Stereotactic radiosurgery (SRS) is an effective and less invasive management option for properly selected brain arteriovenous malformations (AVMs). The primary goal of SRS is total AVM nidus obliteration and elimination of future hemorrhage risk.1–3 Avoidance of treatment-related side effects is an important additional goal. Previous outcomes studies indicate that AVM radiosurgery may be associated with transient or irreversible adverse radiation effects (ARE).4–10 After SRS, serial magnetic resonance imaging (MRI) studies indicate that as many as 30% of patients develop detectable imaging changes adjacent to the treatment volume.4–7 Symptomatic ARE develop in 3% to 11% of patients.1,2,5,7,11,12 Previous publications indicate that AVM anatomic location, nidus size, margin dose,1,5–7,11,12 and the brain volume included in 12 Gy are predictive of symptomatic ARE after AVM radiosurgery.4 The present study was designed to develop a mathematical risk model for AVM radiosurgery.

Methods and Materials
Patient Population
We performed a retrospective review of 918 patients with AVM who underwent single-stage SRS using the Leksell Gamma Knife (Elekta Instruments, Norcross, GA) at our center between 1987 and 2012. We excluded 30 patients who died from hemorrhage within 2 years after SRS and 133 patients who were followed up <2 years despite our efforts to contact patients, families, and referring physicians. We identified a final data set of 755 patients with AVM with at least 2 years of imaging and clinical follow-up. The series included 387 male and 368 female patients. The median patient age was 35 years (range, 3–79 years). No patient underwent previous radiation therapy. Eighty-seven patients (12%) underwent previous resection and 128 (17%) had previous embolization. AVMs were originally diagnosed from imaging performed for brain hemorrhage (364 patients or 48%), seizures (165 patients or 22%), refractory headache (145 patients or 19%), or unrelated complaints (81 patients or 11%). The AVMs were located in the cerebral hemispheres in 486 patients, thalamus in 70, brain stem in 55, cerebellum in 55, basal ganglia in 84

Estimating the Risks of Adverse Radiation Effects After Gamma Knife Radiosurgery for Arteriovenous Malformations
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Background and Purpose—We evaluated risk factors associated with the development of adverse radiation effects (ARE) after stereotactic radiosurgery (SRS) for cerebral arteriovenous malformations (AVMs).

Methods—We evaluated 755 patients with AVM who underwent a single Gamma Knife SRS procedure with at least a 2-year minimum follow-up. Eighty-seven patients (12%) underwent previous resection and 128 (17%) had previous embolization. The median target volume was 3.6 mL (range, 0.1–26.3 mL). The median margin dose was 20 Gy (range, 13–27 Gy).

Results—Fifty-five patients (7%) developed symptomatic ARE at a median follow-up of 75 months. The cumulative rates of symptomatic ARE were 3.2%, 5.8%, 6.7%, and 7.5% at 1, 2, 3, and 5 years, respectively. Factors associated with a higher rate of developing symptomatic ARE included larger AVM volume, higher margin dose, larger 12-Gy volume, higher Spetzler–Martin grade, and higher radiosurgery-based score. The rates of developing symptomatic ARE were higher in the brain stem (22%) or thalamus (16%), compared with AVMs located in other brain locations (4%–8%). Nineteen patients (3%) sustained irreversible new neurological deficits related to ARE, and 1 patient died. The rates of irreversible symptomatic ARE were 0.8%, 1.9%, 2.1%, and 2.8% at 1, 2, 3, and 5 years, respectively. The 5-year cumulative rates of irreversible symptomatic ARE were 9.1% in thalamus, 12.1% in brain stem, and 1.4% in other locations.

Conclusions—The knowledge of ARE risk rates after AVM radiosurgery can assist informed consent for patients with AVM, their families, and healthcare providers. (Stroke. 2017;48:84-90. DOI: 10.1161/STROKEAHA.116.014825.)

Key Words: adverse radiation effects ◼ arteriovenous malformation ◼ complication ◼ Gamma knife ◼ radiation necrosis ◼ stereotactic radiosurgery ◼ T2 changes
Radiosurgery Technique
Our radiosurgical technique has been described in detail in previous reports. The margin SRS dose included the entire AVM nidus volume, defined as the shunt between the afferent arteries and the draining veins. AVM volumes reduced by embolization were not included in the SRS target volume. SRS was performed with either a Model U, B, C, 4C, or Perfexion Leksell Gamma Knife (Elekta Inc, Atlanta, GA).

The median target volume was 3.6 mL (0.1–26.3 mL). The median maximal diameter of the AVM nidus was 2.3 cm (range, 0.5–5.3 cm). The median prescription dose delivered to the nidus margin was 20 Gy (13–27 Gy). The median maximum dose was 38 Gy (22.2–50 Gy). The median number of isocenters was 3 (range, 1–19). The median 12-Gy volume, which is the total volume of tissue including the target and receiving ≥12 Gy, was 7.7 mL (range, 0.3–48.7 mL).

Patient Follow-Up
After radiosurgery, patients were instructed to have clinical and imaging assessments at 6-, 12-, 24-, and 36-month intervals. At the end of 3 years, if MRI suggested complete obliteration, a follow-up angiogram was requested. Complete AVM obliteration was defined as disappearance of the nidus and absence of early venous drainage (using either MRI or angiography). At any time when a new neurological symptom or sign developed, the patient had computed tomography and MRI to rule out hemorrhage or ARE. This retrospective study was approved by the University of Pittsburgh Institutional Review Board.

Table 1. Arteriovenous Malformations Characteristics

<table>
<thead>
<tr>
<th>Location</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal</td>
<td>146</td>
<td>19.3</td>
</tr>
<tr>
<td>Temporal</td>
<td>122</td>
<td>16.2</td>
</tr>
<tr>
<td>Parietal</td>
<td>125</td>
<td>16.6</td>
</tr>
<tr>
<td>Occipital</td>
<td>93</td>
<td>12.3</td>
</tr>
<tr>
<td>Corpus callosum</td>
<td>26</td>
<td>3.4</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>50</td>
<td>6.6</td>
</tr>
<tr>
<td>Thalamus</td>
<td>70</td>
<td>9.3</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>55</td>
<td>7.3</td>
</tr>
<tr>
<td>Brain stem</td>
<td>55</td>
<td>7.3</td>
</tr>
<tr>
<td>Intraventricle</td>
<td>13</td>
<td>1.7</td>
</tr>
<tr>
<td>Presence of varix</td>
<td>85</td>
<td>11.3</td>
</tr>
<tr>
<td>Presence of coexisting aneurysm including clipped or embolized aneurysm</td>
<td>77</td>
<td>10.2</td>
</tr>
<tr>
<td>Spetzler–Martin grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>41</td>
<td>5.4</td>
</tr>
<tr>
<td>II</td>
<td>214</td>
<td>28.3</td>
</tr>
<tr>
<td>III</td>
<td>397</td>
<td>52.6</td>
</tr>
<tr>
<td>IV</td>
<td>103</td>
<td>13.6</td>
</tr>
<tr>
<td>Radiosurgery-based score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1.00</td>
<td>226</td>
<td>29.9</td>
</tr>
<tr>
<td>1.01–1.50</td>
<td>280</td>
<td>37.1</td>
</tr>
<tr>
<td>1.51–2.00</td>
<td>189</td>
<td>25.0</td>
</tr>
<tr>
<td>&gt;2.00</td>
<td>60</td>
<td>7.9</td>
</tr>
</tbody>
</table>

Statistical Analysis
The primary end point for statistical analysis was the development of symptomatic ARE. This was defined as any new neurological symptoms and signs without evidence of a new hemorrhage after SRS. Irreversible symptomatic ARE was defined as the documented persistence of neurological deficits for ≥2 years after the onset of symptoms. Kaplan–Meier survival analysis was performed to calculate the rates of symptomatic ARE. The median follow-up period after SRS was 75 months (range, 24–278 months). Patients were censored when lost to follow-up or at the time of developing symptomatic ARE. The log-rank test was used to assess differences in survival curves and Cox regression was used to assess hazard ratios (HRs) in multivariate analysis. We modeled the end point of symptomatic ARE using a previously described actuarial correction averaging method for multivariable logistic regression analysis. Patients who developed ARE within 2 years after SRS or had >2-year follow-up were incorporated in the logistic regression model. A value of P < 0.05 was used for the statistical significance. The 12-Gy volume was collinear with margin dose, target volume, and maximum diameter. We performed stepwise modeling with each different variable set with 1 and 2 of each of these variables excluded. Each set yielded the same final model with the same values in stepwise multivariate analysis based on survival analysis. Standard statistical processing software (SPSS, version 22.0; IBM Corp., Armonk, NY) was used.

Results
Symptomatic AREs
Fifty-five patients (6%) developed symptomatic ARE after SRS. Thirty-six patients developed transient symptomatic ARE and 19 had irreversible symptomatic ARE. Table 2 shows detailed information on the symptoms and signs related to both transient and irreversible ARE. One patient with an occipital lobe AVM required surgery to reduce brain edema 27 months after SRS. One patient with a midbrain AVM and unrecognized hydrocephalus died because of ARE 35 months after SRS. Table 2 shows the number of patients who developed both transient and irreversible ARE in each location. Eleven of 70 (16%) patients with thalamic AVM developed symptomatic ARE, and 12 of 55 (22%) patients with brain stem AVM developed symptomatic ARE. Patients with AVM in other locations developed symptomatic ARE with a risk of 3.6% to 7.7% depending on the location. The cumulative rates of symptomatic ARE in patients with thalamic AVM at 6, 12, 24, 36, and 60 months were 0%, 7.1%, 12.9%, 14.9%, and 17.1% (Figure 1A). The cumulative rates of symptomatic ARE in patients with brain stem AVM at 6, 12, 24, 36, and 60 months were 8.1%, 10.9%, 18.2%, 22.2%, and 22.2% (Figure 1A). In contrast the 5-year cumulative rate of symptomatic ARE in patients with other non–brain stem–thalamus AVM was only 5.2% (Figure 1A). The odds ratio between thalamus and non–brain stem–thalamus AVM was 3.3 (P < 0.001; 95% confidence interval [CI], 1.65–6.50). The odds ratio between brain stem and non–brain...
stem–thalamus AVM was 4.8 ($P<0.0001$; 95% CI, 2.47–9.30).

In the logistic regression model, Figure 1C shows the probability of both transient symptomatic and irreversible ARE for different single-location sites of thalamus, brain stem, and other locations according to 12-Gy volume (Figure 1C).

The cumulative rates of symptomatic ARE (transient or irreversible) were 1.9% at 6 months, 3.2% at 12 months, 5.0% at 18 months, 5.8% at 24 months, 6.7% at 36 months, 7.3% at 48 months, and 7.5% at 60 months. In univariate analysis based on Cox proportional hazard model, factors associated with a higher rate of symptomatic ARE included larger maximum diameter, larger target volume, higher margin dose, larger 12-Gy volume, AVM location in thalamus or brain stem, and the presence of deep venous drainage, and higher radiosurgery-based score (Figure 2). In multivariate analysis based on Cox proportional hazard model, a greater 12-Gy volume and location in thalamus or brain stem was significantly associated with a higher rate of irreversible symptomatic ARE. Among the group of patients with brain stem AVM, only larger target volume was significantly associated with a higher rate of symptomatic ARE (HR, 1.32; 95% CI, 1.06–1.65) in multivariate analysis based on Cox proportional hazard model (Figure 3). Among the group of patients with AVM in thalamus and the other brain location, there were no factors associated with higher rate of irreversible symptomatic ARE in multivariate analysis.

Five of 70 (7%) patients with thalamic AVM developed irreversible symptomatic ARE, as did 6 of 55 (11%) patients with brain stem AVM. The rates of developing irreversible symptomatic ARE in other locations varied between 0% and 3.2% (Table 2). For patients with thalamic AVM, the cumulative rates of irreversible symptomatic ARE at 6, 12, 24, 36, 48, and 60 months were 0%, 1.4%, 4.5%, 4.5%, 6.7%, and 9.1%, respectively (Figure 1B). For patients with brain stem AVM, the cumulative rates of irreversible symptomatic ARE were 1.9%, 3.8%, 9.8%, 12.1%, 12.1%, and 12.1% (Figure 1B). The 5-year cumulative rate of irreversible symptomatic ARE in patients with other non–brain stem–thalamic and AVM was 1.4% (Figure 1B). The odds ratio between thalamus and non–brain stem–thalamus AVM was 6.1 ($P<0.0002$; 95% CI, 1.98–18.56). The odds ratio between brain stem and non–brain stem–thalamus AVM was 9.7 ($P<0.0001$; 95% CI, 3.37–28.01). In the logistic regression model, Figure 1D shows the probability of irreversible symptomatic ARE for different single-location sites of thalamus, brain stem, and other locations according to 12-Gy volume (Figure 1D).

Table 3 shows the relationship between dose–volume and ARE in each location. A target volume of 1, 4, 13, or 30 mL corresponded to an AVM with an average diameter that was 1.3, 2, 3, and 4 cm in diameter. In the brain stem and thalamic AVMs even smaller target volumes receiving a lower margin dose might develop ARE.

### Discussion

The goal of treatment in cerebral AVMs is complete obliteration to eliminate subsequent intracranial hemorrhage risks while minimizing the risk of developing new treatment-related neurological deficits. The primary disadvantage of SRS lies in the risk of hemorrhage during the latency interval between SRS and total obliteration. Previous SRS outcomes studies indicate that a higher AVM margin dose was significantly associated
with a higher rate of total obliteration. However, the use of higher margin doses also was associated with imaging changes best detected using T2-weighted or fluid-attenuated inversion recovery MR sequences. In the present study, we focused on symptomatic ARE because only such imaging changes after radiosurgery are clinically important only if associated with new neurological symptoms or signs.

The AVM dose, brain volume, and AVM location are the most important factors influencing the risk for delayed radiation-related complications. Strategies to optimize the dose delivered to the target while minimizing dose to the surrounding brain enhance the likelihood of AVM obliteration while balancing the risk of ARE. In our previous study, Flickinger et al. constructed statistical models predicting the risk of irreversible radiation sequelae with a 12-Gy volume, i.e., the volume of tissue (including the AVM target) receiving ≥12 Gy. The relationship between target volume and the occurrence of ARE is considered to be dose dependent. The likelihood of associated symptoms and the type of symptoms that develop depend on the location of the AVM. Flickinger et al. reported that the high-risk group of irreversible symptomatic ARE included the AVM locations in the brain stem and thalamus. In the present study, we reconfirmed that AVM location in either the thalamus or brain stem was significantly associated with higher rate of both transient symptomatic and irreversible ARE.

We constructed logistic risk prediction curves for symptomatic and irreversible symptomatic ARE from this analysis, with dose and volume parameters for the treatment represented by the single parameter, 12-Gy volume. Other factors that are reported to influence the risk of symptomatic ARE include previous hemorrhage and repeat SRS. In the present study, pretreatment hemorrhage was not associated with
symptomatic ARE. Interestingly, in the group of patients with thalamic AVM and brain stem AVM, the 12-Gy volume was not associated with symptomatic ARE, whereas the target volume was the only factor associated with higher rate of symptomatic ARE in multivariate analysis (Table 3).

Symptomatic ARE reportedly occur in 3% to 11% of patients with AVM who undergo SRS.1,2,5–7,11,12 Transient symptomatic ARE may also include headache or seizures (for subcortical lobar AVMs) may also occur after SRS. The higher resolution rates of symptoms such as headache or seizures have been studied in reports of AVMs in certain locations, such as AVMs in the occipitotemporal lobes and near the Sylvian Fissure.5,21,22 But visual field defects (transient versus irreversible=0 versus 5), ocular movement disorders (0 versus 4), and hemiparesis (7 versus 9) tended to be irreversible (Table 2). The higher rate of irreversibility was seen in the brain stem (transient versus irreversible=5 versus 6), thalamus (5 versus 6), occipital (1 versus 3), and cerebellum (1 versus 1; Table 2).

Flickinger et al reported that 102 of 1255 (8%) patients with AVM who underwent SRS in a multicenter study.
developed symptomatic ARE. Eighty of 102 patients who had symptomatic ARE demonstrated evidence of parenchymal radiation injury, 12 had isolated cranial nerve neuropathies, and 10 had new or worsened seizures. Forty-percent of symptomatic ARE had complete symptom resolution. In the present study, patients who developed headache and seizures tended to have transient events, whereas patients who developed cranial nerve or visual field defects proved to have long-lasting AREs. Only 2 patients required surgical resection of their AVM because of persistent ARE symptoms. We prescribe oral corticosteroids for transient (<2 weeks), whereas for persistent symptoms, we prescribe a 90-day trial of vitamin E (400 iu BID) and pentoxifylline (400 mg BID).

Weaknesses of the Present Study
We acknowledge the weaknesses of this retrospective outcome analysis. During our 28-year AVM experience, our knowledge of dose–volume relationships, conformity and selectivity of treatment planning, and reliance on both angiographic and 3-dimensional MRI data, gradually changed. It is likely that patients treated in the latter years of this study benefitted from our expanded knowledge and improving technique. Optimization of target selection and dose planning has reached a mature phase. The incidence of ARE may be slightly under- or overestimated because patients who were followed up <2 years (14%) were excluded in this study.

Conclusions
The knowledge of ARE risk rates after AVM radiosurgery can assist clinical decision making for patients and healthcare providers. We found that the risks of symptomatic ARE from AVM radiosurgery can be predicted according to location and the 12-Gy volume. We anticipate that we will be able to gather additional multicenter experience to verify and extend these predictions.

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We thank Douglas Kondziolka, MD (New York University Langone Medical Center), for significant contributions to patient management at the University of Pittsburgh.

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Disclosures
Dr Lunsford is a stock holder for AB Elekta. The other authors report no conflicts.

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