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Technical Report

Fractionated Gamma Knife Radiosurgery for Optic Nerve Tumors: A Technical Report

Optik Sinir Tümörlerinde Fraksiyone Gamma Knife Radyocerrahi: Teknik Not

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ABSTRACT

AIM: The main purpose of this report is to demonstrate the effects of fractionated radiosurgery regimens in the management of optic gliomas

MATERIALS and METHODS: Two patients suffering from progressive loss of vision due to optic nerve gliomas were treated with Gamma Knife radiosurgery in three fractions within three consecutive days instead of a single dose regimen. Patients were followed for 42 and 39 months respectively.

RESULTS: The treatment modality was well tolerated by the patients with radiological and neurological tumor control after 42 and 39 months of follow up. There were no additional complications.

CONCLUSION: Fractionated regimens of Gamma Knife surgery offer a very good alternative for lesions such as optic glioma and optic nevre sheath meningioma.

KEYWORDS: : Fractionation, Gamma knife radiosurgery, Linear quadratic model, Optic nerve tumors, Stereotactic techniques

ÖZ

AMAÇ: Bu bildirinin temel amacı, optik tümörlerin tedavisinde fraksiyone radyocerrahi rejimlerinin etkilerini ortaya koymaktır.

YÖNTEM ve GEREÇ: Optik sinir kılıf menenjiomu ve optik sinir gliomuna bağlı ilerleyici görme kaybından yakınan iki hasta tek doz rejimi yerine ardışık üç günde ve üç fraksiyonda Gamma Knife radyocerrahi ile tedavi edildi. Hastalar sırasıyla 42 ve 39 ay süre ile takip edildi.

BULGULAR: 42 ve 39 aylık izlemin sonunda tedavi modalitesi, radyolojik ve nörolojik tümör kontrolü ile hastalarca iyi bir şekilde tolere edildi. Herhangi bir ek komplikasyon gelişmedi.

SONUÇ: Gamma Knife cerrahinin fraksiyone rejimleri, optik gliom ve optik sinir kılıf menenjiomu gibi lezyonlarda çok iyi bir alternatif teşkil etmektedir.

ANAHTAR SÖZCÜKLER: Fraksiyonasyon, Gamma knife radyocerrahi, Lineer kuadratik model, Optik sinir tümörleri, Stereotaktik teknikler

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INTRODUCTION

The most common tumor of the optic nerve is the optic nerve glioma which accounts for 66% of all primary optic nerve tumors and about 1% of all intracranial tumors. They may occur at any age, but childhood is the most common period of life for these tumors. While most of the cases are sporadic, there is a well-established relationship between these tumors and neurofibromatosis type 1 (1,12). Gangliogliomas, medullaepitheliomas, hemangioblastomas, schwannomas and hemangiopericytomas are other histopathological diagnoses that can involve optic pathways (12).

Although 10% to 30% are confined to a unilateral optic nerve, the majority involves some combination of optic chiasm, optic tracts, hypothalamus and third ventricle and can virtually be present in any location from eye to the optic cortex along the course of the optic pathway (20).

Another tumoral lesion of the optic nerve is primary optic nerve sheath meningioma (pONSM) which represents approximately 1% to 2% of all intracranial meningiomas. pONSM is the second most common optic nerve tumor after gliomas (6).

The optimal management method for optic pathway tumors remains controversial. Close observation, surgery, chemotherapy and radiotherapy or any combination of these are suggested for patient management (1).

The aim of stereotactic radiosurgery is to precisely deliver a high radiation dose to a well defined target while sparing adjacent normal tissues. A single large dose given during stereotactic radiosurgery treatment is an adequate and effective treatment modality for small arteriovenous malformations, functional disorders and tumors, with good results reported by many authors (17). However, additional measures are needed in some occasions to protect eloquent structures from the dangerous effects of radiation. The basic radiobiological principles and experience accumulated throughout the years have demonstrated that therapeutic ratio of fractionated regimens are superior in treatment of malignancies and the tolerance of eloquent tissues to irradiation can be increased by reducing the dose per fraction (16,17).

Linac-based fractionated stereotactic radiotherapy (FSRT) has been performed for many years, whereas examples of Gamma Knife using fractionation are rare (10). This article describes a different management approach in two patients with optic nerve tumors who were treated with a Gamma Knife (Elekta Instruments, Sweden) unit using fractionated radiosurgery technique. Fractionation was preferred because of the concerns of the toxic effects of the radiation on the optic nerve.

MATERIALS and METHODS

Dose schemes applied to the patients were calculated according to the linear quadratic (LQ) formulation.

In the classic LQ model (10,17), the biological effect is calculated as follows:

$$E = n\left(\alpha d + \beta d^2\right) \qquad (1)$$

Where n is the number of fractions, d is the dose per fraction in Gy, and α and β are two parameters specific to the tissue type. Dividing the Eq. 1 by α gives the biologically effective dose (BED). The final equation is.

$$BED = nd\left(1 + \frac{d}{\alpha/\beta}\right) \qquad (2)$$

The α/β parameter is determined from cell survival curves or in vivo data. The ratio is larger for early reacting tissues such as tumors, than for late reacting tissues such as brain itself. The α/β ratio for the tumors is about 10 Gy, while about 2-3 Gy for the brain. Liu et al. have proposed lookup tables in order to ease the usage of LQ formulation (10).

The safe radiation dose to the optic nerve has not yet been determined and long-term follow-up of radiation related optic neuropathy has not been fully undertaken. Several studies have reported that less than 8 Gy dose to the optic nerve and chiasm is safe. On the other hand there are reports demonstrating doses up to 10 Gy as safe (8,19). In our center, our data and experience suggest 8 Gy is safer than higher doses. Although the dose regimens are selected according to the specific features of each case, 8 Gy is usually our cut off point for the optic nerves.

The first patient was a 29-year-old male referred to our clinic due to progressive deterioration in his vision and ocular movements on the left eye for the last 2 years. He was followed by several clinicians previously and diagnosed as "left optic nerve

tumor". He had refused any surgical intervention due to high risks. When he came to our attention the visual acuity in his left eye was 0.2. He did not have any stigmata of Neurofibromatosis Type 1. Magnetic resonance images demonstrated an optic nerve distortion. The nerve was pushed by a contrast-enhancing lesion along its course. The radiological diagnosis was an optic nerve sheath meningioma (Figure 1). Treatment options and associated risks were discussed with the patient and application of fractionated stereotactic radiosurgery (Gamma Knife Model C, Elekta Instruments, Sweden) was decided on.

Our prescription dose was 13 Gy to the tumor margin (the dose to the 50% isodose line). However, in order to protect the optic nerve as much as possible, we fractionated the treatment. According to the LQ formulation and the lookup tables, we found that 6.2 Gy given in 3 fractions will have the same BED as single 13 Gy treatment.

The second patient was a 37-year-old male referred to our clinic due to progressive loss of vision in both eyes for the last 1 year. His right eye was amaurotic and the visual acuity in his left eye was 0.5. There were no signs of Neurofibromatosis Type 1 on physical examination. His magnetic resonance imaging demonstrated a chiasmatic infiltration suggestive of an optic nerve glioma (Figure 2). Treatment options were discussed with the patient and application of fractionated stereotactic radiosurgery (Gamma Knife Model C, Elekta Instruments, Sweden) was decided on.

The lesion was affecting the chiasm and he had lost vision in his right eye while the visual acuity of the left eye was progressively decreasing. We decided to protect the vision in the left eye as much as possible and to perform a more conservative treatment. Our prescription dose was 8 Gy to the tumor margin (the dose to the 50% isodose line). In order to reduce the negative effects of radiation on the chiasm we fractionated the treatment. Calculations revealed 3.5 Gy in three fractions will produce the same BED as single 8Gy treatment.

The patients were irradiated in three consecutive days, with 24-hour intervals. The Leksell Stereotactic Frame was applied on the first day of the treatment under local anesthesia. After appropriate imaging and calculations in the Leksell GammaPlan software (Elekta Instrument, Sweden) treatments were started. To achieve the same targeting accuracy throughout the treatment days we used the method described by Simonova et al (17). We left the stereotactic frame on the patient's head after initial application for the whole course of treatment (from the first fraction given in the first day to the last given in the last day) and we performed a control procedure as follows to ensure the required accuracy of dose delivery during each fraction:

The Leksell Skull Scaling Instrument (Elekta Instrument, Sweden) was attached to the stereotactic

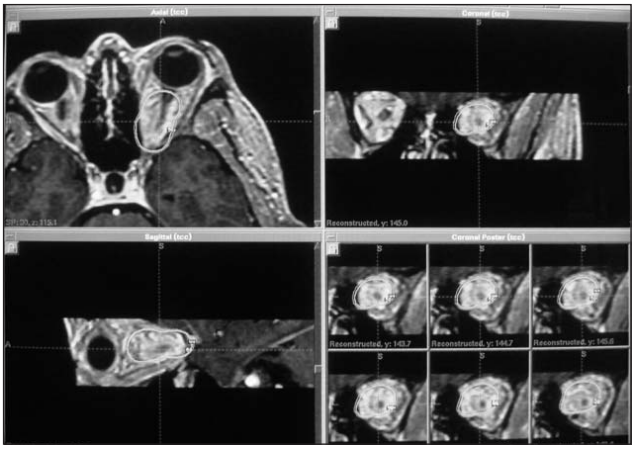

Figure 1: *Snapshot image of the first patient (pONSM) taken during Gamma Knife treatment planning. Images showing axial, coronal, sagittal and coronal poster T1-weighted MRI views of a markedly gadolinium-enhanced homogenous tumor surrounding the left optic pathway, and isodose lines around the mass.*

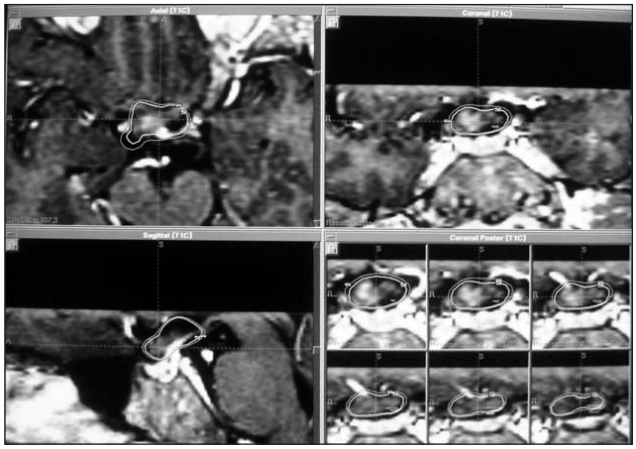

Figure 2: *Snapshot image of the second patient (glioma) taken during Gamma Knife treatment planning. Images showing axial, coronal, sagittal and coronal poster T1-weighted MRI views of a gadolinium-enhanced enlargement suggestive for a glioma within the right side of the optic chiasm, and isodose lines around the mass.*

frame fixed on the patient's head to measure the distances between the centre of the Leksell stereotactic space and certain significant points on the outer boundary of the patient's skull. Measurements were made by insertion of a special probe marked with a scale graduated in millimeter which precisely fit into the 24 holes over the scaling instrument. If the measured distances for all 24 points were identical, the position of the stereotactic frame was accepted as unchanged. If any changes are found in the position of the frame on patient's skull a new radiological investigation and a new dose plan have to be created.

RESULTS

Both treatment procedures were uneventful. Patient compliances were good. The time passed from the application of the Leksell stereotactic frame and to the discharge of the patients was almost 52 hours for both patients. Both patients were administered mild sedatives and analgesics during the treatment time in order to decrease discomfort. Consecutive skull and frame position measurements by the aforementioned method were easily performed and no discrepancies were detected throughout the treatment period. The position of the frames was the same throughout the treatment for both of the patients.

The first case was followed for 42 months after the treatment by radiological and ophthalmological follow up. During this period he did not report any related complications. Additionally his visual acuity in the left eye increased to 0.5. However, radiological appearance of the tumor remained same at the end of the follow up period (Figure 3A,B).

The second patient was followed up for 39 months. Similarly the patient reported no relevant complications. His clinical situation remained stable. Radiological complete disappearance of the tumor was achieved at the end of the follow-up period (Figure 4A,B,C). Additionally, his endocrine work up, due to proximity of the lesion to the pituitary gland demonstrated no endocrinological deterioration.

DISCUSSION

Optic nerve gliomas are rare tumors that usually present in childhood. Although most of the tumors are low-grade gliomas, the clinical course and natural history are highly variable, making decisions for treatment difficult (1,9,13,14). The standard treatment option for these tumors is still controversial. However, there is a general consensus that active treatment should be utilized urgently if signs of significant neurological or visual

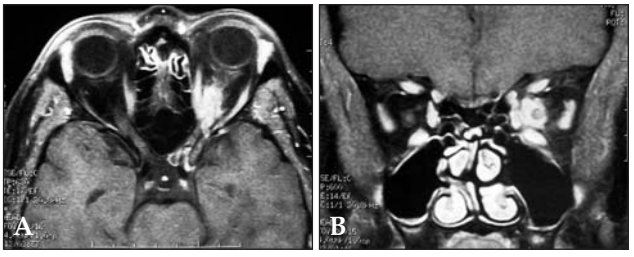

Figure 3: *T1-weighted, gadolinium-enhanced MRI images of the first patient at the end of the 42 months follow-up period.* ***A)*** *Axial.* ***B)*** *Coronal.*

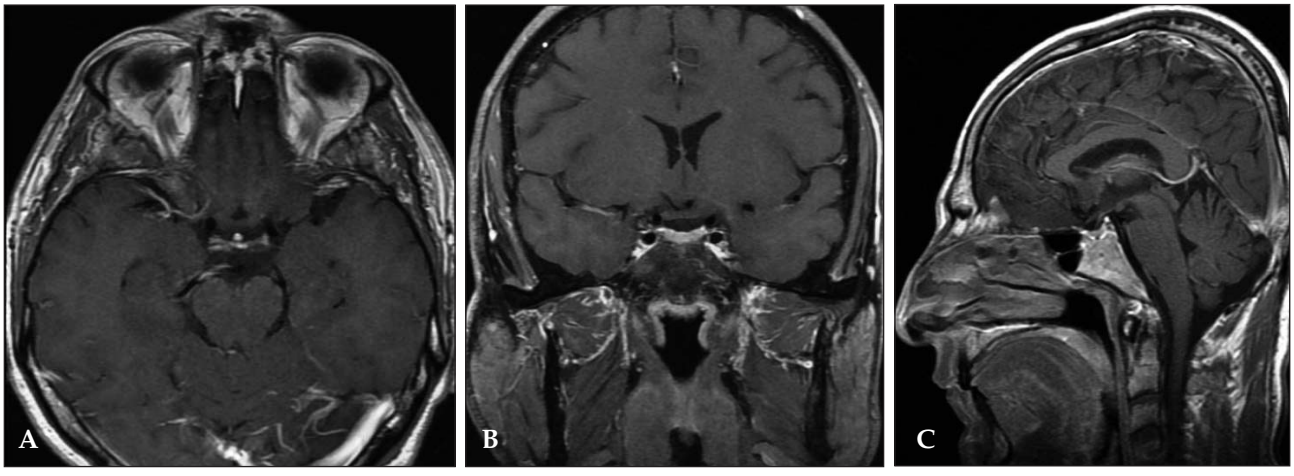

Figure 4: *T1-weighted, gadolinium-enhanced MRI images of the second patient showing complete disappearance of the tumor at the end of the 39 months follow-up period.* ***A)*** *Axial.* ***B)*** *Coronal.* ***C)*** *Sagittal.*

impairment are evident. Surgery is usually preserved for tumors limited to the optic nerves and causing extreme proptosis in patients suffering from blindness. Additionally, tumors extending beyond the optic pathways may benefit from decompressive procedures (3,14). Chemotherapy and radiation are other alternatives. Although chemotherapy is preferred to radiotherapy for the last few years, particularly in children under the age of seven because of high vulnerability to the negative effects of radiation, radiotherapy methods such as stereotactic guidance and fractionation may be used for these patients (4,14).

ONSMs are rare tumors representing 96% of all intraorbital meningiomas. Only 10% of ONSMs are isolated which occur primarily, and the remainder is classified as secondary ONSM. The majority of the patients with pONSM are middle-aged women. They generally present with a painless unilateral loss of visual acuity (6).

Treatment options for pONSM are also controversial as mentioned for optic gliomas. Patients suffering from loss of vision should be treated, but the surgical treatment may result in severe functional deterioration. Up to 95% total loss of vision rates and additional oculoparesis due to damage of nerves and muscles or indirect blockage of pial blood supply have been reported following surgical removal of ONSM. This led the physicians to be more conservative and try to find optimal techniques for irradiation treatment of these tumors. Better results were reported with fractionation of radiation doses using stereotactic radiotherapy or radiosurgery by several authors (5,7,11,15).

It is the best option to utilize any treatment modality after tissue diagnosis; this may not be the case for all patients and pathologies. Optic nerve lesions are one of the examples of such lesions. Their presence in very eloquent areas such as the optic nerve itself or the chiasm may preclude the tissue diagnosis. For these cases, state-of-the-art radiological techniques may help making the diagnosis and guide the further treatment. Advances in neuroimaging have increased the ability to make the right diagnosis and monitor these tumors obviating the need for biopsy (14).

Both of the patients presented in this report were suffering from decreasing visual acuity before they came to our attention. Although their lesions seemed confined to the relevant anatomical structures without any further and aggressive extensions, one to the intraorbital optic nerve and the other to the chiasm, they were evidently causing significant deficits. Presence of lesions in "functionally active" structures precluded delineation of a target for surgery or at least for a biopsy. Taking the progressive deficits into account, our decision was to proceed with radiosurgery. High eloquence of the targets forced us to tailor our treatment strategy to a more safe level. Our first aim for these patients was stabilizing their progressing deficits while preventing any further deterioration. In order to ensure this goal we utilized fractionation.

There are two main goals of fractionation: sparing normal tissue and maximizing tumor control. However, in most circumstances these two goals can not be achieved at the same time and a decision needs to be made (10). For the first patient we performed the treatment with a higher dose since the patient's visual acuity was more encouraging compared with the second patient, whose tumor was confined to the chiasm and causing more deficits. The second patient has already lost his vision in his right eye and loss of vision in the left eye due to radiotoxicity was unacceptable. This concern resulted in dose reduction.

The results achieved after long-term follow-up were encouraging. None of the patients demonstrated any further complication. Moreover, we observed significant improvement in the visual acuity of the first patient and complete radiological disappearance of the tumor at the second patient. These patients are still followed for any late complications of stereotactic radiosurgery.

Simonova et al. (18) have reported partial or complete tumor regression in 83% of their low grade glioma patients with a median time to response of 18 months after treatment with fractionated Gamma Knife radiosurgery. Debus et al. (4) have reported excellent tumor control rates after treatment of optic gliomas with the help of fractionated stereotactic radiotherapy without clinically relevant morbidity.

Fractionated stereotactic radiosurgery performed with Gamma Knife was safe and well tolerated by our patients. Fractionated regimens of Gamma Knife surgery offer a very good alternative for otherwise

untreatable lesions such as optic gliomas and ONSM. Fractionation is advantageous compared to single dose regimens because it reduces the amount of the dose delivered to the normal tissues.

In our opinion, the negative effect of the difference between the "tumor effective dose" and the "optic nerve safe dose" on tumor control can be eliminated using fractionation.

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