# Radiation-Induced Changes After Stereotactic Radiosurgery for Brain Arteriovenous Malformations: A Systematic Review and Meta-Analysis

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**BACKGROUND:** Radiation-induced changes (RICs) are the most common complication of stereotactic radiosurgery (SRS) for brain arteriovenous malformations (AVMs), and they appear as perinidal T2-weighted hyperintensities on magnetic resonance imaging, with or without associated neurological symptoms.

**OBJECTIVE:** To determine the rates of RIC after AVM SRS and identify risk factors.

**METHODS:** A literature review was performed using PubMed and MEDLINE to identify studies reporting RIC in AVM patients treated with SRS. RICs were classified as radiologic (any neuroimaging evidence), symptomatic (any associated neurological deterioration, regardless of duration), and permanent (neurological decline without recovery). Baseline, treatment, and outcomes data were extracted for statistical analysis.

**RESULTS:** Based on pooled data from 51 studies, the overall rates of radiologic, symptomatic, and permanent RIC after AVM SRS were 35.5% (1143/3222 patients, 32 studies), 9.2% (499/5447 patients, 46 studies), and 3.8% (202/5272 patients, 39 studies), respectively. Radiologic RIC was significantly associated with lack of prior AVM rupture (odds ratio [OR] = 0.57; 95% confidence interval [CI]: 0.47-0.69; $P < .001$) and treatment with repeat SRS (OR = 6.19; 95% CI: 2.42-15.85; $P < .001$). Symptomatic RIC was significantly associated with deep AVM location (OR = 0.38; 95% CI: 0.21-0.67; $P < .001$).

**CONCLUSION:** Approximately 1 in 3 patients with AVMs treated with SRS develop radiologically evident RIC, and of those with radiologic RIC, 1 in 4 develop neurological symptoms. Lack of prior AVM hemorrhage and repeat SRS are risk factors for radiologic RIC, and deep nidus location is a risk factor for symptomatic RIC.

**KEY WORDS:** Adverse radiation effect, Gamma Knife, Intracranial arteriovenous malformation, Linear accelerator, Radiation-induced changes, Radiosurgery, Review

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Stereotactic radiosurgery (SRS) is an effective treatment option for the management of brain arteriovenous malformations (AVM), and is particularly favored for small- to medium-sized nidi located in deep or eloquent brain regions.[1-17] As the use of SRS continues to permeate AVM management, recognition and characterization of treatment-specific complications is crucial to optimizing long-term outcomes. The earliest and most frequently observed complication after SRS for AVMs is radiation-induced changes (RICs), which typically manifest 6 to 18 mo after radiosurgery as perinidal T2 signal changes on follow-up neuroimaging.[2,18-26] Although most RICs are asymptomatic, a subset of patients with radiologically evident RIC develop neurological symptoms, such as headache, seizure, and focal neurological deficit.[3,20,21,23,25-31] The

**ABBREVIATIONS: AVM,** arteriovenous malformation; **CI,** confidence interval; **DS-SRS,** dose-staged SRS; **GK,** Gamma Knife; **KPS,** Karnofsky Performance Scale; **LINAC,** linear accelerator; **OR,** odds ratio; **PRISMA,** Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **RBAS,** radiosurgery-based AVM score; **RIC,** radiation-induced change; **SM,** Spetzler-Martin; **SRS,** stereotactic radiosurgery; **SS-SRS,** single-session SRS; **VS-SRS,** volume-staged SRS

majority of symptomatic RIC are transient and can be medically managed, but a minority of SRS-treated AVM patients suffer permanent neurological deterioration secondary to RIC.[2,3,25,27,28] There are considerable variations in the reported rates, durations, and symptoms of RIC.[3,18,19,24,28,32-40] The aims of this systematic review and meta-analysis are to (1) quantify the rates of radiologic, symptomatic, and permanent RIC after SRS for AVMs, and (2) identify risk factors for RIC following SRS for AVMs.

# METHODS

## Literature Search and Inclusion Criteria

This systematic review and meta-analysis follows the guidelines set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement. A literature search was performed using PubMed (November 10, 2016) and MEDLINE (February 10, 2017), using the following search phrase: "(brain OR intracranial) AND arteriovenous malformation AND (gamma knife OR linear accelerator OR stereotactic radiosurgery) AND (cyst OR edema OR necrosis OR radiation-induced change)." The studies underwent screening by title and abstract to ascertain fulfillment of the inclusion criteria, which were as follows: (1) ≥10 patients with AVM treated with SRS; (2) each treated patient must be represented only once among all of the studies included for analysis; (3) all patients who developed radiologic evidence of RIC, RIC-associated symptoms, and/or permanent neurological deficits must be reported; and (4) the study must be written in English. Studies with overlapping published data from the same institution in a more recent study were excluded. In order to mitigate bias, studies that only reported RIC outcomes for a subset of the entire SRS-treated AVM cohort were excluded.

RICs were classified as radiologic, symptomatic, or permanent as follows: (1) radiologic RIC was defined as any MRI evidence of perinidal T2-weighted hyperintensities after SRS; (2) symptomatic RIC was defined as radiologic RIC associated with new or worsening neurological symptoms; and (3) permanent RIC was defined as symptomatic RIC without recovery to a patient's pre-SRS neurological status.

## Data Extraction

Each included study was categorized based on geographic location (dichotomized as SRS performed in a medical center based in the USA or in one outside of the USA), SRS device (dichotomized as Gamma Knife [GK; Elekta, Stockholm, Sweden] or linear accelerator [LINAC] based), SRS approach, and cohort age (dichotomized as exclusively pediatric [age < 18 yr] or inclusive of adult patients). Summary data and, when available, individual patient data regarding demographics, AVM characteristics, SRS treatment parameters, outcomes, and complications were extracted from each study.

Demographic data included the number of AVM patients treated with SRS, gender, and age. AVM characteristics included volume, location, prior rupture, prior embolization, Spetzler-Martin (SM) grade, and radiosurgery-based AVM score (RBAS).[41,42] Deep locations included the basal ganglia, thalamus, peri- and intraventricular regions, and brainstem. SRS treatment parameters included margin dose, maximum dose, and isodose line. Outcome and complication data included radiologic, symptomatic, and permanent RIC, AVM obliteration, time to obliteration, post-SRS hemorrhage, and death. SRS approaches included single-session (SS-SRS), repeat, dose-staged (DS-SRS), or volume-staged (VS-SRS). When available, data regarding RIC-associated symptoms and predictive factors related to RIC were also extracted.

## Statistical Analysis

Descriptive statistics were calculated for baseline and outcomes data using MATLAB (version R2016a, MathWorks, Natick, Massachusetts). Meta-analysis of individual data was performed using RevMan (version 5.3, The Cochrane Collaboration, Copenhagen, Denmark). A univariate logistic regression analysis was performed, for studies with sufficient individual patient data or summary statistical data, to determine the association of RIC with AVM features, patient presentation, treatment characteristics, and outcomes. The principal summary measure was odds ratio (OR) which was analyzed for each association using the generic inverse-variance method.

Due to the assumptions of clinical diversity and differences in methodology among the included studies, the random effects model was implemented. Unclear risks of bias were assumed for retrospective studies. Study heterogeneity was assessed using the $I^2$ and chi-square test statistics. Significant heterogeneity was considered to be present when both the $I^2$ value exceeded 50% and the chi-square value was within the 10% level of significance ($P < .10$). In order to mitigate bias associated with retrospective, nonrandomized studies, only those outcomes with contributions from at least 4 studies were reported. Additionally, publication bias was assessed using funnel plots, which were generated for each outcome measure. Every effort was made to perform a comprehensive review by including studies from both MEDLINE and PubMed. All statistical tests were 2-tailed, and $P < .05$ was considered statistically significant.

# RESULTS

## Study Selection

The literature search yielded a total of 180 studies, 82 of which were excluded after review of abstracts. Of the remaining 98 studies, 51 met the inclusion criteria and were included in our analysis (Figure 1). The reasons for exclusion of the 47 studies after full-text article review included insufficient number of patients with AVMs treated with SRS (n = 7), duplication of patients with RIC (n = 29), and failure to report number of patients with radiologic, symptomatic, and/or permanent RIC (n = 11).

## Baseline and Treatment Characteristics

The 51 included studies comprised a total of 6779 AVM patients treated with SRS.[1,3,21,23,24,28,31-40,43-77] Table 1 summarizes the studies and their respective rates of radiologic, symptomatic, and permanent RIC. Table 2 summarizes the overall patient demographics, AVM features, treatment characteristics, and SRS outcomes. Studies from the USA yielded 50.3% of patients. The frequency of female gender was 46.0%, and 10.3% were pediatric patients. The median age ranged from 9.5 to 43.8 yr, and the median AVM volume ranged

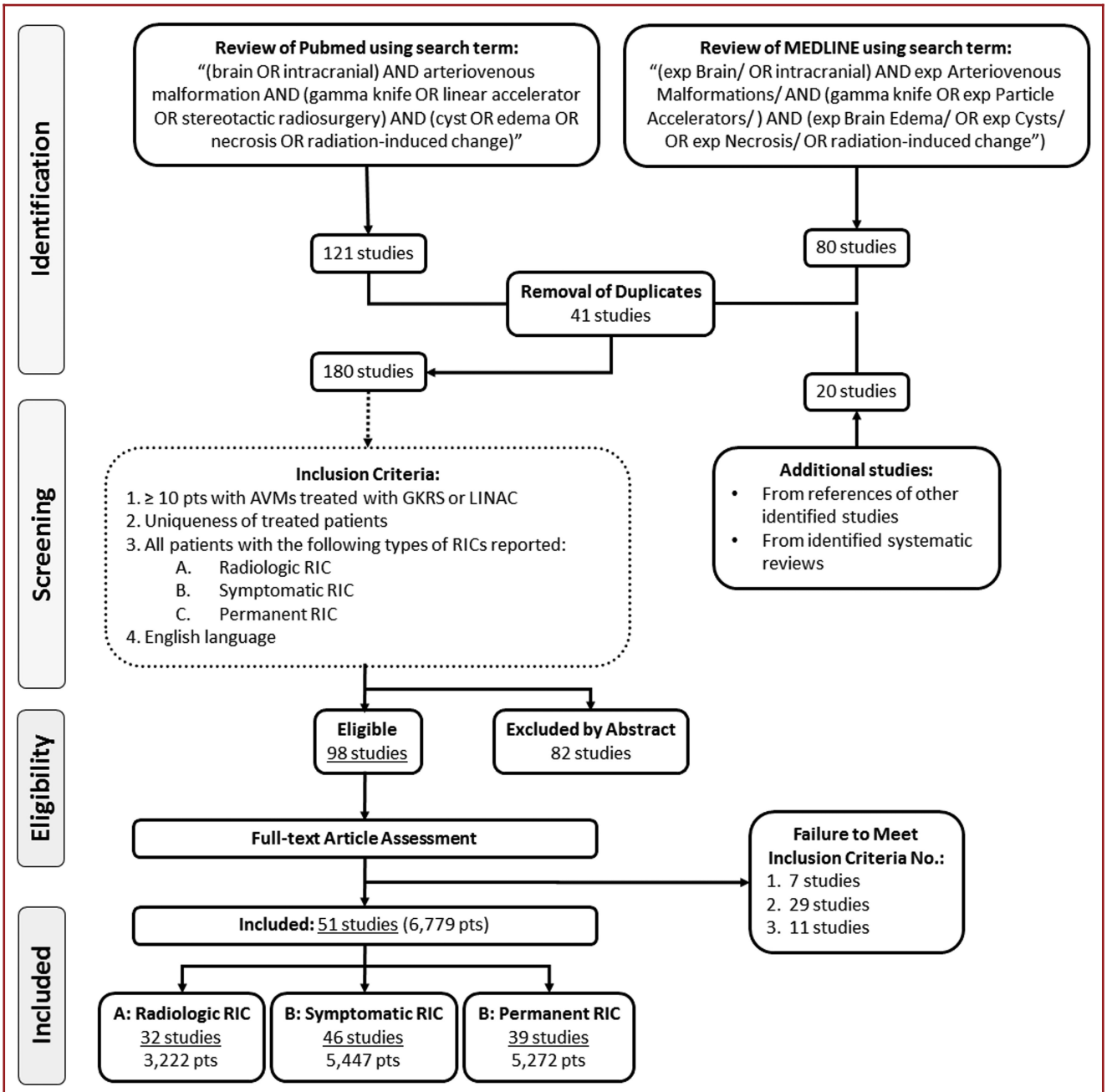


**FIGURE 1.** *Flow diagram showing the selection process for the studies included in the analysis of incidence of radiologic, symptomatic, and permanent RIC following GK SRS (Elekta) or LINAC-based SRS treatment of AVMs.*

from 1.2 to 38.0 $cm^3$. Pre-SRS frequencies of AVM hemorrhage and endovascular treatment were 50.2% and 20.4%, respectively.

SRS modalities were GK (Elekta) and LINAC-based in 83.3% and 16.7% of patients, respectively. The treatment approaches were SS-SRS, DS-SRS, and VS-SRS in 63.1%, 2.3%, and 2.5% of patients, respectively. Repeat SRS was performed in 14.3% of the patients. Across all studies, the median margin and maximum doses ranged from 15.0 to 25.9 Gy and 18.0 to 46.9 Gy, respectively. The median clinical and radiologic follow-up durations were 7 to 187 mo (0.6-15.6 yr) and 5 to 103 mo (0.4-8.6 yr), respectively.

**TABLE 1. Summary of the 51 Studies Included for Analysis, With RIC Categorized Into Radiologic, Symptomatic, and Permanent**

| | Category | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Authors and year | Location of study | Type of SRS | SRS approach | Pediatric study | Year | Radiologic RIC | Symptomatic RIC | Permanent RIC |
| Kano et al, 2017[3] | USA | GK | Single-session | No | 1987-2012 | NR | 55/755 (7.3%) | 19/755 (2.5%) |
| Chen et al, 2016[43] | USA | LINAC | Dose-staged | No | 2004-2007 | NR | 10/34 (29.4%) | 2/34 (5.9%) |
| Hanakita et al, 2016[44] | Not USA | GK | Volume-staged | No | 2005-2012 | 12/18 (66.7%) | 2/18 (11.1%) | 2/18 (11.1%) |
| Nagy et al, 2016[45] | Not USA | GK | Single-session | No | 2000-2007 | NR | 20/124 (16.1%) | 19/124 (15.3%) |
| | Not USA | GK | Volume-staged | No | 2007-2013 | NR | 7/67 (10.4%) | 4/61 (6.6%) |
| Pollock et al, 2016[31,a] | USA | GK | Single-session, volume-staged | No | 1990-1997 | NR | NR | 23/160 (14.4%) |
| [a] | USA | GK | Single-session, volume-staged | No | 1997-2009 | NR | NR | 8/221 (3.6%) |
| Bir et al, 2015[46] | USA | GK | Single-session | No | 2000-2012 | NR | 1/85 (1.2%) | NR |
| Bose et al, 2015[24,b] | Not USA | GK | Single-session | No | 2009-2014 | 9/89 (10.1%) | NR | NR |
| [b] | Not USA | GK | Single-session | No | 2009-2014 | 27/96 (28.1%) | NR | NR |
| Hanakita et al, 2015[47] | USA | GK | Single-session | Yes | 1990-2009 | NR | 9/116 (7.8%) | 7/116 (6.0%) |
| Moraes et al, 2015[48] | Not USA | LINAC | Repeat | No | 2003-2011 | NR | 6/37 (16.2%) | 2/37 (5.4%) |
| Matsuo et al, 2014[49] | Not USA | LINAC | Single-session | No | 1993-2000 | NR | 12/51 (23.5%) | 3/51 (5.9%) |
| Blamek et al, 2013[50] | Not USA | LINAC | Single-session | Yes | 2002-2010 | 5/5 (100.0%) | 0/5 (0.0%) | NR |
| | Not USA | LINAC | Dose-staged | Yes | 2002-2010 | 1/5 (20.0%) | 0/5 (0.0%) | NR |
| Machnowska et al, 2013[39] | Not USA | GK | Single-session | No | 2000-2009 | NR | 17/95 (17.9%) | NR |
| | Not USA | LINAC | Single-session | No | 2000-2009 | NR | 3/66 (4.5%) | NR |
| Parkhutik et al, 2013[35] | Not USA | GK | Single-session | No | 1994-2010 | 59/102 (57.8%) | 7/102 (6.9%) | 3/102 (2.9%) |
| Yen et al, 2013[51] | USA | GK | Repeat | No | 1989-2009 | 482/1426 (33.8%) | 122/1426 (8.6%) | 26/1426 (1.8%) |
| Hayhurst et al, 2012[38] | Not USA | GK | Single-session | No | 2005-2009 | 42/66 (63.6%) | NR | 9/66 (13.6%) |
| | Not USA | GK | Single-session | Yes | 2005-2009 | 7/19 (36.8%) | 4/19 (21.1%) | 0/19 (0.0%) |
| Herbert et al, 2012[52] | Not USA | LINAC | Single-session | No | 1997-2006 | NR | 14/73 (19.2%) | 14/73 (19.2%) |
| Huang et al, 2012[37] | USA | GK | Volume-staged | No | 1998-2011 | 5/18 (27.8%) | 2/18 (11.1%) | 0/18 (0.0%) |
| Kano et al, 2012[53] | USA | GK | Single-session | Yes | 1987-2006 | NR | 8/157 (5.1%) | 2/157 (1.3%) |
| Kano et al, 2012[54] | USA | GK | Repeat | No | 1987-2006 | NR | 16/105 (15.2%) | 4/105 (3.8%) |
| Kano et al, 2012[55] | USA | GK | Volume-staged | No | 1992-2006 | NR | 6/47 (12.8%) | 2/47 (4.3%) |
| Tamura et al, 2012[56,c] | Not USA | GK | Single-session, volume-staged | Yes | 2002-2009 | 2/22 (9.1%) | NR | NR |
| Yeon et al, 2012[57,d] | Not USA | GK | Single-session, volume-staged | Yes | 2002-2008 | 12/39 (30.8%) | 4/39 (10.3%) | 0/39 (0.0%) |
| Zeiler et al, 2011[58] | Not USA | GK | Single-session | No | 2003-2009 | 15/69 (21.7%) | 7/69 (10.1%) | 0/69 (0.0%) |
| Blamek et al, 2010[23] | Not USA | LINAC | Single-session | No | 2001-2005 | 21/62 (33.9%) | 21/62 (33.9%) | NR |
| Buis et al, 2010[28] | Not USA | LINAC | Repeat | No | 1991-2007 | 6/15 (40.0%) | 3/15 (20.0%) | 3/15 (20.0%) |
| Lindvall et al, 2010[59] | Not USA | LINAC | Dose-staged | No | 1986-2008 | NR | 4/56 (7.1%) | 1/56 (1.8%) |
| Ganz et al, 2009[60] | Not USA | GK | Single-session | No | NR | 64/107 (59.8%) | 9/107 (8.4%) | 2/107 (1.9%) |
| Kiran et al, 2009[40,e] | Not USA | GK | Single-session | No | 1997-2005 | NR | 8/53 (15.1%) | 4/53 (7.5%) |
| [e] | Not USA | GK | Single-session | No | 1997-2005 | NR | 13/255 (5.1%) | 2/255 (0.8%) |
| Han et al, 2008[32] | Not USA | GK | Single-session | No | 1997-2004 | 103/157 (65.6%) | 18/157 (11.5%) | 8/157 (5.1%) |
| Pan et al, 2008[61] | Not USA | GK | Single-session | Yes | 1993-2006 | NR | 6/105 (5.7%) | 5/105 (4.8%) |
| Inoue, 2006[62] | Not USA | GK | Single-session | No | NR | NR | 3/114 (2.6%) | NR |
| Moreno-Jiménez et al, 2006[63] | Not USA | LINAC | Single-session | No | 2003-2003 | NR | 3/40 (7.5%) | 2/40 (5.0%) |
| Izawa et al, 2005[64] | Not USA | GK | Single-session | No | 1991-2002 | 9/237 (3.8%) | NR | NR |
| Chang et al, 2004[65] | Not USA | LINAC | Single-session | No | NR | 20/67 (29.9%) | NR | NR |
| | Not USA | LINAC | Dose-staged | No | NR | 19/67 (28.4%) | NR | NR |
| Levegrün et al, 2004[66] | Not USA | LINAC | Single-session | No | 1993-1998 | 58/73 (79.5%) | NR | NR |
| Maity et al, 2004[67] | USA | LINAC | Single-session | Yes | 1994-2002 | NR | 3/17 (17.6%) | 2/17 (11.8%) |
| Veznedaroglu et al, 2004[36,f] | USA | LINAC | Dose-staged | No | NR | 6/7 (85.7%) | 3/7 (42.9%) | 1/7 (14.3%) |
| [f] | USA | LINAC | Dose-staged | No | NR | 7/23 (30.4%) | 3/23 (13.0%) | 2/23 (8.7%) |
| Nataf et al, 2003[68] | Not USA | LINAC | Single-session | Yes | 1984-2000 | 16/29 (55.2%) | NR | NR |
| Pollock et al, 2003[69] | USA | GK | Single-session | No | 1990-1997 | NR | 5/144 (3.5%) | NR |

**TABLE 1. Continued**

| Authors and year | Category: Location of study | Type of SRS | SRS approach | Pediatric study | Year | Radiologic RIC | Symptomatic RIC | Permanent RIC |
|---|---|---|---|---|---|---|---|---|
| Schlienger et al, 2003[70] | Not USA | LINAC | Repeat | No | 1986-2000 | 13/18 (72.2%) | NR | NR |
| Shin et al, 2002[71] | Not USA | GK | Single-session | Yes | 1990-2000 | 28/100 (28.0%) | NR | NR |
| Smyth et al, 2002[72,g] | USA | GK | Single-session, volume-staged | Yes | 1991-1997 | 10/27 (37.0%) | 2/31 (6.5%) | 0/31 (0.0%) |
| Schlienger et al, 2000[1] | Not USA | LINAC | Single-session | No | 1990-1993 | NR | 3/169 (1.8%) | 2/169 (1.2%) |
| Zhou et al, 2000[73,h] | Not USA | GK | Single-session, dose-staged, volume-staged | No | 1996-2000 | 19/87 (21.8%) | NR | 0/132 (0.0%) |
| Miyawaki et al, 1999[33,i] | USA | LINAC | Single-session, volume-staged | No | 1988-1991 | 33/67 (49.3%) | 16/73 (21.9%) | NR |
| Voges et al, 1997[74] | Not USA | LINAC | Single-session | No | 1990-1995 | 22/81 (27.2%) | 13/81 (16.0%) | 7/81 (8.6%) |
| Aoki et al, 1996[21] | Not USA | GK | Single-session | No | 1990-1994 | NR | 24/236 (10.2%) | 10/236 (4.2%) |
| Morikawa et al, 1996[34] | USA | GK | Single-session | No | NR | 8/14 (57.1%) | NR | NR |
| Tanaka et al, 1996[75] | Not USA | GK | Single-session | No | 1991-1994 | NR | 2/76 (2.6%) | NR |
| | Not USA | GK | Single-session | Yes | 1991-1994 | NR | 0/23 (0.0%) | NR |
| Friedman and Bova, 1992[76] | USA | LINAC | Single-session | No | 1988-1991 | NR | 4/80 (5.0%) | 2/80 (2.5%) |
| Loeffler et al, 1990[77] | USA | LINAC | Single-session | Yes | 1986-1988 | 3/10 (30.0%) | 1/10 (10.0%) | 0/10 (0.0%) |

GK, Gamma Knife; LINAC: linear accelerator; NR, not reported; RIC, radiation-induced complication; SRS, stereotactic radiosurgery.
[a]One patient in the upper series had a volume-staged procedure; 22 patients in the lower series had volume-staged procedures.
[b]Upper series represents the subset of patients who underwent draining vein shielding, whereas the lower series did not receive draining vein shielding.
[c]Nine patients were treated with volume-staged SRS.
[d]Two patients were treated with volume-staged SRS.
[e]Upper series represents the subset of patients with basal ganglia AVMs, whereas the lower series represents all other locations.
[f]Upper series represents the subset of patients who received higher treatment dosage (42Gy in 6 sessions), whereas the lower series represents lower dosage (30 Gy in 6 sessions).
[g]Two patients were treated with volume-staged SRS.
[h]Two patients were treated with dose-staged SRS; 1 patient was treated with volume-staged SRS.
[i]Two patients were treated with volume-staged SRS.

## Radiologic, Symptomatic, and Permanent RIC

The overall rates of radiologic, symptomatic, and permanent RIC were 35.5%, 9.2%, and 3.8%, respectively (Table 2). In the subgroup of radiologic RIC, the rates were 34.8% in USA studies, 32.8% in pediatric patients, 33.9% in patients treated with GK-based SRS, and 43.5% in those treated with LINAC-based SRS. In the subgroup of symptomatic RIC, the rates were 8.5% in USA studies, 7.0% in pediatric patients, 8.3% in patients treated with GK-based SRS, and 13.5% in those treated with LINAC-based SRS. In the subgroup of permanent RIC, the rates were 3.1% in USA studies, 3.2% in pediatric patients, 3.5% in patients treated with GK-based SRS, and 6.2% in those treated with LINAC-based SRS. Median time to radiologic and symptomatic RIC formation following SRS ranged from 12 to 13 mo and from 6 to 25 mo, respectively.

Of the 141 patients with symptomatic RIC in whom the specific neurological symptoms were detailed (Figure 2), 69 had hemiparesis (48.9%), 23 had headache (16.3%), 17 had seizures (12.1%), 10 had sensory dysfunction (7.1%), and 5 had ataxia (3.5%). Of the 70 patients with permanent RIC in whom the specific neurological symptoms were described, 37 had hemiparesis (52.9%), 20 had visual field deficits (28.6%), 9 had diplopia (12.9%), 4 had seizures (5.7%), and 3 each had ataxia and sensory dysfunction (4.3%). Among the 4 studies that reported the development of hydrocephalus after SRS, this occurred in 0.5% (5/954 patients). Two of these patients died from acute hydrocephalus, whereas the other 3 underwent cerebrospinal fluid diversion with ventriculoperitoneal shunt placement.

In the meta-analysis for radiologic RIC (Figure 3A), ruptured AVMs were significantly less likely to develop radiologic RIC (OR = 0.57 [0.47-0.69], $P < .001$), whereas patients treated with repeat SRS were significantly more likely to develop RIC, compared to those treated with SS-SRS (OR = 6.19 [2.42-15.85], $P < .001$). In the meta-analysis for symptomatic RIC (Figure 3B), patients with superficially located AVMs were significantly less likely to experience symptomatic RIC (OR = 0.38 [0.21-0.67] $P < .001$). In the meta-analysis for permanent RIC

**TABLE 2. Summary of the Overall Patient Demographics, AVM Features, Treatment Parameters, and SRS Outcomes From the 51 Included Studies**

| Summary statistic | Frequency or range |
|---|---|
| **Demographics** | |
| Total no. of patients | 6779 |
| USA | 3413/6779 (50.3%) |
| Female | 2662/5793 (46.0%) |
| Pediatric | 698/6779 (10.3%) |
| Med age (years) | 9.5-43.8 |
| **AVM features** | |
| Med volume ($cm^3$)[a] | 1.2-38.0 |
| Prior rupture | 3052/6084 (50.2%) |
| Prior embolization | 1187/5828 (20.4%) |
| SM grade | |
| I | 653/4639 (14.1%) |
| II | 1300/4664 (27.9%) |
| III | 2110/4919 (42.9%) |
| IV | 648/4919 (13.2%) |
| V | 89/4919 (1.8%) |
| VI | 57/4994 (1.1%) |
| Location | |
| Lobar | 2407/4235 (56.8%) |
| Cerebellum | 265/4283 (6.2%) |
| Corpus callosum | 168/4179 (4.0%) |
| BG or thalamus | 669/4179 (16.0%) |
| Peri-/intraventricular | 49/2753 (1.8%) |
| Brainstem | 271/4179 (6.5%) |
| **Treatment** | |
| SRS device | |
| GKRS | 5646/6779 (83.3%) |
| LINAC-based | 1133/6779 (16.7%) |
| SRS approach | |
| SS-SRS | 4278/6779 (63.1%) |
| DS-SRS | 158/6779 (2.3%) |
| VS-SRS | 167/6779 (2.5%) |
| Repeat SRS | 648/4522 (14.3%) |
| Med marginal dose (Gy)[a] | 15.0-25.9 |
| Med maximum dose (Gy)[a] | 18.0-46.9 |
| Med isodose line (%)[a] | 40%-89% |
| Med follow-up | |
| Clinical (months)[a] | 7-187 |
| Radiological (months)[a] | 5-103 |
| **Outcome** | |
| RIC | |
| Radiologic | 1143/3222 (35.5%) |
| Symptomatic | 499/5447 (9.2%) |
| Permanent | 202/5272 (3.8%) |
| Complete obliteration | |
| Overall | 2822/4385 (64.4%) |
| Angiographic | 1066/1972 (54.1%) |
| Median time to obliteration (months)[a] | 11.7-50 |
| Other complications | |
| Hemorrhage | 206/2959 (7.0%) |
| Death | |
| Overall | 82/2150 (3.8%) |
| AVM-related | 42/1814 (2.3%) |

Med, median; SM, Spetzler-Martin; BG, basal ganglia; SRS, stereotactic radiosurgery; SS-SRS, single-session SRS; GK: Gamma Knife; LINAC, linear accelerator-based SRS; VS-SRS, volume-staged SRS; DS-SRS, dose-staged SRS; RIC, radiation-induced change; AVM, arteriovenous malformation.
[a]Mean reported when median not available.

(Figure 3C), no factors were found to be associated with experiencing RIC.

## DISCUSSION

### Pathophysiology of RIC Development

RICs are the most frequently observed complication following AVM intervention with SRS, with a time course that generally precedes the other beneficial (ie, obliteration) and harmful (ie, post-SRS hemorrhage, cyst formation) sequelae of SRS treatment.[23,78] The pathophysiology of RIC remains incompletely understood, although several mechanisms have been posited. The classic radiologic appearance of RIC as perinidal T2 hyperintensity on follow-up MRIs may be a product of blood–brain barrier disruption and the ensuing cerebral edema.[3,23] RIC has been associated with SRS-induced obliteration, suggesting that the cellular changes underlying these parallel processes may overlap.[19] SRS achieves AVM obliteration by inducing vascular endothelial damage, which promotes smooth muscle cell proliferation, extracellular collagen formation, and intravascular thrombosis, and progressive arterial and venous stenosis.[79] These same mechanisms can incur perinidal edema, particularly when the venous component is preferentially affected.[80] Therefore, RIC may be a precursor to obliteration, although obliteration is not uniformly achieved in all patients who develop RIC. A better understanding of the pathophysiology of RIC and an ability to modulate its effects could help to improve SRS outcomes for AVM patients.

In addition to favorable outcomes, RIC has also been associated with late complications after AVM SRS, such as cyst formation.[81] Post-SRS cysts typically develop within or adjacent to the site of the original AVM nidus, several years after treatment, and are believed to be related to the formation of telangiectatic perinidal vessels.[78] These fragile vessels are prone to rupture, which promotes serum and protein exudation, edema, cyst formation,

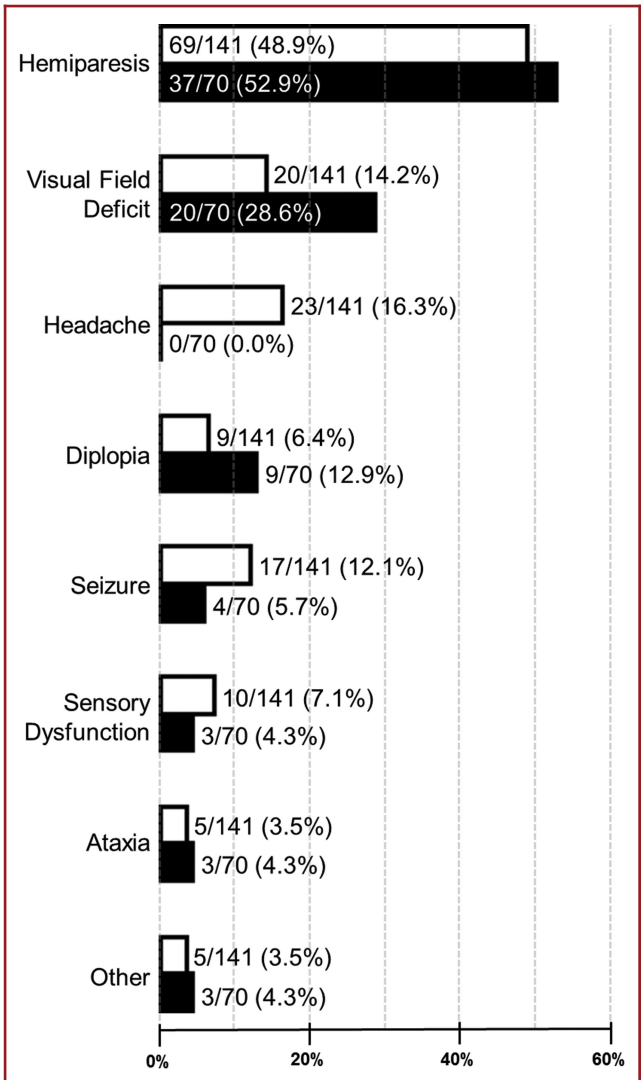


**FIGURE 2.** *Bar graph of incidence of various symptoms in patients with symptomatic (white) and permanent RICs (black). One patient each in the former cohort presented with short-term memory loss and dysphagia. Two patients in the latter cohort presented with aphasia while 1 patient presented with altered mental status.*

and encapsulating hematoma formation. Early complications, such as RIC, may prime the parenchyma surrounding the AVM to the subsequent development of delayed adverse radiation effects. Radiation necrosis represents a severe manifestation of RIC and has been associated with a variety of molecular factors, including the release of inflammatory mediators secondary to brain tissue and vascular endothelial damage, direct glial injury, and perivascular lymphocyte infiltration.[26,82-85]

## RIC Incidence

In our systematic review, the overall rates of radiologic, symptomatic, and permanent RIC following SRS for AVMs were 35.5%, 9.2%, and 3.8%, respectively. Although the strict definition of RIC varied slight across the included studies, in general, RIC includes radiation necrosis, but not post-SRS cyst formation or SRS-induced cavernoma formation.[86] Amongst the studies included in the present systematic review, the rates of radiation necrosis, cyst formation, and cavernoma formation after SRS were 2.9% (40/1360 patients, 15 studies), 3.2% (35/1081 patients, 17 studies), and 2.0% (1/51 patients, one study), respectively. Although there may be an association between RIC and cyst formation, these are 2 radiologically and clinically distinct SRS-induced complications. We recently published a systematic review specifically assessing cyst formation after AVM SRS.[87] We found that the overall incidence of post-SRS cyst formation was 3.0%, with a mean latency period of 78 mo. In general, enlarging or symptomatic cyst underwent surgical intervention, including stereotactic aspiration or craniotomy for lesion resection. In our prior analysis, 33% of post-SRS cyst patients underwent surgical intervention, whereas the remaining 67% were managed conservatively.[87]

There was consistent correlation between RIC risk with larger AVM volume and increasing SRS margin dose among individual analyses.[3,18,19,24,25,28,29,32-40] Recently, Kano et al[3] assessed 755 AVM patients who underwent SS-SRS with ≥2 yr of follow-up, and reported symptomatic and permanent RIC rates of 7% and 3%, respectively. AVM location in the brainstem or thalamus, larger AVM volume and 12-Gy volume, higher margin dose, higher SM grade, and higher RBAS were found to be risk factors for symptomatic RIC. However, in our meta-analyses, neither nidus volume nor margin dose was significantly associated with radiologic or symptomatic RIC. We believe that this is due to (1) lack of individual patient data, (2) differences in the selection of AVM patients for treatment with SRS among the included studies, and (3) variations in SRS devices, techniques, and treatment paradigms among studies; the combination of these factors precluded a sufficiently rigorous analysis of the relationship among nidus volume, margin dose, and RIC.

Although SM grade is an important predictor of radiosurgical outcome, there was an insufficient number of studies to evaluate for an association between SM grade and symptomatic or permanent RIC in our meta-analysis. None of the 5 included studies showed an association between SM grade and radiologic RIC. However, there was significant variation among these studies; 3 were GK (Elekta) SRS studies, while the other 2 were LINAC-based SRS studies, 2 were pediatric studies, 1 each was a DS, VS, and repeat SRS study. In addition to this variability, differences in treatment plans likely accounted for SM grade by lowering treatment doses for higher grade AVMs, which complicates the relationship between SM grade and RIC.

Prior embolization has been shown to adversely affect SRS outcome in prior studies, although the effect of prior embolization remains controversial.[88-90] We did not find an association of embolization with RIC development in the meta-analysis. The majority of the included studies did not report the mean time interval between embolization and SRS. The effect of

**A**

| No. Studies | Radiologic RIC Rate | | Meta-Analysis OR (95% CI) | OR (95% CI) | *P*-value | Heterogeneity | |
|---|---|---|---|---|---|---|---|
| | A | B | 0.01 0.1 1.0 10 100 | | | $I^2$ | $\chi^2$ |
| 7 (1,607 pts) | Male Sex | Female Sex | | 1.03 (0.83-1.27) | 0.79 | 0% | 4.79 (p=0.57) |
| 5 (72 pts) | Spetzler-Martin Grade (*continuous*) | | | 0.97 (0.57-1.67) | 0.92 | 0% | 2.9 (p=0.58) |
| 8 (1,934 pts) | Nidus Volume (*continuous*) | | | 1.16 (0.95-1.40) | 0.14 | 74% | 26.7 (p=0.0004) |
| 6 (220 pts) | Age (*continuous*) | | | 1.02 (0.98-1.06) | 0.41 | 0% | 3.81 (p=0.58) |
| 6 (1,732 pts) | No Prior Embolization | Prior Embolization | | 1.10 (0.87-1.38) | 0.43 | 0% | 3.49 (p=0.62) |
| 8 (1,927 pts) | Unruptured | Ruptured | | 0.57 (0.47-0.69) | **<0.0001** | 0% | 2.39 (p=0.94) |
| 6 (174 pts) | Deep Location | Superficial Location | | 0.78 (0.35-1.72) | 0.54 | 0% | 2.6 (p=0.76) |
| 8 (1,764 pts) | Margin Dose (*continuous*) | | | 0.98 (0.93-1.03) | 0.33 | 0% | 7.49 (p=0.38) |
| 4 (181 pts) | SS-RS | Repeat SRS | | 6.19 (2.42-15.85) | **0.0001** | 0% | 0.64 (p=0.73) |
| 7 (184 pts) | Non-Obliterated | Obliterated | | 1.30 (0.64-2.64) | 0.46 | 0% | 2.02 (p=0.92) |
| | | | A B | | | | |

**B**

| No. Studies | Symptomatic RIC Rate | | Meta-Analysis OR (95% CI) | OR (95% CI) | *P*-value | Heterogeneity | |
|---|---|---|---|---|---|---|---|
| | A | B | 0.01 0.1 1.0 10 100 | | | $I^2$ | $\chi^2$ |
| 11 (2,612 pts) | Nidus Volume (*continuous*) | | | 1.07 (0.97-1.19) | 0.20 | 70% | 33.35 (p=0.0002) |
| 6 (1,000 pts) | Age (*continuous*) | | | 0.99 (0.94-1.06) | 0.87 | 46% | 9.24 (p=0.1) |
| 7 (2,280 pts) | No Prior Embolization | Prior Embolization | | 0.77 (0.57-1.05) | 0.10 | 32% | 8.88 (p=0.18) |
| 9 (2,526 pts) | Unruptured | Ruptured | | 0.55 (0.29-1.03) | 0.06 | 57% | 18.42 (p=0.02) |
| 7 (1,270 pts) | Deep Location | Superficial Location | | 0.38 (0.21-0.67) | **0.0009** | 11% | 6.71 (p=0.35) |
| 6 (2,406 pts) | Margin Dose (*continuous*) | | | 0.94 (0.83-1.07) | 0.35 | 58% | 11.86 (p=0.04) |
| 4 (324 pts) | SS-SRS | Repeat SRS | | 1.73 (0.73-4.14) | 0.21 | 0% | 1.93 (p=0.59) |
| 4 (81 pts) | Non-Obliterated | Obliterated | | 1.19 (0.28-5.01) | 0.81 | 0% | 0.89 (p=0.83) |
| | | | A B | | | | |

**C**

| No. Studies | Permanent RIC Rate | | Meta-Analysis OR (95% CI) | OR (95% CI) | *P*-value | Heterogeneity | |
|---|---|---|---|---|---|---|---|
| | A | B | 0.01 0.1 1.0 10 100 | | | $I^2$ | $\chi^2$ |
| 5 (1,186 pts) | Nidus Volume (*continuous*) | | | 1.02 (0.96-1.09) | 0.53 | 58% | 9.44 (p=0.05) |
| 4 (1,171 pts) | Age (*continuous*) | | | 1.01 (0.98-1.04) | 0.60 | 6% | 3.21 (p=0.36) |
| 5 (1,186 pts) | No Prior Embolization | Prior Embolization | | 0.80 (0.53-1.21) | 0.29 | 0% | 3.04 (p=0.55) |
| 5 (1,186 pts) | Unruptured | Ruptured | | 1.13 (0.78-1.62) | 0.52 | 7% | 4.3 (p=0.37) |
| | | | A B | | | | |

**FIGURE 3.** *Summary of the meta-analysis for the association of various factors with development of* **A** *radiologic,* **B** *symptomatic, and* **C** *permanent RICs. Superficial locations: lobar and cerebellum; deep locations: corpus callosum, basal ganglia or thalamus, periventricular, and brainstem.*

pre-embolization on SRS outcomes remains controversial. In a recent matched cohort study, we did not find pre-SRS embolization to be negatively associated with obliteration in the multivariate analysis.[90] In addition, most studies that analyze the relationship between prior embolization and SRS outcomes do not evaluate the AVM's original angioarchitectural features prior to embolization, but instead focus on the postembolization nidal characteristics. We also found that AVM angioarchitectural complexity, approximated as the sum of the major feeding arteries and draining veins, confounded the interaction between pre-SRS embolization and obliteration.[90] In the same study, we found that prior embolization was a negative independent predictor of radiologic RIC, which suggests that the embolic cast may shield the surrounding brain parenchyma from adverse radiation effects.[90] This potentially protective effect of embolization against SRS-induced complications may serve to partially offset the procedural complications of upfront nidal devascularization. Thus, the relationship between AVM embolization and post-SRS outcomes is multifactorial and complex. Further investigation of embolization effects on RIC formation is warranted in a prospective or controlled fashion.[91]

We found lack of prior AVM hemorrhage ($P < .001$) and treatment with SS-SRS (compared to repeat SRS; $P < .001$) to be significantly associated with radiologic RIC in our meta-analysis. Taken together, these findings suggest that perinidal gliosis, resulting from either AVM rupture or irradiation, may be protective against the development of RIC, which has been shown in prior studies.[38,39,92] Alternatively, fluid-filled space created by the hemorrhage may be inherently protective against RIC.[93] Unfortunately, neither of these hypotheses could be tested in the present review, given the absence of individual patient pathology data. The RIC rates for repeat SRS could also be due to the potentially smaller volumes of residual AVMs vs the larger AVM volumes treated with initial SRS, the difference in which we were unable to control for in the meta-analyses.[94,95] The higher complication rate for SRS of unruptured AVMs should be considered within the context of the management of these patients, which is currently the subject of some debate.[96-100]

Factors such as the geographic location of treatment, patient age, and SRS device, approach, and era of treatment may affect RIC rates, but they were not found to be significant in our meta-analyses. Differences in RIC rates between USA and non-USA studies may be a product of earlier adoption of newer SRS technologies in the USA.[31,101,102] Our findings also indicate that RIC rates may be higher with LINAC-based vs GK SRS. This finding should be interpreted with caution, since none of the included studies made direct comparisons of RIC rates between the 2 modalities; hence, the comparative effectiveness of LINAC-based vs GK SRS for AVMs could not be analyzed in our meta-analysis. Additionally, there were at least 5 times more patients treated with GK compared to LINAC-based SRS in each of radiologic, symptomatic, and permanent RIC subsets of studies. Pediatric patients appeared to have a slightly lower risk of RIC than adults, which is consistent with prior studies.[38,75] We found in single-center, matched cohort studies that prior intervention, either partial resection or embolization, was significantly associated with a lower likelihood of RIC.[7,90] Although the mechanisms for the reduced risk of RIC in previously treated AVMs have not been delineated, we posit that adjacent normal brain parenchyma may be partially shielded from radiation by postoperative gliosis or an embolic cast.[83,103]

## Management of Symptomatic RIC

The most common management of symptomatic RIC is medical therapy with corticosteroids, which may be administered for short (approximately 2 wk) or longer (2-3 mo) courses, depending on the severity and duration of symptoms.[22,26,36,43,45,65,80,82,104] Other medical therapies consist of glycerol infusions, bevacizumab, pentoxifylline, and vitamin E, although these are not routinely used and their efficacy is predominantly anecdotal.[3,22,43,44,54,65,82] Patients who develop new or worsening seizures related to RIC should be initiated on anticonvulsant therapy, or have their pre-existing regimen adjusted in collaboration with an epileptologist.[8,97,105,106]

Although medical therapy alone is sufficient for the vast majority of SRS-treated AVM patients who develop RIC, surgical intervention may be necessary in a few select cases. Cerebrospinal fluid shunting may be required for patients who develop significant post-treatment edema causing ventricular effacement and obstruction with resultant hydrocephalus.[3] Massengale et al[26] evaluated the outcomes of 7 AVM patients who underwent surgical resection of symptomatic radiation necrosis after SRS. Patients with large regions (diameter $\geq$ 4 cm) of suspected radiation necrosis had longer intervals between resection and symptomatic improvement compared to those with smaller regions (diameter $<$ 4 cm) of radiation necrosis (interval $>$ 9 mo vs $\leq$ 2 mo, respectively). The Karnofsky Performance Scale (KPS) improved after resection in patients with a preoperative KPS $\leq$ 50, but failed to improve in those with a preoperative KPS $>$ 70. Postoperative outcomes were not affected by AVM characteristics or SRS treatment parameters.[26]

## Limitations

Since this systematic review pooled data available largely from retrospective, single-center studies, our findings are subject to the selection, treatment, and referral biases which are inherent to their designs. We acknowledge the potential for heterogeneity among the studies included in the meta-analyses, and as such, have quantified the heterogeneities using the $I^2$ and chi-squared statistics. Specifically, variations in the ratios of ruptured to unruptured AVMs, deep-seated to superficially located nidi, and SS-SRS to repeat SRS treatment approaches in each study may have significantly affected the respective stratifications of RIC rate. Additionally, given the delay between the SRS procedure and the onset of RIC, variability in follow-up durations after SRS may affect our pooled estimates of RIC rates. Furthermore, the lack

of sufficient granularity with respect to individual patient data precluded a time-dependent analysis of RIC development.

Due to the lack of detailed neuroimaging data, we were unable to radiologically classify the severity of RIC and correlate it with the likelihood of associated neurological symptoms.[51] Unfortunately, a rigorous assessment of SRS-induced cavernoma formation is beyond the scope of this review. Of studies included the present analysis, only 1 patient in 1 study developed a cavernoma after AVM SRS. Therefore, we were unable to determine the incidence, latency period, and management of SRS-induced cavernomas. Due to the lack of detailed clinical follow-up, we were unable to ascertain the effect of symptomatic RIC on functional outcomes after AVM SRS. The safety, efficacy, and durability of the medical and surgical management options for symptomatic RIC were also unable to be determined.

## CONCLUSION

RICs are the most common adverse effect of SRS for the management of AVMs, and it is radiologically evident in approximately one-third of cases. Most patients with radiologic RIC do not suffer neurological sequelae, and permanent deficits secondary to RIC are uncommon. Unruptured AVM and repeat SRS-treated patients were more likely to have radiologic RIC, whereas those with deep-seated AVMs were more prone to developing symptomatic RIC.

### Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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## COMMENT

This paper is a literature review whose goal was to define the rate of radiation-induced changes and related deficits after SRS for patients with AVMs The English-language literature was searched for papers reporting results on at least 10 patients. Fifty-one papers were identified that included 6779 patients with AVMs who were treated with SRS.

Results found that patients having repeat SRS were more likely to have radiologic RIC, and those with deep-seated targets more likely to have symptomatic RIC. Neither of these conclusions is at all surprising. Patients with ruptured AVMs were less likely to develop radiologic RIC, and the authors suggest that "perinidal gliosis", or a small layer of fluid around the AVM, may be protective.

The authors found that 3.8% of the reported patients sustained a permanent RIC. For this group with a very difficult problem to treat having 24/25 patients without any long-term problems from SRS sounds pretty good. The conclusion one may draw from this review is that for patients with brainstem AVMs, and for sure those that have bled, SRS is a safe treatment method.

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