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PRIMARY INTRACRANIAL GERM CELL TUMORS IN CHILDREN*

A Report of Eight Cases and Review of the Literature

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SUMMARY: Akyüz C, Köseoğlu V, Bertan V, Söylemezoğlu F, Kutluk MT, Büyükpamukçu M. (Department of Pediatric Oncology, Hacettepe University Institute of Oncology, Ankara, Turkey). Primary intracranial germ cell tumors in children: a report of eight cases and review of the literature. Turk J Pediatr 1999; 41: 161-172.

This study was conducted to evaluate the signs and symptoms on admission, diagnosis, localization, therapy, and survival of patients with primary intracranial germ cell tumors (PICGCT). Eight patients with surgically confirmed PICGCTs were treated and followed up at Hacettepe University's Department of Pediatric Oncology between 1974 and 1995.

While one patient was admitted with a second recurrence of her disease, the others were admitted or referred primarily to our institution. In this period, 357 germ cell tumor and 684 primary intracranial malignant tumors were diagnosed and treated at our institution. Thus, PICGCTs comprised 1.1 percent of the primary intracranial malignant tumors and 2.2 percent of the germ cell tumors. There were four females and four males and the median age was eight years (13 months to 12 years). On admission, the most common symptoms were diabetes insipidus (3/8) and vomiting (3/8). One patient also and Down's syndrome. Locations of the tumors were suprasellar in three, in the third ventricle in two, and in the cerebral parenchyma, and pineal and hypothalamic regions in the remainder. There were three germinomas, three malignant teratomas, and two mixed germ cell tumors. Only two patients could be treated with appropriate and adequate chemotherapy and radiotherapy. Three patients died: one in the postsurgical period, one after the third surgical approach and one 11 months after the diagnosis of progressive disease; three were lost to follow-up. The remaining two patients (with second recurrence and disseminated disease) are alive and without disease.

Our experience with these patients demonstrated that appropriate and adequate chemotherapy is as effective a treatment as radiotherapy, even with recurrence of the disease. *Key words: intracranial, germ cell, tumor, children.*

Primary intracranial germ cell tumors (PICGCTs) are very rare heterogeneous neoplasms which more often arise in the suprasellar and pineal regions of the brain, and account for less than five percent of all primary central nervous system tumors of childhood[1,2]. They are more frequently encountered in children than adults and generally become clinically apparent during the second decade of life[1,3]. They are histologically indistinguishable from germ cell tumors of gonads,

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so their histological subtypes such as gonadal germ cell tumors include: germinoma, teratoma, embryonal carcinoma, endodermal sinus tumor and choriocarcinoma. They may secrete substances such as alpha-fetoprotein (αFP) or a beta subunit of human chorionic gonadotropin (βHCG)[1,4].

It has been widely accepted that germinomas should be treated by radiotherapy, mature teratomas by surgical resection and the other malignant tumors by multimodality procedures including surgery, radiotherapy and chemotherapy[5]. However, central nervous system radiation in children has harmful side effects; consequently, other therapy modalities need to be evaluated[1]. A number of chemotherapeutic agents have been used for the treatment of intracranial germ cell tumors and chemotherapy has proved effective in recurrent germinomas[5-7]. The low incidence of PICGCTs makes it difficult for any center to acquire sufficient material for treatment modality and long-term follow-up evaluation[8]. For this reason, we report clinical features and treatment results for eight patients with PICGCTs.

Material and Methods

During the period 1974 to 1995, eight children with PICGCT were treated and followed up at Hacettepe University's Department of Pediatric Oncology in Ankara. Their clinical data, including patient age, sex, location of tumor, histopathological substype, surgical approach and treatment response were reviewed from the medical records.

Case Reports

Case 1

An eight-year-old girl was admitted with ptosis, mydriasis and poor vision in her left eye. Her medical records showed that she had been followed by the Pediatric Endocrinology and Genetic Units for diabetes insipidus and Down's syndrome. On physical examination, signs of Down's syndrome, left ptosis and pupillary dilation were found. Cranial computed tomography (CT) showed a suprasellar mass but other laboratory findings were normal. A biopsy was performed and histology revealed a malignant teratoma. Her parents did not accept any treatment and follow-up was discontinued.

Case 2

A 12-year-old boy was admitted with complaints of headache, vomiting, diplopia and gait abnormality. He was unconscious on his physical examination. Computed tomography of the head demonstrated a huge tumor in the third ventricle. An emergency surgical approach was carried out and partial resection was performed. Twenty-five days later, his cranial CT showed progression of the tumor, his disease progressed and he died on the 30th postoperative day. Histopathological examination of the resected tumor specimen revealed a mixed germ cell tumor.

Case 3

An eight-year-old boy who had been followed by the Pediatric Endocrinology Unit with the diagnosis of precocious puberty was referred to our department after a tumor in the third ventricle was demonstrated on his cranial CT. On admission, his physical findings showed signs of precocious puberty, bilateral grade I papilledema, 6^{th} and 7^{th} cranial nerve palsies, hyperreflexia, weakness of lower extremities, and unilateral Babinski positivity. The tumor was totally removed surgically and its histopathology revealed malignant teratoma. After the diagnosis, chemotherapy (vincristine 1 mg/m^2, procarbazine 50 mg/m^2, CCNU 100 mg/m^2) and radiotherapy were started. In the fifth month of his treatment, the tumor recurred and was again totally removed. Chemotherapy was then changed to cisplatin, vinblastine, and bleomycin (PVB) protocol. After three courses of this protocol, a good response was obtained, but at the end of the 5^{th} course, his disease progressed and he died in the eleventh month after the diagnosis.

Case 4

A seven-year-old boy was referred to our institution for evaluation of a mass located in the left hemisphere of his brain. Complaints were right hemiparesis, strabismus, diminished speech function, vomiting, headache, and seizures. Computed tomography showed a large mass located in the left hemisphere of the brain. On admission, he was unconscious. Craniotomy and total resection were done. Pathologic examination showed a malignant teratoma. His parents did not accept any treatment and the patient was discharged.

Case 5

An 11-year-old girl was referred to our institution for evaluation of her polyuria, polydipsia, diplopia and a suprasellar mass which had been demonstrated on her cranial CT. On admission her physical examination was normal. At that time, her computed tomography and magnetic resonance imaging (MRI) showed a huge suprasellar mass. Alpha-fetoprotein, βHCG and other laboratory findings were also normal. Subtotal resection was performed and histopathology revealed a germinoma. After the diagnosis, cranial and spinal radiotherapy was given at 4500 cGy and 3000 cGy, respectively. After six months, her MRI displayed residual disease. A chemotherapy protocol (BEP) was started and she was given two courses. She then refused the remaining chemotherapy courses.

Case 6

A 13-month-old girl was referred to our department with the diagnosis of intracranial hemorrhage. A pineal tumor with a hemorrhagic component was found on her cranial MRI. Cranial CT revealed the same tumor and hydrocephalus.

Alpha fetoprotein and βHCG of serum were normal. Craniotomy and partial resection of the tumor were performed and a shunt inserted. Histopathology of the tumor revealed a mixed germ cell tumor. On the 20th day following the first surgery, enlargement of the tumor was seen. A second surgical approach was done and the tumor was subtotaly resected again. While under observation in the intensive care unit, the patient became unconscious. She underwent a third surgical procedure, after which she died due to the progressive disease.

Case 7

A nine-year-old girl was admitted to another hospital in 1993 with complaints of left ptosis and mydriasis. At that time, her physical examination was normal except for left ptosis and mydriasis. Cranial MRI showed a suprasellar mass 3x2 cm in diameter (Fig. 1). She underwent surgery, and the tumor was totally

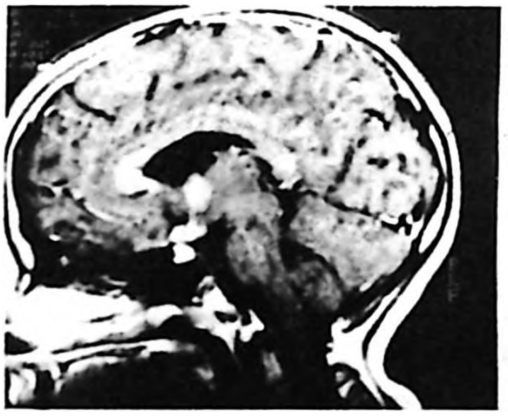

Fig. 1: MRI of the brain on admission demonstrating a suprasellar mass (Case 7).

removed. Histopathology of the tumor specimen revealed germinoma. Her disease relapsed after three months, a second operation was done and partial tumor resection was performed. Postoperatively, craniospinal (3000 cGy, 2500 cGy) radiotherapy was given, in addition to localization of the tumor (4920 cGy). Four months later, in May 1995, she was admitted to our institution with abdominal pain and vomiting. On admission, hepatomegaly, left ptosis and mydriasis were found on physical examination. Plain x-ray of the chest displayed nodular appearance on parenchyma of both lungs. Abdominal ultrasonography showed masses 8x7x8 cm and 11x10 cm in diameter in the right and left lobes of the liver, respectively, and abdominal tomography showed metastatic lesions in the parenchyma of the liver (Fig. 2). Cranial MRI showed a residual mass in the suprasellar region, and chest tomography displayed lymphadenopathy and diffuse parenchymal metastases. In the laboratory investigations, βHCG level was higher than the normal limits (730 mlu/ml). An ultrasonography-guided biopsy from the liver was performed. Histopathology revealed metastases of the germinoma. She was then treated with eleven courses of cisplatin, etoposide,

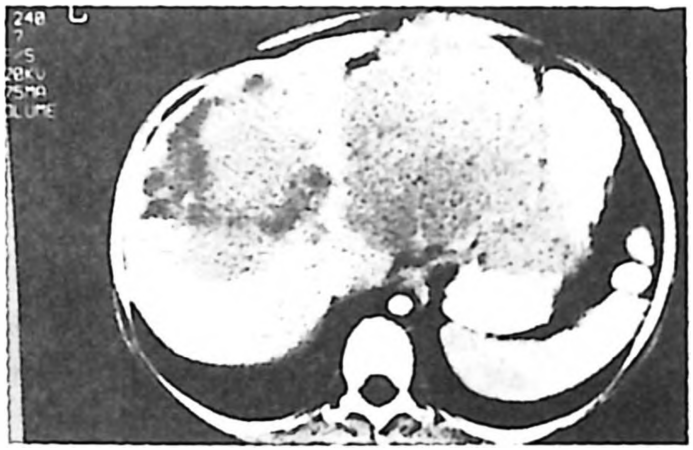

Fig. 2: An abdominal CT scan obtained on admission shows multiple metastatic lesions seen in the liver (Case 7).

and bleomycin (BEP) protocol. At the end of the treatment courses, no liver metastases were found (Fig. 3), and no residual mass was found on primary site (Fig. 4). There was regression of the parenchymal metastases of the lung.

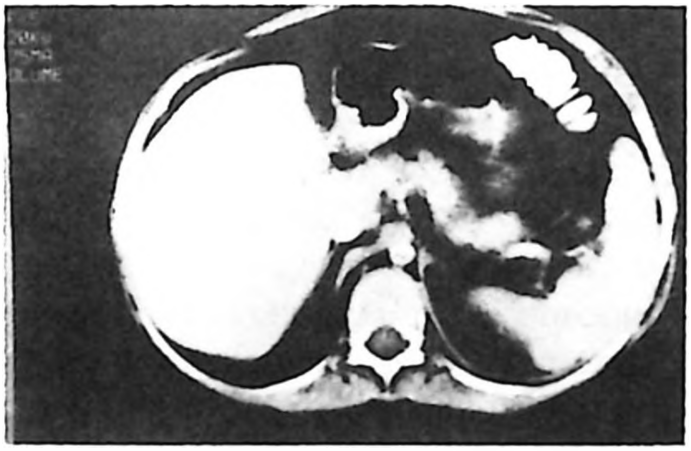

Fig. 3: A CT scan of the abdomen after chemotherapy showing no metastatic lesions of liver (Case 7).

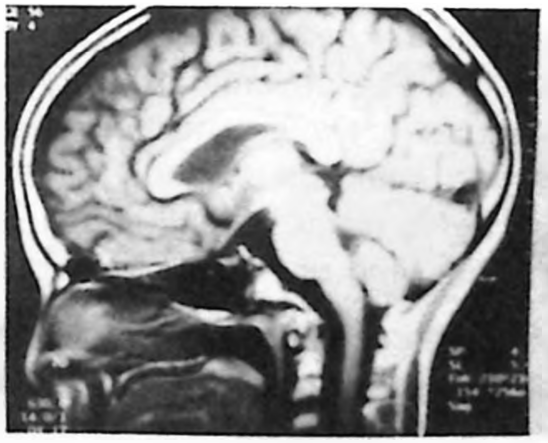

Fig. 4: MRI of the brain after chemotherapy shows no suprasellar mass (Case 7).

Thoracotomy was performed and one nodule was removed. Histopathology did not show any abnormality related to the primary disease. At this moment, she is alive without disease at after 20 months of relapse time.

Case 8

A ten-year-old boy was admitted to another hospital with polyuria and polydipsia. At that time, his physical examination was normal. His cranial MRI showed a mass in the hypothalamic region. He had been followed by the Pediatric Endocrinology Unit after the first admission. Nine months later, he underwent surgery and the mass was partially removed.

Histopathology of the resected specimens revealed a germinoma. After this diagnosis, cranial radiotherapy was given (4400 cGy). He was admitted to our institution following radiotherapy. On admission, his physical examination showed no abnormality. His cranial MRI revealed a mass in the hypothalamic region. BEP protocol was started and five courses were given. The decision was made to stop at the end of five courses of chemotherapy because the cisplatin was causing a decrease in the renal creatinine clearance. Eighteen months after diagnosis, he is alive and free of disease. He has no diminished renal function at this time.

Results

From 1974 to 1995, 357 children with germ cell tumors were treated at the Department of Pediatric Oncology, Hacettepe University. Eight of 357 germ cell tumor cases were diagnosed in an intracranial site. In the same period, 684 children with primary intracranial malignant tumors were diagnosed and treated. Thus, primary intracranial germ cell tumors comprised 2.2 percent of the germ cell tumors and 1.1 percent of the primary intracranial malignant tumors managed and treated in this single institution.

The age range of patients reviewed in this paper (Table I) was 13 months to 12 years, with a median age of eight years. Sex distribution was equal (4 male and 4 female). Of the cases in this group, three had been admitted with diabetes insipidus symptoms; one of these patients also had Down's syndrome. Three had vomiting, two had headache, two had multiple oculomotor palsies, one had visual disturbance, one had diminished speech function, one had a walking disorder, one had cranial nerve palsy, one had hemiplegia, and one had signs of precocious puberty at the time of diagnosis (Table II).

Alpa-fetoprotein and beta-human chorionic gonadotropin could not be measured in four patients. One of the remaining patients had an elevated serum beta-human chorionic gonadotropin level at the time of recurrence, which decreased gradually with chemotherapy and returned to normal limits (Case 7).

Table I: Clinical and Histopathological Findings of Patients with Primary Intracranial Germ Cell Tumor

Case No.	Age at Diagnosis	Sex	Localization	Surgery	Histopathology	Radiotherapy	Chemotherapy	Situation
1	8 years	F#	Suprasellar	Biopsy	Malignant teratoma	–	–	Lost to follow-up
2	12 years	M	Third ventricle	Partial resection	Mixed germ cell tumor	–	–	Died
3	8 years	M	Third ventricle	Total resection	Malignant teratoma	+	+	Relapsed Died
4	7 years	M	Left hemisphere	Total resection	Malignant teratoma	–	–	Lost to follow-up
5	11 years	F	Suprasellar	Partial resection	Germinoma	+	+	Lost to follow-up
6	13 months	F	Pineal	Partial resection*	Mixed germ cell tumor	–	–	Died
7	9 years	F	Suprasellar	Total resection*	Germinoma	+	+	Alive
8	10 years	M	Hypothalamic	Partial resection	Germinoma	+	+	Alive

* At first surgical approach.
\# Down's syndrome.

Table II: Demographic and Clinical Findings of Patients

Age (average)	8 Years (13 Months-12 Years)
Sex (M/F)	4/4 (1/1)
Complaints and physical examination findings	Number of cases
Cranial nerve palsies	4
Diabetes insipidus	3
Vomiting	3
Headache	2
Visual disturbance	2
Speech disorder	1
Precocious puberty	1
Walking disorder	1
Hemiparesis	1
Localization of the tumors	
Suprasellar	3
Third ventricle	2
Cerebral parenchyma	1
Pineal	1
Hypothalamic	1
Surgery	
Total resection	3
Partial resection	4
Biopsy	1
Histopathology	
Germinoma	3
Malignant teratoma	3
Mixed germ cell tumor	2

Locations of the tumors were different. Of the eight patients, three were suprasellar, two were in the third ventricle and the remainder were in the cerebral parenchyma, and pineal and hypothalamic regions. A tissue diagnosis of the tumor was made during surgery in these patients. Three total resections, four partial resections and one biopsy were performed in these cases. These tumors included three germinomas, three malignant teratomas and two mixed germ cell tumors.

Only two patients could be treated with appropriate and adequate treatment protocol in this group (Case 7 and 8). One patient received PVB protocol after the first recurrence of his disease. Two of eight patients are alive, three died, and the others were lost to follow-up.

Discussion

The incidence of primary intracranial germ cell tumors varies geographically and is distinctly higher in childhood than during adult life[9]. In a childhood series in Japan, it accounted for 4.8-15 percent of the primary intracranial neoplasms, which is much higher than the 0.3-3.4 percent reported in a western series[3,4]. Although the Japanase series showed increased incidence, the reason for this is not known[4,5,9]. The incidence was 1.1 percent in our series, lower than that of the Japanese series but similar to findings of the western series. Primary intracranial germ cell tumors tend to demonstrate male predominance in the literature[3,9]. In our series there was no distinction by sex (Table III). Reports of intracranial germ cell tumors have included newborn patients and elderly patients; 68 percent of the patients are between 10 and 21 years of age[9]. The age distribution of our cases agreed with previous reports; the median age was eight years[2,3,9]. To our knowledge there is no reported association between primary intracranial germ cell tumors and chromosomal disorders. However, two patients with primary intracranial germ cell tumors and Down's syndrome were reported separately by Fujita et al.[10] and Wada et al.[11] Our case with Down's syndrome (Case 1) is apparently only the third case in English literature with this association.

Clinical symptomatology varies and depends on the localization of the tumor. The common signs for patients with suprasellar germ cell tumors are chiefly endocrinologic manifestations including diabetes insipidus, hypopituitarism and visual deficit, while the symptoms for germcell tumors located in the pineal region are mainly due to increased intracranial pressure[12]. Growth retardation, precocious puberty and diabetes insipidus with no detectable etiology have been reported as initial symptoms[13-16]. It has been stated that follow-up of children with diabetes insipidus is important for determining whether or not it is idiopathic[17]. In our series, three cases were admitted with diabetes insipidus symptoms and one of these patients also had Down's syndrome. One boy had signs of precocious puberty at the time of diagnosis (Case 3). Precocious puberty is common in boys with hCG-secreting brain tumors, but it is extremely rare in

girls[15]. Signs and symptoms related to precocious puberty usually disappear with regression of the tumor following appropriate treatment[14]. In our case, we could not obtain any improvement because of treatment failure and recurrence of the disease. Vomiting, headache, diplopia and visual disturbance were the other frequent signs on admission.

Table III: Review of the Literature of Primary Intracranial Germ Cell Tumors

Authors	No of Cases	M/F Ratio	Age (Average)	Histopathology	Localization	Ref.
Ho et al.	51	2.6/1	13	30 germinoma 8 teratoma 5 EST 2 CC 6 MGCT 1P+S	17 pineal 14 suprasellar 10BG+T 5 lateral vent. 1 pituitary	9
Yoshida et al.	46	2.0/1	16	19 germinoma 13 EC 2 CC 4 teratoma 8 MGCT	28 pineal 11 suprasellar 4 BG 3 multiple	5
Hoffman et al.	51	1.8/1	10	34 germinoma 7 teratoma 4 EST 2 CC 4 MGCT	32 pineal 16 suprasellar	3
Ono et al.	79	3.0/1	14.2	50 germinoma 5 teratoma 7 extra-embryonic	–	21
Plantaz et al.	35	1.9/1	12	14 germinoma 6 NGGCT 5 P+S	15 pineal 15 suprasellar	22
Kiltie et al.	25	2.5/1	10	10 germinoma 9 NGGCT 6 no histology	14 pineal 9 S+Pt+3rd V 2 P+Pt+S	2
Wolden et al.	48	3.0/1	16	24 germinoma 3 MT 2 CC 1 EC 1 EST 3 MGCT		23
Present study	8	1/1	8	3 germimoma 3 MT 2 MGCT 1 pineal 1 hypothalamic	3 suprasellar 2 third ventricle 1 CP	–

Abb: MT: malignant teratoma, CC: choriocarcinoma, EC: embryonal carcinoma, EST: endodermal sinus tumor, MGCT: mixed germ cell tumor, NGGCT: non-germinomatous germ cell tumor, BG+T: basal ganglia+thalamus, P+S: pineal+suprasellar, BG: basal ganglia, S+Pt+3rd V: suprasellar+pituitary+third ventricle, P+Pt+S: pineal+pituitary+suprasellar, CP: cerebral parenchyma

Diagnosis of primary intracranial germ cell tumors is suggested by the findings on computed tomography and magnetic resonance imaging of the brain[12, 18]; however histopathological examination of the tumor tissue remains necessary for exact diagnosis. Alpha-fetoprotein and beta-human chorionic gonadotropin are useful tools when elevated both for diagnosis and monitoring the results of treatment[3, 8, 19]. They should be measured routinely in both serum and cerebrospinal fluid[3]. In our series, one patient had an elevated serum beta-human chorionic gonadotropin level at the time of recurrence, which decreased gradually and returned to normal limits at the end of therapy.

Primary intracranial germ cell tumors are complex lesions and little is known of their origin[4]. They are thought to derive from trapped germ cells which have failed to migrate. This migration defect of germ cells may explain the occurrence of the tumors in the midline of the brain[4]. Although basal ganlia, fourth and third ventricle, medulla oblongata and both suprasellar and pineal region occurrences are seen, they are generally situated in either the suprasellar or pineal region[9]. In our patients, location of the tumors were different. Of the eight patients, three were suprasellar, two were in the third ventricle and the remainder were in the cerebral parenchyma and pineal and hypothalamic regions. Although the locations of the germ cell tumors in our patients were similar to other studies, to our knowledge, this is the first reported case in English literature of a primary intracranial germ cell tumor located in the cerebral parenchyma.

Because of differences in radiosensitivity among primary intracranial germ cell tumors, histopathological confirmation of the diagnosis and identification of mixed components are essential for optimal treatment and determination of prognosis. For this reason, tissue diagnosis is of critical importance in dealing with primary intracranial germ cell tumors; a stereotactic biopsy or surgical resection should be performed before deciding to schedule treatment[8]. On the other hand, surgical removal may help to obtain better response to local radiotherapy[3]. In our cases, of the eight patients with primary intracranial germ cell tumors, three underwent total resection, four a partial resection and one a biopsy. Histopathological examination showed three germinomas, three malignant teratomas, and two mixed germ cell tumors. These findings were similar to previous reports.

Primary intracranial germ cell tumors are usually treated differently depending on their histopathological subtypes[2, 5]. For germinomas whole brain or whole CNS radiation therapy has been given after the diagnosis is made by surgical biopsy and by characteristic neuroradiological findings on CT and/or MRI. Recurrence rates at five years for completely resected tumors range from 10 to 40 percent in several published reports. Postoperative radiation therapy for all patients with large completely resected germinomas is recommended[1]. However, CNS radiation in children has devastating side effects. Consequently,

new approaches with high remission rate and without any sequelae are needed to treat these tumors. In the past, systemic administration of chemotherapeutic agents has played a limited role in the management of primary or metastatic brain tumors. A variety of agents have been used to treat primary intracranial germ cell tumors. Recently, chemotherapy regimens such as PVB, VP-16/CDDP, etc., which have been demonstrated to be effective in de novo and recurrent primary intracranial germ cell tumors, have been suggested for primary treatment instead of radiotherapy[1, 6, 7, 20]. In our series, two cases, one of them with recurrent disease, were treated effectively using the BEP protocol.

Although primary intracranial germ cell tumors are rare in childhood, they can be treated by appropriate treatment modalities. Our experiences and the data reported previously indicate that chemotherapy, especially BEP protocol, seems to be more effective, even in recurrent disease. It can be used as a first choice of treatment schedule, thus protecting patients from the harmful side effects of radiotherapy. Patients with Down's syndrome and diabetes insipidus with or without Down's syndrome need to be followed in order to determine whether or not they will develop intracranial germ cell tumors.

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