Single-session Gamma Knife radiosurgery for optic pathway/hypothalamic gliomas

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OBJECTIVE Because of their critical and central location, it is deemed necessary to fractionate when considering irradiating optic pathway/hypothalamic gliomas. Stereotactic fractionated radiotherapy is considered safer when dealing with gliomas in this location. In this study, the safety and efficacy of single-session stereotactic radiosurgery for optic pathway/hypothalamic gliomas were reviewed.

METHODS Between December 2004 and June 2014, 22 patients with optic pathway/hypothalamic gliomas were treated by single-session Gamma Knife radiosurgery. Twenty patients were available for follow-up for a minimum of 1 year after treatment. The patients were 5 to 43 years (median 16 years) of age. The tumor volume was 0.15 to 18.2 cm³ (median 3.1 cm³). The prescription dose ranged from 8 to 14 Gy (median 11.5 Gy).

RESULTS The mean follow-up period was 43 months. Five tumors involved the optic nerve only, and 15 tumors involved the chiasm/hypothalamus. Two patients died during the follow-up period. The tumors shrank in 12 cases, remained stable in 6 cases, and progressed in 2 cases, thereby making the tumor control rate 90%. Vision remained stable in 12 cases, improved in 6 cases, and worsened in 2 cases in which there was tumor progression. Progression-free survival was 83% at 3 years.

CONCLUSIONS The initial results indicate that single-session Gamma Knife radiosurgery is a safe and effective treatment option for optic pathway/hypothalamic gliomas.

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KEY WORDS Gamma Knife; optic; hypothalamic; glioma; fractionation; single session; stereotactic radiosurgery

OPTIC pathway/hypothalamic gliomas represent approximately 0.6%–1.2% of all primary intracranial tumors.³⁴ They are rare and account for 1%–5% of all central nervous system tumors in the pediatric group (peak age incidence between 2 and 6 years).^{4,9,48} The most common histopathological grade is low-grade astrocytoma.^{3,5} Although 10%–30% are confined to a unilateral optic nerve, the majority involves some combination of the optic chiasm, optic tracts, hypothalamus, and third ventricle and can be present in virtually any location from the eye to the optic cortex along the course of the optic pathway.⁴⁹

Reports—which overwhelmingly involve the use of external-beam radiotherapy (EBRT)—have indicated that high local tumor control and improved or stable visual function can be achieved in up to 90% of patients.²⁷ The potential late toxicity of EBRT, such as endocrinopathies,

vasculopathies (such as moyamoya disease), secondary malignancies, and neurocognitive deficits, limits its general application, especially in very young children.^{7,12,16,23,39,42} More recently, stereotactic fractionated radiotherapy has been used in the treatment of gliomas in this location.^{8,29,44} There are few case reports on Gamma Knife radiosurgery.^{30,32,33} To the best of our knowledge, this is the first clinical series to investigate the safety and efficacy of single-session stereotactic radiosurgery for optic pathway/hypothalamic gliomas.

Methods

Patient Characteristics

Between December 2004 and June 2014, 22 patients with optic pathway/hypothalamic gliomas were treated by single-session Gamma Knife radiosurgery. Twenty pa-

ABBREVIATIONS EBRT = external-beam radiotherapy; MRS = MR spectroscopy.
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tients who were available for follow-up for a minimum of 1 year after treatment were retrospectively analyzed. The patients were 5 to 43 years (median 16 years) of age. There were 10 male and 10 female patients. The mean follow-up duration was 43 months (range 12–104 months). Gliomas involved the optic nerve in 5 patients (5 eyes) and the hypothalamus/chiasm in 15 patients (30 eyes). Surgical debulking or biopsy was performed in 9 cases (3 cases in the optic nerve, and 6 cases in the hypothalamus/chiasm). Diagnosis was based on MR spectroscopy (MRS) in 7 cases, all of which originated in the hypothalamus/chiasm. In 4 patients (2 patients with gliomas in the optic nerve and 2 patients with gliomas in the hypothalamus/chiasm), there was the typical appearance of the lesions on MRI, so surgical intervention for histological proof of the diagnosis was not performed.

The histopathological grade was pilocytic in 2 patients, low grade in 5 patients, and WHO Grade II in 1 patient. MRS diagnosis was low grade in 4 patients, Grade II in 1 patient, intermediate grade in 2 patients, and Grade III in 1 patient.

One patient underwent EBRT before treatment. His tumor had recurred 3 years after EBRT, although the initial histopathological diagnosis was pilocytic astrocytoma. One patient required ventriculoperitoneal shunt insertion before treatment.

Patient Selection

Patients with optic nerve gliomas were only offered Gamma Knife treatment if the involved eye was blind. In the cases with optic nerve gliomas involving a seeing eye, Gamma Knife radiosurgery was not offered. In patients with hypothalamic/chiasmatic gliomas, Gamma Knife radiosurgery was performed regardless of visual status. Patients harboring tumors that were diagnosed as malignant—either by histopathology or MRS—were not offered Gamma Knife treatment. In patients with neurofibromatosis Type 1, treatment was indicated only when tumor progression was evident on serial imaging.

Treatment Parameters

The Leksell stereotactic head frame was attached to the patient's head after administration of local anesthesia (model G; Elekta AB). In pediatric patients, an additional intravenous sedative was administered prior to frame application. General anesthesia was not used. Imaging was based on contrast-enhanced T1-weighted sequences plus T2-weighted MRI sequences with 1.6-mm-thick slices using high-resolution 1.5-T MRI (Genesis Sigma; General Electric). Stereotactic images were imported into the GammaPlan workstation (Elekta AB). Additional fat-suppression images were obtained when there was tumor extension into the orbit. Treatment was carried out using Gamma Knife model C (Elekta AB). The target volume was drawn on all MRI slices. The critical structure of interest was the optic pathway, and, whenever possible, the functioning part of the pathway was drawn. The prescribed dose was aimed to be 12 to 14 Gy according to the tumor grade. The main determinant of the prescribed dose was keeping the dose to the functioning visual pathway

below the critical threshold, which we considered to be 9 Gy. In cases in which most or all of the tumor involved a functioning visual pathway, or when the functioning visual pathway was not identifiable, the prescription dose was kept at 10 Gy or less to preserve vision.

The tumor volume ranged from 0.15 to 18.2 cm³ (median 3.1 cm³). The administered prescription dose ranged from 8 to 14 Gy (median 11.5 Gy) for isodoses ranging from 50% to 70% with a percent coverage of 80% to 100% (median 94%). The integral dose was 2.8 to 274.5 mJ (median 51.3 mJ). In the 2 cases with purely chiasmatic gliomas, the prescription doses were 8 and 10 Gy, respectively (Table 1).

Follow-Up

Imaging follow-up examinations using contrast-enhanced MRI were carried out at 3-month intervals for the 1st year, 6-month intervals for the 2nd year, and annually thereafter. Additional imaging was obtained when a patient developed new symptoms or experienced the worsening of any preexisting symptoms. Every patient's history and examination findings were recorded and compared with those documented prior to treatment. Radiological follow-up was undertaken by performing contrast-enhanced MRI, including T2-weighted series. A 20% or greater change in the diameter measurements in at least 2 of the largest axes was considered significant. In cases in which the tumor was not sufficiently visible on regular imaging or in doubtful cases, the patient underwent MRI using the same protocol as the one used on the day of treatment. The images were then imported into GammaPlan, fused, and coregistered to the treatment images. The tumor was redrawn on the new images. A volume difference of more than 20% from the day of treatment was considered significant. In addition to imaging, a formal computerized visual field examination was performed, and a complete hormonal profile was determined before treatment and at every follow-up examination. Regular follow-up with an endocrinologist was maintained for hypothalamic/chiasmatic cases. The perimetry findings were compared both in respect to the overall appearance and the quantitative data registered on the forms.

The functional outcome after radiosurgery was determined according to improvement, stability, or worsening of vision and endocrine function.

Informed consent was obtained from all patients or their guardians.

Results

Two patients died during the follow-up period. The first patient had a hypothalamic/chiasmatic glioma, which was histopathologically diagnosed as pilocytic astrocytoma. He received EBRT. Three years after receiving EBRT, the tumor recurred. He underwent Gamma Knife radiosurgery. The tumor remained stable during the course of the follow-up period. Then, tumor progression occurred at 26 months; the patient underwent surgery and eventually died. The other patient had a hypothalamic/chiasmatic glioma diagnosed by MRS as low grade. The tumor had shrunk during follow-up and the patient's last visit was 13

TABLE 1. Summary of the patient and tumor characteristics

Case No.	Age (yrs), Sex	Tumor Location	Diagnosis Method	Tumor Grade	Endocrine Dysfunction	Tumor Vol (cm ³)	Prescription Dose (Gy)	Radiologically Identifiable OC*
1	11, M	ON	Histopathology	Low grade	None	3.4	12	
2	43, F	ON	MRI	Unidentified	None	1.5	11	
3	22, M	OC	Histopathology	Low grade	None	4.2	10	No
4	15, M	Hypo/OC	Histopathology	Grade II	DI+APD	11.7	8	No
5	32, M	ON	Histopathology	Low grade	None	2.4	12	
6	9, F	Hypo/OC	MRI	Unidentified	DI	1.1	11	Yes
7	14, F	Hypo/OC	MRI	Unidentified	DI	18.2	12	Yes
8	15, M	Hypo/OC	Histopathology	Pilocytic	None	15	12	Yes
9	19, M	OC	MRS	Low grade	None	5.2	8	No
10	14, F	Hypo/OC	MRS	Low grade	DI+APD	0.15	12	Yes
11	43, F	ON	MRI	Unidentified	None	1.2	12	
12	17, M	Hypo/OC	MRS	Grade III	None	4.8	14	Yes
13	19, F	Hypo/OC	MRS	Grade II	None	7.2	11	Yes
14	13, M	Hypo/OC	MRS	Low grade	None	6.3	11	Yes
15	28, F	Hypo/OC	MRS	Low grade	DI+APD	0.55	10	No
16	14, F	Hypo/OC	Histopathology	Low grade	None	0.5	10	No
17	31, F	Hypo/OC	MRS	Intermediate grade	DI+APD	1.4	12	Yes
18	15, M	ON	Histopathology	Low grade	None	2.7	14	
19	5, F	Hypo/OC	Histopathology	Pilocytic	APD	4	12	Yes
20	19, M	Hypo/OC	MRS	Intermediate grade	DI+APD	2.7	10	No

APD = anterior pituitary hormone deficiency; DI = diabetes insipidus; hypo = hypothalamus; OC = optic chiasm; ON = optic nerve.

* Blank cells indicate optic nerve tumors without involvement of the chiasm.

months after Gamma Knife treatment. He died 2 months later of an unknown cause.

Imaging Outcome

The tumors shrank in 12 cases, remained stable in 6 cases, and progressed in 2 cases, thereby making the tumor control rate 90% (Table 2). The progression-free survival rate was 83% at 3 years. Temporary tumor swelling occurred in 4 cases; 3 of these cases were associated with edema. The swelling was observed at 2 to 8 months after treatment. All swollen tumors eventually shrank at 12, 13, 15, and 26 months from the time of Gamma Knife treatment. Edema occurred in 4 cases, and all were hypothalamic/chiasmatic. The edema developed at 2, 7, 4, and 8 months after treatment. All of these patients were given steroids and edema completely resolved after 5, 8, 11, and 4 months from the time of onset. Tumor progression was observed in 2 cases. One tumor was initially diagnosed by histopathology as pilocytic astrocytoma and was treated with EBRT. Three years later, there was tumor recurrence that was treated without tumor grade reconfirmation by MRS or biopsy. Tumor progression occurred at 26 months. The other case was treated as a low-grade tumor based only on MRI features. Progression occurred at 24 months.

Clinical Outcome

For statistical purposes, the visual outcome here was reported for each eye when the optic apparatus was involved

in a tumor. This includes 5 eyes with optic nerve gliomas and 30 eyes with hypothalamic/chiasmatic gliomas. The visual field improved in 7 (20%) eyes, remained stable in 26 (74.3%) eyes, and became worse in 2 (5.7%) eyes, thereby demonstrating a visual preservation rate of 94.3%. Visual improvement was observed at 3 to 12 months after treatment in 5 eyes (in 3 different patients). Visual improvement was delayed in 2 other eyes (in 2 different patients), which occurred at 17 and 24 months due to initial transient visual deterioration. Eight eyes had normal vision before treatment, and they remained normal after treatment. Among the 8 blind eyes before treatment, 3 eyes had visual improvement and the rest remained stable (Figs. 1 and 2). Finally, among 19 eyes with pretreatment visual defects, 4 eyes improved, 13 eyes remained stable, and 2 eyes worsened. The 2 eyes with visual deterioration after treatment were both in 1 patient and caused by tumor progression.

Transient visual worsening occurred in 4 patients. These were associated with temporary tumor swelling and lasted for 7, 8, 9, and 8 months. All patients initially had visual defects in both eyes and eventually returned to their pretreatment visual status.

Endocrine dysfunction was present in 8 patients before treatment. This was in the form of diabetes insipidus in 2 patients, anterior pituitary hormone deficiency in 1 patient, and combined diabetes insipidus with associated anterior pituitary hormone deficiency in 5 patients. No new endocrine dysfunction occurred after treatment (Table 1).

TABLE 2. Visual and radiological outcomes in relation to pretreatment visual status, tumor characteristics, and treatment parameters

Case No.	Tumor Location	Visual Status		Temporary Tumor Swelling	Edema	Transient Visual Deterioration	Visual Outcome		Tumor Outcome
		Right Eye	Left Eye				Right Eye	Left Eye	
1	ON	NA	Blind				NA	Stable (blind)	Stable
2	ON	Blind	NA				Stable (blind)	NA	Shrank
3	OC	Blind	Field defect	Yes	Yes	Yes	Improved	Stable	Shrank
4	Hypo/OC	Blind	Field defect				Improved	Stable	Shrank
5	ON	Blind	NA				Stable (blind)	NA	Shrank
6	Hypo/OC	Field defect	Field defect				Worse	Worse	Growth
7	Hypo/OC	Field defect	Field defect	Yes	Yes	Yes	Stable	Stable	Shrank
8	Hypo/OC	Normal	Normal				Stable (normal)	Stable (normal)	Growth
9	OC	Field defect	Field defect				Stable	Stable	Shrank
10	Hypo/OC	Normal	Normal				Stable (normal)	Stable (normal)	Shrank
11	ON	NA	Blind				NA	Stable	Stable
12	Hypo/OC	Normal	Normal		Yes		Stable (normal)	Stable (normal)	Shrank
13	Hypo/OC	Field defect	Field defect				Stable	Stable	Stable
14	Hypo/OC	Blind	Field defect				Improved	Improved	Shrank
15	Hypo/OC	Normal	Normal				Stable (normal)	Stable (normal)	Shrank
16	Hypo/OC	Field defect	Field defect				Stable	Stable	Stable
17	Hypo/OC	Field defect	Field defect	Yes	Yes	Yes	Stable	Stable	Stable
18	ON	Blind	NA				Stable (blind)	NA	Stable
19	Hypo/OC	Field defect	Field defect	Yes		Yes	Improved	Stable	Shrank
20	Hypo/OC	Field defect	Field defect				Improved	Improved	Shrank

NA = not applicable.

Discussion

The disease course of optic pathway glioma, although mostly low grade, is variable and unpredictable, ranging from no progression to rapid progression and resulting in severe morbidity and death.^{4,10,20,21,24,48} The treatment of low-grade astrocytomas remains controversial, especially for optic pathway gliomas.

Chiasmatic/hypothalamic gliomas are not generally amenable to complete excision without incurring unacceptable complications, such as bilateral visual loss or worsening endocrine dysfunction. Debulking of the exophytic or cystic component can be considered in individual cases (especially in those patients with rapid progression), but the indications for surgery are not well defined.⁵⁰ Surgery is generally restricted to partial resection or biopsy.^{14,40} In tumors confined to the optic nerves, complete resection may be curative in most cases.^{1,4,35,36,48}

In the past few decades, chemotherapy has become the first-line treatment of choice. It delays radiotherapy or surgery until the disease has progressed. Nevertheless, although chemotherapy has emerged as a promising therapy, no regimen thus far has been universally accepted.^{11,22,41}

Many studies clearly demonstrate that postoperative radiotherapy directed to the chiasm is much more effective than surgery alone, resulting in a reduced treatment failure rate.^{24,28}

In the treatment of benign lesions, such as low-grade gliomas, the tissue that is desired to be damaged and the surrounding normal tissue that it is desired to be spared are both of the same radiobiological type: i.e., they are

both late-responding tissues. Consequently, one would expect that nothing is to be gained by a fractionated course relative to a single dose. In other words, a change in the fractionation pattern will not preferentially produce more damage in the benign lesion than in the surrounding normal tissues.⁶ Theoretically, fractionated radiation, whether conventional or stereotactic, would not be advantageous over single-dose SRS.

Gliomas in very eloquent areas, such as the optic nerve itself or the chiasm, may preclude tissue diagnosis. Advances in neuroimaging have increased the ability to make the right diagnosis and monitor these tumors, obviating the need for biopsy.³⁵ Sawamura et al. suggested that surgical biopsy appears to be unnecessary for clinically or radiologically typical cases and that curative resection is rarely achieved when the functional outcome of the patients is seriously respected. The role of surgical intervention may be restricted to bulk-reducing surgery only when it is inevitable.³⁸

Tumor control in the current study is on par with studies reporting on other forms of radiation treatment, which range from 75% to 100% (Table 3).^{8,16,21,24,36,42} The good tumor control rates in this study may be related to the fact that most of the tumors were low grade, which is expected with tumors in this location. The 2 cases in which progression occurred were not graded histologically, and both tumors recurred about 2 years after Gamma Knife treatment, raising the possibility of the malignant nature of these tumors.

Visual preservation after radiation therapy has been

FIG. 1. A 17-year-old male patient presented with hydrocephalus and was subsequently underwent shunt treatment. His parents refused surgery. The MRS diagnosis was Grade III hypothalamic glioma. The tumor was treated by a single session of Gamma Knife radiosurgery. **A:** The glioma was 4.8 cm³ in volume and was treated by a prescription dose of 14 Gy to the 50% isodose with 97% coverage. The maximum dose to the visual pathway was 7.9 Gy (*upper*). The visual field examination was normal before treatment (*lower*). **B:** Four years later, the MRI showed that the tumor shrank significantly (*upper*), and the patient's visual field examination remained normal (*lower*).

reported to range from 13% to 81%.^{8,16,21,24,36,42} Our study reports better visual outcome in comparison with these studies. Radiation-induced optic neuropathy is the main concern when treating lesions around or involving the visual pathway. Earlier studies on optic nerve and chiasm tolerance suggested that patients who receive radiation doses exceeding 8 Gy are at risk for developing neuropathy.^{15,43} Several more recent studies that investigated the tolerance of the visual pathway indicated that patients who receive radiation doses of up to 12 Gy to small portions of the optic apparatus have a low risk of developing radiation-induced optic neuropathy.^{31,37} In the current study, almost all of the prescription doses used were 12 Gy or less in order to stay below the optic threshold of the optic apparatus. In the cases in which the tumor was purely chiasmatic or where the tumor could not be differentiated from the chiasm, we limited the dose to 10 Gy or less so as to adhere to the dose constraints of the optic pathway and minimize the risk of optic toxicity. Consequently, we did not observe any cases of radiation-induced optic neuropathy and thus the superior visual outcome. These results question the advantage of administering fractionation over single-session radiosurgery for these tumors.

Stereotactic radiosurgery allows reduction of the dose to the pituitary gland and helps avoid therapy-induced endocrine disorders.³² As in the current study, none of the other studies involving stereotactic radiosurgery for optic pathway gliomas reported clinically relevant morbidity, especially newly developed endocrine dysfunction.^{30,32,33} The incidence of endocrine dysfunction after conventional or stereotactic fractionated radiotherapy is reported to be from 10% to 70%.^{8,10,16,21,24,36,42} Apart from transient visual worsening caused by tumor swelling, no patients suffered any permanent neurological deficit, which establishes single-session Gamma Knife radiosurgery as a safe treatment strategy.

Our study has some limitations. First, the follow-up period was relatively short. Because the majority of treated tumors were considered to be low grade, a longer follow-up period would further consolidate these results. However, the efficacy of Gamma Knife radiosurgery in the treatment of low-grade astrocytomas has been established in several studies.^{13,17–19,25,26,46,47} Second, the histopathological diagnosis was lacking in a number of the patients. Even though some patients were diagnosed with low-grade tumors, they did not have histopathological confirmation

FIG. 2. A 13-year-old male patient presented with visual deterioration. His parents refused surgery. The MRS diagnosis was low-grade hypothalamic glioma. The tumor was treated by a single session of Gamma Knife radiosurgery. **A:** The glioma was 6.3 cm³ in volume and was treated by a prescription dose of 11 Gy to the 50% isodose with 94% coverage. The maximum dose to the functioning visual pathway was 8.4 Gy (*upper*). The patient's visual field examination before treatment showed that the right eye was already blind (*lower*), so the right optic nerve was not delineated during treatment planning. **B:** Two years later, the MRI showed that the tumor shrank (*upper*), and the visual field examination showed that the patient regained some vision in the nasal field of his previously blind right eye (*lower*).

of their grade; however, the lack of recurrence after more than 2 years would at least be an indication of the benign nature of these tumors. An indication of the soundness of this concept would be the 2 cases in which tumor recurred. The first patient experienced recurrence 3 years after EBRT, although the tumor was originally histopatho-

logically diagnosed as pilocytic astrocytoma. Despite the fact that we did not obtain a biopsy before Gamma Knife treatment, tumor recurrence at 2 years after EBRT and then after Gamma Knife treatment would mean it was not a pilocytic astrocytoma at the time of Gamma Knife treatment. The explanation may be that either the tumor had

TABLE 3. Comparison with other studies in which the treatment of the optic pathway/hypothalamic gliomas was fractionated irradiation

Authors & Year	No. of Patients	Follow-Up Duration (yrs)	Dose (Gy)	%			
				10-Yr PFS	Tumor Control	Visual Improvement or Preservation	Endocrine Dysfunction
Tao et al., 1997	29	10	54	100	100	81	72
Horwich & Bloom, 1985	30	10	45–50	90	90	43	33
Jenkin et al., 1993	38	NR	50	73	75	13	NR
Pierce et al., 1990	24	6	54	88	88	30	73
Combs et al., 2005	15	8	52.2	72	80	40	7
Grabenbauer et al., 2000	25	9	45–60	69	86	36	48
Present study, 2016	18	3	11.5	NA	90	94	0

NR = not reported; PFS = progression-free survival.

pathologically transformed to a higher grade in the interval between surgery and Gamma Knife treatment or the initial histopathological diagnosis was incorrect, which is an occurrence that has been reported in 20% to 30% of gliomas.^{2,45} The second patient with tumor progression did not have histopathological confirmation or MRS before treatment to determine the tumor grade. Finally, the follow-up period is relatively short, especially regarding the potential delayed effects of treatment on vision and hormonal status. Radiation-induced optic neuropathy and endocrinopathy may occur years after radiation treatment, and thus a longer follow-up study in the future is essential to further assess these effects.

Conclusions

Our initial results indicate that single-session Gamma Knife radiosurgery is a safe and effective treatment option for optic pathway/hypothalamic gliomas. A longer follow-up is required to assess the prolonged effects of treatment on vision and hormonal status. The results question the advantage that fractionated radiation would provide over single-session stereotactic radiosurgery.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: El-Shehaby. Acquisition of data: El-Shehaby, Abdel Karim, Emad Eldin, Nabeel. Analysis and interpretation of data: El-Shehaby, Abdel Karim, Emad Eldin, Nabeel. Drafting the article: El-Shehaby. Critically revising the article: El-Shehaby, Reda. Reviewed submitted version of manuscript: El-Shehaby, Reda. Statistical analysis: El-Shehaby. Study supervision: Reda.

Supplemental Information

Previous Presentations

Portions of this work were presented in an abstract form and as an oral presentation at the 18th International Leksell Gamma Knife Society Meeting, which was held in Amsterdam, the Netherlands on May 15–19, 2016.

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