Stereotactic radiosurgery for arteriovenous malformations after Onyx embolization: a case-control study

Cheng-Chia Lee, MD,1,3,4 Ching-Jen Chen, MD,1 Benjamin Ball, BS,1 David Schlesinger, PhD,1,2 Zhiyuan Xu, MD,1 Chun-Po Yen, MD,1 and Jason Sheehan, MD, PhD1,2

OBJECT Onyx, an ethylene-vinyl alcohol copolymer mixed in a dimethyl sulfoxide solvent, is currently one of the most widely used liquid materials for embolization of intracranial arteriovenous malformations (AVMs). The goal of this study was to define the risks and benefits of stereotactic radiosurgery (SRS) for patients who have previously undergone partial AVM embolization with Onyx.

METHODS Among a consecutive series of 199 patients who underwent SRS between January 2007 and December 2012 at the University of Virginia, 25 patients had Onyx embolization prior to SRS (the embolization group). To analyze the obliteration rates and complications, 50 patients who underwent SRS without prior embolization (the no-embolization group) were matched by propensity score method. The matched variables included age, sex, nidus volume before SRS, margin dose, Spetzler-Martin grade, Virginia Radiosurgery AVM Scale score, and median imaging follow-up period.

RESULTS After Onyx embolization, 18 AVMs were reduced in size. Total obliteration was achieved in 6 cases (24%) at a median of 27.5 months after SRS. In the no-embolization group, total obliteration was achieved in 20 patients (40%) at a median of 22.4 months after SRS. Kaplan-Meier analysis demonstrated obliteration rates of 17.7% and 34.1% in the embolization group at 2 and 4 years, respectively. In the no-embolization group, the corresponding obliteration rates were 27.0% and 55.9%. The between-groups difference in obliteration rates after SRS did not achieve statistical significance. The difference in complications, including adverse radiation effects, hemorrhage episodes, seizure control, and patient mortality also did not reach statistical significance.

CONCLUSIONS Onyx embolization can effectively reduce the size of many AVMs. This case-control study did not show any statistically significant difference in the rates of embolization or complications after SRS in patients who had previously undergone Onyx embolization and those who had not.


KEY WORDS obliteration; embolization; Gamma Knife; stereotactic radiosurgery; arteriovenous malformation; Onyx; vascular disorders
alone treatment for intracranial AVMs. However, they are increasingly being used in combination, especially for larger and complicated AVMs (e.g., AVMs with perinidal aneurysms or high-flow fistular components). In theory, embolization may reduce the size of the AVM nidus to less than 3 cm in diameter, which would facilitate delivery of a greater effective dose to the residual nidus of a large AVM. A study by Kano et al.27 demonstrated significantly improved results when prior embolization decreased nidus volume to less than 8 cm³.

Nevertheless, the literature regarding benefits of pre-radiosurgical embolization consists of conflicting reports. Several recent series have shown that preradiosurgical embolization may be disadvantageous in AVM patients treated with particle embolization.5,27,55 The lower radiosurgical obliteration rate in patients with prior embolization has been attributed to several potential factors, including recanalization of the embolized AVM,30,36 increased difficulty in AVM delineation and radiosurgical planning,27,30,36,38 and a shielding effect caused by embolization materials with high atomic mass.5

In the era of liquid embolization with materials such as Onyx, several studies have shown that these agents cause less recanalization than previous particle embolic agents did.31,43,45 Additionally, the effects of radiation delivered to the center of AVM models with Onyx were not reduced.9,35 The possible dosage attenuation caused by previous embolic materials can be averted with Onyx embolization.58 The present study aims to evaluate the outcome of SRS treatment of AVMs after Onyx embolization. These cases were matched to a cohort of patients who underwent SRS as an upfront treatment. The rates and timing of obliteration, hemorrhage, and complications were evaluated. To the best of our knowledge, this study is the first report to focus on radiosurgical outcome after Onyx embolization.

Methods
Patient Characteristics

A consecutive series of 199 patients with AVMs underwent Gamma Knife surgery (GKS) between January 2007 and December 2012. From this group of patients, we identified 25 (12.6%) who had prior Onyx embolization before GKS. All of them had at least 1 post-GKS MRI or cerebral angiography follow-up study at the University of Virginia available for analysis. The patients’ clinical data, including demographic characteristics, pre-GKS imaging findings, radiosurgery parameters, and follow-up images, were retrieved from a prospectively collected, institutional review board–approved Gamma Knife database and retrospectively reviewed.

All patients underwent a comprehensive neurological examination and a cerebral imaging evaluation prior to radiosurgery. Bleeding history, the patient’s age, existing comorbidities, location of the nidus, Spetzler-Martin AVM grading, prior treatment history, and clinical symptomatology were reviewed. Stereotactic imaging, including T1-weighted contrast-enhanced 3D volumetric and whole-head T2-weighted fast spin echo imaging sequences and biplane digital subtraction angiography (DSA), was performed for radiosurgical planning.

In addition to the Spetzler-Martin grading system,60 the radiosurgery-based AVM system (RBAS) score,46,47 and the Virginia Radiosurgery AVM Scale score61 were used for the classification of intracranial AVMs in this study. The RBAS was calculated as follows: (0.1 × [AVM volume in cm³]) + (0.02 × [patient age]) + (0.3 × [AVM location score]). The overall scores were then compared with scores of previously treated patients with known outcomes to predict individual outcome.46,47 The Virginia Radiosurgery AVM Scale is based on AVM volume, nidus location, and history of hemorrhage.61 Patients were assigned 0 points if they had an AVM volume of less than 2 cm³, AVM in a noneloquent location, and no history of hemorrhage. Patients were assigned 1 point for each of the following: AVM volume of 2–4 cm³, AVM in an eloquent location, or a history of hemorrhage. They were assigned 2 points if they had an AVM volume greater than 4 cm³.

Prior Embolization

All 25 patients underwent at least 1 embolization using Onyx at the University of Virginia. Five patients with multiple embolizations underwent prior treatments at other institutions. The median interval between the last embolization and SRS was 3 months (range 0–30 months). For embolizations performed at our institution, Onyx 18 (6% EVOH) and Onyx 34 (8% EVOH) were used. The higher concentration of EVOH in Onyx 34 makes the agent more viscous and therefore preferable for forming an Onyx plug at the onset of an embolization. In 1 case, the patient had an intraoperative hemorrhage and postprocedural hemiparesis; in all other cases, the embolization procedure was uneventful. The current report excluded patients who underwent embolization with other embolic materials, such as detachable microcoils, polyvinyl alcohol (PVA), n-buty-2-cyanoacrylate (nBCA), or isobutyl 2-cyanoacrylate.

Gamma Knife Radiosurgery

The procedure for Gamma Knife surgery has been previously described.24,25,56,57 In brief, all patients underwent stereotactic frame placement in the operating room with intravenous monitored anesthesia, and then had stereotactic planning neuroimaging (MRI and DSA). Radiosurgery was performed using the Leksell Gamma Unit Model 4C until 2007 and the Perfexion model (Elekta, AB) thereafter. The AVM nidus was delineated using both stereotactic MRI and cerebral angiography. A dose plan was rendered in a multidisciplinary fashion by a neurosurgeon in conjunction with a radiation oncologist and a medical physicist.

Treatment parameters and dose planning varied according to the patient’s clinical presentation, neurological and ophthalmological examination findings, and AVM nidus location. The dose to the surrounding brain is a critical predictor of adverse radiation effects. Therefore, maximizing conformality to reduce radiation to the eloquent brain tissue is crucial. In this series, the patients who underwent repeated or staged SRS were excluded.

Imaging Evaluations

After SRS, all patients underwent clinical evaluation

Unauthenticated | Downloaded 12/31/21 03:02 PM UTC
and MRI/MRA (MR angiography) studies at 6-month intervals. Once the nidus was believed to be obliterated on MRI/MRA, a cerebral angiogram was recommended. Total obliteration of the AVM was defined as complete absence of filling of the nidus on angiogram. If the patient refused an angiogram, the AVM was deemed obliterated if there was no flow void on MRI or vascular filling on MRA.

Adverse radiation effects (AREs) were defined as newly developed areas of increased T2 signal surrounding the treated AVM nidi following SRS. The grading system described by Yen et al. was used.66 Mild imaging changes with an area of increased T2 signal measuring less than 10 mm in thickness surrounding the treated nidi and imposing no mass effect were considered to represent Grade I AREs. Moderate imaging changes with increased T2 signal in areas of 10 mm thickness or greater, with some mass effect causing effacement of the sulci or compression of the adjacent ventricles, constituted Grade II; and severe imaging changes that caused midline shift of the brain, Grade III.

Statistical Analysis

The 174 patients who had radiosurgical treatment of an AVM during the study period without prior Onyx embolization were eligible to serve as potential case-control matches. We used propensity-score matching between the AVM patients who had Onyx embolization (embolization cohort) and the AVM patients who had no prior embolization (no-embolization cohort). The propensity score was calculated in a logistic regression model with 7 parameters: age, sex, AVM nidus volume (prior to SRS), margin dose, Spetzler-Martin grade, Virginia Radiosurgery AVM Scale score, and duration of follow-up. According to propensity score, a closest-neighbor 1:2 matching algorithm was used. A caliper width of 0.4 times the sample standard deviation of the propensity score was chosen.

The Pearson chi-square test, Fisher exact test, and Mann-Whitney U-test were used for examining the differences between the embolization and no-embolization cohorts. AVM patients who did not undergo prior embolization (no-embolization cohort) were matched to AVM patients who underwent prior Onyx embolization (embolization cohort) by similar age (p = 0.97), sex (p = 1.00), nidus volume before SRS (p = 0.65), margin dose (p = 0.99), Spetzler-Martin grade (p = 0.77), Virginia Radiosurgery AVM Scale score (p = 0.74), and duration of follow-up (p = 0.99).

The demographic data for both the embolization and no-embolization groups are listed in Tables 1 and 2. Descriptive statistics are presented as the median and range for continuous variables and as frequency and percentage for categorical variables.

The rates of obliteration, hemorrhage, AREs, and mortality after SRS were assessed in both patient groups. Kaplan-Meier plots were used to compare the effects of Onyx embolization on SRS efficacy. Statistical significance was indicated by a p value less than 0.05. All analyses were completed using commercial statistical software (version 20.0, IBM SPSS).

### Results

**Patient Demographic and AVM Characteristics**

The embolization group consisted of 15 females and 10 males, with a median age of 42 years (range 8–67 years). In 19 patients (76%), the AVM nidi were located in cerebral hemispheres. Five patients (20%) had AVMs with intranidal aneurysms. The median number of draining veins was 3 (range 1–6). Prior hemorrhage occurred in 9 patients (36%). Two patients underwent resection before SRS, and all 25 patients underwent Onyx embolization at least once (Tables 1 and 2). After Onyx embolization, 18 AVMs decreased in volume; the median nidus volume decreased from 4.9 cm$^3$ (range 0.5–75 cm$^3$) to 3.5 cm$^3$ (range 0.3–33.9 cm$^3$), mean 10.2 cm$^3$).

Spetzler-Martin grade, the radiosurgery-based AVM system (RBAS) score, and Virginia Radiosurgery AVM Scale were used to classify these AVMs. Prior to SRS, 12 nidi were less than 3 cm in maximum diameter, 11 nidi were between 3 and 6 cm, and 2 nidi were larger than 6 cm. Sixteen nidi were located in eloquent areas, and 9 nidi were located in eloquent areas. Nineteen nidi had superficial venous drainage only, and the other 6 nidi had 1 or more deep draining veins. The median RBAS score was 1.4 (range 0.6–4.2), and the median Virginia Radiosurgery AVM Scale score was 2 (range 0–4) (Table 2).

### Table 1. Test results of the matching of 25 GKS-treated AVM patients with prior Onyx embolization and 50 patients without prior embolization (propensity-score matching)*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Embolization</th>
<th>No Embolization</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>25</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Median pt age in yrs</td>
<td>42 (8–67)</td>
<td>40 (10–84)</td>
<td>0.97</td>
</tr>
<tr>
<td>Sex, F:M</td>
<td>15:10</td>
<td>30:20</td>
<td>1.00</td>
</tr>
<tr>
<td>Median AVM nidus vol</td>
<td>3.5 (0.3–33.9)</td>
<td>3.0 (0.1–31.8)</td>
<td>0.65</td>
</tr>
<tr>
<td>(prior to SRS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median margin radiation</td>
<td>22 (13–25)</td>
<td>20 (14–25)</td>
<td>0.99</td>
</tr>
<tr>
<td>dose (Gy)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVM grade (S-M)</td>
<td></td>
<td></td>
<td>0.77</td>
</tr>
<tr>
<td>1–2</td>
<td>18 (72%)</td>
<td>29 (58%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>5 (20%)</td>
<td>16 (32%)</td>
<td></td>
</tr>
<tr>
<td>4–5</td>
<td>2 (8%)</td>
<td>5 (10%)</td>
<td></td>
</tr>
<tr>
<td>Virginia Radiosurgery</td>
<td></td>
<td></td>
<td>0.74</td>
</tr>
<tr>
<td>AVM Scale score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>6 (24%)</td>
<td>17 (34%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>13 (52%)</td>
<td>19 (38%)</td>
<td></td>
</tr>
<tr>
<td>3–4</td>
<td>6 (24%)</td>
<td>14 (28%)</td>
<td></td>
</tr>
<tr>
<td>Median imaging FU (mos)</td>
<td>24.1 (6–61)</td>
<td>25.7 (6–81)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

FU = follow-up; pt = patient; S-M = Spetzler-Martin grade.

* The parameters used in propensity-score matching were age, sex, AVM nidus volume, margin dose, S-M grading, Virginia Radiosurgery AVM Scale score, and median duration of imaging follow-up. Values represent numbers of patients or cases unless otherwise indicated. Values in parentheses are ranges for continuous variables and frequencies or percentages for categorical variables. The p values are for between-groups differences.
Fifty AVM patients with no prior embolization were matched as a control group according to the method described above. The no-embolization group consisted of 30 females and 30 males with a median age of 40 years (range 10–84 years). In 38 patients (76%), the AVM nidus were located in cerebral hemispheres. Eleven patients (22%) had AVMs with intranidal aneurysms. The median number of draining veins was 3 (range 1–6). Prior hemorrhage had occurred in 21 patients (42%). Three patients underwent resection before SRS, 7 patients underwent conventional radiotherapy before SRS, and 40 patients underwent SRS as an upfront treatment; none of the 50 patients in this group underwent any embolization procedure. The median AVM nidus volume before SRS was 3.0 cm³ (range 0.1–31.8 cm³) (Tables 1 and 2).

Because of matching, the distribution of AVM features was similar between the embolization and the no-embolization groups. In the no-embolization group, 31 nidus were less than 3 cm in maximum diameter, 17 nidi were between 3 and 6 cm, and 2 nidus was larger than 6 cm. Thirty-five nidi were located in noneloquent areas, and 15 nidi were located in eloquent areas. Twenty-one nidi had superficial venous drainage only, and other 29 nidi had one or more deep draining veins. The median RBAS score was 1.7 (range 0–4.3), and the median Virginia Radiosurgery AVM Scale score was 2 (range 0–4). (Table 2)

### Radiosurgical Prescription

Table 2 presents the radiosurgical parameters in detail. For the embolization group, the median margin dose was 22 Gy (range 13–25 Gy), the median maximum dose was 44 Gy (range 26–50 Gy), the isodose levels were 50% (no variation), and the median number of shots was 8 (range 1–24). For the no-embolization group, the median margin dose was 20 Gy (range 14–25 Gy), the median maximum dose was 40 Gy (range 28–50 Gy), the median isodose level was 50% (range 50%–65%), and the median number of shots was 8 (range 1–24).

### Imaging Outcome

The median duration of follow-up in the embolization cohort was 24.1 months (range 6–61 months), and the median angiography (DSA) follow-up was 29.8 months (range 6–67 months). Table 3 shows the results of radiological interpretations of MRI/MRA and DSA. In the embolization cohort, MRI/MRA or angiographic obliteration was achieved in 6 patients (24%) at a median of 27.5 months (range 18–61 months) after SRS. Seventeen AVMs (68%) showed partial obliteration, and 2 patients’ AVMs remain widely patent. In the no-embolization group, MRI/MRA or angiographic obliteration was achieved in 20 patients (40%) at a median of 22.4 months. Similarly, there were 28 AVMs that showed partial obliteration and 2 with no appreciable response.

The difference did not achieve statistical significance in either logistic or Cox regression models (p = 0.170 and p = 0.285, respectively) The Kaplan-Meier curve for obliteration is shown in Fig. 1. For the embolization cohort, the obliteration rates were 17.7% and 34.1% at the 2nd and 4th year after SRS, respectively. For the no-embolization cohort, the obliteration rates were 27.0% and 55.9% at the 2nd and 4th year after SRS, respectively.

Figure 2 demonstrates a favorable outcome in a patient who underwent successful treatment combining Onyx embolization and SRS. Preradiosurgical Onyx embolization decreased the size of the AVM, and 22 months after SRS the AVM nidus was totally obliterated.

### Complications

Table 4 displays the complications in both embolization and no-embolization groups. The post-SRS compli-
This approach is believed to lead to less morbidity in the no-embolization group.

...nidal aneurysms. These low-risk features (e.g., perinidal aneurysm) are usually remedied by neurosurgeons. For larger intracranial AVMs with complicated angiography, endovascular embolization prior to radiosurgery has some benefits. Embolization decreases the volume of the AVM nidus, permitting a higher radiosurgical dose to be delivered to the smaller nidus. This approach is believed to lead to less morbidity and a higher obliteration rate following SRS. In addition, embolization can reduce the risk of AVM rupture by eliminating intranidal aneurysms and reduce the flow in shunting vessels by blocking the high-flow fistulas. Moreover, embolization may reduce venous hypertension, which plays a major role in the development of radiation-induced vasogenic brain edema after SRS.

...are classified as Grade I. One hemorrhage episode was noted at 20 months after SRS, and 1 patient had worsening of seizures. No mortality was noted in this cohort.

In the no-embolization cohort, AREs were seen in 25 AVM patients (50%) at a median time of 8 months following SRS (range 2–30 months). They were classified as Grade II in 3 patients and Grade I in 22. There were 3 patients with intracranial hemorrhage and 5 patients with worsening of seizures; 2 patients died due to AVM rupture. The no-embolization group seemed to have a higher rate of AREs, hemorrhage, continued seizure, and mortality, but no statistically significant difference was detected between the two cohorts with respect to these complications (p = 0.624, p = 0.855, p = 0.652, and p = 0.064, respectively).

**Discussion**

Intracranial AVMs vary widely based upon differences in their angioarchitecture: diameter, size, compactness, number of feeding arteries, patterns of venous drainage, and development of perinidal aneurysms. These low-resistance shunting and high-flow vessels within the brain parenchyma are the key features of AVMs that lead to various clinical symptoms because of impaired cerebral perfusion or episodes of hemorrhage. Treatments for previously ruptured AVMs or ones exhibiting threatening features (e.g., perinidal aneurysm) are usually recommended by neurosurgeons.

For larger intracranial AVMs with complicated angioarchitecture, endovascular embolization prior to radiosurgery has some benefits. Embolization decreases the volume of the AVM nidus, permitting a higher radiosurgical dose to be delivered to the smaller nidus. This approach is believed to lead to less morbidity and a higher obliteration rate following SRS. In addition, embolization can reduce the risk of AVM rupture by eliminating intranidal aneurysms and reduce the flow in shunting vessels by blocking the high-flow fistulas. Moreover, embolization may reduce venous hypertension, which plays a major role in the development of radiation-induced vasogenic brain edema after SRS.

However, several authors reported that embolization prior to radiosurgery may reduce the final obliteration rate (Table 5). Andrade-Souza et al. reported on 61 AVM patients who underwent embolization before SRS and observed that the AVM obliteration rate following embolization and radiosurgery was lower than after upfront SRS. Schlienger et al. reported an AVM obliteration rate of 54% for 65 patients with prior embolization compared with 71% for 104 patients with no prior embolization (p = 0.03). The association between lower obliteration rates and previous embolization was statistically significant in multivariate analysis. Miyawaki et al. reported similar results in 43 patients who had previous embolization; the obliteration rates were 26% and 76% for patients with and without previous embolization, respectively. A recent study comprising a large case-matched cohort by Kano et al. also demonstrated that prior embolization reduced the rate of total obliteration after SRS. However, the risk of hemorrhage during the latency period was not affected by prior embolization. Of these articles focusing on the issue of prior embolization and consequent SRS for AVMs, most showed a lower rate of obliteration when comparable AVMs were treated with SRS. Nevertheless, these studies largely involved cases from the pre-Onyx era of embolization.

Several potential mechanisms have been proposed for the diminished rate of SRS-induced obliteration with prior embolization. Recanalization related to the use of PVA, as well as nBCA, has been noted in AVMs treated with embolization prior to radiosurgery. Second, embolization may obscure the targeting of the nidus thereby leading to suboptimal dose planning for radiosurgery; the AVM nidus may be broken apart, and and opaque embolic materials may obscure imaging of the lesion. Third, embolization may induce hypoxia, which makes the tissue less radiosensitive and increases the angiogenic activity of the AVM, rendering it an active instead of a static lesion.

**Table 3. Outcomes of SRS for AVMs**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Embolization</th>
<th>No Embolization</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR/MRA or DSA obliteration*</td>
<td>6 (24%)</td>
<td>20 (40%)</td>
<td>0.17</td>
</tr>
<tr>
<td>Partial obliteration</td>
<td>17 (68%)</td>
<td>28 (56%)</td>
<td></td>
</tr>
<tr>
<td>No response</td>
<td>2 (8%)</td>
<td>2 (4%)</td>
<td></td>
</tr>
</tbody>
</table>

* The median time to obliteration was 27.5 months (range 18–61 months) in the embolization group and 22.4 months (range 6–78 months) in the no-embolization group.
Another possible cause for diminished obliteration in previously embolized AVMs may be the shield effect caused by high atomic number elements in the embolic material and their attenuation of the dose of radiation delivered during radiosurgery.\textsuperscript{54} The shield effect is the subject of controversy, but several reports suggest that embolic material partially decreases the delivered dose.\textsuperscript{4,12,42,66}

With the introduction of Onyx (ev3), clinicians believed that these disadvantages of prior embolic materials would be significantly reduced. First of all, it is well known that embolization with a liquid embolic agent such as Onyx has a lower recanalization rate than embolization with particles.\textsuperscript{41,43,45} In the current study, all patients in the embolization group were treated with Onyx, which probably reduces or eliminates recanalization in the treated component of the nidus.\textsuperscript{5} In addition, the liquid embolic agent is designed to solidify once in the AVM and therefore can be delivered through much smaller microcatheters. The “lava-like flow pattern” within blood vessels of a soft and nonadherent mass does not fragment during the injection. When the Onyx comes into contact with aqueous solutions, the mixer begins to precipitate on the surface while the core remains liquid. Its nonadhesive nature enables longer, slower, and more controlled injection, which allows for the embolization of a larger percentage of the AVM and decreases the probability of breaking a compact AVM apart into noncontiguous residual components of nidus. The difficulties of target delineation appear to be reduced when the residual nidus is compact instead of broken apart. The nonadhesive nature also enables cerebral angiography between injections to monitor the progress of embolization,\textsuperscript{26,40,64,65} which represents a significant advantage over nBCA and other particle embolic materials. Furthermore, this cohesive solution mixed with micron-

<table>
<thead>
<tr>
<th>Complication</th>
<th>Embolization Group</th>
<th>No-Embolization Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Cases</td>
<td>Months Post-GKS</td>
</tr>
<tr>
<td>AREs</td>
<td>11</td>
<td>6.0 (2–19)</td>
</tr>
<tr>
<td>Grade I</td>
<td>10</td>
<td>—</td>
</tr>
<tr>
<td>Grade II</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>Continued seizure</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Mortality</td>
<td>0</td>
<td>—</td>
</tr>
</tbody>
</table>

* Chi-square and Fisher exact test.
### TABLE 5. Review of the literature on prior embolization and embolic materials in the stereotactic radiosurgery for intracranial AVMs

<table>
<thead>
<tr>
<th>Authors &amp; Year (case no.)</th>
<th>No. of Pts</th>
<th>Embolic Materials</th>
<th>Type of SRS</th>
<th>Obliteration Rate</th>
<th>Hemorrhage Rate</th>
<th>Major Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present series, 2014</td>
<td>25*</td>
<td>Onyx</td>
<td>GKS</td>
<td>18% &amp; 34% at 2 &amp; 4 yrs in embolization group (vs 27% &amp; 56% at 2 &amp; 4 yrs in no-embolization controls)</td>
<td>4% (1 pt) in embolization group (vs 6% [3 pts] in no-embolization group)</td>
<td>The rate of total obliteration &amp; risks of hemorrhage after SRS were not affected by prior Onyx embolization.</td>
</tr>
<tr>
<td>Kano et al., 2012&lt;sup&gt;27&lt;/sup&gt;</td>
<td>120</td>
<td>PVA in 20 (17%), nBCA in 38 (32%), isobutyl 2-cyanoacrylate in 14 (12%), &amp; microcoils in 10 pts (8%); none recorded in 38 pts (32%); no Onyx</td>
<td>GKS</td>
<td>35%, 53%, 55%, &amp; 59% at 3, 4, 5, &amp; 10 yrs</td>
<td>8% (9 pts); annual hemorrhage rate 2.7%</td>
<td>Prior embolization reduced the rate of total obliteration after SRS, &amp; the risks of hemorrhage during the latency period were not affected by prior embolization.</td>
</tr>
<tr>
<td>Blackburn et al., 2011</td>
<td>21</td>
<td>nBCA w/ adjunctive use of platinum coils &amp;/or PVA in select cases</td>
<td>LINAC &amp; GKS</td>
<td>81% (13/16) at mean 3.6 yrs</td>
<td>No hemorrhage</td>
<td>Staged endovascular embolization followed by SRS provides an effective means of treating large AVMs not amenable to standard surgical or SRS treatment.</td>
</tr>
<tr>
<td>Izawa et al., 2009</td>
<td>15</td>
<td>Mainly nBCA</td>
<td>GKS</td>
<td>67% (10/15) at mean 2.9 yrs</td>
<td>No hemorrhage</td>
<td>Obliteration &amp; long-term morbidity rates did not differ significantly in patients treated w/ &amp; w/o preradiosurgical nidus embolization.</td>
</tr>
<tr>
<td>Back et al., 2008</td>
<td>15</td>
<td>Not mentioned</td>
<td>GKS</td>
<td>60% (9/15) at min 3 yrs</td>
<td>13.3% (2 pts)</td>
<td>Embolization prior to GKS may reduce AVM obliteration rates.</td>
</tr>
<tr>
<td>Zabel-du Bois et al., 2007</td>
<td>50</td>
<td>nBCA or Ethibloc (Ethicon)</td>
<td>LINAC</td>
<td>67% &amp; 78% at 3 &amp; 4 yrs</td>
<td>125 (6 pts); annual bleeding risk 7.9% after 1 yr &amp; 2.2% after 2 yrs</td>
<td>The rate of obliteration after SRS in AVMs treated after prior partial embolization depends on size as well as S-M grade. The risk of intracranial hemorrhage is not increased after SRS &amp; depends on AVM score, size, &amp; volume, as well as on applied single dose.</td>
</tr>
<tr>
<td>Andrade-Souza et al., 2007</td>
<td>61</td>
<td>nBCA &amp; Lipiodol (Lafayette Pharmaceutical)</td>
<td>LINAC</td>
<td>47% (22/61) at median 44 mos</td>
<td>6% (3 pts) after 3 yrs</td>
<td>Embolization before radiosurgery significantly decreases the obliteration rate, even in AVMs w/ the same volume, location, &amp; marginal dose.</td>
</tr>
<tr>
<td>Schlienger et al., 2000</td>
<td>65</td>
<td>Not mentioned</td>
<td>LINAC</td>
<td>54% &amp; 71% for pts w/ &amp; w/o prior embolization</td>
<td>2.3% (4 pts); not focused on embolization group</td>
<td>Association btw lower obliteration rates &amp; previous embolization is statistically significant in multivariate analysis.</td>
</tr>
<tr>
<td>Miyawaki et al., 1999</td>
<td>43</td>
<td>Not mentioned</td>
<td>LINAC</td>
<td>26% &amp; 76% for pts w/ &amp; w/o prior embolization</td>
<td>2.7% per person-yr for AVMs &lt;14 cm&lt;sup&gt;3&lt;/sup&gt; &amp; 7.5% per person-yr for AVMs &gt;14 cm&lt;sup&gt;3&lt;/sup&gt;; not focused on embolization-treated group</td>
<td>Prior embolization causes lower obliteration rates in multivariate analysis.</td>
</tr>
<tr>
<td>Henkes et al., 1998</td>
<td>64</td>
<td>nBCA, platinum microcoils, &amp;/or PVA</td>
<td>SRS</td>
<td>23% (14/60)</td>
<td>1.7% (1 pt)</td>
<td>AVM obliteration after embolization &amp; radiosurgery is less frequently achieved than after stereotactic irradiation of primarily small AVMs.</td>
</tr>
<tr>
<td>Gobin et al., 1996</td>
<td>125</td>
<td>isobutyl-2-cyanoacrylate &amp; nBCA</td>
<td>LINAC</td>
<td>65%</td>
<td>No hemorrhage</td>
<td>After partial embolization, the risk of hemorrhage from the residual nidus is comparable to the natural history of AVMs, &amp; the residual nidus can be irradiated w/ results almost as good as for a native AVM of the same size.</td>
</tr>
</tbody>
</table>

* Data from 25 cases in which SRS was performed after Onyx embolization were compared with data from 50 propensity-score matched controls.
ized tantalum for radiopacity does not appear to reduce the radiation dose in preclinical study of Onyx and radiosurgery. Shtraus et al. found that the measured attenuation of Onyx placed in a bottle was around 3% higher than the attenuation of water.

The biomaterial properties of Onyx appear to be reflected in the current clinical study. The difference in obliteration rate was not statistically significant between patients who did not undergo prior embolization and those that did, when they had comparable AVM volume, grading, and radiation dose. The post-SRS complications, including ARES, hemorrhage episodes, seizure episodes, and deaths, were also not significantly higher than the patients who did not undergo prior embolization.

**Study Limitation**

This is a case-control study with several limitations. The relatively small number of patients and intermediate length of follow-up preclude appreciable subgroup analyses. In particular, differences in complications or delayed complications related to use of Onyx-treated AVMs may become apparent with longer follow-up. The over time period of the study, more sophisticated MRI sequences (e.g., dynamic studies) and higher field strength magnets have improved the accuracy of treatment planning for an intracranial AVM, which may represent an uncontrolled source of bias. Similarly, embolization techniques, including improvements in catheter delivery technologies, have allowed for more sophisticated delivery of Onyx over time.

**Conclusions**

The current case-control study demonstrated similar results in patients who underwent SRS with and without prior Onyx-based embolization. The post-SRS complication rates, including ARES, intracranial hemorrhage, seizure control, and mortality, were not appreciably different in the Onyx-treated group. Although we did not find that the differences in obliteration rate or post-SRS complications were statistically significant, larger studies with longer follow-up of patients undergoing Onyx-based embolization prior to AVM SRS must be performed to validate these findings. Onyx-based embolization may prove less detrimental to radiosurgical outcomes in comparison with earlier-era embolic materials.

**References**


Author Contributions
Conception and design: Lee. Acquisition of data: Sheehan, Lee, Ball. Analysis and interpretation of data: Lee, Chen, Ball, Xu. Drafting the article: Sheehan, Lee, Chen, Ball, Yen. Critically revising the article: Sheehan, Lee, Chen, Xu. Reviewed submitted version of manuscript: Sheehan, Lee, Chen, Schlesinger, Xu, Yen. Approved the final version of the manuscript on behalf of all authors: Sheehan. Statistical analysis: Lee, Chen, Yen. Administrative/technical/material support: Sheehan, Schlesinger. Study supervision: Sheehan, Yen.

Supplemental Information
Current Affiliation
Dr. Lee: Department of Neurosurgery, Hsinchu Branch, Taipei Veterans General Hospital, Hsinchu, Taiwan, ROC.

Correspondence
Jason Sheehan, Department of Neurological Surgery, University of Virginia Health System, Box 800212, Charlottesville, VA 22908. email: jsheehan@virginia.edu.