Neoplasma 2024; 71(6): 603–609

doi:10.4149/neo_2024_241030N441

Clinical features, treatment modalities, and survival rates of pediatric central nervous system tumors: A retrospective analysis from a single center (2000–2020)

Estera BUBLÁKOVÁ[1], Miroslava MAKOHUSOVÁ[1,*], Anna BALLOVÁ[1], Kristína HUSÁKOVÁ[1], Stanislava HEDEROVÁ[1], Andrea MOCNÁ[1], Robert CHRENKO[2], Svorad TRNOVEC[2], Salome JAKEŠOVÁ[3], Matúš DURDÍK[4,5], Boris RÝCHLY[6], Andrea HRAŠKOVÁ[1], Alexandra KOLENOVÁ[1]

[1]Department of Pediatric Hematology and Oncology, National Institute of Children's Diseases, Faculty of Medicine Comenius University, Bratislava, Slovakia; [2]Department of Pediatric Neurosurgery, National Institute of Children's Diseases, Faculty of Medicine Comenius University, Bratislava, Slovakia; [3]Department of Radiology, National Institute of Children's Diseases, Faculty of Medicine Comenius University, Bratislava, Slovakia; [4]Laboratory of Clinical and Molecular Genetics, Department of Pediatric, National Institute of Children's Diseases, Faculty of Medicine Comenius University, Bratislava, Slovakia; [5]Department of Radiobiology, Cancer Research Institute, Biomedical Research Center, Slovak Academy of Sciences, Bratislava, Slovakia; [6]Diagnostic Centre for Pathology, Unilabs s.r.o., Bratislava, Slovakia

**Correspondence: miroslava.makohusova@gmail.com*

Received October 30, 2024 / Accepted December 20, 2024

Pediatric central nervous system (CNS) tumors represent 20-25% of childhood malignancies, with 35-40 new cases annually in Slovakia. Despite treatment advances, high mortality and poor quality of life in a lot of cases persist. This study assesses the clinical features, treatment modalities, and survival rates of pediatric CNS tumor patients in the single largest center in Slovakia. A retrospective analysis was conducted on pediatric CNS tumors from January 1, 2000, to December 31, 2020, at the Department of Pediatric Oncology and Hematology at the National Institute of Children's Diseases in Bratislava, Slovakia. Among 397 patients (242 males, 155 females), the most common histological types were astrocytomas (42.8%), followed by embryonal tumors (18.4%), brain stem tumors (10.3%), and ependymal tumors (8.1%). Tumor locations were supratentorial (48.1%), infratentorial (46.9%), and spinal (4.3%). Surgical interventions included radical excision (30.2%), subtotal/partial excision (41.8%), and biopsy (9.3%). Treatment modalities varied, with 31.2% receiving combined surgery, chemotherapy, and radiotherapy; 27.5% surgery alone; 9.6% surgery with radiotherapy; 7.8% chemotherapy only; and 6.3% having no treatment. By 2020, 74.3% of patients were alive, with a 25.7% mortality rate. This study outlines the characteristics of pediatric CNS tumors in Bratislava, highlighting the need for multidisciplinary national and international collaboration to advance diagnosis and treatment. Our data align with global findings from other centers.

Key words: CNS tumors; clinical characteristics; survival

Central nervous system (CNS) tumors rank as the second most prevalent cancer in children, accounting for 20–25% of pediatric oncological diseases [1]. The annual incidence rate in Europe is estimated between 4.01 and 5.7 per 100,000 children aged 0–15 years [2]. In Slovakia, approximately 30–35 new cases are diagnosed annually [3]. Significant heterogeneity in this group of tumors, together with limited therapeutic options, is responsible for the fact that brain tumors are the most common cause of death from childhood malignant diseases [4]. The treatment is very challenging due to the developing nervous system, which is damaged by conventional treatment modalities such as neurosurgery, cytotoxic chemotherapy, and craniospinal irradiation [5]. These modalities are still the basis of treatment and improved survival in many cases. However, they cause late side effects, and 50–90% of survivors of childhood brain cancer are diagnosed with a chronic health condition and deterioration in cognitive, behavioral, and emotional functioning [6]. Efforts to improve the survival and quality of life of these children are reflected in a deeper understanding of biology, more accurate diagnosis, and personalized treatment.

Traditional risk stratification schemes have relied on factors such as patient age, tumor histology, and metastatic status at the time of diagnosis to define the treatment. Although these factors are important markers for tumor biology and the subsequent natural history of the disease, they fail to recognize subtle molecular differences that now define the prognosis. The classification system for brain

tumors has undergone a transformative evolution since the introduction of the third edition of the World Health Organization (WHO) classification in 2007, which notably integrated immunohistochemical characteristics [7]. This examination reveals that many of these tumors possess distinct genetic alterations that define their characteristics. Subsequently, the 2016 WHO classification, in its fourth version, incorporated some of the genetic changes within brain tumors, which are crucial for tailoring precise clinical management. Now, we know that even among tumors with similar visual characteristics, the underlying genetic makeup can lead to vastly different clinical outcomes and responses to treatment [8]. The advent of next-generation sequencing technology revolutionized our capacity to analyze extensive portions of the human genome in parallel [9]. The latest release of the fifth edition of the 2021 WHO classification of brain tumors represents a significant leap forward, encapsulating our current understanding of brain tumor biology and routinely employed technologies for investigating molecular alterations [10]. A noteworthy addition to routine laboratory diagnostics is the gradual integration of epigenetic testing, particularly through whole-genome methylation arrays. These arrays offer a nuanced analysis of DNA methylation patterns, crucial regulators of gene expression, thereby enriching our understanding of the molecular landscape of CNS tumors [11].

In our retrospective analyses, we stratify patients according to the fourth edition of the WHO classification of CNS tumors published in 2016.

Patients and methods

Study design. This study retrospectively evaluated patients diagnosed with primary CNS tumors at the Department of Pediatric Hematology and Oncology in Bratislava from January 2000 to December 2020. The study population included individuals aged 0 to 18 years. Additionally, patients diagnosed at other centers across Slovakia who received part of their treatment in Bratislava were included in the analysis. Data were extracted from the Slovak Cancer Registry of Children and Adolescents, medical charts, and hospital health information systems, capturing details on patient gender, age, histology, tumor location, treatment modalities, and overall survival (OS).

CNS tumors were categorized based on the WHO Classification 2016 into the following main groups: low-grade gliomas (LGG, WHO grade I and II), high-grade gliomas (HGG, WHO grade III and IV), embryonal tumors (including medulloblastoma, atypical teratoid rhabdoid tumors – AT/RT, embryonal tumors with multilayered rosettes – ETMRs, and other embryonal tumors), ependymal tumors, germ cell tumors, other tumors and unspecified neoplasms. The unspecified neoplasms category included patients for whom the histological examination was not performed, and a definitive diagnosis could not be established. Patients who did not undergo a biopsy but whose diagnoses were based on clinical or radiologic evaluation were also incorporated into the study.

Statistical analysis. Follow-up started from the date of diagnosis, with patient data being censored at the point of loss follow-up or December 31, 2021, whichever occurred first. The date of diagnosis for each patient was established either as the date of the first surgical resection/biopsy or, in cases where tissue was not obtained, the date of the initial imaging. Survival rates were calculated from the date of diagnosis to the date of either the last follow-up or the patient's death.

The Kaplan-Meier method was employed to estimate survival rates. To compare survival curves across different cohorts, stratified by variables such as period of diagnosis, histological subtypes, tumor localization, type of surgery, therapy used, and clinical characteristics (including sex and age at diagnosis), the log-rank test (Mantel-Cox test) was utilized. A significance level of less than 0.05 was used to determine statistically significant differences in survival between groups. All statistical analyses were conducted using Stata/IC 14.2.

Results

Our analysis revealed 397 patients diagnosed with primary CNS tumors over 20 years. Among them, we have lost the follow-up in 32 (8.0%) patients. The overall male-to-female (M:F) ratio was 1.56:1, with 242 (61.0%) boys and 155 (39.0%) girls. The mean age of patients was 7.67 years. Five age groups were defined: <1 year, 1–4 years, 5–9 years, 10–14 years, and 15–18 years. The highest incidence of cases was observed in the 1–4 years and 5–9 years age groups, with each accounting for 28.2% (112 patients) of the total cohort. In contrast, the lowest incidence was recorded in children under 1 year of age, with 23 cases (5.8%) registered.

We also analyzed the topographic distribution of tumors by age. In children under 3 years, 43 (51.2%) of tumors were supratentorial, 37 (44.0%) were infratentorial, 2 (2.4%) were in the spinal cord, and 2 cases involved both supra- and infratentorial regions. Among children over 3 years, the distribution was nearly equal: 125 (47.8%) infratentorial, 126 (48.2%) supratentorial, and 10 (3.8%) spinal cord tumors. In adolescents, the pattern was similar, with 24 (46.9%) infratentorial, 22 (42.3%) supratentorial, 5 (9.6%) spinal cord tumors, and 1 case of a mixed site tumor. The distribution of patients according to age group and location of the tumors is shown in Table 1.

Astrocytoma was the most common tumor type identified in our analysis, representing 170 patients (42.8%), with this predominance observed across all age groups. These patients were further categorized into three subgroups: astrocytomas grade I and II (n=110), astrocytomas grade III and IV (n=25), and optic pathway gliomas (n=35). Among LGG, the most frequent histopathological type was pilocytic astrocytoma, while in the HGG, anaplastic astrocytoma. These tumors

Table 1. Patients' characteristics, survival rates.

Factor	Category	n	%	Death, n	1 y OS ± SE	2 y OS ± SE	5 y OS ± SE	p-value*
	Total	397	100.0	102	0.8941±0.0155	0.7902±0.0208	0.7662±0.0218	
Period of diagnosis	2000–2010	175	44.1	60	0.8743±0.0251	0.7429±0.0330	0.7200±0.0339	0.0313
	2011–2020	222	55.9	42	0.9098±0.0192	0.8309±0.0258	0.8056±0.0280	
Sex	male	242	61.0	61	0.9008±0.0192	0.7957±0.0264	0.7658±0.0281	0.7736
	female	155	39.0	41	0.8835±0.0258	0.7814±0.0337	0.7662±0.0348	
Age	<1y	23	5.8	8	0.8696±0.0702	0.6848±0.0992	0.6848±0.0992	
	1–4 y	112	28.2	27	0.9018±0.0281	0.8287±0.0358	0.7875±0.0395	
	5–9 y	112	28.2	32	0.8564±0.0332	0.8011±0.0380	0.7402±0.0425	0.5089
	10–14 y	98	24.7	24	0.8980±0.0306	0.8557±0.0357	0.7651±0.0441	
	15–18 y	52	13.1	11	0.9615±0.0267	0.8625±0.0483	0.8194±0.0547	
Age	<10 y	267	67.3	72	0.8762±0.0202	0.7723±0.0262	0.7583±0.0269	0.2324
	≥10 y	130	32.7	30	0.9308±0.0223	0.8273±0.0336	0.7846±0.0369	
Histology	ASTROCYTOMA	170	42.8	26	0.9588±0.0153	0.8780±0.0256	0.8509±0.0282	
	HGG	25	6.3	19	0.7178±0.0905	0.4504±0.1036	0.1501±0.0787	
	LGG	110	27.7	7	1.0000±0.0000	0.9817±0.0128	0.9526±0.0207	
	optic pathway glioma	35	8.8	0	1.0000±0.0000	1.0000±0.0000	1.0000±0.0000	
	OTHER GLIOMAS	25	6.3	0	1.0000±0.0000	1.0000±0.0000	1.0000±0.0000	
	neuronal and mixed glioneuronal tumors	18	4.5	0	1.0000±0.0000	1.0000±0.0000	1.0000±0.0000	
	oligodendroglioma	7	1.8	0	NA	NA	NA	
	EMBRYONAL	73	18.4	30	0.8219±0.0448	0.6935±0.0546	0.6774±0.0557	
	medulloblastoma HR	28	7.1	10	0.8214±0.0724	0.7841±0.0781	0.7057±0.0878	
	medulloblastoma SR	20	5.0	3	0.9090±0.0867	0.8181±0.1162	0.7159±0.1396	
	AT/RT	10	2.5	8	0.600±0.1549	0.2000±0.1265	0.2000±0.1265	
	PNET	13	3.3	7	0.7692±0.1169	0.6923±0.1280	0.6058±0.1382	
	others	2	0.5	2	NA	NA	NA	
	EPENDYMAL	32	8.1	6	0.9688±0.0308	0.9042±0.0526	0.8707±0.0604	
	BRAIN STEM TU	41	10.3	32	0.5610±0.0775	0.2683±0.0692	0.2439±0.0671	
	CHOROID PLEXUS TU	11	2.8	2	0.9091±0.0867	0.9091±0.0867	0.9091±0.0867	
	GERM CELL TU	15	3.8	2	1.0000±0.000	0.8556±0.0950	0.8556±0.0950	
	other tumors and unspecified neoplasm	30	7.6	4	0.9333±0.0455	0.8974±0.0562	0.8476±0.0719	
Localisation	infratentorial	186	46.9	60	0.8548±0.0258	0.7446±0.0322	0.7267±0.0330	
	supratentorial	191	48.1	40	0.9266±0.0189	0.8240±0.0284	0.7912±0.0308	
	supra-infratentorial	3	0.8	1	NA	NA	NA	
	Spinal cord	17	4.3	1	0.9412±0.0571	0.9412±0.0571	0.9412±0.0571	
Surgery	biopsy	37	9.3	17	0.8378±0.0606	0.5313±0.0870	0.5313±0.0870	
	subtotal/partial resection	166	41.8	49	0.8976±0.0235	0.7856±0.0322	0.7513±0.0342	
	total resection	120	30.2	8	0.9833±0.0117	0.9746±0.0145	0.9545±0.0200	
	inoperabile	37	9.3	25	0.5946±0.0807	0.3493±0.0787	0.3202±0.0774	
	without therapy	30	7.6	3	0.9333±0.0455	0.8928±0.0589	0.8928±0.0589	
	NA	7	1.8	0	NA	NA	NA	
Therapy	CHT	31	7.8	3	0.9355±0.0441	0.8930±0.0592	0.8930±0.0592	
	CHT+RAT	29	7.3	27	0.6207±0.0901	0.0503±0.0475	NA	
	CHT+RAT+surgery	124	31.2	44	0.8948±0.0276	0.7611±0.0388	0.7138±0.0417	
	CHT+surgery	21	5.3	4	0.9524±0.0465	0.8444±0.0835	0.8444±0.0835	
	NA	10	2.5	5	0.8000±0.1265	0.5000±0.1581	0.5000±0.1581	
	RAT	10	2.5	6	0.4000±0.1549	0.4000±0.1549	0.4000±0.1549	
	without therapy	25	6.3	5	0.8400±0.0733	0.8000±0.0800	0.8000±0.0800	
	surgery	109	27.5	5	0.9725±0.0157	0.9725±0.0157	0.9619±0.0187	
	surgery+RAT	38	9.6	3	1.0000±0.0000	0.9737±0.0260	0.9459±0.0373	

Note: *the results of the log-rank test between selected categories

Abbreviations: 1 y OS-one-year overall survival; 2 y OS-two-years overall survival; 5 y OS-five-years overall survival; SE- standard error; NA-not applicable/not evaluable; SM-secondary malignancies; CHT-chemotherapy; RAT-radiotherapy

primarily affected children under 14 years of age. Pilocytic astrocytoma was also the most frequent histological type in patients with confirmed optic pathway gliomas; however, histological examination was performed only in 7 patients, with the remaining 28 diagnoses confirmed through imaging. In the optic pathway glioma group, nearly all patients were younger than 9 years (94.0%), with only two cases observed in patients over 10 years old.

Additionally, other gliomas in our cohort included neuronal and mixed glioneuronal tumors (n=18) and oligodendrogliomas (n=7), with an age distribution similar to astrocytomas (1–14 years). Another significant group comprised children with brainstem tumors (n=41; 10.3%). Due to the high surgical risk, not all of these patients underwent biopsy, with the majority being diagnosed by imaging alone. In cases where histology was available, anaplastic, diffuse, pilocytic, and pilomyxoid astrocytomas were identified.

Ependymoma was diagnosed in 32 children (8.0%), with one additional case of subependymoma. The peak incidence occurred in the 1–4-year age range, and all cases were confirmed histopathologically, as surgical removal of the tumor is the primary treatment for these patients. The most common tumor localization was infratentorial, a site associated with a poorer prognosis.

Embryonal tumors constituted the second largest group, affecting 73 children (18.4%). This group primarily comprised medulloblastomas (n=48), followed by supratentorial primitive neuroectodermal tumors (PNETs), including pinealoblastoma, in 13 children and AT/RT in 10 cases. Additionally, there was one case each of medulloepithelioma and ganglioneuroblastoma. These tumors predominantly occurred in children under 9 years of age.

Germ cell tumors were confirmed in 15 patients (3.8%). Of these, 6 were germinomas, 7 were non-germinomas, and in 2 cases, the specific type of germ cell tumor was not further specified. These tumors were diagnosed primarily in the 10–14-year age group.

This series also included 11 cases (2.8%) of choroid plexus tumors, 19 cases (4.7%) of other tumor types (e.g., meningiomas, schwannomas, hemangioblastomas, etc.), and 11 cases (2.8%) of undiagnosed neoplasms.

Biopsy and histological examination were not performed in 67 patients, including those with brainstem tumors (n=28), optic pathway gliomas (n=28), secretory active germ cell tumors (n=2), and other unspecified neoplasm (n=9). Total tumor resection was achieved in 120 patients (30.2%), while subtotal resection (removal of 51–90% of tumor tissue) and partial resection (removal of less than 50% of tumor tissue) were performed in 166 patients (41.8%). The most common treatment approach was surgical resection combined with chemotherapy and radiotherapy, administered to 123 patients (31.2%). The histology of the tumors with treatment modalities are shown in Table 1.

Survival data for 397 patients indicated that 295 patients (74.3%) were alive, while 102 patients (25.6%) had died. The overall survival rate during the follow-up period is presented in Figure 1, with survival further analyzed by age group, as shown in Figure 2.

Among the 102 deaths, brainstem tumors were the leading cause, representing 31.3% (32 patients) of all fatalities and the most commonly reported disease progression. Embryonal tumors accounted for 29.4% (30 patients) of deaths, predominantly medulloblastomas classified as high risk, but also included patients with AT/RT and pinealoblastomas. Of these, 24 patients experienced disease progression during first-line treatment. HGG were responsible for 18.6% (19 patients) of deaths, with an equal number of patients showing disease progression during treatment. LGG accounted for 6.7% (7 patients) of deaths, making this group, in proportion to their total number, the one with the highest survival rate. Disease progression was observed in 9 patients with optic pathway gliomas and in 32 patients with LGG outside the optic pathway. Ependymomas contributed to 5.8% (6 patients) of deaths, with disease progression reported in 5 of these cases during treatment. The remaining deaths included

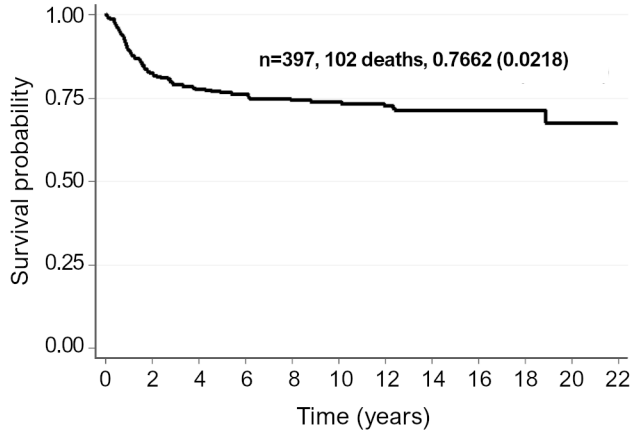

Figure 1. Overall survival during the study period (2000–2021).

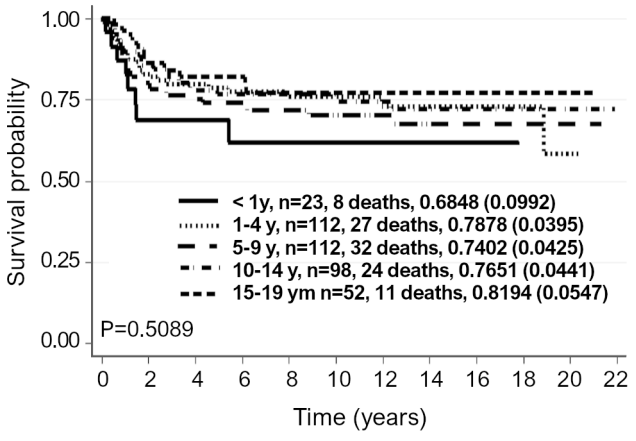

Figure 2. Overall survival based on the age group.

other tumor types, accounting for 3.9% (4 patients), while germ cell tumors were responsible for 1.9% (2 patients) of deaths.

Overall, 132 patients (33.2%) experienced disease progression during treatment, 29 patients (7.3%) had confirmed recurrences, and 4 patients (1.0%) developed secondary neoplasms. Recurrences were most frequently observed in astrocytomas, ependymal tumors, and medulloblastomas, with a recurrence rate for each group of 1.2% (5 patients).

The study also demonstrates an improving survival trend in children with CNS tumors (Figure 3), reflecting advances in biological understanding, more accurate diagnostics, and personalized treatment approaches, all of which contribute significantly to higher survival rates and improved quality of life for these patients.

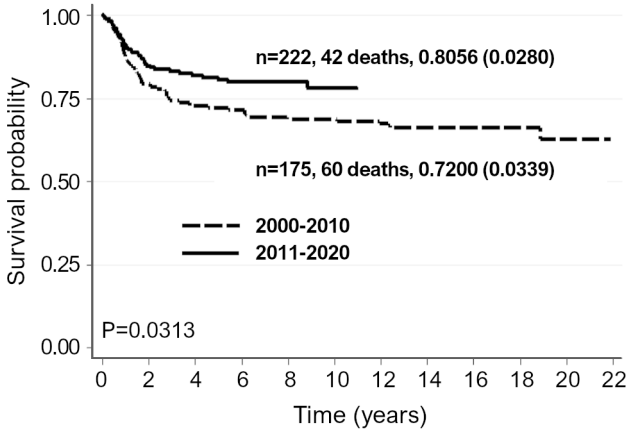

Figure 3. Overall survival based on the study period.

Discussion

This is one of the biggest analyses from our center concerning pediatric brain tumors. The objective of this study was to evaluate the prevalence of childhood CNS tumors in patients who were referred to our center for treatment and follow-up. By evaluating the prevalence of enrolled patients, we can use the data as benchmark information for the cancer registry system of childhood brain tumors in Slovakia. In this way, there should be more investigations about the incidence of childhood CNS tumors in Slovakia, as this is a hospital-based study. Our findings were compared with similar studies globally [12, 13].

Male predominance is a known fact in pediatric CNS tumors, and it is possibly linked to sexually dimorphic tumor cell mechanisms [14]. In all of the reviewed studies [13, 15–18], there was a male predominance, the same as we observed in our study, with a gender ratio of 1.56:1 (M:F). The mean age of diagnosis in our study was 7.67 years, similar to previous findings in other countries, where the mean age ranged from 6.8 to 8.8 years [15, 16, 19]. Next, we compared information about the peak age at which most of the pediatric brain tumors are seen. In the studies, the most commonly affected age group was 5 to 9 years, although the incidence was nearly comparable to the 1 to 4-year age group [15, 17, 20], and in one study from India, the peak incidence was between 11–18 years [18]. In our study, we also have seen the highest frequency in the age groups 1–4- and 5–9-year-old children.

A study from Germany found that supratentorial tumors were more prevalent in older children, which is associated with a more favorable prognosis, compared to infratentorial locations of tumors predominantly seen in children under 3 years old [13]. Some articles have reported that pediatric brain tumors are more commonly found in the supratentorial region [20, 21], while others have presented contrasting findings [22, 23]. In our study, we observed a similar distribution. Under the age of 3, there were 51.2% tumors in the supratentorial compartment, and infratentorial tumors were seen in 44.0% of cases. In older children, the probability was almost the same.

Since neurosurgery is one of the most important procedures in the treatment of brain tumors, we compared surgical approaches in other countries, from which the information was mentioned in their articles. In our center, surgery was not performed in 16.9%, in the article from France, it was 9.74% [12], from China 10.5% [16], and most cases without surgery were stated in the United States in the SEER (Surveillance, Epidemiology, and End Results Program) registry up to 25.4% [24]. Out of proceeded surgeries, in our database, 9.3% were biopsies, 41.8% were subtotal or partial resections, and 30.2% were gross total resections. In an article by Liu et al., the biopsies were performed in 17.1%, subtotal resections in 23.2%, and gross total resections in 49.4% [16]. In the SEER cohort, biopsies or subtotal resections were performed in 21.8% of cases, and gross total resection in 45.1% [24].

Histological data revealed astrocytomas as the most common tumor type, followed by embryonal and ependymal tumors. Our findings were largely consistent with studies from France, Sweden, Germany, and the SEER registry [12, 13, 15, 24]. Brain stem tumors represented another big group of pediatric tumors, comprising 10.3% of the cases. However, comparison with other studies is challenging, as brain stem tumors are not consistently reported as a separate category in the literature. The biggest difference in tumor distribution has been seen in germ cell tumors. In our present study, they comprised only 3.8 %, and this number corresponds with their prevalence in other Western countries. There is a significantly higher incidence of germ cell tumors in Asian countries. In a study from China, it was 21.1% [16], Korea 11.2% [20], Japan 14.3% [25], and Taiwan 14.0% [26]. Choroid plexus tumors (2.8 %) were rare in all of the reviewed articles, ranging from 0.9% in Germany [13] to 2.9 % in France [12]. We saw significant diversity in tumor type distribution, and according to Pinho et al. [27], this variability may be related to racial, environmental, and geographical factors.

According to a study on the prognosis of pediatric brain tumors in the United States, the estimated 5-year survival rate has increased from 55.0% to 76.0% over the last fifty years [28]. Our analysis demonstrated a survival rate of 73.8%, reflecting a trend comparable with the data observed in the US and indicating improved survival rates over the past two decades. Research further suggests that an older age at diagnosis is associated with better survival outcomes compared to a younger age at diagnosis. In our center, in line with the above-mentioned studies, we observed the highest survival rates in patients aged 15–18 years, followed by those aged 5–14 years, with the lowest survival rates reported in the youngest children. However, the difference in survival rates among these age groups was not statistically significant (p=0.5089).

The improving increase in survival rates of pediatric brain tumors, particularly in recent years, underlines significant advancements in diagnosis and treatment. The big leap forward was the integration of novel diagnostic markers – DNA methylation, an epigenetic mechanism, which plays a crucial role in the regulation of gene expression in both normal and cancer cells and has a role in cancer initiation, progression, and maintenance [5]. This examination in brain tumors serves as a diagnostic marker, enabling tumor stratification into relevant subgroups, it also informs us about the prognosis and guiding treatment decisions to avoid over-treatment or ensure appropriate therapy intensity [11]. Additionally, it acts as a predictive biomarker for treatment response and facilitates the development of targeted therapies. Methylation inhibitors also offer a promising approach for therapeutic intervention [29]. The latest WHO classification of CNS tumors, issued in 2021, highlights the importance of these molecular changes, endorsing DNA methylation profiling as a critical tool for CNS tumor stratification [10]. In May 2023, the Genetic Laboratory at the National Institute of Childhood Diseases in Bratislava became the first and only institution in Slovakia to introduce tumor profiling based on DNA methylation. We also analyze CNS tumor tissue samples from other oncology centers across the country. Utilizing the Illumina EPIC methylation SNP array, we generate primary data on methylation profiles of CNS tumors. The primary data are subsequently uploaded to the Classifier, a free online tool developed at the University of Heidelberg, to facilitate the evaluation and interpretation of the findings. In a short time, the report consisting of the most probable methylation class of the tumor, copy number variations profile, and state of MGMT promotor methylation is obtained [30]. Additionally, targeted therapy has revolutionized modern oncology treatment, particularly in addressing LGG, which represents a significant portion of CNS tumors. The direct inhibition of BRAF and/or MEK has emerged as a clinically relevant strategy [31]. Since 2020, our clinic has utilized these inhibitors in indicated cases.

This data is derived from hospital series, and the absence of a population-based study from a centralized registry introduces a high likelihood of selection bias. A key limitation is that not all relevant information was available for patients diagnosed prior to 2003, as a different hospital information system was in use at that time. Children with craniopharyngiomas were excluded from the study, as many are not referred to pediatric oncologists but are managed by pediatric endocrinologists at our center, preventing us from obtaining a complete list of these patients. Additionally, children with hamartomas and neurofibromas were excluded despite some being followed up in our outpatient clinic. Another limitation is that this is a single-center study, and data from other centers across the country were not included. Despite notable advancements in the diagnosis and treatment of pediatric CNS tumors, certain tumor types continue to present a poor prognosis [12]. Slovakia has made significant strides in implementing cutting-edge diagnostic and therapeutic strategies, such as personalized medicine and targeted therapies, including MEK inhibitors. Improved survival rates, particularly for patients with low-grade gliomas and germ-cell tumors, underscore the potential of these advancements. Nevertheless, challenges remain in ensuring equitable access to these innovations, especially in resource-limited settings. Bridging this gap will require collaborative efforts and the sharing of resources and expertise on a global scale. Moving forward, continued research and international cooperation are imperative to optimize outcomes and provide all children with the best possible chance for a cure while minimizing the long-term effects of treatment.

Acknowledgments: The support of grant APVV-23-0657 is highly acknowledged.

References

[1] MCKINNEY PA. Central nervous system tumours in children: epidemiology and risk factors. Bioelectromagnetics 2005; 7: S60–68. https://doi.org/10.1002/bem.20149

[2] RUTKOWSKI S, MODENA P, WILLIAMSON D, KERL K, NYSOM K et al. Biological material collection to advance translational research and treatment of children with CNS tumours: position paper from the SIOPE Brain Tumour Group. Lancet Oncol 2018; 19: e419–e428. https://doi.org/10.1016/S1470-2045(18)30364-4

[3] KAISEROVÁ E, MAKOHUSOVÁ M. [Epidemiology of Childhood Tumors] in ŠAŠINKA M, ŠAGÁT T, LÁSZLÓ KOVÁCS L et al. Pediatria, Herba, 3rd edition, 2019; ISBN 9788089631902

[4] THORBINSON C, KILDAY JP. Childhood Malignant Brain Tumors: Balancing the Bench and Bedside. Cancers (Basel) 2021; 13: 99. https://doi.org/10.3390/cancers13236099

[5] KUMAR R, LIU APY, ORR BA, NORTHCOTT PA, ROBINSON GW. Advances in the classification of pediatric brain tumors through DNA methylation profiling: From research tool to frontline diagnostic. Cancer 2018; 124: 4168–4180. https://doi.org/10.1002/cncr.31583

[6] ALEMANY M, VELASCO R, SIMO M, BRUNA J. Late effects of cancer treatment: consequences for long-term brain cancer survivors. Neurooncol Pract 2021; 8: 18–30. https://doi.org/10.1093/nop/npaa039

[7] LOUIS DN, OHGAKI H, WIESTLER OD, CAVENEE WK, BURGER PC et al. The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol 2007; 114: 97–109. https://doi.org/10.1007/s00401-007-0243-4

[8] LOUIS DN, PERRY A, REIFENBERGER G, VON DEIMLING A, FIGARELLA-BRANGER D et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol 2016; 131: 803–820. https://doi.org/10.1007/s00401-016-1545-1

[9] LORENZ J, ROTHHAMMER-HAMPL T, ZOUBAA S, BUMES E, PUKROP T et al. A comprehensive DNA panel next generation sequencing approach supporting diagnostics and therapy prediction in neurooncology. Acta Neuropathol Commun 2020; 8: 124. https://doi.org/10.1186/s40478-020-01000-w

[10] LOUIS DN, PERRY A, WESSELING P, BRAT DJ, CREE IA et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. Neuro Oncol 2021; 23: 1231–1251. https://doi.org/10.1093/neuonc/noab106

[11] CAPPER D, JONES DTW, SILL M, HOVESTADT V, SCHRIMPF D et al. DNA methylation-based classification of central nervous system tumours. Nature 2018; 555: 469–474. https://doi.org/10.1038/nature26000

[12] DARLIX A, ZOUAOUI S, RIGAU V, BESSAOUD F, FIGARELLA-BRANGER D et al. Epidemiology for primary brain tumors: a nationwide population-based study. Journal of Neuro-Oncology 2017; 131: 525–546. https://doi.org/10.1007/s11060-016-2318-3

[13] KAATSCH P, RICKERT CH, KUHL J, SCHUZ J, MICHAELIS J. Population-based epidemiologic data on brain tumors in German children. Cancer 2001; 92: 3155–3164. https://doi.org/10.1002/1097-0142(20011215)92:12<3155::aid-cncr10158>3.0.co;2-c

[14] SUN T, PLUTYNSKI A, WARD S, RUBIN JB. An integrative view on sex differences in brain tumors. Cell Mol Life Sci 2015; 72: 3323–3342. https://doi.org/10.1007/s00018-015-1930-2

[15] LANNERING B, SANDSTROM PE, HOLM S, LUNDGREN J, PFEIFER S et al. Classification, incidence and survival analyses of children with CNS tumours diagnosed in Sweden 1984–2005. Acta Paediatr 2009; 98: 1620–1627. https://doi.org/10.1111/j.1651-2227.2009.01417.x

[16] LIU APY, LIU Q, SHING MMK, KU DTL, FU E. et al., Incidence and Outcomes of CNS Tumors in Chinese Children: Comparative Analysis With the Surveillance, Epidemiology, and End Results Program. JCO Glob Oncol 2020; 6: 704–721. https://doi.org/10.1200/JGO.19.00378

[17] MEHRVAR N, MEHRVAR A, AKBARI ME, QADDOUMI I. Comprehensive analysis of Iranian reports of pediatric central nervous system tumors. Childs Nerv Syst 2017; 33: 1481–1490. https://doi.org/10.1007/s00381-017-3468-0

[18] KUMAR-MULLAPALLY S, DUSI V, DIGUMARTI R. Clinical Profile, Patterns of Care and Outcomes of Childhood CNS Tumours in India 2022. In: F Birol Sarica (Eds.): Central Nervous System Tumors – Primary and Secondary. https://doi.org/10.5772/intechopen.107356

[19] ARAUJO OL, TRINDADE KM, TROMPIERI NM, FONTENELE JB, FELIX FH. Analysis of survival and prognostic factors of pediatric patients with brain tumor. J Pediatr (Rio J) 2011; 87: 425–432. https://doi.org/10.2223/JPED.2124

[20] CHO KT, WANG KC, KIM SK, SHIN SH, CHI JG et al. Pediatric brain tumors: statistics of SNUH, Korea (1959–2000). Childs Nerv Syst 2002; 18: 30–37. https://doi.org/10.1007/s00381-001-0547-y

[21] BALL WS. Neuroimaging diagnosis of primary brain neoplasms in childhood. In: GK Schulthess, Ch L Zollikofer (Eds.) Diseases of the Brain, Head and Neck, Spine 2004; 107–111.

[22] BECKER LE. Pathology of pediatric brain tumors. Neuroimaging Clin N Am 1999; 9: 671–690.

[23] SIFFERT J, GREENLEAF M, MANNIS R, ALLEN J. Pediatric brain tumors. Child Adolesc Psychiatr Clin N Am 1999; 8: 879–903, x.

[24] HOWLADER N, NOONE AM, KRAPCHO M, MILLER D, BREST A et al. SEER Cancer Statistics Review, 1975–2016, National Cancer Institute Bethesda [As accessed online on April 2019] https://seer.cancer.gov/csr/1975_2016/

[25] MORI K, KURISAKA M. Brain tumors in childhood: statistical analysis of cases from the Brain Tumor Registry of Japan. Childs Nerv Syst 1986; 2: 233–237. https://doi.org/10.1007/BF00272492

[26] WONG TT, HO DM, CHANG KP, YEN SH, GUO WY et al. Primary pediatric brain tumors: statistics of Taipei VGH, Taiwan (1975–2004). Cancer 2005; 104: 2156–2167. https://doi.org/10.1002/cncr.21430

[27] PINHO RS, ANDREONI S, SILVA NS, CAPPELLANO AM, MASRUHA MR et al. Pediatric central nervous system tumors: a single-center experience from 1989 to 2009. J Pediatr Hematol Oncol 2011; 33: 605–609. https://doi.org/10.1097/MPH.0b013e31822031d9

[28] OTTH M, WYSS J, SCHEINEMANN K. Long-Term Follow-Up of Pediatric CNS Tumor Survivors-A Selection of Relevant Long-Term Issues. Children (Basel) 2022; 9. https://doi.org/10.3390/children9040447

[29] GAJJAR A, PFISTER SM, TAYLOR MD, GILBERTSON RJ. Molecular Insights into Pediatric Brain Tumors Have the Potential to Transform Therapy. Clin Cancer Res 2014; 20: 5630–5640. https://doi.org/10.1158/1078-0432.Ccr-14-0833

[30] CAPPER D, STICHEL D, SAHM F, JONES DTW, SCHRIMPF D et al. Practical implementation of DNA methylation and copy-number-based CNS tumor diagnostics: the Heidelberg experience. Acta Neuropathol 2018; 136: 181–210. https://doi.org/10.1007/s00401-018-1879-y

[31] KULUBYA ES, KERCHER MJ, PHILLIPS HW, ANTONY R, EDWARDS MSB. Advances in the Treatment of Pediatric Brain Tumors. Children (Basel) 2022; 10: 62. https://doi.org/10.3390/children10010062