# Treatment results of Stereotactic Radiosurgery for cerebral arteriovenous malformations

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## Abstract

**Background and Purpose**: Stereotactic radiosurgery (SRS) has been widely used for the treatment of cerebral arteriovenous malformations (AVMs), but as for the long term results, little information is available on this relatively new treatment modality. The aim of the current study was to assess the treatment results of SRS for cerebral AVMs in an attempt to identify the possible factors that affected the response (success or failure) to such treatment modality.

**Patients and Methods:** Sixteen patients with angiographically proved cerebral AVMs were enrolled in the study. Pretreatment clinical and radiological data were reviewed. Stereotactic radiosurgery was applied either as an initial treatment (11 patients) or after failure of endovascular embolization (5 patients). Post radiosurgery assessment included evaluation of the clinical outcome, obliteration results, and complications.

**Results:** The follow up period ranged from 25 to 104 months with a median follow up of 72 months. Assessment of the clinical outcome revealed that 11 patients (68.75%) were improved and remained symptom free and 3 patients (18.75%) improved significantly (partial response) with occasional mild headache or disorientation. Two patients (12.50%) were deteriorated clinically (progression) with either progressive persistent headache and/or convulsions. Neuroradiological assessment showed that total obliteration of the AVMs was encountered in 10 patients (62.50%) with a mean duration of 15.9 ± 11.24 months (range 9-47 months) after SRS, subtotal or partial obliteration in 4 patients (25%) and minimal or no obliteration in 2 patients (12.50%). Subgroup analysis revealed that none of the clinical characteristics or treatment parameters influenced significantly the obliteration rate. The progression-free survival (PFS) was 87.50 % and mean time to progression was 91.750 ± 8.103 months (95% CI, 75.869 - 107.631). None of the patients had any permanent radiation induced adverse effects or newly developed neurological deficits.

**Conclusion:** Stereotactic radiosurgery is an effective and safe treatment modality for cerebral AVMs with few complications. Candidates for treatment should be selected on the basis of AVM volume and location, and relative risk analysis compared with surgical and endovascular therapies.

## Introduction

Brain arteriovenous malformations (AVMs) are an important cause of intracranial hemorrhage which accounts for half of the presentations that lead to AVM diagnosis **(1-4).** The main purpose of interventional treatment of AVMs is to prevent first or recurrent intracranial hemorrhage and related death and disability **(5,6).** Microsurgical resection, endovascular embolization, or stereotactic radiosurgery (SRS) are used either alone or in various combinations in an attempt to obliterate the AVM nidus and thereby eliminate the risk of hemorrhage **(2).** However, these interventions are not without risk; new neurological deficits may occur after these procedures in 10% to 42% of patients **(7-10).**

Randomized controlled trials have not informed AVM management so far **(11).** Although A Randomized trial of Unruptured Brain Arteriovenous malformations (ARUBA) is comparing interventional and conservative management, there is no trial randomizing participants between different interventions **(12).** Stereotactic radiosurgery has become an important treatment technique for cerebral AVMs and is believed to result in obliteration of cerebral AVMs by causing endothelial cell proliferation, progressive wall thickening, and eventual luminal closure, thereby preventing hemorrhage. Unlike other treatments, the effects of radiotherapy take months or years. Even with treatment that is highly focused there is some risk of injuring adjacent brain tissue **(13).**

Immediate postradiosurgery complications are rare and adverse effects (e.g. radiation-induced necrosis and vascular changes) may be delayed. Long-term sequential follow-up should be performed after radiotherapy **(14-16).** In investigating causes of treatment failure, several factors have been consistently correlated with incomplete response to radiosurgery; including changes in the nidus morphology after radiosurgery because of resolution of a hematoma, recanalization of a previously embolized portion of the AVMs, technical errors in treatment planning, large nidus size (generally >10 ml)[3] or increasing grade according to Spetzler-Martin grading scale (a scale based on AVM nidus size, pattern of venous drainage, and eloquence of adjacent brain) **(13,17).**

The aim of the current study was to assess the treatment results of SRS for brain AVMs in an attempt to identify the possible factors that affected the response (success or failure) to such treatment modality. The safety and adverse effects of radiosurgery were also assessed.

## Patients and Methods

The current prospective study included 16 patients with angiographically proved cerebral AVMs referred to and treated at Kasr El–Aini Center of Radiation Oncology and Nuclear Medicine (NEMROCK) during the period between July 2000 and August 2006. The study had the institutional ethical review board approval and informed oral consent was obtained from all patients.

The inclusion criteria included: **1-** Age ≤ 65 years old. **2-** Adequate performance status (PS): 0-2 according to World Health Organization (WHO) scale. **3-** Radiological confirmation of the diagnosis by magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA). **4-** Maximum diameter of the cerebral AVM is ≤ 3 cm. **5-** Prior endovascular embolization was failed or contraindicated. **6-** No prior radiation therapy. **7-** No life threatening events and life expectancy > 1 year.

Eligible patients were assessed by careful history-taking, complete physical examination including neurological examination, and neuroradiological investigations. Symptomatic treatment was given when indicated to alleviate neurological symptoms e.g. steroids, sedatives, antiepileptics. Pretreatment clinical and radiological data of the eligible patients were carefully reviewed and recorded before delivery of the planned SRS.

## Stereotactic Radiosurgery Technique

- Immobilization of the head was carried out using a stereotactic head frame screwed to the skull under local anesthesia with or without conscious sedation. The head frame allowed also the localization of the tumor in a three dimensional (3D) coordinate system (the target x, y and z coordinates) and delivery of radiation with precision to a very tightly defined volume.
- Computerized tomography (CT) scan was performed with the head frame in place and cuts were taken every 2 mm with zero angulations. CT images are then transferred to Brain Scan computer workstation (from BrainLAB) under DICOM system and fused with the MRI and MRA performed initially.
- Definition of the nidus, delineation of *the gross target volume (GTV), and volume of risk organs* (ROV) were performed in a 3D configuration for complex dose planning. The maximum target dose was placed at the center of the nidus and at least the 80% isodose curve encompassed the entire nidus. (Figure(1)
- All treatment plans made on Brain Scan 5.31 (BrainLAB) consisted of using multiple noncoplanner arcs of circular beams converging on to the machine isocenter, which is stereotactically placed at the center of imaged target volume. A spherical dose distribution obtained in this case was shaped to fit the GTV more closely by manipulating several parameters; selectively blocking parts of the circular fields, changing arc angles and weights and using more than one isocenter.
- *Arc arrangement was the next step. The arc entrance was selected to be away from risk organs and to avoid an untreatable arc direction because of the table angle or gantry collision or couch angle*. Figure(1)
- Treatment plan intercomparisons were performed using the following criteria: target coverage, *dose volume histogram (DVH)*, conformity index, homogeneity index, and maximum dose in critical organs. Figure (2) all plans had 100% of the dose in the isocenter. Target coverage was defined as the percentage of the GTV covered by the 80% isodose.
- The conformity index (CI) was defined as : **CI = 1 + Vn / Vt ,** where Vn is the volume of normal tissue receiving the prescribed dose and Vt is the volume of the target receiving the prescribed dose. The ideal CI is 1, a CI higher than 1.5 was considered insufficient, and a CI higher than 2 was not accepted. The homogeneity index (HI) for SRS was defined as: **HI = Dmax / Dprescribed ,** where $D_{max}$ and $D_{prescribed}$ are the maximum and the prescribed dose, respectively. The HI should preferably be below 2 and between 2 - 2.5 would be acceptable. **(18)**
- *Dose calculation* (using Clarkson Algorithm), *radiographic verification simulation, and isocenter placement check on the treatment machine preceded the delivery of SRS.*
- The patient's head was then attached to the treatment couch by the stereotactic head frame *and* radiosurgery was delivered in a single session using the 6MV Linear accelerator machine (Varian 600C). The dose ranged from 15-20 Gy depending on age and volume of the AVM. The radiotherapy induced toxicity was assessed according to the Radiation Therapy Oncology Group (RTOG) criteria.

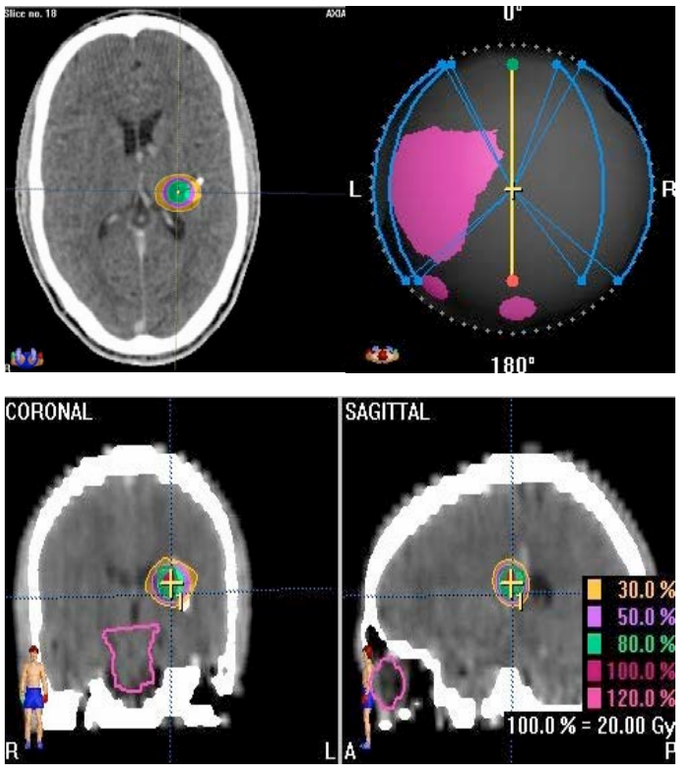



**Fig. 1: Isodose distribution and arc arrangement for a left temporo-parietal AVM**

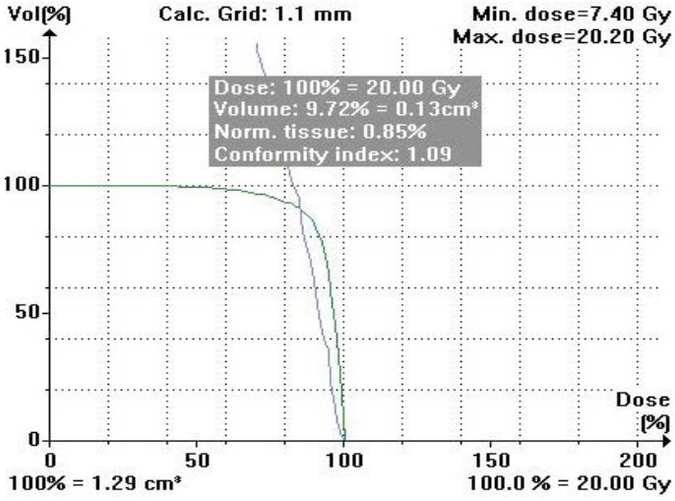



**Fig. 2: Dose volume histogram (DVH) of the left temporo-parietal AVM**

### Assessment of Treatment Response

All patients were put under regular follow up every 3 months for assessment by detailed general and neurological examination in addition to radiological investigations by MRI and MRA every 3-6 months. The clinical outcome (improved, stable, or deteriorated), neuroradiological outcome (total, subtotal or minimal obliteration), and the adverse effects were the main parameters to evaluate the treatment results of SRS.

### Statistical analysis

Data were statistically described in terms of range, mean ± standard deviation (± SD), median, frequencies (number of cases) and percentages when appropriate. Comparison of treatment response between the study groups was done using Chi square ($\chi^2$) test. Exact test was used instead when the expected frequency is less than 5. Survival analysis was done for the different outcome measures using Kaplan Maier statistics calculating the mean and median survival time for each group with their 95% CI and the corresponding survival graphs. A probability value (*p* value) less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel 2007 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

### Results

Sixteen patients (9 males and 7 females) with radiologically proved cerebral AVMs were treated during the period between July 2000 and August 2006. The follow up period ranged from 25 to 104 months with a median follow up of 72 months. The median age of the patients was 24 years (range 14-60 years). Five patients (31.25%) had prior embolization (range 1-4 times). The mean interval between last embolization and SRS was 7.40 ± 5.17 months (range 3-13 months). The commonest initial manifestations were headache in 14 patients (87.50%) and disorientation in 10 patients (62.50%). Seizures and neurological deficit were encountered in 3 patients (18.75%) and 2 patients (12.50%), respectively. The most common AVM location was in the temporal lobes (5 patients) were. Radiologically, 4 patients (25%) had intracerebral hemorrhage which was minimal and did not require surgical intervention. **Table (1)**

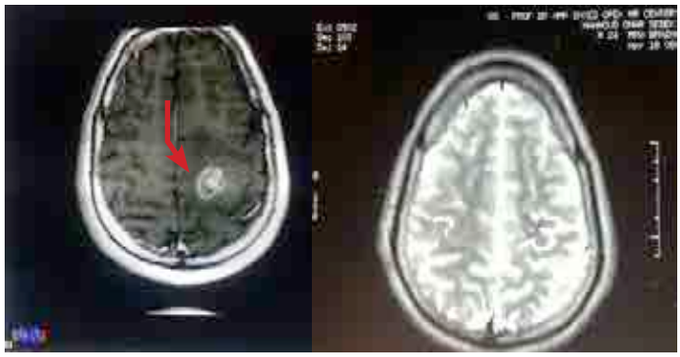
| Characteristics | Incidence (%) |
|---|---|
| **Age (years):** | |
| Median | 24 years |
| Range | 14 - 60 years |
| **Sex:** | |
| Male | 9 (56.25 ) |
| Female | 7 (43.75) |
| **Prior Embolization:** | |
| Yes | 5 (31.25) |
| No | 11(68.75) |
| **Performance Status:** | |
| 0 | 1 (6.25) |
| 1 | 11 (68.75) |
| 2 | 4 (25.0) |
| **Location:** | |
| Temporal | 5 (31.25) |
| Occipital | 4 (25.0) |
| Parietal | 4 (25.0) |
| Temporoparietal | 2 (12.50) |
| Frontal | 1 (6.25) |

The dose of SRS was 20 Gy in 12 patients (75%) and 15 Gy in 4 patients (25%). The mean target volume was 22.9 ± 1.15 mm³ (range 12.5-25 mm³). For most cases adequate target coverage was achieved and the mean value of coverage was 96% ± 2.5 isodose. The mean dose to the center of the AVM (maximum target dose) was 20.5 ± 0.7 Gy and the mean dose to the AVM margin (minimum target dose) was 12.1 ± 2.7 Gy. Twelve patients were planned using one isocenter and 4 patients using two isocenters but 5 noncoplanner arcs were selected to deliver the prescribed dose to each patient. Arc-splitting strategy was applied in two patients in order to spare the brain stem. The mean value for conformity index was 1.1 ± 0.2, while the mean value for homogeneity index was 1.8 ± 0.5. For organs at risk, the optic chiasma and optic nerves didn't receive any dose. In 4 patients, the brain stem and right eye had insignificant dose and the average value of the maximum dose was 1.6 ± 1.7 Gy and 0.4 ± 0.2 Gy, respectively.

Assessment of the clinical outcome revealed that 11 patients (68.75%) were improved and remained symptom free and 3 patients (18.75%) improved significantly (partial response) with occasional mild headache or disorientation. Two patients (12.50%) were deteriorated clinically (progression) with either progressive persistent headache and/or convulsions. During follow up, neuroradiological assessment by MRI and/or MRA showed that total obliteration of the cerebral AVMs was encountered in 10 patients (62.50%), subtotal or partial obliteration in 4 patients (25%) and minimal or no obliteration in 2 patients (12.50%). **Figure (3,4)** The mean duration between the date of SRS and total obliteration of the AVMs was 15.9 ± 11.24 months (range 9-47 months).

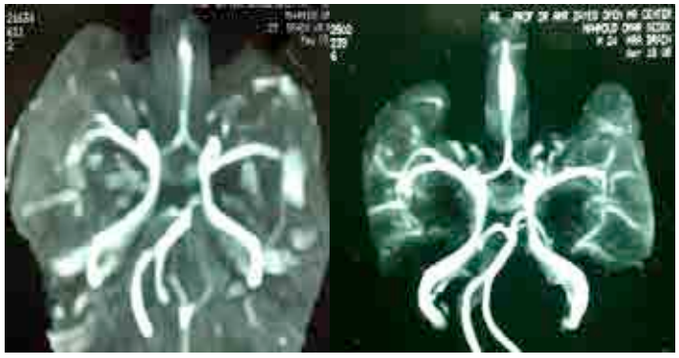
The 10 patients (5 males and 5 females) who had total obliteration were characterized by having prior endovascular embolization (in 4 patients), the dose of SRS was 20 Gy (in 7 patients), and the occipital region was the most common AVM location (in 4 patients). The two patients (1 female, 1 male) who deteriorated clinically and had minimal or no obliteration of their AVMs (6

months after SRS) were 23 and 28 years old, AVMs were located at the occipital and temporal lobes, and clinically presented with severe persistent headache and/or convulsions, respectively. They had no prior endovascular embolization and the dose radiation received was 20 Gy. They were managed by endovascular embolization which was repeated up to 3 times with significant improvement.



**A.** MRI at presentation from BrainLAB

**C.** MRI with total obliteration



**B.** MRA with partial obliteration

**D.** MRA with total obliteration

**Fig. 3: MRI & MRA of a left high parietal AVM with total obliteration 47 months after SRS Arterial supply from the M1 segment of RT. middle cerebral artery & draining into RT. Subependymal veins**

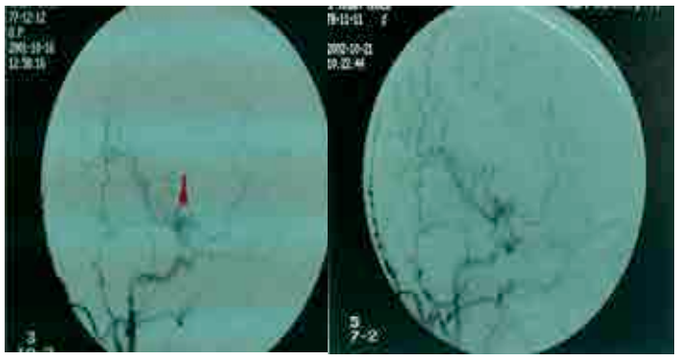


**Fig. 4: Cerebral angiography of a right parietal AVM with minimal obliteration one year after SRS**

Subgroup analysis revealed that none of the clinical characteristics or treatment parameters influenced significantly the response or obliteration rate. The progression-free survival (PFS) was 87.50 % and mean time to progression was 91.750 ± 8.103 months (95% CI, 75.869 - 107.631). **Figure (5)** No patient had any permanent radiation induced adverse effects or newly developed neurological deficits. Five patients (31.25%) experienced transient radiation induced brain edema which was resolved by oral corticosteroids. There was no significant correlation between adverse effects and radiation dose.

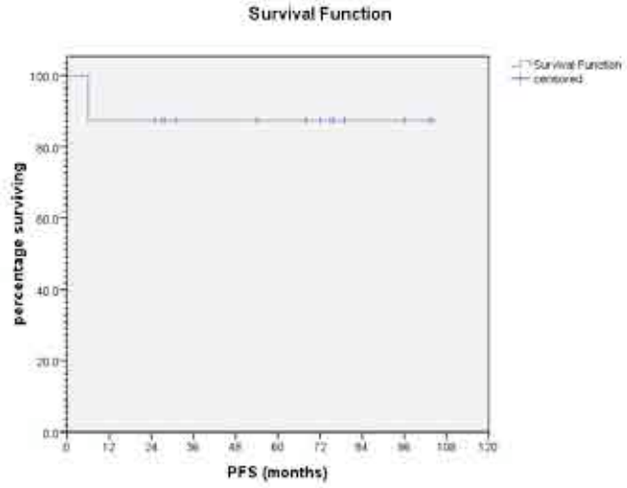



**Fig. 5: Progression-free survival after SRS**

## Discussion

Arteriovenous malformations of the brain, which are probably genetically determined, are errors in the development of the vasculature that, together with the effects of blood flow, may lead to a focal arteriovenous shunt. Clinically, in about half of the patients, the revealing event is an intracranial hemorrhage **(19).** Almost all patients with AVM are subjected to treatment, either by surgery, radiosurgery or embolisation, with the functional aim of reducing the risk of hemorrhage or to alleviate neurological symptoms with an acceptable treatment risk **(11).**

Management strategies obviously differ according to local preferences, but results presented in the literature suggest the following strategy: (**I**) cortically located AVMs with a nidus volume <10 ml could be operated, with or without presurgical embolization, unless there is a single feeder that can easily be catheterized and embolized; (**II**) centrally located AVMs with a nidus volume <10 ml should be treated by radiosurgery, unless suitable for embolisation as indicated above; (**III**) patients harboring AVMs with a nidus volume >10 ml could benefit from targeted partial embolisation followed by radiosurgery or surgery, depending on the angioarchitecture; and (**IV**) AVMs > 20 ml nidus volume usually have a high treatment risk with any treatment modality and are not obvious targets for treatment at all. (**20**)

The current study was designed to assess the outcome of SRS used to treat brain AVMs including its safety and adverse effects. The median age of the patients was 25.6 years (range 14-60 years) with 15 patients (93.75%) younger than 40 years old. Furthermore, 4 patients (25%) were ≤ 18 years old. This observation coincided with the natural history of intracranial AVMs which are occasionally seen in the elderly but are typically diagnosed before the patient has reached the age of 40 years. **(2)**

More than 50% of AVMs present with intracranial hemorrhage and available natural history studies indicated an overall risk of initial hemorrhage of 2-3% per year**. (21, 22)** Mortality from the first hemorrhage is between 10% and 30%,

and 10% to 20% of survivors have long-term disability**. (23, 24)** The lifetime risk of intracranial hemorrhage in a person with an AVM is approximated by the following formula: Lifetime risk (%) = 105 - the patient's age in years**. (25)** The next most common presentation is seizure (either focal or generalized), which occurs in 20- 25% of cases and may be an indicator of the location of the lesion. Other presentations include headaches in 15% of patients, focal neurological deficit in fewer than 5% of cases, and pulsatile tinnitus**. (1, 21)** Patients enrolled in the current study presented mainly with headache (14 patients), disorientation (10 patients), and seizures (3 patients). Fortunately, only 4 eligible patients (25%) had a radiological evidence of intracerebral hemorrhage which was minimal and did not require surgical intervention.

There is an agreement in several studies that the minimum target dose is the most significant factor for the obliteration rate of AVMs. **(26)** The risk for radiation injury, on the other hand, correlated both with doses and with irradiated volumes. **(27, 28)** Therefore, it is possible that the standard dose of 18–20 Gy could cause unacceptable complications if the volumes of AVMs are ignored, because radiation dose outside the prescribed target volume becomes significant in proportion to the treated volume. This could induce unacceptable symptomatic injury especially in central locations. **(29, 30)** The dose of SRS delivered was 20 Gy in 12 patients (75%) and 15 Gy in the other 4 patients (25%) who were younger than 18 years old. The mean dose to the center of the AVM (maximum target dose) was 20.5 ± 0.7 Gy and the mean dose to the AVM margin (minimum target dose) was 12.1 ± 2.7 Gy. No patient had any permanent radiation induced adverse effects or newly developed neurological deficits and there was no significant correlation between adverse effects and radiation dose.

As opposed to surgical resection or embolization, the vasoocclusive effect develops slowly after radiosurgery with the peak between 1 and 2 years after radiosurgery and cerebral AVMs shrink progressively. **(31, 32)** The risk of bleeding persists as long as complete obliteration is not obtained. **(33)** Complete obliteration can occur as early as 4 months or as late as 5 years after treatment and some remain patent. At most institutions, the final result used to be documented by conventional angiography 2 years after treatment. **(34)** Currently, there is an increasing tendency to defer definite labeling of incomplete obliteration until 3 years after treatment. **(35, 36)** In the current study, total obliteration of the cerebral AVMs was encountered in 10 patients (62.50%) after a mean duration of 15.9 ± 11.24 months (range 9-47 months) postradiosurgery. Subgroup analysis revealed that none of the clinical characteristics or treatment parameters influenced significantly the obliteration rate.

Radiosurgery can be considered in lesions thought to be at high risk from a surgical or endovascular standpoint. The overall efficacy of radiosurgery is higher for small lesions, and therefore, this modality may be considered as a primary treatment for smaller as opposed to larger lesions. However, size is not the only factor in the final determination of treatment. The exact location, patient age, symptoms, and angiographic anatomy must be considered in this decision process.

## Conclusion

Stereotactic radiosurgery is an effective and safe treatment modality for arteriovenous malformations of the brain with few complications. Candidates for treatment should be selected on the basis of AVM volume and location, and relative risk analysis compared with surgical and endovascular therapies.

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