Impact of Onyx Embolization on Radiosurgical Management of Cerebral Arteriovenous Malformations: Treatment and Outcome

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■ BACKGROUND: **Stereotactic radiosurgery (SRS) is a well-established treatment modality for cerebral arteriovenous malformations (AVMs). The main limiting factor in the radiosurgical treatment of AVMs is the volume of the nidus, with high-grade lesions often requiring combined treatment to reduce the SRS target volume. To overcome this limitation, we have been using a combined treatment approach consisting of endovascular embolization with Onyx followed by SRS.**

■ OBJECTIVE: **To evaluate our clinical experience for safety and feasibility of this multimodality treatment approach.**

■ METHODS: **This is a retrospective review of all adult patients with cerebral AVMs who received SRS treatment to their AVM after endovascular embolization with Onyx between June 2007 and June 2014.**

■ RESULTS: **Thirty-five consecutive patients were identified. The mean follow-up period was 52.4 ± 22.6 months (range 18–97 months). We confirmed 18 (51.4%) complete nidus closures at a median time of 49.5 months (range 6.5–81 months) from SRS. High-resolution Magnetic resonance imaging/magnetic resonance angiography was performed routinely in all patients until closure of the nidus. Digital subtraction angiography was performed to confirm complete obliteration in 5 of the patients (28%); 13 patients are either planned for digital subtraction angiography or have refused it. In 6 patients (17%) a significant flow reduction was noted after a mean of 32 ± 16 months. No significant improvement was observed in 9 patients (26%) during the follow-up period. Two patients were lost to follow-up.**

■ CONCLUSIONS: **The multimodality treatment of cerebral AVMs using embolization with Onyx followed by SRS is feasible and safe. The use of Onyx significantly reduced the SRS treatment target volume.**

INTRODUCTION

Stereotactic radiosurgery (SRS) is a well-established treatment modality for cerebral arteriovenous malformations (AVMs).[1-3] The primary limiting factor in the radiosurgical treatment of cerebral AVMs is the volume of the lesions. High doses of radiation are required to achieve obliteration[3-6]; however, these are associated with increased risk of radiation-induced complications when delivered in large volumes. Several reports have demonstrated that larger volumes of brain tissue receiving more than 12 Gy increased the risk of radiation-related damage.[7-9] Therefore, larger AVMs require lower-prescription doses to avoid risks of radiation injury, thus limiting the effectiveness of SRS. Moreover, it's been demonstrated that the efficacy of SRS is volume-dependent, and obliteration rates in larger AVMs have been reported as low as 23%–36%.[3,10]

Two approaches have been developed to overcome this limitation. The first is staged-volume SRS,[11-13] whereby the AVM nidus volume is divided and treated sequentially in stages. This

Key words
- Arteriovenous malformations
- AVM
- Embolization
- Onyx
- Radiosurgery
- SRS

Abbreviations and Acronyms
AVM: Arteriovenous malformation
CT: Computed tomographic
DSA: Digital subtraction angiography
MRA: Magnetic resonance angiography
MRI: Magnetic resonance imaging
SRS: Stereotactic radiosurgery

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Citation: World Neurosurg. (2017) 108:656-661.
http://dx.doi.org/10.1016/j.wneu.2017.08.188

Journal homepage: www.WORLDNEUROSURGERY.org

Available online: www.sciencedirect.com

approach, although safe, vis-à-vis radiation morbidity, entails the risk of rebleed until the whole AVM is treated and obliterated. The second, to decrease the treatment volume before SRS, can be accomplished by embolizing the AVM.[14-17] This multimodal approach allows a high-volume AVM to be reduced to a smaller treatment target volume and thus potentially increase the likelihood of obliteration with SRS and decrease the risk of adverse radiation effects.

Onyx is an embolic agent (Micro Therapeutics, Inc., Irvine, California, USA) composed of ethylene-vinyl alcohol dissolved in dimethyl sulfoxide that was approved for neuroendovascular treatment. We have embarked on a combined treatment approach using Onyx for primary closure and as volume reduction before subsequent SRS treatment for niduses that could not be obliterated completely by embolization alone.[18,19] As opposed to earlier available embolization materials (e.g., N-butyl cyanoacrylate), the combination of SRS with Onyx is particularly appealing because it is intended to provide permanent closure if applied correctly by direct intra-nidal injection, with rare instants of recanalization.[20-24] Thus, it allows for a true reduction of the treatment target volume.

However, radiosurgery after embolization with Onyx poses specific challenges due to the artifacts it creates on imaging studies. We previously have described the technical aspects of radiosurgical treatment planning of AVM after embolization with Onyx[25] and the complexity that is imposed on the dose calculation, which is predicated on computed tomographic (CT) Hounsfield units. The purpose of the current study was to evaluate our clinical experience with this multimodality treatment approach of combining embolization with Onyx followed by SRS.

PATIENTS AND METHODS

This was a retrospective review of patients with cerebral AVMs identified in our prospectively maintained SRS database between June 2007 and June 2014. Included were all patients older than 18 years of age who received SRS treatment for their AVM after at least one endovascular embolization procedure with Onyx. Their medical charts, radiosurgical treatment plans, and neuroimaging studies (magnetic resonance, CT, and angiography) were reviewed by a neuroradiologist (S.M.) and a neurosurgeon (A.A.K.). We received approval from our institutional review board to carry out this analysis.

Included were patients with sporadic AVM who had not received previous radiation or radiosurgical treatment. Patients whose endovascular treatment was performed with other embolization materials (e.g., polyvinyl alcohol, coils, or N-butyl cyanoacrylate) and whose follow-up was less than 24 months were excluded.

Endovascular Treatment Procedure

All the endovascular procedures were performed by one experienced invasive neuroradiologist (S.M.). Detailed descriptions of the embolization procedure, clinical outcomes, and risks recently were published by our group.[18,19] All endovascular treatments were performed with the patients under general anesthesia. Catheterization was performed by a transfemoral approach via the use of standard coaxial techniques, in which we navigated the tip of the microcatheter as close as possible to the nidus. Onyx was slowly and progressively injected into the nidus under continuous visual control. We tried to occlude completely the proximal draining veins at the end of treatment. The embolization sessions were halted when the nidus became inaccessible due to unfavorable anatomy of feeders and a high risk/benefit ratio for the patient. At that juncture, other treatment options were considered. Patients with small remnants without bleeding, or with remnants in deep or eloquent areas, were referred to radiosurgery.

Radiosurgical Procedures

Precise target definition of the residual AVM nidus was achieved via stereotactic cerebral digital subtraction angiography (DSA) fused with cranial CT and magnetic resonance imaging (MRI)/magnetic resonance angiography (MRA) scans. All the angiography and embolization procedures were performed by the same invasive senior neuroradiologist (S.M.), who was also involved in the target definition of the nidus before SRS treatment. The embolized portion of the AVM typically was not included in the SRS target volume. When it could be clearly identified, we included the origin of the draining veins into the target volume. The nidus volume was measured with iPlan software (BrainLab, Munich, Germany). The follow-up review of all neuroimaging and the decision-making process for follow-up angiography was likewise performed jointly by the senior neuroradiologist and neurosurgeon.

The details of the SRS treatment procedure have been published elsewhere.[25] To summarize, they were performed with a linear accelerator–based platform (Synergy S, ELEKTA, Stockholm, Sweden), using frame-based head immobilization for registration and treatment. SRS treatment was accomplished using a combination of static fixed beams and/or and static arcs to achieve optimal and conformal target coverage. The treatment dose was typically 15–24 Gy to the defined target volume, with volume, location, and clinical aspects taken into consideration.

Follow-up visits in our outpatient clinic were scheduled after MRI/MRA at 6 months and at 1, 2, 3, 4, and 5 years after the initial SRS procedure. Treatment success was defined when the MRI/MRA indicated significant reduction or absence of the T1-T2 flow artifacts as well as contrast enhancement of pathological vessels.[26,27] Patients also were invited to undergo a diagnostic digital angiography evaluation.

RESULTS

Demographics

We identified 35 adult patients (21 men and 14 women) with cerebral AVMs who underwent a combined treatment approach with SRS after embolization with Onyx. The mean age of the study group at the time of SRS treatment was 38.1 ± 11.8 years. Thirteen (37.1%) patients presented with seizures and 14 (40%) patients had at least one episode of hemorrhage before treatment.

Embolization Procedures

The median Spetzler-Martin grade before the first embolization was 4 (range 2–5, **Table 1**). The location of the AVM was lobar in 26 (74.3%) patients and deep-seated in 9 (25.7%) (i.e., basal ganglia, thalamic/intraventricular). Eighteen AVMs had deep