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Neurosurgical morbidity in pediatric supratentorial midline low-grade glioma: Results from the German LGG studies

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Abstract

Surgical resection is a mainstay of treatment for pediatric low-grade glioma (LGG) within all current therapy algorithms, yet associated morbidity is scarcely reported. As supratentorial midline (SML) interventions are particularly challenging, we investigated the frequency of neurosurgical complications/new impairments aiming to identify their risk factors. Records were retrospectively analyzed from 318 patients with SML-LGG from successive German multicenter LGG studies, undergoing surgery between May 1998 and June 2020. Exactly 537 operations (230 resections, 167 biopsies, 140 nontumor procedures) were performed in 318 patients (54% male, median age: 7.6 years at diagnosis, 9.5 years at operation, 11% NF1, 42.5% optic pathway glioma). Surgical mortality rate was 0.93%. Applying the Drake classification, postoperative surgical morbidity was observed following 254/537 (47.3%) and medical morbidity following 97/537 (18.1%) patients with a 40.1% 30-day persistence rate

Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; GPOH, Gesellschaft fuer paediatrische Onkologie und Haematologie (German Society of Pediatric Oncology and Hematology); HIT, Hirntumorstudien (German brain tumor studies); IOC, intraoperative complication; LGG, low-grade glioma; MRI, magnetic resonance imaging; NF1, neurofibromatosis type 1; OPG, optic pathway glioma; pLGG, pediatric low-grade glioma; POC, postoperative complication; SIOP, Societé Internationale d'Oncologie Pédiatrique (International Society of Pediatric Oncology); SML, supratentorial midline; VPS, ventriculo-peritoneal shunt; WHO, World Health Organization.

Sarah Weiß and Ulrich-Wilhelm Thomale contributed equally to our study.

for newly developed neurological deficits (65/162). Neuroendocrine impairment affected 53/318 patients (16.7%), visual deterioration 34/318 (10.7%). Postsurgical morbidity was associated with patient age <3 years at operation, tumor volume ≥80 cm^3, presence of hydrocephalus, complete resection, surgery in centers with less than median reported tumor-related procedures and during the earlier study period between 1998 and 2006, while the neurosurgical approach, tumor location, NF1 status or previous nonsurgical treatment were not. Neurosurgery-associated morbidity was frequent in pediatric patients with SML-LGG undergoing surgery in the German LGG-studies. We identified patient- and institution-associated factors that may increase the risk for complications. We advocate that local multidisciplinary teams consider the planned extent of resection and surgical skills.

KEYWORDS
child, complication, low-grade glioma, morbidity, neuro-surgery, supratentorial midline

What's new?

Pediatric low-grade gliomas (LGGs) may be associated with high morbidity, despite excellent long-term survival. In particular, LGG along the supratentorial midline (SML) represents a challenging site for intervention, with very rare reporting of neurosurgical complications. Here, the authors analyzed interventions and postsurgical periods in German SML-LGG patients. Postsurgical morbidity was frequent among patients age 3 years or younger and among patients with larger tumor volume and hydrocephalus. Other factors associated with neurosurgical morbidity included complete resection and surgery at institutions where interventions for SML-LGG were carried out less often. The findings highlight areas for consideration in reducing neurosurgical complications in SML-LGG.

1 | INTRODUCTION

Brain and other central nervous system (CNS) tumors are the most frequent solid tumors in children and adolescents and account for the majority of cancer mortality in this age-group.[1] Low-grade gliomas (LGG) account for up to half of all pediatric CNS tumors.[1-3] They are a heterogeneous biologic group characterized by slow growth, in which molecular diagnostics identified an increasing number of distinctive mutations.[4-6] Pediatric LGG (pLGG) are associated with excellent long-term survival,[2,7] but with an often significant morbidity, as well. Over the past decades management of pLGG patients has changed toward integrating surgical and nonsurgical therapies in comprehensive treatment algorithms with the aim of disease control by minimizing long-term toxicity.[8] Neurosurgery remains the mainstay of treatment with a role for diagnosis, tumor control and relief of mass effect,[9] and technical advances supported substantially an improved surgical management.[10-12] Complete resections were confirmed as favorable prognostic factor.[13-17] Key drivers for tumor regrowth or relapse and patterns of behavior of the various tumor subtypes are not fully understood, yet size and site of tumor remnants play a significant role.[15,16,18] Thus, the benefit of extended surgical resection needs to be balanced against the risks of complications and late-effects. They need to be addressed besides all other management issues of pLGG including the indication for and the timing of other therapeutic interventions.

Major sites of pLGG are the supratentorial midline (SML), that is, optic pathways, diencephalon and mesencephalon.[13,14,17] These midline tumors tend to progress following initial management requiring multimodal treatment in a high portion of patients.[14,17,19-21] The aim of performing lesionectomy is challenging considering the deseness of eloquent structures.[22] And specifically for these midline sites, neurosurgical considerations have to address the balance of the risk of surgery-related neurological deficits against the perceived need for a complete vs an incomplete resection, in particular if tumor remnants are likely to be asymptomatic and do not cause mass-effect.[15]

Most studies on pLGG focused on epidemiology, neuropathological features or different nonsurgical treatment approaches.[20,23] Complications and related impairments following neurosurgery in pLGG of these challenging SML regions are rarely reported,[24,25] sometimes only aside to other aspects.[9,26-30] Therefore, we analyzed data from patients treated within the comprehensive therapy algorithm of the successive German pediatric LGG multicenter studies for the frequency of neurosurgical morbidity.[2,13,14] We investigated the association to patient and tumor characteristics as well as to basic surgical data to identify risk factors.

2 | PATIENTS AND METHODS

2.1 | Patients

We retrospectively included patients with pediatric SML-LGG who received at least one neurosurgical intervention within the German

cooperative multicenter LGG studies (Hirntumorstudien – HIT) HIT-LGG 1996[13] or SIOP-LGG 2004[14,23] which prospectively registered patients with LGG of all CNS localizations between 1 October 1996 and 31 March 2012. Initial inclusion criteria comprised age <18 years, histologic diagnosis of LGG according to the respective World Health Organization (WHO) classification and no prior treatment. Central review for neuropathology and neuroradiology was recommended. Follow-up included information up to 4 August 2020.

The German cooperative multicenter LGG studies adhered to the WHO and European Community rules of "Good Clinical Practice" (effective 17 January 1997) as well as the Declaration of Helsinki in its revised version (Edinburgh, Scotland, 2000).

2.2 | Treatment guideline

All patients with SML-LGG followed the study strategy, that is, at diagnosis, best safe resection of the primary tumor was recommended. Following complete or incomplete resection without clinically symptomatic or progressive tumor remnants patients were to be observed. Nonsurgical treatment was indicated for patients with residual tumor and neurological deterioration or continuous tumor progression in whom (re-) resection was deemed unfeasible.[13,14,23] The age limit for primary chemotherapy instead of primary radiotherapy was raised from ≤5 years in the HIT-LGG 1996 study to <8 years in the SIOP-LGG 2004 study. Nonsurgical treatment consisted of primary chemotherapy for all patients with neurofibromatosis type 1 (NF1). Patients ≥8 years were allowed to receive chemotherapy or radiotherapy. Treatment of recurrence or progression following first-line, nonsurgical therapy was not standardized but included the aforementioned therapeutic modalities upon discussion in the local and national reference multidisciplinary tumor boards.[2] Neurosurgical interventions were favored, if feasible.

2.3 | Neurosurgical treatment

All consecutive tumor-related interventions regarding solid as well as cystic tumor components of SML-LGG were included in the analysis, also comprising those beyond adolescence. Decision making may have varied during the study period and among the participating centers. The extent of solid tumor-related neurosurgical intervention was classified as biopsy, partial, subtotal or complete resection based on both, surgical and radiological judgment.[8,31] Extent of resection was defined radiologically as complete, if there was no evidence of residual tumor, and as subtotal, if a small, nonmeasurable tumor rim or lining was visible on the postoperative scans. Measurable, distinct tumor remains were classified as partial resection, while a biopsy left the tumor radiologically unchanged.

All other disease-related interventions, that is, to treat cystic tumor components, cerebrospinal fluid (CSF) circulation disorders as well as operations to apply interstitial radiotherapy were considered as "other interventions."

2.4 | Assessment of neurosurgical morbidity

All available medical/surgical records were reviewed, and all adverse events occurring within 30 days of surgery linked to the appropriate neurosurgical intervention were recorded qualitatively. If a patient suffered from several adverse events due to the same neurosurgical procedure, each event was recorded separately, even if they were mutually dependent.

By definition adverse events, complications and related new impairments, included all deviations from the regular postoperative course. We classified all adverse events according to the Drake classification,[25] a relevant morbidity measure in pediatric neurosurgery.[32] In addition to the Drake classification, we recorded increase of pre-existing deficits, 30 days persistence of a newly developed neurological deficit, and newly developed neuroendocrine impairment with regard to the respective neurosurgical procedure, that is, tumor resection, biopsy or other interventions.

2.5 | Neuroimaging

Central radiologic review was performed at the Reference Center for Neuroradiology of the German Society of Pediatric Oncology and Hematology (GPOH), Wuerzburg, Germany. Neuro-imaging followed recommendations of the German pediatric brain tumor network ("HIT-Netzwerk")[33] and published consensus by the European SIOP Brain Tumor Imaging Group.[8,31] Details are outlined in Figure S1.

2.6 | Statistical analysis

Statistical analyses were performed using IBM SPSS 29 (Armonk, NY) and GraphPad Prism 9.0.0 software (GraphPad Software, San Diego, CA).

Potentially relevant factors that may be associated with the occurrence of surgical morbidity, that is, patient age, NF1 status, tumor location and volume, nonsurgical therapy before surgery, preoperative ventricle width, neurosurgical technique and approach, extent of resection, surgery in centers with less than median/equal to median reported resections/interventions, date of surgical intervention were analyzed. Nonparametric tests were performed, Mann-Whitney *U* or Kruskal-Wallis, followed by Dunn's multiple comparisons test, to analyze possible differences between factors.

Level of significance was assumed in case of a given *P*-value <.05 and is indicated in figures and tables, accordingly.

3 | RESULTS

3.1 | Patient characteristics

A total of 334 patients with pediatric SML-LGG for whom the local team had indicated surgical treatment were identified among 2491

TABLE 1 Characteristics (n = 318 patients, n = 617 interventions)

	All	Optic pathways			Diencephalon (n = 98)	Mesencephalon (n = 85)
		Dodge[a] I (n = 10)	Dodge II (n = 18)	Dodge III (n = 107)		
a. Epidemiology						
Sex						
Male	171 (53.7%)	4	11	64	43	49
Female	147 (46.3%)	6	7	43	55	36
Median age at diagnosis	7.59	7.77	3.57	4.49	9.97	9.46
(IQR), years	(3.78, 11.62)	(4.82, 11.37)	(1.28, 7.50)	(1.24, 8.90)	(5.36, 12.73)	(6.04, 12.50)
Median age for all surgeries (IQR), years	9.51 (6.19, 13.37)	10.84 (6.15, 13.27)	7.55 (4.01, 13.07)	7.6 (3.94, 11.16)	10.43 (6.29, 13.21)	11.05 (7.16, 14.14)
NF1, n (%)						
No	283 (88.9%)	10	15	90	94	74
Yes	35 (11.1%)	0	3	17	4	11
Dissemination, n (%)						
Primary	20 (6.3%)	0	2	11	5	2
Secondary	15 (4.7%)	0	2	8	2	3
No dissemination	283 (89%)	10	14	88	91	80
Histology at first surgery, n (%)						
PA WHO I	223 (70.1%)	10	14	86	59	54
PMA variant of PA	15 (4.7%)	0	2	11	1	1
DG WHO II	26 (8.2%)	0	0	1	16	9
Glioneuronal tumors[b]	16 (5.0%)	0	1	2	8	5
Other LGG[c,d,e]	22 (6.9%)	0	0	4	9	9
No tumor in tissue specimen	15 (4.7%)	0	1	2	5	7
Clinical diagnosis	1 (0.3%)	0	0	1	0	0

	All	Optic pathways			Diencephalon (n = 98)	Mesencephalon (n = 85)
		Dodge[a] I (n = 10)	Dodge II (n = 18)	Dodge III (n = 107)		
b. Of neurosurgical procedures						
Type of intervention (n = 617 surgeries)						
Resections	260					
Complete	48 (7.8%)	5	3	12	21	7
Subtotal	51 (8.3%)	3	1	13	15	19
Partial	161 (26.1%)	1	9	81	34	36
Biopsies	203					
Stereotactic	114 (18.5%)	1	5	29	45	34
Endoscopic	33 (5.3%)	0	3	9	10	11
Open	56 (9.1%)	3	5	20	12	16
Other interventions	154					
Cyst operation	25 (4.1%)	0	3	9	7	6
Endoscopic third ventriculostomy	20 (3.2%)	0	0	1	2	17
Orbital decompression	1 (0.2%)	1	0	0	0	0
Placement of ventriculo-peritoneal shunt	63 (10.2%)	0	4	26	13	20
Placement of ^{125}Iodine seeds	41 (6.6%)	0	3	12	14	12
Other[d]	4 (0.6%)	0	0	1	3	0

TABLE 1 (Continued)

	All	Optic pathways			Diencephalon (n = 98)	Mesencephalon (n = 85)
		Dodge[a] I (n = 10)	Dodge II (n = 18)	Dodge III (n = 107)		
Type of neurosurgical approach (n = 361 surgeries)						
Transcallosal	12	0	2	6	4	0
Transfrontal	100	1	4	40	55	0
Subfrontal	20	4	3	12	1	0
Transcortical-ventricular	11	0	1	6	4	0
Temporal/pterional	107	6	10	65	26	0
Other[e]	3	1	0	2	0	0
Midline	32	0	0	0	0	32
(Sub-)temporal	22	0	0	0	1	21
(Sub-)occipital	54	0	0	0	13	41
Number of interventions (n = 318 patients)						
1 intervention	158 (49.7%)					
Tumor-related	*156 (98.7%)*	7	7	61	52	29
Other	*2 (1.3%)*	0	0	1	0	1
2 interventions	84 (26.4%)					
Tumor-related	84 (100%)	2	8	17	27	30
Other	0	0	0	0	0	0
3 Interventions	44 (13.8%)					
Tumor-related	41	1	2	12	10	16
Other	3	0	0	1	1	1
>3 Interventions	32 (10.1%)					
Tumor-related	32 (100%)	0	1	15	8	8
Other	0	0	0	0	0	0
Nonsurgical therapy prior to first surgery (n = 318 patients)						
No neoadjuvant therapy	281 (88.4%)	7	16	79	97	82
Only chemotherapy	28 (8.8%)	1	1	24	0	2
Only radiotherapy	5 (1.5%)	1	0	2	1	1
Chemoradiotherapy	4 (1.3%)	1	1	2	0	0
Nonsurgical therapy prior to the respective surgical intervention (n = 617 interventions)						
No adjuvant therapy	438 (71%)	8	23	118	139	150
Only chemotherapy	96 (15.5%)	4	6	59	12	15
Only radiotherapy	46 (7.5%)	1	2	15	13	15
Chemoradiotherapy	37 (6.0%)	1	5	21	10	00
Survival status at last follow-up						
Alive	287 (90.3%)	10	16	91	88	82
Dead	31 (9.7%)	0	2	16	10	3

Abbreviations: DG, diffuse glioma; IQR, interquartile range; LGG, low-grade glioma; NF1, neurofibromatosis type 1; PA, pilocytic astrocytoma; PMA, pilomyxoid astrocytoma.

[a]Dodge HW, Love JG, Craig WM, et al. Gliomas of the optic nerves. *AMA Arch Neurol Psychiatry*. 1958;79:607-621. doi: 10.1001/archneurpsyc.1958.02340060003001.

[b]Glioneuronal tumors: Gangliogliomas, dysembryoplastic neuroepithelial tumors and rosette-forming glioneuronal tumors.

[c]Other LGG: Angiocentric glioma, pleomorphic xanthoastrocytoma WHO II and LGG not otherwise specified.

[d]Other: External ventricular drain, evacuation of subdural hygroma.

[e]Other: Transphenoidal and transconjunctival approach.

pLGG patients recruited between 1997 and 2012 into two German LGG studies; 16/334 patients were excluded from analysis for missing sufficient postoperative data within 30 days after surgery (n = 13) or neuropathological reference diagnosis of non-low-grade glioma in retrospect (n = 3). Eventually, our cohort comprised 318 pediatric SML-LGG (Table 1). Exactly 46% of patients (147/318) were female, and 11% had at least clinically confirmed NF1. Median age at first surgery was 9.5 years (range 0.3-25.6 years). Most tumors were localized in the optic pathways (42%) with hypothalamic extension in 107/135 (classified as Dodge III, 79%; Figure 1). Dissemination was present in 20/318 at diagnosis and evolved during follow-up in 15/318. Pilocytic astrocytoma (WHO grade I) was the major neuropathological diagnosis (70%) followed by diffuse glioma WHO grade II (8%). In 5% of all patients, no tumor tissue was detected in the excised specimen.

3.2 | Neurosurgical procedures

Within the observation period, 617 surgical interventions were performed in 318 patients (Table 1). Surgical reports were available for 607 interventions, while accurate postoperative follow-up medical/surgical data were missing for 80/617 procedures. Thus, 537 interventions were analyzed with respect to any surgical related morbidity within 30 days after surgery. Exactly 158/318 patients had just 1 intervention (tumor-related n = 156, other n = 2); 160/318 patients had multiple interventions with successive tumor-related surgeries in 69, solely other interventions in 3 and tumor-related plus other interventions in 88 patients with biopsy followed by other interventions as the most frequent combination.

Preoperative tumor extension was assessed by central neuroradiologic review for 289/617 interventions with tumor volumes ranging from 0.12 to 384.56 cm^3 (median 14.14 cm^3). Neuroradiological reports described preoperatively severe increased ventricle width in 27/537 interventions affecting 27 patients.

Solid tumor-related operations were performed in 397/537 interventions with a majority of biopsies (42.1%, n = 167/397) and 10.3% (n = 41/397) complete resections. Over the years, the percentage of complete and subtotal resections declined.

Other disease-related interventions were performed in 140/537 surgeries. Besides cyst operations, that is, resections, fenestrations or catheter implantations (15.7%, n = 22), most interventions were prompted by the necessity to regulate increased intracranial pressure with endoscopic third ventriculostomy in 14.3% (n = 20), placement of ventriculo-peritoneal shunt (VPS) in 25.7% (n = 36), as well as VPS revision in 12.9% (n = 18) or implantation of transient extraventricular drainage in 2.1% (n = 3). Interstitial radiosurgery with placement of ^{125}Iodine seeds was performed in another 27.8% (n = 39).[34]

The neurosurgical approach was reported for 433 procedures. Interventions were performed via 10 different routes: transcallosal (n = 12), transfrontal (n = 133), subfrontal (n = 20), transcortical-ventricular (n = 11), temporal/pterional (n = 116), transsphenoidal (n = 2), transconjunctival (n = 1), via the midline (n = 58), (sub-)temporal (n = 23) and (sub-)occipital (n = 57).

Neurosurgical interventions were performed in 63 hospitals, 29 of them were university hospitals (226 patients, 474 procedures) and 34 were large, tertiary care hospitals (77 patients, 143 procedures). Fifteen patients received neurosurgical treatment in university and nonuniversity hospitals.

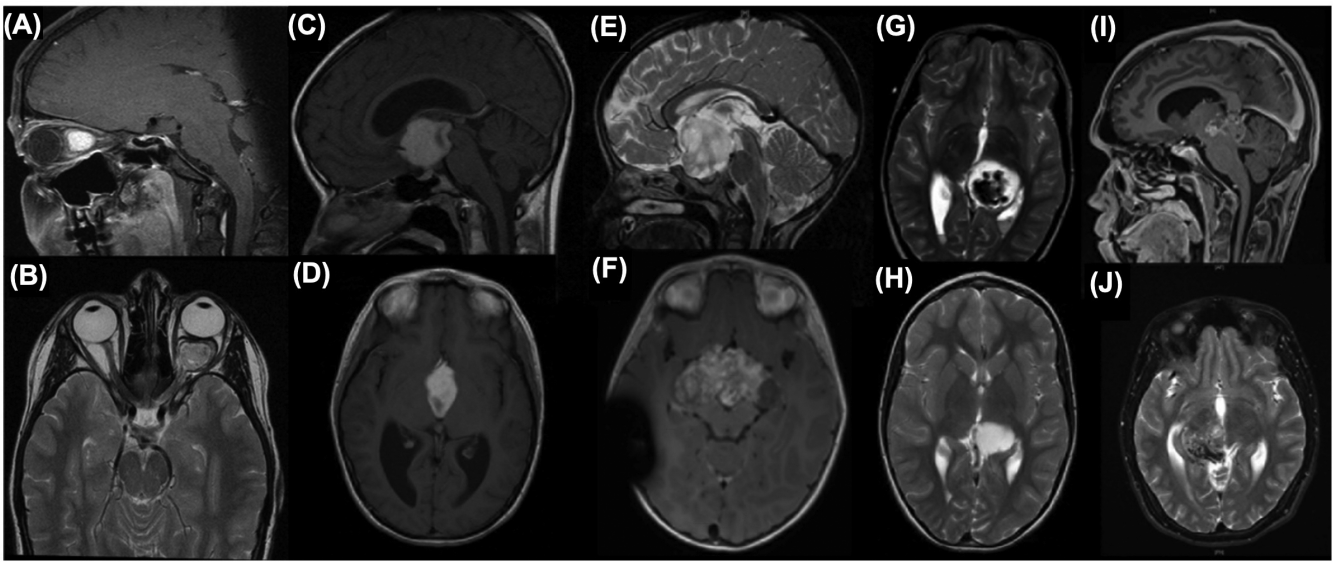

FIGURE 1 MR images of representative examples of the main tumor localizations. (A,B) Isolated optic nerve pilocytic astrocytoma (Dogde I) sagittal and axial T2 weighted images (T2WI). (C,D) Chiasmatic pilocytic astrocytoma with main tumor parts in the third ventricle (Dogde II) sagittal and axial T1 weighted images with contrast enhancement (T1WI CE). (E,F) Intrinsic chiasmatic hypothalamic pilocytic astrocytoma with optic tract involvement (Dogde III) in a shunted patient with valve artifact (F) sagittal T2WI and axial T1WI CE. (G,H) Mesencephalic pilocytic astrocytoma with intratumoral hemorrhage axial T2WI(G). (I,J) Intrinsic diencephalic ganglioglioma with diffuse contrast enhancement and calcification sagittal and axial T1WI.

TABLE 2 Postsurgical morbidity according to the classification by Drake et al[25] (n = 537 interventions).

Surgical morbidity		Medical morbidity	
a. For resections			
Neurological deficit	107	Cardiac	9
Meningitis	12	Respiratory/pneumonia	4
Seizures	21	Gastrointestinal/hepatic	4
Wound infection	2	Renal/genitourinary/urinary tract infection	6
CSF leak	38	Hematological/thromboembolic	3
Shunt blockage	2	Metabolic	0
Shunt infection	1	Cognitive	5
Hemorrhage, managed medically	39	Miscellaneous	0
Hemorrhage, returned to OR	0		
Infarction	36		
Other[a]	66	Other[b]	54
Total	324 (170 patients)	Total	85 (69 patients)
b. For biopsies			
Neurological deficit	31	Cardiac	3
Meningitis	5	Respiratory/pneumonia	0
Seizures	5	Gastrointestinal/hepatic	0
Wound infection	0	Renal/genitourinary/urinary tract infection	3
CSF leak	7	Hematological/thromboembolic	0
Shunt blockage	0	Metabolic	0
Shunt infection	1	Cognitive	3
Hemorrhage, managed medically	8	Miscellaneous	0
Hemorrhage, returned to OR	0	Other	10
Infarction	1		
Other[c]	18	Other[d]	10
Total	76 (57 patients)	Total	19 (15 patients)
c. For other interventions			
Neurological deficit	8	Cardiac	1
Meningitis	2	Respiratory/pneumonia	1
Seizures	3	Gastrointestinal/hepatic	0
Wound infection	3	Renal/genitourinary/urinary tract infection	1
CSF leak	5	Hematological/thromboembolic	0
Shunt blockage	0	Metabolic	0
Shunt infection	2	Cognitive	1
Hemorrhage, managed medically	4	Miscellaneous	0
Hemorrhage, returned to OR	0		
Infarction	1		
Other[e]	8	Other[f]	9
Total	36 (27 patients)	Total	13 (13 patients)

Abbreviation: OR, operating room.

[a]Hygroma (n = 64), cephalic hematoma (n = 4), development of hydrocephalus (n = 15), herniation of the temporal lobe through a bore hole (n = 1), stenosis of the internal carotid and cerebri media artery (n = 1).

[b]Hypothalamic dysregulation of eating behavior (n = 2), central disturbance of hearing perception (n = 1), temperature dysregulation (n = 5), fever of unknown origin (n = 3), inguinal dermatitis (n = 1), colpitis (n = 1), oral candidiasis (n = 1), cutaneous candidiasis (n = 1), aphthous stomatitis (n = 1), acute stress disorder (n = 2), behavioral disorder (n = 1), proptosis (n = 1), propofol-induced rhabdomyolysis (n = 1), diabetes insipidus (n = 25), SIADH (n = 13), hyponatremia of unknown origin (n = 2), hypopituitarism (n = 22), cerebral salt wasting syndrome (n = 16).

[c]Hygroma (n = 15), cephalic hematoma (n = 1), dislocation of extra-ventricular drainage (n = 1), development of hydrocephalus (n = 3).

[d]Fever of unknown origin (n = 4), herpes labialis (n = 1), diabetes insipidus (n = 2), SIADH (n = 1), hyponatremia of unknown origin (n = 2), hypopituitarism (n = 1).

[e]Hygroma (n = 5), development of low pressure hydrocephalus (n = 1), internalization of extra-ventricular drainage (n = 1).

[f]Fever of unknown origin (n = 2), serous conjunctivitis (n = 1), diabetes insipidus (n = 1), SIADH (n = 2), cerebral salt wasting syndrome (n = 2), hyponatremia of unknown origin (n = 2), centrale hyperthermia (n = 1).

TABLE 3 Relation of postsurgical morbidity to clinical risk factors.

	P-value
Analysis of nontumor related interventions ($n = 140$)	
Patient age at intervention	
<3 years vs 3 to <12 years	n.s.
<3 years vs 12-25 years	n.s.
3 to <12 years vs 12-25 years	n.s.
Number of interventions at a given center during the observation period	
≤2 interventions vs >2 interventions	n.s.
Date of surgery	
1998-2006 vs 2007-2009	n.s.
1998-2006 vs 2010-2011	n.s.
1998-2006 vs 2012-2019	n.s.
2007-2009 vs 2010-2011	n.s.
2007-2009 vs 2012-2019	n.s.
2010-2011 vs 2012-2019	n.s.
Preoperatively increased ventricle width	
None to moderate vs severe	n.s.
Analysis of tumor-related procedures ($n = 397$)	
Patient age at intervention	
<3 years vs 3 to <12 years	n.s.
<3 years vs 12-25 years	n.s.
3 to <12 years vs 12-25 years	n.s.
Preoperative tumor volume	
0-39.9 cm^3 vs 40-79.9 cm^3	n.s.
0-39.9 cm^3 vs ≥80 cm^3	**.0036**
40-79.9 cm^3 vs ≥80 cm^3	n.s.
Preoperatively increased ventricle width	
None to moderate vs severe	**.0004**
Number of interventions at a given center during the observation period	
≤4 interventions vs >4 interventions	**.0007**
Extent of resection	
Partial resection vs subtotal resection	n.s.
Partial resection vs complete resection	**.0092**
Subtotal resection vs complete resection	n.s.
Method of biopsy	
Stereotactic biopsy vs endoscopic biopsy	n.s.
Stereotactic biopsy vs open biopsy	**.0078**
Endoscopic biopsy vs open biopsy	n.s.
Type of intervention	
Resections vs biopsies	**<.0001**
Resections vs cyst operations	**<.0001**
Biopsies vs cyst operations	n.s.
Analysis for tumor resections only ($n = 230$)	
Patient age at tumor resection	
<3 years vs 3 to <12 years	n.s.
<3 years vs 12-25 years	**.0025**
3 to <12 years vs 12-25 years	n.s.
Number of tumor resections at a given center during the observation period	
≤3 tumor resections vs >3 tumor resections	**.0040**
Date of surgery	
1998-2006 vs 2007-2009	n.s.
1998-2006 vs 2010-2011	n.s.
1998-2006 vs 2012-2019	**.0216**
2007-2009 vs 2010-2011	n.s.
2007-2009 vs 2012-2019	n.s.
2010-2011 vs 2012-2019	n.s.

Note: Bold values indicate statistical significance ($P < .05$).

Nonsurgical therapy before the first surgery had been given to 37/318 patients (11.6%; chemotherapy n = 28, radiotherapy n = 5, radio- and chemotherapy n = 4). This fraction increased for subsequent interventions over time to 29.0% considering all interventions (chemotherapy n = 96, radiotherapy n = 46, radio- and chemotherapy n = 37) and concerned 94/318 patients (29.6%).

3.3 | Intraoperative complications (for 318 patients and 617 interventions)

A total of 12 intraoperative complications were reported in 617 procedures, 3 of which occurred during complete resections (n = 1 severe arterial bleeding, n = 1 transection of pituitary stalk, n = 1 of optical nerve) and 5 were reported during partial resections (n = 2 severe arterial bleeding, n = 1 transection of the trochlear nerve, n = 1 direct injury of the carotid artery, n = 1 accidental extubation). Four severe bleedings were reported during two open and two stereotactic biopsies. The two hemorrhages during stereotactic biopsies resulted in the termination of the procedure in one case and caused patient death in the other. No intraoperative complication was reported during a subtotal resection.

3.4 | Surgical mortality (for 318 patients and 617 interventions)

Three out of 318 patients died indicating a surgical mortality rate of 0.94%. Dissection of the pituitary stalk resulted in diencephalic dysregulation leading to protracted death in two patients. In one patient bleeding following a biopsy caused death.

3.5 | Postoperative morbidity (for 286 patients and 537 documented postsurgical periods)

Applying the Drake classification[25] postoperative surgical morbidity was observed 436 times and medical morbidity 117 times (Table 2).

Exactly 215 neurological disturbances occurred in 123/286 patients due to the previous operative procedure (Table S1). A total of 162 newly developed deficits occurred in 101 patients with a 30-day persistence rate of 40.1% (65/162 deficits), affecting 47/101 patients. Newly developed focal deficits prevailed with highest rates following complete resections (42 deficits in 20 patients) and open biopsies (8 deficits in 8 patients). Next, 48 preexisting neurological deficits were aggravated after the surgical procedure in 41 patients, mainly following partial resections and stereotactical biopsies. Disturbance of vigilance was reported in 5/286 patients—like somnolence and stupor or prolongated hypersomnia—and only after resections. Seizures were reported in 29/286 patients: after prior resection in 21, following biopsy in 5 and following another intervention in 3 patients. Newly developed endocrine impairments were seen in 53/286 patients (18.5%) with highest occurrence after partial resections and open biopsies.

Deterioration of visual function was reported in 34/286 patients (11.9%), mostly in the context of visual pathway glioma (n = 27/34, 79.4%), without being detailed in most of them.

Space-occupying intracerebral hemorrhages occurred in 14/537 (2.6%) interventions but required no subsequent emergency surgery within 30 days. Clinically relevant infarction developed after 16/537 (3.0%) interventions, hydrocephalus requiring action after 19/537 (3.5%) interventions, hygroma after 84/537 (15.6%) interventions, CNS infections after 19/537 (3.5%) interventions. Infections outside the CNS affected 27 patients. Cardiovascular events, that is, postoperative bradycardia, tachycardia, venous thrombosis, pulmonary artery embolism, stenosis of intracranial arteries, occurred in 17 patients. Twenty-nine patients needed readmission to intensive care within 30 days following surgery.

3.6 | Clinical risk factors for postsurgical morbidity

3.6.1 | Tumor-related interventions

With respect to tumor-related interventions, that is, resections and biopsies, a preoperative tumor volume above 80 cm^3 and preoperatively severely increased ventricle width was noticeably associated with an increased risk for surgery-associated morbidity. Moreover, morbidity due to the tumor-related procedures was increased in institutions with less than median/equal to median reported tumor interventions during the study period. Thirty-two institutions had reported less than median/equal to median tumor interventions. In addition, realization of complete resection vs partial resection predicted noticeably more surgery-associated morbidity. As well, open biopsies vs stereotactic procedures predicted noticeably more surgery-associated adverse events. Endoscopic biopsies showed similar morbidity compared to stereotactic ones but were relatively underrepresented. Patient age was noticeably associated with postsurgical morbidity following tumor resections with more events in younger patients, while

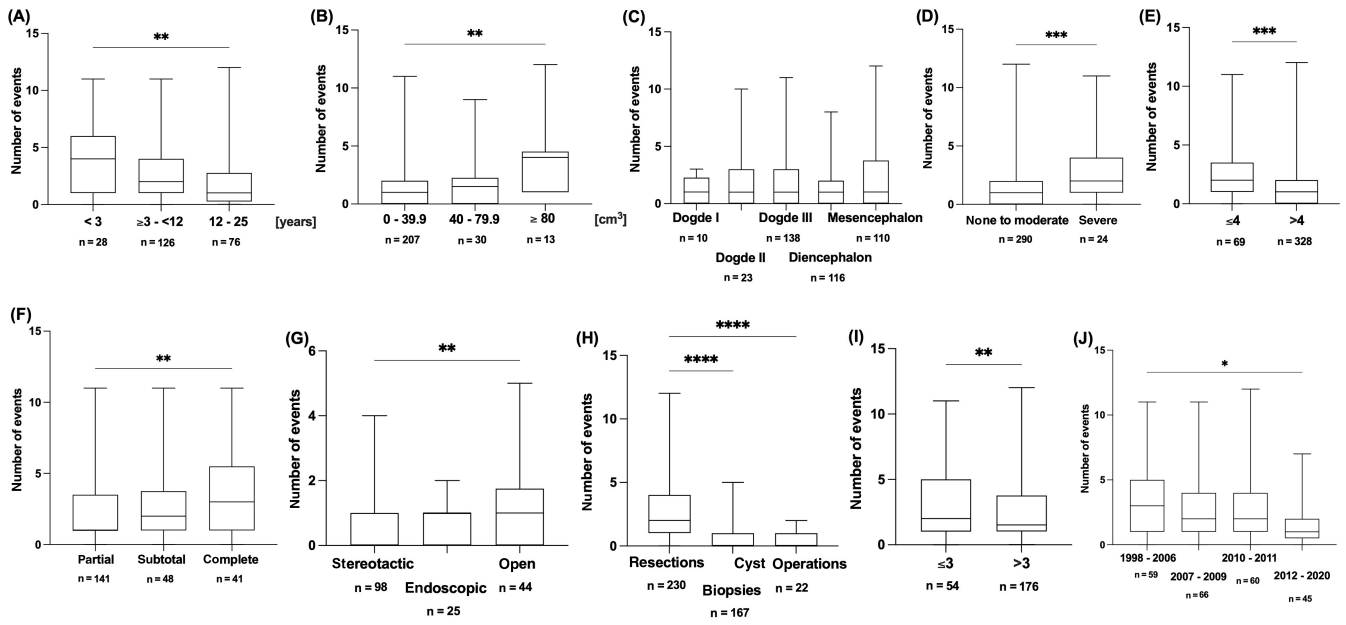

FIGURE 2 Frequency of postsurgical morbidity in relation to clinical factors concerning all tumor-related procedures. Postsurgical complications/new impairments were assessed for dependency to (A) patient age at tumor resection, (B) tumor volume, (C) tumor localization, (D) presence of increased ventricle width preoperatively, (E) surgery in centers with less than median/equal to median vs above median reported interventions, (F) extent of resection, (G) method of biopsy, (H) type of intervention. Only tumor resections were assessed for (I) surgery in centers with less than median/equal to median vs above median reported resections and (J) date of resection. Mann-Whitney *U* and Kruskal-Wallis tests, respectively, with $^{*}P < .05$; $^{**}P < .01$; $^{***}P < .001$; $^{***}P < .0001$. The lines in the boxes are the median. The box height represents the 25th and 75th percentile, respectively. The whisker lengths are the minimal and maximal values (25th and 75th percentile ±1.5-fold interquartile range).

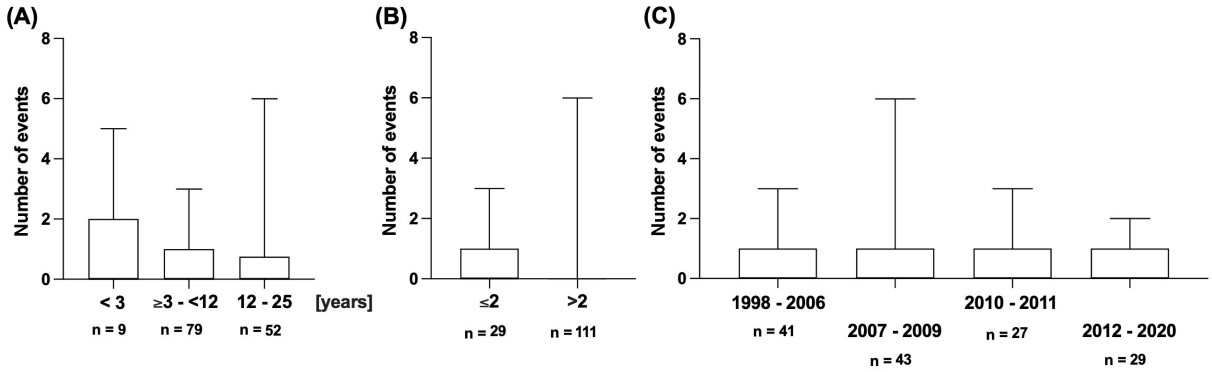

FIGURE 3 Frequency of postsurgical morbidity in relation to clinical factors concerning all nontumor related procedures. Postsurgical complications/new impairments were assessed for dependency to (A) patient age at intervention, (B) surgery in centers with less than median/equal to median vs above median reported interventions and (C) date of surgery. Mann-Whitney *U* and Kruskal-Wallis tests, respectively, with $P > .05$. The box height represents the 25th and 75th percentile, respectively. The whisker length is the maximal value (75th percentile ±1.5-fold interquartile range).

this was lost if all tumor-related interventions were cumulated. Morbidity was higher in institutions with less than median/equal to median reported tumor resections (n ≤ 3) during the observational period. This also applied to solid-tumor related resections during the time interval 1998 to 2006 regarding the date of the surgery (Table 3, Figure 2A-J).

NF1 status, tumor location within the SML, the type of neurosurgical approach and previous nonsurgical treatment did not impact upon the frequency of neurosurgical morbidity events following tumor-related interventions.

3.6.2 | Nontumor related interventions

No corresponding risk factors were identified for the nontumor related interventions. The number of surgical morbidity events was neither associated with patient age at surgery, centers with less than median/equal to median (n ≤ 2) reported interventions during the study period or with different study periods (Figure 3A-C). This also applied to the presence/absence of preoperatively severely enlarged ventricle width (Table 3).

4 | DISCUSSION

Neurosurgical interventions for pediatric LGG are an integral part of all interdisciplinary treatment algorithms.[8,15,16,35,36] Though the extent of surgery represents the pivotal point for subsequent treatment stratification of LGGs, the concomitant effects of neurosurgical interventions are scarcely studied. This report presents the first large-scale analysis of surgical morbidity following operative intervention in a pediatric cohort with supratentorial midline LGG recruited over a 15-year period from 63 hospitals within the population-based German LGG studies.[13,14] The overall frequency of complications or impairments due to the neurosurgical procedure in these challenging regions was high and showed an association to patient, tumor, therapy and institution-related risk factors. Intriguingly, the frequency of postoperative complications and impairments seems to mirror the skills at the treating center.

4.1 | Surgery in pediatric SML-LGG

Our cohort of 318 patients receiving neurosurgical tumor interventions as part of their therapy represented a selected subgroup from the German HIT-LGG 1996 and SIOP-LGG 2004 studies,[13,14] yet comprised the familiar spectrum of age groups, tumor sites within the SML and histologies. Although the majority of NF1-associated visual pathway gliomas were diagnosed radiologically, the cohort included 11% NF1 patients. The 2013 Paris consensus reserved histologic confirmation for chiasmatic-hypothalamic tumors with or without NF1 for tumors with atypical features,[36] while it was generally recommended to attempt resection at other SML sites.[35] The necessity to obtain tissue for subsequent biological stratification[6] had not been an indication to surgery during the recruitment period of both studies.

Comparable to the surgical intervention pattern in recent pediatric SML-LGG cohorts,[15,37] biopsies constituted the majority of tumor-related interventions in our cohort and complete resections amounted to only 10%. This distribution reflects the eloquence of the SML, impeding the attempt for complete resection, which is only justified when achievable with an acceptable functional outcome.[16] Thomale et al[15] reported delayed interventions in almost one-third of SML-LGG following initial observation as stipulated for tumors of small size or in situations with minor or no clinical symptoms. Comparable to the series of Hill et al,[37] CSF flow disorders necessitated frequent interventions in our cohort with increased ventricular width in 2/3 of cases. Low intra- and postoperative morbidity was reported for interstitial radiosurgery (permanent or transient implantation of ^{125}Iodine seeds) for LGG in eloquent areas in small series,[34] which was applied

for focal radiotherapy in suitable tumors and constituted a relevant portion of "other interventions" in our cohort.

Half of our patients had just one intervention, which was tumor-related in almost all cases. The other half had various combinations of tumor-related and other interventions comparable to the report of Hill et al,[37] while Thomale et al restricted analysis to tumor-related surgery.[15]

4.2 | Surgical morbidity

The definition of a complication is distinct from the failure to achieve the surgical goal[38] and encompasses any deviation from the ideal postoperative course that is not inherent in the procedure while not comprising the failure to cure.[24] The classification of surgical complications proposed by Drake et al[25] was specifically designed for neurosurgical patients and has already been adopted by pediatric neurosurgery units. It allows an appropriate grouping of surgical and medical morbidity and identifies same complications occurring with different procedures. Linking each complication to an individual intervention, the Drake system created a countable denominator instead of linking the adverse event rate to individual patients.[24]

4.2.1 | Intraoperative events

Twelve intraoperative complications (IOCs) (2.7%) were reported in our cohort without clear association to a type of tumor-related surgery, but most were classifiable as neurosurgical type of complication. This fraction is identical to the report of van Lindert et al[39] on intra- and postoperative complications in a cohort of 1000 consecutive pediatric neurosurgical procedures. We identified only one anesthesiologic complication corroborating its rarity from other reports.[40,41] Still, attention should be drawn to both types of intraoperative complications with the shared responsibility of the neurosurgeon and anesthesiologist.[40]

The intraoperative mortality rate was 0.94% in our cohort. This appears higher than the 0.3% in a general pediatric neurosurgical cohort,[39] while a recent monocentric study from Scotland reported a mortality rate of 2.1% in 287 neurosurgical operations.[24] But mean age at the time of surgery was lower in the Scottish cohort with 24.6% of procedures performed in infants. In the end, the notion should be challenged that more complications, enhancing the risk of death, may occur in pediatric tumor surgery compared to other neurosurgical interventions.[24,42]

4.2.2 | Postoperative events

Though the frequency of surgical morbidity in our cohort seemed higher opposed to commonly reported complication rates after pediatric neurosurgical procedures,[25,39] only Hill et al[37] addressed the issue of midline locations with their proximity to eloquent areas, thus comparability to other reports is limited.

New neurological deficits occurred more frequently following interventions for brain tumors as compared to other indications in a series of 769 craniotomies in pediatric patients.[42] In another large series of general pediatric neurosurgical interventions, almost half of the complications were cerebrovascular bleedings and only a minor fraction surgical brain injuries.[24,39,40] The prevalence of almost 50% postoperative neurological disturbances in our SML-LGG cohort corroborates findings of a Dutch single-center report on pediatric brain tumor patients.[43] Excluding biopsies from analysis and including tumors outside the SML, neurological complications occurred in 53/121 (44%) patients after first surgery persisting until discharge in 23/121 (19%).[43] Yet, Goodden et al[9] mentioned just 1/21 patients with a transient neurological deficit following debulking procedures in optic pathway/hypothalamic gliomas, although 3 patients had to return to the operating room. None of our patients required a second operation due to postoperative complications (POCs).

Newly developed neurological deficits with highest rates following complete resections and open biopsies (persisting in half of them) prevailed in our cohort, while preexisting neurological deficits aggravated in 15% to 20%, predominantly after partial resections or stereotactical biopsies. In line with the shift on the recommendations for the surgical treatment of optic pathway gliomas (OPGs) within the observation period,[36] this distribution may reflect patient selection for the procedures, limiting the extent of resection for patients with relevant preoperative deficits.

Comparable to other reports,[9,37,43] neuroendocrine impairment in one-fifth of our cohort affected mainly patients with OPG (40/111 patients, 36.0%) with more deficits following resections than biopsies and a high portion of diabetes insipidus and cerebral salt wasting.

4.2.3 | Risk factors

While the unfavorable impact of young age upon progression and survival in pLGG is well recognized, especially for infants with SML tumors,[14] our findings demonstrate that this is true for the rate of postoperative morbidity following resections, as well, and it was indicated even for surgical morbidity in a series of different tumor types.[44] Compared to older children or adolescents, the neurosurgical procedure in infants is hampered by an even smaller size of structures and eminent proximity of functionally critical regions, while at the same time younger patients frequently present with larger chiasmatic-hypothalamic tumors.[36] The enhanced risk for POCs in larger tumors is also supported by our data. As well, the preoperative presence of an increased ventricle width predominantly associated to severe hydrocephalus predisposed to more postoperative morbidity, this was not discussed elsewhere.[9,37,43]

Though the treatment algorithm for pLGG still calls for discussion of resection at presentation, primary resection of chiasmatic-hypothalamic LGG, and many other SML-LGG, is not any more the recommended standard of care.[36] In line with this, of all patient- and procedure-related factors that predicted the development of postoperative complications, preoperative tumor volume >80 cm^3 and

complete resection correlated strongly with an increased number of neurosurgical morbidity. On the other hand, if radical resections are to be avoided, available evidence indicates that the percentage of residual tumor is less important for long-term prognosis.[14,18,45] Thus, (re-) resections have to be restricted with regard to the complication/impairments and the limited options for re-intervention in the SML. This awareness is mirrored by the decreasing rate of extensive resections over time. In addition, throughout the past, improvements of neurosurgical tools and techniques helped to achieve the goals of surgery more safely.[9] This may well explain decreasing complication rates over the past decades, as demonstrated by our findings.

Based on our analysis, NF1 status, did not influence the frequency of neurosurgical morbidity. Although the percentage of NF1 patients was low in our surgical cohort, the distribution of the extent of resection was comparable to non-NF1 patients. Tumor location within the SML as well as the type of neurosurgical approach, for example, midline transcallosal or pterional, were not associated with the frequency of complications. Concerning neurosurgical interventions, a variety of surgical corridors provide access to the deep midline structures, notably the transcallosal, transventricular and skull base approaches. We assume, that the high number of approaches reflects individual selection to reduce potential dangers by respecting tumor location, tumor components like exophytic or cystic extensions, compression of adjacent eloquent structures or perforating arterial branches and by performing necessary interventions to the CSF pathways in the same procedure.

Importantly, previous nonsurgical treatment did not impact upon the frequency of neurosurgical morbidity in our series, and thus does not argue against postponing first-line surgery in SML-LGG.[8,36] It has not yet been investigated, if neo-adjuvant treatment was surgically advantageous in terms of reducing tumor size or lowering vascularity.[46]

The German low-grade glioma studies offered a nationwide frame for patient care in our noncentralized healthcare system.[2] Participation was encouraged for all pediatric oncological units, yet our data indicate a higher rate of postoperative complications for neurosurgical departments performing less than median reported (3 or less) tumor resections and/or less than median reported (4 or less) tumor-related procedures during the observation period. A comparable nationwide U.S. study revealed that the mortality rate for resections of pediatric brain tumors was significantly lower at high-volume hospitals than at low-volume hospitals, as well as after surgery performed by high-volume surgeons.[47] This so-called volume-outcome effect was previously demonstrated for intracranial tumor resection in adults[48] and likewise outlined in a European pediatric series.[43] Following this line, the SIOP working group for pLGG summarized current surgical recommendations for diagnosis and treatment of pediatric LGG in a list of key statements[8,36] urging to agree upon the procedure through the (local or central) multidisciplinary team prior to surgery including the reasons for surgery and the planned extent of resection. Given the results of this multicenter study and the explicit eloquence of pediatric SML-LGG, surgery should be performed by pediatric neurosurgeons with regular experience in microsurgical procedures in children with brain and spinal cord tumors. Otherwise, the patient should be referred to a center with appropriate case-specific expertise and equipment, the goal being to increase patient safety and reduce the risk of permanent neurological deficit.[49]

4.3 | Limitations of our report

As major shortcoming, data acquisition for the German low-grade glioma studies focused upon first-line nonsurgical therapy, and specifically in SIOP-LGG 2004 study, this was first-line chemotherapy within the randomized trial. All other aspects of treatment, including neurosurgical interventions, were prospectively documented with limited data sets only. IOCs were not queried prospectively in our cohort, and both types of IOCs are most likely underreported. As well, specific anesthesiologic or neurosurgical aspects as determents of frequency and type of (post-) surgical complications could not be analyzed.

We also lacked molecular-neuropathological data for most patients. Some have been included in our reports on diffuse glioma WHO grade II, spinal and brainstem LGG. Determining the surgical approach, tumor size and type of infiltration may be related to molecular characteristics.

5 | CONCLUSIONS

We found a remarkable complication rate for neurosurgical procedures in pediatric patients with low-grade glioma of the supratentorial midline. Among the patient- and institution-associated factors that may increase the risk for postsurgical morbidity, pediatric neurosurgical skills at the treating neurosurgical department and extent of resection should be considered before intervention.

Our results need prospective validation in upcoming trials. Data acquisition should be tailored accordingly, since additional factors need consideration, for example, surgical techniques and neurosurgeons' experience, but also non-neurological comorbidities that might influence the postsurgical course. Future studies should include long-term effects of neurosurgical morbidity upon the patient's clinical situation months or years after surgery. Problems may develop after discharge and have an ongoing impact on the patient's quality of survival. A field of possible action may be a registry for complications. Proposed by different centers,[25,39] the collection of procedural complications will be valuable for clinical purposes, research and education. Predicting the quality of pediatric tumor neurosurgery in terms of safety and outcome, comparing centers by quality measurement programs or referring residents and fellows to high-quality centers may impact upon health system management and resource allocation.

AUTHOR CONTRIBUTIONS

Sarah Weiß: Conception and design; Acquisition of data; Drafting article and critically revising. **Ulrich-Wilhelm Thomale:** Conception and design; Analysis and interpretation; Drafting article and critically revising. **Matthias Schulz:** Conception and design; Drafting article and critically revising. **Daniela Kandels:** Acquisition of data; Drafting article

and critically revising. **Martin U. Schuhmann:** Drafting article and critically revising. **Ahmed El Damaty:** Drafting article and critically revising. **Juergen Krauss:** Drafting article and critically revising. **Pablo Hernáiz Driever:** Drafting article and critically revising. **Olaf Witt:** Drafting article and critically revising. **Brigitte Bison:** Acquisition of data; Drafting article and critically revising. **Torsten Pietsch:** Acquisition of data; Drafting article and critically revising. **Astrid Gnekow:** Conception and design; Acquisition of data; Analysis and interpretation; Drafting article and critically revising. **Michèle Simon:** Conception and design; Acquisition of data; Analysis and interpretation; Drafting article and critically revising. The work reported in the article has been performed by the authors, unless clearly specified in the text.

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CONFLICT OF INTEREST STATEMENT

PHD is advisory board member for Bayer and Alexion. OW has consulting agreements with Roche, DayONE, Novartis and Bayer. BB receives a speaker's honorarium from Merck Healthcare Deutschland GmbH. All other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The HIT-LGG 1996[13] study was approved by local and central ethic boards. The SIOP-LGG 2004 study (ClinicalTrials.gov NCT00276640, EudraCT number 2005-005377-29)[14,23] protocol was ethically approved by the Ethical committee of the Ludwig Maximilian's University of Munich, Germany (No. 179-08). Informed consent was obtained from patients, parents and/or guardians.

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SUPPORTING INFORMATION

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

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