

# Primary Intracranial Germ-Cell Tumors

## Birincil Kafa İçi 'Germ' Hücresi Tümörleri

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**Abstract:** Twelve cases of primary intracranial germ-cell tumors including eleven germinomas and one yolk sac tumor out of 2633 primary intracranial tumors are studied. They were evaluated according to their clinical data based on the medical records including the patient's age and sex, location of the tumor, histopathological examination and prognosis with special reference to the incidence. The incidence of primary intracranial germ-cell tumors was 0.45 % in our series. One case with germinoma, a 15 year-old girl had multiple metastases to the frontobasal region, clavicle, lung and spinal cord both by hematogenous route and through the cerebrospinal fluid. This article not only focuses on the incidence and diagnostic technics of intracranial germ-cell tumors, but also presents a rare case of a germinoma with intracranial and extracranial multiple metastases.

**Key Words:** Germinoma, germ-cell tumor, pineal tumor, suprasellar tumor

**Özet:** İkibinaltıyüzotuzüç birincil kafa içi tümör olgusu içinden 11'i germinom, 1'i yolk sac tümörü olan 12 birincil kafa içi germ-hücresi tümörü olgusu incelendi. Bunlar hasta kayıtlarına dayanarak hastanın yaşı, cinsiyeti, tümörün yerleşimi, histopatolojik tanısı, prognozu ve özellikle sıklığı göz önüne alınarak incelendi. Bizim serimizde birincil kafa içi germ-hücresi tümörü sıklığı % 0.45 idi. Germinomlu olgulardan biri frontobazal bölgeye, klavikulaya, akciğere ve omuriliğe kan ve beyin omurilik sıvısı yolu ile çok sayıda metastazı olan 15 yaşında bir kız çocuğu idi. Bu makalede kafa içi germ-hücresi tümörlerinin sıklığı ve tanı yöntemlerini vurgulama dışında kafa içi ve kafa dışında çok sayıda metastazı olan nadir rastlanan bir olguyu bildirdik.

**Anahtar Sözcükler:** Germinom, germ-hücresi tümörü , pineal tümör, suprasellar tümör

### INTRODUCTION

Primary intracranial germ-cell tumors (ICGCT) are rare. They comprise 6 % of all germ-cell tumors (4,6,7). The incidence of intracranial germ-cell tumors has a marked geographic variation. Like the extragonadal germ-cell tumors these tumors are located along the midline. The localizations are pineal (45 %), suprasellar (33.4 %), periventricular (18 %), and intrasellar (3 %) (3,9). Germ-cell tumors usually

occur during the first two decades of life. Male-female ratio is 2:1 (4,6). The new World Health Organisation (WHO) classification of ICGCT is as follows: Germinoma (65 %), embryonal carcinoma (5 %), endodermal sinus tumor (5 %), choriocarcinoma (5 %), teratoma (immature teratoma) (18 %), and mixed tumor (7 %) (9). In this article, we examined 12 cases of ICGCT and emphasized the incidence of ICGCTs .

## PATIENTS AND METHODS

Out of 2633 primary intracranial tumors 12 cases of ICGCTs were diagnosed in the Department of Neuropathology in İstanbul University İstanbul Medical Faculty from 1987 to 1994. These 12 patients included 11 with germinoma and 1 with yolk sac tumor (endodermal sinus tumor, EST). Clinical data including the patient's age and sex, location of the tumor, histopathological evaluation and prognosis were reviewed based on the medical records.

The incidence of ICGCT in our series was 0.45 % . The age range was 8 to 26 years with a mean age of  $16.4 \pm 5.5$  years. There were 8 males and 4 females, male to female ratio was 2 :1.

Germinomas were situated in the suprasellar region in 6 patients and in the pineal region in 5 patients. The EST was localized in the pineal region. Of the 12 patients 8 underwent a total resection whereas 4 of them were verified by stereotactic biopsy.

All resection specimens were fixed in 10 % formalin, embedded in paraffin blocks and stained with hematoxylin and eosin. Stereotactic biopsy specimens were diagnosed by imprint-smear technics. Smears were stained with hematoxylin-eosin.

With regard to morphologic findings, all primary ICGCTs were identical to gonadal germ-cell tumors . Eleven germinomas were composed of lobules or sheets of uniform and large cells surrounded by varying amounts of vascularized connective tissue stroma. The tumor cells were round or oval with centrally located large vesicular nucleus, usually with prominent nucleolus and slightly eosinophilic cytoplasm. Lymphocytic infiltration was present in varying degrees in the fibrous septa (Figures 1, 2).

The endodermal sinus tumor had a reticular pattern with epithelial cells ranging from columnar to cuboidal cells and forming solid and pseudopapillary structures. Papillary structures

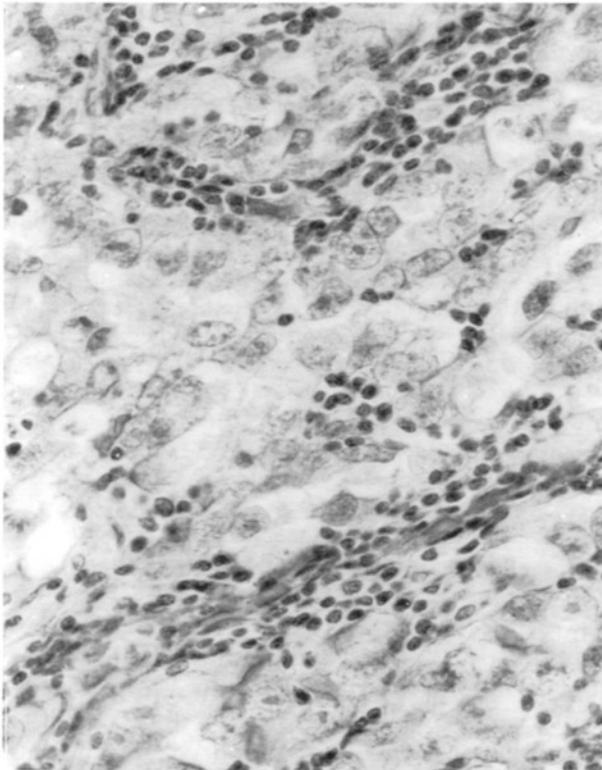


Figure 1. Histologic sections of suprasellar germinoma. The tumor is composed of two cell populations. The first is large cells with clear cytoplasm , large nuclei and prominent nucleoli and the second is clusters of lymphocytes. (H&E, X500)

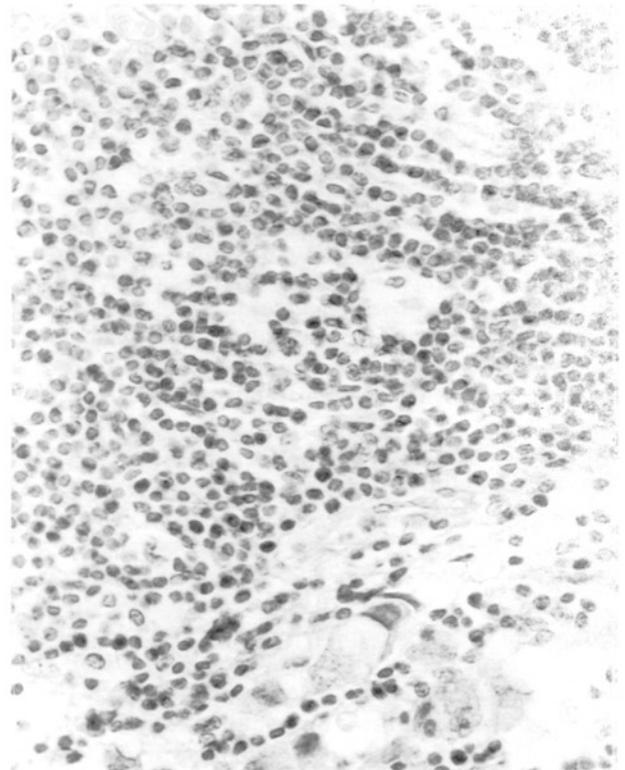


Figure 2. Histologic section of suprasellar germinoma. The tumor cells are dispersed in clusters of lymphocytes. (H&E, X 500)

consisting of columnar cells surrounding glomeruloid blood vessels, which are called Schiller-Duval bodies were present. Periodic acid-Schiff positive (PAS-positive) eosinophilic hyalin droplets were noted in the cytoplasm and in the extracellular spaces (Figure 3).

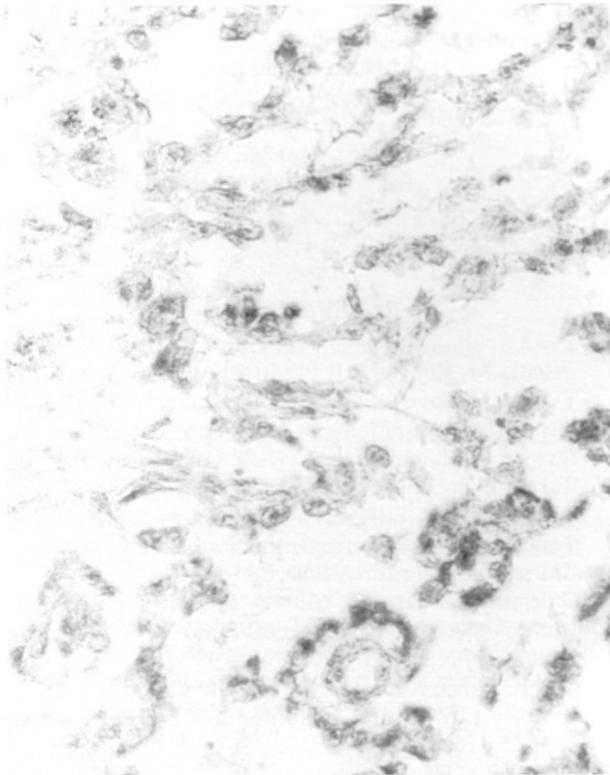


Figure 3. Histologic section of pineal yolk sac tumor. Eosinophilic hyalin droplets are seen in the extracellular spaces of the tumor cells forming papillary structures. (H&E, X500)

The serum alpha feto protein (AFP) and human chorionic gonadotrophin (HCG) levels were measured preoperatively in two patients and postoperatively in five patients with germinomas. They were all within normal range except in one patient with multiple metastases.

Among 11 patients with germinomas 7 were available for follow-up evaluation for periods ranging from 6 months to 7 years. Six patients received only radiotherapy and the patient with metastases received radiotherapy and chemotherapy. This patient, a 15 year-old girl, first had a frontobasal metastasis then an extracranial metastasis in the clavicle, 24 and 36 months after the operation respectively. Morphological examinations

of the primary pineal lesion and the metastatic lesion in the clavicle were consistent with germinoma. Tumor components which may be found in mixed tumors were not present in any of these specimens. During follow-up, pulmonary as well as spinal cord metastases were also detected with conventional radiological methods. She died four years after the first operation. Autopsy was not performed. Other 6 patients with follow-up had neither recurrences and nor metastases.

## DISCUSSION

The incidence of ICGCT varies among Asia, Europe and the western hemisphere (6). The incidence is 0.3-0.5 % in Western series, and 2.1-9.4% in Japan and Taiwan (2,4,5,6,7,10). It appears that there is a racial predilection. Numerous neuropathology specimens from all over the country is referred to our department, so the incidence of ICGCT in our department may be a possible indicator of the incidence in Turkey. The incidence in our series was 0.45 % which is similar to the Western series and lower than the Asian series.

The male to female ratio in a large review series was 2.24 : 1 (4,6,11). The male to female ratio in our series is 2 : 1. This is in line with other reported series.

ICGCTs in the pineal region tend to demonstrate a male predominance, whereas with suprasellar ICGCTs females tend to outnumber the males. In our series there were 4 males, 1 female among the pineal region tumors and 4 males and 2 females among the suprasellar region tumors. So in our series, male predominance in pineal region tumors is consistent with the literature. However, female predominance in suprasellar region tumors in our series is contrary to the reported series.

Stereotactic surgery with 0 % to 0.5 % morbidity provides a safe method of sampling deep intracranial tissues (4,6,7,11). The authors recommend to establish an accurate histological diagnosis to guide the extent of adjuvant therapy. However, because the tumors in the pineal region are of mixed histology a small stereotactic biopsy may not always correctly indicate the nature of the tumor. As pineal region surgery became safe many neurosurgeons began to prefer a direct approach on pineal tumors (5). In our series, 4 tumors were diagnosed with stereotactic biopsy. Three patients out of 4 were available for follow-up evaluation and none of them had recurrences or metastases.

In contrast to gonadal dysgerminomas ICGCT metastasize infrequently. The most common metastatic site is the spinal cord by direct seeding through the cerebrospinal fluid (CSF). There are very few reported cases of primary intracranial germinomas with extraneural metastases. Extraneural metastases of primary intracranial germinomas include lung, bones (femur, vertebra, humerus, scapulae, iliac bones, rib), lymph nodes and the parotid gland (1). In our series, one out of 11 primary intracranial germinomas had spinal, cerebral and extraneural (lung, bone) metastases. This tumor metastasized both by hematogenous route and through CSF. AFP, HCG, carcinoembryonic antigene (CEA), placental alkaline phosphatase, cytokeratin E1/E2 ratio (CKER) levels in serum and CSF are useful diagnostic indicators. These are useful in following the results of the treatment. Increased AFP levels are seen in endodermal sinus tumor, embryonal carcinoma and immature teratoma (5,7,8). Increased HCG levels are detected in choriocarcinoma and other germ-cell tumors that contain syncytiotrophoblastic giant cells (4,10,11). Serum CEA levels may be elevated in various types of carcinomas and teratomas but it has been reported rarely in the literature (4). Germinoma and mature teratoma are not associated with elevation of these markers. In our study, the serum AFP and HCG levels were measured preoperatively in only two patients and postoperatively in seven patients with germinomas. The AFP and HCG levels were all within the normal range except for one patient with multiple metastases. AFP serum level is expected to be high in patient with EST (9,11).

As a result, histopathologic study remains the only means for a correct diagnosis of ICGCTs. However, even though the serum tumor markers are not specific they provide valuable information, especially for small biopsy specimen which sometimes can not include all of the components of a mixed tumor. So with an accurate histologic diagnosis and with the detection of serum tumor markers, a proper therapy can be prescribed and the survival of the patients can be improved.

Some investigators tend to initiate radiotherapy in lesions suspected to be germinomas in the absence of tissue diagnosis, and if the tumor regresses radiotherapy is completed. Recently authors recommend to firmly establish an accurate histological diagnosis to guide the extent of adjuvant

therapy. We have been performing stereotactic biopsy in deep intracranial lesions since 1990 and none of the patients with intracranial tumors have received radiation therapy without a tissue diagnosis since 1990. So the incidence of ICGCTs in our series probably shows the actual incidence of ICGCTs in Turkey.

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