Child's Nervous System (2019) 35:2355–2362
https://doi.org/10.1007/s00381-019-04257-2

ORIGINAL ARTICLE

Risk stratification of pediatric high-grade glioma: a newly proposed prognostic score

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Received: 2 March 2019 / Accepted: 7 June 2019 / Published online: 19 June 2019
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Abstract

Objectives High-grade glioma (HGG) is a clinical challenge. Radiation Therapy Oncology Group Recursive Partitioning Analysis (RTOG-RPA) for HGG remains the standard for assessing the prognosis of adult HGG. This study assesses the validity of the RTOG-RPA to be applied to pediatric HGG.

Methods A retrospective study was conducted on 59 pediatric HGG treated in the Children's Cancer Hospital, Egypt (CCHE) between 2007 and 2016. Several factors were studied as predictors for the disease survival, including age, gender, increased intracranial hypertension, tumor characteristics and pathology, CSF seeding, performance status, post-surgical residual, and radiation dose. The statistically significant results were integrated into a Cox-regression model to develop a prognostic risk score.

Results Kaplan-Meier statistics identified 13 factors that impacted the overall survival. However, Cox model showed that the histological grade IV [HR 14.2, 95%CI; (3.5–57), $P < 0.0001$], thalamic infiltration [HR 8.7; 95%CI; (2.9–25.9), $P < 0.0001$], PS ≥ 60 [HR 0.317; 95%CI; (0.13–0.776); $P = 0.012$], and maximum tumor dimension > 3.3 cm [HR 10.2; 95%CI; (1.58–65.89); $P = 0.015$] were the independent variables that predicted the overall survival. A risk score was proposed based on the presence of one or more of these factors. The median OS for the low risk (score 0–1), the intermediate-low risk (score 2), the intermediate-high risk (score 3), and the high risk (score 4) were 40, 18.5, 9.5, and 2.5 months, respectively, ($P < 0.0001$).

Conclusion The proposed model and risk score could stratify pediatric patients as the RTOG-RPA do for the adults.

Keywords HGG · Pediatric HGG · HGG in children · High-grade glioma in children

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Introduction

High-grade glioma (HGG) represents 20% of the pediatric brain tumors [6, 9]. Roughly, two-thirds of the cases were glioblastoma (grade IV), which is characterized by profound nuclear atypia, mitotic activity, and evident necrosis compared to anaplastic astrocytoma (grade III) [7]. The standard treatment of the disease remains maximum-safe resection followed by adjuvant radiotherapy. The role of chemotherapy is limited to either radiation sensitization or delaying radiotherapy in infants [3, 4]. Despite the emerging therapeutics, the 5-year survival rate is typically below 20% [5]. Since the 1990s, the Radiation Therapy Oncology Group - Recursive Partitioning Analysis (RPA-RTOG) and its revised updates have been used to classify

patients into four classes; each carries a unique survival. The RPA assortment depended on patients' age, performance, tumor grade, disease resectability, and mini-mental status examination [8, 14, 16]. In contrast, there was no robust prognostic stratification for pediatric HGG except for few publications which correlated disease outcome to surgical resectability and histological grade [17]. The study aims to test the idea behind recursive partitioning against pediatric HGG.

Materials and methods

Patient population

A total of 59 patients with pathologically proven high-grade glioma were retrospectively collected from the electronic medical records at Children's Cancer Hospital Egypt (CCHE). The participants were treated between 2007 and 2016. The study excluded children younger than 2 years because of their unique treatment protocols and distinctive disease behavior. The pathology was reviewed according to the World Health Organization (WHO) recommendations.

The patients were classified according to age, gender, site of the disease, presence of thalamic extension, disease crossing to the contralateral hemisphere, maximum tumor dimension, extent of surgical resection, histological grade, Karnofsky-Lansky performance status, presence of neurological symptoms post-resection, radiotherapy dose, dependence of steroids during treatments, concurrent chemotherapy given, and presence of associated hydrocephalus and need for ventriculo-abdominal (VA) shunt.

Radiological assessment

Brain magnetic resonance imaging (MRI) pre- and post-contrast T1-weight sequences were used to assess the tumor's size, location, and extension, as well as the status of the blood-brain barrier. The T2-weight and the fluid-attenuated inversion recovery (FLAIR) sequences were used to characterize the extent of the surrounding edema. The diffusion-weighted sequence was also used to confirm the findings.

Radiotherapy treatment planning

Radiation was administrated using megavoltage linear accelerators with a photon energy of 6 or 10 MV. The target volumes and organ at risk were contoured at the CT simulation images according to the recommendations of the International Commission on Radiation Units and Measurements (ICRU 50/62). MRI fusion and registration was used to enhance the accuracy of the delineation process. The target volumes were defined in all cases according to the RTOG recommendations. Phase I included irradiating the tumor bed, post-surgical residual, and surrounding edema plus 2-cm margin with a dose up to 45–46 Gy followed by exclusion of edema (via fusion with T1-weighted MR images) from the irradiated volume in phase II. Typically, a dose up to 59.4–60 Gy was given in the boost. The radiotherapy was delivered on 1.8–2 Gy per fractions, five fractions per week for 6 weeks, using intensity-modulated radiotherapy (IMRT) technique in 51 patients (86%) and 3D conformal in 8 patients (14%).

Disease follow-up and assessment

The follow-up data were collected for all patients, including the duration of the follow-up, symptoms, steroid dependence during radiation, response of the disease, site and time of disease progression, and time of death, if applicable. Overall survival (OS) was calculated from the time of diagnosis until death or last follow-up while the progression-free survival (PFS) was elaborated from the time of diagnosis to the time of disease progression. The 1- and 2-year survival rates were calculated based on the percentage of patients being alive during the first and second years of diagnosis. Also, the percentage of cases diagnosed with disease progression post-treatment was reported at the same time frame.

Ethics statement

The study was conducted following the approval of the Research Ethics Board in CCHE. The confidentiality was maintained through assigning unique codes, de-identifying the name of the patient.

Statistical analysis

The Kaplan-Meier survival curve and its log-rank test were used to estimate the progression-free survival and overall survival. Receiver operating characteristic (ROC) statistics were used for identifying appropriate cutoff levels for scale data with acceptable sensitivity and specificity. Moreover, Cox-regression model was considered to qualify and quantify the significant variable linked to survival. These significant variables were later used to generate a prognostic score that would predict survival in these patients. An alpha of $P = 0.05$ was used to assess the level of significance. SPSS (23.0) was used for the analysis and the generation of suitable graphs.

Results

Patient demographics and disease characteristics

The median follow-up duration for the treated children was 14.5 (range, 1.5–93.5) months. Basic clinical characteristics are summarized in Table 1.

Disease control and survival outcomes

At the time of analysis, 39 (68.4%) of the patients died from the disease with 1- and 2-year survival rates of 54.4 ± 6.5% and 24.6 ± 5.7%, respectively. Disease progression was reported in 43 (76.8%) of the patients; the median time to progression was 9.5 (range, 0–93) months. The 1-year and 2-year progression-free survival rates were 43.9 ± 6.6% and 19.3 ± 5.2%, respectively. Sixty percent of progression happened within 1 cm from the primary tumor site (local failure), 35% occurred in the ipsilateral lobe or contra-lateral hemisphere (regional), two cases had spinal cord seeding from cranial disease, and one case suffered from a cranial seeding from a spinal disease.

The following parameters were shown to have a significant impact on progression-free survival: CSF seeding, increased intracranial hypertension, presence of V-P shunt, extension of the tumor to the thalamus, higher tumor grade, tumor crossing of the midline, multifocality of the disease, steroid dependence, maximum tumor dimension, presence of residual disease post-surgical excision, performance status, presence of neurological symptoms post-excision, and radiation dose (Table 2). The ROC curve statistics were used to identify the cutoff point with the highest likelihood ratio for the scale data: the maximum tumor dimension (3.3 cm), Karnofsky/Lansky performance scale (60%), and radiation dose (57.7 Gy).

Cox model was built using "Backward Stepwise (Likelihood Ratio) method," (model $P < 0.0001$, likelihood 175.7). Four variables were independent, namely histological grade IV [HR 14.2, 95% CI; (3.5–57), $P < 0.0001$], extension of the tumor to thalamus [HR 8.7; 95% CI; (2.9–25.9), $P < 0.0001$], Karnofsky performance status ≥ 60 [HR 0.317; 95% CI; (0.13–0.776); $P = 0.012$], maximum tumor dimension > 3.3 cm [HR 10.2; 95% CI; (1.58–65.89); $P = 0.015$], (Table 3, Fig. 1a–d). The proposed risk score was generated depending on the presence of one or more of these risk factors. The median overall survival for the low risk (score 0–1), the intermediate-low risk (score 2), the intermediate-high risk (score 3), and the high risk (score 4) were 40, 18.5, 9.5, and 2.25 months, respectively, (log-rank $P < 0.0001$). The 1-year overall survival rates were 90 ± 9.4%, 78 ± 9.7%, 31 ± 11%, and 0 ± 0%, respectively, while the 1-year progression-free survival rates were 90 ± 9.4%, 61 ± 11%, 12.5 ± 8.2%, and 0 ± 0% for the four risk groups, respectively (Table 4, Fig. 2).

Table 1 Patient and tumor characteristics

Age	Median 8 (2–17) years
Gender	
Boys	33 (55.9%)
Girls	26 (44.1%)
ICP	
Normal	36 (62.1%)
Increased pressure	22 (37.9%)
Shunt	
Shunt inserted	20 (35.7%)
No shunts	36 (64.3%)
Neuraxial dissemination	
Positive	4 (6.8%)
Negative	55 (93.2%)
Histology	
Grade III	15 (26.8%)
Grade IV	41 (73.2%)
Tumor site	
Unifocal	56 (94.9%)
Parietal	23 (41.1%)
Frontal	6 (10.7%)
Temporal	5 (8.9%)
Occipital	3 (5.4%)
Primary thalamic	11 (19.6%)
Secondary thalamic infiltration	6 (10.1%)
Infratentorial	8 (14.3%)
Multifocal glioma	3 cases
Tumor dimensions	Median 5.35 (1–11) cm
Size < 3.3 cm	8 (14.8%)
Size ≥ 3.3 cm	46 (85.2%)
Surgical resection	
Gross resection	10 (17.5%)
Subtotal resection	25 (43.9%)
Stereotactic biopsy	22 (38.6%)
Symptoms post resection	
Symptomatic	39 (69.6%)
Asymptomatic	17 (30.4%)
Radiation dose	Median 59.4 (30–60) Gy
Steroids	
Steroid dependent	33 (66%)
Steroid independent	17 (34%)
Karnofsky PS	
< 60	23 (44.2%)
≥ 60	29 (55.8)
Chemotherapy protocol	
Oral etoposide	31 (54.4%)
Oral temozolomide	16 (28.1%)
IV vincristine	5 (8.8)
No chemotherapy	5 (8.8%)

Table 2 Univariate analysis of the study

Variable	Log-rank significance			1-year mortality rates (%)	1-year progression rates (%)
	OS	PFS			
CSF cytology	$P = 0.025$	$P = 0.057$	Positive	75	75
			Negative	53.3	60
			Not done	40	52
Increased intracranial pressure	$P = 0.017$	$P = 0.039$	No	51	66
			Yes	36	41
Thalamic extension	$P < 0.0001$	$P < 0.0001$	Associated thalamic ext.	82	88
			No extension	30	43
Tumor grade	$P = 0.045$	$P = 0.013$	Grade III	33	40
			Grade IV	49	61
Tumor cross midline	$P < 0.0001$	$P < 0.0001$	Not crossing	52	53
			Yes crossing	100	100
Multifocality	$P = 0.005$	$P = 0.005$	Unifocal	44	54
			Multifocal	100	100
Steroid dependence	$P = 0.003$	$P = 0.010$	Independent	35	41
			Dependent	52	64
MTD	$P = 0.005$	$P = 0.014$	< 3.3 cm	25	25
			≥ 3.3 cm	49	62
Extent of resection	$P = 0.001$	$P < 0.0001$	GTR	20	30
			STR	40	52
			Stereotactic biopsy	62	71
Shunt insertion	$P = 0.007$	$P = 0.055$	Shunt inserted	53	58
			No shunt	39	53
Pre-RT neurological status	$P = 0.003$	$P = 0.006$	Free	12	29
			Symptomatic	61	68
Pre-RT performance status	$P < 0.0001$	$P = 0.001$	PS < 60	67	79
			PS ≥ 60	28	40
RT dose	$P = 0.031$	$P = 0.059$	< 57.7 Gy	57	61
			≥ 57.7 Gy	22	41

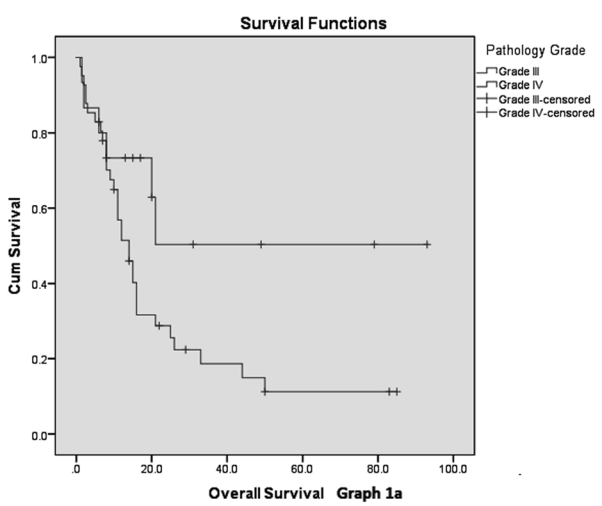
Discussion

HGG remains as a challenging pediatric CNS tumor, especially when it comes to the radiation-induced endocrinopathies, developmental abnormalities, cognitive dysfunction, and short survival. Unfortunately, no key driver mechanism has been identified for this disease. However, some authors suggested a role for neonatal exposure to narcotics, infection, low

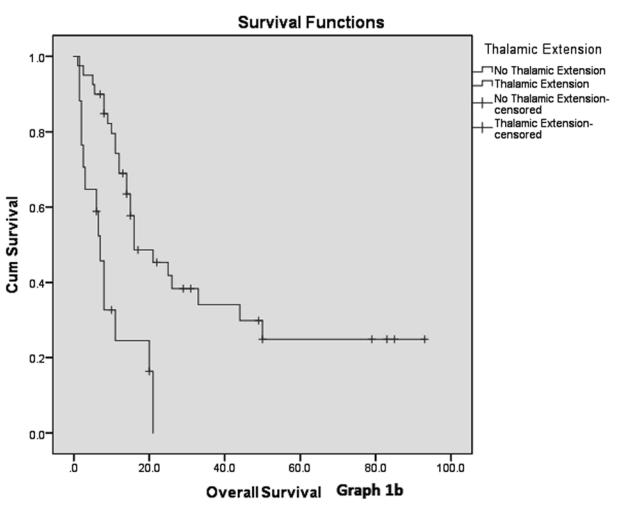
Table 3 Risk stratification and disease survival

		Population percentage	Median OS in months (IQ range)	Median PFS in months (IQ range)	1-year mortality rate ± S.E. (%)	1-year progression rate ± S.E. (%)
Score categories	Low risk (score 0–1)	20	40 (15.7–80)	35 (14.7–80)	10 ± 9	10 ± 9
	Inter. low (score 2)	36	18.5 (12.5–26.7)	13.5 (9.0–22.2)	22 ± 9	39 ± 11
	Inter. high (score 3)	32	9.5 (6.2–13.5)	6.0 (3.2–9.3)	69 ± 11	87.5 ± 8
	Very high risk (score 4)	12	2.25 (1.5–3.0)	0.5 (0.0–3.2)	100 ± 0	100 ± 0

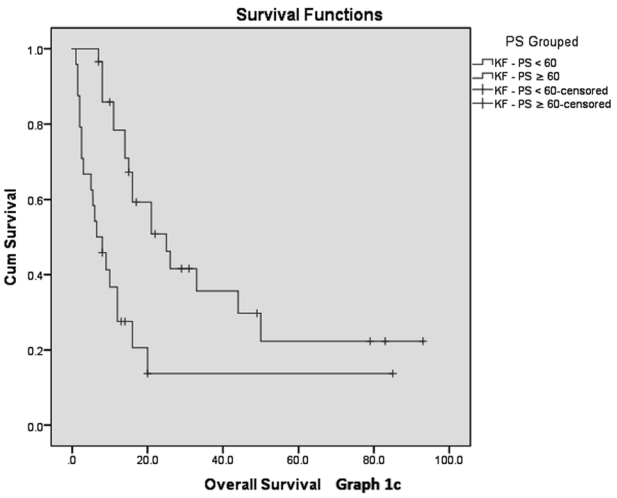
Risk score
- PS-status < 60 = 1 point
- Thalamic extension = 1 Point
- Pathological grade IV = 1 Point
- MTD > 3.3 cm = 1 point



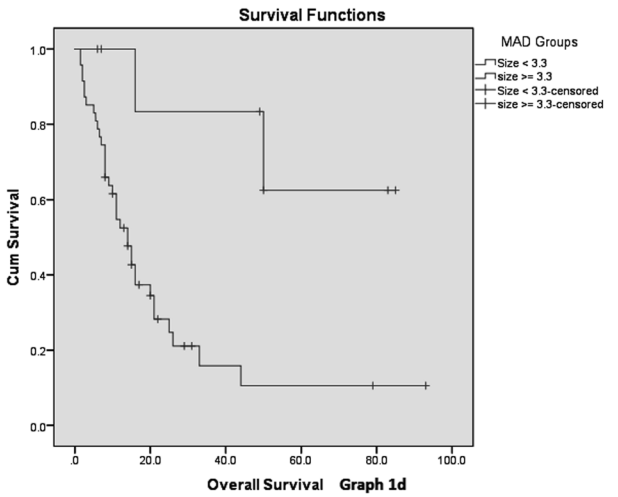
Graph 1a - Kaplan Meier Survival curve shows the difference in OS between grade III and IV histologies



Graph 1b - Kaplan Meier Survival curve shows the difference in OS based on tumor infiltration of the thalamus



Graph 1c - Kaplan Meier Survival curve shows the difference in OS between patient with Karnofsky P.S below 60% and above 60%



Graph 1d - Kaplan Meier Survival curve shows the difference in OS between tumor exceeding and not-exceeding 3.3cm in their maximum dimension

Fig. 1 **a** Kaplan-Meier survival curve shows the difference in OS between grade III and IV histologies. **b** Kaplan-Meier survival curve shows the difference in OS based on the tumor infiltration of the thalamus. **c** Kaplan-Meier survival curve shows the difference in OS between patients with Karnofsky P.S below 60% and above 60%. **d** Kaplan-Meier survival curve shows the difference in OS between tumor exceeding and not exceeding 3.3 cm in their maximum dimension

Apgar score, neonatal distress, or intrauterine exposure to radiation [12, 14, 1].

Previously, the diagnosis of the disease depended solely on the histological diagnosis. However, the recent WHO classification in 2016 has breached through these traditional methods of diagnosis and has incorporated molecular parameters into its classification. It has divided the glioblastoma (GBM) into IDH-wild, IDH-mutant, and NOS based on the presence of the IDH mutation. This mutation identifies GBM that has underwent evolution from a previous low-grade glioma [5]. Furthermore, it has recognized a new disease entity, the diffuse midline glioma, which is characterized by the H3 K27 mutation, and the diffuse growth pattern within the midline structures; such as the thalamus, brainstem, and spinal cord [5, 7]. Despite the expanding molecular characterization of the disease, the therapeutic standards and outcomes have never been changed for many years. These standards are achieving maximum-safe surgical resection and adjuvant chemoradiation [3, 7, 13, 15].

As a part of disease prognostication, several trials were made in the past to identify risk factors linked to poor survival in the adults. The most successful among them were the RPA-RTOG and its updated releases, which investigated the outcome of nearly 3000 adult HGG patients. It recognized that patients' age, performance status, tumor grade, surgical resectability, and mini-mental status

Table 4 Comparison between our study and the Revalidate RTOG-RPA published in 2011

CCHE study		Original RTOG-RPA report	
RPA pediatric risk group	Survival data	Survival data	Patient class
Low risk score ≤ 1	Median OS 40 months	Median OS 17 months	Class III
Intermediate-low risk score 2	Median OS 18.5 months	Median OS 15 months	Class IV
Intermediate-high risk score 3	Median OS 9.5 months	Median OS 10 months	Class V
High risk score 4	Median OS 2.25 months	Median OS 6.4 months	Class VI

examination were the factors that could predict disease outcome. Consequently, they were used to separate the patients into four clusters of different disease outcome, whereby their median survival ranged from 6.5 to 17 months [2, 8, 11, 12, 14]. This revolutionary findings, however, failed to address the pediatric population.

In the present study, we examined the pediatric population treated within the CCHE, and tested the validity of the known findings of the adult recursive portioning analysis. The median follow-up for our patients was 14.5 months. Forty-four (76.8%) of the patients had progression, 26 (60%) due to local failure, 15 (35%) to regional, and 3 (5.4%) cases had neuraxial dissemination. At the time of the last follow-up, 68.4% of the patient died with 1- and 2-year survival rates of 54.4% and 24.6%, respectively.

Through the Cox-regression analysis, we identified the strong influence of higher histological grade [HR 14.2, 95% CI; (3.5–57), $P = 0.000$] and performance status ≥ 60% [HR 0.317; 95% CI; (0.13–0.776); $P = 0.012$] on the overall survival (Table 2). Contrary to the adults, this analysis failed to validate the effect of the age, extent of surgical resection, or mental state examination on disease outcome. However, it identified two other factors: the maximum tumor dimension and the thalamic infiltration. The maximum tumor dimension was associated with a less favorable outcome when it surpassed the 3.3-cm cutoff point [HR 10.2; 95% CI; (1.58–65.89); $P = 0.015$]. In addition, the tumor infiltration to the thalamus was negatively linked to survival [HR 8.7; 95% CI; (2.9–25.9), $P = 0.000$] (Table 2). These findings were consistent with the recently recognized diffuse midline glioma that harbors a drastic behavior and dreadful outcome. However, it is necessary to recognize the emerging importance of H3 K27 mutations as a method to identify this disease moleculary. Also, other mutations, such as POLE/POLD1,

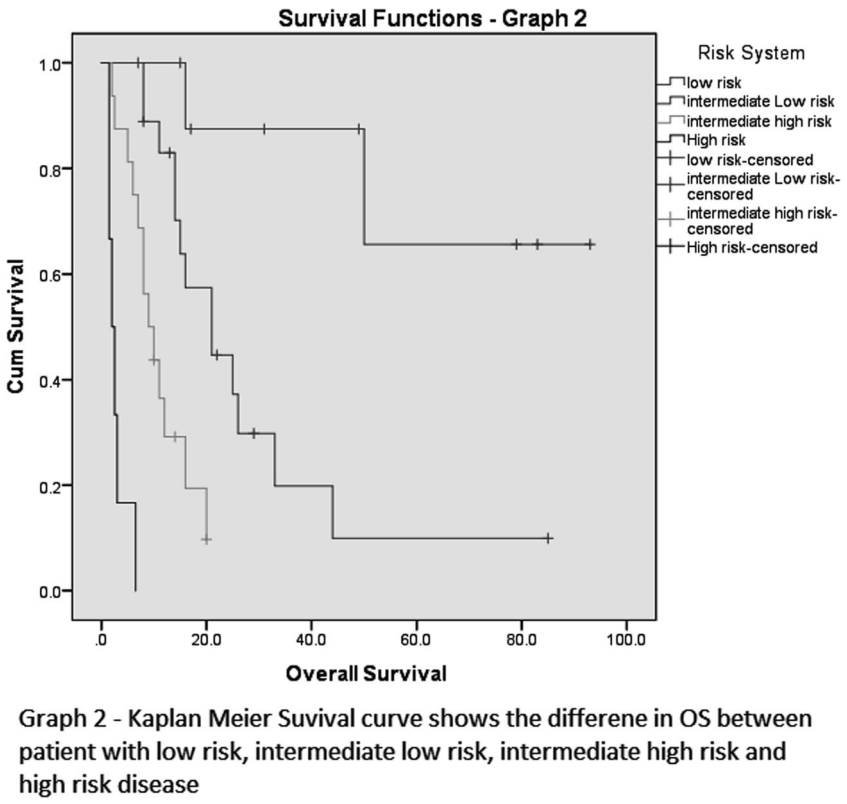


Fig. 2 Kaplan-Meier survival curve shows the difference in OS between tumor patients with low risk, intermediate-low risk, intermediate-high risk, and high-risk disease

Graph 2 - Kaplan Meier Suvival curve shows the differene in OS between patient with low risk, intermediate low risk, intermediate high risk and high risk disease

have been identified supporting the previous context. Not only does this imply a wide biological and clinicopathological diversity of the disease, but it also makes it possible to identify distinct subgroups that defy any improvement to survival [10].

Unfortunately, one of the limitations of this study is the lack of molecular characterization, which might constrain the risk score power by any genetic confounder. However, the proposed score within this study successfully segregated the pediatric patients into four groups with different overall and progression-free survival. The low risk group (score 0–1) was associated with median overall survival and progression-free survival of 40 and 35 months, respectively, and a 1-year mortality rate of 10%. This low risk group enjoyed a better survival outcome compared to the adult counterpart (class III), which had a median survival of 17 months and a 1-year mortality rate of 30% [8, 11].

The median OS and PFS for the intermediate-low risk group (score 2) were 18.5 and 13.5 months, respectively, and a 1-year mortality rate of 22%. This group still had a slightly better survival outcome compared to their adult counterpart (class IV) who had a median overall survival of 15 months and a 1-year mortality rate of 54% [8, 11]. The intermediate-high risk group (score 3) patients were associated with median OS and PFS of 9.5 and 6 months, respectively, and a 1-year mortality rate of 69%. This patient population had a comparable disease outcome to class V adults, who had a median survival of 10 months and a 1-year mortality rate of 72% [8, 11].

The high risk group (score 4) had the worst prognosis with median OS and PFS of 2.25, 0.5 months, and a 1-year survival rate of 0%, which is lower than its comparable class VI adults who had a median OS of 6.4 months and a 1-year survival rate of 15%. This finding may suggest the need for a more intensive treatment strategy to (score 4) children to attain better survival [12].

The survival differences between adult and pediatric population, especially in low risk and high risk groups, urge for exploration of the pediatric disease as a separate disease entity rather than being related to adult HGG. Furthermore, personalized medicine could provide unique protocols for each patients' subgroup, especially with more precise understanding of the biology and cytogenetics of these tumors.

Conclusion

The proposed risk score of HGG based on the performance status, the thalamic extensions, the histological grade, and the maximum tumor dimension have been linked to both the OS and PFS: low risk (40 and 35 months), intermediate-low (18.5 and 13.5 months), intermediate-high (9.5 and 6 months), and high risk (2.5 and 0.5 months) ($P < 0.0001$). The low and intermediate-low risk had a better median OS than adults' classes III and IV in RTOG-RPA reports (40 vs. 17 months) and (18.5 vs. 15). While intermediate-high was quite similar in median OS (9.5 vs. 10.0 months) compared to adult class V. The high risk group was worse in median OS than adults class VI (2.5 vs. 6.4 months).

Recommendation

The developed risk score requires validation in an independent study group of pediatric patients, where the score could tailor therapies accordingly.

Compliance with ethical standards

The study was conducted following the approval of the Research Ethics Board in CCHE. The confidentiality was maintained through assigning unique codes, de-identifying the name of the patient.

Conflict of interest The authors have no conflict of interest to declare.

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