Surgical Management of Adverse Radiation Effects After Gamma Knife Radiosurgery for Cerebral Arteriovenous Malformations: A Population-Based Cohort Study

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■ OBJECTIVE: **The goal of this study is to report our experience in the surgical treatment of cerebral arteriovenous malformations (cAVMs) related permanent symptomatic adverse radiation effects (PSAREs), to clarify an appropriate surgical management and to identify the risk factors related to their development.**

■ METHODS: **We evaluated 549 patients treated with Gamma Knife radiosurgery (GKRS) for cAVMs with a follow-up of at least 8 years. Univariate and multivariate analyses were used to test different risk factors related to the development of PSARE. We retrospectively reviewed the records of these patients to analyze the clinical outcome.**

■ RESULTS: **Fourteen patients (2.5%) developed PSARE and were submitted to surgery. Higher average treated volume represents a significant risk factors for the development of PSARE ($P < 0.05$); on the other hand, older age and higher average dose reduce the risk of PSARE ($P < 0.05$). A favorable clinical outcome was achieved in 13 patients (93%) after surgery; in 1 patient, the unfavorable outcome was due to hemorrhage that occurred months after GKRS. Serial MRI scans following either surgical removal of the nodule or Ommaya reservoir positioning showed progressive reduction of brain edema in all cases.**

■ CONCLUSIONS: **The management of PSARE is controversial, especially for cAVMs treated with SRS. Surgical removal is rarely needed, but—if unavoidable—it can be a valuable option in experienced hands. A careful preoperative planning is always necessary to detect pathologic blood flow through the PSARE.**

INTRODUCTION

Gamma Knife radiosurgery (GKRS), also called stereotactic radiosurgery, constitutes an effective way to treat cerebral arteriovenous malformations (cAVMs), based on a precise delivery of a single, finely focused high dose of radiation to a small, defined intracranial target.[1,2] As reported previously, the physical characteristics of GKRS can induce obliteration of the nidus in 60%–90% of cases over a mean period of 2–4 years, with higher chances of obliteration if the nidus is less than 3 cm in diameter[2,3] and low risks of radiation-induced adverse effects.

Nevertheless, the occurrence of radiation damage to the normal brain tissue surrounding the nidus cannot be excluded, leading to the formation of adverse radiation effects (AREs) associated with edema. AREs can become a severe and late complication of brain radiotherapy, and rarely they can be provoked by specific forms of radiotherapy, including GKRS. AREs generally appear months to

Key words
- Cerebral arteriovenous malformation
- Gamma Knife
- Persistent symptomatic adverse radiation effect
- PSARE
- Surgery

Abbreviations and Acronyms
ARE: Adverse radiation effect
BBB: Blood–brain barrier
BVZ: Bevacizumab
cAVMs: Cerebral arteriovenous malformations
CT: Computed tomography
DSA: Digital subtraction angiography
GKRS: Gamma knife radiosurgery
MRI: Magnetic resonance imaging
PSARE: Persistent symptomatic adverse radiation effect
PTX: Pentoxifylline
SRS: Stereotactic radiosurgery
VEGF: Vascular endothelial growth factor

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years after irradiation, with a peak of onset 12–15 months, and they are considered a chronic inflammatory process ultimately leading to brain parenchymal necrosis.[4-8] Magnetic resonance imaging (MRI) changes after stereotactic radiosurgery (SRS) for AVMs have been reported to occur in 16%–62% of cases, depending on the treatment volume and dose administered; symptomatic AREs have been reported in the range of 3.7%–10.8%, whereas permanent symptomatic adverse radiation events (PSAREs) have been reported in the range of 1%–5.1%.[5,6,9,10]

Recently, the natural history of ARE has been described by a few authors[7,8,11]; various pathogenetic mechanisms and risk factors were proposed and the relation between cAVM obliteration rate and ARE formation was analyzed[12,13]; considering the clinical management of PSARE, there is still a lack of agreement regarding the surgical management of these lesions.[14]

The objective of this study is to evaluate the results of surgical treatment of PSARE, to clarify the management of these lesions in patients who do not respond to medical treatment and to analyze the risk factors connected to their development.

MATERIALS AND METHODS

Patient Population

The study was approved by the local institutional review board. A retrospective, population-based cohort study was conducted on 1076 patients with cAVMs submitted to GKRS at the Neurosurgical Department of Verona between 1993 and 2016. Patients who died from hemorrhage within 2 years of GKSR (32 patients) and patients with a follow-up from GKRS shorter than 8 years (495 patients) were excluded. We identified a final data set of 549 patients with cAVMs. The series included 301 male and 248 female patients; the mean age at GKRS treatment was 33.7 years (range, 5–75 years). No patient underwent previous radiation therapy. All patients were assessed with MRI and digital subtraction angiography (DSA), defining—according to our previous classification[15]—cAVM location and maximum diameter, nidus volume (calculated with the aid of Gamma Plan software), cAVM feeders (superficial vs. deep), cAVM drainage (superficial vs. deep), and extent of the draining system (in 4 grades, according to our classification).[15] Single or multiple endovascular embolizations of the cAVMs were performed in 265 patients (48.2%) before the radiosurgical procedure to reduce the volume of the nidus and the blood flow through the cAVM. Further clinical data are reported in **Table 1**.

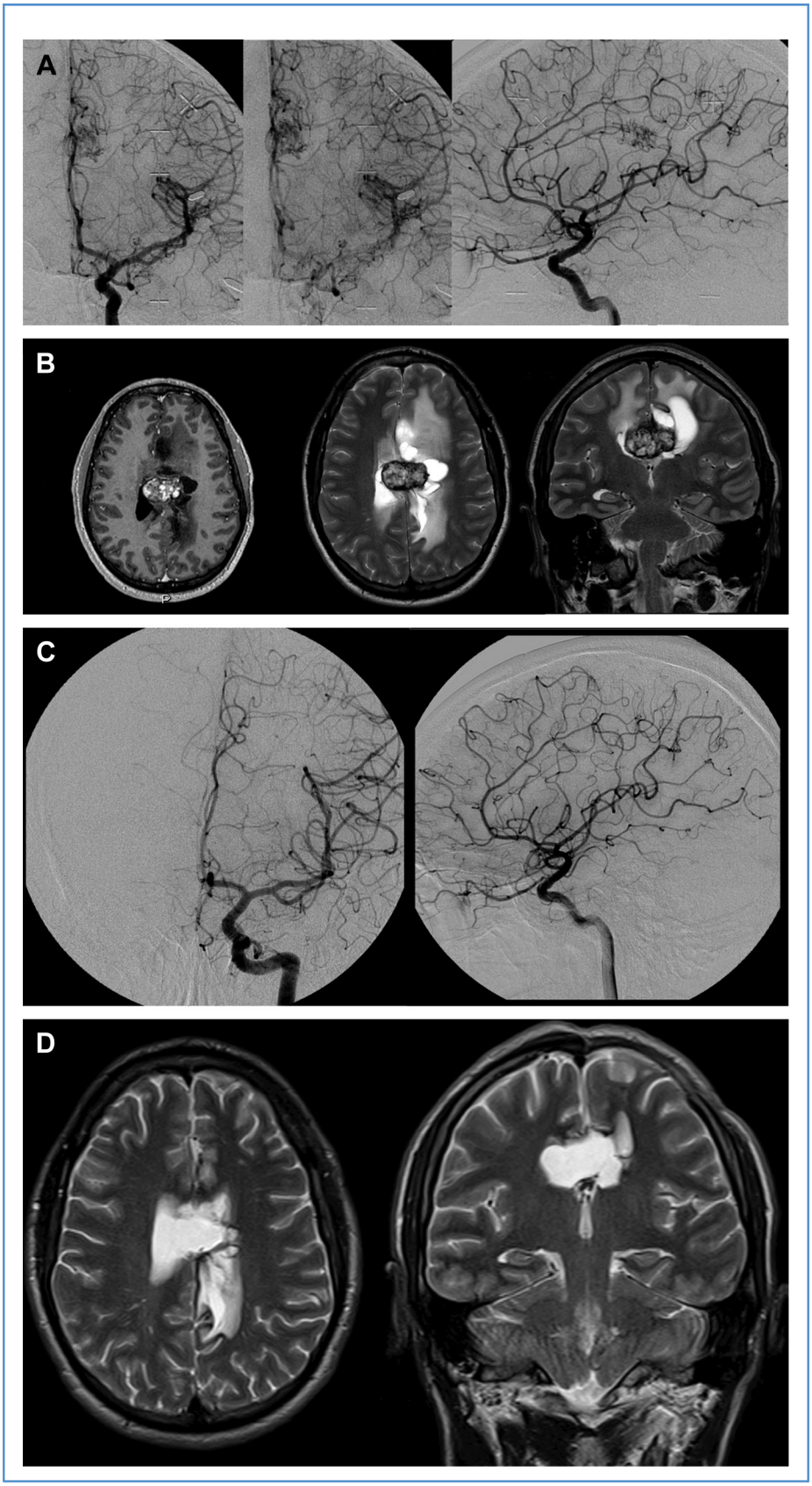
Table 1. Clinical and Radiobiological Data of Patients Who Underwent GKRS for cAVM

	Number of Patients (%)
Clinical onset	
Hemorrhage	295 (54)
Hemorrhage and epilepsy	13 (2)
Epilepsy	151 (28)
Incidental	30 (5)
Other*	60 (11)
cAVM location	
Frontal	47 (8)
Pericentral cortex	100 (19)
Parietal	62 (11)
Peritrigonal area	28 (5)
Occipital	32 (5)
Temporal	96 (18)
Insula	16 (3)
Callosal	14 (2)
Cerebellar	59 (11)
Basal ganglia	66 (13)
Brainstem	19 (3)
Pineal region	4 (0.8)
CP angle	5 (1)
Ventricular	1 (0.2)
Embolization before GKRS	265 (48.2)
Spetzler-Martin grade	
I	40 (7)
II	230 (43)
III	220 (40)
IV	40 (7)
V	0 (0)
Brainstem	19 (3)

GKRS, gamma knife radiosurgery; cAVM, cerebral arteriovenous malformation; CP, cerebello-pontine.
*Headache, neurologic deficit.

Radiosurgery Technique

The radiosurgical technique used in our center has been described in detail in previous reports.[2,3,16-19] All patients underwent GKRS. After the application of the MRI-compatible Leksell Model G stereotactic frame (Elekta Instruments; Stockholm, Sweden), neuroradiologic localization was routinely performed by means of stereotactic 2-dimensional cerebral DSA or, more recently, 3-dimensional rotational stereotactic DSA (with evaluation of the early arterial to late venous phases) to define the cAVMs nidus (target volume), and it was supplemented with stereotactic computed tomography (CT) and MRI, with specific algorithms and sequences, to obtain additional information about the 3-dimensional shape of the cAVMs and the surrounding normal brain structure. The radiosurgical procedure was performed with a model C 201-source Co60 Leksell Gamma Unit (Elekta Instruments) and, since June 2008, with GK Perfexion (Elekta Instruments). Three-dimensional treatment plans were developed using commercially available software: Kula (Elekta Instruments) from February 1993 to February 1998 and Leksell Gamma Plan (versions 4.12, 5.34, and 8.3; Elekta Instruments) after February 1998. The neurosurgeon, radiation oncologist, and medical physicist used multiple collimators to create a highly conformal dose planning and performed the dose selection.


A
B
C
D

The median target volume was 4.64 mL (range, 0.005–37.3 mL). The mean prescription dose delivered to the nidus margin was 21.1 Gy (range, 9–28 Gy); the mean prescription isodose was 54.1% (range, 22%–90%). The mean maximum dose was 39.7 Gy (range, 16–62.5 Gy). The mean number of isocenters was 3.86 (range, 1–28).

Patients Follow-Up After Radiosurgery

After GKRS, patients were evaluated with sequential MRI scans 6 months after SRS and every year thereafter until the disappearance of the nidus. Next, cerebral DSA was performed to confirm the disappearance of the cAVM. Complete cAVM obliteration was defined as disappearance of the nidus and no evidence of early venous drainage (Figure 1). The appearance of new neurologic deficit any time after SRS was followed by CT and MRI scans to rule out hemorrhage or ARE. AREs are defined as any new neurologic symptoms and signs without evidence of a new hemorrhage after SRS.[20] PSAREs are defined as the documented persistence of neurologic deficits despite the medical therapy established; these eventually require surgery for the relief of symptoms. Patients who underwent surgery for the treatment of PSARE represent the material of the study. PSAREs were classified in 3 groups according to their appearance on MRI scans: 1) cyst, 2) gadolinium-enhanced nodule on T1 weighted images, and 3) cyst and nodule.[21] The mean follow-up after radiosurgery was 9.2 years (range, 8–14 years).

Surgical Management of PSARE and Clinical Outcome

Surgery for PSARE was planned after confirmation that conservative therapy had not reached any amelioration of symptoms and further medical therapy would have carried unreasonable risks for the patient. The conservative therapy consisted in dexamethasone (4–8 mg/day for 10–15 days) followed by methylprednisolone (16–25 mg/day) for at least 2 months. The senior author (A.P.) operated on patients harboring nodules with or without cysts. The surgical procedure was constituted by open craniotomy, removal of the nodule, and fenestration of the cysts whenever present. The residual cAVM nidus was also removed whenever present. Patients harboring cysts without evidence of nodule were submitted to stereotactic placement of an Ommaya reservoir to perform repeated drainage of the cysts. (SurgiPlan was used for surgical targeting.)

After surgery, clinical evaluation was assessed with the modified Rankin Scale (mRS) and divided in favorable (score of 0–2) and unfavorable outcome (score $>$ 2). Radiologic evaluation was assessed through MRI studies to evaluate regression of the edema and shrinkage of the cysts (Figure 2).

Statistical Analysis

Univariate and multivariate analyses were applied to factors of age, average treated volume, average periphery dose, average maximum dose, average dose, number of isocenters, and pre-SRS embolization to define their weight on the development of PSARE. The crude odds ratio (95% confidence interval and relative P value) was calculated using a univariate logistic regression model and then a multivariate logistic regression model simultaneously to estimate the effect of the same factors on PSARE development. The correlation between incremental treated volumes at GKRS and the probability of PSARE development was calculated through a simulation based on multivariate logistic model previously estimated. The statistical analysis was performed with STATA software, release 15 (StataCorp, College Station, Texas, USA).

RESULTS

PSARE Group

Of the 549 patients treated with GKRS for cAVMs, 387 patients (70.5%) developed ARE; 374 patients (68.1%) showed transient ARE, and 14 patients (2.5%) complained of PSARE not responding to medical treatment and eventually required surgical intervention. The latter group was consequently considered eligible for the study (see Table 2 and Figure 3 for details in the opposite groups).

The PSARE group comprised 8 male (57%) and 6 female patients (43%) with a mean age of 24.3 years (range, 11–49 years). The initial clinical manifestation of the cAVM included epilepsy in 6 patients (43%), hemorrhage in 5 patients (36%), headache in 2 patients (14%), and 1 patient experienced progressive neurologic deficit (7%). cAVM volume before treatment was 1–10 cm^3 in 7 patients, 11–20 cm^3 in 5 patients, and greater than 30 cm^3 in 2 patients. Applying the Spetzler and Martin scale,[22] 5 patients were grade 1 or 2, 6 patients were grade 3, 2 patients were grade 4, and 1 patient was grade 5. Single or multiple embolizations before GKRS were performed in 11 patients. Regarding GKRS treatment, the average dose at the periphery was 21.06 Gy (range, 15–25 Gy) with an average treated volume of 8.30 cm^3 (range, 2–21 cm^3); two patients underwent a second radiosurgical treatment (Tables 3 and 4).

Twelve patients (85.7%) showed disappearance of flow through the cAVM, whereas 2 patients (14.2%) showed reduced but persistent flow through the malformation after GKRS. Cysts were present in 2 patients, nodules were present in 4 patients, and cysts together with nodules were present in 8 patients. The mean interval between SRS and disappearance of the nidus was 2.54 years, whereas the interval between SRS and appearance of ARE was 8.5 years. The clinical onset of PSARE was represented by epilepsy

Figure 1. (**A**) This 28-years old man previously underwent radiosurgery for a cingulo-callosal arteriovenous malformation (AVM), manifesting with headache and visual disturbances 9 years after SRS; after initial conservative management, the patient did not obtain amelioration of symptoms. (**B**) Axial contrast enhanced magnetic resonance imaging (MRI) T1-weighted and axial and coronal preoperative MRI T2-weighted images showed a callosal nodule surrounded by multiple cysts and edema. (**C**) Preoperative digital subtraction angiography showed no pathologic vessels in the area of the treated AVM. (**D**) Postoperative magnetic resonance imaging 2 months after surgery confirmed the removal of the nodule and showed marked decrease of the edema.

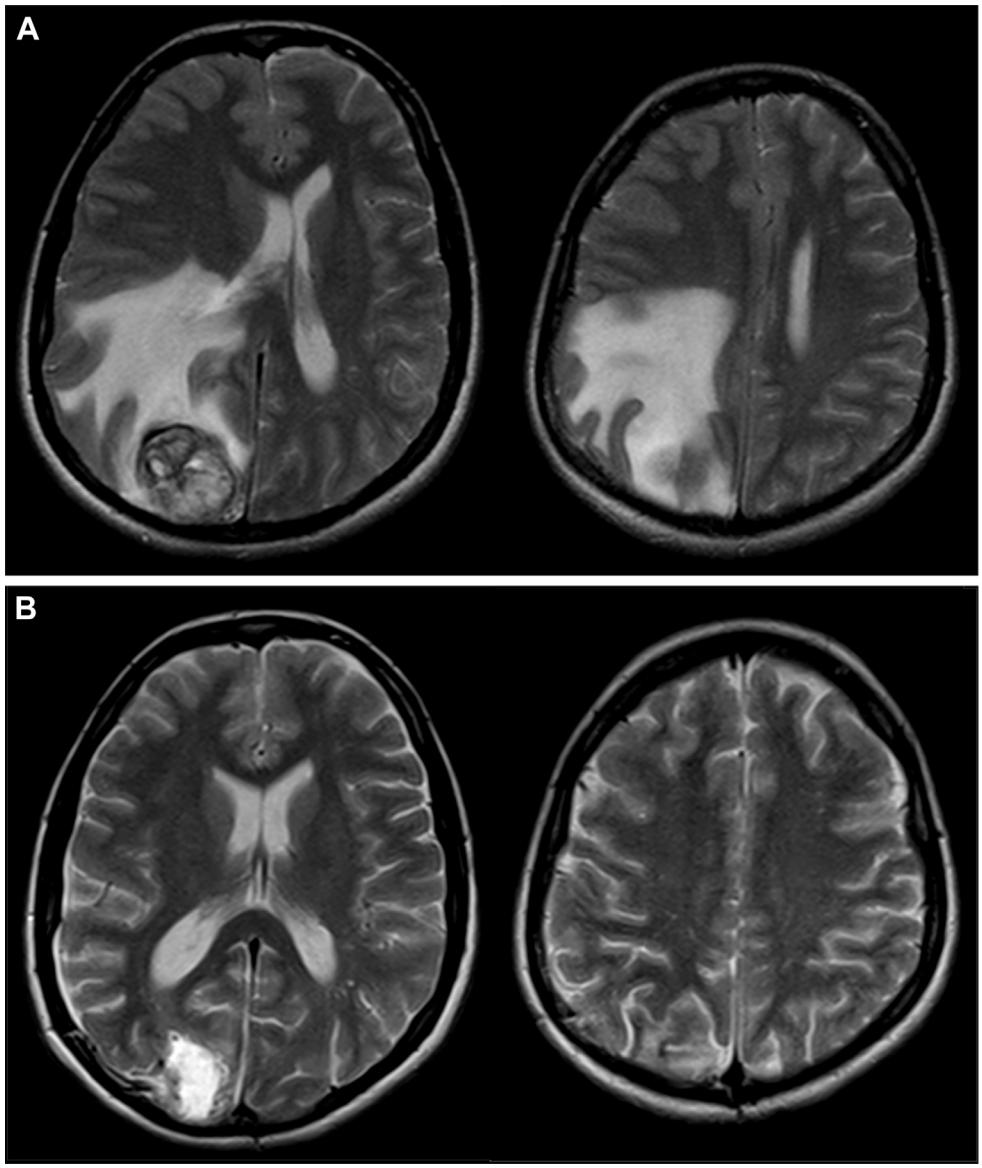


Figure 2. (**A**) A 21-year-old woman with persistent headache and nausea 5 years after SRS. Preoperative T2-weighted magnetic resonance imaging (MRI) showed a right paramedian occipital nodule surrounded by edema. (**B**) Two months after surgery, T2-weighted MRI confirmed removal of the nodule and almost complete disappearance of the T2 hyperintensity. The patient exhibited no neurologic deficits after surgery.

in 6 patients, headache in 5 patients, and a new neurologic deficit (or worsening of a previous deficit) in 3 patients. The mean interval between radiosurgery and the onset of symptoms was 6.7 years (range, 3–11 years), whereas the mean interval between radiosurgery and the surgical procedure was 9.2 years (range, 3–14 years; Table 4).

Surgical Management

Of the 14 patients with PSARE, 12 patients harbored nodules with or without cysts and were submitted to surgical removal of the nodule and cysts fenestration whenever present. Two patients harbored cysts without nodules that were treated with stereotactic placement of an Ommaya reservoir to perform repeated drainage of the cysts. Data regarding clinical and surgical data are presented in Table 4. During surgery, abnormal bleeding was encountered in 1 patient in whom preoperative DSA did not show any injection of a residual nidus. The other 2 cases of incomplete occlusion of cAVMs did not present abnormal bleeding during surgery. Anatomopathologic data obtained are presented in Table 5.

Table 2. Anatomic and Therapeutic Details in the Opposite Groups

	Asymptomatic, Transient ARE (374 Patients)	PSARE (14 Patients)
Average AVM volume (before any treatment)*	8.7 cm^3	14.9 cm^3
Number of patients who underwent embolization before GKRS	167 (44.6%)	11 (78.5%)
Embolization:patient ratio	1.23	1.46
Average prescription dose	21.12 Gy	21.06 Gy
Average treated volume	5.19 cm^3	8.30 cm^3
Average maximum dose	40.25 Gy	40.1 Gy

ARE, adverse radiation effect; PSARE, persistent symptomatic adverse radiation event; AVM, arteriovenous malformation; GK, gamma knife radiosurgery.
*Calculated from the multiplication of the 3 orthogonal diameters and divided by 2.
(Pasqualin A, Barone G, Cioffi F, Rosta L, Scienza R, Da Pian R. The relevance of anatomic and hemodynamic factors to a classification of cerebral arteriovenous malformations. *Neurosurgery.* 1991;28:370-379).

Postoperative complications consisted in bone flap infection in one case (7.1%), with subsequent need for craniectomy and antibiotic therapy for 1 month. Nine months after the first surgery, a custom-made cranioplasty was placed without further complications. In another patient, a persistent urinary infection was diagnosed, with the need for antibiotics therapy for 2 weeks.

Both patients who underwent stereotactic placement of the Ommaya reservoir required multiple aspirations (3 times in the first patient, 2 times in the second one) with a 3-month interval between each other to achieve a complete evacuation of the cysts.

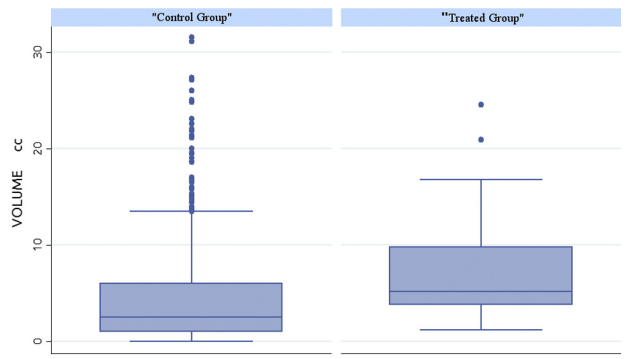


Figure 3. The difference in average treated volumes (in cubic centimeters) between patients who developed transient radiation-induced changes (n = 374 patients, control group) and patients who underwent surgical removal of PSARE (n = 14 patients, treated group).

Outcome and Follow-Up

Surgery-related clinical outcome is shown in Table 4. The postoperative follow-up period ranged from 5 to 72 months (average, 29 months). Thirteen patients (93%) achieved a favorable outcome; mild paresis of the left leg was reported in 1 patient, with mild paresis of the right hand in another patient and mild dysphasia in yet another. It should be noted that in the only case with an mRS score greater than 1, morbidity was due to a previous hemorrhage (occurring months after radiosurgery). Surrounding brain edema decreased rapidly after surgery, and neurologic symptoms quickly resolved in all patients. In 2 patients treated with drainage of the cyst through an Ommaya reservoir, progressive shrinkage of the cyst and disappearance of the surrounding brain edema was observed on MRI.

Risk Factors Evaluation

The effects of different risk factors on the development of PSARE are reported in Table 6. Higher average treated volumes appear as a critical factor in the risk of future PSARE development ($P = 0.03$); on the other hand, older age and higher average dose appear to reduce the risk for PSARE ($P = 0.03$ and $P = 0.001$, respectively).

Multivariate analysis conducted on the same variables tested in the previous univariate model confirmed that average treated volume directly correlates with the future risk of PSARE ($P = 0.04$), whereas age and average dose inversely correlates with the risk of PSARE ($P = 0.05$ and $P = 0.001$, respectively). The simulation based on the previous logistic regression model used to calculate the probability for PSARE development according to incremental values of the average treated volume is reported in Table 7.

DISCUSSION

PSARE after radiosurgery for cAVMs is a rare phenomenon, and the appropriate treatment modality is not clearly defined. Our data confirm than higher average treated volumes represent the leading risk factor for the future development of PSARE; moreover, we showed the incremental probability of PSARE development related to the increase of the average treated volume (Table 7). Interestingly, older age and especially higher average dose seem protective for the development of PSARE. Our clinical results show that surgical removal of PSARE is curative without the need for further treatment for all patients evaluated; moreover, the clinical outcome was good (mRS score ≤ 1) in all patients but one in whom the unfavorable outcome was due to a hemorrhage preceding surgery.

The detailed pathophysiologic mechanism that finally causes the appearance of ARE is not completely understood. Multiple hypotheses have been proposed: radiation injury to glial cells, especially oligodendroglia, can cause demyelinization and subsequent white matter degeneration[23,24]; damage to endothelial cells can lead to the direct alteration of blood–brain barrier (BBB) and the widespread release of proinflammatory cytokines, which finally enhances the alteration of the BBB itself, leading to brain edema and swelling[4]; furthermore, the damage of the cellular wall could provoke an autoimmune reaction as a consequence of the release of antigens from glial and endothelial cells together with

Table 3. Clinical and Radiologic Presentation and Details of Radiosurgical Treatment

				Radiosurgical Details	
Clinical Presentation	AVM Location	AVM Volume (mL)	Number of Prior Embolizations	Periphery Dose (Gy)	Treated Volume (mL)
Headache, visual symptoms	Left occipital	7	2	25	5
Hemorrhage, no deficits	Left frontonuclear	6	1	25	4
Epilepsy, no deficits	Left talamo-capsular	12	1	25	7
Epilepsy, mild hemiparesis	Right rolandic	18	2	21	5
Headache, visual symptoms	Left occipital	6	None	20	6
Epilepsy, no deficits	Left rolandic	35	4	25	5.2
Epilepsy, no deficits	Right frontotemporal	18	1	19	17
Migraine, hemianopia	Right parieto-occipital	15	None	18	10
Epilepsy, no deficits	Right frontal	47	5	16	21 + 24.5
Epilepsy, no deficits	Left temporo-sylvian	3	1	24	2.3
Hemorrhage, no deficits	Left frontocallosal	4	None	22	3.5
Hemorrhage, right hemiparesis	Left thalamocapsular	10	4	23	5
Hemorrhage, no deficits	Left callosal	2	None	22	2
Hemorrhage, hydrocephalus	Left cerebellar	16	1	18	6

Table 4. Clinicopathological and Surgical Data

PSARE			Surgical Details			
Type of Changes	Time from Radiosurgery (Years)	New Symptoms	Time from Radiosurgery (Years)	Procedure	Removal of Residual Nidus	Outcome mRS Score
Cyst	5	Headache, visual symptoms	5	Om	—	0
Nodule + cyst	8	Epilepsy	8	R + F	Yes	0
Cyst	8	Hemiparesis	11	Om	—	0
Nodule + cyst	10	Left leg monoparesis	11	R + F	—	1
Nodule	9	Headache	9	R	—	0
Nodule	9	Epilepsy, hemiparesis worsening	11	R	—	1
Nodule + cyst	3	Epilepsy	3	R + F	—	0
Nodule + cyst	5	Headache, nausea	5	R + F	—	0
Nodule + cyst	7	Epilepsy	8	R + F	—	0
Nodule	12	Epilepsy	13	R	—	1
Nodule + cyst	13	Epilepsy	13	R + F	Yes	0
Nodule + cyst	9	Hemiparesis worsening	14	R + F	—	4*
Nodule + cyst	7	Headache, visual disturbance	9	R + F	—	0
Nodule	5	Headache, disequilibrium	6	R	Yes	0

mRS, modified Rankin Scale; Om, drainage with Ommaya reservoir; R, nodule removal; F, cyst fenestration.
*Preexisting owing to pretreatment hemorrhage.

Table 5. Anatomo-Pathologic Data Obtained From Surgical Specimens (N = 12 Patients)

Anatomo-Pathologic Features	n (%)
Necrosis	11 (91)
Neovascularization	8 (66)
Gliosis	10 (83)
Hemorrhage	6 (50)

the release of free radicals.[25,26] As reported by Shuto et al.,[21] ARE can be visualized on MRI scans as cysts, nodules, and cysts and nodules together. Repeated minor hemorrhages from a nodular lesion that develops within an adjacent brain area are reported to be the main pathologic mechanism that finally causes cyst development.[12] The nodular lesions on MRI scans are the result of late radiation changes mainly consisting of dilated capillary vessels with wall damage.[13]

According to the literature, AREs are related to treatment volume, radiation dose, treatment fractions, and interval between fractions; 12-Gy volume has been related with a high risk of post-radiosurgical complications.[5,27-29] Our data confirm that the target volume is a leading factor in the development of AREs, and a clear trend toward AREs is evident with the enlargement of the average treated volume. Furthermore 8-, 10-, and 12-Gy volumes and mean doses to a specified volume of 16 or 20 cm^3 have been demonstrated as predictors of post-SRS complications.[6] In a multivariate analysis of the risk factors for ARE after SRS for AVMs, Yen et al.[11] highlight that the risk of developing AREs has no relation with previous surgery and hemorrhage, while it is related to a large nidus and the presence of a single draining vein[30]; the authors also reported that symptomatic PSARE were associated with eloquent areas and no pretreatment embolization.[11] However, the lower AVM treated volume reported by Shuto et al.[12] and Pan et al.[31] in their series on cyst formation after GKRS (6.1 and 3.9 ml, respectively) emphasizes that large nidus volume or high radiation dose may be risk factors, but they are not essential. Interestingly, our data show a protective role of higher average dose on the risk of PSARE development. We argued that a possible explanation is related to the higher uniformity of the dose distribution over the nidus. A higher average dose guarantees a homogeneous irradiation of the AVM, thus facilitating its uniform occlusion. On the other hand, a lower average dose is related with a less homogeneous irradiation to the nidus; in this condition, different segments of the AVM receive different doses. This latter condition creates a step by step occlusion of the AVM with different time of occlusion of different segments, possibly leading to ARE formation.

The treatment modality is mainly related to the severity of the phenomenon.[32] Spontaneous resolution usually occurs, but symptoms are progressive in a few cases, necessitating a treatment strategy. Corticosteroids are normally the first line of treatment to control symptoms related to edema, brain swelling, and mass effect, acting through the inhibition of the proinflammatory response, and they are the standard first-line therapy for AREs in our department (e.g., dexamethasone ranging 4–16 mg/day). However, attention must be paid during prolonged therapy with corticosteroids, because they can facilitate the occurrence of wound, cerebral, or systemic infections[33]; in our series, 2 patients required prolonged antibiotic therapy, with craniectomy and subsequent cranioplasty 6 months after the previous revision surgery in 1 patient. We believe that this element constitutes an important factor during the management of PSARE.

Apart from corticosteroids, other therapeutic strategies have been proposed. Rizzoli et al.[34] reported the successful treatment of symptomatic AREs with anticoagulants. Subsequently, Glantz et al.[35] reported that an early institution of anticoagulants (warfarin or heparin) results in a faster clinical improvement. They argued that the reason for the improvement was based on the effect of anticoagulants on the endothelial cells, damaged by radiation, and on the inhibition of platelet aggregation and cytokine release. In addition, the role of antiplatelet medications, such as pentoxifylline (PTX), has been investigated. The ability of PTX in enhancing circulation and tissue oxygenation and reducing radiation-induced fibrosis could lead to amelioration of symptoms[36-38]; furthermore, the association of

Table 6. Univariate and Multivariate Logistic Regression on Factors Related to PSARE Formation

	Univariate			Multivariate		
Factors	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Age	0.95	0.91–0.99	0.03	0.95	0.90–1.00	0.05
Average treated volume	1.07	1.00–1.14	0.03	1.10	1.00–1.22	0.04
Average periphery dose	0.97	0.83–1.14	0.77	1.23	0.96–1.58	0.09
Average maximum dose	0.99	0.92–1.07	0.99	—	—	—
Average dose	0.91	0.87–0.96	0.001	0.91	0.86–0.96	0.001
Number of isocenters	1.07	0.95–1.22	0.23	—	—	—
Embolization before GKRS	2.71	0.84–8.79	0.09	1.97	0.54–7.11	0.3

PSARE, persistent symptomatic adverse radiation event; OR, odds ratio; CI, confidence interval; GKRS, gamma knife radiosurgery.

Table 7. Correlation Between Incremental AVM Volumes at GKRS Treatment and the Probability of PSARE Development

AVM Volume (mL) At GKRS Treatment	PSARE Development Probability (%)	*P* Value
1	1	0.06
2	1.1	0.04
3	1.3	0.03
4	1.5	0.02
5	1.7	0.01
6	1.9	0.01
7	2.1	0.01
8	2.4	0.008
9	2.7	0.007
10	3.1	0.006
11	3.5	0.006
12	3.9	0.007
13	4.4	0.008
14	4.9	0.01
15	5.6	0.01
16	6.3	0.01
17	7	0.02
18	7.9	0.03
19	8.8	0.03
20	9.9	0.04
21	11	0.05
22	12	0.06
23	13	0.08
24	15	0.09
25	17	0.1
26	18	0.11
27	20	0.11
28	22	0.12
29	25	0.13
30	27	0.13
31	29	0.14
32	32	0.14

AVM, arteriovenous malformation; GKRS, gamma knife radiosurgery; PSARE, persistent symptomatic adverse radiation event.

PTX with the free radical scavenger tocopherol (vitamin E) has been used in patients with lung cancer to prevent early and late radiation effects.[39] The role of hyperbaric oxygen—commonly used in treating delayed radiation injury of tissue such as rectum, head, and neck—is still controversial.[40-42] Recently, the introduction of humanized mouse monoclonal antibody against human vascular endothelial growth factor (VEGF)—bevacizumab (BVZ)—increases the options in medical treatment of symptomatic AREs.[43] Based on the inhibition of VEGF, BVZ restores BBB function, thus decreasing cerebral edema and mass effect. Levin et al.[44] reported a neurocognitive improvement in 100% of patients treated with BVZ in a randomized, double-blind study, also with MRI improvement in 63% of patients at an average follow-up of 10 months.

In our department, the rationale for surgical treatment was based on the presence of mass effect and significant edema associated with neurologic signs or intractable epilepsy, and volumetric progression of the nodule in spite of prolonged corticosteroid therapy. Yen et al.[11] proposed a 3-grade scale for AREs based on MRI changes: grade I mild imaging changes (T2 signal thickness of less than 10 mm surrounding the treated nidus, no mass effect), grade II moderate imaging changes (T2 signal thickness of 10 mm or larger with some mass effect), and grade III severe imaging changes with midline shift of the brain.[11] According to this classification, all of our patients were in grade III. However, there is no mention of the presence of a cyst or a nodule in this classification; therefore, it is difficult to draw surgical indications because of the heterogeneity of the lesions and the different causes of mass effect (edema vs. cyst). In our series, cysts were present in 8 patients (61%); in these cases, the volume of the cyst was the leading cause of mass effect and midline shift and eventually the reason for surgery. Furthermore, the relationship between nodule and cyst was the final crucial point: the presence of both of them led to surgery with the aim to remove the nodule. The presence of a cyst alone (2 patients) led to a minimally invasive procedure with placement of an intracystic draining system.

The majority of patients (86%) were treated with open surgery (craniotomy, removal of the nodule and fenestration of the cyst), whereas an intracystic catheter connected to an Ommaya reservoir was positioned in 2 patients. Before surgery, a complete radiologic evaluation of the case is needed (MRI and DSA) to clarify the possible persistent injection of the nidus; in our series of surgical PSARE, incomplete occlusion of the AVM was reported in 2 of the 14 patients (14%) and intraoperative bleeding of the AVM was reported in 1 patient. Yen et al.[11] also reported a lower incidence of incomplete nidus occlusion in patients with AREs after GKRS than in patients without AREs. Furthermore, they highlighted the relationship between cAVM obliteration and development of AREs: 62.8% of nidi with subsequent ARE achieved complete obliteration compared with 52.1% without ARE, with a statistically significant difference ($P < 0.001$). Considering these results, the authors argued that ARE could be a secondary phenomenon of the process of cAVM obliteration. The low incidence of incomplete occlusion in this series, probably related to the small sample size, gives further support to these conclusions. However, it should be noted that in 1 patient with a preoperative DSA showing no nidus injection, a bleeding similar to AVM nidus from the nodule was encountered during surgery. This observation underscores that the surgical management of these lesions could be risky and unpredictable in a small percentage of cases.

The surgical outcome is related to the anatomic location of the ARE and to the previous conditions of the patients.[11,45] In our

series, 3 patients developed postoperative neurologic deficit, and the location of the lesion was rolandic—perirolandic in 2 of them; in the third patient, the location was temporo-uncal, but the clinical condition of the patient was related mainly to the previous post-SRS hemorrhage and to the huge perinodular cysts. The removal of the nodule, the main site of production and release of proinflammatory cytokines,[33] and the fenestration of the cyst causes rapid decrease of brain swelling and amelioration of the symptoms. Therefore, surgery appears to be a reasonable solution for medically intractable patients and, furthermore, is not complicated by hemorrhages or severe postsurgical edema and brain swelling. The less invasive choice of surgical drainage seems reasonable in cases without evidence of a growing mass lesion; in these patients, the drainage of the cyst contents leads to reduced brain swelling and, together with corticosteroid therapy, can lead to regression of AREs. In 2 patients treated with repeated shrinkage of the cyst by external drainage through an Ommaya reservoir progressive, disappearance of the cyst was observed.

MRI follow-up scans showed the effects of surgery on PSARE.[46,47] The gradual disappearance of the T2 signals indicates that the main nature of AREs pathophysiologic mechanism is based on an inflammatory reaction. In addition, the removal of the main site of production of proinflammatory cytokines leads to restoration of the normal BBB and, subsequently, to the disappearance of edema.

A weakness of the present study is the retrospective data analysis. The long-term follow-up period than we choose for the patient selection led us to exclude patients treated with GKRS for AVMs in the last 8 years. During our experience with GKRS, and especially in recent years, our knowledge of radiobiological measures, such as dose—volume relationships and the characteristics of treatment planning, has changed. The true incidence of AREs at our institution might be underestimated or overestimated because of the exclusion of patients treated within the last 8 years.

CONCLUSION

Surgical management of PSARE is safe and advisable in patients who do not respond to previous medical treatment; our experience suggests that early treatment is safer, mainly because of the high risk of infection associated with long-term steroid therapy. The surgical treatment, in experienced hands, bears satisfactory results without significant complications and with regression of the pathologic picture in all cases.

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