Prediction of Obliteration of Arteriovenous Malformations after Radiosurgery: the Obliteration Prediction Index

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ABSTRACT: ***Objective:*** To describe the response to single dose photon stereotactic radiosurgery of arteriovenous malformations (AVMs) so that the probability of success or failure of treatment may be predicted for the individual patient. ***Method:*** The obliteration prediction index (OPI) was calculated for AVMs by dividing the marginal dose of radiation in Gray (Gy) by the lesion diameter in centimetres in cohorts of 42 patients treated with the modified linear accelerator at Toronto-Sunnybrook Regional Cancer Centre and 394 patients treated with the gamma unit at the Royal Hallamshire Hospital, Sheffield, United Kingdom. Patients were grouped into ranges by OPI and the proportion of success and failure was calculated for each group. An exponential function [$P = 1\text{-}A\bullet e^{(-B\bullet OPI)}$] was fitted to the data by the least squares method. ***Results:*** Despite systematic differences in radiation treatment, that is, marginal doses of 15 and 20 Gy in Toronto and most Sheffield patients with a marginal dose of 25 Gy, the resultant data points exhibited similar behaviour. ***Conclusion:*** The function [$P = 1\text{-}A\bullet e^{(-B\bullet OPI)}$] partly describes the biological effect of radiation and is independent of the radiation device used. Radiosurgery centres can use this model to facilitate predictions of successful treatment for individual patients.

RÉSUMÉ: Prédiction de l'oblitération des malformations artério-veineuse après la radiochirurgie: l'indice de prédiction de l'oblitération. ***But:*** De décrire la réponse à la radiochirurgie stéréotaxique utilisant une dose unique de photon au niveau des malformations artério-veineuses (MAV) de telle sorte que la probabilité de succès ou d'échec du traitement puisse être prédite pour chaque patient. ***Méthode:*** L'indice de prédiction de l'oblitération (IPO) a été calculé pour les MAV en divisant la dose marginale de radiation en Gray (Gy) par le diamètre de la lésion en centimètres dans deux cohortes de patients. 42 patients ont été traités au moyen de l'accélérateur linéaire modifié au Toronto-Sunnybrook Regional Cancer Centre et 394 patients ont été traités au moyen de l'unité gamma au Royal Hallamshire Hospital, Sheffield, U.K. Les patients ont été regroupés selon l'IPO et la proportion de succès et d'échecs a été calculée pour chaque groupe. Une fonction exponentielle [$P = 1\text{-}A\bullet e^{(-B\bullet IPO)}$] a été ajustée aux données par la méthode des moindres carrés. ***Résultats:*** Bien qu'il y ait des différences systématiques dans la radiothérapie, soit des doses marginales de 15 et 20 Gy à Toronto et de 25 Gy pour la plupart des patients de Sheffield, l'analyse démontrait que les données étaient comparables. ***Conclusion:*** La fonction [$P = 1\text{-}A\bullet e^{(-B\bullet IPO)}$] décrit partiellement l'effet biologique de la radiation et est indépendante de l'appareil utilisé. Les centres de radiochirurgie peuvent utiliser ce modèle pour prédire plus facilement l'issue du traitement pour chaque patient.

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There is a widespread belief based on reports in the literature[1-4] that approximately 80% of arteriovenous malformations (AVMs) can be obliterated by single dose photon stereotactic radiosurgery. At the time of writing, the most recent report, that of Pollack et al.,[5] documents only 134 angiographically-proven cures of 315 treated AVMs for an obliteration rate of only 43 per cent. If one considers only the 210 patients who underwent post-treatment angiography in that series, the 134 obliterated AVMs still comprise only 64 per cent of that total. What is a reasonable expectation of success in the treatment of AVMs using single dose photon irradiation? Can one make an accurate prediction of the probability of obliteration of an AVM in an individual undergoing stereotactic radiosurgery? What factors influence the likelihood of obliteration?

The probability of obliteration has been thought to depend directly on the minimum or marginal dose of radiation

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administered to the AVM and depends inversely on AVM diameter or volume. What is the evidence?

Marginal dose

The optimal dose of AVM obliteration is still poorly defined. From Engenhart's report[6] of no obliterations in 13 patients treated to a marginal dose of 14 Gy, the minimum effective dose must exceed that. The efficacy of other doses is difficult to determine, given that most centres report the proportion of proven obliteration as a percentage of only those patients who undergo follow-up angiography rather than as a percentage of the entire cohort treated. The widespread practice of decreasing marginal radiation dose as AVM size increases also confounds interpretation of the effects of marginal dose alone. These considerations aside, Engenhart reports approximately 50% obliteration with a 15 Gy marginal dose and an approximately 80% obliteration rate with a 20 Gy marginal dose.

Friedman[2] reports on a mean peripheral dose of 15.6 Gy (10-25 Gy) with the statement that only 15% were treated with 20 Gy or greater "yet the thrombosis rates were high". Details regarding how high are not given. Coffey[7] reported obliteration of lesions greater than 1 cc having no correlation with volume or dose between 16 and 20 Gy. Lunsford[3] reported on patients whose AVMs were treated to a marginal dose of 20 Gy or more, where possible, with no difference in mean marginal dose between those obliterating (mean 23.1, range 18-25.2 Gy) and not (mean 22.1 Gy, range 19-25 Gy). In contrast, Colombo[1] reported that the only significant variable with respect to obliteration was the peripheral dose. Unfortunately, these doses are not explicitly stated. Furthermore, he describes his practice of reducing the marginal dose with increasing AVM volume so that the effect of one factor independent of the other is likely inextricable.

AVM diameter

While larger AVM volumes are thought to be associated with lower obliteration rates, this influence may be difficult to isolate, as noted above, given the concomitant inverse variation in dose with size in many series. Interestingly, Colombo's report[1] shows a striking difference in obliteration rates with different volumes, yet he states that only the marginal dose correlated significantly with outcome. Sebag-Montefiore[8] reported on patients all treated with 17.5 Gy to the margin, regardless of volume, with 25 of 33 lesions < 10 cc obliterating, compared with 9 of 19 lesions > 10 cc.

In summary, although the effects of these two factors may be inextricable, the possibility of using them in combination to predict outcome for patients treated with stereotactic radiation was explored. The objective of this communication is to describe the response to single dose photon stereotactic radiosurgery of AVMs so that the probability of success or failure may be predicted for the individual patient.

Methods

Treatment methods

Toronto stereotactic radiosurgery patients were treated using a linear accelerator and the dynamic rotation technique described by Podgorsak et al.[9,10] Specific modifications as described by O'Brien et al.[11] and by Gillies et al.[12] have been made. Sheffield patients were treated by a gamma unit.[13] Methods and results of the treatment in Sheffield of patients with arteriovenous malformations have been described previously.[14,15]

Determination of AVM diameter

For all cases in both the Toronto and Sheffield series, the diameter used in the calculation was the largest diameter (correcting for the magnification error) visible in the two orthogonal views of the treatment planning angiogram.

Calculation of obliteration prediction index (OPI)

The "obliteration prediction index (OPI)" was calculated for each AVM by dividing the dose of radiation to the margin of the lesion in Gray (Gy) by the lesion diameter in centimetres. Patients were grouped into ranges by OPI and the proportion of success and failure was calculated for each group. The plot of the results had the appearance of an exponential curve with a steep initial rise and then a saturation phase. An exponential function where $[P = 1\text{-}A \bullet e^{(\text{-}B \bullet OPI)}]$ was fitted to the data by the least squares method.

Results

Toronto data

The first 50 patients treated in Toronto followed three years or longer were reviewed. Four patients were excluded from the analysis because there was no three-year imaging. As MRI is less sensitive in the detection of AVM remnants than angiography, two patients were excluded from the analysis because there was MRI evidence of obliteration but no angiographic proof. Patients with MRI evidence of a persistent nidus were included and considered to be failures of treatment. Three Toronto patients with obliteration of the nidus but an early filling draining vein were counted as failures as even the smallest remnant of an AVM constitutes a risk of further bleeding (Guo[16]). Two additional patients who hemorrhaged in the latency period prior to three years of follow-up were also excluded. One of these two patients died and the other had his AVM surgically excised. In all, there were 28 successfully treated patients and 14 whose AVMs failed to obliterate.

The OPI was calculated by dividing the marginal dose of radiation in Gy by the lesion diameter in centimetres. Patients were grouped into ranges by OPI and the proportion of success and failure was calculated for each group. The plot of the results had the appearance of an exponential curve with a steep initial rise and then a saturation phase. An exponential function where $[P = 1\text{-}A \bullet e^{(\text{-}B \bullet OPI)}]$ with $A = 1.14 \pm 0.49$ and $B = 0.114 \pm 0.071$ was found to fit the data best. The ranges for A and B respectively are the standard deviation of that individual fitting parameter. The OPI values for these patients grouped into ranges for plotting and curve fitting are tabulated in the Table and illustrated in the Figure designated as "Toronto data".

Sheffield data

The OPI equation so derived was then tested on a cohort of 394 patients from the Royal Hallamshire Hospital, Sheffield, United Kingdom, where 1534 patients with AVMs have been treated by stereotactic radiosurgery. The fitted parameters were $A = 1.15 \pm 0.14$ and $B = 0.105 \pm 0.017$. The OPI values for these patients grouped into ranges for plotting and curve fitting are tabulated in the Table and illustrated in the Figure designated as "Sheffield data".

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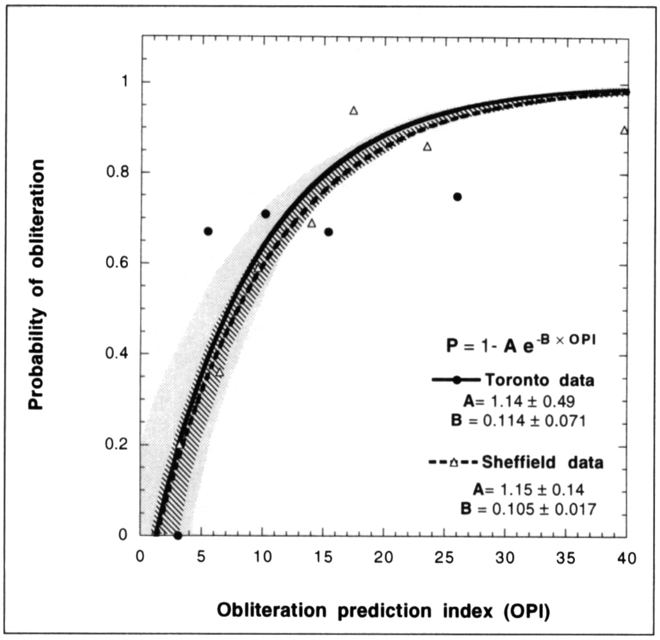

Figure: OPI = marginal dose (Gy)/AVM diameter (cm). The black dots and the open triangles are the data points for the OPI ranges of the Toronto and Sheffield data respectively (tabulated in the Table) plotted against the probability of obliteration for each of these ranges. The solid and dotted lines are the fitted exponential curves for the obliteration prediction index for the Toronto and Sheffield data respectively. For the Toronto data, the 95% confidence limits for the predicted mean are represented by the boundaries of the stippled area in relation to the solid line. The narrower 95% confidence limits for the predicted mean of the Sheffield data are indicated by the boundaries of the cross-hatched area in relation to the dotted curve. Note that the fitted curves overlap.

The OPI ranges were chosen at regular intervals so that the number of subjects in each range was sufficient to make the calculation of the proportion of successful outcomes as stable as possible. In the Toronto series where there were fewer patients than Sheffield the upper four OPI ranges were grouped into two ranges so that there would be sufficient patients in each range. In the Table, the OPI indicated for each range varies from one data set to the other because the number indicated is a weighted average of the points that fell within that range.

Table

TORONTO DATA				SHEFFIELD DATA			
OPI	**N (total)**	**N (oblit)**	**P (oblit)**	**OPI**	**N (total)**	**N (oblit)**	**P (oblit)**
3.1	2	0	0	3.2	5	1	0.2
5.5	6	4	0.67	6.5	88	32	0.36
10.2	21	15	0.71	9.6	118	70	0.59
15.4	9	6	0.67	14.0	67	46	0.69
				17.4	35	33	0.94
26.0	4	3	0.75	23.5	51	44	0.86
				39.7	30	27	0.9

Grouping into OPI ranges as follows:
Toronto: < 4, 4-8, 8-12, 12-20, > 20
Sheffield: < 4; 4-8; 8-12; 12-16; 16-20; 20-30; > 30

In the Figure, the black dots and the open triangles are the data points for the OPI ranges of the Toronto and Sheffield data respectively (tabulated in the Table) plotted against the probability of obliteration for each of these ranges. The solid and dotted lines are the fitted exponential curves for the obliteration prediction index for the Toronto and Sheffield data respectively. For the Toronto data, the 95% confidence limits for the predicted mean are represented by the boundaries of the stippled area in relation to the solid line. The narrower 95% confidence limits for the predicted mean of the Sheffield data are indicated by the boundaries of the cross-hatched area in relation to the dotted curve. Note that the fitted curves overlap.

Discussion

It can be seen that the curves fitted to the data from the Toronto and Sheffield centres are similar despite systematic differences in treatment. The Toronto patients were treated with marginal doses of 15 and 20 Gy whereas the majority of Sheffield patients were treated with a marginal dose of 25 Gy. Forty-seven of the 50 Toronto patients were treated with a single isocentre as the Toronto linear accelerator has collimators available in sizes ranging from one to three centimetres in quarter-centimetre intervals. In Sheffield, an earlier model of the Gamma Knife is used. The largest collimator is 1.8 cm. As is customary with this system, multiple overlapping fields are often used to achieve a conformational dose plan. Kemeny[15] has commented that in the Sheffield experience, there is no difference in the probability of success whether an AVM is treated by single or by multiple fields of radiation.

Although there are clearly other factors that influence the probability of successful treatment of arteriovenous malformations by radiosurgery, the outcome after single dose photon stereotactic radiosurgical treatment of brain arteriovenous malformations may be predicted by the exponential function [$p = 1 - A \cdot e^{(-B \cdot OPI)}$]. In our opinion, this curve partly defines the biological response of brain arteriovenous malformations to stereotactic single dose photon irradiation. The similarity of results from these two centres suggests that it is independent of the device used to produce the radiation.

Conclusion

Individual predictions

If a graph like the Figure is generated, a prediction may be made for an individual patient by calculating the OPI, locating the point on the curve and reading the probability of obliteration from the graph.

Marginal dose determination

The OPI can thus be used to choose an appropriate marginal dose for large AVMs. If the probability of obliteration is predicted to be too low, the dose may be raised as high as necessary within limits dictated by patient safety.[17-19] If obliteration is predicted to be low and adjacent, eloquent brain structures preclude raising the marginal dose sufficiently to lead to a probable successful outcome, then the risk benefit ratio may be considered to be unacceptable and the treatment abandoned.

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Realistic expectations

For smaller arteriovenous malformations, the OPI is helpful in that predictions of the probability of a successful outcome of stereotactic radiosurgery may be made for individual patients with the result that the patients and the physicians treating them may have realistic expectations of outcome.

We suggest that the obliteration prediction index (OPI) is a useful adjunct to clinical practice. If more radiosurgery centres analyse their results in this way then greater certainty regarding the exact curve parameters may derive.

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