Childs Nerv Syst (2015) 31:1447–1459
DOI 10.1007/s00381-015-2800-9

ORIGINAL PAPER

Low-grade gliomas in children: single institutional experience in 198 cases

Magda Garzón[1] · Gemma García-Fructuoso[1] · Mariona Suñol[2] · Jaume Mora[3] · Ofelia Cruz[3]

Received: 16 November 2014 / Accepted: 22 June 2015 / Published online: 9 July 2015

Abstract
Introduction In pediatric population (0–18 years), low-grade gliomas (PLGG) are the most frequent brain tumors and majority are amenable for surgical removal.
Patients and methods A retrospective review of 198 children diagnosed with PLGG between 1980 and 2010 at HSJD was carried out. Several variables were studied to find prognostic factors related to the outcomes (progression-free survival (PFS) and overall survival (OS)).
Results Median age at onset was 88.8 months (3.1 to 214.5 months, SD 53). Surgery was performed in 175 patients (88.4 %), achieving gross total resection (GTR) in 77 (44 %), subtotal resection (STR) in 87 (49.7 %), and 11 (6.3 %) biopsies. Pathological review classified 84 tumors as WHO grade I (48 %) and 89 as grade II (50.8 %). Adjuvant therapy (AT) was given to 75 patients (37.9 %), radiotherapy in 24 (12.1 %), chemotherapy in 33 (16.7 %), and combined in 18 (9.1 %). Sixteen patients (8.1 %) died, 89 (43.4 %) are alive with no evidence of disease, and 93 (47 %) alive with disease, median follow-up 65.2 months. Outcome is significantly correlated with age (p = 0001, worse OS for patients younger than 12 months) and extent of tumor resection (p < 0001). OS for GTR/STR/biopsy was >200, 154.3, and 101.9 months, respectively. Patients treated with AT presented worse OS/PFS (p < 0.001) than those not treated. Histology was non significantly related to outcomes.
Conclusion In our series of PLGG, the best prognostic markers are tumor location (cerebellar) and the extent of tumor resection (GTR). Infants and patients who require adjuvant therapy because of tumor progression or recurrence have worse outcome.

Keywords Pediatric brain tumors · Pediatric low-grade glioma · Outcome studies · Pediatric neurosurgery · Chemotherapy · Radiotherapy

Introduction

Pediatric low-grade gliomas (PLGG) constitute a wide variety of tumors with diverse histology for which the mainstay of treatment is surgical excision. The feasibility to achieve a gross total resection (GTR) has been widely reported as the most relevant prognostic factor. Different rates of progression in residual tumors or recurrence after GTR have been reported [9, 15, 32, 33, 42, 45]. Besides location and extent of tumor resection, other clinical variables, radiological characteristics (such as tumor extent and brain infiltration), and histologic and biological features have been used in the past in an attempt to predict long-term outcomes. Our aim retrospectively reviewing this large cohort of children with PLGG was to

Electronic supplementary material The online version of this article (doi:10.1007/s00381-015-2800-9) contains supplementary material, which is available to authorized users.

✉ Magda Garzón
dendrita07@gmail.com

✉ Ofelia Cruz
ocruz@hsjdbcn.org

[1] Department of Neurosurgery, Hospital Sant Joan de Déu, University of Barcelona, Passeig St. Joan de Déu, 2, 08950 Esplugues de Llobregat, Barcelona, Spain

[2] Department of Pathology, Hospital Sant Joan de Déu, University of Barcelona, Passeig St. Joan de Déu, 2, 08950 Esplugues de Llobregat, Barcelona, Spain

[3] Department of Oncology, Hospital Sant Joan de Déu, University of Barcelona, Passeig St. Joan de Déu, 2, 08950 Esplugues de Llobregat, Barcelona, Spain

analyze the outcomes correlating with potential prognostic variables.

Patients and methods

A retrospective review of the medical and image records for all children and adolescents (0 to 18 years) diagnosed with PLGG at Hospital St. Joan de Drds for all children and adolescents (0 to 18 outcomes. Our aim retrospectively reviewing this large cohort of children with PLGG was to analy [29]. Only when strict criteria had been met, like optic pathway tumors (OPT) in clinically confirmed neurofibromatosis-1 (NF1) patients, tumors were diagnosed solely by neuroimaging. Only patients managed from diagnosis at HSJD were included.

Analyzed variables included demographics (gender and age at diagnosis), clinical (signs and symptoms at presentation and examination findings) association with genetic disorders like NF1 or tuberous sclerosis complex (TSC), neuroimaging (anatomical location, tumor characteristics, and hydrocephalus), pathological (histology and related WHO grade), surgical (extent of resection, hydrocephalus treatment, surgery-related complications), adjuvant therapy (chemotherapy or radiotherapy), and outcome (evidence of recurrence or progression, current status, follow-up time). Informed consent was obtained for all therapies provided, and the HSJD Institutional Review Board approved this study.

Descriptive statistics were used to characterize PLGG patients, and the data is presented in Table 1. Nominal categorical variables were descriptively analyzed regarding the observed frequencies. Numerical variables were evaluated using central tendency and dispersion measures. The co-variables were analyzed using the log-rank test. Date of last clinical assessment was used when onset of event date could not be clearly ascertained. Age at diagnosis, sex, NF1 diagnosis, tumor location, and history of surgery, radiotherapy (RT), or chemotherapy (CT) were all included as candidate independent variables.

Results of Cox multiple regression models within the proportional hazards framework were reported as hazard ratios with 95 % intervals. We evaluated overall survival (OS) and progression-free survival (PFS). An event was defined as death, relapse if previous complete remission was achieved, or progression in patients with a previous partial remission. Progression was defined as evidence of clinical deterioration not related to other causes or increase in the size of the lesion by imaging. OS was defined as the time from diagnosis to date of death and if death had not occurred at the time of analyses were censored at the date of last contact. Similarly, PFS was defined as the time from diagnosis to date of progression, recurrence or death, and all patients surviving at the time of analyses were censored at the date of last contact. For patients who underwent GTR, PFS was defined as the time free of disease since the surgical procedure. Kaplan-Meier plots and estimates were used to describe the survival distributions. Survival was assessed using Kaplan-Meier curves. The results were statistically significant if $p < 0.05$. All information was analyzed and recorded using the Statistical Package for the Social Sciences (SPSS) version 20.0 and R Curve.

Results

The cumulative incidence of tumors and leukemia in our institution between 1980 and 2010 was 2027 cases; of these, 513 were brain tumors (25.3 %). This cohort of 198 PLGG accounts for 9.77 % of all tumors and 38.4 % of all brain tumors in our institution during this period.

Among brain tumors, PLGG were diagnosed in 226 cases (11.1 % of all tumors and 44 % of brain tumors). Data from 198 patients were fully available for analysis and included 98 females (49.5 %) and 100 males (50.5 %). The median age at diagnosis was 88.8 months (range, 3.1 to 214.5 months). Twenty-nine patients (14.6 %) had associated neurocutaneous syndromes (21 NF1 and 8 TSC).

Clinical presentation and radiological features

In our series, by neuroimaging, the anatomical distribution of tumors was 67 cerebellar (33.8 %), 43 hemispheric (21.7 %), 36 optic pathways (OPW) (18.2 %), 32 brainstem (BsT) (16.2 %), 12 spinal (6.1 %), and 8 intraventricular (4 %). Eighty tumors (40 %) were located at the midline (24 OPW, 20 BsT, 11 spinal, and 25 midline cerebellar), 152 (76.7 %) tumors presented with contrast enhancement, and the mean tumor size for the whole cohort was 37 × 33 mm.

The clinical characteristics, like medical history, type and duration of symptoms, and the presence of hydrocephalus at onset are summarized in Table 1.

Histology

Tumor specimen was available in 175 cases (88.4 %), but in 2 cases, histology was inconclusive. The distribution by histology and location is presented in Fig. 1. The WHO classification for the 173 confirmed PLGG was WHO I in 84 cases and WHO II in 89 cases. All the other patients were diagnosed on the basis of neuroimaging (as OPW in patients with NF1 and BsT).). In total, we have diagnosed 70 LGG "*nos*", 54 pylocytic astrocytomas, 31 other LGG (12 gangliogliomas, 8 SEGA, 3 DNET, 3 oligodendrogliomas, 1 oligoastrocytoma, 1 pylomixoid astrocytoma), 14 fibrillary astrocytomas, 4 pleomorphic astrocytomas, and 2 inconclusive (1 BsT and 1 OPW).

Table 1 Descriptive analyses. Tumor location presented by age at onset, duration and type of symptoms, hydrocephalus at onset and history of phacomatoses

Location	Cerebellum	Hemispheres	Optic Pathways (OPW)	Brainstem (BsT)	Spinal	Intraventricular (IV)	Total
Mean age in months	91.4 (21–214)	115.1 (5–212)	49.4 (3–207)	92.1 (14–177)	47.6 (13.6–107)	126.4 (62–203)	88.8 3–214
Mean duration of symptoms (weeks)	4.7 (0–28)	16.3 (0.1–52)	7.3 (0–39)	11.4 (0–52)	23.8 (1.2–210)	25.7 (0–74)	
Type of symptoms (%)	H/V 50 Ataxia 23 Visual 13.5 Motor 13.5	Seizures 77.8 Motor 8.9 H/V 6.7 Other[a] 6.6	Visual 61.1 Other[b] 27.8 H/V 8.3 Seizures 2.8	Motor 36.4 H/V 31.8 Visual 13.6 Ataxia 4.5 Other[c]16.7	Motor 75 H/V 8.3 Scoliosis 16.7	H/V 75 Visual 25	
Phacomatoses	2 NF1	3 NF1 1 TSC	13 NF1	1 TSC	2 NF1	5 NF1 2 TSC	29 (14.6 %)
Hydrocephalus	49 (73.1 %)	4 (8.7 %)	14 (43.75 %)	15 (46.9 %)	0	7 (87.5 %)	88 (44.4 %)
Permanent shunt	14 (20.9 %)	0	12 (33.3 %)	14 shunt +1 ETV (46.9 %)	0	6 (75 %)	47 (23.7 %)
Total number of cases (%)	67 Cases (33.8 %)	43 Cases (21.7 %)	36 Cases (18.2 %)	32 Cases (11.6 %)	12 Cases (6 %)	8 Cases (4 %)	198

H/V headache and vomiting, *NF1* neurofibromatosis type1, *TSC* tuber sclerosis complex

[a] Ataxia, visual alterations

[b] Cranial nerve palsies, endocrine alterations, precocious puberty, macrocraneum

[c] Torticolis and scoliosis

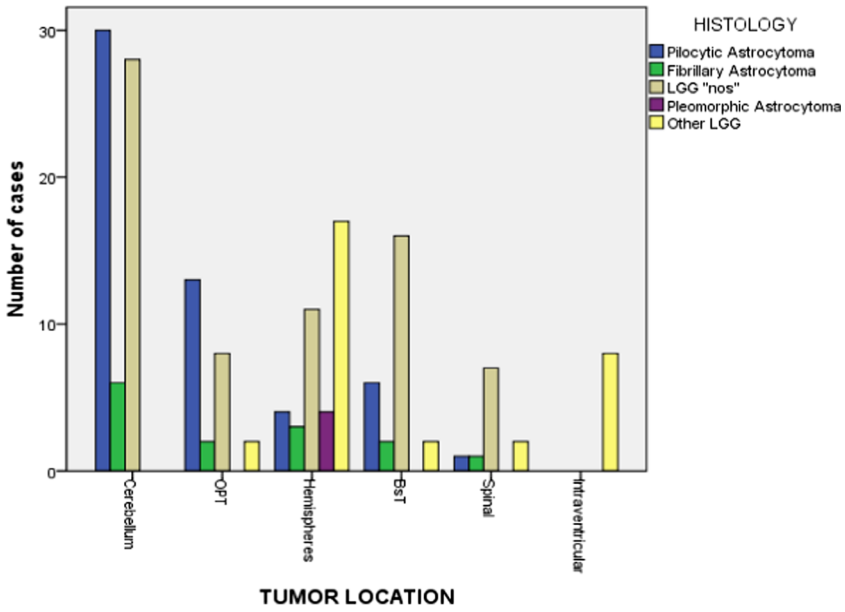


Fig. 1 Histology of the PLGG in our series of 175 tumor specimens analyzed

Treatment

Surgery

Hydrocephalus was present at diagnosis in 88 patients (44.4 % of all PLGG), but only 69 patients presented with signs of acute intracranial hyper pressure and 54 (27.3 %) required a definitive shunt (data summarized in Table 1).

All the PLGG were potential candidates for surgical excision but not all underwent surgery, and the timing of tumor removal was defined by the severity of the neurological compromise. The anatomical location of the tumor and its relationship with eloquent structures were carefully considered before surgical attempt.

Surgical tumor removal

An attempt of surgical tumor removal or biopsy was performed in 175 (88.4 %) patients, achieving gross total resection (GTR) in 77 cases (44 %), subtotal resection (STR) in 87 cases (49.7 %), and biopsy in 11 cases (6.3 %). Table 2 presents the extent of tumor resection related to the anatomical location. Of the 175 patients surgically treated, 109 did not require further treatment (62.3 %).

Infratentorial and hemispheric tumors had the most suitable location for tumor removal. The suboccipital midline was the more frequent surgical approach to remove cerebellar tumors. As expected, the supratentorial midline tumors were the most challenging surgically. However, we encountered a small fraction of cerebellar tumors with a tendency to infiltrate the BsT in which a near total/STR was preferred to avoid functional impairment.

With the aim of improving the amount of tumor removal and reduce morbidity and mortality, over the period of time analyzed newer technical devices like endoscopes, intraoperative ultrasound, ultrasonic aspirator, neurophysiology monitoring, and neuronavigation were progressively incorporated.

Surgical morbidity Intra-operative complications were not assessed. Systemic complications unrelated to the neurosurgical procedure were observed in 28 patients and did not account for the surgical morbidity following the consensus

Table 2 Extent of tumor removal related by tumor location ($p < 0.001$ in univariate analysis, log rank test)

Location	Extent of tumor removal			Total
	Gross total resection	Subtotal resection	Biopsy	
Cerebellum (67 cases)	49 (75.4 %)	16 (24.6 %)	0	65
Hemispheres (46 cases)	23 (57.5 %)	17 (42.5 %)	0	40
OPW (36 cases)	2 (8 %)	20 (80 %)	3 (12 %)	25
BsT (32 cases)	0	20 (76.9 %)	6 (23.1 %)	26
Spinal (12 cases)	2 (18.2 %)	7 (63.6 %)	2 (18.2 %)	11
IV (8 cases)	1 (12.5 %)	7 (87.5 %)	0	8
Total (198 cases)	77 (44 %)	87 (49.7 %)	11 (6.3 %)	175 (88.4 %)

guidance and definitions of complications made by the Canadian Pediatric Neurosurgery Study Group [10], but in many instances caused delayed discharges.

Post-operative local complications or new neurological deficits were observed in a total of 68 (38.8 %) patients; 41 (23.4 %) presented with local complications such as pseudomeningocele, CSF shunt blockage, CSF leak, or wound infection; those complications were all treated successfully and did not lead into long-term sequelae. New neurological deficits were found in 44 (25.1 %) patients, 28 were transient, and 16 (9.1 %) permanent. Intra-operative neurophysiology monitoring was used in some OPW and BsT; however, in this group, a significant number of patients presented new neurological compromise. By location, surgical morbidity was found in 63 % of cerebellar tumors (41/65), 12.5 % of hemispheric (5/40) tumors, 16 % of OPW (4/25), 50 % of BsT (13/26), 27.3 % of spinal cord (3/11), and 25 % of intraventricular tumors (2/8). Tumor location and extent of tumor removal significantly correlated with development of neurological complications ($p < 0.001$). Cerebellar tumors had the highest rate of complications (63 %, majority were local and transient), but also achieved the highest rate of GTR (75.4 %).

Adjuvant treatment

Seventy-five (37.9 %) patients received adjuvant therapy. After surgical removal, 25 patients received chemotherapy, 24 radiotherapy, and 17 combined radio-chemotherapy. Eight patients received single-agent chemotherapy with no previous surgery, and one patient received combined therapy with no previous attempt of tumor removal. The age at onset, anatomical location, and extension of tumor removal were significantly correlated ($p < 0.0001$) with the use of adjuvant therapy.

Chemotherapy

As mentioned, chemotherapy was given as single agent in 8 cases with no previous histological confirmation (5 OPT, 2 hemispheric, and 1 spinal). In other 25 cases, chemotherapy was prescribed after tumor removal, when patients presented with evidence of neurological deterioration or radiological progression. Chemotherapy was the first line of choice and was given with the objective of delaying/avoiding the use of radiotherapy. Many regimens were used including the SIOP LGG protocol [23] or irinotecan + cisplatin according to our institutional protocol [35].

Radiotherapy

Standard fractionated radiotherapy with a varying dose between 45 and 52 Gy was indicated in 24 (12.1 %) patients all with histological confirmation of diagnosis. The mean age for this group was 7.5 years (range, 21.9–191.8 months). Radiotherapy was most frequently used in midline tumors with subtotal resection and recurrent cases. Twelve patients received radiotherapy immediately after tumor removal, and for the rest, radiotherapy was indicated at progression (6 BsT, 4 hemispheric, 1 spinal, 1 OPT, and 1 cerebellar). The use of radiotherapy statistically correlated with anatomical location ($p < 0.001$; log-rank test), since it was indicated in 9 BsT, 7 hemispheric, 3 OPW, 3 cerebellar, and 2 spinal tumors. Histology of those tumors was 12 LGG "*nos*", 3 fibrillary astrocytomas, 3 pilocytic astrocytomas, 2 pleomorphic astrocytomas, and 1 ganglioglioma.

Combined therapy

A combination of radiotherapy and chemotherapy was indicated in 18 cases (9.1 %) with evidence of progression after tumor removal (6 BsT, 11 OPW, 2 hemispheric, and 2 cerebellar tumors). Seventeen cases were confirmed by histology (15 STR and 2 biopsies), but 1 BsT received treatment with no histological confirmation.

The age (older than 3 years, $p = 0.001$), location (midline tumors, $p < 0.0001$), histology (fibrillary astrocytomas, $p = 0.048$), extent of resection (subtotal or biopsied, $p < 0.0001$), and progression or recurrence ($p = 0.023$) statistically correlated with the use of combined therapy.

Conservative management

Twelve patients did not receive any antitumoral treatment, and 2 BsT cases only accepted palliative treatment. Nine (6 OPW with NF1 and 1 TSC) of the 12 had stable visual deficits and never experienced progression. The remaining 3 patients presented with radiological progression but declined further treatment and were lost to follow up.

Long-term follow-up

The median follow-up for all the series was 65.2 months (SD 0.15, CI% 0.39–0.99). Events such as recurrence, relapse, or progression (local or metastatic) are summarized in Table 3.

Progression

Fifty-seven patients (28.8 %) experienced progression; 47 (82.4 %) after partial (43 STR and 4 biopsies) tumor removal. In those cases, histology did not correlate with progression ($p = 0.411$; log-rank test). The other 10 were among the 23 cases in which no surgical removal was attempted in the outset ($p < 0.001$). Anatomical location (mainly OPW and BsT) and the antecedent of phacomatosis statistically correlated with the occurrence of adverse events ($p = 0.001$ and $p = 0.006$; respectively).

Table 3 Adverse events such as progression, metastases, and recurrence observed in all PLGG regarding the anatomical location

Tumor location	Number of cases	Progression	Metastases	Recurrence
Cerebellum	67	7 (10.4 %)	2 (3 %)	1 (1.5 %)
Hemispheres	43	12 (27.9 %)	0	2 (4.6 %)
OPW	36	17(48.6 %)	0	2 (5.7 %)
BsT	32	13 (40.6 %)	2 (6.25 %)	0
Spinal	12	5 (41.7 %)	1 (8.3 %)	2 (16.7 %)
Intraventricular	8	3 (37.5 %)	1 (12.5 %)	–
Total	198	57 (28.8 %)	63 %)	7 (3.5 %)

Fifty-five patients (27.7 %) were transferred to adult care once they were over 18 years old, and further follow-up information was not available.

Metastases and multiple lesions

Metastases and/or multiple lesions were found in 12 (6.1 %) patients. Multiple lesions were found in 6 OPW and metastases in 2 primary cerebellar tumors, 2 BsT, 1 spinal, and 1 IV case. All those cases received adjuvant treatment achieving stabilization in 7 (6 OPW and 1 cerebellar). In 5 patients, further tumor debulking was necessary (twice in 3 cases and thrice in 2 cases). The extent of tumor resection (STR and biopsy, $p < 0.001$)) and recurrence ($p = 0.01$) statistically correlated with the presence of metastases.

Recurrence

Recurrence was defined as new evidence of disease after a period with no evidence of disease whatsoever, clinically or by imaging, during follow-up or after receiving adjuvant or surgical treatment. In our cohort, 7 patients (3.5 % of all PLGG) presented with recurrence. The anatomical location (1 cerebellar, 2 OPW with NF1, 2 hemispheric, and 2 spinal tumors) and the antecedent of NF1 correlated with higher chances of recurrence ($p = 0.006$ and $p = 0.022$).

Mortality

At the end of the study, 16 patients were dead, giving a mortality rate of 8.1 % for all series. The longest follow-up in this group relates to a patient with an OS of 174.2 months. The age at diagnosis and the location of the tumor statistically correlated with mortality ($p < 0.001$; log-rank test). In patients younger than 12 months, mortality was 62.5 % (5 of 8 patients died). By location, mortality was OPW 7/36 cases, BsT 6/32 cases, hemispheric 1/43, spinal 1/12, and intraventricular 1/8. Histology did not correlate with mortality ($p = 0.702$). Fifteen of the 16 patients underwent operations, 11 had a STR, and 4 were biopsied, a second attempt of tumor removal was performed in 5 cases, and a third attempt was performed in 2 cases. Fourteen of those patients received adjuvant therapy, 8 radiotherapy, 4 chemotherapy, and 4 CT.

Survival and sequelae

Quality of life (QOL) is a critical outcome measure that depends on survival and sequelae, determined after years of follow-up. Identification and detailed measurements of the sequelae are limited by time and economic and human resources [3]. Retrospective studies are not ideal to assess accurately this outcome; however, at the end of our study, 182 patients were alive and long-term sequelae (symptoms or neurological deficits) were observed in 93 (46. 9 %). The sequelae were classified as minor in 68, moderate in 21, and severe in 4 cases. Minor sequelae consisted in motor alterations (24/34 cases), sensory/cranial nerve defects (14/18 cases), cognitive impairment (14/17 cases), and others like endocrine disorders, pain, or seizures in 16/24 cases.

The type of sequela distributed by the type of treatment is presented in Table 4. Sixty-nine (63.3 %) of 109 patients treated surgically with no need for further treatment were alive free of disease, 38 presented sequelae, and 2 died as a result of tumor progression; while in the group of 75 patients treated with adjuvant therapy, 14 died, 16 (21.3 %) were alive free of sequelae, and 45 (60 %) presented sequelae. Of the group treated conservatively, no deaths occurred, 10 were alive with sequelae, and 4 were completely asymptomatic.

Neurological sequelae can be related to the tumor itself, but it has been reported that treatment can also generate long-term sequelae [3, 5, 22, 30, 33, 34]. In our series, surgery and the extent of resection were the most important variables correlating with less sequelae ($p < 0.001$; log-rank test), since 72 patients that underwent GTR and 13 with subtotal resection were alive with no evidence of sequelae.

Outcome analysis

With a median follow-up of 65.2 months (SD 0.15 CI 95 % 0.39–0.99), the OS for all patients was 96 % at 3 years, 94.2 % at 5 years, and 89.5 % at 10 years. The estimation of the mean time of OS for the cohort was 168 months, (CI at 95 %, 156.7–

Table 4 Long-term sequelae observed in 93 on 182 patients alive at the end of the study, distributed the type of treatment

Type of treatment	Sensory	Motor	Cognitive	Other[a]	Total
SURG	4	13	8	13	38 (40.8 %)
SURG + RT	1	8	3	2	14 (15 %)
SURG + Ch	1	1	0	2	4 (4.3 %)
SURG + CT	5	8	1	2	16 (17.2 %)
Ch	0	0	0	1	1 (1.1 %)
CT	4	3	2	1	10 (10.7 %)
Conservative	3	1	3	3	10 (10.7 %)
Total	18 (19.3 %)	34 (36.6 %)	17 (18.3 %)	24 (25.8 %)	93 (100 %)

Other sequels registered were pain, seizures, and endocrine disorders

SURG surgical tumor removal, *RT* radiotherapy, *Ch* chemotherapy, *CT* combined therapy (RT + Che)

179.3 months). The mean PFS for the global cohort was 121.3 months, (CI at 95 %, 107–135.61 months).

Progression was observed in 57 patients and most occurred during the first 60 months after diagnosis. Kaplan–Meier curves and statistics are shown in Fig. 2.

In the univariate analysis, tumor location correlated with the clinical variables and was the most important variable to predict outcome ($p = 0.001$, log-rank test). The majority of the tumors located in the midline (e.g., OPW and BsT) were pilocytic astrocytomas and LGG "nos," in which a more benign behavior should be expected; however, the location made complete resection unattainable, worsening the prognosis. The cerebellar tumors had the most suitable location for complete tumor removal but presented the highest rate of surgical complications. Altogether, 76.1 % of patients with cerebellar tumors were alive and with no evidence of disease, with a mean follow-up of 93 months. Only 9.1 % (8/67) required adjuvant treatment.

The histological features did not correlate with prognosis in any of the analysis. The need for adjuvant therapy correlated with worse PFS and OS.

Multivariate analysis is shown in Table 5. Age was one of the most important variables that correlated with prognosis, worse outcomes observed in children younger than 1 year (KM curves and data presented in Fig. 3). History of NF1 and location different of cerebellum were significantly correlated with worse PFS (Fig. 4).

We performed a secondary statistical analysis trying to find the effect of NF1 association with some PLGG like OPW and found a statistically significant relationship between NF1 and the development of progression ($p = 0.047$) and multiple lesions ($p = 0.006$), independent of the type of treatment received. Although this finding is contradictory with other reports, the outcomes for the NF1 subset of patients were similar to other large series published [9, 27].

Shunt dependency, type of treatment, extent of tumor resection, metastases, progression/recurrence, and presence of sequelae correlated with worse outcomes. Treatment-related variables that impacted favorably on outcome were GTR, single modality if adjuvant therapy was given (either radiation or chemotherapy), or no need for any kind of surgical or medical intervention. Patients who underwent a GTR had better OS

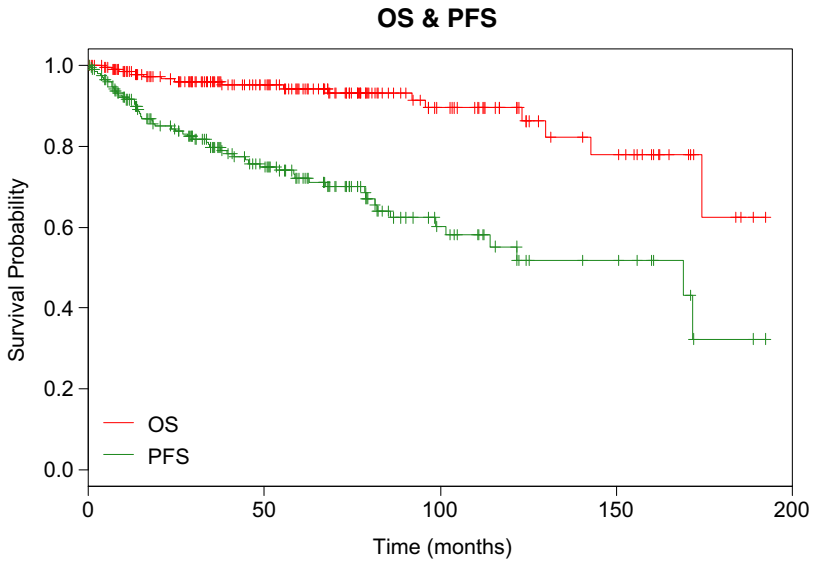
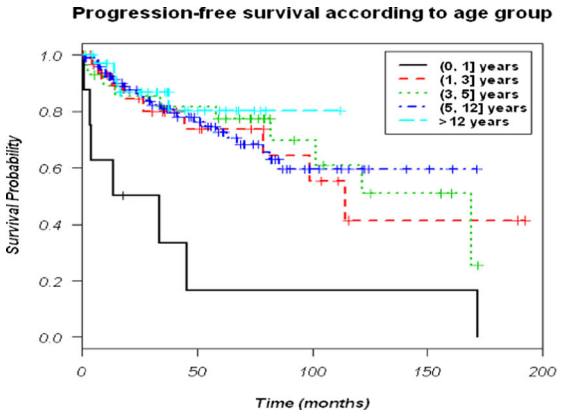
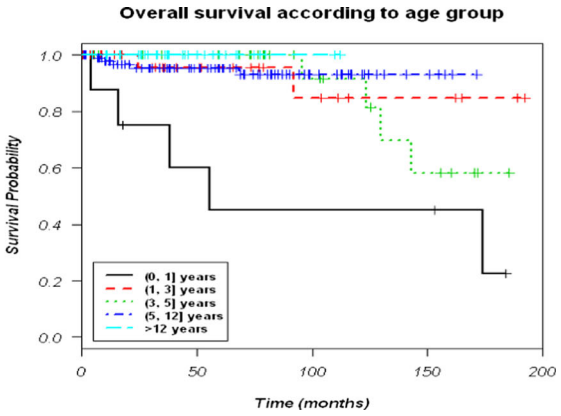


Fig. 2 The Kaplan–Meier curves of OS and PFS for all the cohort. PFS: 60 months 0.7 (SD 0.037, CI 95 % 0.65–0.8), 120 months 0.55 (SD 0.058, CI 95 % 0.55–0.58). OS: 60 months 0.942 (SD 0.019 CI 95 % 0.906–0.980), 120 months 0.895 (SD 0.033 CI 95 % 0.833–0.962)





Age group	Time (years)	Surv.	Std. error	95% CI	
(0, 1]	1	0.62	0.17	0.37	1.00
	3	0.33	0.18	0.12	0.96
	5	0.17	0.15	0.03	0.95
	10	0.17	0.15	0.03	0.95
(1, 3]	1	0.93	0.05	0.84	1.00
	3	0.80	0.08	0.65	0.98
	5	0.74	0.10	0.57	0.95
	10	0.41	0.16	0.20	0.87
(3, 5]	1	0.89	0.06	0.78	1.00
	3	0.82	0.07	0.68	0.98
	5	0.77	0.08	0.63	0.95
	10	0.61	0.12	0.41	0.90
(5, 12	1	0.92	0.03	0.87	0.98
	3	0.81	0.04	0.73	0.90
	5	0.73	0.05	0.63	0.84
	10	0.60	0.07	0.47	0.75
>12	1	0.97	0.03	0.91	1.00
	3	0.87	0.06	0.76	1.00
	5	0.80	0.09	0.65	0.99

Age group	Time (years)	Surv.	Std. error	95% CI	
(0, 1]	1	0.88	0.12	0.67	1.00
	3	0.75	0.15	0.50	1.00
	5	0.45	0.19	0.20	1.00
	10	0.45	0.19	0.20	1.00
(1, 3]	1	1.00	0.00	1.00	1.00
	3	0.95	0.04	0.87	1.00
	5	0.95	0.04	0.87	1.00
	10	0.85	0.11	0.66	1.00
(3, 5]	1	1.00	0.00	1.00	1.00
	3	1.00	0.00	1.00	1.00
	5	1.00	0.00	1.00	1.00
	10	0.92	0.08	0.77	1.00
(5, 12	1	0.98	0.02	0.95	1.00
	3	0.95	0.02	0.91	1.00
	5	0.95	0.02	0.91	1.00
	10	0.93	0.03	0.87	0.99
>12	1	1.00	0.00	1.00	1.00
	3	1.00	0.00	1.00	1.00
	5	1.00	0.00	1.00	1.00

Fig. 3 The dates and Kaplan–Meier curves of PFS and OS by age at onset distributed in groups. In the group of patients aged over 12, the 10-year survival could not be computed since the follow-up in this group was below 120 months and the last observation is censored. Log-rank test, $p = 0.0032$

than those who required adjuvant therapy after a partial surgical tumor removal ($p < 0.0001$; log-rank test). Patients who required adjuvant therapy with previous surgery had longer PFS than patients who did not underwent surgical removal of tumor (86.5 and 78.5 months, respectively, $p < 0.0001$; log-rank test). Survival curves are shown in Fig. 4. No differences in OS or PFS were found regarding the type of chemotherapy given.

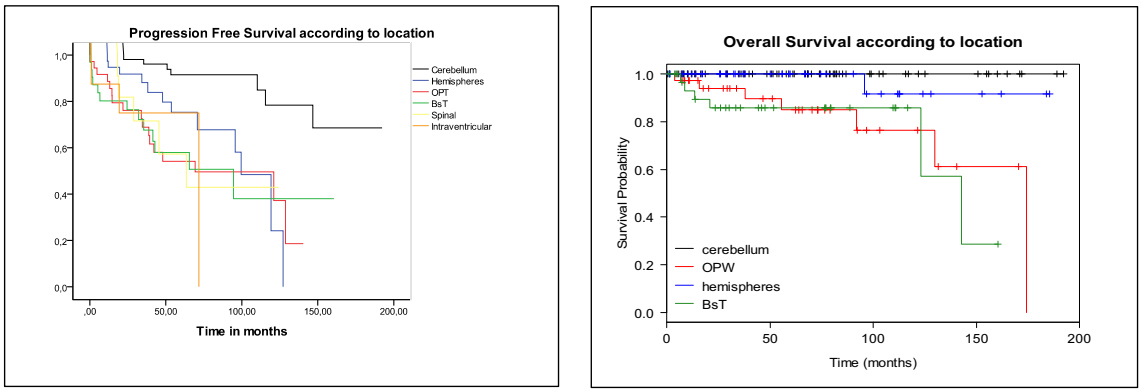
Discussion

We analyzed an institutional cohort of 198 patients with PLGG over a three-decade period and a median follow-up of 5.2 years. This is one of the largest series of PLGG ever reported, and although the retrospective design of the study and the non-unique form of treatment along the years could obscure the analysis, we were able to identify features that exhibited statistically significant associations with OS and PFS.

This cohort of PLGG accounted for 38.4 % of the brain tumors managed at our institution during this period, supporting the fact that PLGG are the most common brain tumors in children, in agreement with the incidence previously reported in Spain and USA [5, 41, 43, 46].

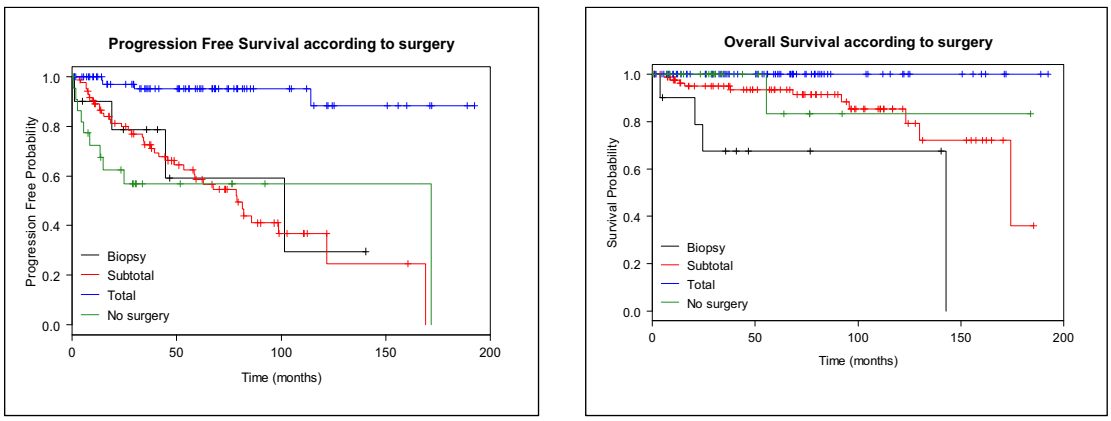
Since the implementation of MRI, more accurate anatomical diagnosis has contributed to a better definition of the characteristics of brain tumors and specifically PLGG, improving their management and prognosis. PLGG distributed by their precise anatomical location present diverse but well-

A



PFS (time in months) Cerebellum: 164.6, Hemispheres: 92.3, OPT: 79.5, BsT: 86.4
OS: Cerebellum: 60, 120 and 180 months 1 (SD 0. CI 95% 1-1). Hemispheres: 60 months 1 (SD 0. CI 95% 1-1), 120 and 180 months 0.917 (SD 0.08. CI 95% 0.74-0.99), OPT: 60 months 0.849 (SD 0.071-0.072. CI 95% 1), 120 months 0.764 (SD 0.103, CI 95% 0.586 – 0.995), BsT 60 and 120 months 0.857 (SD 0.066, CI 95% 0.74–0.997).

B



PFS (time in months) Biopsy: 91.3, STR: 85.7, GTR: 159.4, No Surgery: 100.6
OS: Biopsy: 60 and 120 months 0.675 (SD 0.155, CI 95% 0.43-1)
Subtotal: 60 months 0.934 (SD 0.029, CI 95% 0.88-0.99), 120 months 0.853 (SD 0.052, CI 95% 0.757 – 0.96)
GTR: 60, 120 and 180 months 1 (SD 0, CI 95% 1-1)
No surgery: 60, 120 and 180 months 0.83 (SD 0.152, CI 95% 0.583-1)

Fig. 4 The Kaplan–Meier curves of OS and PFS. **a** By Location and **b** by extent of tumor resection

defined clinical and radiological characteristics including the age at onset, type and duration of symptoms, and the presence of hydrocephalus. In our series we confirm this finding since cerebellar, hemispheric, optic pathways, brainstem, spinal, and intraventricular tumors presented similarly to previously reported studies [4, 5, 19, 20, 24, 35, 37, 41]. In our series, spinal cord tumors presented at the youngest median age. Patients younger than 12 months presented with tumors mainly located in the hemispheres or the optic pathways, with significantly poorer outcomes.

Regarding histology, in our series, more than 60 % of the tumors were pilocytic astrocytomas or LGG "nos", but we found a trend over time of a decreasing incidence of "nos" astrocytoma. For the last decade, this generic diagnosis has been progresively replaced by more specific entities like pilocytic or fibrillary astrocytoma by adding immunohistochemical markers such as GFAP, Ki 67, and p53 [2, 6, 17, 21, 25, 26, 32, 40]. However, in an attempt to standardize the cohort, for this study, we used the basic WHO criteria recommendations as other researchers have previously reported [2, 6, 17, 20, 29, 37, 46, 47].

Despite their potentially common origin, PLGG presented a rather diverse clinical behavior. Recently, a new classification has been proposed considering the categories diffuse and non-diffuse tumors according to the infiltrative nature during growth [31, 46]. This behavior could explain the tendency to progression, recurrence, or metastases. It is now well established that the biology of these tumors is different than

the adult counterpart and is characterized by the MAPK pathway activation (mainly BRAF alterations) predominant in pilocytic astrocytoma and mixed neuronal neuronal-glial tumors; the rarity of malignant transformation, and the uncommonness of other biological characteristics such as IDH1 mutations [31, 37].

The technological advances introduced during the period studied have changed significantly the surgical approach of brain tumors in children, allowing for an increase in the extent of tumor resection and decrease in morbidity and mortality, with a very positive impact on outcome [5, 7, 8, 11, 13, 14, 16, 19, 20, 23, 24, 37, 39, 41, 47, 48]. Currently, surgical excision is the standard of treatment for PLGG; 95.5 % of our patients with cerebellar or hemispheric tumors (105 cases) were offered immediate surgery after diagnosis. However, for selected patients, like those with midline tumors, surgery was deferred until progression or neurological deterioration, as other authors recommend [9, 12, 15, 24, 27, 28]. The extent of tumor removal in our series is similar to data reported in other surgical series [7, 9, 12, 15, 19, 20, 28, 31, 42, 46].

Table 5 List of variables with significant impact on the long-term outcomes (PFS and OS) in patients with PLGG. Multivariate analysis

Variable		PFS			OS		
		p value	Time in months	HR (lower CI95%–higher CI 95 %)	*p* value	Time in months	HR (lower CI95%–higher CI 95 %)
Age	>12 months	$p < 0.0001$	121.9	1(108.4–135.4)	$p < 0.0001$	170.1	1(159.7–180.5)
	<12 months		98	4.49(0–89.2)		98.02	6.6 (41.85–154.19)
Phacomatoses	NO	$p < 0.0001$	127.7	1	n/s		
	NF1		46.7	3.04 (1.65–5.6)			
	TSC		41.8	0.64 (0.09–4.81)			
Anatomical location	Cerebellar	$p < 0.0001$	164.6	0.15 (0.06–0.36)	$p = 0.0006$	<200	0
	OPT		79.5	1		135.3	1
	Hemispheres		92.3	0.53 (0.25–1.12)		162.2	0.11 (0.013–0.89)
	BsT		86.4	0.85 (0.41–1.75)		125.8	1.25 (0.41–3.85)
	Spinal		75.3	0.7 (0.255–1.89)		155.2	0.44 (0.05–3.64)
	Intraventricular		56.3	0.76 (0.22–2.6)		118.3	0.75 (0.09–6.22)
Tentorium location	Infratentorial	$p = 0.008$	139.2	1	$p = 0.323$	170.3	1
	Supratentorial		85.2	2 (1.18–3.4)		154.9	1.64 (0.61–4.42)
Surgical tumor removal	Biopsy	$p < 0.0001$	91.3	1	$p < 0.0001$	101.9	1
	STR		85.7	0.25 (0.08–0.81)		154.3	0.25 (0.08–0.81)
	GTR		159.4	0		>200	0
	Not Surgery		100.6	0.125 (0.01–1.18)		163.2	0.125 (0.013–1.18)
CSF shunt dependence	No	$p = 0.015$	106.7	1	$p = 0.018$	178.6	1
	Yes		126.7	1.93 (1.125–3.3)		147.3	3.12 (1.16–8.4)
Adjuvant therapy	No	$p < 0.0001$	144.7	1	$p < 0.0001$	184.8	1
	Yes		84.9	2.88 (1.67–4.94)		143.0	9.1 (2.06–40.2)
Radiotherapy	No	$p = 0.004$	137.3	1	$p = 0.023$	177.9	1
	Yes		89.9	2.24 (1.28–3.92)		142.6	3.11 (1.116–8.66)
Chemotherapy	No	$p = 0.02$	132.2	1	$p = 0.012$	173.2	1
	Yes		80.6	1.95 (1.10–3.43)		139.9	3.38 (1.24–9.21)
Metastases	No	$p = 0.005$	124	1	$p = 0.079$	168.8	1
	Yes		66.3	2.82 (1.33–5.99)		147.8	2.98 (0.83–10.69)
Recurrence	No	$p < 0.0001$	123.4		n/s		
	Yes		31.1				
Long-term sequels	No	$p = 0.08$	131.8	1	n/s		
	Yes		95.4	1.76 (0.92–3.37)			
Progression	No	n/s	n/s		$p < 0.0001$	188	1
	Yes		n/s			138.2	24.6 (3.22–188.5)

p is the value of the multivariate Cox regression model for PFS and OS (category "NO" as reference)

HR hazard ratio, *n/s* non-significant,

In our experience, surgical tumor removal was a valid prognostic factor. When possible, GTR was the treatment of choice, but in cases with partial resection, a positive prognostic impact was also found for tumor excision and outcome. A satisfactory surgical mortality of zero was encountered but also a surgical morbidity of 38.8 %. Complications, as expected, were related to tumor location and extent of surgical resection. It must be taken into account that this study was not designed to assess complications or sequels, and it was not possible to identify a clear relationship between post-operative complications and long term-sequels. However, the neurological recovery after surgical tumor removal was generally satisfactory. As other authors, we might suggest that the extent of surgical resection is an important factor that should be taken into consideration when trying to avoid functional sequels in those patients with expected long-term survival [10, 11, 15, 33, 34, 36, 41].

The incidence of progression and recurrence in PLGG were particularly high in OPW, BsT, and spinal tumors, since 47 tumors progressed after STR or biopsy; in 77 % of those cases, progression was observed within 60 months from surgery. Other 10 cases of progression were observed in patients treated conservatively at onset, all but one progressed within 25 months from diagnosis [1, 2, 22, 31, 47].

Until 10 years ago, radiation therapy was used in PLGG tumors not amenable for surgical removal. Currently, however, radiotherapy is avoided in all PLGG because of the efficacy of chemotherapy to control the disease and thus prevent the long-term side effects associated with radiation. In some cases, the indication cannot be excluded and more conformational techniques are recommended [9, 12, 18, 20, 22, 30, 33, 42].

Chemotherapy was used upfront to treat BsT and OPW and was indicated to treat recurrence, metastases, or progression in order to delay or avoid radiotherapy [38, 44]. The association of OPW and BsT with NF1 was a factor taken into consideration to delay or avoid radiotherapy or even adjuvant treatment because of its relatively better overall survival [9, 12, 15, 18, 19, 23, 28].

For all the PLGG, age at diagnosis, anatomical tumor location, and extent of surgical resection were highly predictive of PFS and OS (significantly longer OS for cerebellar tumors and those with GTR and shorter for BsT and patients younger than 12 months at diagnosis). The outcomes of our surgical series are similar to other national referral centers in Europe and North America [7, 12, 13, 16, 18, 19, 20, 39, 41, 42, 47]. Satisfactorily, we were able to determinate the PFS and OS, despite the inherent limitations of a retrospective, single institution analysis, with a limited number of cases in comparison to larger multi-institutional series. The p value was not significant, when we discriminated the PFS and OS decade by decade, but both measures have improved over time likely due to refinements in diagnosis, surgical techniques, and treatment modalities (Table 6, supplementary material).

Conclusion

PLGG are the most common brain tumors in childhood. Histologically, they comprise a variety of gliomas, the most frequent type being pilocytic astrocytoma. For these tumors, surgical removal is the treatment of choice. The feasibility of achieving a GTR relates to tumor location and is the strongest prognostic variable. The extent of tumor resection and the neurological risk in case of progression constitutes the basis to prescribe further treatments.

For recurrent or residual tumors located in surgically non-resectable areas and tumors with a tendency to progression, biological studies are expected to provide in the near future with new therapeutic strategies.

Acknowledgments We are grateful to our nursing and multidisciplinary staff for their support in patient care. We thank Daniel Cuadras and Sara Perez Jaume for their support in statistics (Fundació Sant Joan de Déu per la recerca). The authors also thank the institutional Biobank "Biobanc de l' Hospital Materno-Infantil de Sant Joan de Déu per la recerca" as part of the "Red Temática de Biobancos Hospitalarios del ISCIII" and also Miss Sarah Buttler for her valuable help in the edition of this paper.

Conflict of interest The authors declare that they have no competing interests.

References

1. Ater J, Holmes E, Zhou T, et al (2012) Randomized study of two chemotherapy regimens for treatment of low-grade glioma in young children. J Clin Oncol 30(21):2641–2647
2. Bandopadhayay P, Bergthold G, London WB, Goumnerova LC, Morales La Madrid A, Markus K, et al (2014) Long-term outcome of 4040 children diagnosed with pediatric low-grade gliomas: an analysis of the Surveillance Epidemiology and End Results (SEER) database. Pediatr Blood Cancer 61(7):1173–1179
3. Beebe DW, Ris MD, Armostrong FD, Fontanesi J, Mulhern R, Holmes E, Wisoff JH (2005) Cognitive and adaptative outcome in low grade pediatric cerebellar astrocytomas: evidence of diminished cognitive and adaptative functioning in national collaborative research studies (CCG 9891/POG 9130). J Clin Oncol 23:5198–5204
4. Bristol RE (2009) Low-grade glial tumors: are they all the same? Semin Pediatr Neurol 16(1):23–26
5. CBTRUS. Statistical Report (2005) Primary brain tumors in the United States, 1998–2002. Central Brain Tumor Registry of the United States, Hinsdale
6. Choi KC, Kwak SE, Kim JE, Sheen SH, Kang TC (2009) Enhanced glial fibrillary acidic protein-delta expression in human astrocytic tumors. Neurosci Lett 463(3):182–187
7. Colin C, Padovani L, Chappe C, Merciurio S, Scavarda D, Loundou A, et al (2013) Outcome analysis of childhood pilocytic astrocytomas: a retrospective study of 148 cases at a single institution. Neuropathol Appl Neurobiol 39(6):693–705
8. Daumas-Duport C, Scheithauer BW, Chodkiewicz JP, et al (1988) Dysembryoplastic neuroepithelial tumor: a surgically curable tumor of young patients with intractable partial seizures. Report of thirty-nine cases. Neurosurgery 23:545–556

9. De Carli E, Kalifa CM, Raquin J, Lemerle J, Habrand J, Couanet D, et al (2010) Premature deaths and severe morbidity in 192 long-term survivors of pediatric pathway tumors (OPT): a 50-year study. J Clin Oncol 28:15s(suppl; abstr 9555)
10. Drake J, Singhal A, Kulkarni A, De Veber G, Cochrane D, Canadian Pediatric Neurosurgery Study Group (2012) Consensus definitions of complications for accurate recording and comparisons of surgical outcomes in pediatric neurosurgery. J Neurosurg Pediatr 10(2):89–95
11. Due-Tonnessen B, Lundar T, Egge A, Scheie D (2013) Neurosurgical treatment of low-grade cerebellar atrocytoma in children and adolescents: a single consecutive institutional series of 100 patients. J Neurosurg Pediatr 11(3):245–249
12. Fakhreddine M, Mahajan A, Penas-Prado M, Weinberg J, et al (2013) Treatment, prognosis factors and outcomes in spinal cord astrocytomas. Neuro-Oncology 15(4):406–412
13. Fernandez C, Figarella-Branger D, Girard N, et al (2003) Pilocytic astrocytomas in children: prognostic factors—a retrospective study of 80 cases. Neurosurgery 53:544–555
14. Fisher PG, Tihan T, Goldthwaite PT, et al (2008) Outcome analysis of childhood low-grade astrocytomas. Pediatr Blood Cancer 51: 245–250
15. Fouladi M, Wallace D, Langston JW, et al (2003) Survival and functional outcome of children with hypothalamic/chiasmatic tumors. Cancer 97:1084–1092
16. Fouladi M, Jenkins J, Burger P, et al (2001) Pleomorphic xanthoastrocytoma: favorable outcome after complete surgical resection. Neuro-Oncology 3:184–192
17. Gaiser T, Becker MR, Meyer J, Habel A, Siegelin MD (2009) P53-mediated inhibition of angiogenesis in diffuse low-grade astrocytomas. Neurochem Int 54(7):458–463
18. Gajjar A, Bhargava R, Jenkins JJ, Heideman R, Sanford RA, Langston JW, et al (1995) Low-grade astrocytoma with neuraxis dissemination at diagnosis. J Neurosurg 83:67–71
19. Gajjar A, Sanford RA, Heideman R, et al (1997) Low-grade astrocytoma: a decade of experience at St Jude Children's Research Hospital. J Clin Oncol 15:2792–2799
20. Garzon M, Garcia G, Guillen A, Sunol M, Mora M, Cruz O (2013) Brain stem tumors in children and adolescents: single institutional experience. Childs Nerv Syst 29(8):1321–1331
21. Gelpi E et al (2005) Pleomorphic xanthoastrocytoma with anaplastic features presenting without GFAP immunoreactivity: implications for differential diagnosis. Neuropathology 25(3):241–246
22. Gnekow AK, Falkenstein F, Von Homstein S, Zwiener I, Berkefeld S, Bison B, et al (2012) Long-term follow-up of the multicenter, multidisciplinary treatment study HIT-LGG-1996 for low-grade gliomas in children and adolescents of the German Speaking Society of Pediatric Oncology and Hematology. Neuro-Oncology 14(10): 1265–1284
23. Gnekow A, Kandels D, Walker D, Perilongo G, et al (2014) Abstracts from the sixteenth international symposium on pediatric neuro-oncology: a randomized trial of intensification of induction-chemotherapy within an 18 months treatment-strategy on tumor-response at 24 weeks and progression-free-survival in pediatric low grade glioma (LGG). Preliminary results of the SIOP-LGG-2004-Working Group. Neuro-Oncology 16:i60–i70. doi:10.1093/neuonc/nou073
24. Goodden J, Pizer B, Pettorini B, Williams D, Blair J, Didi M, et al (2014) The role of surgery in optic pathway/hypothalamic gliomas in children. J Neurosur Pediatr 13(1):1–12
25. Haapasalo J, Mennander A, Helen P, Haapasalo H, Isola J (2005) Ultrarapid Ki-67 immunostaining in frozen section interpretation of gliomas. J Clin Pathol 58:263–268
26. Hashiba T, Izumoto S, Kagawa N, Suzuki T, Hashimoto N, Maruno M, Yoshimine T (2007) Expression of WT1 protein and correlation with cellular proliferation in glial tumors. Neurol Med Chir (Tokyo) 47(4):165–170
27. Hernaiz-Driever P, Von Hornstein S, Pietsch T, Kortmann R, Warmuth-Metz M, Emser A, Gnekow AK (2010) Natural history and management of low-grade glioma in NF1 children. J Neuro-Oncol 100(2):199–207
28. Listernick R, Ferner RE, Liu GT, Gutmann DH (2007) Optic pathway gliomas in neurofibromatosis-1: controversies and recommendations. Ann Neurol 61:189–198
29. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK (2007) WHO classification of tumours of the central nervous system, 4th edn. IARC, Lyon, p. 309
30. Marcus KJ, Goumnerova L, Billett AL, et al (2005) Stereotactic radiotherapy for localized low-grade gliomas in children: final results of a prospective trial. Int J Radiat Oncol Biol Phys 61:374–379
31. Margraf LR, Gargan L, Butt Y, Raghunathan N, Bowers DC (2011) Proliferative and metabolic markers in incompletely excised pediatric pilocytic astrocytomas—an assessment of 3 new variables in predicting clinical outcome. Neuro-Oncology 13:767–774
32. Maurizi P, Ruggiero A, Attinà G, Cefalo MG, Arlotta A, Riccardi R (2008) The prognostic role of Ki-67 in childhood low-grade glioma. Pediatr Med Chir 30(2):73–78
33. Merchant TE, Conklin HM, Wu S, et al (2009) Late effects of conformal radiation therapy for pediatric patients with low-grade glioma: prospective evaluation of cognitive, endocrine, and hearing deficits. J Clin Oncol 27(22):3691–3697
34. Monje M, Graham Fisher P (2011) Neurosurgical complications following treatment of children with brain tumors. J Pediatr Rehabil Med 4(1):31–36
35. Mora J, Cruz O, Gala S, Navarro R (2007) Successful treatment of childhood intramedullary spinal cord astrocytomas with irinotecan and cisplatin. Neuro-Oncology 9:39–46
36. Neervoort FW, Van Ouwerkerk W, Folkersma H, Kaspers G, Vandertop W (2010) Surgical morbidity of pediatric brain tumors: a single center audit. Childs Nerv Syst 26(11):1583–1592
37. Ohgaki H, Kleihues P (2005) Population-based studies on incidence, survival rates, and genetic alterations in astrocytic and oligodendroglial gliomas. J Neuropathol Exp Neurol 64(6):479–489
38. Packer RJ, Ater J, Allen J, et al (1997) Carboplatin and vincristine chemotherapy for children with newly diagnosed progressive low-grade gliomas. J Neurosurg 86:747–754
39. Palma L, Celli P, Mariottini A (2004) Long-term follow-up of childhood cerebellar astrocytomas after incomplete resection with particular reference to arrested growth or spontaneous tumor regression. Acta Neurochir 146:581–588
40. Pollack F et al (2002) Expression of p53 and prognosis in children with malignant gliomas. N Engl J Med 346(6):420–427
41. Qaddoumi I, Sultan I, Gajjar A (2009) Outcome and prognostic features in pediatric gliomas: a review of 6212 cases from the surveillance, epidemiology, and end results database. Cancer 115: 5761–5770
42. Qaddoumi I, Sultan Y, Broniscer A (2009) Pediatric low-grade gliomas and the need for new options for therapy: why and how? Cancer Biol Ther 8:4–10
43. RNTI-SEHOP, Registro Nacional de tumores en España – Sociedad Española de Hemato-Oncologia Pediátrica. 1980–2012. www.uv.es/rnti/index.html
44. Shaw EG, Wisoff JH (2003) Prospective clinical trials of intracranial low-grade glioma in adults and children. Neuro-Oncology 5: 153–160

45. Sievert AJ, Fisher MJ (2009) Pediatric low-grade gliomas. J Child Neurol 24:1397–1408
46. Stokland T, Liu JF, Ironside JW, Ellison DW, Taylor R, Robinson KJ, Picton SV, Walker DA (2010) A multivariate analysis of factors determining tumor progression in childhood low-grade glioma: a population-based cohort study (CCLG CNS9702). Neuro-Oncology 12:1257–1268
47. Terashima K, Chow K, Jones J, Ahern C, Jo E, Ellezam B, Paulino A, et al (2013) Long-term outcome of centrally located low-grade glioma in children. Cancer 119(14):2630–2638
48. Wisoff JH et al (2011) Primary neurosurgery for pediatric low-grade gliomas: a prospective multi-institutional study from the Children's Oncology Group. Neurosurgery 68(6):1548–1554 discussion 1554–5