

Comparison of the Long-term Efficacy and Safety of Gamma Knife Radiosurgery for Arteriovenous Malformations in Pediatric and Adult Patients

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Abstract

It is debated whether the efficacy and long-term safety of gamma knife radiosurgery (GKRS) for arteriovenous malformations (AVMs) differs between adult and pediatric patients. We aimed to clarify the long-term outcomes of GKRS in pediatric patients and how they compare to those in adult patients. We collected data for 736 consecutive patients with AVMs treated with GKRS between 1990 and 2014 and divided the patients into pediatric (age < 20 years, $n = 144$) and adult (age ≥ 20 years, $n = 592$) cohorts. The mean follow-up period in the pediatric cohort was 130 months. Compared to the adult patients, the pediatric patients were significantly more likely to have a history of hemorrhage ($P < 0.001$). The actuarial rates of post-GKRS nidus obliteration in the pediatric cohort were 36%, 60%, and 87% at 2, 3, and 6 years, respectively. Nidus obliteration occurred earlier in the pediatric cohort than in the adult cohort ($P = 0.015$). The actuarial rates of post-GKRS hemorrhage in the pediatric cohort were 0.7%, 2.5%, and 2.5% at 1, 5, and 10 years, respectively. Post-GKRS hemorrhage was marginally less common in the pediatric cohort than in the adult cohort ($P = 0.056$). Cyst formation/encapsulated hematoma were detected in seven pediatric patients (4.9%) at a median post-GKRS timepoint of 111 months, which was not significantly different from the rate in the adult cohort. Compared to adult patients, pediatric patients experience earlier therapeutic effects from GKRS for AVMs, and this improves long-term outcomes.

Key words: arteriovenous malformation, gamma knife, pediatric patients, stereotactic radiosurgery

Introduction

Most arteriovenous malformations (AVMs) became symptomatic when patients are 30–40 years old,^{1–4} but AVMs are also an important cause of hemorrhagic stroke in younger patients, accounting for approximately half of spontaneous intracranial hemorrhagic strokes in patients younger than 18 years.⁵ Previous reports have suggested that the characteristics and biological behaviors of AVMs differ somewhat between pediatric and adult patients. Briefly, pediatric patients reportedly have stronger hemorrhage tendencies and smaller nidus sizes, are more likely to exhibit deep locations and deep venous drainage, and are less likely to exhibit dangerous angioarchitectural features, such as venous ectasia and feeding artery aneurysms.^{6–9}

Gamma knife radiosurgery (GKRS) is a standard AVM treatment and generally provides a 70–85% obliteration rate after 3–5 years and a low morbidity rate.^{10–38} Some researchers insist that AVMs in pediatric patients are especially sensitive to radiation, which increases the chances of nidus obliteration,^{10,14,39–41} though not all studies have observed this trend.^{20,42–46} However, improved understanding of late radiation-induced complications^{47–64} has illuminated the need to clarify the long-term safety of GKRS, especially in pediatric patients who have much longer residual life expectancies than adult patients do. Given these concerns, we aimed to determine how the long-term outcomes of GKRS for AVMs in pediatric patients compared to those in adult patients.

Materials and Methods

Participants

We collected clinical and radiographic data for consecutive patients who were treated with GKRS

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between 1990 and 2014 and divided the patients into pediatric (age < 20 years) and adult (age ≥ 20 years) cohorts. After we excluded patients who (i) underwent staged GKRS ($n = 21$) or (ii) other radiotherapies ($n = 13$) before the first GKRS in our institution, (iii) received suboptimal (<15 Gy) treatment ($n = 4$), or (iv) received no follow-up care ($n = 17$), 736 patients remained. This sample included 144 pediatric patients (mean follow-up period: 130 months; median follow-up period: 105 months; range: 5–316 months) and 592 adult patients (mean follow-up period: 110 months; median follow-up period: 92 months; range: 1–320 months). The study protocol was approved by our institutional review board and conformed to the principles of the Declaration of Helsinki. All patients provided written informed consent for the use of their data.

Radiosurgical techniques

Details of our hospital's radiosurgical techniques have been previously described.^{27,65,66} In brief, a Leksell stereotactic frame (Elekta Instruments, Stockholm, Sweden) was fixed on the patient's head, and stereotactic imaging was then performed to obtain precise data on the shape, volume, and three-dimensional coordinates of the patient's head. Digital subtraction angiography (DSA) was used before February 1991, computed tomography was used from March 1991 to July 1996, and magnetic resonance imaging (MRI) was used from August 1996 onward. Treatments were planned by dedicated neurosurgeons and radiation oncologists using KULA software until 1998 and the Leksell Gamma Plan thereafter (both software packages are from Elekta Instruments). Radiosurgical dose determinations were mainly based on nidus sizes and proximity to eloquent structures, and the prescribed doses mostly ranged between 18 and 20 Gy. We performed all procedures without general anesthesia. Instead, intravenous sedative agents (i.e., midazolam, thiopental, and/or pentazocine) were used before frame fixation, with support from pediatricians for patients younger than 13–15 years. The procedure was performed with the patient either fully conscious or under sedation, as considered appropriate.

Post-treatment course

Patients were evaluated at regular intervals after GKRS. MRI scans were performed at 6-month intervals for the first 3 years, with confirmatory DSA being performed if the MRI results suggested nidus obliteration. Secondary GKRS was recommended for patients who did not exhibit nidus obliteration within approximately 5 years. Annual MRI check-ups were continued after nidus obliteration to screen

for possible long-term complications. We defined event-free survival (EFS) as survival free from any permanent symptomatic complications that were caused by AVMs themselves or AVM treatments (including surgery, embolization, and radiotherapy) and that were associated with a >1-point deterioration in the patient's modified Rankin Scale (mRS)⁶⁷ score relative to baseline. We also searched for late cyst formation and/or encapsulated hematoma (CF/EH), which was typically characterized by a radiographically-evident enhanced nodular lesion with or without cyst formation with perifocal edema.^{47,49–51,58,59}

Statistical analyses

The examined baseline characteristics included age, biological sex, maximal nidus diameter, nidus volume, radiosurgical dose, depth of location, presence of a deep drainer, eloquent location, history of hemorrhage, surgery, and embolization, the Modified Pittsburgh Radiosurgery-based AVM Grading Scale,⁶⁸ the Spetzler–Martin Grade,⁶⁹ and the Virginia radiosurgical AVM Grading Scale.⁷⁰ Baseline characteristics between the two cohorts were compared using the chi-square test for categorical variables and the Wilcoxon rank sum test for continuous variables. We calculated the actuarial rates of nidus obliteration, post-GKRS hemorrhage, and perifocal edema and the EFS rate with the Kaplan–Meier method and compared the cohorts' curves with the Wilcoxon test. All analyses were performed with JMP Pro 13 software (SAS Institute, Cary, NC, USA). We defined statistical significance as $P < 0.05$.

Results

Baseline characteristics

The patients' baseline characteristics are summarized in Table 1. The median ages were 14.5 years (range: 4–19 years) and 38 years (range: 20–80 years) in the pediatric and adult cohort, respectively. Histories of AVM embolization and hemorrhage were present in 24 (17%) and 102 (71%) pediatric patients, respectively, and 63 (11%) and 311 (53%) adult patients, respectively. Compared to the adult patients, the pediatric patients were significantly more likely to have a history of hemorrhage ($P < 0.001$) or a history of prior embolization ($P = 0.045$). The statistical analysis also revealed the margin dose in pediatric patients which was significantly higher than in adult patients ($P = 0.020$), but the difference was so slight and the median values were the same that no virtual difference was present. There were no observed complications associated with sedation, frame fixation, or GKRS itself.

Table 1 Baseline characteristics and dosimetry data of the two cohorts

Variables	Underage cohort	Adult cohort	P-value
	Value, median (range)		
Follow-up, months	105 (5–316)	92 (1–320)	/
Age (year)	14.5 (4–19)	38 (20–80)	/ [†]
Maximal diameter (mm)	22 (3–68)	22 (5–60)	0.729
Nidus volume (cm ³)	2.1 (0.1–21.5)	2.7 (0.1–44.5)	0.375
Margin dose (Gy)	20 (17–28)	20 (15–28)	0.020 [*]
Central dose (Gy)	40 (27–60)	40 (25–50)	0.946
mPRAS	0.6 (0.2–2.5)	1.2 (0.5–5.5)	/ [†]
Variables	Value, n (%)		P-value
Male sex	71 (49)	344 (58)	0.056
Eloquent location	92 (64)	338 (57)	0.138
Deep location ^{**}	61 (42)	217 (37)	0.205
Presence of deep drainage	86 (60)	308 (52)	0.097
Previous hemorrhage	102 (71)	311 (53)	<0.001 [*]
Prior embolization	24 (17)	63 (11)	0.045 [*]
Prior surgical intervention	20 (14)	52 (9)	0.084
VRAS ≤ 2	96 (67)	397 (67)	0.928
SMG I–II	72 (50)	328 (55)	0.243

mPRAS, modified Pittsburgh radiosurgery-based arteriovenous malformation Grading Scale; SMG, Spetzler-Martin grade; VRAS, Virginia radiosurgical arteriovenous malformation Grading Scale. ^{*}A P-value >0.050 was considered significant. ^{**}Deep location includes basal ganglia, thalamus, brainstem, cerebellum, interventricular regions, and corpus callosum. [†]Not tested because the variable is directly associated with age.

Nidus obliteration

Nidus obliteration was confirmed in 105 pediatric patients (73%) at a median timepoint of 24 months after initial GKRS. The actuarial obliteration rates were 36, 60, 74, and 87% at 2–4, and 6 years, respectively. Secondary GKRS was performed in 16 pediatric patients, with subsequent nidus obliteration confirmed in nine patients. In total, nidus obliteration was confirmed in 114 pediatric

patients (79%). Nidus obliteration was confirmed in 391 adult patients (66%) at a median timepoint of 30 months after initial GKRS. The actuarial obliteration rates were 23, 53, 73, and 85% at 2–4, and 6 years, respectively. A Kaplan–Meier analysis revealed that nidus obliteration occurred significantly earlier in the pediatric cohort ($P = 0.015$, Fig. 1A).

Post-GKRS hemorrhage

Post-GKRS hemorrhage was observed in five pediatric patients (4.0%) at a median timepoint of 59 months after GKRS. All were from unobliterated niduses, except for in one patient who developed a hemorrhage from a recurrent nidus 240 months after the initial GKRS. The actuarial post-GKRS hemorrhage rates were 0.7, 0.7, 2.5, and 2.5% at 1, 2, 5, and 10 years, respectively. Post-GKRS hemorrhage was observed in 38 adult patients (6.4%) at a median timepoint of 13 months after GKRS. The actuarial post-GKRS hemorrhage rates were 2.9, 4.9, 5.5, and 6.4% at 1, 2, 5, and 10 years, respectively. A Kaplan–Meier analysis revealed a tendency toward a lower post-GKRS hemorrhage frequency in the pediatric cohort ($P = 0.056$, Fig. 1B).

Perifocal edema

Post-GKRS perifocal edema was observed in 41 pediatric patients (28%) at a median post-GKRS timepoint of 11 months. The actuarial perifocal edema rates were 23, 30, and 30% at 1–3 years, respectively, which were not significantly different from the adult cohort's actuarial rates of 15, 30, and 32% at 1–3 years, respectively ($P = 0.560$, Fig. 1C).

EFS

Neurological deteriorations (i.e., >1-point mRS score decreases) were observed in four pediatric patients (2.8%). Two of them with niduses located in the thalamus and internal capsule experienced incomplete right hemiparesis 11 months after GKRS, and one of these patients later developed a fatal encapsulated hematoma, as previously reported.⁴⁷⁾ A third patient died due to massive cerebellar hemorrhage at 6 years, and the fourth patient developed diplopia due to an encapsulated hematoma at 75 months, which required surgical resection. The overall pediatric EFS rates were 99, 98, 96, and 96% at 2, 5, 10, and 15 years, respectively. These rates were not significantly different from the adult EFS rates of 97, 96, 96, and 93% at 2, 5, 10, and 15 years, respectively ($P = 0.349$, Fig. 1D).

CF/EH

Cyst formation and/or encapsulated hematoma was detected in seven pediatric patients (4.9%) at

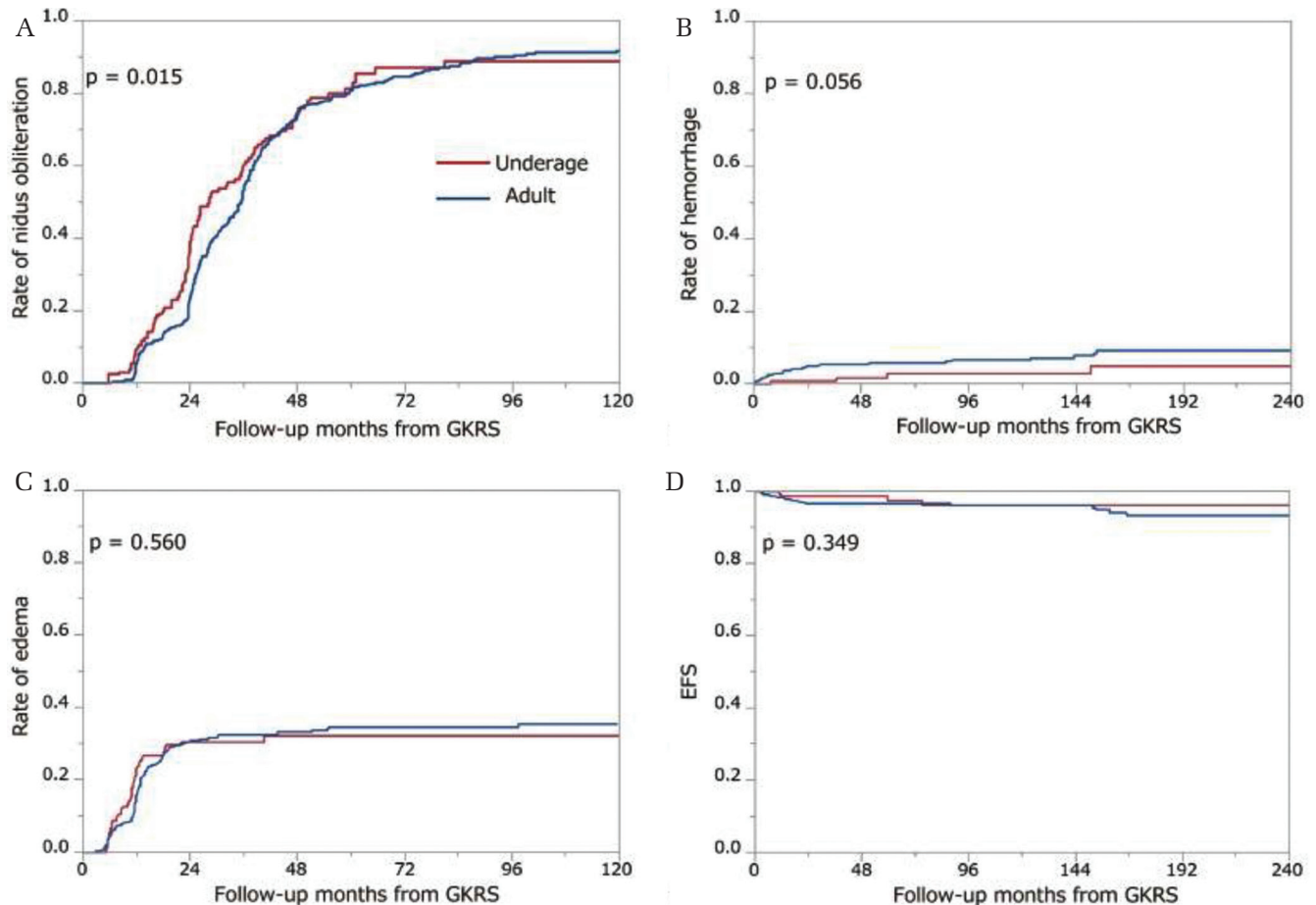


Fig. 1 Kaplan–Meier curves for rates of (A) nidus obliteration, (B) post-treatment hemorrhage, (C) perifocal edema, and (D) event-free survival. EFS, event-free survival; GKRS, gamma knife radiosurgery.

a median timepoint of 111 months (range: 23–243 months) after initial GKRS. These caused mild deficits or no clinical outcomes in six patients but killed the remaining one patient. No radiation-induced tumor was observed in the pediatric patients. On the other hand, CF/EH were detected in 35 adult patients (5.9%) at a median timepoint of 135 months after initial GKRS. No significance between-cohort differences were observed in the CF/EH incidence rates ($P = 0.626$) or the post-GKRS timepoint of CF/EH development ($P = 0.532$).

Discussion

In this study, we compared the outcomes of GKRS for AVMs in pediatric and adult cohorts. Our first major finding was that although the two cohorts' final obliteration rates were almost equal, nidus obliteration occurred earlier in the pediatric cohort than in the adult cohort. Second, post-GKRS hemorrhage occurred less frequently and later in the pediatric cohort than in the adult cohort. These results are

especially impressive given that the pediatric cohort had a significantly higher proportion of hemorrhagic AVMs than the adult cohort did, and that previous hemorrhages are a major risk factor for post-GKRS hemorrhage.^{4,8,71–73} It can obviously be speculated that shorter times to nidus obliteration in the pediatric cohort could have contributed to a reduced frequency of latency-phase hemorrhage. Several previous studies have also confirmed earlier response to radiation in pediatric patients than in adult patients.^{10,14,39–41} One possible explanation for this is that vessels in adult and pediatric patients may differ in sensitivity to radiation-induced damage.¹⁶ For example, AVMs in pediatric patients may have a higher endothelial cell turnover rate in the nidus than AVMs in adults do. The major pieces of evidence for this hypothesis are that AVM recurrence both after radiotherapy and surgery is more commonly observed in young patients^{74–79} and that AVM-affected vessels in pediatric patients tend to have a high Ki-67 index and high vascular endothelial growth factor expression.^{80,81} Interestingly, some previous studies reported that

elderly and non-elderly populations differ in the rate⁷⁰⁾ and timing⁸²⁾ of nidus obliteration, which suggests that radiation sensitivity may depend on age. Further research is necessary.

In this study, we did not observe any complications associated with treatment procedures such as frame fixation; stereotactic imaging studies, including angiography; or irradiation. Nevertheless, meticulous care should be taken to maintain an ideal sedative state, especially in younger children, and effective collaboration with pediatricians is essential. We performed all procedures with the patients under local anesthesia with sedative agents, but the need of general anesthesia should be argued individually.

Cyst formation and/or encapsulated hematoma are rare but possible late radiation-induced complications following GKRS for AVMs.^{51,52,57,60,83–85)} We observed a CF/EH incidence rate of approximately 5% in both the pediatric and adult cohorts. Although fatal outcomes are possible if CF/EH develops in deep brain regions, most CF/EHs developed slowly and caused only mild deficits or even no adverse outcomes. We therefore recommend annual regular imaging follow-up for all treated patients. It remains controversial when follow-up should cease. Because we found that some CF/EHs developed more than 20 years after the initial GKRS, we suggest that follow-up should continue for at least 20 years, but we should conduct further research to stratify the CF/EH risk in different patients and examine whether the follow-up period can be safely shortened.

This study has some limitations. First, its retrospective nature might have introduced selection biases in terms of participants and treatments. Nevertheless, our results are consistent with those of recent studies of pediatric patients,^{19,25,86–92)} which suggests that they are robust and applicable to clinical practice. Second, there was a sample size imbalance between the pediatric and adult cohorts. Sample size uniformity between cohorts is ideal for statistical comparisons, but it is usually an unattainable goal for clinical studies. Hence, we conducted this study in the best available way. Third, we defined EFS as any neurological event that caused a >1-point decrease in mRS scores, which in turn means that subtle complications or controllable epilepsies were not counted. However, because many surgical cohort studies define significant complications as events causing >1 to 2-point decreases in mRS scores or their equivalent,^{93–98)} our EFS definition is acceptable.

Overall, GKRS for AVMs in pediatric patients can provide a favorable nidus obliteration rate within a

shorter timeframe than achieved in adult patients. It also provides a favorable EFS even ≥10 years after treatment. Therefore, GKRS is an optimal treatment for pediatric AVMs. However, additional studies are necessary to further evaluate long-term outcomes, because pediatric patients have long residual life expectancies.

Conflicts of Interest Disclosure

All authors have no conflict of interest.

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