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Favorable prognosis in pediatric brainstem low-grade glioma: Report from the German SIOP-LGG 2004 cohort

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Reports on pediatric low-grade glioma (LGG) of the caudal brainstem are retrospective with heterogeneous cohorts, variable treatments and inconsistent outcome data. We analyzed their natural history and asked whether brainstem location proved unfavorable for survival within the framework of the comprehensive SIOP-LGG 2004 management strategy. Within the prospectively registered, population-based German SIOP-LGG 2004 cohort 116 patients (age 0.2–16.5 years, 10% Neurofibromatosis NF1) were diagnosed with LGG of the pons (27%) and medulla oblongata (73%). After biopsy (23%), variable resection (63%) or radiologic diagnosis only (14%), 59 patients received no adjuvant treatment. Radiologic progression or severe neurologic symptoms prompted chemo- (n = 39) or radiotherapy (n = 18). After further progression (28/57), salvage treatments included multiple treatment lines for 12/28 patients. Five-years event-free survival dropped to 0.40, while 5-years overall survival was 0.95 (median observation time 6.8 years). Higher extent of resection yielded lower progression rate (p = 0.001), but at a cost of 21/100 patients suffering from new postsurgical complications including respiratory insufficiency. Central review confirmed pilocytic astrocytoma (56%), diffuse astrocytoma (8%) or glioneuronal histology (16%) (others 4%, no histology 17%). Malignant evolution was documented in five patients associated with Histone3 mutation in 2/5. Our treatment algorithm conveyed high overall survival for pediatric brainstem LGG. Extensive neurosurgical resection did increase additional postoperative neurologic deficits but not overall survival in this often-chronic disease. More than half of all patients can be

Additional Supporting Information may be found in the online version of this article.

Key words: brainstem low grade glioma, child, surgery, chemotherapy, radiotherapy

Abbreviations: C: carboplatin; DIPG: diffuse intrinsic pontine glioma; E: etoposide; EFS: event-free survival; FET-PET: O-(2-[18F] fluoro-ethyl)-L-tyrosine-positron emission tomography; LGG: low-grade glioma; NF1: neurofibromatosis type 1; OS: overall survival; PA: pilocytic astrocytoma; PFS: progression-free survival; RT: radiotherapy; SD: stable disease; V: vincristine

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[Correction added on December 23, 2019 after first online publication: Figure 1 updated.]

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safely followed by observation, while multimodal adjuvant treatment can control progressive tumors. Molecular assessment should confirm low-grade diagnosis and may detect patterns prognostic for malignant evolution.

What's new?

Outcome studies for pediatric low-grade gliomas (LGG) of the brainstem have generally been small and of low quality, making it difficult to determine prognosis. In this prospective, multicenter study, the authors developed a detailed description of the natural history, treatment response, and prognostic factors associated with favorable survival when a comprehensive treatment strategy was used. This treatment algorithm resulted in high overall survival for pediatric brainstem LGG. The study also emphasizes the importance of the predictive value of molecular patterns, as malignant evolution can occur even in low-grade tumors.

Introduction

Overall survival (OS) of children and adolescents suffering from low-grade glioma (LGG) exceeds 90% at 5 to 10 years.[1,2] Still, the prognostic risk-factors determining natural biology are not fully understood.[1–5] The prognostic impact of young age or germline mutation of neurofibromatosis type 1 (NF1) or of tumor-related criteria like dissemination has been defined consistently.[2,6–11] However, the role of LGG location within the central nervous system (CNS) remains controversial, and this applies in particular to the caudal brainstem where 5–10% of pediatric LGG are found. The natural course of LGG disease is more favorable for cerebral and cerebellar tumor location and after complete resection.[3] In contrast, OS of supratentorial midline and brainstem tumors depends on multi-modal treatment strategies.[2,8,12,13] Long-term prognosis for brainstem LGG disease was found to be lower than for cerebral or cerebellar sites in some cohorts.[3] In larger series, this site did not emerge as a prognostic factor after non-surgical treatment.[1,4,8] Previous reports on pediatric brainstem LGG were confounded by including mesencephalic tumors,[14,15] or high-grade histologies.[16–18] More recent series focused on tumors exhibiting focal or dorsally exophytic growth patterns and/or distinct low-grade histology, excluding tumors with a diffuse intrinsic growth pattern.[14,19] Survival rates ranged from 59% to 100% at 10 years for the low-grade tumor patients.[14,16,19] So far, all reports were compiled retrospectively and the majority of patients had variable treatments.

Therefore, we analyzed the natural history, response to treatment and long-term outcome of 116 pediatric patients with brainstem LGG included in the prospectively registered population-based German cohort of the SIOP-LGG 2004 study when applying a comprehensive treatment strategy.

Patients and Methods

Eligibility

The prospective, multinational and multicenter SIOP-LGG 2004 study registered patients with LGG of all CNS sites from April 1, 2004, until March 31, 2012. Inclusion criteria comprised age <18 years, histologic diagnosis of LGG according to the effective WHO classification (initially 2000, later 2007[20]), without prior nonsurgical therapy. For brainstem location, radiologic diagnosis was accepted, (*i*) if the tumor was not amenable to surgery, and (*ii*) if the imaging pattern clearly distinguished the lesion from diffuse intrinsic pontine glioma (DIPG).[21,22] Central review for pathology and radiology was recommended.

Informed consent was obtained from patients, parents and/or guardians. The Institutional Review Board approved SIOP-LGG 2004 study observed the Declaration of Helsinki in its revised version (Edinburgh, Scotland, 2000), the WHO and European Community rules of "Good Clinical Practice" (effective 17.01.1997). The SIOP-LGG 2004 study was registered at the ClinicalTrials.gov PRS NCT00276640 and had the EudraCT number 2005-005377-29.

Treatment strategy

All patients with brainstem tumor location followed the general study strategy (Supplementary Material Fig. S1): At diagnosis, best safe resection of the primary tumor was recommended. Patients with complete resection were to be observed, as well as patients after incomplete resection, biopsy or radiological diagnosis if no threatening neurological symptoms were present. Severe initial symptoms or clinical or radiological progression during observation were an indication for the start of nonsurgical treatment, if resection remained infeasible. Children <8 years and all children with NF1 were to receive primary chemotherapy. Older children ≥8 years without NF1 were allowed to receive either primary radiotherapy (RT) or chemotherapy.[1] Allocation of non-NF1 patients ≥8 years to the treatment arms was carried out at the discretion of the local treatment center. The nonsurgical treatments are termed "adjuvant" without or with prior surgical intervention. Patients without indication for nonsurgical/adjuvant treatment are termed "observed."

Chemotherapy

Standard chemotherapy with vincristine (V) at 1.5 mg/m^2/dose (maximum 2 mg, i.v. bolus/short-term infusion) and carboplatin (C) at 550 mg/m^2/dose (i.v. 1-hr-infusion) was given for 18 months (induction: 24 weeks, with 7 courses at 3–4 week intervals; consolidation: 10 courses every 6 weeks).[1] For those randomized within the chemotherapy arm of the study etoposide (E) was added with 100 mg/m^2/dose (i.v. 1-hr-infusion) on days 1–3 during induction week 1, 4, 7, and 10.[1] Treatment data were recorded. Dose modifications for children <10 kg of weight and/or <6 months of age and management of toxicity and of hypersensitivity reactions to C were defined.[1]

Radiotherapy

RT was scheduled as conventional external beam radiation with a total dose of 54 Gy (1.8 Gy per fraction). During the study period, proton beam therapy became available for few patients at comparable doses. Brachytherapy/interstitial radiosurgery for suitable tumors was applied with 125-Iodine-seeds.[23]

Radiologic follow-up

Contrast-enhanced MRI was regularly performed at defined intervals in all patients and was planned at week 24, 54 and 85 after the start of adjuvant therapy for response assessment. Complete, partial and objective responses (regression) as well as stable disease (SD) were considered positive responses.[1,24]

Salvage treatment

Treatment for progression after primary radio- or chemotherapy was not standardized, but included all modalities after discussion in local and reference tumor boards.

Statistics

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

The distribution of OS, progression-free survival (PFS) and event-free survival (EFS) were 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). To evaluate OS in the chemotherapy and RT subgroups, OS was in derogation thereof calculated from start of therapy until death (of any cause). EFS was calculated from date of diagnosis until event, defined as relapse after complete resection, clinical or radiological progression, start of non-surgical/adjuvant therapy or death of any cause. To evaluate the variables resection and histology, EFS was in derogation thereof calculated from the date of surgery until event. PFS was calculated from the start of nonsurgical/adjuvant therapy until event, defined as relapse after complete remission, clinical or radiological progression or death of any cause.

Cox regression with forward stepwise selection (inclusion criterion: score test $p \leq 0.05$; exclusion criterion: likelihood ratio test $p > 0.10$) was used to analyze the prognostic value of clinical and biologic variables on EFS. Variables included age (years) at diagnosis (≤1 year, >1 to <8 years, ≥8 years), sex, NF1-status, localization (pons *vs*. medulla oblongata), dissemination, extent of resection and histology (pilocytic astrocytoma [PA] *vs*. diffuse astrocytoma *vs*. glioneuronal tumors). Extent of resection and histology were included as time-dependent variables for EFS from the date of surgery.

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

Data availability

The data sets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Results

Cohort description

Brainstem tumor location was stated for 120 of 1,586 registered patients from the German SIOP-LGG 2004 cohort (77 participating hospitals). Four patients were excluded upon review for diagnosis (n = 1 DIPG, n = 1 Alexander disease) or tumor location (n = 2, primary cerebellar site with brainstem involvement) (Fig. 1). Detailed data for the 116 patients of this report are given in Table 1. Median age at diagnosis was 5.6 years with a clear male preponderance (m:f ratio 1.6:1). NF1 was diagnosed clinically and/or genetically in 12 patients. Only a quarter of tumors originated in the pons (27%), while the majority emerged from the medulla (73%), more than half of the tumors from both sites extended into neighboring structures; for 7 patients primary (n = 4) or secondary (n = 3) dissemination was reported. Central radiologic review of sequential MRIs was performed for 110 patients.

At the time of diagnosis, 106/116 symptomatic patients (5/12 NF1) suffered from single (31/106) or combined (75/106) symptoms related to tumor site. Still, brainstem LGG was an incidental finding in 10 patients (9%, follow-up of surgery for synostosis, imaging for NF1 [4/12], trauma or tics). Besides long-tract signs (n = 47) or cranial nerve palsy (n = 63), increased intracranial pressure (n = 12) and ataxia (n = 10), functional symptoms like newly developed torticollis (n = 31) or isolated vomiting (n = 27) were frequent. No patient presented with the triad of simultaneous long-tract signs, cranial nerve palsies and ataxia.

Surgery

At least one neurosurgical intervention was performed in 100/116 patients (Table 1). Eighteen patients underwent several subsequent resections and biopsies. Twenty-one patients developed significant new postoperative neurologic impairments, including respiratory insufficiency in 5, postoperative cerebellar mutism in 3, and cranial nerve palsy, hemi- or tetra-paresis in 15 patients. Deficits were observed in only 4% of the patients who underwent biopsy (n = 1/27), while they

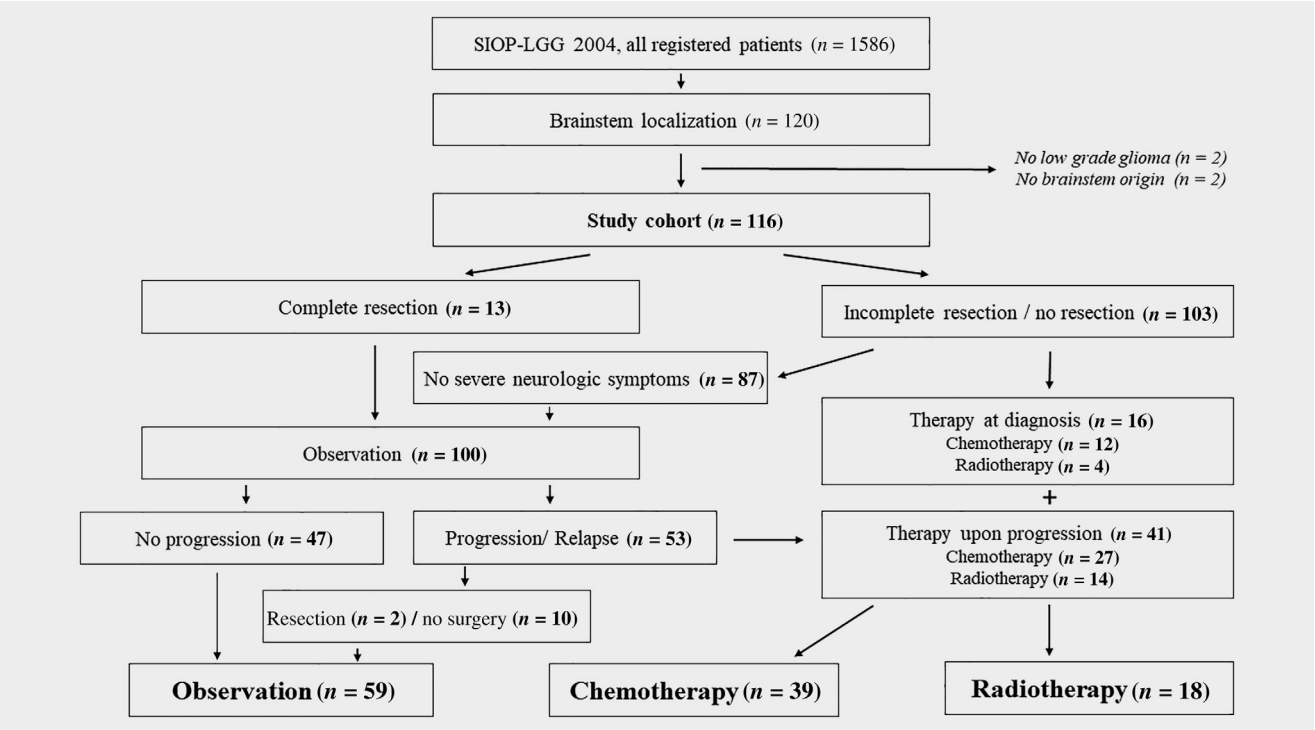

Figure 1. Brainstem LGG cohort. Patient numbers and distribution among strategic subgroups.

occurred in 38% (n = 5/13), 46% (n = 6/13) and 19% (n = 9/47) after initial complete, subtotal or partial resection. Deficits persisted in 18/20 survivors. There were no surgery-associated deaths.

Histologic diagnosis

LGG histology was confirmed upon central review for 96 tumors. In four cases, limited biopsy tissue impeded LGG diagnosis (n = 2) or the sample did not contain tumor tissue (n = 2). Thus, in 20 patients (17%) the diagnosis of LGG relied upon centrally confirmed radiologic criteria. The majority of tumors were PA WHO Grade I. One had a pilomyxoid pattern. Glioneuronal tumors constituted the second largest group and nine tumors were classified as diffuse astrocytoma WHO Grade II. Molecular tumor assessment was performed in 17/96 cases (Table 1): KIAA1549-BRAF-fusion was found in 3 PA, 1 ganglioglioma and 1 diffuse astrocytoma, whereas BRAF-V600E mutation was found in 1 ganglioglioma only. Histone3-K27M mutation was seen in 2 diffuse astrocytomas; another 4 diffuse astrocytomas revealed BRAF/IDH/Histone3-wild type.

Strategic subgroups

During the study period (median follow-up 6.8 years) 59 patients without (n = 11) or with neurosurgical intervention (n = 48) did not receive adjuvant treatment, while 57 patients needed adjuvant treatment (Fig. 1).

Patients remaining observed: during the study period 11/59 patients without adjuvant treatment suffered from tumor progression after initial complete (2/12), subtotal (2/11), and partial resection (5/18) or radiologically diagnosed brainstem LGG (2/11). Tumor growth ceased spontaneously in 5/11; and 2/11 achieved SD after 1–2 re-resections. Three/11 patients had further progression despite surgery, information is missing for one. At last follow-up, 50/59 patients are alive, 3 patients had deceased (1 after tumor-associated respiratory dysregulation, 1 after continuous progression despite multiple resections, 1 with the malignant relapse of a diffuse astrocytoma wild type for BRAF/IDH/Histone3 mutation at retrospective analysis). Six patients were lost to follow-up.

Patients without need for adjuvant treatment within the first three years after diagnosis tended to be older at diagnosis, had more often initial complete/subtotal resection or radiologic diagnosis, and their tumor histology was more often glioneuronal as compared to their counterparts.

Chemotherapy group: primary adjuvant treatment was chemotherapy for 39 patients starting at a median age of 5.7 years. None of them had an initial complete or subtotal tumor resection. Treatment with VC (n = 31) or VCE (n = 8) commenced following a median observation time of 0.7 years for the presence of severe neurologic symptoms in 48% (19/39), radiologic progression in 31% (12/39) and the combination of both in 21% (8/39). Chemotherapy was well tolerated; switching to alternative consolidation was necessary in 14 patients due to C hypersensitivity reactions. Radiologic response after induction at week 24 was tumor regression and

Table 1. Epidemiologic data

Patients characteristic	All patients *n* = 116	Chemotherapy *n* = 39	Radiotherapy *n* = 18
Median age (years, range)			
At diagnosis	5.6 (0.2–16.5)	3.5 (0.2–12.7)	8.1 (0.8–13.6)
At start of therapy	–	5.7 (0.5–15.3)	10.8 (1.2–17.9)
Median interval from diagnosis to start of treatment (years, range)	–	0.7 (0.0–5.9)	1.8 (0.1–7.0)
Age group			
≤1 year	5 (4.3%)	3 (7.7%)	1 (5.6%)
›1 to ‹8 years	68 (58.6%)	31 (79.5%)	7 (38.9%)
≥8 years	43 (37.1%)	5 (12.8%)	10 (55.6%)
Sex			
Male	72 (62.1%)	23 (59.0%)	12 (66.7%)
Female	44 (37.9%)	16 (41.0%)	6 (33.3%)
NF1 status			
NF1	12 (10.3%)	8 (20.5%)	–
Non-NF1	103 (88.8%)	30 (76.9%)	18 (100%)
Not known	1 (0.9%)	1 (2.6%)	–
Localization			
Pons	31 (26.7%)	9 (23.0%)	7 (38.9%)
Medulla oblongata	85 (73.3%)	30 (77.0%)	11 (61.1%)
Local tumor extension			
No extension beyond origin	52 (44.8%)	16 (41.0%)	9 (50.0%)
Dorsal extension	23 (19.8%)	11 (28.2%)	7 (38.8%)
Caudal extension	22 (19.0%)	5 (12.8%)	1 (5.6%)
Cranial extension	14 (12.1%)	3 (7.7%)	1 (5.6%)
Dorsal and caudal extension	1 (0.9%)	1 (2.6%)	–
Dorsal and cranial extension	3 (2.6%)	3 (7.7%)	–
Cranial and caudal extension	1 (0.9%)	–	–
Dissemination			
No	109 (94.0%)	34 (87.2%)	–
Yes	7 (6.0%)	5 (12.8%)	–
Primary surgery			
Complete resection	13 (11.2%)	–	1 (5.6%)
Subtotal resection	13 (11.2%)	–	2 (11.1%)
Partial resection	47 (40.5%) (1 NF1)	20 (51.3%)	9 (50.0%)
Open biopsy	14 (12.1%) (1 NF1)	9 (23.0%)	1 (5.6%)
Stereotactic biopsy	13 (11.2%) (3 NF1)	6 (15.4%)	4 (22.2%)
No surgery[2]	16 (13.8%) (7 NF1)	4 (10.3%)	1 (5.6%)
Histology			
Pilocytic astrocytoma I[1]	65 (56.0%)	23 (59.0%)	13 (72.2%)
Pilomyxoid astrocytoma II	1 (0.9%)	1 (2.5%)	–
Diffuse astrocytoma II[1]	9 (7.6%)	4 (10.3%)	2 (11.1%)
Glioneuronal tumors	18 (15.5%)	4 (10.3%)	2 (11.1%)
Ganglioglioma I[1]	16	3	2
DIG/DIA	2	1	–
Other histologies	3 (2.6%)	2 (5.1%)	–
Astrocytoma NOS	2	1	–
LGG NOS	1	1	–
No histology[2]	20 (17.2%)	5 (12.8%)	1 (5.6%)

(Continues)

Table 1. Epidemiologic data (Continued)

Patients characteristic	All patients $n = 116$	Chemotherapy $n = 39$	Radiotherapy $n = 18$
Observation time from diagnosis to last follow-up (years, range)	6.8 (0.6–15.0)	7.3 (0.7–14.1)	7.8 (0.6–15.0)
Status at last follow-up			
Alive	98	32	16
Without tumor	15	1	5
With stable tumor	80	30	10
With progressive tumor	2	1	–
Evolution of HGG	1	–	1
Lost to follow-up	8	1	1
Status at last follow-up	5CR/SD,2PD,1nn	1PD	1nn
Dead	10	6	1
Tumor progression	5	4	–
Complication[3]	1	–	–
Evolution of HGG	4	2	1

[1]Molecular data from residual tumor tissue available for 8/65 pilocytic astrocytomas (3 KIAA1549-BRAF-fusion, 1 NF1 with CDKN2A mutation, 4 wild type for BRAF/IDH mutation), 7/9 diffuse astrocytomas (2 Histone3-K27M mutation, 1 KIAA1549-BRAF-fusion, 4 wild type for BRAF/IDH/Histone3 mutation) and 2/16 gangliogliomas (1 KIAA1549-BRAF-fusion, 1 BRAF-V600E mutation).
[2]Four patients with biopsy (3 stereotactic, 1 open) but no meaningful histology.
[3]Tumor-associated respiratory dysregulation.
Abbreviations: DIA, desmoplastic infantile astrocytoma; DIG, desmoplastic infantile ganglioglioma; HGG, high-grade glioma; nn, not known; NOS, not otherwise specified.

SD in 12 and 19, respectively, of 37 evaluable patients (84% combined response), while 6/37 showed progressive disease (16%). Two patients had no radiologic assessment at this time point. Further 18 patients developed progression during consolidation ($n = 7$) or surveillance ($n = 11$). Salvage treatment for these 24 progressing tumor patients included one further treatment modality in six patients (proton RT [$n = 2$], photon RT [$n = 3$], chemotherapy [$n = 1$]). Multiple further treatment lines for successive progressions were given in 10 patients combining re-resection plus second chemotherapy ($n = 1$) or proton RT ($n = 2$) or ≥2 adjuvant treatments without or with further resection(s) ($n = 7$, 2/7 photon RT). Eight of 24 patients had no further adjuvant treatment, but partial resection in 4 and spontaneous switch to SD in 3. One of 24 patients died during first-line chemotherapy from rapidly progressing tumor. At the last follow-up, 32 patients were alive and 6 patients had died. In one of them, astrocytoma WHO Grade III had been diagnosed at last biopsy, in another patient suffering from reference-confirmed diffuse astrocytoma retrospective analysis disclosed Histone3-K27M mutation. One patient was lost to follow-up.

RT group: primary adjuvant treatment was RT for 18 patients starting at a median age of 8.7 years, following a median observation time of 1.8 years, due to severe neurologic symptoms in 11% (2/18), radiologic progression/relapse in 67% (12/18) and the combination of both in 17% (3/18) (1 not documented). External fractionated RT with protons ($n = 1$) or photons ($n = 11$) was given at a median dose of 54 Gy (48.4–59 Gy). Six tumors were suitable for interstitial radiosurgery. Tumor response at week 24 was regression and SD in 9 and 4 of 15 evaluable patients, respectively (87%). Two tumors progressed: one tumor exhibited malignant histology at partial resection (ganglioglioma WHO Grade III, BRAF-V600E-mutated), 70 months after initial diagnosis of ganglioglioma WHO Grade I. After chemotherapy with temozolomide, this patient achieved SD. The other tumor met criteria of a highly amino-acid avid tumor at FET-PET assessment (O-(2-[18F] fluoroethyl)-L-tyrosine-PET), progressed rapidly despite further chemotherapy and eventually the patient died. Histone3-K27M mutation was proven retrospectively in this diffuse astrocytoma. Three patients had no radiologic assessment at Week 24. Another 2 tumors progressed 85 weeks and 5 years after the start of RT; complete remission was achieved after multiple resections and chemotherapy in both. At the last follow-up, 16 patients were alive (1 lost to follow-up).

In summary, 27 patients received RT as primary or salvage ($n = 9$) treatment.

Survival data

Survival data, including the results of exploratory univariable analyses, are detailed in Table 2 and illustrated in Figures 2*a*, 2*b* and 3*a*–3*d*. OS for the entire cohort was 0.95 (±0.02) at 5 and 0.86 (±0.05) at 10 years. Five-years OS was 0.89 (±0.05) for the chemotherapy and 0.94 (±0.05) for the RT group. Five-years EFS for the entire cohort was 0.40 (±0.05). It was better for patients older than 8 years, after complete/subtotal resection, without dissemination or for tumors of glioneuronal histology. Multivariable analysis confirmed these characteristics as independent determining factors for EFS (Table 3). Five-years PFS after first adjuvant treatment was

0.42 (±0.08) after chemotherapy and 0.83 (±0.09) after RT. Exclusion of cases with Histone3-mutated tumors and of all cases with malignant evolution did not alter OS, EFS or PFS (Table 2).

Discussion

Our treatment algorithm conveyed high OS and PFS for this prospectively registered cohort with pediatric brainstem LGG comparable to results for other CNS sites. Extensive neurosurgical resection did increase additional postoperative neurologic deficits but not OS in this often-chronic disease. More than half of all patients can be safely followed by observation, while multimodal adjuvant treatment can control progressive tumors despite frequent progressions.

Our cohort is comparable to other series with LGG of all locations[2,8] or of brainstem only[14,15,19] with respect to age, sex ratio and portion of NF1. While the dominant location within the caudal brainstem was either pontine[14,15] or medullary[16,25]

Table 2. Results of univariable survival analysis: 5-year overall survival (OS), 5-year event-free survival and 5-year progression-free survival by subgroups

	All patients $n = 116$	Chemotherapy[1] $n = 39$	Radiotherapy[1] $n = 18$
Overall survival			
All	0.95 (0.02)	0.89 (0.05)	0.94 (0.05)
Histone3 mutations excluded	0.96 (0.02)	0.92 (0.05)	1.00
Malignant histologies excluded	0.96 (0.02)	0.92 (0.05)	1.00
Event-free survival			
All	0.40 (0.05)	–	–
Histone3 mutations excluded	0.41 (0.05)	–	–
Malignant histologies excluded	0.42 (0.05)	–	–
Age	$p = 0.021$	–	–
≤1 year	0.20 (0.18)		
›1–‹8 years	0.33 (0.06)		
≥8 years	0.55 (0.08)		
Sex	$p = 0.061$	–	–
Male	0.48 (0.06)		
Female	0.28 (0.07)		
NF1	$p = 0.095$	–	–
Present	0.25 (0.13)		
Not present	0.42 (0.05)		
Localization	$p = 0.216$	–	–
Pons	0.29 (0.09)		
Medulla oblongata	0.44 (0.06)		
Extent of resection[2]	$p < 0.001$	–	–
Complete	0.76 (0.12)		
Subtotal	0.67 (0.14)		
Partial	0.29 (0.07)		
Biopsy	0.29 (0.09)		
Histology[2]	$p = 0.007$	–	–
Pilocytic astrocytoma	0.36 (0.06)		
Diffuse astrocytoma	0.14 (0.13)		
Glioneuronal tumors	0.61 (0.12)		
Dissemination	$p = 0.046$	–	–
Present	0.00		
Not present	0.43 (0.05)		
Progression-free survival			
All	–	0.42 (0.08)	0.83 (0.09)
Histone3 mutations excluded	–	0.43 (0.08)	0.88 (0.08)
Malignant histologies excluded	–	0.44 (0.08)	0.87 (0.09)

[1]In chemotherapy/radiotherapy subgroups: 5-year OS measured from start of therapy.
[2]Five-year EFS measured from the date of surgery.

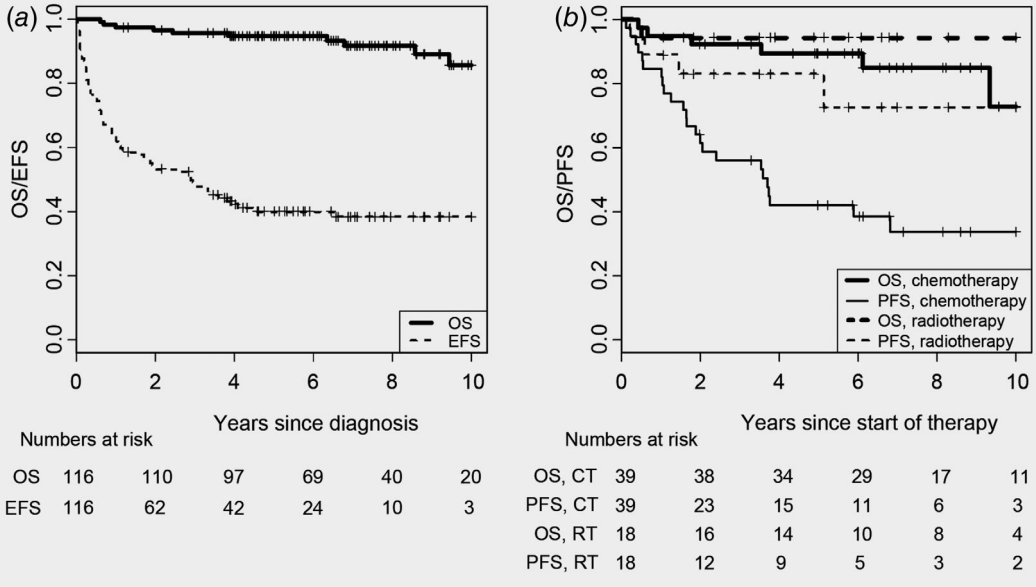

Figure 2. Overall, event-free and progression-free survival. (*a*) OS and EFS for the entire group. (*b*) OS and PFS for the chemotherapy and radiotherapy groups.

in small, not population-based reports, our series confirms that three quarters of brainstem LGG reside in the medulla oblongata, and that more than half of all brainstem tumors extend into neighboring structures clearly limiting attempts of radical resection. As opposed to DIPG the triad of long-tract signs, cranial nerve palsy and ataxia was not present in our patients.[26] Still, 70% had combined symptoms at diagnosis. Being an early symptom for posterior fossa tumors,[27] the high frequency of torticollis in more than 25% of our patients was not described previously highlighting the necessity of neuroimaging in these patients.[28] We attribute the lower frequency of hydrocephalus in our cohort as compared to the series of Klimo *et al.*[14] and Sandri *et al.*[17] to the exclusion of mesencephalic tumors where aqueduct obstruction causes symptoms of increased cranial pressure in more than 80%.[12]

Impact of surgery

For all LGG, surgery tends to be the first procedure. Tumor resection is generally accepted as "treatment of choice," including second interventions or treatment of local relapse.[3,8,29] Anatomical site determines resectability, which, in turn, when complete, is associated with better survival outcomes in both low- and high-grade glioma.[29] Improvement of surgical techniques, use of intraoperative adjuncts, especially neurophysiological monitoring, and referral to specialized pediatric neurosurgical centers contributed to reduced postoperative morbidity after resection for brainstem LGG.[18,30,31] Complete and subtotal resection rates of 16–53% and 24–56%, respectively, were reported in small monocentric series,[14,18,19] but were clearly lower in our cohort with 10% and 16%, respectively. Corroborating the low risk for relapse after complete resection in the series from Pollack *et al.*[32] and Upadhyaya *et al.*,[19] only 3/13 completely resected LGG within our cohort relapsed. However, the risk to damage critical structures upon resection of a brainstem tumor is high[31–33] and critically reflected by a 21% rate of severe postoperative complications being more relevant in complete/subtotal (46%) and less in partial resection (19%) or biopsy (4%) within this protocol. Referral to specialist pediatric centers for brainstem interventions and detailed multidisciplinary team discussion are the most pertinent requests to reduce operative morbidity with its lifelong burden for patients and families in this often-chronic disease.[29]

Impact of histologic confirmation

Nevertheless, confirmation of LGG-histology is warranted and was obtained for 83% tumors within our cohort. Several historic series of pediatric brainstem tumors included low- and high-grade histologies[16–18] and do not allow drawing conclusions about efficacy of treatment for the low-grade cases or analyzing risk factors. On the other hand, radiologic diagnosis was broadly accepted for LGG in the past, especially for NF1-associated tumors of the visual pathways,[34] and radiologic criteria to discriminate DIPG from LGG were established.[21,22] Within our cohort, more than a third of those with radiologic diagnosis were NF1-patients for whom radiologic diagnosis of brainstem LGG has been accepted.[35] Two-thirds of the histologies were PA, and glioneuronal tumors had a share of 20% comparable to other series.[19] The introduction of molecular assessment during the latter part of the study allowed additional confirmation of diagnosis in several cases. Detection of the KIAA1549-BRAF fusion was possible

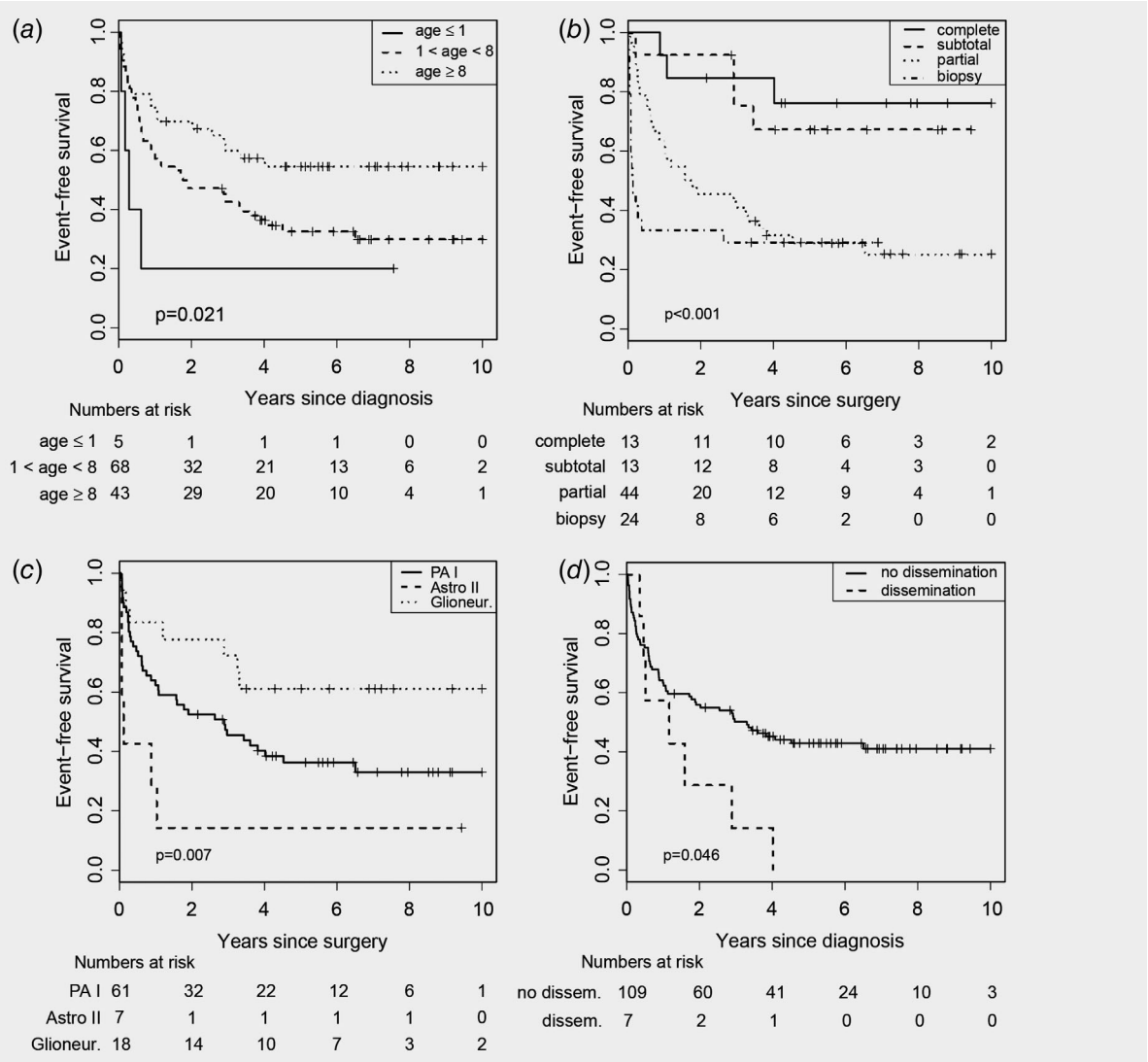

Figure 3. Event-free survival for noticeable prognostic factors. (*a*) EFS for age. (*b*) EFS for extent of resection. (*c*) EFS for histology. (*d*) EFS for dissemination.

in two specimens strengthening the most probable diagnosis of a LGG. In the report of Upadhyaya *et al.*,[19] retrospectively analyzed tissue confirmed KIAA1549-BRAF-fusion in four of seven cases with ganglioglioma and PA, none was BRAF-V600E positive. However, molecular assessment is most imperative in ruling out high-grade histologic features. For two tumors with previous centrally confirmed astrocytoma WHO Grade II, we identified presence of Histone3-K27M mutation, characteristic for diffuse midline glioma.[36] Histone3 mutations have been described in low-grade thalamic and brainstem tumors,[37,38] preceding malignant evolution.[39] Since almost all of these patients eventually die,[38,40] we question the maintenance of the term "low-grade" for these tumors. Yet, their exclusion from survival analysis did not affect OS, underpinning the favorable outcome of this cohort. Malignant progression was additionally seen in three other patients. For those latter patients it is not clear, whether current molecular diagnosis would have revealed relevant mutations. Yet, the relevant frequency of malignant evolution underlines the need for histologic and molecular confirmation of presumably low-grade brainstem lesions; repeat tissue diagnosis is warranted at relapse or unexpected evolution.[41] Stereotactic biopsy is adequate provided sufficient material for detailed analysis can be obtained.[42]

Consequences of patient stratification

Current approaches to adjuvant treatment of LGG in children and adolescents emphasize that there are no apparent differences in long-term OS after immediate post-operative *versus* delayed onset of RT or chemotherapy,[43,44] and relate the choice of the primary adjuvant treatment modality to age, tumor location and size and the time point during the course

Table 3. Multivariable analysis of event-free survival

Predictors	HR	95% CI	*p* value
Age			0.046
≤1 year *vs*. ≥8 years (ref.)	5.68	(1.71–18.92)	
>1 to <8 years *vs*. ≥8 years (ref.)	1.31	(0.69–2.51)	
Sex			N/S: 0.380
Female *vs*. male (ref.)	–	–	
NF1			0.079
Present *vs*. not present (ref.)	2.95	(0.97–9.00)	
Localization			N/S: 0.172
Pons *vs*. Medulla oblongata (ref.)	–	–	
Extent of resection[1]			<0.001
Subtotal *vs*. complete (ref.)	1.25	(0.26–5.91)	
Partial *vs*. complete (ref.)	4.91	(1.39–17.34)	
Biopsy *vs*. complete (ref.)	15.27	(3.91–59.59)	
Histology[1]			<0.001
Diffuse astrocytoma *vs*. pilocytic astrocytoma (ref.)	3.21	(1.14–9.06)	
Glioneuronal tumors *vs*. pilocytic astrocytoma (ref.)	0.23	(0.09–0.59)	
Dissemination			0.009
Present *vs*. not present (ref.)	4.08	(1.60–10.38)	

[1]Treated as time-dependent variable that becomes known at the date of surgery.

of the disease.[1,4,43,45] After the comprehensive treatment algorithm of the SIOP-LGG 2004 study, only 16 of our patients had an indication to start adjuvant treatment at the time of diagnosis, while the majority was initially observed. Over time, many patients, especially if younger at diagnosis, progressed clinically and/or radiologically, resulting in a drop of 5-year EFS to 40%. Events occurred without noticeable differences between primary pontine and medullary site, while a lesser extent of initial resection and astrocytic histology were associated with a clearly higher progression rate, discrepantly discussed in previous reports.[14,15,17,19] But either spontaneous deceleration of tumor growth-rate or neurosurgical re-interventions allowed retaining a further "wait-and-see" conduct for half of our cohort. The higher risk of progression for infants has been uniformly described in various LGG series.[1,2,9,11]

Chemo- and RT: adjuvant treatment started upon defined indications only,[1] and the same principles applied to the management of subsequent progression. For none of the retrospective series, a standardized approach for the initiation of radio- or chemotherapy is detailed[14–19,25,31] impeding the direct comparison of treatment results. In the series of Upadhyaya *et al*.,[19] only 9/25 patients did not receive adjuvant radio- or chemotherapy after successive progressions. In the majority of reports, most patients had primary RT[14–17,19]; few patients were treated with various chemotherapy regimens.[14,16,17,19] The efficacy of V/C for brainstem LGG had been confirmed by Ronghe *et al*. in a series of 16 patients.[46] The favorable outcome of our treatment groups with a 5-year OS 89% and 94% after primary chemotherapy and RT, respectively, underscores the appropriateness of the study strategy for pediatric brainstem LGG. Furthermore, primary RT was delayed to a median age above 8 years in the cohort of 18 patients, and in total only a quarter of all patients had focal irradiation during the course of treatment. Limited by small numbers and being embedded in treatment successions, the relative efficacy of protons, photons and interstitial radiosurgery is difficult to determine. Nevertheless, 22/27 patients irradiated at some point of their treatment course achieved CR and SD. Since early radiation was associated with death mainly attributed to late malignant transformation of primary tumors on long-term follow-up of pediatric LGG patients,[47,48] primary standard chemotherapy is warranted for brainstem LGG. Reflecting stratification within the SIOP-LGG 2004 treatment algorithm median age in the chemotherapy group was lower and young patients needed treatment earlier than in the RT group. Despite a high response rate at Week 24 of 84% of tumors (regression plus SD), the chemotherapy-first strategy came with a 5-year PFS of 42% only compared to 83% for the RT group. As a consequence, primary chemotherapy was associated with multiple lines of treatment for 61% of patients, but this did not compromise survival. No late RT-induced malignancies were observed so far.

Neurofibromatosis: only a smaller fraction of brainstem glioma in NF1-patients was symptomatic and/or progressive and needed treatment in a multi-institutional series.[35] Since the risk for RT-induced late effects is highly increased in NF1, chemotherapy is currently recommended to avoid up-front as well as salvage RT.[49] Eight of our 12 NF1 patients received chemotherapy at tumor progression; none was irradiated and all survived. It cannot be ruled out that referral bias for symptomatic NF1-patients, who otherwise are followed in neuropediatric services, accounts for the higher percentage of treatment indications as compared to the series of Mahdi *et al*.[35]

Functional outcome

Despite detailed documentation of the clinical course of our patients, we lack standardized neurologic assessments during follow-up to complement the radiologic tumor status. While 27/106 survivors reported no neurologic sequelae and we lack information in 9/106, a load of symptoms is reported for the remaining 70/106 patients, among them persistence of long-tract signs (n = 25/70), cranial nerve palsy (n = 41/70), ataxia (n = 30/70), respiratory insufficiency (n = 8/70), difficulties of swallowing (n = 10/70) or speech (n = 5/70). Since most of our pediatric patients have to accept a lifelong impact of their

brainstem LGG upon brain function, future studies should include functional outcome endpoints.[50]

Conclusion

Our data confirm favorable OS for children and adolescents with LGG of the caudal brainstem within the population-based prospective SIOP-LGG 2004 comprehensive treatment strategy. Although EFS is better after more extensive neurosurgical interventions, the extent of resection should be carefully chosen to avoid additional postoperative deficits, and referral to multidisciplinary pediatric neuro-oncology teams is recommended. Even with a high portion of incompletely resected tumors, more than half of the patients in our population-based series can be followed by observation, while the multimodal treatment strategy, including multiple treatment lines, allows controlling even progressive tumors. Radiologic diagnosis of a LGG should be reserved for exceptional cases. We recommend tissue-based histologic and molecular diagnosis for all tumors. Research is needed to detect reliable patterns predictive of possible malignant evolution.

References

1. 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;81:206–25.
2. 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;12:1257–68.
3. 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; 68:1548–54. discussion 54-5.
4. 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;30:2641–7.
5. 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.
6. 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: 4572–8.
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: 1928–36.
8. 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: 1265–84.
9. 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: 457–63.
10. 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;56:1046–54.
11. 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;136:127–34.
12. Kaufmann A, Gerber NU, Kandels D, et al. Management of primary tectal plate low-grade glioma in pediatric patients: results of the multicenter treatment study SIOP-LGG 2004. *Neuropediatrics* 2018;49:314–23.
13. Boesten T, Gerber NU, Kandels D, et al. Management of primary thalamic low-grade glioma in pediatric patients: results of the multicenter treatment studies HIT-LGG 1996 and SIOP-LGG 2004. *Neuro Oncol Practice* 2017;4:29–39.
14. Klimo P Jr, Pai Panandiker AS, Thompson CJ, et al. Management and outcome of focal low-grade brainstem tumors in pediatric patients: the St. Jude experience. *J Neurosurg Pediatr* 2013;11: 274–81.
15. Fried I, Hawkins C, Scheinemann K, et al. Favorable outcome with conservative treatment for children with low grade brainstem tumors. *Pediatr Blood Cancer* 2012;58:556–60.
16. Ahmed KA, Laack NN, Eckel LJ, et al. Histologically proven, low-grade brainstem gliomas in children: 30-year experience with long-term follow-up at Mayo Clinic. *Am J Clin Oncol* 2014;37:51–6.
17. Sandri A, Sardi N, Genitori L, et al. Diffuse and focal brain stem tumors in childhood: prognostic factors and surgical outcome. Experience in a single institution. *Childs Nerv Syst* 2006;22:1127–35.
18. Teo C, Siu TL. Radical resection of focal brainstem gliomas: is it worth doing? *Childs Nerv Syst* 2008;24:1307–14.
19. Upadhyaya SA, Koschmann C, Muraszko K, et al. Brainstem low-grade gliomas in children-excellent outcomes with multimodality therapy. *J Child Neurol* 2017;32:194–203.
20. Louis DN, Ohgaki H, Wiestler OD, et al. The 2007 WHO classification of tumours of the central nervous system. *Acta Neuropathol* 2007;114: 97–109.
21. Moharamzad Y, Sanei Taheri M, Niaghi F, et al. Brainstem glioma: prediction of histopathologic grade based on conventional MR imaging. *Neuroradiol J* 2018;31:10–7.
22. Fischbein NJ, Prados MD, Wara W, et al. Radiologic classification of brain stem tumors: correlation of magnetic resonance imaging appearance with clinical outcome. *Pediatr Neurosurg* 1996;24:9–23.
23. Ruge MI, Simon T, Suchorska B, et al. Stereotactic brachytherapy with iodine-125 seeds for the treatment of inoperable low-grade gliomas in children: long-term outcome. *J Clin Oncol* 2011;29:4151–9.
24. Gnekow AK, Kandels D, Tilburg CV, et al. SIOP-E-BTG and GPOH guidelines for diagnosis and treatment of children and adolescents with low grade glioma. *Klin Padiatr* 2019;231:107–35.
25. Farmer JP, Montes JL, Freeman CR, et al. Brainstem gliomas. A 10-year institutional review. *Pediatr Neurosurg* 2001;34:206–14.
26. Wilne S, Collier J, Kennedy C, et al. Presentation of childhood CNS tumours: a systematic review and meta-analysis. *Lancet Oncol* 2007;8:685–95.
27. Fafara-Les A, Kwiatkowski S, Marynczak L, et al. Torticollis as a first sign of posterior fossa and cervical spinal cord tumors in children. *Childs Nerv Syst* 2014;30:425–30.
28. Tumturk A, Kaya Ozcora G, Kacar Bayram A, et al. Torticollis in children: an alert symptom not to be turned away. *Childs Nerv Syst* 2015;31: 1461–70.
29. Walker DA, Liu J, Kieran M, et al. A multidisciplinary consensus statement concerning surgical approaches to low-grade, high-grade astrocytomas and diffuse intrinsic pontine gliomas in childhood (CPN Paris 2011) using the Delphi method. *Neuro Oncol* 2013;15:462–8.
30. Lundar T, Due-Tonnessen BJ, Egge A, et al. Neurosurgical treatment of pediatric low-grade midbrain tumors: a single consecutive institutional series of 15 patients. *J Neurosurg Pediatr* 2014;14: 598–603.
31. Sinha S, Kale SS, Chandra SP, et al. Brainstem gliomas: surgical indications and technical considerations in a series of 58 cases. *Br J Neurosurg* 2014; 28:220–5.
32. Pollack IF, Hoffman HJ, Humphreys RP, et al. The long-term outcome after surgical treatment of dorsally exophytic brain-stem gliomas. *J Neurosurg* 1993;78:859–63.
33. Jallo GI, Shiminski-Maher T, Velazquez L, et al. Recovery of lower cranial nerve function after surgery for medullary brainstem tumors. *Neurosurgery* 2005;56:74–7. discussion 78.
34. Hernaiz Driever P, von Hornstein S, Pietsch T, et al. Natural history and management of low-grade glioma in NF-1 children. *J Neurooncol* 2010; 100:199–207.
35. Mahdi J, Shah AC, Sato A, et al. A multi-institutional study of brainstem gliomas in

children with neurofibromatosis type 1. *Neurology* 2017;88:1584–9.
36. Louis D, Ohgaki H, Wiestler OD, et al. *WHO classification of tumours of the central nervous system*, 4th edn. Lyon: IARC Press, 2016.
37. Ryall S, Krishnatry R, Arnoldo A, et al. Targeted detection of genetic alterations reveal the prognostic impact of H3K27M and MAPK pathway aberrations in paediatric thalamic glioma. *Acta Neuropathol Commun* 2016; 4:93.
38. Yang RR, Aibaidula A, Wang WW, et al. Pediatric low-grade gliomas can be molecularly stratified for risk. *Acta Neuropathol* 2018;136: 641–55.
39. Ishibashi K, Inoue T, Fukushima H, et al. Pediatric thalamic glioma with H3F3A K27M mutation, which was detected before and after malignant transformation: a case report. *Childs Nerv Syst* 2016;32:2433–8.
40. Ryall S, Tabori U, Hawkins C. A comprehensive review of paediatric low-grade diffuse glioma: pathology, molecular genetics and treatment. *Brain Tumor Pathol* 2017;34:51–61.
41. Kline CN, Joseph NM, Grenert JP, et al. Targeted next-generation sequencing of pediatric neuro-oncology patients improves diagnosis, identifies pathogenic germline mutations, and directs targeted therapy. *Neuro Oncol* 2017;19:699–709.
42. Hamisch C, Kickingereder P, Fischer M, et al. Update on the diagnostic value and safety of stereotactic biopsy for pediatric brainstem tumors: a systematic review and meta-analysis of 735 cases. *J Neurosurg Pediatr* 2017;20:261–8.
43. 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;189:647–55.
44. Fisher PG, Tihan T, Goldthwaite PT, et al. Outcome analysis of childhood low-grade astrocytomas. *Pediatr Blood Cancer* 2008;51:245–50.
45. 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;34:3537–43.
46. Ronghe M, Hargrave D, Bartels U, et al. Vincristine and carboplatin chemotherapy for unresectable and/or recurrent low-grade astrocytoma of the brainstem. *Pediatr Blood Cancer* 2010;55:471–7.
47. 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;61:1173–9.
48. 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;122:1261–9.
49. Kortmann RD, Timmermann B, Taylor RE, et al. Current and future strategies in radiotherapy of childhood low-grade glioma of the brain. Part II: treatment-related late toxicity. *Strahlenther Onkol* 2003;179:585–97.
50. Packer RJ, Pfister S, Bouffet E, et al. Pediatric low-grade gliomas: implications of the biologic era. *Neuro Oncol* 2017;19:750–61.