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COMMENTARY

# Overview of Glioblastoma

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## Introduction

Glioblastoma multiforme (GBM), a rapidly developing and highly aggressive brain tumor, accounts for more than 49 percent of all primary malignant brain tumors (1). Through the extensive research of medical professionals, the scientific community has gained a deeper understanding of GBM, and thus discovered common symptoms, medical treatments, and distinct therapies to attempt to treat the patient. Treatment for GBM is challenging due to the disease's innate resistance to conventional therapy and its propensity for invasive behavior; as a result, more effective neuro-oncological and neurosurgical therapies are required (2).

## History

### *Discovery*

As one of the most complex brain tumors, it isn't a surprise that glioblastomas have a long line of history. Although the origin of these brain tumors is unknown, records that indicate their existence date back to the 1800s. In 1800 and 1804, British scientific reports by Burns and Abernethy displayed the first ever recorded glioblastomas (3). In 1863, Rudolf Virchow, a German physician and founder of social medicine, provided the first comprehensive histomorphological description of this fast-growing malignant tumor (3). Virchow was able to demonstrate the tumor's glial origin which ultimately created the steppingstone for future scientific researchers.

### *Researchers*

Since the initial discovery of GBM, there have been plenty of researchers that continue to investigate the mystery of this deadly brain tumor. In 1914 American Pathologist, Frank Burr Mallory, was credited for coining the term Glioblastoma Multiforme. In 1926, researchers Percival Bailey and Harvey Cushing established the basis of modern classification from gliomas and glioblastomas, which they called GBM. Scherer and Kernohan were the most prolific researchers between the years of 1934 and 1941 and postulated some of the clinic-morphological aspects of glioblastomas (4).

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## Glioblastoma Formation

Glioblastoma is a cancerous tumor that develops in the brain. They form from astrocytes which are star-shaped cells that protect and provide nutrients to the brain. It's common for glioblastoma to grow in the brainstem and cerebellum for most adults. These tumors can also metastasize in multiple areas of the brain, and in some rare cases it can even grow in other parts of the body (5).

## Types of GBM

Glioblastoma has 2 types, primary glioblastoma and secondary glioblastoma. Primary glioblastoma is more common for older people. It's also the common type to have, and with this, your life expectancy will most likely be shortened. Secondary glioblastoma mainly targets younger individuals. It forms from a low-grade glioma which can grow in almost any part of the brain and occasionally in the spinal cord. The survival rate for this type tends to be higher than the primary glioblastoma (5).

## Similarities and Differences

Like any kind of cancer found in the body, there are many differences and similarities between these malignant tumors. Glioblastomas are a type of glioma, which is one of the most common types of brain tumors. With this classification it can be inferred that these tumors are quite similar. The only difference between the two is the severity of the tumor and grade. On the other hand, glioblastomas can be far more complex than other types of brain tumors and can show symptoms rather quickly. All brain tumors range from a grade scale between 1 and 4 (4 being the most dangerous and 1being the least dangerous). Compared to the other brain cancers, all glioblastomas are considered grade IV brain tumors. The reason for this is that they have the most unusual looking cells ultimately making them the most aggressive (6).

## Prognosis

As of now the prognosis states that there is no possible cure for GBM. Treatments are available for patients to keep the tumor in control for a couple of months, and if possible, even years. As glioblastoma continues to grow it creates microscopic branches that can spread to various parts of the brain, which can make it extremely difficult to remove through surgery. Additionally, a single tumor contains different types of cells which can make it almost impossible to treat the whole tumor. For instance, if a drug is being used to treat the tumor, it will only kill a certain cell, not all of them (7).

## GBM Prevalence

### *Rate of GBM*

Glioblastoma multiforme (GBM) is the aggressive, most common brain tumor found in arising adults (8). Every year, more than 13,000 American citizens are diagnosed with glioblastoma, and that's not taking into consideration the amount of people who don't participate in monthly checkups. Glioblastoma has an already low survival rate of 40% within the first year. While things may look good in the beginning, chances decrease to 17% in just the second year, and to a 6.8% chance at the end of 5 years. This cancer has a terrifying population percentage, accounting for almost 50% of all brain cancer cases. In the United States on average there is a slightly higher rate in men than women affected by Glioblastoma. With that Caucasians compared to other ethnic groups such as African Americans, Asians, and American Indians have a greater chance of diagnosis (9).

### *Gender Distribution*

In the gender population, males have a faster exposure to the cancerous cell than females, due to their series of genetic alterations and exposure to growth factors (9). Glioblastoma is more common in older males and begins around the age of 64. Although it only begins at this age, it worsens and gets more fatal as the years pass. Although GBM is found more frequently in men than women, recent studies have shown that females experience a higher intensity in symptoms and their tumors tend to be larger than those in males. The reason for these statistics is still unknown, but researchers are continuing to discover new information about these tumors.

### *Race/ Ethnicity*

Just like age and gender, a patient's race or ethnicity can be an additional factor that may give more information on survival and instances (10). In research studies based on race and ethnicities, it has been found that Asians or Pacific Islanders have the highest 1- year to 5-year survival rate (67.1%, 10.1%). African Americans follow with a 1-year rate of 60.9% and a 5-year rate of 9.9%. Hispanics are second to last with a rate of 60.4% in the first year and 9.5% in the

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fifth year. Lastly, non- Hispanic whites have the lowest survival rate of 57.2% and 6.6% in the 1-to-5-year period. Although race and ethnicity are important to factor in a patient's diagnosis of GBM, there is still extensive research being done in this field for future data.

## Causes & Symptoms

Located either in the brain or spinal cord, this disease comes with many effects and critical symptoms including both psychiatric and neurological (8).

### *Neurological Symptoms*

Neurological symptoms are relatively shown during growth and expansion of the tumor. Around 40 to 60 percent of patients with glioblastomas are prone to show neurological symptoms which include headaches, disorientation, vomiting, seizures, memory loss, and speech difficulties (8). The effect for this is due to the increased intracranial pressure in the frontal lobe and corpus callosum (8). The reason being, of these neurological symptoms are because of the amount of swelling due to the tumor and the desired room when growing (11). The tumor will push on the brain during a fast-spreading process that affects any nearby brain tissue (11).

### *Psychiatriatric Symptoms*

Most cases of glioblastoma show psychiatriatric symptoms and 62 percent of these cases are seen from middle aged to older patients (8). Some primary psychiatriatric symptoms include depression, anxiety, manic-like states, and mood disorders (8). As much as 35% of patients manifest psychiatrist symptoms and are prone to be psychotic, have schizophrenia, resist treatment, and hallucinate (8). The reason for patients with GBM possessing these symptoms is due to tumors predominantly being pushed up against the temporal lobes ultimately affecting the frontal lobe (8).

### *Genetics*

The root cause for glioblastoma is unfortunately unknown and it has shown not to be inherited through genetics (12). Although it is classified as an idiopathic tumor, some individuals with neurofibromatosis type 1, (a genetic cancer syndrome), Turcot syndrome, and Li Fraumeni syndrome can elevate their chances for this disease (13).

## Diagnosis

Due to glioblastoma being classified as a stage four cancer, it is one of the most aggressive and rapidly growing brain tumors (14). If a patient has GBM they will begin to feel symptoms such as headaches, speech, vision, hearing, thinking impairment, and more. A very common symptom in patients is losing vocabulary or forgetting thoughts easily. A way of finding Glioblastomas is by taking an MRI. When the patient feels these symptoms, they will have an MRI taken to see whether there is a tumor in the first place and if they need surgery. In other cases, a surgical biopsy is needed to see if the mass detected is a Glioblastoma or another type of brain tumor. For most patients, the median time it takes to receive a diagnosis is around 330 days; that is almost one full year (15). The time period for diagnosis does range between 156 to 776 days depending on how long it takes an individual to be tested. Unfortunately, the reason it takes a long period of time for an individual to be diagnosed with GBM is because most patients don’t feel symptoms until 100 days after the tumor begins to develop. Although early detection remains difficult, new technologies are being made to help identify early stages of glioblastoma. Developments such as liquid biopsy and serum biomarker may allow for early diagnosis and early treatment in future cases of glioblastoma.

## Treatment/Therapy

The typical course of treatment for a GBM entails surgery, daily radiation, and oral chemotherapy administered over the course of six and a half weeks, followed by a six-month oral chemotherapy regimen administered five days each month (16). Currently, surgery to remove as much of the tumor as possible is the best course of action for glioblastoma, which is then followed by a chemotherapy and radiotherapy regimen.

### *Treatment History*

Many hospitals and research teams have pursued the study of Glioblastomas trying to better treat it and ultimately find a cure. Although this certain tumor is very complex, many breakthrough discoveries have been made. In 1888, physician Byrom Bramwell was one of the first physicians to point out the surgical challenge that these tumors

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brought to the table. He explained that without microscopical examination, it would be quite impossible to spot the transition between the tumorous tissue and normal brain tissue. Furthermore, in our society today many institutes have partnered with universities around the country in hopes to advance medical care for patients who suffer from glioblastomas. The Translational Center of Excellence (TCE) in the Abramson Cancer Center at Penn Medicine has focused on the issues of GBM and have continued to create opportunities to revolutionize treatment. The Penn Medicine team is an international leader in researching and treating Glioblastoma and have made game-changing discoveries. They have ushered in a new era of cellular therapies that treat cancer with a patient's immune system (17). In 2005, Medical Director at the Lou and Jean Malnati Brain Tumor Institute, Roger Stupp, developed a worldwide standard care for Glioblastoma known as the Stupp protocol. His findings in better treatment and new ways of treatment have changed the survival ratio of patients from 1 in 10 that lived longer than two years after diagnosis to now more than 1 in 4 (18). Although there is still much to learn about Glioblastomas, there have been great advancements in treatments. It is only a matter of time before scientific researchers find a cure.

### *Adjuvant Therapy*

Patients with glioblastoma begin chemotherapy 2 to 4 weeks following surgery. Either along with radiation therapy or soon after it (19). GBMs and other advanced brain tumors are frequently treated with temozolomide, a chemotherapeutic medication that the FDA approved in 2013 (16). The medication slows the growth of tumors and is administered orally. Usually, the medication is taken daily during radiation therapy and for six cycles after radiation during the maintenance phase (20). Temozolomide not only has direct anticancer actions but also has immunomodulatory qualities (21). Chemotherapy's effects are influenced by the drug's method of action, dosage, and host immune system (21).

And then of course, there's radiation. Radiation therapy for glioblastoma involves directing X-rays, gamma rays, or photons at a tumor to kill malignant cells (22). The tumor shrinks as cancerous cells are cleared by the body's immune system, which relieves pressure on the brain. If a surgeon decides that removing a tumor would be too dangerous, it may be used as a primary treatment (16). It may also be performed following surgery to eliminate any cancerous cells that the surgeon was unable to see or reach.

### *Surgery*

For surgery, the neurosurgeon will attempt to remove the majority of the tumor (16). However, it is impossible to entirely eradicate GBMs due to a zone of invading tumor cells that assault the tissues around the tumor. The neurosurgeon may also insert medicated wafers into the brain. Over time, these wafers naturally break down and deliver chemotherapy medications into the tumor area (16).

### *Clinical Trials*

All these wonderful treatments, but how effective are they? is the real question. Well, the current standard of care for glioblastoma multiforme is successful and has extended survival times for more patients to two, three, and even four years. Sadly, this treatment is not curative (16). Which basically means that it does not terminate every single tumor cell. However, the outlooks and future for patients with Glioblastoma are expected to improve.

Clinicians and researchers are developing new trials in an attempt to improve the survival rate of patients who have Glioblastoma. A great example of this would be this fairly new clinical trial from a team at the University of Michigan Rogel Cancer Center. This certain clinical trial began in august of 2020 and is led by Daniel Wahl, M.D., Ph.D. They hope to achieve and succeed where several other Glioblastoma treatments have failed. This trial still has a very long way to go (23). In a brilliant ongoing clinical trial which is led by Dr. Andrew B. Lassman, the John Harris Associate Professor of Neurology at Columbia University Vagelos College of Physicians and Surgeons and head of the Neuro-Oncology Division at Columbia University Irving Medical Center/New York-Presbyterian, observed tumor reduction in nearly a third of patients with recurrent glioblastoma, an aggressive brain cancer while using selinexor, the first of a new class of anticancer drugs. (24). These are only a few of the several ongoing clinical trials attempting to alter the course of glioblastoma patients' futures.

### *Mental Health*

Another important aspect that is very crucial to remember is that this patient is not only battling a

deadly unforgiving cancer, but they are also undergoing emotional distress such as anxiety and depression. Any cancer really can have this effect. This is why it is crucial that you care for your patient and have some empathy. To assist patients in coping with the emotional distress and stress caused by cancer and its treatment, palliative care teams frequently include social workers and/or other mental health specialists. To improve the general quality of life for cancer patients, therapists and counselors can provide their services in person or online (25).

## Conclusion

Despite improvements in our understanding of GBM, its inherent invasiveness and resistance to standard treatments makes it extremely difficult to find a cure. It is important to educate healthcare and local communities on the importance of the severity of glioblastomas to inculcate the urgency in patients to seek medical attention once neurological symptoms are detected. In doing so, the patient's overall physical and emotional well-being may be exceptionally improved. As experts continue to advance their medical care for those suffering from GBM, exposing its severity to local communities yields the patient a better prognosis.

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