Clinical Study

Stereotactic and Functional Neurosurgery

Stereotact Funct Neurosurg 2011;89:338–345
DOI: 10.1159/000330837

Received: February 24, 2011
Accepted after revision: July 12, 2011
Published online: October 14, 2011

Linac Stereotactic Radiosurgery for the Treatment of Small Arteriovenous Malformations: Lower Doses Can Be Equally Effective

G.L. Flores[a, b] K. Sallabanda[a, b] M.A. dos Santos[a, c] J. Gutiérrez[a, b]
J.C.B.P. Salcedo[a, b] C. Beltrán[a] C.P. Fernández[a, b] M.G. Atienza[a] J. Samblás[a, b]

[a]Radiotherapy Department, Instituto Madrileño de Oncologia/Grupo IMO, and [b]Neurosurgery Department, Sanatório San Francisco de Asis, Madrid, Spain; [c]Institut de Cancérologie Gustave Roussy, Paris, France

Key Words
Arteriovenous malformation · Stereotactic radiosurgery · Brain · Dose

Abstract
Objective: The purpose of this study was to examine the efficacy and toxicity of treating small arteriovenous malformations (AVMs) (≤3 cm in diameter) with a median marginal applied dose of 14 Gy. ***Methods:*** Two hundred and thirteen patients diagnosed with AVMs were treated between January 1991 and December 2005. Seventy-three percent of the patients had hemorrhaged prior to treatment, 13% had had previous surgery and 19.2% had had previous embolization. The median follow-up duration was 48.1 months. ***Results:*** The Kaplan-Meier analysis estimated that the 36-month obliteration rate was 65.5% for patients undergoing their first stereotactic radiosurgery (SRS) and 68.3% for those undergoing repeated SRS. The Kaplan-Meier analysis estimated the 60-month AVMs obliteration rate for the entire cohort to be 82.4%. The median time to AVM obliteration was 40 ± 2.8 months. We found a statistically significant relationship between the time of obliteration and the following factors: site of the AVMs (sites other than brainstem), a higher prescribed dose and a positive history of previous hemorrhage. Thirteen patients (7.6%) experienced toxicities. ***Conclusions:*** SRS was an effective and safe treatment for AVMs ≤3 cm in diameter, with acceptable toxicity.

Background

For patients with arteriovenous malformations (AVMs), rupture can lead to a neurological deficit and sometimes death. Several treatment options are available, including microsurgery, embolization and stereotactic radiosurgery (SRS). The main objective of SRS is complete obliteration of AVMs. The cure rate in patients with AVMs treated with SRS varies from 50 to 90%, in 3 to 5 years [1–15], and the most accepted incidence of complications varies from 2.4 to 9.4% [3–5, 8, 9, 16]. There are several factors associated with the efficacy of SRS, with the most cited being lower AVM volume, fewer draining veins, younger patient age, superficial lesion location and radiation dose up to 20 Gy [5, 8, 17–25].

The objective of this study was to evaluate the effectiveness of SRS in small AVMs (≤3 cm in diameter) not

KARGER
Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

1011–6125/11/0896–0338$38.00/0

Accessible online at:
www.karger.com/sfn

Marcos Antonio dos Santos, MD
94 Avenue Paul Vaillant Couturier
FR– 94110 Villejuif, Paris (France)
Tel. +33 06 48 31 43 92
E-Mail marcosrxt@gmail.com

amenable to a surgical approach. Because the target volume is known to have significant importance for cure rates, the present study was limited to small AVMs in order to study a relatively homogenous group of patients. A separate study on the treatment of larger AVMs is under way and will be reported soon. Additionally, we aimed to define the relationship between the closure of the AVMs and a series of factors and conditions that the analyses were divided into: (i) pre-treatment factors, which include previous embolization, history of hemorrhage, previous surgery, Spetzler-Martin grade, location and volume of the AVMs; (ii) factors associated with the treatment, which include the dose applied to the margin of the lesion; (iii) post-treatment factors, which include the presence of symptomatic perinidal high-signal-intensity changes (HSIC) on T2-weighted MRI scans associated with toxicity and hemorrhage occurrence.

Methods

This is a retrospective study, which gathered the experiences of the SRS Unit at the San Francisco de Asis Hospital (Madrid, Spain). It focuses on the treatment of AVMs of less then 3 cm in diameter. A total of 213 patients were treated between 1991 and 2005.

All patients were submitted to SRS after the exclusion of any viable surgical approach determined by the location (i.e. regions with difficult surgical access) or because of high functional eloquence. All cases were previously reviewed by the working team, which consisted of neurosurgeons, neuroradiologists and radiation oncologists. All patients had given their informed consent before receiving treatment, according to the protocol established in the SRS Unit. Table 1 describes the pre-treatment symptoms presented by the patients.

Table 1. Clinical characteristics of the patients

Clinical characteristics	n (%)
Previous hemorrhage	157 (73.7)
Headache	47 (22.1)
Neurological deficit	98 (46)
Seizure	30 (14)
Previous surgery	28 (13.1)
Previous embolization	41 (19.2)
Spetzler-Martin grade	
I	18 (8.4)
II	128 (60.1)
III	67 (31.4)
Localization	
Frontal	57 (26.8)
Temporal	36 (16.9)
Occipital	32 (15.0)
Cerebellum	24 (11.3)
Intraventricular	15 (7.0)
Subependymal	14 (6.6)
Brain stem	10 (4.7)
Basal ganglia	10 (4.7)
Thalamus	7 (3.7)
Corpus callosum	5 (2.3)
Parietal	3 (1.4)

Procedures and Treatment Selection

In all cases, SRS was performed with 6-MV linear accelerators with a high precision positioning system with mechanical fixation of the SRS 200 collimator (SRS-200 Radiosurgery System; Philips Medical Systems, Shelton, Conn., USA). To perform the procedure, magnetic resonance imaging (MRI) with a stereotactic localization system was performed on all patients. After attaching the Brown-Roberts-Wells stereotactic ring under local anesthesia, a computed axial tomography (CT) scan, with 1.5 mm slices, and a digital subtraction angiography (DSA) were performed. Both studies, with their own stereotactic system references, were transferred by a network to BrainSCAN 5.32 (Stereotactic Treatment planning Software System; BrainLAB AG, Feldkirchen, Germany). The target definition, the location of the isocenters and the dose planning were performed by a work group, which consisted of a neurosurgeon, a radiation oncologist and a specialized physicist. A dose of 14 Gy was prescribed, usually at the 90% isodose line, although the prescribed dose could vary depending on the eloquence of the treated area and its proximity to the organs at risk. After SRS, the patients were kept under observation in the hospital for 24 h.

Patient Follow-Up

All patients were followed with clinical and imaging evaluations at 6 months, at 1 year and each year thereafter. If there were complications associated with the procedure, the follow-up was changed accordingly. If obliteration of the AVMs was suspected following any test [CT, CT with angiography (Angio-CT), MRI or MRI with angiography (Angio-MR)], a DSA was performed to confirm the AVM obliteration. Using DSA, the AVMs were considered to have been obliterated and healed when all of the following criteria were met: normal cerebral angioarchitecture, complete absence of diseased vessels, absence of arteriovenous nidus and removal or normalization of the veins in the venous drainage areas [26]. For patients in whom the AVM closure was not demonstrated after a minimum follow-up period of 36 months, several options were considered, including irradiation as a second SRS procedure or continuing the observation for another period of time. The presence of new post-SRS hemorrhaging was not considered to be a complication of the procedure.

Toxicity related to SRS was defined as the presence of symptomatic perinidal HSIC on T2-weighted MRI or the appearance of new symptoms in the patients who did not show changes in the imaging, and was defined as transient, if they were present for a period no longer than 6 months.

Statistical Analysis

The SPSS statistics package, version 16.0 for Windows (SPSS Inc., Chicago, Ill., USA), was used to analyze the data. A descriptive analysis was performed for the categorical variables, and a central tendency was performed for the numerical ones. The assumptions of normality and homogeneity of variance were validated, and the appropriate test was selected for each case. The Kaplan-Meier curve was used to analyze the closure time when considering the performance of the SRS as the starting point and 36 months post-SRS as the analysis point. The log rank test was used for comparisons. Other tests, such as Student's t, χ^2 test and ANOVA, were used for the data analysis as appropriate. A probability value <0.05 was considered to be statistically significant.

Results

First SRS

The mean volume of the AVMs before the first SRS was 2.1 cm^3 (range: 1.6–7.8 cm^3). The mean dose to the margin of the AVMs was 14 Gy (range: 12–15 Gy). The median isodose curve was 90%. One isocenter was used for 76.5% the cases, 2 for 20.7% and 3 for 2.8% of the patients. Total covered volume was achieved in 208 (97.7%) of the treated patients, and partial coverage was achieved in 5 patients (2.3%). This partial coverage was secondary to the irregular shape of the malformed nidus and not to the AVM's volume. After SRS, 150 patients achieved obliteration of the AVM.

The cumulative probability of obliteration at 36 months was 65.5%. The mean obliteration time was 27.1 months. Four patients (1.9%) had hemorrhages after the first SRS (all 4 had a history of prior hemorrhages). The time between SRS and the hemorrhage varied from 1 to 87 months. Two of the patients underwent surgery to evacuate the hematoma, and both had a transient neurological deficit.

Second SRS

A second SRS was performed on 23 patients (10.8%). The mean time between the procedures was 49.5 months. The mean volume of the AVMs prior to the second SRS was 2.7 cm^3 (range: 1.6–8.0). The mean dose to the margin of the AVMs was 13.6 Gy (range: 8–14). The median isodose curve was 90%. One isocenter was used for 70% of the patients, 2 isocenters were used for 21.7%, and 3 were used for 8.7% patients. Total coverage of the target volume was achieved in 20 (86.9%) patients, and partial coverage was achieved in 3 (13.1%). Obliteration of the AVMs was observed in 16 cases. In 6 patients, no changes were seen, and they were classified as still open. The cumulative probability of obliteration at 36 months was 68.3%. The majority of these patients (78.2%) had a history of hemorrhage, but none of them hemorrhaged after the second SRS.

Table 2. Obliteration and localization of AVMs

AVMs	Obliteration, %
Frontal	77.2
Temporal	72.2
Occipital	90.6
Cerebellar	66.6
Intraventricular and subependymal	86.6
Brain stem	50
Basal ganglia	100
Thalamus	80
Corpus callosum	71
Parietal	100
Internal capsule	100

Efficacy after the First and Second SRS

The obliteration diagnosis was made in 87% of the patients, using DSA. Obliteration was demonstrated in 166 patients during the follow-up period, including the two SRS procedures. It was considered to have failed in 5 patients, and 42 patients were lost to follow-up. The cumulative probability of obliteration at 60 months was 82.4%. Those 5 patients were kept under surveillance. Surgery was deferred because of difficult accessibility and because of the functional eloquence of the region where the AVMs were located. Two were localized in the temporal lobes in the deep posterior region, one was in the frontal lobe in a motor area, another was in the brainstem in the bulbar region, and the last was located in the deep cerebellar hemisphere. This last patient had two hemorrhages after the first SRS and is currently in a chronic vegetative state. The closure, according to location, is shown in table 2. The mean closure time of the AVMs was 40.5 months (fig. 1). No deaths were registered in the follow-up period.

Pre-, Trans- and Post-Treatment Factors and Their Relationship with the Closure of the AVMs

We found a statistically significant relationship between the site of the lesion and the closure of the AVMs ($p = 0.004$). Those AVMs located in the brainstem had a longer mean and median closure time (86.63 vs. 67.44 months, respectively) when compared to the other ones. We also noted a correlation between a previous history of hemorrhage and earlier obliteration of the AVM ($p = 0.022$) (fig. 2). There were no statistically significant differences between the closure rate and (i) the Spetzler-Martin classification of the AVMs ($p = 0.170$), (ii) the vol-

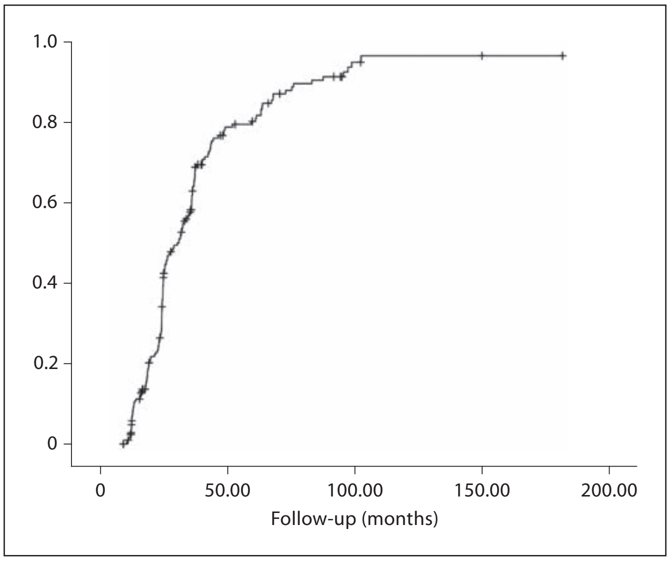

Fig. 1. Probability of AVMs' obliteration for the whole group.

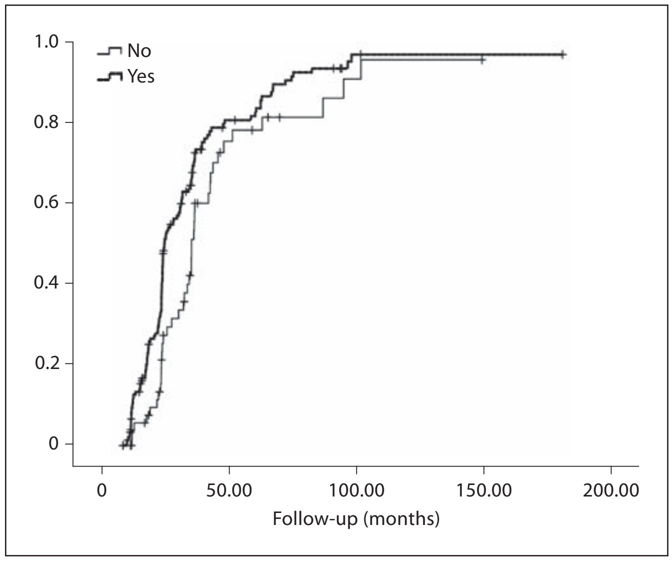

Fig. 2. Probability of AVMs' obliteration according to a previous hemorrhage history.

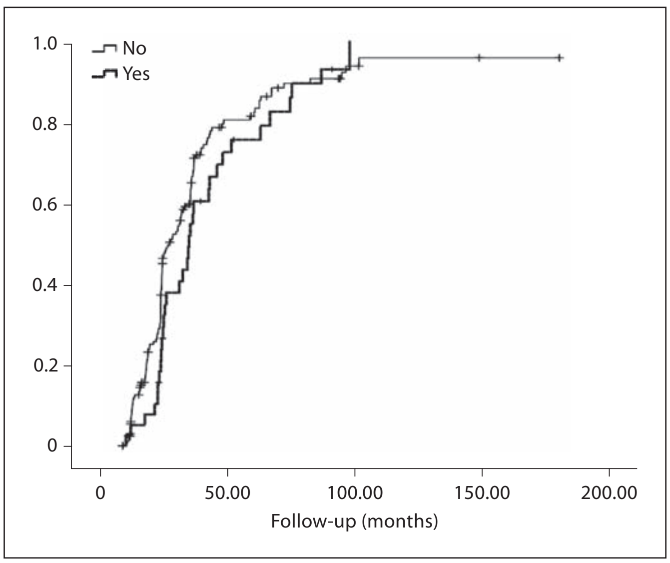

Fig. 3. Probability of AVMs' obliteration according to previous embolization.

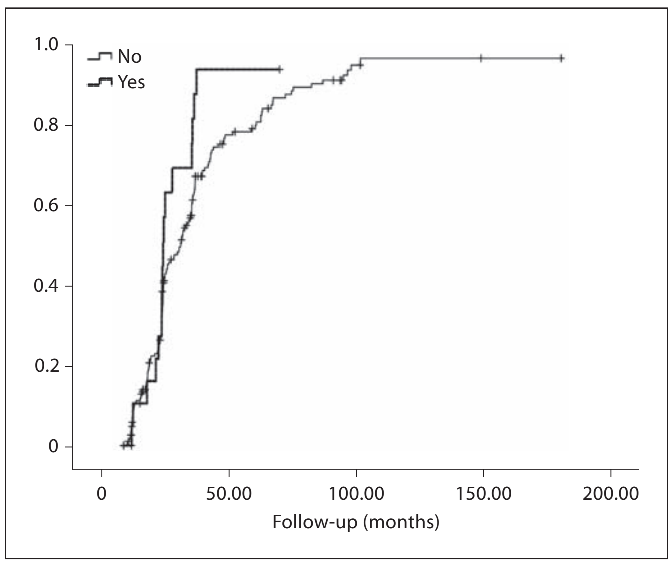

Fig. 4. Probability of AVMs' obliteration according to the presence of symptomatic perinidal HSIC on T2-weighted MRI.

ume range treated ($p = 0.713$), or (iii) the presence of previous embolization ($p = 0.258$) (fig. 3). We saw no statistically significant differences between the closure of the AVMs and the symptomatic perinidal HSIC on T2-weighted MRI ($p = 0.117$) (fig. 4).

Toxicity Associated with the Radiation

There were symptomatic perinidal HSIC on T2-weighted MRI in 11 patients (5.2%) after the first SRS and in 2 (8.7%) after the second SRS. New symptoms that were unrelated with re-bleeding appeared in all of these 13 patients, but all disappeared spontaneously.

Discussion

The major benefit of SRS is to provide an alternative to surgery when it has not been successful due to incomplete removal of the lesion or when the location of the lesion makes surgery impossible. SRS has been shown to be efficient at occluding malformed vessels and controlling related symptoms [7, 8, 15, 17, 21, 22, 27–39]. The variability in AVM size, among other factors, has a decisive influence on the obliteration rate reported in literature (54–92%) [1–6, 8–10, 12–14, 17, 24, 25, 27, 31–34]. We show here that lower doses of radiation obliterate small AVMs with an acceptable rate of complications.

In this series, the most frequent initial symptom was neurological deficit, followed by headaches (46 and 22%, respectively). These data are different from those reported by Steiner et al. [15], who classified hemorrhage as a symptom even when it was confirmed only by tests such as a CT scan or MRI. In this study, 73.7% of patients presented with hemorrhage before SRS, which may be associated with the fact that over 50% of our patients had AVMs in a deep location. The AVMs' cumulative probability of obliteration in five years was 82.47%, results that are similar to those reported by other series [8, 21, 22, 27–34, 40–42]. Complete AVMs occlusion was higher compared with that reported by Skjoth-Rasmussen et al. [42], who reported 78% occlusion in small AVMs of less than 10 cm in volume. Several factors could influence our higher occlusion rate, but the selection of AVM with a diameter of ≤3 cm is probably the main cause.

Factors Related to the Obliteration

Investigators have shown a variety of factors that are predictive of AVM obliteration after radiosurgery. In our study, we found a statistically significant relationship between the time for obliteration and the location of the AVM, the prescribed dose, and a history of previous hemorrhage. These findings are consistent with those reported in other series [4, 13, 16–18, 27, 36, 43–50]. Although the effect of the volume of the AVM did not reach statistical significance, there was a clear trend toward improved obliteration in AVMs with a lower volume. The fact that only small AVMs were admitted in this study clearly limited the interpretations of this result.

Regarding the applied dose, we are aware that a consistent improvement of the obliteration rates has been related to higher applied doses, and in our series, relatively low doses were used, as compared with those reported in the current literature (approximately 20 Gy) [5, 8, 16–17, 24–25]. However, this report includes a series of patients that started around 20 years ago, when such results are not as well established as they are today. Indeed, we found a dose-response relationship, and perhaps our results would be better if higher doses were applied. The obliteration rates presented here raise the hypothesis that lower doses can also be efficient for small AVMs, which can be useful in situations where the target is located near structures that may limit the prescribed dose, such as in the brainstem or the optic chiasm.

Prior hemorrhage has been confirmed as a positive predictor of eventual AVM obliteration by other studies [13, 20]. In this present series, more than half of the patients treated (73.7%) had previously hemorrhaged. Although the exact mechanism of radiation-induced luminal occlusion is still not known, it has been shown that both high-dose radiation [51] and hemorrhage [52] lead to the common activation of transforming growth factor-β, which results in fibroblast transformation and myoblast proliferation. Therefore, the inflammatory response that results from hemorrhage may potentiate the biological effect of radiation treatment.

We found an association between obliteration and prior embolization, but it was not statistically significant. Some authors have reported better results post-SRS in patients who were previously embolized [27, 29]. However, Flickinger et al. [18] have shown that previous embolization is more likely to lead to target miss during radiosurgery by rendering AVM lesions harder to visualize on MR imaging. Accumulating evidence indicates that embolization may reduce the rate of obliteration after radiosurgery, although as retrospective studies, these reports share similar shortcomings. Further studies are necessary to address the impact of embolization on radiosurgical outcomes, which could have important implications for its management [53–60].

Several authors have studied the risk of AVM hemorrhage post-SRS. Kasliwal et al. [61] concluded that prior hemorrhage does not affect the outcome after GKS, in terms of obliteration rate, latency to obliteration or the chances of hemorrhage during the latency period. In our series, the re-hemorrhage rate after SRS was 2.3%, which was somewhat lower than that reported by other centers [16, 18, 27, 54–56]. The annual hemorrhage risk was not determined, considering our low re-hemorrhage rate. Sun et al. [41] illustrated, in two cases, that AVM size is not necessarily predictive of hemorrhage risk and that hemorrhage may still occur after angiographic AVM obliteration. This phenomenon has also been observed in other studies that report an elevated risk of hemorrhage in incompletely obliterated lesions [32, 62, 63]. Although radiosurgery initiates a thickening process of the vascular wall, most authors consider that the risk of bleeding persists until complete occlusion of the malformed vessel. Where there is a venous stenosis, flow reduction can precipitate formation of a thrombus in the drainage vein, raising the pressure inside the *nidus*, thereby also raising the risk of bleeding.

Radiation-Induced Complications

Radiation-induced complications were defined as symptomatic perinidal HSIC on T2-weighted MRI scans. These changes have been reported in relation to gliosis or as a result of ischemia, resulting from arterial steal or after embolization [64]. White matter changes in the direct vicinity of the nidus may appear as a direct consequence of the radiation itself [65]. Vascular edema may arise because of changes in vascular permeability, which is a consequence of the direct action of radiation, and may weaken the blood-brain barrier with a consequent overflow of proteins that will trigger angiogenic edema [66]. Radiation-induced gliosis or demyelination have been reported to occur frequently after high-dose conventional fractionated radiotherapy. However, because of the steep dose gradient and the relatively low treatment dose, it is a very rare complication following SRS [67]. In an analysis of factors that would be useful for predicting complications after SRS, the 12-Gy volume was found to be correlated to its occurrence [5]. Van den Berg et al. [67] reviewed the MR images of 30 patients with T2 HSIC surrounding brain AVMs after the SRS and angiographic studies. They report that fourteen patients (47%) showed HSIC far beyond the 10-Gy isodose area. A single draining vein was present more often in patients with extensive T2 hyperintensity signal changes than in the other patients. Obliteration was achieved in 12 (88%) of the 14 patients with extensive signal intensity changes, as opposed to 8 (50%) of the 16 patients in the other group. They concluded that the HSIC observed in the MRI are most likely related to thrombosis of draining veins at the time of AVM obliteration and are occasionally the cause of neurological symptoms. The higher occlusion rate of brain AVMs under these circumstances was well demonstrated. In our series, the incidence of symptomatic perinidal HSIC on T2-weighted MRI scans associated with transitory deficit was 7.6%, which is similar to the rate reported by other authors [8, 16, 23, 24, 27–29, 68]. Increased toxicity was observed after a second treatment. This finding is also consistent with previous reports in the literature [8, 16, 23, 24, 27, 28, 31, 38, 69].

A larger AVM volume is associated with a higher probability of radiation complications, which has been shown by dose–volume calculations for the AVMs itself and for the surrounding cerebral tissue. In particular, the volume around the AVM's target exposed to 12 Gy or more carries an increased risk of radiological and clinical radiation damage [43, 70–72]. Our limited number of complications is probably related to small volumes treated and to the relatively low doses used.

Limitations of the Study

This study has the evident limitations of a uni-institutional retrospective series of cases collected over a large period of time. Multicenter data collection and collaboration studies are essential to acquire stronger evidence for or against the application of radiosurgery for AVM treatment. We recognize that any conclusion derived from our study must be limited to small AVMs (<3 cm), and we also point out the relatively low dose level used to treat those patients. We reaffirm that better results may be seen with higher doses, based on the results presented previously by other series, but, based on our data, lower doses can be safe and effective in situations when higher doses are difficult to deliver.

Conclusion

SRS with a median marginal applied dose of 14 Gy has offered complete obliteration of small AVMs in 82.4% of the patients, with optimal follow-up. Previous hemorrhage, location of the lesion and marginal dose were positive factors associated with obliteration. Hemorrhage after radiosurgery occurred in 2.4% of patients, whereas 7.6% experienced radiation-induced complications.

References

1 Aoki Y, Nakagawa K, Tago M, Terahara A, Kurita H, Sasaki Y: Clinical evaluation of gamma knife radiosurgery for intracranial arteriovenous malformation. Radiat Med 1996;14:265–268.

2 Betti OO, Munari C, Rosler R: Stereotactic radiosurgery with the linear accelerator: treatment of arteriovenous malformations. Neurosurgery 1989;24:311–321.

3 Coffey RJ, Nichols DA, Shaw EG: Stereotactic radiosurgical treatment of cerebral arteriovenous malformations. Gamma Unit Radiosurgery Study Group. Mayo Clin Proc 1995;70:214–222.

4 Colombo F, Pozza F, Chierego G, Francescon P, Casentini L, De Luca G: Linear accelerator radiosurgery of cerebral arteriovenous malformations: current status. Acta Neurochir Suppl 1994;62:5–9.
5 Friedman WA, Bova FJ, Bollampally S, Bradshaw P: Analysis of factors predictive of success or complications in arteriovenous malformation radiosurgery. Neurosurgery 2003; 52:296–308.
6 Gallina P, Merienne L, Meder JF, Schlienger M, Lefkopoulos D, Merland JJ: Failure in radiosurgery treatment of cerebral arteriovenous malformations. Neurosurgery 1998;42: 996–1004.
7 Karlsson B, Lindquist C, Steiner L: Prediction of obliteration after gamma knife surgery for cerebral arteriovenous malformations. Neurosurgery 1997;40:425–431.
8 Pollock BE, Gorman DA, Coffey RJ: Patient outcomes after arteriovenous malformation radiosurgical management: results based on a 5- to 14-year follow-up study. Neurosurgery 2003;52:1291–1297.
9 Yamamoto M, Jimbo M, Hara M, Saito I, Mori K: Gamma knife radiosurgery for arteriovenous malformations: long-term follow-up results focusing on complications occurring more than 5 years after irradiation. Neurosurgery 1996;38:906–914.
10 Young C, Summerfield R, Schwartz M, O'Brien P, Ramani R: Radiosurgery for arteriovenous malformations: the University of Toronto experience. Can J Neurol Sci 1997; 24:99–105.
11 Fleetwood IG, Steinberg GK: Arteriovenous malformations. Lancet 2002;359:863–873.
12 Lunsford LD, Kondziolka D, Flickinger JC, et al: Stereotactic radiosurgery for arteriovenous malformations of the brain. J Neurosurg 1991;75:512–524.
13 Shin M, Maruyama K, Kurita H, et al: Analysis of nidus obliteration rates after Gamma-knife surgery for arteriovenous malformations based on long-term follow-up data: the University of Tokyo experience. J Neurosurg 2004;101:18–24.
14 Steiner L, Linquist C: Radiosurgery in cerebral arteriovenous malformation; in Tasker RR (ed): Neurosurgery: State of the Art Reviews. Stereotactic Surgery. Philadelphia, Hanley and Belfus, 1987, pp 329–336.
15 Steiner L, Lindquist C, Adler JR, Torner JC, Alves W, Steiner M: Clinical outcome of radiosurgery for cerebral arteriovenous malformations. J Neurosurg 1992;77:1–8.
16 Flickinger JC, Kondziolka D, Lunsford LD, et al: A multi-institutional analysis of complication outcomes after arteriovenous malformation radiosurgery. Int J Radiat Oncol Biol Phys 1999;44:67–74.
17 Flickinger JC, Pollock BE, Kondziolka D, Lunsford LD: A dose-response analysis of arteriovenous malformation obliteration after radiosurgery. Int J Radiat Oncol Biol Phys 1996;36:873–879.
18 Flickinger JC, Kondziolka D, Maitz AH, Lunsford LD: An analysis of the dose-response for arteriovenous malformation radiosurgery and other factors affecting obliteration. Radiother Oncol 2002;63:347–354.
19 Hoh BL, Chapman PH, Loeffler JS, Carter BS, Ogilvy CS: Results of multimodality treatment for 141 patients with brain arteriovenous malformations and seizures: factors associated with seizure incidence and seizure outcomes. Neurosurgery 2002;51:303–309.
20 Liscak R, Vladyka V, Simonova G, et al: Arteriovenous malformations after Leksell Gamma-knife radiosurgery: rate of obliteration and complications. Neurosurgery 2007; 60:1005–1014.
21 Pollock BE: Stereotactic radiosurgery for arteriovenous malformations. Neurosurg Clin N Am 1999;10:281–290.
22 Soderman M, Rodesch G, Karlsson B, Lax I, Lasjaunias P: Gamma knife outcome models as a reference standard in the embolisation of cerebral ateriovenous malformations. Acta Neurochir 2001;143:801–810.
23 Voges J, Treuer H, Lehrke R, et al: Risk analysis of LINAC radiosurgery in patients with arteriovenous malformation (AVM). Acta Neurochir Suppl 1997;68:118–123.
24 Zabel A, Milker-Zabel S, Huber P, et al: Treatment outcome after linac-based radiosurgery in cerebral arteriovenous malformations: retrospective analysis of factors affecting obliteration. Radiother Oncol 2005;77: 105–110.
25 Pollock BE, Flickinger JC, Lunsford LD, Maitz A, Kondziolka D: Factors associated with successful arteriovenous malformation radiosurgery. Neurosurgery 1998;42:1239–1247.
26 Lindquist C, Steiner L: Stereotactic radiosurgical treatment of malformations of the brain; in Lunsford LD (ed): Modern Stereotactic Neurosurgery. Boston, Martinus Nighoff, 1986, pp 491–505.
27 Douglas JG, Goodkin R: Treatment of arteriovenous malformations using Gamma knife surgery: the experience at the University of Washington from 2000 to 2005. J Neurosurg 2008;109:51–56.
28 Flickinger JC, Kondziolka D, Pollock BE, Maitz AH, Lunsford LD: Complications from arteriovenous malformation radiosurgery: multivariate analysis and risk modeling. Int J Radiat Oncol Biol Phys 1997;38: 485–490.
29 Izawa M, Chernov M, Hayashi M, Iseki H, Hori T, Takakura K: Combined management of intracranial arteriovenous malformations with embolization and Gamma knife radiosurgery: comparative evaluation of the long-term results. Surg Neurol 2009;71:43–53.
30 Levegrun S, Hof H, Essig M: Radiation-induced changes of brain tissue after radiosurgery in patients with arteriovenous malformations: dose/volume-response relations. Strahlenther Onkol 2004;180:758–767.
31 Moreno-Jimenez S, Celis MA, Larraga-Gutierrez JM, de Jesus Suarez-Campos J, Garcia-Garduno A, Hernandez-Bojorquez M: Intracranial arteriovenous malformations treated with linear accelerator-based conformal radiosurgery: clinical outcome and prediction of obliteration. Surg Neurol 2007;67: 487–492.
32 Orio P, Stelzer KJ, Goodkin R, Douglas JG: Treatment of arteriovenous malformations with linear accelerator-based radiosurgery compared with gamma knife surgery. J Neurosurg 2006;105:58–63.
33 Schlienger M, Altan D, Lefkopoulos D, et al: Linac radiosurgery for cerebral arteriovenous malformations: results in 169 patients. Int J Radiat Oncol Biol Phys 2000;46:1135–1142.
34 Choe JG, Im YS, Kim JS, Hong SC, Shin HJ, Lee J: retrospective analysis on 76 cases of cerebral arteriovenous malformations treated by gamma knife radiosurgery. J Korean Neurosurg Soc 2008,43:265–269.
35 Izawa M, Hayashi M, Chernov M, et al: Long-term complications after gamma knife surgery for arteriovenous malformations. J Neurosurg (suppl) 2005;102:34–37.
36 Karlsson B, Lax I, Soderman M: Risk for hemorrhage during the 2-year latency period following gamma knife radiosurgery for arteriovenous malformations. Int J Radiat Oncol Biol Phys 2001;49:1045–1051.
37 Inoue HK, Ohye C: Hemorrhage risks and obliteration rates of arteriovenous malformations after gamma knife radiosurgery. J Neurosurg 2002;97:474–476.
38 Bollet MA, Anxionnat R, Buchheit I, et al: Efficacy and morbidity of arc-therapy radiosurgery for cerebral arteriovenous malformations: a comparison with the natural history. Int J Radiat Oncol Biol Phys 2004;58: 1353–1363.
39 Eisenschenk S, Gilmore RL, Friedman WA, Henchey RA: The effect of LINAC stereotactic radiosurgery on epilepsy associated with arteriovenous malformations. Stereotact Funct Neurosurg 1998;71:51–61.
40 Esteves SC, Nadalin W, Piske RL, Benabou S, Souza E, Oliveira AC: Radiosurgery with a linear accelerator in cerebral arteriovenous malformations. Rev Assoc Med Bras 2008; 54:167–172.
41 Sun DQ, Carson KA, Raza SM, et al: The radiosurgical treatment of arteriovenous malformations: obliteration, morbidities, and performance status. Int J Radiat Oncol Biol Phys, in press.
42 Skjoth-Rasmussen J, Roed H, Ohlhues L, Jespersen B, Juhler M: Complications following linear accelerator based stereotactic radiation for cerebral arteriovenous malformations. Int J Radiat Oncol Biol Phys 2010;77: 542–547.

43 Raffa SJ, Chi YY, Bova FJ, Friedman WA: Validation of the radiosurgery-based arteriovenous malformation score in a large linear accelerator radiosurgery experience. J Neurosurg 2009;111:832–839.
44 Han JH, Kim DG, Chung HT, et al: Clinical and neuroimaging outcome of cerebral arteriovenous malformations after Gamma knife surgery: analysis of the radiation injury rate depending on the arteriovenous malformation volume. J Neurosurg 2008;109:191–198.
45 Back AG, Vollmer D, Zeck O, et al: Retrospective analysis of unstaged and staged Gamma knife surgery with and without preceding embolization for the treatment of arteriovenous malformations. J Neurosurg 2008;109:57–64.
46 Fukuoka S, Takanashi M, Seo Y, et al: Radiosurgery for arteriovenous malformations with gamma-knife: a multivariate analysis of factors influencing the complete obliteration rate. J Clin Neuroscience 1998;5(suppl 1):68–71.
47 Chang JH, Chang JW, Park YG, Chung SS: Factors related to complete occlusion of arteriovenous malformations after gamma knife radiosurgery. J Neurosurg 2000;(suppl 3)96–101.
48 Maruyama K, Kondziolka D, Niranjan A, Flickinger JC, Lunsford LD: Stereotactic radiosurgery for brainstem arteriovenous malformations: factors affecting outcome. J Neurosurg 2004;100:407–413.
49 Chang SD, Steinberg GK: Arteriovenous malformations after radiosurgery. J Neurosurg 1998;89:170.
50 Starke RM, Komotar RJ, Hwang BY, et al: A comprehensive review of radiosurgery for cerebral arteriovenous malformations: Outcomes, predictive factors, and grading scales. Stereotact Funct Neurosurg 2008;86:191–199.
51 Major O, Szeifert T, Fazekas I, et al: Effect of a single high-dose gamma irradiation on cultured cells in human cerebral arteriovenous malformation. J Neurosurg 2002;97(suppl 5):459–463.
52 Carmichael ST, Vespa PM, Saver JL, et al: Genomic profiles of damage and protection in human intracerebral hemorrhage. J Cereb Blood Flow Metab 2008;28:1860–1875.
53 Andrade-Souza YM, Ramani M, Scora D, et al: Embolization before radiosurgery reduces the obliteration rate of arteriovenous malformations. Neurosurgery 2007;60:443–451.
54 Nataf F, Ghossoub M, Schlienger M, Moussa R, Meder JF, Roux FX: Bleeding after radiosurgery for cerebral arteriovenous malformations. Neurosurgery 2004;55:298–305.
55 Pollock BE, Flickinger JC, Lunsford LD, Bissonette DJ, Kondziolka D: Factors that predict the bleeding risk of cerebral arteriovenous malformations. Stroke 1996;27:1–6.
56 Friedman WA, Blatt DL, Bova FJ, et al: The risk of hemorrhage after radiosurgery for arteriovenous malformations. J Neurosurg 1996;84:912–919.
57 Pollock BE, Lunsford LD, Kondziolka D, et al: Patient outcomes after stereotactic radiosurgery for ‘operable’ arteriovenous malformations. Neurosurgery 1994;35:1–8.
58 Lax I, Karlsson B: Prediction of complications in gamma knife radiosurgery of arteriovenous malformation. Acta Oncol 1996; 35:49–55.
59 Kwon Y, Jeon SR, Kim JH, et al: Analysis of the causes of treatment failure in Gamma knife radiosurgery for intracranial arteriovenous malformations. J Neurosurg 2000;(3 suppl)104–106.
60 Ondra SL, Troupp H, George ED, Schwab K: The natural history of symptomatic arteriovenous malformations of the brain: a 24-year follow-up assessment. J Neurosurg 1990;73: 387–391.
61 Kasliwal MK, Kale SS, Gupta A, et al: Does hemorrhagic presentation in cerebral arteriovenous malformations affect obliteration rate after gamma knife radiosurgery? Clin Neurol Neurosurg 2008;110:804–809.
62 Lindqvist M, Karlsson B, Guo WY, et al: Angiographic longterm follow-up data for arteriovenous malformations previously proven to be obliterated after gamma knife radiosurgery. Neurosurgery 2000;46:803–810.
63 Shin M, Kawamoto S, Kurita H, et al: Retrospective analysis of a 10-year experience of stereotactic radiosurgery for arteriovenous malformations in children and adolescents. J Neurosurg 2002;97:779–784.
64 Valavanis A, Schubiger O, Wichmann W: Classification of brain arteriovenous malformation nidus by magnetic resonance imaging. Acta Radiol Suppl 1986;369:86–89.
65 Yamamoto M, Hara M, Ide M, Ono Y, Jimbo M, Saito I: Radiation-related adverse effects observed on neuro-imaging several years after radiosurgery for cerebral arteriovenous malformations. Surg Neurol 1998;49:385–397.
66 Flickinger JC, Lunsford LD, Kondziolka D, et al: Radiosurgery and brain tolerance: an analysis of neurodiagnostic imaging changes after gamma knife radiosurgery for arteriovenous malformations. Int J Radiat Oncol Biol Phys 1992;23:19–26.
67 Van den Berg R, Buis DR, Lagerwaard FJ, Lycklama A, Nijeholt GJ, Vandertop WP: Extensive white matter changes after stereotactic radiosurgery for brain arteriovenous malformations: a prognostic sign for obliteration? Neurosurgery 2008;63:1064–1070.
68 Zabel-du Bois A, Milker-Zabel S, Huber P, Schiegel W, Debus J: Stereotactic linac-based radiosurgery in the treatment of cerebral arteriovenous malformations located deep, involving corpus callosum, motor cortex, or brainstem. Int J Radiat Oncol Biol Phys 2006; 64:1044–1048.
69 Touboul E, Al Halabi A, Buffat L, et al: Single-fraction stereotactic radiotherapy: a dose-response analysis of arteriovenous malformation obliteration. Int J Radiat Oncol Biol Phys 1998;41:855–861.
70 Levegrun S, Hof H, Essig M, et al: Radiation-induced changes of brain tissue after radiosurgery in patients with arteriovenous malformations: correlation with dose distribution parameters. Int J Radiat Oncol Biol Phys 2004;59:796–808.
71 Kiran NA, Kale SS, Kasliwal MK, et al: Gamma knife radiosurgery for arteriovenous malformations of basal ganglia, thalamus and brainstem – a retrospective study comparing the results with that for AVMs at other intracranial locations. Acta Neurochir 2009;151:1575–1582.
72 Ganz JC, Reda WA, Abdelkarim K: Adverse radiation effects after Gamma knife surgery in relation to dose and volume. Acta Neurochir 2009;151:9–19.