GAMMA KNIFE RADIOSURGERY FOR CEREBRAL ARTERIOVENOUS MALFORMATIONS IN CHILDREN/ADOLESCENTS AND ADULTS. PART II: DIFFERENCES IN OBLITERATION RATES, TREATMENT-OBLITERATION INTERVALS, AND PROGNOSTIC FACTORS

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Purpose: To evaluate and compare obliteration rates (OBRs) and treatment–obliteration intervals (TOIs) for cerebral arteriovenous malformations (cAVMs) treated with Gamma Knife radiosurgery in children/adolescents and adults; and to determine factors predicting the OBR and TOI in these two populations.

Methods and Materials: This study concerned 62 children/adolescents and 193 adults observed for ≥3 years. Fisher exact two-tailed and Wilcoxon rank–sum tests, multiple logistics, and Cox proportional hazard models were used for statistical analysis.

Results: The overall OBR was 85.5% in children/adolescents and 87.6% in adults (p = 0.671), but children/adolescents showed higher 36-month actuarial OBRs (69.35%) and shorter median TOIs (25.7 months) than adults (66.84% and 28.2 months; p = 0.006 and p = 0.017, respectively). In children/adolescents, lower Spetzler-Martin grades (p = 0.043) and younger age (p = 0.019) correlated significantly with OBRs, and lower Spetzler-Martin grades (p = 0.024) and noneloquent cAVM locations (p = 0.046) with TOIs. In adults, low flow through the cAVM and <6.2-cm³ volume were associated with both OBR and TOI (p = 0.012 and p = 0.002, respectively).

Conclusions: The differences in OBRs within 3 years and TOIs, although slight, seem to show that pediatric cAVMs behave differently from those in adults after Gamma Knife radiosurgery. © 2006 Elsevier Inc.

INTRODUCTION

Cerebral arteriovenous malformations (cAVMs) in children and adolescents present epidemiologic, morphologic, biologic, and clinical characteristics that differ from those in adults, particularly in sex prevalence, brain location, hemorrhagic presentation, and active angiogenesis mediated by humoral factors (1–33). The increasingly widespread use of radiosurgical devices and their increased application to the treatment of cAVMs give rise to the question of whether these different characteristics of cAVMs in children/adolescents and adults could lead to different radiosurgical outcomes. Could radiosurgery have different cAVM obliteration rates (OBRs) and treatment–obliteration intervals (TOIs) in these two populations? Several studies have been reported regarding radiosurgical outcomes and factors predicting the results of radiosurgery on brain angiomas in children (1–12), but the nonpediatric radiosurgical series have included patients of all ages grouped together (34–41), making it impossible to compare the data from children/adolescents with those from adults. To our knowledge, there is only one published study comparing the radiosurgical outcomes of pediatric and adult cAVMs (30), but no detailed statistical analysis was made.

This retrospective study reports our experience with children/adolescents (Group A) and adults (Group B) treated with Gamma Knife radiosurgery (GKR) for cAVMs. A comparison between OBRs and TOIs was undertaken to find any significant differences between these two populations. In addition, the determination of prognostic factors predicting the radiosurgical results in these two groups of patients was performed.

METHODS AND MATERIALS

The calculation and comparison of overall and actuarial OBRs and TOIs, along with statistical evaluation of the parameters po-
tentially correlating with radiosurgical outcomes, were carried out for 62 pediatric/adolescent and 193 adult patients who had been observed for ≥3 years. The numbers of patients in whom cAVM obliteration was achieved within 36 months of GKR were also compared. The median duration of follow-up was 29.0 months in Group A (range, 6.2–77.2 months) and 36.7 months in Group B (range, 6.4–130.7 months). All patients underwent diagnostic four-vessel biplanar or, more recently, rotational three-dimensional digital subtraction angiography, either at the referring center or at our hospital before treatment. Definition of the transit time and blood flow through the cAVM, as well as indications for radiosurgical treatment, radiosurgical technique, and procedure have been described in Part I of this two-part report. The median (range) parameters of dose planning were as follows for Group A: prescription isodose, 55.9% (40–90%); prescription dose (PD), 22.6 Gy (14–26.4 Gy); maximal dose, 41.3 Gy (27–55 Gy); average dose, 29.3 Gy (18.9–36.7 Gy); number of shots, 3.3 (1–9); in Group B these figures were 55% (22–90%), 22.4 Gy (10–28 Gy), 42 Gy (20–62.5 Gy), 29.7 Gy (16.8–43.3 Gy), and 2.9 (1–18), respectively. Patients were generally discharged from hospital on the day after treatment and usually underwent postoperative imaging (MRI and angio-MRI scans) and neurologic evaluations at 6-, 12-, 24-, and 36-month intervals to assess vascular response. When MRI imaging suggested cAVM occlusion (absence of flow-void signal, usually associated with gadolinium enhancement), follow-up angiography was performed to confirm complete obliteration of the angioma. The radiosurgical response of cAVMs was classified as complete obliteration or cure (successful treatment)—defined as normal circulation time, complete absence of pathologic vessels in the former nidus of the malformation, and the disappearance or normalization of draining veins (22, 23)—or as incomplete occlusion, unchanged, or increased cAVM volume (unsuccessful treatment). 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 comparisons between OBR and TOI in children/adolescents and adults (Table 1) were based on the Fisher exact two-tailed test (OBR) and the Wilcoxon rank–sum test (TOI). The cumulative complete occlusion rates were compared by the two-sample binomial exact test. In Fig. 1, the difference between the 36-month OBRs in children and adults was evaluated by assuming that patient follow-up stopped at 36 months and by modeling TOI with classic survival analysis.

Univariate and multivariate statistical analyses (Tables 2 and 3) were performed on 11 independent variables (9 variables adjusted for sex and age) to evaluate whether they correlated significantly with the radiosurgical outcomes, defined as OBR and TOI (dependent variables). The independent variables were selected bearing in mind the most frequently reported differences between the characteristics of cAVMs in children/adolescents and in adults, as well as the most frequently reported prognostic factors associated with radiosurgical obliteration of cAVMs. We also considered the blood flow through the cAVM to be an independent variable, because its potential prognostic power for radiosurgical cure has very seldom been analyzed in previous studies (34). The study was limited to 11 explanatory variables, owing to the limited number of cAVMs available for analysis. Univariate and multivariate analyses of the association between obliteration and clinical characteristics were based on multiple logistic models in Groups A and B separately. In the univariate analysis, variables in each model were the two potential confounders sex and age, together with one of the clinical characteristics. A crucial aspect of the construction of multiple logistic models in multivariate analysis is the selection of variables. Classic stepwise automated variable selection algorithms have a series of well-known disadvantages (42). Therefore, we preferred to adopt the backward and forward bootstrapped stepwise selection of Austin and Tu (43) with 1000 bootstrap samples. The predictive power of the models was assessed by estimating the
area under the receiving operating characteristic curves (together with the 95% bootstrap bias-corrected confidence intervals [CIs]). Accuracy of fit was evaluated by the Hosmer-Lemeshow goodness-of-fit test. We used the classical Cox proportional hazard model on Groups A and B to analyze TOI and to detect potential factors. On the basis of internationally accepted criteria, values of $p < 0.05$ were considered statistically significant. Statistical analysis was performed with Stata version 8.2 (StataCorp, College Station, TX). Because this was a retrospective, single-center study, the possibility of bias in patient selection cannot be ruled out.

**RESULTS**

The subjects of this study were patients with a follow-up period of ≥3 years, or less if obliteration was angiographically documented within 36 months of GKR. This interval was chosen because several investigators (3, 11, 22–24, 26, 35) have maintained that a 3-year latency period constitutes a follow-up long enough to achieve angiographically documented cure of cAVMs or otherwise to declare “radiosurgical failure,” if a patent cAVM nidus persists at angiographic examination, and hence to schedule the patient for retreatment.

**Differences between OBRs and TOIs in Groups A and B**

Overall OBRs were similar ($p = 0.617$) in Groups A (53 of 62, 85.5%) and B (169 of 193, 87.6%) (Table 1). Nevertheless, cAVMs tended to be obliterated earlier in children than adults, with actuarial OBRs at 3 years of 69.35% and 66.84%, respectively (Fig. 1). Analyzing by survival analysis the time interval between GK treatment and obliteration, the $p$ value of the log–rank test on equality of survivor functions truncated at 36 months in children and adults proved to be highly significant ($p = 0.006$). The earlier response to radiosurgery of cAVMs in pediatric/adolescent patients than in adults was confirmed by statistical comparison of the two median TOIs: 25.7 months (range, 6.2–58.2 months) in Group A vs. 28.2 months (range, 6.4–93.6 months) in Group B.

### Table 2. Univariate analysis (adjusted for sex and age) of nine independent variables related to obliteration rate in children/adolescents and adults treated with GKR for cAVMs

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>Children/adolescents</th>
<th>Adults</th>
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<tbody>
<tr>
<td></td>
<td>Patientsa</td>
<td>Odds ratiob</td>
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<tr>
<td>Clinical onset</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2 (13.3)</td>
<td>Reference</td>
</tr>
<tr>
<td>Bleeding</td>
<td>7 (14.9)</td>
<td>2.06</td>
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<tr>
<td>Pre-GK PEE</td>
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<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4 (15.4)</td>
<td>Reference</td>
</tr>
<tr>
<td>No</td>
<td>5 (13.9)</td>
<td>2.02</td>
</tr>
<tr>
<td>SM Location</td>
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<td></td>
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<tr>
<td>Eloquent</td>
<td>9 (15.8)</td>
<td>Reference</td>
</tr>
<tr>
<td>Nonequivalent</td>
<td>0 (0.0)</td>
<td>1.25d</td>
</tr>
<tr>
<td>Location</td>
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<td></td>
</tr>
<tr>
<td>Cortical</td>
<td>8 (18.6)</td>
<td>Reference</td>
</tr>
<tr>
<td>Deep-seated</td>
<td>1 (5.3)</td>
<td>9.64</td>
</tr>
<tr>
<td>SM Grade</td>
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<td></td>
</tr>
<tr>
<td>I–III</td>
<td>7 (11.9)</td>
<td>15.22</td>
</tr>
<tr>
<td>IV–V</td>
<td>2 (66.7)</td>
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<tr>
<td>Blood flow</td>
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<tr>
<td>Low</td>
<td>5 (13.9)</td>
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</tr>
<tr>
<td>Int + high</td>
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<tr>
<td>Volume (cm$^3$)</td>
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</tr>
<tr>
<td>&lt;1.0</td>
<td>1 (5.0)</td>
<td>9.41</td>
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<tr>
<td>1.0–6.2</td>
<td>6 (17.7)</td>
<td>1.70</td>
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<tr>
<td>&gt;6.2</td>
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<tr>
<td>PD (Gy)</td>
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<td>&lt;20</td>
<td>1 (12.5)</td>
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<tr>
<td>20–24</td>
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<td>Reference</td>
</tr>
<tr>
<td>AD (Gy)</td>
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</tr>
<tr>
<td>&gt;30</td>
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<td>Reference</td>
</tr>
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</table>

**Abbreviations:** CI = confidence interval; Reference = reference category; +Inf = unbounded limit; SM = Spetzler-Martin; Int = intermediate flow; PD = prescription dose; AD = average dose; PEE = percutaneous endovascular embolization. Other abbreviations as in Table 1.

* Number (%) of patients with non-obliterated cAVMs.

* Adjusted for sex and age.

* Statistical significance of the odds ratio.

* Calculated by exact methods.
months) in Group B ($p = 0.017$). The radiosurgery-induced obliteration process continued beyond the 3-year period after GKR in several cAVMs in both groups, which had identical actuarial OBRs at 5 years (85.5% in Group A and 85.5% in Group B). After that time, the two curves seem to level off (Fig. 1).

**Differences between prognostic factors in Groups A and B**

In Group A, univariate statistical analysis showed that only Spetzler-Martin (SM) grading correlated significantly with OBR (Table 2): lower SM grades occluded more frequently than grade IV cAVMs ($p = 0.043$). Certain locations in the brain showed higher OBRs, although this was not statistically significant, with deep-seated cAVMs occluding more often than cortical cAVMs ($p = 0.067$). Multivariate analysis confirmed this trend for deep-seated locations and lower SM grades ($p = 0.059$ and $p = 0.058$, respectively) and showed that younger age of children at treatment is the only factor that correlates closely with obliteration ($p = 0.019$) (Table 3).

In Group B, low flow through cAVMs and $<6.2$-cm$^3$ volume correlated significantly with OBR, both at univariate (Table 2) and multivariate analysis (Table 3). In particular, statistical analysis demonstrated that low flow correlated closely with cAVM obliteration only if the volume was $<6.2$ cm$^3$. On the other hand, low flow through the nidus did not show any positive correlation with OBR where cAVM volumes were $>6.2$ cm$^3$. Intermediate and high flow never predicted OBR, either with $<6.2$-cm$^3$ or $>6.2$-cm$^3$ volumes.

As for TOI, statistical analysis adjusted for sex and age showed a significant correlation between TOI and noneloquent sites (hazard ratio [HR] = 2.61; 95% CI, 1.02, 6.72; $p = 0.046$) and lower SM grades (HR = 1.90; 95% CI, 1.09, 3.32; $p = 0.024$) in Group A. That is, children/adolescents treated for cAVMs of grades I to II and in noneloquent sites (according to the SM definition of eloquence) presented an earlier angiographically documented occlusion of the angioma than cAVMs located in eloquent regions and classified as SM grades III to IV. In Group B also, TOI correlated with low flow (HR = 1.89; 95% CI, 1.38, 2.57; $p < 0.001$) and smaller cAVM volume (HR = 1.70; 95% CI, 1.12, 2.56; $p = 0.012$). In other words, radiosurgical obliteration of adult cAVMs was achieved earlier in low-flow angiomas with volumes of $<6.2$ cm$^3$.

**DISCUSSION**

To our knowledge, there has only been one study comparing two distinct groups of pediatric and adult cAVMs treated at the same center (30), but no sophisticated statistical analysis was included. So we thought it would be useful to make a statistical evaluation of OBRs, TOIs, and prognostic factors predicting radiosurgical results in children/adolescents and in adults, to investigate whether different responses to radiosurgical treatment could be found in the two populations.

**OBRs and TOIs**

The aim of radiosurgical treatment of cerebral AVMs is to achieve angiographically documented “complete obliteration” or cure of the angioma. This result is usually achieved within 3 years of radiosurgery, after which period evidence of a patent cAVM nidus at angiography or MRI is defined as a “treatment failure,” both in pediatric patients (3) and in case series including all age groups (35). The Pittsburgh team stated that any patient with a persistent cAVM nidus at $>3$ years after radiosurgery was advised to undergo repeated radiosurgery (26), and several investigators were of the same opinion, both for children (11) and adults (22–24, 35). On the other hand, in a study of a large series of children and adolescents aged $<18$ years, Steiner et al. (4) affirmed that in a few cases obliteration of the cAVM might be delayed, occurring 3–5 years after treat-
ment. In a radiosurgical series including all age groups, Colombo et al. (38) reported that 9 patients who had been considered treatment failures and scheduled for additional irradiation experienced obliteration between 36 and 60 months after radiosurgery. More recently, Shin et al. (14) reported that 25 of 260 cAVMs (9.6%) disappeared, according to angiographic evidence, later than 3 years after radiosurgery. Lindvall et al. (44) reported on 29 patients treated with single-fraction radiotherapy for large cAVMs (mean volume, 11.5 cm³). The actuarial angiographically verified OBRs at 2 years were 56% for cAVMs 4–10 cm³ in volume and 50% for cAVMs >10 cm³. The success rates increased to 81% for cAVMs 4–10 cm³ in volume and 70% for cAVMs >10 cm³ at 5 years after treatment. In our series, the actuarial OBR 3 years after GKR was 69.35% in children/adolescents and 66.84% in adults, but the obliteration process continued during the subsequent period, reaching a 5-year actuarial OBR of 85.48% in Group A and 85.49% in Group B, with the curve leveling off thereafter. These findings suggest that the latency period for evaluating “radiosurgical failure” should be extended to 5 years before radiosurgery is repeated.

The overall OBRs were very similar in pediatric/adolescent populations (61.2–86.6%) (2, 3, 8–10, 12) and in those including all age groups (60%–88%) (14–22, 25, 27, 34, 41). Nevertheless, cAVMs occurred earlier in young patients, with higher actuarial OBRs in children at 2 years (82.3–86%) (4, 6, 23) and 3 years (72–84.1%) (2, 8) than in adults (41.2–80% and 54.7–80%, respectively) (14, 17, 22–26, 37, 38). Treatment–obliteration intervals also seemed to be shorter in children/adolescents than in the series including all age groups. In pediatric studies, several investigators reported a mean/median latency period ranging between 14 months and 21.5 months (2, 11, 23), as against 23–28.5 months in adult patients (14, 22, 27).

Only a few studies have compared these data in adults and children. In one of their initial reports, the Pittsburgh team reported that 11 of 13 children (85%) aged <19 years showed cAVM obliteration within at least 2 years of radiosurgery (23). Their findings supported the claim that (for comparable doses and similar volumes) cAVMs in children are obliterated sooner after treatment than in adults. Tanaka et al. (30) showed that the OBRs at 1 and 2 years after GKR were much higher in children (74% and 95%, respectively) than in adults (45% and 81%, respectively). They concluded that pediatric cAVMs might be more likely to respond to radiosurgery by occlusion than those in adults, but they did not formulate any hypothesis to explain this. In our series, the median TOI was 25.7 months in children/adolescents and 28.2 months in adults (p = 0.017). The difference between the actuarial OBRs at 3 years in Group A (69.35%) and Group B (66.84%) also proved highly significant (p = 0.006).

Our findings and those gathered from the literature seem to suggest a different response to radiation by cAVMs in pediatric and adult patients. As early as 1991, Lunsford et al. (23) postulated that this phenomenon might be related to greater radiation sensitivity in younger patients, although no biologic evidence emerged to support this theory until recently. Histopathologic, immunohistochemical, and electron microscopic examination of cAVM specimens obtained postoperatively 10–60 months after GKR demonstrated that the endothelial damage caused by irradiation induces the proliferation of smooth muscle cells and the production of extracellular collagen by these cells, which leads to progressive stenosis and obliteration of the cAVM nidus (45). In addition, the contractile activity of these gamma ray–activated, spindle-shaped smooth muscle cells and the transformation of the resting cells into an activated form after irradiation might be relevant to the shrinking process and eventual occlusion of AVMs after radiosurgery (46). More recently, Hashimoto et al. (47) identified nonresting endothelial cells by using immunohistochemistry for the Ki-67 antigen from surgical samples of human cAVMs. They showed that the mean Ki-67 index was higher for cAVM vessels than for control brain cortical vessels (0.7% ± 0.6% vs. 0.1% ± 0.2%; p = 0.005), with an approximately sevenfold difference between the number of nonresting endothelial cells in the two samples. In the cAVM group, there was a trend for younger patients to have a wider variation and a higher Ki-67 index than older patients; no trend was evident in the control group. The greater number of nonresting cells found in young patients’ vessels might allow an earlier activation response in case of radiation treatment, inducing more rapid cAVM nidus obliteration in children/adolescents than in adults. The shorter TOI in children/adolescents than in adults has the clinical advantage of a lower risk of bleeding during the latency period in younger patients, as already reported and discussed in Part I of our study.

Prognostic factors for OBR and TOI

Several prognostic factors influencing radiosurgical outcome have been reported. In pediatric series, the factors that have most frequently been found to predict OBR at univariate and multivariate analysis were cAVM volume and PD. Nidus volumes of less than 3 to 4 cm³ and higher PDs (>15–18 Gy) (1, 2, 8–10) correlated closely with OBR. In a large series of 100 cAVMs in children and adolescents, Shin et al. (2) also showed that lower SM grades (I–III), along with patient ages of ≤12 years, were significantly associated with radiologic success. Nataf et al. (9) found a significant correlation between sex and cAVM response to radiosurgery, with 84.2% OBR for boys and 40% for girls. They explained this difference by size stratification, because of the higher mean size of cAVMs in girls in their series.

In series including all age groups, many other independent variables apart from nidus dimensions and increasing PDs proved to be significant predictors for OBR (13, 14, 16–20, 22–24, 34–38). Some investigators found that lower SM grades correlated with OBR (20, 35). Zipfel et al. (13), Shin et al. (14), and Chang et al. (17) demonstrated that compact nidus structure correlated with a higher neuroimaging-defined cure rate than diffuse cAVM structure. The lack of preradiosurgical embolization has been reported to be an independent factor predicting obliteration (18, 19, 36).
Flickinger *et al.* (36) reported that the in-field angiographic OBR was higher in men (114 of 125, 91.2%) than in women (106 of 139, 76.2%), with the difference proving statistically significant at multivariate logistic regression analysis. The Pittsburgh team also found that male patients had a statistically significant higher cAVM OBR compared with female patients aged 12–49 years (89% vs. 78%, *p* = 0.0102) (48). This difference might be due to a potential vascular protective effect of estrogen, which might partially limit radiosurgical cAVM obliteration.

As for blood flow through the cAVM, Petereit *et al.* (49) reported that all nine cAVMs with intermediate or slow flow showed partial or complete obliteration, whereas only three out of five fast-flow cAVMs responded to treatment. But this was a study of only 14 cases, with a median follow-up that was too short (10 months), and with no statistical analysis. More recently, Inoue *et al.* (34) described OBRs of 91.3% and 67.6% in low- and high-flow cAVMs, respectively. They concluded that flow parameters could be used to predict radiosurgical response.

Finally, the correlation between patient age at treatment and OBR should be emphasized. Pollock *et al.* (19) reported that younger patient age was a factor associated with successful cAVM radiosurgery at multivariate linear regression analysis. As early as 1989, Kemeny *et al.* (39) had observed that there was a much better response in patients aged <20 years (75% favorable) than in those aged 20–40 years (45%) or >40 years (approximately 25%).

On the other hand, there have been very few studies of prognosticators for TOI. In the pediatric series, to our knowledge, only Nataf *et al.* (9) investigated factors potentially predicting the TOI; at univariate and multivariate analysis, they found that smaller nidus dimensions, minimum dose >15 Gy, complete cAVM volume coverage, and arteriovenular fistulas at cAVM angioarchitecture correlated significantly with shorter obliteration. In the series including all age groups, factors leading to earlier obliteration of the nidus were smaller size of cAVMs, male sex, hemorrhage before radiosurgery, and higher average dose (14, 16, 37). Meder *et al.* (20) observed that deep-seated cAVMs (Type B) were obliterated faster than others, but they found no convincing explanation for this difference in response. Blood flow through the cAVM also seems to influence the TOI. Petereit *et al.* (49) and Inoue *et al.* (34) noted that slower-flowing cAVMs might be obliterated faster after radiosurgery: they reported that early obliteration (within 12 months) was achieved in 63% of low-flow cAVMs and 28.6% of the intermediate- or high-flow cAVMs. They concluded that to increase the OBR and decrease the TOI, intravascular embolization might be considered before radiosurgery for intermediate- and high-flow cAVMs.

Finally, it is interesting to remember that Lunsford *et al.* (23) described earlier cAVM obliteration after treatment in children than in adults. Kemeny *et al.* (39) and Shin *et al.* (14) also reported a significant correlation between age and TOI. They found that patients aged <20 years had a better chance of radiosurgical success than older age groups and that the difference was statistically significant. Nevertheless, to our knowledge, no studies have made a statistical comparison between prognostic factors for OBR or TOI in pediatric/adolescent patients and adults. Tanaka *et al.* (30) compared the OBR and TOI in pediatric and adult cAVMs treated by GKR. They found shorter TOI and higher OBR in children than in older patients, but no detailed statistical analysis was made.

In our study, the prognostic factors correlating with OBR and TOI were different in children/adolescents and adults. Statistical analysis of data from Group A showed that the younger the patient, the higher the OBR. Higher OBR also seemed to correlate with deep-seated location and lower SM grades, but this did not prove statistically significant when logistic regression analysis was applied. As for TOI, factors leading to earlier obliteration of the nidus were lower SM grades and noneloquent sites.

Noneloquent location has never before been reported to be significantly associated with radiosurgical outcome in pediatric series, and its role as a predictive factor in studies in all age groups is controversial. Meder *et al.* (20) reported that deep-seated cAVMs were obliterated faster than others. These investigators postulated that the different responses to radiosurgery by deep-seated and superficial cAVMs might be related to a difference in local environment. Because deep-seated cAVMs are surrounded by densely packed areas of brain tissue, they might have a different radiosensitivity to cAVMs located in areas in contact with cerebrospinal fluid; there was, however, no evidence to support this hypothesis. Kemeny *et al.* (39) claimed that laterally located AVMs respond better to radiosurgery than those in the midline. According to these investigators, the reason for this difference must be that midline cAVMs are more frequently supplied by afferent vessels arising from several main arterial trunks: in their experience, cAVMs supplied by afferent vessels arising from several main arterial trunks were less likely to be completely obliterated than those supplied by vessels arising from a single arterial trunk. In an earlier study of ours (27), we reported slightly earlier obliteration of the nidus in basal ganglia than in cortical AVMs, but the difference did not prove statistically significant. The earlier obliteration of cAVMs located in noneloquent vs. eloquent sites in children/adolescents could be explained by the higher and more effective radiation dose that can be administered to the margins of cAVMs in critical brain areas. In the present study, for example, a mean maximal dose of 43.2 Gy was administered to cAVMs in noneloquent brain areas, compared with a mean maximal dose of 40.4 Gy elsewhere.

The statistical analysis applied to Group B patients showed that low flow in cAVMs and volume <6.2 cm³ correlated closely with better OBRs and shorter time to obliteration. These results might suggest that intermediate- or high-flow cAVMs should undergo pre-GKR percutaneous endovascular embolization, with the aim of reducing the blood flow to a slower speed and thus increasing radiosurgical effectiveness. However, the true efficacy of this therapeutic strategy needs to be studied on a larger series of
CONCLUSIONS

- Gamma Knife radiosurgery is confirmed as an effective treatment modality for cAVMs, with >85% overall OBRs both in pediatric/adolescent patients and adults.
- The cAVM obliteration process continues for up to 5 years after radiosurgery in some patients. Therefore, we recommend not retracting the incompletely obliterated cAVMs until 5 years have elapsed since the first treatment.
- The higher actuarial OBR at 3 years and the shorter TOI in younger than in older patients, along with the different prognostic factors that significantly correlate with OBR and TOI in children/adolescents and adults, further support the hypothesis that the radiosurgical response of cAVMs might be influenced by patient age at treatment, and suggest that they should be considered two different vascular disorders in the two age groups.
- Therefore, we recommend that cAVMs in pediatric patients should be separated from adult series when studies of radiosurgical outcomes are carried out.

REFERENCES


