Radiosurgery for angiographically occult vascular malformations

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The use of radiosurgery for angiographically occult vascular malformations (AOVMs) is a controversial treatment option for those that are surgically inaccessible or located in eloquent brain. To determine the efficacy of this treatment, the authors reviewed the literature reporting hemorrhage rates, seizure control, and radiation-induced morbidity. They found overall hemorrhage rates of 2–6.4%, overall postradiosurgery hemorrhage rates of 1.6–8%, and stratified postradiosurgery hemorrhage rates of 7.3–22.4% in the period immediately to 2 years after treatment; these latter rates declined to 0.8–5.2% > 2 years after treatment. Of 291 patients presenting with seizure across 16 studies, 89 (31%) attained a seizure-free status and 102 (35%) had a reduction in seizure frequency after radiosurgery. Overall radiation-induced morbidity ranged from 2.5 to 59%, with higher complication rates in patients with brainstem lesion locations. Researchers applying mean radiation doses of 15–16.2 Gy to the tumor margin saw both low radiation-induced complication rates (0–9.1%) and adequate hemorrhage control (0.8–5.2% > 2 years after treatment), whereas mean doses $\geq$ 16.5 Gy were associated with higher total radiation-induced morbidity rates (> 17%). Although the use of stereotactic radiosurgery remains controversial, patients with AOVMs located in surgically inaccessible areas of the brain may benefit from such treatment. (DOI: 10.3171/2009.2.FOCUS0923)

KEY WORDS • angiographically occult vascular malformation • cavernous malformation • Gamma Knife • linear accelerator • radiosurgery

ANGIOGRAPHICALLY occult vascular malformations are a heterogeneous group of lesions that include CMs, cryptic or thrombosed AVMs, capillary telangiectasias, venous malformations, and mixed lesions.^{15,43} Recent reports have indicated that the majority (up to 96%) of AOVMs are CMs,⁶⁰ with prospective natural history data showing symptomatic, radiographically verified, extralesional annual hemorrhage rates ranging from 0.7 to 3.1%.^{32,45} Several authors have described the potential for highly aggressive lesion behavior with accumulating resultant morbidity and even death.^{9,31} Radiosurgery has emerged as a possible therapeutic alternative for such aggressive lesions not amenable to surgical intervention. The initial rationale for the radiosurgical treatment of AOVMs stems from favorable clinical and neuroradiological experience in treating high-flow AVMs.^{2,6,12,13,16,17} However, it becomes more difficult to apply this experience to AOVMs in part because there

are no neuroimaging criteria to gauge their successful obliteration.^{16,31,34,59} Thus, these lesions must be clinically assessed by measuring posttreatment hemorrhage rates as a marker of radiosurgical efficacy. We reviewed results across an accumulating, heterogeneous body of literature detailing radiosurgery for AOVMs, highlighting postradiosurgery hemorrhage, morbidity, and mortality rates; seizure control; and the potential advantages and shortcomings of radiosurgical treatment.

Methods

A MEDLINE search was done for all reports that used the terms “AOVM,” “angiographically occult vascular malformation,” “CM,” or “cavernous malformation” with “radiosurgery.” Surgical series and reviews describing radiosurgical outcomes were reviewed in detail, and references were combed for additional articles not identified on the original MEDLINE search. If patient populations overlapped, the report with the larger population was selected for analysis.

Data extracted from each report included radiation

Abbreviations used in this paper: AED = antiepilepsy drug; AOVM = angiographically occult vascular malformation; AVM = arteriovenous malformation; CM = cavernous malformation.

TABLE 1: Literature review of studies on the radiosurgical treatment of AOVMS*

Authors & Year	Type of Radiation	No. of Patients	Mean Lesion Size (mm ³)	Preradio-surgery Hemorrhage (%)	Mean Max Radiation Dose (Gy)	Mean Tumor Margin Dose (Gy)	Mean Follow-Up (yrs)	Postradiosurgery Hemorrhage (%)†		Overall & Permanent Radiation-Induced Morbidity (%)	Overall Long-Term Morbidity & Mortality (%)
								at 0–2 Yrs	at >2 Yrs		
Amin-Hanjani et al., 1998	PB	95	3.1	17.3‡	18.3§	16.5§	5.4	22.4	4.5	23, 16	49, 8
Chang et al., 1998 ¹⁶	Bragg He, LA¶	57	2.25	—	—	18	7.5	12.3	1.9	8.8, 3.5	32, 3.5
Duma et al., 1993	GK	22	3.62	—	28.6	16.8	2.1	2 cases	0	—, 18	—
Garcia-Munoz et al., 2007	LA	15	1.37	34	19.8	15.9	3.6	7.2**	—	—	17, 8.3
Hasegawa et al., 2002 ^{29,30,40}	GK	82	1.85	34‡	30.6	16.2	4.9	12.3	0.8	13, 7.3	—, 1.2
Huang et al., 2006	LA	30	2.47	—	23.6	15.8	5.0	1.9	—	6.7, 0	0, 0††
Karlsson et al., 1998	GK	22	—	—	33§	18	6.5	11‡‡	6‡‡	27, 23	41, —
Kida et al., 1995, 1999	GK	100	15.3§§	32§ (5.2¶¶)	28.56	15.52	2.2	7.3	5.2	—	8, 1
Kim et al. 2002	GK, LA***	22	1.42	36‡	25.7	16.1	3.2	1.6	—	27, 9.1	9.1, —
Kim et al., 1997	GK, LA†††	17	14.5§§	2.3	—	—	1.8	7.8	—	—	—
Kim et al., 2005	GK	42	—	—	26.8	14.6	2.5	1 case (13‡‡‡)	—	—	—
Liscak et al., 2000, 2005	GK	107	0.9	2	30§	16§	4§	1.6	—	21, 4.5	—, 2
Liu KD et al., 2005	GK	125	3.12	—	—	12.1	5.4	10.3	3.3	2.5, —	17, —
Mathiesen et al., 2003	GK	5	—	—	—	—	5.0	8	—	—	—
Mitchell et al., 2000	GK	18	—	13‡ (6¶¶)	34.4	18.6	4.5	3.7**	—	17, 6	—
Pollock et al., 2000	—	17	2.1	25‡ (6.4¶¶)	32§	18§	4.3§	8.8	2.9	59, 41	—
Regis et al., 2000	GK	49	2.37	0	—	19.2	2.0	1 case (3‡‡‡)	—	14, 0	—
Seo et al., 1995	GK	9	3.6	—	30.2	15.3	2.6	3 cases (5–6‡‡‡)	—	11, 0	—
Shih et al., 2005	GK	30	3.95	—	21.43	13.3	4.4	6 cases	—	3, —	—
Stea et al., 1994	LA	12	17§§	3.6	20–25	14–20	2.4	4**	—	—	—
Tsien et al., 2001	LA	20	20§§	30‡	25§	—	6.4	3.2	—	20, 5	—, 5
Weil et al., 1990	GK	6	—	—	23–50	11.5–25	>2	—	—	—, 50	—
Zhang et al., 2000	GK	53	1.8	—	20–50	20.3	4.2	5 cases (4–39‡‡‡)	—	—	32, —

* Superscripted numbers at the end of some author-year entries refer to other studies in which the same data appear. Abbreviations: Bragg He = helium ion Bragg peak; GK = Gamma Knife; LA = linear accelerator; PB = proton beam; — = not provided.

† Single entries in this column indicate an overall postradiosurgery hemorrhage rate rather than a rate stratified from 0 to 2 years or > 2 years.

‡ Reported from first hemorrhage.

§ Median value. ¶ Helium ion Bragg peak, 82%; LA, 18%.

** Our own calculation based on reported data.

†† Two patients died of unrelated metastatic carcinoma in the follow-up period without rebleeding or neurological deficits.

‡‡ Bleeding from 0 to 4 years, 11%; bleeding after 4 years, 6%.

§§ Value represents the diameter in mm.

¶¶ Rate if lesion considered to be present from birth. *** Gamma knife, 50%; LA, 50%. ††† Gamma knife, 94%; LA, 6%.

‡‡‡ Value in parentheses represents the number of follow-up months at which hemorrhage occurred.

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TABLE 2: Studies including patients who had presented with seizures and subsequently underwent radiosurgery

Authors & Year	No. of Patients Presenting w/ Seizures	Seizure Control (no. of patients)	% Seizure-Free Patients (% w/ Seizure Reduction)
Amin-Hanjani et al., 1998	18	resolved, 1; decreased frequency, 6	6 (33)
Chang et al., 1998 ¹⁶	4	resolved, 2	50
Garcia-Munoz et al., 2007	2	resolved, 1; controlled on AEDs, 1	100
Hsu et al., 2007	14	resolved, 5; decreased frequency, 3	36 (21)
Huang et al., 2006	13	resolved, 8; decreased frequency, 3	62 (23)
Kida et al., 1995, 1999	14	resolved, 3; decreased frequency, 6	21 (43)
Kim et al., 2002	3	controlled on AEDs, 3	100
Kim et al., 2005	12	resolved, 9	82
Liscak et al., 2000, 2005	44	decreased frequency, 20	0 (45)
Liu AL et al., 2005	43	resolved, 12; decreased frequency, 24	28 (56)
Liu KD et al., 2005	28	resolved, 11; decreased frequency, 12	39 (43)
Regis et al., 2000	49	resolved, 26; decreased frequency, 10	53 (20)
Shih et al., 2005	16	resolved, 4	25
Stea et al., 1994	2	resolved, 1; controlled on AEDs, 1	100
Tsien et al., 2001	1	resolved, 1	100
Zhang et al., 2000	28	decreased frequency, 18	0 (64)

type and dosing, lesion characteristics, hemorrhage rates, seizure control, and postoperative morbidity and mortality rates. Two authors independently reviewed all studies that provided any details in these categories, and any discrepancies were resolved by consensus after re-review of primary data before inclusion for analysis. All data were entered into a computerized database (Microsoft Excel) and were analyzed by the authors.

Results

Hemorrhage Rates

Table 1 summarizes data from retrospective studies focused on the radiosurgical treatment of AOVMs. Among studies citing both pre- and posttreatment hemorrhage rates, the annual pretreatment rate ranged from 13 to 36% if the rate was calculated from the first bleeding event or from 2 to 6.4% if the rate was determined based on an assumed lesion presence since birth. Annual hemorrhage rates of 7.3–22.4% were documented in the first 2 years after radiosurgery, decreasing to 0.8–5.2% thereafter. Authors reporting only overall postradiosurgical hemorrhage rates showed annual rates of 1.6–8%.

Bearing a marked resemblance to their AVM counterparts, AOVMs in multiple studies demonstrated a statistically significant decrease in postradiosurgical hemorrhage rates > 2 years after treatment.^{8,31,61} Although increased from a preradiosurgery annual hemorrhage rate of 17.3%, the 22.4% initial annual postradiosurgery hemorrhage rate reported by Amin-Hanjani et al.³ decreased significantly to 4.5% > 2 years after treatment. Hasegawa et al.¹⁹ and Chang et al.⁸ reported similar dramatic decreases from 12.3 to 0.8% and from 12.3 to 1.9%, respectively. Less dramatic, but significant, decreases were seen in the studies of Pollock et al.⁴⁶ and Liu et al.³⁸—from 8.8

to 2.9% and from 10.3 to 3.3%, respectively. Not all studies demonstrated this pronounced decreased hemorrhage rate after 2 years. Karlsson et al.²² showed a decrease in annual hemorrhage rates only after 4 years (from 11 to 6%), whereas Kida et al.²⁴ documented a mild decrease after 2 years (from 7.3 to 5.2%).

Studies with only overall postradiosurgical hemorrhage rates generally demonstrated rate reductions. Nearly 10-fold decreases in overall bleed rates were reported in the studies of Kim et al.²⁶ and Tsien et al.⁶¹ On the other hand, postradiosurgery clinical event rates only decreased from 2.0 to 1.6% in the study of Liscák et al.,³⁵ and data provided by Stea et al.⁵⁷ did not demonstrate a significant decrease in hemorrhage rates.

Some authors reported overall postradiosurgery hemorrhage rates that were greater than those for untreated AOVMs. Mathiesen et al.⁴² reported a greater postradiosurgery bleed rate (8% in 5 patients) compared with bleed rates for incidental cavernomas (2%) or symptomatic cavernomas (7%). Kim et al.²⁷ reported a similar postradiosurgery hemorrhage rate of 7.8% in 17 patients over a follow-up of 1.8 years. Authors of these 2 studies concluded that there was no benefit from radiosurgery and argued against offering it as a treatment modality.

Seizure Control

Table 2 lists data from studies documenting postradiosurgery seizure control. Of the 291 patients across these 16 studies who were treated with radiosurgery, 89 attained a seizure-free status with or without AEDs and 102 had a reduction in the number of seizures experienced, resulting in a postradiosurgical seizure-free rate of 31% and seizure-reduction rate of 35%.

In a study on the radiosurgical treatment of AED-resistant epilepsy caused by AOVMs in 49 patients, Régis et al.⁴⁹ described a seizure-free outcome in 53% of pa-

FIG. 1. Images of a stereotactic radiosurgery plan with low dosimetry and highly conformal treatment planning. The young woman in this case had presented with 3 documented overt symptomatic hemorrhages from a small left thalamic retrolenticular CM associated with an extensive venous developmental anomaly. She had made an excellent recovery from visual and hemisensory symptoms after each bleed. She underwent single-fraction stereotactic radiosurgery (tumor margin dose 13 Gy) for the CM, with a treatment plan to minimize fall-off exposure to the internal capsule and brainstem. She had no further hemorrhage or other clinical setback in the 30 months since treatment.

tients and a reduction in seizures in an additional 20%. Although the authors treated lesions located in both cortical and subcortical structures, they found that the probability of becoming seizure free was significantly higher if a patient's lesion had an extratemporal location. Outcomes were better in patients with simple partial seizures (10 of 13 patients became seizure free) than those with complex partial seizures (5 of 18 patients became seizure free). Régis and colleagues determined that sex, age, and duration of epilepsy held no prognostic value. The mean follow-up period in the study was 2 years.

The study of Liu and associates³⁷ in 43 patients demonstrated a seizure-free outcome in 28% of patients and seizure reduction in 56% over a mean follow-up period of 4.1 years. The study of Liscák and colleagues³⁵ with a mean follow-up period of 4 years revealed postradiosurgery seizure reduction in 45% of 44 patients who had presented with seizures; no patient in this study became seizure free. Authors of smaller studies reported seizure-control results with radiosurgical response rates varying from 25 to 100%.

Some investigators reported worsening seizure control after radiosurgery in some patients. Of the 3 largest studies conducted by Liscák et al.,³⁵ Liu et al.,³⁷ and Régis et al.,⁴⁹ only Liscák et al. reported increased seizure frequency in 2 of 44 patients due to transient radiation-induced edema. In a study of 28 patients, Zhang et al.⁶⁷ described 6 patients whose seizures increased in frequency. Among the smaller studies, Hasegawa et al.¹⁹ noted some worsening seizure control (1 of 4 patients), as did Kida et al.²⁴ (1 of 14 patients) and Kayali et al.²³ (1 of 19 patients).

Radiation-Induced Complications

The overall radiation-induced morbidity rate ranged from 2.5 to 59% across all studies (Table 1). In their study of 125 patients, Liu et al.³⁸ used the lowest mean radiation dose to the tumor margin (12.1 Gy), resulting in one of the lowest reported radiation-induced morbidity rates (2.5%) over a mean follow-up period of 5.4 years. Among the larger studies with mainly deep-seated AOVMS in the basal ganglia, thalamus, or brainstem, total radiation-induced morbidity rates ranged from 8.8 to 27%.^{8,14,19,26,35}

Table 3 stratifies radiation-induced permanent morbidity and mortality rates according to lesion location. Several studies including AOVMS from various locations documented only long-term morbidity rates for patients with lesions in the brainstem. The rate of permanent radiation-induced injury varied from 0 to 54% for the basal ganglia, thalamus, and brainstem structures combined compared with 0 to 13% for lobar structures.

Several large radiosurgical studies including lesions in a variety of locations demonstrated higher complication rates in patients with brainstem lesions than in those with lesions in the deep structures of the thalamus and basal ganglia. In a study of 82 patients, Hasegawa et al.¹⁹ reported permanent radiation-induced complications in 12% of 52 patients with brainstem lesions compared with 0% of patients with deep brain lesions. Similarly, Mitchell et al.⁴⁴ described a complication rate of 25% in cases of brainstem CMs, finding no permanent morbidity associated with irradiating the basal ganglia or thalamus. Duma et al.¹⁴ and Liscák et al.³⁵ described treating AOVMS limited to the brainstem and reported postradiation complication rates of 18 and 8%, respectively. Amin-Hanjani et

Fig. 2. Images of a stereotactic radiosurgery plan with fractionated dosimetry. The young woman in this case had presented with 2 documented gross hemorrhagic events from a large diencephalic CM, each causing hemiparesis with good recovery. Subsequent asymptomatic growth of the lesion was demonstrated on MR imaging. The patient did not want to risk the potential complications of an interhemispheric transcassal resection of this lesion. Thus, she underwent radiosurgery using hypofractionated dosimetry (4-Gy tumor margin dose per fraction in 5 fractions over 2 weeks) to further limit potential radiation toxicity to the hypothalamus. She has remained symptom free and maintained normal neuroendocrine function and weight for 32 months since treatment.

al.³ are the only authors to report a higher complication rate after irradiating deep brain lesions in comparison with brainstem lesions: 22 and 16%, respectively.

Huang et al.²¹ and Seo et al.⁵³ both demonstrated 0% postradiation morbidity rates in patients with a variety of lesions. Interestingly, researchers in these 2 studies used comparatively lower mean radiation doses to the tumor margin: 15.8 and 15.3 Gy, respectively. Anecdotal experience with a limited number of cases in which we used low dosimetry, high conformality, and fractionated dose delivery for larger volumes of radiation treatment has also been favorable, even for lesions that bled repeatedly before treatment and for which the resection risk was prohibitive in highly intact patients (Figs. 1 and 2).

Discussion

As underscored by preradiosurgery hemorrhage rates in the reviewed studies^{3,19,24,26,61} and several natural history reports,^{5,62} a menacing subgroup of AOVMs can follow an aggressive, morbid course. Although surgically accessible lesions can be reflexively managed with excision, the approach to aggressive AOVMs in eloquent parenchyma remains a vexing challenge.

Defining efficacy in the treatment of AOVMs is difficult. Although a decrease in lesion size is an applicable measure of successful treatment for many disease processes, it is unfortunately an unreliable one for AOVMs. Clatterbuck et al.¹⁰ have reported on a series of 76 CMs and observed a mean volume decrease of 991 mm³ over a 26-month period; 55% decreased in size, and 35% increased in size. Kim et al.²⁷ have similarly noted an aver-

age decrease of 9.1 mm³ among 28 CMs compared with a decrease of 8.6 mm³ for lesions treated with Gamma Knife surgery over an average follow-up period of 19.6 months. A reduction in lesion size is an unreliable measure of treatment efficacy.

Because neuroimaging cannot accurately gauge AOVm response, a clinical reduction in the hemorrhage rate is used as an indirect measure of radiosurgical treatment efficacy. The mechanism of a vascular malformation's response to radiosurgery is thought to be due to a progressive hyalinization of the vessel wall, leading to endothelial cell proliferation and eventual luminal closure. This process is likely mediated through radiation-induced vascular effects, which promote a chronic inflammatory response.³² However, AOVMs specifically possess much thinner vascular walls with larger lumen/wall ratios, making them theoretically much more difficult to occlude than AVMs.

Radiosurgery has the advantage of being a minimally invasive procedure for which patients require only a local anesthetic and immediately return to their preoperative functional status with little to no recovery time. Deep and surgically inaccessible malformations can also be managed more safely without violating brain parenchyma. There are, however, unique challenges with radiosurgery. Patients must be carefully selected to most benefit from this radiosurgical option. There is also a direct relationship between the nidus volume and radiosurgical efficacy, with a smaller volume associated with a higher response rate in AVMs and a lower complication rate in AOVMs.^{40,61} Striking a balance between an effective and safe radiation dosage plays a considerable role in treatment, and if the

AOVM is situated within eloquent parenchyma, planning for adequate coverage of the entire lesion can be challenging. Novel radiosurgical strategies with highly conformal dosing, low prescribed dose delivery, and fractionation for larger treatment volumes further enhance the safety of this modality in highly selected cases (Figs. 1 and 2).

Our review of the literature on AOVMs revealed an overall hemorrhage rate of 2–6.4% in radiosurgical studies.^{24,35,44,46,57} Authors reported overall postradiosurgical hemorrhage rates ranging from 1.6 to 8%. This higher range may reflect insufficient follow-up as in the Kim et al.²⁷ study (7.8% over 1.8 years) or a too-small treatment population as in the study of Mathiesen et al.⁴² (8% in 5 patients). Studies that stratified postradiosurgical bleeding demonstrated hemorrhage rates of 7.3–22.4% in the period immediately to 2 years after treatment, and these rates declined to 0.8–5.2% > 2 years after treatment.^{3,19,24,31,46} Because true high-flow AVMs have been obliterated after a 2- to 3-year latency period following radiosurgery,² this change in the AOVm hemorrhage rate may reflect a similar gradual luminal closure response over time and support the use of radiosurgery. However, Barker et al.⁵ have demonstrated that the natural history of aggressive CMs encompasses a temporal clustering of hemorrhages interspersed with long hemorrhage-free intervals. They found that during the first 2.5 years after the first bleeding event, the monthly hemorrhage risk was 2%, which thereafter decreased to < 1%. This natural history parallels many aspects of the latency interval needed before radiosurgical efficacy is seen for vascular malformations.

The role of radiosurgery in the management of these lesions remains controversial. It is possible that if untreated AOVms have a transient 2-year period of increased frequency of hemorrhage events, which then spontaneously returns to a lower rate, the results reported in this review may only reflect this natural history without any truly significant benefit from radiosurgery. Although a prospective randomized controlled trial would be ideal for determining the true efficacy of radiosurgery, one such attempted study was discontinued because of inadequate enrollment.³³

Several patients in some of these studies^{3,8,22,31} underwent surgery for rebleeding or radiation-induced complications, introducing a selection bias into the follow-up of these studies. In the study by Chang et al.,⁸ 8 of 57 patients ultimately underwent surgery for rebleeding (6 patients), radiation necrosis (1 patient), or worsening seizures (1 patient). Karlsson et al.²² have also described 6 of 22 patients who were later treated with surgery for either rebleeding (4 patients) or radiation-induced injury (2 patients). In comparing these patients with those originally selected to undergo lesion excision, some authors have described worse surgical outcomes among patients who had received prior radiosurgical treatment.^{58,65} Pathological reports on these patients described patent vascular channels despite radiosurgery, but these cases by definition were considered to have failed treatment.^{23,58} Karlsson et al., however, reported on 1 CM in a patient treated with Gamma Knife surgery, describing 70% histological occlusion of the lesion. More histological studies are needed to determine

the true effect of radiosurgery on AOVms and whether this treatment modality leads to eventual complete occlusion of these lesions.

The optimal radiation dose, delivering a therapeutic effect while minimizing radiation-induced injury, remains to be determined. Furthermore, while the reduction in hemorrhage rates with radiosurgery has been shown to be statistically significant, its clinical significance is debatable. A postradiosurgery bleeding risk of anywhere between 1.6 and 8% per year in our young AOVm patient population and the psychological toll of continually anticipating long-term radiation-induced morbidity are far from ideal.

Our review showed that radiosurgery confers suitable seizure control even for patients with lesions that are surgically inaccessible or located in or near eloquent brain parenchyma. Of the 291 patients in the 16 studies reviewed, 66% showed a favorable response to radiosurgery either by becoming completely seizure free (31%) or by having a reduction in seizure frequency (35%). Authors of 5 different studies did report worsening seizure control in 11 patients (3.8%). Sex, age, and duration of epilepsy had no prognostic value, but an AOVm that had an extratemporal location increased the probability that a patient would become seizure free. Patients with simple partial seizures also had better outcomes than those presenting with complex partial seizures.⁴⁹

Surgical removal is considered the best treatment for patients with intractable seizures. Cappabianca et al.⁷ have shown that from among a series of 35 patients with solitary supratentorial CMs, 29 became seizure free (83%) after lesionectomy. Cohen et al.¹¹ have also demonstrated that 35 (70%) of 50 patients were seizure free after surgery. In the surgical series of Amin-Hanjani et al.,³ 97% of patients with seizures became seizure free postoperatively with or without AEDs. In our review, we noted that Shih and Pan⁵⁴ had provided both surgical and radiosurgical treatment options for their 30 patients presenting with seizures and had demonstrated a higher seizure-free rate with surgery versus radiosurgery (79 vs 25%, respectively). Some reports have suggested that patients with AOVms associated with epilepsy may naturally experience a decrease in seizure activity over time. Kondziolka et al.³¹ found that among 28 patients with CM who had initially presented with seizures and were conservatively treated, 14% became seizure free. Although this natural history may account for some observed changes in seizure control, all studies included in the current review documented at least a 25% response rate to radiosurgery, demonstrating a potentially true effect of this therapy as an alternative to observing surgically inaccessible lesions.

Radiosurgery must always balance a dose that is therapeutic as well as minimizes adverse sequelae. Delayed neurological deficits are usually corroborated with T2-weighted MR imaging, which in turn confirms a radiation cause of injury and not a repeat hemorrhage. Despite the most careful planning, however, radiation complications do occur at a variable rate depending on dosimetry and location.^{3,19}

As expected, radiation-induced complications were

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more prevalent among studies featuring greater dosimetry, as illustrated by the 2.5% morbidity rate in the study performed by Liu et al.³⁸ (12.1 Gy) compared with a 59% morbidity rate in the study of Pollock et al.⁴⁶ (18 Gy). Furthermore, radiation-induced complication rates were greater in patients with brainstem lesions. In a study of CMs from a variety of locations in 82 patients, Hasegawa et al.¹⁹ described radiation-induced complications only for lesions in the brainstem. Mitchell et al.⁴⁴ demonstrated similar findings in their smaller series of 18 patients, finding permanent morbidities from radiation only in treated patients with brainstem lesions. In studies dedicated to brainstem vascular malformations, complication rates of 8–18% were reported.^{14,36}

Karlsson et al.²² have shown radiation-induced complications in patients with CMs to be 7 times higher than expected when matched against those in similar patients with AVMs. However, the mean radiation dose in that study was 33 Gy. Pollock et al.⁴⁶ have also compared the complication rates of AVMs of the same sizes and in similar locations with AOVMs in their own study. The difference was statistically significant (any complication: 59% for AOVMs vs 10% for AVMs, $p < 0.001$) even though 12 of 17 patients in the Pollack et al. series were treated at or below the tumor margin dose prescribed by Kondziolka et al.³² Although the role of the hemosiderin ring as a radiation sensitizer has been implicated in AOVm complication rates, recent improvements in MR imaging guidance have allowed for better exclusion of this ring in radiation targeting and planning.^{19,55}

The hemorrhage rate has been shown in some studies to be inversely proportional to the radiation dose, suggesting that efforts to reduce radiation-induced morbidities can impede successful hemorrhage reduction.³ In the present review we found that Huang et al.²¹ was able to use a relatively low mean tumor margin dose (15.8 Gy) to achieve a postradiosurgery hemorrhage rate of 1.9% over a mean follow-up period of 5.2 years. The permanent radiation-induced morbidity was 0% in that study. Other authors using mean tumor margin doses of 15–16.2 Gy documented hemorrhage rates of 0.8–5.2% more than 2 years after treatment over mean follow-up periods of 2.2–4.9 years. Permanent radiation-induced morbidity rates were 0–9.1%.^{3,24,26,31,35} Researchers delivering mean radiation doses ≥ 16.5 Gy to the tumor margin recorded total morbidity rates $\geq 17\%$.^{3,14,22,25,44,46} Although radiation-induced injury may be dose-dependent, adequate hemorrhage control can still be realized with moderate doses of radiation. We also noted that many authors did not carefully differentiate posttreatment bleeding from the radiation treatment effect (symptomatic edema). It is hoped that a newly proposed strict definition of hemorrhage is applied in future studies on the outcome of treatment of AOVMs.⁵²

Conclusions

Many studies have shown a decrease in hemorrhage rates following radiosurgery suggesting a protective effect against rebleeding after a latency period of 2 years. Without prospective randomized controlled trials to confirm

this hypothesis, however, we must allow that the reduction could merely reflect the natural history of aggressive lesions as demonstrated by Barker et al.⁵ Radiosurgery may be a suitable alternative to observation in patients presenting with seizures due to AOVMs located in deep or eloquent brain, but microsurgical removal remains the mainstay of treatment. Radiation-induced morbidity is greater for AOVMs than AVMs of similar sizes and locations, and brainstem AOVMs seem to have greater radiation complication rates than do lesions in the lobar or deep brain structures.

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