Acta Neurochir (2015) 157:1251–1266
DOI 10.1007/s00701-015-2444-2

CLINICAL ARTICLE - BRAIN TUMORS

Treatment outcome and patterns of failure in patients of non-pineal supratentorial primitive neuroectodermal tumor: review of literature and clinical experience form a regional cancer center in north India

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Received: 3 March 2015 / Accepted: 5 May 2015 / Published online: 20 May 2015

Abstract
Background Supra-tentorial primitive neuroectodermal tumors (SPNET) are high-grade, hemispheric tumors, which account for around 2–3 % of pediatric brain tumors. We herein intend to report the clinical features and treatment outcome of patients with nonpineal SPNET treated at our institute.
Methods Clinical data were collected by retrospective chart review from 2006 to 2012. Histopathology slides were reviewed, and relevant immunohistochemistry stains were done. Overall survival (OS), recurrence-free survival (RFS) and event-free survival (EFS) were analyzed by the Kaplan-Meier product-limit method.
Results Fifteen patients met the study criterion (male: female=2:1). Median age at presentation was 11 years (range 3–49 years). Surgical resection was gross total in 6 (40 %) and subtotal in 8 (53.33 %) patients. At presentation, two patients had leptomeningeal dissemination. Radiation therapy was delivered in 11 (73.33 %) patients: craniospinal irradiation in 8 (36 Gy/20 fractions/4 weeks to the craniospinal axis followed by a local boost of 20 Gy/10 fractions/2 weeks) and focal RT in 3 patients. Systemic chemotherapy (median 6 cycles; range 1–16 cycles), given in 13 (86.67 %) patients, included the VAC regimen (vincristine, adriamycin, cyclophosphamide) alternating with IE (ifosfamide,etoposide). After a median follow-up of 22.6 months (mean, 24.47 months), complete response and progressive disease were noted in 8 (53.33 %) and 7 (46.67 %) patients, respectively. Median OS was not reached, and estimated median EFS was noted to be 4.12 years (actuarial rate of EFS at 2 years, 55.2 %).
Conclusion Maximal safe resection followed by craniospinal irradiation and systemic chemotherapy with 6–12 cycles of an alternating regimen of VAC and IE is a reasonable treatment strategy in patients with nonpineal SPNET.

Keywords Craniospinal irradiation · Primitive neuroectodermal tumor · Radiotherapy · Supratentorial

Presentation Part of the data was accepted for a poster presentation at the 4th quadrennial meeting of the World Federation of Neuro-Oncology in San Francisco, CA, USA, November 2013. Neuro Oncol 2013; 15 (suppl3): iii79.

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Introduction

Supratentorial primitive neuroectodermal tumor (SPNET) is a high-grade central nervous system malignancy that makes up approximately 2–3 % of all childhood brain tumors [11]. It was first described as a separate disease entity by Hart and Earle in 1973 [17]. According to the classification proposed by Rorke in 1983, intracranial PNET was thought to be a spectrum of disease arising from different parts of the brain [37]. Medulloblastoma, the most common intracranial PNET, is located in the posterior fossa. The diagnostic workup and treatment policy for infra- and supratentorial PNET are not

clearly distinguishable. However, the prognosis in patients with SPNET is worse in comparison to those with posterior fossa PNET [4, 30]. The current study was conducted at our institute to evaluate the clinical features, treatment protocol, patterns of failure and survival outcome in 15 consecutive patients with nonpineal SPNET.

Methods

Patient selection

We performed a comprehensive analysis of patients with nonpineal SPNET undergoing treatment at our institute from January 2006 to December 2012 by retrospective chart review. Demographic features, clinical characteristics including radiological findings, surgical details, histopathological features, adjuvant treatment policy and clinical outcome were recorded in a pre-designed proforma.

Diagnostic workup

Preoperative hemogram, liver and kidney function tests, chest X-ray and contrast-enhanced magnetic resonance imaging (MRI) of the brain were done for all patients. After obtaining the final histopathology report, the patients were evaluated by the neuro-oncologist for adjuvant therapy. Postoperative contrast-enhanced MRI of the entire neuraxis and cerebrospinal fluid (CSF) cytology were done in all patients for risk categorization prior to the start of adjuvant treatment.

Surgical policy

Maximal safe resection was attempted in all patients at the Department of Neurosurgery at our institute. The extent of resection was ascertained from the surgeon's intraoperative notes and postoperative imaging (MRI of the brain). Owing to the aggressive nature and predilection for CSF dissemination in these tumors, adjuvant therapy was administered in all patients expeditiously.

Radiotherapy policy

Adjuvant radiation was started within 4 to 6 weeks after surgery. The clinical target volume (CTV) consisted of the entire brain and spinal axis extending at least 1 cm below the termination of the thecal sac. An isotropic margin of 5 mm was given around the CTV to generate the planning target volume (PTV). Radiation was delivered by a combination of two cranial fields and 1–2 spinal fields with 6 MV X-rays. Radiation planning was done using the Eclipse treatment planning system, version 6.5 (Varian Medical Systems, Palo Alto, CA, USA). Fit patients more than 3 years old were offered craniospinal irradiation: 36 Gy/20 fractions/4 weeks to the entire neuraxis followed by a local boost of 20 Gy/10 fractions/2 weeks usually by three-dimensional conformal radiotherapy on a CL 2300 CD linear accelerator (Varian Medical System, Palo Alto, CA, USA). A boost dose of 5.4–9 Gy at 1.8 Gy per fraction was considered for isolated spinal drop metastasis. In children below 5 years of age, immobilization was achieved with the aid of general anesthesia if required. Blood counts were repeated twice every week, and toxicity charting was done weekly using the RTOG acute radiation morbidity scoring criterion. Radiotherapy was withheld, and appropriate supportive care was given for emergence of grade 3/4 toxicity.

Chemotherapy policy

Adjuvant chemotherapy was administered in all fit patients because of the high propensity of leptomeningeal dissemination and systemic recurrence. The chemotherapy regimen consisted of 12 alternating cycles of VAC (vincristine, 1.5 mg/m^2 IV D1, D8 and D15 with a top dose of 2 mg; adriamycin,75 mg/m^2 IV D1; cyclophosphamide, 1.2 gm/m^2 IV D1 with Mesna uro-protection) and IE (ifosfamide, 1.8 gm/m^2 IV D1–D5 with Mesna uro-protection; etoposide 100 mg/m^2 IV D1–D5) repeated every 3 weeks. Adriamycin was replaced with actinomycin D during the sixth cycle of VAC. Chemotherapy interruption or dose reduction was done in case of emergence of grade 3/4 hematological or non-hematological toxicities.

Follow-up policy

After completion of treatment, all patients were clinically reviewed every 3 months for the first 2 years, then every 6 months from the 3rd to 5th year and annually once thereafter. Contrast-enhanced MRI of the entire neuraxis was done at the time of first follow-up, after 1 year and then only on suspicion of disease recurrence. Response assessment was done as per the modified McDonald criterion [24].

Statistical analysis

An event was defined as death (due to disease progression or treatment-related toxicity), disease progression or recurrence. EFS, RFS and OS were defined as the interval of time from the date of diagnosis to the date of any event, documented disease recurrence or death, respectively. Survival analysis was done by Kaplan-Meier product limit method. Statistical analysis was done using MedCalc software (version 11.3.0). Patients alive at last follow-up were censored.

Results (Table 1)

Patient characteristics

Fifteen patients met the study criterion. A male sex predilection was noted (male:female=2:1). Median age at presentation was 11 years (range 3–49 years). Presenting features included vomiting in six (40 %), headache in five (33.33 %), visual deterioration in five (33.33 %), motor impairment in four (26.67 %), seizures in four (26.67 %) and scalp swelling in three (20 %) patients. Hearing loss and ataxia were noted in one patient each. Median symptom duration was 3 months. Median Karnofsky performance scale (KPS) was 80 (range: 50–90).

Radiology (Fig. 1)

Contrast-enhanced MRI of the brain revealed heterogeneous contrast-enhancing solid cystic supratentorial lesions. Tumor location was frontal in three, temporal in two, occipital in one, multilobed in five, ventricular in one, thalamic in one, midbrain in one and suprasellar in one patient. At presentation, two (13.33 %) patients had leptomeningeal dissemination.

Surgery

All patients underwent maximal safe resection. Surgical resection was gross total in six (40 %) and subtotal in eight (53.33 %) patients. Surgery was not possible in one patient. Large tumor size and extension to eloquent areas often precluded a complete surgical resection. Postoperative residuum was noted in nine patients on imaging. Three patients required the placement of a medium pressure ventriculo-peritoneal (MPVP) shunt for hydrocephalus.

Pathology (Fig. 2)

Postoperative histopathology showed highly cellular, poorly differentiated tumors comprising small round cells with high nucleo-cytoplasmic ratios. The tumor cells were arranged in sheets. The tumors had brisk mitotic activity. All cases were immunopositive for synaptophysin, class III ß-tubulin, neuron-specific enolase (NSE) and neurofilament protein, but immunonegative for glial fibrillary acidic protein (GFAP) and MIC-2. The MIB-1 labeling index was high in all cases (median, 35 %; range, 25–80 %) indicating high proliferative activity of the tumor.

Table 1 Compendium of patient and tumor characteristics, treatment and clinical outcome in 15 consecutive patients with nonpineal SPNET

Serial no.	Age (years)	Sex	KPS	Tumor location	M stage	Surgery	Radiotherapy	Chemotherapy	No. of cycles	Recurrence	FU duration (days)	Status at last FU
1	24	M	90	Temporal	M0	STR	None	VAC/ ICE	6	None	184	CR
2	3	M	70	Parieto-occipital	M3	GTR	None	VAC/ ICE	4	Leptomeningeal	54	PD
3	14	F	70	Lt Ventricle	M0	STR	CSI	VAC/ ICE	6	Local	678	PD
4	5	M	90	Frontal	M0	STR	Local	VAC/ ICE	12	None	781	CR
5	8	F	90	Occipital	M0	GTR	CSI	None	0	None	1502	Expired
6	11	F	80	Frontal	M0	STR	Local	VAC/IE	12	None	883	CR
7	32	M	70	Suprasellar	M0	STR	CSI	VAC/IE	8	Local	569	Expired
8	12	M	70	Parieto-occipital	M1	STR	CSI	VAC/IE	6	None	817	CR
9	49	M	80	Frontal	M0	GTR	CSI	VAC/IE	6	Leptomeningeal	259	Expired
10	3	M	90	Temporal	M0	GTR	Local	VAC/IE	12	None	745	CR
11	40	M	70	Midbrain	M0	GTR	CSI	None	0	Local+ leptomeningeal	2791	PD
12	5	F	50	Fronto-temporal	M0	Not done	None	VAC	1	Local	58	PD
13	3	M	70	Fronto-parietal	M0	STR	CSI	VAC/IE	5	None	246	Expired
14	5	M	80	Gangliothalamic	M0	STR	CSI	VAC/IE	16	None	1277	CR
15	22	F	80	Occipito-parietal	M0	GTR	Due	VAC/IE	4	None	166	CR

KPS Karnofsky performance scale; *FU* follow-up; *M* male; *F* female; *GTR* gross total resection; *STR* subtotal resection; *CSI* craniospinal irradiation; *VAC* vincristine, adriamycin, cyclophosphamide; *IE* ifosfamide, etoposide; *ICE* ifosfamide, carboplatin, etoposide; *CR* complete response; *PD* progressive disease

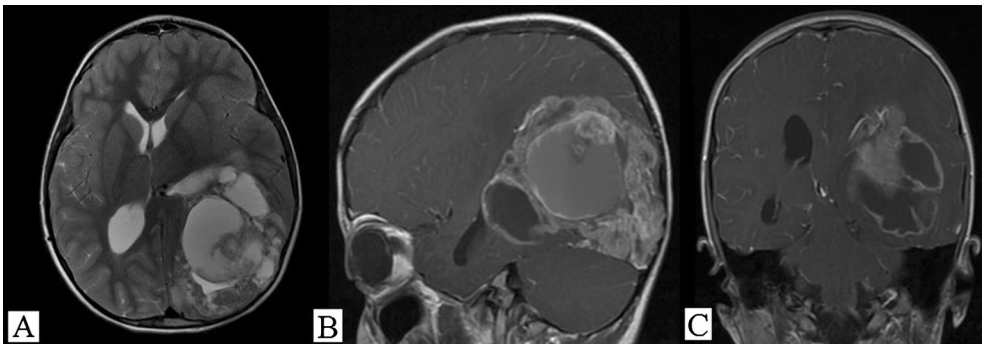

Fig. 1 **a** T2-weighted axial MRI image showing a large, lobulated, solid cystic mass involving the left parieto-occipital lobe, **b** T1-weighted post-gadolinium sagittal image and **c** coronal image show the same mass with a large cystic and solid component with heterogeneous contrast enhancement, mass effect and midline shift

Radiation therapy

Radiation therapy was delivered in 11 (73.33 %) patients: craniospinal irradiation in 8 (36 Gy/20 fractions/4 weeks to the craniospinal axis followed by a local boost of 20 Gy/10 fractions/2 weeks) and focal RT in 3 patients. One patient progressed before initiation of radiotherapy and was lost to follow-up. Radiotherapy-related toxicities included dermatitis: grade 1 in two and grade 3 in one; CNS reaction: grade 1/2 in two; pharyngitis: grade 1 in one; neutropenia: grade 2 in two and grade 3 in one patient.

Systemic chemotherapy

Systemic chemotherapy with an alternating VAC and IE regimen was given in 13 (86.67 %) patients. Though we aimed to give a total of 12 cycles of chemotherapy with an alternating VAC/IE regimen, many of our patients struggled through the course of chemotherapy because of persistent myelosuppression after craniospinal irradiation, further compounded by adjuvant cytotoxic chemotherapy. Median number of cycles administered was six (range 1–16). Chemotherapy-related grade 3/4 toxicity included neutropenia

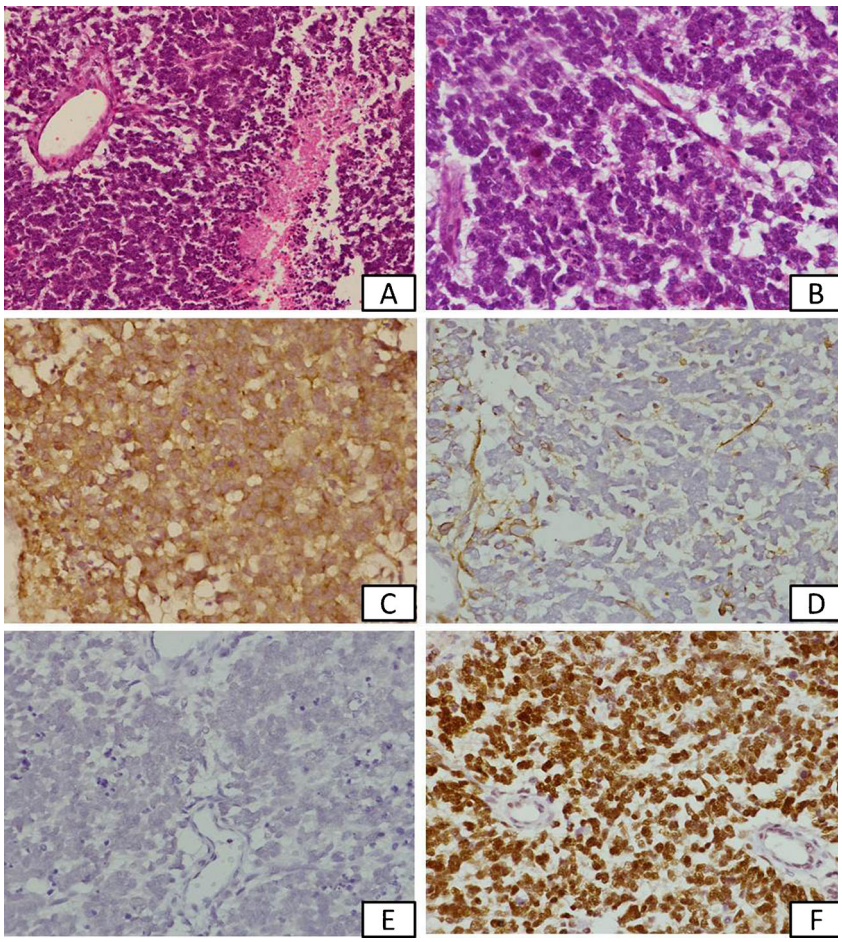

Fig. 2 **a** Photomicrograph showing a highly cellular tumor with tumor cells arranged in diffuse sheets with foci of necrosis (×100); **b** the tumor cells have a high nucleo-cytoplasmic ratio with scant cytoplasm and indistinct cell borders, vesicular nuclei with indistinct nucleoli (×200); **c** the tumor cells are immunopositive for synaptophysin (cytoplasmic staining) (×200); **d** the tumor cells are immunonegative for GFAP (×200); **e** immunostaining for MIC-2 is negative (×200); **f** MIB-1 stain showing high proliferative activity of the tumor (labeling index >90 %) (×200)

in eight (53.33 %), thrombocytopenia in four (26.67 %), anemia in three (20 %) and mucositis in two (13.33 %) patients. Three (20 %) patients had neutropenic fever, and one of them died of sepsis. The most common sequence of treatment was surgery followed by radiotherapy and chemotherapy.

Survival analysis (Fig. 3)

After a median follow-up of 22.6 months (mean, 24.47 months), complete response and progressive disease were noted in eight (53.33 %) and seven (46.67 %) patients, respectively. Four (26.67 %) patients died: three due to disease progression and one due to treatment-related toxicity (neutropenic sepsis). Median OS was not reached (actuarial rate of OS at 1 and 2 years: 81.8 and 72.7 %, respectively), and estimated median EFS was noted to be 4.12 years (actuarial rate of EFS at 1 and 2 years, 70.9 and 55.2 %, respectively).

Patterns of failure

Recurrence was noted in six (40 %) patients: local in three patients, leptomeningeal dissemination in two and both in one. The median time to disease recurrence was 11.12 months (mean, 20.67 months). The actuarial rate of recurrence-free survival at 1 and 2 years was 77 and 57.8 %, respectively.

Salvage treatment

Salvage therapy was offered to one patient with multiagent chemotherapy with a combination of intravenous vincristine, etoposide and carboplatin and weekly intrathecal methotrexate. The patient achieved complete response after six cycles but developed diffuse leptomeningeal disease 6 months after completion of chemotherapy. Best supportive care was given to the remaining five patients with recurrent disease because of poor general health and advanced disease.

Discussion

Hart et al. described supratentorial primitive neuroectodermal tumor (SPNET) as a poorly differentiated intracranial embryonal tumor in 1973 [17]. SPNET is an extremely rare central nervous system (CNS) tumor and constitutes 2.5 % of all pediatric brain tumors [5, 11, 17, 27]. Although histologically indistinguishable from other small round cell tumors of the brain, SPNET is characterized by its distinct aggressive clinical behavior and poorer outcome [19, 33, 37]. There is mounting evidence that SPNET and medulloblastoma (MB) have different molecular alterations and different responses to treatment [4, 5, 19, 38]. Gain of chromosome 17q is more common in MB, whereas loss of chromosome 14q is more common in SPNET [38]. Recently, Picard and colleagues reported three distinct molecular subgroups of central nervous system PNET distinguished by primitive neural (group 1), oligoneural (group 2) and mesenchymal (group 3) lineage with differential expression of cell lineage markers LIN28 and OLIG2 [34]. Patients in group 1 were predominantly females with younger age at presentation and dismal prognosis, the median survival being 0.8 years compared to 1.8 and 4.3 years in group 2 and group 3, respectively.

SPNET is commonly located within the cerebral cortex and pineal region (pinealoblastoma) [9, 36]. These tumors are histologically heterogeneous with variable amounts of glial, neuronal and ependymal differentiation [7]. SPNET commonly affects children and young adults, and the median age at presentation in our study was 11 years. Patients with SPNET present with a wide range of symptoms, which is attributable to their varying locations. Headache, vomiting and visual disturbance were the common presenting features in our study cohort. SPNET shows a high propensity of CSF dissemination (14–20 %) [28, 31]. In the present series, leptomeningeal spread was observed in two patients at presentation and another three at failure.

The management of SPNET has largely evolved based on the treatment philosophy for high-risk medulloblastoma [36].

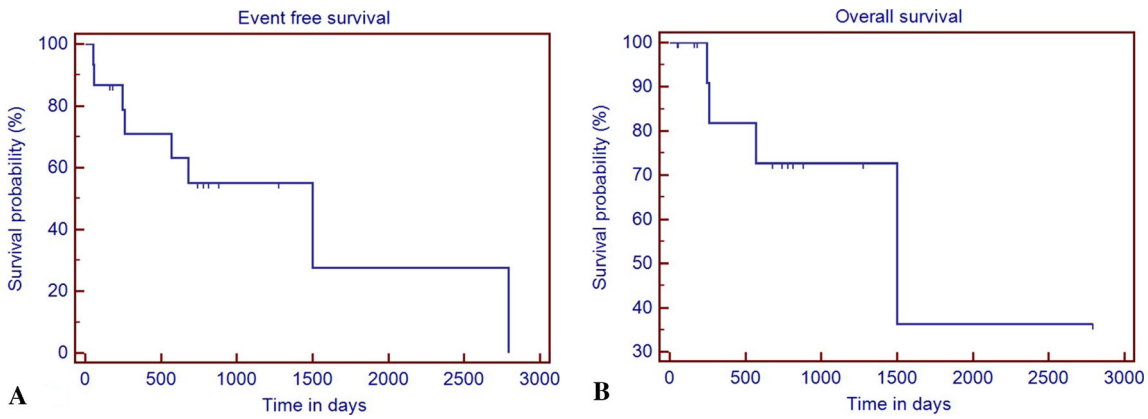

Fig. 3 Kaplan-Meier survival curves depicting (**a**) event-free survival and (**b**) overall survival in this cohort of 15 patients with SPNET

Multimodality management comprising surgery, radiation therapy and systemic chemotherapy is essential for therapeutic success in this rare tumor [28]. Surgery is the cornerstone of management and offers rapid symptom relief and long-term disease control [42]. Variable rates of gross total resection (GTR) have been reported in the literature, ranging from 20 to 53.33 % (Table 2). Young age at diagnosis, large tumor size and extension of the tumor to eloquent areas of the brain often preclude GTR. In the available literature, the prognostic significance of achieving GTR is controversial [6, 7, 21, 22, 28]. Albright et al., in a series of 27 patients with SPNET treated with the CCG-921 protocol, showed that postoperative survival at 4 years was 40 versus 13 % in patients with a postoperative residuum of less than and more than 1.5 cm^2, respectively [1]. There was a trend toward better survival in children undergoing GTR (P=0.08) in a series of 36 patients with SPNET from the Hospital for Sick Children, Toronto, reported by Dirks et al. [7]. In the present study, GTR could only be accomplished in 40 % of patients.

Keeping in mind the natural history of the tumor, craniospinal irradiation (CSI) followed by a local boost to tumor bed is considered standard [31]. The most commonly used time-dose fractionation schedule is CSI to a dose of 36 Gy (range 18–40 Gy) followed by a local boost to 54 Gy (range 45–72 Gy) in conventional fractionation (Table 2). Reduced dose CSI (23.4 Gy) or focal RT alone has been used in very young children (1.5–3 years) in a few studies to minimize the late effects of radiation (Table 2). Paulino et al., in a series of 25 patients with SPNET, reported 5- and 10-year progression-free survival (PFS) rates of 47.1 % in patients treated with CSI compared to 12.5 and 0 %, respectively, in patients undergoing whole-brain RT (WBRT) or focal RT (P=0.02) [31]. Failure at the untreated neuraxis site was the most common cause of progression in six out of eight patients receiving WBRT or focal RT [31]. McBride et al., in a retrospective review of 15 patients with nonpineal SPNET, observed a statistically significant difference in overall survival in patients who received upfront RT versus those who did not (P=0.048) [28]. In our series, radiation therapy was delivered in 11 (73.33 %) patients, comprehensive craniospinal irradiation in 8 and focal RT in 3 patients.

Exploiting the differential repair capacity of normal and tumor tissues, hyperfractionated radiotherapy (HFRT) is an attractive option in this rare tumor, which is believed to be more resistant to conventional radiotherapy and chemotherapy in comparison to medullobastoma [2, 12, 27]. In various studies, CSI (31.2–40 Gy) followed by a local boost (up to 59.7–72 Gy) have been delivered using 1–1.3 Gy per fraction and 2 fractions per day, 6–8 hours apart, with a view to achieving superior tumor control by dose escalation with simultaneous minimization of late morbidities [2, 12, 27] (Table 2). The clinical outcome in these studies has been quite satisfactory with overall survival rates at 3 and 5 years in excess of 60 and 50 %, respectively (Table 2). However, this approach is quite resource intensive, and in young children who require the aid of general anesthesia or conscious sedation for immobilization, delivery of two fractions per day may be quite challenging from the nutritional point of view.

Taking a cue from average-risk medulloblastoma, Chintagumpala et al. explored the efficacy of risk-adapted treatment in patients with SPNET [5]. In a study of 16 patients with SPNET (pineal, 7; nonpineal, 9), eight average-risk patients underwent CSI to a dose of 23.4 Gy, and eight high-risk patients underwent CSI to a dose of 36 Gy in M0 disease with postoperative residuum more than 1.5 cm^2 or 36–39.6 Gy in M2 disease and 39.6 Gy in M3 disease. All patients received a three-dimensional conformal boost to the tumor bed to a dose of 55.8 Gy and to metastatic sites to a dose of 50.4 Gy. After a gap of 6 weeks, all patients received four cycles of non-myeloablative high-dose chemotherapy with cisplatin, vincristine and cyclophosphamide followed by autologous stem cell rescue. After a median follow-up of 5.4 years, 12 patients were alive with a 5-year EFS rate of 75 and 60 % and 5-year OS rate of 88 and 58 % in average- and high-risk patients, respectively. This small pilot study suggests that risk-adapted craniospinal irradiation is feasible in patients with SPNET, provided they receive high-dose chemotherapy in the adjuvant setting (Table 2).

Adjuvant chemotherapy using a multidrug regimen is advocated to enhance systemic control in patients with SPNET [8, 14, 43]. In the CCG 921 trial by Cohen et al., 55 patients with SPNET after surgery were randomized to receive craniospinal radiotherapy followed by eight cycles of lomustine, vincristine and prednisone (standard treatment) or two cycles of 8-in-1 chemotherapy followed by CSI and then eight additional cycles of 8-in-1 [6]. There was no significant difference in overall survival in the two arms, and there was substantial toxicity in the more intensive 8-in-1 chemotherapy arm. In a retrospective analysis of 36 patients with SPNET treated over 25 years, Dirks et al. demonstrated a trend toward better prognosis in children receiving systemic chemotherapy [7]. In the SIOP/UKCCSG PNET 3 trial by Pizer et al., 68 patients with SPNET (pineal, 23 %; nonpineal, 77 %) received postoperative radiation to a dose of 55 Gy/33 fractions at 1.67 Gy/fraction/day (CSI-35 Gy→boost-20 Gy) [35, 40]. Pre-irradiation chemotherapy (4 cycles, alternating vincristine, etoposide, carboplatin and vincristine, etoposide, cyclophosphamide) was administered in 44 patients. The overall 5-year event-free survival (EFS) and OS for the entire cohort were 51.8 and 51.5 %, respectively. The addition of pre-irradiation chemotherapy did not favorably affect survival outcome in this study. In another study of 22 patients, Reddy et al. used eight cycles of a 6-weekly regimen of cisplatin, vincristine and lomustine after maximal safe resection and CSI with satisfactory results (5-year OS, 53 %) [36]. However, in another series of 33 patients with embryonal CNS tumor from

Table 2 Compendium of recent studies using multimodality management for patients with SPNET

Author	No. of patients	Pineal/ nonpineal	Extent of resection	Radiation dose (CSI)	Chemotherapy	Survival outcome	Patterns of failure	Observation
Trials exploring combined modality treatment: radiotherapy (CSI) and conventional chemotherapy								
Cohen et al. (1995) (CCG 921 study) [6]	44	17/27	GTE-13 (30 %) NTE, 12 STE, 11 PE, 3 Biopsy, 5	36 Gy (boost up to 54 Gy) (in children ≥3 years) 23.4 Gy (boost up to 45 Gy in children 1.5–3 years)	Standard arm: CCNU + VCR + prednisone q6wk×8 (after RT) Experimental arm: 8 in 1 chemo with VCR, HU, BCNU, procarbazine,, CDDP, Ara C, prednisone, CTX (2 cycles pre RT and 8 cycles after RT)	3-year PFS, 45 % 3-year OS, 57 %	–	On MVA, pineal location (P=0.011) and M0 disease (P=0.007) significant predictors of improved PFS No significant difference between arm A and B with respect to PFS but arm B associated with higher hematological and non-hematological toxicity
Albright et al. (1995) (CCG 921 study) [1]	27	0/27	GTE-10 (37 %) NTE, 8 STE, 7 Biopsy, 2	36 Gy (boost up to 54 Gy) (in children ≥3 years, N=18) 23.4 Gy (boost up to 45 Gy in children 1.5–3 years, N=9)	Standard arm: CCNU + VCR + prednisone q6wk×8 (after RT) Experimental arm: 8 in 1 chemo with VCR, HU, BCNU, procarbazine, CDDP, Ara C, prednisone, CTX (2 cycles pre RT and 8 cycles after RT)	5-year PFS, 31 % 5-year OS, 34 %	–	PFS significantly improved in patients with M0 disease (P=0.003) and age>3 years (P=0.05) Postoperative survival at 4 years 40 versus 13 % in patients with postoperative residuum <1.5 cm^2 versus >1.5 cm^2 (P=0.19)
Jakacki et al. (1995) (CCG 921 study) [20]	25 (8 infants, 17 older children)	25/0	GTE, 5 (20 %) NTE, 5 STE, 6 PE, 4 Biopsy, 5	36 Gy if age>3 years (boost up to 54 Gy) (n=15) 23.4 Gy if age=1.5–3 years (n=2)	Standard arm: CCNU + VCR + prednisone q6wk×8 (after RT) Experimental arm: 8 in 1 chemo with VCR, HU, BCNU, procarbazine,, CDDP, Ara C, prednisone, CTX (2 cycles pre RT and 8 cycles after RT) All infants (N=8) received 8 in 1 chemo without RT	3-year PFS, 61 % 3-year OS, 73 %	Local, 8 (32 %) Leptomeningeal, 3 (12 %) Local+ leptomeningeal, 3 (12 %)	Among patients >18 months who received CSI and chemo, those with pinealoblastoma fared significantly better than those with nonpineal SPNET (P=0.026) '8 in 1 chemo' without RT ineffective for infants with PB Residual enhancement following RT not predictive of treatment failure
Dirks et al. (1996) [7]	36	10/26	GTE, 7 (19.44 %) STE, 24 Biopsy, 5	25–35 Gy (boost up to 45–54 Gy) (Adjuvant RT in 26 patients; CSI, 19 and WBRT, 7)	(Adjuvant chemo in 13)	3-year OS, 34 % 5-year OS, 18 %	Local, 54 % Leptomeningeal component, 46 %	Significantly worse survival in young children<3 years (P=0.006) Trend toward better survival in children treated since 1984 (P=0.11) and children undergoing GTE (P=0.08) Among the survivors, all received CSI and 4 received chemo
Yang et al. (1999) [44]	28 (all pedia-tric)	3/25	GTE, 17 (60.71 %) NTE, 3 STE, 7 Bx, 1	(Adjuvant RT in 23 patients: CSI, 22; WBRT, 1)	8 in 1 chemo with VCR, HU, BCNU, procarbazine,, CDDP, Ara C, prednisone, CTX (2 cycles pre RT and 8 cycles after RT in 13 patients)	3-year DFS, 60 % 5-year DFS, 38 % 3-year OS, 70 % 5-year OS, 51 %	–	Significantly improved survival in patints undergoing GTE/NTE (3-year OS, 79 %) versus STE/Bx (3-year OS, 0 %) (P=0.04) Significantly worse survival in patients with histological evidence of tumor necrosis (3-year OS 38 versus 100 %) (P=0.0002)

Table 2 (continued)

Author	No. of patients	Pineal/ nonpineal	Extent of resection	Radiation dose (CSI)	Chemotherapy	Survival outcome	Patterns of failure	Observation
								Patients with high MIB1 LI (>10 %) tended to have shorter survival (P=0.095)
Reddy et al. (2000) [36]	22	13/9	GTE/NTE, 10 (45.45 %) PE, 9 Biopsy, 3	34–40 Gy (boost up to 46.8–60 Gy)	CDDP+VCR+CCNU q6wk×8 (post-radiation) Wkly VCR concurrent with RT	5-year PFS, 37 % 5-year OS, 53 %	–	Improved PFS in patients with M0 versus M1 disease (= 0.04) Trend toward improved PFS in patients undergoing complete/near-complete resection versus partial resection/biopsy (P=0.22) No difference in outcome (PFS) in patients with pineal versus nonpineal tumors
Kim et al. (2002) [23]	12 (all adults)	0/12	GTE, 7 (58.33 %) STE, 5	27–36 Gy (mean 32.5 Gy) (boost up to 50.4–55.8 Gy; mean 54.1 Gy) (RT in 10 patients)	VCR+CCNU+CDDP/ procarbazine (No fixed chemo protocol) (Chemo in 5 patients)	3-year PFS, 63 % 3-year OS, 75 %	Local, 3 (25 %) Leptomeningeal, 0 Death, 2	No difference in clinical manifestations, radiological findings and prognosis between adult and pediatric patients with SPNET Intratumoral calcification and MIB1 LI <30 % potential favorable prognostic factors of OS
Paulino et al. (2004) [31]	25	7/18	GTE, 5 (20 %) STE, 10 Biopsy, 10	36 Gy (boost up to 54 Gy) CSI→boost-17 WBRT→boost, 2 Focal RT→6	8 in 1 chemo with VCR, HU, BCNU, procarbazine,, CDDP, Ara C, prednisone, CTX (most common regimen) Chemo in 16 pts (64 %)	5-year PFS, 36 % 10-year PFS, 27 % Primary site control rate, 62 % at both 5 and 10 years	Local, 7 (28 %) Non-primary site in brain, 10 (40 %) Spinal (leptomeningeal), 9 (28 %)	Significantly improved PFS in patients with M0 disease (10-year PFS, 30 %) versus M+ disease (10-year PFS, 0 %) (P=0.01) and patients receiving CSI (10-year PFS, 47.1 %) versus those receiving WBRT/focal RT (10-year PFS, 0 %) (P=0.02) Failure at non-treated neuraxis site most common site of progression in patients receiving WBRT/focal RT (6/8)
Pizer et al. (2006) (SIOP-UKCCSG PNET 3 study) [35]	68	14/54	GTE, 28 (45.16 %) Incomplete excision, 25 Biopsy, 8 Unknown, 1 (Surgical details available in 62 patients)	35 Gy (boost up to 55Gy)	VCR, VP-16, CBDCA alternating with VCR, VP-16, CTX×4 (pre-radiation)	5-year EFS, 47 % 5-year OS, 51.5 %	Local, 18 (26.47 %) Local+ leptomeningeal, 5 (7.35 %) Distant leptomeningeal, 6 (10.3 %) Unspecified, 1 Death, 32	Addition of pre-radiation chemo did not improve OS and EFS 5-year OS, 71.4 % in PB and 40.7 % in nonpineal SPNET
McBride et al. (2008) [28]	15	0/15	GTE, 8 (53.33 %) Incomplete excision, 7	23.4–36 Gy (boost up to 50.4–72 Gy) (Option of focal RT at the discretion of the treating oncologist) (RT in 10/15 patients—upfront in 5 and as salvage treatment in 5)	CDDP, VP-16, CTX, VCR (most common regimen) High-dose chemo→ ASCR in 2	–	Local, 5 (33.33 %) Local+ leptomeningeal, 2 (13.33 %)	OS significantly improved in patients undergoing upfront RT (P=0.048) Trend toward improved OS in patients undergoing GTE (P=0.10) Local recurrence, dominant pattern of failure
Biswas et al. (2009) [4]	14	3/11	GTE, 5 (35.71 %) STE, 5 Bx, 4	35 Gy (boost up to 55 Gy) (RT in 13 patients)	CDDP+VCR+CCNU q6wk×8 (post-radiation) (in 8 patients with nonpineal SPNET) VCR, VP-16, CBDCA alternating with VCR,	5-year OS, 14 %	–	5-year OS significantly better in patients with MB (73 %) versus SPNET (14 %) (P=0.0002) In patients receiving Packer's regimen, 5-year OS significantly better in patients with MB (79 %) versus SPNET (12 %) (P=0.0003)

Table 2 (continued)

Author	No. of patients	Pineal/ nonpineal	Extent of resection	Radiation dose (CSI)	Chemotherapy	Survival outcome	Patterns of failure	Observation
					VP-16, CTX X 4 (pre-radiation) (in 3 patients with PB)			In patients with SPNET receiving Packer's regimen, median PFS and OS, 11.1 and 11.8 months, respectively No significant difference in OS between pediatric (N=8) and adult (N=6) patients with SPNET (5-year OS 25 versus 0 %, respectively) (P=0.92) Median OS in patients with PB and nonpineal SPNET, 20 and 14.8 months, respectively
Jakacki et al. (2015) (COG 99701) [21]	60	23/37	GTE, 25 (54.38 %) Incomplete excision, 21 (Details available only in 46 patients with M0 disease)	36 Gy (boost up to 55.8 Gy)	Concurrent VCR (wkly) and CBDCA (daily) Adjuvant VCR + CTX ±CDDP (×6 months)	5-year OS, 58.7 % 5-year PFS, 48.7 %	Local, 17 (36.17 %) Distant, 5 (10.64 %) Local+distant, 3 (6.38 %) (in 47 patients with M0 disease)	5-year OS and PFS significantly better in patients with PB (81.9 and 62.11 %) versus nonpineal SPNET (44.8 and 39.8 %) (P=0.055 and 0.009, respectively) In patients with PB with M0 disease, extent of resection significant prognostic factor for PFS (P=0.04) and approached significance for OS (P=0.09) In patients with nonpineal SPNET with M0 disease, extent of resection a significant prognostic factor for OS (P=0.017) and approached significance for PFS (P=0.056) No significant difference in outcome in patients with M0 versus M+ disease
Trials exploring deferral/omission of radiotherapy (CSI)								
Duffner et al. (1993) (POG study) [8]	36	–	GTE, 8 (27 %) Incomplete excision, 22 (Surgical details available in 30 patients)	35.2 Gy (boost up to 54 Gy) (in M+/residual or progressive disease after chemo) 24 Gy (boost up to 50 Gy) in patients with no residuum after chemo	CTX+VCR x 2 alternating with CDDP+VP-16×1 till disease progression or 2 years (in patients <2 years) or 1 year (in patients 2–3 years)	2-year PFS, 19 % 2-year OS, 21 %	–	In the entire cohort (N=198), complete resection associated with significantly improved PFS (relative risk, 0.33, 95 % CI 0.2–0.54) Patients with embryonal tumor (PNET) on histopathology had significantly worse PFS (relative risk, 2.2, 95 % CI 1.4–3.4) With the use of postoperative chemo, RT could be deferred for 1–2 years especially in patients who had complete resection of tumor or complete response to chemo
Geyer et al. (1994) (CCG 921 study) [13]	19	8/11	GTE, 6 (31.58 %) NTE, 5 STE, 3 PE, 2 Biopsy, 3	(Focal RT after 2 cycles of 8 in 1 chemo or CSI 1 year after diagnosis at completion of chemo allowed in protocol)	8 in 1 chemo with VCR, HU, BCNU, procarbazine,, CDDP, Ara C, prednisone, CTX	3-year PFS, 0 % (PB) 55 % (nonpineal SPNET)	–	Nonpineal SPNET and M0 disease significant predictors of improved PFS Delayed or reduced volume RT was to be administered in all patients but in fact omitted in most cases In the entire cohort (N=82), only 3 out of 19 event-free survivors 2 years from diagnosis received RT
Mason et al. (1998) [26]	14	3/11	GTE, 7 (50 %) STE, 5 PE, 2	(RT only for PD or residual disease at time of ABMR)	Induction chemo with VCR, CDDP, CTX, VP-16 q3 wk×5 Consolidation chemo with CBDCA, VP-16, thiotepa followed by ABMR in 10/14 patients; 7/14<3 years of age	2-year EFS, 43 % 2-year OS, 64 %	–	Response rate to induction chemo, 67 % In the entire cohort of malignant brain tumor (N=62), response rate and survival better in MB, PNET and ependymoma In the entire cohort, RT only in 19/62 patients Toxic death, 8 %

Table 2 (continued)

Author	No. of patients	Pineal/ nonpineal	Extent of resection	Radiation dose (CSI)	Chemotherapy	Survival outcome	Patterns of failure	Observation
Marec-Berard et al. (2002) (BB SFOP study) [25]	25	4/17 (4, Medullo-epithelioma)	GTE, 9 (36 %) STE, 9 PE, 3 Biopsy, 2 None, 2	Not defined	CBDCA, procarbazine (course 1); CDDP, VP-16 (course 2); CTX, VCR (course 3)—alternating regimens for 18 months	5-year OS, 14 % 2-year OS, 30 % 2-year RFS, 4 %	Local, 15 (60 %) Local+ leptomeningeal, 7 (28 %) Local+ infratentorial, 1 (4 %) Local+distant (peritoneum), 1 (4 %)	Trend toward improved EFS in patients undergoing complete resection Patients with hemispheric tumors had improved OS compared to those with deep tumors
Geyer et al. (2005) (CCG 9921 study) [14]	46	10/36	GTE/NTE, 28 (60.87 %) Incomplete excision, 18	18–30.6 Gy (depending on age and disease status; only in M+/recurrent disease) (boost up to 54 Gy) (focal RT 50.4–54 Gy in M0 disease with residuum after induction chemo)	Induction chemo with VCR, CDDP, CTX, VP-16 (regimen A)/ VCR, CBDCA, ifosfamide, VP-16 (regimen B)×5→ maintenance chemo with VCR, CBDCA, CTX, VP-16×8	5-year OS, 31 % 5-year EFS, 17 %	Local, 23 (50 %) Distant, 5 (10.87 %) Local+distant, 8 (17.39 %) Death, 2	Most survivors (50 % of those alive at 5 years) did not receive RT In the entire cohort of malignant brain tumor (N=299), RR to induction chemo, 42 % No significant difference in between 2 arms in terms of RR/ EFS 1.8 times higher rate of treatment failure in SPNET compared with MB
Timmermann et al. (2006) (HIT SKK87 and HIT SKK 92 trials [41]	29	2/27	GTE, 6 (20.69 %) Incomplete excision, 23	35.2 Gy (boost up to 55.2 Gy) (RT only in 14/29 patients: preventive RT in 10 patients and salvage RT in 4 patients)	HITSKK 87 (N=13): Low risk (R0/M0): Maintenance chemo till age of 3 years or PD High risk (R+/M+): Induction chemo (C1-VCR, procarbazine, MTX and LV rescue; C2-procarbazine, MTX and LV rescue, ifosfamide, VP-16, CDDP, Ara C HIT SKK 92 (N=16): MTX (intravenous and intraventricular), VCR, CTX, CBDCA, VP-16	3-year PFS, 14.9 % 3-year OS, 17.2 %	Local, 13 (44.83 %) Distant, 3 (10.34 %) Local+distant, 8 (27.59 %)	Improved PFS and OS in patients receiving RT Even if intensive chemo is given, omission of RT jeopardizes survival Delay of RT should be limited to a maximum of 6 months
Fangusaro et al. (2008) (Head Start I and II study) [9]	43	13/30	GTE, 21 (48.84 %) Incomplete excision, 22	23.4 Gy (boost up to 55.8 Gy) (RT received in only 16 pts: 14 in salvage setting and 2 as part of primary T/t)	Intensified induction chemo with VCR, CDDP, CTX, VP-16 (and MTX in M+ ds) ×5→high dose myeloablative chemox1 followed by ASCR	5-year EFS, 39 % 5-year OS, 49 %	Local, 17 (39.53 %) Local+distant, 6 (13.95 %) Distant, 2 (4.65 %)	Nonpineal SPNET fared significantly better than PB 12 out of 20 long-term survivors (60 %) did not receive RT Toxic death, 4.7 %
Friedrich et al. (2013) (HIT 2000 trial) [10]	17	8/8 (1, Ependymo blastoma)	GTE, 7 (41.18 %) Incomplete excision, 10	24 Gy (boost up to 54.6 Gy) (In diffuse spinal mets, the entire spinal axis received 36 Gy) (11/17 patients received CSI; 3 as	M0 disease: Adjuvant chemo with VCR, CTX, MTX, CBDCA, VP-16×5 cycles (8 months) (SKK regimen) M+ disease: Induction chemo with CBDCA	5-year EFS, 24 % 5-year OS, 40 %	Local, 9 (52.94 %) Distant, 2 (11.76 %) Local+distant, 2 (11.76 %)	Short intensive induction chemo followed by tandem HDCT superior to prolonged and less intensive induction chemo in CNS PNET/PB (Relapse 3/6 versus 10/11; 5-year EFS 50 versus 9 %; 5-year OS 67 versus 27 %) No significant difference in survival between patients with PB and nonpineal SPNET

Table 2 (continued)

Author	No. of patients	Pineal/ nonpineal	Extent of resection	Radiation dose (CSI)	Chemotherapy	Survival outcome	Patterns of failure	Observation
				part of primary T/t, 8 in salvage setting)	+VP-16 (2–3 months)→ Tandem high-dose chemo (HDCT) (containing intraventricular MTX)			
Trials exploring high-dose chemotherapy followed by ASCR and radiotherapy (CSI)								
Gururangan et al. (2003) [16]	12	12/0	GTE, 5 (41.67 %) Incomplete excision, 7	36 Gy (boost up to 59.4 Gy) (no RT in 2 pts <2 years)	Induction chemo (pre-radiation): Reg A: CTX q4wk×4 (*N*=9) Reg B: CDDP+VCR+ CTX+VP-16 q4wk ×4–6 (*N*=2) Reg C: CBDCA+CTX +VP-16 q 4 wk×4→ Oral VP-16×4 (*N*=1) HD chemo (post-radiation) with CTX+MEL (*N*=11) or BU+MEL (*N*=1)→ASCR	4-year PFS, 69 % 4-year OS, 71 %	Local, 1 (8.33 %) Leptomeningeal, 1 (8.33 %) Local+ leptomeningeal, 1 (8.33 %)	2 infants did not receive RT No toxic death with high-dose chemo→ASCR High-dose chemo may be considered in patients with PB who are infants or have metastatic disease
Trials exploring altered fractionation radiotherapy (CSI) and conventional/high-dose chemotherapy								
Massimino et al. (2006) [27]	15	3/12	GTE, 6 (40 %) PE, 6 Biopsy, 3	31.2 Gy if age <10 years 39 Gy if age >10 years (*N*=6) (HART: Hyperfractionated accelerated radiotherapy, 1.3 Gy/#; 2#/day, 6 h apart) (boost up to 59.7–60 Gy at 1.5 Gy/#; 2#/day, 6 h apart)	High-dose chemo with MTX, CBD-CA, VP-16 and CTX (pre-radiation) Maintenance with VCR/ CCNU or high-dose thiotepa followed by ASCR (post-radiation)	3-year EFS, 34 % 3-year PFS, 54 % 3-year OS, 61 %	Local, 4 (26.67 %) Distant, 1 (6.67 %) Local+distant, 1 (6.67 %) Death, 5	In patients with postoperative residuum (*N*=9), response rate after chemo and HART 44 and 71 %, respectively
Allen et al. (2009) (CCG 9931 study) [2]	36	8/28	R>1.5 cm^2-15 R<1.5 cm^2-18	40 Gy (boost up to 60 Gy to tumor bed and 50 Gy to spinal mets) (HFRT: Hyperfractionated radiotherapy, 1 Gy/#, 2#/day, 6–8 h apart)	CDDP, CTX, VP-16, VCR (regimen A) alternating with CBDCA, VP-16 (regimen B) q 4wk ×5 (Pre-radiation)	5-year PFS, 46 % (in SPNET) and 75 % (in PB) 5-year OS, 48 % (in SPNET) and 86 % (in PB)	–	In the entire cohort (*N*=124), no significant difference in survival with respect to tumor site, postoperative residuum, M stage and response to chemotherapy Overall 85/124 patients (69 %) could complete the planned adjuvant treatment in a median of 6.1 months
Gerber et al. (2014) (GPOH P-HIT 2000-AB4 trial) [12]	26	11/15	GTE, 6 (23.08 %) PE, 16	36 Gy (boost up to 68 Gy to tumor bed and 72 Gy to residuum) (HFRT: Hyperfractionated radiotherapy, 1 Gy/#, 2#/day, 6–8 h apart)	Concurrent wkly VCR Post-radiation CDDP, VCR, CCNU X8	5-year PFS, 58 % 5-year OS, 58 %	Local, 5 (19.23 %) Distant, 4 (15.38 %) Local+distant, 2 (7.69 %) Death, 11 (9 due to PD, 2 toxic death during 2nd line chemo	5-year PFS and OS, both 53% in SPNET versus 64 % in PB Dominant pattern of relapse was distant failure in PB (*N*=4) and local failure in SPNET (*N*=5)

Table 2 (continued)

Author	No. of patients	Pineal/ nonpineal	Extent of resection	Radiation dose (CSI)	Chemotherapy	Survival outcome	Patterns of failure	Observation
Trials exploring risk adapted radiotherapy (CSI) and high-dose chemotherapy								
Chintagumpala et al. (2009) [5]	16	7/9	GTE, 6 (37.5 %) NTE, 1 STE, 2 Biopsy, 7	23.4 Gy if average-risk disease (*N*=8) 36–39.6 Gy if high-risk disease (M1-3, R> 1.5 cm^2) (*N*=8) (boost up to 55.8Gy)	High-dose chemo with CDDP, VCR, CTX ×4 followed by ASCR (post-radiation)	5-year EFS, 75 and 60 % in average- and high-risk patients respectively 5-year OS, 88 and 58 % in average- and high-risk patients, respectively	Local, 1 (6.25 %) CSF, 1 (6.25 %) Distant, 1 (6.25 %) Local+distant, 1 (6.25 %)	5-year EFS, 54 and 78 %; 5-year OS, 67 and 78 % in pineal and nonpineal tumors, respectively
Present study								
Present study (2015)	15	0/15	GTE, 6 (40 %) STE, 8 Bx, 1	36 Gy (boost up to 56 Gy) (Focal RT in 3 patients)	VCR, DOXO, CTX altemating with IFOS, VP-16×6–12 (mostly post-radiation) (Chemo in 13 patients)	2-year OS, 72.7 % 2-year RFS, 57.8 % 2-year EFS, 55.2 %	Local, 3 (20 %) Leptomeningeal, 2 (13.33 %) Local+ leptomeningeal, 1 (6.67 %) Death, 4	Estimated median EFS, 4.12 years

CSI craniospinal irradiation, *WBRT* whole-brain RT, *GTE* gross total excision, *NTE* near total excision, *STE* subtotal excision, *PE* partial excision, *Gy* Gray, *wk* week, *MVA* multivariate analysis, *PFS* progression-free survival, *OS*overall survival, *EFS* event-free survival, *RFS* recurrence-free survival, *PB* pinealoblastoma, *SPNET* supratentorial primitive neuroectodermal tumor, *PNET* primitive neuroectodermal tumor, *MB* medulloblastoma, *RT* radiotherapy, *Chemo* chemotherapy, *RR* response rate, *PD* progressive disease, # fraction, *R* residuum, *CSF* cerebrospinal fluid, *Ara C* cytosine arabinoside, *BCNU* carmustine, *BU* busulfan, *CBDCA* carboplatin, *CCNU* lomustine, *CDDP* cisplatin, *CTX* cyclophosphamide, *DOXO* doxorubicin, *HU* hydroxyurea, *IFOS* ifosfamide, *LV* leucovorin, *MEL* melphalan, *MTX* methotrexate, *VCR* vincristine, *HDCT* high-dose chemotherapy, *ASCR* autologous stem cell rescue, *ABMR* autologous bone marrow rescue

Addenbrooke's Hospital, Cambridge, UK, use of Packer's regimen after surgery and CSI led to dismal results in patients with nonpineal SPNET when compared with MB (5-year OS 12 % versus 79 %; P=0.0003) [4]. The authors opined that nonpineal SPNET, especially in teenagers and young adults, is clinically distinct from MB and resistant to Packer's regimen and suggested the use of alternative chemotherapy (ifosfamide/temozolomide based) regimens [4]. Extrapolating from the data on the use of an alternating VAC and IE regimen in peripheral PNET and Ewing's sarcoma of bone (CCG-7881 and POG-8850 protocol), we follow alternating VAC/IE-based adjuvant chemotherapy for a total of 12 cycles after the completion of radiation therapy, and all but two patients received the aforementioned regimen in the current series [15].

Due to concern about long-term neurocognitive and neuroendocrine sequelae associated with CSI, attempts have been made to eliminate, delay or limit the use of RT (CSI) with the use of prolonged [8, 13, 25] or intensive [41] or high-dose [9, 10, 26] chemotherapy with autologous bone marrow/stem cell rescue (Table 2). Though CSI was avoided or deferred in a subset or majority of patients undergoing prolonged conventional chemotherapy, the clinical outcome was unsatisfactory with 2-year OS rates ranging from 20 to 30 % [8, 13, 25] (Table 2). In the German HIT-SKK87 and HIT-SKK92 trial involving 29 children with SPNET (pineal, 2; nonpineal, 27) <3 years old, use of methotrexate-based intensive chemotherapy led to dismal 3-year rates of overall and progression-free survival (PFS) of 17.2 and 14.9 %, respectively [41]. In this trial overall 14 patients received RT while 15 did not. This perhaps reflects the fact that even if intensive chemotherapy is given, omission of RT jeopardizes survival, and delay of RT should be limited to a maximum of 6 months in SPNET patients. On the contrary, use of postoperative high-dose chemotherapy followed by autologous bone marrow/stem cell rescue in patients with SPNET in the Head Start I and II and HIT 2000 trials led to fairly impressive results with 5-year OS ranging from 40 to 50 % [9, 10]. The majority of the long-term survivors did not receive RT as part of primary treatment (Table 2). However, needless to say that high-dose chemotherapy is resource intensive, has a formidable toxicity profile (myelosuppression, infection, bleeding, mucositis, etc.) and can lead to treatment-related mortality in 5–10 % of patients [9, 26]. In a pertinent study of late effects in 21 survivors of childhood CNS tumor (MB, 13; SPNET, 4; ependymoma, 3; atypical teratoid rhabdoid tumor, 1) treated according to the Head Start I and II protocols, after a median follow-up of 12.6 years, toxicities involving CNS, vision, hearing (grade III/IV) and dentition were noted in 67 %, 67 %, 67 % and 52 % patients, respectively [39]. Hypothyroidism and growth hormone (GH) deficiency were reported in 33 and 48 % of patients, respectively. Irradiation-free survivors (N=10; 48 %), compared to patients who had received RT, had lower rates of hypothyroidism (0/10 versus 7/11; P=0.004) and GH deficiency (2/10 versus 8/11; P=0.03). No case of secondary leukemia or CNS tumor was reported in the survivors.

In summary, in spite of improvement in the treatment modalities of SPNET, the reported clinical outcome is inferior to that of medulloblastoma. The OS rates at 3 and 5 years range from 17.2 to 75 % and 14 to 88 %, respectively, in different studies (Table 2). The PFS/EFS rates at 3 and 5 years range from 0 to 63 % and 17 to 75 %, respectively, in the available literature (Table 2). Tumor recurrence may be local (6.25–60 %), leptomeningeal (0–28 %) or a combination of both (6.25–28 %) (Table 2). Occasionally there may also be distant failure. Local recurrence is the dominant pattern of failure in most studies [10, 21–23, 30, 34, 35]. Gerber et al., in their study of 26 patients, demonstrated that distant failure was more common in patients with pinealoblastoma, whereas local failure was more common in patients with nonpineal SPNET [12]. In an elegant study of 133 patients with pediatric embryonal CNS tumor from North America by Perreault et al., overall 49 (37 %) patients relapsed [32]. The majority of failures were local (79 %) in nonpineal SPNET, diffuse leptomeningeal (100 %) in pinealoblastoma and diverse in medulloblastoma (local, 27 %; distant, 35 %; diffuse leptomeningeal, 38 %). Spinal relapse was noted in 100, 51, 43 and 9 % of patients with pinealoblastoma, medulloblastoma, atypical teratoid rhabdoid tumor and nonpineal SPNET, respectively. In the present study, six (40 %) patients had recurrence: local in three, leptomeningeal in two and both in one. Median time to recurrence in our study was noted to be 11.12 months. Salvage treatment options for recurrent SPNET are limited. Re-excision and second-line systemic chemotherapy may be considered for local and distant failure, respectively.

The various prognostic factors determining improved clinical outcome in patients with SPNET include age (more than 3 years versus less than 3 years) [1, 7], M stage (M0 versus M+ disease) [1, 6, 13, 31, 36], extent of resection (complete versus incomplete resection) [1, 7, 8, 21, 25, 28, 36] and use of radiation therapy (CSI) [28, 31, 41] (Table 2). SPNETs arising in adults and children differ at the molecular level with IDH1 mutation being frequent in adults (42 %) but not in children [3, 18]. In a series of 12 adult patients with nonpineal SPNET reported by Kim et al., clinical outcome was impressive with OS and PFS at 3 years being 75 and 63 %, respectively [23]. However, the authors found no difference in clinical manifestations, radiological findings and prognosis between adults and children with this tumor [23, 44]. In another comprehensive review of 57 adult patients with SPNET, Ohba et al. reported OS rates of 38.2 and 26 % at 3 and 5 years, respectively, and recommended multimodality management consisting of gross total resection (if possible), craniospinal irradiation and systemic chemotherapy for these patients [29]. It is notable that five patients (33.33 %) in our series were adults, with

three having complete response and two progressive disease at last follow-up. There was no significant difference between pediatric and adult patients on univariate analysis of EFS in our series. The impact of tumor location (pineal versus nonpineal) on clinical outcome is unclear with some studies reporting no significant difference [2, 10, 36], while some show superior outcome in patients with pinealoblastoma [6, 12, 20, 21, 35] but others the contrary [5, 9, 13, 25]. Though most single-institute or cooperative trials have grouped patients with both pineal and nonpineal SPNET, we included only patients with nonpineal SPNET in our study. At the present juncture, aggressive multimodality treatment consisting of maximal safe surgery, craniospinal irradiation and adjuvant systemic chemotherapy should be strongly considered in suitable SPNET patients with an aim to achieve an OS rate of 60–70 % at 3 years and 50–60 % at 5 years. With the use of this multimodality approach, the actuarial rates of OS and EFS at 2 years in our series are 72.7 and 55.2 %, respectively. In spite of a few limitations of our study owing to its retrospective nature, relatively short follow-up and treatment heterogeneity, overall compliance with the multimodality treatment approach was noted to be good, and clinical outcome and patterns of failure in patients in this study are in concordance with published results in the medical literature. Moreover, the effectiveness of this combined modality approach in an unselected patient population in the real-world scenario can be considered a strength of our study. Longer follow-up will no doubt lead to unfolding of late recurrence and long-term effects of treatment. More attention needs to be focused on improving treatment effectiveness by innovative study designs such as altered fractionation, radiotherapy dose escalation, use of concurrent chemotherapy along with radiotherapy, intensification of adjuvant chemotherapy, use of high-dose chemotherapy with autologous stem cell rescue and simultaneously minimizing treatment morbidity by use of novel techniques such as intensity-modulated radiation with helical tomotherapy and proton beam therapy. Keeping in mind the scarcity of health resources in developing nations, the cost-benefit ratio of any such future approach needs careful consideration.

Conclusion

Compared to medulloblastoma, the prognosis of SPNET has been historically poor with little improvement over time. Aggressive multimodality management consisting of maximal safe surgery, preferably gross total excision of tumor, followed by craniospinal irradiation and systemic chemotherapy with 6–12 cycles of an alternating regimen of VAC and IE is a reasonable treatment strategy in patients with nonpineal SPNET in a developing nation. However, in young children less than 3 years, an attempt should be made to defer radiation therapy by using prolonged or intensive chemotherapy. In the future, more attention needs to be focused on innovative study designs, quality of life issues and late effects of treatment. A better understanding of the molecular biology of this enigmatic tumor may lead to refinement of the treatment strategy and improvement of clinical outcome.

Conflicts of interest None.

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