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Risk for Hemorrhage the First 2 Years After Gamma Knife Surgery for Arteriovenous Malformations: An Update

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BACKGROUND: Knowledge about the natural course of brain arteriovenous malformations (AVMs) have increased during the past 20 years, as has the number of AVMs treated, especially larger ones. It is thus timely to again analyze the risk for hemorrhage after Gamma Knife Surgery (GKS).

OBJECTIVE: To confirm or contradict conclusions drawn 20 years ago regarding factors that affect the risk for post-GKS hemorrhage.

METHODS: The outcome after GKS was studied in 5037 AVM patients followed for up to 2 years. The relation between post-treatment hemorrhage rate and a number of patient, AVM, and treatment parameters was analyzed. The results were also compared with the results from our earlier study.

RESULTS: The annual post-treatment hemorrhage rate was 2.4% the first 2 years after GKS. Large size, low treatment dose, and old age were independent risk factors for AVM hemorrhage. After having compensated for the factors above, peripheral AVM location and female sex, at least during their child bearing ages, were factors associated with a lower post-GKS hemorrhage rate.

CONCLUSION: Large AVMs (>5 cm^3) treated with low doses (≤16 Gy) had higher and small AVMs treated with high doses a lower risk for hemorrhage as compared with untreated AVMs. This was detectable within the first 6 months after GKS. No difference in hemorrhage rate could be detected for the other AVMs. Based on our findings, it is advisable to prescribe >16 Gy to larger AVMs, assuming that the risk for radiation-induced complications can be kept at an acceptable level.

KEY WORDS: AVM hemorrhage, Gamma Knife Surgery

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A major factor defining the incidence of postradiosurgical arteriovenous malformation (AVM) hemorrhages is the time between treatment and obliteration. The shorter the period studied, the lesser the impact of obliteration on the hemorrhage rate. To minimize the impact of obliteration, we decided to closely study the hemorrhage rate the first 2 years after Gamma Knife (Elekta AB) Surgery (GKS). It coincides with the definition of the latency period stated by Steiner during the earlier days of GKS, and it enables us to compare our findings with an earlier study,[1] hereafter KLS study, when studying factors related to the risk for hemorrhage.

ABBREVIATIONS: GKS, Gamma Knife Surgery.

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The KLS study[1] concluded that the risk for hemorrhage the first 2 years after GKS was strongly correlated with the lowest dose to the AVM nidus (D_{min}), the AVM volume (AVMvol), and the age of the patient.[1] The assumption was, at that time, that the age and AVMvol dependence were caused by inherent features of the AVMs rather than being an effect of the radiation. A recent study has shown these assumptions to be inaccurate and that the risk for hemorrhage in patients with earlier unruptured AVMs is neither related to the AVMvol nor to the age of the patient.[2]

It is therefore timely to reassess the findings from 20 years ago, taking the new information about the natural course into consideration. In addition, GKS has evolved since the earlier study, and better imaging and dose planning have allowed larger AVMs to be treated. The patient

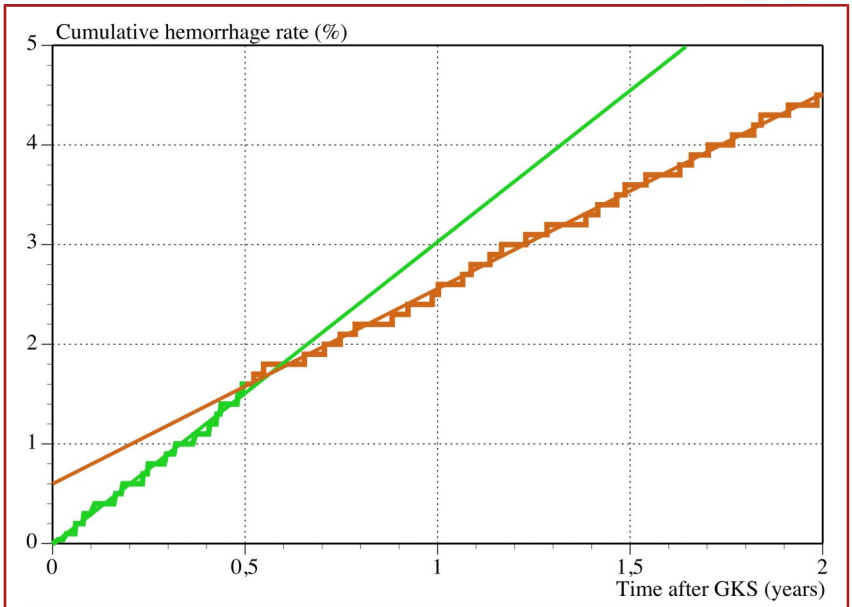

FIGURE 1. *Kaplan-Meier plot for the cumulative hemorrhage rate after GKS. The hemorrhage rate fits well with that of untreated arteriovenous malformations the first 6 months after GKS (green line) to decrease with 1% thereafter (orange line). The straight lines represent the linear curve fits, f(x) = 0.3x − 0.02 for the first 6 months and f(x) = 2x + 0.6 for the following 18 months, R^2 = 0.99 for both. GKS, Gamma Knife Surgery.*

population has also increased. We recently published a study based on the, to the best of our knowledge, largest AVM patient population yet published, assessing the clinical outcome in patients who hemorrhaged after GKS.[3] We decided to closely analyze the hemorrhage rate within the first 2 years after GKS in this patient population to validate or reassess the findings in the KLS study.[1] For completeness, we also added information about the global hemorrhages rate after GKS in the **Supplementary Material**, http://links.lww.com/NEU/D350.

METHODS

Data were extracted from ethics committees approved prospective databases for all AVM patients treated with GKS in the participating centers. All patients with follow-up information were included in this study. Owing to the retrospective design of this study and deidentification of data, the need for patient consent was waived by all IRBs. Data from the KLS study[1] were also included.

Follow-up information was available from 5037 patients. The time at risk was defined as the first 2 years after GKS. The time at risk was shortened if the patients hemorrhaged (213), the AVM obliterated, defined on angiogram or MR imaging (823), or if the follow-up time was <2 years (597). The mean follow-up time for the 597 patients with <2 years follow-up was 1.1 years, and the total number of risk years in the whole patient population was 8792 years. For further information, see the **Supplementary Material**, http://links.lww.com/NEU/D350.

RESULTS

Post-Treatment Hemorrhage Rate

A total of 213 patients (4%) hemorrhaged between 0.1 and 23.9 (mean 10.4 and median 9.4) months after GKS, resulting in an annual hemorrhage rate of 2.4%. The hemorrhage rate was higher for patients with older age, larger AVMs, male sex, and AVMs treated with lower doses, $P < .01$ for all. No significant relation was found between hemorrhage rate and AVM location (central vs noncentral), $P = .16$, embolization, $P = .27$, or history of pre-GKS hemorrhage, $P = .20$. The post-treatment hemorrhage rate was higher among the patients with unruptured AVMs (4.7%) as compared with the other (3.9%).

Figure 1 illustrates a Kaplan-Meier plot of the cumulative hemorrhage rate after GKS. A linear curve fit f(x) = 0.304 * x − 0.0183; R^2 = 0.99 describes the data well the first half year after GKS. This represents a 3% annual risk for hemorrhage (green line). A "knee" in the curve can be seen thereafter, after which it again becomes linear f(x) = 1.96 * x + 0.593; R^2 = 0.99, representing an annual risk of 2% (orange line). It seems to be an "incubation" period of 6 months, during which the risk for hemorrhage is similar as for untreated AVMs and that the risk decreases with 1% thereafter. Thus, the hemorrhage rate P for the whole patient population during the first 2 years after GKS can be expressed by

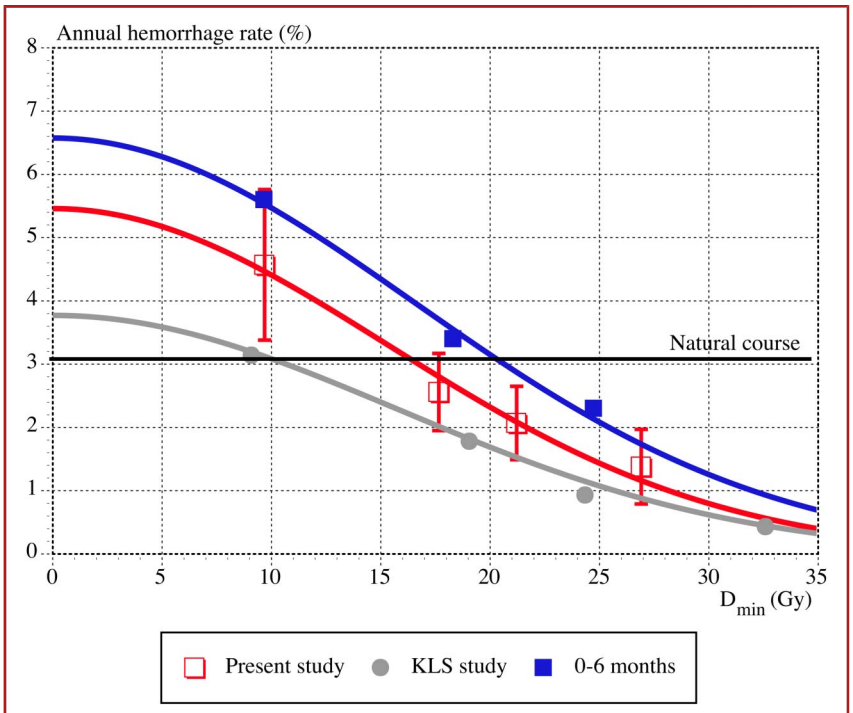

FIGURE 2. *Gaussian curve fits for the first 2 years (red square) and the first 6 months (blue square) after GKS. For comparison, data from the KLS study[1] are included as well (gray circle). The error bars represent the 95% confidence intervals. The curve fit (2) describes the data sets well. The post-treatment risk for hemorrhage is higher than the natural course for D_{min} < 16 Gy, and the relation between D_{min} and hemorrhage rate stronger during the first 6 months after GKS. GKS, Gamma Knife Surgery.*

$$\begin{aligned} P(\%) &= 3 * t \text{ if } t \le 0.5 \text{ year and } P \\ &= 1.5 + 2^*(t\text{-}0.5) \text{ if } 0.5 \le t \le 2 \text{ years} \end{aligned} \quad (1)$$

where t = time after GKS in years. The formula can be used for calculating the expected hemorrhage rate in large patient populations, but because it neither takes D_{min} nor AVMvol into consideration, another prediction model is needed to predict hemorrhage rates at an individual level.

Minimum Dose and Hemorrhage Rate

D_{min} was on average lower for large AVMvol, young patients, embolized AVMs, and unruptured AVMs, $P < .01$ for all. Sex ($P = .90$) and AVM location ($P = .81$) were not significantly related to D_{min}.

The relation between D_{min} and hemorrhage rate was studied by dividing the patient population in 4 groups: D_{min}: ≤15 Gy (N = 692), >15 < 20 Gy (N = 1439), ≥20 < 25 Gy (N = 1314), and ≥25 Gy (N = 880). The relation between D_{min} and the posthemorrhage rate could be accurately described by a Gaussian curve fit with the general function of

$$y = a^*\exp(-b*x^2) \quad (2)$$

where y = annual risk for hemorrhage, x = D_{min}, and a and b are constants. As presented in Figure 2, the curve fits describe all data sets well, with the values a = 5.46 and b = 0.00214 ($R^2 = 0.98$) for the whole patient population (red curve).

There was a strong relation between D_{min} and the hemorrhage rate. This relation is more pronounced during the first 6 months after GKS, contradicting the findings in Figure 1. It seems like the higher risk for patients treated with low D_{min} is balanced by the lower risk for the patients treated with high D_{min}, with 20 Gy being the break point for the first 6 months.

AVM Volume and Hemorrhage Rate

The patient population was divided in 5 groups: AVMvol: ≤2 cm^3 (N = 1022), >2 ≤ 4 cm^3 (N = 761), >4 ≤ 6 cm^3 (N = 461), >6 ≤ 10 cm^3 (N = 520), and >10 cm^3 (N = 761). If the risk for hemorrhage is D_{min} but not AVMvol dependent, then the expected hemorrhage rate, calculated using equation (2), should be similar to the observed number of hemorrhages and independent

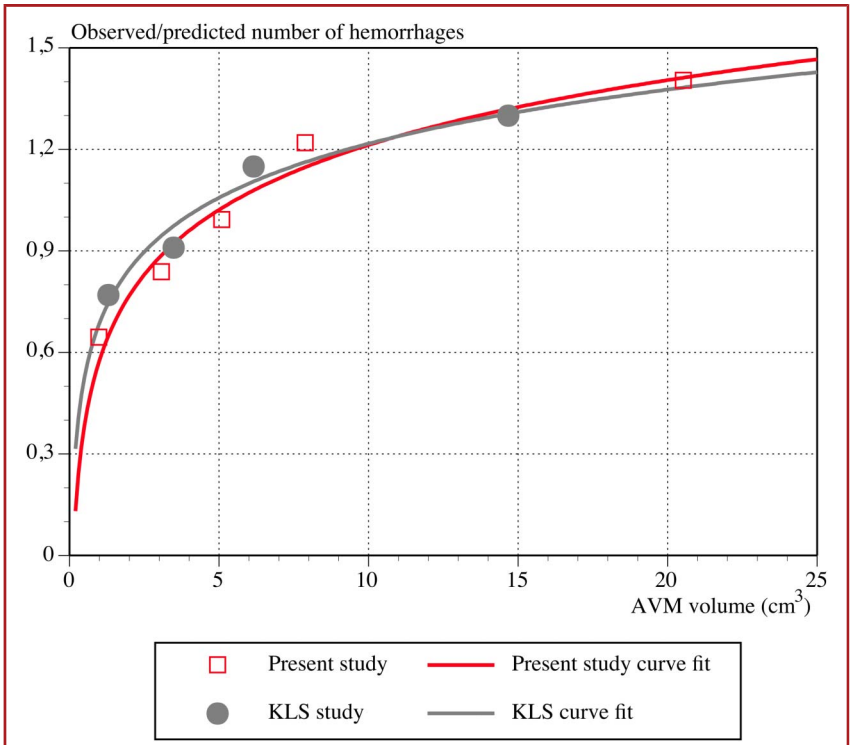

FIGURE 3. *Quotient between observed and predicted number of hemorrhages, using equation (2), compensating for D_{min}. For comparison, data from the KLS study[1] are included as well (gray circle). Larger arteriovenous malformations have a D_{min} independent higher risk for rupture as compared with smaller ones.*

of the AVM volume. This was not the case. We found a D_{min} independent relation between AVMvol and hemorrhage rate.

The results from this study are presented in Figure 3. As seen, both data sets are well described with the logarithmic curve fit.

$$y = a + b*\ln(x) \quad (3)$$

where y = the quotient observed/predicted hemorrhage rate, x = AVMvol, and a and b are constants with the best fit values a = 0.576 and b = 0.277 (R^2 = 0.97) for this study. It is clear that smaller AVMs have a lower and larger AVMs a higher risk for hemorrhage as compared with what is predicted based on D_{min} only.

Hemorrhage Rate Vs Age

To analyze a potential D_{min} and AVMvol independent relation between the age of the patient and the rate of AVM ruptures, the patient population was divided in 5 groups: younger than 18 years (N = 761), 18 years or older and younger than 35 years (N = 1897), 35 years or older and younger than 50 years (N = 1358), 50 years or older and younger than 65 years (N = 810), and 65 years or older (N = 211). The observed/predicted hemorrhage rates were calculated for each group using formulas (2) and (3). As presented in Figure 4, strong age dependence was found, being reasonably well described by a linear curve fit.

$$y = a*x + b \quad (4)$$

where y = the quotient observed/predicted hemorrhage rate, x = age at GKS, and a and b are constants with the best fit values a = 0.0190 and b = 0.404 (R^2 = 0.94) for this study. The lower hemorrhage rates for younger patients do not express a difference between adult and pediatric patients, but a continuously increasing hemorrhage rate with age.

Cumulative Hemorrhage Rate Related to D_{min}, AVMvol, and Age

Based on Figures 2, 3, and 4, the break points between relative increase or decrease in hemorrhage rates are ≤16 Gy, ≤5 cm^3, and 30 years or younger. By using these break points, the patient population can be divided in 8 groups. The relations between time and cumulative hemorrhage rate for all groups are shown in Figure 5. Large AVMs treated with low D_{min} (red lines in the figure) have an age unrelated and twice as high rate for hemorrhage as compared with untreated AVMs. Small AVMs treated with high D_{min} (green lines) have an age unrelated and around half

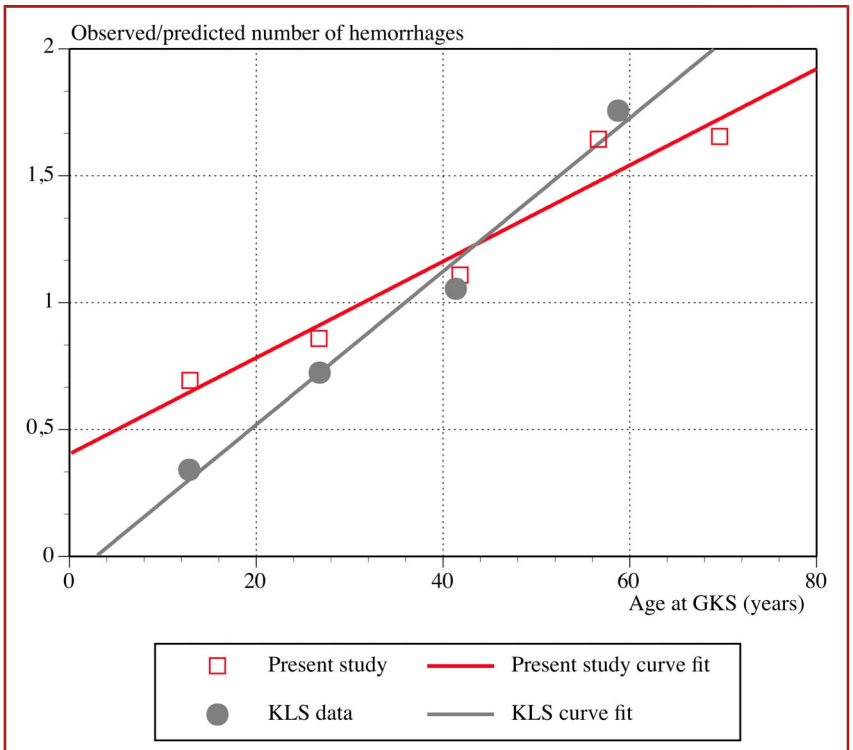

FIGURE 4. *Relation between age of the patient and the quotient observed/predicted number of hemorrhages, compensating for D_{min} and AVMvol by using formulas (2) and (3). For comparison, data from the KLS study[1] are included as well (gray circle). As seen, a liner curve fit describes the relations between age and hemorrhage rate well.*

of the hemorrhage rate as compared with the natural course. Large AVMs treated with high D_{min} (blue lines) have on average a similar hemorrhage rate as untreated AVMs, but with a significant difference between young and old patients. The hemorrhage rate for small AVMs treated with low D_{min} (cyan lines) is close to the natural course.

Other Factors Related to the Hemorrhage Rate

To use the equations (1) and (2-4) to search for other factors that may influence the risk for hemorrhage, their validity must first be confirmed. As presented in Table, equation (1) accurately predicts the total number of hemorrhages but does so poorly when the patient population is divided based on AVM volume, D_{min}, and age of the patient. When using equations (2-4), the predictive power is accurate and unrelated to the 3 parameters above. Thus, only the results based on equations (2-4) will be discussed in the following.

As presented in Table, the observed hemorrhage rate is higher than predicted for central AVMs and lower for female patients in their child-bearing ages. The observed higher rate for central AVMs is in line with the 1% increase in risk for centrally located AVMs found earlier.[2] Thus, this difference is most likely not related to the radiosurgical treatment but to the natural course of AVMs. The lower hemorrhage rate found for women 15 to 40 years implies that hormonal factors may have a protective effect against AVM hemorrhages, at least after GKS.

DISCUSSION

Is Pretreatment Hemorrhage a Risk Factor?

There is a consensus that the risk for AVM hemorrhage is higher after a rupture, at least during the first year after the event. At first glance, this could neither be verified in this study nor in another multicenter study analyzing a large patient population.[4] Actually, nonruptured AVMs hemorrhaged *more* frequently (97/2081) as compared with those who had ruptured within 1 year before GKS (64/1872), $P = .05$. This is to some extent because of unruptured AVMs being larger, on average 8.1 cm^3 as compared with 3.5 cm^3 for the other.

A deeper analysis yields a different result. When equations (2-4) are used, compensating for differences in AVMvol, age, and D_{min}, the number of observed hemorrhages (104) was higher as compared with the predicted number (92) for AVMs which had ruptured before GKS. For unruptured AVMs, the opposite trend was true. Here, we observed a lower number of hemorrhages (88), as compared with the 102 predicted (Table). Thus, it seems that

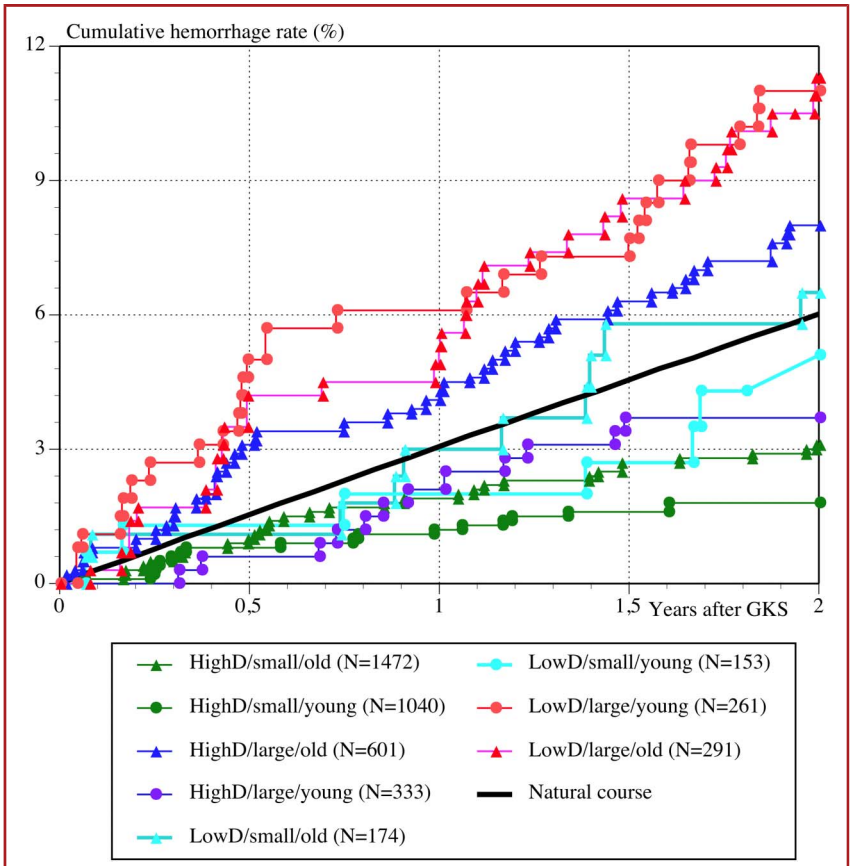

FIGURE 5. *Kaplan-Meier plot of the natural course and the post–Gamma Knife Surgery hemorrhage rates for 8 different groups of arteriovenous malformation (AVM) patients. The graph shows the importance of D_{min} and AVMvol for the hemorrhage rate. The impact of age seems most relevant for large AVMs treated with high doses.*

ruptured AVMs do carry a higher risk for a post-treatment hemorrhage.

These findings have clinical implications. The 2-year hemorrhage rate among small AVMs without a history of a prior hemorrhage was 23/945 (2.4%). Based on our earlier research, the complication rate for small AVMs was 3.4% for the same period.[5] This should be compared with the 6.2% risk for hemorrhage without treatment. It is thus clear that radiosurgery is safer than no treatment for small unruptured AVMs already within the first 2 years after GKS.

Hemorrhage Rate During the First 6 Months After GKS

The risk for hemorrhage has been considered to be unaffected during the first 6 months after GKS.[6] Our findings are consistent with this assumption when looking at the whole patient population (Figure 1). However, as shown in Figure 2, the incidence of hemorrhage is even more dose dependent during the first 6 months as compared with the 18 months thereafter. This must be caused by a short-term radiation response by the AVM. A hypothesis offering an explanation for this is that radiation will more frequently cause inflammatory reactions and acute thrombosis in parts of the AVMs radiated with higher doses.

If so, on the one hand, most, if not all, of an AVM treated with high doses is likely to thrombose, resulting in a decreased flow through the AVM nidus, decreasing the risk for hemorrhage. If, on the other hand, parts of the AVM are treated with high doses and parts with low doses, a redistribution rather than a decrease in the flow is likely to result, changing the hemodynamics, resulting in higher flow in the veins draining the still patent AVM. This could cause a "break through" phenomenon, just as described after surgical removal of large AVMs.[7] Colombo et al[8] suggested a similar mechanism earlier. Further studies are needed before this hypothesis can be verified.

Hemorrhage Rate Vs AVM Volume

We know from earlier studies that the lower the average dose, the longer the time for obliteration to occur.[9] Consequently, larger AVMs will on average be at risk for hemorrhage for a longer

TABLE. Relation Between Observed and Predicted Number of Hemorrhages for Different Patient Categories

Group of patients	N	H	H%	CI	Risk years	Eq. 1	SS	Eq. 2-4	SS
All patients	5037	213	2.4	±28	8792	203	NS	NA	NA
Known D_{min} AVMvol	4325	192	2.5	±27	7636	176	NS	194	NS
AVMvol ≤5 cm^3	2839	76	1.5	±17	4946	114	SS	81	NS
AVMvol >5 cm^3	1486	116	4.3	±20	2690	62	SS	114	NS
D_{min} ≤16 Gy	879	76	4.8	±16	1569	36	SS	73	NS
D_{min} >16 Gy	3446	116	1.9	±21	6067	140	SS	122	NS
Age 34 years or younger	2183	79	2.0	±17	3859	89	NS	80	NS
Age older than 34 years	2142	113	3.0	±20	3777	87	SS	115	NS
Central AVM location	1195	63	3.1	±15	2040	47	SS	43	SS
Noncentral AVM location	3130	129	2.3	±22	5596	129	NS	151	NS
Female patients	2001	73	2.0	±16	3573	82	NS	87	NS
Female 15-40 years	1174	35	1.7	±11	2105	48	SS	48	SS
Male patients	2324	119	2.9	±21	4062	94	SS	107	NS
Prior embolization	874	46	2.9	±13	1575	36	NS	45	NS
No embolization	3451	146	2.4	±23	6060	140	NS	150	NS
Prior hemorrhage	2502	104	2.4	±20	4288	99	NS	92	NS
No prior hemorrhage	1812	88	2.6	±18	3330	76	NS	102	NS

AVM, arteriovenous malformation; Eq, equation; N, number of patients; H, number of hemorrhages, 95% CI.
Predicted and observed number of hemorrhages the 2 first years after GKS for different patient, AVM, and treatment parameters.
SS denotes values outside the 95% CI, while NS denotes a value within the interval. As seen, equations (2-4) compensate accurately for D_{min}, AVMvol, and age but not so for AVM location and female sex.

time as compared with smaller ones. This would contradict the assumption that the volume dependence is radiation related. However, only 25 of the 393 AVMs ≥10 cm^3 that obliterated did so within the first 2 years after GKS, and thus, the impact of this will be limited in this study. One factor speaking for the observed reaction being radiation induced is the strong relation between D_{min} and hemorrhage rate for large AVMs (Figure 5). Large AVMs treated with low D_{min} had a high hemorrhage rate. By contrast, large AVMs in younger patients treated with high doses had a low hemorrhage rate. Furthermore, the pretreatment hemorrhage risk is unrelated to the AVM volume.[2]

Our Findings Compared With Earlier Published Studies

A literature search for articles where the 2-year hemorrhage rate and the number of risk years within the first 2 years after GKS can be extracted, calculated or estimated, with at least 100 patients studied, yielded 12 references.[1,6,8,10-18] The sum of risk years was 9799 and the number of hemorrhages 216, representing an average annual hemorrhage rate of 2.2%, similar to the 2.4% found in our study.

The relation between AVM volume and postradiosurgery hemorrhage rate has been observed by many,[4,14,18-21] as has the relation between prescription dose and hemorrhage rate.[8,10,14,16,21] These factors have, however, not been quantified earlier, except in the KLS study.[1]

Limitations

The definition of the AVM nidus is subjective. Thus, for a given treatment, different definitions of the AVM nidus volume will result in different minimum doses to the AVM nidus. Furthermore, intranidal aneurysms, venous stenosis and other factors that may affect the risk for hemorrhage are not taken into account in this study. This needs to be taken into consideration should the findings in this study be used as a prediction model.

CONCLUSION

Low D_{min}, large AVMvol, and central AVM location are all risk factors for post-treatment AVM hemorrhage. Female sex, at least during their fertile years, and young age seem to protect from hemorrhage. The age dependence seems applicable only for patients with large AVMs treated with high D_{min}. The risk for AVM hemorrhage within the first 2 years after GKS is, as compared with no treatment, lower for small AVMs treated with high doses and higher for large AVMs treated with low doses and unaffected for all other AVMs.

The abovementioned are arguments to prescribe 16 Gy or more to larger AVMs, assuming that the risk for radiation-induced complications can be kept at an acceptable level.

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The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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

Supplementary Material. Materials and Methods, 1 Figure, 1 Table. The Supplemental Digital Content, expands on the Methods provided. Supplemental Figure 1. Relation between the annual post-treatment hemorrhage rate in 27 published articles (X) and our data (+). The data fit reasonably well with the exponential curve fit y = 3.75*exp(− 0.18x).
Supplemental Table 1. Patient characteristics.