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Original Research Article

Frameless versus frame-based stereotactic radiosurgery for intracranial arteriovenous malformations: A propensity-matched analysis

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ABSTRACT

Objective: The frameless linear accelerator (LINAC) based stereotactic radiosurgery (SRS) has been evolving with a reduction in patient discomfort. However, there was limited evidence comparing frame-based and frameless SRS for intracranial arteriovenous malformations (AVM). We aimed to compare the treatment outcomes between frame-based and frameless LINAC SRS.

Materials and Methods: This retrospective cohort compared the outcomes of frame-based LINAC SRS (1998–2009) with frameless LINAC SRS (2010–2020). The primary outcome was the obliteration rate. The other outcomes included the neurological, radiological, and functional outcomes after SRS. A matched cohort was identified by propensity scores for further comparisons.

Results: A total of 65 patients were included with a mean follow-up time of 13.2 years (158.5 months). There were 40 patients in the frame-based group and 25 patients in the frameless group. The overall obliteration rate was comparable (Frame-based 82.5% vs Frameless 80.0%, $p = 0.310$) and not significantly different over time (log-rank $p = 0.536$). The crude post-SRS hemorrhage rate was 1.5% and the incidence was 0.3 per 100 person-years. There were 67.7% of patients with AVM obliteration without new persistent neurological deficits at the last visit and 56.9% of patients with AVM obliteration without any deficits (transient or persistent) during the entire follow-up period. Four patients (8.0%) developed late onset persistent adverse radiation effects (more than 96 months after SRS) among 50 patients with more than 8-year surveillance. In the propensity-matched cohort of 42 patients, there was no significant difference in AVM obliteration (Frame-based vs Frameless, log-rank $p = 0.984$).

Conclusion: Frameless and frame-based LINAC SRS have comparable efficacy in intracranial AVM obliteration. A longer follow-up duration may further characterize the rate of late adverse radiation effects in frameless SRS.

1. Introduction

Stereotactic radiosurgery (SRS) with different energy modalities has been recommended as a safe and effective treatment for intracranial arteriovenous malformations (AVM), especially for the AVMs of Spetzler-Martin grade I and grade II [1–3]. It is a preferred treatment modality for AVMs located in the deep or eloquent brain without evidence of increased bleeding risk [4–8]. The radiosurgery technique has been improving and frameless radiosurgery with mask-based registration has been advocated to reduce patient's discomfort and pain, and to

Abbreviations: ARE, adverse radiation effect; AVM, arteriovenous malformation; HS, Heidelberg score; LINAC, linear accelerator; mRBAS, modified radiosurgery-based arteriovenous malformation grading scale; PRAS, proton radiosurgery arteriovenous malformation score; PSM, propensity score-matched; RIC, radiation-induced change; SM, Spetzler-Martin grade; SMD, standardized mean difference; SRS, stereotactic radiosurgery; VRAS, Virginia radiosurgery arteriovenous malformation scale.

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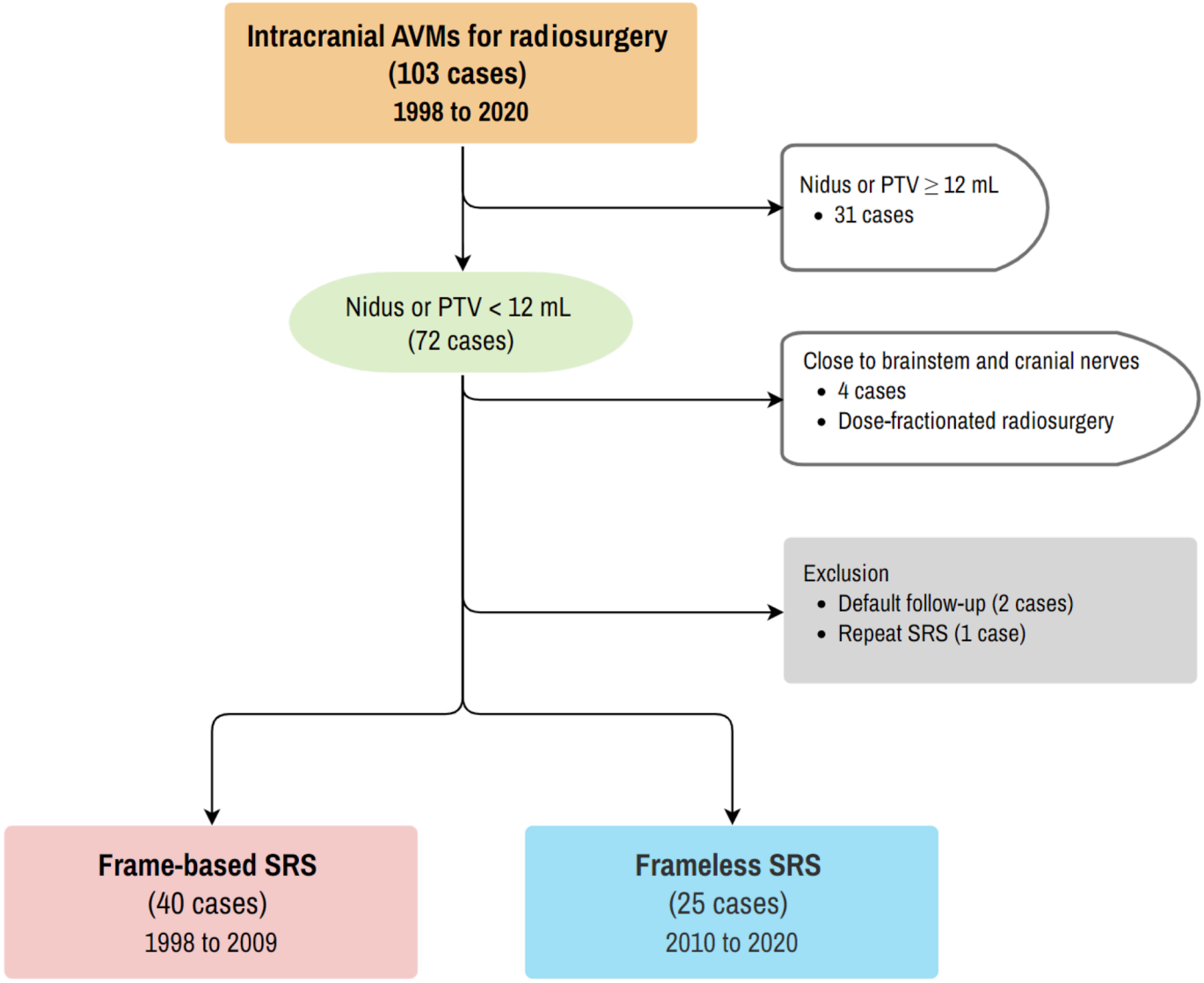

Fig. 1. The flowchart of patients with intracranial arteriovenous malformations (AVM) treated by stereotactic radiosurgery (SRS) from 1998 to 2020.

improve treatment tolerance [9]. The setup accuracy of frameless stereotaxy (mask-based fixation) was comparable to frame-based techniques in localization accuracy though greater motion variations were suggested [10–12]. Frameless radiosurgery techniques have been applied to different pathologies, including trigeminal neuralgia and brain metastasis [13,14]. However, the evidence for frameless SRS for intracranial AVMs is limited. Frameless Gamma Knife SRS for AVM treatment has just been proposed and there is a small number of publications on the treatment outcomes for intracranial AVMs using frameless LINAC SRS [15–17]. We have been utilizing frame-based SRS for AVM since 1998 and the frameless technique was adopted in 2010. In this study, we would like to compare the obliteration rate of intracranial AVMs treated by frameless and frame-based LINAC SRS in a cohort with long follow-up durations.

2. Materials and Methods

This is a retrospective study conducted in a tertiary neurosurgical center for intracranial arteriovenous malformations treated by stereotactic radiosurgery from 1998 to 2020. The frameless stereotactic technique was implemented in 2010. The treatment algorithm for intracranial AVM from 1998 to 2020 is summarized in Fig. 1. Single-fraction radiosurgery was performed for intracranial AVMs balancing the obliteration rate and the risk of neurological deficits, concerning their locations and the 12-Gy volumes [18]. We observed that there was a significant reduction in AVM obliteration when its nidus volume was greater than 12 mL. The optimal cutoff for the AVM obliteration was 12 mL treatment volume, as suggested by the receiver operator characteristic analysis in our internal audit. We decided on dose-fractionated treatment for the AVMs with nidus volume or planned target volume (PTV) $\geq$ 12 mL after 2007. In the current study, we included patients with intracranial arteriovenous malformations less than 12 mL (nidus volume or PTV), treated by single-fraction stereotactic radiosurgery, with post-radiosurgery surveillance imaging performed, and were followed up for at least two years. Patients with previous radiation to the same lesion or insufficient follow-up were excluded from the study. The study protocol was approved by the institutional ethics committee (Ref No. NTWC/REC/22064) with patient consent waived due to its retrospective nature.

2.1. Radiosurgery technique

Linear accelerator (LINAC) based radiosurgery for intracranial AVMs has been performed in our center since 1998. We utilized dynamic conformal arc techniques with multi-leaf collimators (MLC) except that small targets of less than 0.6 mL PTV were treated by cone arcs for a

Table 1
Patient demographics, characteristics, and radiosurgery doses of intracranial arteriovenous malformations treated by frame-based or frameless stereotactic radiosurgery technique.

Demographics		Entire Cohort (65 cases)				PSM Cohort (21 pairs)			
		Total (65)	Frame-based (40)	Frameless (25)	P value	Frame-based (21)	Frameless (21)	P value	SMD
Age (Mean ± SD)		30.6 ± 16.2	30.2 ± 16.3	31.1 ± 16.2	.825	31.1 ± 18.3	30.2 ± 15.8	.872	0.050
Sex (%)								1.000	0.000
Female		33 (50.8%)	18 (45.0%)	15 (60.0%)	.239	12 (57.1%)	12 (57.1%)		
Male		32 (49.2%)	22 (55.0%)	10 (40.0%)		9 (42.9%)	9 (42.9%)		
Previous hemorrhage (%)		36 (55.3%)	23 (57.5%)	12 (48.0%)	.455	9 (42.9%)	10 (47.6%)	.757	0.090
Previous treatment (%)		18 (27.7%)	12 (30.0%)	6 (24.0%)	.599	6 (28.6%)	6 (28.6%)	1.000	0.000
Previous embolization (%)		13 (20.0%)	11 (27.5%)	2 (8.0%)	.065	5 (23.8%)	2 (9.5%)	.410	0.381
Previous excision (%)		6 (9.2%)	2 (5.0%)	4 (16.0%)	.194	1 (4.8%)	4 (19.0%)	.343	0.441
Anatomical Location (%)									
Eloquent area		46 (70.8%)	30 (75.0%)	16 (64.0%)	.343	16 (76.2%)	15 (71.4%)	.726	0.106
Basal ganglia, thalamus, brainstem		14 (21.5%)	10 (25.0%)	4 (16.0%)	.539	5 (23.8%)	4 (19.0%)	1.000	0.113
Primary sensorimotor cortex		9 (13.8%)	3 (7.5%)	6 (24.0%)	.076	1 (4.8%)	5 (23.8%)	.184	
Deep venous drainage (%)		28 (43.1%)	19 (47.5%)	9 (36.0%)	.304	10 (47.6%)	7 (33.3%)	.346	0.287
Diameter (%)					.489			1.000	
0–3 cm		55 (84.6%)	35 (87.5%)	20 (80.0%)		17 (81.0%)	16 (76.2%)		
3–6 cm		10 (15.4%)	5 (12.5%)	5 (20.0%)		4 (19.0%)	5 (23.8%)		
> 6 cm		0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)		
AVM Nidus Volume (mL)									
Mean ± SD		3.54 ± 3.44	3.66 ± 3.50	3.35 ± 3.42	.727	3.96 ± 3.96	3.50 ± 3.49	.699	0.120
Median		2.03	2.02	2.15	.576	2.03	2.15	.597	
Range		0.14–11.50	0.17–11.50	0.15– 11.20		0.17–11.50	0.15–11.20		
Pre-SRS mRS					.524			.893	
0		28 (43.1%)	15 (37.5%)	13 (52.0%)		9 (42.9%)	11 (52.4%)		
1		20 (30.8%)	15 (37.5%)	5 (20.0%)		8 (38.1%)	4 (19.0%)		
2		6 (9.2%)	3 (7.5%)	3 (12.0%)		1 (4.8%)	2 (9.5%)		
3		8 (12.3%)	6 (15.0%)	2 (8.0%)		2 (9.5%)	2 (9.5%)		
4		3 (4.6%)	1 (2.5%)	2 (8.0%)		1 (4.8%)	2 (9.5%)		
5 & 6		0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)		
Dosimetry									
Margin dose (Gy)	Mean ± SD	18.7 ± 1.8	18.0 ± 2.0	18.5 ± 1.4	.384	18.4 ± 1.4	18.6 ± 1.5	.523	0.200
Mean dose (Gy)	Mean ± SD	20.6 ± 2.0	20.8 ± 2.3	20.3 ± 1.4	.274	20.1 ± 1.6	20.4 ± 1.5	.605	
Maximum dose (Gy)	Mean ± SD	22.3 ± 2.4	22.7 ± 2.7	21.7 ± 1.6	.089	21.9 ± 1.9	21.8 ± 1.5	.772	
12-Gy volume* (mL)	Mean ± SD	11.10 ± 8.46	10.32 ± 8.35	12.25 ± 8.67	.384	11.62 ± 9.68	12.89 ± 9.20	.675	
FU time (months)	Mean ± SD	158.5 ± 72.9	202.1 ± 50.3	88.8 ± 42.8	<.001	208.4 ± 47.8	99.0 ± 38.7	<.001	

Abbreviation: AVM, arteriovenous malformation; mRS, modified Rankin Scale; FU, follow-up; PSM, propensity score-matched; SMD, standardized mean difference.
Notes: 1. Total volume of tissue receiving a dose of 12 Gy or more (AVM nidus volume included).

Table 2
The distribution of intracranial arteriovenous malformations across different gradings and prognostic scales.

Prognostic scale	Entire cohort (65 cases)				PSM cohort (21 pairs)		
	Total (65)	Frame-based (40)	Frameless (25)	P value	Frame-based (21)	Frameless (21)	P value
SM (%)				.411			.574
I	6 (9.2%)	3 (7.5%)	3 (12.0%)		1 (4.8%)	2 (9.5%)	
II	35 (53.8%)	21 (52.5%)	14 (56.0%)		11 (52.4%)	11 (52.4%)	
III	23 (35.4%)	15 (37.5%)	8 (32.0%)		8 (38.1%)	8 (38.1%)	
IV	1 (1.5%)	1 (2.5%)	0 (0.0%)		1 (4.8%)	0 (0.0%)	
V	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	
VRAS (%)				.368			.944
0	2 (3.1%)	0 (0.0%)	2 (8.0%)		0 (0.0%)	1 (4.8%)	
1	13 (20.0%)	10 (25.0%)	3 (12.0%)		4 (19.0%)	2 (9.5%)	
2	29 (44.6%)	15 (37.5%)	14 (56.0%)		11 (52.4%)	12 (57.1%)	
3	15 (23.1%)	9 (22.5%)	6 (24.0%)		5 (23.8%)	6 (28.6%)	
4	6 (9.2%)	6 (15.0%)	0 (0.0%)		1 (4.8%)	0 (0.0%)	
HS (%)							.603
1	47 (72.3%)	31 (77.5%)	16 (64.0%)		15 (71.4%)	13 (61.9%)	
2	17 (26.2%)	8 (20.0%)	9 (36.0%)		5 (23.8%)	8 (38.1%)	
3	1 (1.5%)	1 (2.5%)	0 (0.0%)		1 (4.8%)	0 (0.0%)	
mRBAS							
Mean ± SD	1.07 ± 0.47	1.10 ± 0.47	1.01 ± 0.48	.534	1.14 ± 0.52	1.04 ± 0.49	.526
Median	1.07	1.12	0.90	.415	1.08	0.94	.481
PRAS							
Mean ± SD	1.05 ± 0.85	1.13 ± 0.90	0.94 ± 0.76	.364	1.20 ± 0.99	1.01 ± 0.80	.510
Median	0.81	0.84	0.809	.483	0.80	0.81	.642

Abbreviations: SM, Spetzler-Martin grade; mRBAS, modified radiosurgery-based arteriovenous malformation grading scale; VRAS, Virginia radiosurgery arteriovenous malformation scale; PRAS, proton radiosurgery arteriovenous malformation score; PSM, propensity score-matched; HS, Heidelberg scale.

Table 3
The radiosurgery outcomes for intracranial arteriovenous malformations by the conventional classification and the institutional classification.

Outcomes	Description	Original Cohort				PSM Cohort		
		Total (65)	Frame-based (40)	Frameless (25)	P value	Frame-based (21)	Frameless (21)	P value
AVM Obliteration	Overall obliteration	81.5%	82.5%	80.0%	.310	85.7%	81.0%	1.000
	Survival analysis				.536			.984
	Median months to obliteration (95% CI)	34.8 (27.3–42.3)	32.9 (23.9–41.9)	34.8 (22.2–47.4)		29.2 (13.8–44.6)	39.6 (31.4–47.8)	
	1-year obliteration	6.2%	5.0%	8.0%		4.8%	9.5%	
	3-year obliteration	52.5%	52.5%	52.6%		52.4%	48.4%	
	5-year obliteration	74.1%	70.0%	82.9%		71.4%	82.8%	
	7-year obliteration	77.5%	75.0%	82.9%		81.0%	82.8%	
	10-year obliteration	81.1%	77.5%	88.6%		85.7%	88.5%	
	12-year obliteration	85.3%	82.5%	88.6%		85.7%	88.5%	
Institutional classification					.631			.719
A0	Obliteration without new neurological deficit at any time during follow-up	37 (56.9%)	24 (60.0%)	13 (52.0%)		12 (57.1%)	11 (52.4%)	
A1	Obliteration without new neurological deficit at the last follow-up	7 (10.8%)	4 (10.0%)	3 (12.0%)		3 (14.3%)	3 (14.3%)	
A2	Obliteration with a minor neurological deficit at the last follow-up	6 (9.2%)	4 (10.0%)	2 (8.0%)		3 (14.3%)	2 (9.5%)	
A3	Obliteration with a major neurological deficit at the last follow-up	3 (4.6%)	1 (2.5%)	2 (8.0%)		0 (0.0%)	1 (4.8%)	
A4	Obliteration with mortality	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	
B0	Non-obliteration without new neurological deficit at any time during follow-up	11 (16.9%)	6 (15.0%)	5 (20.0%)		2 (9.5%)	4 (19.0%)	
B1	Non-obliteration without new neurological deficit at the last follow-up	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	
B2	Non-obliteration with a minor neurological deficit at the last follow-up	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	
B3	Non-obliteration with a major neurological deficit at the last follow-up	1 (1.5%)	1 (2.5%)	0 (0.0%)		1 (4.8%)	0 (0.0%)	
B4	Non-obliteration with mortality	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	
Conventional classification					.887			.723
Excellent	A0 & A1	44 (67.7%)	28 (70.0%)	16 (64.0%)		15 (71.4%)	14 (66.7%)	
Good	A2	6 (9.2%)	4 (10.0%)	2 (8.0%)		3 (14.3%)	2 (9.5%)	
Fair	A3	3 (4.6%)	1 (5.0%)	2 (5.0%)		0 (0.0%)	1 (4.8%)	
Unchanged	B0 & B1	11 (16.9%)	6 (15.0%)	5 (20.0%)		2 (9.5%)	4 (19.0%)	
Poor	B2 & B3	1 (1.5%)	1 (2.5%)	0 (0.0%)		1 (4.8%)	0 (0.0%)	
Dead	A4 & B4	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	

Abbreviations: AVM, arteriovenous malformation; PSM, propensity score-matched

reduction in neurotoxicity [19]. The target volume was delineated on a set of fused stereotactic computed tomography (CT), magnetic resonance imaging (MRI), and digital subtraction angiograms (DSA) for all cases. We utilized 2-dimensional DSA images (anteroposterior view and lateral view with the localizer) during the imaging fusion for both frame-based and frameless groups. From 1998 to 2009, patients were treated by Varian Clinac 2100CD LINAC (Varian, Palo Alto, California) with a 3-mm MLC. The BrainSCAN planning system (BrainLAB, Munich, Germany) was utilized from 1998 to 2009 and patient immobilization was achieved with a four-point fixation stereotactic frame. In 2010, the ExacTrac X-ray 6D image-guided system (BrainLAB, Munich, Germany) was implemented and it utilized a thermoplastic mask for patient immobilization, with a setup accuracy of 1 mm obtained [11]. A 1-mm PTV margin was applied to account for the setup errors in the frameless treatment plan if deemed safe. No margins were added for AVMs in contact with critical structures (ie, brainstem). Elekta Versa LINAC (Elekta, Stockholm, Sweden) with the Agility 5-mm MLC and the add-on Apex 2.5-mm MLC was installed in 2012 and 2014 respectively. The stereotactic coordinates were generated by the iPlan planning system (BrainLAB, Munich, Germany) and the Monaco planning system (Elekta, Stockholm, Sweden).

2.2. Follow-up protocol

We assessed the patient with radiation oncologists at 1 month, 2 months, and then 4 months after the SRS for any neurological deficits. A yearly follow-up was arranged after the AVM obliteration. The MRI was scheduled every 6 months after SRS before the AVM obliteration, then by a 3-year interval after obliteration or at any time with clinical suspicion for adverse radiation effects (ARE). The obliteration of AVM was assessed by Digital Subtraction Angiography (DSA) in all patients when the MRI suggested obliteration and was reported by a team of neuroradiologists who were not involved in radiosurgery to ensure the objectiveness.

2.3. Outcome assessment

Baseline demographics were retrieved from the radiosurgery records and the clinical management system. Arteriovenous malformations were categorized according to location, venous drainage, size, clinical presentation, and different classification and prognostic scores, including modified Radiosurgery-based AVM score (mRBAS), proton radiosurgery AVM scale (PRAS), Heidelberg score (HS), Virginia Radiosurgery AVM Scale (VRAS), and Spetzler-Martin grade (SM) [20–24]. Primary outcome was the obliteration rate. Other outcomes included the complications after SRS, functional outcomes and retreatment rates. The complications included symptomatic adverse radiation effects (ARE) and radiological changes. The symptomatic AREs were defined as any new focal neurological deficit or seizure after the SRS without evidence of a new hemorrhage. They were further classified into transient AREs (duration less than 2 years) or persistent AREs (duration more than 2 years) [25]. Any new seizure after SRS was defined as a de novo seizure. Radiological changes included radiological radiation-induced changes (RIC), radionecrosis, cyst formation, and chronic encapsulated

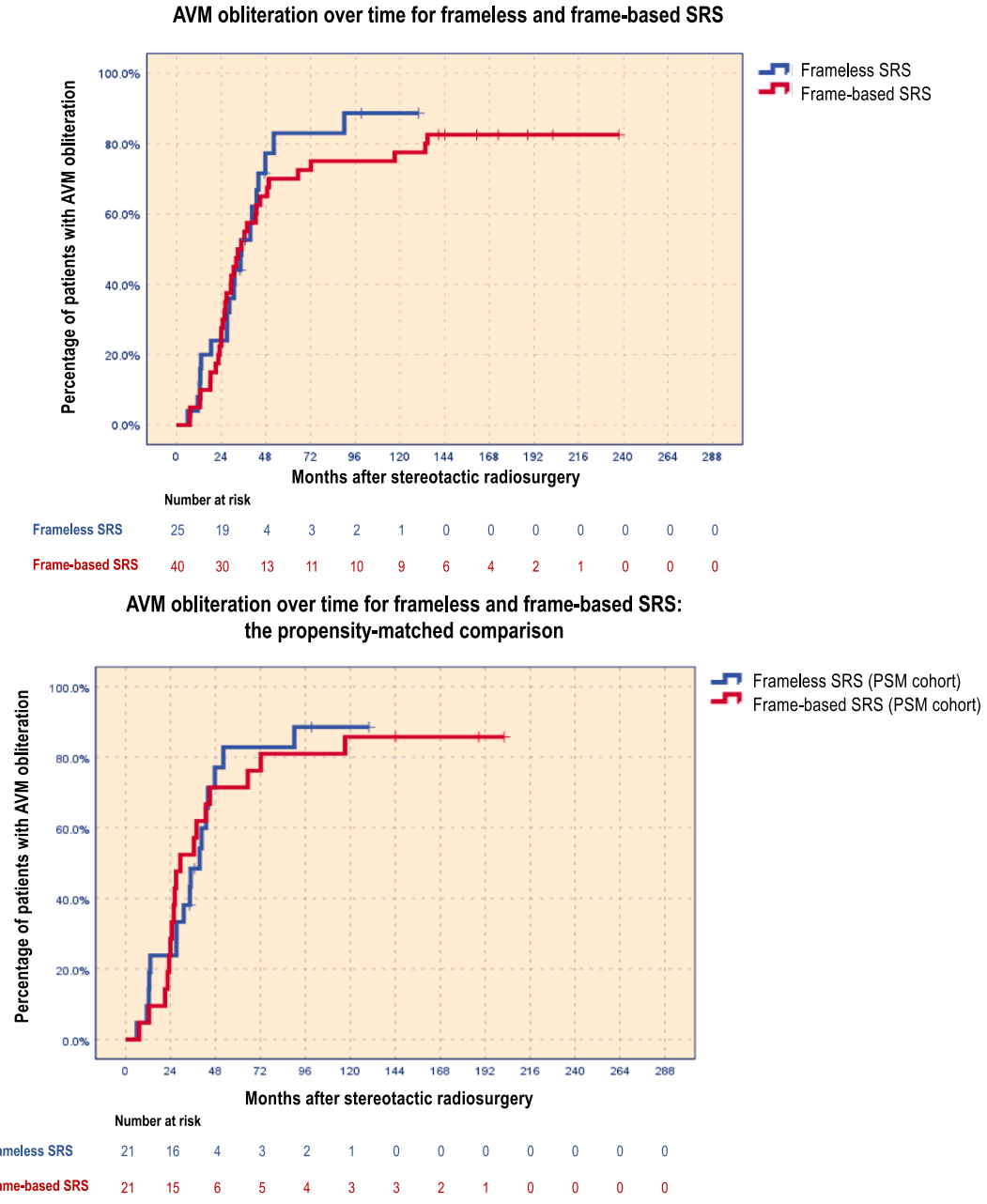

Fig. 2. The obliterations after stereotactic radiosurgery (SRS) for intracranial arteriovenous malformations (AVM). A, Kaplan–Meier curves of frame-based and frameless SRS patients (log-rank p = 0.536); B, Kaplan–Meier curves of the propensity score-matched (PSM) cohort of frame-based and frameless SRS patients (log-rank, p = 0.984);

hematoma. Radiological RICs were defined as any new signal change in the T2 or fluid-attenuated inversion recovery (FLAIR) sequence after the SRS [26–28]. Radionecrosis was defined as a lesion with a central rim or irregular nodular enhancement with or without edema and it was reported by a neuroradiologist [29]. Cyst formation and chronic encapsulated hematoma were subtypes of late AREs [27,30,31]. Hemorrhage in the latency period was defined as any bleeding of AVM after the SRS before complete obliteration was achieved, and its incidence was calculated by 100 person-years at risk. The patient's functional status was assessed by the modified Rankin Scale (mRS) [32].

2.4. Institutional outcome assessment

We classified the SRS treatment outcome based on AVM obliteration and symptomatic AREs (transient or persistent) at our institution. This system primarily dichotomized patients with obliterated AVM (Class A) or non-obliterated AVM (Class B) and subsequently classified them by the presence of any new neurological deficit (transient or persistent) and its severity. A patient without any symptomatic ARE after SRS at any time is considered an A0 outcome. A patient with transient symptomatic ARE but completely resolved at the last assessment is considered an A1 outcome (ie. excellent outcome by Pollock et al) [20]. The difference between A0 and A1 is that a small proportion of patients had mild symptoms for a short period (ie. Transient AREs) during their follow-ups

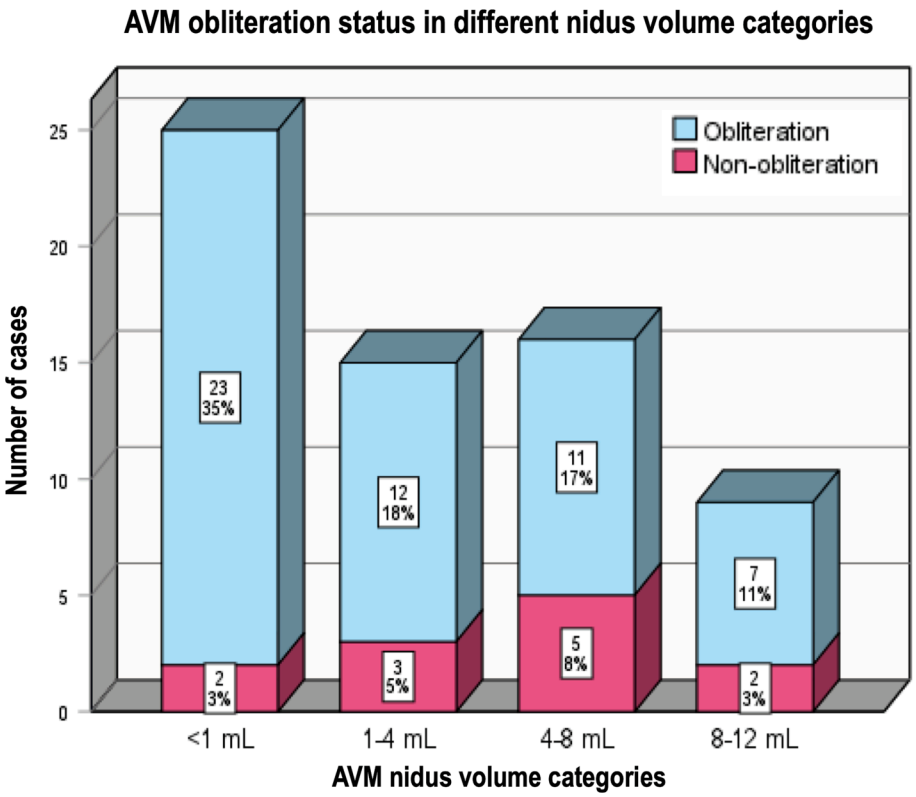

Fig. 3. The distribution of obliteration or non-obliteration by different AVM nidus volume categories.

and their symptoms are often resolved at their last follow-ups. The complete institutional outcome classifications are described in the Supplementary Digital Content.

2.5. Statistical analysis

The continuous outcomes are presented as means with standard deviations or medians. Categorical variables are presented with frequencies and percentages. For the baseline comparison, the continuous variables were compared by independent *t* test while the categorical outcomes were compared by χ^2 tests or Fisher exact tests as appropriate. Ordinal categorical data were compared by the Mann-Whitney *U* test. Kaplan-Meier survival analyses were performed for AVM obliterations, persistent AREs, and symptomatic AREs. The AVM obliteration was compared by the log-rank test between the frameless and the frame-based group. Binary logistic regressions were performed for AVM non-obliterations, symptomatic AREs and AVM obliterations without neurological deficits (transient or persistent) at any time. The identified covariates with $p < 0.15$ entered subsequent multivariate analyses. The propensity-score analysis with 1 to 1 nearest matching was performed with consideration of sample size, to balance the independent baseline covariates and the prescribed dose [33,34]. The propensity score-matched (PSM) analysis included age, gender, previous hemorrhage, previous treatment, nidus volume, venous drainage, anatomical location, eloquence, and margin dose. The standardized mean differences (SMD) of the aforementioned factors were examined in the matched cohort for any residual imbalance. The independent covariates with residual imbalances (SMD > 0.10) underwent double adjustment analysis in the Cox proportional hazards model [35]. Statistical analyses were performed using IBM SPSS Statistics Version 27.0 (Armonk, New York: IBM Corp.). Statistical significance was defined as a P value < 0.05.

3. Results

The different categories of patients treated by stereotactic radiosurgery in our unit from 1998 to 2020 were summarized in Fig. 1. A total of 103 patients received SRS or dose-fractionated radiosurgery. There were 31 patients with AVM nidus volume or PTV greater than 12 mL. There were 4 patients with AVM nidus volume less than 12 mL but were treated by dose-fractionated radiosurgery considering the AVMs' proximity to the brainstem and cranial nerves. Three patients treated by SRS were excluded due to the following reasons: previous radiosurgery to the AVM (1 case) and defaulting follow-ups (2 cases, 1 case in the frame-based group and 1 case in the frameless group). A total of 65 patients were included in the analysis, with 40 patients in the frame-based group and 25 patients in the frameless group.

The mean age at radiosurgery was 30.6 ± 16.2 years old. The average nidus volume of the AVM was 3.54 ± 3.44 mL. There were 46 AVMs (70.8%) located in the eloquent brain and 14 AVMs (21.5%) located in the basal ganglia, thalamus, or brainstem. The mean margin dose, mean dose, and maximum dose were 18.7 Gy, 20.6 Gy, and 22.3 Gy respectively. All patients in the frameless group received the 1 mm PTV margin. There were no statistically significant differences between the frame-based group and the frameless group in the baseline characteristics and different prognostic classification systems (Tables 1 and 2). A higher proportion of patients with previous embolization was noted in the frame-based group ($p = 0.065$), as in the early years embolization before SRS was believed to reduce post-SRS hemorrhage. This practice was discontinued based on the growing evidence for a reduced obliteration rate for combined embolization and radiosurgery [36–38]. The mean follow-up duration was 158.5 ± 72.9 months. There were 21 matched pairs identified by the PSM analysis.

Table 4
Complication rates and functional outcomes for the entire cohort of 65 patients-19012404396480 and the propensity-matched cohort of 42 patients.

	Original Cohort				PSM Cohort		
	Total (65)	Frame-based (40)	Frameless (25)	P value	Frame-based (21)	Frameless (21)	P value
Hemorrhage in the latency period	1 (1.5%)	0 (0.0%)	1 (4.0%)	.385	0 (0.0%)	1 (4.8%)	1.000
Symptomatic AREs*	17 (26.1%)	10 (25.0%)	7 (28.0%)	.789	7 (33.3%)	6 (28.6%)	.739
Persistent	9 (13.8%)	6 (15.0%)	3 (12.0%)	1.000	4 (19.0%)	3 (14.3%)	1.000
Transient	8 (12.3%)	4 (10.0%)	4 (16.0%)	.700	3 (14.3%)	3 (14.3%)	1.000
Median (Range) onset time after SRS (months)	58.0 (6.9–234.2)	105.2 (24.1–234.2)	20.2 (6.9–60.6)		125.1 (33.5–234.2)	22.3 (6.9–60.6)	
Persistent AREs							
Hemiparesis	1 (1.5%)	1 (5.0%)	0 (0.0%)	1.000	2 (9.5%)	0 (0.0%)	.488
Sensory disturbance	1 (1.5%)	0 (0.0%)	1 (4.0%)	.385	0 (0.0%)	1 (4.8%)	1.000
Cerebellar ataxia	2 (3.1%)	2 (5.0%)	0 (0.0%)	.519	1 (4.8%)	2 (9.5%)	1.000
Visual field disturbance	5 (7.7%)	3 (7.5%)	2 (8.0%)	1.000	1 (4.8%)	0 (0.0%)	1.000
Median (Range) onset time after SRS (months)	70.0 (12.1-234.2)	132.0 (24.1–234.2)	20.2 (12.1–60.6)		132.0 (109.0–234.2)	20.2 (12.1–60.6)	
De novo seizure	4 (6.2%)	3 (7.5%)	1 (4.0%)	1.000	2 (9.5%)	1 (4.8%)	1.000
Radiological change							
Radiation-induced changes†	26 (40.0%)	15 (37.5%)	11 (44.0%)	.603	9 (42.9%)	9 (42.9%)	1.000
Radionecrosis	10 (15.4%)	7 (17.5%)	3 (12.0%)	.729	5 (23.8%)	2 (9.5%)	.410
Cyst formation	7 (10.8%)	6 (15.0%)	1 (4.0%)	.235	4 (19.0%)	1 (4.8%)	.343
Chronic encapsulated hematoma	1 (1.5%)	1 (2.5%)	0 (0.0%)	1.000	0 (0.0%)	0 (0.0%)	1.000
Functional status at last FU							
Post-SRS mRS				.438			.802
0	24 (36.9%)	13 (32.5%)	11 (44.0%)		8 (38.1%)	9 (42.9%)	
1	20 (30.8%)	13 (32.5%)	7 (28.0%)		6 (28.6%)	6 (28.6%)	
2	9 (13.8%)	6 (15.0%)	3 (12.0%)		3 (14.3%)	2 (9.5%)	
3	9 (13.8%)	7 (17.5%)	2 (8.0%)		3 (14.3%)	2 (9.5%)	
4	3 (4.6%)	1 (2.5%)	2 (8.0%)		1 (4.8%)	2 (9.5%)	
5 & 6	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	
Decline in mRS				.539			.576
0	58 (89.2%)	35 (87.5%)	23 (92.0%)		18 (85.7%)	19 (90.5%)	
1	5 (7.7%)	3 (7.5%)	2 (8.0%)		1 (4.8%)	2 (9.5%)	
2	2 (3.1%)	2 (5.0%)	0 (0.0%)		2 (9.5%)	0 (0.0%)	
Retreatment‡	3 (4.6%)	2 (5.0%)	1 (4.0%)	1.000	1 (4.8%)	1 (4.8%)	1.000

Abbreviations: ARE, adverse radiation effect; SRS, stereotactic radiosurgery; mRS, modified Rankin Scale; PSM, propensity-score matched.
Notes: * Symptomatic adverse radiation effects (ARE) – Any new neurological deficit or seizure without evidence of hemorrhage. † Radiation-induced changes – T2 hyperintense signal surrounding the nidus of arteriovenous malformations after radiosurgery. ‡ Retreatment – second treatment (surgery, embolization or radiosurgery) performed for arteriovenous malformations with non-obliteration.

3.1. The AVM obliteration rate

The overall obliteration rate was 81.5% for the entire cohort (Frame-based vs Frameless 82.5% vs 80.0% p = 0.310), and the 3-year, 5-year, and 10-year obliteration rate was 52.5%, 74.1%, and 81.1% respectively (Table 3). The median time to obliteration was 34.8 months (Frame-based vs Frameless 32.9 vs 34.8 months, p = 0.536). The 3-year obliteration rates were 52.5% and 52.6% for the frame-based and the frameless groups. No significant difference was revealed in the survival analysis (log-rank p = 0.536, Fig. 2A). In the PSM cohort, there was no significant difference in the AVM obliteration (log-rank p = 0.984, Fig. 2B, HR 1.469, p = 0.348, Supplementary Table 1). The distribution of AVM obliteration by different nidus volume categories is shown in Fig. 3. The AVM retreatment rates were shown in Table 4.

3.2. Adverse radiation effects, hemorrhages, and functional outcomes

The complications after stereotactic radiosurgery are summarized in Table 4. One patient (1.5%) with an unruptured left temporal AVM developed a hemorrhage 3 years after SRS, which corresponded to a post-SRS hemorrhage incidence of 0.3 per 100 person-years for the entire cohort. Subsequent craniotomy with surgical excision of the AVM was performed. This patient had a full recovery without functional impairment. In the long-term follow-up, there were 17 patients (26.1%) who suffered from symptomatic AREs including 8 transient AREs (12.3%) and 9 persistent AREs (13.8%). De novo seizures were identified in 4 (6.2%) patients. Surgical excisions were performed for a chronic encapsulated intracerebral hematoma (1.5%) and a radionecrosis (1.5%) in the frame-based group. There were 4 patients (10.2%) with persistent AREs onset time more than 96 months after SRS, among 39 frame-based patients (97.5%) who completed 8-year surveillance. The rate of persistent AREs at 5 years, 10 years, and 15 years after SRS was 4.6%, 10.2%, and 14.8% respectively (Fig. 4A). No patient developed radiation-induced malignancy. No statistically significant differences were noted in the complication rates between the frame-based group and the frameless group in the original cohort and the PSM cohort (Table 4). The location in the primary sensorimotor cortex was identified to be associated with the development of symptomatic AREs (Table 5, p = 0.022). The symptomatic AREs for the AVMs located at the primary sensorimotor cortex are shown in Supplementary Table 3.

Excellent outcomes (AVM obliteration without new persistent neurological deficits at the last visit) were achieved in 67.7% of patients. There were 89.2% of patients who remained unchanged in the functional status after SRS at the last follow-up. There were 37 patients (56.9%) with the AVM obliterated without any neurological deficit (persistent or transient) at any time after SRS (A0 outcome, Frame-based 60.0% vs Frameless 52.0%, p = 0.631), as shown in Table 3. The rate of A0 outcomes at 5-year and 10-year after radiosurgery was 57.9%, and 53.2% respectively for the entire cohort. The mRBAS has the strongest association with the A0 outcome (Supplementary Table 2).

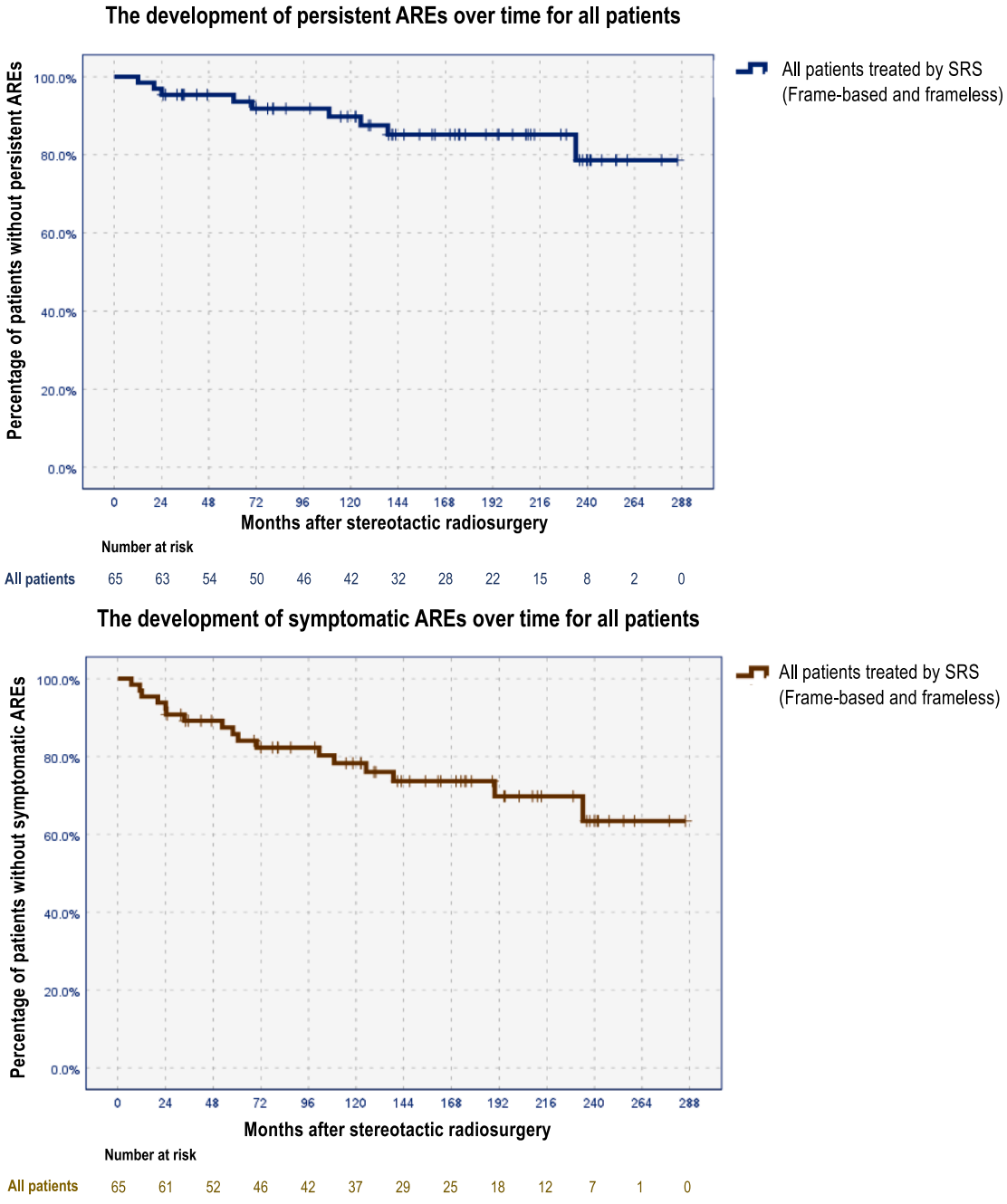

Fig. 4. The development of adverse radiation effects over time for all patients. A, the Kaplan–Meier curve of persistent adverse radiation effects; B, the Kaplan–Meier curve of symptomatic adverse radiation effects.

Table 5
Univariate and multivariate analysis for the risk factors associated with AVM non-obliterations, symptomatic adverse radiation effects, and AVM obliteration without new transient or persistent neurological deficit at any time during follow-up (A0 outcome).

Demographics & dosimetry	AVM non-obliteration					Symptomatic adverse radiation effects					A0 outcome‡				
	Univariate		Multivariate			Univariate		Multivariate			Univariate		Multivariate		
	OR	P	OR	95% CI	P	OR	P	OR	95% CI	P	OR	P	OR	95% CI	P
Age	0.986	.492				1.049	**.011**	1.096	1.027–1.170	**.006**	0.970	.067	0.939	0.894–0.986	**.011**
Sex (Male)	0.688	.563				0.644	.441				2.028	.165			
Rupture	1.250	.730				0.357	.080	1.846	0.300–11.379	.509	2.190	.125	0.597	0.152–2.346	.460
Size (3–6 cm vs < 3cm)	2.190	.315				1.255	.764				0.444	.248			
Nidus Volume	1.120	.201				1.123	.148	0.837	0.400–1.750	.636	0.828	**.018**	0.789	0.524–1.187	.256
Drainage (Deep vs superficial)	1.409	.593				0.453	.191				1.705	.299			
Eloquent	0.503	.300				7.273	.065	9.353	0.837–104.555	.069	0.503	.233			
Primary sensorimotor cortex	0.511	.547				8.182	**.007**	18.111	1.517–216.226	**.022**	0.171	**.038**	0.140	0.018–1.061	.057
Deep location*	3.492	.070	3.228	0.792–13.149	.102	0.721	.651				0.700	.556			
Previous Embolization	0.764	.750				2.083	.265				0.581	.581			
Previous Surgery	0.873	.905				0.000	.999				4.219	.201			
Margin dose	0.613	.068	0.617	0.357–1.065	.083	0.851	.357				1.417	**.039**	1.369	0.848–2.211	.199
12-Gy volume†	1.021	.568				1.060	.082	1.123	0.820–1.537	.469	0.932	**.032**	1.123	0.876–1.440	.361
Frame-based vs Frameless	0.848	.801				0.857	.789				1.385	.527			

Abbreviations: AVM, arteriovenous malformation; CI, confidence interval; OR, odds ratio.
Notes: * Deep location – basal ganglia, thalamus, and brainstem. † Total volume of tissue receiving a dose of 12 Gy or more (AVM nidus volume included). ‡ A0 outcome – AVM obliteration without new neurological deficit (transient or persistent) at any time during follow-up.

4. Discussion

4.1. Key results and interpretation

We have identified comparable obliteration rates between frameless and frame-based stereotactic radiosurgery for intracranial arteriovenous malformations in the original cohort and the matched cohort and reported the rate of long-term adverse radiation effects after LINAC SRS. The overall obliteration rate by frameless SRS was 80.0%. This favorable obliteration rate reflects the accuracy and efficacy of frameless SRS utilizing an image-guided radiation therapy system for intracranial AVMs. Frager et al reported a comparable efficacy in AVM obliteration with reduced radiological RICs in the frameless SRS with 3-dimensional rotational angiography versus the standard frame-based technique [16]. A higher rate of patients with previous radiosurgery (Frame-based 8% vs Frameless 1%) and incidental AVMs (Frame-based 27% vs Frameless 15%) were noted in the frame-based group in Frager et al. [16]. Our study had the advantages of being a more homogenous cohort and performing a matched analysis for the AVM obliteration between the two groups.

The utilization of frameless SRS reduced the necessity of using pins and a skull frame for immobilization, avoided analgesics, local anesthetics, and sedatives, and alleviated the potential pain and prolonged discomfort during the treatment day. The frame-based patient needed 6–8 h to undergo the DSA, contrast CT, and the SRS sequentially (Fig. 5). Kondziolka et al reported a 9% uncomfortable rate during frame application despite using sedatives [39]. Frameless patients, on the contrary, could have their thermoplastic masks prepared and underwent different investigations and the SRS on different days, which provides greater flexibility for the patient and operating logistics. These benefits, though difficult to be quantified, support the convenience of frameless SRS.

There were 20 ARUBA-eligible patients in our cohort [40]. The 10-year AVM obliteration rate of this subset of patients was 89.0%. Considering 1 patient with post-SRS bleeding, the post-SRS hemorrhage incidence was 1.3 per 100 person-years. This finding agrees with Ilyas et al (post-SRS hemorrhage incidence of 1.15 per 100 person-years) and supports that SRS is a feasible intervention for appropriately selected unruptured AVMs considering their natural bleeding risks, as opposed to the ARUBA study [40–42].

Over the entire follow-up period, the crude symptomatic ARE rate was 26.1% with a persistent ARE rate of 13.8%, including hemiparesis (1.5%), sensory disturbance (1.5%), cerebellar ataxia (3.1%), and visual field disturbance (7.7%). The crude rates of symptomatic and persistent AREs were increased due to a long observation interval in the current cohort (Fig. 4). Pollock et al reported a rate of permanent RICs of 4.4% at 4 years, 8.6% at 8 years, and a 15-year late AREs rate of 12.5% [27,43]. We agree with Hasegawa et al that long-term complications after SRS should be monitored [30]. In our series, 8 patients (12.3%) had transient RICs and completely recovered at their last follow-up, including 4 patients (6.2%) with seizures and 4 patients (6.2%) with transient hemiparesis lasting from 1 month to 4 months. In the current study, we did not aim to compare the risk of symptomatic or persistent AREs between the two radiosurgery techniques, as the shorter follow-up duration in the frameless group may underestimate the late AREs. A higher percentage of transient AREs was observed in the frameless group, though not statistically significant ($p = 0.700$). This was attributed to a higher proportion of AVMs located at the primary sensorimotor cortex in the frameless group (Supplementary Table 3). The AVMs located in the primary sensorimotor cortex had higher risks of developing symptomatic AREs (Table 5, $p = 0.022$) while the frame-based or frameless approach did not differ significantly (Table 5, $p = 0.789$).

4.2. Limitation and generalizability

The study is limited by the sample size and its retrospective nature. The case volume and radiosurgery experience were considered

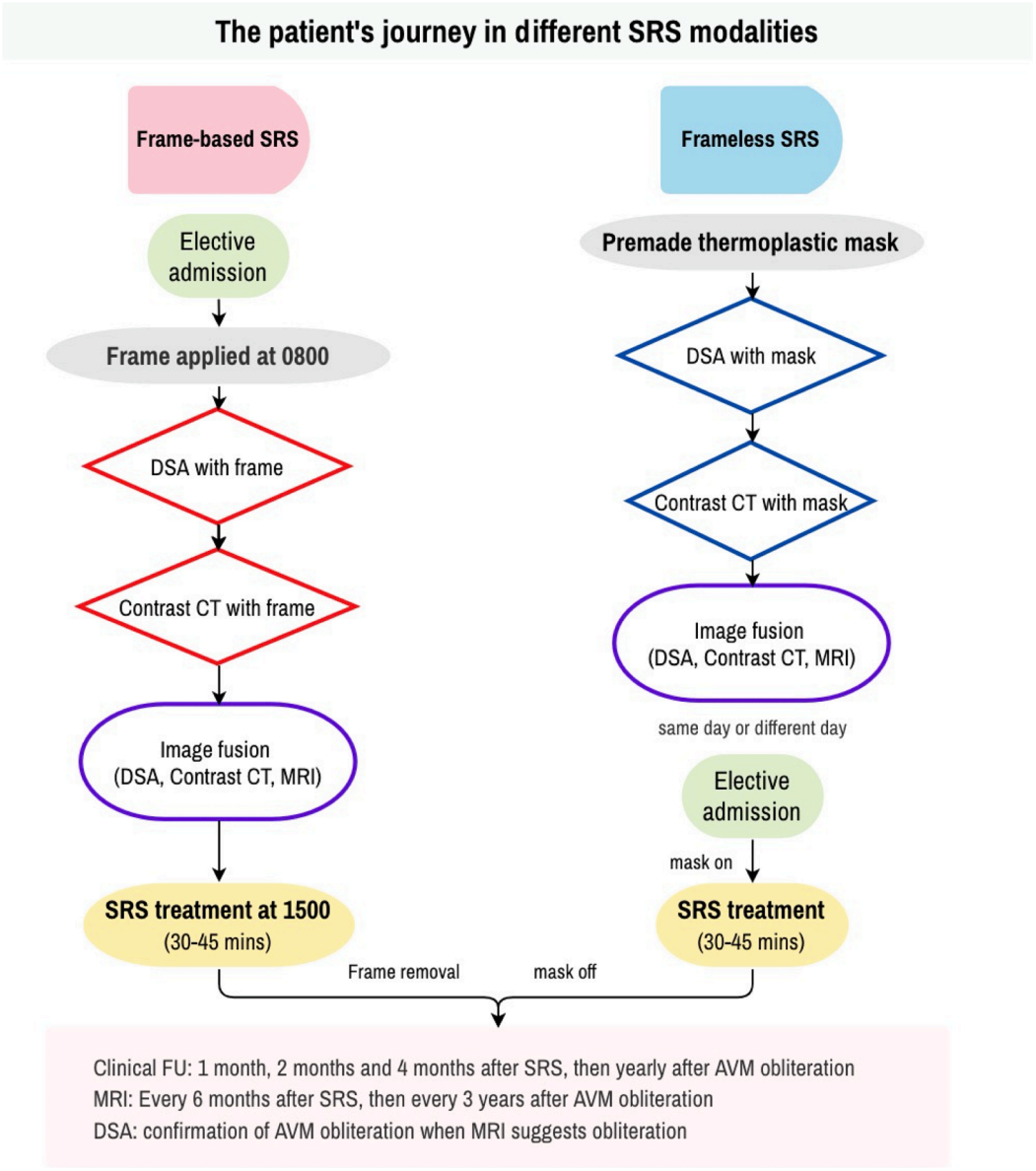

Fig. 5. The patient's treatment journey in frame-based and frameless stereotactic radiosurgery (SRS) for intracranial arteriovenous malformations (AVM). CT, computed tomography; DSA, digital subtraction angiography; MRI, magnetic resonance imaging.

important for the success of radiosurgery. As a low-volume center, we were able to perform long-term surveillance for our patients and recognize the late AREs. The effect of the treatment period may create bias. The cases that received SRS were reduced in the frameless period, which was also noted for the SRS in the modern era by Patibandla et al. [44]. This could be attributed to patients' preferences for other treatment modalities (ie, surgical excision). However, Patibandla et al concluded that the obliteration rate or favorable outcomes did not differ or improve substantially in the modern era while Pollock et al observed a reduction in the obliteration rate despite advances in radiosurgery [43,44]. Further multicenter studies involving frameless and frame-based SRS centers with prospective pain or discomfort assessment may consolidate the comparison on patients' experiences.

5. Conclusions

Frameless stereotactic radiosurgery utilizing an image-guided radiation therapy system achieved a comparable obliteration rate in contrast to frame-based stereotactic radiosurgery for intracranial arteriovenous malformations. Further analysis with a longer follow-up duration would reveal the long-term adverse radiation effects of the frameless stereotactic radiosurgery.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2023.100642.

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