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Clinicopathological analysis of pediatric posterior fossa tumors: insights from a National neurosurgical center

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Abstract

Background. Pediatric posterior fossa tumors are the significant cause of morbidity and mortality in children and adolescents. This study aimed to investigate the characteristics of the patient population and report the experience in managing and treating children with these tumors, as well as their survival outcomes in Kazakhstan.

Methods. This retrospective study analysed data from the archives of the Pediatric Neurosurgery Department and included 214 pediatric patients with PFT in the period from January 2015 to December 2020.

Results. The study included 214 patients with a mean age of 7.29 ± 4.26 years. The most common tumor pathology observed in this study was medulloblastoma (33.18%). Grade I tumors showed a notable median survival of 56.64 months (95% CI, 53.93-59.35), surpassing Grade II tumors at 50.38 months (95% CI, 40.57-60.2). Grade III and IV tumors had median survivals of 38.64 months (95% CI, 31.11-46.17) and 38.76 months (95% CI, 33.96-43.56). Multivariate analysis using Cox regression model revealed significant predictors of overall survival. Grade III-IV tumors (RR = 0.577, 95% CI 0.462-0.720, p = 0.000), delayed resection (RR = 0.950, 95% CI 0.717-1.104, p = 0.000), and brainstem tumors (RR = 2.454, 95% CI 1.791-5.751, p = 0.000) had poorer survival. Tumor volume, age, and adjuvant chemotherapy were not significant predictors of 5-year survival (p > 0.05).

Conclusions. The study found similar death rates in children with pilocytic astrocytoma compared to other population studies. Regrettably, the 5-year survival rate for medulloblastoma and ependymoma indicates a poorer outcome compared to previous reports.

Keywords: pediatric tumor, posterior fossa tumor, surgical treatment, survival.

Introduction

Pediatric posterior fossa tumors (PFT) are a major cause of morbidity and mortality in children and adolescents less than 14 years of age. According to the Central Brain Tumor Registry of the United States (CBTRUS) and the American Cancer Society, PFT of the central nervous system (CNS) is the second leading cause of death in this age group [1–3]. The most common histological type of PFT in children is pilocytic astrocytoma, followed by medulloblastoma, ependymoma, and brainstem glioma [1, 4–15]. Pilocytic astrocytomas alone account for 33.2% of all childhood gliomas. In infants under 1 year of age, gliomas (37.2%) and embryonic tumors (24.9%) are the most frequent types [1, 5, 8, 16–21]. Embryonic PFT are predominantly composed of medulloblastomas (61.9%), atypical teratoid/rhabdoid tumors (ATRT) (15.0%), and primitive neuroectodermal tumors (PNEO) (14.9%). High-grade gliomas are responsible for the greatest number of deaths (43.8%).

PFT are characterized by their rapid growth and the anatomical features of the posterior cranial fossa, which can lead to the rapid onset of symptoms in affected children. Symptoms associated with PFT include headache (31%), vomiting (31%), convulsions (21%), and behavioral changes (11%). At the time

of diagnosis, the most common symptoms observed were headache (51%), vomiting (51%), visual impairment (37%), and seizures (24%) [20, 22]. The timely diagnosis and management of these tumors are critical for improving patient outcomes. Neuroimaging, including CT and MRI, is an essential diagnostic tool for the differential diagnosis of pediatric PFT [23]. Access to accurate and timely neuroimaging data is critical for the timely diagnosis and effective management of these tumors in children.

Despite significant advancements in neuroimaging, surgical techniques, and the development of a multidisciplinary approach to therapy, the survival rate of patients with pediatric PFT remains relatively low due to the aggressive nature of embryonal tumors. The American Cancer Society reports a 5-year survival rate of 74% for children under the age of 14 with CNS tumors and 76% for patients aged 15 to 19 [3]. Despite this, there have been no targeted epidemiological studies conducted on the morbidity and mortality rates of brain tumors, including PFT, in Kazakhstan. In this retrospective study, we aimed to investigate the characteristics of our patient population and report our experience with managing and treating children with PFT, as well as their survival outcomes.

Methods

This retrospective study is based on the archives of the Department of Pediatric Neurosurgery and includes a total of 214 pediatric patients who underwent primary tumor resection for PFT and were included in the study with permission from the Ethics Committee. Inclusion criteria consisted of patients under 18 years of age diagnosed with a PFT after the primary histopathological examination. All patients were admitted to the National Centre for Neurosurgery between January 2015 and December 2020 (Figure 1). This study excluded patients with missing data records, those with secondary tumors (metastases), cranial nerve tumors, and those with tumors located in other areas.

All patients underwent primary tumor resection: gross total resection (GTR) (no residual tumor), subtotal resection (STR) (90% tumor size reduction), partial resection (50–90% tumor size reduction), and biopsy (<50% tumor size reduction). The biopsy specimens from all 214 patients were analyzed and

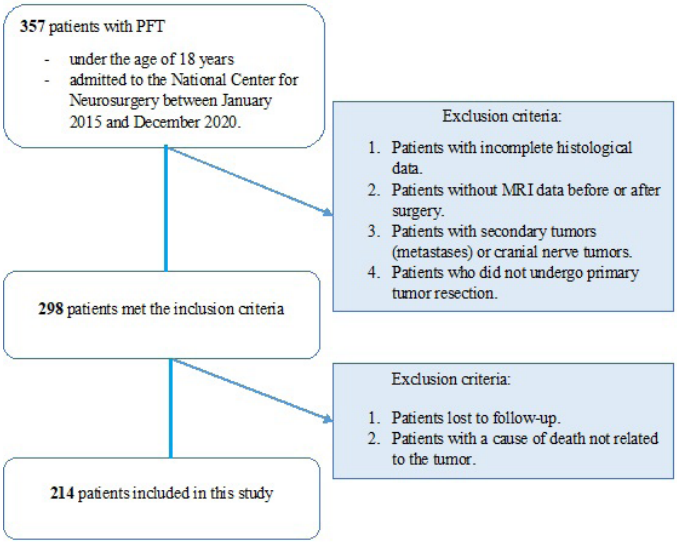

Figure 1 – Types of occluders: A – muscular(symmetric) and B – eccentric(asymmetric)

categorized based on the World Health Organization (WHO) classification of central nervous system tumors for 2007 and 2016. The tumors were classified as either low-grade or high-grade CNS tumors. The extent of resection was assessed through post-operative imaging review in each case.

The study analyzed the post-surgical mortality rate and its correlation with demographic data, clinical characteristics, tumor histology, and the extent of resection. The patients were followed up until September 30th, 2022, which was the date of the last follow-up for surviving patients.

The statistical analysis was performed using the statistical package StataCorp LP (College Station, Texas, 77845, USA). Continuous nonparametric variables are reported as medians (ranges), while categorical variables are reported as numbers and percentages. For categorical data, the Chi-square test was used to evaluate group differences, while the Mann-Whitney U test was used for continuous nonparametric variables. The Kaplan-Meier method was employed to determine overall survival curves. Overall survival was measured from the time of diagnosis to the time of death. Patients without events were censored for PFS at the last follow-up or death. To calculate the hazard ratio and 95% confidence interval for predictors of progression, the Cox proportional hazard model was used, and a p value ≤ 0.05 was considered significant.

Results

From 2015 to 2020, 214 children under the age of 18 underwent primary PFT resection at our clinic. Table 1 displays the patients' characteristics. The median age at diagnosis was 7.29 ± 4.26 years (ranging from 4 months to 17 years). Only six children (2.8%) were infants (less than 1 year of age). Sixty-seven patients (31.31%) were aged between 4 and 7 years, making it the largest proportion within the study population.

Table 1 Patient characteristics (N-214)

Variable		N	%
Age	≤3	50	23.36%
	4-7	67	31.31%
	8-12	57	26.64%
	>13	40	18.69%
Sex	Male	128	59.81%
	Female	86	40.19%
Tumor grade	Grade I	71	33.18%
	Grade II	16	7.48%
	Grade III	38	17.76%
	Grade IV	89	41.59%
Location	Brainstem	25	11.68%
	Cerebellopontine angle	14	6.54%
	Cerebellar hemispere	71	33.18%
	Ventricle+cerebellar vermis	104	48.60%
CSF diversion	Preoperative CSF diversion	147	68.69%
	Intraoperative CSF diversion	3	1.40%
	Postoperative CSF diversion	13	6.07%
	Without CSF diversion	51	28.83%

A significant number of 57 patients (26.64%) were aged between 8 and 12 years. Additionally, the age group comprising patients older than 13 years accounted for 40 individuals (18.69%) of the total participants. Out of the total 214 patients, 128 (59.81%) were male.

Table 2 Clinical Features of Patients with posterior fossa tumors.

Average symptom duration, month	3.78 ± 2.61	
Intracranial hypertension symptoms	192	89.72%
Seizures	10	4.67%
Vision	51	23.83%
Cranial nerves palsy	86	40.19%
Focal weakness	70	32.71%
Cerebellar deficit	176	82.24%

All children were symptomatic, and most had symptoms of intracranial hypertension, such as headache and vomiting (Table 2), which were observed in 192 of 214 children (89.72%). A gait disturbance was present in 176 (82.24%) of the patients. Eighty-six (40.19%) of all cases were associated with cranial nerve palsy, such as strabismus (16.82%), facial nerve palsy (19.16%), hypoacusis (2.80%), and bulbar signs (22.90%). In 23.8% of cases, it was associated with visual impairment. The median time from onset of symptoms to tumor resection was 3.78 ± 2.61 months. In our study, the most prevalent tumor location was the cerebellar vermis and fourth ventricle, accounting for 48.60% of cases. Additionally, the tumor was frequently found in the cerebellar hemisphere in 33.18% of cases. In 25 patients (11.68%), the tumor involved the brainstem, and in 14 cases (6.54%), it was located in the cerebellopontine angle.

Of the 214 children, 87 (40.65%) had CNS WHO low-grade tumors, while 127 (59.24%) were diagnosed with high-grade tumors (Table 3). The most prevalent histologic types were medulloblastoma and pilocytic astrocytoma, which accounted for 33.18% and 32.71% of all cases, respectively, followed by ependymoma (15.42%). The majority of medulloblastoma cases (19.16% of all children) presented as desmoplastic/nodular type. Additionally, 11 incidences (5.14%) of diffuse midline glioma were recorded. Other histologic types in our study include atypical teratoid rhabdoid tumor, pilomyxoid astrocytoma, other high-grade gliomas, and primitive neuro-ectodermal tumor. Of the 214 children, 172 (80.37%) exhibited clinical and radiological findings of hydrocephalus.

Table 3 Histology types of presented tumors

Hystologic types	N=214	%
Pilocytic astrocytoma	71	32.17%
Pilomyxoid Astrocytoma	7	3.27%
Diffuse astrocytoma	6	2.80%
Subependymal giant cell astrocytoma	1	0.47%
Anaplastic Astrocytoma	4	1.87%
Oligoastrocytoma	2	0.93%
Glioblastoma	1	0.47%
Diffuse midline glioma	11	5.14%
Atypical papilloma	1	0.47%
Choriocarcinoma	1	0.47%
Anaplastic ependymoma	33	15.42%
Desmoplastic / nodular medulloblastoma	41	19.16%
Large cell/anaplastic medulloblastoma	4	1.87%
Classic medulloblastoma	14	6.54%
Medulloblastoma NOS	12	5.61%
Atypical teratoid/rhabdoid tumor	3	1.40%
PNET	1	0.47%

Before tumor resection, a total of 147 children (68.69%) underwent hydrocephalus surgery, while 3 patients (1.40%) received CSF diversion surgery at the time of tumor resection. At the time of admission, five patients underwent endoscopic third ventriculostomies (ETV). In most cases, CSF draining operations were performed in regional hospitals before the patients were referred to our clinic. Nevertheless, of the 15 children who received external ventricular drain (EVD) or ETV, 13 had persistent hydrocephalus after tumor resection, requiring the placement of a ventriculoperitoneal shunt (VPS).

All patients underwent primary tumor resection, with subtotal resection (STR) being performed in the majority of cases (77.10%). Gross total resection (GTR) was achieved in 41 children (19.16%). 17 children required a tracheostomy during the postoperative period. After surgery, 120 (56.07%) children received adjunctive radiotherapy, and 131 (61.21%) patients underwent chemotherapy (Table 4).

Table 4 Summary of Patient Characteristics in each Grade group

Treatment	Grade I (N-71)	Grade II (N-16)	Grade III (N-38)	Grade IV (N-89)
Mean age, years (p = 0.018)	8.39±4.14	5.21±3.11	5.69±4.39	7.51±4.17
Average time from onset of symptoms to tumor resection, days (p = 0.000)	144.36 ± 136.52	129 ± 73.75	96.86 ± 91.85	107.25 ± 110.04
Extend of tumor resection (p = 0.000)				
Gross total resection	10 (14.08%)	2 (12.5%)	7 (18.42%)	22 (24.72%)
Subtotal resection	59 (83.1%)	12 (75%)	31 (81.58%)	63 (70.79%)
Partial resection	1 (1.4%)	0	0	3 (3.37%)
Biopsy	1 (1.4%)	2 (12.5%)	0	1 (1.12%)
Intraoperative Blood loss, ml	218.73±120.23	350±310.37	277.02±177.01	267.07± 196.94
Duration of surgery, hours	4.19±1.05	4.62±1.14	4.72±1.34	4.58±1.12
Tracheostomy	3 (4.23%)	1 (6.25%)	5 (13.16%)	8 (8.99%)
Complications				
Neurologic	7 (9.86%)	2 (12.50%)	10 (26.32%)	18 (20.22%)
Non-neurologic	1 (1.41%)	0	1 (2.63%)	6 (6.74%)
Radiotherapy (p = 0.004)	24 (33.8%)	11 (68.75%)	25 (65.79%)	60 (67.42%)
Chemotherapy (p = 0.021)	18 (25.35%)	8 (50%)	30 (78.95%)	75 (84.27%)
Metastasis	2 (2.82%)	2 (12.5%)	0	18 (20.22%)
Tumor progression	8 (11.27%)	4 (25%)	12 (31.58%)	17 (19.1%)

The study included a follow-up period ranging from 21-60 months, during which recurrence or progression was observed in 41 (19.16%) cases, resulting in reoperation for 9 patients. Metastasis was reported in 22 (10.8%) cases. A total of 75 deaths were reported after 60 months from diagnosis.

The study findings reveal distinct survival trends among patients based on tumor grade and histological group. Patients with Grade I tumors demonstrated a notable median survival time of 56.64 months (95% CI, 53.93-59.35 months), surpassing the median survival time of 50.38 months (95% CI, 40.57-60.2 months) observed in patients with Grade II tumors. The median survival time was 38.64 months (95% CI, 31.11-46.17 months) for patients with Grade III tumors, compared with a median survival time of 38.76 months (95% CI, 33.96-43.56 months) for patients with Grade IV tumors. The impact of various risk factors on overall survival rates was analyzed using Kaplan-Meier analyses stratified for each variable (Figure 2).

In the pilocytic astrocytoma group, patients exhibited a median survival time of 56.59 months (95% CI, 53.84-59.34 months), accompanied by an impressive 5-year survival rate of 91.43%. Patients diagnosed with medulloblastoma faced a median survival time of 43.01 months (95% CI, 38.01-48.00 months) and a 5-year survival rate of 56.34%. Within the Anaplastic ependymoma category, the median survival time was 38.13 months (95% CI, 30.03-46.24 months), while the 5-year survival rate stood at 42.42%.

Utilizing a multivariate analysis approach employing the Cox proportional hazards regression model, significant predictors of overall survival emerged. Patients with grade III-IV tumors (RR = 0.577, 95% CI 0.462-0.720, p = 0.000), delayed time to tumor resection (RR = 0.950, 95% CI 0.717-1.104, p = 0.000), and tumors located in the brainstem (RR = 2.454, 95% CI 1.791-5.751, p = 0.000) experienced poorer overall survival rates, as highlighted in Table 5.

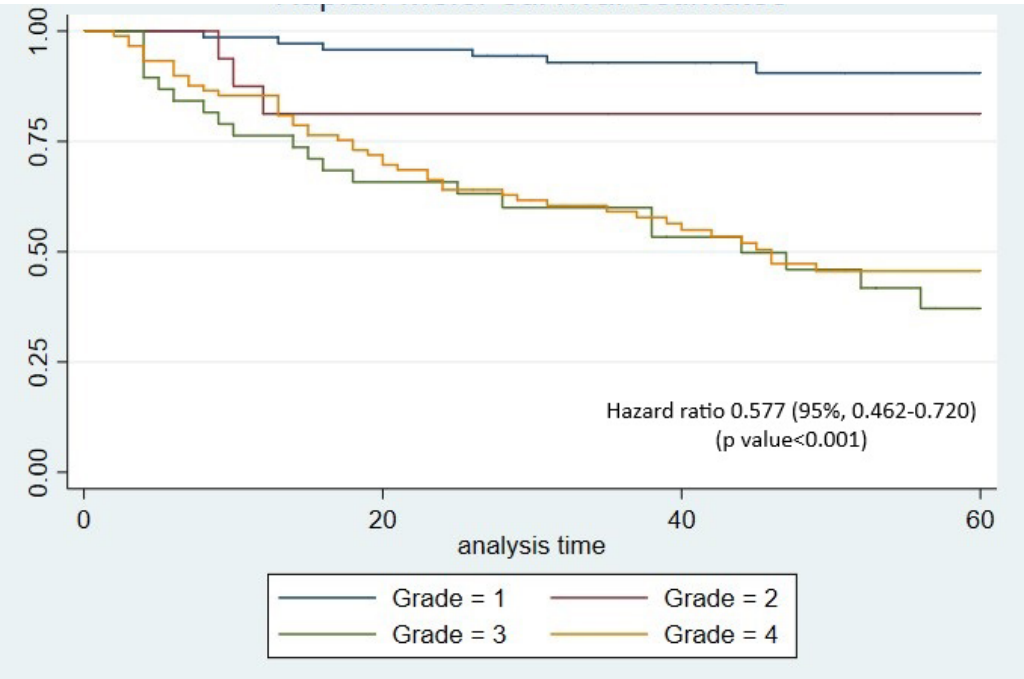

Figure 2 – Kaplan-Meier Survival Estimates

Table 5 Cox regression hazard ratio for poor outcome

	Unadjusted hazard ratio (95% CI)		Adjusted hazard ratio (95% CI)	
Variable	Confidence interval	P value	Confidence inter-val	P value
Tumor volume	0.987(0.973-1.001)	0.079		
Histology	0.577(0.462-0.720)	0.000	0.514(0.406-0.651)	0.000
Pilocytic astrocytoma			0.081(0.031-0.211)	0.000
Medulloblastoma			0.646(0.364-1.148)	0.137
Anaplastic ependy-moma			0.415(0.250-0.581)	0.018
Other			0.585(0.297-1.153)	0.000
Sex	1.816(0.836-2.185)	0.218		
Age	0.933(0.881-0.988)	0.018		
Time to surgery				
(Low-grade/ High-grade)	0.950(0.717-1.104)	0.000		
Radiotherapy	0.792(0.304-0.796)	0.004	0.481(0.297-0.779)	0.003
Chemotherapy	1.824(1.093-3.044)	0.021		
Location-CPA	1.784(1.049-2.903)	0.032	1.714(1.030-2.852)	0.038
Location-brainstem	2.454(1.791-5.751)	0.000	2.549(1.362-4.771)	0.003
Extent of tumor re-section	0.095(0.030-0.300)	0.000	0.098(0.034-0.281)	0.000

The extent of tumor resection demonstrated a substantial impact on overall survival, with a noteworthy relative risk (RR) of 0.098 and a tight 95% confidence interval (CI) of 0.034 to 0.281 ($p < 0.001$). Notably, tumor volume (RR = 0.987, 95% CI 0.973-1.001, p = 0.079), age (RR = 0.933, 95% CI 0.881-0.988, p = 0.018), and adjuvant chemotherapy (RR = 1.824, 95% CI 1.093-3.044, p = 0.021) did not emerge as significant predictors of 5-year survival.

Postoperative neurologic complications were observed in 17.29% of patients, comprising oculomotor nerve palsy (2.33%), facial nerve palsy (0.93%), bulbar sign (3.27%), ataxia (0.46%), limb weakness (3.74%), and Posterior fossa syndrome (0.93%). Non-neurologic complications, predominantly pneumonia, observed in 3.74% cases.

Discussion

Brain tumors account for a significant proportion of cancer cases in Kazakhstan, with an estimated prevalence of 15.7% on average and ranking second in malignant tumors affecting children [24,25]. Despite this, no targeted epidemiological studies have been conducted on the morbidity and mortality rates of brain tumors, including PFT, in Kazakhstan.

To address this gap in knowledge, our study provides a comprehensive analysis of a large cohort of PFT patients, represented by data collected from the National Center of Neurosurgery database, which caters to over 90% of Kazakhstan children with this pathology who receive surgical care. Our study evaluated the demographics, clinical data, histological types, and surgical treatment of children with PFT. To the best of our knowledge, this is the first analysis of the incidence and survival of children with PFT in Kazakhstan.

In our study, the three most prevalent histological types of PFT were pilocytic astrocytomas (32.71%), medulloblastomas (33.17%), and anaplastic ependymomas (15.42%). These findings are consistent with previous studies, indicating that these types of tumors are the most commonly occurring in the posterior fossa [1, 6, 23, 26–29].The prevalence of other tumor types, such as atypical rhabdoid/teratoid tumors, hemangioblastomas, vestibular schwannoma, gangliocytomas of the cerebellum, and meningiomas, was relatively low, accounting for 18–19% of cases.

Several investigators have reported that embryonal tumors are more commonly found in infants [1, 4, 5]. This is consistent with our findings that infants under the age of one have the highest incidence of central nervous system malignancies (6.22 per 100,000) and PFT is the most prevalent tumor in children aged 1-4 years (22.1%), especially in the cerebellum [1, 23, 30].

Our study found that the median age at the time of diagnosis of PFT in children in Kazakhstan was 7.29 ± 4.26 years, which is consistent with previous studies [16, 30, 31]. However, we observed that the median age of children with grade II and grade III tumors was lower, at 5.21 and 5.69 years, respectively. This difference in age may be attributed to the tumor's location and earlier manifestation of hydrocephalus symptoms.

There have been conflicting reports regarding the gender distribution of PFT in children across various studies. In line with the findings of some earlier studies [32], we discovered that there were more male children than female children in our study. Though more female patients with PFT were reported by Picariello et al.[11, 30]. Certain types of PFT have been reported to be more common in either males or females. For example, Ostrom et al. discovered that medulloblastomas and ependymomas are more common in males than in females [1, 9]. Pilocytic astrocytoma, on the other hand, impacts both genders equally [33].

The reasons for these gender distribution differences are unclear and require further investigation. For patients to receive a successful course of treatment, early PFT diagnosis is essential. However, the diagnosis of PFT is frequently difficult because of the early nonspecific clinical signs, particularly in infants. The most typical signs of tumors in the cerebellum are increased intracranial pressure and symptoms of cerebellar dysfunction. The most common clinical signs of PFT in our study, as well as earlier studies, were intracranial hypertension symptoms like headache, vomiting, and vision impairment, as well as anorexia, behavioral abnormalities, irritability, and lethargy [21-22, 30, 34, 35]. A neurologist is consulted because of these symptoms, which are present in about 89.72% of patients. Other clinical manifestations of cranial nerve involvement are less frequent and more prevalent in older kids [23].

The influence of the duration of time between symptom onset and tumor diagnosis on survival prognosis in patients with pediatric brain tumors is a topic of ongoing debate. In our study, the average time from symptom onset to tumor removal was 3.78 ± 2.61 months, which is longer than the 4 weeks reported in a previous study [22]. The longer diagnostic delay in our study may be attributed to the level of knowledge of malignant brain tumors among the general population and healthcare professionals, as well as the availability of diagnostic tools such as CT and MR examinations of the brain.

In our study, an extended diagnostic delay was found to exert a substantial impact on the overall survival of patients. The lack of availability of CT and MR examinations of the brain in many regional centers is a significant challenge that further delays tumor detection in our country. Strategies to improve access to diagnostic tools and increase awareness of malignant brain tumors among healthcare professionals and the general population are needed to facilitate early diagnosis and improve overall survival in patients with pediatric brain tumors.

In our study, the majority of deaths were observed in children under 5 years old, which is consistent with the findings of Aras et al. [20]. This highlights the importance of early detection and timely treatment to improve survival outcomes, particularly in young children who may be more vulnerable to the effects of these tumors.

Previous research has shown that the histological type, tumor size, and location are all important factors in predicting mortality rates for brain tumors [32, 36, 37]. In our study, we found that while tumor size did not significantly affect survival rates (p=0.079), tumors located in the brainstem had a higher mortality rate compared to tumors in the ventricle and cerebellum, consistent with previous findings [1]. This underscores the importance of accurate diagnosis and prompt treatment, especially for tumors in critical brain regions.

Embryonic tumors and ependymomas are known for their aggressive biology and high lethality, despite advancements in diagnosis and treatment [3]. Previous studies have shown a strong correlation between tumor histology and patient outcomes [18, 32, 38, 39]. Surgery and adjuvant therapies, such as chemotherapy and radiation, are the mainstay of treatment for these tumors. Achieving maximum safe resection through surgery is critical for successful treatment, and the extent of resection is directly related to patient outcomes [20, 21, 31, 40-43].

Pilocytic astrocytomas are generally associated with favorable outcomes in pediatric patients. Previous studies have reported 10-year survival rates exceeding 90% [44]. Our analysis of 5-year overall survival rates for pilocytic astrocytomas aligns with these findings, showing a promising 91.43% survival rate. Prior research has indicated that the 10-year overall survival of pediatric ependymoma was around 50 ± 5% [45]. In our study, we observed a 5-year overall survival rate of 42.42%. These results highlight the persistent challenge in achieving favorable outcomes for patients with posterior fossa ependymoma. Long-term survival rates for Medulloblastoma have been reported to be approximately 70-85% [21]. However, our study's 5-year overall survival rate (56.34%) for Medulloblastoma indicates a poorer outcome compared to these previous reports.

The significant effect of postoperative adjuvant radiotherapy on patient survival is also highlighted by our study. However, we were unable to locate any solid proof supporting the necessity of postoperative chemotherapy. Due to this, chemotherapy regimens for ependymomas and embryonic tumors in our country may need to be revised.

Our research emphasizes the value of early detection, aggressive surgical resection, and suitable adjuvant therapy for the treatment of PFT. The results of this study can help clinicians and researchers better understand the clinical and pathological characteristics of PFT in the pediatric population of Kazakhstan. A more thorough and systematic epidemiological analysis of brain tumors in the Kazakh pediatric population is also required, as our study's findings show.

The main limitation of this study is its retrospective design. In addition to survival, the variety of tumors and the limited sample size restricted us from doing a thorough investigation of prognostic factors in this carefully chosen cohort of children. Despite these drawbacks, we offer a large descriptive sample of PFT diagnosed in our country. These findings highlight the necessity of additional study as well as the application of present knowledge and clinical practice.

Conclusion

In this study, we have analyzed data from the National Center of Neurosurgery database, providing insights into pediatric brain tumors, particularly those located in the posterior fossa. Our findings indicate that pilocytic astrocytomas exhibit favorable outcomes, with a 5-year survival rate comparable to data from other population studies. Unfortunately, our study's findings reveal that the 5-year survival rate for medulloblastoma and ependymoma is less favorable when compared to earlier documented reports. These results highlight the need for further research and improved treatment strategies to enhance survival rates for this aggressive tumor. Modern oncology urgently needs to do a systematic epidemiological analysis of the morbidity and mortality from malignant tumors in the Kazakh children's population.

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Statement of Ethics: The Institutional Review Board of the National Center for Neurosurgery reviewed and exempted the study due to the retrospective study design. All participants in this study provided written informed consent prior to accessing their CT, MRI scans or identifying personal characteristics in this study.

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