Neurochirurgie 65 (2019) 63–68

Disponible en ligne sur ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com

Original article

Pediatric high grade gliomas: Clinico-pathological profile, therapeutic approaches and factors affecting overall survival

O. Boudaouara [a,*], S. Charfi [a], M. Bahri [b], J. Daoud [b], M.Z. Boudawara [c], N. Gouiaa [a], T. Sellami Boudawara [a]

[a] Laboratoire d'anatomie et de cytologie pathologique, CHU Habib Bourguiba, route Aïn km 0.5, 3029 Sfax, Tunisia
[b] Service de radiothérapie, CHU Habib Bourguiba, 3029 Sfax, Tunisia
[c] Service de neurochirurgie, CHU Habib Bourguiba, 3029 Sfax, Tunisia

ARTICLE INFO

Article history:
Received 7 May 2018
Received in revised form 19 January 2019
Accepted 9 March 2019
Available online 29 March 2019

Keywords:
Pediatric high grade glioma
Glioblastoma
Surgical resection
Radiation therapy
Treatment response
Overall survival

ABSTRACT

Introduction. – Pediatric high grade gliomas are rare tumors of the central nervous system. Treatment is multidisciplinary, comprising surgical excision followed by radiotherapy and/or chemotherapy.
Objectives. – describe these tumors' characteristics as seen in our institution, and identify factors associated with better overall survival.
Patients and methods. – We conducted a retrospective study of 30 cases of pediatric high grade glioma treated consecutively in our institution over a 20-year period. Brainstem tumors and patients aged more than 22 years were excluded. Univariate analysis was conducted to determine factors associated with better overall survival.
Results. – The series comprised 30 pediatric high grade gliomas: 27 glioblastomas and 3 anaplastic astrocytomas. The sex ratio was 1.7. Mean age was 13 years. Tumors were mainly located in the cerebral hemispheres (63.3%). Median tumor size was 5 cm. Glioblastomas were subdivided into 26 cases of classical subtype (96.3%) and 1 case of epithelioid subtype (3.7%). Surgical strategy consisted in tumor resection in 24 cases (80%). Twenty-one patients (70%) received postoperative radiotherapy. Therapeutic response at end of treatment was complete in 7 cases (23.3%). Postoperative radiation therapy and complete treatment response were significantly associated with improved overall survival in all high grade gliomas and also specifically in glioblastomas ($P < 0.001$ and $P = 0.005$, respectively).
Conclusion. – Our results suggest that postoperative radiotherapy and complete treatment response are predictive factors for better overall survival in pediatric high grade glioma.

1. Introduction

Pediatric high grade gliomas (HGG) are relatively infrequent, accounting for 6.5% to 12% of all central nervous system tumors in children [1–6]. Excluding brainstem HGGs, location is most commonly supratentorial, with 30–50% arising in the cerebral hemispheres [5,7]. HGG encompass World Health Organization (WHO) grade III tumor, comprising mainly anaplastic astrocytomas, and WHO grade IV tumors consisting in glioblastomas [5,7]. Due to the rarity of these childhood neoplasms, studies of prognostic factors and optimal treatment strategies are limited, and adult treatment paradigms are often extrapolated to children, even though there is data indicating that these diseases are biologically distinct [7,8]. The current standard of care is multimodal, combining maximal safe resection when technically feasible followed by radiation therapy (RT) and chemotherapy [4,5,9]. In spite of aggressive treatment, 5-year overall survival (OS) is poor, not exceeding 35% [4].

We conducted a single-center study to describe clinic-pathological features, treatment patterns and outcomes in pediatric HGG. We also explored prognostic factors affecting OS.

2. Patients and methods

2.1. Patients

A retrospective database search for the period 1997–2017 identified 30 pediatric patients with HGG consecutively treated at our institution. We included histologically proven HGG in patients aged 22 years old or younger. Brainstem gliomas were excluded.

* Corresponding author.
E-mail address: annoussa1988@hotmail.com (O. Boudaouara).

https://doi.org/10.1016/j.neuchi.2019.03.001
0028-3770/

Clinico-pathological and treatment characteristics as well as survival outcomes were retrieved from review of medical records. Surgical intervention was classified as simple biopsy, subtotal resection or gross total resection. Resection extent was assessed on early postsurgical cerebral computed tomography (CT) and/or surgical report. Gross total resection (GTR) was defined as a total macroscopic removal of the mass, and subtotal or incomplete resection as a surgery which had leaved a tumor residue. Biopsies were performed without tumor debulking, and were either open or stereotactic. Treatment response was evaluated on the basis of a cerebral CT or magnetic resonance imaging (MRI) within 2 months of diagnosis. Complete response was defined as no radiological evidence of the tumor, with disappearance of any tumor cells from the cerebrospinal fluid. Otherwise, response was classified as incomplete. In the absence of timely cerebral imaging, treatment response was considered non-assessable.

2.2. Statistical analysis

Descriptive analyses used percentages to describe categorical variables. For continuous variables, mean and standard deviation (SD) were calculated in normal distributions, and median and range in non-normal distributions.

OS was defined as the time from initial surgery to date of death or last follow-up. Kaplan–Meier curves were used to obtain median OS. Univariate analysis on log-rank test screened for prognostic factors associated with improved OS in the whole cohort and in each histological grade subgroup. *P*-values < 0.05 were deemed statistically significant.

3. Results

3.1. Population

Mean age at diagnosis was 13 ± 6.3 years; 4 patients (13.3%) were 4 years old. The sex ratio was 1.7. HGG was de novo in 26 cases (86.7%) and derived from WHO grade II astrocytoma in 4 cases (13.3%). None of our patients presented an inherited HGG predisposing syndrome. Clinical characteristics are shown in Table 1. Nineteen tumors (63.3%) were located in the cerebral hemispheres.

Histology showed that the majority of cases (27 cases, 90%) were glioblastoma (WHO grade IV), comprising 26 classical subtypes (96.3%) and one epithelioid subtype (3.7%) (Fig. 1a). In the glioblastoma subgroup, histopathological evidence of necrosis (Fig. 1b) and microvascular proliferation (Fig. 1c) was found in 19 and 22 cases respectively (70.4% and 81.5% of all glioblastomas). The case of epithelioid glioblastoma showed strong immunoreactivity for INI-1 (Fig. 1d).

Surgical management consisted in tumor resection in 24 cases (80%). GTR was achieved in 10 cases (33.3%), while resection was subtotal in 14 cases (46.7%). Three of the 9 patients with thalamic HGG underwent subtotal resection and GTR was feasible in one case. Stereotactic needle biopsy was the only surgical option in the 5 remaining cases. In cerebral gliomas, tumor resection was performed in 18 cases and was complete in 9 cases among them. The remaining patient with cerebral HGG was eligible only for open needle biopsy. Both patients with cerebellar HGG had subtotal resection.

The supine position, a modification of dorsal decubitus, was used to manage accessible supratentorial lesions involving the thalamus (4 cases) and cerebral hemispheres (18 cases). The park bench position, an adjustment of the lateral position, was adopted for tumors arising in the cerebellar hemispheres (2 cases). In both surgical positions, once the tumor was visualized, it was fragmented and removed completely or partially, in a piecemeal fashion in all cases (24 cases).

Twenty-one patients (70%) received postoperative RT, with a median dose of 60 Gy.

Treatment response assessment found complete response in 7 cases (23.3%), 4 of which with GTR; complete response was more frequent when GTR had been achieved, but the difference was not statistically significant (*P* = 0.18). Treatment response was incomplete in 18 cases (60%). In 5 patients (16.7%), response could

Table 1
Patient characteristics.

	n (%)
Mean age at diagnosis ± standard deviation	13 ± 6.3 years
Gender	
Male	19 (63.3%)
Female	11 (36.6%)
Secondary high grade glioma	
No	26 (86.7%)
Yes	4 (13.3%)
Symptoms	
Focal neurological deficit	20 (66.7%)
Symptoms of raised intracranial pressure	20 (66.7%)
Seizures	10 (33.3%)
Cranial nerves paralysis	2 (6.7%)
Isolated headaches	2 (6.7%)
Cerebellar syndrome	2 (6.7%)
Tumor location	
Cerebral hemispheres	19 (63.3%)
Diencephalon	9 (30%)
Cerebellar hemispheres	2 (6.7%)
Median tumor size (range)	5 cm (3–12 cm)
Annular ring-like enhancement on imaging	23 (76.7%)
WHO tumor grade	
Grade IV	27 (90%)
Grade III	3 (10%)
Extent of surgical resection	
Gross total resection/complete resection	10 (33.3%)
Incomplete/subtotal resection	14 (46.7%)
Biopsy only	6 (20%)
Postoperative radiation therapy	21 (70%)
Postoperative chemotherapy	3 (10%)
Complete treatment response	7 (23.3%)
Progression	22 (73.3%)
Recurrence	3 (10%)
Secondary metastasis	7 (23.3%)
Death due to disease	18 (60%)

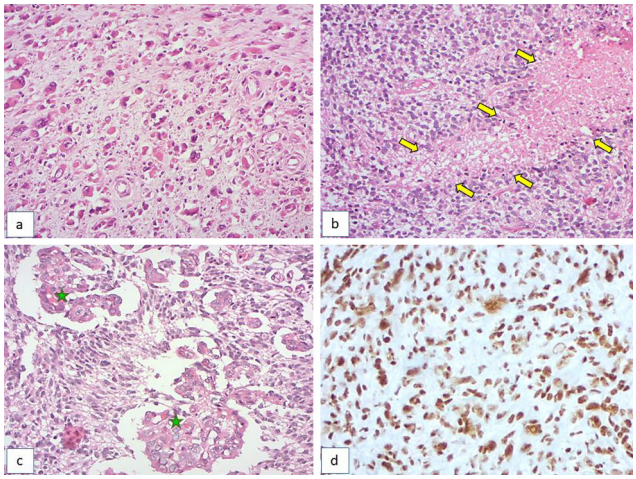

Fig. 1. a: epithelioid glioblastoma: area of discohesive epithelioid cells with abundant eosinophilic cytoplasm. These cells sometimes have excentric nuclei mimicking rhabdoid cells, hematoxylin eosin ×100; b: tumor necrosis area lined by a palisade of glial tumor cells (arrows), hematoxylin eosin ×200; c: microvascular proliferation with glomeruloid feature within a glioblastoma (star), hematoxylin eosin ×200; d: immuno-staining of tumor cells with INI-1 in an epithelioid glioblastoma, ×200.

Table 2
Prognostic factors: univariate analysis of overall survival for the whole cohort and grade IV gliomas.

Variable	Whole cohort	($n=30$)		Grade IV gliomas	($n=27$)	
	Median OS (%)	95% CI	*P*-value[a]	Median OS (%)	95% CI	*P*-value[a]
Age			0.73			0.85
< 12 years (median)	20	0–47		20	0–44.9	
≥ 12 years (median)	13	5–21		13	5.1–20.8	
Gender			0.55			0.42
Male	17	8.1–25.8		17	0–35.5	
Female	7	0–17.4		7	0–17.4	
Symptoms						
Seizures			0.55			0.75
Yes	12	2.4–21.5		12	0–24.8	
No	17	2.9–31		17	2.8–31.1	
Duration of symptoms before diagnosis			0.22			0.31
< 6 weeks (median)	7	4.6–9.3		7	4.4–9.5	
≥ 6 weeks (median)	20	10.2–29.7		20	10.2–29.8	
Tumor location			0.62			0.45
Diencephalon	20	0–48.1		20	0–47.4	
Cerebral and cerebellar hemispheres	13	1.7–24.2		13	1.7–24.2	
Tumor size			0.70			0.56
< 5 cm (median)	17	0–38		17		
≥ 5 cm (median)	12	2.6–21.3		13	0–26	
WHO tumor grade			0.39			
Grade III	3					
Grade IV	17	4.5–29.4		NA		
Extent of surgical resection			0.70			0.95
Total or subtotal resection	13	0–28		13	0–28	
Biopsy only	6	0–19.7		17	0–34.6	
Postoperative treatment						
Radiation therapy			< 0.001			< 0.001
Yes	30	11.8–48.1		30	11.9–48	
No	5	0–10.9		2	0.7–3.2	
Radiation dose			0.63			0.75
< 60 Gy	7	0.6–13.4		7	13.7–46.2	
≥ 60 Gy	30	13.7–46.2		30		
Treatment response			0.005			0.005
Complete	49			49		
Incomplete or non-assessable	8	5.8–10.1		8	5.8–10.1	

OS: overall survival; 95% CI: 95% confidence interval; NA: non-applicable test.
[a] *P*-value calculated on log-rank test.

not be evaluated due to early death (3 cases) or loss to follow-up (2 cases).

Median follow-up was 8 months (range: 0–144 months). Table 1 details treatment outcomes during follow-up.

3.2. Overall survival (OS) and prognostic factors

Median OS was 13 months, [95% CI (confidence interval): 0–26]. On univariate analysis, patients who had received postoperative RT and those who had complete treatment response showed longer OS in both whole cohort and WHO grade IV astrocytomas ($P < 0.001$ and $P = 0.005$ respectively) (Table 2; Figs. 2 and 3). Other factors (clinical features, treatment patterns and outcomes) did not result in any significant impact on OS, whether in the whole cohort or in the glioblastomas subgroup (Table 2).

4. Discussion

4.1. Pediatric HGG features

HGG are very infrequent tumors in pediatric populations, believed to constitute 6.5% to 12% of all childhood intracranial neoplasms [1–6]. Their Onset under the age of 4 years is even less common, comprising 10–20% of all pediatric HGG [10,11]. In adults, HGG often arise from a low grade glioma that has progressed to a higher grade, but this phenomenon is extremely rare in children; nearly all pediatric HGG are diagnosed in a primary setting [1,7]. Although rare, few inherited syndromes increasing patients' risk of developing HGG have been reported These syndromes typically comprise cell proliferation and apoptosis disorders such as Li-Fraumeni syndrome, neurofibromatosis type 1 or Turcot syndrome [1,7,12].

Symptoms and signs at presentation are non-specific and very polymorphous, depending on tumor location. Excluding brainstem tumor, the cerebral hemispheres represent the main location of pediatric HGG (35–69%) followed by the diencephalon (20%) [4,5,13,14].

Similarly to their adult counterparts, necrosis and/or microvascular proliferation are histologic features of glioblastomas in children [7]. Epithelioid glioblastoma is a new entity, described recently in the fourth edition of the WHO classification [7]. This variant of HGG presents distinctive histological features; it comprises a dominant population of closely packed epithelioid cells showing focal discohesion and sometimes displaying a rhabdoid phenotype. These cells do constitutively express INI-1; this fundamental immunohistochemical feature allows the crucial distinction between epithelioid glioblastoma and atypical teratoid/rhabdoid tumor which demonstrates a universal lack of INI-1 expression.

The current treatment regimen consists in surgical resection as the cornerstone of management of HGG in both children and adults [1,5]. The purpose of resection is to remove as much tumor as possible to alleviate the mass effect, obtain tissue for pathological analysis and cytoreduce the tumor [1].

Nevertheless, true complete resection can be rarely achieved in pediatric HGG, since the tumor is frequently deep-seated in the neuraxis and local recurrence is the dominant pattern of failure

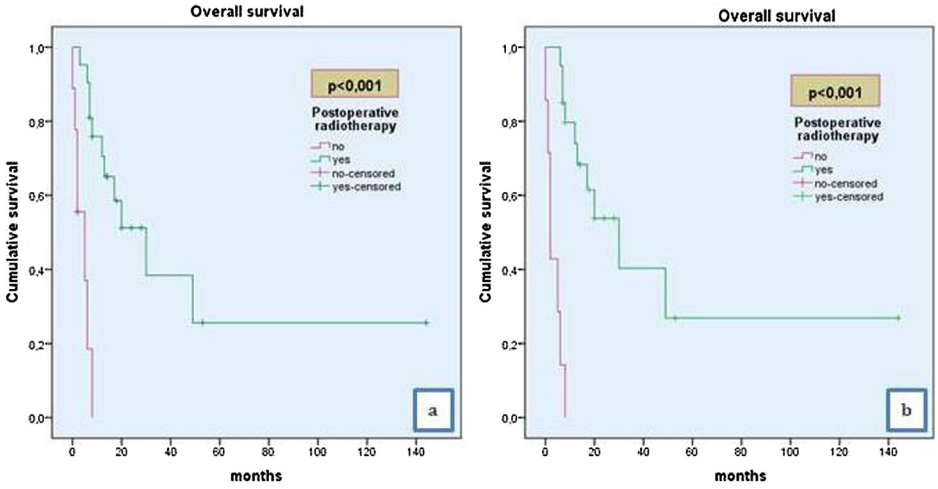

Fig. 2. Overall survival curve according to postoperative radiotherapy administration (a) for the whole cohort, (b) for glioblastomas.

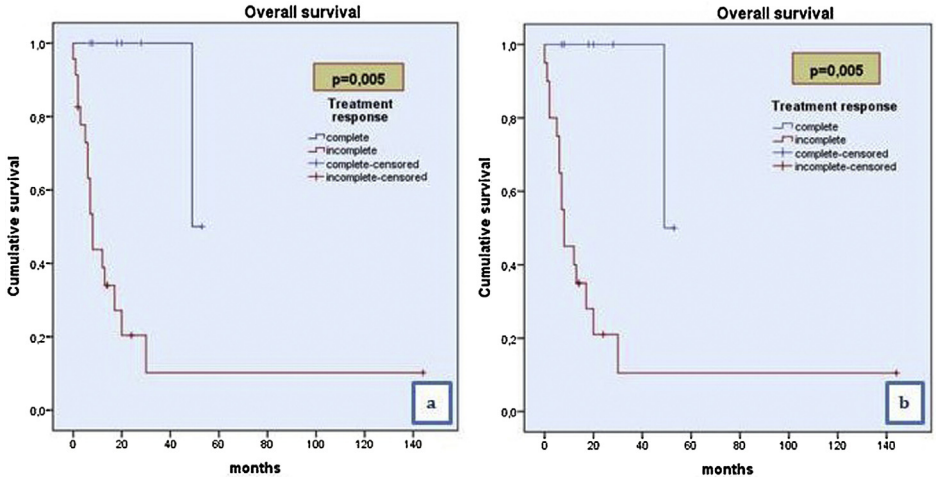

Fig. 3. Overall survival curve according to treatment response (a) for the whole cohort, (b) for glioblastomas.

[4,15–17]. Postoperative RT is the second standard of care for children aged more than 3 years old. The usefulness of chemotherapy in conjunction with RT in pediatric HGG is controversial.

Due to its retrospective design, there are inherent limitations to the present study. In fact, We collected from our database HGG cases treated over a 20-year period; meanwhile several attempts to perfect oncologic protocols have been undertaken, although treatment guidelines have generally remained unchanged over the years.

Kramm et al. [15] and Karremann et al. [3] reported complete treatment response in 7–40% of cases, compared to 23.3% in the current series. Thus, our findings agree with those of the literature affirming that response is often incomplete at the end of treatment.

Frequent leptomeningeal and cerebral spread via cerebrospinal fluid is a feature of HGG in children compared to adults: 30% in the present series, versus 15% in the literature [7,18].

4.2. Overall survival (OS) and prognostic factors

Median OS was estimated to 13 months, in line with previous reports of median OS ranging from 13 to 27.6 months [4,16,19–24].

In the current series, HGG patients had clinical and pathological distributions comparable to those in previous pediatric HGG studies. Likewise, treatment strategies and outcomes agree with previous reports.

While prognostic factors have been widely investigated in the adult HGG population, studies in pediatrics are scarce.

Our analysis revealed that postoperative RT and complete treatment response were prognostic factors for OS in pediatric HGG. The other factors (clinico-pathological features and treatment patterns) showed no significant association with outcomes.

4.2.1. Radiation therapy (RT)

While the role of postoperative RT in the treatment of adult HGG is well-established [25], benefit in pediatric HGG and glioblastomas remains uncertain and has been rarely explored in the literature [19]. In the present study, patients who received postoperative RT showed a significantly better OS than those who did not, in both the overall HGG group and the glioblastomas subgroup.

However, several previous studies [4,19,23] reported no difference in survival between pediatric HGG or glioblastomas undergoing RT or not. Lam et al. [19] ($n = 302$ pediatric glioblastomas) found the same median OS of 20 months with or without RT. Additionally, type of RT does not seem to be a relevant factor for OS in children with glioblastoma, as shown by Perkins et al. [23] ($n = 24$ pediatric glioblastomas) and Nikitović et al. [24] ($n = 15$ glioblastomas). Walston at al. [4] ($n = 51$ HGGs), demonstrated that receiving a dose at or above the median dose of 59.4 Gy was not associated with improved OS in their overall HGG cohort or in WHO grade IV tumors ($n = 28$). However, for the subgroup with

incompletely resected HGG radiation dose at or above 59.4 Gy provided significant improvement in OS in both HGG and glioblastomas.

Further randomized trials are urgently required to establish the real impact of postoperative RT on survival in pediatric HGG and glioblastoma.

4.2.2. Treatment response

In the current study, complete response at the end of treatment was associated with improved OS in pediatric HGG and in glioblastomas subgroup. These findings are consistent with those of Kramm et al. [15] in their cohort of 99 thalamic HGG.

4.2.3. Tumor location

The impact of tumor site on outcomes seems equivocal. In the pediatric HGG and glioblastoma literature, several authors reported deep tumor location to be associated with worse OS in comparison with superficial locations, perhaps due to decreased accessibility and hence extent of resection [6,15,21,22]. Patients with cerebellar HGG or glioblastoma exhibited a poorer OS compared with locations in the cerebral hemispheres [3,19]. In the present study, the two subgroups (HGG and glioblastomas) did not differ significantly with respect to tumor site.

4.2.4. WHO tumor grade

According to the literature, patients with WHO grade III HGG show a significantly longer OS than those with WHO grade IV tumors [3,4,15]. Unfortunately, tumor grade did not emerge as prognostic of OS in the present study, perhaps due to the small number of WHO grade III tumors ($n = 3$).

4.2.5. Extent of surgical resection

An attempt at a primary GTR is the typical standard of care in HGG. It was clearly established in previous studies that extent of resection is highly predictive of improved OS in pediatric HGG, regardless of histological grade [3,4,6,15,16,19,21–23]. In their studies of 302 and 15 pediatric glioblastomas respectively, Lam et al. [19] and Nikitović et al. [24] found that OS was significantly longer in children with GTR than in case of subtotal resection. Likewise, McCrea et al. [6] and Adams et al. [8] showed, in their respective cohorts of 97 pediatric HGG and 342 pediatric glioblastomas, that extent of resection was predictive of outcome, with a trend for longer OS following GTR than subtotal resection or simple biopsy.

In the present study, median OS in HGG with tumor resection was better than in those with simple biopsy (13 months versus 6 months), but extent of resection did not have a significant impact on OS, perhaps due to the small size of our cohort ($n = 30$).

4.2.6. Molecular landscapes

Although childhood and adult HGG share similar histopathological appearances and comparable clinical features, it is now believed that these tumors are molecularly distinct entities [26–28]. Almost half of pediatric HGG have recurrent hotspot mutations in histone H3-encoding genes (H3.3K27 mutation and, less frequently, H3.3G34 mutation), confirming their prominent biological significance in the genesis of pediatric glioblastomas [7,27,28]. While H3.3K27M mutations have been reported in midline HGG, H3.3G34R mutations have been found in gliomas arising from the cerebral hemispheres. This molecular subset of tumors harbors the most unfavorable outcomes in terms of OS and post-treatment craniospinal spread. Moreover, given the lack of MGMT-promoter methylation in this category, H3.3 K27 mutant HGG exhibits a poor responsiveness to temozolomide-based chemotherapy [7,8,26–28].

IDH1 and IDH2 mutations are rare in pediatric tumors, at less than 10% of pediatric glioblastomas [26–28]. Unlike in adults, where IDH mutations are a signature of secondary glioblastomas, pediatric glioblastomas harboring these aberrations arises de novo without evidence of a precursor lesion [7,27]. This subset of tumors shows the most favorable outcomes and the longest OS. MGMT-promoter methylation is an epigenetic phenomenon that occurs frequently in IDH1 or H3.3 G34 mutant HGG, entailing a potentially better response to temozolomide in these molecular subgroups [27].

The last genetic subgroup comprises approximately 40% of pediatric HGG and includes tumors heralding neither histone H3 nor IDH mutations. H3/IDH wild type HGG shows intermediate prognosis, while several oncogene amplifications may delineate poorer outcomes [26,27].

Identification of combined histo-molecular HGG subgroups has enhanced understanding of this devastating disease. Integrating molecular sub-classifications in routine HGG neuropathological diagnosis is a crucial step to improve patient management and conduct future clinical trials.

5. Conclusion

HGG in children comprise a wide group of WHO grade III or IV astrocytic tumors exhibiting unfavorable outcomes. Although better than in adults, OS in pediatric HGG remains poor, at a median of 13 months in the present study. Our analysis identified postoperative RT and complete treatment response as prognostic factors for OS in pediatric HGG and glioblastomas. Given that pediatric HGG are clinically and biologically heterogeneous, improvements in therapy and consequently in outcomes may require patients stratification on the basis of molecular hallmarks. Historical treatment algorithms derived from adult HGG studies seem to be inappropriate for what appears to be a distinct disease on the basis of its molecular signature and clinical course.

Financial and technical support

None.

Disclosure of interest

The authors declare that they have no competing interest.

References

[1] Braunstein S, Raleigh D, Bindra R, Mueller S, Haas-Kogan D. Pediatric high-grade glioma: current molecular landscape and therapeutic approaches. J Neurooncol 2017;134:541–9, http://dx.doi.org/10.1007/s11060-017-2393-0.
[2] Ganigi PM, Santosh V, Anandh B, Chandramouli BA, Sastry Kolluri VR. Expression of p53, EGFR, pRb and bcl-2 proteins in pediatric glioblastoma multiforme: a study of 54 patients. Pediatr Neurosurg 2005;41:292–9, http://dx.doi.org/10.1159/000088731.
[3] Karremann M, Rausche U, Roth D, Kühn A, Pietsch T, Gielen GH, et al. Cerebellar location may predict an unfavourable prognosis in paediatric high-grade glioma. Br J Cancer 2013;109:844–51, http://dx.doi.org/10.1038/bjc.2013.404.
[4] Walston S, Hamstra DA, Oh K, Woods G, Guiou M, Olshefski RS, et al. A multi-institutional experience in pediatric high-grade glioma. Front Oncol 2015;5:1–7, http://dx.doi.org/10.3389/fonc.2015.00028.
[5] Fangusaro J. Pediatric high grade glioma: a review and update on tumor clinical characteristics and biology. Front Oncol 2012;2:47–51, http://dx.doi.org/10.3389/fonc.2012.00105.
[6] McCrea HJ, Bander ED, Venn RA, Reiner AS, Iorgulescu JB, Puchi LA, et al. Sex, age, anatomic location, and extent of resection influence outcomes in children with high-grade glioma. Neurosurgery 2015;77:443–53, http://dx.doi.org/10.1227/NEU.0000000000000845.
[7] Louis DN, Ohgaki H, Cavenee WK, Ellison DW, Figarella-Branger D, Perry A, et al. WHO classification of tumors of the central nervous system. 4th ed. Lyon, France: IARC; 2016.
[8] Adams H, Adams HHH, Jackson C, Rincon-Torroella J, Jallo GI, Quiñones-Hinojosa A. Evaluating extent of resection in pediatric glioblastoma: a multiple propensity score-adjusted population-based analysis. Child's Nerv Syst 2016;32:493–503, http://dx.doi.org/10.1007/s00381-015-3006-x.

[9] Fangusaro J, Warren KE. Unclear standard of care for pediatric high grade glioma patients. J Neurooncol 2013;113:341–2, http://dx.doi.org/10.1007/s11060-013-1104-8.
[10] Sung T, Miller DC, Hayes RL, Alonso M, Yee H, Elizabeth W. Preferential inactivation of the p53 tumor suppressor pathway and lack of EGFR amplification distinguish de novo high grade pediatric astrocytomas from de novo adult astrocytomas. Brain Pathol 2000;10:249–59, http://dx.doi.org/10.1111/j.1750-3639.2000.tb00258.x.
[11] Pollack IF, Finkelstein SD, Burnham J, Holmes EJ, Hamilton RL, Yates AJ, et al. Age and TP53 mutation frequency in childhood malignant gliomas: results in a multi-institutional cohort. Cancer Res 2001;61:7404–7.
[12] Fangusaro J. Pediatric high-grade gliomas and diffuse intrinsic pontine gliomas. J Child Neurol 2009;24:1409–17, http://dx.doi.org/10.1177/0883073809338960.
[13] Wakefield A, Pignata A, Ghazi A, Ashoori A, Hegde M, Landi D, et al. Is CMV a target in pediatric glioblastoma? Expression of CMV proteins, pp65 and IE1-72 and CMV nucleic acids in a cohort of pediatric glioblastoma patients. J Neurooncol 2015;125:307–15, http://dx.doi.org/10.1007/s11060-015-1905-z.
[14] Suri V, Das P, Jain A, Sharma MC, Borkar SA, Suri A, et al. Pediatric glioblastomas: a histopathological and molecular genetic study. Neuro Oncol 2009;11:274–80, http://dx.doi.org/10.1215/15228517-2008-092.
[15] Kramm CM, Butenhoff S, Rausche U, Warmuth-Metz M, Kortmann R-D, Pietsch T, et al. Thalamic high-grade gliomas in children: a distinct clinical subset? Neuro Oncol 2011;13:680–9, http://dx.doi.org/10.1093/neuonc/nor045.
[16] Yang T, Temkin N, Barber J, Geyer JR, Leary S, Browd S, et al. Gross total resection correlates with long-term survival in pediatric patients with glioblastoma. World Neurosurg 2013;79:537–44, http://dx.doi.org/10.1016/j.wneu.2012.09.015.
[17] Wolff JEA, Driever PH, Erdlenbruch B, Kortmann RD, Rutkowski S, Pietsch T, et al. Intensive chemotherapy improves survival in pediatric high-grade glioma after gross total resection: results of the HIT-gBM-c protocol. Cancer 2010;116:705–12, http://dx.doi.org/10.1002/cncr.24730.
[18] Broniscer A, Tatevossian RG, Sabin ND, Klimo J, Dalton J, Lee R, et al. Clinical, radiological, histological and molecular characteristics of paediatric epithelioid glioblastoma. Neuropathol Appl Neurobiol 2014;40:327–36, http://dx.doi.org/10.1111/nan.12093.
[19] Lam S, Lin Y, Zinn P, Su J, Pan I. Patient and treatment factors associated with survival among pediatric glioblastoma patients: a Surveillance, Epidemiology, and End Results study. J Clin Neurosci 2018;47:285–93, http://dx.doi.org/10.1016/j.jocn.2017.10.041.
[20] Antonelli M, Buttarelli FR, Arcella A, Nobusawa S, Donofrio V, Oghaki H, et al. Prognostic significance of histological grading, p53 status, YKL-40 expression, and IDH1 mutations in pediatric high-grade gliomas. J Neurooncol 2010;99:209–15, http://dx.doi.org/10.1007/s11060-010-0129-5.
[21] Song KS, Phi JH, Cho B-K, Wang K-C, Lee JY, Kim DG, et al. Long-term outcomes in children with glioblastoma. J Neurosurg Pediatr 2010;6:145–9, http://dx.doi.org/10.3171/2010.5.PEDS09558.
[22] Das KK, Mehrotra A, Nair AP, Kumar S, Srivastava AK, Sahu RN, et al. Pediatric glioblastoma: clinico-radiological profile and factors affecting the outcome. Child's Nerv Syst 2012;28:2055–62, http://dx.doi.org/10.1007/s00381-012-1890-x.
[23] Perkins SM, Rubin JB, Leonard JR, Smyth MD, El Naqa I, Michalski JM, et al. Glioblastoma in children: a single institution experience. Int J Radiat Oncol 2011;80:1117–21, http://dx.doi.org/10.1016/j.ijrobp.2010.03.013.
[24] Nikitović M, Stanić D, Pekmezović T, Gazibara MS, Bokun J, Paripović L, et al. Pediatric glioblastoma: a single institution experience. Child's Nerv Syst 2016;32:97–103, http://dx.doi.org/10.1007/s00381-015-2945-6.
[25] Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJB, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352:987–96, http://dx.doi.org/10.1056/NEJMoa043330.
[26] J.E. M. Gliomas in children. Curr Treat Options Neurol 2013;15:316–27, http://dx.doi.org/10.1007/s11940-013-0225-x.
[27] Korshunov A, Ryzhova M, Hovestadt V, Bender S, Sturm D, Capper D, et al. Integrated analysis of pediatric glioblastoma reveals a subset of biologically favorable tumors with associated molecular prognostic markers. Acta Neuropathol 2015;129:669–78, http://dx.doi.org/10.1007/s00401-015-1405-4.
[28] Bozkurt SU, Dagcinar A, Tanrikulu B, Comunoglu N, Meydan BC, Ozek M, et al. Significance of H3K27M mutation with specific histomorphological features and associated molecular alterations in pediatric high-grade glial tumors. Child's Nerv Syst 2018;34:107–16, http://dx.doi.org/10.1007/s00381-017-3633-5.