Chapter 3
Arteriovenous Malformation

Katelyn M. Atkins, Marc Bussière, and Helen A. Shih

Neurosurgeon Lars Leksell first described radiosurgery in 1951 [1] and the first clinical application involved GammaKnife-based treatment of benign conditions such as trigeminal neuralgia and arteriovenous malformations [2]. Importantly, the principles of SRS have been applied to fractionated stereotactic radiotherapy techniques for treatment of a variety of commonly treated benign tumors and functional disorders of the CNS. This chapter summarizes hypofractionated radiotherapy techniques, including SRS and FSRT, for arteriovenous malformations.

3.1 Pearls

- Cerebral AVMs are abnormal vascular lesions that bypass the capillary network by shunting blood from feeding arteries to draining veins via a tortuous nidus of vascular connections.
- The point prevalence is 18 in 100,000, accounting for 1–2% of all strokes and 9% of subarachnoid hemorrhages.
- The majority (80–90%) are supratentorial and isolated in nature, while up to 9% occur in multiple.

K. M. Atkins
Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA, USA
e-mail: kmatkins@partners.org

M. Bussière · H. A. Shih (✉)
Department of Radiation Oncology, Massachusetts General Hospital, Francis H. Burr Proton Therapy Center, Boston, MA, USA
e-mail: bussiere.marc@mgh.harvard.edu; hshih@mgh.harvard.edu

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- While generally considered sporadic congenital malformations, the presence of multiple AVMs is predictive of hereditary hemorrhagic telangiectasia (also termed Osler-Weber-Rendu syndrome).
- Brain AVMs generally present between the ages of 10 and 40 years.
- The most common presenting symptoms are:
  - Intracranial hemorrhage (usually intraparenchymal)
  - Seizure (more likely with large, cortical AVMs with superficial drainage)
  - Headaches
  - Focal neurologic deficits (secondary to mass effect, hemorrhage, or vascular steal)
- AVMs carry an estimated risk of hemorrhage of 1–4% per year:
  - The strongest predictors of hemorrhage include prior hemorrhage (at presentation, or clinically silent), deep location, exclusively deep drainage, and associated aneurysms.
- Medical workup: H&P, including assessment of performance status, with emphasis on preceding neurological symptoms (headaches, seizures, focal neurologic deficits) and thorough neurologic examination.
- Imaging workup:
  - CT: Lesions are typically identified on CT, which demonstrate strong contrast enhancement and appear as isodense or hyperdense tortuous vessels. There may be areas of hemorrhage surrounding the nidus. More sensitive imaging (see below) is usually required.
  - MRI/MRA: Increased sensitivity for evaluating the nidus, which demonstrate strong contrast enhancement and appear as hypointense flow voids on both T1- and T2-weighted series.
  - Angiography: The gold standard modality for AVM diagnosis and nidus delineation.
- Given the morbidity and mortality of hemorrhage, treatment is often considered for asymptomatic patients.
- Management strategies include observation, surgical resection, SRS, and embolization.
- For resectable lesions, surgery is the treatment of choice—as the risk of hemorrhage is immediately removed.
- For unresectable lesions or those with high associated surgical risk, SRS is a well-established alternative.
  - High-dose RT is presumed to result in a fibrointimal reaction with associated thrombosis and eventual obliteration of the AVM nidus often within the first 3 years (typical single-fraction SRS dose of 15–24 Gy with higher doses more effective but also with higher risk of morbidity).
- Endovascular treatment or embolization (while rarely curative as an isolated intervention) can be a useful adjuvant technique prior to surgery or SRS.

Table 3.1 Spetzler-Martin grading scale[a]

Size	
0–3 cm	1
3.1–6.0 cm	2
>6 cm	3
Brain location	
Non-eloquent	0
[b]Eloquent	1
Venous drainage	
Superficial	0
Deep	1

[a]Modified from Spetzler et al. [3]
[b]Involving or directly adjacent to primary motor or somatosensory cortex, primary visual cortex, Broca'a area, Wernicke's area, hypothalamus, thalamus, deep nuclei, brainstem, or cerebellar nuclei

3.2 Staging, Grading, and Other Classifications

Classically, the surgical risk associated with AVMs has been classified based on the 1986 Spetzler-Martin grading scale, which accounts for multiple or large lesions, those in eloquent brain regions, and superficial versus deep drainage, to predict surgical outcomes (Table 3.1, [3]). The total score is the sum in all categories (e.g., grade I = 1 point, grade V = 5 points), where the higher the score, the higher the risk of operative morbidity and mortality [4].

More recently, several radiosurgery-based AVM scoring systems have been developed to more effectively predict outcomes following AVM radiosurgery. The most commonly used is the modified radiosurgery-based AVM score that incorporates AVM nidus volume, patient age, and AVM location by the following equation: AVM score = (0.1) (volume, mL) + (0.02) (age, year) + (0.5) (location; hemispheric/corpus callosum/cerebellar = 0, basal ganglia/thalamus/brainstem = 1) [5].

3.3 Patient Selection

- Factors influencing treatment recommendations include patient age, medical comorbidities, cranial nerve deficits, AVM size and/or growth rate, presenting symptoms, competing symptoms (i.e., contralateral hearing or vision loss), and proximity to critical organs at risk (OAR, such as brainstem, cochlea, optic apparatus, and eloquent brain).
- Single-fraction SRS for low-grade or small-volume AVMs (SM Grade I–II, low AVM score, nidus volume <10–15 cc), including those in eloquent or deep locations not amenable to surgical resection.
- For single-fraction SRS, targets should generally be:

  - <3 cm.
  - Not directly abutting critical OARs.
  - >3–5 mm from the optic apparatus (optic chiasm, optic nerves) to achieve adequate dose falloff between the prescription dose and OAR tolerance (<8–10 Gy for single-fraction SRS).

- For FSRT, tumors may be larger (> 3–4 cm), in closer proximity to or involving OARs.
- For large or high-risk AVMs, the optimal treatment approach remains controversial, but includes FSRT versus volume-staged SRS:
  - FSRT: Total dose is divided into ≥2 equal fractions delivered approximately weekly [6].
  - Volume-staged SRS: The AVM nidus is divided into several regions based upon branches of vascular flow (typically 2–4), each of which is treated to an effective single-fraction dose, commonly with a 3–9-month break interval [7, 8].

3.4 Treatment Planning Considerations

Treatment planning considerations, including critical components of simulation, target delineation, coverage considerations, and planning strategies are described in (Table 3.2) and depicted in (Fig. 3.2).

Table 3.2 Treatment planning considerations

Simulation instructions	**Position**: Supine, arms at sides, head and neck neutral. **Immobilization**: A rigid (frame or frameless) stereotactic immobilization system[a]. – GaK: Head frame in conjunction with a metal collimator helmet. – Linac based: Various, including rigid frame with external skull fixation, noninvasive modified GTC frame (noninvasive fixation by use of a dental plate), or a three-point thermoplastic mask with a modified stereotactic frame (Fig. 3.1). **CT**: Thin-cut CT images (1.0–3.0 mm slice thickness) ideally with IV contrast spanning from vertex to mid-cervical spine. **Diagnostic imaging**: Co-registration of planning CT with the appropriate diagnostic imaging (contrast-enhanced MRI or CT) for target and OAR delineation. – MRI sequences should include pre- and post-contrast T1-weighted, pre-contrast T2-weighted and FLAIR, and multi-planar (axial, sagittal, and coronal) post-contrast T1-weighted images. Post-contrast T1-weighted images with thin (1 mm) sectioning ideally should be obtained.
Image guidance	Imaging options include CBCT, orthogonal KV X-rays; misalignment corrections via positional systems with four or six rotational axes of the patient couch/platform.

Table 3.2 (continued)

Target delineation	Target is the entire nidus (see Fig. 3.2a), delineated by co-registration with brain MRI/MRA and/or CT angiography. Draining veins best visualized during arterial phase of angiogram are not part of the target.
Margins	The target is the nidus (GTV = CTV). PTV = CTV plus 0–5 mm uniform expansion (depending on institutional setup error, including accuracy and reproducibility of immobilization). For standard thermoplastic mask, generally CTV plus 3–5 mm uniform expansion. For stereotactic frame, generally CTV plus 0–2 mm uniform expansion.
Tumor/target coverage considerations	≥98% of the GTV/CTV should receive the prescription dose. ≥95% of the PTV should receive the prescription dose.
Treatment modality	Linac, GaK, CyK, proton beam
Planning strategies/ assessment	Steep PTV to OAR dose gradients are generated using multiple beam arrangements or non-coplanar arcs together with dose prescription to the steepest portion of the beam profile (often the 50% IDL for GaK or the 80–90% IDL for linac based). For linac-based SRS, the standard beam profile is shaped by collimation with cones or MLCs. An example treatment plan is depicted in Fig. 3.2b. Notably, as target size increases, the dosimetric advantages of SRS tend to decline—as the sharp dose falloff becomes shallower and the higher doses to adjacent normal tissue become prohibitive, thereby generally precluding safe and effective SRS delivery to targets >3 cm in diameter. The following indices should be generated [9]: **Conformality index**: Prescription isodose volume/target volume (ideally ≤2). **Heterogeneity index**: Maximum dose to target volume/prescription dose (ideally ≤2). **Gradient index**: Volume receiving half the prescription isodose/ volume receiving the full prescription isodose (ideally ≥3).

[a]Based on delivery system and institutional protocol. *GaK* GammaKnife, *GTC* Gill-Thomas-Cosman, *FLAIR* fluid-attenuated inversion recovery, *CBCT* cone beam CT, *CyK* CyberKnife

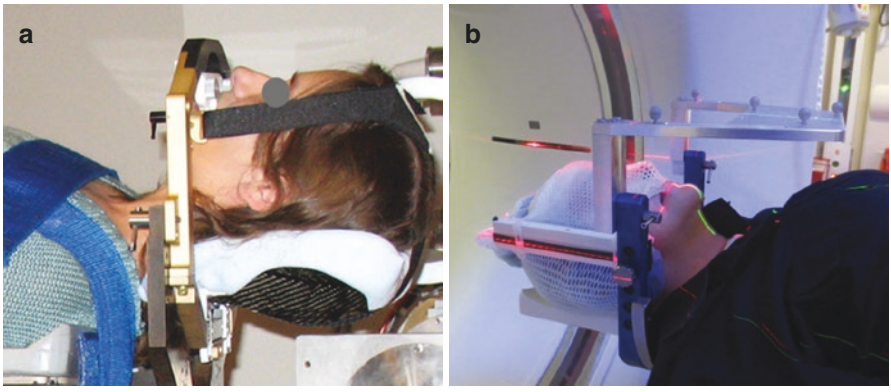

Fig. 3.1 Immobilization depicted using (**a**) a modified Gill-Thomas-Cosman (mGTC) frame (Integra NeuroSciences, USA) and (**b**) a thermoplastic mask (Brainlab, Germany)

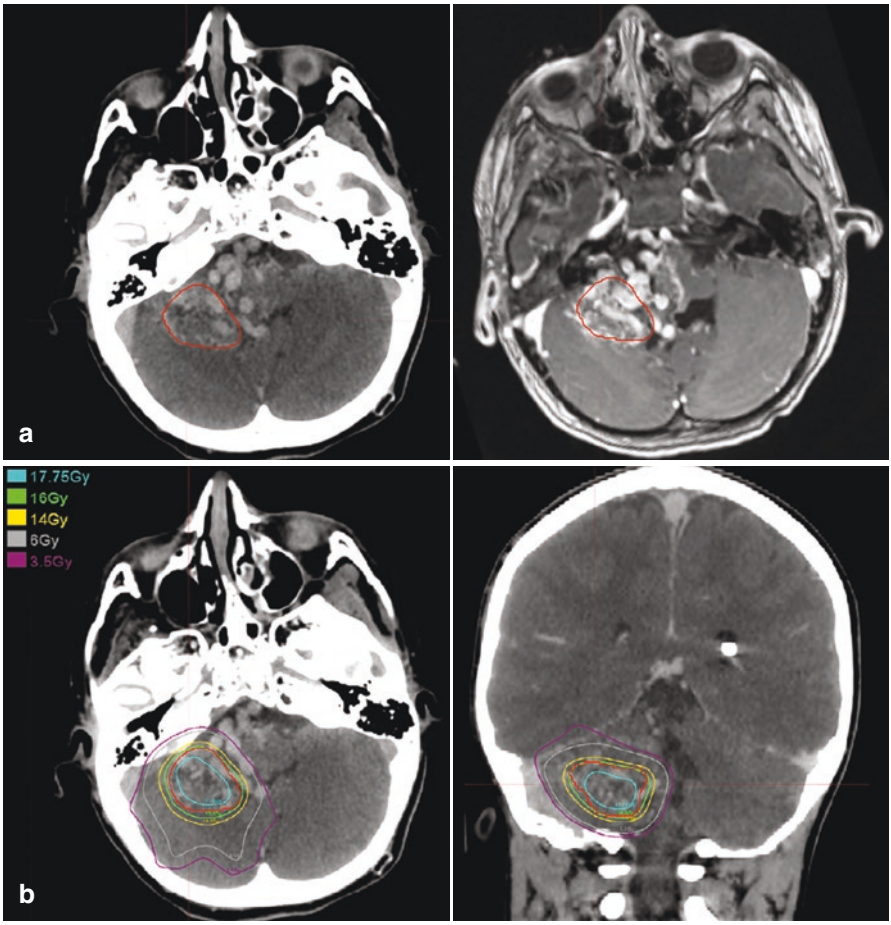

Fig. 3.2 A 6.5 cc right cerebellar AVM in a 12-year-old child; GTV target delineation in red. (**a**) Simulation CT (left), 3D FSPGR MRI sequence (right). (**b**) Treatment plans with prescription IDL in green, effective normalization 90%. SRS, 8 GyRBE protons × 2 fx (16 GyRBE total). Simulation CT axial (left) and coronal (right). *IDL* isodose line

3.5 Commonly Used Dose/Fractionation Schemes

Commonly utilized dose/fractionation schemes for SRS and FSRT are described in Table 3.3.

3.6 Normal Tissue Tolerances

Normal tissue tolerances for SRS and FSRT are described in Table 3.4. In particular, the estimated rates of radiation-induced optic neuropathy are very rare <8–10 Gy but reach >10% at single-SRS doses between 12 and 15 Gy [13, 14].

Table 3.3 Commonly used dose/fractionation schemes

Commonly used dose/fractionation schemes		
	Patient selection considerations	Dose/fractionation
SRS	SM Grade I–II, low risk	15–24 Gy × 1 fx [10, 11]
FSRT	Large lesion, high risk	12–28 Gy, in 2–4 fx ≥7 days apart [6, 12]
Volume staged	Large lesion, high risk	13–18 Gy, in 2–4 sessions, 3–9 months apart [7, 8]

SM Spetzler-Martin

Table 3.4 Normal tissue tolerances for SRS and FSRT

Dmax[a] (Gy) in critical structures for SRS and FSRT							
Organ	Authors' recommendations			TG101 [16]			QUANTEC [17]
Fractions	One	Three	Five	One	Three	Five	One
Brainstem	≤12 Gy	≤21 Gy	≤30 Gy	15 Gy	23.1 Gy	31 Gy	<12.5 Gy
Cochlea	<4.2Gy	–	–	9 Gy	17.1 Gy	25 Gy	≤14 Gy
Optic apparatus	≤8 Gy	≤16.5 Gy	≤25 Gy	10 Gy	17.4 Gy	25 Gy	–
Optic chiasm	≤8 Gy	–	–	–	–	–	<12 Gy
Optic nerve	≤8 Gy	–	–	–	–	–	–

[a]Maximum point dose

In a study by Kano et al., patients with vestibular schwannomas treated with GammaKnife SRS who received a central cochlea dose <4.2 Gy had better hearing preservation [15].

3.7 Patient Management Considerations

- Premedication/prophylactic medication:
  - There is no standard premedication regimen.
  - Consideration of steroids, benzodiazepines, and/or anticonvulsants is dependent on severity and tempo of symptoms or neurologic deficit(s), treatment volume/location and number of fractions, if known prior seizures, as well as patient age and/or medical comorbidities.
- Acute toxicity:
  - Generally well tolerated; expected higher risk of toxicity with high-grade AVMs requiring FSRT or volume-staged radiotherapy.
  - Headaches (<5–15%), transient neurologic changes (<1–10%) [10, 11, 18]:

    Consider short-course dexamethasone 2–4 mg QD (can increase to BID), taper, and/or discontinue as soon as feasible.
    Second line: Referral to neurology.
  - Seizures (<10–15%) [10, 11, 18]: Referral to neurology.

- Late toxicity:
  - Headaches (<10–15%), seizures (<5–10%), neurologic changes (<10%) [6, 7, 10–12, 19, 20].
  - To note, there remains an inherent risk of hemorrhage until obliteration occurs, including any hemorrhage (LG 0–6%, HG 2–22%) and fatal hemorrhage (LG 0–3%, HG 0–15%) [6, 7, 10–12, 19, 20].

3.8 Follow-Up

- H&P every 6–12 months, or as needed.
- MRI with contrast annually (CT with contrast if non-tolerant or MRI contraindicated).
  - At the time of apparent radiographic resolution, perform angiography to confirm obliteration.
- For base of skull locations, monitor for hypopituitarism with regular serum analyses annually.
  - Recommend endocrinologist for long-term management and monitoring of endocrine dysfunction.

3.9 Relevant Literature

- Low-grade AVMs (SM Grade I–II, low AVM score, nidus volume <10–15 cc) are effectively treated with single-fraction SRS (general dose 15–24 Gy). Typical reported obliteration rates are 70–90%, including those in eloquent or deep locations not amenable to surgical resection ([10, 11, 18] and see Table 3.5).
- For large or high-risk AVMs, the optimal treatment approach remains controversial, as delivery of effective single-fraction SRS doses is limited by increasing treatment volumes and associated risk of treatment-related toxicity. To mitigate this, there are two main strategies, FSRT or volume-staged SRS.
  - In FSRT, the total dose is divided into ≥2 equal fractions delivered weekly, with the rationale of improving tolerance of adjacent normal brain tissue to higher doses, however at the expense of obliteration rates (15–27%) [6, 12, 19].
  - For volume-staged SRS, the AVM nidus is divided into several regions (typically 2–4), for which each section is treated to an effective single-fraction dose, typically with a 3–9-month interval to allow for normal brain tissue recovery [7, 8, 21].

Table 3.5 Relevant literature

Study	Patients (*n*)	Median follow-up (months)	Median AVM vol (cm^3)	Modality, median marginal dose, fractionation	Obliteration rate (%)
Pan (2000) [22]	240	26 (12–73)	32% >10	GaK, 15–18 Gy × 1 fx	– vol 10–15 cm^3: 77% at 40 months – vol >15 cm^3: 25% at 40 months – 58% at 50 months
Flores (2011) [23]	213	48	2.1 (mean)	Linac, 14 Gy × 1 fx	– 66% at 3 years – 82% at 5 years
Kano (2012) [18]	217 (SM I-II)	64	2.3	GaK, 22 Gy × 1 fx	– 58% at 3 years – 87% at 4 years – 90% at 5 years – 93% at 10 years
Stark (2013) [24]	1012	96	3.5 (mean)	GaK, mean 21.1 Gy × 1 fx	69% overall
Hattangadi-Gluth (2014) [11]	248	35	3.5	Protons, 15 Gy (RBE) × 1 fx	– 65% at 2.9 years – 70% at 5 years
Ding (2014) [10]	502 (SM I-II)	48 (radiographic) 62 (clinical)	2.4	GaK, 23 Gy × 1 fx	– 66% at 5 years – 80% at 10 years
Silander (2004) [19]	26	NA	13	Protons, FSRT, 20–25 Gy (RBE) total in 2–4 fx	– vol <25 cm^3:70% – vol ≥25 cm^3: 30%
Vernimmen (2005) [25]	64	62	41% <14, 59% ≥14	Protons, FSRT, 2–3 fx – Volume <14 cm^3: Minimum target vol total dose—15 Gy (RBE) – Volume ≥14 cm^3: Minimum target vol total dose—10.4 Gy (RBE)	– vol <14 cm^3: 75% – vol ≥14 cm^3: 43%
Hattangadi (2012) [12]	59	56	22.9	Protons, FSRT, 8 Gy (RBE) × 2 fx	Total 15%, partial 34%, stable 51%
Blamek (2013) [6]	49 (37% SM III)	29	18	19.9 Gy total dose in 2–4 fx	1 year 7% 2 years 11% 3 years 21%

- Notably, a recent literature review by Moosa et al. suggests that the higher delivered BED in volume-staged SRS may result in higher obliteration rates compared to FSRT (47 vs. 22%), with the noted disadvantage that partial obliteration may result in altered blood flow patterns and an uncertain impact on the risk of hemorrhage, although rates of hemorrhage do not appear to be increased [20].

References

1. Leksell L. The stereotaxic method and radiosurgery of the brain. Acta Chir Scand. 1951;102(4):316–9.
2. Leksell L. Trigeminal neuralgia. Some neurophysiologic aspects and a new method of therapy. Lakartidningen. 1971;68(45):5145–8.
3. Spetzler RF, Martin NA. A proposed grading system for arteriovenous malformations. J Neurosurg. 1986;65(4):476–83.
4. Hamilton MG, Spetzler RF. The prospective application of a grading system for arteriovenous malformations. Neurosurgery. 1994;34(1):2–6; discussion-7
5. Pollock BE, Flickinger JC. Modification of the radiosurgery-based arteriovenous malformation grading system. Neurosurgery. 2008;63(2):239–43; discussion 43
6. Blamek S, Larysz D, Miszczyk L, Idasiak A, Rudnik A, Tarnawski R. Hypofractionated stereotactic radiotherapy for large or involving critical organs cerebral arteriovenous malformations. Radiol Oncol. 2013;47(1):50–6.
7. Kano H, Kondziolka D, Flickinger JC, Park KJ, Parry PV, Yang HC, et al. Stereotactic radiosurgery for arteriovenous malformations, part 6: multistaged volumetric management of large arteriovenous malformations. J Neurosurg. 2012;116(1):54–65.
8. Seymour ZA, Sneed PK, Gupta N, Lawton MT, Molinaro AM, Young W, et al. Volume-staged radiosurgery for large arteriovenous malformations: an evolving paradigm. J Neurosurg. 2016;124(1):163–74.
9. Balagamwala EH, Suh JH, Barnett GH, Khan MK, Neyman G, Cai RS, et al. The importance of the conformality, heterogeneity, and gradient indices in evaluating Gamma Knife radiosurgery treatment plans for intracranial meningiomas. Int J Radiat Oncol Biol Phys. 2012;83(5):1406–13.
10. Ding D, Yen CP, Xu Z, Starke RM, Sheehan JP. Radiosurgery for low-grade intracranial arteriovenous malformations. J Neurosurg. 2014;121(2):457–67.
11. Hattangadi-Gluth JA, Chapman PH, Kim D, Niemierko A, Bussiere MR, Stringham A, et al. Single-fraction proton beam stereotactic radiosurgery for cerebral arteriovenous malformations. Int J Radiat Oncol Biol Phys. 2014;89(2):338–46.
12. Hattangadi JA, Chapman PH, Bussiere MR, Niemierko A, Ogilvy CS, Rowell A, et al. Planned two-fraction proton beam stereotactic radiosurgery for high-risk inoperable cerebral arteriovenous malformations. Int J Radiat Oncol Biol Phys. 2012;83(2):533–41.
13. Mayo C, Martel MK, Marks LB, Flickinger J, Nam J, Kirkpatrick J. Radiation dose-volume effects of optic nerves and chiasm. Int J Radiat Oncol Biol Phys. 2010;76(3 Suppl):S28–35.
14. Tishler RB, Loeffler JS, Lunsford LD, Duma C, Alexander E 3rd, Kooy HM, et al. Tolerance of cranial nerves of the cavernous sinus to radiosurgery. Int J Radiat Oncol Biol Phys. 1993;27(2):215–21.
15. Kano H, Kondziolka D, Khan A, Flickinger JC, Lunsford LD. Predictors of hearing preservation after stereotactic radiosurgery for acoustic neuroma. J Neurosurg. 2009;111(4):863–73.
16. Benedict SH, Yenice KM, Followill D, Galvin JM, Hinson W, Kavanagh B, et al. Stereotactic body radiation therapy: the report of AAPM task group 101. Med Phys. 2010;37(8):4078–101.

17. Marks LB, Yorke ED, Jackson A, Ten Haken RK, Constine LS, Eisbruch A, et al. Use of normal tissue complication probability models in the clinic. Int J Radiat Oncol Biol Phys. 2010;76(3 Suppl):S10–9.
18. Kano H, Lunsford LD, Flickinger JC, Yang HC, Flannery TJ, Awan NR, et al. Stereotactic radiosurgery for arteriovenous malformations, Part 1: management of Spetzler-Martin Grade I and II arteriovenous malformations. J Neurosurg. 2012;116(1):11–20.
19. Silander H, Pellettieri L, Enblad P, Montelius A, Grusell E, Vallhagen-Dahlgren C, et al. Fractionated, stereotactic proton beam treatment of cerebral arteriovenous malformations. Acta Neurol Scand. 2004;109(2):85–90.
20. Moosa S, Chen CJ, Ding D, Lee CC, Chivukula S, Starke RM, et al. Volume-staged versus dose-staged radiosurgery outcomes for large intracranial arteriovenous malformations. Neurosurg Focus. 2014;37(3):E18.
21. Pollock BE, Kline RW, Stafford SL, Foote RL, Schomberg PJ. The rationale and technique of staged-volume arteriovenous malformation radiosurgery. Int J Radiat Oncol Biol Phys. 2000;48(3):817–24.
22. Pan DH, Guo WY, Chung WY, Shiau CY, Chang YC, Wang LW. Gamma knife radiosurgery as a single treatment modality for large cerebral arteriovenous malformations. J Neurosurg. 2000;93(Suppl 3):113–9.
23. Flores GL, Sallabanda K, dos Santos MA, Gutiérrez J, Salcedo JCBP, Beltrán C, et al. Linac stereotactic radiosurgery for the treatment of small arteriovenous malformations: lower doses can be equally effective. Stereotact Funct Neurosurg. 2011;89(6):338–45.
24. Starke RM, Yen CP, Ding D, Sheehan JP. A practical grading scale for predicting outcome after radiosurgery for arteriovenous malformations: analysis of 1012 treated patients. J Neurosurg. 2013;119(4):981–7.
25. Vernimmen FJ, Slabbert JP, Wilson JA, Fredericks S, Melvill R. Stereotactic proton beam therapy for intracranial arteriovenous malformations. Int J Radiat Oncol Biol Phys. 2005;62(1):44–52.