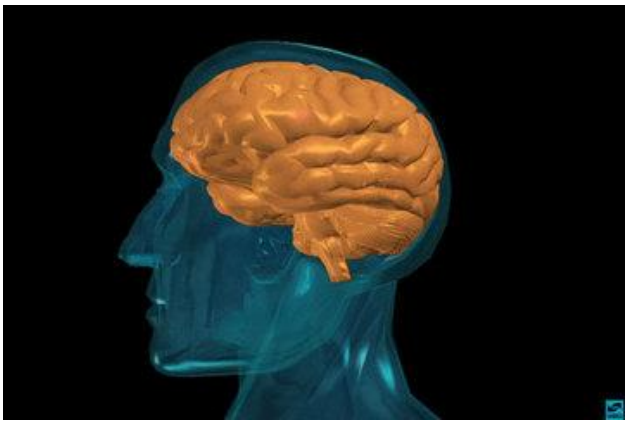
Cancer Association of South Africa (CANSA)

Research • Educate • Support

Fact Sheet on Cancer of the Brain and Central Nervous System

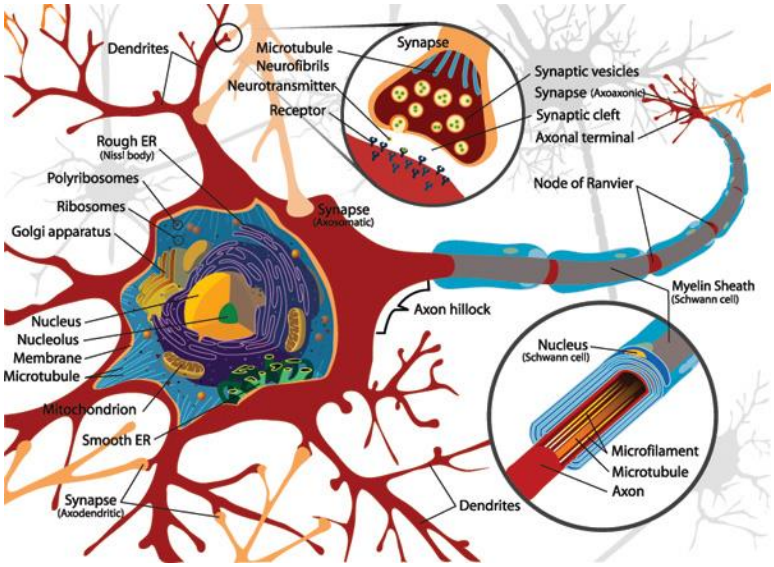
Introduction

The brain is the center of the nervous system in all vertebrate and most invertebrate animals - only a few invertebrates such as sponges, jellyfish, adult sea squirts and starfish do not have a brain, even if diffuse neural tissue is present. The brain is located in the head, usually close to the primary sensory organs for such senses as vision, hearing, balance, taste and smell. The brain of a vertebrate is the most complex organ of its body.



[Picture Credit The Brain]

[Picture Credit: Neuron]



In a typical human the cerebral cortex (the largest part) is estimated to contain 15 to 33 billion neurons, each connected by synapses to several thousand other neurons. These neurons communicate with one another by means of long protoplasmic fibers called axons, which carry trains of signal pulses called action potentials to distant parts of the brain or body targeting specific recipient cells. The human brain has the same general structure as the brains of other mammals, but is larger than any other in relation to body size. (Wikipedia).

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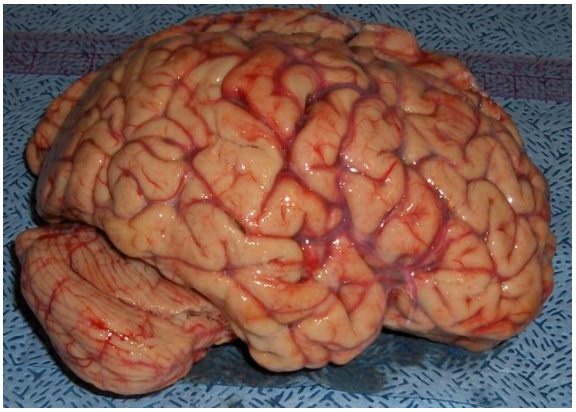
The Human Brain

Every animal one can think of - mammals, birds, reptiles, fish, amphibians - has a brain. The human brain, however, is unique. The brain gives humans the power to speak, imagine and problem solve.



[Picture Credit: Human Brain]

The brain performs an incredible number of tasks including the following:

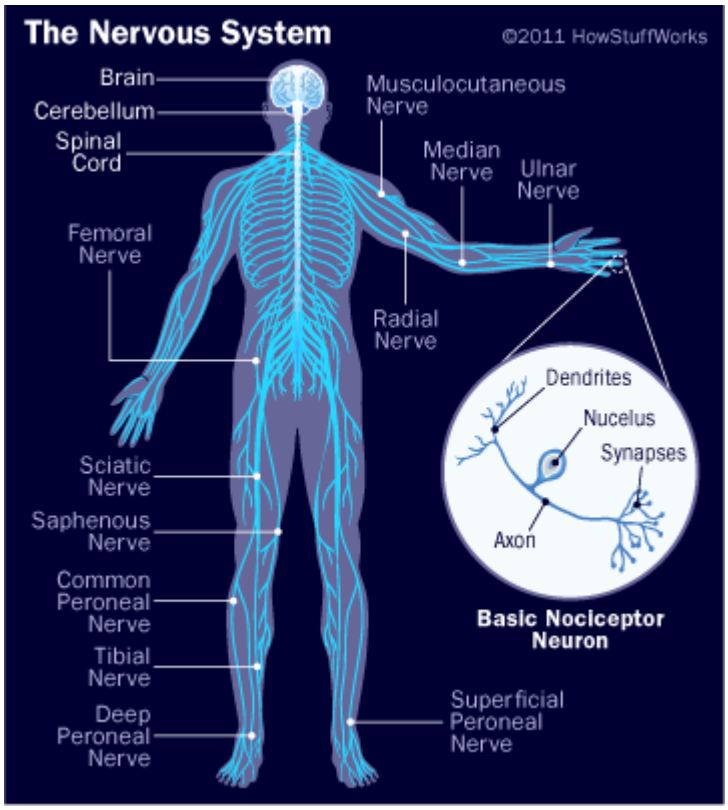
- It controls body temperature, blood pressure, heart rate and breathing
- It accepts a flood of information about the world from various senses (seeing, hearing, smelling, tasting and touching)
- It handles physical movement like walking, talking, standing or sitting
- It lets individuals think, dream, reason and experience emotions

All of these tasks are coordinated, controlled and regulated by an organ that is about the size of a small head of cauliflower.

The brain, spinal cord and peripheral nerves make up a complex, integrated information-processing and control system known as the **central nervous system**. In tandem, they regulate all the conscious and unconscious facets of one's life. The scientific study of the brain and nervous system is called **neuroscience** or **neurobiology** (HowStuffWorks).

The Nervous System

The Central Nervous System is effectively the centre of the nervous system, the part of it that processes the information received from the peripheral nervous system. The CNS consists of the brain and spinal cord. It is responsible for receiving and interpreting signals from the peripheral nervous system and also sends out signals to it, either consciously or unconsciously. This information highway called the nervous system consists of many nerve cells, also known as neurones (BiologyOnLine).



[Picture Credit: The Human Nervous System]

Cancer of the Brain

Brain cancer is a disease of the brain in which cancer cells (malignant cells) arise in the brain tissue and multiply in an uncontrolled fashion. Cancer cells grow to form a mass of cancer tissue (tumour) that interferes with brain functions such as muscle control, sensation, memory and other normal body functions.

[Picture Credit: Brain Cancer]

Tumours composed of cancer cells are called malignant tumours, and those composed of mainly non-cancerous cells are called benign tumours. Cancer cells that develop from brain tissue are called primary brain tumours while tumours that spread from other body sites to the brain are termed metastatic brain tumours (MedicineNet.Com).

Incidence of Brain and Central Nervous System Cancer in South Africa

According to the National Cancer Registry (2013) the following number of brain and central nervous system cases was histologically diagnosed in South Africa during 2013:

Group - Males 2013	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	206	1:944	0,57%
Asian males	8	1:682	1,00%
Black males	63	1:3 093	0,59%
Coloured males	25	1:798	0,59%
White males	110	1:265	0,54%

Group - Females 2013	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	140	1:1 727	0,38%
Asian females	4	1:1 845	0,40%
Black females	50	1:4 827	0,32%
Coloured females	24	1:775	0,58%
White females	62	1:490	0,39%

The frequency of histologically diagnosed cases of cancer of the brain and central nervous system in South Africa for 2013 was as follows (National Cancer Registry, 2013):

Group - Males 2013	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All males	42	17	14	32	41	39	17	3
Asian males	1	1	1	1	1	2	1	0
Black males	21	6	5	12	10	6	0	0
Coloured males	5	1	2	6	4	5	1	0
White males	12	8	6	13	24	25	15	3

Group - Females 2013	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All females	28	10	21	14	22	29	14	2
Asian females	0	1	0	1	0	2	0	0
Black females	20	5	8	4	5	4	3	0
Coloured females	1	2	2	3	4	9	2	0
White females	4	2	10	6	13	14	9	1

N.B. In the event that the totals in any of the above tables do not tally, this may be the result of uncertainties as to the age, race or sex of the individual. The totals for 'all males' and 'all females', however, always reflect the correct totals.

Causes of Brain Cancer

In most cases, doctors do not know what causes a brain tumour. It is known that brain tumours are not infectious. One cannot, therefore, catch a brain tumour. Cancerous brain tumours are more common in males than females. Non-cancerous brain tumours, and tumours where the diagnosis is unknown, are more common in females. There are some risk factors that are known:

Age - people can get brain tumours at any age. Generally speaking, as one gets older the risk for brain tumours increases. There are many different types of brain tumours and some are more common in younger adults.

Genetic conditions and family history - a small proportion of brain tumours are related to known genetic conditions. People who have one of these rare syndromes have an increased risk of getting a brain tumour. These syndromes cause a number of different medical problems, and so individuals may already know if any of these run in their family. Examples are:

- Neurofibromatosis type 1 (von Recklinghausen disease) - this is the most common syndrome linked to brain or spinal cord tumours. It is often inherited from a parent, but it can also start in some children whose parents don't have it. Children with this syndrome may have optic gliomas or other gliomas of the brain or spinal cord, or neurofibromas (benign tumours of peripheral nerves). Changes in the *NF1* gene cause this disorder

- Neurofibromatosis type 2 - less common than von Recklinghausen disease, this condition can also either be inherited or may start in children without a family history. It is associated with cranial or spinal nerve schwannomas, especially vestibular schwannomas (acoustic neuromas), which almost always occur on both sides of the head. It is also linked to an increased risk of meningiomas, as well as spinal cord gliomas or ependymomas. Changes in the *NF2* gene are responsible for neurofibromatosis type 2

- Tuberous sclerosis - children with this condition may develop subependymal giant cell astrocytomas (SEGAs), as well as other benign tumors of the brain, skin, heart, or kidneys. It is caused by changes in either the *TSC1* or the *TSC2* gene

- Li-Fraumeni syndrome - people with this syndrome have an increased risk of gliomas, as well as breast cancer, soft tissue sarcomas, leukaemia, and adrenal gland cancers. It is caused by changes in the *TP53* gene

- Von Hippel-Lindau syndrome (VHL) - children with this disease tend to develop haemangioblastomas (blood vessel tumours) of the cerebellum, spinal cord, or retina, as well as tumours in the kidney, pancreas, and some other parts of the body. It is caused by changes in the *VHL* gene

- Turner syndrome - Turner syndrome (TS) is a medical disorder that affects about 1 in every 2 500 girls. Although researchers do not know exactly what causes Turner syndrome, they do know that it is the result of a problem with a girl's chromosomes. Girls with Turner syndrome are usually short in height. Those who are not treated for short stature reach an average height of about 1,4 metres. When Turner syndrome is diagnosed while a girl is still growing, she can be treated with growth hormones to help her grow taller

- Turcot syndrome - Turcot syndrome is a condition in which cells become abnormal and form masses called polyps. A polyp is benign (non-cancerous) but can eventually turn malignant (cancerous, meaning it can spread to other parts of the body). Turcot syndrome is rare and is considered to be an alternative form of two more common syndromes associated with polyp formations: Lynch syndrome and familial adenomatous polyposis (FAP)

  People with Turcot syndrome have multiple adenomatous colon polyps (polyps in the colon made up of cells that form mucous), an increased risk of colorectal cancer, and an increased risk of brain cancer. The type of brain cancer generally depends on whether the Turcot syndrome is more similar to Lynch syndrome or FAP. The two most common types of brain tumours in Turcot syndrome are:

  - Glioblastoma. This type of brain tumour is a very aggressive form of astrocytoma that is commonly found in families who have features of Lynch syndrome
  - Medulloblastoma.This type of brain tumour begins in granular cells in the cerebellum (back of the brain). Medulloblastoma most often occurs in children and is commonly found in families who have features of FAP

- Gorlin syndrome – Gorlin syndrome, also known as nevoid basal cell carcinoma syndrome, is a condition that affects many areas of the body and increases the risk of developing various cancerous and non-cancerous tumours

  In people with Gorlin syndrome, the type of cancer diagnosed most often is basal cell carcinoma, which is the most common form of skin cancer. Individuals with Gorlin syndrome typically begin to develop basal cell carcinomas during adolescence or early adulthood. These cancers occur most often on the face, chest and back. The number of basal cell carcinomas that develop during a person's lifetime varies among affected individuals. Some people with Gorlin syndrome never develop any basal cell carcinomas, while others may develop thousands of these cancers. Individuals with lighter skin are more likely to develop basal cell carcinomas than are people with darker skin

<u>Family history</u> - if one has a parent, brother or sister diagnosed with a brain tumour, the risk is higher than for other people in the general population

Medical radiation - exposure to radiation is one of the definite known risk factor. Types of brain tumours called meningiomas and, to a lesser extent, cancerous (malignant) gliomas, are more common in people who have had radiotherapy, CT scans or X-rays to the head in the past. Doctors keep medical exposure to radiation as low as possible

Previous cancers - people who have had cancer as a child have a higher risk of developing a brain tumour later in life. People who have had leukaemia or non-Hodgkin lymphoma as an adult also have an increased risk. There is some evidence that there is an increased risk of brain tumours in adults who have had other types of cancer, but more research is needed to confirm this

The increase in brain tumour risk may be due to the treatment for the previous cancer. For example, radiotherapy to the head. Intrathecal methotrexate for the treatment of leukaemia has also been shown to increase the risk of brain tumours. It is important to remember that any increase in brain tumour risk from cancer treatment is small compared to the risk of not having the treatment for the original cancer

People with HIV or Aids – these individuals have a double the risk of being diagnosed with a brain tumour compared to the general population

Post-menopausal women who are taking hormone replacement therapy (HRT) – these women may have a slightly increased risk of developing meningioma, compared with women who have never taken HRT. Women taking oral contraceptives might also have a higher risk of meningioma, but more research is needed to confirm this link

Body size - larger people - individuals with a larger waist size or greater body mass index (BMI) have a slightly higher risk of meningioma compared with the smallest people. But this does not seem to affect glioma risk

Children weighing 4kg or more at birth – Large birth weight babies have a small increased risk of some brain tumour types, compared with lighter babies

Electromagnetic radiation - Numerous epidemiological (population) studies and comprehensive reviews have evaluated magnetic field exposure and risk of cancer in children. Since the two most common cancers in children are leukaemia and brain tumours, most of the research has focused on these two types

[Picture Credit: Power Lines]

A study in 1979 pointed to a possible association between living near electric power lines and childhood leukaemia.

Among more recent studies, findings have been mixed. Some have found an association; others have not

Mobile phones – according to award-winning scientist and author, Devra Lee Davis: all studies that have been able to examine people a decade after heavy use of mobile phones began have found increased risk of brain tumours.

[Picture Credit: Mobile Phone Use]

Dr Davis is Founder of Environmental Health Trust, a National Book Award finalist, Carnegie Science Medal winner, author of "Disconnect" - the truth about cell phone radiation and health, what the industry has done to hide it, and what you can do to protect your family. She is also Visiting Professor, Georgetown University. She was the Founding Director of the Board on Environmental Studies and Toxicology at the U.S. National Academies of Sciences, 1983-1993, a Presidential appointee in the Clinton Administration to the National Chemical Safety and Hazard Investigation Board, and Founding Director of the Center for Environmental Oncology at the University of Pittsburgh Cancer Institute, 2004-2009.

Professor Joel Moskowitz of University of California Berkeley combined information from all other studies ever done on brain tumours and cell phones and found 'consistent evidence that heavy cell phone use for a decade or longer increases brain tumour risk at least 30%' (Huffington Post).

A landmark court case in Italy has ruled that there is a 'causal link' between using a mobile phone and brain tumours. Mr Innocente Marcolini, a 60-year old Italian businessman, fell ill after using a mobile phone at work for up to 6 hours every day for 12 years (The Telegraph)

Smoking and alcohol – it is not yet clear whether smoking affects brain tumour risk. Some studies have shown increased risks for some types of brain tumour. Drinking alcohol does not seem to affect risk
(Cancer Research UK; National Cancer Institute; Huffington Post; American Cancer Society; TeensHealth; Cancer.Net; Genetics Home Reference).

Signs and Symptoms of Brain Cancer in Adults

The brain is contained within the skull and has a fixed amount of space. If a tumour grows in the brain it will often cause an increase in pressure within the skull, which can cause symptoms to develop. An increase of pressure in the skull is called increased intracranial pressure (ICP). The most common symptoms of raised pressure within the brain are headaches, feeling sick (nausea) and being sick (vomiting).

Many other things can cause headaches or feelings of sickness, but if one has either of these for over a week with no sign of getting better, it is important that one sees a doctor to get it checked out.

Headaches - a pressure headache is usually dull and constant and occasionally throbbing. Severe headaches are uncommon. A headache may get worse when one coughs, sneezes, bends down or does any hard physical work. All of these tend to raise pressure in the brain. Headaches may be worse at night and may wake the person up.

Feeling sick (nausea) and vomiting - if the raised pressure makes one sick, it may be worse in the morning than during the day. It may also get worse if one suddenly changes position, for example from sitting or lying to standing.

Seizures - seizures (fits) are another common symptom of brain tumours. Some people may experience muscle spasms, which could be twitching or jerking of an arm or leg, or sometimes the whole body. Occasionally they can cause moments of unconsciousness.

A seizure can be a frightening experience. If one has a seizure he/she should seek medical help so that the cause can be diagnosed and treated. A seizure can be caused by medical conditions other than a brain tumour.

Drowsiness - another possible symptom is drowsiness. This can happen as the pressure in the skull increases. One may find that one sleeps more or that one drops off during the day when one would normally not do so.

Raised intracranial pressure can also cause changes to one's sight, such as blurred vision, 'floating objects' and tunnel vision. It may also make one confused or affect one's balance. (MacMillan Cancer Support).

Symptoms Connected with the Tumour's Position in Adults

Some symptoms may be caused by tumours in particular parts of the brain. Sometimes a headache can feel worse on the same side of the head as the tumour. In general, each area of the brain controls different functions. A tumour in a particular part of the brain may prevent that area of the brain from working normally.

- Frontal lobe − changes in personality and intellect; uncoordinated walking or weakness of one side of the body; loss of smell; occasional speech difficulties
- Parietal lobe − difficulty speaking or understanding words; problems with writing, reading or doing simple calculations; difficulty coordinating certain movements, and finding one's way around; numbness or weakness on one side of the body
- Temporal lobe − seizures, which may cause strange sensations: a feeling of fear or intense familiarity (*déjà vu*), strange smells or blackouts; speech difficulties; memory problems
- Occipital lobe − loss of vision to one eye, which the person may not notice at first and may sometimes be discovered during routine eye tests
- Cerebellum − lack of coordination; slurred speech (dysarthia); unsteadiness; flickering involuntary movement of the eyes (nystagmus); vomiting and neck stiffness
- Brain stem − unsteadiness and an uncoordinated walk; facial weakness, a one-sided smile or drooping eyelid; double vision; difficulty speaking and swallowing; vomiting or headache just after waking (this is rare). Symptoms may appear gradually
- Meninges – headaches, vomiting and problems with sight and movement

- Pituitary gland – the pituitary gland produces lots of different hormones so a tumour in the gland can cause a variety of symptoms including: irregular periods; infertility; weight gain; lethargy; high blood pressure; diabetes; mood swings; and enlarged hands and feet. A tumour in the pituitary gland can also cause pressure on the nerves to the eyes, causing tunnel vision
- Celebral hemispheres - Sometimes brain tumours may cause changes in personality or behaviour. This usually happens when the tumour is in the brain's cerebral hemispheres

All the above symptoms may also be caused by conditions other than a brain tumour. If any of the symptoms described above are present it is important to see a medical practitioner. (MacMillan Cancer Support).

Signs and Symptoms of Brain Cancer in Children

The following are the most common symptoms of a brain tumour in children. However, each child may experience symptoms differently. Symptoms vary depending on the size and location of the tumour. Many symptoms are related to an increase in pressure in or around the brain. There is no spare space in the skull for anything except the delicate tissues of the brain and its fluid. Any tumour, extra tissue, or fluid can cause pressure on the brain and result in the following symptoms:

Increased intracranial pressure (ICP) - caused by extra tissue or fluid in the brain. Pressure may increase because one or more of the ventricles that drain cerebrospinal fluid (CSF, the fluid that surrounds the brain and spinal cord) has been blocked, causing the fluid to be trapped in the brain. Increased ICP can cause the following:

- Headache
- Vomiting (usually in the morning)
- Nausea
- Personality changes
- Irritability
- Drowsiness
- Depression
- Decreased cardiac and respiratory function and eventually coma if not treated

Symptoms vary depending upon which part of the brain the tumour is found. Symptoms of brain tumours in the cerebrum (front of brain) may include:

- Seizures
- Visual changes
- Slurred speech
- Paralysis or weakness on half of the body or face
- Increased intracranial pressure (ICP)
- Drowsiness and/or confusion
- Personality changes

Symptoms of brain tumours in the brainstem (middle of brain) may include:

- Seizures
- Endocrine problems (diabetes and/or hormone regulation)

- Visual changes or double vision
- Headaches
- Paralysis of nerves/muscles of the face, or half of the body
- Respiratory changes
- Increased intracranial pressure (ICP)

Symptoms of brain tumours in the cerebellum (back of brain) may include:

- Increased intracranial pressure (ICP)
- Vomiting (usually occurs in the morning without nausea)
- Headache
- Uncoordinated muscle movements
- Problems walking (ataxia)

The symptoms of a brain tumour may resemble other conditions or medical problems – a doctor should be consulted if any of the above symptoms occur and persist.
(Children's Hospital of Wisconsin).

Types of Tumours that can Form in the Brain or Spinal Cord
The following types of tumours can form in the brain and spinal cord:

Astrocytic Tumours
An astrocytic tumour begins in star-shaped brain cells called astrocytes, which help keep nerve cells healthy. An astrocyte is a type of glial cell. Glial cells sometimes form tumours called gliomas. Astrocytic tumours include the following:

- Brain stem glioma (usually high grade): A brain stem glioma forms in the brain stem, which is the part of the brain connected to the spinal cord. It is often a high-grade tumour, which spreads widely through the brain stem and is hard to cure. Brain stem gliomas are rare in adults. (See the PDQ summary on Childhood Brain Stem Glioma Treatment for more information.)
- Pineal astrocytic tumour (any grade): A pineal astrocytic tumour forms in tissue around the pineal gland and may be any grade. The pineal gland is a tiny organ in the brain that makes melatonin, a hormone that helps control the sleeping and waking cycle.
- Pilocytic astrocytoma (grade I): A pilocytic astrocytoma grows slowly in the brain or spinal cord. It may be in the form of a cyst and rarely spreads into nearby tissues. Pilocytic astrocytomas can often be cured.
- Diffuse astrocytoma (grade II): A diffuse astrocytoma grows slowly, but often spreads into nearby tissues. The tumour cells look something like normal cells. In some cases, a diffuse astrocytoma can be cured. It is also called a low-grade diffuse astrocytoma.
- Anaplastic astrocytoma (grade III): An anaplastic astrocytoma grows quickly and spreads into nearby tissues. The tumour cells look different from normal cells. This type of tumour usually cannot be cured. An anaplastic astrocytoma is also called a malignant astrocytoma or high-grade astrocytoma.
- Glioblastoma (grade IV): A glioblastoma grows and spreads very quickly. The tumour cells look very different from normal cells. This type of tumour usually cannot be cured. It is also called glioblastoma multiforme.

Oligodendroglial Tumours

An oligodendroglial tumour begins in brain cells called oligodendrocytes, which help keep nerve cells healthy. An oligodendrocyte is a type of glial cell. Oligodendrocytes sometimes form tumours called oligodendrogliomas. Grades of oligodendroglial tumours include the following:

- Oligodendroglioma (grade II): An oligodendroglioma grows slowly, but often spreads into nearby tissues. The tumour cells look something like normal cells. In some cases, an oligodendroglioma can be cured.
- Anaplastic oligodendroglioma (grade III): An anaplastic oligodendroglioma grows quickly and spreads into nearby tissues. The tumour cells look different from normal cells. This type of tumour usually cannot be cured.

Mixed Gliomas

A mixed glioma is a brain tumour that has two types of tumour cells in it — oligodendrocytes and astrocytes. This type of mixed tumour is called an oligoastrocytoma.

- Oligoastrocytoma (grade II): An oligoastrocytoma is a slow-growing tumour. The tumour cells look something like normal cells. In some cases, an oligoastrocytoma can be cured.
- Anaplastic oligoastrocytoma (grade III): An anaplastic oligoastrocytoma grows quickly and spreads into nearby tissues. The tumour cells look different from normal cells. This type of tumour has a worse prognosis than oligoastrocytoma (grade II).

Ependymal Tumours

An ependymal tumour usually begins in cells that line the fluid -filled spaces in the brain and around the spinal cord. An ependymal tumour may also be called an ependymoma. Grades of ependymomas include the following:

- Ependymoma (grade I or II): A grade I or II ependymoma grows slowly and has cells that look something like normal cells. There are two types of grade I ependymoma — myxopapillary ependymoma and subependymoma. A grade II ependymoma grows in a ventricle (fluid-filled space in the brain) and its connecting paths or in the spinal cord. In some cases, a grade I or II ependymoma can be cured.
- Anaplastic ependymoma (grade III): An anaplastic ependymoma grows quickly and spreads into nearby tissues. The tumour cells look different from normal cells. This type of tumour usually has a worse prognosis than a grade I or II ependymoma.

Medulloblastomas

A medulloblastoma is a type of embryonal tumour. Medulloblastomas are most common in children or young adults.

Pineal Parenchymal Tumours

A pineal parenchymal tumour forms in parenchymal cells or pineocytes, which are the cells that make up most of the pineal gland. These tumours are different from pineal astrocytic tumours. Grades of pineal parenchymal tumours include the following:

- Pineocytoma (grade II): A pineocytoma is a slow-growing pineal tumour.

- Pineoblastoma (grade IV): A pineoblastoma is a rare tumour that is very likely to spread.

Meningeal Tumours

A meningeal tumour, also called a meningioma, forms in the meninges (thin layers of tissue that cover the brain and spinal cord). It can form from different types of brain or spinal cord cells. Meningiomas are most common in adults. Types of meningeal tumours include the following:

- Meningioma (grade I): A grade I meningioma is the most common type of meningeal tumour. A grade I meningioma is a slow-growing tumour. It forms most often in the dura mater. A grade I meningioma can be cured if it is completely removed by surgery.
- Meningioma (grade II and III): This is a rare meningeal tumour. It grows quickly and is likely to spread within the brain and spinal cord. The prognosis is worse than a grade I meningioma because the tumour usually cannot be completely removed by surgery.

A haemangiopericytoma is not a meningeal tumour but is treated like a grade II or III meningioma. A haemangiopericytoma usually forms in the dura mater. The prognosis is worse than a grade I meningioma because the tumour usually cannot be completely removed by surgery.

Germ Cell Tumours

A germ cell tumour forms in germ cells, which are the cells that develop into sperm in men or ova (eggs) in women. There are different types of germ cell tumours. These include germinomas, teratomas, embryonal yolk sac carcinomas, and choriocarcinomas. Germ cell tumours can be either benign or malignant.

Craniopharyngioma (Grade I)

A craniopharyngioma is a rare tumour that usually forms just above the pituitary gland (a pea-sized organ at the bottom of the brain that controls other glands). Craniopharyngiomas can form from different types of brain or spinal cord cells. They begin in the centre of the brain, just above the back of the nose.

Recurrent Brain Tumours

A recurrent brain tumour is a tumour that has recurred (come back) after it has been treated. Brain tumours often recur, sometimes many years after the first tumour. The tumour may recur at the same place in the brain or in other parts of the central nervous system.

The following tumour types are more common in children than in adults:

- Brain stem glioma
- Craniopharyngioma
- Ependymoma
- Juvenile pilocytic astrocytoma (JPA)
- Medulloblastoma
- Optic nerve glioma

- Pineal Tumour
- Primitive neuroectodermal tumours (PNET)
- Rhabdoid tumour

(National Cancer Institute; National Brain Tumor Society; Cancer Research UK).

Staging of Brain Cancer in Adults

Brain and spinal cord tumours are named based on the type of cell they formed in and where the tumour first formed in the CNS. The grade of a tumour may be used to tell the difference between slow-growing and fast-growing types of the tumour. The grade of a tumour is based on how abnormal the cancer cells look under a microscope and how quickly the tumour is likely to grow and spread.

Tumour Grading System:

Grade I (low-grade)
The tumour grows slowly, has cells that look a lot like normal cells, and rarely spreads into nearby tissues. Grade I brain tumours may be cured if they are completely removed by surgery.

Grade II
The tumour grows slowly, but may spread into nearby tissue and may recur (come back). Some tumours may become a higher-grade tumour.

Grade III
The tumour grows quickly, is likely to spread into nearby tissue, and the tumour cells look very different from normal cells.

Grade IV (high-grade)
The tumour grows and spreads very quickly and the cells do not look like normal cells. There may be areas of dead cells in the tumour. Grade IV tumours usually cannot be cured.
(National Cancer Institute).

Staging of Brain Cancer in Children

The stage of a cancer in children is a measure of how far it has spread. The extent of spread is based on the results of imaging tests and any other tests that have been done.

For most types of cancer, the stage of the cancer is one of the most important factors in selecting treatment options and in determining the outlook (prognosis). But tumours of the brain and spinal cord differ in some important ways from cancers in other parts of the body. One of the main reasons other cancers are dangerous is that they can spread throughout the body. Tumours starting in the brain or spinal cord can spread to other parts of the central nervous system, but they almost never spread to other organs. These tumours are dangerous because when they grow, it can interfere with essential functions of the brain.

Because most tumours in the brain or spinal cord do not usually spread, they are not formally staged. Some of the most important factors that determine a child's prognosis include:

- The type of tumour (such as astrocytoma and ependymoma)
- The grade of the tumour (how quickly the tumour is likely to grow, based on how the cells look under a microscope)
- The location of the tumour
- How much of the tumour can be removed by surgery (if it can be done)
- The child's age
- The child's functional level (whether the tumour has started to interfere with normal brain functions and everyday activities)
- Whether or not the tumour has spread through the cerebrospinal fluid (CSF) to other parts of the brain and/or spinal cord
- Whether or not tumour cells have spread beyond the central nervous system

(American Cancer Society).

Treatment of Brain Cancer

Treatment for brain tumours depends on a number of factors including the type, location and size of the tumour as well as the patient's age and general health. Treatment methods and schedules differ for children and adults.
(University of California San Francisco).

Treatment of Brain Cancer in Adults

Different types of treatment are available for patients with adult brain and spinal cord tumours. Some treatments are standard (the currently used treatment), and some are being tested in clinical trials. A treatment clinical trial is a research study meant to help improve current treatments or obtain information on new treatments for patients with cancer. When clinical trials show that a new treatment is better than the standard treatment, the new treatment may become the standard treatment. Patients may want to think about taking part in a clinical trial. Some clinical trials are open only to patients who have not started treatment.

The types of standard treatment used:

Watchful waiting - watchful waiting is closely monitoring a patient's condition without giving any treatment until symptoms appear or change.

Surgery - surgery may be used to diagnose and treat adult brain and spinal cord tumours. Even if the doctor removes all the cancer that can be seen at the time of the surgery, some patients may be given chemotherapy or radiation therapy after surgery to kill any cancer cells that are left. Treatment given after the surgery to lower the risk that the cancer will come back, is called adjuvant therapy.

Radiation therapy - radiation therapy is a cancer treatment that uses high-energy x-rays or other types of radiation to kill cancer cells or keep them from growing. There are two types of radiation therapy. External radiation therapy uses a machine outside the body to send radiation toward the cancer. Internal radiation therapy uses a radioactive substance sealed in needles, seeds, wires, or catheters that are placed directly into or near the cancer. The

way the radiation therapy is given depends on the type of tumour and where it is in the brain or spinal cord.

The following ways of giving radiation therapy to the tumour cause less damage to the healthy tissue that is around the tumour:

- 3-dimensional conformal radiation therapy: A procedure that uses a computer to create a 3-dimensional (3-D) picture of the brain or spinal cord tumour. This allows doctors to give the highest possible dose of radiation to the tumour, with as little damage to normal tissue as possible. This type of radiation therapy is also called 3-dimensional radiation therapy and 3D-CRT.
- Intensity-modulated radiation therapy (IMRT): A type of 3-D radiation therapy that uses a computer to make pictures of the size and shape of the brain or spinal cord tumour. Thin beams of radiation of different intensities (strengths) are aimed at the tumour from many angles. This type of radiation therapy causes less damage to healthy tissue near the tumour.
- Stereotactic radiosurgery: A type of radiation therapy that uses a head frame attached to the skull to aim a single large dose of radiation directly to a brain tumour. This causes less damage to nearby healthy tissue. Stereotactic radiosurgery is also called stereotaxic radiosurgery, radiosurgery, and radiation surgery. This procedure does not involve surgery.

Chemotherapy - chemotherapy is a cancer treatment that uses drugs to stop the growth of cancer cells, either by killing the cells or by stopping them from dividing. When chemotherapy is taken by mouth or injected into a vein or muscle, the drugs enter the bloodstream and can reach cancer cells throughout the body (systemic chemotherapy). When chemotherapy is placed directly into the cerebrospinal fluid, an organ, or a body cavity such as the abdomen, the drugs mainly affect cancer cells in those areas (regional chemotherapy).

Combination chemotherapy is treatment using more than one anticancer drug. To treat brain tumours, a wafer that dissolves may be used to deliver an anticancer drug directly to the brain tumour site after the tumour has been removed by surgery. The way the chemotherapy is given depends on the type of tumour and where it is in the brain.

Anticancer drugs given by mouth or vein to treat brain and spinal cord tumours cannot cross the blood-brain barrier and enter the fluid that surrounds the brain and spinal cord. Instead, an anticancer drug is injected into the fluid-filled space to kill cancer cells there. This is called intrathecal chemotherapy.

Chemotherapy wafer implants (Gliadel wafers) - Wafer implants are a way of giving chemotherapy for brain tumours into the area of the tumour. The wafer is made of gel that contains a chemotherapy drug. During brain surgery to remove some or all of a tumour, the doctor puts up to 8 wafers in the space where the tumour was. Over the next few days, the wafers slowly release a chemotherapy drug called carmustine (BCNU) into this area. The wafers dissolve over 2 to 3 weeks.

Using chemotherapy wafers as well as surgery and radiotherapy can help some people with glioma to live longer. At the moment wafers are licensed for people with either:

- High grade malignant glioma
- Glioblastoma multiforme which has come back after treatment

Studies so far have shown that people who have chemotherapy wafers manage with them quite well. But like any chemotherapy treatment, they do have side effects. These include:

- Feeling sick, and being sick
- A skin rash
- Hair loss
- Infections
- Headaches
- Forgetfulness or sleepiness
- Mood changes
- Feeling weak and lacking in energy

There are also side effects after surgery to the brain. Some of these side effects are slightly more likely to happen if you have chemotherapy wafers put in during your surgery. These side effects include weakness or paralysis on one side of your body and convulsions or fits (seizures). But whether you have these side effects will depend more on the position of your tumour, and on the exact type of the operation you have. Your brain surgery wound may also take a bit longer to heal if you have Gliadel wafer treatment.
(Cancer Research UK).

Proton beam radiation therapy - proton beam radiation therapy is a type of high-energy, external radiation therapy that uses streams of protons (small, positively-charged pieces of matter) to make radiation. This type of radiation kills tumour cells with little damage to nearby tissues. It is used to treat cancers of the head, neck, and spine and organs such as the brain, eye, lung, and prostate. Proton beam radiation is different from x-ray radiation.

Biologic therapy - biologic therapy is a treatment that uses the patient's immune system to fight cancer. Substances made by the body or made in a laboratory are used to boost, direct, or restore the body's natural defences against cancer. This type of cancer treatment is also called biotherapy or immunotherapy.

Biologic therapy is being studied for the treatment of some types of brain tumours. Treatments may include the following:

- Tyrosine kinase inhibitor therapy.
- Vascular endothelial growth factor (VEGF) therapy.
- Dendritic cell vaccine therapy.
- Gene therapy.

Targeted therapy- targeted therapy is a type of treatment that uses drugs or other substances to identify and attack specific cancer cells without harming normal cells.

Supportive care is given to lessen the problems caused by the disease or its treatment.

This therapy controls problems or side effects caused by the disease or its treatment and improves quality of life. For brain tumours, supportive care includes drugs to control seizures and fluid build-up or swelling in the brain.
(National Cancer Institute).

Treatment of Brain Cancer in Children
Specific treatment for brain tumours will be determined based on:

- The child's age, overall health, and medical history
- The type, location, and size of the tumour
- Extent of the disease
- The child's tolerance for specific medications, procedures, or therapies
- Expectations for the course of the disease

Treatment may include alone or in combination.

Surgery - surgery is usually the first step in the treatment of brain tumours. The goal is to remove as much of the tumour as possible while maintaining neurological function. Surgery for a biopsy is also done to examine the types of cells the tumour is made of for a diagnosis. This is frequently done if the tumour is in an area with sensitive structures around it that may be injured during removal

Chemotherapy - chemotherapy (chemo) uses anti-cancer drugs that are usually given into a vein (IV) or taken by mouth. These drugs enter the bloodstream and reach almost all areas of the body. However, many chemo drugs are not able to enter the brain and reach tumour cells.

For some brain tumours, the drugs may be given directly into the cerebrospinal fluid (CSF) in the brain or into the spinal canal below the spinal cord. To help with this, a thin tube, known as a *ventricular access catheter*, may be inserted through a small hole in the skull and into a ventricle during a minor operation.

In general, chemotherapy is used for faster growing tumours. Some types of brain tumours, such as medulloblastoma, tend to respond well to chemotherapy. It is most often used along with other types of treatment such as surgery and radiation therapy. It may be used instead of radiation therapy in children 3 years and younger.

Some of the chemotherapy drugs used to treat children with brain tumours include:

- Carboplatin
- Carmustine (BCNU)
- Cisplatin
- Cyclophosphamide
- Etoposide
- Lomustine (CCNU)
- Methotrexate
- Temozolomide
- Thiotepa

- Vincristine

These drugs may be used alone or in various combinations, depending on the type of brain tumour. Chemotherapy is given in cycles. Each cycle generally lasts about 3 to 4 weeks and is followed by a rest period to give the body time to recover.

Radiation therapy - radiation therapy uses high-energy x-rays or small particles to kill cancer cells. This type of treatment is given by a doctor called a *radiation oncologist*. Radiation therapy may be used in different situations:

- After surgery to try to kill any remaining tumor cells
- As part of the main treatment if surgery is not a good option
- To help prevent or relieve symptoms from the tumor

Children younger than 3 years, however, are usually not given radiation because of possible long-term side effects with brain development. Instead, their treatment relies mainly on surgery and chemotherapy. Radiation treatment can also cause some problems in older children. Radiation oncologists try very hard to deliver high doses of radiation to the tumor while limiting the radiation to normal surrounding brain areas as much as possible.

Types of radiation therapy

In most cases, the radiation is focused on the tumor from a source outside the body. This is called *external beam radiation therapy (EBRT)*.

Before your child's treatments start, the radiation team will take careful measurements to determine the correct angles for aiming the radiation beams and the proper dose of radiation. In most cases, the total dose of radiation is divided into daily fractions (usually given Monday through Friday) over several weeks. For each session, your child lies on a special table while a machine delivers the radiation from a precise angle. Each treatment is much like getting an x-ray, but the dose of radiation is much higher. It is not painful. Some younger children might need to be sedated to make sure they don't move during the treatment. Each session lasts about 15 to 30 minutes, but most of the time is spent making sure the radiation is aimed correctly. The actual treatment time each day is much shorter.

Radiation therapy can damage normal brain tissue, so doctors try to deliver high doses of radiation to the tumor with the lowest possible dose to normal surrounding brain areas. Several techniques can help doctors focus the radiation more precisely:

Three-dimensional conformal radiation therapy (3D-CRT): 3D-CRT uses the results of imaging tests such as MRI and special computers to precisely map the location of the tumor. Several radiation beams are then shaped and aimed at the tumor from different directions. Each beam alone is fairly weak, which makes it less likely to damage normal tissues, but the beams converge at the tumor to give a higher dose of radiation there. Your child may be fitted with a plastic mold resembling a body cast to keep him or her in the same position so that the radiation can be aimed more accurately.

Intensity modulated radiation therapy (IMRT): IMRT is an advanced form of 3D therapy. In addition to shaping the beams and aiming them at the tumor from several angles, the intensity (strength) of the beams can be adjusted to limit the dose reaching the most sensitive normal tissues. This may let the doctor deliver a higher dose to the tumor. Many major hospitals and cancer centers now use IMRT.

Conformal proton beam radiation therapy: Proton beam therapy is related to 3D-CRT and uses a similar approach. But instead of using x-rays, it focuses proton beams on the tumor. Protons are positive parts of atoms. Unlike x-rays, which release energy both before and after they hit their target, protons cause little damage to tissues they pass through and then release their energy after traveling a certain distance. Doctors can use this property to deliver more radiation to the tumor and do less damage to nearby normal tissues.

This approach may be more helpful for brain tumors that have distinct edges (such as meningiomas), but it is not clear if this approach will be useful with tumors whose edges are mixed with normal brain tissue (such as astrocytomas or glioblastomas). There are only a handful of proton beam centers in the United States at this time.

Stereotactic radiosurgery/stereotactic radiotherapy: This type of treatment delivers a large, precise radiation dose to the tumor area in a single session (radiosurgery) or in a few sessions (radiotherapy). (There is no actual surgery in this treatment.) It may be useful for some tumors in parts of the brain or spinal cord that can't be treated with surgery or when a child is not healthy enough for surgery.

First, a head frame is attached to the skull to help precisely aim the radiation beams. Once the exact location of the tumor is known from CT or MRI scans, radiation is focused at the tumor from many different angles. This can be done in 2 ways.

In one approach, radiation beams are focused at the tumor from hundreds of different angles for a short period of time. Each beam alone is weak, but they all converge at the tumor to give a higher dose of radiation. An example of such a machine is the Gamma Knife.

Another approach uses a movable linear accelerator (a machine that creates radiation) that is controlled by a computer. Instead of delivering many beams at once, this machine moves around the head to deliver radiation to the tumor from many different angles. Several machines with names such as X-Knife, CyberKnife, and Clinac are used in this way for stereotactic radiosurgery.

Stereotactic radiosurgery typically delivers the whole radiation dose in a single session, though it may be repeated if needed. Sometimes doctors give the radiation in several treatments to deliver the same or a slightly higher dose. This is called *fractionated radiosurgery* or *stereotactic radiotherapy*.

Brachytherapy (internal radiotherapy): Unlike the external radiation approaches above, brachytherapy involves inserting radioactive material directly into or near the tumor. The radiation it gives off travels a very short distance, so it affects only the tumor. This technique is most often used along with external radiation. It provides a high dose of radiation at the tumor site, while the external radiation treats nearby areas with a lower dose.

Whole brain and spinal cord radiation therapy (craniospinal radiation): If tests such as an MRI scan or lumbar puncture find the tumor has spread along the covering of the spinal cord (meninges) or into the surrounding cerebrospinal fluid, then radiation may be given to the whole brain and spinal cord. Some tumors such as ependymomas and medulloblastomas are more likely to spread this way, and therefore may require craniospinal radiation.

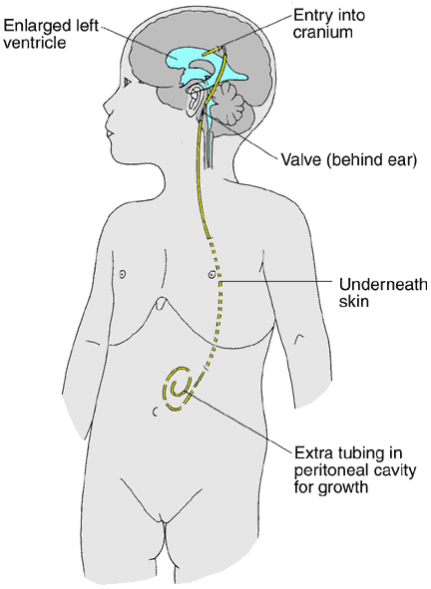
Steroids - to treat and prevent swelling especially in the brain

Anti-seizure medication - to treat and prevent seizures associated with intracranial pressure

Ventriculoperitoneal shunt (also called a VP shunt.) - a VP shunt may be placed in the head to drain excess fluid from inside the brain. A VP shunt helps control the pressure inside the brain

[Picture Credit: Ventriculoperitoneal Shunt]

Ventriculoperitoneal Shunt Placement



Lumbar puncture/spinal tap - to test pressure in the central nervous system, to look for suspicious cells, and give medication if needed. There may be situations in which a lumbar puncture would be contraindicated in brain tumours

Bone marrow transplantation - the goal of a bone marrow transplant is to cure many diseases and types of cancer. Some of the diseases that have been treated with bone marrow transplant include the following:

- leukaemia
- lymphomas
- some solid tumours i.e., neuroblastoma, rhabdomyosarcoma, brain tumours
- aplastic anaemia
- immune deficiencies (severe combined immunodeficiency disorder, Wiskott-Aldrich syndrome)
- sickle cell disease
- thalassemia
- Blackfan-Diamond anaemia
- metabolic/storage diseases i.e., Hurler's syndrome, adrenoleukodystrophy disorder
- cancer of the kidneys

Supportive care - for the side effects of the tumour or treatment

Rehabilitation - to regain lost motor skills and muscle strength; speech, physical, and occupational therapists may be involved in the healthcare team

Antibiotics - to treat and prevent infections

Continuous follow-up care - to manage disease, detect recurrence of the tumour and to manage late effects of treatment
(Children's Hospital of Wisconsin; Lucile Packard Children's Hospital at Stanford; American Cancer Society; MacMillan Cancer Support).

About Clinical Trials
Clinical trials are research studies that involve people. These studies test new ways to prevent, detect, diagnose, or treat diseases. People who take part in cancer clinical trials have an opportunity to contribute to scientists' knowledge about cancer and to help in the development of improved cancer treatments. They also receive state-of-the-art care from cancer experts.

Types of Clinical Trials
Cancer clinical trials differ according to their primary purpose. They include the following types:

Treatment - these trials test the effectiveness of new treatments or new ways of using current treatments in people who have cancer. The treatments tested may include new drugs or new combinations of currently used drugs, new surgery or radiation therapy techniques, and vaccines or other treatments that stimulate a person's immune system to fight cancer. Combinations of different treatment types may also be tested in these trials.

Prevention - these trials test new interventions that may lower the risk of developing certain types of cancer. Most cancer prevention trials involve healthy people who have not had cancer; however, they often only include people who have a higher than average risk of developing a specific type of cancer. Some cancer prevention trials involve people who have had cancer in the past; these trials test interventions that may help prevent the return (recurrence) of the original cancer or reduce the chance of developing a new type of cancer.

Screening - these trials test new ways of finding cancer early. When cancer is found early, it may be easier to treat and there may be a better chance of long-term survival. Cancer screening trials usually involve people who do not have any signs or symptoms of cancer. However, participation in these trials is often limited to people who have a higher than average risk of developing a certain type of cancer because they have a family history of that type of cancer or they have a history of exposure to cancer-causing substances (e.g., cigarette smoke).

Diagnostic - these trials study new tests or procedures that may help identify, or diagnose, cancer more accurately. Diagnostic trials usually involve people who have some signs or symptoms of cancer.

Quality of life or supportive care - these trials focus on the comfort and quality of life of cancer patients and cancer survivors. New ways to decrease the number or severity of side effects of cancer or its treatment are often studied in these trials. How a specific type of cancer or its treatment affects a person's everyday life may also be studied.

Where Clinical Trials are Conducted

Cancer clinical trials take place in cities and towns in doctors' offices, cancer centres and other medical centres, community hospitals and clinics. A single trial may take place at one or two specialised medical centres only or at hundreds of offices, hospitals, and centres.

Each clinical trial is managed by a research team that can include doctors, nurses, research assistants, data analysts, and other specialists. The research team works closely with other health professionals, including other doctors and nurses, laboratory technicians, pharmacists, dieticians, and social workers, to provide medical and supportive care to people who take part in a clinical trial.

Research Team

The research team closely monitors the health of people taking part in the clinical trial and gives them specific instructions when necessary. To ensure the reliability of the trial's results, it is important for the participants to follow the research team's instructions. The instructions may include keeping logs or answering questionnaires. The research team may also seek to contact the participants regularly after the trial ends to get updates on their health.

Clinical Trial Protocol

Every clinical trial has a protocol, or action plan, that describes what will be done in the trial, how the trial will be conducted, and why each part of the trial is necessary. The protocol also includes guidelines for who can and cannot participate in the trial. These guidelines, called eligibility criteria, describe the characteristics that all interested people must have before they can take part in the trial. Eligibility criteria can include age, sex, medical history, and current health status. Eligibility criteria for cancer treatment trials often include the type and stage of cancer, as well as the type(s) of cancer treatment already received.

Enrolling people who have similar characteristics helps ensure that the outcome of a trial is due to the intervention being tested and not to other factors. In this way, eligibility criteria help researchers obtain the most accurate and meaningful results possible.

National and International Regulations

National and international regulations and policies have been developed to help ensure that research involving people is conducted according to strict scientific and ethical principles. In these regulations and policies, people who participate in research are usually referred to as "human subjects."

Informed Consent

Informed consent is a process through which people learn the important facts about a clinical trial to help them decide whether or not to take part in it, and continue to learn new information about the trial that helps them decide whether or not to continue participating in it.

During the first part of the informed consent process, people are given detailed information about a trial, including information about the purpose of the trial, the tests and other procedures that will be required, and the possible benefits and harms of taking part in the trial. Besides talking with a doctor or nurse, potential trial participants are given a form,

called an informed consent form, that provides information about the trial in writing. People who agree to take part in the trial are asked to sign the form. However, signing this form does not mean that a person must remain in the trial. Anyone can choose to leave a trial at any time—either before it starts or at any time during the trial or during the follow-up period. It is important for people who decide to leave a trial to get information from the research team about how to leave the trial safely.

The informed consent process continues throughout a trial. If new benefits, risks, or side effects are discovered during the course of a trial, the researchers must inform the participants so they can decide whether or not they want to continue to take part in the trial. In some cases, participants who want to continue to take part in a trial may be asked to sign a new informed consent form.

New interventions are often studied in a stepwise fashion, with each step representing a different "phase" in the clinical research process. The following phases are used for cancer treatment trials:

Phases of a Clinical Trial

Phase 0. These trials represent the earliest step in testing new treatments in humans. In a phase 0 trial, a very small dose of a chemical or biologic agent is given to a small number of people (approximately 10-15) to gather preliminary information about how the agent is processed by the body (pharmacokinetics) and how the agent affects the body (pharmacodynamics). Because the agents are given in such small amounts, no information is obtained about their safety or effectiveness in treating cancer. Phase 0 trials are also called micro-dosing studies, exploratory Investigational New Drug (IND) trials, or early phase I trials. The people who take part in these trials usually have advanced disease, and no known, effective treatment options are available to them.

Phase I (also called phase 1). These trials are conducted mainly to evaluate the safety of chemical or biologic agents or other types of interventions (e.g., a new radiation therapy technique). They help determine the maximum dose that can be given safely (also known as the maximum tolerated dose) and whether an intervention causes harmful side effects. Phase I trials enrol small numbers of people (20 or more) who have advanced cancer that cannot be treated effectively with standard (usual) treatments or for which no standard treatment exists. Although evaluating the effectiveness of interventions is not a primary goal of these trials, doctors do look for evidence that the interventions might be useful as treatments.

Phase II (also called phase 2). These trials test the effectiveness of interventions in people who have a specific type of cancer or related cancers. They also continue to look at the safety of interventions. Phase II trials usually enrol fewer than 100 people but may include as many as 300. The people who participate in phase II trials may or may not have been treated previously with standard therapy for their type of cancer. If a person has been treated previously, their eligibility to participate in a specific trial may depend on the type and amount of prior treatment they received. Although phase II trials can give some indication of whether or not an intervention works, they are almost never designed to show whether an intervention is better than standard therapy.

Phase III (also called phase 3). These trials compare the effectiveness of a new intervention, or new use of an existing intervention, with the current standard of care (usual treatment) for a particular type of cancer. Phase III trials also examine how the side effects of the new intervention compare with those of the usual treatment. If the new intervention is more effective than the usual treatment and/or is easier to tolerate, it may become the new standard of care.

Phase III trials usually involve large groups of people (100 to several thousand), who are randomly assigned to one of two treatment groups, or "trial arms": (1) a control group, in which everyone in the group receives usual treatment for their type of cancer, or 2) an investigational or experimental group, in which everyone in the group receives the new intervention or new use of an existing intervention. The trial participants are assigned to their individual groups by random assignment, or randomisation. Randomisation helps ensure that the groups have similar characteristics. This balance is necessary so the researchers can have confidence that any differences they observe in how the two groups respond to the treatments they receive are due to the treatments and not to other differences between the groups.

Randomisation is usually done by a computer program to ensure that human choices do not influence the assignment to groups. The trial participants cannot request to be in a particular group, and the researchers cannot influence how people are assigned to the groups. Usually, neither the participants nor their doctors know what treatment the participants are receiving.

People who participate in phase III trials may or may not have been treated previously. If they have been treated previously, their eligibility to participate in a specific trial may depend on the type and the amount of prior treatment they received.

In most cases, an intervention will move into phase III testing only after it has shown promise in phase I and phase II trials.

Phase IV (also called phase 4). These trials further evaluate the effectiveness and long-term safety of drugs or other interventions. They usually take place after a drug or intervention has been approved by the medicine regulatory office for standard use. Several hundred to several thousand people may take part in a phase IV trial. These trials are also known as post-marketing surveillance trials. They are generally sponsored by drug companies.

Sometimes clinical trial phases may be combined (e.g., phase I/II or phase II/III trials) to minimize the risks to participants and/or to allow faster development of a new intervention.

Although treatment trials are always assigned a phase, other clinical trials (e.g., screening, prevention, diagnostic, and quality-of-life trials) may not be labelled this way.

<u>Use of Placebos</u>

The use of placebos as comparison or "control" interventions in cancer treatment trials is rare. If a placebo is used by itself, it is because no standard treatment exists. In this case, a trial would compare the effects of a new treatment with the effects of a placebo. More often, however, placebos are given along with a standard treatment. For example, a trial might compare the effects of a standard treatment plus a new treatment with the effects of the same standard treatment plus a placebo.

Possible benefits of taking part in a clinical trial

The benefits of participating in a clinical trial include the following:

- Trial participants have access to promising new interventions that are generally not available outside of a clinical trial.
- The intervention being studied may be more effective than standard therapy. If it is more effective, trial participants may be the first to benefit from it.
- Trial participants receive regular and careful medical attention from a research team that includes doctors, nurses, and other health professionals.
- The results of the trial may help other people who need cancer treatment in the future.
- Trial participants are helping scientists learn more about cancer (e.g., how it grows, how it acts, and what influences its growth and spread).

Potential harms associated with taking part in a clinical trial

The potential harms of participating in a clinical trial include the following:

- The new intervention being studied may not be better than standard therapy, or it may have harmful side effects that doctors do not expect or that are worse than those associated with standard therapy.
- Trial participants may be required to make more visits to the doctor than they would if they were not in a clinical trial and/or may need to travel farther for those visits.

Correlative research studies, and how they are related to clinical trials

In addition to answering questions about the effectiveness of new interventions, clinical trials provide the opportunity for additional research. These additional research studies, called correlative or ancillary studies, may use blood, tumour, or other tissue specimens (also known as 'biospecimens') obtained from trial participants before, during, or after treatment. For example, the molecular characteristics of tumour specimens collected during a trial might be analysed to see if there is a relationship between the presence of a certain gene mutation or the amount of a specific protein and how trial participants responded to the treatment they received. Information obtained from these types of studies could lead to more accurate predictions about how individual patients will respond to certain cancer treatments, improved ways of finding cancer earlier, new methods of identifying people who have an increased risk of cancer, and new approaches to try to prevent cancer.

Clinical trial participants must give their permission before biospecimens obtained from them can be used for research purposes.

When a clinical trial is over

After a clinical trial is completed, the researchers look carefully at the data collected during the trial to understand the meaning of the findings and to plan further research. After a phase I or phase II trial, the researchers decide whether or not to move on to the next phase or stop testing the intervention because it was not safe or effective. When a phase III trial is completed, the researchers analyse the data to determine whether the results have medical importance and, if so, whether the tested intervention could become the new standard of care.

The results of clinical trials are often published in peer-reviewed scientific journals. Peer review is a process by which cancer research experts not associated with a trial review the study report before it is published to make sure that the data are sound, the data analysis was performed correctly, and the conclusions are appropriate. If the results are particularly important, they may be reported by the media and discussed at a scientific meeting and by patient advocacy groups before they are published in a journal. Once a new intervention has proven safe and effective in a clinical trial, it may become a new standard of care.
(National Cancer Institute).

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World Health Organization Classification of the Tumours of the Central Nervous System

The following is a simplified version of the last WHO classification of the tumours of the central nervous system. For each tumour there are the WHO official name, the ICD-O code (with Arabic numeral, where /0 indicates 'benign' tumour, /3 malignant tumour and /1 borderline tumour), and with Roman numeral the WHO Grade (a parameter connected with the 'aggressiveness' of the tumour).

1. Tumours of neuroepithelial tissue

1.1. **Astrocytic tumours**
1.1.1 Pilocytic astrocytoma (ICD-O 9421/1, WHO grade I)
1.1.1a *Pilomyxoid astrocytoma* (ICD-O 9425/3, WHO grade II)
1.1.2 Subependymal giant cell astrocytoma (ICD-O 9384/1, WHO grade I)
1.1.3 Pleomorphic xanthoastrocytoma (ICD-O 9424/3, WHO grade II)
1.1.4 Diffuse astrocytoma (ICD-O 9400/3, WHO grade II)
1.1.5 Anaplastic astrocytoma (ICD-O 9401/3, WHO grade III)
1.1.6.Glioblastoma (ICD-O 9440/3, WHO grade IV)
1.1.6a *Giant cell glioblastoma* (ICD-O 9441/3, WHO grade IV)
1.1.6b *Gliosarcoma* (ICD-O 9442/3, WHO grade IV)
1.1.7 Gliomatosis cerebri (ICD-O 9381/3, WHO grade III)

1.2. **Oligodendroglial tumours**
1.2.1 Oligodendroglioma (ICD-O 9450/3, WHO grade II)
1.2.2 Anaplastic oligodendroglioma (ICD-O 9451/3, WHO grade III)

1.3. **Oligoastrocytic tumours**
1.3.1 Oligoastrocytoma (ICD-O 9382/3, WHO grade II)
1.3.2 Anaplastic oligoastrocytoma (ICD-O 9382/3, WHO grade III)

1.4. **Ependymal tumours**
1.4.1 Subependymoma (ICD-O 9383/1, WHO grade I)
1.4.2 Myxopapillary ependymoma (ICD-O 9394/1, WHO grade I)
1.4.3 Ependymoma (ICD-O 9391/3, WHO grade II)
1.4.4 Anaplastic ependymoma (ICD-O 9392/3, WHO grade III)

1.5. **Choroid plexus tumours**
1.5.1 Choroid plexus papilloma (ICD-O 9390/0, WHO grade I)
1.5.2 Atypical choroid plexus papilloma (ICD-O 9390/1, WHO grade II)
1.5.3 Choroid plexus carcinoma (ICD-O 9390/3, WHO grade III)

1.6. **Other neuroepithelial tumours**
1.6.1 Astroblastoma (ICD-O 9430/3, WHO grade I)
1.6.2 Chordoid glioma of the third ventricle (ICD-O 9444/1, WHO grade II)
1.6.3 Angiocentric glioma (ICD-O 9431/1, WHO grade I)

1.7. **Neuronal and mixed neuronal-glial tumours**
1.7.1 Dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos) (ICD-O 9493/0)
1.7.2 Desmoplastic infantile astrocytoma/ganglioglioma (ICD-O 9412/1, WHO grade I)
1.7.3 Dysembryoplastic neuroepithelial tumour (ICD-O 9413/0, WHO grade I)
1.7.4 Gangliocytoma (ICD-O 9492/0, WHO grade I)
1.7.5 Ganglioglioma (ICD-O 9505/1, WHO grade I)
1.7.6 Anaplastic ganglioglioma (ICD-O 9505/3, WHO grade III)
1.7.7 Central neurocytoma (ICD-O 9506/1, WHO grade II)
1.7.8 Extraventricular neurocytoma (ICD-O 9506/1, WHO grade II)
1.7.9 Cerebellar liponeurocytoma (ICD-O 9506/1, WHO grade II)
1.7.10 Papillary glioneuronal tumour (ICD-O 9509/1, WHO grade I)
1.7.11 Rosette-forming glioneuronal tumour of the fourth ventricle (ICD-O 9509/1, WHO grade I)
1.7.12 Paraganglioma (ICD-O 8680/1, WHO grade I)

1.8. **Tumours of the pineal region**
1.8.1 Pineocytoma (ICD-O 9361/1, WHO grade I)
1.8.2 Pineal parenchymal tumour of intermediate differentiation (ICD-O 9362/3, WHO grade II, III)
1.8.3 Pineoblastoma (ICD-O 9362/3, WHO grade IV)
1.8.4 Papillary tumors of the pineal region (ICD-O 9395/3, WHO grade II, III)

1.9. **Embryonal tumours**
1.9.1 Medulloblastoma (ICD-O 9470/3, WHO grade IV)
1.9.1b *Medulloblastoma with extensive nodularity* (ICD-O 9471/3, WHO grade IV)
1.9.1c *Anaplastic medulloblastoma* (ICD-O 9474/3, WHO grade IV)
1.9.2. CNS Primitive neuroectodermal tumour (ICD-O 9473/3, WHO grade IV)
1.9.2a *CNS Neuroblastoma* (ICD-O 9500/3, WHO grade IV)
1.9.3 Atypical teratoid/rhabdoid tumour (ICD-O 9508/3, WHO grade IV)

2. Tumours of cranial and paraspinal nerves

2.1 Schwannoma (IDC-O 9560/0, WHO grade I)
2.2 Neurofibroma (IDC-O 9540/0, WHO grade I)
2.3 Perineurioma (IDC-O 9571/0, 9571/3, WHO grade I, II, III)
2.4 Malignant peripheral nerve sheath tumour (MPNST) (IDC-O 9540/3, WHO grade II, III, IV)

3. Tumours of the meninges

3.1 **Tumours of meningothelial cells**
3.1.1 Meningioma (IDC-O 9530/0, WHO grade I)
3.1.1l *Atypical meningioma* (IDC-O 9539/1, WHO grade II)
3.1.1o *Anaplastic meningioma* (IDC-O 9530/3, WHO grade III)

3.2 **Mesenchymal tumours**
3.2.1 Lipoma (IDC-O 8850/0)
3.2.2 Angiolipoma (IDC-O 8861/0)
3.2.3 Hibernoma (IDC-O 8880/0)
3.2.4 Liposarcoma (IDC-O 8850/3)
3.2.5 Solitary fibrous tumour (IDC-O 8815/0)

3.2.6 Fibrosarcoma (IDC-O 8810/3)
3.2.7 Malignant fibrous histiocytoma (IDC-O 8830/3)
3.2.8 Leiomyoma (IDC-O 8890/0)
3.2.9 Leiomyosarcoma (IDC-O 8890/3)
3.2.10 Rhabdomyoma (IDC-O 8900/0)
3.2.11 Rhabdomyosarcoma (IDC-O 8900/3)
3.2.12 Chondroma (IDC-O 9220/0)
3.2.13 Chondrosarcoma (IDC-O 9220/3)
3.2.14 Osteoma (IDC-O 9180/0)
3.2.15 Osteosarcoma (IDC-O 9180/3)
3.2.16 Osteochondroma (IDC-O 9210/0)
3.2.17 Haemangioma (IDC-O 9120/0)
3.2.18 Epithelioid hemangioendothelioma (IDC-O 9133/1)
3.2.19 Haemangiopericytoma (IDC-O 9150/1, WHO grade II)
3.2.20 Anaplastic haemangiopericytoma (IDC-O 9150/3, WHO grade III)
3.2.21 Angiosarcoma (IDC-O 9120/3)
3.2.22 Kaposi Sarcoma (IDC-O 9140/3)
3.2.23 Ewing Sarcoma - PNET (IDC-O 9364/3)

3.3 **Primary melanocytic lesions**
3.3.1 Diffuse melanocytosis (IDC-O 8728/0)
3.3.2 Melanocytoma (IDC-O 8728/1)
3.3.3 Malignant melanoma (IDC-O 8720/3)
3.3.4 Meningeal melanomatosis (IDC-O 8728/3)

3.4 **Other neoplasms related to the meninges**
3.4.1 Haemangioblastoma (IDC-O 9161/1, WHO grade I)

4. Tumors of the haematopoietic system

4.1 Malignant Lymphomas (IDC-O 9590/3)
4.2 Plasmocytoma (IDC-O 9731/3)
4.3 Granulocytic sarcoma (IDC-O 9930/3)

5. Germ cell tumours

5.1 Germinoma (IDC-O 9064/3)
5.2 Embryonal carcinoma (IDC-O 9070/3)
5.3 Yolk sac tumour (IDC-O 9071/3)
5.4 Choriocarcinoma (IDC-O 9100/3)
5.5 Teratoma (IDC-O 9080/1)
5.6 Mixed germ cell tumours (IDC-O 9085/3)

6. Tumours of the sellar region

6.1 Craniopharyngioma (IDC-O 9350/1, WHO grade I)
6.2 Granular cell tumour (IDC-O 9582/0, WHO grade I)
6.3 Pituicytoma (IDC-O 9432/1, WHO grade I)
6.4 Spindle cell oncocytoma of the adenohypophysis (IDC-O 8991/0, WHO grade I)

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