ABSTRACT
The gamma knife treatment of cerebral arteriovenous malformation (AVM) has been studied at the Karolinska Hospital in Stockholm, Sweden, since 1970. In this review we evaluate the probability of total obliteration, the risk of radioinduced complications and the probability of post treatment of AVM. Applying this, the physician may be able to estimate the expected results following GK surgery for AVM.

Keywords: Brain arteriovenous malformation, gamma knife, prediction radiosurgery, risk complications, risk estimation formula.

The first gamma knife (GK) treatment of a cerebral arteriovenous malformation (AVM) was performed at the Karolinska Hospital in Stockholm, Sweden by Steiner in 1970. Since that time more than 1300 AVM have been treated in Sweden with GK surgery. Much has happened from the first treatment to the present time with the advent of radiosurgery as an established treatment modality for AVM. To define the role of GK surgery in comparison to microsurgery and embolization in the management of AVM an evaluation of the expected treatment results, following the different treatment modalities, has to be carried out. Ideally, this should be carried out for each case individually as it should be possible to predict the results prior to treatment. This is true in the case of GK surgery. Here, the probability for total obliteration, the risk of radioinduced complication and the probability for post treatment hemorrhage can be calculated. The aim of this review is to describe the facts and findings these calculations are based upon, making it possible for the reader to estimate the expected results following GK surgery for his own patients.

(A) AVM obliteration following GK surgery
The first report of an AVM obliteration following GK surgery was published in 1972. It was a case report of a patient treated with “gamma ligation.” The rationale was to ligate the feeders, and this was carried out by using one isocenter directed towards the feeding artery. An angiography carried out 19 months later revealed total obliteration. This case was followed by others treated with the same philosophy, but the results were not satisfactory. The treatment strategy was therefore changed to radiation of the whole AVM nidus volume, when possible.

In 1984 Steiner reported the results following different treatment strategies. The report was based on angiography follow-ups 192 (64%) of the patients and the treatments were divided into four groups: A: total; B: partial radiation cover of the nidus; C: coverage of all; D: some feeders. The two year angiography follow-up results were: 90/104 (86%) obliteration in group A: 0/10 in group B; 1/3 in group C and 0/4 in group D. The definition of the two year angiography follow-up being the endpoint to evaluate the treatment result has since become generally accepted for radiosurgery. The result in Group A=80% obliteration rate, has been accepted as the result expected following optimal radiosurgery. The Pittsburgh group published their first major AVM publication in 1991. Of 227 patients treated, 46 (20%) were followed up with a two-year angiography. They concluded that the results were AVM volume dependent, the obliteration rate decreasing with increasing AVM volume. Recently, the first 20 years of experience in GK treatments of AVM were analyzed. We concluded that the treatment result was both dose and AVM volume dependent. as described below.

The patient material consisted of 1319 consecutive AVM patients treated from 1970-1990. Included in the study were all patients with an angiography verifying total obliteration and all patients with evidence of persisting malformation ≥ 2 years after treatment were defined by either MR images, angiography or hemorrhage, in total
945 patients. Excluded were cases who had received radiotherapy before GK surgery and the results following a second GK treatment. Fifteen patients had 2 AVM’s and in this study each AVM was considered separately. Therefore, of the 1183 patients eligible for the study 945 (80%) were included. To estimate the volume of the AVM nidus, an indirect method was used. In GK surgery, the aim of the dose planning was to describe the whole AVM nidus periphery in line with the prescription isodose line. Therefore the volume within this isodose line can be used as an approximation of the AVM nidus volume. In this study, the AVM volume was defined as being equal to the volume within the best isodose line. In this material, the mean AVM nidus volume was 3.6 (1-50) cm³. Both the average and the minimum (=lowest periphery) dose given to the AVM nidus were related to the treatment outcome. The higher the dose given, the higher the incidence of obliteration. Additionally, the obliteration rate was inversely related to the AVM volume. These three parameters were, however, interdependent. By letting two parameters vary and keeping the third constant, it was obvious that the minimum dose was the decisive parameter for the treatment result. The relation between the minimum dose and the obliteration rate is illustrated in Fig. 1. It can be described quite accurately by a logarithmic function, \( f(x) = 3.57 \ln(x) - 0.4 \) (R²=0.99).

![Graph showing obliteration rate versus minimum dose.](image)

Fig. 1 The obliteration rate is plotted against the minimum dose in this graph. No dose threshold can be seen. The higher the minimum dose, the better the results.

The average dose, reflecting the amount of energy delivered to the malformation, was closely related to the obliteration time, defined as the time between treatment and the angiography proving obliteration. The relation between the average dose and the obliteration time (in months) could be described by a linear function, \( f(x) = -0.21x + 30 \) (R²=0.99). This suggests that the obliteration process is linearly energy dependent. A consequence therefore is that the expected time of obliteration is AVM size dependent, with a longer expected time for larger malformations. This suggests that the arbitrarily defined two year endpoint for the treatment result, defined above, may be too short for larger AVM. It has also been shown that a significant number of obliterations will take place two years or more after treatment. Today, most centers agree that three years latency is required before treatment failure can be concluded. Radiation causes damage in the AVM vessel wall. The damage initiates a repair process resulting in a continuous increase in thickness of the intima, which may result in total obliteration. For each part of an AVM vessel, a number of factors, such as radiation sensitivity, dose and vessel wall thickness, determine the end result of the repair process following radiation damage. Theoretically, it is sufficient with total closing in one spot of each vessel constituting the malformation to obliterate a malformation. Due to the inhomogenous dose distribution following GK surgery, it can be assumed that larger AVM may require lower radiation doses to the AVM periphery than smaller ones. This is compatible with the findings in the material. For the obliterated cases, the minimum dose decreased with increasing AVM volume. It is therefore possible that the length of each AVM vessel is a factor of importance for obliteration. The average vessel length can be estimated by (AVM volume)\(^2\)\(^3\) and, if it is multiplied with the minimum dose a product, named the K index, is obtained. The relation between the K index and the obliteration rate is illustrated in Fig. 2. It seems that the chance for obliteration increases linearly with the K index up to a break point, whereafter the chance for obliteration does not increase further. The coordinates for the intersection between the linear regressions for these two parts are (27:80). Thus, the highest probability for obliteration is obtained when K
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index \( \geq 27 \) and that a treatment dose resulting in a K index of 27 results in a high chance of obliteration and the lowest possible risk of complications.

(B) Risk for radio-induced complication following GK surgery. The limiting factor in radiosurgery is the risk of complications. It is therefore important to be able to estimate this risk factor prior to treatment. The first model reported was based on the results from proton beam therapy.8 In this report, the 1 and 99 percentile for isoeffective dose were given in a log-log plot, where the beam diameter was plotted on the x-axis, and the dose on the y-axis. These results were based on 74 patients, out of whom 8 did suffer from radiation induced complications. Flickinger published in 1989 an integral logistic formula for prediction of complications in radiosurgery.9 This model was based on information from the literature and it has been used to predict a 3% probability for brain necrosis following radiosurgery treatment of acoustic neuromas,10 meningiomas11 and AVM.4 A more accurate risk prediction model is possible to determine by using the dose distributions and other data from a large patient material. We therefore decided to analyze all AVM patients treated at the Karolinska Hospital from 1970 - April 1992. A total of 862 patients were eligible and included in the study. It could be shown that the only factor related to the incidence of complications was the average dose to the radiated volume.13 Based on this finding a risk estimation model was determined which would predict the risk for complications prior to the treatment.13 To check if any factors other than the dose distribution were of importance for the treatment risk, the predicted number of complications were compared to the observed number in a larger patient material.14

The fact that two years observation time was sufficient for almost all complications to occur,13 made us evaluate all AVM patients treated with the Karolinska GK from 1970 - 1993. Ten patients had more than one AVM where the distance between the malformations was such that the overlap between the dose plans was negligible. Each AVM in this study was considered separately for these patients. To avoid any influence of impact from previous radiation, patients who underwent previous radiation therapy after the second GK treatment were excluded from the study. Thus, 1024 of 1112 patients were eligible and included in the study. In 19 of the patients, all treatment parameters could not be evaluated. The complication risk in these patients was defined as being the average risk in the studied patient population (5.3%). In the study, a complication was defined as radiation induced new or aggravated neurological symptoms or signs, transitory or permanent occurring together with radiological evidence of edema or radionecrosis. The possible impact of parameters other than the dose distribution were investigated by comparing the observed number of complications to the predicted number. The predicted number of complications was determined by adding the calculated probability of complication for the population group to be studied and complete it to the nearest integer. A significant difference was defined to exist if the predicted number of complications was not within the 95% confidence interval of the observed number. The following parameters were analyzed: radiation given before GK radiosurgery; patient gender and age; AVM location and hemorrhage; whether present or absent before treatment.

The analysis of the importance of different parameters revealed that AVM location and previous hemorrhage were important factors for the risk of complications. Central AVM location was associated with a higher risk of complications, while previous hemorrhage was related to a lower risk. Thus, a more accurate risk prediction model must also take these two factors into consideration. To comply with this, the AVM material was divided into three groups: central AVM location; peripheral location with and without previous hemorrhage. The fact that 91% of the patients harboring a central AVM had suffered from a previous hemorrhage made further division of this group less meaningful. The relation between the average dose in 20 cm² and the incidence of complications for the three groups are illustrated in Fig. 3. For clarity, the 95% confidence intervals are illustrated in one group, but the magnitude of the intervals are similar for the other two groups. The relatively large
Table 1 - Influence on the risk for post treatment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>p-value</th>
<th>Significance</th>
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</thead>
<tbody>
<tr>
<td>Gender</td>
<td>0.89</td>
<td>ns</td>
</tr>
<tr>
<td>Localization</td>
<td>0.75</td>
<td>ns</td>
</tr>
<tr>
<td>Initial symptom</td>
<td>0.47</td>
<td>ns</td>
</tr>
<tr>
<td>AVM volume</td>
<td>0.0008</td>
<td>significant</td>
</tr>
<tr>
<td>Time hemorrhage - y</td>
<td>0.85</td>
<td>ns</td>
</tr>
<tr>
<td>Age at treatment</td>
<td>0.007</td>
<td>ns</td>
</tr>
<tr>
<td>Maximum dose</td>
<td>0.24</td>
<td>ns</td>
</tr>
<tr>
<td>Average dose</td>
<td>&lt;0.0001</td>
<td>significant</td>
</tr>
<tr>
<td>Minimum dose</td>
<td>&lt;0.0001</td>
<td>significant</td>
</tr>
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uncertainty is due to the fact that only about 300-400 patients were included in each group. A new risk estimation formula was developed taking also the AVM location and previous history into account. To control its accuracy, the calculated probability of complication was compared to the observed incidence. The risk of complications were therefore calculated in a subset of 90 randomly selected patients. The results are shown in Fig. 4, where the lines represent the functions fitted to the clinical data from Fig. 3. The points are the calculated risk of complication. It seems that the model predicts the risk in an accurate way with one exception. There is a disagreement between the calculated complication probability and the 6 incidence data for low doses. This inconsistency is dependent on the fact that none of the equations used to describe the clinical data can be perfectly fitted to this data. However, the inconsistency Fig. 4 illustrates is only at low doses, and it has a consequence only for risk predictions at the order of some percent. Thus, this will not be a restriction for the applicability of the model. It is obvious that one risk estimation model cannot describe the treatment risk following GK surgery for AVM accurately. AVM location and previous hemorrhage must be taken into consideration. Thus, the accuracy when using the risk estimation model above for other pathologies than AVM is uncertain.

(C) Risk for hemorrhage in the latency period

The opinion as to whether the natural course is affected or not in the post treatment period varies. Statements of increased, unchanged and decreased risk for hemorrhage as compared to the natural course are all represented in the literature.3,4,16-20 It is not within the scope of this review to compare the pre and post treatment incidence for hemorrhage but to estimate the magnitude of the risk itself, and the factors influencing it. This information is available in one of our papers, from which the following is extracted.20

The time period studied was the first two years following GK treatment in 1604 consecutive patients. All hospital records of the patients were studied. In 1403/1604 patients (87%), the result of a post treatment radiology examination was known. For the remaining 201 cases letters were sent and phone calls made, resulting in information from most, but not all, of the patients. It could be argued that the patients lost to any kind of follow-up did suffer from a lethal hemorrhage. If so, the percentage of patients reported dying from a hemorrhage in this series would have been lower than expected. This was not the case. In the series, 29% of the patients with rupture died due to the hemorrhage. This is within the range previously reported, 20 to 41%.2,21-25

To investigate if any factors could be related to the incidence of post treatment rupture, a number of parameters, listed in Table 1 were analyzed. Age at treatment, AVM volume, average and minimum dose significantly correlated to the incidence of hemorrhage, which was higher in older patients and larger in AVM. It was lower when higher average doses or higher doses to the AVM periphery were used. In other words, if the whole malformation was included in the radiation field a lower post treatment incidence of hemorrhage was observed. Due to the fact that the three parameters AVM volume, thus minimum and average dose are interdependent, a
multivariate analyzer was performed. The p-values were 0.95; 0.12 and 0.24, respectively. Thus the minimum dose seems to be the major decisive parameter. The mean time between initial hemorrhage and GK treatment was 2.5 years (one week-36.3 years, median eight months). There was no significant correlation between incidence of post treatment hemorrhage and time elapsed between the presenting hemorrhage and treatment (p=0.85). The risk of post treatment hemorrhages are illustrated in Fig. 5. The material is divided according to the minimum dose and it is obvious that the risk for hemorrhage increases with decreasing minimum doses. Based on this graph, an estimation of the total risk for post treatment hemorrhage can be calculated, assuming a two year delay between treatment and obliteration.

References

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