Volume-staged versus dose-staged stereotactic radiosurgery outcomes for large brain arteriovenous malformations: a systematic review

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OBJECTIVE Several recent studies have improved our understanding of the outcomes of volume-staged (VS) and dose-staged (DS) stereotactic radiosurgery (SRS) for the treatment of large (volume > 10 cm³) brain arteriovenous malformations (AVMs). In light of these recent additions to the literature, the aim of this systematic review is to provide an updated comparison of VS-SRS and DS-SRS for large AVMs.

METHODS A systematic review of the literature was performed using PubMed to identify cohorts of 5 or more patients with large AVMs who had been treated with VS-SRS or DS-SRS. Baseline data and post-SRS outcomes were extracted for analysis.

RESULTS A total of 11 VS-SRS and 10 DS-SRS studies comprising 299 and 219 eligible patients, respectively, were included for analysis. The mean obliteration rates for VS-SRS and DS-SRS were 41.2% (95% CI 31.4%–50.9%) and 32.3% (95% CI 15.9%–48.8%), respectively. Based on pooled individual patient data, the outcomes for patients treated with VS-SRS were obliteration in 40.3% (110/273), symptomatic radiation-induced changes (RICs) in 13.7% (44/322), post-SRS hemorrhage in 19.5% (50/256), and death in 7.4% (24/323); whereas the outcomes for patients treated with DS-SRS were obliteration in 32.7% (72/220), symptomatic RICs in 12.2% (31/254), post-SRS hemorrhage in 10.6% (30/282), and death in 4.6% (13/281).

CONCLUSIONS Volume-staged SRS appears to afford higher obliteration rates than those achieved with DS-SRS, although with a less favorable complication profile. Therefore, VS-SRS or DS-SRS may be a reasonable treatment approach for large AVMs, either as stand-alone therapy or as a component of a multimodality management strategy.

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KEY WORDS Gamma Knife; arteriovenous malformation; radiosurgery; volume-staged; dose-staged; review; vascular disorders; stereotactic radiosurgery

The optimal management of large (volume > 10 cm³) brain arteriovenous malformations (AVMs) is controversial. Options for intervention include resection, embolization, and stereotactic radiosurgery (SRS), alone or in combination.5,16,17,26,64,79 As stand-alone treatment modalities for large AVMs, microsurgery is associated with relatively high rates of morbidity and mortality, whereas embolization results in low rates of complete nidal obliteration.35,39,41 Single-session SRS (SS-SRS) is effective for many small- to medium-sized AVMs but yields lower obliteration rates for large AVMs with increased rates of neurological morbidity.22,25,28,31,32,34,45,47,65,74,76 Volume-staged (VS) and dose-staged (DS) SRS are multisession techniques devised to improve the risk-to-benefit profile for the radiosurgical treatment of large AVMs.5,48,51,68,78,82 Volume-staged SRS divides large AVMs into distinct volumes, each of which is independently targeted by SRS with 2- to 9-month intervals until the entire treatment is completed.5,48,51,68,78,82
AVM is treated. In contrast, DS-SRS involves repeated delivery of radiation to the entire AVM until a cumulative total dose has been delivered in a period of a few weeks. Either technique can be used as a stand-alone approach to achieve obliteration. Alternately, they can be used in conjunction with embolization or as a prelude to resection after regression of the nidus.

Unfortunately, a direct comparison between VS-SRS and DS-SRS is difficult given the substantial variability in treatment parameters, rates of salvage therapy among existing studies, and definitions and confirmations of complete and partial obliteration. A recent systematic review by Moosa et al. revealed that DS-SRS appears to be associated with lower obliteration rates, lower post-SRS hemorrhage mortality rates, and similar rates of symptomatic SRS-related complications compared with VS-SRS. However, since the aforementioned comparison of these 2 SRS techniques, several additional studies of VS-SRS or DS-SRS for the treatment of large AVMs have been published. Therefore, the aim of the current systematic review is to provide an updated comparison of these outcomes after VS-SRS and DS-SRS for large AVMs.

Methods

Literature Search and Inclusion Criteria

No registered review protocol was used in this study. This review follows the guidelines set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. A literature review was performed on March 20, 2016, using PubMed with the following search phrase: “arteriovenous malformations AND (radiosurgery OR radiotherapy) AND (stage OR staged OR staging OR hypofractionated OR fraction OR fractionated OR fractionation).” The remaining studies underwent screening by title and abstract to determine inclusion plausibility, and the resultant relevant articles were scrutinized to ascertain fulfillment of inclusion criteria. In an attempt to capture the largest possible patient population, maintain a relatively homogeneous cohort, and adequately assess outcomes, we devised the following inclusion criteria for this systematic review: 1) at least 5 patients treated with either VS-SRS or DS-SRS, 2) a mean AVM volume of at least 10.0 cm³ prior to SRS, 3) available posttreatment data, and 4) a study written in English. Studies pertaining to repeat SRS for AVMs or to SRS for indications other than large AVM treatment were excluded from this review.

Data Extraction

Patient demographics, AVM characteristics, SRS treatment parameters, and data regarding outcomes and complications were extracted from each of the included studies. Demographic data included number of patients treated with staged SRS, sex, age, clinical presentation, and follow-up duration. The AVM characteristics included nidus volume, Spetzler-Martin grade, prior hemorrhage, and prior embolization. Stereotactic radiosurgery treatment parameters included margin dose for VS-SRS or total dose for DS-SRS, isodose line, number of treatment stages, and interval between SRS procedures. Outcome and complication data included complete and partial AVM obliteration, time to obliteration, symptomatic radiation-induced changes (RICs), post-SRS hemorrhage, and death. The definition of partial obliteration was non-uniform across all studies but was reported for each study when possible. Radiation-induced changes were defined as perinidal T2-weighted hyperintensities on follow-up MRI, and only clinically symptomatic RICs from each study were recorded.

Statistical Analysis

All statistical analyses were performed using SPSS Statistics (version 22.0.0.0, IBM Corp.). Descriptive statistics were calculated as regards the rates of complete obliteration, partial obliteration, symptomatic RIC, post-SRS hemorrhage, and mortality in each of the VS-SRS and DS-SRS groups. Pooled data on the study level as well as reported means from the individual studies were used in our descriptive statistics. All studies were retrospective in design, and unclear risks of bias were assumed for retrospective studies.

Results

Study Selection

The search yielded 25 additional studies that were published after the last analysis by Moosa et al. Of these, 6 met the inclusion criteria for analysis, including 4 VS-SRS studies comprising 194 patients and 2 DS-SRS studies comprising 62 patients (Fig. 1). These additional studies were combined with the prior comparative analysis by Moosa et al., resulting in a total of 11 VS-SRS and 10 DS-SRS studies. Notable differences between the new set of DS-SRS studies and those previously identified by Moosa et al. were an older patient population (mean age in new studies 44.7 years [95% CI 43.5–45.9 years] vs prior studies 37.7 years [95% CI 35.7–39.6 years]) and smaller AVM sizes (mean nidus volume in new studies 15.0 cm³ [95% CI 10.0–19.9 cm³] vs prior studies 28.7 cm³ [95% CI 20.8–36.6 cm³]). Both new and prior DS-SRS studies were comparable with regard to mean total radiation dose, number of SRS stages, mean time between stages, and prior AVM hemorrhage and embolization rates. The new DS-SRS studies yielded higher obliteration rates than the prior studies (total 71.2%, mean 70.5%, 95% CI 65.2–75.8% vs total 18.6%, mean 22.8%, 95% CI 4.4–41.1%, respectively). Both new and prior DS-SRS studies had comparable rates of symptomatic RIC, hemorrhage, and mortality. The new set of VS-SRS studies comprised 194 patients. Both new and prior VS-SRS studies were comparable regarding baseline and outcome data.

Overall Demographic and Treatment Characteristics

Tables 1 and 2 summarize the patient, AVM, and treatment characteristics of the VS-SRS and DS-SRS studies included for analysis, respectively. From a total of 11 VS-SRS and 10 DS-SRS studies meeting the inclusion criteria, 299 and 219 patients were eligible for analysis, respectively. Female sex accounted for 43.7% (121/277 patients).
and 53.2% (149/280 patients) of the VS-SRS and DS-SRS groups, respectively. The mean age ranged from 26 to 37 years and from 34 to 46 years in the VS-SRS and DS-SRS groups, respectively.

Mean AVM volume was 23.8 cm$^3$ (95% CI 17.4–30.2 cm$^3$) and 26.2 cm$^3$ (95% CI 19.0–33.4 cm$^3$) in the VS-SRS and DS-SRS studies, respectively. Prior AVM hemorrhage occurred in 44.5% (154/346 patients) and 44.8% (116/259 patients) of VS-SRS and DS-SRS patients, respectively. Prior embolization was performed in 31.7% (108/341 patients) and 46.8% (96/205 patients) of VS-SRS and DS-SRS patients, respectively.

Stereotactic radiosurgery was delivered via Gamma Knife (GK) in all 4 new VS-SRS studies and via linear accelerator (LINAC) in both new DS-SRS studies. Overall, 11 VS-SRS studies used GK, and 8 of the 10 DS-SRS studies used LINAC. The mean VS-SRS margin dose delivered to each volumetric component ranged from 15 to 20.8 Gy, with the entire AVM being treated in 2–4 stages at 1- to 9-month staged intervals. The mean DS-SRS total margin dose ranged from 20 to 42 Gy, delivered in 2–12 stages with at least 1 day between stages.

Obliteration Rates

Tables 3 and 4 summarize the posttreatment outcomes for the VS-SRS and DS-SRS studies, respectively. In all new VS- and DS-SRS studies, complete AVM obliteration was confirmed with angiography, although MRI was used for routine follow-up evaluation. Overall, the mean complete obliteration rates for VS-SRS and DS-SRS were 41.2% (95% CI 31.4%–50.9%) and 32.3% (95% CI 15.9%–48.8%), respectively, after follow-up durations ranging from 28 to 130 and 29 to 102 months, respectively. Based on pooled individual patient data, complete obliteration was achieved in 40.3% (110/273 patients) of the VS-SRS group and in 32.7% (72/220 patients) of the DS-SRS group with sufficient follow-up.

Two new VS-SRS and 1 new DS-SRS study reported time to AVM obliteration. Overall, the mean times to obliteration for the 5 VS-SRS and 5 DS-SRS studies with available data were 69.0 months (95% CI 43.9–94.1 months) and 32.4 months (95% CI 24.3–40.4 months), respectively. The mean partial obliteration rates, which were defined individually for each study and inhomogeneously across studies, for the VS-SRS and DS-SRS groups were 75.0% (95% CI 54.3%–95.6%) and 47.4% (95% CI 28.9%–65.9%), respectively. Based on pooled individual patient data, partial obliteration was achieved in 56.3% (67/119 patients) of the VS-SRS group and in 36.8% (43/117 patients) of the DS-SRS group. Neither of the 2 new DS-SRS studies reported partial obliteration rates.

Complication Rates

The rates of symptomatic RIC were reported in all new studies. The overall mean symptomatic RIC rates were 14.0% (95% CI 7.2%–20.8%) and 12.5% (95% CI 7.4%–17.7%) in the VS-SRS and DS-SRS groups, respectively. The overall mean post-SRS hemorrhage rates were 18.8% (95% CI 14.4%–23.2%) and 11.6% (95% CI 3.5%–19.7%) in the VS-SRS and DS-SRS groups, respectively. The overall mean mortality rates were 6.4% (95% CI 3.6%–9.2%) and 4.8% (95% CI 0.6%–9.0%) in the VS-SRS and DS-SRS groups, respectively.

Based on pooled individual patient data, symptomat-
TABLE 1. Summary of patient and treatment characteristics in 4 new VS-SRS studies, presented individually and pooled with prior data adapted with permission from Moosa et al., 2014*

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Pts in Study†</th>
<th>No. of Females</th>
<th>No. of Pts Meeting Criteria‡</th>
<th>Mean Age (yrs)§</th>
<th>Mean AVM Vol (cm³)$</th>
<th>Mean Margin Dose (Gy)§</th>
<th>Isodose Line</th>
<th>No. of Tx Stages</th>
<th>Mean Time Btw Stages (mos)$</th>
<th>Spetzler-Martin Grade</th>
<th>No. w/ Previous Hemorrhage</th>
<th>No. w/ Previous Embolization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seymour et al., 2016</td>
<td>38¶</td>
<td>NR</td>
<td>33</td>
<td>27.3</td>
<td>15.5</td>
<td>NR</td>
<td>2–3</td>
<td>5.8</td>
<td>I: 0%; II: 0%; III: 11.4%; IV: 40.4%; V: 48.6%</td>
<td>15/38 (39.5%)</td>
<td>20/38 (52.6%)</td>
<td></td>
</tr>
<tr>
<td>Hanakita et al., 2015</td>
<td>18</td>
<td>5/18 (27.0%)</td>
<td>18</td>
<td>33</td>
<td>38.0</td>
<td>16.0</td>
<td>40%</td>
<td>2–3</td>
<td>6.0</td>
<td>I: 0%; II: 0%; III: 22.2%; IV: 38.9%; V: 39.8%</td>
<td>12/18 (66.7%)</td>
<td>5/18 (27.8%)</td>
</tr>
<tr>
<td>Nagy et al., 2015</td>
<td>84</td>
<td>37/84 (44.0%)</td>
<td>76</td>
<td>37</td>
<td>19.7</td>
<td>17.5</td>
<td>NR</td>
<td>2–3</td>
<td>NR</td>
<td>I: 0%; II: 8.4%; III: 45.8%; IV: 36.1%; V: 9.6%</td>
<td>37/84 (44.0%)</td>
<td>12/84 (14.3%)</td>
</tr>
<tr>
<td>Chytka et al., 2015</td>
<td>23</td>
<td>10/23 (43.5%)</td>
<td>22</td>
<td>26</td>
<td>23.3</td>
<td>17.0</td>
<td>50%</td>
<td>2–3</td>
<td>6.0</td>
<td>NR</td>
<td>7/23 (30.4%)</td>
<td>15/23 (65.2%)</td>
</tr>
<tr>
<td>Huang et al., 2012</td>
<td>18</td>
<td>10/18</td>
<td>18</td>
<td>35</td>
<td>22.9</td>
<td>15.0–18.0</td>
<td>50%</td>
<td>2–4**</td>
<td>3–9</td>
<td>I: 0%; II: 0%; III: 10.6%; IV: 55.6%; V: 33.3%</td>
<td>10/18 (55.6%)</td>
<td>8/18 (44.4%)</td>
</tr>
<tr>
<td>Kano et al., 2012†</td>
<td>47</td>
<td>21/47 (44.7%)</td>
<td>47</td>
<td>33</td>
<td>22</td>
<td>16.0</td>
<td>NR</td>
<td>2**</td>
<td>4.9</td>
<td>I: 0%; II: 0%; III: 10.6%; IV: 55.6%; V: 29.8%</td>
<td>18/47 (38.3%)</td>
<td>21/47 (44.7%)</td>
</tr>
<tr>
<td>Amponsah et al., 2011</td>
<td>5</td>
<td>4/5 (80.0%)</td>
<td>5</td>
<td>31</td>
<td>37.2</td>
<td>18</td>
<td>50.0%</td>
<td>2 or 4</td>
<td>10</td>
<td>I: 0%; II: 0%; III: 0%; IV: 60%; V: 40%</td>
<td>2/5 (40.0%)</td>
<td>NR</td>
</tr>
<tr>
<td>Lee et al., 2009</td>
<td>23</td>
<td>7/23 (30.4%)</td>
<td>5</td>
<td>34</td>
<td>16.8</td>
<td>20.8</td>
<td>53%</td>
<td>2</td>
<td>1–7</td>
<td>I: 0%; II: 30.4%; III: 43.5%; IV: 21.7%; V: 4.3%</td>
<td>18/23 (78.3%)</td>
<td>3/23 (13.0%)</td>
</tr>
<tr>
<td>Chung et al., 2008</td>
<td>7</td>
<td>4/6 (66.7%)</td>
<td>6</td>
<td>33</td>
<td>60</td>
<td>16.0–18.6</td>
<td>NR</td>
<td>2</td>
<td>6.9</td>
<td>I: 0%; II: 0%; III: 16.7%; IV: 50%; V: 33.3%</td>
<td>3/6 (50.0%)</td>
<td>0/6 (0.0%)</td>
</tr>
<tr>
<td>Back et al., 2008</td>
<td>23††</td>
<td>8/19 (42.0%)</td>
<td>19</td>
<td>33</td>
<td>20.2</td>
<td>16.5–19.0</td>
<td>NR</td>
<td>2–3</td>
<td>2</td>
<td>NR</td>
<td>8/19 (42.1%)</td>
<td>0/19 (0.0%)</td>
</tr>
<tr>
<td>Sirin et al., 2006</td>
<td>37</td>
<td>12/28 (42.9%)</td>
<td>14</td>
<td>37</td>
<td>24.9</td>
<td>16.0</td>
<td>50%</td>
<td>2–3</td>
<td>5</td>
<td>I: 0%; II: 0%; III: 7.1%; IV: 39.3%; V: 53.6%</td>
<td>13/28 (46.4%)</td>
<td>13/28 (46.4%)</td>
</tr>
<tr>
<td>Total</td>
<td>361</td>
<td>121/277 (43.7%)</td>
<td>299</td>
<td>62.8</td>
<td>23.80</td>
<td>17.1</td>
<td>(31.0–34.6)</td>
<td>(17.4–30.2)</td>
<td>(16.4–17.8)</td>
<td>46.4%</td>
<td>31.7%</td>
<td>(38.6–54.2%)</td>
</tr>
</tbody>
</table>

NR = not reported; Pts = patients; Tx = treatment.

* All patients in the tabulated VS-SRS studies were treated with GK radiosurgery.
† Includes patients lost to follow-up.
‡ Having large AVMs treated using VS-SRS with appropriate follow-up.
§ Median reported when mean not available; range indicated when neither was available.
¶ Thirty-eight patients were treated in "Era 1" from 1992 to March 2004, while 30 patients were treated in "Era 2" from May 2004 to 2008. The latter focused on decreasing per-stage treatment volume, shortening interval time between stages, and encouraging margin dose prescriptions ≥ 17 Gy.
** Some were re-treated.
†† Twenty-three patients had embolization prior to VS-SRS; 7 patients did not.
### TABLE 2. Summary of patient and treatment characteristics in 2 new DS-SRS studies, presented individually and pooled with prior data adapted with permission from Moosa et al., 2014

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Pts in Study</th>
<th>No. of Females</th>
<th>Mean Age (yrs)</th>
<th>Mean AVM Vol (cm³)</th>
<th>Treatment Modality</th>
<th>Mean Total Dose (Gy)</th>
<th>Isodose Line</th>
<th>No. of Tx Stages</th>
<th>Mean Time Btw Stages (days)</th>
<th>Spetzler-Martin Grade</th>
<th>No. w/ Previous Hemorrhage</th>
<th>No. w/ Previous Embolization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen et al., 2016</td>
<td>38</td>
<td>13/38 (34.2%)</td>
<td>34</td>
<td>43.8</td>
<td>LINAC</td>
<td>35</td>
<td>80%</td>
<td>5</td>
<td>NR</td>
<td>NR</td>
<td>17/38 (44.7%)</td>
<td>8/38 (21.1%)</td>
</tr>
<tr>
<td>Lindvall et al., 2015</td>
<td>24</td>
<td>13/24 (54.2%)</td>
<td>24</td>
<td>45.6</td>
<td>LINAC</td>
<td>32.9</td>
<td>NR</td>
<td>5</td>
<td>1–2 NR</td>
<td>I: 0%; II: 30.6%; III: 36.7%; IV: 24.5%; V: 8.2%</td>
<td>9/24 (37.5%)</td>
<td>16/24 (66.7%)</td>
</tr>
<tr>
<td>Blamek et al., 2013</td>
<td>49</td>
<td>25/49 (51.0%)</td>
<td>49</td>
<td>36</td>
<td>LINAC</td>
<td>20.0</td>
<td>NR</td>
<td>2–4 ≥7</td>
<td>NR</td>
<td>I: 0%; II: 0%; III: 0%; IV: 0%; V: 65%</td>
<td>18/49 (36.7%)</td>
<td>28/49 (57.1%)</td>
</tr>
<tr>
<td>Xiao et al., 2010</td>
<td>24</td>
<td>13/20 (65.0%)</td>
<td>20</td>
<td>34</td>
<td>LINAC</td>
<td>25.0–30.0</td>
<td>90%</td>
<td>5–6 1</td>
<td>NR</td>
<td>I: 0%; II: 0%; III: 0%; IV: 35%; V: 65%</td>
<td>11/20 (55.0%)</td>
<td>10/20 (50.0%)</td>
</tr>
<tr>
<td>Zabel-du Bois et al., 2016</td>
<td>15</td>
<td>9/15 (60.0%)</td>
<td>15</td>
<td>37</td>
<td>LINAC</td>
<td>26.0</td>
<td>80%</td>
<td>4–5 1</td>
<td>NR</td>
<td>I: 0%; II: 0%; III: 33%; IV: 40%; V: 26.7%</td>
<td>8/15 (53.3%)</td>
<td>4/15 (26.7%)</td>
</tr>
<tr>
<td>Karlsson et al., 2005</td>
<td>28</td>
<td>15/28 (53.6%)</td>
<td>24</td>
<td>35</td>
<td>LINAC</td>
<td>41.0–50.0</td>
<td>90%</td>
<td>12 3.5</td>
<td>NR</td>
<td>I: 0%; II: 0%; III: 0%; IV: 0%; V: 0%</td>
<td>13/28 (46.4%)</td>
<td>NR</td>
</tr>
<tr>
<td>Veznedaroglu et al., 2004</td>
<td>7§</td>
<td>4/7 (57.1%)</td>
<td>6</td>
<td>38</td>
<td>LINAC</td>
<td>42.0</td>
<td>89%</td>
<td>6 2</td>
<td>I: 0%; II: 0%; III: 28.6%; IV: 57.1%; V: 14.3%</td>
<td>2/7 (28.6%)</td>
<td>6/7 (85.7%)</td>
<td></td>
</tr>
<tr>
<td>Silander et al., 2004</td>
<td>23§</td>
<td>13/18 (72.2%)</td>
<td>18</td>
<td>42</td>
<td>LINAC</td>
<td>30.0</td>
<td>80%</td>
<td>6 2</td>
<td>I: 4.3%; II: 0%; III: 43.5%; IV: 43.5%; V: 8.7%</td>
<td>10/23 (43.5%)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Lindvall et al., 2003</td>
<td>36</td>
<td>18/29 (62.1%)</td>
<td>10</td>
<td>43</td>
<td>LINAC</td>
<td>30.0–35.0</td>
<td>90%</td>
<td>5 1–2 1</td>
<td>I: 31%; II: 31%; III: 34.5%; IV: 3.4%; V: 0%</td>
<td>14/29 (48.3%)</td>
<td>11/29 (37.9%)</td>
<td></td>
</tr>
<tr>
<td>Lindqvist et al., 1986</td>
<td>26</td>
<td>14/26 (53.8%)</td>
<td>5</td>
<td>35</td>
<td>LINAC</td>
<td>42.0</td>
<td>NR</td>
<td>12 3.5</td>
<td>NR</td>
<td>I: 0%; II: 0%; III: 0%; IV: 0%; V: 0%</td>
<td>14/26 (53.8%)</td>
<td>NR</td>
</tr>
<tr>
<td>Total</td>
<td>296</td>
<td>149/280 (53.2%)</td>
<td>219</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>116/259 (44.8%)</td>
<td>96/205 (46.8%)</td>
</tr>
</tbody>
</table>

- **Mean (95% CI)**: 39.0 (36.7–41.2), 26.2 (19.0–33.4), 32.4 (27.7–37.0), 44.8% (39.8–49.8%), 50.2% (37.9%–62.5%)

**Note:**
- PBI = proton beam irradiation.
- * Includes patients lost to follow-up.
- † Having large AVMs with DS-SRS treatment with appropriate follow-up.
- ‡ Median reported when mean not available.
- § Seven patients were treated to a total of 42 Gy; 23 patients to 30 Gy.
TABLE 3. Summary of outcomes in the 4 new VS-SRS studies, presented individually and pooled with prior data adapted with permission from Moosa et al., 2014

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Mean FU Duration (mos)*</th>
<th>Mean Time to Complete Obliteration (mos)*</th>
<th>Complete Obliteration Rate</th>
<th>Partial Obliteration Rate†</th>
<th>Symptomatic RIC Rate</th>
<th>Post-SRS Hemorrhage Rate</th>
<th>Mortality Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seymour et al., 2016‡</td>
<td>130.2</td>
<td>118.8</td>
<td>5/38 (13.2%)</td>
<td>17/33 [≥25%] (51.5%)</td>
<td>11/33 (33.3%)</td>
<td>11/33 (33.3%)</td>
<td>4/24 (16.7%)</td>
</tr>
<tr>
<td>Huang et al., 2012</td>
<td>&gt;36</td>
<td>NR</td>
<td>11/18 (61.1%)</td>
<td>NR</td>
<td>1/22 (4.5%)</td>
<td>1/22 (4.5%)</td>
<td>1/22 (4.5%)</td>
</tr>
<tr>
<td>Kano et al., 201246</td>
<td>87</td>
<td>NR</td>
<td>17/47 (36.2%)</td>
<td>5/30 [≥75%] (16.7%)</td>
<td>6/47 (12.8%)</td>
<td>10/47 (21.2%)</td>
<td>5/47 (10.6%)</td>
</tr>
<tr>
<td>Amponsah et al., 2011</td>
<td>76.5</td>
<td>NR</td>
<td>2/5 (40.0%)</td>
<td>3/3 [NR] (100.0%)</td>
<td>2/5 (40.0%)</td>
<td>1/5 (20.0%)</td>
<td>0/5 (0.0%)</td>
</tr>
<tr>
<td>Lee et al., 2009</td>
<td>41.2</td>
<td>NR</td>
<td>2/5 (40.0%)</td>
<td>3/3 [NR] (100.0%)</td>
<td>0/23 (0.0%)</td>
<td>2/23 (8.7%)</td>
<td>2/23 (8.7%)</td>
</tr>
<tr>
<td>Chung et al., 2008</td>
<td>28</td>
<td>53</td>
<td>2/6 (33.3%)</td>
<td>4/4 [NR] (100.0%)</td>
<td>0/6 (0.0%)</td>
<td>1/6 (16.7%)</td>
<td>0/6 (0.0%)</td>
</tr>
<tr>
<td>Back et al., 2008</td>
<td>&gt;36</td>
<td>NR</td>
<td>18/25 (72.0%)</td>
<td>NR</td>
<td>3/25 (12.0%)</td>
<td>4/25 (16.0%)</td>
<td>0/25 (0.0%)</td>
</tr>
<tr>
<td>Sirin et al., 2006</td>
<td>50</td>
<td>NR</td>
<td>7/14 (50.0%)</td>
<td>7/7 [NR] (100.0%)</td>
<td>7/28 (25.0%)</td>
<td>4/28 (14.3%)</td>
<td>2/28 (7.1%)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>110/273 (40.3%)</td>
<td>67/119 (56.3%)</td>
<td>44/322 (13.7%)</td>
<td>50/256 (19.5%)</td>
<td>24/323 (7.4%)</td>
</tr>
<tr>
<td>Mean (95% CI)</td>
<td>59.6 (44.2–75.0)</td>
<td>69.0 (43.9–94.1)</td>
<td>41.2% (31.4%–50.9%)</td>
<td>75.0% (54.3%–95.6%)</td>
<td>14.0% (7.2%–20.8%)</td>
<td>18.8% (14.4%–23.2%)</td>
<td>6.4% (3.6%–9.2%)</td>
</tr>
</tbody>
</table>

* Minimum of range was used when mean or median was not available.
† Percentages in brackets indicate study authors’ definition of partial obliteration.
‡ Thirty-eight patients were treated in “Era 1” from 1992 to March 2004, while 30 patients were treated in “Era 2” from May 2004 to 2008.

Discussion
Reframing Staged SRS Outcomes
Since the systematic review by Moosa et al., there have been 2 additional DS-SRS and 4 additional VS-SRS studies. Altogether, these new studies help to improve our understanding of the role of staged SRS in the management of large AVMs. An analysis of mean reported values and of pooled data suggests that VS-SRS may afford higher rates of both complete and partial obliteration than DS-SRS. However, one should note that complete obliteration rates were inclusive of salvage therapy, which confounds any assessments of comparative effectiveness. The mean and pooled rates of symptomatic RIC, post-SRS hemorrhage, and mortality appear to be higher for VS-SRS than DS-SRS. The mean time to obliteration was longer in the DS-SRS group. Prior embolization was more common in the DS-SRS group; however, since the effect of prior embolization on staged SRS outcomes is poorly defined, it is unknown if this discrepancy contributed to the poorer obliteration results in the DS-SRS group.4,10

Optimizing Staged SRS Approaches
The patient, AVM, and treatment characteristics that yield the best outcomes for either VS-SRS or DS-SRS remain incompletely defined. Seymour et al. showed that a margin dose ≥ 17 Gy for VS-SRS was associated with double the rate of at least a partial response, less than half the time to complete obliteration, and higher probabil-
Role of Staged SRS in the Management of Large AVMs

The management of large AVMs is challenging, and the role of staged SRS continues to evolve as outcomes data accrue. Rather than being the sole modality for achieving AVM obliteration, staged SRS may be an effective up-front therapy for volume reduction and downgrading of large, Spetzler-Martin Grade IV and V AVMs, allowing the residual nidi to subsequently become more favorable candidates for definitive occlusion with resection, SS-SRS, or curative embolization.1 Stereotactic radiosurgery may improve an AVM’s resectability by inducing arteriolar in-

### TABLE 4. Summary of outcomes of 2 new DS-SRS studies, presented individually and pooled with prior data adapted with permission from Moosa et al., 2014

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Mean FU Duration (mos)*</th>
<th>Mean Time to Complete Obliteration (mos)*</th>
<th>Complete Obliteration Rate</th>
<th>Partial Obliteration Rate†</th>
<th>Symptomatic RIC Rate</th>
<th>Post-SRS Hemorrhage Rate</th>
<th>Mortality Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen et al., 2016</td>
<td>87.5</td>
<td>NR</td>
<td>26/35 (74.3%)</td>
<td>NR</td>
<td>9/35 (25.7%)</td>
<td>2/35 (5.7%)</td>
<td>2/34 (5.9%)</td>
</tr>
<tr>
<td>Lindvall et al., 2015</td>
<td>NR</td>
<td>35.2</td>
<td>16/24 (66.7%)</td>
<td>NR</td>
<td>1/24 (4.2%)</td>
<td>3/24 (12.5%)</td>
<td>4/24 (16.7%)</td>
</tr>
<tr>
<td>Blamek et al., 2013</td>
<td>29</td>
<td>16</td>
<td>6/49 (12.2%)</td>
<td>13/43 [NR] (30.2%)</td>
<td>0/49 (0.0%)</td>
<td>2/49 (4.1%)</td>
<td>0/49 (0.0%)</td>
</tr>
<tr>
<td>Xiao et al., 2010</td>
<td>32</td>
<td>NR</td>
<td>0/20 (0.0%)</td>
<td>8/20 (&gt;50%)</td>
<td>0/20 (0.0%)</td>
<td>2/20 (10.0%)</td>
<td>0/20 (0.0%)</td>
</tr>
<tr>
<td>Zabel-du Bois et al., 2006</td>
<td>31</td>
<td>29</td>
<td>3/15 (20.0%)</td>
<td>10/12 (&gt;50%)</td>
<td>2/15 (13.3%)</td>
<td>3/15 (20.0%)</td>
<td>0/15 (0.0%)</td>
</tr>
<tr>
<td>Karlsson et al., 2005</td>
<td>&gt;36</td>
<td>NR</td>
<td>2/24 (8.3%)</td>
<td>5/22 (&gt;50%)</td>
<td>2/24 (13.3%)</td>
<td>5/24 (21.7%)</td>
<td>5/24 (21.7%)</td>
</tr>
<tr>
<td>Veznedaroglu et al., 2004</td>
<td>102/82‡</td>
<td>27/48‡</td>
<td>9/24 (37.5%)</td>
<td>NR</td>
<td>6/30 (20.0%)</td>
<td>0/30 (0.0%)</td>
<td>0/30 (0.0%)</td>
</tr>
<tr>
<td>Silander et al., 2004</td>
<td>40</td>
<td>NR</td>
<td>2/14 (14.3%)</td>
<td>4/12 (&gt;50%)</td>
<td>5/26 (19.2%)</td>
<td>0/26 (0.0%)</td>
<td>0/26 (0.0%)</td>
</tr>
<tr>
<td>Lindvall et al., 2003</td>
<td>38</td>
<td>39</td>
<td>7/10 (70.0%)</td>
<td>NR</td>
<td>4/29 (13.8%)</td>
<td>2/29 (6.9%)</td>
<td>0/29 (0.0%)</td>
</tr>
<tr>
<td>Lindqvist et al., 1986</td>
<td>&gt;60</td>
<td>NR</td>
<td>1/5 (20.0%)</td>
<td>3/4 (&gt;10%)</td>
<td>3/26 (11.5%)</td>
<td>4/26 (15.4%)</td>
<td>2/26 (7.7%)</td>
</tr>
<tr>
<td>Total</td>
<td>50.0</td>
<td>32.4</td>
<td>32.3%</td>
<td>47.4%</td>
<td>12.5%</td>
<td>11.6%</td>
<td>4.8%</td>
</tr>
<tr>
<td>Mean (95% CI)</td>
<td>34.8–65.2</td>
<td>24.3–40.4</td>
<td>15.9%–48.8%</td>
<td>28.9%–65.9%</td>
<td>7.4%–17.7%</td>
<td>3.5%–19.7%</td>
<td>0.6%–9.0%</td>
</tr>
</tbody>
</table>

* Minimum of range was used when mean or median was not available.
† Percentages in brackets indicate study authors’ definition of partial obliteration.
‡ Seven patients in the study were treated to a total dose of 42 Gy and had a mean follow-up of 102 months and time to obliteration of 27 months; 23 patients in the study were treated to a total dose of 30 Gy and had a mean follow-up of 82 months and a mean time to obliteration of 48 months.

Regarding DS-SRS, it is important to consider both the total delivered dose as well as the dose per stage. Studies have shown that a higher total dose incurs an increased risk of complications without improving the potential for obliteration. Therefore, it has been suggested that the total dose for DS-SRS should be limited to < 35 Gy.5,56,80 Data suggest that the optimal dose per stage is 6–7 Gy.13,77 Thus, an efficient DS-SRS schedule appears to be 4 fractions at 7 Gy per fraction or 5 fractions at 6–6.5 Gy per fraction.13,77
timal hyperplasia and tissue gliosis, potentially improving intraoperative blood vessel coagulability and tissue plane dissection, respectively.60,69,77 However, the downgraded AVMs appear to have higher surgical morbidity than estimated by the Spetzler-Martin grading system.1

One must also consider, particularly for VS-SRS, that the time to obliteration may be considerably longer than that for SS-SRS. And since complete protection from AVM hemorrhage is only conferred when the entirety of the nidus is obliterated, patients undergoing VS-SRS may be exposed to a prolonged latency interval during which the risk of AVM rupture remains. Therefore, alternatives to staged SRS, such as repeat SS-SRS or combined embolization and SS-SRS, also warrant consideration in the treatment of large AVMs.7,49,58,62,64 Ultimately, these high-risk lesions are probably best managed by an experienced, multidisciplinary team at a high-volume cerebrovascular center.

Study Limitations

Although our analysis comprised a greater quantity of data than the prior review by Moosa et al., the interpretation of its findings is constrained by similar limitations. Heterogeneity of the baseline and outcomes data among the constituent studies limits our ability to draw definitive conclusions regarding the superiority of one staged SRS paradigm over the other with respect to obliteration or adverse events. Even within each staged SRS approach, different treatment regimens were used in each study. In addition, there were wide variations in prior embolization rates, utilization of salvage therapy, methods for confirming total AVM obliteration, and definitions of partial obliteration.

Since the data for unruptured and ruptured AVMs were not typically segregated, we were unable to ascertain the outcomes for the subgroup of large, unruptured AVMs treated with either VS-SRS or DS-SRS. Given the considerable degree of current controversy regarding the management of unruptured AVMs, data supporting or refuting the benefit of staged SRS for these lesions would have been very interesting.2,23,27,33,59,75,84 We encourage future VS-SRS or DS-SRS studies to specifically assess the risk-to-benefit profile of these therapies for large, unruptured AVMs, which are more commonly selected for conservative management rather than intervention. Furthermore, detailed neurological outcomes, such as those pertaining to seizure remission in patients with AVM-associated epilepsy, could not be extracted from many studies and are therefore largely unknown in these cohorts of large AVMs treated with staged SRS.12,20,21,24,44,57,83 National SRS registries such as the American Association of Neurological Surgeons (AANS) and American Society for Radiation Oncology (ASTRO) SRS registries may provide more robust data regarding the outcomes of staged SRS for large AVMs.71

Conclusions

An updated comparison of VS-SRS and DS-SRS for large AVMs continues to support higher complete and partial obliteration rates with VS-SRS. However, the complication profiles of the 2 approaches with regard to symptomatic RIC, post-SRS hemorrhage, and mortality may favor DS-SRS. New studies have offered further insight regarding the optimization of both radiosurgical techniques. Currently, either VS-SRS or DS-SRS may be a reasonable treatment strategy for large AVMs when intervention is deemed appropriate, either as stand-alone therapy or as a component of multimodality management.

References


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

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