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ORIGINAL ARTICLE - PEDIATRIC NEUROSURGERY

Survival and functional outcomes in paediatric thalamic and thalamopeduncular low grade gliomas

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Abstract

Background Childhood thalamopeduncular gliomas arise at the interface of the thalamus and cerebral peduncle. The optimal treatment is total resection but not at the cost of neurological function. We present long-term clinical and oncological outcomes of maximal safe resection.

Methods Retrospective review of prospectively collected data: demography, symptomatology, imaging, extent of resection, surgical complications, histology, functional and oncological outcome.

Results During 16-year period (2005–2020), 21 patients were treated at our institution. These were 13 girls and 8 boys (mean age 7.6 years). Presentation included progressive hemiparesis in 9 patients, raised intracranial pressure in 9 patients and cerebellar symptomatology in 3 patients. The tumour was confined to the thalamus in 6 cases. Extent of resection was judged on postoperative imaging as total (6), near-total (6) and less extensive (9). Surgical complications included progression of baseline neurological status in 6 patients, and 5 of these gradually improved to preoperative status. All tumours were classified as low-grade gliomas. Disease progression was observed in 9 patients (median progression-free survival 7.3 years). At last follow-up (median 6.1 years), all patients were alive, median Lansky score of 90. Seven patients were without evidence of disease, 6 had stable disease, 7 stable following progression and 1 had progressive disease managed expectantly.

Conclusion Paediatric patients with low-grade thalamopeduncular gliomas have excellent long-term functional and oncological outcomes when gross total resection is not achievable. Surgery should aim at total resection; however, neurological function should not be endangered due to excellent chance for long-term survival.

Keywords Childhood glioma · Low-grade astrocytoma · Survival · Extent of resection · Thalamus

Abbreviations

cDNA	Complementary deoxyribonucleic acid
CST	Cortico-spinal tract
DNA	Deoxyribonucleic acid
EOR	Extent of resection
ETV	Endoscopic third ventriculostomy
FLAIR	Fluid-attenuated inversion recovery
GTR	Gross total resection
LGG	Low-grade glioma
MCS	Milan Complexity Scale
MRI	Magnetic resonance imaging
NTR	Near total resection
OS	Overall survival
PCR	Polymerase chain reaction
PFS	Progression-free survival
PR	Partial resection
RNA	Ribonucleic acid
RT PCR	Reverse transcriptase polymerase chain reaction
STR	Subtotal resection

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Introduction

Childhood tumours of the thalamic region are rare, representing less than 5% of brain tumour histopathology [6, 8, 14, 39]. They either arise directly at the thalamus or at the junction of thalamus and cerebral peduncle, so-called thalamopeduncular tumours [25]. Historically, surgery for these tumours was more conservative due to proximity of internal capsule, cortico-spinal tract (CST), hypothalamus, mesencephalon and other vital neurovascular structures and was thus deemed very high risk. Progress in neuroimaging allowing detailed presurgical planning, advanced microsurgical techniques and intraoperative neuromonitoring along with image guidance and postoperative care have shifted the balance towards more extensive resection in recent decades [4, 7, 20, 34, 36, 43]. More extensive surgery was associated with acceptable rates of surgical morbidity-mortality and excellent long-term survival especially in low-grade tumours.

Children with low-grade gliomas (LGG) have a very high chance of reaching adulthood, and in case of pilocytic astrocytoma histology, complete cure can be achieved with total resection, usually without the need for adjuvant oncological treatment [40]. In these patients, surgery should aim at maximal safe resection, that is surgery guided by intraoperative neuromonitoring and image guidance, where maintaining preoperative level of function takes precedence over resection extent. The goal of surgery is not a postoperative image where total resection is achieved but the patient is left severely disabled; rather, the goal is stable or improved neurological status regardless of resection extent.

The purpose of this study was to assess our surgical philosophy and strategy of maximal safe resection as described above in children harbouring thalamic and thalamopeduncular LGGs.

Patients and methods

Patient population

Patients treated for thalamic and thalamopeduncular LGG between 2005 and 2020 at our institution were identified in a prospectively collected database. Lesions originating from adjacent structures (optic pathways, hypothalamus, basal ganglia, brainstem, ventricles, pineal region or cerebellum) and merely extending into the thalamus or cerebral peduncle were excluded. Patients treated surgically elsewhere and referred to our tertiary centre for oncological treatment were excluded as well.

Clinical data and outcome assessment

Collected data included basic demography (gender, age) at presentation, duration and type of symptoms, and school attendance. Follow-up visits were scheduled postoperatively at 6 weeks, 3 months, 6 months, 1 year and annually thereafter. Clinical status of the patient was assessed preoperatively and at follow-up visits using the Lansky scale [18]. Current school type, grade and/or highest attained education or current employment was also noted. Neurological status was assessed preoperatively, postoperatively (usually on postoperative day one), at discharge and during follow-up visits. Permanent surgery-related neurological deficit was defined as absent on baseline examination and present at 3 months follow-up. Surgical mortality was defined as any death within 30 days of surgery. At each follow-up visit, patients were also classified according to disease status: complete remission with no residual tumour, stable disease and progressive disease. Disease progression was defined as tumour recurrence after gross-total or near-total resection, progression of residual tumour by more than 25% [10] after subtotal or partial resection or metastatic disease distant from the primary surgery site.

Neuroimaging

Each patient underwent detailed magnetic resonance imaging (MRI) preoperatively. In recent cases, diffusion tensor imaging was also used to assess the course of the CST and other relevant neural pathways (e.g. optic tract). Details noted on MRI included presence of cysts, calcifications, oedema, character of contrast media uptake, extension into surrounding structures and presence of hydrocephalus. For the purpose of preoperative volumetric analysis, the tumour was depicted on T1-weighted gadolinium enhanced, T2-weighted or fluid-attenuated inversion recovery (FLAIR) sequences depending on properties of the tumour. The 3D Slicer software [11] was used to quantify tumour volume on serial axial slices (0.7-mm or 1-mm cuts). Two clinicians (one experienced neurosurgeon not involved in the surgery and one neuroradiologist) blinded to the patient information performed the analysis. If the values differed substantially, a third independent analysis was performed. The final volume was calculated as mean from two most similar values (of the eventual three performed). Identical approach was used to calculate postoperative tumour volume on MRI performed on the first or second postoperative day (no later than 48 h). Extent of resection (EOR) was then calculated using the equation: $100 - (\text{postoperative volume}/\text{preoperative volume} \times 100)$ with the result expressed in percentage of resection. EOR

was classified using MRI volumetry as gross-total resection (GTR): no residual tumour on postoperative MRI; near-total resection (NTR): 95–99% resection; subtotal resection (STR): 80–95% resection; and partial resection (PR): less than 80% resection [17]. Surgical complications (e.g. haematoma or ischemia) were also assessed on postoperative MRI. Follow-up MRI was used to evaluate eventual tumour progression as described above.

Surgery

Surgery aimed at achieving GTR whenever deemed feasible and safe. Surgery was performed using standard microsurgical techniques under electrophysiological monitoring and image guidance. Decrease in amplitude (< 50%) of somatosensory evoked potentials, significant increase of transcranial threshold stimulation (20% of baseline value), decrease of amplitude (< 50%) or change in latency of motor evoked potentials warned the surgeon against pursuing further resection. Further increase in threshold stimulation (50% of baseline value) and/or decrease of amplitude (< 20%) was signal for immediate stop of resection. Similarly, direct stimulation of CST using a monopolar electrode was considered safe up to 5 mA. If clear tumour margin could be maintained, resection was pursued unless deterioration of electrophysiology occurred. Care was taken to respect electrophysiological and image-guided presence of descending white matter tracts or eloquent cortical areas. Various surgical approaches were used according to the extent of the tumour. Approach was tailored specifically to the lesion and included transsylvian/pterional, middle-temporal gyrus, transcortical/transventricular, transcallosal/transventricular and supracerebellar-infratentorial with various modifications according to tumour extension. When appropriate, surgery was performed in staged fashion. The complexity of surgery was assessed retrospectively through the Milan Complexity Scale (MCS) [12] according to preoperative MRI images and surgical notes. This scale can evaluate the risk of postoperative neurological worsening after brain tumour surgery according to five parameters: involvement of major brain vessels, posterior fossa location, cranial nerve manipulation, tumour eloquent location and tumour size greater than 4 cm. The resulting sum ranges from 0 to 8 points and higher values have increased risk of postoperative worsening (Table 1).

Hydrocephalus was managed preoperatively by external ventricular drainage, endoscopic third ventriculostomy (ETV) or postoperative shunting as the clinical situation demanded.

Genetic analysis

Diagnostic evaluation to detect LGG-associated molecular alterations was performed in a stepwise manner. Most common alterations were detected by direct sequencing from tumour DNA (*BRAF V600E*) or reverse transcriptase-PCR (RT-PCR) cDNA achieved by reverse transcription of tumour RNA (*KIAA1549-BRAF*) as previously described [37]. Wild-type cases were subjected to panel RNA sequencing using ArcherDX Lung panel kit (ArcherDX, CO, USA).

Table 1 Milan Complexity Scale (MCS) [12] and the number of patients positive for each variable

Variable	Score	Number of patients (%)
Major brain vessel manipulation[a]		
No	0	
Yes	1	15 (71)
Posterior fossa		
No	0	
Yes	1	9 (43)
Cranial nerve manipulation		
No	0	
Yes	2	7 (33)
Eloquent area[b]		
No	0	
Yes	3	21 (100)
Tumour size		
0–4 cm	0	
4.1 cm +	1	11 (52)
Total score	0–8	Mean score: 5, range 3–8

[a]Major vessels include: internal carotid artery; anterior, middle and posterior cerebral artery; anterior and posterior communicating artery; anterior choroidal artery; ophthalmic artery; vertebral artery; basilar artery; superior, anterior inferior and posterior inferior cerebellar artery; superior sagittal, transverse, sigmoid sinus; internal cerebral veins; vein of Galen

[b]Eloquent areas include motor, sensory, language, visual cortex, hypothalamus, thalamus, internal capsule, brainstem, pineal region

Statistical analysis

The risk for immediate postoperative worsening was compared for MCS scores 0–4 vs. MCS scores 5–8. Comparison of categorical variables was performed using Fisher's exact test. The Kaplan–Meier method was used to estimate the probability of 5-year overall survival (OS) and 5-year progression-free survival (PFS). *p*-value of less than 0.05 was considered significant.

Results

During the study period, 21 patients were treated at our institution, 11 during the last 5 years (Tables 2 and 3). There were 13 girls and 8 boys (mean age 7.6 years; range 1.25–15.9 years). Presentation included progressive hemiparesis in 9 patients

Table 2 Basic characteristics of the study population

Number of patients	21
Male:female	8:13
Mean age (range); years	7.6 (1.25–15.9)
Mean duration of symptoms (range); days	54.2 (0–180)
Location	
Thalamus (bilateral)	6 (2)
Thalamopeduncular	15
Tumour extension	
Tentorial incisura	5
Pineal region	3
Basal ganglia	2
Third ventricle	2
Cerebello-pontine angle	2
Radiological features	
Contrast enhancement	21
Heterogeneous appearance	16
Cystic tumour	16
Calcifications	4
Mean tumour volume (range); cm^3	29 (3.9–96.6)
Hydrocephalus present	14
External ventricular drainage	5
Endoscopic ventriculostomy	8
Eventual shunting	7

(Fig. 1), symptoms of raised intracranial pressure in 9 patients (Fig. 2) and cerebellar symptomatology in 3 patients due to tumour extension into the posterior fossa. Mean symptom duration was 54.2 days (range 0–180). The tumour was confined to the thalamus in 6 patients (bilateral involvement in 2 patients); in 15 patients, simultaneous involvement of the cerebral peduncle was evident. Homogenous appearance was noted in 5 tumours and calcifications in 4 tumours, all but 5 tumours were cystic and all showed evidence of contrast enhancement on MRI. The mean preoperative tumour volume was 29 cm^3 (range 3.9 cm^3–96.6 cm^3). Most common tumour extension was into the tentorial incisura (5 cases), followed by pineal region (3 cases), basal ganglia, third ventricle and cerebello-pontine angle (2 cases each). Diffusion tensor imaging and fibre tractography were utilised in the last 3 patients and showed anteromedial CST displacement in relation to the tumour in two patients and split CST in the last patient (Fig. 3).

Preoperatively, hydrocephalus was present in 14 patients. Initial treatment included temporary external ventricular drainage in 5 patients. Definite hydrocephalus treatment required ETV in 8 patients and eventual shunt implantation in 7 of these patients.

In 2 patients, stereotactic biopsy was performed as a first procedure; both underwent subsequent transcortical/transventricular resection. The most common approach was supracerebellar-infratentorial (12 patients) followed by transcortical/transventricular (4 patients), pterional/transsylvian (3 patients), middle temporal gyrus (1 patient) and transcallosal/transventricular (1 patient). The mean MCS score was 5 points (range 3–8) (Table 1). There was no surgical mortality. Surgical complications included immediate worsening of the postoperative neurological status and Lansky score progression in 6 patients (28.6%); 5 of these returned to preoperative level at 3 months follow-up. The rate of permanent surgical morbidity in this study was thus 4.7%. These complicated patients were distributed evenly across the study period and no relation was found to EOR (GTR/NTR vs. STR/PR: 4/12 vs. 2/9; $p = 0.659$, Fisher's exact test).

Tumour histology revealed LGG in all patients (grade II in 5 patients, all remaining were classified as grade I pilocytic astrocytomas). All tumours were examined for proliferation activity using the Ki67 marker; mean positivity detected was 2.5% (range 0–4%).

Underlying molecular alteration was successfully identified in 17 patients (81%). Majority of patients harboured *KIAA1549-BRAF* fusion ($n = 10$) or *BRAF V600E* mutation ($n = 3$). Receptor tyrosin kinase–associated alteration was uncovered in three patients (*FGFR1*, *NTRK1* and *ROS1*). One patient was diagnosed with germ line *NF1* mutation resulting in neurofibromatosis type 1. Three patients (19%) did not have any alteration revealed due to insufficient tumour tissue ($n = 3$) or negative results of all used tests including RNA sequencing ($n = 1$).

GTR was achieved in 6 patients (28.6%), NTR in 6 patients (28.6%), STR in 5 patients (23.8%) and PR in 4 patients (19%). Mean residual tumour volume was 2.2 cm^3 (range 0 cm^3–9.5 cm^3). Disease progression was observed in 9 patients with a median progression-free survival of 7.3 years: recurrence after NTR in 4 patients and residual tumour progression in 5 patients after STR or PR. All recurrent tumours were asymptomatic and diagnosed on routine follow-up MRI. Additional surgery for tumour progression was performed in 5 patients (1 subsequent GTR), 3 of these received additional chemotherapy and 2 patients received additional chemotherapy only without surgery. Chemotherapy regime included combination of carboplatine and vincristine in 3 patients and vinblastine only in 2 patients. Two patients experienced allergic reaction to carboplatine and this was substituted by cyclophosphamide. No further serious chemotherapy-related adverse events were recorded. The last patient with tumour progression is managed expectantly due to excellent functional status and involvement of eloquent areas. No patient received radiotherapy. At last follow-up (median 6.1 years), all patients were alive, 7 without evidence of disease, 6 with initial residual but stable disease, 7 with stable disease after progression and therapy and one patient as progressive disease managed expectantly (Fig. 4, Table 3).

Table 3 Individual data for each patient

Patient	Gender; age (years)	Symptomatology	Duration (days)	Location	Extension	Preoperative hydrocephalus	Approach	Milan Complexity Scale[12]
1	F; 9.0	Raised ICP	60	Thalamus bilateral	Third ventricle	Yes	Biopsy; transcortical/transventricular	3
2	M; 14.1	Hemiparesis	30	Thalamus (right)		No	Biopsy; transcortical/transventricular	3
3	M; 8.6	Raised ICP	60	Thalamopeduncular (left)		Yes	SCIT	5
4	F; 9.4	Raised ICP	30	Thalamus (left)	Third ventricle	Yes	SCIT	5
5	M; 4.6	Hemiparesis	54	Thalamopeduncular (right)		No	Pterional/transsylvian	6
6	F; 2.7	Hemiparesis	90	Thalamus (left)		No	Transcallosal/transventricular	4
7	F; 5.9	Raised ICP	45	Thalamopeduncular (left)		Yes	SCIT	4
8	F; 12.4	Hemiparesis	90	Thalamopeduncular (left)		Yes	SCIT	4
9	M; 6.1	Hemiparesis	3	Thalamopeduncular (right)		No	Transcortical/transventricular	4
10	M; 4.2	Cerebellar	120	Thalamopeduncular (left)		Yes	SCIT	5
11	F; 15.9	Raised ICP	5	Thalamopeduncular (left)		Yes	SCIT	4
12	F; 5.5 (Fig. 1)	Hemiparesis	21	Thalamus (left)	Basal ganglia	No	Pterional/transsylvian	7
13	F; 11.3	Raised ICP	7	Thalamopeduncular (right)		Yes	Transcortical/transventricular	5
14	F; 9.6	Cerebellar	180	Thalamopeduncular (right)	Tentorial incisura, CP angle	Yes	SCIT	7
15	F; 10.6	Raised ICP	30	Thalamus bilateral	Tentorial incisura, pineal region	Yes	SCIT	6
16	M; 1.3	Raised ICP	0	Thalamopeduncular (left)	Tentorial incisura, pineal region	Yes	SCIT	6
17	M; 7.4 (Fig. 2)	Raised ICP	7	Thalamopeduncular (left)		Yes	SCIT	4
18	F; 3.4	Hemiparesis	7	Thalamopeduncular (right)	CP angle	No	SCIT	8
19	M; 5.6	Hemiparesis	180	Thalamopeduncular (left)	Basal ganglia	Yes	Middle temporal gyrus	7
20	F; 3.3	Hemiparesis	60	Thalamopeduncular (right)	Tentorial incisura, sellar region	No	Pterional/transsylvian	7
21	F; 9.7 (Fig. 3)	Cerebellar	60	Thalamopeduncular (right)	Tentorial incisura, pineal region	Yes	SCIT	8

Table 3 (continued)

Patient	Resection extent	Permanent hydrocephalus management	Histology	Molecular alteration	Postoperative progression	Recurrence (months)	Recurrence management	Oncological status	Follow-up (months)	Lansky score
1	PR	ETV, VPS	Grade 1	*BRAF V600E*	Transient			Stable initial residual	187.5	100
2	GTR		Grade 2	Insufficient material				No evidence of disease	101.8	90
3	STR	ETV, VPS	Grade 2	Receptor tyrosin kinase (*NTRK1* fusion)				Stable initial residual	116.5	100
4	PR	ETV	Grade 1	*BRAF V600E*		84.7	Observation, stable afterwards	Stable after progression/therapy	118.3	90
5	STR		Grade 1	*KIAA1549-BRAF* fusion	Permanent	91.1	CHT	Stable after progression/therapy	116.4	90
6	NTR		Grade 2	Insufficient material		2.9	Surgery, CHT	Stable after progression/therapy	108.3	70
7	STR	ETV, VPS	Grade 1	Germ line *NF-1* mutation		11.2	Surgery, CHT	Stable after progression/therapy	110.8	90
8	PR	ETV, VPS	Grade 2	*BRAF V600E*				Stable initial residual	93.1	100
9	STR		Grade 1	*KIAA1549-BRAF* fusion		5.9	CHT	Stable after progression/therapy	93.6	100
10	GTR		Grade 1	*KIAA1549-BRAF* fusion	Transient			No evidence of disease	90.3	90
11	GTR	ETV, VPS	Grade 1	negative				No evidence of disease	73.2	100
12	GTR		Grade 1	*KIAA1549-BRAF* fusion				No evidence of disease	62.9	100
13	NTR		Grade 2	Insufficient material				Stable initial residual	72.8	100
14	NTR	ETV, VPS	Grade 1	*KIAA1549-BRAF* fusion		22.3	Surgery (GTR)	No evidence of disease	63.6	90
15	PR		Grade 1	*KIAA1549-BRAF* fusion		2.66	Surgery	Stable after progression/therapy	46.5	100
16	NTR	ETV, VPS	Grade 1	*KIAA1549-BRAF* fusion	Transient			Stable initial residual	33.3	70
17	GTR		Grade 1	Receptor tyrosin kinase (*FGFR1* fusion)				No evidence of disease	23.0	100
18	NTR		Grade 1	*KIAA1549-BRAF* fusion		6.5	Observation	Observed progression	9.3	90
19	STR		Grade 1	*KIAA1549-BRAF* fusion				Stable initial residual	3.2	90
20	NTR		Grade 1	Receptor tyrosin kinase (*ROS1* fusion)	Transient	2.0	Surgery, CHT	Stable after progression/therapy	5.1	90
21	GTR		Grade 1	*KIAA1549-BRAF* fusion	Transient			No evidence of disease	5.1	80

F female, *M* male, *ICP* intracranial pressure, *SCIT* supracerebellar infratentorial, *PR* partial resection, *STR* subtotal resection, *NTR* near-total resection, *GTR* gross total resection, *ETV* endoscopic third ventriculostomy, *VPS* ventriculoperitoneal shunt, *CHT* chemotherapy

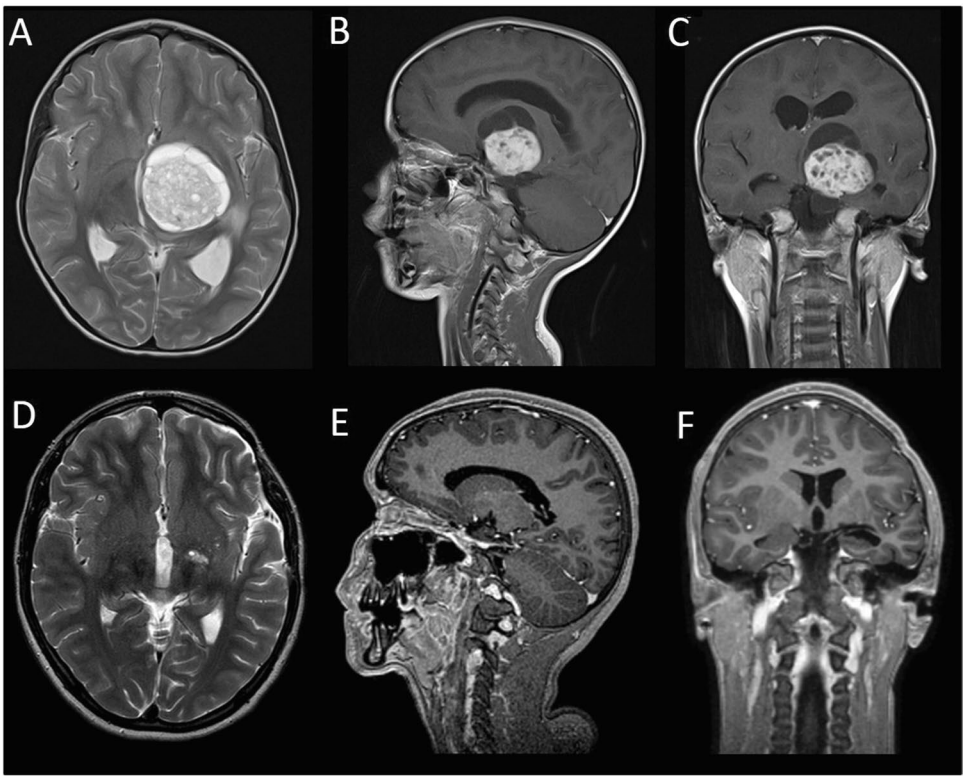

Fig. 1 A 5-year-old girl presenting with hemiparesis. Preoperative magnetic resonance imaging depicts tumour of the left thalamus extending into the basal ganglia. **A** Preoperative T2-sequences in the axial plane, **D** corresponding postoperative image. Contrast-enhanced preoperative images in the sagittal (**B**) and coronal planes (**C**) and corresponding postoperative images (**E**, **F**) show gross total resection via the pterional/transsylvian approach

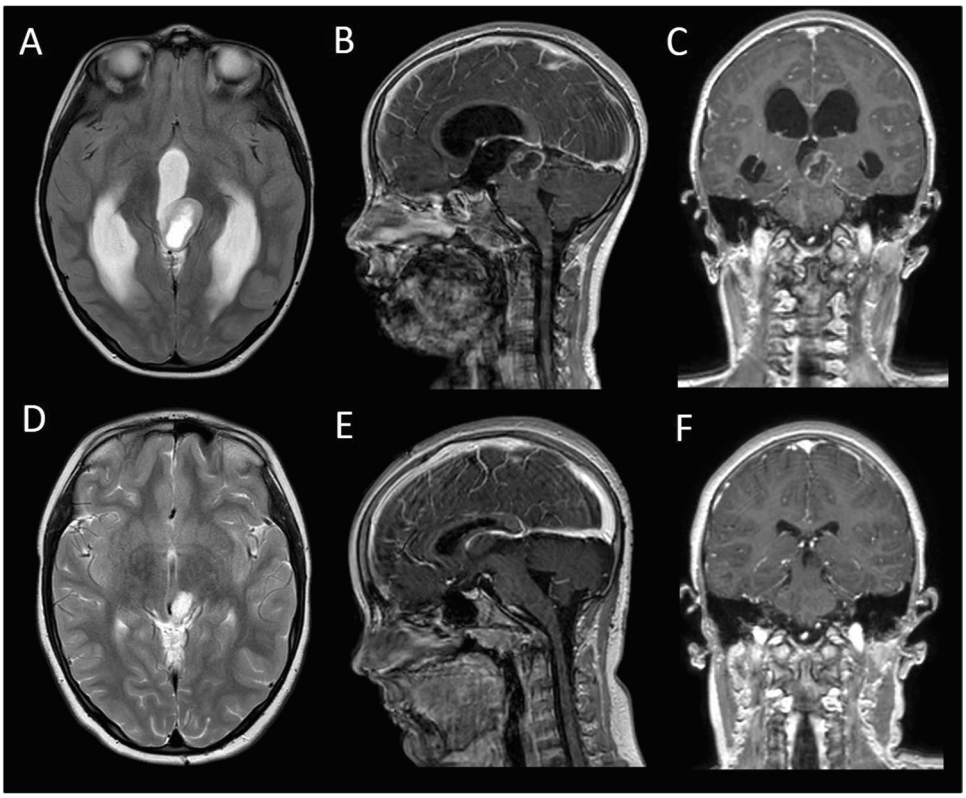

Fig. 2 A 7-year-old boy presenting with raised intracranial pressure due to aqueduct obstruction. Preoperative magnetic resonance (**A**–**C**) shows solid-cystic tumour with peripheral contrast enhancement (**B**, **C**). Gross total resection was achieved via supracerebellar-infratentorial approach (**D**–**F**)

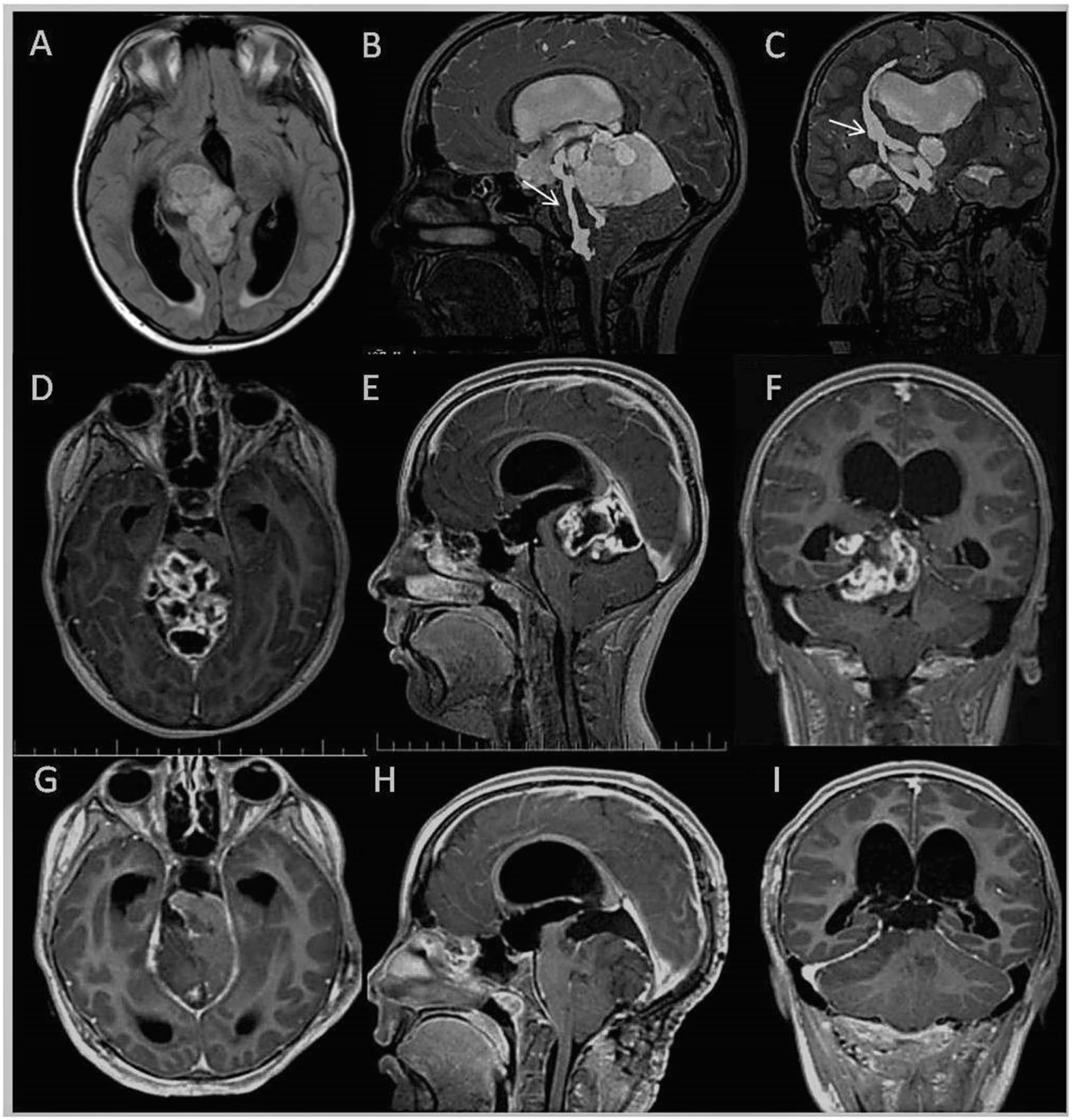

Fig. 3 A 9-year-old girl presenting with cerebellar symptomatology. Preoperative magnetic resonance imaging depicts tumour originating in the right thalamus (**A** axial fluid attenuated inversion recovery image), the course of cortico-spinal tract (arrow on **B**, **C**; T2-sequences with diffusion tensor imaging) in relation to the tumour. Preoperative 3D Turbo Field Echo sequences with contrast enhancement of the multicystic tumour (**D**, **E**, **F**) and corresponding postoperative imaging confirming gross total resection (**G**, **H**, **I**)

Last median Lansky score was 90 (70–100), 10 patients are attending elementary school (4 have individual study plans), 5 have either finished or are attending high-school, one is studying university and one is employed; the last 4 patients have yet to reach school age.

Statistical analysis

Comparing patients with MCS scores 0–4 (1/8 patients with immediate complication) to patients with MCS scores 5–8 (5/13 patients with immediate complication) did not reach

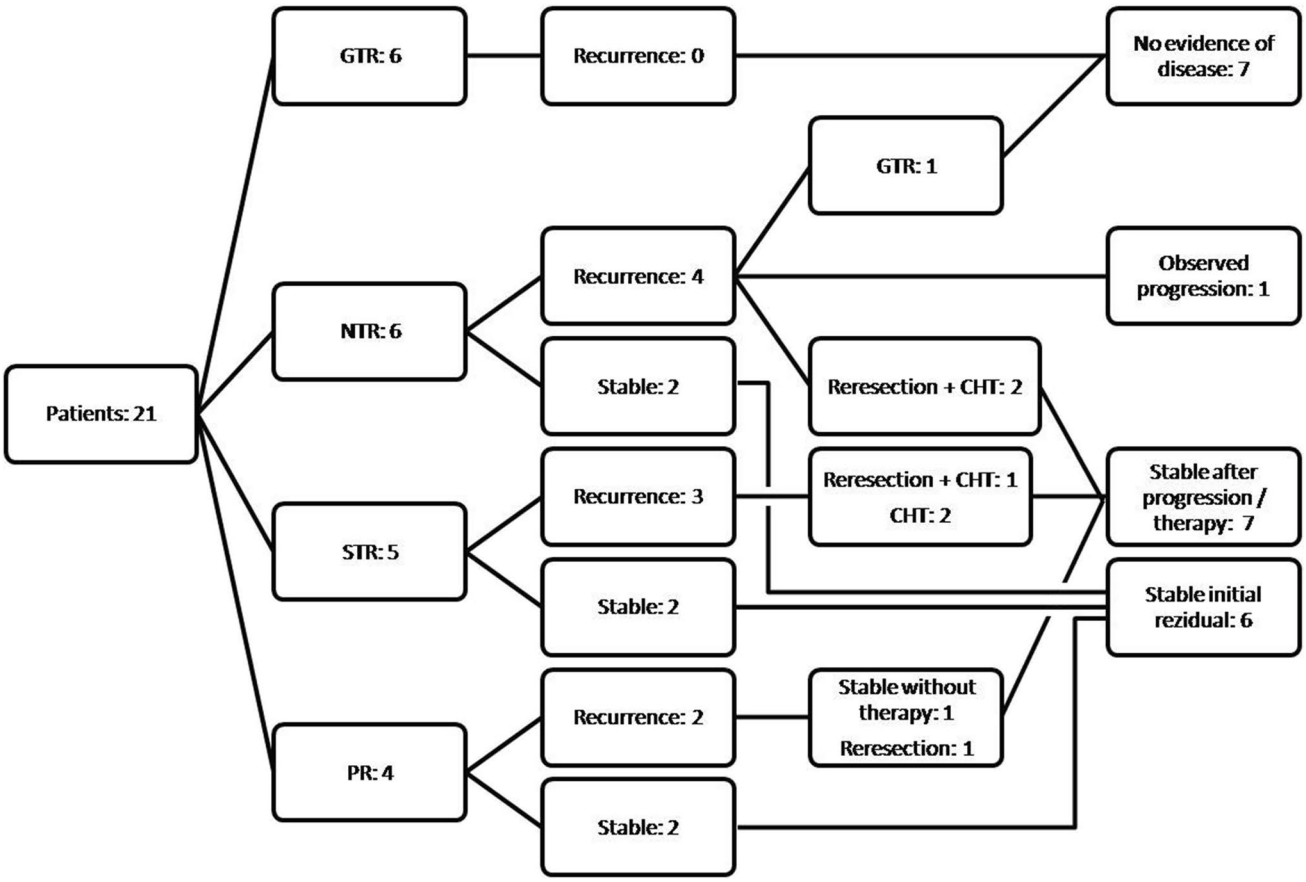

Fig. 4 Flowchart depicting extent of resection, recurrence and additional therapy. GTR, gross total resection; NTR, near total resection; STR, subtotal resection; PR, partial resection; CHT, chemotherapy

statistical significance ($p=0.336$, Fisher's exact test). Five-year OS in this patient cohort was 100%, and 5-year PFS was 64% (Fig. 5). No patient who underwent initial GTR (6 patients) experienced disease progression in comparison to 9/15 patients with less extensive EOR ($p=0.019$, Fisher's exact test).

Discussion

Natural history of paediatric LGGs is rather favourable and children have excellent survival prognosis in comparison to adults. OS rates at 10 and 20 years range from 80 to 90% [1, 13, 31] and adult surviving patients have low probability of glioma-related death [1]. Contrary to their adult counterparts [16, 28, 41], paediatric LGGs very rarely undergo malignant transformation in adulthood [1, 21, 33]. Furthermore, pilocytic histology was identified as a favourable prognostic factor in comparison to non-pilocytic histology [1, 33] and pilocytic astrocytomas have a very low mortality rate (3.1%) [30]. Thus, children with pilocytic astrocytomas (and LGGs) have a very high probability of reaching advanced adulthood and not succumbing to their glioma. All these facts have to be factored into a treatment plan which should aim at maximising tumour control and minimising treatment-related complications and toxicity.

The cornerstone of treatment is surgery. Surgery obtains representative histological samples, relieves tumour-associated mass effect and addresses hydrocephalus which is often present due to aqueduct obstruction. The location of thalamopeduncular astrocytomas is highly eloquent and surgically challenging. The borders of the thalamus comprise hypothalamus (inferior), third ventricle (medial), lateral ventricle and stria medullaris (superior), posterior limb of internal capsule (lateral), foramen of Monro (anterior) and posterior commissure (posterior). These borders also define thalamic surfaces that can be reached through transcisternal or transcallosal/transverntricular approaches avoiding the need to transgress brain parenchyma: the posteriorly projecting cisternal surface through modifications of supracerebellar infra-/transtentorial or posterior interhemispheric transtentorial subsplenial approach; the lateral-ventricular and velar surfaces through the anterior interhemispheric transcallosal approach; the third ventricular surface through the contralateral supracerebellar suprapineal approach. These accessible

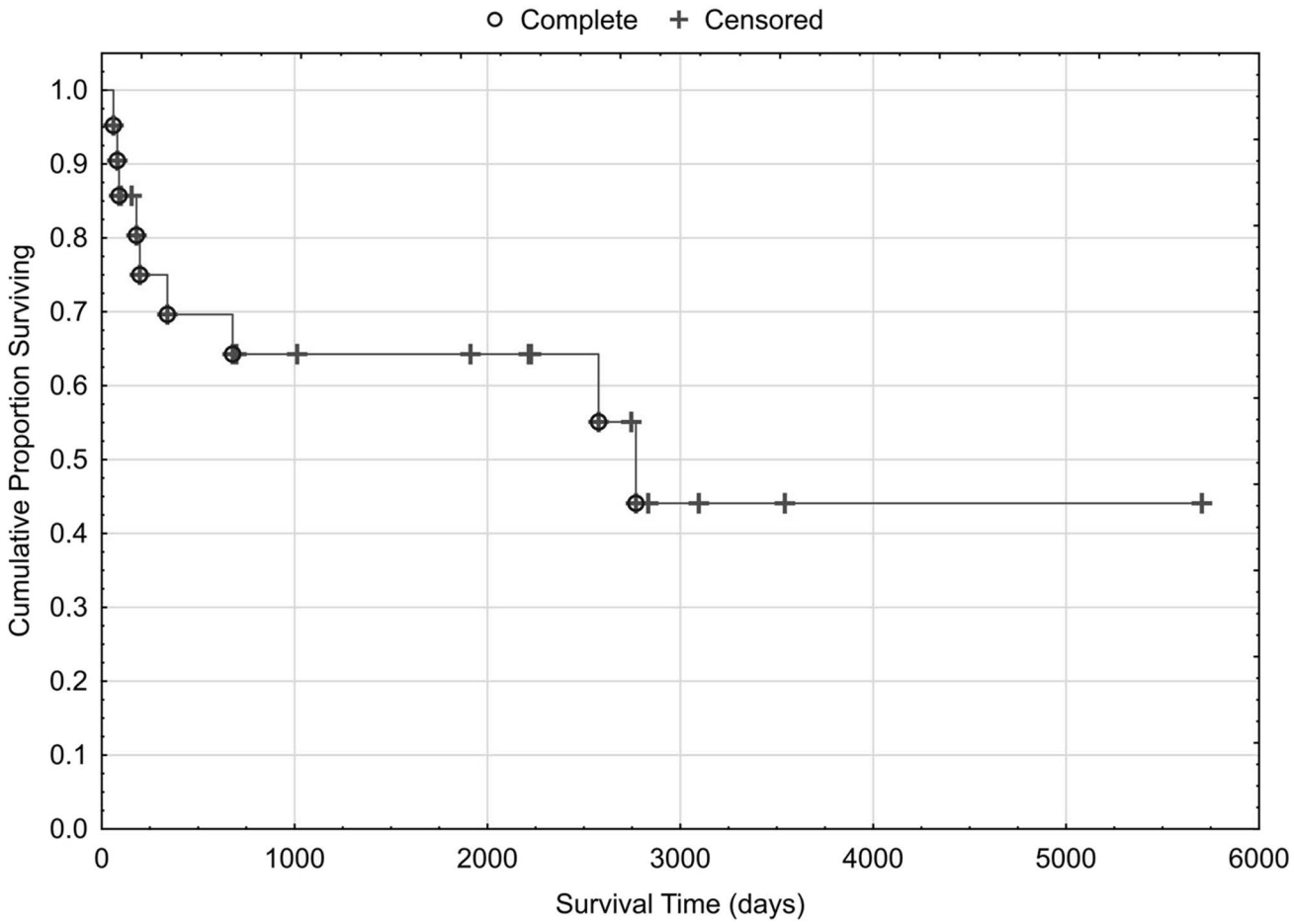

Fig. 5 Progression-free survival of the patient cohort using the Kaplan–Meier method

thalamic surfaces allow the surgeon to safely reach most tumours confined within the thalamus and in effect dictate the approach according to the closest surface to the lesion [34]. Alternatively, thalamus can be divided into six segments and each of these can be reached by a corresponding approach: anteroinferior (orbitozygomatic approach), medial (anterior ipsilateral transcallosal approach), lateral (anterior contralateral transcallosal approach), posterosuperior (posterior transcallosal approach), lateral posteroinferior (parietooccipital transventricular approach) and medial posteroinferior (supracerebellar-infratentorial approach) [27].

Furthermore, thalamopeduncular astrocytomas tend to expand outwardly and compress surrounding eloquent areas (e.g. basal ganglia, CST, hypothalamus, optic pathways and aqueduct) or stretch critical neurovascular structures (e.g. optic nerve, oculomotor nerve, deep venous system, posterior cerebral artery). Extension into the tentorial incisura and cerebello-pontine angle endangers additional cranial nerves and cerebral vessels. Intraoperative injury is more likely because these structures are sometimes at their functional limit (particularly the oculomotor nerve) and any additional manipulation can lead to mechanical or vascular damage. These pitfalls are very relevantly reflected in the Milan Complexity Scale [12]. Indeed 13 of our patients scored 5 or more points and had higher probability of immediate postoperative worsening, although this difference did not reach statistical significance, due to small sample size. Fortunately, all but one postoperative decline in functional status improved at follow-up with time and physiotherapy. Other studies also confirm this extraordinary plasticity of children's nervous system [2, 7] where postoperative deficits (although likely to occur after surgery for midline tumours) usually improve during follow-up.

Detailed knowledge of the relevant anatomy, intraoperative image guidance, neuromonitoring of somatosensory and motor evoked potentials and cortical as well as CST mapping are prerequisites for safe surgery in and around the thalamic region. Several approaches to the thalamus and cerebral peduncles are feasible [3, 8, 24, 25, 35]; however, no approach is universal and needs to be adjusted individually. Recently, preoperative diffusion tensor imaging of CST was reported to analyse its displacement [4, 5, 22]. The direction

of CST displacement varies widely; anterior or anterolateral being the most common [4, 5, 20, 22]. Additionally, the location of the optic tract and visual pathway needs to be considered. Eventual extracerebral extension of the lesion can also guide the approach. Thus, preoperative approach planning should take into account (among other factors) displacement of CST, visual pathway and extracerebral projection of the tumour (Table 4). Despite using fibre tractography in our last cases only, we did not encounter increased risk of postoperative decline in the earlier part of the study period, probably due to careful approach selection based on known anatomical landmarks and surgeon's familiarity with the approach.

Majority of tumours (12) were addressed by the supracerebellar-infratentorial approach which is familiar to most neurosurgeons, keeps anatomical orientation relatively simple and allows the surgeon to easily reach parts of the tumour extending into the incisura, posterior fossa, cerebello-pontine angle and with tentorial section into supratentorial space.

Table 4 Simplified approaches to thalamic and thalamopeduncular tumours

Tumour confined to the thalamus
- Reaches (or closest) thalamic surface
o Lateral ventricle
■ Transcallosal/transventricular
■ Transcortical/transventricular
o Third ventricle
■ Contralateral supracerebellar suprapineal
o Cisternal
■ Supracerebellar infra-/transtentorial
■ Posterior interhemispheric transtentorial subsplenial
- Thalamic region
o Anteroinferior
■ Orbitozygomatic
o Medial
■ Anterior ipsilateral transcallosal
o Lateral
■ Anterior contralateral transcallosal
o Posterosuperior
■ Posterior transcallosal
o Lateral posteroinferior
■ Parietooccipital transventricular
o Medial posteroinferior
■ Supracerebellar infratentorial
Extracerebral extension
- Tentorial incisura
o Supracerebellar-infratentorial
o Retrosigmoid extension if cerebello-pontine angle involved
o Transtentorial if supratentorial extension
- Anterior
o Pterional/transsylvian
- Lateral
o Middle temporal gyrus

Displacement of corticospinal tract and visual pathway depicted on diffusion tensor imaging needs to be considered

Following gravity retraction of the cerebellum, and elevation of the tentorium with retention sutures, a wide corridor is developed which allows ample space for tumour dissection. Deep venous system is usually dislocated superiorly, posterior cerebral arteries laterally and superior cerebellar arteries caudally. These structures (along with the fourth nerve at the edge of the tentorium) need to be identified early and vigorously protected. Furthermore, as tumour dissection and resection proceeds, cerebral peduncles and thalami are identified and tumour can be removed at this location under electrophysiological monitoring. This approach is optimal to use if the CST is displaced anteriorly or anterolaterally. On the other hand, even a discrete presence of normal tissue dorsal to the tumour identifiable on preoperative MRI suggests the course of eloquent tracts and if no dorsal tumour extension outside of the peduncle or thalamus is clearly visible, other surgical route should be chosen according to the principle discussed above.

The rates of gross total resection of thalamic tumours vary in the literature from 0 [15] to 81% [14] or 92% if NTR is included as well [34]. Such a wide range of reported GTR can be attributed to GTR definition criteria, combined reporting of both low- and high-grade tumours, inclusion of bilateral lesions, surgeon's experience, choice of surgical approach, intraoperative deterioration of electrophysiological monitoring and other factors [7, 25, 29, 34, 43]. Our rate of GTR of 28.6% and combined GTR/NTR rate of 57.2% falls in line with the literature. The main reason for less extensive resection in this series is our philosophy where postoperative function has priority over resection extent, particularly in the setting of low-grade tumours. The decision on EOR is modified by the surgeon during surgery based mainly on clearly defined tumour margins and electrophysiological monitoring. Taking into consideration deterioration of somatosensory and motor evoked potentials and proximity of CST by direct stimulation, we were able to prevent long-term postoperative neurological decline in all but one patient. Of note, in this and another patient, further resection was abandoned when direct subcortical stimulation of CST showed its proximity (5 mA positive response) and no clear tumour margin could be identified. This is contrary to our attitude to high-grade lesions (such as anaplastic ependymoma) where the difference between GTR and STR has significant implications for survival [26, 42] more extensive surgery and even severe postoperative deficit is acceptable given the discussed plasticity of children's nervous system. With this conservative approach, we were able to achieve a 4.7% rate of permanent surgery-related neurological deficit and median Lansky score of 90, which both compares favourably to contemporary literature [4, 7, 20, 25, 38, 43]. It is necessary to emphasise that no significant difference was found between surgical morbidity and EOR; however, only GTR proved to be significant for preventing disease recurrence and achieving complete cure.

The advances in oncological therapy and biological treatment further support our surgical philosophy of putting

quality of life first. Many residual tumours can be observed with serial MRI, and upon progression or clinical manifestation, further surgery and/or oncological therapy can be considered depending on tumour location and patient functional status. Long-term tumour control with modern agents can be achieved without significant treatment-related side effects [9]. In fact, no patient in this series experienced serious chemotherapy-related morbidity. Radiotherapy was avoided completely in this patient cohort, considering its deleterious long-term effects on developing brain.

Molecular genetics evaluation of the tumour tissue provided important insight into the biology of thalamopeduncular LGGs. Histologically, the majority of tumours were classified as pilocytic astrocytoma or diffuse astrocytoma. This was reflected by the distribution of molecular alteration with *BRAF* alterations being the most prevalent; *KIAA1549-BRAF* a *BRAF V600E* accounted for 76% molecular changes. These findings correlated with previously published evidence of alterations among LGGs located within midline brain structures [32, 44]. In our cohort, molecularly confirmed thalamopeduncular LGGs harboured excellent prognosis with no patient succumbing to the disease with the median time of follow-up of 6.1 years. This underscored the need for complex histopathological and molecular evaluations confirming the diagnosis of LGG. Our data support the strategy of less aggressive approach in the LGG of midline locations where incomplete resection is acceptable in exchange for better neurological outcome with maintained excellent prognosis. Similarly, approaches for progressive cases should account for radiation sparing therapies in order to avoid deleterious long-term side effects. Moreover, molecular testing is critical to identify targets for novel targeted therapies that offer further options for non-surgical therapies with acceptable toxicities. In our cohort, no patient was treated with any of the targeted agents (yet), but *KIAA1549-BRAF* cases would be suitable candidates for the use of MEK inhibitors, *BRAF V600E* for BRAF inhibitors in case of tumour progression and/or clinical manifestation [19, 23].

Limitations of this study must be kept in mind. This is a single-centre retrospective analysis spanning many years and with a limited number of patients. Although the basic surgical strategy remained unchanged, unknown bias could have been introduced. Multicentre collaboration and large sample size would address most of these shortcomings and help identify other factors relevant to surgical morbidity and oncological prognosis.

Conclusion

Childhood thalamopeduncular low-grade astrocytomas can be treated surgically with acceptable extent of resection and surgery-related permanent complications. Due to their indolent biological course and long-term survival, maximum emphasis should be placed on postoperative quality of life. Aggressive treatment endangering function should be avoided since residual/recurrent tumours can be safely managed expectantly, surgically resected or controlled with modern oncological therapy; however, only GTR offers the best chance of achieving complete cure.

Author contribution All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Vladimir Beneš 3rd, Michal Zápotocký, Petr Libý, Jakub Táborský, Jana Blažková Jr., Jana Blažková Sr., David Sumerauer, Adéla Mišove, Ivana Perníková, Martin Kynčl, Lenka Krsková, Miroslav Koblížek, Josef Zámečník, Ondřej Bradáč and Michal Tichý. The first draft of the manuscript was written by Vladimír Beneš 3rd and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials Available from the corresponding author upon reasonable request.

Code availability Not applicable.

Declarations

Ethics approval Ethical approval was waived by the local Ethics Committee of Second Faculty of Medicine, Charles University and Motol University Hospital in view of the retrospective nature of the study and all the procedures being performed were part of the routine care.

Conflict of interest The authors declare no competing interests.

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Comments This manuscript describes a series of 21 children with thalamic and thalamopeduncular low grade gliomas treated between 2005 and 2020. The authors provide a good description of their patients and their surgical technique, emphasising their choice of operative approach, their use of adjunctive methods to maximise surgical safety and the fact that a good long term neurological and oncological outcome does not necessarily require a complete resection of the tumour. The authors have addressed comments from the initial reviewers. Although other similar series have been described, these are rare tumours and a relatively large well-described and well-managed series such as this one is still a useful addition to the literature. Within the current paradigms of chemotherapy and targeted therapy for low grade gliomas, their emphasis on surgical safety rather than complete resection is important. This is not always clarified in surgical series.

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