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Supratentorial primitive neuroectodermal tumors in children

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Abstract

A retrospective review of 36 children diagnosed with a supratentorial primitive neuroectodermal tumor (PNET) at the Hospital for Sick Children was performed for the period 1970–1995. All children but one received their initial treatment at our institution. There were 18 males and 18 females and the median age at diagnosis was 35 months. Twenty-two PNETs were lobar, 3 were deep in the hemisphere, and 10 were located in the pineal region. One child presented with intracranial leptomeningeal disseminated disease. The tumors were mostly undifferentiated although 22 had some evidence of differentiation along one or more neuroepithelial lines. Five children had a biopsy, 24 had subtotal resection, and 7 had gross total resection. Twenty-six children had adjuvant radiotherapy and 13 had chemotherapy. At last follow-up 30 patients were dead and 6 were alive. The median survival was 23 months and the 2, 3, and 5 year survivals were 50%, 34%, and 18% respectively. All of the survivors received craniospinal radiation and 4 received chemotherapy. There was a statistically significantly worse survival in young children. There was a trend to better survival in children treated since 1984, and in children undergoing gross total resection. Because of the extremely poor survival, we recommended that all children undergo gross total resection followed by chemotherapy. For children older than 3 years of age craniospinal radiation should also be given.

Introduction

Primitive neuroectodermal tumors (PNET) are rare but highly malignant primary central nervous system tumors which occur predominantly in children. Controversy remains over whether these tumors of similar histology can all be classified under the single term PNET, which reflects a belief that the undifferentiated progenitor cell occurs in all parts of the nervous system, or whether these tumors are truly distinct entities arising from progenitor cells unique to the site of origin [1, 2]. It is clear that all these tumors share a similar histologic appearance, consisting of predominantly a dense population of small cells with little cytoplasm with or without areas of differentiation into cells resembling neurons, astrocytes, oligodendrocytes, or ependymal cells. It has been suggested by some investigators that tumors which exhibit prominent differentiation, especially along neuronal lines, may have a better natural history [3, 4]. In addition, supratentorial PNETs and medulloblastomas, apart from their potentially different cell origins, may also be considered to be distinct tumors because they have markedly different survival rates. Despite the controversy surrounding their histogenesis and classification, all PNETs have a tendency to spread along CSF pathways and long term survivors are rare despite surgery, radiation therapy, and chemotherapy.

Nosological arguments aside, we performed a retrospective review of all children presenting with a supratentorial PNET at the Hospital for Sick Children between 1970 and 1995. Our review included

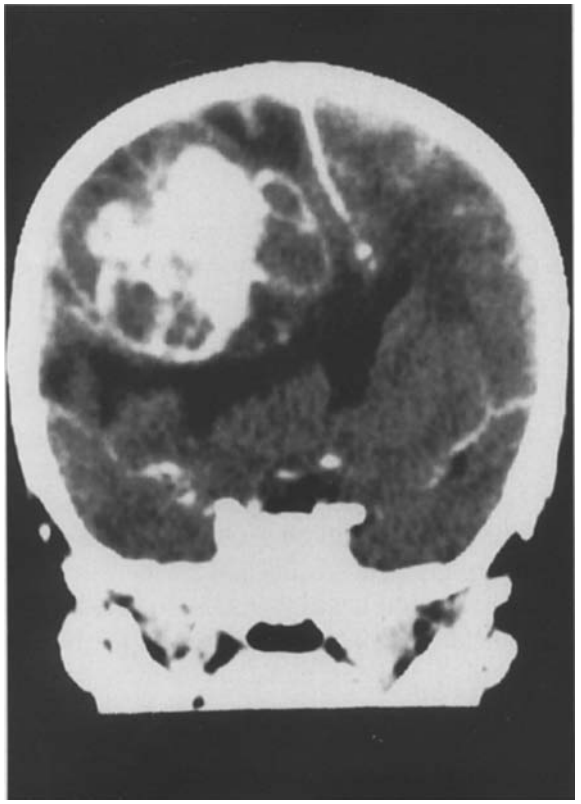


Fig. 1. Coronal contrast enhanced CT scan in a 22 month old girl who presented with a 2 week history of vomiting and increasing lethargy. The CT scan showed features characteristic of a lobar supratentorial PNET. There is a large heterogeneous mass in the right frontal lobe, with a solid enhancing region and multiple cystic areas. There is edema surrounding the mass as well as massive shift of the midline structures. This child has a gross total removal of her lesion followed by craniospinal radiation and chemotherapy. An asymptomatic local recurrence was found 18 months after surgery and she underwent a repeat resection followed by chemotherapy. She remained well 16 months after this treatment.

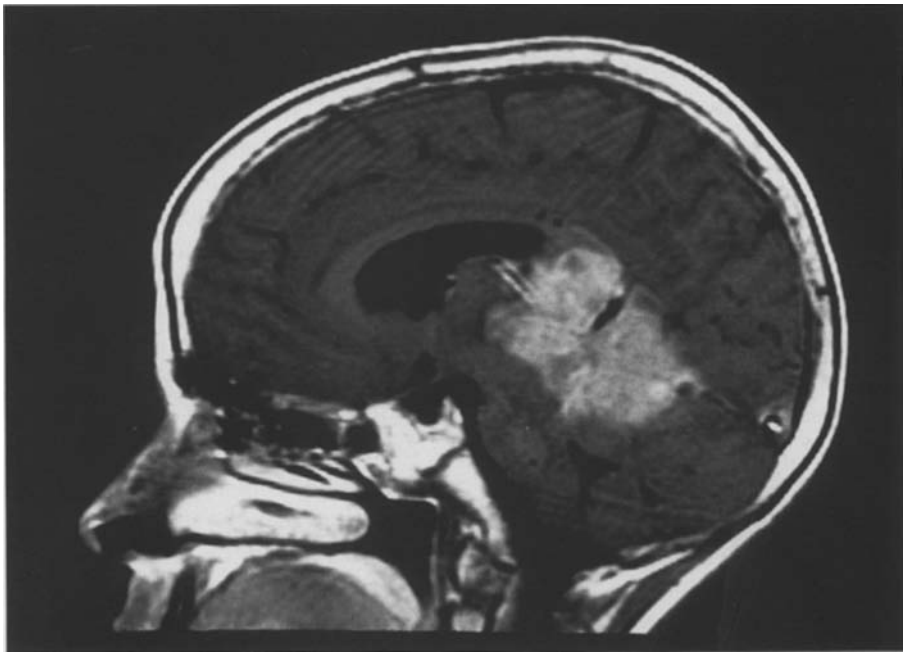
all PNETs occurring in the supratentorial compartment, including PNETs of the cerebral hemispheres, basal ganglia, and diencephalon. Tumors also known as pineoblastomas, ependymoblastomas, and neuroblastomas were also included in our review. Our review attempts to identify factors correlated with survival and we give recommendations for treatment of these extremely malignant neoplasms.

Patient selection

A retrospective review of all patients less than eighteen years of age presenting with a supratentorial PNET to the Hospital for Sick Children between 1970–1995 was performed. Thirty-six children were identified and 35 received their initial treatment at the Hospital for Sick Children. PNETs were pathologically classified as either undifferentiated or differentiated with the cell type specified as recommended by Rorke and Becker [2, 5]. Medulloblastomas and retinoblastomas were not included in this review. Pineoblastomas having pineocytic differentiation were also excluded. One child diagnosed with a medulloepithelioma of the left parietal lobe was included.

Patient characteristics and surgical treatment

The clinical characteristics of the patients reviewed are shown in Table 1. There were eighteen males and eighteen females. The mean age at diagnosis was 52 months (median 35 months) with a range from 1 month of age to 154 months. Eighteen patients were less than 3 years of age at diagnosis. Twenty-two were lobar in location, 10 were in the pineal region, 3 were deep, and 1 was disseminated over both cerebral convexities as well as the basal leptomeninges without an apparent focal primary site. The majority of children presented with signs and symptoms of raised intracranial pressure (ICP). Typically, the duration of symptoms before diagnosis was short, with headache or irritability for 2–4 weeks followed by nausea, vomiting, and increased lethargy. Four children had a precipitous decline prior to surgery as a result of hemorrhage into their tumor. Imaging studies characteristically revealed large, well-circumscribed heterogeneous masses [6]. These tumors usually had both solid and cystic components and calcification was frequently present on noncontrast CT. Heterogeneous enhancement was usually apparent after contrast injection on CT or MRI, and gadolinium enhanced MRI showed leptomeningeal dissemination in several cases. Imaging studies and clinical presentations of 2 patients with supratentorial PNETs are shown in



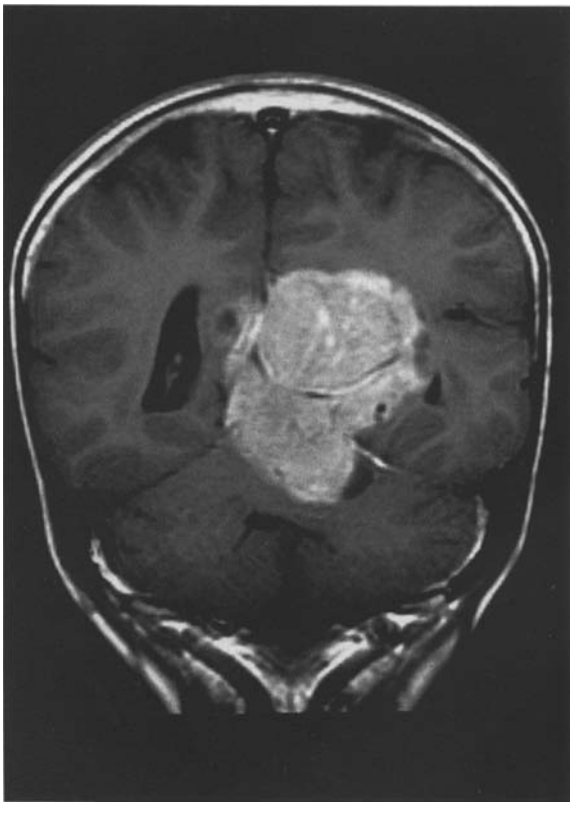


Fig. 2 (a and b). Sagittal and coronal gadolinium enhanced MRI scans of a 12 year old boy who presented with Parinaud's syndrome and signs and symptoms of raised intracranial pressure. The MRI scan shows a massive, uniformly enhancing lesion in the pineal region. He underwent a subtotal (80%) resection of a PNET. Interestingly, he presented with a similar tumor 8 years previously and was treated with a ventriculoperitoneal shunt and craniospinal radiation without a tissue diagnosis. His tumor was observed to completely disappear on follow up examination. Following surgery of recurrence he was treated with chemotherapy, but, his tumor progressed and he died after a further 18 months.

Figs 1 and 2. At the time of original diagnosis, 18 patients had undergone a post-operative metastatic work-up by cerebrospinal fluid cytology, CT-myelography, or gadolinium enhanced MRI. Eleven of these patients were found to have localized disease, and the remaining had evidence of intracranial dissemination (4 patients), or spinal dissemination (3 patients). In the remaining eighteen patients it could not be unequivocally determined from the records whether or not there was neuraxis dissemination at the time of diagnosis.

The different treatments performed on these children are shown in Table 1. Five patients had an open or stereotactic biopsy alone, 24 patients had subtotal resection, and six patients had a gross total resection (3 by surgeon's impression, 3 by post-operative imaging). One patient presented at age 4 with a large pineal tumor and he was treated with a ventriculoperitoneal shunt or craniospinal radiation therapy without a confirmed histological diagnosis. His tumor disappeared and he remained well for 8 years until he presented with massive recurrence of his pineal region tumor which was then removed by gross total resection (see Fig. 2). Histologic examination at that time confirmed a PNET. Five patients had a repeat resection for their PNET at the time of recurrence, an total resection was achieved in two.

The 30 day postsurgical mortality was 8.3% (3 patients). These 3 patients all presented in coma secondary to raised intracranial pressure associated with large tumors.

Review of pathologic reports revealed that 22 tumors were undifferentiated and 14 had differentia-

Table 1. Patient characteristics and treatment

	No. of cases		No. of cases
Sex		**Pathology**	
Male	18	*Differentiated*	22
Female	18	1 line	14
		2 or more lines	7
Age		neuronal	9
(months)		astrocytic	14
Median = 35		ependymal	5
Mean = 53		oligodendroglial	2
Age 3 and up	18	*Undifferentiated*	14
Age less than 3	18		
Location		**Surgery**	
Nonpineal	26	Biopsy	5
Lobar		Subtotal Resection	24
Frontal	10	Total Resection	7
Temporal	4		
Parietal	3		
Occipital	2	**Radiation Therapy**	
Hemisphere	3	Craniospinal	19
Deep		Brain only	7
Basal Ganglia	1	None	10
Diencephalon	1		
Corpus callosum	1	**Chemotherapy**	
Leptomeningeal	1	yes	13
		no	26
Pineal region	10		
Symptoms and Signs			
Raised ICP	31		
Seizures	8		
Focal deficit	9		

tion into a one or more neuroepithelial cell types. In the majority of tumors with areas of differentiation the greatest portion of the tumor was still undifferentiated. Nine tumors had neuronal differentiation, although it was prominent in only one tumor, 14 had astrocytic differentiation, 5 had ependymal differentiation, and 2 had oligodendrocytic differentiation. Fourteen tumors had differentiation into one cell type and 7 had differentiation into 2 or more cell types. There was one case of classic medulloepithelioma in a 2 year old girl which was characterized by a papillary and tubular arrangement of columnar epithelial cells resembling the primitive medullary epithelium. There was no evidence of melanocytic or muscle differentiation in any supratentorial PNET in this series.

Of those patients who did not suffer inexorable progression of their disease shortly after diagnosis, the frequency of intracranial or spinal dissemination was found to be 46% at the time of recurrence (compared to 39% at diagnosis). The five patients who came to autopsy all showed extensive spread of PNET over the leptomeninges of the brain and spinal cord. There were no extraneural metastases and no peritoneal metastases occurred in patients with ventriculoperitoneal shunts.

Adjuvant treatment

Twenty six patients received radiation therapy post-operatively. Nineteen patients underwent craniospinal radiation (4500–5400 cGy local and 2500–3500 cGy to the remaining neuraxis) and 7 patients either had whole brain radiation or local radiation (4500–5400 cGy) to the area of the tumor. Seven patients did not receive radiation therapy because of persistent severe post-operative neurologic deficit and one patient's parents refused radiation. All of these patients presented in extremis. Two patients did not receive radiation therapy post-operatively because they were under two years of age and instead they received chemotherapy as the primary adjuvant therapy. These two children received craniospinal radiation therapy at recurrence. Thirteen patients received chemotherapy post-operatively, and recently all children with PNETs

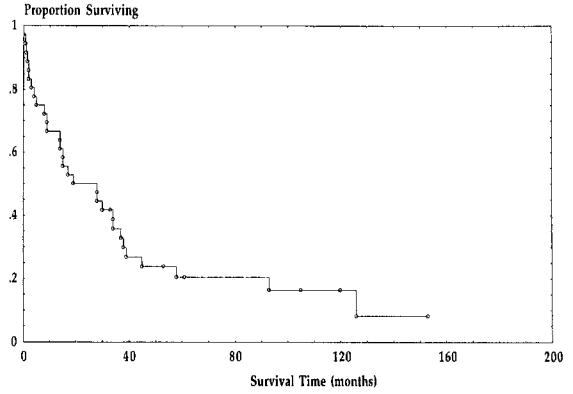


Fig. 3. Kaplan-Meier plot showing overall post-operative survival of all 36 patients with supratentorial PNETs.

treated at the Hospital for Sick Children have been receiving adjuvant chemotherapy. Fifteen patients received chemotherapy at recurrence.

Statistical analysis

Survival curves were made using the Kaplan-Meier method [7]. Patients lost to follow up were censored at the time of last examination. A series of univariate analyses using the log rank test was performed to determine the effect of different parameters on outcome [8].

Results

Thirty patients are dead and six patients were alive at the last follow up. Three of the surviving patients were examined in the last three months, two were lost to follow up after more than 10 years of disease free survival, and one patient was lost to follow up four years ago after more than four years of disease free survival.

The median survival of the 36 children diagnosed with a supratentorial PNET was 23 months (mean 35 months), and the 2, 3, and 5 year survival rates were 50%, 34%, and 18% respectively. The Kaplan-Meier survival curve for the whole group is shown in Fig. 3. The median time to recurrence was 14 months (mean 19 months).

The six surviving patients all received craniospi-

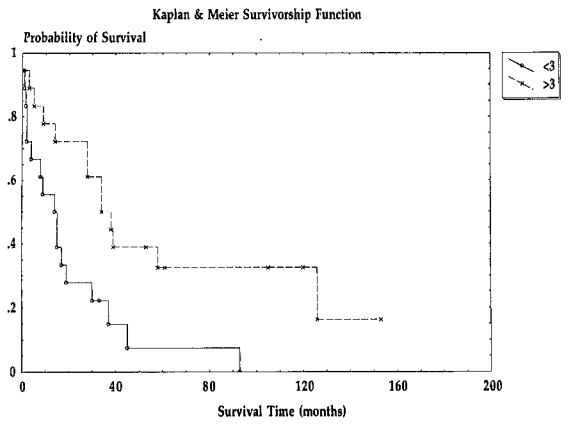


Fig. 4. Kaplan-Meier plot showing overall post-operative survival for patients under 3 years of age (< 3) or 3 years of age and older (> 3). There were 18 patients in each group. Log-rank analysis revealed a significant difference between the two groups with p = 0.006.

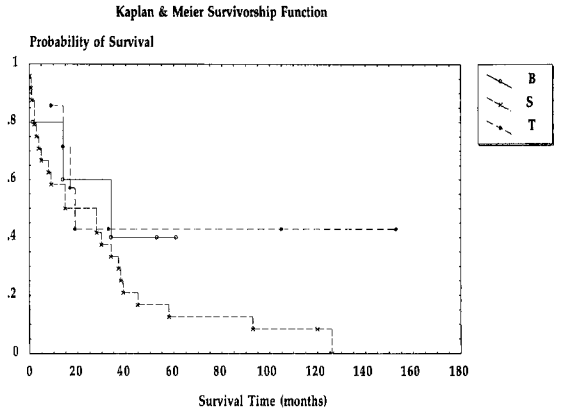


Fig. 5. Kaplan-Meier plot showing overall post-operative survival for patients undergoing biopsy (B, n = 5), subtotal resection (S, n = 24), and total resection (T, n = 7). There was a trend to increased survival in patients undergoing total resection (p = 0.08) and 3 out of six survivors had total resection.

nal radiation therapy and four patients also received chemotherapy. According to the Glasgow Outcome Scale, 2 patients have had a good outcome and have normal intelligence [9]. Two patients have moderate disability with mildly impaired cognitive ability and mild endocrinopathy. Two patients are severely disabled and have markedly decreased intelligence and severe endocrinopathy.

There was a strong association between age at diagnosis and survival, with younger children clearly having a worse prognosis. For analysis, two equal groups of patients were created by grouping children according to age under 3 or age 3 and older. The 2 and 5 year survival rates for children under 3 years of age were 28% and 5.8% respectively, and for children three years of age and older the survival rates were 72% and 29% respectively. Kaplan-Meier survival curves for these two groups are shown in Fig. 4, and log rank analysis showed that the observed difference in these two curves was statistically significant (p = 0.006). There was a significant difference in survival between younger and older children up to the age of 7. Five out of the 6 survivors in this series were diagnosed at 5 years of age and older (mean age 74 months). Young age was also associated with a shorter time to recurrence.

There was no significant difference in survival according to patient sex, tumor pathology (differentiated vs. undifferentiated, or neuronal differentiation vs. other histology), or stage of disease at time of diagnosis (as determined by metastatic work up in 18 patients). Interestingly, the 5 year survival of pineal PNETs (pineoblastomas) compared to non-pineal region PNETs was 30% vs. 12%. This difference, however, did not reach statistical significance in an analysis of their survival curves (p = 0.26). Two of the survivors had pineoblastomas, three had lobar PNETs, and one survivor presented with intracranial leptomeningeal dissemination. The mean patient ages were similar in the groups of undifferentiated tumors vs. differentiated (54 vs. 51 months) and in pineal vs. non-pineal region PNETs (55 vs. 52 months). The mean patient age in neuronally differentiated tumors was slightly higher than non-neuronal tumors (64 vs. 49 months).

The 5 year survival of patients diagnosed and treated in the last decade (since January 1984), compared to the first 14 years of study (1970–1983), was also similar, 15% vs. 19% respectively, although analysis of their survival curves suggested there was a trend towards better survival in the past decade (p = 0.11). Four out of the 6 survivors were treated since 1984. The mean age in the 1984–1995 group was slightly higher (60 vs. 47 months). Ten out of 13 patients who received adjuvant chemotherapy were also diagnosed and treated after 1984.

A comparison was made between patients who

underwent gross total resection with patients who had either a biopsy or subtotal resection. Statistical analysis showed that there was a trend to increased survival in those patients undergoing total resection ($p = 0.08$). Interestingly, 3 out of the 6 survivors had total resection. The mean age of patients undergoing total resection was 54 months compared with 52 months in the subtotal resection/biopsy group. The survival curves for each type of surgical treatment are shown in Fig. 5.

Seven out of the 10 patients who did not receive radiation therapy had severe post-operative neurologic disabilities and radiation therapy was not indicated. Therefore, a comparison was not made between those who received radiation and those who did not. However, survival of patients receiving craniospinal radiation was compared to those who received brain radiation only, and no statistical difference was found ($p = 0.24$). A comparison was also made for survival of those who received chemotherapy initially with those who did not. This analysis revealed that there was a trend to better survival in those patients who received adjuvant chemotherapy ($p = 0.07$), although if the same 7 patients were excluded from analysis as above, then there was clearly no difference.

Discussion

Supratentorial PNETs are extremely rare brain neoplasms and at the Hospital for Sick Children we have observed only 36 cases over the past 25 years, or approximately 3 cases every two years. A decade ago we reported on 144 children diagnosed with medulloblastoma over a 30 year period, suggesting that medulloblastomas are 3–4 times more common than supratentorial PNETs [10]. Supratentorial PNETs, including pineoblastomas, likely represent only 2–4% of all brain tumors in children [11].

Previous studies have reported dismal survivals for children with supratentorial PNET. In the original paper by Hart and Earle only one patient survived to 5 years and the remainder were dead at an average of 10 months [12]. Kosnik *et al.* in 1978 reported on 15 cerebral PNETs (excluding pineoblastomas) occurring in children of mean age 3.1 years [13]. The survival at 1 year was only 10%. In more recent series, survival has been reported to be better, although these series are heterogeneous and difficult to compare. The two most recently reported series most closely resemble our own. Albright *et al.* reported on 27 patients with supratentorial PNET, excluding pineoblastoma [14]. All of their patients were children (only 1 patient older than 9 years), although none were less than 1.5 years of age. The overall 5 year survival was 34% and all patients received craniospinal radiation and chemotherapy. Children 1.5–3 years old had a significantly worse survival compared to older children. Children with disseminated disease on post-operative staging examinations also had worse survival. There was a trend to better survival in those children with smaller amounts of post-operative residual disease. This same group has also reported on the survival of children with pineoblastomas [15]. Twenty-three patients with pineoblastomas of mean age 3.1 years were treated with surgery and chemotherapy. Craniospinal radiation was also given to children older than 18 months. The 3 year survival was 74%. Another abstract has reported 48% 5 year survival for children with pineoblastoma [16]. Both abstracts suggest that survival has improved because of craniospinal radiation and chemotherapy.

Two year survival in a second recent series was 47% and at 5 years was between 6 and 30% [17]. This series also excluded children with pineoblastoma but was otherwise similar in that the mean age of the children was 3.3 years. There was no correlation between survival and tumor differentiation or extent of resection. Local recurrence, however, seemed to correlate with extent of primary resection.

Other series of PNETs are quite different because they examine a different patient population. Gaffney *et al.* reported a 25% 5 year survival rate on a group of patients whose mean age was 17.3 years [18]. In their series, they also identified that degree of differentiation correlated with survival. The review of primary cerebral neuroblastomas by Berger *et al.* suggested that these tumors were a distinct clinicopathologic entity [4]. The mean age of patients in their series was 9.9 years and they identi-

fied that cystic tumors and gross total resection were associated with better survival. Another series of cerebral neuroblastomas reported 30% 5 year survival although 13% of their patients were older than 20 years of age [3].

It is clear from our study that age has a significant impact on survival, and therefore comparisons between different studies must pay very close attention to age. Perhaps differences in survival between two groups are more a function of age of the patient as opposed to the intrinsic biology of the tumor. Patient age is known to have a significant impact on survival in supratentorial high grade astrocytomas [19]. Interestingly, our series had a very high proportion of patients at a very young age, with 36% of patients less than two years of age. Only six patients (17%) were older than 9 years of age and the oldest patient was 12 years old. In our series of 41 patients with intracranial neoplasms in the first year of life, 19% were supratentorial PNETs [20]. In other series, the incidence of supratentorial PNETs in the first 1–2 years of life was lower, ranging from 1%–14% [21–25]. The overall survival in our series may be lower than other series because of the higher proportion of younger patients.

Presence or absence of any type of differentiation or neuronal differentiation had no impact on survival in our series. In medulloblastomas, differentiation has been reported to be associated with both a worse and a better prognosis [26, 27]. Only one report of supratentorial PNETs has suggested that degree of differentiation may correlate with survival [18]. Location of PNET also did not have any significant impact on survival, but there is suggestion that pineoblastomas may have a better survival compared to cerebral hemisphere or deep PNETs. In addition, in this review, we did not demonstrate a difference in survival in patients with localized disease at presentation compared to those with disseminated disease. Also, at recurrence, disease remained local in 54% of patients and suggests that patients may benefit from repeat resection. In the 5 patients that came to autopsy, leptomeningeal dissemination was present in every case, however, 4 of these patients were already known to have disseminated disease. Therefore, we were unable to ascertain whether patients with only clinically apparent local recurrence actually have widespread disseminated disease. Because all children now uniformly undergo a post-operative staging assessment, we are likely to obtain a better assessment of the impact of tumor stage on survival in the future. Advanced disease stage is known to contribute to a worse survival in children with medulloblastom [28, 29].

Although it did not reach statistical significance, there is a trend to better survival following gross total resection. Three of the six survivors in this series had a gross resection. The impact that gross total resection has on survival makes intuitive sense, because PNETs on pathologic examination tend to be sharply demarcated from the surrounding brain [5]. Type of radiation therapy and chemotherapy did not have an impact on survival although it is noted that 4 of the 6 survivors received chemotherapy following diagnosis. The increasing use of chemotherapy and improved microsurgical resection in the past decade may have contributed to the trend to increased survival seen since 1984. Conversely, the fact that the overall survival is not statistically better after 1984, despite more aggressive treatment, emphasizes the extremely aggressive biologic nature of these lesions.

Summary and treatment recommendations

Supratentorial PNETs are highly malignant neoplasms which have a much worse prognosis than medulloblastoma. Recent studies show that the 5 year survival rate for medulloblastoma is 60–80% [28, 29]. Because of the rarity of these tumors, the controversies in opinion of pathologic classification, and the retrospective nature of past reviews of supratentorial PNETs, we have a poor understanding of the natural history of these lesions in children. Children usually present after a brief illness with signs and symptoms of raised intracranial pressure and imaging studies frequently reveal large tumors. Intracranial or spinal subarachnoid dissemination is estimated to be present in 20–40% of patients at the time of diagnosis. The overall 5 year survival of patients with supratentorial PNETs is 18% and young children have a worse prognosis.

We recommended that all children with a supratentorial PNET undergo gross total resection. If residual tumor is demonstrated on post-operative contrast enhanced neuroimaging studies, strong consideration should be given to performing a repeat resection. Because of the extremely poor survival of children with this disease, we recommended that all children receive post-operative chemotherapy. Radiation therapy should be withheld in patients under the age of 3 years because of its long term adverse effects on the developing central nervous system, but it should be used for patients who fail chemotherapy. Craniospinal radiation with a local boost to the primary tumor site should be given to all children over 3 years of age, regardless of post-operative staging examination. With aggressive resection, craniospinal radiation, and chemotherapy, we have seen a progressive increase in survival of patients with medulloblastoma over the past decade. Hopefully, with a similar aggressive treatment plan, we will observe increased survival in the next decade in children with supratentorial PNETs.

Acknowledgement

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