to assess whether additional treatment options were warranted. Total obliteration using cerebral angiography was defined as failure to visualize the nidus as well as early venous drainage. Whenever a new neurological symptom or sign developed, the patient had a CT and/or MR imaging study to rule out bleeding or ARE. Adverse radiation effect was diagnosed if the patient developed clinically symptomatic reactive imaging changes at the target site, which typically appeared on MR imaging as an area of irregular contrast enhancement associated with disproportionate surrounding T2 signal change and mass effect compatible with perilesional edema. We evaluated the AVM volume reduction rate, which was estimated using the following formula: target volume at time of initial SRS/target volume at time of repeat SRS.

TABLE 3: Initial and repeat radiosurgery parameters in 105 patients

Parameter	Median (range)	
	Initial SRS	Repeat SRS
max diameter of nidus in mm	29.0 (7.8–48.0)	20.0 (7.4–45.0)
target vol in cm^3	6.4 (0.2–26.3)	2.3 (0.1–18.2)
margin dose in Gy	18.0 (13.5–25)	18.0 (12.5–23)
max dose in Gy	35.0 (18–50)	36.0 (22.2–46)
no. of isocenters	3 (1–12)	3 (1–11)

Statistical Analysis

Actuarial analysis with the end point of AVM obliteration differs from survival analysis by requiring greater care to avoid potential bias. While dates of death are narrowly defined for a survival analysis, AVM obliteration is measured by either angiographic or MR imaging at a discrete time. The exact time of AVM obliteration is not known. A number of patients in this series disappeared from follow-up and had no imaging in the 2- to 5-year interval after repeat radiosurgery. Eventually these patients had delayed follow-up angiography 5–10 years after repeat radiosurgery. In such cases, the actual time of AVM obliteration is unknown, but it is likely to have been earlier than the date of the angiography. In addition, patients with residual AVMs at 3–4 years after repeat SRS routinely underwent a third radiosurgery procedure at that time with all further follow-up thereafter censored. This study reports the outcomes after the second SRS procedure only; we did not calculate the effects of the third AVM radiosurgery on eventual obliteration in this report. We used MR imaging alone to calculate obliteration rates if additional angiographic confirmation was not available. The combined effects of censoring follow-up for retreatment after 3–4 years and the "delayed follow-up" AVM patients (those having confirmatory imaging at intervals well beyond 3–4 years) might artificially elevate the 10-year actuarial obliteration rate calculations. To try to avoid this bias in calculating obliteration rates, we therefore defined the estimated obliteration time as the halfway point between the time that the last MR imaging study showed a patent nidus and the time that an angiogram or MR imaging study documented obliteration. To account for the 97% reliability of MR imaging in establishing AVM obliteration, the following correction factor (mrCF) can be applied to the combined obliteration rates documented by either MR imaging (65 cases) or angiography (47 cases): mrCF = 1.0 – 0.03 × MR obliterations/(MR obliterations + angio obliterations) = 0.983.

We identified a second potential statistical bias in calculating obliteration rates using angiography alone as opposed to defining it with either MR imaging or angiography. While angiography is the "gold standard" for

obliteration, Pollock et al.[29] reported that only 3 of 100 patients with MR imaging–defined obliteration undergoing angiography had a residual nidus. Approximately 60% of the patients in this series did not undergo angiography after their follow-up MR imaging study revealed obliteration. In contrast, almost all patients with an MR imaging–defined residual nidus underwent angiography, often followed by repeat SRS. This artifact of patient management leads to a greater proportion of patients with unobliterated AVMs undergoing angiograms. Although we agree that angiography remains the best measure to define AVM obliteration, MR imaging remains a highly accurate close-approximation alternative to assess obliteration.[29]

Kaplan-Meier survival analysis was carried out to calculate rates of hemorrhage and obliteration. In the assessment of hemorrhage, patients were censored on loss of follow-up or at the time of hemorrhage. As such, rates of hemorrhage reflect a single hemorrhage experienced by a patient even if he or she had multiple hemorrhages. Annual hemorrhage rates were calculated based on years of follow-up and total number of hemorrhages; as such, this accounts for the total number of hemorrhages experienced by patients. The log-rank test was used to assess differences in survival curves and Cox regression was used to assess hazard ratios in multivariate analysis. Relevant factors affecting total AVM obliteration and hemorrhage after repeat SRS included the following: age and sex, AVM location (brainstem, thalamus, and basal ganglia vs other locations), target volume at repeat SRS, the initial AVM volume percentage (continuous number, ≥ 50% reduction vs < 50% reduction), margin dose at repeat SRS (continuous number, ≥ 16 Gy vs < 16 Gy), presence of a venous varix, presence of a proximal arterial aneurysm, number of bleeding events before initial SRS, number of bleeding events before repeat SRS, prior embolization, prior resection, Spetzler-Martin grade at the time of repeat SRS, and modified Pollock-Flickinger score at the time of repeat SRS. In multivariate analysis using the Cox proportional hazards model, we analyzed the following variables: target volume at repeat SRS, AVM reduction rate, margin dose at repeat SRS, number of bleeding events before repeat SRS, and prior embolization. The Mann-Whitney U-test was used to evaluate the relationship between 1) AREs and delayed cyst formation after initial and repeat SRS, and 2) patient and AVM characteristics (age, sex, AVM location, target volume, AVM reduction rate, 12-Gy volume, margin dose, presence of a varix or proximal arterial aneurysm, prior hemorrhage, prior embolization, prior resection, Spetzler-Martin grade, and Pollock-Flickinger score). A value of $p < 0.05$ was defined as statistically significant.

Results

At the time of assessment, 96 patients were alive and 9 had died. Six patients died due to hemorrhage from their AVM. Three patients died of other causes unrelated to AVM bleeding or AREs (myeloma in 1 case, chronic obstructive pulmonary disease in 1, and unknown causes in 1). The median interval between repeat SRS and the most recent follow-up was 80 months (range 6–205 months).

Factors Associated With Incomplete Obliteration After Initial SRS

Factors that affected treatment planning and were associated with incomplete obliteration after the initial SRS procedure are shown in Table 4. Recanalization of a previously embolized nidus occurred in 12 patients. Reemergence of compressed AVM vessels after prior hemorrhage was noted in 9 patients. An insufficient radiosurgical dose (< 17 Gy) was implicated in 17 patients. Inadequate assessment of the AVM 3D morphology (including factors such as incomplete cerebral angiography or lack of axial plane CT or MR imaging) was observed in 18 patients. Suspected subtotal obliteration (persistent early venous drainage without visible nidus) occurred in 18 patients. In 31 patients we were unable to retrospectively identify any specific factor that led to treatment failure.

Outcome of Initial SRS

The median AVM volume change rate after the first procedure was 50% (range 2%–909%). Nineteen patients had larger target volumes identified at the time of the repeat procedure than the volume identified at the time of initial SRS. Five of these 19 patients had recanalization after prior embolization before initial SRS and 8 had additional AVM components that became apparent after a compressive hematoma regressed. Two were childhood AVMs that may have progressed spontaneously during the latency interval.[13] In 4 patients the apparent AVM enlargement between procedures may also be related to vascular growth factors or recruitment of additional vascular blood supply. Seven patients (7%) sustained a hemorrhage between their initial SRS and repeat SRS at a median of 12 months (range 2.6–69 months).

Total Obliteration Rate After Repeat SRS

Magnetic resonance imaging after repeat SRS confirmed total obliteration in 65 patients (62%). Eighteen patients declined further angiography. Forty-seven patients underwent angiography at 3–10 years after repeat SRS. Postradiosurgery obliteration rates (based on either angiography or MR imaging criteria) were 35%, 68%, 77%, and 80% at 3, 4, 5, and 10 years, respectively. The median time until total obliteration on MR imaging was 38.9 months (95% CI 36.34–41.46 months). Figure 1 also shows the effect of assuming that obliteration occurred exactly when it was documented by angiography. The uncorrected obliteration probability calculations are lower at 3, 4, and 5 years (28%, 55%, and 68% vs 35%, 68%, and 77% with corrected calculations) but higher at 10 years (86% vs 80% with correction). The actuarial total obliteration rates based on angiography alone were 26%, 58%, 63%, and 66% at 3, 4, 5, and 10 years, respectively, at a median of 44.3 months after SRS (95% CI 38.05–50.55 months) using corrected obliteration times. Any obliteration rates calculated by angiography alone from this series are biased (artificially lowered) by exclusion of patients with MR imaging–defined obliteration who refused angiography.

In univariate analysis, the factors associated with a higher rate of total obliteration using MR imaging included smaller target volume at the time of repeat SRS (p

TABLE 4: Factors associated with incomplete obliteration of AVMs after initial radiosurgery*

Factor	No. of Pts	Prior Hemorrhage	Prior Embolization	Margin Dose (Gy)	Target Vol (cm^3)	SRS Planning by Angiography Alone
recanalization of nidus after embolization	12	6	12	19	6.9	8 (67)
reappearance of compressed vessels after prior hemorrhage	9	9	0	20	2.3	4 (44)
lower radiation dose	17	4	6	15	10.3	5 (29)
inadequate assessment of 3D AVM morphology	18	4	3	19	5.1	14 (78)
subtotal obliteration	18	7	4	18	5.7	6 (33)
unknown causes	31	13	9	20	5.1	16 (52)

* Values represent numbers of patients (%) unless otherwise indicated. Abbreviation: Pts = patients.

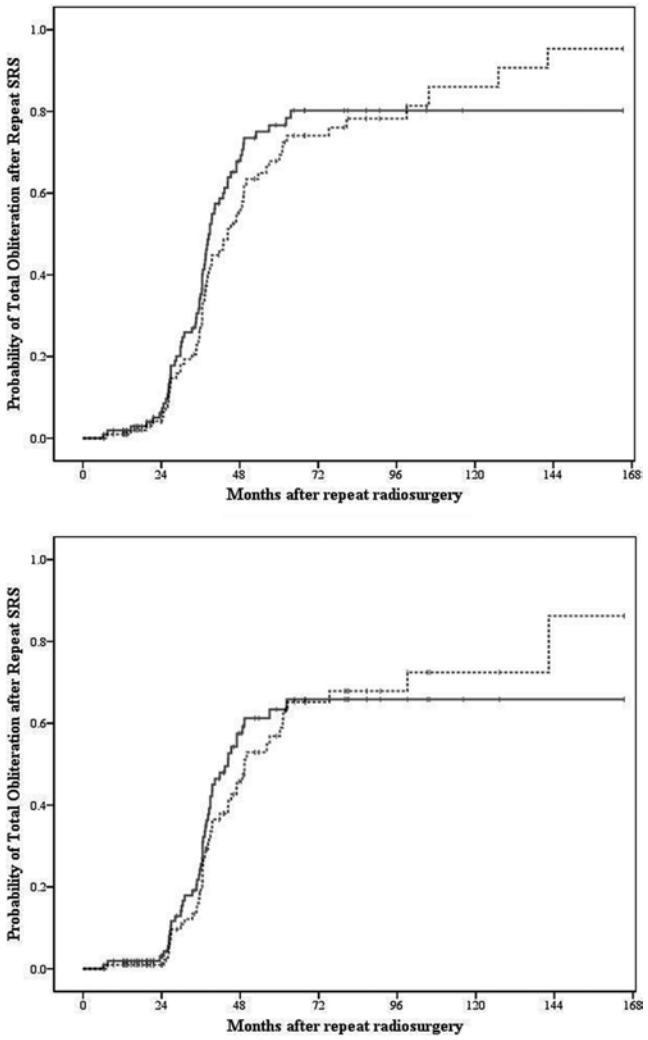

Fig. 1. Upper: Kaplan-Meier curves for total obliteration as documented by MR imaging or angiography after repeat SRS for AVMs with corrected time *(solid line)*. Uncorrected Kaplan-Meier curves for total obliteration by MR imaging or angiography after repeat radiosurgery for AVMs with uncorrected time *(broken line)*. **Lower:** Kaplan-Meier curves for total obliteration by angiography alone after repeat radiosurgery for AVMs with corrected time *(solid line)*. Uncorrected Kaplan-Meier curves for total obliteration by angiography alone after repeat radiosurgery for pediatric AVMs with uncorrected time *(broken line)*.

= 0.038) and a greater AVM volume reduction (continuous number, p = 0.035; ≥ 50% AVM reduction after the initial SRS, p = 0.014). The only factor associated with a higher rate of total obliteration on angiography was AVM volume reduction of 50% or more after initial SRS (p = 0.015) (Table 5). In the multivariate analysis, AVM volume reduction of 50% or more after initial SRS was associated with a higher rate of total obliteration when either MR imaging and angiography were used to confirm obliteration (total obliteration on angiography or MR imaging: p = 0.014, HR 1.86, 95% CI 1.14–3.06; total obliteration on angiography: p = 0.015, HR 2.07, 95% CI 1.15–3.72) (Table 6). The other variables (target volume at the time of repeat SRS, margin dose at the time of repeat SRS, number of prior bleeding events before repeat SRS, and prior embolization) were not associated with eventual total obliteration.

Hemorrhage After SRS

During the latency interval after initial SRS, 7 patients (7%) had a hemorrhage. Despite the second SRS, 17 patients (16%) had a bleeding event, and 2 patients had 2. Three patients suffered a hemorrhage both before and after repeat SRS. None of the patients who had hemorrhages had total obliteration on MR imaging or angiography. After imaging confirms AVM obliteration, we recommend that patients continue to have MR imaging studies at 3- to 5-year intervals to assess long-term risks such as late cyst development, AVM reappearance, or radiation-related neoplasia. To date we have not seen recurrent AVM development or radiation-related neoplasia in any of the 105 patients included in this study. In 512.1 patient-years of theoretical risk of hemorrhage (interval from the date of repeat SRS to the date of total obliteration on angiography or the date that the last follow-up images showed a residual AVM), 17 patients experienced 19 bleeding events, yielding an annual hemorrhage rate of 3.7% until obliteration occurred. The cumulative rates of hemorrhage in patients with persistent AVMs despite repeat SRS were 0%, 1.9%, 8.1%, 10.1%, 10.1%, and 22.4% at 0.5, 1, 2, 3, 5, and 10 years, respectively (Fig. 2). These actuarial numbers translate to annual hemorrhage rates of 4.05% and 1.79% of patients developing new post–repeat-SRS hemorrhages per year for Years 0–2 and 2–10 following repeat SRS. These actuarial bleeding calculations show the proportion of patients who make it to 2,

TABLE 5: Univariate analysis of total obliteration and bleeding after repeat radiosurgery in 105 patients*

Variable	p Value		
	Total Obliteration		
	Angiography or MRI	Angiography Alone	Bleeding After Repeat SRS
age	0.281	0.205	0.777
sex	0.504	0.223	0.818
location (BS, TH, BG)	0.374	0.306	0.217
target vol at initial SRS	0.470	0.619	0.010
target vol at repeat SRS	0.038	0.048	0.002
AVM reduction rate (TV_{GK2}/TV_{GK1})	0.035	0.145	0.760
AVM reduction rate (≥50%)	0.014	0.015	0.019
margin dose at repeat SRS	0.244	0.264	0.373
margin dose at repeat SRS ≥16 Gy	0.084	0.515	0.283
presence of venous varix	0.163	0.216	0.161
feeding artery aneurysm	0.199	0.278	0.523
no. of hemorrhages before initial SRS	0.919	0.950	0.024
no. of hemorrhages before repeat SRS	0.504	0.522	0.008
prior embolization	0.295	0.733	0.094
prior resection	0.071	0.129	0.572
Spetzler-Martin grade	0.457	0.268	0.291
Pollock-Flickinger score at repeat SRS	0.147	0.187	0.010

* BG = basal ganglia; BS = brainstem; TH = thalamus; TV = target volume; TV_{GK1} = target volume at the time of initial SRS; TV_{GK2} = target volume at the time of repeat SRS.

5, and 10 years without hemorrhage but do not count any subsequent bleeding events. The crude rates of all hemorrhages following radiosurgery (counting all multiple hemorrhages) were 8.8%, 2.1%, and 6.5% (for 9, 2, and 6 hemorrhages per 102.7, 95.3, and 92.2 patient-years of follow-up) for Years 0–2, 2–5, and 5–10, respectively.

In the univariate analysis, factors associated with a higher rate of hemorrhage after repeat SRS included larger target volume at initial SRS (p = 0.010), larger target volume at repeat SRS (p = 0.002), less than 50% AVM volume reduction after initial SRS (p = 0.019), greater number of hemorrhages before initial SRS (p = 0.024) or before repeat SRS (p = 0.008), and higher Pollock-Flickinger score (p = 0.010) (Table 5). In the multivariate analysis, factors associated with a higher rate of hemorrhage included larger target volume at the time of repeat SRS (p = 0.004, HR 1.16, 95% CI 1.05–1.28) and a higher rate of hemorrhage before repeat SRS (p = 0.015, HR 1.63, 95% CI 1.10–2.41) (Table 6). The other variables (≥ 50% AVM volume reduction after initial SRS, margin dose at the time of repeat SRS, and prior embolization) were not associated with a change in risk of hemorrhage after repeat SRS.

The Influence of AVM Volume Reduction by the First SRS Procedure

When the first procedure led to a volume reduction of 50% or more, the rates of total obliteration on angiography or MR imaging were 44%, 68%, and 72% at 3, 4, and 5 years after the second procedure. The median time until total obliteration documented by angiography or MR imaging after repeat SRS was 39.5 months (95% CI 33.06–45.94 months). The rates of total angiographically confirmed obliteration following repeat SRS in pa-

TABLE 6: Multivariate analysis of total obliteration and hemorrhage after repeat radiosurgery in 105 patients*

Variable	Total Obliteration						Hemorrhage After Repeat SRS		
	Angiography or MRI			Angiography					
	p Value	HR	95% CI	p Value	HR	95% CI	p Value	HR	95% CI
target vol at repeat SRS	0.289	NA	NA	0.337	NA	NA	0.004	1.16	1.05–1.28
AVM reduction rate (≥50%)	0.014	1.86	1.14–3.06	0.015	2.07	1.15–3.72	0.515	NA	NA
margin dose at repeat SRS	0.422	NA	NA	0.479	NA	NA	0.425	NA	NA
no. of hemorrhages before repeat SRS	0.936	NA	NA	0.924	NA	NA	0.015	1.63	1.10–2.41
prior embolization	0.091	NA	NA	0.334	NA	NA	0.198	NA	NA

* NA = not applicable.

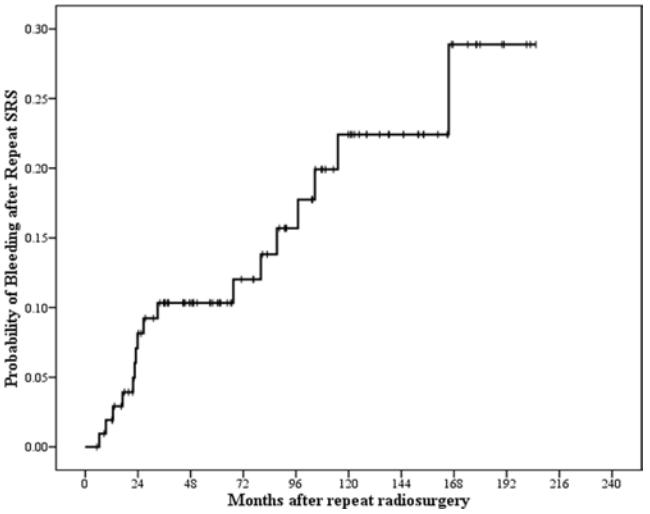

Fig. 2. Kaplan-Meier curve for bleeding rate after repeat SRS for residual AVMs.

tients whose AVM volume was reduced by less than 50% after the first procedure were 7%, 47%, and 55% at 3, 4, and 5 years. The median time until total obliteration on angiography or MR imaging after repeat SRS was 49.3 months (95% CI 33.21–65.39 months). An AVM volume reduction rate of 50% or more after the first procedure was significantly associated with higher total obliteration on angiography or MR imaging ($p = 0.014$) after the second SRS (Figs. 3 and 4).

The actuarial rates of new AVM bleeding after repeat SRS in patients whose AVM volume was reduced 50% or more by the first procedure were 0%, 0%, 2.2%, 2.2%, and 14.4% at 1, 2, 3, 5, and 10 years, respectively. The actuarial rates of new AVM bleeding after repeat SRS in patients whose AVM volume was reduced by less than 50% after the first procedure were 3.8%, 16.5%, 17.5%, 17.5%, and 28.7% at 1, 2, 3, 5, and 10 years, respectively. An AVM volume reduction rate of 50% or more after the first SRS was significantly associated with a lower bleeding risk after repeat SRS ($p = 0.034$).

Adverse Radiation Effects

Five patients (4.8%) developed AREs between the time of initial SRS and the time of repeat SRS. The median time until development of symptoms after initial SRS was 24.5 months (range 3.8–44.1 months). In the univariate analysis, a higher margin dose at the time of initial SRS ($p = 0.029$) was significantly associated with a higher risk of AREs after initial SRS. Factors associated with a higher rate of AREs after repeat SRS included prior embolization ($p = 0.022$) and higher Spetzler-Martin grade ($p = 0.004$) (Table 7). Symptoms of temporary AREs after initial SRS included the development of seizures in 2 patients, hemiparesis in 2, and headache and vertigo in 1. All suspected ARE symptoms were successfully managed with corticosteroids and resolved before repeat SRS. Ten patients (9.5%) developed AREs after repeat SRS at a median of 10.5 months after treatment (range 3.4–64.5 months). Temporary symptomatic AREs after repeat SRS included seizures with headache in 2 patients, upper-extremity weakness in 2 patients, headache with sensory dysfunction in 1 patient, seizure in 1 patient, and ataxia in 1 patient. All patients were treated with temporary administration of oral corticosteroids. In addition we often prescribe a combination of vitamin E and pentoxifylline for 3 months.[37] Permanent neurological deficits related to AREs included hemiparesis with homonymous hemianopsia in 1 patient, a partial visual field cut in 1 patient, and hemiparesis with impaired vision in 1 patient (Table 8). No radiation-related neoplasms were detected during follow-up.

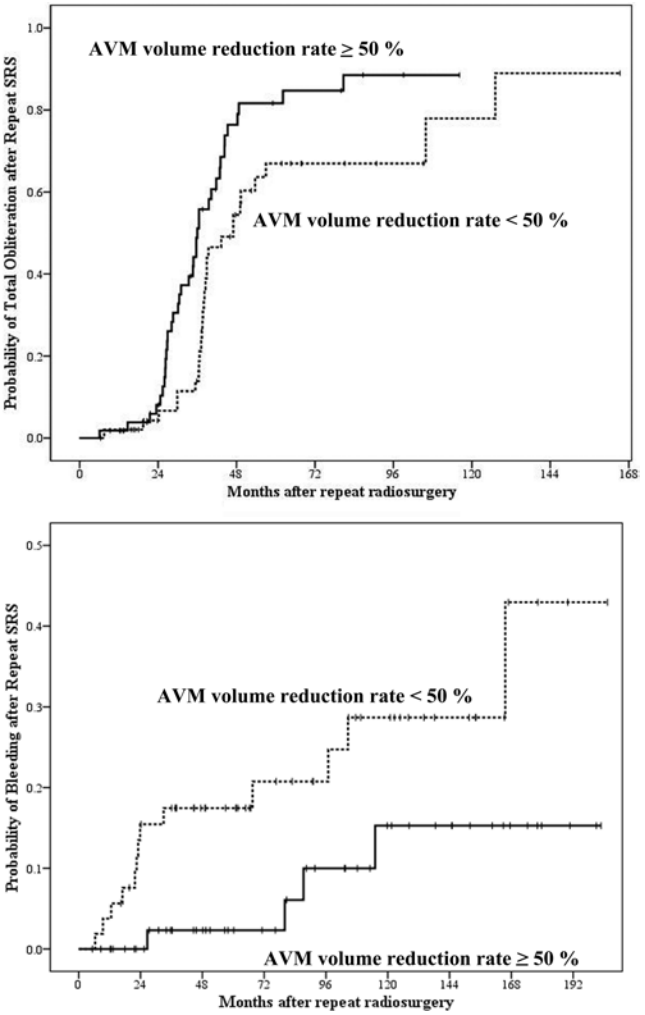

Fig. 3. Upper: Kaplan-Meier curves for total obliteration on angiography or MR imaging after repeat SRS for residual AVMs with a volume reduction rate of 50% or more versus less than 50%. A volume reduction rate of 50% or more after initial SRS was significantly associated with higher total obliteration rate on angiography or MR imaging ($p = 0.014$). **Lower:** Kaplan-Meier curves for bleeding rate after repeat SRS for residual AVMs with a volume reduction rate of 50% or more versus less than 50%. A volume reduction rate of 50% or more after initial SRS was significantly associated with lower bleeding rate ($p = 0.019$).

Delayed Cyst Formation

One patient who had a prior hemorrhage experienced delayed cyst formation 67 months after initial SRS but

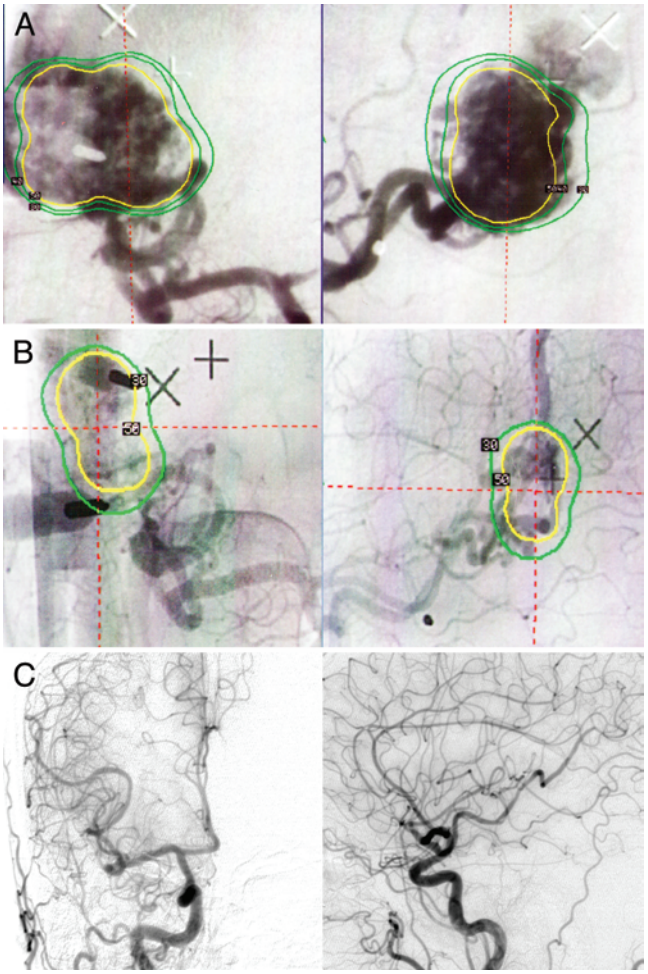

Fig. 4. **A:** Anterior and lateral carotid artery angiograms obtained in a 48-year-old man documenting the right frontal AVM with a volume of 10 cm^3 at the time of SRS. The margin dose was 17 Gy. **B:** Anterior and lateral carotid artery angiograms obtained 43 months after initial SRS showing a residual nidus with a volume of 2.9 cm^3 in the SRS field. This residual nidus was treated by the second SRS with a margin dose of 18 Gy. **C:** Anterior and lateral carotid artery angiograms obtained 3 years after the second SRS showing the absence of nidus.

still underwent repeat SRS 74 months after the initial radiosurgery because of residual AVM filling. The cyst decreased in size without any surgical procedure 13 months after repeat SRS. Delayed cyst formation occurred in 5 patients (4.8%) at a median of 108 months after repeat SRS (range 47–184 months). One patient required placement of an Ommaya reservoir 176 months after repeat SRS. A higher number of prior bleeding events was significantly associated with delayed cyst formation after repeat SRS ($p = 0.025$).

Additional Treatment After Repeat SRS

Twelve patients underwent a third SRS procedure because of identification of residual AVM despite 2 prior SRS procedures. The third procedure was performed at a median of 64.6 months (range 9.9–120 months) after the second SRS. Total obliteration after the third SRS was documented by MR imaging in 5 patients (range 6.5–55.5 months) and by angiography in 3 (range 6.5–55.5 months).

TABLE 7: Univariate analysis of AREs after radiosurgery in 105 patients

Variable	p Value	
	Btwn Initial & Repeat SRS	After Repeat SRS
age	0.821	0.643
sex	0.178	0.175
location (BS, TH, BG)	0.286	0.462
target vol	0.155	0.185
AVM reduction rate		
TV_{GK2}/TV_{GK1}	NA	0.488
<50% reduction	NA	0.975
12-Gy vol	0.090	0.252
margin dose	0.029	0.487
presence of varix	0.018	0.283
coexisting aneurysm	0.397	0.444
prior bleeding		
before initial SRS	0.565	0.925
before repeat SRS	NA	0.736
prior embolization	0.710	0.022
prior resection	0.459	0.957
Spetzler-Martin grade	0.128	0.004
Pollock-Flickinger score	0.088	0.631

One patient developed homonymous hemianopsia due to ARE 14.5 months after the third SRS. Two patients underwent a fourth SRS because of identification of residual AVM. One patient had a hemorrhage 23.3 months after the third SRS and underwent a fourth SRS 75.8 months after the third SRS. Another patient underwent a fourth SRS 37.8 months after the third SRS and had total obliteration confirmed by angiography 35.3 months after the fourth SRS.

Two patients underwent resection for AVM because of hemorrhages occurring at 21.8 and 42.6 months, respectively, after repeat SRS. One patient underwent surgical hematoma removal 12.6 months after repeat SRS, but died 6 months later as a result of another hemorrhage.

Discussion

Intracranial bleeding is the most feared complication of intracranial AVMs. In the absence of treatment, the overall risk of a spontaneous hemorrhage from a brain AVM appears to range from 2% to 5% per year.[1,2,11,23] In a 24-year follow-up assessment, Ondra et al.[23] reported that AVMs have a relatively constant annual death risk of approximately 1% and a risk of bleeding of approximately 4% per year. Da Costa et al.[3] reported that a hemorrhagic presentation was a significant independent predictor of future bleeding (rate of bleeding 7.5% per year, HR 2.15, $p < 0.01$), whereas associated aneurysms, deep venous drainage, and prior embolization were not significantly associated with future bleeding. In our experience, a prior bleeding event increased the rebleeding rate to approximately 10% in the first 6 months.[27] In addition reduced

TABLE 8: Clinical characteristics of cases in which patients experienced AREs after repeat radiosurgery

Case No.	AVM Nidus Location	Target Vol at Initial SRS/Repeat SRS (cm^3)	Margin Dose at Initial SRS/Repeat SRS (Gy)	Interval Btwn Repeat SRS & Symptomatic AREs (mos)	Temporary or Permanent	Symptoms
1	corpus callosum	9.1/4.7	18/15	13.2	temporary	upper-extremity weakness
2	thalamus	5.4/1.5	25/20	5.9	temporary	upper-extremity weakness
3	basal ganglia	0.4/3.0	20/18	3.4	permanent	hemiparesis, homonymous hemianopsia
4	parietal lobe	12.2/3.8	17/18	9.9	temporary	headache & arm paresthesias
5	thalamus	8.4/5.2	15/14	13.1	permanent	hemiparesis, impaired vision
6	temporal lobe	2.7/5.7	20/18	64.5	temporary	headache, seizure
7	temporal lobe	5.3/9.4	18/16	15.6	permanent	partial visual field cut
8	cerebellum	6.4/2.8	18/17	6.0	temporary	imbalance, dizziness
9	motor strip	6.1/1.5	20/20	5.1	temporary	seizure
10	occipital	8.5/2.0	16/18	11.1	temporary	seizure, headache

venous outflow and a diffuse AVM nidus also increased the odds ratio for new AVM hemorrhage.

Why Initial Radiosurgery Fails

Successful AVM radiosurgery requires accurate stereotactic localization of the nidus, image-integrated dose planning, and precise delivery of an adequate radiation dose to the chosen target.[30] Before 1991, we relied on biplane angiography alone for dose planning. The 3D volume of the AVM is best depicted by a combination of angiography and high-resolution MR imaging for dose planning. However, some patients cannot undergo MR imaging, and in such patients we add axial-plane CT imaging. Improper assessment of the 3D AVM morphology is a common factor associated with failed initial SRS.[18,30,39] In the present series, 78% of the patients with inadequate assessment of the AVM volume at the time of initial SRS had angiography alone; these patients were treated relatively early in our SRS experience. Recanalization of the AVM after embolization is also a cause of initial treatment failure. Embolization is used as an adjunct to SRS for large AVMs in an effort to reduce the AVM volume. Embolization more commonly reduces flow through the AVM but leaves the treatable AVM volume unchanged. Recanalization has been reported after embolization with virtually all agents, although improved obliteration rates have been reported using liquid embolic agents.[9,12,35] Patients with AVMs in whom initial SRS fails may become candidates for resection.[4] Sanchez-Mejia et al.[31] reported that radiosurgery facilitated subsequent AVM microsurgery and decreased operative morbidity.

Total Obliteration Rate

Although we concur that cerebral angiography is the gold standard to confirm complete obliteration of an AVM, it is has proved impossible to obtain post-SRS angiograms in all patients with AVMs. The reasons are multiple but include patient satisfaction with MR imaging as a modality with better than 90% correlation with prediction of angiographic obliteration, the diverse geographic origin of our patient population, and patient unwillingness to undergo yet one more angiogram despite less than 1% risk of a neurological event afterward. With respect to the value of MR imaging, Pollock et al.[28] reported an uncorrected positive predictive value of 84%. They also noted that in those patients whose angiogram showed a persistent early draining vein, complete nidus obliteration was evident at the time of repeat angiography 6–12 months later. After correcting for this additional data, the overall predictive value of MR imaging obliteration rose to 97%.

In the present report, both MR imaging and angiographic data were included. It would be optimal to have all patients undergo follow-up angiography 4–5 years after repeat radiosurgery. The potential slight overestimation of obliteration rates by using MR imaging is balanced by the tendency to underestimate long-term obliteration rates based only on early follow-up examinations. We believe it is both reasonable and necessary to use MR imaging evidence of obliteration to evaluate the outcomes of repeat SRS, although we continue to report the outcomes of repeat SRS based on both MR imaging and angiographic criteria. The timing of documentation of obliteration is variable since patients may have delayed imaging performed months to years after the requested time of 3 years.

Karlsson et al.[14] reported the results of repeat SRS using Gamma Knife for AVMs and reported a 58% obliteration rate after more than 2 years of follow-up. Schlienger et al.[32] reported the results of repeat SRS using LINAC-based SRS for AVMs and reported a 59% (19 of 32 patients) obliteration rate at a median follow-up of 19.5 months. Yen et al.[39] recently reported a 55% rate of total obliteration at a mean follow-up of 48.2 months after repeat SRS using the Gamma Knife. In the present study, the rate of total obliteration after repeat SRS that was documented by angiography was 45% (45 of 105 patients). The total obliteration rate confirmed using MR imaging was 62% (65 of 105 patients) at a median follow-up of 80 months after repeat SRS. The 5-year total obliteration rates as documented by MR imaging and angiography were 67.9% and 56.8%, respectively.

Yen et al.[39] reported that factors associated with a higher rate of total obliteration in multivariate analysis included a margin dose greater than 20 Gy and nidus volume less than 1.5 cm^3. In the present series, factors

associated with a higher rate of total obliteration on MR imaging or angiography included smaller target volume at the time of repeat SRS ($p = 0.038$) and ≥ 50% AVM volume reduction after initial SRS ($p = 0.014$) in the univariate analysis. In the multivariate analysis, however, only ≥ 50% AVM volume reduction after initial SRS ($p = 0.014$, HR 1.86, 95% CI 1.14–3.06) was significantly associated with a higher rate of total obliteration on MR imaging or angiography.

Corrected Versus Uncorrected Obliteration Times

When we calculated obliteration rates using either MR imaging or angiography follow-up data, we found that the corrected obliteration times varied by only a few percentage points. The 5-year obliteration rate was elevated from 68% to 77% and the 10-year obliteration rate was reduced (from 86% to 80%). We believe that the actuarial calculations for AVM obliteration defined by MR or angiography using corrected obliteration times provide the most accurate portrait of AVM obliteration within this patient population. The magnitude of the effect of using uncorrected obliteration rates defined by angiography alone was more pronounced and raised the 5- and 10-year obliteration rates from 63% to 66%.

Bleeding After Repeat SRS

Yen et al.[39] reported that the annual incidence of bleeding during the latency period after initial and repeat SRS remained unchanged (at 3% in still-patent AVM residuals), thereby indicating no protective effect of SRS. Karlsson et al.[14] reported that the annual incidence of bleeding during the first 2 years of the latency period was 1.8%. In the present series, the annual incidence of bleeding during the latency period after repeat SRS was 3.7%. The cumulative rates of patients developing new AVM hemorrhages after repeat SRS were 1.9%, 8.1%, 10.1%, 10.1%, and 22.4% at 1, 2, 3, 5, and 10 years after treatment, respectively. The annual risk of new post–repeat-SRS hemorrhage in the first 2 years after radiosurgery (4.05% per year) was greater than the risk after 2 years had elapsed (1.79% per year for Years 2–10).

We found that the factors statistically associated with a higher rate of bleeding included larger target volume at the time of repeat SRS ($p = 0.004$, HR 1.16, 95% CI 1.05–1.28) and a greater number of bleeding events before repeat SRS ($p = 0.015$, HR 1.63, 95% CI 1.10–2.41 in the multivariate analysis). We found no statistically significant relationship between any AVM treatment factors and the risk of hemorrhage in the interval between initial SRS and repeat SRS. It is possible that either the small number of bleeding events in this interval or the death of some patients after their initial SRS may obscure a relationship that would emerge in a larger patient experience.

Complications of Repeat SRS

Our data further confirm that higher doses and larger volumes increase the risk of AREs after SRS. Flickinger et al.[7] reported in a multiinstitutional study that 80 of 1255 patients with AVMs developed AREs or had other effects including delayed cyst formation after SRS. Flickinger et al.[6] also reported in another multiinstitutional study that the risks of developing permanent symptomatic sequelae from AVM radiosurgery varied dramatically with location and, to a lesser extent, volume. These risks could be predicted according to the 12-Gy volume. In the present study, 10 of 105 patients developed symptomatic AREs, but only 3 patients had permanent neurological deficits (Table 8). A higher margin dose was associated with a higher rate of AREs after initial SRS ($p = 0.029$), and prior embolization ($p = 0.022$) and higher Spetzler-Martin grade ($p = 0.004$) were associated with a higher rate of developing AREs after repeat SRS. In the present series, there was no statistically significant correlation between the 12-Gy volume and the risk of AREs after either initial or repeat SRS.

Delayed cyst formation and even chronic expanding hematoma have been reported after SRS-induced AVM obliteration, although these sequelae are uncommon.[16,25,38] The actual risk of delayed cyst formation is unknown, since some patients with an obliterated AVM do not undergo late imaging follow-up. The phenomenon has been observed at several SRS centers, including our own, and the reports indicate that this complication may occur many years after SRS. In the present series, 5 patients (4.8%) had documented delayed cyst formation at a median of 108 months after repeat SRS (range 47–184 months). One patient required placement of an Ommaya reservoir and the others were simply observed. In the present study a higher number of hemorrhages was significantly associated with delayed cyst formation after repeat SRS ($p = 0.025$). We suspect that residual iron pigment deposition from repeated bleeding events may serve as a radiation sensitizer that increases the risk of this complication in selected patients.

Additional Treatment After Additional SRS

Patients in whom repeat SRS fails remain at risk and may warrant additional intervention. Options include a third SRS procedure, embolization (in selected cases), or resection. In the present series, 12 patients underwent a third SRS procedure and 2 patients underwent resection. A future report will assess the long-term outcomes in patients who have undergone more than 2 SRS procedures.

Weaknesses of the Current Study

We acknowledge certain weaknesses of this retrospective outcome analysis. In this study, the exclusion of patients who were lost to follow-up might produce bias. During our 23-year AVM experience, our knowledge of dose-volume relationships, conformality and selectivity of treatment planning, and reliance on angiographic and then MR imaging data gradually changed. It is likely that patients treated in the later years of this study benefited from our expanded knowledge and improving technique. Optimization of target selection and dose planning have reached a mature phase.

Conclusions

Repeat SRS for incompletely obliterated AVMs sig-

nificantly improves the eventual obliteration rate of AVMs that are not occluded after the first procedure. The risk of delayed hemorrhage and death are reduced over time, but persist if this additional treatment does not result in obliteration of the AVM. The most effective candidates for repeat SRS are patients with smaller residual AVM volumes after the first procedure and those who have not had a prior bleeding event.

Appendix

This article is one of a series. The complete series is as follows.

Sheehan J: Editorial. Radiosurgery. **J Neurosurg** [epub ahead of print November 11, 2011. DOI: 10.3171/2011.6.JNS11844]

Bambakidis NC, Selman WR: Editorial. Stereotactic radiosurgery for arteriovenous malformations. **J Neurosurg** [epub ahead of print November 11, 2011. DOI: 10.3171/2011.6.JNS11842]

Lanzino G: Editorial. Role of radiosurgery for arteriovenous malformations. **J Neurosurg** [epub ahead of print November 11, 2011. DOI: 10.3171/2011.8.JNS11843]

Kondziolka D, Kano H, Lunsford LD: Response to editorials. Arteriovenous malformations and radiosurgery. **J Neurosurg** [epub ahead of print November 11, 2011. DOI: 10.3171/2011.8.JNS111498]

Kano H, Lunsford LD, Flickinger JC, Yang HC, Flannery TJ, Awan NR, et al: Stereotactic radiosurgery for arteriovenous malformations, Part 1: management of Spetzler-Martin Grade I and II arteriovenous malformations. Clinical article. **J Neurosurg** [epub ahead of print November 11, 2011. DOI: 10.3171/2011.9.JNS101740]

Kano H, Kondziolka D, Flickinger JC, Yang HC, Flannery TJ, Awan NR, et al: Stereotactic radiosurgery for arteriovenous malformations, Part 2: management of pediatric patients. Clinical article. **J Neurosurg Pediatr** [epub ahead of print November 11, 2011. DOI: 10.3171/2011.9.PEDS10458]

Kano H, Kondziolka D, Flickinger JC, Yang HC, Flannery TJ, Awan NR, et al: Stereotactic radiosurgery for arteriovenous malformations, Part 3: outcome predictors and risks after repeat radiosurgery. Clinical article. **J Neurosurg** [epub ahead of print November 11, 2011. DOI: 10.3171/2011.9.JNS101741]

Kano H, Kondziolka D, Flickinger JC, Yang HC, Flannery TJ, Niranjan A, et al: Stereotactic radiosurgery for arteriovenous malformations, Part 4: management of basal ganglia and thalamus arteriovenous malformations. Clinical article. **J Neurosurg** [epub ahead of print November 11, 2011. DOI: 10.3171/2011.9.JNS11175]

Kano H, Kondziolka D, Flickinger JC, Yang HC, Flannery TJ, Niranjan A, et al: Stereotactic radiosurgery for arteriovenous malformations, Part 5: management of brainstem arteriovenous malformations. Clinical article. **J Neurosurg** [epub ahead of print November 11, 2011. DOI: 10.3171/2011.9.JNS11176]

Kano H, Kondziolka D, Flickinger JC, Park KJ, Parry PV, Yang HC, et al: Stereotactic radiosurgery for arteriovenous malformations, Part 6: multistaged volumetric management of large arteriovenous malformations. Clinical article. **J Neurosurg** [epub ahead of print November 11, 2011. DOI: 10.3171/2011.9.JNS11177]

Disclosure

The work described in this report was funded by a research grant to Dr. Kano from Elekta AB, Stockholm, Sweden. Drs. Lunsford, Kondziolka, Niranjan, and Novotny are consultants for Elekta AB, and Dr. Lunsford is a stockholder.

Author contributions to the study and manuscript preparation include the following. Conception and design: Lunsford, Kano, Kondziolka, Flickinger. Acquisition of data: Kano, Flickinger, Flannery, Awan. Analysis and interpretation of data: Kano. Drafting the article: Lunsford, Kano, Kondziolka, Flickinger. Critically revising the article: Lunsford, Kano, Kondziolka, Flickinger, Flannery, Niranjan, Novotny. Statistical analysis: Kano, Flickinger. Study supervision: Lunsford, Kano, Kondziolka, Flickinger.

References

1. Auger RG, Wiebers DO: Management of unruptured intracranial arteriovenous malformations: a decision analysis. **Neurosurgery 30:**561–569, 1992
2. Brown RD Jr, Wiebers DO, Forbes G, O'Fallon WM, Piepgras DG, Marsh WR, et al: The natural history of unruptured intracranial arteriovenous malformations. **J Neurosurg 68:**352–357, 1988
3. da Costa L, Wallace MC, Ter Brugge KG, O'Kelly C, Willinsky RA, Tymianski M: The natural history and predictive features of hemorrhage from brain arteriovenous malformations. **Stroke 40:**100–105, 2009
4. Firlik AD, Levy EI, Kondziolka D, Yonas H: Staged volume radiosurgery followed by microsurgical resection: a novel treatment for giant cerebral arteriovenous malformations: technical case report. **Neurosurgery 43:**1223–1228, 1998
5. Fleetwood IG, Steinberg GK: Arteriovenous malformations. **Lancet 359:**863–873, 2002
6. Flickinger JC, Kondziolka D, Lunsford LD, Kassam A, Phuong LK, Liscak R, et al: Development of a model to predict permanent symptomatic postradiosurgery injury for arteriovenous malformation patients. **Int J Radiat Oncol Biol Phys 46:**1143–1148, 2000
7. Flickinger JC, Kondziolka D, Lunsford LD, Pollock BE, Yamamoto M, Gorman DA, et al: A multi-institutional analysis of complication outcomes after arteriovenous malformation radiosurgery. **Int J Radiat Oncol Biol Phys 44:**67–74, 1999
8. Flickinger JC, Kondziolka D, Maitz AH, Lunsford LD: An analysis of the dose-response for arteriovenous malformation radiosurgery and other factors affecting obliteration. **Radiother Oncol 63:**347–354, 2002
9. Fournier D, TerBrugge KG, Willinsky R, Lasjaunias P, Montanera W: Endovascular treatment of intracerebral arteriovenous malformations: experience in 49 cases. **J Neurosurg 75:** 228–233, 1991
10. Gobin YP, Laurent A, Merienne L, Schlienger M, Aymard A, Houdart E, et al: Treatment of brain arteriovenous malformations by embolization and radiosurgery. **J Neurosurg 85:** 19–28, 1996
11. Graf CJ, Perret GE, Torner JC: Bleeding from cerebral arteriovenous malformations as part of their natural history. **J Neurosurg 58:**331–337, 1983
12. Jayaraman MV, Marcellus ML, Hamilton S, Do HM, Campbell D, Chang SD, et al: Neurologic complications of arteriovenous malformation embolization using liquid embolic agents. **AJNR Am J Neuroradiol 29:**242–246, 2008
13. Kader A, Goodrich JT, Sonstein WJ, Stein BM, Carmel PW, Michelsen WJ: Recurrent cerebral arteriovenous malformations after negative postoperative angiograms. **J Neurosurg 85:**14–18, 1996
14. Karlsson B, Kihlström L, Lindquist C, Steiner L: Gamma knife surgery for previously irradiated arteriovenous malformations. **Neurosurgery 42:**1–6, 1998
15. Karlsson B, Lindquist C, Johansson A, Steiner L: Annual risk for the first hemorrhage from untreated cerebral arteriovenous malformations. **Minim Invasive Neurosurg 40:**40–46, 1997
16. Kihlström L, Guo WY, Karlsson B, Lindquist C, Lindqvist M: Magnetic resonance imaging of obliterated arteriovenous malformations up to 23 years after radiosurgery. **J Neurosurg 86:**589–593, 1997
17. Lunsford LD, Kondziolka D, Flickinger JC, Bissonette DJ, Jungreis CA, Maitz AH, et al: Stereotactic radiosurgery for

arteriovenous malformations of the brain. **J Neurosurg 75:** 512–524, 1991
18. Maesawa S, Flickinger JC, Kondziolka D, Lunsford LD: Repeated radiosurgery for incompletely obliterated arteriovenous malformations. **J Neurosurg 92:**961–970, 2000
19. Maruyama K, Kawahara N, Shin M, Tago M, Kishimoto J, Kurita H, et al: The risk of hemorrhage after radiosurgery for cerebral arteriovenous malformations. **N Engl J Med 352:**146–153, 2005
20. Maruyama K, Shin M, Tago M, Kishimoto J, Morita A, Kawahara N: Radiosurgery to reduce the risk of first hemorrhage from brain arteriovenous malformations. **Neurosurgery 60:** 453–459, 2007
21. Ogilvy CS, Stieg PE, Awad I, Brown RD Jr, Kondziolka D, Rosenwasser R, et al: AHA Scientific Statement: Recommendations for the management of intracranial arteriovenous malformations: a statement for healthcare professionals from a special writing group of the Stroke Council, American Stroke Association. **Stroke 32:**1458–1471, 2001
22. Ogilvy CS, Stieg PE, Awad I, Brown RD Jr, Kondziolka D, Rosenwasser R, et al: Recommendations for the management of intracranial arteriovenous malformations: a statement for healthcare professionals from a special writing group of the Stroke Council, American Stroke Association. **Circulation 103:**2644–2657, 2001
23. Ondra SL, Troupp H, George ED, Schwab K: The natural history of symptomatic arteriovenous malformations of the brain: a 24-year follow-up assessment. **J Neurosurg 73:**387–391, 1990
24. Paulsen RD, Steinberg GK, Norbash AM, Marcellus ML, Marks MP: Embolization of basal ganglia and thalamic arteriovenous malformations. **Neurosurgery 44:**991–997, 1999
25. Pollock BE, Brown RD Jr: Management of cysts arising after radiosurgery to treat intracranial arteriovenous malformations. **Neurosurgery 49:**259–265, 2001
26. Pollock BE, Flickinger JC: A proposed radiosurgery-based grading system for arteriovenous malformations. **J Neurosurg 96:**79–85, 2002
27. Pollock BE, Flickinger JC, Lunsford LD, Bissonette DJ, Kondziolka D: Hemorrhage risk after stereotactic radiosurgery of cerebral arteriovenous malformations. **Neurosurgery 38:**652–661, 1996
28. Pollock BE, Flickinger JC, Lunsford LD, Maitz A, Kondziolka D: Factors associated with successful arteriovenous malformation radiosurgery. **Neurosurgery 42:**1239–1247, 1998
29. Pollock BE, Kondziolka D, Flickinger JC, Patel AK, Bissonette DJ, Lunsford LD: Magnetic resonance imaging: an accurate method to evaluate arteriovenous malformations after stereotactic radiosurgery. **J Neurosurg 85:**1044–1049, 1996
30. Pollock BE, Kondziolka D, Lunsford LD, Bissonette D, Flickinger JC: Repeat stereotactic radiosurgery of arteriovenous malformations: factors associated with incomplete obliteration. **Neurosurgery 38:**318–324, 1996
31. Sanchez-Mejia RO, McDermott MW, Tan J, Kim H, Young WL, Lawton MT: Radiosurgery facilitates resection of brain arteriovenous malformations and reduces surgical morbidity. **Neurosurgery 64:**231–240, 2009
32. Schlienger M, Nataf F, Lefkopoulos D, Mammar H, Missir O, Meder JF, et al: Repeat linear accelerator radiosurgery for cerebral arteriovenous malformations. **Int J Radiat Oncol Biol Phys 56:**529–536, 2003
33. Sinclair J, Kelly ME, Steinberg GK: Surgical management of posterior fossa arteriovenous malformations. **Neurosurgery 58 (4 Suppl 2):**ONS-189–ONS-201, 2006
34. Spetzler RF, Martin NA: A proposed grading system for arteriovenous malformations. **J Neurosurg 65:**476–483, 1986
35. Weber W, Kis B, Siekmann R, Kuehne D: Endovascular treatment of intracranial arteriovenous malformations with onyx: technical aspects. **AJNR Am J Neuroradiol 28:**371–377, 2007
36. Wegner RE, Oysul K, Pollock BE, Sirin S, Kondziolka D, Niranjan A, et al: A modified radiosurgery-based arteriovenous malformation grading scale and its correlation with outcomes. **Int J Radiat Oncol Biol Phys 79:**1147–1150, 2011
37. Williamson R, Kondziolka D, Kanaan H, Lunsford LD, Flickinger JC: Adverse radiation effects after radiosurgery may benefit from oral vitamin E and pentoxifylline therapy: a pilot study. **Stereotact Funct Neurosurg 86:**359–366, 2008
38. Yamamoto M, Jimbo M, Hara M, Saito I, Mori K: Gamma knife radiosurgery for arteriovenous malformations: long-term follow-up results focusing on complications occurring more than 5 years after irradiation. **Neurosurgery 38:**906–914, 1996
39. Yen CP, Jain S, Haq IU, Jagannathan J, Schlesinger D, Sheehan J, et al: Repeat Gamma Knife surgery for incompletely obliterated cerebral arteriovenous malformations. **Neurosurgery 67:**55–64, 2010

Manuscript submitted October 11, 2010.
Accepted September 7, 2011.
Please include this information when citing this paper: published online November 11, 2011; DOI: 10.3171/2011.9.JNS101741.

Address correspondence to: L. Dade Lunsford, M.D., Department of Neurological Surgery, University of Pittsburgh, Suite B-400, UPMC Presbyterian, 200 Lothrop Street, Pittsburgh, Pennsylvania 15213. email: lunsfordld@upmc.edu.