Pineoblastoma: prognostic factors and survival outcomes in young children

Boran Chen, Yanjie Zhao, Chaoyue Chen

Department of Neurosurgery, West China Hospital of Sichuan University, Chengdu, Sichuan 610041, China.

To the Editor: Pineoblastoma (PB) is a rare embryonal tumor of pineal parenchymal origin, which is a World Health Organization grade IV lesion frequently diagnosed in children and adolescents. A literature-based study revealed that patients aged ≤5 years have a worse prognosis compared with patients aged >5 years (5-year survival rate: 15% *vs.* 57%, $P < 0.001$).[1] Thus, younger children and older children with PB should be treated separately. Maximal safe surgical resection followed by craniospinal irradiation and chemotherapy is recommended for the treatment of PB, and treatment protocols are highly age dependent. Abdelbaki *et al*[2] reviewed 23 patients aged <6 years in the Head Start I–III trials and found that craniospinal irradiation and high-dose induction chemotherapy followed by marrow-ablative chemotherapy and autologous hematopoietic cell rescue (HDCx/AuHCR) were associated with better survival. Several population-based studies have evaluated the prognostic factors in pediatric and adult patients using data from the Surveillance, Epidemiology, and End Results (SEER) database. Selvanathan *et al*[3,4] included pediatric patients and adult patients between 1990 and 2007 from the SEER database; their results showed that older age was the only positive prognostic factor for pediatric patients, and younger age and localized disease were associated with improved survival in adult patients. Given the rarity of PB, the poor prognosis of young children with PB and the paucity of studies specific to young children with PB, we aimed to determine the prognostic factors and survival outcome of PB patients aged ≤5 years using data from the SEER database.

We derived data from the SEER 18 Registry database between 1975 and 2016. Data in the SEER database are free to the public, so ethics approval and informed consent are not required.

In this study, we included patients aged ≤5 years with a first and primary diagnosis of PB, according to the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) – Histology Code 9362/3. Patients without a histologically confirmed diagnosis of PB or active follow-up were excluded. We obtained the following variables from the SEER database: age at diagnosis (patients aged <1 year were assigned to the infant group, and those aged ≥1 year were assigned to the children group), sex, race (white, black, or other [American Indian/Alaskan Native, or Asian/Pacific Islander]), tumor size (<30 mm or ≥30 mm), metastasis status (yes or no), the extent of resection (biopsy, subtotal resection, or gross total resection), and therapy mode (both radiotherapy and chemotherapy, radiotherapy only, chemotherapy only, or neither).

The outcomes of interest were overall survival (OS) and disease-specific survival (DSS). OS was defined as the time from diagnosis to death of any cause, and DSS was defined as the time from diagnosis to death due to PB. We performed the Kaplan–Meier curve analysis to estimate the OS and DSS and assessed the significance of the intergroup difference with log-rank tests. The univariate Cox proportional-hazard regression model was used to assess the prognostic value of each variable. To identify the independent prognostic factors of OS and DSS, variables that were significantly associated with OS or DSS in the univariable Cox regression model were then analyzed in the multivariate Cox regression model. Hazard ratio (HR) and the corresponding 95% confidence interval (CI) were calculated in the univariate and multivariate Cox regression models. The nomograms to predict 1-year, 3-year, and 5-year OS and DSS rates were developed based on the independent prognostic factors. The developed nomograms were then calibrated with bootstrap resampling repeated 1000 times by assessing Harrell's concordance index (C-index) and calibration curve, which depicts the comparison between predicted survival and observed survival. Statistical significance was set at a *P* value of < 0.05. All the analyses were conducted

Access this article online

Quick Response Code:

Website:
www.cmj.org

DOI:
10.1097/CM9.0000000000002063

using Stata (version 15.1, Stata Corp., College Station, TX, USA) and packages of RMS, survival, and survminer in the R program (version 3.6.3, http://www.r-project.org/).

We identified 424 PB patients from the SEER 18 Registry database between 1975 and 2016. Overall, 78 patients with a diagnosis of PB aged <5 years were included in the study [Supplementary Figure 1, http://links.lww.com/CM9/A984]. The baseline characteristics of the patients are presented in Supplementary Table 1, http://links.lww.com/CM9/A984.

Kaplan–Meier curves were plotted to illustrate OS and DSS of all patients, shown in Supplementary Figures 2A and 3A, http://links.lww.com/CM9/A984. Among the patients who were dead during follow-up, five had an unknown cause of death. These patients were excluded from the analyses of DSS. The median OS of all patients was 24 (95% CI, 13–35) months, and the median DSS of all patients was 26 (95% CI, 12–40) months. The 1-year, 3-year, and 5-year OS rates were 67.6% (95% CI, 55.7–77.0%), 41.3% (95% CI, 29.8–52.5%), and 36.6% (95% CI, 25.4–47.8%), respectively. The 1-year, 3-year, and 5-year DSS rates were 71.0% (95% CI, 58.7–80.2%), 43.7% (95% CI, 31.4–55.4%), and 38.5% (95% CI, 26.6–50.3%), respectively. We used the Kaplan–Meier method with log-rank tests to compare the OS and DSS values in subgroups of patients stratified by age, sex, race, tumor size, metastasis status, the extent of resection, radiotherapy, and chemotherapy. Results of log-rank tests revealed that patients of different ages had significantly different OS ($P < 0.001$; Supplementary Figure 2B, http://links.lww.com/CM9/A984) and DSS ($P < 0.001$; Supplementary Figure 3B, http://links.lww.com/CM9/A984). Radiotherapy and chemotherapy were potential prognostic factors for both OS ($P < 0.001$; Supplementary Figure 2H and 2I, http://links.lww.com/CM9/A984) and DSS ($P < 0.001$; Supplementary Figure 3H and 3I, http://links.lww.com/CM9/A984), whereas the significance were not shown when patients were stratified by other variables [Supplementary Figures 2C-G and 3C-G, http://links.lww.com/CM9/A984].

Univariate Cox proportional-hazard analysis was conducted to identify the important prognostic factors associated with OS and DSS. As shown in Table 1 and Supplementary Table 2, http://links.lww.com/CM9/A984, patients aged 2 years and older had better OS ($P = 0.002$) and DSS ($P < 0.001$) compared with patients aged < 1 year. The results of univariate Cox analysis revealed that radiotherapy and chemotherapy were both favorable prognostic factors for OS (radiotherapy: HR, 0.321, 95% CI, 0.170–0.608, $P < 0.001$; chemotherapy: HR, 0.412, 95% CI, 0.203–0.835, $P = 0.014$) and DSS (radiotherapy: HR, 0.301, 95% CI, 0.154–0.587, $P < 0.001$; chemotherapy: HR, 0.369, 95% CI, 0.180–0.758, $P = 0.007$). Age at diagnosis, radiotherapy, and chemotherapy were then fed into multivariate Cox analysis. Age at diagnosis was an independent prognostic factor for OS ($P = 0.018$) and DSS ($P < 0.001$) in the multivariate Cox analysis. Similar to the univariate Cox analysis, radiotherapy and chemotherapy were independent favorable prognostic factors for OS (radiotherapy: HR, 0.407, 95% CI, 0.206–0.805, $P = 0.010$; chemotherapy: HR, 0.311, 95% CI, 0.144–0.671, $P = 0.003$) and DSS (radiotherapy: HR, 0.395, 95% CI, 0.191–0.814, $P = 0.012$; chemotherapy: HR, 0.272, 95% CI, 0.123–0.600, $P = 0.001$) in the multivariate Cox analysis.

The independent prognostic factors identified by the univariate and multivariate Cox proportional-hazard analyses were integrated to develop the nomogram to predict 1-year, 3-year, and 5-year OS and DSS. In the nomogram, the score of each variable is the projection of the value of each variable onto the points scale, and the total points are the sum of the scores of the three variables. The total points are then projected onto the OS or DSS scales to obtain the predicted 1-year, 3-year, and 5-year OS or DSS of each individual [Supplementary Figure 4A and 4B, http://links.lww.com/CM9/A984]. The C-indexes of OS (0.785, 95% CI, 0.722–0.849) and DSS (0.812, 95% CI, 0.753–0.872) indicated that the two nomograms were of acceptable calibration. The calibration curves showed that the predicted 1-year, 3-year, and 5-year OS and DSS were generally in agreement with the actual OS

Table 1: Multivariate Cox proportional-hazard models for OS and DSS.

Variables	OS		DSS	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (years)		0.018		<0.001
<1	Reference		Reference	
1	0.903 (0.345–2.358)	0.834	0.404 (0.144–1.129)	0.084
2	0.307 (0.115–0.817)	0.018	0.122 (0.041–0.362)	<0.001
3	0.373 (0.145–0.957)	0.040	0.136 (0.046–0.405)	<0.001
4	0.171 (0.042–0.694)	0.014	0.074 (0.017–0.318)	<0.001
5	0.228 (0.078–0.666)	0.007	0.099 (0.031–0.316)	<0.001
Radiotherapy				
No	Reference		Reference	
Yes	0.407 (0.206–0.805)	0.010	0.395 (0.191–0.814)	0.012
Chemotherapy				
No	Reference		Reference	
Yes	0.311 (0.144–0.671)	0.003	0.272 (0.123–0.600)	0.001

CI: Confidence interval; DSS: Disease-specific survival; HR: Hazard ratio; OS: Overall survival.

and DSS [Supplementary Figure 4C and 4D, http://links.lww.com/CM9/A984].

It is better not to mix younger patients (aged ≤5 years) and older patients (aged ≥5 years) because this heterogeneity of age may alter the variability of treatment response and reduce the likelihood of demonstrating treatment benefit.[1] Our results showed that age, radiotherapy, and chemotherapy were independent prognostic factors in young children (age ≤5 years), whereas the extent of resection, tumor size, and metastasis status were not associated with survival, neither in the univariate analysis nor in the multivariate analysis.

Age at diagnosis was the strongest prognostic factor, and several studies revealed that younger children (age <5 years or 6 years) had a significantly lower survival rate compared with older children.[2,4,5] In our study of patients aged ≤5 years, we further stratified patients by single age and found that patients aged <1 year had worse survival outcomes compared with patients aged ≥2 years. Of note, 37 out of 54 patients aged ≥2 years received radiotherapy, and 2 out of 11 patients aged <1 year received radiotherapy. Patients aged ≥2 years were more likely to receive radiotherapy than patients aged <1 year (odds ratio: 9.79, 95% CI: 1.70–98.94, $P = 0.0019$). Radiotherapy was not recommended for infants due to the deleterious effects of radiotherapy on developing brains. The low treatment rate of radiotherapy may partially explain the poor survival of infants with PB.

Our results of the role of radiotherapy in the treatment of young children with PB suggested that PB in young children is radiosensitive. However, evidence from the literature is controversial. Results of the study by Mynarek et al[5] indicated that there were potential benefits of radiotherapy for OS in patients aged <4 years (HR: 0.605, 95% CI: 0.283–1.290, $P = 0.193$). Abdelbaki et al[2] found that radiation was an independent prognostic factor for OS in young children (HR: 0.06, 95% CI: 0.01–0.34, $P = 0.0014$), whereas not for progression-free survival (PFS) (HR: 0.40, 95% CI: 0.14–1.15, $P = 0.09$). Results of the HIT 88/89 and HIT 91 trials revealed that dose and volume of radiation had a significant impact on survival and suggested local doses of at least 54 Gy and craniospinal doses of at least 35 Gy.[6]

The efficacy of chemotherapy was also controversial. Abdelbaki et al[2] demonstrated the benefit of HDCx/AuHCR on both PFS and OS, whereas Jin et al[7] claimed no benefit of chemotherapy. In our study cohort, most (83.3%) patients received chemotherapy, and chemotherapy was significantly associated with improved OS (HR: 0.311, 95% CI: 0.144–0.671, $P = 0.003$) and DSS (HR: 0.272, 95% CI: 0.123–0.600, $P = 0.001$).

This study has several limitations that should be acknowledged. First, this is a retrospective study with inevitable selection bias, which is a common limitation in studies using data from the SEER database. Second, there is a lack of doses of radiotherapy and specific regimens of chemotherapy in the SEER database, which restricted further analysis. Third, molecular information that may affect the survival of PB patients was not recorded in the SEER database.

In conclusion, the results of our study suggest that age at diagnosis, radiotherapy, and chemotherapy are independent prognostic factors of OS and DSS for PB patients aged ≤ 5 years. We developed two nomograms with acceptable calibration to make individualized predictions of OS and DSS. The optimal doses of radiotherapy and regimens of chemotherapy need further research.

Conflicts of interest

None.

References

1. Tate M, Sughrue ME, Rutkowski MJ, Kane AJ, Aranda D, McClinton L, et al. The long-term postsurgical prognosis of patients with pineoblastoma. Cancer 2012;118:173–179. doi: 10.1002/cncr.26300.
2. Abdelbaki MS, Abu-Arja MH, Davidson TB, Fangusaro JR, Stanek JR, Dunkel IJ, et al. Pineoblastoma in children less than six years of age: the head start I, II, and III experience. Pediatr Blood Cancer 2020;67:e28252. doi: 10.1002/pbc.28252.
3. Selvanathan SK, Hammouche S, Smethurst W, Salminen HJ, Jenkinson MD. Outcome and prognostic features in adult pineoblastomas: analysis of cases from the SEER database. Acta Neurochir (Wien) 2012;154:863–869. doi: 10.1007/s00701-012-1330-4.
4. Selvanathan SK, Richards O, Alli S, Elliott M, Tyagi AK, Chumas PD. Outcome and prognostic features in paediatric pineoblastomas: analysis of cases from the surveillance, epidemiology, and end results registry (1990-2007). Acta Neurochir (Wien) 2019;161:1799–1807. doi: 10.1007/s00701-019-03909-1.
5. Mynarek M, Pizer B, Dufour C, van Vuurden D, Garami M, Massimino M, et al. Evaluation of age-dependent treatment strategies for children and young adults with pineoblastoma: analysis of pooled European Society for Paediatric Oncology (SIOP-E) and US head start data. Neuro Oncol 2017;19:576–585. doi: 10.1093/neuonc/now234.
6. Timmermann B, Kortmann RD, Kühl J, Meisner C, Dieckmann K, Pietsch T, et al. Role of radiotherapy in the treatment of supratentorial primitive neuroectodermal tumors in childhood: results of the prospective German brain tumor trials HIT 88/89 and 91. J Clin Oncol 2002;20:842–849. doi: 10.1200/jco.2002.20.3.842.
7. Jin MC, Prolo LM, Wu A, Azad TD, Shi S, Rodrigues AJ, et al. Patterns of care and age-specific impact of extent of resection and adjuvant radiotherapy in pediatric pineoblastoma. Neurosurgery 2020;86:E426–E435. doi: 10.1093/neuros/nyaa023.