Predictors for complete obliteration of arteriovenous malformations following stereotactic radiosurgery

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ABSTRACT

Objective: Radiosurgery is one of the management options used to treat cerebral arteriovenous malformation (AVM). The primary goal of treatment is the complete obliteration of AVM. Multiple factors have been proposed predicting complete AVM obliteration. This meta-analysis aims to assess the predictors of complete obliteration following stereotactic radiosurgery.

Materials and Methods: A literature search was conducted using the databases PubMed, Cochrane Central Register of Controlled Trials and EMBASE. Articles discussing predictors of obliteration of AVM following radiosurgery were included. Odd ratio and 95% confidence intervals were used to assess the predictive ability of identified predictors.

Results: Higher obliteration rates were observed in previously ruptured AVM (OR: 1.21, 95% CI, 1.02–1.43, $p = 0.03$), lower Spetzler-Martin grade (OR: 1.66, 95% CI, 1.11–2.50, $p = 0.01$), and in AVM receiving a higher marginal dose (OR: 1.18, 95% CI, 1.11–1.24, $p < 0.001$). In contrast, deep AVM location (OR: 0.51, 95% CI, 0.39–0.67, $p < 0.001$), eloquence (OR: 0.67, 95% CI, 0.42–1.06, $p = 0.09$), prior embolization (OR: 0.83, 95% CI, 0.72–0.95, $p = 0.006$), larger target volume (OR: 0.82, 95% CI, 0.71–0.95, $p = 0.009$), and a higher Radiosurgery-based AVM score (RBAS) (OR: 0.48, 95% CI, 0.36–0.65, $p < 0.001$) were associated with lower obliteration rates.

Conclusions: A previously ruptured AVM, a lower Spetzler-Martin grade, a higher marginal dose, non-deep location, no prior embolization, smaller target volume, and lower RBAS were identified as positive predictors for obliteration. Particularly, patients with AVM categorized as having a lower RBAS, radiosurgery should be considered as a first management option for a higher obliteration rate. However, factors such as age, eloquence and sex were not found to influence obliteration rates.

INTRODUCTION

Cerebral arteriovenous malformation (AVM) represent an abnormal collection of arteries and veins without an intervening capillary bed [1]. High blood flow and elevated pressure increase the risk of rupture and subsequent hemorrhage. Ruptured AVM is a major cause of secondary intracranial hemorrhage. AVM rupture is associated with high mortality and morbidity rates,

29% and 23%, respectively [2–4]. Several therapeutic methods are used to treat AVM, including radiosurgery, embolization, surgical resection or combination of several methods [5]. Radiosurgery is being used more frequently, particularly in patients with surgically inaccessible lesions. Radiosurgery has been shown to be a low risk procedure that is associated with high obliteration rates [6–8]. The primary aim of radiosurgery is to prevent hemorrhage by achieving complete AVM obliteration.

Once complete obliteration is identified on angiography, the overall risk of hemorrhage drops to 1% [9]. However, an interval period exists from the time of radiosurgery until complete obliteration is achieved, during which the risk of hemorrhage remains. Proper selection of patients undergoing radiosurgery is paramount in predicting success of radiosurgery. Multiple factors have been proposed as positive predictors for complete AVM obliteration such as the volume of AVM [10–12] and history of prior embolization [11, 13–15]. However, some inconsistencies exist in the literature. For instance, some reports [15, 16] suggested a high predictive ability (odds ratio: 1.4) of prior embolization for complete obliteration, while other studies [10, 11, 13, 14] demonstrated no significant difference in obliteration rates with or without prior embolization.

Therefore, we conducted a meta-analysis to evaluate the factors predicting complete obliteration which will help identify the patients with a higher chance of complete obliteration following stereotactic radiosurgery.

RESULTS

Literature research

A total of 926 articles were available from the electronic databases, of which 31 articles were selected after reviewing the titles and abstracts. Six-hundred and seventy (670) unrelated articles were excluded. After reviewing the full texts of the 31 selected articles, 10 articles [10–16, 19–21] met the inclusion criteria and were selected for the analysis. From the selected articles, 10 predictive factors were identified and subsequently analyzed, including rupture of AVM, deep location, non-eloquence, craniotomy surgery, prior embolization, volume of AVM, max diameter, gender, age, and high margin dose.

Characteristics of included studies

Ten retrospective studies with 2280 patients were included in this analysis (Table 1). The majority of the included articles were conducted between 2012 and 2017. Three studies were conducted in North America, two studies were done in Asia, and six studies were done in Europe. The mean of age ranged from 33 to 40 years. The mean radiosurgery-based arteriovenous malformation score (RBAS) was about 1.4 in all included studies, and the mean of margin dose utilized ranged from 15 to 25 Gy. Complete obliteration rate ranged between 59% and 87%. AVM obliteration was identified using CTA, MRA or DSA. All analyzed studies had a high quality with a NOS score > 6.

Rupture of AVM

Four studies [10, 11, 13, 14] including 1346 patients presented AVM rupture as a predictor for obliteration.

After pooling the data of these studies with fixed-effect model, ruptured AVM demonstrated higher obliteration rates than unruptured AVM, with pooled OR of 1.21 (95% CI, 1.02–1.43, $p = 0.03$, Figure 1A). There was no significant heterogeneity between these studies ($p = 0.32$ and $I^2 = 14\%$).

Deep location

Two studies [10, 14] of 826 subjects reported the association between AVM location (basal ganglia, thalamus, or brainstem) and obliteration. These two studies showed a negative association between deep location and obliteration with multivariate logistic regression, and had no significant heterogeneity ($p = 0.28$ and $I^2 = 15\%$). Using fixed-effect model analysis, the pooled results suggested that deep AVM location was associated with a lower obliteration rate (OR: 0.51, 95% CI, 0.39–0.67, $p < 0.001$, Figure 1B).

Eloquent AVM

In four studies [11, 13, 14, 20] of 1302 patients, the pooled OR of eloquent cortex AVM location for obliteration was 0.67 (95% CI, 0.42–1.06, $p = 0.09$). With sensitivity analysis, the high heterogeneity ($p = 0.04$ and $I^2 = 65\%$) was attributed to the study by Pollock [14], and the random-effects model was used. After excluding the study by Pollock, the heterogeneity significantly decreased ($p = 0.32$ and $I^2 = 13\%$) and AVM located in the eloquent location were associated with lower obliteration rates (OR: 0.55, 95% CI, 0.37–0.84, $p = 0.005$, Figure 1C). The subgroup analysis by techniques showed that the pooled OR of eloquent cortex AVM location for obliteration was 0.64 (95% CI, 0.43–0.96, $p = 0.03$) in the LINAC group, while no association was found in Gamma Knife group with OR of 1.02 (95% CI, 0.78–1.33, $p = 0.89$).

Prior resection

Two studies [11, 14] including 801 subjects reported an association between prior surgical resection and obliteration rates. There was no significant heterogeneity ($p = 0.33$ and $I^2 = 0\%$) and the fixed-effects model was used. After pooling the ORs of two studies and 801 subjects, the results showed that the prior craniotomy surgery was not associated with a higher obliteration rate (OR: 1.19, 95% CI, 0.82–1.73, $p = 0.37$, Figure 1D).

Prior embolization

There were six studies [10, 11, 13–16] of 1625 subjects reporting the OR and 95% CI for the relationship between prior embolization and AVM

Table 1: Characteristic of included articles

Author	Year	Country	Study design	Patients (n)	Sex (M/F)	Mean age (years)	Mean RBVS	Techniques	Mean dose (Gy)	Study period	Obliteration (%)	Detection of obliteration	NOS score
Thenier-Villa, J. L.	2017	Spain	Retrospective	195	110/85	37.6	1.70	LINAC	16.75	1998–2013	81	DSA or MRA	8
Pollock, B. E.	2016	USA	Retrospective	381	169/212	39.5	1.37	GK	19.2	1990–2009	85	DSA or MRA	9
Paul, L.	2014	Spain	Retrospective	662	362/300	37.1	/	GK	18.9	1993–2005	71	DSA or MRA	8
Hattangadi-Gluth, J. A.	2014	USA	Retrospective	248	124/124	39	1.33	Proton beam linac	15	1991–2010	70	MRA or CTA	7
Fokas, E.	2013	Germany	Retrospective	164	89/75	36	1.41	LINAC	19	1998–2008	61	MRA	7
Taeshineetanakul, P.	2012	Canada	Retrospective	139	75/64	35.5	1.30	LINAC and GK	18.8	2000–2009	69	DSA or MRA	8
Kano, H.	2012	China	Retrospective	120	61/59	33	1.43	GK	18	1987–2006	59	DSA or MRA	8
Cetin, I. A.	2012	Turkey	Retrospective	92	49/43	35	1.36	Proton beam linac	20	2000–2006	80	DSA or MRA	7
Zabel, A.	2005	Germany	Retrospective	110	50/60	40	/	LINAC	18	1998–2001	87	CTA, MRA and DSA	7
Schlienger, M.	2000	France	Retrospective	169	62/107	33	/	LINAC	25	1990–1993	64	DSA or MRA	7

RBAS: radiosurgery-based arteriovenous malformation score; LINAC: linear accelerator; GK: Gamma knife.

obliteration. In two studies, prior embolization was associated with lower obliteration rates, while in the remaining four studies, no such association was identified. The fixed-effects model was used and found no significant heterogeneity ($p = 0.12$ and $I^2 = 43\%$). The results suggested that prior embolization significantly reduces obliteration rates (OR: 0.83, 95% CI, 0.72–0.95, $p = 0.006$, Figure 1E).

Target volume

Three studies [10–12] of 395 patients presented the OR of the relationship between higher target volume and obliteration rate. All of these studies suggested that a higher target volume was associated with lower the obliteration rate. Two studies [11, 12] suggested the cut-off values of target volume at 4ml and 8ml. The pooled OR of higher target volume for obliteration was 0.82 (95% CI, 0.71–0.95, $p = 0.009$, Figure 1F) by a random-effects model ($p = 0.14$ and $I^2 = 50\%$).

Spetzler-martin (SM) grade

The Spetzler-Martin grade was considered an independent predictor in two studies of 334 patients [11, 19]. These studies showed the patients with a lower SM grade (I, II and III) had a higher obliteration rate than higher SM grade (IV and V). After pooling the results, there was no heterogeneity ($p = 0.95$ and $I^2 = 0\%$) between the two studies and the AVM with lower SM grade was associated with a higher obliteration rate (OR: 1.66, 95% CI, 1.11–2.50, $p = 0.01$, Figure 1G).

Radiosurgery-based arteriovenous malformation score (RBAS)

Three studies [10, 11, 15] of 413 patients presented the OR for the relationship between RBAS and obliteration rates. Two [10, 15] of these studies demonstrated that AVM with lower RBAS had a higher obliteration rates. One study [11] found no such association. For the heterogeneity of these studies ($p = 0.13$ and $I^2 = 51\%$), the random-effects model was conducted and the results suggested the higher RBAS was associated with a lower obliteration rate (OR: 0.48, 95% CI, 0.36–0.65, $p < 0.001$, Figure 1H). The subgroup analysis by techniques suggested the pooled OR of higher RBAS for obliteration was 0.42 (95% CI, 0.34–0.52, $p < 0.01$) in the proton beam linac group, but no significance in LINAC group (OR: 0.75, 95% CI, 0.45–1.25, $p = 0.27$).

Gender

The ORs and 95% CIs for relationship between gender and obliteration were reported in six studies of 1548 subjects [10–15]. There was no difference in obliteration rate between males and females (OR: 1.04, 95% CI, 0.90–1.20, $p = 0.63$, Figure 1I). For the significant heterogeneity ($p = 0.24$ and $I^2 = 26\%$), the fixed-effects model was used.

Age

Five studies [10, 11, 13–15] of 1456 patients included analyzed the relationship between age at the

time of radiosurgery and the obliteration rate. Only one study [15] showed that an older age was associated with the lower obliteration rate, while the remaining studies found that there was no difference. The pooled results also showed there was no difference in patients with different age (OR: 1.00, 95% CI, 0.99–1.01, $p = 0.90$, Figure 1J), without significant heterogeneity ($p = 0.16$ and $I^2 = 38\%$).

High marginal dose

The ORs and 95% CIs of marginal dose utilized and obliteration were reported in seven studies of 1254 subjects [10–13, 15, 20, 21]. A higher marginal dose was associated with higher obliteration rates (OR: 1.22, 95% CI, 1.11–1.34, $p < 0.001$, Figure 1K). For the heterogeneity ($p = 0.06$ and $I^2 = 51\%$), the random-effects model was used and the study by Cetin [15] was found to be the origin of the heterogeneity. After excluding the study by Cetin, the heterogeneity decreased ($p = 0.66$ and $I^2 = 0\%$) and the higher marginal dose was still a predictor for higher obliteration rate (OR: 1.18, 95% CI, 1.11–1.24, $p < 0.001$). The subgroup analysis by techniques suggested that higher marginal dose was associated with higher obliteration rates in the proton beam linac group (OR: 1.47, 95% CI, 1.11–1.93, $p = 0.006$), LINAC group (OR: 1.20, 95% CI, 1.09–1.32, $p < 0.001$) and Gama Knife group (OR: 1.17, 95% CI, 1.10–1.26, $p < 0.001$).

Publication bias

Begg's test conducted by STATA 13.0 also showed no evidence of publication bias ($p = 0.764$, Figure 2) for higher marginal dose, which involved the largest number of articles.

DISCUSSION

Implications

The primary goal of treatment for AVM is the complete obliteration of the AVM, so that the risk of hemorrhage is eliminated [9]. Thus, identifying of the factors associated with higher obliteration rates is important. To the best of our knowledge, this is the first meta-analysis performed that looks at the positive predictors for obliteration of AVM following radiosurgery. The obliteration rates of AVM following radiosurgery range between 59% and 87% [12, 19]. After pooling the results of ten articles with 2280 patients, we found that lower obliteration rates were reported in patients with unruptured AVM, AVM located in deep cerebral locations, prior embolization, larger AVM volume, a higher SM grade or RBAS, and a lower marginal dose.

Multiple reports [22, 23] have suggested that ruptured AVM are associated with higher obliteration rates. This is thought to be related to better visualization

of the nidus following AVM rupture, thus making it easier to target the AVM with radiosurgery [22, 23]. Three [10, 11, 13] of the four analyzed studies looking at the association between AVM rupture and concluded that a trend towards higher obliteration rates in previously ruptured AVM exists. However, Ding et al. [22] showed the ruptured AVM had significantly higher complete obliteration rates (68%) than the unruptured AVM (48%) using univariate logistic regression. Pooling the data from the four studies with minimal heterogeneity demonstrated higher obliteration rates in previously ruptured AVM. The inconsistencies observed could be attributed to limited number of patients included in the analyzed studies.

AVMs located in deep locations, such as the thalamus, brainstem, or basal ganglia, are associated with high rates of mortality and morbidity [24]. Moreover, deep AVM are reported to have lower obliteration rates after radiosurgery [10, 25–27]. Hattangadi-Gluth et al. [10] reported an obliteration rate of 62% in AVM located in deep structures. In contrast, the obliteration rates of AVM located in other locations was 67%. Pollock et al. [14] also reported the deeply located AVM had lower complete obliteration rates compared to those located in the cerebral hemispheres or the cerebellum (77.8% VS 86.5% at 8 years), which was consistent with our findings.

Some researches [11, 13, 14, 20] looked at whether obliteration rates varied depending on the eloquent location of the AVM. An eloquent location refers to highly functional cortical areas of the brain such as the sensorimotor, language, or visual cortex [14]. Ding et al. [28] demonstrated that 28% of AVM located in eloquent areas were completely obliterated 5 years after radiosurgery, which was significantly lower than the obliteration rates of AVM located in non-eloquent areas (43%). The result of LINAC group were also consistent with these studies, while there was no association of eloquent location and obliteration in Gama Knife group.

SM grade was initially proposed to determine the operative risks in patients undergoing surgery for AVM [29]. The factors considered in the grading system are size of nidus, the type of venous drainage (superficial vs deep) and the location of AVM in terms of eloquence. Obliteration rates reported following radiosurgery for SM grades I and II range between 80% and 93% [9, 30]. The obliteration rates following radiosurgery for SM grades III ranged from 60% to 72% [22, 23]. Obliteration rates for SM grades IV and V are reported to be around 43.6% [31]. Although two studies [11, 19] showed that there was no association between the SM grade and obliteration rate, we found that AVM with lower SM grade had a higher obliteration rate. This may be related a smaller AVM volume observed in lower SM grade [21]. Although the SM grade could be an independent predictor for obliteration, RBAS had a stronger predictive ability than SM grade, with OR of 2.08 and 1.66 respectively. The RBAS [32] was generally used to predict the obliteration rate. The criteria utilized includes age, location and the

A **B** **C** **D** **E** **F**

G

H

I

J

K

Figure 1: Forest plots for relationship between obliteration rates and rupture of AVM (A), deep cerebral locations (B), eloquent locations (C), prior resection (D), prior embolization (E), larger AVM volume (F), lower SM grade (G) or RBAS (H), gender (I), age (J) and lower marginal dose (K).

size of AVM. Patients with RBAS of 0.01–1.50, 1.51–2.00 and > 2.00 had obliteration rates of 63%, 60% and 28%, respectively [11]. We found that a higher RBAS had the highest predictive ability of all the factors with OR of 2.08 for complete obliteration, however, the included studies did not provide cut-off values of RBAS that can be used to identify patients with the best chance of complete obliteration following radiosurgery. Moreover, we found the higher RBAS predicted the obliteration in the proton beam linac group, but not in LINAC group. For only one study in LINAC group, the prediction of RBAS in patients with LINAC treatment needs more studies to evaluate in future.

Few studies discussed the effect of surgical resection on the outcomes following radiosurgery. The two studies [11, 14] suggested the prior surgery had no influence on obliteration rate, and analysis demonstrated similar results. However, the effect embolization on obliteration was assessed in many articles. Cetin et al. and Schlienger et al. [15, 16] demonstrated that previously embolized AVM were significantly less likely to obliterate compared to unembolized AVM (54% VS 71%, respectively). Three articles [10, 11, 14] demonstrated a trend towards lower obliteration rates in previously embolized AVM, however, there results didn't reach statistical significance. Embolization could result in making the nidus more diffuse, making targeting the nidus

at the time of radiosurgery more difficult [21]. However, Zabel-du et al. [33] suggested that the AVM of ≥ 3 cm in diameter had lower obliteration rates than AVM with a smaller diameter < 3 cm (92% VS 60%). Izawa et al. [34] demonstrated that following AVM embolization, radiosurgery for malformations 12 mm^3 or larger were more likely to obliterate compared to lesions less than 12 mm^3 in 90% vs 10%, respectively. We found that prior embolization was associated with lower complete obliteration rates in patients following radiosurgery. Thus, it is important to appropriately choose patients undergoing embolization prior to radiosurgery so that the benefits of embolization outweigh the risks associated with lower obliteration rate.

Target volume was considered as an independent predictor for obliteration in many studies [10–12]. Fokas [11] suggested that AVM with a target volume smaller than 4 cc would have a higher complete obliteration rate, while Kano [12] showed the cut-off was between 6 and 8 mm^3 with univariate analysis. Another study [35] demonstrated that the complete obliteration rates were 67%, 58% and 23% in treatment volumes of < 4 mm^3 , 4– 14 mm^3 and > 14 mm^3 , respectively.

Kano et al. [12] found that females were more likely to have complete obliteration compared to males, with a HR of 2.384. The remaining studies [10, 11, 13–15] did not find such a correlation. Moreover, we

Figure 2: The Begg publication bias plot of the studies reporting the association of obliteration rate and higher marginal dose with $P = 0.764$.

found no significant association between gender and obliteration.

The margin dose commonly ranged from 16 to 25 Gy, and almost all of the included studies that higher obliteration rates are achieved by utilizing higher margin doses. Our results also showed higher margin doses were associated with higher obliteration rates, regardless of the techniques (proton beam linac, LINAC OR Gama Knife). However, margin doses higher than 25 Gy were associated with minimal effects on obliteration rates, while also being associated with higher rates of adverse radiation effects [36]. Kano et al. [12] suggested a cut-off value of margin dose of 18Gy with OR of 1.197. Although Cetin et al. [15] suggested 20Gy as the cut-off value with OR of 2.09. More evidence is still required to set the margin dose that is associated with the highest obliteration rates and the lowest risk of adverse radiation effects.

Limitation

The included articles were all retrospective studies, which might result in the selection bias and the high-quality studies are needed. Several factors influencing

clinical outcomes, such as post-radiosurgery hemorrhage and radiation-induced changes, were not covered in the report. However, the assessment of factors for complete obliteration, the major aim of radiosurgery, was necessary to identify the patients with a higher chance of favorable outcomes following radiosurgery. Appropriate patient selection prior to radiosurgery would improve the outcomes. Third, for the limited data, we could not identify the factors affecting the interval of time from first radiosurgery to complete obliteration.

MATERIALS AND METHODS

Collect the eligible articles

This study was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Figure 3). A literature search was conducted using the search engines PubMed, Cochrane Central Register of Controlled Trials and EMBASE from the beginning of indexing to Sep 12, 2017 using the keywords: obliteration, arteriovenous malformations and radiosurgery. The reference of included articles were checked to find additional related studies.

Figure 3: The flow diagram of procedures to search the included studies.

Inclusion and exclusion criteria

Initial review consisted of reviewing the titles and abstracts of all available studies. The full texts of selected studies were independently reviewed by two neurosurgeons. The eligibility of the selected studies and disagreements were discussed. The inclusion criteria consisted of: 1-Studies reporting on patients diagnosed with intracerebral AVMs and treated with radiosurgery; 2- Studies which had the odds ratio (OR) and 95% CI of variables for the obliteration available, or the original data included is sufficient to calculate the OR and 95% CI; 3- Case-control, cohort studies or randomized controlled studies (RCTs) were included. Articles reporting outcomes of radiosurgery for AVM in children, articles not in English, case reports, and animal studies were excluded.

Data extraction

The data from the included studies were extracted by two authors independently and the disagreements were discussed. The following data were extracted from eligible studies: author, year of publication, country, study design, number of patients, gender, study period, rate of obliteration, detection method, year of follow up, and the ORs and 95% CI of variables for obliteration. Obliteration of AVM identified by Computed Tomography Angiography (CTA), Magnetic Resonance Angiography (MRA) or Digital Subtraction Angiography (DSA) was considered the end points. The techniques of radiosurgery included linear accelerator (LINAC), Gamma Knife, and proton beam linac. The values of multivariate regression analysis were first choice when the ORs of univariate regression analysis and multivariate regression analysis coexisted.

Quality assessment of the included articles

The quality of the included studies were evaluated by two authors independently using the Newcastle-Ottawa Scale (NOS) [17]. The score ranged from 0 to 9 points. The quality of study was considered high if the score was higher than 6 points.

Data analysis

The software Review Manager Version 5.3 (Cochrane collaboration, Oxford, UK) was used to pool the OR of the variables for obliteration, and the STATA 13.0 (STATA Corporation, College Station, TX) was used to assess the publication bias of the included studies. The pooled ORs and 95% CIs were used to evaluate the efficiency of variables for obliteration. The fixed-effects would be used when the heterogeneity was not significant with the $I^2 < 50\%$ or $p > 0.10$, otherwise, the random-effects would be used. The sensitivity analysis was used

to confirm the robustness of the pooled results in analysis with significant heterogeneity [18]. The subgroup analysis by different techniques of radiosurgery would be conducted if there was a significant heterogeneity ($I^2 > 50\%$ or $p < 0.10$) between the included studies. Funnel plot with Begg rank correlation was used to assess the publication bias of included studies. If $p > 0.05$, there was no significant difference.

CONCLUSIONS

The results of this meta-analysis suggest that unruptured AVM, deep location, prior embolization, higher target volume, higher SM grade or RBAS, and lower marginal dose were associated with lower complete obliteration rate. RBAS had the highest predictive ability in present study, and more studies are required to evaluate the optimal cut-off score of RBAS for complete obliteration. However, age, eloquent location and gender were not a predictor for complete obliteration in patients with AVMs.

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CONFLICTS OF INTEREST

No conflicts of interest.

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