Low Dose Gamma-knife Radiosurgery for Diffuse Brainstem Gliomas

Radiocirurgia Gamma Knife com Dose Baixa em Gliomas Difusos do Tronco Cerebral

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ABSTRACT

Introduction: Diffuse brainstem glial tumors remain a challenge. Despite many advances in neurosurgical techniques, no effective treatment is currently available. Recently, some authors showed beneficial results with gamma-knife radiosurgery (GK) for focal brainstem tumors. Objective: to analyze safety and effectiveness of GK in patients with diffuse brainstem gliomas. Methods: Eleven patients with diffuse brainstem gliomas treated with Gamma-knife from November 2001 to June 2009 were included. Complete data such as age, gender, symptoms, tumor size, prescription dose, adverse radiation effects and an early late follow-up were analyzed. Results: The mean age was 28.7 years (ranging from 1y 7m to 62y). Six patients were female and 5 were male. The gamma-knife prescription dose ranged from 6 to 7 Gy. All patients had clinical and imaging improvement at an early follow-up, although in 6, there was a late increase in tumor size and death. The others remained clinically stable or better. Larger tumors had a direct relationship with a poorer prognosis. No patient developed complications related to the radiosurgical treatment. Conclusion: Gamma-Knife is a safe and effective treatment for selected patients with diffuse brainstem tumors. The authors propose lower doses. Further studies are mandatory in order to analyze which patients could benefit from this treatment.

Key words: Brainstem glioma; Gamma Knife; Radiosurgery; Stereotactic surgery; Pediatrics

RESUMO

Introdução: Gliomas difusos de tronco cerebral continuam a ser um desafio. Apesar dos avanços em técnicas neurocirúrgicas, atualmente não há tratamento eficaz disponível. Recentemente, alguns autores mostraram resultados benéficos com radiocirurgia Gamma Knife (GK) para tumores focais. Objetivo: analisar a segurança e a eficácia de GK em pacientes com gliomas difusos de tronco cerebral. Métodos: Foram incluídos onze pacientes com gliomas de tronco cerebral difusos, tratados com radiocirurgia de novembro de 2001 a junho de 2009. Dados completos foram analisados, tais como idade, sexo, sintomas, tamanho do tumor, dose prescrita, efeitos adversos da radiação e um follow-up tardio. Resultados: A idade média foi de 28,7 anos (variando de 1a 7m a 62a). Seis pacientes eram do sexo feminino e 5 eram do sexo masculino. A dose prescrita de radiocirurgia GK variou de 6 a 7 Gy. Todos os pacientes apresentaram melhora clínica e de imagem em um acompanhamento precoce; entretanto, 6 apresentaram aumento final no tamanho do tumor e chegaram ao óbito. Os outros pacientes permaneceram clinicamente estáveis ou melhoraram. Tumores maiores tinham uma relação direta com um prognóstico mais pobre. Nenhum paciente desenvolveu complicações relacionadas ao tratamento radiocirúrgico. Conclusão: Gamma-Knife é um tratamento seguro e eficaz para pacientes selecionados com tumores difusos de tronco cerebral. Os autores propõem o uso de doses mais baixas. Outros estudos são necessários para analisar quais pacientes poderiam se beneficiar deste tratamento.

Palavras-chave: Glioma do tronco cerebral; Gamma Knife; Radiocirurgia; Cirurgia estereotáxica; Pediatría

INTRODUCTION

Gliomas are the most common tumor lesions arising in the brainstem. Clinical and radiological appearance may vary, from small focal lesions to diffuse, infiltrative tumors. Both children and adults can be affected. Gliomas account for 10-20% of central nervous system tumors in childhood while in the adult population, they correspond to about 1.5-2.5%21,26.

Symptoms such as long tract pathways, cranial nerve deficits and disturbances in motor coordination commonly occurs due to compression of neural structures in the brainstem. Magnetic Resonance Imaging (MRI) is the method of choice in the diagnosis as well as in the evaluation of tumor size and location. Treatment modalities include surgery (especially when they are focal and located in accessible areas), chemotherapy, radiotherapy and radiosurgery10,31.

Gamma Knife surgery (GK) is a radiosurgical procedure using photon emission from 201 cobalt-60 sources, disposed in a spherical arrangement that targets one or more intracranial points, with minimal damage to surrounding structures. Since Leksell, in the late 1960s it has been used in the neurosurgical...
armamentarium.

Although GK is generally indicated for benign lesions, little has been published using this treatment on brainstem gliomas. Typically, tumors with good responses are brain metastasis, pituitary adenomas, meningiomas and vestibular schwannomas. Recently, some authors described their results using GK for focal brainstem gliomas, usually with a 12 Gy dose\(^5,13-16,19,22,29\).

The authors analyzed the outcome of eleven patients with clinical and radiological signs of diffuse brainstem gliomas, in which GK had been used as the main treatment, in order to evaluate its safety and effectiveness.

**MATERIALS AND METHODS**

**Study population**

This retrospective study included 11 patients with clinical and radiological diagnosis of diffuse brainstem gliomas treated in the Gamma Knife Unit at the Fleni Institute, in Buenos Aires, between November 2001 and June 2009. Both children and adults have been included.

**Imaging studies**

All patients had a positive 1.5 Tesla MRI, showing a tumor lesion in the brainstem, including midbrain, pons and medulla oblongata. Only cases with no contrast-enhancement were included. The tumor volume for treatment and follow-up was based on areas of both hypointensity at T1 and hyperintensity at T2 MRI images. Total volume was calculated on a computerized program (Leksell Gamma Plan® Elekta).

**Gamma Knife surgery**

Gamma Knife is a radiosurgical procedure consisting of a highly focused radiation therapy delivered to one or more selected targets inside the brain. The radiation source comes from 201 Cobalt-60 seeds arranged in a convergent pattern. In every case, the procedure and their results were fully explained to the patients and their families.

Typically, a Gamma Knife session consists of four steps: frame fixation, neuro-imaging, treatment planning and the treatment itself. All patients were treated in a LGK B2 model (Elekta AB, Stockholm).

The patients were discharged on the same day, unless in case of any clinical or neurological issues (not related to the procedure). Due to the low doses of radiation prescribed, the patients did not receive steroids or anticonvulsants unless in the presence of symptoms of increased intracranial pressure or seizures.

**Follow-up**

After Gamma Knife treatment, patients were evaluated monthly for the first three months and then every three months. Additional images were included if there was clinical deterioration. Evaluation was done both clinically and through MRI. In the event that a patient was unable to be present for an evaluation, they were contacted either by telephone or e-mail. Information was gathered either with the patient or his/her family, as well as the referring physician.

Clinical improvement was defined as one of the following outcomes: 1. sustained increase in the Karnofsky Performance Scale of at least 20 points; 2. improvement in the level of consciousness defined by a longstanding increase in the Glasgow Coma Scale (at least 1 point) or marked reversal of motor deficits.

Radiological outcome was also based on a computerized program (Leksell Gamma Plan® Elekta). Pre-treatment tumor volume was compared with those found in further exams, and tumor increase was considered when there was at least a 10% increase in the tumor volume. Radiological tumor decrease was defined as a tumor volume decrease when higher than 10%. In contrast, with minor changes (<10 % volume) or no changes, the tumor was considered stable.

**RESULTS**

**Study population**

The study analyzed 11 patients with brainstem tumors, and diagnosed through clinical symptoms and imaging compatible with diffuse glioma. In two cases, a biopsy was done, the
other nine had diagnosis based on an extensive analysis of the clinical manifestations and MRI. This diagnosis was done by neuroradiologists and the neurosurgical team.

There were 5 male (45%) and 6 female (55%) patients with a mean age of 28.7 years (ranging from 1y/7m to 62y). Most common symptoms were gait instability in 7 patients (64%), dizziness in 6 (55%) and diplopia in 7 (64%) (Table 1). Duration of symptoms before treatment ranged from 14 days to 7 months.

Table 1. Data including age, volume, dose, symptoms and outcome of patients.

<table>
<thead>
<tr>
<th>NUMBER</th>
<th>AGE</th>
<th>VOLUME (mm³)</th>
<th>DOSE (Gy)</th>
<th>SYMPTOMS</th>
<th>EARLY FOLLOW-UP</th>
<th>LATE FOLLOW-UP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>62 y</td>
<td>86.3</td>
<td>7.0</td>
<td>Diplopia, gait instability, diplopia</td>
<td>Clinical improvement. Mld radiological improvement</td>
<td>Progression after 17 months. Death after 24 months</td>
</tr>
<tr>
<td>2</td>
<td>1 y/7m</td>
<td>32.3</td>
<td>0.0</td>
<td>Diplopia, gait instability, diplopia</td>
<td>Clinical improvement. Mld radiological improvement</td>
<td>Progression after 19 months. Death after 27 months</td>
</tr>
<tr>
<td>3</td>
<td>15 y</td>
<td>53.7</td>
<td>0.5</td>
<td>Diplopia, diplopia, gait instability</td>
<td>Major clinical improvement. Mld radiological improvement</td>
<td>Progression after 11 months. Death after 26 months</td>
</tr>
<tr>
<td>4</td>
<td>15 y</td>
<td>4.2</td>
<td>0.5</td>
<td>Diplopia, gait instability</td>
<td>Clinical improvement.</td>
<td>Clinically stable. Mld symptoms</td>
</tr>
<tr>
<td>5</td>
<td>15 y</td>
<td>5.1</td>
<td>0.5</td>
<td>Diplopia, diplopia, cranial nerves II, IV and VI dysfunction</td>
<td>Clinical improvement.</td>
<td>Clinical improvement. Rmnae minimal symptoms</td>
</tr>
<tr>
<td>6</td>
<td>52 y</td>
<td>21.3</td>
<td>0.5</td>
<td>Dysarthria, Gait instability, low-grade glioma</td>
<td>Clinical improvement.</td>
<td>Clinical improvement. Rmnae minimal symptoms</td>
</tr>
<tr>
<td>7</td>
<td>21 y</td>
<td>41.3</td>
<td>0.5</td>
<td>Diplopia, swallowing disturbance</td>
<td>Clinical improvement.</td>
<td>Progression after 2 months. Death due to aspiration pneumonitis after 6 m</td>
</tr>
<tr>
<td>8</td>
<td>2 y/7m</td>
<td>14.3</td>
<td>0.5</td>
<td>Diplopia, gait instability</td>
<td>Clinical and radiological improvement</td>
<td>Progression after 3 months. Hydrocephalus. Death after 76 months</td>
</tr>
<tr>
<td>9</td>
<td>45 y</td>
<td>17.4</td>
<td>0.5</td>
<td>Hemispheric spasm, dizziness</td>
<td>Clinical and radiological improvement</td>
<td>Maintain clinical and radiological improvement. Hemispheric spasm</td>
</tr>
<tr>
<td>10</td>
<td>45 y</td>
<td>23.8</td>
<td>0.5</td>
<td>Diplopia</td>
<td>Clinical improvement.</td>
<td>Progression after 6 months.</td>
</tr>
<tr>
<td>11</td>
<td>18 y</td>
<td>12.1</td>
<td>0.5</td>
<td>Diplopia, gait instability</td>
<td>Clinical and radiological improvement</td>
<td>Progression after 11 months. Death after 16 months</td>
</tr>
</tbody>
</table>

Gamma Knife Prescription

The recommended prescription dose was usually 6 to 7 Gy at 50% isodose. The dose distribution per patient was 6 Gy in one case (9%), 6.5 Gy in nine (82%) and 7 Gy in one (9%). GK treatment volume ranged from 4.1 to 86.3 mm³ (a mean volume of 30.5 mm³).

Outcome

All patients had clinical and radiological improvement at an early follow-up. However, seven developed clinical worsening after a period of 2-19 months, with MRI exams depicting tumor increase. Six of these seven patients died during the long-term follow-up period (55%), with an interval of 8-76 months. In four of these cases, death was due to intracranial hypertension and neurological impairment secondary to tumor enlargement. In the fifth patient, death was caused by aspiration pneumonia, with concurrent signs of tumor recurrence. Progression-free survival from these patients ranged from 2 to 19 months (a mean of 9.9 months). In all these cases, the lesion volume was higher than 40 mm³ at the time of GK. Mean time to death in these patients was 29 months.

The other 6 patients remained clinically stable with mild to moderate neurological deficits. Serial MRI depicted no major tumor growth, with a follow-up ranging from 7 to 80 months (a mean of 30.4 months).

Complications

None of the patients who had received 6 to 7 Gy dose developed any complication, including those who treated bigger volumes.

Illustrative cases

Case #2: IH, female, 1 year and 7-month-old. According to her mother, seven months before GK, the patient began to have a progressive deficit of motor coordination, vomiting and diplopia. Computed tomography (CT) scan and MRI depicted hydrocephalus and a brainstem expansive lesion predominantly in the pontine region without contrast-enhancement. An endoscopic third ventriculostomy was performed and she was referred for GK treatment.

The prescribed dose was 6 Gy at 50% isodose. The tumor volume was 53.2 mm³ delivered in 19 isocenters. Integral dose was 430.5 mJ.

After one month, bouts of vomiting had improved as well as headaches. Two months after GK, there was also improvement in ocular movements. At that time, the patient could walk with minor instability, presented a normal cranial nerve examination and speech was adequate for her age. The MRI showed a slight decrease in tumor size (Figures 1 and 2).

The patient persisted with minor symptoms until 19 months after GK, when she experienced a clinical deterioration with the MRI showing tumor re-growth. At that time, the tumor had...
heterogeneous areas of contrast-enhancement. A second GK session was performed with no improvement. The patient died 27 months after GK treatment.

**Case #5:** RF, female, 18 year-old. Six months before GK, the patient started with dizziness that developed to diplopia and gait instability. At the first GK consultation she had multiple cranial nerve palsies (especially III, IV and VI) and quadriparesis. Imaging studies showed a diffuse ponto-mesencephalic tumor lesion with no contrast enhancement.

At GK treatment, the tumor volume was 5.1 mm³. A dose of 6.5 Gy at 50% isodose was given in a total of 12 target points. The integral dose was 44.1 mJ (Figures 5, 6 and 7).

The patient had significant clinical and radiological improvement. After 2 years and 9 months with minor symptoms of gait instability she continues to have a good recovery.

**Case #8:** MAL, male, 2 years and 9-month-old. The parents complained that three months before GK treatment, the boy had begun with gait instability and diplopia. MRI showed a large diffuse tumor in the brainstem, mostly located in the pons region. There was a mass effect. No surgery was undertaken and the patient was referred to the GK Unit.

The prescribed dose at 50% isodose was 6.5 Gy delivered in 12 target points. The tumor volume was 14.3 mm³. The integral dose was 124.9 mJ (Figures 3 and 4).

The first six months post-GK showed no intercurrence, and then he had a hydrocephalus that was treated with a ventriculo-peritoneal shunt. Further clinical and radiological improvement were achieved in the next eight months, but later he had a quick clinical deterioration, dying nine months after GK treatment.
Brainstem tumors are well recognized neoplastic diseases affecting both in pediatric and adult population. Many classification schemes have been proposed\(^1,6-8,30,36\). One of the most recent classification to pediatric brainstem tumors has been developed by Choux et al., 2000\(^3\) advocating the use of four categories: type I (diffuse); Type II (focal intrinsic); Type III (focal exophytic); and Type IV (cervicomedullary)\(^10\). More recently, Kumar and Kalra proposed a new scoring system\(^20\).

Histologically, many tumors may be found in the brainstem region, but mostly they have a glial origin\(^4\). These gliomas can
vary from pylocitic astrocytomas to malignant glioblastoma multiforme. Differential diagnosis includes encephalitis, demyelination, histiocytosis, hamartomas, vascular malformations and tuberculomas.

Focal brainstem tumors have a much better prognosis and if located in accessible regions, surgery can be a reasonable option. However, when brainstem gliomas are diffuse, the treatment is challenging. In most brain tumor centers, the treatment includes radiotherapy (usually when there are radiological signs of malignancy) or clinical observation. In diffuse tumors, surgery has a role in the diagnosis (biopsy). Subtotal resection of the tumor is controversial, since in most cases they cannot achieve a significant decrease in tumor size. Chemotherapy may be an acceptable therapy, but its role in controlling tumor cells is debated. New drugs and therapeutic schemes have been proposed but need further investigation. They include temozolamide, carboplatin, etoposide, ifosfamide, bevacizumab, irinotecan, tipifarnib and imatinib.

Natural history of diffuse brainstem tumors

Kesari et al. in 2008, analyzed 101 patients with focal and diffuse brainstem gliomas and found some indicators relating to a poorer prognosis: a non-caucasian ethnicity, tumor location at the pons, more than 10 years of age and higher grade on histology. In diffuse tumors, however, children had a poorer outcome.

Diffuse intrinsic tumors in children have a poor prognosis and have a higher level of morbidity. The median progression time is 5-6 months with a median survival time of only 9-12 months despite appropriate treatment. The prognosis for adults with diffuse brainstem tumors is better, with a median survival time of 59 months.

Salmaggi et al. illustrated the natural history of brainstem gliomas in adults, describing the outcome of 34 patients from an Italian retrospective study. There was no complete response after radiotherapy alone or with chemotherapy. Nine patients experienced an initial clinical improvement with stable imaging studies. In the late follow-up (9-180 months), the majority of the patients improved, two remained stable and 14 died (12 due to tumor progression).

Results

Our series included two children, 1.7y and 2.9 years old. Both showed clinical and radiological improvement at an early follow-up. An additional Gamma Knife treatment was performed on one of the children after recurrence with tumor enlargement and contrast enhancement but failed to bring any favorable result. Both died at late follow up after 2.3 and 3.4 years, respectively.

Six out of nine adults in our group are still alive with adequate tumor control. The other three died after 26, 20 and 8 months. Larger tumors had a direct correlation with poorer results. All patients that remain alive showed a permanent clinical and radiological improvement.

Gamma knife for gliomas

For a long time, GK has not been used in the treatment of gliomas, in part due to conflicting results. However, recent studies have shown beneficial effects of GK therapy in selected cases.

Heppner et al. published their analysis of 49 patients with low-grade gliomas, including 11 patients with tectal and brainstem lesions. Supra- and infratentorial lesions had similar results. Their initial conclusions were that GK was safe and should be considered in cases where residual or recurrent lesions were found.

Kano et al., in 2009, also showed good results using GK in pilocytic astrocytomas including those located in the brainstem, both in adults and in children. The effectiveness was higher with small residual tumors, while cases with lesion associated to cystic changes experienced poorer results.

Yen et al. published in 2007, the results of 20 patients treated with GK radiosurgery for focal brainstem gliomas with varying doses ranging from 10 to 18 Gy. Mean tumor size was 2.5 cm. In their paper, they stated that “in diffuse intrinsic tumors (...) radiosurgery is not an appropriate alternative”. Our initial results showed that this statement should be reviewed.

In malignant gliomas, the results are much more controversial. Kondziolka et al., in 1997, used GK at a later time after initial diagnosis and found a longer survival time when compared with a historical control group. Souhami et al., in 2004, conducted a multicentric study, randomly choosing patients.
to receive GK as part of the initial therapy. The authors did not find any significant difference. Other authors have shown beneficial effects of GK in the treatment of malignant gliomas when used as part of a comprehensive therapy methodology \(^{13,19,21}\). Nwokedi et al.\(^{22}\), in 2002 compared two groups of patients with glioblastoma multiforme, using external beam radiotherapy with or without GK. The group treated with GK had a significantly longer overall survival time (25 months versus 13 months in the conventional treatment group).

**Complications**

In 1994, Kihlström et al., reported on 7 patients with tectal tumors treated with GK at doses ranging from 14 to 45 Gy. However, radio-induced changes were seen with these higher doses. They suggested a dosage limit of 14 Gy to the brainstem\(^{18}\). Furthermore, Sharma et al.\(^{28}\), suggested a limit of 12 Gy to the brainstem region.

In our study, when lower doses were used (6-7 Gy) there was no adverse radiation effect (ARE) at early or late follow-up, even in large tumors. This confirms the statement proposed by Ganz et al.\(^{11}\), in 2009, that the relationship between target-volume and the risk of ARE may not be applied with lower prescription doses.

Additionally, after gamma knife treatment with low dose, a new treatment after relapse could be possible.

**Limitations**

This is a non-randomized retrospective study with a small number of patients. Further studies are needed.

**CONCLUSIONS**

Diffuse brainstem tumors remain a major neurosurgical challenge. Currently, many treatments have failed to improve significantly the outcome and survival rate. An individualized combination of radiotherapy, chemotherapy and surgery is still usually recommended.

A short-term response has been seen in almost every patient after radiation therapy, showing good response to low doses treatment.

In our series of patients with neoplastic lesions, Gamma Knife radiosurgery significantly improved the clinical and radiological outcome and should be considered in select cases. Larger tumors had a poorer outcome. Further studies are needed in order to achieve the ideal radiation dose and to select those patients who would benefit the most from this modality of treatment.
REFERENCES


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