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# Patterns of Failure after LINAC Radiosurgery for Cerebral Arteriovenous Malformations

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## Short Title : AVM Radiosurgery : Pattern of Failures

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# **Patterns of Failure after LINAC Radiosurgery for Cerebral Arteriovenous Malformations**

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## **ABSTRACT**

### **Background**

Numerous studies have assessed the predictive factors of the arteriovenous malformation (AVM) response to stereotactic radiosurgery (SRS) but only a few have discussed the causes of failure. The aim of this study was to evaluate the patterns of failure in patients with AVM who had undergone LINAC SRS.

### **Methods**

We performed a retrospective analysis of 288 patients treated by LINAC SRS in our institution from 1995 to 2011. Failure was defined on the basis of the control angiogram at 5 years and identified in 44 patients. The distribution of causes was estimated by a descriptive analysis of literature-based causes: minimal margin dose < 18 Gy, residual nidus outside the initial targeted volume, prior embolization, recanalization and size of the target volume. We also analyzed associations between causes.

### **Results**

Incomplete nidus identification (41%) and prior embolization (77%) were the most frequently observed conditions in cases of failure. Previously embolized patients, in whom the cause of failure was always identified ( $p=0.001$ ), were younger ( $p=0.004$ ) and had larger nidus volumes (0.025). Recanalization was rare (5/34) and exclusively in females ( $p=0.048$ ). Larger nidus volumes were less frequent ( $2.18 \text{ cm}^3 \pm 2.2 / [0.13-10.8]$ ) and observed mainly in females when  $> 2 \text{ cm}^3$  ( $p=0.012$ ). Insufficient dose was observed in 9 patients and found in case of larger volume ( $p=0.031$ ) leading to dosimetry constraints (3 cases) and vicinity of eloquent zones (6 cases). No known causes were found in 5 patients, 4 of whom had low Spetzler-Martin grades (I and II,  $p=0.003$ ) suggestive of radioresistance.

### **Conclusion**

Detailed analysis highlighted the distribution of causes and the potential role of radioresistance.

## **INTRODUCTION**

Cerebral arteriovenous malformations (AVM) have a significant cumulative risk for hemorrhage<sup>1</sup>. Several treatment options are possible: observation, microsurgical resection, stereotactic radiosurgery (SRS), embolization, and multimodal treatment<sup>2</sup>. Open AVM resection is considered the gold standard treatment because of its ability to immediately relieve the risk of hemorrhage<sup>3</sup>. However, when the risk of microsurgery is too great, SRS has proven to be a favorable alternative. The rates of AVM obliteration after primary SRS varies from 43% to 92%<sup>4-10</sup>. Most SRS-treated AVMs are obliterated within 3 years<sup>11</sup>. When the nidus is still present 5 years after SRS, treatment is considered to have failed. The diagnosis of failure is established by angiogram<sup>12</sup> or by angio-magnetic resonance imaging (MRI) in the event of contraindications or patient refusal<sup>13</sup>. Numerous studies<sup>14,15</sup> have assessed the predictive factors of AVM response to SRS (clinical features, imaging and dosimetry) but only a few have investigated the specific patterns of failure<sup>16,17</sup>. Our aim was to analyze the patterns of AVM treatment failure at 5 years after linear accelerator (LINAC) SRS.

## **MATERIAL AND METHODS**

### **❖ Population and Radiosurgery**

From September 1995 to December 2011, 288 patients were treated in our institution with LINAC SRS for cerebral AVM. SRS was performed on a Varian® Clinac 2100C (Varian Medical Systems, Palo Alto, CA). We used cylindrical collimators (diameters: 6 to 24 mm) from 1995 to 2000 (n=50) and micro-multileaf collimators with a conformal arc technique from 2000 to 2011 (n= 238), (Brainlab, Feldkirchen, Germany). A Leksell stereotactic head frame was placed under local anesthesia for all treatments. Delineation and treatment planning were performed with BrainScan software (Brainlab, Feldkirchen, Germany). The planning target volume (PTV) consisted of the AVM nidus without any additional margin, which was identified on a multimodal imaging approach including angio computed tomography (CT) scan (1.25-mm slice thickness), angio-MRI (1-mm slice thickness) and an angiogram. In case of prior embolization, the non-flowing embolized zones were excluded from the target volume. All AVM nidi were delineated by both a neurosurgeon and a neuroradiologist. The prescribed dose was 25 Gy at the isocenter with a marginal dose of 22 Gy. The marginal dose was reduced on a case-by-case basis according to the size of the target volume and the surrounding organs at risk (OAR). Each treatment plan was reviewed and approved by a radiation oncologist, neurosurgeon and physicist.

### ❖ Failures of Radiosurgery

Follow-up consisted in clinical examination and angio-MRI 6 months, 1 year and each year up to 5 years after SRS. At 5 years, a systematic angiogram was performed. Fourteen patients (4.9%) were lost to follow-up (cylindrical collimators n=2, micro-multileaf collimators n=12). At the 5-year control angiogram, 44 patients (15.3%) were considered to have experienced therapeutic failure if incomplete nidus obliteration with persistence of an early filling draining vein<sup>12</sup>. The characteristics of the 44 patients are shown in **Table 1**.

Thirty-five patients (80%) had received treatment before SRS1, consisting in embolization in 94% of cases. The residual AVM nidus volume at the 5-year control angiogram was < 50% in 28 patients (64%), > 50% in 14 patients (31 %) and unchanged in 2 patients (5%).

Of the 44 patients, 22 (50%) (13 women, mean age 40.8 years) underwent a second SRS (SRS2) at the same facility with the same strategy. Of the 22 non re-irradiated patients, 1 underwent successful surgery, 6 were successfully re-embolized, 1 died (of causes unrelated to AVM), 3 refused a second radiosurgery treatment, 2 were treated in another center, 4 were lost to follow-up and 5 had no further treatment (maximum reasonable dose reached and no alternative therapy available). Failure was defined on the basis of the SRS2 5-year control arteriogram.

Of the 22 patients with SRS2, 20 underwent the 5-year control angiogram and were analyzed. The mean time between SRS1 and SRS2 was 6.7 years (range 5-16 years) and the mean follow-up after SR2 6.6 years (range 5-12 years). Seven patients were embolized between the two SRS (1 to 5 embolizations). The mean minimum marginal dose was 19.6 Gy  $\pm$ 3.9 (range 11.5-24). In 16 patients (80%) treatment was successful and in 4 (20%) a failure. In 13 of the 14 patients who had a > 50% reduction after SR1 treatment was successful (cure rate of 93%). In the 6 patients with >50% residual nidus (reduction <50 %) after SR1, treatment was successful in 3 and a failure in 3 (cure rate of 50%). (**Figure 1: Flow Chart**)

### ❖ Data analysis

After a case-by-case assessment, the distribution of patterns of AVM treatment failure at 5 years after SRS was estimated retrospectively by a descriptive analysis of literature-based causes: minimal margin dose < 18 Gy<sup>18,19</sup>, residual nidus outside the initial target volume (i.e. insufficient nidus targeting)<sup>16,17,20</sup>, the size of the targeted volume<sup>19,21-24</sup>, prior embolization<sup>25,26</sup> and recanalization<sup>27,28</sup>. We elected to study the mean volume (cm<sup>3</sup>) of the

targeted volume, the Spetzler-Martin grading scale, and AVMs with a volume greater than 2 cm<sup>3</sup> and greater than 4 cm<sup>3</sup><sup>23,24</sup>. We also recorded absence of cause of failure.

Data are shown as numbers with associated percentages for categorical data and as means with associated standard deviations ( $\pm$  SD) and range [minimum – maximum] for continuous data.

Associations between patterns of failure were analyzed by chi-squared test or Fisher's exact test when appropriate. Comparisons of means were performed by Student's t-test or Mann & Whitney's test if the distribution of data was not normal.

Statistics were computed with STATA (version 12, StataCorp, College Station, US). All tests were two-sided and a p-value < 5% was considered statistically significant.

The study received full ethical review and approval.

## RESULTS

Insufficient nidus targeting was observed in 18 patients (41%). In 8 of the 18, the targeted volume was reduced (mean targeted volume = 0.9 cm<sup>3</sup>) because of the vicinity of eloquent areas: precentral region (n=2), brainstem (n=1), corpus callosum (n=2), deep gray nuclei (n=1) and optical tracts (n=2). In the remaining 10 patients, determination was insufficient because parts of the nidus were not identified: a draining vein (n=1), no clear boundaries of the nidus (n=3, no previous treatment), nidus partially masked by prior embolization (n=5) and a split nidus after prior embolization with one part being masked (n=1).

Prior embolization was performed in 34 patients (77%). Recanalization was visualized in 5 patients, which was systematically located in a previously embolized area not included in the targeted volume as it was not permeable at the time of SRS. These 5 patients were embolized 3, 3, 5, 7 and 9 times, respectively, with histoacryl before SRS. The mean time between the last embolization and radiosurgery was 6.8 months (range 4-12).

The mean size of the targeted volume in the failed treatment group (n=44) was 2.18 cm<sup>3</sup>  $\pm$  2.22 (SD), range 0.13-10.8. On the Spetzler-Martin scale, 2 patients (5%) had grade I AVMs, 13 (30%) grade II, 15 (34%) grade III and 14 (32%) grade IV. Sixteen patients had a volume greater than 2 cm<sup>3</sup> (36%) and 9 a volume greater than 4 cm<sup>3</sup> (20%).

For 9 patients (20%) the minimum marginal dose was insufficient (< 18 Gy, range [11.3 – 17.3]). Three patients had an insufficient dose because of large volume AVMs (10.8 cm<sup>3</sup>, 5.8

cm<sup>3</sup> and 5.4 cm<sup>3</sup>). Six patients had lesions in the vicinity of eloquent areas: capsulo-thalamic (n=1), corpus callosum (n=2) and central region (n=3).

In 5 patients (11%) no cause of failure was identified. In these patients, the minimum marginal dose was sufficient (>18Gy), targeting was suitable and no prior embolization had been performed (i.e. no recanalization). Volume was lower than 2 cm<sup>3</sup> with a mean volume of 0.57 cm<sup>3</sup> ± 0.35 (SD), range [0.23-1.14].

Previously embolized patients were younger (p=0.004, Mann & Whitney), the volume of their nidus was larger (p=0.025, Mann & Whitney) and they all had an identified cause of failure (p=0.001, Fisher). Recanalization was exclusively observed in females (p=0.048, Fisher). Low Spetzler-Martin grades were predominantly observed in patients without an identified cause (p=0.003, Fisher). Volumes > 2 cm<sup>3</sup> were preferentially observed in females (p=0.012, Chi2). Low doses (<18Gy) were preferentially observed for larger volumes (p=0.031; Mann & Whitney). When no cause was identified the volume was smaller (0.57 cm<sup>3</sup> ± 0.35, range [0.23-1.14]; p=0.013, Mann & Whitney) with low Spetzler-Martin grades (p=0.003, Fischer). All associations of causes are given in **Table 2**.

## DISCUSSION

The aim of this study was to analyze patterns of AVM treatment failure at 5 years after LINAC SRS. Incomplete nidus identification and prior embolization were the most frequently observed conditions, in 41% and 77%, respectively, of patients with failed treatment. Previously embolized patients were younger (p=0.004) and had larger volumes of nidus (0.025) and an identified cause of failure (p=0.001). Recanalization was rare (5 out of 34) and exclusively in females (p=0.048). Large volumes of nidus were less frequent (mean value = 2.18 ± 2.2 (SD) range [0.13-10.8]) and observed mainly in females when > 2 cm<sup>3</sup> (p=0.012). Nine patients with larger volumes (3.66 cm<sup>3</sup> ± 3.20 (SD) versus 1.80 cm<sup>3</sup> ± 1.77 (SD); p=0.031) had received insufficient doses, which led to dosimetry constraints in 3 and vicinity of eloquent zones in 6. In 5 patients, 4 of whom had low Spetzler-Martin grades (I and II, p=0.003), no known causes were identified.

Incomplete nidus identification in AVM treatment has been documented elsewhere<sup>16,17,20</sup>. It can be the consequence of a targeting mistake, as seen in 10 of 18 patients in our series, a ratio similar to that of Ellis et al<sup>16</sup>. It could have been avoided with better technical tools that provide a comprehensive overview of the nidus in 3D. Modern imaging and planning technologies we systematically used (2D angiogram, co-registered angio CT-Scan and angio



MRI) were however limited in our 10 patients. Historical series<sup>27</sup> using only angiograms recorded incorrect definitions of nidus in 33 of 45 cases. One imaging modality is known to be prone to errors in the identification of the nidus<sup>29,30</sup>. The lack of full nidus identification could also be investigator-dependent<sup>31</sup> or in some cases due to non-utilization of supra-selective arteriography<sup>32,33</sup>. Prior embolization, which was very frequent in our series, can interfere with nidus definition<sup>18,25</sup> and consequently affect failure<sup>26</sup>. In our series, on this particular point, patients were younger, nidus were bigger and a cause of failure was always found. The incidence of prior embolization in the literature is variable but the procedure can be beneficial in carefully selected patients, in particular for large AVMs<sup>34,35</sup>. Finally, the concentration of histoacryl could influence the obliteration rate<sup>36</sup> and chronic hypoxia due to embolization could be suspected to enhance cell resistance to radiation<sup>37</sup>.

The incidence of recanalization is rather low<sup>26–28,38</sup>. Lesions related to embolic agents<sup>26,38,39</sup> and neoangiogenesis secondary to transient regional nidus hypoxia<sup>40</sup> can take part in the recanalization process. Hematoma resorption (21/44, Table I) could lead to recanalization, although rare, 9%<sup>27</sup>. However in our series, we took care to wait for complete resorption before undertaking SRS, which on average was performed 6.8 months after embolization. Surprisingly, we observed recanalization in females only, which suggests a potential link with hormones<sup>41–43</sup>.

In 9 of 44 patients, the mean minimum marginal dose was low (<18 Gy) and likely contributed to failure according to the demonstrated dose-dependent efficiency<sup>18,22,44,45</sup>. Moreover, the mean volume of these 9 patients was larger (3.67 cm<sup>3</sup>) than for the rest of the SRS failures (2.39 cm<sup>3</sup>). There is inconclusive evidence in the literature on the predictive value of volume for treatment failure<sup>19,21–23</sup>, which therefore is perhaps not an independent factor.

In 5 patients we found no definite causes of failure and their nidus volumes were small (Spetzler-Martin grades I and II). Radioresistance could have been a factor since it has been reported that a plateau of a maximum obliteration rate of 75%-88% is observed at 25Gy<sup>18,19</sup>. Beyond that, endothelial cells could die without cellular proliferation and vessel occlusion. There is no study available of intrinsic endothelial cell sensitivity to single high dose radiation. Experimental data suggest that a 10 Gy single dose is a minimum threshold required for inducing massive endothelial cell apoptosis<sup>46</sup>, which is due to radiation-induced activation of acidic sphingomyelinase and leads to the production of ceramide, a pro-

apoptotic sphingolipid<sup>47</sup>. An increase in total plasma ceramide following stereotactic high dose radiation therapy for lung or liver metastases was recently reported as a promising biomarker of tumor response<sup>48</sup>. These results and others suggest that vascular cell ability to synthesize ceramide in response to single high dose radiation could be a major determinant of vessel radiosensitivity and hence the efficacy of AVM SRS.

Repeat radiosurgery succeeded in decreasing SRS1 failures since we obtained an occlusion rate of 80%, which is consistent with that in the literature<sup>49-51</sup>. Kano et al<sup>49</sup> reported, in line with our observations, that a decrease in the nidus of at least 50% after SRS1 could be a predictive occlusion factor for SRS2.

## CONCLUSION

This study assessed the patterns of failure after LINAC SRS for the treatment of AVM. Despite our limited data, detailed analysis established the distribution of causes and identified the potential role of radioresistance and the future interest of individual radiosensitivity measurements. Further studies are required to elucidate the intricate mechanisms of failure.

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### **Figure Legends**

**Figure 1** : Flow chart of the study population

**Table 1** : Characteristics of the population of failure

**Table 2** : Associations of causes of failure

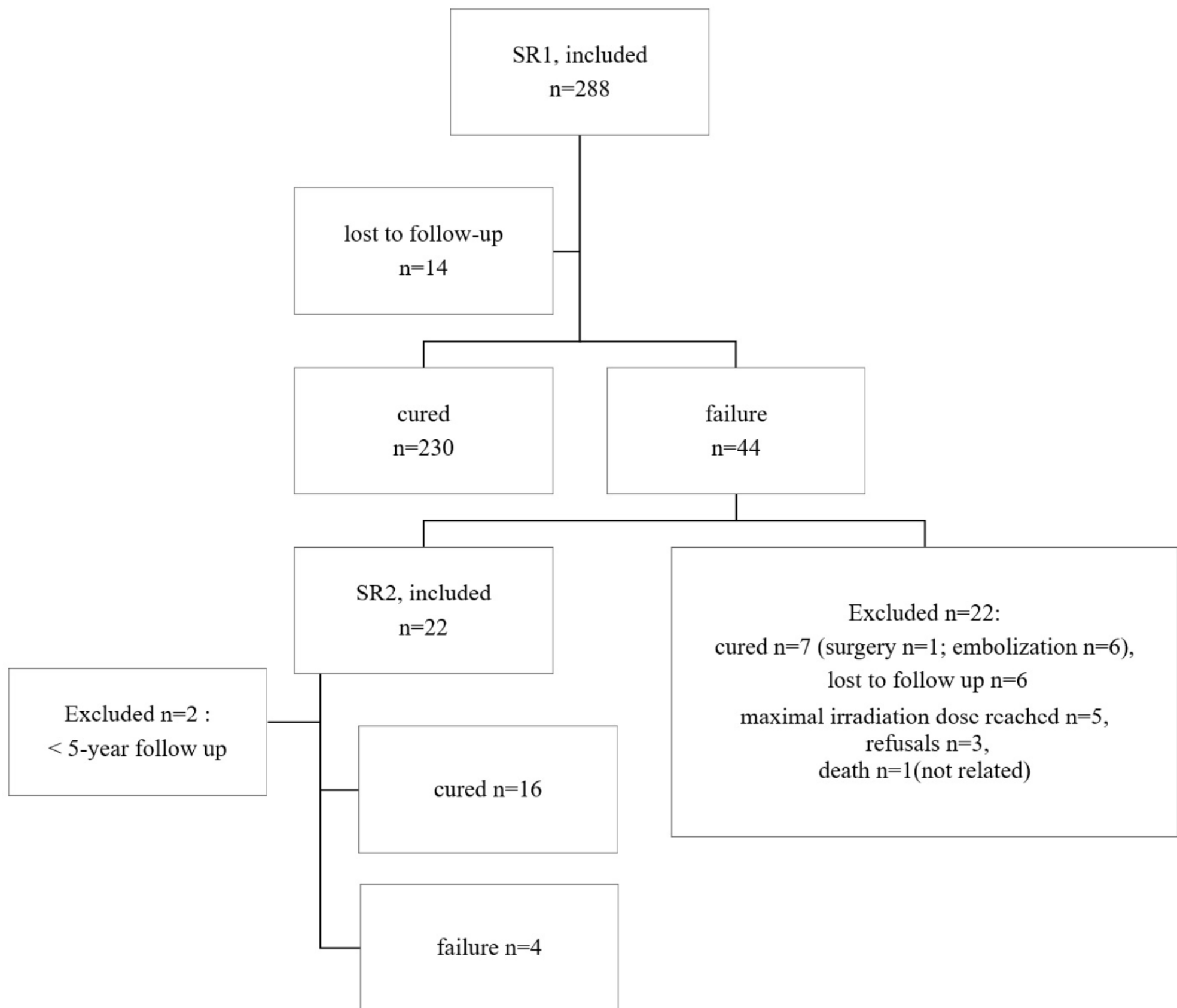


Table 1 : Characteristics of the population of failure

<b>Population of Failure</b>	
<b>Age (years), mean <math>\pm</math>sd / [range]</b>	36 $\pm$ 14.7 / [13-61]
<b>Gender, n (%)</b>	
male	22 (0.50)
Female, n (%)	22 (0.50)
<b>Clinical feature, n(%)</b>	
hemorrhage	21 (0.48)
seizure	10 (0.23)
headache	9 (0.20)
progressive motor deficit	1 (0.02)
incidental finding	3 (0.07)
<b>Previous Treatments, n (%)</b>	
embolization	32 (0.73)
microsurgery	2 (0.05)
embolization + microsurgery	2 (0.05)
<b>Location (eloquence), n (%)</b>	
eloquent zone	32 (0.73)
non eloquent zone	12 (0.27)
<b>Location, n (%)</b>	
Frontal lobe	7 (0.16)
Parietal lobe	6 (0.14)
Temporal lobe	7 (0.16)
Occipital lobe	4 (0.09)
Cerebellum	1 (0.02)
Corpus callosum	2 (0.05)
Basal ganglia	3 (0.07)
brainstem	2 (0.05)
<b>Spetzler &amp; Martin, n (%)</b>	
I	2 (0.05)
II	13 (0.30)
III	15 (0.34)
IV	14 (0.32)
<b>Pollock score, mean <math>\pm</math>sd / [range]</b>	1.17 $\pm$ 0.417 / [0.324-2.220]
<b>Dosimetrics Parameters, mean <math>\pm</math>sd / [range]</b>	
Targeted Volume (cm <sup>3</sup> )	2.18 $\pm$ 2.2 / [0.13-10.8]



Table 1 : Characteristics of the population of failure

Minimal Marginal Dose (Gy)	20.72 ±3.6 / [11.3-25.7]
Maximal Marginal Dose (Gy)	28.56 ±6.8 / [20-63.7]
Reference Dose (Gy)	24.18 ±4.0 / [20-27]
ICRU (Gy)	26.36 ±1.1 / [22-27]

		female	age (years)	Patterns of failure											
				Insufficient nidus coverage	prior embolization	recanalization	Volume (cm <sup>3</sup> )	Spetzler & Martin				Volume > 2 cm <sup>3</sup>	Volume > 4 cm <sup>3</sup>	Dose min < 18Gy	No cause
								I	II	III	IV				
		n (percentage)	SD; [range]	n (percentage)			(SD; range)	n (percentage)							
<b>Insufficient nidus coverage</b>	yes	7 (0.39)	33.83 +/- 12.73; [24-43]		15 (0.83)	0 (0)	1.52 +/- 1.49 [0.72-2.03]	0 (0)	6 (0.33)	5 (0.28)	7 (0.39)	5 (0.28)	1 (0.06)	2 (0.11)	0 (0)
	no	15 (0.58)	36.27 +/- 15.29; [22-45]		19 (0.73)	5 (0.19)	2.64 +/- 2.55 [0.61-4.23]	2 (0.08)	7 (0.27)	10 (0.38)	7 (0.27)	11 (0.42)	8 (0.31)	7 (0.27)	5 (0.19)
<b>prior embolization</b>	yes	18 (0.53)	<b>31.28 +/- 11.90</b> [22-		15 (0.44)	5 (0.15)	<b>2.50 +/- 2.33 [0.635-3.34]*</b>	0 (0)	9 (0.26)	11 (0.32)	14 (0.41)	15 (0.44)	8 (0.24)	7 (0.21)	<b>0 (0)*</b>

			<b>40]</b> <b>*</b>												
	no	4 (0.40)	<b>48</b> <b>+/-</b> <b>14.</b> <b>51</b> <b>[36-</b> <b>60]</b> <b>*</b>	3 (0.30)		0 (0)	<b>1.10 +/- 1.40</b> <b>[0.45-1.06]*</b>	2 (0.20 )	4 (0.40 )	4 (0.4 0)	0 (0)	1 (0.1 0)	1 (0.1 0)	2 (0.20 )	<b>5</b> <b>(0.50</b> <b>)*</b>
<b>recanalizat</b> <b>ion</b>	yes	<b>5 (1)*</b>	35. 40 <b>+/-</b> 6.2 3 <b>[34-</b> <b>38]</b>	0 (0)	5 (1)		2.18 +/- 2.22 <b>[0.64-3.34]</b>	0 (0)	1 (0.20 )	3 (0.6 0)	1 (0.2 0)	3 (0.6 0)	2 (0.4 0)	2 (0.40 )	0 (0)
	no	<b>17</b> <b>(0.44)</b> <b>*</b>	35. 26 <b>+/-</b> 14. 97 <b>[22-</b> <b>45]</b>	18 (0.46)	29 (0.74)		2.03 +/- 2.21 <b>[0.61-2.47]</b>	2 (0.05 )	12 (0.31 )	12 (0.3 1)	13 (0.3 3)	13 (0.3 3)	7 (0.1 8)	9 (0.23 )	5 (0.13 )
<b>Spetzler &amp;</b> <b>Martin</b>	I	0 (0)	44. 50 <b>+/-</b> 31. 81 <b>[22-</b> <b>67]</b>	0 (0)	0 (0)	0 (0)								0 (0)	<b>2</b> <b>(1)*</b>

	II	6 (0.46)	39. 15 +/- 15. 37 [32- 52]	6 (0.46)	9 (0.69)	1 (0.08)								0 (0)	<b>2</b> <b>(0.15)</b> )*
	III	7 (0.47)	35. 00 +/- 14. 04 [26- 40]	5 (0.33)	11 (0.73)	3 (0.20)								5 (0.33 )	<b>1</b> <b>(0.07)</b> )*
	IV	9 (0.64)	30. 64 +/- 10. 35 [22- 42]	7 (0.50)	14 (1)	1 (0.07)								4 (0.29 )	<b>0</b> <b>(0)*</b>
<b>Volume &gt; 2 cm<sup>3</sup></b>	yes	<b>12</b> <b>(0.75)</b> *	35. 06 +/- 10. 93 [28- 41]	5 (0.31)	15 (0.94)	3 (0.19)								5 (0.31 )	0 (0)
	no	<b>10</b> <b>(0.36)</b> *	35. 39 +/- 15.	13 (0.46)	19 (0.68)	2 (0.07)								4 (0.14 )	5 (0.18 )

			95 [21. 5- 44. 5]												
<b>volume &gt; 4 cm<sup>3</sup></b>	yes	7 (0.78)	34. 89 +/- 15. 39 [22- 45]	1 (0.11)	8 (0.89)	2 (0.22)								4 (0.44 )	0 (0)
	no	15 (0.43)	36. 78 +/- 8.5 4 [34- 40]	17 (0.49)	26 (0.74)	3 (0.09)								5 (0.14 )	5 (0.14 )
<b>Dose min &lt; 18Gy</b>	yes	7 (0.78)	33. 56 +/- 11. 66 [30- 40]	2 (0.22)	7 (0.78)	0 (0)	<b>3.66 +/- 3.20 [1.60-5]*</b>	0 (0)	0 (0)	5 (0.5 6)	4 (0.4 4)	5 (0.5 6)	4 (0.4 4)		0 (0)
	no	15 (0.43)	35. 71 +/- 14. 90	16 (0.46)	27 (0.77)	5 (0.14)	<b>1.80 +/- 1.77 [0.60-2.10]*</b>	2 (0.06 )	13 (0.37 )	10 (0.2 9)	10 (0.2 9)	11 (0.3 1)	5 (0.1 4)		5 (0.14 )

			[23-45]												
<b>No cause of failure</b>	yes	1 (0.20)	48.40 +/- 18.22 [38-60]	0 (0)	<b>0 (0)*</b>	0 (0)	<b>0.57 +/- 0.35</b> <b>[0.42-0.61]*</b>	<b>2</b> <b>(0.40)</b> <b>)*</b>	<b>2</b> <b>(0.40)</b> <b>)*</b>	<b>1</b> <b>(0.20)</b> <b>)*</b>	<b>0</b> <b>(0)*</b>	0 (0)	0 (0)	0 (0)	
	no	21 (0.54)	33.59 +/- 12.94 [23-43]	18 (0.46)	<b>34</b> <b>(0.87)*</b>	5 (0.13)	<b>2.38 +/- 2.28</b> <b>[0.74-3.65]*</b>	<b>0</b> <b>(0)*</b>	<b>11</b> <b>(0.28)</b> <b>)*</b>	<b>14</b> <b>(0.36)*</b>	<b>14</b> <b>(0.36)*</b>	16 (0.41)	9 (0.23)	9 (0.23)	