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CLINICAL STUDY - PATIENT STUDIES

Supratentorial primitive neuroectodermal tumors: a Canadian pediatric brain tumor consortium report

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Abstract *Introduction* Supratentorial primitive neuroectodermal tumors (SPNET) are rare tumors accounting for only 2.5% of childhood brain tumors. The purpose of this study was to describe the range of treatment regimens used to treat pediatric SPNET in Canada and to identify prognostic factors for overall survival in this population. *Methods* This study was a retrospective clinical analysis of SPNET patients treated over the last 10 years in Canada. A questionnaire was developed and distributed to all institutions in Canada who treat pediatric patients. Data were collected for patients <19 years of age who were diagnosed and treated for SPNET between 1995 and 2005. *Results* Data were obtained for 48 eligible patients. The stages of patients for whom complete data were provided were 80, 3, and 16% for metastatic stage M0, M1, and M2/3, respectively. The best responses to therapy included complete response in 44%, partial response in 8%, still on therapy in 2%, progressive disease in 31%, toxic death in 2%, and no therapy given in 12%. The 4-year survival was 37.7 ± 7.6%. The factors associated with an increase in survival were the use of radiation therapy and chemotherapy, and age >2 years. Overall survival was not affected by metastatic disease at diagnosis, tumor site, or degree of initial resection. *Conclusions* Survival is poor in SPNET

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patients but highest in those who received chemotherapy and radiation therapy. Further studies are needed to improve the survival of these patients.

Keywords Brain · Child · Supratentorial primitive neuroectodermal tumor

Introduction

Supratentorial primitive neuroectodermal tumors (SPNET) are embryonal tumors of the central nervous system that account for ~2.5% of childhood brain tumors [1]. The mean age at diagnosis for SPNET is 3 years and there is no sex predilection [2]. These tumors bear some similarities to posterior fossa medulloblastomas, but they exhibit important differences with respect to outcome and response to therapy which is much poorer [1, 3, 4]. SPNET also share many morphological features with medulloblastoma, but they have many different biological features including transcriptional and cytogenetic profiles [5]. Despite evidence of biological distinctness, SPNETs continue to be stratified as high-risk medulloblastoma in most cooperative group trials globally.

In two large reported series on SPNETs, improved survival rates were seen in older children and in those whose tumors were completely resected [6, 7]. In one of these studies the absence of metastatic disease and pineal tumor location were also associated with a better outcome [7].

Currently no established standard of care for patients with SPNET exists. A variety of therapeutic strategies ranging from radiation therapy with chemotherapy, to high-dose chemotherapy with autologous stem cell transplantation are currently followed by different treatment centers. Clearly, there is a substantive gap in knowledge about determinants of treatment outcomes in this group of tumors.

The purpose of this multicenter study was to review a large series of children with SPNET to obtain information about current treatment regimens and to determine if other disease and treatment factors affected survival. We found that there was an increase in survival in patients who received radiation therapy and chemotherapy, and in patients over the age of 2 years. In contrast to earlier works though, we did not find that survival was affected by metastatic disease at diagnosis, tumor location or degree of resection.

Methods

The Canadian Pediatric Brain Tumor Consortium is composed of the 17 centers in Canada that care for all children with brain tumors in the country. All of the centers were asked to participate in this study.

A questionnaire was developed by the principal investigator (DJ), which was based on input from the members of the Consortium.

Each of the participating centers received approval from their local Research Ethics Review Board prior to participating in this survey. No patient identifiers were included in the questionnaire or included in the central data collection.

Data were collected for all patients <19 years of age, diagnosed at their institution with SPNET between 1995 and 2005 by chart review. Information collected included categories of: presentation, anatomical location, MRI description, extent of surgical resection (based on post-operative imaging and the surgeon's report), histopathologic description and diagnosis, treatment including chemotherapy, high-dose chemotherapy with stem cell rescue and radiation therapy, and overall survival.

Overall survival was defined as date from diagnosis to death or last follow-up, and was described using the Kaplan Meier method. Survival between groups was compared using the log rank test. Those factors significantly associated with survival were then entered into a multiple regression Cox proportional hazards model to explore whether these were independently associated with survival. All statistical analysis was performed using the SAS statistical program (SAS-PC, Version 9.1; SAS Institute Inc., Cary, NC, USA). All tests of significance were two-sided and statistical significance was defined as $P < 0.05$.

Results

Thirteen of the seventeen centers (76%) responded to the survey and data were obtained on 50 patients. Two patients were excluded because one had a mid-brain tumor and one had an esthesioneuroblastoma. Thus, the analysis was performed on 48 eligible patients. All of these patients were evaluated for overall survival. A summary of patient characteristics is listed in Table 1.

The median age of the patients at the time of diagnosis was 49.5 months and ranged from 0 to 214 months. Twenty-four (50%) of the patients were male. The symptoms at presentation are listed in Table 2. The most frequent presenting symptoms were nausea or vomiting and headache. The median time from first presenting symptom to diagnosis was 1 month (range 0–6 months).

The locations of the lesions were mostly hemispheric (81%) with only nine (19%) of the tumors located in the pineal region. From the cases for which it was provided, imaging of the lesions revealed gadolinium enhancement in 89%, intra- and peri-tumoral hemorrhage in 37%, leptomeningeal disease in 18%, and calcifications in 41%. The mean maximal tumor dimension was 5.9 cm with a range of 1.5–11 cm.

Table 1 Summary of patient characteristics

Age	Location	Initial resection	Stage	Chemo drugs	Radiation site	Radiation dose (cGy)	Best response to therapy	Outcome	Time diagnosis to follow up	Time diagnosis to death	Failure type
8	Pineal	Complete	M0	E, Ci, Cy, V	None	N/A	N/A	Died		5	Septic shock
11	Pineal	Incomplete	Unk	None	None	N/A	N/A	Died		5	Cardiac arrest
17	Pineal	Subtotal	M2	None	None	N/A	N/A	Died		1	Unk
26	Pineal	Incomplete	M0	Cy, V, C	Tumor	4,200	PD	Died		5	Disseminated
31	Pineal	Incomplete	M0	E, Ci, Cy, V, L, Pr	CSA + tumor	5,300	CR	Alive	83		N/A
60	Pineal	Unk	Unk	V, C, Cy, Ca, P, H, Ci, A, Pr, T	Tumor	5,400	PD	Died		12	Distant progression
79	Pineal	Incomplete	M0	E, Ci, Cy, V	CSA + tumor	5,400	CR	Alive	4		N/A
94	Pineal	Biopsy	M3	None	CSA	5,400	PR	Died		17	Disseminated
175	Pineal	Incomplete	Unk	Ci, L, V	CSA + tumor	5,580	CR	Alive	21		N/A
13	Frontal	Complete	M0	E, Ci, Cy, V	None	N/A	PD	Died		8	Unk
18	Frontal	Complete	M0	E, Ci, Cy, V	None	N/A	PD	Died		6	Disseminated
21	Frontal	Complete	M0	Ci, Cy, E, V, HD	None	N/A	PD	Died		17	Local relapse
22	Frontal	Complete	M0	I, C, E	CSA	3,600	PD	Died		26	Disseminated
26	Frontal	Complete	Unk	Ci, Cy, E, V	None	N/A	CR	Alive	76		N/A
31	Frontal	Subtotal	Unk	V, Ci, Cy, E	CSA + tumor	5,040	PD	Died		9	Disseminated
33	Frontal	Subtotal	M0	E, Ci, Cy, V	CSA + tumor	5,580	CR	Alive	25		N/A
34	Frontal	Incomplete	M0	E, Ci, Cy, V	CSA + tumor	5,400	PD	Died		21	Local progression
49	Frontal	Incomplete	M0	E, Ci, Cy, V	CSA + tumor	5,400	PD	Died		6	Local and disseminated
50	Frontal	Incomplete	M0	None	None	N/A	N/A	Died		2	Palliative
50	Frontal	Complete	M0	I, C, E	CSA + tumor	5,040	PD	Died		8	Unk
51	Frontal	Complete	M0	V, Ca, P, H, Ci, A, Pr, Cy	CSA + tumor	5,400	CR	Alive	170		N/A
63	Frontal	Subtotal	M0	V, C, Cy	CSA + tumor	5,580	CR	Died		21	Disseminated
68	Frontal	Complete	M0	V, L, Pr	CSA + tumor	5,040	CR	Alive	123		N/A
106	Frontal	Incomplete	M3	V, L, Ci, Cy	CSA + tumor	5,580	CR	Alive	135		N/A
106	Frontal	Incomplete	M0	E, Ci, Cy, V	CSA + tumor	6,000	CR	Alive	39		N/A
128	Frontal	Complete	M0	V, L, Ci, Ca	CSA + tumor	5,580	CR	Alive	76		N/A
139	Frontal	Complete	M0	V, D, Cy, I, E	Brain	Unk	CR	Alive	13		N/A
142	Frontal	Subtotal	Unk	E, Ci, Cy, V	CSA + tumor	7,200	CR	Alive	107		N/A
0	Parietal	Biopsy	Unk	None	None	N/A	N/A	Died		3	Unk
10	Parietal	Subtotal	Unk	None	None	N/A	N/A	Died		6	Local progression
19	Parietal	Subtotal	M0	L, V, Pr	CSA + tumor	4,750	CR	Alive	209		N/A
22	Parietal	Complete	M0	E, Ci, Cy, V	Brain	5,000	PD	Died		12	Local progression
30	Parietal	Subtotal	M0	E, Ci, Cy, V	Brain	3,400	PD	Died		6	Disseminated
32	Parietal	Subtotal	Unk	C, E, I, V	Tumor	5,040	CR	Alive	33		N/A
49	Parietal	Complete	M0	E, Ci, Cy, V	None	N/A	CR	Alive	5		N/A

Table 1 continued

Age	Location	Initial resection	Stage	Chemo drugs	Radiation site	Radiation dose (cGy)	Best response to therapy	Outcome	Time diagnosis to follow up	Time diagnosis to death	Failure type
67	Parietal	Complete	M0	V, L, Ci	CSA + tumor	5,400	CR	Died		92	Local progression
127	Parietal	Complete	M0	I, C, E, HD	Tumor	5,400	PR	Died		57	Distant progression
140	Parietal	Incomplete	M0	V, L, Ci	CSA + tumor	5,400	PR	Died		8	Disseminated
154	Parietal	Subtotal	M0	E, Ci, Cy, V	CSA + tumor	5,400	On Tx	Alive	2		N/A
214	Parietal	Subtotal	M0	C, L, V	CSA	3,600	CR	Alive	15		N/A
10	Temporal	Complete	M0	None	Brain	5,000	CR	Alive	97		N/A
55	Temporal	Complete	M1	E, Ci, Cy	CSA + tumor	5,400	PD	Died		18	Disseminated
72	Temporal	Incomplete	M3	Given - unk	Given - unk	Unknown	CR	Alive	2		N/A
95	Temporal	Subtotal	Unk	V, Ci, Ca	CSA + tumor	5,580	CR	Alive	73		N/A
160	Temporal	Subtotal	M2	E, Ci, Cy, V	CSA + tumor	5,400	PD	Died		22	Disseminated
10	Occipital	Incomplete	M3	None	None	N/A	N/A	Died		0	Local progression
25	Occipital	Incomplete	Unk	C, E, V, Cy	Tumor	2,300	PR	Died		7	Disseminated
180	Occipital	Biopsy	M0	E, Ci, Te	CSA + tumor	5,400	PD	Died		9	Local progression

C carboplatin, *E* etoposide, *I* ifosfamide, *V* vincristine, *Cy* cyclophosfamide, *Ca* carmustine, *P* procarbazine, *H* hydorxyurea, *Ci* cisplatin, *A* cytarabine, *Pr* prednisone, *T* thiotepa, *HD* high dose with stem cell rescue, *L* lomustine, *Te* temozolamide, *D* doxorubicin, *CSA* craniospinal axis, *N/A* not applicable, *Unk* unknown, *CR* complete response, *PR* partial response, *PD* progressive disease

Table 2 Symptoms of patients at presentation of SPNET

Symptom	Number of patients	Percentage
Nausea/vomiting	29	59
Headache	28	57
Seizure	13	27
Ataxia	5	10
Visual difficulties	6	12
Focal neurological signs	7	14
Hemiparesis	6	12
Irritability	7	14
Lethargy	6	12
Other symptoms[a]	All <4	All <8

[a] Other symptoms include somnolence, bradycardia, hypertension, fixed/dilated pupils, decreased sleep, ear pain, dizziness, speech difficulty, personality changes, increased head circumference, loss of consciousness, polyuria/polydipsia, hemianopsia, hearing loss, ptosis, and skull swelling

As part of the staging workup, some patients underwent cerebrospinal fluid analysis ($n = 32$), MRI of the spine ($n = 34$), bone marrow analysis ($n = 13$), and bone scan ($n = 11$). Cerebrospinal fluid was positive for malignant cells in three (9%) of the 32 patients. MRI of the spine at diagnosis was normal in 30 of 34 patients (88%). Bone marrow and bone scan analyses were negative in all patients. One patient who did not have a bone scan had obvious skull bone erosion on plain radiograph. The overall stage of disease was reported by institutions on a higher number of patients ($n = 37$) as M0 in 30 (81%), M1 in one (3%), M2 or M3 in six (16%), and M4 in none.

All patients underwent a surgical procedure: biopsy only (<10% of tumor resection) in 6% (3/48), incomplete resection (10–90% of tumor removed) in 29% (14/48), subtotal resection (91–99% of tumor removed) in 27% (12/48), and complete resection (100% of tumor removed) in 35% (18/48). In 2% (1/48) the extent of surgical resection was not recorded.

Pathological information was obtained for all patients. Forty-three patients had PNET with glial, astrocytic or neuronal differentiation. Two patients had PNET with rhabdoid like cells but neither patient had tumors that fulfilled the diagnostic criteria for atypical teratoid rhabdoid tumor. Two patients were had ependymoblastoma and one a central ganglioneuroblastoma.

The post-operative therapy given to these patients was varied and some patients received more than one type of therapy (such as chemotherapy and radiation therapy). Five received chemotherapy alone, two received high-dose chemotherapy with stem cell rescue (one also had radiation therapy), two received radiation therapy alone, 33 received both chemotherapy and radiation therapy, and six received supportive care only. The median dose of radiation given was 5,400 cGy with a range of 2,300–7,200 cGy. Of the 36 patients who received radiation therapy, 26 received radiation that included the cranisospinal axis, four received whole brain irradiation, focal radiation was given to five patients, and in one the radiation field was not noted.

The responses to therapy varied. There were six patients (12%) who had no therapy given and one patient who was still on therapy who are not included in the response calculations. Of the remaining 41 patients, 21 had a complete response to treatment; of these two relapsed and died. Four patients had a partial response and all of them ultimately died of progressive disease. There was progressive disease or relapse in 21 patients (51%) (including the six who had an initial response), and toxic death (from sepsis) in one patient (2%). The pattern of relapse for the patients who experienced disease progression was disseminated in 11/21, local in 5/21, local and disseminated in 1/21, and distant in 2/21. For 2/21 the location of relapse was not noted.

The five patients who received focal radiation included one who survived their disease and four who died of progressive disease. Focal radiation was used in two patients with pineal region tumors (both of whom died of disease) while the other four patients with pineal tumors who received radiation had craniospinal radiation and three of these survived their disease.

The 4-year survival was 37.7 ± 7.6% and the median follow up time for survivors was 42 months (range 2–134 months). Table 3 illustrates that age, chemotherapy, radiotherapy, and treatment with both chemotherapy and radiotherapy were associated with improved survival (Figs. 1, 2, 3, respectively), whereas metastatic disease, pineal location, and complete resection were not prognostic factors.

In a multiple regression model including age over 24 months, chemotherapy and radiotherapy, only the use of radiotherapy was significantly associated with improved survival with an adjusted hazards ratio of 0.23 ((95% CI 0.09–0.58; $P = 0.002$) for radiotherapy, 0.83 (95% CI 0.30–2.29; $P = 0.7$) for age over 24 months, and 0.40 (95% CI 0.14–1.11; $P = 0.08$) for chemotherapy).

Discussion

This survey summarizes the data for 48 pediatric patients with SPNET treated in 76% of Canadian pediatric oncology centers from 1995 to 2005. This survey represents one of the larger series in the literature. The 4-year survival of our patients was 37.7 ± 7.6%, within the range of previously published survival rates of 17–57% [6–14]. We found a significantly longer survival in patients treated with chemotherapy and radiation therapy. Factors found by

Table 3 Four years overall survival in different subgroups

	Present	Absent	*P*-value
Age >24 months (n = 35)	49.2 ± 9.1	8.3 ± 8.0	0.002
Metastatic disease (n = 7)	17.9 ± 16.0	39.1 ± 9.9	0.4
Pineal tumor location (n = 9)	25.4 ± 15.5	40.8 ± 8.5	0.2
Complete or subtotal resection (n = 30)	44.9 ± 9.8	27.3 ± 11.6	0.1
Radiation (n = 36)	48.1 ± 9.2	8.3 ± 8.0	<0.0001
Chemotherapy (n = 40)	42.9 ± 8.6	12.5 ± 11.7	0.003
Both radiation and chemotherapy (n = 34)	48.0 ± 9.6	14.3 ± 9.4	0.0008

Percent survival ±SE

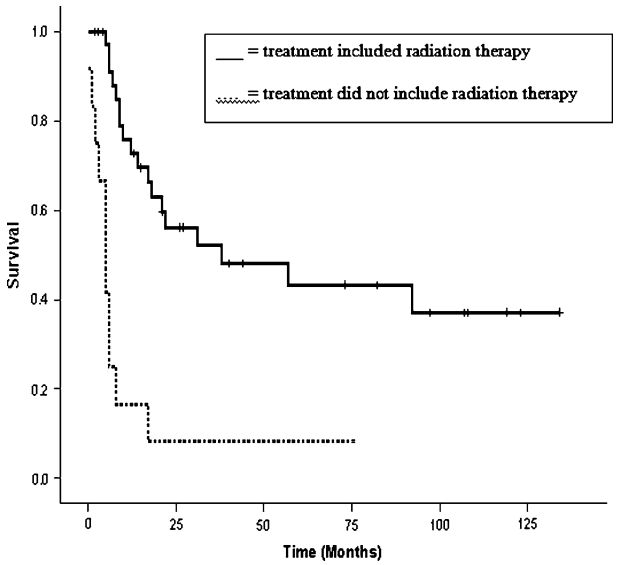

Fig. 1 Comparison of survival for patients who received radiation versus no radiation

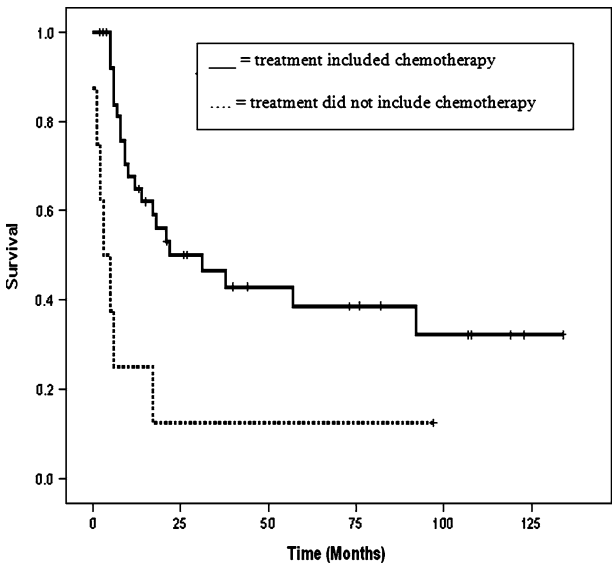

Fig. 2 Comparison of survival for patients who received chemotherapy versus no chemotherapy

others to be associated with a poor prognosis in SPNET (location of tumor, extent of resection, presence of metastatic disease) [6, 7] were not found to affect survival in our population. Children <2 years of age have previously been found to have a poor prognosis [6, 7] and we also found a worse survival in this age group.

The extent of surgical resection, whether gross total, at least 90% resection or resection leaving <1.5 cm^2 of residual disease, has been shown by several authors to improve survival rates [2, 6, 7, 10, 12]. We found no difference in survival based on extent of resection, similar to a recent publication from the SIOP [14]. This is likely due to the effectiveness of chemotherapy and radiation therapy in treating this tumor.

Nor did we find an association of improved survival in patients with nonmetastatic disease, a finding that has previously been reported [7, 12]. It is possible that the impact of surgery was lost in the various treatments our patients received. The lack of impact of metastases on survival may be due to the imbalance of our population toward M0 stage. As well, given the variability in the staging workup, this must be interpreted with caution.

Not surprisingly, we found a significant survival benefit when chemotherapy and radiation therapy were used concurrently. Multiple regression analysis found that only radiation therapy was independently significantly associated with improved survival. Results of this multiple regression, though, must be viewed cautiously given the number of children included in this study. Nonetheless, previous studies have shown that children with SPNET who were not treated with radiation therapy had a high-relapse rate [5, 15–18]. A recent CCG infant brain tumor study included 46 patients with SPNET, and only four of these patients who did not receive radiation therapy were event free at 5 years [12]. As well, a recent SIOP study of 68 patients with SPNET randomized patients to pre-radiation chemotherapy followed by radiation versus radiation therapy alone and there was no difference in survival

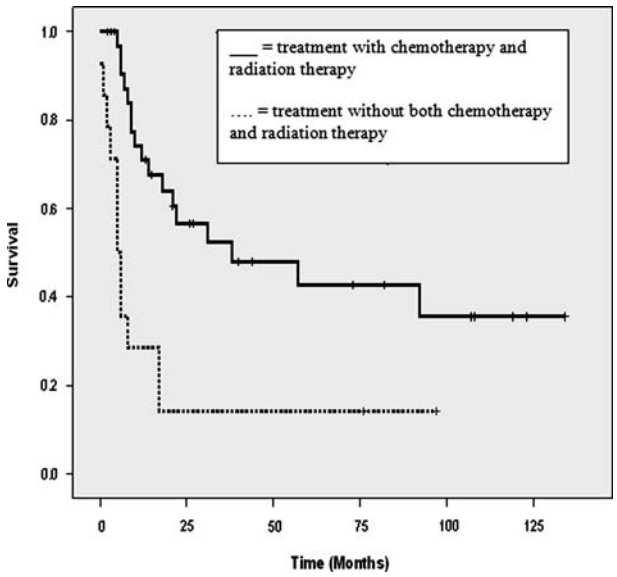

Fig. 3 Comparison of survival for patients who received both chemotherapy and radiation therapy versus those who did not receive both therapies

between these two groups, again emphasizing the role of radiation therapy [14]. Our findings also strengthen the argument that radiation therapy is of benefit to survival in SPNET, however there are a few long-term survivors in patients who did not receive radiation, suggesting there are likely biological differences in this tumor.

One interesting finding regarding radiation was the use of focal or brain irradiation as opposed to craniospinal radiation. In this series three of the nine patients treated with focal or brain irradiation survived, which is similar to the overall survival in this study. Thus, this type of radiation deserves consideration in patients who clinicians are reluctant to treat with craniospinal irradiation.

The fact that only radiation therapy was associated with increased survival in multiple regression analysis, and not age or chemotherapy emphasizes the issue of potential confounders. Clinicians are generally reluctant to treat young children with radiation to the central nervous system given the profound effects on brain development. Thus, the result that young age was associated with a significant decrease in survival was possibly related to the fact that clinicians are hesitant to use this therapy in this age group and thus these young patients were not offered the best therapy for survival. It is also possible that younger children present with very aggressive disease in which a decision is made to treat the patient with supportive care alone without radiotherapy or chemotherapy.

There were many different chemotherapy protocols used in this survey, and we cannot thus comment on the specific regimen. In a previous randomized CCG study that included patients with SPNET, different chemotherapy regimens did not influence survival [7]. Regimens in this survey were moderate to high-intensity therapy employing vincristine, platinum-based compounds, and alkylating agents, and we support use of types of regimens.

The majority of children in our study presented with signs of increased intra-cranial pressure, as well 28% presented with seizures. In previous reviews of children with SPNET, seizures were present in 22% of patients [6] and focal neurological deficits in 25% [10]. Seizures are reported to occur in ~15% of patients with supratentorial lesions [19], and patients with SPNET have an incidence of seizures that is somewhat higher than this.

In our study, we examined the workup of patients for metastatic disease. Only a minority of patients underwent a bone marrow analysis or bone scan (27 and 23%, respectively), and these tests were negative in all circumstances. Reviewing 222 SPNET patients from other series showed that <0.5% of patients presented with metastases outside of the CNS [6, 7, 14, 15]. We believe that bone marrow analysis and bone scan are unnecessary for patients newly diagnosed with SPNET, unless they have symptoms and signs to strongly suggest involvement of these sites.

Children with SPNET located in the pineal region have previously been reported to have better outcomes compared to children with SPNET in other locations [7, 14, 16]. Our study show contrary results such that patients with hemispheric tumors had a higher 4-year survival than patients with pineal tumors (41% vs. 24%, respectively), but the difference did not reach statistical significance ($P = 0.2$). However, there were only nine patients with pineal tumors in this study and only five of these patients were treated with chemotherapy and radiation therapy. Of these five patients three survived their disease and so pineal tumors treated with the combination of chemotherapy and radiation therapy had a survival of 60% supporting this type of therapy for these tumors.

This study is somewhat limited by its retrospective nature and small sample size. Given the small sample size, the results of multiple regression analysis should be viewed cautiously. This is a rare tumor and survival is similar in most studies, so the heterogeneity of treatments in this study may not be a major limitation. The lack of central pathology review is another limitation, as information from this would have enabled a more detailed analysis on outcome compared to pathological subtype. These patients are an unselected series of all patients seen at the participating institutions during the study time period. Thus, the information obtained may be slightly different from other studies, which are based on protocols with eligibility requirements. Despite these limitations this is one of the largest series of SPNET patients, and the results provide useful information.

Conclusions

This study of 48 pediatric patients with SPNET treated between 1995 and 2005 found a 4-year survival of 37.7%. This is similar to survival rates from previous studies published as early as 10 years ago. This study demonstrated that chemotherapy combined with radiation therapy was associated with a significant increase in survival. Although the patients who received a combination of chemotherapy and radiation therapy had a higher 4-year survival rate, the number of patients and the variation in chemotherapy protocols makes it difficult to assess the preferred treatment modality. Based on the survival of patients who received radiation therapy, there appears to be a consensus that this modality needs to be included in whatever chemotherapy protocol is developed. Stage of disease, location of the tumor, and extent of resection were not associated with a difference in survival. The results of this review reinforce the need for specific SPNET studies utilizing different treatment regimens, which include a combination of chemotherapy and radiation therapy, in order to improve the survival of these children. New strategies for infants are needed.

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