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Long-term natural history of neurofibromatosis Type 2—associated intracranial tumors

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Abstract

Object—Neurofibromatosis Type 2 (NF2) is a heritable tumor predisposition syndrome that leads to the development of multiple intracranial tumors, including meningiomas and schwannomas. Because the natural history of these tumors has not been determined, their optimal management has not been established. To define the natural history of NF2-associated intracranial tumors and to optimize management strategies, the authors evaluated long-term clinical and radiographic data in patients with NF2.

Methods—Consecutive NF2 patients with a minimum of 4 years of serial clinical and MRI follow-up were analyzed.

Results—Seventeen patients, 9 males and 8 females, were included in this analysis (mean follow-up 9.5 ± 4.8 years, range 4.0–20.7 years). The mean age at initial evaluation was 33.2 ± 15.5 years (range 12.3–57.6 years). Patients harbored 182 intracranial neoplasms, 164 of which were assessable for growth rate analysis (18 vestibular schwannomas [VSs], 11 nonvestibular cranial nerve [CN] schwannomas, and 135 meningiomas) and 152 of which were assessable for growth pattern analysis (15 VSs, 9 nonvestibular CN schwannomas, and 128 meningiomas). New tumors developed in patients over the course of the imaging follow-up: 66 meningiomas, 2 VSs, and 2 nonvestibular CN schwannomas. Overall, 45 tumors (29.6%) exhibited linear growth, 17 tumors (11.2%) exhibited exponential growth, and 90 tumors (59.2%) displayed a saltatory growth

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Disclosure

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pattern characterized by alternating periods of growth and quiescence (mean quiescent period 2.3 ± 2.1 years, range 0.4–11.7 years). Further, the saltatory pattern was the most frequently identified growth pattern for each tumor type: meningiomas 60.9%, VSs 46.7%, and nonvestibular schwannoma 55.6%. A younger age at the onset of NF2-related symptoms ($p = 0.01$) and female sex ($p = 0.05$) were associated with an increased growth rate in meningiomas. The identification of saltatory growth in meningiomas increased with the duration of follow-up ($p = 0.01$).

Conclusions—Neurofibromatosis Type 2–associated intracranial tumors most frequently demonstrated a saltatory growth pattern. Because new tumors can develop in NF2 patients over their lifetime and because radiographic progression and symptom formation are unpredictable, resection may be best reserved for symptom-producing tumors. Moreover, establishing the efficacy of nonsurgical therapeutic interventions must be based on long-term follow-up (several years).

Keywords

neurofibromatosis Type 2; intracranial tumor; natural history; vestibular schwannoma; meningioma; tumor growth; oncology

Neurofibromatosis Type 2 is an autosomal dominant, heritable multiple neoplasia syndrome that predisposes patients to tumors of the central and peripheral nervous systems.⁴ The syndrome has variable phenotypic expression. Central and peripheral NF2-associated tumors include schwannomas, meningiomas, and ependymomas. The hallmark of NF2 is the development of bilateral VSs, which occurs in 90%–95% of patients.^{11,25,29} Other intracranial NF2-associated tumors include meningiomas and nonvestibular CN schwannomas. Many patients with NF2 harbor a significant intracranial tumor burden and manifest symptoms that make clinical treatment challenging. Management options for NF2-associated intracranial tumors include conservative observation, surgery, radiation, and chemotherapy.

Because the natural history of intracranial NF2-associated tumors has not been determined,⁸ their optimal management, including the type and timing of treatment, has not been established. Furthermore, the long-term effectiveness of nonsurgical therapies (radiation and chemotherapy), in which the absence of tumor growth or progression has been considered an effective outcome, cannot be accurately assessed until the precise long-term patterns of tumor progression have been established. To better define the long-term natural history of intracranial tumors in NF2, we evaluated growth patterns, new tumor development, and clinical characteristics in NF2 patients with long-term clinical and radiographic follow-up. We then analyzed the findings to determine precise growth patterns and associated features predictive of progression.

Methods

All patients consented to and were enrolled in local institutional review board–approved clinical protocols.

Patient Population

Patients with 4 or more years of serial cranial MRI studies who were followed up at the National Institutes of Health were included in the study. Neurofibromatosis Type 2 was diagnosed based on clinical criteria and confirmed at the National Institutes of Health.⁶

Clinical Evaluation

A complete clinical evaluation, including history, audiology testing, and neurological examination, was performed during follow-up. Karnofsky Performance Scale scores and neurological findings were derived from clinical examinations and augmented by personal interviews and historical assessments of functional status.

Imaging Evaluation

Magnetic resonance imaging studies, including post-contrast T1- and T2-weighted sequences, were analyzed. Imaging studies were performed at the Clinical Center of the National Institutes of Health and elsewhere. Outside images were digitized, and measurement bars were calibrated across all images. Outside digital studies with thin-slice thickness (≤ 3 mm) were coregistered to ensure that precise measurement comparisons were made over the longitudinal follow-up.

Volumetric Analysis of Tumors

Tumors were classified as cranial meningiomas, VSs, or nonvestibular CN schwannomas based on imaging characteristics. Tumor measurements were obtained utilizing multiplanar postcontrast T1-weighted MR images.³⁵ Volume was calculated using the following formula for an ellipsoid: $(A \times B \times C)/2$.²² Multilobulated tumors were divided into individual compartments to increase accuracy; compartmental volume was determined using the above equation. Volumetric measurements for VSs were divided into posterior fossa and canalicular components when these tumors extended into both areas. Total tumor volume was determined by summing the volumes of the individual compartments.

Determination of Growth Rate and Patterns

Tumors that were treated with radiotherapy (proton beam or radiosurgery) were excluded from growth rate and pattern analysis. Imaging data available before surgical debulking or resection of tumors were used, but data for residual or recurrent tumors were not assessed. Tumors that developed during the course of the imaging follow-up or were resected before achieving serial longitudinal follow-up were excluded from growth pattern analysis. At least 2 imaging time points were necessary for growth rate analysis, and at least 3 were necessary for growth pattern analysis.

Absolute tumor growth rate was calculated using the following formula: $(\text{final volume} - \text{initial volume})/\text{follow-up interval}$. Before acquiring tumor measurements, the interrater error for the measurement of tumors was determined through an analysis of variance in multiple tumor measurements. The standard error for our volumetric measurements was 0.015 cm^3 . Tumor growth was defined as an increase in tumor size of at least 0.03 cm^3 (2 SDs) over a measurement interval. Tumor quiescence was defined as $< 0.03 \text{ cm}^3$ of growth over an

approximately 6-month interval (Fig. 1). Tumors that displayed alternating periods of growth and quiescence were determined to have a saltatory growth pattern. For all tumors without quiescent periods, regression curves were fitted to the measurement data. Growth patterns were determined to be linear or exponential based on the best-fit R^2 value. The relative growth rate was determined based on the percentage growth (as a function of volume at the beginning of the measurement interval) per year, weighted by the duration of each imaging interval.

Factors Affecting Tumor Growth Rate or Pattern

Clinical and radiographic features previously related to tumor growth in the literature were recorded for the patients in this study.^{7,17,19} The patient factors evaluated for impact on tumor growth rate and pattern included age, sex, and family history of NF2. The duration of follow-up and its relation to the identification of a saltatory growth pattern was also determined. Two historical markers used to characterize disease severity in patients with NF2, including age at onset of NF2-related symptoms and presence of intracranial meningiomas, were also evaluated for their association with growth rate and specific patterns of growth.⁵ For meningiomas, additional imaging features were assessed, including tumor location, T2-weighted tumor signal hyperintensity, presence of a peritumoral cyst, and peritumoral edema.

Statistical Analysis

The relative rate and pattern of growth for each tumor was assessed using statistical methods to determine possible associations with patient factors, markers of disease severity, or tumor imaging characteristics. Since most patients had multiple tumors, a mixed model was used to account for patient effect and initial tumor volume. Multivariate analysis was performed using a linear mixed model for the quantitative outcome (relative growth rate) and a generalized mixed model for the nominal outcome (growth pattern). A forward method was applied for model selection. The final model was selected based on the model 1) with the smallest Akaike information criterion or pseudo-Akaike information criterion and 2) containing all variables with a p value ≤ 0.1 . The p values for the variables excluded from the final model were calculated by aggregating each to the final model. Statistical analysis was performed using SAS Version 9.2 (SAS Institute, Inc.). Analysis was considered statistically significant for $p \leq 0.05$. Values were expressed as the means $\pm$ standard deviations, unless indicated otherwise.

Results

Patient Demographics

Seventeen patients, 9 males and 8 females, were included in this study. The mean age at initial evaluation was 33.2 ± 15.5 years (range 12.3–57.6 years). Eleven patients (65%) had a family history of NF2, and 6 patients (35%) did not. Collectively, the number of intracranial tumors identified in patients at any given time point was 182, including 32 VSs (17.6%), 11 nonvestibular CN schwannomas (7.6%), and 139 intracranial meningiomas (76.4%). Sixteen patients had bilateral VSs. One patient who met the clinical diagnostic criteria (family history of NF2, spinal cord ependymoma, and intracranial meningioma) did

not have a VS identified on high-resolution MRI. Four patients (23.5%) had nonvestibular CN schwannomas, and 13 (76.5%) harbored intracranial meningiomas. The mean duration of follow-up was 9.5 ± 4.8 years (range 4.0–20.7 years). Magnetic resonance imaging was obtained every 1.5 ± 1.1 years on average (range 0.4–4.1 years).

Clinical Findings

The mean age at the onset of NF2-related symptoms was 27.7 ± 15.3 years (range 5–55 years). Initial symptoms that led to diagnosis included hearing loss (10 patients [59%]), visual disturbance (2 patients [12%]), enlarging subcutaneous mass (2 patients [12%]), seizure (1 patient [6%]), and headache (1 patient [6%]). One patient (6%) remains asymptomatic. With the progression of symptoms over the study period, the median KPS score decreased from 90 (range 60–100) at the initial evaluation to 80 (range 60–100) at the last follow-up. The number of patients unable to work due to NF2-related disability (KPS score ≤ 70) increased from 3 patients (17.6%) to 7 patients (41.2%) over the study period. At the last follow-up, 2 patients (1 without VS) retained normal hearing bilaterally. The remaining patients had bilateral complete hearing loss (9 patients), unilateral complete hearing loss (4 patients), or bilateral partial hearing loss (2 patients).

No patient received chemotherapy during the follow-up. Thirteen patients received focused treatment either prior to or during the follow-up period for 23 VSs, 7 of which were treated with SRS and 16 with resection. Four VSs (4 patients) treated with SRS required subsequent resection due to radiographic progression that had resulted in significant brainstem compression and/or symptom development (Fig. 2). The 3 remaining SRS-treated VSs (2 patients) continue to be monitored expectantly despite radiographic progression because no new symptoms have developed.

Six patients received treatment for 11 intracranial meningiomas either prior to or during the follow-up period, 2 of which were treated with SRS and 9 with resection. Reasons for resecting the meningiomas included headache (6 tumors [66%]), seizures (3 tumors [33%]), paresthesias (1 tumor [11%]), and to facilitate removal of a deep VS (2 tumors [22%]). Three tumors caused headache and seizure. Both SRS-treated meningiomas revealed progressive growth within 4 years after radiosurgical treatment. One tumor revealed an early response (reduction in size) that persisted for 3 years and then progression.

Intracranial Meningiomas

One hundred thirty-nine intracranial meningiomas were present in 13 patients (10.7 ± 13.2 tumors/patient). They occurred in multiple locations (Table 1), the most common being convexity (44 tumors [31.6%]), parasagittal (23 tumors [16.5%]), and falx (20 tumors [14.4%]) locations. Radiographically, meningiomas vividly enhanced with contrast administration and were associated with adjacent parenchymal edema (7 tumors [5.0%]), peritumoral cysts (7 tumors [5.0%]), and/or T2 hyperintensity (3 tumors [2.2%]) in some cases.

On initial imaging, 71 tumors (51.1%) were identified. Sixty-six new intracranial meningiomas developing in 11 patients (47.5% of total intracranial meningiomas; 6.0 ± 5.9 new tumors/patient, range 1–18 new tumors/patient) were identified during follow-up. Two

convexity meningiomas were resected prior to the initial imaging study. Note that 5 meningiomas (3.6%) were excluded from growth pattern analysis given their development at more recent imaging time points. Seven intracranial meningiomas (5.0%) were resected during follow-up. The location of these tumors resected during the course of imaging follow-up included the posterior fossa (5 tumors [71% of resected tumors]) and the lateral ventricle (2 [29%]). Two of the tumors resected during the follow-up were excluded from growth pattern analysis because at least 3 imaging time points were not available before resection.

Overall, 135 tumors (97.1% of all meningiomas identified during the course of the study) were evaluable for growth rate analysis, and 128 tumors (92.1%) were evaluable for growth pattern analysis. One hundred thirty-four intracranial meningiomas (99.3%) displayed growth during the follow-up period. The mean absolute growth rate for intracranial meningiomas was $0.4 \pm 0.8 \text{ cm}^3/\text{year}$ (range 0.01–6.7 cm^3/year). Analysis of volumetric-based growth patterns revealed that 7.8% (10) of intracranial meningiomas grew exponentially, 31.2% (40) grew linearly, and 60.9% (78) displayed a saltatory pattern (Fig. 1) characterized by intervening absolute quiescent periods. The mean duration of quiescent periods was 2.4 ± 2.3 years (range 0.4–11.7 years).

Analysis revealed that more rapid growth was associated with a younger age at the onset of NF2-related symptoms ($p = 0.01$) and with female sex ($p = 0.05$; Table 2). Additionally, the likelihood of observing saltatory growth increased with a longer duration of follow-up ($p = 0.01$). Indeed, 84% of tumors with more than 10 years of imaging follow-up exhibited a stuttering pattern.

Vestibular Schwannomas

Thirty-two VSs were present in 17 patients. Twenty-three VSs were present on initial imaging (7 tumors in 6 patients had been resected by the time of initial imaging). Two new tumors developed in 1 patient during the course of follow-up. Seven VSs initially treated with SRS before available imaging were excluded from statistical analysis. Eighteen VSs in 12 patients were evaluable for growth rate analysis, and 15 tumors in 9 patients were evaluable for growth pattern analysis. Three tumors resected during the course of imaging follow-up were excluded from growth pattern analysis, because at least 3 imaging time points were not available prior to surgery.

Over the evaluation period all VSs (100%) displayed growth that was variable with respect to rate and pattern. The mean absolute growth rate for VSs was $0.6 \pm 0.9 \text{ cm}^3/\text{year}$ (range 0.01–3.2 cm^3/year). Analysis of volumetric-based growth patterns revealed that 13.3% (6 tumors [40%]) of VSs grew exponentially, 13.3% (2 tumors) grew linearly, and 46.7% (7 tumors) displayed a saltatory pattern characterized by intervening absolute quiescent periods. The mean duration of the quiescent periods was 2.8 ± 2.2 years (range 0.4–6.9 years). Analysis revealed that the VS growth rate and pattern showed no statistically significant ($p > 0.05$) association with examined patient factors, markers of disease severity, or tumor imaging characteristics.

Nonvestibular CN Schwannomas

Eleven nonvestibular CN schwannomas in 4 patients were evaluated. Two such lesions developed in 2 patients during the course of imaging follow-up at 3 and 7 years after the initial imaging evaluation was performed. No treatment was provided for these lesions during the follow-up period, and the tumors remained asymptomatic during the study period. All 4 patients with nonvestibular CN schwannomas were male and also had intracranial meningiomas. The most common location for the nonvestibular CN schwannomas was the CN IX, X, XI complex (36.4%). Other locations included CNs V (27.3%), XII (27.3%), and III (9.1%).

Nine nonvestibular CN schwannomas (82%) exhibited growth during follow-up. The mean absolute growth rate was $0.2 \pm 0.4 \text{ cm}^3/\text{year}$ (range 0–1.2 cm^3/year). Analysis of volumetric-based growth patterns revealed that 11.1% (1) of tumors grew exponentially, 33.3% (3) grew linearly, and 55.6% (5) displayed a saltatory pattern characterized by intervening absolute quiescent periods. The mean duration of quiescent periods was 4.0 ± 4.3 years (range 0.8–11.3 years). Nonvestibular schwannoma growth rate and pattern showed no statistically significant ($p > 0.05$) association with examined patient factors, markers of disease severity, or tumor imaging characteristics.

Discussion

Neurofibromatosis Type 2

Neurofibromatosis Type 2 is a tumor predisposition syndrome caused by mutation of the *NF2 tumor suppressor gene*, located at 22q12.2.^{32,37} Approximately half of the cases are inherited in an autosomal dominant fashion, and the remainder represent new spontaneous mutations. The incidence is approximately 1 case in 25,000 live births, and the prevalence is 1 case in 100,000–200,000 persons.¹² Patients harbor central and peripheral nervous system tumors and demonstrate nonneoplastic ocular manifestations, including retinal hamartomas, epiretinal membranes, and early development of cataracts. More recently, tumor-independent peripheral neuropathy has been described in patients with NF2.^{14,15}

Previous Studies

Despite the significant morbidity and mortality caused by NF2-associated intracranial tumors, the natural history of these lesions is unknown. Specifically, previous studies evaluating NF2-related VSs,^{1,7,16,19,24,36} nonvestibular CN schwannomas,¹³ and intracranial meningiomas are limited by several critical factors. First, they have been focused primarily on the growth of VSs,^{1,7,16,19,24,36} and data and conclusions from these studies have been conflicting because of the limited follow-up. Second, NF2-related nonvestibular schwannomas have not been studied extensively. Only one study has documented the natural history data for these lesions, and the follow-up was limited.¹³ Finally, despite the prevalence, multiplicity, and associated morbidity of intracranial meningiomas in NF2, no specific studies have examined the natural history of NF2-related meningiomas. Previously reported data come from a single study in which findings on 2 patients with NF2 were included with data on patients with sporadic meningiomas.²⁷

Because patients with NF2 most frequently have multiple intracranial tumors and will demonstrate new tumors of variable histological types over their lifetime, they present a unique clinical circumstance as compared with patients with similar isolated sporadic tumors. Patients with NF2 often require multiple operations or adjuvant treatments for intracranial tumors over their lifetime. Consequently, it is critical to develop insight into the long-term natural history of the various types of intracranial tumors in NF2. Long-term natural history findings should have direct implications for the timing, type, and effectiveness of treatment for the various tumor types in NF2. Here, we discuss the clinical and imaging findings of NF2 patients with long-term follow-up to provide a deeper understanding of the natural history of these lesions.

Clinical Findings

The mean age at the onset of disease-related symptoms in our study patients was 27.7 years (range 5–55 years), which is representative of the disease among the general population as described in population-based studies of NF2.^{11,25,29} Moreover, a similar proportion of male/female patients (9 males and 8 females) were represented. Thirteen (76.5%) of 17 patients harbored intracranial meningiomas and most often in multiples; only 4 patients had singular intracranial meningiomas. In the 1990s, the median life expectancy after diagnosis was 15 years, and virtually all patients with NF2 progressed to bilateral deafness.¹¹ Despite significant advances in disease diagnosis and the surveillance of at-risk populations through presymptomatic MRI studies and genetic testing as well as improved microsurgical, rehabilitative, and radiation delivery techniques, the majority of patients in our study had bilateral hearing loss (15 patients [88.2%]) and were rendered unable to work as a result of an NF2-associated disability (KPS score = 70 in 7 patients [46.7%]).

Radiosurgery in NF2

Over the course of the imaging follow-up, 9 tumors (7 VSs and 2 meningiomas) in 6 patients were treated with SRS. All VSs treated with SRS as a first-line treatment displayed continuous radiographic progression, and 4 (57%) required resection due to tumor progression and symptom development. Both meningiomas treated with SRS displayed progressive growth within 4 years after radiosurgery but remain under observation only because there has been no symptom development.

Findings in the current study underscore the complexity in managing NF2. Contrary to reports of the long-term success of the radiosurgical management of sporadic VSs and meningiomas, data in the present study indicate that the long-term benefit of radiosurgery for tumors in NF2 is less than for their sporadic counterparts. While prior studies of SRS for NF2-related VSs with approximately 5 years of follow-up have documented local control rates of 74%–100%,^{20,21,23,34} data from the current study (7 of 7 VSs demonstrated progression after treatment) and a report by Rowe and colleagues³³ (50% control with 8-year follow-up) indicates that NF2-associated acoustic schwannomas are not nearly as responsive to SRS as their sporadic counterparts with longer periods of evaluation.

Tumor Growth Rate and Patterns

Intracranial Meningiomas—Data on the growth rates of NF2-associated intracranial meningiomas in 2 patients, as part of a larger group of patients with sporadic meningiomas, have been reported.²⁷ In that study, NF2-associated intracranial meningiomas grew at a rate of 0.3 cm³/year. In the current study (135 tumors), the growth rate for intracranial meningiomas was similar (mean 0.4 cm³/year) and is also consistent with other studies that describe the growth rate of sporadic meningiomas (0.2–2.5 cm³/year).^{27,28}

Previously, authors studying sporadic meningiomas noted variations in growth patterns and rates, but no data exist regarding the pattern of growth for NF2-associated intracranial meningiomas. Hashiba and colleagues¹⁷ found that 37% of sporadic meningiomas did not grow during an average follow-up of 3.3 years. Likewise, other sporadic meningioma studies documented variable growth patterns, including periods of no tumor growth.^{27,28,38} Over the course of the present study, 99% of intracranial meningiomas exhibited growth, and 60.9% displayed extended quiescent periods (mean 2.4 years). This finding suggests that the quiescence described in prior studies with shorter follow-ups probably represents intervals between growth periods and is part of a saltatory growth pattern—a fact further supported by the association between the duration of follow-up and the identification of saltatory growth.

Vestibular Schwannomas—Consistent with previously reported growth rates for NF2-related VSs (0.3–0.7 cm³/year),^{7,16} we found long-term mean absolute growth rates for VSs to be 0.6 cm³/year. While previous NF2-related VS studies have described variable tumor growth patterns (linear and exponential) as well as no tumor growth,^{19,36} a saltatory growth pattern has not been described. In the current study we found that 46.7% of VSs demonstrated a saltatory growth pattern that included periods of quiescence lasting a mean of nearly 3 years. These findings further suggest that previous studies with shorter durations of follow-up may have incorrectly classified tumors as nongrowing or with consistent growth (linear/exponential), while the saltatory pattern may best describe the growth of the majority of these tumors. This incorrect classification of growth patterns can also lead to an overestimation of the efficacy of nonresective treatments, such as SRS and chemotherapy, which incorporate a lack of tumor growth as an efficacious treatment outcome.

Nonvestibular CN Schwannomas—The current findings demonstrated that nonvestibular CN schwannomas are the most indolent intracranial tumor type in NF2 (mean growth rate 0.2 cm³/year). Despite the slow rate of growth, 9 (82%) of the 11 nonvestibular CN schwannomas revealed growth over the study period. Data also showed that the majority (55.6%) of nonvestibular CN schwannomas in NF2 have a saltatory growth pattern with relatively long quiescent periods (mean quiescent period 4.0 years). Findings indicated that these schwannomas do not display significant growth over short observation periods (< 3 years),¹³ but instead show indolent growth interrupted by periods of quiescence that is better appreciated with long-term follow-up.

Factors Affecting Tumor Growth Rate or Pattern

Intracranial Meningiomas—Because previous studies have not specifically examined factors affecting the natural history of NF2-associated intracranial meningiomas, there is no information regarding the factors that influence the lesion's growth rate. Current study data indicated that an increased growth rate is associated with female sex ($p = 0.05$) and a younger age at symptom onset ($p = 0.01$). Specifically, studies have shown a potential progesterone influence in the development of sporadic meningiomas based on the propensity of these tumors to occur in females and the presence of progesterone receptors in the majority of meningiomas.^{9,18,26,30} Histopathological studies have also revealed that higher WHO grade lesions (atypical, anaplastic) are more commonly identified in pediatric patients with NF2.³¹ Data in the current study corroborated these findings, indicating that meningiomas in patients with a younger age at the onset of NF2-related symptoms also have an increased growth rate.

Meningiomas in NF2 exhibit differences in growth rates and patterns, even among tumors within the same patient. Additionally, we found variability in the growth rate of individual tumors observed over time, including saltatory growth patterns. The majority of NF2-associated meningiomas (60.9%) exhibited this growth pattern, and there was a strong correlation between periods of quiescence and a longer duration of follow-up ($p = 0.01$). The association between the duration of follow-up and periods of quiescence suggests that with even longer follow-ups, a higher percentage of tumors will exhibit a saltatory growth pattern. Moreover, the greater likelihood of identifying extended periods of quiescence with longer durations of follow-up has significant implications for clinical management, timing of the intervention, and evaluation of the efficacy of therapeutic interventions.

Vestibular Schwannomas—No patient factors, markers of disease severity, or imaging characteristics were associated with tumor growth rate or pattern in the current study. Similarly, Ito and colleagues¹⁹ found that there was no relationship between clinical factors and tumor growth rate in untreated NF2-associated VSs. Other groups have reported conflicting relationships between patient age and the growth rates of NF2-associated VSs, ranging from an increasing growth rate with increasing age to a decreasing growth rate with increasing age.^{1,7,8,24} Because of conflicting and inconclusive retrospective data, the identification of factors that predict the behavior of VSs in NF2 will require a large, long-term prospective natural history study.

Nonvestibular CN Schwannomas—Although nonvestibular CN schwannomas appear to be the most indolent subset of tumors in NF2, growth is readily appreciated in most tumors over the long-term follow-up. While these tumors grew during the study period, no tumor became symptomatic and required surgery. An analysis of clinical factors as they relate to nonvestibular CN schwannoma growth rate or pattern has not been conducted. Given the number of tumors and the frequent occurrence of saltatory growth (5 of 9 tumors), no statistical correlation between tumor growth rate and patterns, and patient factors or markers of disease severity were made.

Development of New Tumors

Neurofibromatosis Type 2 is characterized by progressive disability caused by the growth of central and peripheral nervous system–associated tumors. New tumors will also develop in the majority of patients with NF2 during the course of their lifetime. Over a period of approximately 10 years, 11 (64.7%) of 17 patients in this study demonstrated new tumors that were not present on initial MRI. Sixty-six meningiomas, 2 VSs, and 2 nonvestibular schwannomas were not evident when initial imaging was performed. Given that new tumors will occur in most patients during the course of long-term follow-up, prophylactic targeted treatments (radiosurgery, surgery) aimed at MRI-demonstrated tumors will only address a fraction of the tumors that will be evident at later time points. Furthermore, many of these tumors do not appear to require treatment (as they remain asymptomatic), as shown in this long-term follow-up study.

Implications for Clinical Management

Adjuvant Therapies—Because the natural history of NF2 causes progressive disability and involves multiple surgeries for many patients, the impetus for developing nonsurgical therapies has increased. Consequently, the number of clinical trials aimed at nonsurgical treatment has increased. Various end points to determine the efficacy of nonsurgical treatment methods have been proposed, including local tumor control (quiescence of growth).¹⁰ Our study demonstrates that tumor quiescent periods, such as those included in the course of saltatory growth, occur in most NF2-associated intracranial tumors regardless of histological type. Therefore, using the cessation of growth (quiescence) as a measure of therapeutic efficacy could lead to an inaccurate overestimation of success and could merely reflect the natural history of NF2-associated tumors.

Based on data in the current study, the long-term efficacy of SRS in the management of NF2-associated VSs diminishes with a longer follow-up. Current findings are also consistent with a recent assessment of the long-term utility of SRS for VHL-associated hemangioblastomas.³ Similar to intracranial NF2-associated neoplasms, cranial hemangioblastomas in VHL disease spontaneously stop growing for periods of time and exhibit saltatory growth.² Despite numerous reports demonstrating high rates of control over a short-term follow-up (< 5 years), the long-term follow-up of patients with VHL disease has revealed that control rates for hemangioblastomas treated with SRS diminishes over time (local control rates of 70%, 61%, and 51% at 8, 10, and 15 years after treatment, respectively). These findings indicate that surgery remains the first-line strategy for managing symptomatic tumors, and SRS treatment should be reserved for non-operative patients. Regardless of the chosen intervention, these data support a lengthier duration of follow-up to discern the treatment effect from quiescence associated with the natural history of tumors in NF2.

Surgical Indications—Variability in growth rates among individual tumors over time also suggests that past behavior does not predict future growth. Because the imaging findings that predict tumor growth and quiescence are unknown, developing a targeted preventative management paradigm is currently impossible. Therefore, tumor growth in the absence of symptoms is not an indication for treatment. Data from this study clearly indicate

that the majority of NF2-associated intracranial tumors will grow for a period of time and then display extended periods of quiescence while remaining asymptomatic. Because nearly all tumors (98.2%) display radio-graphic progression over a long-term follow-up, resecting NF2-associated tumors on the basis of growth alone will subject patients to additional procedures over finite periods of time and expose them to the accompanying morbidities associated with resection. Specifically, if tumor progression alone were used as an indication for surgery in patients in the current study, each patient would have undergone an additional 9 unnecessary resections over the study period.

Conclusions

Neurofibromatosis Type 2-associated intracranial tumors display substantial variability in growth rate and pattern. The most common growth pattern across all intracranial tumors associated with NF2 was a saltatory pattern characterized by periods of growth and quiescence. These extended periods of quiescence and different growth patterns have important implications for clinical management, timing of intervention, evaluation of therapeutic efficacy, and the design of future clinical trials on NF2.

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Abbreviations used in this paper

CN	cranial nerve
KPS	Karnofsky Performance Scale
NF2	neurofibromatosis Type 2
SRS	stereotactic radiosurgery
VHL	von Hippel-Lindau
VS	vestibular schwannoma

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Fig. 1.

Upper: Graph of planum meningioma growth revealing an extended period of quiescence (5.5 years). Growth rate from Time Point 1 to 2 averaged $< 0.02 \text{ cm}^3/\text{year}$. **Lower:** Axial contrast-enhanced registered MR images demonstrating the absence of tumor growth between Time Points 1 (*left*) and 2 (*right*).

Fig. 2.

Upper: Graph depicting tumor growth following SRS for the management of VS in a patient with NF2. Stereotactic radiosurgery was performed for the right VS immediately before the first available imaging studies. The left VS was untreated until resection (X). *Vertical line* at the 2-year mark indicates how much the left tumor grew (natural history) versus the right radiated tumor in the same interval. **Lower:** Axial contrast-enhanced registered MR images demonstrating growth of the right VS (*left, asterisk*) after SRS and the natural history of the

contralateral VS (*left and right*). Note multiple histologically proven posterior fossa meningiomas (*arrows*) that were removed at the time of the VS surgeries.

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TABLE 1
Location of 139 intracranial meningiomas

Location	No. of Tumors (%)
convexity	44 (31.6)
parasagittal	23 (16.5)
falx	20 (14.4)
posterior fossa	16 (11.5)
tentorium	16 (11.5)
sphenoid wing	8 (5.8)
ventricle	5 (3.6)
planum/olfactory groove	4 (2.9)
cavernous sinus	2 (1.4)
optic sheath	1 (0.7)

TABLE 2
Probability values for growth rate and pattern associations for intracranial meningiomas*

Variable	Relative Growth Rate (faster growth rate)	Growth Pattern (presence of stuttering growth pattern)
no. of patients	134	128
patient		
age	0.6237	0.8697
sex	0.0466	0.1244
family history	0.5873	0.5246
duration of FU	†	0.0123
disease severity	0.0144	0.6785
age at onset		
tumor		
location [‡]	0.1136	0.3808
T2 hyperintensity	0.8854	0.2913 [§]
peritumoral cyst	0.9408	0.9619
peritumoral edema	0.4977	0.4922

* FU = follow-up.

† Not examined for association with growth rate because it was used in the calculation of growth rate.

‡ Twenty tumors in the 5 locations with fewer than 10 tumors were excluded from analysis. Thus, the location variable in the analysis includes 5 categories.

§ The p value was calculated from the Fisher exact test, because the generalized mixed model did not converge.