PROBABILITY OF OBLITERATION AND MANAGEMENT RISK FOLLOWING GAMMA KNIFE SURGERY FOR CEREBRAL AVM

Bengt Karlsson, Ingmar Lax

*Department of Neurosurgery (BK) and Hospital Physics (IL)
Karolinska Hospital, Stockholm, Sweden*

Abstract : In order to define the optimal treatment for an AVM patient, the probability of cure and the management risk following the treatment must be estimated before the treatment. Here, Gamma Knife surgery has an advantage over microsurgery and embolization with its reproducibility within the variability of the individual radiation sensitivity. Based on more than 2000 treatments, we have developed models to predict the probability for obliteration, the risk for radioinduced complications and the probability for a post treatment hemorrhage within the first two years following a Gamma Knife treatment. The factors determining the overall outcome are the absorbed dose in the target and the brain, the AVM volume and location and the age and clinical history of the patient. The probability for obliteration equals $35,69 * \ln(D_{\min}) - 39,66$ and is AVM volume independent. The risk for radioinduced complications relates to the average dose in the 20cm³ tissue receiving the most radiation, and it is also related to the clinical history of the patient and the AVM location. Finally, the risk for post treatment hemorrhage increases with the age of the patient, and is higher for larger AVM. It decreases with increasing amount of radiation given, and it is independent of the clinical history of the patient. For retreatments, the model for prediction of obliteration is valid, but the risk for radioinduced complications is higher and the risk for post treatment hemorrhage lower as compared to following the first treatment.

Key words : Brain arteriovenous malformation, Gamma Knife, Prediction, Radiosurgery, Risk, Complications, Risk estimation formula

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A. Prediction of obliteration

The first report of an AVM obliteration following GK surgery was published in 1972¹⁾. It was a case report of a patient treated with "gamma ligation". The rationale was to ligate the feeders, and it was performed by using one isocenter directed towards the feeding artery. An angiography 19 month later revealed total obliteration. This case was followed by others treated with the same philosophy, but the results were not satisfactory²⁾. The treatment strategy was, when possible, therefore changed to radiation of the whole AVM nidus volume. In 1984 Steiner reported the results following different treatment strategies³⁾. The report was based on angiography follow ups in 192/300 (64%) of the patients, and the treatments divided

into four groups : A : total ; and B : partial radiation cover of the nidus. C : coverage of all ; and D : some feeders. The two years 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 years angiography follow up being the endpoint to evaluate the treatment result has since become generally accepted for radiosurgery. The result in group A, $\approx 80\%$ obliteration rate, has also been accepted as what can be expected following optimal radiosurgery. The results above has also been used to support the opinion that larger malformations are less likely to obliterate following radiosurgery, although this was not expressed in the publication.

The Pittsburgh group published their first major AVM publication in 1991⁴⁾. Of 227 patients treated, 46

(20%) were followed up with a two-year angiography. They concluded that the results are AVM volume dependent, i.e. the obliteration rate decreased with an increasing AVM volume. They also recently published a model to predict the probability of obliteration following radiosurgery for AVM⁵.

The opinion that the AVM size has an independent importance for the outcome is also represented in another publication⁶. Recently Schwarz et al pooled their own data with the Sheffield data, and related the outcome to a prediction model based on the assumption that the chance for cure is related to the lowest periphery dose ($D_{\min}$) and the largest AVM nidus diameter.

Recently, the first 20 years of experience following GK treatments of AVM at the Karolinska and University of Virginia was analyzed^{7,8}. Two models to predict the probability of obliteration were published, one based on $D_{\min}$ only and the other on $D_{\min}$ and the average radius of the AVM nidus.

A model has to predict the probability for obliteration reasonable accurate before the treatment in every case. If this is the case, then the model also has the ability to accurately predict the number of obliterations in a group of patients, independent of how the group is selected. We can therefore check the accuracy of the model by comparing the predicted with the observed number of obliteration in different subgroups of patients in a large patient material. This was done by comparing the predictions to the outcome in different subgroups of the 830 AVMs with adequate follow up out of 1033 treated with Gamma Knife surgery at the Karolinska Hospital 1970-1993.

For the model published by Schwarz et al⁶, a significant difference was found between the number of observed and predicted obliterations. The other three models predicted the total number of obliterations accurately, i.e. within the 95% confidence interval of the observed number.

The model by Flickinger et al underestimated the number of obliterations for AVMs treated with low doses ($D_{\min} \leq 22\text{Gy}$) and overestimated the number of obliterations for high dose treatments. In addition, the number of obliterations for small AVMs was overestimated. Thus, this model does not accurately predict the probability for obliteration.

There are two different philosophies behind the two models described by Karlsson et al^{7,8}. One model is based on the assumption that the larger the AVM volume, the longer in average the vessels forming it. Taking the fact that it is sufficient to occlude a vessel on one spot only, it seems reasonable that a longer vessel given the same dose of radiation as a shorter has

a higher probability for occlusion. If this is true, then both the dose and the AVM volume is related to the outcome. An index, K index, was defined based on the assumptions above.

The model did, however, underestimate the probability for obliteration for small AVM and overestimate it for larger. It also overestimated the probability for obliteration for low dose treatments. Thus, the assumptions the model was based on does not seem to be accurate, and the model should therefore not be used.

The other model is based on the curve fit ($R^2 = 0.99$) to the relation found between $D_{\min}$ and the incidence of obliteration^{7,8}. The equation of the curve fit is:

$$P = 35,69 * \ln(D_{\min}) - 39,66$$

where P = the probability for obliteration (%). This model predicts the probability for obliteration accurately for the whole patient material. In addition, it accurately predicts the probability for small or large AVM treated with high or low doses. Furthermore, age, gender, maximum dose, average dose, AVM location, previous treatment and history of bleeding does not affect the accuracy of the prediction⁹. Therefore, it seems that the model above is accurate and can be used to predict the treatment results prior to the treatment. It can also be used to predict the probability for obliteration when treating previously irradiated malformations¹⁰.

Both the observation that the result of the prediction is independent of the AVM volume and the observation that a previous treatment, resulting in a size decrease of the AVM, does not affect the accuracy of the prediction model strongly indicate that the probability for obliteration is dose dependent only. The AVM volume itself does not directly affect the treatment results, only indirectly, as a larger malformation is usually treated with a lower dose of radiation in order to keep the risk for complications at an acceptable level.

B. Prediction of the risk for complications

The limiting factor in radiosurgery is the risk for complications. It is therefore important to accurately estimate this risk prior to the treatment. The first model reported was based on the results from proton beam therapy¹¹. In this report, the 1 and 99 percentiles for isoeffective doses were given in a log-log plot, where the beam diameter was plotted on the x-axis, and the dose on the y-axis. This graph was based on the treatment results in 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 radiosurgery¹²⁾. 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 neuromas¹³⁾, meningiomas¹⁴⁾, and AVMs⁴⁾. The Pittsburgh group has now abandoned the concept that one risk estimation model can be used for different diagnoses¹⁵⁾.

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 1970–April 1992. A total of 862 patients were eligible for 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, including both the target and the brain volume adjacent to the target¹⁶⁾. Based on this finding, a risk estimation model was determined which could predict the risk for complications prior to the treatment¹⁶⁾.

It is obvious that a complication occurs from the brain tissue and not from the pathology treated. It can therefore be argued that it is only the radiation delivered to the brain tissue, and not to the target volume, that is of importance for the risk for complications. This concept was used in the integral logistic formula¹²⁾. We did not believe that this was accurate. We felt that a complication may also be caused by the indirect effects of the radiation, such as swelling, changed microcirculation, increased local pressure etc.¹⁶⁾. If so, the amount of radiation to the target volume is also of interest. We therefore calculated the average dose in a volume large enough to cover both the target volume and the surrounding brain volume receiving a high dose of radiation, and we arbitrarily chose 20cm³ as this volume. It could be shown that the average dose in this volume was related to the incidence of complications. The Pittsburgh group have now accepted our philosophy, and the now agree with the concept that all radiation delivered is of importance for the risk for complications¹⁵⁾.

Using the same concept as in the previous paragraph (A), the accuracy of the model was checked by comparing the observed with the predicted number of complications in different subgroups of the material, and thereby define if any other factor than the dose distribution is of importance for the risk for complications. This was done in a patient material of 1128 patients treated in a 24 years period¹⁷⁾.

It could be shown that previous radiation given

increases the risk for complications^{10,17)}. It could also be shown that a central location increases the risk for complications, and that a previous hemorrhage decreases the risk. The latter was not detected when a multivariate analysis was performed, the reason being that 90% of the centrally located malformations have a hemorrhage as the initial symptom. However, when central and peripheral AVM were analyzed separately, the impact of a previous hemorrhage became obvious for peripheral AVM.

It is obvious that one risk estimation model cannot accurately predict the risk for complications in all AVMs, but that at least three models are needed. It is equally obvious that a risk estimation model based on the results following AVM treatments cannot directly be used to predict the risk for complications when other pathologies are treated. In this matter, there was previous a disagreement between the Karolinska and Pittsburgh group. When we published our first risk estimation model, a caveat was given to use it for other diagnoses than AVM¹⁶⁾. One example hereof is the around 8 times higher risk seen when cavernous malformations are treated¹⁸⁾. The Pittsburgh group recommended earlier the use of the integral logistic model¹²⁾ for all diagnoses^{4,13,14)}, but in their latest paper they agree with our opinion and write that the risk is different for different diagnoses¹⁵⁾.

The fact that the Pittsburgh group, after having compared the predicted and observed outcome in their own patient material, has accepted and agreed to the concepts published earlier by us makes the probability high that our risk estimation model is reasonable accurate. This is, however, of little help for a radiosurgery center if they cannot use the model when treating their own patients. A reasonable accurate estimation can be obtained by using the graph in figure 1, where the average dose to 20cm³ is plotted against the risk for complications for different AVM locations.

A more accurate prediction can be obtained by using the software written by us that is presently used at the Karolinska Hospital and the Gamma Knife centers in München, San Diego and Madrid. This software can easily be implemented in the Gamma-Plan, and it can be obtained from one of the authors (Lax).

C. Risk for hemorrhage in the latency period

The opinion 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^{3,4,11,19–21)}. It is not within the scope of this review to compare the pre- and post

treatment incidence for hemorrhage, just 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 extracted²¹⁾.

The time period studied was the first two years following the 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 patient with rupture died due to the hemorrhage. This is within the range previously reported, 20 to 41%^{4,11,22-25)}.

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, D_{min} and average dose significantly correlated to the incidence of hemorrhage, which was higher in older patients and larger 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, D_{min} and average dose are interdependent a multivariate analysis was performed. The P-values were 0.95; 0.12 and 0.24, respectively. Thus, D_{min} seems to be the major decisive parameter.

The median time between initial hemorrhage and GK treatment was 8 months (one week-36.3 years, mean 2.5 years). 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 hemorrhage is illustrated in figure 2. The material is divided according to D_{min} , and it is obvious that the risk for hemorrhage increases with decreasing D_{min} . Based on this graph, an estimation of the total risk for post treatment hemorrhage can be calculated, assuming a two years delay between treatment and obliteration.

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Fig. 1 Incidence of complications in relation to the average dose in the 20cm³ brain and AVM tissue receiving the most radiation in previously not irradiated patients. A linear curve fit is plotted for peripheral AVM with bleeding, and an exponential fit for the two other. For clarity, the 95% confidence interval bars are plotted for centrally located AVM only, but they are in the same magnitude for the two other groups.

Table 1 Relation between patient, AVM and treatment parameters to the risk for post treatment hemorrhage. Larger AVM volume and high age of the patient are both related to a higher risk for hemorrhage, while a high average and a high minimum dose both decrease the risk for hemorrhage.

parameter	p	significance
gender	0.89	n.s.
localisation	0.75	n.s.
initial symptom	0.47	n.s.
AVM volume	0.0008	significant
time hemorrhage-?	0.85	n.s.
age at treatment	0.007	significant
maximum dose	0.24	n.s.
average dose	<0.0001	significant
minimum dose	<0.0001	significant

Fig. 2 Annual risk for hemorrhage per 6 months period after the treatment. The area marked with///represents the risk for hemorrhage in untreated patients. By using this graph, the risk for post treatment hemorrhage can be calculated.