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Section I - Introduction

Voices Against Brain Cancer Foundation www.voicesagainstbraincancer.org

Voices Against Brain Cancer (VABC) was started in loving memory of Gary Lichtenstein, who lost his valiant battle against brain cancer on October 1, 2003. Gary was diagnosed with a glioblastoma multiforme, an aggressive type of brain tumor, in March 2003, at the age of 24. *Our mission is to find a cure for brain cancer by advancing scientific research, increasing awareness within the medical community and supporting patients and families afflicted by this disease*. This binder has been created to give you—the patients and caregivers—an understanding of what a brain tumor diagnosis means and how you can fight and overcome this disease. We have included information on diagnosis to prognosis to social support systems in the area—it is our hope that no one will have to face this disease alone.

VABC would like to welcome you to our community where you can channel your energy into positive initiatives to fight brain cancer, speak with people who have been through what you are going through and learn more about living with brain cancer. We envision a community in which people can connect and share resources in order to get through this illness.

For more information on Voices Against Brain Cancer and how you can help contribute to the cause, please visit our website or email us at info@voicesagainstbraincancer.org.

VABC funds the Columbia University Medical Center Neurological Institute Brain Tumor Center's (BTC) various research programs. In addition, to ensure that current studies are moving forward, VABC has agreed to fund clinical studies on generic medicines that show promise in the laboratory in inhibiting brain tumor growth. The BTC is led by Dr. Steven Rosenfeld, who dedicated his medical career to brain cancer after his mother passed away from the disease in 1978. After completing his medical studies, Dr. Rosenfeld became the Director of the Brain Tumor Program at the University of Alabama in 1995, and presided over an expansion of the program to national prominence. Dr. Rosenfeld is also Columbia University's Head of Neuro-Oncology (the study of brain tumors) and a Fellow of the American Neurological Association. Suffice to say, Columbia University's BTC is one of the foremost centers of research and treatment for brain tumors in the world, and all of the accrued knowledge and expertise of this center will be assisting you in fighting this disease.

The BTC is located in the Neurological Institute of New York Building at the Columbia University Medical Center at 710 W. 168th St., on the corner of 168th Street and Fort Washington Avenue. To make an appointment, please call Raisa Perez at (212) 305-1718.

Section II - What Is Cancer?

Cancer - A Definition

Cancer is a collection of many related diseases that are all characterized by one common feature—the inappropriate and chaotic growth of cells. Under normal conditions, cells grow only when needed; for example, during the healing of a wound. However, when cells become cancerous, they lose the ability to be controlled by the body's needs, and continue to grow. The mass of cells that results from this uncontrolled growth is called a "tumor." While some of these tumors do not spread beyond their point of origin, others are capable of spreading large distances, often to other organs and tissues. This process is called "metastasis," and tumors that metastasize are called "cancers".

Brain Tumors

Brain tumors can either originate from within the brain ("primary brain tumors") or from cancer cells that have metastasized from other organs or tissues ("secondary brain tumors"). Primary brain tumors can be derived from the over twenty different cell types that make up the brain. They are named and categorized by the type of cells that produce them. The most common forms of cancer that produce secondary brain tumors include lung, breast, kidney, and skin (melanoma) cancer.

While primary brain tumors rarely metastasize outside of the central nervous system ("CNS"), they all have the propensity to spread within the normal brain, and are all, therefore, cancerous. However, primary brain tumors do vary significantly in terms of how rapidly they grow and spread. Thus, most primary brain tumors are described in terms of "grade." Low-grade tumors tend to grow slowly and frequently remain dormant for long periods of time, while high-grade tumors grow and spread rapidly. The ability of all of these tumors to invade normal brain tissue means that surgery is rarely able to cure them, since it is generally not possible for the surgeon to remove all of the cancerous cells without removing an unacceptably large amount of normal brain tissue as well.

By contrast, metastatic brain tumors tend not to invade normal brain tissue, but rather push it aside as they continue to grow. This means that surgery and focused forms of radiation therapy, such as Gamma Knife, proton beam, and Stereotactic Radiosurgery, can often completely remove or destroy the metastatic tumor.

Brain Tumor Statistics

Each year, more than 190,000 people in the United States and 10,000 people in Canada will be diagnosed with a brain tumor. Over 40,000 will be primary brain tumors.

In the United States, the overall incidence of all primary brain tumors is 14.1 per 100,000 people per year. Primary brain tumors are the leading cause of solid tumor cancer deaths in children under the age of 20, now surpassing acute lymphoblastic leukemia (“ALL”), and are the third leading cause of cancer death in young adults ages 20 to 39. Although as many as 70% of children diagnosed with primary brain tumors will survive, they are often left with long-term side effects.

Over 150,000 secondary (“metastatic”) brain tumors occur yearly in the United States. Secondary brain tumors occur at some point in 10%-15% of people with cancer.

Primary Brain Tumor Types in Adults

As noted above, brain tumors are characterized by the presumed cell of origin. While there are over 120 different types of brain tumors, most occur from a very limited set of cell types. Listed below are the most common primary brain tumor types in adults.

Gliomas

Glial cells are the “connective tissue” of the brain, providing crucial support for the nerve cells that do the actual work of the brain. Glial cells come in several different types. The most common of these include astrocytes, oligodendrocytes, and ependymal cells. Each of these glial cell types can produce brain tumors, referred to as “gliomas.” Gliomas are the most common of primary brain tumors, and they are named for their cell of origin as follows:

Tumors derived from astrocytes:

Astrocytomas represent the most common type of glioma. They develop from glial cells called astrocytes. They can arise anywhere in the brain and are most common in areas that have the largest number of astrocytes, namely the frontal, temporal, and parietal lobes of the brain. These tumors can be very low-grade (“pilocytic astrocytomas,” also called “grade I astrocytic tumors”), low-grade (“astrocytomas,” also called “grade II astrocytic tumors”), intermediate-grade (“anaplastic astrocytomas,” also called “grade III astrocytic tumors”) or high-grade (“glioblastoma multiforme,” also called “grade IV astrocytic tumors”). The risk of tumor growth, spread, and patient death increases as the tumor grade increases. Furthermore, a significant number of low-grade astrocytomas become a higher grade over time. Hence, even low-grade astrocytomas have the potential to have serious, malignant consequences, and these tumors should never be called or considered “benign.”

Pilocytic astrocytomas (“grade I”) are relatively uncommon in adults. A high percentage of these tumors can be effectively treated with surgery alone. However, a subset of these tumors (10%-20%) can spread and become aggressive. If you are diagnosed with such a tumor, it is important to have regular examinations by your physician to detect any possible recurrence.

Astrocytomas ("grade II") tend to grow relatively slowly, and depending on their location, can initially be treated with surgical removal ("resection") alone. However, while surgery can often remove much or all of the *visible* tumor, it should be remembered that small nests of tumor cells are almost always left behind, since these tumors can and often do invade normal brain tissue. Thus, it is sometimes necessary as well to treat these tumors with additional therapies, including radiation therapy and/or chemotherapy. The median survival rate with this tumor is in the range of five to seven years, which means that approximately 50% of patients with this disease are alive at least this long or longer. If you have a low-grade astrocytoma, you should be seeing your treating physician on a regular basis (every three to four months) with MRI scans, since *early detection* of tumor regrowth or progression to a higher tumor grade can often be effectively treated with surgery, radiation therapy, and chemotherapy.

Anaplastic astrocytoma ("grade III") and glioblastoma multiforme ("grade IV," also called "GBM") are the more aggressive versions of astrocytomas. In addition, GBMs are the most common of primary brain tumors. Median survival for these tumors is in the range of two years for the former and one year for the latter. However, it should be kept in mind that these numbers reflect the results of studies that are rapidly becoming out of date, as significant advances in treating these diseases are regularly being made. Nevertheless, either type of tumor still carries with it a serious risk of death or disability, and patients with either tumor need to be closely followed by physicians who specialize in the treatment of these diseases. Treatment of either type of tumor generally involves surgery, radiation therapy, and chemotherapy. The advances in the treatment of these tumors that have occurred have resulted from studies of novel therapies in patients who have enrolled in clinical trials. If you have been diagnosed with either of these tumor grades, you should ask your physician if you qualify for a clinical trial in your area and if so, should seriously consider enrolling in one.

In children, astrocytomas can occur in some places that rarely harbor tumors in adults. These include the brainstem and the hypothalamus. These are structures near the base of the brain that control appetite, heart rate, breathing, sleep/wake cycles, eye movements, speech, and swallowing. Surgery is most likely not an option for these tumors, since they occur in portions of the brain that are essential for life. Treatment generally involves radiation therapy, although chemotherapy can be used as well.

Tumors derived from oligodendrocytes:

Oligodendrocytes are the cells that produce the "insulation" that surrounds nerve cells. When oligodendrocytes become cancerous, they can produce tumors called oligodendrogliomas. When these tumors take on more aggressive features, they are called anaplastic oligodendrogliomas.

Oligodendrogliomas tend to be slow growing, indolent tumors that constitute about 8% of all primary brain tumors. Because they grow so slowly, these tumors are also associated with a fairly long median survival of about 11 years. Depending on their size and behavior, these tumors can be treated by close monitoring, surgery, or radiation therapy. Anaplastic oligodendrogliomas have a shorter median survival (approximately three years)—a reflection of their more rapid growth. About 85% of these tumors have specific deletions of parts of their chromosomes (called “1p/19q deletions”), and when these deletions occur, the tumor is quite sensitive to chemotherapy. Hence, anaplastic oligodendrogliomas can be treated with surgery, radiation therapy, and/or chemotherapy. If you have an anaplastic oligodendroglioma, you should ask your doctor if you are eligible for any chemotherapy protocols in your community.

Tumors derived from ependymal cells:

Ependymal cells form the lining of fluid-filled spaces in the brain called the “ventricles.” When these cells become cancerous, they are called ependymomas, and when ependymomas become aggressive, they are called anaplastic ependymomas.

Ependymomas are relatively uncommon tumors in adults, constituting about 5% of primary brain tumors. They can occur in the brain or the spinal cord. They are generally slow growing. Treatment can consist of surgical removal of all visible parts of the tumor, followed by a close follow-up with brain or spinal cord MRI scans. Radiation therapy is sometimes added to reduce the chance of tumor recurrence. When the tumor cannot be completely removed, radiation therapy is generally prescribed to reduce the chance of tumor growth.

Anaplastic oligodendrogliomas constitute a minority of ependymomas (about 15%). These are more aggressive tumors, and generally require surgery, radiation therapy, and chemotherapy. If you are diagnosed with an anaplastic ependymoma, you should ask your doctor if you qualify for any clinical investigations in your community.

<u>Meningiomas</u>

The meninges form a set of linings around the brain that protect it from mechanical injury. When tumors develop from the meninges, they are called meningiomas.

Meningiomas are the second most common form of primary brain tumor (after GBM), and increase in frequency with age. They typically grow very slowly, and can stop growing for periods of time altogether. It is estimated that approximately 20% of people above the age of 80 have meningiomas, and for the vast majority of these individuals, these tumors are of no concern or consequence. However, when meningiomas occur near important neurological structures, such as the optic nerves, brainstem, hypothalamus, or important blood vessels, they can compress and damage these structures and cause significant neurological disability or even death. In these cases, the treatment typically consists of complete surgical removal, when possible. If complete surgical removal is not possible, radiation therapy is often added to prevent or slow the growth of the remaining tumor. In some cases, it may be possible to treat problematic meningiomas without surgery, using forms of focused radiation therapy such as Gamma Knife, proton beam, or Stereotactic Radiosurgery. These treatments are generally given over several hours, and do not require extensive hospitalization.

Meningiomas can become aggressive, and when they do, they often invade normal brain tissue. These tumors are called “atypical meningiomas” and generally are treated with surgery and radiation therapy. The role of chemotherapy in atypical meningiomas is unclear, and is being investigated in several clinical studies.

For more information on primary brain tumors in adults, you should explore the following web sites: American Brain Tumor Association (www.abta.org), The Brain Tumor Society (www.tbts.org), The National Brain Tumor Foundation (www.braintumor.org), and The Brain Tumor Funders’ Collaborative (www.braintumorfunders.org), and a federal government-sponsored clinical investigative consortia for brain tumor research (www.nabtt.org)

Primary Brain Tumors in Children

Several features distinguish brain tumors in children from those that occur in adults. First, some of the most common tumors seen in adults are relatively uncommon in children, and vice versa. Second, most primary brain tumors in adults occur in the cerebral hemispheres, which make up the majority of the mass of the brain. However, primary brain tumors in children tend to occur in the base of the brain, in the cerebellum, brain stem, and hypothalamus. An extensive discussion of childhood brain tumors is beyond the scope of this chapter, and if you are interested, you should explore several user-friendly websites, including The Pediatric Brain Tumor Foundation (www.curethekids.org), and The Pediatric Brain Tumor Consortium (www.pbtc.org).

Chapter III — Surgery

Surgery for Primary Brain Tumors

Surgery has traditionally been, and remains, the first line of therapy for patients with primary brain tumors. For some tumors, complete surgical removal is often possible. However, even for tumors that cannot be completely removed, surgery can have a major beneficial effect on symptoms and on the effectiveness of other treatments, such as radiation therapy and chemotherapy.

The Role of Surgery

Surgery has several goals in the treatment of all primary brain tumors, and these include the following:

a. **Complete tumor removal:** Tumors which can often be removed entirely include some meningiomas, grade I astrocytomas, and ependymomas. However, complete removal does not mean the patient can forget about the tumor completely, because these tumors can come back even if all visible signs of the tumor are removed by the surgeon. For this reason, it is important that you follow up regularly with your neurosurgeon so any tumor recurrence can be detected early.

b. **Partial tumor removal:** Even for tumors that cannot be completely removed, partial removal has a role. There is increasing evidence that the more tumor removed during surgery, the better your chances that other therapies, including radiation therapy and chemotherapy, will be effective. Neurosurgeons in general will recommend as complete a surgical resection as possible, so long as the tumor can be removed *safely*—i.e., without leaving you with an unacceptable neurological deficit. Tumors that are in deep parts of the brain or which involve critical brain structures, such as those that allow you to speak and understand, however, may not be even partially resectable. Furthermore, tumor debulking is a major surgical procedure, and like any other major operation, has certain risks which become significant if your general medical condition is severely compromised (such as congestive heart failure, kidney failure, severe lung disease, and so on). In these cases, the surgeon may recommend a stereotactic biopsy instead. In this procedure, the surgeon uses a pencil-thin biopsy probe to remove a small amount of tissue, under computer guidance. This small amount of tissue is used for pathological evaluation, under minimally invasive conditions that, in general, places the body under far less stress than surgery. There are however, two general risks of stereotactic biopsy. First, because it removes only a small amount of tissue, it is possible to miss the tumor entirely or remove a fragment of tissue that is not representative of the overall tumor. Second, it is possible to produce local bleeding from the procedure. Both of these problems can be dealt with effectively, however. When you first meet with your neurosurgeon, be sure to discuss the pros and cons of partial removal versus stereotactic biopsy in your particular case.

c. Pathological identification: As our treatments of primary brain tumors become more sophisticated and tailored to the individual tumor, it is becoming increasingly important to have adequate amounts of tissue for review by neuropathologists. For example, over the last several years, specific markers that predict how well you will respond to specific treatments have become routinely available, and this technology will certainly be expanded as we learn more about tumors and their appropriate treatments. The only way to access this information, however, is by examining tumor tissue, which is provided by the neurosurgeon during an operation, either by partially removing the tumor or by a stereotactic biopsy.

d. Removal of hypoxic tissue: As primary brain tumors grow, their ability to nourish themselves with nutrients and oxygen (provided by blood flow) becomes increasingly compromised. As the oxygen delivery decreases, these tumors become more and more deficient in oxygen—a condition called "hypoxia." Hypoxic tissue is remarkably resistant to other forms of therapy, particularly radiation therapy. The only way to get rid of this especially dangerous part of the tumor is for the neurosurgeon to remove it during an operation.

e. Symptomatic improvement: Primary brain tumors cause symptoms in part by compressing the normal brain and thereby interfering with normal brain function. By partially removing the tumor, neurosurgeons can relieve this compression and markedly improve symptoms and the quality of life. This is true even in situations where the tumor has become resistant to all other forms of treatment.

Surgery Risks and Side Effects

Surgery on the brain is a major procedure, and depending on the extent of the procedure, can be associated with a variety of risks and side effects. Fortunately, these are all relatively uncommon, but you should nonetheless discuss them with your neurosurgeon before your operation.

a. Infection: An infection of the surgical site or brain is very uncommon. More common are infections of other parts of the body that may develop because you are staying in bed after the procedure, such as lung infections or bladder infections. This is why it is important to be mobile—spend as much time out of bed as possible—as soon as your surgeon feels it is safe. All of these infections are generally treatable with antibiotics, but an infection can still prolong your hospital stay (*see below*).

b. Blood clots: Having a brain tumor by itself increases your risk of developing a blood clot in your legs, and staying in bed after an operation markedly increases that risk. Blood clots in the veins of the legs can be carried by the bloodstream to the lungs, where they are called “pulmonary thromboemboli.” This is a serious problem that can be fatal if not prevented or adequately treated. This underscores the importance of being mobile as soon as it is safely possible. If this cannot be done, your surgeon may prescribe compression to your legs, to prevent blood from pooling there, or may administer some blood thinners to keep your blood from clotting.

c. Temporary neurological deficits: It is not uncommon for the surgical procedure itself to increase the amount of swelling in the surrounding normal brain tissue. Depending on where in the brain this occurs, this may lead to a temporary worsening of your neurological symptoms. This will often improve over time, particularly with the use of steroids, such as Decadron or prednisone.

d. Permanent neurological deficits: There is always the risk of damaging part of your normal brain tissue during the surgery, and depending on the location of this injury, this could leave you with a permanent neurological deficit. Neurosurgeons work very hard to prevent this, but you should still discuss what the chances of this happening are in your case. In certain circumstances, when the neurosurgeon feels that this is an appreciable risk, he/she may elect to perform your surgery with you awake (*see below*).

e. Bleeding into the surgical site: Several types of primary brain tumors have abnormal blood vessels that are easily damaged and can bleed. Some bleeding typically can occur after any brain tumor operation, but this is usually minor, temporary, and causes no appreciable problems. On rare occasion, however, this can become more serious, and can require another operation.

f. Seizures: Blood is very irritating to the brain, and even a trivial amount of bleeding can induce seizures. Your surgeon may choose to start you on anti-seizure medication before the operation in order to prevent this problem from occurring.

g. Prolonged hospitalization: Typically, a stereotactic brain biopsy requires one day of hospitalization, and a tumor resection requires three to five days in the hospital. However, any of the above complications will increase the time you have to spend in the hospital. Prolonged hospitalization by itself is a problem, since it increases your risk of acquiring a hospital-acquired infection (typically more resistant to antibiotics than a community-acquired infection) and can make it harder for you to readjust emotionally and physically to life at home. If your hospitalization has been prolonged for any reason, your neurosurgeon may prescribe a brief stay in a rehabilitation hospital or may have you do home rehabilitation. This can significantly accelerate your return to a normal life.

Newer Surgical Methods

Surgical Navigation: As with any other type of surgery, neurosurgery continues to make technological advances in the procedures used for brain tumor biopsies and resections. Many of the recent advances involve marrying neurosurgical techniques with a variety of sophisticated brain imaging methods. These advances give the surgeon detailed, real-time anatomic views of the tumor and surrounding brain in the operating room that can guide how the surgery is performed. In addition, several of these imaging techniques provide the surgeon with information on where certain important neurological functions are controlled in the brain and how close these regions are to the tumor.

Surgical Drug Delivery: Another area of neurosurgical advances involves marrying surgical technology to drug delivery technology. One of the problems in effectively treating brain tumors with chemotherapy is the "blood brain barrier." This is a normal feature of the blood vessels in the brain, which are surrounded by cells that prevent many substances in the blood from entering the brain. This barrier exists so that the brain can be insulated from a variety of chemicals that circulate in your blood and which could impair normal brain function if they got into the brain. However, this barrier also blocks the entry of a variety of chemotherapeutic agents that are active against brain tumors in the laboratory. Several methods of getting around this problem through the use of neurosurgical techniques are either available or under active investigation. These include the following:

a. Gliadel®: During a brain tumor removal procedure, the neurosurgeon generates a "resection cavity"—i.e., a hole in the brain where the visible tumor used to be. In most primary brain tumors, however, we know that malignant tumor cells are left behind within a centimeter or less from the edge of the resection cavity. One option now available to the surgeon is to line this cavity with a biodegradable wafer that contains high concentrations of BCNU, a chemotherapy drug. As the wafer is slowly dissolved by the surrounding brain tissue, it releases high local concentrations of BCNU. This preparation was approved by the Food and Drug Administration over a decade ago for use in patients with malignant gliomas, and it is marketed under the name Gliadel®. While this is a very promising technology, Gliadel® use is associated with some complications, and prior use of this agent may prevent you from enrolling in certain investigational clinical trials.

b. Convection enhanced delivery: In this procedure, a small catheter is inserted into or surrounds the brain tumor, and chemotherapy is slowly pumped into the tumor directly. This method of drug delivery has the advantage over Gliadel® because it covers large areas of brain tissue surrounding the tumor, where microscopic nests of tumor cells frequently can be found. It is still considered an investigational procedure, however, and whether it will find its way into the mainstream of neurosurgical techniques will depend on a number of clinical trials that are ongoing. If you are interested in considering this option, you should ask your neurosurgeon for the nearest center that is investigating this technology.

Cortical Mapping: Sometimes, removing or partially removing a tumor involves operating on a regions of the brain that are involved in critical functions, such as moving parts of the body, speaking or reading. In these situations, the neurosurgeon may elect to remove the brain tumor under local anesthesia, with you at least partially awake. During such a procedure, he/she will map exactly where your ability to speak or move is controlled in the brain and where these brain regions are located relative to the tumor. During the tumor removal, the surgeon will monitor your ability to perform these normal functions. This procedure has the potential to significantly reduce your risk of suffering a permanent neurological deficit during the surgery. While the prospect of having your brain operated on while you are awake may sound gruesome, patients are typically treated with sufficient medication to be completely comfortable and generally have little memory of the procedure after it is over.

Surgery for Secondary Brain Tumors

It used to be assumed that surgical removal had no role in the treatment of cancers that had metastasized (i.e., spread) to the brain, and that the only appropriate treatment for this problem is radiation therapy. However, several studies performed in the late '80s and early '90s have clearly shown that removal of brain metastases, when they are limited in number, can significantly improve survival and quality of life in patients with brain metastases, particularly when combined with radiation therapy. More recent studies in patients with spinal cord compression—another complication of metastatic cancer—have also shown that surgery has a definite role in well-selected patients. It is now standard practice to remove large or symptomatic brain metastases in patients whose cancer elsewhere (e.g., lung, bone, breast, etc.) is under good control.

Chapter IV – Radiation Therapy

Background

The term "radiation therapy" actually denotes a variety of treatments that utilize subatomic particles or the radiation that these particles release to treat cancer. The concept of using radiation to treat cancers goes back to the discovery of X-rays in the 19th century. However, its development rapidly advanced after World War II, when interest in nuclear energy in general, stimulated by the Manhattan Project and the development of the atomic bomb, led to intensive research on the effects of radiation on cells.

Radiation therapy (also known as "radiotherapy") comes in a variety of forms, and it can kill cancer cells by a variety of mechanisms. A detailed discussion of these various types of radiation therapy is beyond the scope of this chapter. However, for patients with primary brain tumors, there are a few forms of radiotherapy that are commonly used, and in this chapter, we will focus on these.

External beam, fractionated radiotherapy

This form of therapy uses high-energy radiation, which is administered from a source that is located outside of the body ("external beam") to damage the DNA of tumor cells. Tumor cells in general are not as efficient as normal cells in repairing the damage that this form of radiation inflicts. Thus, giving this form of radiation in small doses spaced out over time ("fractionation") allows the normal cells to recover from whatever damage is caused while tumor cells are unable to recover. Furthermore, the fact that most of the normal cells in the brain are not actively dividing protects them further from the damaging effects of radiation. Typically, primary brain tumors are treated with a course of external beam radiation that is given in approximately 30 treatments ("fractions"), with one fraction given per day, five days per week, for approximately six weeks of treatment. A significant amount of work is required to determine exactly how this radiation is to be administered in each patient's case, and this radiation planning can take up to one week before treatment can begin. Once treatment does begin, it is important to continue with it until it is concluded, without major interruptions, since this would give the tumor cells a chance to recover from the damage produced by the radiation.

Given that primary brain tumors invade normal brain tissue, it is important to be sure that regions of the brain that contain microscopic amounts of invasive tumor cells are treated with radiation. This means that some normal brain tissue surrounding the tumor needs to be treated. Minimizing this treatment of normal brain tissue has been a goal of investigators in the field for some time. Over the last decade, there have been significant technical advances that have involved combining state-of-the-art imaging technology (mostly with CT scans) with external beam radiation therapy. These advances now spare more of the normal tissue, which should reduce radiation therapy-related side effects (*see below*). These techniques are referred to as “conformal therapy” since they allow the radiation to better “conform” to the region of brain that has the tumor. They include “intensity modulated radiotherapy” (IMRT) and CT TomoTherapy. You should ask your radiation therapist if these methodologies are available and can be used in your treatment.

Other forms of radiation therapy

Brachytherapy:
This involves the placement of a source of radioactivity directly into the tumor to deliver a high local dose of treatment. Brachytherapy was extensively used in the past for treatment of high-grade gliomas, but has generally fallen out of favor. This is because it also significantly damages normal brain tissue, and can produce a significant amount of neurological disability. More recently, brachytherapy has been re-explored by new technologies that might be safer for normal brain tissue. One of these is an inflatable balloon which is filled with radioactive material (“GliaSite”) and which is inserted into the cavity that the neurosurgeon creates after removing the tumor.

Gamma Knife, Stereotactic Radiosurgery:
Both Gamma Knife and Stereotactic Radiosurgery use the same principle—multiple beams of radiation are administered that converge on a defined volume within the brain. The dose of each individual beam is very small, so any normal brain outside of this volume receives a trivial dose of radiation. However, any tissue within the defined volume receives a very high dose—high enough to effectively kill any tissue within this volume. This type of therapy is highly effective for treating metastatic brain tumors, since these tumors do not invade brain tissue, but rather tend to push normal brain tissue aside. Hence, if the defined volume is limited to the metastatic tumor, this type of treatment will effectively destroy the cancer while leaving the surrounding brain tissue unaffected. However, primary brain tumors invade normal brain tissue, and it is therefore impossible to treat such tumors with Gamma Knife or Stereotactic Radiosurgery effectively without also killing a significant amount of healthy brain tissue. This means that Gamma Knife or Stereotactic Radiosurgery is generally not appropriate for high-grade gliomas and similar primary brain tumors.

Proton beam:
This form of therapy involves radiating the affected tissue with a beam of protons, which are subatomic particles. The technology for generating proton beams is complex, expensive, and not widely available. However, proton beam therapy has several advantages over more conventional forms of radiation therapy. First, proton beams can kill tumor cells by multiple mechanisms that do not apply to external beam fractionated radiotherapy, which may enhance the effectiveness of this therapy. In particular, proton beams can kill tumor cells which are relatively deprived of oxygen (“hypoxic”). A hypoxic

tumor is typically resistant to external beam radiation therapy. In addition, it is possible to control how much volume of tissue receives the proton beam in a way that is not possible with external beam radiation, and this may reduce the toxicity to normal surrounding brain tissue. As noted above, proton beams are not widely available. However, if you are interested in finding out more about this treatment possibility, you should ask your radiation therapist. It should be noted that some of the recent technical advances in external beam radiation, including CT TomoTherapy, are approaching proton beams in terms of their ability to spare normal brain tissue, and you should expect these technical advances to continue to become available.

Radiation Therapy Side Effects

Local and short-term side effects:

Skin irritation:
Radiation therapy to the head can produce side effects to the skin that resemble those from excessive sun exposure. Scalp redness, drying, and itching are common, and can respond to topical ointments. Be sure to ask your radiation therapist which remedies are recommended and which ones should be avoided.

Hair loss:
The hair follicles are particularly sensitive to radiation therapy, and loss of hair over the treated area is nearly universal. Hair regrowth will frequently occur, but can take a year or longer to do so, and regrown hair may be gray or white. Some things you can consider include the following:

- Do not over-shampoo your hair.
- Use a mild shampoo, such as a baby shampoo.
- Do not use hot rollers, curling irons, hairsprays or dyes.
- Consider purchasing a wig, scarves, or caps. Hairpieces and wigs might be tax-deductible or covered by insurance.
- If your wig is covered by insurance, get a prescription for a wig from the physician.

Dry mouth, altered taste:
Some radiation is invariably administered to the salivary glands and to the tongue and palate. The former can produce mouth dryness, while the latter will alter your ability to taste food. Many patients complain that food has a “metallic” taste. Both of these effects are temporary and will improve over the three to six months following the radiation. Things to keep in mind include the following:

- Drink plenty of water.
- Suck on sugar-free hard candy or ice pops, or chew sugar-free gum.
- Rinse with a mouthwash recommended by the doctor.

- Serve foods with sauces, gravies, and salad dressings to make them moist and easier to swallow.
- Drink liquids with meals.
- Thrush is a superficial yeast infection of the mouth and throat. If you notice a white coating on your tongue or have problems swallowing, call your doctor. Treatment is easy and effective. Using Biotene or a similar mouthwash and practicing good oral hygiene may help prevent this in the first place.

Fatigue:
This typically becomes apparent after three to four weeks of treatment. Many patients find that they need to take a nap during the middle of the day. This side effect is the major reason we recommend that patients take a leave of absence from work during the course of radiation treatment. Fatigue typically improves by about three months after the end of radiation therapy. However, for those who choose to work through their treatment or who do not completely recover from this symptom, there are medications that can be prescribed that are very effective in helping with fatigue.

Long-term side effects

These problems tend not to become apparent until at least one year after treatment. They include the following:

Hormonal problems, including early menopause, loss of libido, and hypothyroidism:
When the tissue radiated includes the base of the brain, some radiation will be unavoidably administered to the hypothalamus. This region of the brain controls the release of a variety of hormones that are important for normal functioning. Some of these hormones are needed for normal reproductive and sexual functioning, and their loss can lead to premature menopause in women and loss of sex drive in men and women. Some of these problems can be addressed with hormone replacement or other medication, and you should check with your neuro-oncologist or primary care physician if you are concerned. Loss of thyroid function can lead to fatigue, weight gain, as well as other problems. Doctors routinely check thyroid function in patients, since low thyroid levels can be easily and effectively treated.

Intellectual problems, including memory loss:
When portions of the brain that control memory receive radiation therapy, the result can be a slow decline in memory and intellectual function. This has provided the major impetus to find newer forms of radiation administration, such as conformal therapies, that spare as much normal brain tissue as possible (*see above*). This problem has become less severe as these methodologies have become generally available. How much of a problem this will be for any individual patient will depend on the location of the tumor and on how much radiation will be given. You should discuss this concern with your radiation therapist at the onset of your treatment. Neuropsychological testing

can be useful in identifying specific problematic areas (language, reasoning, memory, spatial skills, etc.) and can be used in conjunction with cognitive, speech, or vocational therapy to develop a plan to address these problems. Medications have also been used to varying degrees of success in the treatment of radiation-related memory problems, and you should ask your neuro-oncologist or radiation therapist about these. You should also remember that a number of medical and emotional problems, including low thyroid, uncontrolled diabetes, and depression can produce difficulty with memory and intellectual function, and these need to be evaluated and treated if they are present.

Secondary tumors

It has been known for some time that radiation to the head can lead to the formation of several types of tumors. The most common of these are acoustic neuromas and meningiomas, and both are generally treatable with surgery or Gamma Knife radiotherapy. The risk of this is still relatively low, and should not be used as a reason to avoid radiation therapy for treatment if you have a high-grade glioma.

Chapter V – Chemotherapy

What is chemotherapy?

This may seem like a simple question to answer. However, there has been a veritable explosion of new drugs and new methods of administering these drugs that were not available or even imaginable ten years ago. Hence, the content of this chapter must now include a variety of treatments that for most of the public may not come to mind when they hear the term "chemotherapy." For the purposes of this chapter, we will define chemotherapy as any medication, administered by mouth, intravenously, or directly into the brain, which prevents tumor growth or spread. As will become apparent in the following sections, this definition includes a large and diverse list of medications, and this list will in all likelihood continue to rapidly expand as progress in the treatment of brain tumors continues to advance. Indeed, new treatments for brain tumors are now appearing every six to 12 months—a rate of progress that was unimaginable one decade ago.

How does chemotherapy work?

Classical chemotherapy: Most of the drugs that typically come to mind when one hears the term "chemotherapy" work by a similar mechanism. They damage important cellular machinery and thereby induce the cells to undergo a process called "apoptosis." Apoptosis occurs in normal cells when their DNA—which is the cells' genetic "blueprint"—is severely damaged ("mutated"). Under these conditions, cells activate a series of processes that ultimately lead to their death, so they do not pass on their damaged DNA to their progeny cells, and do not interfere with normal bodily function. In other words, apoptosis is a form of cellular "suicide" designed to protect our bodies from the dangerous effects of harboring mutant DNA. By damaging DNA or interfering with the duplication of DNA that occurs when cells multiply, these chemotherapeutic drugs induce the tumor cells to undergo apoptosis—leading ultimately to the death of the tumor.

Signal transduction inhibitors: Although classical chemotherapy has a role in the treatment of brain tumors, there has been much interest recently in examining newer anti-cancer drugs that work by other mechanisms. Most of these interfere with another important cellular function called "signal transduction." Signal transduction refers to the process by which cells regulate their internal functioning. This functioning includes cell growth, cell division, cell migration, as well as the synthesis of important cellular components. In many types of cancers, including any brain tumors, the process of signal transduction is abnormal. In some instances, signal transduction components are abnormally active—causing cancer cells to multiply inappropriately and in an uncontrolled manner. Because abnormalities in the signal transduction process are so common in cancer, many drug companies have invested considerable effort in developing medications that block these abnormalities, and the resulting drugs have had a major impact on the treatment of a variety of cancers, including cancers of the breast, lung, colon, and kidney. The role of these drugs in treating brain tumors is under very active investigation.

Antiangiogenesis: In order for tumors to grow, they need to develop a blood supply to provide them with nourishment. Many tumors, including most brain tumors, are quite adept at producing their own blood supply. This observation has led to a great deal of effort at finding ways of blocking the production of new blood vessels ("angiogenesis"). Several of these are in clinical trial now, and one (Avastin®) is routinely used by many neuro-oncologists.

Targeted therapeutics: One of the major problems with classical chemotherapies, and one that applies as well to signal transduction inhibitors, is that they can have significant side effects. Classical chemotherapies are completely incapable of distinguishing normal brain tissue from tumor tissue. These drugs are used only because tumor tissue is generally more sensitive and less able to repair the damage that classical chemotherapies produce. Likewise, since signal transduction is a process found in normal tissue, as well as in cancerous cells, drugs that interfere with signal transduction are expected to have some side effects (although these are generally much milder than those produced by classical chemotherapies). An alternative approach would be to identify some cellular component that is expressed in tumor cells but not normal cells. Drugs that target such a component might therefore kill tumor cells selectively, and leave normal cells alone. This "magic bullet" approach has always been an ideal for brain tumor researchers, but in recent years, we have come to learn that brain tumors have unique targets not found in normal brain tissue, and in several cases, new drugs that attack these unique targets have been developed. This approach is referred to as "targeted therapeutics," and specific examples will be included in the following sections.

Cell-based therapies: These treatments use cells to attack the tumor, either by delivering toxic chemicals to the tumor or by directly attacking tumor cells through the immune system. Examples include bone marrow or neural stem cells, as well as dendritic cells. The latter are a form of immune system cell that can be programmed to recognize tumors as foreign and destroy them. Each of these therapies is still experimental, but clinical trials utilizing stem cells and dendritic cells are currently open, and you should ask your physician if any are available in your vicinity.

How can we make chemotherapy work better?

A major problem in the use of any of these chemotherapies is that they do not always work, and do not work indefinitely. This is the major reason why glioblastoma multiforme, anaplastic astrocytoma, and other aggressive brain tumors are so difficult to treat. However, in the last several years, we have learned a great deal about how brain tumor cells become resistant to chemotherapy, and have developed new methods of predicting which tumors are likely to be resistant and how to overcome this resistance.

Classical chemotherapy resistance: Brain tumor cells have evolved several mechanisms to overcome the damage that classical chemotherapy produces. The most significant of these is an enzyme called “methylguanine methyltransferase” (MGMT for short), which undoes the damage produced by classical chemotherapy drugs like temozolomide (Temodar®), BCNU, CCNU, and procarbazine. We now know from several recently-published studies that brain tumors which express high levels of MGMT are likely to be resistant to these classical chemotherapies. It is likely that before too long, testing your tumor for MGMT expression will become routine and will be used to determine which type of chemotherapy will be most useful against your tumor. Furthermore, there are now ways of getting around the problem of MGMT expression, two of which are being actively investigated. The first is through the use of a drug that blocks MGMT, which renders tumor cells sensitive to Temodar® and other classical chemotherapies. One of these, O^{6-}benzylguanine (O6BG for short) is in clinical trials at several institutions, and you should ask your physician if any institutions in your vicinity are using this agent. The second method is to administer chemotherapy in small doses on a daily basis. This type of chemotherapy administration is called “metronomic dosing,” and it appears to also be effective at inactivating MGMT and enhancing the chance that your tumor will respond to drugs like Temodar®.

Concurrent chemotherapy and radiation therapy: We now know that there is a positive interaction (“synergy”) between Temodar® and radiation therapy, due to a large multi-institutional clinical trial that was conducted several years ago in Canada and Europe. The study found that patients who received a course of Temodar® during their six weeks of radiation therapy did better than those patients who received radiation therapy alone, and this has now become the standard of care for patients with glioblastoma multiforme and anaplastic astrocytoma.

Signal transduction inhibitor resistance: Although signal transduction inhibitors have great promise for enhancing the treatment of brain tumors, not every tumor is sensitive to this class of drugs. It is now possible to characterize brain tumors on the basis of their “gene expression profiling.” This technique allows scientists to characterize brain tumors based on which of the tumor’s 50,000+ genes are abnormally “turned on” and which are abnormally “turned off.” Although this technology is too complex to discuss in detail in this chapter, it does have the potential of providing a “tumor fingerprint” that will eventually give doctors a way of tailoring treatment to a particular tumor’s gene expression. In general, this technology is still investigational. However, it has already yielded practical information in one specific situation. In a recent study, scientists utilized gene expression profiling to see if they could predict which patients with brain tumors responded to a specific class of signal transduction inhibitors—those which target the epidermal growth factor receptor. These drugs, which include Tarceva® and Iressa®, were found to produce responses in only some patients with brain tumors. Gene expression profiling determined why. Those patients who responded were by and large the ones whose tumors expressed two genes—a mutant epidermal growth factor receptor called EGFRvIII; and PTEN, which is a component of the signal transduction process. It is likely that future gene expression profiling studies will identify other predictors of signal transduction inhibitor responsiveness. Although gene expression profiling is still a research tool, it may eventually become a standard test that will allow the physician to tailor the treatment of a brain tumor to its specific characteristics.

Blood-brain barrier resistance: The brain is insulated from many of the molecules that circulate in the blood, due to a structure called the "blood-brain barrier." This prevents the normal brain from being damaged by molecules that are toxic to the brain and which are routinely found in the bloodstream. However, the blood-brain barrier presents a problem for treating brain tumors. This is because it prevents the delivery of chemotherapies that would be effective if they could only get into the brain. Two methods have been developed to get around this problem. The first is a technique called "blood-brain barrier disruption." In this method, the patient is given a medication that temporarily opens up the blood-brain barrier, and chemotherapy is then administered while the blood-brain barrier is open. The second is a technique called "convection-enhanced delivery" in which the chemotherapy is directly pumped into the brain by means of one or more small tubes that are inserted into the tumor by a neurosurgeon, and removed once the treatment has stopped (usually several days). Both of these techniques are investigational and you should discuss these with your physician if you are interested in considering these.

What chemotherapies are currently available for treating brain tumors?

Classical chemotherapies:

Some of the classical chemotherapies chemically damage DNA and ultimately lead to apoptosis. These include the following:

- Temodar®
- BCNU
- CCNU
- Procarbazine
- Cisplatin
- Carboplatin
- Melphalan

Others prevent DNA from being replicated, which occurs as cancer cells try to multiply. These include the following:

- Irinotecan (also known as “CPT 11”)
- Etoposide
- Topotecan
- Vincristine
- Hydroxyurea

As a group, these drugs will tend to depress the number of blood cells in your bloodstream. Lowering your white blood cell count increases your risk of getting an infection, while lowering your platelet count increases your risk of bleeding. A drop in your red blood cell count (“anemia”) is less common, but can occasionally occur, and can reduce the oxygen carrying capacity of your blood. By and large, these potential complications are treatable if diagnosed early. Hence, it is very important that you work closely with your physician so any potentially dangerous change in your blood counts can be anticipated and treated effectively.

Nausea is a common side effect of many of these drugs. However, there are now several medications that are generally quite effective in preventing nausea. Chemotherapies that damage DNA have the potential of causing changes in the DNA structure (“mutations”) in normal cells that can cause these cells to eventually become cancerous. These “secondary malignancies” are fortunately rare, and the risk of developing one of these is related to the duration of exposure to chemotherapy—the longer you receive these types of chemotherapies, the greater the risk. This is why a patient will not use drugs like Temodar® indefinitely.

Signal transduction inhibitors

As noted above, these include a number of drugs that have only recently been available for patients with brain tumors. Several of the more common of these include the following:

- Tarceva®
- Iressa®
- Gleevec®
- Sirolimus
- Sutent®

Generally, the side effects of these drugs are milder than those for the classical chemotherapies, and they vary from one signal transduction inhibitor to another. The most common of these include rash, diarrhea, blood clots, bleeding, high blood pressure (“hypertension”), and swelling of the ankles. Most of these side effects are readily manageable with regular visits to your physician. What role these and related drugs will play in the management of brain tumors is a subject of intensive investigation, and you should check regularly with your physician as new information comes in. In addition, newer signal transduction inhibitors are being studied in both brain tumors as well as other cancers, and you should check with your physician about the status of clinical trials in your vicinity for which you may be eligible.

Antiangiogenesis

Drugs that target the process of angiogenesis have received a great deal of attention recently, as they have shown activity against recurrent brain tumors—the hardest tumors to treat. As noted above, these drugs interfere with the tumor's ability to create its own blood supply. Several antiangiogenic drugs are FDA-approved for other cancers, and others are being actively investigated in clinical trials for patients with brain tumors. These include the following:

- Avastin®
- VEGF Trap
- Cilengitide
- Sutent®
- Gleevec®

Avastin®, Sutent®, and Gleevec® are FDA-approved, while Cilengitide and VEGF Trap (among others) are in late-phase clinical trials. Avastin® has shown particular promise in patients with recurrent brain tumors, and is now used by many neuro-oncologists for patients for whom Temodar® no longer works. It is administered intravenously, and its side effects include high blood pressure ("hypertension"), blood clots, bleeding within the tumor, protein in the urine ("proteinuria"), and congestive heart failure. In general, as with the signal transduction inhibitors, these side effects are either rare or manageable.

Targeted therapeutics

Drugs that fall within this category are all investigational at the present time. These chemotherapies target unique molecules that are expressed in tumor cells but not, or only to a very small degree, in normal brain tissue. This approach kills tumor cells by one of several mechanisms. One approach involves the formation of a hybrid drug that has two functions—one part binds the tumor cell specifically and the other part kills the cell once contact has been made. These molecules have been investigated in several clinical trials and are referred to as "immunotoxins". Another approach involves using the immune system to recognize a target found only on tumor cells through the use of a tumor-specific vaccine. A third utilizes "monoclonal antibodies"—protein molecules made by the immune system that recognize unique targets on the tumor and which interfere with tumor growth by blocking this target function.

What are clinical trials and why should I care about them?

It should be apparent from this chapter that much of the progress over the last decade in the development of effective chemotherapies for brain tumors has occurred as a result of research by many scientists. Most of these new treatments are based on findings in the laboratory that were eventually shown in animal studies to be effective in killing brain tumor cells. However, humans are not laboratory rats, and just because a drug looks promising in a rat or mouse with a tumor does not mean it will work in humans. The only way to know is to test promising chemotherapies in real people who are afflicted by real brain tumors, in a process called a “clinical trial.” Before a chemotherapy drug can be approved by the Food and Drug Administration (FDA), it needs to be investigated in a series of clinical trials. Clinical trials are highly regulated and closely monitored in order to protect patients from harm and in order to ensure that their care is not compromised.

There are at least two reasons to consider participating in a clinical trial. The first is altruistic. As is apparent from the above, the only way we will make progress in treating brain tumors is if courageous individuals who are afflicted by this disease volunteer to participate in a clinical trial. While every effort is taken to assure patients of their safety and while a clinical trial on a drug is not initiated unless there is compelling evidence that the drug may be effective, there is no guarantee that the drug will work in humans—hence the need to conduct the trial. The second reason is more out of self-interest. As is apparent from this chapter, there are many new promising approaches for the treatment of brain tumors. However, getting these new drugs approved by the FDA can take years, and therefore, the only way to be treated by them now is to enroll in a clinical trial.

Chapter VI – Complications of Having a Brain Tumor

Having a brain tumor puts you at an increased risk of developing other problems

In previous chapters, we have described problems associated directly with having a brain tumor (seizures, personality change, memory loss, etc.) as well as potential problems produced by the treatment of a brain tumor (neurological deficits from surgery, hair loss from radiation therapy, low blood counts from chemotherapy, etc.). However, there are other problems that patients with brain tumors are at increased risk for. Nearly all of these are manageable, and the purpose of this chapter is to alert you to them so you will know to discuss them with your doctor early on—before they cause serious problems.

Blood clots: Simply having a brain tumor places you at a significantly higher risk of developing blood clots. These clots are called “deep venous thrombosis” (or DVTs for short) and occur in the veins of the legs. Symptoms of DVTs include calf pain, swelling, and discoloration of the legs, although DVTs can also occur without any symptoms. The danger of DVTs is that they can break off and be carried by the bloodstream to the lungs, where they cause “pulmonary thromboemboli” (or PTEs for short)—blood clots in the pulmonary arteries. PTEs can be deadly, and are a major cause of sudden death in hospitalized patients in general. The best way of treating PTEs is to prevent them from occurring in the first place. Hence, if you do develop pain, swelling, or discoloration of your legs, you need to contact your doctor as soon as possible. Your doctor may decide to perform a “Doppler ultrasound” which is a non-invasive test that can determine if you indeed have DVTs. If you do, there are two options to treat them. Some patients can be safely treated with blood thinners (“anticoagulants”) that eventually cause the blood clots to dissolve. These blood thinners can be given by vein (“intravenously”), by daily local injection (“subcutaneously”) and by mouth, and which choice of treatment is used is something your doctor should explain to you. However, not all patients with brain tumors can be safely treated with blood thinners, since these medications can cause bleeding into the brain tumor itself. In this situation, your doctor may instead decide to insert a special type of filter into the major vein in your abdomen, know as the “inferior vena cava.” This device, known as a “Greenfield filter” or “Inferior vena cava filter” keeps blood clots from reaching the lungs. A major problem with these filters is that they can cause permanent swelling in the legs. For this reason, it is generally preferred to use blood thinners for treating DVTs so long as they can be used safely.

Depression: It goes without saying that having a potentially life-threatening disease can shake your sense of security to the core. This is made even worse by all of the sudden changes in your routine that come hand-in-hand with being diagnosed with a brain tumor. You may have been working full-time one month only to find yourself recovering from surgery in the next month, going to daily radiation therapy treatments, dealing with side effects of chemotherapy, and seeing doctors far more often than you were used to doing. It is thus not surprising that most patients go through a period of reactive depression, which tends to get better once they adapt to the changes in lifestyle that their disease brings on. However, for some patients, the depression does not go away. Furthermore, several of the medications doctors use to treat brain tumor side effects, such as steroids, can make depression worse.

Depression can manifest itself in a variety of ways. We commonly think of tearfulness, sadness, and social withdrawal as signs of depression. Indeed, for many patients affected by this problem, it is obvious to everyone that depression is present. However, depression can also appear as irritability, anxiety, decreased sex drive ("libido"), sleep problems, and inappropriate social behavior. If you have a brain tumor and are experiencing any of these problems, be sure to talk to your doctor as soon as they become apparent. As with most things, depression is easier to treat early on. In the BTC clinic, we routinely have our patients meet with a social worker as soon as they are diagnosed, so that we can get an assessment of our patient's level of social support. We do not hesitate to prescribe antidepressants and/or refer the patient to a psychiatrist when depression is suspected, and we find that depression in our patients responds well to these interventions.

Rash: Several of the medications that we prescribe for managing the symptoms of brain tumors can produce an allergic reaction. This is generally manifested by a rash that can develop over your arms, chest, abdomen, and back, and frequently itches. It is even possible to develop allergies to medications that you have taken for years under certain circumstances, such as radiation therapy. We know that patients undergoing radiation therapy can become allergic to medications that they had tolerated well before the radiation therapy. The most common medication to fall in this category is Dilantin, which is used to control seizures. This is why we generally want to switch patients who are about to undergo radiation therapy and are taking Dilantin to another anti-seizure medication.

We generally manage medication-related rashes by immediately stopping the likely offending medication(s) and prescribing anti-histamine and steroid medications. Most of these rashes typically resolve after several weeks. However, on rare occasions, the rash can become very severe, involve the entire body, and be associated with fever and with several laboratory abnormalities. In general, if you develop a rash while under treatment for your brain tumor, you should notify your doctor. If your rash is not getting any better despite adjusting your medication, or is associated with fever or a general "sick" feeling, call your doctor immediately in order to prevent more serious complications from developing.

Premature menopause/infertility: Both radiation therapy to the brain as well as chemotherapy can accelerate the onset of menopause. Likewise, chemotherapy can reduce sperm count and reduce male fertility as well. If you think that you may wish in the future to conceive, you may wish to bank your ova/sperm in a facility that specializes in this process.

Steroid-related complications: We use steroids for reducing the swelling ("edema") in the brain that is associated with brain tumors. Steroids can be extremely effective in reducing swelling and improving symptoms and quality of life. However, their use can be associated with several side effects, most of which are readily reversed once the steroids are withdrawn. These side effects include the following:

a. Diabetes: Steroids make you relatively resistant to the effects of the insulin that your body makes, and this can raise your blood sugar, sometimes to very high levels. Your doctor will want to know if there is any history of diabetes in your family, which increases the risk that you may develop this "steroid-induced" diabetes. This condition is generally managed the same way that spontaneous diabetes is managed—i.e., with diet, oral medications, and sometimes, insulin injections. Frequently, reducing the steroid dosage to the minimum required dose will often reduce the severity of this side effect or eliminate it altogether.

b. Obesity and hypertension: Steroids are potent appetite-stimulants, and weight gain is common once you start taking them for this reason alone. The weight unfortunately is in the form of fat, which in addition to being deposited in the usual places (belly and buttocks), can also be deposited around your face and along the upper part of your back, giving you a characteristic "round" face appearance. Fortunately, as with the diabetes, this problem is reversible once the steroid dosage is reduced. Steroids also cause you to gain weight by inducing your body to retain salt. This can cause swelling in your ankles (different from and not to be confused with the swelling in your ankles that comes from a blood clot in your leg veins) and can raise your blood pressure ("hypertension"). As with diabetes, a prior history or family history of elevated blood pressure increases your risk of developing this problem. The hypertension associated with steroid use can be readily treated with medication, and will get better and possibly go away altogether once the steroids are withdrawn or their dose reduced. By inducing your body to retain salt, steroids can also increase the pressure in your eye, which can lead to a condition called "glaucoma." As with hypertension, steroid-induced glaucoma is most common in people who have a family history of glaucoma or who have a history of borderline elevation of eye pressure. If either of these apply to you, you should have your eyes examined regularly by your ophthalmologist while you are taking steroids.

c. Pneumocystis pneumonia: Steroids reduce immunity, and they increase your risk of developing infections that occur in people whose immune system is suppressed ("opportunistic infections"). The most common of these (which is still very uncommon) is a type of pneumonia caused by the organism *Pneumocystis carinii*. This can be effectively prevented by taking regular doses of certain antibiotics. The most commonly used medication for this is Bactrim, which is a member of the sulfa group of antibiotics. Be sure to tell your doctor if you are allergic to sulfa, as there are other equally effective antibiotics that can also be used to prevent Pneumocystis pneumonia. As with the other steroid side effects, this one is reversible once the steroids are withdrawn.

d. Osteoporosis: Steroids suppress the maintenance of osteoid—the material that makes up bones—and can accelerate the thinning of bones that occurs with age ("osteoporosis"). If you have been on steroids for a prolonged period of time (longer than three months) you should discuss with your doctor whether a bone density test would be appropriate. If you are developing osteoporosis, this can be treated with available medications.

e. Muscle weakness: Prolonged use of steroids weakens the muscles of the shoulder joint and thigh, and can affect your ability to perform activities that use these muscle groups, including walking up stairs, running, brushing your teeth, and applying makeup. This effect is less pronounced with some steroids (e.g., prednisone) and more of a problem with others (e.g., Decadron). As with other steroid side effects, this one is also responsive to lowering the dose of steroid. In addition, if you are taking Decadron and are experiencing this type of weakness, you may wish to have your doctor switch you to an equivalent dose of prednisone (6 milligrams of prednisone is equivalent to 1 milligram of Decadron).

f. Mood and sleep changes: We have already noted above that depression can be worsened by steroids. Other mood disorders, including bipolar disorder ("manic depression") and generalized anxiety disorder can also be worsened by the addition of steroids to your treatment. As with other steroid-induced problems, the risk of developing worsening depression, anxiety, or bipolar disorder are increased if you have a family history of any of these. Be sure to discuss any history of emotional or mood problems with your physician so that steps can be taken to minimize the risk of emotional/mood problems from developing. Steroids can also interfere with your ability to sleep. Changing the time you take your steroids in relation to when you go to bed, or prescribing sleep aids, can often reduce this side effect.

Frequently Asked Questions

What is a brain tumor?

A brain tumor consists of a collection of abnormally functioning brain cells that have begun to grow and reproduce inappropriately. As this group of cells grows, it compresses and damages normal brain structures, which causes a variety of neurological symptoms.

How is a brain tumor recognized?

There are no symptoms that are unique to brain tumors. When symptoms do occur, they are due to damage to the region of the brain where the tumor happens to be located. Thus, tumors in the front of the brain can produce personality changes while tumors in the middle of the brain can affect strength, sensation, and vision. Seizures can also occur with brain tumors, as can headaches. However, a variety of other neurological diseases can cause each of these symptoms. Recognizing that neurological symptoms are due to a brain tumor requires several tests (see below).

Does a severe headache indicate the presence of a brain tumor?

Not necessarily. Headaches do occur with brain tumors, typically when they become large and are associated with swelling, but they are still an uncommon symptom. Headaches are far more common in other diseases, including migraines and arthritis of the neck. If you are now having headaches that you never had before, you should see your doctor. However, the probability is still relatively low that the onset of headaches is caused by a brain tumor.

How is a definitive diagnosis of a brain tumor made?

Any of the above symptoms may lead your doctor to perform a study that produces an image of the brain. The most commonly used method to do this is magnetic resonance imaging (MRI). This imaging technique can produce high-resolution images of tumors, and can provide some information on the nature and behavior of a brain tumor. However, as with the symptoms listed above, a variety of other diseases can also produce changes on the MRI that can resemble a brain tumor. Ultimately, making the diagnosis of a brain tumor requires examining the abnormal tissue shown by the MRI under a microscope. This is routinely done by performing a brain biopsy, in which a neurosurgeon removes the abnormal tissue from the brain and has it evaluated by a neuropathologist under the microscope. A variety of sophisticated tests can be performed on the tissue to not only identify what type of tumor is present, but what types of treatment are most appropriate. When a tumor is suspected after performing the MRI, the neurosurgeon may also recommend a "resection"—i.e., removing as much tumor as can be done safely. Current data suggests that patients do better when as much of their tumor as possible can be removed.

What is the difference between a benign and malignant brain tumor?

The terms benign and malignant can be misleading when applied to brain tumors. These terms were first developed to apply to other cancers elsewhere in the body. “Benign” tumors remain localized and do not spread elsewhere in the body (“metastasize”), and can often be cured by complete surgical removal; “malignant” tumors characteristically spread to other organs and tissues, including the brain. By contrast, even the most aggressive primary brain tumors rarely metastasize outside of the brain and central nervous system. However, both high-grade, aggressive brain tumors and low-grade, indolent brain tumors can and often do invade normal brain tissue, and this invasiveness can produce a great deal of neurological disability or even death. Thus, even non-invasive brain tumors can have malignant consequences if they occur in an important part of the brain. Therefore, rather than use the terms “benign” and “malignant,” we use the term “high-grade” to describe rapidly growing, aggressive brain tumors and “low-grade” to describe slowly growing, more indolent brain tumors.

How many different types of brain tumors are there?

Each of the cell types in the brain can become “transformed” (i.e., cancerous) and produce a brain tumor, and these tumors are classified by the type of cell of origin. While there are over twenty different types of brain tumors based on the cell type that creates the tumor, only a handful of these are commonly seen. These are called “primary brain tumors,” since they originate in the brain. In addition, however, the brain can often be a location where tumors from elsewhere in the body spread. These are called “metastatic brain tumors.”

What are the most common brain tumors?

In adults, the most common brain tumors are derived from astrocytes (the cells that make up the “connective tissue” of the brain) and meningeal cells (the cells that make up the lining of the brain). Tumors derived from astrocytes include astrocytomas, anaplastic astrocytomas, and glioblastoma multiforme. Tumors derived from meningeal cells are called meningiomas. In children, a different group of tumors are seen, which are rarely seen in adults and derived from cells that are normally present only in the fetus, but abnormally retained after birth.

What factors affect the chances for survival for patients after a malignant brain tumor?

For primary brain tumors, the most important factors that affect survival are the following: grade of tumor (more aggressive tumors have a worse prognosis); location of the tumor (tumors which the surgeon can remove almost completely because of their location are associated with a better prognosis); and age (younger patients tend to do better).

For metastatic tumors, the most important prognostic factors are: location of the brain metastasis (completely removable tumors or tumors that can be treated with a Gamma Knife or stereotactic radiosurgery are associated with a better prognosis); and the amount of cancer elsewhere in the body (patients whose cancer elsewhere in the body is well-controlled do better).

What options are there to treat a metastatic tumor in the brain?

The two main options are to remove the metastatic tumor by surgery, or to destroy it by focused radiation (Gamma Knife, stereotactic radiosurgery, or proton beam therapy). Conventional radiation therapy, or external beam therapy, is also used to improve the prognosis and prevent recurrences.

What tests are needed to determine if a patient would be appropriate for Gamma Knife?

Gamma Knife is an appropriate treatment for metastatic brain tumors (as opposed to primary brain tumors) if the tumor is not too big, if there are not too many tumors, and if the tumor is located in a region of the brain that can handle the temporary swelling that often develops after treatment. All of these issues need to be evaluated by the treating neurosurgeon and radiation oncologist to decide if Gamma Knife is appropriate.

Will the patient be awake during Gamma Knife treatment?

Yes.

Will the patient's head be shaved for Gamma Knife treatment?

Generally not.

What can the patient expect after Gamma Knife treatment?

The Gamma Knife typically produces some brain swelling after treatment. This is generally mild and temporary, resolves after several weeks, and can be treated with medication.

Will my insurance cover Gamma Knife treatment for brain metastases?

It should. If your insurance rejects your application, you should appeal this decision, since the efficacy of Gamma Knife treatment for brain metastases has been established.

What are the complications of radiation/chemotherapy treatments?

Conventional radiation therapy (often referred to as “external beam radiation therapy”) has both short-term and long-term complications. The short-term complications are typically temporary, and include fatigue, loss of taste, and a skin rash over the treated area. Hair loss over the treated area is almost always seen, and may be reversible over the subsequent year. The long-term complications include some loss of memory and higher cognitive function. The severity of these symptoms is determined by how much normal brain tissue is also treated. Newer methods of applying radiation therapy have significantly lessened the severity of long-term complications. You should ask your radiation therapist if these newer methods (including “conformal radiation therapy,” “intensity-modulated radiation therapy,” and “CT TomoTherapy”) are available in your case.

Conventional chemotherapy typically affects the ability of normal tissue to grow. Thus, bone marrow, which produces white blood cells (which fight off infection), red blood cells (which carry oxygen to the tissues), and platelets (which prevent bleeding) can be suppressed with chemotherapy. This suppression can lead to low white blood cell, red blood cell, and platelet counts. These problems can be treated with growth factors (Neulasta for white blood cells and Epogen for red blood cells) and platelet transfusions. However, the newest chemotherapy drugs used for treating primary brain tumors are far less likely to produce these problems. These newer drugs do have their own side effects, which are generally mild and treatable. You should ask your doctor in detail what these various side effects are and what interactions (if any) there are with any other medications you are taking.

What causes brain tumors?

A history of radiation to the brain does increase the risk of all types of primary brain tumors. **This should not be a reason to avoid radiation therapy if your doctor prescribes it, since the risk of this complication is still low.** In about 10% of patients there is a strong family history, implying genetic factors may have a role in this small subset of patients. Other epidemiologic studies have failed to reveal any common explanation for brain tumors, so in most cases, we have no explanation for what causes primary brain tumors in most patients.

The risk of developing a specific type of brain tumor is related to age. Older patients tend to have more aggressive primary brain tumors, and younger patients tend to get less aggressive forms. However, we are noticing an increase in the frequency of the more aggressive tumors in younger patients, which may suggest that some environmental factors contribute to the formation of brain tumors. Unfortunately, we do not have any good indication of what these factors are.

What does it mean when a brain tumor is in remission?

It means that all signs of the tumor (as evaluated by MRI) are gone. This does not mean that the tumor is cured. Rather, it means that our current imaging techniques, including MRI, are not sufficiently sensitive to pick up any remaining few malignant tumor cells. This is why we often continue to treat brain tumors with chemotherapy once all signs of the tumor are gone.

What are recurrent tumors?

These are tumors that have come back after remission. This is a common event for high-grade astrocytomas (anaplastic astrocytomas and glioblastoma multiforme), and these recurrences are now treated with a variety of new drugs that were not available as recently as five years ago. This implies that if you have a recurrent primary brain tumor, you should aggressively seek a physician who is comfortable treating this problem with the latest agents that are available (see below).

How is a brain tumor treated?

Treatment depends on the nature of the tumor. For high-grade primary brain tumors, treatment typically consists of surgery, radiation therapy, and chemotherapy. For low-grade tumors, treatment might consist of surgery and/or radiation therapy. For metastatic brain tumors, treatment typically consists (when possible) of surgery and radiation therapy. Chemotherapy for the treatment of metastatic brain tumors is currently being investigated.

How do I choose the best doctor and medical center?

Brain tumors are not common diseases. The experience of your treating physician or physicians matters a lot. Hence, adequately taking care of patients with brain tumors requires the involvement of physicians who are current on the latest information about these type of cancers, and are experienced in treating them. This generally means getting care from faculty of a university-affiliated hospital or medical center. You should ask any potential treating physician how many patients with brain tumors they have cared for over the last year, how many experimental or investigational protocols in brain tumor therapy they are running (centers at the cutting edge will be performing clinical investigative studies, since the optimal treatment for brain tumors is constantly changing), and what their experience with your particular type of tumor has been. Getting a second opinion is definitely a good idea—this will allow you to check out the reputations of the other physicians you have seen by asking their colleagues, and will give you a sense of the range of treatment choices for your particular tumor.

Once a brain tumor is removed or biopsied, how long does it take to identify how aggressive a tumor it is?

The tissue removed during surgery is reviewed immediately by the pathologist using a technique called “frozen sectioning.” This provides the pathologist with a rough idea as to whether the tissue contains the tumor and whether the tissue is adequate to make a diagnosis. However, a final diagnosis requires more detailed examination and a process called “paraffin embedding and sectioning,” which takes one to two days. This yields material that is generally adequate to determine if the tumor is aggressive or low-grade, and which type of tumor it is. Additional testing is occasionally performed to determine if the tumor contains markers that predict its responsiveness to chemotherapy, and these tests generally take one week.

What is the average length of hospitalization and recovery time after brain tumor surgery?

When the surgeon performs a biopsy, the hospitalization is typically one day, and recovery is very fast. More extensive procedures that involve removal of all or some of the readily visible tumor involve longer hospital stays (four to six days) and a longer recovery period (three to six weeks). While these may be issues for you to discuss with your neurosurgeon, you should remember that patients tend to do better when as much of the tumor as possible is removed.

What are some suggestions for telling family members about the diagnosis of a brain tumor?

The diagnosis of a high-grade brain tumor is a serious business, and carries with it a heavy emotional burden for patients and their families. It is important for doctors who are caring for these patients to keep a balanced perspective when discussing the diagnosis of a brain tumor and its implications. In addition to emphasizing the seriousness of the diagnosis and the potential for disability and death, it is also important to emphasize that progress in understanding and treating aggressive brain tumors has been accelerating over the last decade. What is considered the “optimal” treatment for these diseases changes every six months to one year. This is a reflection of the intensive research being performed by clinicians and scientists around the country, most of whom have been supported by research grants from the National Institutes of Health (NIH). Recently, these funds have become much harder to obtain because of inadequate appropriations to the NIH budget from the federal government. Hence, for progress to continue in brain tumor research, it will remain important for patients and their families to lobby for continued support of brain tumor research through the current patient advocacy groups. These include the American Brain Tumor Association (www.abta.org), The Brain Tumor Society (www.tbts.org), The National Brain Tumor Foundation (www.braintumor.org), The Pediatric Brain Tumor Foundation (www.curethekids.org), The Pediatric Brain Tumor Consortium (www.pbtc.org), The Brain Tumor Funders’ Collaborative (www.braintumorfunders.org), and others available on the web.

How are tumors graded?

Typically, primary brain tumors are graded based on how aggressive they appear under the microscope. Signs of aggressiveness include an increase in the number of cells in the tissue ("hypercellularity"), abnormal cell shape ("pleomorphism"), evidence of blood vessel growth ("angiogenesis"), and cell death ("necrosis"). The more of these features that are present, the more aggressive a tumor is likely to behave and the higher the grade. It should be kept in mind that many primary brain tumors have some regions that have only a few of these features, while other regions have more. Neuropathologists typically grade brain tumors by their most aggressive-looking regions, since this predicts likely tumor behavior.

What are clinical trials and how do I find one?

Finding the best treatments for brain tumors still requires investigations of novel, promising drugs in humans with these diseases. While laboratory investigations in experimental animals provide valuable information on how such drugs might work in humans, the final proof is to study these drugs in patients with brain tumors. In order for a drug to enter a human clinical investigative trial, it has to pass a series of rigorous reviews to ensure that the patients who enroll in these trials are adequately protected.

In order for a promising drug to be approved by the Food and Drug Administration (FDA) for use in humans with brain tumors, it must be examined in three types of clinical trials. Phase I trials attempt to determine if the drug is safe, and what the maximum tolerated dose (MTD) of the drug is. Once the MTD is determined, a phase II trial is undertaken, and its goal is to determine how frequently patients respond to the drug when it is administered at the MTD. This leads to a phase III trial, where the drug in question is compared to the current standard of therapy to see how it compares. Completing these three phases can take as long as five to ten years, and is generally required before the drug can be approved by the FDA.

Progress in brain tumor treatment will only occur with ongoing clinical trials that are designed to improve how we treat this disease. There are several ways to find out what trials are available near you. One is to check the websites of the two NIH-supported brain tumor clinical research consortia (www.nabtt.org). A second is to review the NIH website on clinical trials (www.clinicaltrials.gov). A third is to ask your doctor for referral to a medical center that conducts clinical trials in brain tumor therapy.

What supportive services are available for brain tumor patients?

This can vary enormously from region to region. Several of the patient advocacy groups referenced above have information on support services available in your community. Alternatively, you can ask your doctor for a list of available services.

What are steroids and can they have an adverse effect on a patient?

Steroids are drugs that are commonly used for patients with brain tumors. They are used to reduce the swelling ("edema") that occurs as brain tumors grow. Brain edema frequently causes neurological problems, and can rapidly respond to the use of steroids. Common steroid drugs include dexamethasone (Decadron) and prednisone.

However, steroids are not without side effects. Prolonged usage can cause weight gain, difficulty with sleep, depression, hypertension, diabetes, thinning of the bones ("osteoporosis"), thinning of the skin and easy bruising, and other side effects. Doctors use these drugs for as short a period of time as possible, and only because prolonged brain edema is more dangerous than many of these side effects.

Clinical trials are currently underway to examine other drugs that could substitute for steroids and help patients avoid many of these side effects. You should check with your doctor to see if you might be eligible for any such trials in your community.

How can the patient cope with fatigue?

Fatigue is common after radiation therapy, and is seen as well with some prolonged chemotherapy treatment schedules. It is often self-limited and can improve somewhat with mild regular exercise. For patients who need to work through periods of fatigue, doctors can prescribe medications that aid in overcoming this symptom. These medications include Ritalin, Cylert, Provigil, and Amantadine. You should ask your doctor if any of these medications would be appropriate for your situation.

You should also be aware that other diseases can cause fatigue, including hypothyroidism, diabetes, malnutrition, and depression. Your doctor should be considering these diseases as well when you discuss your symptoms of fatigue.

Will I lose permanent function in the part of the brain that the tumor is in?

That depends. Part of the damage from brain tumors is due to the edema that these tumors can produce. Edema is generally reversible, particularly with steroids and surgery, and the affected region of the brain will recover once the edema has resolved. However, some of the damage is produced by the tumor itself, particularly if the tumor is aggressive and has been growing rapidly, and this damage is generally permanent, since the brain cannot regrow after it has been damaged. Nevertheless, it should be kept in mind that the brain retains a remarkable degree of plasticity—i.e., it can be retrained after an injury, even in adults. This can only happen with rehabilitation. Hence, physical therapy, occupational therapy, and speech and cognitive therapy all are essential treatments that are commonly used to help brain tumor patients recover as completely as possible.

What kinds of doctors treat brain tumors?

The optimal treatment of brain tumors requires a multi-disciplinary team of physicians who work together to bring the most effective treatment to a patient. These physicians include neuro-oncologists; neurosurgeons; radiation oncologists; neuropathologists; neuropsychologists; psychiatrists; nurse practitioners; social workers; and speech, occupational, and physical therapists. The key is that all of these practitioners need to interact together. This typically occurs in brain tumor specialty centers through a weekly meeting, called a “brain tumor board” where ongoing clinical issues are discussed and a consensus on the treatment of each patient is developed.

How is sexuality and fertility affected by brain tumors, radiation and chemotherapy?

Sexuality is very dependent on the patient’s general state of health and well-being. It should therefore not be surprising that being given the diagnosis of an aggressive brain tumor temporarily reduces sex drive (“libido”). This can often be helped with short-term counseling. The diagnosis of a brain tumor can also stress the most stable of relationships, and if this is a contributing issue, it can often be addressed by marital or couples counseling.

Brain tumors themselves can affect sexuality, particularly if the tumor involves regions of the brain that control the release of hormones that affect libido, including estrogen, progesterone, and testosterone. These same regions of the brain can be damaged by radiation therapy, leading to the same set of problems.

Fertility in both males and females can be affected by chemotherapy. Male patients who are interested in having children during or after their treatment with chemotherapy should consider banking their sperm prior to treatment. Banking of ova for women about to begin chemotherapy is less routine, but can be considered if facilities are available in your community. Chemotherapy and radiation therapy can accelerate the onset of menopause in women, and loss of periods (“amenorrhea”) is common in women undergoing treatment.