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Review

Repeat radiosurgery for cerebral arteriovenous malformations

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ABSTRACT

We perform a systematic review of repeat 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, repeat 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 (PRISMA) 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 repeat 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 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.

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, repeat 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 repeat radiosurgery for cerebral AVM with an emphasis on lesion obliteration rates and complications.

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2. Methods

2.1. Literature search

A systematic review was performed in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) 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 repeat 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 repeat stereotactic radiosurgery for their AVM. Confidence interval (CI) for the final obliteration rate was computed using Fieller's method of a 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 GammaKnife (Elekta, Stockholm, Sweden) (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 repeat radiosurgery for AVM included hemorrhage and RIC as summarized in Table 2. In pooling all reported data from the repeat 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