

Making stereotactic radiosurgery decisions by calculating the probability of perilesional edema in cavernomas

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Abstract. – OBJECTIVE: Stereotactic radiosurgery is a therapeutic modality for cavernomas that is associated with certain adverse effects, such as perilesional edema. In this study, we aimed to estimate the presentation of perilesional edema using imaging techniques, considering its location, proximity to major venous and arterial structures, size, depth, and eloquent location.

PATIENTS AND METHODS: The radiographic evaluation included their sizes, localization of the lobes, whether they were in the deep or superficial regions, eloquent areas, and their proximity to the major arteries and venous sinuses.

RESULTS: As the size increased, the time to edema increased at the same rate ($r=0.972$, $p=0.001$). We determined that the duration of edema increases as it attaches to the great venous structures, and edema occurs over a longer time ($r=-0.761$, $p=0.001$). Cavernomas >13 mm had a high probability of causing edema ($p=0.0014$). Edema occurred with a high probability in patients with an arterial distance <5.69 mm and a venous/arterial distance ratio >8.93 (specificity 100%, selectivity 98.2%).

CONCLUSIONS: When recommending stereotactic radiosurgery treatment, the possibility of edema formation should be calculated based on the location, size, and proximity of the cavernoma to the vascular structures, and the choice of treatment should be made accordingly.

Key Words:

Cavernous cerebral malformations, Spetzler-Martin Scale, Intracranial hemorrhage, Stereotactic radiosurgery, Perilesional edema.

Introduction

Cavernous cerebral vascular malformations (CCVM) are benign lesions that may continue to grow and tend to bleed. The disease prevalence ranges from 0.16-0.5%, with an annual rate of 0.56/100.000 years in adults^{1,2}. The annual risk of bleeding from cavernous cerebral malformations

(CMs) is reportedly up to 3%. The risk of rebleeding varies widely and ranges from 4.5-23% per year³. Although clinical findings vary based on the lesion location and bleeding status, CMs are often identified incidentally using progressive imaging methods in daily life⁴.

Among individuals with symptomatic CMs, 50% are diagnosed with seizures, 25% with focal neurological deficits due to bleeding, and 25% with focal neurological deficits without bleeding. Most of these cases are diagnosed in adulthood, while 25% are diagnosed in childhood. Although CMs are low-flow vascular malformations, individuals who exhibit symptoms may require appropriate medical interventions⁵. The autosomal dominant familial form of the disease commonly presents with multiple CMs (CCMI mutations), whereas the sporadic form typically manifests as a solitary cavernous malformation (CM)⁶.

The three therapeutic options for CM lesions are microsurgical excision, stereotactic radiosurgery, and conservative care. Stereotactic radiosurgery (SRS) is a treatment option for CMs, particularly when they are small, non-symptomatic, or non-hemorrhagic and when they cannot be removed with microsurgery. SRS is generally safe; however, perilesional edema (PLE) is a rare but potentially fatal complication that can lead to headaches and neurological deficits, which can cause morbidity⁷. Studies⁸ have shown that perilesional edema develops in 17% of patients after stereotactic radiosurgery, and it reaches its maximum size in an average of 6 months. Studies⁹ have also focused on predicting perilesional edema in meningiomas after SRS and have shown that the treatment is related to the localization and structural features of the tumor rather than its type. The possibility of perilesional edema formation has also been associated with invasion and size increase in the venous sinuses^{10,11}.

Among patients who underwent SRS for high-risk CM lesions, 18.4% experienced adverse radiation consequences¹². These findings demonstrate that PLE, one of the unanticipated consequences of SRS, decreases living standards and causes continuing neurological impairments. Although findings demonstrate that PLE, one of the unanticipated consequences of SRS, decreases living standards and causes continuing neurological impairments, it is difficult to understand and predict the outcome of SRS. Therefore, this work establishes a scoring system called the cavernoma perilesional edema (CPE) score, which can be used to predict the potential of PLE in CMs based on specific parameters.

This study aimed to elucidate the distinctive features of CMs that predict PLE and to clinically decide whether to use SRS as a treatment option, considering their location, proximity to major venous and arterial structures, size, depth, and eloquent location.

Patients and Methods

Study Design

A total of 78 individuals diagnosed with CM who underwent SRS between June 2018 and September 2021 were enrolled in this study. Our study included male and female patients over the age of 18 who decided to have SRS due to cavernoma, those who had no other malignancy or lesion in the brain, those who had no other malignancies in the body, those who were not under immune suppression, and those who did not receive steroid therapy. Exclusion criteria included individuals dealing with other malignancies or brain lesions, having malignancies elsewhere in the body, receiving immune suppression for various etiologies, and using steroid therapy. The PLE duration ranged from 1 to 24 months. The participants were monitored for 24 months.

All procedures were conducted in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and the Helsinki Declaration. Ethics committee approval was taken from Istanbul Medeniyet University ethical committee No.: 580/2023.

Radiological Imaging Before SRS

Cranial Magnetic Resonance Imaging (MRI) (1.5 Tesla) and its sequences, susceptibility-weighted (SWI) MRI, and gradient recalled

echo (GRE) were used to detect radiological features. A neuroradiology specialist performed the radiological procedures. Measurements were taken at the distances closest to the vascular structures. The distances to the great venous sinuses (transverse, cavernous, greater, and lesser petrosal, sphenoparietal, sigmoid and basilar, superior and inferior sagittal, straight, occipital, and intercavernous) and the closest detectable arterial distance were measured, and the venous distance/arterial distance (VAD score) was calculated from these results.

The superficial and deep locations were recorded (“superficial location” refers to a cortical area of the brain that is easily accessible, while “deep location” refers to the presence of a lesion situated within the subcortical white matter of the brain). The classification of brain regions as eloquent or non-eloquent was based on their anatomical location [the primary motor cortex (precentral gyrus), the primary somatosensory cortex (postcentral gyrus), the primary visual cortex, the primary auditory cortex, Broc’s area (located in the posterior inferior frontal gyrus, specifically in the pars opercularis and pars triangularis), and Wernicke’s area were considered as eloquent areas]. Solitary or multiple CMs and hemosiderin rings before SRS were recorded prior to SRS.

Evaluation After SRS

Patients presenting with perilesional edema after SRS treatment were documented. The diameter of the edema and formation time after treatment were recorded. The peripheral location of the cavernoma was determined in the 3D T2-weighted and gradient-Echo MRI. The dimensions of the cavernoma were determined based on its maximum diameter. The nearest arterial and venous distances were ascertained through MRI angiography and venography. Then, the measurement of distance was conducted. The measurement of cavernomas that induce edema involved determining their maximum width in conjunction with the associated edema’s diameter while excluding the cavernoma’s diameter. In addition, the localization of the CM and the timing and magnitude of edema following SRS were documented.

Stereotactic Radiosurgery

The CyberKnife radiosurgery system (Accuracy Inc., Sunnyvale, CA, USA) was used for stereotactic radiosurgery. It operates at a 6-MV energy level and possesses a sensitivity of 0.1 mm.

Statistical Analysis

All analyses were performed using SPSS version 25 (IBM Corp., Armonk, NY, USA). Histograms, Q-Q plots, and Shapiro-Wilk tests were used to determine whether the variables were normally distributed. Data are presented as median (1st-3rd quartile) for continuous variables and frequencies (percentages) for categorical variables. Between the two independent groups, continuous variables were analyzed using Student's *t*-test or Mann-Whitney U test, depending on the normality of distribution. Categorical variables were analyzed using the Chi-squared test or Fisher's exact test. Additionally, VAD, arterial distance, and size cut-off points were determined to predict edema. The optimal cut-off values were defined as the points on the receiver operating characteristic (ROC) curve closest to the 0% false positive and 100% true positive marks. Spearman's correlation coefficient was used to test the relationships between numerical variables that did not demonstrate a normal distribution. The strength of the correlation coefficient was interpreted as poor (0.2-0.4), moderate (0.4-0.6), strong (0.6-0.8), and very strong (0.8-1.9). Statistical significance was set at $p < 0.05$.

Results

Overall, 78 patients were enrolled in this study. The age of the patients ranged from 32 to 50 years, with a median of 44. Of these, 28 (35.9%) cases were located in the frontal lobe and 12 (14.4%) in the parietal lobe. Edema was observed in 21 (26.9%) patients. The mean great venous distance was 28.9 mm (range, 20-42.6 mm), the closest arterial distance was 7.98 mm (2.9-14.4), the venous/arterial ratio was 4.51 (1.09-10.11), the mean edema diameter was 40.9 mm (23.6-80.9 mm), the mean size was 10 mm (816 mm), and the mean duration of edema was 10 months (5-11 months). A deep location was observed in 42 (53.8%) patients, an eloquent location in 18 (23.1%), a single CCM in 66 (84.6%), and a hemosiderin ring in 48 (61.5%) (Table I).

A comparison was made between patients with and without edema for each variable. The arterial distance (1.58; range, 2.9-0.1) and venous/arterial distance (16.33; range 288-10.86) of the patients with edema were significantly higher ($p < 0.001$) than those of patients without edema. In addition, the size of CCMs with edema (15, range 21-8) was significantly larger than those without

edema ($p = 0.004$). A statistically significant difference exists in the location of the lobes, their presence in the eloquent region, and whether they are solitary or multiple. No edema was observed in the brainstem or pons. All lesions in the thalamus showed edema. Additionally, the prevalence of deep (85.7%), eloquent (42.9%), single (100%), and hemosiderin rings (85.7%) was significantly higher in patients with edema ($p < 0.05$).

The performances of VAD, size, and arterial distance in predicting edema were evaluated based on the ROC curves. According to the ROC analysis, the optimal cut-off value for VAD was > 8.93 . The area under the curve (AUC) was 0.99 (95% CI: 0.97-1) ($p < 0.001$) (sensitivity; 100%, specificity of 98.2%) (Figure 1).

In the diagnosis of edema, the cut-off point of the size parameter was > 13 , and the AUC was 0.71 (95% CI: 0.58-0.85) ($p = 0.004$; specificity, 71%; selectivity, 79%). In the diagnosis of edema, the arterial distance parameter cut-off point was < 5.69 , the AUC was 0.95 (95% CI: 0.9-0.99), ($p < 0.001$; specificity, 100%; selectivity 90%) (Table II).

A strong statistically significant positive correlation was found between the size and presentation time of edema ($r = 0.972$, $p = 0.001$). Additionally, there was a strong correlation between the size of the cavernoma and the diameter of the edema. Negative and strong statistically significant correlations were observed between the presentation time of edema and its size and the great venous distance ($r = -0.761$ and $r = -0.642$, respectively). Moreover, strong statistically significant negative correlations were found between venous/arterial distance and arterial distance ($r = -0.847$; $r = -0.642$, respectively) (Table III) (Figure 2).

When the hemosiderin ring was examined, the presentation time of edema was significantly longer, 13 months (10-16.5 months), in patients with a hemosiderin ring compared to others, 10 months (9-11 months) (Figure 3) (Figure 4).

Discussion

Brain vascular malformations were examined in all five groups. These include aneurysms, arteriovenous malformations, developmental venous anomalies, capillary malformations, and cavernous malformations. CMs are vascular abnormalities with gliotic borders in the form of lumps containing hyalinized vascular structures and hemosiderin deposits. It can occur sporadically

Table I. Summary of patient's characteristics and the relationship between edemas.

	Total (n=78) N (%) / M [Q1-Q3]	Edema (n=21) N (%) / M [Q1-Q3]	No edema (n=57) N (%) / M [Q1-Q3]	p
Male	42 (53.8)	15 (71.4)	27 (47.4)	0.059 ^a
Female	36 (46.2)	6 (28.6)	30 (52.6)	
Age	44 [32-50]	37 [27-57]	45 [32-55]	0.111 ^b
Great venous distance (mm)	28.9 [20-42.6]	28.8 [44-25.8]	29 [42.6-15.4]	0.335 ^b
Arterial distance (mm)	7.98 [2.9-14.4]	1.58 [2.9-0.1]	9.6 [22.03-7.05]	<0.001 ^b
Venous/Arterial Distance ratio (VAD)	4.51 [1.09-10.11]	16.33 [288-10.86]	1.91 [4.87-0.99]	<0.001 ^b
Size (mm)	10 [8-16]	15 [21-8]	10 [11-7]	0.004 ^b
<i>Brainstem</i>	4 (5.1)	0 (0)	4 (7)	0.023 ^a
<i>Frontal Lobe</i>	28 (35.9)	6 (28.6)	22 (38.6)	
<i>Multiple</i>	8 (10.3)	0 (0)	8 (14)	
<i>Occipital Lobe</i>	6 (7.7)	3 (14.3)	3 (5.3)	
<i>Parietal Lobe</i>	12 (15.4)	3 (14.3)	9 (15.8)	
<i>Pons</i>	3 (3.8)	0 (0)	3 (5.3)	
<i>Cerebellum</i>	6 (7.7)	3 (14.3)	3 (5.3)	
<i>Thalamus</i>	3 (3.8)	3 (14.3)	0 (0)	
<i>Temporal Lobe</i>	8 (10.3)	3 (14.3)	5 (8.8)	
Deep White Matter	42 (53.8)	18 (85.7)	24 (42.1)	0.001 ^a
Superficial	36 (46.2)	3 (14.3)	33 (57.9)	
Eloquence				
Yes	18 (23.1)	9 (42.9)	9 (15.8)	0.012 ^a
No	60 (76.9)	12 (57.1)	48 (84.2)	
Single	66 (84.6)	21 (100)	45 (78.9)	0.022 ^a
Multiple	12 (15.4)	0 (0)	12 (21.1)	
Hemosiderin Ring				
Yes	48 (61.5)	18 (85.7)	30 (52.6)	0.008 ^a
No	30 (38.5)	3 (14.3)	27 (47.4)	
Edema diameter (mm)	40.9 [23.6-80.9]			
Edema (month)	10 [5-11]			

^aPearson's Chi-square test; ^bMann-Whitney U test. Data are given as median (M) [1st quartile (Q1)- 3rd quartile (Q3)] for continuous variables and as frequency (percentage) for categorical variables.

cally and familiarly. With the expansion of the usage areas of imaging methods, the incidence of incidental detection has been increasing. It occurs in 0.01-0.05% of the general population and accounts for approximately 10-15% of all vascular malformations¹³.

SRS aims to eliminate the CM by directing a radiation source directly into the CM. However, there remains a need for a consensus on the effectiveness of SRS^{14,15}. Niranjan et al¹⁶ prepared a protocol and guidelines for the treatment of SRS of CMs. According to these guidelines, while asymptomatic cases without hemorrhage risk are followed up, SRS is recommended for single lesions in eloquent regions with hemorrhage risk and for two or more lesions that are difficult to surgically remove¹⁶.

Although SRS is considered safe, complications can develop. Between 5% and 40% of patients may encounter treatment-related complications, such as seizures, heightened headaches, temporary or sustained muscle weakness or neurological deficits, and PLE. Radiotherapy-induced MRI changes have been reported in 36% of patients after arteriovenous malformations (AVM) treatment¹⁷. These changes were accompanied by the appearance of PLE.

PLE is a complication commonly observed in radiosurgery and is typically associated with high-dose radiation¹⁸. Although the occurrence of PLE is believed to be lower in patients with CMs, a significant number of cases show radiological evidence of edema. A few individuals may ex-

Figure 1. Receiver operative characteristic curve analysis of edema estimation with arterial distance, venous/arterial distance, and size.

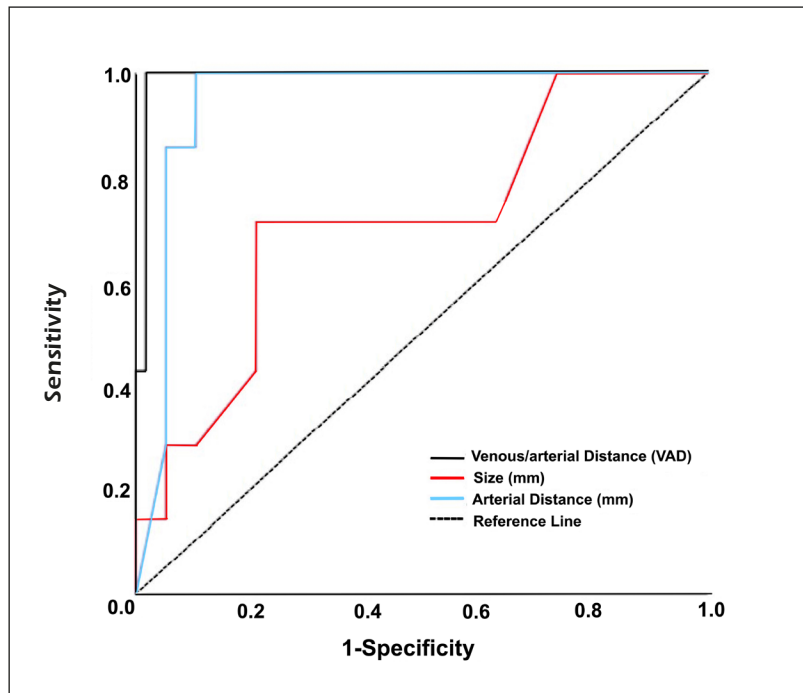


Table II. Cut-off points for edema estimation with ROC curve, VAD ratio, size, and arterial distance values.

Cut-off	AUC (95% CI)	Std Error	Sensitivity	Specificity	p
VAD>8.93	0.99 (0.97-1)	0.01	100%	98.2%	<0.001
Size>13 mm	0.71 (0.58-0.85)	0.07	71%	79%	0.004
Arterial Distance <5.69 mm	0.95 (0.90-0.99)	0.03	100%	90%	<0.001

CI: Confidence Interval, VAD: Venous/arterial distance ratio, AUC: Area under the curve.

Table III. Relationship between edema time, great venous distance, arterial distance, size, and VAD ratio variables in cases with edema.

		EDEMA (months)	Size (mm)
NSize (mm)	r	0.972	
	p	0.001	
Great venous distance (mm)	r	-0.761	-0.642
	p	0.001	0.002
Arterial distance (mm)	r	-0.073	-0.046
	p	0.752	0.843
Venous/Arterial Distance (VAD)	r	-0.382	-0.418
	p	0.088	0.059

hibit no symptoms, whereas others may manifest symptoms. Moreover, patients may exhibit neurological impairment and experience headaches. PLE is diagnosed 9.7% of PLE cases radiologically. Among these cases, 6.9% of the symptoms were temporary, and 2.7% were permanent¹⁸.

Greater peritumoral imaging changes were observed in SRS-treated meningiomas with convexity, parasagittal region, or falx cerebri localization. Additionally, venous obstruction, pial supply, location, tumor volume, tumor grade with histological subtype, vascular endothelial growth

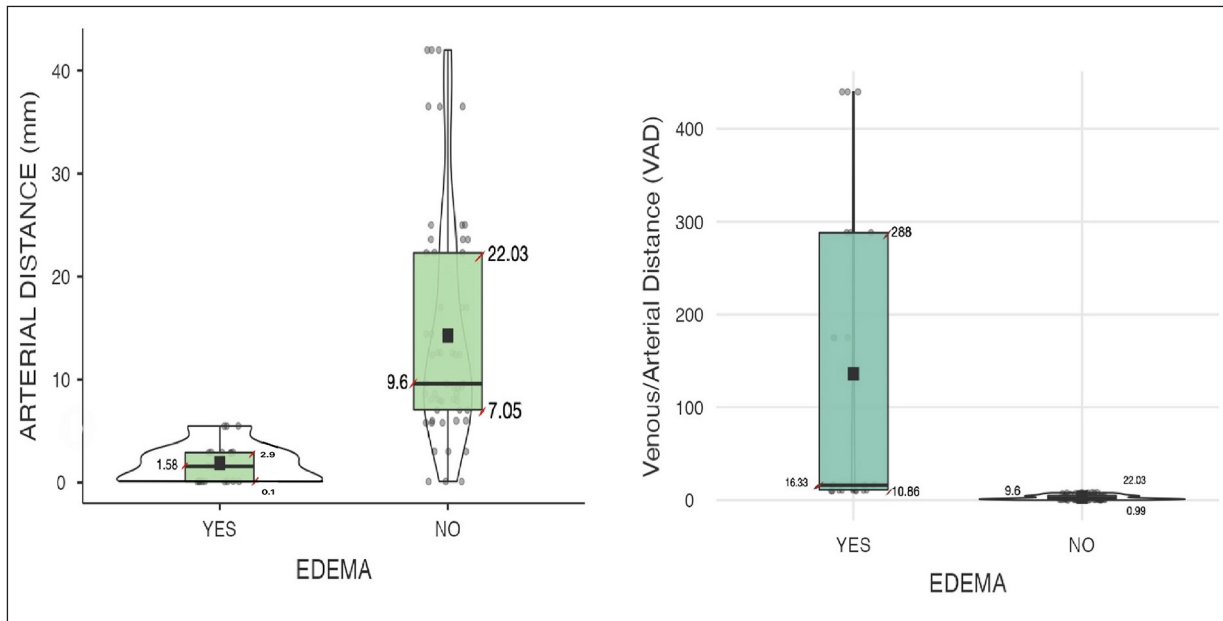


Figure 2. Boxplot graph showing the relationship of cavernoma with arterial distance, venous/arterial distance, and perilesional edema.

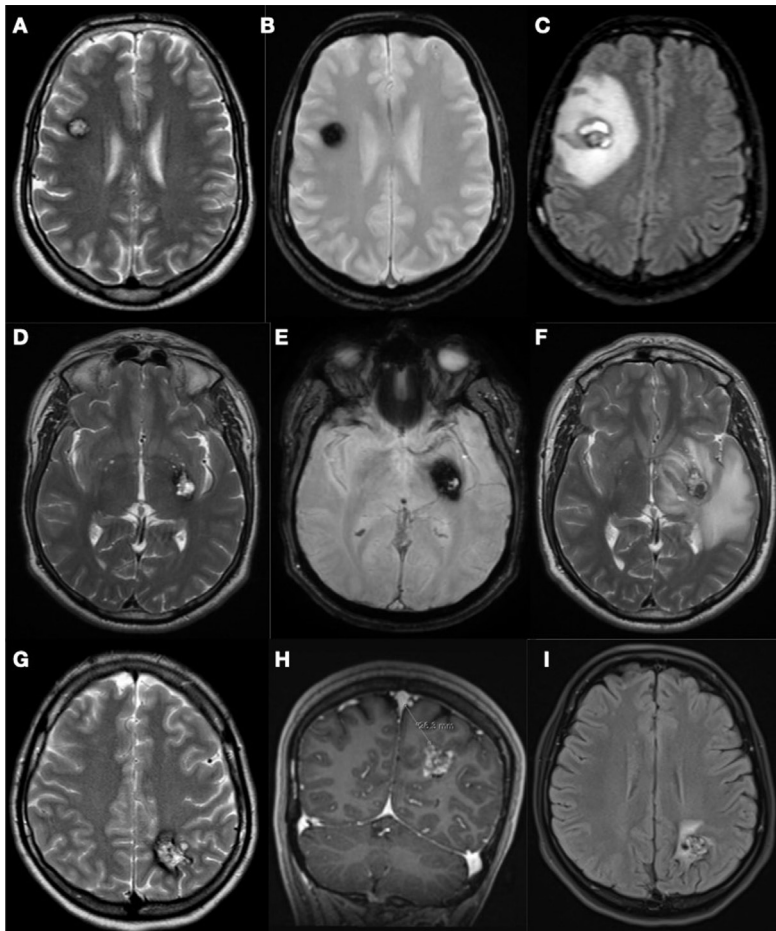


Figure 3. A-C, Perilesional edema MRI image of right frontal cavernoma after SRS. D-F, Perilesional edema MRI image of left thalamic cavernoma after SRS. G-I, MRI of perilesional edema after SRS, a left parietal cavernoma at a distance of 26.3 mm from the superior sagittal sinus. SRS, stereotactic radiosurgery; MRI, magnetic resonance imaging.

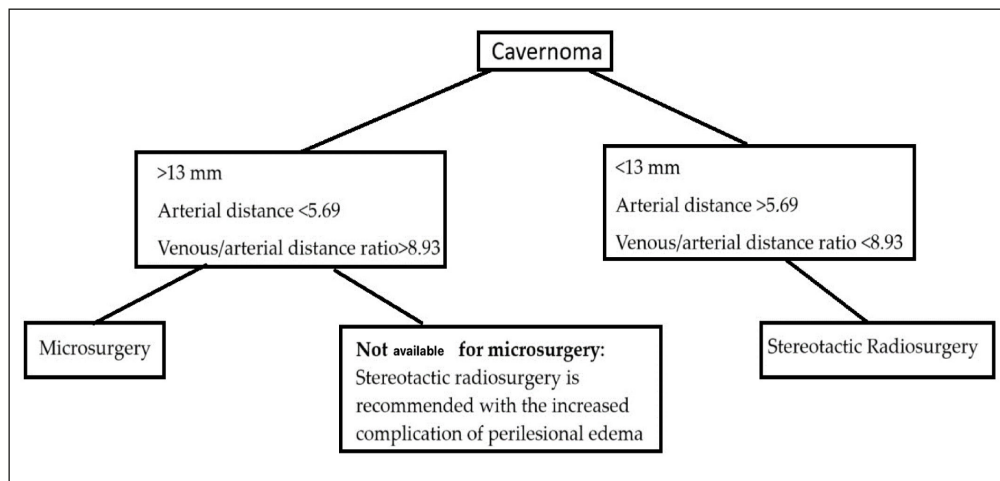


Figure 4. Diagram showing treatment selection methods against the possibility of perilesional edema.

factor (VEGF) receptor expression, and patient age were associated with PLE in meningioma studies. Conti et al⁹ identified PLE in 19 of 229 meningioma cases. Our results showed that the volume of the tumor, specifically non-basal tumors, was a potential contributing factor to the development of edema. Specific factors such as location, a close association between the brain and tumor, and the presence of atypical histology have been identified as potential contributors to the development of PLE^{9,19}. However, studies on CMs are lacking. After examining the parameters of the literature on tumors, we identified unfamiliar categories. Several parameters employed in the Spetzler-Martin grading system²⁰, commonly utilized for the management of AVMs, can be used to predict the occurrence of PLE after SRS treatment of CMs.

Liscák et al²⁰ reported a 27% prevalence of PLE in CMs after gamma knife radiosurgery, which is consistent with the 26.9% prevalence observed in our study²¹. In the present study, PLE tended to occur more frequently in the frontal region (28.6%) and was absent in patients with brainstem or pons involvement. The occurrence of PLE is believed to be uncommon because of the distinct characteristics of the brainstem and pons compared to other cortical cellular structures.

GRE-MRI effectively reveals hemosiderin pigments and microhemorrhages. Similarly, the SWI sequence is effective in showing deoxyhemoglobin and iron content and is more effective than GRE in imaging non-hemorrhagic CMs. The hemosiderin ring manifests as a hemosiderin pigment emerging from the vascular bed on

MRI^{22,23}. Hemosiderin rings were observed in 61.5% of patients. Additionally, the presence of a hemosiderin ring was observed in 85.7% of the PLE cases. The association between the hemosiderin ring and edema can be anticipated, given the implication of VEGF as a contributing factor to PLE and the reported efficiency of the VEGF inhibitor bevacizumab in its therapeutic intervention^{24,25}. Therefore, the presence of a hemosiderin ring, characterized by the occurrence of cavernous hemorrhage foci, increases the possibility of edema, which was detected in the deep white matter (85.7%) and non-eloquent regions (84.2%) in most patients. This situation is further linked to the proximity of deep-seated major arterial vascular structures and their corresponding blood supplies.

Noteworthy findings were observed when the influence of radiological proximity to vascular structures was eliminated as a factor. Although there was no statistically significant difference in the distance to the great venous sinuses between patients with and without edema, the measurable arterial distance in patients without edema (9.6 mm) was significantly different from that in patients with edema (1.58 mm). Moreover, upon calculating the vascular supply ratio for each lesion, the venous/arterial distance ratio was markedly elevated in patients with edema (16.33/1.91). An arterial distance of less than 5.69 mm exhibits a method characterized by 100% sensitivity and 90% specificity in the estimation of perilesion. Furthermore, upon integrating the VAD ratio, we observe a method exhibiting a specificity of 98.2%. There was a positive correlation between lesion size and

the presence of PLE. It is possible to predict that PLE may occur in CMs larger than 13 mm, with a sensitivity of 71% and specificity of 79%.

The presentation time of edema was observed in patients with hemosiderin rings for an average of 10 months. Further, a significant correlation was observed between edema size and the distance to the major venous sinuses based on the presentation time of edema.

Limitations

This study has certain limitations. Although our data provide strong statistical results, it is necessary to compare them with other patient groups and cohorts using the same parameters and discuss their effectiveness. Therefore, further studies on this topic are important.

Conclusions

Recommending SRS treatment, the possibility of edema formation should be calculated according to the location, size, and proximity of the cavernoma to the vascular structures, and the choice of treatment should be made accordingly.

Conflict of Interest

No conflict of interests declared.

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Informed Consent

Written informed consent was obtained from each patient.

Ethics Approval

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Ethics Committee approval was taken from Istanbul Medeniyet University, approval No.: 580/2023.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' Contributions

Research concept and design: HSC, EU, CS.
Data analysis and interpretation: HSC, EU, CS.
Collection and/or assembly of data: HSC, EU, CS.
Writing the article: HSC, EU, CS.
Critical revision of the article: HSC, EU, CS.
Final approval of the article: HSC, EU, CS.

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