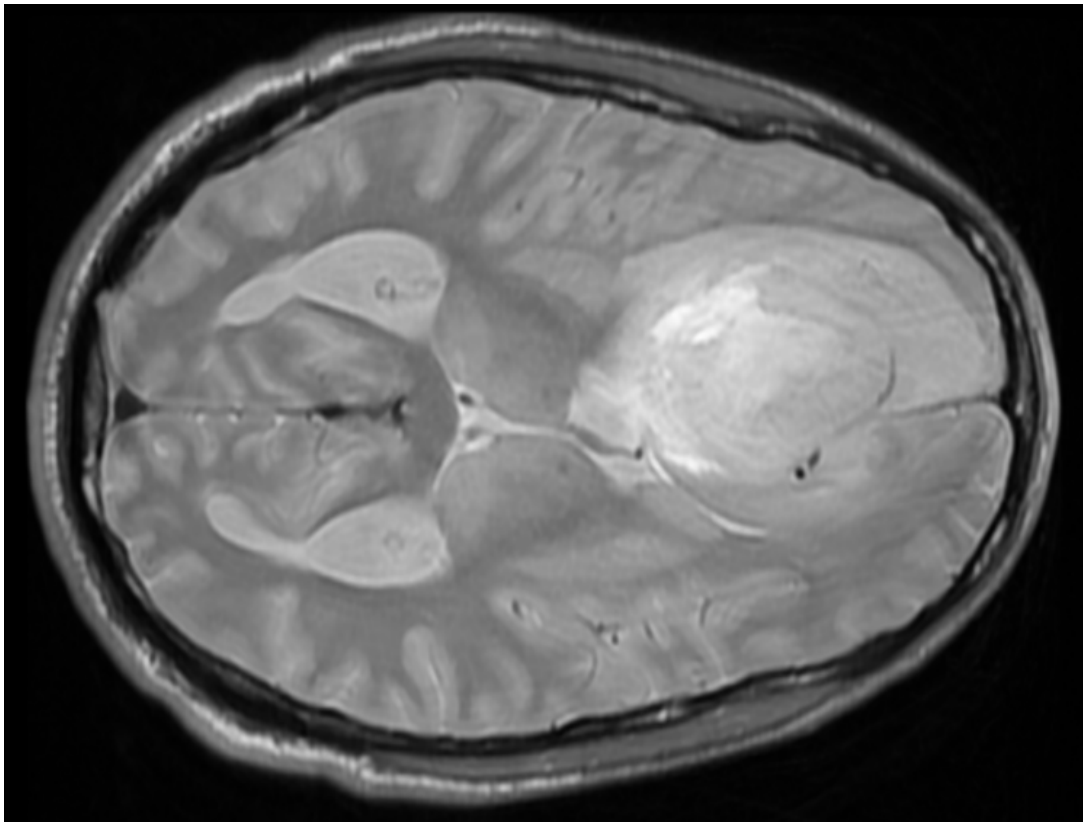


Central Nervous System Cancers — Diagnosis and Treatment

[See online here](#)

This article explains basic facts about tumors of the CNS. It includes neuroepithelial tumors like astrocytomas and fibrillary astrocytomas. It also runs through oligodendroglioma, medulloblastoma and meningeal tumors like meningioma and primary CNS lymphoma. The article covers the definition, epidemiology, etiology, and causes of CNS tumors, in addition to classification, pathophysiology, symptoms, diagnosis (including history and examination), therapy and prognosis.



Definition and Epidemiology of Central Nervous System Cancers

Brain tumors are a dysfunctional and abnormal growth of tissue in the cranium. They can either be primary or secondary (although they are five times more likely to be secondary).

Most (85 %) of CNS tumors will be **metastases** from other cancers. As such, investigations for a suspected CNS tumor should also include tests for other organs'

function to rule out metastases.

Of primary brain tumors, **gliomas** account for the significant majority (70%) and **glioblastomas** make up the largest proportion in this group. Of patients diagnosed with glioblastoma, only 3% are still alive in 5 years.

Etiology of CNS Cancers

Tumors will have varying etiology dependent on the specific tumor classification. Around 50 % of all tumors are secondary, following malignancy elsewhere in the body.

Neurocutaneous syndromes can also cause CNS tumors. These are inherited, autosomal dominant conditions that lead to both benign and malignant tumors. They are caused by a **mutation in tumor suppressor genes**.

Neurocutaneous disorders include **neurofibromatosis type I and type II**. Type I typically causes **meningiomas** and **optic tract astrocytomas**. This is the result of a mutation in the neurofibromin gene. Type II neurofibromatosis results in **vestibular schwannomas** amongst other manifestations and results from a mutation in the Merlin gene.

Von Hippel-Lindau disease can cause tumors in the CNS (typically **hemangioblastomas** and **ocular angiomas**) but also causes a number of renal cancers.

Classification of CNS Cancers

As noted before, brain tumors are far more likely to be secondary to primary malignancies elsewhere in the body. Below are common primary tumors you will be expected to know.

Classification of primary tumors

Neuroepithelial tumors:

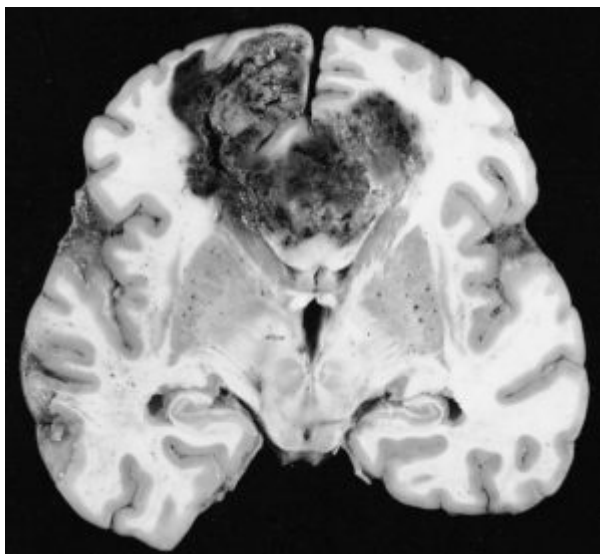


Image: "CNS: glioblastoma multiforme. This typical untreated glioblastoma, here with the classic "butterfly" configuration, is a necrotic hemorrhagic mass." By The Armed Forces Institute of

- Astrocytic tumors
- Oligodendroglial tumors
- Ependymal tumors
- Choroid-plexus tumors
- Embryonal tumors (medulloblastoma)

Meningeal tumors:

- Meningiomas
- Hemangioblastoma

Primary CNS lymphoma

Germ-cell tumors:

- Germinoma
- Choriocarcinoma
- Teratoma

Sellar region tumors:

- Pituitary adenomas
- Craniopharyngioma
- Pinealoma/pinealoblastoma

Gliomas are a group of malignant tumors that include **astrocytomas** (like glioblastoma multiforme) and **oligodendrogliomas**. They can be associated with **neurofibromatosis** but are more regularly idiopathic. They are unlikely to metastasize.

Astrocytomas are graded I-IV. Grade I tumors grow very slowly over the span of years. Grade IV tumors (also known as glioblastoma multiforme) are far faster growing and can cause mortality within a year. **Oligodendrocytes** are far slower growing.

Meningiomas are benign tumors. They grow over many years from the [meninges](#) and are found (usually) below the tentorium. They usually form in the pituitary fossa, skull base, parasagittal region, sphenoid ridge, and subfrontal region.

Schwannomas arise from the cerebellopontine angle. They are benign tumors of Schwann cells. They can be caused by **neurofibromatosis type II** but will be bilateral. If you see bilateral vestibular schwannomas of the VIII nerve think of neurofibromatosis!

Pathophysiology of CNS Cancers

As with many tumors, the development of symptoms is caused by the expanding size of the tumor. Either cancer cells invade normal neuronal tissue, or pressure from the growing tumors can cause **focal neurological deficits**.

Patients will typically present with **seizures** ([epilepsy](#)) and signs of **raised intracranial pressure**. These include [headache](#), vomiting, intellectual deterioration. A headache can be worse on [coughing](#), bending or in the morning. Patients can also present with **focal (localized) deficits** due to pressure from the expanding tumors. These can vary dependent on the site of the tumor.

Diagnosis of CNS Cancers

A **full history and examination** should be taken in any patients presenting with symptoms suggestive of a brain tumor.

As mentioned previously, patients will complain of headaches, seizures, vomiting and focal deficits (for instance, cranial nerve VI palsies where patients will complain of **diplopia**). Asking for **specifics about a headache** is important. Patients will describe a headache that is worse with coughing, bending or in the morning (typical of raised intracranial pressure).

Patients presenting with headaches are a common occurrence, and the majority of patients will have a non-sinister reason behind the headaches. It is therefore important to be able to differentiate sinister from non-sinister presentations.

The **headaches** are **usually constant and dull** and patients are unlikely to present with acute severe pain. Other concerning factors are nausea and vomiting and a worsening headache. Patients can report worsening headaches on bending over, coughing or sneezing, all of which are indicators of raised intracranial pressure.

Often patients will complain their **headache is worse at night**, and if patients are waking from sleep to a headache, they have severe pain. This pattern has been suggested to arise from diurnal variations in PCO_2 which causes **vasodilation**, a drop in blood pressure and potential headache.

Identifying the **course of symptoms** can also be telling. A direct effect of mass lesion will often cause a progressive loss of function and worsening symptoms (as the tumor slowly grows).

On examination, **papilloedema** may be present (due to raised intracranial pressure). In the early stages of CNS tumor development, you might expect to see **mild venous engorgement** and some **loss of venous palpation**.

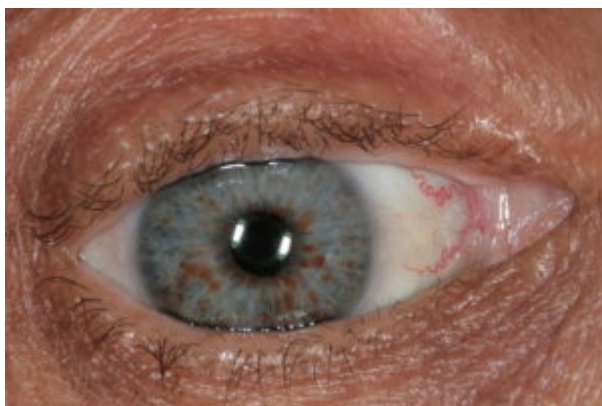


Image: "Lisch nodules are numerous nodules of dendritic melanocytes in aggregates within the iris. They are brown-yellow, round-shaped, raised papules as seen with slit lamp examination in the iris of patients with Neurofibromatosis type 1 (>90% of the cases) together with scattered café-au-lait pigmented skin lesions and multiple neurofibromas (superficial or deep) in skin or other organs." By Dimitrios Malamos - Own work. License: [CC BY 4.0](https://creativecommons.org/licenses/by/4.0/)

Late CNS tumors will have a **blurred disc margin, pronounced venous engorgement** and signs of **hemorrhage**. An eye examination is imperative to a good examination when a CNS tumor is suspected. Patients with neurofibromatosis type I can have **Lisch**

nodules in the iris. These patients also have **café-au-lait patches** and **axillary freckling**.

CT head is the most common diagnostic investigation. Some tumors are hard to see on an unenhanced CT, so **enhanced CT** is commonly ordered. Oligodendrogliomas can show **calcification** on a CT.

MRI may also be used (particularly good for diagnosing **posterior fossa masses**). A **stereotactic guided biopsy** can also be taken for histology.

Histology of CNS Cancers

- **Glioblastoma multiforme** (astrocytoma grade IV): Tumor cells are “pseudopalisading” and are seen bordering central areas where necrosis and hemorrhage are found.
- **Meningioma**: Spindle cells are seen arranged in concentric circles. Sometimes known as a “whorled pattern.” Psammoma bodies (calcified areas) are also seen.
- **Hemangioblastoma**: These are tumors of the capillaries found in the cerebellum. On histological examination, capillaries with minimal parenchyma are seen.
- **Oligodendroglioma**: Under the microscope, oligodendrocytes are often described as looking like fried eggs. These are calcified in oligodendroglioma.
- **Pilocytic astrocytoma** (low grade): “Rosenthal” fibers are eosinophilic, corkscrew-like fibers.
- **Medulloblastoma**: Show Homer Wright rosettes where tumor cells surround a neuropil.
- **Ependymoma**: Show characteristic rosettes perivascularly. Basal ciliary bodies are found near the nucleus of the tumors.
- **Craniopharyngioma**: Calcification is commonly seen.

Therapy of CNS Cancers

Different aspects of the patient’s issues can be treated differently. If the patient has **cerebral edema** (possibly caused by raised intracranial pressure) **steroids** (for instance Dexamethasone) can be given orally or intravenously. If the patient is suffering from epilepsy as a result of the tumor, **antiepileptic drugs** are recommended.

After the initial management, one should consider whether **surgery** is a realistic option. In some cases, it is not necessary. Slow-growing benign tumors like gliomas can often be followed up with frequent imaging and left. Some benign tumors are regularly removed, for instance, acoustic neuromas.

Malignant tumors are harder to deal with as they often cannot be totally removed. The surrounding neural tissue will often be infiltrated and cannot be removed as it has a functional use in the patient.

Radiotherapy only has small use in tumors of the CNS. It can improve survival in gliomas and secondary metastases from a primary tumor but not drastically.

Chemotherapy has little use; however, temozolomide is used in glioblastomas and has been shown to improve survival.

Prognosis of CNS Cancers

Malignant tumors of the CNS typically have a poor prognosis, whilst some benign tumors can be left with little loss of quality of life in the patients.

The prognosis for **glioblastoma multiforme** is poor, and most patients die within one year.

Patients with **meningioma** can have a resection. This often depends on the location of the tumors.

Schwannoma patients can have surgery and prognosis is often good.

Oligodendroglioma is a slow-growing glioma and as such has a good prognosis.

CNS Cancers in Children

Primary CNS tumors of childhood occur in up to 4.5 cases per 100,000 per year. Pediatric brain cancer is the leading cause of pediatric cancer-related morbidity and mortality.

Half of CNS cancers in children arise below the tentorium. The current classification of CNS tumors in children takes into account the histologic pattern and the presumed site of origin in the brain. Pediatric CNS cancers can be generally classified into embryonal tumors and non-embryonal tumors.

EMBRYONAL TUMORS IN CHILDREN

Medulloblastoma, CNS primitive neuroectodermal tumors, and atypical teratoid or rhabdoid tumors belong to this family of CNS tumors.

Medulloblastoma

- Up to 40% of pediatric CNS tumors are medulloblastomas. The molecular classification of these tumors is very important in terms of prognosis and likelihood of distant metastasis at the time of presentation.
- Tumors with **Wnt** mutations occur in older children, usually do not show distant metastasis, and have an excellent prognosis.
- Tumors with **sonic hedgehog** mutations occur in infants, usually do not metastasize, and generally, have a good prognosis.
- Tumors with **MYC** overexpression tend to have anaplastic tumors on histology, dissemination at the time of diagnosis is common, and patients have a poor prognosis. These tumors are more common in infants.
- Finally, patients with medulloblastomas with unknown genetic mutations tend to have an intermediate prognosis.

CNS primitive neuroectodermal tumors

- Tumors that belong to this group include **supratentorial** tumors, **medulloepithelioma**, and **ependymoblastoma**.
- These tumors should be treated aggressively.
- Total resection, if possible, is the treatment of choice for these tumors.
- The prognosis is usually poor for these tumors.

Atypical teratoid/rhabdoid tumors

- These tumors have **rhabdoid cells** intermixed with elements from CNS

primitive neuroectodermal tumors.

- These tumors are more common in infants and young children.
- These tumors are usually hyper-dense on CT and have calcification.
- Treatment includes multi-agent chemotherapy, however, the prognosis is generally poor.

Nonembryonic pediatric CNS tumors

Gliomas

- **Pilocytic astrocytoma**, which is a low-grade glial tumor, is the most common type of glioma seen in children.
- Low-grade gliomas account for up to 40 % of pediatric brain tumors.
- Unlike adults, low-grade glioma in children rarely progresses to high-grade glioma.
- Pilocytic astrocytoma never progresses to high-grade glioma!
- Multiple chemotherapy regimens are effective in the treatment of low-grade gliomas in children.

Germ cell tumors

- Tumors that belong to this group include **germinoma**, **syncytiotrophoblastic** tumors, **embryonal carcinoma**, **yolk sac** tumors, **choriocarcinoma**, and **teratoma**.
- Germinoma has an excellent prognosis. Patients typically have an elevated beta-HCG level.
- Syncytiotrophoblastic tumors also have an excellent prognosis and they have the same biomarker as germinoma.
- Embryonal carcinoma presents with an elevated beta-HCG level plus an elevated alpha-fetoprotein level. The prognosis is poor.
- Yolk sac tumors have the same biochemical signature as embryonal carcinoma. They also have a poor prognosis.
- Choriocarcinoma presents with markedly elevated beta-HCG levels. The prognosis is somewhat intermediate.
- Immature teratoma has a poor prognosis, whereas, mature teratoma typically has an excellent prognosis.

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