

AMERICAN BRAIN TUMOR ASSOCIATION

Glioblastoma and Malignant Astrocytoma



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To learn more about the ABTA, visit www.abta.org.

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Glioblastoma and Malignant Astrocytoma

ABOUT THIS PUBLICATION

This brochure is about glioblastoma (also called grade IV astrocytoma) and malignant astrocytoma (grade III astrocytoma). Collectively, these are both “high-grade” astrocytomas.

INTRODUCTION



Astrocyte

Any tumor that arises from the glial (from the Greek for “glue”), or supportive tissue, of the brain is called a “glioma.” One type of glioma is the astrocytoma.

Astrocytomas are named after astrocytes, the star-shaped cells from which they grow.

Astrocytomas are graded to describe their degree of abnormality. The most common grading system uses a scale of I to IV. Tumors also may be grouped by their rate of growth: low grade (slow growth), mid grade (moderate) and high grade (rapid). On that scale, a grade I glioma is accurately considered benign, in that complete surgical excision is considered curative. These tumors, however, are diagnosed almost exclusively in childhood. Grade II gliomas are often designated “low-grade,” as the label “benign” fails to reflect the common tendency of these tumors to recur. Many patients with grade II gliomas are done

a great disservice by being told that their tumors are benign. Patients with grade II gliomas require serial monitoring by MRI or CT scan for surveillance of tumor recurrence. The terms “malignant glioma” and “high-grade glioma” encompass both grade III and IV gliomas, and reflect the fact that management of these tumors is fairly similar, with some important exceptions. The word “anaplastic” means malignant. An anaplastic astrocytoma is a grade III or mid grade tumor and diffusely infiltrates neoplasm that demonstrates focal or dispersed anaplasia and an increased growth index compared with grade I and II astrocytoma. The histological diagnosis is based on nuclear atypia and mitotic activity.

Glioblastoma or glioblastoma multiforme (“multiforme” is no longer part of the WHO designation, though glioblastoma is still often abbreviated “GBM”) is the highest grade glioma (grade IV) tumor, is the most malignant form of astrocytoma, and is synonymous with a grade IV glioma. The histologic features that distinguish glioblastoma from all other grades are the presence of necrosis (dead cells) and increase of blood vessels around the tumor. Grade IV tumors are always rapidly growing and highly malignant tumors.

In this new era, molecular markers have been intensively explored to overcome the limitation in the histopathological diagnosis of gliomas. Gene expression profiling has given rise to new molecular classification schemes. This classification by gene expression profiling has also revealed molecular classes not detected by traditional methods of looking at tumor samples under a microscope. The promoter methylation of the O6-methylguanine methyltransferase (MGMT) gene has been found to predict a longer length of survival, and a person’s response to

certain chemotherapeutic agents in the treatment of glioblastoma.

In early studies in 1984, EGFR (*epidermal growth factor receptor*) expression or overexpression was found in glioblastoma. *IDH1* (Isocitrate dehydrogenase) and some *IDH2* were found in certain subsets of glioblastoma. These markers are beginning to be used as a diagnostic test for predicting longer survival and for evaluating the efficacy of new targeted molecular drugs. The Cancer Genome Atlas (TCGA), a project of the National Institutes of Health (NIH), led to new development of the classification of glioblastoma. Four distinct molecular types of glioblastoma became apparent. These specific glioblastoma types may lead to different treatment regimens. Incorporating molecular techniques into patient's tumor analysis will allow for the promise of personalized medicine by targeted cancer drugs.

INCIDENCE

About 50% of gliomas are glioblastomas. They are most common in adults ages 45–65, and affect more men than women. Glioblastomas arise from normal brain tissue. They may invade and migrate away from the main tumor within the brain; however, glioblastoma will rarely spread elsewhere in the body. There are two subtypes of glioblastoma: *de novo* (new or primary) and secondary. *De novo* tumors arise quickly and tend to make their presence known abruptly. They are the most common, and a very aggressive form of glioblastoma. *De novo* tumors account for the majority of glioblastomas in persons age 55 and older. Secondary glioblastomas, most often found in patients ages 45 and younger, typically start as low-grade or mid-grade astrocytoma which have been genetically programmed to eventually transform into malignant, rapidly growing glioblastomas. Anaplastic astrocytomas occur more often in younger adults.

Anaplastic astrocytomas occur more often in younger adults. About 9% of childhood brain tumors are glioblastomas. Scientists are now developing tests that may help better identify these two subcategories of glioblastoma.

Between 1% and 7% of people with glioblastomas and about 4% of people with anaplastic astrocytomas are found to have multiple tumors at the time of diagnosis.

CAUSE

Brain tumors cannot be prevented. The cause of these tumors and other types of brain tumors is unknown. Genes are the fundamental building blocks found in all body cells. Scientists have identified abnormalities in the genes of different chromosomes which may play a role in the development of tumors. However, what causes those abnormalities is still uncertain.

Scientists are conducting environmental, occupational, familial and genetic research to identify common links among patients. Despite a great deal of research on environmental hazards, no direct causes have been found.

The majority of brain tumors are not hereditary. Brain tumors can be caused by a genetically inherited syndrome, such as Neurofibromatosis, Li-Fraumeni, Von Hippel-Lindau, Turcot and Tuberous Sclerosis, affecting only 5% of patients.

SYMPTOMS

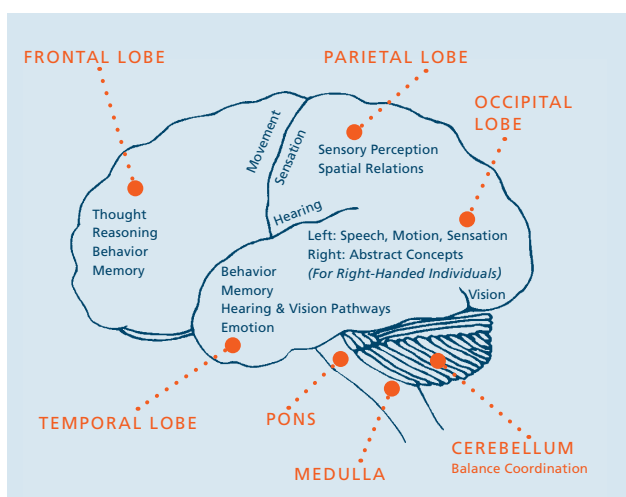
As a brain tumor grows, it may interfere with the normal functions of the brain (see diagram at right). Symptoms are an outward sign of this interference.

Since the skull cannot expand in response to the growth of a tumor, the first symptoms are usually due to increased pressure in the brain. Headaches, seizures,

memory loss and changes in behavior are the most common symptoms. Loss in movement or sensation on one side of the body, language dysfunction and cognitive impairments are also common. Other symptoms may also occur depending on the size and location of the tumor.

DIAGNOSIS

To obtain an accurate diagnosis, your doctor will begin with a neurological examination followed by an MRI or CT scan. The scan may be done with a contrast dye that makes the border and details of the tumor more visible. If you have a tumor, the scan will help your doctor determine the size, location and probable type of tumor. Some physicians may also request an MRS (magnetic resonance spectroscopy) scan which measures chemical and mineral levels in a tumor. Those measurements may give a suggestion as to whether a tumor is malignant or benign. It may also help distinguish a brain tumor from other medical problems, such as infection (tuberculosis, parasite, bacterial and fungus), demyelination (a disease that damages the myelin, or protective sheath, of a brain's neurons) or a stroke. On MRI with contrast, high grade gliomas show brightly (this is called enhancement); low



Functions of the lobes of the brain

grade gliomas frequently do not enhance with contrast, or slightly enhance. However, only the examination of a patient's tumor tissue under a microscope can confirm an exact diagnosis.

TREATMENT

SURGERY

Generally, the first step in the treatment of glioblastomas is surgery. With today's modern techniques, surgery is generally safe for most patients. The goals of surgery are to obtain tumor tissue for diagnosis and treatment planning, to remove as much tumor as possible, and to reduce the symptoms caused by the presence of the tumor. In some circumstances, such as certain medical conditions or concerns about the location of the tumor, a biopsy may be done in place of the surgery. The tissue obtained during the biopsy is then used to confirm the diagnosis. Diagnosis is based upon the most visible cell structure change and growth activity seen in the tissue, even if the features are found in only a few cells. Performing a surgical resection provides a larger number of cells, leading to a more accurate diagnosis, which can greatly influence management and treatment options.

Optimally, the neurosurgeon would like to remove as much of the tumor as possible. However, due to the location of the tumor – where movement, sensation or speech would be affected – some tumors cannot be completely removed. Partial tumor removal may be performed to decrease the amount of swelling in the brain or to reduce seizure activity.

Surgery to remove a brain tumor is carried out by making an opening in the skull over the tumor in what is known as a craniotomy. Several specialized pieces of equipment are available to the neurosurgeon. Brain mapping and functional MRIs help the neurosurgeon

determine and avoid vital areas of the brain during surgery. Stereotactic computerized equipment, image-guided techniques or an intra-operative MRIs can be used by the surgeon as navigational tools – much like a GPS system. These tools help to guide the neurosurgeon's access into some of the difficult or deep areas in the brain. Lasers may be used during surgery to vaporize tumor cells. Ultrasonic aspirators are tools which break apart and suction out the tumor. High-powered microscopes help the neurosurgeon to better see the tumor.

Because the tentacle-like cells of an astrocytoma grow into the surrounding tissue, these tumors cannot be totally removed. Surgery is helpful, however, as partial removal can help decrease symptoms and the tissue obtained during the surgery confirms the type of tumor. Radiation, chemotherapy and/or bio-therapy are then used to treat the remaining tumor.

RADIATION

In adults, radiation therapy usually follows a biopsy or surgery. There are different types of radiation which may be given using various doses and schedules.

Conventional fractionated external beam radiation is “standard” radiation given five days a week for five or six weeks. External beam radiation is actually the same radiation you get with a simple chest X-ray. Conventional radiation for high-grade astrocytomas is usually aimed at the tumor site and the area around the tumor.

A form of “local radiation” may be used to boost conventional radiation. Most forms of local radiation treat the tumor while protecting the healthy cells surrounding the tumor. They include:

- Conformal photon radiation, also known as intensity-modulated radiation therapy (IMRT) or 2-D and 3-D conformal radiation therapy, conforms radiation beams to match a tumor's shape and size.

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- Image-guided radiation therapy (IGRT) is the technique of using image technology at the time of each treatment to verify accurate position of tumor.
 - Proton beam therapy provides optimal dose distribution when protons are attracted to a specific tumor target.
 - Interstitial radiation, in the form of solid or liquid radiation, may be implanted into the tumor during surgery.
 - Stereotactic radiosurgery (SRS) and Fractionated stereotactic radiosurgery (FSRS) are special forms of precisely focused, high-dose radiation for delivery to a small, localized tumor as a single dose treatment or fractionated treatment over four to five days.
 - Photodynamic therapy uses a sensitizing drug and laser light to destroy tumor cells.
 - Boron neutron capture therapy releases radioactive compounds within the tumor.

Radiation sensitizing drugs, chemotherapy during radiation therapy, and drugs that increase oxygen levels in the brain are being studied as ways of making tumor cells more sensitive to radiation or enhancing the effects of radiation. Monoclonal antibodies may be capable of carrying radiation or drugs to the tumor site.

Many of these radiation techniques are investigational and offered in organized testing plans called “clinical trials.” Your doctor can tell you if the radiation technique you are considering is a standard treatment or an investigational treatment.

CHEMOTHERAPY

For newly diagnosed GBM, a six-week course of temozolomide is given concurrently with radiation. Temozolomide is an alkylating agent with reasonable blood-brain barrier penetration. Some oncologists recommend taking temozolomide one hour prior

to radiation therapy to maximize its purported radiosensitizing effect, though for practical reasons nighttime administration may be more feasible for some patients. For more information on Temozolomide, visit the ABTA website at www.abta.org.

Researchers continue to look for new drugs to treat glioblastoma and anaplastic astrocytoma, and there are many drugs under investigation. Some of these drugs have proven useful in treating other types of tumors in the body, and still others are standard brain tumor drugs given in a different way. Because chemotherapy drugs can affect normal cells, patients can expect side effects such as hair loss or lack of appetite from treatment.

Most chemotherapy drugs fall into one of two groups: *cytotoxic* drugs and *cytostatic* drugs. Cytotoxic drugs are designed to destroy tumor cells. They work by making tumor cells unable to reproduce themselves. Carmustine (Gliadel or BCNU), Lomustine (CCNU), temozolomide (Temodar) procarbazine, cisplatin, carboplatinum, Etoposide and irinotecan are examples of cytotoxic drugs.

Cytostatic drugs are used to alter the behavior of a tumor. These drugs work by changing the tissue in and around the tumor. There are several different types of cytostatic drugs. For example, angiogenesis inhibitors are cytostatic drugs that stop the growth of new blood vessels around a tumor. Differentiating agents, such as phenylbutyrate, phenylacetate or retinoid are cytostatic drugs which make malignant cells look and act like normal cells. Sometimes, cytotoxic and cytostatic chemotherapy drugs are combined in an attempt to increase both of their effectiveness.

Some of these drugs have been approved by the Food and Drug Administration (FDA) for the treatment of high-grade brain tumors. Others have received approval in the treatment of other cancers, and thus must be prescribed “off-label” for brain tumor use.

Researchers are also developing new ways of delivering drugs to the tumor. Convection-enhanced delivery, or CED, uses a pump to slowly “flow” a chemotherapy drug or biologic substances into the tumor site. In another method, a biodegradable carmustine wafer is left in the tumor cavity after surgery to release a chemotherapy drug into the remaining tumor tissue. Other researchers are working with microparticles which release drugs into the tumor at a pre-determined rate.

Chemotherapy may be used in infants and very young children to delay radiation therapy until the age of three or four. At that point, the child’s brain is more fully developed and better able to tolerate radiation therapy. Clinical trials are underway to evaluate the most effective ways of treating these tumors in infants and children.

SYMPTOMS MEDICATION MANAGEMENT

There are several drugs used to relieve the symptoms of a brain tumor. Steroids are drugs used to decrease swelling (edema) around the tumor. The most frequently prescribed steroid for brain tumor patients is dexamethasone. Steroids should be tapered to the lowest dose necessary to alleviate symptoms. In some cases, this can be done rapidly, though in other cases, it is necessary to maintain patients on a standing steroid dose. Many patients, particularly those with tumors associated with significant mass effect, require a low dose of steroids at least through radiation therapy.

Anti-epilepsy drugs control seizures, although special precaution must be taken to achieve optimal dosing while maintaining the effectiveness of chemotherapy. Patients who present with seizures should be treated with antiseizure medications indefinitely. However, patients without a seizure history who are placed on antiepileptic medications prior to surgery should be tapered off, as the relatively small benefit of preventing a first-time seizure is generally outweighed

by potential adverse drug effects. There are no strict guidelines that establish an antiseizure medication of choice; however, there has been a general shift away from phenytoin in favor of levetiracetam. Both agents are effective, but levetiracetam has a favorable adverse effect profile, minimal drug-drug interactions (an important consideration for chemotherapy) and does not require routine drug level monitoring.

During the treatment, the degree of fatigue that patients experience ranges from minimal (e.g., not affecting the ability to perform full-time work) to profound (e.g., spending the majority of the day in bed), though generally is tolerable. Brain activating agents such as modafinil and methylphenidate can occasionally reduce fatigue. Most patients adjust their lifestyles to accommodate for fatigue. Regular exercise has been shown to decrease fatigue. Anti-emetic drugs prevent vomiting and help control nausea. Anti-depressant, anti-anxiety medications or sleeping medications may be also considered to improve quality of life during the treatment.

BIOLOGIC AND TARGETED THERAPIES

Purposeful altering of the natural behavior of tumor cells is a newer area of medicine called “biologic” or “targeted therapy.” Some of the substances used in this type of therapy are found in nature, others in chemicals with side effects that may alter tumor cells. These new molecular targeted therapies, which are still under investigation, are designed to stop messages going into the tumor cell, which will subsequently halt growth. Several pathways in the brain encourage cell growth. The relevant growth factor pathways in malignant glioma include EGF (epidermal growth factor), PDGF (platelet derived growth factor), VEGF (vascular endothelial growth factor), IGF (insulin-like growth factor) and HGF/SF (hepatocyte growth factor/scatter factor). In GBM, several growth factor receptors (e.g. EGFR, VEGFR, PDGFR) are overexpressed or mutated, which causes cells to grow

out of control, increased survival of abnormal cells and increased blood supply to the tumor. Specific drugs that inhibit these growth receptors have been developed in clinical trials. Cellular signaling pathways – pathways where one reaction causes another reaction in the cells – are very important in cell growth, not stopping abnormal cells from dying, causing tumor invasion into normal tissue and stimulating a new blood supply to tumors. Drugs to counteract these abnormal reactions are being developed.

Vaccine immunotherapy is a new and exciting area of treatment designed to trigger the body's own immune system to fight and halt tumor growth. Recent breakthroughs in understanding of the mechanisms, leading to full T-cell activation and recognition of the importance of overcoming tumor-induced immunosuppressive mechanisms, have shed a new light on how to generate effective anti-tumor response and sparked a renewed and enthusiastic effort to apply this method as a treatment for malignant brain tumors. These treatments include cancer vaccines that utilize a tumor's antigens. Antigens have signals that alert the system there are abnormalities in cells. The vaccine attacks the cells by using a genetically engineered dendritic cells to stimulate the immune system and cause a response. Dendritic cells are potent immunostimulatory cells that continuously look for antigens, and then activate a strong immune response. Immunotherapy may represent the next frontier of the most promising personalized therapies.

Other researchers are using gene therapies as a way of controlling tumor growth. In one method, specially-engineered genes make tumor cells more susceptible to drug therapy. In another method, gene therapy is used to stimulate the body's natural production of immune substances. Or, gene therapy may be used to restore

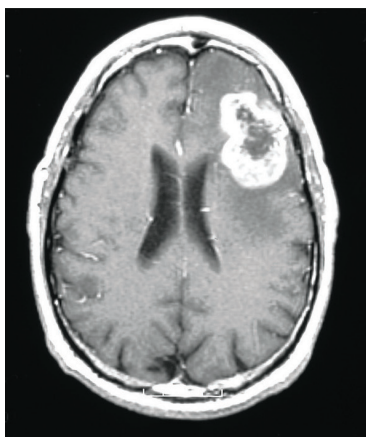
the normal function of tumor suppressing genes within tumor cells.

Recent evidence has suggested a subset of brain cancer cells, variably termed brain cancer-propagating cells (BCPCs) or cancer stem cell may underlie the growth of GBM and be responsible for their resistance to therapy. Key signaling pathways essential for the development and regulation of neural stem cells are active in BCPCs of GBM. Targets for new treatments will be found in these signaling pathways. It is unclear whether BCPCs are the only source of growth of GBM because there are other types of tumor cells that may be causing growth. A combination of several treatments may be required to manage the various origins of tumor growth.

CLINICAL TRIALS

Several of the treatments discussed in this publication are available to patients through clinical trials. Trials are open for both patients with newly-diagnosed tumors and those with recurrent tumors.

Clinical trials test the safety and effectiveness of treatments that have already shown significant promise in laboratory studies. For patients, they provide access to



Contrast-enhanced MRI scan of a glioblastoma multiforme
Photo courtesy of Jeffrey Bruce, MD

therapies that would otherwise be unavailable. All clinical trials, conducted in phases – I, II and III – are overseen by government and local hospital boards, and are subject to rigorous regulation and oversight.

The American Brain Tumor Association's TrialConnect® service matches patients with appropriate clinical trials based on tumor type and treatment history. Patients or families can contact a TrialConnect® specialist at 877-769-4833, Monday through Friday, from 8:30 a.m. to 6:30 p.m. EST, or create a patient profile at: www.abtatrialconnect.org.

EVALUATING A TREATMENT

When evaluating a treatment, ask your doctor how the recommended treatment will affect your prognosis. What are the expected benefits of this treatment? What are the risks? What quality of life can you expect during and after the treatment? If this is an investigational treatment, how many patients with your tumor type have received this treatment, and what were their results?

Before evaluating any treatment in clinical trials, ask your doctor the same questions about prognosis, benefits and risks that you would ask when evaluating another treatment.

Also understand in which phase (I, II or III) of this investigation you would be participating.

RECURRENCE

To measure effectiveness of treatment and to monitor for possible tumor recurrence, an initial follow-up scan will be done about two to six weeks following completion of radiation therapy. The scan will be repeated every two to three months for about a year, then on a schedule set by your doctor.

During this time, some patients may continue to receive ongoing temozolomide chemotherapy

treatment, which is typically administered each month as a monthly maintenance five day schedule for 6–12 months.

High-grade astrocytomas can be aggressive tumors. Over time they may recur, and when they do, it may be as a higher grade tumor. Sometimes the tumor cells move, or migrate, into the surrounding tissue and give rise to another tumor. Most high-grade astrocytomas recur at, or near, the original site. While tumor recurrence on the opposite side of the brain and outside of the central nervous system is rare, it is occurring more often as patients live longer.

Recurrent tumors can be treated. Depending on the patient's overall medical condition and the growth characteristics of the tumor, a second surgery may be considered. Although a course of conventional radiation can be given only once, a form of stereotactic radiation may be given after conventional radiation. Therapy with a second drug (such as bevacizumab or carmustine) may be considered even if prior drug treatment was not effective. In addition, implanted biodegradable wafers (Gliadel) containing the chemotherapy drug BCNU may be considered for glioblastoma patients undergoing surgery for removal of a recurrent tumor. Most biological, targeted drug and vaccine therapies are available to those with recurrent tumors as part of clinical trials.

PROGNOSIS

“Prognosis” means a prediction of outcome. This information is usually based on information gathered from *groups* of people with the same disease. It is important to remember these statistics are not individualized. How well a person responds to treatment is affected by the grading of malignancy of the tumor cells, the amount of tumor removed and their general health. Age also plays a key role in outcome. Younger adults and children tend to have a better prognosis.

Because these tumors are apt to grow into surrounding tissue, anaplastic astrocytomas and glioblastomas can be very difficult to treat. Without treatment, these aggressive tumor cells multiply rapidly. The goal of treatment is to slow down that process, control tumor growth and improve life quality.

Prognosis is usually reported in years of “median survival.” Median survival is the time at which *an equal number of patients do better and an equal number of patients do worse*. With standard treatment, median survival for adults with an anaplastic astrocytoma is about two to three years. For adults with the more aggressive glioblastoma, treated with concurrent temozolamide and radiation therapy, median survival is about 14.6 months with a two-year median survival rate of 30%. However, a 2009 study reported that almost 10% of patients with glioblastoma may live five years or longer.

Children with high-grade tumors (grade III and IV) tend to do better than adults; five year survival for children is about 25%.

In addition, glioblastoma patients who have had their MGMT gene shut off by a process called methylation, also have prolonged survival rates. The MGMT gene is thought to be a significant predictor of response.

However, not all glioblastomas have the same biologic abnormalities. This may be the reason different patients respond differently to the same treatments and why different patients with the same tumor have different outcomes. Researchers continue to study the common characteristics of long-term brain tumor survivors, and how personalized and targeted treatments may be more optimally used to treat brain tumor patients.

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are available at www.abta.org.*

AMERICAN BRAIN TUMOR ASSOCIATION

8550 W. Bryn Mawr Avenue, Suite 550
Chicago IL 60631

**For more information contact
an ABTA Care Consultant at:**

CareLine: 800-886-ABTA (2282)

Email: abtacares@abta.org

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