

Long term effects of Gamma knife Radiosurgery for treatment of cerebral arteriovenous malformations

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Abstract

Background: The Gamma Knife Radiosurgery (GKR) is an established management option for Cerebral Arteriovenous Malformations (AVMs). Therapeutic benefits of radiosurgery for arteriovenous malformations are complete obliteration of nidus with minimal neurological deficit.

Methods: Radiosurgery was performed between February 2003 and April 2010 at Kamraniye day clinic, Tehran, Iran, using the Leksell gamma knife model B (Elektra Instruments AB, Stockholm, Sweden) on 82 consecutive patients with AVMs. The male-to-female ratio was 1.4:1 (48M, 34F). The age of the patients ranged from 9 to 70 years (mean, 28.5±12 years). The marginal dose to the AVM nidus was 45 to 85% (median, 60%) isodose and ranged from 14 to 30 Gy (mean, 20.57±13Gy). The maximum dose ranged between 20 to 60 Gy (mean, 37.5 Gy ± 10.17Gy). Follow up of patients for complete AVM obliteration and in the case of complications MRI were performed.

Results: Complete obliteration of AVM was achieved in 56 cases (68.29%). It was marked in average 3.62 [SD=3.19] years (from 1 to 5 years) after GKR. Partial obliteration (≥50% reduction of the nidus volume) was marked in 24 cases (31%), and less than 50% reduction of the nidus volume was marked in 2 cases (2.4%) with a follow-up of 5 years. Complete obliteration of AVM had statistically significant associations with smaller score of Spetzler-Martin arteriovenous malformation grading system for AVMs. ($p < 0.05$)

Conclusion: The Gamma Knife Radiosurgery can offer total and partial obliteration to acceptable percent of treated AVM with a low risk of morbidity. Higher success observed in patients with Spetzler-Martin Grade I and II AVMs, which was attributed to smaller volume of AVMs in this group.

Keywords: Gamma Knife Radiosurgery (GKR), Arteriovenous malformations, Obliteration rate

Introduction

The Cerebral arteriovenous malformations (AVMs) are vascular anomalies that cause abnormal pathway between arterial system and venous system [1]. Despite the low prevalence (0.06% up to 0.11%) in the gen-

eral population, AVMs are one of the main cause of intracranial hemorrhage in people younger than 35 years old, and therefore the main goal of treatment is to prevent the bleeding caused by rupture of the pathological vessel pathways [2-5].

Available treatments for AVMs include

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microsurgery, embolization, Stereotactic radiosurgery or a combination of these methods [6].

The Gamma Knife Radiosurgery (GKR) is an established management option for Cerebral Arteriovenous Malformations. It can be used as an alternative method to microsurgery in low-grade lesions as a modality of choice for Intermediate grade AVMs and as a part of a combined treatment of high-grade AVMs. In up to 90% of cases, the treatment results in complete obliteration of the AVM within several years after treatment [7-14].

Therapeutic benefits of radiosurgery for arteriovenous malformations are the complete obliteration of nidus with minimal neurological deficit.

Early complications are associated with hemorrhage from the nidus during latency period [10,15]. When complete obliteration is achieved within several years, the risk of hemorrhage becomes very low; but the possibility of several other complications exists on the long-term follow up [10,15]. The incidence of delayed radiation induced complications range from 3.2 to 12.5%, which have been experienced by all investigators

performing radiosurgery for the AVMs using a gamma knife [16,17]. One of the most frequent and important of delayed radiation induced complications is cyst formation in the vicinity of the target area [10, 18-20].

We conducted this study to evaluate long term effects of gamma knife radiosurgery for treatment of cerebral arteriovenous malformations.

Methods

Radiosurgery was performed between February 2003 and April 2010 at Kamraniye day clinic, Tehran, Iran, using the Leksell gamma knife model B (Elektra Instruments AB, Stockholm, Sweden) on 82 consecutive patients with AVMs.

The stereotactic frame was fixed to the patient's head under local anesthesia (general anesthesia was generally used for children younger than 10 years of age) and the position of frame was adjusted on the head of patients according to the location of the AVM in the brain to bring the nidus of the AVM closer to the center of the stereotactic system.

Table 1. Distribution of symptoms for patients with AVM.

Presenting symptoms	Percent
Headache	68%(56)
Hemorrhage	54%(45)
Seizures	30%(24)
Transient neurologic deficits	40%(32)
Decreased mental status	10%(8)
Visual deficits	7%(5)
Others	10%(8)

Data are presented as frequency percentage (NO.).

Table 2. Arteriovenous malformation localization.

Site	percent
Parietal	20.75%(17)
Occipital	15.9%(13)
Temporal	14.6%(12)
Frontal	9.8%(8)
Thalamus	7.3%(6)
Cerebellum	4.9%(4)
Corpus Callosum	9.8%(8)
Basal Ganglia	2.4%(2)
Brain Stem	3.7%(3)
Intraventricular	11%(9)

Data are presented as frequency percentage (NO.).

Table 3. Spetzler Martin arteriovenous malformation classification

Grade	Percent
I	14.6%(12)
II	34.1%(28)
III	35.4%(29)
IV	14.6%(12)
V	1.2%(1)

Data are presented as frequency percentage (NO.).

Table 4. The AVM obliteration after the gamma knife radiosurgery treatment in 82patients

Years after GKS	Total obliterated	Not total obliterated	Cumulative Obliteration Rate (%)
1	9	73	10.97 %
2	20	53	35.36 %
3	15	38	53.65 %
4	7	31	62.19 %
5	5	26	68.29 %

Stereotactic localization of the AVMs was done with angiography alone (28 patients) angiography plus computed tomography (9 patients), angiography with magnetic resonance imaging (30 patients) and MRI alone (15 patients).

The male-to-female ratio was 1.40: 1 (48M, 34F). The age of the patients ranged from 9 to 70 years (mean, 28.5 ± 12 years).

Previous microsurgical resection was performed on 5 (6.09% patients), embolization performed on 9 (10.97% patients), stereotactic radiotherapy performed on 1 (1.21% patients), and 3(3.63%patients) had history of CVA and ICH. 7 of these patients (8.53%) had undergone a combination of surgery plus embolization before the gamma knife treatment.

Gamma knife radiosurgery was the primary treatment for 60 (73.17%) patients.

Various symptoms, localization of the AVM and the Spetzler grade are summarized in Tables 1, 2, 3.

The diameter of the AVM nidus ranged between 0.9 and 5.9 cm (mean, 2.7 ± 0.5 cm).

The marginal dose to the AVM nidus was 45 to 85% (median, 60%) isodose and ranged from 14 to 30 Gy (mean, 20.57 ± 3.13 Gy). The maximum dose ranged between 20 to 60 Gy (mean, $37.5 \text{ Gy} \pm 10.17$ Gy).

In one case in which obliteration was not achieved 3.5 years after radiosurgery in an-

other center, gamma knife was repeated in our center.

Follow up patients for complete AVM obliteration and in the case of complications (for example, post irradiation edema or re-bleeding) MRI were performed. The MRI scans were performed after the complete obliteration only in cases in which the clinical status was suspicious.

Statistical Analysis

Statistical analysis was carried out using SPSS v.13 software. Data were presented as number, percent, mean and standard deviation (SD). The statistical analysis was conducted using the T test and the p-value < 0.05 was considered statistically significant.

Results

Complete obliteration of AVM was achieved in 56 cases (68.29%). It was marked in average 3.62 [SD=3.19] years (from 1 to 5 years) after GKR. Partial obliteration ($\geq 50\%$ reduction of the nidus volume) was marked in 24 cases (31%), and less than 50% reduction of the nidus volume was marked in 2 cases (2.4%) with a follow-up of 5 years (Table 4).

Complete obliteration of AVM had statistically significant associations with smaller score of Spetzler-Martin arteriovenous malformation grading system for AVMs [Fig. 1] ($p < 0.05$).

Table 5- Results after Radiosurgery of arteriovenous malformations

Series (ref.no)	No. of patients	Obliteration (%)	Complications (%)	Fatal rebleeding (%)
Bollet et al., 2004 (8)	112	54	2	0
Pollock et al., 2003 (13)	144	73	10	3.5
Friedman, 2002 (15)	436	67	2	1.2
Inoue and Ohye, 2002 (36)	80	81.3	----	----
Chang et al., 2000 (37)	128	78.9	4.7	----
Touboul et al., 1998 (38)	100	51	8	----
Sasaki et al., 1998 (39)	66	85.7	6.7	0
Karlsson et al., 1997 (40)	945	56	5	----
Colombo et al., 1994 (41)	180	80	2	2.8
Kondziolka et al., 199 (28)	112	71	4.4	1.7

Table 6. Number of patients undergone GKRS separated according to years

2003	2004	2005	2006	2007	2008	2009	2010
8(9.5%)	13(16%)	11(13.5%)	12(15%)	5(6%)	14(17%)	11(13.5%)	8(9.5%)

There was not any statistical significant relationship between age, clinical symptoms, sex and complete obliteration rate.

In 3 patients, the microsurgical removal of the incompletely obliterated AVM was done 5 years after GKR. Treatment was performed within less than 3 years only in cases in which a new nidus had developed which was not observed in our patients.

Before radiosurgery, hemorrhage from AVMs occurred in 45patients (54%). The number of bleedings in a single patient ranged between one and three times, with a mean of one bleeding episode.

Rebleeding was seen in the latent period before AVM obliteration in 9 patients (11%) within 3.5 to 37 months (mean, 11.5 months) after the GKS. The neurodeficit after rebleeding impaired in 2 patients (2.4%), and 1 patient (1.2%) died as the consequence of the rebleeding. (only patient who died in our study).

The neurological symptoms induced by the AVM was detected prior to gamma knife treatment in 65 patients (79.26%). In 42 patients (51.2%), these neurological symptoms improved significantly after GKS within 6 to 35 months (mean, 12 month). Radiosurgery induced cerebral edema and rebleeding caused worsening of clinical symptoms in 11 cases (13.4%).

The cause of morbidity was cerebral edema induced by radiosurgery in 2 patients and

rebleeding in 9 patients. Finally, morbidity was observed in 8 patients which represented a cumulative risk of 10% in the group of 82 patients available for evaluation.

Epilepsy was detected in 24 patients (30%) before radiosurgery.

Termination of the seizures or improvement in seizure frequency was observed in 18 patients 4.2 to 48 months (mean, 16 month) after radiosurgery. A worsening of epilepsy after radiosurgery was detected in 2 patients after radiosurgery because of cerebral edema, and 4 patients (4.8%) had persistent seizure attacks before surgery.

Edema was detected by MRI in 15 patients (18.20%) within 3 to 30 months (mean, 11months) after the procedure. Edema was symptomatic only in 2 patients representing a 2.43% morbidity rate. The corticosteroid therapy was given in all 15 patients for a period of 12 months. Edema later resolved in 13 of these 15 patients.

The Gamma knife radiosurgery was repeated only in 1 patient (1.2%) because complete obliteration was not achieved within 3.5 years of the first treatment in another center.

Number of patients undergone GKRS is separated according to years (from 2003 to 2010) and is shown in table 6.

Discussion

The annual rate of bleeding from an un-

Table 7. Spetzler-Martin AVM grading system

Spetzler-Martin AVM grading system. The Spetzler-Martin AVM grading system allocates points for various features of intracranial AVM's to give a score between 1 and 5 in order to estimate the risk of surgery for that patient.	
Size of nidus	small (<3 cm) = 1 medium (3-6 cm) = 2 large (>6 cm) = 3
Eloquence of adjacent brain	non-eloquent = 0 eloquent = 1
Venous drainage	superficial only = 0 deep = 1

ruptured Arteriovenous malformation is reported up to 4% and may significantly increase by coexistent factors (for example, deep venous drainage, venous stenosis, aneurysm, high mean arterial pressure, diffuse morphology, periventricular location, and larger size of the nidus)[5,6,11,14,21-23]. Approximately 18% of the first hemorrhages are fatal [21], in addition mortality and morbidity associated with hemorrhages varying between 6–29% and 50–70% in various reported series [11,27,28]. The AVMs can also cause seizures, transient neurologic deficit, headache and decreased mental status [1,5,24].

The AVMs are typically found in young individuals (20-40 years) so life-long probability for various complications is considered to be high enough to give active treatment [15,25,26].

The AVMs with small-to-intermediate size can be effectively treated either by surgery or gamma knife radiosurgery but management of large lesions represents a significant challenge [25, 26, 29-34].

The microsurgical resection for AVMs in the eloquent area can be associated with a high morbidity and mortality.

Embolization of cerebral AVMs has been performed for nearly 40 years to reduce the risk of bleeding. Despite advances in the technique, reformation of AVMs after complete endovascular treatment is a well-known problem. Thus GKS is accepted as an alternative to microsurgery and embolization for the treatment of AVMs, particularly for those in eloquent area. Radiosurgery could be beneficial in the complete obliteration of

the AVMs, with a 1 to 4 year latency period in most cases.

The purpose of this study was to assess the benefit of radiosurgery in patients with AVM. Unlike microsurgery or embolization, the AVM obliteration after radiosurgery cannot be evaluated immediately after the procedure, so it is impossible to evaluate the effectiveness of treatment in all patients, but delay in the AVM obliteration despite the risk of rebleeding, can have some advantages (for example, gradual restoration of the circulation in the collateral vessels) [35].

Complete obliteration of AVM was achieved in 56 cases (68.29%) in our study that is similar to other studies (Table 5). The maximum obliteration rate was reported by Sasaki et al., 1998 [39] that was 85.7%, and minimum obliteration rates was 51% that reported by Touboul et al., 1998 [38].

It was marked in average 3.62 years (from 1 to 5 years) after GKR that other articles also emphasize on this latent period.

Complete obliteration of AVM had statistically significant associations with smaller score of Spetzler-Martin arteriovenous malformation grading system for AVMs (table7) ($p < 0.05$). Higher success was observed in patients with Spetzler-Martin Grade I and II AVMs, which is attributed to smaller volume of AVMs in this group. Since the Spetzler-Martin AVM grading system, considered the diameter of the AVM nidus, its localization in the eloquent areas, and the type of venous drainage [42], it proved to be useful for the prognosis and result of the microsurgical resection [43].

There was not any statistical significant

relationship between age, clinical symptoms, sex and complete obliteration rate in our study, however some authors emphasized on effect of these factors for determining positive treatment outcomes [12,13,40].

Complications after radiosurgery are classified as acute, subacute, and delayed. Acute complications associated with the performance of the treatment itself, are part of the treatment procedure. However, these complications were not seen in our study and are mentioned infrequently in other articles.

Subacute complications are caused by postirradiation edema, which can be observed after a delay of several months, usually within 6 to 24 months, but most frequently within 1 year after radiosurgery. The radiosurgery induced cerebral edema caused worsening of clinical symptoms in 2 cases (2.4%) in our study.

Edema observed after radiosurgery occurs at a time when the AVM vessels show continual flow void and obliteration is not accomplished; thus, the reasons are not hemodynamic changes caused by obliteration but rather a toxic effect on the surrounding tissue or the AVM itself [44].

Rebleeding caused worsening of clinical symptoms in 9 cases (10.9%) and 1 patients (1.2%) died as the consequence (the only patient died in our study). The risk of rebleeding during the latency period of the healing process after radiosurgery can be evaluated only in terms of the potential cure rate of alternative treatment methods that cannot calculated in present study.

Although the percentage of patients with rebleeding after radiosurgery varies between 3.4 to 10%, the number of fatal hemorrhages is reported between 0 to 3.5%. These percentages are alike our findings.

Conclusion

Gamma knife radiosurgery can offer total and partial obliteration to acceptable percent of treated AVM with a low risk of morbidity.

Higher success was observed in patients with Spetzler-Martin Grade I and II AVMs, which is attributed to smaller volume AVMs

in this group.

Radiosurgery induced cerebral edema and rebleeding caused worsening of clinical symptoms in 11 cases (13.4%). The cause of morbidity was cerebral edema induced by radiosurgery in 2 patients and rebleeding in 9 patients. Finally, morbidity was observed in 8 patients which represented a cumulative risk of 10% in the group of 82 patients available for evaluation.

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