Hypofractionated stereotactic radiotherapy for large arteriovenous malformations

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Abstract

Cerebral arteriovenous malformations (AVMs) are abnormal connections between the arteries and veins, with possible serious consequences of intracranial hemorrhage. The curative treatment for AVMs includes microsurgery and radiosurgery, sometimes with embolization as an adjunct. However, controversies exist with the treatment options available for large to giant AVMs. Hypofractionated stereotactic radiotherapy (HSRT) is one treatment option for such difficult lesions. We aim to review recent literature, looking at the treatment outcome of HSRT in terms of AVM obliteration rate and complications. The rate of AVM obliteration utilizing HSRT as a primary treatment was comparable with that of stereotactic radiosurgery (SRS). For those not totally obliterated, HSRT makes them smaller and turns some lesions manageable by single-dose SRS or microsurgery. Higher doses per fraction seemed to exhibit better response. However, patients receiving higher total dose may be at risk for higher rates of complications. Fractionated regimens of 7 Gy x 4 and 6–6.5 Gy x 5 may be accepted compromises between obliteration and complication. Embolization may not be beneficial prior to HSRT in terms of obliteration rate or the volume reduction. Future work should aim on a prospectively designed study for larger patient groups and long-term follow-up results.

Key Words: Arteriovenous malformation, hypofractionated stereotactic radiotherapy, radiosurgery

INTRODUCTION

Cerebral arteriovenous malformations (AVMs) are congenital lesions in which abnormal collections of blood vessels composed of dilated arteries and draining veins with dysplastic vessels are present without interposed capillary beds and intervening neural parenchyma. The annual incidence is estimated at 1 person per 100,0006,17 and prevalence at 18 per 100,000 population.1,2 Hemorrhage rate is usually quoted to be 2–4% per year with a cumulative risk when left untreated.5,10 The curative treatment for AVMs includes microsurgery and radiosurgery, sometimes with embolization as an adjunct. The successful treatment of large AVMs remains a challenging task. No single treatment for large or giant AVMs can provide satisfactory results. Many of them were previously considered inoperable, especially those classified as Spetzler–Martin Grade IV or V.30,31 Although
the optimal management is still controversial,15,18 many clinicians now accept treatment of properly selected patients with large inoperable AVMs. However, treatment could lead to high mortality and morbidity. Experiences from a high-capacity medical center reported complete cure in only 36% of patients while adopting multimodality treatment for giant AVMs, at the cost of 15% mortality and another 15% long-term morbidity.17

Single-fraction stereotactic radiosurgery (SRS) has been proven effective in treating small AVMs, with complete obliteration rates of 72–96%.18 Dose–volume relationship is unfavorable for large AVMs and the effective dosage might result in unacceptably high complication rates.11,13,27 However, volume reduction was found even in AVMs that failed to completely obliterate,19 making low-dose SRS with repeated treatments a viable option. Alternatively, large inoperable AVMs may be treated with radiosurgical techniques in dose or volume fractionation schemes to avoid damage to the surrounding tissue.18

Since the earliest attempt, fractionated stereotactic radiotherapy has been used in the treatment of large AVMs for over 20 years.22,24 The obliteration rate was low after fractionated radiotherapy with a dose per fraction of 2–4 Gy to a total dose of up to 50 Gy and such treatment may cause significant side effects.21 Therefore, the use of fractionated radiotherapy with lower doses per fraction cannot be recommended.

In contrast, fractionated stereotactic radiosurgery, also known as hypofractionated stereotactic radiotherapy (HSRT), usually involves delivering higher fraction dose to the target for up to 5 or 6 fractions. It can now be readily delivered by commercially available devices such as CyberKnife (Accuray Inc., Sunnyvale, CA, USA) and Novalis/Tx (BrainLAB AG, Feldkirchen, Germany; and Varian Medical Systems, Palo Alto, CA, USA). The objective of this article is to review recent literature for the treatment outcome of HSRT in terms of AVM obliteration rate and complication.

INDICATION AND PATIENT SELECTION

Unlike intracranial aneurysms, there is still no consensus in the definition of large or giant AVMs. The most widely accepted surgical grading system of AVM is the Spetzler–Martin classification,10 where the size of the AVM is determined by the maximum diameter as small (<3 cm), medium (3–6 cm), or large (>6 cm). The last category was also known as “giant AVM” by some authors.7,42

Unfortunately, this grading scale does not seem to correlate with successful AVM radiosurgery because it is insensitive to important factors such as AVM volume. Pollock and Flickinger proposed a radiosurgery-based scoring system,28 which is calculated by AVM volume, patient age, and AVM location. Because they used a continuous scale, there was no specified threshold for AVM volumes. Since a ball of 3 cm in diameter has an approximate volume of 14 mL, it is not uncommon to see 14 mL as a threshold for large AVMs in radiosurgical literatures.26,35,39 However, there were many other definitions for large, extra-large, or giant AVMs.1,4,9,27,37,41

The major indication for HSRT, just like other alternative radiosurgical techniques, is large inoperable AVMs. As there is no consensus in definition, large AVMs refer to those too large to be effectively and safely treated with single-fraction SRS in this article. The term inoperable is also disputable. However, most authors preferred not to operate on AVMs of Spetzler–Martin Grade IIIB, IV, and V.31

Not all patients with large inoperable AVMs require aggressive treatment, including HSRT. On the contrary, treatment is not recommended for such patients with minimal or only mild symptoms. Accepted indications for treatment include repeated hemorrhage, progressive neurological deficits, intractable seizures, and other severe symptoms.17

TREATMENT DELIVERY

Radiobiologically, the linear-quadratic formulation is a model describing the cell survival curve. The α/β ratio is the dose where cell killing due to the linear and quadratic components are equal. Typically, the target cells for the obliteration of AVMs have a small α/β ratio in the dose–response curve, like late-responding normal tissues, so that fractionation is unfavorable for the obliteration of an AVM nidus. The real α/β ratios of AVMs, normal vessels, and normal neural structures are in fact not well known. Qi et al. reviewed HSRT literature and reported the α/β ratio of 2.2 ± 1.6 Gy.29 While using the derived α/β ratio of 2.2 Gy, they proposed the fractionated regimens of 7.0 Gy × 4, 5.6 Gy × 6, 4.7 Gy × 8, and 4.2 Gy × 10.29 The benefit of fractionation depends on the relative relationship between the AVM and the late-responding normal tissue in the irradiated area. As long as the α/β ratio for AVMs is larger than the surrounding brain tissue, fractionation schemes should, in principle, have therapeutic advantages over single-dose schemes.4,29

Generally, the fraction doses in the literature were within 4–7 Gy per fraction. Four to six fractions were delivered daily or every other day, making the whole course up to 2 weeks. The total doses usually ranged from 28 to 42 Gy. Some authors determined the dose according to the AVM volume and location, while others adjusted the dosage as the experience accumulated.25,35 Since the AVM is a benign vascular lesion with a sharp border, the gross target volume (GTV) should be equal to the clinical target volume (CTV), i.e., the AVM nidus. However, dependent of the irradiation techniques, a margin of up...
to 5 mm might be added to generate the planning target volume (PTV). [32]

Because the technical advancement in radiation delivery is very fast, we believe that, at the time being, most HSRT for AVMs are delivered by CyberKnife or Novalis/Tx systems. However, older techniques were utilized in most available literature. Newer techniques, such as RapidArc (Varian Medical Systems), are also being applied, but only short-term outcome is available.[32]

Due to limited availability, as well as radiophysical and radiobiological differences, proton and heavy-particle treatments were excluded from our review.

**OBLITERATION RATE**

Single-fraction SRS has proved to be an effective method, especially in smaller AVMs. Several studies demonstrated both non-obliteration and complication rates rise when AVMs exceed 10 mL in size, with only a 32% obliteration rate after receiving single-dose SRS in one study of Gamma knife radiosurgery.[27] The two-year obliteration rate of AVMs larger than 4 mL is reported to be 40–58% in comparison to smaller AVMs, for which the obliteration rate is reported to be 85–100%.[14,24]

Comparison of the effects between SRS and HSRT showed no inferiority of AVM obliteration rate in the HSRT group. Aoyama and Chang used HSRT for patients with larger AVMs or AVMs at the eloquent area; even though the crude obliteration rate seemed lower in the HSRT group, statistical analysis did not reveal significant difference [Table 1]. The effectiveness of HSRT may be underestimated by the selection bias.[43]

Regardless of the total irradiation dose given, there seems to be a minimal dose per fraction required to obtain the desired high obliteration rates. A 7.2-fold greater obliteration rate of 7-Gy over 5-Gy cohorts was reported by Veznedaroglu et al.,[35] and other studies also reported obliteration rate of 50–83% for doses of 7 Gy versus 8–22% for doses less than 7 Gy.[14,23] The difference between the 7-Gy and ≥7-Gy groups was not statistically significant.[18] For lower doses tested, Xiao et al. reported that 6-Gy group showed better response rate than 5-Gy group.[37]

A pooled analysis of previous reports has shown the HSRT of 7-Gy fraction to be superior with a AVM obliteration rate of 65% compared to 38.5% of single treatment, 25% of volume fractionation, and 58% of salvage treatment.[18]

For smaller AVMs, several studies have suggested that embolization is a negative predictor of obliteration.[16,25,40] However, reduction of size by embolization increased the obliteration rate in large AVMs as reported by Veznedaroglu et al.[15] The benefit was not observed by another report.[37] The tendency of suboptimal response of embolized AVMs might be caused by more difficult target definition and subsequent volumetry due to image artifacts caused by embolization materials. It is also possible that AVMs undergoing embolization are simply more complicated AVMs accompanied by fistulae and aneurysms, making them worse responders.

In general, the use of routine pre-HSRT embolization is questionable due to the lack of solid evidence of benefit in different studies. Embolization may be reserved for AVMs associated with aneurysms or large arteriovenous fistulae.

**COMPLICATIONS**

Eliminating the risk of hemorrhage in patients with AVMs through obliteration is the primary goal of therapy. Latency period between irradiation and eventual obliteration is cited as the chief disadvantage when compared to microsurgery. There was a decrease in the incidence of hemorrhage as compared to the natural course according to one report.[20] However, several confounding variables in the literature make it difficult to determine the real hemorrhage rate following irradiation, especially when patients presented with rupture prior to the treatment, or received embolization, surgery, previous radiosurgery while entering the studies. Several of the reports also failed to report the risk of bleeding in person-year expression, making it difficult to compare the differences across the studies. Comparing the annual bleeding risk of AVMs after HSRT and SRS, the reported figure of 3–9% in the HSRT group seems slightly higher than most SRS series. However, the comparison might be an invalid one because HSRT is usually reserved for larger AVMs or AVMs in the eloquent area in these studies.[25,37]

Radiation-related adverse effects also constituted another category of commonly seen complications after HSRT. Transient symptoms are usually associated with increased signal change on T2-weight magnetic resonance image, while radiation necrosis or cyst formation may also develop.[12,33,36] HSRT does not cause increased incidence of T2 signal change, which typically produces clinically silent or mild symptoms, and is usually transient.[4] Radiation necrosis, in contrast, is the most serious type of late radiation change. The rates of radiation necrosis in patients treated with radiosurgery are usually quoted to range from 3 to 7%.[12,25,31] A high total dose of HSRT does not seem to correlate well with obliteration, but may be more responsible for a higher rate of complications. Veznedaroglu et al. reported relatively high adverse effects (86% radiographic, 28% symptomatic) with 7-Gy fraction for a total dose of 42 Gy. Among these were one patient with venous infarction outside the 10% isodose prescription line, which developed 10 months after receiving HSRT, and the patient subsequently remained vegetative.[35] Other studies in which 28–35 Gy was used
have reported low rates of radiological changes and mild symptoms despite the same per fraction doses.\cite{4,8,23}

**STAGED TREATMENT**

While other reports compared the effects of HSRT with SRS for large AVMs, Xiao et al. viewed HSRT as a first stage of the multimodality treatment for large inoperable AVMs.\cite{37} They followed Wowra et al.,\cite{36} analyzing the obliteration dynamics of AVMs after irradiation. The time-dependent regression of transnodal flow after irradiation, or obliteration dynamics, is a determinant of the latency period. Xiao et al. also measured the volume changes and fit the numbers into the exponential decay model.\cite{37} After HSRT, large inoperable AVMs decreased 44% in volume annually. Therefore, HSRT turns some of these AVMs into manageable lesions, which could then be treated by single-dose SRS or microsurgery.\cite{37} Although this approach seems to be reasonable for really large lesion, it apparently prolongs the latency period and additional bleeding during this period can be expected.

**CONCLUSION**

The rate of AVM obliteration utilizing HSRT as a primary treatment was comparable with that of SRS. For

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**Table 1: Studies of hypofractionated stereotactic radiotherapy series**

| Study            | No.    | Size/volume              | Total dose/fractions | Prior treatment | Follow-up time | Obliteration rate | Complication |
|------------------|--------|--------------------------|----------------------|-----------------|----------------|------------------|--------------|
| Aoyama, 2001[4]  | HSRT: 26 | Eloquent area or >2.5 cm, mean: 2.26 cm | 24–28.8 Gy/4 (mean: 26.8 Gy) | Embolization: 11% Surgery: 9% | >1 year (mean: 35.4 months) | At 3 years: 53% | Hemorrhage: 12% Radiation necrosis: 0% |
| SRS: 27 | Non-eloquent area or <2.5 cm, mean: 1.78 cm | 12–20 Gy (mean: 18.5 Gy) | >1 year (mean: 34.6 months) | At 3 years: 71% | Hemorrhage: 7% Radiation necrosis: 8% |
| Lindvall, 2003[23] | HSRT: 29 | Mean: 11.5 mL (median: 32.6 Gy) | 30–35 Gy/5 (mean: 19.3 Gy) | Embolization: 17% Surgery: 38% | 8 years (mean: 38 months) | At 2 years: 56% (4–10 mL) 50% (>10 mL) At 5 years: 81% (4–10 mL) 70% (>10 mL) | Hemorrhage: 7% Epilepsy: 7% Radiation necrosis: 7% |
| Veznedaroglu, 2004[35] | Mean: 23.8 mL (6 patients) | 42 Gy/6 | Embolization: 86% | >5 years (mean: 102 months) | 83% (at mean latency 108 ± 52 weeks) | 14% (86% with radiographic change) | 8.7% (30% with radiographic change) |
| Mean: 14.5 mL (18 patients) | 50 Gy/6 | Embolization: 57% | >5 years (mean: 82 months) | 22% (at mean latency 192 weeks) | Hemorrhage: 22% 5 years Radiation necrosis: 3% |
| Chang*, 2004[8] | HSRT: 33 | Eloquent area or >2.5 cm | 20–28 Gy/4 (mean: 25.9 Gy) | Embolization: 10% Surgery: 15% | Mean: 52 months | At 3 years: 32% At 5 years: 61% At 6 years: 71% | Hemorrhage: 8%/5 years Radiation necrosis: 10% Epilepsy: 2% |
| SRS: 42 | Non-eloquent area or <2.5 cm | 12–20 Gy (mean: 19.3 Gy) | Embolization: 10% Surgery: 15% | Mean: 52 months | At 3 years: 52% At 5 years: 81% At 6 years: 81% | Hemorrhage: 20% Radiation necrosis: 0% |
| Zabel-du Bois, 2006[41] | HSRT: 15 | > 4 cm Median: 27 mL | 20–32.5 Gy/4–5 (median: 26 Gy) | Embolization: 27% Surgery: 0% | Median: 2.6 years | At 3 years: 17% At 4 years: 33% | Hemorrhage: 21% Radiation necrosis: 0% |
| SRS: 33 | Median: 7 mL | 15–19 Gy (median: 17 Gy) | Embolization: 24% Surgery: 3% | At 3 years: 47% At 4 years: 60% | 0% Hemorrhage: 4% Ischemic stroke: 5% |
| Xiao, 2010[17] | HSRT: 20 | >5 cm, median: 46.84 mL | 25–30 Gy/5–6 (median: 30 Gy) | Embolization: 50% | Median post-treatment volume: 13.51 mL | Increase seizure: 5% Hemorrhage: 2.06%/year |

\*Continuum of the Aoyama et al. study, HSRT: Hypofractionated stereotactic radiotherapy
those not totally obliterated. HSRT makes them smaller and turns some lesions manageable by single-dose SRS or microsurgery. Higher doses per fraction seemed to exhibit better response. However, patients receiving higher total dose may be risked for higher rate of complication. Fractionated regimens of 7 Gy × 4 and 6–6.5 Gy × 5 may be accepted compromises between obliteration and complication. Prior embolization may not be beneficial prior to HSRT in terms of obliteration rate or the volume reduction. Future work should focus on a prospectively designed study, for larger patient groups and long-term follow-up results.[16]

REFERENCES

1. Al-Shahi R, Bhattacharyya JJ, Currie DG, Papantastsiou V, Ritchie V, Roberts RC, et al. Prospective, population-based detection of intracranial vascular malformations in adults: The Scottish Intracranial Vascular Malformation Study (SIVMS). Stroke 2003;34:1163-9.
2. Al-Shahi R, Warlow CA. A systematic review of the frequency and prognosis of arteriovenous malformations of the brain in adults. Brain 2001;124:1900-26.
3. Amapolski K, Ellis TL, Chan MD, Bourland JD, Glazier SS, McMullen KP, et al. Staged gamma knife radiosurgery for large cerebral arteriovenous malformations. Stereotact Funct Neurosurg 2011;89:365-71.
4. Aoyama H, Shirato H, Nishioka T, Kagie K, Onimaru R, Suzuki K, et al. Treatment outcome of single or hypofractionated single-isocentric stereotactic irradiation (STI) using a linear accelerator for intracranial arteriovenous malformation. Radiat Oncol 2001;59:323-8.
5. Brown RD Jr; Wiebers DO, Forbes G, O'Fallon WM, Pegras DG, Marsh WR, et al. The natural history of unruptured intracranial arteriovenous malformations. J Neurosurg 1988;68:352-7.
6. Brown RD Jr; Wiebers DO, Torner JC, O'Fallon WM. Frequency of intracranial hemorrhage as a presenting symptom and subtype analysis: A population-based study of intracranial vascular malformations in Olmsted County, Minnesota. J Neurosurg 1996;85:29-32.
7. Chang SD, Marcellus ML, Marks MP, Levy RP, Do HM, Steinberg GK. Multimodality treatment of giant intracranial arteriovenous malformations. Neurosurgery 2003;S3:1-11; discussion 11-3.
8. Chang TC, Shirato H, Aoyama H, Ushikoshi S, Kato N, Kuroda S, et al. Stereotactic irradiation for intracranial arteriovenous malformation using stereotactic radiosurgery or hypofractionated stereotactic radiotherapy. Int J Radiat Oncol Biol Phys 2004;60:861-70.
9. Chung WY, Shiu CY, Wu HM, Liu KD, Guo WY, Wang LW, et al. Staged radiosurgery for extra-large cerebral arteriovenous malformations: method, implementation, and results. J Neurosurg 2008;109 Suppl:S65-72.
10. Crawford PM, West CR, Chadwick DW, Shaw MD. Arteriovenous malformations of the brain: Natural history in unoperated patients. J Neurol Neurosurg Psychiatry 1986;49:1-10.
11. Flickinger JC, Kondziolka D, Maizt AH, Lunsford LD. An analysis of the dose-response for arteriovenous malformation radiosurgery and other factors affecting obliteration. Radiat Oncol 2002;63:347-54.
12. Flickinger JC, Kondziolka D, Pollock BE, Maizt AH, Lunsford LD. Complications from arteriovenous malformation radiosurgery: Multivariate analysis and risk modeling. Int J Radiat Oncol Biol Phys 1997;38:845-90.
13. Flickinger JC, Kondziolka D, Lunsford LD. A dose-response analysis of arteriovenous malformation obliteration after radiosurgery. Int J Radiat Oncol Biol Phys 1996;36:873-9.
14. Friedman WA, Bova FJ, Mendenhall WM. Linear accelerator radiosurgery for arteriovenous malformations: The relationship of size to outcome. J Neurosurg 1995;82:180-9.
15. Han PP, Ponce FA, Spetzler RF. Intention-to-treat analysis of Spetzler-Martin grades IV and V arteriovenous malformations: Natural history and treatment paradigm. J Neurosurg 2003;98:3-7.
16. Jayaraman MV, Marcellus ML, Do HM, Chang SD, Rosenberg JK, Steinberg GK, et al. Hemorrhage rate in patients with Spetzler-Martin grades IV and V arteriovenous malformations: Is treatment justified? Stroke 2007;38:325-9.
17. Jessurun GA, Kamphuis DJ, van der Zande FH, Nossent JC. Cerebral arteriovenous malformations in The Netherlands Antilles. High prevalence of hereditary hemorrhagic telangiectasia-related single and multiple cerebral arteriovenous malformations. Clin Neurol Neurosurg 1993;95:193-8.
18. Jones J, Jang S, Gretch CC, Kepka AG, Marymont MH. Advances in the radiosurgical treatment of large inoperable arteriovenous malformations. Neurosurg Focus 2007;23:E7.
19. Karlsson B, Kihlstrom L, Lindquist C, Steiner L. Gamma knife surgery for previously irradiated arteriovenous malformations. Neurosurgery 1998;42:1-5; discussion 5-6.
20. Karlsson B, Lindquist C, Steiner L. Effect of Gamma Knife surgery on the risk of rupture prior to AVM obliteration. Minim Invasive Neurosurgery 1996;39:21-7.
21. Karlsson B, Lindquist M, Blomgren H, Wan-Yeo G, Soderman M, Lax I, et al. Long-term results after fractionated radiation therapy for large brain arteriovenous malformations. Neurosurgery 2005;57:42-9; discussion 42-9.
22. Lindqvist M, Steiner L, Blomgren H, Arndt J, Berggren BM. Stereotactic radiation therapy of intracranial arteriovenous malformations. Acta Radiol Suppl 1986;369:610-3.
23. Lindvall P, Bergstrom P, Lofroth PO, Hariz MI, Henriksson R, Jonasson P, et al. Hypofractionated conformal stereotactic radiotherapy for arteriovenous malformations. Neurosurgery 2003;53:1036-42; discussion 1042-3.
24. Lunsford LD, Kondziolka D, Flickinger JC, Bissouette DJ, Jungreis CA, Maizt AH, et al. Stereotactic radiosurgery for arteriovenous malformations of the brain. J Neurosurg 1991;75:512-24.
25. Miyamoto S, Hashimoto N, Nagata I, Nozaki K, Morimoto M, Taki W, et al. Posttreatment sequelae of palliatively treated cerebral arteriovenous malformations. Neurosurgery 2000;46:589-94; discussion 594-5.
26. Miyawaki L, Dowd C, Wara W, Goldsmith B, Albright N, Gutin R et al. Five year results of LINAC radiosurgery for arteriovenous malformations: Outcome for large AVMs. Int J Radiat Oncol Biol Phys 1999;44:1089-106.
27. Pan DH, Guo WY, Chung WY, Shiu CY, Chang YC, Wang LW. Gamma knife radiosurgery as a single treatment modality for large cerebral arteriovenous malformations. J Neurosurg 2000;93 Suppl 3:5113-9.
28. Pollock BE, Flickinger JC. A proposed radiosurgery-based grading system for arteriovenous malformations. J Neurosurg 2002;96:79-85.
29. Qi XS, Schultz CJ, Li XA. Possible fractionated regimens for image-guided intensity-modulated radiation therapy of large arteriovenous malformations. Phys Med Biol 2007;52:5667-82.
30. Spetzler RF, Martin NA. A proposed grading system for arteriovenous malformations. J Neurosurg 1986;65:476-83.
31. Starke RM, Komotar RJ, Hwang BY, Fischer LE, Garrett MC, Otten ML, et al. Treatment guidelines for cerebral arteriovenous malformation microsurgery. Br J Neurosurg 2009;23:376-86.
32. Subramanian S, Srinivas C, Ramalingam K, Babaih M, Swamy ST, Arun G, et al. Volumetric modulated arc-based hypofractionated stereotactic radiotherapy for the treatment of selected intracranial arteriovenous malformations: Dosimetric report and early clinical experience. Int J Radiat Oncol Biol Phys 2012;82:1278-84.
33. Toublou E, El Halabi A, Buffat L, Merienne L, Huard J, Schlienger M, et al. Single-fraction stereotactic radiotherapy: A dose-response analysis of arteriovenous malformation obliteration. Int J Radiat Oncol Biol Phys 1998;41:855-61.
34. Valentinio V. Stereotactic radiation therapy in arteriovenous malformations and brain tumors using the Fixster system. Acta Radiol Suppl 1986;369:608-9.
35. Veznedaroglu E, Andrews DW, Benitez RP, Downes MW, Werner-Wasik M, Rosenstock J, et al. Fractionated stereotactic radiotherapy for the treatment of large arteriovenous malformations with or without previous partial embolization. Neurosurgery 2004;55:59-30; discussion 330-1.
36. Wowra B, Muacevic A, Tonn JC, Schoenberg SO, Reiser M, Herrmann KA. Obliteration dynamics in cerebral arteriovenous malformations after cyberknife radiosurgery: Quantification with sequential nidus volumetry and 3-tesa 3-dimensional time-of-flight magnetic resonance angiography. Neurosurgery 2009;64 Suppl 2:A102-9.
37. Xiao F, Gorgulho AA, Lin CS, Chen CH, Agazaryan N, Vinuela F, et al. Treatment of giant cerebral arteriovenous malformation: Hypofractionated stereotactic radiation as the first stage. Neurosurgery 2010;67:1253-9; discussion 1259.
38. Yamamoto M, Jimbo M, Hara M, Saito I, Morii K. Gamma knife radiosurgery for arteriovenous malformations: Long-term follow-up results focusing on complications occurring more than 5 years after irradiation. Neurosurgery 1996;38:906-14.
39. Yang SY, Kim DG, Chung HT, Paek SH, Park JH, Han DH. Radiosurgery for large cerebral arteriovenous malformations. Acta Neurochir (Wien) 2009;151:113-24.

40. Yuki I, Kim RH, Duckwiler G, Jahan R, Tatoshima S, Gonzalez N, et al. Treatment of brain arteriovenous malformations with high-flow arteriovenous fistulas: Risk and complications associated with endovascular embolization in multimodality treatment. Clinical article. J Neurosurg 2010;113:715-22.

41. Zabel-du Bois A, Milker-Zabel S, Huber P, Schlegel W, Debus J. Linac-based radiosurgery or hypofractionated stereotactic radiotherapy in the treatment of large cerebral arteriovenous malformations. Int J Radiat Oncol Biol Phys 2006;64:1049-54.

42. Zhao J, Yu T, Wang S, Zhao Y, Yang WY. Surgical treatment of giant intracranial arteriovenous malformations. Neurosurgery 2010;67:1359-70; discussion 1370.

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