Acta Neurochirurgica (2019) 161:1799–1807
https://doi.org/10.1007/s00701-019-03909-1

ORIGINAL ARTICLE - PEDIATRIC NEUROSURGERY

Outcome and prognostic features in paediatric pineoblastomas: analysis of cases from the Surveillance, Epidemiology, and End Results registry (1990–2007)

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Received: 21 November 2018 / Accepted: 10 April 2019 / Published online: 18 May 2019

Abstract

Background Paediatric pineoblastomas are rare central nervous system tumours. Patient and treatment factors associated with outcome are poorly defined and limited to small retrospective case series and single case reports.

Methods Using the Surveillance, Epidemiology, and End Results (SEER) cancer registry, we investigated clinical and pathological factors associated with outcome in paediatric pineoblastomas. Paediatric patients (< 16 years old) with pineoblastomas diagnosed between 1990 and 2007 were identified from the SEER database. Kaplan-Meier survival analysis and Cox models were used to examine the effect of variables on overall survival. The variables analysed included patient's age at diagnosis, gender, race, tumour spread and size, surgical resection and the use of adjuvant radiotherapy.

Results Seventy-eight patients were identified from the database. Twelve patients were excluded as 11 had no surgery and one patient was excluded as the surgical status was unknown. Analysis of the remaining 66 patients revealed a median age at diagnosis of 5.5 years. Three patients underwent biopsy. Seventeen patients underwent full and partial resection, respectively. A further 46 patients underwent surgery the nature of which was not recorded. Thirty-nine patients (59.1%) received adjuvant radiotherapy. Eight patients (12.1%) had both surgery (full or partial resection) and radiotherapy. The median overall survival was 40.5 months. Univariate analysis demonstrated that older age at diagnosis was the only positive predictor of overall survival.

Conclusion This study represents the largest analysis of paediatric pineoblastomas to date. The only clinically relevant prognostic factor was older age at diagnosis. The role of surgery and adjuvant radiotherapy on overall survival remains to be defined.

Keywords Pineoblastomas · SEER · Epidemiology · Survival · Outcome

Abbreviations

CCLG	Children's Cancer and Leuakaemia Group
CI	Confidence interval
CSF	Cerebrospinal fluid
HR	Hazard ratio
ICD	International classification of diseases
MGMT	O^6-methylguanin-DNA-methyltransferase
NCI	National Cancer Institute
OS	Overall survival
PBL	Pineoblastoma
SEER	Surveillance, Epidemiology, and End Results
sPNET	Supratentorial primitive neuroectodermal tumour
UK	United Kingdom
US	United States
WHO	World Health Organisation

This article is part of the Topical Collection on *Pediatric Neurosurgery*

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Introduction

Pineoblastoma (PBL) is considered to be a World Health Organisation (WHO) Grade IV lesion [1, 2]. It is categorised as a supratentorial primitive neuroectodermal tumour (sPNET) localised to the pineal gland [3]. Histologically, PNET lesions are characterised as being highly cellular and have a high mitotic index. These tumours often disseminate widely within the central nervous system via the cerebrospinal

fluid (CSF) pathways [4]. Despite their similarities, significant differences exist between different PNETs. Patients with PBL are known to have poorer outcomes in comparison to patients with infratentorial PNETs (i.e. medulloblastomas). Although they share common histological features, there is increasing evidence that these tumours differ in their structural, biological and immunohistochemical characteristics. Furthermore, responses to treatment also differ. PBL has a poorer outcome following surgical resection and radiotherapy than medulloblastoma [2, 5].

There are molecular genetic differences between PBL and other supratentorial and infratentorial PNETs. Genetic differences can even be found between different PBL subgroups. However, unlike in medulloblastomas, there are no studies that have characterised PBL into different molecular genetic subtypes due to small patient numbers. Cytogenetic studies of the PNET tumours have shown a range of abnormalities even within a particular histological subtype as detailed below (Table 1). There are discrete cytogenetic aberrations in PNET cells dependent on anatomical site with no particular common cytogenetic aberration.

In terms of incidence, the literature suggests that pineal region tumours are 10 times more common in the paediatric population than they are in adults. Paediatric cases of PBL account for more than 90% of published cases [10]. The peak incidence of PBL is in the first 4 years of life and the tumour is uncommon in infants (less than 1 years old) [11, 12]. The above figures are however based on analysis of published cases. Interestingly, analysis of the Surveillance, Epidemiology, and End Results (SEER) database revealed 78 cases of paediatric pineoblastoma (< 16 years old) recorded between 1990 and 2007, which is smaller than the number of adult cases recorded over the same period [13]. This suggests that PBL may not be a predominantly paediatric tumour.

Factors influencing survival are also poorly understood. Due to limited data, little is known of the clinical course and outcomes of paediatric patients with PBL [14]. There are several reasons for this. These patients tend to be analysed in series that include adults or alongside patients with other types of pineal region tumours (e.g. germinomas). Furthermore, treatment approaches for this patient group are varied and this complicates interpretation of the literature. Reported treatment strategies range from localised radiotherapy to the pineal region [15–18] to multi-modality treatment with surgery, radiotherapy and chemotherapy [6, 19]. Lastly, previous series were published without central histological review [20–22].

Despite these shortcomings, the biggest hindrance to establishing optimal therapy is the small number of patients. Prior to this study, the largest reported series of PBL was of 95 patients [13]. However, this series was only limited to adult patients. The median overall survival was 176 months. Factors that were found to be associated with poor survival included widespread dissemination and older age at diagnosis (> 60 years old). The next biggest series is by Lutterbach et al. of 64 adult patients [14]. The reported median overall survival was only 35 months, however all patients presented with disseminated disease in their series. Factors that were important in determining prognosis were poor tumour differentiation and presence of residual disease following surgery [14].

Lee et al. utilised data from the Brain Tumour Registry of Japan, and examined patient, tumour and treatment factors that influenced survival in 34 adult patients (> 16 years old) who presented with PBL [2]. There were a higher proportion of males (22 patients) with a median age of 35 years. The median survival from the time of diagnosis was only 25.7 months with a median follow up of 20.5 months. In the final multivariate analysis, radiotherapy (≥ 40 Gy) and gross total resection were associated with increased survival. Chemotherapy did not improve overall survival but this should be interpreted with caution as chemotherapy data were only available for 10 patients [2].

As radiotherapy and chemotherapy have proven benefit in children with medulloblastoma, Gururangan et al. proposed that children and adults with PBL should be treated with high-dose chemotherapy and radiotherapy followed by autologous stem cell rescue [22]. Hinkes et al. have noted that the efficacy of chemotherapy is age-dependent and more effective in older children (> 3 years old) in comparison to younger ones (< 3 years old) in maintaining these patients in remission [23]. At the same time, the younger patients in the above cohort only received radiotherapy after the age of three and therefore the oncological management of the patient groups was different and this may well explain the different outcomes. No study has conclusively established the role of chemotherapy in PBL either retrospectively or prospectively. This issue is complicated by small patient numbers and a variety of chemotherapeutic agents used in the literature.

In the United Kingdom (UK) and the United States (US), there are now national guidelines to standardise the management of these patients. These guidelines are based on evidence from randomised controlled trials from three relatively large sPNET studies which included small numbers of patients with

Table 1 Cytogenetic abnormalities across the PNET family of brain tumours

Tumour type	Cytogenetic abnormality
Medulloblastoma	Unbalanced translocations or deletions of chromosomes 8, 10q, 11p, 11q, 16p and 17p [6]
Pineoblastoma	Deletion of long arm of chromosome 11 [7]; gain in chromosome 17q and 1p deletion [8]
sPNET	17p and 2p deletion [9]

PBL. These series were the CCG (1995), HIT (2007) and SIOP-PNET3 (2006) trials which included 25, 11 and 14 PBL patients, respectively. Interpretation and extrapolation of these trials in the context of PBL is difficult as analysis was performed for sPNET as a whole.

In the UK, Children's Cancer and Leukaemia Group (CCLG) guidelines recommend post-surgical chemotherapy and radiotherapy. The chemotherapy regime consists of vincristine, etoposide, carboplatin and cyclophosphamide and should commence within 28 days of surgery. Radiotherapy should commence within 4 weeks of the last dose of chemotherapy and should involve craniospinal axis with a boost to the pineal region. In the US, the National Cancer Institute (NCI) protocol is similar however patients receive radiotherapy prior to chemotherapy. Tarbell et al. did not find any difference in the event-free survival between the two groups of patients with regard to timing of radiotherapy and chemotherapy [7]. It is important to note that the above guidelines are only for those patients above the age of 3 years. With regard to patients below the age of three, there are no national guidelines in the UK. In the US, biopsy is performed first to diagnose pineoblastoma. The patients are then treated initially with chemotherapy with the view of delaying, if not obviating, the need for radiation therapy. In children not responding to chemotherapy, there is no guidance on the appropriate timing and dose of radiation therapy.

As detailed above, the systematic study of paediatric PBL is hindered by the low incidence of the tumour and importantly, by the lack of patient registries detailing patient, tumour and treatment details. Studies of extremely rare tumours like PBL are only made possible by utilising large national databases [2, 14]. The National Cancer Institute's Surveillance, Epidemiology, and End Results database (SEER) is considered the gold standard of all cancer registries. This database provides researchers with data that are sufficiently powered to conduct statistical analysis to characterise rare tumours. Due to the paucity of paediatric PBL cases in the literature, we have utilised the SEER database to investigate the epidemiology, natural history and prognostic factors to further our understanding of these rare tumours.

Methods

Information was extracted from the SEER database which is maintained by the US-based NCI. SEER-STAT version 6.6.2 (Surveillance Research Program, National Cancer Institute, Bethesda, MD, USA) was utilised to extract the data. The SEER 17 Registries (1973–2007) dataset was utilised. All patients with PBL aged less than 16 years diagnosed from 1990 to 2007 were identified. The International Classification of Diseases for Oncology (ICD) code (Pineoblastoma: 9362/3) was used. Patients were excluded if they did not have surgery or if the surgical status was unknown. Statistical analysis was performed using SPSS Statistics 22 (IBM Corporation, Chicago, IL, USA) software.

Kaplan-Meier survival analysis was used to assess the overall survival (OS). Patients were not censored and the only event considered was death. The Mantel-Cox log-rank test was utilised to determine differences in the survival curves. Univariate and multivariate Cox proportional hazard models were utilised to determine the hazard ratios (HR) and their 95% confidence intervals (CIs), to ascertain the effect of individual variables on overall survival. Only statistically significant variables in univariate analysis were considered for multivariate analysis. Possible explanatory clinical variables assessed included age at diagnosis, sex, race, tumour size, extent of tumour spread, surgical resection and the use of adjuvant radiotherapy. Ethical approval or informed consent was not required for this study as the SEER database contains fully anonymised data.

Results

Patient and tumour characteristics

Between 1990 and 2007, 78 paediatric patients (< 16 years old) were registered on the SEER database with a diagnosis of PBL. Twelve patients were excluded from further analysis as 11 did not have surgery and in one patient the surgical status was unknown (Fig. 1).

Outcome and prognostic analysis was therefore performed on the remaining 66 patients. The incidence rate was 0.02 cases per million per year. Median follow up period was 40.5 months (range 2–313 months) with a median age at diagnosis of 5.5 years. The patient, tumour and treatment characteristics are displayed below. There was no significant sexual predilection and the tumour occurred more commonly in younger patients below the age of 5 years.

Factors associated with survival

Univariate analysis identified older age ($p = 0.01$) as the only factor associated with improved prognosis (Table 2).

Since only one variable reached significance, multivariate analysis was not performed. Within the whole patient group, 10 and seven patients underwent full and partial resection, respectively. In the < 3 years of age, four and five patients underwent full and partial resection, respectively (Table 3).

A further 46 patients underwent surgery the nature of which was not recorded. Thirty-nine patients (59.1%) received adjuvant radiotherapy. Only eight patients (12.1%) had both surgery (full or partial resection) and radiotherapy. There was no statistically significant survival benefit from

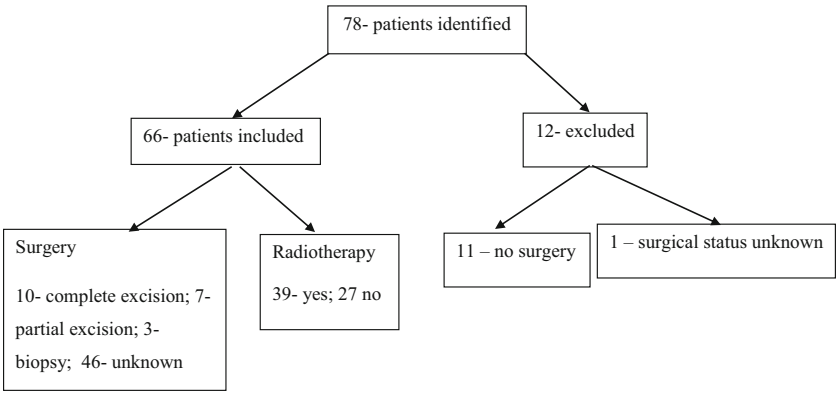

Fig. 1 Study profile

both surgery and radiotherapy; however, there was a trend towards improved prognosis from combined modalities.

The 5-year overall survival rate was 55.9% and the median overall survival was 40.5 months. Kaplan-Meier curve was used to illustrate overall survival for the full cohort (Fig. 2). Survival curves stratified based on patient's age demonstrated that older paediatric patients (> 3 years old) had a better prognosis ($p = 0.008$) (Fig. 3).

Table 2 Patient, tumour and treatment characteristics

Patient characteristics	
Age	*N* (%)
0–1	11 (16.7)
0–3	25 (37.9)
0–5	33 (50.0)
6–10	18 (27.3)
11–15	15 (22.7)
Sex	*N* (%)
Male	31 (47.0)
Female	35 (53.0)
Tumour characteristics	
Number of primaries	*N* (%)
1	62 (94.0)
2	4 (6.0)
Spread	*N* (%)
Localised	41 (62.1)
Regional	12 (18.2)
Distant	7 (10.6)
Unknown	6 (9.1)
Tumour size (mm)	*N* (%)
< 10	0(0.0)
10–19	3 (4.5)
20–29	14 (21.2)
30–39	9 (13.6)
40–49	6 (9.1)
50–59	5 (7.6)
60-	2 (3.0)
Unknown	27 (40.9)
Treatment characteristics	
Type of surgery	*N* (%)
Biopsy	3 (4.5)
Partial resection	7 (10.6)
Complete excision	10 (15.2)
Surgery (type not specified)	46 (69.7)
Radiotherapy	*N* (%)
Yes	39 (59.1)
No	27 (40.9)

Discussion

The biological behaviour of paediatric PBL is poorly understood due to the rare nature of the disease. To date, the incidence and prevalence remains unknown. Furthermore, the current clinical management of paediatric PBL is based on retrospective case series and extrapolation from treatment experiences from other PNET lesions such as medulloblastoma. There are limited data on prognostic factors and prognosis. Utilising the large number of patients provided by the SEER database, this study investigated epidemiology, natural history and prognostic factors that affect outcome in paediatric patients with PBL.

Patient and tumour characteristics

The median overall survival in our series was only 40.5 months. This is shorter than 66 months reported by Cuccia et al. 2006 in their small Argentinean series of 12 paediatric patients with PBL [1]. In a larger series of 64 adult patients (≥ 18 years old), the median survival was even longer at 77 months [14]. Survival in our patient group was longer than the reported median survival of 25.7 and 30 months by Lee et al. and Chan et al. respectively [2, 24]. These data values are however from much smaller series of 34 and 11 patients, respectively, and they only included adult patients. The apparent difference in median survival times between the different studies may be impacted by differences in age, treatment strategies and maybe even diagnostic accuracy between centres. Furthermore, the proportion of patients with disseminated disease in the above series is significantly higher in comparison to ours. Finally, the study period for all of the above series is also different, ranging from 1969 to 2001 and therefore these series are significantly older than ours.

It appears from our data that a significant proportion (72.7%) of patients appear to be above the age of 2 years

Table 3 Univariate analysis of the effect of patient, tumour and management factors on overall survival (hazard ratio ± confidence interval)

Univariate analysis					
Variable		Hazard ratio	Overall *p* value	95% confidence interval for the hazard ratio	
Age	≤ 3[a]	*0.37*	*0.01*	*0.17*	*0.79*
	> 3				
Tumour size	Per 1-mm increase	1.02	0.24	0.99	1.06
Spread of tumours	Localised[a]	1.00	0.56	0.55	6.42
	Metastasis	0.92	0.85	0.38	2.21
	Unknown	1.87	0.32		
Radiotherapy	Yes[a]	1.00	0.27	0.72	3.30
	No	1.54			
Surgery	Excision[a]	1.00	0.28	0.41	3.92
	Partial and biopsy	1.26			

[a] Reference category

*Statistically significant

- Unable to analyse

with a median age of diagnosis of 5.5 years. This is similar to Cuccia et al. who also noted a significant proportion of their patients to be above the age of 2 years (75%) with a median age of diagnosis of 6.6 years [1]. It is also in keeping with previous publications that noted a tendency for PBL to occur in children especially in the first and second decades of life, while being uncommon in infants [1, 12].

In our series, the proportions of male (47.0%) and female (53.0%) patients were not dissimilar. This is in concordance with other series such as Lutterbach et al. [14]. The slight increase in the proportion of females was also noted by Fauchon et al. in their series [21]. They noted that this difference was even more significant in higher grade pineal parenchymal tumours [21]. This finding is not replicated in all

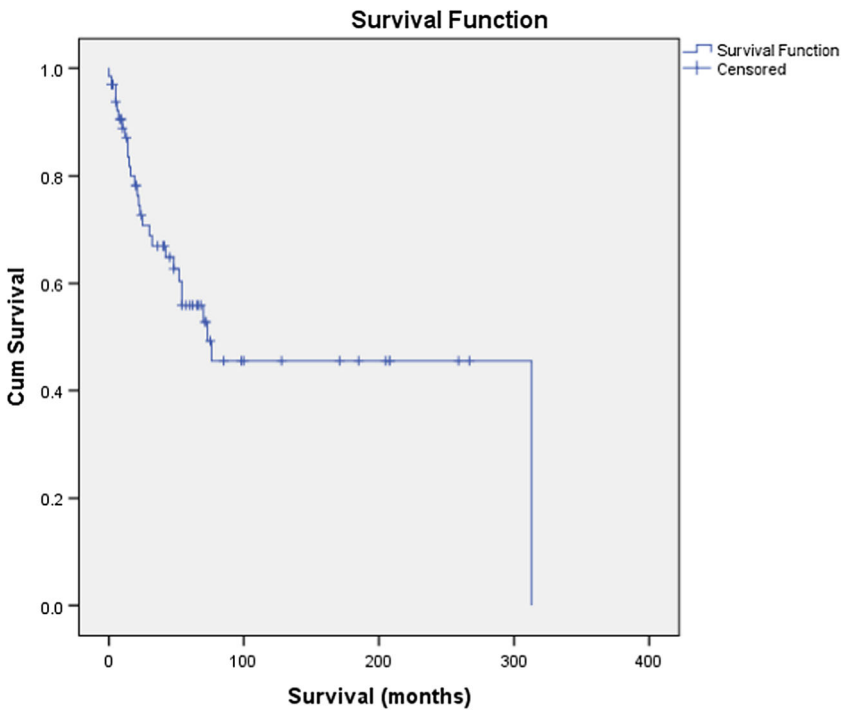

Fig. 2 Overall survival for patient cohort

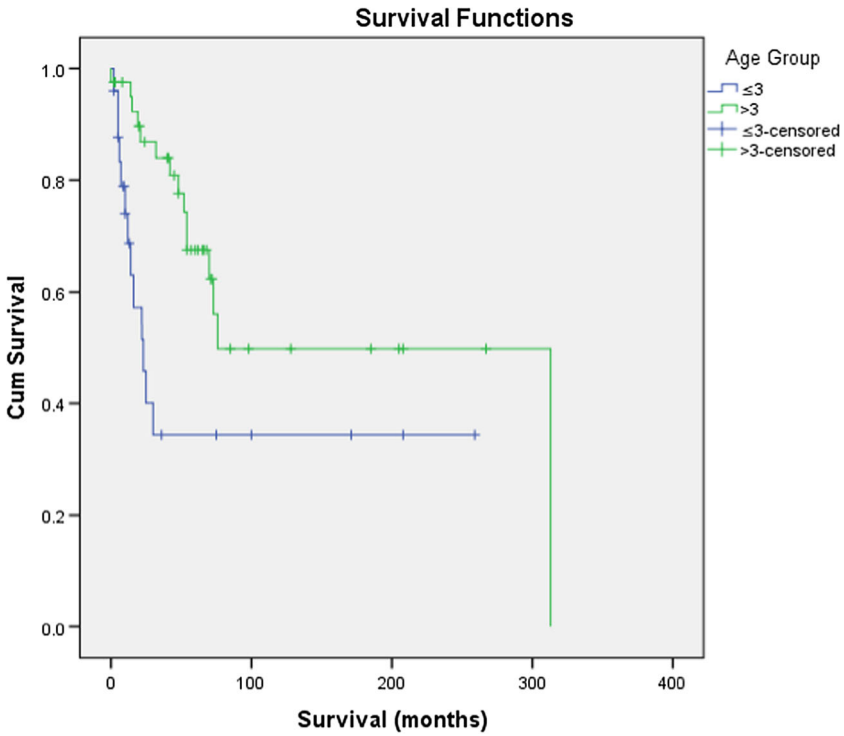

Fig. 3 Survival curves stratified on age

series: Cuccia et al. reported a significantly larger proportion of males (67%) in their cohort [1].

Factors associated with survival

In the univariate analysis, we have shown that older age is associated with a significantly better prognosis. This is likely due to a larger proportion of patients who received full resections (60%) and radiotherapy (84.8%) in the older age group (> 3 years old). Although not statistically confirmed, Cuccia et al. in his series of 12 PBL patients similarly noted poorer survival in younger children, especially in those below the age of 3 years [1]. Interestingly, the above finding is also echoed in the series of 11 children with PBL by Hinkes et al. [23]. Furthermore younger patients tended to present with larger tumours - an observation replicated in our study. They also found that patients above the age of three responded more favourably to chemotherapy and radiotherapy post-surgery. Fauchon et al. showed that the PBL tumours of younger patients tended to exhibit more mitoses and tumour necrosis and were also larger at presentation [21]. Interestingly, the effect of age on prognosis was not replicated by Lutterbach et al. [14]; however, the data should be interpreted with caution as their adult series contained patients with histological diagnosis of both PBL and pineal parenchymal tumour with intermediate differentiation and univariate analysis was performed for both types of patients as a single group. Nevertheless, the series show a trend towards poorer overall survival in older adult patients, although this was not significant [14]. Lee et al. reported that age was not an important predictor of survival in their smaller series of 34 adult patients [2]. However, the author has failed to publish his *p* value and confidence interval for this variable.

Tumour management

In the univariate analysis, tumour resection did not improve survival. The current literature on the benefits of surgery in patients with PBL is non-statistical, anecdotal and based on single-institution experience describing either surgical [3, 25] or non-surgical treatment [1, 23, 26–28]. Several authors have reported no benefit with aggressive surgical resection in patients with PBL, suggesting a non-resective route (biopsy and CSF diversion) instead [1, 21, 29, 30]. In a series of 12 paediatric patients with PBL by Cuccia et al., the benefit of surgery and moreover degree of resection were not apparent [1]. The benefits of surgery were also not seen in the mixed series of pineal parenchymal tumours by Fouchon et al. [21]. Subgroup analysis based upon histological subtype with regard to benefit from surgery was not performed due to small patient numbers. The SIOP-PNET 3 study found that in the sPNET group, the presence of residuum did not affect prognosis. This finding was echoed by the Children's Cancer Group Randomised Trial (1995). They also found that the size of the residuum did not affect prognosis [31]. Lee et al. reported statistically significant benefit of surgical resection on univariate analysis; however, on multivariate analysis, the hazard ratio was undefined and the Cox regression was unable to

generate a *p* value. The authors failed to publish the hazard ratio and its corresponding confidence interval for the univariate analysis. Lee et al. argue that this was because no patient died following tumour resection [2]; however, this may just reflect a type 2 error due to a small sample size. Statistically significant benefits have been noted in children and adults with medulloblastomas [24, 32], although the evidence for surgical resection should be interpreted with caution, as selection bias was not eliminated. Due to lack of randomisation, the patients who have had surgery may have been fitter with more accessible, unifocal lesion.

In our study, there was no statistically significant difference in the overall survival between the patients who underwent adjuvant radiotherapy and those who did not. There was a trend towards longer survival in patients who received adjuvant radiotherapy, and the lack of statistical significance may reflect the small sample size. Similar, however more significant, observations have also been made in adult and paediatric patients with medulloblastomas [24, 29, 30, 33].

The benefits of radiotherapy have been noted in adult and paediatric populations with PBL [23, 25, 34, 35]. Although not statistically evaluated due to small sample sizes, the published findings nevertheless are rather interesting. In their series of six older children (aged 3–17 years old), Hinkes et al. reported that radiotherapy helped to achieve and maintain remission [23]. It is unclear if it could be attributed to radiotherapy alone as patients received a combination of chemotherapy and radiotherapy. Chang et al. noted the benefits of radiotherapy in their 11 patients, although this was not assessed statistically due to a small cohort size [4]. In their adult series, Lee et al. report that cranial radiation therapy conferred increased survival that was statistically significant [2]. This analysis involved comparison between those receiving ≥ 40 Gy and those receiving lesser doses. Interestingly, a similar radiation dose threshold was noted in children with medulloblastoma [36]. Because of limitations of the SEER database, we were unable to ascertain the radiation doses in our patient group.

The utilisation of chemotherapy was not assessed in our study as this intervention modality is not recorded on the SEER database. The benefits of chemotherapy in paediatric series is yet to be statistically confirmed retrospectively or prospectively due to the limited number of patients highlighting the need for international multicentre collaboration. So far, the benefits of chemotherapy have been demonstrated in case reports and case series [11]. In their series of six patients with PBL, Schild et al. noted a partial response to chemotherapy [30]. In the series by Chang et al. consisting of 11 patients who had both surgery and radiotherapy, seven underwent additional chemotherapy. It was noted that utilisation of the aforementioned adjuvant modality did not confer survival advantage [4]. In a retrospective review of older studies, chemotherapy has been shown to be non-beneficial. This has to be interpreted with caution due to the wide variety of chemotherapy regimens available [35]. Some significant benefits were seen in the context of other PNETs like medulloblastoma [22]. The role of brachytherapy in the context of PBL should also be investigated further; isolated case reports and case series suggest possible benefits with this modality [21].

Limitations of the SEER database

The SEER database provides invaluable data on rare brain tumours and enables analyses of large series. This would not otherwise be possible from institutional studies. However, the database holds limited information on tumour size, extent of resection, dose and type of radiotherapy and the use of chemotherapy. There were no data available on time to tumour recurrences (which would enable calculation of progression-free survival), performance status complications or comorbidities. Given the recently developed prognostic factors for gliomas, i.e. performance status, age, extent of resection and O^6-methylguanin-DNA-methyltransferase (MGMT) status, the omission of these factors is a limitation of this study [37]. Furthermore, given the rarity of paediatric PBL, the pathological diagnosis has not been subjected to scrutiny by an independent pathologist. The SEER database does not undertake a centralised review of the tumour tissue prior to entry into the database. As a result, no pathological confirmation is undertaken.

Finally, the main concern the authors had is coding accuracy. A significant proportion of patients (15.4%) in our series with diagnostic coding of pineoblastoma were not reported as having any form of surgery. It may be that these patients had surgery but were coded inaccurately. Inaccurate coding may also account for the disproportionately fewer number of paediatric cases in comparison to adult cases contradictory to published literature.

Nevertheless, despite several shortcomings above, our study is the most thorough analysis of paediatric PBL to date and provides relevant insights into prognosis and management of these rare tumours. The anecdotal observations from previously published case series and isolated case reports are confirmed by our study.

Conclusions

This study emphasises the role of national tumour databases in furthering our understanding of rare brain tumours and determining management options. The authors recommend that in cases of exceptionally rare brain tumours, the registry should have their cases centrally reviewed including their histological diagnosis, staging, extent of resection, chemotherapy regime, radiotherapy doses and most importantly the coding process. This would minimise discrepancies between units and

countries with regard to diagnosis and intervention. This is an important issue highlighted by the differences in the incidence of grade 1 and grade 3 ependymomas in different countries.

In summary, our data suggests that overall survival is better in older children. Furthermore, it suggests that in paediatric patients with PBL, the role of surgery and adjuvant radiotherapy remains undefined. Based on our limited data, there is no survival advantage with radiotherapy and surgery. This may reflect a type 2 error despite the study being the largest series to date. Certainly, anecdotally and based on the experience of individual institutions, the benefits of surgery and radiotherapy can be seen, albeit not as significantly so as in medulloblastoma. Based on the limitations described above, it is appropriate to manage PBL according to the existing protocols until a larger retrospective or ideally prospective analysis can be performed.

Compliance with ethical standards

Conflict of interest All authors certify that they have no affiliations with or involvement in any organisation or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest and expert testimony or patent-licencing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

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