DIFFERENT concepts can be used to overcome the volume limitation in AVM radiosurgery. One is staged radiosurgery, in which the AVM nidus is divided into smaller subvolumes and each of them is treated as an independent AVM, separating the treatments by approximately 6 months. This assumes that the previously irradiated parts will completely occlude, which is not always the case; it was shown in a recently published study that the majority of AVMs did not occlude following staged radiosurgery. In addition, the obliteration rate might have been even lower if there had been any patients in whom the staged radiosurgical treatment was initiated but not completed.

Another method of overcoming the volume limitation is to use conventional fractionated radiotherapy. We have shown earlier that the obliteration rate following radiotherapy in which standard doses per fraction are used is low. In another study based on a retrospective analysis in which the results following AVM radiosurgery were compared with the ones following fractionated radiotherapy, it was suggested that the obliteration rate decreases with increasing total dose and increases with increasing dose per fraction. If correct, the obliteration rate following a fractionated treatment with a given dose per fraction will be similar if a radiosurgical treatment with the same dose has been used instead.

The Taipei group has also shown that it is possible to obliterate large AVMs with conventional radiosurgery. We showed in an earlier study that most AVMs that do not obliterate decrease in size. We found that a dose of 10 Gy decreases the AVM volume by an average of 40%, and a dose of 15 Gy by 50% (B. Karlsson, unpublished data). We have also shown that the obliteration rate following repeated treatment is the same as for untreated AVMs.

Taking all these observations together, it is tempting to suggest a novel concept: repeated radiosurgery. The idea is to irradiate the whole AVM nidus with a low dose of radiation, wait 3 to 4 years, and then treat the remaining AVM portion, if there is any, again. This idea was suggested by one of the authors (H.J.), who prospectively started to evaluate this concept. The criticism most pertinent to such a treatment strategy is that most of the aforementioned radiosurgical results are based on small- to medium-sized AVMs, and that it is unclear whether these results can be extrapolated to larger AVMs.

We therefore decided to analyze this further by evalu-
ating the results in the larger AVMs treated. To get a sufficiently large patient cohort for a meaningful analysis, all cases fulfilling the AVM definitions given in the following section and treated at the Karolinska Hospital, Katsuta Hospital, and Furukawa Seiryo Hospital were included in the study.

Clinical Material and Methods

All patients with an AVM nidus volume of 9 ml or more who were treated with GKS (Gamma Knife, Elekta AB) with a prescription dose of 10 Gy or more were included in the study if the prescription dose covered the whole AVM nidus. There were 28 patients treated at the Karolinska Hospital between 1980 and 1995, 28 treated at Katsuta Hospital between 1992 and 2003, and 83 treated at Furukawa Seiryo Hospital between 1992 and 2005, for a total of 139 patients. No follow-up information of any kind was available for six patients, who were therefore excluded from this study. Thus, 133 patients were eligible for and included in the study.

There were 71 male (53%) and 62 female patients, the mean age was 31 years (range 5–68 years), and the median age was 29 years. The majority (75 patients) had not suffered a hemorrhage before the treatment, whereas 58 patients had hemorrhages before and after treatment. The average AVM nidus volume was 16 ml (range 9–56 ml), and the median volume was 14 ml. The prescription dose at the first treatment varied between 10 and 25 Gy (mean 16 and median 15 Gy), and the dose at the second treatment was between 15 and 25 Gy (mean and median, 18 Gy). The prescription isodose lines varied between 30 and 70% (mean and median, 50%).

The study was divided into clinical and angiographic assessments. In the clinical part, we analyzed the posttreatment hemorrhage rate and the incidence of radiation-induced complications. The end point of the angiographic part was either complete obliteration of the AVM nidus as verified by angiography or any imaging findings suggesting a patent AVM nidus 35 months or more after the treatment. The AVM was considered patent if the lesion hemorrhaged more than 3 years after the treatment, and its size was assumed to be the same as that on the most recent radiological examination. The angiography results after the first treatment were defined as unchanged if there was a less than 10% decrease; a bit smaller if there was an 11 to 50% decrease; much smaller if the decrease was 51 to 99%; and obliterated if the whole nidus was completely obliterated.

All 133 patients were included in the clinical study, whereas 89 patients were included in the angiography part of the study. The reasons for excluding the 44 patients were as follows: repeated treatment less than 35 months after the initial treatment (one patient); no imaging information (18 patients, of whom seven experienced hemorrhage within 6 months posttreatment); imaging information obtained less than 2 years after the treatment (13 patients); and imaging information obtained 2 to 3 years after the treatment (12 patients).

Forty-two patients were treated with GKS a second time, and two of these patients received this treatment a third time. Nineteen of the repeatedly treated patients were examined using angiography, which yielded conclusive results. Seventeen of the remaining 23 patients were treated after August 1, 2004.

For statistical analysis, the Mann–Whitney U-test was used to evaluate continuous and nominal data. The Fisher exact test was used to analyze two sets of nominal data. Kaplan–Meier analysis was used to assess the risk of posttreatment hemorrhage. A result was considered statistically significant if the probability value was less than 0.01.

Results

Obliteration Rate After the First Treatment

Following the first treatment, three AVMs (3%) were unchanged, 21 (24%) were a bit smaller, 40 (45%) were much smaller, and 25 (28%) were obliterated. There was a statistically significant relationship between the peripheral dose and obliteration (p = 0.03).

Obliteration Rate After the Second Treatment

In 19 (45%) of the 42 patients who underwent a second GKS treatment, angiography revealed AVM obliteration or a patent AVM 35 months or more after the second treatment. Of these 19 patients, in one (5%) the AVM was a bit smaller, in five (26%) it was much smaller, and the nidus was obliterated in 13 (68%). We could not see either a relationship between obliteration and prescription dose (p = 0.22) or one between obliteration and absolute volume decrease after the first treatment (p = 0.51). It is noteworthy that the results are so much better after the second treatment, despite the small difference in prescription dose (mean 16 Gy compared with 18 Gy).

Obliteration Results After the Third Treatment

Two patients were treated a third time, and in one of them, an angiogram obtained 15 months after the third treatment verified a complete occlusion of the nidus. In the other patient, an angiogram obtained 26 months posttreatment revealed a small AVM remnant.

Obliteration Rate After Repeated Radiosurgery

The results following repeated radiosurgery are illustrated in Fig. 1. The first treatment resulted in 25 obliterations, leaving 64 patients with a patent AVM. Of those, 42 underwent repeated treatment, resulting in 13 oblations in the 19 patients in whom angiography was performed. If we assume the same rate for the 23 patients not examined, another 16 obliterations will occur. Two patients were treated a third time; in one the AVM was obliterated. Thus, the total number of obliterations following repeated radiosurgery is expected to be 55, or 62% of the patients.

Posttreatment Complication Rate

A total of nine (7%) adverse radiation effects occurred in the 133 patients. Four (3%) of the patients developed neurological deficits, and another five developed late cysts, of which two were symptomatic, necessitating treatment. It seems that the tolerance for doses of approximately 15 Gy when treating large AVMs might be higher than previously assumed.

Posttreatment Hemorrhage Rate

Among the 58 patients in whom a hemorrhage occurred before the treatment, 13 (22%) also suffered a hemorrhage after the treatment. In the 75 patients in whom a hemor-
rhage did not occur before the treatment, 18 (24%) suffered a posttreatment hemorrhage. There was no significant difference in the incidence of posttreatment hemorrhage between patients who had experienced a hemorrhage before the treatment and those who had not (p = 0.83). Eleven (35%) of the hemorrhages occurred within the 1st year, nine (29%) between Years 1 and 2, and 11 (35%) 2 to 10 years after the treatment. Figure 2 illustrates the posttreatment hemorrhage rate in a Kaplan–Meier plot, showing that the 10-year nonhemorrhage rate was 47%, corresponding to a 7% annual incidence of hemorrhage. Another way to calculate the annual incidence of hemorrhage is to divide the number of hemorrhages (31) by the total number of risk years (466), again resulting in a 7% annual risk of hemorrhage.

Discussion

Repeated Radiosurgery as a Management Concept

The management of large AVMs is controversial. Combined treatments, fractionated radiation treatment, staged radiosurgical treatment, and other management strategies have all been recommended. Some investigators have also claimed that no treatment might be the best option, because the risk of hemorrhage for large AVMs has been considered to be low, an assumption that has been much debated. Actually, some studies suggest the opposite, which is in agreement with the findings in the present study. In an earlier study, we showed that low-dose fractionated radiation treatment is suboptimal. The high incidence of hemorrhage in this series raises a caveat against no treatment, because it leaves the AVM at risk for future hemorrhages. Our study shows that repeated radiosurgery might be a reasonable option for large AVMs, based on the relatively high estimated obliteration rate (62%) in this small series of patients.

Is the Obliteration Rate Different for Large and Small AVMs?

One interesting observation is the difference in the obliteration rate between the first and second treatment, despite the small difference in prescription dose. This may be due to a better response to radiation in patients with smaller AVMs, but it could also be a cumulative effect from the first and the second treatments, which might increase the obliteration rate.

How does this fit with earlier observations? We have shown in earlier studies that the probability for AVM obliteration is unrelated to the lesion’s volume and that the relationship between peripheral dose and obliteration rate is independent of the prior radiation given. We have also shown that the lower the amount of radiation given to the AVM nidus, the longer the time to obliteration. Also, the obliteration rate following fractionated radiotherapy is similar to the one following radiosurgery if the same dose per fraction is given.

The difference in obliteration after the first and second treatment reported in this study is incompatible with some of the earlier statements. For example, due to the longer time to obliteration for large AVMs, it might not be sufficient to wait just 3 years before the final result is assessed. Therefore, some of the repeated treatments might have been avoided if the AVMs had been monitored for a longer time. One can speculate that for larger AVMs, it might be better to minimize the target volume, running the risk of leaving parts of the AVMs outside the target volume rather than overtreating. The opposite is true for small AVMs.

We have already mentioned that the obliteration rate after a second radiosurgical treatment is comparable to the results after the first treatment. If larger AVMs had an inherent radioresistance factor, the result following the second treatment for small AVMs would be better than for larger ones. This was not the case; in the present study, an obliteration rate of 68% was found, compared with 61% in our series of repeatedly treated small AVMs. Therefore, we believe that the AVM volume effect is limited, but that further research is needed before a definite conclusion can be drawn.

Is the Hemorrhage Rate Different for Large and Small AVMs?

Some authors have concluded that small AVMs carry a
Repeated GKS compared with staged GKS for very large brain AVMs

higher risk of hemorrhage than large ones. This is based on the observation that small AVMs are more frequently diagnosed as being due to a hemorrhage than large ones. This, however, does not necessarily mean that smaller AVMs carry a higher risk of hemorrhages than larger ones. This difference could just as well be explained by the fact that small AVMs seldom cause seizures, migraine, neurologic deficits, or other symptoms often seen in patients harboring large AVMs. In an earlier study, we showed that large AVMs carry a higher risk of hemorrhage than do small ones. An annual incidence of hemorrhage of 6% was found in a series of 28 very large AVMs treated with fractionated radiotherapy and followed for up to 20 years after the treatment, suggesting the same conclusion.10 The higher risk of hemorrhage in larger AVMs is also supported by the findings in this paper, in which 11 (8%) of 133 patients suffered a hemorrhage within the 1st year after the treatment. Thus, the posttreatment hemorrhage rate is a more serious threat to patients with large AVMs than the risk of radiation-induced complications after repeated radiosurgery.

Could the High Posttreatment Hemorrhage Rate be Caused by Radiation?

Some suggest that the risk of AVM hemorrhage may be higher during the latency period between the radiosurgical treatment and its final outcome, compared with the rate occurring in the natural course of the disease. If so, the high incidence of hemorrhages in this cohort should be taken as a relative contraindication for repeated AVM radiosurgery. However, if the hemorrhage rate represents the natural course of the disease, the opposite is true. It is therefore important to discuss this issue further.

Let us assume that the risk of hemorrhage is at least as high for smaller AVMs as for the larger ones studied here. Let us further assume that radiation does increase the risk of hemorrhage. If so, we would expect at least the same rate of hemorrhage following AVM radiosurgery for smaller AVMs compared with larger ones. We would also expect that the risk of hemorrhage would increase with increasing treatment doses. Our earlier research has shown the opposite: when we analyzed 1593 AVMs treated with conventional GKS,4 the incidence of posttreatment hemorrhage was 2% and 1% for the 1st and 2nd year after the treatment, respectively, which should be compared with the 8% and 7% found here. In addition, the risk of hemorrhage decreased with increasing treatment doses. Furthermore, the incidence of posttreatment hemorrhage increased with increasing AVM volume after the differences in treatment doses had been taken into consideration. Thus, our controversial conclusion is that large AVMs do carry a higher risk of hemorrhage than smaller ones.

Revised Radiosurgery Compared With Staged Radiosurgery

Sirin et al.11 reported that one third of the analyzed AVMs were obliterated after staged radiosurgery. It should be noted that the majority of obliterations were based on magnetic resonance imaging and not on angiography, making a lower obliteration rate possible. Thus, the assumption that the subvolume(s) previously treated would be obliterated was proven wrong in the majority of cases. If so, it seems reasonable to wait until the final result of the prior treatment is available before an additional treatment is given. The disadvantage with this approach is that the latency time between the first treatment and obliteration will increase, increasing the risk of hemorrhage. For us, the higher obliteration rate as well as the aforementioned considerations suggest that repeated radiosurgery may be more appealing than staged radiosurgery.

It is noteworthy that 10% of the patients treated with repeated radiosurgery experienced hemorrhaging within the 1st year after the treatment, compared with 0% following staged radiosurgical treatment. One would expect a higher hemorrhage rate in the staged radiosurgery group, because a part of the AVM is left untreated for a period of time, and because a partial treatment may cause hemodynamic changes that increase the risk of hemorrhages. Could this be explained by an increased hemorrhage risk initially after a radiosurgical treatment? Probably not, because there is evidence that the risk of AVM hemorrhage is lower after compared with before a radiosurgical treatment.6 How can this difference be explained? One possible explanation would be that patients who experience a hemorrhage before the last staged procedure may not complete the staged treatment, and if so, will not be included in the study.11 Another is that the difference is caused by random factors. Further studies are necessary before this very important issue can be clarified.

Conclusions

Large AVMs carry a high risk of hemorrhage. Thus, an aggressive approach is necessary. We believe that repeated radiosurgery is a viable option for some AVMs that in earlier times were considered to be too large to benefit from radiosurgical treatment. It seems that the risk of posttreatment hemorrhage is a larger clinical problem than the risk of radiation-induced complications. Further studies are necessary before this very important issue can be concluded whether repeated radiosurgery is a better treatment than staged radiosurgery for large AVMs.

Dedication

We dedicate this publication to Melker Lindqvist, our mentor in neuroradiology, who passed away much too early. We not only miss his excellence, expertise, and scientific approach to radiosurgery and neuroradiology, but we miss much more a very good friend whom we had the pleasure to work with for many years.

References


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