Artigo Original

RADIOSURGERY WITH A LINEAR ACCELERATOR IN CEREBRAL ARTERIOVENOUS MALFORMATIONS

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SUMMARY

Objective. To evaluate results achieved with radiosurgery and complications of the procedure when treating arteriovenous malformations with linear accelerator.

Methods. This retrospective study was conducted between October 1993 and December 1996. Sixty-one patients with arteriovenous malformations were treated with radiosurgery utilizing a 6MV energy linear accelerator. Ages of the 32 female and 29 male patients ranged from 6 to 54 years (mean: 28.3 years). The most frequent initial symptom was cephalea (45.9%), followed by neurological deficit (36.1%). Cerebral hemorrhage diagnosed by image was observed in 35 patients (57.3%). Most arteriovenous malformations (67.2%) were graded Spetzler III and IV. Venous stenosis (21.3%) and aneurysm (13.1%) were the most frequent angioarchitecture changes. The dose administered varied from 12 to 27.5Gy in the periphery of the lesion.

Results. Out of twenty-eight patients that underwent conclusive angiography control, complete obliteration was achieved in 18 (72%) and treatment failed in 7 (absence of occlusion with more than 3 years of follow-up). Four were submitted to a second radiosurgery, and one of these has shown obliteration after 18 months of follow-up.

Discussion. Several factors were analyzed regarding the occlusion rate (gender, age, volume, localization, Spetzler, flow, embolization, total of isocenters, prescribed dose and chosen isodose) and complications (total of isocenters, localization, volume, maximum dose, prescribed dose and chosen isodose). Analyzed variables showed no statistical significance for obliteration of the vessel, as well as for treatment complications. The largest diameter of the arteriovenous malformation, its volume and the dose administered did not influence time of obliteration.

Conclusion. Radiosurgery is effective in the treatment of arteriovenous malformations and can be an alternative for patients with clinical contraindication or with lesions in eloquent areas. In the studied variables no statistically significant correlation was observed between occlusion and treatment complications.

Key Words: Stereotactic radiosurgery. Linac radiosurgery. Linear accelerator. Arteriovenous malformations. Radiation.

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Introduction

Cerebral arteriovenous malformation is a morphologic, functional and very rare change, present in less than 0.8% of the population, and only 10% of the patients present symptomatology [1, 2]. Among its manifestations, the scariest is bleeding, with a 2% to 4% yearly risk [3-5], which makes it a very peculiar infirmity due to its localization and consequent risk of sequels. There is a 10% risk of mortality in the first bleeding [6], and up to a 30% risk of morbidity.

Considering microsurgery, the classical treatment, associated or not to embolization, radiosurgery is an alternative in situations of clinical contraindication, because of the unfavorable location for surgery or even due to the patient's choice for a less invasive treatment.

Radiosurgery is capable of occluding approximately 70% to 80% of the arteriovenous malformations treated in the most experienced centers of the world (Karolinska, Pittsburgh, Vicenza, and Harvard, among others).

Objective

This study aims to disclose results obtained with radiosurgery in Brazil and to analyze several factors that could be associated with the obliteration rate and complications of the procedure in the treatment of arteriovenous malformations with a linear accelerator.

Methods

Patient population

Between October 1993 and December1996, sixty-one arteriovenous malformation patients were treated with radiosurgery at the Beneficência Portuguesa Hospital of São Paulo.

Ages of the 32 female and 29 male patients ranged from 6 to 54 years with a mean of 28.3 years (median 29 years).

Cephalea was the most common symptom (45%; n = 28), followed by motor deficit (36%; n = 22) and collapse and convulsion (23%; n = 14). Cerebral hemorrhage was diagnosed by tomography or resonance in 35 patients (Table1).

The anatomic region most frequently affected by arteriovenous malformations was that of the base nuclei (36%; n = 22). Embolization was the previously utilized procedure in 35 patients (57%). Diameters of the lesions varied from 0.4 to 8.0cm (mean 3.02cm) and the volume from 0.3 to 37.5 cm^3 (mean volume = 4.74cm^3).

Most patients were graded initially as Spetzler III (37%) and IV (29%).

Before embolization, the flow of the arteriovenous malformations was found to be high in 11%, low in 21% and medium in 52%.

In association with arteriovenous malformations the most frequently found angioarchitecture change was venous stenosis (21%), followed by aneurysm (8%). Fourteen patients were submitted to surgical procedures before radiosurgery, six for removal of clots and eight for removal of arteriovenous malformations.

After embolization, there was a change in the Spetzler grading variable due to reduction of the arteriovenous malformation diameters, increasing predominance of grades II (29%) and III (50%).

Procedures

The equipment utilized for treatment of patients was the 6MV linear accelerator, linked to the Radionics planning system.

The collimators used varied in number and diameter for the 61 patients treated. From 1 to 3 isocenters with diameters ranging from 1.25 to 3.0cm were utilized.

Patients selected for radiosurgery were submitted early in the morning, under local anesthesia, to fixation of the stereotaxy frame Brown Roberts Wells (BRW) in the skull, with placement of screws by the team's neurosurgeon. Afterward, tests of tomography, magnetic resonance and angiography were performed. For each test, this study utilized accessories corresponding to the respective parameters, for image reception by the computerized program. Analysis of the test and delimitation of the arteriovenous malformations volume by the neuroradiologist were performed prior to transference of the angiographic images.

The administered dose ranged from 12 to 27.5Gy in the chosen isodose (periphery of the lesion) and from 18.33 to 47.22Gy at the peak. We have followed the risk estimated by Kjellberg for radionecrosis due to the irradiated volume[7].

Principal measurements

After radiosurgery, patients were followed up with clinical-neurological and image tests.

Magnetic resonance was performed every 6 months on the average and for suspicion of occlusion, an angiography was performed. Timing of these tests was somewhat flexible.

Control angiography was performed in 31 patients (these patients have also undergone other tests such as resonance and tomography); 24 patients were followed-up with only resonance and angioresonance; and 6 patients have missed follow-up.

The occlusion rate in the 31 patients that underwent angiography was analyzed as well as complications in the 55 patients that underwent clinical follow-up.

Out of the 31 patients that underwent angiography, 6 were considered inconclusive, meaning that no occlusion was observed in the interval up to 3 years after radiosurgery.

Table 1 - Frequency distribution of the initial symptoms (n=61)

Initial Symptoms	Frequency	%
Hemorrhage	35	57.3
Cephalea	28	45.9
Motor deficit	22	36.1
Collapse/convulsion	14	23

Table 2 - Radiosurgery result for the different AVM diameters (n=25)

AVM Diameter	Failure	Total Occlusion
<15mm	0	6(100%)
15 to 25mm	4	6(60.0%)
>25mm	3	6(66.6%)
Total	7	18(72.0%)

AVM = arteriovenous malformations.

In 25 patients, it was possible to conclude whether treatment had been a failure or a success, for in these patients, occlusion (cure) was observed, as well as arteriovenous malformation persistence in the 3 years after radiosurgery (failure).

Cure was considered whenever the angiography showed a normal aspect, with the complete absence of pathological vessels, of the *nidus* pattern of the arteriovenous malformation and disappearance or normalization of the area's venous drainage[8].

Statistical methods

Data analysis was performed using the chi-square test or the Fisher's exact test. For comparison of related measurement proportions, the Stuart-Maxwell test was used, and measurement comparisons between two groups was performed by Mann-Whitney test. The Kruskal-Wallis test was utilized for comparison of 3 or more independent groups. The level of significance used was 5%.

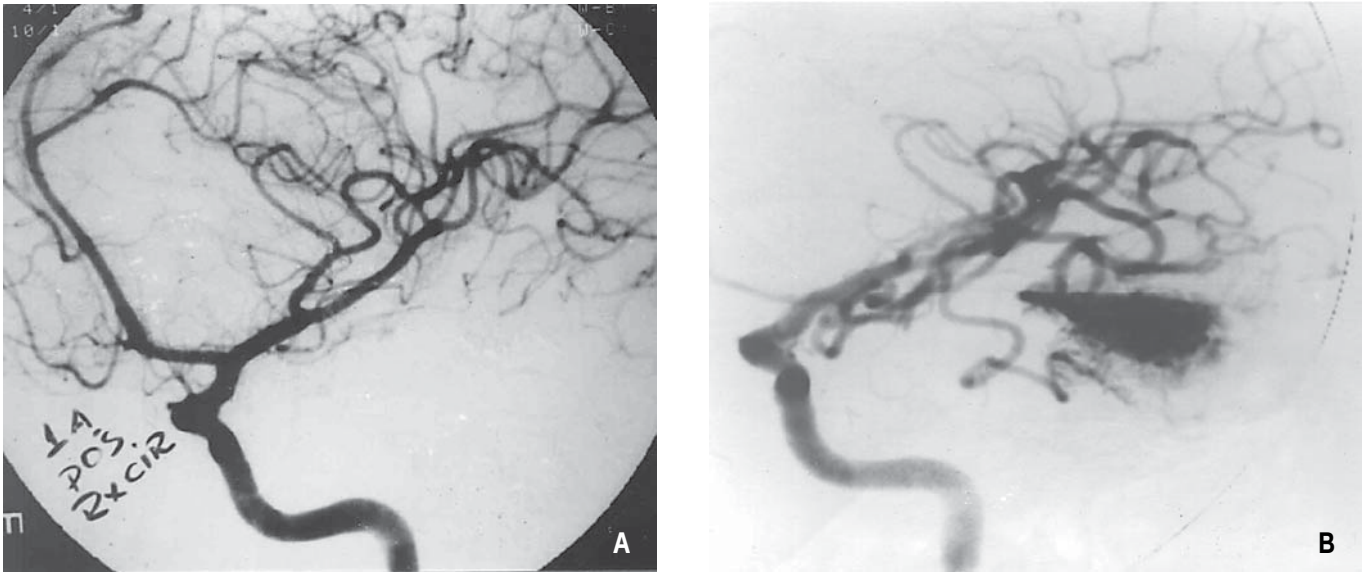
RESULTS

Of the twenty five patients analyzed conclusively in relation to occlusion or failure, success was achieved in 72%, with the lesions up to 15mm of diameter (n=6), occluded in 100% (Table 2). Time of occlusion, following angiography ranged from 12 to 48 months (mean: 28.8 months).

The arteriovenous malformations of the temporal region were those that, proportionally, most occluded (100%) (Figure 1), followed by those of the parietal region (80%) and base nuclei (66%). Location of arteriovenous malformations was not correlated to the occlusion rate (p=0.561) nor to the Spetzler grading (p=0.412). Other factors evaluated did not correlate significantly with the arteriovenous malformation occlusion rate: age (p=0.060), gender (p=0.659), volume of the lesion (p=0.9999), flow (p=0.281), embolization (p=0.352), total of isocenters (p=0.528), prescribed dose (p=0.2861) and chosen isodose (p=0.0869).

In this study it was noted that time of occlusion was not directly

Figure 1 - A) AVM of left temporal region submitted to radiosurgery with a 25Gy dose in the periphery. B) Complete AVM occlusion 12 months after radiosurgery



related to the administered dose, nor to the volume of the arteriovenous malformations.

Radiosurgery complications observed were motor deficit in 4 patients (7.2%), perilesional edema in 4 patients (7.2%), and low memory in 1 patient (1.8%). Four patients presented bleeding after radiosurgery (7.2%). Two patients died, one of bleeding and the other of liver transplant.

At follow-up, clinical evaluation showed that 23 patients were asymptomatic, taking no medications, 13 presented deficit, 11 asymptomatic with medication, 6 symptomatic without deficit, 6 missed follow-up, and 2 died.

Seven patients that did not achieve occlusion in 3 years of post-radiosurgery follow-up were considered to be a failure. Four, out of these seven were submitted to a second radiosurgery and one achieved occlusion at 18 months post-treatment.

Patients treated with 3 isocenters presented a higher complication rate (28%), but no significant correlation was found ($p = 0.52$).

The anatomic regions that presented more complications were those of the frontal and parietal base nuclei. No statistically significant difference was found ($p = 0.358$).

Other analyzed factors did not influence significantly the complications rate either: the volume ($p = 0.0798$), the chosen isodose ($p = 0.7444$), the prescribed dose ($p = 0.0554$), and the maximum dose ($p = 0.7846$).

DISCUSSION

This study presents a peculiar sample of arteriovenous malformation patients. Most of them had already experienced contraindication of other potentially curable procedures. Many of them with not surgically treatable lesions, others with clinical contraindication for surgery or even the desire of not being operated and also those that were operated but total exeresis of the arteriovenous malformation had not been possible.

Occlusion rate was 72%, equivalent to the rates found in the best series in literature (Colombo et al. - 75%; Betti et al. - 66%; Souhami et al. - 43% in one year; Lunsford et al. - 80% with a gamma knife)[9-12].

This study has questioned whether the linear accelerator would be equivalent to the *gamma knife* regarding effectiveness and accuracy. Podgorsak et al. analyzed the physical characteristics of the two techniques and concluded that, when utilizing multiple frames with the rotatory technique, distribution of isodoses, the dose in the target and its decay at a few millimeters distance are equivalent[13, 14]. In the 1980's, first results with the linear accelerator were very promising because they proved the equivalence between the different radiosurgery techniques[9, 10].

Radiosurgery has been found to be very effective for occlusion of malformed vessels as well as for control of symptoms [15]. There is evidence that radiosurgery would act on the neurons, thus contributing to control of epilepsy[16].

Some authors have shown equivalence of result between radiosurgery and microsurgery[17, 18]. The major benefit of radiosurgery is to provide a treatment, alternative to surgery and complementary to embolization, when it is not successful in lesions with difficult surgical access or in eloquent areas. Another factor to be considered regarding radiosurgery is how easy it is for the patient. The method does not require hospitalization, and treatment is only slightly invasive. Nevertheless, the time needed for occlusion of the vessel, that may take up to three years, should be considered as a drawback of the method.

Radiosurgery is an adequate treatment for arteriovenous malformations, for, in addition to precision, which preserves

normal tissues, the high single dose, administered to the late response tissues (low alfa/beta), presents a greater biological effect. As such, theoretically, radiosurgery is much more effective for the treatment of arteriovenous malformations than for high grade metastases and gliomas [19].

In this study, mean age of patients at onset of the disease was 28.3 years. The youngest patient was 6 years old and the dose utilized was not changed because of age. Kondiziolka et al. utilized doses that range from 16 to 25Gy in children. The most frequent initial symptom was cephalea, followed by neurological deficit (45.9% and 36.1% respectively) [20]. These data are similar to those found by Steiner et al [15]. Some authors classify hemorrhage as a symptom, even when confirmed only by tests such as tomography and resonance. In our study, 57% of the patients presented hemorrhage. Kondiziolka et al. showed a higher incidence of hemorrhage (82%) among children from 2 to 18 years of age [21].

The lesions presented a diameter varying from 0.4 to 6cm (mean: 2.3cm) at the moment of radiosurgery. The larger lesions complicate radiosurgery technically, with a greater chance for formation of hot spots due to the combination of collimators, forcing reduction of the prescribed dose. These situations might suggest selecting specific points within the arteriovenous malformation, such as the nourishing arteries, aiming to reduce toxicity of the method. However, Steiner showed that if the whole volume of the *nidus* is not included, radiosurgery will not bring about good results [22].

Colombo et al. established a direct correlation between diameter of the arteriovenous malformation and success of therapy [23]. For this author, the smaller lesions close more than the larger ones. Another frequently found correlation is that of the given dose with the probability of occlusion. Smaller lesions allow for bigger doses, due to the low risk of complications. Therefore, it becomes difficult to distinguish whether success is due to the dose or to the diameter of the lesion. Some authors consider the absence of a well established minimal dose for the occlusion of the arteriovenous malformation [24]. Steiner suggested that the minimal peripheral dose favorable for occlusion would range from 20 to 25Gy [25]. Colombo et al suggested doses from 22 to 30Gy for lesions up to 15mm in diameter [9, 23].

Our study did not find a relation between dose and probability of occlusion. The lowest effective dose utilized was 15Gy, in which a 3.75cm collimator was used in the 80% isodose with a maximum dose of 18.75Gy.

Since the structure of the arteriovenous malformation vascular wall varies considerably, presenting with different proportions of elastic and muscular layers, it is possible that the greater response to radiosurgery is associated to predominance of the muscular layer.

Seventy percent of the patients in this study were graded Spetzler III, IV and V, which translates into the non-surgical indication for these patients.

Spetzler grading [26] is not the best parameter to compare treatment results between radiosurgery and surgery. This grading was elaborated aiming to predict the surgical risks of the procedure and so must be taken into account for the therapeutic decision. Complication risks in radiosurgery are related to other factors not included in the Spetzler grading. In radiosurgery, the diameter is of great significance in relation to the complication rates, as well as to success of the therapy (probability of occlusion). The difference is that in radiosurgery, the dose can be adjusted in order to keep the complication rate a constant. For example, when using a collimator with 2cm diameter and prescribing 20Gy, the expected risk of complications is 3%. When using a collimator with 3cm diameter for the same 3% complication risk, the prescribed dose should be reduced to 15Gy. In eloquent areas or sensory innervation areas, the dose administered should depend not only on the diameter of the collimator, but also on the tolerance dose of these structures. Lesions graded Spetzler I can present several different diameters. An arteriovenous malformation located in a non-eloquent area, with superficial venous drainage and with a 3cm diameter is considered grade I. In this same situation, changing only the diameter to 1cm, this arteriovenous malformation continues to be graded Spetzler I. Cure rate with surgery is of 94% in both situations [27] and, for radiosurgery, cure rate of a 3cm arteriovenous malformation can be of 33% and for a 1cm arteriovenous malformation the rate reaches up to 96% [9].

The radiosurgery utilized varied considerably with respect to the total of isocenters, the prescribed dose and the chosen dose. Definition of these data depended basically on the volume and format of the *nidus* and of its anatomic location. Combination of two isocenters was the most utilized technique, with doses varying from 12 to 27.5Gy (mean: 21.29Gy). The minimal dose is normally a factor of concern, especially in the association of isocenters. In this study, the maximum dose ranged from 18.33 to 47.22Gy (mean: 29.30Gy) and this variable was not related to the complications.

Clinical improvement was observed in the majority of series that studied this variable [10, 12, 15, 28]. These data are in accordance with our study. Many symptoms of the initial clinical status are transitory making it difficult to evaluate the real contribution of radiosurgery to control these deficits. In our study, we observed that of the 22 patients initially presenting deficit, 9 have achieved full recovery of the symptoms during follow-up. Among the 13 that developed the deficit, 3 presented complications from embolization, 3 presented complications from surgery and 4 presented complications from radiosurgery. These data disclose that the therapy applied brought about high morbidity.

Signal changes are the main findings of resonance observed in the complications (hypersignal in T2), and they can correspond to an edema, to demyelination or gliosis. The edema can arise because of vascular permeability changes due to direct action of radiation, leading to barrier breaking and a consequent overflow of proteins that would originate the angiogenic edema [29]. Lately, changes of the cerebral parenchyma after radiosurgery have been observed [30].

The bleeding rate during the six years was 7% (n = 4), with 5, 14, 17 and 28 month intervals, respectively, between radiosurgery and bleeding. Although radiosurgery initiates a thickening process of the vascular wall, most authors consider that the risk of bleeding persists until complete occlusion of the malformed vessel occurs [31]. Kjellberg stated that radiosurgery contributes to protection of the vessel, stopping bleeding, even without complete occlusion [32]. This can occur, theoretically, through reduction of the flow inside the *nidus*. On the other hand, upon existence of venous stenosis, flow reduction can precipitate formation of thrombus in the drainage vein, culminating in pressure increase inside the *nidus* and consequent bleeding.

The analyzed variables showed no statistical significance for obliteration of the vessel (gender, age, volume, region, Spetzler, flow, embolization, total of isocenters, prescribed dose, and chosen dose) as well as for complications of the treatment (total of isocenters, region, volume, prescribed dose, maximum dose, and chosen isodose). The largest diameter of the arteriovenous malformation, its volume and administered dose did not influence time of obliteration.

CONCLUSION

This study shows the effectiveness of a consecrated therapeutic method for treatment of arteriovenous malformation, achieving occlusion and complication rates within the values obtained to date in literature.

Such data accredit radiosurgery with a linear accelerator for the treatment of arteriovenous malformation as an alternative for the lesions located in areas of difficult surgical access, or for patients with clinical contraindication for microsurgery, or still, for those that have been treated with embolization or even surgery, that were not able to achieve complete occlusion of the arteriovenous malformation.

Conflict of interest: none

RESUMO

RADIOCIRURGIA COM ACELERADOR LINEAR EM MALFORMAÇÕES ARTERIOVENOSAS CEREBRAIS

OBJETIVO. Analisar os resultados obtidos com radiocirurgia e as suas complicações do procedimento, no tratamento das malformações arteriovenosas com acelerador linear.

MÉTODOS. Este é um estudo retrospectivo. Entre Outubro de 93 e Dezembro de 96, sessenta e um pacientes com malformações arteriovenosas foram tratados, utilizando um acelerador linear com 6MV de energia. As idades variaram de 6 a 54 anos (média: 28,3 anos), 32 pacientes mulheres e 29 pacientes homens. O sintoma inicial mais freqüente foi cefaléia (45,9%), seguido de déficit neurológico (36,1%). Hemorragia cerebral diagnostica por exame de imagem foi observada em 35 pacientes (57,3%). A maioria das malformações arteriovenosas (67,2%) eram graus III e IV de Spetzler. Estenose venosa (21,3%) e aneurisma (13,1%) foram as mais freqüentes alterações da arquitetura vascular. A dose administrada variou de 12 a 27,5Gy na periferia da lesão.

RESULTADOS. Dos vinte e oito pacientes que se submeteram a controle angiográfico conclusivo, 18 tiveram obliteração completa (72%) e 7 falharam ao tratamento (ausência de oclusão com mais de três anos de seguimento). Quatro pacientes foram submetidos a uma segunda radiocirurgia, e um paciente deste grupo apresentou obliteração em 18 meses de seguimento.

DISCUSSÃO. Vários fatores foram analisados em relação ao grau de oclusão (sexo, idade, volume, localização, Spetzler, fluxo, embolização, total de isocentros, dose prescrita e isodose escolhida) e complicações (total de isocentros, localização, volume, dose máxima, dose prescrita e isodose escolhida). As variáveis analisadas não mostraram significância estatística para a obliteração do vaso, bem como para as complicações de tratamento. O maior diâmetro da malformação arteriovenosa, seu volume e a dose administrada não influenciaram no tempo de obliteração.

CONCLUSÃO. Radiocirurgia é eficiente no tratamento das malformações arteriovenosas e pode ser uma alternativa para pacientes com contra-indicações clínicas ou com lesões em áreas eloqüentes. Não foram observadas correlações estatisticamente significativas entre as variáveis estudadas entre oclusão e complicações do tratamento.[Rev Assoc Med Bras 2008; 54(2): 167-72]

UNITERMOS: Radiocirurgia estereotáxica. Radiocirurgia com acelerador linear. Radioterapia. Malformações arteriovenosas. Radiação.

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