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# Central Nervous System Germinomas

## A Review

Michael Bruce Horowitz, MD, Walter A. Hall, MD

• **The germinoma represents a less malignant form of germ cell tumor. Depending on the individual's age, this neoplasm constitutes approximately 0.1% to 3.4% of all intracranial tumors. The embryologic origin remains a mystery; however, current theories implicate an aberration in primordial germ cell migration. Clinical presentation depends on tumor location and may involve endocrine, hypothalamic, visual, and cognitive dysfunction. In evaluating midline intracerebral masses, it is imperative that one be aware of the various radiologic appearances, endocrinologic changes, and chemical markers that help to distinguish germinomas from other neoplasms that appear in the pineal, suprasellar, and periventricular regions. Only through the careful evaluation of all available studies can the physician institute appropriate therapies such as biopsy, radiation, and chemotherapy. This article focuses on the epidemiology, embryology, clinical presentation, means of diagnosis, treatment, and outcome of this rare neoplasm.**

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The germ cell tumor, a rare finding in the neuraxis, represents a neoplasm that, if properly diagnosed and managed, can be eradicated or controlled in the adult and pediatric populations.[1,2] Under this broad category, in order of frequency of appearance in the central nervous system in all age groups, lie the subcategories of germinoma (40%); mixed tumor (30%); teratoma (20%); and yolk sac tumor, embryonal carcinoma, and choriocarcinoma (10%).[2] These neoplasms most often involve the reproductive organs but may also appear in extragonadal sites such as the sacrococcygeal region, intracranial region, abdomen, retroperitoneum, thoracic cavity, pharynx, neck, thyroid, spinal cord, meninges, bladder, prostate, and soft tissues of the occipital region. Germ cell tumors arising within the ovary rarely occur before the fifth year of life. In contrast, testicular germ cell tumors are frequently found before the fifth year of life and present as a painless mass with an associated hydrocele. Pure germinomas are rare in children younger than 5 years.[1]

Pure germ line tumors are called germinomas. Differentiated germ cell tumors may be divided into embryonic (embryonal carcinoma and mature or immature teratoma) and extraembryonic (choriocarcinoma and yolk sac or endodermal sinus tumors) growths. When organized according to increasing malignant potential, these tumors are germinoma, teratoma, embryonal carcinoma, embryonal sinus tumor, and choriocarcinoma.[3] Each tumor represents the malignant correlate of a normal stage of embryonic development.[3] Germinomas arise from the primordial germ cell; teratomas arise from the differentiated embryonic cell layers; embryonal carcinoma develops from a pluripotential cell of the embryo proper; endodermal sinus tumors represent tissue from extraembryonic yolk sac endoderm; and choriocarcinoma arises from extraembryonic trophoblastic tissue.[3] This article focuses on the epidemiology, embryology, clinical presentation, means of diagnosis, treatment, and outcome of a rare treatable neoplasm, the germinoma.

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From the Department of Neurological Surgery, University of Pittsburgh (Pa) School of Medicine, University Health Center of Pittsburgh.

Reprint requests to Department of Neurological Surgery, 9402 Presbyterian-University Hospital, 230 Lothrop St, Pittsburgh, PA 15213 (Dr Horowitz).

### EPIDEMIOLOGY

The incidence of germinomas varies among Asia, Europe, and the Western Hemisphere. Depending on an individual's age, germinomas constitute 0.1% to 3.4% of all intracranial tumors.[1,3-5] The Armed Forces Institute of Pathology reported that germ cell tumors represented 1.8% of primary intracranial tumors in individuals younger than 20 years, and germinomas represented 16.7% of these tumors.[6] Other reports indicate that germ cell tumors represent 6.5% of intracranial tumors seen during the first two decades of life.[6] Studies evaluating individuals of all ages, however, have shown germinomas to represent up to 65% of intracranial germ cell tumors.[3] The incidence of germ cell tumors in Japan far exceeds that found in other nations. A review of 20 192 brain tumors in Japan between 1969 and 1978 revealed 435 germinomas (2.7%) in all age groups, 184 of which were in children (7.8% of primary pediatric brain tumors).[7] Other series report that 0.3% to 9.4% of intracranial neoplasms in Japan are germinomas.[3-5] Just as it appears that there is a predilection for race, there also seems to be a tendency for these tumors to develop in males. Germ cell tumors have a male-female ratio of 2.24:1, while germinomas have a male-female distribution of 1.88:1.[3]

### EMBRYOLOGY

Germ cell tumors arise because of neoplastic changes during embryonic development. Intracranial germ cell tu-

mors occur in the pineal region, suprasellar-retrochiasmal area, pituitary fossa, posterior third ventricle, interpeduncular and quadrigeminal plate region, cerebellar vermis, thalamus, and walls of the lateral and third ventricles.[8] How these neoplasms come to develop in the various intracranial sites is not known.

Mature male and female germ cells are derived from primordial germ cells that appear in the yolk sac wall at the end of the third week of development.[9] The development and migration of these cells has been studied in a variety of organisms. In ascarides and in insects, at the point of the first egg division, long V-shaped chromosomes are found in blastomeres giving rise to germ cells. Blastomeres destined to become somatic cells contain fragmented versions of these chromosomes. In birds and reptiles, primordial germ cells are located in the extraembryonic blastoderm. These cells migrate into spaces between endoderm and mesoderm, penetrate blood vessels of the area vasculosa, and eventually reach the germinal ridges. Cells that stray during migration later degenerate.[10,11] In man, the origin of primordial germ cells in the embryo has not been studied. These cells are located in the endodermal epithelium of the yolk sac near the allantoic stalk. From here, cells migrate into the adjoining mesenchyme and eventually settle in the germinal ridges.[10]

Primitive germ cells arise from endoderm, migrate into adjacent mesoderm, stimulate blood vessel formation, and disseminate throughout the embryo.[8] Work performed in birds and reptiles has led to the idea that intracranial germinomas develop secondary to circulatory dispersion of cells in the embryo. An alternative theory, proposing that intracranial germinomas arise from misplaced multipotential fragments of the embryonic primitive streak, was supported by the close proximity of the most rostral portion of the primitive streak to the pineal anlage.[2,8-11] Hypothalamic and retrochiasmal tumors are not explained by this theory. Jennings et al[9] stated that the appearance of the ventral hypothalamus at 35 to 38 days coincided with the major migration phase of human germ cells. The presence of germ cell tumors in diencephalic loci suggested that local ontogenic, synaptic, and functional interrelationships may exist between the developing diencephalic structures, the pineal gland, the suprasellar region, and germ cells.[3]

## CLINICAL PRESENTATION

Signs and symptoms associated with germinomas most commonly include diabetes insipidus (41%), visual field defects (33%), and hypothalamic/pituitary dysfunction (33%). Pituitary/hypothalamic abnormalities include delay or regression of sexual development (16%); hypopituitarism (16%); growth failure (9%); precocious puberty (5%); fluctuations in blood pressure, heart rate, respiration, and temperature; gastric motility; and alterations in memory, mood, appetite, and emotional behavior. Additional clinical features associated with germinomas are hydrocephalus (21%), obtundation (15%), Parinaud's syndrome (14%), pyramidal tract signs (14%), ataxia (9%), diplopia (10%), seizures (3%), choreoathetosis (2%), dementia (2%), and psychosis (1%).[2,3] Pineal region tumors generally present first with Parinaud's syndrome and hydrocephalus, while suprasellar tumors present with endocrinopathy, visual loss, and diabetes insipidus.[12]

Germinomas disseminate from the suprasellar and pineal regions by direct infiltration or spread along cerebrospinal fluid pathways.[3] Distant sites of spread include the cavernous sinus,[13] hypothalamus,[3,12] thalamus,[12,14,15] basal ganglia,[12,14-16] septum pellucidum,[12] ventricular system near the foramen of Monro and the trigone of the lateral ventricle,[15] parietal region,[17] cerebellar vermis,[15] frontal lobe,[15] and paraventricular region.[15] Cavernous sinus involvement[13] presents with headache, decreased visual acuity, third nerve palsy, orbital pain, complete ophthalmoplegia, and facial numbness. Coffey[12] described a 24-year-old woman with a hypothalamic germinoma who had anterograde and retrograde amnesia, hyperphagia, visual obscurations, headache, and normal endocrine function. Damage to the fornix, mamillothalamic tracts, and ventromedial thalamus was presumably responsible for the patient's symptoms.

Ono et al[14] described eight patients with germinomas of the thalamus and basal ganglia (third most common site of occurrence). These patients presented with hemiparesis (100%), mental disturbance (63%), increased intracranial pressure (38%), and progressive dystonia with involuntary movements (25%). Tumor affecting the cerebellum can cause dizziness, tinnitus, and gait abnormality.[15]

The endocrinologic presentation and evaluation of germinomas is an interesting and important topic. With proper diagnostic testing and institution of appropriate treatment, the patient can be returned to normal hormonal balance. Multiple endocrine abnormalities may develop as a consequence of tumor infiltration. Because of this infiltration, germinomas have a greater incidence of endocrinopathy than do craniopharyngiomas.[18] Diabetes insipidus with polyuria and polydipsia occurs in 93% of suprasellar germinomas and in 41% of germinomas, regardless of location.[3,16] Growth hormone release is impaired earlier than gonadotropin release. Low levels of luteinizing hormone and follicle-stimulating hormone and poor response to luteinizing hormone–releasing hormone have been seen. Thyroid-stimulating hormone and adrenocortical hormone are less frequently affected. Some studies have shown delayed and/or exaggerated plasma thyroid-stimulating hormone response to thyroid-releasing hormone. In these patients, despite an elevated level of thyroid-stimulating hormone, a hypothyroid state often exists because the thyroid-stimulating hormone is biologically less active.[18] For unknown reasons, adrenocortical hormone response to exogenous corticotropin-releasing factor is often delayed in persons with hypothalamic germinomas.[18] Growth hormone release in response to exogenous gonadotropin-releasing factor is another indicator of hypothalamic invasion.[18] With hypothalamic destruction or interruption of the hypothalamic-pituitary axis, prolactin secretion is increased. Despite an increase in prolactin, galactorrhea may not be seen with hypothalamic destruction due to an absence of sex hormones crucial for milk production.[4,18]

Germinomas may have their course complicated by other extracranial manifestations such as genetic abnormalities and metastases. Two genetic diseases seen with germinoma are Klinefelter's syndrome and de Lange's syndrome. Klinefelter's syndrome, originally described in 1942, affects 0.6% of live male neonates and is characterized by gynecomastia, small atrophic testicles, absent spermatogenesis, high urinary excretion of gonadotropins, and eunuchoid habitus.[19] This syndrome has a high association with breast cancer, lymphoma, leukemia, transitional cell carcinoma of the bladder, and prostatic cancer and was first associated with extragonadal germ cell tumors in 1972. Germinoma and choriocarcinoma have both been associated with Klinefelter's syndrome. An alteration in gonadal ridge differentiation leading to malinduction and dyssynchronization of migration of primordial germ cells may explain the association between these maladies.[20-22] De Lange's syndrome was first described in 1933 in two infants with mental retardation, delayed growth and development, short stature, low body weight, bushy eyebrows fused at the midline, long upturned eyelashes, small

nose with a low bridge, anteverted nostrils, crescent-shaped mouth, hirsutism, hypoplastic nipples and umbilicus, proximally implanted thumbs, bilateral simian creases, flexion contractions of the elbows, and decreased quantity of pubic hair.[23]

Although intracranial germinomas rarely spread outside the central nervous system, there have been reported cases of distal metastases, mostly from pineal lesions.[24] Because pineal metastases predominate, extracranial metastases from a suprasellar germinoma should suggest that the original tumor contained foci of more malignant germ cell elements.[24] Metastatic sites include lung, kidney, bladder, mediastinum, paratracheal lymph nodes, breast, peritoneum, bone, skin, stomach, small bowel, mesentery, and diaphragm.[24-27] Although peritoneal, pulmonary, and cardiac metastases have been reported in patients without spinal fluid shunting devices, they have been speculated to occur in patients with such systems as a result of seeding from the central nervous system cavity.[25,28,29]

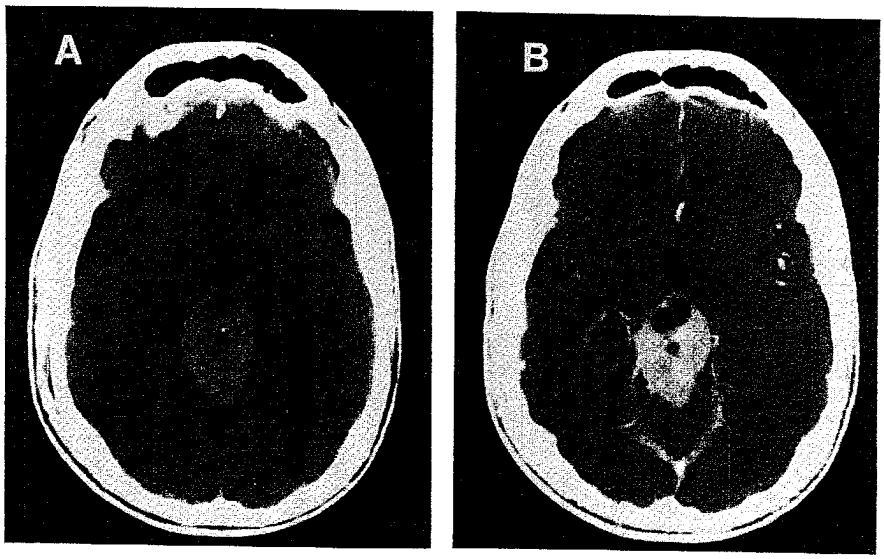


Fig 1.—A, Nonenhanced computed tomographic image of a pineal region germinoma (General Electric Model 9800). Notice increased density in relation to surrounding brain tissue and the presence of intratumoral cysts. B, Contrast-enhanced computed tomographic scan (Isovue 300, Squibb Diagnostics, New Brunswick, NJ).

## DIAGNOSIS

### Radiologic Evaluation

When the findings of the neurologic examination are abnormal, computed tomography or magnetic resonance imaging is usually the first diagnostic test that is performed. Ganti et al[30] evaluated 16 pineal germinomas by computed tomography and found that 94% percent were denser than brain on unenhanced computed tomographic scan, 88% showed moderate to marked contrast enhancement, 38% showed prominent and slightly enlarged pineal calcification, 63% showed parenchymal calcification with a coarse nodular pattern, and 32% showed meningeal and ependymal seeding. Kageyama et al[31] describe three types of pineal calcifications. Type 1 involves tumor within and around the calcified pineal body. There is no capsule between the mass and the surrounding brain. Type 2 represents several calcified areas that, following radiotherapy, form a single mass. This lesion most likely represents encapsulated tumor growing within the pineal body. Type 3 calcifications appear after radiotherapy. Their pathogenesis remains uncertain; however, they most likely represent intrapineal tumor. Abu-Yousef and Hitchon,[32] in three patients with germinoma, found no evidence of abnormal calcification. Other studies have emphasized the occasional presence of hemorrhage.[33]

While moderate inhomogeneous enhancement after administration of contrast is possible, nonhomogeneous enhancement should suggest another type of lesion.[34,35] An irregular border may represent infiltration.[36] In contrast to germinomas, teratomas are sharply demarcated from the surrounding brain, contain fat, have no significant contrast enhancement, may be cystic, and exhibit linear and nodular calcific deposits on computed tomograms.[30] Cysts may also be found with germinomas and are thought to represent proteinaceous fluid or liquified necrosis (Fig 1).[32] Embryonal cell carcinoma and choriocarcinoma are hyperdense before contrast administration, enhance markedly, and exhibit no abnormal pineal or parenchymal calcification.[30]

Basal ganglia and thalamic germinomas may be associated with ipsilateral cerebral hemiatrophy.[33,36] Wallerian degeneration secondary to the destruction of subcortical structures may be responsible for this wasting.[33] Chang et al[35] state that germinomas in the basal ganglia and thalamus are irregular and demonstrate intratumoral cysts and calcification.

Magnetic resonance imaging represents another method of evaluation. On both long and short repetition time spin echo series in four patients reviewed by Kilgore et al,[37] the signal from germinomas was isodense in comparison with normal brain. The tumor can displace cerebrospinal fluid (CSF) and adjacent structures such as the quadrigeminal plate, sylvian aqueduct, and posterior third ventricle.[37] Germ cell tumors with embryonal cell elements had long $T_1$- and $T_2$-weighted signals.[37] Magnetic resonance imaging offers the advantage of easily acquiring images in the coronal and sagittal planes. The disadvantage is the inability to image calcium.

### Markers

Cerebrospinal fluid examination for cytologic and marker studies is useful in the evaluation of a patient with a suspected germ cell tumor if samples can be obtained without precipitating herniation. Elevated levels of human chorionic gonadotropin (HCG) and α-fetoprotein (AFP) are more closely correlated with malignant germ cell tumors such as embryonal carcinoma, endodermal sinus tumors (yolk sac tumors), and choriocarcinoma,[2,38-40] with HCG and AFP elevated in the former two and HCG alone elevated in the latter. The level of HCG is only occasionally elevated with germinomas, while the level of AFP is rarely elevated. α-Fetoprotein is usually more specific for highly malignant neoplasms, and HCG is associated with more benign neoplasms, although it can be produced by the most malignant masses. Recently, it has been proposed that absolute levels of AFP should not be used, but rather an AFP index calculated as (CSF/serum AFP)/(CSF/serum albumin), with a value greater than 1.42 indicating local synthesis of AFP in the central nervous system.[41] When present, markers are a useful indicator of tissue type; however, CSF marker levels are not elevated in 10% to 20% of the more malignant germ cell tumors.[38] Measurement of AFP is often unreliable

(1) because there is cross-reactivity of the assay with other CSF proteins, (2) because there is evidence that three types of human AFP exist (one of which may be a normal CSF component), and (3) because many normal individuals and individuals with nonmalignant conditions have elevated levels of AFP.[41] In addition to helping the physician diagnostically, marker levels can be used to evaluate the effectiveness of treatment. Anecdotal reports state that a lack of return of markers to normal levels after treatment indicates a poor prognosis.[38]

Markers other than AFP and HCG have recently been associated with germinomas. The level of angiotensin I–converting enzyme was elevated in the plasma of one patient with a suprasellar germinoma who did not have sarcoid, granulomatous disease, hyperthyroidism, or diabetes, diseases commonly associated with elevated levels of this enzyme. Angiotensin I–converting enzyme was also found in tumor cells obtained by biopsy.[42] Interestingly, an isomeric form of kidney and lung angiotensin I–converting enzyme is present in normal testes and sperm. Another marker, placental alkaline phosphatase was recently found to be associated with germinoma.[5,39] In the past, elevated levels of this enzyme were associated with pregnancy, testicular seminoma, and ovarian, lung, breast, pancreatic, and adrenal cancers.[5,39] Shinoda et al[39] found levels of serum placental alkaline phosphatase that were less than 0.2 IU/mL in patients with teratoma, metastatic choriocarcinoma from the testis, glioma, meningioma and acoustic neurilemoma. Three patients with germinoma had serum levels ranging from 0.52 to 3.78 IU/L, and two had elevated CSF values of 0.83 and 9.83 IU/L (normal, <0.20 IU/L in serum and <0.11 IU/L in CSF). Melatonin has been studied in patients with pineal region tumors. Low melatonin levels are associated with pineal destruction, and high levels suggest the presence of a melatonin-secreting neoplasm. An increase in melatonin has been seen with germinoma. Some argue that such elevation is a consequence of laboratory error.[43]

## HISTOPATHOLOGIC EXAMINATION

Germinomas characteristically infiltrate locally and spread by dissemination through the craniospinal and subarachnoid spaces. Parenchymal metastases and extradural spread are rare.[40] Grossly, solid tumor tissue can be soft and purplish-gray.

Microscopically, these tumors consist of large polygonal cells surrounded by fibrous connective tissue. Lymphocytic infiltration is most prominent around blood vessels. Cells tend to organize in sheets and lobules and are characterized by large round or oval vesicular nuclei, prominent irregular nucleoli, pale ill-defined cytoplasm, rich stores of glycogen, and coarse or fine granular chromatin.[15,24,27,44,45] Mitotic figures can be present (Fig 2).[24,44]

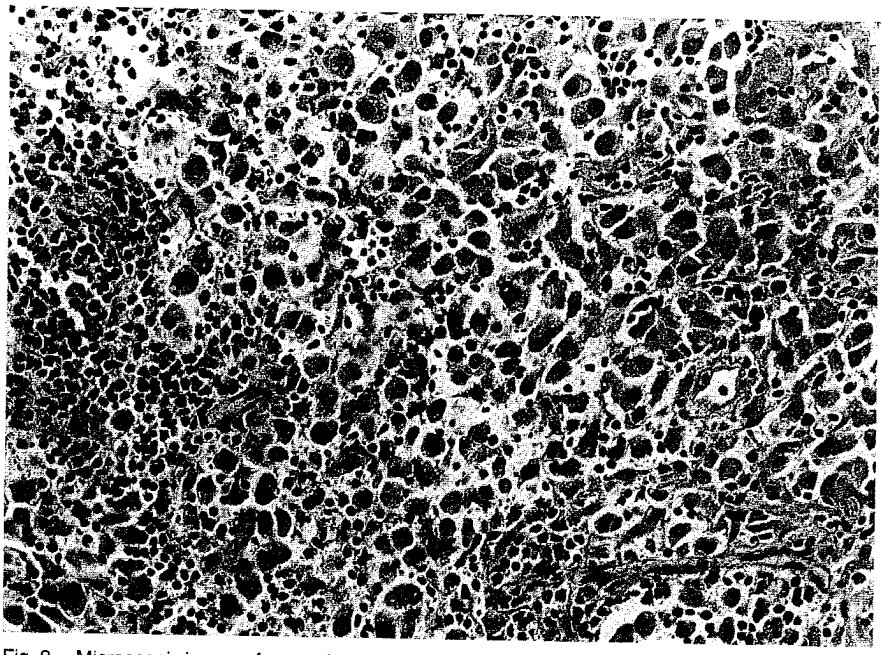

Fig 2.—Microscopic image of a germinoma demonstrating two cell populations. The first consists of large cells with well-defined cell borders, large nuclei, and prominent nucleoli. The second consists of small, round tumor-infiltrating lymphocytes. Occasional mitoses can be seen (hematoxylin-eosin, ×250).

Ultrastructurally, germinomas display scanty cytoplasm, few organelles, and abundant glycogen. The cytoplasm contains poorly developed Golgi complexes, distorted and aggregated mitochondria, and moderately developed rough and smooth endoplasmic reticulum. Cell membranes are occasionally fused by desmosomes or tight junctions.[15,44] An additional interesting finding is that of intranuclear membranes, structures adjacent to electron-lucent spaces measuring 20 to 100 nm in width and 3 μm in length. Thick layers of chromatin surround these membranes, which are arranged parallel, perpendicular, or oblique to the nuclear envelope. Such structures are sometimes interrupted at regular intervals and occasionally are contiguous with the nuclear envelope over a 20- to 100-nm distance. The significance of these intranuclear membranes is unknown, yet a role in nucleocytoplasmic material exchange has been suggested. They may also be involved with accelerated protein synthesis or abnormal DNA metabolism.[46]

Lymphocytic infiltration of germinomas has been demonstrated by light and electron microscopy. Tumor-infiltrating lymphocytes have been characterized using monoclonal antibodies. In intracranial germinomas, 70% to 80% of tumor-infiltrating lymphocytes were T lymphocytes, and the remainder were B lymphocytes. Cytotoxic/suppressor and helper/inducer T-cell types were intermingled.[47] Cravioto and Dart[48] and Hassoun et al[49] have speculated on the significance of lymphocytes within a tumor. They believe that the activity of tumor-infiltrating lymphocytes may represent a host immunologic response to tumor antigens.

## TREATMENT

Past surgical treatment of germinomas by open biopsy or resection was fraught with danger, especially prior to the advent of microsurgical technique. The 30% to 70% morbidity associated with biopsy prompted Torkildsen in 1948 to propose empiric shunting and irradiation for suspicious lesions.[50] More recently, neurosurgeons have relied on other modes of therapy to diagnose and manage this type of germ cell tumor.

Computed tomographic–guided stereotaxis is now an accepted method for obtaining diagnostic tissue. This procedure can provide a sample within 1 to 3 mm of a desired target. However, because the average sample size is 2 to 4 mm in greatest diameter, sampling

error can occur when a heterogeneous tumor is encountered.[51] Nevertheless, stereotactic surgery, with a 0% to 0.5% morbidity, provides a safe method of sampling deep intracranial tissues.[50] Linstadt et al[52] followed up 33 patients with germinoma for a median of 5.3 years (range, 0.1 to 27.5 years). At 5 years, all patients with stereotactic biopsy-proved germinomas were alive, while only 73% of the patients who did not undergo biopsy were alive after the same period. An initial incorrect diagnosis was believed to be responsible for this difference, since 66% of those with recurrent disease were found to harbor an ependymoma or a pinealoblastoma. Biopsy, therefore, may increase survival by increasing diagnostic accuracy and as a result allow for the institution of proper therapy.[52]

The extreme radiosensitivity of germinomas has led some to initiate radiation therapy of suspected lesions without a tissue diagnosis. Biopsy studies, however, have shown that only 61% of lesions suspected to be of germ cell origin on the basis of imaging studies will actually be germ cell tumors.[50] Fifteen percent will be of pineal parenchymal origin (pineocytoma or pinealoblastoma), 17% will be gliomas, and 7% will represent other lesions.[50] Tumor regression after a maximum dose of 2000 cGy supports the presence of a germinoma.[34] Tumors that do not respond to such doses may represent mixed tumors, choriocarcinomas, embryonal carcinomas, endodermal sinus tumors, pinealomas, teratomas, and glial tumors. Pinealoblastoma and histiocytosis may respond to radiation treatment.[63]

Radiation regimens for germinoma therapy vary. Most studies recommend 4000 to 6000 cGy to the primary intracranial site[52,54-56] and approximately 3000 cGy to the remainder of the uninvolved brain.[54,56] Recurrence-free rates are reported to be 85% to 100% at 5 to 10 years posttreatment.[50] Local control appears to improve from about 50% with 40 Gy or less to 90% with 50 Gy or more.[50] Some investigators believe that spinal irradiation should be reserved (1) for lesions that demonstrate clear CSF invasion by myelography, cytology, magnetic resonance imaging, or computed tomography; (2) for extensive intracranial disease; (3) for multiple foci of tumor; (4) for ventricular or meningeal seeding; and (5) after tumor spillage at surgery.[50] Cerebrospinal fluid invasion can be expected in 6% to 85% of patients with histologically proved germinomas.[52-55,57] In such situations, dosages vary between 3600 and 4500 cGy.[53,55] Controlled prospective studies have not been performed to determine the value of adjuvant spinal irradiation.[52] Linstadt et al[52] claimed that 8% of their study patients who underwent radiation therapy to the cord developed spinal metastases, while 23% of those who did not undergo radiation therapy developed metastases. In their minds, the 15% benefit provided by radiation therapy did not justify the attendant risks, such as growth retardation and myelitis.[52] Shibamoto et al[56] further complicated the decision-making process by citing their findings in which six patients had positive CSF cultures, did not receive spinal irradiation, and had no spinal involvement over a 6- to 12-year follow-up period. These favorable outcomes may be secondary to decreased viability of free-floating cells or irradiation of cells as they circulate within the CSF and enter an irradiated field.[48] Nevertheless, despite their observations, Shibamoto and colleagues recommend radiation therapy for all individuals with evidence of spinal compartment involvement.

Despite the efficacy of radiation therapy in the treatment of germinomas, chemotherapy has recently been advocated as an adjuvant therapy to decrease the total dose of radiation necessary to induce tumor resolution. This would be especially useful for germinomas in areas where radiation therapy could cause endocrinopathies, cognitive deficits, or other untoward side effects.[58-60] Allen et al[58] described the use of two courses of cyclophosphamide administered as 900 mg/m$^2$ over 2 days (1800 mg/m$^2$ total). A complete response to chemotherapy was reinforced by 3000 cGy over 4 weeks, while less than complete resolution was coupled with 5000 cGy over 5 to 6 weeks in 160- to 180-Gy fractions.[58] If the neoplasm was disseminated, spinal irradiation was added. Ninety-one percent of patients had complete resolution and 9% had total regression of the intracranial mass with subsequent positive CSF cytologic studies. Disease-free survival ranged from 23 to 89 months. Complications included neutropenia secondary to marrow toxicity. As a consequence of their findings, Allen and colleagues recommended that the following protocol be carried out when treating any germ cell tumor: (1) biopsy; (2) staging by computed tomography, myelography, CSF markers, and magnetic resonance imaging; (3) chemotherapy; and (4) radiation therapy.

An alternate chemotherapy regimen for the treatment of initial, recurrent, and metastatic germinomas includes bleomycin, cisplatin, and vinblastine sulfate or cisplatin and etoposide.[60-64] The former involves the same chemotherapeutic combination used for testicular tumors. Pharmacokinetic studies have shown significant CSF penetration by cisplatin and bleomycin, but not by vinblastine.[61] Blood-brain barrier penetration is apparently made possible by effects from previous irradiation and/or tumor factors.

As a consequence of improved means of diagnosis and innovative therapies, the current survival rate for patients with germinoma ranges from 66% to 86% after a median follow-up of 5 years or longer.[65] It is these results that make germinomas rewarding tumors to treat, for with proper early diagnosis and appropriate treatment, the patient, who is most often a child, can return to a normal life-style with minimal to little deficit.

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