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Repeat radiosurgery for cerebral arteriovenous malformations

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Abstract

We perform a systematic review of repeated radiosurgery for cerebral arteriovenous malformations (AVM) with an emphasis on lesion obliteration rates and complications. Radiosurgery is an accepted treatment modality for AVM located in eloquent cortex or deep brain structures. For residual or persistent lesions, repeated radiosurgery can be considered if sufficient time has passed to allow for a full appreciation of treatment effects, usually at least 3 years. A systematic review was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. References for this review were identified by searches of MEDLINE, Web of Science and Google Scholar databases. A total of 14 studies comprising 733 patients met the review criteria and were included. For series that reported target dose at both first and repeat treatments, the weighted means were 19.42 Gy and 19.06 Gy, respectively. The mean and median obliteration rate for the repeat radiosurgery treatments were 61% (95% confidence interval 51.9–71.7%) and 61.5%, respectively. The median follow up following radiosurgery ranged from 19.5 to 80 months. Time to complete obliteration after the repeat treatment ranged from 21 to 40.8 months. The most common complications of repeated radiosurgery for AVM included hemorrhage (7.6%) and radiation-induced changes (7.4%). Repeat radiosurgery can be used to treat incompletely obliterated AVM with an obliteration rate of 61%. Complications are related to treatment effect latency (hemorrhage risk) as well as radiation-induced changes. Repeat

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radiosurgery can be performed at three years following the initial treatment, allowing for full realization of effects from the initial treatment prior to commencing therapy.

Keywords

Arteriovenous malformation; Gamma knife; LINAC; Neurosurgery; Retreatment; Stereotactic radiosurgery

1. Introduction

Cerebral arteriovenous malformations (AVM) are pathologic vascular lesions found in children and adults with a prevalence in adults of approximately 18 per 100,000.[1] AVM are defined by an abnormal connection between the venous and arterial circulation resulting in an arteriovenous shunt and the gross appearance of a tangle of blood vessels. The angioarchitecture of these lesions puts them at risk for hemorrhage as well as subjecting the adjacent parenchyma to the potential for ischemia and seizure. [2, 3] AVM have an annual hemorrhage rate of 2–3% that persists as long as the lesion exists.[4, 5] Management of these lesions can be observational, although lesion obliteration is typically considered to mitigate these risks. The exact treatment modality, or combination of treatment modalities, is highly debated and is dependent on lesion specific factors, patient specific factors and surgeon experience.[6-9] Radiosurgery is an accepted treatment modality for AVM located in eloquent cortex or deep brain structures.[10-14]

In general, radiosurgery results in either complete obliteration of the AVM or reduction in its size. Rarely, there is no change in the lesion characteristics following radiosurgery. For residual or persistent lesions, repeated radiosurgery can be considered if sufficient time has passed to allow for a full appreciation of treatment effects, usually at least 3 years.[15-17] Herein, we perform a systematic review of repeated radiosurgery for cerebral AVM with an emphasis on lesion obliteration rates and complications.

2. Methods

2.1. Literature search

A systematic review was performed in accordance with the preferred reporting items for systematic reviews and meta-analyses guidelines.[18] References for this review were identified by searches of MEDLINE, Web of Science and Google Scholar for relevant articles using the search terms "repeat* radiosurgery arteriovenous malformation" and "repeat* radiosurgery AVM", where * is a truncation character that retrieves all word endings. Only articles published in English up to 15 August 2014 were included. We identified only articles relevant to the repeated radiosurgical treatment of incompletely obliterated AVM where initial treatment of the entire lesion was performed with radiosurgery.

Reports with insufficient outcome data or series smaller than 10 patients were excluded. Articles with overlapping data from the same institution (reporting on the same patients) were excluded. Reports of planned staged-volume radiosurgery were excluded.

Additionally, reports with multiple fraction treatments, where the total dose of a treatment is divided over a short time period, were excluded.

2.2. Data extraction

No registered review protocol was utilized in this study. Data extraction was independently performed by the authors AJA and BPW. The authors extracted methodological and demographic data including study design, patient age, nidus size (volume and maximal diameter), Spetzler–Martin grade [19] and time range from first radiosurgery to repeat radiosurgery. Radiosurgery treatment planning data of target (prescription) dose, maximal dose, isocenter line and delivery unit (radiation source) were also identified. Additionally, we analyzed nidus size reduction, length of follow up, and calculated the obliteration rate after repeat radiosurgery and complications resulting from stereotactic radiosurgery.

In terms of post-treatment outcomes and complications, recorded data included number and percentage of post-treatment patients demonstrating angiographic or other imaging evidence of complete obliteration, mean/median time to obliteration and number and percentage of patients with hemorrhage and radiation-induced changes (RIC) following repeat treatment. RIC was defined as imaging findings of edema, cyst formation or necrosis correlated with patient reported symptoms or worsening of neurologic deficits, or seizures as a result of radiation treatment.

2.3. Statistical analyses

Statistical analyses in this review were performed using SPSS Statistics (version 22.0.0.0, IBM Corporation, Armonk, NY, USA). Descriptive statistics were obtained for obliteration rate, RIC rate, hemorrhage rate and mortality rate in the group of patients who underwent repeated stereotactic radiosurgery for their AVM. Confidence interval for the final obliteration rate was computed using Fieller's method of a confidence interval (CI) for the ratio of two means.[20]

3. Results

3.1. Study selection

The initial search yielded 319 reports published between 1989 and 2014. After removing duplicated records, 103 reports were then screened of which 31 full-text articles met screening criteria for eligibility. Subsequently, 17 articles were excluded due to insufficient outcome data (n = 10) and overlapping data published from the same institution (n = 7). Two studies reporting on the same cohort of patients but with supplementary outcome measures were condensed into a single series.[21, 22] Figure 1 shows a flow chart of the systematic review process.

3.2. Repeat AVM radiosurgery series included for analysis

A total of 14 studies comprising 733 patients meeting review criteria were included.[11, 15-17, 21, 23-31] All studies were retrospective in design. The number of patients in individual studies ranged from 11 to 140 with a median age ranging from 35 to 43 years old.

The radiation delivery platform used was a gamma knife ($n = 7$), linear particle accelerator ($n = 6$), or both ($n = 1$).

3.3. Treatment planning details

The time interval between radiosurgery sessions ranged from a median of 38 to 108 months. For series that reported target dose at both first and repeat treatments, the weighted means were 19.42 Gy (range: 12.6–23) and 19.06 Gy (range: 13.6–22.8), respectively. When reported, the majority of patients treated had AVM with high Spetzler–Martin scores; 53% of patients had grade III lesions although there were patients with grades ranging from I to VI. The nidus size reduction between first and repeat treatments ranged from 29.7 to 65.9% with a weighted mean reduction of 61.6%. Treatment planning details are summarized in Table 1.

3.4. Outcome details

Complete obliteration rates following initial radiosurgery in this highly selected group varied widely between 35.7 and 86.0%. The mean and median obliteration rate for the repeat radiosurgery treatments were 61% (95% CI 51.9–71.7%) and 61.5%, respectively. The median follow up ranged from 19.5 to 80 months. Time to complete obliteration after the repeat treatment ranged from 21 to 40.8 months (Table 2).

The consistent reported complications of repeated radiosurgery for AVM included hemorrhage and RIC as summarized in Table 2. In pooling all reported data from the repeated radiosurgery studies, the hemorrhage rate was reported in 12 of the 14 studies with a mean of 7.6% (95% CI 1.9–18.9%), RIC rates were reported in 11 of the 14 studies with a mean of 7.4% (95% CI 3.7–17.5%).

4. Discussion

4.1. Treatment options after failed radiosurgery for AVM

Treatment of persistent AVM following radiosurgery can be performed with repeat radiosurgery (the focus of this review) but consideration can also be given to microsurgical resection or subsequent endovascular embolization to occlude the still-patent nidus. [32] AVM characteristics may change significantly from the time of initial treatment as a result of the initial radiosurgery and must be considered when selecting subsequent treatment modalities.[33, 34] Altogether, management decisions must be made based on the final characteristics of the AVM following radiosurgery and include the size, location, venous drainage characteristics, associated aneurysms, eloquence of involved cortex and rate of arteriovenous shunting. The decision to pursue any given modality of retreatment is also a function of the perceived hemorrhage risk, likelihood of cure and estimation of procedural complications associated with interventional treatment. Observation can also be a management option, particularly when the AVM characteristics following radiosurgery dramatically change the size and hemodynamics of the lesion. Lesions that have reduced considerably in size and have reduced flow characteristics (slow arteriovenous shunting) demonstrated on digital subtraction angiography may be appropriate candidates for further observation. In our own experience and the published experience of others, certain

characteristics of treated AVM which demonstrate complete or near-complete nidus obliteration with a persistent early draining vein demonstrate low rates of hemorrhage and may even go on to complete obliteration at long term follow up. [35]

4.2. Reasons of failure after first radiosurgery

Complete AVM obliteration is traditionally defined as angiography (gold standard) with normal circulation time, complete absence of any abnormal vessels around the previously defined nidus and normalization of the draining veins. Authors of large series have reported that the complete obliteration rate following radiosurgery is as high as 80%. [10, 36] However, this cure rate depends on many unavoidable and avoidable factors. Patient age, volume and location of AVM nidus, length of follow up and radiobiological resistance are considered unavoidable factors. [15, 37, 38] Radiobiological resistance is the failure to obliterate the nidus of AVM despite proper treatment planning and delivery. [37] Avoidable factors include inadequate target localization and inadequate dose delivery to the nidus. [38, 39] Generally, a higher rate of complete obliteration is associated with younger patient age, higher dose, longer follow up period, hemispheric AVM location, smaller AVM volume, the presence of only a single draining vein and no history of prior embolization. [40, 41]

4.3. Complications of repeat radiosurgery

While radiosurgery is a noninvasive treatment modality, it is associated with known complications. In our systematic review, hemorrhage is the most frequent complication ranging from 4.4 to 16% in individual series. High-grade and large AVM are associated with increased likelihood of incomplete obliteration and complications. [26, 30] In pooling all reported data, the most consistently associated complications with repeat radiosurgery are intracerebral hemorrhage (7.6%) and RIC (7.4%).

Traditionally, reduced doses were prescribed for repeat AVM treatments in order to avoid complications. [16] Lisack and colleagues reduced the prescription dose for the repeated radiosurgery treatment, however, the cumulative risk of morbidity in both groups of patients was the same. [23] On the other hand, because target (nidus) volume of a repeated treatment is often smaller, some centers consider higher prescription doses to maximize chances for obliteration [16, 22, 23] in concordance with the known relationship between dose and volume. [42]

4.4. Timing of repeat radiosurgery

The timing of further treatment following stereotactic radiosurgery is a function of the latency seen in both the effects and complications inherent to radiosurgery. Since the treatment effect period following radiosurgery for AVM is delayed and is thought to be maximal within the first three years, [43] further interventions are reserved until after this time period if they are necessary. Simply stated, repeat radiosurgery is typically delayed for a period of 3 years to allow for full realization of any beneficial treatment effect before subjecting the patient to the additional risk of a second treatment. Similarly, the compounding of any potential central nervous system toxicity such as radiation necrosis is avoided by increasing the interval between treatments. Repeat radiosurgery has been safely demonstrated not only with AVM, but also with the treatment of brain tumors where a

rigorous dose escalation study has defined maximum acute and chronic tolerable doses of 15–24 Gy, depending on the size of the treatment target. [44] In the various series of repeat radiosurgery for AVM that we reviewed, an average of at least 38 months elapsed between treatments.

Following radiosurgery, any persistent AVM nidus has the ongoing potential for hemorrhage. Regardless of the debate whether the initial radiosurgical treatment modifies the natural history of hemorrhage during the latency period in these patients,[45–47] a risk of hemorrhage does exist as long as the nidus persists. For patients undergoing repeat radiosurgery, this risk is magnified since there is more time that passes from initial diagnosis to eventual AVM obliteration. The percentage of patients experiencing hemorrhage in the series reviewed was similar to the rates seen following primary radiosurgery treatment, ranging from no hemorrhage events in smaller series[25, 31] up to 16% in the largest series. [16] The risk of hemorrhage during an extended treatment time interval must therefore be considered when evaluating patients for repeat radiosurgery.

4.5. Study limitations

This systematic review is limited by its retrospective study design, the limited granularity of individual patient characteristics and the single center nature of many of the studies. Additionally, the method of neurovascular imaging and follow up protocols performed at each center may vary widely, confounding obliteration and complication rates. Although the majority of series used angiography to confirm complete obliteration, a few studies included small percentages of patients where obliteration was assessed based on MRI.[16, 22, 24] Baseline characteristics of patients also varied and were difficult to account for. Namely, some patients had prior microsurgery or embolization in addition to their radiosurgery treatment.

5. Conclusion

Repeat radiosurgery for AVM can be used to treat incompletely obliterated lesions with a complete obliteration rate of 61%. Complications are related to treatment effect latency (hemorrhage risk) as well as RIC. Repeat radiosurgery can be performed at 3 years following the initial treatment allowing for full realization of effects from the initial treatment prior to commencing therapy.

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Highlights

- Repeat radiosurgery for AVM is relatively safe and effective procedure
- Repeat radiosurgery achieves a complete obliteration rate of 61%
- The most common complications are hemorrhage and radiation-induced changes
- Repeat radiosurgery can be performed at three years following the initial treatment

Fig. 1. Preferred reporting items for systematic reviews and meta-analyses flow chart for the systematic review process.

Table 1

Arteriovenous malformation patient treatment planning parameters

Author, year	Patient s, n	SRS delivery unit	Time to repeat SRS (months)	Initial SRS				Repeat SRS					
				Volume	Max diameter	Prescription dose	Max dose	Isodose line (%)	Volume	Max diameter	Prescription dose	Max dose	Isodose line (%)
Karlsson, 1998 [15]	101	GK	46.8 ^a	—	—	—	—	—	3.2 ^a	—	20 [*]	—	—
Pollock, 2003 [25]	21	GK	43 [*]	5.7 [*]	—	18 [*]	36 [*]	—	4.3 [*]	—	18 [*]	36 [*]	—
Schlienger, 2003 [29]	32	LINAC	52 [*]	2.75 [*] 3.8 ^a	2.7 [*]	24.5 [*] 23a	35.7 [*] 34 ^a	67 [*]	4.2 [*] 6.2 ^a	3 [*]	25 [*] 22.8 ^a	35.7 [*] 34.3 ^a	70 [*]
Mirza-Aghazadeh, 2006 [27]	15	LINAC	46 [*]	8.30 [*] 8.9 ^a	2.73 [*] 2.54 ^a	15 [*] 18 ^a	22 [*] 27 ^a	70 [*]	2.07 [*] 3.6 ^a	1.58 [*] 1.68 ^a	15 [*] 16 ^a	22 [*] 21 ^a	67 [*]
Liscak, 2007 [23]	68	GK	—	3.9 [*]	—	20 [*]	38 [*]	50 [*]	2.9 [*]	—	18 [*]	34 [*]	50 [*]
Raza, 2007 [30]	14	GK or LINAC	40.6 ^a	24.87 ^a	—	11 [*]	13.8 [*] 15.6 ^a	80 [*] 80.7 ^a	17.47 ^a	—	11 [*]	13.5 [*] 16 ^a	80 [*] 80.4 ^a
Jokura, 2009 [24]	71	GK	—	7.0 ^a	—	20.4 ^a	—	—	2.7 ^a	—	—	—	—
Buis, 2010 [28]	15	LINAC	52 ^a	4.6 ^a	—	18 [*]	—	—	2.1 ^a	—	21 [*]	—	—
Yen, 2010 [17]	140	GK	55.2 ^a	4.1 ^a	27.1 ^a	20.6 ^a	38.5 ^a	54 [*]	1.4 ^a	1.54 [*]	20.3 ^a	36.4 [*]	58 [*]
Flores, 2011 [31]	23	LINAC	49.5 ^a	2.1 ^a	—	14 ^a	—	90 [*]	2.7 ^a	—	13.6 ^a	—	90 [*]
Hauswald, 2011 [26]	11	LINAC	108 [*]	13 [*]	—	18 [*]	22.5 [*] 22.5 ^a	80 [*]	1.75 [*]	—	15.5 [*] 15.9 ^a	19.4 [*] 19.9 ^a	80 [*]
Stahl, 2012 [22] & Raffa, 2009 [21]	73	LINAC	38 [*] (44 ^a)	12.7 [*] 14.3 ^a	—	—	15 [*]	—	4 [*] 6.5 ^a	—	15 [*]	—	—
Kano, 2012 [16]	105	GK	40.9 [*]	6.4 [*]	29 [*]	18 [*]	35 [*]	—	2.3 [*]	20 [*]	18 [*]	36 [*]	—
Nagy, 2012 [11]	44	GK	60 [*]	—	—	—	—	—	—	—	—	—	—

— = no data, GK = gamma knife, LINAC = linear particle accelerator, Max = maximal, SRS = stereotactic radiosurgery.

^{*} Median.^a Average.

Table 2

Arteriovenous malformation patient outcomes and complications

Author, year	Patients, n	Age (years)	Delivery unit	Spetzler–Martin grade: n (%)	Complication: n (%)	Follow-up (months)	Complete obliteration rate after repeat SRS, n (%)	Time to complete obliteration (months)	Method for determining AVM obliteration ^a
Karlsson, 1998 [15]	101	35 [*]	GK	—	hemorrhage: 6 (6)	—	62 (61)	—	angiogram
Pollock, 2003 [25]	21	—	GK	—	no hemorrhage	—	18 (86)	—	angiogram
Schlienger, 2003 [29]	32	36 [*]	LINA _C	—	hemorrhage: 3 (9); RIC: 3 (9)	19.5 [*]	19 (59.3)	21 [*]	angiogram
Mirza-Aghazadeh, 2006 [27]	15	39 ^a	LINA _C	II: 7 (46.7), III: 8 (53.3)	hemorrhage: 2 (13); RIC: 2 (13)	39 [*] 43.8 ^a	10 (66.6)	—	angiogram
Liscak, 2007 [23]	68	35 [*]	GK	—	hemorrhage: 3 (4); RIC: 2 (3)	73.5 [*]	47 (69)	—	angiogram
Raza, 2007 [30]	14	29 ^a	LINA _C or GK	III: 5 (35.8), IV: 8 (57.1), V: 1 (7.1)	hemorrhage: 2 (14); RIC: 2 (14)	30.5 ^a	5 (35.7)	40.8 ^a	angiogram
Jokura, 2009 [24]	71	36 ^a	GK	—	—	—	33 (46.47)	—	angiogram (majority) or MRI
Buis, 2010 [28]	15	41 [*]	LINA _C	I: 7 (46.7), II: 4 (26.7), III: 3 (20), IV: 1 (6.7)	no hemorrhage; RIC: 6 (40)	49 [*]	9 (60)	50 [*]	angiogram
Yen, 2010 [17]	140	32.9 ^a	GK	I: 18 (12.9), II: 42 (30), III: 76 (54.3), IV: 4 (2.9)	hemorrhage: 8 (6); RIC: 4 (3)	84.2 ^a	77 (55)	—	angiogram
Flores, 2011 [31]	23	—	LINA _C	—	no hemorrhage; RIC: 2 (8.7)	—	16 (69.5)	—	angiogram
Hauswald, 2011 [26]	11	35 [*]	LINA _C	III: 10 (91), V: 1 (9)	hemorrhage: 1 (9); RIC: 2 (18)	26 [*]	5 (56)	26 [*]	—
Stahl, 2012 [22] & Raffa, 2009 [21]	73	43 [*]	LINA _C	I: 12 (11.7), II: 37 (35.9), III: 41 (39.8), IV: 13 (12.6)	hemorrhage: 5 (7); RIC: 4 (5)	37 [*]	51 (70)	—	angiogram (majority) or MRI
Kano, 2012 [16]	105	35 [*]	GK	I: 5 (5), II: 20 (19), III: 53 (59), IV: 15 (14), V: 1 (1), VI: 11 (10)	hemorrhage: 17 (16); RIC: 10 (9.5)	80 [*]	65 (62)	38.9 [*]	angiogram (majority) or MRI
Nagy, 2012 [11]	44	—	GK	—	hemorrhage: not reported; RIC: 3 (7)	—	30 (68)	—	angiogram

— = no data, AVM = arteriovenous malformation, GK = gamma knife, LINA_C = linear particle accelerator, RIC = radiation-induced changes, SRS = stereotactic radiosurgery.

^{*} Median.

^a Average.

Angiogram refers to catheter based diagnostic cerebral angiography.

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