Pathology & Oncology Research (2020) 26:2693–2701
https://doi.org/10.1007/s12253-020-00875-3

ORIGINAL ARTICLE

The Role of Time as a Prognostic Factor in Pediatric Brain Tumors: a Multivariate Survival Analysis

Eduardo Javier Barragán-Pérez[1] · Carlos Enrique Altamirano-Vergara[1] · Daniel Eduardo Alvarez-Amado[1,2] · Juan Carlos García-Beristain[1] · Fernando Chico-Ponce-de-León[3] · Vicente González-Carranza[3] · Luis Juárez-Villegas[4] · Chiharu Murata[5]

Received: 27 March 2020 / Accepted: 9 July 2020 / Published online: 13 July 2020

Abstract

There is no evidence that prolonged pre diagnostic symptomatic intervals (PSI) increases the risk of death in pediatric brain tumors. When investigating the role of time previous research had not controlled for confounding variables or measured the pretreatment interval (PTI). We use the term global delay interval (GDI) to describe the sum of PSI and PTI. The aim of this research was to evaluate whether there was a decrease in the probability of survival in children with brain tumors due to a prolonged PSI, PTI and GDI, using a multivariate survival analysis. We retrospective review 127 clinical records labeled with the diagnosis of CNS tumors attended at a specialized pediatric center in Mexico City from January 2008 to December 2012. Patients with PSI and GDI diagnosed between 3 and 6 months showed statistical lower probability of surviving that those with intervals <3 months even when adjusting for age, sex, localization and tumor grade. When stratified for the place of residency and adjusted for sex, age, localization, grade of tumor, type of surgery and coadjuvant therapy, a GDI between 3 and 6 months showed to be a risk factor for the overall survival of brain tumors compared with an interval < 3 months. When analyzing the interaction, high grade tumors are at more risk of dying when GDI was between 3 and 6 months compared to <3 months. Prolonged PSI and GDI showed to be a potential prognostic factor for survival in CNS tumors, especially in high grade tumors. Future prospective research should measure the PSI, PTI and GDI and adjust for covariates in order to properly infer the effect of time in pediatric brain tumors.

Keywords Symptomatic interval · Delayed diagnosis · CNS tumors · Survival outcome

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s12253-020-00875-3) contains supplementary material, which is available to authorized users.

✉ Daniel Eduardo Alvarez-Amado
alvarezamado@hotmail.com

[1] Pediatric Neurology Department "Hospital Infantil de México Federico Gómez", Mexico City, Mexico

[2] Hospital Infantil de México Federico Gómez, Calle Doctor Márquez 162, Alcadía Doctores, Cuauhtémoc, 06720 Ciudad de México, Mexico

[3] Pediatric Neurosurgery Department "Hospital Infantil de México Federico Gómez", Mexico City, Mexico

[4] Pediatric Oncology Department "Hospital Infantil de México Federico Gómez", Mexico City, Mexico

[5] Research Methodology Department, Instituto Nacional de Pediatria, Mexico City, Mexico

Abbreviations

CNS	Central Nervous System
USA	United States of America
PSI	Prediagnostic Symptomatic Intervals
PTI	Pretreatment Interval
GDI	Global Delay Interval
GDP	Gross Domestic Product
HIMFG	Hospital Infantil de México Federico Gómez
IQR	Interquartile Range
CI	Confidence Interval
OS	Overall Survival
CNS ET/RF	CNS Embryonal tumor with rhabdoid features

Introduction

Central Nervous System (CNS) tumors are the second most common cancer in children (26%) followed by leukemias

(28%) [1]. They have an incidence of 3.3 to 4.5 cases per 100,000 people per year in the United States of America (USA) [1] and are the leading pediatric cause of death from neoplasm [2]. In this country, between 1970 and 2012, there was a 31% reduction in the mortality of children with CNS tumors compared to a 76% reduction in leukemia [3]. The variability of the presenting symptoms makes the accurate diagnosis a clinical challenge [4]. In Latin America, there is little information about their global survival and associated prognostic factors, and no data reported from Mexico [5].

The prediagnostic symptomatic intervals (PSI) are more prolonged in CNS tumors than in other pediatric neoplasms [6]. It may vary from several weeks to months [4, 7–21] but it has not yet demonstrated that prolonged intervals can increase the risk of death [11]. However, it has shown to have implications in the functional prognosis of the patients [22]. The time that elapses between the early symptoms and the first treatment includes the PSI and the pretreatment interval (PTI) [23–25]. Therefore, we consider the hypothesis that the sum of the PSI and PTI was a more accurate measurement of the potential influence of time in brain tumors and used the term global delay interval (GDI) to describe it. The GDI includes the delays caused by the individual health system of each country [6].

When investigating the role of time previous research had not controlled for confounding variables or measured the PTI. Therefore, the main objective of this research was to retrospectively evaluate whether there was a decrease in the probability of survival in children with brain tumors due to a prolonged PSI, PTI and GDI, using a multivariate survival analysis. As a secondary goal, and due to a lack of reports in Mexico, we describe the global five year survival rate and prognostic factors of the brain tumors attended in a specialized third level pediatric center in Mexico City.

Methods

Setting

Mexico has a population of little more than 126 million people [26], 31.4% of which are between 0 and 17 years [27]. It is an upper middle income country with a Gross Domestic Product (GDP) per capita of $9715 USD in the fourth quarter of 2018 [28]. Of the total population, 48.8% have an income below the poverty line and 16.2% have no access to healthcare services [29]. The "Hospital Infantil de México Federico Gómez" (HIMFG) is a specialized third level pediatric center located in Mexico City, in the central area of the country. It was founded in 1943, as the first National Institute of Health in Mexico [30]. The HIMFG oversees attending the most vulnerable population, children without insurance or social medical care. Between 1970 and 2004 the most common reported cases of brain tumors ($n = 810$) were astrocytomas (32%), medulloblastoma (19%), craniopharyngioma (11%), ependymomas (10.24%) and germinomas (4%), with an important increase in the number of surgical procedures in those years [31].

Patients and Data Collection

We conducted a retrospective study and reviewed the clinical records of patients between one month and sixteen years labeled with the diagnosis of CNS tumors attended the HIMFG from January 2008 to December 2012. A total of 253 cases were found with only 127 meeting the inclusion criteria. The reasons for exclusion were: Tumor with extracerebral origin ($n = 32$), incomplete data because of treatment in other health center ($n = 26$), a final diagnosis that ruled out a brain tumor ($n = 25$), incomplete data ($n = 22$), neurocutaneous syndrome ($n = 16$) and family members did not accepted treatment and were lost in follow up ($n = 5$).

Demographic characteristics were collected, survival time, PSI and PTI was calculated from the moment of the neuroimaging diagnosis either by Computed Tomography or Magnetic Resonance Imaging. The PTI was defined as the first treatment indicated. This treatment could have been a total or partial surgical resection and in the case of biopsy or no surgical procedure, radiotherapy or chemotherapy. Brain tumors were classified according to histopathological characteristics and in the cases that there was none, neuroimaging was evaluated by two neuroradiologists. The names of the tumors were standardized to be in line with the International Classification of Diseases for Oncology, 3rd Edition, codes can be found in Supporting Information Table S1. The main categories for analysis were High and Low grade tumors (grade I-II and III-IV respectively) according to the WHO 2007 classification. Total resection was defined as a surgical intervention that resected more than 80% of the tumor.

Statistical Analysis

Statistical analysis was performed using R (version 3.6.2) and RStudio (Version 1.2.5001). The survival 2.44–1, flexsurv 1.1.1, KMsurv 0.1–5 and survminer 0.4.3 packages were used. Numeric data were analyzed using the median and interquartile range (IQR) as a measure of dispersion due to skewed data. Survival was censored to the right until March 2018. The survival rate was calculated using the Kaplan-Meier estimates and the log-rank test was used to compare the survival of different groups. The hazard ratio was analyzed using Cox regression. Only p values <0.05 were considered statistically significant.

The proportional hazards assumption was evaluated based on the scaled Schoenfeld residuals. The variables PSI, PTI and GDI were converted from days to categorical intervals of

Table 1 Summary of patient, tumor, and treatment details

	Tumor Grade	
	Low	High
n	67	60
sex = Male (%)	35 (52.2)	33 (55.0)
Age (median [IQR])	6.00 [4.00, 9.00]	5.00 [3.00, 7.00]
Categorical age (%)		
>6 years	31 (46.3)	19 (31.7)
<=3 years	11 (16.4)	22 (36.7)
3–6 years	25 (37.3)	19 (31.7)
Place of residency (%)		
Mexico City	30 (44.8)	27 (45.0)
State of Mexico	19 (28.4)	19 (31.7)
Other areas	18 (26.9)	14 (23.3)
Survival time (median [IQR])	96.00 [84.00, 120.00]	24.00 [7.00, 99.00]
Deceased (%)	9 (13.4)	31 (51.7)
Type of tumor (%)		
Pilocytic Astrocytoma	36 (53.7)	0 (0.0)
Classic Medulloblastoma	0 (0.0)	23 (38.3)
Classic Ependymoma	12 (17.9)	0 (0.0)
Craniopharyngioma	9 (13.4)	0 (0.0)
Diffuse Midline Glioma	0 (0.0)	15 (25.0)
CNS ET/RF*	0 (0.0)	8 (13.3)
All other tumors	10 (14.9)	14 (23.3)
Localization = Supratentorial (%)	32 (47.8)	14 (23.3)
Tumor Grade = High (%)	0 (0.0)	60 (100.0)
Type of surgery (%)		
Total resection	27 (40.3)	13 (21.7)
Biopsy	9 (13.4)	4 (6.7)
None	3 (4.5)	14 (23.3)
Partial resection	28 (41.8)	29 (48.3)
Coadjuvant treatments (%)		
Both	29 (43.3)	51 (85.0)
Chemotherapy alone	2 (3.0)	3 (5.0)
None	18 (26.9)	3 (5.0)
Radiation therapy alone	18 (26.9)	3 (5.0)
Prediagnostic symptomatic intervals [days] (median [IQR])	120.00 [60.00, 180.00]	90.00 [52.50, 150.00]
Prediagnostic symptomatic intervals [categorical] (%)		
<=3 months	33 (49.3)	31 (51.7)
3–6 months	19 (28.4)	22 (36.7)
>6 months	15 (22.4)	7 (11.7)
Pre treatment interval [days] (median [IQR])	13.00 [10.00, 18.00]	14.00 [10.00, 20.00]
Pre treatment interval [categorical] = >13 days (%)	31 (46.3)	31 (51.7)
Global delay interval [days] (median [IQR])	128.00 [68.00, 198.00]	115.00 [60.50, 170.00]
Global delay interval [categorical] (%)		
<=3 months	21 (31.3)	23 (38.3)
3–6 months	24 (35.8)	25 (41.7)
>6 months	22 (32.8)	12 (20.0)

*CNS Embryonal tumor with rhabdoid features

months in order to fulfill the proportional hazards assumption. Due to the clinical relevance, the median (90 days) of the PSI was used as a base (3 months) for the construction of the PSI and GDI categories. Surgery and coadjuvant treatment showed to be time dependent variables. The place of residence of the patients was used as strata in order to include them as important confounding variables. This correction was not achieved for the main categorical tumor type, so we used the grade in order to include the type of tumor in the cox regression analysis. Hazard estimates were similar across place of residence (log-rank test $p = 0.23$) and within each stratum the impact of the covariate of interest on the hazard ratio was not statistically different ($p > 0.05$). There was no multicollinearity between the variables that were included in the final models. All multivariate analyses were evaluated using the survival::cox.zph function and we reported only the models with global values with $p > 0.05$.

Results

Demographic and Clinical Characteristics

Demographic and clinical characteristics of the patients can be seen in Table 1. The median age at diagnosis was 5 years (IQR: 3–8) with 68 males (53.5%) and 59 females (46.5%). High grade tumors accounted for 47.2% ($n = 60$) of the total sample and 52.3% ($n = 67$) were low grade tumors. A detailed summary of the main tumors can be found in the Supporting Information Table S2.

The total pre symptomatic interval median was 90 days (IQR: 60, 180; Max-Min: 5–1440) and 13 days (IQR: 10, 20; Max-Min: 1–200) for the pretreatment interval. When we took into account both, we got a median global delay interval of 120 days (IQR: 68, 190; Max-Min: 15–1500). The median PSI for low grade tumors was 120 days (IQR: 60, 180) and for high grade tumors 90 days (52.5, 150). PTI has a median of 13 days (IQR: 10, 18) for low grade tumors and 14 days (10, 20) for high grade tumors. Median GDI was 128 (IQR: 68, 198) and 115 days (60.5, 170) respectively.

Survival Analysis

The Kaplan-Meier Curve with their respective survival table for the main categories are shown in Fig. 1. At five years, the overall survival (OS) was 70% ($n = 127$; 95% confidence interval, CI = 0.63–0.79). The shortest median survival time observed was 5.5 months (IQR: 3.5–19.5) for patients with Embryonal Tumor with Rhabdoid Feature followed by Diffuse Midline Glioma with 7 months (IQR: 5.0–8.5). The five year OS for patients with low grade tumors was 88% (n = 67, OS = 0.88; CI = 0.80–0.96) and 50% for those with high grade tumors

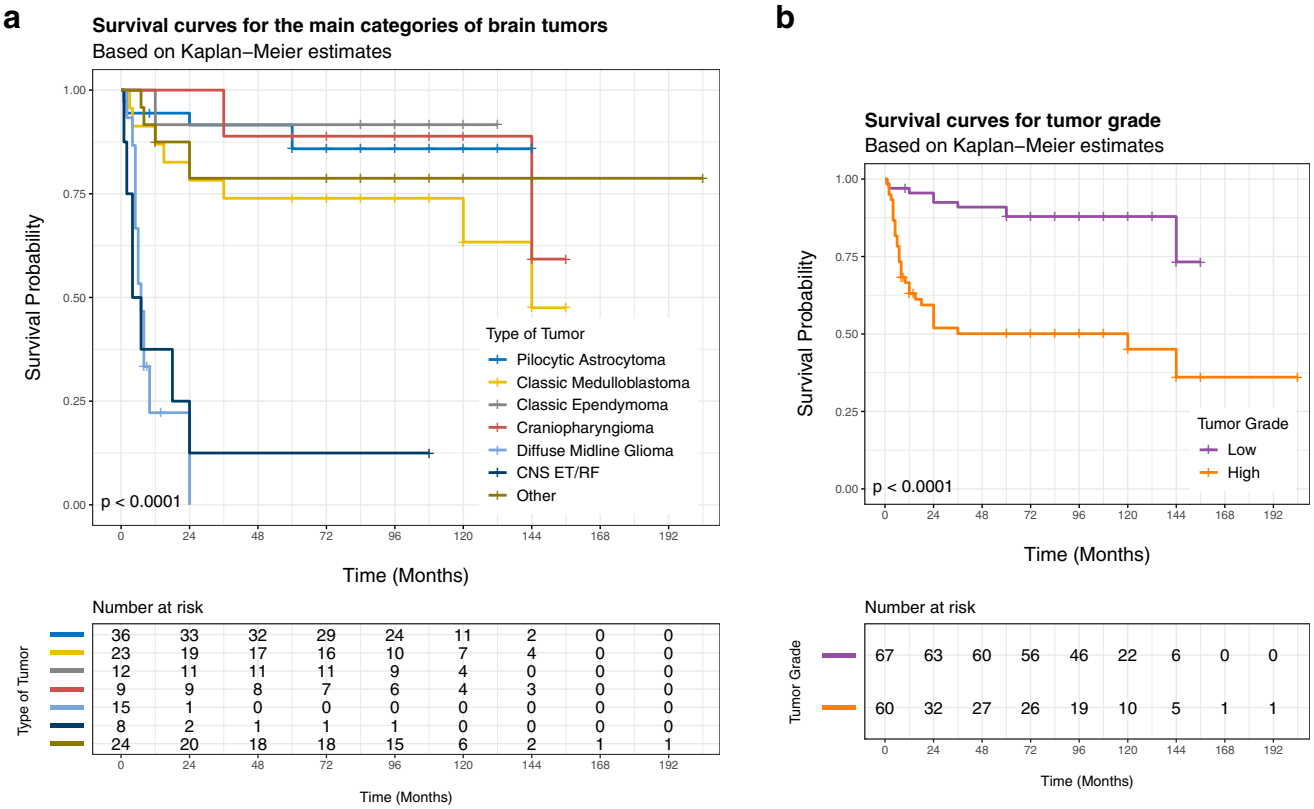

Fig. 1 Kaplan Meier survival curve and table for the main categories of brain tumors (**A**) and tumor grade (**B**)

($n = 60$, OS = 0.50; CI = 0.39–0.65), the log-rank test showed a statistical significant difference ($p < 0.0001$).

In respect of the patients with tumors from the category others, five-year after diagnosis the number of patients who were alive was as follows: Anaplastic Ependymoma 1 of 4 (75%), Primitive Neuroectodermal Tumor 3 of 5 (60%), Diffuse Astrocytoma 2 of 3 (67%) and Glioblastoma Multiforme 1 of 2 (50%). All the patients with Anaplastic Astrocytoma ($n = 2$), Choroid Plexus Papilloma ($n = 3$), and patients with Undifferentiated Tumors ($n = 5$) were all alive at the five-year cut. A summary of the category others can be found in the Supporting Information Table S3.

Prognostic Factors

Factors predicting poor outcome by univariate analysis were localization, grade of tumor and pre symptomatic interval (Table 2). They maintained their influence in outcome when we stratified for the place of residency in order to include the time dependent variables. (Table 2). In the univariate stratified analysis type of surgery and coadjuvant therapy had an influence on outcome. The multivariate stratified model was used as the final model in order to allow the adjustment for the type of surgery and coadjuvant therapy as well for the other clinically relevant variables (Table 3).

When adjusted for sex, age, localization, grade of tumor, type of surgery and coadjuvant therapy, the pre symptomatic interval and pretreatment interval showed no statistical difference in their hazard risk in the stratified model. Those diagnosticated between 3 and 6 months ($n = 41$, hazard ratio, HR = 1.61; 95% CI = 0.71–3.68, $p = 0.257$) and > 6 months ($n = 22$, HR = 0.65; 95% CI = 0.21–2.02, $p = 0.460$) showed no difference when compared with those diagnosticated <3 months ($n = 64$). Finally, the adjusted stratified model showed that patients that were treated >13 days ($n = 62$) showed no difference (HR = 1.02; 95% CI = 0.48–2.17, $p = 0.963$) in comparison with those treated <=13d ($n = 65$).

When a global delay interval between 3 and 6 months ($n = 49$) was included in the stratified model as a separate factor, the univariate analysis did not show it to influence survival (HR = 1.88; 95% CI = 0.89–4.01; $p = 0.100$) when compared with those with a delay <3 months ($n = 44$). However, when we adjusted for all the other prognostic factors, a global delay between 3 and 6 months showed to be a risk factor for the overall survival (n = 49, HR = 2.46; 95% CI = 1.04–5.83; $p = 0.040$) when compared with an interval < 3 months (n = 44). Additional factors that predicted poor outcome on this multivariate stratified model were: High grade tumors ($n = 60$, HR = 4.99; 95% CI = 1.55–16.04; $p = 0.007$) when compared to low grade tumors ($n = 67$) and partial resection ($n = 57$, HR = 16.18; 95% CI = 2.82–92.82; $p = 0.002$), biopsy ($n = 13$, HR = 46.98; 95% CI = 6.41–344.39; $p < 0.001$) and no surgical intervention ($n = 17$,

Table 2 Multivariate survival model

Overall survival		n (%)	HR (Univariable)	HR (Base model)	HR (Model 1)	HR (Model 2)
Age	Mean (SD)	6.0 (3.4)	0.98 (0.89–1.07, $p = 0.609$)	1.05 (0.95–1.15, $p = 0.323$)	1.07 (0.97–1.19, $p = 0.153$)	1.09 (0.98–1.20, $p = 0.103$)
Sex	Female	59 (46.5)	–	–	–	–
	Male	68 (53.5)	1.43 (0.76–2.69, $p = 0.274$)	1.32 (0.69–2.53, $p = 0.396$)	1.29 (0.67–2.49, $p = 0.444$)	1.05 (0.52–2.13, $p = 0.888$)
Localization	Infratentorial	81 (63.8)	–	–	–	–
	Supratentorial	46 (36.2)	0.29 (0.13–0.66, $p = 0.003$)	0.40 (0.17–0.94, $p = 0.034$)	0.41 (0.18–0.97, $p = 0.042$)	0.36 (0.15–0.88, $p = 0.026$)
Tumor Grade	Low	67 (52.8)	–	–	–	–
	High	60 (47.2)	5.36 (2.54–11.30, p < 0.001)	4.84 (2.23–10.52, $p < 0.001$)	5.27 (2.35–11.81, $p < 0.001$)	6.10 (2.68–13.90, $p < 0.001$)
Prediagnostic symptomatic intervals	<=3 m	64 (50.4)	–	–	–	–
	3-6 m	41 (32.3)	2.20 (1.13–4.30, $p = 0.021$)	–	–	2.92 (1.35–6.34, p = 0.007)
	>6 m	22 (17.3)	0.82 (0.30–2.27, $p = 0.707$)	–	–	1.15 (0.38–3.50, $p = 0.810$)
Pre treatment interval	<=13d	65 (51.2)	–	–	–	–
	>13d	62 (48.8)	1.02 (0.55–1.89, $p = 0.956$)	–	–	0.90 (0.45–1.80, $p = 0.758$)
Global delay interval	<=3 m	44 (34.6)	–	–	–	–
	3-6 m	49 (38.6)	1.88 (0.89–4.01, p = 0.100)	–	2.22 (1.02–4.84, $p = 0.046$)	–
	>6 m	34 (26.8)	0.99 (0.40–2.43, $p = 0.977$)	–	1.41 (0.56–3.57, $p = 0.464$)	–

Table 3 Multivariate survival stratified model

Overall survival		n (%)	HR (Univariable)	HR (Base model)	HR (Model 1)	HR (Model 2)
Age	Mean (SD)	6.0 (3.4)	0.98 (0.89–1.07, p = 0.609)	0.98 (0.86–1.12, p = 0.790)	0.99 (0.87–1.13, p = 0.900)	1.02 (0.89–1.18, p = 0.754)
Sex	Female	59 (46.5)	–	–	–	–
	Male	68 (53.5)	1.43 (0.76–2.69, p = 0.274)	0.91 (0.44–1.88, p = 0.794)	0.79 (0.37–1.71, p = 0.551)	0.91 (0.43–1.93, p = 0.809)
Localization	Infratentorial	81 (63.8)	–	–	–	–
	Supratentorial	46 (36.2)	0.29 (0.13–0.66, p = 0.003)	0.38 (0.13–1.05, p = 0.062)	0.44 (0.16–1.23, p = 0.117)	0.36 (0.13–1.00, p = 0.050)
Tumor Grade	Low	67 (52.8)	–	–	–	–
	High	60 (47.2)	5.36 (2.54–11.30, p < 0.001)	5.35 (1.74–16.44, p = 0.003)	4.99 (1.55–16.04, p = 0.007)	6.03 (1.94–18.79, p = 0.002)
Type of surgery	Total resection	40 (31.5)	–	–	–	–
	Biopsy	13 (10.2)	17.95 (3.71–86.81, p < 0.001)	32.88 (4.98–217.26, p < 0.001)	46.98 (6.41–344.39, p < 0.001)	39.53 (5.78–270.43, p < 0.001)
	None	17 (13.4)	39.81 (8.85–179.11, p < 0.001)	44.43 (8.21–240.56, p < 0.001)	53.30 (9.08–313.02, p < 0.001)	39.35 (7.11–217.73, p < 0.001)
	Partial resection	57 (44.9)	6.91 (1.59–29.95, p = 0.010)	11.51 (2.21–59.96, p = 0.004)	16.18 (2.82–92.82, p = 0.002)	12.44 (2.30–67.42, p = 0.003)
Coadjuvant treatments	Both	80 (63.0)	–	–	–	–
	Chemotherapy alone	5 (3.9)	2.11 (0.64–6.92, p = 0.217)	2.69 (0.58–12.38, p = 0.204)	1.75 (0.34–9.07, p = 0.503)	1.97 (0.39–9.96, p = 0.410)
	None	21 (16.5)	0.19 (0.04–0.78, p = 0.021)	0.85 (0.13–5.57, p = 0.864)	0.81 (0.12–5.69, p = 0.832)	1.04 (0.15–7.16, p = 0.968)
	Radiation therapy alone	21 (16.5)	0.09 (0.01–0.64, p = 0.016)	0.27 (0.03–2.39, p = 0.239)	0.15 (0.02–1.39, p = 0.095)	0.31 (0.03–2.86, p = 0.302)
Prediagnostic symptomatic intervals	<=3 m	64 (50.4)	–	–	–	–
	3-6 m	41 (32.3)	2.20 (1.13–4.30, p = 0.021)	–	–	1.61 (0.71–3.68, p = 0.257)
	>6 m	22 (17.3)	0.82 (0.30–2.27, p = 0.707)	–	–	0.65 (0.21–2.02, p = 0.460)
Pre treatment interval	<=13d	65 (51.2)	–	–	–	–
	>13d	62 (48.8)	1.02 (0.55–1.89, p = 0.956)	–	–	1.02 (0.48–2.17, p = 0.963)
Global delay interval	<=3 m	44 (34.6)	–	–	–	–
	3-6 m	49 (38.6)	1.88 (0.89–4.01, p = 0.100)	–	2.46 (1.04–5.83, p = 0.040)	–
	>6 m	34 (26.8)	0.99 (0.40–2.43, p = 0.977)	–	0.86 (0.31–2.37, p = 0.769)	–

HR = 53.30; 95% CI = 9.08–313.02; p < 0.001) when compared to those who had a total surgical resection (n = 40). When analyzing the interaction between grade of tumor and the categorical GDI we found that high grade tumors are at more risk of dying when GDI was between 3 and 6 months compared to <3 months (HR = 4.05; 95% CI = 1.13–14.46; p = 0.03) contrary to low grade tumors (HR = 0.50; 95% CI = 0.064–3.84; p = 0.50).

Discussion

Survival Analysis

Our patients overall five year survival of 70% (n = 127, OS = 0.70; 95% CI = 0.63–0.79) approximates the one reported from the USA between 2000 and 2015 of 73% (n = 9699; OS = 0.73, 95% CI = 0.72–0.74) for children of 0–14 years [32]. Other high income countries have reported similar data [33–35]. It is important to note that there is a great variability between countries even of the same region, as can be seen in Europe [36, 37]. In Latin America, Brazil reported a five year survival of 45% (n = 103, OS = 0.45; 95% CI, 0.37–0.57) [38], the only other survival research in our region (Colombia) did not report global survival [39]. It also should be considered that our results are a reflection of the children that attend our specialized pediatric center (HIMFG) in Mexico City, as there is regional variability in different institutions even from the same country [40–42].

Prognosis Factors

Surgery was the major therapeutic intervention that influenced survival in children diagnosed with brain tumors, as has been previously reported [43, 44]. In our sample, comparing those that had total resection, the ones who had partial resection, biopsy and no surgical treatment had more risk of dying. When controlling for other confounding variables anatomical localization had no influence on outcome, but these results should be interpreted cautiously as the category was too broad to detect change (infratentorial and supratentorial). More Importantly, it should be reminded that neuroanatomical restrictions are the major determinant in what type of surgery is performed [45].

Being a retrospective study where the main goal was not to find the true effect of treatment modalities limits the scope of the results in respect of chemotherapy and radiotherapy. We did not control the type, doses or the location in the case of radiotherapy. In addition to this, we had a group of heterogeneous tumors. However, the resistance of brain tumors and the toxic profile of these coadjuvant treatments could be one of the reasons for the slow reduction in mortality in comparison to leukemia and why are the main causes of death secondary to neoplasms in children [46].

Without adjusting by type of tumor, prolonged PSI had already been associated with a better survival probability in pediatric brain tumors [47]. Patients with low-grade tumors have shown a higher PSI that is considered due to their low growth and the presence of atypical symptoms that makes their diagnosis difficult [48]. Prolonged survival in patients diagnosed >6 months may be because of patients with low-grade tumors. It is considered that this effect may be due to the slow growth and less aggressive nature of low grade tumors [47].

Previous research found a subset of pediatric patients that can benefit from an earlier diagnosis in terms of survival that included brain tumors [49]. In our sample high grade tumors had a lower probability of survival in comparison to low grade tumors. When we test for the interaction of GDI we found that this group had a lower probability of survival when the interval was between 3 and 6 months compared with those with GDI below 3 months. In children with medulloblastoma (the most common pediatric high grade brain tumor), PSI had no influence on survival [50]. However, PTI was not taken into account and their sample had a PSI of 2 months (n = 224; IQR: 1.0–3.0) [50]. This shorter interval in comparison to ours could explain why they did not find an effect. In addition to this, they did not report the adjusted hazard risk and used the univariate log-rank analysis to conclude that patients with longest PSI had the best survival outcome (PSI = > 4.0 months: 10-year OS rate, 71%; PSI <4.0 months, 10-year OS, 61%; p = 0.056) [50].

Limitations

Some of the limitations of our study had already been discussed. In addition to them, it should be considered that we had a small heterogeneous sample and used a retrospective design. However, these findings are the first one to show evidence of an effect of time using a multivariate cox regression model. This allowed us to control for confounding variables and found a higher risk in high grade SNC tumors in children diagnosed between 3 and 6 months compared with those <3 months. Another important limitation regarding the GDI is that his role could be because of the effect of PSI, although these changes depending on the variables that are controlled. Nevertheless, this study is the first research that attempts to investigate the role of PTI and GDI as a prognostic factor.

In conclusion prolonged PSI and GDI showed to be potential prognostic factors for survival in pediatric patients with high grade tumors. Early detection should remain a priority, but it should also take into account if the workflow in each country's healthcare system ensures an early treatment. When investigating the time since the start of symptoms and his

influence in the survival of pediatric CNS tumors previous research considered only the pre symptomatic interval. In low middle countries such as Mexico, the timing of the first therapeutic intervention could be more prolonged due to problems within the healthcare systems. Future prospective research should measure the PSI, PTI and GDI and adjust for covariates in order to properly infer the effect of time in pediatric brain tumors.

Acknowledgements We are thankful to our patients and their families for the support to carry out this research. To the team of the Pediatric Neurology Department of HIMFG and their continuous search for excellence, kindness and integrity.

Compliance with Ethical Standards

Conflict of Interest There is no financial interest or benefit to disclose.

References

1. Wells EM, Packer RJ (2015) Pediatric brain tumors. Continuum 21: 373–396
2. Siegel RL, Miller KD, Jemal A (2019) Cancer statistics, 2019. CA Cancer J Clin 69:7–34
3. Siegel RL, Miller KD, Jemal A (2016) Cancer statistics. CA Cancer J Clin 66:7–30
4. Wilne S, Collier J, Kennedy C, Koller K, Grundy R, Walker D (2007) Presentation of childhood CNS tumours: a systematic review and meta-analysis. Lancet Oncol 8:685–695
5. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A (2018) Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68:394–424
6. Dang-Tan T, Franco EL (2007) Diagnosis delays in childhood cancer. Cancer. 110:703–713
7. Crawford JR, Santi MR, Vezina G, Myseros JS, Keating RF, LaFond DA et al (2007) CNS germ cell tumor (CNSGCT) of childhood: presentation and delayed diagnosis. Neurology. 68:1668–1673
8. Patel V, McNinch NL, Rush S (2019) Diagnostic delay and morbidity of central nervous system tumors in children and young adults: a pediatric hospital experience. J Neuro-Oncol 143:297–304
9. Shay V, Fattal-Valevski A, Beni-Adani L, Constantini S (2012) Diagnostic delay of pediatric brain tumors in Israel: a retrospective risk factor analysis. Childs Nerv Syst 28:93–100
10. Sethi RV, Marino R, Niemierko A, Tarbell NJ, Yock TI, MacDonald SM (2013) Delayed diagnosis in children with intracranial germ cell tumors. J Pediatr 163:1448–1453
11. Kukal K, Dobrovoljac M, Boltshauser E, Ammann RA, Grotzer MA (2009) Does diagnostic delay result in decreased survival in paediatric brain tumours? Eur J Pediatr 168:303–310
12. Flores LE, Williams DL, Bell BA, O'Brien M, Ragab AH (1986) Delay in the diagnosis of pediatric brain tumors. Am J Dis Child 140:684–686
13. Handayani K, Sitaresmi MN, Supriyadi E, Widjajanto PH, Susilawati D, Njuguna F, van de Ven PM, Kaspers GJL, Mostert S (2016) Delays in diagnosis and treatment of childhood cancer in Indonesia. Pediatr Blood Cancer 63:2189–2196
14. Dobrovoljac M, Hengartner H, Boltshauser E, Grotzer M (2002) Delay in the diagnosis of paediatric brain tumours. Eur J Pediatr 161:663–667
15. Molineus A, Boxberger N, Redlich A, Vorwerk P (2013) Time to diagnosis of brain tumors in children: a single-Centre experience. Pediatr Int 55:305–309
16. Azizi AA, Heßler K, Leiss U, Grylli C, Chocholous M, Peyrl A, Gojo J, Slavc I (2017) From symptom to diagnosis—the Prediagnostic symptomatic interval of pediatric central nervous system tumors in Austria. Pediatr Neurol 76:27–36
17. Mehta V, Chapman A, McNeely PD, Walling S, Howes WJ (2002) Latency between symptom onset and diagnosis of pediatric brain tumors: an eastern Canadian geographic study. Neurosurgery. 51: 365–373
18. Stocco C, Pilotto C, Passone E, Nocerino A, Tosolini R, Pusiol A, Cogo P (2017) Presentation and symptom interval in children with central nervous system tumors. A single-center experience. Childs Nerv Syst 33:2109–2116
19. Wilne S, Collier J, Kennedy C, Jenkins A, Grout J, Mackie S, Koller K, Grundy R, Walker D (2012) Progression from first symptom to diagnosis in childhood brain tumours. Eur J Pediatr 171:87–93
20. Reulecke BC, Erker CG, Fiedler BJ, Niederstadt T-U, Kurlemann G (2008) Brain tumors in children: initial symptoms and their influence on the time span between symptom onset and diagnosis. J Child Neurol 23:178–183
21. Elhassan MMA, Mohamedani AA, Osman HHM, Yousif NO, Elhaj NM, Qaddoumi I (2019) Patterns, treatments, and outcomes of pediatric central nervous system tumors in Sudan: a single institution experience. Childs Nerv Syst 35:437–444
22. Fukuoka K, Yanagisawa T, Suzuki T, Shirahata M, Adachi J-I, Mishima K, Fujimaki T, Matsutani M, Nishikawa R (2014) Duration between onset and diagnosis in central nervous system tumors: impact on prognosis and functional outcome. Pediatr Int 56:829–833
23. Walker D, Wilne S, Grundy R, Kennedy C, Neil DA et al (2016) A new clinical guideline from the Royal College of Paediatrics and Child Health with a national awareness campaign accelerates brain tumor diagnosis in UK children - "headSmart: Be Brain Tumour Aware". Neuro-Oncology 18:445–454
24. Abdelmabood S, Kandil S, Megahed A, Fouda A (2017) Delays in diagnosis and treatment among children with cancer: Egyptian perspective. East Mediterr Health J 23:422–429
25. Njuguna F, Martijn H, Langat S, Musimbi J, Muliro H, Skiles J, Vik T, Sitaresmi MN, van de Ven PM, Kaspers GJL, Mostert S (2016) Factors influencing time to diagnosis and treatment among pediatric oncology patients in Kenya. Pediatr Hematol Oncol 33:186–199
26. INEGI. Encuesta Intercensal 2015. In: Instituto Nacional de Estadística y Geografía [Internet]. 14 Mar 2015 [cited 28 Jan 2020]. Available: https://www.inegi.org.mx/programas/intercensal/2015/
27. CONAPO. 31.4 por ciento de la población en México son niñas, niños y adolescentes, de 0 a 17 años. In: Consejo Nacional de Población [Internet]. 30 April, 2019 [cited 28 Jan 2020]. Available: https://www.gob.mx/conapo/prensa/31-4-por-ciento-de-la-poblacion-en-mexico-son-ninas-ninos-y-adolescentes-de-0-a-17-anos-198293?idiom=es
28. INEGI. Por actividad económica. In: Instituto Nacional de Estadística y Geografía [Internet]. 2018 [cited 28 Jan 2020]. Available: https://www.inegi.org.mx/temas/pib/
29. CONEVAL. Medición de Pobreza 2008-2018, Estados Unidos Mexicanos. In: Consejo Nacional de Evaluación de la Política de Desarrollo Social [Internet]. 2018 [cited 28 Jan 2020]. Available: https://www.coneval.org.mx/Medicion/PublishingImages/Pobreza_2018/Serie_2008-2018.jpg
30. Santos-Preciado JI (2008) El Hospital Infantil de México y su Boletín Médico: un hito en la historia de la pediatría mexicana. Bol Med Hosp Infant Mex 65:81–82

31. de León Castro-Sierra Eduardo FC-P, Perez Peña-Diazconti M et al (2006) Bol Med Hosp Infant Mex 63:367–381
32. Ostrom QT, Gittleman H, Truitt G, Boscia A, Kruchko C, Barnholtz-Sloan JS (2018) CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2011–2015. Neuro Oncol 20:iv1–iv86
33. Rivas-Vilela S, Rubió-Casadevall J, Fàbrega-Ribas A, Joly-Torta C, Vilardell L, Marcos-Gragera R (2019) Incidence and survival of central nervous system tumors in childhood and adolescence in Girona (Spain) 1990–2013: national and international comparisons. Clin Transl Oncol 21:1177–1185. https://doi.org/10.1007/s12094-019-02043-9
34. Desandes E, Guissou S, Chastagner P, Lacour B (2014) Incidence and survival of children with central nervous system primitive tumors in the French National Registry of childhood solid tumors. Neuro-Oncology 16:975–983
35. Farinotti M, Ferrarini M, Solari A, Filippini G (1998) Incidence and survival of childhood CNS tumours in the region of Lombardy. Italy Brain 121(Pt 8):1429–1436
36. Magnani C, Aareleid T, Viscomi S, Pastore G, Berrino F, Oberaigner W et al (2001) Variation in survival of children with central nervous system (CNS) malignancies diagnosed in Europe between 1978 and 1992: the EUROCARE study. Eur J Cancer 37: 711–721
37. Robertson PL, Zeltzer PM, Boyett JM, Rorke LB, Allen JC, Geyer JR, Stanley P, Li H, Albright AL, McGuire-Cullen P, Finlay JL, Stevens KR, Milstein JM, Packer RJ, Wisoff J, _ _ Survival and prognostic factors following radiation therapy and chemotherapy for ependymomas in children: a report of the Children's Cancer group. J Neurosurg 1998;88: 695–703
38. de Araujo OL, da Trindade KM, Trompieri NM, Fontenele JB, Felix FHC (2011) Analysis of survival and prognostic factors of pediatric patients with brain tumor. J Pediatr 87:425–432
39. María GVM, Francis ERN, Nelson UL, Gutiérrez E, Gimón AV, Barboza D et al (2013) Tumores cerebrales pediátricos experiencia de 10 años. Revista Venezolana de Oncologia 25:85–97
40. Zareifar S, Rowshani F, Haghpanah S, Bordbar M (2018) Five-year survival rate of children with central nervous system tumors in shiraz, Iran. Iranian Journal of Pediatric Hematology and Oncology 8:1–11
41. Mehrvar A, Faranoush M, Hedayati Asl AA, Tashvighi M, Fazeli MA, Qaddoumi I, Mehrvar N, Sobuti B, Jafarpour A, Ravan parsa R, Zangooei R, Alebouyeh M, Vossough P (2014) Childhood central nervous system tumors at MAHAK's pediatric Cancer treatment and research center (MPCTRC), Tehran. Iran Childs Nerv Syst 30:491–496
42. KA R (2011, 810) Epidemiology and survival of childhood primary central nervous system malignancies in Iran: Results from a single center. Pediatr Blood Cancer 57
43. Grob ST, Levy JMM (2017) Improving diagnostic and therapeutic outcomes in pediatric brain tumors. Mol Diagn Ther 22:25–39. https://doi.org/10.1007/s40291-017-0299-3
44. Pogorzala M, Styczynski J, Wysocki M (2014) Survival and prognostic factors in children with brain tumors: long-term follow-up single center study in Poland. Anticancer Res 34:323–326
45. Segal D, Karajannis MA (2016) Pediatric brain tumors: an update. Curr Probl Pediatr Adolesc Health Care 46:242–250
46. Rey-Casserly C, Diver T (2019) Late effects of pediatric brain tumors. Curr Opin Pediatr 31:789–796
47. Chen J, Mullen CA (2017) Patterns of diagnosis and misdiagnosis in pediatric Cancer and relationship to survival. J Pediatr Hematol Oncol 39:e110–e115
48. Qaddoumi I, Merchant TE, Boop FA, Gajjar A (2019) Diagnostic delay in children with central nervous system tumors and the need to improve education. J Neuro-Oncol 145:591–592
49. Ferrari A, Lo Vullo S, Giardiello D, Veneroni L, Magni C, Clerici CA, Chiaravalli S, Casanova M, Luksch R, Terenziani M, Spreafico F, Meazza C, Catania S, Schiavello E, Biassoni V, Podda M, Bergamaschi L, Puma N, Massimino M, Mariani L (2016) The sooner the better? How symptom interval correlates with outcome in children and adolescents with solid tumors: regression tree analysis of the findings of a prospective study. Pediatr Blood Cancer 63:479–485
50. Gerber NU, von Hoff K, von Bueren AO, Treulieb W, Deinlein F, Benesch M, Zwiener I, Soerensen N, Warmuth-Metz M, Pietsch T, Mittler U, Kuehl J, Kortmann RD, Grotzer MA, Rutkowski S (2012) A long duration of the prediagnostic symptomatic interval is not associated with an unfavourable prognosis in childhood medulloblastoma. Eur J Cancer 48:2028–2036