Radiotherapy of Pineal and Ectopic Pineal Tumors

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From December 1984 to February 1990, 16 patients with tumors of pineal and suprasellar location were treated with radiation therapy. Tissue diagnoses were obtained before radiation therapy in 5 patients and 11 were irradiated without histologic confirmation. Initial treatments for these patients were craniospinal plus boost primary irradiation (six), whole brain plus boost primary irradiation (nine), primary tumor site irradiation (one). The 5 year actuarial survival rate is 71%. Three cases with elevated beta-human chorionic gonadotropin (HCG) responded favorably to radiation, but pineal tumors with elevated alpha-fetoprotein (AFP) did not respond well. Spinal metastasis developed in 2 cases (2/15) with elevated AFP : one received prophylactic spinal irradiation, another did not. Our studies suggest that more aggressive treatment would be necessary in patient with elevated AFP and in this patient, radiation therapy may be initiated without pathologic confirmation. From the result of our study, routine use of prophylactic spinal irrdiation for all patients with pineal region tumor is not indicated and use of prophylactic spinal irradiation is considered for the patients with positive craniospinal fluid cytology, meningeal seeding, disease extension along the ventricular wall and biopsy proven germinoma.

Key Words: Pineal tumor, Radiation therapy, Surgery, Tumor markers

INTRODUCTION

Because of the histologic diversity of pineal tumors, the choice of the treatment for pineal region tumors remain controversial[1]. Primary removal of pineal region tumors had been associated with a 25% to 70% mortality[5]. Most tumors in this region are radiosensitive. Therefore, treatment with shunt operation and radiation therapy without a tissue diagnosis had been advocated[13].

But recent advances in surgical techniques have significantly lowered the mortality and morbidity associated with surgery in the pineal region. With this advancement, there is growing consensus that a tissue diagnosis should be made for the more rational approach and individualized treatment according to each pathology. It is necessary to differentiate radiosensitive germinoma from the bening and radioresistant malignant tumors. If this differentiation can be made on the basis of clincal, biochemical, and radiological studies, it would be of value.

The purpose of our study is to assess (1) the necessity of tissue diagnosis (2) the optimum radiation therapy (3) the sensitivity and specificity of CT scanning and tumor marker studies in making a presumptive diagnosis

METHODS AND MATERIALS

1. Patient Characteristics

Between December 1984 and February 1990, 16 patients with tumors of pineal (12) and suprsellar location (4) were irradiated at the Department of Therapeutic Radiology of Pusan Paik Hosptial. The age range of patients was 2 to 30 years with a median of 13 years (Table 1). Only 2 patients were over 20 years of age. Most patients were in the second decade (69%). The predominant incidence of pineal region tumros in young men is similar to that reported by other authors[2]. There were 13 males and 3 females.

The tumors were located in the pineal region in 12 cases and in the suprasellar region in 4 cases (Case 1, 2, 3, 4 Table 3). Case 2 showed a metastatic tumor mass in the posterior fossa on the CT scans obtained in 2 months after the radiation therapy. Histology was confirmed in all of four cases of supreasellar tumor and 1 case of twelve pineal region tumors. The remaining 11 cases were treated without tissue confirmation.

Common presenting symptoms were headache, nausea, vomiting, and visual disorder (Table 2). Parinaud's syndrome which is considered to be a pathognomonic sign of tumor in the pineal region was present in nine of 12 patients with pineal region

Table 1. Age & Sex Distribution

Age	Male	Female	Total
0 – 5	1		1
6 – 10	1	1	2
11 – 15	7	1	8
16 – 20	3		3
21 – 30	1	1	2
Total	13	3	16

Table 2. *Presenting Symptoms and Signs*

	Pineal	Suprasellar
Symptom		
Headache	4	3
Nausea and Vomiting	5	2
Lethargy and Drowsiness	4	1
Visual Problem (diplopia, blurring)	7	2
Sign		
Upward gaze limitation	9	1
Diabetes insipidus	3	1
Optic atrophy		2
Hemiparesis	2	
Sluggish light reflex	4	

tumor. Diabetes insipidus was observed in 3 of 4 patients with suprasellar germinoma, but was seen in only three of 12 patients with tumors in the pineal region.

The cytology of cerebrospinal fluid was examined in 9 of 16 patients. One of the 9 patients was positive for malignant cells. Serum levels of beta-HCG or AFP were measured in 15 patients (Table 3).

Radiographic studies included skull x-rays, 4-vessel angiography, myelography, and CT scans of brain. All of the patients were initially examined by the CT scans.

2. Treatment

1) Surgery

Five of 16 patients underwent surgical procedures before radiation therapy: of 4 patients with supreasellar mass, 2 with suprasellar mass and biopsy was performed in one case. One case of pineal tumor was confirmed by stereotactic biopsy. Ventriculoperitoneal shunts were performed in 6 patients.

Table 3. Results of Evaluation

Case No.	Tissue Diagnosis	CSF Cytology	Myelography	HCG	AFP
1	*germinoma*	*negative*		N	N
2	germinoma	positive			
3	germinoma	negative		N	N
4	EST		WNL	N	E
5		negative	WNL	E	N
6					E
7	pineocytoma		WNL	N	N
8		negative			N
9					N
10				N	N
11		negative		N	N
12		negative		E	E
13		negative		N	E
14				E	N
15		negative			
16				E	N

HCG : human chorionic gonadotropin, AFP : alpha-fetoprotein, EST : endodermal sinus tumor, WNL : within normal limit, N : normal, E : elevated

2) Radiation Therapy

All patients were treated with cobalt-60 gamma ray. 9 patients were treated with whole brain irradiation followed by reduced fields to the primary site given by opposed lateral fields. 6 patients received craniospinal irradiation. One patient (case 4) was given a radiation therapy to the primary site only with wide field. The total dose ranged from 2000 to 3960 cGy to the whole brain, 3650 to 5940 cGy for the primary site, and 2100 to 3000 cGy to the spinal cord. Details of radiation therapy are shown in Table 4.

Folow up CT scans of brain during and after radiation therapy were available in 9 patients. The CT scan was repeated after 2000 to 2500 cGy and patients with tumors (*e.g.*, germinoma, pineoblastoma). Because these tumors have a high likelihood of seeding in the central nervous system, the spine was then irradiated.

Survival was calculated from the begining of radiation therapy by the life table method.

RESULTS

1. Treatment and Outcome

Actuarial survival curve in all patients is present-

ed in the Fig. 1. Eleven of 16 patients are alive without evidence of recurrence with follow up intervals of 19 to 79 months with median 36 months. Actuarial survival rate at the 79 months was 71%. Of 5 deaths, one patient (2 year old) died of infection 4 months postoperatively and this patient was eliminated from the survival analysis. Four patients (case 4, 10, 12, 13) died of recurrence between 4 and 12 months after treatment: two patients (case 12, 13) developed primary relapse with simultaneous spinal metastasis, and two patient (case 4, 10) developed primary recurrence alone. Initial treatment for these four patients included craniospinal plus boost irradiation to the primary site (case 13), whole brain irradiation followed by reduced fields to the primary site (case 4, 10, 12).

Table 4. Details of Radiation Therapy

Case No.	Cranial Irradiation (cGy)		Spinal Dose
	WB	Boost	(cGy)
1	3960	540	
2	2100	2200	2100
3	3600	1400	3000
4	* 5040	900	
5	3600	1440	
6	3600	900	
7	3700	1400	3000
8	3450	1050	
9	3600	900	
10	3600	1260	
11	2000	1650	
12	3960	1080	
13	2400	2600	2550
14	3000	2000	3000
15	3600	1440	
16	3000	2000	3000

* cranial irradiation of case 4 was wide field
WB : whole brain

No patient showed spinal metastasis alone. Incidence of spinal metastasis in this study was 13.3% (2/15). None of two patients with spinal metastasis received surgery previously. Of six patients receiving spinal irradiation, only one developed spinal metastasis coexisting with primary recurrence. No patients with biopsy proven germinoma (0/4) had spinal metastasis; two received craniospinal irradiation, remaing two did not.

2. Results of Evaluation

Results of tissue diagnosis is presented in table 3. Myelography was performed in 4 cases and negative in all cases. Craniospinal fluid cytology studies demonstrated the presence of neoplastic cells in one of 8 evaluable patients.

9 patients had follow up CT scan after 2000 to 2500 cGy given to the whole brain. Significant regression of tumor size was demonstrated in 7 patients. One patient who showed no response died 4 months later. Of 8 patients who showed good response, 6 patients are alive.

Of 4 patients whose serum alphafetoprotein (AFP) was elevated, three patients died. The first patient (case 4) with a endodermal sinus tumor was treated with only local field irradiation. When the radiation therapy was completed, the value of AFP

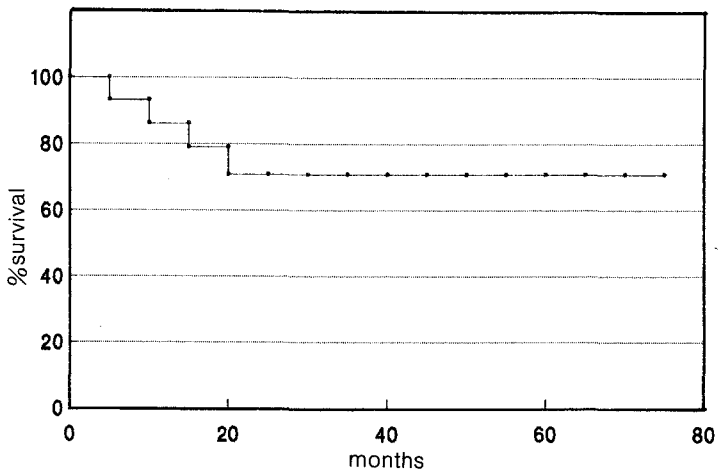

Fig. 1. Actuarial survival in all patients. —— n=15

was decreased from 700 ng/ml to 38.7 ng/ml and CT scan showed that the tumor mass was reduced in size. But the serum AFP was returned to initial value of 70 ng/ml after four and half months of radiation therapy and CT scan showed a regrowing tumor mass. This patient died 12 months later with recurrent tumor in the primary site. The second patient (case 12) presented with precocious puberty and elevated levels of serum beta-human chorionic gonadotropin (HCG), and radiation therapy was given to the whole brain and primary site boost (5040 cGy). Both AFP and beta-HCG were decreased from the value of 150 ng/ml and 1000 mIU/ml to 3.86 ng/ml and 10 mIU/ml respectively. This patient died 4 months later with spinal metastasis. The case 13 who received craniospinal irradiation showes a elevated value of the AFP (700 ng/ml) and follow up CT scan showed partial response. This patient died 8 months later with local tumor recurrence, subarachnoid seeding and multiple spinal metastasis. AFP was not checked after completion of radiation therapy.

Before radiation therapy, all patients underwent CT scans with and without contrast enhancement. The CT findings in all 16 patients are summarized in table 6. Presumtive diagnosis on the base of age, sex, tumor marker, and CT findings was made in six patients. Of six patients, three patients were germ cell tumor, one teratoma, one embryonal carcinoma and one endodermal sinus tumor.

Table 5. Recurrence Related to Tumor Dose

Tumor Dose (cGy)	Number of case	Recurrence
< 4000	1	0
4000 – 4499	1	0
4500 – 4999	5	1 (20%)
5000 – 5499	8	* 3 (38%)
> 5500	1	0

* pathologies were nongerminomatous germ cell tumors in all three cases

DISCUSSION

1. Role of Surgery

Because of the high percentage of radiosensitive tumors occuring in this region and the high mortality and morbidity associated with surgery, shunt operation followed by radiation therapy without tissue diagnosis had been advocated. This had led to the use of the radiation test. Rich et al[18] suggested to put a patient with a solitary tumor in the pineal or suprasellar area without endocrine or tumor marker abnormalities in the therapeutic trial of radiation with 2000 to 3000 cGy followed by reassessment with CT scan. If there is no tumor regression, a histologic confirmation with biopsy is needed to make therapeutic decisions.

But this method was criticized by Edwards et al [1] with following reasons. First, this approach submits the patient to 2000 cGy of unnecessary radia-

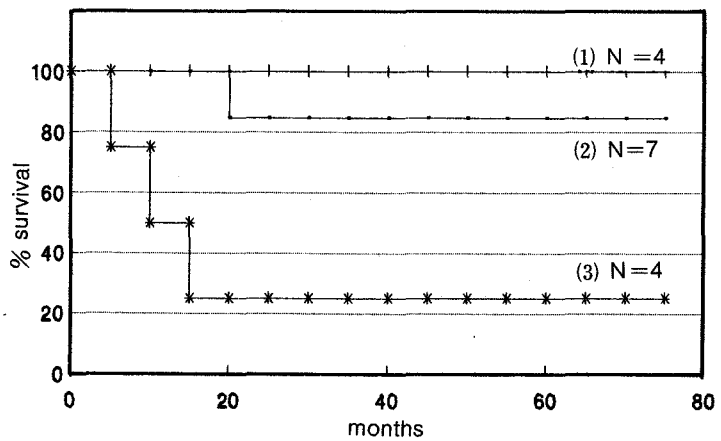

Fig. 2. Comparison of survival between patients with increased HCG and AFP.
—•— normal T.M. —⊥— increased HCG —•— increased AFP
TM: tumor marker, HCG: human chorionic gonadotropin, AFP: alphafetoprotein

Table 6. Presumptive Diagnosis on the Base of Age, Sex, Biochemical & CT Finding

Case No.	Sex & Sex	CT finding			TM		Presumptive Diagnosis
		TD	CE	C	HCG	AFP	
5	M/19	H		+	E	N	GCT
6	F/10	H	+	+		E	Teratoma
8	M/ 2	H	+		N	N	
9	M/13	H	+	+	N	N	
10	M/11				N	N	
11	M/16	I			N	N	
12	M/11	I	+++		E	E	Embry. Ca
13	M/ 9	I	+	+	N	E	EST
14	F/30	I	++		E	N	GCT
15	M/14	I	+++	+			
16	M/23	I+H	+++	+	E	N	GCT

TD : tumor density, CE : contrast enhancement, C : calcification, TM : tumor marker, HCG : human chorionic gonadotropin, AFP : alphafetoprotein, H : hyperdense, I : isodense, + : mild, ++ : moderate, +++ : well enhancement, E : elevated, N : normal, GCT : germ cell tumor, EST : endodermal sinus tumor

tion in the case of benign lesion. The incidence of the benign lesion in the pineal region is reported as 20~25%[3,5]. Second, in the case of partial response, it is difficult to make a therapeutic decision. Therefore, he insisted that histologic diagnosis should be made in all patients. Chapman[10] also recommended the tissue diagnosis in order to make a distinction between germinoma, endodermal sinus tumor and pineoblastoma, because radiation test can not distinguish germinoma from endodermal sinus tumor or pineoblastoma. With a tissue diagnosis, more aggressive treatment to pineoblastoma and endodermal sinus tumor can be offered. Necessity of histologic diagnosis in all patients is discussed in the following section of the tumor markers and CT scans.

However, some authors did not recommend a tissue diagnosis because of incresed risk of spinal metastasis. Wara et al[12] reported an spinal metastasis rate of 14% in biopsied germinomas versus 1. 7% in the no-biopsy group and several reports suggested an increased incidence of spinal metastasis in operated cases[4,9,28]. But the contradictory report can be found in the literature[3,17]. In our 2 patients who developed spinal metastasis, none had been operated. In two patients with biopsy proven suprasellar germinoma who did not received spinal irradiation, none developed spinal metastasis. Thus, the relationship between operation and spinal metastasis is unclear in our study.

2. Optimum Radiation Therapy

Yuta, et al[18] reported the treatment results among different treatment volume groups. He suggested that for cytology-negative cases without metastasis, irradiation of the tumor plus wide margin was sufficient. Others also reported excellent results when local field encompassing either the tumor plus margin or the entire ventricular system followed by a boost to the primary tumor was used[13,17]. A correlation study between field size and survival has been found that a field including the ventricular system is generally acceptible [16,17,28,29].

Prophylactic spinal irradiation remains controversial. Wara et al[12] reported that the 8% incidence of spinal metastasis in his study does not warrant routine prophylactic spinal irradiation. Our studies showed spinal metastasis in 2 cases (2/15) with AFP positivity: one received prophylactic spinal irradiation, another did not. The results from other studies[2,9,16,18] indicate that the risk of spinal metastsis from intracranial germinoma is too low to warrant routine prophylactic spinal irradiation. Therefore, craniospinal irradiation should be administered only to those patients with positive cytology, meningeal seeding, multiple germinoma, hypothalamic invasion or disease extended along the ventricular walls[2,17,18,19]. But the specificity of cytologic studies of CSF is less well established with pineal tumors[22] and negative cytology dose

not exclude subarachnoid seeding[3,10]. In our cases, cytologic examination was negative in both of 2 patients who developed spinal metastasis later. This implies that negative cytology should be interpretated with caution.

Analysis of the dose response and survival rate for pineal region tumors indicates greater survival rate with higher dose[4]. High radiation dosages (5000 to 5500 cGy) have reduced local recurrence rates from 47% to 10%[27]. Other author also reported that doses of greater than 5000 cGy are necessary to control these tumors[4,9]. In our data, if we eliminate 3 cases with nongerminomatous germ cell tumor from the analysis of recurrence rate, we can get the control rate of 100% in patients who received radiation greater than 5000 cGy (Table 5).

3. Tumor Markers and CT Scans

An elevation of HCG can occur in germinomas [3,5,24,25] and often in other germ cell tumors such as choriocarcinomas[25], embryonal carcinomas[24,26], and teratomas[3], whereas AFP which is secreted from the yolk sac elements is found in endodermal sinus tumor and embryonal cell tumor[2,11,21-23]. When the level of both AFP and beta-HCG is elevated, embryonal carcinoma is suggestive[2,20]. Therefore germinoma and benign teratoma can be excluded if AFP is present. In these cases, Histologic confirmation has not been found to be beneficial[8,20]. In our study, 4 cases with elevated AFP (case 4, 6, 12, 13) can be diagnosed as an embryonal carcinoma or endodermal sinus tumor and case 12 (both HCG and AFP are elevated) as an embryonal carcinoma. The presence of these tumor markers has been shown to be a grave prognostic sign in patients with testicular germ cell tumor[30]. Fig. 2 demonstrates the superior survival rates for patients with normal tumor marker or elevated level of beta-HCG compared with those with elevated level of AFP.

This reflects the generally poorer prognosis of tumors with intracranial nongerminomatous elements. However, except one patient (case 12) who had elevated levels of both AFP and beta-HCG, all of three patients with elevated level of beta-HCG alone are alive (case 5, 14, 16).

CT scanning also can be used in making a presumtive histological diagnosis. Zimmerman RA[15]. insisted that the CT findings when considered together with the patient's age and sex can be extremly useful in deciding on surgery and/or radiation therapy. Consideration of CT scans together with the clinical features, CSF cytology, tumor markers will usually allow a specific diagnosis with a high degree of probability[3]. The tissue density and enhancement characteristics alone do not differentiate lesions of pineal cell origin from germinal tumors, but calcification throughout the tumor of a female patient points to the diagnosis of a pineal cell tumor[15]. In this way, we tried to determine the pathology without a tissue diagnosis. The result is presented in table 6. In the patient with normal tumor marker (case 8, 9, 10, 11), we could not make any presumptive diagnosis on the basis of CT findings alone. Unfortunately, radiation test of case 8, 9 did not provide any clue for the presumptive diagnosis. Response to radiation in these cases was minimal.

On the basis of clinical, biochemical and radiologic studies, we can choose the following patients who benefit from initial radiation therapy without a tissue diagnosis. (1) those patients who show the elevation of the AFP. The finding of elevated AFP is sufficient for diagnosis, and radiation or chemotherapy may be initiated without surgical intervention[14]. (2) those patients who have a coexisting mass in the pineal and suprsellar area, suggesting germinoma. (3) those female patients who have a calcification throughout the tumor on CT scan. The diagnosis can be pineal cell tumor[7,15]. Initial surgical biopsy or excision is beneficial in the following patients. (1) those patients with a solitary tumor in the pineal or suprasellar area without tumor marker abnormalities, (2) those patients with fat density or ossification on the CT scanning. (3) those patients with elevated level of beta-HCG alone. Because elevated levels of beta-HCG have been associated not only with germinoma but also with choriocarcinoma, malignant teratoma and rarely with benign teratoma[22].

In conclusion, more aggressive radiation treatment such as the combination with chemotherapy would be necessary for the patient with elevated AFP and in this case, radiation therapy can be initiated without surgical intervention. From the result of our study and review of the literature, authors conclude that the routine use of prophylactic spinal irradiation for all patients with pineal region tumor is not indicated and use of prophylactic spinal irradiation is considered for the patients with positive CSF cytology, meningeal seeding, disease extension along the ventricular wall and biopsy proven germinoma.

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＝국문초록＝

송과선종 및 이소성 송과선종의 방사선 치료

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1984년 12월 부터 1990년 2월까지 인제대학교 의과대학 부산 백병원 치료방사선과에서 송과선 및 뇌하수체상부에 위치한 종양으로 진단받은 16명의 환자에 대하여 외부 방사선 조사를 시행하였다. 조직학적 진단은 5명에서 가능했고 나머지 11명의 환자는 조직학적 진단없이 치료를 시작하였다.

방사선조사는 전뇌－척수부위(6명), 전뇌부위(9명), 종양부위(1명)로 시행하였다. 생명표에 의거한 환자의 생존율은 71%였다. 조직학적 진단이 가능했던 3명, 종양 marker 정상소견을 보인 7명 그리고 beta-HCG 증가를 보인 환자들은 방사선치료에 좋은 반응을 보였으나, AFP의 증가를 보인 환자에서는 방사선치료에 대한 반응이 좋지 않았다. 척수전이는 AFP 증가를 보인 2예에서 관찰되었다. : 1명은 예방적 척추조사를 받았으나, 다른 한명은 받지 않았다.

이상의 고찰을 통하여 AFP의 증가를 보이는 환자에서는 방사선치료 외에 보다 적극적인 치료가 간구되어야 하며, 이런 환자에서는 조직학적 진단 없이 방사선 치료를 시작할 수 있다. 그리고 예방적 목적으로 척수조사를 하는 것은 뇌척수액 세포검사의 양성, 뇌 척수막으로의 전이, 뇌실 침범, 조직학적으로 입증된 생식세포종일 경우에는 고려할 수 있다.