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LOW GRADE BRAIN TUMOR GUIDE

PLEASE SEE THE HELPFUL,
PRACTICAL ADVICE ON PAGE 17
FOR WHAT YOU SHOULD DO FIRST AFTER A DIAGNOSIS.

Al Musella, DPM

ABOUT THE MUSELLA FOUNDATION

The Musella Foundation for Brain Tumor Research & Information, Inc., is a 501(c)3 nonprofit public charity dedicated to accelerating the search for the cure of brain tumors and to helping families deal with a brain tumor diagnosis. We create and distribute educational materials, help match patients to clinical trials, provide emotional and financial support to brain tumor patients, raise awareness for brain tumor community challenges, lobby for expedited access to promising treatments, and give grants for brain tumor research. We maintain several websites to serve brain tumor patients and families:

Brain Tumor Information and Treatment - virtualtrials.org
Co-pay Assistance - braintumorcopays.org
Fundraising - walktoendbraintumors.org

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Low Grade Tumor Book 1st edition Musella Foundation for Brain Tumor Research & Information

An up-to-date and essential guide to

Tools for getting organized

Understanding brain tumors

Molecular markers

Your medical team

Questions to ask

Standard-of-care treatment

Alternative and complementary treatments

Common medicines for treating symptoms

"Real world" and online support groups

Insurance management

Al Musella, DPM

First edition

LOW GRADE

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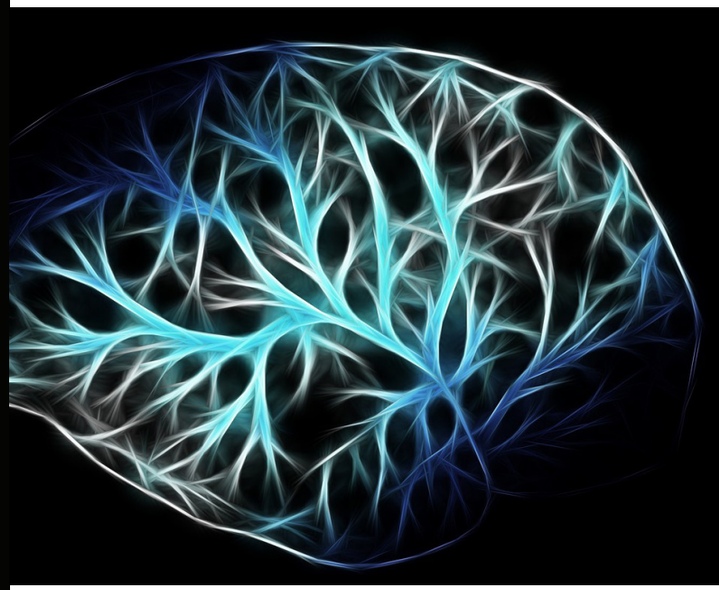

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Brain tumors and their diagnoses

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Photo By Dave Royko

Introduction

Al Musella, DPM

If you have this book in your hands, it is possible that you or someone close to you have just received one of the biggest shocks of your life: the diagnosis of a brain tumor. And as if that shock were not enough, let me add another: you now have to make immediate and important decisions about your brain tumor treatment. The medical team who made the diagnosis will provide advice and guidance. But because so many options exist — what doctors to choose, where to be treated, what treatments are available, what clinical trials can be entered — you need to become as informed as possible in order to make the best and most rational decisions.

The goal of this ***Low Grade Brain Tumor Guide*** is to provide you, your family, and your friends with a basic primer on the "brain tumor" terrain. This book provides tools for getting organized and delivers information about low grade brain tumors, your medical team, brain tumor treatment, clinical trials, and sources of support. This book can be a vital first resource as you begin the fight against your brain tumor by providing context for the world of low grade brain tumor treatment.

A special feature of this Guide is that it is written with explicit reference to the virtualtrials.org website run and managed by the Musella Foundation for Brain Tumor Research and Information. The virtualtrials.org website was begun in the 1990s to list clinical trials and host online support groups for brain tumor patients. Since then, the website has grown steadily. There were over 150,000 visitors in the past year, from 217 different countries. For many people, the website has become an essential portal to brain tumor information and a place of shared experience. The website lists brain tumor centers, hosts and manages online support groups, keeps an up-

to-date catalog of brain tumor clinical trials, and describes current and experimental brain tumor therapies. The website also provides links to, and actually gives, financial assistance.

A final word. Although it might feel otherwise right now, you are not alone. However difficult your next months or years will be as you fight your brain tumor, there are others who have lived through the experience and have a lot to share with you. Please reach out. There is a community that can support you — that wants to support you — beginning with the wonderfully resourceful Musella Foundation.

We wish you peace and health.

Photo By Steve Tilkin

ABOUT THIS GUIDE

Forward

We are sensitive to the fact that if you are reading this Guide, you could be experiencing some of the most stressful and difficult days of your life. We have produced this Guidebook to let you know you are not alone in your challenges.

A diagnosis of a low grade tumor can be worrisome for the patient and the entire family. Currently available information on the Internet is confusing and at times contradictory. We understand that simply hearing a tumor described as 'low grade' does little to alleviate the anxiety, frustration, or fear you may experience when you do not understand what it means. In this Guide, we attempt to tackle many commonly asked questions to ease some of the burden of the unknown and give you some of the information you will need to have effective discussions with your or your loved one's doctor. It is our hope that this Guidebook will somehow make the path ahead of you smoother.

Applicability

This Guide discusses low grade tumors (Grades 1 and 2) in children and adults. Individuals needing information about Grades 3 and 4 – high grade tumors – should refer to the document entitled "Brain Tumor Guide for the Newly Diagnosed" which is available at this website: https://virtualtrials.org

Personalized Help

If you have any questions or comments, or if you have just been told that you need brain surgery, please call us at the Musella Foundation at 888-295-4740 at any time during normal business hours, US Eastern time zone. You can also submit questions by means of our website. Go to: https://virtualtrials.org

Glossary

We understand that you are likely to encounter a number of unfamiliar terms and abbreviations. At the back of this Guide is a glossary of terms and abbreviations as well as a link to the National Cancer Institute's Dictionary of Cancer Terms.

Internet Links

This Low Grade Brain Tumor Guide contains many up-to-date Internet links to different sections of the virtualtrials.org website of the Musella Foundation and to other websites.

Due care has been taken to ensure that the Internet links are accurate. But as we know, such links are sometimes changed by the organizations that originally posted them. At the virtualtrials.org website of the Musella Foundation, a PDF version of this book is available, which is both searchable and has activated Internet links. There is also a separate webpage on which all the website links in this book are routinely kept up to date. To access that page to see a complete listing of the website links in this book, go to:
https://virtualtrials.org/booklinks.cfm.

Scientific Advances/Studies

This Guide is based on the most up-to-date information known at the time. However, the field of medicine is constantly expanding and improving its knowledge about brain tumors such that what may be standard today is considered obsolete later. This is why treatment by a doctor specializing in brain tumors is so important; specialist doctors are on the leading edge and are themselves driving the direction of advanced treatment against brain tumors.

You should also know that one or even a few studies contradicting a current standard practice does not necessarily warrant a change in medical direction. Often, more studies are needed to completely check all factors and verify the data found in the contradictory study. Your best resource for resolving any apparent conflicts in medical thought is your doctor.

Informational Only

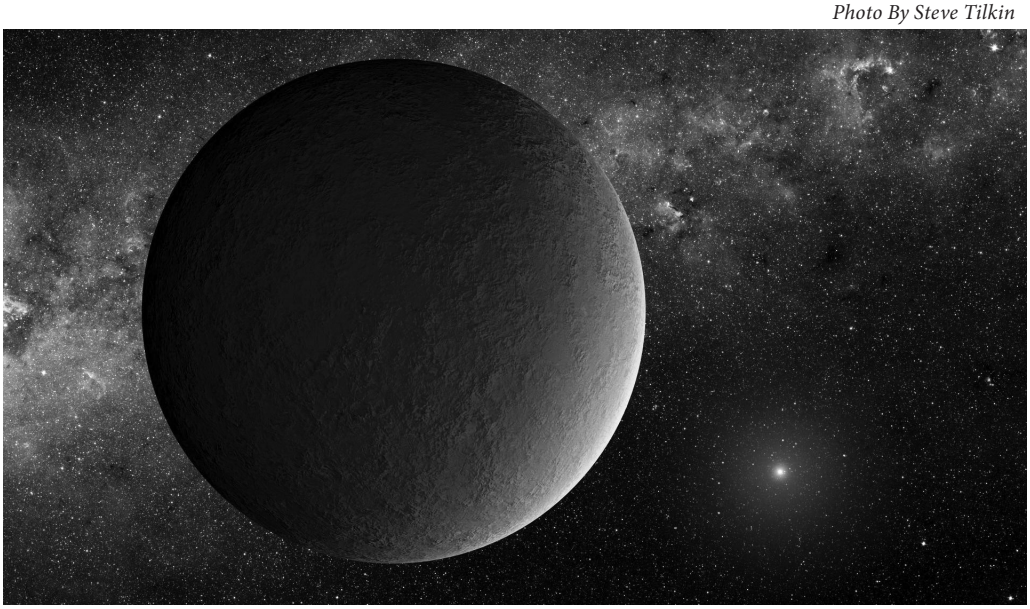
The information provided in this ***Low Grade Brain Tumor Guide*** ("Guide") and at the virtualtrials.org website (the website) reflects the diverse opinions of many different people, most of whom are not physicians or nurses trained to practice oncology, neuro-oncology, or neurosurgery.

Neither this Guide nor the website provides any medical advice from any person at the Musella Foundation or associated with the Guide or website.

The information in this Guide and at the website should, therefore, be considered simply as ideas for further exploration with your personal doctors. You should never ignore professional medical advice in seeking treatment because of something you have read in this Guide or on the website. Always consult your doctor for your care.

If you find any errors, disagree with what we say, or have suggestions to improve it, please contact us by email at musella@virtualtrials.org or phone toll free at 888- 295-4740.

Photo By Steve Tilkin



Introduction to Low Grade Tumors

Understanding Brain Tumors

A brain tumor is an abnormal mass of tissue located within the skull in which cells grow and multiply uncontrollably, having escaped the mechanisms that produce normal cells. Not all brain tumors are the same.

Brain tumors are identified by grade, as opposed to stage. Tumor grade is different from cancer stage. Cancer stage refers to the size and/or extent of the original (primary) tumor and whether cancer cells have spread in the body.

The grade of a tumor means how different the tumor cells look from the normal cells of origin when the pathologist reviews the tumor tissue under a microscope. Lower grade tumors may appear similar to surrounding normal brain but may have a slightly higher density of cells or mutations that do not appear in normal brain cells. Higher grade tumors have a higher density of cells and the cells are reproducing at a much higher rate, often with many more mutations not found in normal cells.

Grading Brain Tumors

The World Health Organization (WHO) defines the grading system for brain tumors and how doctors (pathologists) are to classify tumors based on those grades. The grading system allows doctors to identify the nature of tumors and may help to indicate prognoses and treatment options.

WHO classifies all brain cancers on a grade of 1 to 4. Brain cancer tumors vary from Grade 1 (least aggressive) to Grade 4 (most aggressive) based on the rate of their

uncontrolled growth and invasiveness to nearby tissues. The grade levels are as follows:

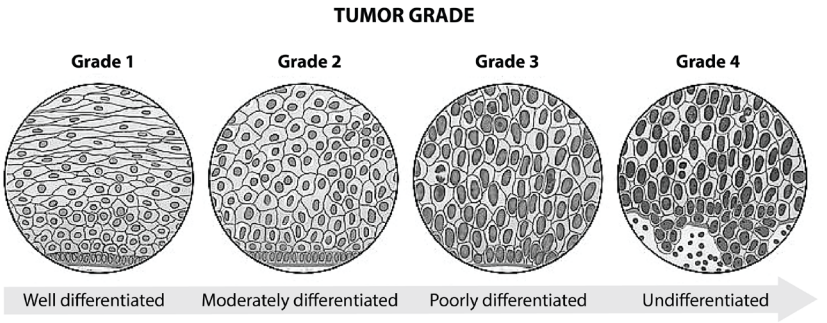
Grade X: Grade cannot be determined yet.

Grade 1 means a tumor that is very slow growing and well differentiated (see definition below). Such tumors are usually associated with long-term survival and are most common in children. Grade 1 tumors often do not need additional therapy after surgery. This is the grade level meant when a tumor is called benign.

Grade 2 means a tumor that has slightly abnormal characteristics, is considered moderately differentiated, and is relatively slow growing. It is considered a cancerous tumor. Most of these tumors are infiltrative, which means they spread into nearby normal tissue, and over time can transform into a higher grade tumor. Grade 2 tumors may or may not require additional therapy after surgery.

Grades 3 and 4 are tumors that have very abnormal cells, are poorly differentiated or entirely undifferentiated and are able to grow and spread quickly. These tumors actively reproduce abnormal cells that invade nearby tissue. They tend to recur. Grade 3 and 4 tumors always require additional therapy after surgery that typically involves radiation and chemotherapy.

The term "differentiation" refers to how much the cells of a sample of tumor tissue look normal. Well differentiated tumor cells look more like normal cells of origin. These tend to grow and spread more slowly than poorly differentiated or undifferentiated cancer cells, which often do not resemble the normal cell of origin and may vary widely in sizes and shape.



Low Grade Tumors

Tumors categorized as Grade 1 or Grade 2 are considered low grade tumors.

Low grade tumors are masses that typically originate in the brain and tend to be slow growing. They often arise in young, otherwise healthy patients and generally have a slow course with longer-term survival in comparison with high grade gliomas.
Low grade tumors are the most common type of brain tumor in children, representing 40% of all childhood brain and spinal cord tumors. Although adults also develop low grade gliomas, they behave and are treated very differently.

Treatment options for brain tumors include observation ("watch & wait"), surgery, radiation, chemotherapy (or other medications), or a combined approach, and management is personalized based on tumor location, histology (its appearance under the microscope), molecular profile (the unique DNA features or mutations), and patient characteristics. Moreover, in a low grade brain tumor with a relatively good prognosis and prolonged survival, the potential benefits of treatment must be carefully weighed against potential treatment-related risks.

Although those with low grade tumors are only rarely cured, most are able to work, attend school, and perform other tasks for a number of years. Careful management of seizures, brain swelling, and other symptoms with medications, combined with the timely use of the appropriate treatment can help preserve a high quality of life and minimize symptoms related to cognitive or neurological deficits.

In general, we often don't know how long a low grade glioma has been developing. Sometimes a doctor can estimate how long it has been there based on how it looks on an MRI or because of symptoms a person has experienced in the past.

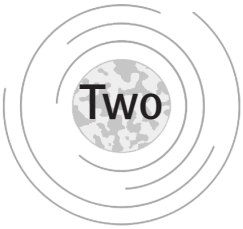
Origination of Brain Tumors

More than 150 different brain tumors of all 4 grades have been identified. About 20 percent of those tumors are low grade. All tumors are divided into two main groups: primary and metastatic (sometimes called secondary).

Primary brain tumors originate in the brain and rarely migrate outside of the central nervous system (i.e., the brain, spinal cord and nearby structures).

Secondary or metastatic brain tumors form from a cancer that originates elsewhere in the body, most often from lung, breast, or skin. The cancer cells migrate to the brain, usually through the bloodstream. Metastatic tumors are considered cancerous (malignant). Secondary tumors are more common and typically require treatment that is different from primary tumors.

Photo By Steve Tilkin



Signs, Symptoms, and Diagnosis

Common Signs and Symptoms of Low Grade Tumors

Low grade tumors typically do not spread outside the brain, but instead grow into the normal brain tissue, creating symptoms as the tumor grows locally. This can disrupt connections between normal brain cells and can also create pressure on the nearby brain tissues. Since the tumor's growth is restricted by the skull, even a small tumor can cause significant issues, particularly if the tumor is in a critical area of the brain.

Low-grade tumors can cause a range of symptoms, which can be similar to the symptoms experienced due to high grade tumors. The most common symptoms are:

- Headaches, especially a morning headache or a headache that goes away after vomiting (affects 50% to 60% of patients);
- Seizures (as defined in the Glossary below). About 20 to 50% of patients will experience one or more seizures. These can be minor or "focal" seizures that are barely noticeable, resulting in unusual smells, funny feelings in the stomach or brief spells that are not easily explained. Low grade gliomas can also result in seizures that produce a more severe electrical disturbance causing disruption of consciousness, shaking or uncontrolled movements of the arms and legs, and affecting the ability to talk;
- Focal neurologic deficits such as memory loss, motor weakness, aphasia (difficulty speaking or understanding speech), visual symptoms, and cognitive and personality changes. (This symptom is more common with higher grade tumors but can occur with low grade tumors);

- Nausea and vomiting;
- Unusual smells;
- Anxiety or anxiety attacks;
- Unusual sleepiness or change in activity level;
- Loss of balance (especially weakness on one side of the body), lack of coordination, or trouble walking;
- Increase in head size (in infants);
- Numbness/sensory loss.

The brain has specialized areas that help us control individual functions, so if a tumor develops in the part of the brain that controls the right leg, you may have weakness, numbness or seizures in that leg. If a tumor develops in the part of the brain that controls language, you may have trouble speaking or understanding. Most tumors are found because they cause a symptom that leads your doctor to request an MRI or CT of the brain.

Diagnostic Tests and Procedures

Most brain tumors are diagnosed after symptoms appear. Often a brain tumor is first suspected by an internist like a primary care physician or a neurologist or, if the symptoms are severe enough, by an emergency room physician. An internist is a doctor who specializes in treating adults. A neurologist is a doctor who specializes in problems with the brain and central nervous system.

In addition to obtaining a detailed medical history and a standard physical examination, the doctor may recommend the tests and procedures described below. The doctor will likely consider several factors when choosing which diagnostic test(s) or procedures to employ:

The type of tumor suspected;
Symptoms;
The person's age and general health;
The results of any earlier medical tests.

These tests are to further evaluate the patient's symptoms and determine whether a brain tumor or another conditions may be present.

Neurological Exam

A neurological exam is a series of questions and tests to check the brain, spinal cord, and nerve function. The exam checks for the issues listed below, which can help the doctor understand whether a neurological condition is present.

- Tests for eye movement, pupil reaction, and eye reflexes;
- Vision tests and examination of the optic nerve;
- Hearing tests;
- Tests of involuntary muscle reflexes;
- Balance and coordination tests;
- Tests for sense of touch using sharp and blunt objects;
- Tests of facial muscles, tongue movements, and gag reflexes;
- Mental status examination and memory tests.

Blood tests

At present, blood tests are not used to diagnose brain tumors. There are efforts underway that may make blood tests part of the diagnostic process. However, blood tests are routinely done to provide a baseline before any planned treatment. They can provide helpful information about general health, how other organs are functioning, other medical conditions and the possible risks of treatment. Blood tests may include:

- A complete blood count (CBC), which measures the number and quality of white blood cells, red blood cells and platelets;
- Blood chemistry tests, which measure certain chemicals in the blood to show how well certain organs, such as the liver and kidneys, are working.

Imaging: Overview

Imaging studies help to identify a variety of abnormal conditions in the brain, such as a stroke, infection, or a tumor. The size, location, and other characteristics of a tumor may assist in determining its cell of origin and grade. Imaging studies are also useful in determining whether swelling or bleeding in the brain may be causing symptoms.

Imaging: CT Scans

Brain tumors may first be identified by means of a computed tomography (CT) scan. CT scan uses x-rays to make detailed cross-sectional images of the brain and spinal cord. Unlike a regular x-ray, a CT scan creates a rapid, three-dimensional representation of the brain and skull. However a CT scan does not show very much detail, so if a mass is suspected based on the CT scan, the doctor will likely request a magnetic resonance imaging (MRI) scan of the brain.

For brain and spinal cord tumors, CT scans are not used as often as MRI scans. Still, there are instances where CT scans may have advantages over MRI scans:

CT scans take much less time than MRIs, which can be particularly helpful for children who have trouble staying still; and

CT scans provide greater detail of the bone structures than MRIs.

Imaging: MRI Scans

An MRI scan of the brain is often the only imaging required. This procedure does not use radiation, but instead uses a magnet, radio waves, and a computer to make a series of detailed pictures of the brain and spinal cord.

The doctor may ask that a dye called gadolinium be injected during the MRI, which improves the visibility of inflammation, the mass and blood vessels. Disease of the cerebral tissue frequently impairs the integrity of the blood-brain barrier allowing gadolinium to leak through and increase the signal of the images compared to unaffected regions of the brain. It is crucial to recognize that contrast imaging studies can be misleading since multiple brain pathologies can disrupt the integrity of the brain-blood barrier causing contrast enhancement. Furthermore, static contrast enhancement alone cannot discriminate between low-grade and high-grade tumors so once a lesion is identified, a resection or a biopsy is required for diagnosis based on the tumor tissue. A biopsy is preferred to a resection in those with a less common presentation such as young age.

Some patients may have pacemakers or other implanted devices that are incompatible with MRI. Such patients should undergo head computed tomography (CT) with contrast dye.

Under some circumstances, the doctor may ask that the whole body is scanned to check for cancer elsewhere in the body.

While the MRI is a good technique for confirming the presence of a brain mass, it does not identify the type of mass. The mass may be benign, malignant, primary, or metastatic or may even be indistinguishable from an infection.

A biopsy or resection is needed to confirm the diagnosis and to grade the tumor.

Imaging: Considerations for Pediatric MRIs

An MRI is used to help diagnose brain tumors in children because of its ability to see through the skull and the bones of the skull and spine without radiation. To date, no adverse side effects from the magnetic fields and radio waves of the MRI have been reported, so an MRI is generally considered safe for children.

However, some children cannot remain still for an MRI scan, which usually takes a minimum of 15 minutes but may last for more than an hour. MRIs depend on the stillness of the patient for image clarity, so a child may require medication to help them relax or sleep during the procedure. Where sedation is needed, the child may be administered a liquid sedation medicine to swallow about 20 to 45 minutes before the scan is scheduled. Several factors are considered when determining if a child will need sedation, including the age and developmental level of child.

Imaging: PET Scan

Positron Emission Tomography (PET) does not provide the kind of visual representations of tumors that a CT or MRI image might, but it provides insights into a brain tumor that can help in differential diagnosis (e.g., deciding if a suspected area is tumor or scar tissue, or if a tumor has grown or merely changed in reaction to treatment). A visual reading of PET images correlated to MRI imaging can considerably improve the certainty of the diagnosis. PET may suggest that the tumor has higher grade areas not always apparent on the MRI.

For a PET scan, a radioactive substance (usually a type of sugar known as FDG) is injected into the blood. The amount of radioactivity used is very low and passes out of the body within a day or so. Because rapidly growing tumor cells consume more glucose, the difference in radioactive glucose uptake can be detected with a special camera that detects radiation. The variability in radioactive glucose in normal and abnormal brain cells may suggest whether a tumor is low grade (low glucose uptake) or high grade (high glucose uptake). PET may also be useful in determining whether high grade tumor remains after treatment.

PET scans tend to be more costly than other diagnostic tools and insurance companies typically only approve the procedure for specific indications.

As with an MRI, some children might need medicine to help them relax or even go to sleep during a PET scan.

Lumbar Puncture

Under certain circumstances, the doctor may recommend a lumbar puncture.

The lumbar puncture, also called a spinal tap, is used to collect cerebrospinal fluid (CSF) from the spinal column. This is done by placing a needle between two vertebrae in the lower spine and into the lining around the spinal cord to remove a sample of the CSF. The sample of CSF is checked under a microscope for the presence of tumor cells. Note that this evaluation would not necessarily provide the level of biomarker information for the mass that a biopsy or resection (both described below) would.

This procedure may help to distinguish between certain diseases and a tumor. Some types of tumors can even be diagnosed with spinal fluid alone, such as lymphoma. However, most low grade brain tumors cannot be diagnosed with spinal fluid analysis alone. Diseases where the symptoms may mimic those of a tumor are:

- **Meningitis.** This is an inflammation of the membrane covering the brain and spinal cord. The inflammation is usually the result of a viral, bacterial, or fungal infection. However, the presence of cancer cells in the spinal fluid is called carcinomatous meningitis and may cause similar symptoms to an infection.
- **Encephalitis.** An inflammation of the brain that is usually caused by a virus.

If the individual is fragile (i.e., very young, very old or has underlying health concerns, or could be susceptible to a brain bleed or stroke if a biopsy is undertaken) then the doctor may order a lumbar puncture.

Molecular Evaluation

The diagnosis of a brain tumor is based principally on the molecular evaluation of tumor tissue. The molecular evaluation and classification of brain tumor tissue is the corner stone upon which the medical diagnosis and treatment rests. In this evaluation, the pathologist's goal is to determine the tumor's growth pattern (circumscribed versus infiltrative, solid versus cystic), enhancement pattern (non-enhancing versus enhancing), and the presence or absence of edema, necrosis, and calcification.

A molecular evaluation includes two aspects: a review of the tumor tissue, referred to as a histological evaluation, and the determination of the DNA biomarkers.

The histological features evaluated include cytological atypia, mitotic activity,

anaplasia, microvascular proliferation, and necrosis. All these features are present in high grade gliomas, and either none or only cytological atypia in the lower grade tumors.

For that reason, the evaluation of the microscopic structure of a tumor's tissue and an identification of the biomarkers (discussed below) by a qualified pathologist becomes extremely important for an accurate diagnosis, which in turn, drives decisions about treatment, and in some cases, a prognosis. A prognosis is the medical estimate of how the tumor will behave in the future and how quickly it may grow.

A biomarker is any gene mutation, pattern of tumor gene expression, and nongenetic changes in the DNA of a tumor. Many different biomarkers have been characterized for brain tumors and are in clinical use. Treatment often targets a particular biomarker that is known or theorized to be effective in curbing the growth of a tumor. These are called targeted therapies.

The tumor tissue required for the molecular evaluation is made available currently to the pathologist by two methods: biopsy or surgery. The biopsy technique is described below. For more detailed information about surgery please see the Section entitled "Surgery".

Biopsy

Overview

Brain biopsies are performed by highly specialized doctors called neurosurgeons. A description of the types of biopsies that may be performed can be found below. While this section presents the technical aspects of a biopsy, we remain sensitive to the fact that undergoing this procedure can be quite stressful both prior to and after the event, and hopefully the information presented here will address some of your concerns.

Prior to the biopsy, the neurosurgeon is likely to request that use of all blood thinners including aspirin, ibuprofen, as well as all herbs and supplements that thin the blood be ceased.

Biopsy During Surgery

When the tumor is considered operable based on the neurosurgeon's review of the MRI image, the surgery to remove the tumor becomes the biopsy. Before removing the tumor, but while the surgery is underway, the neurosurgeon will likely obtain a small tissue sample to provide a working diagnosis to help make decisions during the remainder of the surgery. This tissue sample is submitted to the pathologist, rapidly frozen and processed so that microscopic examination can be done immediately. The pathologist's analysis may be helpful to the neurosurgeon in determining whether a complete resection is possible.

After surgery, the entire resected tumor is sent to the pathologist, who will process the remainder of the tumor for permanent microscope slides, for molecular testing, or even for research.

A surgery that involves cutting an opening in the skull is called a craniotomy. Removal of all visible tumor is called a gross total resection and removal of a portion of the tumor is called a partial resection. For more information, please see the section in this Guide entitled "Surgery."

Needle Biopsy

Where the tumor is considered inoperable by the neurosurgeon or there is a location or condition that makes surgery not feasible, the neurosurgeon will recommend a needle biopsy. A needle biopsy may also be referred to as a stereotactic biopsy or guided needle biopsy, depending on the specific technique planned.

It should be noted that pathologists tend to get less data about the tumor from tissue obtained by a needle biopsy than from the greater quantity of tumor tissue taken during a surgery.

In a needle biopsy, the neurosurgeon drills a small hole into the skull and inserts a thin hollow needle into the tumor. A tiny amount of tissue is extracted through the needle. The scalp incision is usually very small—only a few millimeters.

To ensure stability and accuracy of the procedure, the person's head may be secured

with a frame. In a frameless biopsy, the neurosurgeon will use a neuronavigational system like a CT or MRI to identify the exact location of the tumor within the brain.

The CT or MRI images and coordinates are used to guide a needle to the tumor through a small opening in the skull. The neurosurgeon will usually extract several samples from various locations within the tumor for ensuring maximum diagnostic accuracy.

Many patients tolerate this biopsy under light sedation and local anesthesia instead of general anesthesia.

A needle biopsy typically takes 2 to 3 hours.

The greatest risk of a biopsy is bleeding in the brain, and about 5% of cases may have some bleeding. Bleeding can cause symptoms ranging from mild headache to serious stroke-like effects. To manage any risks, most neurosurgeons will ask their patients to remain overnight following a biopsy, but a few individuals may be asked to stay for a couple of days. The majority of people are discharged after the one-night stay.

After the biopsy, the person may be given a steroid (e.g., dexamethasone) to help minimize swelling caused by the biopsy and an antibiotic or antimicrobial to help guard against post-operative infection.

Liquid Biopsy

Genetic material from the tumor may be shed into the blood and, therefore, available for detection by means of a "liquid biopsy". A liquid biopsy can provide key genetic information about the tumor. Currently, liquid biopsies are not yet routinely used, but they have been implemented in various clinical scenarios, including the non-invasive diagnosis of brain cancer, subtyping the brain tumor, and prognosis prediction. Because it is considered a minimally invasive procedure, it can be done more frequently than standard biopsies. It can also be performed when surgical biopsies cannot, such as when tumors are difficult to reach or when a patient would be unable to tolerate the biopsy procedure.

Importance of Early Detection and Diagnosis

More timely diagnosis of brain tumors could improve patient outcomes, yet patients and their primary physicians may find it difficult to recognize the early symptoms of brain tumors. In primary care, patients can present with symptoms that seem to be common manifestations of benign conditions making the diagnostic process very challenging. Often patients brush off their symptoms as normal if they consider them part of an expected ageing process, or if symptoms are vague, intermittent, or non-threatening.

Eventually symptoms can become too troublesome to ignore which begins a more intense medical evaluation to determine the cause. The starting point for the improvement of the wellbeing and survival of patients with brain tumors is the accurate and early medical diagnosis. Diagnostic testing consists of:

- Review of medical history;
- Physical exams;
- Neurological exams;
- Imaging studies (e.g., MRI scans);
- Biopsy or Resection (for harvesting tumor cells/tissue);
- Lumbar Puncture (in some cases) (if biopsy or resection cannot be performed).

Some doctors may request an electroencephalogram (EEG) to detect possible seizures or abnormalities in the electrical activity of the brain.

After the medical team completes all tests, many of the premier brain tumor hospitals will convene, either actually or virtually, a "tumor board". A tumor board consists of several doctors of differing specialties who will weigh all the evidence (e.g., pathology findings, MRI/CT Scan images and medical history) to discuss the diagnosis and proposed treatment.

The rate for accurately determining the diagnosis of a brain tumor is at least 95%. Occasionally, there can be uncertainties. In those cases, it is highly advisable to request a second opinion from a highly rated brain cancer center.

For a list of major brain tumor centers by state and country, please go to:

https://virtualtrials.org/Brain_Tumor_Centers.cfm.

If possible, all brain tumor patients should receive at least one second opinion from a brain tumor center.

A correct and timely diagnosis can help patients receive accurate treatments which, in turn, supports their wellbeing and maximum survival. Over time, greater than 70% of low grade gliomas can transform into a higher grade or become aggressive in behavior within a decade. As a result, expert treatment and monitoring is essential.

First Things After Diagnosis

Getting Organized

Organization is your key to obtaining the information you will need for ensuring the proper management of your care or your loved one's care. This information can help you with many actions including monitoring side effects, planning doctor visits, tracking medical bills and insurance claims and supporting referrals to specialists for second (or third) opinions. Such referrals are often delayed by the need to obtain records that may have been lost along the way. Maintaining your own copies of the items described below items will ensure that your consulting physicians have access to all of your important documents at the time of your appointment.

Since many low grade tumor journeys can be quite long, some exceeding a decade or more, maintaining a notebook binder for safeguarding and retrieving the information about your tumor is key in ensuring effective and efficient communications with medical professionals when needed.

Setting Up Your Document Binder

A three-ring binder can become your best friend. Items to keep in your treatment binder include:

Medical history. Start with a copy of the first medical history form you are asked to fill out. This will list past medical problems, such as diabetes or heart problems, which may affect the treatment choice, as well as any allergies you have. An important allergy to note is one to either iodine or shellfish, as the dyes (contrast agents) used in some brain scans contain iodine. Having a copy of your first medical history will be helpful when you have to fill out similar forms. Keep your medical history

updated as things change. You can also ask your doctor for a copy of your examination records.

Copies of imaging films and reports. Most radiological centers today can provide you with a copy of your imaging scans on a CD that can be viewed on any computer. When you check in at the MRI radiology facility, it is very important to request a copy of the film or a CD along with the written report of the radiologist's findings. (Most office supply stores carry special three-hole vinyl pages that hold multiple CDs safely within a binder.)

Ask for a CD of your images BEFORE you go into the scanner, as it is easier for the staff to handle the request then than if you tell them afterward.

All routine laboratory reports (e.g., blood tests). Different members of your medical team will benefit from receiving recent laboratory results that may have been initially ordered by another physician. Having your own personal copies of all routine laboratory reports so that they are available for review on demand, will save time, increase your own understanding, and in some cases eliminate the need for unnecessary blood work. As a bonus, if you are computer literate, keep track of lab results in a spreadsheet so you can graph results over time and see how you are doing.

All pathology reports, cytology reports, and molecular genetic analysis reports from all biopsies and CSF analyses. If you have had more than one biopsy, or have a history of another cancer, keep these records in this section. Also, if the biopsy was reviewed by more than one pathologist, keep both reports.

List of Medications. It is important to disclose all the medications you take to your doctors and care team members. Keeping an up-to-date medication record in your treatment binder (including all vitamins, herbal supplements, and over-the-counter items) can provide a quick and clear snapshot of your daily meds at a glance, reducing the chance of error when more than one physician is involved with your care. Without this information, you may experience symptoms that are medication-related or side effects of a medication that one member of your medical team may not realize you are taking, with the consequence that you may be incorrectly diagnosed or treated.

Take your treatment binder to every appointment with every doctor and request that this list be reviewed before any new medication is prescribed. You should also request a copy of the drug formulary — a list of covered medications — from your insurance company and keep it in your treatment binder. Knowing in advance about the need for prior authorization can save you time and expense.

Many people maintain their binder virtually on their computer, stored the data on a flash drive, and occasionally print the data out and store them in the binder as needed — since it is easier to carry a binder around.

Please note that the Musella Foundation's Patient Navigation Program (as described later in this Guidebook) can help you organize your medical records.

Additional Practical Tips

Emergency Note. You should produce and print out a list of your current medications and allergies to store in your wallet or pocketbook in case of emergency.

Phone Numbers. Record the names, addresses, phone numbers, email addresses, and a short description of all of your important contacts. Be sure to include your family members who should be contacted in an emergency, all of your doctors, your lawyer, your financial advisor and/or insurance agent, and any clergy.

Classifications and Types of Low Grade Tumors

Benign vs Malignant

The World Health Organization divides brain tumors into two main categories: benign and malignant. Both types can cause life altering symptoms, so both require qualified medical attention.

Benign Tumors: These are slow-growing and less likely to invade normal tissue. The term 'benign' is less used nowadays as it can be misleading. Low grade brain tumors can still be serious. Due to the limited space capacity inside the skull, even the growth of a 'benign' brain tumor can cause harm by pressing on and damaging areas of the brain. Such tumors may also obstruct the flow of cerebro-spinal fluid (CSF), which nourishes and protects the brain, leading to a build-up of pressure that can cause significant symptoms. "Benign" tumors are normally classified as a Grade 1.

Malignant Tumors: These consist of rapidly dividing abnormal cells that invade normal brain tissue, leading to symptoms and damage. However, they rarely spread beyond the brain. Depending on molecular evaluation, malignant tumors can be designated any Grade between 2 and 4.

Mixed Tumors: Tumors may contain areas with different grades. In such cases, a tumor is assigned the highest grade level present, even if most of the tumor cells are of a lower grade.

Photo By Dave Royko

Differentiating low-grade from high-grade tumors

Determining the difference between low and high grade tumors can be challenging, especially when the person's medical history cannot provide distinguishing information. Both low and high grade tumors may have similar symptoms, growth patterns and may exhibit extensive swelling (edema) on the MRI scan which can make it more difficult for the doctors to assess the image.

Among the distinguishing features identifiable when the tissue is analyzed by a pathologist in the lab are:

67% of low grade tumors have a mild quantity of tumor infiltrating lymphocytes in their tissues whereas high grade tumors will have significant lymphocyte infiltration;

The number of tumor cells exhibiting high PD-1 is significantly lower in low grade gliomas. PD-1 is a protein found on T cells, which are a type of immune system cell. When present, PD-1 may block T cells from protecting the body from cancer and infections; and

Low grade tumors have a lower Ki-67, which is an index indicating the proliferation (growth) rate of the tumor. Ki-67 is often less than 5% for low grade tumors. Because there are so many other factors (like age, tumor type and location), the Ki-67 index does not appear to have a correlation with survival.

Types and Characteristics of Grade 1 Tumors

Chordomas

A Chordoma is a primary bone cancer that develops from remnants of embryonic notochord in the skull-base (head) and spine. Chordomas are generally slow growing and are most commonly found within the head at the base of the skull near a bone called the clivus and in the lower portion of the spine. Chordomas are extremely rare with a yearly incidence in the US of approximately 1 in one million (300 new cases each year). Because they are usually very slow to grow, they are often quite large by the time they are discovered. Usually, symptoms develop and worsen over time. Common symptoms include headache or double vision. Less frequently seen symptoms are visual loss, hearing loss, difficulty swallowing, hoarse voice, facial numbness, incoordination, motor weakness and memory disturbance. These tumors can be very destructive, invading bones and putting pressure on vital brain structures.

In most cases, aggressive surgical removal followed by radiation therapy to remaining tumor offers the best chance of long-term control. Because chordomas invade the bone, complete removal is often impossible. Additionally, chordomas are relatively resistant to radiation therapy and are located adjacent to important and deli-

cate brain structures, such as the brain stem and cranial nerves, which limits the dose of radiation that can be given. For these reasons, highly-focused radiation must be used to treat these tumors. Stereotactic radiosurgery and proton beam are the two most effective methods.

There are no known chemotherapy drugs that are particularly effective in the treatment of chordomas.

Chordomas are malignant and potentially life threatening tumors. Currently the median survival in the United States is about 7 years. The overall survival rates are 68% at 5 years and 40% at 10 years. Complete surgical resection offers the best chance for long-term survival. In many cases, radiation therapy can also increase local control rates and prolong survival. Even after surgery and/or radiation, chordomas tend to return locally - in the same location or in the areas around the original tumor. Many patients undergo multiple surgeries over several years to treat local recurrences. After a local recurrence, the chances of achieving a cure are significantly diminished. Distant metastasis (spreading to other body parts) occurs in 20-40% of patients with chordomas of the spine and less than 10% of patients with skull-base tumors. The most common sites of distant metastasis are the lungs, liver, bones, and skin.

Craniopharyngiomas

A craniopharyngioma is not a pituitary tumor per se, but rather a tumor that develops near the pituitary gland and above it, at the base of the brain near the optic nerves that connect the eyes to the brain. Therefore, it can cause a wide variety of hormone and neurologic problems and treatment requires surgical and medical expertise. In addition, many of these tumors present in children, and the hormonal problems caused by the tumor or by its treatment requires expert management by doctors in many different areas of medicine.

A craniopharyngioma is a benign tumor that will not spread like cancer, but because it tends to grow insidiously and surround very important nerves and blood vessels at the base of the brain, as well as near the pituitary gland and hypothalamus, these tumors can eventually grow large enough to compress the normal pituitary gland, leading to loss of normal hormones that are important for normal life and reproduction. If the tumor gets very large, it can cause compression of other nerves or arteries

that are located near the pituitary gland, especially the optic nerves which connect the eyes to the brain; this can cause slow but progressive loss of vision.

Unlike pituitary adenomas, craniopharyngiomas are thought to come from an abnormal remnant or "left-over" of when the pituitary gland and hypothalamus were being created during development before birth. As a consequence, it is likely that the tumor has been present in some form since birth, but for whatever reason it lay "dormant" until it started to grow and cause symptoms.

When the tumor is small and has not grown to involve important arteries or nerves near the pituitary gland, it can be removed safely and completely, although the concern always exists that microscopic parts of the tumor may remain. For that reason, even after a complete removal, patients need to have yearly MRI scans to make sure the tumor does not come back. If the tumor is large and deemed unsafe for complete removal, it may still be important to get out some of the tumor to relieve symptoms, and to also make what is left behind small enough to treat with radiation, which is usually very effective at preventing growth of what is left behind.

The cause of these tumors remains unknown, although it is thought to be a abnormality of development in the normal pituitary gland or hypothalamus. Because this is an abnormality in development, it is unlikely that anything after birth can be done to prevent their formation, although what causes them to grow and cause symptoms is an active area of research. As far as anyone can tell, there is no known genetic cause for these tumors.

Gangliocytomas and Gangliogliomas

Gangliocytomas and gangliogliomas are rare tumors that include neoplastic nerve cells that are relatively well-differentiated. People of any age may have a gangliocytoma, but this type of brain tumor develops most often in people between the ages of 10 and 30. Gangliocytomas most often form in the brain's temporal lobes, which sit behind the ears and process sensory input, including memory, hearing and emotion. The tumor may also form in these locations:

- Brainstem: This is the part of the brain that connects the cerebrum (uppermost portion), to the spinal cord and cerebellum. It sends signals to control things like breathing and heart rate.

Photo By Dave Royko

- Cerebellum: Located at the back of the brain. The cerebellum controls balance, movement and vision.
- Floor of the third ventricle: This narrow cavity in the front of the brain protects it from trauma and helps transport nutrients and waste.
- Spinal cord: The spinal cord carries nerve signals between the brain and the body. These signals enable sensations and movement.

Early, noticeable symptoms for these rare tumors may include the following:

Movement changes, including loss of muscle control, tremors, paralysis, weakness;
Seizures;
Sensation changes, including numbness;
Speech difficulties;
Vision changes.

Diagnosis of such tumors will include the tests and imaging described earlier in the Diagnostic Tests and Procedures section.

Glomus jugulare

Glomus jugulare tumors most frequently are benign and typically are located just under the skull base, at the top of the jugular vein. They are the most common form of glomus tumor. However, glomus tumors, in general, contribute to only 0.6 percent

of tumors of the head and neck.

Hemangioblastoma

A hemangioblastoma is a rare tumor that grows in the blood vessels of the brain, spinal cord or retina. It isn't cancerous, but it may grow and press on surrounding tissues. They originate from blood vessels, can be large in size and often are accompanied by a cyst. These tumors are most common in people ages 40 to 60 and are more prevalent in men than women. Usually, healthcare providers recommend removing a hemangioblastoma with surgery. After removal, a hemangioblastoma is unlikely to grow back. If surgery is not enough to control this disease, a new drug called belzutifan (Welireg) can be use. Belzutifan is approved for patient with Von Hippo Laudau (VHL) disease. VHL may cause the development of cysts or tumors in the body. Common areas for the development of these cysts or tumors are brain and spinal cords, kidney and pancreas.

Lhermitte-Duclos disease (LDD)

Lhermitte-Duclos disease (LDD) is a very rare benign tumor in the cerebellum. It may also be called dysplastic gangliocytoma of the cerebellum. Researchers do know that Cowden syndrome, which is linked to Lhermitte-Duclos disease, happens when a gene called PTEN mutates. PTEN makes a protein that helps control how cells grow and divide. When the PTEN gene mutates, it stops making the protein, enabling cells to grow uncontrollably, which may lead to the development of this tumor.

Meningiomas

Meningiomas arise from the meninges, the layer of cells that cover the brain and spinal cord, and account for approximately 30% of all brain tumors. 85% of meningiomas are a benign, non-cancerous tumor. However, in rare cases, they become a malignant cancer.

There is no obvious cause of a meningioma; most are sporadic or random diseases. However, this type of brain tumor is more common in women than men, with a 3:1 ratio, and in people between the ages of 40 and 70. Other risk factors include:

- Genetic inheritance of neurofibromatosis, a rare nervous system disorder

which can cause benign tumors throughout the body.
- Exposure to radiation, such as was given in the 1950's to control head lice in some countries. Radiation therapy to the head can be used to treat an infection of the scalp or tumors of the head, brain, or neck.

Overall, 99% of meningiomas represent pure chance. There does not appear to be any link to smoking, diet, or other lifestyle risks that are associated with other types of tumors.

Meningiomas compress parts of the brain or spinal cord as they grow, often achieving great size before they put enough pressure on the brain or spine to cause any symptoms at all. Most often, meningiomas are found incidentally on MRIs. If symptoms do present, they generally appear slowly and may be slight at the onset.

Most often, meningiomas are found incidentally on MRIs during a patient visit that was unrelated to the meningioma itself. Because meningiomas arise separately from the brain itself, they usually display a very sharp border between the brain and tumor both on MRI imaging and on microscopic appearance. The microscopic appearance of the tumor determines its grade, a measure of how cancerous the tumor is. The majority of meningiomas are Grade 1, benign tumors, but occasionally can be Grade 2 (atypical) or Grade 3 (malignant), which are more cancerous.

The grades for meningiomas are as follows:

- Grade 1 – Benign meningioma: Represent 78-81% of meningiomas. Benign meningiomas are non-cancerous and are recognized for their slow growth and distinct borders.

- Grade 2 – Atypical meningioma: Represent 15-20% of meningiomas. Atypical meningiomas are made up of tumor cells that do not appear typical or normal. They have a higher recurrence rate and tend to grow faster. They are neither malignant (cancerous) nor benign but may become malignant in the future.

- Grade 3 – Malignant or anaplastic meningioma: Represent 1-4% of meningiomas. This is an aggressive type of brain tumor, most often invading the parts of the brain closest to the tumor.

The treatment for a meningioma depends on several factors: the location of the brain tumor, whether the tumor is benign or malignant, and the patient's general health and preferences.

The majority of meningiomas can be cured or controlled through a combination of surgery and radiation therapy. The mainstay of therapy for meningiomas is surgical removal. Because meningiomas arise from the covering over the brain, rather than the brain itself, they can usually be successfully removed through an operation known as a craniotomy. The type of craniotomy and approach used by the surgeon to access and remove the tumor depends on its location in the brain, with the risks of surgery generally increasing for larger tumors and for tumors that grow closely to critical brain structures such as major blood vessels and nerves. In some instances the risk of injuring these critical structures may prevent a surgeon from removing a tumor in its entirety.

In the event that a tumor can't be removed completely or for small tumors that are found asymptomatically, another approach that is very successful uses stereotactic radiosurgery with tumor control rates >90%. Additional radiation and/or chemotherapy is sometimes also prescribed for tumors in the Grade 2 or Grade 3 classes if they fail to respond or are resistant to surgery and radiosurgery.

Sometimes very small tumors require no treatment at all. It is not uncommon to find tumors on CT or MRI scans that are ordered for other reasons. If the tumor is small and is not causing any symptoms, doctors may decide to observe and monitor it by taking pictures of it every 6-12 months to make sure it's not growing, holding off on any surgery or treatment until the tumor shows signs that it is actively getting bigger.

Optic pathway gliomas

Optic pathway gliomas are a type of low-grade tumor found in the optic nerve or chiasm, where they often infiltrate the optic nerves, which send messages from the eyes to the brain. Optic pathway gliomas most commonly affect children under ten years old and account for 3 to 5% of childhood central nervous system tumors; however, in very rare cases, individuals as old as 79 years old can be diagnosed. In the case of older patients, the optic pathway glioma tends to be a high grade malignant tumor (Grade 3 or 4).

People with neurofibromatosis are more likely to develop an optic pathway glioma. These gliomas can cause vision loss and hormone problems since these tumors are often located at the base of the brain where hormonal control is located. Gliomas affecting hormone function may be known as hypothalamic gliomas. Optic pathway gliomas are usually a Grade I pilocytic astrocytoma (see description below) with immature astrocytes.

Overall, 85% of patients with optic pathway gliomas will lose some vision, and over time, approximately 25% will retain vision between 20/20 and 20/40. About 60% of patients will develop vision worse than 20/300. Patients may have an afferent pupillary defect (a condition in which pupils respond differently to light stimuli shone in one eye at a time), and where visual field assessment is possible, there may be visual field defects.

Both optic nerve gliomas and meningiomas can show a diffuse enlargement of the optic nerve, and both may also show a globular or fusiform enlargement of the optic nerve. However, meningiomas will show "tram-tracks," which are caused by the thickened and denser optic nerve sheath resulting in a central lucency (less dense region). Calcification is seen in 20 to 50% of meningiomas but very rarely in gliomas. Optic nerve gliomas will show an isointense or slightly hypointense signal on T1 but hyperintense on T2 sequences on an MRI.

Treatment is ideally managed by an interdisciplinary team of neuro-ophthalmologists, hematology-oncologists, oculoplastic surgeons, and radiation-oncologists, depending on the case. Management is tailored based upon all the relevant factors such as symptoms, nature of the tumor, tumor progression, vision and vision change, clinical course, NF1 status, neoplasm genetics, patient's age, and patient (or parent) preference. Observation is often the first choice until significant visual deficits or progression is seen on MRI imaging.

Pilocytic astrocytomas

Pilocytic astrocytomas are slow-growing, benign brain or spine tumors that often take the form of fluid-filled sacs called cysts, although they can also take on solid forms. They generally occur in the lower half of the brain including the cerebellum, brain stem, and around the pituitary gland or hypothalamus. They tend to not infiltrate surrounding tissues; however, they can increase pressure on brain tissue and

block the flow of cerebrospinal fluid (CSF). This may cause symptoms of headaches, personality changes, disequilibrium, and nausea.

Pineocytomas/Pineal Astrocytomas

Pineocytomas also called Pineal Astrocytomas are generally benign lesions that arise from the pineal cells, occurring predominantly in adults. They are most often well-defined, noninvasive, homogeneous and slow-growing. Pineal tumors arise in the region of the pineal gland, a small structure deep within the brain. This gland is thought to be involved in the sleep-wake cycle, though its exact function remains unclear. There are at least 17 different types of tumors that may occur in this region and these tumors range from more aggressive gliomas to benign cysts. The three most common categories of pineal region tumors are gliomas, germ cell tumors (germinomas, embryonal cell carcinoma, teratomas) and pineal cell tumors (pineocytoma and pineoblastoma). Others include meningioma, lymphoma, metastatic tumors, and pineal cysts.

The pineal gland is located deep within the brain near the aqueduct of Sylvius, a passageway through which newly produced cerebrospinal fluid (CSF) travels as it exits the center of the brain. As pineal region tumors grow, they often put pressure on this passage, thus blocking the flow of the CSF. As CSF flow is blocked, pressure builds up in the brain and creates hydrocephalus. Symptoms of hydrocephalus include headache, nausea and vomiting, memory difficulties and imbalance. Severe intracranial (inside the head) pressure may even be life threatening and require immediate attention.

In some cases, a ventriculoperitoneal (VP) shunt will be placed in order to alleviate the pressure. During this procedure, a small catheter is placed into the fluid space of the brain and is tunneled under the skin and usually into the empty spaces in the abdomen. The extra fluid that builds up in the head is thus diverted into the belly where it is easily reabsorbed by the body. Another way to alleviate the pressure is through a procedure called a third ventriculostomy. In this procedure, a small hole is made at the base of the brain to allow better flow of the CSF.

Pineal region tumors can also cause abnormalities in vision because they can arise in an area of the brain which controls eye movement. Some symptoms may include inability to focus, double vision, or the inability to move the eyes.

Germ cell tumors of the pineal region can secrete hormones which could lead to disturbances in endocrine function, particularly by causing early puberty in children.

Pineal cysts may have been present since birth. Other types of pineal region tumors would have developed more recently.

Surgery is the first step in the diagnosis and treatment of these tumors. The exact pathology determines the recommended course of treatment. Some less aggressive tumors only require removal while others may require radiation therapy and/or chemotherapy. One common aggressive pineal region tumor, germinoma, can be successfully treated in approximately 90% of cases.

Pituitary adenomas

Pituitary adenomas are the most common intracranial tumors after gliomas, meningiomas and schwannomas. The large majority of pituitary adenomas are benign and fairly slow-growing. Adenomas are the most common disease affecting the pituitary. They commonly affect people in their 30s or 40s, although they are diagnosed in children, as well. Most pituitary tumors can be cured or controlled with appropriate treatment. There are different types of treatments, utilized depending on your tumor type and symptoms. Treatment options include:

- Observation over a period of time to see if treatment is needed;
- Medications;
- Surgery;
- Radiation therapy.

The most common surgical procedure is performed through the nose called a transsphenoidal operation.

Some pituitary tumors may be observed without treatment because they grow very slowly. This may also be recommended if other medical conditions seriously increase the risk of surgical or other treatments. Because pituitary tumors are slow growing, patients can often be observed without treatment for long periods of time without the tumor causing serious problems. This is often the recommended form of treatment for patients who are age 75 or older (however, there is no specific age limit for

pituitary surgery) or who have a serious medical illness such as heart disease. If a decision is made to observe the tumor without treatment, you may need continued hormone testing coordinated by a Neuroendocrine clinic, and you may need periodic visual testing with an ophthalmologist. CT or MRI scans are performed three to six months after initial diagnosis and every six to 12 months thereafter until the situation has been clarified. This period of observation without treatment provides information which helps the doctors decide if it is necessary to use other treatments which carry more risk.

One type of pituitary tumor in particular, prolactinomas, can be successfully treated with drugs. Prolactinomas secrete a hormone called prolactin and can often be controlled by a drug called bromocriptine or a newer medication called cabergoline. These drugs often cause a reduction in the tumor size and at the same time decrease the abnormally high level of prolactin in the blood. Although bromocriptine or cabergoline may control the tumor and bring the levels of prolactin in the blood back to normal, they most likely will not make the tumor disappear unless the tumor is very small. Treatment with these drugs often must be continued for many years or indefinitely. However, some patients can develop rare, severe adverse effects over time, so communication between the patient and their doctor is essential for safe and effective treatment.

In most cases, bromocriptine is an effective treatment for prolactin secreting tumors and has few side effects. However, some patients taking bromocriptine develop nausea, headache, dizziness, and weakness. Usually these symptoms can be avoided by taking small doses of the drug at first and slowly increasing the dosage up to the needed level over a period of several weeks or months. Side effects are similar with cabergoline but less common. Bromocriptine and cabergoline will not control all prolactin secreting tumors, and approximately 20 percent of patients with prolactinomas may need surgery or radiation therapy.

There are other drugs that may aid in the control of tumors that produce excess growth hormone. These drugs are used only if surgery and/or radiation therapy fail to cure the tumor, or during the period while the patient is waiting for radiation therapy to take effect. However, if a patient cannot have surgery, drugs can sometimes be an effective alternative treatment.

Another treatment option for pituitary tumors is radiation therapy, which is most

commonly used after surgery. Most people think of radiation therapy as a treatment for malignant tumors (cancer) but pituitary tumors (which are NOT cancerous) also respond well to radiation treatment. Some tumors have roots in the bone or coverings around the brain that involve vital nerves or blood vessels in such a way that surgical removal would cause significant damage to these important structures. In these cases, it is best to treat the main part of the tumor with surgery and to use radiation therapy for the roots or remaining tumor.

Radiation therapy, given under the direction of a radiation oncologist, is most effective after surgery has reduced the size of the tumor. The smaller the tumor is at the time of radiation therapy, the more effective the treatment is. Radiation usually requires a series of treatments that last a few minutes each day for four to six weeks. In most cases, the treatment is painless and is done on an outpatient basis. Radiation treatments generally begin a few weeks or months after surgery to allow time for incisions from the surgery to heal.

The ability of the gland to produce hormones often decreases slowly after radiation therapy. Twenty percent of patients who have normal pituitary function soon after the radiation therapy ends will require hormone replacement after two years. This figure rises to 50 percent after five years.

A specialized form of radiation therapy called radiosurgery can be used in selected cases. Radiosurgery involves a single, highly focused radiation treatment. The patient often can return home after the single treatment, which is done on an outpatient basis. Which form of radiation treatment (fractionated radiotherapy or radiosurgery) depends on recommendations of the neurosurgeon and the radiation oncologist.

A tumor in the pituitary gland causes symptoms by either stimulating the gland to release too many hormones or by pressing on the gland, causing it to release too few.

A pituitary tumor can cause an increase in any of the anterior pituitary hormones listed in the table. Examples include:

- An increase in the amount of growth hormone (GH) causes the body to grow at an abnormally fast rate. Bones become thicker, the hands and feet may appear wider or thicker and the jaw may protrude. This condition is called acromegaly.

- If a tumor releases adrenocorticotrophic hormone (ACTH), it causes the adrenal glands to secrete too much cortisol; this leads to fat deposits, especially in the shoulders, face, and abdomen. It can also cause diabetes, osteoporosis, abnormal hair growth (especially in women), and stretch marks called striae. This condition is called Cushing's disease.

- Elevated levels of prolactin may cause secretion of breast fluids in women and decreased sexual drive in men and women. It also may cause irregular or absent menstrual periods in women, and difficulty in having an erection in men.

Because the pituitary gland is located within the skull, when a tumor becomes large it may cause headaches that worsen as it grows. Also, since the pituitary gland is located near the nerves that connect the eyes to the brain, a pituitary tumor can press on the nerves and cause vision loss. Loss of peripheral vision may occur first and be undetectable, but it may progress to eventual blindness if the pressure is not removed from the nerve. The tumor may also press on the nerves that move the eye and cause double vision. If the tumor is very large, it may press on other parts of the brain and cause problems with memory, weakness, or numbness.

Schwannomas

Schwannomas are common benign, slow growing brain tumors in adults. They arise along nerves, comprised of cells that normally provide the "electrical insulation" for the nerve cells. Schwannomas often displace the remainder of the normal nerve instead of invading it. Although these tumors are benign, they can cause complications, such as nerve damage and loss of muscle control, which may affect swallowing, eye movement or causes facial paralysis, depending on where the tumor is located. Sciatic nerve schwannomas can mimic disk herniation with low back pain, with radiating pain down your leg. In about 5% of cases, a schwannoma can become malignant and become a cancerous soft tissue sarcoma or malignant nerve sheath tumor. Some of these tumors can be aggressive and call for a prompt, comprehensive treatment plan that could include surgery, chemotherapy, radiation therapy or a combination of these approaches.

Types and Characteristics of Grade 2 Tumors

Overview of Gliomas

Low-grade gliomas represents a spectrum of tumor types with diverse tissue and DNA features. Gliomas are the most prevalent type of adult brain tumor, accounting for 78 percent of malignant brain tumors. There are approximately 12,000 new cases every year. Even the most aggressive gliomas almost never spread into other parts of the body, and in this sense they differ from cancers in that they typically remain confined to the central nervous system.

Low grade (Grade 2) malignant tumors are divided based on the type of glial cells they arise from. There are three main types of glial cells: astrocytes, oligodendrocytes, and ependymal cells.

Astrocytomas, which arise from astrocytes, are the most common type of glial cells. Oligodendrogliomas, which arise from oligodendrocytes, are less common but tend to be more responsive to treatment. Ependymomas, which arise from ependymal cells, are rare and often occur in the lining of the ventricles in the brain. Discussions of these three follow.

Astrocytomas

Astrocytomas are the most common primary tumor; about 50% are astrocytomas. People of all ages can develop astrocytomas, but they are more prevalent in adults, particularly middle-aged men and women older than 45.

This type of tumor originates from astrocytes, which are star-shaped glial cells found in the supporting tissue of the brain. Astrocytes are very busy cells in the brain. They are involved with the biochemical support of neurons and other brain cells, support of certain cells which form the blood-brain barrier, a major role in the repair and scarring pro¬cess of the brain and spinal cord following mechanical / inflammatory injuries and providing a “guidance” for growing neurons / axons during the development of the brain.

Astrocytes can be readily identified histologically since they have a filament called a

glial fibrillary acidic protein (GFAP), and typically also have mutations in the IDH gene, but have intact 1p and 19q chromosomes as well as loss of ATRX.

Astrocytomas are most commonly found in the cerebrum. Astrocytomas in the base of the brain are more prevalent in children or younger people and account for most children's brain tumors. In children, most of these tumors are considered low-grade, while in adults, most are high-grade.

Based on their histological features, astrocytomas are classified based on their structural abnormalities and the speed of their growth. Commonly occurring astrocytomas include:

Diffuse or Fibrillary astrocytoma (Grade 2): this is the most common form of low-grade astrocytoma. It occurs in the brain stem. Diffuse astrocytoma most often occurs in young male adults. Although these tumors grow slowly and have low cell-division activity, they can infiltrate into neighboring brain structures. In 40% of cases, this type of tumor causes seizures. It may also cause headaches, hydrocephalus, and personality changes.

Pilocytic astrocytoma. This type of tumor is typically a Grade 1.

Pineal astrocytoma. This form can have any Grade, depending on its aggressiveness.

Oligodendrogliomas

Oligodendrogliomas are brain tumors that come from a type of brain cell known as an oligodendrocyte. These tumors are known for having the appearance of many small "fried eggs" when looked at under a microscope. The slowest growing of these tumors is described as a low grade oligodendroglioma (Grade 2); the faster growing type is the anaplastic oligodendroglioma (Grade 3).

Some oligodendrogliomas also contain astrocytes. In the past these were referred to as oligoastrocytomas, but under current WHO classification guidance the preferred terms for these mixed gliomas are diffuse astrocytoma/anaplastic astrocytoma or oligodendroglioma/anaplastic oligodendroglioma, depending on the predominance of their genetic material.

Most of the time we can't tell how long a brain tumor has been there. Sometimes doctors can tell based on how long you may have had symptoms before you were diagnosed. If you have a low grade oligodendroglioma, it is possible that the tumor has been there for many years before it started causing any symptoms. If you have an anaplastic oligodendroglioma, it is possible that it started out as a low grade oligodendroglioma and has been there for many years.

Low grade oligodendrogliomas are usually treated with a combination of surgery and radiation. If the tumor is located in an area where it is safe to remove, then the neurosurgeon will attempt to remove as much as possible, and sometimes this is all the treatment you will need at the beginning. The doctors will monitor the tumor with MRI scans every few months and if the tumor appears to be growing, the doctors will then consider additional surgery or starting treatment with radiation. Anaplastic oligodendrogliomas are known for being very responsive to chemotherapy. For this reason, after surgery, patients will often receive a combination of radiation therapy and chemotherapy.

Ependymomas

Ependymomas originate from a transformation of ependymal cells, which line the ventricular system of the brain and have numerous small hair-like structures called cilia. These cells secrete cerebrospinal fluid that fills the ventricles in the brain and beat their little cilia to keep that fluid properly circulating. They are a type of glioma that develops from ependymal cells. Ependymal cells are found in the lining of the ventricles and spinal cord. These tumors are more common in children than adults. In children, they are often found in the cerebellum, the brain's coordination center. In adults, they are often found in the spinal cord.

Ependymal cells line the fluid filled spaces of our brain and spinal cord. Because of its location, the tumor often blocks the flow of the cerebrospinal fluid (CSF), the fluid that bathes the brain and spinal cord. This can cause fluid to build up and cause increase pressure in the brain and spinal cord. The most common symptoms associated with ependymomas are headache, back pain, numbness, weakness, and sometimes double vision. If the pressure becomes too high, this can cause nausea and vomiting as well as decreased consciousness.

Ependymomas are generally slower growing than other gliomas. Most ependymomas are myxopapillary ependymomas that occur in the lowest portion of the spinal column. These tumors are generally less aggressive, although once treated they can grow back. For some ependymomas, surgery may be the only treatment you need. Others may need to be treated with radiation or possibly chemotherapy. If the tumor grows back, it usually becomes more aggressive.

Ependymomas account for two to three percent of all brain tumors. Most are well-defined, but some are not. Ependymomas can be either low or high grade tumors. The low grade forms are these:

Low grade Ependymoma (Grade 1): The cells reproduce slowly. There are two subtypes:

Subependymoma: a rare form that develops in glial cells in the spinal cord and brain.

Myxopapillary ependymoma: typically develops in the lower spine.

Low grade Ependymoma (Grade 2): These ependymomas can occur in the brain or the spine.

No one knows for sure what causes ependymomas. We do know that exposure to radiation may increase the chances of developing tumors in general. While scientists have looked at other possible causes such as aspartame (NutraSweet®), cell phones and power lines, no one has been able to show that any of these are clear causes of ependymomas.

Prognosis & Treatment Implications for Low Grade Tumors

The prognosis (chance of recovery) and treatment options for a low grade tumor depends on a number of different factors, including:

- the age and overall health of the individual;
- type of tumor;
- tumor grade;
- the extent of the disease (infiltrative or not);

- the size and location of the tumor;
- the presence or absence of metastasis;
- the tumor's response to therapy;
- the extent of surgical resection;
- tolerance for recommended medications, procedures or therapies;
- new developments in treatment.

In general, low-grade gliomas tend to be readily treatable. Prompt medical attention and appropriate therapy are important for the best prognosis.

A surgical gross total resection appears associated with better survival for patients able to undergo such a procedure but this has not been and is unlikely to be formally established.

Randomized clinical trials suggest radiation therapy prolongs time to recurrence but not overall survival and may be associated with quality of life and cognition compromises.

Prognosis for Low Grade Gliomas

A spectrum of outcomes is seen in patients with low-grade gliomas. Patient groups can be recognized with a median survival as low as two years to greater than 12 years, depending on the grade and other factors. A good understanding of the prognostic factors is thus critical in making a treatment decision and patient education in the overall management of these tumors. The clinical prognostic factors include:

- Age: Younger patients do better compared to older patients, with some studies classifying the age of below and above 40 years being low and high risk, respectively

- Symptoms at presentation: Presenting symptoms like seizures are associated with a good prognosis as well, likely due to the earlier diagnosis of the condition leading to close monitoring - this could well be due to lead-time bias, while fixed neurological deficits are associated with a poor prognosis.

- Tumor size and area involved: Tumor size is also important, with larger tumors associated with a poor prognosis, and involvement of the corpus callosum is

associated with adverse outcomes.

The molecular factors are as follows:

- The presence of 1p/19q co-deletion (which leads the classification to be an oligodendroglioma) is associated with the most favorable diagnosis. These tumors were also associated with mutations in CIC, FUBP1, NOTCH1, and the TERT promoter. These patients had the most favorable prognosis among the gliomas. One study showed that the median survival for 1p/19q co-deleted tumors was 12 years compared to 8 years in non-codeleted gliomas.

- Mutations in either IDH1 or IDH2 occur in up to 80% of grade 2 and 3 diffuse gliomas and carry a favorable prognosis compared with IDH wild-type (non-mutated) tumors, but are not usually as favorable as the oligodendroglioma.

- Patients with tumors characterized by mutations of IDH and TP53 with ATRX inactivation but without 1p/19q codeletion have an intermediate level of prognosis.

- The patients with the least favorable outcomes had low-grade gliomas without IDH mutations but with mutations in PTEN, EGFR, NF1, TP53, PIK3Ca, PTPN11, and PLCG1. These are molecularly similar to a Grade 4 glioblastoma.

Finding out you have a low grade glioma can be scary. The good news is that these tumors are almost always slow-growing. Your medical team will help you determine the best treatment plan for you, whether that means simply observing the tumor, surgically removing it, or something else. Don't be afraid to ask questions. Your doctor is committed to helping you.

Quality of Life

The prognosis of patients with a low-grade tumor is affected by multiple variables and can vary greatly, from 2 years to decades. Because of this, quality of life and neurocognition are becoming increasingly important factors in treatment decision making. Studies now are evaluating neurocognitive function, quality of life, and seizure control in patients with low-risk low grade tumors after surgery. There have been several studies demonstrating that there are significantly higher levels of cogni-

tive impairment in patients who receive radiation compared with those who do not undergo radiation. Therefore, treatment strategies that delay the use of radiation to preserve cognitive function are appealing. As more treatment options for low-grade tumors become available, quality-of-life measures and outcomes will play key roles in disease management recommendations.

Molecular Evaluation of Common Grade 1 Tumors

Pilocytic and Diffuse Astrocytomas

Genomic alterations involving activation of BRAF and the ERK/MAPK pathway are very common in sporadic cases of pilocytic astrocytoma, a type of low-grade glioma.

BRAF-KIAA1549 alterations

BRAF activation in pilocytic astrocytoma occurs most commonly through a *BRAF-KIAA1549* gene fusion, producing a fusion protein that lacks the BRAF regulatory domain. This fusion is seen in most infratentorial and midline pilocytic astrocytomas but is present at lower frequency in supratentorial (hemispheric) tumors.

Presence of the *BRAF-KIAA1549* fusion predicted a better clinical outcome (progression-free survival [PFS] and overall survival [OS]) in one report that described children with incompletely resected low-grade gliomas. However, other factors such as *CDKN2A* deletion, whole chromosome 7 gain, and tumor location may modify the impact of the *BRAF* mutation on outcome. Progression to high-grade glioma is rare for pediatric low-grade glioma with the *BRAF-KIAA1549* fusion.

BRAF activation through the *BRAF-KIAA1549* fusion has also been described in other pediatric low-grade gliomas (e.g., pilomyxoid astrocytoma). Other genomic alterations in pilocytic astrocytomas that can activate the ERK/MAPK pathway (e.g., alternative *BRAF* gene fusions, *RAF1* rearrangements, *RAS* mutations, and *BRAF V600E* point mutations) are less commonly observed.

BRAF V600E mutations

BRAF V600E point mutations are occasionally observed in pilocytic astrocytoma; the mutations are also observed in nonpilocytic pediatric low-grade gliomas, including ganglioglioma, desmoplastic infantile ganglioglioma, and approximately two-thirds of pleomorphic xanthoastrocytomas.

Studies have observed the following:

- In a retrospective series of more than 400 children with low-grade gliomas, 17% of tumors were *BRAF V600E* mutant. The 10-year PFS rate was 27% for *BRAF V600E*–mutant cases, compared with 60% for cases whose tumors did not harbor that mutation. Additional factors associated with this poor prognosis included subtotal resection and *CDKN2A* deletion. Even in patients who underwent a gross-total resection, recurrence was noted in one-third of these cases, suggesting that *BRAF V600E* tumors have a more invasive phenotype than do other low-grade glioma variants.
- In a similar analysis, children with diencephalic low-grade astrocytomas with a *BRAF V600E* mutation had a 5-year PFS rate of 22%, compared with a PFS rate of 52% in children who were *BRAF* wild-type.
- The frequency of the *BRAF* V600E mutation was significantly higher in pediatric low-grade glioma that transformed to high-grade glioma (8 of 18 cases) than was the frequency of the mutation in cases that did not transform to high-grade glioma (10 of 167 cases).

Other mutations

Activating mutations in *FGFR1, PTPN11,* and *NTRK2* fusion genes have also been identified in noncerebellar pilocytic astrocytomas. In pediatric grade 2 diffuse astrocytomas, the most common alterations reported (up to 53% of tumors) are rearrangements in the MYB family of transcription factors.

Angiocentric gliomas

Angiocentric gliomas typically arise in children and young adults as cerebral tumors presenting with seizures.

Two reports in 2016 identified MYB gene alterations as being present in almost all cases diagnosed as angiocentric glioma, with *QKI* being the primary fusion partner

in cases where fusion-partner testing was possible. While angiocentric gliomas most commonly occur supratentorially, brain stem angiocentric gliomas with *MYB-QKI* fusions have also been reported.

Painting by Linda Singer

Astroblastomas

Astroblastomas are defined histologically as glial neoplasms composed of GFAP-positive cells and contain astroblastic pseudorosettes that often demonstrate sclerosis. Astroblastomas are diagnosed primarily in childhood through young adulthood.

The following studies have described genomic alterations associated with astroblastoma:

- A report describing a molecular classification of CNS primitive neuroectodermal tumors (PNETs) identified an entity termed CNS high-grade neuroepithelial tumor with MN1 alteration (CNS HGNET-MN1) that was characterized by gene fusions involving MN1. Most tumors with a histologic diagnosis of astroblastoma (16 of 23) belonged to this molecularly defined entity.

- A report of 27 histologically defined astroblastomas found that 10 cases had MN1 rearrangements, 7 cases had BRAF rearrangements, and 2 cases had RELA rearrangements. Methylation array analysis showed that the cases with MN1 rearrangements clustered with CNS HGNET-MN1, the BRAF-mutated cases clustered with pleomorphic xanthoastrocytomas, and the RELA cases clustered with ependymomas.

- Genomic evaluation of eight cases of astroblastoma identified four with MN1 alterations. Of the remaining four cases, two had genomic alterations consistent with high-grade glioma and two cases could not be classified on the basis of their molecular characteristics.

- A study described eight cases of astroblastoma. All five cases that underwent fluorescence in situ hybridization analysis showed MN1 rearrangements.

These reports suggest that the histologic diagnosis of astroblastoma encompasses a heterogeneous group of genomically defined entities; astroblastomas with MN1 fusions represent a distinctive subset of histologically diagnosed cases.

Neurofibromatosis type 1 (NF1)

Children with NF1-associated low-grade gliomas often have tumors in the optic pathway that are not biopsied. In a series of pediatric patients (n = 17; median age, 10 years) with NF1-associated low-grade gliomas in which tissue was collected and subjected to whole-exome sequencing, the number of mutations was very low (median, 6 per case).

Germline NF1 mutations were observed in 88% of patients, and the most common somatic alteration was loss of heterozygosity for NF1, with a smaller number of cases showing inactivating mutations in the second NF1 allele. CDKN2A loss was observed in 1 of 17 patients (6%). Alterations in TP53 and ATRX were not observed among the 17 pediatric patients with NF1-associated low-grade gliomas. Activating BRAF genomic alterations are uncommon in pilocytic astrocytoma and other low-grade gliomas occurring in children with NF1.

Tuberous sclerosis

Tuberous sclerosis complex (TSC), also known as tuberous sclerosis, is a rare genetic disease that causes non-cancerous (benign) tumors to grow in the brain and several areas of the body, including the spinal cord, nerves, eyes, lung, heart, kidneys, and skin. Most children with tuberous sclerosis have a germline mutation in one of two tuberous sclerosis genes (TSC1 or TSC2). Either of these mutations results in activation of the mammalian target of rapamycin (mTOR) complex 1. These children are at risk of developing subependymal giant cell astrocytomas, cortical tubers, and subependymal nodules. Because subependymal giant cell astrocytomas are driven by mTOR activation, mTOR inhibitors are active agents that can induce tumor regression in children with these tumors.

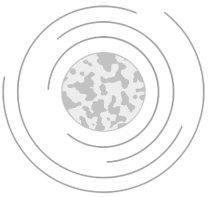
Photo By Dave Royko

Molecular Evaluation of Common Grade 2 Gliomas

Most Grade 2 gliomas have DNA mutations in the IDH1 or IDH2 gene. Gliomas with an IDH mutation grow more slowly than gliomas without one.

Some Grade 2 gliomas, the oligodendrogliomas, have an IDH mutation and an additional DNA irregularity called the 1p/19q codeletion. These gliomas can respond well to chemotherapy.

For pediatric diffuse astrocytomas, rearrangements in the MYB family of transcription factors (MYB and MYBL1) are the most commonly reported genomic alteration. Other alterations observed include FGFR1 alterations (primarily duplications involving the tyrosine kinase domain), BRAF alterations, NF1 mutations, and RAS family mutations. IDH1 mutations, which are the most common genomic alteration in adult diffuse astrocytomas, are uncommon in children with diffuse astrocytomas and, when present, are observed almost exclusively in older adolescents.



Treatment for Low Grade Tumors

Treatment for low grade tumors normally includes a combination of symptom management, chemotherapy, radiation therapy, surgical intervention, and monitoring. Given the typically slower growing time for low grade tumors, all relevant factors must be considered to appropriately manage and improve overall outcomes. The optimal treatment of low grade gliomas, particularly the timing of treatment, is controversial, and treatment decisions must balance the benefits of therapy against the potential for treatment-related complications.

For that reason, treatment options are evolving. In some cases, monitoring rather than treatment is adopted. Some low grade tumors present few, if any, symptoms and cause few problems with little or no pain. They may even remain inactive for long periods of time. Treatment in those cases usually does not enhance quality of life.

Although management strategy for low-grade glioma has been controversial due to the heterogeneity of these tumors, natural history of these tumors and variability in the practice patterns of providers, the recent FDA approval of Voranigo, an IDH1/2 inhibitor for the treatment of low-grade astrocytoma and oligodendroglioma, will provide another option for management of these diseases. The advantages of Voranigo over the other treatment options such as radiation or traditional chemotherapeutics agents such as PCV or Temozolomide is its limited side effects profile. Voranigo, based on a recent INDIGO data, demonstrated a profound impact on the rate of tumor progression while being well tolerated and not limiting quality of life. This therapy was also shown to delay neurocognitive side effects that are typically associated with patients who receive radiation treatment.

For more information about Vorasidenib, please see: https://www.tandfonline.com/doi/full/10.1080/23808993.2024.2316347 and https://www.nejm.org/doi/full/10.1056/NEJMoa2304194.

Symptom Management

Seizures, cerebral edema (swelling in the brain around the tumor), and obstructive hydrocephalus (increased pressure within the brain due to blockage of the flow of cerebrospinal fluid within the brain) are the most serious symptoms.

In the case of seizures, symptoms may include:

Temporary confusion;
Staring;
Rapid eye blinking;
Not responding to words or noises for a short period;
Stiffening of the body;
Sudden falling for no apparent reason;
Breathing problems (lips may turn blue);
Loss of bowel or bladder control;
Uncontrollable jerking movements of the arms and legs;
Loss of consciousness; and/or
Psychological symptoms such as fear, anxiety or deja vu.

Edema (swelling) may be manifested by headaches, nausea or other side effects dependent upon which brain tissue is being compressed.

Each of these requires a different therapeutic approach:

- Seizures. The same medications used to treat epilepsy are usually successful in controlling seizures associated with brain tumors. However, seizures may be more difficult to control in people with brain tumors, particularly low grade gliomas. If medications are not effective, surgery to remove part of the tumor may be recommended in an attempt to reduce seizure activity.

- Swelling. Cerebral edema usually can be treated successfully with steroids; the most commonly used steroid is dexamethasone (brand name: Decadron).

Dexamethasone use can be temporary if specific treatment of the tumor is planned, and the treatment is expected to decrease edema. Dexamethasone may be used for a more prolonged period of time if treatment is not currently planned. Dexamethasone may be particularly useful in the late phases of the illness, such as if the tumor recurs and there is no other way to control cerebral edema. One of the problems with long-term use of dexamethasone (particularly high doses) is the potential for side effects (e.g., ulcers, bleeding from the gastrointestinal tract, behavioral changes, thinning of the skin, loss of bone strength, high blood sugar). Thus, the dose of dexamethasone is tapered to achieve the lowest dose that effectively controls symptoms yet minimizes long-term complications.

Obstructive hydrocephalus may require surgery to bypass the blockage and lower the pressure within the brain.

Standard of Care

Standard of care for low grade gliomas includes maximal safe surgical resection. Prior trials divided patients on the basis of extent of resection and age and resulted in patients grouped into low risk (age younger than 40 years and gross total resection) and high risk (age older than 40 years or subtotal resection).

Patients who are low risk ideally undergo routine magnetic resonance imaging surveillance after resection. On the basis of recently published data, it is now recommended that high risk patients undergo a combination of both radiation and chemotherapy after surgery.

The studies, however, do not address the management of patients with low-grade gliomas in the era of genomic medicine. These treatments can also have great impact on quality of life, and therefore treatment recommendations should be done on an individual basis considering the tumor's classification, the person's age, extent of resection, as well as current and preferred future quality of life.

Patient Navigation Program

Program Overview

The Brain Cancer Support and Solutions Alliance (BCSSA) has been established through a collaborative effort of three leading non-profits: Head for the Cure, the Musella Foundation, and Cancer Commons. This alliance aims to provide comprehensive support, education, and guidance to brain cancer patients and their caregivers.

BCSSA Dedicated Neuro-Oncology Nurse Navigator

The BCSSA funds a specialized Neuro-Oncology Nurse Navigator to offer critical support for brain cancer patients and their caregivers. This role is designed to address both the psychological and practical needs of those affected by brain cancer.

The Nurse Navigator offers a range of services to alleviate the unique challenges faced by brain cancer patients:

- **Personalized Support:** Tailored resources to help patients and caregivers navigate treatment options, medical appointments, symptom management, and access to specialized services.

- **Emotional and Psychological Assistance:** Crucial psycho-social support to help patients and families cope with emotional distress, including guidance on accessing counseling and mental health services.

- **Practical and Educational Guidance:** Patient education throughout the care experience, explaining medical terminology, treatment regimens, and recovery expectations, while also connecting patients to financial and logistical resources.

Cancer Commons Staff Scientists

In conjunction with the Nurse Navigator services, patients will also have access to the knowledge and expertise of Cancer Commons' staff scientists. The scientists, in consultation with external experts, help each patient identify and access an indi-

vidualized regimen of therapies that specifically target the molecular drivers of their disease. Treatment guidance is informed by the clinical experiences of previous patients, such that each patient contributes to a learning system benefitting future patients. Specifically, the scientists can provide:

- Expert, personalized treatment recommendations;
- Guidance on clinical trials; and
- Resources for precision oncology.

How to Access the Program

All services provided by the BCSSA and Cancer Commons are offered free of charge. These services are available to both high-grade and low-grade brain tumor patients, including international cases. Patients and caregivers seeking support can access these services by visiting this site:

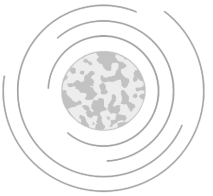
https://cancercommons.org/bcssaregistration/.

Privacy Protection

BCSSA and Cancer Commons value the privacy of the individuals choosing to access their services. The use and protection of personal data under the program is as described in the privacy policy found here:
https://cancercommons.org/privacy-policy/

For questions about registration and/or this privacy policy, please feel free to email: info@cancercommons.org .

Photo by Linda Singer



Surgery

Overview

Surgical resection in eligible patients is the cornerstone of treatment with low-grade tumors. The objective of surgery is to remove as much of the tumor as possible while minimizing damage to the normal brain.

Traditionally, surgery has been the mainstay of treatment for most benign and low grade brain tumors. More recently, there has been some movement toward a "watch and wait" approach (as more thoroughly discussed in the section entitled "Monitoring" below) for some of these tumors rather than immediate surgical intervention. Whether or not all patients should have surgery after initial diagnosis is an area of controversy:

- Some doctors recommend removal of as much tumor as possible in all patients as soon as the diagnosis of a brain tumor is made. This recommendation is based upon studies suggesting that patients who have immediate surgery survive longer, possibly because the tumor is less likely to change into a more aggressive form.

- Other doctors recommend that carefully selected patients initially be monitored without therapy, until the tumor grows or symptoms worsen despite medical therapy. The rationale behind this approach is that low grade gliomas may progress very slowly, so surgery may create more symptoms than are caused by the tumor, and surgery done later may be equally effective in prolonging survival.

The doctor and patient should discuss the matter and evaluate balancing the benefits of removing tumor versus the potential for surgery to damage healthy brain tissue. The amount of tissue removed and whether surgery is possible are influenced heavily by the location of the tumor within the brain:

- If the tumor is in an area of the brain controlling one or more critical functions (e.g., swallowing), surgery may result in severe damage. In this event, the doctor may recommend against surgery or may recommend limiting the amount of tumor removed during surgery.

Photo By Dave Royko

- If the tumor is in a less critical area of the brain, the doctor may recommend trying to remove as much of the tumor as possible.

Despite the lack of evidence, surgery serves as both a diagnostic and therapeutic procedure. Sufficient tissue is obtained not only to confirm the diagnosis but also to perform molecular testing, and the resection (defined below) may help relieve the effects of the tumor, including hydrocephalus and edema.

In many cases, low grade brain tumors can be removed by surgery, and surgery may actually "cure" some low-grade tumors.

A good surgery can increase the response to chemo and radiation. This is why one of the single most important decisions you have to make is WHERE and by WHOM you will have brain surgery. A more experienced neurosurgeon may consider relatively easy what another neurosurgeon might consider "inoperable" (see the section below for the definition of "inoperable"). If you have been told your tumor is "inoperable", it is a wise idea to obtain a second opinion from another neurosurgeon.

The use of surgery varies by brain tumor type and location. Some brain tumors are easily separated from the healthy tissue of the brain and are in an accessible area where surgery can be recommended. Other tumors may have extensively invaded healthy tissues and would prove to be difficult to safely separate and remove. Additionally, some patients are not candidates for surgical resection because the tumor is located next to critical brain structures, such as those responsible for the senses or for speaking, or because the patient is in poor medical condition. A highly qualified neurosurgeon is able to evaluate all these factors and determine the appropriateness of surgery.

Low grade tumors (particularly gliomas) can recur years to decades after initial treatment. Re-resection can be considered when the complete resection of the tumor is possible. The completeness of resection at primary treatment and re-resection influences overall survival. The evidence does not suggest a decrease in overall survival with recurrent patients undergoing multiple resections. However, it must be emphasized that a diligent preoperative evaluation is required to determine the probability of a successful complete resection.

Need for Expertise

When it is appropriate, surgery is performed by a neurosurgeon. Neurosurgery, as a profession, runs the entire length of the central nervous system - from head to the bottom of the spine. Certain neurosurgeons are experts at certain forms of surgery to be performed around the head and others perform interventions on the spine. A general neurosurgeon may not have adequate experience in the removal of brain tumors and may be less informed regarding current treatment therapies. Because most neurosurgeons do not see many brain tumors, you need to find one that specializes in brain tumors. The website of your selected treatment facilities should list all the neurosurgeons practicing there; carefully review their expertise to make sure that "brain tumors" is listed as one of the main areas of expertise.

Within the group of neurosurgeons who deal with brain tumors, you want to find an expert. An "expert" neurosurgeon is one who performs a minimum of 25 surgeries per year. Typically, these neurosurgeons are associated with major brain tumor centers, which have the qualified medical personnel, state-of-the-art equipment and other resources necessary to treat brain tumors. Such centers can be identified using this link:

https://virtualtrials.org/Brain_Tumor_Centers.cfm.

Studies indicate that major brain tumor centers and/or surgical teams that perform 50 or more surgeries a year achieve better survival rates with fewer complications. In brain surgery, experience matters A LOT. Neurosurgeons who have operated on many similar tumors can usually remove more of the tumor, with fewer side effects, than neurosurgeons who have operated on only a few tumors. They are also much more likely to have access to and training on the latest high-tech surgical tools.

While there are over 4500 neurosurgeons in the United States, only 125 (approximately) are considered experts in the removal of brain tumors. Because choosing an experienced neurosurgeon can greatly affect the quality of tumor removal and your recovery, finding an expert and getting a second opinion about which neurosurgeon to choose is vital.

Only an expert neurosurgeon can assess how much of the tumor is considered oper-

able. Any tumor can theoretically be removed, but a skilled neurosurgeon uses his or her experience to make a judgment on the risks of removal versus the benefits of removal. Each brain tumor is different, and the neurosurgeon can usually predict if — and how much — neurological damage will occur if the brain tumor is removed.

However, keep in mind that some neurosurgeons may be overly aggressive. Discuss the expected risks of the surgery to make sure your neurosurgeon understands your views on how aggressive you want him or her to be.

If your tumor is considered truly "inoperable," you may be offered alternatives to surgery, such as stereotactic radiosurgery as described under the Radiation section of this Guide. These techniques are generally available at a major brain cancer clinic.

Selected Definitions

Some terms unique to brain surgery follow:

Craniotomy: The most common type of brain tumor surgery. A craniotomy involves a neurosurgeon making an incision in the scalp, removing a piece of bone from the skull to give the neurosurgeon access to the tumor and then removing as much of the tumor as is deemed safe.

Debulking: surgical reduction in the size of the tumor. Debulking may be done in the case of benign tumors to relieve symptoms. Debulking may also be done in the case of high-grade tumors with the goal of increasing the chance that chemo or radiation will kill more cells of the tumor but must be done so with utmost care to avoid bruising the tumor and causing complications. Second opinions are highly recommended prior to debulking a high-grade tumor.

Eloquent area: The area of the brain which supports language, motor, sensory or other important function. Surgery near or within an eloquent area presents a challenge for neurosurgery because of the risk of neurological damage to an important function.

Inoperable: an expert neurosurgeon has concluded surgery should not be performed on the tumor for a reason such as one of these:

- the tumor does not have clear borders (sometimes referred to as "margins") and is hard to distinguish from health brain tissue;
- the tumor is too close to parts of the brain that control vision, speech, mobility;
- there are multiple tumors;
- the surgery is likely to result in a significant loss of function; or
- the person's underlying health is insufficient for the surgery (e.g., person is quite elderly or has other health problems that make surgery unsafe for them).

Some tumors are labeled "inoperable," but can be removed by neurosurgeons with specialized expertise. If you've been told your tumor is inoperable, consider seeking a second opinion at a large, multidisciplinary brain tumor center. These teams typically offer advanced surgical techniques that allow greater access to hard-to-reach sections of the brain.

Illustration by Margo Singer

Operable: a qualified neurosurgeon has concluded surgery may be performed on the tumor and is reasonably (based on the doctor's considerable experience) expected to result in greater benefits than risk to the patient, all factors having been carefully considered.

Resection: surgical removal of a tumor. A resection may be partial (also called "sub-total") or total.

Total or Gross Total Resection: Surgical removal of every visible portion of a tumor. Surgical removal is not considered "complete" since microscopic portions are left no matter how precise the surgery has been. This is why there is a need for additional treatment following surgery.

When Surgery is Necessary

For small, benign (non-cancerous) tumors, like most meningiomas, that do not cause symptoms and are not expected to grow into a critical area, the doctor may suggest a "Watch & Wait" approach (detailed in the section entitled "Monitoring" below). In those cases, only if the tumor grows enough that it creates symptoms, then the doctor may recommend surgical removal.

If the benign tumor does cause symptoms, a neurosurgeon is likely to recommend removal in order to relieve or reduce your symptoms. Benign tumors can often be removed surgically and do not usually grow back after surgery. In such cases, surgery is considered curative.

For Grade 2 tumors that are located in an area of the brain that is accessible to surgery, the neurosurgeon will thoroughly evaluate the possibility of removing the tumor or as much of the tumor as possible to improve neurological function and obtain an exact diagnosis of the brain tumor. The neurosurgeon's goal will be to completely remove the brain tumor (i.e., perform a total resection) while protecting, to the maximum extent possible, the person's functions and quality of life.

Accepted reasons for surgery include increased pressure within the brain, intolerable symptoms caused by the tumor or a bleed (hemorrhage) into the tumor, or seizures that are unresponsive to medications.

Pre-Surgery

Pre-Surgery Health Checks

You should expect to be run through a battery of tests designed to determine your ability to handle the anesthesia that will be given to you during surgery and your ability to recover from the procedure.

Unless you have recently had such tests, your neurosurgeon will likely order some or all of the following:

Blood tests for general health check
Urine test for kidney operations
Electro-Cardiogram to check your heart.
Chest X-ray to check your lungs.
Additional Contrast MRI for the Neurosurgeon's planning
Vitals: Height, Weight, Temperature, Heartrate

If you have not been admitted to the hospital, these tests can be conducted prior to surgery on an outpatient basis.

Pre-Surgery Treatments

Before surgery occurs, carefully discuss treatment options with your neurosurgeon. Certain treatments are available only prior to or in conjunction with surgery.

There may be certain advanced treatments that can only be received at the time of surgery or for which registration must be made prior to surgery, such as radioactive GammaTile therapy, as described below. Ask if the GammaTiles would be appropriate in your case.

Pre-Surgery Discussions, Prep and Check-In

Prior to your surgery, the neurosurgeon will meet with you to describe the proce-

dure from his or her viewpoint and provide you with any instructions.

If you are on an aspirin routine or if you are taking any herbs or supplements, you should make sure your neurosurgeon knows. Your neurosurgeon is likely to request that you cease the use of all blood thinners including aspirin, ibuprofen, as well as all herbs and supplements at least one week prior to surgery, assuming there is enough time. Aspirin, ibuprofen, and many supplements promote bleeding by slowing your platelets which will discourage healing of your incision after surgery.

You will be told when and where to show up for hospital admission and the surgery. Prior to your surgery, to help you reduce the risks of infection, it is recommended that you take a good, long shower and clean yourself well with soap from head to toe.

Anyone who accompanies you to the hospital for check-in will be shown where they can wait; they will be told when your surgery has been completed and when they can visit you in the recovery room.

Post-Surgery Preparations

While surgery of a brain cancer is an essential for those tumors deemed operable, even a total resection will not remove all the brain tumor cancer cells. For that reason, other treatments are needed.

So even before surgery, you need to be preparing with your medical team a list of options for postsurgical treatment. Here are some of the things you should request and/or ask about even before surgery occurs.

Before surgery, verify that the neurosurgeon will order a molecular evaluation of the tumor tissue. As noted in the section of this Guidebook above entitled "Diagnosis Scope/Delays", there are molecular markers in brain tumors that are essential for diagnosis, may indicate resistance to certain treatments, may determine eligibility for clinical trials or for repurposed drugs that are approved for types of cancer other than brain tumors. Major brain tumor centers routinely perform a diagnostic level genetic evaluation of tumors, but you should ask anyway.

Before surgery, find out how your brain tumor tissue will be preserved after extraction. If the specimen will not be immediately used either to create a custom-made

vaccine or to serve for molecular-marker testing, ask if the specimen can be frozen for future use if needed, and ask about the costs involved.

Pre-Surgery Anxiety

The thought of being scheduled for brain surgery can be one of the most anxiety-producing events. "Brain surgery" sounds like a very scary thing. It is. But it is now much safer and easier than ever. Moreover, the goal of a maximally safe resection is now more often reached with the help of intraoperative imaging or by means of fluorescence-guided visualization of tumor tissue, which represents an important advance.

During surgery, it is sometimes extremely difficult to distinguish tumor and infiltrated tissue from surrounding healthy brain. An oral drug called Gleolan is now available for causing tumor cells to become fluorescent — that is, to light up under a microscope with a special blue light — thereby helping neurosurgeons remove as much tumor as possible without harming healthy tissue. (See the paragraph entitled "Fluorescence-guided neurosurgery" below for more information.)

There are still some brain tumors that are too dangerous to remove because of their size or location, but the limits to what is possible, safely, are shrinking every year. If you are told that your tumor is inoperable, or that a total resection of the brain tumor is not possible, get another opinion.

You should be aware that the surgical competency available at the top brain cancer clinics today is nothing short of extraordinary. One of the leading neurosurgeons at the University of California at San Francisco is Dr. Mitchel Berger and he has produced with his colleague Dr. Shawn Hervey-Jumper a video describing the outcomes of the current trend in extensive resections (removals) of brain tumors. That video can be accessed at the link in the box below.

WARNING: VIDEO CONTAINS IMAGES THAT MAY BE DISTURBING TO SENSITIVE INDIVIDUALS
https://www.youtube.com/watch?v=RtICiRVcKlI

There was a long term (20+ year) survivor of a high grade brain tumor (a Grade 4 glioblastoma) who had undergone 6 brain surgeries. Her name was Cheryl Broyles.

The advice from this undoubted hero-veteran of brain surgeries can be found at the link in the box below.

WARNING: VIDEO CONTAINS IMAGES THAT MAY BE DISTURBING TO SENSITIVE INDIVIDUALS
https://www.youtube.com/watch?v=rOD2n9e5Lt0

Types of Surgery

The techniques and tools available to neurosurgeons are rapidly evolving today. As a result, there are several different types of surgery available to patients. Your neuro¬surgeon will carefully review your MRI images, medical file, and will discuss with you to determine what type is best for your particular situation.

Emergency Surgery

In a few rare cases, emergency surgery at a local hospital might be the only immediate option because of symptoms related to brain swelling caused by the tumor or because of some acute risk of brain injury. Typically, however, the good news is that there is usually sufficient time to locate the doctors who are most experienced in the treatment of brain tumors and to gather information that can assist in your decision-making process.

Craniotomy

The current trend in neurosurgery is for highly skilled neurosurgeons to attempt to resect tumors to the greatest extent as deemed advisable by means of a craniotomy. In a craniotomy, the neurosurgeon removes a section of the skull (referred to as a flap) to extract as much of the tumor as possible, then replaces the flap.

During the procedure, the neurosurgeon may use a variety of tools including:

- **Ultrasonic aspiration** (UA). This is a device that uses vibrating sound waves to break up the tumor and then gently suctions the tumor tissue. A UA device limits damage to adjacent healthy tissue and blood vessels and nerve fibers in the area. Plus, the duration of the surgery and therefore time the person must

be under anesthesia is reduced.

- **Microsurgery**. This is a special, high-powered microscope to look at the brain tissue to distinguish between tumor tissue and healthy tissue and enable the neurosurgeon to separate between the two with extreme delicacy.

- **Fluorescence-guided neurosurgery.** In certain cases, prior to the resection of a high-grade tumor, the neurosurgeon will have you drink a liquid solution of five-aminolevulinic acid (5-ALA) hydrochloride, commonly referred to as "Gleolan", a few hours prior to surgery. During surgery, the neurosurgeon will then use a fluorescent light with special blue filters to expose the tumor. The Gleolan helps the tumor glow a brilliant blue or hot pink, enabling the neurosurgeon to better distinguish between tumor and healthy tissue.

Interoperative MRI. In this approach, the neurosurgeon uses an MRI to remove as much tumor material as is deemed safe. The goal may be to remove not just the tumor material that lights up on the MRI image when a contrast dye is used, but also the area around the tumor that does not light up in the image. This form of surgery is used to increase the extent of resection, which has recently been shown to significantly improve the overall survival of high-grade patients. The risk is that an increased resection can cause a new postoperative deficit. For this reason, the neurosurgeon works with great care.

At the conclusion of the procedure, the bony flap may be secured with small metal brackets or staples and the skin of the scalp is pulled back over it. This will leave a scar, but hair hides it in many cases.

Awake Surgery/Intraoperative Brain Mapping

A neurosurgeon may perform an awake surgery, also known as intraoperative brain mapping, when the tumor is very close to an eloquent part of the brain (area of the brain which supports language, motor, sensory or other important function). An awake surgery is designed to allow the neurosurgeon to electrically stimulate part of the brain during the surgery.

This craniotomy procedure is performed while the patient is awake but sedated. Some people are awake and conscious for part of the operation. Other people are

awake throughout the whole procedure.

Special Surgical Considerations for Low Grade Astrocytoma and Oligodendroglioma Gliomas

While people with pilocytic astrocytomas do particularly well after removal of their tumors, the benefit of surgery on survival with other types of low grade glioma is less clear.

Low grade astrocytoma IDH-mutant and oligodendroglioma IDH-mutant 1p19q-codeleted gliomas are diagnosed in 20,000 people, mostly young adults and those in midlife, each year in the United States. These types of low grade gliomas grow into healthy brain tissue, and there is often no distinct boundary between the tumor and healthy tissue. As a result, efforts to remove all tumor cells inevitably remove some of the healthy brain tissue and can leave behind tumor cells.

After surgery, undetectable pockets of tumor cells grow slowly. This leads to recurrence and eventually malignancy and death, often in less than two years. A study published January 2023 in the *Journal of Clinical Oncology* that evaluated hundreds of cases over a long period of time has revealed that resecting (removing) as much as possible of the tumor soon after diagnosis offers a distinct survival advantage.

Patients who had larger post-operative and/or pre-operative astrocytomas lived a median of nine years after diagnosis, compared to more than 20 years for those with smaller residual tumors. Patients with larger post-operative and/or pre-operative oligodendroglioma lived a median of almost 20 years, compared to more than 20 years with smaller pre- and post-operative tumors, according to the study.

The completeness of resection has been shown to impact overall and progression-free survival. For glioma patients with greater than or equal to 90% resection of the tumor, the 5-year overall survival was 97% versus 76% for those with less than 90%. Based on the overall experience, most authorities in the field favor a maximal safe resection over biopsies.

Patients who had a potentially riskier procedure, called gross total resection (GTR), lived longer than those with residual tumors. In GTR, surgeons remove all of the tumor visible on an MRI.

An even more significant surgical procedure called GTR-plus, which includes removing a margin of healthy tissue, extended the survival of astrocytoma patients, but not oligodendroglioma patients.

Photo by Steve Tilkin

Surgery for Pituitary Tumors

Surgery is the preferred treatment for most pituitary tumors. Two types of surgeries are offered for pituitary tumor removal.

Transsphenoidal Surgery

Most pituitary tumors are removed by the transsphenoidal method of surgery, directed through the nose to the bottom of your skull where the pituitary gland is located. In the past, transsphenoidal surgery was started by making a one to-two inch incision under your lip at the top of your upper gum or within the front part of the nose.

In recent years, the surgery has been modified so that there is no need for an incision under the lip or in the front part of the nose. The new procedure is called an endonasal procedure because the tumor is approached through the nasal cavity without an incision.

The tumor is reached by working through one nostril and making a hole in the back of the nose into the bottom of the skull. Through this hole, the surgeon can see the bottom of the pituitary gland and the tumor and can thus remove the tumor. The endonasal procedure reduces operating room time by as much as two hours, reduces the discomfort associated with the surgery, and allows for a quicker recovery compared to the older techniques. In fact, most patients now go home the next day or the day after that.

Often, the surgeon will remove a small piece of fat from just below the skin on the abdomen to fill the cavity created by the tumor removal. The bottom of the skull is sometimes reconstructed using an absorbable man-made mesh. This will help bolster the strength of the repair of the hole made in the bottom of the skull and helps prevent leakage of cerebrospinal fluid (CSF). The CSF fluid surrounds the brain, spinal cord, and pituitary gland and acts as a cushion, and provides nutrients to the nervous system.

In a small number of patients, the fat or muscle packing will not hold and CSF may leak from the nose. If the drainage continues, it may allow bacteria into the CSF and may result in an infection called meningitis. Sometimes waiting a few days, or treat-

ment with a small drainage tube in the lower back, will allow this drainage to stop so that no further treatment is needed. However, in a few patients (less than 2%), another procedure may be necessary to seal the hole at the bottom of the skull.

Sedated (i.e., quiet but not asleep) at the beginning and end of the surgery and awake during tumor removal: You would receive a scalp block and a little anesthesia for sedation (but not enough for you to sleep or become unconscious) at the opening procedure at the commencement of the surgery. The anesthesiologist supporting the neurosurgeon will then stop the sedation when the neuro¬surgeon signals that he or she is ready to remove the brain tumor, so that you will be awake during the removal. Once the neurosurgeon says that he or she has completed the removal, the anesthesiologist will sedate you again for the closure procedure and you will be allowed to come out of sedation once that process is done.

Asleep at the beginning and end of the surgery and awake during tumor removal: At the commencement of the surgery, you will receive a nerve block and general anesthesia, which will render you unconscious. When the neuro¬surgeon signals that he or she is ready to remove the brain tumor, the anesthesiologist will wake you up. Once the neurosurgeon says that he or she has completed the process, the anesthesiologist will again put you to sleep for the closure procedure and you will be awakened for recovery once that process is done.

Your neurosurgeon will have a discussion with you to reach agreement on which approach will work best for your surgery.

Responses during the awake period helps guide the neurosurgeon in removing or substantially reducing tumors that might otherwise be considered inoperable due to their location or size, while at the same time avoiding damaging eloquent areas of the brain. During the surgery, the neurosurgeon will stimulate the area around the tumor with small electrodes and will ask you to perform tasks such as talking, moving a specified part of your body, counting (maybe even doing simple math), and looking at pictures. Some individuals with unique talents, such as singers and musicians, have sung or played their instruments during their surgery.

The neurosurgeon will use computerized maps of the brain taken before and during the procedure (this is why this surgical procedure is also called interoperative brain mapping). Your responses will create a map of the functional areas of your brain,

which will provide the neurosurgeon additional guidance for removing as much of the tumor as possible while avoiding the eloquent areas.

While this sounds like a scary approach, it is actually a common practice and is becoming increasingly common as neurosurgeons attempt to achieve the extent of resection, which, as earlier mentioned, correlates to significant improvements in the overall survival of high-grade patients.

Neurosurgeons and their anesthesiologists are skilled in ensuring patients do not experience pain during the procedure and are able to remain comfortable through¬out. Typically, a nurse is dedicated to a patient throughout the surgery with the sole job of helping the person to feel safe and calm.

The only areas of the body involved in this surgery that can feel pain are the scalp and muscles at the site; the brain itself has no pain receptors.

It is recognized that awake surgery is not for everyone. Some of the factors restricting the application include if the person has certain types of sleep disorders (like sleep apnea) or is unlikely to respond calmly to the procedure and the neurosurgeon.

Debulking/Partial Resection

When an entire tumor cannot be removed, but is causing intolerable functional deficits, a neurosurgeon may perform a surgery to debulk the tumor. Debulking or partial resection refers to reducing the size of a brain tumor.

The following are usually NOT candidates for surgical debulking:

- The tumor is large and invasively dominating one hemisphere of the brain;
- The tumor is a large butterfly glioma;
- The patient is elderly (65 or over);
- The patient has an infiltrating tumor, is already taking steroids and has a Karnofsky score of less than 70. (See the Section entitled Karnofsky Performance Status for the score chart.) Typically, in this circumstance, the patient's condition is unlikely to be improved with surgery; or
- The tumor is a multicentric glioma. A multicentric glioma produces two or more tumors, all of which are in separate locations of the brain.

It is highly recommended that you obtain a second opinion from a highly qualified neurosurgeon prior to receiving a debulking of a tumor. A debulking that expects to leave more than 25-30% of the tumor intact also leaves residual vascular tumor that has the propensity to produce brain edema and intratumoral hemorrhage (a condition referred to as "wounded glioma syndrome"). Several studies have established that patients with Grade 2 (or greater) gliomas who undergo debulking/partial resection can experience greater neurological morbidity than do patients who undergo gross total resection.

LITT Laser Surgery

If a tumor is small enough and in accessible locations whether near the surface or even deep inside, it may be possible for the neurosurgeon to use a surgical technique called by several names: "Laser Interstitial Thermal Therapy (LITT) ablation", "stereotactic laser thermoblation", or "MRI guided laser ablation." This Guide will just use "LITT".

LITT surgery may be available for tumors previously thought to be inoperable. In this technique, the neurosurgeon makes a small incision (coverable by a small, nor¬mal bandage), then makes a small hole through the bone. Through this access point and while the head is secured in place, the neurosurgeon uses an MRI to guide a 1.6 mm thick laser device (about the thickness of a pencil) precisely into the tumor.

The neurosurgeon then uses the MRI to obtain real time thermometry measuring the temperature of the tumor and the normal surrounding tissue. This enables the neurosurgeon to heat up the laser just enough to destroy the tumor (basically by cooking it from the inside out). The neurosurgeon turns off the laser before the heat reaches the normal surrounding tissue, reducing the likelihood of damage to nearby healthy brain tissue.

This procedure has been used with thousands of patients and has been shown to be successful in reducing or removing diseased tissue.

The LITT system used by neurosurgeons consists of a laser system, workstation, and an MRI. There are two FDA-approved LITT systems in the United States: Visualase (Visualase, Inc.) and NeuroBlate (Monteris Medical, Inc.). The main differences

between the two systems are the laser wavelength, cooling method, heat production, and distribution pattern. The NeuroBlate system, approved by FDA in 2009, has a 1064-nm diode pulsed laser with a CO2-cooled side-firing probe or diffusing tip probe. The Visualase system, approved by the FDA in 2007, has a 980-nm diode continuous laser with a saline cooled diffusing applicator tip.

LITT systems are more likely to be available at a major brain cancer center. Its main advantage over conventional surgery is that it is minimally invasive. Only a small hole is needed; the neurosurgeon does not have to remove a portion of the skull to access the tumor, which reduces recovery time considerably. However, based on decades of experience that tells them about the effectiveness of conventional surgery, most neurosurgeons will still prefer to extract a tumor by a scalpel when they can.

Neuroendoscopy/ Key-Hole Surgery/ Neurosurgical Tubular Retractor System

Neuroendoscopy, also known as key-hole surgery, is a minimally invasive surgery technique developed in the 1990s and received benefit of rapid developments since. This surgical technique utilizes an endoscope; this form of surgery is used for very limited types of surgical challenges.

An endoscope is a medical instrument, which is a long tube with a camera attached to a monitor and an eyepiece through which the neurosurgeon looks. At the end of the endoscope are tiny forceps and scissors the neurosurgeon can use to perform a microsurgery. An endoscope may be either flexible or rigid and is inserted through a small hole made in the skull or through the mouth or nose.

Neuroendoscopy can be used to remove some or all of a small tumor located in difficult places such as many midline skull base, some parenchymal lesions, and tumors within the fluid filled spaces deep within the brain called ventricles.

The neurosurgeon may also use neuroendoscopy to help relieve hydrocephalus, which is a buildup of excess fluid in the ventricles sometimes caused by a tumor that generates an excess of edema/inflammation. When excess fluid expands the size of the ventricles, this causes the pressure in the brain to increase which in turn can cause a person to experience a variety of intolerable symptoms.

A form of surgery that is a type of neuroendoscopy is the neurosurgical tubular retractor system. In this type of surgery, the neurosurgeon extracts the tumor through a tube. A retractor which is part of this system pushes or holds delicate brain tissue aside to enable the neurosurgeon to reach the target tumor. This is of important benefit because it is thought to cause less damage than other surgical options since it is moving tissue away rather than cutting through it. This system may be very helpful in situations when a tumor is located deep within the brain. Like neuroendoscopy, it also offers a less invasive option than a traditional craniotomy.

Photodynamic Therapy

A form of therapy called photodynamic therapy (PDT) was first developed in the 1980's and is now being used in combination with surgery. PDT is a combination of a photosensitizer drug, light, and molecular oxygen. Owing to its low toxicity, this therapy is being tested on both children as well as adults.

PDT takes advantage of the fact that a photosensitizer, a light-activated drug, accumulates more readily in tumors. The patient would be given the photosensitizer a few days prior to surgery. This time allows the drug to collect in the tumor and when later exposed to a specific wavelength of light, the drug produces free radicals that kill the tumor cells. After the tumor that has been treated with PDT is removed, the neurosurgeon would irradiate the cavity with a laser to destroy any residual cancer cells that are beyond the margin of the tumor.

Therefore, PDT, optimizes the removal of the tumor and ablation (cleaning) of the tumor site while minimizing damage to healthy tissue. Unlike surgical resection and radiotherapy, PDT can treat micro-invasive areas, which is a serious benefit in treating the thin outgrowth patterns of gliomas.

One photosensitizer is called porfimer sodium ("Photofrin") and is currently being tested on patients. Another agent being evaluated is Gleolan. In order to achieve a greater accumulation of a photosensitizer drug in the tumor, nanotechnology is being researched (e.g., Ce6/PTX2-Azo Nanoparticles).

Currently, no device allows the use of PDT without direct, surgical access to the tumor; the light used in PDT is not strong enough to go through more than 1 cm of tissue. Also, PDT is not currently FDA approved, so access to this therapy is through

clinical trial, however, it is an emerging technology and is worth discussing with your neurosurgeon.

Shunt Implantation

In some cases, the brain tissue reacts to the presence of the tumor and to treatments such that it produces an excessive amount of fluid. Too much fluid in the enclosed area of the cranium can oversaturate the brain tissue causing symptoms like nausea, headaches, and drowsiness. It can even become life threatening in extreme cases.

Since this fluid cannot be re-absorbed by the body as quickly as it is produced, the situation requires medical intervention. If available medications (such as dexamethasone or Avastin) do not satisfactorily control the situation, the neurosurgeon may recommend the installation of a shunt.

A shunt is a small valve that is installed surgically under the skin right behind an ear. A tube is attached to the shunt internally and drains the extra fluid from the brain into the abdomen where the body can then dispose of it in the normal course.

The surgery for installing a shunt is a true surgery. There will be a few stitches behind the ear, a couple of staples possibly in the torso (to permit the doctor to snake the tube into position in the abdomen) and then a couple of staples where the shunt ends in the abdomen. While there is always a risk of infection with any surgery, the incisions for this surgery are pretty limited, which limits the infection risk.

Shunts come in programmable and non-programmable types. The instructions for either the program or settings (depending on the type of shunt) tell the shunt how much fluid to remove from the brain so that it doesn't remove too much or too little. Shunts do not necessarily come out of surgery adjusted perfectly because it can be a trial-and-error process to get the shunt to drain the right amount. The neurosurgeon is the one who will first set the shunt's meter – usually at a conservative best guess rate - and then make any necessary adjustments afterwards, which is done in the doctor's office by the doctor manipulating the shunt under the skin. (This is typically painless.)

Shunts do malfunction and when they do, a range of symptoms result like headache, vomiting, visual issues, fatigue, irritability, loss of balance, fever, and redness. (This

is not a comprehensive list, but you get the idea.) If there is redness along the track of the shunt, then that could mean there is an infection brewing. If anything like these symptoms show up, you should call the doctor's office right away and they will probably want to see the patient urgently.

Ventricular Access Device Installation

The posterior fossa is a small space found near the brainstem and cerebellum. The cerebellum is that part of the brain responsible for controlling balance, coordinated movements and vital body functions, such as breathing. A tumor can grow in this area. Most posterior fossa tumors that appear as a meningioma, schwannoma, epidermoid, cholesteatoma, chordoma, and chondrosarcoma are more common in adults, whereas other rare tumors, such as Ewing's sarcoma, are more common in children. About 70% of posterior fossa tumors are diagnosed in children.

When a brain tumor grows in the posterior fossa area, its critical location leads to brainstem compression and herniation. It can block the flow of spinal fluid and cause increased pressure on the brain and spinal cord, which can produce an array of serious symptoms.

In order to treat this type of tumor, a neurosurgeon may decide to install a ventricular access device if the tumor does not exceed size recommendations. This device, also called an Ommaya reservoir, is placed under the scalp with tubing going to the brain's fluid-filled spaces (ventricles) so the neurosurgeon can sample the fluid, drain it or deliver chemotherapy into the fluid.

GammaTiles (also called Surgically Targeted Radiation Therapy or STaRT)

When deemed appropriate to the case, neurosurgeons can imbed radioactive seeds called GammaTiles to deliver radiation directly to the site. GammaTiles are one-inch square collagen tiles that deliver radiation to the tumor environment. Each GammaTile has four, tiny radioactive seeds that have been shown to delay tumor regrowth and avoid typical side effects of radiation like hair loss. The GammaTile delivers radiation immediately upon placement and is focused right where it is needed.

With GammaTile Therapy, there is no need for patients and their caregivers to travel

to and from a radiation treatment center. Patients receive treatment at home while going about their daily life. In a clinical study, GammaTile treatment resulted in nearly twice as many tumor-free months. There are risks with this therapy that should be discussed with the neurosurgeon.

Neuroplastic Surgery

You may wish to discuss with your neurosurgeon about having a neuroplastic surgeon involved with your surgery. This specialist surgeon can help minimize scar visibility and aid in wound healing. For tumors involving the bone or the scalp, a neuroplastic surgeon can assist with creating personalized implants to help replace removed bone to prevent visible deformity to the head.

Length of Brain Tumor Surgery

A craniotomy and removal of your tumor typically takes 4 to 6 hours. Remember that brain tumor surgery involves an entire team of people, as well as monitoring of vital signs, positioning of equipment and ensuring you are comfortable before your procedure begins. The time elapsed between your room being cleared of visitors to the actual start of surgery can be up to two hours alone. If you have people waiting for you, they should be aware of this extra time on top of the actual surgical procedure time.

Hospital Stays

Years ago, patients with brain tumors would stay in the hospital for a week or more after the procedure. Over the last two decades, doctors have been able to steadily decrease the amount of time patients need to remain in the hospital following surgery. Now, the average stay for brain surgery is three (3) days and two (2) nights with the first night in ICU for maximum observation.

Risk of Complications

Surgery on the brain is serious and complicated surgery. The neurosurgeons performing these types of surgeries in the US today are among the brightest, most competent, and best equipped doctors in the world, thereby reducing the risks associated with this major medical event. Nonetheless, some post-surgery complications hap-

pen as a direct result of surgery and are expected in some cases, but just moving brain tissue around during the surgery can cause other temporary symptoms.

While most people leave surgery in as good a functional state or better than when they went in, about 18% of the individuals who receive brain surgery develop impairments from the surgery, despite all the best training, planning and efforts by the neurosurgeon. Those most at risk for complications are those who are older and those who have a Karnofsky score of less than 70. The Karnofsky scale can be found at Table 1 of this National Institutes of Health document:

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3837542/

Impairments include motor weakness, sensory deficits (e.g., hearing loss or degradation), aphasia/language difficulty, visual deficits, confusion, and ataxia (lack of muscle control or coordination of voluntary movements). It is strongly recommended that the person proceed to rehabilitation as soon as the neurosurgeon approves.

One complication to be mindful of is the risk of infection. Any surgery depletes the immune system, which can give infection a foothold. This is especially true for repeat surgeries because the neurosurgeon is cutting through skin tissues which have been radiated, making those areas more susceptible to post surgery infections. It is important to carefully follow the neurosurgeon's instruction for post-surgery care.

Immediate Post Surgery Care

After your brain tumor surgery, you will most likely spend the night in a neuro-critical or intensive care unit (NCCU or ICU) for observation. You may be connected to an intravenous (IV) line through which you will receive a constant drip of fluid, a heart monitor, a urinary catheter, and an oxygen mask. You will also have a dressing (bandage) on your head for a day or two.

The purpose of your NCCU/ICU stay is to prevent or minimize any complications you may have to the anesthesia and the surgery itself. Anyone emerging from brain surgery is under a significant amount of physiologic stress that can be seen with fluctuations in blood pressure, blood glucose, heart rate and variations in oxygen consumption, so you deserve careful attention and prompt intervention for anything that may arise. This often translates into a nurse checking your vitals every

15-30 minutes immediately upon recovery from anesthesia for the first 1-2 hours, and then once per hour for the next 6 hours. (Do not plan on getting much sleep in the NCCU/ICU.) Once everything stabilizes, then you are ready to leave the NCCU/ICU for a regular hospital room.

When you leave the NCCU or ICU, you will continue recovery at a neurosurgery nursing unit. You should be able to be out of bed eating and taking short walks the day after surgery. Once you are eating and drinking normally, the IV will be removed from your arm.

You should not experience a lot of pain after surgery. Most people take acetaminophen for minor discomfort, but stronger pain relievers may be appropriate as recommended or approved by your doctor.

Post-Surgery Home Care and Other Topics

Post-Surgery Doctor Visit. After you are released from the hospital, you can continue your recovery at home with home-based or outpatient therapy, as needed. You will need to return for a follow-up visit with your neurosurgeon in about a week or so to assess your health and remove any staples or stitches. In some cases, they will need to stay in for longer.

Pathology Report. Be sure to ask your neurosurgeon for a copy of the pathology report from the procedure. Although it may be expensive to do so, you can readily get a second opinion on the reading of the pathology slides. There is a lot of interpretation put into the reading of the pathology slides, and this is the single most important diagnosis you will ever have in your life, so it may be worth the money to double-check it. Best of all, getting a second opinion will not involve any pain — and can be accomplished by mail, so there will be no need for additional travel.

Steroid. If you have been prescribed a steroid to help control the swelling, check with the doctor about when you can taper (slowly!) from use. (The most commonly prescribed steroid for brain tumor patients is called dexamethasone.) While a steroid is a great help, it can lead to issues with both short and prolonged use, which are described below in the section entitled "Medications for Swelling"

For steroid use lasting longer than a few days, it is VERY important to follow your doctor's instructions about decreasing your steroid dosage. Stopping steroids abruptly can lead to numerous withdrawal symptoms including an adrenal crisis which is a rare but fatal reaction to a lack of steroid in your body.

Healing. It will take time to return to your usual level of energy. Be patient. Healing requires extra rest, and the surgery probably took more out of you than you might think. The amount of time required to recover after brain surgery is different for each person, and it depends on:

- The procedure used to remove the brain tumor;
- The location of the tumor within the brain;
- Areas of the brain affected by the surgery;
- Your age and your overall health going into the surgery.

Preventing Post-Surgery Constipation. When they give you anesthesia, they typically also give you a medication like Ondansetron (commonly called Zofran) to help avoid nausea from the anesthesia. Zofran (or similar meds) can cause significant constipation making it very hard for you to relieve yourself for days, can cause you to feel sluggish, and can dampen your appetite at a time when you should eat well. Eating fibrous foods and taking a stool softener approved by the neurosurgeon can help.

Hydration. Keep yourself well hydrated with lots of plain WATER during your recovery. Drinking lots of water helps to flush any medication residues from the body and aids in avoiding the constipation. Fruit juices, sodas, off-the-shelf ice teas and coffees should be limited because of their high sugar content. The best drink always is good old plain water.

Sleep Position. Sleep with your head propped slightly upright. The body always sends fluid to the site of a wound, and in this case, the fluid can build up pressure, so you want the fluid to be able to drain downward.

Radiation Treatment

Overview

Surgical removal of the tumor is highly advantageous to the patient, but is insufficient for removing the non-visible, microscopic cancer cells that remain. At the right dosage, radiation will kill brain cancer cells almost as effectively as surgery but will also kill the invisible cells.

The radiation does so by damaging the DNA with¬in the cancer cell, which then stops them from growing and dividing. The injured cell perishes leaving no descendant cells to continue the growth of the tumor.

Depending on the kind of tumor, a person may only get radiation therapy. Radiation treatment must be tailored for each person based on the type, status (e.g., resected or not), the location of the tumor or tumor cavity, and the characteristics of the individual (e.g., age, health status).

Radiation therapy is typically performed under the care of a radiation oncologist at a radiation facility or by a neurosurgeon either during surgery when radioactive materials are implanted or during radiosurgery when conventional surgery is not an option.

The objective is to deliver radiation, consisting of a powerful targeted beam, only to the tumor and a small margin around the tumor. There are numerous technologies, with increasing precision, available that offer this approach, which is applicable when there is a single tumor or just a few tumors. Side effects from this form of

therapy are reduced.

The radiation oncologist, and possibly also a neurosurgeon, will decide which approach is best based on all factors of the particular case given the twin goals of improving longevity by increasing the effectiveness of the treatment against the dis¬ease while at the same time preserving to the maximum extent possible quality of life by decreasing treatment toxicity.

Radiation Technologies

The field of radiation has become the beneficiary of rapid and amazing enhancements in its technology over the last 30 years. As a result, there are a variety of types of technologies employed today. Not all brain cancer centers will have every technology, but a major brain cancer center is likely to have excellent, state of the art radiation technology.

Prior to the start of your therapy, you should find out exactly what type of technology will be used.

These are the types of technologies you may encounter. The equipment used by each are described below.

- Stereotactic Radiosurgery (SRS)
- External beam radiation therapy (EBRT)
- Internal radiation therapy (Brachytherapy)

Stereotactic Radiosurgery (SRS)

Overview of SRS

Although no "knife" or incision is used to expose the brain during stereotactic radiosurgery (SRS) but rather a precise high-dose beam of radiation, SRS is considered "surgical" because of the degree of change that takes place after the procedure. Although not part of the standard-of-care treatment, it is good to know about SRS.

SRS is a noninvasive approach to treat brain tumors using pencil-thin beams of radiation directed only at the tumor. SRS is a standard treatment for selected primary

and metastatic brain tumors and may be delivered as:

- An addition to conventional EBRT (described below), called local "boost" radiation, when the patient has already received the maximum safe dose of conventional radiation therapy, or
- The only technique used to deliver radiation therapy to some brain tumors, or
- A substitute for surgery for a metastatic brain tumor or a benign tumor (such as a pituitary, pineal region, or acoustic tumor).

This focused technique allows radiation to be delivered in an area of the brain or spinal cord that might be considered inoperable and can be delivered to tumors that are small (generally 2 centimeters or less).

SRS can involve one treatment session or several (fractionated) sessions over a period of several days or weeks, assisted by computer-aided planning. SRS delivers a much higher dose of radiation to the target than conventional radiation therapy. For some low grade tumors, SRS can be curative. SRS is also sometimes used for small tumor recurrences.

Prior to SRS, the patient is fitted with a head frame, although some forms of SRS are frameless. CT and/or MRI scans are performed with the head frame in place to locate the tumor and obtain information necessary for computerized treatment planning. Treatment is totally non-invasive and painless, although the headframe may be somewhat uncomfortable for some people.

Patients maintain their normal function and are completely awake and alert throughout the entire procedure.

Radiation is generally given in a series of treatments over several weeks. The total radiation dose, which is based upon the number of treatments and the amount of radiation administered per treatment, is carefully calculated to maximize the killing of tumor cells and minimize damage to the normal brain.

Types of SRS Devices

Many different manufacturers have developed devices for administering SRS. Some of the notable brands are Gamma Knife, CyberKnife and ZAP-X. Other systems

which may be used for both SRS as well as External Beam Radiation Therapy (EBRT) are Novalis Tx, LINAC and TrueBeam. These are not the only SRS devices available; the information below is solely to provide some representative information to understand the state of the advances in radiation technology.

Each SRS device has its own advantages and disadvantages. Just know that if you are told your tumor is too large or the wrong shape for SRS, get another opinion from a doctor who uses a different type of SRS device.

GammaKnife

The Gamma Knife is an instrument that was developed by researchers in Sweden nearly three decades ago. It delivers 201 beams of radiation using radioactive cobalt that are focused by a computer so that they intersect at the precise location of the cancer. The patient is placed on a couch and then a large helmet is attached to the head frame. Holes in the helmet allow the beams to match the calculated shape of the tumor.

The most frequent use of the Gamma Knife has been for small, benign tumors, particularly acoustic neuromas, meningiomas, and pituitary tumors. For larger tumors, partial surgical removal might be required first. The Gamma Knife is also used to treat solitary metastases and small malignant tumors with well-defined borders.

CyberKnife

Like Gamma Knife, CyberKnife delivers sub-millimeter accuracy, but is enabled by an enhanced tumor tracking technology and real-time imaging so that a person does not have to be immobilized during treatment. CyberKnife, which was first used in the US in 2001, offers flexible treatment options. A person can have a single high dose treatment, or two to five lower dose treatments, generally completed within a week. CyberKnife uses electrically generated photon beams.

ZAP-X

The ZAP-X system is a new addition to radiosurgery. It is based on state-of-the-art linear accelerator (LINAC) technology and has a novel, fully integrated dosimetry validation system that monitors and verifies delivered radiation in real time. It uses

a gyroscopic motion to direct high dose beams from a multitude of unique angles to precisely aim at the tumor, resulting in less healthy brain tissue exposure. The system has unique self-shielding technology (like a bank vault) so that radiology departments do not need to build a special room and bunkers for it. ZAP-X does not use Cobalt-60, avoiding the costs involved in licensing, storing, and replacing radioactive isotopes, so it may be a less costly alternative for some.

Novalis Tx

Novalis Tx is a highly sophisticated SRS/EBRT device developed by NASA engineers. It is equipped with "Novalis Body" software for image-guided radiotherapy delivery. Its X-ray-based localization technology allows the doctor to treat the tumor with sub-millimeter accuracy. The system includes a 6-dimensional robotic couch that positions patients automatically and with the highest degree of precision. It has high dose conformity within a shorter period of time making treatment times shorter.

Photo by Steve Tilkin

LINAC

Also used for SRS and EBRT, an adapted linear accelerator can deliver a single, high-energy beam that is computer-shaped to the tumor. The patient is positioned on a sliding bed around which the linear accelerator circles. The linear accelerator directs arcs of radioactive photon beams at the tumor. The pattern of the arc is computer-matched to the tumor's shape. This reduces the dose delivered to surrounding normal tissue. LINAC radiation therapy may be used in the treatment of metastatic cancer or some benign brain tumors.

TrueBeam

TrueBeam is a system with a sophisticated architecture that was engineered with motion management technologies, advanced 3D imaging and patient comforts in mind. It is able to provide pinpoint accuracy with less time on the treatment couch; treatments that may take another system 15 minutes or more may take the TrueBeam two minutes. TrueBeam uses a cone-beam computer tomography (CT) that uses 25 percent less of an X-ray dose than other image-guided technologies. It is a quiet machine and has built-in music to provide a more relaxing therapy experience. TrueBeam can be used for both SRS and EBRT.

Side Effects of SRS

Possible side effects of SRS include edema (swelling), occasional neurological problems, and radiation necrosis (an accumulation of dead cells). A second surgery to remove the build-up of dead tumor cells may be required.

EBRT Radiation (Proton, 3D-CRT, IMRT)

Overview

EBRT (which may also be referred to as Stereotactic Radiation Therapy or SRT) involves directing radiation beams from outside the body into the tumor. Machines called linear accelerators produce the high-energy radiation beams that penetrate the tissues and deliver the radiation dose directly to the cancer.

EBRT divides treatment into multiple sessions. This approach is best for large tumors

or tumors within or close to critical brain structures that cannot tolerate a large radiation dose. This form of radiation technology significantly reduces side effects while improving the ability to deliver a high total amount of radiation directly to the tumor.

EBRT is typically delivered as an outpatient procedure a few minutes per day, every day (often weekends are excepted) or approximately six weeks. EBRT begins with a planning session, or simulation, during which the radiation oncologist takes measurements in order to line up the radiation beam in the correct position for each treatment. During treatment, you would lie on a table and the radiation will be delivered from multiple directions. The actual area receiving radiation treatment may be large or small, depending on the features of the brain tumor.

Proton Beam

Proton beam therapy is a form of EBRT. It offers excellent dose localization that permits treatment of brain cancer by administration of a high dose to the tumor while minimizing damage to surrounding normal tissues. A proton beam has a sharp energy peak called the Bragg peak, which spreads out to cover the tumor volume. The energy behind the peak is nearly zero, unlike some other forms of EBRT. This means that the dose to normal tissue around the tumor can be less than that experienced in other forms of radiation therapy.

Note that proton beam radiation is more expensive than conventional photon beam used in most of the other technologies and as a result, not all insurance companies will approve use of proton beam therapy. Some insurance companies have approved use after appeals.

Proton radiation therapy may have a role in the treatment of unusually shaped tumors and small tumors that are located deep in the skull, such as skull base tumors or pituitary tumors. Proton radiation therapy has been evaluated in the treatment of meningiomas and appears to be effective in a high percentage of cases.

Proton or Photon?

In several of the top brain cancer centers, the radiology department has both pro¬ton beam as well as photon beam technology and patients may be perplexed about which

is best for them. The best answer can only come from the radiation oncologist, who will evaluate the location, type, and shape of the tumor, as well as your age and underlying health and other factors. However, here are some considerations you may wish to discuss with your radiation oncologist.

Proton radiation has the physical advantage of better spatial selectivity (i.e., this form of radiation can offer a more condensed "hit"). Plus, proton beam radiation seems to also have better radiobiological efficacy than photon type radiation, meaning that it is better suited for the treatment of radioresistant tumors (e.g., a tumor that might be hard or dense compared to one that might be soft and jelly like or a tumor which is located near the eloquent (sensitive) parts of the brain.)

Though protons may release a larger mean energy per unit length, the radiobiologic properties or protons and photons are not all that different.

In proton beam radiation, there is less radiation "spillage" into neighboring areas because the treatment is highly localized. This is a desirable feature if the tumor's margins are well defined.

However, photon therapy may be more helpful in the case of a diffuse tumor; that is, one which has finger-like tentacles extending some distance from the main tumor mass and invading healthy areas. Since the particles emitted by photon beam radiation "bounce around" a little more than proton radiation, photon beam may present an advantage for those dealing with a diffuse tumor because the radiation will have a greater opportunity to deliver destruction to those invasive, tentacles of the tumor.

3D-CRT

Three-dimensional conformal radiation therapy (3D-CRT) is another form of EBRT. This technology conforms a specific arrangement of x-ray beams to the tumor's shape to maximize tumor dose and minimize exposure to normal tissue. This treatment is tailored to your specific anatomy and tumor location. Your doctor may use CT and/or MRI scanning to plan your treatment. The use of 3D-CRT is believed to reduce the chance of injury to nearby normal tissues.

IMRT

Intensity-modulated radiation therapy (IMRT) is another form of EBRT. This is an advanced mode of high-precision radiotherapy that uses computer-controlled x-ray accelerators. The accelerators conform and deliver a precise radiation dose, some¬times referred to as "beamlets", to the three-dimensional (3-D) shape of the tumor. The machines control the intensity of the radiation beam to focus a higher dose on the tumor and minimize radiation exposure to healthy cells.

At Brigham's and Women's Hospital, researchers conducted randomized controlled trials comparing IMRT to 3D-CRT. They found that IMRT results in significantly less changes to the salivary glands in patients with head and neck cancers.

Brachytherapy

Brachytherapy is internal radiation treatment. The most common form of brachytherapy places radioactive material directly into or near the tumor. In those cases, the radioactive material is often referred to as "implants" or "seeds." A new, alternate radiation technique involves the insertion of a balloon at the tumor site during site and administering radiation through a catheter into the balloon.

Brachytherapy is used in the treatment of newly diagnosed or recurrent brain tumors. It may be administered as the primary radiation therapy or as a "boost" of additional radiation delivered before or following standard ERBT.

For boost therapy to be effective, the tumor must be no more than 2 inches in diameter and accessible by surgery. Larger tumors may require surgery to reduce the size of the tumor before the Brachytherapy is applied. Brachytherapy is a local therapy; it is not commonly used for widely spread or multiple tumors.

While standard radiation aims rays at the tumor from outside the body, brachytherapy attacks the tumor from the inside. The advantages to this internal delivery of radiation are:

- Reduced damage to normal tissue, and therefore, reduced side effects. This technique limits radiation exposure to a localized area around the radiation

sources, minimizing exposure of healthy tissues away from the tumor,
- More concentrated delivery of radiation to the area where the cancer is mostly likely to recur, and
- Reduced risk of damage to normal brain tissue makes brachytherapy an option for patients with recurrent tumors who have undergone radiation treatment for recurrent brain tumors and may not be able to tolerate additional EBRT.

Radiation Seeds

To implant radiation "seeds" in the tumor, catheters (tubes) are placed into the tumor bed using surgical techniques that are directed by CT and MRI. The radiation "seeds" are placed in the catheters. Depending on the isotopes used, the implant is removed either after a few days, after several months or is left in place permanently. Steroids are commonly used with this therapy to decrease brain swelling. In rare instances, implantation might be repeated. Brachytherapy implants are typically temporary and are removed once treatment is completed. In some cases, an implant may be permanent.

Considerations for the Use of Radiation for Low Grade Gliomas

The precise, optimal management of patients with low grade gliomas after surgery remains debated. The risk-benefit ratio of treatment with radiation and chemotherapy must be weighed for each individual patient. A large study of patients with low-risk low grade glioma younger than 40 years who had gross total resections reported 52% of patients had recurrence within 5 years of surgery. On the basis of this data, in patients who are considered low risk, defined as age younger than 40 years with a gross total resection, it is an attractive option to forgo further treatment with radiation and chemotherapy at the time of diagnosis and instead undergo "Watch and Wait" surveillance (described in the section entitled "Monitoring" below.)

In people with low grade gliomas, radiation may be recommended in three circumstances:

- Radiation can be given after surgery, with the objective of eradicating tumor cells that were not removed at the time of surgery. The effectiveness of immediate radiation therapy after surgery is unclear. Because the benefit is uncertain

and radiation has the potential for long-term neurologic side effects, postoperative radiation is sometimes delayed.

- Radiation may be the preferred treatment when a low grade glioma has been diagnosed in a critical area of the brain that cannot be surgically removed, and therapy is felt to be necessary.

- Radiation can be used later in the course of the illness, when there is evidence that the tumor is growing and is causing symptoms. The use of radiation at this time will depend upon how much radiation was given previously, since radiation cannot usually be given in full doses to the same area of the brain more than once.

Treatment Schedule

The NCCN recommendations mention two different types of radiation therapy — standard and hypofractionated.

When you receive standard radiation, the total radiation dose is fractionated, which means the dose is often split into many smaller portions or fractions delivered over several weeks. This is done in order to maximize damage to the cancer cells while minimizing damage to healthy brain tissue.

In hypofractionation, the total radiation dose is divided into fewer, larger fractions given in less time.

Standard, fractionated radiation therapy usually starts a few weeks after surgery, normally as soon as the surgical wound heals. Normal EBRT is usually given in 30–40 sessions over a 6-week period, 5 days a week (usually Monday through Friday). The actual treatment may take only a few minutes, but you should expect to spend 30 to 45 minutes preparing before each treatment session.

You would also take a low dose of the chemo Temodar each day throughout the 6 weeks. After the completion of the 6 weeks, you will often be given a 4-week break for recovery.

Brachytherapy may be administered for only a few days, followed by removal of the

radioactive “seed”.

Stereotactic radiosurgery is typically conducted in one single session that may last an hour or more.

What to Expect During Treatment

The first step in radiation treatment is a consultation with the radiation oncologist. In this important visit, you and your radiation oncologist will meet each other and discuss your situation. During the consultation, the radiation oncologist will review your medical history and perform a physical examination. If your radiation oncologist is not associated with the treatment facility where you had your diagnosis and surgery, you should bring any images, records, referral forms, list of medications you are taking and your insurance information.

The radiation oncologist is likely to impact a great deal of information to you in your consultation, so it would be helpful to take someone with you to help you remember all the details. Also, this is when you bring out any questions you may have. Below you will find some sample questions you may wish to ask.

The radiation oncologist may order additional images or tests before radiation begins. Your sessions will be scheduled once these additional results are in, and the doctor has had a chance to review them. The radiation oncologist most likely will make his treatment recommendations to your neurosurgeon and/or neuro-oncologist to ensure a multi-disciplinary consensus. Once this is achieved, the radiation oncologist will communicate the plan with you and seek your consent to commence radiation treatment.

Planning Session

At this point, you can expect to be asked to come in for a planning session. During this session, you will become acquainted with the treatment facility, equipment and you may undergo a radiation simulation. You will not receive any radiation during this planning simulation, but you may be fitted with a mask that will help hold your head steady during treatments.

The skin of your head may also be marked (temporarily) as the radiation oncologists

maps out the alignment and delivery plan for the radiation beams. You may have some low energy red laser lights appear on your head when they completely darken the room, but these will not be emitting any radiation and you will probably not even feel them; they are just for alignment and planning purposes.

You should expect to spend quite a bit of time at the planning session as the radiation oncologist and staff the prepare a highly precise, highly sophisticated computerized program for your radiation sessions. It may take a few days for that program to be prepared and double checked. Once that is done, then your sessions can begin.

Radiation Sessions

To prepare, you'll be positioned on a table. Cushions and restraints will be used to hold your head and body still. Then you'll undergo an imaging test, such as an X-ray or CT scan, to make sure you are in the same precise position before each treatment.

During radiation treatment, you must lie very still on the treatment table while the radiation beam is targeted to the exact area of the tumor. Depending on the equipment used, the machine and treatment table may rotate on a gantry up to 360 degrees so that the radiation hits the tumor from all angles.

The radiation oncologist and technologists will not be in the room during the treatment, but they will be watching you via a video camera and can hear you through an audio connection with the treatment room so if you have an issue, you will be able to communicate with them. You'll probably hear the machine when it's turned on and delivering your radiation, but you will not feel the radiation as it is being delivered.

Once your treatment session is complete, you can go about your day. You won't be radioactive or give off radiation or glow green.

Weekly Checks

You may undergo weekly CT scans to see if the dose you receive needs to be recalculated based on any changes in weight, or tumor size and shape. You probably will meet with your radiation oncologist weekly for a quick check to see if you are having any issues that need discussing.

Post-Radiation MRIs

Expect that any MRI taken within a month or even two after radiation treatment may contain a significant amount of swelling (edema) that could cause the image to be very cloudy. In terms of understanding if the tumor is active, this (or these) MRI images could be inconclusive and not worth the anxiety. However, the imaging is important for the future comparison purposes.

Pre-Radiation Therapy Questions to Ask

Questions About Treatment Equipment & Techniques

- Do you treat many patients with this type and size of tumor, and in a similar location often?
- What type of equipment do you plan to use for my radiation?
- How do you ensure my safety and the accuracy/ consistency of daily treatment?
- Will treatment be tailored with different doses, margins, depending on proximity of tumor to adjacent Organs at Risk (OAR)?
- How will OAR be protected? e.g., Optic nerve, hippocampus, temporal lobe, frontal lobe, cavernous sinus, carotid artery, pituitary gland, cognitive abilities, etc.?
- How will tumor target volume be determined? Who interprets and reviews the clinical target volume (CTV) prior to treatment?
- How will the tumor boundaries be determined for bone and dural tails to ensure nothing is missed? Will MRI, CT, PET/CT, PET/MRI be used? (A dural tail is a thickening of the membranes next to the tumor.)
- Will the "radiation plan" be explained? (Including how much radiation exposure does healthy brain tissue and OAR receive?)
- Are there any medications that will maximize the effectiveness of the radiation and will they be used?

Questions About Side Effects Of Treatment & Management Of Side Effects

- What healthy areas are most at risk from the radiation plan? (Identify areas of hair loss, skin irritation, muscles, ears, nose, eyes, lacrimal gland, pituitary gland, etc.)
- What potential neurological deficits risks/side effects/complications are associ-

ated with the treatment?
- Can I develop seizures as a result of radiation treatment? (Answer should be yes but perhaps as a rare occurrence because the brain is likely to swell some and swelling may trigger a seizure.)
- What functions/ parts of my brain may be injured temporarily or permanently by this treatment? Odds?
- What about the development of necrotic tissue as a result of treatment? Odds? (Answer should be between 20 and 30%)
- What emotional side effects can I expect to have from this treatment? How soon, how far into the future?
- How will these issues be managed, near term, long term?
- What side effects from treatment can I expect to have?
- How much medical care & assistance might I need during the worst side effects of his treatment?
- Are there medications/supplements that will help prevent or minimize expected side effects before, during, after treatment? For how long?
- What are the side effects of these medications?
- What vitamins/supplements can be taken during treatment? (Expect that the answer is "None whatsoever" because vitamins/supplements can interfere with or un-do the beneficial effects of the radiation treatment.)
- (If applicable:) What effect will radiation have on any other medical problems I have and medications I take?
- Can I continue to work and drive during treatment? (Neither is a good idea because a person receiving radiation will likely be fatigued from the treatment, but you should be guided by what the doctor says.)
- What will be my follow-up care after all radiation sessions are complete and who does that?

Side Effects to Expect From Radiation Treatment

A major problem with radiation therapy is treatment-related side effects. Radiation kills both tumor cells and normal cells, although tumor cells are somewhat more sensitive to the effects of radiation. Nevertheless, radiation cannot kill all tumor cells without damaging adjacent normal brain, and this results in treatment-related side effects.

The most common side effect is damage to the surrounding normal brain cells,

resulting in gradually worsening impairment of mental sharpness and ability to think and concentrate (called impaired cognition). This tends to be worse with larger radiation fields, tends to worsen over time, and is more of a problem in people who survive for several years after radiation treatment. It is difficult to know for certain whether impaired cognition results from the radiation or whether it might be due to the disease itself. Nevertheless, the possibility of impaired cognition is one of the main reasons why radiation therapy is often delayed until it is absolutely necessary.

The most common side effects of radiation follow.

Scalp problems. Your scalp may be red, irritated, or sensitive where the radiation beam goes through the scalp. If the tumor site is closer to the outside of the brain, the beam may be more intense.

Hair loss. Where the radiation beam goes through the scalp hair may be lost, most likely temporarily. You might want to find a very gentle shampoo to use during radiation. Avoid all shampoos that are harsh and have alcohol, salicylic acid, grapefruit juice, or strong fragrances in them. (Check the ingredients of any shampoo). Go for organic, natural shampoos, and don't waste money on products like Nioxin and Rogaine to restore hair after radiation. Those products don't work for radiation hair loss.

Photo by Steve Tilkin

Swelling (edema). Swelling in the brain at or near the treatment site can cause signs and symptoms such as headaches, nausea, maybe even some weakness. If you are having to travel any distance in the car to get to the daily radiation appointments, you should consider having supplies ready in case of nausea. The movement of the car, plus intracranial swelling stimulated by radiation, can sometimes (but not always) result in spontaneous vomiting.

Symptoms from swelling are likely to increase across the period radiation is given as the irritation to the brain increases across time. In short, the last 3 weeks of radiation (in a 6-week schedule) and a few weeks afterwards are probably going to be the most sensitive time. Be aware that the swelling in the brain may cause a seizure during this period, especially if the patient overexerts themselves. Not everyone experiences serious symptoms like that, but it is a good idea to be aware and watching.

The radiation oncologist may prescribe an anti-inflammatory medication (such as the steroid dexamethasone commonly referred to as "dex") to treat symptoms caused by too much swelling if they appear. Ideally, you should only take the least amount of dex for the least amount of time necessary to manage symptoms.

Fatigue. Tiredness and fatigue may occur during radiation and/or for the first few weeks afterwards. The way the brain heals from any injury is to rest, particularly within deep sleep. So, you should not be worried about tiredness; it is a sign that the brain is doing what it should to respond to the radiation and heal.

Necrosis. A possible complication associated with radiation is the build-up of dead tissue called necrosis. The radiation therapy being administered kills the cancer cells, and in some cases, this may cause dead cells to build up faster than the body can remove them. Large amounts of necrosis can cause complications. Some patients may require follow-up surgery to remove the necrosis. Necrosis happens in around 25% of cases and can show up on an MRI at any time after radiation.

The typical time to first see radiation-induced necrosis is about three (3) months after radiation has finished, but it can appear as late as 18 months or even longer. Radiation necrosis has been reported to occur between 3% and 24% of patients and there are no known predictive factors for radiation necrosis.

Radiation Injury. Over time, it becomes apparent that the tissue irradiated is damaged, hence the drive to radiation technologies that minimize effects to health brain tissue. Radiation damaged tissue will generally lose blood supply and becomes oxygen deprived. There can be chronic radiation complications result from scarring and narrowing of the blood vessels within the area which has received the treatment.

Post-Radiation Self Care Tips

Here are some simple things that you can do to help your brain heal after radiation:

- Sleep at least 8 hours every night, at the same time, preferably starting early (like at 8PM).
- Sleep with your head slightly elevated. That will help with any swelling.
- Take a good, 2-hour power nap in the afternoon starting not later than 4:30PM (or else you may not sleep that well at night).
- Eat healthy. Include lots of fruits and veggies. The brain likes fish and dark berries (dark cherries, blackberries, blueberries, strawberries)
- Meditating about 15-20 minutes a day helps calm down any built-up stress (which inhibits healing) and....it can help boost the immune system.
- Do some physical exercise/activity every day. Follow the guidance of the doctor for physical activity and do what is safe but avoid (to the extent possible) taking root in a recliner. Sensible physical activity will help the brain recover after radiation.
- Do some mental exercise/activity. You need to do something every day that you think is fun and stimulating such as painting/drawing, putting puzzles together, making scrap books, building model cars, anything that makes you think. The brain likes to have its neurons stimulated, which helps with recovery and if you enjoy what you are doing, it is likely a good, restorative activity.

Radiation Limits

For patients with low grade tumors, the dosage for any radiation therapy they may be prescribed is usually expressed in Gray (Gy) with a standard treatment typically ranging from 45 to 60 Gys and delivered in fractions over several weeks. However, specific treatment plans are tailored to each individual.

After receiving the standard treatment, there are limits to the amount of radiation a

person with a low grade brain tumor can receive. Such limits are not strictly specified, but rather are determined on a case-by-case basis. The factors the radiation therapist will considered are:

Protecting Healthy Tissue: Radiation can damage not only cancer cells but also surrounding healthy cells. Limiting the dose helps to minimize side effects and preserve normal brain function.

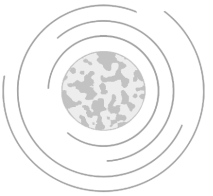
Side Effects Management: Higher doses of radiation can lead to acute and chronic side effects, such as fatigue, cognitive changes, and neurological deficits. By adhering to dosage limits, radiation therapists aim to reduce these risks.

Tumor Response: Low-grade tumors often respond well to lower doses of radiation. High doses may not significantly improve outcomes and could increase the risk of complications.

Cumulative Exposure: If a patient has received radiation in the past (for instance, for a different condition), there may be limits on how much more radiation they can safely receive to avoid cumulative damage.

Individual Variability: Each patient's anatomy, tumor type, and overall health can influence how much radiation they can safely tolerate. Personalized treatment plans help ensure the best balance between effectiveness and safety.

These factors make careful planning and monitoring essential in radiation therapy. In cases where patients may require additional radiotherapy after the initial treatment, additional treatments, such as re-irradiation or Gamma Knife, may be considered based on individual circumstances, but this would depend on factors like the patient's overall health, response to previous treatments, and specific clinical guidelines. However, additional radiation carries risks and is not suitable for everyone.



Chemotherapy

Overview

Chemotherapy or "chemo" refers to the use of medicines to stop or slow the growth of cancer cells. Chemotherapy works by interfering with the ability of rapidly growing cells (like cancer cells) to divide or reproduce themselves. Chemo is occasionally used in an effort to shrink benign masses. Because most of an adult's normal cells are not actively growing, they are not affected by chemotherapy, with the exception of bone marrow (where the blood cells are produced), the hair roots (follicles), and the lining of the gastrointestinal tract.

Distinguishing Low Risk from High Risk in Low Grade Tumors

Low-grade brain tumors are a heterogeneous group. Because of the heterogeneity of these tumors, chemos may work on some, but not all of the cells of a tumor. For this reason, certain tumors, despite their low grade, present a higher risk of recurrence and poorer prognoses. Treatment decisions must be made factoring the potential risk.

However, how to identify high-risk patients remains controversial: molecular tumor markers play an important role, whereas clinical and radiologic characteristics have additional value. This section is based on current understandings.

Use for Low Risk, Low Grade Tumors

A low risk, low grade tumor would be a benign or Grade 1 tumor. There is no estab-

lished protocol for the use of chemotherapy in treating such tumors.

Use for Uncertain Risk, Low Grade Tumors

The management of patients younger than 40 years of age who have had a gross total resection of a grade 2 astrocytoma that is IDH wild type remains unclear. Observation via "Watch & Wait" (discussed in the section entitled "Monitoring" may not be prudent, and, in these cases, immediate radiation with concomitant chemotherapy is typically used.

Photo By Steve Tilkin

Use for High Risk, Low Grade Tumors

If a patient is deemed high risk, defined as older than 40 years or having a subtotal resection, treatment with radiation and chemotherapy at diagnosis should be considered. However, because of the potential of short- and long-term adverse effects with radiation (which are detailed in the Chapter entitled "Radiation"), initial use of chemo alone has also been investigated for treatment in certain cases. For instance, in high-risk patients with the more prognostically favorable oligodendroglioma diagnosis, if there is concern for long-term effects of radiation, one may consider treatment with chemotherapy alone at initial diagnosis. There have been several small phase II trials that suggest that treatment with temozolomide has similar response rates to that of radiation with tumor stabilization of between 3 and 5 years for these high risk patients.

Use for Recurrent Disease

In all cases, chemo is considered the primary option later in the course of illness, when there is evidence that the tumor has recurred and is causing symptoms and certainly when surgery or radiation are not feasible.

Benefits

Chemotherapy is not curative, but it can improve survival by several years in some low grade tumor patients. Tumor shrinkage (which may be accompanied by an improvement in symptoms) has been seen in selected patients using various drugs or combinations, such as temozolomide (brand name: Temodar) or the "PCV" combination (procarbazine, Lomustine, and vincristine). Patients with oligodendrogliomas (tumors with co-deletions of 1p/19q) are most likely to benefit from chemotherapy.

In a long term study, patients with low-risk, low grade tumors that receive both radiation and chemotherapy have demonstrated a median of 13.3 years in overall survival versus an overall survival of 7.8 years in patients treated with radiation alone.

In a shorter term study, progression-free survival at 10 years was 21% in patients with low risk, low grade tumors who received radiation alone, compared with 51% in the patients who received both radiation and chemotherapy. The benefit of radiation and chemotherapy was seen in all histologic subgroups but did not reach sig-

nificance in patients with astrocytomas, hence the need for careful surveillance of these tumors. Further studies continue to identify the molecular subtypes of tumors that derive the greatest benefit from chemotherapy and radiation at initial diagnosis.

How It Is Administered

Some chemotherapy drugs that are used for the treatment of brain tumors are given by infusion into a vein, and some like temozolomide are given by mouth.

Dosages

Doctors typically follow the FDA approved dosage regime. During radiation, adjuvant temozolomide is given at a low dose. If the tumor grows despite radiation and the low dose adjuvant chemo normally prescribed during radiation, the doctor may decide to prescribe higher dose chemo. Dosages at other times are at a higher dose which is calculated on the basis of body mass.

Side Effects

The effects of chemotherapy on normal tissues cause side effects during treatment. In general, side effects are more frequent when two or more drugs are administered simultaneously and with higher versus lower doses of chemo.

Challenges in Pediatric Treatments

Breathtaking advances in brain cancer treatment over the past 20 years have nonetheless left gaps, and a notable one is the need for more options for children with brain tumors. These young patients face hurdles at every turn. Even for adults, brain cancer is notoriously hard to treat; the blood-brain barrier that spares the brain and spinal cord injury from harmful agents also blocks most types of therapy. Depending on where the tumor sits, surgery can be a challenge, and radiation runs the risk of damaging bits of healthy tissue.

Given safety concerns, trials for new treatments in pediatric cancers generally lag behind studies in adults. Advocacy groups for pediatric cancer highlight the dearth of research dollars that flow to this area, despite unmet need—and they note the funding chasm relative to research dollars for cancers common in adults.

Thus, therapeutic options for children are very limited. Typically the only clear standard of care today for children who have a low grade glioma is chemotherapy. The duration of chemotherapy that can be administered for children is limited, because of the toxicities, which include bone marrow suppression, cardiotoxicity, and a whole host of other of other adverse effects plus long-term side effects that may include changes in growth and metabolism, secondary malignancies at times, and long-term cardiovascular toxicity.

As a result, the degree of unmet need in pediatric cancers is extraordinary, particularly relative to adult cancers. In recent decades, we've seen numerous drug approvals—in the adult setting, but very few new drugs are approved for pediatric patients.

Most patients that are treated for pediatric brain tumors are in clinical trials because there aren't existing therapeutic options that are effective. There are real opportuni-

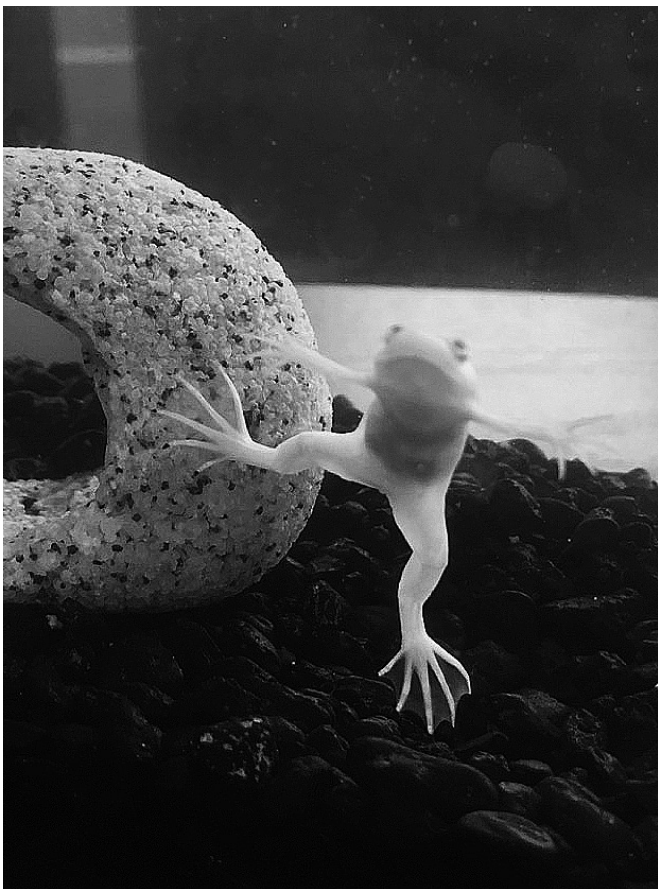
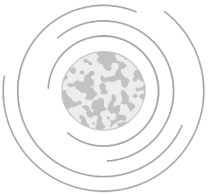


Photo by Margo Singer

ties to improve patient outcomes in brain tumors in children who have identifiable driver mutations that can be targeted, including the most frequent brain tumor in children, which is a low grade glioma.

Despite all these challenges, in the past decade, the survival of certain pediatric tumors has advanced 80% and 90%, which is amazing for a malignant brain tumor. Unfortunately, there are a few tumors that are still quite lethal and their diagnosis is a terrible thing. These are the tumors researchers are working on diligently to harness all the science possible to develop innovative therapies to treat these tumors. Science definitely has a way to go, but progress is being made constantly.



Monitoring

Overview

Management of low grade brain tumors depends on the kind of tumor. In the case of Grade 2 astrocytomas with an unmutated IDH gene, it is important that patients undergo long-term close surveillance, because recurrence is nearly universal. These patients should not go longer than twelve months between MRI scans to ensure continuous monitoring.

Low grade brain tumors which are benign, Grade 1 or gliomas with favorable genetics are typically slow growing, unlikely to spread and may cause no or few symptoms for very long periods, sometimes as long as 10 years after the original diagnosis. However, even these tumors can progress over time despite treatment, so monitoring these tumors is also important.

There are two different approaches to monitoring of low grade tumors: Watch & Wait and Regular Surveillance.

Watch and Wait

A 'Watch and Wait' approach is used when it is deemed safe and appropriate to postpone treatment, rather than provide treatments that could cause side-effects that may be worse than those caused by the tumor itself. Examples where the Watch & Watch approach makes sense include:

- Tumors with no symptoms that were discovered by accident, for example, as a result of a scan given to check for a potential head injury following a fall.

- Tumors in which the symptoms are tolerable and do not, in the opinion of the person diagnosed with the tumor, significantly affect quality of life. An example would be headaches or seizures that are well controlled with medication.

- The tumor is growing in an area that is not very accessible surgically and intervention would be likely to cause more harm than doing nothing.

- The person has another medical condition that may be made worse by treatment, e.g., individual is elderly and frail.

Under the Watch & Wait approach, the individual will see the doctor for scheduled check-ups and MRI scans. The current scans are compared with the previous set(s) to confirm the tumor remains stable. The frequency of these check-ups can vary from every few months to every couple of years. Sample frequencies, subject to the doctor's adjustment, for stable tumors are:

Low-grade tumor: every 6 months
Benign: every year

Regular Surveillance

The regular surveillance approach is used as a matter of course when the individual is currently undergoing treatment or has recently completed a biopsy or surgery. In this case, the doctor will often assign a somewhat greater frequency until a number of consecutive check-ups indicate that the tumor is stable.

In the event that a scheduled checkup reveals the tumor is no longer stable, then treatment may be necessary. The doctor may recommend the start of some form of treatment if:

- It is evident (or strongly suspected) from the scans that the tumor is growing;
- Symptoms develop or worsen that degrade quality of life, e.g., headaches or seizures become uncontrollable.

Scheduling MRI Appointments

Especially after the initial MRIs, the days before any MRI and the time waiting for the results can be a period of extreme anxiety. It is recommended to schedule MRIs and doctor visits as close together as possible to reduce anxious waiting time.

Emotional Impact of Watch and Wait Approach

Being told that you have a brain tumor, but agreeing with the doctor's recommendation that no active treatment will be given until it shows growth can be very upsetting. Most people, when they hear they have a growth of any kind in their brain want it removed and it takes an adjustment just to go along with a Watch & Wait approach.

In addition, the time between appointments for monitoring what the tumor is doing (or not doing) can also seem (or be) long. The stress can be intense. People who have been put on Watch & Wait have told us about what they have found to help. These include:

- Learn more about your tumor to help you understand this tumor could be kept in check for a long time.
- Have the doctor explain more about the Watch & Wait approach and how far apart your appointments for check-ups will be so that you feel more in control.
- Learn more about available treatment options before you have to make any decisions about how you want to proceed. Having a Plan B will help relieve any anxiety over what you might expect.
- Ask your doctor about when you should call his/her office if you experience a new or changing symptom.
- Keep a notebook in which you can write any questions that you have for your next appointment. Write them down as they come to mind.
- Keep your own files of every appointment and what was discussed so that you can review them when you feel the need.
- Talk to your family and friends you know are caring and trustworthy about the risks and benefits and how you're feeling.

- Speak to others who are in the same situation. There is online support you can access to communicate with others who share the same types of concerns you have.
- Ask the doctor if there is a social worker or counselor you could access to talk things over if you feel overloaded emotionally.

Managing Symptoms and Side Effects

Coping with Cognitive Changes and Memory Difficulties

Our brain is our thinking tool. When a tumor damages the brain and treatments like surgery, radiation, and chemo assault it, our ability to remember and think clearly can be impacted. Memory and thinking are susceptible functions that rely on many parts of the brain, so it may not be possible to determine if the issue one is experiencing is related to the tumor or to treatment or is a combination of both.
Regardless of how they arise, memory and cognitive effects can be a frustrating and sometimes debilitating side effect. They may manifest themselves in a general mental fogginess or confusion, and in a slower than normal functioning of these sorts of skills:

Language (reduced ability to think of a word or name or recall a conversation or event);
Concentration/focus or ability to pay attention;
Ability to plan and organize;
Decision making;
Controlling impulses.

In addition to the impact of those functions, there also can be an effect called cognitive fatigue. When the brain is fending off a tumor, it is working very hard and the brain's ability to work at that level is limited. Individuals may signal a halt when their mental stamina reach a subjective limit. They may describe their condition as exhausted, "maxed out", drained or even burned out, or they may say nothing but simply reduce their activities or responsiveness to expectations. Cognitive fatigue is not always easily recognized because it can change from day to day and may be

impacted by needs for sleep, food, a shift in medications or even emotions. Generally, you may find that if you or your loved one have tasks to handle, they are best done earlier in the day, if possible.

Memory and cognitive issues may occur gradually over time. Once your recovery from surgery and radiation have concluded and your life begins to return to normal, you may notice some changes, or you may identify changes shortly after starting a new medication.

In addition to discussing these changes with your doctor, who may suggest a cognitive rehabilitation program or a change in your medications, there are some practical things you can do on a day-to-day basis to reduce the frustration associated with these changes:

Pace Yourself. Don't try to do too much and make sure you get regular sleep. Exhaustion does nothing to help a struggling memory.

Think When You're Fresh. Memory often works best when you feel at your best, which is typically earlier rather than later for most, so plan to do your heavy thinking tasks early.

Focus on One Thing. Trying to multi-task only overloads the brain's circuitry.

Stay organized. Do your best to keep essential and common use things in the same place (e.g., like your medications, house keys, TV remote, etc.).

Write Notes. Anyone with a slow memory will tell you they write lots of notes to help them remember things. Make "to-do" lists.

Timers and Alarm Clocks. Use timers and alarms to remind you when you have to do something.

Exercise. Talk to your doctor about starting (or continuing) with an exercise program. Exercise, done safely, can help you feel sharper and somewhat strengthen your memory and cognitive functioning.

Coping with Seizures

Overview

Between 20 and 50% of people diagnosed with a low grade brain tumor will experience some level of seizure activity and will require medical intervention. The nature and severity of these seizures will vary from person to person, depending on the region of the brain that is affected.

In some cases, a seizure will appear as something slight and quick — muscle or eye twitching, or a sense of being "out of the moment" mentally and/or physically for a brief time, or a blank stare or sudden pause without response. These are called focal seizures, which may present themselves prior to a more serious seizure later on, so even focal seizures should be discussed with your doctor. For others, seizures will involve full body activity, often categorized as grand mal seizures. Unprovoked recurrent seizures are a serious problem and can have a big impact on quality of life.

First Aid for Seizures

In the US, call 911 and get medical help to your house. (Certain people who routinely have seizures may not need a call for medical help, but if your loved one has a significant seizure, medical assistance is appropriate.)

Gently roll your loved one onto one side and put something soft under their head.

Loosen anything tight around their neck.

Don't put anything in their mouth — the tongue can't be swallowed, and objects placed in the mouth can be bitten or inhaled.

Don't try to restrain them - you'll only end up injuring them and/or yourself. Note how long the seizure lasts so that you can tell the doctor afterwards.

What To Do About Seizures

The first thing you should do is discuss any seizure with your doctor. Your doctor is able to prescribe anti-seizure drugs. There are many to select from and it may take some trial & error to find the drug that controls seizures effectively with the least amount of side effects.

Photo by Margo Singer

Safety is a serious concern. One of the major problems with seizures is the unpredictability of occurrence. It is a good idea to discuss the following precautions with your doctor if you experience or are at risk for seizures:

Working at heights/ climbing tall structures;

Driving;
Cooking using the oven or a fire;
Using heavy machinery and other power tools;
Taking a bath unsupervised;
Swimming unattended.

Your doctor may recommend that an Occupational Therapist visit your home to identify ways to improve safety in the event of a seizure. The University of Virginia Department of Neurology offers safety guidance, which can be accessed at this link:

https://med.virginia.edu/neurology/wp-content/uploads/sites/235/2015/11/patient-safety-in-adults.pdf

It is important to understand that although lifestyle changes and safety precautions are needed, one should avoid becoming too controlling and rigid.

Tips For How To Avoid Seizures

In addition to taking any anti-seizure medication prescribed by the doctor, here are some practical tips for avoiding seizure triggers:

Sleep: goal should be to achieve the number of hours recommended per night (e.g., 8 hours for adults). Need to pick a schedule and stick with it. Sleep deprivation or even changes in sleep schedules can trigger seizures. Sleep deprivation is a *huge* trigger. Not getting 8 hours of sleep doesn't immediately mean that you'll have a seizure that next day, but it can make you susceptible.

Limit Computer Time: Watch out about getting overly tired by working too much on a computer. An estimated 30% of seizures these days are triggered by people working on their computer. Too much. Get up, look away frequently, and limit time spent on the computer and similar electronic devices.

Stress. Goal is to avoid as much stress (e.g., emotional drama) as possible. Ideal would be to learn stress management and meditative techniques.

Avoid use of alcohol. Some people are fine with a glass or two of wine or maybe a cocktail, but some people cannot have any alcohol. Be reasonable and be guided by

the advice from your doctor.

Avoid drugs (other than the prescribed ones).

Avoid flashing lights or other visual stimulations, whether on TV or elsewhere. Avoid playing videos or computer games, especially those with flashing lights. Avoid even looking at the flashing lights on emergency vehicles or firework finales. Know also that some people can be triggered into a seizure by flashing lights with loud noises or music (e.g., sensory over-stimulation.)

Eat a healthy diet. There are studies that suggest that minimizing carbohydrates (e.g., avoiding gorging on junk food like potato chips) can reduce the risk.

Avoid getting overly heated. Saunas, Turkish baths, super-hot showers, Jacuzzis, etc. are not a good idea for those with brain tumors. The heat has been known to trigger a seizure.

Avoid overindulging in caffeine. This includes sodas, teas, coffees, and chocolates. Caffeine stimulates the central nervous system. For coffee, overindulging means consuming more than 2 to 4 cups per day (dependent on a person's size and prior typical consumption.) One of the triggers of seizures from caffeine is the interference with sleep, so you should avoid consuming so much caffeine in any form that have insomnia or become irritable and restless.

Thirteen

Survivorship and Long Term Care

Overview

Survivorship focuses on the health and well-being of a person from the moment of their cancer diagnosis. This includes the physical, mental, emotional, social, and financial effects of cancer through treatment and beyond. The survivorship experience includes issues related to follow-up care (including regular health and wellness checkups), late effects of treatment, cancer recurrence, second cancers, and quality of life. Family members, friends, and caregivers are also considered part of the survivorship.

Both benign and malignant brain tumors can potentially affect the overall quality of life of patients. The majority of patients diagnosed with a primary brain tumor will have significant impacts from their tumor. The table below illustrates some benign tumor types and their associated impacts.

TUMOR TYPE	IMPACTS
Vestibular schwannoma/acoustic neruroma	Hearing and balance problems
Meningioma	Headache, confusion, vision changes, hearing loss, seizures
Low-grade glioma (WHO grades I and II)	Headache, weakness, numbness, seizures, edema
Pituitary adenoma	Endocrine problems
Craniopharyngioma	Headache, loss of balance, vision, problems, increased thirst and urination, mood swings

Treatment of these brain tumors may consist of surgical resection and/or radiation treatment. Treatment-related effects may include deficits in cognition, mood changes, and a decline in mobility.

Phases of Adult Survivorship

Currently, three phases of survivorship exist: acute, extended, and permanent or long-term survivorship.

Acute survivorship is focused on cancer treatment and is initiated at diagnosis through the end of treatment.

Extended survivorship occurs after the end of treatment and focuses on the effects of treatment and follow-up care.

Permanent survivorship focuses on the years after cancer treatment has ended. It is important to note that in this phase the focus shifts from recurrence to the long-term effects of cancer and treatment.

Pediatric Survivorship

Many children diagnosed with and treated for certain low grade brain tumors become long term survivors. Because survivorship comes with numerous complex issues, including possible long-term effects of treatment and social and psychological concerns, having specialized support that focuses on the needs of such survivors and their parents to navigate life after a tumor can be a significant benefit. The field of pediatric brain tumor survivorship is much more developed; there are recently published guidelines and many of the top brain cancer clinics can offer such support. The range of services includes assistance for scheduling follow-up screening, education of patients and parents, specialist referrals as needed, and psychological and school-related counseling.

Survivorship Plan of Care and Treatment Options

Patients with extended life expectancy can benefit from survivorship-focused care. In particular, patients and their families can benefit mentally, emotionally, and physically by developing a plan to minimize negative symptoms associated with the malignancy and treatment. An optimized state of wellness can also be beneficial in

dealing with health-related challenges that may lie ahead.

In brain tumor survivors, symptoms are often clustered together, with fatigue, cognitive impairment, and depression being a common example making it essential to address symptoms holistically. Each symptom can interact with and magnify the others, and thus, optimal outcomes result from addressing all symptoms. A comprehensive survivorship plan can create a roadmap to wellness. Symptoms need to be systematically measured to determine symptom severity. Serial measurement will allow for tracking of progress. Frequent touchpoints in the survivorship journey create opportunities for readjustment and optimization of the plan if meaningful progress is not being demonstrated.

Treatment options are extensive and dependent on the presenting issue(s). Options include mindfulness and meditation training, yoga, social support, cognitive behavioral therapy, family/caregiver counseling, rehabilitation (e.g., vestibular rehab for balance, speech therapy or occupational therapy), hearing aids, sleep assessment and aids, physical activity, healthy nutrition, antidepressant medication, and anti-anxiety medication.

Role of Caregivers

Brain tumors and subsequent treatment often create neurocognitive deficits that may impact daily functional status. As such, caregivers may play a very important role in the patient's recovery and the needs of both the patient and the caregiver should be addressed during survivorship care.

The Musella Foundation can guide you through the consenting process and submission of your medical records, help you understand your treatment options, and facilitate access to those treatments through clinical trials and expanded access programs.

"Prehabilitation" for Low Grade Tumor Patients

Prehabilitation is a concept that is being applied more frequently in the care of low grade tumor patients. There is a cohort of patients that have an extended period of time between diagnosis and surgery. This period of time allows for optimization of health before surgical intervention. The goal of prehabilitation in the low grade

patient population is to identify health-related impairments for early intervention and to maximize health to improve treatment-related outcomes.

A majority of prehabilitation programs have been developed and studied by surgical oncology specialties with the focus of improving surgical outcomes. Comprehensive prehabilitation programs incorporate exercise, nutritional optimization, smoking cessation, and psychological support to relieve anxiety. Your neurosurgeon can discuss with you what prehabilitation needs you may have and refer you to the appropriate healthcare professionals to address your specific physical, emotional and nutritional requirements. Patients often appreciate the supportive environment that prehabilitation programs offer and feel empowered to participate in their care.

With the knowledge that survivorship starts at the time of diagnosis, collaboration with a prehabilitation program may be an optimal means in which to minimize treatment-related side effects later on. Research is currently lacking in the use of prehabilitation in the brain tumor population. However, these individuals may be well suited for this type of supportive service. Patients often undergo a 'Watch & Wait' period (as further described in the "Monitoring" section) before surgery, which provides an opportunity to focus on improving physical and mental wellness.

Nutrition

Attention to nutrition or dietary intake is an important part of survivorship care, with current guidelines supporting a plant-based diet that is composed mostly of vegetables and fruits (2.5 cups per day) and choosing whole grains over refined grains. Additionally, there should be limited intake of processed and red meats, refined sugars, and alcohol. All survivors are encouraged to achieve and maintain a normal body mass index (BMI). Adherence to these recommendations has been associated with an absolute risk reduction of death at 5 years in patients with certain types of cancer.

The Mediterranean diet and the Dietary Approaches to Stop Hypertension (DASH) diet are both plant-based diets, rich in fruits and vegetables and low in red and processed meats that are well known for their benefits on cardiovascular health. They have also been found to have positive effects on cancer mortality and risk of certain cancers, with the highest amount of evidence for colorectal cancer and breast cancer.

Less is known about the effects on brain tumor patients. A study in glioma patients showed that individuals with the greatest adherence to the DASH diet were 72% less likely to have a glioma compared with those with the lowest adherence. Intake of red meats and salt was positively associated with glioma, whereas consumption of nuts, legumes, and fruits were inversely associated with glioma. Fish intake has been associated with several types of cancer and is beneficial for brain development. A meta-analysis of nine observational studies in patients with brain cancer suggests that fish intake might be associated with a lower risk of brain cancer. In addition, in the glioma population, there has been interest in the ketogenic diet.

Residual treatment-related effects may affect a survivor's nutritional status including swallowing problems, nausea, dry mouth, altered taste and smell, loss of appetite, and cognitive challenges that may interfere with effective grocery shopping and cooking. Evaluation by an oncology-certified dietician can be helpful in creating a patient-centered plan with appropriate goal setting.

Food Styling by Andy Singer

Natural Treatments/ Supplements

With regard to dietary supplements, the NCCN finds that there is currently no clear evidence that they are effective for cancer prevention, control, or recurrence, and

nutrients should be acquired from food over supplements.

Brain tumors do not materialize overnight. They could have been developing since embryonic times and gaining more DNA mutations to develop across time. Not only that, but the brain tumor is the product of many factors including immune system dysfunction, exposures to toxic substances, diet, level of inflammation, other genetics, stress, and other things all coming together. Despite that, after a diagnosis almost everyone rushes to find the natural supplements with the intent of undoing all those years of complex, interlocked factors. You may decide to do the same and there is much to be said about being an empowered patient or caregiver, which may include the use of supplements to aid in dealing with the side effects of treatment. However, just be aware that some supplements can interfere with medical treatment.

For example: Most radiation oncologists do not allow patients to take any supplements of any kind during radiation treatment because it can inadvertently reverse the beneficial effects of treatment.

Researchers have found that patients using probiotic supplements were 70 percent less likely to respond to anti-PD-1 checkpoint inhibitors - a type of immunotherapy. It was discovered that the greater the bacterial diversity in the gut, the more the person responds to immunotherapy. Most probiotic pills add billions of only certain selected bacteria into the system, decreasing that diversity. So, the immunotherapy does not work as well. (On the other hand, patients who ate a high-fiber diet were five times more likely to respond to immunotherapy treatment with anti-PD-1 checkpoint inhibitors.)

> It is important that you check with the doctor on the appropriateness of using any natural treatment or supplement, and if it is permissible, what dosage the doctor views as appropriate before buying or using any such products.

Exercise

NCCN Guidelines recommend cancer survivors participate in at least 150–300 minutes of moderate-intensity activity or 75 minutes of vigorous-intensity activity per week, along with 2–3 sessions of strength/resistance training per week. Randomized trials have shown exercise to be safe, tolerable, and effective for most cancer survi-

Food Styling by Andy Singer

vors, with positive effects on fatigue, emotional well-being, balance, and quality of life.

Additionally, many studies have shown a decrease in overall mortality and cancer recurrence. However, many of these studies have focused on survivors of breast cancer and Hodgkin's lymphoma, with very limited studies done in brain tumor patients. Currently, no specific exercise guidelines exist for neuro-oncology patients. This is especially concerning since brain tumor patients may have increased levels of fatigue, memory impairment, and balance issues as compared with the general cancer survivor population.

Capozzi et al. performed a feasibility study in which 24 patients with a diagnosis of brain cancer participated in a 12-week exercise program. Participants exercised weekly in a group setting with other brain cancer patients, focusing on both aerobic exercise and resistance training. Patients were also given an at-home exercise program that was done an additional 2 times per week. Improvements in total grip

strength, sit-to-stand test, and waist circumference were noted, along with decreased tiredness, depression, drowsiness, and concern with well-being. However, the lack of a control or comparison group, along with a small sample size, highlights the importance of further research in this population.

While these studies provide promise for the benefits of exercise in survivors of brain tumors, further research is clearly needed in this population. It is recommended that patients at increased risk of falls, due to balance concerns, peripheral neuropathy, or other neurologic deficits, be evaluated by an exercise physiologist and participate in a supervised exercise program.

Neurological Considerations for Low Grade Meningioma Patients

The goal in management of "benign" or low-grade primary brain tumors is survival without cognitive or behavioral dysfunction. Tumor location does matter in terms of specific cognitive and behavioral symptom outcomes.

Skull-based meningiomas as compared with convexity meningiomas are more likely to cause significant impairment in verbal memory, information processing capacity, and psychomotor speed, but both skull-based and convexity meningiomas lead to general impairments in executive dysfunction and working memory. This difference may be due to the proximity of skull-based meningiomas to the memory hub, the hippocampus, while convexity meningiomas tend to occur near white matter tracts underlying executive functions.

Of particular importance for return to work, family relationships, and social engagement, are the behavioral and personality changes that may result from tumors and their treatment. Anterior skull base meningiomas frequently lead to alterations in personality and behavior due to their location near the ventromedial cortex.

Primary Care

A large percentage of brain tumors patients either do not have a primary care physician or feel that their primary care physicians were not well-versed in the long-term effects of their tumor treatment. A goal of any good survivorship plan should include

support from a family medicine physician, ideally one with additional training and experience in cancer survivorship, who can treat minor conditions and make direct referrals as required for needed non-oncology medical services.

Coping Emotionally

Individuals with a low grade brain tumor often experience emotional and social effects after their diagnosis. This may include dealing with a variety of emotions, such as uncomfortable changes to their self-image, sadness, anxiety about the future, fear, or anger. Sometimes, people find it difficult to express how they feel to their loved ones. Some have found that enlisting the support of a social worker, counselor, or member of the clergy can help them develop more effective ways of coping with their diagnosis.

It is recommended that patients, caregivers, as well as families and friends avoid "doomscrolling" – going online to read a lot of horrific things about brain tumors and their prognoses. Not every patient fits into the same bucket, each tumor is uniquely constructed and each tumor is going to respond differently to treatment. There's no guarantee, but we do know that with the proper medical support a significant numbers of patients are able to achieve long-term survival with good quality of life.

Being diagnosed with a brain tumor can be stressful for you and your caregiver. Practicing mindfulness and relaxation techniques can help calm your mind, reduce stress and help sharpen your mental focus. Practicing mindfulness involves controlled breathing methods, guided imagery, and other practices to relax the body and mind and help reduce stress. Some of the steps you can take are:

1. Slow down and breathe, then take a deep breath.
2. Remind yourself that your thoughts are "just thoughts." Thoughts come and go. We all have thoughts but having a thought doesn't mean that it's true or that it will last forever.
3. Take another deep breath and move on with your day.
4. Take some time to do something that you enjoy, like a hobby, going for a walk, taking a warm bath, calling a friend, going to a movie, or playing with a child or a pet. Give yourself the gift of thinking about something else other than the tumor.

For those who may prefer a guided mindfulness exercise, the University of Utah has published this video entitled "Leaves on a Stress" available at this link:

https://www.youtube.com/watch?app=desktop&v=x4Zt1ZBzMps

Rehabilitation and Long Term Care

Many low grade brain tumor survivors face physical, psychological, social, and intellectual challenges related to their tumor and its treatment and will require ongoing assessment and specialized care. Long-term health care and social services for individuals and families of low grade brain tumors are often required. Such services may need to include:

- Periodic, scheduled MRI scans to monitor for tumor recurrences;
- Intellectual function evaluation;
- Endocrine evaluation and treatment;
- Neurologic assessment;
- Psychosocial care;
- Hearing, vision monitoring;
- Ovarian dysfunction evaluation and treatment;
- Motor function evaluation and physical therapy;
- Complementary medicine.

Pediatric Considerations in Long Term Care

As a result of treatment, children may experience changes in intellectual and motor function. They may need certain individualized services, such as those listed above, to ease children's return to school and maximize their ability to learn. Families may need ongoing education to stay abreast of developments in long term care.

Supportive Care and Resources

Caregiving for Someone with a Low Grade Tumor

Although those with many types of low grade tumors are only rarely cured, many people with such tumors are able to work, attend school, and perform other tasks for a number of years and need little or no caregiving by another person.

In certain cases, such as a Grade 2 glioma, the tumor may recur requiring additional treatment; it may even advance to a higher grade level resulting in assistance by a caregiver. In addition to physical changes, such patients may experience changes in mood, personality, and thinking. As a result, caregiving by a loved one or family member may be challenging.

Caregiving (when required) often includes a variety of responsibilities. Planning for your role as a caregiver will help you take good care of your loved one and support your own health and wellbeing. These steps can make the task more manageable:

- Learn as much as you can about your loved one's diagnosis, treatment options, and chance of recovery. Even though low grade tumors tend to change very gradually, you will need to stay up to date on a continuous basis because as the disease and its treatment changes, so will your role.

- Get to know your loved one's health care team. If possible, request a meeting with the team. Ask for clear, accurate information about the illness and treatment. Also, learn what each professional on the team does.

- Ask the health care team about the medical, financial, and coping resources available to you and your loved one.

- Ask family and friends for help. Figure out what tasks need to be done and organize a network of people to help you. Some people create an email list, text chain, or web page. There are also websites available to make this process easier at this link:

- https://www.cancer.net/coping-with-cancer/finding-social-support-and-information/online-communities-support

- Learn how to provide routine, day-to-day care. Ask your loved one's health care team for details on the best ways. This may include bathing, dressing, and giving meals. Also ask how to provide basic medical care that may be needed, such as wound care.

- Consider professional caregivers if the load becomes overwhelming. Medical

Photo by Margo Singer

professionals can help with medical care that you are not comfortable doing. Home care aids can help with everyday caregiving tasks, such as grooming and cooking. Your loved one's health insurance may pay for these services.

- Explore community resources. Many communities have available resources for caregivers. These include case management, legal aid, financial assistance, and counseling. Ask your loved one's health care team for local referrals.

- Stay organized. Please see the suggestions in the section above entitled "First Things After Diagnosis - Getting Organized" for how to keep track of important information that will enable it to be available when you need it.

Caregivers Fatigue

At times it can be quite a challenge when one is providing care day after day without sufficient breaks, and this can lead to a syndrome called caregiver's fatigue. This can manifest itself in some of the following ways:

Physical symptoms
Sleep is no longer regular; routinely fail to get at least seven hours undisturbed sleep per night;
Feeling ill; getting sick more frequently;
Lack of energy;
Change in eating patterns/appetite;
Stomach/digestive issues;
Losing weight or hair;
Having back problems.

Emotional symptoms
Feeling edgy, irritable, argumentative, or losing your temper more often, even with the loved one you are caring for; displaying episodes of rage (e.g., yelling at other drivers);
Experiencing crying spells;
Feeling sad or depressed much of the time or having mood swings;
Having a sense of anxiety and hopelessness about the future;
Having a sense of loneliness;
Feeling overwhelmed; want to just curl up into a ball and cry;

Experiencing a decline in your prior level of concern.

Psychological symptoms
Withdrawal from family and friends; not seeking or accepting offers of help;
Not feeling satisfied with support from family and friends;
Not taking, or not having, at least 15-20 minutes of personal time each day;
Neglecting your own needs;
Feeling like caregiving is running a bulldozer over your life;
Looking for the exit (even to the point of wishing your loved one would perish sooner);
Feeling strained in balancing work and caregiver responsibilities;
Displaying more forgetfulness than before;
Experiencing more difficulty in concentrating or making decisions (e.g., inability to plan meals, sometimes even when they are sorely needed);
Needing prescription drugs, alcohol or more coffee, cigarettes, or other substances to make it through the day.

First Aid for Caregiver's Fatigue

If you recognize that you are showing signs of caregiver's fatigue, it might be time to apply some caregiver First Aid. Your first aid kit includes:

Ask for help. Do not try to be a hero. Acknowledge you cannot do it alone and recruit people to help you, even if you have to force yourself. Make a list of daily activities and tasks. See if you can delegate any of it. Work hard to delegate parts of your work. Brain cancer takes a village.

Give yourself permission to take breaks. Get out of the house. Visit with friends. Pamper yourself with a long bath. Of course, this means others have to step in to watch your loved one while you are on R&R.

Take care of yourself. Exercise; meditate/pray; eat well; don't sacrifice sleep; take your vitamins; get yourself to your doctor and dentist for regular check-ups or to address any issues. Do not let some urinary tract infection linger until you pee blood or let that back problem get worse.

Journal about your struggles and feelings for a few minutes every day. It helps to

get it out. Do a Journal online. Others will read your struggles and be inspired by them or maybe have ideas for you that could lessen your load.

Practice Gratitude. At the end of each day, take a few minutes to write down 3 to 5 things for which you are grateful. If this sounds like a silly waste of time you don't have, don't give in to that thought. This simple, quick step can make a huge difference in your attitude. It literally changes your brain's chemistry to more positive and more energetic thinking.

Work/Life Balance. If you are still working, check into family-leave benefits from your place of work. If available, this might be able to open up your schedule considerably and give you some breathing room.
Share. Keep sharing your frustrations with other caregivers. Communicating with them will remind you that you are not alone and that there really are people who understand what you are going through.

Mind, Body, Soul: Faith In Healing And Emotional Wellness

While your primary physician may appear anything but spiritual in his or her approach to your brain tumor, some within the medical community are aware, and in support of, the power of prayer. Prayer, while very personal, may be empowering and proactive at times when "control" seems out of reach.

Also do not neglect the rest of your body. When facing a major problem like a brain tumor, the smaller problems sometimes get overlooked. You have enough problems to handle without having a "minor" problem blossom into a "major" problem. Be especially mindful of swelling and/or pain in the legs (which may indicate blood clots, unfortunately common with brain tumors), dental problems (some treatments may hurt the gums and teeth), and rashes (indicating allergic reactions to treatments).

Your life, as you once knew it, may change throughout the journey. Things may not seem normal, but there will be a new "normal" for you and your family. The new normal will be what you and your family make it. It will take time, but you will settle into a routine that is comfortable for you. As with anything that is lost, you will

go through a grieving process. Although everyone experiences grief and loss differently, you will probably experience some of the universal steps in this process, which may include shock, denial, anger, depression, and acceptance.

How you work through this process will be highly personal and individual. As you work through each step, you will probably have some additional feelings that may at times present conflicts for you. These emotions are many and can be unpredictable. Neither right nor wrong, they just are, and you are entitled to feel the way you do. They may include feelings of loneliness, sorrow, anger, sadness, blame, or shame, which may lead to anxiety and stress. Sometimes you will feel helpless.

To combat such emotions, concentrate on wellness and try to work through each of the feelings rather than denying them. Have a set of coping strategies that will guide you through each step. These strategies may include: (1) accept and understand your limitations, and set realistic goals; (2) get as much up-to-date expert information about your condition as you possibly can so you don't fear the unknown, and be proactive in your treatment plan; (3) take good care of yourself by eating well, getting exercise and rest, and not self-medicating with alcohol; (4) see a mental health provider if you feel it necessary, as he or she can help you handle your emotions and stress; (5) record your feelings in a journal; and (6) try exercise, yoga, massage therapy, and/or meditation.

Accessing Support Networks and Patient Advocacy Groups

Table 1: Organizations that can provide support for caregivers

Organization	Website
Musella Foundation for Brain Tumor Research & Information	https://forum.virtualtrials.org
Clinical Trials & Noteworthy Treatments For Brain Tumors	https://www.facebook.com/groups/13657508258
Novocure, Optune Support For Glioblastoma	https://www.facebook.com/groups/347097922150691
Glioblastoma - GBM SURVIVORS TO THRIVERS!	https://www.facebook.com/groups/197153540892173
Surviving Glioblastoma (GBM)	https://www.facebook.com/groups/353827365003
American Brain Tumor Association	http://www.abta.org/
American Cancer Society Cancer Survivors Network (for Brain Cancer)	https://csn.cancer.org/forum/165
National Brain Tumor Society (NBTS) Support Groups	https://braintumor.org/support-services/support-groups/
Smart Patients Brain Tumor Community	https://www.smartpatients.com/communities/brain-tumor

Financial and Legal Considerations

The Costs Of Cancer Care

Even with insurance coverage, cancer care can be expensive and result in financial hardship. Many people have insurance plans with yearly deductibles, specified amounts of expenses they must pay out of pocket each year before the insurance plan will begin paying any costs. After the yearly deductible is met, insurance plans also often require co-insurance payments. For example, with a typical 80/20 coinsurance rate, the insurance plan will pay 80% of approved medical costs while the patients must pay the remaining 20% of medical costs out of pocket. Finally, many insurance plans require co-payments. A co-payment is a set fee, like $30, that an insurance plan requires the patient to pay out of pocket each time the patient visits a physician.

Consequently, considering deductibles, co-insurance payments, and copayments, the amount of out-of-pocket costs for direct medical care — visits to physicians, surgery, radiation therapy, chemotherapy — can add up to a considerable amount even for patients with excellent insurance plans. But in addition to direct medical costs, there are also many nonmedical expenses associated with cancer treatment. These include transportation, hotels, meals, and childcare.

The Centers for Disease Control (CDC) determined in 2021 that out-of-pocket costs per person for medical services were highest in the initial and end-of life phases of care for brain cancer, among a few other cancers.

The investigators found that the monthly median out-of-pocket expense for these patients was nearly $2000 (remember, the median is the middle value in a set of measurements, with half the values above that middle value and half below). Within that monthly median out-of-pocket amount, the highest components were payments for medication ($710), hospital bills ($403), and transportation ($327). These expenses decreased after 3 months, suggesting that expenses were reduced after the completion of radiation therapy. The investigators also found that median lost wages were $7500, and that median lost work time was 12.8 days.

The American Society of Clinical Oncology sponsors a website for patients called Cancer.net. This website has an excellent section on financial considerations related to cancer care, including a video presentation. Especially relevant is the page entitled "Questions to Ask About Cost." Go to: https://www.cancer.net/navigating-cancer-care/financial-considerations.

Financial Assistance

There are many organizations and even individuals that provide financial assistance to patients with brain tumors and their families. Miles for Hope, for example, provides flight assistance to those participating in clinical trial treatment. Other organizations might not provide direct help with expenses but can help reduce the costs associated with medical care. Angel Flight was created by a group of volunteer pilots to provide for free air transportation for medically related needs when time is important, but the trip is not an emergency. The organization called Mission4Maureen has funds to cover an array of expenses, from travel for treatment, to maintaining a place to live, to paying medical bills not covered by insurance.

If a low grade tumor progresses to a high grade tumor, the Musella Foundation may provide (subject to available funds) co-pay assistance program for people with health insurance for one or more of the following treatments: Avastin, Lomustine (aka CCNU or Gleostine), Temodar, and the Novocure Optune device. To find out about this program, go to: https://braintumorcopays.org.

For people without insurance, we have a Musella Foundation Drug Discount Card that can save everyone — not just patients with brain tumors — up to 80% or more off the cost of prescription medicines, over-the-counter medicines (that is, medicines not needing a prescription), and even prescription medicines for pets. There is no cost for the card, there is no risk in using it, and it is immediately available online, with no registration required. You take the card to your pharmacy and ask how much the prescription would cost using this card compared with how much it would cost without it. If using the card is less expensive for the prescription, then use it.

The Musella Foundation Drug Discount Card can also be used by patients who have insurance, but you cannot combine the discount this card provides with the discount your insurance provides. Sometimes the card discount will be greater than your insurance discount.

The Musella Foundation provides a Musella Foundation Drug Discount Card for all patients, but especially those patients without insurance. To get the card immediately, go to: https://virtualtrials.org/Drug_Discount_Card.cfm

Table 2 below provides a list of some of the organizations that can help you. As a reminder, if you receive Medicare or Medicaid benefits from the US Centers for Medicare & Medicaid services, you can also contact those agencies directly for help paying some of your health care and prescription drug costs. For Medicare call 1-800-Medicare (1-800-633-4227).

Photo by Margo Singer

Table 2: Organizations that can provide financial advice and support

Organization	Website	Description
• **Angel Flight Travel Assistance**	• **www.angelflight.com**	• Arranges free air transportation for any legitimate, charitable, medically related need
• **CancerCare**	• **www.cancercare.org**	• Offers financial assistance for cancer-related costs and co-pays, and professional oncology social workers can help guide to additional resources
• **Darren Daulton Foundation**	• **www.darrendaultonfoundation.org**	• Provides financial assistance to those who suffer from brain cancer, brain tumors, and brain injuries
• **Drug Assistance Programs from Pharmaceutical Companies**	• **www.cancersupportivecare.com drug_assistance.html**	• Lists pharmaceutical company programs intended to facilitate access to needed medications for patients who have financial difficulties and are not eligible for Medicare, Medicaid, or private insurance
• **Glenn Garcelon Foundation**	• **www.glenngarcelonfoundation.org**	• Gives grants to people with primary brain tumor of any type (malignant or non-malignant)
• **Medicare Rights Center**	• **www.medicarerights.org**	• Ensures access to affordable health care for older adults and people with disabilities
• **Mission for Maureen Travel Assistance**	• **www.mission4maureen.org**	• Provides financial assistance to families burdened with the cost of brain cancer treatment. Financial aid is available for medical bills as well as child care, housing payments, utility bills, transportation, medication and other areas of assistance
• **NeedyMeds**	• **www.needymeds.org**	• Maintains website of programs that help people who cannot afford medications and healthcare costs and provides a free drug discount card
• **Patient Advocate Foundation**	• **www.copays.org**	• Provides financial assistance to patients, including those insured through plans like Medicare, for co-payments, co-insurance and deductibles required by a patient's insurer

Social Security (When Unable to Work)

If, as a result of a brain tumor diagnosis and treatment, you can no longer work, either temporarily or permanently, you may be entitled to Social Security benefits.

These benefits may be Social Security Disability Insurance (SSDI) and/or Supplemental Security Income (SSI).

There is a confidential online tool provided by Social Security that would be able to tell you what benefits you may be eligible for. You can access that tool at the link below. You just answer their questions about your situation and the tool will tell you what benefits may apply:

https://ssabest.benefits.gov

If a person has earned enough, they may qualify for SSDI, but if they do not have sufficient credits for SSDI, they can still apply for SSI. SSI is not dependent on any earnings history.

You can apply online or by phone. You should know that there is a 5-month waiting period before benefits will start, so you should apply as soon as they realize they cannot work.

It is not required but may speed up the process if you ask the doctor for a letter with the diagnosis to give to Social Security. When Social Security has a doctor's letter with the diagnosis specifically stated, the process seems to be given maximum attention.

You can begin the application with Social Security on-line at this link: https://www.ssa.gov/applyfordisability/

OR…. you can start the application process by phone. To do that, you would call 1-800-772-1213. Someone from Social Security will then follow up with a call to complete the application process.

Benefits for Children of Disabled Parent

As soon as your Social Security benefit is approved, if you have children at home, you should apply for benefits for them. Once you are approved, your children under age 18 (or 19 if still in high school) are eligible for benefits as children of a disabled parent.

Crowd Funding

Some individuals elect to obtain the funds they need to cover the expenses they incur for brain cancer treatment (e.g., travel to major brain cancer clinic, cost of drugs not covered by insurance).

It is advisable that prior to proceeding, you consider the taxable nature of any funds you might obtain. While some of these sites state that the money provided through their organization are "gifts" and are, therefore, not taxable, this declaration is not binding on the US Internal Revenue Service (IRS).

Crowd funding organizations usually send recipients 1099-Ks if the fund-raising campaign raised more than $20,000 and had more than 200 donors, which may then attract the scrutiny of the IRS. The proceeds may end up being deemed to be taxable income, so you might want to get competent tax advice before proceeding.

Legal Matters

Overview

It is important to have certain legal documents in place to protect you, your privacy, and your loved ones, and some of these documents you have been intending to put in place, but they were not a priority at the time. Now they are.

The first time you are admitted to a hospital, you will be asked if you have an Advanced Directive or a Medical Power of Attorney. Most people don't. If the hospital offers to help you put some of these documents in place, do it and ask for copies and keep them in your binder.

Other ways of getting these documents in place is to access document drafts online

for your specific locale (each State has different laws and forms). You may talk to a lawyer or the doctor's/hospital's social worker about how to get these documents in place.

If you do already have the documents in place of most concern to hospitals and doctors, bring them with you, and the staff will make copies for your files and return the originals to you.

Documents to Have in Place

Other than your Will, financial beneficiary statements, and Financial Power of Attorney, medical service providers will want to see all the rest of these documents:

Last Will and Testament. Make sure your Will is current.

Financial Beneficiary Statements. Make sure you have a current designated beneficiary on any 401(k), IRA and life insurance policy. The Will does NOT govern these. If your beneficiary is still the friend you started a rock band with years ago in your garage, that friend will get the 401(k) or life insurance proceeds no matter what the Will says. Remember that accounts like 401(k)s, IRAs, and annuities can often just be re-named in the event of a passing so that someone inheriting those accounts might be able to minimize or avoid paying taxes on the amounts until withdrawn.

Durable Medical Power of Attorney. You should execute a Durable Medical Power of Attorney (Medical POA) so that someone you trust can make medical decisions in case you are not capable of making those decisions for yourself. (A power of attorney that is "durable" refers to the fact that the POA will remain in effect for your lifetime unless you revoke it, which you always can.)

It is very important to tell your family who you have designated to be your medical power of attorney and to tell them what your values are and what kinds of medical treatment you would want or not want, including breathing machines and feeding tubes, if your condition were to worsen and you were unable to communicate or were in a coma.

Another reason for the Medical POA is that many doctors' offices, MRI centers, etc., will not let a family member fill out the medical history or other pre-procedure

forms unless they are the designated Medical POA.

HIPAA Disclosure. In order to have enough information about your condition to be able to make good decisions under a Medical POA, whoever you designate under that Medical POA should be designated under a HIPAA disclosure.

Every doctor who treats you will ask you to sign a HIPAA privacy form indicating who you allow to know and discuss details of your case with that doctor (or facility). You will need to list each person by name (e.g., your spouse, parents, children and maybe a friend.) Ask for a copy of the completed form, as the original will be kept by the physician in each case. Having the copy of the executed HIPAA form will help save time when you need to send someone to pick up reports or films or to ask questions for you. When medical personnel tell you they cannot give your children something for you or talk about something to anyone other than you, having the copy of the HIPAA form available for them to see will enable them to meet your request without delay.

Advance Directive. You need to express how you want things handled if things get tough. Basically, an Advance Directive and Palliative Care counseling are needed. We all hate to think about these things, but it can save a lot of trouble later if you handle this now. An advance directive, also called a living will, tells your medical team what kind of care you would like to have if you become unable to make medical decisions for yourself. Such decisions include:

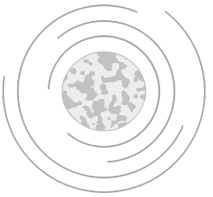
- Do you want to be resuscitated?
- Do you want aggressive treatment like ventilation and intubation?
- Do you want tube or intravenous feeding?

If this very tough and delicate conversation is too much to take on by yourself, it can be facilitated by a social worker or other person experienced in handling these discussions with perhaps the support of clergy, if needed. The person designed under the Medical POA should be present to hear the responses so that he/she can execute your wishes.

> Best rule of thumb: Palliative Care Counseling should occur so promptly after diagnosis that you feel like it is a waste of time.

Durable Financial Power of Attorney designates a person of your choice to manage your finances if you become incapacitated and are unable to make financial decisions for yourself. Your financial power of attorney document should not contain any medical directives, which are covered in your Medical POA document. Standard Durable Financial Power of Attorney forms are available online or through an attorney. They are straightforward and easy to complete. If you have special circumstances, you may wish to consult with an attorney.

Please be aware that companies like cable TV, electricity, gas (for cooking/heating), water, etc. will not even speak to anyone else if those accounts are in your name - even if they are told you are in the ICU. You should consider either getting those accounts transferred or make sure you have a Durable Financial Power of Attorney in case you become unable to do whatever is necessary under those accounts.



Promising Research and Advances in Low-Grade Gliomas

Research Initiatives and Treatment Breakthroughs

CHARM

A new tool, called CHARM for "Cryosection Histopathology Assessment and Review Machine", developed by researchers at Harvard Medical School uses artificial intelligence (AI) to determine the molecular profile of a patient's brain tumor during surgery. The advance can help neurosurgeons know how much tissue to remove during surgery or whether to place tumor-killing drugs directly in the brain while the patient is still on the operating table.

At present, even state-of-the-art clinical practice cannot profile tumors molecularly during surgery. The CHARM tool overcomes this challenge by extracting thus-far untapped biomedical signals from frozen pathology slides. This advance is important as neurosurgeons want to have as much information as possible during tumor resection to remove the right amount of brain tissue. Removing too much can affect a patient's neurologic and brain function, while removing too little may allow the cancer to grow and spread. The ability to determine intraoperative molecular diagnosis in real time, during surgery, can propel the development of real-time precision oncology.

Bionaut

Bionaut Labs is developing a tiny micro-robot smaller than a grain of rice that is guided through a patient's central nervous system into a targeted spot in the brain where it can perform minor surgery, deliver therapeutic drugs, or return with tissue for a biopsy.

The Bionaut can release a payload of targeted therapy directly into a tumor– even deep inside the brain – and head for home. Each tiny Bionaut contains a powerful magnet that allows it to be remotely controlled from outside the body. The patient has an MRI or CT scan, which the physician uses to plan the safest route to the affected area and then loads the route onto a computer. The patient is sedated and the Bionaut is injected into the central nervous system at the entry point worked out in advance. Then the computer takes over, guiding the probe to its destination while causing the least possible damage to surrounding tissue as the physician monitors its progress via x-ray.

Because low grade tumors are often smaller than high grade tumors, this development may have broader application for those with low grade tumors.

The company is testing its technology at a Mayo Clinic facility and is poised to begin clinical trials with five top-tier US medical centers as it applies for FDA approval. The company is in discussions with the FDA to begin clinical trials within the next year.

Voranigo (vorasidenib)

Voranigo has been approved by the FDA for the treatment of adult and pediatric patients 12 years and older. Voranigo targets a mutation in the IDH genes, which are present in 80% of low-grade gliomas. IDH-mutant gliomas make up about 20% of diffuse gliomas in adults, by far the most common malignant primary brain tumors. The latest research suggests that Voranigo can delay the progression of some low-grade gliomas with IDH1 or IDH2 mutations and postpone the need for additional therapies. Voranigo, a tablet that patients take by mouth, blocks the activity of abnormal IDH1 and IDH2 proteins in cancer cells, largely sparing healthy cells. Unlike other drugs that target mutant IDH proteins, this one can cross the blood-

brain barrier.

In the international clinical trial, called INDIGO, patients with Grade 2 gliomas and IDH1 or IDH2 mutations who received Voranigo lived much longer without the disease worsening than participants who received a placebo, researchers reported at the American Society of Clinical Oncology (ASCO) annual meeting in Chicago. The median time until the disease worsened or death from any cause—a measure called progression-free survival—was estimated to be 27.7 months for people in the Voranigo group versus 11.1 months for those in the placebo group, the researchers found. The results were concurrently published in the New England Journal of Medicine June 2023.

The FDA approved Voranigo for the treatment of low-grade astrocytomas and oligodendrogliomas.

Tovorafenib ("Ojemda" or "Day One")

Investigators observed fast onset responses with tovorafenib in the treatment of pediatric patients with heavily pre-treated low grade gliomas, according to findings from the Phase 2 FIREFLY study. According to the most recent analysis of that trial, Ojemda shrank tumors in 51% of the 77 patients who received the drug, with responses lasting a median of 13.8 months. Individuals aged 6 months to 25 years were enrolled in the study. Results were presented at the 2023 American Society of Clinical Oncology (ASCO) Annual Meeting. In April 2024, the US Food and Drug Administration (FDA) granted an Accelerated Approval of this drug; if a further trial confirms the anticipated clinical benefit, the FDA is expected to provide its full approval.

Tovorafenib is an oral, selective, central nervous system–penetrant, type II RAF inhibitor with activity against monomeric and dimeric forms of RAS signaling. Unlike type I BRAF inhibitors, tovorafenib does not lead to paradoxical activation of the MAPK pathway. Tumor response occurred independent of histologic subtype, BRAF alteration type, number of prior lines of therapy, or prior MAPK inhibitor use.

This drug can be administered in tablet form and as an oral suspension with once a week dosing.

Dabrafenib (Tafinlar) and trametinib (Mekinist)

On March 16, 2023, the U.S. Food and Drug Administration approved a new treatment combination that will now be available as an option for pediatric patients 1 year of age and older with low-grade glioma (LGG, grade 1 or 2) that have a mutation called BRAF V600E. This marks the first FDA approval of a treatment option for patients of this age group with LGG that have this mutation, including gangliogliomas, pleomorphic xanthroastrocytoma (PXA), as well as certain other astrocytomas and oligodendrogliomas.

The drug combination, Dabrafenib (Tafinlar, Novartis) and trametinib (Mekinist, Novartis), has also been approved in new oral formulations for patients who cannot swallow pills, which is critical for this population. In June 2022, the FDA approved the combination of these same oral drugs for treatment of both adult and pediatric (older than 6 years of age) patients with high- and low-grade gliomas with the BRAF V600E mutation.

Ivosidenib (Tibsovo)

Over the last decade, there has been a strong interest in targeting these mutations in both hematologic malignancies and solid tumors, including gliomas. This has led to the US FDA's approval of Ivosidenib (AG-120, an IDH-1 inhibitor) for adult patients with acute myeloid leukemia. Ongoing trials are investigating the role of IDH inhibitors in solid tumors, including gliomas. Certain of those trials involve Ivosidenib.

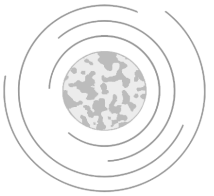
Ivosidenib is a targeted, potent, oral inhibitor of the mutant IDH-1 protein. In a Phase I, perioperative study of Ivosidenib and Vorasidenib (described above) in recurrent IDH-1-mutant, low-grade glioma, both drugs demonstrated central nervous system penetration and lowered 2-Hydroxyglutarate level >90% in tumor tissue compared with untreated samples. Ivosidenib and Vorasidenib showed a manageable safety profile.

LOGLIO

Since the survival time for patients with a low grade glioma is generally longer than for patients with high grade glioma, much of the funding for glioma treatment

research has focused on high grade tumors, resulting in a slower pace of research for low grade tumors. The Loglio consortium, a coalition of investigators dedicated to improving diagnosis and treatment for lower grade glioma, was formed by philanthropists Ashley and Alan Dabbiere in order to connect brain tumor researchers all over the US to tackle the problem of low grade glioma research in collaborative groups. Loglio provides funding for novel, high-risk research that may not be eligible for traditional funding mechanisms. Successful preliminary results from Loglio studies have been leveraged into nearly $39 million of additional funding for low grade glioma research from the National Institutes of Health and other funding sources.

Photo by Margo Singer



Glossary of Terms and Abbreviations

Below you will find the definitions of selected terms and abbreviations used in this Guidebook or that is it expected you will encounter with your doctors.

Access to the complete Dictionary of Cancer Terms is available at the National Cancer Institute website: www.cancer.gov/dictionary.

Alkylating agent: a type of drug (i.e., chemotherapy) that interferes with the DNA of cancer cells, thereby inhibiting their growth.

Anaplastic: An adjective denoting a tumor as cancerous; a term used to describe cancer cells that divide rapidly and have little or no resemblance to normal cells.

Antibiotic: A drug used to treat infections caused by bacteria.

Antimicrobial: A drug used to prevent or treat infections caused by a variety of organisms such as bacteria, fungi, or viruses.

Aphasia: A loss or impairment in using words or comprehending what other people are saying.

ASCO: American Society for Clinical Oncology, a US national organization.

Astrocytoma: A tumor that begins in the brain or spinal cord in astrocytes.

Avastin: See Bevacizumab

BBB: Blood-Brain Barrier: A network of tissues and blood vessels that helps keep harmful substances from reaching the brain. The BBB can also decrease the ability of certain treatments from getting to the brain, hence the research into nanoparticles.

BCNU: The brand name for the chemo Carmustine.

Bevacizumab: A drug used alone or with other drugs to treat certain types of cervical, colorectal, lung, and kidney cancer, and glioblastoma. It is used under the brand name Avastin to treat these cancers. Bevacizumab binds to a protein called vascular endothelial growth factor (VEGF). This may prevent the growth of new blood vessels that tumors need to grow.

Biopsy: The removal of cells or tissue to allow for evaluation by a pathologist.

CBC: Complete Blood Count. The CBC test evaluates the quantity of red blood cells, various white blood cells, and platelets.

CCNU: Another name for the chemo called Lomustine or Gleostine.

Centimeter or “cm”: A unit of measure. There are 2.54 centimeters in one inch; said another one, there are .3937 inches in one centimeter. For example, a tumor with a length of 5cms would, therefore be about 1.97 inches long.

Chemotherapy or “chemo”: Treatment with drugs that kill cancer cells.

Chromosomes. Chromosomes are structures found in the center (nucleus) of cells that carry long pieces of DNA. DNA is the material that holds genes. It is the building block of the human body. Chromosomes also contain proteins that help DNA exist in the proper form.

Clinical Trial: A protocol to evaluate the effectiveness and safety of drugs or devices developed in a laboratory by monitoring their effects on humans. Drugs or devices that are being tested under clinical trials have not been approved by the US Food and Drug Administration. In the US, strict rules for conducting clinical studies have been put in place by the National Institutes of Health and the Food and Drug Administration. Other countries regulate clinical trials in accordance with their laws; clinical trial regulations in the United Kingdom are similar to those in the US. See also Randomized Clinical Trial.

CNS: The Central Nervous System, which consists of the brain and the spinal cord.

Cognitive: The mental process of thinking, learning, remembering, being aware of surroundings, and using judgment.

Contrast agent or dye: When referring to a medical imaging scan, it is a substance that radiologists use to see tissues more clearly in the images.

Cranium/ Cranial: The bones that form the head and surround the brain.

Craniotomy: An operation in which a piece of the skull is removed. A craniotomy may be done so doctors can remove a brain tumor or abnormal brain tissue.

CSF: Cerebral Spinal Fluid. It is made by tissue that lines the ventricles (hollow spaces) in the brain. The CSF flows in and around the brain and spinal cord to help cushion them from injury and provide nutrients.

CT Scan: Computed Tomography scan. A procedure that uses a computer linked to an x-ray machine to make a series of detailed pictures of areas inside the brain or the body.

Cystic: A closed, sac-like pocket of tissue. It may be filled with fluid, air, pus, or other material. A cystic glioma is a descriptive term for one form of glioma that contains a large cystic component.

Debulking: Surgical reduction in the size of the tumor. Debulking may be done in the case of benign tumors to relieve symptoms.

Differentiation: How much or how little the tumor tissue looks like the normal tissue it came from.

Diffuse: Widely spread; not localized or confined.

DNA: Deoxyribonucleic acid. One of two types of molecules that contain genetic information. The other is RNA. Most DNA is found inside the nucleus of a cell, where it forms the chromosomes.

Edema: Swelling caused by excess fluid trapped in tissues like the brain.

EGFR: Epidermal Growth Factor Receptor. EGFR is a protein found on certain types of cells that binds to a substance called epidermal growth factor. The EGFR protein is involved in cell signaling pathways that control cell division and survival. When mutated, EGFR can be a potent contributor to the development of a brain cancer. Drugs that block EGFR proteins are being used in the treatment of some types of brain cancer. EGFRs are a type of receptor tyrosine kinase. Also called, ErbB1, and HER1.

Eloquent area: The area of the brain which supports language, motor, sensory or other important function.

Epigenetic alteration: A change in the chemical structure of DNA that does not change the DNA coding sequence. Epigenetic alterations occur in the body when chemical groups called methyl groups are added to or removed from DNA or when changes are made to proteins called histones that bind to the DNA in chromosomes. These changes may occur with age and exposure to environmental factors, such as diet, exercise, drugs, and chemicals.

FDA: The US Food and Drug Administration.

Generic: Official nonbrand names by which medicines are known. Generic names usually refer to the chemical name of the drug.

GFAP: Glial Fibrillary Acidic Protein, which is a protein that is encoded by the GFAP gene in humans. It is expressed by numerous cell types of the central nervous system, including astrocytes and ependymal cells during development. The finding of GFAP in a pathology evaluation is usually indicative of a primary brain tumor.

Gleostine: The brand name for the chemo referred to as Lomustine or CCNU.

Glioma: Any cancerous (anaplastic) brain tumor. A glioma begins in glial cells (cells that surround and support nerve cells.)

Heterogeneity: Made up of different elements. GBMs have significant inter and intra--tumoral molecular heterogeneity making them tough to treat since one or a few parts of the tumor will be susceptible to a certain treatment, but other parts will remain unaffected.

HIPAA: Stands for the Health Insurance Portability and Accountability Act of 1996, which derives from Public Law 104-191. Sections 261 through 264 of the HIPAA law requires certain standards for the electronic exchange, privacy, and security of health information. As it relates to brain cancer patients, the most common effect of the HIPAA law is safeguarding the privacy of their medical information. As a result, individuals need to designate in writing to whom medical service providers may provide their personal medical information.

Hippocampal avoidance: An advancement in whole brain radiation which uses intensity-modulated radiotherapy, a technique to pinpoint certain regions of the brain while avoiding others, to help preserve a patient's cognitive abilities.

Histology: The study of tissues and cells under a microscope.

Immunocompromised: Having a weakened immune system.

Immunohistochemistry: A lab test that uses antibodies to test for certain antigens (markers) in a sample of tissue. Immunohistochemistry is used to help diagnose diseases, such as cancer. It may also be used to help tell the difference between different types of cancer.

Immunotherapy: A type of therapy that uses substances to stimulate or suppress the immune system to help the body fight brain cancer. Some types of immunotherapies only target certain cells of the immune system. Others are intended to affect the immune system in a general way.

Infiltration/ infiltrative: Infiltration is the movement of cancer cells from their normal location into the surrounding healthy tissue. Another word for infiltration is invasion. Infiltration is an important feature that pathologists look for when trying to decide if a brain tumor is benign (non-cancerous) or malignant (cancerous).

Inoperable: An expert neurosurgeon has concluded surgery should not be performed on the tumor.

Intracranial: Existing or occurring within the cranium.

Intracranial pressure (ICP): Intracranial pressure is the pressure within the cranio-spinal environment, which is a closed system that holds a fixed, optimal volume of neural tissue, blood, and cerebrospinal fluid (CSF). When the ICP increases owing to edema or tumor growth, symptoms like headaches, nausea and others can develop as brain tissues are compressed.

Ischemia: Lack of blood flow. See also Transient Ischemic Attack.

IV: Intravenous. IV generally refers to a device to administer fluids into a blood vein.

Lesion: An area of abnormal tissue. A lesion may be either benign (not cancerous) or malignant (cancerous).

Malignant: A term synonymous with cancer. Malignant cells grow in an uncontrolled way and can invade nearby tissues.

Mass: A lump or swelling that may or may not be cancerous.

Meninges: The three thin layers of tissue that cover and protect the brain and spinal cord.

Metastatic: The spread of cancer cells from the place where they first formed to another part of the body. In a metastasis of the brain, cancer cells have broken away from the original (primary) tumor, traveled through the blood or lymph system, and formed a new tumor in the brain.

Methylation: A complex chemical reaction in which a small molecule called a methyl group is added to other molecules. In the treatment of brain cancer, it is generally believed that having a methylated MGMT gene provides a benefit because it interferes with the cancer's ability to regrow after chemo treatment.

Mitotic activity: The presence of dividing (proliferating) cells. Cancer tissue generally has more mitotic activity than normal tissues.

Monotherapy: The use of a single chemo or device during treatment.

MRI: Magnetic resonance imaging; a diagnostic and monitoring technique in which radiowaves and a powerful magnet linked to a computer are used to create detailed pictures of areas inside the body. These pictures can show the difference between normal and diseased tissue.

Mutation: Any change in the DNA sequence of a cell. Mutations may be caused by mistakes during cell division, or they may be caused by exposure to DNA-damaging agents in the environment. Mutations can be harmful, beneficial, or have no effect.

Myelination: The formation of the myelin sheath around a nerve fiber. (See also sheath).

NCI: The US National Cancer Institute at the National Institutes of Health.

Necrosis: The death of living cells. It occurs when too little blood and oxygen flows to the tissue. It can be triggered by injury or radiation. A necrotic area in the brain can grow but will do so at a slower pace than cancer. If the area of necrosis become large enough and symptomatic, surgery may be the best treatment.

Neuro or Neurological: Related to or affecting the central nervous system.

Neuro-oncologist: A doctor who specializes in diagnosing and treating brain tumors and other tumors of the nervous system using chemical agents.

Neurosurgeon: A doctor who specializes in diagnosing and treating brain tumors and other tumors of the nervous system by means of surgical intervention.

Oncogene: A gene that, if mutated, may cause the growth of cancer cells.

Operable: A qualified neurosurgeon has concluded surgery may be performed on the tumor and is reasonably (based on the doctor's considerable experience) expected to result in greater benefits than risk to the patient, all factors having been carefully considered.

OS: Overall survival.

Palliative Care: Care given to improve the quality of life of patients who have a serious or life-threatening disease. Also called comfort care, supportive care, and symptom management.

Pathologist (may also be referred to as a neuropathologist): A specialized doctor who identifies diseases of the nervous system by studying cells and tissues under a microscope.

Peer-reviewed Scientific Journal: A publication that contains original articles that have been written by scientists and evaluated for technical and scientific quality and correctness by other experts in the same field.

Perfusion: Refers to the passage of blood through the circulatory system. A perfusion MRI, therefore, attempts to identify blood stream activity in a tumor environment.

PET Scan: Positron Emission Tomography scan. A procedure in which a small amount of radioactive glucose (sugar) is injected into a vein, and a scanner is used to make detailed, computerized pictures of areas inside the body where the glucose is taken up. Because cancer cells often take up more glucose than normal cells, the pictures can be used to find cancer cells in the body.

PFS: Progression Free Survival. The length of time during and after treatment that the disease remains stable and does not grow.

POA: Power of Attorney. A power of attorney may be issued/obtained for medical, financial, or other reasons. A POA enables the trusted, designated person to make decisions and perform in place of the person making the designation.

Primary: With reference to a tumor, it is one that is at the original site at which it arose.

Progress / Progression: When in the course of a disease, it recurs, grows, or otherwise becomes worse.

Pseudo-progression: A phenomenon in which an initial increase in tumor size is observed but is later followed by a decrease in the tumor. Pseudo-progression is among the most common causes of misdiagnosed tumor recurrence.

Recur, Recurrence: The return of a tumor after a period of stability or remission.

Resectable: Able to be removed by surgery.

Resection: Surgical removal of a tumor. A resection may be partial (also called “subtotal”) or total.

RNA: Molecules of nucleic acid. RNA is also the genetic material of some viruses used for treatment instead of DNA.

Seizure: a burst of uncontrolled electrical activity between brain cells (also called neurons or nerve cells) that causes temporary abnormalities in muscle tone or movements (stiffness, twitching or limpness), behaviors, sensations, or states of awareness. Seizures are not all alike.

Sheaths: when referring to nerves, these are enveloping tubular structures. The destruction of this sheath by disease or injury can slow or stop the impulses traveling along that nerve resulting in a decrease of the function served by that nerve.

SOC: Standard of Care. Means the treatment protocol that is accepted by medical experts as the proper treatment for a brain tumor and that is widely used by doctors worldwide.

SSDI: US Social Security Disability Insurance.

SSI: US Supplemental Security Income.

Stereotactic: Referring to precise positioning in three-dimensional space. For example, biopsies, surgery, or radiation therapy can be done stereotactically.

Surgically Targeted Radiation Therapy or STaRT: A procedure whereby collagen tiles are inserted during surgery to the tumor site to delivery radiation.

Thrombocytopenia: A condition in which there is a lower-than-normal number of platelets in the blood. It may result in easy bruising and excessive bleeding from wounds or bleeding in mucous membranes and other tissues.

TMZ: Abbreviation for Temozolomide, also known as Temodar or Temodal.

Total or Gross Total Resection: Surgical removal of every visible portion of a tumor.

Transient Ischemic Attack or TIA: A temporary period of symptoms similar to those of a stroke. A TIA usually lasts only a few minutes and doesn't cause permanent damage. Often called a ministroke, a TIA may be a warning, so the doctor should be promptly informed of any strike like episodes, no matter how temporary.

Tumor: Can be non-cancerous (benign) or malignant (cancerous).

Unresectable: Not able to be removed surgically.

Vascular: Of or pertaining to the blood vessels.

WHO: World Health Organization, which issues the guidance by which brain tumors are diagnosed and classified.

Photo By Brian Singer

Al Musella's Story

Al Musella, DPM is a retired podiatrist. He worked his way through school as a computer programmer for medical research projects.

His interest in brain tumors started when his sister-in-law, Lana, was diagnosed with a GBM in 1992. Lana had surgery and radiation, but then the first MRI scan after radiation showed that the tumor had grown even larger. This was before Temodar, the Gliadel Wafer, and Avastin were available. So, the outlook for Lana was bleak. Her doctors told her there were no clinical trials that would take her because of the size of her tumor. Although they were at a major brain tumor center, they basically gave up on her. She was told she only had a few weeks left to live, and the only treatment option was a standard course of BCNU, which had no chance of helping her beyond a few extra weeks.

At that time, there was no world wide web! Version 1 of Netscape was released on December 15, 1994. Al was an active member of Compuserve, and Compuserve had a cancer forum, with sections devoted to the top 10 cancers (but no brain tumor section). Al created and ran the Brain Tumor Forum on Compuserve in January 1993. He organized the members and had them help survey every major hospital in the USA to find what treatments were available. That list was posted on Compuserve and became the basis for the first Internet database of clinical trials!

Back then, the National Cancer Institutes (NCI) only maintained lists of clinical trials that they funded, not the trials sponsored by the drug companies or the individual doctors or hospitals. (They do most now). And the only way to access them was to call the NCI and they would mail them to you. The NCI invited Al to demonstrate his technology to them, and the clinicaltrials.gov website was partially modelled after virtualtrials.org!

Despite being told by a few major brain tumor centers that there were no clinical trials that would accept Lana, (because her tumor was too large and multifocal), Al found a few She did very well for a while, getting to see her 4 kids grow up, then unfortunately died of a recurrence on October 25, 2000. She lived over 8 years after

being told she only had a few weeks left. Many of those years she was in excellent condition, taking care of her kids, working, driving and enjoying life.

In 1998, Al started the Musella Foundation as a not-for-profit charity dedicated to speeding up the search for cures of brain tumors and to helping families deal with the diagnosis of brain tumor. Ironically, Al's father was diagnosed with a GBM in 1999, a year after Al formed the Musella Foundation. Al and his family were more prepared than previously to deal with this diagnosis, but it was still a horrendous experience for Al to go through. His father died quickly, in about 4 months.

Since its inception, a lot has been accomplished by the Musella Foundation:

The virtualtrials.org website continues to expand in terms of services provided and the community served (in 2021 the website had over 250,000 visitors from 217 different countries).

The Foundation's co-payment assistance program has awarded more than $10 million in grants to over 2,000 brain tumor patients in this life-saving program.

The Foundation created and runs the Brain Tumor Virtual Trial, a study of brain tumor patients, as well as the long-term glioblastoma outcome project.

The Foundation helped accelerate FDA approval of Temodar, Avastin, Gleolan and Optune for brain tumor patients, and helped convince Medicare to pay for Temodar, Gliadel, Avastin, and Optune.

In the 30 years that Al has been immersed in the world of brain tumors, he has seen an amazing change in attitude among brain tumor researchers. There has been an unprecedented burst of progress in identifying new approaches. He is convinced that we are in the home stretch and a cure is within sight. It is now only a matter of time and money.

Through the Musella Foundation, we have a chance to speed up the search for a cure, by funding selected research that complements, without duplicating, research funded by the government.

To that end, Al needs your help. Donations to the Musella Foundation can be general or can be dedicated to specific ends, like brain tumor research or co-payment

assistance. For more details on how you can help us speed up the search for the cure, please visit the virtualtrials.org website.

Photo by Paolo Salcido, Salcido Photography, IBTA's First World Summit of Brain Tumour Patient Advocates

Al Musella, DPM
Founder and President
The Musella Foundation for Brain Tumor Research and Information

Recent Grants Made By The Musella Foundation

2024 Grant Awards

$100,000 to **Imaging Biometrics** for the project titled: **"Expanded access program of Oral Gallium Maltolate for the Treatment of Relapsed and Refractory Glioblastoma"**.

$4,000 to **Imaging Biometrics** to help patients pay for the treatment from the project titled: **"Expanded access program of Oral Gallium Maltolate for the Treatment of Relapsed and Refractory Glioblastoma"**.

$75,000, in collaboration with **Stache Strong, to Constantinos Hadjipanayis, MD, PhD, UPMC Brain Tumor Center** to fund the project titled: **"A Multicenter Study to Assess the Feasibility of Gleolan® (ALA / Aminolevulinic Acid HCl) in Pediatric Brain Tumor Patients After Delayed Administration"**.

$50,000 grant to **Katherine Onk and David Needham at DNKO LLC** to fund the project: **Effective Delivery of Doxorubicin to Invasive Margins in GBM: Establishing Optimal Warming Criteria for a Thermal Sensitive Liposome with Laser Interstitial Thermal Therapy in a Porcine Brain Model.** [The Musella Foundation only partially funded the grant which requested $322,000 and are saving up for the rest.]

$48,836.91 grant to **Dr. Ekokobe Fonkem at Medical College of Wisconsin** to fund the project: **Advancing Immunotherapy for Glioblastoma: Pre-Clinical Development of a Novel PI3K Inhibitor**. This grant was from the Melissa Bloom-Brand Fund of the Musella Foundation!

$40,000 to **Dr. Ekokobe Fonkem at Medical College of Wisconsin** for the project titled: "**Combination of PI3Kinase Inhibitors with Immune Check Point Inhibition as a Potential Therapeutic Target for DIPG"**.

$35,000 grant to **Dr. Haack at Beth Israel Deaconess Medical Center to fund the project: Computer modeling of tumor treating fields.**

$25,000 to **DIPG Collaborative** to help fund research into pediatric DIPGs.

$25,000, in collaboration with **Stache Strong, to Dr. Jessica Tsai Children's Hospital Los Angeles and Dr. Orly Alter at the University of Utah** to fund the project titled: **"Experimental validation of AI/ML-identified therapeutic targets in glioblastoma"**.

$10,053.52 to **Dr. Samuel Singer at The Feinstein Institutes for Medical Research** for the project titled: **"Assessment of sST2 Staining in Tumor Tissue from Glioblastoma, IDH-Mutant High Grade Glioma and High Grade Meningioma"**.

$5,000 to **DDRFA (DIPG / DMG Research Funding Alliance)** to fund DIPG / DMG Virtual Tumor Boards!

$5,000 to the **Central Brain Tumor Registry of the United States** for the project titled: **"Provision of the most current population-based statistical information for all primary brain and other central nervous system (CNS) tumors in the United States."** This is an annual grant to help support this important ongoing project.

Total for 2024 (year to date): $356,223.43 (Only includes The Musella Foundation's portion for collaborative grants)

ACKNOWLEDGMENTS

This Low Grade Brain Tumor Guide was directed by Al Musella, DPM; written by Channah Piscioneri, patient advocate; and the graphic design was provided by Linda Singer of www.LcsProductionDesign.com.

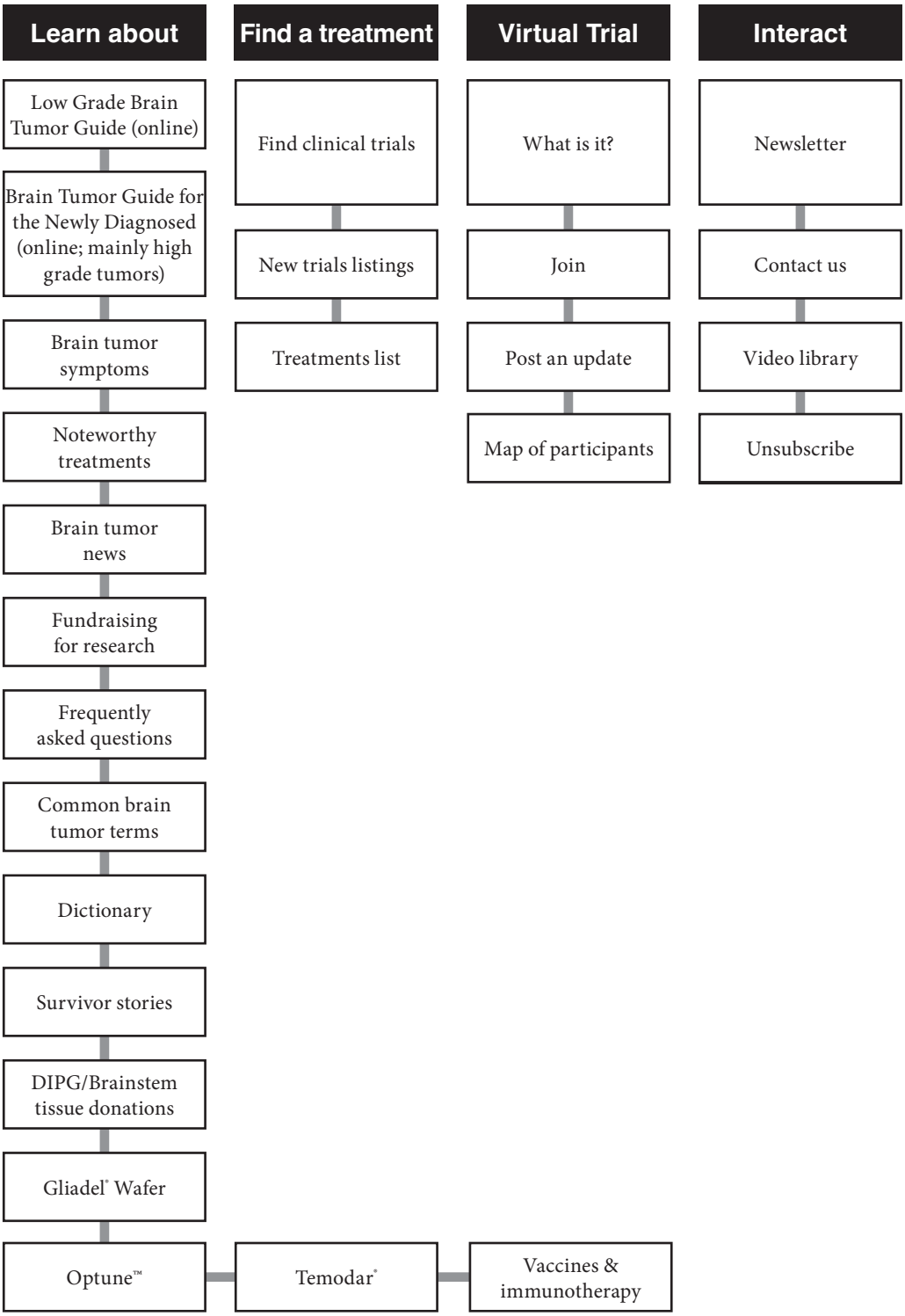
The Musella Foundation for Brain Tumor Research & Information, Inc., sponsors this book.

The Musella Foundation is a 501(c)(3) nonprofit public charity dedicated to speeding up the search for the cure of brain tumors and to helping families deal with brain tumors.

For brain tumor information or to make a donation, please go to: https://virtualtrials.org.

All proceeds from the sale of this ***Low Grade Brain Tumor Guide*** are used to fund brain tumor research.

Site Map of Virtualtrials.org



Site Map of Virtualtrials.org

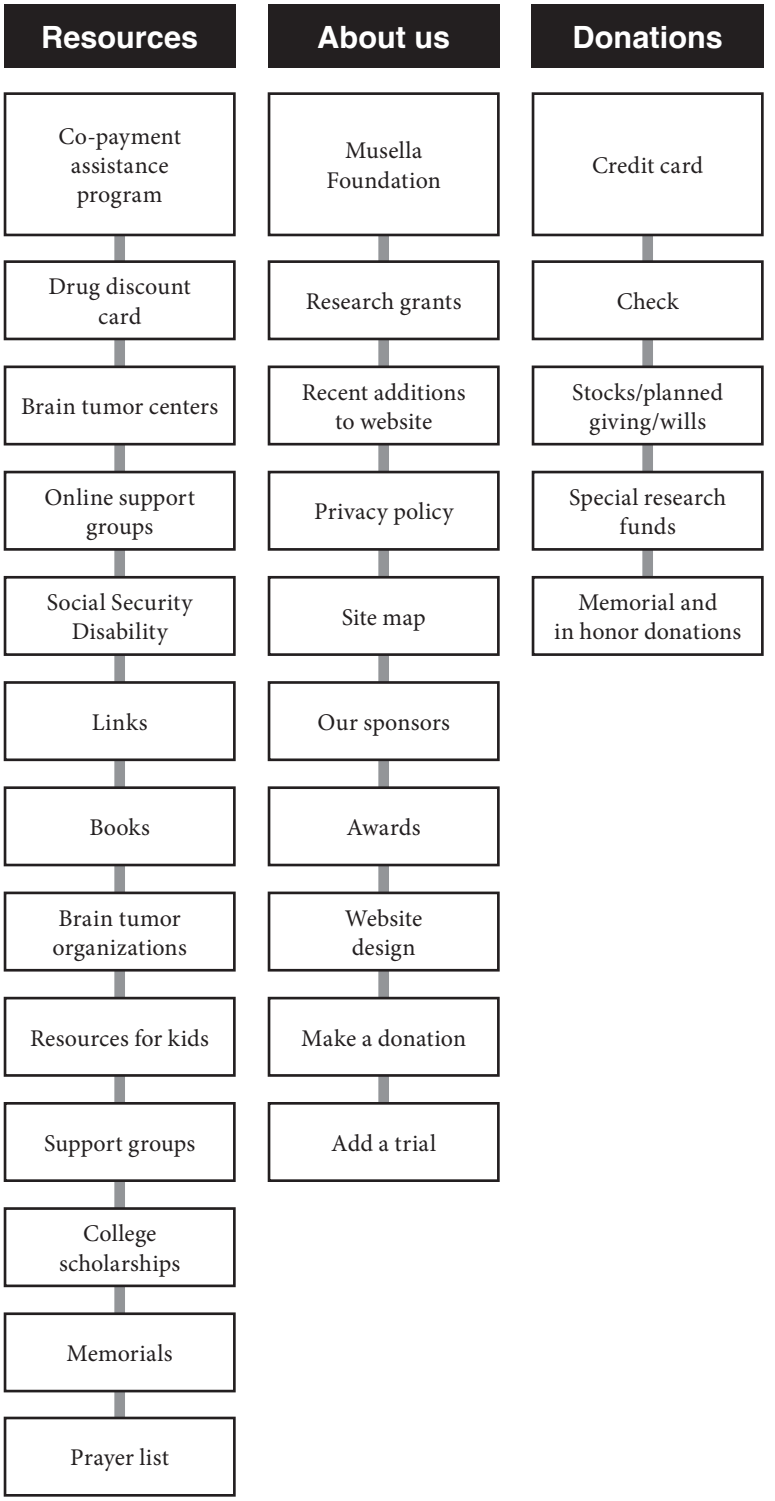


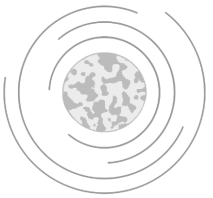
Photo By Dave Royko

ANNEX A: What is the pituitary gland?

The pituitary gland, located at the base of the brain, is a small organ about the size of an acorn. It is surrounded by a bony saddle like structure called the sella turcica, which resides above the sinuses at the back of the nose. The pituitary gland is sometimes referred to as the "master gland" because it releases substances that control the basic functions of growth, metabolism, and reproduction, including substances that change the activity level of the thyroid and adrenal glands, the testicles in the male, and the ovaries in the female.

The pituitary gland is divided into two parts, called lobes. These are referred to as the anterior (front) and the posterior (back) lobes. Each lobe releases hormones, which control basic activities within the body. The specific hormones and their activities are shown in this table.

ANTERIOR LOBE HORMONES	FUNCTIONS
Thyroid Stimulating Hormone (TSH)	Causes the thyroid gland to grow and releases thyroid hormones (called T4 & T3)
Adrenocorticotrophic Hormone (ACTH)	Causes the adrenal gland to release several hormones; the major one is cortisol
Growth Hormone (GH)	The main hormone for general body growth (in children) and body composition (in adults)
Follicle Stimulating Hormone (FSH)	Stimulates ovulation in women and the production of sperm in men
Luteinizing Hormone (LH)	Stimulates ovulation in women and testosterone production in men
Prolactin (prl)	Responsible for breast milk production in women
POSTERIOR LOBE HORMONES	
Antidiuretic Hormone (ADH)	Controls thirst and the amount of water released into the urine
Oxytocin	Stimulates uterine contractions in women



The diagnosis of brain tumor is a life-shaking event, compounded by the need to make important decisions such as what doctors to choose, where to be treated, and what treatments are available. To make the most rational decisions for yourself or for a loved one, you need to become as informed as soon as possible.

The goal of this **Low Grade Brain Tumor Guide** is to provide a vital first resource with tools for learning about the diagnostic processes, the tumor itself, and for engaging with a medical team on the complex array of treatment options.

This **Low Grade Brain Tumor Guide** is a wealth of helpful and hopeful information and is being presented by the Musella Foundation for Brain Tumor Research & Information, an organization that since the 1990's has been dedicated to the cure of brain tumors.

The Musella Foundation maintains a website, virtualtrials.org, that is focused on brain tumor information and treatment; a co-pay assistance website, braintumorcopays.org; and a fundraising website, walktoendbraintumors.org.