The gold standard for diagnosing an arteriovenous malformation (AVM) nidus and evaluating its obliteration after stereotactic radiosurgery (SRS) is digital subtraction angiography (DSA). Recently, MRI and MR angiography (MRA) have become increasingly popular imaging modalities for the follow-up of patients with an AVM because of their convenient setup and noninvasiveness. In this study, the authors assessed the sensitivity and specificity of MRI/MRA in evaluating AVM nidus obliteration as assessed by DSA.

METHODS The authors study a consecutive series of 136 patients who underwent SRS between January 2000 and December 2012 and who underwent regular clinical examinations, several MRI studies, and at least 1 post-SRS DSA follow-up evaluation at the University of Virginia. The average follow-up time was 47.3 months (range 10.1–165.2 months). Two blinded observers were enrolled to interpret the results of MRI/MRA compared with those of DSA. The sensitivity, specificity, positive predictive value, and negative predictive value for the obliteration of AVM were reported.

RESULTS On the basis of DSA, 73 patients (53.7%) achieved final angiographic obliteration in a median of 28.8 months. The sensitivity (the probability of finding obliteration on MRI/MRA among those for whom complete obliteration was shown on DSA) was 84.9% for one observer (Observer 1) and 76.7% for the other (Observer 2). The specificity was 88.9% and 95.2%, respectively. The false-negative interpretations were significantly related to the presence of draining veins, perinidal edema on T2-weighted images, and the interval between the MRI/MRA and DSA studies.

CONCLUSIONS MRI/MRA predicted AVM obliteration after SRS in most patients and can be used in their follow-up. However, because the specificity of MRI/MRA is not perfect, DSA should still be performed to confirm AVM nidus obliteration after SRS.

KEY WORDS obliteration; Gamma Knife; stereotactic radiosurgery; arteriovenous malformation; MRI; digital subtraction angiography; vascular disorders
MRA has been used with minimal adverse effects in the routine radiological follow-up of patients with an AVM. Once the nidus has been shown on MRA images to be obliterated or the nidus has been persistently patent for the maximal follow-up time, patients are recommended to undergo DSA examination. In the current study, we retrospectively assessed the sensitivity and specificity of MRI/MRA in evaluating nidus obliteration and compared its efficacy to that of the gold standard, DSA. Factors associated with false-positive or -negative obliterations using MRI/MRA were also analyzed.

Methods
Patients
A consecutive series of 483 patients with an AVM underwent Gamma Knife surgery (GKS) between January 2000 and December 2012. Of these patients, 136 (28%) with regular clinical examinations, several MRI studies, and at least 1 post-GKS DSA follow-up at the University of Virginia were included in this study. Clinical data, including patient demographics, imaging results, and radiosurgical parameters, were reviewed retrospectively from a database prospectively approved by the University of Virginia institutional review board.

Each patient underwent a comprehensive neurological examination and a cerebral imaging evaluation before radiosurgery. Bleeding history, age of the patient, existing comorbidities, location of the nidus, Spetzler-Martin grade of the AVM, previous treatment history, and clinical symptomatology were reviewed. Neurodiagnostic imaging included both an intravenous paramagnetic contrast-enhanced 3D volumetric MRI scan and a whole-head T2-weighted fast spin-echo (FSE) imaging sequence. Subsequently, each patient underwent biplanar DSA. MRI scans with DSA images are more helpful in developing 3D conformal plans than using 2D angiography only.

Stereotactic Radiosurgery
Our SRS technique was described previously. Radiosurgery was performed by using a Leksell gamma unit model 4C between 2000 and 2007 and the Perfexion model (Elekta) thereafter. Because precise localization of portions of the nidus was not achieved by using DSA in the anterior-posterior plane, 3D imaging via MRI was necessary to establish better localization. Radiosurgical parameters and dose plans were formulated by the treating neurosurgeon in consultation with a medical physicist and a radiation oncologist. The dose to the surrounding brain is a critical predictor of adverse radiation effects; therefore, one should carefully consider maximizing conformity and avoiding any identifiable portion of eloquent brain parenchyma.

Imaging Evaluations
After SRS treatment, each patient underwent clinical evaluation and MRI/MRA studies at 6-month intervals. To minimize the MRI sequencing difference from other institutions, we included only the patients who underwent a series of neuroimaging studies at the University of Virginia. At the University of Virginia during the study period, the MRI/MRA protocol was fairly consistent, with minor variations resulting from improvements in MRI technology. The protocol for MRI/MRA follow-up in patients after GKS for an AVM is distinct from that in patients after GKS for other conditions; this follow-up includes evaluation for the presence of not only abnormal vasculature but also perinidal parenchymal edema. The flow of the abnormal vessels and the content of draining veins were also important. Therefore, the MRI/MRA protocol included thin-sliced T1-weighted imaging (T1WI) with and without contrast, FSE T2-weighted imaging (T2WI), and 3D time-of-flight (TOF) MRA source images. T1WI helps to interpret the possibility of the presence of subacute hematoma/thrombus and hemosiderin-laden gliotic brain tissue. T2WI helps clinicians to evaluate the severity of perinidal brain edema. 3D-TOF MRA displays the flow and existence of the nidus.

Total obliteration of the AVM after radiosurgery was defined as the complete absence of the former nidus, normalization of afferent and efferent vessels, and normal circulation time as determined with high-quality rapid-sequence DSA. Any remaining nidus, regardless of its size, was considered “patent” in this study, including the existence of early-filling draining veins. Although it may be difficult to determine the existence of early-filling draining veins with MRI/MRA, we shared the same rationale when we interpreted obliteration of an AVM on a MRI/MRA study; any residual nidus was considered patent in this study. Original interpretation of the angiograms to determine patency or obliteration of the nidus was performed by a senior neurologist (M.W.) and a senior neurosurgeon (J.S.).

For the sake of assessing the predictive value of MRI/MRA, 2 observers were enrolled in the study: an experienced neuroradiologist (C.C.L.) and an experienced neuroradiologist (M.A.R). These observers were blinded to patient name, clinical conditions, and image reports. For the assessments for obliteration, the observers were also blinded to the DSA results previously interpreted by the senior neuroradiologist and the senior neurosurgeon. The results were analyzed by the other coauthors.

To analyze the potential factors that cause false-positive and -negative determinations of obliteration in MRI/MRA studies, radiological features in these studies that can affect imaging interpretation were collected. These features include the presence and numbers of draining veins, the presence of brain edema as determined by T2WI, and the presence of contrast enhancement within the nidus. The interval between the MRI/MRA and DSA studies was also analyzed.

Statistical Analysis
Descriptive statistics for all data are presented as medians and ranges for continuous variables and as numbers and percentages for categorical variables. Potential prognostic variables associated with false-positive and -negative results, including the nidus volume, AVM grade, previous hemorrhage, previous resection, previous embolization, presence of a draining vein, presence of T2 signal changes, presence of contrast enhancement, and interval between the MRI and DSA studies, were evaluated using logistic univariate and multivariate analyses. Statistical
significance was defined as a p value of < 0.05. All analyses were completed by using commercial statistical software (IBM SPSS version 20.0).

In this study, the sensitivity, specificity, positive predictive value, and negative predictive value for an AVM obliteration were reported. Sensitivity was defined as the probability of finding obliteration on MRI/MRA among those for whom complete obliteration was shown on DSA. Specificity was defined as the probability of finding a patent nidus among those for whom a patent nidus was shown on DSA. Positive predictive value was defined as the probability of finding a case in which the nidus was diagnosed as obliterated on MRI/MRA and in which it was confirmed on DSA. Negative predictive value was defined as the percentage of cases in which the nidus was diagnosed as patent on MRI/MRA and in which it was confirmed on DSA. For differentiating a patent from an obliterated AVM on MRI/MRA compared with those determined on DSA, each observer also performed receiver operating characteristic (ROC) analysis.

**Results**

**Patient Demographics and AVM Characteristics**

The median age of the patients was 36 years (range 4–73 years), and the female/male sex distribution was 73:63. The median nidus volume, based on volumetric calculations from MR images, was 2.1 cm³ (range 0.1–21.0 cm³). Most patients (n = 106, 77.9%) had an AVM nidus located in a hemispheric lobe. Spetzler-Martin grades were used to classify the AVMs of these patients: 115 nidi (84.6%) were < 3 cm, 20 nidi (14.7%) were between 3 and 6 cm, and 1 nidus (0.7%) was > 6 cm; 70 nidi (51.5%) were located in a noneloquent area, and 66 nidi (48.5%) were located in an eloquent area; and 77 nidi (56.6%) had superficial venous drainage only, and the other 59 nidi (43.4%) had ≥ 1 deep draining veins.

Fifty-eight patients (42.6%) had hemorrhage episodes before SRS, and 30 patients (22.1%) had seizure episodes; other symptoms included headache in 30 (22.1%), cranial nerve palsy in 10 (7.4%), visual field deficits in 8 (5.9%), dysphasia in 6 (4.4%), cerebellar sign in 5 (3.7%), and long tract sign in 5 (3.7%), among others. Fourteen patients (10.3%) had received microsurgical AVM nidus resection with residue, whereas 31 (22.8%) had ≥ 1 previous embolization intervention. Fifteen patients (11.0%) had previous fractionated radiation therapy. The median clinical follow-up time was 47.3 months (range 10.1–165.2 months), the median MRI follow-up duration was 42.6 months (range 8.6–147.3 months), and the median DSA follow-up time was 31.7 months (range 8.6–105.6 months) (Table 1). To validate the predictability of MRI/MRA in determining the obliteration of intracranial AVMS, we reviewed the pre-DSA MRI images, and the median pre-DSA MRI was performed 27.6 months (range 5.8–115.0 months) after SRS. The interval between the immediate previous MRI/MRA and the subsequent DSA was 2.1 months (range 0–24.4 months).

**Imaging Outcome**

Table 2 shows the interpretations of the MRI/MRA and DSA images according to the 2 observers. In the current series, final angiographically determined obliteration was achieved in 73 patients (53.7%) in a median of 28.8 months. In the other 63 patients a patent nidus was diagnosed as patent on MRI/MRA and in which it was confirmed on DSA. However, discrepancies between the 2 observers occurred when they used MRI/MRA to determine the obliteration of a post-GKS nidus. For Observer 1, 7 cases were false positive when interpreted using MRI/MRA and 11 cases were false negative when interpreted using MRI/MRA. For Observer 2, 3 cases were false positive when interpreted using MRI/MRA and 17 cases were false neg-
TABLE 2. Determination of nidus on MRI/MRA and DSA and predictive value of MRI/MRA for definitive obliteration in comparison with DSA

<table>
<thead>
<tr>
<th>DSA</th>
<th>MRI/MRA</th>
<th>MRI/MRA</th>
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<tbody>
<tr>
<td></td>
<td>Observer 1</td>
<td>Observer 2</td>
</tr>
<tr>
<td>Patent (no.)</td>
<td>56</td>
<td>60</td>
</tr>
<tr>
<td>Obliterated (no.)</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Prevalence (%)</td>
<td>53.7</td>
<td>53.7</td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>84.9</td>
<td>76.7</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>88.9</td>
<td>95.2</td>
</tr>
<tr>
<td>Positive predictive rate (%)</td>
<td>89.9</td>
<td>94.9</td>
</tr>
<tr>
<td>Negative predictive rate (%)</td>
<td>83.6</td>
<td>77.9</td>
</tr>
<tr>
<td>False-positive rate (%)</td>
<td>10.1</td>
<td>5.1</td>
</tr>
<tr>
<td>False-negative rate (%)</td>
<td>16.4</td>
<td>22.1</td>
</tr>
</tbody>
</table>

* Prevalence of obliteration after SRS for an intracranial AVM.

Discussion

Complete AVM obliteration after SRS is critical for reducing the risk of hemorrhage from the nidus. Thus, the primary end point in AVM radiosurgery is usually complete obliteration. Because of its high spatial and temporal resolution, DSA is the gold standard diagnostic modality for determining nidus obliteration. Previous studies have recommended that clinicians acquire follow-up DSA images for AVM patients for 2 to 4 years after SRS to determine the appropriate management strategies, such as observation, repeat SRS, embolization, and resection. Although the morbidity and mortality rates associated with DSA are low, several studies involving DSA have found significant complication rates and decreased compliance of patients in continuing with the recommended treatment. In contrast, the complication rate for MRI is lower than that for DSA. In several small reports, MRA-based images might be used as the sole follow-up imaging modality for radiosurgery of AVMs that are less than 3 cm³ when they are in a noneloquent location.

In this study, we evaluated whether MRI/MRA can replace DSA for determining AVM obliteration after SRS. For patients who were believed to have nidus obliteration shown on MRI/MRA, high positive predictive values of 89.9% and 94.9% were observed between the 2 observers. MRI/MRA seems to be a reasonable but imperfect modality for determining nidus obliteration in patients with an AVM treated by SRS. Although we did not specifically address the value of DSA targeting at the time of SRS, the value of DSA for confirming obliteration intuitively seems to convey an importance for DSA targeting along with routine stereotactic MRI at the time of SRS.

However, false-positive and -negative interpretations of MRI/MRA were still evident, which may carry important implications. Partial obliteration of an intracranial AVM may be detrimental to the patient, because false-positive obliteration according to MRI/MRA can result in suboptimal salvage therapy. Several authors have suggested that after SRS, progressive narrowing of the vessel caliber is a key factor for false interpretation of nidus obliteration. Factors that may be detrimental to the patient include large nidus size, previous radiotherapy, AVM location, presence of draining veins, perinidal edema on T2WI, and time interval between MRI/MRA and DSA. In contrast, the presence of draining veins, perinidal edema on T2WI, and time interval between MRI/MRA and DSA were significantly associated with false-negative interpretations. The other factors we evaluated were not significantly associated with false-negative interpretations.

For differentiating a patent nidus from an obliterated nidus on MRI/MRA in comparison with DSA, ROC analysis resulted in areas under the ROC curve for predicting obliteration of 0.861 for Observer 1 and 0.844 for Observer 2 (Fig. 3).
not become 100% until the nidus diameter was 0.36 cm, whereas compared with DSA results, 1.5-T MRA without contrast detected 81%–99% of intracranial vessels with a diameter of ≤1 mm.34

In addition to vessel diameters and blood flow velocity, there are multiple factors that may influence the visibility of vessels in MRI/MRA, including the intensity of the magnetic field, parameters of echo time, repetition time, and flip angle, the use of saturation band, the thickness of every slice, the direction of blood flow, and the image angle of the blood flow.26,36 Even the type of flow, such as turbulent flow, may decrease the signal intensity.37 Accompanying the dynamic changes of AVM after SRS, the signal intensity changes continuously, which makes the interpretation of MRA challenging. Finally, the AVM and normal brain may have common draining veins, which causes difficulties in interpreting obliteration of the nidus. In theory, these veins will never disappear completely. Nevertheless, from the factors analyzed in this study, the presence of a draining vein, perinidal edematous changes on T2WI, and contrast enhancement were not related to false-positive interpretations, which also reflects the meticulous interpretations of the neurosurgeons and neuroradiologists at our center.

In contrast to false-positive results, false-negative results are often overlooked in current and previous reports.4 The false-negative interpretation of obliteration on the basis of MRI/MRA may result in a patient receiving unnecessary interventions, leading to extraneous potential risks associated with these interventions. In earlier studies, the precontrast high-intensity signals and contrast enhancement within the nidus of AVMs caused by hematoma or thrombus formation interfered with the interpretation of AVM obliteration.38 In current clinical practice, we recommend reviewing the spin-echo T1WI, FSE T2WI sequences, and 3D-TOF MRA sequences simultaneously to better exclude the presence of a subacute hematoma/thrombus and hemosiderin-laden gliotic brain tissue, which all have a high signal intensity in lesions in TOF MRA images. Because 3D-TOF MRA is also a T1-based technique, coagulated or slow-flowing blood might present as a hyperintense signal as well. The combination of T1WI and 3D-TOF MRA might overcome the misinterpretation of stagnant nidal blood flow as persistent flow.4 According to our analysis, the presence of a draining vein and interference of perinidal edema on T2WI were related to false-negative interpretations, which indicates that the presence of a drainage vein may occur when an intracranial AVM is obliterated, and the extent of perinidal edema may be independent of AVM obliteration. Another factor associated with false-negative interpretations is prolonged time intervals (>6 months) between MRI and DSA. A lon-
Prediction of AVM obliteration by MRI/MRA

The changes in AVM angioarchitecture after SRS may be more rapid than previously believed. Therefore, we recommend that DSA be performed within 3 months of obliteration confirmation via MRI/MRA.

Although we did not exclude the AVMs with previous embolization, we initially expected the embolic agents to affect the interpretation of obliteration. However, previous embolization was not related to either false-positive or negative interpretation according to logistic model analysis (p = 0.803 and 0.300, respectively). Although reports do not definitively show that embolic agents influence the interpretation of AVM obliteration, several studies demonstrated that embolic agents, including detachable microcoil, polyvinyl alcohol, N-butyl-2-cyanoacrylate, and isobutyl-2-cyanoacrylate, may interfere with SRS dose planning.9,11,27,28 For instance, embolization may obscure the margin of the nidus and thereby mislead to an optimal interpretation.27 Also, dose planning may be more difficult if the AVM nidus is segmented into discrete noncontiguous portions, and the nidus may be obscured on MRI and even biplanar angiography when microcoil or other embolic materials are used. Second, embolization may induce hypoxia, which makes the tissue less radiosensitive and increases the angiogenic activity of the AVM,2,35 rendering it a more active lesion.1,23 Therefore, these physical and biological effects should be considered carefully by the radiologist or neurosurgeon who reviews the postembolization AVMs.

The higher rate of false-negative than false-positive interpretations reflects the fact that our clinicians were looking carefully for radiological evidence of nidus obliteration and were likely biased to avoid false-negative interpretations before the patients underwent DSA. We tend to wait longer and collect more MRI evidence to prove that the SRS was successful before ordering DSA. In particular, MR sequences may prove helpful when clinicians face the dilemma of near-obliteration. For example, cine phase-contrast MRI may be an effective pulse sequence for helping us to investigate the hemodynamics of radiosurgical AVMs.14,24 Phase-contrast MRI offers co-registered morphological images and velocity data within a single acquisition. After acquiring and processing the data in morphological and phase-difference images, various visualization strategies enable qualitative analysis of hemodynamics. A number of quantitative parameters, such as pulse wave velocities and estimates of wall shear stress, which might serve as future biomarkers, can be extracted.10

FIG. 2. Illustration of a case with false-negative interpretation of AVM nidus obliteration in an 11-year-old boy with a 0.7-cm³ AVM nidus in the right frontal region. Because of a persistent fine, linear, branching contrast enhancement (probably vessels) that is not present on T1WI (A), T1WI with contrast (B), T2WI (C), or TOF MRA (D and E) and may be related to slow flow, both observers had difficulty judging whether this AVM was obliterated. In addition, an unchanged susceptibility artifact in this region was consistent with hemosiderin-laden gliotic brain tissue. The T2 signal hyperintensity surrounding the nidus also confounded the accurate interpretation. DSA performed 2 weeks after MRI (F and G) shows no evidence of shunting or a nidus, thereby confirming AVM obliteration. Red arrows in A–G point to the location of the nidus. Figure is available in color online only.
rent 2D sequences, the short scan time for a target vessel and the acquisition plane (should be vertical to the blood flow) limit the use of phase-contrast MRI. With the refinement of imaging techniques, future techniques in 3D or 4D phase-contrast flow studies may enable better assessment of AVM nidi after SRS.

Study Limitations

There were several limitations in this retrospective study, which involved a large number of patients treated at the University of Virginia, many of whom were from outside the United States or who traveled long distances for treatment. To avoid misinterpreting the MRI/MRA or DSA images from variable sequences that were set by different hospitals, we included only the patients who were regularly followed up with neuroimaging studies at the University of Virginia (28% of the total number of patients with an AVM during 2000–2012). These stringent criteria may have resulted in unintended selection bias. Although this was not a rigorously controlled study, the information provided remains precise and extensive for such a study design. In addition, over the time span of the study, more sophisticated MR sequences (e.g., cine phase-contrast studies) and higher-field-strength magnets (3-T vs 1.5-T MR machine) have improved the detection rate of small residual blood flow within nidi. Hence, image quality and nidus-obliteration detection may have varied slightly between earlier and more recently obtained MRI/MRA studies.

Conclusions

MRI/MRA offers reasonable sensitivity and specificity for detecting nidus obliteration in patients with an AVM treated with SRS. The approximate sensitivity and specificity of MRI/MRA in this study were 80% and 90%, respectively. The determination of obliteration by MRI/MRA was limited by the presence of draining veins, T2 signal changes around the nidus, and prolonged time intervals between MRI/MRA and DSA acquisitions. Despite recent improvements in MRI techniques, DSA remains the definitive diagnostic modality for assessing complete AVM nidus obliteration after radiosurgery.

References

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TABLE 3. Influential factors of false-positive and -negative interpretations of AVM obliteration on MRI/MRA (logistic regression model)

<table>
<thead>
<tr>
<th>Factor</th>
<th>False-Positive Obliteration*</th>
<th>False-Negative Obliteration†</th>
</tr>
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<tbody>
<tr>
<td>AVM vol (cm³)</td>
<td>0.840</td>
<td>0.778</td>
</tr>
<tr>
<td>S-M grade</td>
<td>0.347</td>
<td>0.404</td>
</tr>
<tr>
<td>Previous hemorrhage</td>
<td>0.255</td>
<td>0.883</td>
</tr>
<tr>
<td>Previous resection</td>
<td>0.845</td>
<td>0.423</td>
</tr>
<tr>
<td>Previous embolization</td>
<td>0.803</td>
<td>0.300</td>
</tr>
<tr>
<td>Previous radiotherapy</td>
<td>0.793</td>
<td>0.283</td>
</tr>
<tr>
<td>AVM location (lobar vs no lobar)</td>
<td>0.276</td>
<td>0.125</td>
</tr>
<tr>
<td>Presence of draining vein</td>
<td>0.637</td>
<td>0.057</td>
</tr>
<tr>
<td>Presence of T2 changes</td>
<td>0.051</td>
<td>0.018‡</td>
</tr>
<tr>
<td>Presence of enhancement</td>
<td>0.712</td>
<td>0.583</td>
</tr>
<tr>
<td>MRI/MRA-to-DSA interval</td>
<td>0.150</td>
<td>0.048‡</td>
</tr>
</tbody>
</table>

* Nine cases and 10 observations.
† Nineteen cases and 28 observations.
‡ Boldface indicates statistical significance.

FIG. 3. ROC curves show good discriminating power, with areas under the curve of 0.861 (Observer 1) and 0.844 (Observer 2) for MRI/MRA differentiating obliteration of intracranial AVMs after SRS.
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Author Contributions
Conception and design: Sheehan, Lee, Reardon. Acquisition of data: Lee, Reardon, Ball. Analysis and interpretation of data: Lee, Reardon, Ball, Chen. Drafting the article: Lee, Reardon, Chen, Yen, Xu. Critically revising the article: Sheehan, Lee, Reardon, Chen, Yen, Xu. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Sheehan. Statistical analysis: Sheehan, Lee, Yen, Xu, Wintermark. Administrative/technical/material support: Sheehan, Wintermark. Study supervision: Sheehan, Wintermark.

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