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Clinical Study

Adult supratentorial extra-pineal primitive neuro-ectodermal tumors

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ABSTRACT

Primitive neuro-ectodermal tumors (PNET) are rare malignant brain tumors, mostly undifferentiated, that tend to spread through the cerebrospinal fluid (CSF). Extra-pineal supratentorial PNET in adults are very rare. Published guidelines for adult PNET were not available until 2011, and at our institute surgeons and oncologists did not have consensus on imaging evaluation or treatment protocols between 1994 to 2008. Twenty-two consecutive adult patients with extra-pineal supratentorial PNET from this period were reviewed in this retrospective study. Their clinical profiles and radiologic images were evaluated. A pathological review based on the 2007 World Health Organization criteria was also conducted. Prognostic factors were analyzed. The 1 and 3 year overall survival rates were 64% and 32% for adult extra-pineal supratentorial PNET, respectively. Limited by the small number of tumors in this series, we suggest that negative prognostic factors are multiplicity at onset, initial CSF seeding, and tumor differentiation. Although age of onset, extent of resection, radiation and chemotherapy were assumed to be good prognostic factors, the analysis did not reveal strong significance for overall survival with univariate and multivariate analysis. We believe more detailed investigations on the genetic/molecular basis of supratentorial PNET and their clinical outcomes are warranted.

1. Introduction

Primitive neuro-ectodermal tumors (PNET) are relatively rare brain tumors, particularly in adults. These tumors are highly malignant, undifferentiated neoplasms that arise from the germinal matrix cells of the primitive neural tube. They are occasionally multicentric at the time of diagnosis, and sometimes seed within the central nervous system [1]. Hart and Earle first described the subgroup of supratentorial PNET. They are defined as poorly differentiated, embryonic tumors outside the cerebellum that closely resemble medulloblastomas [2]. While PNET account for 20% of pediatric brain tumors [3], adult supratentorial PNET constituted less than 1% of adult brain tumors in 2011, according to the British Neuro-oncology Society [3]. Treatment options for adult patients have not been clearly outlined due to their low incidence. This retrospective study reviewed 22 adult patients with extra-pineal supratentorial PNET at Chang Gung Memorial Hospital, Taiwan, over a 14 year period. Despite the lack of consensus regarding the optimal treatment strategy, this study also attempted to analyze the prognostic factors in these patients.

2. Methods and materials

During the period from July 1994 to September 2008, 22 patients aged >18 years at the time of diagnosis were included in this study. Their pathologic and radiologic data were retrospectively analyzed. All patients underwent surgical intervention and the diagnosis of supratentorial PNET was confirmed by a neuro-pathologist based on the 2007 World Health Organization (WHO) classification. Tumor size and location, surgical procedures, and adjuvant therapies were documented, as well as the progression-free survival (PFS) of each patient. These patients were followed up in the outpatient clinic or through telephone interviews.

Statistical analyses were performed using the chi-squared test or Fisher's exact test, with Kaplan–Meier survival analysis for the categorical variables. All significance tests were one-sided. Statistical significance was set at $p < 0.05$.

3. Results

3.1. Clinical data at presentation

The age of the patients at diagnosis ranged from 19 to 81 years (median, 52 years). Twelve (55%) were female. The most frequent symptoms or signs were headache, increased intracranial pressure,

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Table 1
Symptoms and signs of primitive neuro-ectodermal tumor in adult patients upon initial presentation.

Symptoms/signs	n	%
Headache	11	50
Nausea/vomiting	10	45
Motor disturbance	10	45
Cranial nerve palsy	7	32
Frontal syndrome	4	18
Aphasia	3	14
Seizure	1	5
Other symptoms[a]	5	23

[a] Included memory defects, disorientation, eye pain, blurred vision, vertigo, lethargy, and neck pain.

and motor disturbance (Table 1). The median time from the first presenting symptom to diagnosis was 42.3 days (range, 3–365 days).

The lesions were mostly located in the brain parenchyma (77.3%), including the frontal, temporal, parietal, and occipital lobes. Four (18.2%) tumors were located primarily in the ventricles and one in the corpus callosum (4.5%). Fifteen (68%) patients initially presented with a single tumor while seven (32%) had multiple tumors. Nine tumors were in the right hemisphere, nine in the left hemisphere, and four (18%) were bilateral. The temporal lobe was the most frequent tumor site (n = 10, 45%). There were no pineal supratentorial PNET in this study. The mean maximum tumor dimension was 3.8 cm, with a range of 1–7 cm. A summary of the patient characteristics is listed in Table 2.

Of the 14 patients who underwent initial cerebrospinal fluid (CSF) analysis, bone scan, or MRI of the spine, CSF spread was identified in five (36%) patients. Pathologic diagnoses, along with immunohistochemical evaluations, were reviewed by a neuropathologist to confirm the original diagnosis (Table 2, Fig. 1A). Eighteen out of 20 patients (90%) had glial or neuronal differentiation. Immunohistochemical glial fibrillary acidic protein (GFAP) expression was positive in nine (45%) patients (Fig. 1C) and synaptophysin (Syn) expression was noted in 13 (76%). One patient demonstrated morphologic glial differentiation and nine patients demonstrated neuronal differentiation. Two patients did not have neuronal or glial differentiation.

3.2. Initial treatment

In terms of initial surgical procedure, five patients (23%) underwent stereotactic biopsy (<10% tumor resection), four (18%) underwent incomplete resection (10–90% tumor resection) due to profuse bleeding or proximity to an eloquent area, six (27%) underwent subtotal resection (90–99% tumor resection), and seven (32%) underwent gross total resection (100% tumor removal).

Adjuvant therapies during this period varied. Seven patients received chemotherapy (CT) and 16 received external radiation to either the brain alone, or combined with the cranio-spinal axis (Table 3). Five patients (22.7%) did not receive post-operative adjuvant therapy for various reasons, including major neurologic disabilities after the initial surgery or patient choice. For these patients, supportive care was provided. In patients who received adjuvant therapy, seven (41%) received CT and then radiation therapy.

One patient received radiation at their local hospital and the details were not available. Among the 16 patients (72.7%) who received radiotherapy (RT) at our institute, three (18.8%) received cranio-spinal axis radiation with an additional boost to the tumor bed, six (37.5%) received whole brain RT, and seven (44%) were treated with only focal RT to the tumor bed. The median radiation dose was 5700 cGy (range, 1700–6100 cGy).

3.3. Outcome

The mean follow-up duration was 24 months (range, 1–102 months). The 1 and 3 year PFS rates were 59% and 27.2%, respectively. The 1 and 3 year overall survival (OS) rates were 63.6% and 31.8%, respectively (Fig. 2). The median overall PFS was 16 months, while the median OS was 24 months. At the last follow-up (102 months), 17 (77%) patients had died and five (23%) were still alive. All except one of the survivors were in complete remission 30 months after treatment.

Table 2
Summary of primitive neuro-ectodermal tumor patient characteristics.

Patient	Age	Sex	Multiplicity	Tumor size, cm	Tumor localization	Initial CSF spreading	Immuno-histochemical study	Initial resection
1	29	F	S	7	L; T	N/A	None	STR
2	63	F	Mu	3.5	R; P	N/A	GFAP+, NSE+	SB
3	75	M	S	4	R; T	Y	None	GTR
4	46	M	Mu	4	B; V	N/A	GFAP−, NF−, NSE+	SB
5	29	M	S	4	L; T	N/A	CK−, GFAP−, NSE+, Syn+, Vimentin+	STR
6	76	M	S	2.5	R; Fr	Y	CK−, GFAP−, NSE+,	GTR
7	81	M	Mu	1	Corpus callosum	N/A	CK−, GFAP−, Syn−,	SB
8	20	F	S	4.5	L; T	N	CK−, GFAP−, Desmin−, NSE+, Syn+	GTR
9	77	M	S	4.5	L; T	N	GFAP+, NSE+, Syn+	SB
10	61	M	S	3	B; V	Y	GFAP−, NSE+, Syn+	IR
11	55	F	S	3	R; Fr	N/A	GFAP−, Desmin−, NSE+, Syn+, Vimentin+	STR
12	31	F	S	4	R; Fr	N	GFAP−, Desmin-NF+, Syn−	GTR
13	19	M	S	1.5	L; V	N	EMA−, GFAP+, Syn−, Vimentin+	STR
14	26	F	Mu	5.6	L; V	N	GFAP+, NSE+, Syn+	IR
15	62	F	Mu	2.5	B; T	Y	GFAP−, NSE+, Syn+	IR
16	66	F	Mu	1.5	L; T	Y	CK−, GFAP−, NSE+, Syn+	IR
17	39	F	S	5.3	R; P	N	CK−, EMA−, GFAP+, Syn+, Vimentin+	GTR
18	49	M	Mu	4	B; T; R; V	N/A	GFAP+, Syn+	GTR
19	41	F	S	5	L; O	N	GFAP+, NSE+, Syn−,	STR
20	37	M	S	6	R; Fr	N	Chromogranin A−, EMA−, GFAP+, Syn+,	GTR
21	75	M	S	4	L; T	N/A	EMA−, GFAP+, Syn+	STRl
22	70	M	S	2.8	R; T	N	GFAP+, Syn+	SB

B = bilateral, CK = cytokeratin, EMA = epithelial membrane antigen, GTR = gross total resection, F = female, Fr = frontal lobe, GFAP = glial fibrillary acid protein, IR = incomplete resection, L = left, M = male, Mu = multiple, N = no, N/A = not available, NF = neuro-filament, NSE = neuron specific enolase, O = occipital lobe, P = parietal lobe, R = right, S = single, SB = stereotactic biopsy, STR = sub-total resection, Syn = synaptophysin, T = temporal lobe, V = ventricle, Y = yes, − = negative, += positive.