# Long-Term Risks of Hemorrhage and Adverse Radiation Effects of Stereotactic Radiosurgery for Brain Arteriovenous Malformations

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**BACKGROUND:** The information about long-term risks of hemorrhage and late adverse radiation effects (AREs) after stereotactic radiosurgery for brain arteriovenous malformations (AVMs) is lacking.
**OBJECTIVE:** To evaluate the long-term risks of hemorrhage and late ARE rates in patients with AVM treated with Gamma Knife surgery (GKS).
**METHODS:** We examined 1249 patients with AVM treated with GKS. The Spetzler–Martin grade was I in 313 patients (25%), II in 394 (32%), III in 458 (37%), and IV/V in 84 (7%). The median treatment volume was 2.5 $cm^3$, and the median marginal dose was 20 Gy.
**RESULTS:** The median follow-up period was 61 months. The 5- and 10-year nidus obliteration rates were 63% and 82%, respectively. The 5- and 10-year cumulative hemorrhage rates were 7% and 10%, respectively. The annual hemorrhage rate was 1.5% for the first 5 years post-GKS, which decreased to 0.5% thereafter. During the follow-up period, 42 symptomatic cyst formations/chronic encapsulated hematomas ([CFs/CEHs], 3%) and 3 radiation-induced tumors (0.2%) were observed. The 10- and 15-year cumulative CF/CEH rates were 3.7% and 9.4%, respectively.
**CONCLUSION:** GKS is associated with reduced hemorrhage risk and high nidus obliteration rates in patients with AVM. The incidence of late AREs tended to increase over time. The most common ARE was CF/CEH, which can be safely removed; however, careful attention should be paid to the long-term development of fatal radiation-induced tumors.

**KEY WORDS:** Adverse radiation effect, Arteriovenous malformation, Gamma Knife, Intracranial hemorrhage, Stereotactic radiosurgery, Vascular malformation

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Stereotactic radiosurgery (SRS) is a standard treatment for brain arteriovenous malformations (AVMs), especially those in eloquent or deep regions such as the basal ganglia, thalamus, and brainstem. Although many studies have reported the safety and efficacy of SRS for AVMs,[1-6] some patients have developed late adverse radiation effects (AREs) such as cyst formation (CF), chronic encapsulated hematoma (CEH), and, very rarely, radiation-induced tumor (RIT).[7-10] As most AVMs are intra-axial and require relatively high-dose irradiations, surrounding normal brain tissues are more prone to damage compared with SRS for other lesions. In addition, unlike brain metastases that similarly require high-dose irradiation, most patients with AVM live long after achieving complete nidus obliteration. Accordingly, it is important to ascertain the long-term safety and efficacy of SRS for brain AVMs for clinical decision making. This study, therefore, aimed to evaluate the long-term nidus obliteration rates, hemorrhage risk, and late AREs of Gamma Knife surgery (GKS) and identify their associating factors from the 30-year experience with GKS for AVM at our institute.

**ABBREVIATIONS: AHR,** annual hemorrhage rate; **AREs,** adverse radiation effects; **CEH,** chronic encapsulated hematoma; **CF,** cyst formation; **GKS,** Gamma Knife surgery; **RIT,** radiation-induced tumor; **SRS,** stereotactic radiosurgery.

Supplemental digital content is available for this article at neurosurgery-online.com.

## METHODS

### Patient Characteristics

Patient data were obtained from an institutional review board–approved database. All patients with AVM treated with GKS were included while those who



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had prior radiotherapy and those initially treated with volume-staged GKS were excluded. Between May 1991 and December 2015, 1393 patients with AVM underwent GKS at our institute. Among them, 10 had prior radiotherapy, 8 were treated with volume-staged GKS, and 126 had no clinical follow-ups; 1249 patients were thus eligible for this study. All patients provided informed consent. The patient characteristics are summarized in Table 1.

### Radiosurgical Techniques

The details of the radiosurgical procedure are summarized in Table 1. See **Text, Supplemental Digital Content 1**, http://links.lww.com/NEU/C986.

### Follow-up Evaluation

Clinical follow-up data were obtained either during patient visits to our hospital or from referring doctors. We requested MRI every 3 years for the first year post-GKS, every 6 months for the second and third years, and then every year. Angiography recommended after nidus obliteration was strongly suggested from MRI. The definition of nidus obliteration was an absence of anomalous arteriovenous shunting on angiography or a lack of abnormal flow void on MRI. Repeat GKS was recommended when MRI or angiography indicated residual nidi >3 years after the previous GKS. However, it depended on patient age or preference, particularly when the residual nidi were tiny or a high risk of radiation injury was predicted in the eloquent area. Surveillance was selected for patients who refused repeat GKS.

### Statistical Analysis

The pre-GKS annual hemorrhage rate (AHR) was calculated by dividing the total number of pre-GKS hemorrhages by the total person-years at risk before GKS. The at-risk pre-GKS interval was considered as the patient's age at the time of GKS, assuming that the AVMs were present from birth. The overall or latency interval of post-GKS AHR was calculated by dividing the total number of post-GKS hemorrhages by the total person-years at risk, which were defined as the duration from GKS to the last follow-up or nidus obliteration, respectively. Late ARE was defined as symptomatic CF/CEH or RIT that met the Cahan criteria as follows: (1) the tumor must be absent at the time of treatment and localized within the radiation field, (2) there must be a sufficient latency interval between radiation therapy and tumor development, and (3) the patient must not have a genetic predisposition to neoplasms.[11] The cumulative hemorrhage rates, nidus obliteration rates, and CF/CEH rates were calculated using the product limit of Kaplan and Meier. To analyze the factors that correlated with hemorrhages, nidus obliteration, and CF/CEH after single or repeated GKS, the following were assessed: age, sex, history of hemorrhage (ruptured vs unruptured AVM), prior craniotomy, prior embolization, Spetzler–Martin grade[12] (grades I-III vs grades IV and V), direction of drainers (superficial vs deep), eloquent areas (eloquent vs noneloquent), nidus location (deep, including the basal ganglia, thalamus, brainstem, and corpus callosum vs others), treatment year (1991-1999 vs 2000-2015), maximum dose, marginal dose, treatment volume, isodose line (%), and number of shots and procedures.[5] The factors associated with hemorrhages, nidus obliteration, and CF/CEH after GKS were determined using the log-rank test and the Cox proportional hazards model. Hazard ratios were reported with 95% CIs. The optimal cutoff point was determined using the receiver operating characteristic curve analysis. All statistical analyses were performed using SPSS Statistics for Windows, version 21.0 (IBM Corporation), with $P < .05$ considered significant.

**TABLE 1. Patient Characteristics, AVM Angioarchitectural Features, and Radiosurgical Parameters in 1249 Patients**

| Characteristic | Value |
|---|---|
| Sex | |
| Man | 759 (60.8%) |
| Woman | 490 (39.2%) |
| Age (y) | |
| Median | 33 (range, 2-84) |
| Presenting symptoms | |
| Ruptured | 762 (61.0%) |
| Unruptured | 487 (39.0%) |
| Epilepsy | 187 (15.0%) |
| Headache | 106 (8.5%) |
| Focal neurological sign | 54 (4.3%) |
| Others | 14 (1.1%) |
| Asymptomatic | 126 (10.1%) |
| Prior treatment | |
| Craniotomy | 175 (14.0%) |
| Embolization | 222 (17.8%) |
| AVM location | |
| Supratentorial lobar | 828 (66.3%) |
| Cerebellum | 110 (8.8%) |
| Thalamus | 100 (8.0%) |
| Basal ganglia | 87 (7.0%) |
| Brainstem | 76 (6.1%) |
| Corpus callosum | 48 (3.8%) |
| Spetzler–Martin grade | |
| I | 313 (25.1%) |
| II | 394 (31.5%) |
| III | 458 (36.7%) |
| IV | 77 (6.2%) |
| V | 7 (0.6%) |
| Direction of venous drainage | |
| Superficial only | 685 (54.8%) |
| Deep | 564 (45.2%) |
| Eloquent location | |
| Noneloquent | 452 (36.2%) |
| Eloquent | 797 (63.8%) |
| Mean diameter, median (mm) | 16.9 (range, 3.6-47.3) |
| Treatment volume, median ($cm^3$) | 2.5 (range, 0.1-55.3) |
| Maximum dose, median (Gy) | 38 (range, 16-55) |
| Marginal dose, median (Gy) | 20 (range, 11-30.6) |
| % isodose, median | 50% (range, 40-95) |
| Number of shots, median | 3 (range, 1-63) |

AVM, arteriovenous malformation.

### Data Availability Statement

The data that support the findings of this study are available from the corresponding author (T.H.) on reasonable request.

## RESULTS

The median clinical follow-up period was 61 months (interquartile range: 30-115). Of the 1249 patients, 645, 295, 98, and 43 patients were followed up beyond 5, 10, 15, and 20 years, respectively.



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## Survival

During the follow-up period, 7 patients died of AVM rupture, 9 of systemic diseases, 2 of suicide, 3 of suspected radiation-induced brain tumors, and 7 of unknown causes. The actuarial 5- and 10-year survival rates were 98.1% and 96.6%, respectively. There were no significant differences between the survival of patients with ruptured and unruptured AVM ($P$ = .84).

## Annual Hemorrhage Rates Before and After GKS

During the 43 590 patient-years from birth to GKS, 880 hemorrhages occurred in 762 patients. Before GKS, 670 patients experienced a single hemorrhagic episode, 72 experienced 2 episodes, 16 experienced 3 episodes, and 4 experienced ≥4 episodes. The pre-GKS AHR was 2.0% overall and was 3.6% in patients with ruptured AVMs. AVM rupture occurred in 69 patients within 5 years post-GKS and in 17 patients beyond 5 years post-GKS. The AHRs within 5 years post-GKS were 1.5% for all patients (69 hemorrhages/4525 patient-years), 1.7% for patients with pre-GKS ruptured AVMs (46 hemorrhages/2772 patient-years), and 1.5% for patients with pre-GKS unruptured AVMs (23 hemorrhages/1752 patient-years) while the AHRs beyond 5 years post-GKS decreased to 0.5% (17 hemorrhages/3332 patient-years), 0.6% (12 hemorrhages/2161 patient-years), and 0.4% (5 hemorrhages/1171 patient-years), respectively. During the latency period from GKS to nidus obliteration, the AHRs within 5 years were 1.9% for all patients (59 hemorrhages/3093 patient-years), 2.2% for patients with pre-GKS ruptured AVMs (39 hemorrhages/1812 patient-years), and 1.7% for patients with pre-GKS unruptured AVMs (23 hemorrhages/1353 patient-years) while those beyond 5 years post-GKS were 2.0% (16 hemorrhages/804 patient-years), 2.8% (12 hemorrhages/432 patient-years), and 1.1% (4 hemorrhages/373 patient-years), respectively. No hemorrhages were reported after nidus obliteration, except for CEHs.

## Cumulative Hemorrhage Rate

The cumulative hemorrhage rates post-GKS were 4.9%, 6.9%, 9.7%, 11.2%, and 13.0% at 3, 5, 10, 15, and 20 years, respectively (Figure 1A). The factors associated with post-GKS hemorrhage are summarized in Table 2 (detailed in **Text, Supplemental Digital Content 2**, http://links.lww.com/NEU/C987 and **Figure, Supplemental Digital Contents 3**, http://links.lww.com/NEU/C988). Treatment volume alone was significantly associated with AVM rupture ($P$ = .003, hazard ratio 1.040, 95% CI: 1.013-1.068). Treatment volume ≥3 $cm^3$ affected a higher risk of post-GKS hemorrhages significantly, compared with treatment volume <3 $cm^3$ ($P$ < .001, Figure 1B).

## Nidus Obliteration Rates

Follow-up radiological data for the evaluation of nidus obliteration were either insufficient (with MRI results only) or unavailable in 144 patients, who were thus excluded from this stage of the study. Eventually, nidus obliteration was evaluated in 1105 patients. During the follow-up period, 662 patients (60%) achieved complete nidus obliteration, which was confirmed on angiography and MRI in 508 and 154 patients, respectively, while incomplete obliteration was observed in 443 patients (40%) up to the last follow-up. The actuarial 5-, 10-, 15-, and 20-year nidus obliteration rates after initial or repeated GKS were 62.6%, 82.4%, 86.1%, and 89.9%, respectively (Figure 2). The factors associated with nidus obliteration are summarized in Table 2 (detailed in **Text, Supplemental Digital Content 4**, http://links.lww.com/NEU/C989 and **Figures, Supplemental Digital Contents 5**, http://links.lww.com/NEU/C990, **Supplemental Digital Content 6**, http://links.

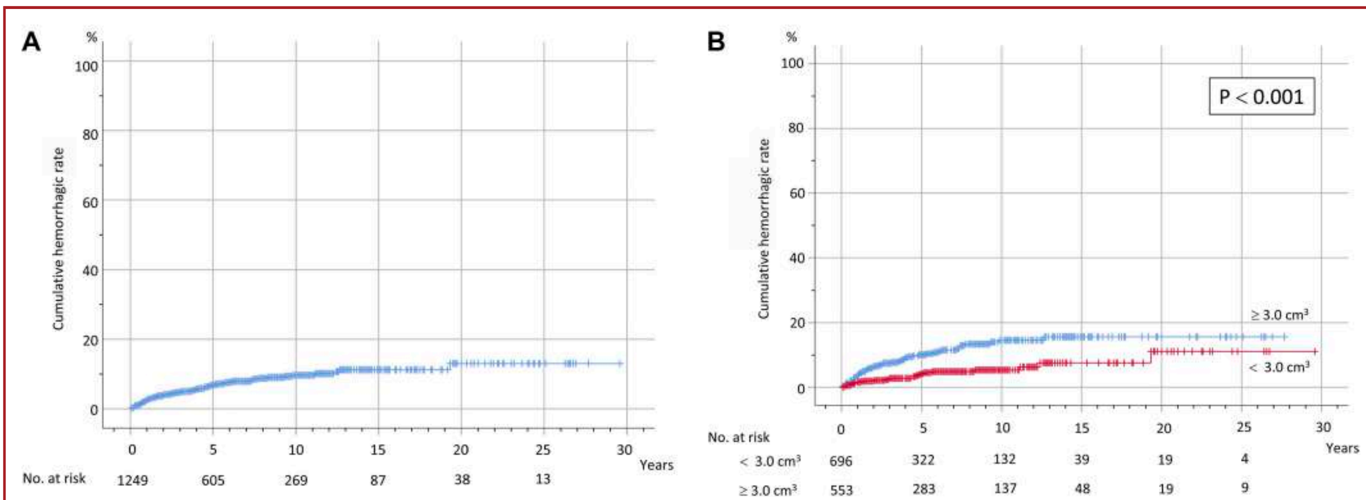


**FIGURE 1.** *Kaplan–Meier curves demonstrating the cumulative post-GKS hemorrhage rates in 1249 patients* **A** *and the cumulative post-GKS hemorrhage rates based on treatment volume (<3 $cm^3$ vs ≥3 $cm^3$,* **B***). GKS, Gamma Knife surgery.*



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**TABLE 2.** **Factors Related to Post-GKS Hemorrhage, Nidus Obliteration, and the Development of CF/CEH**

| | Hemorrhage | | | Nidus obliteration | | | CF/CEH | | |
|---|---|---|---|---|---|---|---|---|---|
| Factor | Univariate *P* value | Multivariate *P* value | Hazard ratio (95% CI) | Univariate *P* value | Multivariate *P* value | Hazard ratio (95% CI) | Univariate *P* value | Multivariate *P* value | Hazard ratio (95% CI) |
| Age | 0.11 | NT | | 0.58 | NT | | 0.06 | NT | |
| Sex | 0.51 | NT | | 0.52 | NT | | 0.10 | NT | |
| Hemorrhage before GKS | 0.29 | NT | | 0.005[a] | 0.15 | | 0.017[a] | 0.39 | |
| Craniotomy before GKS | 0.96 | NT | | 0.15 | NT | | 0.025[a] | 0.15 | |
| Embolization before GKS | 0.48 | NT | | <0.001[a] | 0.003[a] | 0.719 (0.579-0.892) | 0.09 | NT | |
| Spetzler–Martin grade (I-III vs IV, V) | 0.001[a] | 0.53 | | 0.005[a] | 0.004[a] | 0.539 (0.355-0.818) | 0.25 | NT | |
| Eloquent area | 0.060 | 0.31 | | 0.62 | NT | | 0.89 | NT | |
| Drainer (superficial only vs deep) | 0.008[a] | 0.11 | | 0.72 | NT | | 0.90 | NT | |
| Location (deep vs not deep) | 0.28 | NT | | 0.63 | NT | | 0.43 | NT | |
| Treatment year (1991-1999 vs 2000-2015) | 0.82 | NT | | 0.51 | NT | | 0.043[a] | 0.20 | |
| Maximum dose (Gy) | 0.61 | NT | | <0.001[a] | 0.089 | | 0.10 | NT | |
| Marginal dose (Gy) | 0.023[a] | NT | | <0.001[a] | NT | | 0.002[a] | NT | |
| Treatment volume ($cm^3$) | <0.001[a] | 0.004[a] | 1.040 (1.012-1.068) | <0.001[a] | <0.001[a] | 0.964 (0.946-0.982) | <0.001[a] | 0.002[a] | 1.059 (1.022-1.097) |
| % isodose line | 0.10 | NT | | 0.001[a] | NT | | 0.23 | NT | |
| No. of shots | 0.090 | 0.70 | | 0.001[a] | 0.63 | | <0.001[a] | 0.16 | |
| No. of GKS | NT | NT | | NT | NT | | 0.08 | NT | |

CEH, chronic encapsulated hematoma; CF, cyst formation; CI, confidence interval; GKS, Gamma Knife surgery; NT, not tested.
[a]Significant.

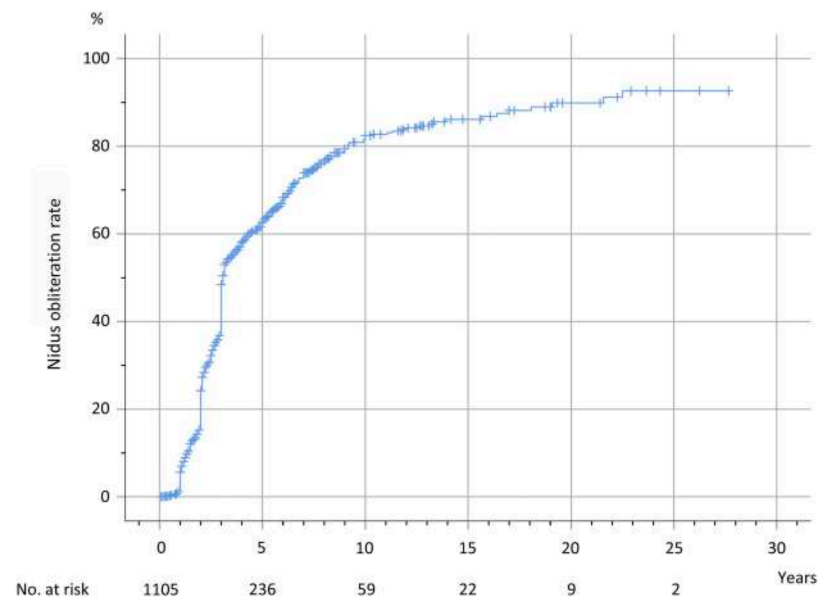


**FIGURE 2.** *Kaplan–Meier curves demonstrating the cumulative nidus obliteration rates in 1105 patients.*

lww.com/NEU/C991, and **Supplemental Digital Content 7**, http://links.lww.com/NEU/C992).

## Late Adverse Radiation Effects

Symptomatic CF/CEH occurred in 42 patients (3%) with a median period of 133 months (range, 40-287 months). Three patients (0.2%) developed RITs within the 10 Gy isodose line, including a glioblastoma multiforme at 7 years (Figure 3A), an anaplastic oligodendroglioma at 7 years (Figure 3B), and an angiosarcoma at 13 years post-GKS (Figure 3C), all of whom died. Of these 45 patients who developed late AREs, 18 (39%) received repeated GKS, with 13 receiving a second GKS, 4 receiving a third GKS, and 1 receiving a fourth GKS. Using the Kaplan–Meier method, the cumulative incidences of CF/CEH at 5, 10, and 15 years were 0.4%, 3.7%, and 9.4%, respectively (Figure 4A). In the multivariate analysis, larger treatment volume ($P = .002$, hazard ratio 1.059, 95% CI: 1.022-1.097) was significantly associated with the development of CF/CEH (Table 2). The actuarial 10- and 15-year cumulative CF/CEH rates in patients with treatment volumes <7.8 $cm^3$ were 1.3% and 5.4%, respectively, compared with 12.3% and 21.8% in those with volumes ≥7.8 $cm^3$ ($P < .001$, Figure 4B). Among 42 patients who developed CF/CEH, 15 (36%) had radiation-induced perilesional edema within 2 years after the first or second GKS and 5 of 21 patients (24%) who experienced a third or fourth GKS developed CF/CEH with a mean period of 155 months. Multiple logistic regression analysis in those 42 patients demonstrated that deep location ($P = .02$, odds ratio 8.774, 95% CI: 1.362-56.539) and men ($P = .04$, odds ratio 4.712, 95% CI: 1.116-19.890) were significantly associated with the development of CF rather than CEH.

## Salvage Treatment

Salvage treatments are summarized in Table 3. Salvage surgery was required for symptomatic CF/CEH in 17 patients (neurological deficits 13, headache 4), all of whom had rapid improvement of their symptoms.

# DISCUSSION

## Hemorrhage Risk after Stereotactic Radiosurgery

There is currently no discussion on the indication of interventional therapy for ruptured AVMs. On the other hand, interventional therapy for unruptured AVMs has been controversial following a randomized trial of unruptured brain AVMs (ARUBA) that demonstrated the superiority of medical management alone to interventional therapy for the prevention of death or symptomatic stroke in unruptured patients with AVM.[13] Prior knowledge of the natural history of AVMs is essential in evaluating the efficacy of interventional therapy. In a systematic review of the natural history of AVMs (involving 3894 ruptured and 4524 unruptured AVMs),[14] AHRs ranged from 0.9% to 7.5% (mean, 4.3%) and 1.3% to 4.3% (mean. 2.2%), respectively, while the 5-year cumulative hemorrhage risks after diagnosis ranged from 13% to 42.5% (mean, 26.5%) and 6% to 21.5% (mean, 11.3%), respectively. According to the review, the AHRs of ruptured



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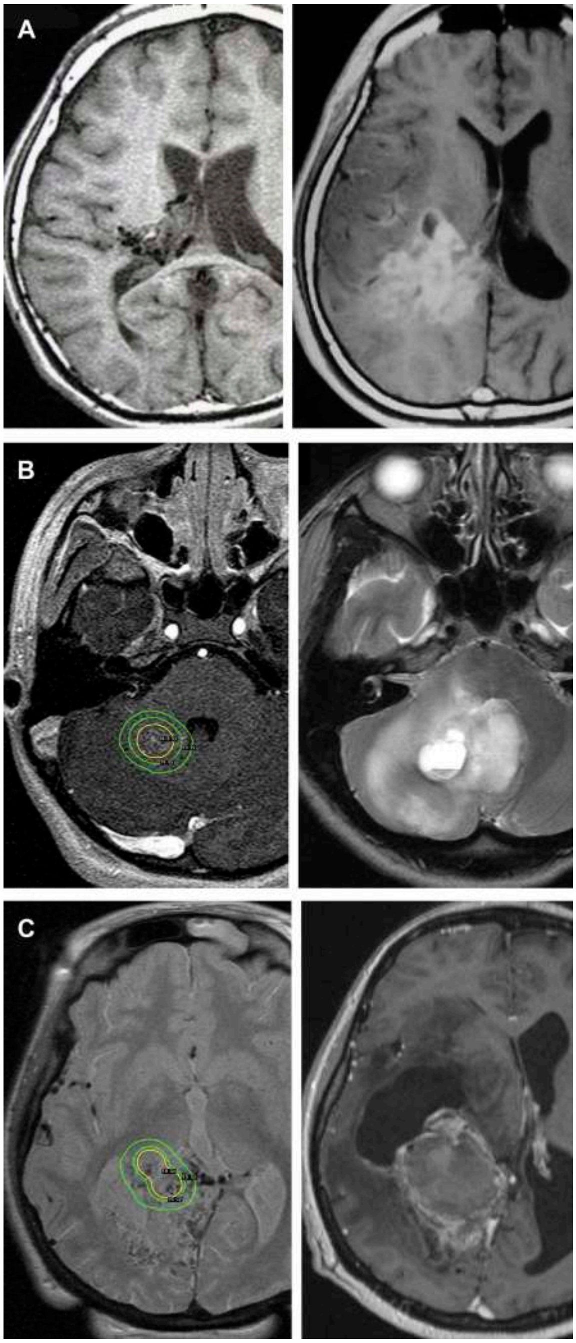


**FIGURE 3.** *Radiation-induced malignant tumors.* **A**, *Pre-GKS at the age of 14; the nidus with a treatment volume of 8.8 $cm^3$ was treated at a margin dose of 20 Gy (left), and a glioblastoma multiforme developed 7 years post-GKS (right).* **B**, *Pre-GKS at the age of 12 showing isodose lines at marginal dose (24.8 Gy), 15, and 10 Gy; the treatment volume was 2.2 $cm^3$ (left) and an anaplastic oligodendroglioma developed at 7 years (right).* **C**, *Pre-GKS at the age of 28 showing isodose lines at marginal dose (18 Gy), 15, and 10 Gy; the treatment volume was 14.1 $cm^3$ (left) and an angiosarcoma developed at 13 years (right). GKS, Gamma Knife surgery.*

AVMs were approximately twice as high as those of unruptured AVMs. In our study, the AHRs were lower than those of the natural course of AVM, with AHRs within 5 years post-GKS being 1.7% and 1.5% for ruptured and unruptured AVMs, respectively, which decreased to 0.6% and 0.4%, respectively, thereafter. Even during the latency interval, the AHRs remained lower than those of the natural course of AVM. These findings suggest the effects of GKS in reducing hemorrhage risk. According to the final follow-up of the ARUBA study,[15] the incidence of death or symptomatic stroke was 3.39 per 100 patient-years (15 of 110 patients) with medical management alone and was 12.32 per 100 patient-years (41 of 116 patients) in the interventional group. Similarly, in patients with unruptured AVM of our study, the incidence of death or AVM rupture (not including symptomatic cerebral infarction) was 1.20 per 100 patient-years (35 of 487 patients), suggesting less incidence than that of medical management alone in the ARUBA study. The ARUBA study demonstrated that death or symptomatic stroke occurred in one-third of the interventional group, indicating that more events developed after intervention than commonly considered.

## Late Adverse Radiation Effects

Although CF/CEH has been reported as late AREs by many studies,[7-9,16] the risk of their development several decades later remains unknown. Several doctors have, therefore, been skeptical about performing SRS on younger patients, especially those with surgically accessible AVMs. For the past 3 decades, SRS has been performed for various intracranial lesions. Notably, the management of AVM differs from that of other lesions in 2 distinct ways. First, unlike malignant brain tumors, patients with AVM are expected to survive for several decades on successful treatment and prevention of hemorrhages. Second, as most AVMs are intra-axial, unlike most extra-axial benign brain tumors (such as meningiomas, vestibular schwannomas, and pituitary adenomas), the brain parenchyma is more prone to radiation damage. In this context, addressing late AREs is critical because of the risk of long-term neurological deficits, which can compromise the quality of life.[8] Our study demonstrated a relatively high incidence of late AREs beyond 10 years, with 10- and 15-year cumulative rates of 4.2% and 10.6%, respectively. However, this may have been an overestimation because most patients without late AREs are unlikely to visit hospitals or undergo further radiological imaging after achieving complete nidus obliteration. As a result, long-term follow-ups tend to be maintained only in patients who have developed late AREs. As has been reported, the incidence of CF/CEH varies from 1.2% to 7.4%, depending on the length of follow-up.[8,17-21] However, fear for the development of CF/CEH is unwarranted because they can be easily and safely removed even if patients have developed neurological deficits. Our concerns revolve around the long-term risk of malignant RITs. To date, the risk of RITs after conventional fractionated radiotherapy has been reported to range from 1% to 4% at 10 to 20 years, depending on the radiation dose.[22,23] By contrast, SRS-induced tumors have been considered extremely rare, accounting for <1% of patients



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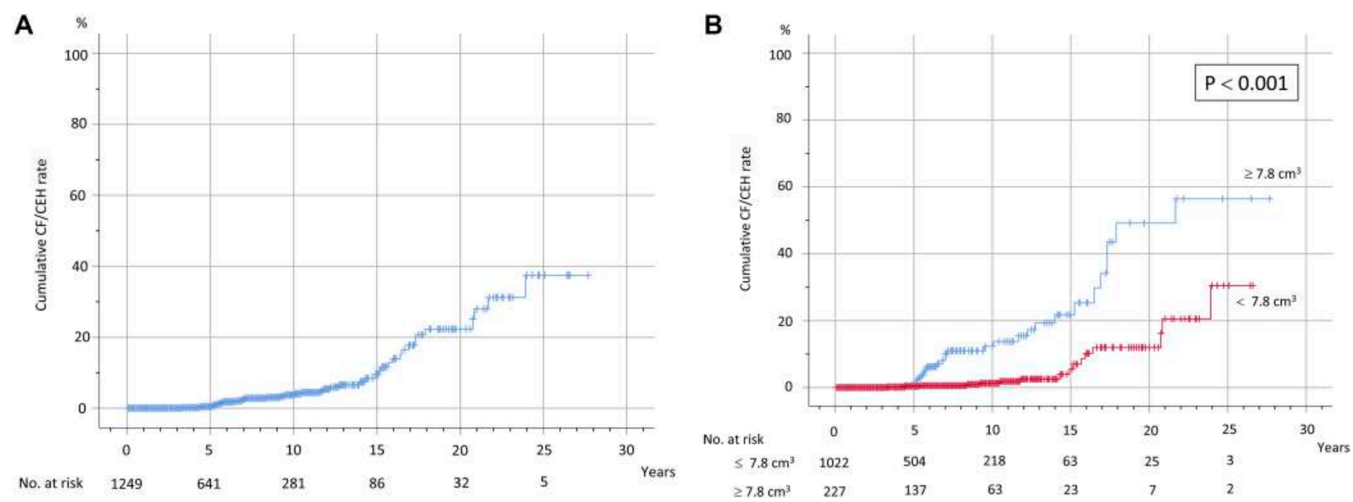


**FIGURE 4.** *Kaplan–Meier curves demonstrating the cumulative ARE rates in 1249 patients* **A** *and the cumulative ARE rates based on treatment volume (<7.8 cm$^3$ vs ≥ 7.8 cm3,* **B***). ARE, adverse radiation effect; CEH, chronic encapsulated hematoma; CF, cyst formation.*

who underwent SRS.[24-29] Wolf et al[28] also reported in a retrospective, multicenter cohort study that overall incidence of RITs was 6.80 per 100 000 patients-years or a cumulative incidence of 0.045% over 10 years. To the best of our knowledge, 8 cases of malignant RITs after AVM radiosurgery, including 3 from our study (4 glioblastomas, 1 anaplastic astrocytoma, 1 anaplastic oligodendroglioma, 1 high-grade glioma, and 1 angiosarcoma), have been reported within an interval of 6 to 24 years after SRS.[7,30-34] This study calls for attention to the long-term risk of malignant RITs after SRS.

**TABLE 3.** **Salvage Treatment After Gamma Knife Surgery**

| Salvage treatment | No. of patients (%) | Mean interval from initial GKS (m) |
|---|---|---|
| Repeat GKS | 215 (17.2) | 51 |
| 2nd | 194 (15.5) | |
| 3rd | 18 (1.4) | |
| 4th | 3 (0.2) | |
| Embolization | 24 (1.9) | 43 |
| Surgery | 52 (4.2) | 73 |
| Craniotomy for AVM rupture | 28 (2.2) | |
| Removal of CF/CEH | 14 (1.1) | |
| Ommaya reservoir placement | 3 (0.2) | |
| Cyst peritoneal shunt | 1 (0.1) | |
| Ventriculoperitoneal shunt | 2 (0.2) | |
| Ventricular drainage | 1 (0.1) | |
| Brain tumor removal | 3 (0.2) | |

AVM, arteriovenous malformation; CEH, chronic encapsulated hematoma; CF, cyst formation; GKS, Gamma Knife surgery.

## Study Limitations

Because this was a single-center study, some biases because of patient selection or radiosurgical techniques may have affected our results. In addition, clinical and radiological data were unavailable in 126 patients. Therefore, the incidence of post-GKS hemorrhages or late AREs may have been underestimated because of a lack of essential clinical information or radiological images. By contrast, many doctors tend to discontinue radiological imaging in patients who have achieved nidus obliteration, which may have resulted in the overestimation of late ARE rates because patients who developed symptomatic AREs are more likely to undergo radiological imaging in the long term.

# CONCLUSION

GKS represents a reasonable treatment option for the prevention of hemorrhages in patients with AVM, particularly those in deep or eloquent regions where safe removal of the nidus with microsurgery is often considered impossible. More than 80% of patients with AVM eventually achieved nidus obliteration beyond 10 years post-GKS and associated with reduced hemorrhage risk with an AHR of 0.5% after 5 years. The incidence of late AREs tended to increase with longer follow-up. CF/CEH is the most common ARE and can be safely removed, but careful attention should be paid to the development of malignant RITs, which can be fatal.

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## Disclosures

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## REFERENCES


1. Chen CJ, Lee CC, Ding D, et al. Stereotactic radiosurgery for unruptured versus ruptured pediatric brain arteriovenous malformations. *Stroke*. 2019;50(10):2745-2751.
2. Daou BJ, Palmateer G, Thompson BG, et al. Stereotactic radiosurgery for brain arteriovenous malformations: evaluation of obliteration and review of associated predictors. *J Stroke Cerebrovasc Dis.* 2020;29(8):104863-104869.
3. Ding D, Yen CP, Xu Z, Starke RM, Sheehan JP. Radiosurgery for patients with unruptured intracranial arteriovenous malformations: clinical article. *J Neurosurg.* 2013;118(5):958-966.
4. Hasegawa H, Hanakita S, Shin M, et al. Long-term outcomes of single-session stereotactic radiosurgery for cerebellar arteriovenous malformation, with a median follow-up of 10 years. *World Neurosurg.* 2017;98:314-322.
5. Hasegawa T, Kato T, Naito T, et al. Long-term outcomes for pediatric patients with brain arteriovenous malformations treated with gamma knife radiosurgery, part 1: analysis of nidus obliteration rates and related factors. *World Neurosurg.* 2019;126:e1518-e1525.
6. Starke RM, Kano H, Ding D, et al. Stereotactic radiosurgery for cerebral arteriovenous malformations: evaluation of long-term outcomes in a multicenter cohort. *J Neurosurg.* 2017;126(1):36-44.
7. Hasegawa H, Hanakita S, Shin M, et al. A comprehensive study of symptomatic late radiation-induced complications after radiosurgery for brain arteriovenous malformation: incidence, risk factors, and clinical outcomes. *World Neurosurg.* 2018;116:e556-e565.
8. Hasegawa T, Kato T, Naito T, et al. Long-term outcomes for pediatric patients with brain arteriovenous malformations treated with gamma knife radiosurgery, part 2: the incidence of cyst formation, encapsulated hematoma, and radiation-induced tumor. *World Neurosurg.* 2019;126:e1526-e1536.
9. Ilyas A, Chen CJ, Ding D, et al. Radiation-induced changes after stereotactic radiosurgery for brain arteriovenous malformations: a systematic review and meta-Analysis. *Clin Neurosurg.* 2018;83(3):365-376.
10. Shuto T, Ohtake M, Matsunaga S. Proposed mechanism for cyst formation and enlargement following gamma knife surgery for arteriovenous malformations. *J Neurosurg.* 2012;117(suppl):135-143.
11. Cahan WG, Woodard HQ, Higinbotham NL, Stewart FW, Coley BL. Sarcoma arising in irradiated bone: report of eleven cases. *Cancer*. 1998;82(1):8-34.
12. Spetzler RF, Martin NA. A proposed grading system for arteriovenous malformations. *J Neurosurg.* 1986;65(4):476-483.
13. Mohr JP, Parides MK, Stapf C, et al. Medical management with or without interventional therapy for unruptured brain arteriovenous malformations (ARUBA): a multicentre, non-blinded, randomised trial. *Lancet*. 2014;383(9917):614-621.
14. Goldberg J, Raabe A, Bervini D. Natural history of brain arteriovenous malformations: systematic review. *J Neurosurg Sci.* 2018;62(4):437-443.
15. Mohr JP, Overbey JR, Hartmann A, et al. Medical management with interventional therapy versus medical management alone for unruptured brain arteriovenous malformations (ARUBA): final follow-up of a multicentre, non-blinded, randomised controlled trial. *Lancet Neurol.* 2020;19(7):573-581.
16. Pollock BE, Link MJ, Branda ME, Storlie CB. Incidence and management of late adverse radiation effects after arteriovenous malformation radiosurgery. *Neurosurgery*. 2017;81(6):928-934.
17. Bir SC, Ambekar S, Maiti TK, Nanda A. Clinical outcome and complications of gamma knife radiosurgery for intracranial arteriovenous malformations. *J Clin Neurosci.* 2015;22(7):1117-1122.
18. Matsuo T, Kamada K, Izumo T, Hayashi N, Nagata I. Cyst formation after linac-based radiosurgery for arteriovenous malformation: examination of predictive factors using magnetic resonance imaging. *Clin Neurol Neurosurg.* 2014;121:10-16.
19. Meneghelli P, Pasqualin A, Zampieri P, et al. Surgical management of adverse radiation effects after gamma knife radiosurgery for cerebral arteriovenous malformations: a population-based cohort study. *World Neurosurg.* 2018;114:e840-e850.
20. Nakajima H, Yamanaka K, Ishibashi K, Iwai Y. Delayed cyst formations and/or expanding hematomas developing after gamma knife surgery for cerebral arteriovenous malformations. *J Clin Neurosci.* 2016;33:96-99.
21. Shuto T, Yagishita S, Matsunaga S. Pathological characteristics of cyst formation following gamma knife surgery for arteriovenous malformation. *Acta Neurochir (Wien)*. 2015;157(2):293-298.
22. Minniti G, Traish D, Ashley S, Gonsalves A, Brada M. Risk of second brain tumor after conservative surgery and radiotherapy for pituitary adenoma: update after an additional 10 years. *J Clin Endocrinol Metab.* 2005;90(2):800-804.
23. Armstrong GT, Liu Q, Yasui Y, et al. Long-term outcomes among adult survivors of childhood central nervous system malignancies in the childhood cancer survivor study. *J Natl Cancer Inst.* 2009;101(13):946-958.
24. Rowe J, Grainger A, Walton L, Silcocks P, Radatz M, Kemeny A. Risk of malignancy after gamma knife stereotactic radiosurgery. *Neurosurgery*. 2007;60(1):60-66; discussion 65-66.
25. Patel TR, Chiang VL. Secondary neoplasms after stereotactic radiosurgery. *World Neurosurg.* 2014;81(3-4):594-599.
26. Hasegawa T, Kida Y, Kato T, Iizuka H, Kuramitsu S, Yamamoto T. Long-term safety and efficacy of stereotactic radiosurgery for vestibular schwannomas: evaluation of 440 patients more than 10 years after treatment with gamma knife surgery. *J Neurosurg.* 2013;118(3):557-565.
27. Ding D, Yen CP, Starke RM, Lee CC, Sheehan JP. Unyielding progress: recent advances in the treatment of central nervous system neoplasms with radiosurgery and radiation therapy. *J Neurooncol.* 2014;119(3):513-529.
28. Wolf A, Naylor K, Tam M, et al. Risk of radiation-associated intracranial malignancy after stereotactic radiosurgery: a retrospective, multicentre, cohort study. *Lancet Oncol.* 2019;20(1):159-164.
29. Pollock BE, Link MJ, Stafford SL, Parney IF, Garces YI, Foote RL. The risk of radiation-induced tumors or malignant transformation after single-fraction intracranial radiosurgery: results based on a 25-year experience. *Int J Radiat Oncol Biol Phys.* 2017;97(5):919-923.
30. Berman EL, Eade TN, Brown D, et al. Radiation-induced tumor after stereotactic radiosurgery for an arteriovenous malformation: case report. *Neurosurgery*. 2007;61(5):E1099.
31. Kaido T, Hoshida T, Uranishi R, et al. Radiosurgery-induced brain tumor. *J Neurosurg.* 2001;95(4):710-713.
32. Starke RM, Yen CP, Chen CJ, et al. An updated assessment of the risk of radiation-induced neoplasia after radiosurgery of arteriovenous malformations. *World Neurosurg.* 2014;82(3):395-401.
33. Xhumari A, Rroji A, Enesi E, Bushati T, Sallabanda Diaz K, Petrela M. Glioblastoma after AVM radiosurgery. Case report and review of the literature. *Acta Neurochir (Wien)*. 2015;157(5):889-895.
34. Yoshida K, Ichikawa T, Kurozumi K, Yanai H, Onoda K, Date I. Fatal glioblastoma after Gamma Knife radiosurgery for arteriovenous malformation in a child. *J Clin Neurosci.* 2014;21(8):1453-1455.


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**Supplemental Digital Content 1. Text.** Radiosurgical techniques.
**Supplemental Digital Content 2. Text**. Factors associated with post-GKS hemorrhage.
**Supplemental Digital Content 3. Figure**. Kaplan–Meier curves demonstrating the cumulative post-GKS hemorrhage rates based on the Spetzler–Martin grading scale.
**Supplemental Digital Content 4. Text.** Factors associated with nidus obliteration.
**Supplemental Digital Content 5. Figure**. Kaplan–Meier curves demonstrating the cumulative nidus obliteration rates based on the Spetzler–Martin grading scale.
**Supplemental Digital Content 6. Figure.** Kaplan–Meier curves demonstrating the cumulative nidus obliteration rates based on pre-Gamma Knife surgery embolization.
**Supplemental Digital Content 7. Figure.** Kaplan–Meier curves demonstrating the cumulative nidus obliteration rates based on treatment volume (<4 $cm^3$ vs ≥ 4 $cm^3$).

## COMMENT

During the interval studied, 1393 patients underwent SRS of whom 126 had no definitive follow-up, 93% had smaller volume AVMS



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(SM grades 1-3), 61% had at least 1 prior hemorrhage. A few take home messages include:

1. Larger volume AVMS had an increased risk of bleeding during the latency interval after SRS.
2. The eventual complete obliteration rates varied from 82% to 86% at 10 years with 215 (17%) having >1 procedure.
3. The margin dose was relatively consistent (20 Gy if the volume was <10 cc)
4. Despite evolving dose planning technologies, the success rate did not differ significantly between early and later years.
5. Late complications included late cyst development (1%-3%) and chronic expanding encapsulated hematomas (CEEHs). Three patients developed malignant glial neoplasms likely radiation related. In this series, no additional cases of meningioma after AVM radiosurgery are reported.[1a]
6. Embolization prior to SRS-reduced obliteration rates. Multidisciplinary decision making in advance of the first procedure makes a lot of sense.[1b]

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