DOI: 10.31276/VJSTE.64(3).44-48

Effective treatment for symptomatic brain tumours and arteriovenous malformation in children by radiosurgery with a rotating gamma system

Khoa Mai Trong[1], Phuong Pham Cam[2*], Luan Nguyen Duc[2], Hung Nguyen Quang[2], Phuong Dao Manh[2], Thai Pham Van[1]

[1]*Hanoi Medical University*
[2]*The Nuclear Medicine and Oncology Centre, Bach Mai Hospital*

Received 1 October 2021; accepted 3 December 2021

Abstract:

To assess the effectiveness of radiosurgery with a rotating gamma system (RGS) for paediatric brain tumours and arteriovenous malformation (AVM), this work was carried out on 123 patients with brain tumours or AVM received radiosurgery at Bach Mai hospital. The median dose was 13 Gy from a range of 8 to 20 Gy. Endpoints include the effects of increased intracranial pressure, seizures, hemiplegia, and tumour size on the syndrome. Results exhibited that the percentages of patients with complete response, partial response, and disease progression out of 59 patients with headache accounted for 11.9, 69.5, and 18.6%, respectively. Of the 20 patients with seizures, 30% had complete response, 65% partial response, and 5% stable disease. Regarding brain tumour size, 9 months after treatment, those with complete response, partial response, stable disease, and disease progression made up 18.7, 50.4, 14.6, and 16.3% of the total patients, respectively. There was no statistically significant effect of radiation dose on the results. This study showed a high percentage of children with brain tumours and AVM undergoing radiosurgery with a RGS had symptomatic responses after treatment.

Keywords: **arteriovenous malformation, brain tumours in children, headache, hemiplegia, radiosurgery, rotating gamma system, seizures, symptom relief.**

Classification number: **3.2**

Introduction

Brain tumours are the second most common group of tumours in children following only after hematologic cancers. This group of diseases originates from an abnormal proliferation of nerve cells, astrocytes, dendritic cells, or neuroblastoma. Brain tumours may also be secondary from many types of cancer elsewhere in the body. Depending on the location, size, and nature of the tumour, the primary treatment for a brain tumour may be surgery, radiotherapy, or chemotherapy. In addition, surgery is difficult to conduct in cases of brainstem tumours or tumours in some other locations because serious complications can occur. In those cases, radiosurgery using a rotating gamma knife (RGK) is a safe and effective option that has been proven in many studies [1-3]. Meanwhile, brain AVM includes lesions that are defined by the presence of arteriovenous (AV) shunting through a nidus of coiled and tortuous vascular connections that connect feeding arteries to draining veins [4]. Brain AVM is considered congenital vascular lesions that can be present at any age. AVM was reported to have a higher rate of rupture than in adults [5]. RGK radiosurgery is one of the most effective treatment methods for this disease, which has been known for a long time [6].

Today, along with advances in medicine, many new types of radiotherapy machines and methods have been introduced to focus the dose on lesions while minimizing the radiation dose to surrounding healthy tissues. Since then, radiation therapy for the treatment of brain tumours and AVM in children has been increasingly studied. Radiation therapy plays an important role especially for patients with large tumours, deep tumour sites, or tumours on important organs such as the brainstem, ventricles, etc., which are all very difficult places to perform surgery. Gamma knife radiosurgery (GKRS) has been used by Swedish professor Lar Leksell to treat brain tumours since 1968 with very good results. The gamma knife system used by Lar Leksell at that time contained 201 sources of Cobalt-60 arranged on a spherical hood containing directional envelopes. These radiation sources

*Corresponding author: Email: phamcamphuong@gmail.com

were directed through directional gates so that the beams were focused on the pathological point in the brain [7, 8]. The RGS uses 30 sources of Cobalt-60 symmetrically distributed around a hemisphere between latitude angles of 13 to 43º as measured from the sagittal plane. The sources within the single housing helmet rotate at a speed of approximately 2 to 4 rotations per minute. Inside the source hemisphere, a concentric collimating hemisphere is co-rotating with the sources and exposes the desired beam diameter such as 4, 8, 14, or 18 mm. The rotating sources of RGS simulate an infinite number of beams and promote extremely high target-to-surface dose ratios [9]. Since July 2007, the Nuclear Medicine and Oncology Centre at Bach Mai hospital has used the Gamma ART 6000, an American radiosurgery system, which is a hybrid with features of both the gamma knife and LINAC radiosurgery systems to treat brain tumours and AVM. More than 6000 patients, including children, with brain tumours and intracranial diseases have been treated with the RGK. This group has conducted a thesis to assess the role of this treatment method in the treatment of brain tumours and intracranial diseases in children.

Patients and study methods

From July 2007 to December 2020, 123 paediatric patients (≤15 years old) included in this prospective interventional study received radiosurgery for brain tumours and intracranial diseases with RGS at the Nuclear Medicine and Oncology Centre, Bach Mai hospital, Hanoi. The patients had symptomatic tumours of the brain or AVM. Their lesions had specific features on magnetic resonance imaging (MRI), computed tomography (CT), or magnetic resonance spectroscopy (MRS) [10, 11]. Specifically, the lesions had a maximum diameter of 3 cm, and in a few cases, we accepted tumours with sizes of no greater than 5 cm with no severe comorbidity. The ages of the patients were no greater than 15 years old. The patients were without pregnancy or lactation. There were indications for the subjects to be treated with RGK given by the Hospital Medical Council. All patients gave consent to join in the study.

In this study, we used the Gamma ART 6000, an American Radiosurgery system. We gave patients a single dose of radiosurgery from 8 to 20 Gy. The dose was defined to the outer margin of the tumour representing 50% isodose. The radiation oncologists decided the specific radiation dose for each patient. We then grouped patients according to the treated dose with a threshold of 14 Gy (median value of the range from 8 to 20 Gy) to test whether the radiation dose affected the treatment outcome.

The primary endpoint was a response in clinical symptoms in a follow-up period of 9 months after treatment, which included the syndrome of increased intracranial pressure, seizures, and hemiplegia. When compared to symptoms before treatment, the patient might have either complete response (complete relief of symptoms), partial response (partial relief of symptoms), stable disease (no change in symptoms), or progressive disease (an increase in symptoms). Another study endpoint was the change in the size of tumours on the MRI scans after 9 months.

The data were coded and analysed by SPSS 16.0 using statistical algorithms. A p-value of less than 0.05 was considered significant.

Results

Patient characteristics

Out of 123 paediatric patients that met the criteria in this study, 45 patients were female (36.6%) and 78 patients were male (63.4%). The median age was 10 years in a range from 4 to 15 years. Diagnosis beginning with the highest rate: astrocytoma in 29 patients (23.6%), AVM in 20 patients (16.3%), pineal gland tumour in 18 patients (14.6%), and brainstem tumour in 14 patients (11.4%). The tumour was in the temporal lobe in 21 patients (17.1%), in the frontal lobe in 20 patients (16.3%), in the pineal gland in 18 patients (14.6%), and other positions accounted for less percentage.

Clinical symptoms prior to RGK

The clinical symptoms of the 123 patients are shown in Table 1. Prior to RGS irradiation, 59 patients (48%) had a significant headache, 20 patients (16.3%) had significant seizures, and 17 patients (13.8%) had significant hemiplegia.

Table 1. Clinical symptoms prior to RGK.

Symptom	Number of patients	Proportion (%)
Increased intracranial pressure	59	48.0
Seizures	20	16.3
Hemiplegia	17	13.8
Puberty early	4	3.3
Double vision	3	2.4
Blurred vision	7	5.7
Cross-eyed	1	0.8
Drooping eyelids	4	3.3
Tinnitus	1	0.8
Cerebellum syndrome	6	4.8
Absence of consciousness	1	0.8
Total	123	100.0

Response at 9 months after RGS irradiation

Of the 59 patients who suffered significant intracranial pressure prior to RGS irradiation, the rates of complete response, partial response, and disease progression at 9 months after RGS irradiation were 11.9, 69.5, and 18.6%, respectively (Fig. 1).

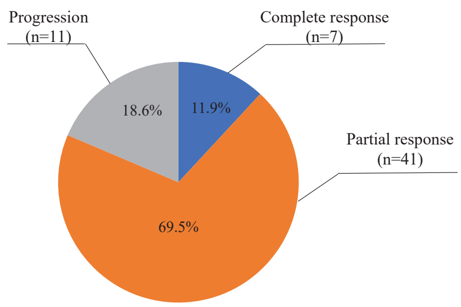

Fig. 1. Syndrome of increased intracranial pressure: response at 9 months after RGS irradiation.

Of the 20 patients who experienced seizures prior to irradiation, 6 patients (30%) achieved complete response, 13 patients (65%) had partial response, and one patient (5%) maintained stable disease at 9 months following RGS irradiation, respectively (Fig. 2).

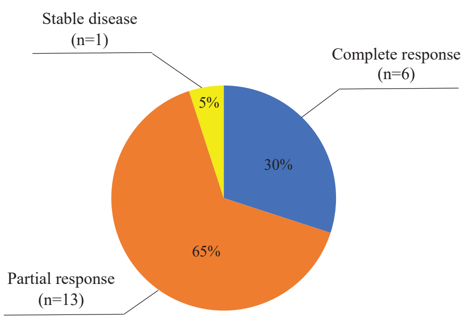

Fig. 2. Seizures: response at 9 months after rotating gamma system (RGS) irradiation.

Of the 17 patients who experienced hemiplegia prior to irradiation, 3 patients (17.6%) achieved complete response, 10 patients (58.9%) had partial response, and 4 patients (23.5%) had disease progression at 9 months following RGS irradiation, respectively (Fig. 3).

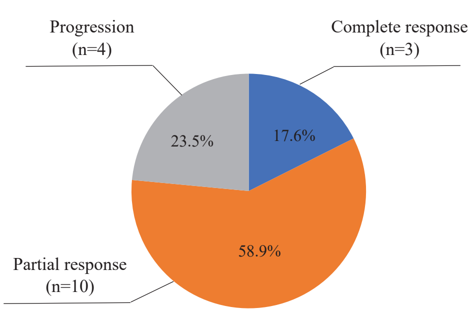

Fig. 3. Hemiplegia: response at 9 months after RGS irradiation.

In terms of sizes of the tumours 9 months after treatment: we achieved complete response in 23 out of the 123 patients (18.7%), partial response (with median decrease in size by 20%) in 62 patients (50.4%), and stable disease in 18 patients (14.6%). In 20 patients (16.3%), the lesion appeared larger than prior to RGS irradiation. Brainstem tumours had the highest rate of recurrence, which occurred in 13 out of 14 patients (92.8%). Patients with AVM had the best response. Of the 20 patients who experienced AVM prior to irradiation, at 9 months following RGS irradiation, 12 patients (60%) achieved a complete response, 5 patients (25%) had a partial response, and 3 patients (23.5%) maintained stable disease (Fig. 4). About side effects after radiosurgery, 27.6% of patients had symptoms of increased intracranial pressure. However, the symptoms were controlled with medical treatment.

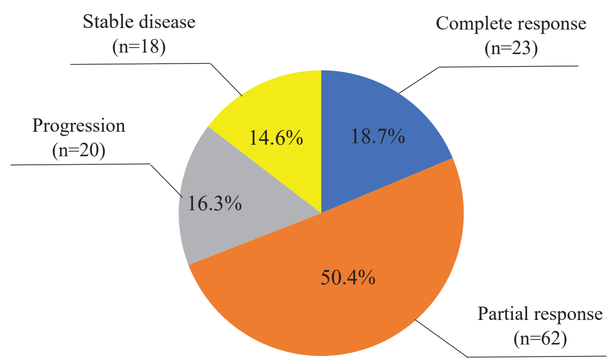

Fig. 4. Size tumours: response at 9 months after RGS irradiation.

Response rates related to different doses of rotating gamma system radiosurgery

Complete response was defined as complete relief of symptoms or complete disappearance of the brain tumours and intracranial diseases. The overall response was defined as complete or partial symptom relief or decrease in size of the brain tumours and intracranial diseases. p-values were calculated with the Chi-square test. The best response to RGS irradiation regarding the syndromes of increased intracranial pressure, seizures, hemiplegia, and decrease of tumour size were compared for RGS doses of ≤14 Gy (n=58), and >14 Gy (n=65). The results of this subgroup analysis are summarised in Table 2. The rotating gamma system dose had no significant impact on outcomes.

Table 2. Treatment response according to the radiation dose threshold of 14 Gy.

Endpoint	≤14 Gy	>14 Gy	p-value
Syndrome of increased intracranial pressure			
Complete response rate	3.4% (2/59)	8.5% (5/59)	0.17
Overall response rate	39% (23/59)	42.4% (25/59)	0.45
Seizures			
Complete response rate	10% (2/20)	20% (4/20)	0.14
Overall response rate	20% (4/20)	75% (15/20)	0.27
Hemiplegia			
Complete response rate	0% (0/17)	17.6% (3/17)	0.02
Overall response rate	17.6% (3/17)	58.8% (10/17)	0.03
Brain tumours size			
Complete response rate	4.9% (6/123)	13.8% (17/123)	0.003
Overall response rate	29.1% (36/123)	39.8% (49/123)	0.21
AVM size			
Complete response rate	2% (2/20)	50% (10/20)	0.47

Discussion

Brain tumours ranked second in childhood cancers (only after hematologic cancers), account for 15% of cancers in children under 16 years of age. Childhood central nervous system tumour incidence varies by country from 1.12-5.14 cases per 100,000 persons, with the highest rate of incidence being in the United States [12]. Tumour resection surgery is the first treatment of choice. However, it is difficult to achieve a R0 resection in many cases due to the high risk of complications. For these cases, the indication for alternative treatment with radiosurgery using RGK is reasonable and has been proven to be safe and effective in many studies [1-5]. The classical radiosurgery system and accelerated radiotherapy were introduced in the late 1960s and 1980s, respectively. The RGK radiosurgery system incorporates the advantages of both methods and was introduced in the late 1990s [9]. This system is currently only available in a few large treatment centres around the world as well as in Vietnam. At the Nuclear Medicine and Oncology Centre, Bach Mai hospital, there have been more than 6,000 patients including children with brain tumours and AVM treated with the RGK.

Rotating gamma radiosurgery resulted in very high rates of symptomatic response in syndromes of increased intracranial pressure or seizures. Overall complete and partial response rates were 81.4 and 95%, respectively, in which AVM and astrocytoma had the highest response rates. Of the 29 patients with astrocytoma 9 months after surgery, 24 patients had a partial response (82.8%). In 20 patients with AVM, the response rate was 85% where 12 patients achieved complete response and 8 patients had partial response, which accounts for 60 and 40%, respectively.

In terms of tumour size, an overall response was observed in 69.1% of patients. However, in 16.3% of the cases, lesions appeared larger than prior to RGS irradiation. Patients with AVM and astrocytoma had the best response. Of the 20 patients who experienced AVM prior to irradiation, 12 patients (60%) achieved complete response, 5 patients (25%) had partial response, and 3 patients (23.5%) maintained stable disease, respectively at 9 months following RGS irradiation. In 29 patients with astrocytoma, 16 patients (55.2%) had partial response, 8 patients (27.6%) maintained stable disease, and 5 patients (17.2%) had disease progression 9 months after radiosurgery. Response to treatment depends on many factors including the grade of malignancy of the lesion. That is probably the reason why AVM, benign lesions, had better responses than other tumours. Besides, the location of the lesion is also a factor related to the effectiveness of treatment. Perhaps this is why brainstem tumours are generally less responsive.

When comparing RGS doses of ≤14 Gy and >14 Gy, it is seen that dose had no significant impact on outcomes. One reason for this may be that the study subjects were not a diagnostically homogeneous group. With each type of brain tumour, and especially with different histopathology, different tumour locations likely have different responses to radiation therapy. Therefore, in order to better understand the dose-response relationship in paediatric brain tumour patients, further studies in each disease group should be conducted.

Other studies also showed the effectiveness of radiosurgery with AVM and brain tumours in children. A study from the University of Pittsburgh reviewed 135 children treated with GKRS. The median GKRS prescription dose to the nidus margin was 20 Gy (from 15 to 25 Gy), which correlated with the median maximum target dose of 40 Gy (from 30 to 50 Gy). A reduced dose was prescribed for large AVMs and niduses located in an eloquent area as per published risk/benefit prediction curves based on the 12 Gy volume. Paediatric AVM obliteration rates at 3, 4, 5, and 10 years were 45, 64, 67, and 72%, respectively [6]. In 2017, C.P. Pham, et al. (2017) [13] reported a mean reduction in tumour size from 1.87 to 1.15 cm after 36 months of treatment when performing radiosurgery with a dose of 12 Gy for 37 patients with low-grade brainstem glioma. Based on these results, RGK should be considered in selected patients with astrocytomas. The most appropriate indication may be for patients who are inoperable or have residual lesion after surgery. We may need more research to confirm this claim. C.G. Hadjipanayis, et al. (2002) [14] conducted a study at the University of Pittsburgh on 37 patients with unresectable or recurrent pilocytic astrocytomas. In the study, 68% of the patients were 18 years old or younger. The median radiation dose was 15 Gy and 48.6% of the patients achieved a complete or partial response. Neurological symptoms worsened in only 2 patients after radiosurgery. In another study, J. Boethius, et al. (2002) [15] performed radiosurgery on 19 patients including 16 children with radiation doses from 9 to 20 Gy (median of 10 Gy). The author followed the group of patients for a median time of 4.7 years and concluded that tumour size was moderately reduced in 85% of patients while the disease was controlled in 18 out of 19 patients. J.A. Barcia, et al. (1994) [16] studied radiosurgery performed with the mean dose of 21.7 Gy in 16 patients with inoperable low-grade gliomas. The author reported that 50% of tumours had a complete response and 31% had partial response or stable disease.

When researching the literature, there were a few studies with comparable indicators as those presented in this study. For example, B. Mirza, et al. (2010) [17] treated 6 children with AVMs and 12 children with tumours using stereotactic radiotherapy and radiosurgery. They reported a rate of 83% in control or regression in patients with tumours, and all children with AVMs. In 2003, A. Hirth, et al. [18] conducted a study of 12 children with cerebral or skull base tumours with a mean tumour margin dose of 13.8 Gy. After a mean follow-up of 78.6 months, they found that seven patients remained stable.

The overall response rates in our present study were higher than other studies. This showed that radiosurgery using RGK is an effective treatment for brain tumours and intracranial diseases. It should be added, however, that there may be a risk of bias since the studies are retrospective.

Conclusions

In conclusion, this study shows that treatment with a RGK system helps children with brain tumours and intracranial diseases achieve high symptom response rate and reduce tumour size after radiosurgery. Therefore, it is a suitable alternative treatment when surgical removal of the entire tumour is not possible.

COMPETING INTERESTS

The authors declare that there is no conflict of interest regarding the publication of this article.

REFERENCES

[1] A.S. Plant, et al. (2018), "Safety and efficacy of gamma knife radiosurgery for pediatric brain tumours", *Neuro-Oncology*, **20(2)**, DOI: 10.1093/neuonc/noy059.536.

[2] D. Weintraub, et al. (2012), "Gamma knife surgery of pediatric gliomas", *J. Neurosurg. Pediatr.*, **10(6)**, pp.471-477.

[3] N. Massager (2012), "Gamma knife radiosurgery", *Rev. Med. Brux.*, **33(4)**, pp.367-370.

[4] M. Gaballah, et al. (2014), "Intraoperative cerebral angiography in arteriovenous malformation resection in children: A single institutional experience", *J. Neurosurg. Pediatr.*, **13(2)**, pp.222-228.

[5] T.E. Darsaut, et al. (2011), "Management of pediatric intracranial arteriovenous malformations: Experience with multimodality therapy", *Neurosurgery*, **69(3)**, pp.540-556.

[6] J.H. Suh, G.H. Barnett (2003), "Stereotactic radiosurgery for brain tumours in pediatric patients", *Technology in Cancer Research & Treatment*, **2(2)**, pp.141-146.

[7] L. Leksell (1951), "The stereotactic method and radiosurgery of the brain", *Acta. Chir. Scand.*, **102(4)**, pp.316-319.

[8] L. Leksell (1983), "Stereotactic radiosurgery", *J. Neurol. Neurosurg. Psychiatry,* **46(9)**, pp.797-803.

[9] A. Wu (1992), "Physics and dosimetry of the gamma knife", *Neurosurgery Clinics of North America*, **3(1)**, pp.35-50.

[10] L. Yin, L. Zhang (2013), "Correlation between MRI findings and histological diagnosis of brainstem glioma", *Can. J. Neurol. Sci.*, **40(3)**, pp.348-354.

[11] J.C. Flickinger, et al. (2000), "Development of a model to predict permanent symptomatic postradiosurgery injury for arteriovenous malformation patients", *Int. J. Radiat. Oncol. Biol. Phys.*, **46(5)**, pp.1143-1186.

[12] K.J. Johnson, et al. (2014), "Childhood brain tumour epidemiology: A brain tumour epidemiology consortium review", *Cancer Epidemiol. Biomarkers Prev.*, **23(12)**, pp.2716-2736.

[13] C.P. Pham, et al. (2017), "Rotating gamma system irradiation: A promising treatment for low-grade brainstem gliomas", *In Vivo*, **31(5)**, pp.957-960.

[14] C.G. Hadjipanayis, et al. (2002), "Stereotactic radiosurgery for pilocytic astrocytomas when multimodal therapy is necessary", *J. Neurosurg.*, **97(1)**, pp.56-64.

[15] J. Boethius, et al. (2002), "Gamma knife radiosurgery for pilocytic astrocytomas", *J. Neurosurg.*, **97(5)**, pp.677-680.

[16] J.A. Barcia, et al. (1994), "Stereotactic radiosurgery of deeply seated low grade gliomas", *Acta Neurochir. Suppl.*, **62**, pp.58-61.

[17] B. Mirza, et al. (2010), "Stereotactic radiotherapy and radiosurgery in pediatric patients: Analysis of indications and outcome", *Childs Nerv. Syst.*, **26(12)**, pp.1785-1793.

[18] A. Hirth, et al. (2003), "Gamma-knife radiosurgery in pediatric cerebral and skull base tumours", *Med. Pediatr. Oncol.*, **40(2)**, pp.99-103.