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An Overview On Brain Tumor

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Abstract:

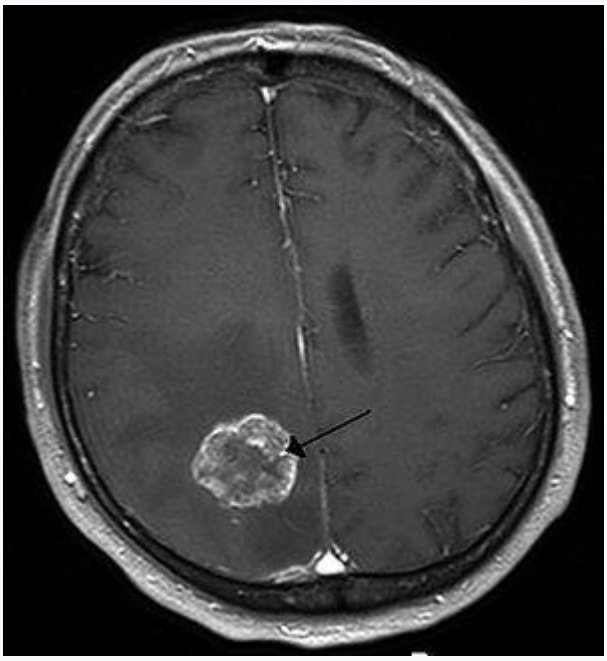
Brain tumors are common, requiring general medical providers to have a basic understanding of their diagnosis and management. The most prevalent brain tumors are intracranial metastases from systemic cancers, meningiomas, and gliomas, specifically, glioblastoma. Central nervous system metastases may occur anywhere along the neuroaxis, and require complex multidisciplinary care with neurosurgery, radiation oncology, and medical oncology. Meningiomas are tumors of the meninges, mostly benign and often managed by surgical resection, with radiation therapy and chemotherapy reserved for high-risk or refractory disease. Glioblastoma is the most common and aggressive malignant primary brain tumor, with a limited response to standard-of-care concurrent chemoradiation. The new classification of gliomas relies on molecular features, as well as histology, to arrive at an "integrated diagnosis" that better captures prognosis. This manuscript will review the most common brain tumors with an emphasis on their diagnosis, oncologic management, and management of medical complications. Early diagnosis and treatment are important in diminishing the morbidity and mortality rates in the latter group and in providing better palliative management in the former. Advances in neuroradiology, particularly the development of CT, have made early diagnosis possible, given clinical awareness of the syndromes of brain tumour on the part of the physician. New methods of accurate CT-controlled surgery for glioma have also been introduced.

Advances in adjuvant methods of radiotherapy, with radiation sensitizers or interstitial implantation, and of chemotherapy by tailoring the drug regimen to an individual patient and by targetting agents specifically to brain tumour, are being sought while the feasibility of fresh modes of immunotherapy has been tested. These developments hold some hope that results for malignant glioma may improve in the forseeable future.

Key word:

Introduction, risk factors, pathology ,diagnosis, treatment, research A **brain tumor** occurs when abnormal cells form within the brain. There are two main types of tumors: malignant tumors and benign (non-cancerous) tumors. These can be further classified as primary tumors, which start within the brain, and secondary tumors, which most commonly have spread from tumors located outside the brain, known as brain metastasis tumors. All types of brain tumors may produce symptoms that vary depending on the size of the tumor and the part of the brain that is involved. Where symptoms exist, they may include headaches, seizures, problems with vision, vomiting and mental changes. Other symptoms may include difficulty walking, speaking, with sensations, or unconsciousness.

Brain tumor	
Other names	Intracranial neoplasm, brain tumour



Brain metastasis in the right cerebral hemisphere from lung cancer, shown on magnetic resonance imaging

Specialty	Neurosurgery, Neuro-oncology
Symptoms	Vary depending on the part of the brain involved, headaches, seizures, problem with vision, vomiting, mental changes
Types	Malignant, benign
Causes	Usually unknown
Risk factors	Neurofibromatosis, exposure to vinyl chloride, Epstein–Barr virus, ionizing radiation
Diagnostic method	Computed tomography, magnetic resonance imaging, tissue biopsy
Treatment	Surgery, radiation therapy, chemotherapy
Medication	Anticonvulsants, dexamethasone, furosemide
Prognosis	Average five-year survival rate 33% (US)
Frequency	1.2 million nervous system cancers (2015)
Deaths	228,800 (worldwide, 2015)

The cause of most brain tumors is unknown, though up to 4% of brain cancers may be caused by CT scan radiation. Uncommon risk factors include exposure to vinyl chloride, Epstein–Barr virus, ionizing radiation, and inherited syndromes such as neurofibromatosis, tuberous sclerosis, and von Hippel-Lindau Disease. Studies on mobile phone exposure have not shown a clear risk. The most common types of primary tumors in adults are meningiomas (usually benign) and astrocytomas such as glioblastomas. In children, the most common type is a malignant medulloblastoma. Diagnosis is usually by medical examination along with computed tomography (CT) or magnetic resonance imaging (MRI). The result is then often confirmed by a biopsy. Based on the findings, the tumors are divided into different grades of severity.

Treatment may include some combination of surgery, radiation therapy and chemotherapy. If seizures occur, anticonvulsant medication may be needed. Dexamethasone and furosemide are medications that may be used to decrease swelling around the tumor. Some tumors grow gradually, requiring only monitoring and possibly needing no further intervention. Treatments that use a person's immune system are being studied. Outcomes for malignant tumors vary considerably depending on the type of tumor and how far it has spread at diagnosis. Although benign tumors only grow in one area, they may still be life-threatening depending on their size and location. Malignant glioblastomas usually have very poor outcomes, while benign meningiomas usually have good outcomes. The average five-year survival rate for all (malignant) brain cancers in the United States is 33%.

Secondary, or metastatic, brain tumors are about four times as common as primary brain tumors, with about half of metastases coming from lung cancer. Primary brain tumors occur in around 250,000 people a year globally, and make up less than 2% of cancers. In children younger than 15, brain tumors are second only to acute lymphoblastic leukemia as the most common form of cancer. In NSW Australia in 2005, the average lifetime economic cost of a case of brain cancer was AU$1.9 million, the greatest of any type of cancer.

Overview...

The World Health Organization (WHO) first published a universal classification system for CNS tumors in 1979.

This system classifies tumors according to there microscopic characteristics and has been accepted as the universal method of classification of brain tumor.

Tumors were classified into 2 categories :

1. Primary Brain Tumors
2. Secondary Brain Tumors

Types of Primary Brain Tumors

There are many type of primary brain tumors. they are named according to the type of cells or the part of the brain in which they begin. for example : most primary brain tumors begins in glial cell and are called *Glioma*.

1. Gliomas (A)
2. Astrocytomas (A)
3. Glioblastoma Multiforme
4. Oligodendrogliomas (A)
5. Ependymomas & Ependymoblastomas (C)
6. Medulloblastomas (C)
7. Meningiomas (A)
8. Pituitary adenomas
9. Schwannomas
10. Primary CNS lymphoma

- Malignant brain tumors (Also called *Brain Cancer*) contain cancer cells :
  - More serious and often are threat to life
  - Rapid Growth
  - Invade or crowd nearby healthy brain tissue
  - Cancer cell may spread to other parts of the brain or to the spinal cord
  - rarely spread to other parts of the body.

Primary Brain Tumors :

- These tumors can be *Benign* or *Malignant*.
- Primary tumors originates in the CNS

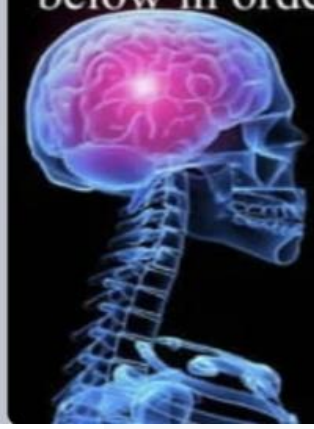
- Benign brain tumors do not contain *cancer* cells :
  - Usually, benign tumors can be removed and the rarely grow back.
  - Benign brain tumors have an obvious border or edge.
  - They dont spread to other parts of the body
  - They don't invade tissues around them
  - However, benign tumors can press on sensitive area of brain and can cause serious health problems.
  - Unlike benign tumor of other parts of the body, benign tumor of the brain are sometimes life threatening.
  - with time benign brain tumors can become malignant.

Secondary Brain Tumor :

Secondary brain tumors also called as *Metastatic Brain Tumor* originates from malignancies outside of the CNS and spread to the brain, typically through arterial circulation.

•Approx. 25% of individual with systemic cancer develop metastatic brain tumor approx. 80% in cerebral hemisphere and 20% in the posterior fossa.

•1/3rd of bin metastases orginate in lungs and followed in manner below in order of frequency :



Lungs→Breast→Skin→GI tract→Kidney

•Frontal lobe is the most common site

•Average survival with the treatment is approx. 6 months but varies widely by the extent of other systemic metastases.

Tumor Grade

Doctors group brain tumor by *grade*. the grade of a tumor efers to the way cells look under a microscope:

- **Grade I**: The tissue is benign. The cells look nearly like normal brain cells, and they grow slowly.
- **Grade II**: The tissue is malignant. The cells look less like normal cells than do the cells in a Grade I tumor.
- **Grade III**: The malignant tissue has cells that look very different from normal cells. The abnormal cells are actively growing (*anaplastic*).
- **Grade IV**: The malignant tissue has cells that look most abnormal and tend to grow quickly.

RISK FACTORS

- A risk factor is something that may increase the chance of getting a disease.
  - Studies have found the following risk factors for brain tumors:

1. Ionizing Radiations : especially from high dose x-rays and other sources can cause cell damage that leads to a tumor. most common types are meningioma or glioma.
2. Family History : It is rare for brain tumors to run in a family. only a very few number of families have several member with brain tumors

** Studies have not shown consistent links between these possible risk factors and brain tumors, but additional research is needed.

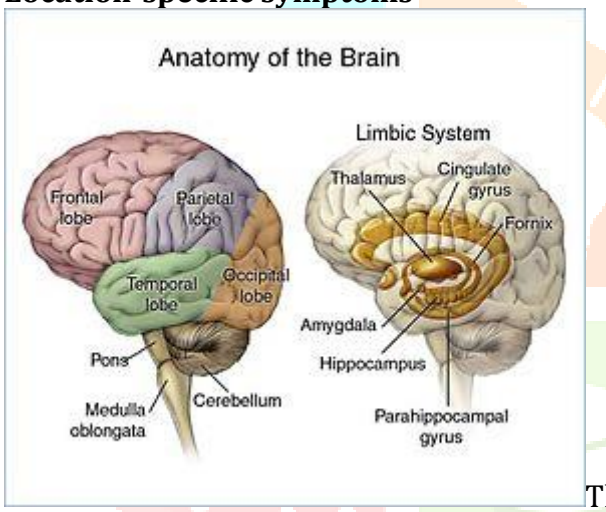
Signs and symptom

The signs and symptoms of brain tumors are broad. People may experience symptoms regardless of whether the tumor is benign (not cancerous) or cancerous. Primary and secondary brain tumors present with similar symptoms, depending on the location, size, and rate of growth of the tumor. For example, larger tumors in the frontal lobe can cause changes in the ability to think. However, a smaller tumor in an area such as Wernicke's area (small area responsible for language comprehension) can result in a greater loss of function.

Headaches

Headaches as a result of raised intracranial pressure can be an early symptom of brain cancer. However, isolated headache without other symptoms is rare, and other symptoms including visual abnormalities may occur before headaches become common. Certain warning signs for headache exist which make the headache more likely to be associated with brain cancer. These are, as defined by the American Academy of Neurology: "abnormal neurological examination, headache worsened by Valsalva maneuver, headache causing awakening from sleep, new headache in the older population, progressively worsening headache, atypical headache features, or patients who do not fulfill the strict definition of migraine".Other associated signs are headaches that are worse in the morning or that subside after vomiting.

Location-specific symptoms



The main areas of the brain and Limbic system

The brain is divided into lobes and each lobe or area has its own function.[18][19] A tumor in any of these lobes may affect the area's performance. The symptoms experienced are often linked to the location of the tumor, but each person may experience something different.

- Frontal lobe: Tumors may contribute to poor reasoning, inappropriate social behavior, personality changes, poor planning, lower inhibition, and decreased production of speech (Broca's area).
- Temporal lobe: Tumors in this lobe may contribute to poor memory, loss of hearing, and difficulty in language comprehension (Wernicke's area is located in this lobe).
- Parietal lobe: Tumors here may result in poor interpretation of languages, difficulty with speaking, writing, drawing, naming, and recognizing, and poor spatial and visual perception.
- Occipital lobe: Damage to this lobe may result in poor vision or loss of vision.
- Cerebellum: Tumors in this area may cause poor balance, muscle movement, and posture.
- Brain stem: Tumors on the brainstem can cause seizures, endocrine problems, respiratory changes, visual changes, headaches and partial paralysis.

Behavior changes

A person's personality may be altered due to the tumor damaging lobes of the brain. Since the frontal, temporal, and parietal lobes control inhibition, emotions, mood, judgement, reasoning, and behavior, a tumor in those regions can cause inappropriate social behavior, temper tantrums, laughing at things which merit no laughter, and even psychological symptoms such as depression and anxiety. More research is needed into the effectiveness and safety of medication for depression in people with brain tumors.

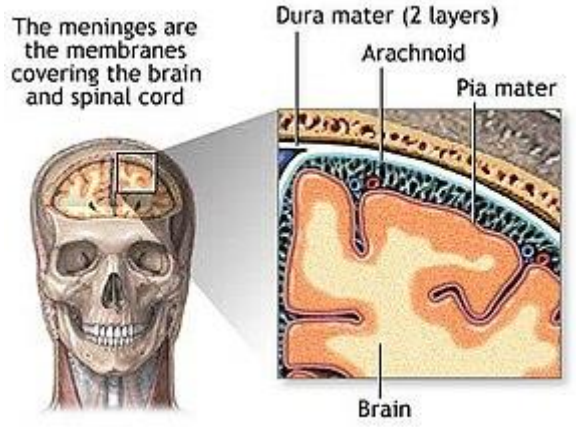
Personality changes can have damaging effects such as unemployment, unstable relationships, and a lack of control.

Cause

Epidemiological studies are required to determine risk factors. Aside from exposure to vinyl chloride or ionizing radiation, there are no known environmental factors associated with brain tumors. The best known cause of brain cancers is ionizing radiation. Approximately 4% of brain cancers in the general population are caused by CT scan radiation. For brain cancers that follow a CT scan at lags of 2 years or more, we estimate that 40% are attributable to radiation. Mutations and deletions of tumor suppressor genes, such as P53, are thought to be the cause of some forms of brain tumor. Inherited conditions, such as Von Hippel–Lindau disease, tuberous sclerosis, multiple endocrine neoplasia, and neurofibromatosis type 2 carry a high risk for the development of brain tumors. People with celiac disease have a slightly increased risk of developing brain tumors. Smoking has been suggested to increase the risk but evidence remains unclear.

Although studies have not shown any link between cell phone or mobile phone radiation and the occurrence of brain tumors, the World Health Organization has classified mobile phone radiation on the IARC scale into Group 2B – possibly carcinogenic. The claim that cell phone usage may cause brain cancer is likely based on epidemiological studies which observed a slight increase in glioma risk among heavy users of wireless phones. When those studies were conducted, GSM (2G) phones were in use. Modern, third-generation (3G) phones emit, on average, about 1% of the energy emitted by those GSM (2G) phones, and therefore the finding of an association between cell phone usage and increased risk of brain cancer is not based upon current phone usage.

Meninges



The meninges lie between the skull and brain matter. Tumors originating from the meninges are meningiomas.

Human brains are surrounded by a system of connective tissue membranes called meninges that separate the brain from the skull. This three-layered covering is composed of (from the outside in) the dura mater, arachnoid mater, and pia mater. The arachnoid and pia are physically connected and thus often considered as a single layer, the *leptomeninges*. Between the arachnoid mater and the pia mater is the subarachnoid space which contains cerebrospinal fluid (CSF). This fluid circulates in the narrow spaces between cells and through the cavities in the brain called ventricles, to support and protect the brain tissue. Blood vessels enter the central nervous system through the perivascular space above the pia mater. The cells in the blood vessel walls are joined tightly, forming the blood–brain barrier which protects the brain from toxins that might enter through the blood.

Tumors of the meninges are meningiomas and are often benign. Though not technically a tumor of brain tissue, they are often considered brain tumors since they protrude into the space where the brain is, causing symptoms. Since they are usually slow-growing tumors, meningiomas can be quite large by the time symptoms appear.

Brain matter

The brains of humans and other vertebrates are composed of very soft tissue and have a gelatin-like texture. Living brain tissue has a pink tint in color on the outside (gray matter), and nearly complete white on the inside (white matter), with subtle variations in color. The three largest divisions of the brain are:

- Cerebral cortex
- Brainstem
- Cerebellum[35]

These areas are composed of two broad classes of cells: neurons and glia. These two types are equally numerous in the brain as a whole, although glial cells outnumber neurons roughly 4 to 1 in the cerebral cortex. Glia come in several types, which perform a number of critical functions, including structural support, metabolic support, insulation, and guidance of development. Primary tumors of the glial cells are called gliomas and often are malignant by the time they are diagnosed.

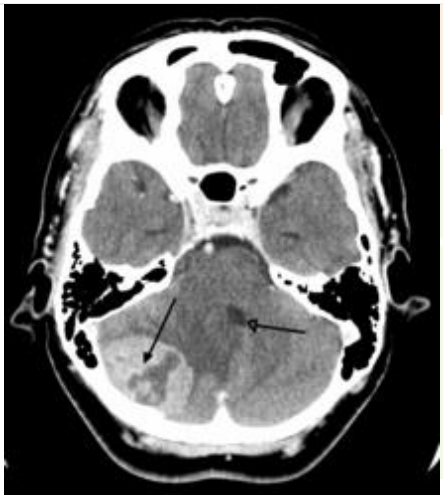
The thalamus and hypothalamus are major divisions of the diencephalon, with the pituitary gland and pineal gland attached at the bottom; tumors of the pituitary and pineal gland are often benign.[*citation needed*]

The brainstem lies between the large cerebral cortex and the spinal cord. It is divided into the midbrain, pons, and medulla oblongata.

Spinal cord

The spinal cord is considered a part of the central nervous system. It is made up of the same cells as the brain: neurons and glial cells.

Diagnosis



A posterior fossa tumor leading to mass effect and midline shift

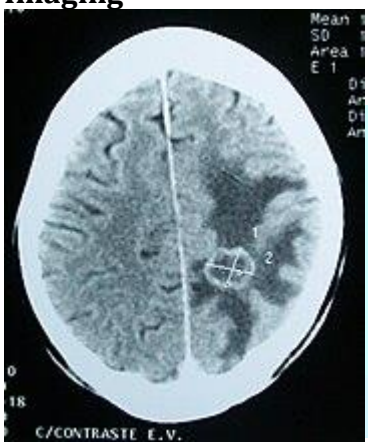
Although there is no specific or singular symptom or sign, the presence of a combination of symptoms and the lack of corresponding indications of other causes can be an indicator for investigation towards the possibility of a brain tumor. Brain tumors have similar characteristics and obstacles when it comes to diagnosis and therapy with tumors located elsewhere in the body. However, they create specific issues that follow closely to the properties of the organ they are in.

The diagnosis will often start by taking a medical history noting medical antecedents, and current symptoms. Clinical and laboratory investigations will serve to exclude infections as the cause of the symptoms. Examinations in this stage may include the eyes, otolaryngological (or ENT) and electrophysiological exams. The use of electroencephalography (EEG) often plays a role in the diagnosis of brain tumors.

Brain tumors, when compared to tumors in other areas of the body, pose a challenge for diagnosis. Commonly, radioactive tracers are uptaken in large volumes in tumors due to the high activity of tumor cells, allowing for radioactive imaging of the tumor. However, most of the brain is separated from the blood by the blood–brain barrier (BBB), a membrane that exerts a strict control over what substances are allowed to pass into the brain. Therefore, many tracers that may reach tumors in other areas of the body easily would be unable to reach brain tumors until there was a disruption of the BBB by the tumor.

Disruption of the BBB is well imaged via MRI or CT scan, and is therefore regarded as the main diagnostic indicator for malignant gliomas, meningiomas, and brain metastases.
Swelling or obstruction of the passage of cerebrospinal fluid (CSF) from the brain may cause (early) signs of increased intracranial pressure which translates clinically into headaches, vomiting, or an altered state of consciousness, and in children changes to the diameter of the skull and bulging of the fontanelles. More complex symptoms such as endocrine dysfunctions should alarm doctors not to exclude brain tumors.[*citation needed*]
A bilateral temporal visual field defect (due to compression of the optic chiasm) or dilation of the pupil, and the occurrence of either slowly evolving or the sudden onset of focal neurologic symptoms, such as cognitive and behavioral impairment (including impaired judgment, memory loss, lack of recognition, spatial orientation disorders), personality or emotional changes, hemiparesis, hypoesthesia, aphasia, ataxia, visual field impairment, impaired sense of smell, impaired hearing, facial paralysis, double vision, or more severe symptoms such as tremors, paralysis on one side of the body hemiplegia, or (epileptic) seizures in a patient with a negative history for epilepsy, should raise the possibility of a brain tumor.[*citation needed*]

Imaging



CT scan of a brain tumor, with its diameters marked as an X. There is hypoattenuating (dark) *peritumoral edema* in the surrounding white matter, with a "finger-like" spread.
Medical imaging plays a central role in the diagnosis of brain tumors. Early imaging methods – invasive and sometimes dangerous – such as pneumoencephalography and cerebral angiography have been abandoned in favor of non-invasive, high-resolution techniques, especially magnetic resonance imaging (MRI) and computed tomography (CT) scans,[39] though MRI is typically the reference standard used.[42] Neoplasms will often show as differently colored masses (also referred to as processes) in CT or MRI results.[*citation needed*]

- Benign brain tumors often show up as hypodense (darker than brain tissue) mass lesions on CT scans. On MRI, they appear either hypodense or isointense (same intensity as brain tissue) on T1-weighted scans, or hyperintense (brighter than brain tissue) on T2-weighted MRI, although the appearance is variable.
- Contrast agent uptake, sometimes in characteristic patterns, can be demonstrated on either CT or MRI scans in most malignant primary and metastatic brain tumors.
- Pressure areas where the brain tissue has been compressed by a tumor also appear hyperintense on T2-weighted scans and might indicate the presence of a diffuse neoplasm due to an unclear outline. Swelling around the tumor known as *peritumoral edema* can also show a similar result. This is because these tumors disrupt the normal functioning of the BBB and lead to an increase in its permeability.

More recently, advancements have been made to increase the utility of MRI in providing physiological data that can help to inform diagnosis and prognosis. MRI itself is sufficient in identifying the brain tumor's location and morphology, but other types of MRI may be used on top of that, such as MRA, MRS, pMRI, fMRI, and DWI. These imaging techniques help doctors and surgeons to diagnose the type of tumor, to plan for surgery, and to assess treatment and radiation/chemotherapy.

Different Types of MRI Scans

Magnetic Resonance Angiography (MRA)- looks at the blood vessels in the brain. In the diagnosis of brain tumor, MRAs are typically carried out before surgery to help surgeons get a better understanding of the tumor vasculature. For example, a study was done where surgeons were able to separate benign brain tumors from malignant ones by analyzing the shapes of the blood vessels that were extracted from MRA.[43] Although not required, some MRA may inject contrast agent, gadolinium, into the patient to get an enhanced image

Magnetic Resonance Spectroscopy (MRS)- measures the metabolic changes or chemical changes inside the tumor. The most common MRS is proton spectroscopy with its frequency measured in parts per million (ppm). Gliomas or malignant brain tumors have different spectra from normal brain tissue in that they have greater choline levels and lower N-acetyl aspartate (NAA) signals.[44] Using MRS in brain tumor diagnosis can help doctors identify the type of tumor and its aggressiveness. For example, benign brain tumors or meningioma have increased alanine levels. It can also help to distinguish brain tumors from scar tissues or dead tissues caused by previous radiation treatment, which does not have increased choline levels[45] that brain tumors have, and from tumor-mimicking lesions such as abscesses or infarcts.

Perfusion Magnetic Resonance Imaging (pMRI)- assess the blood volume and blood flow of different parts of the brain and brain tumors. pMRI requires the injection of contrast agent, usually gadopentetate dimeglumine (Gd-DTPA) into the veins in order to enhance the contrast. pMRI provides a cerebral blood volume map that shows the tumor vascularity and angiogenesis. Brain tumors would require a larger blood supply and thus, would show a high cerebral blood volume on the pMRI map. The vascular morphology and degree of angiogenesis from pMRI help to determine the grade and malignancy of brain tumors. For brain tumor diagnosis, pMRI is useful in determining the best site to perform biopsy and to help reduce sampling error. pMRI is also valuable for after treatment to determine if the abnormal area is a remaining tumor or a scar tissue. For patients that are undergoing anti-angiogenesis cancer therapy, pMRI can give the doctors a better sense of efficacy of the treatment by monitoring tumor cerebral blood volume.[46]**Functional MRI (fMRI)**- measures blood flow changes in active parts of the brain while the patient is performing tasks and provides specific locations of the brain that are responsible for certain functions. Before performing a brain tumor surgery on patients, neurosurgeons would use fMRI to avoid damage to structures of the brain that correspond with important brain functions while resecting the tumor at the same time. Preoperative fMRI is important because it is often difficult to distinguish the anatomy near the tumor as it distorts its surrounding regions. Neurosurgeons would use fMRI to plan whether to perform a resection where tumor is surgically removed as much as possible, a biopsy where they take a surgical sampling amount to provide a diagnosis, or to not undergo surgery at all. For example, a neurosurgeon may be opposed to resecting a tumor near the motor cortex as that would affect the patient's movements. Without preoperative fMRI, the neurosurgeon would have to perform an awake-craniotomy where the patient would have to interact during open surgery to see if tumor removal would affect important brain functions.[47]

Diffusion Weighted Imaging (DWI)- a form of MRI that measures random Brownian motion of water molecules along a magnetic field gradient. For brain tumor diagnosis, measurement of apparent diffusion coefficient (ADC) in brain tumors allow doctors to categorize tumor type. Most brain tumors have higher ADC than normal brain tissues and doctors can match the observed ADC of the patient's brain tumor with a list of accepted ADC to identify tumor type. DWI is also useful for treatment and therapy purposes where changes in diffusion can be analyzed in response to drug, radiation, or gene therapy. Successful response results in apoptosis and increase in diffusion while failed treatment results in unchanged diffusion values.[48]

Other Types of Imaging Techniques

Computed Tomography (CT) Scan- uses x-rays to take pictures from different angles and computer processing to combine the pictures into a 3D image. A CT scan usually serves as an alternative to MRI in cases where the patient cannot have an MRI due to claustrophobia or pacemaker. Compared to MRI, a CT scan shows a more detailed image of the bone structures near the tumor and can be used to measure the tumor's size.[49] Like an MRI, a contrast dye may also be injected into the veins or ingested by mouth before a CT scan to better outline any tumors that may be present. CT scans use contrast materials that are iodine-based and barium sulfate compounds. The downside of using CT scans as opposed to MRI is that some brain tumors do not show up well on CT scans because some intra-axial

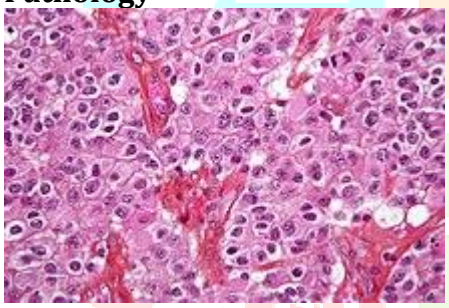
masses are faint and resemble normal brain tissue. In some scenarios, brain tumors in CT scans may be mistaken for infarction, infection, and demyelination. To suspect that an intra-axial mass is a brain tumor instead of other possibilities, there must be unexplained calcifications in the brain, preservation of the cortex, and disproportionate mass effect.

CT Angiography (CTA)- provides information about the blood vessels in the brain using X-rays. A contrast agent is always required to be injected into the patient in the CT scanner. CTA serves as an alternative to MRA.

Positron Emission Tomography (PET) Scan- uses radioactive substances, with the most common one being a sugar known as FDG, while more specific tracers for glioma are emerging. This injected substance is taken up by cells that are actively dividing. Tumor cells are more active in dividing so they would absorb more of the radioactive substance. After injection, a scanner would be used to create an image of the radioactive areas in the brain. PET scans are used more often for high-grade tumors than for low-grade tumors. It is useful after treatment to help doctors determine if the abnormal area on an MRI image is a remaining tumor or a scar tissue. Scar tissues will not show up on PET scans while tumors would.

However, these techniques cannot alone diagnose high- versus low-grade gliomas, and thus the definitive diagnosis of brain tumor should only be confirmed by histological examination of tumor tissue samples obtained either by means of brain biopsy or open surgery. The histological examination is essential for determining the appropriate treatment and the correct prognosis. This examination, performed by a pathologist, typically has three stages: interoperative examination of fresh tissue, preliminary microscopic examination of prepared tissues, and follow-up examination of prepared tissues after immunohistochemical staining or genetic analysis.[*citation needed*]

Pathology



Micrograph of an oligodendroglioma, a type of brain cancer. Brain biopsy. H&E stain

Tumors have characteristics that allow the determination of malignancy and how they will evolve, and determining these characteristics will allow the medical team to determine the management plan.[*citation needed*]

Anaplasia or dedifferentiation: loss of differentiation of cells and of their orientation to one another and blood vessels, a characteristic of anaplastic tumor tissue. Anaplastic cells have lost total control of their normal functions and many have deteriorated cell structures. Anaplastic cells often have abnormally high nuclear-to-cytoplasmic ratios, and many are multinucleated. Additionally, the nucleus of anaplastic cells is usually unnaturally shaped or oversized. Cells can become anaplastic in two ways: neoplastic tumor cells can dedifferentiate to become anaplasias (the dedifferentiation causes the cells to lose all of their normal structure/function), or cancer stem cells can increase their capacity to multiply (i.e., uncontrollable growth due to failure of differentiation).[*citation needed*]

Atypia: an indication of abnormality of a cell (which may be indicative of malignancy). Significance of the abnormality is highly dependent on context.

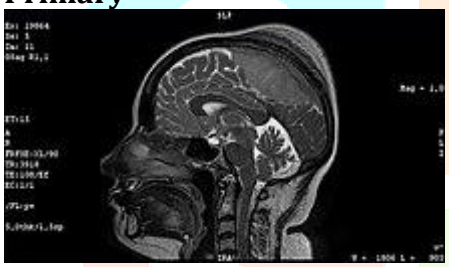
Neoplasia: the (uncontrolled) division of cells. As such, neoplasia is not problematic but its consequences are: the uncontrolled division of cells means that the mass of a neoplasm increases in size, and in a confined space such as the intracranial cavity this quickly becomes problematic because the mass invades the space of the brain pushing it aside, leading to compression of the brain tissue and increased intracranial pressure and destruction of brain parenchyma. Increased intracranial pressure (ICP) may be attributable to the direct mass effect of the tumor, increased blood volume, or increased cerebrospinal fluid (CSF) volume, which may, in turn, have secondary symptoms.[*citation needed*]

Necrosis: the (premature) death of cells, caused by external factors such as infection, toxin or trauma. Necrotic cells send the wrong chemical signals which prevent phagocytes from disposing of the dead cells, leading to a buildup of dead tissue, cell debris and toxins at or near the site of the necrotic cells
Arterial and venous hypoxia, or the deprivation of adequate oxygen supply to certain areas of the brain, occurs when a tumor makes use of nearby blood vessels for its supply of blood and the neoplasm enters into competition for nutrients with the surrounding brain tissue.[54] More generally a neoplasm may cause release of metabolic end products (e.g., free radicals, altered electrolytes, neurotransmitters), and release and recruitment of cellular mediators (e.g., cytokines) that disrupt normal parenchymal function.[*citation needed*]

Classification

Tumors can be benign or malignant, can occur in different parts of the brain, and may be classified as primary or secondary. A primary tumor is one that has started in the brain, as opposed to a metastatic tumor, which is one that has spread to the brain from another area of the body.[56] The incidence of metastatic tumors is approximately four times greater than primary tumors. Tumors may or may not be symptomatic: some tumors are discovered because the patient has symptoms, others show up incidentally on an imaging scan, or at an autopsy.[*citation needed*]
Grading of the tumors of the central nervous system commonly occurs on a 4-point scale (I-IV) created by the World Health Organization in 1993. Grade I tumors are the least severe and commonly associated with long-term survival, with severity and prognosis worsening as the grade increases. Low-grade tumors are often benign, while higher grades are aggressively malignant and/or metastatic. Other grading scales do exist, many based upon the same criteria as the WHO scale and graded from I-IV.

Primary



Meningioma of the middle third of the sagittal sinus with large hyperostosis
The most common primary brain tumors are:[58]

- Gliomas[59] (50.4%)
- Meningiomas[59] (20.8%)
- Pituitary adenomas[59] (15%)
- Nerve sheath tumors (10%)

These common tumors can also be organized according to tissue of origin as shown below:[60]

Tissue of origin	Children	Adults
Astrocytes	Pilocytic Astrocytoma (PCA)	Glioblastoma Multiforme (GBM)
Oligodendrocytes		Oligodendroglioma
Ependyma	Ependymoma	
Neurons	Medulloblastoma	
Meninges		Meningioma

Secondary

Secondary tumors of the brain are metastatic and have invaded the brain from cancers originating in other organs. This means that a cancerous neoplasm has developed in another organ elsewhere in the body and that cancer cells have leaked from that primary tumor and then entered the lymphatic system and blood vessels. They then circulate through the bloodstream, and are deposited in the brain. There, these cells continue growing and dividing, becoming another invasive neoplasm of primary cancer's tissue. Secondary tumors of the brain are very common in the terminal phases of patients with an incurable metastasized cancer; the most common types of cancers that bring about secondary

tumors of the brain are lung cancer, breast cancer, malignant melanoma, kidney cancer, and colon cancer (in decreasing order of frequency).[*citation needed*]
Secondary brain tumors are more common than primary ones; in the United States, there are about 170,000 new cases every year. Secondary brain tumors are the most common cause of tumors in the intracranial cavity. The skull bone structure can also be subject to a neoplasm that by its very nature reduces the volume of the intracranial cavity, and can damage the brain.

By behavior

Brain tumors or intracranial neoplasms can be cancerous (malignant) or non-cancerous (benign). However, the definitions of malignant or benign neoplasms differ from those commonly used in other types of cancerous or non-cancerous neoplasms in the body. In cancers elsewhere in the body, three malignant properties differentiate benign tumors from malignant forms of cancer: benign tumors are self-limited and do not invade or metastasize. Characteristics of malignant tumors include:

- uncontrolled mitosis (growth by division beyond the normal limits)
- anaplasia: the cells in the neoplasm have an obviously different form (in size and shape). Anaplastic cells display marked pleomorphism. The cell nuclei are characteristically extremely hyperchromatic (darkly stained) and enlarged; the nucleus might have the same size as the cytoplasm of the cell (nuclear-cytoplasmic ratio may approach 1:1, instead of the normal 1:4 or 1:6 ratio). Giant cells – considerably larger than their neighbors – may form and possess either one enormous nucleus or several nuclei (syncytia). Anaplastic nuclei are variable and bizarre in size and shape.
- invasion or infiltration (medical literature uses these terms as synonymous equivalents. However, for clarity, the articles that follow adhere to a convention that they mean slightly different things; this convention is not followed outside these articles):
    - Invasion or invasiveness is the spatial expansion of the tumor through uncontrolled mitosis, in the sense that the neoplasm invades the space occupied by adjacent tissue, thereby pushing the other tissue aside and eventually compressing the tissue. Often these tumors are associated with clearly outlined tumors in imaging.
    - Infiltration is the behavior of the tumor either to grow (microscopic) tentacles that push into the surrounding tissue (often making the outline of the tumor undefined or diffuse) or to have tumor cells "seeded" into the tissue beyond the circumference of the tumorous mass; this does not mean that an infiltrative tumor does not take up space or does not compress the surrounding tissue as it grows, but an infiltrating neoplasm makes it difficult to say where the tumor ends and the healthy tissue starts.
- metastasis (spread to other locations in the body via lymph or blood).

Of the above malignant characteristics, some elements do not apply to primary neoplasms of the brain:

- Primary brain tumors rarely metastasize to other organs; some forms of primary brain tumors can metastasize but will not spread outside the intracranial cavity or the central spinal canal. Due to the BBB, cancerous cells of a primary neoplasm cannot enter the bloodstream and get carried to another location in the body. (Occasional isolated case reports suggest spread of certain brain tumors outside the central nervous system, e.g. bone metastasis of glioblastoma multiforme.
- Primary brain tumors generally are invasive (i.e. they will expand spatially and intrude into the space occupied by other brain tissue and compress those brain tissues); however, some of the more malignant primary brain tumors will infiltrate the surrounding tissue.

By genetics

In 2016, the WHO restructured their classifications of some categories of gliomas to include distinct genetic mutations that have been useful in differentiating tumor types, prognoses, and treatment responses. Genetic mutations are typically detected via immunohistochemistry, a technique that visualizes the presence or absence of a targeted protein via staining.

- Mutations in IDH1 and IDH2 genes are commonly found in low-grade gliomas
- Loss of both IDH genes combined with loss of chromosome arms 1p and 19q indicates the tumor is an oligodendroglioma
- Loss of TP53 and ATRX characterizes astrocytomas
- Genes EGFR, TERT, and PTEN, are commonly altered in gliomas and are useful in differentiating tumor grade and biology

Specific types

Main article: WHO classification of the tumors of the central nervous system

Anaplastic astrocytoma, Anaplastic oligodendroglioma, Astrocytoma, Central neurocytoma, Choroid plexus carcinoma, Choroid plexus papilloma, Choroid plexus tumor, Colloid cyst, Dysembryoplastic neuroepithelial tumour, Ependymal tumor, Fibrillary astrocytoma, Giant-cell glioblastoma, Glioblastoma multiforme, Gliomatosis cerebri, Gliosarcoma, Hemangiopericytoma, Medulloblastoma, Medulloepithelioma, Meningeal carcinomatosis, Neuroblastoma, Neurocytoma, Oligoastrocytoma, Oligodendroglioma, Optic nerve sheath meningioma, Pediatric ependymoma, Pilocytic astrocytoma, Pinealoblastoma, Pineocytoma, Pleomorphic anaplastic neuroblastoma, Pleomorphic xanthoastrocytoma, Primary central nervous system lymphoma, Sphenoid wing meningioma, Subependymal giant cell astrocytoma, Subependymoma, Trilateral retinoblastoma.

Treatment

A medical team generally assesses the treatment options and presents them to the person affected and their family. Various types of treatment are available depending on tumor type and location, and may be combined to produce the best chances of survival:

- Surgery: complete or partial resection of the tumor with the objective of removing as many tumor cells as possible.
- Radiotherapy: the most commonly used treatment for brain tumors; the tumor is irradiated with beta, x rays or gamma rays.
- Chemotherapy: a treatment option for cancer, however, it is not always used to treat brain tumors as the blood–brain barrier can prevent some drugs from reaching the cancerous cells.
- A variety of experimental therapies are available through clinical trials.

Survival rates in primary brain tumors depend on the type of tumor, age, functional status of the patient, the extent of surgical removal and other factors specific to each case.[65]

Standard care for anaplastic oligodendrogliomas and anaplastic oligoastrocytomas is surgery followed by radiotherapy. One study found a survival benefit for the addition of chemotherapy to radiotherapy after surgery, compared with radiotherapy alone.[66]

Surgery

The primary and most desired course of action described in medical literature is surgical removal (resection) via craniotomy. Minimally invasive techniques are becoming the dominant trend in neurosurgical oncology. The main objective of surgery is to remove as many tumor cells as possible, with complete removal being the best outcome and cytoreduction ("debulking") of the tumor otherwise. A Gross Total Resection (GTR) occurs when all visible signs of the tumor are removed, and subsequent scans show no apparent tumor. In some cases access to the tumor is impossible and impedes or prohibits surgery.

Many meningiomas, with the exception of some tumors located at the skull base, can be successfully removed surgically. Most pituitary adenomas can be removed surgically, often using a minimally invasive approach through the nasal cavity and skull base (trans-nasal, trans-sphenoidal approach). Large pituitary adenomas require a craniotomy (opening of the skull) for their removal. Radiotherapy, including stereotactic approaches, is reserved for inoperable cases.
Several current research studies aim to improve the surgical removal of brain tumors by labeling tumor cells with 5-aminolevulinic acid that causes them to fluoresce. Postoperative radiotherapy and chemotherapy are integral parts of the therapeutic standard for malignant tumors.

Multiple metastatic tumors are generally treated with radiotherapy and chemotherapy rather than surgery and the prognosis in such cases is determined by the primary tumor, and is generally poor.

Radiation therapy

The goal of radiation therapy is to kill tumor cells while leaving normal brain tissue unharmed. In standard external beam radiation therapy, multiple treatments of standard-dose "fractions" of radiation are applied to the brain. This process is repeated for a total of 10 to 30 treatments, depending on the type of tumor. This additional treatment provides some patients with improved outcomes and longer survival rates.[*citation needed*]
Radiosurgery is a treatment method that uses computerized calculations to focus radiation at the site of the tumor while minimizing the radiation dose to the surrounding brain. Radiosurgery may be an adjunct to other treatments, or it may represent the primary treatment technique for some tumors. Forms used include stereotactic radiosurgery, such as Gamma knife, Cyberknife or Novalis Tx radiosurgery.[73][*unreliable medical source?*]
Radiotherapy is the most common treatment for secondary brain tumors. The amount of radiotherapy depends on the size of the area of the brain affected by cancer. Conventional external beam "whole-brain radiotherapy treatment" (WBRT) or "whole-brain irradiation" may be suggested if there is a risk that other secondary tumors will develop in the future.[74] Stereotactic radiotherapy is usually recommended in cases involving fewer than three small secondary brain tumors. Radiotherapy may be used following, or in some cases in place of, resection of the tumor. Forms of radiotherapy used for brain cancer include external beam radiation therapy, the most common, and brachytherapy and proton therapy, the last especially used for children.
People who receive stereotactic radiosurgery (SRS) and whole-brain radiation therapy (WBRT) for the treatment of metastatic brain tumors have more than twice the risk of developing learning and memory problems than those treated with SRS alone. Results of a 2021 systematic review found that when using SRS as the initial treatment, survival or death related to brain metastasis was not greater than alone versus SRS with WBRT.
Postoperative conventional daily radiotherapy improves survival for adults with good functional well-being and high grade glioma compared to no postoperative radiotherapy. Hypofractionated radiation therapy has similar efficacy for survival as compared to conventional radiotherapy, particularly for individuals aged 60 and older with glioblastoma.

Chemotherapy

Patients undergoing chemotherapy are administered drugs designed to kill tumor cells. Although chemotherapy may improve overall survival in patients with the most malignant primary brain tumors, it does so in only about 20 percent of patients. Chemotherapy is often used in young children instead of radiation, as radiation may have negative effects on the developing brain. The decision to prescribe this treatment is based on a patient's overall health, type of tumor, and extent of cancer. The toxicity and many side effects of the drugs, and the uncertain outcome of chemotherapy in brain tumors puts this treatment further down the line of treatment options with surgery and radiation therapy preferred.
UCLA Neuro-Oncology publishes real-time survival data for patients with a diagnosis of glioblastoma multiforme. They are the only institution in the United States that displays how brain tumor patients are performing on current therapies. They also show a listing of chemotherapy agents used to treat high-grade glioma tumors.
Genetic mutations have significant effects on the effectiveness of chemotherapy. Gliomas with IDH1 or IDH2 mutations respond better to chemotherapy than those without the mutation. Loss of chromosome arms 1p and 19q also indicate better response to chemoradiation.

Other

A shunt may be used to relieve symptoms caused by intracranial pressure, by reducing the build-up of fluid (hydrocephalus) caused by the blockage of the free flow of cerebrospinal fluid.

Prognosis

The prognosis of brain cancer depends on the type of cancer diagnosed. Medulloblastoma has a good prognosis with chemotherapy, radiotherapy, and surgical resection while glioblastoma multiforme has a median survival of only 12 months even with aggressive chemoradiotherapy and surgery. Brainstem gliomas have the poorest prognosis of any form of brain cancer, with most patients dying within one year, even with therapy that typically consists of radiation to the tumor along with corticosteroids. However, one type, focal brainstem gliomas in children, seems open to exceptional prognosis and long-term survival has frequently been reported.[82]
Prognosis is also affected by presentation of genetic mutations. Certain mutations provide better prognosis than others. IDH1 and IDH2 mutations in gliomas, as well as deletion of chromosome arms 1p and 19q, generally indicate better prognosis. TP53, ATRX, EGFR, PTEN, and TERT mutations are also useful in determining prognosis.

Glioblastoma multiforme

Glioblastoma multiforme (GBM) is the most aggressive (grade IV) and most common form of a malignant brain tumor. Even when aggressive multimodality therapy consisting of radiotherapy, chemotherapy, and surgical excision is used, median survival is only 12–17 months. Standard therapy for glioblastoma multiforme consists of maximal surgical resection of the tumor, followed by radiotherapy between two and four weeks after the surgical procedure to remove the cancer, then by chemotherapy, such as temozolomide.[83] Most patients with glioblastoma take a corticosteroid, typically dexamethasone, during their illness to relieve symptoms. Experimental treatments include targeted therapy, gamma knife radiosurgery,[84] boron neutron capture therapy, gene therapy, and chemowafer implants.

Oligodendrogliomas

Oligodendrogliomas are incurable but slowly progressive malignant brain tumors. They can be treated with surgical resection, chemotherapy, radiotherapy or a combination. For some suspected low-grade (grade II) tumors, only a course of watchful waiting and symptomatic therapy is opted for. These tumors show a high frequency of co-deletions of the p and q arms of chromosome 1 and chromosome 19 respectively (1p19q co-deletion) and have been found to be especially chemosensitive with one report claiming them to be one of the most chemosensitive tumors. A median survival of up to 16.7 years has been reported for grade II oligodendrogliomas

Acoustic neuroma

Acoustic neuromas are non-cancerous tumors.[89] They can be treated with surgery, radiation therapy, or observation. Early intervention with surgery or radiation is recommended to prevent progressive hearing loss.[90]

Epidemiology

Figures for incidences of cancers of the brain show a significant difference between more- and less-developed countries (the less-developed countries have lower incidences of tumors of the brain This could be explained by undiagnosed tumor-related deaths (patients in extremely poor situations do not get diagnosed, simply because they do not have access to the modern diagnostic facilities required to diagnose a brain tumor) and by deaths caused by other poverty-related causes that preempt a patient's life before tumors develop or tumors become life-threatening. Nevertheless, statistics suggest that certain forms of primary brain tumors are more common among certain populations.
The incidence of low-grade astrocytoma has not been shown to vary significantly with nationality. However, studies examining the incidence of malignant central nervous system (CNS) tumors have

shown some variation with national origin. Since some high-grade lesions arise from low-grade tumors, these trends are worth mentioning. Specifically, the incidence of CNS tumors in the United States, Israel, and the Nordic countries is relatively high, while Japan and Asian countries have a lower incidence. These differences probably reflect some biological differences as well as differences in pathologic diagnosis and reporting.[93] Worldwide data on incidence of cancer can be found at the WHO (World Health Organization) and is handled by the IARC (International Agency for Research on Cancer) located in France

United States

In the United States in 2015, approximately 166,039 people were living with brain or other central nervous system tumors. Over 2018, it was projected that there would be 23,880 new cases of brain tumors and 16,830 deaths in 2018 as a result,[92] accounting for 1.4 percent of all cancers and 2.8 percent of all cancer deaths.[95] Median age of diagnosis was 58 years old, while median age of death was 65. Diagnosis was slightly more common in males, at approximately 7.5 cases per 100 000 people, while females saw 2 fewer at 5.4. Deaths as a result of brain cancer were 5.3 per 100 000 for males, and 3.6 per 100 000 for females, making brain cancer the 10th leading cause of cancer death in the United States. Overall lifetime risk of developing brain cancer is approximated at 0.6 percent for men and women.

UK

Brain, other CNS or intracranial tumors are the ninth most common cancer in the UK (around 10,600 people were diagnosed in 2013), and it is the eighth most common cause of cancer death (around 5,200 people died in 2012. White British patients with brain tumour are 30% more likely to die within a year of diagnosis than patients from other ethnicities. The reason for this is unknown.

Children

In the United States more than 28,000 people under 20 are estimated to have a brain tumor About 3,720 new cases of brain tumors are expected to be diagnosed in those under 15 in 2019. Higher rates were reported in 1985–1994 than in 1975–1983. There is some debate as to the reasons; one theory is that the trend is the result of improved diagnosis and reporting, since the jump occurred at the same time that MRIs became available widely, and there was no coincident jump in mortality. Central nervous system tumors make up 20–25 percent of cancers in children

The average survival rate for all primary brain cancers in children is 74%.[99] Brain cancers are the most common cancer in children under 19, are result in more death in this group than leukemia. Younger people do less well.

The most common brain tumor types in children (0-14) are: pilocytic astrocytoma, malignant glioma, medulloblastoma, neuronal and mixed neuronal-glial tumors, and ependymoma

In children under 2, about 70% of brain tumors are medulloblastomas, ependymomas, and low-grade gliomas. Less commonly, and seen usually in infants, are teratomas and atypical teratoid rhabdoid tumors.[106] Germ cell tumors, including teratomas, make up just 3% of pediatric primary brain tumors, but the worldwide incidence varies significantly.

In the UK, 429 children aged 14 and under are diagnosed with a brain tumour on average each year, and 563 children and young people under the age of 19 are diagnosed.

Research

Immunotherapy

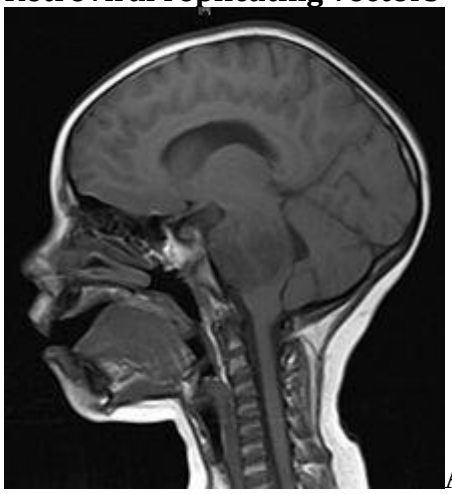
Cancer immunotherapy is being actively studied. For malignant gliomas no therapy has been shown to improve life expectancy as of 2015.

Vesicular stomatitis virus

See also: Oncolytic virus

In 2000, researchers used the vesicular stomatitis virus, or VSV, to infect and kill cancer cells without affecting healthy cells.

Retroviral replicating vectors


A brainstem glioma in four-year-old. MRI, sagittal, without contrast

Led by Prof. Nori Kasahara, researchers from USC, who are now at UCLA, reported in 2001 the first successful example of applying the use of retroviral replicating vectors towards transducing cell lines derived from solid tumors. Building on this initial work, the researchers applied the technology to *in vivo* models of cancer and in 2005 reported a long-term survival benefit in an experimental brain tumor animal model. [*unreliable medical source?*] Subsequently, in preparation for human clinical trials, this technology was further developed by Tocagen (a pharmaceutical company primarily focused on brain cancer treatments) as a combination treatment (Toca 511 & Toca FC). This has been under investigation since 2010 in a Phase I/II clinical trial for the potential treatment of recurrent high-grade glioma including glioblastoma multiforme (GBM) and anaplastic astrocytoma. No results have yet been published.

Non-invasive detection

Efforts to detect and monitor development and treatment response of brain tumors by liquid biopsy from blood, cerebrospinal fluid or urine, are in the early stages of development.

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