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CLINICAL ARTICLE

Neurofibromatosis type 2–associated meningiomas: an international multicenter study of outcomes after Gamma Knife stereotactic radiosurgery

Nasser Mohammed, MD, MCh,[1] Yi-Chieh Hung, MD,[1] Zhiyuan Xu, MD,[1] Tomas Chytka, MD,[2] Roman Liscak, MD, PhD,[2] Manjul Tripathi, MBBS, MCh,[3] David Arsanious, MD,[4] Christopher P. Cifarelli, MD, PhD,[4] Marco Perez Caceres,[5] David Mathieu, MD,[5] Herwin Speckter, MSc,[6] Gautam U. Mehta, MD,[7] Gregory P. Lekovic, MD, PhD,[7] and Jason P. Sheehan, MD[1]

[1]Department of Neurological Surgery, University of Virginia Health System, Charlottesville, Virginia; [2]Department of Neurological Surgery, Na Homolce Hospital, Prague, Czech Republic; [3]Department of Neurological Surgery, Postgraduate Institute of Medical Education and Research, Chandigarh, India; [4]Department of Neurological Surgery, West Virginia University, Morgantown, West Virginia; [5]Department of Neurological Surgery, Université de Sherbrooke, Centre de recherche du CHUS, Sherbrooke, Quebec, Canada; [6]Department of Neurological Surgery, CEDIMAT Hospital, Santo Domingo, Dominican Republic; and [7]Department of Neurological Surgery, House Ear Institute, Los Angeles, California

OBJECTIVE The management of neurofibromatosis type 2 (NF2)–associated meningiomas is challenging. The role of Gamma Knife radiosurgery (GKRS) in the treatment of these tumors remains to be fully defined. In this study, the authors aimed to examine the role of GKRS in the treatment of NF2-associated meningiomas and to evaluate the outcomes and complications after treatment.

METHODS Seven international medical centers contributed data for this retrospective cohort. Tumor progression was defined as a ≥ 20% increase from the baseline value. The clinical features, treatment details, outcomes, and complications were studied. The median follow-up was 8.5 years (range 0.6–25.5 years) from the time of initial GKRS. Shared frailty Cox regression was used for analysis.

RESULTS A total of 204 meningiomas in 39 patients treated with GKRS were analyzed. Cox regression analysis showed that increasing the maximum dose ($p = 0.02$; HR 12.2, 95% CI 1.287–116.7) and a lower number of meningiomas at presentation ($p = 0.03$; HR 0.9, 95% CI 0.821–0.990) were predictive of better tumor control in both univariable and multivariable settings. Age at onset, sex, margin dose, location, and presence of neurological deficit were not predictive of tumor progression. The cumulative 10-year progression-free survival was 94.8%. Radiation-induced adverse effects were noted in 4 patients (10%); these were transient and managed medically. No post-GKRS malignant transformation was noted in 287 person-years of follow-up.

CONCLUSIONS GKRS achieved effective tumor control with a low and generally acceptable rate of complications in NF2-associated meningiomas. There did not appear to be an appreciable risk of post–GKRS-induced malignancy in patients with NF2-treated meningiomas.

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KEYWORDS neurofibromatosis type 2; NF2; Gamma Knife radiosurgery; multiple meningiomas; stereotactic radiosurgery

Neurofibromatosis type 2 (NF2) is an autosomal dominant condition resulting in the development of multiple central nervous system tumors due to the loss of a copy of the tumor suppressor gene *NF2* on chromosome 22.[1] Currently, NF2 is not a curable disease. The diagnosis of NF2 is based on the Manchester clinical criteria.[2] It is estimated that two-thirds of patients with NF2 will eventually develop meningiomas.[3] Baser et al. found that in patients with NF2, the relative risk of mortality was 2.5 times greater in patients with meningiomas

ABBREVIATIONS GKRS = Gamma Knife radiosurgery; NF2 = neurofibromatosis type 2; PFS = progression-free survival; SRS = stereotactic radiosurgery.

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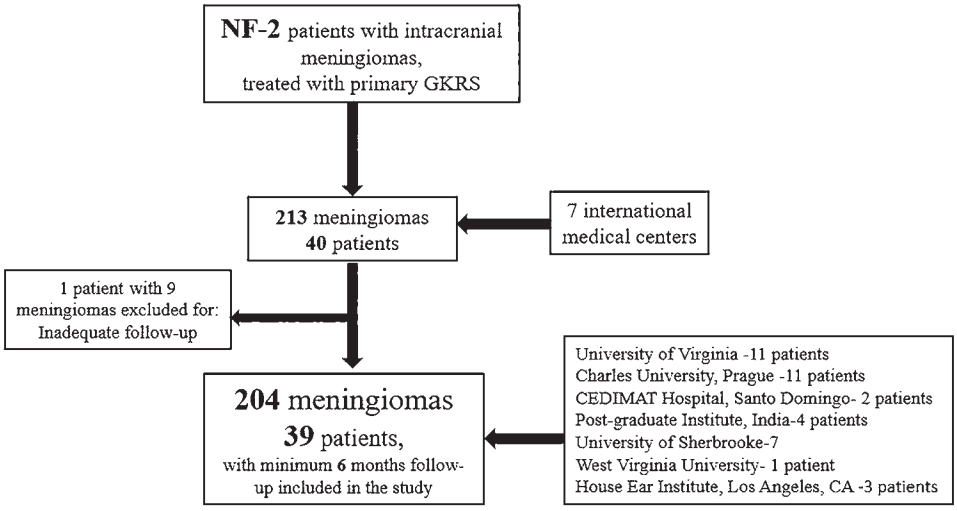

FIG. 1. Figure showing the selection of cases included in the study.

than in those without such lesions.[4] The age at onset has been described as a predictor of disease severity.[5]

The treatment of multiple tumors separated in time and space poses a significant clinical challenge. Patients may require multiple surgeries and additional treatments to control the disease. With multiple tumors, less invasive treatments are often preferable. The present treatment options for meningiomas in this patient population include surgery, postsurgical radiotherapy, upfront or salvage stereotactic radiosurgery (SRS), and chemotherapy. A review of the literature results in only a few SRS studies that have dealt with this rare disease, for which multicenter studies are lacking.[6–8] The present multicenter study is aimed at examining the role of Gamma Knife radiosurgery (GKRS) in the treatment of NF2-associated meningiomas and evaluating the complications of the treatment.

Methods

Patient Selection

From the database contributed by 7 medical centers participating in the International Radiosurgery Research Foundation (IRRF), 40 patients with 213 meningiomas treated with primary GKRS were pooled together. One patient was excluded because of inadequate follow-up information. Thus, 39 NF2 patients with 204 intracranial meningiomas treated with primary GKRS were included in the present study. The number of patients contributed by each center are as follows: University of Virginia, 11; Na Homolce Hospital, Prague, 11; CEDIMAT hospital, Santo Domingo, 2; Postgraduate Institute, India, 4; University of Sherbrooke, 7; House Ear Institute, Los Angeles, 3; and West Virginia University, 1 (Fig. 1).

The study was approved by each participating institution's review board and by the IRRF review committee. The data from each center were de-identified and pooled. The pooled data were analyzed. As this is a retrospective study, patient consent was not deemed necessary.

Patients with NF2 who had at least one intracranial meningioma treated with primary GKRS were included in the study. The indication for treatment was either symptomatic tumors or a progressive increase in tumor size. There was no age limit for inclusion. The radiological diagnosis of meningioma was considered adequate for study inclusion. A follow-up of at least 6 months was required. Patients with a history of prior surgery for the treated meningioma were excluded.

Baseline Assessment

Clinical data on different baseline parameters such as age at diagnosis, age at first GKRS, sex, location, tumor size, symptoms, and neurological deficits were collected. Since some NF2 patients had more than one meningioma treated with GKRS, characteristics such as size, location, and symptoms were collected separately for each of the tumors treated.

Radiosurgical Attributes

The Gamma Knife (Elekta AB) technique used for the treatment has been previously described in detail.[9] Briefly, the stereotactic G frame was fixed under sedation and local anesthesia. Stereotactic contrast-enhanced MRI was performed to define the tumor. Various models of Leksell Gamma Knife units (model B, U, 4C, Perfexion, and Icon) were used depending on the available technology at the time of radiosurgery. A team comprising a radiation oncologist, a radiation physicist, and neurosurgeons were involved in the treatment planning. Tumor volume was measured using GammaPlan software (Elekta AB) after contouring the tumor shape on multiple slices.

Follow-Up Assessment

Patient follow-up included both clinical assessment and radiological serial imaging. Tumor progression was defined as an increase of ≥ 20% of tumor volume from baseline pre-GKRS tumor volume. The time to tumor progression was calculated from the date of GKRS. A need for post-GKRS surgery, repeat GKRS, or adjuvant chemotherapy was noted. Adverse radiation reactions were

TABLE 1. Patient demographics and clinical features

Characteristic	Value
No. of patients	39
Total no. of meningiomas	386
No. of meningiomas treated w/ GKRS	204
Median age at diagnosis, yrs	30 (8–65)
Median age at GKRS, yrs	38 (10–72)
Preexisting neurological deficit due to meningiomas	15 (39)
Signs or symptoms prior to GKRS	
Asymptomatic	14 (35)
Headache	10 (26)
Seizures	2 (6)
Gait instability	3 (8)
Visual disturbance	6 (15)
Motor weakness	3 (8)
Hearing loss	4 (10)
Sensory deficit	1 (3)
Median no. of meningiomas per patient	6 (1–46)
No. of patients w/ ≤10 meningiomas	23 (59)
No. of patients w/ ≥11 meningiomas	16 (41)
Location (among 204 meningiomas)*	
Convexity	122 (60)
Parasagittal	12 (6)
Falcine	16 (7.8)
Anterior cranial fossa	10 (5)
Sphenoid/middle cranial fossa	10 (5)
Posterior fossa	32 (15.6)
Median follow-up after initial GKRS, yrs	8.5 (0.6–25.5)

Values represent the number (%) or median (range).
* Percentages are based on 204 meningiomas.

TABLE 2. Radiosurgical and outcome details

Variable	Value
Median treatment vol, cm^3	1.33 (0.10–21.20)
Median max dose, Gy	26 (20–50)
Median margin dose, Gy	12.5 (10–25)
No. of tumors w/ post-GKRS progression	10/204 (4.9)
Median time to progression, yrs	3 (0.5–3.9)
Repeat GKRS	2/39 (5)
Post-GKRS	2/39 (5)
Adjuvant chemotherapy	2/39 (5)
Radiation-induced adverse effect	4/39 (10)
Nature of adverse radiation effect	
Edema	3/39 (8)
Radiation necrosis	1 (2.5)
Malignant transformation in treated tumors	0
Mortality due to meningioma-related causes	0

Values represent the number of patients (%) or median (range).

documented. Mortality directly related to meningiomas, or their treatment with GKRS, was evaluated.

Statistical Analysis

Continuous variables are described using median and range. Since each patient had more than one tumor, observations from each patient were dependent in nature. Dependency for individual patient-level tumor characteristics was analyzed using shared-frailty Cox regression analysis. A shared-frailty model involves regression models with random effects. Shared-frailty models are used to model within-group correlation; in the present case, tumors from the same patient are correlated because they share the same frailty. STATA statistical software version 16.1 (StataCorp) was used for statistical analysis. A two-sided p value < 0.05 was considered to be statistically significant.

Results

Demographics and Clinical Features

Thirty-nine patients with the diagnosis of NF2 who collectively had 204 intracranial meningiomas treated primarily with GKRS were included in the study. The median age at diagnosis was 30 years (range 8–65 years). At the time of radiosurgery, 16 patients (41%) had more than 10 meningiomas. The median age at the time of GKRS was 38 years (range 10–72 years). Fifteen patients (39%) presented with neurological deficits due to meningiomas. Fourteen patients (35%) were asymptomatic due to the meningiomas. Headache was the most common clinical symptom, occurring in 10 patients (26%). Seizures occurred in 2 patients (6%). Cerebral convexity was the most common tumor location (122/204 tumors, 60%). The median follow-up after the initial GKRS was 8.5 years (0.6–25.5 years) (Table 1).

Radiosurgery Management

The median treatment volume was 1.31 cm^3 (range 0.1–21.2 cm^3). The median maximum radiation dose administered was 26 Gy (range 20–50 Gy). The median margin dose was 12.5 Gy (range 10–25 Gy) (Table 2).

Tumor Control Outcomes and Factors Predicting Tumor Control

Tumor progression (defined as ≥ 20% increase in size from baseline at the time of GKRS) was seen in 10 (4.9%) of the treated tumors in 10 patients. The median time to progression was 3 years (range 0.5–3.9 years). Two patients required repeat GKRS due to tumor progression. Two patients required post-GKRS surgery, and adjuvant chemotherapy was used in 2 patients. There were 4 cases of marginal failure and 3 cases of in-field failure. A shared frailty Cox proportional hazards model was used to investigate factors predictive of tumor control. Increasing the maximum dose ($p = 0.02$; HR 12.2, 95% CI 1.287–116.7) and a lower number of meningiomas at presentation ($p = 0.03$; HR 0.9, 95% CI 0.821–0.990) were predictive of better tumor control in both the univariable and multivariable settings. Age at onset, sex, margin dose, location, and pres-

TABLE 3. Cox regression analysis with shared frailty analysis for factors predictive of tumor control after GKRS

Variable	Univariate			Multivariate		
	p Value	HR	95% CI	p Value	HR	95% CI
Age at diagnosis	0.406	0.974	0.917–1.035			
Female sex	0.642	1.766	0.160–19.47			
Neurological deficit	0.514	0.451	0.041–4.936			
Maximum dose	**0.029**	12.26	1.287–116.7	**0.03**	10.66	1.235–80.89
Margin dose	0.781	1.010	0.940–1.085			
No. of meningiomas	**0.03**	0.901	0.821–0.990	**0.01**	0.905	0.834–0.981
Location	0.450	1.121	0.832–1.511			

Boldface type indicates statistical significance.

ence of neurological deficit were not predictive of tumor progression (Table 3). The actuarial 10-year progression-free survival (PFS) was 94.3% (Fig. 2).

Radiation-Induced Adverse Events and Risk of Post-GKRS Malignant Transformation

Radiation-induced adverse effects were noted in 4 patients (10%). Three patients had radiation-induced perilesional edema, and 1 patient developed radiation necrosis. All of these adverse effects were transient and managed medically with steroids. No malignant transformation was noted in any patient. No mortality was directly caused by the treated meningiomas or arose due to GKRS.

Discussion

Patients with NF2 have tumors of varied histology occurring over time and space. The present study is focused on evaluating the outcomes after upfront GKRS in NF2-associated meningiomas. Clinicians must often balance between the number of interventions performed and close observation in managing these tumors. The ability to treat multiple tumors over time and space and its minimally invasive nature has made GKRS a valuable option in treating NF2-associated meningiomas.

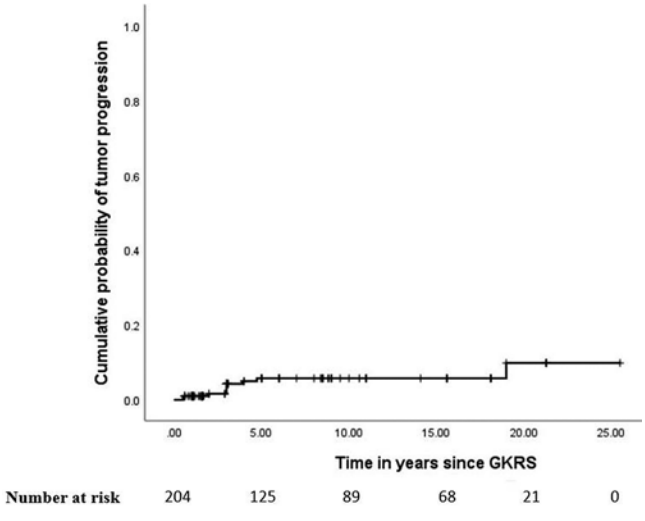

FIG. 2. Graph showing survival analysis with cumulative probability of tumor progression after GKRS.

Meningiomas in NF2 typically occur in a much younger patient population compared with sporadic meningiomas.[10,11] The median age at the time of GKRS in the present study was 38 years. The age at GKRS in previous studies has been reported to range from 27 to 54 years.[6,7] Given the potential for multiple lifetime treatments, typically only growing and symptomatic tumors are given consideration for treatment. Most patients with NF2 have a long follow-up due to their predisposition to new tumor formation, and the median follow-up in the present study was 8.5 years (range 0.6–25.5 years).

The 10- and 20-year PFS rates in the present study were 94.8% and 90.6%, respectively, and within the current study period for this cohort, no mortality was noted due to NF2 disease. Birckhead et al. evaluated 15 NF2 patients with 62 intracranial meningiomas treated with GKRS.[7] The 5- and 10-year tumor control rates were both 96%. Radiation adverse events occurred in 13% of patients. Four patients had died at last follow-up. There were no cases with GKRS-induced secondary malignancies in their median follow-up period of 9.25 years. Liu et al. studied 12 patients with NF2 who had 125 treated meningiomas with a median follow-up of 43 months. The overall local control rate was 92% in their study; 25% of the patients developed adverse radiation effects following radiosurgery. Four patients had died at follow-up. No malignant transformation was noted in their patients.[6]

A smaller number of intracranial meningiomas present at the time of initial GKRS was predictive of better tumor control after radiosurgery in logistic regression analysis. In the present study, 59% of the patients had ≤ 10 meningiomas. It can be hypothesized that patients with fewer meningiomas at presentation have a milder disease, with tumor biology more amenable to control by radiosurgery, compared with those patients presenting with a greater tumor burden. Differences in the radiobiological responsiveness of NF2 subtypes should be explored in future studies.

Increasing the maximum radiation dose was also found to be predictive of better tumor control after GKRS in the present study. The treatment planning of GKRS incorpo-

rates a wide variation of isocenters with differing sizes, shapes, and weights. Millar et al. suggested that the biological effectiveness may vary due to these variations.[12] Differing maximum doses in GKRS are a result of fairly fixed margin doses, but various prescription isodoses are used to treat the target. Typical prescription isodoses in GKRS vary from 40% to 60%. Dose heterogeneity arises from the varied prescription doses and number of isocenters in GKRS. With GKRS, some portions of the target volume have relative "hot spots" and maximal doses within the tumor may impact target response. Lucia et al. reported the impact of inhomogeneous versus homogenous dose distribution on local control of brain metastasis after SRS.[13] They found that inhomogeneous dose distribution resulted in better local control. Similar findings were reported by Langenhuizen et al. in the treatment of vestibular schwannomas with GKRS.[14] A higher maximum dose may also be effective at overcoming late-responding tissue typical of a grade I meningioma.[15] However, a higher maximum dose has, at times, been associated with an increased rate of radiation adverse events. Balagamwala et al. analyzed 145 patients for the importance of conformity index, heterogeneity index, and gradient index in treating intracranial meningiomas with GKRS.[16] They found that a higher heterogeneity index and a lower gradient index were associated with an increased rate of complication. However, conformity index was not associated with toxicity. We analyzed central failure versus marginal failure rates among tumors that progressed and correlated them with the maximum dose and the margin dose. There were 4 cases of marginal failure and 3 cases of in-field failure. In NF2, meningiomas may arise congruently and it often becomes difficult to determine where one tumor ends and another begins. Margin failure versus new tumor growth therefore becomes difficult to analyze.

GKRS-Induced Secondary Malignancy in Treating NF2-Associated Meningiomas

NF2 genomics obey the Knudson's two-hit hypothesis. The first hit is usually a germline mutation, and the additional somatic mutation is the second hit, resulting in inactivation of the tumor suppressor gene and its function.[17,18] The concern with GKRS is the possibility of the second hit mutation occurring due to radiosurgery, leading to radiation-induced tumorigenesis in the background of the *NF2* mutation. Patients with NF2 are subjected to radiation therapy at a much younger age compared with patients with sporadic meningiomas. They may also require multiple radiosurgery procedures over time. This could potentially increase the cumulative risk of radiation-induced secondary malignancy in NF2 patients. Fortunately, in the median follow-up period of 8.5 years (range 0.6–25.5 years), there were no cases of secondary malignancies developing within the field of radiation. Previous studies on SRS for NF2-associated meningiomas have also demonstrated no secondary malignancies.[6,7] However, a longer follow-up period extending over decades is required to validate the current findings, but there does not appear to be an appreciable increase in malignancy (new or transformed) in the post-GKRS NF2 patients.

Study Limitations

The limitations of a retrospective analysis apply to this study. The WHO grade of the tumors was not known in patients treated with primary GKRS. Incorporation of the WHO classification of the tumors could give a better understanding of tumor progression. Longer follow-up is required to rule out the effects of GKRS in patients with NF2 and the possibility of induction of secondary malignancies. Although the present study involved a small number of patients, the median number of meningiomas per patient was high. The present study also incorporated a diverse NF2 patient population in a wide geographic distribution giving a greater generalizability to its conclusions.

Conclusions

GKRS is an effective treatment for NF2-associated meningiomas with a 10-year PFS rate of 94.8% and a reasonable rate of complications, most of which are temporary. GKRS is a valuable adjunct for treating multiple meningiomas occurring over time and space in patients with NF2. For this patient population, with a median follow-up period of 8.5 years in the current study, there does not seem to be an appreciable risk of secondary malignancy following GKRS.

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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: Sheehan, Mohammed, Hung, Xu, Liscak. Acquisition of data: Sheehan, Mohammed, Hung, Chytka, Liscak, Tripathi, Arsanious, Cifarelli, Perez Caceres, Speckter, Lekovic. Analysis and interpretation of data: Sheehan, Mohammed, Hung, Xu, Mathieu, Mehta. Drafting the article: Sheehan, Mohammed, Hung. Critically revising the article: Sheehan, Mohammed, Hung, Xu, Chytka, Tripathi, Mathieu, Speckter, Mehta. Reviewed submitted version of manuscript: Sheehan, Mohammed, Xu, Chytka, Liscak, Tripathi, Arsanious, Cifarelli, Perez Caceres, Mathieu, Speckter, Mehta, Lekovic. Approved the final version of the manuscript on behalf of all authors: Sheehan. Statistical analysis: Sheehan, Mohammed, Xu. Administrative/technical/material support: all authors. Study supervision: all authors.

Correspondence

Jason P. Sheehan: University of Virginia Health System, Charlottesville, VA. jsheehan@virginia.edu.