Role of Stereotactic Radiosurgery in the Treatment of High-Grade Cerebral Arteriovenous Malformation

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Abstract

Arteriovenous malformation (AVM) with a small nidus located in the cortical eloquent areas is difficult to surgically resect without neurological complication, but is a suitable target for stereotactic radiosurgery (SRS). However, lesions with large nidus volume or with deeply located nidus are difficult to safely treat, even by SRS. To explore the optimal treatment strategies for such high-grade cerebral AVM, we reviewed treatment outcomes of SRS using gamma knife surgery (GKS) for patients with high-grade AVM at our institute and in published reports. Although lesions in the thalamus and the brainstem carried higher risk of morbidity after SRS, accumulation of technical knowledge and experience about SRS and technological advances in dose planning have enabled safer treatment of AVM in these locations. Large AVM presents another challenge to SRS treatment. Multimodal treatment, including surgery and endovascular treatment, should be considered. In this setting, staged SRS using GKS or CyberKnife may achieve safer treatment of large cerebral AVM. Further progress in SRS is anticipated to enhance the treatment efficacy for high-grade cerebral AVM while reducing treatment morbidity.

Key words: cerebral arteriovenous malformation, gamma knife surgery, stereotactic radiosurgery

Introduction

Stereotactic radiosurgery (SRS) is widely accepted to be among the least invasive treatment modalities for small arteriovenous malformation (AVM), even AVM located in the cortical eloquent areas.¹ In contrast, AVM in deep locations such as the brainstem and thalamus still presents a therapeutic challenge, with a high risk of life-threatening latency hemorrhage, and the accompanying higher risks associated with SRS.¹,36) According to the recommendations of the American Stroke Association, radiosurgery for cerebral AVM can be considered for lesions thought to present high risk to surgical or endovascular treatment.¹,36) The grading system by Spetzler and Martin has been widely used to assess the surgical difficulty of cerebral AVM.⁴⁷) Spetzler-Martin grade 3 or higher lesions are considered to have higher risk for surgery, and also have higher risk of morbidity associated with SRS because of the usually large size or location in cortical eloquent areas.¹,36) Since SRS using gamma knife surgery (GKS) is designed to deliver high dose irradiation to a small target, AVM with a large nidus volume is not an ideal target.⁴⁷) Among the eloquent areas defined by Spetzler-Martin grading,⁴⁷) AVM in deep locations such as the thalamus and brainstem have higher risks of morbidity even with GKS.¹,36,47) Therefore, it is not always true that SRS is the best option for surgically intractable small AVM. The role of SRS in modern multidisciplinary treatment strategy for AVM remains controversial.

This review examines our experience of SRS using GKS for AVM and previous cases¹,4,6,23,33,34,36,37,47,48) to clarify the role of SRS in the modern therapeutic strategy for such intractable AVM. Furthermore, we discuss advances in the technology of SRS, which may contribute to safer treatment of cerebral AVM, especially high-grade
lesions.

**SRS for AVM**

I. **AVM in the basal ganglia and thalamus** (Fig. 1)

AVM located in the basal ganglia and thalamus have annual rates of bleeding of 9.8% to 11.4%.\(^{13,51,55}\) In our series of 48 patients with thalamic AVM, the annual bleeding rate was 14%.\(^{19}\) Since high risks of morbidity and mortality occur together, earlier extirpation is desirable before repeated hemorrhages.\(^{40}\) However, surgery for AVM in the thalamus frequently causes neurological deterioration because of the proximity to critical structures.\(^{40}\) This danger is sufficient justification for hesitation before recommending this therapeutic option.\(^{41}\) In our experience, microsurgical resection with preoperative embolization and intraoperative electrophysiological monitoring can achieve acceptably low complication rates for small AVM, especially AVM associated with hematomas.\(^{40,41}\) Therefore, even with challenging AVM, microsurgery can be the first choice for treatment in selected patients during the acute phase of the disease. On the other hand, SRS reduced the risks of mortality and morbidity in patients with surgically intractable small AVM, and in patients without severe neurological deficits, who had been observed conservatively before the advent of alternative treatments.

![Fig. 1 A–D: Right carotid angiograms (A: anteroposterior view, B: lateral view) and gadolinium enhanced time of flight imaging (C: axial section, D: coronal section) before radiosurgery showing an arteriovenous malformation in the thalamus. Marginal dose of 20 Gy was prescribed for the 3.4 cm³ nidus. Corticospinal tractography was integrated in dose planning. E, F: Right carotid angiograms (E: anteroposterior view, F: lateral view) 25 months after stereotactic radiosurgery showing complete nidus obliteration without neurological complication.](image)

![Fig. 2 A–D: Left carotid angiograms (A: anteroposterior view, B: lateral view) and gadolinium enhanced time of flight imaging (C: axial section, D: sagittal section) before radiosurgery showing an arteriovenous malformation in the medulla oblongata. Marginal dose of 20 Gy was prescribed for the 0.3 cm³ nidus. E, F: Left carotid angiograms (E: anteroposterior view, F: lateral view) 12 months after stereotactic radiosurgery confirming complete nidus obliteration.](image)
of SRS.\textsuperscript{41} SRS achieves nidus obliteration rates for thalamic AVM of 45\% to 62\% at 3 years, and obliteration rates without neurological complication of 39\% to 55\%.\textsuperscript{1,36} In our experience with longer follow-up intervals, the angiographical obliteration rate by the Kaplan-Meier method was 67\% at 3 years and 82\% at 5 years.\textsuperscript{19} Among 43 patients who were observed for more than 12 months, 24 patients (56\%) had absolute obliteration of AVM without neurological complications.\textsuperscript{19} The morbidity rates after SRS for these lesions are 12\% to 19\%, higher than those of AVM in other parts of the brain, which are 2.7\% to 8\%.\textsuperscript{13,25,35,46} In our experience, the morbidity rate was not negligible at 17\%,\textsuperscript{19} consistent with previous reports, and factors affecting neurological deterioration after SRS in the multivariate analysis were higher margin dose, treatment using the first generation dose planning system, and nidus fed by the thalamogeniculate artery. Analyses of our data showed that the rate of adverse events in the group of patients who underwent treatment based on newer planning software (Leksell GammaPlan; Elekta Instruments AB, Stockholm, Sweden), which enables display of multiple radiographic images on the computer screen and simultaneous superimposition of isodose lines, was significantly lower compared with the group of patients treated with older planning tools (KULA; Elekta Instruments AB) in which the prescribed dose planning was manually superimposed on radiographic imaging films. This result suggests that technical advances will be very important in increasing the safety of GKS and strenuous efforts should be made to reduce the complications.

II. AVM in the brainstem (Fig. 2)

The annual bleeding rate of untreated brainstem AVM is 15.1\%\textsuperscript{33} and the annual rate of rebleeding is 17.8\%.\textsuperscript{32} These significant rates of bleeding and events directly linked to the morbidity and mortality of patients are concerns in the consideration of SRS. In our 44 patients with brainstem AVM, the annual hemorrhage rate was 17.5\%,\textsuperscript{20} which is consistent with previous findings, and four (9\%) of the patients died of bleeding even after SRS. Thus, earlier exirpation is desirable for brainstem lesions as well as for thalamic AVM. However, surgery may be applicable only for some cases of brainstem lesions, and morbidity and mortality associated with surgical removal is significant, ranging from 20\% to 25\% and 0\% to 20\%, respectively.\textsuperscript{3,33,46} The risks largely depend on the nidus location within the brainstem. Safe removal is not feasible for AVMs located in the ventral midbrain, pons, and medulla oblongata.\textsuperscript{33} In our experience of patients with brainstem AVM, we found no significant difference in outcomes with location within the brainstem, and the associated morbidity was 5\%, which was less than the rate of morbidity associated with surgical resection.\textsuperscript{20} Therefore, brainstem AVM would be a good candidate for SRS, especially in the ventral midbrain, pons, and medulla oblongata, for which total surgical removal is difficult. Our study revealed that SRS significantly reduced the annual risk of hemorrhage, from 17.5\% before treatment to 2.4\% after treatment, but latent hemorrhage from incompletely obliterated nidus could be critical. Since higher dosage was significantly associated with higher obliteration rate,\textsuperscript{20} adequate marginal dose must be delivered for small AVMs, ideally more than 18 Gy, to achieve complete nidus obliteration. From our experience, patients with brainstem AVM with nidus volume smaller than approximately 10 cm\textsuperscript{3} are good candidates for SRS.\textsuperscript{20} Serious neurological complications can be anticipated in cases with larger lesions in the brainstem,\textsuperscript{42} so a multimodal treatment strategy in combination with SRS, microsurgery, and endovascular treatment should be discussed.\textsuperscript{24,26,33}

III. AVM with large nidus volume (Fig. 3)

The natural history of Spetzler-Martin grade 4 and 5 AVMs remains controversial. The annual hemorrhage risk has been reported as 1.5\% to 10.4\%.\textsuperscript{5,8,22} For patients with history of hemorrhage, the annual risk of hemorrhage was calculated as 6\% to 13.9\%.\textsuperscript{5,8,22} Therefore, such AVMs might carry potential risk of hemorrhage. Limitations of GKS include the size of lesions. Large lesions cannot be adequately treated by single fractionated radiosurgery because high-dose irradiation in one session for larger lesions increases the undesirable effect of irradiation of the surrounding brain structure.\textsuperscript{12} To overcome this limitation, several treatment strategies have been proposed, including dose fractionation.\textsuperscript{9} Since AVM is not a proliferative disease, dose fractionation seems to be an inappropriate approach for this disease.\textsuperscript{14,38,50,52} Another method is volume-staging,\textsuperscript{12,37,45} in which a part of a lesion is irradiated over a series of sessions. Volume-staged radiosurgery has recently been tried for large, aggressive AVM. As an innovative modality, some favorable outcomes have been reported for SRS, using CyberKnife for large AVM.\textsuperscript{53} Additional analyses of these options are necessary. The correct combination of surgery and endovascular treatment to treat large lesions must be determined. The complete obliteration rate after volume-staging radiosurgery was low,\textsuperscript{12,45} but surgical removal of incompletely obliterated nidus after this approach appears to be a good treatment strategy because surgical resection of an ir-
Fig. 3 A 31-year-old man presented with a large arteriovenous malformation (AVM) located in the left parietal lobe which was detected incidentally. This patient was managed conservatively at first, but he suffered intracerebral hemorrhage 13 years later. A–D: Left carotid angiograms (A: anteroposterior view, B: lateral view) and T2-weighted magnetic resonance images (C, D) before radiosurgery showing a large AVM. This patient received 2-staged volume stereotactic radiosurgery. The total target volume was 33 cm³ and the marginal dose was 16 Gy for both stages. E, F: T2-weighted magnetic resonance images 44 months after first treatment showing slight detection of the nidus. Further response is expected in time.

radiated nidus is feasible and safe. Recently, the combination of initial embolization for large AVM to reduce the nidus volume, followed by SRS, resulted in 76% obliteration of the total nidus on imaging, which might be acceptable for such challenging lesions. On the other hand, the morbidity according to treatment was described as 18% per procedure. Historically, the hemorrhagic risks were considered to be lower for most cases of AVM with larger nidus compared to other grades of AVM, and observation is usually recommended as a first choice of treatment option. In contrast, one report showed relatively higher hemorrhagic risk for patients with large nidus. Caution must be taken when considering SRS as a treatment option, by estimating the hemorrhagic risks and weighing the risks and benefits of the intervention.

Advances in Technology

Technological development of SRS is still in progress, and continues to contribute to better treatment outcomes of SRS for AVM. As an example of refined treatment planning, integration of diffusion tensor tractography (DTT) into radiosurgical treatment planning was started in 2004 at our institute. For the time being, we have started to integrate tractography of the corticospinal tract (CST), optic radiation, and arcuate fasciculus, as these are critical white matter structures to be preserved. By analyzing the relationship between the occurrence of radiation-induced neuropathy and the maximum dose received by each tract, tolerable doses of each white matter tract could be estimated. The estimated tolerable dose was approximately 20 Gy for the CST, 8 Gy for the optic radiation, and 8 Gy and 20 Gy for temporal and frontal fibers of the arcuate fasciculus, respectively. Among the 144 patients with AVM who underwent radiosurgical procedures after integration of tractography at our institute, the rate of radiation-induced neuropathy was 2.8%, which was significantly lower than the previously reported complication rate of 5% to 20%. Our more precise analysis of outcomes of patients with lesions adjacent to the CST found that integrating DTT of the CST into treatment planning significantly reduced motor complication without compromising the obliteration. Certain points require attention when applying DTT. For patients with a history of infarction, edema, hemorrhage, and craniotomy that was repaired with metallic materials, DTT is sometimes difficult to create because of severe degradation of images. The accuracy of tractography should also be considered. We know that the anatomical CST is not exactly the same as DTT-CST. Further accumulation of cases using DTT is necessary for more meticulous and safer treatment.

Conclusions

Deeply located high-grade AVM is still challenging, even for SRS. Although the rate of neurological complications for patients with thalamic AVM was higher, reflecting the proximity to vital structures,
advances in the radiosurgical technologies have contributed to reducing morbidity. Brainstem AVMs in the ventral midbrain, pons, and medulla oblongata, for which total surgical removal is difficult, would be good candidates for SRS. For large AVM, volume-staged radiosurgery could be a treatment option as a part of multimodal treatment. Further technological progress in SRS, as exemplified by tractography-integrated treatment, may contribute to safer treatment of high-grade AVM.

References


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