Growth Dynamics of Intracranial Tumors in Patients with Neurofibromatosis Type 2

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■ OBJECTIVE: **Patients with neurofibromatosis type 2 (NF2) are prone to develop multiple intracranial neoplasms, such as schwannomas of the cranial nerves and meningiomas. The aim of our study was to investigate 1) the median growth rate per year, 2) the growth-free interval, and 3) the growth patterns of NF2-associated intracranial tumors.**

■ METHODS: **All available magnetic resonance (MR) images of patients from the regional neurofibromatosis center were collected. The depicted tumors' volumes were then calculated if the tumors met the following inclusion criteria: contrast enhanced T1-weighted MRI datasets had to be available from at least two investigations and tumors had to be measurable on at least two slices.**

■ RESULTS: **One-hundred and eighty-eight tumors from 52 patients (20 male, 32 female) met the inclusion criteria for volumetric analysis. Overall, the median follow-up time was 76.5 months per patient (range 13–199 months). After 5 years, the median tumor size was 196% ± 338% for vestibular schwannomas (VS), 204% ± 702% meningiomas (M), 128% ± 64.9% for non-vestibular schwannomas (NVS) and 139% ± 270% for pre-operated tumors of the cerebellopontine angle (TX), respectively. The median time to 20% tumor progression was 21 months for VS, NVS and TX, and 17 months for M. Overall, saltatory growth was the most common growth pattern (46.9%).**

■ CONCLUSIONS: **Most NF2-associated tumors display a saltatory growth pattern. Meningiomas and untreated vestibular schwannomas grow rapidly and overall at similar rates. Tumors of the CPA that have been operated on and non-vestibular schwannomas show less relative growth per year.**

INTRODUCTION

Neurofibromatosis type 2 (NF2) is an autosomal-dominant genetic disorder characterized by the development of multiple neoplasms affecting the central nervous system. According to the latest findings, NF2 has an incidence of 1 in 25,000 live births and a prevalence of 1 in 100,000,[1] which makes it a rare disease.

NF2 is caused by a mutation of the NF2 gene on locus 22q12 that encodes the tumor suppressor protein merlin (moesin-ezrin-radixin-like protein), which is localized in the cytoskeleton. A mutation in this gene locus can lead to various lesions, including schwannomas of the cranial nerves, meningiomas, and intraspinal and subcutaneous tumors.

Patients with this disorder depend on the advice and guidance of dedicated and experienced physicians. In order to evaluate the course of an individual's disease progression and to assess the effectiveness of treatment, it is crucial to be aware of the natural history of those tumors associated with NF2.

In the past, there have been studies investigating the natural history of tumor growth in patients suffering from NF2.[2-7] These studies were mostly limited to certain subsets of tumors or small groups of patients. Additionally, in recent years there has been a dramatic improvement in technologies that facilitate exact volumetric determination of tumor size, which makes it possible to assess tumor growth patterns in larger groups of patients.

Our aim was to gain a better understanding of the growth dynamics of the most common NF2-related intracranial neoplasms by evaluating 1) the median growth rate per year, 2) the growth-free intervals,

Key words
- Growth dynamics
- Magnetic resonance imaging
- Natural history
- Neurofibromatosis
- Tumors

Abbreviations and Acronyms
CPA: Cerebellopontine angle
M: Meningioma
MRI: Magnetic resonance imaging
NF2: Neurofibromatosis type 2
NVS: Nonvestibular schwannoma
TX: Tumor of the cerebellopontine angle that has previously undergone surgery
VS: Vestibular schwannoma

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and 3) the growth patterns. To this end, we analyzed 188 tumors in 52 patients over the course of 359 patient-years of follow-up.

METHODS

This retrospective study was approved by the Ethics Committee of the State Chamber of Medicine in Thuringia. Patient records from all patients of the local Neurofibromatosis Center at the HELIOS Klinikum Erfurt, who were diagnosed with definite NF2 on the basis of clinical criteria, were screened for biotechnical data and information on previous treatment. All available magnetic resonance imaging (MRI) data from the patient group were collected and, if necessary, digitized.

First, the number of distinct tumors per patient was quantified. Second, we evaluated the tumors on the basis of digital volumetric datasets, which were uploaded into iPlan Net software (Brainlab, Munich, Germany). Tumors were then outlined on each slice using semiautomated segmentation. The software's Smart Brush tool was first used to outline the tumors. The tumor shapes were then manually adjusted in order to improve contouring accuracy. Tumor volumes were automatically calculated from area and slice distance by the software.

Tumors were included in this study if they met the following criteria:

1) Only intracranial schwannomas of the cranial nerves and meningiomas were present.
2) Tumors had to be visible on 2 investigations that had been taken no more than 36 months apart from each other.
3) Tumors had to be visible on at least 2 slices.
4) Tumors must not have undergone previous treatment, including radiotherapy, medical therapy, and/or surgery. Excluded from this rule were tumors of the cerebellopontine angle (CPA) that had previously undergone surgery, as they formed a separate group.

Criterion 2 was chosen to introduce a maximum time interval and to reduce loss-to-follow-up bias. Loss-to-follow-up bias has not been accounted for in previous studies investigating the growth dynamics of these tumors over time.

Only tumors that could be outlined clearly, and which were not part of conglomerates, were included in this analysis in order to minimize intraobserver variability.

The tumors were measured on postcontrast T1-weighted MRI datasets, preferably with small slice thickness. In one case, tumors were measured without contrast because there was insufficient enrichment with gadolinium contrast agent.

All tumors were measured by the same rater in favor of measurement error. Datasets from all 3 orientations were used for this study (axial, coronal, and sagittal), none of which were reconstructions. The slice thickness varied from 0.5–7.0 mm.

Third, we measured the greatest transverse diameter of tumors that could be seen on volumetric datasets and that could additionally be found on historic, nonvolumetric MR images in order to investigate 1) if linear measurements show the same growth patterns as volumetric measurements and 2) if change can be seen in the patterns of growth over longer follow-up periods. The greatest transverse diameter of these tumors was measured on axial slices.

All measured tumors were consecutively divided into 4 groups: untreated vestibular schwannomas (VS), untreated meningiomas (M), untreated nonvestibular schwannomas (NVS), and tumors of the cerebellopontine angle that previously had undergone surgery (TX).

Statistical analysis was performed in the R software environment (R Development Core Team 2015). The median growth per year was used for descriptive analysis of the data. The tumor volume at the time of first-available investigation was considered the baseline. Consecutive volumes were grouped according to when they were taken. All datasets recorded within 12 months after the first investigation were considered together, as were the datasets obtained within 13–24 months after the first investigation and so on.

Progression-free intervals were calculated using the Peña-Strawderman-Hollander model for recurrent survival analysis that has previously been described by Baethge et al.[8] This method is based on the Kaplan-Meier model of survival analysis.[9] However, Kaplan-Meier survival analysis was devised for studies that had death as their primary outcome, and it therefore focuses exclusively on the first event of its kind and neglects any recurrent events. The more recent Peña-Strawderman-Hollander model, additionally, takes recurrent events into account.[10]

The "survrec" package for R offers the option to analyze data according to the Peña-Strawderman-Hollander method. In accordance with previous studies[11] and results from internal validation at our institution, any growth of $\geq$20% was considered an "event." Groups were compared by log-rank test using the "TestSurvRec" package.

Tumors which had datasets from at least 3 time points available were suitable for growth pattern analysis. Growth patterns were determined by visual judgment of the relative volume changes. Growth patterns were grouped according to their appearance: 1) saltatory growth (**Figure 1A**); 2) linear growth (**Figure 1B**); 3) exponential growth (**Figure 1C**); 4) stable size (**Figure 1D**); and 5) decreasing in size (**Figure 1E**).

RESULTS

Fifty-two patients (20 male, 32 female) were included in this study. The median age at first available investigation of the brain was 27 years (range 10–62 years). The median follow-up time was 76.5 months per patient (range 13–199 months).

Quantification of Tumor Burden

Fifty-two patients harbored 293 tumors at the time of first investigation. Over the course of follow-up, they developed 237 additional tumors, resulting in a total of 530 tumors (**Table 1**).

Of these, 342 tumors were excluded because they did not meet inclusion criteria. The reasons for exclusion were: 1) 226 were part of conglomerates and could not be outlined clearly; 2) 47 could only be measured on 1 dataset; 3) 25 were visible on only 1 slice; 4) 22 could not be outlined clearly owing to their position; 5) 12 had undergone previous treatment (and were also not part of the TX group); 6) 7 were tumors of the CPA that had undergone surgery