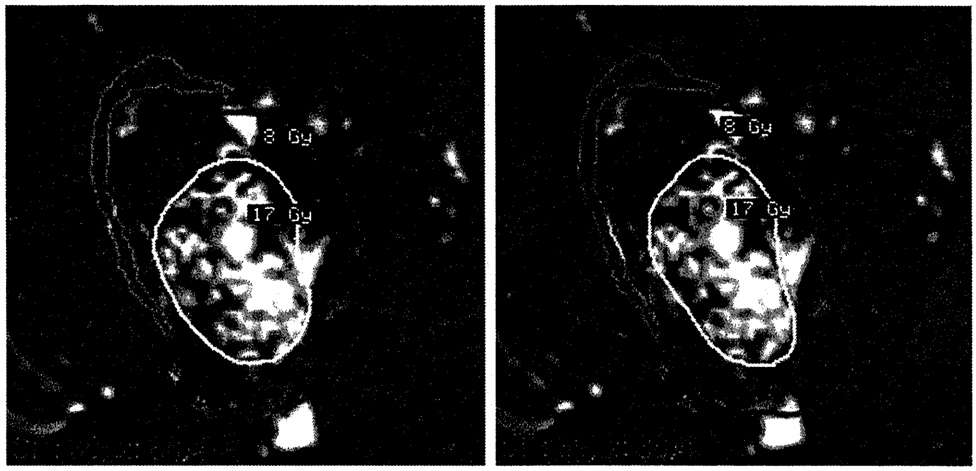

Fig. 2. Radiosurgical dosimetry of 33-year-old woman with unruptured arteriovenous malformation in the right occipital lobe. Dose delivered to the optic radiation before referring to tractography (a) was intentionally reduced after its integration (b).

follow-up at 45 months. This was the only patient who developed permanent morbidity after the prospective integration of tractography. Another patient exhibited mild transient hemiparesis 12 months after treatment prospectively integrating pyramidal tractography but fully recovered after administration of oral corticosteroid agents. Frequency of pre-existing epileptic attacks increased in 3 patients, and new onset of convulsive seizure was observed in 1 patient after radiosurgery. Nidus obliteration was confirmed by magnetic resonance imaging or angiography in 42 patients (29%) until last follow-up. Posttreatment hemorrhage was observed in 2 patients during 319 patient-years. Neither of them exhibited radiation-induced neuropathy before their subsequent hemorrhage. The other patients had no complications throughout the follow-up period.

DISCUSSION

By integrating diffusion tensor tractography of the brain white matter to radiosurgery, permanent and transient morbidity could be reliably prevented in our patients with brain arteriovenous malformations. Although many results of utilizing diffusion tensor–based tractography for diagnostic purposes have been reported (17), its integration into treatment planning of radiosurgery is our original technique and has not been performed at any other institute. Therefore, though this is a retrospective case series, reporting our results would be the most appropriate means to evaluate its efficacy.

Although there are a variety of white matter fiber tracts, we considered that the pyramidal tract would be the most important tract in preventing morbidity of radiosurgery because its injury causes motor paresis and leads to decline of activities of daily living (18, 19). At the same time, the pyramidal tract was practically the easiest one to draw from the technical point of view (17). The optic radiation and the arcuate fasciculus would be next important and are more difficult to draw (20, 21). Injury of the optic radiation causes visual disturbance. Verbal function requires participation of a distributed neural system in the dominant hemisphere, and we integrated the arcuate fasciculus tractography to preserve this function as much as practically possible. For the time being, we are introducing the above three tracts, considering them as critical white matter structures to be preserved. Technical difficulty is also a consideration, as mentioned above. Confirming above three tracts along with anatomically identifiable critical structures of the brain would be sufficient to prevent major disabling morbidity.

Integration of tractography into intraoperative navigation was also developed at our institute (13). However, it contains risks of inevitable brain shift caused by craniotomy or tumor removal, thus leading to poorer accuracy. On the other hand, such a shift does not occur in the setting of integration of tractography into radiosurgery. Therefore, we believe this would be the most suitable clinical application of diffusion tensor tractography in treating brain disorders.

Our study has several potential limitations. Our follow-up period was not long enough to evaluate late adverse events after radiosurgery (6), although it would be appropriate to observe early radiation injury that usually occurs 6 months to 2 years after radiosurgery (2, 6). Longer follow-up would be necessary to investigate whether delayed radiation-induced neuropathy does not affect our result.

Furthermore, the obliteration rate in this study group was low, probably because the median follow-up period of 23 months was shorter than that usually necessary for nidus obliteration, which is 3–5 years (22). One concern is that obliteration on imaging or subsequent prevention of future hemorrhage, which is the therapeutic goal of radiosurgery for arteriovenous malformations, can be compromised by modification of treatment planning by referring to tractography. Therefore, we need to prove, by longer follow-up, that this technique can provide morbidity prevention without lowering the obliteration rate.

Another limitation of tractography is its reliability. There is no guarantee that fibers do not exist where the tracts is not drawn (17, 23). However, tractography has been proven to reflect anatomic pyramidal tract functioning in intraoperative fiber stimulation analysis (24). Therefore, as indicated in this study, irradiation while paying attention to firmly depicted fibers could sufficiently prevent morbidity, and practically this is the best and the only way to prevent morbidity.

The fact that the rate of tractography integration was higher in the last 2 years suggests the feasibility and usefulness of the procedure. We hope our technique will also be applied to future treatment planning software so that even physicians who are unfamiliar with complicated imaging processing can utilize our methodology (10).

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Outcomes of Radiosurgery for Brainstem Arteriovenous Malformations

Tomoyuki Koga, MD*
Masahiro Shin, MD, PhD*
Atsuro Terahara, MD, PhD‡
Nobuhito Saito, MD, PhD*

Departments of *Neurosurgery and ‡Radiology, University of Tokyo Hospital, Tokyo, Japan

Correspondence:
Tomoyuki Koga, MD,
Department of Neurosurgery,
University of Tokyo Hospital, 7-3-1
Hongo, Bunkyo-ku,
Tokyo 113-8655, Japan.
E-mail: kouga-tky@umin.ac.jp

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BACKGROUND: Arteriovenous malformations (AVMs) in the brainstem yield a high risk of hemorrhage. Although stereotactic radiosurgery (SRS) is accepted, because of high surgical morbidity and mortality, outcomes are still unclear.

OBJECTIVE: We previously reported the early results of SRS for brainstem AVMs. Here, we obtained data from a longer follow-up for a larger number of patients and present precise outcomes based on the latest follow-up data.

METHODS: Forty-four patients with brainstem AVMs were treated by SRS. Outcomes such as the rates of obliteration, hemorrhage after treatment, and adverse effects were retrospectively analyzed.

RESULTS: The annual hemorrhage rate before SRS was 17.5%. The mean follow-up period after SRS was 71 months (range, 2-168 months). The actuarial obliteration rate confirmed by angiography was 52% at 5 years. Factors associated with higher obliteration rate were previous hemorrhage ($P = .048$) and higher margin dose ($P = .048$). For patients treated with a margin dose of ≥ 18 Gy, the obliteration rate was 71% at 5 years. Persistent worsening of neurological symptoms was observed in 5%. The annual hemorrhage rate after SRS was 2.4%. Four patients died of rebleeding, and disease-specific survival rate was 86% at 10 years after treatment.

CONCLUSION: Nidus obliteration must be achieved for brainstem AVMs because they possibly cause lethal hemorrhage even after SRS. Treatment with a high margin dose is desirable to obtain favorable outcomes for these lesions. Additional treatment should be considered for an incompletely obliterated nidus.

KEY WORDS: Arteriovenous malformation, Brainstem, Gamma knife, Stereotactic radiosurgery

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Arteriovenous malformations (AVMs) involving the brainstem yield a high risk of hemorrhage and are often life-threatening.[1-4] Treatment modalities for these lesions include surgery, as reported in several series.[3-5] Stereotactic radiosurgery (SRS) is another option to treat brainstem AVMs to avoid risks of surgical removal. Although there are several reports of results of SRS for brainstem AVMs,[1,2,6,7] the precise outcomes are largely unknown because of the rarity of these lesions. We previously reported the results of SRS for 30 patients with brainstem AVMs and concluded that lower-dose treatment leads to treatment failure.[1] Thereafter, we have principally treated brainstem AVMs with enough margin ≥ 18 Gy on the basis of previous experience. To reevaluate the treatment outcomes of SRS for brainstem AVMs using the latest data available, we retrospectively analyzed outcomes of 44 patients with brainstem AVMs who underwent SRS at our institute.

ABBREVIATIONS: AVM, arteriovenous malformation; **SRS,** stereotactic radiosurgery

PATIENTS AND METHODS

Clinical Materials

Between July 1990 and October 2009, 44 patients with brainstem AVMs were treated by SRS at our institute with the Leksell Gamma Knife. The AVMs with a nidus that was partially or entirely located in the midbrain, pons, and medulla oblongata were defined as brainstem AVMs. The AVMs in the cisternal portion without involvement of brainstem parenchyma were excluded from this study. In all patients, diagnosis was confirmed with cerebral angiography in combination with computed tomography (CT) or magnetic resonance imaging (MRI). Patients with an AVM nidus that had a largest diameter of < 3 cm were treated by SRS. One patient underwent evacuation of a hematoma in the cerebellum before SRS. One patient required ventricular drainage for acute hydrocephalus caused by intraventricular hemorrhage, and the other underwent ventriculoperitoneal shunt for obstructive hydrocephalus. Two patients were treated by endovascular approach before SRS. No patient underwent surgical removal of the nidus before SRS. The extent of the nidus was visually confirmed by at least 2 neurosurgeons on CT or MRI. The volume of this visually confirmed nidus was then calculated with computer software (Leksell GammaPlan, Elekta Instruments AB, Stockholm, Sweden) and was defined as AVM volume in this study. The modified radiosurgery-based grading system scores (AVM scores) proposed by Pollock and Flickinger[8] were also used to evaluate patient outcomes, calculated according to the following equation in brainstem AVMs: $0.1 \times$ (AVM volume in cm^3) + $0.02 \times$ (patient age in years) + 0.3×2.

The clinical characteristics are summarized in Table 1. Locations of AVMs were ventral midbrain, dorsal midbrain, pons, cerebellopontine angle, and medulla oblongata in 8, 8, 13, 8, and 6 patients, respectively. Forty-four patients were followed up for 2 to 168 months (mean, 71 months; median, 49 months) after SRS. Among them, 41 patients were followed up for > 1 year. Patient age at the time of SRS ranged from 5 to 68 years (mean, 40 years; median, 39 years). The mean largest diameter of the nidus was 16 mm (range, 7.5-27 mm). The mean nidus volume was 1.3 cm^3 (range, 0.1-3.9 cm^3). The mean radiosurgery-based AVM score was 1.52 (range, 0.75-2.13). Thirty-six patients (82%) experienced 46 hemorrhages before SRS. Between the time of diagnosis and SRS, excluding the first bleedings in patients who presented with hemorrhage, 10 hemorrhages were observed during 57 patient-years. By the person-years method, the annual hemorrhage rate after initial presentation until SRS was 17.5%. At the time of SRS, 31 patients (72%) showed neurological deficits caused by past hemorrhage. They presented with motor weakness in 10 (23%), sensory disturbance in 9 (20%), cerebellar ataxia in 11 (25%), and cranial nerve symptoms in 25 (57%). For SRS with the Gamma Knife, the maximal dose ranged from 20 to 50 Gy (mean, 37 Gy; median, 40 Gy) and margin dose ranged from 10 to 20 Gy (mean, 19 Gy; median, 20 Gy).

TABLE 1. Clinical Characteristics and Radiosurgical Dosimetry for Patients With Brainstem Arteriovenous Malformations

Characteristics	Value
No. of patients in analysis	44
M/F ratio	29/15
Age, y	
Range	5-68
Mean	40
Median	39
Clinical presentation, n (%)	
Hemorrhage	36 (82)
Headache	4 (9)
Incidental	2 (5)
Neurological deficit, n (%)	
No deficit	12 (27)
Motor deficit	10 (23)
Sensory disturbance	9 (20)
Cerebellar ataxia	11 (25)
Cranial nerve symptoms	25 (57)
Previous treatment, n (%)	
No previous treatment	39 (89)
Endovascular embolization	2 (5)
Hematoma evacuation	1 (2)
Ventricular drainage	1 (2)
Ventriculoperitoneal shunt	1 (2)
AVM score	
Range	0.75-2.13
Mean	1.52
Median	1.51
Radiosurgical dosimetry	
Maximum dose, Gy	
Range	20-50
Mean	37
Median	40
Margin dose, Gy	
Range	10-20
Mean	19
Median	20

Radiosurgical Treatment

After the Leksell stereotactic frame was fixed on the patient's head, the patient underwent stereotactic imaging to obtain precise information on the shape, volume, and 3-dimensional coordinates of the AVM nidus. Only biplanar stereotactic cerebral angiography was used for radiosurgical dose planning until February 1991. Thereafter, CT or MRI was used in combination with angiography. Treatment planning was jointly performed by neurosurgeons and radiation oncologists using commercially available software. The first-generation treatment planning software (KULA, Elekta Instruments AB), with which prescribed dose planning was manually superimposed on radiographic imaging films, was used until September 1998. Advanced planning software (Leksell GammaPlan, Elekta Instruments AB), which enabled us to display multiple radiographic images on the computer screen and simultaneously superimpose isodose lines on them, was used thereafter. In principle, the ideal dose applied to the margin of each AVM nidus was ≥ 18 Gy. However, 7 of 9 patients (78%) who underwent treatment until August 1991 were treated by margin doses < 17 Gy to avoid the risk of radiation injury.

Follow-up Evaluation and Statistical Analysis

After SRS, follow-up clinical examinations were performed at our hospital or by referring physicians. Serial cerebral angiography was performed every year until 1992. After 1993, the patients underwent CT or MRI with contrast enhancement every 6 months, and angiography was performed when obliteration of the AVM nidus was strongly suggested on those images.

Excellent outcome was defined as complete nidus obliteration without hemorrhage after treatment or adverse events.

Statistical analyses were performed with JMP 8 (SAS Institute Inc, Cary, North Carolina). The actuarial obliteration rate was calculated with the Kaplan-Meier method. The Cox proportional hazard model was used for univariate and multivariate analyses to evaluate factors potentially affecting nidus obliteration and adverse effects.

RESULTS

Obliteration Rate

Complete nidus obliteration was confirmed on angiography studies (Figure 1) in 20 patients (45%) within 6 to 75 months (median, 24 months) after SRS. The actuarial rates of AVM obliteration confirmed by angiography were 44% at 3 years and 52% at 5 years. In 2 cases, MRI demonstrated complete obliteration of the AVM nidus without angiographic confirmation. When these cases are counted as having complete obliteration of the nidus, the obliteration rates were 48% at 3 years and 57% at 5 years.

In other patients, no radiological change in nidus was confirmed in 4 patients by angiography and 1 patient by MRI. Reduction of nidus volume was confirmed in 5 patients by angiography (Figure 2) and 13 patients by MRI. One patient died of hemorrhage before a follow-up imaging study was performed. If complete obliteration was not obtained, all patients were conservatively observed without additional treatment.

Factors significantly associated with higher obliteration rate in the multivariate analysis were hemorrhagic onset (P = .048) and higher margin dose (P = .048; Table 2). For 37 patients who underwent treatment with a margin dose ≥ 18 Gy, the actuarial obliteration rate was 57 at 3 years and 71% at 5 years (Figure 3). Among 8 patients without prior hemorrhage, 6 patients were prescribed ≥ 18 Gy. On the other hand, 31 of 36 patients with a history of hemorrhage underwent treatment with a margin dose

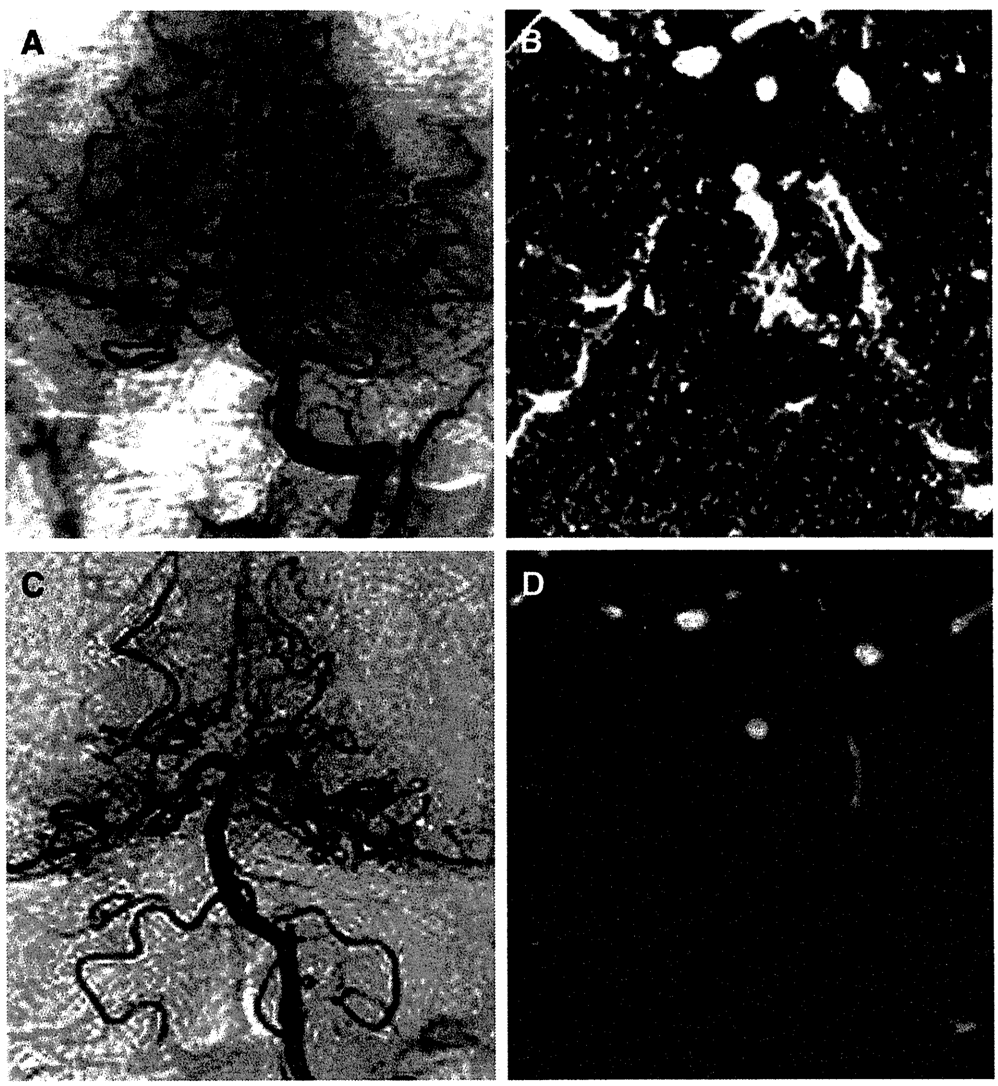

FIGURE 1. **A** *and* **B**, *pretreatment angiography* (**A**) *and MRI* (**B**) *of an arteriovenous malformation in the midbrain that presented with hemorrhage. A margin dose of 20 Gy was prescribed for the 2.9-cm*^{3} *nidus.* **C** *and* **D**, *complete nidus obliteration was confirmed 24 months after stereotactic radiosurgery by angiography* (**C**) *and MRI* (**D**).

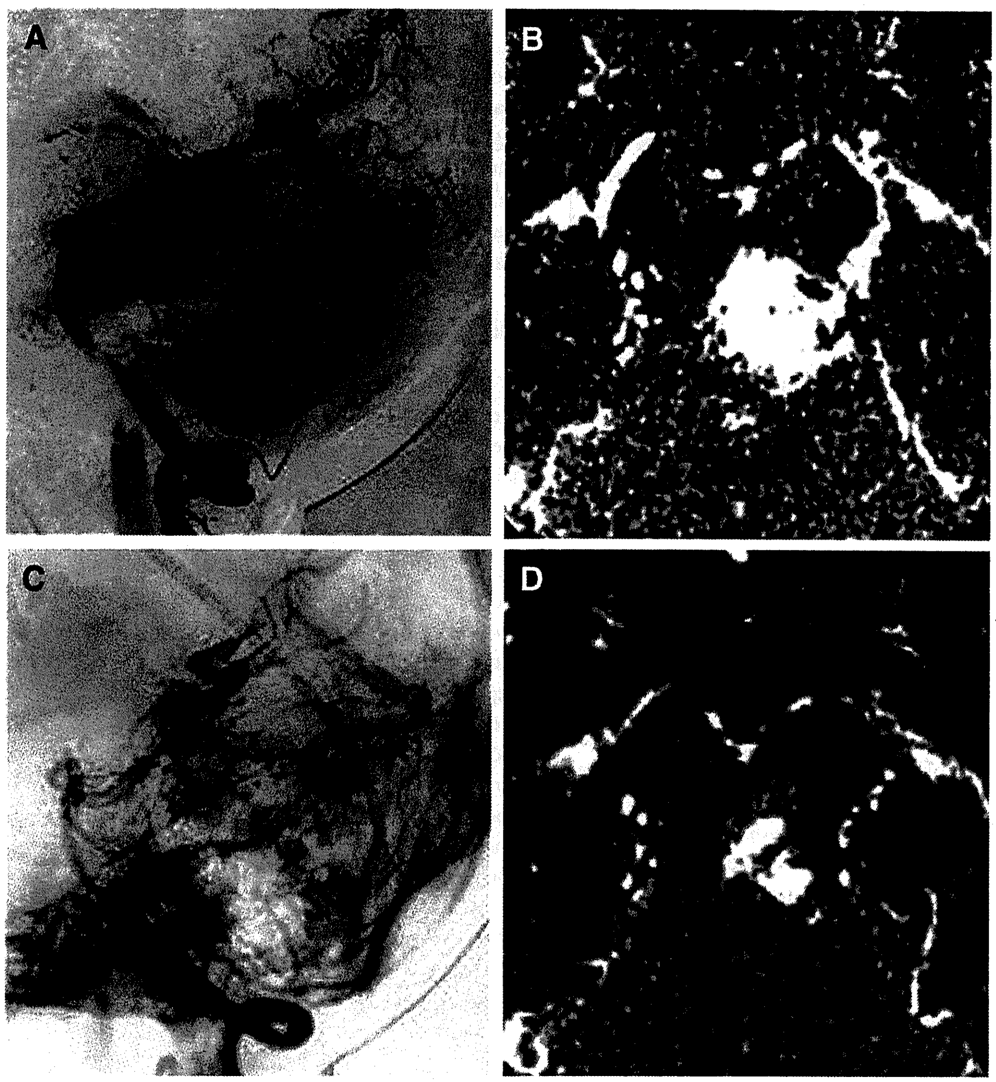

FIGURE 2. **A** *and* **B**, *pretreatment angiography* (**A**) *and MRI* (**B**) *of an arteriovenous malformation in the midbrain that presented with hydrocephalus. A margin dose of 17 Gy was prescribed for the 1.9-cm*^{3} *nidus.* **C** *and* **D**, *incomplete nidus obliteration was confirmed 48 months after stereotactic radiosurgery by angiography* (**C**) *and MRI* (**D**).

≥ 18 Gy. There was no significant correlation between history of hemorrhage and applied margin dose.

Complications and Hemorrhagic Events

Five patients (11%) developed T2-hyperintensity regions around an irradiated field confirmed by MRI 5 to 12 months (median, 7 months) after SRS. Neurological deterioration caused by radiation injury was observed in 2 patients (5%) 7 months after SRS. Of these 2 patients, 1 experienced transient ptosis, which lasted for 1 month, and the other presented permanent upward-gaze palsy.

Six patients experienced 6 hemorrhages 1 to 93 months (median, 15 months) after treatment during 253 patient-years. The annual hemorrhagic risk after SRS was 2.4%. All post-treatment hemorrhages occurred before angiographic confirmation of nidus obliteration. There was no bleeding after nidus obliteration in this cohort during 77 patient-years. The characteristics of the patients who suffered from hemorrhage after treatment are described in Table 3. Although age, volume, location of the nidus, AVM score, and number of hemorrhages before treatment were examined, there was no statistically significant factor associated with hemorrhage after treatment. Four

TABLE 2. Factors Associated With Angiographically Confirmed Obliteration of the Arteriovenous Malformation Nidus After Stereotactic Radiosurgery[a]

Factor	P		95% Confidence Interval	
	Univariate	Multivariate	Lower	Upper
Sex	.72	.83	0.413	3.312
Hemorrhage before treatment	.049[b]	.048[b]	1.013	104.870
AVM score	.99	.37	0.476	7.015
Use of advanced software in dose planning	.94	.88	0.247	2.860
Margin dose	.001[b]	.048[b]	1.169	4.032

[a]AVM, arteriovenous malformation.
[b]$P < .05$.

patients died of rebleeding 1 to 93 months (median, 27 months) after SRS. Therefore, the disease-specific survival rate at 3, 5, and 10 years was 95%, 92%, and 86%, respectively. Of the 4 patients who died of hemorrhage after treatment, 2 patients had lesions in the pons, 1 had a dorsal midbrain lesion, and the other had a lesion in the ventral midbrain. There was no correlation between nidus location and death. There was no significant factor associated with each radiation-induced neurological adverse effect and mortality caused by rebleeding in this cohort.

For 37 patients who underwent treatment with a margin dose ≥ 18 Gy, nidus obliteration without adverse events or hemorrhage after treatment (excellent outcome) was achieved in 20 (54%) (5 of 7, 2 of 6, 5 of 10, 4 of 8, and 4 of 6 in patients with ventral midbrain, dorsal midbrain, pons, cerebellopontine angle, and medulla oblongata AVMs, respectively; Figure 4).

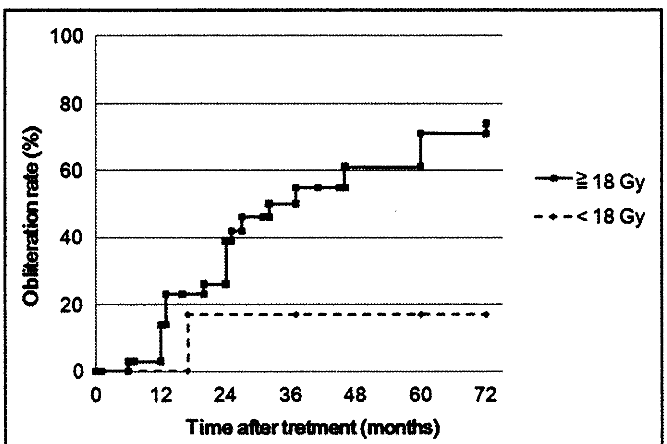

FIGURE 3. *Kaplan-Meier curve showing cumulative rate of complete nidus obliteration stratified by margin dose.*

There was no statistical difference between locations. Excellent outcome was achieved in 10 of 20 patients (50%) whose AVM score was < 1.5 and 10 of 24 patients (42%) whose AVM score was ≥ 1.5. There was no statistical difference between these 2 groups. Furthermore, excellent outcome was achieved in 1 of 6 patients (17%) who underwent treatment planned only by angiography and in 19 of 38 patients (50%) who underwent treatment planned by angiography plus CT or MRI, although it was not statistically different ($P = .20$).

DISCUSSION

Deep-seated AVMs possess higher hemorrhagic risk and are more likely to cause devastating hemorrhage.[9-12] The annual bleeding rate of untreated brainstem AVMs is reported to be 15.1%,[3] which is consistent with our results, and the annual rate of rebleeding is 17.8%.[13] Considering this high risk of hemorrhage associated with brainstem AVMs, earlier extirpation is desirable before repeated hemorrhages. For this purpose, microsurgical resection can be a preferable treatment option. However, surgery can be applicable for only limited cases, and morbidity and mortality associated with surgical removal are not negligible, ranging from 20% to 25% and from 0 to 20%, respectively.[3,4,14] Because the associated risks depend largely on the nidus location within the brainstem, safe removal is not feasible for AVMs located in the ventral midbrain, pons, and medulla oblongata.[3] On the other hand, as for SRS, we found that there was no significant difference in outcomes among each location within the brainstem, and the associated morbidity was less than that with surgical removal, which was reported to range from 5% to 12%.[1,2,6,7] Despite the result that annual bleeding rate was reduced from 17.5% to 2.4% after SRS, hemorrhage from incompletely obliterated nidus can be critical and remains an issue of major concern. The rate of complete obliteration was 52% at 5 years and was lower than that of AVMs in other locations. This lower obliteration rate is consistent with other reports of results of radiosurgery for deeply located AVMs involving brainstem AVMs, which were 43% to 66%.[2,6] As discussed in other reports,[6] the intention to reduce the treated volume to reduce the risk of complications might have led to insufficient coverage of the entire nidus and thus resulted in a lower obliteration rate. At present, it is important to deliver a sufficient margin dose for small AVMs, ideally > 18 Gy, to achieve complete nidus obliteration on SRS. Radiation tolerance limit of the brainstem is controversial despite precise analyses.[15] However, a higher margin dose may cause severe radiation adverse events. Because the evidence of SRS for brainstem AVM is limited, we should carefully apply higher doses, and cautious follow-up is mandatory. An AVM score > 2.25 was associated with poor outcomes in a previous report,[6] although no patients in our series had a score > 2.25. For brainstem AVMs, an AVM score of 2.25 corresponds to a 12.5-cm^3 nidus in a 20-year-old patient, a 8.5-cm^3 nidus in a 40-year-old patient, or a 4.5-cm^3 nidus in a 60-year-old patient. Therefore, an AVM with a score

TABLE 3. Characteristics of the Patients Who Suffered From Hemorrhage After Treatment[a]

Age, y	Location	Volume, cm^3	AVM Score	No. of Hemorrhages Before Treatment	Timing of Hemorrhage After Treatment, mo	Outcomes After Treatment
24	Dorsal midbrain	0.4	1.12	1	1	Alive
56	Dorsal midbrain	3.6	2.08	0	93	Dead
37	Pons	0.2	1.36	1	1	Dead
53	Pons	0.4	1.70	2	37	Dead
45	Ventral midbrain	0.5	1.55	2	16	Dead
64	Cerebellopontine angle	2.5	2.12	1	13	Alive

[a]AVM, arteriovenous malformation.

< 2.25 or a nidus volume that is smaller than approximately 10 cm^3 might be a good candidate for SRS. For larger lesions, multimodality treatment strategy combined with SRS, surgical removal, and endovascular treatment should be discussed.[3,5,16] Because there was no evidence regarding repeated treatment for brainstem AVMs, we conservatively observed the patients for whom complete obliteration could not be achieved. However, concerning the aggressive nature of brainstem AVMs even after SRS, additional treatment should be considered because the safety and efficacy of repeated radiosurgery or surgical removal for incompletely obliterated AVMs in other locations have been established.[17,18] Although obliteration rates changed from 57% to 71% between 3 and 5 years after treatment, it is not clear whether this result warrants observation even 3 years after treatment. Concerning aggressive hemorrhage from an incompletely obliterated nidus, retreatment or microsurgical resection might be considered for incompletely obliterated lesions at about 3 years after first SRS.[18] In our series, previous hemorrhage was associated with higher obliteration rate, consistent with previous reports.[19,20] Although the reasons for this association are not clear, the endothelial damage caused by the hemorrhage possibly promotes occlusion of the internal lumen and thrombosis of AVMs, as indicated in previous studies.[21-23]

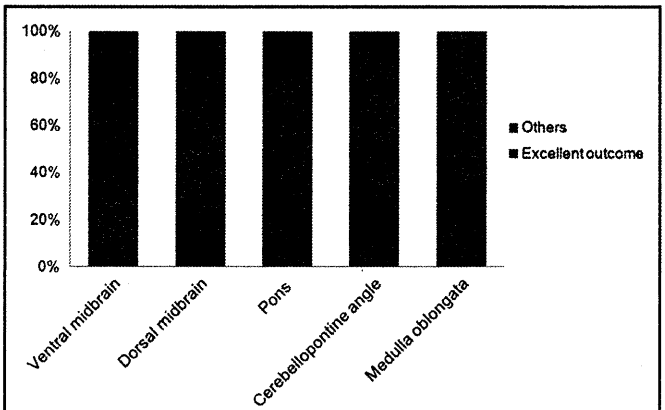

FIGURE 4. *The number and rate of patients for whom complete nidus obliteration without new deficit or rebleeding was achieved in each location.*

Delayed complications such as hemorrhage from obliterated AVMs, chronic encapsulated expanding hematoma, and delayed cyst formation were not observed in our cohort, probably owing to the relatively small size and deep location, because it is known that larger AVMs at lobar locations are at higher risk for those adverse events.[24] However, these late complications occur even > 10 years after treatment, and evaluating the incidence now is premature. At present, those complications are reported as relatively rare phenomena,[24] but the cumulative risk might be much higher in young patients with long lives ahead of them. Therefore, continual follow-up is recommended even after AVM obliteration has been demonstrated on angiography. In this study, we presented the outcomes of SRS for brainstem AVMs on the basis of our maximum follow-up data, but SRS is a relatively new treatment modality, and our knowledge of its long-term risks is still limited. We need to observe patients carefully for longer periods.

CONCLUSION

From the long-term follow-up data, we confirmed that a sufficient margin dose was necessary to effectively obliterate brainstem AVMs. Even with sufficient doses, radiation-related morbidity was relatively low, and SRS was considered to be acceptable as an alternative treatment for small brainstem AVMs. Because incompletely obliterated lesions could cause lethal hemorrhage, additional treatment, including reirradiation and surgical resection, should be considered when complete obliteration cannot be achieved by first SRS. Arteriovenous malformations, especially in the ventral midbrain, pons, and medulla oblongata, where total surgical removal is difficult, would be a good candidate for SRS. However, for large AVMs or lesions in the dorsal midbrain or cerebellopontine angle, surgical removal or a combination of SRS, surgery, and endovascular treatment might be appropriate. The incidence and the risk of delayed complications are still not clear, and we should continue to observe patients carefully, even after angiographic obliteration has been confirmed after SRS.

patients remained neurologically worse, and 2 died of rebleeding (4,4%). In line with Koga et al, we think that our series demonstrates that much better results may be obtained with the use of a higher dose in the treatment regimen. Instead of a dramatic reduction in the marginal dose, safety must be ensured by a cautious analysis of the angioarchitecture on the stereotactic angiography and magnetic resonance imaging and confinement of the treatment volume to the nidus proper with the exclusion of arterial feeders, draining veins, and perinidal angiogenesis. Risk prediction models like the one reported by Flinkinger et al[2] are very useful, but they must not be misused. They must be applied with the following 2 major principles kept in mind: These models do not take into account the role of the degree and extent of restrictive definition of the target to the nidus proper, and the worst postradiosurgery complication is bleeding in the brainstem.

Jean Regis
Marseille, France

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Koga et al report the outcomes of Gamma Knife radiosurgery in a select group of patients with arteriovenous malformation (AVMs) in critical areas of the brainstem. Because of these locations, optimal doses for obliteration have to be tempered by the risk of adverse radiation effects in valuable real estate. They confirm that a minimal dose to the AVM margin of ≥ 18 Gy can enhance the obliteration rate. In this series, the rate by 5 years is as high as 57% of patients. We believe that the radiosurgical technology must provide excellent conformality of the 3-dimensional dose delivery and high selectivity of the dose, so that critical structures receive tolerable doses of radiation. Both volumetric magnetic resonance imaging and angiography must be used to target the AVM. Residual AVMs after a period of 3 to 5 years must have additional options considered because the hemorrhage rate continues to present major morbidity or mortality risks to the patient. Relatively few patients will benefit from endovascular techniques because total obliteration is almost never achieved and volumes are frequently the same after embolization, even if flow is reduced to a component of the AVM. Some patients may become eligible for surgery at centers with excellent microsurgical skills. Some patients will benefit from repeat radiosurgery. The risk-benefit analysis in brainstem AVM patients is quite complex.

L. Dade Lunsford
Pittsburgh, Pennsylvania

特集 …第40回放射線による制癌シンポジウム―基礎と臨床の対話―…

2. 寡分割照射の基礎と臨床

ガンマナイフによる定位手術的照射（SRS）

寺 原 敦 朗[*1]

Stereotactic Radiosurgery with Gamma Knife: Terahara A[*1] ([*1]Department of Radiology, Toho University Omori Medical Center)

The first Gamma Knife in Japan was installed in 1990. Treatment methods and strategies have changed mainly based on a lot of clinical experience and data accumulated in the past 20 years, not on basic data from radiation biology. The prescribed peripheral doses for radiosurgery, for instance, were selected and changed based on a thorough consideration of clinical results for desired endpoint such as obliteration of AVM and tumor control and also adverse effect including brain necrosis and cranial nerve injury, taking into account dose-volume analysis. Since there are still many unresolved questions for radiosurgery, approach from a standpoint of basic radiation biology will be also required.

Key words: Gamma Knife, Radiosurgery, SRS, AVM

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はじめに

スウェーデンの脳神経外科医であったレクセルが，1951年に定義した定位手術的照射（SRS: stereotactic radiosurgery）を実現するために考案されたのがガンマナイフであり，1968年にその最初のユニットが誕生している．当初は三叉神経痛，癌性疼痛などといった通常の脳外科的治療によってコントロールできない機能的障害を治療する目的で用いられたが，CT, MRIといった画像診断の発達もあり，現在では小さな脳動静脈奇形（AVM）や脳腫瘍などの治療に広く用いられるようになっている．

日本においては，1990年に東京大学医学部附属病院に最初のガンマナイフが導入され，今年で20年となる．導入当初はAVMおよび聴神経腫瘍，髄膜腫といった良性腫瘍の治療に主に用いられていたが，高度先進医療から保険適応となった頃から，転移性脳腫瘍の治療にも広く用いられるようになり，導入施設も急速に増加し，2010年12月の時点で，56施設に設置されている．その放射線治療における役割についても一定の評価が得られ，確立した治療方法として認められている．

日本に最初に導入された当時は，まだ臨床データも少なく，1回大線量照射であるため通常分割照射のデータを応用することも難しく，その適応や治療効果，有害事象，適切な照射法や処方線量などについて明らかでない点も多かった．治療計画システムも現在のような洗練されたものではなく，ある断面における線量分布を紙にプロットして画像フィルムに重ねて評価するという原始的な方法であった．治療計画に用いる画像の質も含めて，治療の質は現在よりもやや劣っていたと思わ

*1 東邦大学医療センター大森病院放射線科

れる.

この20年間の臨床経験の蓄積により，様々な知見が得られ，一部では治療方法の改良，変更も行われてきた．この稿ではその歩みを振り返ってみたい.

1 ○ AVMに対するガンマナイフSRS

AVMに対するSRSの目的は，出血を予防するためにnidusの閉塞を得ることである．1990年当時，辺縁線量20〜25 Gyで治療を行えば，2年後に8〜9割に閉塞が得られ，有害事象発生率は3%と言われていた.

当初は血管造影検査の画像のみで治療計画を行っていたが，それだけではターゲットとなるnidusの3次元的形状が分からないため，造影CTを参考とするようになった．さらに定位的画像としての造影CTやMRIを併用して治療計画を作成するようになり，nidus部をより正確に同定して治療を行うことが可能となり，nidus閉塞率も向上している[1)]．治療計画システムが前世代のKulaから現在のGammaPlanに変更され，各種画像を直接システム内で連携して扱えるようになったことも大きな改善であった.

Nidus閉塞率は，当初言われていた数字よりはやや低く，3年で7割程度，5年で8〜9割程度であり，閉塞までにかなり長期間かかる場合があることもわかってきた[1)]．また，治療後の出血のリスクについてもデータが集積され，nidusの閉塞が得られる前にも出血のリスクは5割ほど減少していることが示された[2)]．逆にnidus閉塞が得られた後も出血リスクは完全になくなるわけではなく，9割程度のリスク減少が得られ[2)]，年に0.3%，10年で2.2%の累積リスクがあることもわかってきた[3)]．Nidusが小さく，辺縁線量が高い方が有意に閉塞率が高いというデータも出ているが，小さなAVMは高い線量で照射されることが多かったことと，線量分布の不均一性の影響も含めて検討するため，容積で補正したEUD（equivalent uniform dose）を用いた解析を行った．その結果，治療容積およびEUDが閉塞率に関する有意な因子であり，辺縁処方線量は有意ではなかった．また容積の大きなAVMでは，閉塞するまでの期間が長い傾向はあるものの，最終的な閉塞率はあまり変わらなかったこと，また23 Gy以上の線量増加では閉塞率の向上はほとんど認められないという報告もあり，有害事象のリスクも考慮して，東大病院では原則として辺縁線量20 Gyにて治療を行っている.

症候性の有害事象発生率については，実際にはやや多く，当初は12%程度に認められていたが，7%程度に減少しており，治療計画の改善や線量の低減によるものと思われる．永続的な有害事象は1.5%であった[1)].

晩発性の有害事象については，長期経過観察によって遅発性嚢胞形成や慢性被膜化血腫などのまれな有害事象も明らかになってきた.

2 ○ 聴神経腫瘍に対するガンマナイフSRS

聴神経腫瘍に対しては，当初は辺縁線量18〜20 Gyが用いられていた．しかしながら，聴神経に平行して走行している顔面神経や三叉神経の有害事象が2〜3割に発生したことから，現在は12〜14 Gyが用いられている．また，治療計画画像にMRIを用い，処方線量域が腫瘍の形状に可及的に一致するように多数のショットを用いるといった治療法の改善とあいまって，有害事象発生率は数パーセントのレベルまで減少している．有用な聴力が残っている場合には，治療後の聴力温存が5〜8割程度で可能となっている．処方線量を下げても，局所制御率（良性腫瘍であるので腫瘍が消失する必要はないため，治療が必要となる腫瘍の増大が認められていない率）は，85〜97%と良好な成績が報告されている[4)].

3 ○ 髄膜腫に対するガンマナイフSRS

髄膜腫に対しても当初は18〜20 Gy程度の辺縁線量が用いられていたが，最近では14〜18 Gy程度のやや低めの線量が用いられ，聴神経と同様の定義での局所制御率は，85〜95%と報告されている．さらにより低線量でも局所制御可能との

報告もあり，辺縁線量12～14 Gyにて治療を行っている施設もある．手術による全摘が困難な頭蓋底部の髄膜腫に対しては，SRSが良い適応とされ，小さな腫瘍であればSRS単独で，大きな腫瘍であれば可及的切除後に残存腫瘍に対してSRSが行われる．腫瘍摘出後の残存腫瘍再増大，再発腫瘍に対しても有用である．また，傍矢状洞部付近の腫瘍に対するSRSでは，症候性の脳浮腫をきたす頻度が高いため，注意が必要であることもわかってきた．

4 下垂体腫瘍に対するガンマナイフSRS

下垂体腫瘍に対しては，ホルモン非産生腫瘍の場合は辺縁線量15～20 Gy程度の照射を行うことで，局所制御率は95%以上との良好な報告が多いが，ホルモン産生腫瘍の場合は辺縁線量25～35 Gy程度の照射が必要とされ，クッシング病や成長ホルモン産生腫瘍といったホルモン産生腫瘍におけるホルモン値についての奏効率は，報告によって差があるが，5～8割程度の奏効率となっている[5]．また，視力低下を避けるために，視神経から視交叉への線量を8～10 Gy以下におさえる必要があるとされている．

5 転移性脳腫瘍に対するガンマナイフSRS

転移性脳腫瘍は悪性腫瘍であるが，数として数個程度までで，径3 cm以内であれば，その他の条件も考慮した上でガンマナイフSRSの良い適応になると考えられる．ガンマナイフSRSが保険適応となったこともあり，日本においては，現在最もSRS患者数が多い疾患であり，全体の約6割を占めている．

辺縁線量としては18～25 Gy程度がよく用いられ，局所制御率は8～9割程度と報告されており，外科的手術と同程度の制御率が得られているが，大きな腫瘍ほど，制御率が低い傾向であることが報告されている．短期間で治療が終了し，症状の改善も比較的早期に得られる場合が多いことと，全脳照射のみよりも局所制御率が高い上に，正常脳全体への影響が少なくできることから，QOLの面からもより好ましい治療として広く用いられている．また，施設によっては，多数の脳転移に対しても全脳照射を行わず，積極的にSRSを用いた治療を施行している．脳転移の個数についてなど，ガンマナイフSRSの適応限界を明確にすることなどを目的として，Japan Leksell Gamma Knife Society Study Groupによる多施設共同臨床試験も行われている．

6 ガンマナイフSRSにおける容積効果（volume effect）

ガンマナイフを用いたSRSでは，1回大線量放射線照射が行われるが，この線量は，通常の放射線治療に用いられる線量に比較してかなり高い．このような治療が許される背景には，照射容積が小さい場合には，正常組織の耐容線量が高くなるという，いわゆる“容積効果（volume effect)”がある．SRSの治療容積は径3 cm以下であることが多いが，この程度の小さな容積の範囲においても，容積が小さければ高線量の照射が可能であり，容積が大きくなるにしたがって，線量を下げるべきであるという，線量―容積関係が存在していると考えられている．ガンマナイフ治療においては，治療後の画像上の変化の発生率が他の腫瘍症例に比較して高いAVM症例において，主にこの件に関する検討が行われてきた．

Kjellbergらは，陽子線を用いたAVMに対するSRSの結果を1983年に報告しており[6]，臨床および実験データをもとに，1%線量容積等効果ラインを設定している．これは照射ビームの径と線量をそれぞれ対数軸にとり，径7 mmで50 Gy，径50 mmで10.5 Gyの点を結んだ直線で，これより低い線量にて治療を行えば，障害発生率は1%以下になるというものである．

Flickingerらは，SRSの障害を予測するための線量容積効果モデルを提唱している[7]．これはロジスティックモデル（logistic model）をもとにしたもので，正常の脳組織は障害発生に関しては，同様に反応すると考え，あるレベルの線量が

照射された場合には，ある一定の確率で壊死が起こるとして計算されている．このモデルによる3%の障害発生確率を示す線量容積等効果ラインが，Kjellbergらの提唱した1%線量容積等効果ラインとも良く一致していたため，このラインがSRSにおいて線量を決定する際のガイドラインの一つとして用いられていた．但し，このモデルでは，正常組織の部位の違いによる照射に対する反応の違いは考慮されておらず，また，実際には，このラインの下側で治療を行った場合でも，3%よりも多い有害事象の発生が認められていた．

Flickingerらは，AVMに対するSRS後の画像上の変化について，線量容積データとの関係を解析し，1992年に報告している[8]．画像上の変化の出現と様々な線量容積パラメーターやその他の因子との関係を解析した結果，多変量解析では，治療容積のみが有意な因子であり，線量容積効果モデル（integrated logistic formula）はそれ以上の障害発生予測因子とはなっていなかった．元々この障害発生確率は，治療後の画像変化の発生確率ではなく，永続的な症状を発現する確率を算出するモデルとして考案されているため，この報告の中で使われていたパラメーターの値が適切でなかった可能性もある．

そこで，その後Flickingerらは，さらに症例を集積し，より臨床において用いやすいモデルについて検討している．AVMに対するガンマナイフSRS後の画像上の変化出現には12 Gy以上が照射された容積（V12）が，症候性の有害事象にはそれと部位が有意な因子であったと報告している[9]．さらに，永続的な症状発現に関して，V12と部位による危険度スコアを用いた予測モデルを提唱している[10]．それによれば，前頭葉部は部位としては最もリスクが低く，橋/中脳部が最も高くなっていた．このモデルを用いて計算された予測リスクは，上記のガイドラインによって線量を設定していても，容積と部位によって大きく異なることが示されている[11]．

まとめ

ガンマナイフSRSは，我が国へ導入されてから20年が経過しているが，本稿で振り返ったように，基礎的あるいは実験的データではなく，あくまでも臨床経験やデータの蓄積をもとに，処方線量の変更や照射法の修正といった治療方針の見直しが行われ，徐々に変遷してきたというのが実情である．

ガンマナイフも新しい機種(パーフェクション)では照射可能領域が拡大し，将来的にはエクステンドという新しい固定器具の使用によって分割照射も可能となる見込みであり，頭部のみならず，上頸部領域の病変に対する少回数分割照射による定位放射線治療（SRT）も可能となるものと思われ，ますます適応範囲が拡大することが期待されている．その際にどのような分割回数および線量を用いるのが適切であるのかなど，まだ不明な点も多い．臨床面からのみならず，基礎面からのアプローチも重要であると思われる．

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