Glioblastoma & High-Grade Astrocytoma
ACKNOWLEDGEMENTS

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INTRODUCTION

This brochure is about glioblastoma (also known as glioblastoma multiforme or astrocytoma grade IV) and anaplastic astrocytoma (also known as astrocytoma grade III or high-grade astrocytoma), which belong to a group of primary brain tumors called gliomas. Primary brain tumors start in the brain¹ and rarely spread to other organs.² Gliomas are one of the most common types of brain tumors.¹,³

While there are several different kinds of gliomas, this publication discusses only two types: glioblastomas and anaplastic (refers to very abnormal looking cells) astrocytomas. Both are considered cancerous (malignant) tumors.

TUMOR TYPE

Gliomas are classified based on how they look under the microscope.⁴ It is believed that glioblastomas and anaplastic astrocytomas arise from glial cells called astrocytes.⁵,⁶ That is why glioblastomas have sometimes been referred to as grade IV astrocytomas.⁵ However, their exact origin is still unknown.¹
The World Health Organization (WHO) has developed a classification system for brain tumors. In 2016 the WHO classified glioblastoma and anaplastic astrocytoma into the following genetic subtypes:\(^7\)
- IDH-mutant
- DH-wildtype
- IDH NOS

IDH stands for isocitrate dehydrogenase. If there is a mutation (a change in a gene) specifically in the IDH gene, the tumor is considered IDH-mutant.\(^4\) If no mutation exists, the tumor is classified as IDH-wildtype. IDH NOS, which stands for not otherwise specified, means that the type of IDH mutation is unclear.\(^3\) In 2016, the WHO further divided IDH-wildtype glioblastoma into epithelioid glioblastoma, giant cell glioblastoma, and gliosarcoma.\(^7\)

In 2021 the WHO again updated CNS tumor classification, incorporating new knowledge gained from additional molecular markers and new diagnostic techniques. Tumors are now listed as “CNS grade 1-4” with the presence or absence of IDH mutation, a key factor in glioma classification. This update provides more flexibility in using grade relative to tumor type and to emphasize biological similarities within tumor types instead of clinical behavior. Therefore, this change to tumor type grading replaced the term anaplastic astrocytoma with IDH-mutant astrocytoma, grade 3, and glioblastoma with IDH-wildtype glioblastoma, grade 4, and IDH-mutant astrocytoma, grade 4. This brochure will use the 2016 tumor classifications as the 2021 classifications continue to be incorporated into practice.

In the past, the diagnosis of brain tumors relied more heavily on how the tumor cells look under the microscope. While that information is still important,
it is more common today to include a tumor's genetic or molecular information to help make a diagnosis.\textsuperscript{8}

For glioblastoma and anaplastic astrocytoma, the discovery of the mutation in the IDH gene may lead to a more accurate diagnosis, can help determine an individual's prognosis (the chance of recovery or survival from a disease), and may predict response to treatment.\textsuperscript{8,9}

For patients diagnosed with glioblastoma or anaplastic astrocytoma, it is important to have the tumor molecularly tested to determine the diagnosis under the current classification system. Molecular parameters were added to the 2021 WHO update as biomarkers for grading and further estimating prognosis within these tumors.

TUMOR LOCATION

Glioblastoma and anaplastic astrocytoma are most commonly found in the cerebrum, the largest part of the brain that is divided into four lobes.

Glioblastoma and anaplastic astrocytoma IDH-mutant are commonly found in the frontal lobe,\textsuperscript{7} which controls reasoning, emotions, problem-solving, speech, and movement.\textsuperscript{1}

Glioblastoma IDH-wildtype typically occurs in the temporal lobe, followed by the parietal lobe, frontal lobe, and occipital lobe.\textsuperscript{7} The temporal lobe processes memories with special senses like hearing and understanding words.\textsuperscript{1} The parietal lobe mainly processes sensory information such as touch, temperature, and pain. The occipital lobe controls vision.

TUMOR GRADE

In 2016 The WHO used a grading system with a scale of I to IV for brain tumors. In general, as the grade increases, the prognosis worsens.\textsuperscript{1} Tumor grade dictates treatment options.
Although glioblastoma is a grade IV tumor and anaplastic astrocytoma is a grade III tumor, they are both considered to be high-grade gliomas. That means they are both generally fast growing and aggressive, but glioblastoma is more aggressive than anaplastic astrocytoma.

The 2021 WHO updates changed from Roman Numeral grading (I, II, III, IV) to Arabic grading (1, 2, 3, 4) as this is what is currently done for all other tumors.

IDH-wildtype glioblastoma is a grade 4 tumor. IDH-mutant astrocytoma can be a grade 2, 3 or 4 tumor. Grades 3 and 4 are considered to be high-grade gliomas. This means they are both generally fast growing and aggressive, but IDH-wildtype glioblastoma is more aggressive than a grade 3 or 4 IDH-mutant astrocytoma.

Finding out the grade, subtype, and location of your high-grade glioma through molecular testing will help you and your doctor to make more informed treatment decisions.

**INCIDENCE**

Incidence refers to how often a disease occurs.

Glioblastomas account for nearly 15% of all primary brain tumors. They are most common in adults, usually occurring in slightly older people. The median age at diagnosis is 65 years, with the highest rates occurring in individuals 75 to 84 years. Although these tumors are found in both men and women, they tend to occur more often in men. Glioblastomas occur more commonly in white people than those of other races.

Glioblastomas are rare in children. They account for only 3% of primary brain tumors in children and teens.
Anaplastic astrocytomas account for nearly 2% of all primary brain tumors. More common in adults, the median age at diagnosis is 53 years. Anaplastic astrocytomas are more evenly distributed in men and women than glioblastomas, but still occur slightly more often in men. Anaplastic astrocytomas occur more commonly in white people than those of other races.

Anaplastic astrocytomas are even more rare in children and teens than glioblastomas, with nearly half the number of cases.

An estimated 13,000 people are diagnosed with glioblastoma each year; about 1,400 are diagnosed with anaplastic astrocytoma.

CAUSE

Like other types of brain tumors, the exact cause of most glioblastomas and anaplastic astrocytomas is unknown. Scientists have identified abnormalities in the genes of different chromosomes that may play a role in how brain tumors develop. But what causes normal brain cells to change into abnormal tumor cells remains unclear.

Anything that can increase a person’s chance of developing a brain tumor is called a risk factor. Risk factors often influence the development of a brain tumor, but don’t directly cause it to develop. Some people with many risk factors never get a brain tumor, while others without any risk factors do develop a brain tumor.

Risk factors that may raise a person’s chance of developing glioblastoma or anaplastic astrocytoma include exposure to radiation, such as x-rays, and rare genetic disorders. Among the latter are Li-Fraumeni syndrome, neurofibromatosis, and Turcot syndrome.

But very few patients have a genetic disorder that...
increases their chance of developing either of these high-grade gliomas.

Researchers have not linked environmental or occupational factors, such as exposure to electromagnetic radiation or certain chemicals, cell phones, or head injury to the growth of high-grade gliomas, but they continue to study that possibility.8,9

SYMPTOMS

As a high-grade glioma grows, it spreads into normal brain tissue, which may increase pressure on the brain4-6 or disrupt connections between normal brain cells. Symptoms are the result of this pressure and interference with brain function.

Generally, the most common signs of glioblastoma as well as anaplastic astrocytoma are seizures, headaches, and cognitive problems related to thinking, learning, concentrating, remembering, problem-solving, and decision-making.4,5 Seizures and headaches occur in about half of patients with a high-grade glioma.4,8 Other general symptoms include nausea/vomiting, vision problems, and fatigue (tiredness even after sleeping).5,6

Each person will experience unique or different symptoms depending on the location and size of the tumor.5,6,8 The location of a tumor is linked to the symptoms a person may have because the lobes of the brain control different functions. Although the frontal and temporal lobes are the most common locations for glioblastoma and anaplastic astrocytoma, these tumors can be found anywhere in the brain.7

Tumors in the frontal lobe may cause:5

- Memory problems
- Changes in personality and behavior
- Muscle weakness or paralysis
Changes in judgment
Fatigue

Tumors in the temporal lobe may cause:\(^6,18\)

- Seizures
- Memory problems
- Issues with coordination
- Speech, hearing, and vision problems

Large high-grade gliomas tend to be associated with a lot of swelling in the brain near the tumor (known as edema) and pressure inside the skull caused by the growing tumor (known as mass effect or intracranial pressure).\(^8\)

Some people do not have any symptoms and are diagnosed with a brain tumor based on results of tests done for other reasons, such as trauma or migraines. This is called an incidental finding. Others have symptoms that worsen over the course of days to weeks, leading them to seek treatment.\(^8\)

Tell your doctor about all of your symptoms, as this information can inform a diagnosis and help design a treatment plan to relieve symptoms.\(^18\)
DIAGNOSIS

Doctors use different types of tests to find, or diagnose, a brain tumor and learn what type it is and where in the brain it is located. Tests are often done by different specialists and providers who are part of the healthcare team.

**Different Tests**

After getting a thorough medical history from the patient, the doctor will do a physical examination. Neurological exams test a patient’s eye movements, vision, hearing, balance, coordination, and reflexes as well as cognitive skills, such as awareness, attention, speech, language, memory, and judgment. These tests, which are used to help determine which part of the brain the tumor is affecting, are typically done by a clinical neuropsychologist, a psychologist who specializes in understanding the relationship between the brain and behavior.

A computed tomography (CT) scan, a form of imaging, is often ordered first as it is very helpful in identifying the presence of the tumor. But a magnetic resonance imaging (MRI) scan is the preferred test for further evaluating brain tumors because it is more sensitive than CT for identifying important features. Patients with a pacemaker or other artificial metal parts typically cannot have an MRI, so they would have a CT scan. These imaging tests can be used with or without contrast, which is a dye that makes the scanned images clearer.
Positron emission tomography (PET) scans and MR spectroscopy—two other forms of imaging—can help identify glioblastomas in difficult cases, such as those that involve radiation necrosis (death of healthy tissue caused by radiation therapy) or intracranial hemorrhage (bleeding in the brain).

Although imaging tests may give the doctor an educated idea of the tumor type, a biopsy or surgical resection is needed to be sure of the diagnosis. During a biopsy, the neurosurgeon (a doctor who specializes in surgery of the nervous system) surgically removes a small piece of the tumor tissue and sends the sample to a pathologist who will examine it under a microscope. The pathologist will indicate the tumor type and grade in a pathology report sent to the neurosurgeon. When the neurosurgeon removes the entire tumor, or nearly all of it, to send it for pathology testing, it is known as a surgical resection.

If the tumor cannot be reached surgically or the patient is not healthy enough to have surgery, the neurosurgeon may do a stereotactic biopsy, which uses a computer and a 3-dimensional scanning device to help guide the removal of tissue for a biopsy.

Doctors are increasingly using molecular testing to diagnose high-grade gliomas because they pick up on certain mutations or biomarkers found in both glioblastoma and anaplastic astrocytoma. A biomarker is a gene, protein, or other molecule found in blood, other body fluids, or tissues that may be a sign of an underlying condition or disease; the IDH mutation is a biomarker.

All patients with anaplastic astrocytoma and glioblastoma should be tested for an IDH mutation to determine the tumor subtype with immunohistochemistry (IHC) staining. If the staining is negative for IDH mutation, gene sequencing should be completed for anaplastic astrocytoma and younger patients (under 55 years of age) with glioblastoma. Sequencing patients older than 55
years of age with glioblastoma is not required because IDH mutations rarely occur in this age group. The IDH-wildtype subtype is found in about 90% of all glioblastomas while the IDH-mutant subtype makes up the remaining 10%.7

In addition to helping with the diagnosis, knowing the tumor subtype can help the doctor select the best treatment options and offer insight into the tumor’s response to certain treatments.8,9,20

For example, patients with larger glioblastomas also should be tested for MGMT (which stands for O6-methylguanine-DNA methyltransferase) promotor methylation status8; some patients have methylated MGMT tumors and others have unmethylated MGMT tumors. Researchers have found that MGMT-methylated tumors tend to respond well to chemotherapy.20

Molecular testing may involve getting a blood test or sending a tissue sample to a specialty lab.21 While a basic diagnosis is often available within a week, further molecular tests can take several weeks.

Talk to your doctor about conducting molecular tests as they are key to making an accurate diagnosis.

**Tumor Grading**

Primary brain tumors, unlike other cancers, are graded rather than staged because they generally do not travel to other parts of the body. Tumor stage tells where the tumor cells have traveled in the body. A tumor grade tells how normal the tumor cells look when viewed under a microscope.16 Using the WHO’s grading system of I through IV, the higher the grade, the less normal the cells look and the quicker the tumor grows.
Glioblastoma and anaplastic astrocytoma are considered grade IV and grade III tumors, respectively.\(^7\) Grade IV is the highest a tumor can be graded. These high-grade gliomas grow more quickly than low-grade gliomas (grades I and II).\(^1\) Glioblastoma is the most aggressive type of glioma.\(^9\)

As a reminder, in 2021 the WHO decided to change from Roman Numeral grading (I, II, III, IV) to Arabic grading (1, 2, 3, 4) as this is what is currently done for all other tumors. This change may take time to become fully integrated into practice.

Your initial diagnosis of a glioma may change to glioblastoma or anaplastic astrocytoma after the biopsy/surgical resection and test results are complete.

**TREATMENT**

In general, current treatment options (often referred to as standard of care) for glioblastoma and anaplastic astrocytoma are surgery, radiation therapy, and chemotherapy.\(^{20,22}\) Typically, these treatments are used in combination.

Treatment options will depend on many factors. Among them are:\(^6,23\)

- The tumor size, type, and grade
- Where the tumor is located
- If the tumor has invaded other parts of the brain
- Genetic mutations and biomarkers found in the tumor cells
- Symptoms caused by the tumor
- Possible side effects of treatment
- Previous treatments
• The patient’s age, overall health, and treatment preferences
• Prognosis

Although medical and surgical advances in the past two decades have improved survival rates and quality of life for people with glioblastoma or anaplastic astrocytoma, currently there is no cure for these high-grade gliomas. Therefore, treatment goals may be to eliminate or control the tumor, relieve symptoms, improve functioning, prolong life, and/or provide comfort.

No matter what type of treatment a patient decides on, follow-up is essential. During treatment, patients should have a brain MRI every two to three months to assess how well the therapy is working. Generally, repeat MRIs will need to be done less often over time.

Discuss your goals for treatment and quality of life with your doctor, weighing the benefits and risks of surgery as well as other treatment options.

Surgery

Surgery remains the first step in the treatment of glioblastoma and anaplastic astrocytoma. The purpose of having surgery is to:

• Obtain tumor tissue for diagnosis and treatment planning (if a biopsy was not already done)
• Remove as much tumor as possible
• Reduce symptoms caused by the tumor
• Prolong survival
• Reduce the need for corticosteroids

Thanks to recent medical advances, many tools are available to help the neurosurgeon surgically remove as
much of the tumor as possible. These include brain-mapping tools, enhanced imaging devices, and special dyes.

When the whole tumor is removed, the surgery is called a gross total resection.

However, some tumors cannot be fully removed because of their location. In particular, high-grade gliomas are difficult to remove completely because the tumor grows with tentacle-like branches into different areas of the brain. The tumor could be hard to reach or near a vital area in the brain that, if damaged, could affect the patient’s movement, sensation, or speech. Or the patient may not be a good candidate for surgery because of existing health problems. Removing only part of the tumor is called a subtotal resection.

Following surgery, patients should be given an MRI within days to determine how much of the tumor was removed. Studies have shown that patients with high-grade gliomas who had a gross total resection had better outcomes than those who had a subtotal resection.

Common side effects of surgery include pain, edema, scarring, headaches, and scalp pain. Rare side effects include infection, major bleeding, blood clots, seizures, and brain damage.

To learn more, read the ABTA’s Surgery brochure.

Radiation

In most cases, the doctor will recommend radiation therapy to slow or stop the glioblastoma or anaplastic astrocytoma from growing. Though the whole tumor may appear to have been removed during surgery, tumor cells may have grown into the surrounding brain tissue and tiny pieces of the tumor likely remain undetected;
they are too small to be seen on MRI or removed during surgery.\textsuperscript{4,8}

Radiation therapy uses high-energy, very focused rays (either x-rays, photons, or protons) to kill the tumor cells that remain in the brain.\textsuperscript{16} A doctor who specializes in planning radiation therapy treatment is called a \textit{radiation oncologist}.

The most common type of radiation used to treat high-grade gliomas is known as \textit{external beam radiation therapy} (EBRT).\textsuperscript{16,23} There are different methods for doing EBRT, but all of them involve using a machine to deliver the radiation through the skin directly to the high-grade glioma. These include:

- Conventional radiation therapy
- Three-dimensional conformal radiation therapy
- Intensity modulated radiation therapy
- Proton therapy
- Stereotactic radiosurgery (SRS)

All these techniques deliver a precise amount of radiation to the tumor and limit the amount of radiation to nearby healthy brain tissue.\textsuperscript{16,23} Depending on the size and location of the tumor, the radiation oncologist may choose one or a combination of these

Proton therapy: the gantry rotates and directs the protons to the tumor. Photo courtesy of MD Anderson Proton Therapy Center.
radiation techniques. Generally, radiation therapy is given in a series of daily treatments over several weeks.\textsuperscript{4}

Studies suggest that having radiation therapy after surgery increases survival for patients with glioblastoma and anaplastic astrocytoma.\textsuperscript{4,9}

**Common side effects** from radiation therapy include fatigue, hair loss, mild skin reactions, upset stomach, and loss of appetite.\textsuperscript{5,23} While radiation can be very effective in killing tumor cells, it also can harm normal cells.\textsuperscript{4} This damage may result in cognitive changes, such as a decline in mental sharpness, thought processes, and memory.\textsuperscript{4,23}

Patients experience side effects differently. Most side effects go away shortly after treatment is completed.\textsuperscript{23} But some people may experience long-term side effects such as cognitive changes and hormonal problems.

To learn more, read the ABTA’s Conventional Radiation Therapy, Proton Therapy and Stereotactic Surgery brochures.

**Systemic Therapy**

Systemic therapy uses medication to kill tumor cells.\textsuperscript{23} These therapies are usually prescribed by a medical oncologist or neuro-oncologist. A medical oncologist is a doctor who specializes in treating tumors with drugs. A neuro-oncologist is a doctor who specializes in treating
tumors in the central nervous system (referring to the brain and spinal cord) with drugs.

Systemic therapy are medications delivered by an intravenous tube into one’s vein, usually in the arm, or by a pill that is swallowed. Chemotherapy is usually scheduled for a specific number of cycles given over a set time frame.

Systemic therapies used to treat high-grade gliomas are chemotherapy and targeted therapy, both effective methods of cancer treatment. The main difference between them is that chemotherapy kills both cancer cells and healthy cells, while targeted therapy kills mainly cancer cells.

Chemotherapy uses medications to stop or slow the growth of cancer cells.4,23 Temozolomide (also known as TMZ) is an oral chemotherapy drug that has been approved by the U.S. Food and Drug Administration (FDA) to treat glioblastoma and anaplastic astrocytoma.5,6 Most clinicians have adopted temozolomide as the standard chemotherapy for treating patients with high-grade gliomas.9,22

Woman receiving chemotherapy.

Patients with glioblastoma and anaplastic astrocytoma are often prescribed temozolomide as part of a treatment plan that includes surgery and/or radiation therapy.20,22 It may be given at the same time the patient
is undergoing radiation therapy and then following radiation therapy.\textsuperscript{4}

When chemotherapy is used in combination with surgery and radiation therapy, it may improve survival and quality of life in some patients with high-grade gliomas.\textsuperscript{4} Studies have shown that adding chemotherapy to radiation therapy, following surgery, improves survival over radiation therapy alone for newly diagnosed patients with IDH-mutant and MGMT-methylated anaplastic astrocytoma and MGMT-methylated glioblastoma.\textsuperscript{20}

Evidence also suggests that more than 25\% of patients with glioblastoma have a significant survival benefit from adding chemotherapy to their treatment regimen.\textsuperscript{9}

Some patients with glioblastoma and anaplastic astrocytoma with IDH-wild type or MGMT-unmethylated tumors may also benefit from adding chemotherapy to radiation therapy.\textsuperscript{27,28}

Another chemotherapy medication, \textit{carmustine}, is sometimes used to treat high-grade gliomas.\textsuperscript{16} In rare cases, during surgery, carmustine wafers are placed in the area where the tumor was removed. The wafers release chemotherapy directly to the tumor site and eventually dissolve.\textsuperscript{23}

Research has shown that the use of carmustine wafers, which attack any tumor cells that remain in the brain, helps prolong a person’s life.\textsuperscript{16,29,30} There are risks associated with the use of carmustine wafers, so patients should discuss the pros and cons with their doctor.

\textbf{Common side effects} of temozolomide include fatigue, nausea and vomiting, mouth sores, risk of infection, hair loss, loss of appetite, constipation, and diarrhea.\textsuperscript{16,23} Side effects usually stop after the treatment is finished. Common side effects of carmustine wafers may include new or worse seizures within days of having surgery, edema, wound healing issues, nausea, vomiting, constipation, and depression.\textsuperscript{16}
To learn more, read the ABTA’s Chemotherapy brochure.

**Targeted Therapy**

Targeted therapy refers to treatments that target certain proteins that help cause the high-grade glioma to grow and survive.\(^2\) Unlike chemotherapy that can kill all cells, targeted therapy is more precise in killing specific tumor cells with a specific abnormal protein. Currently, there are only a few targeted therapies that will reach the brain tumor at high enough amounts to kill the cancer cells. **The doctor can run molecular tests to identify which proteins the tumor is made of to help determine the best targeted therapy for each patient.**

**Bevacizumab** is an antibody targeted therapy that has been approved by the FDA to treat glioblastoma.\(^5\) It works by targeting a protein known as vascular endothelial growth factor.\(^1\) This protein triggers the making of new blood vessels, which in turn, feed the tumor enabling it to spread and grow.\(^2\) Essentially, the targeted therapy starves the tumor. Studies have shown bevacizumab, which is given intravenously, can improve the quality of life for patients with glioblastoma, but it does not improve survival.\(^3,4\) Typically, it is recommended when other treatments have failed.\(^2\) **Common side effects** of bevacizumab include high blood pressure, diarrhea, fatigue, and weakness.\(^1\) Rare, but severe side effects, include heart issues, stroke, kidney damage, and bleeding.\(^4,1\)

Other targeted therapies are being studied and have shown some promise for treating a small number of glioblastomas.\(^9\) Most of these are given as part of clinical trials.
Ask your doctor if molecular testing can help identify a targeted therapy to treat the tumor.

**Alternating Electric Field Therapy**

Alternating electric field therapy may be a treatment option for patients with either newly diagnosed or recurrent glioblastoma. It involves wearing a portable, battery-operated device that creates low-intensity electric fields, known as Tumor Treating Fields (TTFields), that interfere with the tumor cells’ ability to grow and divide. Using the TTFields device requires placing transducer arrays (adhesive patches) on the patient’s head and using the device for at least 18 hours a day.

Approved by the FDA for the treatment of glioblastoma, research suggests that this device may prolong survival and maintain quality of life when used with temozolomide after radiation therapy plus temozolomide in patients with newly diagnosed glioblastoma. The most common device-related side effects are mild to moderate skin irritation on the scalp and headache. Other side effects are malaise, muscle twitching, fall, and skin ulcers. Side effects of the device when used together with temozolomide are low red blood cell count, nausea, constipation, vomiting, tiredness, seizure, and depression.
STANDARD TREATMENT APPROACHES

**IDH-mutant Anaplastic Astrocytoma**

For patients newly diagnosed with IDH-mutant anaplastic astrocytoma, experts at the National Comprehensive Cancer Network recommend surgery followed by radiation therapy and temozolomide, regardless of how much tumor was removed.\textsuperscript{22} Carmustine wafers may be an option.\textsuperscript{16}

**IDH-wildtype Anaplastic Astrocytoma**

Recommended treatment for patients with IDH-wildtype anaplastic astrocytoma is surgery followed by radiation therapy plus temozolomide during and after radiation therapy.\textsuperscript{22} Ongoing clinical trials are assessing whether taking temozolomide during radiation therapy improves survival for these patients; it has been demonstrated for patients with IDH-mutant anaplastic astrocytoma.

**IDH-mutant and IDH-wildtype Glioblastoma**

Standard treatment for patients with glioblastoma consists of surgery followed by radiation therapy plus temozolomide during and after radiation therapy.\textsuperscript{9} Carmustine wafers or the TTFFields device may be options.\textsuperscript{16}

**Older Patients and Those Less Fit**

In general, patients older than 70 years of age and those who have a harder time performing normal daily activities, sometimes referred to as poor functional status, may be treated less aggressively.\textsuperscript{9,25} Like younger patients, older patients will likely benefit from removing as much tumor as possible during surgery. However, they may have worse side effects from general anesthesia and complications following surgery. Other
medical conditions and medications they take for them can further complicate treatment decisions for older patients.

Therefore, subtotal resection or stereotactic biopsy alone may be a better option than gross total resection for these patients, depending on the tumor's location and size, the patient's overall health, and the treatment goals. They may be given either temozolomide or radiation therapy alone as these patients, in general, tend to tolerate one treatment better than combined treatments. A shortened combination treatment also may be helpful.

Supportive care is essential for all high-grade gliomas.

**PALLIATIVE CARE**

Glioblastoma and anaplastic astrocytoma and their treatments cause physical symptoms and side effects. Relieving them is an important part of supportive care, sometimes referred to as palliative care. Palliative care is for anyone, regardless of their age, or tumor type and stage. It should be started shortly after diagnosis for best results. People who receive palliative care often have less severe symptoms, better quality of life, and are more satisfied with treatment.

Palliative care may include medications, nutritional changes, relaxation techniques, and emotional and spiritual support, among others. As an example, the same drugs used to treat epilepsy may help control seizures caused by the high-grade glioma. Corticosteroids may be used to reduce edema. Antiemetic medications prevent vomiting and help control nausea. Antidepressants may be used to help with depression and anxiety. Sleep aids also may be used as needed.

**CLINICAL TRIALS**

Clinical trials offer individuals the chance to use new or experimental (meaning it has not yet been proven) tests
and treatments before they are available to the public. Many of the treatments discussed in this brochure are available to patients through clinical trials.

Additional targeted therapies and immunotherapies are being studied as possible treatment options for glioblastoma and anaplastic astrocytoma. As researchers learn more about specific gene mutations and other biomarkers, they are pursuing new targeted therapies directed at them. Immunotherapies refer to drugs that enlist the body’s own immune system to fight the tumor. Some types of immunotherapy only target certain cells of the immune system, whereas others affect the immune system in a general way.

In addition to new treatments, some clinical trials focus on new ways to relieve symptoms and side effects while others test new medications and treatment combinations specifically for recurrent tumors. New ways to deliver chemotherapy, which often cannot break through the blood-brain barrier to work, are being studied for the treatment of glioblastoma.

People who want to join a clinical trial volunteer and must meet certain criteria, such as having a specific type of tumor or not having been treated with a certain therapy before. Most clinical trials cover treatment costs.

To learn more, read the ABTA’s Clinical Trials brochure.

Treatments evaluated in clinical trials may or may not be effective or may cause severe side effects. Talk to your doctor to see if a clinical trial is right for you.
**RECURRENT**

Following treatment for a high-grade glioma, patients should schedule regular appointments with their healthcare team to check if the tumor has returned, manage any side effects that continue after the treatment has ended, and monitor their overall health. This follow-up care may include regularly scheduled physical examinations, blood tests, and MRIs.

Follow-up care is an important part of a person’s overall care plan because even if the whole tumor appears to have been removed, high-grade gliomas are likely to recur. The tumor tends to return near the same place where it was first found.

If, and when, a high-grade glioma returns, the doctor will perform a new round of tests to learn as much about the recurrent tumor as possible to help figure out the best treatment options. In addition to an MRI or CT scan, tests may include an MR spectroscopy, MR perfusion, or PET scan.

Sometimes, what appears to be a recurrence is actually a phenomenon known as pseudoprogression or radiation necrosis which is when the area around the tumor mimics tumor growth on an MRI. Pseudoprogression tends to occur closer to the completion of radiation therapy, whereas radiation necrosis tends to occur later.

Radiation changes can be hard to tell from disease progression and may contribute to pseudoprogression seen on a scan. Distinguishing pseudoprogression and radiation necrosis on imaging test results from actual tumor growth is important as it can affect the diagnosis and treatment options.

In general, treatments for a recurrent high-grade glioma may include additional surgery, radiation therapy...
(depending on whether or how much radiation was given after the original diagnosis), chemotherapy, targeted therapy, and clinical trials.\textsuperscript{4,22,42}

Patients may benefit more from re-treatment if they have:\textsuperscript{4}
- Good overall health
- A smaller amount of tumor present
- A longer time between original treatment and recurrence

The best candidates for having additional surgery are individuals with a large, well-defined high-grade glioma that can be removed entirely or close to it, and whose tumor has recurred after a longer time has passed since the original tumor was treated.\textsuperscript{42} These patients then are evaluated for the next treatment based on prior treatments. About 20\% to 30\% of patients with recurrent glioblastoma are candidates for a second surgery.

The benefits of re-treating patients with radiation therapy for a recurrent high-grade glioma is being evaluated in clinical trials.\textsuperscript{25} Re-irradiation may benefit select patients, such as those with a small recurrent tumor and good functional status.\textsuperscript{42} If re-irradiation is suggested, advanced forms of radiation, such as stereotactic radiosurgery or brachytherapy, may be used to deliver very high doses of radiation with great accuracy, while minimizing the amount of radiation to nearby healthy tissue.\textsuperscript{42,43}

There is some evidence to suggest that these advanced forms of radiation may prolong the lives of patients being treated for recurrent high-grade glioma.\textsuperscript{42} Younger patients with better functional status and a longer time between treatment for the original and recurrent tumor may be the best candidates for re-irradiation.\textsuperscript{44}
Temozolomide, lomustine, and bevacizumab are the standard systemic therapies used to treat recurrent high-grade glioma. They may be used alone or in combination, depending on a patient's treatment history, functional status, side effects experienced in the past, tumor size and surrounding edema, corticosteroid needs, and patient preferences.

In general, bevacizumab may be a better option for patients who have significant edema or side effects from corticosteroids, whereas temozolomide may be better for patients whose tumor has returned after a period of observation. Observation is when a patient's condition is carefully watched, but the patient is not given treatment unless the tumor grows, or symptoms change.

Temozolomide also may be an option for some patients, such as those who have relapsed several months after completing treatment with temozolomide for an MGMT-methylated tumor. In general, however, chemotherapy is not as effective in treating recurrent high-grade glioma as it is treating the original tumor. That is likely because the recurrent tumor cells become resistant to the temozolomide.

Bevacizumab has shown promising results for alleviating symptoms in recurrent anaplastic astrocytoma and glioblastoma. In most studies, it has improved quality of life, but not overall survival.

TTFields also may benefit patients with recurrent glioblastoma. Research suggests that patients who used a TTFields device lived as long as individuals who received chemotherapy for a recurrent glioblastoma as well as had fewer side effects and a better quality of life in certain cases.

Clinical trials are often important in the treatment of recurrent tumors. This is especially true when standard options are limited.
Treatments aimed at relieving a person’s symptoms and side effects should be part of the care plan for all patients with recurrent glioblastoma and anaplastic astrocytoma.42

Talk to your doctor about the risk of your tumor returning and discuss how to monitor it with your healthcare team.

PROGNOSIS

Prognosis refers to the chance of recovery or survival from a disease. A prognosis is based on statistics that look at a large group of people with the same disease over time. Keep in mind that statistics on survival rates are estimates. Typically, they are measured every five years, so the latest estimates may not include the most current methods of diagnosing and treating glioblastoma and anaplastic astrocytoma.45

A patient’s prognosis should consider the following factors:

- **How much tumor remains in the brain after surgery**
  The prognosis is better when all or most of the tumor can be surgically removed.2,8,9

- **The tumor's genetic subtype**
  IDH-mutant high-grade gliomas have better outcomes than IDH-wildtype tumors8,20,22 and MGMT-methylated glioblastomas have a better prognosis than MGMT-unmethylated tumors.20

- **Age**
  Generally, younger people tend to have a better prognosis than older adults.9,20,37
  However, older adults tend to receive less aggressive therapy, which may play a role in this poorer prognosis.34
• Functional status

Overall, people who are better able to carry out daily activities have a better prognosis than those who cannot.\textsuperscript{20}

During the past 20 years, more refined surgeries, a better understanding of the types of tumors that respond to different treatments, and more precise radiation therapy have significantly prolonged the lives of many people with high-grade glioma and improved their quality of life.\textsuperscript{23} Still, recovery from glioblastoma or anaplastic astrocytoma is not always possible.\textsuperscript{4}

When the tumor cannot be cured or controlled, the cancer is called advanced or terminal.\textsuperscript{23} Hospice care offers the best possible quality of life for people who are not expected to live longer than six months.\textsuperscript{4,23} Hospice care can be provided at home or in a healthcare setting. In-home hospice care requires nursing care and special equipment. Support services are available that can help individuals cope with an advanced tumor diagnosis.

The following are the 1-year, 5-year and 10-year survival rates for individuals diagnosed with glioblastoma or anaplastic astrocytoma, as presented by the Central Brain Tumor Registry of the United States.

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>1-Year Survival Rate</th>
<th>5-Year Survival Rate</th>
<th>10-Year Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glioblastoma</td>
<td>43%</td>
<td>7%</td>
<td>5%</td>
</tr>
<tr>
<td>Anaplastic Astrocytoma</td>
<td>66%</td>
<td>31%</td>
<td>23%</td>
</tr>
</tbody>
</table>

Source: CBTRUS, 2018

Talk to your doctor about your prognostic factors, as listed above, to get a more individualized prognosis.
FUTURE DIRECTIONS

The growing knowledge of the molecular make-up of tumors and their role in brain tumor development has allowed researchers to further categorize glioblastoma and anaplastic astrocytoma in ways that are having a significant impact on both treatment and survival. But there is much more work to be done.

Knowing the genetic and biological make-up of the tumor is an important first step in developing drugs that target and kill the cancer cells. Molecular testing is playing an increasingly greater role in helping make that determination. In addition to MGMT promoter status and the known mutations in the IDH gene, researchers are discovering new genetic mutations and biomarkers linked to high-grade gliomas. They continue to identify additional subtypes that were just added to the 2021 WHO classification update and will likely identify more that will be added to the next update.

The hope is that this better understanding will lead to better and more precise treatment. Together, the medical and scientific communities, supporting organizations, and the patients and their families are building on past successes toward a better cure for all persons diagnosed with glioblastoma and anaplastic astrocytoma.
AMERICAN BRAIN TUMOR ASSOCIATION
INFORMATION, RESOURCES AND SUPPORT

Educational brochures are available on our website or can be requested in hard copy format for free by calling the ABTA. Most brochures are available in Spanish, with exceptions marked with an asterisk.

General Information
About Brain Tumors: A Primer for Patients and Caregivers
Brain Tumor Dictionary*
Brain Tumors Handbook for the Newly Diagnosed*
Caregiver Handbook*

Tumor Types
Ependymoma
Glioblastoma and Anaplastic Astrocytoma
Medulloblastoma
Meningioma
Metastatic Brain Tumors
Oligodendroglioma and Oligoastrocytoma
Pituitary Tumors

Treatment
Chemotherapy
Clinical Trials
Conventional Radiation Therapy
Proton Therapy
Stereotactic Radiosurgery*
Steroids
Surgery
Information
ABTA WEBSITE | ABTA.ORG
Offers more than 200 pages of information, programs, support services and resources, including: brain tumor treatment center and support group locators, caregiver resources, research updates and tumor type and treatment information across all ages and tumor types.

Education & Support

• ABTA Educational Meetings & Webinars
  In-person and virtual educational meetings led by nationally-recognized medical professionals.

• ABTA Patient & Caregiver Mentor Support Program
  Connect with a trained patient or caregiver mentor to help navigate a brain tumor diagnosis.

• ABTA Connections Community
  An online support and discussion community of more than 25,000 members.

• ABTA CareLine
  For personalized information and resources, call 800-886-ABTA (2282) or email info@abta.org to connect with a CareLine staff member.

Get Involved

• Join an ABTA fundraising event.

• Donate by visiting abta.org/donate.

Contact The ABTA
CareLine: 800-886-ABTA (2282)
Email: info@abta.org
Website: abta.org
REFERENCES


11. CBTRUS, p.17.

12. CBTRUS, p.21.

13. CBTRUS, p.46.

14. CBTRUS, p. 53.

15. CBTRUS, p.84.


