

Glioblastoma & Anaplastic Astrocytoma



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Glioblastoma & Anaplastic Astrocytoma

ABOUT THIS PUBLICATION

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

INTRODUCTION



Astrocyte

Any tumor that arises from the glial (from the Greek word 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 growth) and high-grade (rapid growth).

On that scale, a grade I glioma is accurately considered benign. With these tumors, a complete surgical excision is considered curative; however, they are diagnosed almost exclusively in childhood.

Grade II gliomas are often designated as *low-grade* tumors because the label “benign” fails to reflect the common tendency of these tumors to recur. Patients with grade II gliomas require serial monitoring by MRI or CT scan for surveillance of tumor recurrence every 6-12 months.

The terms *malignant glioma* and *high-grade glioma* encompass both grade III and IV gliomas. Management of these tumors is fairly similar, but there are some important exceptions.

The word *anaplastic* means malignant. An anaplastic

astrocytoma is a grade III or high-grade tumor that demonstrates focal or dispersed anaplasia (abnormal, irregular shape) cells and an increased growth index compared to grade I and II astrocytoma. The pathological diagnosis is based on appearance of cells (nuclear atypia) and growth rate (mitotic activity).

Glioblastoma (often abbreviated *GBM*) is a grade IV glioma tumor. It is the most malignant form of astrocytoma. The features under the microscope that distinguish glioblastoma from all other grades is the presence of necrosis (dead cells) and the increase of abnormal growth of blood vessels around the tumor. Grade IV tumors are always rapidly growing and highly malignant tumors.

In the past, brain tumor diagnoses were made by examining the physical appearance of the tumor cells under a microscope. In addition to this information, it is more common today to incorporate a tumor's molecular and genetic information into its diagnosis. This extra information leads to greater diagnostic accuracy, more accurate prognosis and treatment response, and improved disease management.

For example, tumors with methylated MGMT (inactive gene) have been found to predict a longer length of survival and tend to respond better to chemotherapy like temozolomide (Temodar).

The IDH1 gene encodes for a metabolic enzyme called isocitrate dehydrogenase 1, which catalyzes the conversion of isocitrate to alpha-ketoglutarate as part of normal function of brain metabolism. A mutation in this gene was discovered in a small percentage of glioblastoma samples in 2008 and has since been found in a majority of low-grade gliomas and secondary high-grade gliomas.

The IDH1 gene is used to further classify GBM into two subtypes:

- > **Glioblastoma, IDH-wildtype:** Occurs in about 90% of cases, usually in people age 55 or older.
- > **Glioblastoma, IDH-mutant:** Occurs in about 10% of

cases, commonly in people age 45 or younger. This subtype often progresses from a lower grade glioma.

Anaplastic astrocytoma tumors are also classified as IDH-mutant and IDH-wildtype. The IDH-wildtype anaplastic astrocytomas could be considered “pre-glioblastomas,” because they have a poorer prognosis than those with the IDH mutation. IDH mutations tend to occur in younger brain tumor cases, most commonly between the ages of 20 and 40. The mutation is also associated with tumors of the frontal lobe, with approximately 70% of IDH-mutated gliomas located there. IDH1 mutations may serve as a predictive biomarker to guide aggressive surgical resection.

Incorporating molecular techniques into a patient’s tumor analysis will allow for the promise of precision medicine by combination of targeted cancer drugs.

INCIDENCE

An estimated 26,170 new cases of primary malignant brain tumors are expected to be diagnosed in the US in 2019. About 56% of gliomas are glioblastomas with 13,310 new cases predicted in 2019. They are most common in adults ages 45–65 and affect more men than women. Glioblastomas arise from normal brain tissue. Glioblastomas may migrate away from the original tumor site, but they rarely spread elsewhere in the body.

Glioblastomas are more common in older adults and less common in children. These tumors comprise approximately 3.1% of all brain and other central nervous system tumors reported among ages 0-19.

CAUSE

Brain tumors cannot be prevented. The cause of these tumors and other types of brain tumors is unknown. 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.

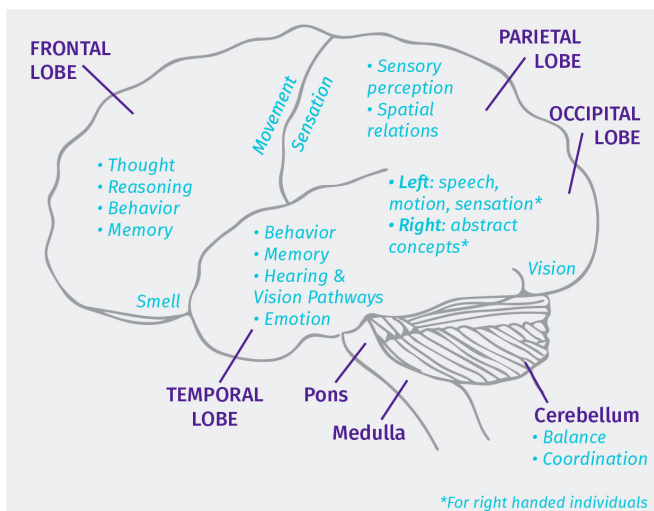
Scientists are conducting environmental, occupational, familial and genetic research to identify common links among patients. Despite a great deal of research on

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, but these only affect 5% of patients.

SYMPTOMS

As a brain tumor grows, it takes up space in the skull. Since the skull cannot expand in response to this growth, pressure is placed on brain tissue. Symptoms are the result of this pressure interfering with brain function. 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, a 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 grade gliomas frequently do not enhance with contrast or only slightly enhance. However, only the examination of a patient's tumor tissue under a microscope and molecular analysis can confirm an exact diagnosis.

TREATMENT

Surgery

Generally, the first step in the treatment of glioblastomas and anaplastic astrocytomas 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; thus, a more accurate diagnosis can be made. This 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, MRI tractography (photo) and functional MRIs help the neurosurgeon determine and avoid eloquent, or functional, areas of the brain that are associated with language, vision and mobility. Stereotactic computerized equipment, image-guided techniques or intra-operative MRI 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 to reach or deep areas in the brain. Lasers may be used during surgery to vaporize tumor cells. Ultrasonic aspirators are tools that break apart and suction out the tumor. High-powered microscopes help the neurosurgeon to better see the tumor.

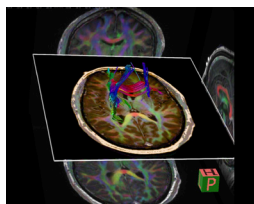


Image courtesy of Surasak Phuphanich, MD, FAAN.

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. Radiation, chemotherapy and/or tumor treating fields (TTFields) 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 the same type of radiation as a simple chest X-ray. Conventional radiation for glioblastoma and anaplastic astrocytoma 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 can be delivered by several methods, including intensity-modulated

radiation therapy (IMRT) and 3-D Conformal radiation therapy. Conformal photon radiation contours the radiation beams to match a tumor's shape and size.

- > Image-guided radiation therapy (IGRT) is the technique of using imaging technology at the time of each treatment to verify that patients are in the right position within a millimeter.
- > Proton beam therapy is an alternative to the standard radiation. It provides superior dose distribution for a higher dose at the tumor, avoids healthy tissue and reduces overall toxicity.
- > 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 typically used for 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 during surgery.
- > Boron neutron capture therapy releases radioactive compounds within the tumor.

Chemotherapy

For newly diagnosed GBM, a six-week course of temozolomide (Temodar) is given concurrently with radiation. Temozolomide is an alkylating agent with reasonable blood-brain barrier penetration. In poorly performing patients or patients over 70 years old, a hypofractionated course may be used to reduce the treatment time to 2-4 weeks. Radiation treatment is given daily, Monday through Friday. Oncologists recommend taking temozolomide one hour prior to radiation therapy to maximize its effect. Although, for practical reasons, nighttime administration may be more feasible for some patients. Early results from the ongoing clinical "CATNON" study showed benefit of adjuvant and concurrent radiation with temozolomide.

Because chemotherapy drugs can affect normal cells, patients can expect side effects from treatment, such as low white blood cell or platelet count, fatigue, hair loss, or lack of appetite.

Most chemotherapy drugs are cytotoxic drugs. Cytotoxic drugs are designed to destroy tumor cells. They work by making tumor cells unable to reproduce themselves. There are a number of different cytotoxic drugs used to treat brain tumors.

Only temozolomide, BCNU/CCNU and carmustine have been approved by the Food and Drug Administration (FDA) for the treatment of high-grade brain tumors. Other drugs have received approval in the treatment of other cancers; therefore, they must be prescribed “off-label” for brain tumor use.

Researchers are also developing new ways of delivering drugs to the tumor. Convection-enhanced delivery (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 nanoparticles that release drugs into the tumor at a pre-determined rate with good penetration through blood-brain barrier.

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.

Management of Symptoms with Medication

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; however, 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 without a seizure history who are placed on antiepileptic medications prior to surgery should be tapered off because 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 (Keppra). Both agents are effective, but levetiracetam has a favorable adverse effect profile, has minimal drug-to-drug interactions (an important consideration for chemotherapy), and does not require routine drug level monitoring.

During treatment, the degree of fatigue that patients experience ranges from minimal (not affecting the ability to perform full-time work) to profound (spending the majority of the day in bed). Brain stimulating agents – such as modafinil (Provigil) and methylphenidate (Ritalin) – 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 or sleeping medications may also be considered to improve quality of life during the treatment.

Biologic, Targeted, and Immuno Therapies

Purposeful altering of the natural behavior of tumor cells is a newer area of medicine called *biologic* or *targeted therapy* or *immunotherapy*. 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 are still under investigation, but they are designed to stop signals going into the tumor cell, which

halts growth. Several pathways in the brain encourage cell growth. In GBM, several growth factor receptors (EGFR, VEGF, PDGFR) are overexpressed or mutated, which causes rapid cell growth, 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.

Immunotherapy is a new promising area of treatment designed to trigger the body's own immune system to fight and halt tumor growth. Recent breakthroughs in understanding some of these mechanisms has shed a new light on how to generate effective anti-tumor response. This has sparked a renewed and enthusiastic effort to apply this method as a treatment for malignant brain tumors.

These treatments include checkpoint inhibitors and cancer vaccines that utilize a tumor's antigens. Antigens are signals that alert the system there are abnormalities in cells. The vaccine attacks the cells by using 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. Immune checkpoint inhibitors are drug-antibodies which unleash T-cells attack on cancer cells.

Checkpoint proteins tell the immune system that a cell is healthy. There may be other molecules signaling that the cell is cancerous, but if there are enough checkpoint proteins on the cell surface, the immune system may overlook the "bad" signals. The best known example of a checkpoint protein is PD-L1 (for Programmed Death Ligand 1; its receptor is PD-1). The body needs PD-L1 to keep the immune system T-cells from attacking healthy cells. Cancer cells may upregulate (speed up the production of) PD-L1 as a protective mechanism. When PD-L1 activates the PD-1 receptor on the surface of a T-cell, the T-cell is signaled to destroy itself. The FDA recently approved checkpoint inhibitors Opdivo (Nivolumab), Keytruda (Pembrolizumab) and Tecentriq (Atezolizumab) for the treatment of metastatic melanoma, lung cancer, Hodgkins' lymphoma, kidney and bladder cancer. These new drugs are now being

studied in newly diagnosed and recurrent glioblastoma. Immunotherapy may represent the next frontier of the most promising personalized therapies in this new decade.

Other researchers are using gene or oncolytic virus (polio or adeno or herpes virus) 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.

Tumor Treating Fields (TTFields)

TTFields are an FDA-approved novel therapeutic option. Studies have shown TTFields slow and reverse tumor growth by inhibiting mitosis (the process by which cells divide and replicate).

TTFields are used in combination with temozolomide for the treatment of glioblastoma in newly diagnosed adult patients. Usually treatment with TTFields follows surgery and radiation therapy.

TTFields are also approved in the U.S. for treatment of recurrent GBM as a monotherapy after surgical and radiation options have been exhausted.

Adhesive bandages hold insulated ceramic discs (transducer arrays) that deliver electricity transformed into electromagnetic energy to the scalp. The battery operated-TTF device generates low intensity, intermediate frequency, alternating electrical fields to the brain. These electrical fields exert selective toxicity in proliferating cells thereby halting cell division and destroying the cancer cells.

Currently, a physician must prescribe the TTField device. The prescribing physician will provide instructions for using the device, replacing transducer arrays (every 4 to 7 days), and recharging and replacing batteries.

Patients must wear the device for at least 18 hours a day, taking only short breaks for personal needs, and use the

device for at least four weeks.

This should be discussed with your doctor as a treatment option.

Clinical Trials

Several of the treatments discussed in this publication are available to patients through clinical trials. Clinical trials are open to 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 therapies that would otherwise be unavailable. All clinical trials, conducted in phases – 0, I, II and III – are overseen by government (FDA) and local hospital boards (IRB) and are subject to rigorous regulation and oversight.

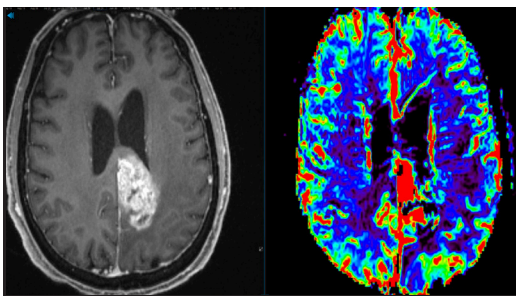
The American Brain Tumor Associations TrialConnect® service matches patients with appropriate clinical trials based on tumor type and treatment history. Patients or families can contact a TrialConnect® specialist at 877-769-4833, Monday through Friday, from 8:30 a.m. to 6:30 p.m. EST, or create a patient 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? How many patients with your tumor type have received this treatment, and what were their results? Is this covered by insurance and a research fund?

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 (0, I, II or III) of this investigation you would be participating.



Contrast-enhanced MRI scan and perfusion MRI with increased cerebral blood volume (cbv) of active tumor (not radiation necrosis or pseudo tumor progression), glioblastoma Photo courtesy of S. Phuphanich, MD

RECURRENCE

To measure effectiveness of treatment and to monitor for possible tumor recurrence, an initial follow-up scan is 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 a 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 to 12 months.

Anaplastic astrocytomas are aggressive tumors and can recur over time. In some cases, anaplastic astrocytomas develop into glioblastoma. However, glioblastoma cannot become 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 for small a tumor. Therapy with a second line drug, such as lomustine (also known as CCNU), Gleostine (generic CCNU), bevacizumab (Avastin), low-dose

temozolomide (Temodar), or a combination of these drugs 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 or immunotherapies 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 tumor growth and improve quality of life.

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 IDH mutant anaplastic astrocytoma is about three to five years. For adults with glioblastoma, treated with concurrent temozolomide and radiation therapy, median survival is about 15 to 18 months with a five-year survival of 10%. However, there are case reports of patients surviving for 10 to 20 years. Younger age and complete tumor resection are associated with longer survival.

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 have prolonged survival rates. The MGMT gene is thought to be a significant predictor of response to chemotherapy agents.

However, many glioblastoma and anaplastic astrocytoma tumors are biologically different from one another. 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 individual personalized therapy may be more optimally used to treat brain tumor patients.

THE ABTA IS HERE FOR YOU

You don't have to go through this journey alone. The American Brain Tumor Association is here to help.

Visit us at www.abta.org to find additional brochures, connect with a support community, join a local event and more.

We can help you better understand brain tumors and support resources. Our team of caring professionals are available via email at abtacares@abta.org or via our toll-free CareLine at 800-886-ABTA (2282).

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PUBLICATIONS

About Brain Tumors: A Primer for Patients and Caregivers

Brain Tumor Dictionary*

Brain Tumors - a handbook for the Newly Diagnosed*

Caregiver Handbook*

Tumor Types:

Ependymoma

Glioblastoma and Anaplastic Astrocytoma

Medulloblastoma

Meningioma

Metastatic Brain Tumors

Oligodendroglioma and Oligoastrocytoma

Pituitary Tumors

Treatments:

Chemotherapy

Clinical Trials

Conventional Radiation Therapy

Proton Therapy

Stereotactic Radiosurgery*

Steroids

Surgery

*All publications are available for download in Spanish. (exception is marked *)*

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