

Treatment of Supratentorial Primitive Neuroectodermal Tumors (PNETs) in Children

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Objective : Strategies for managing supratentorial primitive neuroectodermal tumors(PNETs) in children include surgical resection, craniospinal irradiation and chemotherapy. This study is performed in order to compare the efficacy of various methods of treatment and to describe its optimal management.

Methods : We have reviewed all medical records and pathology slides of six children(four males and two females) with supratentorial PNET from November, 1987 to May, 2003. The extent of resection was confirmed by computed tomography and magnetic resonance studies.

Results : The patients were aged 1 to 13 years and treated postoperatively with/without adjuvant therapy. Tumor location included was four cortical, one gangliobasal, and one pineal region. The presenting symptoms and signs consisted of increased intracranial pressure and focal neurological deficits such as seizure and hemiparesis. The treatment consisted of surgical resection alone in one patient, postoperative radiotherapy in one patient, postoperative chemotherapy in one, and postoperative radiotherapy with chemotherapy in three. Five patients lived more than 12 months after diagnosis and one patient among them has been living more than 5 years after diagnosis.

Conclusion : We can improve the survival and prognosis of supratentorial PNET patients by radical gross total resection of tumor followed by craniospinal irradiation and aggressive chemotherapy. First of all, gross total resection of tumor is the most important among many factors.

KEY WORDS : Primitive neuroectodermal tumor · Surgical resection · Radiotherapy · Chemotherapy.

Introduction

Most embryonal tumors of the central nervous system in childhood occur in the posterior fossa and the most common one is medulloblastoma¹⁾. Histologically similar lesions occasionally arise above the tentorium and Hart and Earle introduced the term "primitive neuroectodermal tumor(PNET)" describing embryonal tumor outside the cerebellum, morphologically similar to medulloblastoma²⁾.

In 1993, the World Health Organization(WHO) classification of brain tumors defined all PNETs of central nervous system as PNET, regardless of the location³⁾. PNETs are clinically characterized by their aggressive clinical behavior and high incidence of leptomeningeal dissemination.

Supratentorial PNETs in children have a poor prognosis even after multimodal treatment including surgical resection, chemotherapy and radiotherapy.

We retrospectively studied the treatment outcomes in supratentorial PNET patients to define which treatment strategies can improve the outcome.

Materials and Methods

Six patients, treated at our hospital, were entered in this study. We have reviewed the outcome of six children(four males and two females) with supratentorial PNET from November, 1987 to May, 2003. All medical records and pathology slides were reviewed. The patients were aged 1 to 13 years with three children under 3 years of age. All patients underwent surgery for histologic diagnosis and the tumor was removed as much as possible. The extent of resection was confirmed by computed tomography(CT) or magnetic resonance(MR) studies and was classified as gross total, subtotal(greater than 90%) and partial. Five patients were

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Supratentorial PNET

Table 1. Clinical features and outcome of six patients with supratentorial primitive neuroectodermal tumor

	Age/Sex	Tumor location	Operation	Radiotherapy	Chemotherapy	Survival period(month)
1	5/M	Lt.F	1987.11(STR) 1988.11(STR)	5400cGy		13, dead
2	13/M	Lt.FP	1993.6(STR) 1994.4(STR) 1995.2(STR)	9000cGy *	POG 9060(ifosfamide) POG 8731(MTX)	20, dead
3	1/F	Rt.BG	1995.8(PR)			5, dead
4	2/F	Rt.TP	1998.5(GTR) 1999.12(GTR)	5400cGy	POG 9135 (cisplatin, BCNU)	60, alive
5	1/M	Pineal	1998.8(GTR)		POG 9135 (cisplatin, BCNU)	12, dead
6	9/M	Rt.TP	2002.1(GTR) 2003.4(STR)	5400cGy	POG 9031 (vincristin, cyclophosphamide)	17, alive

M : male, F : female, Rt. : right, Lt. : left, F : frontal, T : temporal, P : parietal, GTR : gross total resection, STP : subtotal resection, PR : partial resection, POG : pediatric oncology group, MTX : methotrexate * whole brain irradiation 4500cGy, spinal irradiation 3600cGy, tumor bed 900cGy

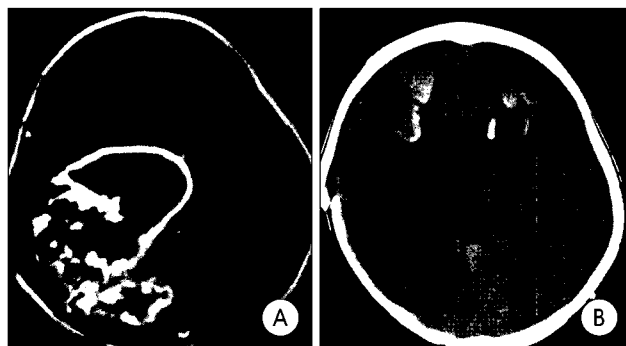


Fig. 1. case 4. A : Brain magnetic resonance image showing a heterogeneously enhanced mass lesion in the right temporoparietal area and midline shift to left side. B : Follow-up brain computed tomography, six years after the operation, showing no local recurrence with diffuse mineralized calcifications along the corticomedullary junction site of the both cerebral hemispheres and tip of shunt catheter in left lateral ventricle.

treated postoperatively with adjuvant therapy including chemotherapy and radiotherapy. The image follow-ups of the brain had been performed every 3~6 months after initial surgery for the first two years and then yearly.

Results

The presenting symptoms and signs consisted of increased intracranial pressure and focal neurological deficits such as seizure and hemiparesis. Four patients presented with headache, nausea and vomiting and two with lethargy. Motor signs were presenting problems in two patients. Seizures were noted in four patients.

Tumor location was four cortical, one gangliobasal, and one pineal region. A gross total removal of the tumor was achieved in three patients(case 4, case 5, case 6); a subtotal resection in two(case 1, case 2); a partial resection in one(case 3). Four of them had multiple craniotomies for local recurrence. Case 2 and case 6 received postoperative radiotherapy followed by chemotherapy; case 4 received postoperative chemotherapy followed by radiotherapy; case 1 received only radiotherapy and case 5 only chemotherapy, respectively; case 3 had neither radiation therapy nor chemotherapy.

Radiation was delivered to the tumor bed 5400cGy in three patients(case 1, case 4, case 6) and case 2 received postoperative craniospinal irradiation(whole brain irradiation 4500cGy, spinal irradiation 3600cGy and tumor bed 900 cGy). The chemotherapy was performed according to pediatric oncology group(POG) protocol(POG 8731; methotrexate, POG 9031; vincristin, cyclophosphamide, POG 9060; ifosfamide, POG 9135; cisplatin, BCNU). Four of six patients died. Five patients lived more than 12 months after diagnosis and one of them has been living more than 5 years after diagnosis(Table 1).

Case Illustration

Case 4

This 2 year-old girl was admitted to our hospital due to headache, nausea and vomiting. Brain MR image showed a heterogeneously enhanced mass lesion in the right temporoparietal area with midline shift to left(Fig 1A). After total removal of the mass, chemotherapy using POG 9135 protocol(cisplatin, BCNU) was administered. Postoperative 17 months follow-up brain MR image revealed a recurred mass lesion. Prompting a second craniotomy was done and the mass lesion was totally removed. Then she underwent radiotherapy(5400cGy). Postoperative 6years follow-up brain CT showed no local recurrence(Fig 1B).

Case 6

This 9 year-old boy was admitted to our hospital due to

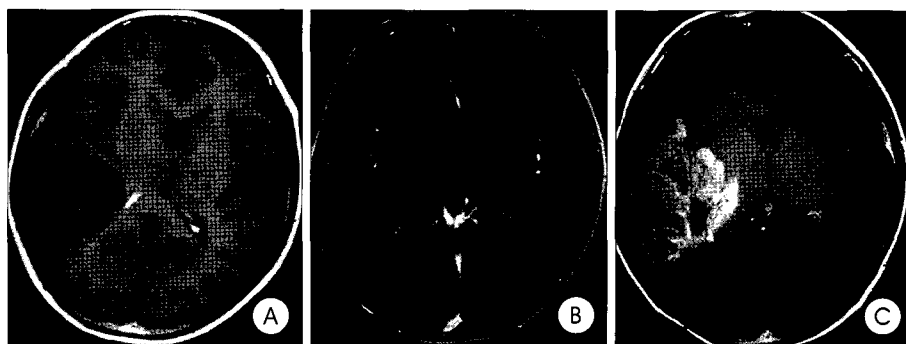


Fig. 2. case 6. A : Brain magnetic resonance(MR) image showing a heterogeneously enhanced round mass lesion on the right temporoparietal area. B : Follow-up brain MR image, 14 months after the operation, showing no local recurrence. C : Follow-up brain MR image, 16 months after the operation, showing recurrence on the right temporoparietal area.

seizure attack and headache. Brain MR image showed a heterogeneously enhanced round mass lesion in the right temporoparietal area(Fig. 2A). The mass lesion was totally removed. Histopathologic finding showed sheets of undifferentiated small round tumor cells(Fig. 3). He took postoperative radiotherapy(5400cGy) and POG 9031 protocol(vincristin, cyclophosphamide) chemotherapy.

Postoperative 14 months follow-up brain MR image showed no local recurrence but postoperative 16 months follow-up brain MR image showed mass recurrence so he underwent second craniotomy and the mass lesion was subtotally removed(Fig. 2B, C).

Discussion

PNET is the most common malignant brain tumor in children, which was first introduced by Hart and Earle in 1973 to describe a particular small round-cell neoplasm of the cerebral hemispheres⁴. Microscopically, PNETs are composed predominantly of small undifferentiated cells with dark, oval to irregular nuclei without observable cytoplasm. PNETs can occur anywhere in the nervous system and are identified historically according to the tumor site : the medulloblastoma(posterior fossa), pineoblastoma(pineal gland), and central neuroblastoma(cortical)^{2,9,12}.

Supratentorial PNETs are highly malignant primary central nervous system tumors accounting for 2.5% of childhood brain tumors, with 80% of cases occurring in the first decade, in contrast to medulloblastoma accounting for 20%^{2,3,10,11,13}.

These tumors grow rapidly and the duration of symptoms before diagnosis is brief, ranged from 1 to 12 weeks, with a mean of 6 weeks, and the tumors are often large at the time of diagnosis¹. In our cases, the duration of symptoms before

parietal lobes.

The outcome of supratentorial PNETs are poor in spite multimodal treatments including surgical resection, radiation therapy and chemotherapy^{11,12}. Hart and Earle reported only one patient survived to 5 years and the remainder(five patients) were dead at an average of 10months⁴. Kosnik et al reported 15 cerebral PNETs and 40% of the patients were alive at 6 months, only 10% at 1 year and all patients had died within 2 years after diagnosis⁹. Albright et al. reported 27 patients of cerebral PNETs and overall 5 year survival rate was 34%³.

Many factors affect the prognosis of supratentorial PNETs. First, the degree of tumor resection affect the prognosis. Patients with complete or nearly complete resection of tumor have a trend for better prognosis, therefore many reports recommend aggressive tumor resection as much as possible without neurologic deficits^{1,3,9,10}. In our cases, total or subtotal resection cases have better prognosis than partial resection case(more than 12 months vs. 5 months). Second, postoperative craniospinal radiation and chemotherapy improve survival^{1,3,10-13}. Some authors suggested immediate radiotherapy followed by maintenance chemotherapy was superior to preirradiation chemotherapy because progression of disease before and during radiotherapy occurred predominantly in children who received early chemotherapy.

Therefore they

diagnosis ranged from 1 to 4 weeks. Supratentorial PNETs are located most frequently in the frontal and parietal lobes and, on CT, are iso- or hyperintense lesions that enhance heterogeneously after administration of contrast agents. A relatively distinct boundary between tumor and brain is generally seen on both CT and MR scans. Approximately half are large, solid tumors and half are cystic. In our cases, four of six cases are located in the frontal and

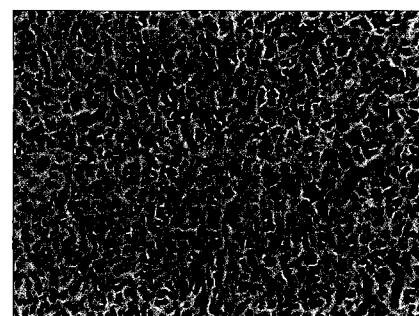


Fig. 3. case 6. Histopathologic finding showing sheets of undifferentiated small round tumor cells(H & E, ×400).

recommended radiotherapy should immediately follow surgery in children with supratentorial PNETs even if aggressive chemotherapy is applied^{11,13}. In our cases, post-operative radiotherapy and/or chemotherapy performed cases have better prognosis and combination of radiotherapy and chemotherapy cases have better prognosis than others. In multiple craniotomies for local recurrence cases, combination of radiotherapy and chemotherapy cases (case 2, case 4, case 6) have longer survival period than only radiotherapy case (case 1). Third, tumor location affect the prognosis. Some authors reported pineal PNETs have a better prognosis than nonpineal PNETs^{2,11}. Timmermann et al. reported 3-year progression free survival rate for pineal and nonpineal PNETs revealed a significant advantage 64% vs 34%¹¹. Cohen et al. reported similar result (61% vs 33%)². Dirks et al found 30% vs 12% 3-year survival for pineal and nonpineal PNETs. In our cases, pineal PNET case (case 5) has a better prognosis than nonpineal PNET case (case 3) but this is not apparent due to the difference of surgical extent and other treatment modalities (other cases were excluded from this comparison due to the difference of age). Fourth, the age of patients affect prognosis. Younger patients have a poor prognosis than older patients^{1,3,7}. Albright et al. reported children 1.5~3 years old had a significantly worse survival compared to older children. Other reports demonstrate that age under 5 years is a poor prognostic factor for supratentorial embryonal tumors^{3,6,8}. In our cases, older children (case 1, case 2, case 6) have a better prognosis than younger children (case 3, case 5) except case 4.

Case 4 showed very long survival period compared with other cases and the extent of surgical resection is the most important among many factors compared with case 2 and case 6. In addition, the Ki-67 labelling index of case 4 was 5 but the reported mean Ki-67 labelling index of PNET ranges from 17.2 to 30.9¹⁴. The low Ki-67 labelling index also contributed to the long term survival of case 4.

Although statistical significance was not reached due to the small number of cases, there were some trends; gross total resection cases, postoperation chemotherapy and radiotherapy performed cases, pineal PNETs or older children have better outcomes in our cases.

Conclusion

The prognosis of the patients with supratentorial PNETs remains poor despite treatment including surgical

resection, radiotherapy and/or chemotherapy. However we can improve the survival and prognosis of supratentorial PNET patients by radical resection of tumor followed by radiotherapy except for very young patients who cannot perform radiotherapy and aggressive chemotherapy. First of all, gross total resection of tumor is the most important among many factors.

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