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# Characteristics, survival and incidence rates and trends of pilocytic astrocytoma in children in the United States; SEER-based analysis

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ABSTRACT

*Introduction:* Pilocytic astrocytoma (PA) is a neurological neoplasm and a common neurological tumor among children. No recent reports have studied the recent demographic characteristics of PA cases in the US.
*Methodology:* We used the Surveillance, Epidemiology, and End Results (SEER) Program to retrieve data on children diagnosed with PA between 2000 and 2015. We calculated the incidence, annual percentage changes (APC), and survival.
*Results:* Our study included 3084 children with PA, with an incidence of 8.227 per 1,000,000 person-years, being highest among whites (9.062), and children aged 1–4 year (11.175). Overall incidence in children increased significantly over the study period, with an APC of 0.825% (95% CI[0.027–1.630], $P = .044$). Moreover, incidence among blacks increased significantly over the study period (APC = 3.466%, 95% CI[0.342–6.688], $P = .032$), but did not change among other races. The relative 5-year survival of included patients was 95.3%, with patients younger than 1 year having the worst survival.
*Conclusions:* Overall PA incidence and incidence among blacks has been increasing last decade. Additionally, PA survival was found to be worse among infants. Further studies are also needed to investigate the effect of the age and race on the incidence and survival of PA.

## 1. Introduction

Pilocytic astrocytoma (PA) is a neurological neoplasm that represents 20% of total central nervous system (CNS) tumors among children [1]. It is predominantly seen in the pediatric population and considered the most common brain tumor in children aged between 5 and 14 years, and the second most common between 0 and 4 years. However, it uncommonly affects the adolescent and adult populations [2–5]. The Central Brain Tumor Registry of the United States (CBTRUS) reported the incidence of PA in the United States to be 2.9 per million [6]. Increasing incidence trends have been reported during the last decades in the USA and in Europe [7–11].

While most PA cases are classified as WHO grade 1, histologically anaplastic PA are classified as WHO grade 3 tumors [12]. Pilomyxoid astrocytomas have a worse prognosis and have recently been distinguished from PA by many histological features [13] [14].

PA is known to have a relatively benign clinical course and an excellent prognosis, with a 5-year survival of 80–90%. They are mostly cured by total surgical resection, with 75% progression-free survival rate and 95.8% overall survival after 10 years [15]. Tumor-specific characteristics, like the percentage of resection, location, and pathologic features have been reported to influence the prognosis of PA after resection [16]. While radiation therapy is usually preserved for the cases of recurrent or progressive tumors where the option of additional surgery is not possible [17].

Over the last decade, only a few reports have studied the characteristics and survival in Pas in children and infants in the US. During the last 7 years, a few studies have reported the incidence and survival of PAs patient in adults, but none have focused on the incidence of PA in children and infants.

Continuous observation of patterns of such diseases on populations level is essential as it helps scientists assess the delivery of healthcare and improve our understanding of diseases [18]. In this study, we aim to provide an in-depth assessment and analysis of the distribution, trends in the incidence, and survival (overall and PA-specific) of this tumor using a large patients' cohort that covers the period from 2000 to 2015.

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## 2. Methods

### 2.1. Study design

We did a retrospective cohort that follows the guidelines of the STROBE checklist [19].

### 2.2. Data source

We got a permission from the National Cancer Institute (NCI) to use the Surveillance, Epidemiology, and End Results (SEER) database and access the incidence-SEER 18 registries. These registries cover up to 27.8% of the general population in the US between the years 2000 and 2015 [20]. Data obtained from the SEER program is anonymized. Therefore, it is waived from IRB approval.

### 2.3. Study population

We included PA cases that were diagnosed in patients aged < 20 years between 2000 and 2015. 'Histology recode - Brain grouping: Pilocytic astrocytoma' variable was used to make this selection. This SEER variable is based on the international classification of the disease (ICD-O-3/WHO 2008 Definition). We excluded cases with diagnosis based only on autopsy or death certificates (cases without pathological confirmation), as well as cases with unknown age at diagnosis.

Within included patients, we looked into the following variables: sex, age at diagnosis of pilocytic astrocytoma, race, state, survival months, current vital status, cause of death, association with other malignancies, and site of malignancy (using primary site variable).

### 2.4. Outcomes

We calculated PA incidence rates in individuals younger than 20 years between 2000 and 2015. We adjusted rates to the US standard population and expressed them by 1,000,000 person-years. Overall incidence rates and incidence rates according to demographic factors and tumor-related factors were calculated. Then, we calculated the Annual Percentage Changes (APCs), which represented the change of incidence between the years 2000 and 2015.

We also measured overall survival and PA-specific survival. Survival was measured as the period in months between the date of diagnosis and the date of death. Patients were followed until the date of death, or they were censored by the end of 2015. In the case of PA-specific survival, patients were censored if they died because of any cause other than pilocytic astrocytoma.

### 2.5. Statistical analysis

We used SEER*stat software to access and extract the data and calculate incidence rates and relative 5-year survival [21]. We used the Joinpoint Regression software to calculate APCs. The Joinpoint Regression program uses (t) tests to detect statistical significance of APCs [18]. We used IBM SPSS 23 software to perform multivariable covariate-adjusted Cox models, in which we adjusted for sex, age at diagnosis, and race. All statistical tests we performed were two-sided, and a $P$ value of < .05 was considered statistically significant.

## 3. Results

### 3.1. Baseline characteristics

Our study included 3084 pilocytic astrocytoma patients younger than 20 years old and diagnosed between 2000 and 2015. Baseline characteristics are summarized in Table 1. The mean age at diagnosis was 8.54 years, with a standard deviation of 5.388. Most patients were whites (81.32%) and were in California (39.81%). About 3.15% of cases had other primary malignancies. The most common site for pilocytic astrocytoma was the cerebellum (36.22%).

**Table 1**
Baseline characteristics and incidence rates of pediatrics pilocytic astrocytoma cases ($n$ = 3084).

| | *N* (%) | Rate[a] (95% CI)[b] |
|---|---|---|
| Total | 3084 (100) | 8.227 (7.939–8.523) |
| Association with other malignancies | | |
| One primary malignancy only | 2987 (96.8) | 7.969 (7.686–8.260) |
| Associated with other primary malignancies | 97 (3.15) | 0.258 (0.209–0.315) |
| Sex | | |
| Male | 1575 (51.07) | 8.203 (7.803–8.619) |
| Female | 1509 (48.92) | 8.251 (7.840–8.679) |
| Age at diagnosis | | |
| < 1 year | 97 (3.15) | 5.268 (4.272–6.426) |
| 1–4 years | 817 (26.50) | 11.175 (10.421–11.968) |
| 5–9 years | 863 (28) | 9.366 (8.752–10.013) |
| 10–14 years | 763 (24.74) | 7.965 (7.410–8.550) |
| 15–19 years | 544 (17.64) | 5.656 (5.191–6.152) |
| Race | | |
| White | 2508 (81.32) | 9.062 (8.711–9.424) |
| Black | 325 (10.54) | 5.825 (5.209–6.495) |
| American Indian/Alaska native | 25 (0.81) | 3.412 (2.208–5.044) |
| Asian or Pacific Islander | 159 (5.16) | 4.543 (3.864–5.308) |
| State | | |
| California | 1228 (39.81) | 7.439 (7.029–7.867) |
| Connecticut | 145 (4.7) | 9.928 (8.376–11.693) |
| Georgia | 374 (12.13) | 8.762 (7.896–9.697) |
| Hawaii | 31(1) | 5.826 (3.958–8.280) |
| Iowa | 137 (4.44) | 10.505 (8.819–12.424) |
| Kentucky | 185 (6) | 10.281 (8.852–11.875) |
| Louisiana | 153 (4.96) | 7.779 (6.595–9.116) |
| Michigan | 133 (4.31) | 7.687 (6.436–9.114) |
| New Jersey | 292 (9.47) | 7.968 (7.080–8.937) |
| New Mexico | 56 (1.82) | 6.181 (4.668–8.033) |
| Utah | 148 (4.8) | 10.154 (8.581–11.937) |
| Washington | 196 (6.36) | 10.835 (9.371–12.465) |
| Alaska | 6 (0.19) | 8.001 (2.935–17.560) |
| Site of malignancy | | |
| Cerebrum | 245 (7.94) | |
| Frontal lobe | 89 (2.89) | |
| Temporal lobe | 131 (4.25) | |
| Parietal lobe | 61 (1.98) | |
| Occipital lobe | 31 (1) | |
| Ventricles | 155 (5.03) | |
| Cerebellum | 1117 (36.22) | |
| Brain stem | 334 (10.83) | |
| Overlapping lesions in the brain | 82 (2.66) | |
| Unknown in the brain | 489 (15.86) | |
| Spinal cord | 118 (3.83) | |
| Optic nerve | 218 (7.06) | |

[a] Rates were calculated as number of cases per 1,000,000 person-years and age adjusted to the 2000 US standard population.
[b] 95% confidence interval.

### 3.2. Incidence rates and trends of pilocytic astrocytoma in children

The incidence of pilocytic astrocytoma in patients younger than 20 years was 8.227 per 1,000,000 person-years (95% CI, 7.939–8.523) (Table 1). This incidence was highest among in whites (9.062), and children aged 1–4 years (11.175). The highest incidence was in the states of Washington (10.853), Iowa (10.505), Kentucky (10.281), and Utah (10.154), whereas Hawaii was the state with lowest incidence rates (5.826).

Overall incidence of pilocytic astrocytoma in patients younger than 20 years increased significantly over the study period, with an APC of 0.825% (95% CI [0.027–1.630], $P = .044$). However, the incidence among both sexes did not significantly change over the study period; APC = 0.837% (95% CI [−0.440–2.131], $P = .182$), and APC = 0.849% (95% CI [−0.371–2.085], $P = .158$), for males and females, respectively. Incidence among blacks increased significantly over the study period (APC = 3.466%, 95% CI [0.342–6.688], $P = .032$), but did not change among other races. Incidence of pilocytic astrocytoma increased significantly over the study period in children aged between 15 and 19 years (APC = 1.726%, 95% CI [0.228–3.246], $P = .027$), but did not significantly change in other age groups.

### 3.3. Survival and prognostic factors of pilocytic astrocytoma in children

The relative 5-year survival of children with pilocytic astrocytoma was 95.3%. After adjustment for age, sex, race, cox models showed no significant difference in both overall and PA-specific survival between sexes and races. However, diagnosis of pilocytic astrocytoma at less than 1 year of age, was associated with significantly worse overall and PA-specific survival outcomes (HR = 3.830, 95% CI [2.074–7.072], $P < .001$, and HR = 4.843, 95% CI [2.436–9.629], $P < .001$, respectively) (Table 2).

## 4. Discussion

In this report, we identified 3084 cases with histologically-confirmed pilocytic astrocytoma, diagnosed between 2000 and 2015. Our analysis showed a significant increase in the overall incidence of PA over the study period, and in the incidence of PA in blacks. Moreover, it showed that a diagnosis of PA in an age younger than 1 year was associated with significantly worse overall and PA-specific survival outcomes.

We found the incidence of PA to be higher in white patients with no difference between males and females. In a previous population-based study conducted on adult patients in the United States in 2011; the incidence of PA was higher in non-Hispanic White patients than other ethnic groups. While the incidence rate of PA was found to be higher in male patients, there was no difference in the incidence between males and post-menopausal females [22]. The lack of difference between males and females before puberty and in the post-menopausal age may suggest an effect of hormones on the incidence of PA [22,23]. As our study focuses on the population of children and neonates, we were not able to test such a hypothesis. Although this hypothesis was further investigated in a study in 2011, where there was no statistically significant difference between male/female RR for peri- and post-menopausal ages and this for only pre-menopausal ages [22].

The most common site for PA in our sample was in the cerebellum, followed by the frontal lobe, the temporal lobe, and the partial lobe. A previous population-based study in 2016, found similar results after analyzing and comparing the data of patients in the United States and 12 countries in the Southern and Eastern Europe, and more than one third of cases diagnosed with PA were located in the cerebellum, except for infants; where most of the PA was located in the supratentorial and optic nerve area [24]. Similarly, in 2003 a study in Switzerland found that PA developed most frequently in the cerebellum (42%) and supratentorial structures (36%) [15]. Some studies have suggested a correlation between the age and the site of the tumor, where the majority of PAs in children were usually located in the cerebellum, those in adult are mostly located in the supra-tentorial area, while in infants where PAs of the supratentorial area and optic nerve were predominant with a lower proportion of cerebellar tumors [15,25–27]. Interestingly, previous studies have found cerebellar PAs to have better survival outcomes than other non-cerebellar PAs (10-year survival exceeding 99%) [16,25,28], this was explained as cerebellar tumors are mostly treated by gross or total resection, and this allows a greater percentage of tumor to be resected which lead to better prognosis and higher possibility of cure, and cause less possible neurological deficits [29–33].

We report that the overall incidence of PA in children was 8.22 per million per year, the incidence in children aged 1–4 years was significantly higher than other age groups. These incidence rates are similar to previous ones in Switzerland, and the UK in 2009, and 2003 respectively [15,34]. However, when analyzing the data from the European SEE database, PA incidence was lower in this age group. This could be due to the late detection of the tumors; meaning that the tumor might develop during the childhood period, but discovered and diagnosed at later age leading to this disparity [25]. Another possible explanation could be the underreporting and flows in the registration system; PA is considered a treatable tumor, and usually not managed within oncology clinics and centers [25].

We noticed a significant increase in PA incidence since 2000 in black children. While there are no previous studies on the effect of the race/ethnicity on the incidence of PA specifically, many papers studied the relation between race and incidence/survival of neurological tumor in general and found blacks to have higher risk and worse survival of deferent neurological malignancies [35,36]. The association between the race and the incidence of PAs was explained by many theories and hypothesis, a previous article in 2006 suggested that this could be related to differences in the histological classification of brain tumors between different races [37]. Other theory explained this difference by the interaction between the higher prevalence of AIDS/HIV infection among black populations and the CNS tumors [38,39]. Other

**Table 2**
Multivariable covariate-adjusted Cox models for overall and PA-specific survival with adjustment for the following factors: age at diagnosis of pilocytic astrocytoma, sex, and race.

| Patient characteristics | All-cause HR[a] (95% CI)[b] | All-cause P[‡] | PA-specific HR[a] (95% CI)[b] | PA-specific P[‡] |
|---|---|---|---|---|
| Age (vs. 15–19 years) | | | | |
| 10–14 years | 0.684 (0.399–1.174) | .168 | 0.630 (0.324–1.223) | .172 |
| 5–9 years | 0.742 (0.442–1.245) | .258 | 0.876 (0.480–1.598) | .665 |
| 1–4 years | 0.552 (0.315–0.969) | .039 | 0.739 (0.394–1.389) | .348 |
| < 1 year | 3.830 (2.074–7.072) | < .001 | 4.843 (2.436–9.629) | < .001 |
| Sex (vs. Male) | | | | |
| Female | 1.105 (0.777–1.571) | .579 | 1.127 (0.756–1.681) | .556 |
| Race (vs. white) | | | | |
| Black | 1.567 (0.959–2.561) | .073 | 1.443 (0.816–2.550) | .207 |
| Asian or Pacific Islander | 0.504 (0.160–1.589) | .242 | 0.630 (0.199–1.997) | .432 |
| American Indian/Alaska Native | 2.504 (0.616–10.190) | .2 | 1.572 (0.218–11.332) | .654 |

[a] The hazard ratio for all-cause and PA-specific death for the above co-variables. all statistical tests were two-sided.
[b] 95% confidence interval.
[‡] Two-sided P value was calculated from multivariable covariate-adjusted Cox models.

hypotheses explained this incidence by the difference in socio-economic status between different racial populations in some regions rather than a difference in genetic susceptibility [40,41].

Patients with PA have an excellent prognosis; the 5-year survival rate of children with PA was 95.3% in our study. The 10-year survival of PA in Europe and the United States was reported to be 94% and 95%, respectively. These survival rates are significantly better than those observed before the year 2000 [24]. This improvement in PA survival rates is believed to be related to the advances in diagnostic and surgical techniques, accompanied by improved pediatric neurosurgical establishments, and improved follow up.

In our sample, only 3% of patients had another primary malignancy. No previous data is present on the association of PA with other malignancies. However, a recent SEER-based analysis has shown that about 6% of patients with glioblastoma multiforme (GBM) have a prior primary malignancy before their GBM diagnosis [42]. This lower number of cases associated with other malignancies in our sample could be attributed to the relatively shorter follow-up period.

We found that PA at an age younger than a year was associated with the worst survival outcomes. This might be due to the suggested relation between the younger age at diagnosis and difference in the treatment protocols than the ones used in adults.

Ideally, surgery is considered to be the first and best line of treatment in cases of PAs. Usually, it is associated with a higher survival rate than other non-invasive modalities, but have more neurological complications. Another less offensive treatment modality is radiation, it is used in the non-operable cases and in the extremity of age. The last line of treatment is chemotherapy, which is associated with the least complications but has the worst survival rates of all treatment modalities [17,43–46].

In cases of juvenile PAs, surgical treatment is generally avoided in infants and young patients to avoid neurological complications [43,44]. Moreover, radiation, which is considered the most effective treatment modality in the non-operable PA cases is usually avoided in infants and young patients, and replaced by chemotherapy [45]. On the other hand, a study in Switzerland, 2005, found different results where older age was significantly associated with worse survival. These results were explained as older patients are less frequently treated by surgical intervention and radiotherapy, and those who are treated show better survival than those who are not [47].

Another aspect which must be taken into consideration is the molecular and genetic aspect of the development of PA. Recently, studies found that PA shows mutational activity on many genes, including BARF/Ras/ERK/MAPK genes. Unfortunately, the SEER database does not offer any information about genetic and mutational activity. Further studies are recommended in order to investigate the effect of certain mutations and its effect on the incidence and survival of PA, as well as any prognostic effect or therapeutic strategies regarding this lesion.

Our study has many strength points. We used the most recent up-to-date available version of the SEER database, whose data is known to be reliable, of high quality, and generalizable to the United States Population. Our sample size provided enough power to notice the differences in the incidence and survival outcomes associated with different variables. However, our study still has some limitations, such as the retrospective nature which allows for selection bias, and the lack of reliable data regarding chemotherapy and radiotherapy. The data in SEER on chemotherapy and radiotherapy are not sensitive enough to generate reliable information and to be used in group comparison. Another point is the lack of data regarding the genetic and molecular aspect of tumors. In addition, the database does not include information on the extent of resection. Furthermore, SEER does not provide data about the medical history of registered cases, the method of diagnosis, and treatment modality, leading to possible confoundings in survival analyses. Finally, the SEER program does not cover some of the relatively populous states in the US like Texas, Florida, New York, Illinois, Pennsylvania, Ohio, and other states.

## 5. Conclusion

We provide a thorough analysis of PA cases diagnosed in children between the years 2000 and 2015 in the United States. Overall PA incidence and incidence among blacks has been increasing over the study period. Additionally, PA survival was found to be worse among infants. We recommend further study of the relation between the topography distribution and racial differences of tumors and the survival. Further studies are also needed to investigate the effect of the age and race on the incidence and survival of PA. More investigation is needed to determine the effect of the different modalities of treatment and other previously existing conditions such as HIV and other chronic diseases on the incidence and survival of PA.

## Declaration of interests

The author declares no conflict of interest.

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