

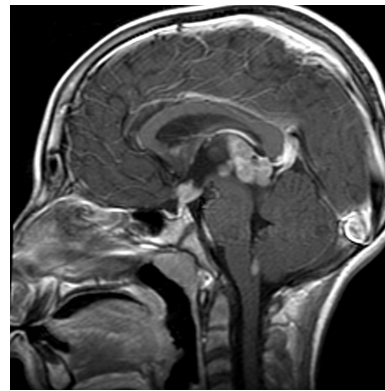
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Germ Cell Tumors of the Brain

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The family of tumors known as germ cell tumors can develop anywhere in the body, most commonly in the male testicles and female ovaries, but also in other locations in the pelvis, abdomen, chest and brain. These tumors are considered to arise from nests of embryonic cells that were traveling along the primitive notochord during early fetal development down to their usual locations (ie. to the genitals), but somehow became arrested in their migration. Those tumors arising in the brain do so mainly from mid-line locations of the pineal gland (at the rear end of the third ventricle) and the suprasellar and hypothalamic region (at the front end of the third ventricle).

What causes these primitive embryonic cells to undergo transformation into cancers is not known. These tumors are found only very rarely in more than one family member, so a genetic association is not the usual reason. Of interest, however, is that these tumors are far more common in South-East Asian countries than in North or America or in Europe. No environmental factor has been linked to the development of these except that the drug diethylstilbestrol (DES) used several decades ago to stabilize unstable pregnancies, and known to be associated with the development of vaginal cancer in offspring of woman taking the drug during pregnancy, has also been less convincingly linked to testicular cancer in offspring. Testicular cancer (but not other forms of germ cell cancers) has been clearly associated with the failure of testicles to descend from the abdomen into the scrotal sac of young boys.



Pineal tumor with metastases to the anterior third ventricle/hypothalamus, also to the fourth ventricle.

(Image provided by Gilbert Vézina, M.D. Children's National Medical Center, DC)

The average age at which germ cell tumors of the brain present is around the onset of puberty. However, some will present in infancy and early childhood, and others present in adult life. The age at onset is important in that younger, pre-pubertal children will experience more profound damaging effects of radiation therapy - and such younger children are usually the very ones that harbor the most malignant types of CNS germ cell tumors that require more aggressive treatments in order to cure them.

The germ cell tumors of the brain represent less than 5% of childhood brain tumors, and yet are also one of the most curable of brain tumors, being exquisitely sensitive to both radiation therapy and chemotherapy. However, their very rarity, and the complex heterogeneous forms they take, has led to a poor understanding of these tumors and how

best to diagnose them and treat them. Debates ensue as to when surgery should be used for these tumors, when radiation therapy should be used alone or in combination with chemotherapy (and what doses and fields of irradiation should be used), and when can milder forms of chemotherapy suffice as opposed to more intensive chemotherapies.

The Different Types (Pathology) of Germ Cell Tumors of the Brain:

One significant difficulty in understanding germ cell tumors arising in the brain is that they often contain more than one type of germ cell tumor. The most widely accepted classification of such tumors is as follows:

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|---|----------------------------------|
| Pure Germinoma | 65% approx. of all CNS GC Tumors |
| Germinoma with Mature and/or Immature Teratoma | 15% approx. |
| Mixed Malignant Germ Cell Tumors (containing one or more of the types: Yolk sac tumor- also known as Endodermal Sinus Tumor) Choriocarcinoma Embryonal carcinoma Germinoma Mature Teratoma Immature Teratoma | 20% approx. |

Therefore, in over one third of cases, the patient will have tumors composed of more than one type of germ cell tumor. It is critical for treating physicians to be aware of this, because each of these components is best treated in differing ways!

Diagnosis of Germ Cell Tumors of the Brain:

Patients with **pineal region tumors** usually present with the acute effects of these tumors compressing and obstructing the nearby ventricular system, causing hydrocephalus (excess fluid in the chambers of the brain), raised pressure within the entire brain and consequently headaches and vomiting. Characteristically, certain eye changes are also noted due to downward compression of the tumor on the midbrain (Parinaud’s Syndrome). A magnetic resonance imaging (MRI) scan will reveal a tumor in the pineal region – but that in itself does not confirm the diagnosis of a germ cell tumor. Other tumors can look virtually identical on MRI, such as pineoblastoma (pineal PNET), ependymoma and malignant gliomas.

Patients with **suprasellar/hypothalamic region tumors** present usually with a much longer history, sometimes over many months or even years, of vague symptoms including increased thirst and urination, increased fatigue, poor growth and declining school performance. These signs are largely due to destruction of the hormone-producing cells located in the hypothalamus and its connection down to the pituitary gland (the pituitary

stalk or infundibulum). Again, an MRI scan will demonstrate a tumor in this location, but this does not confirm the diagnosis of a germ cell tumor; gliomas of the optic pathway are not infrequently confused with germ cell tumors in this location, as can other types of tumors.

One of the unique characteristics of germ cell tumors arising in the brain is their production and release of chemicals into the blood and the cerebrospinal fluid (CSF) called **tumor markers**. The presence of these tumor markers in either location can often confirm that a tumor seen in the pineal or suprasellar regions on MRI is indeed a germ cell tumor. However, nothing is ever quite that easy! There are two germ cell tumor markers in common use today, but not all germ cell tumors produce them, and some do so only in small amounts. The presence of such markers and the levels at which they are present in the blood or CSF are not absolutely diagnostic of specific germ cell tumor types. These tumor markers can thus be misleading in identifying germ cell tumors and specific germ cell tumor types, so that the results of germ cell tumor marker tests must be interpreted with caution. The germ cell tumor markers and their associated tumor types are shown below:

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|---|---|
| Alpha-fetoprotein (AFP) | considered diagnostic of Yolk Sac Tumor (but also seen at low levels in some cases of Immature Teratoma and Embryonal carcinoma). |
| Human Chorionic Gonadotropin Beta (HCG-β) | Once considered diagnostic of Choriocarcinoma, but now recognized to be produced at “low” levels in pure Germinoma, as well as some cases of Immature Teratoma and Embryonal Carcinoma. |

A significant problem that now exists is that some children with pure germinomas are being over-treated as more malignant tumors. This is because an HCG-β level in excess of 25mg/dl is currently, on North American and European (but not Japanese) trials, considered diagnostic of a more malignant choriocarcinoma tumor. There is no basis in fact for such an arbitrary cut off. On the contrary, it is clear that children with pure germinomas can have much higher levels of HCG-β in their blood or CSF. At Childrens Hospital of Los Angeles, biopsy proven children with germinomas and with HCG-β up to almost 200mg/dl have been successfully cured with the less intensive germinoma treatments.

The Role of Surgery in the Treatment of Germ Cell Tumors of the Brain:

Unfortunately, the germ cell tumors of the brain arise in deep-seated locations that, even with modern day neurosurgical and imaging techniques, can lead to significant damage if operated upon by inexperienced hands. The rarity of these tumors means that only those neurosurgeons – and largely pediatric neurosurgeons – who work in major medical centers, have sufficient experience and expertise to tackle these tumors.

In general, **a biopsy (a small sample of tumor tissue) is essential if the MRI scan shows a tumor in the pineal or suprasellar regions, and the tumor markers in both serum and CSF are not elevated.** Patients with pineal region tumors usually present with hydrocephalus that needs to be corrected by placement of a shunt; accordingly, many skilled neurosurgeons today will combine the placement of a third ventriculostomy (a totally internalized shunt) with a tiny biopsy of the tumor, performed through a much less invasive endoscopic procedure. However, the tumor tissue sample is often extremely small by this approach, and may not be representative of the entire tumor, thereby failing to recognize an additional component of a mixed germ cell tumor.

Attempts to remove most of the tumor by radical surgical resection have NOT been shown to improve the cure rate of patients with germ cell tumors of the brain, and are associated with higher complication rates, some of which may be very serious and irreversible. However, in the case of tumors consisting of mature or immature teratoma components, these components are not so responsive to irradiation or chemotherapy, and are indeed best eradicated by surgical resection. The best time to undertake such a surgical resection is not at initial diagnosis, but through **delayed surgical resection**, after initial chemotherapy (or in some cases initial radiation therapy) have shrunk down the other elements of the germ cell tumor, and a residual tumor mass remains indicative most likely of mature or immature teratoma.

Sometimes, the mature or immature teratoma component of the tumor is so substantial, that the tumor actually increases in size with initial chemotherapy. This uncommon but well recognized scenario is known as **“The Growing Teratoma Syndrome”**, and when this happens, it is critical that the treating physicians recognize it for what it is, a situation requiring prompt surgical resection. It is NOT an indication that chemotherapy has failed, and all hope for cure is lost unless immediate high dose radiation therapy or – even worse – far more intensive chemotherapy – is implemented! Resection of the teratoma should be undertaken, and then the original plan of treatment continued.

The Role of Radiation Therapy and Chemotherapy in the Treatment of Germ Cell Tumors of the Brain.

Germinomas of the brain are amongst the most radiation-curable of all tumors. The current “gold standard” is clearly radiation therapy, delivered to encompass the ventricular system of the brain (NOT the entire brain or the spinal cord, unless the patient has evidence of tumor spread to these regions) with an additional boost of irradiation to the site of the tumor. This approach will produce cure of the tumor in over 90% of cases of germinoma of the brain. However, in pre-pubertal children, as well as children already presenting with some damage as a consequence of their tumor, even the current standard of radiation therapy treatment alone can produce some impairment of learning abilities, memory and intellectual functions. Accordingly, studies in North America, Europe and Japan in recent years have been trying to reduce the doses of radiation therapy down to a safer level, by giving the radiation therapy after a few courses of chemotherapy. Studies from New York University (Dr Jeffrey Allen) have suggested that such an approach,

combining chemotherapy followed by radiation therapy *localized only to the tumor site*, will result in over 90% cure rate in select children with localized brain germinomas. At my own institution (Childrens Hospital of Los Angeles) we have used the same chemotherapy as Dr. Allen, but followed by low dose *ventricular* field irradiation and a small boost to the tumor site –with 100% survival without any relapse of the tumor. Recently, the North American Childrens Oncology Group (COG) have open a national study in which children with germinoma of the brain are randomly assigned to receive either radiation therapy alone (to the ventricular system of the brain plus a boost to the tumor site) or to receive Dr. Allen’s chemotherapy followed by just local field irradiation.

Finally, the optimal treatment for those children with the more difficult **mixed malignant germ cell tumors** of the brain, continues also to be somewhat controversial. These tumors are far less sensitive to chemotherapy than germinomas, and are not cured by radiation therapy alone. The currently accepted treatment approach is to use several cycles of more intensive chemotherapy, followed by radiation therapy. Results from such an approach indicate cure rates of around 60% to 80%. The controversy surrounds how wide a field of radiation therapy needs to be applied. My own studies as well as those from European investigators, would indicate that only high dose radiation therapy *directed only to the tumor site*, need be employed (with the addition of low doses of irradiation to the ventricular system to “cover” any germinoma component). However, the current national COG trial administers full doses of irradiation to the entire brain and spine to these children – many of whom are pre-pubertal and therefore at much greater risk for long term toxicities of the radiation therapy. Even the COG Committee is now considering eliminating whole brain and spinal cord irradiation in their next Mixed Malignant Germ Cell Tumor trial, following completion of the present trial.

The Management of Children with Recurrent Germ Cell Tumors of the Brain:

Only a minority of patients with brain germinomas will develop a recurrence. This is likely to happen in patients who have received irradiation to the tumor site only (with or without chemotherapy) or, for whatever reason, have received chemotherapy only. Such patients can be virtually uniformly cured by appropriate radiation therapy. However, for those patients who have already received focal irradiation, the toxicities of the added irradiation are not minor, and must be considered carefully. For children who do develop recurrence of tumor despite prior irradiation and chemotherapy, an approach incorporating very high dose (marrow destructive) chemotherapy and blood cell rescue has been shown to be associated with 80% cure rates.

The treatment of children with recurrence of mixed malignant germ cell tumors depends upon the predominant cell type at recurrence. If germinoma, then treatment should be as indicated above for pure germinomas. If teratoma, then surgical resection will be the crucial form of treatment. If the more malignant GCT elements predominate (eg. yolk sac tumor, choriocarcinoma, embryonal carcinoma) then one has a much tougher battle ahead. The best approach employs two stages; the first, use of chemotherapy to achieve a state of minimal residual tumor; the second stage, the use of marrow ablative chemotherapy with blood cell rescue as indicated above for pure germinomas. This

approach has resulted in about 50% cure rates for children with recurrent mixed malignant germ cell tumors of the brain. A critical component here is the ability to achieve a state of minimal residual tumor with further chemotherapy. It is imperative that new drugs and drug combinations be identified that will have the best chance of achieving such tumor responses. One approach that a number of institutions in North America are considering as a pilot is the combination of gemcitabine, paclitaxel and oxaliplatin –drugs that have been shown effective in recurrent germ cell tumors arising outside the brain in adults.

Conclusion:

The treatment of these rare germ cell tumors of the brain is associated with high cure rates, but their rarity and complexity demand that diagnosis and treatment be undertaken at major pediatric-oriented medical centers, or at the very least, in consultation with physicians from such centers. One must remember that one may be treating several different germ cell tumor components within the same patient's tumor, each with different biological behaviors and therefore demanding different approaches to treatment at the same time.

It is essential that an accurate diagnosis is made to ensure that a patient is neither under-treated nor over-treated. Finally, new drug programs must be developed in order to improve the cure rate for children whose germ cell tumors of the brain recur, and ultimately to employ more effective drug treatments in the initial management of such children to prevent any recurrences from the outset.

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