

# Glioblastoma

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Glioblastomas are the most common primary brain tumours in adults. (Primary means the tumour starts in the brain, rather than starting elsewhere in the body then spreading to the brain). It is the most aggressive form of adult brain tumour.

The information in this fact sheet gives an overview of glioblastoma in adults and answers some of the questions you may have about this type of tumour.

## **In this fact sheet:**

- What is a glioblastoma?
- What causes glioblastoma?
- How are glioblastoma diagnosed?
- How are glioblastoma treated?
- What is the prognosis for glioblastoma?
- How common are glioblastoma?

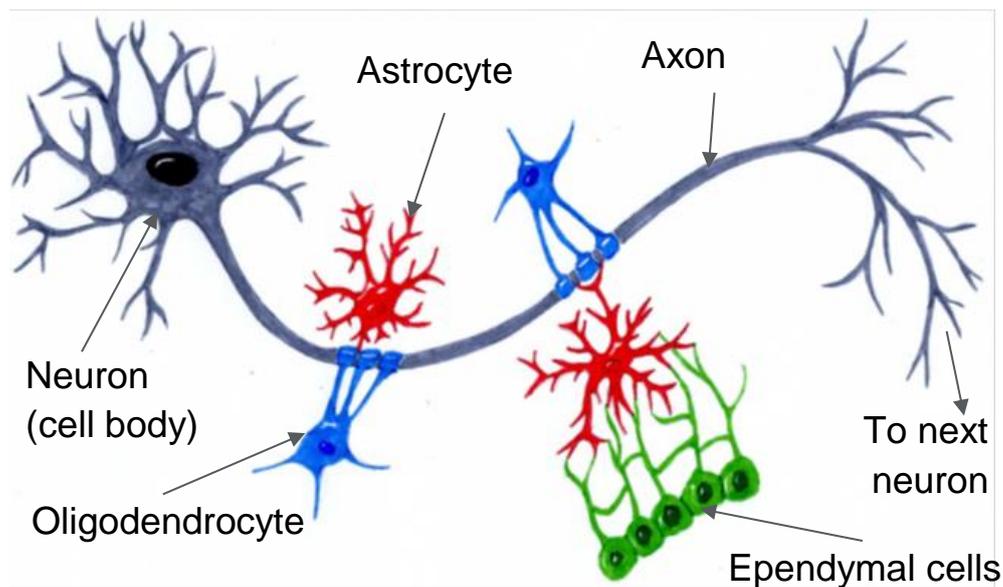
## **What is a glioblastoma?**

Glioblastoma is the more common name for a type of brain tumour called a grade 4 astrocytoma. (You may sometimes hear it called glioblastoma multiforme, or GBM for short, though these terms are less used nowadays).

## What is a grade 4 astrocytoma (glioblastoma)?

Throughout the brain and spinal cord we all have nerve cells called 'neurons' which transmit 'messages' (electrical and chemical signals). Surrounding our neurons are cells called glial cells. Glial cells provide our neurons with oxygen and nutrients and remove dead cells, supporting and protecting the neurons. Glial cells are much smaller than neurons and we have many more glial cells than neurons.

There are different types of glial cell, each of which play a different role in supporting the neurons. The main types are astrocytes, oligodendrocytes and ependymal cells. (See diagram below).



Brain tumours can develop from any of these types of glial cells. (Glioma is the collective name for this group of tumours, so you may also hear glioblastomas referred to as a type of glioma).

However, gliomas will also have a more specific name depending on which type of glial cell the tumour grows from. Brain tumours that grow from astrocytes will be called astrocytomas; brain tumours that grow from oligodendrocytes will be called oligodendrogliomas; and tumours that grow from ependymal cells will be called ependymomas.

Astrocytomas are the most common type of glioma.

Astrocytomas themselves are divided into 4 grade, according to how the tumours behave:

- Pilocytic astrocytoma (Grade 1)
- Diffuse or low grade astrocytoma (Grade 2)

- Anaplastic astrocytoma (Grade 3)
- Grade 4 astrocytoma, or glioblastoma

(Brain tumours are graded by the World Health Organisation (WHO) from 1- 4 according to their behaviour, such as the speed at which they grow and how likely they are to spread. Grades 1 and 2 are low-grade, slow-growing and sometimes referred to as benign; grades 3 and 4 are high-grade, fast-growing and often referred to as malignant. For more information, see our 'What is a brain tumour?' fact sheet).

In summary, a glioblastoma is a high grade (Grade 4), fast growing tumour that develops from cells in the brain known as astrocytes.

## **Types of glioblastoma (grade 4 astrocytoma)**

There are two main types of glioblastomas: primary (sometimes called 'de novo' meaning 'from new') and secondary.

### **Primary glioblastoma**

The use of the word 'primary' here can be a bit confusing, as it is used differently when referring to primary brain tumours in general.

'Primary brain tumours' start in the brain, rather than spreading from another part of the body. A 'primary glioblastoma' however, is a glioblastoma which develops 'spontaneously'.

This means that the first appearance of the tumour is as a glioblastoma.

Primary glioblastomas usually grow rapidly. There can be less than three months between no obvious brain abnormality to a fully developed tumour.

### **Secondary glioblastoma**

In contrast, secondary glioblastomas develop from lower grade brain tumours i.e. grade 2 diffuse astrocytomas or grade 3 anaplastic astrocytomas.

The time these take to go from the earliest detection of a brain tumour to glioblastoma varies considerably - from less than one to more than ten years. The change from these other tumour types to glioblastoma can be rapid however, once it occurs. They have a much better prognosis than primary glioblastomas.

### **Glioblastoma sub-types**

Research has shown that glioblastomas can be divided into different sub-types according to the type of genetic changes they show within the tumour cells.

The most commonly used scheme, provided by The Cancer Genome Atlas, divides glioblastomas into four sub-types: 'Classical', 'Proneural', 'Mesenchymal' and 'Neural' groups.

Another classification system is by the so-called 'methylation status' of the tumour. This refers to the way a particular gene called MGMT is 'expressed' (i.e. how it functions). (See the 'How are glioblastomas treated?' section later in this fact sheet).

In addition to this, glioblastomas are 'genetically diverse'. This means that the cells within the tumour are not all of the same type, and each person's tumour will be different. You may hear this referred to as 'heterogeneity'.

## **Causes of glioblastoma**

It is still not known exactly why glioblastomas begin to grow. The reason for their development is under ongoing investigation, and research is looking at genetic and molecular changes in the cells.

Normal cells grow, divide and die in a controlled way, in response to signals from your genes. These signals tell the cells when to grow and when to stop growing. If these signals are absent, our bodies also have further 'checkpoints' to limit the ability of cells to divide in an uncontrolled way.

Mutations in specific genes can lead to tumour growth by causing cells to behave as if they are receiving a growth signal even when they are not, or by inactivating the checkpoints that would normally stop the cells from dividing. As a result the cells continue to divide and can develop into a tumour.

Research is gradually discovering genes which are involved in different types of tumours.

In glioblastoma, 70–80% are characterized by loss of chromosome 10 and the genes it carries, and gain of chromosome 7. (Chromosomes are the parts of the cell which carry the genes. We have 23 pairs of chromosomes, numbered 1 - 22, plus X and/or Y in every cell).

At the level of the genes (which are often known by abbreviations of their name), several genes are coming to the fore as possibly being involved in the initial development of glioblastomas. These include the checkpoint genes 'TP53', 'PTEN', 'NF1' and 'p16-INK4A' which appear to be inactivated

in some glioblastomas; and also the growth-signal stimulating genes, 'EGFR' and 'PDGFRA', that have been found to be over-activated in some glioblastomas.

Each of the four sub-types of glioblastoma has a different level of mutation in these genes. This may be able to be used in the future, after more research, to predict how people may respond to certain treatments and also the length of their overall survival.

Research, including pioneering programmes funded by The Brain Tumour Charity, is also looking at how the genetic and molecular changes in tumour cells affect the ongoing development and growth of the tumour development (as opposed to why these changes occur in the first place).

These findings could lead to treatments that are tailored to the genetic make-up of each patient's tumour.

## **How are glioblastomas diagnosed?**

If your doctor (GP or A&E doctor) suspects you have a brain tumour, they may examine the back of your eye and look for changes caused by increased pressure in the skull. If they still suspect a tumour, they will refer you to a specialist - a neurologist or neurosurgeon (specialists in brain and nerve disorders).

### **Neurological examination**

The specialist will ask questions about your health and give you a physical examination. They will also test your nervous system (called a 'neurological examination'). This involves looking at your vision, hearing, alertness, muscle strength, co-ordination and reflexes.

They may also look at the back of your eyes to see if there is any swelling of the optic disc. (The optic disc is where the optic nerve from the brain enters the eye). Any swelling is a sign of raised pressure inside the skull, which could be a sign of a brain tumour.

### **Scans**

You will then have one or more further tests, such as an MRI (magnetic resonance imaging) or CT (computerised tomography) scan to establish whether a brain tumour is present. (For more information, please see the 'Scans' fact sheet).

For some people, their first symptom may be a seizure, so they are seen as an emergency. In this case they may be given a scan as their first test, after which their case will be referred to a neuro-oncology 'MDT' (multi-disciplinary team) followed by a consultation with the neurologist/neurosurgeon. (Please see 'The Multi-Disciplinary Team (MDT)' fact sheet for more information).

Some GPs can also refer you directly for a scan.

## **Biopsy**

If, following the scan, a tumour is found and the tumour is in

an area of the brain which can be operated on, a biopsy (small sample of the tumour) may be taken from your tumour. It is important to realise that a biopsy is an operation that takes several hours. Any risks will be explained to you by your surgical team.

## **Surgery**

Alternatively to a biopsy, and if possible, the surgical removal of as much of the main part of the tumour will be undertaken at the same time. This is known as 'debulking'. It is difficult to remove the whole tumour in the case of glioblastomas as they are 'diffuse', meaning they have threadlike elements that spread out into the brain.

## **Biobanking**

In both cases of biopsy or surgery, you may like to ask, before your operation, about the possibility of 'biobanking' some of the tissue from your tumour.

A key to accelerating research towards improving survival and quality of life for people with brain tumours, is for researchers to have access to centralised tissue banks containing patients' tumour samples so they can carry out more research.

Currently there is no centralised tissue bank and not all centres are able to take and store samples, as they need to be licenced under the Human Tissue Act, with ethical approvals in place. As a result, routine collection of tissue for research is not yet

a reality.

The Brain Tumour Charity is committed to establishing a centralised tissue bank with simpler access arrangements. As there are many types of brain tumour, some of which are very rare, we need to ensure that we learn from every patient. This will require systems and cultural changes in the approach to collecting samples. By asking about biobanking some of your tumour, you may help with the move towards this.

Speak to us and to your health team if this is something you are interested in doing. (The Brain Tumour Charity Support & Info Line - 0800 800 0004 or [support@thebraintumourcharity.org](mailto:support@thebraintumourcharity.org))

## **Laboratory analysis**

Following biopsy or surgery, cells from the tumour will be analysed in a laboratory by a neuropathologist. (Please see 'The Multi-Disciplinary Team (MDT)' fact sheet).

The neuropathologist will examine the cells, looking for particular cell patterns. In a glioblastoma, they would be looking for the following:

- glial cells that have unusual shapes or characteristics - these are called 'anaplastic glial cells'
- cells that are dividing rapidly - this is called 'mitotic activity'
- the appearance of new and extensive blood-transport pathways that are bringing blood to the tumour allowing it to grow faster - this is called 'microvascular proliferation'
- large zones of uncontrolled cell death - this is called 'cell necrosis'

If these are found, the diagnosis will be glioblastoma.

It may be that other patterns are also seen, which are characteristic of another type of tumour. In such instances of a 'mixed cell tumour', the diagnosis given is that of the highest grade tumour cells.

It is important that a detailed diagnosis of the exact tumour type is made as this will allow your medical team to determine the best course of treatment for you.

## **Biomarker testing**

As part of this analysis, you may like to ask about 'biomarker testing'. This is where the doctors look for markers (changes) in certain genes in the tumour cells that may indicate how well you will respond to certain treatments.

For people with glioblastomas, there is a biomarker test called MGMT, which can show how well you are likely to respond to the chemotherapy drug temozolomide. (See 'Temozolomide and the MGMT gene' in the 'Effectiveness of treatment' section in this fact sheet).

Some neuro-oncology centres carry out this test as a matter of course. You can ask if this is done in your centre and for the results if it is. If it is not routinely done at your centre and you are interested in having this test, ask your health team. (Please also see the 'Biomarkers' fact sheet for more information).

## **How are glioblastomas treated?**

The current 'gold standard' (ideal) treatment for patients diagnosed with glioblastoma is surgery to remove as much of the tumour as possible, followed by chemoradiation (chemotherapy and radiotherapy) as soon as the surgical wound is healed. (For more information about these therapies, please see the 'Chemotherapy' and the 'Radiotherapy' fact sheets).

### **Surgery**

As glioblastomas are diffuse (have threadlike tendrils extending into other areas of the brain) it is not possible to remove all of the tumour, but your surgeon will try to remove as much as it is possible to do safely.

However, it can be difficult to identify the edges of the main part of the tumour. Recent advances (funded by The Brain Tumour Charity and Cancer Research UK) have improved surgeons' ability to remove more of the tumour.

Prior to surgery, patients are given a drink containing a substance called 5-ALA. Sometimes known as the 'pink drink', even though it is not pink, this causes the tumour cells in the brain to glow pink under ultra-violet light. This allows the surgeon to tell the tumour cells apart from the normal cells and so remove more of the tumour.

The extent to which the tumour can be removed safely will also depend on its location in the brain i.e. how deep in the brain it is and whether it is near to any important parts of the brain.

### **Chemoradiation**

The chemoradiation is used to slow the growth of any tumour cells that cannot be removed by surgery.

Chemoradiation comprises radiotherapy over a period of weeks and rounds of the chemotherapy drug temozolomide (TMZ). Temozolomide works by stopping tumour cells from making new DNA (the material that carries all their genetic information). If they cannot make DNA, they cannot divide into two new tumour cells, so the tumour cannot grow. TMZ is also thought to sensitise the tumour cells to the radiation.

Temozolomide is usually taken for a further 6 months after radiotherapy has finished.

## **Effectiveness of treatment**

Unfortunately glioblastomas are aggressive tumours and often appear resistant to treatment. It is believed that the heterogeneity (variety) of cells in a glioblastoma is one of the reasons for this. We do not yet have effective treatments against all the cell types in the tumour. As a result not all cell-types will be targeted by the current treatments, allowing the tumour to regrow.

Also some of the tumour cells appear to be stem-cell-like. Stem cells are unspecialised cells that can grow into any cell-type and have the ability to regenerate. This suggests that these tumour cells play a role in tumour regeneration even after therapy.

Recent advances, however, are starting to give us information about who may respond better to certain treatments.

### **Temozolomide and the MGMT gene**

It has been found that some glioblastomas are less sensitive to temozolomide (TMZ), making treatment with this drug less effective for some people.

The MGMT gene produces a protein (also often referred to as MGMT). This protein is involved in repairing the DNA in your cells and so helps to protect you against the development of tumours.

However, it also helps the tumour cells to repair themselves, making the temozolomide less effective.

People with less of the MGMT protein, therefore, respond better to chemotherapy and generally survive longer, as the tumour cells cannot repair themselves so well.

You can ask for a 'biomarker' test called the 'MGMT methylation test' to establish your level of the MGMT protein and see how likely you are to respond to temozolomide. This can then be used to help plan a suitable, individualised treatment plan.

As many centres will treat all glioblastomas with TMZ as a matter of course, speak to us and to your neuro-oncologist for more information and advice,

(The Brain Tumour Charity Support & Info Line - 0800 800 0004 or [support@thebraintumourcharity.org](mailto:support@thebraintumourcharity.org))

## **IDH-1 gene and TERT gene**

Mutations in the IDH-1 gene have been found to be frequent

in secondary glioblastomas, but rare in primary glioblastomas, apart from the proneural sub-type.

Mutations in the region of the TERT gene have been found to be the other way round i.e. common in primary glioblastomas but less frequent in secondary glioblastomas.

Both are associated with effects on overall survival. Mutations of the IDH-1 gene are often linked with longer-term survival rates. Conversely mutations in the TERT gene have been shown to predict poorer survival.

However, tumours that had mutations in both these genes had survival rates even longer than those who had the IDH-1 mutation alone.

If you would like to have a biomarker test for IDH-1, ask your neuro-oncologist for information and advice about whether you are suitable for an IDH-1 test.

(For more information about biomarkers, please see the 'Biomarkers' fact sheet).

The Brain Tumour Charity's research funding has contributed to the development of the MGMT and IDH-1 tests.

## **Other treatments**

### **Avastin®**

You may have heard that the use of another drug, called Bevacizumab (Avastin®) may be helpful in the treatment of glioblastomas. However, the evidence for this is not clear and for this reason it is not licensed for use with brain tumours in

the UK. (Please see the 'Bevacizumab (Avastin®)' fact sheet for more information).

Deciding on the treatment that is best for you can often be confusing. Your team will recommend what they think is the

best treatment option, but the final decision will be yours. You can also call our Support & Info Line for advice and information and to discuss any concerns you may have. Tel: 0800 800 0004 or [support@thebraintumourcharity.org](mailto:support@thebraintumourcharity.org).

## Ongoing research into treatment

Research is ongoing to find the keys to tumour progression in glioblastomas. The functioning of genes and their associated proteins, both within cells and on their surface, are important areas of research.

Identifying these key substances and mechanisms will help to lead to new drugs that are targeted at these elements and lead to more individualised treatment. Much of this research is still in the laboratory.

However other research, often on drugs or combinations of drugs, is at the clinical trial stage where patients can take part if they like. (For more information about clinical trials, including the pros and cons, please see our 'Clinical trials' fact sheet).

For example, research following on from, or related to, research that The Brain Tumour Charity has funded includes:

- a trial of hydroxychloroquine (HCQ) with radiotherapy for high grade gliomas in people aged 70 or over
- a study looking at the effects of a drug called Reolysin in people with cancer affecting the brain

Other trials include:

- a trial looking at Sativex with temozolomide for glioblastoma brain tumours
- a trial of a vaccine called DCVax-L for glioblastoma

Clinical trials are vital if we are to establish new and better treatments for brain tumours.

If you take part in a clinical trial, it may give you access to a drug or combination of drugs that you would not normally be offered and, if the trial treatment is an improvement, you may be one of the first people to benefit from it. In addition, some patients report that they are pleased to be helping to advance science, even if they do not benefit directly. Yet in a UK-wide survey in 2013, 73% of brain tumour patients said their medical team had not discussed clinical trials with them.

If you would like to take part in a clinical trial, ask your clinician about trials that may be suitable for you.

You can also talk to us at The Brain Tumour Charity via our Research & Clinical Trials Info Line - call 01252 749 999 or email [clinicaltrials@thebraintumourcharity.org](mailto:clinicaltrials@thebraintumourcharity.org), where we can help answer your

questions and any concerns. In addition, The Brain Tumour Charity has an online clinical trials database that you can use to search for clinical trials for your specific tumour type anywhere in the world. You can find it on our website [thebraintumourcharity.org/about-brain-tumours/clinical-trials](http://thebraintumourcharity.org/about-brain-tumours/clinical-trials)

You can also find out more about clinical trials in our 'Clinical trials and brain tumours' fact sheet.

It is important to be aware that every trial has a set of 'entry criteria' that you must fit to be able to enter.

## **How common are glioblastomas?**

Glioblastomas are the most common type of primary brain tumour in adults and account for 12-15% of all brain tumours. (Primary, in this instance, means the tumour starts in the brain rather than growing elsewhere in the body and spreading to the brain). However, with about three to four new cases of glioblastoma diagnosed each year per 100,000 people in the UK, glioblastoma is still classed as a rare cancer.

Glioblastoma primarily affects adults aged between 45 and 75 years old and it is slightly more common in men than in women.

Primary ('de novo') glioblastomas represent over 90% of all glioblastomas and are typically found in older people (the average age is 62 years old).

Secondary glioblastomas represent less than 10% of all glioblastomas and are typically found in younger people (the average age is 45 years old).

## **Resources**

People with glioblastomas may be interested in the following resource. This resource comes in the context of poor survival rates, the slow pace of innovation in developing new treatments and the lack of options that many patients face at the end of life.

Surviving "Terminal" Cancer, by Ben A. Williams PhD. Fairview Press, 2002

### **Disclaimer:**

*Each of these resources feature academics that have received a terminal diagnosis for glioblastoma, who after much research and consultation of medical advice, resorted to self-medication to manage their condition and extend their life, using a large number of treatments simultaneously over a number of years. These academics describe this as an act of desperation, and had the benefit of clinical training and knowledge to aid their decision-*

*making. The vast majority of brain tumour patients do not have such expertise to draw on.*

*We would like to make it clear that The Brain Tumour Charity does not recommend that patients self-medicate to manage their condition at any stage of their care pathway, especially with treatments that have not passed minimum standards of clinical safety through a peer review and clinical trial process.*

## **What if I have further questions?**

If you require further information, any clarification of information, or wish to discuss any concerns, please contact our Support and Information Team.

Call 0808 800 0004 (free from landlines and most mobiles including 3, O2, Orange, T-mobile, EE, Virgin and Vodafone)

- Email: [support@thebraintumourcharity.org](mailto:support@thebraintumourcharity.org)
- Join our closed Facebook group:  
[bit.ly/supportonfacebook](https://bit.ly/supportonfacebook)

## **About us**

The Brain Tumour Charity makes every effort to ensure that we provide accurate, up-to-date and unbiased facts about brain tumours. We hope that these will add to the medical advice you have already been given.

Please do continue to talk to your doctor if you are worried about any medical issues.

The Brain Tumour Charity is at the forefront of the fight to defeat brain tumours and is the only national charity making a difference every day to the lives of people with a brain tumour and their families. We fund pioneering research to increase survival, raise awareness of the symptoms and effects of brain tumours and provide support for everyone affected to improve quality of life.

We rely 100% on charitable donations to fund our vital work. If you would like to make a donation, or want to find out about other ways to support us including fundraising, leaving a gift in your will or giving in memory, please visit us at [www.thebraintumourcharity.org](http://www.thebraintumourcharity.org), call 01252 749043 or email [fundraising@thebraintumourcharity.org](mailto:fundraising@thebraintumourcharity.org)

## **About this fact sheet**

This fact sheet has been written and edited by The Brain Tumour Charity's Support and Information Team. The accuracy of medical information has been verified by a leading health professionals specialising in neuro-oncology. Our fact sheets have been produced with the assistance of patient and carer representatives and up-to-date, reliable sources of evidence. If you would like a list of references for any of the fact sheets, or would like more information about how we produce them, please contact us.

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**Your notes**



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