Received: 29 April 2020 | Revised: 2 June 2020 | Accepted: 10 June 2020

DOI: 10.1002/ijc.33170

CANCER THERAPY AND PREVENTION

IJC International Journal of Cancer

Loss of efficacy of subsequent nonsurgical therapy after primary treatment failure in pediatric low-grade glioma patients—Report from the German SIOP-LGG 2004 cohort

Daniela Kandels[1] | Torsten Pietsch[2] | Brigitte Bison[3] | Monika Warmuth-Metz[3] | Ulrich-Wilhelm Thomale[4] | Rolf-Dieter Kortmann[5] | Beate Timmermann[6] | Pablo Hernáiz Driever[7] | Olaf Witt[8] | René Schmidt[9†] | Astrid K. Gnekow[1†]

[1]Swabian Children's Cancer Center, Medical Faculty, University of Augsburg, Augsburg, Germany

[2]Institute of Neuropathology, DGNN Brain Tumor Reference Center, University of Bonn, Bonn, Germany

[3]Institute of Diagnostic and Interventional Neuroradiology, University Hospital Würzburg, Würzburg, Germany

[4]Pediatric Neurosurgery, Charité Universitaetsmedizin Berlin, Corporate Member of Freie Universitaet Berlin, Humboldt-Universitaet zu Berlin, and Berlin Institute of Health, Berlin, Germany

[5]Department of Radio-Oncology, University Hospital Leipzig, Leipzig, Germany

[6]Department of Particle Therapy, University Hospital Essen, West German Proton Therapy Centre Essen (WPE), West German Cancer Center (WTZ), German Cancer Consortium (DKTK), Essen, Germany

[7]Department of Pediatric Oncology/Hematology, Charité Universitaetsmedizin Berlin, Corporate Member of Freie Universitaet Berlin, Humboldt-Universitaet zu Berlin, and Berlin Institute of Health, Berlin, Germany

[8]Hopp Children's Cancer Center Heidelberg (KiTZ), German Cancer Research Center (DKFZ), and Heidelberg University Hospital, Heidelberg, Germany

[9]Institute of Biostatistics and Clinical Research, University of Münster, Münster, Germany

Abstract

First-line treatment of pediatric low-grade glioma using surgery, radio- or chemotherapy fails in a relevant proportion of patients. We analyzed efficacy of subsequent surgical and nonsurgical therapies of the German cohort of the SIOP-LGG 2004 study (2004-2012, 1558 registered patients; median age at diagnosis 7.6 years, median observation time 9.2 years, overall survival 98%/96% at 5/10 years, 15% neurofibromatosis type 1 [NF1]). During follow-up, 1078/1558 patients remained observed without (n = 217), with 1 (n = 707), 2 (n = 124) or 3 to 6 (n = 30) tumor volume reductions; 480/1558 had 1 (n = 332), 2 (n = 80), 3 or more (n = 68) nonsurgical treatment-lines, accompanied by up to 4 tumor-reductive surgeries in 215/480; 265/480 patients never underwent any neurosurgical tumor volume reduction (163/265 optic pathway glioma). Patients with progressing tumors after first-line adjuvant treatment were at increased risk of suffering further progressions. Risk factors were young age (<1 year) at start of treatment, tumor dissemination or progression within 18 months after start of chemotherapy. Progression-free survival rates declined with subsequent treatment-lines, yet remaining higher for patients with NF1. In non-NF1-associated tumors, vinblastine monotherapy vs platinum-based chemotherapy was noticeably less effective when used as second-line treatment. Yet, for the entire cohort, results did not favor a certain sequence of specific treatment options. Rather, all can be aligned as a portfolio of choices which need careful balancing of risks and benefits. Future molecular data may predict long-term tumor biology.

Abbreviations: BBSFOP, Baby Brain protocol of the French Society of Pediatric Oncology; CI, confidence interval; CNS, central nervous system; EC, European community; EFS, event-free survival; HR, hazard ratio; LGG, low-grade glioma; MRI, magnetic resonance imaging; NF1, neurofibromatosis type 1; OPG, optic pathway glioma; OS, overall survival; PA, pilocytic astrocytoma; PFS, progression-free survival; PFS-1, progression-free survival after first-line nonsurgical therapy; PFS-2, progression-free survival after second-line nonsurgical therapy; PFS-3, progression-free survival after third-line nonsurgical therapy; PFS-4, progression-free survival after fourth-line nonsurgical therapy; SML, supratentorial midline; WHO, World Health Organization.

[†]Joint senior authors.

[Correction added on 28 September 2020, after first online publication: Projekt Deal funding statement has been added.]

Correspondence
Daniela Kandels, Swabian Children's Cancer Center, Medical Faculty, University of Augsburg, Stenglinstraße 2, 86156 Augsburg, Germany.
Email: lgg-studie@uk-augsburg.de

Funding information
Deutsche Kinderkrebsstiftung, Grant/Award Numbers: 2004.5, 2007.10, 2010.08;
Open access funding enabled and organized by Projekt DEAL.

KEYWORDS
chemotherapy, pediatric low-grade glioma, progression, radiotherapy, surgery

1 | INTRODUCTION

Pediatric low-grade gliomas (LGGs) are heterogeneous at a clinical, neuropathological and molecular level. They occur at all ages and sites of the central nervous system (CNS)[1,2] with a low risk for malignant transformation.[3,4] Comprehensive treatment strategies have been developed for pediatric LGG integrating various therapeutic approaches.[1,2,5-14]

Whereas neurosurgical resection is considered the treatment of choice, a relevant portion of tumors is not amenable to complete resection. Tumors may grow and alternate with phases of proliferative arrest. Unresectable tumors and residues pose a risk for nonsurgical treatment upon clinical and/or radiological progression.

Current treatment strategies schedule chemotherapy as first-line treatment for most, in particular for the younger patients,[6,8,10,15] to avoid radiation. Radiotherapy is used more often in older patients.[12,13]

Most nonsurgical treatment modalities have shown high initial response rates exceeding 90%. Still, these fail in a relevant proportion of patients. More than half of patients suffer from tumor progression after first-line chemotherapy[16,17] and up to 30 % following first-line radiotherapy.[12,13,18,19] Using a multistate model for analysis of our study cohort, Goebel et al identified patients with multiple interventions after 2 years of diagnosis at increased risk for a highly progressive disease biology and death.[20] Although radiotherapy is superior to chemotherapy in terms of progression-free survival (PFS),[12,13,21] concerns regarding long-term sequelae[3,18,19,22-25] limit its application as an approach especially in the very young. Thus, we and others recommended front-line chemotherapy for all patients[26] accepting more and earlier tumor progressions. Salvage chemotherapy upon further progression was shown to be effective.[9,16,17,27]

Most salvage treatments have been analyzed for response to therapy, whereas long-term follow-up data are scarce.[16,17,28] So far, a comprehensive strategy for patients with repeatedly progressive or relapsing LGG has yet to be defined. Despite repeated progressions, overall survival (OS) for these patients remains acceptable[2,25,29] and most patients reach adulthood. LGG is a life-long disease for patients whose tumor location or dissemination do not allow surgical resection.[20] All therapeutic efforts have to minimize long-term sequelae due to disease and therapy.

We report the largest population-based and prospectively registered cohort with extended follow-up. We examined the effect of subsequent surgeries and nonsurgical therapies for pediatric LGG of all histologies and locations. We analyzed risk factors for repeatedly progressive disease.

What's new

For some patients with pediatric low-grade glioma, first-line treatment isn't enough. Here, the authors evaluated the effectiveness of various second-line strategies, including surgical and non-surgical therapies, in a German cohort. Risk factors for tumor progression included age under 1 year at diagnosis, early treatment failure, and tumor dissemination. Over the entire cohort, the results did not clearly support one specific treatment strategy as the best choice, although platinum-based therapy performed better than vinblastine in non-NF1 tumors. This is the first long term analysis of comprehensive treatment strategies in recurrent tumors in a population-based, prospectively registered pediatric low-grade glioma cohort.

2 | PATIENTS AND METHODS

2.1 | Eligibility

The prospective multinational/multicenter study SIOP-LGG 2004 registered patients with LGG of all CNS localizations from 2004 to 2012. Follow-up included information up to 10 July 2019. Inclusion criteria were age < 18 years at diagnosis and histologic diagnosis of LGG according to the respective World Health Organization (WHO)-classification of CNS tumors without prior nonsurgical therapy. In defined cases, radiological diagnosis was accepted.[15] Central review for pathology and radiology was recommended.

2.2 | Treatment strategy

At diagnosis, best safe resection of the primary tumor was recommended. Patients with complete resection were to be observed, as well as patients following incomplete resection, biopsy or radiological diagnosis, provided they did not suffer from tumor-related, severe neurologic symptoms. Upon clinical or radiological progression,[15] nonsurgical treatment was indicated if resection was deemed unfeasible. For patients <8 years and for all patients with NF-associated LGG chemotherapy as first-line

treatment was recommended, whereas older children could receive primary radiotherapy instead[15] (Figure S1).

2.3 | Treatment modalities

For this report, surgical interventions were divided into "therapeutic" surgery, if relevant tumor volume reduction was achieved (ie, partial, subtotal and complete resection), and "diagnostic" surgery for biopsies. Extent of resection was confirmed by early postoperative scanning (obtained within the first 48 hours after surgery, up to 72 hours in exceptional circumstances) and combined surgical and radiological judgement.[26] Additional surgery for regulation of increased cranial pressure (ie, ventriculostomy, external cerebrospinal fluid drainage or ventricular-peritoneal shunting) was not considered for analysis.

First-line chemotherapy consisted of vincristine and carboplatin given for 18 months. Additional etoposide was given during the induction period to patients allocated into the interventional arm of the randomized study.[15]

Focal radiotherapy by either photon or proton external beam radiation was applied with a total dose of 54 Gy (1.8 Gy per fraction), whereas individual concepts were used in case of craniospinal radiation for disseminated disease. Brachytherapy/interstitial radiotherapy for suitable tumors was applied with 125-iodine seeds, but restricted to small and circumscribed tumors of selected sites.

Treatment for progression following primary radio- or chemotherapy was not standardized, but included all modalities, including published and individualized regimens (Table S1), following discussion in local and reference tumor boards.

Nonsurgical treatment modalities (chemotherapy and radiotherapy) are referred to as "adjuvant" treatment. Patients receiving everolimus for subependymal giant cell astrocytoma associated with tuberous sclerosis were allocated to the observation group.

2.4 | Neuroimaging

Radiologic diagnosis was accepted, if the tumor was not amenable to surgery, for hypothalamic-chiasmatic tumors associated with neurofibromatosis type 1 (NF1), or for tumors extending along visual pathways and demonstrating hypodensity on a native computed tomography scan. Contrast-enhanced magnetic resonance imaging (MRI) was performed at defined intervals in all patients and was planned at Week 24, 54 and 85 after the start of nonsurgical therapy for response assessment. Definitions for radiological response followed published consensus.[26,30-32]

2.5 | Statistics

For continuous variables, median and range are given. Categorical variables are indicated in absolute or relative frequencies.

The distribution of survival times was estimated with the Kaplan-Meier method and compared between independent groups using log-rank test. OS was calculated from date of diagnosis until death of any cause. Event-free survival (EFS) was calculated from date of diagnosis until event, defined as relapse after complete resection, clinical or radiological progression, start of nonsurgical/adjuvant therapy or death of any cause. Patients without event were censored at the date of last MRI. To evaluate the variable "extent of resection," EFS and OS were in derogation thereof calculated from the date of surgery until event.

Progression-free survival after first-line therapy (PFS-1) was calculated from the start of first nonsurgical/adjuvant therapy until event, defined as relapse after complete remission, clinical or radiological progression or death of any cause. Analogously, progression-free survival after second-line (PFS-2), third-line (PFS-3) and fourth-line therapy (PFS-4) was calculated from the start of second, third and fourth nonsurgical/adjuvant therapy until event, respectively.

Radiation-free survival (RFS) was calculated from the start of first chemotherapy until start of first radiotherapy or death of any cause.

Cox regression with forward stepwise selection (inclusion criterion: score test $P \leq .05$; exclusion criterion: likelihood ratio test $P > .10$) was used to analyze the prognostic value of clinical and biologic variables on PFS-1 and PFS-2. Multivariable analysis of PFS after first-line/second-line chemotherapy or radiotherapy included all variables indicated in Table 3 and 4, respectively. For the final multivariable models, hazard ratios (HRs) of selected variables with their 95% confidence intervals (CIs) and likelihood ratio *P* values are shown.

Kaplan-Meier estimates for PFS-1, PFS-2, PFS-3 and PFS-4 were based on a common set of patients and thus stochastically dependent. Accordingly, statistical tests to compare PFS-1, PFS-2, PFS-3 and PFS-4 rates were calculated while adjusting for the worst-case dependence structure (adjusted *P* values).

Analyses were exploratory, and *P* values were considered as descriptive measures to detect and study meaningful effects. In particular, no significance level was fixed.

3 | RESULTS

3.1 | Epidemiologic data

From 2004 to 2012, 1586 previously untreated children and adolescents with LGG from 81 German centers were registered. Twenty-eight patients were excluded for inconsistent diagnosis, missing data, displaying WHO-grade II H3.3K27M mutation upon molecular-genetic testing,[33] receiving first-line nonsurgical therapy without specified[15] or nonprotocol first-line chemotherapy (Figure 1). Thus, analysis is based on 1558 patients; epidemiological data are given in Table 1. Median age at diagnosis was 7.6 years. No age peak was noted for non-NF1 patients, whereas two thirds of the NF1 patients (62%) were aged 1 to 5 years at diagnosis (Figure S2).

Tumor location differed with NF status: In non-NF1 patients, most tumors (34%) were located in the cerebellum, followed by the

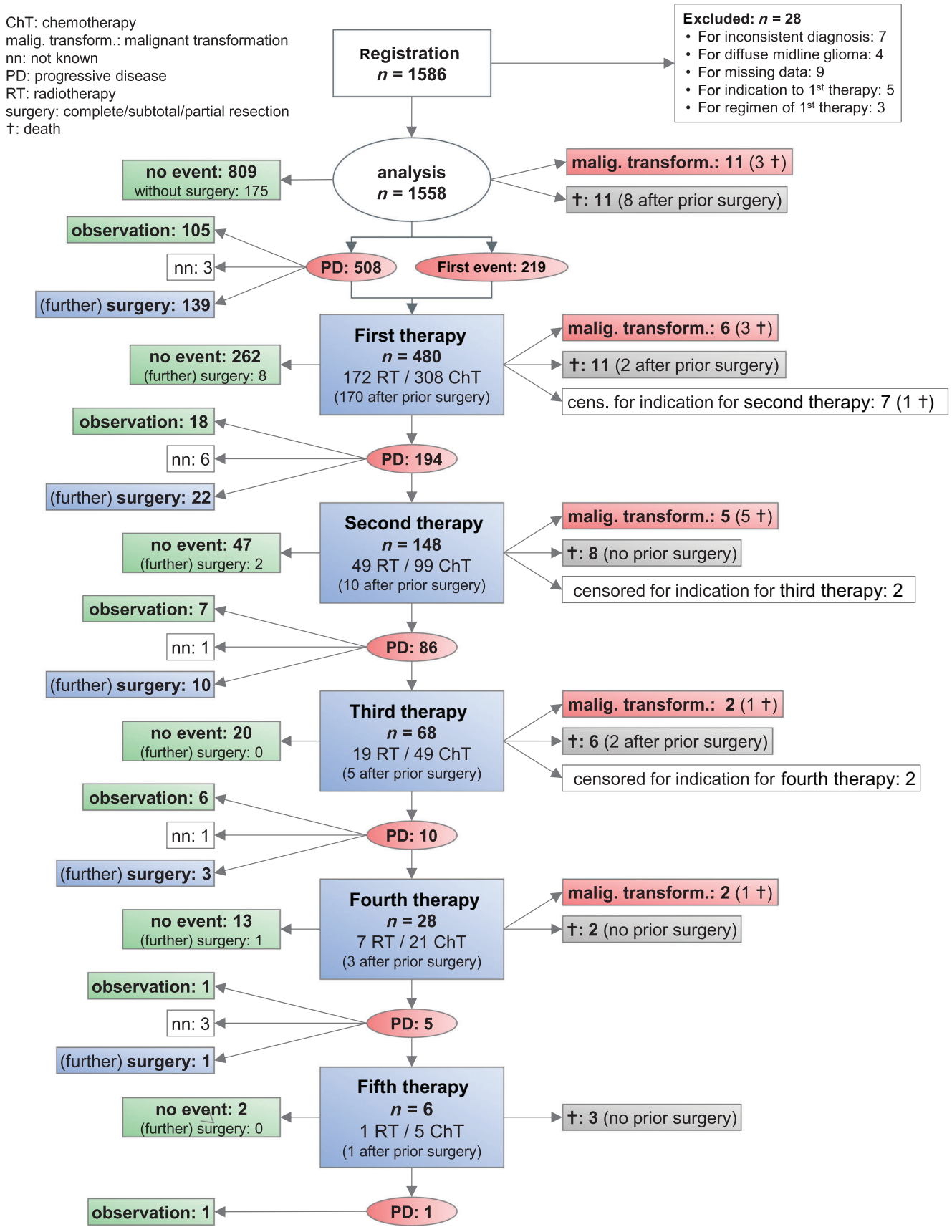

FIGURE 1 Course of disease and treatment cascade with patient numbers throughout the lines of therapy. "Surgery" comprises relevant tumor reduction in terms of complete, subtotal or partial resection, but neither biopsies nor interventions for regulation of increased cranial pressure

TABLE 1 Epidemiologic data

	All patients n = 1558	NF1 (n = 228)	No nonsurgical therapy		One nonsurgical therapy		Two nonsurgical therapies		≥3 nonsurgical therapies	
			All patients (n = 1078)[a]	NF1 (n = 92)	All patients (n = 332)	NF1 (n = 99)	All patients (n = 80)	NF1 (n = 23)	All patients (n = 68)	NF1 (n = 14)
Median age (y) (range)										
At diagnosis	7.6 (0.1-17.9)	4.8 (0.6-16.6)	8.8 (0.1-17.9)	5.7 (1.1-16.6)	6.1 (0.3-17.5)	5.1 (0.6-16.1)	4.1 (0.4-16.6)	2.9 (0.9-15.3)	1.8 (0.2-13.0)	2.8 (0.8-11.4)
At start of first-line therapy (n = 480; 136 NF1)	6.9 (0.3-25.9)	6.0 (1.3-17.2)	—	—	8.5 (0.6-25.9)	6.4 (1.7-16.8)	5.8 (0.4-18.0)	5.0 (1.4-17.2)	2.6 (0.3-14.0)	3.0 (1.3-11.8)
At start of second-line therapy (n = 148; 37 NF1)	8.2 (0.7-21.2)	9.0 (3.1-18.7)	—	—	—	—	9.8 (1.1-21.2)	9.5 (3.4-18.7)	5.9 (0.7-15.9)	6.9 (3.1-14.5)
At start of third-line therapy (n = 68; 14 NF1)	8.4 (1.1-18.9)	9.6 (4.6-15.5)	—	—	—	—	—	—	8.4 (1.1-18.9)	9.6 (4.6-15.5)
Median interval from diagnosis to start of first-line therapy (y) (range)	—	—	—	—	0.8 (0.0-14.3)	0.7 (0.0-14.3)	0.1 (0.0-9.5)	0.6 (0.0-9.5)	0.1 (0.0-12.5)	0.1 (0.0-2.9)
Age group										
<1 y	75	3	33	0	14	1	8	1	20	1
≥1 to <8 y	735	167	449	60	192	79	53	19	41	9
≥8 y	748	58	596	32	126	19	19	3	7	4
Sex										
Male	831	116	582	48	176	53	40	10	33	5
Female	727	112	496	44	156	46	40	13	35	9
Localization										
Cerebral hemispheres[b]	359	6	328	5	25	1	6	0	0	0
Optic pathways	330	176	96	66	147	80	39	19	48	11
SML outside the optic pathways[c]	237	21	134	7	75	10	21	3	7	1
Cerebellum	460	9	428	8	28	1	3	0	1	0
Caudal brainstem	117	13	59	4	41	6	9	1	8	2
Spinal cord	54	3	33	2	16	1	2	0	3	0
No PT assessable	1	0	0	0	0	0	0	0	1	0
Dissemination										
None	1483	227	1064	92	311	99	67	22	41	14
Primary/secondary	48/27	0/1	10/4	0/0	14/7	0/0	7/6	0/1	17/10	0/0
Extent of first surgery										
Complete resection[d]	518	7	499	7	15	0	3	0	1	0
Subtotal resection	137	1	115	1	20	0	1	0	1	0
Partial resection	353	16	222	7	84	3	18	3	29	3

(Continues)

TABLE 1 (Continued)

	All patients n = 1558	NF1 (n = 228)	No nonsurgical therapy		One nonsurgical therapy		Two nonsurgical therapies		≥3 nonsurgical therapies	
			All patients (n = 1078)[a]	NF1 (n = 92)	All patients (n = 332)	NF1 (n = 99)	All patients (n = 80)	NF1 (n = 23)	All patients (n = 68)	NF1 (n = 14)
Biopsy	255	30	79	1	108	15	42	8	26	6
Not known	2	1	2	1	0	0	0	0	0	0
No surgery	293	173	161	75	105	81	16	12	11	5
Extent of maximum surgery										
Complete resection	579	9	548	8	25	1	4	0	2	0
Subtotal resection	150	2	118	2	27	0	3	0	2	0
Partial resection	343	21	192	6	92	6	25	5	34	4
Biopsy	189	22	56	0	82	11	32	6	19	5
Not known	4	1	3	1	1	0	0	0	0	0
No surgery	293	173	161	75	105	81	16	12	11	5
Histology										
PA WHO-grade I[e]	841	47	581	14	170	15	43	11	47	7
DG WHO-grade II[f]	102	4	69	2	20	1	9	0	4	1
PXA WHO-grade II	14	0	11	0	3	0	0	0	0	0
Ganglioglioma WHO-grade I	143	0	122	0	13	0	5	0	3	0
DNT WHO-grade I	48	1	45	1	1	0	2	0	0	0
SEGA WHO-grade I	27	1	27	0	0	0	0	0	0	0
Other glioma[g]	70	1	50	0	14	1	4	0	2	0
No histology[h]	313	175	173	75	111	82	17	12	12	6
Observation time from diagnosis to last follow-up (y) (range)	9.2 (0.0-25.4)	9.8 (0.3-20.3)	8.8 (0.3-15.3)	9.0 (0.3-14.3)	10.7 (0.0-20.3)	11.3 (1.2-20.3)	10.1 (0.7-17.9)	8.9 (6.3-17.9)	9.8 (1.8-25.4)	9.6 (5.7-13.4)
Status at last follow-up										
Alive	1503	221	1064	92	317	96	67	20	55	13
Without tumor	618	10	574	8	38	2	5	0	1	0
With stable/regressing tumor	813	203	451	82	265	91	55	17	42	13
with progressive tumor	32	4	14	0	7	2	4	2	7	0
Evolution of high grade glioma	13	1	8	0	3	1	0	0	2	0
Not assessable	27	3	17	2	4	0	3	1	3	0
Dead	55	7	14	0	15	3	13	3	13	1
Tumor-/therapy-associated	27	2	4	0	7	0	6	1	10	1
Evolution of high grade glioma	13	1	3	0	3	0	5	1	2	0

TABLE 1 (Continued)

			No nonsurgical therapy		One nonsurgical therapy		Two nonsurgical therapies		≥3 nonsurgical therapies	
	All patients n = 1558	NF1 (n = 228)	All patients (n = 1078)[a]	NF1 (n = 92)	All patients (n = 332)	NF1 (n = 99)	All patients (n = 80)	NF1 (n = 23)	All patients (n = 68)	NF1 (n = 14)
Other cause of death	8	3	4	0	3	3	1	0	0	0
Cause of death not assessable	7	1	3	0	2	0	1	1	1	0

Abbreviations: DG, diffuse glioma; DNT, dysembryoplastic neuroepithelial tumor; NF1, neurofibromatosis type 1; NOS, not otherwise specified; PT, primary tumor; PXA, pleomorphic xanthoastrocytoma; SEGA, subependymal giant cell astrocytoma; SML, supratentorial midline.

[a]Administration of everolimus for subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis is not counted as chemotherapy – these patients are therefore assigned to this group.

[b]Including tumors of the lateral ventricles in 45 patients.

[c]Including thalamus, hypothalamus, basal ganglia, corpus callosum, mesencephalon.

[d]Including 2 patients with complete resection of primary tumor, but remaining meningeosis.

[e]Including pilomyxoid astrocytoma in 19 patients.

[f]Including diffuse astrocytoma, oligoastrocytoma, oligodendroglioma.

[g]Comprising: astrocytoma NOS (n = 21), desmoplastic infantile ganglioglioma/astrocytoma WHO-grade I (n = 12), angiocentric glioma WHO-grade I (n = 6), rosette-forming glioneuronal tumor WHO-grade I (n = 5), papillary glioneuronal tumor WHO-grade I (n = 1), low-grade glioma NOS (n = 25).

[h]Including 20 patients without evidence of tumor cells in the biopsy specimen and 2 further patients in which histology was not taken until 7 and 14 years after clinical diagnosis and revealed a high grade histology.

supratentorial midline (SML) (28%) and cerebral hemispheres (27%), while 87% of NF1-associated tumors evolved from the SML and affected the optic pathways in 78%.

Dissemination was detected in 75 patients (5%). Infants diagnosed within the first year of life were more likely to develop dissemination (17%) when compared to patients aged 1 to <8 years or ≥8 years (5% or 4%, respectively). Although dissemination was present in 13/36 infants with chiasmatic-hypothalamic LGG, it was seen in none of 39 infants with tumors in in other CNS regions (Figure S3). Just one NF1 patient developed secondary dissemination.

Histological diagnosis of a LGG was confirmed in 1245 patients (centrally reviewed: 1136), whereas 20 patients had inconclusive histological results and 293 were diagnosed upon radiological criteria only (173/293 NF1).

Progression to high-grade histology evolved in 26/1558 patients (2 NF1) after up to 14 years from first diagnosis, resulting in a 10-years malignant transformation rate measured from diagnosis of 1.8%. Malignant transformation occurred more often in spinal (4/54), caudal brainstem (4/117) and hemispheric tumors (11/359), but in none of 460 cerebellar tumors. Initial histologic diagnosis had been pilocytic astrocytoma WHO-grade I (PA) in 9, diffuse glioma WHO-grade II in 11 and ganglioglioma WHO-grade I in 4. Two patients with optic pathway glioma (1 NF1) underwent first tumor-related surgery for progression 6.1 and 14.0 years after radiological diagnosis, revealing high-grade histology. After malignant transformation, all patients followed high-grade glioma protocols and were censored for further analysis.

3.2 | Outcome data

3.2.1 | OS and current status

Median observation time was 9.2 years. OS was 98% at 5 years and 96% at 10 years; 55 patients died after median 3.9 years, one as late as 17.9 years from initial diagnosis. Survival was inferior for patients aged <1 year at diagnosis, with disseminated tumor, with tumor location in the caudal brainstem and spinal cord, and for patients without therapeutic surgery. Patients with early events within 18 months from start of first-line chemotherapy had a distinctly increased mortality (Table 2). At last follow-up, 1503/1558 patients were alive; median observation time for surviving patients was 9.3 years; median age at last contact was 17.6 years.

3.2.2 | Surgical and nonsurgical treatment from diagnosis

Until last follow-up, 1078 patients remained observed without initiation of nonsurgical treatment. Of these, 217 never underwent therapeutic surgery, whereas 707 and 124 had 1 or 2 surgeries, respectively. Another 30 patients had 3 to 6 therapeutic surgical interventions.

TABLE 2 Overall (OS) and event-free survival (EFS)

	OS				EFS		
	n	5 years (%) (SD)	10 years (%) (SD)	Log rank (*P* value)	n	5 years (%) (SD)	Log rank (*P* value)
All	1558	98.1 (0.4)	96.3 (0.5)	–	1558	54.1 (1.3)	–
Sex				.921			.259
Male	831	98.1 (0.5)	96.1 (0.7)		831	55.4 (1.8)	
Female	724	98.1 (0.5)	96.5 (0.7)		724	52.7 (1.9)	
Age at diagnosis				.001			<.001
<1 y	75	90.7 (3.4)	87.7 (3.9)		75	22.5 (5.0)	
≥1 to <8 y	735	98.2 (0.5)	96.7 (0.7)		735	48.8 (1.9)	
≥8 y	748	98.6 (0.4)	96.8 (0.7)		748	62.6 (1.8)	
Neurofibromatosis status[a]				.510			<.001
Non-NF1	1329	97.8 (0.4)	96.1 (0.6)		1329	57.4 (1.4)	
NF1	228	99.6 (0.4)	98.0 (1.0)		228	35.1 (3.2)	
Tumor location[b]				<.001			<.001
Cerebral hemispheres[c]	359	99.4 (0.4)	97.6 (1.0)		359	67.5 (2.6)	
Optic pathways	330	96.7 (1.0)	93.8 (1.4)		330	26.8 (2.5)	
SML outside the optic pathways[d]	237	96.6 (1.2)	94.8 (1.5)		237	44.4 (3.3)	
Cerebellum	460	99.8 (0.2)	99.8 (0.2)		460	74.2 (2.1)	
Caudal brainstem	117	96.6 (1.7)	91.7 (2.9)		117	39.3 (4.6)	
Spinal cord	54	92.6 (3.6)	92.6 (3.6)		54	38.5 (6.7)	
Dissemination status				<.001			<.001
No dissemination	1483	98.6 (0.3)	97.4 (0.5)		1483	56.5 (1.3)	
Dissemination	75	86.7 (3.9)	75.6 (5.3)		75	8.0 (3.1)	
Histology[e]				.033			.031
PA WHO grade I[f]	841	98.4 (0.4)	96.3 (0.7)		841	54.1 (1.7)	
Diffuse glioma WHO grade II	102	93.0 (2.5)	88.8 (3.4)		102	44.8 (5.1)	
PXA WHO grade II	14	100 (0.0)	100 (0.0)		14	50.0 (13.4)	
DNT WHO grade I	48	97.9 (2.1)	97.9 (2.1)		48	69.5 (6.8)	
Ganglioglioma WHO grade I	143	99.3 (0.7)	98.1 (1.4)		143	66.2 (4.0)	
Other	97	94.7 (2.3)	93.5 (2.6)		97	56.5 (5.3)	
Extent of first surgery[g,h]				<.001			<.001
Complete resection	518	99.4 (0.3)	98.4 (0.7)		496	83.6 (1.7)	
Subtotal resection	137	100	100		134	64.5 (4.2)	
Partial resection	353	97.1 (0.9)	93.5 (1.5)		335	44.1 (2.8)	
Biopsy	255	94.4 (1.5)	91.2 (1.8)		183	29.1 (3.4)	
Time to event after primary radiotherapy[i]				.682			–
Event ≤18 mo. after start of therapy	20	70.0 (10.2)	70.0 (10.2)			–	
Event >18 mo. after start of therapy	15	78.8 (11.0)	78.8 (11.0)			–	
Time to event after primary chemotherapy[i]				<.001			–
Event ≤18 mo. after start of therapy	55	65.4 (6.5)	52.9 (7.4)			–	
Event >18 mo. after start of therapy	121	94.3 (2.3)	92.2 (3.1)			–	

Abbreviations: DNT, dysembryoplastic neuroepithelial tumor; NF1, neurofibromatosis type 1; PA, pilocytic astrocytoma; PXA, pleomorphic xanthoastrocytoma; SML, supratentorial midline.

[a]Excluded: one male patient with neurofibromatosis type 2, radiological diagnosis of optic pathway glioma at the age of 12 years; he died of another tumor without nonsurgical therapy for his optic pathway glioma.

[b]Excluded: one patient whose primary tumor was not assessable.

[c]Including tumors of the lateral ventricles.

[d]Including thalamus, hypothalamus, basal ganglia, corpus callosum and mesencephalon.

[e]Excluded: 313 patients without histological diagnosis.

[f]Including: 19 patients with pilomyxoid astrocytoma.

[g]Excluded for OS: two patients with extent of surgery not assessable; OS calculated from date of surgery.

[h]Excluded for EFS: 115 patients with event prior to surgery, two patients with extent of surgery not assessable; EFS calculated from date of surgery.

[i]Including patients with event after start of nonsurgical therapy; OS calculated from date of event.

TABLE 3 Progression-free survival after first-line (PFS-1) and second-line chemotherapy (PFS-2)

	PFS-1				PFS-2[a]		
	n	3 years (%) (SD)	5 years (%) (SD)	Log rank (*P* value)	n	3 years (%) (SD)	Log rank (*P* value)
All[b]	307	65.7 (2.7)	53.2 (2.9)	—	96	28.1 (4.8)	—
Sex				.449			.573
Male	157	63.7 (3.8)	55.9 (4.0)		51	31.5 (6.7)	
Female	150	67.7 (3.8)	50.5 (4.1)		45	24.0 (7.0)	
Neurofibromatosis status				<.001			.007
Non-NF1	181	53.5 (3.7)	39.9 (3.7)		66	23.0 (5.3)	
NF1	126	83.2 (3.3)	72.4 (4.0)		30	40.3 (10.2)	
Age at diagnosis				<.001			.290
<1 y	37	37.8 (8.0)	24.3 (7.1)		25	18.8 (8.3)	
≥1 to <8 y	228	71.0 (3.0)	58.5 (3.3)		54	30.9 (6.7)	
≥8 y	42	61.2 (7.6)	50.8 (7.9)		17	33.1 (11.8)	
Age at start of first-line therapy				<.001			.114
<1 y	29	24.1 (7.9)	10.3 (5.7)		22	18.2 (8.2)	
≥1 to <8 y	206	70.9 (3.2)	58.1 (3.4)		53	31.1 (6.9)	
≥8 y	72	67.7 (5.6)	57.2 (5.9)		21	31.7 (10.4)	
Tumor location[c]				.433			.083
Cerebral hemispheres	11	72.7 (13.4)	54.5 (15.0)		1	0 events[d]	
Optic pathways	188	66.8 (3.4)	53.1 (3.7)		65	27.4 (5.9)	
SML outside the optic pathways[e]	46	63.0 (7.1)	54.0 (7.4)		14	42.9 (13.2)	
Cerebellum	11	81.8 (11.6)	81.8 (11.6)		2	1 event[d]	
Caudal brainstem	40	57.4 (7.8)	44.3 (7.9)		10	0.0	
Spinal cord	10	60.0 (15.5)	60.0 (15.5)		3	2 events[d]	
Dissemination status				<.001			.067
No dissemination	261	72.3 (2.8)	60.4 (3.1)		65	30.6 (6.2)	
Dissemination	46	28.3 (6.6)	12.2 (5.0)		31	22.6 (7.5)	
Histology[f]				.698			.469
PA WHO-grade I[g]	151	50.7 (4.1)	36.9 (4.0)		60	21.8 (5.5)	
Diffuse glioma WHO-grade II	14	50.0 (13.4)	35.7 (12.8)		6	0.0	
Ganglioglioma WHO-grade I[h]	7	57.1 (18.7)	28.6 (17.1)		7	28.6 (17.1)	
Other[h]	15	60.0 (12.6)	53.3 (12.9)				
Extent of maximum surgery before start of first-line chemotherapy				<.001			—
Complete resection	6	83.3 (15.2)	83.3 (15.2)			—	
Subtotal resection	13	76.9 (11.7)	76.9 (11.7)			—	
Partial resection	75	60.0 (5.7)	42.3 (5.7)			—	
Biopsy	65	47.2 (6.2)	37.4 (6.1)			—	
None	148	74.9 (3.6)	62.4 (4.0)			—	
Time from diagnosis to first treatment				<.001			.560
<3 mo.	133	49.2 (4.4)	36.6 (4.2)		57	24.0 (5.9)	
3 to <12 mo.	74	78.4 (4.8)	70.3 (5.3)		16	16.7 (9.9)	
12 to <24 mo.	33	72.7 (7.8)	57.4 (8.6)		9	50.0 (17.7)	
2 to <5 y[i]	46	82.5 (5.6)	64.2 (7.2)		14	47.6 (14.0)	
≥5 y[i]	21	76.2 (9.3)	66.7 (10.3)				

(Continues)

TABLE 3 (Continued)

		PFS-1			PFS-2[a]		
		n	3 years (%) (SD)	5 years (%) (SD)	Log rank (*P* value)	n	3 years (%) (SD)	Log rank (*P* value)
Type of second-line chemotherapy								.291
Platinum-based combinations[j]						56	24.1 (5.8)	
Vinblastine mono						28	27.7 (9.6)	
All others						12	53.0 (15.5)	
Type of second-line chemotherapy with respect to NF status								.005
Platinum-based combinations[j]	Non-NF1 patients					46	23.9 (6.3)	
	NF1 patients					10	18.0 (15.1)	
Vinblastine mono	Non-NF1 patients					12	8.3 (8.0)	
	NF1 patients					16	47.9 (14.4)	
All others	Non-NF1 patients					8	50.0 (17.7)	
	NF1 patients					4	66.7 (27.2)	

Abbreviations: n.a., not applicable; NF1, neurofibromatosis type 1; PA, pilocytic astrocytoma; SML, supratentorial midline.
[a]First-line chemo- or radiotherapy.
[b]Excluded for missing follow-up data following the start of therapy: one patient for PFS-1, three patients for PFS-2.
[c]Excluded: one patient whose primary tumor was not assessable.
[d]Not included in analysis due to small group size; the number of events up to Year 3 is indicated.
[e]Including thalamus, hypothalamus, basal ganglia, corpus callosum and mesencephalon.
[f]Excluded: 120 patients without histological diagnosis (PFS-1), 23 patients (PFS-2).
[g]Included: 14 patients with pilomyxoid astrocytoma (PFS-1), nine patients (PFS-2).
[h]Pooled for analysis of PFS-2: three patients with ganglioglioma WHO-grade I and four patients with other histologies.
[i]Pooled for analysis of PFS-2: all patients with time since diagnosis to first treatment ≥2 years.
[j]Including: vincristine/carboplatin ± etoposide; vincristine/cyclophosphamide/cisplatin.

A total of 480 patients had at least one nonsurgical therapy (261 after prior radiologic progression). Of these, 332 patients received 1, 80 patients 2 and 68 patients 3 or more nonsurgical treatment lines (Figure 1).

Prior to first adjuvant treatment, 170/480 patients had 1 to 4 therapeutic surgeries, while in 45/480 patients without up-front tumor reduction, it was eventually performed after 1 to 4 nonsurgical therapies. Still, 265/480 patients never had any surgical tumor volume reduction (226/265 SML, 163 of these in the optic pathways). Modes of applied treatments and indications for first nonsurgical therapy are displayed in Tables S1 and S2.

Most of the total of 1382 therapeutic surgeries was performed for tumors in the cerebral hemispheres (391/1382; 28%) and cerebellum (552/1382; 40%). At times, complete resection required repeated interventions and was achieved in 579 patients; the majority had tumors in the cerebral hemispheres (206/579; 36%) or cerebellum (314/579; 54%).

Within the observation time, a total of 730 nonsurgical therapies were applied. The majority was given to patients with optic pathway glioma (OPG; 394/730; 54%), with tumors in the SML outside the optic pathways (ie, thalamus, hypothalamus, basal ganglia, corpus callosum, mesencephalon; 143/730; 20%) or the caudal brainstem (87/730; 12%) (Table S3).

3.2.3 | Event-free survival

With a median follow-up of 8.3 years to last neuroimaging, EFS was 54% at 5 years and 49% at 10 years for the entire cohort (range: 0.0-13.4 years). EFS was lower in patients aged <1 year, with OPG, with dissemination and with a lesser extent of first resection (Table 2). At last follow-up, 809/1558 patients were alive without event after complete (n = 422), subtotal (n = 80) or partial (n = 123) tumor resection, or without therapeutic surgery (n = 182; extent or resection unknown: n = 2).

3.2.4 | Treatment following first event

During follow-up, 749/1558 patients experienced an event, which was start of first nonsurgical therapy in 219 (14%) and radiological progression/relapse in 508 (33%), associated with malignant transformation in another 11 (1%) and 11 patients (1%) died (tumor progression: 2, diencephalic dysfunction after complete tumor resection: 2, major seizure: 1, sepsis: 2, malignant peripheral nerve sheath tumor: 1, unknown reason: 3).

Progression/relapse occurred up to 13.4 years from diagnosis and was seen in 80/508 patients after initial complete resection, in 225 after prior debulking, while 203 had been observed without therapeu-

TABLE 4 Progression-free survival after first-line (PFS-1) and second-line radiotherapy (PFS-2)

	PFS-1			PFS-2[a]		
	n	5 years (%) (SD)	Log rank (*P* value)	n	5 years (%) (SD)	Log rank (*P* value)
All[b]	171	80.1 (3.2)	—	46	48.7 (7.7)	—
Sex			.923			.097
Male	91	78.8 (4.5)		20	36.9 (11.3)	
Female	80	81.6 (4.5)		26	58.1 (10.2)	
Neurofibromatosis status			.978			.056
Non-NF1	162	79.6 (3.3)		41	52.4 (8.2)	
NF1	9	88.9 (10.5)		5	20.0 (17.9)	
Age at diagnosis			.038			.882
<1 y	5	30.0 (23.9)		2	2 events[c]	
≥1 to <8 y	56	85.3 (4.8)		36	49.9 (8.6)	
≥8 y	110	79.6 (4.0)		8	60.0 (18.2)	
Age at start of first non-surgical therapy			.686			.463
<1 y	2	2 events[c]		2	2 events[c]	
≥1 to <8 y	29	86.2 (6.4)		32	53.1 (9.2)	
≥8 y	140	80.2 (3.5)		12	46.9 (15.0)	
Tumor location			.200			.913
Cerebral hemispheres	19	68.4 (10.7)		3	1 event[c]	
Optic pathways	45	77.3 (6.3)		20	47.8 (11.5)	
SML outside the optic pathways[d]	57	81.2 (5.4)		12	38.7 (16.3)	
Cerebellum	21	95.0 (4.9)		2	1 event[c]	
Caudal brainstem	18	82.4 (9.2)		7	57.1 (18.7)	
Spinal cord	11	75.0 (15.8)		2	1 event[c]	
Dissemination status			<.001			.004
No dissemination	156	83.3 (3.0)		38	53.9 (8.6)	
Dissemination	15	36.2 (15.4)		8	25.0 (15.3)	
Histology[e]			.001			.371
PA WHO grade I[f]	109	82.4 (3.8)		28	44.2 (9.7)	
Diffuse glioma WHO grade II	19	77.8 (9.8)		7	50.0 (20.4)	
Ganglioglioma WHO grade I[g]	14	46.2 (13.8)		7	33.3 (19.2)	
Other[g]	10	77.8 (13.9)				
Extent of maximum surgery before start of first-line radiotherapy			.941			—
Complete resection	13	76.2 (12.1)			—	
Subtotal resection	10	80.0 (12.6)			—	
Partial resection	52	79.2 (5.9)			—	
Biopsy	56	83.0 (5.2)			—	
None	40	78.6 (6.7)			—	
Time from diagnosis to first treatment			.960			.009
<3 mo.	49	80.7 (5.8)		24	61.4 (10.2)	
3 to <12 mo.	34	81.3 (6.9)		10	53.3 (17.6)	
12 to <24 mo.[h]	19	78.9 (9.4)		12	18.5 (11.8)	
2 to <5 y[h]	42	81.6 (6.3)				
≥5 y[h]	27	77.0 (8.3)				
Mode of radiotherapy			.516			—
Interstitial radiosurgery (brachytherapy)	59	83.9 (4.9)			—	

(Continues)

TABLE 4 (Continued)

	PFS-1			PFS-2[a]		
	n	5 years (%) (SD)	Log rank (*P* value)	n	5 years (%) (SD)	Log rank (*P* value)
Photon-beam therapy, focal	93	81.9 (4.1)			—	
Proton-beam therapy, focal	15	70.6 (12.6)			—	

Abbreviations: NF1, neurofibromatosis type 1; PA, pilocytic astrocytoma; SML, supratentorial midline.
[a]After first-line chemotherapy.
[b]Excluded for missing follow-up data following the start of therapy: one patient for PFS-1, three patients for PFS-2.
[c]Not included in analysis due to small group size; only the number of events up to Year 5 is indicated.
[d]Including thamalus, hypothalamus, basal ganglia, corpus callosum, mesencephalon.
[e]Excluded: 19 patients without histological diagnosis (PFS-1), four patients (PFS-2).
[f]Included: three patients with pilomyxoid astrocytoma (PFS-1), one patient with pilomyxoid astrocytoma (PFS-2).
[g]Pooled for analysis of PFS-2: four patients with ganglioglioma WHO-grade I and three patients with other histologies.
[h]Pooled for analysis of PFS-2: all patients with time since diagnosis to first treatment ≥12 months.

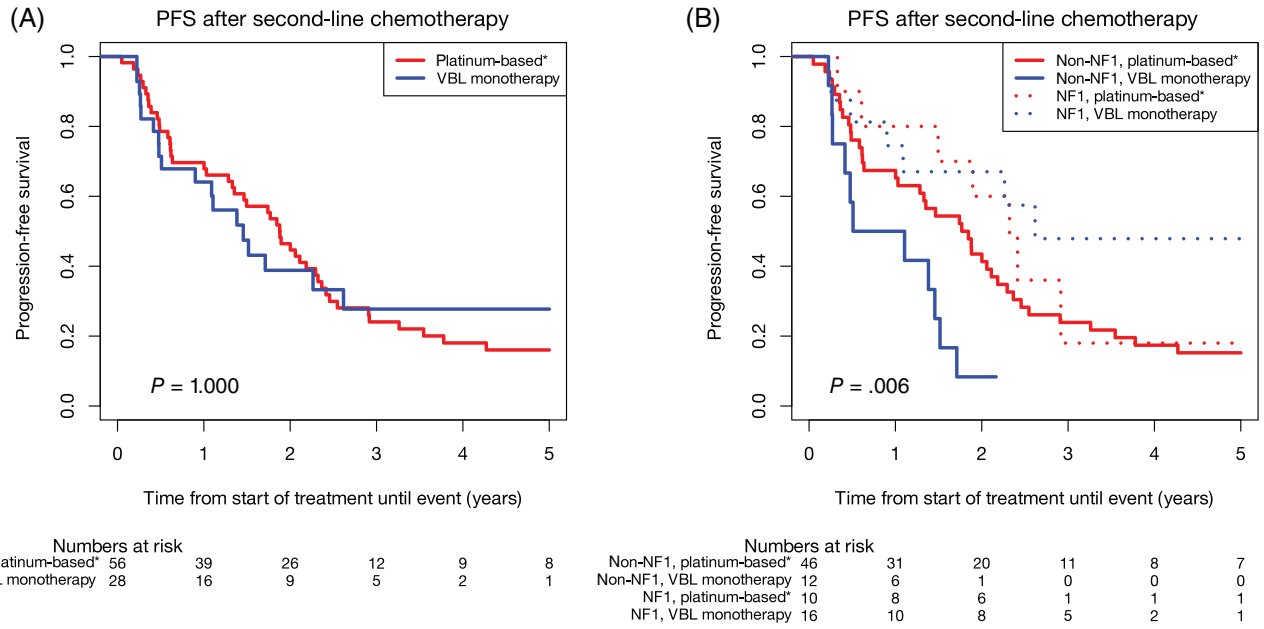

FIGURE 2 PFS after second-line chemotherapy. A, For platinum-based* vs VBL monotherapy; B, for platinum-based* vs VBL monotherapy and for NF1 status. * including: vincristine/carboplatin ± etoposide and vincristine/cyclophosphamide/cisplatin; results for other regimen are not shown due to small group size. NF1, neurofibromatosis type 1; PFS, progression-free survival; VBL, vinblastine

tic surgery (62 with biopsy). Following progression/relapse, 139/508 patients had further debulking and 105 remained observed only, whereas 261 patients received first-line nonsurgical therapy; for three patients no information was available (Figure 1).

Thus, nonsurgical treatment was given to 480/1558 patients defined as first event for 219 patients and following progression/relapse in 261.

3.2.5 | Progression-free survival after first nonsurgical therapy (PFS-1)

With a median follow-up of 8.5 years (range: 0.0-14.6 years) from start of therapy to last neuroimaging, 5-years PFS-1 was 53% after first-line chemotherapy and 80% after first-line radiotherapy. PFS-1 following chemotherapy was noticeably higher for NF1-associated tumors. It was lower for patients with dissemination and for patients who started treatment within the first year of life. For patients with chemotherapy, 5-years-PFS-1 was lower for those with lesser extent of resection and for those who started therapy within 3 months after diagnosis, whereas PFS-1 after primary radiotherapy was neither associated with the extent of prior resection nor with the interval between diagnosis and start of treatment. PFS-1 after primary radiotherapy did not differ with respect to radiation mode (Tables 3 and 4).

Multivariable analysis confirmed four prognostic factors for an event: (a) following first-line chemotherapy: non-NF1 status, start of chemotherapy within 3 months of diagnosis and disseminated tumors

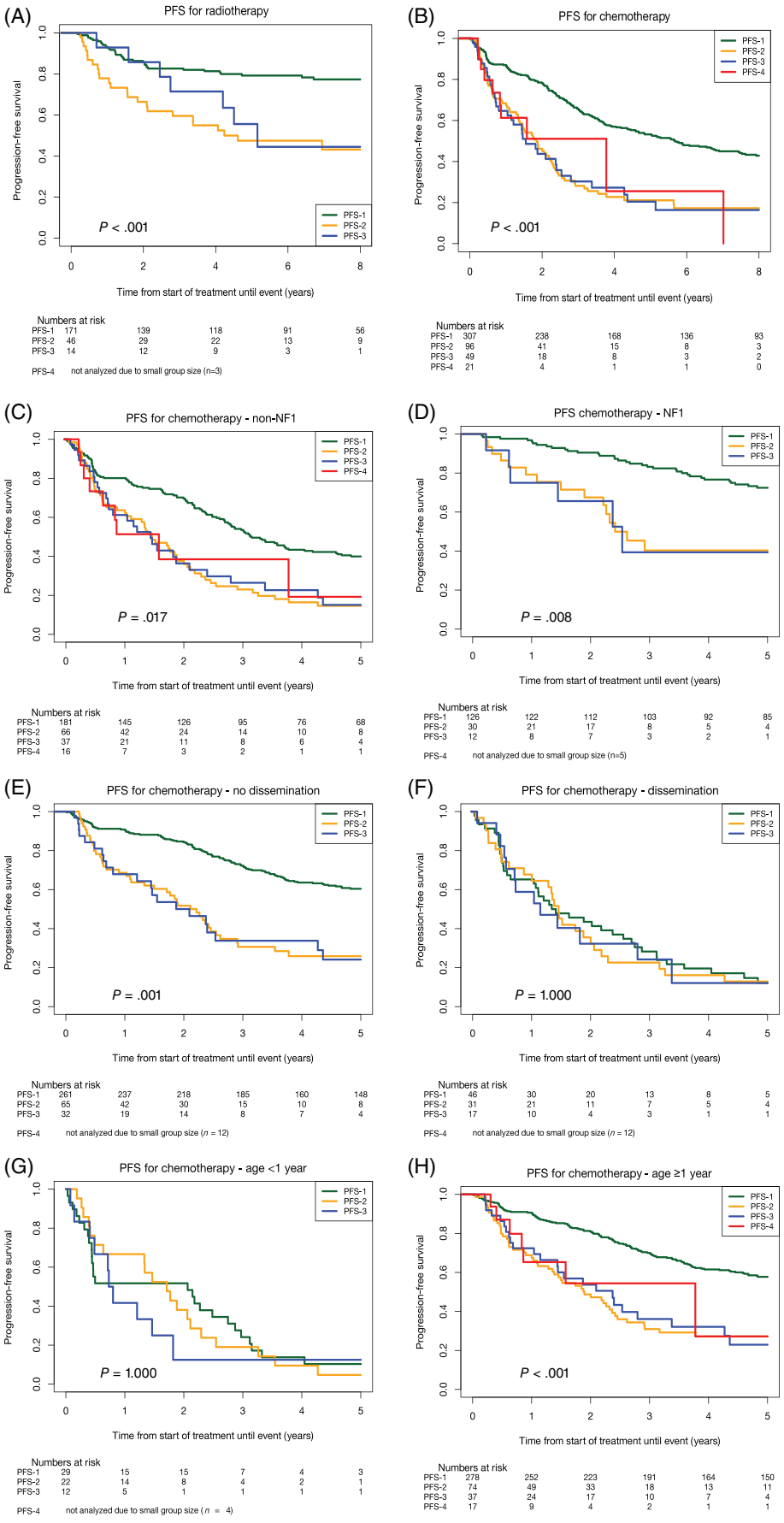

FIGURE 3 PFS for first-line and rescue (second-line, third-line and forth-line) therapies. A, PFS for radiation (irrespective of the modality of previous treatments); B, PFS for chemotherapy (irrespective of the modality of previous treatments); C, PFS for chemotherapy for non-NF1 patients; D, PFS for chemotherapy for NF1 patients; E, PFS for chemotherapy for patients without tumor dissemination; F, PFS for chemotherapy for patients with disseminated tumor; G, PFS for chemotherapy for patients aged < 1 year at start of first treatment; H, PFS for chemotherapy for patients aged ≥ 1 year at start of first treatment. NF1, neurofibromatosis type 1; PFS, progression-free survival

($P < .001$; HR 2.95; CI 2.02-4.30, vs no dissemination); (b) following first-line radiotherapy: ganglioglioma ($P = .010$; HR 4.20; CI 1.81-9.75, vs PA) (Table S4).

3.2.6 | Treatment following first nonsurgical therapy

Following first nonsurgical therapy, 262/480 patients stayed observed without further event. Tumor progression occurred in 194 patients at an interval of up to 14.1 years, associated with malignant transformation in another six. Seven patients were censored for further analysis as second-line treatment was started without radiological or clinical progression. Eleven patients died (primary tumor: 4, sepsis: 2, other malignant neoplasia associated with NF1: 3, unknown reason: 2).

Following progression, 22/194 had further tumor surgery and 18 remained observed with spontaneous tumor stabilization, whereas 148 patients received second-line nonsurgical therapy; for six patients no information was available (Figure 1). Median time from progression to start of second-line therapy was 0.17 years (range: 0.0-6.8 years).

3.2.7 | Progression-free survival after second nonsurgical therapy (PFS-2)

With a median follow-up of 5.7 years (range: 0.0-13.1 years) from start of second therapy to last neuroimaging, PFS-2 was 28% at 3 years for all patients receiving second-line chemotherapy and 49% at 5 years for patients receiving radiation as second-line treatment.

After second-line chemotherapy, 3-years PFS-2 differed with respect to NF1 status (Table 3). No relevant differences in PFS-2 were seen with respect to age at diagnosis, age at start of first treatment, dissemination or time from diagnosis to first nonsurgical treatment. The mode of pretreatment did not affect PFS-2 after second-line chemotherapy, being 33% or 27% at 3 years after first-line-radiotherapy or first-line chemotherapy, respectively.

The choice of the chemotherapeutic regimen for second-line treatment did not influence PFS-2, if the cohort was analyzed in its entirety. Yet, 3-years PFS-2 after therapy with vinblastine reached 48% for patients with NF1, but dropped to 8% for non-NF1 patients (Table 3, Figure 2A,B). Multivariable analysis confirmed a noticeably higher risk for progression following vinblastine monotherapy salvage approach in non-NF1 patients when compared to vincristine/carboplatin or vincristine/cisplatin/cyclophosphamide treatment ($P = .003$; HR 2.80; CI 1.43-5.50) (Table S4).

After second-line radiotherapy, 5-years PFS-2 reached 49% for all. It was lower for patients with disseminated tumors, but did not show differences with respect to tumor location or histology (Table 4).

3.2.8 | Subsequent treatment following second nonsurgical therapy

Following second nonsurgical therapy, 47/148 patients stayed observed without further event. Tumor progression was diagnosed in 86 patients at an interval of up to 8.1 years, associated with malignant transformation in another five. Two patients were censored for further analysis as third-line therapy was started without radiological or clinical progression. Eight patients died (primary tumor: 6, seizures: 1, unknown reason: 1).

Following tumor progression, 10/86 patients underwent therapeutic tumor surgery, whereas seven remained observed with spontaneous tumor stabilization (in 1/7 patient the tumor progressed again after a 10-years interval); for one patient, no information was available. In 68 patients, third-line adjuvant treatment was started. Median time from progression to start of third-line therapy was 0.1 years (range: 0.0-3.5 years).

3.2.9 | Progression-free survival after first (PFS-1), second (PFS-2), third (PFS-3) or further rescue treatments for sequence of treatments

PFS changed with progressing treatments (Figure 3A-H): Three-years PFS was 66% after first-line chemotherapy (PFS-1), but dropped to 28% after second-line chemotherapy (PFS-2). Subsequent chemotherapies reached a PFS in the same range. This pattern was modified slightly by the modality of previous treatments (ie, radiation or chemotherapy). Three-years PFS-3 was 30% for all patients with third-line chemotherapy, but was lower for patients being pretreated with two chemotherapies (26%) in contrast to patients who had received radiotherapy as part of their prior treatments (42%) (Table S5). A similar trend was seen in patients with NF1-associated tumors after multiple rescue chemotherapies, but at a higher level for all PFS-curves: PFS-1 was higher compared to PFS after rescue therapies, which were quite parallel for second- and third-line chemotherapy ranging from 39% to 47% (Table S5). Of note, for patients with tumor dissemination or age < 1 year at start of first treatment, PFS-1 was already as low as PFS-2 and PFS-3. Small sample size precluded further analysis of a possible impact of histology or tumor location.

Five-years PFS was 80% after first-line radiotherapy (PFS-1) and dropped to 49% for second-line radiotherapy after prior chemotherapy (PFS-2), but did not decrease further after two or more prior chemotherapies (Table S6). Further subgroup analyses for rescue radiotherapy could not be performed due to small patient numbers.

4 | DISCUSSION

This report presents the first population-based, prospectively registered pediatric LGG cohort which allowed long-term analysis of the course of disease focusing upon repeatedly progressing tumors within

a comprehensive treatment strategy. The sequence of surgical and nonsurgical therapies in our cohort mirrored tumor location with emphasis of surgical therapy for cerebral hemispheric and cerebellar LGG, whereas SML tumors including OPG were predominantly treated nonsurgically.

4.1 | Initial management

Our cohort was comparable to previously published series with respect to age distribution, sex and portion of NF1 as well as distribution of tumor sites and the various low-grade histologies and 10-years OS above 95%.[1,2,14,29]

Corroborating previous series, the extent of tumor removal impacted strikingly upon overall and EFS. Progression was less frequent in cerebellar and hemispheric sites than in LGG of the SML, caudal brainstem or spinal cord where limited surgical approaches resulted in mostly incompletely resected LGG.[1,14,34-36] Yet, relapse in our cohort was observed in one out of six patients even after complete resection, implying an invasive growth pattern on the microscopic level even in LGG.[37,38] Though there was a trend for more frequent progressions/relapses in pediatric LGG WHO-grade II and less in glioneuronal tumors, the impact of histology has to be related to its frequency at certain tumor sites.[1,14,29] Nonetheless, the majority of our patients (69%) with LGG at all CNS sites remained observed without need of nonsurgical treatment following diagnosis with or without any tumor-related therapeutic surgery.

Radiologic tumor progression or severe or progressive neurologic, ophthalmologic or clinical symptoms prompted nonsurgical treatment in 31% of all patients corresponding to the fraction reported in previous population-based[1,2] or large institutional[29,34] cohorts. Of note, more than a third of patients receiving adjuvant therapy had up to four prior attempts of surgical tumor removal, whereas resection during the further course was attempted in less than 10%. Nevertheless, in the course of the cascade of treatment lines, growth arrest was reached for a third of patients at each stage. Even tumors with intermittent progressions did not always prompt further intervention but stabilized spontaneously in some patients.

4.2 | First-line nonsurgical treatment

Current treatment strategies schedule chemotherapy as first-line adjuvant treatment at least for the younger patients to avoid or defer radiotherapy,[2,5,6,8,10,15] reflected in a share of 64% receiving first-line vincristine/carboplatin chemotherapy in our cohort, whereas 36% had first-line radiotherapy. Besides being younger, the chemotherapy cohort comprised patients with disseminated tumors, representing 36% of those <1 year at diagnosis with LGG of the optic pathways. This corroborates previous data of a cohort of disseminated LGG; 24/28 patients with nonsurgical treatment received first-line chemotherapy, eight of these being infants.[39]

PFS following front-line radiotherapy was 80% at 5 years in our cohort confirming results of previous series with 70% to 85% 5-years PFS.[12,13,21,40] PFS did not differ between the radiation modalities, but was lower for patients with ganglioglioma or disseminated disease. The extent of prior resection did not impact upon the risk of progression or death in our cohort. Larger tumor size trended with a higher progression rate in the ACNS0221-study. Both tumor size and nonpilocytic histology were associated with compromised survival, yet only 49/85 patients had radiation as first-line treatment.[13]

First-line chemotherapy is associated with a higher initial progression rate resulting in 5-years PFS between 34% and 60% for various regimens[2,5,6,8,10,15] and was 53% for vincristine/carboplatin (+/− etoposide) in our cohort. As previously reported, progression was more frequent among patients with dissemination and very young patients, especially if treatment started early after diagnosis or within the first year of life.[1,2,6,15,39,41] Although smaller postsurgical residues prior to the start of chemotherapy proved favorable for PFS, surgery-associated morbidity should preclude the attempt of radical resection in critical regions.[36,42,43]

Mortality for the entire cohort was increased for patients experiencing progression during or early after first chemotherapy. This expands the result from the European randomized chemotherapy trial, identifying progression at Week 24 as most important risk factor for death.[15] This aspect has not been detailed by de Haas et al although their OS was in the same range as for our subgroup.[16]

4.3 | Salvage chemotherapy

Our data confirm the feasibility to apply consecutive lines of chemotherapy to further postpone radiation, as has been demonstrated by others.[16,17] Yet, PFS following second-, third- or fourth-line treatment dropped to less than half compared to first-line—irrespective of the choice of the successive chemotherapy regimens. Of note, PFS remained in a comparable range for later treatment lines independent from the modality of the prior treatment (chemo- or radiotherapy). This contrasts sharply with the results from Scheinemann et al, where progression rates were comparable for first- and second-line chemotherapy (5-years PFS-2 was 37% ± 8%) and did not reveal changes upon further progressions either.[17] In addition, their patient cohort was younger both at diagnosis and progression and their relapsed cohort only comprised 4/38 patients with NF1. Thus, Scheinemann's cohort was enriched for subgroups for which our results predicted an inferior outcome. Though, in the report of de Haas et al, PFS following salvage chemotherapy showed a decline similar to our results in 44 patients with relapse following Baby Brain protocol of the French Society of Pediatric Oncology (BBSFOP) first-line treatment.[5,16]

The decline of PFS between first and subsequent treatment lines was not seen in our patient groups with tumor dissemination or age < 1 year at diagnosis, specifically for infants starting their initial treatment within the first year of life. For them, PFS following first-line treatment was very low already and did not drop further. This corresponds to the results of Laithier et al and de Haas et al.[16,17] For the

subgroup of 26 infants, PFS was 34% at 3 years following first-line chemotherapy[5] corresponding to the PFS in the report of de Haas et al.[16] The relapsed BBSFOP cohort included 17/44 infants at diagnosis and half of the patients were still younger than 5 years at first relapse.[16]

In our cohort, lower PFS was only seen in infants with OPG, whereas infants with tumors in other regions of the brain (cerebellum, cerebral hemispheres, mesencephalon) had an outcome equivalent to older children and their tumors did not develop dissemination. This aspect was not detailed in the literature so far.

Of note, PFS following third-line chemotherapy was better if radiotherapy had been part of the prior sequence of treatments, specifically in the non-NF1 cohort. We do not know whether reactions to the radiation interfered with the interpretation of tumor response vs growth on MRI and prompted premature initiation of the next rescue chemotherapy[44]; however, the disparate distribution of risk factors precludes direct comparison. Although more than half of the patients in the "chemotherapy-only" group were infants and/or had disseminated tumors, the group with prior chemo- and radiotherapy included no infants and only three patients with dissemination, and thus, comprised less patients with high risk for progression.

The type and sequence of the most commonly used chemotherapy regimens[2,6,9,10,15,27,45] reached comparable PFS in the salvage settings for our patients with just one exception. Although vinblastine monotherapy achieved a satisfactory PFS for patients with NF1-associated tumors, this was not the case for patients with sporadic LGG. This effect had been observed in a small number of relapsed patients and following primary treatment, as well.[8,9] For non-NF1 patients, PFS after second-line treatment was noticeably inferior for vinblastine monotherapy as compared to all platinum-based combination regimens in the multivariate analysis. This result is in contrast to the report of Scheinemann et al.[17] The majority of their relapsed patients had been pretreated with carboplatin with or without vincristine (32/38) and received vinblastine as salvage therapy (23/38).

4.4 | Salvage radiotherapy

During the observation time of up to 25 years from diagnosis, just 64 patients of the chemotherapy-first group received radiotherapy, resulting in "radiotherapy-free" survival of 81% at 5 years and 71% at 10 years corresponding to previous reports[5,8,10] (Table S7). Due to the decreasing number of patients throughout time, our analysis cannot answer the potential role of early radiotherapy for patients at risk for multiple progressions following chemotherapy.

A higher risk for earlier progression following first and further lines of chemotherapy raised debate about an earlier positioning of radiotherapy to prevent the detrimental effect of progressive disease.[46,47] Modern photon and proton therapy reduce the radiation dose to developing brain tissue, diminishing toxicities without compromising disease control. Still, cognitive, endocrine and clinical late effects have been reported for highly conformal therapies but not in older children and after reduced doses to organs at risk.[13,18,40] Currently, limitation of its use in young children is recommended.[13,22,48]

Contrasting the report of Mueller et al[21] with an equivalent outcome for patients with PA following radiotherapy as first-line or salvage treatment, our data stress a decline for 5-years PFS from 80.1% for first-line radiotherapy to 48.7% after second- and 51.3% for third-line and successive lines, as well. This pattern has been described previously[23] and appears comparable, though on a higher level, to the decline of PFS after salvage chemotherapy.

Just recently, Acharya et al recommended early radiation for a high-risk group defined as patients with diffuse astrocytoma and/or midbrain/thalamic tumors, since delayed radiotherapy after at least one line of chemotherapy was associated with a significant decrement in OS in their cohort.[47] Yet, their series did not comprise disseminated and spinal LGG and very young patients and is thus not comparable to our cohort. Of note, a higher risk for progression was retained in the chemotherapy-pretreated patients with disseminated tumors and after early start of first treatment. We would argue that the decline of PFS after salvage therapy mirrors the selection of more aggressive tumors needing multiple treatment-lines for disease control, for chemo- and radiotherapy alike.

4.5 | Response to salvage treatment and biology

We would not interpret the shorter PFS time after salvage therapy (irrespective of the type of previous treatment) as tumor resistance in the wake of pretreatment. The pattern rather corresponds to more aggressive tumor types not identifiable by conventional histologic criteria, up to now.[38,49-53] Disseminated PAs of the optic pathways in infants constitute the largest portion of this high-risk group with (frequent) early progression and impaired OS. Unfortunately, no tissue for molecular analysis had been secured from our patients. Risk stratification of pediatric LGG by molecular findings could associate clinical features like age, sex, tumor site, extent of resection and histology with distinct molecular patterns and survival parameters in a large retrospectively collected cohort,[50] but patients did not follow a defined treatment algorithm. Similarly, progression to high-grade histology, which occurred predominantly, but not exclusively, in diffuse glioma WHO-grade II,[33] may be anticipated in the presence of specific molecular genetic changes.[50,54]

4.6 | Neurofibromatosis type 1

Patients with NF1-associated LGG constituted 15% of the entire patient group, comparable to other reports[1,2,5,8]; their median age at diagnosis was almost 3 years below the non-NF1 cohort. More than half of NF1-associated tumors (60%) were progressive or received adjuvant treatment early after diagnosis, resulting in 5-years EFS of 35%. This apparently opposes the 5-years EFS of 57% for non-NF1 patients. Yet, in line with previous findings,[55] the majority of NF1-associated tumors were located in regions hardly amenable for

therapeutic surgery (77% in the optic pathways, 9% in other SML structures, 6% in the caudal brainstem) increasing the need for non-surgical interventions.

If only OPG are considered, patients with NF1-associated tumors received treatment less often (63%) as compared to those with sporadic OPG (81%), possibly reflecting a less aggressive growth behavior. Since NF1 patients are not systematically registered in Germany, we also assume a registration bias for NF1-associated OPG. In addition, the cohort of sporadic OPG is enriched for infants with diencephalic syndrome and dissemination; however, these data should not mislead to postpone the start of treatment in symptomatic patients. In line with others,[56] almost three quarters of our OPG patients started adjuvant treatment for visual impairment. Long-term survival did not differ with respect to NF1 status.

Corroborating previous reports, PFS following first-line vincristine/carboplatin chemotherapy was noticeably higher for NF1 patients compared to non-NF1 patients.[2,7,8] But as for non-NF1 patients, PFS dropped to half after further lines of rescue chemotherapy for NF1-associated tumors, though the absolute level remained higher and no specific risk factors were obvious. Salvage radiotherapy was used exceptionally only, but was less effective in extensive tumors.

Molecular genetic data point to specific mutations in addition to the underlying NF1-gene mutation which may herald an unfavorable course of disease.[57] Since the quest for molecular data to identify patients at risk for multiple progressions requires submission of adequate tumor tissue, even NF1-associated OPG may need biopsy in the future.

4.7 | Limitations of our study

Our analysis has a pertinent shortcoming: The initial SIOP-LGG 2004 study focused upon first-line chemotherapy within the randomized trial and not upon multiple lines of treatment or the comparison of late effects of chemo- vs radiotherapy. The study collected only limited data on salvage therapies with respect to response assessment and toxicity, clinical sequelae and late effects, and neuropsychological development.

We also lack molecular-neuropathological data for most patients, though they have been reported for the subgroup of diffuse glioma WHO-grade II.[33]

A comparison of the efficacy of the three major radiation techniques is beyond the scope of this report; the choice of the treatment option was determined by individual tumor and patient characteristics and accessibility.

5 | CONCLUSION

The majority of pediatric LGG patients can be successfully managed within the current European treatment recommendations including first- and further-line options. Results of first-line treatment confirm previously identified risk factors like young age at diagnosis or start of treatment, tumor dissemination or early treatment failure.

Patients progressing after front-line adjuvant treatment are at risk of suffering multiple subsequent progressions, many of whom carry up-front identified risk factors. Those base cases may contribute to lower PFS rates with subsequent treatments. Nevertheless, a portion of progressing tumors may stabilize spontaneously.

Customized treatment strategies including the careful consideration of surgical and nonsurgical interventions have to be tailored for tumor site, age and other epidemiologic preconditions and must be decided in a multidisciplinary approach repeatedly during follow-up. In view of the often "chronic" nature of LGG, each patient is entitled to a thorough assessment of possible benefits vs their long-term sequelae throughout the whole course of different treatments.

Our results do not set priority to a certain sequence of specific treatment options, since none proved superior in preventing another progression. Rather, all can be aligned as portfolio of choices which need balancing risks and benefits of each element. Although vinblastine monotherapy may be the more effective regimen for NF1-associated tumors, non-NF1 patients seem to profit from platinum-based combination regimens—at least when given second-line. A randomized comparison has to test this assumption.

Patients without NF1, with disseminated tumors or those requiring therapy early after diagnosis are at risk for multiple progressions requiring repeated treatments. Further research including the correlation of molecular-genetic and clinical data has to carve out the determinants of this tumor biology. Since pediatric LGG has to be regarded as a chronic, life-long disease for a large portion of patients, a population-based registry covering a broad range of clinical aspects should accompany all randomized trials, for which only a small subgroup will be eligible.

ACKNOWLEDGMENTS

Open access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST

O. W. has contracts for AdBoards and consultancy with Novartis, Roche, BMG, SK Life science, Janssen and receives a research grant from BVD. The other authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data sets for the current study are available from the corresponding author on reasonable request.

ETHICS STATEMENT

Informed consent was obtained from patients, parents and/or guardians. The SIOP-LGG 2004 study observed the Declaration of Helsinki in its revised version (Edinburgh, Scotland, 2000), the WHO and EC rules of "Good Clinical Practice" (effective 17 January 1997), and was ethically approved. It was registered at ClinicalTrials.gov PRS NCT00276640, EudraCT number 2005-005377-29.

ORCID

Daniela Kandels https://orcid.org/0000-0002-8631-868X

Pablo Hernáiz Driever https://orcid.org/0000-0003-3135-3872

REFERENCES

1. Stokland T, Liu JF, Ironside JW, et al. A multivariate analysis of factors determining tumor progression in childhood low-grade glioma: a population-based cohort study (CCLG CNS9702). *Neuro Oncol*. 2010;12:1257-1268.
2. Gnekow AK, Falkenstein F, von Hornstein S, et al. Long-term follow-up of the multicenter, multidisciplinary treatment study HIT-LGG-1996 for low-grade glioma in children and adolescents of the German Speaking Society of Pediatric Oncology and Hematology. *Neuro Oncol*. 2012;14:1265-1284.
3. Bandopadhayay P, Bergthold G, London WB, et al. Long-term outcome of 4,040 children diagnosed with pediatric low-grade gliomas: an analysis of the Surveillance Epidemiology and End Results (SEER) database. *Pediatr Blood Cancer*. 2014;61:1173-1179.
4. Sturm D, Pfister SM, Jones DTW. Pediatric gliomas: current concepts on diagnosis, biology, and clinical management. *J Clin Oncol*. 2017;35:2370-2377.
5. Laithier V, Grill J, Le Deley MC, et al. Progression-free survival in children with optic pathway tumors: dependence on age and the quality of the response to chemotherapy—results of the first French prospective study for the French Society of Pediatric Oncology. *J Clin Oncol*. 2003;21:4572-4578.
6. Ater JL, Zhou T, Holmes E, et al. Randomized study of two chemotherapy regimens for treatment of low-grade glioma in young children: a report from the Children's Oncology Group. *J Clin Oncol*. 2012;30:2641-2647.
7. Ater JL, Xia C, Mazewski CM, et al. Nonrandomized comparison of neurofibromatosis type 1 and non-neurofibromatosis type 1 children who received carboplatin and vincristine for progressive low-grade glioma: a report from the Children's Oncology Group. *Cancer*. 2016;122:1928-1936.
8. Lassaletta A, Scheinemann K, Zelcer SM, et al. Phase II weekly vinblastine for chemotherapy-naive children with progressive low-grade glioma: a Canadian Pediatric Brain Tumor Consortium study. *J Clin Oncol*. 2016;34:3537-3543.
9. Bouffet E, Jakacki R, Goldman S, et al. Phase II study of weekly vinblastine in recurrent or refractory pediatric low-grade glioma. *J Clin Oncol*. 2012;30:1358-1363.
10. Massimino M, Spreafico F, Riva D, et al. A lower-dose, lower-toxicity cisplatin-etoposide regimen for childhood progressive low-grade glioma. *J Neurooncol*. 2010;100:65-71.
11. Mishra KK, Puri DR, Missett BT, et al. The role of up-front radiation therapy for incompletely resected pediatric WHO grade II low-grade gliomas. *Neuro Oncol*. 2006;8:166-174.
12. Merchant TE, Kun LE, Wu S, Xiong X, Sanford RA, Boop FA. Phase II trial of conformal radiation therapy for pediatric low-grade glioma. *J Clin Oncol*. 2009;27:3598-3604.
13. Cherlow JM, Shaw DWW, Margraf LR, et al. Conformal radiation therapy for pediatric patients with low-grade glioma: results from the Children's Oncology Group phase 2 study ACNS0221. *Int J Radiat Oncol Biol Phys*. 2019;103:861-868.
14. Wisoff JH, Sanford RA, Heier LA, et al. Primary neurosurgery for pediatric low-grade gliomas: a prospective multi-institutional study from the Children's Oncology Group. *Neurosurgery*. 2011;68:1548-1554.
15. Gnekow AK, Walker DA, Kandels D, et al. A European randomised controlled trial of the addition of etoposide to standard vincristine and carboplatin induction as part of an 18-month treatment programme for childhood (≤16 years) low grade glioma - a final report. *Eur J Cancer*. 2017;81:206-225.
16. de Haas V, Grill J, Raquin MA, et al. Relapses of optic pathway tumors after first-line chemotherapy. *Pediatr Blood Cancer*. 2009;52:575-580.
17. Scheinemann K, Bartels U, Tsangaris E, et al. Feasibility and efficacy of repeated chemotherapy for progressive pediatric low-grade gliomas. *Pediatr Blood Cancer*. 2011;57:84-88.
18. Greenberger BA, Pulsifer MB, Ebb DH, et al. Clinical outcomes and late endocrine, neurocognitive, and visual profiles of proton radiation for pediatric low-grade gliomas. *Int J Radiat Oncol Biol Phys*. 2014;89:1060-1068.
19. Huynh-Le MP, Walker AJ, Burger PC, et al. Management of pediatric intracranial low-grade gliomas: long-term follow-up after radiation therapy. *Childs Nerv Syst*. 2016;32:1425-1430.
20. Goebel AM, Gnekow AK, Kandels D, Witt O, Schmidt R, Hernaiz Driever P. Natural history of pediatric low-grade glioma disease - first multi-state model analysis. *J Cancer*. 2019;10:6314-6326.
21. Muller K, Gnekow A, Falkenstein F, et al. Radiotherapy in pediatric pilocytic astrocytomas. A subgroup analysis within the prospective multicenter study HIT-LGG 1996 by the German Society of Pediatric Oncology and Hematology (GPOH). *Strahlenther Onkol*. 2013;189:647-655.
22. Merchant TE, Conklin HM, Wu S, Lustig RH, Xiong X. Late effects of conformal radiation therapy for pediatric patients with low-grade glioma: prospective evaluation of cognitive, endocrine, and hearing deficits. *J Clin Oncol*. 2009;27:3691-3697.
23. Tsang DS, Murphy ES, Merchant TE. Radiation therapy for optic pathway and hypothalamic low-grade gliomas in children. *Int J Radiat Oncol Biol Phys*. 2017;99:642-651.
24. Aarsen FK, Paquier PF, Arts WF, et al. Cognitive deficits and predictors 3 years after diagnosis of a pilocytic astrocytoma in childhood. *J Clin Oncol*. 2009;27:3526-3532.
25. Krishnatry R, Zhukova N, Guerreiro Stucklin AS, et al. Clinical and treatment factors determining long-term outcomes for adult survivors of childhood low-grade glioma: a population-based study. *Cancer*. 2016;122:1261-1269.
26. Gnekow AK, Kandels D, van Tilburg C, et al. SIOP-E-BTG and GPOH guidelines for diagnosis and treatment of children and adolescents with low grade glioma. *Klin Padiatr*. 2019;231:107-135.
27. Gururangan S, Fangusaro J, Poussaint TY, et al. Efficacy of bevacizumab plus irinotecan in children with recurrent low-grade gliomas—a Pediatric Brain Tumor Consortium study. *Neuro Oncol*. 2014;16:310-317.
28. Azizi AA, Schouten-van Meeteren AYN. Current and emerging treatment strategies for children with progressive chiasmatic-hypothalamic glioma diagnosed as infants: a web-based survey. *J Neurooncol*. 2018;136:127-134.
29. Fisher PG, Tihan T, Goldthwaite PT, et al. Outcome analysis of childhood low-grade astrocytomas. *Pediatr Blood Cancer*. 2008;51:245-250.
30. D'Arco F, Culleton S, De Cocker LJL, Mankad K, Davila J, Tamrazi B. Current concepts in radiologic assessment of pediatric brain tumors during treatment, part 1. *Pediatr Radiol*. 2018;48:1833-1843.
31. Tamrazi B, Mankad K, Nelson M, D'Arco F. Current concepts and challenges in the radiologic assessment of brain tumors in children: part 2. *Pediatr Radiol*. 2018;48:1844-1860.
32. Warren KE, Poussaint TY, Vezina G, et al. Challenges with defining response to antitumor agents in pediatric neuro-oncology: a report from the response assessment in pediatric neuro-oncology (RAPNO) working group. *Pediatr Blood Cancer*. 2013;60:1397-1401.
33. Falkenstein F, Gessi M, Kandels D, et al. Prognostic impact of distinct genetic entities in pediatric diffuse glioma WHO-grade II - report from the German/Swiss SIOP-LGG 2004 cohort. *Int J Cancer*. 2020. https://doi.org/10.1002/ijc.32995
34. Garzon M, Garcia-Fructuoso G, Sunol M, Mora J, Cruz O. Low-grade gliomas in children: single institutional experience in 198 cases. *Childs Nerv Syst*. 2015;31:1447-1459.

35. Roder C, Breitkopf M, Bisdas S, et al. Beneficial impact of high-field intraoperative magnetic resonance imaging on the efficacy of pediatric low-grade glioma surgery. *Neurosurg Focus*. 2016;40:E13.
36. Holzapfel J, Kandels D, Schmidt R, et al. Favorable prognosis in pediatric brainstem low-grade glioma: report from the German SIOP-LGG 2004 cohort. *Int J Cancer*. 2020;146:3385-3396.
37. Matyja E, Grajkowska W, Stępień K, Naganska E. Heterogeneity of histopathological presentation of pilocytic astrocytoma - diagnostic pitfalls. A review. *Folia Neuropathol*. 2016;54:197-211.
38. Louis DN, Ohgaki H, Wiestler OD, et al. *WHO Classification of Tumours of the Central Nervous System*. 4th ed. Lyon, France: IARC Press; 2016.
39. von Hornstein S, Kortmann RD, Pietsch T, et al. Impact of chemotherapy on disseminated low-grade glioma in children and adolescents: report from the HIT-LGG 1996 trial. *Pediatr Blood Cancer*. 2011;56:1046-1054.
40. Indelicato DJ, Rotondo RL, Uezono H, et al. Outcomes following proton therapy for pediatric low-grade glioma. *Int J Radiat Oncol Biol Phys*. 2019;104:149-156.
41. Mirow C, Pietsch T, Berkefeld S, et al. Children <1 year show an inferior outcome when treated according to the traditional LGG treatment strategy: a report from the German multicenter trial HIT-LGG 1996 for children with low grade glioma (LGG). *Pediatr Blood Cancer*. 2014;61:457-463.
42. Dodgshun AJ, Hansford JR, Sullivan MJ. Risk assessment in paediatric glioma-time to move on from the binary classification. *Crit Rev Oncol Hematol*. 2017;111:52-59.
43. Balogun JA, Rutka JT. Surgery of intracranial gliomas in children. *Prog Neurol Surg*. 2018;30:204-217.
44. Tsang DS, Murphy ES, Lucas JT Jr, Lagiou P, Acharya S, Merchant TE. Pseudoprogression in pediatric low-grade glioma after irradiation. *J Neurooncol*. 2017;135:371-379.
45. Gururangan S, Fisher MJ, Allen JC, et al. Temozolomide in children with progressive low-grade glioma. *Neuro Oncol*. 2007;9:161-168.
46. Bitterman DS, MacDonald SM, Yock TI, et al. Revisiting the role of radiation therapy for pediatric low-grade glioma. *J Clin Oncol*. 2019;37:3335-3339.
47. Acharya S, Liu JF, Tatevossian RG, et al. Risk stratification in pediatric low-grade glioma and glioneuronal tumor treated with radiation therapy: an integrated clinicopathologic and molecular analysis. *Neuro Oncol*. 2020. https://doi.org/10.1093/neuonc/noaa031
48. de Blank P, Bandopadhayay P, Haas-Kogan D, Fouladi M, Fangusaro J. Management of pediatric low-grade glioma. *Curr Opin Pediatr*. 2019;31:21-27.
49. Fouladi M, Hunt DL, Pollack IF, et al. Outcome of children with centrally reviewed low-grade gliomas treated with chemotherapy with or without radiotherapy on Children's Cancer Group high-grade glioma study CCG-945. *Cancer*. 2003;98:1243-1252.
50. Yang RR, Aibaidula A, Wang WW, et al. Pediatric low-grade gliomas can be molecularly stratified for risk. *Acta Neuropathol*. 2018;136:641-655.
51. Ho CY, Mobley BC, Gordish-Dressman H, et al. A clinicopathologic study of diencephalic pediatric low-grade gliomas with BRAF V600 mutation. *Acta Neuropathol*. 2015;130:575-585.
52. Bergthold G, Bandopadhayay P, Hoshida Y, et al. Expression profiles of 151 pediatric low-grade gliomas reveal molecular differences associated with location and histological subtype. *Neuro Oncol*. 2015;17:1486-1496.
53. Ryall S, Tabori U, Hawkins C. Pediatric low-grade glioma in the era of molecular diagnostics. *Acta Neuropathol Commun*. 2020;8:30.
54. Frazao L, do Carmo Martins M, Nunes VM, et al. BRAF V600E mutation and 9p21: CDKN2A/B and MTAP co-deletions - markers in the clinical stratification of pediatric gliomas. *BMC Cancer*. 2018;18:1259.
55. Campen CJ, Gutmann DH. Optic pathway gliomas in neurofibromatosis type 1. *J Child Neurol*. 2018;33:73-81.
56. Fisher MJ, Loguidice M, Gutmann DH, et al. Visual outcomes in children with neurofibromatosis type 1-associated optic pathway glioma following chemotherapy: a multicenter retrospective analysis. *Neuro Oncol*. 2012;14:790-797.
57. D'Angelo F, Ceccarelli M, Tala, et al. The molecular landscape of glioma in patients with neurofibromatosis 1. *Nat Med*. 2019;25:176-187.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Kandels D, Pietsch T, Bison B, et al. Loss of efficacy of subsequent nonsurgical therapy after primary treatment failure in pediatric low-grade glioma patients—Report from the German SIOP-LGG 2004 cohort. *Int. J. Cancer*. 2020;147:3471–3489. https://doi.org/10.1002/ijc.33170