Introduction

The primitive neuroectodermal tumor (PNET) is the subject of much debate among neuropathologists. PNETs, regardless of site of origin, are composed of “undifferentiated” neuroepithelial cells, and frequently also contain one or more populations of “differentiated” neoplastic cells [1]. The controversy revolves around whether the tumor arises from a multipotential cell unique to the particular area of the central nervous system (e.g. medulloblastomas from external granule cells in the cerebellum, pineoblastomas from pineoblasts) or whether it arises from a primitive cell common to all sites. PNETs, regardless of location, are morphologically similar, if not identical, and all have the propensity to spread within the central nervous system through subarachnoid pathways [2]. It is becoming increasingly apparent, however, that there are also biological differences. Supratentorial PNETs (SPNETs) do not appear to have a sex predilection, whereas medulloblastomas occur twice as frequently in males as in females. Cytogenetic abnormalities differ between the infratentorial and supratentorial counterparts [3]. Most importantly, the prognosis following therapy is not the same for PNETs arising in different locations [4, 5]. Even within the supratentorial compartment, PNETs arising within the pineal region (pineoblastomas) appear to respond differently to treatment than the nonpineal supratentorial PNETs [4, 6]. Except for the recent prospective study from the Children’s Cancer Group [4, 6], the studies reported in the literature have mostly been retrospective studies of small numbers of patients treated in a heterogeneous fashion.

Cerebral PNETs account for approximately 2–3% of childhood brain tumors [7, 8]. Pineal region PNETs or pineoblastomas are even rarer. The cerebral hemispheres account for the majority of SPNETs, with the frontal, temporal and/or parietal lobes most frequently involved. The patients usually present with nonspecific symptoms

Abstract Pineal region supratentorial primitive neuroectodermal tumors (SPNETs; pineoblastomas) and nonpineal SPNETs are rare tumors that historically have carried a very poor prognosis. With multimodality therapy, including maximal surgical resection, craniospinal radiation therapy and chemotherapy, the survival for patients with pineal PNETs has significantly improved. Chemotherapy alone, at least in conventional doses, appears to be insufficient treatment for younger children with pineoblastomas, in whom there is almost universal rapid tumor progression and death. Survival of patients with nonpineal SPNETs remains in the order of 30–35% despite multimodality therapy. Unlike those with pineal SPNETs, a significant percentage of infants with nonpineal SPNETs who undergo gross total surgical resection followed by chemotherapy will be long-term survivors. This article gives an overview of the natural history, prognostic factors and treatment of both pineal and nonpineal SPNETs.

Key words Supratentorial primitive neuroectodermal tumor · SPNET · Pineoblastoma · Treatment · Prognosis
referrable to their tumors’ mass effect, including headaches, vomiting, seizures and, occasionally, hemiparesis. Radiographically, the tumors are typically large, well-circumscribed, occasionally cystic and/or necrotic, masses that enhance with contrast administration [9]. In the CCG study, 40% of the nonpineal tumors were >6 cm in maximal diameter [10].

The exact incidence of dissemination throughout the subarachnoid space and CSF, whether at diagnosis or at the time of recurrence, has not been established, since complete staging evaluations have not been uniformly obtained in published reports. In the reports that do give sufficient detail about sites of recurrence, local recurrence is frequently reported to have been accompanied by diffuse subarachnoid spread [11, 12]. In the Children’s Cancer Group study, metastatic spread at the time of diagnosis was seen in 4 of the 26 patients (19%) with nonpineal SPNETs and 4 of the 24 patients (17%) with pineoblastomas [4, 6]. Seven of 18 (38.9%) completely staged patients with nonpineal SPNETs in the series reported by Dirks et al. had either intracranial (n=4) or spinal dissemination at the time of diagnosis, and 46% had dissemination at the time of recurrence [13]. Systemic metastases are not common, but have been reported, usually at the time of recurrence [7, 11].

In the past, both nonpineal and pineal SPNETs carried an extremely dismal prognosis despite treatment, with most patients succumbing within 2 years [14–16]. Recent aggressive multimodality treatment strategies have produced more optimistic results, particularly for pineal region SPNETs. A report from the Children’s Cancer Group showed a 3-year progression-free survival (PFS) of 61±13% for patients with pineal PNETs treated with craniospinal radiation therapy and adjuvant chemotherapy [6]. The corresponding 3-year PFS for patients with nonpineal PNETs treated according to the same protocol was 33±9% (P=0.026). All infants with pineal PNETs treated with 8-in-1 chemotherapy alone, however, developed progressive disease at a median of 4 months, suggesting that age and/or the use of radiation are important determinants of survival. Interestingly, infants with nonpineal SPNETs treated with 8-in-1 chemotherapy according to the same protocol (n=11) had a 3-year PFS of 55±16%, significantly better than infants with pineal PNET (P<0.01) [17]. In the subsequent CCG infant study, utilizing more intensive chemotherapy, 2-year PFS was 34% for patients with nonpineal SPNET (67% for those with gross total surgical resections), while for infants with pineal region PNETs the corresponding PFS was 9% [18].

**Prognostic factors**

Due to the rarity of these tumors and the heterogeneity of treatments used in retrospective studies, the ability to perform statistically meaningful multivariate analyses of risk factors has not been possible.

**Age**

Young age has consistently been shown to be an adverse prognostic factor in pineal SPNETs [6, 19]. Whether this is due to biologically more aggressive tumors in infants or because these patients usually receive lower doses of radiation, if they receive any radiation at all, is not known. In both cooperative group studies, all infants with pineal SPNETs developed progressive disease within 2–14 months of diagnosis and died. In the Pediatric Oncology Group study, 5 of 11 infants had metastatic disease at diagnosis and all 8 patients who underwent metastatic staging at recurrence had leptomeningeal disease. Six of the 11 received radiation therapy after developing progressive disease, but died 4–23 months (median 10 months) later [19].

It is less clear whether age is an adverse prognostic factor for nonpineal SPNETs. In the CCG study, patients 19–36 months of age received 45 Gy to the primary tumor site and 23.4 Gy to the craniospinal axis (rather than 54 Gy and 36 Gy, respectively). Progression-free survival was significantly worse for these patients, with all 9 of them dying of progressive disease, than for older patients who received full-dose radiation [10]. However, infants treated with 8-in-1 chemotherapy alone (n=8) had a 3-year PFS of 55±16% [17], which appears to be at least as good as the survival in older children following full-dose radiation and the same adjuvant chemotherapy.

**Radiation therapy**

Radiation therapy is the gold standard for treatment of central nervous system tumors and generally is at least temporarily effective in halting tumor growth and/or bringing about clinical and radiographic improvement. In a historical review of patients with pineal region PNETs, patients who received radiation therapy survived longer than patients who did not [16]. In older retrospective studies of SPNETs, involved field, whole-brain and craniospinal radiation at varied doses were administered without a clear advantage to any one approach [7, 15, 20, 21]. Long-term survivors after surgery and varied doses and fields of radiation have been reported, albeit only a minority.

The propensity for subarachnoid dissemination has led to the standard use of craniospinal radiation in older children, regardless of metastatic stage at diagnosis. It is difficult to say how much this has contributed to the recent reports of improved survival, since patients now typically also receive adjuvant chemotherapy, as well as maximal surgical resection. Whether all patients require...