

# Natural history and management of low-grade glioma in NF-1 children

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**Abstract** Pediatric neurofibromatosis type 1 (NF-1) patients are prone to developing low-grade glioma (LGG). The HIT-LGG study 1996 aimed to observe the natural history of pediatric LGG and to postpone irradiation in younger children by using carboplatinum and vincristine in case non-surgical treatment was required. A total of 109 of 1,044 (10.4%) protocol patients had a genetic NF-1 trait [57 female patients; median age 5.1 years (range 1–15.4 years)]. Eighty-three patients (76%) suffered from an optic pathway

tumor. Neuroimaging only allowed diagnosis in 67 patients. Histology revealed pilocytic astrocytoma WHO grade I in 38 of 42 biopsied patients. Sixty-five (60%) patients received non-surgical treatment, either chemotherapy ( $n = 55$ ) or irradiation ( $n = 10$ ). The overall survival rate of 96% after a median observation time of 5.25 years contrasts with an event free survival rate (EFS) of 0.24 at 5 years. Progressive LGG were observed even in children older than 11 years. Chiasmatic/postchiasmatic localization was a univariate risk factor for progressive disease. In the chemotherapy group, we observed a 5-year progression-free survival (PFS) rate of 0.73. Similarly, the PFS rate in the irradiation group was 0.78. Multivariate analysis revealed surgical intervention and localization within the optic pathway as factors that increased the risk of tumor progression. In this large prospective multinational study, LGG in NF-1 patients did progress in 75% of patients. Chemotherapy yielded acceptable PFS. The biological factors determining progression remain poorly understood.

This study was conducted on behalf of the HIT-LGG study group for Children and Adolescents with a Low Grade Glioma. P. Hernáiz Driever and S. von Hornstein contributed equally to this work.

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## Introduction

Up to 15% of all neurofibromatosis type 1 (NF-1) patients will develop a cerebral tumor within the first two decades [1–7], the majority of which are low-grade glioma (LGG) with pilocytic astrocytoma histology. They are predominantly located along the optic pathway [2–6]. The management challenges [8] are: (1) the natural history of these tumors is not fully understood, (2) impairment of visual acuity in optic pathway lesions affects only a

portion of NF-1 patients, (3) NF-1 patients may develop serious complications after irradiation, (4) the diagnosis of a brain tumor may lead to the diagnosis of NF-1, whereas in other patients the lesion may be diagnosed through screening, and (5) NF-1 patients often suffer from concurrent disease-related problems like cognitive impairment, seizures, and the disposition to develop additional neoplasms.

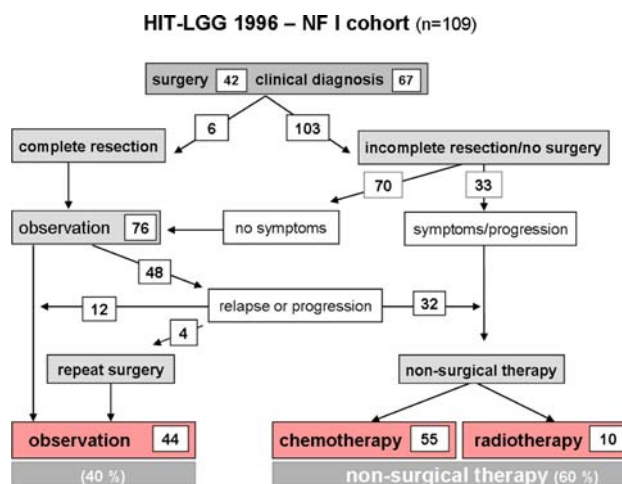
Several studies focused on the biological differences between histologically identical tumor lesions in children with and without the NF-1 trait [9–12]. In a systematic review of prognostic factors for progression of childhood optic pathway glioma, three clinical reports demonstrated an improved progression free survival (PFS) for NF-1 patients using a multivariate analysis, whereas in six other studies NF-1 trait was not a significant prognostic factor [12]. Current clinical recommendations remain unclear as to whether the presence of NF-1 itself should be considered for stratification of therapy if treatment is necessary [8]. In addition, several medical subspecialties care for pediatric NF-1 patients, each with their own experience and perspective.

The primary aim of the prospective HIT-LGG-1996 study was to establish a common therapeutic strategy for pediatric LGG patients, including NF-1 patients with a symptomatic LGG, in the countries of the German-speaking Society of Pediatric Oncology and Hematology (GPOH). Hence, by reporting the results on NF-1 patients of the HIT-LGG study, we inform on the largest comprehensively treated cohort so far, and seek to answer questions on the factors determining clinical biology of NF-1 associated LGG.

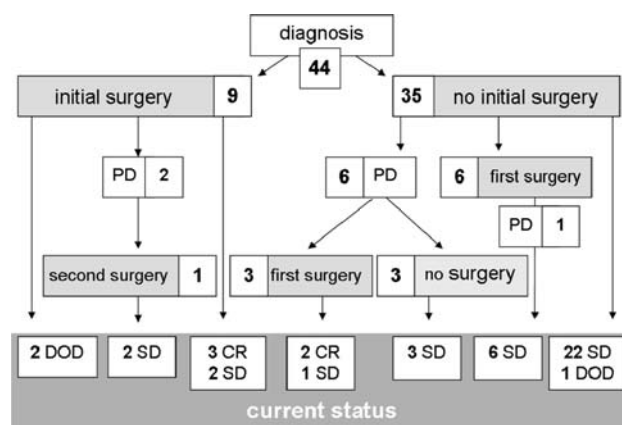
## Patients and methods

### Eligibility

The HIT-LGG 1996 study was designed as a comprehensive treatment strategy for all participating centers in the German speaking countries of the Society of Pediatric Oncology and Hematology (GPOH). The eligibility criteria included children and adolescents younger than 17 years of age suffering from a LGG. The radiological diagnosis of a LGG was accepted for NF-1 patients either with optic pathway gliomas or isolated hypothalamic chiasmatic tumors that demonstrated hypo/isodensity on non-enhanced computed tomography after central review by one of us (M.W.-M.). Patients were recruited between October 1st, 1996 and March 31st, 2004, and followed till March 2008. Patients' parents or guardians gave their informed consent. Central (Augsburg) as well as participating centers ethics board approval was obtained.



**Fig. 1** Study group flow chart



**Fig. 2** Observation group flow chart. NF-1 patients received neither chemotherapy nor radiotherapy within the study period, i.e. observation group; *DOD* death of disease, *SD* stable disease, *PD* progressive disease, *CR* complete remission

### Study strategy

After initial complete surgical resection a “wait and see” strategy was adopted. Adjuvant therapy was recommended in case of severe neurologic or ophthalmologic symptoms at diagnosis or, if surgery was not an option, upon clinical, ophthalmologic or radiological progression following a period of observation (Figs. 1 and 2). Adjuvant therapy consisted of either radiotherapy or chemotherapy with an age limit for stratification at 5 years. At the beginning, only children younger than 5 years were planned to receive chemotherapy. As the study continued, an increasing number of older patients received chemotherapy.

### Adjuvant treatment

Non-surgical therapy was administered as described in detail elsewhere [13, 14]. The chemotherapy regimen

consisted of vincristine (1.5 mg/sqm intravenous bolus) and single dose carboplatin (550 mg/sqm as a 1-h infusion with appropriate hydration). During the 10 weeks induction, vincristine was given weekly and carboplatin on day 1 of weeks 1, 4, 7, and 10. Both drugs were given concomitantly at 4-week intervals during weeks 13 to 53. Radiotherapy was given as local radiation to the primary tumor region at a total dose of 54 Gy. Children younger than 5 years received a reduced dose of 45.2 Gy. No age restriction was given for brachytherapy [15].

## Methods

### *Biostatistics*

All patients having a genetic NF-1 trait meeting the NIH-criteria for a NF-1 diagnosis were included. The functions of survival (OS), event-free survival (EFS) and progression-free survival (PFS) were calculated by the method of Kaplan and Meier. OS was calculated from the date of diagnosis until the death of the patient regardless of its cause. EFS was determined from the date of diagnosis until relapse, progression, death of any cause, and the necessity to start non-surgical treatment [16]. PFS was estimated from the initiation of non-surgical treatment to progression of a residual tumor, relapse following previous complete remission, evidence of new or progression of existing metastases or death of any cause. We differentiated between subgroups in response to EFS, PFS and OS using the log-rank test.

The potential influence of resection (as time dependent variable), age at diagnosis (continuous and age groups), sex, type of NF-1 trait inheritance, histology [pilocytic astrocytoma (PA) vs clinical diagnosis vs other] and tumor site (optic pathway glioma vs other supratentorial midline localization vs other) on EFS was analyzed by multivariate Cox regression analysis. The final model was built by forward stepwise variable selection. Estimated hazard ratios of variables of the final model were given.

All analyses were explorative. Therefore no significance level was fixed. The *P* values were given for descriptive reasons.

### *Response assessment*

Assessment of tumor response using neuroimaging was recommended at certain time intervals, MRI being the preferred mode of investigation as described in detail elsewhere [13, 14]. The radiological assessment of tumor response by contrast enhanced MRI followed recommended criteria [17]. Complete, partial, and objective response as well as stable disease were considered positive responses within the protocol [13, 14]. Objective response is considered >25% but <50% change of tumor size radiographically.

## Results

### Patients

Ninety pediatric treatment centers in Germany, Switzerland, Austria, and Belgium adhered to the treatment strategy of the HIT-LGG 1996 study. A total of 109 LGG patients with clinically diagnosed NF-1 were registered (10.4% of protocol patients, *n* = 1,044) and followed prospectively for a median of 5.3 years (1.9–12.2 years) (Table 1, Fig. 1). The slight female predominance in the cohort was even more prominent in the adjuvant therapy subgroups. None of the patients enrolled were younger than 1 year of age. Fifty patients were younger than 5 years and 25 patients (23%) were older than 11 years. Histology was centrally reviewed by one of us (T.P.). Only one patient had a pleomorphic xanthoastrocytoma WHO II in the cerebral hemisphere. Sixty-seven patients were diagnosed by neuroimaging only. Three tumors with astrocytoma WHO II were found in the cerebellum (*n* = 1) and the optic chiasm (*n* = 2). Seventy-six percent of patients (*n* = 83) had LGG affecting the optic pathway, the majority comprising Dodge III tumors (*n* = 45) [18]. Ninety-three patients had supratentorial midline tumors. None of the NF-1 patients had diencephalic syndrome and neither disseminated nor spinal disease was reported. Brainstem localization was found in 3 patients. Twelve patients (11%) developed more than a single primary LGG in the brain. The true incidence was not assessed systematically. Concerning NF-1 diagnostic NIH criteria, the patients did not differ from previous characterizations.

### Surgery

Due to the clinical diagnosis of NF-1, 67 patients (61%) who met the neuroradiological diagnosis did not undergo surgery (Figs. 1, and 2). The tumors of 27 patients (25%), including 5 of 6 patients with hemispheric tumors, were amenable to surgery. Biopsy only was performed in 15 (14%) patients.

### Strategy groups

Eighteen patients remained observed following surgery, as were 26 patients with a neuroradiological diagnosis of LGG (Fig. 2). Nine patients had surgery within 3 months of presentation. In another 6 patients, the decision to subject patients to surgery was taken after 3 months of diagnosis. Three patients underwent surgery after developing progressive disease (Fig. 2). At occurrence of tumor progression or clinical deterioration, 65 patients (60%) were treated non-surgically (Fig. 1). Seven of the ten irradiated patients received conventional radiotherapy and 3 brachytherapy.

**Table 1** Patients and treatments included in study

Strategy group	NF-1 cohort	Observation	Chemotherapy	Radiotherapy
Number of patients <sup>a</sup>	109	44	55	10
Sex (female:male)	57:52	19:25	32:23	6:4
Age at diagnosis	5.2 y (1.0–19.8)	7.1 y (1.6–19.8)	3.7 y (1.7–12.9)	10.8 y (1.0–14.7)
Histology				
PA WHO I	38	17	13	8
A WHO II	3	0	3	0
PXA WHO II	1	1	0	0
Clinical + imaging diagnosis only	67	26	39	2
Localization				
Cerebral hemispheres	7	6	0	1
SML	93	32	53	7
Optic nerve	16	8	8	0
Chiasm	21	10	9	2
Dodge III	45	8	33	4
Hypothalamus	1	1	0	0
3rd ventricle	1	1	0	0
Thalamus	1	0	1	0
Basal ganglia	3	2	1	0
Tectum	1	0	1	0
Mesencephalon	3	2	0	1
Cerebellum	5	3	1	1
Brainstem	4	2	1	1
Unknown	1	1	0	0
First resection				
Complete <sup>b</sup>	6	5	0	1
Subtotal	6	4	1	1
Partial	15	9	6	0
Biopsy <sup>c</sup>	15 (10)	0	9 (5)	6 (5)
No histology	67	26	39	2
Age at start of therapy			5.2 y (1.7–14.9)	1.2 y (1.1–14.8)
Overall interval from diagnosis to therapy			2.6 m (0.0–61.3)	3.2 m (0.8–44.4)
<3 months			<i>n</i> = 28	<i>n</i> = 5
>3 months			1.0 m (0.0–2.6)	1.1 m (0.8–2.6)
			<i>n</i> = 27	<i>n</i> = 5
			17.4 m (3.1–61.3)	32.0 m (3.7–43.8)
Interval until best response			3.4 m (0.8–24.4)	5.0 m (2.5–10.3)
Best response				
CR			0	1
PR/OR			24	2
SD			29	5
PD			1	1
Unknown			1	1
PD in observation		9		
Followed by no surgery		3		
Followed by surgery <sup>d</sup>		4		
Unknown		2		
Progression after adjuvant therapy			17	3
Interval until progression after first therapy			1.7 y (1.6 m – 7.4 y)	7.4 m/31.1 m/46.1 m

**Table 1** continued

Strategy group	NF-1 cohort	Observation	Chemotherapy	Radiotherapy
Current status				
CR	7	7	0	0
PR/OR	3	0	2	1
SD	90	34	48	8
PD	5	0	4	1
DOD	4	3	1 (OS 4.4 years)	0
Follow-up period	5.3 y (1.9 m – 12.2 y)	4.6 y (1.9 m – 9.7 y)	5.7 y (8.8 m – 12.2 y)	5.2 y (2.3–7.4)

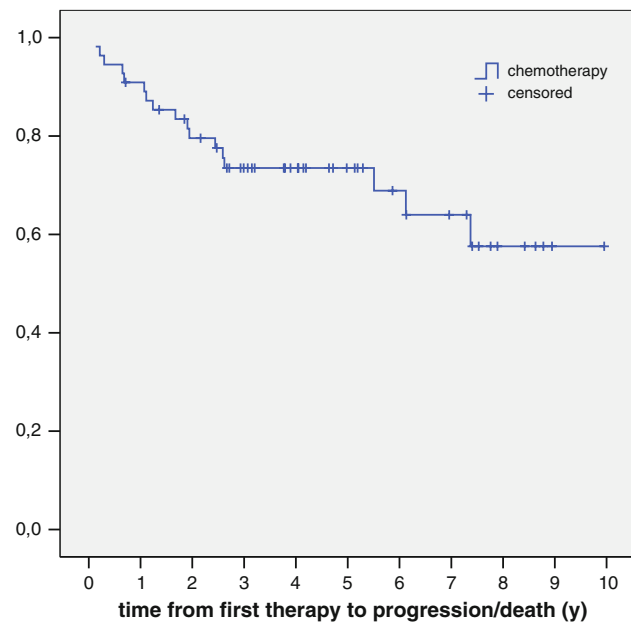
PA Pilocytic astrocytoma, A astrocytoma, PXA pleomorphic xanthoastrocytoma, CR complete remission, PR partial remission, OR objective response, SD stable disease, PD progressive disease, DOD dead of disease, OS Overall survival, y years, m months

- <sup>a</sup> In the radiotherapy group, 7 patients received conventional percutaneous radiotherapy, 3 patients received brachytherapy
- <sup>b</sup> In the radiotherapy group, 1 patient had a complete resection after having had subtotal resection, progressive disease treated with irradiation and response to the adjuvant therapy
- <sup>c</sup> Numbers in parentheses indicate stereotactic biopsy
- <sup>d</sup> Three patients had PD before primary surgery, 1 patient was submitted to a second surgery after PD

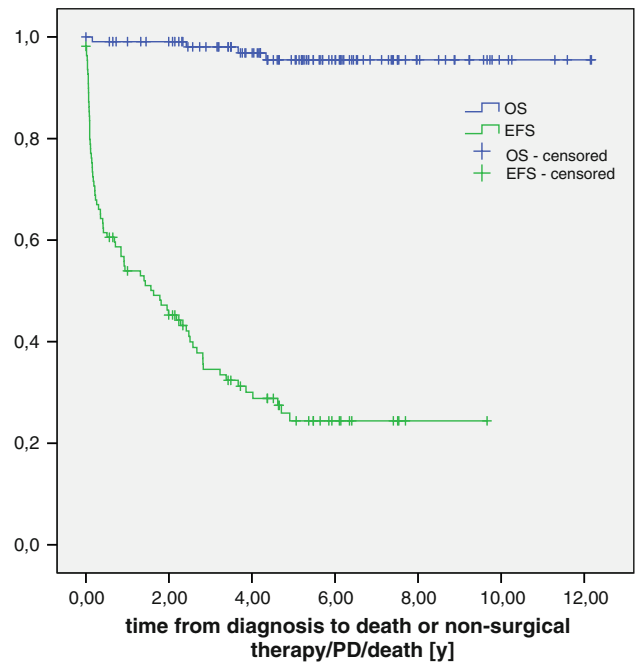
Following protocol’s recommendations, the median age of patients in the chemotherapy group was expectedly lower than in the radiotherapy group with 5.2 years and 12.2 years, respectively. In both adjuvant treatment groups, half of all patients started therapy within 3 months of LGG diagnosis. The 5-year PFS of the adjuvant treatment group was 0.72 and 0.56 at 9.95 years (Fig. 3).

**Overall and event-free survival**

Four patients of the NF-1 cohort died during follow-up, resulting in an OS of 0.96 at 12 years (Fig. 4). Three of the



**Fig. 3** Progression-free-survival for NF-1 patients with primary chemotherapy (n = 55)



**Fig. 4** Event-free-survival and overall-survival for the whole NF-1 cohort (n = 109)

patients who died of the disease were in the observation group (0.16, 2.41 and 3.67 years after diagnosis). All had optic pathway tumors involving either the chiasm alone (n = 1) or as a Dodge III tumor (n = 2). They died from an Addison crisis (n = 1) and cardiovascular failure (n = 2), i.e. disease-related complications. One patient in the chemotherapy group died 4.34 years after the initial diagnosis of a LGG in the 3rd ventricle due to progression of disease. Kaplan–Meier analysis revealed that the OS of the cohort was not influenced by gender, age (when comparing younger and older patients, </> 10 years of age),

mode of NF-1 trait inheritance (familiar vs sporadic), histology (pilocytic astrocytomas vs no histology or others), and localization (optic pathway vs other sites). Seventy-seven events were recorded, resulting in an EFS of 0.24 at 5 years after median observation time of 5.25 years that was followed up to 9.66 years (Fig. 3).

#### Observation group ( $n = 44$ )

After a median follow up time of 4.6 years, 37% of all patients were successfully treated without adjuvant treatment (CR: 7 and SD: 34 patients). In this group, 9 patients had either a relapse or progressive disease and were treated with surgery in 5 cases during the observation time. All eventually experienced a stable disease state (Fig. 2). However, 3 patients died from disease-related complications and not from disease progression.

#### Chemotherapy group ( $n = 55$ )

Almost all patients (98%) responded to this first therapy except for two patients (1 PD and 1 not evaluated). Best response to chemotherapy was recorded after a median treatment time of 3.6 months with the latest response after 48.3 months. Nine patients had their best response after the end of chemotherapy. Of 24 patients who received a scan at 24 weeks after start of chemotherapy, PR/OR and SD were noted in 3 and 21 patients, respectively. Therapy was well tolerated. However, 20 patients developed an allergy to carboplatin. Substantial vincristine toxicities were not reported. Sixteen patients progressed after a median time of 3.8 months. Seven of these patients were treated again with chemotherapy. One of these 7 patients was eventually treated with radiotherapy 35.2 months after start of adjuvant chemotherapy. Another 4 patients with PD received radiotherapy as second line treatment. The primary aim of postponing radiotherapy in this group was achieved for 3 patients, postponing it by 4, 6.3, and 13.1 months after the start of chemotherapy. This corresponds to a median delay of radiotherapy after start of chemotherapy of 9.7 months for the whole chemotherapy group. One patient of this cohort eventually died of the tumor and 4 patients experienced progressive disease after a median follow-up of 5.7 years. The 5 years, PFS rate of the chemotherapy group was 0.73, and 0.57 after 9.95 years.

#### Radiotherapy group ( $n = 10$ )

Best response to treatment was observed after 5.1 months in 8 of 10 patients. Progressive tumors were observed in 2 patients following conventional external radiotherapy to the chiasm and the cerebellum, and in 1 patient following brachytherapy of a Dodge III optic pathway tumor. One of

the patients with PD was then treated with chemotherapy and the other two were observed (one of them had a CR following surgery). The 5-year PFS rate of the radiotherapy group is 0.78, and 0.59 after 7.36 years. None of the patients developed any unwanted irradiation-associated acute or late effects.

#### Prognostic factors

Univariate analysis of the EFS for the whole NF-1 cohort by log-rank test revealed significantly worse outcome for tumors located within the optic pathway especially if these tumors were Dodge stage II/III (Table 2). However, gender, age, and histological type and mere clinical/imaging diagnosis did not influence EFS. When analyzing the EFS of the chemotherapy group for single variables, no influence was found for age, gender, start of therapy, and extent of surgery, histology, and response to therapy at week 24. Risk factors were also not found for the EFS of the radiotherapy group patients.

Multivariate EFS analysis of the whole NF-1 cohort revealed that patients who had a biopsy had the highest risk for progressive disease (Table 3). The risk of PD in the group of patients who underwent a more extensive surgery was still significantly higher than those whose diagnosis was made by clinical examination and neuroimaging only. Tumors located outside the optic pathway had a significantly reduced risk of progression after all histologies were included. After excluding patients with tumors of PXA WHO II or A WHO II histology, localization did not play

**Table 2** Univariate analysis (log-rank test) of the risk factors for event free survival of the NF-1 cohort of the HIT-LGG 1996 protocol

Factor	EFS at 5 years	SE at 5 years	$n$	$P$ value
Gender				0.3234
Male	0.29	0.07	52	
Female	0.20	0.05	57	
Localization				0.0334
Optic pathway	0.19	0.04	82	
Other	0.34	0.10	26	
Optic pathway localization				0.015
Dodge I	0.50	0.12	16	
Dodge II/III	0.11	0.05	66	
Other	0.34	0.10	26	
Histology				0.986
PA	0.18	0.07	38	
Clinical diagnosis only	0.27	0.06	67	
Other	0.25	0.21	4	

EFS Event free survival, SE standard error,  $n$  number of patients, PA pilocytic astrocytomas WHO I

**Table 3** Multivariate analysis of the risk factors for the EFS of the NF-1 cohort of the HIT-LGG 1996 protocol

Variable	Comparison	HR	95% CI	P value of likelihood ratio test
Extent of surgery	Biopsy vs no/prior to surgery	6.45	(2.93; 14.20)	$P = 0.001$
	Resection vs no/prior to surgery	1.24	(0.63; 2.42)	
Localization <sup>a</sup>	Other vs optic pathway	0.44	(0.23; 0.84)	$P = 0.007$

HR Hazard ratio, CI confidence interval

<sup>a</sup> This variable was not significant when the 4 patients with histologies other than pilocytic astrocytomas or clinical diagnosis only were excluded

**Table 4** Multivariate analysis of the risk factors for the EFS of NF-1 patients treated with adjuvant therapy

Variable	Comparison	HR	95% CI	P-value of likelihood ratio test
Extent of surgery	Biopsy vs no/prior to surgery	3.66	(1.59; 8.42)	$P = 0.005$
	Resection vs no/prior to surgery	2.53	(1.15; 5.58)	
Localization <sup>a</sup>	Other vs optic pathway	0.27	(0.11; 0.67)	$P = 0.001$
Histology <sup>b</sup>	Pilocytic astrocytoma vs clinical diagnosis only	0.25	(0.10; 0.63)	$P = 0.001$

HR Hazard ratio, CI confidence interval

<sup>a</sup> This variable was in the final model when patients with histologies other than pilocytic astrocytomas and clinical diagnosis only were excluded

<sup>b</sup> This variable was in the final model when the 4 patients with histologies other than pilocytic astrocytomas or clinical diagnosis only were excluded

any significant role. Similar results were obtained with multivariate analysis for the combined adjuvant treatment group and for the chemotherapy group alone (Table 4). A further multivariate analysis of the combined adjuvant treatment group and the chemotherapy group revealed that, after exclusion of patients suffering from tumors with PXA WHO II or A WHO II histology, localization outside the optic pathway and PA WHO I histology were significantly associated with lower risk of PD when compared with patients diagnosed by clinical and imaging findings only. Other risk factors, such as type of NF-1 trait inheritance, gender, and age, were included but did not display significance in the multivariate analysis of any group.

Univariate Kaplan–Meier estimates of PFS for the chemotherapy group showed no influence of age, gender, mode of NF-1 trait inheritance, localization, histology, initial time interval from diagnosis to therapy, or response to therapy. Twenty events in 65 patients with adjuvant therapy and 17 events in 55 patients receiving chemotherapy did not allow multivariate regression analysis.

## Discussion

The group of NF-1 patients with LGG in this study is one of the very few prospectively registered cohorts and was collected within the first multi-center cooperative trial of the German Speaking Society of Pediatric Oncology and Hematology (GPOH) to optimize LGG therapy in children and adolescents. In contrast to earlier studies stating that LGG in NF-1 patients arises at an age of less than 5 years,

in our cohort LGG arose throughout the first two decades of life and became symptomatic [3, 5]. Nearly 25% of patients diagnosed with a tumor were older than 11 years of age. This underscores the risk of new symptomatic LGG, especially within the optic pathway of pediatric NF-1 patients during the second decade of life [8, 19].

Female patients dominated all strategy groups, especially the adjuvant treatment groups. This supports epidemiologic findings that female NF-1 patients are more prone to develop tumors than male NF-1 patients [20]. However, this dominance was not significant in terms of EFS or PFS.

The group is characterized by a majority of optic pathway lesions (76%) corroborating other studies [2–5]. NF-1-associated optic glioma were mainly reported in the optic nerve itself, yet the LGG of our cohort were predominantly detected in the chiasmatic and postchiasmatic area (80%), and lesions restricted to the optic nerve were rather rare. Furthermore, our cohort lacked patients with adverse risk factors such as age under 1 year at diagnosis, disseminated disease pattern and diencephalic syndrome [12, 21]. Also, the frequency of brain stem involvement was lower (3/109) than reported by Guillamo et al. [3] (17%), whereas hemispheric localization was comparable (7/109). We found that the involvement of the chiasm, especially the postchiasmatic area, was associated with worse EFS in the univariate analysis. Two out of eight studies in the meta-analysis by Opocher et al. [12] support our findings, identifying Dodge II/III tumors versus Dodge I tumors as an independent risk factor for progression of optic pathway glioma in multivariate analysis, whereas the remainder did not.

In our cohort, one patient suffering from a hemispheric tumor was diagnosed with a pleomorphic xanthoastrocytoma WHO grade II. To our knowledge, this is the first report of such histology in a pediatric NF-1 patient. Furthermore, despite progression in 3 out of 4 patients, none in the cohort was diagnosed with a high-grade brain tumor within the follow-up period [22]. Only a quarter of all patients had tumors that were amenable to surgical therapeutic intervention. Surgery sufficed as sole therapy in only 18 of 27 patients, similar to reports from other groups [3, 23–25]. In almost 2 out of 3 patients, diagnosis and decision on therapy were based upon clinical and imaging findings only, echoing other reports [22].

Sixty percent of our patient cohort received adjuvant treatment, 55 of whom were treated with chemotherapy. Until now, many clinicians have given radiotherapy similar or higher importance than chemotherapy [3, 5, 6, 12]. Thus, our cohort is the first to report the results of NF-1 patients with a LGG treated predominantly with chemotherapy.

Earlier reports on pediatric NF-1 patients indicated that LGG largely remained asymptomatic [3–6]. However, EFS of our patients was low (5-year EFS 0.24). We cannot exclude a registration bias due to the reporting system as most patients with a more aggressive course were probably registered. The marked tendency of LGG progression in our cohort may also be due to the fact that hypothalamic tumors with a more aggressive biology prevail [16]. On the other hand, our large observation group also contained one case of spontaneous regression (signal alteration in the optic tract that did not fulfill criteria of an unidentified bright object) [26].

Response within the NF-1 cohort to vincristine/single dose carboplatin chemotherapy was promising and comparable to responses reported by other groups using combinations of 2 drugs [16, 21, 27, 28]. Compared with these studies, we were able to achieve high 5-year PFS rate of 0.73 [16, 21, 27, 28].

Three of the children of the radiotherapy group received radioiodine seed implantation. This approach is considered very safe but has its limitations concerning tumor size and location [15]. To date, radiotherapy in our cohort was not associated with risks reported in other NF-1 patients [29–32]. The small number of patients treated with this approach limits the assertions that can be made about its safety.

LGG located within the optic pathway, especially within the chiasmatic and postchiasmatic area, were more likely to be associated with tumor growth according to univariate analysis. This was further corroborated by multivariate analysis. These findings are in line with clinical studies reporting hypothalamic and optic pathway LGG to be generally more aggressive [16]. Experimental studies demonstrate that spatiotemporal differences of CXCL 12 expression contribute to the unique pattern of NF-1-

associated optic pathway tumors [33]. A risk factor more strongly associated with progressive LGG was biopsy and surgical intervention versus clinical and imaging diagnosis only. Our preliminary understanding of this observation is that clinicians may prefer more invasive surgery for tumors that appear abnormal on imaging [22]. Another explanation may be that tumors, when submitted to surgery, responded to inflammatory mediators set free by the surgical trauma with cellular growth. A third interpretation is that tumors diagnosed with imaging only may be biologically less aggressive.

Despite a countrywide trial and children's cancer registry we cannot exclude that NF-1 children with non-progressive tumors are followed by medical specialties outside pediatric oncology though we believe that our study included the relevant patients. Another limitation is that at the beginning of the study a central review of radiology had yet to be established.

In summary, NF-1 patients have a strong tendency to develop a progressive LGG throughout the first two decades of life. A high percentage of our cohort needed therapy. Chemotherapy achieved satisfactory PFS. Irradiation seems to reach similar PFS rates. Tumor response to chemotherapy was good and delayed irradiation. The biological risk factors that determine progression remain unknown. NF-1 patients should follow current treatment recommendations until separate strategies respecting such biological aspects will have been developed.

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