



Evaluation of Treatment Response, Side Effects, and Prognostic Factors in AVM Patients Treated with Stereotactic Radiosurgery using Filter-Free Energies on LINAC

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OBJECTIVE

Arteriovenous malformations (AVMs) are rare vascular pathologies that can be treated with surgery, embolization, and stereotactic radiosurgery (SRS). Most of the data about SRS applied for AVM treatment belong to Gamma Knife. In this study, the patients who were treated with linear accelerators with filter-free energies (FFF) were retrospectively analyzed.

METHODS

In this study, 19 patients with AVM diagnosis who underwent SRS with FFF and VMAT technique between 2014 and 2022 were evaluated. The clinical features and radiotherapy planning data of the patients were analyzed. The treatment response was evaluated with angiography/MR angiography results performed at 6, 12, and 24 months after SRS. The duration until the treatment response, side effects, and the factors affecting them were examined.

RESULTS

The median age of the patients was 33 (12–64) years. Embolization was performed before SRS in 12 patients, while seven received SRS only. Nine patients were treated with 6X-FFF and 10 with 10X-FFF energy. The median PTV was 7.30 cc (1.20–37.60). The median treatment dose was 20 Gy (15–20 Gy). Median follow-up was 20 (5–81) months. Symptoms disappeared after the treatment in twelve patients (63%) and the median time to symptom disappearance was 4.5 (1–12) months. Median follow-up was 20 (5–1) months. Complete obliteration was seen in twelve patients and median time to obliteration was 11.5 (3–31) months. Partial obliteration was achieved in five patients. Based on the radiological evaluation, the obliteration rates were 6/18 (33%), 6/14 (43%), and 8/13 (62%) at 6, 12, and 24 months, respectively. Complete obliteration was obtained in six patients who reached a 3-year follow-up period. Brain necrosis was observed in three patients (16%) at 11, 27, and 30 months.

CONCLUSION

In patients diagnosed with AVM, the treatment outcomes of SRS with LINAC-based FFF are similar to those achieved with other systems. A longer follow-up period is required for evaluating the side effects.

Keywords: Arteriovenous malformation; filter-free energies; LINAC; stereotactic radiosurgery.

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INTRODUCTION

Arteriovenous malformations (AVMs) are abnormal vascular formations that are rare congenital pathologies characterized by the absence of capillaries between arteries and veins. Although approximately 1/5 of them are asymptomatic, they may present with intracranial bleeding, seizures, headache, and focal neurological deficits. Intracranial bleeding is the most common clinical presentation.[1]

Preventing intracranial bleeding is the primary objective of AVM treatment. Microsurgery, radiosurgery and endovascular embolization may be used alone or in combination for this purpose. Radiosurgery is the least invasive method among these. It prevents bleeding by causing vascular obliteration, but the time until occlusion can take up to 1 year according to some sources, while others state it may take 3–5 years.[2,3] A successful surgical resection rapidly eliminates the risk of bleeding. The treatment decision should be made with a multidisciplinary team considering the bleeding risk of the lesion in short and long-term, its impact on patient's daily activities, treatment options and the risks of the treatment.[4]

The use of radiosurgery in AVM treatment was firstly reported as a case study by Steiner et al.[5] in 1972. The developments in technology for linear accelerator based radiosurgery advanced in early 1980s. As linear accelerator based radiosurgery is becoming more popular, most of the articles published about AVMs are presenting Gamma Knife (GK) treatment results.[6]

Some of the current linear accelerators have the capacity of treatment using flattening filter and flattening filter free (FFF) photon beams. FFF beams used in stereotactic radiotherapy provide a rapid dose reduction, protect the organs at risk better than filtered beams and have 2–4 times higher dose rate, significantly reducing beam-on-time. The dosimetric results of the treatment plans with FFF have been observed to be similar or better than the plans delivered with FF beams.[7] In a study by Mamballikalam et al.,[8] it was indicated that FF and FFF beam models and different irradiation techniques can be equivalent in stereotactic radiosurgery (SRS) applied to small lesions. It has been stated that the only possible advantage of the filter free energies may be the short treatment duration due to the high dose rate. However, in their study, Nakano et al.[9] concluded that the dose delivery duration is important in the effects of radiotherapy. Besides, it should be kept in mind that the short irradiation time may be important in reducing errors that can arise from busy work schedules and patient movements.[10]

In this retrospective study, we compared the AVM obliteration rates and radiation induced damages in result of the treatment delivered with filter free energies in LINAC based device with the current literature.

MATERIALS AND METHODS

Nineteen patients with AVM who underwent SRS (with Varian TrueBeam STX) with filter-free energies (FFF) in LINAC between 2014 and 2022 were included in this study. The patient group consisted of those with residual nidus after the embolization, those were not suitable for embolization/surgery or those who refused these procedures.

Demographic characteristics, clinical symptoms of the patients, and the information about other treatments administered to the patients before radiotherapy (embolization/surgery) were obtained from archive records. Radiological stages were determined using digital angiography/magnetic resonance (MR) imaging/MR angiography/computed tomographic (CT) angiography imaging techniques. Spetzler-Martin (SM) staging system was used.

Simulation CT images of the patients were obtained using Siemens Somatom Definition AS device with a slice thickness of 1 mm. Thermoplastic head masks were used for immobilization of the patients. CT images were transferred to the Treatment Planning System (TPS) and fused with diagnostic MR angiography images. The AVM nidus was contoured as GTV with a radiologist. PTV was created by giving a 1 mm margin to GTV. Treatments were planned using VMAT technique (2 or 3 arcs) with a LINAC (Fig. 1). The device has 2.5 mm HD MLCs. For the treatments, 6X or 10X FFF energies were used. It was aimed to comply with ICRU 91 [11] criteria for dosimetric evaluations. The treatment dose was targeted to cover 98% of the PTV volume (D98). It was intended not to exceed the dose limitations in Timmerman's table [12] for organ at risk doses. Brain tissue volumes receiving 8 Gy, 10 Gy, abs 12 Gy (V8, V10, and V12) were tried to be kept as low as possible. Dosimetric QA was performed before every treatment. IGRT technique was used in the treatment. The simulation CT images were matched with CBCT images to ensure that set up errors were <1 mm.

The clinical information of the patients (age, gender, SM stage, location of the lesion, symptoms, the modality of treatment before SRS, symptom persistence after the treatment, steroid use, the presence of edema or necrosis...), and radiotherapy planning data

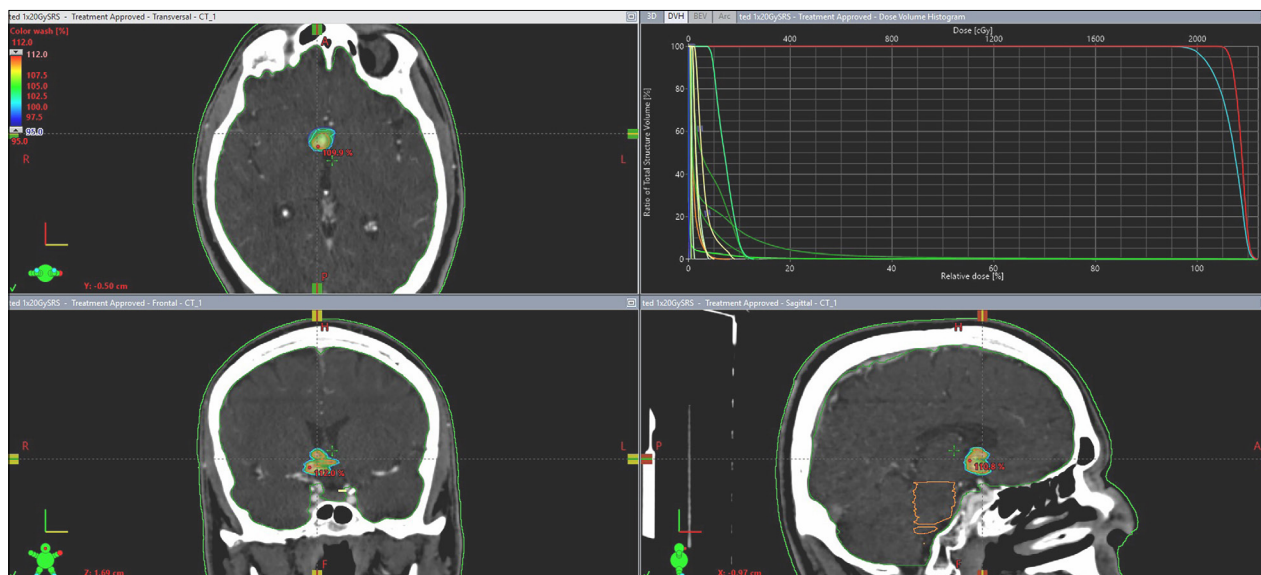


Fig. 1. Planning views and DVH table(upper right) of a case. 47 years old, man. In September 2017 complained seizure. AVM has been seen at cerebral angiography but was not suitable for embolization because of the location. So that 1x20 Gy SRS has been applied and 9 months after SRS total obliteration has been found at cerebral angiography. DVH: Dose-volume histogram; AVM: Arteriovenous malformations; SRS: Stereotactic radiosurgery.

(technique, number of arcs, treatment dose, GTV, PTV, V8, V10, and V12...) were investigated as the factors affecting prognosis. Treatment response was evaluated by comparing MR/MR angiography/digital angiography images before the treatment and during follow-up. These data were obtained from the Radiation Oncology archive, TPS (Eclipse, Version 11 and 15), radiation therapy information system (ARIA, Version 11 and 15), hospital information system, and PACS (Secra IDS7, Version 20.2.10.3376).

After the treatment, the follow-up intervals were 3 months for the 1st year, 6 months for the 2nd year and then annually. Symptom evaluation and physical examination were performed during routine outpatient clinic visits. Obliteration levels were evaluated with digital or MR angiography every 6 months in the first 2 years after treatment and annually thereafter.

Treatment response, time to response, side effects, and factors affecting these outcomes were evaluated. Treatment response analyses and the effects of the variables on the response were conducted using the Kruskal-Wallis test.

RESULTS

In our study, median age of the patients was 33 (12–64) years. Ten(53%) of the patients were women and 9 (47%) of them were men. Eight of them (42%)

were diagnosed by angiography, 5 (26%) by MRI and 6 (32%) by MR angiography. The distribution of SM stages was as follows: stage I 2 (11%), stage II 3 (16%), stage III 4 (21%), stage IV 9 (47%), and stage V 1 (5%). Sixteen (84%) patients were presented with headache, 4 (21%) with seizure and 1 (5%) with loss of vision. At the time of diagnosis 5 patients (26%) had intracranial bleeding. SRS was applied to 7 of the patients as the only treatment method and 12 patients were treated with SRS after embolization (Table 1). Nine patients were treated with 6X-FFF and 10 patients with 10X-FFF energies. All the treatment plans were made using VMAT technique with 2 arcs used in 17 plans and 3 arcs used in 2 plans. Median PTV was 7.30 cc (1.20–37.60 cc), median treatment dose was 20 Gy (15–20 Gy). Less than 20 Gy dose were applied to six of the patients (18 Gy to 5, 15 Gy to 1 patient). Median brain V8 value was 2.76% (0.70–10.93), V10 was 1.83% (0.48–7.41) and V12 was 1,50 (0.36–5.54). Median Conformity Index calculated with *Peddick* formula was 1.01(0.56–1.24) and median Gradient Index (GI) was 4.41(2.82–8.97).

Median follow-up was 20 (5–81) months. The total obliteration rates at the 6th, 12th, 24th months of follow-up were 6/18 (33%), 6/14 (43%), and 8/13 (62%), respectively. All six patients who reached a 3-year follow-up had achieved complete obliteration. The median time to complete obliteration was 11.5 (3–31) months.

Table 1 Patients characteristics

Characteristics	n	%
Gender		
Male	9	47
Female	10	53
SM grade		
I	2	11
II	3	16
III	4	21
IV	9	47
V	1	5
Symptom		
Headache	16	84
Seizure	4	21
Vision loss	1	5
SRS timing		
After embolization	12	63
Only SRS	7	37

SRS: Stereotactic radiosurgery

In twelve patients (63%) symptoms disappeared after the treatment and median time to recovery was 4.5 (1–12) months. Brain edema occurred in 8 patients (42%), 3 (16%) of them had intracranial bleeding after SRS. Grade 3 or more serious side effects have not been observed. Brain necrosis was observed in three patients (16%) at the 11th, 27th and 30th months after SRS. Lesions of these patients were localized at right temporooccipital paramedian region, prefrontal cortex, and right parietooccipital region, respectively. Embolization before SRS has been applied to all three of them. The patient who developed necrosis at the 30th month underwent surgical excision due to the lack of response to medical treatment. PTV in this patient's SRS plan was 30.60 cc and the brain V8, V10, and V12 values were 7.71%, 5.72%, and 4.59%, respectively. The patient who developed necrosis at the 27th month of follow-up was treated with high-dose methylprednisolone and the symptoms were controlled. PTV in this patient's SRS plan was 5.10 cc and the brain V8, V10, and V12 values were 2.76%, 1.83%, and 1.32%, respectively. Radynecrosis was observed in a patient at the 10th month after treatment, and PTV in this patient's SRS plan was 31.20 cc. The brain V8, V10, and V12 values were 10.93%, 7.41%, and 5.54%, respectively. The patient's clinical condition was improved after 5 months of corticosteroid use.

The factors that are associated with the time to total obliteration were statistically analyzed. No significant relationship was found between GTV or radiotherapy

dose and the time to treatment response ($p=0.11$ and $p=0.39$; respectively). The use of embolization before SRS or SM stage alone did not show a significant contribution to treatment success ($p=0.70$ and $p=0.37$; respectively). There was no significant relationship between PTV and the presence of side effects (bleeding or necrosis) ($p=0.46$).

DISCUSSION

The main objective of AVM treatment is to prevent intracranial hemorrhage by stopping the blood flow to the nidus. Microsurgery, endovascular embolization and radiosurgery are the methods that can be used to achieve this goal individually or in combination. The size, complexity, venous drainage, depth, and localization of AVM, material used for embolization (which can change the radiation doses to the nidus when SRS is applied), amount of the material used, whether or not revascularization occurs after embolization affects treatment success and some of the risk factors patients have before the diagnosis of AVM. These factors include intracranial bleeding, seizures, vascular diseases, neurological deficits, and stroke.[13] The most important factor among these predicting the treatment success alone is the size of AVM. Factors such as the number of feeding arteries, having seizures, and presence of headache are associated with the size of the lesion. Independent factors that influence the success include deep venous drainage, extension to the surrounding brain tissue and location in the dominant hemisphere.[14] In a study, it was concluded that SM stage does not predict the stroke or death risk in patients with unruptured and untreated AVM.[15] In our study, embolization before SRS or the SM stage did not show a significant contribution to the treatment success alone ($p=0.70$; $p=0.37$, respectively). Furthermore, the presence of hemorrhage before the treatment was not found to be a statistically significant factor for the treatment success ($p=0.15$).

SRS prevents bleeding by obliterating the vessels. According to some sources, the time to vascular obliteration may take up to 1 year, while in others this duration is shown as 3–5 years.[2,3] In our study, the median time to complete obliteration was calculated to be 11.5 (3–31) months. This was considered shorter compared to other studies in the literature.

Some of the current linear accelerators have the capacity to treat with both flattening filtered and flattening filter free photons. FFF photons used in stereotactic radiotherapy provide a better protection for the organs

at risk by providing a sudden dose fall-off. They have 2–4 times higher dose rate than filtered beams which reduces the *beam-on* time significantly. Dosimetric results of treatment plans using FFF have been shown to be similar or better than those with FF beams.[7] A study by Mamballikalam et al.,[8] which applied SRS to very small (≤ 1 cc) and small (≤ 3 cc) lesions in brain with different techniques, established that the dosimetric properties (dose conformity, heterogeneity, dose fall-off characteristics, organs at risk doses) of FF and FFF beams as a function of application technique showed a minimal variation. The only difference observed was that FFF provides slightly more monitor units than FF beams for volumes up to 2 cc with *rapidarc* technique, but the situation was reversed for 3 cc target volume. In conclusion, this study demonstrated that FF and FFF beam models and different irradiation techniques for SRS in small tumor volumes may be equivalent. The only possible advantage of FFF was stated to be the short treatment times due to high dose rates. However, Nakano et al.[9] showed that the increased time of dose delivery in photon irradiations reduced the relative biological effectiveness. Therefore, it was concluded that FFF beams could be used for effective radiotherapy with shorter dose delivery times. In addition, it should be kept in mind that the delivery time is shorter in treatment plans using FFF, which can be important for reducing the device density and errors caused by patient movements.[10] All patients in our study were treated with FFF and had similar treatment success compared to treatments using FF in the literature.

A review published by Yahya et al.[16] concluded that while treatments with GK systems provide a better Conformity Index (CI) and GI, LINAC-based SRS can achieve better dose homogeneity in the target and better protection of critical organs. GI in this study was reported to have a median of 4.3 (2.0–9.9). In our study, median GI was calculated to be 4.41 (2.82–8.97) with LINAC-based FFF, which is similar to values achieved with GK. In a study by Orio et al.,[17] the median CI for GK treatments was reported to be 1.1; while in our study with LINAC-based FFF, the median CI was calculated to be 1.01.

According to a study which used only LINAC based radiosurgery and had a median follow up of 15.6 years, it was deduced that the positive treatment outcomes are associated with a target volume of < 4 cm³ and a marginal dose greater than 12 Gy.[18] Ding et al.[19] showed in one of their studies that ≥ 20 Gy margin dose provided better control. Our study has a median follow-up of 20 (5–81) months. Median GTV was 4.20 cc (0.70–22.70), median PTV was 7.30 cc (1.20–37.60)

and median treatment dose was 20 Gy (15–20). In contrast to the literature, GTV or the applied dose did not show a significant relationship with the treatment outcome ($p=0.11$ and $p=0.39$ respectively). That result may be due to the small number of patients, 20 Gy being administered to 68% (13/19) of the patients and the relatively short follow-up period.

In a study conducted by Esteves et al., which includes patients who were treated with a 6 MV linear accelerator, they reported a 72% occlusion rate, which is similar to some other studies (Colombo et al. 75%; Betti et al. 66%; Souhami et al. 43% in a year; Lunsford et al.[20–24] 80% with GK). This study mostly comprised of patients with surgically inaccessible lesions, contraindications for surgery and failed total obliteration after embolization. The authors reported that the widest diameter, volume of the malformation and applied dose did not affect the time of the obliteration.[20] Twelve of the patients in our study received SRS after embolization, while seven of them did not receive any treatment before SRS. Nine patients were treated with 6X-FFF and ten of them were treated with 10X-FFF energy. All six patients who reached a 3 year follow-up had achieved complete obliteration. The patients were evaluated radiologically at 6, 12, 24 months. The obliteration rates were 6/18 (33%), 6/14 (43%), and 8/13 (62%), respectively. These results are similar to the literature.

Orio et al.[17] did not find a statistically significant difference in the AVM obliteration rates between radiosurgery performed with GK and LINAC. They reported high obliteration rates in both groups at 3–4 years after treatment. They also noted that the rates of treatment-related toxicity were similar in both groups. Multivariate analyses indicated that the most significant predictor of chronic toxicity was previous SRS. Unlike previous studies, treatment volume was not found to be a statistically significant risk factor for chronic toxicity. This may be due to the use of more tightly restricted dose limits based on the previous studies. They stated that the similar toxicity rates of two treatment modalities may be due to differences in patient groups and treatment parameters. The biggest difference between two groups was found to be the median applied dose. It should be noted that lower median treatment doses were applied with LINAC due to a lack of sufficient clinical experience, particularly before 2002. The median treatment dose was 16 Gy for LINAC and 20 Gy for GK. In our study which consisted of patients treated in a single fraction with LINAC using FFF, median treatment dose was 20 Gy (15–20 Gy). These results suggest that with the advances in LINAC

technology, similar results can be achieved with treatments applied at equivalent doses to those used in GK.

A meta-analysis based on data from 51 studies, classified the complications associated with radiotherapy as radiological, symptomatic and permanent. These side effects were reported as 35.5%, 9.2% and 3.8% respectively in patients treated with radiotherapy with AVM diagnosis. The incidence of these complications was 33.9% in GK based SRS and 43.5% in LINAC based SRS. Symptomatic radiation related complications were as follows: hemiparesis (48.9%), headache (16.3%), seizures (12.1%), sensory loss (7.1%), and ataxia (3.5%). Permanent complications included hemiparesis (52.9%), visual field loss (28.6%), diplopia (12.9%), seizures (5.7%), and ataxia and sensory loss (4.3%). It was noted that fewer radiological anomalies were seen during follow-up in ruptured AVMs.[25]

In a study examining radiation induced changes following GK radiosurgery, acute side effects after SRS appeared as peri-nidal hyperintensity that could be visualized in T2-weighted or FLAIR MR within the first 2 years after treatment. The breakdown of the blood-brain barrier following endothelial damage and subsequent development of demyelination is the suggested pathophysiological mechanism of radiation induced damage. The average time for the onset of acute side effects is 13 months. According to the authorities, 83% of changes in MR disappear spontaneously within an average of 22 months. While the frequency of observed acute side effects in MR is 30%, symptoms can develop in 10% of patients. Acute side effects can be permanent in 3% of patients. Corticosteroids or antiepileptics are used for the treatment of the symptoms. The hospitalization rate is very low.[26] AVM localization, nidus size, margin dose, and brain volume receiving a dose over 12 Gy can predict the symptom presence. Symptomatic damage is more common in deep localizations (thalamus, basal ganglia and brainstem).[27] In our study, brain edema developed in eight patients (42%) and intracranial hemorrhage developed in three patients (16%) after the treatment. In patients with brain edema, corticosteroids were prescribed and symptoms regressed in all of them. No grade 3 or higher side effects were observed in the acute period.

Late onset side effects are rarely seen. Persistent brain edema, radiation necrosis and cystic vascular formation are some of the late onset side effects that typically appear 5 years or later after the treatment. The incidence of late onset side effects is around 2–6% and depends on the follow-up duration.[28] Delayed cyst formation has been associated with larger AVM volumes, higher

radiation doses, complete obliteration, and lobar localization.[29] It can be treated with drainage, shunt placement or resection when it causes symptoms. Radiation necrosis can be visualized as edema and mass effect on MRI. Resection can be applied if it causes symptoms and is located in a “non-eloquent” area. Secondary tumors related to radiation can also be seen as late side effects, but their frequency is unknown. It has been established that the risk of secondary malignancies is lower in single fraction than fractionated treatments.[30] In our study, grade 3 or more serious side effects were observed in three patients (16%). In the 11th, 27th, and 30th months, these three patients showed signs of brain necrosis. The patient who experienced necrosis in the 30th month did not respond to medical treatment, and surgical excision was performed. PTV in this patient’s treatment plan was 30.60 cc. V8, V10, and V12 of the brain volume are 7.71%, 5.72%, and 4.59%, respectively. The patient who developed necrosis in the 27th month was treated with high-dose methylprednisolone and then was monitored closely. PTV in the treatment plan of this patient is 5.20 cc. V8, V10, and V12 of the brain volume are measured as 2.76%, 1.83%, and 1.32%, respectively. In the treatment plan of the patient who developed radiation necrosis in the 10th month after treatment, it was observed that the PTV was 31.20 cc. V8, V10, and V12 of the brain volume are 10.93%, 7.41%, and 5.54%, respectively. The clinical symptoms of this patient improved after 5 months of steroid use. No permanent neurological damage was observed in our patient group but longer follow-up periods are needed. Two studies conducted with LINAC-based devices showed a median V12 value of 4.5 cc[31] and 5.97 cc, respectively. In the first study, radiation necrosis rate was found to be 20% but there was no relationship with the irradiated volume ($p=0.21$). In the second study, it was observed that one patient developed radiation-induced necrosis and the V12 value for this patient was 18.5 cc.[16] In our study, the V12 values of our patients who developed radiation necrosis at 11th, 27th, and 30th months after treatment were measured as 75.34 cc; 17.53 cc; and 63.22 cc, respectively. These values are higher than those reported in other studies in the literature.

CONCLUSION

Treatment results of SRS with LINAC based devices using FFF in AVM patients are similar to those applied with other methods. Longer follow-up periods are needed in terms of side effects.

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Conflict of Interest: All authors declared no conflict of interest.

Ethics Committee Approval: The study was approved by the Dokuz Eylül University Non-interventional Research Ethics Committee (no: 2023/03-10, date: 18/01/2023).

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