Cyst formation after stereotactic radiosurgery for brain arteriovenous malformations: a systematic review

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OBJECTIVE Cyst formation can occasionally occur after stereotactic radiosurgery (SRS) for brain arteriovenous malformations (AVMs). Given the limited data regarding post-SRS cyst formation in patients with AVM, the time course, natural history, and management of this delayed complication are poorly defined. The aim of this systematic review was to determine the incidence, time course, and optimal management of cyst formation after SRS for AVMs.

METHODS A literature review was performed using PubMed to identify studies reporting cyst formation in AVM patients treated with SRS. Baseline and outcomes data, including the incidence and management of post-SRS cysts, were extracted from each study that reported follow-up duration. The mean time to cyst formation was calculated from the subset of studies that reported individual patient data.

RESULTS Based on pooled data from 22 studies comprising the incidence analysis, the overall rate of post-SRS cyst formation was 3.0% (78/2619 patients). Among the 26 post-SRS cyst patients with available AVM obliteration data, nidus obliteration was achieved in 20 (76.9%). Of the 64 cyst patients with available symptomatology and management data, 21 (32.8%) were symptomatic; 21 cysts (32.8%) were treated with surgical intervention, whereas the remaining 43 (67.2%) were managed conservatively. Based on a subset of 19 studies reporting individual time-to-cyst-formation data from 63 patients, the mean latency period to post-SRS cyst formation was 78 months (6.5 years).

CONCLUSIONS Cyst formation is an uncommon complication after SRS for AVMs, with a relatively long latency period. The majority of post-SRS cysts are asymptomatic and can be managed conservatively, although enlarging or symptomatic cysts may require surgical intervention. Long-term follow-up of AVM patients is crucial to the appropriate diagnosis and management of post-SRS cysts.

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KEY WORDS cyst; stereotactic radiosurgery; arteriovenous malformation; complication; incidence

STEREOTACTIC radiosurgery (SRS) is widely used as a treatment option for brain arteriovenous malformations (AVMs), particularly for small- to moderate-sized nodi located in deep or eloquent brain areas associated with an elevated surgical risk.^{10,11,16,25,49,60} Cyst formation after SRS for AVM is an uncommon, delayed complication, which can become symptomatic and necessitate surgical intervention.^{34,42,54,55,63,64} The current literature on post-SRS cyst formation in AVM patients is limited by a paucity of studies reporting the incidence of cyst

formation, the prolonged temporal relationship between SRS and cyst formation, and the clinical manifestations and management of post-SRS cysts.^{4,7,8,14,22,27,28,32,35–37,41,42,54,63,64,69} Additionally, there is considerable variation in the data regarding cyst formation because of differences in baseline patient and AVM characteristics, SRS modalities and treatment strategies, follow-up durations, and reporting of radiological and clinical end points.^{4,30,35,44,54} Overlap of study cohorts further confounds our ability to ascertain meaningful relationships between preoperative

ABBREVIATIONS AVM = arteriovenous malformation; GKRS = Gamma Knife radiosurgery; LINAC = linear accelerator; RIC = radiation-induced change; SRS = stereotactic radiosurgery.

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factors and post-SRS cyst formation.^{26,34,54} Therefore, the aims of this systematic review were to 1) quantify the incidence of cyst formation after SRS for AVM, 2) determine the latency period between AVM SRS and cyst formation, and 3) evaluate the management options for post-SRS cysts in AVM patients.

Methods

Literature Search and Inclusion Criteria

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 using PubMed on September 1, 2016, with the following search phrase: “arteriovenous malformations AND radiosurgery AND cyst.” The studies were screened by title and abstract to ascertain fulfillment of inclusion criteria, which were as follows: 1) number of AVM patients who developed a cyst after SRS was reported; 2) each patient with a post-SRS cyst was represented only once among all of the studies included for analysis; 3) size of the overall cohort of AVM patients treated with SRS was reported; 4) patients were treated with SRS using the Gamma Knife (GKRS), linear accelerator (LINAC), or proton beam systems, in a single session or a dose- or volume-staged approach; 5) follow-up duration after SRS was reported; and 6) study was written in English. To meet the aforementioned inclusion criteria, only the most recent study with the greatest number of patients diagnosed with post-SRS cysts was used from a set of overlapping studies.

Data Extraction

Patient demographics, AVM characteristics, SRS treatment parameters, and outcome and complication data were extracted from each of the eligible studies. Demographic data included the number of AVM patients treated with SRS, sex, age, and follow-up duration. Arteriovenous malformation characteristics included nidus volume, prior AVM hemorrhage, and prior nidus embolization. Stereotactic radiosurgery treatment parameters included margin dose, maximum dose, and isodose line. Outcome and complication data included AVM obliteration, time to obliteration, post-SRS cyst formation, latency period between SRS and cyst formation, symptomatic radiation-induced changes (RICs), post-SRS hemorrhage, and death. Radiation-induced changes were defined as perinidal T2-weighted hyperintensities on follow-up MRI, and only clinically symptomatic RICs were recorded from each study. For those patients who developed post-SRS cysts, data regarding the time interval between SRS and cyst formation, association with complete nidus obliteration, presence or absence of symptoms associated with the cyst, and management of the cyst were recorded, when available. We defined post-SRS cyst formation as the de novo development of a fluid-filled, proteinaceous, and/or hemorrhagic sac within or adjacent to the site of the original AVM nidus.

Statistical Analysis

All statistical analyses were performed using MATLAB

(version R2016a, MathWorks). For studies included in the analysis of cyst incidence, descriptive statistics were calculated for baseline and post-SRS outcomes data. Post-SRS cyst data were pooled from all eligible studies for the calculation of cyst incidence. The incidence of cyst formation was calculated by dividing the total number of AVM patients who developed a cyst after SRS by the total number of AVM patients treated with SRS. For the studies with individual patient data regarding the time interval between SRS and cyst formation, the mean latency period to cyst formation was calculated.

Results

Study Selection

The literature search yielded a total of 59 studies, from which 52 were selected based on title and abstract; 20 studies were then eliminated based on a failure to meet the inclusion criteria, yielding 32 studies eligible for at least one analysis. Of the 32 eligible studies, 22 studies reported sufficient data to allow inclusion in the analysis for post-SRS cyst incidence, and 19 studies reported sufficient data to allow inclusion in the analysis for latency period to cyst formation (Fig. 1).

Overall Demographic and Treatment Characteristics

Table 1 summarizes the patient, AVM, and treatment characteristics of the 22 studies, comprising a total of 2619 AVM patients treated with SRS, which were included in the cyst incidence analysis. The frequency of the female sex was 46.8% (962/2053 patients). The median age ranged from 12 to 46 years. The median AVM volume ranged from 1.4 to 48.8 cm³. Prior AVM hemorrhage had occurred in 41.8% of patients (920/2200), and the proportion of ruptured AVMs ranged from 0% to 83.3%, among the studies. Prior embolization had been performed in 21.6% of patients (462/2135 patients), and the proportion of embolized AVMs ranged from 0% to 100.0%.

Gamma Knife radiosurgery was exclusively used in 20 studies (90.9%), and LINAC was exclusively used in 2 studies (9.1%). Volume-staged SRS was used in 1 study, dose-staged or hypofractionated SRS was used in 1 study, and repeat SRS was used in 2 studies. The median margin and maximum doses ranged from 16 to 24 Gy and 28 to 44 Gy, respectively. The median isodose line ranged from 50% to 80%. The median follow-up duration of all SRS-treated AVM patients in each cohort ranged from 31 to 199 months (2.6–16.6 years).

Cyst Formation Incidence, Latency, and Management

The data regarding post-SRS cyst formation are summarized in Table 2. The mean incidence of cyst formation for all studies was 4.4% (95% CI 2.0%–6.8%). Cyst formation rates were 4.1% (95% CI 1.5%–6.7%) in the 20 studies using GKRS, compared with 6.9% (95% CI 6.4%–7.4%) in the 2 studies using LINAC. Based on pooled data, the incidence of post-SRS cyst formation was 3.0% (78/2619 patients) for all studies. The pooled rates of cyst formation were 2.9% (74/2562 patients) in the studies using GKRS and 7.0% (4/57 patients) in the studies using LINAC. Of the 26 post-SRS cysts for which AVM oblit-

FIG. 1. Flow diagram showing the selection process for studies included in analyses of cyst incidence and latency period.

eration data were available, 76.9% (20/26) were associated with complete nidus obliteration. Of 64 post-SRS cysts for which the symptomatology and management data were reported, 32.8% (21/64) were symptomatic. Of these 64 cysts, 16 cases (25.0%) underwent craniotomy for cyst resection, 4 (6.2%) underwent stereotactic decompression, 3 (4.7%) underwent cystoperitoneal shunt placement, and 1 (1.6%) underwent Ommaya reservoir placement. In total, 21 patients underwent surgical intervention (32.8%), and the remaining 43 (67.2%) were managed conservatively. Specific symptoms were attributed to 6 post-SRS cysts and included seizures (3 [50.0%] of 6 cysts), hemiparesis (2 [33.3%] of 6 cysts), psychological changes (1 [16.7%] of 6 cysts), aphasia (1 [16.7%] of 6 cysts), headache (1 [16.7%] of 6 cysts), and death secondary to status epilepticus (1 [16.7%] of 6 cysts).

Table 3 summarizes the time-to-cyst-formation data from the 19 studies that reported individual patient data, comprising a total of 63 patients with post-SRS cysts. The mean latency period between SRS and cyst formation was 78 months (6.5 years), and individual latency periods ranged from 6 to 240 months (0.5–12.0 years). Figure 2 is a histogram of the incidence of cyst formation in these 63 patients.

Obliteration and Complication Rates

The posttreatment data from the 21 studies included

in the cyst incidence analysis are summarized in Table 2. The mean complete AVM obliteration rate was 65.4% (95% CI 56.3%–74.6%). Based on pooled data, obliteration was achieved in 65.5% (1450/2215 patients). The median time to obliteration ranged from 2.5 to 8.3 years. The mean rates of symptomatic RIC, post-SRS hemorrhage, and mortality were 8.5% (95% CI 4.9%–12.0%), 13.2% (95% CI 3.3%–23.2%), and 6.9% (95% CI 4.1%–9.8%), respectively. Based on pooled data, the rates of symptomatic RIC, post-SRS hemorrhage, and mortality were 8.6% (165/1907 patients), 8.8% (191/2162 patients), and 6.0% (92/1542 patients), respectively.

Discussion

Cyst formation following SRS treatment of AVM is one of the least common complications.^{18,24,54,61} Because of its relative rarity and the prolonged follow-up duration necessary to detect its occurrence, the pathobiology, clinical implications, and overall impact of delayed cyst formation on the risk-to-benefit profile of SRS for AVM remain incompletely defined.^{50,58} Given our synthesis of the available literature, we estimate that approximately 3% of AVM patients will develop a cyst after SRS. However, since 70% of post-SRS cysts were asymptomatic, the rate of symptomatic cyst formation after SRS for an AVM may only be 1%.

TABLE 1. Summary of patient and treatment characteristics for the 22 studies included in the analysis of cyst incidence, presented individually and pooled together

Authors & Year	No. of Pts in Study†	No. of Females	Median Age (yrs)†	Median AVM Vol (cm ³)†	No. w/ Previous Hemorrhage	No. w/ Previous Embolization	Treatment Modality§	Median Margin Dose (Gy)†	Median Maximum Dose (Gy)†	Isodose Line	Median FU Duration†
Malikova et al., 2016	35	21/35 (60.0%)	46	2.6	18/35 (51.4%)		GKRS	22	44		199 mos (16.6 yrs)
Nakajima et al., 2016	404			4.4			GKRS	19.1			59 mos (4.9 yrs)
Bir et al., 2015	85	42/85 (49.4%)	41	13.5	26/85 (30.6%)	8/85 (9.4%)	GKRS	18	36	50%	33 mos (2.7 yrs)
Bowden et al., 2014	87	47/87 (54.0%)	38	3.85	40/87 (46.0%)	19/87 (21.8%)	GKRS	20	36		64 mos (5.3 yrs)
Ding et al., 2014 ¹⁸	60	35/60 (58.3%)	34	2.3	44/60 (73.3%)	15/60 (25.0%)	GKRS	22	40.1	50%	39 mos (3.3 yrs)
Ding et al., 2013 ²⁷	444	222/444 (50.0%)	36	3.6	0/444 (0.0%)	122/444 (27.5%)	GKRS	20	40	50%	76 mos (6.3 yrs)
Kano et al., 2012 ³⁵	120	59/120 (49.2%)	33	6.6	64/120 (53.3%)	120/120 (100.0%)	GKRS	18	35.7		70 mos (5.8 yrs)
Kano et al., 2012 ³⁷	135	60/135 (44.4%)	12	2.5	87/135 (64.4%)	25/135 (18.5%)	GKRS	20	40		71 mos (5.9 yrs)
Kano et al., 2012 ⁴⁰	67	25/67 (37.3%)	41	1.4	51/67 (76.1%)	11/67 (16.4%)	GKRS	20	36.4		73 mos (6.1 yrs)
Kano et al., 2012 ³⁶	47	21/47 (44.7%)	33	22	18/47 (38.3%)	21/47 (44.7%)	VS-SRS (GKRS)	16			87 mos (7.3 yrs)
Kano et al., 2012 ³⁸	105	52/105 (49.5%)	31	6.4	43/105 (41.0%)	34/105 (32.4%)	Repeat GKRS	18	35		80 mos (6.7 yrs)
Kano et al., 2012 ⁴¹	217	106/217 (48.8%)	38	2.3	78/217 (35.9%)	0/217 (0.0%)	GKRS	22	40		64 mos (5.3 yrs)
Yen et al., 2011	85	30/85 (35.3%)	33	1.9	54/85 (63.5%)	9/85 (10.6%)	GKRS	19.9	33.9	61%	102 mos (8.5 yrs)
Kim et al., 2010	44	21/44 (47.7%)	27	48.8	24/44 (54.5%)	7/44 (15.9%)	GKRS	13.9	28		109 mos (9.1 yrs)
Yen et al., 2010	186	88/186 (47.3%)	13	3.2	133/186 (71.5%)	38/186 (20.4%)	GKRS	21.9	40.1	56%	80 mos (6.7 yrs)
Buis et al., 2010	15	9/15 (60.0%)	31	4.6		7/15 (46.7%)	Repeat LINAC	18			103 mos (8.6 yrs)
Izawa et al., 2009	15	4/15 (26.7%)	34	9.9	7/15 (46.7%)	15/15 (100.0%)	GKRS	19.9	39.4		79 mos (6.6 yrs)
Maruyama et al., 2006	27	8/27 (29.6%)	37	2.6	16/27 (59.3%)		GKRS	20			70 mos (5.8 yrs)
Izawa et al., 2005	237	93/237 (39.2%)	30	4.7	130/237 (54.9%)	0/237 (0.0%)	GKRS	20.2	42.8		82 mos (6.8 yrs)
Chang et al., 2004	42	19/42 (45.2%)			22/42 (52.4%)	4/42 (9.5%)	SS-SRS & DS-SRS (LINAC)	24.1		80%	31 mos (2.6 yrs)
Pollock et al., 2003	144		36	5.7	50/144 (34.7%)	7/144 (4.9%)	GKRS	18	36		86 mos (7.2 yrs)
Kihlström et al., 1997	18		29	2	15/18 (83.3%)		GKRS				168 mos (14.0 yrs)
Total	2619	962/2053 (46.8%)			920/2200 (41.8%)	462/2135 (21.6%)					
Range	18–444	26.7–60.0%	12–46	1.4–48.8	0.0–83.3%	0.0–100.0%		16–24	28–44	50–80%	31–199 mos (2.6–16.6 yrs)

FU = follow-up; Pt = patient; SS-SRS = single-session SRS; DS-SRS = dose-staged or hypofractionated SRS; VS-SRS = volume-staged SRS.

Blank cells represent data that were not reported.

† Includes patients who were lost to follow-up.

‡ Mean reported when median not available.

§ Data describe the primary treatment modality; salvage therapy is not presented here but included repeat SRS, embolization, and resection.

TABLE 2. Summary of outcomes after SRS, including cyst-specific data, for the 22 studies included in the analysis of cyst incidence, presented individually and pooled together

Authors & Year	Complete Obliteration Rate	Median Time to Complete Obliteration†	RIC Rate	Hemorrhage Rate	Mortality Rate	No. of Cyst-Developing Pts	No. of Prior Obliterations	No. Symptomatic	Symptom	Cyst Management
Malikova et al., 2016	35/35 (100.0%)	43 mos (3.6 yrs)	1/35 (2.9%)			1/35 (2.9%)	1/1 (100.0%)	1/1 (100.0%)	Psy, Sz: 1	Res: 1
Nakajima et al., 2016						18/404 (4.5%)		7/18 (38.9%)		Obs: 10; StD: 1; Res: 7
Bir et al., 2015	67/85 (78.8%)	35 mos (2.9 yrs)	1/85 (1.2%)	5/85 (5.9%)	3/85 (3.5%)	1/85 (1.2%)	0/1 (0.0%)	1/1 (100.0%)	ME: 1	Res: 1
Bowden et al., 2014	43/87 (49.4%)		3/87 (3.4%)	4/87 (4.6%)	6/87 (6.9%)	3/87 (3.4%)		1/3 (33.3%)	ME: 1	Obs: 2; StD: 1
Ding et al., 2014 ¹⁸	43/60 (71.7%)		4/60 (6.7%)	3/60 (5.0%)		0/60 (0.0%)				
Ding et al., 2013 ²⁷	275/444 (61.9%)		61/444 (13.7%)	32/444 (7.2%)		10/444 (2.3%)		0/10 (0.0%)		Obs: 10
Kano et al., 2012 ³⁵	70.8/120 (59.0%)		10/120 (8.3%)	9/120 (7.5%)	13/120 (10.8%)	1/120 (0.8%)	1/1 (100.0%)	1/1 (100.0%)	Aph, HmP: 1	StD: 1
Kano et al., 2012 ³⁷	97.2/135 (72.0%)	71 mos (5.9 yrs)	8/135 (5.9%)	8/135 (5.9%)	4/135 (3.0%)	1/135 (0.7%)		0/1 (0.0%)		Obs: 1
Kano et al., 2012 ⁴⁰	63/67 (94.0%)	40 mos (3.3 yrs)	11/67 (16.4%)	4/67 (6.0%)	10/67 (14.9%)	2/67 (3.0%)	2/2 (100.0%)	0/2 (0.0%)		Obs: 2
Kano et al., 2012 ³⁶	17/47 (36.2%)		3/47 (6.4%)	10/47 (21.3%)	8/47 (17.0%)	0/47 (0.0%)				
Kano et al., 2012 ³⁸	65/105 (61.9%)	39 mos (3.3 yrs)	15/105 (14.3%)	24/105 (22.9%)	9/105 (8.6%)	6/105 (5.7%)		1/6 (16.7%)		Obs: 5; OmR: 1
Kano et al., 2012 ⁴¹	201.8/217 (93.0%)	30 mos (2.5 yrs)	5/217 (2.3%)	13/217 (6.0%)	20/217 (9.2%)	2/217 (0.9%)		1/2 (50.0%)	HmP: 1	Obs: 1; StD: 1
Yen et al., 2011	50/85 (58.8%)	36 mos (3.0 yrs)	10/85 (11.8%)	10/85 (11.8%)	2/85 (2.4%)	1/85 (1.2%)	0/1 (0.0%)	0/1 (0.0%)		Obs: 1
Kim et al., 2010	15/44 (34.1%)			3/44 (6.8%)		2/44 (4.5%)		0/2 (0.0%)		Obs: 2
Yen et al., 2010	109/186 (58.6%)		13/186 (7.0%)	10/186 (5.4%)	0/186 (0.0%)	5/186 (2.7%)				
Buis et al., 2010	9/15 (60.0%)	99 mos (8.3 yrs)	3/15 (20.0%)	0/15 (0.0%)		1/15 (6.7%)	0/1 (0.0%)			
Izawa et al., 2009	10/15 (66.7%)	35 mos (2.9 yrs)	0/15 (0.0%)	0/15 (0.0%)		1/15 (6.7%)	1/1 (100.0%)	1/1 (100.0%)		Res: 1
Maruyama et al., 2006	5/27 (18.5%)			27/27 (100.0%)	1/27 (3.7%)	2/27 (7.4%)	1/2 (50.0%)	1/2 (50.0%)		Obs: 1; Res: 1
Izawa et al., 2005	130/237 (54.9%)			8/237 (3.4%)	3/237 (1.3%)	8/237 (3.4%)	8/8 (100.0%)			
Chang et al., 2004	34.02/42 (81.0%)		12/42 (28.6%)	10/42 (23.8%)		3/42 (7.1%)	1/3 (33.3%)	1/3 (33.3%)	HA: 1; Sz: 2; Dth: 1†	Obs: 3
Pollock et al., 2003	92/144 (63.9%)		5/144 (3.5%)	11/144 (7.6%)	13/144 (9.0%)	5/144 (3.5%)	5/5 (100.0%)	5/5 (100.0%)		CPS: 3; Res: 4§
Kihlström et al., 1997	18/18 (100%)	48 mos (4.0 yrs)	0/18 (0.0%)			5/18 (27.8%)	5/5 (100.0%)	0/5 (0.0%)		Obs: 5
Total	1450/2215 (65.5%)		165/1907 (8.6%)	191/2162 (8.8%)	92/1542 (6.0%)	78/2619 (3.0%)	20/26 (76.9%)	21/64 (32.8%)	Sz: 3	Obs: 43 (67.2%)
Mean	65.4%		8.5%	13.2%	6.9%	4.4%		36.1%	ME: 2	StD: 4 (6.3%)
95% CI	56.3%–74.6%		4.9%–12.0%	3.3%–23.2%	4.1%–9.8%	2.0%–6.8%		35.2%–37.0%	HmP: 2	CPS: 3 (4.7%)
Range	18.5–100.0%	30–99 mos (2.5–8.3 yrs)	0.0–28.6%	0.0–100.0%	0.0–17.0%	0.0–27.8%			Psy: 1	OmR: 1 (1.6%)
									Aph: 1	Res: 15 (23.4%)
									HA: 1	
									Dth: 1	

Aph = aphasia; CPS = cystoperitoneal shunt; Dth = death; HA = headache; HmP = hemiparesis; ME = mass effect; Obs = observation; OmR = Ommaya reservoir; Psy = psychological changes; Res = resection; StD = stereotactic drainage; Sz = seizures.

Blank cells represent data that were not reported.

† Mean reported when median not available.

‡ One patient died secondary to status epilepticus.

§ CPS only: 1 patient; CPS followed by Res: 2 patients; Res only: 2 patients.

TABLE 3. Time to cyst formation for 63 patients from the 19 studies reporting individual patient data for follow-up after SRS

Authors & Year	Pt No.	Time to Cyst (mos)
Malikova et al., 2016	1	240
Bir et al., 2015	2	12
Shuto et al., 2015	3	13.2
	4	31.2
	5	37.2
	6	38.4
	7	42
	8	42
	9	49.2
	10	54
	11	54
	12	60
	13	60
	14	60
	15	64.8
	16	74.4
	17	74.4
	18	85.2
	19	94.8
	20	97.2
	21	97.2
	22	121.2
	23	123.6
	24	134.4
	25	135.6
	26	144
	27	144
	28	162
	29	180
	30	192
Bowden et al., 2014	31	6
	32	31
	33	67
Matsuo et al., 2014	34	8
	35	39.6
	36	50.4
	37	60
	38	126
Kano et al., 2012 ³⁵	39	8
Kano et al., 2012 ³⁷	40	56
Kano et al., 2012 ⁴⁰	41	8.8
	42	166
Kano et al., 2012 ⁴¹	43	38
	44	74
Al Hinai et al., 2011	45	36
	46	144
	47	156
Yen et al., 2011	48	72

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TABLE 3. Time to cyst formation for 63 patients from the 19 studies reporting individual patient data for follow-up after SRS

Authors & Year	Pt No.	Time to Cyst (mos)
Buis et al., 2010	49	47
Kim et al., 2010	50	36
	51	42
Izawa et al., 2009	52	72
Liu et al., 2008	53	60
Inoue, 2006	54	120
Flickinger et al., 1999	55	57
	56	64
	57	83
	58	84
	59	120
Kim et al., 1999	60	11
Yamamoto et al., 1998 ⁶³	61	60
	62	84
	63	120

Mean latency of cyst formation: 78.2 mos (6.5 yrs).

Factors Associated With Post-SRS Cyst Formation

We found a mean latency period of 6.5 years between SRS and cyst formation. In general, cyst formation occurs later than more common post-SRS complications, such as RICs and post-SRS hemorrhage.^{19,20,21,23,29,53,67} Therefore, studies with longer follow-up periods tended to report a higher incidence of cyst formation, which emphasizes the importance of long-term surveillance after SRS for AVM. Specifically, patients who develop new neurological symptoms after AVM obliteration should undergo neuroimaging to screen for cyst formation. Pan et al. reported an overall post-SRS cyst incidence of 1.6%, which increased to 3.6% if only those patients with at least 5 years of follow-up were considered.⁵⁴ This suggests that the rate of cyst detection may positively correlate with follow-up duration.

Several demographic factors, AVM angioarchitectural features, treatment parameters, and post-SRS outcomes have been associated with cyst formation.^{26,34,54} Ding et al. reported a cyst incidence of 2.3% at a mean follow-up of 7.9 years in a cohort of 444 unruptured AVMs; in their analysis, radiological evidence of RIC was significantly associated with cyst formation.²² Izawa et al. reported a cyst incidence of 3.4% at a mean follow-up of 6.8 years; their analysis found higher SRS maximal dose, larger nidus volume, lobar AVM location, and obliteration to be predictors of cyst formation.³⁴ In our analysis, we found that the majority of post-SRS cysts (77%) occurred in patients with obliterated nidi, which suggests that follow-up of AVM patients treated with SRS should not be abandoned after obliteration is achieved. Pan et al. found RIC and prior nidal embolization to be significantly associated with cyst formation, while the relationship between prior AVM hemorrhage and cyst formation approached

FIG. 2. Histogram of the number of newly discovered cysts biennially since SRS treatment in 63 patients from 19 studies with individual patient time-to-cyst-discovery data. The mean time to cyst formation is 78 months (6.5 years).

statistical significance.⁵⁴ These findings suggest that the pathophysiology of delayed cyst formation is distinct from that of post-SRS hemorrhage.^{2,15,34,65,66} Indeed, histopathological examination of resected cysts suggests that cyst formation occurs secondary to a chronic, organized response to radiation-induced vascular telangiectasia and wall damage, which promotes microhemorrhage and protein exudation.⁵⁹ It is possible that prior AVM hemorrhage and embolization increase tissue susceptibility to damage, thereby increasing the risk of cyst formation.^{6,52} The risk of cyst formation was found to be higher for AVM patients treated with LINAC than in those treated with GKRS (7% vs 3%, respectively, in the pooled analysis). Because of the insufficient statistical power of the available literature, additional data are necessary to perform a more rigorous evaluation of the relationship between the SRS treatment modality and cyst formation. Differences in dosimetry not only in the immediate planned target volume but also at the lower isodose lines such as the 12-Gy isodose volume should be examined as potential contributing factors for discrepancies in cyst formation between SRS delivery platforms.

Kihlström et al. reported the highest rate of cyst formation (28%) among the studies included in our analysis, a rate that was more than 3 times higher than the second highest rate of cyst incidence (7.4%) documented by Maruyama et al.^{42,47} We offer the following observations to put these findings into perspective. First, the Kihlström study had a particularly lengthy mean follow-up duration of 14 years. Second, only patients who attained complete AVM obliteration were included in that study, and cyst formation may correlate with nidus occlusion.³⁴ Third, their study reported the highest proportion of ruptured AVMs treated with SRS (83.3%) among the included studies. Since prior AVM hemorrhage may be correlated with cyst formation, the high rate of prior hemorrhage could also partially account for the elevated post-SRS cyst incidence.⁵⁴ However, all 5 cysts in the study were between 1 and 2 cm in diameter, asymptomatic, and managed conservatively.

Management of Post-SRS Cysts

The optimal management of post-SRS cysts is not well defined. In general, asymptomatic cysts should be managed conservatively, and some cysts have been shown to spontaneously regress over time. However, enlarging cysts may require treatment, even in the absence of symptoms, particularly if the cyst is located in the vicinity of deep or eloquent brain area.^{28,47,59,62} Significant mass effect secondary to the cyst, intracystic loculations and septations, and residual AVM nidus adjacent to the cyst are all factors that may favor craniotomy for cyst resection.^{33,55} Simple cyst anatomy, significant medical comorbidities, or refusal of craniotomy may favor cystoperitoneal shunt or Ommaya reservoir placement. Stereotactic drainage alone may be less effective than shunting since cysts have the potential to recur.^{51,55}

Currently, no medical therapy is known to be effective for post-SRS cysts given our incomplete understanding of cyst pathogenesis. Shuto et al. analyzed the histopathology of 28 post-SRS cysts and identified angiogenic and inflammatory components.⁵⁹ These authors postulated that post-SRS cysts were on the opposite end of the same pathobiological spectrum as chronic encapsulating hematomas. Future studies may seek to investigate the effect of antiangiogenic (for example, bevacizumab) or antiinflammatory (for example, dexamethasone) medications on cyst size and morphology.¹²

In the context of the aforementioned surgical and medical therapeutic uncertainty regarding optimal cyst management, we recommend surgical intervention for an enlarging cyst with a volume > 8 cm³ and for any cyst causing newfound neurological signs or symptoms. Specifically, we typically recommend shunt placement or aspiration for deep-seated cysts and resection for superficially located ones. Small, asymptomatic cysts can generally be observed with serial neuroimaging studies and correlated with the patient's neurological examination.

Study Limitations

Heterogeneity of the baseline and outcomes data among the studies limits our ability to draw definitive conclusions regarding the incidence of cyst formation after SRS for AVM. Variability in follow-up durations after SRS may affect our estimates of cyst incidence. Specifically, the inclusion of studies with a median follow-up of less than 5 years may have resulted in an underestimation of cyst incidence, whereas reporting bias of cyst complications may have resulted in an overestimation. Additionally, given the paucity of data regarding post-SRS cysts, we included studies that used a variety of both primary SRS treatment paradigms and salvage therapies.^{3,49}

Several of the studies included in this review identified various risk factors for cyst formation (for example, RIC, SRS dose, AVM volume and location, obliteration rate, and prior nidus embolization). Unfortunately, given the lack of individual patient data, especially for patients who did not develop post-SRS cysts, we were unable to perform analyses of the pooled data to identify predictors of cyst formation. Specifically, we were unable to ascertain the effect of nidus morphology, SRS dose planning, number and timing of SRS treatments, and time interval between prior AVM

interventions and SRS on cyst formation. Additionally, the lack of sufficient granularity with respect to individual patient data prevented us from performing a time-dependent analysis (for example, Kaplan-Meier method) for cyst formation. We were unable to ascertain the specific clinical manifestations of symptomatic cysts (for example, seizure, focal neurological deficit, headache).^{9,13,14,17,57} The safety, efficacy, and durability of the various surgical options for cysts requiring intervention could not be determined. All studies were retrospective in design, and unclear risks of bias were assumed for retrospective studies.

Conclusions

The incidence of cyst formation after SRS for AVM is 3%, with a latency period of approximately 7 years. Therefore, long-term follow-up is paramount for AVM patients treated with SRS because of the substantial delay between treatment and cyst development. The majority of post-SRS cysts are asymptomatic and require only observation. Surgical intervention should be considered for symptomatic or enlarging cysts, with options including craniotomy for resection, cystoperitoneal shunt placement, stereotactic drainage, and Ommaya reservoir implantation.

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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. Analysis and interpretation of data: Ilyas, Chen. 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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