Intracranial arteriovenous malformations (AVMs) most commonly present with hemorrhage, which carries a mortality rate of 10%–15% and a morbidity rate of up to 50%. The annual hemorrhage rate for AVMs is between 2% and 4% per year. The ultimate goal of treatment in intracranial AVMs is complete obliteration of the nidus, and thus reducing the risk of hemorrhage.

Stereotactic radiosurgery (SRS) is an approved treatment option for intracranial AVMs that are not treatable via microsurgery. For low-grade deep AVMs smaller than 3 cm, SRS alone can be performed when microsurgery is not possible. Smaller AVMs allow large doses of radiation to be applied safely and thus have a higher obliteration rate. Given the concomitant increased risks of adverse radiation effects, high doses of radiation cannot be safely used in large AVMs, thereby resulting in a worse obliteration rate. Thus, a multimodal approach consisting of a combination of embolization and SRS has been widely used.

Embolization before SRS significantly decreases the AVM obliteration rate. However, there is no significant difference in the risk of hemorrhage and permanent neurological deficits after SRS alone and following embolization. Further validation by well-designed prospective or randomized cohort studies is still needed.

**Object.** The effectiveness and risk of stereotactic radiosurgery (SRS) in the management of partially embolized intracranial arteriovenous malformations (AVMs) remain controversial. The aim of this analysis was to assess current evidence regarding the efficiency and safety of SRS for AVM patients with and without prior embolization.

**Methods.** To compare SRS in patients with and without embolization, the authors conducted a meta-analysis of studies by searching the literature via PubMed and EMBASE for the period between January 2000 and December 2013, complemented by a hand search. Primary outcome was the rate of AVM obliteration on a 3-year follow-up angiogram. Secondary outcome was the rate of hemorrhage at 3 years after SRS. Tertiary outcome was permanent neurological deficits related to radiation-induced changes.

**Results.** Ten studies eligible for analysis included 1988 patients: 593 had undergone embolization followed by SRS and 1395 had undergone SRS alone. The AVM obliteration rate was significantly lower in patients who had undergone embolization followed by SRS than in those who had undergone SRS alone (41.0% vs 59%, OR 0.46, 95% CI 0.37–0.56, p < 0.00001). However, the rates of hemorrhage (7.3% vs 5.6%, OR 1.17, 95% CI 0.74–1.83, p = 0.50) and permanent neurological deficits related to radiation-induced changes (3.3% vs 3.4%, OR 1.41, 95% CI 0.64–3.11, p = 0.39) were not significantly different between the two groups.

**Conclusions.** Embolization before SRS significantly decreases the AVM obliteration rate. However, there is no significant difference in the risk of hemorrhage and permanent neurological deficits after SRS alone and following embolization. Further validation by well-designed prospective or randomized cohort studies is still needed.

**Key Words.** arteriovenous malformation • embolization • outcome • stereotactic radiosurgery

**Abbreviations used in this paper:** AVM = arteriovenous malformation; SRS = stereotactic radiosurgery.

*Drs. Xu and Zhong contributed equally to this work.*
Methods

A detailed protocol that included the methods for a literature search, inclusion and exclusion criteria, an assessment of the quality of reporting, and data extraction and analysis was developed before we conducted this systematic review.33,37 This article was prepared in accordance with the guidelines outlined in the “Meta-Analysis of Observational Studies in Epidemiology” and “Preferred Reporting Items for Systematic Reviews and Meta-Analyses.”

Search Strategy

Two reviewers (F.X. and J.Z.) performed a comprehensive review of articles in the literature published between January 2000 and December 2013. An electronic search of PubMed and EMBASE was conducted. This search was supplemented by hand searching the five journals in which most studies were published (Neurosurgery, Journal of Neurosurgery, Acta Neurochirurgica, American Journal of Neuroradiology, and Stroke) and the reference lists of identified articles. Key words and free text searches, used in combination with the Boolean operators “or” and “and,” were as follows: “intracranial arteriovenous malformations,” “brain arteriovenous malformations,” “cerebral arteriovenous malformations,” “radiosurgery,” “stereotactic radiosurgery,” “radiotherapy,” “linear accelerator (LINAC),” “Gamma Knife,” “CyberKnife,” “embolization,” “particles,” “N-butyl cyanoacrylate,” and “Onyx.” When multiple publications described the same cohort, we included the study with the largest cohort.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: 1) studies published in the English language, 2) all available randomized controlled trials and comparative studies (cohort studies) that compared SRS with and without embolization for intracranial AVMs, 3) reporting on at least 10 consecutive patients of any age undergoing the two treatment modalities, 4) reported duration of follow-up, and 5) explicitly reported obliteration rate or hemorrhage risk or permanent neurological deficits.

The exclusion criteria were as follows: 1) studies describing other intracranial vascular malformations (dural arteriovenous fistulas, cavernous malformations, developmental venous anomalies, vein of Galen malformations, and angiographically occult vascular malformations), 2) studies with insufficient data, 3) studies with substantial imbalance of clinical characteristics or absence of baseline information, and 4) editorials, letters, review articles, case reports, and animal experimental studies.

Data Extraction

Two authors (F.X. and J.Z.) independently reviewed all searched articles and extracted data using a structured data extraction form. In cases of disagreement, consensus was reached through discussion with the senior author (N.C.B.).

Outcomes

The primary outcome was the rate of AVM obliteration on a 3-year follow-up angiogram. The secondary outcome was the rate of hemorrhage at 3 years after SRS. The tertiary outcome was permanent neurological deficits related to radiation-induced changes. Because most included studies did not report mortality rates, we did not evaluate the mortality outcomes.

Statistical Analysis

Using the software package RevMan 5.2 (Cochrane Collaboration), we performed a meta-analysis on studies that provided data on the outcomes of SRS in patients with and without embolization. Dichotomous variables were presented as odds ratios (embolization followed by SRS vs SRS alone) with a 95% confidence interval. Heterogeneity between studies was assessed by the calculation of I², which describes the proportion of total variation that is attributable to differences among trials rather than sampling error (chance). Values of I² < 25%, 25%–50%, and > 50% are defined as low, moderate, and high heterogeneity, respectively. The random-effects model was used if heterogeneity between studies was > 50%. Otherwise, the fixed-effects model was used. The odds ratio was estimated (significance set at p < 0.10) if the 95% CI did not include the value 1. Funnel plots were used to screen for potential publication bias. Although a different nidus size or AVM volume affected the selection of treatment and clinical outcomes, subgroup analysis could not be conducted because of insufficient data.

Results

Study Selection

Figure 1 shows a flow diagram according to the Quality of Reporting of Meta-analyses statement. A total of 795 articles were retrieved from the PubMed and EMBASE databases. After removing duplicated articles, we screened 731 titles and abstracts. The full-text publications of 57 potentially eligible studies were reviewed in detail. Of these, 47 were excluded based on the inclusion and exclusion criteria. No new studies were found in the five journals or the reference lists. As a result, 10 studies were included in this analysis. Overall, these studies included 1988 patients; 593 had undergone embolization followed by SRS, and 1395 had undergone SRS alone.

Study Characteristics

Of all the included studies, none was a randomized controlled trial, 1 (10%) was a prospective study, and 9 (90%) were retrospective studies. The studies had been performed in the United States (4), Canada (1), France (1), the United Kingdom (1), Japan (1), Korea (1), and Puerto Rico (1). Various embolic materials were used, including...
coils, silk, polyvinyl alcohol particles, Lipiodol, N-butyl cyanacrylate, isobutyl 2-cyanacrylate, and Onyx liquid embolic. Radiosurgical treatment consisted of charged-particle radiation, LINAC, Gamma Knife, or CyberKnife treatments. Study and patient characteristics and clinical outcomes are summarized in Table 1.

Quality of Included Studies

The quality of observational studies was assessed using the Newcastle-Ottawa Scale. We evaluated the studies with regard to three items: patient selection, comparability, and outcome (Table 2). A study can be awarded a maximum of one star for each numbered item within the selection and outcome categories. A maximum of two stars is given for comparability. Studies with more than six stars are considered high quality.

Study Outcomes

Ten studies including 1988 patients reported the rate of AVM obliteration on a 3-year follow-up angiogram. The obliteration rate was significantly lower in patients who had undergone embolization followed by SRS than in those who had undergone SRS alone (41.0% vs 59%, OR 0.46, 95% CI 0.37–0.56, p < 0.00001; Fig. 2). The heterogeneity was moderate (p = 0.07, I² = 43%).

Seven studies including 1699 patients reported the rate of hemorrhage at 3 years after SRS. There was no difference between patients who had undergone embolization followed by SRS and those who had undergone SRS alone (7.3% vs 5.6%, OR 1.17, 95% CI 0.74–1.83, p = 0.50; Fig. 3). The heterogeneity was low (p = 0.34, I² = 12%).

Four studies including 1336 patients reported permanent neurological deficits related to radiation-induced changes. There was no difference between patients who had undergone embolization followed by SRS and those who had undergone SRS alone (3.3% vs 3.4%, OR 1.41, 95% CI 0.64–3.11, p = 0.39; Fig. 4). The permanent neurological deficits demonstrated no heterogeneity (p = 0.57, I² = 0%).

Sensitivity Analysis and Publication Bias

The results were similar when fixed- or random-effects models were used. Funnel plot analysis on the rate of obliteration and hemorrhage indicated significant publication bias (Figs. 5–7).

Discussion

A previous meta-analysis showed that preradiosurgical embolization was associated not only with an increased hemorrhage rate and higher risk of complications but also with a greater chance of complete obliteration. However, that analysis used indirect comparison to evaluate the outcomes of SRS in AVM patients with and without prior embolization. The two groups were chosen from different
### TABLE 1: Design and baseline characteristics of included trials*

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Study Period</th>
<th>No. of Patients</th>
<th>Age (yrs)</th>
<th>No. of Males (%)</th>
<th>No. of Hemorrhages (%)</th>
<th>Nidus Size (cm)</th>
<th>Vol (ml)</th>
<th>No. w/ SM Grade ≥III (%)</th>
<th>Margin Dose (Gy)</th>
<th>Duration of FU (yrs)</th>
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<td>1989–2000</td>
<td>47/47</td>
<td>NA</td>
<td>NA</td>
<td>53.2/38.3</td>
<td>2.49/2.30</td>
<td>7.42/6.66</td>
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<td>16.7/16.7</td>
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<tr>
<td>Back et al., 2008</td>
<td>1994–2004</td>
<td>15/54</td>
<td>40.5/36.3</td>
<td>44.4/46.7</td>
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<td>NA</td>
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<tr>
<td>Darsaut et al., 2011</td>
<td>1985–2009</td>
<td>17/25</td>
<td>NA</td>
<td>NA</td>
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<tr>
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<td>1991–2002</td>
<td>15/237</td>
<td>35.3/30.1</td>
<td>73/61</td>
<td>47/55</td>
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<td>NA</td>
<td>NA</td>
<td>9.94/7</td>
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<td>Kano et al., 2012</td>
<td>1987–2006</td>
<td>120/120</td>
<td>33/33</td>
<td>50.8/49.2</td>
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<td>1980-2008</td>
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<td>1990–1993</td>
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<td>29.5</td>
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</table>

*All studies were retrospective, except the one by Nataraj et al., which was prospective. Values are expressed as the mean of the cohort or the median if the mean was not available. EMB = embolization; FU = follow-up; NA = information not available; SM = Spetzler-Martin.

### TABLE 2: Risk of bias in the observational studies using the Newcastle-Ottawa Scale

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Representation of Exposed Cohort</th>
<th>Selection of Nonexposed Cohort</th>
<th>Ascertaintment of Exposure</th>
<th>Demonstration That Outcome of Interest Not Present at Start of Study</th>
<th>Control for Important or Additional Factor</th>
<th>Assessment of Outcome</th>
<th>FU Long Enough for Outcomes to Occur</th>
<th>Adequacy of FU of Cohorts</th>
<th>Total Score</th>
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Stereotactic radiosurgery with and without embolization

**Fig. 2.** Forest plot of obliteration rate comparing combined treatment (EMB+SRS) versus SRS alone. A fixed-effects model was applied. "Total" refers to the total number of patients; "Events," to the obliteration rate; and "Weight," to the weight that each study contributes to the pooled estimate. EMB = embolization; M-H = Mantel-Haenszel method.

**Fig. 3.** Forest plot of hemorrhage rate comparing combined treatment (EMB+SRS) versus SRS alone. A fixed-effects model was applied. "Events" refers to hemorrhage rate.

**Fig. 4.** Forest plot of permanent neurological deficits comparing combined treatment (EMB+SRS) versus SRS alone. A fixed-effects model was applied. "Events" refers to permanent neurological deficits.
studies instead of the same study. Here, via direct comparison, our meta-analysis systematically summarized the available evidence on outcomes in AVM patients who underwent embolization followed by SRS or SRS alone. We found that embolization before SRS significantly decreases the obliteration rate while not affecting the risk of hemorrhage and permanent neurological deficits.

Our results should be interpreted with caution, however. An important limitation of our meta-analysis is that most of the included studies were retrospective, and none of them had a randomized design. Thus, the baseline characteristics vary among the included studies. Treatment selection bias may be particularly problematic in these observational studies because of patient and AVM characteristics, thus hampering comparison of treatments. Nidus size, AVM volume, Spetzler-Martin grade, and margin dose were the most prominent differences between the two groups (Table 2). Andrade-Souza and colleagues performed a retrospective study in which two groups were matched according to anatomical location, AVM volume before radiosurgery, and margin dose. Not all of the embolized patients could be matched with similar nonembolized patients. The percentage of Spetzler-Martin Grades III–V was higher in the embolized group (68.1%) than in the nonembolized group (59.6%) because of differences in nidus size and AVM volume. In the study by Back and colleagues, the AVM volume in the embolized group was significantly greater than in the nonembolized group. In the study by Schwyzer and colleagues, the percentage of Spetzler-Martin Grades III–V was significantly higher in the embolized group (58.6%) than in the nonembolized group (48.8%). Moreover, the two groups demonstrated significant differences in Gamma Knife surgery parameters, including maximum diameter, nidus volume, and prescription dose.

Kano and colleagues performed a propensity score case-control matched study to reduce bias. They showed that prior embolization reduced the rate of total obliteration after SRS. However, they reported a low rate of nidus obliteration (35%) after this combined treatment. They showed that a target volume smaller than 8 cm³ was associated with a higher rate of obliteration. As previously demonstrated, the size of the AVM after embolization and before radiosurgery was significantly associated with the obliteration rate. Zabel-du Bois and colleagues reported that the obliteration rate is significantly higher in AVMs with a diameter < 3 cm than in AVMs with a diameter ≥ 3 cm (92% vs 60%). Izawa and colleagues showed that the obliteration rate after embolization before SRS was significantly higher in AVMs (90%) with a nidus volume smaller than 12 ml than in AVMs with a nidus volume more than 12 ml (10%). Blackburn and colleagues recently showed that staged embolization followed by SRS provides an effective means of treating large AVMs, obtaining a high rate of obliteration after this combined treatment (81%). Given a lack of data, we were unable to perform subgroup analysis. Therefore, a well-designed prospective randomized study is needed to evaluate the benefit of preradiosurgical embolization.

Our study demonstrated that although the risk of hemorrhage after SRS was higher in the group with previous embolization, the difference was not statistically significant. In theory, the risk of hemorrhage may be reduced by targeting associated aneurysm or venous ectasia while awaiting the delayed occlusion achieved from SRS. Wikholm and colleagues demonstrated that protection from bleeding can be attained only if at least 90% of the AVM is obliterated. However, achieving this goal is unlikely in most large AVMs. Other studies revealed no protective
role of partially obliterated AVMs. The risk of hemorrhage after SRS persists as long as the nidus remains patent. The relative higher hemorrhage rate after combined treatment may be partially explained by the fact that nidus size and AVM volume were larger in the embolized group than in the nonembolized group. Obliteration may be attained later or not at all. There is no evidence that partial embolization reduces long-term hemorrhagic risk.

The rate of permanent neurological deficits did not differ significantly between the two groups. Despite advances in endovascular techniques and embolic materials, the permanent disabling morbidity or mortality rates vary at different centers from 1.6% to 15.5%. In addition, combined management with embolization and SRS may also result in increased risks of each treatment modality. In this meta-analysis, the reported rate of permanent neurological deficits after SRS in the embolized groups was higher, equal, or lower than that in the nonembolized groups. In the study by Andrade-Souza and colleagues, the rate of permanent neurological deficits associated with radiation-induced changes following combined treatment was higher than after SRS alone. It may be caused by impaired venous drainage attributable to embolization or deflection of radiation to the surrounding normal brain tissue. In the study of Izawa and colleagues, no major neurological deterioration was found in any case after embolization. The authors explained that this finding may reflect careful case selection and nonaggressive strategy of endovascular treatment.

Conclusions

In summary, the results of our meta-analysis show that embolization before SRS significantly decreases the obliteration rate. In addition, there is no significant difference in the risk of hemorrhage and permanent neurological deficits between combined treatment (embolization followed by SRS) and SRS alone. Further validation through well-designed prospective or randomized cohort studies is still needed.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following: Xu, Zhong; Acquisition of data: Xu, Zhong; Ray, Manjila; Analysis and interpretation of data: Xu, Zhong, Ray, Manjila; Drafting the article: Xu, Zhong; Ray, Manjila; Critically revising the article: Xu, Zhong, Ray. Reviewed submitted version of manuscript: Bambakidis. Approved the final version of the manuscript on behalf of all authors: Bambakidis. Statistical analysis: Xu, Zhong. Administrative/technical/material support: Xu, Zhong.

References