

Glioblastoma (cancer affecting the brain)

*A guide for journalists on glioblastoma
and its treatment*



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Overview

Glioblastoma (GBM) is a devastating disease for both patients and caregivers. It is the most aggressive primary brain tumour – a tumour that originates in the brain – and despite available therapies, prognosis is extremely poor. The majority of patients do not survive for more than two years following diagnosis, and the median survival is generally less than a year.¹ The average 5-year survival rate is less than 3%.²

Worldwide, there are an estimated 240,000 cases of brain and nervous system tumours per year – GBM is the most common, and the most lethal, of these tumours.³ The treatment a patient receives depends on the location of the tumour in the brain and their overall health and age, but the current standard of care for GBM is surgery followed by treatment with both chemotherapy and radiotherapy, after which patients continue with chemotherapy alone. Biological therapies (also called targeted therapies) are a relatively new approach to GBM treatment and have shown promise in clinical trials.

GBM progresses rapidly and patients can deteriorate quickly. Common symptoms include headaches, seizures, nausea, weakness, paralysis and personality or cognitive changes such as losing the ability to speak or think clearly.⁴ Unfortunately, most patients ultimately lose their life to GBM; therefore, maintaining optimal quality of life is very important to patients and their caregivers and is a significant consideration when selecting potential treatment options.

This guide provides an overview of glioblastoma, including its incidence, risk factors, symptoms, diagnosis and treatment options.

Section 1

Glioblastoma

i. About the brain

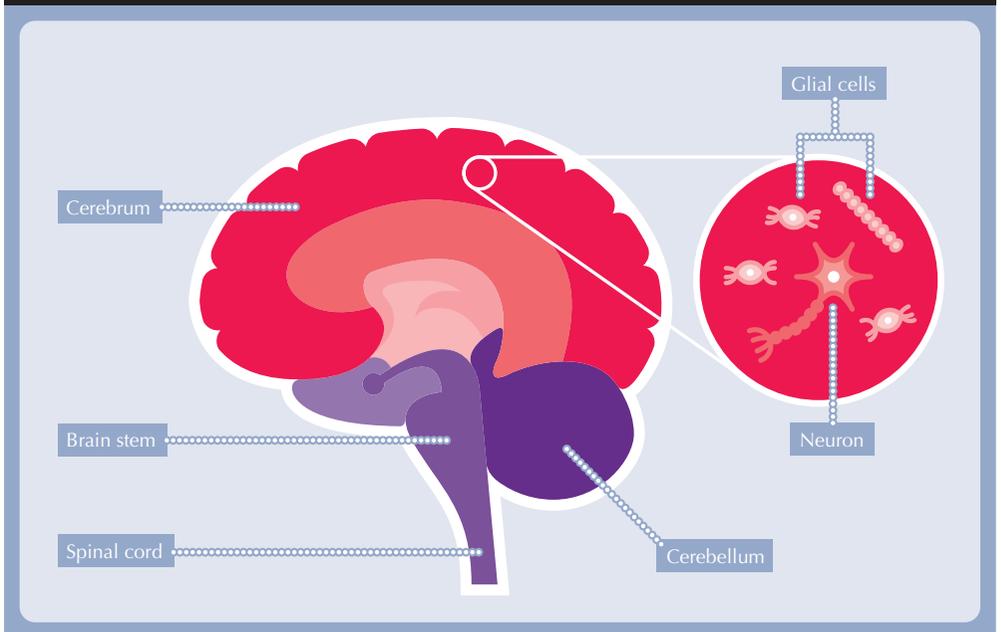
Along with your spinal cord, the brain makes up your body's central nervous system (CNS), which controls and regulates body functions and processes – from what we think to how we move. The human brain can be divided into a number of distinct regions based on anatomy, structure or the activities controlled by the region (see Figure 1).

- The forebrain consists primarily of the cerebrum, which is the largest part of the brain and controls thoughts and speech.
- Situated at the back of the brain underneath the cerebrum is the cerebellum. The cerebellum is the second largest region of the brain, controlling voluntary movement and balance.
- The brainstem connects the cerebrum to the spinal cord and consists of the midbrain, pons and medulla oblongata. The brainstem is associated with involuntary functions, such as breathing and swallowing.⁵

The brain has two main types of cells; neurons and glial cells.⁶ Neurons act as 'messenger' cells, relaying and transmitting signals from the body to the regions of the brain where they are processed. Neurons are highly specialised cells that process and transmit information throughout the nervous system by electrical and chemical signaling.⁶ Glial cells provide support for the neurons and help to regulate the signal transmission (from the word glial meaning 'glue' in Greek). It is estimated that there are 10 times as many glial cells as neurons in the nervous system.⁶

Cells in the brain are protected from the body's circulating bloodstream by the blood brain barrier (BBB), a network of tightly joined specialised cells that form the wall of the capillary and an additional layer outside the capillary. The vast majority of drugs (such as monoclonal antibodies) cannot cross an intact BBB.⁷ However, the BBB is thought to be impaired in GBM, which may allow some drugs that are larger in molecular size to enter the brain.

Figure 1 Anatomy of the brain



ii. What is brain cancer?

Cancer is the term used to describe a variety of diseases in which cells escape the control mechanisms that normally limit growth and division.⁸ Primary brain tumours are caused by the uncontrolled replication and growth of cells originating in the brain. They can develop in both neuron and glial cells. Glioma (cancer developing from glial cells) is the most common type of primary brain tumour (a tumour that originates in the brain), accounting for approximately one third of all cases diagnosed. Glioma also represents approximately 80% of all primary malignant brain cancers.⁹

Glioblastoma (formerly glioblastoma multiforme; GBM) is the most common and most aggressive type of glioma.⁹ GBM is often located in a region of the forebrain known as the cerebrum, which controls some of the most advanced processes such as speech and emotions.^{6,10} While GBM is highly locally invasive (invading normal brain tissue), it rarely spreads to other organs beyond the brain. GBM is

a highly aggressive, fast-growing cancer and treatment is often limited by the tumour location and the ability of a patient to tolerate surgery. Consequently, it is a particularly difficult cancer to treat.¹²

iii. Causes and risk factors

GBM generally occurs spontaneously and without an identifiable cause, however, certain factors have been linked to an increased risk of developing the disease:

- **Age:** Although GBM can occur at any age, including in infants and children, the risk increases with age – the average age at diagnosis is 64 years.⁹
- **Gender:** GBM is more frequently diagnosed in men, though the reason for this is unknown.¹⁰
- **Genetics:** There is an increased incidence of GBM in families with a very rare hereditary disorder called Li-Fraumeni syndrome (LFS), the incidence and prevalence of which is unknown.¹³ Patients with LFS are susceptible to a variety of different cancers, including brain cancer, breast cancer and

leukaemia. The syndrome is thought to arise from mutations in a gene which plays a role in tumour suppression.¹⁴

- **Radiation:** Evidence suggests that exposure to ionising radiation (for example, previous radiotherapy to the head or working in the nuclear industry) may increase the risk of developing GBM.¹⁵
- **Other factors:** There has been much speculation over a link between mobile phone use and brain tumours and many studies have found conflicting results. No definitive association between the two has yet been found. The long-term risks of mobile phone use remain unknown.¹⁶⁻¹⁸

iv. Symptoms

As GBM is an aggressive disease that progresses rapidly, patients can deteriorate quickly. The symptoms of GBM can vary depending on the size and location of the tumour in the brain. The following are common symptoms:^{10,19-21}

- Increased intracranial pressure (pressure build-up in the head) manifesting as headaches, nausea and vomiting
- Cognitive impairment or slowing of cognitive function (e.g. losing the ability to speak or think clearly)
- Changes in personality, mood or concentration
- Visual impairment
- Seizures
- Motor dysfunction such as paralysis
- Sensory loss e.g. numbness, weakness

The symptoms of GBM are often distressing to patients and their caregivers as they significantly and negatively impact on quality of life as well as ability to carry out activities of daily living. Because of this, symptom management can be as important as treatment of the disease.

v. Diagnosis

If patients present symptoms that suggest a brain tumour, they usually undergo a Magnetic Resonance Imaging (MRI) scan, which produces a detailed picture of the brain, enabling any abnormalities to be seen.²²

Diagnosis is confirmed by a biopsy, where sample tissue is taken from the suspected lesion.²³ Biopsy of a brain tumour must be undertaken with caution to limit damage to normal brain function.

Brain tumour classification and grading is defined by the World Health Organization (WHO) classification of nervous system tumours.²⁴ There are four grades of brain tumours which are classified on a scale

according to the presence of certain criteria, such as growth rate and cell differentiation (how 'normal' a cell looks under a microscope).

- Grade I tumours are slow growing, non-malignant and are associated with long-term survival
- Grade II tumours are slow growing but generally return more frequently than grade I tumours
- Grade III lesions are malignant, fast growing and poorly differentiated
- Grade IV tumours are the fastest growing, highly malignant and are poorly differentiated.

GBM is classified as a grade IV brain tumour.^{24,25}

Section 2

Epidemiology and prognosis

i. Incidence and mortality

Worldwide, there are an estimated 240,000 cases of brain and nervous system tumours per year – GBM is the most common, and the most lethal, of these tumours.³ In the US alone, approximately 18,000 people are diagnosed with GBM every year. GBM accounts for 13,000 cancer deaths in the US annually.²⁶ In most European countries, new cases of GBM occur in approximately 2–3 people in every 100,000 each year.²⁷

ii. Prognosis

Cancer statistics often use an ‘overall 5-year survival rate’ to give a better idea of the longer term outlook for people with a particular cancer. It is almost impossible to predict how long an individual patient might live, but 5-year survival rates can give an approximate range. As GBM is a ‘high grade’ and advanced disease, the average 5-year survival rate for patients is particularly poor, at less than 3%.² The majority of GBM patients do not live over a year.²⁴

Figure 2 Incidence and mortality of some of the most common cancers worldwide

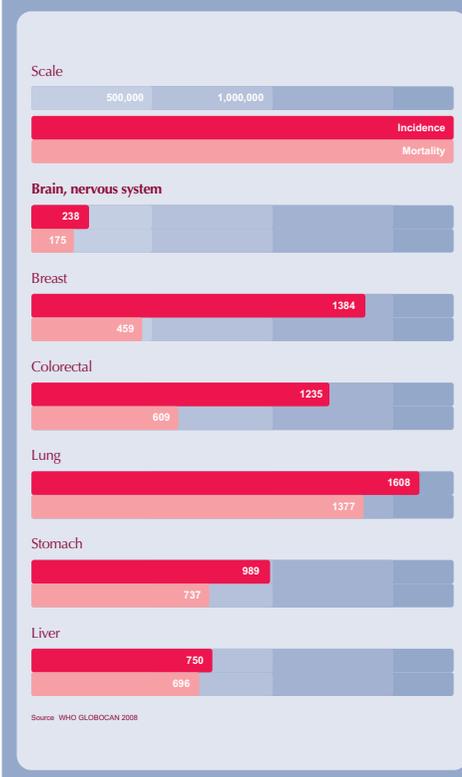
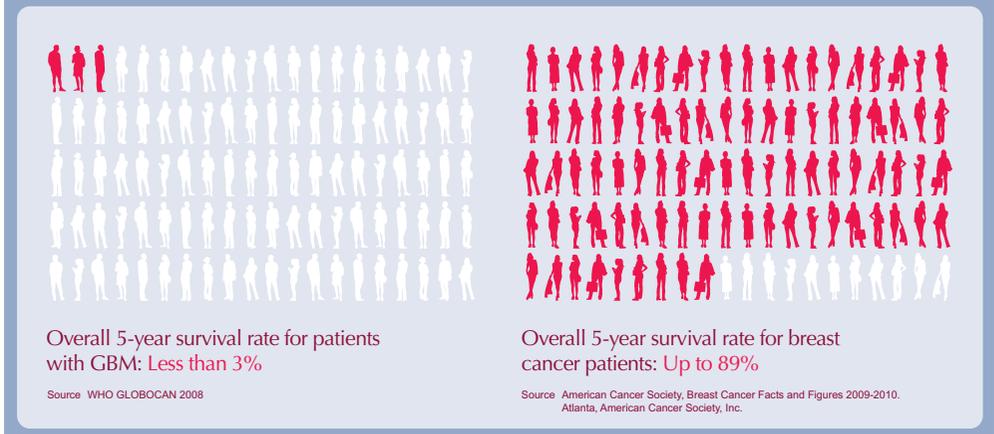


Figure 3 Comparing 5-year survival rate of GBM to other cancers worldwide



However, the prognosis of GBM does vary depending on the age of the patient, the tumour size and location, the amount of tumour that can be removed during surgery and the neurological performance status of the patient which may impact on their treatment options (i.e. the ability for patients to live a ‘normal’ life and carry out day-to-day tasks).²⁴

Section 3

Treatment

Treatment options for GBM vary depending on a number of factors – tumour size, position, whether it has spread to other regions of the brain and the performance status of the patient. The current standard of care for GBM is surgery, chemotherapy and radiotherapy.²⁸ More recent treatments are biological (targeted) therapies, which can be used alone or in combination with chemotherapy or radiotherapy.

Arguably the most important factor of GBM treatment is the physical, emotional and psychological support a patient receives, as GBM is such an aggressive disease which can severely affect a patient's quality of life.

i. Surgery

If the tumour is located in a part of the brain where it can be removed without risking damage to the brain itself or subsequent brain function, then surgery will typically be undertaken to remove as much of the tumour as possible.²⁹ This procedure is known as debulking surgery

or resection. Due to the sensitive nature of the operation it is very rare that the entire tumour is removed during debulking surgery, however, the greater the amount of tumour that can be removed, the better the prognosis for the patient.²⁸

Depending on the health and age of the patient, surgery is usually followed by radiotherapy and chemotherapy followed by maintenance chemotherapy treatment to control the tumour or prevent tumour regrowth.²⁸

ii. Radiotherapy

Along with surgery, radiotherapy is routinely given to patients with the aim of controlling tumour growth, reducing the chance of the cancer coming back (recurring) and alleviating symptoms.^{28,30} In cases where surgery is inadvisable due to risk of damage to the brain, radiotherapy is recommended as a primary treatment and is widely accepted as the standard of care.³¹

iii. Chemotherapy

Although chemotherapy has shown limited success in the treatment of GBM, the combination of radiotherapy and chemotherapy is the established standard of care in patients with newly diagnosed GBM.¹ Chemotherapy does not distinguish between normal healthy cells and cancer cells, which can lead to unwanted side effects.

Unfortunately, in almost all cases, GBM will return or progress following treatment (known as recurrent disease). Some patients will undergo second surgery or a second course of radiotherapy or chemotherapy. Prognosis at this stage remains extremely poor³² and patients sometimes consider participating in clinical trials.³⁰

iv. Biological (targeted) therapy

Biological (targeted) therapies are a relatively new approach to cancer treatment and target specific biological processes that are often essential to tumour growth. Biological therapy can include use of monoclonal antibodies, vaccines and gene therapies. As biological therapies precisely target cancer-specific processes, they may be less toxic to non-cancerous, healthy cells than other types of treatment (such as chemotherapy and radiotherapy).³³

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