Commentary: Systematic Review and Meta-Analysis of the Dose-Response and Risk Factors for Obliteration of Arteriovenous Malformations Following Radiosurgery: An Update Based on the Last 20 Years of Published Clinical Evidence

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Contemporary cerebrovascular disease has seen rapid clinical advancement. Increased knowledge in pathobiology has facilitated developments in the diagnosis and management of multisystemic disease states associated with relatively high rates of morbidity, mortality, and economic stress.1 Such trends are consequent of continued multidisciplinary translational work in related basic science and clinical fields.

Specific to cerebrovascular disease, rapid expansion of minimally invasive surgery (MIS) alternatives to pathology historically treated via transcranial approaches has supported an accumulating market of fellowship training and device development.2,3 The majority of advancements have been associated with ischemic-occlusive and aneurysmal pathology in the context of neuroendovascular intervention, resulting in a shift in management.4-7 Growth in this sector is indicative of clinical progress, but the steep rise of endovascular volume has shadowed previously established noninvasive methods, specifically the use of stereotactic external beam radiation therapy (XRT), with consequent paucity of novel literature despite evolving technology.

Intracranial arteriovenous malformations (AVMs) represent pathophysiologically complex lesions historically treated via microsurgical resection and are subject to individualized treatment in the context of clinical presentation.8 Endovascular techniques have shown limited success outside of adjunct treatment in the majority of lesions.8 Radiation therapy via single-dose or fractioned stereotactic radiosurgery (sSRS and fSRS, respectively) has been described to provide definitive therapy for small- and medium-sized unruptured and ruptured AVMs with obliteration rates reported as high as 60% to 80%.8 Due to inherent delay, the patient remains at risk during the latency period.8 Larger AVMs may be amenable to volume-staged SRS, although outcomes are inconclusive and treatment is reserved for salvage therapy.9,10 SRS demonstrates a sigmoid dose-response relationship between radiosurgical margin dose and obliteration rates and the balance between obliteration and adverse radiation effects (AREs) remains under active investigation.8

Two commonly used systems in SRS are the linear accelerator (LINAC), which mechanically orbits a target while delivering a controlled and shaped photon beam generated by the bremsstrahlung process, and Gamma systems (Gamma Knife [GK]), which apply therapeutic gamma radiation produced in cobalt beta decay via rotating or fixed converged beams.9-13 Controversies exist in the durability and safety of SRS vs standard measures.8 Literature reviews provide concise and relevant presentations of knowledge in pathogenesis and treatment, facilitating practitioners and scientists in quality improvement and patient selection.

The authors14 provide an informative comprehensive literature review with quantitative meta-analysis examining factors contributing to dose-responses and subtotal obliteration using data abstracted from available reports of patients with ruptured and unruptured AVMs who underwent sSRS (dose-response) or sSRS/fSRS (risk factors). Multivariate dose-response meta-analysis via equivocal Poisson and linear-quadratic regression models demonstrated favorable (>60%) obliteration rates with marginal doses over 18 Gy with a plateau at 20 Gy, a pattern lower albeit consistent with existing literature.14,15 Results strengthen reports that marginal dose positively correlates with obliteration before approaching the characteristic horizontal asymptote at levels considered to be relatively low risk for the development of delayed and acute AREs.10-16 The authors note a steeper dose-response curve in lesions treated with GK vs LINAC, attributed to proportional differences in marginal to isodose line secondary to discrepancies in beam generation and delivery. Risk factor analysis was conducted in a univariate manner, a limitation acknowledged by the authors, due to the
heterogeneity of available data. Parameters, including increased AVM volume/diameter, Spetzler-Martin (SM) and radiosurgical AVM scores, and prior embolization, were reported as negatively associated with obliteration via odds ratios. The presence of a compact nidus signaled a 3-fold increase in obliteration rates vs diffuse lesions, calculated from an unknown percentage of 1041 patients across 3 studies. No significant differences were found between ruptured/unruptured lesions, eloquent locations, and the presence of AVM-associated/incidental aneurysms. The authors note potential publication bias in all significant univariate associations evidenced by funnel plot analysis of combined standard error with respect to odds ratios, and caution that volume correlations were produced by arbitrarily categorizing “larger” or “smaller” individual lesions with a threshold volume of 3.5 cc. Although outside the scope of the paper, no correlations were made between parameters and functional outcome, AREs, or rupture/rupture post-treatment.

SRS represents an MIS option widely employed in neurooncology and with expanding potential in functional and cerebrovascular neurosurgery. However, the field has not seen a relatively high volume of cerebrovascular academic interest as compared to alternatives, specifically endovascular and transcranial microsurgical approaches. Notably, only 8 (13.3%) of the 60 reports included in the meta-analysis have been published over the last 5 yr (2016 or later). The authors should thus be commended for providing a contemporary summarization of factors associated with obliteration rates. Cumulatively, results indicate a positive association of a marginal dose of 18 Gy at variable follow-ups with obliteration rates greater than 60% in ruptured and unruptured AVMs treated with single-dose SRS. Additionally, univariate evidence is provided with the caveat of publication bias for positive associations of AVM decreased volume or diameter, SM or radiosurgery scores, lack of prior embolization, and a compact nidus with obliteration rates. Clarification of necessary dose-responses provides evidence for clinically significant results achieved with relatively acceptable toxicity profiles, and identification of factors potentially affecting obliteration, facilitating patient selection. Interestingly, the factors associated with increased obliteration are likewise associated with effective and safe surgical resection.

Perhaps more so than any other cerebrovascular pathology, AVMs are highly complex and structurally unique lesions, with individual patients requiring focused multidisciplinary planning and consideration of conservative, microsurgical, radiosurgical, and endovascular options. Thus, the discrepancy in relevant radiosurgical literature is disappointing, making the provided review critical for practicing physicians and academics to succinctly evaluate available evidence. Further studies should seek to interrogate and expand provided results, with additional studies querying clinical outcomes, latency periods to obliteration, and the involvement of ruptured/unruptured associated aneurysms. Continued progression in effective and durable MIS cerebrovascular techniques is a trend that will arguably dominate future treatment patterns. Speculatively, the majority of patients would likely prefer lying on a table for 45 min of outpatient SRS in place of more invasive therapy if outcomes are similar. It is imperative for academics to evaluate if such techniques can be optimized to have similar treatment and safety profiles.

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