Surgical Outcome of Pediatric Posterior Fossa Tumors in Shiraz, Southern Iran: A Brief Report

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Abstract

Posterior fossa tumors (PFTs) are prevalent in children, and about half of all childhood brain tumors arise from the structures of the posterior fossa. Studies on PFTs in Iranian children have mainly focused on epidemiological characteristics. This study aimed to evaluate surgical outcomes and predictive factors for survival in children with PFTs in Shiraz, Iran. A prospective cohort study was conducted from March 2014 to September 2019 in Namazi Hospital affiliated with Shiraz University of Medical Sciences (Shiraz, Iran). A total of 87 pediatric patients under the age of 16 who were diagnosed with PFT and had undergone surgery were recruited. The children were followed up for postoperative outcomes such as mortality and neurological complications. Data were analyzed using SPSS software (version 20.0) and R software (version 3.3.1). P<0.05 was considered statistically significant. The mean age of the patients was 6.49±4.14 years and 64.4% were male. Sixteen patients were lost to follow-up, 31 died after surgery, and 40 were in remission during phone calls. The median survival time of the patients was four years. The most common type of PFT was medulloblastoma (n=46, 53%). The result of the multivariate Cox proportional hazards model showed that age (P=0.034) was correlated with postoperative survival, hazard ratio 0.90 (95% confidence interval 0.82 to 0.99). Among various predictive factors, lower age was associated with poor outcomes in pediatric children with PFTs.

Keywords
● Brain neoplasms
● Child
● Medulloblastoma
● Survival rate
● Iran

What’s Known

• Factors affecting surgical outcome and recurrence of different types of pediatric posterior fossa tumors (PFTs) were reported.
• Studies on PFTs in Iranian children have mainly focused on epidemiological characteristics. So far, no prospective results are available.

What’s New

• Over 60% of our pediatric patients recovered from surgery with a median survival time of four years.
• Medulloblastoma, the most common PFT, was present in over 50% of the patients.

Introduction

Posterior fossa tumors (PFTs) are prevalent in children, and about half of all childhood brain tumors arise from the structures of the posterior fossa. Clinical manifestations of brain tumors vary and can be non-specific. The symptoms may appear months before the final diagnosis.1 Surgical treatment of PFTs represents a significant challenge for neurosurgeons, since resection can damage the brainstem and cerebellum. In addition, age-related changes in the physiology of pediatric patients exacerbate the challenge. However, recent advances in medical treatments have improved the outcome for children with PFTs. Factors affecting surgical outcomes and the recurrence of different types of PFTs have been reported.2 However, studies on PFTs in Iranian children have mainly focused on epidemiological characteristics.3
Therefore, the present study aimed to evaluate surgical outcomes and predictive factors for survival in pediatric patients with PFTs.

**Materials and Methods**

A prospective cohort study was conducted from March 2014 to September 2019 in Namazi Hospital, a major referral center for pediatric neurosurgical conditions, affiliated with Shiraz University of Medical Sciences (Shiraz, Iran). The target population was pediatric patients under the age of 16 who were diagnosed with PFTs and had undergone surgery. The exclusion criteria were patients with incomplete records and those with brainstem tumors. The parents of these children were contacted by phone and asked for information about the surgical outcome (recurrence, complications, death) at least six months after surgery. The six months was set as a minimum requirement but was longer in some cases, since the participants were recruited at different time periods. The obtained data included demographic characteristics, the medical history of the patient, the results of the physical examination, and information about the surgery and outcome. The patients whose parents were not available for the interview were also excluded from the study. The study was approved by the Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.MED.REC.1399.118). Verbal consent was obtained from the parents of the patients for their participation in the study and publication of the data.

**Statistical Analysis**

Data were analyzed using SPSS software, version 20.0 (SPSS Inc., Chicago, IL). Initially, univariate analysis, including cross-tabulation and independent samples t test, was used to determine factors associated with deaths and complications. Then, the binary logistic regression (Forward: Wald) of the factors correlated with each recurrence, death, and complication at P<0.20 was fitted. The Kaplan-Meier estimator was utilized to estimate the survival rate in each period. In addition, the R software, version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria) was used to analyze the collected and coded data. To fit the semi-parametric Cox proportional hazards model, the log-rank test of equality across strata was used for categorical data. For continuous variables, a univariate Cox proportional hazard regression was used. A predictor was included if the test had a P<0.2. Variables with statistical significance were used in the multivariate analysis for the final Cox proportional hazards model. The hazard ratio (HR) obtained for each variable was also used to analyze the results. The baseline risk level was set at 1, and HR above or below 1 indicated that the risk level for the study group is greater or smaller than the baseline, respectively. P<0.05 was considered statistically significant.

**Results**

In total, 87 pediatric patients who were diagnosed with PFTs and underwent surgery were included in the study. The baseline characteristics of the patients are presented in table 1.

After the surgical intervention for PFT, 16 (18.4%) patients were lost to follow-up due to the unavailability of phone calls. Of the remaining 71 patients, 31 (43.7%) died after surgery (8 (11.3%) died during their index admission, and 23 (32.4%) after discharge). Of the 31 deceased patients, 5 (7.0%) had tumor recurrence. Moreover, of all patients, 40 (56.3%) were in clinical remission at the time of phone calls. All deaths were related to the disease or treatments. The most common postoperative complication was speech disorder (n=12, 17%).

The results of the univariate analysis showed that sex (P=0.02), headache (P=0.02), chemotherapy (P<0.001), length of intensive care unit stay (P=0.13), and age (P<0.001) were correlated with postoperative complications, whereas other factors did not have any correlation. The results of multiple logistic regression analysis indicated that age (P=0.03, odds ratio [OR]=4.00), chemotherapy (P=0.03, OR=0.22), and headache (P=0.03, OR=3.85) were the predictors of complications after surgery. Furthermore, the results also revealed that headache (P=0.002), failure to thrive (P=0.05), and age (P=0.007) correlated with death, whereas other factors did not have any correlation. The results of multiple logistic regression analysis showed that headache (P=0.02, OR=0.85) and age (P=0.02, OR=3.20) were predictors of deaths after PFT surgery.

As mentioned, 16 (18.4%) patients were lost to follow-up and thus excluded from the final survival assessment. The median survival time of the remaining 71 patients was four years (range: 1 to 7 years) (figure 1), and the mean duration of follow-up was 3.47 years. The 1-, 2-, and 3-year survival rate for these children was 87%, 66%, and 47%, respectively. Medulloblastoma, astrocytoma, ependymoma, and other tumors (most common in pathology reports) accounted for 46 (53%), 21 (24.1%), 16 (18.4%), and 4 (4.5%) of the cases, of which 20, 3, 4, and 4 patients died after surgery, respectively.
The results of the univariate Cox analysis indicated that age, headache, hydrocephalus, and tracheostomy were correlated with postoperative survival rates in our patients (table 2). The multivariate Cox model indicated that age was correlated with postoperative survival: HR 0.90 (95% confidence interval 0.82 to 0.99) (P=0.034).

### Discussion

The present study investigated the life expectancy of pediatric patients diagnosed with PFTs in Southern Iran. In line with the results of a previous study, the median tumor-free survival time of our patients was four years (range: 1-7 years), of which 14 children died under the age of two. Age is an important prognostic indicator of survival rate in PFT patients. However, the results of multiple logistic regression analysis did not reflect such a correlation; probably due to the low sample size. We also found that chemotherapy was not a significant predictor of survival in children with PFTs. Nonetheless, this finding could have been negatively influenced by parents’ decision not to opt for long-course chemoradiotherapy due to its significant economic and psychosocial burden. In this regard, an interdisciplinary approach for Iranian children with PFTs is strongly recommended.

The significance of morbidities after surgery (e.g., executive function deficits) in long-term survivors of PFTs has been recognized as an important issue. In line with a previous study, we found speech disorder in our patients (18%).

### Table 1: Characteristics of pediatric patients with PFTs (n=87)

| Characteristic                     | Median (IQR) or n (%) |
|-----------------------------------|-----------------------|
| Age (years)                       | 6 (2-9)               |
| Number of children in the family  | 2 (2-3)               |
| Ordinal position of the child     | 1 (1-3)               |
| Blood loss during surgery (cc)    | 400 (200-650)         |
| Sex                               |                       |
| Male                              | 56 (64.4)             |
| Female                            | 31 (35.6)             |
| Place of residence                |                       |
| Shiraz                            | 28 (32.2)             |
| Outside Shiraz                    | 59 (67.8)             |
| Symptoms before surgery           |                       |
| Vomiting                          | 55 (63.2)             |
| FTT                               | 2 (2.3)               |
| Weakness                          | 5 (5.7)               |
| Imbalance                         | 39 (44.8)             |
| Spinal cord involvement           | 1 (1.2)               |
| Cranial nerve disorders (except papilledema) | 11 (12.6) |
| Decreased level of consciousness  | 12 (13.8)             |
| Hydrocephalus                     | 68 (78.2)             |
| Involvement of other areas of the brain | 2 (2.4)   |
| Procedures during hospitalization and after discharge | |
| VP shunt                          | 36 (41.4)             |
| Tracheostomy                      | 6 (6.9)               |
| Radiotherapy                      | 45 (51.7)             |
| Chemotherapy                      | 55 (63.2)             |
| Chemoradiotherapy                 | 43 (49)               |

IQR: Interquartile range; FTT: Failure to thrive; VP: Ventriculoperitoneal

### Table 2: The results of univariate Cox analysis in pediatric patients with posterior fossa tumors after surgery

| Variable    | Hazard Ratio | Lower 95% | Upper 95% | P value |
|-------------|--------------|-----------|-----------|---------|
| Age         | 0.88         | 0.80      | 0.98      | 0.019   |
| Headache    | 0.40         | 0.19      | 0.85      | 0.017   |
| Hydrocephalus| 1.40       | 0.99      | 2         | 0.05    |
| Tracheostomy| 3.17         | 1.08      | 9.30      | 0.035   |
as the most prevalent postoperative executive dysfunction. The significance of this disorder will appear once the surviving children reach school age. The results of logistic regression analysis showed that none of the variables were correlated with postoperative complications in our patients. However, the univariate Cox model revealed that age, headache, and tracheostomy had significantly affected the survival rate in these children. Tracheostomy tube placement could be considered one of such morbidities, since it is an inevitable procedure in PFT patients after the removal of the tumor. On the other hand, the univariate Cox model showed that headache, as one of the early symptoms, was significantly related to a poor outcome. A previous study reported that headache is one of the main symptoms of PFTs. However, Kakar and colleagues found that the absence of papilledema, hemiparesis, and meningism is associated with satisfactory surgical outcomes. Therefore, headaches in pediatric patients with a brain tumor should be considered chronic rather than just a generalized non-specific symptom.

Our results showed that an increase in age by one year resulted in a decrease in HR of about 0.1. Indeed, lower age was the only predictor of poor survival in the multivariate Cox model of pediatric PFTs. Based on the type of PFT, age might affect the survival rate. For example, older pediatric patients with medulloblastoma have better prognostic outcomes and those aged under four years with ependymoma have lower progression-free survival. However, a previous study reported that age did not affect the outcome of patients with cerebellar astrocytoma. In the present study, medulloblastoma was the dominant tumor type, which may explain our results on the effect of age on the outcome. Further studies with larger sample size and multicenter trials are required to substantiate our findings. Utilization of recent advances in immunohistochemical methods, especially in medulloblastoma, will provide more evidence about the effect of age on various types of PFTs.

Despite the non-significant results from multiple regression analysis, in line with previous studies, we found that the inclusion of permanent cerebrospinal fluid (CSF) diversion in the univariate regression analysis predicted a poor outcome. The effect might be due to a more severe disease course in patients undergoing permanent CSF diversion. However, in the case of hydrocephalus associated with PFTs, pediatric neurosurgeons consider a transient CSF diversion instead of a permanent ventriculoperitoneal shunt insertion. These findings indicated that severe ventriculomegaly prior to surgery could potentially lead to a poorer outcome.

As confirmed by our neuropathologist, the most common pathological finding was medulloblastoma (grade IV). However, as the main limitation of our study, no methylation profiling was available at our center. In addition, some of the parents were scattered across a large geographical area, which hindered their availability during follow-up. As a direct result, the outcomes were presented annually rather than at the exact time.

### Conclusion

Surgical treatment of PFTs represents a significant challenge for neurosurgeons. Among various predictive factors, lower age was associated with poor outcomes in patients with PFT. A better understanding of the factors affecting surgical outcomes would lead to the most effective treatment methods.

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### Authors’ Contribution

A.R: Study design, interpretation of data, drafting, and critically revision; M.J: Conceptualization, validation, and drafting, and critically revision; F.B: Data acquisition, data analysis, drafting, and critically revision; R.T: Interpretation of data, drafting, and critically revision; A.S: Interpretation of data, validation, and drafting, and critically revision; K.E: Interpretation of data, drafting, and critically revision; SG: Conceptualization, validation, and drafting; All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

### Conflict of Interest:

None declared.

### References

1. Pollack IF, Jakacki RI. Childhood brain tumors: epidemiology, current management.
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and future directions. Nat Rev Neurol. 2011;7:495-506. doi: 10.1038/nrneurol.2011.110. PubMed PMID: 21788981.

2 Tabatabaei SM, Seddighi A, Seddighi AS. Posterior fossa tumor in children. Iranian Journal of Child Neurology. 2012;6:19-24.

3 Rahmanian A, Rakei SM, Mehrabani G. Prevalence of Medulloblastoma in Shiraz, Southern Iran. Middle East Journal of Cancer. 2013;4:135-6.

4 Stensvold E, Myklebust TA, Cappelen J, Due-Tonnesen BJ, Due-Tonnessen P, Kepka A, et al. Children treated for medulloblastoma and supratentorial primitive neuroectodermal tumor in Norway from 1974 through 2013: Unexplainable regional differences in survival. Pediatr Blood Cancer. 2019;66:e27910. doi: 10.1002/pbc.27910. PubMed PMID: 31264356.

5 Palmer SL, Glass JO, Li Y, Ogg R, Qaddoumi I, Armstrong GT, et al. White matter integrity is associated with cognitive processing in patients treated for a posterior fossa brain tumor. Neuro Oncol. 2012;14:1185-93. doi: 10.1093/neo/ncs335. PubMed PMID: 22898373; PubMed Central PMCID: PMC3424215.

6 Zali A, Farzan A, Ramandi M. Prevalence of Childhood Brain Tumors at MOPHID hospital in Tehran (1996-2002). Journal of Medical Council. 2006;24:119-22. Persian.

7 Kakar J, Ashraf J, Khan AA, Imran M, Rehmani MA, Ghorii SA, et al. The Satisfactory Surgical Outcome of Posterior Fossa Brain Tumors in Children at Civil Hospital, Karachi. Asian J Neurosurg. 2020;15:377-81. doi: 10.4103/ajns.AJNS_56_19. PubMed PMID: 32656135; PubMed Central PMCID: PMCPMC7335127.

8 Lanphear J, Sarnaik S. Presenting symptoms of pediatric brain tumors diagnosed in the emergency department. Pediatr Emerg Care. 2014;30:77-80. doi: 10.1097/PEC.0000000000000074. PubMed PMID: 24457493.

9 Jenkin D, Shabanah MA, Shail EA, Gray A, Hassounah M, Khafaga Y, et al. Prognostic factors for medulloblastoma. Int J Radiat Oncol Biol Phys. 2000;47:573-84. doi: 10.1016/s0360-3016(00)00431-4. PubMed PMID: 10837938.

10 Figarella-Branger D, Civatte M, Bouvier-Labit C, Gouvernet J, Gambarelli D, Gentet JC, et al. Prognostic factors in intracranial ependymomas in children. J Neurosurg. 2000;93:605-13. doi: 10.3171/jns.2000.93.4.0605. PubMed PMID: 11014538.

11 Desai KI, Nadkarni TD, Muzumdar DP, Goel A. Prognostic factors for cerebellar astrocytomas in children: a study of 102 cases. Pediatr Neurosurg. 2001;35:311-7. doi: 10.1159/000050443. PubMed PMID: 11786699.

12 Butt B, Sheik MM, Anwar H, Chudary MA, Butt RM. Six months Analysis of Posterior Fossa Surgery in Neurosurgery Unit-I, Punjab Institute of Neurosciences (PINS). Pakistan Journal of Neurological Surgery. 2018;22:7-16.