

Glioblastoma

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's the most aggressive form of adult brain tumour. They can also occur rarely in children.

This fact sheet gives an overview of glioblastomas 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 glioblastomas?
- How are glioblastomas diagnosed?
- How are glioblastomas treated?
- Answers to some commonly asked questions that you may have about glioblastomas

What is a glioblastoma?

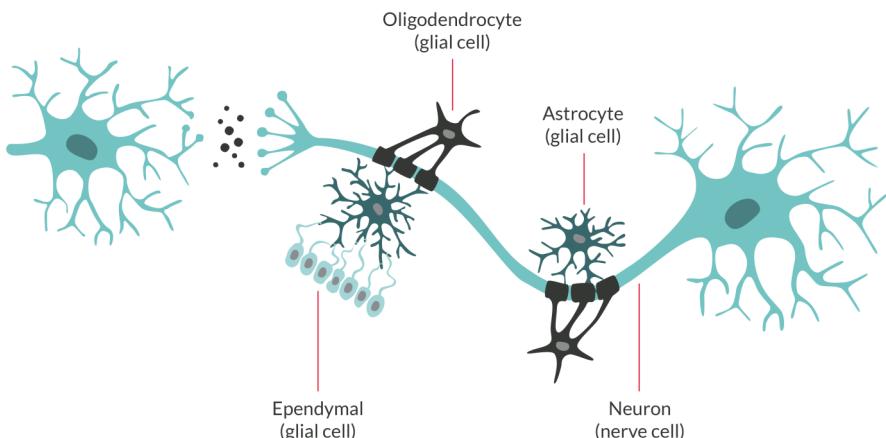
Glioblastoma is the more common name for a type of brain tumour called a grade 4 astrocytoma. (You may sometimes hear it called glioblastoma multiforme, or GBM / GBM4 for short, though these terms are less used nowadays.)

What is a grade 4 astrocytoma (glioblastoma)?

Throughout the brain and spinal cord we all have nerve cells, called neurons. 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.

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



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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 the following 4 grades, according to how the tumours behave:

- pilocytic astrocytoma (Grade 1)
- diffuse or low grade astrocytoma (Grade 2)
- anaplastic astrocytoma (Grade 3)
- glioblastoma (Grade 4 astrocytoma).

Grading

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 less likely to spread to other parts of the brain. There is less chance of them returning if they can be completely removed.

They are sometimes referred to as benign, though this is misleading, as they can still be serious. They can cause harm by pressing on the brain directly, or indirectly by causing a build-up of fluid within the skull.

Grades 3 and 4 are high-grade, fast growing and more likely to spread to other parts of the brain. They may come back even if intensively treated.

They are often referred to as malignant or cancerous.

For more information, see our *What is a brain tumour?* webpage and 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 3 months between no obvious brain abnormality to a fully developed tumour.

Most glioblastomas are primary glioblastomas.

Secondary glioblastoma

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

It's important to know that not all low grade brain tumours will transform into high grade tumours.

If a lower grade tumour does progress, the time they take to go from a lower grade astrocytoma to a glioblastoma varies considerably. It can range from less than 1 year to more than 10 years. However, once the change starts, it can be rapid.

Secondary glioblastomas tend to occur in younger people and have a slightly 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. Depending on the changes found, these can affect the likely response to some treatments and prognosis.

However, glioblastomas are genetically diverse. This means that the cells within the tumour are not all of the same type and may have different mutations. You may hear this referred to as heterogeneity. As a result, everybody's tumour is different.

What causes glioblastomas?

It's still not known exactly why glioblastomas begin to grow.

There's no evidence to suggest that the tumour could have been caused by anything you have done (or not done).

The reasons why glioblastomas develop are under ongoing investigation, and research is looking at genetic and molecular changes that can occur 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 not there, our bodies also have further checkpoints to stop cells dividing in an uncontrolled way.

When a cell divides, mistakes can sometimes be made when copying the genes into the new cell. These mistakes are called mutations.

If a mutation happens in certain genes, it can lead to tumour growth by causing cells to behave as if they are receiving a growth signal even when they're not, or by deactivating the checkpoints that would normally stop the cells from dividing. As a result, the cells continue to divide and can develop into a tumour.

It's important to know that these mutations are mistakes that are found in the tumour, and will not be inherited by your children.

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

This could 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 (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 make an urgent oncology referral either directly for a scan or to a specialist, such as a neurologist (a specialist in diagnosis and non-surgical issues of the brain and nerves).

For more information , see the *Your health team (MDT) for adults* webpage and fact sheet.

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's 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.

Sometimes you are sent for the scan directly by your GP, so you may have this before you see the specialist for the neurological examination.

For some people, their first symptom may be a seizure, so they are seen as an emergency. In this case they may also 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.

For more information, please see the *Scans for adults with brain tumours* webpage and fact sheet.

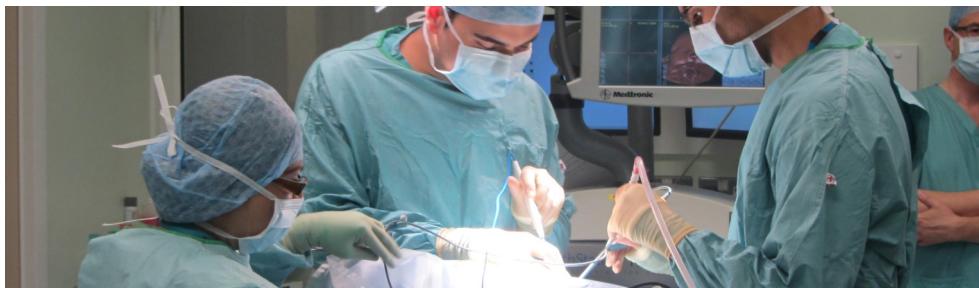
Biopsy/surgery

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 to allow for more accurate diagnosis of the tumour type.

It's important to realise that a biopsy is an operation that takes several hours. The risks will be explained to you by your surgical team.

If it can be done, surgery to remove as much of the tumour as possible will be carried out at the same time. This operation is called a craniotomy.

For more information, see the *Neurosurgery for adults with brain tumours* webpage and fact sheet.



Biobanking



Before a biopsy or surgery, you may like to ask about the possibility of biobanking some of the tissue from your tumour.

Biobanking means storing a sample of your tumour. Doing this may enable you to be a candidate for clinical trials in the future and also have any relevant genetic (biomarker) tests.

Different trials may require your sample to be stored in a particular way. Speak to your healthcare team, to make sure your sample is stored in a way that doesn't prevent you from taking part in certain trials or having certain treatments, e.g. immunotherapy.

See the *Other treatments* section later in this fact sheet.

Your sample could also be used by scientists for research towards improving survival and quality of life for people with brain tumours.

Currently not all centres are able to take and store samples, as they need to be licensed under the Human Tissue Act, with ethical approvals in place. As a result, routine collection of tissue for research is not yet a reality.

Speak to us and to your healthcare team if this is something you're interested in doing.

**The Brain Tumour Charity Information and Support Line:
support@thebraintumourcharity.org or 0800 800 0004.**

Laboratory analysis

Following biopsy or surgery, cells from the tumour will be analysed in a laboratory by a neuropathologist.

For more information, see *Your health team for adults (MDT)* webpage and 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
- 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's 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 of 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 your results if it is. If it's not routinely done at your centre and you're interested in having this test, ask your healthcare team.

Please see the Biomarkers webpage and fact sheet for more information.

How are glioblastomas treated?

The current gold standard (ideal) treatment for patients diagnosed with glioblastoma, if they're well enough, 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** webpages and fact sheets.

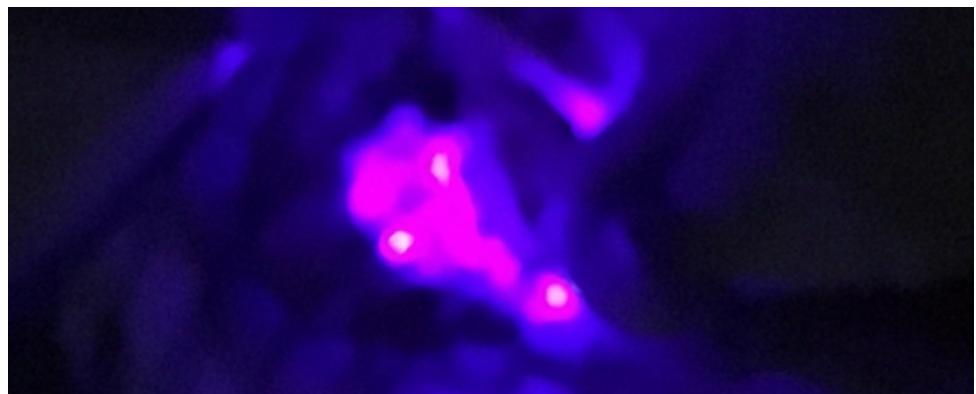
Surgery

Your surgeon will try to remove as much of the tumour as possible. This is known as debulking.

It is difficult to remove the whole tumour in the case of glioblastomas because:

- they are diffuse, meaning they have threadlike elements that spread out into the brain
- it can be hard to tell the difference between the edges of the main part of the tumour from normal brain tissue.

This means parts of the tumour may get left behind after surgery.



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 in some hospitals are given a drink containing a substance called 5-ALA. Often known as the "pink drink", even though it is not pink, this causes the tumour cells in the brain to glow pink under violet light. This allows the surgeon to tell the tumour cells apart from the normal cells and so remove more of the tumour. It has proven to be beneficial for adults with high grade gliomas such as glioblastomas.

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's near to any important parts of the brain.



Currently, the pink drink is not fully available in almost 50% of neurocentres.

We are working alongside healthcare professionals and the government to ensure that everyone who should have access, will have access .

Chemoradiation

Chemoradiation comprises radiotherapy over a period of weeks and rounds of the chemotherapy drug temozolomide (TMZ).

It's used to slow the growth of any tumour cells that cannot be removed by surgery.

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 new tumour cells, so the tumour cannot grow. TMZ is also thought to make the tumour cells sensitive to the radiation.

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

For more information, please see the *Temozolomide* and the *Radiotherapy for adults with brain tumours* webpages and fact sheets.

Gliadel® wafers

Gliadel® wafers are small wafers, coated with the chemotherapy drug carmustine, that are put directly into the brain at the end of surgery. This means the treatment gets round the blood-brain barrier that prevents many chemotherapy drugs from entering the brain.

The wafers are only licensed in the UK for use in recurrent glioblastomas (glioblastomas that have come back) and when the surgeon is confident that at least 90% of the tumour has been removed.

For more information, see our *Chemotherapy for adults with brain tumours* webpage and fact sheet.

Effectiveness of treatment

Unfortunately glioblastomas are aggressive tumours and often appear resistant to treatment.

It's 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, many 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's 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 may hear this referred to as having methylated MGMT.

Conversely, people with unmethylated MGMT have higher protein levels and so respond less well to TMZ.

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 temozolamide. This can then be used to help plan a suitable, individualised treatment plan.

Many centres will treat all glioblastomas with TMZ as a matter of course as there is no other effective drug. Also, some people with unmethylated MGMT do respond to TMZ, so there's still a chance it will prolong survival.

Speak to your neuro-oncologist or to our Information and Support team for more information:

**The Brain Tumour Charity Information and Support Line:
- 0800 800 0004 or 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 rarely in primary glioblastomas.

Conversely, mutations in the region of the TERT gene have been found to be 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'd 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* webpage and fact sheet.

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

Avastin®

You may have heard that the use of another drug, called bevacizumab (Avastin®), may be helpful in the treatment of glioblastomas. However, in Europe it is felt that there is insufficient evidence for its effect on brain tumours and for this reason it is not licensed for use with brain tumours in the UK.

See the *Bevacizumab (Avastin®)* webpage and fact sheet for more information.

Emerging treatments

Tumour Treating Fields (TTF)

Also known as Optune®, TTF is a relatively new, non-invasive technique for adults with glioblastoma. It uses alternating electrical fields, delivered via a set of adhesive patches worn like a skull cap, to disrupt tumour cell division, or cause cell death. This helps to prevent the tumour from growing or spreading so quickly.

It's not currently available through the NHS.

For more information, see our *TTF* webpage.

Immunotherapy (DCVax®-L)

DCVax®-L is a personalised cancer vaccine that is made from each patient's own dendritic cells. (Dendritic cells are a type of immune cell that help the body's immune system recognise and attack tumour cells.)

In May 2018, interim results from a clinical trial showed increased overall survival for patients with glioblastoma. However, as of June 2018, it's not currently available on the NHS, and the trial, though ongoing, is not recruiting any more people. It may be possible to access it privately and you may have to go abroad for the initial treatment. You will need to have a sample of your tumour flash frozen. Speak to your healthcare team if you are interested.

For more information, see our news article about DCVax®, or contact The Brain Tumour Charity Information and Support Line - 0800 800 0004 or support@thebraintumourcharity.org

Deciding on the treatment that is best for you can often be confusing. Your healthcare team will recommend what they think is the best treatment option, but the final decision will be yours.

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.

Research is also ongoing into treatments used for other illnesses, and into other organisms, such as Zika and polio viruses.

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 lab.

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 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.

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 wouldn't 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'd like to take part in a clinical trial, ask your clinician about trials that may be suitable for you, or contact The Brain Tumour Charity Information and Support Line.

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

For more information about clinical trials, including the pros and cons, please see our *Clinical trials* webpage and fact sheet.

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 3 to 4 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 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



Glioblastoma: a guide for patients and loved ones.

Gideon Burrows, NGO Media, 2017

The following resources come in the context of the slow pace of innovation in developing new treatments.

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

Surviving “Terminal” Cancer
A patient advocacy film, produced by Dominic Hill.
survivingterminalcancer.com

Disclaimer:

Each of these resources features 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 or need other support?

You can contact our Information and Support Team in the following ways:



0808 800 0004

(Free from landlines and most mobiles:
3, O2, EE, Virgin and Vodafone)



support@thebraintumourcharity.org



Live Chat

Get in touch with us online via
thebraintumourcharity.org/live-chat



Join one (or more) of our
closed Facebook groups:
bit.ly/FBSupportGroups



thebraintumourcharity.org/getsupport

Disclaimer:

This resource contains information and general advice. It should not be used as a substitute for personalised advice from a qualified specialist professional. We strive to make sure that the content is accurate and up-to-date, but information can change over time. Patients must seek advice from their medical teams before beginning or refraining from taking any medication or treatment. The Brain Tumour Charity does not accept any liability to any person arising from the use of this resource.

About this information resource

The Brain Tumour Charity is proud to have been certified as a provider of high quality health and social care information by The Information Standard - an NHS standard that allows the public to identify reliable and trustworthy sources of information.

Written and edited by our Information and Support Team, the accuracy of medical information in this resource has been verified by leading health professionals specialising in neuro-oncology.

Our information resources have been produced with the assistance of patient and carer representatives and up-to-date, reliable sources of evidence.

We hope that this information will complement the medical advice you have already been given. Please do continue to talk to your medical team if you are worried about any medical issues.

If you would like a list of references for any of our information resources, or would like more information about how we produce them, please contact us.

We welcome your comments on this information resource, so we can improve. Please give us your feedback via our Information and Support Team on **0808 800 0004** or **support@thebraintumourcharity.org**

Your notes:

About The Brain Tumour Charity

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 worldwide, raise awareness of the symptoms and effects of brain tumours and provide support for everyone affected to improve quality of life.

We wouldn't be able to make the progress we have without the incredible input we receive from you, our community. Whether it's reviewing our information resources, campaigning for change, reviewing research proposals or attending cheque presentations, everything you do helps to make a difference. To find out more about the different ways you can get involved, please visit thebraintumourcharity.org/volunteering

We rely 100% on charitable donations to fund our work.

If you would like to make a donation, or find out more about other ways to support us, including leaving a gift in your Will or fundraising through an event, please get in touch:

Visit
thebraintumourcharity.org/get-involved
call us on 01252 749043 or email
fundraising@thebraintumourcharity.org



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