Skull Base Meningiomas in Patients with Neurofibromatosis Type 2: An International Multicenter Study Evaluating Stereotactic Radiosurgery

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Abstract

Objective Meningiomas are the second most common tumors in neurofibromatosis type 2 (NF-2). Microsurgery is challenging in NF-2 patients presenting with skull base meningiomas due to the intrinsic risks and need for multiple interventions over time. We analyzed treatment outcomes and complications after primary Gamma Knife radiosurgery (GKRS) to delineate its role in the management of these tumors.

Methods An international multicenter retrospective study approved by the International Radiosurgery Research Foundation was performed. NF-2 patients with at least one growing and/or symptomatic skull base meningioma and 6-month follow-up after primary GKRS were included. Clinical and radiosurgical parameters were recorded for analysis.

Results In total, 22 NF-2 patients with 54 skull base meningiomas receiving GKRS as primary treatment met inclusion criteria. Median age at GKRS was 38 years (10–79 years). Most lesions were located in the posterior fossa (55.6%). Actuarial progression free survival (PFS) rates were 98.1% at 2 years and 90.0% at 5 and 10 years. The median follow-up time after initial GKRS was 5.0 years (0.6–25.5 years). Tumor volume at GKRS was a predictor of tumor control. Lesions >5.5 cc presented higher chances to progress after radiosurgery ($p = 0.043$). Three patients (13.64%) developed adverse radiation

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effects. No malignant transformation or death due to meningioma or radiosurgery was reported.

Conclusions GKRS is effective and safe in the management of skull base meningiomas in NF-2 patients. Tumor volume deserve greater relevance during clinical decision-making regarding the most appropriate time to treat. GKRS offers a minimally invasive approach of particular interest in this specific group of patients.

Introduction

Neurofibromatosis type 2 (NF-2) is an autosomal dominant syndrome characterized by the presence of multiple benign tumors such as bilateral vestibular schwannomas, meningiomas, ependymomas, and astrocytomas.[1] Meningiomas are the second most common tumors in NF-2, presenting in up to 80% of patients by 70 years of age.[2,3] These lesions have been associated with increased morbidity as well as a 2.51-fold increase in mortality risk when comparing NF-2 patients with and without meningiomas.[4]

Meningiomas of the skull base are ideally approached with surgery; however, they tend to abut or encase neurovascular structures complicating the chances of achieving gross total resection (GTR), which is the most important predictive factor of tumor control.[5–12] Sporadic meningiomas of the skull base are frequently treated with GKRS, and studies have demonstrated long-term tumor control and neurological preservation or improvement in the majority of patients.[13–18] However, for NF-2 patients, particular genetic alterations, histology types and potentially natural history advocate for a different meningioma biology,[19–22] and questions remain about the value of GKRS for skull base meningiomas in NF-2 patients. NF-2 patients usually present with several lesions and are more prompt to recur and diachronically develop new tumors over time, which represents a challenging clinical scenario where less invasive treatments should be better analyzed. Our study presents outcomes from an international multicenter cohort of skull base NF-2 associated meningiomas treated with upfront Gamma Knife radiosurgery (Elekta AB, Stockholm) to identify treatment outcomes and its predictors, as well as complications rates on this specific group of patients.

Methods

Patient Selection

This is an international multicenter retrospective study. Data about patient epidemiology and treatment outcomes were collected from seven medical centers participating in the International Radiosurgery Research Foundation after institutional review board (IRB) approval in each institution and patient consent was waived by each IRB. The data were de-identified and pooled; thereafter, the pooled data were analyzed. Reporting of the data has been performed according to the most updated (Strengthening The Reporting of OBservational Studies in Epidemiology) STROBE statement.

Eligibility criteria included NF-2 patients of any age with at least one skull base meningioma treated with upfront Gamma Knife radiosurgery (GKRS). As patients who undergo GKRS as primary treatment lack a definitive pathological diagnosis, a radiological diagnosis of meningioma was deemed adequate for patient inclusion. Radiological features consistent with meningioma such as extra-axial location, dural attachment, intratumoral calcifications, and/or contrast enhancement were considered relevant for diagnosis. The indication for GKRS was the presence of either symptomatic or progressively growing lesions. A follow-up of at least 6 months was required. A longer follow-up was not considered appropriate as this might have introduced study bias in actuarial results by excluding earlier failures, which did occur in this study (►**Supplementary Fig. S1** [available in the online version]). Exclusion criteria included previous radiation or surgical resection of the meningiomas (►**Fig. 1**). Vestibular schwannomas were not included in this analysis.

Baseline Data and Variables

Clinical baseline parameters including sex, age at diagnosis, age at first GKRS, total number of meningiomas, location, symptoms, and neurological deficits were recorded. GKRS treatment parameters including treatment volume, maximum dose, and margin dose were also noted directly from the medical records.

Follow-Up and Outcomes

Clinical and radiological follow-up was recorded. Time to tumor progression was calculated from the date of GKRS by using radiographic data. Tumor progression was based on volumetric analysis, and was defined as an increase of $\geq$20% over the baseline pre-GKRS tumor volume (original volume), on any follow-up MRI. The need for post-GKRS surgery, repeated radiation, or adjuvant chemotherapy was also recorded. Radiation adverse effects and time to its development were documented. Radiation necrosis was defined on the basis of either neuroimaging studies or tissue pathology. Relevant MRI findings for radiographic diagnosis of radiation necrosis are the characteristic enhancement of central necrosis on T1-weighted images and/or the central high signal intensity proper to the necrotic tissue surrounded by a low signal intensity proper to the solid non-necrotic peripheral portion on T2-weighted images.[23] Mortality due to the treated lesions or their treatment with GKRS was evaluated. As most NF-2 patients present with multiple meningiomas,

information about each specific lesion was collected independently.

Radiosurgical Technique

Details of the single fraction Gamma Knife technique employed for the treatment of the lesions included in this study have been widely described.[24,25] Briefly, thin-slice axial and/or coronal MRI images were obtained after a stereotactic G frame (Elekta AB) was placed under sedation and local anesthesia. Additionally, computed tomography imaging was fused to the MRI to optimize imaging of the skull base (soft tissue and bony structures) for treatment planning and delivery. Different models of Leksell Gamma Knife units (model B, U, 4C, Perfexion and Icon; Elekta instrument, Inc.) were used upon the available technology at the medical center and the time of the procedure. A multidisciplinary team of radiation oncologists, radiation physicists, and neurosurgeons were involved in the treatment planning. It was important to place the frame's base ring at the level of C-2 to treat the lower extension of some tumors effectively.

Statistical Analysis

Descriptive statistics were performed according to each variable type; numerical variables were described by using median and range. Gaussian distribution and homogeneity of variance were tested accordingly when needed. Mann–Whitney U test was performed to compare continuous variables. Kaplan–Meier analysis and the log rank test were performed to independently analyze the cumulative probability of tumor progression and progression free survival (PFS). Multivariable analysis was performed via Cox proportional hazards model to further investigate adjusted predictive factors. When a patient presented more than one tumor, each lesion was considered individually for analysis of tumor control or progression. Statistical analysis was performed by using SPSS (version 25, IBM, Armonk, New York, United States), a $p < 0.05$ was required to account for statistical significance.

Results

Patients and Tumor Attributes

A total of 40 NF-2 patients and 213 associated meningiomas treated with primary GKRS were identified and examined for eligibility. One patient presenting with inadequate follow-up was excluded. The final study cohort included 22 patients with at least one skull base meningioma, and 54 lesions (►**Fig. 1**). From these, one patient was recruited from West Virginia University (USA), eight from University of Virginia (USA), two from the CEDIMAT Hospital (Dominican Republic), four from University of Sherbrooke (Canada), four from Charles University (Czech Republic), one from the Post Graduate Institute of Medical Education and Research (India), and two from the House Ear Institute (USA). Patient attributes and tumor characteristics are described in ►**Table 1**. In total, 14 out of 22 patients were females (63.6%), and the median cohort age at diagnosis was 25.5 years (8–65 years). Patients were symptomatic in a 63.6% of cases. The most common symptoms were headaches (27.3%), visual disturbances (18.2%), and motor weakness (13.6%). The number of skull base meningiomas treated with GKRS per patient ranged from one to eight lesions (median = 2, mean = 2.46). In total, 10 meningiomas were located in the anterior cranial fossa (18.5%), 3 in the cavernous sinus (5.6%), 11 in the sphenoid wind/middle cranial fossa (20.4%), and 30 in the posterior cranial fossa (55.6%), which represented the most common location for these lesions. The median age at GKRS was 38 years (10–79 years).

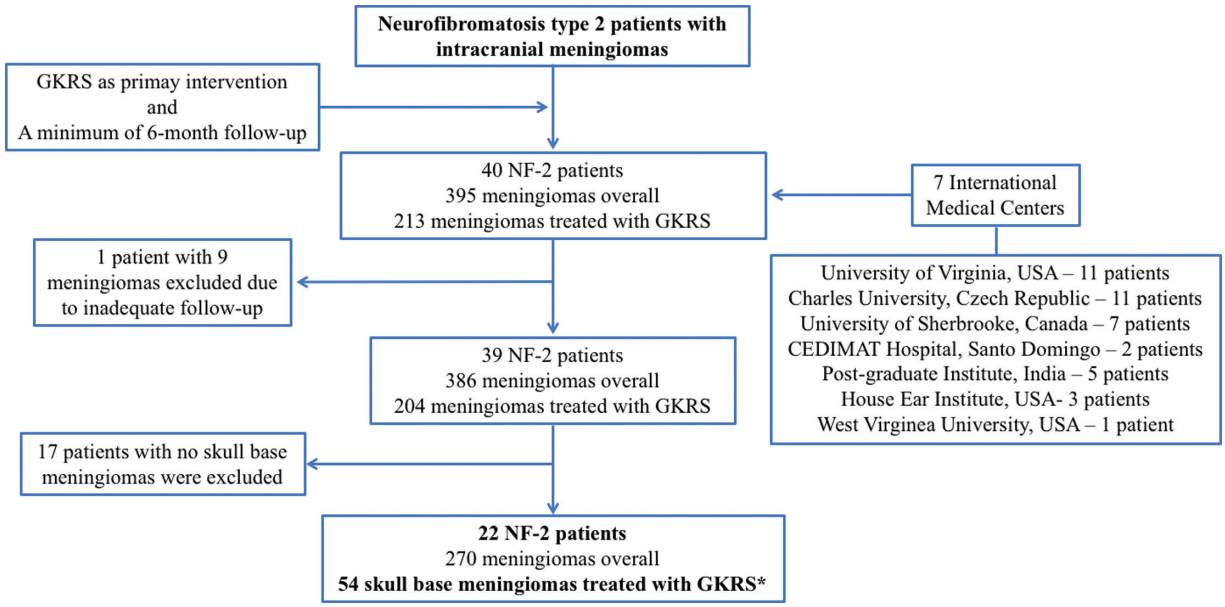

Fig. 1 Patient selection algorithm. *Final number of patients recruited from each specific center for the cohort with 54 skull base lesions included in the analysis is described in the results (section: patients and tumor attributes).

Table 1 Demographics and clinical features of patients with neurofibromatosis type 2 presenting with skull base meningiomas

Clinical characteristics	
Number of patients	22
Sex (M/F)	8/14
Age at diagnosis in years, median (range)	25.5 (8–65)
Age at GKRS in years, median (range)	38 (10–79)
Total number of skull base meningiomas treated with GKRS	54
Total number of meningiomas in included patients	270
Number of skull base meningiomas treated with GKRS per patient, Median, mean (range)	2, 2.46 (1–8)
Number of meningiomas per included patient, median (range)	11 (1–46)
Signs or symptoms prior to GKRS	
Patients with preexisting neuro-deficit due to meningiomas, *n* (%)	10 (45.5%)
Asymptomatic, *n* (%)	8/22 (36.4%)
Headache, *n* (%)	6/22 (27.3%)
Seizures, *n* (%)	3/22 (13.6%)
Gait instability, *n* (%)	1/22 (4.6%)
Visual disturbance, *n* (%)	4/22 (18.2%)
Motor weakness, *n* (%)	3/22 (13.6%)
Hearing loss, *n* (%)	3/22 (13.6%)
Sensory deficit, *n* (%)	1/22 (4.6%)
No. of patients with $\leq$10 meningiomas[a]	10/22 (45.5%)
No. of patients with $\geq$11 meningiomas[a]	12/22 (54.5%)
Tumor location (among 54 skull base meningiomas)	
Anterior cranial fossa, *n* (%)	10/54 (18.5%)
Cavernous sinus, *n* (%)	3/54 (5.6%)
Sphenoid wind/middle cranial fossa, *n* (%)	11/54 (20.4%)
Posterior cranial fossa, *n* (%)	30/54 (55.6%)
Median follow-up after initial GKRS in years (range)	5.0 (0.6–25.5)

Abbreviations: GKRS, Gamma Knife radiosurgery
[a]Refers to total tumor burden disease

Table 2 Radiosurgical and outcome details for patients with neurofibromatosis type 2 presenting with skull base meningiomas treated with upfront Gamma Knife radiosurgery

Radiosurgical parameters and outcomes	
Treatment volume, median (range) in cc	3.5 (0.20–75)
Maximum dose, median (range) in Gy	25.5 (20–50)
Margin dose, median (range) in Gy	12.0 (10–25)
No. of tumors with post-GKRS radiographic progression, *n* (%)	4 (7.4%)
Anterior cranial fossa, *n* (%)	1 (10.0%)
Cavernous sinus, *n* (%)	0 (0.0%)
Sphenoid wind/middle cranial fossa, *n* (%)	2 (18.1%)
Posterior Cranial fossa, *n* (%)	1 (3.3%)
Time to progression, median (range) in years	3 (0.58–3.9)
No. of patients with repeat GKRS, *n* (%)	0/22 (0%)
No of patients undergoing post-GKRS surgery, *n* (%)	1/22 (4.55%)
No. of patients receiving adjuvant chemotherapy, *n* (%)	1/22 (4.55%)
Radiation induced adverse effects[a], *n* (%)	3/22 (13.64%)
Nature of adverse radiation effects[a]	
Edema, *n* (%)	1/22 (4.55%)
Radiation necrosis, *n* (%)	1/22 (4.55%)
Radiation-induced changes on temporal lobe pole (NOS), *n* (%)	1/22 (4.55%)
Malignant transformation in the treated tumors, *n* (%)	0
Mortality due to meningioma related causes	0

Abbreviations: GKRS, Gamma knife radiosurgery; NOS, no otherwise specified.
[a]Each case represents a different patient (three in total).

Radiosurgical Treatment Attributes

The median treatment volume for the studied cohort was 3.5 cc (0.20–75 cc). The median maximum dose delivered was 25.5 Gy (20–50 Gy) and the median margin dose was 12.0 Gy (10–25 Gy; ►**Table 2**).

Gamma Knife Radiosurgery Outcomes and Tumor Volume as Predictor of Tumor Progression

Specific parameters of tumor control are depicted in ►**Table 2**. The overall tumor control rate was 92.6% (54 lesions), with a median follow-up time after initial GKRS of 5.0 years (0.6–25.5 years). Overall, actuarial PFS rates were 98.1% at 2 years and 90.0% at 5 and 10 years (►**Fig. 2**). Four patients demonstrated treatment failure with a median time to progression of 3 years (0.58–3.9 years). One of these patients required post-GKRS surgery and another received adjuvant chemotherapy.

Univariate and multivariate regression analyses were performed to identify any predictor for tumor progression; the Cox proportional hazards model was used for this purpose (►**Table 3**). After adjusting for clinically relevant confounding factors, tumor volume (cc) was the only predictor of tumor progression, accounting for 4.7% higher chances of progression per each additional cc (hazard ratio: 1.047 5; 95% confidence interval: 1.011–1.083; $p = 0.009$). Once we identified tumor volume as predictor, we inquired for the cut-off value that granted higher odds of tumor progression

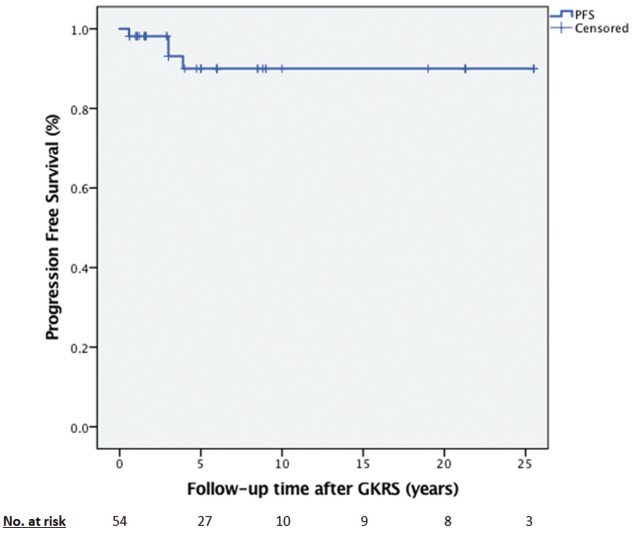

Fig. 2 Progression free survival on patients with neurofibromatosis type 2 presenting with skull base meningiomas.

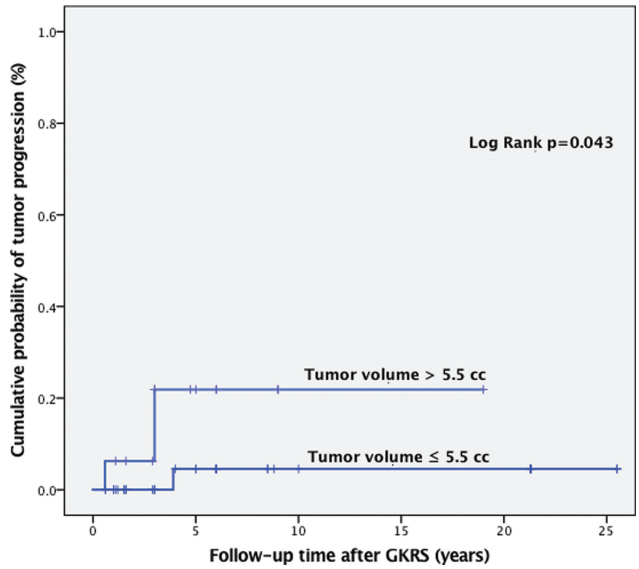

Fig. 3 Cumulative probability of tumor progression on patients with neurofibromatosis type 2 presenting with skull base meningiomas according to volume per tumor analysis.

through Kaplan–Meier analysis, and found that tumors greater than 5.5 cc convey a significantly higher chance of progression over time (►**Fig. 3**, $p = 0.043$). However, there were no differences between tumors with volumes ≤5.5 cc and those with volumes >5.5 cc in regard to maximal or margin dose ($p > 0.05$).

Radiation-Induced Adverse Effects, Malignant Transformation, and Death

GKRS for skull base meningiomas was generally well tolerated. Radiation-induced adverse effects (RAE) were noted in three patients (13.64%). One patient had radiation-induced perilesional edema 3.5 months after therapy, one patient developed biopsy-proven radiation necrosis developed 6 months after GKRS, and other one receiving radiation for a meningioma on the sphenoid wing/middle cranial fossa presented nonspecified changes on temporal lobe tip. All the RAE were transient and medically managed with steroids. No cases of malignant transformation after GKRS or death due to the meningiomas or their treatment were reported.

Discussion

Patients with NF-2 present with multiple central and peripheral nervous system neoplasms. The results from this international multicenter study provide estimates of long-term outcomes and complications for this specific group of patients presenting with skull base meningiomas treated with primary GKRS. Furthermore, we have identified and confirmed the role of tumor volume as a predictor of treatment response in this cohort of NF-2 patients with a mean follow-up of 5 years.

Skull Base Meningiomas on Neurofibromatosis Type-2 Patients

Meningiomas are the second most common tumor type in NF-2 patients; they are associated with increased tumor burden of intracranial and spinal neoplasms, higher mortality, and grant a greater likelihood of undergoing more surgical procedures.[4,26] In general, 33 to 50% of nonsyndromic meningiomas present in the skull base. Li et al described that in NF-2, the skull base location is significantly more common in pediatric patients, with rates of 30.9 and 19.1% for pediatric and adult population,

Table 3 Univariate and Multivariate analysis of relevant factors predicting tumor progression after Gamma knife radiosurgery

Variable	Univariate			Multivariate		
	p-Value	HR	95% CI	*p*-Value	Hazard ratio	95% CI
Age at diagnosis	0.541	1.018	0.962–1.076			
Female sex	0.163	0.241	0.033–1.775			
Neurological deficit	0.300	0.302	0.031–2.913			
Tumor volume (cc)	0.005	1.049	1.014–1.084	0.009	1.047	1.011–1.083
Maximum dose (Gy)	0.011	1.125	1.027–1.231	0.904	0.816	0.030–22.24
Margin dose	0.035	1.248	1.015–1.534	0.846	1.927	0.003–1430.3
No. of meningiomas	0.847	1.013	0.886–1.159			

Abbreviations: CI, confidence interval; HR, hazard ratio; cc, cubic centimeters; Gy, gray.

respectively.[27] NF-2 associated skull base lesions, and particularly those arising from the petrosal region, would possess faster absolute and relative annual growth than tumors from nonskull base locations.[27,28]

The therapeutic goals for meningiomas of the cranial base should account for relief of neurological deficits, prevention of tumor progression or recurrence, and survival improvement while still offering minimal to no morbidity. Although recent technical adjuvants to surgery have allowed for better surgical approaches and outcomes, these lesions represent a formidable challenge as they tend to abut and/or encase critical neurovascular structures as well as to extend to more than one region. Additionally, meningiomas in NF-2 patients present at a younger age when compared with sporadic meningiomas, resulting in NF-2 associated skull base lesions being even more prevalent in pediatric patients.[27] Thus, given the potential of requiring multiple treatments since very early in life and the increased odds of additional surgery across the entire lifespan, and in more than one location, treatment selection for NF-2 associated meningiomas is of particular importance.

Resection for Neurofibromatosis Type-2 Associated Skull Base Meningioma

Microsurgical resection has historically been considered the gold standard treatment for skull base meningiomas due to its potential to relieve mass effect, provide histologic diagnosis, and immediately improve symptoms. However, these lesions may be associated with substantial morbidity and mortality after surgery and even delayed recurrence after complete or partial resection. In this setting, the value of aggressive resections must be weighed against the indolent course of the disease and potentially associated neuro-deficits. Overall, the anatomic constraints of the skull base limit GTR rates to 20 to 100% of cases, with complication rates from complete resection of 10 to 96%.[11,18,24,29–34] These numbers may vary according to each specific region and improve according to the date of the published series. Currently, microsurgery embraces the concept of safe maximal resection, where the quality of life of the patients is prioritized.

As most patients with NF-2 are under continuous and long-term follow-up, the likelihood of detecting small skull base meningiomas is high. In our series, 81.5 and 96.3% of lesions had <10 cc and <15 cc, respectively. Nanda et al analyzed a cohort of patients with sporadic small skull base lesions (<3 cm) that were surgically resected, and compared their outcomes with matched lesions treated with radiosurgery. The group reported comparable results, with a GTR rate of 65.3%, 8-year tumor control rate of 86.4%, overall survival rate of 87.2% at 50 months, and need of second surgery due to recurrence in 7.6% of cases. Nonetheless, special attention should be paid in NF-2 patients presenting with meningiomas, where the benefits from surgery need to be well weighed as multiple surgical treatments are usually required due to the high tumor burden.[4,26]

Gamma Knife Radiosurgery for Neurofibromatosis Type-2 Associated Skull Base Meningioma

To date, there are no series looking specifically into the role of GKRS in NF-2 associated skull base meningiomas. However, the role of radiosurgery on sporadic skull base meningiomas has been widely explored.[13,15–18,24,35–63]

The cohort of patients described here has a median age at the time of GKRS of 38 years (10–79 years), which is in line with what has been described for NF-2 associated meningiomas in general[64,65] and the fact that treatment is needed at a younger age when compared with sporadic meningioma populations. Our cohort of patients demonstrated a 2-year PFS of 98.1% and 5-, 10-, and 20-year rates of 90.0%. Thus, PFS in this group of patients would be comparable to that among sporadic skull base meningiomas, which demonstrate 5- and 10-year actuarial control rates around 91 to 96% and 79 to 87.6%, respectively.[17,66] These results are also similar to control rates for NF-2 meningiomas of all brain locations at 5 years (92–97%) and 10 years (90–96%).[64,65,67] Furthermore, despite the anecdotal concern that GKRS can increase the risk of malignancy in a group of patients already predisposed to develop tumors, no malignant transformation was identified in our cohort. Similarly, none of the patients from three series of GKRS on NF-2 meningiomas, with 286 treated meningiomas in total, developed malignant transformation.[64,65,67] No death associated with a meningioma was reported in our cohort.

Predictors of Tumor Progression: The Role of Tumor Volume

In contrast to other series analyzing GKRS for sporadic skull base meningiomas, we did not find that variables such as age, sex, maximal dose, or margin dose were significant predictors of tumor progression.[13,15–18,24,35–63] However, tumor volume remained as a strong predictor even after multivariate analysis, adding 4.7% risk per each additional cc of volume. This finding could be explained by the therapeutic constraints imposed by bigger tumors, as they are more likely to require sparing of important organ-at-risk which lead to consider conservative doses. In our cohort, which presents acceptable outcomes, the median treatment volume was 3.5 cc (0.20–75 cc), the median maximum dose was 25.5 Gy (20–50 Gy), and the median margin dose was 12.0 Gy (10–25 Gy). These radiosurgical parameters are in line with previously conservative values reported on other series that also present acceptable outcomes for sporadic skull base meningiomas.[16–18,25,66] Overall, this would support the idea that NF-2 skull base associated meningiomas do not require higher radiation doses than those delivered to sporadic lesions, and consequently do not represent additional risk to the surrounding critical neurovascular structures. The rate of adverse radiation effects in our series was 13.6% (3 out of 22 patients), and all the events were medically managed with steroid therapy. In addition to the predictive value of the pre-GKRS volume on tumor progression, we identified that tumors with a volume greater than 5.5 cc might harbor greater likelihood of progression. This finding suggests that early intervention may be beneficial even during a watchful waiting period, as once a tumor reaches a certain volume (5.5 cc, 31.5% of cases in our cohort), its probability to recur after GKRS has already increased. The relationship between volume and GKRS treatment outcomes in sporadic skull base meningiomas has also been described in previous reports.[18,42,68,69]

Study Limitations

This study harbors the limitations of a retrospective approach. No information about the World Health Organization grade or specific histology type was available for analysis as patients were treated with primary GKRS. Thus, it is possible that these tumors were not meningiomas or that they were higher grade meningiomas. Higher grade meningiomas would have biased the study's PFS to a worse outcome; however, the risk of image misdiagnosis in a contemporary series was 2.3%.[70] Also, skull base location for a meningioma was noted to be predictive of a lower grade tumor.[71] Although our follow-up time was long, we would still benefit from longer follow-up periods, specifically for data about rates of post-GKRS malignant transformation.

Conclusion

Gamma knife stereotactic radiosurgery represents a safe and effective primary treatment option for skull base meningiomas in patients with NF-2. Tumor control is achieved at comparable rates with sporadic skull meningiomas without the need for increasing radiosurgical doses. GKRS should be considered as an important minimally invasive strategy in the management of these lesions, which is particularly relevant in the setting of patients with NF-2, with the potential need for multiple surgical interventions during their lifetime. Early treatment in NF-2 patients when the tumor is smaller may portend a more favorable prognosis for long-term tumor control post-GKRS.

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Conflict of Interest
None declared.

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