Stereotactic Radiosurgery for Arteriovenous Malformations: The Effect of Treatment Period on Patient Outcomes

Bruce E. Pollock, MD*‡

Michael J. Link, MD*§

Scott L. Stafford, MD‡

Yolanda I. Garces, MD‡

Robert L. Foote, MD‡

Departments of *Neurological Surgery, ‡Radiation Oncology, and §Otorhinolaryngology, Mayo Clinic College of Medicine, Rochester, Minnesota

Correspondence:
Bruce E. Pollock, MD,
Department of Neurological Surgery,
Mayo Clinic,
Rochester, MN 55905.
E-mail: pollock.bruce@mayo.edu

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BACKGROUND: Stereotactic radiosurgery (SRS) has been performed on patients with cerebral arteriovenous malformations (AVMs) for over 40 years.

OBJECTIVE: To evaluate the impact of treatment period on obliteration, intracranial hemorrhage (ICH), and radiation-induced complications (RICs).

METHODS: Retrospective comparison of 381 AVM patients having SRS during a 20-year period (group 1, January 1990 through March 1997, n = 160; group 2, April 1997 through December 2009, n = 221). The median radiological and clinical follow-up after initial SRS was 77 months and 93 months, respectively.

RESULTS: Obliteration was 59.1% at 4 years and 85.1% at 8 years. Obliteration was more common in patients with hemispheric or cerebellar AVMs ($P = .001$), smaller prescription isodose volume (PIV) ($P < .001$), and group 1 patients ($P < .001$). The ICH rate was 7.7% at 4 years and 10.6% at 8 years. ICH was more common in older patients ($P = .02$), patients with deep AVM ($P = .01$), and larger PIV ($P < .001$). There was no difference in the ICH rate between the treatment groups ($P = .18$). The rate of permanent RICs was 4.4% at 4 years and 8.6% at 8 years. RICs were more common with larger PIVs ($P < .001$) and group 1 patients ($P = .02$). There was no difference in the number of patients having obliteration without new deficits between the 2 treatment periods (68.8% vs 73.3%, $P = .33$).

CONCLUSION: Advances in SRS procedures over the past 20 years have resulted in a lower risk of RIC, but fewer patients had AVM obliteration. Increasing the prescription dose for patients with medium- and large-volume AVMs by using current conformal dose-planning techniques may improve the obliteration rate while maintaining a low risk of RICs.

KEY WORDS: Arteriovenous malformation, Complications, Hemorrhage, Obliteration rate, Stereotactic radiosurgery

Stereotactic radiosurgery (SRS) is an accepted management option for many patients with cerebral arteriovenous malformations (AVMs). Over the past 40 years, SRS has been shown to be effective for both ruptured[1] and unruptured AVMs,[2,3] pediatric AVMs,[4] and AVMs located in deep and critical locations.[5-9] More recently, staged-volume SRS has been used to manage patients with large AVMs that historically were considered too big for single-fraction SRS.[10-12] In addition to advancements in neuroimaging and more sophisticated radiation delivery systems over this time frame, there has been an increased base of knowledge on obliteration,[13-18] radiation-induced complications (RICs),[19-22] and post-SRS intracranial hemorrhage (ICH).[23-27] In this study, we analyzed AVM patients having SRS at our center during our first 20 years (1990-2009), and compared our early patients (January 1990 through March 1997) with more recently treated patients (April 1997 through December 2009) with regard to obliteration, ICH, and RICs.

ABBREVIATIONS: AVM, arteriovenous malformation; **ICH,** intracranial hemorrhage; **LINAC,** linear accelerator; **mRS,** modified Rankin Score; **PIV,** prescription isodose volume; **RBAS,** radiosurgery-based AVM score; **RIC,** radiation-induced complication; **SRS,** stereotactic radiosurgery; **STO,** subtotal obliteration

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METHODS

Patient Population

All aspects of this retrospective study were approved by the Institutional Review Board, Mayo Clinic, Rochester, Minnesota (#14-007333). From a prospective registry, 471 AVM patients were identified having SRS from 1990 to 2009. Patients included in this study had sporadic AVM, no prior radiation, and a minimum of 2 years of follow-up. A total of 90 patients (19.1%) were excluded (Figure 1). Of note, every patient who experienced a decline in their functional status as defined by a reduction in their modified Rankin Score (mRS) regardless of their follow-up interval were included. The remaining 381 patients were divided into 2 groups based on the date of their initial SRS procedure. Group 1 patients (n = 160) had SRS from January 1990 through March 1997; group 2 patients (n = 221) had SRS from April 1997 through December 2009. The patient characteristics are detailed in Table 1. Group 1 patients had a greater median maximum diameter (28 mm vs 24 mm, $P < .001$), a higher percentage of Spetzler-Ponce class C AVMs (21.9% vs 13.1%, $P = .02$),[28] and a higher median radiosurgery-based AVM score (RBAS) (1.46 vs 1.31, $P < .001$).[29] Group 2 patients had a higher percentage of Spetzler-Ponce class A AVMs (48.4% vs 32.5%, $P = .002$).
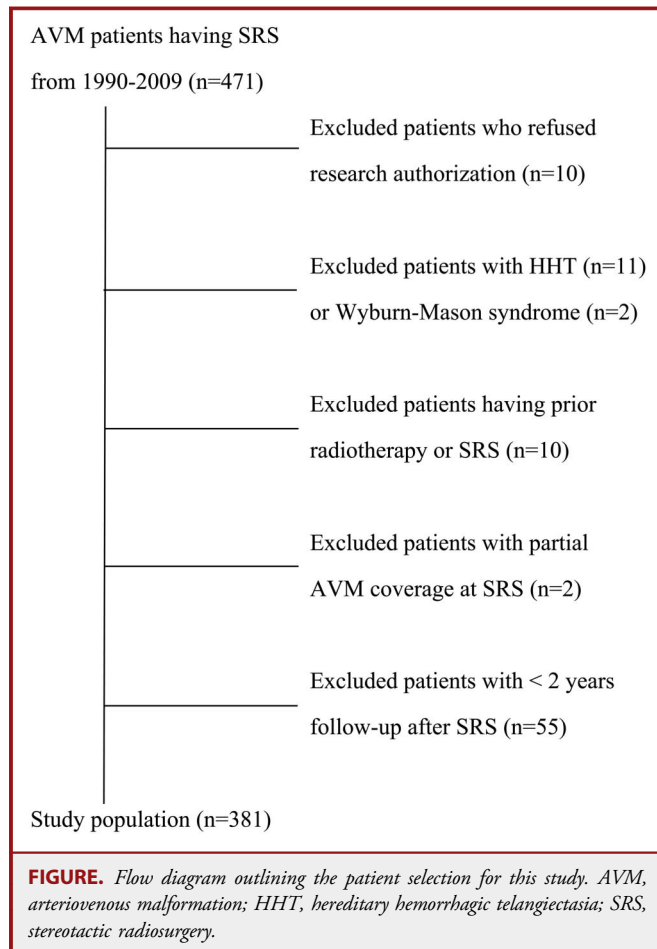
TABLE 1. Patient Characteristics[a]

Factor	Group 1 (n = 160)	Group 2 (n = 221)	P Value
Sex (M/F)	76/84	93/128	.29
Median age, y (range)	36 (3-82)	42 (5-71)	.29
Prior hemorrhage, n (%)	55 (34.4)	63 (28.5)	.22
Prior resection, n (%)	15 (9.4)	15 (6.9)	.36
Prior embolization, n (%)	12 (7.5)	8 (3.6)	.09
Eloquent location, n (%)[b]	128 (80.0)	165 (74.7)	.22
Deep location, n (%)[c]	32 (20.0)	30 (13.6)	.09
Median diameter, mm (range)	28 (9-62)	24 (6-61)	<.001
Spetzler-Ponce class, n (%)[d]			
A	52 (32.5)	107 (48.4)	.002
B	73 (45.6)	85 (38.5)	.16
C	35 (21.9)	29 (13.1)	.02
Median RBAS (range)[e]	1.46 (0.41-5.92)	1.31 (0.21-4.40)	<.001

[a]AVM, arteriovenous malformation; RBAS, radiosurgery-based arteriovenous malformation score.
[b]Eloquent location defined as sensorimotor, language, or visual cortex, hypothalamus, thalamus, brainstem, cerebellar nuclei, or regions directly adjacent to these structures.
[c]Basal ganglia, thalamus, or brainstem.
[d]Based on the 3-tiered system of Spetzler and Ponce.[28]
[e]Based on the modified radiosurgery-based AVM score of Pollock and Flickinger.[29]

AVM patients having SRS from 1990-2009 (n=471)

Excluded patients who refused research authorization (n=10)

Excluded patients with HHT (n=11) or Wyburn-Mason syndrome (n=2)

Excluded patients having prior radiotherapy or SRS (n=10)

Excluded patients with partial AVM coverage at SRS (n=2)

Excluded patients with < 2 years follow-up after SRS (n=55)

Study population (n=381)

FIGURE. *Flow diagram outlining the patient selection for this study. AVM, arteriovenous malformation; HHT, hereditary hemorrhagic telangiectasia; SRS, stereotactic radiosurgery.*

Radiosurgery Technique

SRS was initially performed by using the Model-U Leksell Gamma Knife (Elekta Instruments, Norcross, Georgia). From the beginning of our AVM practice, dose planning was based on a combination of stereotactic biplanar angiography and either contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) to more effectively exclude the adjacent parenchyma and draining veins from the prescription isodose volume (PIV).[30,31] A small number of patients (<10) in our early practice underwent embolization to reduce the nidus volume in preparation for SRS; no patient after 1995 underwent planned embolization before SRS. Dose planning was performed using KULA (Elekta Instruments) from January 1990 until April 1993. After April 1993, versions of Leksell GammaPlan (Elekta Instruments) were used for dose planning. Dose selection to the AVM margin from January 1990 until April 1997 was based on the PIV guided by models that estimated the risk of radiation necrosis to 3% or less (<4.2 cm^3, 20 Gy; 4.2-14.1 cm^3, 18 Gy; >14 cm^3, 16 Gy). A number of seminal articles were published in the mid-1990s increasing the knowledge of factors associated with obliteration,[14,15] RICs,[19-21] and post-SRS hemorrhage,[23,24,26] which were critical in guiding patient selection and dose prescription for later AVM SRS.

In April 1997, a number of changes were introduced to the AVM SRS practice including upgrading from the model U to the model B Gamma Knife, changing the MRI imaging protocol from 3-mm gadolinium-enhanced T1-weighted axial and coronal spin-echo sequences to a 1-mm gadolinium-enhanced axial 3-dimensional spoiled gradient recalled acquisition in steady state sequence, and revising the dose prescription protocol so that small-volume AVMs (≤4.0 cm^3) received a margin dose of 20 to 25 Gy, medium-volume AVMs (4-8 cm^3) received 18 Gy, and

larger-volume AVMs (>8 cm) received 15 to 16 Gy. Patients with AVMs located in deep locations generally were treated with 15 to 18 Gy. Also in 1997, the routine use of staged-volume SRS was introduced for large-volume AVMs to accomplish the simultaneous goals of delivering an effective dose (15-18 Gy) to the entire nidus while limiting the radiation exposure to the surrounding normal brain. Patients with AVMs >15 cm³ in hemispheric or cerebellar locations were considered for staged-volume SRS, as were patients with deep AVM over 8 cm³. Subsequent upgrades in the Leksell Gamma Knife to the current version (Perfexion) provided automation in patient positioning, which increased the precision of radiation to the target. Over time, dose plans have used a higher number of isocenters per plan and the liberal use of beam-blocking techniques to increase the conformality of the treated volume.[32]

Table 2 outlines the radiosurgical dosimetry for the AVM patients at the time of their initial SRS. Group 2 patients had a higher median number of isocenters (6 vs 4, $P < .001$) to treat smaller median volumes (3.6 cm³ vs 5.7 cm³, $P < .001$). Group 2 patients had a higher median margin (20.0 Gy vs 18.0 Gy, $P < .001$) and maximum dose (40.0 Gy vs 36.0 Gy, $P < .001$). Ten percent of group 2 patients were managed using a staged-volume approach, compared with less than 1% of group 1 patients ($P < .001$). The median number of sessions was 2 (range, 2-4) to cover a median volume of 20.2 cm³. The median time between fractions was 6 months (range, 3-9). There were no differences in heterogeneity index, gradient index,[33] or 12-Gy volumes between the groups. Conformality indices have not been routinely calculated in our practice because of concerns about the reliability of target volume (nidus) definition during AVM dose planning.[34,35]

Additional Procedures

Sixty-four patients (16.8%) underwent repeat SRS at a median of 42 months (range, 35-108) after their initial SRS. A median of 5 isocenters

(range, 1-12) was used to cover a median PIV of 2.4 cm³ (range, 0.2-17.2). The median margin dose was 18.0 Gy (range, 14.0-20.0); the median maximum dose was 36 Gy (range, 25.0-44.0).

Ten patients (2.6%) had AVM resection performed at a median of 24 months (range, 7-70) after an ICH. Four patients (1.0%) had AVM resection performed at a median of 48 months (range, 31-67) owing to residual nidus. One patient (0.3%) had AVM resection performed at 29 months because of symptomatic radiation necrosis. Eight patients (2.1%) had AVM resection performed at a median of 110 months (range, 66-200) because of symptomatic cyst formation or edema. In total, 23 patients (6.0%) underwent a craniotomy and AVM resection after SRS. One patient (0.3%) had placement of a ventriculoperitoneal shunt placed following ICH 50 months after staged-volume SRS.

Follow-up

In neurologically stable patients, follow-up consisted of MRI and clinical examination at 1, 2, and 3 years after SRS. If follow-up MRI was consistent with obliteration, then angiography was requested 2 or more years after SRS to confirm obliteration. Although cerebral angiography remains the gold standard to confirm obliteration after SRS, a few study patients refused to undergo follow-up catheter angiography. For those patients, obliteration was evaluated based on most recent MR results. Patients with MRI showing persistent nidus and patients with residual AVM on follow-up angiography 3 or more years after SRS were evaluated for repeat SRS or surgical resection based on their age, clinical condition, and the AVM response from the first SRS procedure.

Data collection for this study was completed in December 2014. Obliteration was defined on MRI as an absence of flow voids on T1-and T2-weighted images.[36-38] Although lack of abnormal arteriovenous shunting is the definition of angiographic obliteration, we also classified patients with subtotal obliteration (STO) on follow-up angiography as obliterated based on the growing amount of information that such patients are essentially cured of the future risk of bleeding,[38-40] and the fact that no further AVM-directed therapy is recommended for these patients. Patients having surgery because of ICH or residual AVM (n = 14) were defined as having incomplete obliteration and the mRS was based on their preoperative status. Likewise, patients having repeat SRS at other centers (n = 3) were defined as having incomplete obliteration and their mRS was based on their preoperative status. Patients having surgery secondary to late RICs (n = 8) all had angiographic obliteration and the mRS was based on their preoperative status. The final patient outcomes were classified as excellent (complete obliteration, no new deficit), good (complete obliteration, minor deficit), fair (complete obliteration, major deficit), unchanged (residual AVM, no deficit), poor (persistent AVM, any new deficit), and dead. The median radiological follow-up after patients' first SRS was 77 months (range, 7-252); the median clinical follow-up was 93 months (3-290). One hundred eight patients (28.3%) had more than 10 years of follow-up.

Statistical Analysis

Continuous variables between the treatment groups were compared with the Student t test; nonparametric variables were compared with use of the χ^2 test. Confidence intervals were calculated using the modified Wald method. Kaplan-Meier survival analysis was performed to determine the rates of obliteration, ICH, RIC, and mRS decline after SRS. Although the time to ICH and RICs are typically well defined, the time to obliteration is never clearly known and must be estimated based on the timing of follow-up imaging studies. The log-rank test was used to

TABLE 2. Radiosurgical Parameters[a]			
Factors	Group 1 (n = 160)	Group 2 (n = 221)	P Value
Median no. of isocenters (range)	4 (1-14)	6 (1-26)	<.001
Median PIV, cm³ (range)	5.7 (0.4-45.8)	3.6 (0.1-35.4)	<.001
Median margin dose, Gy (range)	18.0 (15.0-22.0)	20.0 (15.0-25.0)	<.001
Median maximum dose, Gy (range)	36.0 (22.7-44.0)	40.0 (28.6-50.0)	<.001
No. of staged-volume procedures	1 (0.6%)	22 (10.0%)	<.001
Median heterogeneity index[b]	2 (1.25-2)	2 (1.25-2.22)	.12
Median gradient index[c]	2.76 (2.23-3.71)	2.81 (2.25-3.33)	.24
Median 12 Gy volume, cm³ (range)	8.35 (0.7-56.2)	7.50 (0.4-47.2)	.06
Repeat SRS	26 (16.3%)[d]	38 (17.2%)	.81

[a]PIV, prescription isodose volume; SRS, stereotactic radiosurgery.
[b]Heterogeneity index = maximum dose/prescribed dose.
[c]Gradient index = volume of half of the prescription isodose/volume of the entire prescription isodose.
[d]Two group 1 patients (1.3%) underwent a third SRS procedure.

evaluate for differences in obliteration, ICH, and RICs for the following patient and AVM factors (sex, age, prior hemorrhage, prior resection, prior embolization, deep location, and eloquent location). To avoid colinearity due to the interrelationship between dosimetry parameters (number of isocenters, PIV, margin dose, maximum dose, 12-Gy volume), only PIV and date of initial SRS (group 1 vs group 2) were analyzed as treatment variables. Factors with a P value of .15 or less on univariate testing were placed into a Cox proportional hazards model. Statistical significance was defined as $P < .05$. All statistical tests were two-sided.

RESULTS

AVM Obliteration

Two hundred fifty-four patients (66.7%) had obliteration confirmed by angiography (n = 176) or MRI (n = 79) after initial SRS. Forty-four of 64 patients (68.8%) having repeat SRS achieved obliteration (angiography, n = 33; MRI, n = 11), for an overall crude obliteration rate of 78.2%. One hundred thirty group 1 patients (81.3%) had obliteration compared with 168 group 2 patients (76.0%) (P = .22). Obliteration after SRS was 59.1% at 4 years and 85.1% at 8 years.

Table 3 outlines the factors associated with obliteration after SRS. Multivariate analysis found deep AVM location (P = .001) and increasing PIV ($P < .001$) were negative predictors of obliteration. The obliteration rate of patients with deeply located AVMs was 47.0% at 4 years and 77.8% at 8 years, compared with 61.5% at 4 years and 86.5% at 8 years for patients with AVMs located in the cerebral hemispheres or cerebellum. The 4-year obliteration rate was 66.8%, 57.4%, and 44.7% for AVMs with PIV of <4 cm^3, 4 to 10 cm^3, and >10 cm^3, respectively. At 8 years the obliteration rate was 88.3% for AVMs <4 cm^3, 82.7% for AVMs from 4 to 10 cm^3, and 80.5% for AVMs >10 cm^3.

Date of initial SRS was also correlated with obliteration. The 4-year and 8-year obliteration rate of group 1 patients was 67.9% and 86.1%, respectively, compared with 52.7% and 84.3% for group 2 patients ($P < .001$). Subset analysis showed no difference in the obliteration rate between the treatment groups for patients with PIV <4 cm^3 (86.7% vs 84.3%, P = .68) and for PIV >10 cm^3 (70.0% vs 64.1%, P = .86). Group 1 patients with PIV 4 to 10 cm^3 had a higher obliteration rate (86.8%) compared with group 2 patients with PIV 4 to 10 cm^3 (68.7%) (P = .02).

Hemorrhage After Radiosurgery

Thirty-four patients (8.9%) had an ICH at a median of 25 months (range, 3-168) after initial SRS. Of the patients who bled, 11 (32.4%) had no deficit, 11 (32.4%) developed new deficits (hemiparesis, n = 5; ataxia, n = 2; vegetative state, n = 2; diplopia, n = 1; visual field loss, n = 1), and 12 (35.2%) died. Three of 64 patients (4.7%) having repeat SRS had an ICH at 11, 17, and 27 months, respectively. Two patients developed a hemiparesis and 1 patient died. Twenty-six patients (6.8%) either died or developed a new deficit related to post-SRS ICH. Overall, 37 patients (9.7%) had an ICH after SRS in 2966 person-years of follow-up (1.3% per year). The rate of ICH after SRS was 7.7% at 4 years and 10.6% at 8 years.

Table 4 outlines the factors associated with ICH after SRS. Multivariate analysis found that increasing age (P = .02), deep AVM location (P = .01), and increasing PIV ($P < .001$) were predictors of ICH. The ICHs of patients ≤ 40 years of age was 5.5% at 4 years and 7.9% at 8 years, compared with 10.0% at 4 years and 13.4% at 8 years for patients >40 years of age. The ICHs of patients with deeply located AVM was 9.9% at 4 years and 14.2% at 8 years, compared with 7.2% at 4 years and 9.7% at 8 years for patients with AVMs located in the cerebral hemispheres or cerebellum. The 4-year ICH rate was 4.0%, 8.2%, and 14.2% for AVMs with PIV of <4 cm^3, 4 to 10 cm^3, and >10 cm^3, respectively. At 8 years the ICH rate was 4.9% for AVMs <4 cm^3, 9.4% for AVMs from 4 to 10 cm^3, and 22.2% for AVMs >10 cm^3. Treatment group was not associated with post-SRS ICH.

Radiation-Induced Complications

Twenty-three patients (6.0%) developed a permanent RIC at a median of 27 months (range, 8-111) after initial SRS. The deficits

TABLE 3. Analysis of Factors Associated With Obliteration[a]

Factor	Univariate Analysis HR (95% CI), P Value	Multivariate Analysis HR (95% CI), P Value
Sex	0.96 (0.76-1.20), 0.70	NT
Age	1.01 (0.99-1.01), 0.83	NT
Prior hemorrhage	1.08 (0.86-1.35), 0.52	NT
Prior resection	1.31 (0.86-1.35), 0.21	NT
Prior embolization	0.62 (0.35-1.11), 0.11	0.69 (0.38-1.25), 0.22
Deep location	0.66 (0.48-0.92), 0.01	0.57 (0.41-0.80), 0.001
Eloquent location	1.02 (0.77-1.33), 0.91	NT
PIV	0.97 (0.96-0.99), 0.002	0.96 (0.95-0.98), <0.001
Treatment group[b]	0.69 (0.55-0.88), 0.002	0.57 (0.45-0.73), <0.001

[a]CI, confidence interval; HR, hazard ratio; NT, not tested; PIV, prescription isodose volume; SRS, stereotactic radiosurgery.
[b]Group 1 patients had their initial SRS between January 1990 and March 1997; group 2 patients had their initial SRS between April 1997 and December 2009.

TABLE 4. Analysis of Factors Associated With Hemorrhage[a]

Factor	Univariate Analysis HR (95% CI), P Value	Multivariate Analysis HR (95% CI), P Value
Sex	1.35 (0.70-2.63), 0.34	NT
Age	1.02 (1.00-1.05), 0.03	1.03 (1.01-1.05), 0.02
Prior hemorrhage	0.93 (0.45-1.83), 0.84	NT
Prior resection	0.74 (018-3.06), 0.68	NT
Prior embolization	2.11 (0.75-5.95), 0.16	NT
Deep location	1.82 (0.88-3.77), 0.11	2.56 (1.21-5.42), 0.01
Eloquent location	1.27 (0.56-2.90), 0.57	NT
PIV	1.07 (1.04-1.10), <0.001	1.06 (1.04-1.09), <0.001
Treatment group[b]	0.61 (0.32-1.19), 0.18	NT

[a]CI, confidence interval; HR, hazard ratio; NT, not tested; PIV, prescription isodose volume.
[b]Group 1 patients had their initial SRS between January 1990 and March 1997; group 2 patients had their initial SRS between April 1997 and December 2009.

included hemiparesis (n = 7), visual field loss (n = 4), new seizures (n = 4), sensory loss (n = 3), aphasia (n = 2), ataxia (n = 1), and diplopia (n = 1). One patient (0.3%) died of complications related to the treatment of radiation necrosis. Eight of 64 patients (12.5%) developed a permanent RIC at a median of 14 months (range, 9-134) after repeat SRS. The deficits included hemiparesis (n = 4), ataxia (n = 2), visual field loss (n = 1), and diplopia (n = 1). The rate of RIC after SRS was 4.4% at 4 years and 8.6% at 8 years. No radiation-induced tumors were noted after SRS.

Table 5 outlines the factors associated with permanent RICs after SRS. Multivariate analysis found increasing PIV ($P < .001$) and treatment group ($P = .02$) to correlate with RICs. The incidence of permanent RICs was 2.3% for PIV <4 cm^3, 7.5% for PIV 4 to 10 cm^3, and 20.9% for PIV >10 cm^3. Group 1 patients had a greater incidence of permanent RICs (14.4%) compared with group 2 patients (3.6%). Subset analysis showed no difference in the RICs between treatment groups for patients with PIV <4 cm^3 (3.3% vs 1.7%, $P = .50$) and for PIV 4 to 10 cm^3 (11.3% vs 4.5%, $P = .16$). Group 1 patients with PIV >10 cm^3 had a higher incidence of RICs (31.9%) compared with group 2 patients with PIV >10 cm^3 (7.7%) ($P = .006$).

Functional Status

The patients' mRS scores before SRS were 0 (n = 119, 31.2%), 1 to 2 (n = 252, 66.2%), and ≥3 (n = 10, 2.6%). After SRS, 20 patients (5.2%) showed improvement in their mRS scores, primarily from 1 to 0 because they had resolution of headaches (n = 11), seizures (n = 8), or trigeminal neuralgia (n = 1), and 304 patients (79.8%) were unchanged. Fifty-seven patients (15.0%) had a decline (median, −2) in their mRS at a median of 29 months (range, 3-168) after SRS, and 14 patients died (3.7%) of either ICH (n = 13) or complications related to the treatment of radiation necrosis (n = 1). The actuarial rate of mRS decline after SRS was 9.8% at 4 years and 15.3% at 10 years. Group 1 patients had a crude risk of mRS decline of 23.8% vs 8.6% for patients in group 2 ($P < .001$). Risk stratification based on the RBAS showed no difference in mRS decline between group 1 (8.4%) and group 2 (3.8%) for patients with RBAS ≤1.50 ($P = .17$). Alternatively, group 1 patients with RBAS >1.50 had a higher rate of mRS decline (40.3%) compared with group 2 patients (15.6%) ($P < .001$).

Table 6 outlines the final patient outcomes after radiosurgical treatment. Overall, 272 patients (71.4%) achieved an excellent

TABLE 5. Analysis of Factors Associated With Permanent RIC[a]

Factor	Univariate Analysis HR (95% CI), P Value	Multivariate Analysis HR (95% CI), P Value
Sex	1.11 (0.54-2.30), 0.77	NT
Age	1.01 (0.98-1.03), 0.65	NT
Prior hemorrhage	0.82 (0.37-1.81), 0.62	NT
Prior resection	0.45 (0.06-3.29), 0.43	NT
Prior embolization	1.36 (0.32-5.70), 0.68	NT
Deep location	1.50 (0.65-3.51), 0.35	NT
Eloquent location	1.42 (0.54-3.71), 0.48	NT
PIV	1.08 (1.05-1.11), <0.001	1.07 (1.03-1.10), <0.001
Date of Treatment[b]	0.28 (0.12-0.63), 0.002	0.38 (0.16-0.88), 0.02

[a]CI, confidence interval; HR, hazard ratio; NT, not tested; PIV, prescription isodose volume; RIC, radiation-induced complication.
[b]Group 1 patients had their initial SRS between January 1990 and March 1997; group 2 patients had their initial SRS between April 1997 and December 2009.

TABLE 6. Patient Outcomes			
Outcome	Group 1 (n = 160), n (%)	Group 2 (n = 221), n (%)	P Value
Excellent	110 (68.8)	162 (73.3)	.33
Good	11 (6.9)	5 (2.3)	.03
Fair	9 (5.6)	1 (0.5)	.002
Unchanged	13 (8.1)	40 (18.1)	.005
Poor	9 (5.6)	7 (3.2)	.24
Dead	8 (5.0)	6 (2.7)	.24

outcome. There was no difference between treatment groups with regard to excellent outcomes (P = .33). Group 1 patients were more likely to have obliteration with a new deficit (good or fair outcome) compared with group 2 patients, whereas group 2 patients were more likely to have persistent AVMs without a new deficit (unchanged outcome).

DISCUSSION

Early AVM Radiosurgery

Stereotactic radiosurgery has been performed for over 40 years as an alternative to observation or surgical resection for patients with intracranial AVMs. Steiner et al[41] from the Karolinska Institute in 1972 reported that single-fraction, high-dose irradiation caused the progressive obliteration of AVMs and subsequent cure from the risk of later hemorrhage. Based on the fact that AVMs could be visualized using angiography before the development of CT and MRI, AVMs were one of the most frequent conditions treated during the early Gamma Knife experience: 204 of the first 762 patients (27%) having Gamma Knife radiosurgery by Leksell had AVM.[42] During that same period, Kjellberg and Fabrikant were using protons and heavy charged particles instead of photons to irradiate AVMs,[43,44] and other centers soon modified linear accelerators (LINACs) to perform SRS.[45,46]

After the introduction of SRS, it was a number of years until different centers started to publish their results for patients with intracranial AVMs. In 1991, Lunsford et al[16] reviewed 227 patients having SRS during the initial 3-year experience at the University of Pittsburgh. Total nidus coverage was possible in 216 patients (95%) during single-session SRS. The 2-year angiographic obliteration rates according to volume were: <1 cm^3 (8/8, 100%), 1 to 4 cm^3 (22/26, 85%), >4 cm^3 (7/12, 58%). The overall angiographic obliteration rate was 80%. MRI showed areas of increased signal in 38 of 161 patients (24%) at a mean interval of 10 months after SRS, but only 10 patients (6%) were symptomatic, and only 2 patients (1%) had permanent treatment-related deficits. Two patients died of ICH. In 1992, Steiner et al[17] reported the clinical outcomes of 247 consecutive patients having SRS from 1970 and 1983 at the Karolinska Institute. Obliteration was achieved in 81% of

cases. The annual risk of hemorrhage after SRS was 3.7% until 5 years. Post-SRS ICH was the cause of death in 5 patients (2%). Symptom resolution or significant improvement was noted in almost 70% of patients with headaches, motor deficits, seizures, or language or memory deficits after SRS. A full working capacity was reported by 162 of 228 patients (71%). In 1994, Colombo et al[13] reported 180 AVM patients having LINAC-based SRS from 1984 to 1992. Twenty-seven patients (15%) with large or irregularly shaped AVMs underwent partial treatment. The complete obliteration rate was 80% at 2 years. Fifteen patients (8%) bled after SRS. In patients having total AVM coverage, the bleeding risk decreased from 4.8% in the first 6 months, to 0% starting from 1 year after SRS. Patients with partially irradiated AVMs had an annual bleeding rate from 4% to 10% over the first 2 years, then no bleeding thereafter. In 1995, Friedman et al[15] analyzed 158 AVM patients having LINAC-based SRS between 1988 and 1993 at the University of Florida. Forty-eight of 60 patients (80%) were noted to have an angiographic cure. Complete obliteration was obtained in 81% of AVMs between 1 and 4 cm^3, 89% of AVM between 4 and 10 cm^3, and 69% of AVM greater than 10 cm^3. Six patients (4%) had an ICH after SRS (2 patients had deficits, 1 patient died). Two patients had permanent radiation-related complications. To summarize, the early studies on AVM SRS provided valuable information on this management approach, but some of their conclusions (ie, 80% of patients achieved angiographic obliteration) were premature and required further detailed examination.

Evolution of AVM Radiosurgery Knowledge

Following the publication of individual experience with AVM SRS by the different centers, the next articles analyzed in greater detail the 3 elements associated with successful AVM SRS: obliteration rate, the risk of radiation-related complications, and the chance of a post-SRS hemorrhage. Each of these factors has now been well studied and a more complete knowledge foundation has developed that serves as an effective guide for AVM SRS. It is now accepted that there is a correlation between AVM obliteration and radiation dose. Assuming that the radiation is well targeted, the chance of AVM cure is approximately 65% to 70% at 15 Gy, 75% to 80% at 18 Gy, and 85% to 90% at 20 to 25 Gy.[14] Next, the chance of RICs after AVM SRS relates to some measure of the radiation dose to the surrounding tissue and the location of the AVM.[19-21] The most commonly cited parameter is the 12-Gy volume, which is the total volume (AVM plus surrounding tissue) that receives a radiation dose of 12 Gy or more. Also, patients with AVMs in deep locations (thalamus, basal ganglia, and brainstem) are more likely to develop neurological deficits secondary to imaging changes noted on MRI.[19] Finally, SRS does not increase the bleeding rate of AVMs.[23,24,26] Early studies may have noted elevated bleeding rates related to the timing of the procedure. If patients were treated soon after an ICH, the natural history of AVM would predict that these patients should have a greater chance of rebleeding during the latency interval after SRS before the nidus

has obliterated. More recent articles have provided additional support for the results of these seminal works on obliteration, post-SRS hemorrhage, and RICs.[1-9,22,25,27]

Another significant advancement over the past 20 years has been a better appreciation and understanding of post-SRS imaging and how it relates to the risk of ICH risk. The primary goal of AVM SRS is to eliminate a patient's risk of future ICH, and for many years the only accepted end point of treatment was complete obliteration as defined by Lindquist and Steiner in 1988.[47] They defined AVM obliteration as "when the arteriogram has shown a normal circulation time, complete absence of pathological vessels in the former nidus of the malformation, and the disappearance or normalization of draining veins from the area." Since that time, it has been shown that, even in the absence of complete AVM obliteration, the risk of hemorrhage may be reduced if not completely eliminated. Pollock et al[38] reported 19 patients who had a STO (an early draining vein without residual nidus) identified on follow-up angiography. Every patient who underwent repeat angiography (n = 7) attained complete AVM obliteration, and no hemorrhages were observed in the remaining 12 patients at a median follow-up interval of 27 months. Yen et al[40] identified 159 patients (8% of treated cases) with a STO after AVM SRS at the University of Virginia. Twenty-three patients had repeat SRS, whereas 136 received no further treatment. They found that 66 of 90 patients (73%) who underwent later angiography had complete obliteration: no instances of ICH were noted in these patients in 767 patient-years of follow-up, showing that the protection from later ICH is significant in patients with a subtotal obliteration after SRS. Abu-Salma et al[39] described 121 patients having a STO after AVM SRS. The majority of patients (71%) later progressed to complete obliteration; no patient bled in 322 years of follow-up after STO was noted. Consequently, it is now recognized that STO may represent either a transition of an AVM on the way to complete obliteration or a final angiographic outcome. Regardless, the annual ICH risk for such patients is very low, as demonstrated by the absence of any bleeding events in more than 1100 patient-years of follow-up in these 3 studies (95% confidence interval, 0.0-0.4). Based on these results, further AVM-directed treatment is no longer recommended for patients noted to have a STO following SRS.

MRI is also now recognized as providing satisfactory evidence of AVM obliteration after SRS. In 1996, Pollock et al[38] compared 164 angiograms with MRI to determine the diagnostic accuracy after AVM SRS. MRI correctly predicted patency in 64 of 64 cases (positive predictive value, 100%) and obliteration in 84 of 100 cases (negative predictive value, 84%), for an overall diagnostic accuracy of 90%. O'Conner and Friedman[37] from the University of Florida reviewed 120 patients having SRS between 1990 and 2010 and found a negative predictive value of 82%. The accuracy of MRI improved over the study interval and MRI was more accurate in predicting obliteration in patients with larger AVM volumes. More recently, Khandanpour et al[36] compared 23 patients having angiography and 3T MRI after AVM SRS. At a mean interval of 33 months after SRS, 10 patients (43%) had complete angiographic obliteration. In this series, there was complete concordance (100% accuracy) between the 2 imaging techniques. Therefore, as a safer, less invasive, and cheaper alternative to conventional angiography, MRI is now accepted as a reliable method to assess the obliterative status in contemporary studies on AVM SRS.[1-11,48]

Factors Related to Obliteration and Functional Decline

Our results provide further evidence on the importance of AVM size and location with regard to obliteration and RIC after SRS. It has been known since the earliest SRS articles that the obliteration rate is inversely related to AVM size/volume.[13-18,49] In 2 recent articles from the University of Pittsburgh on postgeniculate visual pathway AVM[5] and Spetzler-Martin Grade I to II AVM,[48] they noted a higher rate of obliteration for lesions less than 5 cm^3. Paúl et al[50] analyzed the angioarchitectural and hemodynamic factors predictive of obliteration in 662 AVM patients having SRS between 1993 and 2005. Even after controlling for other factors associated with obliteration (nidus morphology, feeding artery dilation, margin dose), smaller AVM volume remained a positive predictor of obliteration. Similar to other reports,[7-9] patients with AVMs located in the basal ganglia, thalamus, or brainstem had lower obliteration rates and a greater chance of RIC than patients with more superficial lesions. Conversely, eloquent location alone was not associated with worse outcomes in our series. Ding et al[6] performed a matched cohort study comparing 134 patients with AVMs located in the primary sensorimotor cortex with patients with noneloquent lobar AVMs. The median AVM volume was 4.1 cm^3; the median margin dose was 20 Gy. Eighty-four patients (63%) had AVM obliteration and 8 patients (6%) had permanent new deficits after SRS. No difference was noted in the obliteration rate or clinical outcomes between the 2 groups. They concluded that eloquent location does not appear to confer the same negative prognostic value for SRS that it does for microsurgery.

The finding that patients treated early in our AVM series had higher obliteration and RIC rates than more recently treated patients may provide some useful information to improve SRS outcomes in the future. Analyzing the 2 treatment groups by PIV shows that there was no difference in the obliteration rates for patients with PIV <4 cm^3 and for patients with PIV >10 cm^3, whereas permanent RICs occurred more frequently in group 1 patients with PIV >10 cm^3, but not for group 1 patients with PIV <10 cm^3. Although it is not possible to pinpoint which of the changes in our practice correlate with these observations, the probable explanation is 2-fold and relates to the goal of reducing the incidence of RIC. First, advances in neuroimaging and dose planning software combined with more sophisticated radiation delivery devices have all contributed to improved dose conformality in AVM SRS. By more accurately targeting the nidus and excluding the adjacent brain, feeding arteries and draining veins, the same AVM treated in 1990 would likely have a larger PIV than if the same AVM was treated in 2009. As such,

a prescribed dose of 18 Gy with less conformal planning often meant that the nidus was actually receiving a margin dose of 20 Gy or more. Second, the reduction in dose prescription for AVM with a PIV of 8 to 14 cm^3 from 18 Gy to 15 to 16 Gy should also result in a higher obliteration rate for our group 1 patients. Based on these findings, we believe that going back to margin doses of 18 Gy for PIV up to 10 cm^3, and consideration of staged-volume SRS for AVM between 10 and 15 cm^3 with the goal of providing 18 Gy during each session, may accomplish the goal of increasing obliteration for these patients while maintaining a low risk of RIC. Patients with larger-volume AVMs in deep locations will still be managed by the same method using an initial margin dose of 15 Gy and performing repeat SRS later if the AVM fails to obliterate.

Nagy et al[51] reported 492 patients with larger-volume AVMs (>10 cm^3) having single-session SRS and divided them into 3 groups based on the time of SRS and the method of dose planning. The first group (1986-1993), labeled "nonconformal" angiography, used a median of 2 isocenters to cover between 45% and 70% of the AVM volume (median, 15.7 cm^3). The second group (1994-2000), labeled "conformal" angiography, used a median of 5 isocenters to cover between 64% and 95% of the AVM volume (median, 14.6 cm^3). The third group (2001-2007), labeled "MRI," used a median of 7 isocenters to cover between 62% and 94% of the AVM volume (median, 14.3 cm^3). The mean AVM margin dose was >20 Gy for all 3 groups. The rate of obliteration increased over the study period from 27% to 53%, and the number of significant adverse radiation-induced side effects (defined as a decline of mRS ≥2) was highest in the "nonconformal" angiography group (14%). In summary, conformal 3-dimensional dose planning and appropriate dose prescription are the most important technical considerations in SRS, and, in that regard, SRS procedures performed today are superior in comparison with procedures performed 2 or more decades ago. This sentiment was also stated by Kano et al[52] who said "During our 23-year AVM experience, our knowledge of dose-volume relationships, conformality and selective 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 benefitted from our expanded knowledge and improving technique."

Radiosurgery of Large-Volume AVM

One consideration, we believe, that has clearly resulted in a reduction in RICs has been the appreciation of the risk of single-fraction SRS to large-volume AVMs. In 1995, Yamamoto et al[18] provided an interim report on the first 121 AVM patients having SRS at our center between 1990 and 1993. Thirty-one patients (26%) had AVMs ≥10 cm^3, receiving AVM margin doses of 16 to 18 Gy. At the time of that study (follow-up, 12-60 months), no difference was noted in the rate of RICs for these patients compared with patients with AVMs <10 cm^3. However, longer follow-up showed that a number of these patients required prolonged corticosteroid treatment or surgical resection for radiation necrosis, cyst formation, or symptomatic areas of T2 signal abnormali-

ties.[53,54] These late complications have also been noted at other centers,[6,52,55] and, therefore, we now continue to follow patients with MRI even after obliteration has been documented.

In an effort to limit the short- and long-term risk of radiation-related complications, we began treating patients with larger AVM using a staged-volume approach to limit the radiation exposure of the surrounding brain. Analysis of our first 10 AVM patients having staged-volume SRS showed that the 12-Gy volume was reduced by an average of 11%, and the non-AVM 12-Gy volume was reduced by an average of 27%.[12] Over time, improvements in the dose-planning software have made interpolation of previous dose plans onto to current imaging much simpler, and we currently treat approximately 10% of our AVM patients in a staged fashion. Staged-volume SRS has been reported by a number of centers with mixed results. Kano et al[11] reported 47 patients having staged-volume SRS at the University of Pittsburgh between 1992 and 2006. The median combined volume of the AVM was 21.0 cm^3; the median margin dose was 16 Gy. The 5-year actuarial rate of obliteration was 28%. Patients receiving a margin dose ≥17 Gy had a higher obliteration rate. Symptomatic adverse radiation effects were noted in 2 patients (4%). Huang et al[10] described 18 patients with AVM >15 cm^3 having staged-volume SRS between 1998 and 2011. The median AVM volume was 22.9 cm^3; the prescribed AVM margin dose was 15 Gy for all the procedures. The 5-actuarial obliteration rate was 29%. Obliteration was higher in patients with nonembolized AVM at 5 years (57% vs 14%), but it did not reach statistical significance. Only 1 patient (6%) developed a permanent radiation-related deficit. These early reports show that the risk of RIC has been reduced for patients with large-volume AVM, but further follow-up is needed to determine whether refinements in this technique will provide higher rates of AVM obliteration.

Relevance and Limitations of This Study

Understanding contemporary outcomes for various AVM management strategies is critical. Despite the numerous problems with the study (failure to randomly assign a large number of eligible patients, lack of standardized treatments, short follow-up), the recent publication of A Randomized trial of Unruptured Brain Arteriovenous Malformations (ARUBA) has placed tremendous pressure on neurosurgeons to justify their interventions for patients with unruptured AVMs.[56] However, comparisons based on the results of patients managed 20 years ago may result in the incorrect conclusion that observation is superior to treatment if the outcomes are below the current standard of care. Our results show that more recently treated patients had a significantly lower chance of mRS decline, primarily because of a reduction in the incidence of RICs, especially for patients with AVMs >10 cm^3. Compared with the medical group in ARUBA (10% incidence of stroke or death), only 3.8% of group 2 patients with a RBAS ≤1.50 had a mRS decline. Group 2 patients with RBAS >1.50 had a higher rate of mRS decline (15.6%) than the medical arm of ARUBA. It should be noted that the median clinical follow-up in the current series is significantly longer than ARUBA (93 months vs 33 months), so it

is likely that with an additional 5 years of observation the incidence of stroke or clinical impairment would exceed the risk of SRS for these patients as well.

This study is susceptible to a number of biases inherent to any retrospective review including treatment selection bias, patients lost to follow-up, and outcome assessment often performed by the treating physicians. Another weakness in our analysis was the inability to test the effect of conformality on outcomes. Although it was possible to acquire the other dosimetric factors for evaluation, it was not feasible to compare the target volume with the PIV for 2 reasons. First, we were not able to reconstruct dose plans for patients treated early in our series. Second, it has been recognized that variation in defining the AVM nidus is often noted between different observers. However, this flaw is not unique to this study and no AVM article to date has used conformality measures as a predictor of SRS outcomes. Finally, our criteria of obliteration, which included patients with MRI alone and patients with STO on follow-up angiography, may overestimate the true incidence of obliteration within our series. However, most current studies on AVM SRS incorporate obliteration data for both angiography and MRI,[1-11,48,52] and it has been estimated that the inclusion of MRI obliteration introduces a potential overestimation error of obliteration of 1% to 2%.[48] Likewise, the annual ICH risk of patients with STO on angiography after SRS is sufficiently low ($<0.4\%$ per year) that including these patients would also have a negligible effect on our results.

CONCLUSION

Radiosurgery has withstood the test of time and is a safe and effective treatment option for many patients with cerebral AVMs. Advances in SRS procedures over the past 20 years have resulted in a lower risk of RICs, but fewer patients had AVM obliteration. Increasing the prescription dose for patients with medium- and large-volume AVMs by using current conformal dose-planning techniques may improve the obliteration rate while maintaining a low risk of RIC.

Disclosure

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

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COMMENTS

The current study represents a robust, 20-year single-center, retrospective review of all intracranial AVMs (31% ruptured) treated using the SRS from 1990 to 2009 (group 1: 1990-1997; group 2: 1997-2009). A total of 471 patients were identified, for a final cohort of 381 patients. The overall obliteration rate was 59.1% at 4 years, and increased up to 85.1% at 8 years post-SRS. The relatively low incidence of post-SRS AVM hemorrhage (4.4% at 4 years, 10.6% at 8 years) was similar between the study subgroups. The rate of radiation-induced complications (RICs) was 4.4% at 4 years and 8.6% at 8 years. Prescription isodose volume (PIV) was directly proportional to the incidence of RIC, but indirectly proportional to overall obliteration rate. Group 1 was associated with higher obliteration rates and higher risk of RICs, which the authors correlated to multifactorial improvements on the SRS treatment including new Gamma Knife equipment, staged-volume SRS, higher number of isocenters per plan, and better conformality index.

One of the most interesting findings on the current article, though, can be seen on its subgroup analysis based on PIV. The obliteration rates for patients with PIV <4 cm³ or >10 cm³ were similar between groups 1 and 2, despite a lower incidence of RICs on patients treated by using contemporary techniques (group 2). Paradoxical, though, is the fact that patients in group 1 with PIV 4 to 10 cm³ had higher obliteration rates, but a similar incidence of RICs in comparison with group 2. Taken together, those findings corroborate how, in a large subset of patients, the advances on SRS techniques have made the radiosurgical treatment of selected AVMs safer without compromising its obliteration rates. Nonetheless, it also suggests that prior institution-specific protocols for a certain subgroup of patients may still provide adequate treatment response with acceptable morbidity rates. It will be interesting to see if the authors can identify in their practice factors that would elucidate their current data for this subgroup of patients.

In those times where the indications and modalities of treatment for unruptured cerebral AVMs have been questioned by recent studies with nonnegligible methodological flaws, we congratulate the authors for a very relevant contribution to the cerebrovascular literature.

Louis Whitworth
Dallas, Texas

In this comprehensive, retrospective review, the authors share their experience of 381 AVM patients treated with stereotactic radiosurgery (SRS) over a 20-year period. Not only is the number of patients in this review significant, but the extended follow-up period is also impressive. The median radiological follow-up after initial SRS was 77 months; the median clinical follow-up was 93 months. These prolonged follow-up data importantly provide long-term data demonstrating obliteration rates beyond 5 years after treatment.

In the discussion the authors eloquently describe the evolution of SRS treatment for AVM.

The key issues that are relevant to radiosurgery for AVM are nicely covered: the obliteration rate of the nidus, the risk of radiation-related

complications, and the incidence of post-SRS hemorrhage from the residual AVM nidus.

The authors show that dose planning and appropriate dose prescription are the 2 most important factors in SRS treatment. Importantly, deep-seated AVMs and increased size and number of isocenters have been noted to be negative predictors of obliteration. Not surprisingly, higher-grade AVMs (large, deep-seated, and with more isocenters) fared worse, both in terms of obliteration rate and complication rate.

The authors divided the cohort into 2 groups based on the date of initial SRS treatment—before and after March 1997. At that time point, the treatment protocol was changed by reducing the prescription dosage, which mainly affected middle- to large-sized AVMs (8-14 cc), reducing the dose from 18 Gy to 15 to 16 Gy.

Complete obliteration in small (<4 cc) and large (>10 cc) lesions were similar in both groups; however, in middle-sized AVMs (4-10 cc) obliteration rates were higher in the early group that received the higher radiation dose, while radiation-induced complications were similar in these subset of patients.

The results emphasize that AVMs can be treated effectively using SRS, but one must treat the lesions with the maximally safe radiation dose to achieve obliteration.

We agree with the authors' conclusion that, with modern neuro-imaging techniques and advances in SRS planning software, it should be feasible to increase the treatment dose for middle- to large-sized AVMs (4-10 cc) to 18 Gy.

Risk of hemorrhage was reduced, if not completely eliminated, even in the absence of complete nidus obliteration; hence, further treatment was unnecessary in most subobliterated cases. Although this observation is not a new finding, it is an important addition to the accumulating literature regarding the extent to which full treatment needs to be pursued.

Last, automatization of the treatment procedure, one of the changes in practice over recent years, has been shown to be a useful tool, notably reducing the incidence of the radiation-induced complications of single-fraction SRS to large-volume AVMs.

The take-home message of this noteworthy review is that, over time, technical improvements, implementation of treatment modifications, and adaptation lead to decreases in morbidity and radiation toxicity without compromising efficacy.

Andrew A. Kanner
Ido Strauss
Tel Aviv, Israel

The authors present their 20-year experience of AVM radiosurgery analyzing 381 patients addressing long-term outcome in terms of obliteration, posttreatment hemorrhage, and radiation-induced complications (RICs). Comparing early (group 1, treated between January 1990 and March 1997) and more recently treated patients (group 2, April 1997 through December 2009), the article clearly demonstrates the impact of technical developments and increasing institutional experience on outcome. It was found that deep AVM location and increasing prescription isodose volume were significant negative predictors of obliteration. The negative impact of volume on obliteration is widely accepted. At the same time, it is generally practiced in the radiosurgical community to apply lower prescription doses to larger lesions (in the present study, 15-16 Gy to lesions >8 cm³) to avoid complications. In Sheffield we have always been reluctant to prescribe marginal doses lower than 17.5 Gy, and we found that improving treatment planning resulted in better outcomes without the need for significant dose reduction even in the large AVM group

(>10 cm³).[1] Similarly to single-stage treatments, early attempts at staged-volume radiosurgery of large AVMs used lower prescription doses, thus compromising successful obliteration.[2] We found this an unnecessary precaution (our experience with staged-volume radiosurgery is in publication). Likewise, while the authors adopted a cautious policy treating deep AVMs with lower prescription doses (15-18 Gy), we treat them more aggressively, applying 17.5 to 25 Gy to the margin depending on size and are able to achieve better obliteration without higher complication rates.[3] As it is concluded in the Discussion, a more cautious dose prescription applied more recently may contribute to slightly lower obliteration rates in their group 2, and, with advanced treatment planning, one may afford application of higher prescription doses (not less than 18 Gy), thus improving obliteration rate without an increase of complications in the future. Based on our experience, we can only encourage the radiosurgical community to prescribe not less than 17.5 to 18 Gy even in large and deep AVMs.

Nearly 70% of the treated AVMs in this study were unruptured and the actuarial rate of mRS decline was 15.3% at 10 years. In the light of the recent ARUBA trial[4] this poses the question to the radiosurgical community of whether the long-term benefits of securing a previously unruptured AVM really outweigh short-term side effects of an active management. Because of a short follow-up time, ARUBA does not answer this question. As it is emphasized in the Discussion, more recently treated patients (group 2) with a radiosurgery-based AVM score (RBAS) ≤1.5 had a lower chance of mRS decline compared with the medical group in ARUBA (3.8% and 10% incidence of stroke or death, respectively), while patients with RBAS >1.50 had 15.6% mRS decline. There are 3 points to make here. First, as mentioned in the article, with an additional 5 years of observation of the medical arm, the incidence of clinical decline might exceed the risk of radiosurgery for high-risk patients also. Second, deep-seated AVMs behave more aggressively if left untreated,[5] and these patients are more likely in the RBAS >1.50 group. The long-term benefits of an active treatment would certainly appear after a longer follow-up time than in the ARUBA study (33 months follow-up). Third, RICs in group 2 patients are low (3.6%), and subset analysis showed that the rate of RICs in this group was 1.7% with volumes <4 cm³, 4.5% for 4 to 10 cm³, and 7.7% for >10 cm³. Thus, long-term protection from hemorrhage soon outweighs the risk of treatment-related morbidity in small AVMs, but for large AVMs future studies with longer follow-up are needed.

Gábor Nagy
Budapest, Hungary
Andras A. Kemeny
Sheffield, United Kingdom

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