CLINICAL INVESTIGATION

GAMMA KNIFE RADIOSURGERY FOR CEREBRAL ARTERIOVENOUS MALFORMATIONS IN CHILDREN/adolescents AND ADULTS. PART I: DIFFERENCES IN EPIDEMIOLOGIC, MORPHOLOGIC, AND CLINICAL CHARACTERISTICS, PERMANENT COMPLICATIONS, AND BLEEDING IN THE LATENCY PERIOD

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Purpose: To compare the epidemiologic, morphologic, and clinical characteristics of 92 children/adolescents (Group A) and 362 adults (Group B) with cerebral arteriovenous malformations (cAVMs) considered suitable for radiosurgery; to correlate radiosurgery-related permanent complication and post-radiosurgery bleeding rates in the 75 children/adolescents and 297 adults available for follow-up.

Methods and Materials: Radiosurgery was performed with a model C 201-source Co60 Leksell Gamma Unit (Elekta Instruments, Stockholm, Sweden). Fisher exact two-tailed, Wilcoxon rank–sum, and two-sample binomial exact tests were used for statistical analysis.

Results: There were significant differences between the two populations in sex (p = 0.015), clinical presentation (p = 0.001), and location (p = 0.008). The permanent complication rate was lower in younger (1.3%) than in older patients (5.4%), although the difference was not significant (p = 0.213). The postradiosurgery bleeding rate was lower in Group A (1.3%) than in Group B (2.7%) (p = 0.694), with global actuarial bleeding rates of 0.56% per year and 1.15% per year, respectively.

Conclusions: The different characteristics of child/adolescent and adult cAVMs suggest that they should be considered two distinct vascular disorders. The similar rates of radiosurgery-related complications and latency period bleeding in the two populations show that gamma knife radiosurgery does not expose young patients to a higher risk of sequelae than that for older patients. © 2006 Elsevier Inc.

Cerebral arteriovenous malformations, Gamma knife radiosurgery, Children, Adults, Outcomes.

INTRODUCTION

The epidemiologic, morphologic, and clinical characteristics of cerebral arteriovenous malformations (cAVMs) in children and adolescents might differ from those in adults (1). In 1999, terBrugge (2) claimed that “brain vascular disorders in the pediatric age group are genuinely different from those in adults, despite the fact that they carry the same name.” Cerebral arteriovenous malformations are more often deep-seated or located in eloquent brain regions in pediatric cases (3–13) than in older patients (14–28). Intracerebral hematomas due to rupture of cAVMs are more frequent in children than adults (29, 30), and clinical presentation as spontaneous hemorrhage is reported in up to 80–100% of pediatric cases (4, 6, 10, 13, 30–32), potentially exposing these young patients to a higher risk of rebleeding during the latency period after radiosurgery than adults. Furthermore, cAVMs that recur after complete resection or obliteration at the original site, or the de novo appearance of an ectopic angioma, have been described in children or adolescents but never in adults (33, 34).

The risks of potentially severe long-term sequelae related to neurocognitive and pituitary dysfunctions after radiation treatments, as well as the occurrence of radiation-induced brain tumors, are reported to be much more frequent among patients irradiated during childhood or adolescence than among those irradiated as adults (35, 36). As a consequence, there is a general consensus in the various brain tumor treatment protocols to avoid radiation treatment in patients aged <5 years (6, 37).

The question of whether cAVMs in children and adults
really constitute two distinct vascular disorders has become more urgent with the increasingly widespread use of radiosurgical devices. Does radiosurgical treatment expose children/adolescents with cAVMs to higher risks of permanent complications and postradiosurgery bleeding than adults? Apart from the strictly pediatric series, radiosurgical reports have usually analyzed children and adolescents and adults as a single group, avoiding comparison of their results. To our knowledge, only one published study has compared the radiosurgical outcomes of pediatric and adult cAVMs (31), but no detailed statistical analysis was made comparing the two groups of patients.

This retrospective study reports our experience with children/adolescents and adults treated with gamma knife radiosurgery (GKR) for cAVMs. A comparison between the epidemiologic, morphologic, and clinical characteristics of the cAVMs and between treatment parameters was made to investigate whether there were any significant differences between the two groups. The GKR-related permanent complication and postradiosurgery bleeding rates were also compared, to assess whether there might be any significant difference in the responses to GKR by the two populations.

METHODS AND MATERIALS

From February 1993 to December 2004, one-stage GKR treatment was performed at our department on 454 patients, of whom 92 were aged <21 years (Group A), and 362 were aged ≥21 years (Group B). All patients underwent diagnostic four-vessel planar (two-dimensional [2D]) or, more recently, three-dimensional (3D)-rotational angiography at the referring center or at our hospital before treatment. Transit time through the cAVM was defined as the interval between initial visualization of the injected contrast agent entering the arterial segment and its subsequent passage into the venous drainage threshold (38). Blood flow through the cAVM was defined as low, intermediate, or high, in accordance with earlier studies (39). As is well known, circulation time within cAVMs ranges from 1 to 4.4 s (40). Blood flow was arbitrarily classified as low for a circulation time <2 s, intermediate between 1 and 2 s, or high for <1 s. Fractionated radiation therapy was not administered to either group before or after radiosurgery.

Group A

The median age in Group A was 14 years (range, 5–20 years). Most patients were female (50 of 92, 54.5%) (Table 1). Bleeding represented the clinical presentation in 65 of 92 patients (70.6%). Before radiosurgery, percutaneous endovascular embolization procedures were undertaken with the aim of reducing the cAVM to a volume more suitable for GKR in 38 of 92 patients (41.3%), whereas microsurgical incomplete cAVM resection was carried out in 3 patients (3%). No other treatments were performed before GKR in the remaining patients. Eloquent brain sites according to Spetzler-Martin’s (SM) definition were involved in most cases (84 of 92, 91.3%), and 29.4% of the cAVMs (27 of 92) were located in deep-seated areas—the corpus callosum, pineal region, basal ganglia, thalamus, or brainstem. The SM classification of 7.6% of the angiommas was Grade 4, and there were no Grade 5 cAVMs. The numbers of the 92 cAVMs assigned to low, intermediate, and high flow subgroups were very similar. The median cAVM volume before GKR was 2.93 mL (range, 0.1–25.0 mL). The median and range parameters of dose planning were as follows: prescription isodose, 54.3% (40–90%); prescription dose, 22.0 Gy (13.5–26.4 Gy); maximal dose, 40.6 Gy (27–55 Gy); average dose, 29.1 Gy (12–37.1 Gy); number of shots, 4 (1–16). Endotracheal neuroanesthesia was needed in 40 of 92 patients, usually in those aged <13 years.

Group B

The median age in Group B was 36 years (range, 21–75 years) (Table 1). Most patients were male (216 of 362, 59.7%). Bleeding represented the clinical presentation in 189 patients (52.2%). Before radiosurgery, percutaneous endovascular embolization procedures were performed in 178 (49.2%) adults, and microsurgical incomplete cAVM resection was undertaken in 11 patients (3.0%). Seven patients had undergone previous linear accelerator radiosurgery elsewhere. Gamma knife radiosurgery was the only treatment in 170 patients (47.0%). Eloquent brain sites were involved in 313 patients (86.5%), and 62 cAVMs (17.1%) were located in deep-seated areas. The SM classification of 6.9% of the angiommas was Grade 4, with no Grade 5 cAVMs. The three blood-flow subgroups were very similar in size. The median cAVM volume at GKR was 2.53 mL (range, 0.05–31.5 mL). The median and range parameters of dose planning were as follows: prescription isodose, 54.2% (22–90%); prescription dose, 22.0 Gy (10.0–28.0 Gy); maximal dose, 40.5 Gy (20–62.5 Gy); average dose, 28.6 Gy (16.8–43.3 Gy); number of shots, 3.5 (1–23). No endotracheal neuroanesthesia was needed.

Radiosurgical technique

By definition, GKR implies a single session of external irradiation performed under stereotactic conditions. The indications for radiosurgical treatment were as follows: deep-seated or eloquent location; surgical or embolization remnants; microsurgery/embolization refused or too risky; volume <10 mL or, in rare cases, also ≥10 mL, when other treatments were not feasible or too risky, or were refused; severe medical conditions that precluded general endotracheal anesthesia. Radiosurgical technique and procedure with a model C 201-source Cs137 Leksell Gamma Unit (Elekta Instruments, Stockholm, Sweden) have been described previously (24). Neuroradiologic localization was routinely performed by means of stereotactic 2D cerebral angiography or high-resolution magnification subtraction stereotactic angiograms or, more recently, 3D rotational stereotactic angiography (with evaluation of the early arterial to late venous phases) to define the cAVM nidus (target volume) and to determine target coordinates. Angiographic examination was supplemented with stereotactic CT/MRI, with specific algorithms and sequences, to obtain additional information about the 3D shape of the cAVM and the surrounding normal brain structure.

Patients were generally discharged from hospital on the day after treatment. In the follow-up period, patients usually underwent postoperative imaging (MRI and angio-MRI scans) and neurologic evaluations at 6- and 12-month intervals to assess vascular response, to identify delayed or late radiation injury and/or edema of the brain, and to guide appropriate management. When MR images suggested cAVM occlusion, follow-up angiography was performed to confirm complete obliteration of the angiomma. Thereafter, patients were advised to have further MR imaging every 5 years because of the reported risk of delayed postradiosurgical adverse effects (41).
Complications after radiosurgical treatment were classified as early (within 24–48 hours), delayed (within 6 months), or late (after more than 6 months) (24). Neurologic morbidity was defined as transient or permanent, and the modified Rankin outcomes scale (42) was used to grade its severity. Any episodes of bleeding during the latency period were registered. Follow-up data were obtained from hospital notes, imaging studies, and contact with relatives and family physicians. Medical records, MRI, and angiography images for all patients were carefully reviewed.

Statistical analysis

In Tables 1, 2, and 3, the statistical comparisons between parameters in the two groups of patients were based on the Fisher exact two-tailed test (discrete variables) and the Wilcoxon rank-sum test (continuous variables). Person-years and actuarial rates of bleeding were determined according to the method described by Nataf et al. (43). Actuarial post-GKR bleeding rates were compared with the two-sample binomial exact test. On the basis of internationally accepted criteria, values of \( p \leq 0.05 \) were considered statistically significant. Statistical analysis was performed with Stata software, version 8.2 (Stata Corporation, College Station, TX). Because this was a retrospective, single-center study, the possibility of bias in patient selection cannot be ruled out.

RESULTS

Epidemiologic, morphologic, and clinical characteristics and treatment parameters were compared and statistically analyzed for the whole series of 92 children/adolescents and 362 adults (Table 1). The frequency and statistical correlation of GKR-related complications and posttreatment hem-
orrhages were evaluated in the 75 children/adolescents and 297 adults who were available for follow-up (Tables 2 and 3, Fig. 1).

Epidemiologic, morphologic, and clinical characteristics and treatment parameters in Groups A and B

In Group A, female patients predominated, whereas there were more male patients in Group B ($p = 0.015$). In the pediatric/adolescent age group, hemorrhagic onset occurred much more frequently than among adults ($p = 0.001$), and deep-seated cAVMs were twice as common in children as in adults ($p = 0.008$). No significant differences emerged in the numbers of pre-GKR embolizations, the numbers of cAVMs in eloquent sites, or the SM grades. The numbers of cAVMs with low, intermediate, or high flow were similar in the two groups. There were no significant differences between median cAVM volumes or their division into the three arbitrarily chosen subgroups. As for the selected treatment parameters, neither the median values nor the subgroups within prescription dose and average dose showed any significant differences between children and adults. Therefore, the two groups presented a well-matched distribution of cAVM volumes, prescription doses, and average doses, thus excluding any possible biases that might have skewed the results of our statistical analysis.

GKR-related complications in Groups A and B

Early complications after GKR were very rare in both Groups (1 of 92 in Group A and 8 of 362 in Group B); they were always transient and essentially consisted of nausea/vomiting or epilepsy. Permanent neurologic sequelae were less frequent among young patients (1 of 75, 1.3%) than among older ones (16 of 297, 5.4%), although the difference was not statistically significant (Table 2). Most of these patients (10 of 17) presented minor neurologic handicaps, classified as Grades 1 to 2 on the modified Rankin outcomes scale. To date, neither GKR-related

<table>
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<th>Year after GKR</th>
<th>No. of pt-years</th>
<th>No. of pts with bleeding</th>
<th>Actuarial rate</th>
<th>95% CI</th>
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<td>70.57</td>
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<td>0.0</td>
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<td>2</td>
<td>57.95</td>
<td>0</td>
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<td>3</td>
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<td>4</td>
<td>13.28</td>
<td>1</td>
<td>7.5</td>
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<td>5</td>
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<td>6</td>
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<td>&gt;7</td>
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Abbreviations: pt/pts = patient/patients; CI = confidence interval; No = no observations. Other abbreviations as in Table 1.
mortality nor radiosurgery-induced brain tumors have occurred in either group.

**Bleeding rate during the latency period in Groups A and B**

Hemorrhages during the latency period were very rare in both groups. Hemorrhagic presentation of cAVMs was much more frequent in children than in adults, yet the bleeding rate during the latency period was lower in children/adolescents (1 of 75, 1.3%) than in adults (8 of 297, 2.7%), though the difference did not prove to be statistically significant (Table 2). The global actuarial rate of bleeding after GKR was also lower in Group A (0.56% per year; 1 patient with hemorrhage; 178.35 patient-years) than in Group B (1.15% per year; 8 patients with hemorrhage; 692.79 patient-years). The difference was not significant (95% confidence interval, 0.001–0.040 in Group A and 0.006–0.023 in Group B, p = 0.55), probably because of the small number of events in both groups (Table 3). It is noteworthy that 6 of the 9 cases of hemorrhage occurred in low-flow cAVMs. Statistical comparison of the median latency periods (Table 2) and the post-GKR actuarial hemorrhage rates (Fig. 1) of the two groups showed no significant p values. However, the analysis might not be reliable because there was only one event in Group A. This patient, a 9-year-old boy whose cAVM rebled 37 months after GKR, had no permanent neurologic worsening. In Group B, five of eight hemorrhages were rebleedings, and six of eight occurred within 12 months from GKR. There was only one bleeding-related death, 7.8 months after GKR; the patient died 2 days after a hemorrhagic stroke in the intensive care unit of our department. Two other adults showed permanent worsening of their condition after bleeding, whereas the remaining 5 patients presented a negative neurologic examination at their latest follow-up.

**DISCUSSION**

**Epidemiologic, morphologic, and clinical characteristics and treatment parameters**

Only a few investigators have claimed that cAVMs in children might behave differently than those in adults (12, 34, 44). Recently Stapf et al. (1) statistically analyzed the effect of age on demographic, morphologic, and clinical cAVM characteristics at the time of diagnosis. They found statistical correlations between patient age and clinical and morphologic features of cAVMs: in particular, between the different age groups and hemorrhagic and epileptic onset rates, nidus size, anatomic location, and the relative frequency of concurrent arterial aneurysms. Although the incidence of cAVMs is very similar in children/adolescents and adults, amounting to 1/100,000 child-years (45) and 0.94–1.11/100,000 person-years, respectively (46), they more often become symptomatic in children and young adults than in older patients (1, 3, 32, 45).

Radiosurgical studies did not generally show any sex preponderance, either in children/adolescents (3–8, 10, 11, 13) or adults (14, 15, 18, 19, 21–24, 26, 28, 47–51). In our experience, there was a preponderance of female patients among children/adolescents and of male patients in the adult group (p = 0.015).

Many investigators decided to include patients aged <5 years in their radiosurgical series, both in pediatric studies and in those including all age groups (3, 4, 12, 14, 15, 17, 18, 22, 24, 27, 31, 47–49). Other investigators (6, 8, 10, 11, 13, 19, 21, 23, 26, 28, 50, 51) refused to treat children aged <5 years with radiosurgery, on the basis of previous publications describing the development of mental retardation after conventional radiotherapy in such patients. We also chose not to treat patients aged <5 years.

In the radiosurgical studies, between 58% and 100% of patients in the pediatric age group presented as bleeding (3, 4, 6, 7, 10–13), whereas the incidence ranged between 30% and 66% if all age groups were included in the analysis (14–16, 18–25, 27, 28, 47, 52). In 99 cAVMs treated with GKR, Tanaka et al. (31) reported previous bleeding in 91.3% of patients aged <16 years and in 73.7% of patients aged ≥16 years. Pollock et al. (53) found that hemorrhagic onset was much more frequent in pediatric than adult patients, but it was unclear whether the changes in cAVM morphology occurring throughout childhood and adolescence might affect the risk of hemorrhage.

In the nonradiosurgical series involving pediatric cAVMs exclusively (30, 32), child/adolescent vs. adult cAVMs (29, 44), or studies including only patients aged >18 years (54), bleeding onset occurred in 68–90% of younger and 48–62% of older patients. However, none of these studies included a statistical comparison of the two populations. In our experience, the different incidence of hemorrhagic presentation in children/adolescents and adults proved to be statistically significant (p = 0.001). However, the lower incidence of bleeding at presentation in adults than in younger patients could also be explained by the fact that the
adult population is more apt to have scans done for alternative reasons and therefore might present a higher percentage of patients diagnosed incidentally.

Nevertheless, in our study, the rates of cAVMs incidentally discovered were very similar in children/adolescents (1%, 1 of 92 patients) and adults (2.2%, 8 of 362). The difference did not prove significant at statistical analysis.

Deep-seated and midline location of cAVMs was found in 38% to 67% of cases in radiosurgical studies of pediatric patients (3–8, 11–13), compared with 16.6–36% of cases in series that included all age groups (14–25, 27, 28). We recently published the results of GKR in 33 basal ganglia and 209 supratentorial cortical AVMs. The difference between the proportion of pediatric patients (aged <18 years) and adults (aged >18 years) in the two subgroups proved to be highly significant (p = 0.004) (28). In the present study population, deep-seated cAVMs were twice as frequent in children/adolescents as in adults (p = 0.008). A relationship between age, hemorrhagic onset, and cAVM location was posited by Karlsson et al. (55). They found a mean age of 26.8 years at the first episode of bleeding in 686 patients with deep-seated cAVMs, a mean age of 30.9 years in 680 patients with peripherally located cAVMs, and a mean age of 33.8 years in 113 patients with cerebellar angiomas (p < 0.001). The higher frequency of deep-seated and midline-located cAVMs among young patients might be explained by the fact that in such cases every occurrence of bleeding, even minimal, becomes clinically manifest due to their critical location.

As for other cAVM characteristics and radiosurgical parameters, no important differences emerged from the literature on pediatric/adolescent patients or the series including all age groups. The number of patients undergoing pre-radiosurgical embolization was very similar in both pediatric/adolescent (0–35%) (3–5, 8, 10–12, 31) and adult (21–45.1%) (15–18, 20, 25, 27, 31, 47–49, 55) series. In our study, the incidence of pre-GKR embolization was >40% in both groups; it was slightly higher among adults (49.2%) than children (41.3%), but the difference was not statistically significant (p = 0.177). The large number of patients who underwent pre-GKR embolization in our series might be due to the presence in our department of a neuroradiological team skilled in these endovascular procedures and with long experience with AVM embolization. The reason why pre-GKR embolizations were performed less frequently in children than in adults could be related to the higher incidence of deep-seated and midline cAVMs among children/adolescents. It is well known that endovascular embolization of these cAVMs is hazardous, bearing notable technical difficulties due to the anatomic characteristics of the afferent vessels supplying these angiomas (28).

Spetzler-Martin Grades 1–3 were predominant in all the radiosurgical series, varying between 60% and 92% of child cases (3–5, 7, 10–12) and between 59.6% and 92.5% of adult cases (14–19, 21, 23, 24, 26, 47, 48, 52). Tanaka et al. (31) reported SM Grades 2 to 3 in 22 of 23 patients aged <16 years (96%) and SM Grades 1–3 in 68 of 76 patients aged >16 years (89.5%). In our study, too, the number of cases of SM Grades 1–3 was very similar in the two groups of patients, without any significant difference (p = 0.814).

No particular differences in mean cAVM volume were noted in the various radiosurgical series. The mean cAVM treated volumes ranged between 1.99 mL and 9.9 mL in children/adolescents (3, 5, 7, 10, 11, 13) and between 2.7 mL and 9.4 mL in the series including all age groups (14, 20–23, 25–27, 49, 52). Tanaka et al. (31) found that the mean volumes of cAVMs treated with GKR in pediatric and adult patients were 4.8 mL and 4.3 mL, respectively. In our study, they were 2.93 mL in Group A and 2.53 mL in Group B (p = 0.09).

The mean and median prescription doses delivered to the cAVMs were similar in the different radiosurgical studies, ranging between 15.9 Gy and 22.7 Gy in pediatric/adolescent series (3–5, 10, 12, 13) and between 15 Gy and 21.5 Gy in the studies including all age groups (14–16, 18–20, 22–27, 47). Tanaka et al. (31) reported very similar mean prescription doses in the pediatric (20.5 Gy) and adult (20 Gy) groups. In our experience, exactly the same median prescription dose (22 Gy) was calculated in younger and older patients (p = 0.527).

To our knowledge, the radiosurgical pediatric series gave no data regarding blood flow through the cAVMs or the average dose to the angioma. In the studies including all age groups, Chang et al. (18) reported that it was possible to determine the flow pattern at angiography in 240 patients undergoing GKR and that only 35 of them (14.2%) had low-flow cAVMs. However, Petereit et al. (39) and Inoue and Ohye (56) found low-flow cAVMs in 21–41% of patients treated with radiosurgery. Low-flow cAVMs represented one-third of cases in both groups in our series; the numbers of cAVMs assigned to low, intermediate, and high flow subgroups, along with the median average doses, were very similar in the pediatric/adolescent and adult groups (p = 0.633 and 0.149, respectively).

In summary, the findings reported in the literature, along with those in our experience, provide a compelling argument against the assumption of uniform cAVM characteristics across different age groups at the time of initial presentation, as far as sex, onset, and location are concerned.

**GKR-related complications**

The most dangerous complications of radiation treatment of cAVMs are cognitive and endocrinologic deficits and radiation-associated carcinogenesis, particularly in children/adolescents, owing to their still-ongoing brain development and long life expectancy. However, to our knowledge, cognitive and endocrinologic deficits after radiosurgery have not been observed to date. Steiner et al. (6) reported neither cognitive nor endocrinologic deficits after GKR on 114 patients aged 5–17 years. Riva et al. (9) treated 8 patients aged 9–18 years with GKR for cAVMs. Neuropsychological tests were administered to these young patients at an average of 6 years after radiosurgery; when compared with
a control group, they showed no neurologic, cognitive, memory, or attention deficits. More recently, Steinworth et al. (57) evaluated long-term cognitive function in 39 pediatric and adult patients treated with linear accelerator radiosurgery for cAVMs and followed for at least 2 years. No cognitive decline was noted during follow-up. On the contrary, significant improvements occurred in intelligence, memory, and attention, especially among patients who had had no intracranial hemorrhages.

Radiation-associated carcinogenesis seems to be very rare but possible. Over a period of 19 years, no radiation-induced tumors were observed in >1,300 patients treated with GKR in Steiner et al.’s series (6). However, because the latency period for radiation-induced tumors is 8–26 years (6), the investigators were not able to give a definitive assessment of their incidence after radiosurgery. More recently, Pollock et al. (16) reported three cases of radiation-induced tumors after radiosurgery in the 43,177 patients remaining after the exclusion of more recently treated patients, patients with limited life expectancy due to treated malignant brain tumors, and the patients who died or were lost to follow-up after GKR. The investigators calculated an incidence of radiation-induced tumors after radiosurgery of 0.007%.

Loeffler et al. (58) maintained that radiation-associated tumors might theoretically occur after radiosurgery. Nevertheless, it seems that the relative risk of tumor formation after GKR is substantially lower than that seen in patients treated with larger-volume radiation. The high single dose of radiation given to the target volume during radiosurgery should lead to cytotoxicity rather than mutagenicity, and volumes and doses of radiation along the entrance and exit pathways during convergent-beam radiosurgery are so small that the likelihood of tumorigenesis is remote. However, because of the risk of radiosurgery-induced tumors, the investigators suggest that long-term surveillance is prudent for all surviving patients, regardless of the outcomes of their radiosurgical treatment. They conclude that although patients will increasingly be reported with radiation-induced tumors after radiosurgery in the future, the overall incidence seems quite low and should not alter current radiosurgical practice. Since 1993, when GKR treatments started at our department, no case of radiation-induced tumor has been documented.

Other radiosurgery-related permanent complications occurred very rarely, whether in series of children/adolescents (0–5.9%) (3, 8, 10–13, 31) or those including all age groups (0–5.0%) (15, 17, 18, 20, 22–24, 27, 28, 48, 50–52). In a retrospective analysis of 100 cAVMs in children and adolescents treated with GKR, Shin et al. (4) showed that risk factors found to be associated with neurologic deterioration after radiosurgery were nidus location in the brainstem (p = 0.0285) and a maximum radiation dose of >40 Gy (p = 0.0447). In the series including pediatric and adult age groups, the most frequently reported risk factors for radiosurgery-related permanent symptomatic complications were large cAVM volume, deep-seated and critical brain locations, and the overall tissue volume receiving ≥12 Gy (19, 24, 52, 59, 60).

In our series, univariate statistical analysis to identify any potential risk factors predicting radiosurgery-associated permanent complications was not considered applicable, owing to the small number of events in both groups. On the basis of academic or work performance and behavior in the family, along with observations by relatives, referring physicians, and ourselves, we can say that none of the patients in our series showed any radiosurgery-related permanent cognitive and/or endocrinologic deficits. Delayed and late permanent GKR-related complication rates were very low in both Group A (1.3%) and Group B (5.4%), and most complications (10 of 17) consisted of minor neurologic morbidity (Rankin Grades 1 and 2). We observed a lower permanent morbidity rate in children than in adults, although the difference did not prove significant (p = 0.213). These extremely favorable results in child/adolescent cAVMs might be due to their frequent hemorrhagic onset, which leaves a residual necrotic area around the angioma, radiation of which should not involve the appearance of new neurologic deficits or the worsening of existing ones (28).

**Bleeding during the latency period**

Halim et al. (61) recently performed a statistical analysis to estimate the longitudinal risk of intracranial hemorrhage in 790 patients with cAVMs within a defined population. At multivariate analysis, they found that patients who presented with intracranial hemorrhages had a higher rate of subsequent bleeding than those who presented without (p < 0.032). The investigators concluded that clinical manifestation of cAVMs as intracranial hemorrhage was the most important predictor of future intracranial hemorrhage. Therefore, because cAVM hemorrhagic onset is much more frequent in children than adults, one would expect higher rates of bleeding during the latency period after radiosurgery in children/adolescents than in older patients. Surprisingly, the various radiosurgical series reported very similar crude bleeding rates in both groups, ranging between 4.0% and 16.1% in pediatric series (3–5, 8, 11, 12) and between 1.9% and 16% in those including all age groups (14, 16, 17–19, 22–26, 28, 43, 48, 50, 52, 56, 62). Most pediatric radiosurgical series did not record any cases of bleeding in the latency period (6, 7, 10, 13, 31). In the series including all age groups, only Kemeny et al. (51) reported no hemorrhages after GKR on 52 patients, but these had a very young mean age (29.7 years) and were followed for only 1 year. Furthermore, the annual bleeding rate was lower in pediatric/adolescent (2.5–2.7% per patient per year) (11, 12) than adult (3.08–5.5%) (19, 43, 48) series. In a study of 31 patients aged <18 years, Smyth et al. (3) reported a cumulative post-GKR hemorrhage rate of 3.2% per patient per year in the first year and a rate of 4.3% per patient per year over the first 3 years. On the other hand, Pollock et al. (25) analyzed the effect of GKR on the hemorrhage rate in 315 cAVM patients with a mean (± SD) age at the time of
radiosurgery of 35.0 ± 15.2 years. They found that the annual hemorrhage rate until cAVM obliteration was 4.8% during the first 2 years after radiosurgery and 5.0% per year during the 3–5 years after GKR.

Friedman et al. (52) and Zipfel et al. (14) performed a multivariate analysis on several independent variables to discover whether any of them could be considered risk factors influencing the occurrence of bleeding in the latency period, but none of the parameters analyzed was predictive of hemorrhage after radiosurgery. When Shin et al. (4) made a retrospective study of 100 cAVMs in children and adolescents who were followed for a median period of 21.5 months, they found that feeding arteries located in the posterior fossa (p = 0.0071) and cAVM nidus location in the cerebellum (p = 0.001) were significantly associated with the risk of hemorrhage in the latency period. In radiosurgical series including all age groups, several factors were found to predict the risk of hemorrhage during the latency period at unimultivariate analysis: large cAVM volume, presence of unsecured intranidal or paranidal aneurysms, partial irradiation of the nidus, and low prescription doses (17, 19, 25, 43, 50, 56, 62). In a series of 115 cAVMs treated with GKR, 68 of moyamoya type (low-flow) and 47 shunt (high-flow) or mixed type, Inoue and Ohye (56) reported no hemorrhages during the latency period among the slow-flow group and bleeding in 8 of 47 patients (17%) with mixed- and shunt-type cAVMs (p = 0.0002).

Karlsson et al. (62) and Shin et al. (15) described a statistically significant correlation between patient age at treatment and the incidence of postradiosurgery hemorrhage: at unimultivariate analysis, patient age >60 years significantly increased the risk of latency-period hemorrhage. Tanaka et al. (31) compared 23 patients aged <16 years and 76 patients aged ≥16 years who were treated with GKR for cAVMs. The only two bleedings during the latency period occurred in adults.

In our study, we did not undertake statistical analysis to discover potential risk factors for bleeding after GKR because we considered that the low incidence of bleeding in our series would not allow reliable results. Nevertheless, bleeding during the latency period was twice as frequent in adults (2.7%) as in children/adolescents (1.3%), although the difference was not statistically significant (p = 0.694). In addition, younger patients showed a lower global risk of hemorrhage after GKR (0.56% per year) than older ones (1.15% per year), although, again, the difference was not significant (p = 0.55). In 6 of 9 patients in our series, the hemorrhage occurred in low-flow cAVMs, and most of them showed a deep venous drainage. Possibly stenosis of the venous drain opening in the deep-vein system induces slowing of the blood flow, giving rise to increasing pressure within the cAVM nidus and facilitating hemorrhages (28, 48). The fact that overall and actuarial bleeding rates during the latency period were lower in children/adolescents than in adults could be explained by the shorter treatment–obliteration interval achieved in pediatric patients, as discussed in part II of our report: the earlier the obliteration, the shorter the latency period, and, consequently, the lower the risk of bleeding after GKR. This hypothesis was supported by the observation that the very few pediatric hemorrhages reported showed a median latency period varying between 40.5 months and 62 months (4, 11, 12), suggesting that only the most radiation-resistant, long-term treatment failure cAVMs were at risk of bleeding in children/adolescents. In contrast, in the series including all age groups, bleedings usually occurred within 1 year of radiosurgery (mean/median interval, 4.5–13 months) (15, 23, 25, 48), showing a slower response to radiation treatment by cAVMs in adults. In the present study, we observed only one rebleeding during the latency period, 37 months after GKR, in a 9-year-old boy in Group A, whereas the median time for bleeding during the latency period among the 8 patients affected in Group B was 7.6 months. Statistical comparison between the median latency periods in the two groups showed no significant p values. However, the analysis might have been skewed because there was only one event in Group A.

**CONCLUSIONS**

- The finding that cAVMs in children/adolescents and adults showed significantly different characteristics of gender, clinical onset, and location suggests that they should be considered two different vascular disorders.
- Gamma knife radiosurgery is confirmed as a safe treatment modality for cAVMs, with no mortality, extremely low permanent morbidity rates, and, to date, no radiation-induced tumors either in children/adolescents or adults.
- Similar overall rates of GKR-related permanent complications and of overall and annual bleedings during the latency period in younger and older patients seem to demonstrate that children/adolescents are not exposed to higher risks than adults after radiosurgical treatment.

**REFERENCES**


5. Hoh BL, Ogilvy CS, Butler WE, *et al.* Multimodality treat-


