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

Clinical trials

Alternative and complementary treatments

Common medicines for treating symptoms

Assistance Programs

13th Edition

BRAIN TUMOR GUIDE

for the

NEWLY DIAGNOSED



MUSELLA
FOUNDATION FOR BRAIN TUMOR RESEARCH & INFORMATION, INC.

Brain Tumor Guide for the Newly Diagnosed

Thirteenth edition

A comprehensive and essential guide to understanding:

Brain tumors and their diagnoses

Genetic markers

Your medical team and questions to ask

Standard-of-care treatment

Clinical trials

Alternative and complementary treatments

Common medicines for treating symptoms

"Real world" and online support groups

Al Musella, DPM
The Musella Foundation

MUSELLA FOUNDATION
FOR BRAIN TUMOR
RESEARCH & INFORMATION

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, provide help matching patients to clinical trials, give emotional and financial support to brain tumor patients, support awareness and advocacy for brain tumor issues, and give grants for brain tumor research. We maintain 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.

Copyright/Permission Statement

This Brain Tumor Guide for the Newly Diagnosed ("Guidebook") and its contents are copyrights of the Musella Foundation for Brain Tumor Research & Information, Inc.

© 2026 The Musella Foundation, 1100 Peninsula Boulevard, Hewlett, NY 11557, 888-295-4740

https://virtualtrials.org

First Edition Published January 1, 2010
Thirteenth Edition Published May 14, 2026

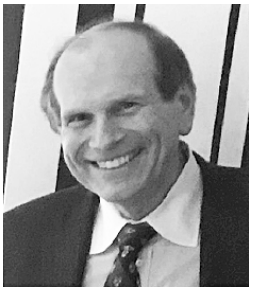
You may print, copy, or download extracts solely for your personal and non-commercial use.

You may not, except with the prior written permission of the Musella Foundation copy, distribute, commercially exploit, publish, store in a retrieval system, or otherwise disclose this Guidebook or any portion thereof.

All rights reserved.

ISBN 978-0-9899740-6-6

Introduction



Steven Brem, MD

Receiving a brain tumor diagnosis often brings uncertainty and raises important questions about the next steps, diagnosis, and treatment. Making informed decisions can be critical, even lifesaving. As the saying goes, information is power. In today's digital era, with abundant online resources, social media, and artificial intelligence, there is a vast amount of both accurate information and misinformation available.

This guide, now in its 13th edition, has been carefully updated and rewritten with your needs in mind. It is intended for patients, families, caregivers, and healthcare professionals: physicians, nurses, advanced practice practitioners, social workers, psychologists, and other members of the care team. Achieving optimal outcomes for brain tumor patients depends on a collaborative, interdisciplinary approach and a supportive community.

If a clinical trial is available, you are encouraged to consider enrolling, as clinical trials offer access to tomorrow's medicines today. The Musella Foundation, established in the 1990s, assists in finding suitable trials through its patient navigation program. This program, available at no cost, provides personalized nurse navigation services and expert treatment guidance. The program team uses the latest, evidence-based medical research to help patients make informed decisions about their care. The Foundation's website provides instructions for enrolling in the program.

The website also provides a comprehensive directory of brain tumor centers, giving patients and families access to specialized medical facilities across the country, as well as links to valuable resources and programs designed to support individuals facing a brain tumor diagnosis. These resources cover a range of needs, including financial assistance programs to help ease the burden of medical expenses.

Whenever possible, the registry number for national clinical trials (NCT#) is provided in this guide, allowing you to look up eligibility criteria, contact details, and information about new treatments. The Musella Foundation shares this information through its weekly newsletter. This guide presents the latest information, focusing on best practices and standards of care defined by evidence-based guidelines from the National Comprehensive Cancer Network (NCCN).

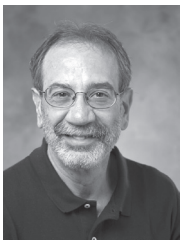
Information for this guide was gathered using AI tools (such as Google Gemini) to collect documents, websites, and publications, and was then independently verified by consulting original references in the National Library of Medicine (PubMed®). The advice offered is informed by the Musella Foundation's years of experience advising thousands of patients, collaborating with leading centers nationwide, and consulting its distinguished Medical Advisory Board.

Serving as the Chief Medical Advisor for the Musella Foundation is a great honor, and it is a privilege to work alongside a dedicated team. Patients are viewed as partners and stakeholders in the pursuit of a cure for brain tumors. Advancing the fight against brain cancer begins with knowledge, inspiring physicians, scientists, industry, academia, and both private and public entities to work together in a coordinated effort toward a cure. Please feel free to reach out with your ideas and questions.

Wishing you peace of mind and hope for the future,

Steven Brem, MD,
Penn Brain Tumor Center, University of Pennsylvania
Chief Medical Advisor for the Musella Foundation

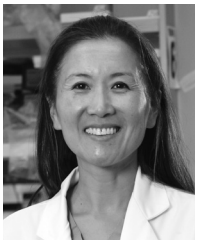
In addition to the comprehensive review and invaluable scientific guidance of Dr. Steven Brem during the drafting of this Edition 13, members of the Musella Foundation's Medical Advisory Board also reviewed and approved the contents of this Guide. We are especially grateful to Dr. Henry Friedman, Dr. Isabelle Germano, Dr. Linda Liau, and Dr. Michael Schulder for enriching the value of this document with their collective wisdom.



Henry S. Friedman, MD, is deputy director of the Preston Robert Tisch Brain Tumor Center at the Duke University Medical Center in Durham, North Carolina. An internationally recognized neuro-oncologist, Dr. Friedman has a long-standing career in the treatment of children and adults with brain and spinal cord tumors. He has written hundreds of research articles, and his work has been showcased on several segments of the CBS program *60 Minutes*. Dr. Friedman strongly believes that there is hope for patients who are being treated for brain cancer.



Isabelle M. Germano, MD, MBA, is Professor of Neurosurgery, Neurology, Oncological Sciences, Radiation Oncology, and Global Health at the Icahn School of Medicine at Mount Sinai in New York, NY. She serves as Director of the Comprehensive Brain Tumor Program and Co-Director of the Radiosurgery Program. A pioneer in image-guided neurosurgery, her clinical practice focuses on minimally invasive surgery for brain and spine tumors. Dr. Germano has authored six neurosurgical books, and her translational research and clinical work has been published in more than 200 peer-reviewed articles. Recognized nationally and internationally as an educator, her work has also been featured in the media. She is an elected member of the American Academy of Neurological Surgeons.



Linda Liau, MD, PhD, MBA, is the chair of the Department of Neurosurgery at UCLA in Los Angeles, California, and director of the UCLA Specialized Program of Research Excellence (SPORE) in Brain Cancer. She is a neurosurgeon with a clinical expertise in intraoperative functional brain mapping for resection of brain tumors. Dr. Liau's research is focused on clinical neuro-immunology, immunotherapy, and brain cancer vaccines. Her work has been published in major journals and textbooks and has been highlighted nationally and internationally. She is an elected member of the National Academy of Medicine.



Michael Schulder, MD, is Director of the Brain Tumor Center at the Northwell Neuroscience Institute and Professor and Vice Chair of Neurosurgery at the Zucker School of Medicine at Hofstra/Northwell. He also serves as the Residency Program Director and co-Director of the Center for Stereotactic Radiosurgery. Dr. Schulder initiated the academic brain tumor program at Northwell Health, including among other projects, building a robust clinical trials program. He has done pioneering research on techniques of image-guided neurosurgery including intraoperative MRI, and new techniques of radiosurgery. He has authored many peer-reviewed publications and book chapters and argues strongly for an unremitting effort to find new and better treatments for people with brain tumors.

Table of Contents

About the Musella Foundation ii
Introduction iii
Forward xii
Applicability xii
Personalized Help xii
Glossary xiii
Internet links xiii
Scientific Advances/Studies xiii
Survivor stories xiii
Informational Only xiv

CHAPTER 1: WHAT YOU NEED TO KNOW WHEN A BRAIN TUMOR IS FOUND 1

Discovery of a Cranial Mass 1
Diagnostic Process 3
Biopsy 6
Diagnosis Scope/Delays 8
Diagnosis Results 19
Primary Versus Metastatic Tumors 20
Most Common Primary Brain Tumors 23
How Long Has the Tumor Been There? 30
Grade Levels (Defined) 32
Grade Levels (How Determined) 33
What are Survival Statistics for Those with Brain Tumors? 35
Coping with a Brain Tumor Diagnosis (Practical) 37
Coping with a Brain Tumor Diagnosis (Emotional) 41
Hope 47
SURVIVOR STORY #1 49
KEY TAKEAWAYS TO REMEMBER 51

CHAPTER 2: TREATMENT FACILITIES 53

Brain Tumor Centers 53
NCI Designated Cancer Centers 54
Brain Cancer SPORE Locations 55
Clinics Offering Alternative Treatments 56

CHAPTER 3: UNDERSTANDING BRAIN TUMORS 61

Overview of Your Medical Team 61
Typical Types of Doctors 62
Additional Specialists 63
Need for Expertise 64
Criteria for Selecting a Doctor 65
What questions should I ask my medical team? 65
Second Opinions (Diagnosis/Genetic Study) 66
Second Opinions (Treatment) 67
SURVIVOR STORY #2 69
KEY TAKEAWAYS TO REMEMBER 71

CHAPTER 4: PROTECTING YOURSELF AND FAMILY DURING TREATMENT 73

Health Maintenance Vaccines ... 73
Fertility Protection ... 74
Insurance Management ... 75
Financial Matters ... 81
Legal Matters ... 86
SURVIVOR STORY #3 ... 90
CHECKLIST OF TOP TEN FIRST THINGS ... 92

CHAPTER 5: TREATMENTS OVERVIEW 97

General ... 97
Patient Navigation Program ... 99
SURVIVOR STORY #4 ... 113
KEY TAKEAWAYS TO REMEMBER ... 118

CHAPTER 6: SURGERY 119

Overview ... 119
When Surgery is Necessary ... 123
Types of Surgery ... 128
Key-Hole Surgery ... 135
Treatment Implants During Surgery ... 140
Post-Surgery Home Care and Other Topics ... 144
SURVIVOR STORY #5: BEN WILLIAMS ... 146
KEY TAKEAWAYS TO REMEMBER ... 148

CHAPTER 7: RADIATION 149

Overview ... 149
What to Expect During Treatment ... 161
Pre-Radiation Therapy Questions to Ask ... 164
Side Effects to Expect From Radiation Treatment ... 165
Post-Radiation Self Care Tips ... 167
Lifetime Brain Radiation Tolerance ... 168
SURVIVOR STORY #6 ... 171
KEY TAKEAWAYS TO REMEMBER ... 173

CHAPTER 8: CHEMOTHERAPY 175

Overview ... 175
Is My Chemo Working? ... 176
Temozolomide (Temodar or Temodal) ... 176
Lomustine/CCNU/Gleostine ... 182
Carmustine/BCNU ... 184

CHAPTER 9: IMMUNOTHERAPY 185

Overview ... 185
Personalized Vaccines ... 188
Monoclonal Antibodies/Immune Checkpoint Inhibitors ... 202
CAR T-Cell Therapy: An Evolving Treatment ... 208
Oncolytic Viral Therapy ... 212
SURVIVOR STORY #7 ... 218
KEY TAKEAWAYS TO REMEMBER ... 220

CHAPTER 10: OPTUNE GIO®/TTFIELDS DEVICE 221

Overview ... 221
How it Works ... 221
Initial Testing Results ... 223
Latest Results and Trials ... 223
Optune Gio® Availability and Use ... 226

CHAPTER 11: HOW BEVACIZUMAB (AVASTIN®) WORKS 229

Effects, Use in Pediatrics, Biosimilars, and Side Effects ... 229

CHAPTER 12: FOCUSED ULTRASOUND (FUS) 239

CHAPTER 13: MEDICATIONS FOR SYMPTOM MANAGEMENT 243

Common Medications ... 245
KEY TAKEAWAYS TO REMEMBER ... 258

CHAPTER 14: CLINICAL TRIALS 259

Importance of Clinical Trials ... 259
Understanding Clinical Trials ... 260
Why Should You Consider Participating In A Clinical Trial? ... 261
When Should You Consider A Clinical Trial? ... 262
How Do You Assess A Clinical Trial? ... 263
How Do You Find Clinical Trials? ... 263
Treatments, Trials and the Food and Drug Administration ... 265
Alternative And Complementary Treatments ... 271
SURVIVOR STORY #8 ... 277
KEY TAKEAWAYS TO REMEMBER ... 279

CHAPTER 15: DIET 281

Overview ... 281
Why Consider Dietary Changes? ... 281
Gut-Brain Immune Relationship ... 281
The Inflammation Factor ... 283
First Fix ... 284
Diet Mix ... 284
Calories/ What To Do About Lack Of Appetite ... 284
Proteins ... 285

CHAPTER 16: IMAGING AND MONITORING 295

Overview ... 295
CT Scan ... 295
Magnetic Resonance Imaging (MRI) ... 296
Blood Tests ... 305
SURVIVOR STORY #9 ... 306

CHAPTER 17: SIDE EFFECTS 309

Memory and Cognitive Effects ... 309
Tumor Side Effects ... 311
Side Effects of Treatment ... 319
Hair Loss During Treatment ... 321
SURVIVOR STORY #10 ... 326
KEY TAKEAWAYS TO REMEMBER ... 328

CHAPTER 18: SURVIVORSHIP 329
Survivorship Programs ... 330
When Does Survivorship Begin in High-Grade Brain Cancer? ... 332
Understanding The Prognosis Without Letting It Define You ... 332
Handling the Fear of Recurrence ... 333
The Physical Reality of Survivorship With a High-Grade Tumor ... 335
Living Well With Long-Term Optune Gio® Use ... 337
Reducing Your Risk of Stroke with Brain Cancer ... 340
Mitigating Long-Term Cognitive Effects of Radiation & Other Brain Cancer Treatments 342
Emotional Survivorship Under a Shadow of Recurrence ... 347
Medical Care as a Lifelong Companion ... 352
Living Fully Without False Promises ... 352
The Power and Limits of Survivor Stories ... 353
Conclusion: Survivorship as Courage, Not Outcome ... 354

CHAPTER 19: CAREGIVING AND SUPPORT GROUPS 355
Caregiving ... 356
Caregivers Fatigue ... 356
First Aid for Caregiver's Fatigue ... 357
Mind, Body, Soul: Faith In Healing And Emotional Wellness ... 358
Impairments And Strategies For Coping ... 363
Support Groups ... 365
Online Support Groups ... 367
SURVIVOR STORY #11: YARON BUTTERFIELD ... 368
KEY TAKEAWAYS TO REMEMBER ... 372

CHAPTER 20: LATE STAGE 373
Intubation and Ethical Considerations ... 373
Hospice ... 374
Practical Tips ... 375

CHAPTER 21: PASSING 381
Where Has My Loved One Gone? ... 388
Disposal of Unused Medications ... 388
Identify Theft of Deceased ... 390
Brain Donation ... 392

CHAPTER 22: GRIEVING 393
Overview ... 393
Anticipatory Grief ... 394
Grief After the Passing ... 395
Prolonged Grief Disorder ... 399

CHAPTER 23: HOPE FOR THE FUTURE 401

GLOSSARY OF TERMS AND ABBREVIATIONS 403

AL MUSELLA'S STORY 419

RECENT GRANTS MADE BY THE MUSELLA FOUNDATION 422

APPENDIX A: MOLECULAR CHARACTERISTICS OF A GBM 427

Subtypes of GBMs 427
Immunosuppressive Environment Differences in GBMs 428

APPENDIX B: BRAIN FUNCTIONS AND DYSFUNCTIONS BY LOCATION 429

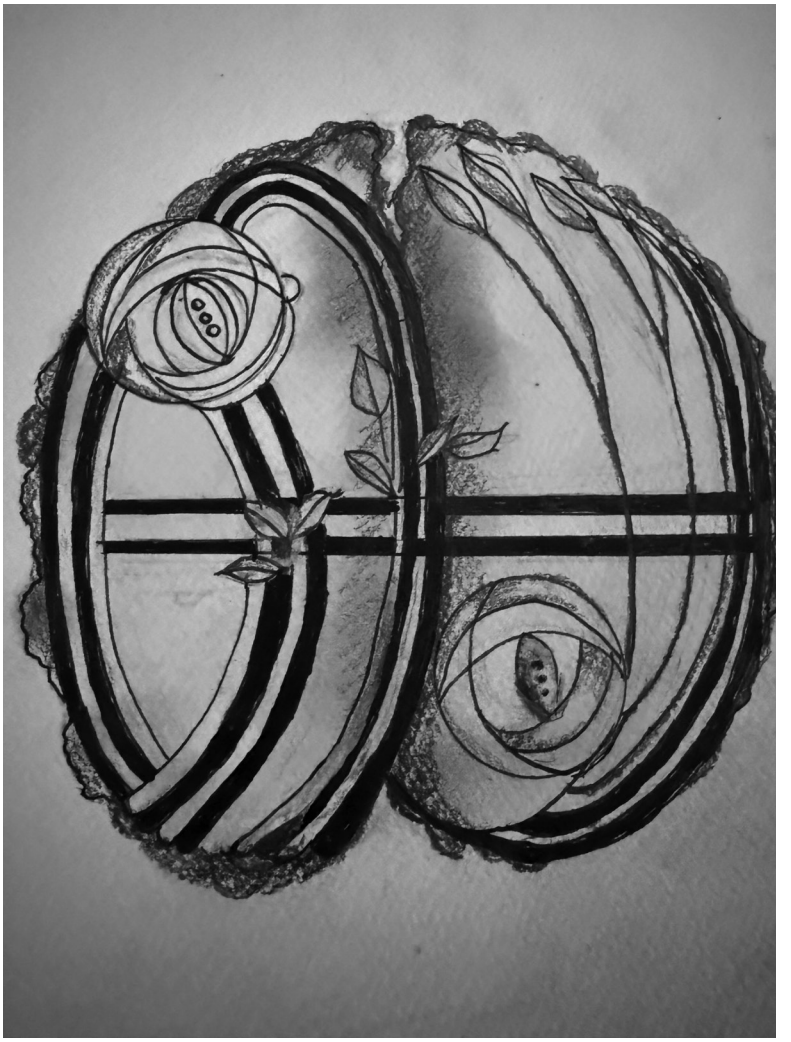
Hemispheres Of The Brain 431
Diagnosing Dysfunctions 431
Rehabilitation 436

APPENDIX C: CAUSES OF BRAIN TUMORS 438

Overview 438

ACKNOWLEDGMENTS 447

Drawing by Julia Rawlinson



ABOUT THIS EDITION

Forward

We are sensitive to the fact that if you are reading this Guidebook, 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. We are here to help you sort through various treatment options and to be a resource for you so that you can further understand your disease. It is our hope that this Guidebook will somehow make the path ahead of you smoother.

Applicability

This Guidebook is intended to primarily address adult malignant brain tumors. Infant and early childhood brain tumors are of different types, and have different characteristics, symptoms, and prognoses. Because of these differences, individuals caring for children with brain tumors are encouraged to access doctors, facilities and resources that specialize in such brain tumors.

For parents whose child has received a diagnosis of DIPG (Diffuse Intrinsic Pontine Glioma) or DMG (Diffuse Midline Glioma), an excellent resource to reach out to for comprehensive information about research, treatment and the latest clinical trials is DIPG.org at this link: https://dipg.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 Guidebook 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 thirteenth edition of the Brain Tumor Guide for the Newly Diagnosed 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 Guidebook 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. Your best resource for resolving any apparent conflicts in medical thought is your doctor.

Survivor stories

The survivor stories in this book are real but have been edited for this book format to highlight general themes and the specific interests of book chapters in which they appear. You can find the full stories for these survivors — as well as stories for other survivors — at the virtualtrials.org website of the Musella Foundation: https://virtualtrials.org/survive.cfm.

The Musella Foundation is deeply appreciative of all the people who have shared their stories at our website and in this Guidebook. Please share your story, too.

Informational Only

The information provided in this ***Brain Tumor Guide for the Newly Diagnosed*** (the Guidebook) 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 Guidebook nor the website provides any medical advice from any person at the Musella Foundation or associated with the Guidebook or website.

The information in this Guidebook 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 Guidebook 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.

NCCN Guidelines

The recommendations here are intended to align with current and advanced recommendations as described in the NCCN Brain Cancer Glioma guidelines, which are available online for professionals and for patients at: nccn.org/patients/guidelines/content/PDF/brain-gliomas-patient.pdf



One

What You Need To Know When A Brain Tumor Is Found

Discovery of a Cranial Mass

It may have been persistent headaches, blurred vision, an episode of confusion, loss of balance, even back pain, a seizure, or some other unusual symptom, all of which might be caused by a brain tumor but could also be caused by something else, that made you concerned enough to visit a doctor or hospital emergency room. Most brain tumors are found after symptoms appear, although some may even be discovered during a routine physical or eye examination.

Upon presentation of the possibility of a tumor the doctor may first order a CT or MRI scan and, if it is detected, return with the news that a "mass" has been found in the brain. The next step is obtaining a tissue sample by surgery or biopsy for histopathologic and molecular analysis by a neuropathologist. Without examination of a tissue sample by a neuropathologist, a brain tumor cannot always be definitely diagnosed.

You may feel a flood of emotions, such as disbelief, fear, and anger at this news because it may sound life-threatening to you. While any mass in the brain is likely to produce the same symptoms, they are not all the same.

There are around 120 different types of brain tumors. All tumors start with defective cells that acquire the ability to rapidly grow in an uncontrolled manner, forming the lumps we call tumors. Just because the doctor may use the term "tumor" does not mean it is cancerous. Tumors in the brain can be non-cancerous (benign) or malignant (cancerous).

Benign tumors most commonly stem from the meninges (layers of tissue that cover the brain), from nerve sheaths (layer surrounding nerves), or from the pituitary gland. Roughly 70 percent of masses will turn out to be benign (non-cancerous) growths that do not spread and may not even require surgery.

However, even a benign tumor can cause serious symptoms and damage within the brain. Because the brain is enclosed in a rigid container (the skull), there is no space for a tumor mass to grow. As a tumor (even a benign tumor) grows, it builds up intracranial pressure and compresses everything around it, and this process can lead to neurological problems and even death, so getting medical management is important. Fortunately, there has been a lot of progress in the treatment of benign brain tumors.

Meanwhile, although malignant brain tumors may also originate from the same tissues as a benign tumor, malignant tumors more commonly arise from glial cells (comprising neuronal supportive tissues) and are named according to their cell of origin. These tumors typically grow rapidly, invade surrounding healthy brain tissue and are life threatening.

No matter what your tumor turns out to be, please know that you are not alone, even though a brain tumor is considered a rare condition. The chance that a person may develop a cancerous tumor of their brain or spine is less than 1%. And yet, every year around 25,000 adults will be diagnosed in the US with a tumor that originates in the brain and many more will be diagnosed with a cancer that has spread to the brain from another organ such as the lung or breast. In addition, each year about 5,000 parents will hear those two devastating words — brain tumor — about one of their children.

Since by the time most brain tumors are found, they have become well entrenched, researchers are attempting to develop techniques to screen for brain tumors during routine physical exams to find and treat them early before the tumor spreads and may become harder to contain. Clinical tests based on liquid blood or urine biopsies are under study. The use of fluid-based clinical tests—including samples from blood, urine, or cerebrospinal fluid—represents an exciting and emerging technology. Known as "liquid biopsy," this approach holds the promise for revolutionizing how brain tumors are diagnosed, monitored, and treated. As liquid biopsy technology advances and becomes suitable for widespread clinical use, it is expected to offer

a highly sensitive and specific tool that provides clinically relevant information in a cost effective manner. The use of fluid-based clinical tests—including samples from blood, urine, or cerebrospinal fluid—represents an exciting and emerging technology. Known as "liquid biopsy," this approach holds the promise for revolutionizing how brain tumors are diagnosed, monitored, and treated. As liquid biopsy technology advances and becomes suitable for widespread clinical use, it is expected to offer a highly sensitive and specific tool that provides clinically relevant information in a cost effective manner. This technology could greatly benefit the evaluation of new drug efficacy, as well as the ongoing monitoring of patients receiving standard treatments or participating in clinical trials.

Diagnostic Process

When a mass is found by a doctor, the doctor will recommend several tests to determine if it is benign or cancerous, and if cancerous what form of cancer it is. The evaluation of a patient with a suspected brain tumor should include a detailed patient history, a comprehensive neurological examination, and a general examination of other body systems. Most patients with high-grade malignant gliomas will have no family history of brain tumors or identifiable risk factors for glioma.

An official diagnosis is based principally on the molecular evaluation of the tumor tissue, but the diagnostic procedure typically follows these steps:

Neurological Exam

The doctor will perform a neurological exam that will consist of items like those listed of listed below. Issues with any of these areas help the doctor understand the scope of effect of the mass.

- 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

When there is a growth on the brain, symptoms can arise from excessive fluid (edema) or from increased intracranial pressure within the skull. Specific symptoms may also arise from the location of the growth. The most common presenting symptoms of high-grade gliomas include:

- Headache (50% to 60% of patients)
- Seizures (20% to 50% of patients)
- Focal neurologic deficits such as memory loss, motor weakness, aphasia (difficulty speaking or understanding speech), visual symptoms, and cognitive and personality changes (10% to 40%)

Focal neurologic deficits are more common with high-grade than with low grade gliomas. In contrast, seizures are less common with high-grade than with low-grade gliomas.

Imaging

Imaging studies help to identify and localize brain masses and offer clues as to what type of mass is present. They are also useful in diagnosing certain complications of brain masses, such as hydrocephalus and hemorrhage. A brain magnetic resonance imaging (MRI) scan with contrast is often the only study required prior to surgery. However, with the growing adoption of neuronavigation during surgery, your neurosurgeon may request specialized imaging studies to pinpoint essential functional regions of the brain that must be preserved. These tests are crucial for ensuring that critical areas are avoided during the surgical procedure. These additional sequences include: a) functional MRI (fMRI) which is task-based, to identify hubs that are "eloquent" (critically important) and identify speech and motor areas; b) diffusion-weighted MRI (dw-MRI) – needed for tractography to identify the "eloquent" white matter tracts that support functions such as speech, motor movement, and vision; and c) resting state fMRI (rs-fMRI) which can be used for mapping the functional connectome, which is a picture of the functional brain networks. However, with the growing adoption of neuronavigation during surgery, your neurosurgeon may request specialized imaging studies to pinpoint essential functional regions of the brain that must be preserved. These tests are crucial for ensuring that critical areas are avoided during the surgical procedure.

These additional sequences include: a) functional MRI (fMRI) which is task-based, to identify hubs that are "eloquent" (critically important) and identify speech and motor areas; b) diffusion-weighted MRI (dw-MRI) – needed for tractography to identify the "eloquent" white matter tracts that support functions such as speech, motor movement, and vision; and c) resting state fMRI (rs-fMRI) which can be used for mapping the functional connectome, which is a picture of the functional brain networks. Patients who should not have an MRI should undergo head computed tomography (CT) with contrast.

The doctor may ask that your whole body be scanned to check if there is cancer elsewhere in the body. A contrast agent called gadolinium may be injected during the MRI, which improves the visibility of inflammation, the tumor and blood vessels.

The urgency of a neurosurgical evaluation for a suspected brain tumor depends on the clinical stability of the patient, symptom severity, and tumor size and location. Patients with large symptomatic tumors, including those with signs and symptoms of elevated intercranial pressure, require emergent evaluation and neurosurgical attention.

Patients with smaller tumors or with minimal symptoms can often be safely and effectively evaluated in the outpatient setting.

For more detailed information about imaging please see the Section entitled "Imaging and Monitoring".

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 cornerstone upon which the medical diagnosis and treatment rests. In this evaluation, the pathologist considers 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.

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

Biopsies are performed by highly specialized doctors called neurosurgeons.

Prior to the biopsy, 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 that thin the blood.

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, the neurosurgeon will usually obtain a frozen-section biopsy to provide a working diagnosis. This tissue sample is rapidly frozen and stained so that microscopic examination may be completed while the patient is still under anesthesia. Following this, the neurosurgeon will continue to remove as much of the tumor as possible.

After surgery, the entire resected tumor is sent to the neuropathologist for final examination, during which tissue samples are permanently preserved in paraffin (a petroleum-based wax) or frozen for future use.

A craniotomy and removal of your tumor typically takes 4 to 6 hours. For more information, please see the section in this Guidebook entitled "Surgery."

Stereotactic 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 stereotactic biopsy. A stereotactic biopsy may also be referred to as a guided needle biopsy.

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

In a stereotactic biopsy, your neurosurgeon drills a hole into the skull and inserts a thin hollow needle into the tumor. The size of the hole will range from about 2.5-5mm in diameter for a twist-drill style opening to around 10-14mm (roughly half an inch) for a standard burr hole, depending on the biopsy system and whether additional instruments are needed. The opening is kept as small as possible because stereotactic navigation allows the neurosurgeon to guide the needle very precisely to the target inside the brain.

To ensure stability and accuracy of the procedure, your 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 extract several samples from various locations within the tumor for ensuring maximum diagnostic accuracy.

Many patients can tolerate this form of biopsy while only under light sedation with local anesthesia as opposed to general anesthesia.

A stereotactic 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, you 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.

Alternate Biopsy

If a biopsy is considered too dangerous (e.g., the individual is fragile/has underlying health concerns, or could be susceptible to a brain bleed or stroke due to the biopsy) then the doctors may turn to evaluation of the cerebral spinal fluid (CSF). This would be done by a lumbar puncture (also called a spinal tap). The theory is that elements of the tumor may be found in the CSF and aide doctors in determining what the mass is. Note that this evaluation would not necessarily provide the level of biomarker detail for the mass that a biopsy would.

Diagnosis Scope/Delays

Overview

The molecular evaluation is a complex process and can take many days, even a few weeks to complete. The World Health Organization (WHO) classification of tumors is the standard and universally used diagnostic system. The basis of the information used in this Guidebook is the fifth edition of the WHO Classification of Tumors of the Central Nervous System (CNS), which was published in 2021.

Scope of Evaluation

The most recent WHO guidelines require histology with molecular testing to create a "layered" integrated diagnosis. The three layers that are combined to make an integrated diagnosis are:

Histologic type: This means the type of cell from which the cancer most likely originated. Cell type is normally ascertained by microscopy of stained biopsy tissue sections, immunohistochemistry analysis, and examination of the inner cell structure. A section below entitled Types of Primary Tumors provides further details.

Histologic grade: This means a description of a tumor based on how abnormal the cells and tissue look under a microscope and how quickly the cells are likely to grow and spread. The histologic grade is a measure of malignancy. Low-grade cancer cells look more like normal cells and tend to grow and spread more slowly than high-

grade cancer cells. The histologic grading system is used for planning treatment. A section below on Grade Levels provides further details.

Molecular characterization: Cancer cells typically contain some changes to the DNA of the cells that helps them grow out of control. These changes, or more technically "genetic alterations", hijack the cell's regulation of growth and division. These alterations may involve making multiple copies of a gene (so called "amplification") or fusing different unrelated genes together (called "translocations" or "fusions") or changing the sequence of a gene (called "mutation"). When proteins are then produced based on this altered genetic blueprint, the control of the cell lifecycle is disturbed, and the cell can learn survival behaviors that lead to cancer.

Genetic alterations range in size; they can affect anywhere from a single DNA building block to a large segment of a chromosome that includes multiple genes. Using a normal phrase as a baseline the examples below give an idea of the various possible alterations to DNA coding:

THE BOY PLAYED WITH THE DOG – normal gene coding
THC BOY PLAYED WITH THE DOG - missense
THE PBYL OAY DWE ETH OGD TI – mutation
THE YO ADP TH HEW GT – deletion/loss

Plus, there can be an amplification of a gene. Gene amplification is an increase in the number of copies of a gene without a proportional increase in other genes. This can result from duplication of a region of DNA that contains a gene through errors in DNA replication and repair machinery as well as through fortuitous capture by selfish genetic elements.

Part of the molecular characterization will be the identification of any epigenetic alteration. These are changes in how your behaviors and environment can cause changes that affect the way your genes work. Unlike the genetic alterations described above, epigenetic changes are reversible and do not physically change your DNA sequence, but they can change how your body reads a DNA sequence. For example, a person's diet and exposure to pollutants, can impact their epigenetics.

For purposes of performing a molecular evaluation, the pathologist will seek to identify any epigenetic signatures (e.g., DNA methylation, mRNA, and microRNA expression, etc.) which may help with disease classification (and may later provide

potential targets for therapy.)

Key Genetic Markers That Enable and Stimulate Tumor Growth

Different tumors will have different molecular and genetic profiles. There are two major classes of genes critical for the development and diagnosis of brain tumors:

Tumor Suppressor Genes: these are genes that are supposed to inhibit cell proliferation and tumor development, but go awry opening the path to tumor development, and

Oncogenes: these genes produce the proteins that stimulate tumor activities important for invasion, the growth of new blood vessels to support the growth and nourishment of the tumor (a process called "neoangiogenesis"), the ability of the tumor to escape the functions of the immune system, and other characteristics.

Generic alterations in tumor cells that include mutations in certain genes, deletions of chromosomal regions, and epigenetic changes to DNA structure can identify the status of these tumor suppressor genes and the oncogenes, which drive the characteristics of the tumor. By testing for these genetic alterations in your brain tumor, your medical team can generate a genetic and epigenetic profile of your tumor to achieve a “layered” integrated diagnosis that can guide treatment choices.

To this end, these are the certain, basic genetic alterations that are routinely tested for an integrated diagnosis:

Mutations in IDH-1 and IDH-2

Mutations in the isocitrate dehydrogenase 1 and 2 (IDH-1 and IDH-2) genes cause the production of flawed enzymes that interfere with cell metabolism and promote the growth of tumors. Studies have shown that IDH-1 mutations are present in approximately 85-90% of secondary GBMs (i.e., glioblastomas arising from a progression of a lower Grade astrocytoma) but are rarely present in primary GBMs. Despite being a cause of tumors, mutations in IDH-1 and IDH-2 are associated with longer survival.

Although certain tumors contain IDH1/2 mutations, in astrocytic gliomas, IDH mutations are typically associated with mutations in TP53 and ATRX genes. In fact, the absence of the ATRX protein and the abundance of p53 protein are required for the diagnosis of an astrocytoma.

Modification of MGMT Gene and Methylation

The status of the MGMT gene predicts, at least to some degree, the sensitivity of the tumor to treatment with some of the standard brain cancer chemotherapies. Knowing the MGMT status provides the doctor with some insights as to best treatments and course of the disease. Here's how that happens.

An important brain cancer treatment drug is temozolomide (often called Temodar), which is a standard chemo for high-grade malignant gliomas. Temodar works by stopping the replication of a cancer cell's DNA. If the cancer cells cannot make more DNA, it cannot split into 2 new cells and, therefore, the cancer cannot grow. What the chemo is actually doing is putting alkyl (referred to as a methyl group by biochemists) on the O6 atoms of guanine on the DNA strand. This change severely damages the DNA of the cancer cells and if this change is not repaired, the cancer cells will die, which is what we want.

However, a protein (enzyme) produced by the MGMT gene is designed to protect the DNA of cells against damage from things like ionizing radiation, but it also protects cells from damage done by alkylating chemos. That repair enzyme is called O6-methylguanine-DNA methyltransferase or just "MGMT" for short. In short, the DNA repair enzyme produced by the MGMT gene can cause resistance to alkylating chemos like Temodar. This MGMT repair enzyme does its repair work by transferring the methyl group it finds at the O6 site of guanine to its cysteine residues. This avoids the desired genetic mutation of the cancer cell and its inevitable death. Clearly, this repair enzyme un-does at least some of the beneficial effects of Temodar or another alkylating chemo.

In some people with high-grade malignant gliomas, there are decreased levels of this MGMT repair enzyme because the DNA elements that promote the production of the MGMT repair enzyme have been changed due to an epigenetic modification of the MGMT gene. Many studies have shown that the loss of MGMT expression and decrease in repair enzyme production is not due to gene deletion, mutation, rear-

rangement, or unstable RNA, but rather to an epigenetic modification.

An epigenetic modification can be caused by exposure to environmental mutagens, such as UV radiation and N-nitroso compounds (e.g., foods containing sodium nitrites like processed meats and imported beers); these exposures are thought to account for 80% of the human cancer incidence.

For more information about epigenetic modifications, please go to this CDC site:

https://www.cdc.gov/genomics/disease/epigenetics.htm

The epigenetic modification to the MGMT gene impairs its production of repair enzyme. That is a good thing in the context of gliomas being treated with Temodar. When the tumor is said to be methylated, that means the amount of the DNA repair enzyme normally produced by the MGMT gene is reduced. Less MGMT repair enzyme = less interference with the cancer cell killing effects of Temodar or other alkylating chemo.

It then can be understood why tumors said to be unmethylated were twice as likely to progress during radiation as those with a mutated MGMT gene. Plus, the median time interval between resection and tumor progression of unmethylated tumors was also nearly half that of methylated tumors. In other words, unmethylated MGMT tumors generally tend to progress sooner following tumor resection than methylated MGMT tumors.

Nearly half of glioblastomas have MGMT promoter methylation. If the MGMT promoter test is "negative", your oncologist may still treat you with temozolomide as the tumor is heterogeneous and there may be variations within the tumor. Thus, temozolomide could be effective for a subpopulation of the GBM tumor cells. Studies show that temozolomide may be more effective in patients older than 65 years of age. Finally, patients whose tumors show the MGMT promoter is unmethylated could be eligible for specific clinical trials in which temozolomide is withheld in favor of a novel agent such as a targeted therapy or an immune modulatory agent.

Ki-67 or MIB-1 Index

Ki-67 or the MIB-1 index is a critical biomarker used in pathology to assess the aggressiveness of brain tumors. Ki-67 is a nuclear protein that is present during active phases of the cell cycle but is absent in resting cells. It is detected using immunohistochemistry on tumor tissue samples allowing pathologists to quantify the proportion of cells undergoing division. This assessment helps to differentiate between various tumor types and grades and measures the proliferation (growth) rate of tumor cells. A higher percentage, e.g. >5%, indicates a faster-growing tumor and can be used to help predict the tumor's aggressiveness and risk of recurrence. The specific numerical values as well as prognostic significance can vary between different tumor types and grades. For example, for meningiomas, a Grade I (benign) will have an average Ki-67 value of 3%; grade II (atypical), an average of 8%, and a grade III (malignant) an average of 17%. Some studies suggest a cutoff of 3% or 4% suggests a higher rate of recurrence, especially in Grade 1 tumors. For gliomas, based on WHO grade, for oligodendroglioma, the median ki-67 index is 4.4%, for WHO grade III, for anaplastic astrocytoma or anaplastic oligoastrocytoma, the median ki-67 is ~13%. For glioblastoma (IDH wild-type), a 15% threshold is being investigated as a prognostic marker, where a lower index could correlate with a longer survival time.

Codeletion of 1p/19q Chromosomes

During cell division, pieces from two different chromosomes sometimes switch places with each other. In some cases, when this rare event occurs, the chromosome pieces are jointly deleted. Codeletion of 1p/19q is an example of this type of chromosomal abnormality; part of chromosome 1 is switched with chromosome 19, and then both parts are removed.

In the 2021 WHO classification, codeletion of 1p/19q serves as a diagnostic biomarker for oligodendrogliomas. Tumors that have codeleted 1p/19q are more sensitive to chemo than those that lack the codeletion, and the presence of codeleted 1p/19q is associated with longer survival times.

Mutations of CDKN2A, CDKN2B

Among the mutations known to increase the risk of glioma development in adults are

cyclin-dependent kinase inhibitor 2A and B (CDKN2A, CDKN2B). CDKN2A loss is considered the most common mechanism for cell cycle dysregulation. Such a loss occurs in slightly more than 50% of GBM cases. Variants to three tumor suppressor genes close to both the CDKN2A and CDKN2B genes (on the chromosomal locus 9p21) are known to increase the risk for glioma, basal cell carcinoma, and melanoma. Untreated, a cancer exhibiting this biomarker can ultimately accelerate in growth.

Mutations of EGFR

Epidermal growth factor (EGF) is a protein that stimulates cell growth by binding to a receptor — conveniently called the epidermal growth factor receptor (EGFR). Many different types of cancer produce abnormally high levels of EGFRs, and when these EGFRs are stimulated by EGF proteins, they cause the cancer cells to divide and grow excessively. EGFR has been identified as a known oncogene for some forms of brain tumor. In an estimated 57% of GBMs, the EGFR gene is amplified. This means that there is an abnormally high number of copies of the EGFR gene in a cell, a situation that can lead to overproduction of the EGFR protein, signaling the tumor to grow.

High levels of EGFR are not found in normal cells, so controlling EGFR has been identified as a path to slowing down tumor growth. Because stopping the production of excessive amounts of EGFR or preventing EGF from binding to excessive amounts of EGFR could restrain the growth of tumor cells, EGFR has long been a target of several potential therapies for brain cancer.

There is a variant called EGFR Variant III (EGFRvIII) for which there are targeted treatments in development. EGFRvIII positive tumor cells are known to be resistant to cell death, have a faster growth rate and tend to be more invasive. About 30% of glioblastomas contain this variant, so researchers are targeting this factor in their treatment development efforts.

Mutations of TERT

TERT stands for telomerase reverse transcriptase. It is a gene that increases telomerase expression. The prevalence of TERT promoter mutations has been found in about 70-80% in GBMs of adults. The presence of TERT helps to confirm the fact that the tumor is primary (i.e., originating in the brain.) TERT mutations at

124C and 146C are considered "hot spots" for mutations and have been known to give rise to other cancers (i.e., ovarian, thyroid, melanoma). It is currently thought that the presence of TERT is not an early event in the development of a brain tumor. Primary GBMs without TERT mutations appear to behave more like high-grade astrocytomas, which generally lack TERT mutations. This possibility is supported by the observation that those primary GBM patients without TERT mutations had a longer survival, on average, than other primary GBM patients.

Mutations of p53

A tumor suppressor gene frequently identified in the development of astrocytomas is p53 (sometimes referred to as TP53), located on chromosome 17p. The p53 protein has been found to influence multiple functions including progression through the cell cycle, DNA repair after damage, gene stability, and the tendency for a cell to undergo cell death (apoptosis) following treatment. One of this gene's major functions is to prevent abnormal cells with damaged DNA from reproducing. It does so by releasing a protein referred to as p53. When the p53 gene is mutated, the p53 protein is inactive. Since mutant p53 cannot bind to the DNA in an effective way, cells with damaged DNA are allowed to proliferate without check and form tumors. p53 mutations have been reported in approximately 40% of astrocytic tumors of all grades.

A certain, rare variant of TP53 has been implicated in the development of Li-Fraumeni syndrome. Li-Fraumeni predisposes carriers to a variety of cancers, including brain cancer, throughout their lifetime. More than half of all families with Li-Fraumeni syndrome have inherited mutations in the TP53 gene.

H3K27 mutations

There are mutations in histones — specialized proteins around which the DNA in our cells are wound — that can contribute to the pathogenesis of cancer and other genetic diseases. These mutations are found in most of the diffuse gliomas arising in midline brain structures, such as the thalamus, brainstem, and spinal cord. Tumors in these locations occur primarily in children but also sometimes in adults. These tumors have a Grade 4 classification. If your pathology report indicates that you have this mutation, please contact the Musella Foundation to learn about experimental therapies targeted to this mutation.

Mutations of BRAF

Primary brain tumors can exhibit alterations in the v-raf murine sarcoma viral oncogene homolog B1 (BRAF) gene. Under normal conditions, the unmutated BRAF gene encodes a protein that plays a crucial role in a cell signaling pathway responsible for regulating healthy cell growth and division. When mutated, however, the BRAF gene may send persistent signals, resulting in uncontrolled cell proliferation and tumor development.

The two most frequent BRAF alterations in brain tumors are the BRAF V600E point mutation and the KIAA1549-BRAF fusion. The BRAF V600E mutation is most often identified in pleomorphic xanthoastrocytoma (PXA), ganglioglioma, epithelioid glioblastoma, and gliomas diagnosed in younger patients. In contrast, the KIAA1549-BRAF fusion predominates in pilocytic astrocytoma. While BRAF V600E mutations are uncommon in adult glioblastomas, their presence in certain adult gliomas has been associated with improved survival. Targeted therapies that address these alterations present significant treatment opportunities for patients with BRAF-driven brain tumors.

Several BRAF-targeted therapies have received FDA approval for gliomas. Notably, the combination of dabrafenib and trametinib is approved as first-line systemic therapy for pediatric low-grade gliomas in patients aged one year and older with BRAF V600E mutations. Clinical studies demonstrated an objective response rate (ORR) of 47%, compared to 11% with standard chemotherapy. This combination also holds accelerated approval for both adult and pediatric patients (over 6 years old) with BRAF V600E-mutated, unresectable, or metastatic solid tumors, including high-grade gliomas (HGG) following recurrence.

Tovorafenib (Ojemda) has received accelerated approval for patients as young as six months with BRAF fusions, rearrangements, or V600 mutations. Unlike earlier (Type I) BRAF inhibitors, tovorafenib is a Type II RAF inhibitor and is effective against tumors with BRAF fusions, such as KIAA1549-BRAF, which are common in pilocytic astrocytomas. Consequently, targeted therapy is increasingly considered standard-of-care for BRAF-altered low-grade gliomas (LGG), offering superior progression-free survival and response rates compared to traditional carboplatin/vincristine regimens.

For high-grade gliomas, although BRAF V600E mutations are rare (approximately 1–3%), targeted therapies provide a vital alternative for these aggressive tumors, which often respond poorly to standard treatment. Additionally, BRAF-targeted agents are being used more frequently in recurrent cases for both adults and children with relevant genetic alterations (BRAF V600E mutations, fusions, or rearrangements).

Importantly, modern BRAF inhibitors, such as dabrafenib and investigational agents like PF-07284890 (NCT0453188), can cross the blood-brain barrier and have demonstrated activity even in leptomeningeal disease. A significant challenge with all targeted therapies is the development of acquired resistance, often due to reactivation of the MAPK pathway. While these drugs can induce substantial tumor shrinkage, they are typically cytostatic rather than cytotoxic or curative, raising debate over optimal treatment duration and the potential for "rebound" tumor growth upon abrupt discontinuation. Side effects from BRAF-targeted therapies are generally manageable and may include fever, skin rash, headache, or fatigue.

+7/-10 Chromosomal Changes

The simultaneous loss of chromosome 10 (-10) and gain of chromosome 7 (+7) in gliomas represents the most common loss-gain chromosomal pair observed in human cancers. This pattern has been studied since the 1980s and is recognized as an early event in the development of IDH-wild type glioblastomas. Chromosome 7 gain often includes the region encoding the epidermal growth factor receptor (EGFR), a well-established oncogene, while chromosome 10 loss typically affects the phosphatase and tensin homologue (PTEN), a known tumor suppressor gene. Although the precise functions of these genetic changes are not fully understood, their presence is generally linked to a poorer prognosis.

The World Health Organization (WHO) now recognizes the "+7/–10 signature" as an official criterion for diagnosing IDH-wildtype (IDH-wt) glioblastoma, even if the tumor appears to be lower grade by histological examination. This chromosomal signature is highly specific to glioblastoma and is associated with aggressive clinical behavior, reduced response to radiation therapy, and decreased survival rates. Patients exhibiting both chromosome 10 loss and chromosome 7 gain have a

significantly worse prognosis compared to those with only one or neither of these alterations.

Timing/Delays

Depending on the checks to be done on the harvested tissue, the results of the evaluation (and therefore the diagnosis) may take anywhere from a few days to even a few weeks to be complete. The uncertainty and anxiety waiting for results can be stressful, so it is helpful to discuss with the doctor some notion of when you might expect to have a diagnosis.

Some reasons for delays include but are not limited to the need to use special stains to differentiate cellular components which may have to be freshly acquired, the need for larger samples than were initially provided to the lab (these will be obtained from the stored biopsy or surgical sample), or advanced tests like flow cytometry and electron microscopy. In the case of rare or unusual findings, the pathologist may seek a second opinion before entering their conclusion in the record to ensure maximum accuracy of the conclusions.

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 disciplines who will weigh all the evidence (e.g., pathology findings, MRI/CT Scan images and medical history) to agree on the diagnosis and proposed treatment.

The accuracy rate for diagnosing a brain tumor varies significantly depending on the diagnostic methods used, the tumor type, its location, the volume of tissue removed, etc. Sampling errors can occur because of the heterogeneity of tumors, the presence of necrosis, cysts, or inflammation. MRI and CT scans are the primary tools to detect the presence of a brain tumor and can be highly accurate (greater than 85%) for extra-axial (i.e., outside of the brain tissue) tumors such as meningiomas and pituitary adenomas. However, there is lower accuracy, sometimes less than 70%, for intra-axial tumors (within brain tissue) for certain types of gliomas and those in complex areas such at the pineal area or intraventricular zones. A glioblastoma might have a diagnostic accuracy, for example, of 73%. It is often prudent, if there is ambiguity as to the pathological diagnosis, to send the tissue to a center of excellence that sees a high volume of brain tumors with special expertise in neuropathology.

Diagnosis Results

The diagnosis will provide the name of the type of tumor (out of the 130+) available and the grade level.

Even though a brain tumor may have the same name as another, each brain tumor is unique with a highly variable molecular design and its own equally unique immune system environment. Understanding both the molecular composition of the tumor and the various immune infiltrates (or lack of them), are pivotal in treatment selection.

Owing to the diversity among tumors, being overly distracted by what worked for the uncle of a friend, or what is written in some long-term survivor's blog may turn out to be a disservice to you because it is highly unlikely that the two tumors are an exact match in their molecular/DNA structure and the immunosuppressive environments. Then when one considers other factors like age, tumor location and operability, gender, health, etc., the differences between one tumor and another grows even more.

Based on these various studies, the best strategy appears to be to ensure the characteristics of your unique tumor is defined with the most appropriate level of detail and clarity as recommended by the attending doctor, and that this definition is the basis for treatment selection.

Your unique tumor will be described to an extent in a pathology report, which formed the basis of your diagnosis. If you don't have a copy, you may wish to ask for it for your files and future reference.

For more information about the genetic structure of GBMs please see Appendix A entitled "Molecular Characteristics of GBMs" at the back of this Guidebook.

Get The Facts About Your Cancer Diagnosis

Try to obtain as much basic, useful information about your cancer diagnosis as you need to make decisions about your care. Write down your questions and concerns beforehand and bring them with you. Consider asking:

- What kind of cancer do I have?
- Where is the cancer?
- Has it spread?
- Can my cancer be treated?
- What is the chance that my cancer can be cured?
- What other tests or procedures do I need?
- What are my treatment options?
- How will the treatment benefit me?
- What can I expect during treatment?
- What are the side effects of the treatment?
- When should I call the doctor?
- What can I do to prevent my cancer from recurring?
- How likely are my children or other family members to get cancer?

Consider bringing a family member or friend with you to your first few doctor appointments to help you remember what you hear.

You might also want to consider how much you want to know about your cancer. Some people want all the facts and details, so they can be very involved in the decision-making process. Others prefer to learn the basics and leave details and decisions to your doctor. Think about which approach works best for you. Let your health care team or caregiver know what you'd prefer.

Primary Versus Metastatic Tumors

If conclusive, the diagnosis would identify if the tumor originated in the brain or elsewhere in the body. A tumor originating in the brain is considered primary; those originating elsewhere are identified as metastatic.

Primary Tumors

Primary brain tumors start from brain cells, nerves, glands (like the pituitary) or from the membranes that surround the brain (called the meninges). Not all primary brain tumors are cancerous.

93% of primary brain tumors are diagnosed in people over 20 years old; people over

85 have the highest incidence. The average age at diagnosis is 57.

Medical professionals widely believe that primary, malignant brain tumors do not metastasize outside the central nervous system. However, there are exceptions in approximately 0.5% of cases.

Metastatic Tumors

A metastatic brain tumor is a tumor that develops from cancer cells originating elsewhere in the body that have spread to the brain. Metastatic brain tumors are named for the location in which they originate and are all considered cancerous. Approximately 20-40% of people with cancer will see their cancer spread to the brain, often depending on the originating cancer. For instance, close to 40% of people with lung cancer will develop metastatic brain tumors.

The likelihood that a brain lesion is metastatic should be assessed before proceeding to biopsy or surgery.

Metastatic brain tumors are four times more common than primary brain tumors in adults. Although metastatic brain tumors usually occur in the context of known systemic cancer, they can also occur as the first sign of a systemic cancer. If any aspect of the clinical or neurodiagnostic evaluation suggests that a brain tumor is a metastatic rather than a primary lesion, systemic evaluation, including CT scan of the chest, abdomen, and pelvis or a PET scan of your entire body should be performed.

Treatment for metastatic brain tumors is dependent upon the treatment of the originating, primary cancer. As a result, an individual with a metastatic brain tumor will need the support of a closely coordinated team of doctors to include the oncologist for the originating, primary cancer, and a neuro-oncologist for guidance in treating the brain tumor.

Recently, trying to understand why a tumor in one part of the body will transition to another, researchers have learned that cancers are able to hijack a metabolic pathway that breaks down fats and proteins, which boosts the levels of a byproduct called methylmalonic acid. We have also learned that as people age, their bodies produce more methylmalonic acid. This methylmalonic acid drives cancer progression and

invasion in another location. In that process, the cancer must suppress the activity of a key enzyme and when that suppression happens, the cancer becomes more aggressive and invasive.

Metastasis is responsible for the majority of cancer-related mortality, so researchers are working on finding ways to predict who might have the tendency to produce metastatic lesions and on developing new therapeutics to discourage the metastasis in the first place.

In the last few years, there have been dramatic advances for the treatment of brain metastases, including the use of immunotherapy and brain-penetrant, targeted therapy. The development of small-molecule tyrosine kinase inhibitors (TKIs) has been a significant breakthrough, especially for non-small cell lung cancer (NSCLC) and melanoma. For NSCLC, specific EGFR inhibitors (e.g., osimertinib [Tagrisso], which is brain penetrant, and ALK inhibitors (e.g., crizotinib [Xalkori] can be effective against brain metastases, sometimes delaying the need for radiation therapy. For patients with breast cancer, the combination of tucatinib, capecitabine and trastuzumab has demonstrated significant activity in the central nervous system for HER2-positive cancer, improving progression-free survival. For patients with melanoma, BRAF inhibitors (e.g., dabrafenib [Tafinlar®]) or vemurafenib[Zelboraf®] plus MEK Inhibitors (e.g., trametinib [Mekinist®]) have shown remarkable intracranial activity in patients with BRAFV6004-mutant tumors.

Immunotherapy, using immune checkpoint inhibitors (ICIs), has been highly effective for metastatic melanoma to the brain, and at times, for NSLC. This is especially true of the combination of anti-CTLA-4 (ipilimumab [Yervoy®]) and anti-PD-1 (e.g., nivolumab [Opdivo®]. There have been durable responses, i.e., long-term survivors who appeared to be cured of intracranial disease, and significant responses in a subset of patients with asymptomatic brain metastases. New immunotherapeutic approaches, such as anti-LAG-3 (e.g., relatlimab) are being explored, in combination with nivolumab [Opdualag®] to further enhance efficacy.

Additionally, more sophisticated diagnostic tools are available today, in addition to innovative surgical and radiation approaches, which have helped survival rates expand in the last years. These improvements also provide for better quality of life for patients following diagnosis.

Most Common Primary Brain Tumors

Overview of Gliomas

In this Guidebook, the focus is on gliomas, a category of CNS tumors that arise from glial cells. Glial cells are the "support cells" of the CNS, helping neurons and nerve cells do their jobs. Glial cells are subdivided into astrocytes, ependymal cells and oligodendroglial cells (or oligos). Primary tumors are identified by the predominance of the type of cells found in the tumor tissue.

Gliomas are the most common type of primary brain tumors, accounting for 78 percent of malignant brain tumors. These are serious tumors with the capability of producing a combination of problems for people ranging from memory loss to seizures resulting from the compression of brain tissue as the growing tumor competes for space and from tumor infiltration into the surrounding healthy brain tissue, so they require expert medical intervention.

A landmark publication in The New England Journal of Medicine (NEJM) distinguished three genetic subsets of gliomas: (1) IDH wild-type gliomas, the most common and lethal type; (2) IDH mutant astrocytomas, which have longer survival; and (3) oligodendrogliomas, with both IDH mutations and 1p/19q co-deletions, which have the longest survival.

A description of some of the most common glial tumors follow below.

Astrocytomas

Astrocytomas are the most common primary tumor. Most occur in men and women older than 45. About 50% of primary brain tumors are astrocytomas. This type of tumor originates from astrocytes, which are star-shaped glial cells found in the supporting tissue of the brain. Astrocytes can be readily identified histologically since they have a filament called a glial fibrillary acidic protein (GFAP). 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 process of the brain and spinal cord following mechanical / inflammatory injuries and providing a "guidance" for

growing neurons / axons during the development of the brain.

Astrocytomas may occur in many parts of the brain but are most commonly found in the cerebrum. People of all ages can develop astrocytomas, but they are more prevalent in adults, particularly middle-aged men. 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:

WHO Grades 1 through 4: Pineal astrocytoma (a tumor that forms in the pineal gland). This form can have any Grade, depending on its aggressiveness.

WHO Grades 1 and 2 (Low grade): These occur more frequently in children or young adults and include:

- Astrocytoma (Grade 4) which is a fast-growing tumor. It is different from a Glioblastoma in that the Astrocytoma Grade 4 has a mutated IDH-1 gene, whereas a Glioblastoma does not. It is also differentiated from a Grade 3 Astrocytoma owing to its greater aggressiveness in growth and invasiveness due to its CDKN2A/B deletions.

Glioblastomas (GBM)

Glioblastomas (GBM) are the most common, fastest growing and the most invasive type of brain tumor in adults. GBMs account for nearly 50 percent of all primary brain tumor cases. In a few rare cases, a secondary GBM may progress from a lower grade astrocytoma. GBMs can occur anywhere in the brain, but most typically forms in the frontal or temporal lobes.

Glioblastomas, like astrocytomas, develop from astrocytic cells but are characterized by significant cellular heterogeneity (diversity) and typically contain several different types of malignant cells, including those with features resembling the progenitor cells of oligodendrocytes (OPCs). Recent single-cell RNA sequencing (sc-RNAseq) reveal that malignant cells within a GBM exist in four main, highly plastic cellu-

lar states that mimic normal developing brain cell types. In addition to the OPCs, there are neural progenitor cells, mesenchymal-like cells and astrocyte-like cells. This plasticity is a major reason why single-target drug therapies often fail, as the glioblastoma can adapt and escape the treatment.

Slightly more men develop GBMs than women, and the risk of occurrence increases with age. Most people are diagnosed between the ages of 50 and 70, but they can occur at any age. Doctors diagnose about 15,000 glioblastoma cases in the U.S. each year.

These tumors are:

- aggressive, fast growing.
- diffuse; GBMs spread into nearby regions of the brain erratically and sometimes to the opposite side of the brain. They can be surgical challenges.
- likely to return, even if totally removed and intensively treated.
- have a distinctive appearance that helps neuropathologists distinguish them from a lesser Grade tumor.

Prior to the 2021 WHO classification update, Grade 4 astrocytomas (not in the pineal gland) were all classified as a Grade 4 Glioblastoma. With the 2021 classification, tumors classed as Grade 4 Glioblastomas are limited to tumors found to be negative for mutations in the IDH-1 gene, owing to the substantial differences in the course of the disease and treatment challenges. As a result of this change, aggressive astrocytomas with a mutated (positive) IDH-1 gene are no longer classified as Grade 4 Glioblastomas, but rather are classified as Grade 4 astrocytomas.

Based on the 2021 WHO classification, a typical GBM has alterations in EGFR, no mutations in the IDH-1 gene, and alterations (even losses) in chromosomes 7p and 10q or the TERT promoter.

GBMs can be resistant to treatment. One of the reasons for that resistance is that a GBM is a very complex cancer. As its full name - Glioblastoma Multiforme- suggests, this tumor is multiforme in its gross structure; it has not just tumor tissue, but

necrosis (clumps of dead cells) and areas of hemorrhage. The tumor is multiforme in its microscopic structure; it has regions of elongated and compressed necrosis and tumor cells, plus cell nuclei of substantial variation in size and shape. The tumor is multiforme genetically with a variety of genetic alterations, deletions, and amplifications.

One of the challenges in treating GBMs is that a GBM is not a homogeneous tumor. A GBM has been described as a cluster of different cancers. Cells within the same tumor will display distinct characteristics that affect their growth rate, survival, migration, and therapy-response.

These cells have the ability to change depending on factors within a tumor and outside of the tumor. Analysis shows that GBM cells exist in at least four different cellular states and can change between them. As a result, treating a GBM is like trying to shoot a moving target. One treatment that might shrink and contain the GBM for a few months, killing susceptible cells, may leave surviving cells that are resistant to that treatment.

Currently, there are three subtypes of glioblastoma: classical, proneural, and mesenchymal. This widely accepted triparte scheme excludes tumors with a mutated IDH gene, which is not characteristic of a glioblastoma under the latest WHO standards. For more information about GBMs please see Appendix A entitled "Molecular Characteristics of a GBM."

The challenges presented by GBM are motivating researchers to find new and sophisticated ways of treating this cancer. One promising new treatment approach for cancer is microRNAs (miRNAs). One miRNA can target multiple miRNA transcripts, which allows the targeting of multiple cancer-producing pathways using a single drug. This will not just enhance the effectiveness against the whole GBM but will reduce the chances the GBM regrows.

RNA science is being used to develop novel vaccines directed against glioblastoma. Using similar technology developed for the COVID vaccine, leading to the 2023 Nobel Prize in Medicine and Physiology, researchers are using miRNA vaccines and nanoparticles to treat glioblastoma in preclinical models with early, promising success in human clinical trials in glioblastoma and pancreatic cancer.

Oligodendrogliomas

Oligodendrogliomas account for less than 10% of all primary brain tumors. This type of tumor also accounts for 4% of primary brain tumors in children. They originate from oligodendrocytes, which are cells with a cross-section that look like trees with only a few branches. Oligodendrocytes are the myelinating cells of the central nervous system (CNS), so they are quite vulnerable. (Myelination is the insulation wrapping found around the axon, which is a long and spindly part of nerve cells.)

Oligodendrogliomas can be low or high grade:

- WHO Grade 2 (low grade): are slow-growing tumors with relatively better prognosis than the same grade astrocytomas (pilocytic and diffuse astrocytoma) and roughly the same symptoms as low-grade astrocytoma.

- WHO Grade 3:(high grade): as referred to as oligodendrogliomas. These are rapid growing and often consist of a combination of cancerous astrocytes and oligodendrocytes.

Oligodendrogliomas can occur anywhere within the CNS but are primarily found in the frontal and temporal lobes of the cerebral hemispheres.

Medulloblastomas

A medulloblastoma is the most common pediatric brain cancer, accounting for 10% to 15% of pediatric central nervous system tumors. They are high-grade (Grade 3 or 4) tumors and are thought to originate in embryonic tissue. Owing to that, they are likely to be discovered in the first five (5) years of life and be exceptionally rare in adults. More boys have this type of tumor than girls.

Almost all medulloblastomas arise in the cerebellum at the back and base of the brain. They are typically treated with surgery, chemo, and radiation.

Ependymomas

Ependymomas, which 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.

Ependymomas account for two to three percent of all brain tumors. Most are well-defined, but some are not. There are three grades of ependymoma:

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.

High grade Ependymoma (Grade 3): Known as anaplastic ependymomas, these are malignant tumors that mostly occur in the brain (versus the spine).

Surgery, ideally resulting in a gross total removal, is the essential initial treatment of ependymomas in adults and children. In children with intracranial ependymomas of WHO grades 2 or 3, surgery is followed by local radiotherapy regardless of residual tumor volume. In adults, radiotherapy is used for patients with anaplastic ependymoma WHO grade 3 and in case of an incomplete resection of WHO grade 2 ependymoma. Chemotherapy alone is used in children younger than 12 months old and in adults with recurrent disease when additional surgery and irradiation are no longer feasible. A gross total removal is the cornerstone of treatment for spinal ependymomas with radiotherapy used for incompletely resected tumors.

Meningiomas

Meningiomas are not gliomas but are among the most common brain tumor in adults, accounting for 20-30% of all primary brain and spinal cord tumors. A meningioma develops on the brain's meninges (the tissue around the outer part of the brain and spinal cord) and is a tumor of leptomeningeal origin.

The meninges consist of the outer three layers (dura mater, arachnoid mater, and pia

mater) of a thin tissue designed to protect the brain and is found just under the skull. Meningiomas commonly form in areas populated with heavy amounts of arachnoid villi (located in the second layer which covers the brain).

Meningiomas are almost invariably benign, but some can be cancerous. Elderly patients are more frequently affected. It is believed that meningiomas might be caused by a genetic abnormality or chromosomal defects (e.g., partially or completely missing chromosome 22), however, other studies show that meningiomas reacts to hormonal changes or trauma. Ultimately, we are not sure what causes these tumors. However, those diagnosed with Neurofibromatosis Type 2 may be affected by multiple meningiomas and bilateral vestibular schwannomas. Neurofibromatosis Type 2 has been proven to be hereditary.

The risk of developing a meningioma increases with age. They occur 2 to 4 times as often in women than men, partly because meningiomas have progesterone and estrogen receptors, therefore, female hormones promote the growth of these tumors. This mechanism is supported by the fact that pregnancy can accelerate the growth of meningiomas, and the tumors are more common in menopausal women taking hormone replacements.

Pediatric Brain Cancers/DMG/DIPG

Brain cancer is the second-most common type of cancer in children, surpassed only by leukemia and is the leading cause of deaths among children.

Diffuse Midline Glioma (DMG) is a serious pediatric glioma that arises at the critical connection point linking the brain cortex—an area responsible for complex information processing, logical reasoning and thinking—to the spinal cord. A DMG in the pons is referred to as a Diffuse Intrinsic Pontine Glioma (DIPG).
Because those tumors are buried deep inside the brain, surgery is often impossible, and they are usually non-responsive to radiation. However, there is a lot of research going on for this time of tumor in the areas of immunotherapy and targeted treatments.

Recently, researchers have discovered that DMG's are uniquely dependent on methionine. Methionine is one of nine amino acids that our bodies use to make proteins. Since we are unable to make methionine, we must obtain our methionine from foods

with this amino acid, such as poultry and legumes. Researchers are now understanding that controlling methionine in the diet may help extend survival of the children with this disease and may make other therapies more effective.

For more information about different specific types of CNS tumors and how they are treated, visit the section on brain tumors on the website of the National Cancer Institute (NCI). The NCI is the principal agency for cancer research and training of the United States federal government. The section on CNS tumors is located at: www.cancer.gov/types/brain.

How Long Has the Tumor Been There?

Development and Growth Patterns of Glioblastoma

Glioblastoma is a highly aggressive type of brain tumor that typically develops over a span of months to a few years, depending on its underlying biological pathway. Most glioblastomas emerge suddenly and without any clear early warning signs; these are known as primary, or de novo, glioblastomas. In such cases, the malignant transformation likely occurs within just a few months.

Research has shown that, on average, the time from the initial onset of symptoms to a clinical diagnosis of glioblastoma is approximately four months. By the time patients notice symptoms, the tumor is often already growing rapidly. The precise factors that can cause a previously dormant or undetectable tumor to suddenly begin aggressive growth remain unknown. Notably, glioblastomas are recognized for their swift progression; once they become malignant, the tumor can demonstrate significant growth within weeks. Cell-division rates typically range from 1.1% to 2.2% per day, and the tumor may double in size every three to eight weeks.

Interestingly, as the tumor increases in size, the growth rate tends to slow down—a phenomenon known as Gompertzian growth. For instance, a small glioblastoma (less than 4 mL in volume) may exhibit a daily growth rate of 3.9%, whereas a much larger tumor (greater than 37 mL) may grow at only 0.3% per day.

Additionally, different regions of the tumor can grow at varying rates. The non-

contrast enhancing compartment, which is visible on FLAIR MRI sequences, often grows more quickly (2.2% per day) compared to the contrast-enhancing compartment (1.0% per day). This observation provides support for "supratotal" surgical resections, where both the contrast-enhancing tumor and the adjacent FLAIR abnormality are removed.

Primary Versus Secondary Glioblastoma

A smaller proportion of glioblastoma cases follow a different course. These are called secondary glioblastomas, which originate as lower-grade gliomas and gradually progress into a more aggressive form. This transformation typically occurs over five to ten years before the tumor evolves into a glioblastoma. Secondary glioblastomas are more frequently seen in younger adults.

The traditional classification distinguishing primary (de novo) from secondary (progressed) glioblastomas has evolved into a molecular-based distinction. Tumors now categorized as GBM, IDH-wildtype, refer exclusively to what was previously known as primary glioblastoma. These tumors generally affect older adults and are marked by their pronounced aggressiveness and rapid onset.

Tumors once identified as secondary glioblastomas are now classified as Astrocytoma, IDH-mutant, CNS WHO grade 4. Although these tumors appear identical to glioblastoma under the microscope, their distinct IDH mutation is associated with a different growth pattern and, as a result, a better prognosis.

Clinical Presentation and Detection

In general, by the time patients experience symptoms such as headaches, seizures, or neurological changes, the glioblastoma has likely been growing for several months at a size that could be detected. However, because the earliest stages of development do not produce symptoms and are not visible on imaging, determining the exact moment the tumor first began to form is extremely challenging.

Grade Levels (Defined)

Brain tumors are given grades, as opposed to stages. Tumor grade is not the same as a cancer stage. Cancer stage refers to the size and/or extent (reach) of the original (primary) tumor and whether cancer cells have spread in the body. The grade of a brain cancer is indicative of its current speed of growth and the potential to interfere with brain function. Grading is a determination of what stage the tumor is at, or how advanced (bad) it may be in its development.

The WHO classifies all cancers on a grade of 1 to 4. Brain cancer tumors vary in their malignancy, from Grade 1 (least aggressive) to Grade 4 (most aggressive). The grade levels are as follows:

- Grade 1 means a very slow growing tumor that is "well differentiated" and is unlikely to spread much, if at all. They can often be cured with surgery. This is the grade level meant when a tumor is called benign. Long term survival is likely.

- Grade 2 means a tumor that has slightly abnormal characteristics and is slow growing. It is considered "moderately differentiated." It is considered a cancerous tumor, but of a low grade. This tumor might regrow after treatment at a more life-threatening grade.

- Grade 3 means a tumor whose cells look abnormal. It is actively growing but may have little or has no dead cells. This tumor is considered a "poorly differentiated" high grade cancer. This tumor tends to regrow after treatment at a more life-threatening grade.

- Grade 4 means an "undifferentiated", high grade tumor where its cells are abnormal and actively dividing. Plus, the tumor has abnormal blood vessel growth and areas of dead tissue (sometimes called necrosis). Grade 4 tumors can grow and spread quickly.

Classification Summary Table

The table below displays a summary of the WHO classification of brain tumor grades and their general characteristics.

Grade	Tumor Types	Characteristics
Low Grades		
Grade 1	Craniopharyngioma Chordomas Ganglioglioma Gangliocytoma Pilocytic astrocytoma	Possibly curable via surgery alone Long-term survival Least malignant (benign) Non-infiltrative
Grade 2	Pineocytoma "Diffuse" astrocytoma Pure oligodendroglioma	Slightly infiltrative Relatively slow growing Can recur as higher grade
High Grades		
Grade 3	Anaplastic ependymoma Astrocytoma Anaplastic oligodendroglioma	Malignant Infiltrative Tend to recur as higher grade
Grade 4	Glioblastoma multiforme/ GBM Astrocytoma Medulloblastoma Ependymoblastoma Pineoblastoma	Malignant Rapidly growing and aggressive Widely infiltrative Recurrence is common Tendency for necrosis

Grade Levels (How Determined)

Overview

Grading a specific tumor type has been described as a process that is as much an "art form" as a science and typically involves a determination made by a pathologist after a biopsy or surgery.

If the tumor tissue has been obtained by biopsy, grading can be somewhat

controversial depending on the size of biopsy specimen obtained. One part of the tumor may have smaller lower-grade cells, while larger more aggressive cells may be present in a different location in the tumor.

Furthermore, tumors initially assigned a low grade can become aggressive in growth, changing the status of the grade even during treatment. It is important to have your biopsy examined by a neuropathologist who sees a large number of brain tumors, always requesting a copy of the report for your records and comparison.

Factors in Grade Determination

The determination of Grade level is based on factors that include, but are not limited to these:

- The presence or absence of mutations of the IDH-1, MGMT Promoter and TP53 genes.

- The presence or absence of other mutations that will contribute to the doctors' understanding of the aggressiveness of the tumor. If a pathologist has access to sufficient tumor tissue, the presence of mutations/biomarkers can be checked (e.g., EGFR, GFAP, PTEN, MDM2, H3K27M, PDL1, NF1, PIK3CA, etc.).

- Mitotic index (or MIB factor or Ki-67 index). This index offers a view in terms of the rate at which the tumor cells replicate/grow. This is often shown on the pathology report.

- Tumor size and observable diffusion through the brain based on contrast MRI images. Experienced neurosurgeons and neuro-oncologists can often accurately predict the official diagnosis from the images but are obliged to withhold final judgment until the pathology report is issued.

- Histological Factors. Sometimes when the slides of the tissues are examined under the microscope, certain characteristics are observed that provide some important clues as to aggressiveness, such as invasiveness, angiogenesis, necrosis (tissue death), mitosis, nuclear atypia (abnormal cell nuclei) or cellular proliferation. In addition, the pathologist may search for other proteins that provide

clues to the origin and aggressiveness (grade) of the brain tumor. These include:

a) GFAP (glial fibrillary acidic protein) which is routinely used in histology to identify and grade gliomas as it is highly expressed in glial cell, which are the cells of origin for gliomas; and

b) synaptophysin, which is often positive in oligodendrogliomas (especially when combined with other molecular markers such as IDH mutation and 1p/19q co-deletion) but can be negative in higher-grade gliomas. Expression of synaptophysin can be variable, so a negative result does not exclude an oligodendroglioma; and

c) cytokeratin, which can be a marker for carcinomas, and is often found in metastatic cancer to the brain, but may also be found in gliomas, especially high-grade gliomas, thus the overlap can make it difficult to distinguish a primary (glioma) from a secondary (metastatic cancer).

Importantly, no single tissue marker such as synaptophysin nor cytokeratin alone is sufficient for a definitive diagnosis, but the actual diagnosis relies on the integration of multiple layers of evidence by the pathologist, including histology, immunohistochemistry (e.g., GFAP, synaptophysin, and cytokeratin) and molecular-genomic testing.

For a detailed discussion about the molecular characteristics of a Grade 4 Glioblastoma, please see Appendix A entitled "Molecular Characteristics of a GBM".

What are Survival Statistics for Those with Brain Tumors?

Nobody knows how long you are going to live with your brain tumor. Statistics are a tool used for comparing treatments and for describing what has happened in the past to groups of people with your tumor type. Statistics cannot predict how long any individual person will live.

There are two important survival statistics that you will commonly see in research about brain tumors:

- Overall survival (OS): OS is the average survival time of a group under study — such as 1 or 2 years. Just because a 1-year or 2-year survival statistic is reported does not mean that you will live for 1 or 2 years. Rather, it means that on average the people described in that particular research lived for that length of time; and

- Progression-free survival (PFS). PFS is reported either as the percentage of people who reach a milestone without having tumor progression — such as 6 months or 1 year — or as the average number of months before tumor progression for the entire group. Progression means tumor growth or regrow.

The survival statistics of OS and PFS are commonly used in medical research, and you can compare treatments by looking at either number. We feel that PFS is the more important survival statistic because after people experience tumor progression, they usually move on to other treatments. In that case, relying on the OS survival statistic to evaluate a treatment may be misleading. As you read about survival statistics, keep in mind that they fail to take into consideration many factors that are extremely important on a case-by-case patient basis — such as age, general health, tumor size and location within the brain, the extent of tumor surgical removal, and much more, including access to the care of brain tumor experts.

Surgical technologies and the ability to accurately diagnose brain tumors have improved dramatically, and ongoing clinical trials are leading the way to new and better treatments. Your ability to challenge survival statistics will greatly depend on surrounding yourself with a medical team that is not influenced negatively by such numbers. Importantly, there are increasing numbers of long-term survivors found in the "tail" of the Kaplan-Meier survival curves that should provide hope, and these long-term survivors may not be reflected in the numbers generated in the median 'overall survival' (OS). The median OS represents, statistically, the number which half of the patients achieve, and does not, by itself, report these long-term survivors.

Try to avoid those within the medical community who have an unfortunate and bleak outlook and may not be current in their understanding of advanced, new treatments. Physicians associated with, and in consultation with, leading brain tumor medical centers are your best defense against negative survival statistics and will enhance your ability to remain positively engaged during your journey through

treatment. An overly pessimistic outlook, or therapeutic nihilism, can lead to self-defeating behavior and self-fulfilling, negative predictions which taken together, can also precipitate depression—a common, unfortunate consequence of having a brain tumor, especially a glioblastoma.

Look for people with your tumor type who are leading normal lives. These people prove that no tumor type is completely hopeless. Participate in online and real-world support groups, discussed later in this book, to meet others who have gone through the same medical crisis as you but are now many years out and doing well. It is important to see and acknowledge that there are people with brain tumors who do well.

If you want to see brain tumor survival statistics, go to the website of the Central Brain Tumor Registry of the United States:

https://cbtrus.org/cbtrus-fact-sheet/

Coping with a Brain Tumor Diagnosis (Practical)

The diagnosis of a brain tumor can leave patients and their loved ones in a mental fog, a fog so thick with questions that simply determining where to begin can be debilitating. There are ways in which you can regain control, step out from the fog, and achieve some much-needed clarity.

Use Your Hospital's Health Portal. If your hospital or clinic offers a "MyChart" or "Health Portal", it is advisable to sign up for use. With just a few clicks, you can view test results, schedule appointments, request prescription refills, and communicate directly with your care team—anytime and anywhere. It's a convenient way to stay informed, stay connected, and manage your care online.

Ask Your Doctor for a Case Manager (or Nurse Navigator). Not all the brain tumor clinics have them, but some do, and if you can get one assigned to you, they can be a major asset for you. A case manager serves as a link between you, the doctors, and other service providers (e.g., insurance companies) throughout your care, and can be especially helpful when one of the thousand questions emerge for which you need guidance but not necessarily from the doctor. They cannot treat you

or provide medical direction, but they can provide education and information to enable you to obtain your medical services more efficiently and effectively.

Organize A Binder. Organization is your key to obtaining the information you will need for finding the proper treatment necessary for your specific type of tumor. The following are approaches that have helped other brain tumor patients:

A three-ring binder can become your best friend and treatment partner for safeguarding and promptly retrieving all the necessary information about your tumor type and treatment plan. Referrals to specialists or for second (or third) opinions are often delayed by the need to obtain records sometimes caused by records that 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.

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) and pathology reports from biopsies. 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 as well as pathology reports from biopsies, 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.

● 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.

Photo Credit Brian Singer



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 on Page 99 of this Guidebook) can help you organize your medical records.

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.

Know The Location. Knowing the exact location of your tumor will assist you in many ways. By researching the functions of that part of the brain, you can more clearly understand — and be prepared for — many of the symptoms you are experiencing or might expect to experience. Ask your physician to be specific about the location. Perhaps he or she can provide you with a diagram of the brain with a penciled-in identification of the tumor site. For a detailed discussions of what symptoms can be expected from what location, please see Appendix B "Brain Functions and Dysfunctions by Location" at the back of this Guidebook.

A Personal Diary. Beginning on day one, keeping a diary is very important as you review various treatment options with specialists. Recording your specific questions and concerns will help ensure that your medical team provides the answers you and your loved ones or caregivers need. You may want to create a separate section for each team member, writing down which doctor is responsible for the various aspects of your care, medication refills, routine lab work, referrals, and what was discussed at appointments. Questions can often arise after you leave an appointment and being able to refer to these pages later may be helpful. It is critical that you maintain monthly calendar pages to record the start of new medications or therapies and

any bad reactions to them. The starting times of symptoms and side effects may be difficult to recall at a later date, but it is important to distinguish their origins.

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.

Coping with a Brain Tumor Diagnosis (Emotional)

Love. When you are diagnosed with a brain tumor, especially a high-grade tumor, those closest to you are also diagnosed. Everyone is affected in some way. The way to move through this journey with as much strength and stability as possible is to make kindness and love a central part of the daily routine with each other.

Avoid Isolating. Keep the lines of communication open. Maintain honest, two-way communication with your loved ones, doctors, and others after your cancer diagnosis. If needed, try to find a new openness with loved ones. You may feel particularly isolated if people try to protect you from bad news or if you try to put up a strong front. If you and others express emotions honestly, you can all gain strength from each other. Communication can help reduce the anxiety and fear that cancer can cause.

Let Family and Friends Help You. Often friends and family can run errands, provide transportation, prepare meals, and help you with household chores. Learn to accept their help. Accepting help gives those who care about you a sense of contributing at a difficult time. Also encourage your family to accept help if it's needed. A cancer diagnosis affects the entire family and adds stress, especially to the primary caregivers. Accepting help with meals or chores from neighbors or friends can go a long way in preventing them from developing caregiver fatigue.

When Family/Friends Fall Short. Don't be shocked or dismayed if some dear friend or a certain family member doesn't call, doesn't help, changes the topic when you are talking. Plenty of people do not know how to handle this kind of diagnosis or don't have the strength. Don’t press them. Take heart because friends and family might not to act the way you think they should, and you will be left bruised in the

middle of the road if you expect too much from them. Don't worry. Perfect strangers often show up and help in meaningful ways.

Anticipate possible physical changes. Now — after your cancer diagnosis and before you begin treatment — is the best time to plan for changes. Prepare yourself now so that you'll be better able to cope later. Ask your doctor what changes you should anticipate. If drugs will cause hair loss, advice from image experts about clothing, makeup, wigs and hairpieces may help you feel more comfortable and attractive. Insurance often helps pay for wigs, prostheses, and other adaptive devices. Members of cancer support groups may be particularly helpful in this area and can provide tips that have helped them and others.

Fear of Being a Burden. Especially if you have a high-grade tumor, you may be looking at periods in your future where you are dependent on others to care for you. Many people in that situation develop a fear of being a burden. That thinking is stunningly flawed.



When you have periods of dependency, it is an act of tremendous generosity on your part to allow the people who love you to take care of you. If you ask caregivers who have done this, even in intense and demanding situations, they will describe their time with their dependent loved ones as "poignant", "special" or even "sacred". The

opportunity to comfort and care for an ailing loved one resonates at the deepest parts of the human heart and soul and the experience adds to the lives of people who would care for you; it does not diminish it.

So, every moment you fight this disease and live to your fullest extent within the bounds of this disease, even if it means you need lots of help from others, is an act of love from you that matters in the deepest ways.

Review your goals and priorities. Determine what's really important in your life. Find time for the activities that are most important to you and give you the most meaning.

Consider potential lifestyle changes. Maintain your normal lifestyle but be open to modifying it as necessary. Consider how treatment will impact your daily activities. Ask your doctor whether you can expect to continue your normal routine. You may need to spend time in the hospital or have frequent medical appointments. If your treatment will require a leave of absence from your normal duties, plan for this.

Obtaining Sufficient Sleep. Patients with a brain tumor often experience anxiety and depression which can interrupt the normal sleep cycle, and lack of sleep (insomnia) is a common symptom. It can be made worse by taking steroids designed to decrease brain swelling but the steroids themselves can have the side effect of causing insomnia. Furthermore, stress will raise serum cortisol levels which has numerous additional side effects such as reduction of immunity, metabolic disorders (elevated blood glucose levels, pre-diabetes or worsening of diabetes), and negative effects on behavior, cognition, and metabolism. Each person may have a different requirement for hours of sleep; there is no "magic number". Literature supports a minimum of seven hours per day, but some of us benefit from 8 or even 9 hours. If sleep is interrupted, then naps during the day can help restore brain and immune function. During sleep, the brain rewires itself, removes toxins that normally accumulate or are the byproduct of the brain tumor and possibly radiation treatment effects. Sleep may counter 'chemo fog.' Much is written on techniques to obtain a good night's sleep, but a dark room, comfortable bedding, a temperature that is normal or slightly cool, noise reduction, avoidance of the "blue light" from a personal computer, and avoidance of "doom scrolling" on your personal device—all of these adjustments may contribute to a restorative, healthy night's sleep. If you are having

persistent problems with insomnia, please see your primary care physician or oncologist as to the possibility of taking medication to relieve anxiety and promote sleep.

Maintain a healthy lifestyle. This can improve your energy level. Choose a healthy diet consisting of a variety of foods and get adequate rest in order to help you manage the stress and fatigue of the cancer and its treatment. Exercise and participating in enjoyable activities also may help. Continuing study data suggest that people who maintain some physical exercise during treatment not only cope better but also may live longer.

Questioning. You must learn to question your doctors what you are told initially and, as treatment plans are put into place, to ask what qualifying factors your diagnosis and treatment plan are based upon.

However, we understand that some of the first questioning you will do has to do with how this could have happened in the first place. In short: why you? and how is it that you have a brain tumor. This is an especially urgent question if the brain tumor turns out to be malignant. At the back of this Guidebook is Appendix C entitled "Causes of Brain Tumors" which describes what is known about the complex conditions that lead to the formation of a brain tumor.

Reaching And Internet Researching. Because not all brain tumors are the same, when confronted with wildly encouraging or wildly discouraging statements about this drug or that treatment, just recognize that the statement might not be true in your loved one's case. Anything that sounds too good to be true – in either direction – should be treated with suspicion and followed with rational fact-finding, including especially consultation with the doctor.

Also know that statements and statistics on the Internet may be old, irrelevant for the specific type of brain tumor, and without benefit of the results of the latest treatments.

Since our society is increasingly dependent on Internet searches, when you do your searches, seek trustworthy content such as the Musella Foundation site, NCI (National Cancer Institute), WebMD, Oncolink (Brain Tumor Section), and CancerQuest ". Signs that the site/article you are reading is trustworthy are:

Recently Dated. Look first to see how recent the information is. Any worthy article will be dated; if you can't find a date, the information risks being bogus. Brain tumor research changes constantly; if the article was written several years ago, the data is likely obsolete.

Written/Reviewed by Experts. Verify that the article was written and reviewed by qualified experts. You should be able to easily find the names and professional qualifications of the author or reviewer.

Some papers are written by people who have themselves tackled a brain tumor. While these papers or sites are a fantastic source for inspiration and practical tips on your day-to-day journey, the experiences of others should not be taken as sound medical advice for you.

Be aware that in certain countries, candidates for medical certifications must publish a paper to complete their certification process and some of those candidates will employ papermills to produce unverified "medical" papers that then can be found online.

Contents Based on Well-Respected, Independent Research. You should look for the sources of the research that forms the basis of the paper. The sources you want to see are respected and independent medical journals, government health sites, academic institutions, hospitals, or expert health organizations.

Certain companies, particularly those selling home remedies or supplements, will produce papers extolling the benefits of their products and get those papers published online as a marketing ploy. These papers may sound very detailed and scientific, but the underlying data will not have been verified by any independent research.

Making sure the data you find on the Internet is trustworthy will help you have more useful and satisfying conversations with your doctor.

A good way to ensure you are looking at trustworthy data is to sign up for the Musella Foundation brain tumor news blasts, which presents the latest news about brain tumor research with knowledgeable comments to help you keep that news in proper perspective. You can sign up at this link:

https://virtualtrials.org/newsblast.cfm

Depression. Depression is probably the first symptom of this disease, but we tend to look at depression as "normal" and overlook it. If your loved one is depressed, you should bring it up with the doctor (privately if need be). Brain cancer patients can be depressed because the tumor changes the chemistry of their brain. During treatment, anti-depressants are often prescribed, and some of those anti-depressants can sometimes help in the fight against the cancer by making the cancer cells more sensitive to the chemo.

Quality Of Life. When the treatment plan is being discussed (especially after Standard of Care), make sure that your loved one's objective for quality of life (QOL) is considered. There may be trade-offs. Your loved one might prefer to get to play in a golf tournament with friends rather than schedule a certain phase of treatment.

The preferences of the loved one with the brain tumor needs to be your #1 priority, even if you might disagree for whatever reason. It's your loved one's disease, your loved one's skin and is the one who would endure the side effects. The one with the disease needs to be provided with the dignity and compassion of handling treatment the way they want. It is hard sometimes to stand back and just be the advocate of the wishes of a loved one with this disease, but that may be what is required.

Prayer. If you have a religious tradition, recruit prayer warriors. You will be praying for your loved one, but it's wonderful to have little (or big) armies of people praying for you and your loved one, too. If your loved one is or has been religiously engaged, get their priest, minister, spiritual director involved NOW. Have that person visit regularly. This journey is deeply spiritual in nature.

Future. Do not think about the future any more than you have to. Do everything you can to live in the present moment. This is harder to do than to say because the nature of a human being is to be focused on the future; however, you do not want to give up your time with your loved one today by worrying excessively about tomorrow.

Feelings. Just know that it is perfectly okay for you to feel overwhelmed, angry, sad, alone, confused, anguished, in denial, and really angry all in the space of an hour and then do it all over again 2 hours later. That's pretty normal.

Telling People. After the diagnosis, you might feel compelled to share it with

others. It's a good idea to start sharing slowly. Many people who hear of the diagnosis will have their own opinions, suggestions, anecdotes, and feelings they will then flood you with when you are still trying to absorb all sorts of new thoughts and information yourself. When you have given yourself the chance to find your own equilibrium, start sharing with those caring people closest to you first and ask them for their support. Then, share the diagnosis with those in the next layer of your life. Avoid feeling as though you have to share every detail; just remember that you can always provide more details later.

Hope

Any of us confronting a brain tumor, especially a high grade one, feel a strong need to find any reason to be hopeful. This craving that exceeds anything we have experienced in the past. We hope the treatments will work; we hope the tumor will stay gone after surgery or if it is not removable, we hope the radiation kills it. We hope to qualify for a clinical trial that we hope will be that special, silver bullet that destroys the disease. Above all, we hope that our lives can get back to the way it was before the diagnosis.

All these hopes turn to an externally driven source. They are dependent upon test results, treatment response, treatment research and availability, etc. and if they do not come to fruition as all of us might like, we can find ourselves in a deep emotional ditch. To be clear, these are all good goals, but these forms of hope are simply insufficient for this journey. Individuals relying on these factors can set themselves up to experience a crushing anxiety if they are told what they have hoped for has not happened.

The challenge of hope must include the realization that there just is no such thing as a Life without its challenges, and brain cancer is one of those challenges, certainly one of its fiercest. So, pinning one's hopes to external factors over which we have only the barest control (if any) in the face of such a serious challenge like brain cancer is simply not enough to sustain a person – at least not well.

The option to an externally driven hope is an internally driven one. This is hope that comes from our deepest, most authentic parts, and is the fruit of our attitudes and philosophy of Life. It is not as dependent on what happens. It rests instead on an

understanding of our lives as being a part of the huge tapestry of Life, which includes an understanding that no physical life is infinite and a recognition of our place in human history and in this wide, awesome universe. For the religiously inclined, it includes a recognition of our valued place in God's unfolding plan.

Central to an internally driven hope is the development of new attitudes and probably a new meaning to a person's Life. This form of hope, obviously to be developed within the context of a person's personal philosophical/spiritual/religious views, is vital for this sort of a journey. Because of the powerful connection between our minds and our bodies, an attitude of hopelessness can actually predict a poorer outcome against the disease. Of course, feeling hopeful in the face of all the obstacles throughout diagnosis and treatment is truly difficult. Therefore, devoting some time and effort to pursuing and nurturing hope is a worthy endeavor.

Only a hope based on a deep, personal philosophy will produce the resilience necessary to allow a person to face the challenges of brain cancer with the strength and sturdiness that will offer future opportunities to undergo continued treatment and live longer.

Good places to start or continue the process of developing a strong, internal hope for this journey include:

- Discussions with clergy or spiritual counselors, especially those associated with the chaplain's office at your hospital.

- Discussions with palliative care counselors or social workers at your hospital.

- Logotherapy. Logotherapy derives from the works of Frankl, a neurologist and psychiatrist, who survived severe suffering in the Holocaust and concluded that "Everything can be taken from a man but one thing: the last of the human freedoms—to choose one's attitude in any given set of circumstances, to choose one's own way." Finding a counselor with competency in logotherapy can help with hope. Reading stories of brain cancer survivors - people who have faced the same types of challenges you are facing and have learned to cope. This Guidebook contains many such stories.

SURVIVOR STORY #1

It started with small things in 1999, mostly visual. My wife thought I was experiencing a stroke.

I called my doctor at home on a Sunday. He had a scan set for Wednesday; my wife and I saw the neurologist and neurosurgeon on Thursday, and surgery was on the following Tuesday. I had glioblastoma. I received radiation and chemotherapy as well as stereotactic radiation. I was very fortunate to be at a teaching hospital. I had a recurrence in 2001 with successful resection during which Gliadel Wafers were implanted.

In 2002, they thought I had another recurrence, but it was only scar tissue and radiation necrosis.

I am currently a 19-year survivor of glioblastoma. I still deal with several medical issues associated with my tumor treatment, including some loss of peripheral vision and neuropathy in my right foot, which affects my balance. Most important to me are conversations I have with brain tumor patients and their caregivers. On average, I talk to two or three patients in a given month. I always point them to the virtualtrials.org website as the best resource for all things brain tumor. I do not give medical advice, but I do answer questions as best I can. What I hear quite often is the hope they feel when they meet someone who has survived glioblastoma for as long as I have. I make sure they know that there are many long-term survivors and that there is hope based on new treatments and research.

I have learned a lot of things from my experiences; these are just a few of them:

- You will learn quickly who is comfortable and who is not comfortable in dealing with issues of mortality.

- Have someone with you to listen, ask questions, and remember. Several times the neurosurgeon told my wife that no one had ever asked him a particular question before.

- Don't fear knowledge. As my wife said many times, "There is nothing you can tell

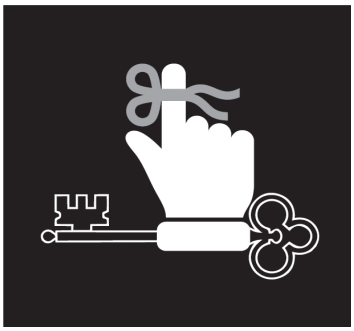
us that is worse than we can imagine."

- God gave us the gift of life that brings uncertainty. When tough times hit, He can comfort us much as we can comfort each other.

Painting by Julia Rawlinson



KEY TAKEAWAYS TO REMEMBER



About 70% of masses in the brain are benign (non-cancerous) growths that do not spread and may not even require surgery.

Metastatic (secondary) brain tumors are about four times more common than primary brain tumors. The likelihood that a mass in the brain is metastatic should be assessed by the doctor before biopsy or surgery.

An integrated diagnosis consists of a full neurological exam, imaging of the site, and a molecular evaluation of tissue obtained by biopsy or surgery.

The molecular evaluation can take up to a few weeks to complete.

By testing for molecular markers, your medical team can generate a profile of your tumor cells that achieves a reliable diagnosis and can help guide treatment choices.

If diagnosed with a brain tumor, especially a malignant one:

Get organized from Day #1 with a binder to keep track of everything, including especially your medications, and

Know the exact location of your tumor.

Survival statistics do not necessarily consider all factors; your ability to challenge survival statistics will greatly depend on surrounding yourself with a medical team that is not influenced negatively by such numbers.





Two

Treatment Facilities

Brain Tumor Centers

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.

Major Clinic Benefits

The most accurate diagnoses and resources for the best, most expert treatment across the multiple medical disciplines you will need on your medical team is most often found at a brain tumor center. Any brain tumor is complex, but Grade 3 or Grade 4 tumors are exceptionally complex diseases requiring the high level of expertise available at a brain cancer center.

The reasons you want to go to a brain cancer center are these:

- The neurosurgeons and team members at brain cancer centers perform over 50 brain surgeries annually (as many as five surgeries per week at some centers) and may offer the most technologically advanced procedures with higher rates of survival and lowest postoperative deficits. Your choice of surgeon and post-surgical treatment team can profoundly affect the outcome of your care. In addition to having the best neurosurgeons and

neuro-oncologists, the top brain clinics also have the latest technologies and equipment to help those expert doctors.

- The most advanced clinical trials are for GBMs, but the majority of openings for those trials are available at the well-resourced, top brain clinics. So, if your loved one has a high-grade brain tumor, you want to set them up in a system where they may get access to advanced treatments when they are needed.

Many of these specialized centers allow you to directly submit imaging scans and even tissue samples, if you have them, for further examination without a referring physician.

If the nearest brain tumor center is far from where you live, the staff there should be able to coordinate some of your treatment with doctors more local to you, so that extended stays near the brain tumor center may not be necessary.

NCI Designated Cancer Centers

The United States is fortunate to have a number of superb brain cancer centers with world-class capabilities. The National Cancer Institute (NCI) has designated cancer centers in the U.S. Most of these centers are part of a university or large medical center; all have a high degree of cancer competency. You can locate a NCI designated cancer center at this website:

https://www.cancer.gov/research/infrastructure/cancer-centers/find

For information about consultations with the neuro-oncology branch of the National Cancer Institute, go to: ccr.cancer.gov/Neuro-Oncology-Branch. Then, select the box on the left marked "Information for Patients," and click "Read more."

Brain Cancer SPORE Locations

In 2002, the NCI established the Brain Cancer Specialized Programs of Research Excellence (SPORE) program. The Brain Cancer SPORE program objectives include improved prognostic testing, tumor vaccines, and other immunotherapeutic approaches, as well as enabling the rapid and efficient movement of scientific findings into clinical settings.

Current Brain Cancer SPORE grant clinics are:

Brigham and Women's Hospital
Northwestern University at Chicago
University of California at Los Angeles
University of California at San Francisco
University of Texas MD Anderson Cancer Center

Travel and Housing Discounts

Those needing to travel to a medical facility should ask about available discounts for travelers.

Air carriers may offer a discount to those traveling for medical reasons. Generally, this discount is obtained at the time the reservation is being made, so you should ask at the time you make flight arrangements.

Many of the top brain cancer clinics have discounts at local motels and hotels. For patients undergoing radiotherapy requiring multiple visits or traveling long distances (more than 40 miles) from home, almost all of the major medical centers and brain tumor programs have provisions for affordable housing. Importantly, the American Cancer Society sponsors the "Hope Lodge" program in over 30 centers. (See https://www.cancer.org/support-programs-and-services/patient-lodging/hope-lodge.html.) Other specific examples include:

Near Duke University's Cancer Institute is a facility called the Caring House which has affordable housing for patients and their caregivers that travel to Duke for their outpatient treatments. The website for this facility is:

https://caringhouse.org

Near MDAnderson, where about 150,000 people each year get cancer treatment, there is the Jesse H. Jones Rotary House International, the Hope Lodge from the American Cancer society, the Halo House, the Aishel House, Joe's House, Matthew's Miracle House, the ASCF (A Shelter for Cancer Families), plus Comfortable Home (furnished apartments), not to mentioned reduced rates at the nearby luxury hotels like Marriott, Hilton, or Wyndham.

In short, if you know you will need to be treated as an outpatient at one of the brain cancer centers, it is advisable to ask if they have facilities that may reduce the costs of the stay.

Clinics Offering Alternative Treatments

A diagnosis of a high-grade brain cancer can be devastating. The panic and anguish that ensue may cause a person to look beyond established medical facilities.

There are private clinics that will present very compelling assurances. Their personnel seem compassionate, understanding, and competent. Their clinic has a reassuring, restful, spa-like ambiance to it. Testimonials are published online by very enthusiastic, grateful clients. The treatments often blend unusual drugs that not otherwise available with innovative "healthy" approaches to diet and elevate hope.

These private clinics are typically but not exclusively outside of the US; they operate under laws or loopholes in laws that enable the clinic to provide compassionate care to patients who have been diagnosed with a terminal illness. Doctors with variable qualifications are allowed to provide unproven or disproven treatments without any regulations or requirements to report on their results.

All of these clinics charge exorbitant prices, which insurance companies generally do not cover, in the range of $60,000 to $120,000 for their treatments. Also, treatments may require the patient and family to remain in the clinic's country for several weeks at a time, incurring not just the basic treatment costs, but also the costs of travel, ground transport, hotels, and meals during the stay. Treatments will often

need to be repeated at another round of similar charges.

Amid other concerns is the potential that a patient may experience a medical crisis while abroad. Standard commercial air carriers may not accept transporting a medically fragile person, which will then necessitate a medical evacuation flight. Getting back home by "med-evac" plane may easily run into the tens of thousands of dollars, and most insurance companies, including travel insurance companies are not likely to cover such costs.

It is highly advisable that if you are seriously considering seeking treatment at a clinic offering alternate treatments that you thoroughly investigate everything about the clinic. No one can presume to make crucial decisions for a person when they or their loved one is ill but having one's eyes wide open is the best path to the best outcome.

Some questions to ask to identify clinics that are not likely to provide treatments supporting the best outcome are these:

- Is the clinic regulated by the relevant government or an independent, rigorous medical oversight agency? Do they report results? If not, why not?

- If the clinic describes its treatment as a "miracle," "scientific breakthrough", or containing "secret ingredients", please read the section in this Guidebook entitled "Alternative Treatments."

- Where does the clinic get the drugs used in their treatments? (Clinic may use drugs harvested from failed, terminated clinical trials and will not be keen to disclose that.)

- Does the clinic use the same treatment for all types of cancers? (There is no such thing as one size fits all with cancer.)

- How does the clinic ensure the safety of the treatment? Some clinics will claim the treatment is "natural." Not everything that is natural is safe, especially for cancer patients.

- Does the personnel and marketing videos and literature use a lot of medical jargon and talk about "curing" the disease or other strong words

appealing to the emotions? How reliable are the testimonials in their marketing brochures? (If researched, you may find that some of the patients in the testimonials have either been deceased for years or were simply paid actors.)

- What is their explanation for why their products are not supported by conventional doctors? (A questionable clinic may claim that their treatment challenges modern practices and, therefore, the medical industry conspires together to silence them.)

- Can they back up their claims of outcomes? (Questionable clinics may make claims of impressive outcomes but can provide no specifics even if they claim people have been "cured" of brain cancer using their treatment.)

- Will you have to sign a non-disclosure? Many questionable clinics require clients to sign a non-disclosure agreement prohibiting them from talking about the clinic and their treatment outcome.

Before proceeding, and certainly before giving a clinic offering an alternate treatment any money, it is wise to strongly consider the factors described above and speak to your neurosurgeon or neuro-oncologist about any complementary medicine (e.g., herbal supplements) you are currently taking or wish to take. Contact the Musella Foundation to see what we know about the particular treatment.



Painting by Linda Singer





Three

Understanding Brain Tumors

Overview of Your Medical Team

Typically, the physician discovering your tumor will refer you to a doctor with expertise in neuro medicine for a consultation regarding treatment.

Treatment of brain tumors often consists of a number of different types of interventions: brain surgery to biopsy or remove the tumor and obtain a tissue sample; radiation therapy; chemotherapy; alternating electric field therapy with a device called the Optune; different drugs for managing symptoms caused not only by the tumor but also by the tumor's treatment; and even enrollment in a clinical trial.

This large number of different possible treatments means that you will need a team of specialized doctors— preferably associated with a single medical center experienced in treating brain tumors — that will be able to coordinate and administer the most up-to-date treatments with precision and care.

Your medical team should include several experts experienced in different medical specialties. The make-up of your medical team will vary depending on the type and location of your tumor, and it may include specialists representing a variety of different medical cross-specialties.

It is essential that your medical team include experts with current and comprehensive experience in the treatment of your specific type of brain tumor and that have a communication process to remain inter-connected about your care.

Typical Types of Doctors

Among the doctors you may encounter are:

Neurosurgeon. A neurosurgeon is someone who performs biopsies and surgery involving the nervous system, typically specializing in one particular area or system, such as the brain or the spine. Before considering any surgical procedure, it is important to established that your neurosurgeon has substantial and up-to-date experience in your condition. It is also wise to obtain a second opinion from a similarly qualified neurosurgeon associated with a major brain tumor center.

While some neurosurgeons also practice neuro-oncology and oversee the administration of chemotherapy treatments, most confine their practice to surgical therapy and follow-up care.

Neuro-oncologist. If the tumor is found to be cancerous, you will need a neuro-oncologist on your team.

A medical board-certified oncologist treats many forms of cancer; however, not all oncologists are experts in treating brain tumors. As part of your medical team, your general oncologist can assist you with obtaining second opinions and researching available treatment options, but he or she should refer you to a neuro-oncologist experienced specifically in the treatment of brain tumors.

Many neuro-oncologists are also neurologists, doctors who treat disorders of the nervous system (some also started as general oncologists) as well as general cancer. It is important that your selected neuro-oncologist has substantial and up-to-date experience in treating your type of tumor and is up to date on advances in both surgery and alternative treatments.

If your primary brain tumor physician is not familiar with the most current treatments or clinical trials you should request a second opinion. Even if you are diagnosed by a major brain tumor center, you may still wish to get a second opinion from another major brain tumor center to confirm your diagnosis, to confirm a treatment plan, and/or to locate a clinical trial. It is your right to have a second opinion. (See sections below on Second Opinions.)

Neuroradiologist. This is a specialist in the area of reading MRI and CT scans involving the nervous system. Your MRI or CT scans should always be reviewed by a neuroradiologist experienced with tumors within the brain.

Radiation oncologist. This is a doctor specializing in the administration of radiation therapy (solely and specifically) and should work in cooperation with your neuro-oncologist/ surgeon to develop an appropriate course for the duration and intensity of your radiation therapy.

Neurologist. Neurologists have expertise in treating a variety of neurological symptoms found in patients with brain tumors, which could include headaches, seizures, or impairment of vision, speech and strength. In your management team for a benign tumor, you may be treated by a neurosurgeon (for diagnosis and/or removal of the tumor), a neurologist, a medical oncologist (who also treats benign tumors) and/or a radiation oncologist (if you have had radiation therapy, e.g, gamma knife or are a candidate for radiation therapy). It is important that you have continuity of care by someone who is familiar with your situation, and ideally someone who has expertise in the care of brain tumors. If you live far from a medical center with a center of excellence in neuro-oncology, you could be followed regularly with MRIs and have a primary care physician who treats symptoms such as headaches. Alternatively, you could be followed by a neurologist, especially if you have seizures. It is important that you set up a follow-up plan so there is frequent monitoring while you resume a normal life.

Additional Specialists

From time to time you may have a requirement for complementary care during your treatment and recovery, such as:

- Rehabilitation specialists (physical/speech therapist, occupational therapist)
- Neuropsychologists and psychiatrists

- Endocrinologists
- Ophthalmologists (eye doctors) or Neuro-Ophthalmologists (eye doctors specializing in eye problems in patients with neurological illnesses)
- Dentists (especially important prior to chemotherapy)
- Pharmacists
- Nutritionists
- The group of doctors at your hospital of care who might undertake the tumor board review of your tumor treatment

Need for Expertise

You must seek out the foremost expert advice. Because diagnosing a specific type of brain tumor is complicated, it is essential to get confirmation of a diagnosis. Second, third, or even fourth opinions should come from experts within a specific area, such as those who are experts in the removal of brain tumors: neurosurgeons performing at least 25 brain surgeries per year, or experts in neuropathology who can qualify the diagnosis of your tumor biopsy. It is estimated that as many as 25 percent of brain tumor patients will have their diagnosis changed upon further examination by a second, expert opinion, which can drastically alter not only the prognosis but also the recommended treatment plan.

A review of your MRI or CT scans, tests, and pathology reports, along with an overview of new resources and treatment programs can be obtained through many of the leading major brain tumor centers. Your physician can also consult with the National Cancer Institute (see discussion under "Treatment Facilities"). They will also review your case for free. They have excellent adult and pediatric brain tumor specialists available to help you.

Most pathologists do not see enough brain tumors to allow them to make the subtle distinctions that may be necessary for diagnosis. You can also ask for a second opinion on the reading of the biopsy slides from a major brain tumor center.

There is a cost, but the process is easy; your hospital just mails the slides. If you do need to travel for a second or third opinion, there are many organizations that provide financial assistance specifically for brain tumor patients. Please check the information on insurance and financial help in the next chapter (entitled “Protecting Yourself and Your Family During Treatment”) of this book.

Criteria for Selecting a Doctor

It is advisable that you look for a doctor who:

- **Listens.** It's important to find a doctor who will listen to your concerns. It will be easier for you to ask this doctor questions.

- **Explains.** You want a doctor who can use plain language to explain what you have, what the treatment options are and what your prognosis is in terms you can understand.

- **Understands.** You want that elusive quality of chemistry between you and your doctor — a doctor who understands you. If it isn't there, find someone else. He or she may have all of the credentials, but if the chemistry between you and that doctor isn't positive, you might do well to switch.

Make the relationship with your doctor a working partnership. The best treatment relationship is one where you ask questions and participate in your care.

What questions should I ask my medical team?

Some of the questions you may wish to ask your medical team are:

- What type of brain tumor do I have?
- What is the grade of the brain tumor?
- Are any additional tests needed?
- How many tumor types like this do you treat each year?
- Will the brain tumor board review my case? How often?
- Where would you recommend I get a confirming/second opinion?
- Do you have any written information about my type of brain tumor?
- How will the brain tumor affect my functioning?
- What are my treatment options?
- Which treatment do you recommend? Why?
- Which clinical trials do I qualify for, and which do you recommend?
- Can you recommend a neuro-oncologist who specializes in this type of brain tumor?

- What other specialists will be part of my care?
- What is the timeline for treatment(s)?
- Where will I get the treatment?
- Will I be able to drive myself to and from treatment?
- Will my medical insurance cover this type of treatment?
- How will this type of treatment affect my work schedule?
- Will I need to apply for disability? Social Security disability?
- Will I need to take medications? If so, what kinds and how often?
- Are there any side effects? What kind?
- Are there short-term and long-term side effects?
- How can side effects be managed? By medicines? By physical therapy?
- Will my quality-of-life change? Will I function differently?
- Will I see a change in my personality? Appetite? Sleep habits? Memory?
- What can I expect before, during, and after treatment?
- What is the follow-up plan if this treatment doesn't work?
- How often will I need follow-up imaging scans? What kind of scans?
- Do you think I should attend a support group now? Are there any support-groups nearby?

Second Opinions (Diagnosis/Genetic Study)

The initial tumor molecular evaluation done following a hospital biopsy or surgery is done to the extent needed to reach a conclusive diagnosis and enable the doctor to commence treatment of the disease.

The key genetic characteristics ("biomarkers") that are of most interest at the initial stage are these: IDH-1 gene status, MGMT promoter gene status, presence/absence of chromosome 1p and/or 19q deletions, and the mitotic index (or Ki-67 index).

These are just the absolute basic data points needed at the commencement of diagnosis and medical treatment. However, should the tumor prove to be resistant to the first-line treatment or regrow, as many high-grade tumors do, an in-depth evaluation of the tumor tissue may enable your doctors to identify more effective, alternate treatments such as those available in a clinical trial.

Your neuro-oncologist should discuss with you the option of having your tumor genetically profiled. If your doctor does not present the topic, you may wish to

inquire your doctor about genetic testing.

Companies that do this type of work include:

- FoundationOneCDx (FDA approved in 2011 for tumor mutation profiling; most often recommended)
- CARIS Molecular Intelligence (well-recommended)
- Guardant360CDx (first FDA-approved tumor mutation profiling via liquid biopsy)
- MSK IMPACT (Integrated Mutation Profiling Of Actionable Cancer Targets at Memorial Sloan Kettering) FDA-approved profiling of variants, insertions, deletions, and microsatellite instability
- CeGat (Tubingen, Germany)

Tumor mutation profiling services performed by these companies can be expensive, take time (notionally 4-6 weeks), costs are often not covered by insurance and the attending neuro-oncologist may prefer the results of one service over another. The timing for requesting this second evaluation should be discussed with the doctor, because initial chemo treatments are likely to alter the molecular characteristics of the tumor.

Second Opinions (Treatment)

It is reasonable and common to obtain a second opinion for treatment from a different neurosurgeon or neuro-oncologist at a hospital other than your current one. See the Section entitled "Treatment Facilities" for suggestions of highly rated options. For a second opinion on your treatment options, you may also turn to the Patient Navigation Program described on Page 99 of this Guidebook.

The purposes of a second opinion include but are not limited to: confirming the diagnosis, obtaining recommendations regarding surgery, ensuring the current treatment plan is correct, and learning about opportunities for other advanced treat-

ments relevant to your tumor.

The process for a second opinion typically involves a review of your medical history, current diagnosis and all images that have been taken.

You would initiate a second opinion by calling the appointment desk at the brain cancer clinic you wish to have the second opinion from and informing them you need a second opinion. Appointments for second opinions are usually scheduled promptly.

In the event you do not want to travel to the clinic from which you are requesting the second opinion, you may ask them if they would perform the second opinion by means of a virtual, online visit or by a "desk review" of your files and images. Many clinics will accommodate such a request.

While second opinions are reasonable, it is not advisable to waste time and energy by going to six or seven different cancer centers to see several doctors who may all tell you the same thing. If the two opinions are similar, it's likely that all other neurosurgeons or neuro-oncologists will tell you the same thing.

Photo Credit Linda Singer



SURVIVOR STORY #2

On the night of December 25, 2012, I went to bed and had a grand mal seizure for the first time ever. The only thing I remember was waking up on a stretcher as I was being lifted into an ambulance. I failed to answer basic questions. I was confused and had no idea what was happening. I was rushed to the local hospital to undergo a CT scan. The results showed an 8-cm tumor on the right frontal lobe of my brain.

This news left my wife and me speechless. It was so much to digest. She cried, and I sat in disbelief. I was then transported by ambulance to another hospital where an MRI scan and another CT scan were performed. Unfortunately, the imaging interpretation at the first hospital was confirmed. I was told that I needed to be operated on as soon as possible. Luckily, one of the best neurosurgeons in the state was on call that night. After quick but thorough research, my family and I decided to go ahead with the surgery. My neurosurgeon and his team were able to remove the entire tumor. During recovery I had several more seizures and received the antiepileptic medication levetiracetam (Keppra). A week or so after discharge, while still recovering in bed, I received the phone call that no one wants. My pathology report was back. I had a grade 3 anaplastic astrocytoma.

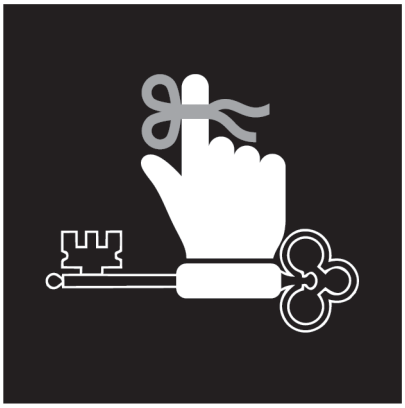
My family and I were devastated. Before that first seizure my life was great. I had just turned 31 years old, I had a great job, my wife and I had just purchased our first home, and we had a beautiful one-year-old boy. Life seemed perfect, then the curve ball.

My first reaction was, Why me? What did I do to deserve this? My wife and I went to see the neurosurgeon for a follow-up appointment, and he recommended a comprehensive cancer center. Our appointment came quickly. We received detailed information about my diagnosis and my treatment schedule. I did not like hearing the statistics, especially when they confirmed what Dr. Google seemed to be reporting on the Internet, but we decided to take the brain tumor head on. My treatment was 30 days of radiation therapy with weekends off, 6 weeks of temozolomide (Temodar) every day, and then 12 months of adjuvant temozolomide with the cycle of 7 days on, 23 days off.

The radiation therapy was difficult to tolerate near its end. Because I did not like watching my hair fall out, I shaved all my hair off. Chemotherapy, however, was not too hard to tolerate, and I went back to my job on light duty toward the end of treatment.

Throughout all this, I recognized how blessed I am. I had such an awakening. I started to take charge of my health in ways I never thought possible. I no longer procrastinated. I no longer put anything on hold. The experience gave "living life" a whole new meaning to me. I received many miracles on my journey. Although not everything was easy, especially at the beginning, I can say that my diagnosis saved me.

KEY TAKEAWAYS TO REMEMBER



The most important decisions you have to make are WHERE and by WHOM to be treated.

The best, most expert treatment is most often found at a major brain tumor center. In addition to having the best neurosurgeons and neuro-oncologists, top brain clinics also have the latest technologies and equipment.

Get copies of your brain scans (or a CD of them) and their interpretations, and share them with other members of your medical team to ensure that they agree with the interpretations.

Understand the different functions of the members of your medical treatment team.

If considering alternate treatment facilities, ask lots of in-depth questions before paying any money.

It is essential that your medical team include experts with current and comprehensive experience in the treatment of your specific type of brain tumor and that have a communication process to remain inter-connected about your care.

It is reasonable and common to obtain a second opinion for treatment from a different neurosurgeon or neuro-oncologist at a hospital other than the one you are currently going to.





Four

Protecting Yourself and Family During Treatment

Health Maintenance Vaccines

You may want to discuss with your doctor getting certain vaccines that may help you maintain your underlying health. Because the benefits and safety of vaccines vary from person to person, only your doctor can determine the appropriateness and timing of you getting these certain vaccines.

In general, vaccines are not recommended during chemo or radiation therapy. For that reason, the scheduling of vaccines may need to be made prior to the start of those procedures, so discussing the issue of vaccines early is recommended.

The vaccines you may wish to explore with your doctor include the following:

COVID-19. Many medical experts recommend that those with cancer should get the COVID-19 vaccine but be sure to talk to your doctor first.

Influenza. It is a good idea for patients to be protected from the flu. You can typically get the flu vaccine at least two (2) weeks before chemo or between chemo cycles. Your doctor may have specific instructions for how you get this vaccine. The nasal mist flu vaccine may not be recommended because it contains the weakened flu virus and can lead to an infection. The injectable vaccine has the dead flu virus and is believed by more doctors to be safer for their cancer patients. Unless your doctor suggests otherwise, your family members should also get the injectable flu vaccine instead of the nasal mist. By protecting themselves from the flu, they're also protecting you from getting it from them.

Shingles. Shingles is a reactivation of the herpes zoster (chicken pox) virus in patients. Those who have had chicken pox at any time in their life may get Shingles, which produces large, painful welts on the body that can last for weeks. Shingles may occur more frequently with people with compromised immune systems such as those with cancer or those going through cancer treatment. There is a particular vaccine against Shingles that some doctors believe would be safe for individuals with brain cancer to take to prevent Shingles, but other vaccine forms that most doctor agree are not recommended for brain cancer patients. It is important to discuss with the doctor first.

Pneumococcal Pneumonia. A person's immune system becomes compromised by the combined assault of the disease and treatments and pneumonia can follow, with consequences that may be serious. The pneumococcal vaccine helps to prevent serious lung, blood or brain infections caused by certain bacteria. As with all vaccines, it is important to discuss this one with your doctor first, as recommendations may vary depending on your particular case. But generally, patients with cancer should receive two types of pneumococcal vaccine. These vaccines should be given 2 weeks prior to chemo.

Others. The doctor may recommend that you are re-vaccinated for certain illnesses (e.g., tetanus) or may tell you that you do not need or should not get certain vaccinations (e.g., polio, MMR -measles, mumps, rubella). Ask the doctor also what vaccines your family members should get if they are expected to be around you during your treatment.

Fertility Protection

Radiation to the head, surgery, and most medications (except chemotherapy drugs) used to treat brain tumors do not pose a threat to fertility. If radiation therapy is aimed at locations other than the head, you should consult your radiation oncologist about fertility concerns prior to beginning treatment. Often, a lead apron can provide adequate protection to sex organs during radiation treatments.

Chemotherapy can have a real and permanent effect on fertility in men, reducing or eliminating sperm production. While this effect is reversible in most cases, it may

be a number of years before sperm counts return to normal. In women, chemotherapy can temporarily halt menstrual periods, but normal menses should resume after treatments are concluded. Alkylating agents, however, can affect egg production (effects worsen for older women).

If your brain tumor requires certain forms of treatment such as chemo, you may have difficulty becoming pregnant or fathering a child. You should discuss with your doctor before starting treatment if you think you may want to have a baby in the future. Men may be able to store sperm and women may be able to store eggs prior to treatment, and then use those stored resources to have a baby once treatment has concluded. These services are not always offered at every hospital, but your doctor's office may be able to recommend a clinic that specializes in this kind of service.

The importance of fertility is a personal choice. While it is not always the priority of the medical team who are basing their treatment on life-saving measures, it should be discussed before beginning any form of chemotherapy. If necessary, you should insist on having that discussion.

Fertility experts can provide advice about the possibility of sperm banking for men or egg harvesting and fertilization techniques for women. Sperm banks typically suggest a minimum sperm count to be frozen for use at a later date, but a low count alone should not discourage you. A fertility expert can give guidance regarding your chances of success in the case of a low sperm count and other options available to you.

Although rarely the result of brain tumor treatments, impotence can occur as a result of depression. If you experience more than the occasional sexual dysfunction that is normal with aging, you should consult your medical team about medications and other available treatment avenues.

Insurance Management

Effects of the Affordable Care Act (ACA)

Some people with brain tumors are afraid that their health insurance will be

cancelled because they have become sick. Others are afraid that the cost of their medical treatment during a year or over a lifetime will exceed dollar pay-out limits set by their health insurance plan, thereby depleting life savings, or even bankrupting them. Others are afraid that if they lose their job plus the health insurance that goes with the job, while being treated for a brain tumor, they will not be able to find new health insurance because of the preexisting condition. Or they are afraid that they will not be able to afford the health insurance even if they can continue with their existing policy or if they do find new coverage.

The Patient Protection and Affordable Care Act (ACA), the federal law passed in 2010 that is often also referred to as Obamacare, was enacted to help displace such fears. Many national cancer organizations have evaluated the ACA. According to the American Cancer Society, for example, the ACA has helped and will help people with brain tumors in the following ways:

- Upon passage, the law immediately stopped insurance companies from dropping patients from coverage just because they got sick.
- Upon passage, the law immediately banned health insurance companies from having lifetime pay-out limits. In 2014, the law banned health insurance companies from having annual pay-out limits.
- Upon passage, the law immediately banned health insurance companies from denying coverage to children with preexisting conditions. In 2014, the law banned health insurance companies from denying coverage to adults with preexisting conditions, like cancer.
- Upon passage, the law immediately banned health insurance companies from denying coverage to patients who participate in clinical trials.
- Upon passage, the law immediately banned health insurance companies from charging patients for cancer screening tests, such as mammograms and colonoscopies.
- In 2014, the law required all states to create online health insurance marketplaces (usually called "exchanges") so that people without insurance through employment can compare and buy coverage from health insurance companies.

With passage of the ACA, if you had health insurance through your employment, you kept your current health insurance. However, your health insurance plan now has to abide by the provisions of the ACA law, such as following the ban on lifetime

and annual pay-out limits and providing free cancer-screening tests, among others.

Understanding your insurance

Insurance laws vary from state to state. Also, your health insurance policy may be under state or federal guidelines depending on where you work and whether your employer is self-insured. A large employer who is self-insured is not considered an insurance company but rather writes its own policy that is in turn managed by an oversight organization, which may be a health maintenance organization (HMO) operating within your state. The self-insured policies are governed by federal laws, and even state laws such as in California — with strict HMO laws protecting consumers — are not available to those covered by self-insured federally regulated plans.

Complicating things even further, plans such as HMOs and preferred provider organizations (PPOs) often fall under different jurisdictions as well. Your human resources department at your employer can often tell you if your plan is self-insured, whether it is governed by state or by federal regulations, and the contact information for the proper agency.

Most insurance plans contain a specific list of "covered" medications and those that are excluded from coverage, called a "formulary," and by law must provide you with a copy upon request. Many of the drugs used in the treatment of brain tumors are approved by the FDA for other conditions but are not approved for treatment of conditions associated with brain tumors. When a physician prescribes a medication for a condition that falls outside the FDA-approved guidelines, it's called an "off label" use, and in many cases is not covered.

Many states provide an appeal process for challenging an off-label denial that may assist you in obtaining coverage. You may be required (if for no other reason than your immediate need of the drug) to pay for the prescription out of pocket, as the process may take several weeks for a decision. If your employer or the insurance company will allow you to upgrade your prescription coverage to one that will allow for off-label medication coverage, you would be wise to do so now, regardless of whether or not you require such coverage at this time — it's likely you will need it in the future.

Request a copy of your insurance plan's formulary and keep it in your treatment binder. Have your physician check the formulary when prescribing a new medication to ensure coverage, or perhaps select a like drug (if available) from the formulary to avoid unnecessary out-of-the-pocket expense.

Information regarding the laws that govern switching plans during treatment or "continuity of care" issues when policies change with new employment can best be answered by calling the office of your state's insurance commissioner. Many states, such as California, have specific departments for patient advocacy that can help you work through these issues, or direct you to the proper federal agency if your plan is governed by federal regulations. Such patient advocates within your state health insurance department can help you with the necessary paperwork for filing appeals or complaints when your insurance company denies coverage for specific treatments or medications.

- All communications (from making claims to general inquiries) should be in writing.
- When communicating by phone or in person, be sure to record and confirm your understanding of the conversation in a letter sent certified with confirmation of receipt and keep a copy of the letter in your file.
- Scrutinize everything you receive from the insurance company and hospital — for example, bills, payments, and credits for mistakes — they DO happen! Do not be afraid to ask for explanations for items that are unclear or unspecified.
- Read your policy thoroughly so that you are aware of what benefits you are entitled to and what items are excluded, paying special attention to areas involving clinical trials or experimental treatments. Be prepared to ask your physician to write a letter on your behalf explaining why you should be allowed coverage for these items. It is helpful to have an "understanding" with your physician as to when consideration of experimental therapies would take place, rather than waiting for that day to arrive, only to find an unsupportive care partner.
- Health insurance companies can assign a case manager to you so that you can talk to the same person each time you call. Ask your insurance company whether you can be assigned a case manager.
- Do not hesitate to ask to deal with a "superior" of the person handling your

account and keep accurate information regarding the names of all persons (and their positions) involved with your claims.

- Before making a request, make sure that the person you are dealing with has the authority to grant it.
- Do not be intimidated.
- Do not hesitate to challenge anything that doesn't sound right to you.
- If you are unsure about anything, check with the State Insurance Department and then, if necessary, with a lawyer. If you do not think you can afford a lawyer, you may be able to get low-cost or free legal help. Try calling the local bar association to ask about legal aid (available through nonprofit organizations in most major communities) or a local law school to ask if they have a student law clinic.
- Most states have nonprofit advocacy organizations that are dedicated to access and continuity of care issues and are able to discuss your legal rights and avenues for contesting insurance decisions on your behalf. You can search the Internet using words like: "insurance denials", "HMO", "continuity of care", or "healthcare access" along with "patient advocates." In California, Citizens for the Right to Know is an excellent resource.
- Set up and keep a file of all correspondence and phone communications relating to your claims. The file should include, but not be limited to: bills, payments, claims, letters you send, letters you receive, checks, contacts, and your policy.
- Be sure that all of your premiums are paid on time. You may have trouble getting insurance again if you let your policy lapse.
- Keep track of all of your unreimbursed medical expenses. You might be able to claim these expenses on your tax returns.

Medicare coverage

In the United States, Medicare starts at age 65 years for persons eligible to receive it. Medicare comes in several distinct parts. Part A covers hospital expenses, an optional part B covers doctor expenses and outpatient care, and an optional part D covers prescription drug expenses. Part A is free for Medicare patients, but it pays only 80% of hospital inpatient care and has a deductible. Part B charges a means-based monthly fee starting at $202.90 in 2026 (deducted from Social Security benefits if they are being received), but it also pays only 80% of expenses and has a deductible. Parts A and B are called "original Medicare." Part D requires enrolling in a Medicare prescription drug

plan provided by a private company, which charges a monthly premium.

Because parts A and B pay only 80% of medical expenses, another part of Medicare, the missing part C, is designed to cover much of that 20% gap and lower deductible exposure. These are Medicare Advantage Plans, offered by private companies. A person must be in original Medicare before joining a part C plan. Medicare Advantage Plans often have monthly premiums (in additional to the part B premium), but many of these plans also include part D drug coverage as well as extra benefits, like vision, hearing, and dental coverage. Medicare Advantage Plans, however, typically operate with provider networks — that is, they are either HMOs or PPOs. That means that covered services will be less expensive to you as long as you see doctors or use hospitals that belong to the plan's network.

As an alternative to Medicare Advantage Plans, Medicare supplemental insurance (Medigap) policies are available from private companies to cover the 20% gap that original Medicare leaves. There are a variety of these supplemental plans, offering different benefits. These plans generally cost more than Medicare Advantage Plans, and they are not bundled with a part D prescription drug plan, which will have to be acquired separately. But supplemental plans do not attempt to limit the choice of doctors or facilities, exposing you to more expense if you choose to use doctors or medical care centers outside a plan's provider network.

As a brain tumor patient, you will need to seek out the best care possible for your brain tumor at a comprehensive cancer center — or at more than one center over the course of your treatment — wherever possible in the country. Consequently, if you are enrolled in Medicare, or will soon be, it might be prudent during the next annual enrollment period to seek out the best supplemental insurance (Medigap) policy you can afford because Medicare Advantage Plans are designed to limit choices to a preferred provider network. One place to begin a search for supplemental insurance (Medigap) policies is at the website of the American Association of Retired Persons (AARP) here:

https://www.aarpmedicareplans.com/shop/medicare-supplement-plans.html

Insurance Paperwork Organization

From an insurance standpoint, a brain tumor diagnosis could cover the gamut from surgery to lab reports, chemo, radiation, prescriptions (e.g., for anti-seizure meds,

anti-nausea pills), long term care, hospitalization, palliative/hospice care. Fighting a brain cancer often means touching everything medical.

The insurance and other paperwork might be overwhelming. If you can, find someone competent – like someone in the family or a trustworthy friend - who agrees to be in charge of dealing with the insurance paperwork and insurance companies. The one diagnosed with the brain cancer should not have to deal with any of it.

Financial Matters

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.

The Musella Foundation runs a co-pay assistance program for people with health insurance for one or more of the following treatments: Avastin, Temodar, Modeyso (dordaviprone), Lomustine (CCNU or Gleostine) and the Optune device. To find out about this program, go to: https://braintumorcopays.org.

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. In the medical journal Neuro-Oncology Practice, investigators analyzed the out-of-pocket expenses for 43 patients diagnosed with malignant glioma between August 2008 and May 2012. Of these 43 patients, 35 (81%) were newly diagnosed with malignant glioma. The majority had private medical insurance, 10 (23%) had Medicare or Medicaid coverage, and 2 (5%) were uninsured.

The investigators found that the monthly median out-of-pocket expense for these patients was $1342 (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.

The Musella Foundation runs two different programs to help you with treatment costs. For people with insurance, we have a co-pay assistance program for one or more of the

following treatments: Avastin, Temodar, Modeyso (dordaviprone), Lomustine (CCNU/Gleostine) and the Optune device.

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 1 on the next page 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).

Table 1: 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	https://www.cms.gov/medicare/coverage/prescription-drug coverage/patient-assistance-program	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

In the case of a high-grade brain tumor, i.e., a Grade 3 or Grade 4 (including GBM), Social Security guidelines (as of this writing) provide for immediate approval for benefits. For that reason, there is no need to secure the services of an attorney to obtain benefits to which you are entitled. These benefits are automatic for high grade tumors and the application process is straightforward.

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. A person under the age of 65 may qualify for Medicare if they have been receiving SSDI for 24 months. Coverage usually starts in the 25th month of SSDI entitlement and enrollment in Medicare Part A (Hospital Insurance) and Part B (Medical Insurance) is typical. Individuals under 65 with end stage renal disease (ESRD) or ALS may be eligible for Medicare earlier.

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?

Most hospitals will not resuscitate or intubate a person with what is considered a life-threatening diagnosis like a high-grade brain tumor unless that person expresses this desire in writing.

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.

In 2010, Massachusetts General Hospital found that patients with life threatening diagnoses who received early palliative care counseling stopped chemo sooner, entered hospice earlier, experienced less suffering at the end of their life, but lived 25% longer than those who received such counseling late (e.g., when ending treatment).

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.



SURVIVOR STORY #3

I am now a multi-year survivor of my brain tumor. I remember being seated in the emergency department in May 2009 as a nurse pushed a sedative into my IV line to control my shaking before transporting me into the room with an MRI scanner. The CT image in front of me displayed a lesion that would later be diagnosed as anaplastic astrocytoma. At that moment, I was a 23-year-old biomedical engineer working for a medical device company, I had recently moved in with my girlfriend, and I had always been healthy. Everything changed; I become a cancer patient overnight.

The events following my diagnosis were a blur. After neurosurgery to remove the tumor performed with a procedure called an "awake" craniotomy — during which the neurosurgeon administered verbal tests to see what areas of the brain had been affected by the tumor — I began treatment, which included radiation therapy and concurrent chemotherapy with temozolomide (Temodar).

After that initial treatment, I began adjuvant therapy with temozolomide on the cycle of 5 days on, 23 days off. During adjuvant therapy I was fortunate to have no delays due to the emergence of side effects like neutropenia (an abnormally low count of a type of white blood cell).

Fast forward a year and one brain-tumor recurrence scare (a second opinion was invaluable in avoiding a second surgery), I found myself in a completely different state and city with my now fiancé starting medical school. I was looking for a job, continuing my temozolomide regimen, and trying to answer the ever-present question in my mind, "What do I want to do with my life?" Ironically, I had never been much for introspection before I was diagnosed, when my perceived "time" seemed to be in oversupply. The answer I came up with is that I wanted to matter — I wanted my life to have more meaning. That sounds a little ridiculous and dramatic, but that was truly how I felt. And so over the next year I began volunteering in medical clinics and mobile hospitals in underserved neighborhoods. Eventually this culminated in my decision to become a physician and provide care to those who are diagnosed with cancer. My motivation came from a strong desire to reciprocate the heartfelt compassion and support I received during the treatment of my brain tumor.

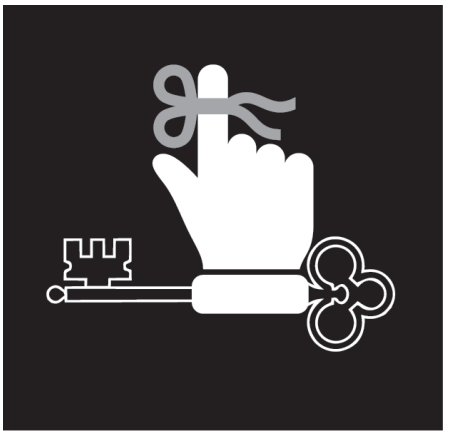
Six years later and a score of clean MRI scans, I have graduated from medical school and am now in the last year of my residency in the field of radiation oncology. I have found

fulfillment in life that I would not have had otherwise. The future is always uncertain, for cancer survivors and for everyone else, and I am still learning how to balance living for the moment with planning for the time ahead. Those diagnosed with a brain tumor may tread very different paths, but we are all survivors beginning on Day 1.

Painting by Linda Singer



CHECKLIST OF TOP TEN FIRST THINGS



Here is the Musella Foundation's most important first things checklist:

1. BEST CARE. Seek out the most advanced and the most specialized brain tumor care available to you.

Facility: Many smaller and local hospital systems may offer neurosurgery and treatment for brain tumors. However, these systems do not usually have the same state-of the-art facilities, technologies, and doctors specializing in different tumor types that large brain tumor centers have. Even if that means travelling a distance from home, bear in mind that larger brain tumor centers will have (1) more advanced pathology facilities for diagnosis; (2) greater capacity for storing tumor tissue for future testing; (3) better familiarity with the latest surgical and treatment practices; and (4) more clinical trial options to offer.

Doctors: You should find the most experienced neurosurgeon and neuro-oncologist you can who specialize in the treatment of your type of brain tumor, and you should ensure your doctors team together to coordinate and administer the different types of treatment your brain tumor will require.

Treatment Options: Engaging with our Patient Navigation Program (described below) helps you learn more about your cancer and your treatment options.

2. BEFORE SURGERY. Before surgery occurs, carefully consider various treatment options. There are some clinical trials that require registration before surgery of a

brain tumor occurs. In some trials, such as for certain types of immunotherapies, treatment begins before surgery. There are also treatments, such as Gliadel Wafers or GammaTiles, that can only be received at the time of surgery. For trials related to custom-made vaccines, the tumor sample obtained during surgery needs to be handled in a special way. Discuss your options with your neurosurgeon before surgery.

3. OPTUNE/TTFIELDS. Ask whether treatment with the Optune/TTFields' alternating electric-field therapy is available in your case. The Optune device, which treats brain tumors by delivering alternating electric fields called tumor treatment fields (TTFields), is a therapy approved by the US Food and Drug Administration (FDA) for newly diagnosed and recurrent glioblastoma (the most common type of primary brain tumor).

In addition to being a non-toxic and a non-invasive form of treatment, a recent study conducted by the University of Florida has found that Optune/TTFields dually activates certain pathways (i.e., STING and AIM2) that drive early anti-tumor immune responses.

Not all treatment centers offer the Optune/TTFields and this cap is not appropriate for all patients, but it is worth the discussion with your doctor. A detailed description of this treatment can be found in the section entitled "Optune/TTFields Device" of this Guidebook.

4. MOLECULAR TESTING. Make sure your tissue sample, whether obtained by biopsy or surgery, is subjected to comprehensive molecular-marker testing. Ask your doctor if the extent of testing adequately supports treatment decisions now and in the future. If you are treated at a major brain tumor center, the sample of your tumor tissue may be tested for molecular markers that can guide treatment choices.

5. TUMOR TISSUE PRESERVATION. Ask your surgeon how your tumor tissue will be preserved. The preservation of your tumor tissue should be discussed with your neurosurgeon before surgery. Brain tumor tissue is commonly preserved by the formalin fixed paraffin-embedded method. A better alternative is for the tumor tissue to be flash-frozen in liquid nitrogen. One advantage of freezing is that the tumor tissue is preserved intact and can be later used to create personalized cancer vaccines.

6. EDUCATE YOURSELF. Read this guide and visit the virtualtrials.org website. In

the "Learn About" section of the website, there is an archive of articles called "Noteworthy Treatments." In the "Interact" section, there is a video library of talks and presentations on all things brain-tumor related. You can also subscribe to our "Brain Tumor News Blast," which carries news stories about brain tumors: https://virtual-trials.org/newsblast.cfm.

7. JOIN A SUPPORT GROUP. The Musella Foundation operates online discussion forums covering numerous brain tumor topics. Additionally, Facebook has many brain tumor groups. Some of our favorites are:

Clinical Trials & Noteworthy Treatments For Brain Tumors,
Novocure, Optune Support For Glioblastoma,
Glioblastoma - GBM SURVIVORS TO THRIVERS!, and
Surviving Glioblastoma (GBM).

The website addresses for all these and more can be found in the section of this Guidebook below entitled "Support Groups."

8. THE PAPERWORK.

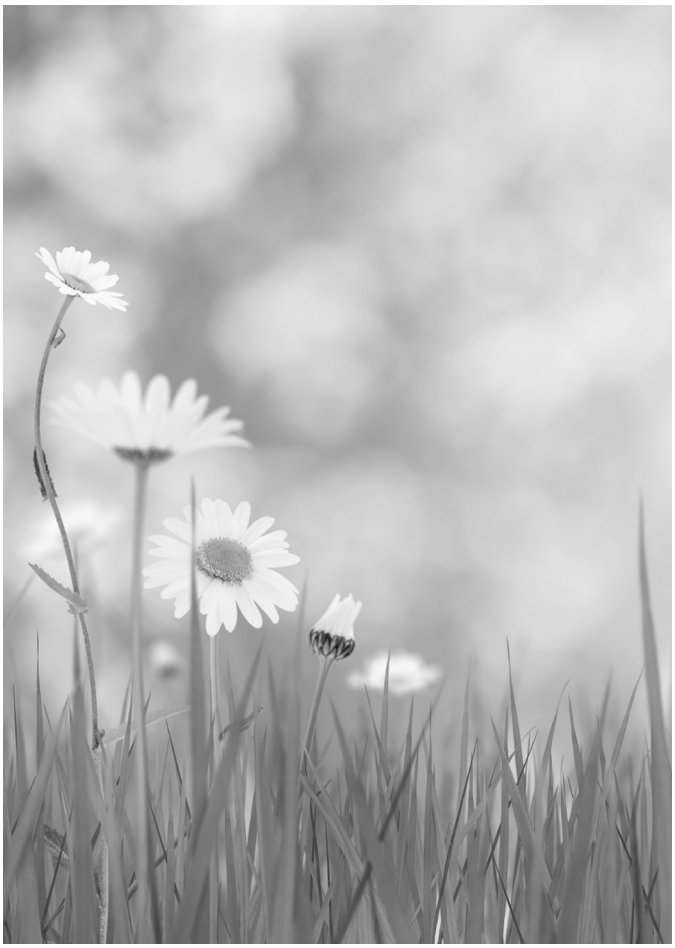
Get organized: Request, record, organize and keep all brain-tumor–related documents and information. Request all documents related to your diagnoses and treatment, including all pathology reports, and keep these documents organized in a binder. This binder can also contain whatever notes you take along the way. You may also consider making audio recordings (e.g., on your cell phone) of appointments with your doctors for future reference and review. It might also be good to bring a friend or family member with a good memory to all medical appointments.

Execute the Documents: Think about and sign such necessary legal documents as an advance directive, a durable medical power of attorney, and a durable financial power of attorney.

9. DESIGNATE A SUPPORT TEAM. Receiving a diagnosis of brain tumor is an exceptionally emotional and confusing situation. Unless you are especially skilled and motivated to do your own medical research, it may be best to designate a friend or family member to research treatment options and all things tumor-related on

your behalf. Please give this person this Guidebook to read and direct him or her to the virtualtrials.org website. Another person might be designated to relay news to your larger network of family and friends.

10. INSURANCE. Upgrade your insurance and know that some financial support is available. Upgrade to the best medical insurance that you can afford. If you are enrolled in Medicare, seek out the best supplemental policy you can afford but avoid Medicare Advantage Plans because they limit the choice of doctors. The Musella Foundation runs a co-pay assistance program for people with insurance to help with expenses related to the Optune/ TTFields device and several common chemotherapy treatments. For people without insurance, the Musella Foundation offers a Drug Discount Card that gives discounts for prescription and non-prescription medications.







Five

Treatments Overview

General

Newly diagnosed brain cancer is treated in accordance with a well-established Standard of Care protocol as described below. This protocol was established in 2005 and adopted by the worldwide neuro-oncology discipline following the release of a landmark study headed by Dr. Roger Stupp, a Swiss doctor who currently practices at Northwestern University in Illinois.

Dr. Stupp's study demonstrated a statistically significant survival advantage to those individuals newly diagnosed with GBM, while affording only minimal additional toxicity. That study employed the use of a chemo drug called Temozolomide (commonly referred to as Temodar) concurrent with radiation of the tumor site.

This protocol applies to adults with a cancerous tumor; it excludes pediatric cases. It is also important to note that there is no set protocol for the treatment of brain cancer in those 70 years old or above. Despite so many elderly people making up the bulk of brain cancer cases, medicine remains fluid about how to best treat them; doctors will examine all factors including such matters as the person's physical frailty and cognitive functioning, as well as the scope of the disease and may decide to tailor the Standard of Care to the person.

It is likely that you have heard of the term "clinical trial" and have recognized that the most advanced treatments are accessible through such a trial. You should be aware that all clinical trials have qualifying requirements and that many, but not all, clinical trials require the completion of the Standard of Care protocol.

There are nearly a dozen cancer treatments approved by the FDA for brain cancer, hundreds of clinical trials at countless locations throughout the US, any number of possible combination therapies, plus more than 150,000 new cancer treatment articles published each year. The neuro-oncologist will present you with selected options he/she believes may work, but there may be other options at other locations.

The latest anti-cancer targeted therapies and immunotherapies are directed at the genetic DNA mutations that underlie the development and progression of the brain tumor. Most high-grade brain tumors, especially glioblastomas, carry a wide range of genetic alterations, but the number that translate into meaningful treatment options is surprisingly small.

A large percentage of high-grade gliomas contain at least one genomic alteration (up to 84% in one study of glioblastoma), which could theoretically be actionable. However, many of the alterations are lower-tier targets (ESCAT IIIA-IV), meaning there is less clinical evidence for using targeted therapy. Another study found that only 7.2% of patients had an actionable mutation per EANO (European Association of Neuro-Oncology) guidelines and a mere 3.1% received targeted therapy. The median number of total genomic alterations can be as high as 8 per tumor, but the vast majority of these are merely descriptive and potentially useful in the interpretation of clinical trials and drug development, but very few are considered high-tier targets for currently available therapies.

In practical terms, most patients end up having one, maybe two, and in many cases no truly actionable mutations at all. Here's why:

The genetic landscape of a high grade tumor tends to revolve around several major regulatory pathways. The first is the RTK/RAS/PI3K signaling network, which is altered in the vast majority of glioblastomas. Mutations or amplifications in genes like EGFR, PIK3CA, or the loss of NF1 fall into this category. Although these changes are common and biologically important, therapies targeting them have had limited success so far. Still, they represent some of the few targets with available drugs or ongoing clinical trials.

Another major pathway involves p53, the cell's central guardian against DNA damage. Mutations in TP53 are widespread in high-grade gliomas, but currently they offer little in terms of actionable treatment. Only certain tumors with MDM2

amplification may be treated with targeted drugs, and even then, these therapies remain experimental.

Many tumors also carry disruptions in the genes that control cell-cycle progression—such as CDK4/6 amplification or CDKN2A loss—and these can sometimes be paired with inhibitors in clinical trials. Yet again, this typically represents just one potential target in a tumor filled with many other untreatable genetic biomarkers.

A small number of tumors harbor DNA-repair defects or become "hypermutated" after treatment with temozolomide. These cases may respond differently to certain immunotherapies, but they are the exception rather than the rule.

Taken together, high-grade brain tumors are genetically chaotic but therapeutically lean. Even though scientists can identify numerous mutations scattered across key pathways, only one to three of these alterations—at most—tend to suggest a possible targeted therapy, and many tumors present no actionable mutations whatsoever. This mismatch between biological complexity and clinical opportunity remains one of the central challenges in treating aggressive brain cancers today.

Clearly, you need to know the best options for your specific case so that you can make the best treatment decisions possible. You can make these decisions yourself or with your support team, or you can access the Musella Foundation Patient Navigation Program, described below, to help you make these complex decisions at no cost.

Patient Navigation Program

Program Overview

The Musella Foundation has joined forces with Head for the Cure and Cancer Commons to form the Brain Cancer Support and Solutions Alliance (BCSSA). United by a shared commitment to support individuals from diagnosis through treatment, the BCSSA brings together the strengths of each organization to provide timely, personalized nurse navigation and expert guidance from PhD scientists. This one-on-one support is grounded in the latest evidence-based science and medical research and is offered at no cost to patients and families.

By consenting to participate and granting access to your medical records, you enroll in personalized, evidence-based support and contributing to a broader community that advances care through shared real-world data. Support services are tailored to each individual and may include nurse navigation and advocacy, help understanding treatment options and potential next steps, review of genetic and molecular information by PhD clinical scientists, and identification of relevant clinical trials or expanded access opportunities. The program can also assist in identifying financial assistance options, emotional support resources, and additional services that may be helpful along the way.

How to Access the Program

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.

To get started, please visit: https://virtualtrials.org/navigation.cfm and click on the link stating, "Click HERE to get started with our patient navigation program"
This link will take you to a form where you can register for Expert Guidance via the BCSSA: https://www.cancercommons.org/bcssaregistration

When entering the program, you will be asked to register, consent, and submit your medical records. You can submit the records manually, or if it is easier, give your BCSSA Nurse Navigator the login credentials for your medical portal and they can import and organize the records for you. Importantly, if you choose to share credentials, you must also disable 2-factor authentication.

If you have any questions contact a BCSSA Nurse Navigator at (877) 971.1200.

Confidentiality

The Musella Foundation and Cancer Commons will take precautions to keep your health information confidential and not disclose it without your consent. You are also protected under the federal Health Insurance Portability and Accountability Act ("HIPAA") and any other applicable federal and state laws related to protection of patient information. You can review the most up-to-date version of Cancer

Commons' Privacy Policy on its website.

Geographic Limitation

These program services are intended for use only within the United States and its territories. The program services may not be appropriate or available for use outside the US.

Treatment Development Challenges

It is recognized that brain cancer needs more treatments and therapeutics. These needs are being addressed in the research labs throughout the world that are working constantly to produce a wave of better treatments and therapeutics.

Among the perplexing challenges faced by researchers is the fact that cell lines and tissue culture plates are not the same environments as the cancer itself, and animal models are not able to adequately mimic the disease in humans. As a result, advances in research technology are increasingly focused on modeling - either in vitro or by computation. These processes require a more profound understanding of the brain's environment such as the tumor-stroma interactions including neural tissue, extracellular matrix, the blood-brain barrier, astrocytes, and microglia.

Just by way of one example, the blood-brain barrier ("BBB") has been the nemesis of many promising cancer drugs. The human brain is encased not only in a boney structure but is protected by the BBB which is a highly selective network of blood vessels and tissue that keeps harmful substances from entering the brain. The BBB will allow certain substances like water, oxygen, carbon dioxide, and general anesthetics, pass into the brain. However, it keeps out bacteria and other substances, such as many drugs intended to treat brain cancer. Researchers are now turning to nanoparticle technologies as a way of producing treatments that will be more effective against brain cancer, thus finally defeating the interference of the BBB.

NCCN Guidelines for Treatment

The National Comprehensive Cancer Network (NCCN) is a not-for-profit alliance of 31 leading cancer centers dedicated to improving the quality, effectiveness, and efficiency of care so that patients can live better lives. The NCCN issues peer-reviewed

and consensus-based guidelines— based on published medical evidence and expert opinion — about what is the best treatment for typical patients with newly diagnosed or recurrent brain tumors.

The standard-of-care treatment for high-grade glioma that is described in this Guidebook is based on the NCCN Guidelines which were issued December 5, 2025. The NCCN Guidelines represent a general standard of care, although there may be some variations in "standard" treatment among the participating cancer centers. These Guidelines are available online to patients at the link given in the box below. For professionals with NCCN registration, the full guidelines (Version 3.2026) are available on line at: https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf.

To access the NCCN Guidelines, please go to this website:

https://www.nccn.org/patients/guidelines/content/PDF/brain-gliomas-patient.pdf

You may have to register before downloading the guideline.

In the NCCN Guidelines, treatment of newly diagnosed high-grade malignant glioma is determined on the basis of three different characteristics:

- The person's age (70 years old or younger and older than 70 years), and
- The person's Karnofsky Performance Status (KPS) score (See the Section entitled "Karnofsky Performance Status" for details), and
- The tumor's methylated (favorable) versus unmethylated (unfavorable) promoter status. (See the Section entitled "Modification of MGMT Gene and Methylation" for details.

The recommended NCCN treatments for primary malignant brain tumors can be found in the Journal of the NCCN. This Journal is a peer-reviewed, medical journal read by 25,000 oncologists and cancer care professionals and is the official journal of the NCCN. The Clinical Practice Guidelines can be accessed at this link:

https://jnccn.org/view/journals/jnccn/18/11/article-p1537.xml

By way of a summary, for every category of brain cancer patient, the NCCN recommends enrollment in a clinical trial. The next most common treatment recommendation after surgery consists of:

- Standard radiation therapy
- Oral chemotherapy with temozolomide (Temodar) during radiation therapy (which is called concomitant therapy) and then after radiation therapy (which is called adjuvant therapy)
- Alternating electric field therapy (the Optune/TTFields device) after radiation therapy (as an adjuvant therapy).

Each of these are described in Sections that follow.

Because patients newly diagnosed with high-grade malignant glioma will be seen by multiple different medical specialists, the NCCN strongly recommends close and regular communication among all medical service providers across the different medical disciplines involved, including physical and occupational therapists, psychologists, and social workers. Bear in mind that this type of interaction is more likely to occur at comprehensive cancer centers and at hospital systems with established brain tumor boards.

The virtualtrials.org website hosts a video library, with up-to-date videos from medical and patient brain tumor conferences that cover all aspects of brain tumor treatment, from radiation therapy to the latest chemotherapeutic drugs. To view a menu of these videos and to start watching them, go to: https://virtualtrials.org/video.cfm.

Standard Of Care (SOC)

Below are the current standards for care. If the applicable standard-of-care treatment is not offered to you, you should ask why not. If cost is the barrier to receiving any part of this standard-of-care treatment, contact us. The Musella Foundation has a co-payment assistance program that may be able to help you in some circumstances with your out-of-pocket expenses.

If the diagnosis comes back as a Grade 2, the doctor will decide what treatment protocol to follow depending on the specific type of tumor, its location, symptoms,

and other factors.

If the diagnosis comes back as a Grade 3 or Grade 4, the Standard of Care (SOC) treatment consists of:

- **Surgery** to the extent possible. (See the Section entitled "Surgery" for detailed information.). Surgery is followed by a period, usually a month, to enable the incision to heal.

- **Radiation with concurrent chemo**. In most cases, radiation will be administered daily (except for weekends) for approximately 6 weeks. Radiation is provided concurrent with a low dose of a systemic chemo called Temozolomide ("Temodar" or "TMZ"). Statistically, through numerous studies, use of Temodar in conjunction with radiation has been shown statistically to be the best initial treatment. For more information about radiation, see the Section entitled "Radiation" and for more information about the chemo Temozolomide, see the Section entitled "Temodar".)

- **Maintenance Chemo**. Following radiation, you may be prescribed a maintenance dose of Temodar which you would take 5 consecutive days out of every 28 days.

- **Optune/TTFields Device**. Certain studies show that use of the Optune/TTFields cap which treats brain tumors by delivering alternating electric fields, enhances the outcome of radiation and chemo. Not every tumor is located where this cap is useful, but where it is and if the person is diligent in use, the Optune/TTFields cap can help fight against the disease.

Although the above standard-of-care protocol has been found in clinical trials to extend survival time after the diagnosis of high-grade malignant glioma — sometimes considerably — nevertheless it only actually “cures” brain tumors in a relatively small number of persons. For that reason, all persons newly diagnosed with high-grade malignant glioma should consider enrollment in a clinical trial of an experimental therapy. There is evidence that patients on clinical trials have superior health outcomes (overall survival) even if the experimental therapy ultimately proves to be ineffective, possibly because the intensity of medical care and the monitoring within a trial is robust, so that adverse events and other complications of care

are noted and treated immediately. Clinical trial enrollment can occur at the very start of your treatment, or it can occur later. Clinical trials and their importance are discussed in the Section entitled "Clinical Trials."

Considerations Regarding SOC for High Grade Tumors

Many patients upon hearing a high-grade tumor diagnosis want the doctor to order up the strongest, most potent chemo to "blast" the disease away. While the sentiment is understood, there are ramifications that do not make that strategy workable. All treatments have side effects, and a protocol of maximum strength is likely also to be highly toxic and wear the patient's underlying health out. The recurrence or "progression" of malignant gliomas (Grade 3 and 4 Astrocytomas and Glioblastomas) is high. Within two years of initial diagnosis, over 90% of glioblastomas will recur even with aggressive standard therapy, and the probability is high that a Grade 3 or 4 Astrocytoma may recur. As a result, strategies to regularly monitor and treat the tumor while maintaining a high quality of life are essential.

For that reason, neuro-oncologists prefer to administer a generally tolerable chemo to control the disease immediately after diagnosis. Temozolomide (Temodar) has been used as the standard treatment for newly diagnosed GBMs since 2005. This chemo limits the amount of toxicity from treatment and preserves the patient's health for ongoing and future treatment.

Medicine, however, does apply the research developments for many second line treatments for GBM (subject to other factors like patient age, condition, anticipated responsiveness to treatment, etc.). There is an ongoing emergence of targeted treatments for GBM, and these are reflected in the clinical trials being conducted at the major brain cancer clinics.

General Treatment Considerations

When discussing treatment options with your doctor, you should understand that treatment is evolving. Traditionally, surgery has been the mainstay of treatment for most cancers. More recently, as it relates to benign and low-grade tumors, there has been a movement toward "watch and wait" rather than immediate surgical intervention. In some cases, watching rather than treatment is enough. Some tumors present few, if any, symptoms and cause few problems with little or no pain. They

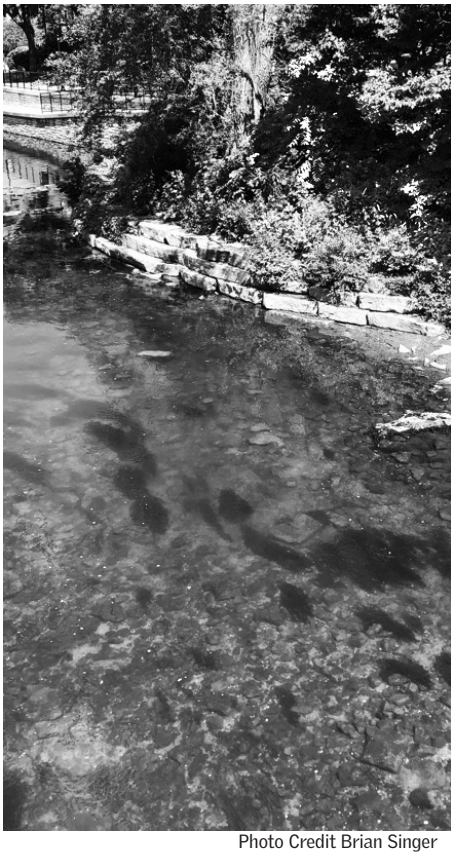


Photo Credit Brian Singer

may even remain inactive for long periods of time. Treatment in those cases usually do not enhance your quality of life. Treatment options vary. Learn about your disease and the approaches commonly used to treat it.

Some tumors respond better to radiation, others to chemotherapy or hormonal treatments. Some require one type of therapy, others a combination.

High grade tumors are aggressive and are assumed to cause major problems. Aggressive medical intervention in those cases is warranted.

Ask what would happen without any treatment and compare the answer with the expected results of treatment.

Not all cancer treatments have disrupting side effects; those that do are often predictable. Your doctor can outline a plan to prevent many side effects and otherwise treat or lessen others. In general, side effects are reversible, and helping you cope with them should be a focus of your doctor.

Take the potential side effects into consideration when choosing a treatment, but also know that most aren't as bad as you've heard. Ask your doctor what you can expect, for example:

- How sick are you going to be?
- How much energy are you going to have during treatment?
- If you work 50 hours a week now, will you be able to work 50 hours a week during treatment? Will you be able to work 20 hours?

Find out the answers to these and other questions you have. Treatment is your decision.

Family/Friends Considerations

You will have to decide the role your family and friends can play. They may have the best of intentions, but family and friends may overwhelm you with their research efforts. And they can be overly enthusiastic in advocating aggressive treatment when they don't fully understand the side effects and outcomes.

However, friends and family are crucial to supporting the best outcome. Numerous studies have correlated best cancer outcomes with social networks and support. But know your limits. It's OK to take a rest and regroup. You set the priorities and your limitations.

Work Considerations

Many people can work during treatment following surgery and radiation provided that their work schedule allows for their doctor visits and their reaction to the treatment is not so overwhelming that it interferes with their ability to work.

Many employers are required by law to change your work schedule to meet your needs during your cancer treatment. Talk with your employer about ways to adjust your work during treatment. You can learn more about these laws by talking with a social worker that may be part of the staff at your doctor's office.

Additionally, under the Americans with Disabilities Act (ADA) those diagnosed with cancer have certain rights if they are applying for work, if they wish to keep their cancer diagnosis confidential, and if they need accommodations at work for periodic breaks or a change in schedule. The ADA is administered by the US Equal Employment Opportunity Commission which publishes guidance for dealing with cancer in the workplace. That guidance can be found at this link:

https://www.eeoc.gov/laws/guidance/cancer-workplace-and-ada

Financial Considerations

For help with paying for medications that insurance does not cover, the section in Chapter 4 entitled "Financial Assistance" identifies resources that are prepared to assist.

Quality of Life Considerations

It is reasonable to consider your quality-of-life goals when considering treatment.

All treatments have side effects and brain tumor treatments have to be as aggressive as the disease itself. Unlike normal, off-the-shelf medications one might buy at a retail store, the side effects for brain tumor treatments can arise more often than not. It is highly recommended that you have a discussion with your doctor about what side effects you can expect and then reach an agreement with the doctor about what you are, and are not, willing to tolerate.

Absent a frank and open conversation with the doctor, the doctor is professionally bound to place the highest priority on managing the disease with a lower priority on quality of life. This does not mean quality of life is unimportant to the doctor. It simply means that given a choice between extending life by even a little bit or avoiding a treatment that may reduce a person's mobility and produce joint pain, the doctor will choose to extend life.

If, however, mobility is as important to you as extending your life, then the doctor needs to know that to see what adjustments, if any, can be made to the treatment protocol.

Understanding what side effects to expect and what benefits the treatment offers will help you avoid wondering why you are getting certain treatments should the side effects become manifest.

The goals of therapy can vary, and only you can decide what side effects you're willing to accept to achieve them. If you're a young person with a curable disease, you may be willing to tolerate very severe, short-term side effects for a chance of eliminating your disease. But if you are 85 and have an incurable disease, you may decide not to accept bad side effects if the goal is to live only an additional month or two.

Ask your doctor what the treatment is expected to accomplish. For example, the doctor's statement that treatment will increase survival by 50 percent sounds great. But if 50 percent means increasing life from eight weeks to 12 weeks, and those remaining weeks are spent vomiting and battling nausea, weakness, and fatigue,

maybe you haven't gained much.

Making Hard Treatment Decisions

From time to time, you may find yourself in the position of having to make some very hard choices. For example, the MRI says that tumor is probably progressing, and the medical team recommends surgery with a certain clinical trial drug administered during surgery. But the trial is not going to open up for a month. Do you wait for the trial or do the surgery now to stop the growth of the tumor?

Here are some pointers for how to make tough treatment decisions:

- **What does your doctor/medical team recommend**? Having enough support and advice to make a choice is important. Do you even want to make the decision? Or do you prefer to leave the decision up to your medical team? If you want to make or contribute to the decision, continue reading...

- **Does your hospital have a health decision aid** you could use? Some top hospitals have a written decision aid you can use to help you to weigh the important factors and make your decision.

- **Gather the facts (even if you have to push your doctor some)**. Examples:

    - What are the progression free and overall survival statistics for the treatment options? Were the studies done relevant to someone of your age, your diagnosis and your brain tumor's genetic make-up?

    - Are there any other options you should consider?

    - What are all the eligibility and disqualifying criteria for trial enrollment?

- **Learn the benefits and risks** of each option. Decide which of the benefits matter the most to you.

- **Be prepared for trade-offs**. Example: The good news is that a certain drug has a great progression free status, but the bad news is that it might give you non-

stop diarrhea for a month. Be very clear about what you will tolerate and what you won't.

- **Listen to your emotions**. "Gut feels" really have validity. We process a myriad of factors subconsciously. We have to be careful that we are not swayed solely by how we feel, but it is reasonable to consider how we feel instinctively.

Long Term Treatment Side Effects

In the past, the consequences of long-term side effects were never a big concern because people with newly diagnosed high-grade gliomas did not live long enough for them to be a concern. Fortunately, there has been a steady rise in the number of long-term survivors of brain tumors, largely due to the success of the standard-of-care treatment described in this section. Now long-term side effects have to be considered when choosing a treatment.

A long-term side effect of radiation is cognitive loss, which varies with the volume of the targeted area, the dose of radiation, the number of fractions, the location of the radiation field, and the delivery system. Whole brain therapy, used traditionally for brain metastases, invariably causes some cognitive decline after one year due to demyelination of white matter tracts and disconnection of neural networks with loss of the white matter integrity. Accordingly, there is an increasing use of focal radiation therapy (i.e., stereotactic radiosurgery) with a single fraction (gamma knife) or three to five fractions (CyberKnife®), or other forms of conformal radiation with a tight, targeted field and sparing of the white matter (Novalis). Intensity modulation radiation therapy (IMRT) is another option to minimize brain injury while targeting the tumor. Finally, proton therapy can minimize injury to the normal brain because of the Bragg peak effect, in which the radiation enters the brain normally, reaches the target, but does not exit, minimizing injury to surrounding tissue as the energy is deposited into the target. Finally, there are computer and imaging-based techniques, such as hippocampal sparing, designed to protect the hippocampus, a key structure for memory. Furthermore, for radiation-induced necrosis (tissue death) which may occur between 3 months and 2 years after radiation, treatment with bevacizumab, steroids (like dexamethasone), supportive treatments (pentoxifylline or vitamin E), memantine, or hyperbaric oxygen may be of value.

Another potential risk of risk of radiation therapy is the potential to develop

cerebrovascular disease and stroke later in life, especially for those treated at a young age or treated with high doses of radiation in the vicinity of major arteries and those with other vascular risk factors (hypertension, diabetes, smoking, high cholesterol). Radiation-related vascular problems typically arise 5–20+ years after treatment, though earlier changes can occur. Your radiation oncologist will carefully plan radiation so that the dose delivered to major arteries, such as the carotid artery, is quite low. In large population studies of survivors of adult brain tumors, the overall death directly caused by stroke is low; death from the brain tumor itself is by far the greater danger. Long-term complications of radiation can occur years after treatment due to a process called radiation-induced vasculopathy which accelerates atherosclerosis and causes narrowing of blood vessels. Because of this risk, careful monitoring and control of other stroke risk factors is advised to prevent this rare complication.

Another concern of radiation is that soon after radiation (days, weeks, or months—not years later) there can be a treatment effect known as radiation-induced edema, or swelling. This phenomenon is generally transient, but may require steroids or in severe cases the use of a drug such as bevacizumab (Avastin). It may lead to radiation-induced necrosis and breakdown of the blood-brain barrier, which can be difficult to distinguish on an MRI image from tumor progression; therefore, it is called "pseudoprogression". A follow-up MRI will generally show improvement when the cause is radiation, and will show tumor enhancement with true tumor progression. This phenomenon of pseudoprogression may be more common in patients who have a methylated MGMT promoter and are taking temozolomide (TMZ) as TMZ is a radiosensitizer, making radiation therapy more powerful and sometimes modestly increasing the side effects. The survival benefit of concurrent TMZ and radiation is substantial enough that the combination remains the global standard of care.

Chemotherapy, for example temozolomide (Temodar or TMZ), is selected because it kills dividing cells (cytotoxic) and penetrates the blood-brain barrier. TMZ is relatively nontoxic, but like all cytotoxic chemotherapy it may have side effects such as fatigue, nausea/vomiting, or suppression of the immune system with lowering of white blood cells. TMZ is generally well tolerated during treatment, but some effects can persist or appear months to years later. The most significant long-term concern is its impact on bone marrow. TMZ suppresses blood-cell production, and while this usually improves after treatment stops, a small number of patients develop prolonged or even permanent marrow dysfunction. This can show up as chronic low

blood counts (particularly lymphopenia), increased susceptibility to infections, or rarely, serious conditions such as myelodysplastic syndrome (MDS) or acute leukemia. These complications are uncommon, but they are documented.

Another long-term effect involves the immune system. Even after blood counts normalize, some patients have persistent lymphopenia, especially low CD4 T-cell levels. This can increase vulnerability to viral infections or reactivation of infections like shingles. Because of this, clinicians may monitor blood counts for months or years after therapy, particularly if a patient experiences recurrent infections.

Fatigue is one of the most commonly reported lingering effects. Even after active treatment has ended, many patients describe a chronic, low-grade fatigue that can affect daily functioning. This may overlap with other factors—recovery from radiation, stress, sleep disruption, or the underlying illness—but TMZ appears to contribute in some people.

Gastrointestinal effects such as nausea typically resolve after treatment, but some individuals develop longer-term changes in appetite or digestion. Hair thinning rarely persists long term, but nail changes or skin sensitivity can occasionally continue.

Finally, fertility effects deserve mention. TMZ can reduce sperm count and motility in men, and although this is often reversible, long-term or permanent infertility is possible. The effect on female fertility is less clearly defined, but ovarian reserve may be affected. For this reason, fertility preservation discussions with your oncologist are typically recommended before treatment.

There are also rare cases of myelodysplasia or "preleukemia" or secondary cancers–conditions related to chemotherapy, particularly with alkylating agents such as temozolomide (Temodar). So, although the optimal duration of temozolomide treatment remains unknown, staying on temozolomide for prolonged periods could increase the risk of injury to the bone marrow. More research is needed on this question.

SURVIVOR STORY #4

My brain tumor story began in late 2006, when I suffered a series of debilitating seizures. Such symptoms would typically result in emergency treatment, but my case was complicated by the fact that I had suffered from epilepsy since childhood. It had been kept under control with medication, and by 2006 I had been seizure-free for years. Nonetheless, my physicians attributed these new seizures to my old epilepsy condition. Medication was increased but the convulsions grew progressively worse. One day in early 2007, I awoke to find the right half of my face paralyzed, with generalized stiffness on the right side of my body. My wife took me to the emergency room. I underwent a CT scan, which showed a large tumor in my left frontal lobe along the motor strip.

In February 2007, I had a total resection. Before the operation, the surgeon had requested my permission to be as aggressive as possible (permission I granted) but warned me to be prepared for deficits, including the possibility of paralysis of one side of the body. In reality, my only postoperative deficits were similar to the preoperative ones: facial paralysis, right-side weakness, and minor aphasia. These problems gradually improved in the weeks, months, and years following the operation.

I was sent home to await the pathology report, which arrived within a few days. The diagnosis was glioblastoma, a conclusion confirmed by two other laboratories, which independently analyzed the tumor tissue on paraffin slides. I received the usual prognosis for this disease: almost certain recurrence within 1 year, with slim odds of surviving more than 3 years. Molecular testing reported that the MGMT status of my tumor was unmethylated, meaning that my tumor was less likely to respond to chemotherapy with alkylating agents like temozolomide (Temodar).

I sought out therapeutic options. At that time where I lived abroad, what is now the current standard-of-care therapy for glioblastoma was not widely applied. But I found and read the famous paper by Stupp et al entitled "Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma," which showed benefit for concurrent administration of daily temozolomide during a 6-week period of radiotherapy followed by adjuvant therapy with temozolomide. I found two radiation oncologists who were willing to offer this therapy to me, and I got started immediately. Even before the radiation phase, I had begun to read everything I could find about brain tumors, searching for ways to improve my survival probabilities. The website PubMed (www.pubmed.com), the US National Library of Medicine index of medical articles published worldwide, was an

invaluable resource. At some point I stumbled on the Musella Foundation virtualtrials.org website, which also provided me with substantial information about my illness. I found Ben Williams's story on that website to be particularly interesting and the logic behind his treatment approach compelling. I read Ben's book and his periodic updates, which led to an exchange of email, followed by several telephone conversations. Throughout my ordeal Ben has been an invaluable source of knowledge and support for me, as he has been for many other patients.

I was in the fortunate position of having had a total resection of my brain tumor. However, I was aware that the odds of recurrence within 1 year were extremely high, and that a recurrent tumor is more difficult to control than a newly diagnosed tumor due to its acquired resistance to first-line therapies. My goal, therefore, became that of postponing a recurrence for as long possible and to do so by all means at my disposal. The approach was along the lines of that advocated by Ben Williams: to block multiple tumor growth mechanisms by means of a "cocktail" of agents that have shown some evidence of efficacy against glioblastoma or other types of cancer.



Photo Credit Steve Tilkin

During the 6 weeks of radiation, I had ample time to start planning for the next treatment phase. My oncologist proposed 8 28-day cycles of temozolomide on the standard schedule of drug administration on days 1 to 5 of each cycle followed by 23 days off. I had read that this schedule provided limited benefit for someone like me, whose tumor MGMT status was unmethylated. But there were some positive reports of experiments using a low dose daily (metronomic) schedule, in which MGMT methylation status had less of an effect on patient outcomes.

Based on this argument, I lobbied my physicians to try the metronomic schedule, and they said that they would consider it. In 2007 the drug bevacizumab (Avastin) was becoming popular as an experimental treatment for recurrent glioblastoma. Bevacizumab is an anti-angiogenesis drug that inhibits the growth of new blood vessels to feed the tumor. Based on positive results from various early studies, I wanted to add bevacizumab to the proposed metronomic therapy for temozolomide. This highly anti-angiogenic approach was attractive to me because it had the potential to forestall recurrence by delaying the growth of blood vessels in the tumor area. I discussed the idea with some prominent neuro-oncologists around the world and received encouragement from many quarters. Physicians at one particular comprehensive cancer center were particularly enthusiastic and generously offered to write letters of support for my plan. With help from a researcher, I drafted a proposal for my bevacizumab/metronomic temozolomide treatment plan, which I presented to my oncologists. They were interested in seeing whether such a treatment plan could work in a case like mine. Provided that I sign a consent form, they were willing to send the proposal through the hospital's internal review board, which approved it as a one-person experiment.

Things were looking good, but I wanted to pursue a more aggressive strategy. I added chloroquine to the therapy, after reading papers that showed that it improved results for chemotherapy. I likewise included verapamil, which could potentially inhibit extrusion of chemotherapy agents from cancer cells and help prevent multidrug resistance. Another addition was aspirin (200 mg/day), mainly as a prophylactic against blood clots from bevacizumab, but it had potential anti-cancer benefits in its own right. The drug celecoxib was also included early on due to promising results from small clinical trials for brain tumors and other cancers. Before going further, I compiled a list of 60-plus agents that could potentially contribute to the therapy, which fell into three categories: (a) they had shown efficacy against some form of cancer, either in clinical or preclinical settings; (b) they had been shown to be synergistic with chemotherapy or other substances already in my therapy; or (c) they had demonstrated positive effects in building up the immune

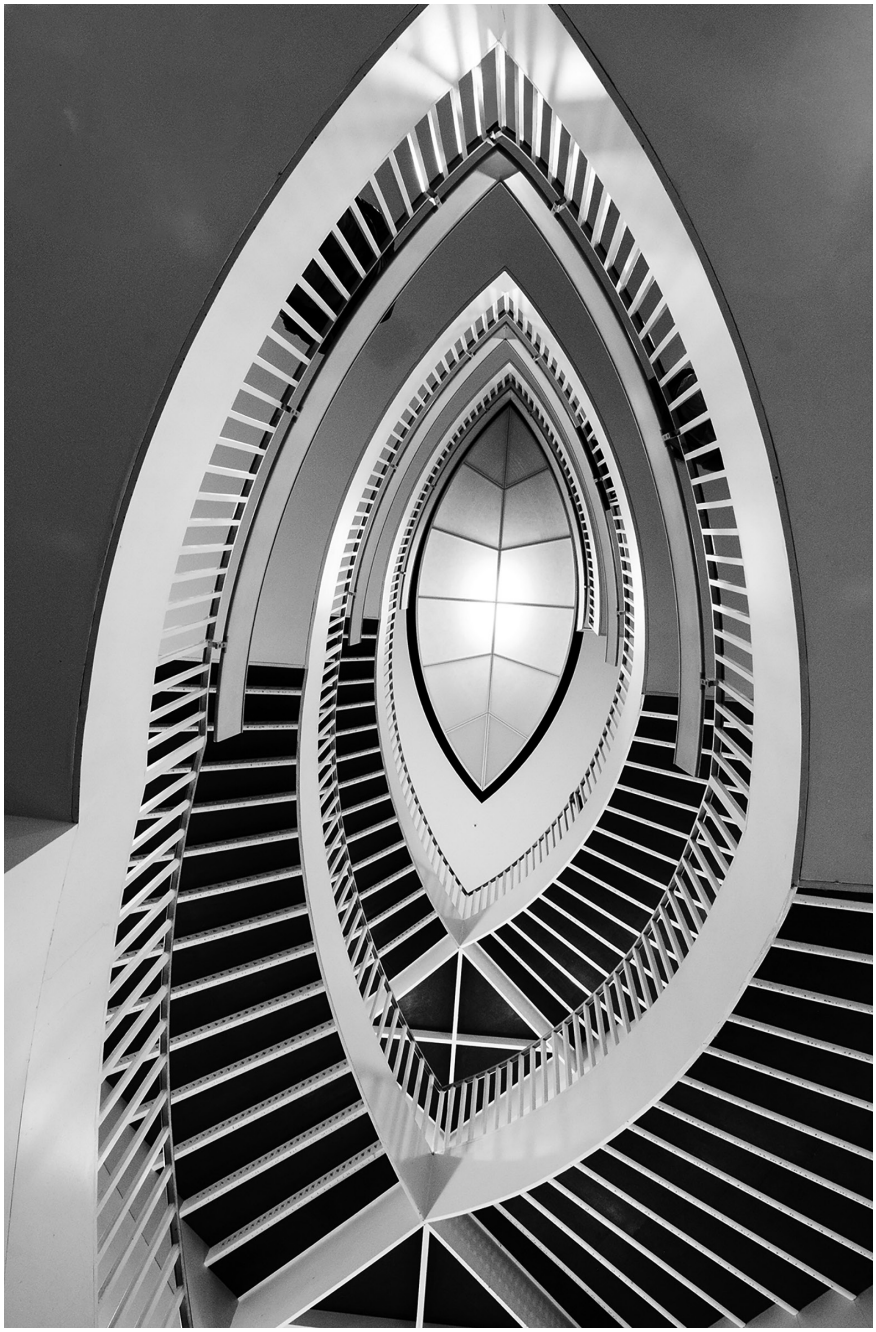
system. The list was eventually refined to 27 substances, many of which were natural supplements, for example, green tea extract, fermented papaya extract, omega-3 fish oils, resveratrol, melatonin, mushroom extracts, selenium, and so on. With minor exceptions, my MRI scans have been clear since the summer of 2007. There were a few scares during the first 2 years, with images showing small degrees of enhancement in and around the tumor cavity. But these abnormalities, which could indicate recurrence, were likely due to radiation damage. In any case they have disappeared over time. I now get yearly MRI scans, and no changes have been noted for many years.

Note that if I had to go through this again, I would alter many of the details in my treatment plan based on discoveries made in years subsequent to my diagnosis. I would not, however, change my treatment approach — that is, to battle the tumor aggressively using multiple agents simultaneously, thereby inhibiting as many growth pathways as possible.

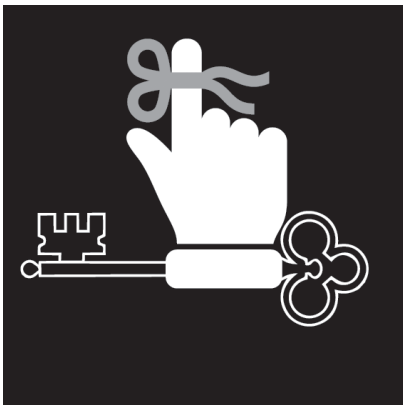
It has been over 9 years since my diagnosis without any signs of recurrence. After I have passed the 10-year survival point, I will switch from once-per-year to every-other year MRI scans. I still believe that my approach was the most effective way to treat a glioblastoma. For other patients with brain tumors, I thus advise the following:

- Become as educated as possible about this disease and participate in formulating your treatment plan to the best of your ability.
- Make your voice heard.
- Never be afraid to ask questions or offer suggestions, based on what you have learned from other sources (including other patients).
- Finally, if you feel like your input is being ignored, find another physician who will listen to you.

Photo Credit Steve Tilkin



KEY TAKEAWAYS TO REMEMBER



The current standard-of-care treatment for newly diagnosed high-grade malignant glioma consists of 4 different treatments, depending on patient and tumor characteristics: (1) surgery; (2) radiation therapy; (3) systemic chemotherapy with temozolomide during radiation therapy and then after at a maintenance dose; and (4) alternating electric field therapy (the Optune device) after radiation therapy.

If the standard-of-care treatment is not offered to you, ask why not.

Use the Optune website to find doctors who are trained in administering the device.

Make certain that the members of your medical team are experienced in the treatment of your specific type of brain tumor.

Enroll in the Patient Navigation Program to explore all your treatment options. To get started, please access this link: https://virtualtrials.org/xcelsior.cfm

Using the questions in this book as a guide, prepare your own list of questions, being sure to ask the members of your medical team about your treatment options.

Consider entering a clinical trial.



Six

Surgery

Overview

Surgery is one of the main treatments for brain tumors. In many cases, brain tumors can be removed by surgery and surgery may actually "cure" some low-grade tumors. For high-grade tumors, surgery alone is not a cure, but it does buy time for other treatments to work and offers a lot of opportunities. For example, a tissue sample from surgery can be analyzed for the molecular contents of the tumor and be tested for resistance to certain drugs. This analysis may point to specific treatments that will best manage the disease. In addition, there are some therapies that require prior surgery and removal of the tumor to make use of the tumor tissue in producing a personalized treatment.

A well-performed surgery is the #1 contributor to the best outcome when a cancerous tumor is first diagnosed. A 2020 study led by the Johns Hopkins Kimmel Cancer Center found that, among those diagnosed with the most aggressive form of brain cancer, median survival after diagnosis was 8 months for those who had a biopsy but no surgery; 11 months with partial tumor removal; and about 16 months for those whose tumor was completely removed.

Additionally, in high-grade tumors, a good surgery will 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, particularly cancerous ones, 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.

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. 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 operable. 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. Since surgery of high-grade brain tumors is not a cure, sometimes brain tumors are considered inoperable if the expected neurological damage arising from the surgery would create unacceptable problems for the patient.

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 Guidebook. 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;
- the tumor has spread along the lining of the ventricles that make cerebrospinal fluid (ependymal spread) or the coverings of the brain (leptomeningeal spread).This finding can be detected, often by MRI, and rarely by glioma cells in the CSF using a spinal tap (lumbar puncture);
- 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.

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 "subtotal") 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 and wait" approach. 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 malignant 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.

For high-grade malignant brain tumors, surgery may relieve symptoms caused by too much pressure in the brain and allow time for other treatments to work. Malignant brain tumors can grow so fast that without surgery, other treatments might not have the time to work. Surgery is also an opportunity to try experimental treatments that require direct access to the brain.

A common problem with malignant brain tumors is recurrence (regrowth). Tumors often come back within a short period of time, even if they have been surgically removed and treated with radiation and chemo. When they do recur, they usually

grow in or near the same place as the original tumor. Over 80% of recurrences are within 2 centimeters of the original tumor location. Researchers and doctors are hard at work developing ways to discourage tumor regrowth or lengthen the time before the tumor again grows.

The challenge of this disease is sometimes having to experience repeated surgical procedures, radiation, and chemo. For this reason, the better a person maintains their underlying health with a good diet, exercise (to the extent recommended by their doctor) and good emotional support, the better they are able to withstand the repetitive treatments often needed to manage the disease.

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
- Blood tests to evaluate the clotting ability of blood (the 'coagulogram'), which includes platelet count, Prothrombin Time (PT) and Partial Thromboplastin Time (PTT), are particularly important if patient has been on blood thinners, or there is a history of excessive bleeding or a blood disorder
- Urine test for kidney operations
- Electro-Cardiogram to check your heart
- Chest X-ray to check your lungs
- Additional MRI used by the neurosurgeon for surgical planning. These additional modalities may include contrast enhancement, high-definition MRI for neuronavigation, resting-state or task-based functional MRI to identify "eloquent" areas that control speech or movements, or diffusion-weighted MRI to identify white matter tracts that connect the vital "hubs" of the brain "connectome"

- 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 are certain advanced treatments or clinical trials that require registration prior to surgery.

For example, certain types of immunotherapies need to begin before surgery. For trials related to custom-made vaccines, the tumor sample obtained during surgery needs to be stored in a special way, so those needs must be known to the neurosurgeon prior to surgery.

There are also treatments that can only be received at the time of surgery, such as implantation of Gliadel Wafers or radioactive GammaTile therapy, as described below. Ask if the Gliadel Wafers or 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 procedure 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.

- Before surgery, ask about personalized vaccine therapy, which requires a tumor sample.

- Before surgery, ask about clinical trials that require registration even before surgery occurs.

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.)

Most long-term survivors of high-grade malignant glioma have had multiple surgeries. Usually, surgery will not be as bad as you expect. The worst part may just be worrying about it the night before. There are risks to surgery anywhere in the body, but surgery today is much safer and easier than it was even 10 years ago. Serious side effects are much less common than they used to be, so don't let horror stories from the past bother you. Problems do still occur but not as frequently as in the past.

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 23-year survivor of GBM who underwent 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=r0D2n9e5Lt0

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 neurosurgeon 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 some circumstances, 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.



Intraoperative 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 postopera-

tive 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. Options include:

- Awake throughout the surgery: You would receive an injection of a local anesthesia to numb a small part of your scalp, called a scalp block.

- 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 neurosurgeon 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 neurosurgeon 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

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 intraoperative 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 maximal safe resection because the extent of resection, as noted previously, correlates with significant improvement in overall survival.

Neurosurgeons and their anesthesiologists are skilled in ensuring patients do not experience pain during the procedure and are able to remain comfortable throughout. 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 surgically, but is causing intolerable functional deficits due to 'mass effect' from compression or invasion of the brain's white matter (fiber tracts), or raised intracranial pressure, the neurosurgeon may perform an operation to debulk the tumor. Partial resection is performed only in special circumstances, as maximal safe resection is the gold standard, and wherever possible, a gross total resection (GTR), is the objective. A GTR is defined as a gross total removal where there is no visible tumor seen on the postoperative, contrast-enhanced MRI.

How much of the tumor can safely be removed without harming normal, surrounding, functional brain tissue and the normal blood supply to the brain is an important decision that is made by the surgeon after a discussion with patient and caregivers, and is also based on the intraoperative surgical findings, the texture of the tumor, its attachment to critically important blood vessels, and the degree of invasion into neighboring structures. The benefit of a GTR, or an extent of resection that is 80% or higher, is diminished if in the process of surgical removal, a functional deficit is created. For a surgeon, it is a delicate balancing act between increasing EOR (Extent of Resection or 'maximal') and avoidance of injury and further neurological deficit (safety).

The determinants of the EOR depend on many factors, but one of the key factors is location of the tumor. Tumors that invade the deep structures near the midline of the brain, such as the thalamus or the brainstem, can be removed in rare circumstances, but usually removal of these intrinsic tumors are formidable. It also depends on if the tumor is focal, with a discrete border, or more likely has many "finger-like" extensions into the surrounding brain or is diffusely infiltrative. The presence of hydrocephalus or proximity to the ventricular lining is another consideration.

The functional status of the patient, measured by the Karnofsky Performance Score (KPS) [or, alternatively their ECOG score] is a useful barometer to guide the decision-making process. (See the Section entitled Karnofsky Performance Status for the score chart.) Clearly, the higher the KPS prior to the surgery, the more likely there will be a benefit from surgery, and the more likely the patient will make a meaningful recovery after surgery. The KPS can be a surrogate marker for the extent of the disease, its invasion into "eloquent" brain centers (speech, vision, and motor areas),

and the extent of injury. The brain has some degree of recovery and retraining, known as neuroplasticity. One of the reasons for surgical debulking is to maximize the brain's ability to heal itself, a process which is just beginning to be understood. Relief of hydrocephalus, mass effect, etc. will all tilt the odds of a high-quality, prolonged survival in favor of the patient. Historically, many clinical trials used a KPS of 70 or greater as a cutoff value for trial eligibility. There is no single KPS value that would preclude surgery, although a KPS of 50 or less would mean that the chances of improvement from surgery alone are poor. The decision to operate is made on a case-by-case basis, often with the input from an interdisciplinary neuro-oncology team (Neurosurgery, Neuro-oncology, Radiation Oncology, Radiology, etc) and multiple factors, beyond the KPS score, are considered.

Generally, the neurosurgeon will decide if the tumor is "operable" or "inoperable" due to its pattern of growth, location, etc. For example, a tumor that is dispersed in many locations (multicentric) and is not "nodular" but rather grows as a spider web, or a film, may not be resected totally. Removing only a portion of the tumor, for example 25- 50% of the tumor, can be futile for two reasons. First, if only half of the tumor is removed, the tumor can grow back rapidly, as the doubling time of a malignant glioma can be as rapid as 6 weeks and often regrows after 6 months. The extent of tumor removal during surgery has a significant impact on the tumor doubling time, which is the duration it takes for a tumor's volume to double. When only 50% of the tumor is resected, the time to recurrence is equivalent to one doubling time of tumor growth. If 75% of the tumor is removed, the progression-free survival is extended to two doubling times. In cases where 95% of the tumor is successfully resected, the time to recurrence increases substantially, corresponding to five doubling times. This demonstrates that a greater percentage of tumor removal can dramatically prolong the period before the tumor begins to regrow.

A second danger of a suboptimal (< 80% removal) of the tumor is the "wounded glioma syndrome" ("WGS") which can occur if 25- 50% of the tumor remains intact. This rare, but potentially fatal postoperative complication, is characterized by the rapid onset (hours to days) of severe cerebral edema (brain swelling) and/or hemorrhage (bleeding) within the surgical bed in distant, unoperated regions of the brain. The mechanism is uncertain but factors that contribute to the WGS included: i) disruption of the delicate network of fragile blood vessels (angiogenesis) with a tendency to bleed easily; ii) local changes in the hemodynamics with changes in blood flow (called 'normal perfusion pressure breakthrough') into already compromised

surrounding brain tissue, which has poor autoregulation; iii) the tumor can induce a thickening of the blood, a coagulopathy, where small blood vessels become blocked or thrombosed, leading the residual tumor susceptible to bleeding.

Another consideration influencing the neurosurgeon's decision on the EOR is the IDH-mutational status of the tumor, if known. The IDH-mutant tumors, now classified as Grade 4 astrocytomas, have sharper margins and a more predictable spread, making extensive removal (including into the surrounding brain), known as "supratotal" or "supramaximal" resection feasible, and significantly improving survival. For the more common, IDH-wildtype glioblastoma, the focus is often to remove the contrast-enhancing tumor by 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 Guidebook 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, normal 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. In the NCCN guidelines (version 3, 2025), MRI-guided LITT is a category 2B recommendation (evidence-based, but not uniform consensus) as a consideration for patients who are poor surgical

candidates for a craniotomy with tumor resection. Potential, evidence-based indications include relapsed brain metastases, radiation-induced necrosis, glioblastoma, or other gliomas.

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.

Minimally Invasive Surgery/Neuroendoscopy/ Key-Hole Surgery

The Goals & Challenges of Neurosurgical Tumor Removal

Neurosurgery involves a delicate balance. Evidence demonstrates that removing as much of a brain tumor as possible improves patient outcomes, including survival rates, neurological function, and symptom relief. Reducing tumor volume also enhances the effectiveness of chemotherapy, immunotherapy, and radiation by minimizing tumor burden and limiting residual disease to the smallest possible amount. For benign tumors that exert pressure on the brain and are located outside the brain and brainstem—such as meningiomas, acoustic neuromas, and pituitary tumors—complete removal can be curative. However, microscopic tumor cells may remain in the surrounding brain, attached to blood vessels, or even invade bone (as seen in meningiomas), making truly curative surgery difficult. As a result, postoperative monitoring and scheduled follow-up ("active surveillance") are crucial for detecting

and intercepting potential recurrence. In cases of well-localized, low-grade gliomas, surgery can also be curative. Many low-grade gliomas, however, are diffuse and infiltrate surrounding tissue microscopically, challenging total removal. Maximally safe resection is the cornerstone of treatment for many brain tumors, including malignant gliomas and glioblastomas. Glioblastomas, which are "multiforme," vary in resection extent depending on their location, invasion into deep structures (such as the brainstem, thalamus, or hypothalamus), crossing the midline, or being multicentric rather than localized.

Technological Advances in Neurosurgery

The turn of the century saw the development of innovative surgical techniques, including MRI-guided surgery and intraoperative navigation systems—akin to GPS in cars—that provide neurosurgeons with a "roadmap" to the tumor while avoiding critically important (eloquent) areas responsible for speech, movement, and vision. Peter Huber, a leading cancer researcher, envisioned modern medicine as enabling tumor surgery with the human body remaining completely intact. Minimally invasive surgery utilizes precise incisions and minimal tissue injury, leading to faster recovery, shorter hospital stays, and improved functional outcomes. Tools facilitating these procedures include advanced surgical microscopes, endoscopes, and exoscopes. The exoscope, equipped with computer-assisted robotic arms, allows neurosurgeons greater freedom and precision. Both the microscope and exoscope can be paired with techniques that illuminate the tumor using fluorescent dyes (such as 5-ALA), and intraoperative ultrasound provides real-time feedback about residual tumor, hemorrhage, or cysts. Preoperative functional MRI and diffusion-weighted MRI help identify active (eloquent) brain areas and essential fiber tracts, guiding the neurosurgeon in avoiding damage to vital neural networks. The gold standard for brain mapping remains awake craniotomy, where electrical stimulation confirms areas controlling brain function during tumor resection. These advanced mapping procedures are performed in specialized centers with experienced teams including neuroanesthesia and nursing.

Minimally Invasive Approaches and Keyhole Craniotomies

Increased precision from preoperative and intraoperative mapping allows for minimally invasive scalp incisions and bone removals (craniotomies). When bone removal is less than 3 cm (about one or two inches), the procedure is termed "keyhole."

Larger bone flaps, up to 7 cm, may be used in cases of large, superficial tumors. Keyhole craniotomies are preferred due to reduced postoperative scalp swelling, superior cosmetic and psychological outcomes, and earlier discharge to home. However, the primary focus remains cancer control and removing the majority of the tumor. Resections exceeding 80% generally result in significantly longer survival, while gross total removal (99–100% of contrast-enhancing tumors) consistently leads to better survival outcomes. These benefits may be negated if surrounding vessels are damaged, causing stroke, or if eloquent brain regions or white matter are injured, resulting in neurological deficits.

Protecting Brain Structures During Surgery

Various tools and strategies have been developed to avoid injury to deep white matter, fiber tracts, and surrounding brain. Atraumatic suction devices help mobilize critical structures, such as blood vessels, reducing the need for retractors that can cause swelling (edema). Tubular retraction systems displace fiber tracts to the side while preserving white matter integrity and providing a safe pathway to the target tumor. These "parafascicular approaches," which run parallel to white matter tracts, are integral to the paradigm shift toward minimally invasive neurosurgery and increase the feasibility and safety of removing small, deep tumors.

Endoscopic Surgery for Skull Base and Deep Brain Tumors

For tumors of the pituitary gland and surrounding skull base, endoscopes have been developed. These devices, consisting of a long tube with a camera and monitor, may be flexible or rigid and are inserted through a small hole at the base of the skull, often with collaboration from the otolaryngology (ear/nose/throat or ENT) team. The endoscope, equipped with tiny forceps and microscissors, enables more complete surgery with bright illumination and a 360-degree view of the tumor edges, surpassing the limits of conventional microscopes. Endoscopes can also be used to biopsy or resect deep brain tumors via a small opening ("burr hole") at the top of the skull. Additionally, endoscopic techniques are effective in treating obstructive hydrocephalus by creating an opening in the floor of the third ventricle—an operation known as endoscopic third ventriculostomy (ETV)—to restore normal cerebrospinal fluid flow and alleviate hydrocephalus symptoms. After microsurgical tumor removal, the endoscope can be used to inspect the surgical field for residual tumor, bleeding, and to ensure a clean and dry environment.

Adjuncts to Surgery: Local Tumor Control

Upon completion of surgery, neurosurgeons may place FDA-approved polymer "wafers" containing chemotherapy (Gliadel) to delay local recurrence in newly diagnosed malignant gliomas. Other promising approaches for local control, such as radioactive seeds (GammaTile), are in early clinical trials but not yet FDA-approved. Photodynamic therapy (PDT) using talaporfin sodium is available in Japan, but not in the United States; PDT is most effective for superficial tumors due to limited laser penetration (0.75 to 1.5 cm), making it less suitable for deep, infiltrating glioma cells.

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, then you should call the doctor's office right away and they will probably want to see the patient pretty immediately.

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.

Treatment Implants During Surgery

Neurosurgeons can surgically implant chemo into the brain tumor or may place chemo into the tumor site after a tumor has been removed in order to discourage future growth. The neurosurgeon can also imbed radioactive seeds to deliver radiation directly to the site. The options are further described below.

Gliadel Wafers (also called Carmustine Wafers)

Before surgery, ask about the possibility of implantation of Gliadel Wafers within the brain tumor cavity during surgery.

Gliadel Wafers are dime-sized wafers containing polifeprosan 20 with a chemo called carmustine. Gliadel Wafers may be appropriate for those with a newly diagnosed, high-grade tumor or those about to undergo surgery for a regrowth of a high-grade tumor.

These Wafers are implanted by the neurosurgeon during surgery at the tumor site. The Wafers are placed onto the walls and floor of the space made available when the tumor was removed. As many as eight (8) Wafers may be used; the number of Wafers will depend on the size of the tumor cavity.

They are left in place and over the following 2 to 3 weeks, the Wafers slowly dissolve, delivering carmustine to the tumor environment. The goal is to kill tumor cells left behind after surgery.

In the NCCN guidelines, Gliadel Wafers are considered optional for patients who receive a maximally safe resection. Be aware that implantation of Gliadel Wafers during surgery may make you ineligible for some clinical trials further on in your treatment, so plan ahead.

GammaTiles (also called Surgically Targeted Radiation Therapy or STaRT)

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.

More than 1,000 patients have been treated with GammaTile to date, and several publications have described technical aspects of the device, workflow and clinical outcomes.

Neuroplastic Surgery

For complex tumors, such as those penetrating the skull or at the skull base, your neurosurgeon may work closely with a colleague who is an expert in plastic surgery or in ENT (otolaryngology). If the tumor is near or in the orbit of the eye, the neurosurgeon will likely work with an oculoplastic surgeon – an ophthalmologist (eye doctor) who has extra training in plastic and reconstructive surgery for the eye socket. Likewise, if there is a large tumor involving the skull, a plastic or "neuroplastic" surgeon (with dual expertise in plastic surgery and neurosurgery) may be involved in the surgical approach, obtaining skin grafts, and assisting in the repair. Neurosurgeons may remove bone during the operation if there is brain swelling or if the bone is invaded by cancer, although this is relatively rare. In situations where the bone is removed, a second operation, called a cranioplasty, can be scheduled and a form-fitting, synthetic plate obtained by using 3-D scanning. The personalized implant will prevent visible deformity to the skull.

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 remain in the hospital for a week or more after the procedure. However, with improved techniques in neuroanesthesia and neurosurgery, including brain mapping, the length of stay has been significantly reduced. The average length of stay may be as short as three (3) days or two (2) nights. However, the length of stay is variable and depends on the location of the tumor, the age of the patient, co-existing conditions (e.g., heart or lung), the baseline neurological conditions and performance score, and whether the patient has unsteadiness. While early mobilization of patients after surgery is desirable and avoids complications related to prolonged bed rest, such as constipation, depression, deconditioning of muscle, urinary retention, and early pneumonia (atelectasis)—it is also important to prevent premature discharge to home as a patient who is weak is vulnerable to falls, which could lead to a readmission due to head trauma. Frequently, an independent evaluation by nursing or physical therapy/occupational therapy can be helpful in determining the discharge date.

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 happen 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. (See the Section entitled Karnofsky

Performance Status for the score chart.)

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 detect early changes in your Neuro vital signs, level of consciousness, or any other changes in vital signs (blood pressure, blood glucose, heart rate, oxygen consumption). Anyone emerging from brain surgery is under a significant amount of physiological stress. One of the more serious, but fortunately rare, complication is hemorrhage near the surgical site; most hemorrhages will occur within 6 hours of surgery. A postoperative MRI as early as 12 hours and up to 48 hours after surgery is recommended to gauge the extent of resection and ensure there is not any significant, but silent, hemorrhage.

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.

SURVIVOR STORY #5: BEN WILLIAMS

At the age of 50, I had surgery for glioblastoma on March 31, 1995, after an MRI scan in the emergency room the preceding day. The tumor was located in my right parietal cortex and was very large (it was approximately 180 cc and described as the "size of a large orange"). My neurosurgeon later told me that I would have been dead within two weeks had I not had the surgery when I did.

During the first two months after my diagnosis, I spent many hours on the Internet and in our medical school library, learning all that I could about possible treatment options. While I initially entertained boron neutron capture therapy, gene therapy, and radiation-loaded monoclonal antibodies as much more promising than conventional treatment, I finally rejected all of these based on likely problems of various sorts. I therefore opted for conventional chemotherapy but in combination with other agents that seemed likely to improve the effectiveness of chemotherapy over that which typically occurs.

All of my MRI scans since chemotherapy have been free of any sign of tumor. Throughout my first year of treatment, I added various nutritional supplements that can be obtained at most health food stores. The inspiration for the various treatments and health food commodities I opted for has come from many different sources. Much of it came from my own research on Medline, sometimes after hearing about a treatment in passing from participants in an online support group. I also found the webpage of the Musella Foundation as a source of leads to follow up on.

My treatment philosophy has been very similar to the treatment approach that has developed for AIDS. Both HIV and cancer involve biological entities that mutate at high rates, so unless a treatment is almost instantaneously effective, the dynamics of evolution will create new forms that are resistant to whatever the treatment may be. However, if several different treatments are used simultaneously (instead of sequentially, which is typically the case), any given mutation has a much smaller chance of being successful.

A second feature of my treatment philosophy is that any successful treatment will need to be systemic in nature since it is impossible to identify all of the extensions of the tumor into normal tissue.

Ben Williams, a 31-year survivor of glioblastoma, is the author of the 2002 book Surviving Terminal Cancer: Clinical Trials, Drug Cocktails, and Other Treatments Your Oncologist Won't Tell You About. At the virtualtrials.org website, he has posted various updates of this book as well as a 2017 update of the long report entitled "Treatment options for malignant gliomas." To access these important sources, go to:

https://virtualtrials.org/williams.cfm

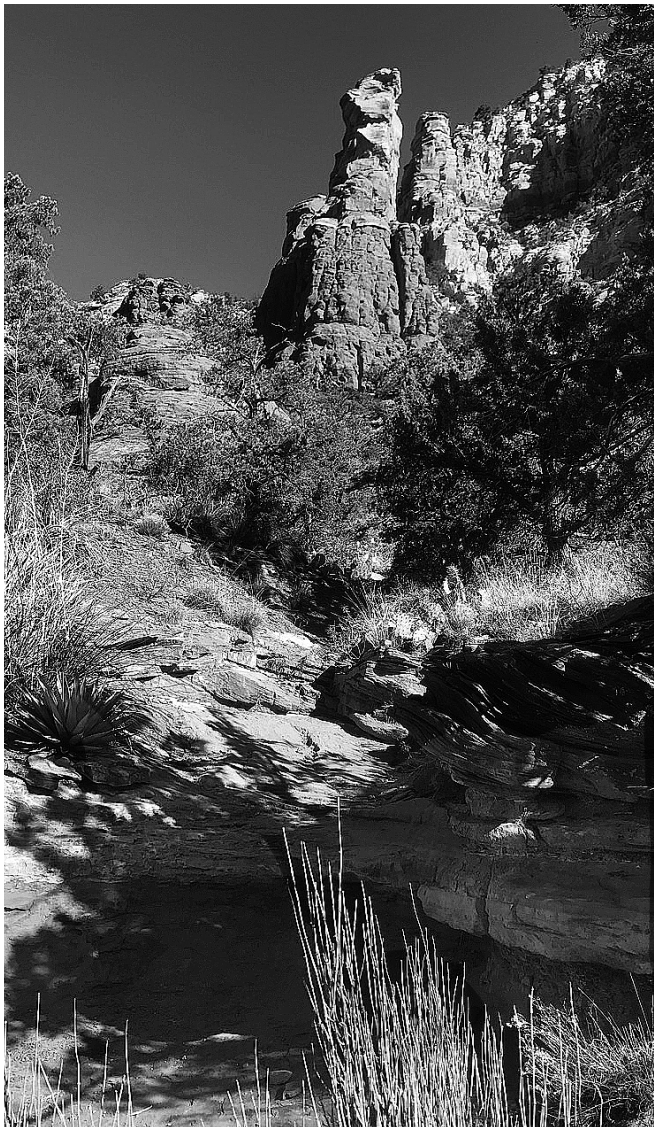
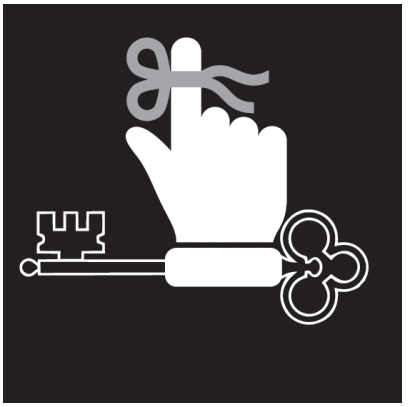


Photo Credit Margo Singer

KEY TAKEAWAYS TO REMEMBER



Find an expert neurosurgeon specializing in brain tumors – someone who performs a minimum of 25 surgeries per year. Typically, expert neurosurgeons are associated with major brain tumor centers..

If you are told that your brain tumor cannot be maximally resected or is inoperable, seek a second opinion.

Before surgery takes place, ask about molecular-marker testing, enrollment in clinical trials, custom-made vaccines, and implantation of Gliadel Wafers.

Note that if you are interested in treatment with a personalized vaccine, you must make arrangements **before surgery** to have the vaccine made or to have frozen tissue stored so that you can have the vaccine made later.



Seven

Radiation

Overview

Many decades ago, upon the diagnosis of a GBM, neurosurgeons would try a few times to remove the entire half of the brain in which the GBM was located. It was determined that even with such a radical surgical approach, the disease would return, infect the remaining half brain and lead to the patient's demise. Doctors realized that removal of the visible part of the disease was not enough. It was essential to treat also the non-visible, microscopic cancer cells that continued to be present. Radiation therapy was then employed.

At the right dosage, radiation will kill brain cancer cells almost as effectively as surgery but will kill the invisible cells. The radiation does so by damaging the DNA within 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. In the case of high-grade tumors, patients will receive radiation, unless some health problem precludes them from getting radiation (e.g., extreme old age.)

Radiation treatment must be tailored for each person based on the type, status (e.g., resected or not) and location of the tumor or tumor cavity.

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 tumor and a small margin around the tumor are usually targeted by a powerful beam of radiation.

Because tumor cells reproduce more rapidly than normal brain cells, they are more affected by radiation than normal cells. The radiation disrupts the DNA of the cells that are reproducing. Compared to tumor cells, normal cells are also better able to repair damage caused by radiation.

Radiation Approaches

There are three main approaches used in radiation treatment:

Radiosurgery. As the name implies, this is the use of selected radiation technologies to perform surgery-like treatment on a lesion or tumor. It is nonsurgical in the sense that no incision is made, but the tumor is so damaged that the treatment goal is removal. Radiation is often delivered at a single high dose in a one-day session, but can be delivered in several session (e.g., 3 to 5) of smaller dosages, called fractionated stereotactic radiotherapy, for larger tumors. Radiosurgery is appropriate for only tumors such as those one and one-half inches in diameter or smaller.

Whole-Brain Radiation Therapy (WBRT) administers radiation to the entire brain. This approach is used when there is widespread cancer in the brain (e.g., numerous tumors or metastatic lesions) or when a cancer in another part of the body is metastasizing to the brain. Recent studies have demonstrated that WBRT may have more disadvantages owing to its tendency to produce cognitive neurotoxicity, which is an overall decline in brain function, and WBRT may not necessarily offer corresponding improvements in the control of the cancer when compared to the next approach, which focuses radiation on the tumor. However, studies have also found that in the case of brain metastasis, if a person has just one metastatic lesion which is removed surgically, and then is treated with WBRT, they are likely to have increased survival. In addition, safer ways to administer WBRT have been developed. By blocking out the memory structures from the radiation fields (sometimes referred to as Hippocampal Avoidance) and the use of certain medications during therapy, a person's memory can be protected.

Localized Radiation Therapy is the other approach. In the late 1990s through early

2000s, the use of localized radiation became more prevalent than WBRT. In this approach, the objective is to deliver radiation only to 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 disease while at the same time preserving to the maximum extent possible quality of life by decreasing treatment toxicity.



Photo Credit Dave Royko

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. (This is one of the many questions suggested below under the section "Pre-Radiation Questions to Ask.")

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

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 the definition of surgery extends to the concept of focused energy precisely applied to an anatomic target. SRS was first developed by a Swedish neurosurgeon, Lars Leksell, who developed the GammaKnife system over fifty years ago.

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 effectively controlling or eliminating tumors like pilocytic astrocytomas, benign tumors (meningiomas, acoustic neuromas, hemangioblastomas); the effect, however, is gradual and shrinkage can occur over months to years, so if there is mass effect, or compression of CSF flow (obstructive hydrocephalus), then surgery is favored. 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.

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.

Gamma Knife

Gamma Knife: 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

The Novalis TX is an image-guided radiosurgery and radiotherapy system developed by a partnership between Varian Medical Systems (for the linear accelerator hardware) and BrainLab (for treatment planning software and image guidance). 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.

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 Therapy

Proton 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. Photon therapy 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 therapy 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 therapy. Some insurance companies have approve use of proton therapy.

Proton 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 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 proton 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.

Proton therapy is also effective at preserving white matter fiber tracts in the brain compared to traditional (photon) therapy because its precision minimizes radiation to surrounding healthy tissue, leading to superior long-term cognitive outcome with less white matter injury, especially in children.



Photo Credit Linda Singer

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, sometimes 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."

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.

Brachytherapy may be permanent or temporary. In permanent brachytherapy, the radioactive seeds are left in place permanently. Some radiation oncologists may advise patients to avoid close contact with young children or pregnant women for the initial several weeks, but after that time the radioactivity diminishes to such a low level that it would not be harmful.

In temporary brachytherapy, the radioactive materials are inserted for a specified period of time and then removed before you would go home. Temporary brachytherapy may be administered at a lower dose over a longer period of time or a higher dose over a shorter period of time.

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.



Photo Credit Steve Tilkin

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.



Photo Credit Steve Tilkin

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 associated 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 undo 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

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.

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 7 to 9 hours for adults 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.

Lifetime Brain Radiation Tolerance

Radiation therapy is an important and often life-saving treatment for brain tumors. Because the brain is a delicate and complex organ, doctors carefully consider not only how much radiation is needed to treat the tumor, but also how much the brain can safely tolerate over a person's lifetime.

What "lifetime tolerance" means

Lifetime brain radiation tolerance refers to the maximum amount of radiation that brain tissue can safely receive over time without an unacceptably high risk of permanent injury. Unlike some other tissues in the body, the brain has a limited ability to repair radiation damage. For this reason, radiation effects can accumulate and is planned by radiation therapists with the future in mind.

There is no single number that applies perfectly to every situation, but decades of experience have helped doctors understand safe boundaries.

The practical lifetime limit for the brain

For large portions of the adult brain, a total dose of about 60 Gray (Gy), given in small daily treatments over several weeks, is generally considered near the brain's lifetime tolerance. This is why standard radiation courses for aggressive brain tumors usually stop around the 60 Gy level. Although this amount of radiation is delivered over a relatively short period of time, it counts toward the brain's lifetime exposure. Higher doses have not been shown to clearly improve outcomes and the risk of long-term side effects rises significantly beyond this point.

Some elderly and all pediatric patients have a lower tolerance, so dosages are reduced. In the case of pediatric patients, long term neurodevelopment is a leading concern.

Why there is no "annual limit"

In cancer treatment, radiation is not given in a small amount each year. Instead, the full treatment dose is typically delivered over weeks. It is important to know that the brain does not "reset" its tolerance over time, so prior radiation exposure is always considered in future treatment decisions. This is why radiation plans are designed as if they may be the only opportunity to treat that area of the brain safely.

Whole brain vs. focused radiation

Lifetime tolerance also depends on how much of the brain is treated. Treating the entire brain with whole brain radiation (e.g., for brain metastases) reaches tolerance more quickly. Treating smaller, targeted areas allows more protection of healthy tissue. Modern radiation technology aims to limit exposure to critical regions involved in memory, vision, balance, and thinking. Radiation plans are constrained by organs at risk (OARs) as shown below:

Structure	Typical Max Dose
Optic nerves/chiasm	≤ 54 Gy
Brainstem	≤ 54-60 GY
Hippocampus (memory)	Kept as low as possible
Cochlea (hearing)	≤ 45 Gy
Pituitary/hypothalamus	≤ 45-50 Gy

What happens if tolerance is exceeded

Exceeding the brain's tolerance increases the risk of long-term complications, which may develop months or years after treatment. These can include changes in memory or thinking, localized brain injury, or persistent swelling. For this reason, radiation oncologists carefully balance tumor control with long-term brain health.

Can radiation ever be given again?

In some cases, additional radiation may be considered later, but this is done cautiously and only for small areas using very precise techniques. There is no second "allowance"—each situation is evaluated individually, weighing potential benefit against risk.

Why this matters for patients' survivorship

Understanding lifetime brain radiation tolerance helps explain why radiation doses are carefully limited and some treatments are not repeated. Protecting quality of life is a central goal of care. Radiation therapy is planned not only to treat cancer today, but to protect the brain you will rely on for the rest of your life.

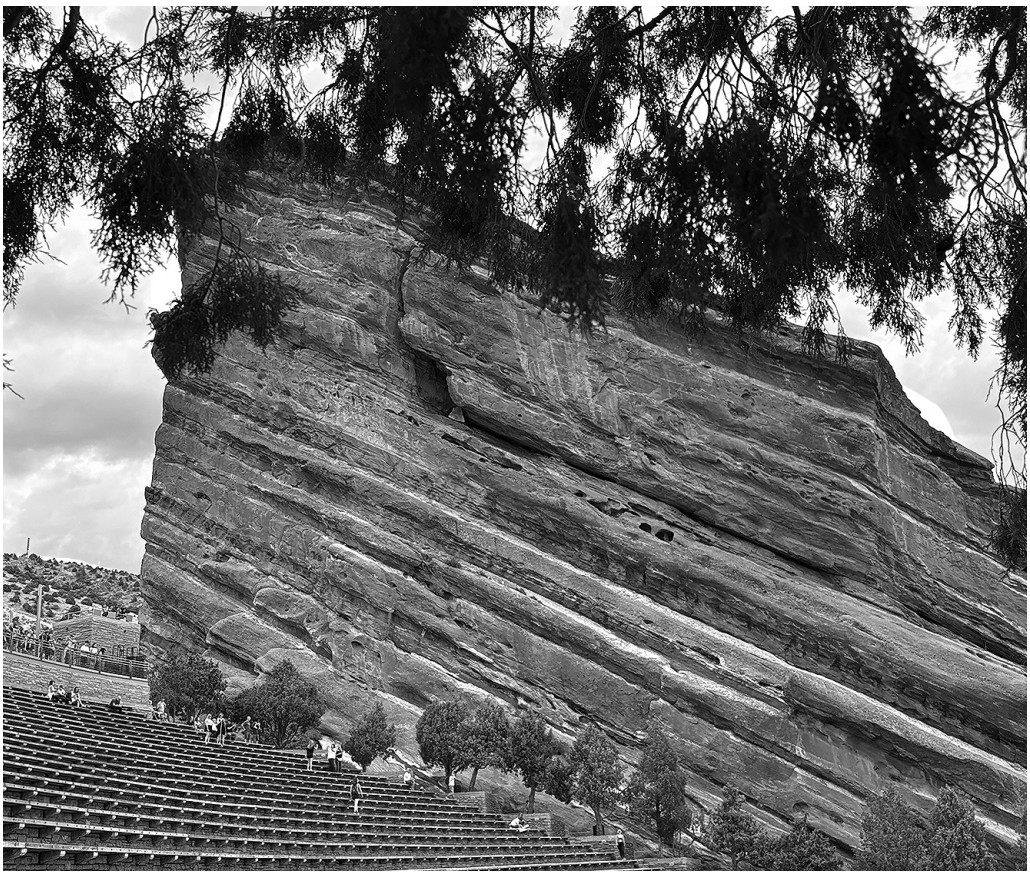


Photo Credit Linda Singer

SURVIVOR STORY #6

On September 19, 2012, I had a grand mal seizure. It was during my lunch break at work, and I was talking with a coworker when I started feeling strange. It felt as if my eyes were crossing each other. It seemed like just a minute, but the next thing I knew was that I was lying on the floor, with an emergency technician asking me whether I could see him. My co-worker was also looking down at me, and he seemed scared. I was 35 years old, the mother of two young girls, and in good health. I rarely even had headaches, let alone a seizure.

I spent several days at the local hospital. More seizures followed. A biopsy revealed that I had a grade IV glioblastoma in my left parietal lobe. Family and friends researched our options, and we selected a comprehensive cancer center as the best place for my treatment. My doctor there told me that with a tumor the size of the one I had, I should have undergone immediate surgical resection rather than first having a biopsy.

At the comprehensive cancer center, I did undergo surgery to remove as much of the tumor as possible. During surgery, the neurosurgeon placed Gliadel Wafers in the tumor cavity. After surgery, I completed 4-weeks of radiation treatment with concomitant temozolomide (Temodar). After radiation, I continued with adjuvant temozolomide at home and had an MRI scan every 2 months.

Seven months after my first diagnosis, I had recovered well enough to run a 5K race with my family. But the adjuvant therapy with temozolomide left me feeling weak, and the MRI scans indicated that my tumor had recurred at the original site. When I was initially diagnosed, the molecular profile of my tumor indicated that it might not be as responsive as possible to alkylating agents like temozolomide because my MGMT status was unmethylated.

By fall 2013, my family and I began an intensive search for a clinical trial for me. We felt that the type of clinical trial that would offer the most hope would be one that enhanced my own immune system to combat cancer cells. We searched websites, especially the listing of clinical trials on the clinicaltrials.gov website of the US National Library of Medicine, and eventually narrowed down a list of potential clinical trials.

To find a clinical trial, I needed to consider my eligibility as well as the nature of the study itself. I applied to several clinical trials and came close to entering two of them

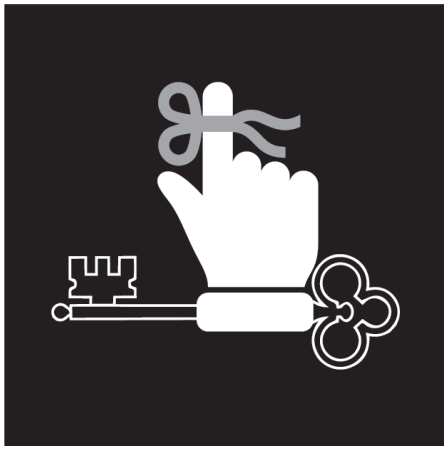
before I was accepted for a clinical trial at a comprehensive cancer center in Los Angeles that seemed the best fit for me. My husband and I flew out there, and I underwent surgery again to remove the recurrent tumor and to have a port inserted. After cells were collected from my tumor, killer T immune cells taken from my body as well as from donors were "trained" to attack the tumor. The concept was that these modified T immune cells could be inserted every two months through the implanted port to help my body fight any residual cancer cells.

After the second resection, I returned home to await my flight back to Los Angeles for the first treatment session. I had lost vision in my right eye as a result of the second surgery, and I also had a low-grade fever, but nonetheless I was ready to proceed. I flew to California and received the first injection through the port. Unfortunately, my fever became worse, and it was discovered that meningitis had developed because my body was rejecting the implanted port. I thus had another surgery to remove the port, and the decision was made to place the modified T immune cells directly on the site of the tumor.

It took a stay in intensive care, time, and antibiotics. Luckily, after several weeks I recovered from the meningitis. I was disappointed to learn that I could not continue in the clinical trial. But my MRI scans showed no sign of tumor. The decision was made for me to go home to wait and see. I have been waiting and seeing for four and a half years. So far, my MRI scans show no sign of recurrent tumor.

The cancer and the surgeries have taken a toll. Although I am on antiepileptic drugs, I still have seizures. I have no vision in my right eye, and I have not been able to return to my former career as a mechanical engineer. But I am lucky. I am a stay-at home mom to two wonderful girls. I can sew and work in my garden. I spend time with my friends and family and enjoy my life. I hope that sometime soon we will all have treatments that are more effective than chemotherapy.

KEY TAKEAWAYS TO REMEMBER



If at all possible, have your radiation administered at a top brain cancer clinic because they are most likely to have the latest, most advanced radiation equipment which can best treat your tumor and preserve the healthy parts of your brain.

Find out exactly what type of radiation technology will be used.

Talk to your radiation oncologist about what side effects that you may expect.

If you have not been prescribed the chemo Temozolomide (Temodar) to take concurrently with your radiance, ask why. This chemo has been shown to sensitize cancer cells to the radiation leading to a better outcome.





Eight

Chemotherapy

Overview

Chemotherapy (often referred to as "chemo") is the use of a drug or combination of drugs to kill tumor cells. In the case of malignant high-grade tumors, the chemo lessens the chances the tumor will return or grow. In other cases, chemo may stop the growth of the tumor entirely.

Chemo is considered a "systemic" therapy because the drugs will go throughout the body, which is a benefit if any cancer cells have moved away from the original tumor (a process called metastasis).

Not all chemo drugs work the same way. Depending on the particular type of chemo, the drug may damage the cancer by (1) destroying the tumor's DNA directly; (2) restricting the tumor cell's ability to divide, grow, and invade healthy tissue; or (3) blocking the blood supply to the tumor itself and inhibiting the growth of new blood vessels that would otherwise feed the tumor.

When a brain tumor requires treatment with chemo, doctors will be reluctant to use the word "cure", although their objective has a curative intent. The realistic goal of chemo treatment with brain cancer is to control and manage the disease by discouraging further growth and spread.

Chemo for brain cancer is given in different ways. Many chemos are administered at home orally in pill or capsule form. Other chemos are delivered in an infusion room at the clinic or hospital intravenously through a thin needle placed directly into a vein. In very rare cases, the chemo may be delivered intra-arterially, that

is, injected directly into an artery that travels to the tumor. How you receive your chemo depends on what specific chemo you have been prescribed.

Is My Chemo Working?

The only way you and the doctor will be able to determine if the chemo you are taking is working is by observing the reaction of the disease. If your regular MRIs are returning absent evidence of disease, or showing signs of stability/no growth, then it is understood your chemo is working.

The side effects you may experience to the chemo are not indicative of its effect on the cancer. Some people have no/few side effects, but the chemo is slamming the cancer. The effects of the treatments on you are independent from the effects of the treatments on the disease.

The most common prescribed chemotherapies for brain tumors follow.

Temozolomide (Temodar or Temodal)

Overview of Temozolomide

Temozolomide (typically referred to as "Temodar" or "Temodal") is the standard, most prescribed first chemo for brain cancer. It is a derivative of a class of drugs called imidazotetrazines. Temodar entered critical trials in 1985 and was released to the market by Schering-Plough in 1999. Since then, it has been widely used in combination with radiation as the standard first-line treatment for brain cancer.

Temodar has excellent characteristics. It has 100% oral bioavailability which means that it can be administered in pill form. Also, Temodar usually produces only moderate side effects relative to other chemos.

Absorption is rapid; the peak concentration in the blood happens between 30 minutes and 2 hours after the Temodar is taken, and then its by-products are quickly excreted in the urine. When Temodar is at its peak and as it circulates through the body, it immediately kills any rapidly dividing cells, most notably cancerous

cells. However, Temodar will kill other rapidly dividing cells like hair follicles, cells in the gut, and blood cells. This is why hair loss should be expected with Temodar treatment and also why blood tests are needed during Temodar treatment.

Temodar is an alkylating agent. It kills the cancer cells by disrupting the DNA replication happening in the cancer cell, thus causing programmed cell death (apoptosis).

For a tumor to be most responsive to Temodar treatment, the tumor should be deficient in MGMT (O6-methylguanine-DNA methyltransferase) but proficient in MMR (DNA mismatch repair proteins). For alkylating agents like Temodar and like Carmustine (the chemotherapeutic agent used in the Gliadel wafer), methylation of the promoter of MGMT is a major favorable prognostic factor, and it is found in approximately 35% to 45% of patients with Grade 3 and 4 gliomas. That is, if you have an MGMT-methylated tumor, Temodar (or Carmustine) is more likely to provide a greater magnitude of progression-free and overall survival than if you have an MGMT unmethylated tumor. Consequently, if you are among the majority of patients with an MGMT-unmethylated tumor, you should seriously consider enrollment in a clinical trial because it is likely that you will derive less benefit from standard of- care treatment.

Temodar rapidly crosses the blood-brain barrier (BBB) and has been shown to induce tumor regression in patients with high-grade astrocytomas and GBM.

Dosage and Frequency

The dose for Temodar is dependent on the phase. There are two phases for Temodar administration during SOC: an initial phase and a maintenance phase.

In the initial phase, a low dose of Temodar is usually prescribed to be taken daily concurrently with radiation, which generally consists of 42 sessions and runs about 6 weeks. Treatment with the combination of radiation plus Temodar has been found to improve survival in all patient groups, even elderly patients, because it has been found to be a sensitizer that makes the radiation more effective. As an adjuvant to radiation, Temodar is administered daily (even on weekends when radiation might not be administered).

Unless otherwise directed by the neuro-oncologist, the maintenance phase of

Temodar begins after a 4-week break commencing at the end of radiation. In the maintenance phase, a higher dose of Temodar is prescribed and is taken for 5 consecutive days out of every 28 days.

The exact quantity of Temodar to be taken during each phase is calculated based on Body Surface Area, taking into consideration your bone marrow toxicity (as determined by blood tests) and your tolerance (e.g., absence of abnormal or intolerable side effects).

Body Surface Area (BSA) is determined by weight and surface area in square meters. The BSA for the average adult male is 1.9 and for the average female is 1.6.

For the initial phase, the daily dose of Temodar in milligrams is calculated using this formula:

- 75 mg/m2/day (where m2 is your BSA).

- For instance, for a person with a BSA of 1.84, the dosage would be calculated as follows: 1.84m2 x 75 mg/m2 = 138mg. This would be rounded up to 140 mg/day.

For the maintenance phase, Temodar dosage is higher, but the chemo is not taken daily as it was during radiation. It is taken for 5 consecutive days every 28 days, which is called a cycle. The dosage for the first maintenance cycle will be lower than the other maintenance cycles to enable the doctor to judge your tolerance level for Temodar. The formula for the maintenance phases of Temodar are as follows:

- First maintenance cycle: 150 mg/m2/day (where m2 is your BSA.)

- Subsequent cycles: Assuming you show acceptable levels of tolerance, the Temodar is increased to 200 mg/m2/day for each of the remaining cycles (where m2 is your BSA. This is considered the maximum amount.

For a reality check on your Temodar dosage, please see the dosage calculator on the Musella Foundation website at this link:

https://virtualtrials.org/temodar/dose.cfm

Length Of Maintenance Phase

Your doctor will decide how many cycles of Temodar you will receive in the maintenance phase, depending on how you respond to and tolerate treatment. The standard number of cycles is six (6) but may be increased to twelve (12) cycles.

Evidence from studies suggests that there may be an improvement in progression-free survival for those who take more than 6 cycles, but there could also be a higher risk of significant hematological toxicity with no increase in overall survival. For that reason, the doctor has to carefully assess your tolerance to the chemo and the tumor's responsiveness and decide if you should continue Temodar for some other period such as 12 or 18 months. In other cases, the doctor may prescribe Temodar until it stops working or causes side effects or until the tumor is either completely gone or sufficiently stable.

Side Effects and Toxicity

Temodar is considered somewhat less toxic and better tolerated than many other chemos but does have the common side effects of weakness and fatigue, nausea and vomiting, constipation, gastrointestinal upset, alopecia, and low blood cell counts caused by bone marrow suppression.

Temodar may increase the risk of infection by lowering the number of white blood cells you have in your blood. Symptoms mimic those of a cold or flu: a change in your temperature, general muscles aches, headaches, feeling cold, shivering. Your doctor may prescribe a mild, generic anti-microbial like Bactrim to help guard against infection.

Contact your doctor or physician's assistant/nurse immediately if you develop signs of an infection which includes a temperature of 100.4 ° Fahrenheit or 37.5° Celsius, or an alternate temperature advised by your doctor.

Temodar may cause your gums or nose to bleed. This is caused by a drop in the number of platelets in your blood. Platelets help form clots when we cut ourselves. You may notice bloody gums when you brush your teeth, or you may see small bruises or spots on your arms and legs.

Because a simple cavity or early gum infection (gingivitis) can quickly escalate into an acute infection, you should obtain a thorough dental examination prior to beginning Temodar treatment and follow up regularly with your dental care team.

You may also lose your appetite when on Temodar. The fatigue or feeling sick can decrease one's appetite.

You may also have headaches. You should tell your doctor's office if you keep getting headaches so that the doctor can recommend treatment.

Less common but potentially severe adverse events included severe myelosuppression, myelodysplastic syndromes, pneumocystis pneumonia, hepatotoxicity, and embryo-fetal toxicity.

How To Take Temodar (Sample Protocols for Information Only)

Your doctor is going to give you specific instructions for how and when to take the Temodar you are prescribed, and those instructions must be carefully followed. To give you an idea of what you might expect, sample protocols are provided below solely for informational purposes,

Low Dose

During radiation, Temodar is taken daily throughout the period of radiation treatment. A low dose of Temodar is usually taken every morning in order to sensitize the tumor to the radiation.

High Dose

General Notes

- Temodar should be taken on an empty stomach in the evening. This means you shouldn't eat anything for two hours before and an hour after you take it. You can drink water during this time but should not have any solid food.

- It is important not to open or split the capsules. Temodar should be

swallowed whole with water. Never chew the capsules.

- If you miss a dose, contact your doctor or nurse. Do not make up the missed dose by taking a double dose.

A sample, time-ordered schedule based on going to sleep at 9 PM follows. This schedule would need to be adjusted based on your specific time to go to sleep.

- 6PM: Only if your doctor so instructs you, you would first take your Nexium/Pepcid or whatever the doctor recommends to coat the stomach. Some leading doctors do not consider this step necessary for those without stomach problems.

- 6:30PM: dinner. Must be only light and white, easy to digest foods. No heavy dinners. No red meats (e.g., no burgers, no steak), no red sauces.

- 7PM (or 30 mins after finishing dinner): take one (1) Zofran pill. Zofran is the anti-nausea pill prescribed by the doctor.

- 7:30PM (or 30 mins after Zofran): Only if your doctor so instructs you, take the sleep aide your doctor may have suggested to help you sleep through any breakthrough nausea. This pill may be a mild herbal sleep aide. Many people do not need this pill. If you can handle the high dose Temodar without this sleep aide, it is good to avoid it, but if nausea wakes you up, this is the solution.

- 8PM (or 30 mins after taking your sleep aide): take your prescribed daily dosage of Temodar with a full (8 ounce) glass of water. (No other liquid; just water.)

- Only if your doctor so instructs you, sit upright for one (1) hour after taking Temodar. Your doctor may consider this step important if the doctor thinks that by laying down right away after taking the Temodar, you might cause the Temodar to splash back and damage your upper gastro-intestinal system. People who suffer from gastroesophageal reflux disease (GERD) may need to do this step.

- 9pm (or after one hour of sitting upright). Go to bed for sleep.

- Next morning: Because Zofran constipates with a vengeance, drink a glass of MiraLAX or some other anti-constipation aide, as recommended by the doctor. Many also use a stool softener like docusate or Senna. (For Senna a typical schedule for taking it is at 8am and 8pm.

As mentioned, the doctor will go through the process he or she wants you to follow in detail. Since the above schedule has a few practical concepts woven into it based on practical experience, it might be helpful to copy this, take it to the doctor's office when you have your discussion, and then find out from the doctor what changes the doctor wants. The doctor's word, of course, is the final authority on how you should take the Temodar.

FDA Data Sheet

The official FDA approved Data Sheet on Temodar is available online at this link:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021029s031lbl.pdf

Lomustine/CCNU/Gleostine

Lomustine, also referred to as CCNU or Gleostine, is another chemo that, like Temodar, is an alkylating agent (i.e., it interferes with the DNA of cancer cells, thereby inhibiting their growth). Whereas Temodar acts by alkylation of guanine, Lomustine also introduces interstrand crosslinks and leads to carbamoylation of amino acids, which interferes with certain processes necessary for the replication of cancer cells.

Lomustine is probably the most prescribed chemo for brain cancer second only to Temodar, and it is usually prescribed in the following situations:

- For those diagnosed with a newly diagnosed high-grade tumor, some doctors, notably those in the UK or Europe, may prescribe a combination of Lomustine with Temodar. In small studies, the overall survival has been superior in those receiving the combination therapy, however, toxicity is

higher compared to those taking Temodar as a monotherapy, so further study comparing these treatments is needed.

- For those diagnosed with a recurrent high-grade tumor and previously treated with Temodar, many doctors will prescribe Lomustine, absent other treatments (e.g., clinical trial).

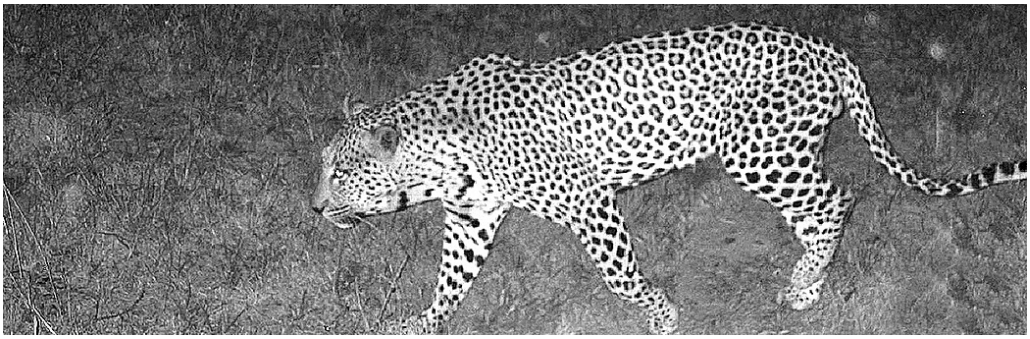
- For those newly diagnosed with Oligodendroglioma, doctors may prescribe a combination of Procarbazine hydrochloride, Lomustine (CCNU), and Vincristine sulfate, a combination known as PCV. PCV may also be prescribed for those with a recurrent high-grade glioma which is not an Oligodendroglioma. Lomustine is considered the most active ingredient of the three (3) chemos.

Lomustine is a moderately emetogenic chemo, that is, it can cause vomiting that requires a standard anti-emetic medication, which is usually sufficient. The most relevant adverse effect is thrombocytopenia (lower than normal number of platelets, which may result in easy bruising and bleeding). Neutropenia, which is a lower-than-normal number of a certain type of white blood cell, can be seen, often in a delayed time frame, that can make a patient at a higher risk for infection.

Certain studies have shown that the combination of Lomustine and Avastin may effectively increase overall survival (OS), progression-free (PFS), and 6-month PFS in patients with GBM.

The official FDA approved Data Sheet on Lomustine/CCNU/Gleostine is available online at this link:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/017588s042lbl.pdf

Photo Credit Linda Singer



Carmustine/BCNU

Carmustine is another common alkylating-type chemo for high-grade brain cancers. Its brand name is BCNU.

It has been given to brain cancer patients by IV, but that approach produces what some doctors consider an unacceptable level of toxicity. For that treason, Carmustine is most often used by wafer implantation in the resection cavity in conjunction with surgery, whether at the time of initial diagnosis or recurrence.

Biodegradable wafers impregnated with Carmustine (referred to as Gliadel® wafers) is thought to provide a therapeutic bridge during the healing period between surgical resection and the onset of radiation.

For more information, please refer to the discussion of Gliadel Wafers in the section above entitled "Surgery".





Nine

Immunotherapy

Overview

In the past few decades, there has been rapid development in tumor immunotherapy, which is recognized as a key strategy to treating malignant tumors. Normally, the immune system recognizes and eliminates foreign or abnormal cells, like bacteria, viruses, and even cancer cells before they can harm us. However, once a brain tumor reaches a certain point in its development, chemical signals from the tumor prohibit the immune system from recognizing tumor cells. Some tumor cells are able to escape detection by the immune system and continue growing and invading. (For more information about tumor cells' ability to escape the immune system, please see Appendix C entitled "Causes of Brain Tumors" at the back of this Guidebook.)

Knowing this, researchers and doctors have led efforts in the specialty of immunotherapy to stimulate and activate the patient's immune system in a manner to "wake up" the immune system to kill tumor cells. Other cancers have used immunotherapies with success, which encouraged work to direct this line of therapies toward brain cancers.

However, treating the brain with immunotherapy presents problems not found with other organs. The brain is protected by a blood-brain barrier (BBB) which can prevent certain drugs from entering the brain and it has a unique immune environment. There is a strong presence of cells in the tumor environment that are immunosuppressive (resistant to the beneficial actions of the immune system), plus there are few T cells (critical immune cells that react against foreign antigens. In addition, gliomas are composed of glioma cells with a high degree of microheterogeneity (i.e., differences in structure) even within the same tumor, making some cells responsive to a certain treatment and others less so.

Glioblastoma is a highly heterogeneous cancer, characterized by significant variations in its cellular composition, biological behavior, and the surrounding tumor microenvironment. These differences manifest not only between individual tumors but also within the tissues surrounding the brain, leading to unique challenges in treatment and management. Recognizing the complexity and variability of glioblastoma, specialized centers of excellence are pioneering advanced immunotherapeutic strategies. These efforts are driven by multidisciplinary teams composed of neurosurgeons, oncologists, neurologists, and immunologists.

Through close collaboration, these experts design and implement innovative treatment protocols and combinations, tailored to address the individual characteristics of each patient's tumor and immune response. The development of personalized immunotherapy protocols is informed by the understanding that each patient's immune system and tumor environment are distinct. By adapting approaches to these variations, medical professionals aim to better decode tumor behavior and improve patient outcomes.

A key objective of these immunotherapeutic strategies is to shift a glioblastoma tumor from being an immunologically "cold" tumor, which is unresponsive to immune interventions, to an immunologically "hot" tumor, which is receptive and responsive to such treatments. This transformation holds the promise of enhancing the effectiveness of immunotherapy in combating the disease.

Some approaches they are now using to overcome these various problems are improved grooming of the native immune system cells (i.e., natural killer cells, macrophages) and the adaptive immune system (i.e., cytotoxic T lymphocytes, B lymphocytes) to basically wake them up to do their jobs and "marking" of epitopes (that part of an antigen that the immune system is able to detect) so that the immune system recognize the cell with that antigen as being foreign. To accomplish these tasks, researchers are pursuing novel approaches, including combination therapies which are likely to show improved results against brain cancer.

Dexamethasone and Immunotherapy

Dexamethasone is commonly prescribed for individuals with brain tumors due to its ability to reduce brain swelling and inflammation. These effects are particularly beneficial in managing symptoms caused by tumors themselves, as well as reactions

following surgery and radiation therapy. However, dexamethasone is often described as "a double-edged sword," since its prolonged administration or use at high doses can lead to significant unwanted side effects.

The metabolic side effects of dexamethasone include elevated blood sugar levels, which can negatively impact patient health. Additionally, dexamethasone can suppress the immune system, posing challenges for individuals undergoing tumor immunotherapies. The mechanisms underlying this immunosuppressive effect involve a reduction in lymphocyte counts, including key immune cells such as T cells, CD3, CD4, CD8, and NK cells. Dexamethasone also decreases levels of anti-tumor cytokines, such as interferon-gamma (IFN-γ).

Due to its immunosuppressive properties, dexamethasone can interfere with a range of immunotherapy treatments. These include dendritic cell vaccines, CAR T cell therapy, DNA vaccines, mRNA vaccines, peptide vaccines, viral oncolytics, gene therapies such as CAN-2409, and immune checkpoint inhibitors. In addition, dexamethasone-induced hyperglycemia can further suppress tumor immunity through multiple mechanisms, including T cell impairment and exhaustion, macrophage reprogramming, reduced immune cell infiltration, resistance to immunotherapy, and alteration of metabolic signaling pathways. For all these reasons, a discussion with your treating physician should include the optimal dosage and duration of steroids.

Many of the types of immunotherapies being developed against GBMs are described below.

Image by Ryan McGuire, Pixabay



Personalized Vaccines

Selected Definitions

Antigen: An antigen is any substance (like a virus, bacteria, toxin, pollen, or your blood type markers [ABO/Rh]) that your immune system recognizes as foreign or potentially harmful, triggering a defense response, mainly the creation of specific antibodies, but also the recruitment of specific lymphocytes, with the aim of neutralizing or eliminating the threat, keeping you in good health. The origin can be external (pathogens, allergens) or within the human body (cancer cells) and the composition of the antigen can be a protein (such as the spike protein on a virus) but also sugars (polysaccharides, lipids, or nucleic acids). An antigen can be compared to a unique "ID tag" perceived by the immune system as an invader to your body's defenses, differing from the normal antigens that reside within your body, so the immune system recognizes what is "self" and what is "foreign" to the body, in order to maintain good health.

Autologous: cells obtained from the patient themselves.

Dendritic cell: A special type of immune cell that is found in body tissues and that enhances an immune response by showing antigens on its surface to other cells of the immune system. A dendritic cell is a type of phagocyte and a type of antigen-presenting cell (APC).

Neoantigen. A neoantigen is a novel, tumor-specific antigen that may arise from a mutation, genetic alteration, or viral infection within malignant cells. Unlike the normal "self" proteins, these altered proteins are recognized as "foreign". Therefore, these antigens will bypass normal immune tolerance and trigger strong, specific T-cell responses against tumor cells. Because neoantigens are expressed only on tumor cells, they are ideal targets for personalized immunotherapy. Neoantigens are used to develop cancer therapies and immune checkpoint inhibitors.

Primary endpoint: means the result of a trial measured at the end to see if the treatment being tested worked, i.e.., that there was a positive and clinically significant difference in survival between the group of patients getting the treatment and a control group of patients who did not.

Overview

Emerging as a potential addition to the Standard of Care in the treatment of GBM is a form of immunotherapy that involves personalized vaccines that use the patient's own dendritic cells. The antigens these dendritic cells collect are designed to stimulate an immune response, thereby activating the powerful killer T immune cells to destroy the tumor. Results from vaccine trials suggest that patients with GBM receiving such a personalized vaccine may survive significantly longer that patients receiving the current Standard of Care treatment.

Please note: If you are interested in treatment with a personalized vaccine, you must make arrangements before surgery to have the vaccine made or to have frozen tissue stored so that you can have the vaccine made later.

Dendritic cells were first observed in 1868 by the German pathologist Paul Langerhans, who described branched cells in the skin but mistakenly thought they were nerve cells. Their immunological role remained unclear until 1973, when Ralph Steinman and Zanvil Cohn identified and named "dendritic cells" in the mouse spleen and, through subsequent work, demonstrated their extraordinary ability to activate naïve T cells, laying the foundational groundwork for modern cellular immunology.

Due to the way these cells are shaped, they have a very large surface area which enable them to contact many other immune system cells such as T- cells, natural killer cells, neutrophils, epithelial cells. Recent research highlights the critical function of dendritic cells (DCs) in orchestrating the immune response against solid tumors. For DCs to effectively eliminate such tumors, they must interact with two distinct populations of T cells: CD4+ helper T cells and CD8+ killer (effector or cytotoxic) T cells. This interaction leads to the formation of a three-cell cluster, commonly referred to as a "triad." Within these triads, CD4+ T cells play a vital role in "licensing" other T cells by delivering essential signals through the dendritic cell. This process reprograms the T cells, enhancing their potency and enabling them to overcome T cell exhaustion. As a result, T cells regain their cytotoxic function, allowing them to efficiently target and destroy tumor cells. In the context of brain cancer, the presence of these triads has significant implications for treatment outcomes. Specifically, the formation of triads influences the response to immune checkpoint inhibitors (ICI), indicating that effective T cell engagement by dendritic cells is crucial for successful immunotherapy.

Dendritic cells play a central role in the immune response to tumors as "professional" antigen-presenting cells (APCs). They possess a high capacity to sample their environment and initiate immune responses by activating T cells through three key mechanisms:

DCs express MHC class II molecules (in addition to class I), allowing them to present antigens and neoantigens to CD4+ helper T cells;

They display co-stimulatory molecules such as CD80/CD86 (B7 complex) and CD40, which interact with T cell receptors to facilitate activation; and

DCs secrete cytokines, including interleukin-12 (IL-12), which enhance the strength and effectiveness of the T cell response.

Building on Ralph Steinman's discovery that dendritic cells are key activators of T-cell immunity, subsequent researchers demonstrated that dendritic-cell stimulation could drive the expansion of T cells targeting specific tumor antigens and neoantigens - work that, alongside Carl June's independent development of CAR-T cell engineering, contributed to modern cancer immunotherapy.Other studies have shown that a single dendritic cell can activate anywhere from 10 to as many as 3,000 T cells. This remarkable efficiency underscores why current immunotherapy strategies are focused on harnessing dendritic cells and activating T cells together. By doing so, T cells can be "retrained" to attack tumor neoantigens, including those associated with malignant brain tumors such as glioblastoma.

DC Vax®-L Vaccine (Murcidencel)

It made sense to researchers to capitalize on these sentinels of the immune system and manipulate them into stimulating the immune system against brain tumors. Research on this approach has been well underway for many years, and one of the research products is DCVax-L, an autologous (made from the patient's own cells) dendritic cell vaccine. DCVax is a personalized immunotherapy designed to give the immune system a better chance at recognizing and fighting brain tumors like glioblastoma.

Unlike conventional drugs or chemotherapy, the DCVax-L vaccine is tailored for



Photo Credit Steve Tilkin

each individual patient, utilizing their own cells. The process begins when physicians collect immune cells—specifically dendritic cells—from the patient's blood. These cells are then matured in the laboratory and "pulsed" with lysate derived from the patient's own surgically removed tumor, enabling the immune cells to recognize neoantigens unique to that tumor. In the laboratory, scientists combine these elements by teaching the dendritic cells to identify the distinct proteins present on that specific patient's tumor. Once the dendritic cells have been trained to recognize these tumor-associated proteins, they are transformed into a customized vaccine. The finished vaccine is administered to the patient via intradermal injection, aiming to prompt an immune response targeted specifically at the patient's brain tumor.

Inside the body, the vaccine's purpose is to alert the immune system to the presence of tumor cells that it might otherwise overlook. Glioblastoma is notorious for hiding in healthy brain tissue, making it difficult for immune cells to detect. The dendritic cells in DCVax essentially act as messengers, showing T-cells what the tumor looks like and directing them to attack it. By doing this, DCVax aims not only to target the main tumor but also to seek out the microscopic cancer cells that remain after surgery and standard treatment.

Clinical trials have produced encouraging results. The phase III trial results for DCVax®–L indicated a significant improvement in median survival for both newly diagnosed and recurrent glioblastoma, with an excellent safety profile. Patients with newly diagnosed GBM receiving the vaccine had a median survival of 19.3 months compared to a median survival of 13.2 months based on comparison with contemporaneous, external control populations. For patients with recurrent glioblastoma, the median OS was 13.2 months compared with 7.8 months among control patients. Importantly, in a subpopulation of patients, there was a "tail" of long-term survivors, exceeding 5 years, and in some cases, over 10 years, which is consistent with an immune-mediated effect, as a vaccine will be like a continuous drug due to immunological memory and proliferation of T cells to provide the durable, sustained effect. At the time of this publication, the DCVax-L is undergoing regulatory review in England by the MHRA and has not yet been approved by the FDA in the United States.

Because of the complexity of the glioblastoma (multiforme) and the individual variation amongst patients, a single vaccine, based on dendritic cells or T cells, may be a "platform technology" that can be used in combination with other approaches such as modulation of cytokines, or given with booster of T cells, or mRNA. Since the publication of the landmark JAMA Oncology paper (Liau L, Ashkan K, Brem S et al, 2023), additional studies have shown an increase in survival combining the DCVax-L vaccine with immune checkpoint inhibition or an immune stimulator (poly-ICLC) can "supercharge" the immune system and increase the potency of the vaccine. Also, there is an intense search for a biomarker, such as interferon– gamma (IFN-γ), that can be used to monitor individual patients receiving an immune therapy.

The intricate nature of glioblastoma, coupled with significant variability among patients, presents challenges for treatment. A single vaccine platform, such as one based on dendritic cells or T cells, serves as a foundational technology that can be

integrated with other therapeutic strategies. For example, it may be paired with cytokine modulation or administered alongside boosters like T cells or mRNA approaches to enhance effectiveness.

Since the publication of the landmark JAMA Oncology paper by Liau, Ashkan, Brem, and colleagues in 2023, further research has demonstrated improved survival rates when the DCVax-L vaccine is combined with immune checkpoint inhibitors or immune stimulators like poly-ICLC. These combination therapies act to "super-charge" the immune system, thereby increasing the potency and potential benefits of the vaccine for patients with glioblastoma.

In addition, there is ongoing research dedicated to identifying reliable biomarkers to monitor individual responses to immunotherapy. One such candidate is interferon-gamma (IFN-γ), which may help clinicians track and assess the effectiveness of immune-based treatments in real time.

For the latest information about the DCVax-L vaccine, please go to this link:
https://virtualtrials.org/dcvax.cfm

DC Vaccine -mRNA Combination (Dubodencel, DOC1021)

DOC1021 (Dubodencel)is an investigational, personalized immunotherapy being developed for glioblastoma. It belongs to a newer generation of dendritic cell (DC) vaccines designed to stimulate the patient's own immune system to recognize and attack tumor cells. This approach involves the use of patient-derived, autologous tumor lysate, amplified mRNA, and gamma interferon to enhance the body's immune response against tumor cells. The therapy is created by fusing the patient's dendritic cells (DCs) with proteins and mRNA extracted from their own tumor, aiming to provoke a robust and tumor-specific immune reaction. This dual-loading strategy is intended to expose the immune system to a broad and highly personalized set of tumor antigens, including those unique to that individual's cancer. By doing so, the vaccine aims to overcome one of glioblastoma's key challenges: its genetic diversity and ability to evade immune detection.

Once administered, DOC1021 is designed to activate both helper (CD4+) and killer (CD8+) T cells and promote the formation of immune memory, potentially allowing the immune system to continue surveilling for tumor recurrence over time. The

approach seeks to mimic aspects of a viral infection, which is known to generate strong and durable immune responses, without requiring genetic modification of immune cells or highly toxic preparative treatments.

Promising findings from a multicenter Phase II clinical trial (NCT0685305) were presented at the ASCO 2025 annual meeting. DOC1021 demonstrated a favorable safety profile. Notably, the 12-month overall survival (OS) rate among trial participants was 88%, substantially higher than the historical survival rate of 53-60% observed with SOC treatments. Of the sixteen patients evaluated, fifteen were MGMT unmethylated. Importantly, post-vaccination analysis revealed a significant expansion of both CD4+ and CD8+ memory T-cells, indicating the activation of all three critical components of the "immune triad." This immune triad engagement is recognized as a key prerequisite for successful immunotherapy against solid tumors. Additionally, researchers observed intense expression of CD25+ (IL-2Rα)—a marker of activated T-cells—alongside effector memory T-cell and migratory tumor-infiltrating lymphocyte co-expression, as well as NK cells and microglia, following vaccination. These findings were consistent with an active immune response, which was not present prior to vaccination.

While further study is required to confirm its clinical benefit, it exemplifies the growing effort to bring precision immunotherapy to patients with brain cancer, a field in urgent need of new and effective treatments.

mRNA Vaccine Technology

In the ongoing fight against cancer, one of the most exciting frontiers of research lies in the use of mRNA technology. While mRNA's role in vaccine development became widely known during the COVID-19 pandemic, its application in cancer therapy, particularly for brain cancers like glioblastoma, has opened up new possibilities for treatment. One of the leaders in this field is Dr. Elias Sayour, a pioneering pediatric neurosurgeon and researcher dedicated to using mRNA-based vaccines. Dr. Elias Sayour's research is particularly focused on glioblastoma.

Messenger RNA (mRNA) is a molecule that serves as a blueprint for making proteins in cells. In cancer treatment, scientists have harnessed the power of mRNA to instruct the body's immune system to recognize and attack cancer cells. Instead of directly targeting the tumor with traditional therapies like chemotherapy or radia-

tion, mRNA vaccines work by teaching the immune system to fight the cancer itself.

Dr. Sayour and his team are working on developing personalized mRNA cancer vaccines designed specifically for each patient's unique cancer profile. In cancer vaccines, the mRNA is crafted to encode proteins, or antigens, found on the surface of tumor cells. The body's immune system recognizes these foreign proteins as a threat and mounts an immune response specifically aimed at attacking the cancer cells that produce them, potentially leading to better outcomes with fewer side effects compared to traditional treatments.

What makes these mRNA vaccines different is their ability to target specific tumor markers. By customizing the vaccine to each patient's genetic profile, these treatments aim to create a more personalized and effective immune response. Unlike conventional therapies that indiscriminately affect healthy and cancerous cells alike, mRNA vaccines can be designed to target only the cancer cells, sparing the healthy tissues.

Trials are being held that combine the mRNA with other immunotherapies, such as checkpoint inhibitors, which remove the natural "brakes" on the immune system. This combination aims to boost the vaccine's ability to trigger an immune attack on the tumor. Early results from these trials have been encouraging, with some patients showing promising immune responses, though more research is needed to confirm the long-term effectiveness of these treatments.

IMVAX and the Goldspire™ Platform

Another promising effort in vaccine research is the development of IGV-001, which is a first-in-class autologous tumor cell vaccine developed using IMVAX's proprietary Goldspire™ immuno-oncology platform. This approach seeks to turn the patient's own tumor into the source of a personalized immunotherapy. Unlike many therapies that target a single antigen or mutation, IGV-001 captures the full antigenic signature of a patient's tumor and uses it to stimulate an immune response tailored to that individual's cancer.

The manufacturing process is both unique and intricate: tumor cells harvested during surgical removal are combined with IMV-001, an antisense oligonucleotide targeting IGF-1R a receptor implicated in tumor progression) and placed into spe-

cialized biodiffusion chambers. These chambers are exposed to low-dose irradiation to trigger stress and immunogenic cell death, which helps release an array of tumor antigens. The chambers are then temporarily implanted in the patient's abdomen, allowing antigenic material and immunomodulatory signals to diffuse into the body and educate the immune system to recognize tumor cells as hostile.

Early clinical testing has demonstrated that IGV-001 is well tolerated in patients with newly diagnosed GBM and has shown encouraging signals of immune activation and clinical benefit beyond standard therapy.

The Imvax approach stands out for its personalized nature and its potential to engage the immune system against a tumor's entire antigen landscape—a strategy particularly appealing in cancers like GBM that are highly heterogeneous and notoriously resistant to single-target therapies. If additional testing results confirm the signals seen in earlier studies, this could mark a pivotal moment in brain tumor immunotherapy.

Survivin-Targeting Vaccines

Survivin is a key protein involved in regulating apoptosis (programmed cell death). Under normal conditions, survivin is active primarily during early human development and is nearly absent from healthy adult brain tissue. However, in many brain tumors—especially high-grade gliomas and glioblastoma—survivin becomes reactivated. This reactivation allows cancer cells to evade death, proliferate rapidly, and resist the harmful effects of radiation and chemotherapy.

The marked presence of survivin in tumor cells, contrasted with its near absence in healthy adult brain cells, makes it a compelling target for therapy. Treatments designed to target survivin aim not only to directly kill cancer cells, but also to dismantle the cellular mechanisms that allow these malignant cells to survive.

One of the most promising strategies in survivin-targeted therapy is the development of therapeutic cancer vaccines. These vaccines work by training the immune system to recognize survivin as a marker of tumor cells. When the immune system is exposed to a survivin-based signal, it generates immune cells that can specifically seek out and destroy survivin-expressing cancer cells. Because normal brain cells do not express survivin, this approach is intended to maximize precision while mini-

mizing harm to healthy tissue.

Early clinical studies of survivin-targeted immunotherapies for brain cancer have shown that these treatments are generally well tolerated. When combined with standard therapies such as surgery, radiation, and chemotherapy, survivin-targeted approaches may help extend survival for some patients. As research advances, these strategies could become increasingly important in personalized care for individuals with brain cancer.

Researchers have developed a synthetic survivin vaccine called SurVaxM to stimulate the immune system to target this cancer-associated molecule. In a phase II trial involving patients with newly diagnosed glioblastoma, adding the survivin vaccine to standard-of-care treatment provided a survival benefit even for patients with an MGMT unmethylated promoter status. Additional trials are underway to assess SurVaxM as an adjunctive therapy for high-grade glioma.

Another approach uses a viral vaccine that incorporates the survivin promoter alongside a fiber protein polylysine modification (pk7), which is believed to have antitumor potential. This oncolytic adenoviral virotherapy enters and destroys glioma tumor cells. For detailed information, refer to ClinicalTrial.gov: NCT03072134.

In 2025, the pivotal phase 2b SURVIVE Trial (NCT05163080) for newly diagnosed glioblastoma completed a successful interim analysis. Among more than 200 patients, the trial met predefined benchmarks for potential benefit. The FDA has granted SurVaxM both Fast Track Designation and Orphan Drug Status. Earlier results from a Phase 2a study (NCT02455557) showed that 51% of patients receiving SurVaxM survived at least two years, with a median overall survival of 25.9 months—almost double the historical average of 12–15 months. Notably, a five-gene expression signature and increased intratumoral memory B cell populations have been identified as predictors of vaccine response, paving the way for future personalized therapies. For glioblastoma, the vaccine is typically administered subcutaneously in combination with chemotherapy (temozolomide) and radiation.

Survivin-targeting vaccines are also being investigated for other conditions, including pediatric brain tumors. An ongoing trial (NCT04978727) is enrolling children diagnosed with medulloblastoma, ependymoma, high-grade glioma, and newly diagnosed diffuse intrinsic pontine glioma (DIPG). The vaccine has continued to

show a strong safety profile, with side effects mainly limited to mild local injection site reactions.

Anktiva (N-803)

Anktiva, also known by its research name, N-803, is an investigational immunotherapy designed to strengthen the body's own immune response against cancer. It has been approved by the FDA for the treatment of bladder cancer (NMIBC). Rather than directly attacking tumor cells, Anktiva works by stimulating specific immune cells that are critical for recognizing and destroying cancer, particularly natural killer (NK) cells and CD8+ cytotoxic T cells. These immune cells are often suppressed or exhausted in patients with aggressive cancers, including high-grade brain tumors such as glioblastoma.

At the molecular level, Anktiva is a modified interleukin-15 (IL-15) superagonist complex. IL-15 is a naturally occurring immune signaling protein that plays a key role in the survival, activation, and persistence of NK cells and memory CD8+ T cells. However, native IL-15 is difficult to use therapeutically because it is short-lived in the body and can be toxic at higher doses. Anktiva was engineered to overcome these limitations by stabilizing IL-15 and enhancing its biological activity while allowing for more controlled dosing. The result is a therapy that can produce a sustained immune-activating signal without some of the drawbacks seen with earlier cytokine treatments.

In brain cancer, immune-based therapies face unique challenges. The central nervous system has long been considered an immune-restricted environment, and brain tumors actively create local immune suppression through multiple mechanisms. Glioblastoma, in particular, reduces immune cell infiltration, secretes immunosuppressive factors, and promotes immune exhaustion. Anktiva is of interest in this setting because it aims to expand and re-energize immune cells systemically, increasing the number and functional capacity of NK cells and T cells that may then traffic into the tumor and its surrounding environment.

Another reason Anktiva has drawn attention in brain cancer research is its potential to complement other immunotherapies. By increasing the pool of activated NK and CD8+ T cells, Anktiva may help overcome this limitation and make other immune therapies more effective. For this reason, it is being explored primarily

in combination strategies, rather than as a stand-alone treatment. In a pilot study (NCT06061809), 5 of 5 patients achieved 100% disease control with a regimen that combined ANKTIVA and Optune Gio® Tumor Treating Fields. Three of those patients had a near complete response and the other 2 achieved disease stability as of the report date. This finding is highly encouraging. Ongoing and planned studies are helping to clarify how best to dose and schedule Anktiva in patients with brain tumors. It is important to emphasize that Anktiva remains investigational for brain cancer. While its immune-stimulating mechanism is scientifically compelling, its true impact on survival, quality of life, and long-term disease control in glioblastoma and other brain tumors is still being studied.

CeGaT Personalized Peptide Vaccines

CeGaT is a German precision-medicine company that has developed a highly personalized peptide vaccine approach for cancer, including aggressive brain tumors such as glioblastoma. Unlike traditional "one-size-fits-all" cancer vaccines that target a single shared tumor antigen, the CeGaT strategy is built around the unique molecular fingerprint of an individual patient's tumor. The goal is to train the immune system to recognize that patient's cancer as foreign and mount a sustained, tumor-specific immune response.

The process begins with comprehensive genomic and transcriptomic sequencing of the patient's tumor tissue, usually obtained at surgery. CeGaT analyzes DNA and RNA from the tumor and compares it to normal tissue from the same patient. This allows researchers to identify tumor-specific mutations and abnormal protein expressions—features that do not exist in healthy cells. From this analysis, CeGaT selects a set of short protein fragments, or peptides, that are predicted to be most visible to the patient's immune system when presented on their individual HLA (Human Leukocyte Antigen) molecules.

These selected peptides are then manufactured into a custom vaccine, typically consisting of multiple tumor-derived peptides rather than a single target. This multi-peptide design is especially relevant in brain cancer, where tumors are highly heterogeneous and capable of evolving under treatment pressure. By targeting several antigens at once, the vaccine aims to reduce the likelihood that the tumor can escape immune detection by simply shedding one antigen.

Once administered—usually by subcutaneous injection along with an immune-stimulating adjuvant—the peptide vaccine is intended to prime and expand tumor-specific T cells, particularly CD8+ cytotoxic T lymphocytes. These activated T cells can then recognize tumor cells displaying the corresponding peptide antigens. In theory, this creates an ongoing immune surveillance effect, allowing the immune system to continue recognizing residual or recurring tumor cells long after standard treatments such as surgery, radiation, and chemotherapy have been completed.

Clinical experience with CeGaT's personalized peptide vaccines has come primarily from early-phase trials and observational studies, including patients with glioblastoma. These studies have demonstrated that the vaccines can reliably induce measurable immune responses against tumor-specific peptides. Some patients have shown prolonged disease control compared with historical expectations, although results vary and definitive survival benefits have not yet been proven in randomized trials. As with most cancer vaccines, the strongest signals appear in patients who are able to mount a robust immune response and who are not heavily immunosuppressed. Researchers increasingly view the CeGaT vaccine platform as a foundational immunotherapy that may work best in combination with other treatments. Strategies under investigation include pairing peptide vaccines with checkpoint inhibitors, cytokine-based immune stimulants, or therapies that reduce immune suppression in the tumor microenvironment.

While still investigational, the CeGat vaccine embodies a shift in neuro-oncology toward individualized, immune-based strategies aimed at achieving longer-term tumor control by transforming the patient's immune system into an active and informed participant in the fight against brain cancer.

Inovio's DNA Vaccine Platform

Inovio Pharmaceuticals has developed a distinctive DNA-based immunotherapy platform in which small, circular DNA molecules called plasmids are engineered to encode cancer-associated proteins (antigens). These plasmids act as "software" that tells human cells to produce specific cancer antigens internally, mimicking what happens in an infection or in cancer, thereby teaching the immune system to recognize and attack tumor cells displaying those antigens

Rather than injecting the antigen itself (as many traditional vaccines do), Inovio's

approach relies on in vivo protein production, that is, the patient's own cells become antigen factories once the DNA plasmids enter them. To enhance plasmid uptake into cells, Inovio uses a proprietary electro-delivery device (called CELLECTRA®) that delivers brief electrical pulses at the injection site, transiently opening cell membranes to allow DNA entry.

For glioblastoma, Inovio developed a multi-target DNA immunotherapy regimen centered around two key plasmids:

INO-5401: This vaccine encodes multiple tumor-associated antigens found on GBM cells, such as proteins like WT-1, human telomerase reverse transcriptase (hTERT), and prostate-specific membrane antigen (PSMA), which are expressed in GBM tumors but less so in normal tissues. By presenting several antigens, INO-5401 aims to broaden the immune response and reduce the chance that tumors can evade detection by down-regulating a single target

INO-9012: Instead of encoding a tumor antigen, this DNA plasmid encodes interleukin-12 (IL-12), a cytokine that acts as a potent immune stimulant. IL-12 promotes the activation and expansion of T cells and helps polarize them toward an antitumor state, potentially overcoming immune suppression.

Together, these plasmids are administered intramuscularly with CELLECTRA® to drive both antigen presentation and immune activation. These responses are designed to generate cytotoxic T cells capable of recognizing and attacking GBM cells.

Because the approach is still investigational, its ultimate role in standard GBM therapy depends on confirmatory results from larger, controlled studies.

Other Personalized Vaccines

Other products using personalized vaccines include vaccine pulsed with lysate or peptides, again showing how researchers are working creatively to combine approaches and technologies. Exploiting the potency of dendritic cells holds promise for brain cancer treatment, so those looking for novel, advanced therapy should watch for developments in this technology.

Monoclonal Antibodies/Immune Checkpoint Inhibitors

A vital capability of the immune system is to be able to tell the difference between a normal cell and a cancerous one. Doing so enables the immune system to destroy the cancerous ones while leaving the normal cells alone. One of the ways in which the body does this is by targeting a particular checkpoint protein, which acts as a type of switch turning the immune system on and off. The class of medicine that does this is called a monoclonal antibody.

In cancer treatment, monoclonal antibodies are used to remove the "brakes" and turn on the immune system so that the system can perform its function of destroying the cancer. By blocking particular checkpoint proteins, the body's natural, pre-existing anti-cancer immune responses are unleashed.

There are several monoclonal antibodies being used in brain cancer treatment and they are known by the specific checkpoint protein they target.

Malignant gliomas are recognized as immunologically "cold" tumors, characterized by an immunosuppressive microenvironment. These attributes present significant challenges for immunotherapeutic approaches, necessitating innovative strategies to achieve effective and sustained anti-tumor responses.

Monoclonal antibodies, including immune checkpoint inhibitors (ICIs), are considered essential components of combination therapies that aim to maintain remission or, ideally, cure high-grade gliomas. The concept of combination therapy has a strong precedent in the medical field, exemplified by the successful use of "triple therapy" to combat previously intractable diseases such as HIV/AIDS. Furthermore, dual or combination therapies are routinely employed to suppress the immune system for organ transplantation, manage malignant hypertension, and treat refractory infections.

Clinical trials have demonstrated evidence of efficacy for combination immunotherapy in gliomas. Notable examples include the use of dendritic cell (DC) vaccines in conjunction with mRNA, or other immune stimulators such as ICIs and poly ICLC. Recent advances have highlighted the increased effectiveness of viral oncolytic therapy when combined with ICIs.

The field faces the daunting challenge of identifying the optimal combination among hundreds, even thousands, of potential therapeutic options. Achieving an FDA-approved immunotherapy for glioblastoma remains a "holy grail" in neuro-oncology. Given glioblastoma's multiform nature—reflected in its cellular, genetic, and immunological diversity—a sustainable immune response will likely require ongoing monitoring and an adaptive treatment approach. This paradigm is analogous to current HIV/AIDS management strategies, where initially effective regimens are modified over time to address mutations or other changes in the disease.

PD-1/PD-L1 Checkpoint Inhibitors

The use of PD-1/PD-L1 (Programmed Death-1 and Programmed Death Ligand-1) checkpoint inhibitors in brain cancer treatment represents one of the most exciting and innovative developments in the field of oncology. These inhibitors, which essentially work by blocking the immune system's checkpoint mechanisms that cancer cells exploit to evade detection, have shown promising results in a variety of cancers, including melanoma, lung cancer, and bladder cancer. However, brain cancer, especially glioblastoma (GBM), remains one of the most challenging areas for immunotherapy.

In the immune system, PD-1 is a receptor on T-cells (immune cells responsible for attacking foreign bodies, like cancer cells), and its ligand, PD-L1, is often overexpressed on the surface of tumor cells. When PD-1 binds with PD-L1, it acts as a "brake" on the immune response, preventing T-cells from attacking the tumor effectively. The PD-1/PD-L1 checkpoint inhibitors, such as pembrolizumab (Keytruda) and nivolumab (Opdivo), work by blocking this interaction, thereby allowing the immune system to mount a stronger defense against cancer.

However, brain cancer, particularly glioblastoma, presents unique challenges. The brain is protected by the blood-brain barrier (BBB), a selectively permeable barrier that prevents many immune cells, antibodies, and therapies from entering the brain. This makes it difficult for PD-1/PD-L1 inhibitors to reach brain tumors in sufficient concentrations. Additionally, brain tumors are known to create their own immunosuppressive environment, which complicates the effectiveness of immune checkpoint inhibitors. Inhibitors directed at the PD-1 protein include pembrolizumab (Keytruda®), nivolumab (Opdivo®), and cemiplimab (Libtayo®); inhibitors directed

at the PD-L1 protein include durvalumab (Imfinzi®), atezolizumab (Tecentriq®) and avelumab (Bavencio®).

What is the difference between these two proteins? PD-L1 (Programmed Death-Ligand 1) is frequently found on the tumor cells themselves. The "L" stands for "ligand". Therefore, glioblastoma cells overexpress PD-L1, and this protein can also be found in the tumor microenvironment, such as macrophages. Up to 40% of the glioblastoma volume is composed of white cells, often derived from bone marrow. These macrophages also have PD-L1 on their cell surface; another name for PD-L1 are the terms CD274 or B7-H1. Higher PD-L1 expression is associated with improved survival and, in some cases, better responses to ICIs in patients with brain metastases.

The initial trials of PD-1/PD-L1 inhibitors for GBM were promising, but results have been mixed. While some patients experience durable responses, the overall response rate to checkpoint inhibitors in GBM remains relatively low. For example, in early-phase clinical trials, nivolumab and pembrolizumab have shown limited success in terms of progression-free survival in GBM patients, with some reports of partial responses but little evidence of long-term survival benefits in the majority of cases.

The effectiveness of ICIs in treating malignant gliomas is limited by several factors:

Low Mutational Burden: Unlike cancers such as melanoma or lung cancer, glioblastoma (GBM) typically has a lower number of mutations. This reduced mutational load makes it more challenging for the immune system to recognize the tumor as "foreign," resulting in a less robust immune response.

Deficient Mismatch Repair (dMMR): ICIs have shown high effectiveness in solid tumors featuring a specific DNA repair deficiency known as dMMR (deficient mismatch repair). dMMR is a molecular phenotype in which cancer cells cannot correct errors that occur during DNA replication, leading to high mutation rates and what is termed microsatellite instability-high (MSI-H). Tumors with high MSI and dMMR generate many neoantigens, making them immunologically "hot" and more likely to be infiltrated by immune cells, causing strong responses to ICIs such as pembrolizumab or nivolumab. As a result, dMMR serves as an important predictive biomarker for positive and often durable responses to immunotherapy in various solid cancers—for example,

approximately 15% of newly diagnosed colorectal cancer (CRC) cases, where immunotherapy is frequently a first-line treatment. However, while dMMR is associated with high sensitivity to immunotherapy, some patients still develop resistance, which has prompted ongoing research into effective combination therapies.

Researchers are actively exploring new treatment regimens to improve the immunogenicity of gliomas and increase the effectiveness of ICIs. The primary goal is to convert immunologically "cold" tumors into "hot," immunoresponsive tumors. Several promising approaches are being investigated:

TTFields + Immunotherapy: The addition of pembrolizumab to Tumor Treating Fields (TTFields) and chemotherapy (as studied in the 2-THE-TOP trial, NCT03405792) has been associated with a 70% increase in overall survival (OS) in certain patient populations, notably in those with a large tumor burden who could only undergo biopsy. This combination demonstrated signs of enhanced anti-tumor immunity.

Triplet Blockade: There is growing interest in "triplet" therapy, which combines three ICIs—anti-PD-1, anti-CTLA-4, and anti-LAG-3—administered before surgery (neoadjuvantly). Early results show that this approach leads to increased activation of tumor-infiltrating lymphocytes when compared to baseline biopsy samples, indicating a stronger immune response.

Synergies of ICIs with Viral Oncolytics and Vaccines: Trials are underway combining ICIs with oncolytic viruses (such as CAN-3110/rQNestin34.5v.2, NCT03152318) or with personalized cancer vaccines like DCVax-L. These strategies are designed to prime the immune system prior to administering ICIs, potentially increasing the likelihood of a robust anti-tumor immune response.

Despite the hurdles, the potential for PD-1/PD-L1 inhibitors in brain cancer is still considered significant. The remarkable success of ICIs to treat melanoma metastatic to the brain is exemplified by the amazing recovery of President Jimmy Carter, who received immunotherapy with pembrolizumab combined with targeted radiation to 4 tumors in the brain, leading to a complete disappearance of these tumors and no recurrence enabling him to survive another 9 years and reaching the age of 100!

One promising avenue is the use of biomarker-driven patient selection. The development of companion diagnostics to identify which patients are most likely to benefit from checkpoint inhibition is an area of active research. For instance, tumors that express high levels of PD-L1 or show certain genetic mutations may be more likely to respond to PD-1/PD-L1 inhibitors. New emerging predictive biomarkers include a) DNA Replication Stress. A gene signature that predicts functional defects in the DNA replication stress response has emerged as a predictor of better outcomes; b) Advanced Neuroimaging. "Radiomic" features (such as shape, intensity, and texture on MRI) show promise as non-invasive biomarkers to predict survival and response early in treatment; c) Gut Microbiome. Specific gut bacteria are linked to improved immune response and overall survival in patients with glioblastoma and also associated with positive responses for a PD-L1 inhibitor (such as atezolizumab) whereas other types of microbiome have poor response to the ICI. Though we are not yet at a point where PD-1/PD-L1 inhibitors are the standard of care for brain tumors, their potential to transform treatment options for cancers like glioblastoma remains an exciting prospect.

CTLA-4 Inhibitors

Interest in using CTLA-4 (cytotoxic T-lymphocyte protein 4) inhibitors for brain cancer grew as scientists recognized that the brain is not completely isolated from the immune system, as was once believed. Immune cells can cross the blood–brain barrier, and brain tumors can express antigens that are detectable by T cells. This provided a biological rationale for testing immunotherapies, including CTLA-4 blockade, in both primary brain tumors and brain metastases.

Clinical experience, however, has shown that CTLA-4 inhibitors on their own have limited effectiveness in most primary brain cancers, particularly glioblastoma. These tumors create a strongly immunosuppressive environment and often require treatment with corticosteroids to control swelling, which can blunt immune responses. As a result, single-agent CTLA-4 inhibition has not become a standard treatment for these tumors.

More encouraging results have been seen when CTLA-4 inhibitors are used in combination with other therapies. Pairing CTLA-4 blockade with PD-1 or PD-L1 inhibitors can produce a stronger and more sustained immune response. Combining immunotherapy with radiation or experimental tumor vaccines has also been

explored as a way to make brain tumors more visible to the immune system. In patients with brain metastases—especially from melanoma—CTLA-4 inhibitors, particularly in combination regimens, have demonstrated meaningful tumor responses within the brain in some cases.

Overall, CTLA-4 inhibitors currently play a limited and mostly experimental role in the treatment of primary brain cancers. Their greatest potential appears to lie in combination strategies and in the treatment of brain metastases rather than as stand-alone therapies. Ongoing research continues to focus on improving their effectiveness, identifying which patients are most likely to benefit, and reducing treatment-related toxicity.

LAG-3 Inhibitors

Along with PD-1 and PD-L1, another immune checkpoint protein is LAG-3 (lymphocyte-activation gene-3). LAG-3 is an inhibitory receptor found on T cells that, when activated by binding to its ligands (such as MHC II), suppresses the immune response and leads to "T-cell exhaustion." Approximately 10% of glioblastoma express LAG-3; in this circumstance, Relatlimab, a monoclonal antibody that works as an ICI by blocking the LAG-3 protein, could be considered. It currently is FDA-approved in combination with nivolumab (Opdualag®) for unresectable or metastatic melanoma but is being evaluated in clinical trials for numerous cancers (lung, liver, breast, GI, leukemia, lymphoma). A phase II trial (NCT06325683) is comparing relatlimab + nivolumab against chemotherapy (lomustine) in patients with recurrent glioblastoma.

CAR T-Cell Therapy: An Evolving Treatment

Overview of CAR T-Cell Therapy in Brain Cancer

One of the most active areas of brain cancer research today focuses on teaching the immune system to recognize and attack tumor cells with greater precision. Among the most innovative strategies is CAR T-cell therapy, a personalized immunotherapy that has already transformed the treatment of certain blood cancers and is now being adapted for brain tumors.

Pioneers of CAR T-Cell Therapy

Three notable pioneers in CAR T cell therapy are Zelig Eshar, who developed the

first CARs in the late 1980s; Steven Rosenberg, who pioneered adoptive T-cell therapy and provided clinical settings for CAR T-cell testing; and Carl June, who led clinical breakthroughs for B-cell malignancies. Additional contributors include Patrick Hwu, Michael Sadelain, and Renier Brentjens, who advanced CAR T cell technology with novel designs and enhanced immune functions.

Antigen Recognition and Immune Activation

CAR T cell therapy is based on the recognition of antigens on the surface of malignant cells, known as tumor-associated antigens, tumor-specific antigens, or neoantigens. Each T cell carries a receptor that identifies antigens on cancer cells. When a T cell is alerted by an antigen-presenting cell, mainly a dendritic cell, it attaches to and destroys the cancer cell, while signaling other immune components to attack the cancer cell as a foreign invader.

Overcoming Immune Evasion in Glioblastoma

Glioblastoma and other brain cancers can evade the immune system by releasing chemicals that confuse T cells, preventing recognition of foreign antigens and allowing cancerous cells to grow unchecked. Malignant cells can also recruit bone marrow-derived white cells that suppress T cells. These myeloid-derived suppressor cells, together with microglia in the brain, create an immunosuppressive environment that exhausts T cells. Modern immunotherapy aims to reactivate T cells and increase their infiltration into tumors. CAR T cells are engineered to turbocharge T cells and direct them toward tumor-associated antigens.

CAR T-Cell Therapy Process

In CAR T-cell therapies, T cells are collected from the patient's blood through apheresis. These T cells are modified in the lab by adding a chimeric antigen receptor. Once modified, the CAR T cells are multiplied and infused back into the patient, where they seek out and destroy tumor cells bearing the targeted marker. To increase the proportion of CAR T cells relative to untreated lymphocytes, chemotherapy may be used to deplete other lymphocytes. In patients with malignant brain tumors, lymphodepletion may be adjusted or omitted, since lymphocyte counts are often already reduced due to the tumor, radiation, chemotherapy, or steroids. The CAR T cell therapy process can take between three and five weeks.

Targeting Tumor Markers in Brain Cancer

In brain cancer research, attention has been given to targets commonly present on

tumor cells but rare or absent on normal brain tissue, such as EGFRvIII, IL13Rα2, HER2, and others. Early clinical trials have demonstrated that CAR T cells are capable of reaching tumors within the brain and, in some patients, producing meaningful tumor responses.

Initial human trials with CAR T cells has shown dramatic effectiveness against otherwise incurable tumors. Different approaches target distinct antigens, such as IL-13α2 (overexpressed in 75–80% of glioblastomas) and EGFR variant III (found in 30% of glioblastomas). IL-13α2 is favored because it is rarely present in normal brain tissue, reducing off-target risks. Early studies have demonstrated tumor shrinkage or disappearance, increased T cell infiltration, and a favorable immune environment. Due to immunological memory, the immune system can recognize tumor antigens in the future, potentially allowing for long-term responses from a short course of therapy.

Additional and Emerging Targets

Beyond IL-13 and EGFRvIII, other targets include HER2 (overexpressed in up to 80% of glioblastomas), GD2 (found in pediatric brain tumors), B7-H3 (an immune checkpoint protein), EphA2 (involved in tumor migration), Tenascin-C (extracellular matrix molecule), MMP2 (promotes tumor invasion), CD70 (promotes immune escape), CD147 (linked to tumor growth), MUC1 (reduces immune cell killing), and NKG2D (activates natural killer cells). Multiple clinical trials are underway for these targets.

Recent Innovations and Ongoing Challenges

Recent trials in 2024 and 2025 have shown that second-generation CAR T cell therapies targeting both EGFR and IL-13α2 receptors are highly effective. These bispecific T cell engagers (BiTEs) prevent tumors from escaping by "turning off" a single protein. Administration via direct injection into the cerebrospinal fluid, often using a subcutaneous reservoir, appears more effective. However, dramatic responses are often transient. Brain tumors present distinct challenges due to their biological complexity, variability among cells, and the protective nature of the brain's immune environment. Tumor cells may lose or alter their target markers over time, allowing them to escape immune detection. These challenges have prompted the development of next-generation CAR T strategies. Combining CAR T cell therapy with immune checkpoint inhibitors has not promoted effectiveness but pairing with monoclonal antibodies that block immunosuppressive molecules may hold promise. Antigen

escape remains a challenge, as glioblastoma's heterogeneity allows tumor cells to evade detection. Careful screening is essential to confirm the presence of target antigens.

Third-Generation CAR T-Cell Therapies

The next generation of CAR T cell therapies will test innovations such as allogeneic T cells (from healthy donors, allowing for "off-the-shelf" use), upfront therapy (as a second-line option for newly diagnosed glioblastoma), in vivo production of CAR T cells (circumventing traditional manufacturing), and improved target identification using AI and single-cell analysis.

Extending CAR T-Cell Therapy to Other Brain Tumors

Advances in CAR T cell therapy for glioblastoma may also benefit pediatric brain tumors and other malignant brain tumors, including aggressive meningiomas. Mesothelin has emerged as a promising target, with preclinical studies showing tumor elimination. Early-phase clinical trials are planned, and human studies using B7-H3-targeted CAR T cells delivered via Ommaya port have demonstrated safety. Other antigen targets identified by "antigen atlas" approaches, such as NMNA2 and WNT5A, may elicit synergistic immune responses.

Advances: Synthetic CAR Systems

To address the limitations of traditional CAR T-cell therapy, researchers have also created synthetic CAR systems, such as syn-CAR or synNotch-CAR platforms. These approaches incorporate biological "logic" into immune cell behavior.

Instead of activating T cells based on a single tumor marker, syn-CAR systems allow T cells to sense combinations of signals within the tumor environment, creating a more refined response—similar to needing multiple keys to unlock a door.

In a syn-CAR approach, a T cell may first encounter one tumor-associated signal, which then activates the cell to express a second CAR targeting another tumor antigen. This sequential activation ensures that T cells respond only in the presence of true tumor tissue, reducing the risk of damage to healthy brain cells and improving precision.

This logic-gated strategy is particularly important in brain cancer, where safety is critical and tumor cells are often highly heterogeneous.

Toxicities and Risks of CAR T-Cell Therapy

The most concerning toxicities of CAR T-cell therapy include cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). CRS, well-characterized in blood cancers, is manageable in glioblastoma patients and marked by fever, low blood pressure, and, in severe cases, multi-organ failure. ICANS can cause neurological symptoms such as confusion, headaches, and seizures. Recent bivalent CAR-T trials reported grade 3 neurotoxicity in 56% of participants.

Current Status and Future Directions

While these therapies remain predominantly experimental and are mainly accessible via clinical trials, they mark an important evolution in brain cancer management. Instead of exclusive dependence on surgery, radiation, and chemotherapy, ongoing research is steadily attempting to enhance the scope of brain cancer treatment.



Photo Credit Margo Singer

Oncolytic Viral Therapy

Oncolytic virus therapy uses a modified virus that can cause tumor cells to self-destruct and stimulates the body's natural, pre-existing immune response against the cancer.

Oncolytic viruses - viruses that are able to infect and break down cancer cells but not healthy cells - are able to selectively replicate within and cause the death of cancer cells. Brain cancer cells have defects in them that allow for invasion by viral proteins. It is believed that oncolytic viruses will infect tumor cells and block the replication of those tumor cells. Through a process called lyses, the presence of the oncolytic virus may then cause the infected cancer cell to break down.

Several viruses, including adenovirus, measles virus, polio virus, parvovirus, HSV, and retroviral replicating vectors (RRVs) have been engineered to treat GBM. Below are described a few of these efforts.

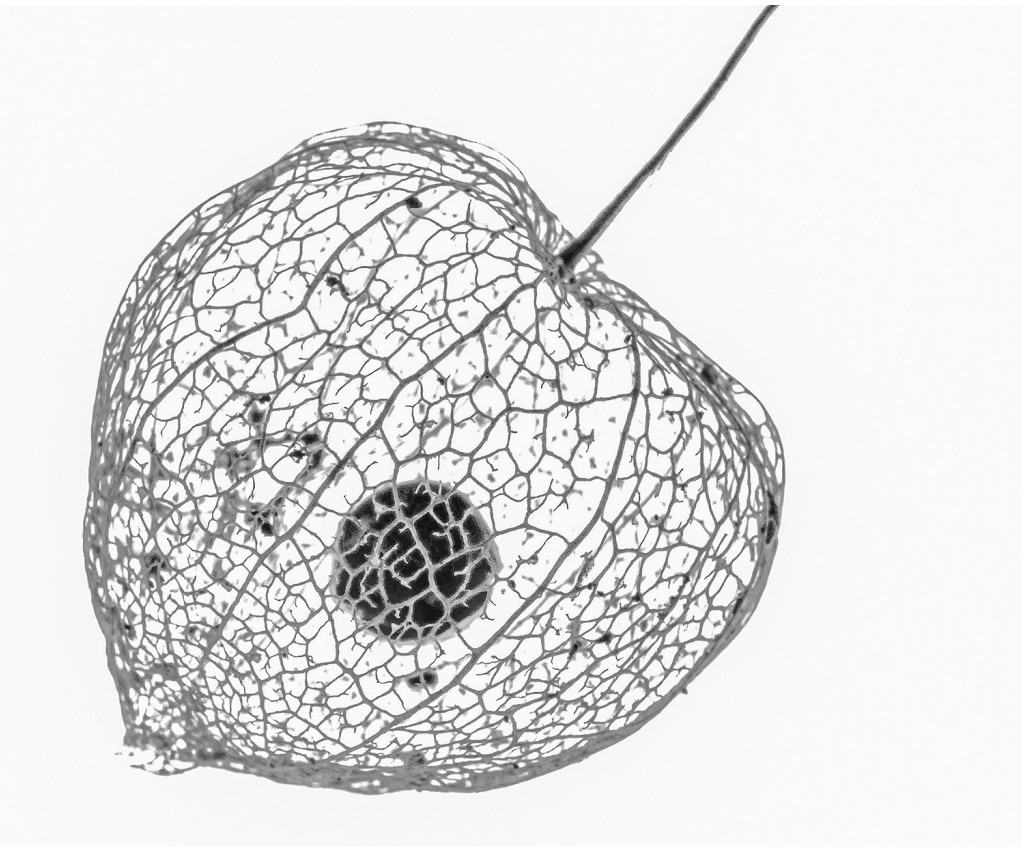


Photo Credit Steve Tilkin

Polio-Rhinovirus Chimera (Lerapolturev)

Lerapolturev is a vaccine currently undergoing rigorous investigation for its potential in treating glioblastoma. This therapy consists of the live attenuated (Sabin) type 1 poliovirus vaccine, which has been genetically engineered to include an internal ribosomal entry site (IRES) from human rhinovirus type 2. This modification creates a chimeric organism—a chimera—meaning it contains two or more genetically distinct sets of DNA.

Clinical studies have demonstrated that Lerapolturev is safe for patients with recurrent glioblastoma multiforme (GBM), and initial results indicate that it may provide extended survival compared to current treatments. The vaccine is designed to specifically target malignant glioma cells, as it recognizes CD155, a receptor for poliovirus that is frequently expressed on GBM cells. Once Lerapolturev enters these tumor cells, it is believed to trigger an immune response, enabling the body's own immune system to identify and destroy the cancerous cells.

Owing to encouraging evidence from ongoing Phase I clinical trials, the U.S. Food and Drug Administration (FDA) has designated Lerapolturev as a breakthrough therapy for patients with recurrent glioblastoma.

Lerapolturev is currently being assessed in a multicenter Phase 2 trial that focuses on safety and overall survival in adults with recurrent WHO grade IV malignant glioma (NCT02986178). In pediatric populations, results from a Phase 1b trial (NCT03043391) have confirmed the safety and feasibility of administering lerapolturev to children with recurrent high-grade gliomas. In this heavily pretreated group, the median overall survival was 4.1 months, with some patients surviving more than 22 months.

Researchers are also exploring the combination of lerapolturev with pembrolizumab (anti-PD-1, Keytruda®). The aim is to determine whether the virus can enhance the immune response in patients with recurrent glioblastoma, thereby improving the efficacy of checkpoint inhibition therapy, as part of the LUMINOS-101 trial (NCT04479241).

The current clinical protocols utilize convection-enhanced delivery (CED), a

neurosurgical technique in which a catheter is used to infuse the virus slowly and directly into the tumor over approximately 6.5 hours, thereby bypassing the blood-brain barrier. Results from earlier Phase 1 studies revealed promising long-term benefits in a subset of patients: 21% of adults treated with the modified virus survived three years, compared to a historical median survival of only four months. Remarkably, a few participants in the early trial survived for more than 70 months following infusion, which is highly uncommon for recurrent glioblastoma.

The most frequent side effects associated with lerapolturev are linked to the body's inflammatory reaction to the virus. These include severe headaches (Grade 3), seizures, and, in rare cases, hemiparesis (weakness on one side of the body). To manage treatment-related swelling in the brain, many patients require low-dose bevacizumab (Avastin®).

Adenovirus

Adenovirus treatment for brain cancer represents an innovative approach that blends virology, genetics, and immunotherapy in an effort to more precisely target tumor cells while preserving healthy brain tissue. This form of treatment uses a modified version of a common virus—the adenovirus—that has been carefully engineered so it cannot cause ordinary viral illness. Instead, it is repurposed to recognize, enter, and disrupt cancer cells in ways that conventional therapies often cannot.

Once introduced into the brain tumor—most often directly into the tumor itself or the surgical cavity after tumor removal—the adenovirus preferentially infects cancer cells. Many brain tumors, particularly aggressive types such as glioblastoma, have genetic abnormalities that allow the virus to replicate inside them. As the virus multiplies, the infected tumor cell eventually bursts, releasing new viral particles that can then spread to nearby cancer cells. This localized cycle of infection and destruction allows the virus to act as a self-amplifying treatment within the tumor environment.

Beyond directly killing tumor cells, adenovirus therapy plays an important role in activating the immune system. Brain tumors are known for their ability to hide from immune surveillance, creating a highly suppressive environment that limits the effectiveness of many immunotherapies. When adenovirus-infected tumor cells die, they release tumor antigens and danger signals that alert the immune system.

This process can recruit immune cells such as T cells and natural killer cells to the tumor site, helping the body recognize the cancer as a threat and potentially mount a longer-lasting immune response.

In some treatment strategies, adenoviruses are also used as delivery vehicles for therapeutic genes. These may include so-called "suicide genes," which make tumor cells vulnerable to specific medications, or immune-stimulating genes that increase local inflammation and immune activity within the tumor. Other approaches aim to restore tumor-suppressor functions that are lost in cancer cells. By confining these genetic effects to the tumor itself, adenovirus therapy seeks to minimize harm to surrounding brain tissue.

Clinical research into adenovirus therapy for brain cancer has been most extensive in glioblastoma. Early trials of certain adenovirus-based treatments have shown that a subset of patients experience meaningful tumor control and, in rare cases, long-term survival. These results are particularly notable given the aggressive nature of high-grade brain tumors and their resistance to standard treatments.

Several adenovirus-based therapies have been studied, particularly in glioblastoma:

DNX-2401 (tasadenoturev)

Tasadenoturev (DNX-2401) remains the most clinically advanced oncolytic adenovirus for GBM. A recent phase I-II trial (CAPTIVE/ KEYNOTE-192, NCT02798406) showed that the combination of DNX-2401 with the checkpoint inhibitor pembrolizumab (Keytruda®) for recurrent glioblastoma is safe and yields a promising survival: i) the 12-month OS was 52.7%, significantly higher than the 20% seen with standard of care; ii) importantly, a subset of patients achieved a durable, complete response, with a few remaining alive 45 to 60 months after treatment. The virus uses an RGD-motif to target integrins frequently found on glioma cells, inducing a direct cell death (oncolysis) and stimulating an influx of CD8+(cytotoxic) T cells into the tumor.

Suicide Gene Therapy (ADV-TK) [thymidine kinase adenovirus]

Another key adenoviral approach involves AdV-tk (adenoviral vector with HSV-tk gene), frequently used in combination with the antiviral drug valacyclovir. The virus delivers a "suicide gene" that converts the non-toxic prodrug (valacyclovir) into a toxic substance within the tumor, killing local cancer cells

and activating the immune system. A phase 2 trial (NCT00589875) in newly diagnosed GBM reported an increase in median survival from 13.5 months to 17.1 months when AdV-tk was added to standard radiation and chemotherapy. A genetically modified adenoviral vector with HSV-tk gene (CAN-2409, GMCI) when given together with nivolumab (Opdivo®) to patients with newly diagnosed GBM in a multicenter study (ABTC 1603, NCT03576612) was well tolerated and generated measurable immune activation. Notably, a subset of patients had a median OS of 30.6 months with other favorable prognostic factors such as gross total resection (GTR) and tumors with methylated MGMT promoters.

The treatment is generally well tolerated, but side effects can occur, most commonly as a result of immune activation rather than viral infection. Patients may experience fever, headache, fatigue, or temporary worsening of neurological symptoms due to inflammation in the brain. Imaging changes after treatment can sometimes resemble tumor growth, requiring careful interpretation by experienced clinicians.

At present, adenovirus therapy for brain cancer remains largely investigational and is most often available through clinical trials. Researchers continue to study why some patients respond better than others and how best to combine adenovirus therapy with surgery, radiation, chemotherapy, and newer immunotherapies.

Ongoing advances in viral engineering and immune science are steadily refining this approach. While it is not yet a standard therapy, it offers a promising avenue of hope, particularly for patients facing tumors that have limited response to conventional options.

Retroviral Replicating Vectors (RRVs)

Another approach, combining virotherapy and gene therapy, uses an RRV. The theory in this approach is that the virus will integrate into the host genome and spread through rapidly proliferating cells. Early phases of clinical trials evaluating the RRV called Toca 511 in recurrent high-grade glioma patients showed the virus was safe and persistent in the tumor, but the trial failed to meet its goals for effectivity, so the developers have returned to the lab with this one.

Nonetheless, the survival data in the application of oncolytic viruses suggest that certain individuals will benefit from this technology. They key will be finding the

genetic traits in the tumors that can predict which patients are more likely to respond to this form of therapy.

While the Phase III Toca 5 trial (NCT02414165) for recurrent high-grade glioma did not meet its primary endpoint, subgroup analysis showed potential efficacy, with a durable complete response in a subset of patients, leading to ongoing investigation of newer RRV platforms, such as DB107-RRV (NCT06504381) for newly diagnosed glioblastoma) and next-generation vectors targeting immune modulation. Preclinical studies of RLI (receptor-linker-interleukin-15), an IL-15 superagonist, show that RRVs can improve survival by modulating the tumor microenvironment and stimulate CD4+/CD8+ T cells. "Split-genome" RRV systems (spRRV) are being developed to improve the safety and efficacy of gene transfer and the spread of virus within tumor tissues.

For more information about Immunotherapy including a listing of clinical trials, please go to this website:

https://virtualtrials.org/Immunotherapy_treatments.cfm

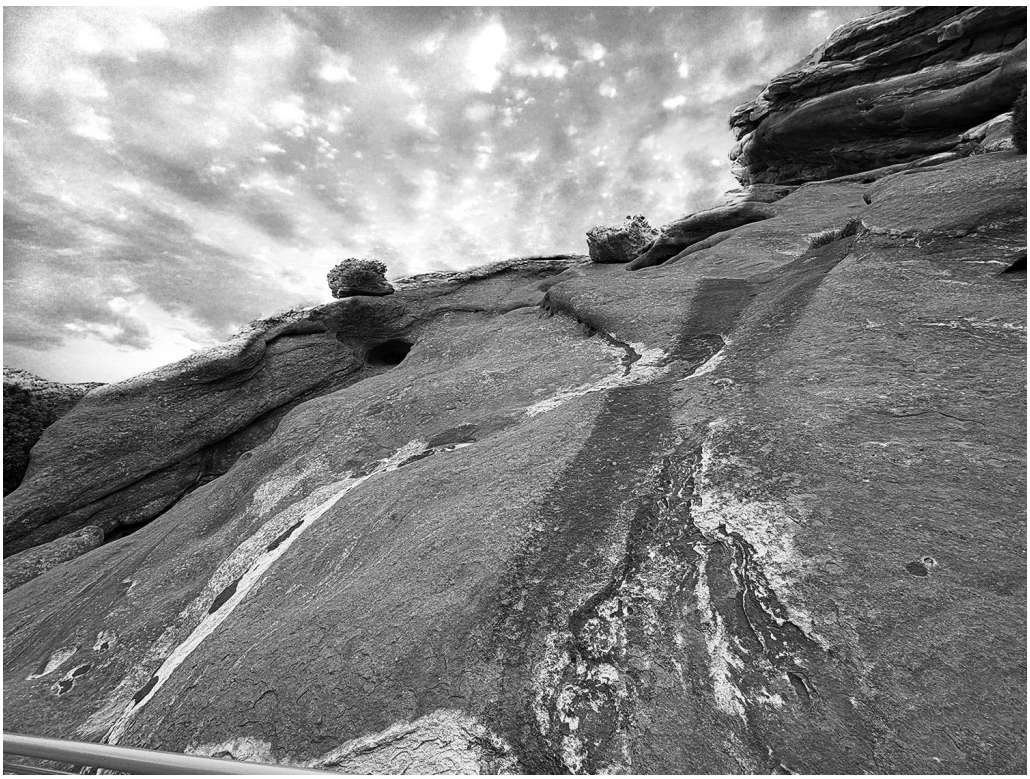


Photo Credit Linda Singer

SURVIVOR STORY #7

In September 2008 I had dizzy spells and a heightened sensitivity to bright lights. Upon visiting my family doctor, he ordered blood work and asked me to wear a Holter monitor, thinking that I might have a heart problem. I was 43 years old, and other than having low blood pressure I was in good health.

On October 2, 2008, I woke up at my usual time, 6:30 AM, went about my routine, got the kids up, made breakfasts, lunches, etc., feeling fine to this point. Around 8:00 AM, I felt dizzy again and began banging into door frames and tripping as I walked from the carpet onto the hardwood floors. My daughter, 11 years old, was talking to me and I couldn't understand what she was saying. I started to panic and I was sweating. I had to get my daughter to the bus stop and figure out what was going on. I came home from the bus stop shaking and afraid. My left side went all tingly. I thought I was having a stroke.

I called my husband at work and told him I needed to go to the emergency room. He rushed home and took me to the hospital, where I was taken for an electrocardiogram right away. They told me that I had not had a stroke and that there was nothing wrong with my heart, and they were getting ready to send me home, thinking I may have had just a fainting spell. With pressure from my husband and my family doctor, I was sent for a CT scan. Soon after came the news: a 3-cm brain tumor. The tumor was located close to the surface in the left parietal region, just above my ear. We were told to go directly and immediately to the regional neurological center.

Shocked and dazed, we first picked up our children at high school and elementary school, told them what was happening, had a group cry, dropped them off at home, and then went to the center. I had surgery 5 days later. The surgeon was able to remove only about 25% of the growth as the tumor mimicked the appearance of the brain and in places he was unable to differentiate between the tumor and healthy brain tissue. While we were obviously distressed by this, the surgeon told us to take heart because in these types of cases, surgery is not the primary determinant of the final outcome. After a week in hospital, I was sent home to recover and await the results of the biopsy. I was diagnosed with a grade III anaplastic astrocytoma and was referred to a cancer center for further treatment.

In the early days, we were sometimes disheartened, especially as we learned more about

this disease. In particular, while the Internet can be a tremendous source of information, it can also contain information that may be misleading. One of the scarier things to read about was the statistics, which can seem very grim. I made a conscious decision not to even think about statistics, and I encourage anyone going through the experience of a brain tumor to do the same, because we are not statistics.

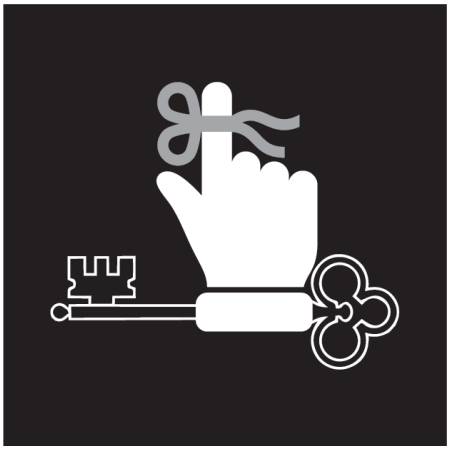
My initial assessment at the cancer center was on October 30. My radiation oncologist and the medical oncologist felt that because I was young and strong I could handle the most aggressive treatment. On November 17, I began a treatment regimen of radiation and chemotherapy together. I had radiation treatments Monday to Friday and took a low dose of temozolomide (Temodar) 7 days a week. I had a short break from radiation over Christmas and finished this phase of treatment on January 5. Overall, I tolerated it very well. Other than losing my hair, the biggest adverse effect I felt was increased fatigue. Also, the steroids I was taking to relieve headaches and pressure in my brain caused bloating and affected my sleep patterns.

After a four-week recovery period, I had an MRI that showed that the tumor had shrunk. That day I began the next phase of my treatment, which consisted of a higher dose of temozolomide for 12 months on the cycle of 5 days on and 23 days off. There was a target dose of chemotherapy toward which my doctors gradually brought me. At the lower doses, I tolerated the chemotherapy except for nausea and vomiting, but as I was brought to the target dose, my entire body became itchy, I became tired, and my level of blood platelets was greatly reduced. After a break to recover, I received again a lower dose of chemotherapy, which I remained on until my treatment finished. I have had no further treatments since then.

I am now a 10-year survivor of grade III anaplastic astrocytoma. I have difficulty dealing with multiple things at the same time, and I have problems with short-term memory, which means I have to make notes for everything. This has been my "new normal," but I am not complaining.

One thing I did not mention, which I think is very important, is having a positive attitude, and for me personally, the power of faith. I was surrounded by people who kept my spirits up and always encouraged me. I thank God each day for the miracle of healing that I have received.

KEY TAKEAWAYS TO REMEMBER



To date, only a few drugs and devices have been approved by the Food and Drug Administration specifically for the treatment of brain tumors, but research is ongoing, including in the area of immunotherapy.

Immunotherapy works by enhancing the body's own immune system response against cancer cells, and there are many immunotherapy trials for brain tumors underway.

If you are interested in treatment with a personalized vaccine, you must make arrangements **before surgery** to have the vaccine made or to have frozen tissue stored so that you can have the vaccine made later.





Ten

Optune Gio®/TTFields Device

Overview

Optune Gio® is a wearable battery-operated device that has been approved by the Food and Drug Administration (FDA) for the treatment of newly diagnosed glioblastoma. The device is approved for use in combination with the chemo, temozolomide (Temodar), after concurrent radiation therapy and temozolomide treatments are completed. The Optune Gio® device has also been approved by the FDA for treatment of recurrent glioblastoma.

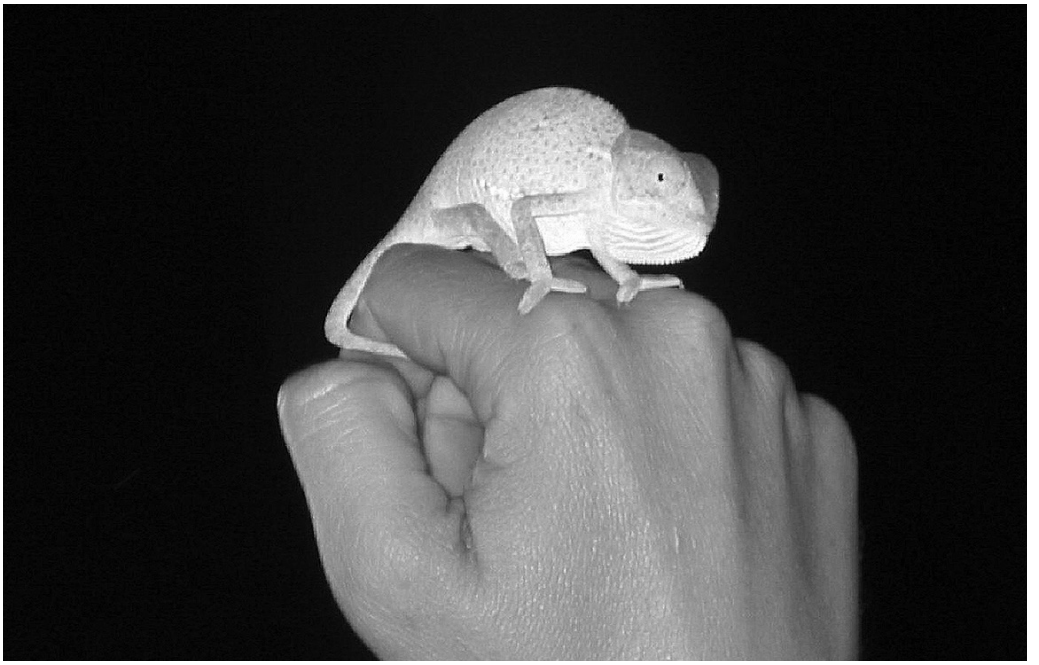
How it Works

The Optune Gio® device delivers alternating electric fields (called Tumor Treating Fields or "TTFields") through four insulated transducer arrays. These arrays are worn on a shaved scalp and are connected with a battery-operated electrical-field-generating device, which can be carried as a travel case or backpack. The transducer arrays can be worn continuously for 3 to 4 days before they need to be removed for hygienic care of the scalp, re-shaving of hair, and reapplication with a new set of arrays. Loose-knit wigs, hats, or other head coverings can all be worn over the arrays. The photograph at the end of this chapter shows a man wearing the Optune Gio® array and carrying case.

The Optune Gio® device utilizes low intensity (1-3V/cm), intermediate frequency (200 kHz) electric fields, which alternate 200,000 times per second, to disrupt cancer cells. These electric fields work through several distinct biophysical and biological mechanisms. When the electric fields enter a cancer cell, they attract and repel charged proteins during cell division, selectively interfering with the process by

delivering low-intensity, intermediate frequency alternating current.

Since alternating electric fields do not enter the bloodstream like drugs, they do not affect cells in other parts of the body. The most common side-effects Optune device users experience are mild-to-moderate scalp irritation, headaches, and logistical difficulties.



Key Mechanisms of Action

Antimitotic Effect. The primary mechanism targets the physical structure of dividing cells. Alternating electric fields specifically affect dividing cells, whereas non-dividing cells remain unaffected. This selectivity provides a significant advantage for treating brain tumors. The healthy tissue of the surrounding brain, including blood vessels, neurons, and connective tissue (glia), divides infrequently, unlike other organs such as skin, bone marrow, or gut, which are more mitotically active. As a result, toxicity to surrounding brain tissue is minimal. Tumor treating fields (TTFields) also impair the cancer cell's ability to replicate and repair its DNA.

Enhanced Antitumor Immunity. TTFields transform an immunologically resistant, or "cold," glioblastoma multiforme (GBM) into an immunoresponsive, or "hot," state. Under stress, cancer cells release molecular signals that cause cal-

reticulin to move to the cell surface, alerting immune cells to target the tumor. TTFields activate the STING pathway, promote tumor-associated macrophages to adopt the M1 immunostimulatory state rather than the M2 immunoresistant state, and stimulate the type I interferon (T1IFN) pathway via DNA sensor-dependent inflammasome. This promotes in situ immunization against glioblastoma.

Inhibition of Cell Motility and Spread of Cancer Cells. By disrupting the microtubule and actin cytoskeleton, TTFields impair the ability of malignant cells to move and invade adjacent tissue. Because invasion is a hallmark of cancer—and a primary driver of glioma spread throughout the brain—suppressing cell motility could potentially translate into a survival benefit for patients.

Initial Testing Results

A large, randomized trial (NCT00916409, EF-14) was conducted to compare the use of the Optune Gio® device plus adjuvant temozolomide (Temodar) versus the use of Temodar alone in patients with newly diagnosed glioblastoma who had received radiation therapy along with concurrent Temodar. The FDA actually stopped this trial early because there were clearly evident increases in progression-free and overall survival in the group treated with Optune Gio® device plus Temodar compared with the Temodar-only group. The FDA stated that all of the patients in the trial should be allowed to benefit from Optune Gio® treatment. This FDA action might be the first time ever that a brain tumor trial was stopped early because a treatment was found to be so clearly effective.

Latest Results and Trials

Based on the EF-14 Phase 3 pivotal study in those with newly diagnosed GBMs, Optune Gio® is proven to extend survival.

Overall Survival	Temodar Only	Temodar plus Optune Gio®
24 months/ 2 years	31%	43%
60 months/5 years	4.5%	13%

The 5-year probability of survival when Optune Gio® was used with 90% compliance is 29.3% versus 4.5% when using Temodar alone.

An important phase 2 trial (NCT03405792, 2-THE-TOP) evaluates the safety and efficacy of the combination of Optune Gio® (TTFields), temozolomide (Temodar®) and an immune checkpoint inhibitor (ICI), Keytruda® (anti-PD-1, pembrolizumab). As of 2026, final analysis of this trial have been reported, showing improved progression-free survival (12.0 months compared with 5.8 months in controls) and overall survival (24.8 months compared to controls, 14.6 months). Importantly, immune studies using single-cell analysis and T cell clonotyping of blood and tumor samples showed expansion of T cell clones via a T1 interferon-driven trajectory, supporting an immune-mediated mechanism, sustaining the activation of T cells and formation of immunological memory. There were striking results observed in patients who had complex glioblastomas that could be treated with biopsy only, yet these "inoperable" tumors showed dramatic responses consistent with an immune-mediated as well as TTFields response. These results suggest that TTFields can enhance the effectiveness of ICIs, offering a promising new treatment avenue for glioblastoma. Due to the results of the 2-THE-TOP study, a larger Phase 3 trial (NCT06556563, EF-41/KEYNOTE D58) has been initiated for newly diagnosed glioblastoma, randomizing Optune Gio® and temozolomide with pembrolizumab or with a placebo.

The Anktiva trial is currently evaluating Optune Gio® (TTFields) as an immune-stimulating device. Preliminary data from a pilot study (NCT06061809, QUILT-3.078), which included Anktiva (NAI, N-803 or nogapendekin alfa inbakicept-pmln), an IL-15 superagonist that activates natural killer (NK) cells and T cells, demonstrated promising results. When combined with TTFields, bevacizumab (Avastin®), and PD-L1 targeting high-affinity NK (t-haNK) cells, a 100% disease control rate was observed in five patients with recurrent glioblastoma multiforme (GBM) who were treated with a "chemo-free" regimen. Notably, Anktiva increased the absolute lymphocyte count (ALC) in these patients, who had previously experienced lymphopenia following standard of care (SOC) treatments such as radiation and chemotherapy. Beyond its role in GBM, Anktiva is also being investigated for its ability to stimulate the proliferation of NK and T cells in muscle-invasive bladder cancer or metastatic bladder cancer (NCT03022825). Further studies will evaluate its efficacy in other cancer types, including head and neck cancer (NCT04247282), non-Hodgkin lymphoma (NCT05618925), and bowel cancer

(NCT04491955).

Optune Gio®(TTFields) may play an important role in the treatment of metastatic cancer to the brain. The final results of the randomized Phase 3 METIS trial (NCT02831959), which compared stereotactic radiosurgery (SRS) alone to SRS combined with TTFields, recently demonstrated that the study met its primary endpoint. There was a statistically significant delay in the time to intracranial progression for patients with brain metastases from non-small cell lung cancer (NSCLC), and this benefit was achieved without a decline in quality of life or cognitive function. Consequently, TTFields has emerged as a new treatment option for patients with brain metastases from NSCLC, including those receiving immune checkpoint inhibitors. An FDA decision regarding this indication is expected in 2026.

Recent advances in neuroimaging are paving the way to refine Optune Gio®(TTFields) therapy into a personalized delivery system. High-resolution 3D echo planar MR spectroscopy (3DEPSI) has been utilized to monitor Novo-TTF responses in patients with GBM (NCT02441322), revealing a direct correlation between TTFields dose distribution and tumor response. These findings confirm the therapeutic activity of TTFields and support the strategy of optimizing scalp array placement to maximize TTFields dosing in areas at highest risk of progression. Additionally, customizing and adapting the array layout after tumor progression is being explored.

These concepts are now being further developed in an ongoing trial (NCT05086497) that combines MRI imaging with metabolic mapping. Whole brain MRI is used to provide a more comprehensive picture of malignant cell spread within the brain, with the goal of enhancing TTFields effectiveness. In related research, a gene-based biomarker panel has been identified that can predict individual patient responses to TTFields based on immunological activity. TTFields cause malignant glioma cells to rupture, releasing antigens that, in preclinical models, induce memory immune responses to the tumor. This process activates STING and AIM2 inflammasomes, triggers adjuvant immunity, and may prevent future recurrence.

Another Phase 2 study is testing a new high intensity array concept in recurrent GBMs, given recent in vitro data that suggests an increase in effectiveness may be

possible with higher intensity.

Optune Gio® Availability and Use

Doctors must be trained and certified to prescribe the Optune Gio® device, however, its use has been expanding over the last decade so that it is now available for prescription from most major brain tumor centers as well as some smaller hospitals in the US and in over 260 centers outside the USA.

The device is intended to be worn continuously for at least 18 hours per day, and a shaved scalp must be maintained for the duration of therapy. If that seems burdensome, recent studies clearly indicate a dose-response curve with alternating electric-field therapy: patients who have the highest compliance (greater than 90%) in wearing the device for 18 or more hours per day have the best outcomes, including, as mentioned above, in one sub analysis, a 5-year survival rate in a group of patients in the Phase 3 Trial (EF-14, NCT00916409) who were highly compliant and wore the Optune device more than 90% of the time (approximately 22 hours/day). Patients who choose not to use the Optune Gio® device should therefore not feel guilty about seeking other treatments. The best time to start Optune Gio® has been at the completion of radiation therapy. However, an ongoing Phase 3 trial (NCT04471844, TRIDENT) is evaluating the benefit of starting Optune Gio® concurrently with radiation and temozolomide in patients with newly diagnosed GBM. Enrollment is complete, and top-line results are expected soon. One consideration is that the use of Optune Gio® can potentially make the patient ineligible for certain clinical trials.



The Optune Gio® array and carry case / backpack. Courtesy of Novocure, Inc.





Eleven

How Bevacizumab (AVASTIN®) Works

Overview of Bevacizumab (Avastin®)

Bevacizumab, commonly known by the brand name Avastin®, is a targeted cancer treatment that changed the way many doctors manage certain brain tumors, including recurrent high-grade brain cancers and, in some cases, pediatric low-grade tumors. It was first approved by the U.S. FDA in 2004 for colon cancer and later approved in 2009 for recurrent glioblastomas. Researchers developed Avastin after discovering that many tumors survive by creating new blood vessels to feed themselves.

How It Works

Unlike traditional chemotherapy, Avastin is not designed to directly kill tumor cells. Instead, it works by blocking a protein called VEGF (vascular endothelial growth factor). VEGF signals the body to grow new blood vessels. Tumors need oxygen and nutrients to grow. To do that, tumors release signals that stimulate the formation of new blood vessels, a process called angiogenesis. Brain tumors often produce large amounts of VEGF for angiogenesis. Avastin blocks this signal, helping "starve" the tumor by reducing blood vessel growth and decreasing edema-causing leakage from abnormal vessels in the brain. The resulting edema can cause headaches, cognitive changes, weakness, and reduced mobility. By decreasing this fluid leakage, Avastin can relieve symptoms and may reduce the need for steroid medications. Some patients notice improvement after one or two intravenous infusions.

Effects and Benefits

By limiting blood vessel growth, Avastin can reduce the tumor's access to oxygen and nutrients, which may slow progression. In brain tumors, one of its most important effects is reducing swelling (edema) around the tumor. This can lower intracranial pressure and mass effect, which often improves neurological symptoms.
For many brain cancer patients, the benefit of Avastin is improved quality of life. Some patients experience clearer thinking, better strength, less dependence on steroids like dexamethasone, and temporary slowing of tumor progression. In some cases, patients who were struggling to walk or function improve noticeably after treatment begins. However, Avastin does not work for everyone, and tumors can eventually adapt and continue growing despite treatment.

Possible Mechanisms of Action

Avastin may work through several complementary mechanisms. As with many powerful medications, Avastin may have several mechanisms of action. In addition to "starving" the tumor of its blood supply (anti-angiogenesis), Avastin may also temporarily normalize tumor blood vessels, which are often leaky and disorganized. By reducing this leakiness, it may improve blood flow and oxygen delivery in the tumor area, potentially making treatments such as chemotherapy or radiation more effective when used together. Avastin could also enhance immune responsiveness and immunotherapy by activating dendritic cells and T-cells (VEGF itself is immunosuppressive), or iv) act on stem cells located in the lining of the ventricles (subventricular zone).

Clinical Uses

Clinically, Avastin is FDA-approved for recurrent glioblastoma and is also used in selected newly diagnosed glioblastoma cases, particularly when there is bulky disease, significant mass effect, increased intracranial pressure, or a deep tumor that cannot be safely removed. It may also be used palliatively during radiation therapy and temozolomide treatment or during episodes of rapid neurological decline.
In selected patients with bilateral vestibular schwannomas, Avastin may also be considered when preserving hearing is a major priority and surgery carries a high risk of deafness.

What Patients Should Expect

It is important to understand that Avastin is a disease-controlling treatment, not a cure. In conditions such as glioblastoma, it can improve symptoms and delay tumor progression, but it has not consistently been shown to extend overall survival. Its greatest benefit is often improved quality of life through better control of swelling and stabilization of disease.

Use in Pediatrics

Currently, Avastin® is used in pediatric neuro-oncology mainly as an off-label treatment, as it is not FDA-approved for children. For pediatric low-grade gliomas (LGG), it can be used to treat aggressive or recurrent tumors, especially when these tumors cannot be surgically removed or threaten critical functions like vision. Sometimes, it is administered with chemotherapy (irinotecan) as a third-line therapy. While it may provide short-term tumor control, progression often occurs after treatment stops (median progression-free survival is about 8 months after stopping treatment). Gliomas can develop resistance mechanisms, such as changing from a solid, spherical mass to a more diffuse, infiltrative pattern, or recruiting other angiogenic pathways besides VEGF to bypass Avastin®'s effects.



Photo Credit Ethan Brooke on Unsplash

The use of Avastin® in pediatric high-grade gliomas (PHGG) and diffuse intrinsic pontine gliomas (DIPG) has been less successful. Major clinical trials have found that adding Avastin® does not significantly improve overall survival for most newly diagnosed PHGG patients.

In a small subset of patients (10-15%) whose tumors have MAPK network (BRAF V600E, NF1, KIAA1549:BRAF fusion, FGFR1) mutations or alterations, Avastin®

can provide a potential survival benefit of up to 16 months longer. In these cases, the benefit is not only anti-angiogenic but also immunological, as Avastin® helps CD8+ cytotoxic T cells enter the tumor and overcome the immunosuppressive microenvironment often found in high-grade tumors. Avastin® may also be considered as a palliative or salvage therapy for heavily pre-treated, recurrent, high-grade tumors to reduce swelling and steroid dependence.

Biosimilars

With the expiration of Avastin's patents, more than a dozen companies have begun developing biosimilar products. A biosimilar is a product approved based on its substantial similarity to the original approved product, with the same mechanism of action, administration method, dosage form and strength, and no meaningful differences in safety or effectiveness. Biosimilars are often less expensive, making insurance companies more likely to approve their use.

Currently, Avastin biosimilars are available, and for simplicity, the term "Avastin" in this chapter refers to both Avastin and its biosimilars.

Biosimilar Name	Non-Proprietary Name	Company	FDA Approval Date
Mvasi	bevacizumab-awwb	Amgen	September 14, 2017
Zirabev	bevacizumab-bvzr	Pfizer	June 27, 2019
Alymsys	bevacizumab-maly	Amneal Pharmaceuticals	April 13, 2022
Vegzelma	bevacizumab-abcd	Celltrion	September 27, 2022
Avzivi	bevacizumab-tnjn	Bio-Thera Solutions	December 6, 2023
Jobevne	bevacizumab-nwgd	Biocon Biologics	April 9, 2025

Avastin Administration

Before reviewing the administration information about Avastin (bevacizumab), please remember that this information is for general knowledge only and should not be considered medical advice. It is essential to consult with a healthcare provider for any health concerns or before making any decisions related to your health or treatment.

Avastin is generally administered about once every two (2) weeks but may be given every three (3) weeks based on the specific clinical situation. Avastin® is given as an intravenous (IV) infusion. The duration of treatment is typically continued until there is disease progression or unacceptable side effects (toxicity) occur. While specific schedules are commonly used, variations may be explored in clinical practice or in a specific clinical trial. It is crucial to consult with your oncologist to determine the most suitable treatment schedule based on your individual medical condition and overall treatment plan.

Success Rate/Predicting Success

What is the success rate of Avastin®? For patients with newly diagnosed or malignant brain tumors, a substantial portion of patients (up to 40%) do quite well on Avastin® and patients benefiting may go as long up to 66 weeks, and occasionally longer. Treatment duration depends upon many factors, and long-term use may be more common in patients with recurrent GBM rather than those newly diagnosed. Numerous institutional studies have reported an objective response rate (tumor shrinkage of more that 50%) in 35 -40% of patients treated with Avastin®. A much higher percentage realize some benefit, but not 50% tumor size reduction. Also, because of the effect of Avastin® on the leakiness of small blood vessels, there may be a "pseudo-response" which confounds the MRI interpretation as the GBM appears to shrink when it is merely less visible, similar to a "steroid effect" that confounds the interpretation of a MRI. Furthermore, the 6-month progression-free survival (PFS) – meaning the GBM did not grow for at least half a year –– typically ranges between 29% and 50%.

While there is no single FDA-approved test to definitively predict an individual's

response to Avastin®, clinical research and emerging molecular profiling have identified several potential indicators to help gauge both benefit and risk. As indicators of potential benefit, genomic analyses suggest certain genetic biomarkers that point to a "long-term responder" (providing a benefit for a year or more): i) CDK4 amplification; ii) MGMT methylation; iii) SETD2 mutations; and iv) LRIG3 or DDIT3 amplification. Furthermore, a high baseline level of the target protein, VEGF-A, may correlate with a better response to anti-angiogenic therapy with Avastin®.

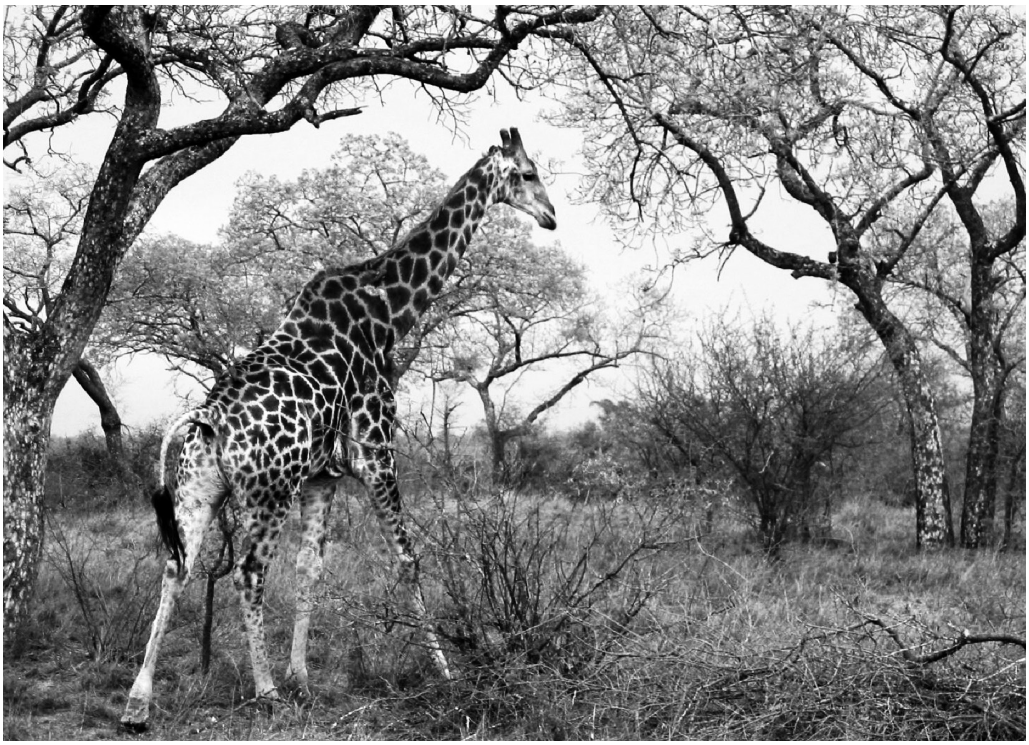


Photo Credit Linda Singer

Advanced neuroimaging may reveal predictors of efficacy, including: i) edema volume and edema index, generated by machine learning models, which can predict a favorable response, especially as the drug's most immediate effect, as noted previously, can be the reduction of peritumoral swelling (vasogenic edema). Advanced neuroimaging can differentiate between highly vascularized tumors (measured by rCBVmax on MRI) and low-vascularity tumors (low rCBVmax on MRI) with the more vascularized tumors responding better to Avastin®. Because VEGF is involved in controlling blood pressure, and Avastin® specifically blocks VEGF, hypertension is a side effect of Avastin®; paradoxically, there is evidence that hypertension during treatment is a positive clinical marker that portends a favorable response with

increased OS in patients with recurrent GBM.

Predicting which patients are at higher risk for serious complication of Avastin® is an important area of current neuro-oncology research. To predict which patients are at risk for vascular toxicity (hypertension or thrombosis), there are genetic germline variants (single nucleotide polymorphisms, SNPs), such as MED13L, FGF14, and RGS10 that have been linked to a higher risk of Avastin®-induced hypertension. Variants in genes such as TSPAN33 and MYL1are linked to a higher risk of blood clots (thrombosis) during Avastin® therapy.

The risk of neurocognitive decline may be due to progressive disease, age, radiation-effect, seizures, medications, chemotherapy ('chemo-fog'), but if patients start with a lower baseline of cognitive function or those with an early cognitive decline within the first 10 weeks of treatment, then they have a higher risk of continued cognitive decline and a shorter survival.

While the potential benefits from Avastin are great, Avastin is a powerful drug that, like any drug, may cause some serious side effects.

Please be aware that Avastin use may disqualify a person from certain clinical trials, or its use must be stopped for a certain period of time before joining a clinical trial.

When Best to Use Avastin

For the reasons given above, it is best used in one of the following situations:

- When everything else has been tried and the disease keeps growing. In such cases, Avastin has been shown to improve progression free survival, but it has not demonstrated an improvement in overall survival.

- In very carefully selected newly diagnosed patients with bulky inoperable tumors or multi-focal tumors. In these cases, Avastin has been shown to prolong neurologic preservation and reduce the need for steroid use (which can be a problem if used long term).

- When the tumor regrows and the intracranial swelling is so great that unwant-

ed symptoms (like immobility) occur but can no longer be controlled by use of safe dosages of a corticosteroid like dexamethasone.

- To treat the formation of necrosis for a limited period.
- In conjunction with a clinical trial which requires use of Avastin.
- Because of some unique situation where the doctor believes the Avastin is the best treatment option, such as using Avastin as a "super steroid" to prevent or treat swelling from immunotherapies.

Side Effects

Like any powerful drug, Avastin can cause a range of side effects. Most are toler-



Photo Credit Linda Singer

able. Common side effects include:

- Fatigue. About 45% of patients experience fatigue, which can also result from various medical or lifestyle factors such as depression, immobility, insomnia, anemia, inflammation, "chemo brain," radiation, seizures, or medications.
- Hypertension (High Blood Pressure). Occurs in about 30–40% of patients and is generally managed with anti-hypertensive medication. Interestingly, hypertension during treatment is linked to a better response to Avastin because the

VEGF pathway is involved in both tumor growth and blood pressure regulation.

- Wound Healing Complications. VEGF is important for normal wound healing, so minor cuts may heal slowly while on Avastin. The drug should not be used for at least 28 days before or after surgery, unless the surgery is an emergency.

- Thromboembolism (Blood Clots). There is an increased risk of arterial and venous blood clots, such as deep vein thrombosis, though these events are relatively uncommon. Symptoms can include swelling in a leg (rarely both legs), pain (often in the calf), red or bruised skin, and warmth in the swollen area.

- Nosebleeds (Epistaxis). Minor nosebleeds may occur, often related to elevated blood pressure or the effects of Avastin on blood vessels. These usually stop on their own but should be monitored, especially blood pressure.

- Proteinuria. An increase in protein excretion in the urine, indicating possible kidney stress, is seen in about 25% of patients but is generally not clinically significant.

- Joint (arthralgia) and Muscle (myalgia) Pain. About one-third of patients may experience joint or muscle pain, which can sometimes require medical treatment or discontinuation of the drug. Pain usually begins after several cycles of treatment and can persist for months after stopping the drug. Standard painkillers, anti-inflammatory drugs, or low-impact exercises can help manage these symptoms.

Rare but serious side effects of Avastin® include:

- Gastrointestinal (GI) Perforation. A hole or ulcer may develop in the stomach or intestine. This is more common in patients taking steroids, those who are older, or those with a history of inflammatory bowel disease or gastrointestinal problems. Posterior Reversible Encephalopathy Syndrome (PRES). A rare but serious neurological disorder marked by brain swelling, seizures, confusion, and vision loss.

- Serious Bleeding (Hemorrhage). Major, life-threatening bleeding in the brain (intracranial hemorrhage) is rare (about 1%) and typically occurs in patients with residual or recurrent brain tumors or after surgery, especially in highly vascular tumors. Hypertension or concurrent anticoagulation can increase the risk.

- Serious Headaches. Severe headaches can occur in about half of patients. While headaches are common with brain tumors, a new, excruciating headache during Avastin treatment could be related to infusion reactions, hypertension, or rarely, PRES. Persistent headaches should be promptly evaluated to rule out serious complications like intracranial bleeding.

Please call your doctor's office right away (even after hours) if you suspect any GI perforation or deep vein clot, especially if your symptoms appear suddenly. Call 911 if you experience coughing up blood, shortness of breath, pain when breathing, sharp chest pain, rapid heart rate, or serious lightheadedness.





Focused Ultrasound (FUS)

Focused ultrasound (FUS) is a developing, minimal invasive cancer treatment that aims to kill cancer cells with high frequency sound waves. FUS was first used in the treatment of brain tumors during the late 1960s and early 1970s, but it was not until the advancement of adjacent technologies (e.g., MRI guidance systems and robotic manipulators) did researchers return to FUS to further explore its clinical applications, including as a treatment for GBMs (as further described below) and as an alternative to stereotactic radiosurgery (SRS) for brain metastasis.

Recently, FUS is being practiced on other cancers and the results to date are encouraging. When FUS is turned on a solid tumor within the body, the cancer cells die and turn to foam, but the healthy cells are not impacted.

In the case of brain cancer, researchers are attempting to use FUS in a few new ways such as to open the blood-brain barrier (BBB) temporarily and reversibly in GBM patients who are undergoing standard chemo treatment to see if doing so will improve the effectiveness of the chemo treatment. The BBB is a protective layer of tightly joined cells that lines the blood vessels of the brain to prevent harmful substances from getting into brain tissues. However, this barrier can also prevent therapeutic agents like chemos from getting into the brain. Currently, FUS is available only by clinical trial.

Pivotal Clinical Trial Evidence in FUS for Glioblastoma

A recent pivotal trial (BTN009NA, NCT03551249) has yielded promising results that support the advancement of focused ultrasound (FUS) for the treatment of newly diagnosed glioblastoma. In this multicenter Phase I/II clinical trial,

researchers targeted high-grade gliomas (HGG) using the 2016 diagnostic criteria for glioblastoma multiforme (GBM). The study employed microbubble (MB)-enhanced transcranial FUS in combination with temozolomide (TMZ) chemotherapy. The results demonstrated a median overall survival (OS) of 31.3 months, which is notably superior compared to an external, matched control group that had a median OS of 13.5 months.

Importantly, the trial also assessed enriched plasma biomarkers, specifically cell-free DNA (cf-DNA). These biomarkers showed a close correlation with both progression-free survival and overall survival, indicating that sono-liquid biomarker analytics could potentially serve as a tool for longitudinal, non-invasive monitoring of disease status. Building on these findings, a larger Phase 3 trial is planned to further evaluate the efficacy and safety of this approach.

Additionally, a follow-up pivotal trial of sono-liquid biopsy (LIBERATE/NCT05383872) is being planned. This trial will investigate the concordance between molecular findings in plasma cell-free DNA following MB-FUS and those found in resected tumor tissues in patients with high-grade glioma. The outcomes of these studies may serve as the impetus for further clinical trials targeting high-grade gliomas with adjuvant chemotherapy, including agents previously considered to have limited brain penetration.

Potential Roles of FUS in Brain Tumor Management

Taken together, there are currently four potential roles for FUS in the management of brain tumors:

- **Blood-Brain Barrier (BBB) Opening:** Low-intensity FUS, used with microbubbles, can transiently open the BBB. This allows for up to 5.9 times higher concentrations of drugs such as temozolomide or carboplatin to reach tumor tissue.

- **Thermal Ablation:** Similar to Laser Interstitial Thermal Therapy (LITT), high-intensity focused ultrasound (HIFU) can be used to directly destroy tumor tissue through heat. This is especially relevant for deep-seated brain tumors or tumors in locations that are difficult or risky to access with standard surgical techniques.

- **Immune Modulation of the Tumor Microenvironment (TME):** FUS may "prime" the TME by releasing neoantigens from destroyed tumor cells, potentially enhancing the effectiveness of immunotherapies such as dendritic cell vaccines, CAR-T cell therapy, cytokine reprogramming, or anti-CD47 antibodies.

- **Non-Invasive "Sonobiopsy":** By disrupting the BBB and destroying tumor cells, FUS releases circulating tumor DNA (ct-DNA) into the bloodstream. This enables real-time monitoring of tumor progression or response to therapy without additional surgery. A specific, sensitive, reproducible, cost-effective, and clinically relevant biomarker is considered a "holy grail" in neuro-oncology, as it would support adaptive and dynamic clinical trials with actionable "stop" and "go" decisions based on liquid biopsy results.

Although numerous MRI technologies play a crucial role in clinical decisions regarding tumor progression or pseudoprogression, distinguishing between these states remains a challenging aspect of neuro-oncology.

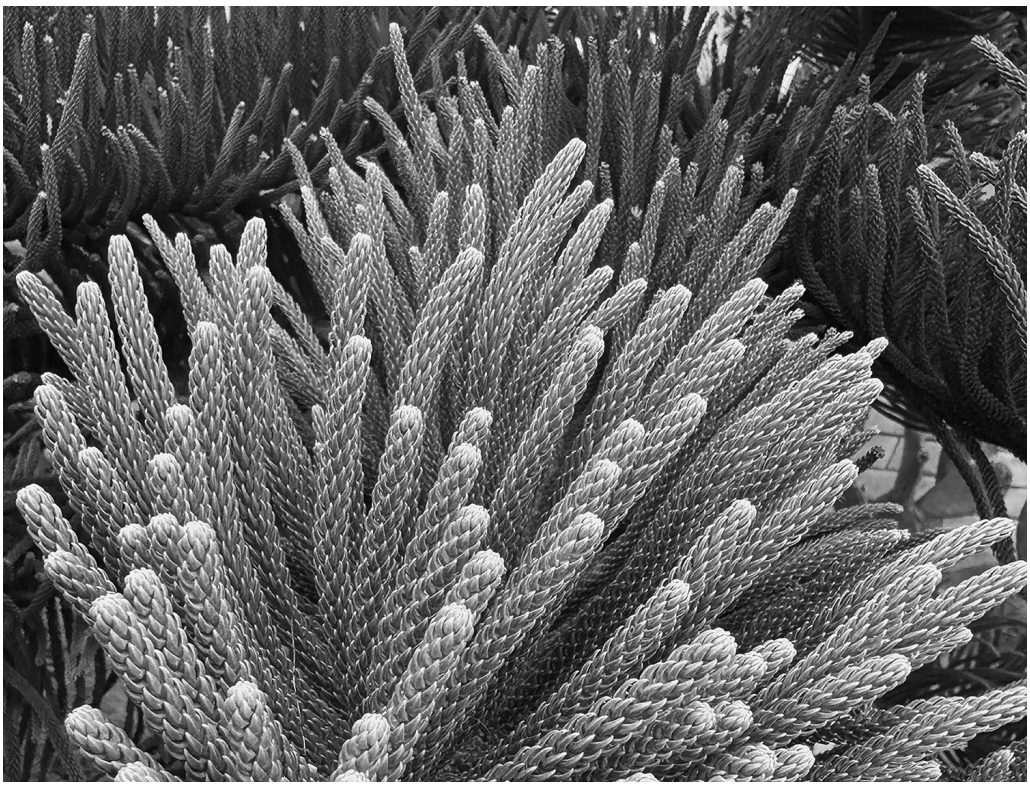


Photo Credit Stuart Volkow





Thirteen

Medications For Symptom Management

In the treatment of brain tumors, not unlike the treatment of any other acute or chronic illness, a variety of medications are used to combat symptoms, such as pain, fatigue, swelling, and seizures. The medications may include antibiotics, steroids, analgesics or narcotics, and anticonvulsants. It is necessary to take responsibility for your medications to ensure your safety. As your medical team will be made up of physicians from various specialties, all of whom may prescribe different medications or alter dosages in the context of your care, it is vital that you keep ongoing and accurate (up to date) records in your treatment binder and on your phone regarding your medications, including:

- Medications you are currently taking (including dosages) and who is responsible for monitoring you (prescribing physician) or providing refills. This information can be very helpful to any caregiver seeking information or assistance on your behalf.

- Medications you have taken in the past, noting their value (e.g., "was most helpful for sleep").

- Medications discontinued due to negative side effects.

- Any allergic or adverse reactions, mild or otherwise, noted in RED.

You should always:

- Ask your doctors to review your list of current medications prior to prescribing something new.

- Check to ensure that the recommended drug is covered on your insurance plan's drug formulary, or if you'll need a prior authorization.

- To avoid receiving the wrong medication at the pharmacy, write down the specific medication and dosage as stated on your prescription before submitting it to a pharmacist and compare this information to the label on the bottle you receive to ensure it is the same drug as stated on the prescription.

- Your prescription might be filled with a generic substitution if your doctor did not prescribe it to be "dispensed as written." If the medication you receive is different from what was written on the original prescription by your physician, ask the pharmacist. Also ask the pharmacist for his/her thoughts on the generic. Most generic drugs are okay to use, but for some drugs that have a very narrow effectiveness range, such as anti-seizure drugs, it may be worthwhile to pay the extra for the brand name or insist on the same brand of generic each time.

Whenever possible, having all your prescriptions filled through a single pharmacy source can be an additional safeguard against medical errors, preventing adverse drug interactions, as most pharmacies now use computer systems that automatically flag dangerous interactions based upon your previous medications. Should your physician fail to recall a particular medication that might present a problem, chances are your pharmacist will catch it. Still, asking your physician(s) to review your medication sheet in your treatment binder — each and every time a new drug is prescribed — is an important, potentially life-saving step.

It is important that you understand the side effects and drug interactions of all the medications you are prescribed. Most of the drugs we use have very scary package inserts and list every side effect ever reported to happen in people who were taking the drugs — whether the drug caused it or not. Our point is to be aware of the most common side effects and watch for them, not to be scared away from using the drugs.

Additional information regarding your medications and drug interactions can be found at websites like Drugs.com (www.drugs.com).

Common Medications

The following is a general description of medications commonly used to treat symptoms and/or conditions caused by a brain tumor itself or resulting from surgery and/or other standardized treatments of brain tumors. Many of the significant/ common side effects associated with a particular medication are noted, but the list may be incomplete. Your physician may recommend medications not covered within this general guide. You are advised to thoroughly discuss and understand all the benefits and side effects with your physician before a prescription is issued. Medicine is dynamic and there are new medications appearing all the time for symptoms of patients with brain tumors. Your physician may have a favorite regiment, but physicians keep an open mind to progress, so don't be afraid to ask your physician about alternatives.

Always ask your doctor before taking anything, even over-the-counter pain medications.

Medications for Heartburn/Acid Reflux

A good example demonstrating why your doctor must be consulted before taking ANY medication is the situation with over-the-counter medications for treating heartburn or acid reflux, which are referred to as a Proton Pump Inhibitor (PPI). The best-known PPIs are Prilosec, Prevacid, Protonix, Dexilant, Nexium and Acidphex, but there are others.

Researchers have been surprised recently to find that PPIs (particularly omeprazole and pantoprazole) significantly increase the production of a certain enzyme called ALDH1A1. A vast number of reports from other studies demonstrates that ALDH1A1 is a contributor to cancer therapy resistance and is associated with poor prognosis across a variety of human cancers.

When this surprising finding appeared, some researchers recommended an immediate change in the clinical practice of routinely prescribing PPI's for neuro-

oncology patients. It turns out that among other activities both good and bad, when it comes to brain cancer treatment, some of the data suggests that PPIs contribute to supporting tumor regrowth and recurrences of GBM.

A meta-analysis of five prospective clinical trials with approximately 3,000 patients confirmed that the use of potent ALDH1A1-activating PPIs (e.g., omeprazole-Prilosec; pantoprazole- Protonix, etc.) led to inferior outcomes in patients with glioblastoma, including worse PFS and OS. These patients had a higher risk of death, even when accounting for other risk factors such as age, steroid use, gender, and MGMT promoter methylation status. Indeed, a separate study using the XCELSIOR nationwide cancer registry found a negative impact in survival especially pronounced in patients with MGMT-methylated tumors - exactly the group that typically benefits from standard chemotherapy (temozolomide). Importantly, these negative associations were not found with other types of antacids (e.g., H2 blocker or locally acting antacids).

Because of these findings, prevailing advice is to limit the use of potent ALDH1A1-activating PPIs in patients with glioblastoma. While PPIs are often prescribed to prevent gastric complications caused by steroids in the context of brain edema, alternative agents are available that do not appear to carry the same risk. It is important that you first discuss with your doctor the appropriateness of taking PPIs, as well as ANY over the counter medication, vitamin, herb, or supplement.

Medications For Pain Relief

Because the brain itself does not feel pain, studies show that physicians treating patients for brain tumors often overlook pain. However, pain as a by-product of disease or due to complications from surgery or other forms of treatment is very real and deserves real attention. Headaches from brain inflammation or tension, scalp sutures, muscular pain, and hairline fractures due to steroid therapy, and pressure points on arms and hips from extended bed rest require medication. Pain left untreated can slow healing, deplete emotional reserves, exacerbate depression, and sleep deprivation, and detract from your quality of life.

Mild pain. The lowest level of pain can usually be managed with Tylenol (acetaminophen), Advil (ibuprofen), or Aleve (naproxen). Note that aspirin can affect

how fast your blood clots, which may be bad or good. Always ask your doctor about it first.

Moderate pain. More powerful prescription medication, such as Percocet (the combination of oxycodone and acetaminophen) and Percodan (the combination of oxycodone and aspirin), can be taken as directed by a physician.

Severe pain. Codeine, Vicodin (the combination of hydrocodone and acetaminophen), oxycodone, and stronger, morphine-type medications are typically long acting and are taken less frequently. Many also come in "patch" form for slow absorption and continuous relief. Ritalin (methylphenidate) is used to treat attention-deficit hyperactivity disorder (ADHD). If taken in small doses with pain medication, Ritalin can increase the narcotic effect (enhancing pain relief) while reducing the drowsiness commonly associated with these drugs. Ritalin has also been shown to benefit patients who suffer from fatigue. According to package inserts for drugs that contain morphine, such drugs should not be used in patients with brain tumors. The reason is that they can hide symptoms. However, they are still commonly used, and the benefits may outweigh the risks when you are in severe pain. Discuss any concerns you might have with your physician.

Medications For Swelling

Steroids are powerful anti-inflammatory drugs typically prescribed to reduce swelling in the brain (cerebral edema) before and/or after surgery, during radiation treatments, or to relieve symptoms such as memory loss and limb (arm/leg) weakness caused by brain swelling. While common, swelling can be harmful if excessive and must be controlled.

Synthetic steroids such as Decadron and Hexadrol (dexamethasone) are man-made hormones similar to cortisol, which is produced naturally by your body. Taken orally, these steroids create higher levels in the body than what is normally secreted, reducing inflammation but also causing the body to temporarily stop natural production on its own. For this reason, it is very important to "wean" yourself (cut back slowly) when stopping oral steroid therapy. Always follow your physician's recommended schedule for reducing dosages. During this reduction period, your body will slowly come back "online" and begin to produce normal cortisol levels again.

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 adrenal crisis which is a rare but fatal reaction to a lack of steroid in your body.

While the benefits of steroids are undeniable, often unmatched by any other medication, they are not without short and long-term side effects.

Long-term side effects can include (but are not limited to) diabetes, muscle pain/weakness, osteoporosis (bone loss) leading to fractures, and susceptibility to infections. Short-term effects can include (but are not limited to) increased appetite, weight gain, and indigestion; swollen or "moon-faced" appearance; stretch marks, rash/flushing of skin, and acne; increase in blood sugar; brittle bones; depression and/or behavioral changes; anxiety and/or paranoia; and suppressed immune system.

Other oral steroidal therapies include prednisone or prednisolone. While not as strong as Decadron or Hexadrol, side effects are generally the same, although perhaps not as severe in most cases. There are nonsteroidal medications that can help with swelling, such as Avastin (bevacizumab).

Medications For Reducing Seizures

Roughly 30 to 40 percent of patients will experience some level of seizure activity and require medication to reduce electrical responses in the brain. Due to the location and/or size of some tumors, many neurosurgeons will prescribe anti-seizure medication as a matter of routine before, during, and/or after surgery when the risk of seizure is considered high. In the past, all brain tumor patients were put on anti-seizure medications routinely for life, but since they can have a lot of side effects, many doctors now try to do without these drugs until seizures occur.

Recent research has highlighted a significant overlap in the pathogenic pathways of seizures and gliomas, suggesting that these two conditions may not only share underlying mechanisms but may also influence each other's development and progression. One of the central explanations for the close association between glioma growth and seizure activity centers on the presence of elevated glutamate levels within the tumor microenvironment (TME). This increase in glutamate is

attributed to enhanced expression of the cystine-glutamate transporter, which leads to excessive glutamatergic signaling in affected tissues.

The surplus of glutamate in the TME has several important consequences. Not only does it contribute to the abnormal electrical activity associated with seizures, but it also promotes the polarization of tumor-associated macrophages. This polarization results in a state of immunosuppression within the TME, ultimately supporting tumor invasion and progression. With the recent discovery of the glutamatergic neuroglioma synapses, glutamate has emerged as a promising target for therapeutic intervention. Targeting glutamate signaling presents an opportunity to address both seizure control and the management of glioma growth, providing hope for improved outcomes in affected patients.

There are 20+ antiseizure medications available; the list below highlights commonly prescribed options for adults, but this is not an exhaustive list.

First-Line & Broad-Use Medications for Adults

These are often used as first choices or for many seizure types:

Levetiracetam (Keppra)– widely prescribed for partial-onset, generalized tonic-clonic, and myoclonic seizures. Probably the most prescribed anti-seizure. The reasons this drug is often prescribed is because it inhibits malignant glioma cell proliferation and increases glioma cell sensitivity to the chemo Temodar and does not interfere with chemos. This benefit is maximized in patients whose tumors are methylated. (For a full discussion of methylation, please see the section entitled " Key Genetic Markers That Enable and Stimulate Tumor Growth" above.) Keppra is generally safe, effective, and well-tolerated; however, it can cause fatigue, moodiness, and even heightened irritability / anger in some people.

Lamotrigine (Lamictal)– effective for focal and generalized seizures; often a preferred choice due to a favorable long-term safety profile in many patients. This is the antiseizure drug that pregnant women will take; however, can cause rashes in some people.

Valproic Acid / Divalproex sodium (Depakote)– broad-spectrum medication effective for multiple types including generalized seizures, though not suitable for all (especially pregnancy). Commonly prescribed for focal seizures and require periodic blood levels to ensure adequate dosage and guard against liver damage. Because Depakote interacts with many medications, make sure your physician reviews your current medication list, including over the counter and herbal supplements, at the time of recommendation.

Topiramate (Topamax)– another broad-spectrum option used for focal and generalized seizures. Unlike many seizure drugs that target a single pathway, Topamax stabilizes brain activity through four primary methods: a) sodium channel blockage; b) GABA enhancement- increasing the activity of gamma-aminobutyric acid (GABA), the brain's primary "calming" neurotransmitter; c) glutamate antagonism—it blocks glutamate receptors (AMPA/kainite), which otherwise stimulate nerve signaling. Given the importance of glutamate in glioma progression, it may theoretically have anti-tumor effects; and d) carbonic anhydrase inhibition- it weakly inhibits this enzyme, which could further dampen electrical activity in the brain. Topamax may cause language ("word-finding") and memory difficulties. Topamax is effective against several different types of seizures in both adults and children age 2 and older, including focal (partial onset) seizures; primary generalized tonic-clonic seizures ("grand mal" seizures), and a rare childhood-onset epilepsy, the Lennox- Gastaut Syndrome. Of note, those patients that experience too much moodiness on Keppra often turn to Topamax.

Other Frequently Used Antiseizure Drugs

Depending on seizure type and patient needs:

Carbamazepine (Tegretol)– often used for focal seizures. Some with repetitive seizures use this one with reasonable success. Tegretol (carbamazepine) is an anticonvulsant that is also prescribed in the treatment of manic depression and other psychiatric disorders. Effective in its ability to control grand mal seizures, Tegretol must be monitored closely with frequent

blood-level measurements, since in rare cases it may suppress bone marrow production. You should report any onset of a rash to your physician immediately. Tegretol also reduces or increases the effects of many medications. Double vision, pounding or slow heart rate, and nausea are noted side effects with this drug.

Oxcarbazepine (Trileptal)– similar use to carbamazepine; sometimes better tolerated. Sometimes the doctor will add Trileptal to another drug, like Keppra.

Lacosamide (Vimpat)– used in focal seizures as monotherapy or add-on. Like most anti-seizures, it may cause dizziness, double vision, nausea when first starting, but after a while, these symptoms should lift. Often used in combination with Lamictal.

Gabapentin (Neurontin) and Pregabalin (Lyrica)– can be used (often as adjunct therapy) especially in focal seizures, though gabapentin is now commonly prescribed for many off-label uses as well. Recent evidence suggests that gabapentin, in addition to seizure control, could provide a survival benefit in patients with glioblastoma by disrupting the "conversation" between neurons and tumor cells. A retrospective study of over 1,000 patients at Mass General Brigham and UCSF found that patients taking gabapentin lived an average of 4 to 6 months longer than those who did not. Preclinical studies in mouse models show that gabapentin limits the growth of human glioblastomas. A possible mechanism in patients is that gabapentin inhibits neuronal hyperactivity, as gliomas "hijack" brain network, creating a feedback loop where cancer cells stimulate nearby neurons to become hyperactive. The primary driver of this interaction is a protein called TSP-1 (thrombospondin-1) which helps tumors form synaptic connections with health neurons; gabapentin acts a TSP-1 antagonist. Patients treated with gabapentin show significantly lower levels of serum TSP-1, suggesting that the drug successfully blocks this target in patients. A prospective clinical trial, GLUGLIO (NCT05664464), is an ongoing randomized trial to explore the use of gabapentin as part of a triple-drug combination (gabapentin, memantine, and sulfasalazine) to target these glutamatergic pathways.

Older or Less Commonly Used Agents

Used in specific scenarios or when other drugs aren't effective:

Phenytoin (Dilantin)– older drug still used, especially in emergency settings or specific seizure types. This is one of the longest used standard drugs for those with epilepsy/seizures. Phenytoin, otherwise known as Dilantin, is a commonly used medication to prevent full-body seizures in high-risk patients. People metabolize Dilantin differently, so periodic blood levels are taken to ensure that dosages are adequate and stable. Side effects of Dilantin include muscle fatigue, dizziness, and loss of coordination, as well as tooth decay and gum problems. Regular dental checkups and extra attention to oral hygiene are advised. Long-term use of Dilantin can cause a decrease in certain nutrients, such as folic acid and calcium. Ask your physician about supplements if necessary. Dilantin can also interact with other medications, including over-the-counter drugs, birth control pills, and herbal supplements. Dilantin can also make some chemotherapy drugs less effective. Because phenytoin increases the production and activity of liver enzymes like Cytochrome P450 (CYP450) and the CYP3A4 isoenzyme, this drug activates the liver's metabolic machinery, which causes the liver to break down and clear chemotherapy much quicker. A faster metabolism leads to significantly lower levels of chemotherapy in the bloodstream. For example, phenytoin can decrease plasma levels of etoposide by up to 50%. When drug levels drop below a 'therapeutic window', the chemotherapy may be rendered useless, failing to control tumor growth, and potentially leading to disease progression or reduced survival.

Phenobarbital– effective but less used due to sedation and side effects. This is a barbiturate and strong depressant and is less frequently prescribed, as the effectiveness of other anticonvulsants can be more easily achieved without the potentially addictive qualities of these drugs. Phenobarbital is the oldest anti-seizure medication and still is in common use today to control various types of seizures and provide sedation. It is known to cause drowsiness and may be used before medical procedures. It is primarily in use for generalized tonic-clonic ('grand mal') seizures or focal seizures. It is a first-line treatment for neonatal seizures.

Clobazam / Clonazepam– benzodiazepines sometimes used as add-on or for specific epilepsy syndromes.

For more information about seizures, please see the section in this Guidebook entitled "Seizures" under "Side Effects."

Medications For Reducing Nausea

Nausea is common with brain tumors, as both a part of the disease process itself and as a by-product of radiation and chemotherapy treatment. The most commonly prescribed medications for reducing nausea are:

Zofran (Ondansetron) is used to control nausea caused by chemotherapy or radiation. It is usually administered intravenously prior to treatment and can be taken orally after treatment, if necessary. Effective for only a few hours, Zofran is limited to nausea caused by chemotherapy and radiation only and is not to be taken for motion sickness or other generalized conditions related to nausea. While mild in nature, side effects of Zofran include headache, fatigue, diarrhea, and constipation, and the drug may exacerbate pre-existing liver disease.

Kytril (Granisetron) is similar to Zofran in both treatment administration and side effects, although it may also cause abdominal pain. It lasts up to 12 hours. Granisetron is also available in a patch (called Sancuso). Using a patch formulation of nausea medication may be a good option if you cannot swallow due to nausea or vomiting.

Compazine (prochlorperazine) is a commonly prescribed medication for the treatment of generalized nausea and is given orally, intravenously, or as a suppository. Compazine belongs to a family of antipsychotic agents called "phenothiazines" and may cause drowsiness, low blood pressure, dizziness, constipation, dry mouth, blurred vision, and sensitivity to light. While effective in the management of nausea, Compazine should not be used in conjunction with alcohol, may interact with other medications, and could potentially cause an irreversible condition called tardive dyskinesia — involuntary movements or twitches of the face, tongue, or arm muscles.

Haldol (Haloperidol) is another antipsychotic medication that is used to control nausea and has risks and side effects similar to those of Compazine. Haldol and Compazine should not be taken without a detailed discussion with your physician.

Transderm Scop contains the seasickness drug scopamine, which can sometimes be used for nausea. Transderm Scop is a patch formulation of the drug that is applied to the skin and works for 3 days per patch. A main side effect is dry mouth, which can be a benefit when there is difficulty swallowing and too much saliva is being produced.

There are also many alternative treatments. Some patients report that acupuncture, biofeedback, and hypnosis provide nausea relief with no side effects and are much cheaper than most commonly used drugs.

Medications For Improving Mood

Being diagnosed with a brain tumor alone is enough to create overwhelming anxiety and stress. It is important to understand that during the course of treatment, intense and seemingly "over-emotional" reactions — such as acute

Photo Credit Linda Singer



depression, sexual dysfunction, sudden outbursts, and visual or audio hallucination — may be the result of medication or a condition stemming from the tumor itself, not necessarily an emotional response. It is also important to communicate about these emotional changes with your medical team in order to seek proper assistance and guidance to help you distinguish the many moods of treatment and recovery, and to help you cope.

A psychiatrist is a medical doctor who can assist with the mood-related conditions directly caused by the tumor or its treatment. Psychologists can also provide help with coping difficulties and with mild depression due to issues of long-term care, financial strain, or the stress placed upon family and other important relationships. Ask your medical team to refer you to a psychiatrist or psychologist experienced in treating brain tumor patients.

Herbal remedies may be of some benefit. However, herbal mixtures can adversely interact with other prescription medications and should always be discussed with your medical team for safety and adequate dosing information. If you are thinking of taking hypericin, one of the principal active compounds of St. John's wort, make sure to ask your medical team first, for hypericin can interfere with other drugs.

Medications For Reducing The Formation Of Blood Clots

Brain tumor patients are at a higher-than-normal risk for developing dangerous blood clots. Blood clots commonly start in the legs as deep vein thrombosis (DVT). Symptoms of DVT may include pain, tenderness, swelling, discoloration of the affected leg, and skin that is warm to the touch. If you develop these symptoms, you must call your doctor and get it checked quickly. Left untreated, blood clots can break away and travel to the lungs where they may cause a pulmonary embolism, which can be rapidly fatal. Symptoms of a pulmonary embolism include sudden shortness of breath, chest pain (worse with breathing), and rapid heart and respiratory rates. If you develop any of these symptoms, you must go to the emergency room immediately.

Medications called anticoagulants help to thin the blood and reduce clotting, the body's normal response to help stop bleeding. Heparin is an anticoagulant that is given by injection, usually for a short period of time to prevent or treat blood clots. Warfarin (commonly referred to as coumadin) is an oral medication that can be

taken over a long period of time to prevent blood clots. Warfarin can have many drug interactions and requires monitoring of blood levels. Another class of oral anticoagulant that may be used are called DOACs (Direct Acting Oral Anticoagulant.)

Medications in this class of DOACs include: apixaban (Eliquis), rivaroxaban (Xarelto) and edoxaban (Savaysa). A study showed that DOACs were safer compared to low-molecular weight heparin (LMWH) in terms of a much-reduced risk of intracranial hemorrhage (brain bleeds) in patients with glioblastoma. Aspirin also reduces the risk of blood clots, but it does not actually make the blood "thinner". Rather, it inhibits a molecule, thromboxane, a chemical that causes platelets to clump together; therefore, aspirin makes the blood less 'sticky' and less likely to form dangerous clots.

Plavix (clopidogrel) is another antiplatelet drug, but much more powerful than aspirin. Patients with glioblastoma who undergo neurosurgical procedures should discontinue aspirin or Plavix about one week before surgery to minimize the risk of serious bleeding in the brain. Plavix may be prescribed by a physician in a patient with a recent heart attack to minimize the risk of a second cardiac event, but the risks of a brain bleed need to be carefully balanced with the potential cardiac benefit.

When you are taking anticoagulants, normal cuts and scrapes may take longer to stop bleeding or heal, and there is an increased risk of the tumor bleeding into the brain — so these drugs are double-edged swords and should be taken exactly as prescribed. Warfarin interacts with many medications and should be discussed thoroughly with your medical team before treatment. Your doctor will also order periodic blood tests to ensure that appropriate medication levels are maintained.

It is important to note that changes to your diet can have a negative effect on the blood-thinning measures of anticoagulant medication. Suddenly increasing foods such as spinach in your diet can adversely affect bleeding times. The sudden introduction of fish-oil capsules as a dietary supplement, which are full of omega-3 fatty acids, can also alter bleeding times. While there is no need to eliminate spinach and other healthy items (including supplements) from your daily routine, you are advised to maintain your normal diet and not increase or decrease items significantly or add new supplements without discussing them with your physician. This

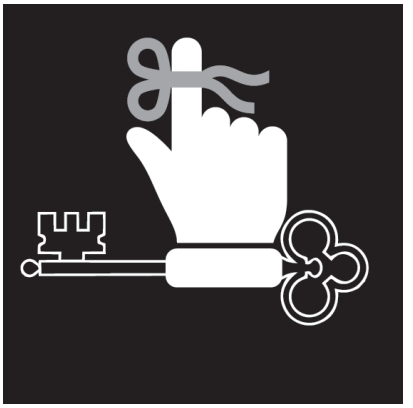
is not the time to begin a new diet for weight loss without consulting your physician.

It is always a good idea to wear a medical alert bracelet informing medical personnel that you are taking anticoagulants in the case of an emergency. They are widely available in most retail pharmacies and on the Internet, inexpensive, and an important safeguard for your health.

Of course, you should take your medicines as directed, not changing the frequency or dosage without talking to your doctor. If you need help with co-payments for drugs, please go to needymeds.org and look up each drug you take. If you cannot afford a drug, don't stop taking it. Instead, speak to your doctor about a less expensive alternative.

To get additional information about any medication, go to the drug information site Medline Plus: https://medlineplus.gov/druginformation.html. Medline Plus is provided as a service of the US National Library of Medicine. On this website, drugs can be looked up by their brand or generic names.

KEY TAKEAWAYS TO REMEMBER



Always follow your doctor's instructions when decreasing your dosage of any medication, especially steroids.

Always check with your doctor before taking any over-the-counter medications.

Because your medical team will be made up of doctors of different specialties, it is vital that you take responsibility for keeping an ongoing and accurate record of the medications you are taking, including their dosage and the names of the physicians who prescribed them.

Always ask your medical team to review your complete list of medications before they prescribe anything new.

If possible, always fill your prescriptions at the same pharmacy to safeguard against medical errors and adverse drug interactions.

Make yourself knowledgeable about the most common possible side effects and drug interactions of the medications you are taking.



Fourteen

Clinical Trials

Importance of Clinical Trials

Clinical trials offer experimental treatments that may provide new inroads for extending life expectancy and improving quality of life. Understanding the current availability of clinical trials requires time and due diligence. Each brain cancer center will have its own clinical trial offerings; what is available at center may not be available at another. We hate to say this, but some doctors are reluctant to refer you to other treatment centers. You must search out for yourself the appropriate clinical trials available for your specific tumor type, always advocating in your own best interests toward a cure. A clinical trial is the best way of trying experimental therapies because the doctors will watch you very carefully for signs of side effects.

There are other ways to gain access to an experimental treatment in the United States. That is the Right to Try law and expanded access program, which allows terminally ill patients access to experimental drugs and devices. The Right to Try law and expanded access program are discussed below.

People in clinical trials seem to do better than people who choose not to participate. Even if the drug or other agent ultimately proves to be ineffective, merely by being in a clinical trial, there is evidence that survival is increased, possibly due to the added intensity, observation, and monitoring to improve the overall medical care, and detect complications early. This is why the NCCN guidelines for patients with brain tumors recommend a clinical trial whenever possible. Furthermore, a clinical trial represents "tomorrow's medicines, today!" And once a cure is actually found, the first people to get it will be those in the clinical trial for it. Cures have been found for other types of cancer, and we all hope it will happen for brain tumors, someday soon.

Understanding Clinical Trials

Clinical trials have a designation — phase I, phase II, or phase III — that is based upon the specific types of questions that are being asked about the treatments in question. These clinical trial phase designations are defined by the US Federal Drug Administration (FDA) and published in the Code of Federal Regulations. A summary of the definitions follows. For the most current, full definitions, please go to this site:

https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-312/subpart-B/section-312.21

In a phase 0 trial, also referred to as Early Phase I. This phase differs significantly from other phases of clinical trials as it is not a required part of testing for a new drug. However, the purpose of this phase is to expedite the drug approval process. Phase 0 studies use only a small dose of the new drug in fewer than 15 patients over a short period of time. The goal is to determine if the new drug or agent behaves in human subjects as is expected based on preclinical studies. In Phase 0 clinical trials, researchers gather data to see if the drug reaches the intended target tissue and how it interacts with the body or tumor, providing "proof of concept" before large-scale trials are initiated

In a phase I trial, a new drug or treatment is studied in a small group of people (20 to 80 patients or volunteers) for the first time to evaluate its safety, determine a safe dosage range and identify potential side effects.

In a phase II trial, the study drug or treatment is given to a larger group of people (100 to 300 patients) and further assessed for effectiveness and safety. The dosage of medication may be increased to determine toxicity levels.

In a phase III trial, the study drug or treatment is given to large groups of people (300 to 3000 patients) to confirm its effectiveness within a sizable population, monitor side effects and toxicity levels, compare it with standard treatments, and further determine safety.

Statistics are used to try to make sense of the trial results. A number is calculated called the significance level. The number usually chosen as the benchmark is 0.05, which means that there is a 95% chance that the effect seen in the trial was caused by the treatment and not by chance alone. Conversely, this means that if you run 100 trials of a worthless drug, about 5 of those trials may report success even though there is none. This is why multiple trials are needed, and it is best if they are conducted by different centers.

The FDA will approve a drug that is better than standard treatment, or is at least as good as standard treatment, if it has fewer side effects. Once a treatment is approved by the FDA, everyone can get access to it, not just those in clinical trials.

Why Should You Consider Participating In A Clinical Trial?

Clinical trials provide access to some of the newest and most promising treatments for diseases that have no cure. In many cases, these trials, guided by experts, may represent your best possible chance for survival or for a better quality of life. By participating in a clinical trial, you help researchers take one small step, or even a giant leap, closer to a cure. Aside from helping yourself, your experiences can support advances in the state of the art in the field, leading to improved treatments for others in the future.

Earlier (under the "Treatment Overview" section), this Guidebook discussed the brain cancer guidelines developed by the National Comprehensive Cancer Network (NCCN), the not-for-profit alliance of 33 leading cancer centers. For every patient category in the NCCN guidelines, enrollment in a clinical trial is recommended for those who are eligible.

Another advantage to enrolling in a clinical trial is the cost. Brain tumor treatments are very expensive. In general, the experimental treatment used in a clinical trial is free to you. There may, however, be charges for associated costs of treatment — such as surgery, doctor's consultations and visits, MRI scans, and blood tests — so, ask about costs and what your insurance will pay and what your out-of-pocket expenses will be. If you have no insurance, there may be clinical trials available that cover all the costs.

When Should You Consider A Clinical Trial?

The decision of when to participate in a clinical trial should be discussed with your medical team. Some patients and physicians feel more comfortable exhausting possibilities with the standard-of-care treatment first. Others choose right away to participate in trials from the onset of diagnosis. You may wish to discuss certain points of progress (or lack of progress) with your medical team as a guideline to help you with your decision. Obviously, if you have a low-grade tumor for which good treatments are available, you will be less likely to try something experimental. If you have a high-grade malignant tumor and the expected outcome of the standard-of-care treatment is not acceptable to you, it is easier to make the decision to try something experimental.

Some clinical trials are conducted specifically for treatment of recurrent tumors rather than treatment of newly diagnosed tumors. Whether or not you decide to wait or move forward, it is important to research available trials early for your specific type of tumor and to know in advance if, or when, you might qualify. Be especially careful not to miss trial-entry deadlines. Some trials require that you sign up for them before surgery. Others require that you sign up before radiation therapy ends. One thing to keep in mind is to plan ahead and think through a large range of contingencies. Among those contingencies are the trial eligibility requirements and disqualifiers.

Each clinical trial has their own set of eligibility requirements that might include the age range of participants, location of the tumor, grade and/or type of tumor, the presence of specific molecular markers, or the requirement of a specific degree of stabilization as a trial enrollment criterion.

Clinical trials also have their own sets of disqualifiers which may include another form of treatment. In some cases, the trial coordinator may agree to a "washout period" - a period of time during which you do not take that certain other treatment before being enrolled in the trial. Both the eligibility requirements and the disqualifiers are included in the description of the clinical trial on the National Cancer Institute's website (see below for how to find trials).

In the old days, it was an easy decision. The standard-of-care treatment provided so little hope that you had nothing to lose by joining a trial. But the current standard-

of-care treatment has progressed to the point where you now have a difficult decision to make about when to enter a clinical trial, since the standard-of-care treatment does help some people for a long time and new trials with advanced treatments are opening up continuously.

How Do You Assess A Clinical Trial?

The best way to evaluate if a clinical trial is right for you is to speak with your primary physician, your neuro-oncologist or neurosurgeon, and other members of your medical team, including those to whom you have turned for second opinions. You might also contact one of the major brain tumor centers for additional insight into a specific clinical trial. You should also consult with the physician in charge of the trial. It is always helpful to know how earlier trials of the proposed treatment came out. Lastly, it is important to ask any physicians not in favor of your participation: Why not? What would they recommend instead, and why?

Although individual case results are meaningless statistically, the experiences of others may help give you enough information to choose between two treatments that are otherwise a toss-up. You can find these individual experiences in the online support groups, in real-world support groups, and in the results of the Brain Tumor Virtual Trial, a study run by the Musella Foundation (see below).

How Do You Find Clinical Trials?

You can find listings for clinical trials at the resources described below.

Musella Foundation Resources

At the virtualtrials.org website of the Musella Foundation, clinical trials can be located in two ways online. To access either method, go to: https://virtualtrials.org, then click on the box on the middle right that says, "Find Treatments!".

> Patient Navigation Program is the first option. As earlier described in detail in this Guidebook, this program uses the xCures platform which is loaded with all the currently available knowledge about brain cancer treatments and matches it to the details about your tumor to help you quickly find promising treatments. This service is provided at no charge.

Clinwiki is another option. Using a few details about your tumor that you key in to this online system, treatment options can be found.

The Musella Foundation can also be directly called at 1-888-295-4740.

National Cancer Institute

The National Cancer Institute is not specific to brain tumors, but it does maintain a powerful clinical-trials search engine. In addition to allowing you to search by cancer type, location, and other variables, it also allows you to search by the type of trial (that is, whether it is a phase I, phase II, or phase III trial). To access the National Cancer Institute clinical-trial search engine, go to: https://www.cancer.gov/about-cancer/treatment/clinical-trials/search.

Clinicaltrials.gov

Clinicaltrials.gov is the world's largest clinical trials database, currently holding registration from 572,000 trials conducted across all 50 U.S. states and in 225 countries and territories. You can search for trials by condition, intervention, sponsor, location, and type of trial. To access this resource, go to: https://www.clinicaltrials.gov.

DIPG/DMG Trials

For parents whose child has received a diagnosis of DIPG (Diffuse Intrinsic Pontine Glioma) or DMG (Diffuse Midline Glioma), a resource for comprehensive information about the latest clinical trials can be found at this link: https://dipg.org/dipg-treatment/active-clinical-trials/.

The Brain Tumor Virtual Trial

The Brain Tumor Virtual Trial is a registry managed and run by the Musella Foundation. The virtual trial consists of a database of brain tumor patients, the treatments they are using, and their outcomes. Participants record the treatments that they and their medical teams decide to pursue. The Musella Foundation does not tell participants what treatments to receive; we just record the outcomes. There is no cost to participate in the virtual trial. The patient or caregiver records information on

simple forms right on the virtualtrials.org website and posts an update each month. We send email reminders on the first of each month. The patient or caregiver also sends in copies of MRI reports (not the MRI films) and pathology reports so that information can be verified. Participants are able to view the ongoing results of the project.

The concept behind the Brain Tumor Virtual Trial is to identify which treatments, or which combinations of treatments, are working the best. In addition to providing greater insight for researchers about beneficial therapies in the real world, the virtual trial also supports participants in learning how to become expert managers of their own conditions. For example, participants can generate reports on the information they have entered, such as a graph of their status over time. For more information on the Brain Tumor Virtual Trial, please go to: https://virtualtrials.org/brain/index.cfm.



Photo Credit Stuart Volkow

Treatments, Trials and the Food and Drug Administration

When considering clinical trials, it is useful to understand the difference between approved and experimental treatments. In general, there are two general classes of treatment: (1) those approved by the US Food and Drug Administration (FDA) specifically for brain tumors on the basis of evidence from clinical trials; and (2) experimental treatments, sometimes with drugs approved by the FDA for other types of cancers or other diseases, and sometimes with drugs not yet approved at all by the FDA.

The virtualtrials.org website of the Musella Foundation has separate sections, each with extensive information, about several of the key brain tumor treatments. Be sure to visit each of the following sections for the latest updates about these treatments:

- **Immunotherapy:** https://virtualtrials.org/Immunotherapy_treatments.cfm
- **Optune device:** https://virtualtrials.org/optune
- **Temodar (temozolomide):** https://virtualtrials.org/temodar
- **DCVax:** https://virtualtrials.org/dcvax

FDA Approved Treatments for Brain Tumors

At the time of the issuance of this edition of the Guidebook, these are the FDA approved treatments for brain tumors. Treatments not on this list are repurposed/"off label" drugs (as described in the following) or treatments found in clinical trials.



Photo Credit Margo Singer

Name(s) of Drug/Treatment Approved	What is it Approved For?	FDA Approval Date	Comments
Afinitor/Everolimus	Subependymal giant cell astrocytoma	August 30, 2012	Approved for adults and children aged 1 year or older who have tuberous sclerosis and are not able to have surgery.
Belzutifan/Welireg	Brain/spinal cancers linked to Von-Hippel-Lindau disease including hemangioblastoma	August 13, 2021	
Bevacizumab/Avastin	Recurrent GBM	May 5, 2009	For use in adults. This use is approved for the Avastin, Zirabev, and Mvasi brands of Bevacizumab
BiCNU/BCNU/Carmustine (Non wafer form)	Approved for glioma patients, and most often used in low-grade gliomas and in recurrent GBM patients	March 1977	Carmustine is used in the treatment of certain types of brain tumors, including glioblastoma, brainstem glioma, medulloblastoma, astrocytoma, ependymoma, and metastatic brain tumors
Carmustine Implants/Gliadel Wafers (Wafer form)	Recurrent GBM and untreated malignant high-grade glioma	Sept.1996 for rGBM and 2003 for newly diagnosed high-grade gliomas	rGBM: Used with surgery; glioma: used with surgery and radiation therapy
Dordaviprone (Modeyso), originally known as ONC201	Adult and pediatric patients (age 1 and older) with H3K27M-mutant DMG who have experienced disease progression following therapy	August 6, 2025	Mechanism: small molecule that acts as a protease activator of mitochondrial ClpP and an antagonist of dopamine receptor D2 (DRD2)
Gleostine/Lomustine/CCNU (Originally marketed as CeeNu but rebranded Gleostine in 2014)	Recurrent (non-specified) brain tumors	August 5, 1976	For those who have already been treated with surgery or radiation; this is an orally active nitrosourea chemotherapeutic agent

Name(s) of Drug/Treatment Approved	What is it Approved For?	FDA Approval Date	Comments
Optune (formerly NovoTTF-100A System)/ Tumor Treatment Fields	Recurrent and newly diagnosed GBM	April 8, 2011 for rGBM; in 2015 approved for newly diagnosed GBM	For treatment for adult patients (22 years of age or older) with histologically confirmed GBM. The device is intended to be used as a monotherapy and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted.
PCV (P=Procarbazine Hydrochloride, C= Lomustine/CCNU, V= Vincristine Sulfate	Certain types of brain tumors	Combo approved in 2015	Often used with radiation therapy
Pembrolizumab/ Keytruda	For unresectable or metastatic solid tumors with high tumor mutational burden. (GBMs are generally low mutational burden when initially diagnosed but may change over time.)	June 16, 2020	For adult and pediatric patients
Temozolomide/ Temodar	Anaplastic astrocytoma and GBM	March 15, 2005	For Astrocytomas, approved for patients with refractory disease that got worse during therapy that included a nitrosourea and procarbazine hydrochloride. For GBMs, used with radiotherapy in patients with newly diagnosed disease and then alone as maintenance therapy
Vorasidenib: dual inhibitor of mutant IDH1 and IDH2 enzymes.	Adult and pediatric patients (12 years and older) with Grade 2 astrocytoma or oligodendroglioma that have a susceptible IDH1 or IDH2 mutation	August 6, 2024	Used following surgery (biopsy or resection) to delay the need for more aggressive treatments like chemotherapy and radiation

Repurposed / Off Label Drugs

Even if an FDA-approved drug is not approved specifically for "brain tumors," your medical team is still able to prescribe it for your brain tumor. When doctors prescribe a drug for a therapeutic purpose other than the one approved by the FDA, it is called "off-label" prescribing. Many drugs commonly used for brain tumors are prescribed off label. Although the use of these drugs by your medical team is legal, and the drugs are easily available, you might nonetheless have trouble getting your insurance company to pay for off-label usage of a drug because it will argue that such off-label treatment is experimental. In such cases, know that you can fight the insurance company's denial. You should enlist your neuro-oncologist to help get the drug approved by your insurance company.

The Right to Try law and Expanded Access Program

In 2018, the US Congress passed the Right to Try law, allowing terminally ill patients to try experimental therapies (drugs and devices) that have completed phase I FDA testing but have not yet been approved by the FDA. Before the federal law was



Photo Credit Margo Singer

approved, 41 states had passed Right to Try laws.

To be eligible for a right to try a drug that is not approved for any use, a patient must meet the following conditions: (1) be diagnosed with a life-threatening disease or condition; (2) have exhausted approved treatment options; (3) be unable to participate in a clinical trial involving the eligible investigational drug, as certified by a doctor; and (4) give written informed consent regarding the risks associated with taking the investigational treatment. To request a drug or device under the Right to Try law, the patient, the patient's representative, or the patient's physician has to send a letter to the director of compassionate use or to some other designated representative at the drug or device manufacturer to discuss options for access to the drug or device.

Please note that drug and device companies are not required to provide treatments to patients under Right to Try laws. Each company is responsible for developing its own processes and procedures for approving Right to Try requests. It is reasonable that companies should not be forced to provide treatments when they do not think the treatments are appropriate or when they have limited supplies of the treatments apart from their use in clinical trials. In addition, doctors who do not think that a treatment will be helpful have no obligation to request a Right to Try treatment for a patient.

The Expanded Access Program is another pathway that may permit a patient to obtain investigational drugs or devices outside of a clinical trial. The same drugs or devices that would be available under the Right to Try law may be available under the Expanded Access Program and the conditions for use are generally the same as described above for the Right to Try. As with Right to Try, the investigational drugs or devices under this Program have not yet been approved by the FDA and have not yet been determined to be safe or effective. However, if you and your doctor believe the emerging drug or device may help in your case, you should consider contacting the Expanded Access Program. Contact information follows below:

- Oncology drugs: 240-402-0004 or www.fda.gov/media/144400/download
- Investigation drugs: 301-796-3400 or www.fda.gov/patients/learn-about-expanded-access-and-other-treatment-options/understanding-investigational-drugs

Alternative And Complementary Treatments

Discussing alternative and complementary treatments is a little like discussing religion and politics. These topics are hard and emotional, there is often a lot of fear associated with them, and there can be many points of view.

This Guidebook will give you an understanding of alternative and complementary treatments, but as with anything else, the final decision to use them must be yours.

Alternative treatments are treatments that have not yet been proven to work based on scientific testing and are used INSTEAD of mainstream treatments.

Complementary treatments have also not yet been proven to work but are used IN ADDITION to mainstream treatments. Once a treatment has been shown to work, it crosses over from "alternative"/"complementary" to "mainstream."

The Mainstream Path Of Treatment Development

When someone invents or discovers a therapy that he or she thinks might effectively treat a brain tumor, the path to the treatment's becoming part of mainstream medicine begins with laboratory testing on cell cultures and/or on animals. If the treatment still seems promising, human trials are started. We discussed clinical trials in an earlier section, but basically the treatment is tested on people with a brain tumor and is compared with either historical controls or with a control group.

The early stages of a trial, when only a few people are tested, cannot really show how well the treatment actually works. All phase III trials have had successful phase I and phase II trials leading up to them. However, most phase III brain tumor trials have failed to show significant benefit compared to standard treatment even though a new tested treatment looked very good in early trials. The reason for this is that the course of a brain tumor is variable. A small percentage of patients will do well no matter what treatment you give them, and the natural history is a roller coaster —you have wild ups and downs. If you happen by chance to select a handful of brain tumor patients who happen to have the right subtype, genetics, age, resection extent, Karnofsky Performance Status score, and other prognostic factors, and are on the right track of the roller coaster at the time, they may do well in a small trial even if the treatment is not as good as the standard treatment.

The next step is to test the treatment in a large group. This is when you conduct a randomized clinical trial, in which patients are assigned by chance to receive treatment with either the new therapy or placebo (an inactive substance that looks just like the new therapy) or standard treatment. Then, when the two groups are compared, you get a much better feel for how the new therapy works, since all the other variables are controlled. The trials need to be repeated a few times on large numbers of patients treated before you will know if the effect is treatment related or chance related.

Statistics are used to try to make sense of the trial results. A number is calculated called the significance level. The number usually chosen as the benchmark is 0.05, which means that there is a 95% chance that the effect seen in the trial was caused by the treatment and not by chance alone. Conversely, this means that if you run 100 trials of a worthless drug, about 5 of those trials may report success even though there is none. This is why multiple trials are needed, and it is best if they are conducted by different centers.

The Food and Drug Administration (FDA) will approve a drug that is better than standard treatment, or is at least as good as standard treatment, if it has fewer side effects. Once a treatment is approved by the FDA, everyone can get access to it, not just those in clinical trials.

How Alternative Treatments Are Developed

An alternative treatment is developed when someone has an idea that a certain therapy may help a brain tumor, or the researchers notice that a brain tumor survivor has tried a certain therapy. They then try the treatment on a few more brain tumor patients and see that some of them get better. (As mentioned before, some brain tumor patients are on the upswing of the roller coaster and would have been doing better even without the treatment.)

At that point, the researchers are convinced the treatment works, and they try to promote it so that more people can benefit from it. In many cases, these are the most well-meaning people with the best of motives. They saw something work in a few patients and want others to do well also. However, the difference is in the science. At this point, it would be good to follow the mainstream path and do rigorous trials

of a new treatment, and if it passes the tests, the novel treatment will become mainstream and help everyone. However, that is often not the path taken. Instead, many promoters of alternative and complementary therapies skip the proof and go on to marketing. They use individual case reports or small trials to justify the treatment.

On the Internet we read about many of these types of treatments, but these stories introduce a huge new problem: selection bias. This means that you hear from and see the people who do well with a treatment, but you do not see the ones who died. For example, if the standard treatment for a brain tumor has an average survival period of 5 years (and some of the experimental treatments exceeds that), an alternative treatment needs to reach that point to just say it is as good as standard treatment.

Put another way: If you take 1000 patients and put them on standard treatment, you expect 500 of them to be alive in 5 years. If you take the same 1000 patients and give them a treatment that is half as effective as standard treatment, you expect to see 250 alive at 5 years. If you see 250 people telling you that this miracle alternative treatment worked for them, you may tend to believe them. But you are not seeing the 750 who died — they can't tell you that it didn't work for them. So, at that point, what question should you ask? If they tell you they have 250 5-year brain tumor survivors, ask out of how many started? If it is 250 out of 250, it is a miracle. If it is 250 out of 1000, it is only half as good as standard treatment.

Frequently, those who recommend alternative treatments for serious illness will say "It doesn't hurt to try since the standard treatment does not result in a cure." This statement is erroneous, because even if the treatment itself is not toxic or dangerous, the use of such treatment often works against the science-based treatment, or sometimes is even used as a sole approach (stopping the scientific treatment that, while not curative, may extend their life and temporarily bring some relief to patients).

Also, the high cost of alternative treatment, usually not covered by health insurance, can cause serious financial pain to families and patients who desperately cling to straws of a "cure" offered by those who sell these nonscientific treatments.

There are "red flags" to watch out for when dealing with non-scientifically based treatments. The following are some of the most common "red flags" associated with alternative treatments:

- They are proprietary (available from one source or a limited number of sources) and are not available on the standard pharmaceutical market (which is subject to government supervision and regulation).

- They are expensive, and patients and their families must usually "pay up" in advance before the treatment can be started or continued. Most true clinical trials are licensed and supervised by government entities and are backed with public or private grants so that patients pay little or nothing for the treatment. Most legitimate studies are run in or by major universities or other institutions of higher learning, whereas the majority of alternative schemes are run by for-profit entities.

- The results of the alternative programs have not stood the test of review by a **peer-reviewed scientific journal** (in most cases, the data have not even been submitted to peer-reviewed scientific journals for publication). The alternative programs rely on "testimonials" by patients or former patients, and these are highly unreliable, especially when the diagnosis (of cancer) has not been based on scientific diagnostic techniques, such as pathological examination of tissue.

- There is often a tendency for the providers of alternative treatment to speak ill of traditional scientific medicine, frequently asserting that organized medicine is involved in a conspiracy to force patients to get orthodox treatment for the economic gain of the medical profession.

Brain tumor patients contact us frequently at the Musella Foundation. Many of them have tried just about every alternative treatment ever proposed for brain tumors. Some of them do well. Most do not. We track them with our Brain Tumor Virtual Trial project. Analyzing our data for this project, we found that not one of the alternative treatments reported had any positive effect on the outcome of the cases.

We still keep an eye on the patients who do not join the project. The ones that use mainstream treatments do better than the ones who use alternative treatments alone. We have seen many people decline and die rapidly when refusing standard treatments. They usually change their minds near the end and start standard treatments, but of course it is too late. Unfortunately, they then blame the standard treatments for the death.

However, when it comes to complementary treatments, when you use mainstream treatments but add to them, you may see some positive results. There may be some complementary treatments that do help with treatment side effects and possibly may make treatments more effective. However, keep in mind that if you feel a complementary treatment is powerful enough to change the course of your tumor in a positive way, it is just as likely — or more so — to be able to change it in a negative way. The body is very complicated. You cannot predict what would happen if you change one thing, because one small change can upset the delicate balance of the body and have unseen consequences. The only way to tell is by trying it in a well-designed trial. Proponents may say there is no money in it so no one would fund the trial. That is not true. The Musella Foundation, as well as most of the over 100 other brain tumor foundations worldwide, fund research projects like this.

Conspiracy theories may be put to rest by these two simple thoughts: (1) there is no way the medical industry is organized enough to keep away from the public a cure that would be the biggest boon to society (and biggest money maker) in the world; and (2) there are many researchers who dedicate their lives to finding the cure.

Patients need to learn to ask the right critical questions. These are some to consider:

- What exactly is this treatment?
- Who has received it?
- How many brain tumor patients have had documented responses, and how many patients have tried it?
- How are responses assessed?
- Why is it not given as part of mainstream practice in the United States?
- How was the diagnosis of brain tumor made? In some countries, MRI scans are not routine for brain tumor patients, and even if there is an MRI, there are some diseases that look similar to a brain tumor. A biopsy is the best way to tell if the diagnosis is a brain tumor and which type it is.
- Have the treatment results been published in a peer-reviewed scientific journal? If not, why not?

Natural Treatments/ Supplements

High grade brain tumors do not materialize overnight. They could have been developing for as long as 7 years and gaining more DNA mutations to become more aggressive 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 that will undo 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.)

Researchers have found that cannabis use has been associated with shorter time to progression and shorter overall survival among patients with advanced cancer who received anti-PD-1 checkpoint inhibitors (like Keytruda). Preclinical studies indicate that cannabinoids can suppress the antitumor activity of T cells—the primary cells activated by PD-1 inhibitors—by inhibiting the JAK/STAT signaling pathway through the cannabinoid receptor-2 (CNR2/CB2). Retrospective studies found that patients using cannabis had significantly lower response rates (RR) to checkpoint inhibitors like nivolumab, 15.9% compared to 37.5% for non-users. Furthermore,

prospective observational studies showed a shorter median OS (e.g. 6.4 months compared to 28.5 months) and a reduced time to tumor progression in users of cannabis.

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.

SURVIVOR STORY #8

In April 1989, asked by the girls' softball coach to demonstrate a slide (I had played softball in high school and college), I spent an afternoon practicing and banged my head on the gym floor. I was 27 years old at the time, living at home with my parents, recently engaged to the love of my life. My family physician told me to rest, but I was suffering migraines and was very tired.

The following Thursday I drove home from work with a friend. During the drive, I had another migraine, but this time the left side of my body was going numb. We went straight to the emergency room. In the meantime, my mother described my signs and symptoms to a neurologist, and he told her to have me carry over my CT scans to him. When he looked at them, he told me that I had a tumor that needed to be removed.

On May 2 the neurosurgeon did a craniotomy and removed a cystic astrocytoma from my right frontal lobe. I opted to not receive radiation therapy for there was no guarantee that the tumor would not reoccur. My husband to be and I wanted to start having children; our physicians felt that the tumor had been sufficiently well contained within the cyst. Wasting no time, we began trying right away to conceive a child.

In January when I went for an MRI scan, my pregnancy test was positive. Two more children followed. My neurologist retired. When I met my new neurologist, he shockingly asked whether my husband was ready to raise our children without me. He stated that no one survives the type of brain tumor I had. My husband and I were then contemplating having a fourth child, and I had mentioned that to the new neurologist. He felt we were being foolish.

That's when I discovered the virtualtrials.org website of the Musella Foundation. I went on a rampage to learn more about brain tumors than I ever cared to know. I read many articles and emails. Some made me laugh, some made me cry. It is all such real-life stuff.

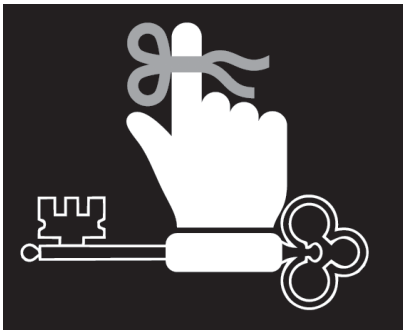
I fired the neurologist and spoke with my former neurologist, telling him that I needed a physician that knew that I was going to survive. We had a fourth child.

Since the removal of the tumor 27 years ago, I am alive and well. I have added survival of a hurricane to my life's story, when Hurricane Sandy flooded my home and my four boys, and I were not able to evacuate. But the fact that I had already survived a brain tumor made even that horrific storm just another day that God has blessed me with. I continue to have clear MRI scans, and my newest neuro-oncologist has called me an outlier, a designation with which I am perfectly content. I am blessed with good health and an interesting life. Indeed, overcoming a glioma has become the measure by which I readily estimate everything else that God has sent my way.

Photo Credit Linda Singer



KEY TAKEAWAYS TO REMEMBER



Clinical trials may provide your best possible survival or for a better quality of life. At the virtualtrials.org website of the Musella Foundation, you can have access to important resources for locating clinical trials, including:

Patient Navigation Program, which uses the xCures platform loaded with all the currently available treatments and matches it to the details about your tumor to help you quickly find promising treatments, and

Clinwiki which uses details about your tumor that help you find treatment options.

Alternative treatments have not yet been proved to work based on scientific testing and are used instead of mainstream treatments.

Complementary treatments have not yet been proved to work based on scientific testing, but they are used in addition to mainstream treatments.

There are several "red lights" to watch out for if you look at using non-scientifically based treatments — few sources for the products; an expensive cost; reliance on patient "testimonials" rather than publication of data in peer-reviewed scientific journals; and conspiracy talk.

Learn to ask the right critical questions about alternative and complementary treatments. What is it? Who and how many have received it? How were responses assessed? Why is it not part of mainstream practice? How was the diagnosis of brain tumor confirmed? And have the treatment data been published in a peer-reviewed scientific journal?





Fifteen

Diet

Overview

The impact of diet on brain tumors remains an area of ongoing research. Scientists have yet to fully understand the interplay between dietary changes and brain tumor development or treatment. Some dietary adjustments may provide benefits, while others could potentially have negative effects. The recommendations discussed here are generally considered healthy, but it is important to remember that nutritional guidance often evolves as new evidence emerges. For the latest updates, consider subscribing to our Brain Tumor News Blast.

Why Consider Dietary Changes?

If you have been diagnosed with brain cancer, you may be searching for actionable steps to help manage the disease and maintain your quality of life. One practical and particularly relevant, measure to consider is adjusting your diet.

Gut-Brain Immune Relationship

Dietary changes may be especially important in defending the brain against the cancer. Recent research from the National Institutes of Health and Cambridge University indicates that certain immune cells tasked with protecting the brain first undergo a training phase in the gut. These "gut-educated" antibody-producing immune cells then migrate to defend areas around the brain and the rest of the central nervous system.

Gut-Brain-Immune Axis in Glioma and Treatment Response

Additionally, current research increasingly points to the gut-brain-immune axis as a major factor influencing glioma progression, responsiveness to therapy, and patient survival. The gut microbiome not only impacts the body's response to tumors but also shapes the brain's immune environment, potentially either suppressing or encouraging tumor growth. An imbalance in gut bacteria can create an "immune-cold" tumor microenvironment (TME) in the brain. New studies have identified genetic and cellular connections between gut bacteria and glioma behavior.

Metabolites produced by gut bacteria, such as short-chain fatty acids (SCFAs) like butyrate, can regulate tumor suppressor genes. Consuming dietary fiber increases SCFA production; these metabolites can then travel to the brain and convert "pro-tumor" M2 macrophages into "anti-tumor" M1 macrophages, improving survival outcomes. Conversely, a lack of these protective metabolites due to gut dysbiosis may foster a tumor-promoting environment.

The effectiveness of immune checkpoint inhibitors (ICIs) in treating glioblastoma (GBM) is also strongly affected by the gut microbiome. For instance, tryptophan supplementation can restore a healthy microbiome, increase circulating cytotoxic T cells, and enhance immunotherapy results.

Microbiome Diversity, Chemotherapy, and New Research

High baseline levels of certain bacteria, such as Ruminococcus , are associated with better responses to immunotherapy across multiple cancer types, including GBM, by promoting B cell infiltration into the tumor. Changes in the gut microbiome can also reduce the efficacy of standard chemotherapies, while some bacteria may help alleviate chemotherapy side effects. Patients with GBM often have lower microbial diversity compared to healthy controls. A recent Mendelian randomization study identified 53 specific microbial populations that may increase or decrease glioma progression risk, suggesting they could serve as useful prognostic biomarkers.

In preclinical models, interventions aimed at "rebalancing" the gut microbiome—such as introducing specific bacteria like Duncaniella dubosii—have replicated the benefits of dietary changes and extended survival by strengthening the body's natural defenses. An ongoing clinical trial (THERApeutic Outcomes, NCT05326334) is

currently studying how the gut microbiome and dietary patterns affect clinical outcomes in newly diagnosed GBM patients.

Multiple studies have shown a close association between specific gut microbiota and treatment effects. Other findings demonstrate that adjusting the gut microbiota can enhance the effectiveness of immunotherapy and reduce resistance to treatment. Diet is a major factor enabling these benefits. Therefore, steps to improve gut health and the immune response through dietary changes can play a significant role in a brain cancer patient's overall disease management.

Sustaining Underlying Health. What also matters is recognizing that the brain cancer is less than 1% of the body's weight and the remaining 99% of the body needs, more than ever when a brain cancer fight is on, as good a nourishment as you can give it (and tolerate). Another important benefit of a good diet is maintaining one's underlying health during what can be a vigorous fight. A good diet can help stave off some treatment side effects.

Many clinics and hospitals have classes for cancer patients on how to eat better. It is a good idea to see if your clinic or hospital has such classes and attend one. Another option is locating a clinical nutritionist for individualized assistance.

If you are a caregiver of a person who has no interest in changing their diet, understand that cleaning up your loved one's diet, while important, is a bonus. So, if your loved one refuses, it is better not to fight over it. Keep the bigger picture in mind.

The Inflammation Factor

In those studies that seem to produce the best evidence of effect between diet and brain cancer, the top issue is reducing inflammation. Why is that?

Inflammation in the brain, being encased in a boney container, has nowhere to go. Plus, if there is too much of it, the pressure it puts on the brain can create an array of unwelcome symptoms. Plus, when inflammation happens there is a release of substances that promote cell division, which can trigger the cancer's growth.

How can a person best reduce their inflammation? Turn to mostly plant-based foods. It won't eliminate your risk, but it will reduce it.

First Fix

SOME nutrition experts believe that the first thing any cancer patient needs to do is cut out all ultra-processed foods from their diet. To know what an ultra-processed food is, this is a quick definition: If it comes in a box or a can, and the ingredient label is long and filled with chemical names you can't easily pronounce, and don't recognize as healthy — it's probably ultra-processed.

Diet Mix

The ideal diet for an adult should be about 25% of calories from protein, 50% from high fiber fruits and veggies, and 25% of calories from whole grain carbs or starches like peas, corn, potatoes. In addition, most guidelines also recommend that 20 to 35% of your calories come from healthy fats like olive oil, fish oils (omega-3-fatty acids), nuts, and avocado oil, which need to be integrated into these portions.

Calories/ What To Do About Lack Of Appetite

Cancer can cause a person's metabolic processes to affect how the person's body uses proteins, fats, and carbs. (The condition is called hypermetabolism. It is important to get the required amount of food each day.)

A rough estimate of caloric needs would be between 11.5 and 16 calories for every pound of weight (25 to 35 calories per kilogram of weight). For determining what should be your personal caloric target, a discussion with your doctor or nutritionist/ dietician is best.

Calorie restrictive diets should be avoided, unless the doctor says otherwise, because that could lead to an unhealthy decrease in weight and muscle mass during treatment. Statistically, those who do better in the long run are those who maintain a healthy weight.

Sometimes a person just does not feel like eating, for example, when nauseated from treatment. But they still need the calories. In those times, it is advisable to try having smaller more frequent meals, avoid filling up on liquids at your meals, and consider supplementing a meal with one of those meal replacement milk shakes

sold in pharmacies. Look for those with the lowest sugar content. A person should not exceed one of these shakes per day and only for the purposes of ensuring an adequate caloric intake.

Proteins

The current recommended daily allowance for protein is 45 to 60 grams per day (or whatever it takes to get your intake to be about 25% of your calories). More than what you need makes your body have to process all that extra protein; less than that may make it hard for your body to protect itself from infection and heal (e.g., lowered blood cell counts may result because your body cannot make blood cells.) This is another area where your personal target should be set with your doctor or nutritionist.

The ideal in protein consumption is to look for low fat/ high protein foods such as skinless chicken, fish, turkey, low fat dairy, nuts, and seeds.

Red Meat

Red meat contains hormones which can stimulate cancer growth. It also contains endocrine disrupting chemicals and iron which is a potentially gene-damaging oxidant. Then, if the meat is cooked on a grill, it develops heterocyclic amines, which in lab studies has been shown to increase the cancer risk.

High-temperature, dry-heat cooking—such as grilling, frying, or roasting—dramatically increases Advanced Glycation End products (AGEs) in food. AGEs and the compound methylglyoxal (MGO) can increase the invasiveness of GBM cells by triggering inflammatory signaling and altering the extracellular matrix, highlighting a link between metabolic byproducts and cancer progression. AGE accumulation promotes oxidative stress and inflammation, and can upregulate specific proteins (such as TGFβ, brevican, and tenascin C) that facilitate GBM growth and invasion.

To minimize dietary AGE exposure, prioritize cooking methods and habits that prevent their formation. For example, replace high-heat, dry methods (grilling, frying, broiling, roasting) with moist-heat techniques such as boiling, steaming, poaching, or stewing. Cook food at lower temperatures for shorter durations. Avoid the "crust" or "char" on foods which can promote inflammation that can drive cancer progres-

sion. Marinate meats in acidic ingredients like lemon juice, tomato juice, vinegar, before cooking to reduce AGEs. Focus on plant-based foods (vegetables, fruits, whole grains) which naturally contain fewer AGEs than processed foods or animal-derived products high in fat and protein.

Fish

In addition to being a good non-meat source of protein, fish has anti-inflammatory properties in the form of polyunsaturated fatty acids (PUFAs). Best fish for PUFAs are the cold-water fatty fish such as tuna (the light 'skipjack' tuna, but not the albacore tuna, since the bigger the fish, the more possibility it will have mercury), sockeye salmon, sardines, herring, and mackerel.

Eggs

Eggs are a good source of non-meat protein and are rich in choline, lutein, and zeaxanthin, which are all micronutrients believed to have disease-fighting properties. A couple of eggs per week is generally recommended.

Yogurt

While even a small amount of normal dairy milk may increase the risk of triggering cancer growth due to the hormones in the milk, once that milk is fermented into yogurt, the risk is reduced or removed. Yogurt, which is a good source of calcium and protein, contains beneficial bacteria (probiotics). Yogurt may help reduce inflammation and aid against the cancer.

Soy, Hormones and Brain Tumors

Many individuals choose soy as an alternative source of protein. Some medical professionals have expressed concerns that the phytoestrogens present in soy might stimulate tumor growth, especially among postmenopausal women diagnosed with meningiomas. These tumors can contain estrogen receptors, which may respond to hormone-like compounds. Despite these concerns, there is currently no evidence that consuming soy or soy-based products promotes the growth of brain tumors, including both meningiomas and gliomas.

It is important for postmenopausal women to be cautious about hormone replacement therapy (HRT), as research has shown a higher incidence of meningiomas in women who use HRT. Similarly, women of child-bearing age are advised to avoid oral contraceptives containing estrogens, as these hormones may also have the potential to promote meningioma growth.

Current Research on Soy and Tumors

Recent research suggests that consuming soy and tofu products may actually reduce the risk of developing meningiomas. One study found that estrogen-like compounds in soy could compete with the body's own estrogen, potentially acting as antiproliferative agents and lowering tumor risk. Furthermore, phytoestrogens such as daidzein and genistein, which are found in soy, have been inversely associated with the risk of adult gliomas, indicating that increased intake might help reduce risk.

Major health organizations, including the American Cancer Society, support the safety of soy for cancer patients and survivors. They recommend that consuming one to three servings of whole soy foods daily—such as tofu, edamame, or soy milk—is safe for these populations.

Carbohydrates

Carbohydrates are essential for providing energy; however, both the type and amount of carbohydrate intake warrant careful consideration in patients with brain tumors. The Academy of Nutrition and Dietetics advises that individuals with cancer should not generally restrict carbohydrate consumption below recommended healthy levels, unless specifically directed by a healthcare professional or registered dietitian for medical indications such as significant glycemic concerns.

Carbohydrates serve as a vital energy source for all individuals, including those receiving cancer treatment. They support physiological processes by fueling the brain and immune system, sustaining energy during therapy, and preserving protein reserves for tissue repair and healing. Nutritional guidance emphasizes the selection of nutrient-dense carbohydrates, such as whole grains (e.g., quinoa, oats), vegetables, and fiber-rich fruits, over refined sugars, white bread, or processed snack foods.

Presently, the Academy does not prescribe a specific carbohydrate percentage for

cancer patients. Nonetheless, moderation is advised, as excessive carbohydrate intake may lead to elevated blood glucose and insulin levels, which could potentially encourage tumor proliferation—particularly in aggressive forms such as glioblastoma that readily utilize glucose. Very low-carbohydrate diets are not recommended unless closely supervised by healthcare professionals. In general practice, many dietitians recommend that approximately 50–60% of total energy be derived from carbohydrates, with emphasis on whole grains, fruits, vegetables, legumes, and other fiber-rich foods.

The Academy underscores the importance of prioritizing carbohydrate quality rather than focusing on quantity; concern about the role of carbohydrates in cancer cell metabolism is discouraged. Nutritional goals should center on maintaining a balanced diet, meeting energy requirements, and limiting added sugars and highly processed foods that offer limited nutritional benefit. Intake of simple sugars and sugar-sweetened beverages should be reduced due to their minimal nutrient value and potential to contribute to weight gain and related health issues.

Crucially, the Academy and other professional bodies advocate for individualized nutrition plans. Registered dietitian nutritionists (RDNs) who specialize in oncology will evaluate patients' dietary patterns, symptoms, treatment side effects, weight fluctuations, and metabolic status to tailor recommendations for carbohydrate and caloric intake. This personalized approach ensures optimal nutritional support throughout the cancer treatment continuum.

Vegetables

Veggies should make up half of your plate at meals. Studies show that people who consume 1-2 servings of leafy greens each day experience fewer memory and cognitive issues than people who rarely eat them.

Leafy green and cruciferous veggies (broccoli, cabbage, spinach, kale, Brussels sprouts, Bok choy, arugula, collard greens, and cauliflower.) are excellent; those in the cabbage family contain some cancer fighting substances called indoles and isothiocyanate that have been widely studied.

Fruits

Some people avoid fruits to avoid sugar, but many fruits are supportive of memory and mental acuity thanks to their high vitamin and antioxidant content. If you are

concerned about sugar, choose low glycemic fruits like berries, apples, and watermelon.

The brain appreciates berries like dark cherries, black berries, strawberries – the darker the better.

Be careful of citrus (orange, grapefruit, lemon) during chemo cycles only to avoid having to have your stomach deal with the extra acid. Citrus after chemo cycles are good, but please be aware that grapefruit occasionally interferes with medications doctors may prescribe.

Whole grains (like oatmeal, brown rice, quinoa, whole wheat breads and pasta) are good carbs and 25% of your diet should consist of them. Refined grains (such as white flour, white pasta, white rice, and white breads) are best left on the shelf. There has been some debate about whole grains being bad for the brain. The latest studies do not suggest they are but talk to your doctor or nutritionist on this question.

Legumes (peas, beans, lentils, peanuts, etc.) and starches like sweet potatoes are also excellent sources of good carbs.

Antioxidants

Even under normal circumstances the brain is most sensitive to oxidative stress. Add some surgery, radiation and chemo, and the brain is really stressed.

An answer to all that oxidative stress is to add some antioxidants. Most of the fruit and veggie items mentioned above are going to provide excellent sources of antioxidants.

Some people feel the need to add more to their diet via supplements of the most powerful antioxidants (vitamins C, E, beta-carotene, selenium, lycopene, and anthocyanins.) Plus, there are supplements that are popular with those dealing with brain cancer such as Curcumin (Turmeric), Boswellia, Berberine, and others.

It is a wise idea to discuss your diet and supplementation frankly with the doctor because during certain phases of treatment (most notably during radiation) the supplementation of antioxidants may undo the beneficial effects of treatment.

Consuming antioxidants via what you eat is not an issue (as far as I know), but supplementation via pills/capsules might harm, not help, so the doctor should be involved in deciding what antioxidants you take and when.

Not only that but there is a debate among scientists. It is well understood that as a cancer preventive, antioxidants are beneficial, but once cancer is present, some doctors feel that the antioxidants could aid the cancerous processes and not the person. Again, the issue is not the antioxidants a person is consuming via the diet, but rather the additional amount obtained through supplements. Your doctor or nutritionist would be able to guide you.

Fats

We need fats in our diet, but they need to be healthy fats.

Unsaturated fats are the "good" fats, and they are chiefly found in nuts, olive oil, peanut oil, canola oil, avocados, tuna, and salmon... as long as those oils are not superheated by high heat cooking which then changes their chemistry.

There are the saturated fats, which can be found in meat and other animal products, such as butter, cheese, and all milk except skim. Palm and coconut oils are also high in saturated fats and can be found in a variety of the baked goods sold in groceries. (Check the labels!) These are not desirable fats for your diet, so watch your consumption of these.

Lastly, there are trans fats, which are found in limited amounts in meat and other animal products, such as butter, cheese, and all milk, but can be found in large amounts in processed foods, fried foods, some types of margarines, snack foods, and baked goods. If the label says "hydrogenated" or "partially hydrogenated" then that food contains trans fats no matter what else the label says. It is best not to consume any trans fats, but if you do, limit your daily intake to no more than 120 calories (which is probably just one or two commercially baked cookies).

As previously mentioned, the single most important diet principle that someone dealing with brain cancer needs to follow is avoid eating ultra-processed foods, especially those containing trans fats.

Keto Diet

Some brain cancer patients believe switching to the keto diet has benefited them. A few studies in humans with certain types of brain tumors have shown some promise in controlling the growth of those tumors on this diet. Depending on your type of treatment and other personal medical issues, your body may not be able to metabolize the proteins and fats that are used in abundance in a keto diet, so definitely talk to your doctor first before trying this diet.

Sugars

Some people say that it is essential to eliminate all sugar in all its forms (glucose, glutamate, fructose, corn syrups,) because sugars are thought to fuel cancer. Actually, all of our cells need sugar (glucose) to function, and there is no way for our bodies to give the needed glucose to our healthy cells but not give it to our cancerous cells. The trick is to limit as many added sugars as is possible (and tolerable).

Hydration

It is vitally important to stay well hydrated, especially during treatment. Drinking lots of water helps to flush the chemo residue from the body and aids in avoiding the constipation that treatment can cause. However, fruit juices, sodas and 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.

For those looking for some taste to their water, Green Tea, which contains an antioxidant that de-toxify cell-damaged free radicals, is an excellent option. If the Green Tea is taken as a supplement by capsule, you should speak to your doctor first because of the antioxidant nature of the Green Tea which may interfere with certain treatments, particularly if you are taking other antioxidants.

Alcohol

Alcohol consumption should be eliminated or at the very least reduced. Alcohol can cause the liver to be inflamed, can interfere with certain medications (e.g., CCNU/Lomustine and Procarbazine) and could impair the liver's ability to breakdown the chemo. Chances are that your doctor will try to encourage a "no alcohol' policy

while during treatment.

What To Avoid

The presence of brain cancer means there is a compromise of the immune system. This being the case, it would be wise to avoid foods associated with a high risk of food contamination, including:

- Unwashed fresh fruits and veggies especially those with leaves that can hide dirt raw or lightly cooked sprouts like alfalfa or beansprouts
- Unpasteurized drinks of any kind whether juices or milk and all products made from them (e.g., cheese or yoghurt made from unpasteurized milk)
- Soft, slow-ripened, or blue-veined cheeses (e.g., brie, camembert, Danish blue, stilton, and gorgonzola)
- Eggs that are not fully cooked such as soft boiled, over easy, and poached; raw, unpasteurized eggs; or foods made with raw egg, such as homemade raw cookie dough and homemade mayonnaise. When making a cake, do not lick the bowl
- Refrigerated pate. Pate in a can might be alright but read the label to see if it is safe.
- Rare or undercooked meat and poultry. Investigating in a meat thermometer is smart.
- Cold hot dogs or cold cuts from the deli; if you are going to eat them (despite their overabundance of chemicals), hot dogs must be steaming hot.
- Uncooked shellfish (e.g., oysters).
- Smoked fish and raw fish like that in sushi and sashimi. There are some fish labeled "sushi grade" and "sashimi grade" that might be okay, but ask your doctor first.
- Avoid all the deli prepared salads with egg, ham, chicken, seafood as any of these can teem with bacteria, especially if not properly refrigerated before you get them.

Strange And Useless

The following diets or dietary devices have no proven value and may be harmful:

Budwig Diet. This is a diet of flaxseed and cottage cheese and includes several restric-

tions. The flaxseed and cottage cheese may be fine for some people, although the flaxseed may interfere the absorption of some medications and the cottage cheese may produce intestinal issues. The restrictions of the diet are a mix of healthy and unhealthy. Taken as a whole, the restrictions of the diet may put you at risk of certain vitamin and mineral deficiencies, so if you want to proceed with this diet, talk to your doctor or nutritionist first.

Alkaline Water. There are devices ranging in price from $50 to $5,000 to produce alkaline water. While some will claim that alkaline water inhibits the growth of cancer, this concept is unproven. The fact is that the minute the water we drink mixes with the ever-present acid in the stomach, it loses its alkalinity.

The Gerson Therapy. This protocol includes thirteen (yes -13) glasses of fruit/veggie juice per day plus many coffee enemas, which can be quite harmful. (This last therapy didn't much help the developer, Dr. Gerson, when he contracted cancer himself).

The bottomline is that there are lots of weird and costly programs out there, some of which are just designed to put your money in their pockets. Talk to your doctor or nutritionist before you buy or start anything that is or seems off the main road.





Sixteen

Imaging and Monitoring

Overview

Brain scans allow doctors to get an idea of what is going on inside the head non-invasively. No scan is 100% accurate, and each is open to interpretation. The more experienced the doctor is at interpreting brain scans, the more confident you can be about the results of that interpretation. Also, the more the doctor knows your personal history, the more accurately that doctor is able to put new scans into their proper context.

As mentioned elsewhere, it is a good idea to get a personal copy of the films (or a CD of them) and the radiology report. You can share these documents with your medical team to make sure they agree on the reading of the scans. Having copies of the scans will also be useful if you need a quick second opinion from another brain tumor center, or if the original scans are lost, as happens more than you would think.

CT Scan

A CT scan (or CAT scan, a computerized axial tomogram) is a non-invasive imaging technology that uses x-rays to generate a computer simulation picture of the cross section of your head. Usually, a contrast agent (a dye) is injected into your arm halfway through the test to enable the tumor to show up better. A CT scan can be readily available and much cheaper than an MRI scan.

A CT scan shows some things very well, such as bleeding into the brain and signs of swelling, and it is sometimes used for planning surgery and radiation. Since CT scans use x-rays, there is a tiny risk with their use, so they are usually limited to only

when they are absolutely needed, especially in children.

If you are having a CT scan performed on a child, ask the radiology technician whether the level of exposure dosage can be reduced appropriately for children. On some older CT scanners, such a reduction is not possible. In such cases, you should select a different imaging facility.

Magnetic Resonance Imaging (MRI)

Overview

Magnetic resonance imaging (MRI) is a non-invasive imaging technology that produces three dimensional detailed anatomical images. It is currently the most used technology for disease detection, diagnosis, imaging support for biopsy and surgery, and treatment monitoring; doctors prefer the MRI because it is more detailed than a CT Scan image and avoids ionizing radiation from X-rays. An MRI also is able to find smaller tumors than a CT Scan.

Frequencies

MRIs are usually performed regularly at a frequency recommended by the doctor to monitor the status of the tumor or tumor site. Sample frequencies, subject to the doctor's adjustment, for stable tumors are:

- High grade tumor every 2 to 3 months
- Low-grade tumor every 6 months
- Benign every year

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.

How an MRI Works

An MRI scan uses magnetism and radio waves to create a “picture” of the inside of your head. It employs powerful magnets which produce a strong magnetic field that forces protons in the body to align with that field. When a radiofrequency

current is then pulsed through the patient, the protons are stimulated, and spin out of equilibrium, straining against the pull of the magnetic field. Physicians are able to tell the difference between various types of tissues based on the energy released as the protons realign with the magnetic field.

To obtain an MRI image, a patient is placed inside a large magnet and must remain very still during the imaging process in order not to blur the image. MRI is potentially one of the best imaging technologies for children since, unlike CT, it does not have any ionizing radiation that could potentially be harmful. However, one of the most difficult challenges that MRI technicians face is obtaining a clear image, especially when the patient is a child or has some kind of ailment that prevents them from staying still for extended periods of time. As a result, many young children require anesthesia, which increases the health risk for the patient.

Contrast Agents

When an MRI is performed, a contrast dye (usually gadolinium) may be injected intravenously to increase the speed at which protons realign with the magnetic field of the MRI machine. The faster the protons realign, the brighter the image.

Side effects of the gadolinium are typically transient; they may include headache, dizziness, pain at the injection site, rash, itching, and nausea. A severe adverse reaction is extremely rare. A different contrast agent is used for MRI scans than for CT scans, so if you had an allergic reaction to the dye used for a CT scan, you may still be able to use the contrast agent for an MRI scan (and vice versa).

This dye is often used after a round of images have already been taken so that the new images with the contrast dye can be compared to see if there are any important details to be see. With a contrast agent, non-growing ("non-enhancing") tumors will appear "isodense" meaning that it looks rather dull and dark just like the same as the first series of images taken without the dye.

A growing ("enhancing") tumor will appear hyperdense (bright) and show off other changes. Changes may reflect blood perfusion (growth of additional blood vessels), vascular permeability (microleaks of blood) and extracellular space of the tumor. One way to understand these changes is to remember that a tumor needs a lot more blood supply that normal tissue needs, so if there is an increase in blood perfusion

and more blood in the tumor, that is indicative of an enhancing tumor or one that is getting ready to grow.

Considerations for Use

When having an MRI scan, the following should be taken into consideration:

- Although an MRI does not emit the ionizing radiation that is found in x-ray and CT imaging, it does employ a strong magnetic field. The magnetic field extends beyond the machine and exerts very powerful forces on objects of iron, some steels, and other magnetizable objects; it is strong enough to fling a wheelchair across the room. As a result, people with implants, particularly those containing iron, including but not limited to pacemakers, vagus nerve stimulators, implantable cardioverter- defibrillators, loop recorders, insulin pumps, cochlear implants, deep brain stimulators, and capsules from capsule endoscopy should not enter an MRI machine without supervision and/or a specific protocol, as there are modern technologies to perform MRIs and mitigate the risk.

- Noise—loud noise commonly referred to as clicking and beeping, as well as sound intensity up to 120 decibels (which is loud) in certain MRI machines. If noise bothers you, it is recommended that you inform the imaging technician who can give you ear protection.

- Nerve Stimulation—a twitching sensation sometimes results from the rapidly switched fields in the MRI.

- Pregnancy—while no effects have been demonstrated on the fetus, it is recommended that MRI scans be avoided as a precaution especially in the first trimester of pregnancy when the fetus' organs are being formed and contrast agents, if used, could enter the fetal bloodstream.

- Claustrophobia—people with even mild claustrophobia may find it difficult to tolerate long scan times inside the machine. Familiarization with the machine and process, as well as visualization techniques, sedation, and anesthesia provide patients with mechanisms to overcome their discomfort. Additional coping mechanisms include listening to music or watching

a video or movie, closing, or covering the eyes, and holding a panic button. The open MRI is a machine that is open on the sides rather than a tube closed at one end, so it does not fully surround the patient. It was developed to accommodate the needs of patients who are uncomfortable with the narrow tunnel and noises of the traditional MRI and for patients whose size or weight make the traditional MRI impractical. Newer open MRI technology provides high quality images for many but not all types of examinations.

Other than as may be noted above, MRI scans are thought to be safe.

Types of MRIs

There are different kinds of MRI scans. Here are some of the important ones:

- MRA (magnetic resonance angiography) shows details of the blood vessels.

- MRS (magnetic resonance spectroscopy) shows the chemical makeup of the brain, which can sometimes be used to tell the difference between radiation necrosis, normal brain, swelling, and tumor. Sometimes MRS can distinguish between low-grade and high-grade tumors, a distinction that is helpful when the best area for a biopsy is being selected. MRS can also detect whether a treatment is working much more rapidly than regular MRI can and comparing repeated MRS scans can be especially useful for tracking tumor status. MRS is available at most brain tumor centers and is starting to become available everywhere.

- fMRI (functional MRI) measures blood flow in the brain and is used to map which areas of your brain control which functions. For example, if the tumor is near your speech area, you will be asked to talk while the scan is performed to highlight the areas you use while talking, and to see if the tumor invades that area.

- Diffusion MRI, which measures water movement in the brain, can be used to determine how well the treatment is working.

MRI Interpretation Basics

MRI images are taken in sequences. When MRIs of the brain are being made, there are typically two sequences: T1 and T2.

T1-weighted images are produced in shorter repetitions (referred to as TR) and shorter time between the delivery of the RF pulse and the receipt of the echo signal (referred to as TE). T1 is useful for demonstrating the underlying anatomy of the brain and associated structures.

If a structure is dark on the T1 sequence, the image may be displaying additional water (edema/swelling), inflammation, tumor, hemorrhage. If a structure is bright white on the T1, the image may be indicating, among other things, the presence of fat, proteins and protein-rich fluids like slow moving blood, subacute hemorrhage, melanin, necrosis, and gadolinium.

T2-weighted images use longer TRs and TEs than the T1 sequence.

If a structure shows up as dark on the T2 sequence, the image may be displaying melanin, protein-rich fluids like slow moving blood. If a structure shows up as bright on the T2 sequence of images, then it is probably indicating the presence of blood and water (e.g., edema/swelling), inflammation, tumor hemorrhage.

Fluid-attenuated inversion recovery (FLAIR) is contrast technique for the T2 MRI sequence. It shows certain areas revealed in the T2 sequence with the cerebrospinal fluid (CSF) from the ventricles dampened or removed. This allows for any brain abnormalities like tumors to appear more conspicuous, while the CSF appears dark or subdued. The FLAIR signal is particularly helpful for detecting subtle changes in tumors.

"Diffusion weighted imaging" is a term that shows up frequently in MRI reports. This imaging simply helps show the cellular structure of the brain.

There are a few new experimental MRI techniques that may be able to better distinguish pseudo progression from true progression, and to tell earlier if a treatment is working or not. See our video library for details: https://virtualtrials.org/video.cfm

Common Findings

The first one or two MRIs following surgery or radiation are likely to be filled with evidence of edema/inflammation, making the MRI inconclusive. In the interest of controlling pre-scan anxiety, it is useful to be aware that MRI results are not always clear, so you should not expect too much from early MRIs. The results are often anti-climactic. Only successive, comparative MRIs will be able to be conclusive.

Sometimes MRIs identify a "suspicious spot." Spots may be tumor recurrence, but it may also be necrosis. Necrosis is the presence of a clump of dead cells. These are deposits of cancer cells that have been killed off by the radiation and/or chemo and that accumulate in a given location. Comparisons to future scans should enable the doctor to conclude what the spot is.

Sometimes MRIs identify an enlargement of the tumor. This puffiness looks like it may be tumor recurrence to the doctor analyzing the MRI without your treatment history, but that puffiness may not be tumor recurrence. In 20% to 30% of cases the enlargement is something called pseudo-progression. The tumor tissue sort of blows up in response to the treatments, shows up as an enlargement in your scan, but subsequent follow-up scans show either tumor stability or shrinkage.

Perfusion MRI

For this form of MRI, a contrast dye is injected quickly into a vein. A special type of MRI image is then obtained that looks at the volume of blood going through the brain and tumor/tumor environment. Tumors, particularly high-grade tumors, typically require much more blood than normal brain tissue. A perfusion MRI can help detect changes in blood amounts, which in turn can help assess the status of the tumor.

Magnetic Resonance Spectroscopy (MRS)

This test can be done as part of an MRI. It measures biochemical changes in an area of the brain (displayed in graph-like results called spectra). By comparing the results for a tumor to that of normal brain tissue, it can help tell the difference between any dead tissue caused by previous radiation treatments and new tumor

cells. The sensitivity, specificity, and accuracy of MRS is 84-87.5%, 75-93.3%, and 81-92.1% respectively. Plus, MRS has a higher sensitivity and specificity than a T2 MRI sequence.

Pseudo-Progression/ Treatment Effects

Due to treatments like surgery, radiation, chemos or immunotherapies, fluid soaks the tissues around the tumor site. This fluid (called edema or more medically speaking a "T2/Flair signal") looks very cloudy on an MRI image, and the doctors who look at the image cannot tell if the cloud is itself tumor progression, or if that cloud is hiding tumor progression, or if the cloud is just a bunch of fluid, or if the area being seen is a clump of necrotic tissue. This is why the doctor will say something like "We'll have a better idea after the next MRI" (leaving us biting our fingernails for the next 30 or 60 or 90 days).

In approximately 20% to 30% of GBM cases, the first MRI obtained after radiation therapy and concurrent temozolomide meets the criteria for progressive disease. Additionally, it is not uncommon for MRI images during treatment to have an increase in T2/FLAIR sensitivity, which raises the possibility of tumor progression. The radiologist who first views the MRI images and sends the MRI report to your doctor is probably going to mention the potential of tumor progression.

Your personal doctor, who best knows the phase of treatment you are in and how you have been responding to treatment so far, may tell you he or she disagrees with the report. It is not uncommon for subsequent follow-up MRIs to prove him or her right by showing tumor shrinkage or stability.

This phenomenon has been termed either "treatment effect" or "pseudo progression" and is among the most common causes of misdiagnosed tumor recurrence. This is of concern at most stages of treatment because pseudo progression following chemo can happen in the early months and later there can be radiation-induced necrosis six (6) months or more after radiation, especially for persons with an IDH-1/wild type/ unmutated gene in the tumor.

However, development of a new enhancement outside the original tumor site most likely does represent tumor progression and should be treated accordingly.

PET Scans in Neuro-Oncology: Applications and Advances

When Are PET Scans Ordered?

In certain situations, to better interpret MRI images and address uncertainties caused by pseudo-progression, a physician may recommend a PET scan

How PET Scans Work

A PET scan (positron emission tomography) involves injecting a small amount of a radioactive substance into a vein, usually in your arm. This tracer combines a low-dose radioisotope with sugar, making it generally safe and causing minimal to no side effects. However, PET scans may pose risks for people who are allergic to sugar substitutes or iodine, or for those with diabetes. For diabetic patients, it is important to keep blood sugar levels under control, ideally below 180 mg/dL, to prevent the tracer from being distributed improperly and to ensure high-quality imaging. If blood sugar is elevated, the tracer could be absorbed by fat or muscle tissue instead of the tumor, which diminishes the scan's effectiveness. Despite these considerations, the amount of radioactive tracer is minimal and is not considered dangerous for patients with diabetes.

What PET Scans Show

PET scans reveal the metabolic activity of different regions of the brain by measuring glucose (sugar) utilization. A computer reconstructs the PET image, displaying cellular activity as "hot spots" (higher activity) or "cold spots" (lower activity). Cancer cells, which consume more glucose than normal cells, appear as bright areas on the scan due to the radiotracer's accumulation.

Clinical Value of PET Scans

By identifying variations in metabolic activity, PET scans help differentiate between tumor presence and other conditions, such as necrosis. However, PET scan availability can be limited and costs are often high. As PET technology becomes more mainstream in neuro-oncology, costs are expected to decrease. This underscores the importance of



Photo Credit Margo Singer

receiving care at a specialized medical center with a dedicated neuro-oncology team and access to advanced imaging technologies.

Types of PET Scans and Tracers

Several types of PET scans are commonly used for diagnosing and monitoring brain tumors. These include fluoro-L-phenylalanine (F-DOPA or 18F-DOPA) and fluorodeoxyglucose (FDG), one of the original tracers. Other options are MET and FET tracers. The adoption of 18F-Fluciclovine and other amino-acid-based PET tracers (such as 18F-FET and 18F-DOPA) is rapidly advancing from experimental research to becoming a critical diagnostic standard in neuro-oncology. These newer tracers are especially valuable due to their specificity, sensitivity, and accuracy; they offer high tumor-to-brain contrast and are not restricted by the blood-brain barrier.

International Recommendations and Clinical Benefits

Amino acid PET imaging is now recommended by international working groups, such as PET-RANO, because of its exceptional clinical value for glioma patients compared to standard anatomical MRI. Its widespread clinical use at all disease stages is justified by the significant advantages it provides, which include:

- **Differentiating Recurrence (Progression) from Treatment Effects (Pseudoprogression):** PET scans use lesion-to-normal brain tissue ratios to distinguish progressive disease from necrosis, making them a strong predictor of tumor progression. Traditionally, the sensitivity of FDG-PET for differentiating tumor recurrence from necrosis ranges from 81% to 86%, with some suggesting even higher accuracy. Tumor volume affects accuracy, and PET is generally less useful for small, low-volume tumors. The PURSUE trial (NCT04410367) established a criterion (SUVmax > 4.8) to achieve 80% sensitivity and 85% specificity for identifying recurrent metastases. Fluciclovine has demonstrated 90% sensitivity and 83% specificity in distinguishing glioblastoma recurrence from treatment effects, and it often detects metabolically active tumor regions not visible on MRI.
- **Improved Accuracy Over Traditional Tracers:** Fluciclovine typically provides a higher lesion-to-normal brain ratio than older tracers like 11C-Methionine (MET).
- **Surgical and Radiation Planning:** PET imaging helps define Biological Tumor Volume (BTV), often revealing tumor infiltration beyond what is

visible on T1-weighted MRI, which allows for more targeted biopsies and surgical resections.

Theranostics and Future Directions

The concept of "theranostics"—combining therapy and diagnostics—using amino acid tracers is an emerging area in neuro-oncology. Amino acid PET can act as a biomarker for treatment response; patients who are "metabolic responders" (those with decreased tracer uptake) have shown significantly longer survival, even when MRI findings are unclear. These tracers target specific biological pathways (such as LAT1 and ASCT2 transporters), which may become targets for future radioligand therapies.

Blood Tests

Your doctor will probably ask you to take regular blood tests during treatment. This is to monitor the effects of treatment on your blood since treatments like chemo can discourage your bone marrow from producing enough blood cells at the level necessary for a reasonable degree of health.

Each type of blood cell has a range that's considered normal or healthy. Ranges are used rather than a specific number because the number can vary from person to person or within the same person from day to day.

The three blood cell types and their optimal ranges are:

- Platelets, which help blood clot. The normal range for platelet count is 150,000/milliliter (mL) to 400,000/mL.

- Red blood cells, which deliver oxygen throughout your body. Red blood cells may be measured in two different ways. Hematocrit is the proportion of red blood cells in your blood. The normal range for men is 40% to 55% and for women is 36% to 48%. Hemoglobin is a protein in red blood cells. The normal range for men is 13.0/deciliter (dL) to 17.0 g/dL and for women is 11.5/dL to 15.5 g/dL.

- White blood cells, which fight infection. The normal range for white blood

cells is 5,000/mL to 10,000/mL.

If your doctor says you're fine but your tests results are somewhat different from the ranges shown here, don't be alarmed. Some labs interpret test results a bit differently from others, so these figures are not absolutes.

If, however, your doctor feels that one or more of your blood cells are too low, the doctor may want to delay your next chemo cycle until your blood cells have had more time to recover from the last treatment.

SURVIVOR STORY #9

In June 2000, when I was 33 years old, my life quickly changed. I began having headaches that felt as if my skull were going to explode. An MRI scan showed that my brain was hemorrhaging, and I went immediately into surgery. An acorn-sized glioblastoma tumor was found in my left temporal lobe. I was told I had less than a year to live.

I quit my job to be a stay-at-home mom, wanting to spend every precious moment with my boys. I went into conformal brain radiation. I refused chemotherapy because standard treatment at that time had seriously bad side effects and would only add a few months to my life.

In July 2004, the glioblastoma came back. I had awake surgery since the glioblastoma was located in my left temporal lobe and there was a high risk of my losing the ability to speak. After surgery I went on the 5-day, 23-week temozolomide (Temodar) schedule.

Again, the glioblastoma came back, and I went into brain surgery a third time. The tumor was only the size of a "pea," but during surgery a buffer around the tumor was removed. After surgery I again went back on temozolomide.

In March 2009, the glioblastoma came back a fourth time. This time the tumor was not even located in my brain but in the meninges (the layer of tissue that covers the brain). I went into surgery a fourth time and all "visible" tumor was removed. The brain itself looked nice and clear, no visible tumor in the brain itself. After surgery, I could not go back on temozolomide since it had quit working for me, and I did not qualify for

any clinical trials because of the third reoccurrence of the cancer and my treatment history. We decided to keep an eye on the tumor with MRI scans every 2 months. Now, fast forward to 2018, I have endured three more recurrences of my brain tumor. The last recurrence was last year, when it was discovered that I had a grade 3 anaplastic pleomorphic xanthroastrocytoma (a rare type of anaplastic astrocytoma) located in my pituitary gland. Because the tumor was inoperable I went through four weeks of radiation therapy. At the end of the year, my MRI scan looked clear, with no glioblastoma or xanthroastrocytoma seen.

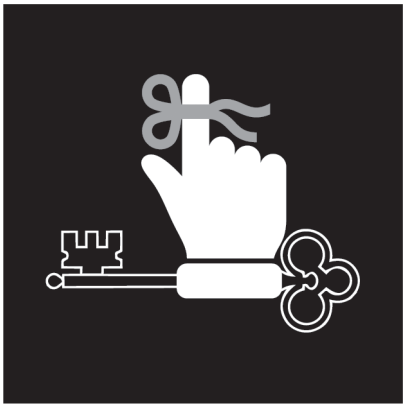
Over time I have experienced many deficits. Some of these have been challenging, others I have managed. Most people would never know that I am battling brain tumors. I seem normal. However, my family and good friends know I am seriously suffering in the fight.

But I love life, and I will never regret this fight: it has been well worth it. Since my last recurrence, I have had fun with my family, hugged my boys goodbye at college, celebrated holidays, and enjoyed the beauty around me. During these years, connecting with others battling brain tumors has inspired me so much. Al Musella and the virtualtrials.org website have been so helpful. Reading survivor stories is encouraging. Please don't feel it is over. Don't listen to the statistics. We can still love life and have fun even as brain tumor patients.

Photo Credit Linda Singer



KEY TAKEAWAYS TO REMEMBER



A healthy diet can help reduce treatment side effects. Many clinics offer nutrition classes for cancer patients, so consider attending one.

Always consult your doctor or nutritionist before using antioxidants, as timing and dosage matter during treatment.

Staying hydrated during treatment helps flush chemo residue and prevent constipation.

The link between diet and brain tumors isn't clear. As studies come out, the Musella Foundation will keep you abreast through its news Blasts. You can sign up for the Blasts at this link: https://virtualtrials.org/newsblast.cfm

Expect that your doctor will order regular scans like MRIs to monitor the disease.

Early MRIs after surgery and radiation may be unclear due to inflammation and could be inconclusive.

Pseudo-progression—tumor puffiness from treatment—occurs in 20-30% of cases. Your doctor may wait for follow-up scans to make a clear interpretation.

Get copies of your brain scans and interpretations to share with your medical team for a second opinion to ensure that they agree with the interpretations.



Seventeen

Side Effects

Memory and Cognitive Effects

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.

Tumor Side Effects

Karnofsky Performance Status

A rating system, called the Karnofsky Performance Status (KPS), was developed in the late 1940's by Drs. David Karnofsky and Joseph Burchenal to aid doctors in assess the functionality of a person due to their brain tumor, since a brain tumor can present a complex of conditions. The KPS, which remains in use today, allows a doctor to rapidly classify a patient and their treatment needs. The KPS is presented below.

SCORE	GENERAL CONDITION	COMMENTS
100	Able to carry on normal activity and to work. No special care is needed.	Normal, no complaints, no evidence of disease
90		Able to carry on normal activity, minor signs, or symptoms of disease.
80		Normal activity with effort, some signs, or symptoms of disease.
70	Unable to work. Able to live at home, care for most personal needs. A varying degree of assistance is needed.	Cares for self, unable to carry on normal activity or to do active work.
60		Requires occasional assistance but is able to care for most of his needs.
50		Requires considerable assistance and frequent medical care.
40	Unable to care for self. Requires equivalent of institutional or hospital care. Disease may be progressing rapidly.	Disabled, requires special care and assistance. [In bed more than 50% of the time].

30		Severely disabled, hospitalization is indicated although death not imminent. [Almost completely bedfast].
20		Hospitalization necessary, very sick, active supportive treatment necessary. [Totally bedfast and requiring extensive nursing care by professionals and/or family].
10		Moribund, fatal processes progressing rapidly. [Comatose or barely arousable].

ECOG Performance Status Scale

A patient's functional status may, as an alternate to the KPS, be evaluated in accordance with the ECOG Performance Status Scale. This scale was developed by the Eastern Cooperative Oncology Group (ECOG), now the ECOG-ACRIN Cancer Research Group, and was published in 1982. This scale, which is also called the WHO Performance Status or Scale, is used by researchers when planning cancer clinical trials to study new treatments. The ECOG Scale is presented below.

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours

3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Deceased

Seizures

Roughly 30 to 40% of people diagnosed with a 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.



Photo Credit Linda Singer

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. A list of the most commonly prescribed anti-seizure medications can be seen in the section entitled "Medications for Reducing Seizures".

What Causes Seizures

There are star-shaped cells involved with any glioma called astrocytes. The astrocytes that surround the remaining piece of tumor or are in the tumor environment take on a strange shape and act very differently. These weird and dysfunctional astrocytes mimic the response of the brain to some injury or trauma, and they cause swelling. They will do this in reaction to the presence of any part of the tumor, and/or to treatment effects from radiation or chemo. Basically, anything that makes these odd astrocytes unhappy will turn them into swelling producers.

That swelling, which is liquid suspended between brain cells, interferes with the delicate balance brain cells need between excitability and inhibition in order to function properly. That lack of balance can trigger harmful levels of excitability, which in turn can be enough to spark a seizure.

Plus, gliomas try to take over the brain's microvasculature system so that they can get a fresh supply of nutrients to grow. As they grow, they release toxic levels of glutamate, an excitatory neurotransmitter, which can kill off healthy neurons, making space for the cancer to grow. An abundance of glutamate can also cause more neurons to become electrically active, which can result in seizures. Ordinarily, one would expect the astrocytes, which are supposed to protect healthy brain cells from the high levels of glutamate by acting like a mini-vacuum cleaner and vacuuming up the excess glutamate, but the astrocytes are dysfunctional as previously described.

Introduction to Cancer Neuroscience

An emerging frontier of research, "cancer neuroscience", has led to a clinical trial with "gabapentinoids", including gabapentin and pregabalin, which are FDA-approved agents commonly prescribed for seizures and neuropathic pain. In a recent study, patients who were administered gabapentin after the surgical removal of newly diagnosed glioblastoma showed improved survival rates compared to those who did not receive the medication. This finding supports the theory that seizures may contribute to the growth of glioma. As a result, controlling seizures is emphasized as a crucial component of care for patients with gliomas.

Currently, the clinical trial NCT05664464 is underway to examine the effects of drugs that can cross the blood-brain barrier and target glutamate. Additional future studies are planned to evaluate the impact of gabapentin on overall survival for patients with glioblastoma. These studies will focus on dose-response relationships, long-term follow-up, and progression-free survival.

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: Sleep goal should be to achieve the number of hours recommended per night (e.g., 7 to 9 hours for adults). Need to pick a schedule and stick with it, as consistency is key. Sleep deprivation or even changes in sleep schedules can trigger seizures. Sleep deprivation is a huge trigger. Not getting 7 to 9 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.

Photo Credit Margo Singer



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



Photo/Styling Andy Singer

(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 could lead to insomnia, irritability, or restlessness.

Hiccoughs/Hiccups

Hiccoughs (hiccups) do happen in some people. It does help to avoid acidic, greasy, and spicy foods. Really persistent hiccoughs (sometimes lasting days) can be associated with neural dysfunction caused by the tumor (or its residue). When this happens, the hiccoughs are being caused by what could be thought of as a tiny epileptic event. They are not necessarily harmful by themselves but can be terribly annoying and can interfere with sleep. When that occurs, the doctor needs to get involved. Drugs that are used to treat this kind of hiccoughs would be a muscle relaxer like Baclofen (Lioresal/Gablofen, etc.), or an anti-epileptic like Carbamazepine (Tegretol). In really severe cases, the doctor might prescribe even stronger medications like Lorazepam (Ativan) or Haloperidol (Haldol).

Steroid-Induced Hiccups

Steroids, with dexamethasone in particular, are frequently recognized as triggers for hiccups in patients with cancer, especially those diagnosed with brain tumors. This adverse effect is well documented and is considered to be dose-dependent, typically occurring at doses above 10 mg per day. However, hiccups may arise at various dosage levels. Notably, steroid-induced hiccups are significantly more common in men compared to women.

Management Strategies

The management of steroid-induced hiccups usually involves one of three main strategies:

1. Discontinuation – Simply stopping the steroid medication often leads to resolution of hiccups within one to three days. (Make sure your doctor approves with pausing this medication before you do so.)

2. Dose Reduction – Lowering the steroid dose may relieve hiccup symptoms while still maintaining the desired therapeutic effects.

3. Steroid Rotation – Switching the patient from dexamethasone to methylprednisolone or prednisolone can resolve hiccups without sacrificing the anti-inflammatory benefits of steroid treatment.

Pharmacological Options

When modification of steroid therapy is not possible, several medications may be considered to manage steroid-induced hiccups:

1. Metoclopramide (Reglan) – This medication is often chosen first due to its effectiveness and favorable safety profile.



Photo Credit Stuart Volkow

2. Baclofen – A muscle relaxant that is commonly prescribed for persistent hiccups.

3. Chlorpromazine – The only FDA-approved medication for intractable hiccups. It must be used cautiously because it can cause sedation and lower blood pressure.

4. Gabapentin – This medication is emerging as an effective option for treating neurogenic hiccups.

Side Effects of Treatment

Fatigue

Fatigue resulting from chemo, radiation, and poor nutritional status is very common in cancer patients. The following describes some ways in which you can get some relief from this symptom:

Physical Pain. If you are experiencing a physical pain somewhere, tell your doctor and get it treated. Do not suffer in silence. Pain is a fatigue producer.

Emotional Pain. If you are experiencing anxiety or depressive emotions, tell your doctor and get it treated. Certain medications actually can both lift your mood and sensitize the cancer cells so that your chemo works more effectively.

Get moving. Planting yourself in a recliner is not a recipe to success; it is a fast track to fatigue. Those with the least fatigue stay active and engaged.

Eat well. For its size, even a healthy brain slurps up more than its fair share of calories than the other organs of the body and for a brain fighting back against cancer, the caloric requirements are as serious as if your brain was cycling up a steep hill. There is a section in this Guidebook that covers diet.

Eat well (again). Your bone marrow is busy trying to make new blood cells to replace those destroyed by chemo and it needs good nutrition to do that. You need to be eating sufficient, lean, good quality protein in order to have the building blocks (amino acids) required to make new blood cells. Most cancer

treatments decrease the number of red blood cells, which causes a decrease in the amount of oxygen that gets delivered throughout the body and when the oxygen in the tissues is low, fatigue follows.

Sleep. The brain heals and regroups during sleep, and if it doesn't get sleep, fatigue is sure to follow. However, treatments can really cause problems with sleep. Make sure to go to bed at exactly the same time every night, even on weekends. This is a really important because it programs/reprograms your body into how to go to sleep; sometimes after a trauma like surgery, the body just forgets how to go to sleep and stay asleep for the requisite amount of time. If you find that you are just unable to restore a good sleeping pattern after two weeks of trying, tell your doctor and get his or her advice for getting you back to your much needed sleep.

Behavioral Changes

A person who has had a tumor removed from their brain and is potentially facing a tough diagnosis can be expected to have their personality impacted. Not many people would take that sort of an experience with a carefree attitude. Some of the changes you can expect include the following:

Depression. Depression is actually one of the first symptoms of the disease owing to the stress the brain is under owing to the presence of a tumor. The reasons for the depression are not clear, but apart from the obvious turbulence on the physical organ-brain from the disease, depression is probably linked to these kinds of factors:

- The psychological/ spiritual load of being diagnosed with this disease;
- Concerns about work and financial concerns;
- The effects of some drugs required for treatment (some drugs, like certain anti-seizure meds can have a depressive effect. If this is noticed and is intolerable, discuss with the doctor.);
- Wanting to return to one's prior normal life and vitality;
- The effects of medical procedures (e.g., some people are offended/ humiliated by having to dress into hospital gowns and get transported by

wheelchair through hospital hallways in public; others feel demeaned by losing their hair from chemo, having a scar on their head, and having to put up with stares and well-meaning but hurtful comments from others);

- Concerns about possible pain and loss of dignity.

There are probably other factors that others may bring up, but just those are enough for anyone. This is not a symptom that should be ignored but rather should be discussed with the doctor. Some neuro-oncologists report writing more prescriptions for anti-depressants than for chemo plus some anti-depressants can help sensitize the cancer cells to chemo, so an anti-depressant can provide two benefits.

Irritability/Anger. Some medications, notably steroids and anti-seizures, may elevate a person's irritability or anger threshold. Keppra (Levetiracetam), the most often prescribed anti-seizure med, can produce serious levels of anger and irritation in sensitive individuals. Dexamethasone, the most often prescribed steroid, can make a person very nervous, agitated, and unable to get a solid night's sleep leaving them irritable. If you notice unusual levels of irritability or anger, you should discuss the matter with the doctor who may be able to adjust your dosage or switch your medication to a more tolerable one.

Hair Loss During Treatment

What Causes Hair Loss?

Some hair loss may occur with radiation, but it is more commonly associated with high doses of chemotherapy. This side effect is one of the most visible and emotionally difficult aspects of cancer treatment. Many patients experience feelings of lost privacy, identity, or control. Knowing the reasons for hair loss, what to expect, and how to cope can help you feel more prepared throughout your treatment journey.

Chemotherapy targets rapidly dividing cells, which includes cancer cells as well as healthy cells like those in hair follicles. When these healthy cells are affected, hair can thin or fall out. The extent of hair loss depends on the chemotherapy drugs used, the dosage, and your individual response. Not all chemotherapy medications cause hair loss. Your oncology team can give you information about the likelihood of hair loss with your specific treatment plan.

What to Expect

Hair loss usually begins two to four weeks after starting chemotherapy. Some people notice gradual thinning, while others see their hair come out quickly, sometimes in clumps. Before hair loss starts, you may feel tenderness or sensitivity on your scalp. Hair loss can affect not only the scalp, but also eyebrows, eyelashes, and other body hair.

While losing your hair can be upsetting, remember that chemotherapy-related hair loss is typically temporary. Most people see hair starting to regrow one to three months after treatment ends, but full regrowth may take six to twelve months. Hair may feel different at first—softer, curlier, straighter, or even a different color—but these changes are usually temporary as your hair continues to recover.

Preparing for Hair Loss

Many patients find it helpful to plan for hair loss before it begins. Some choose to cut their hair shorter to make thinning less noticeable, while others explore wigs or head coverings in advance. Insurance plans may cover part of the cost of a wig, often referred to as a "cranial prosthesis." Organizations such as the American Cancer Society provide information, support programs, and wig resources.

Head coverings are a personal decision. Some people prefer wigs, while others are more comfortable with scarves, turbans, hats, or caps. There is no right or wrong choice—the best option is what makes you feel most comfortable and confident.

Caring for Your Scalp and Hair

During chemotherapy, your scalp may become dry or sensitive. Gentle care is essential. Use a mild, fragrance-free shampoo and pat your hair dry instead of rubbing. Avoid heat styling tools and use a soft brush to minimize irritation. Protect your scalp from sun exposure with sunscreen or a hat and keep your head warm in cold weather.

After shampooing, use a conditioner designed for fine or limp hair. Avoid hair curlers, though gentle use of sponge curlers may be acceptable as long as you don't sleep in them. Do not color, bleach, or process your hair, and avoid vigorous brushing.

Try to avoid using hair dryers, but if you must, use the lowest heat setting possible.

Avoid hot water on your scalp—tepid or cool water is best, as coolness can be stimulating.

Products advertised to regrow hair are not effective for hair loss from cancer treatment and are not worth the expense.

There is a cap called the DigniCap that is designed to reduce hair loss, but it is not recommended for patients with brain tumors or central nervous system malignancies.

Save some of your fallen hair if you plan to buy a wig—it can help you match your natural color. If you decide to shave your head, use an electric razor rather than a manual razor to avoid nicks and infection. It's best to have someone you trust help you with shaving.

Eating healthy foods supports hair follicle recovery. Daily scalp massage with a drop or two of olive oil can stimulate circulation and may help speed up regrowth, though the difference may not be obvious. Vibrating head massagers are also available. The key to regrowing your hair is stimulating circulation in your scalp.

Use a cotton or satin pillowcase to avoid irritating your scalp while sleeping. If you go outside without a head covering, apply sunscreen to your scalp, which will be very sensitive to sunlight.

Most hospitals have wig salons, and the staff are familiar with caring for sensitive scalps, such as using cotton liners under wigs. The American Cancer Society can recommend wig salons and may help with the cost. Insurance may cover the expense, and wigs may be tax-deductible medical expenses—keep your receipts for any out-of-pocket payments.

Emotional Support

The emotional effects of hair loss should not be underestimated. It is normal to feel sadness, frustration, or anxiety. Talking openly with your care team, joining a support group, or meeting with a counselor can be helpful. Many cancer centers offer patient support services, counseling, and image recovery programs to help you manage these changes.

When to Contact Your Care Team

If you notice redness, itching, rash, severe scalp pain, or signs of infection such as warmth or drainage, contact your healthcare provider right away. Your care team is there to help you manage side effects and keep you comfortable during treatment.



Photo Credit Steve Tilkin

Effects Of Treatment And Medication On Libido and Sex

For patients undergoing treatment for a brain tumor, a decrease in sexual desire or in the ability to enjoy normal sexual activity is common. Deciphering the origin of these changes can be difficult, for many factors can be involved. While surgery causes postoperative fatigue and temporary physical weakness, chemotherapy and radiation can greatly affect and reduce your desire for sexual stimulation because of adverse effects on hormone production. So, too, can medications prescribed for the symptoms of brain tumors, such as swelling, seizures, nausea, anxiety, and depression.

Physical changes, such as hair loss and weight gain, can further undermine your sense of attractiveness and desirability, deepening the emotional separation from sexual contact. Individually or in various combinations, these side effects create in some cases a daunting puzzle that requires patience and communication to piece together.

Depression is common among brain tumor patients, a condition often controlled with antidepressant medication — for example, with selective serotonin reuptake inhibitors like Paxil (paroxetine) or Zoloft (sertraline). These medications can reduce sexual desire. A simple change in dosage or medication may help restore sexual desire and should be discussed with your prescribing physician.

While most treatment-associated dysfunction or lack of desire is temporary, being able to openly discuss difficulties and options for sexual intimacy with your partner and with your medical team can help in managing the extent of disruption and being able to resume normal sexual relations after treatment. Unfortunately, discomfort among health professionals in discussing sex with the same openness and honesty with which they discuss nausea, diarrhea, and even expectations for recovery can complicate your ability to understand — and prepare emotionally for — how treatment might affect sexual desire. For this reason, patients often find it beneficial to discuss issues of intimacy with other members of their medical team, such as counselors or neuropsychologists. These healthcare professionals will be familiar not only with the impact of brain trauma and the effects of medication but also with the emotional toll borne by the patient.

Birth Control

If you take birth control pills, it is important to discuss the potential effects of your treatment with your gynecologist and with your medical team for your tumor. Chemotherapy may halt menstrual periods temporarily, but precaution against pregnancy must be maintained due to the devastating effects of chemotherapy for an unborn fetus. Some chemotherapy medications, as well as anti-seizure drugs, can interact with the effectiveness of birth control pills. Likewise, some form of contraception is often required to participate in a clinical trial to avoid unintended harm to a fetus. A thorough discussion with your medical care team is essential.

Sex, Surgery, And Brain Tumor Treatment

In most cases, there are few reasons why you cannot have sexual relations while undergoing radiation therapy or after surgery. However, you should always consult with your medical team regarding any precautions against strenuous activity, including sex. Both radiation therapy and surgery can result in fatigue, making any strenuous physical activity difficult. As your strength returns, normal sexual activity can resume.

Likewise, unless your medical team specifically warns you against sexual activity while undergoing chemotherapy, normal relations are limited only by the precautions associated with the drugs themselves. Because chemotherapy drugs can be

transferred through sperm, in some cases they can also be harmful to sperm and also damage a fetus. Condoms should thus always be used during both intercourse and oral sex to eliminate the possibility of exposing another person either vaginally or orally to the harmful effects of chemotherapy drugs.

Because sperm can live for up to three months, condoms should be used until three months have passed since the last chemotherapy treatment. Although dry orgasms can occur naturally on occasion as men age, chemotherapy can also cause this syndrome. The lack of ejaculation during orgasm is not cause for alarm and should have no adverse effect on pleasure.

Women receiving chemotherapy must take extra precaution against pregnancy, for birth defects can result from these drugs. Discuss your method of birth control with your medical team and be sure to specifically discuss whether there might be any possible reduction in the effectiveness of your birth control pills during chemotherapy. Chemotherapy can also dry out mucus membranes within the nose, mouth, and vaginal area. Non-petroleum over-the-counter vaginal lubricants can assist with the temporary dryness associated with chemotherapy, relieving the discomfort and pain often experienced during sexual relations while on chemotherapy. Because petroleum-based products can irritate the vaginal area and also weaken condoms, they should be avoided.

SURVIVOR STORY #10

On June 1, 2005, just five weeks after the birth of my first child, I was diagnosed with glioblastoma. This malignant and deadly type of brain tumor was the size of a woman's fist. Glioblastoma patients are told that "it's not a matter of if, it's a matter of when" the tumor will come back.

I quickly underwent brain surgery to remove the glioblastoma. The problem with brain surgery is that the doctors don't know what they will find until they cut into your head and take a look. After discovering that removing the tumor could cause a loss of mobility on my left side, the surgeons removed only half of it. I was told I would be lucky to live a year. I kept telling the doctors that that couldn't be right, because I had just had my first child.

My husband and I were not going to give up easily. We hit the road to visit some prestigious cancer centers after receiving the worst possible pathology report. Both brain tumor clinics recommended that I "re-do" my brain surgery to complete the removal of the tumor. I chose one of these centers to coordinate all of my treatment. I also went on long-term disability to cover my medical bills and keep my business afloat. In July 2005, surgeons operated again to remove the remaining tumor, a procedure that was successful.

At that time, I entered a clinical trial that involved the implantation of a drug locally at the affected areas in my brain, treatment that required a four-day stay in a neuro-intensive care unit. Most brain surgeries remove the tumor but not all the damaged cells. The new procedure was a way to kill off the remaining damaged cells and prevent the tumor from coming back. I was lucky that my health insurance paid for the hospital stay and all expenses. Frequently, we had no idea whether our health insurance would pay for an experimental treatment if needed.

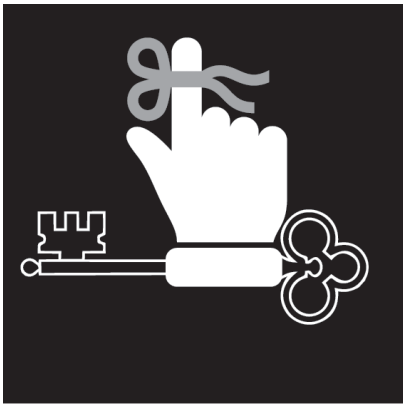
The surgeries and experimental drug procedure were a success. Nonetheless, I lost a lot of my cognitive function, and it took weeks for me to recover.

As if the brain surgeries weren't enough, my family and I moved to the location of the cancer center to receive a complete series of radiation treatment. After radiation, I then began a year of chemotherapy. I returned to work during this important recovery period.

Because of my disability insurance, I didn't have to come back to work, but I love what I do. But without the disability income, I would not have been able to keep my business afloat. It was a life saver.

Now, in 2018, I have had clean MRI scans for 13 years. I attribute my success to mindset, resilience, and tenacity — all of the qualities than enabled me to see beyond a terrible diagnosis in 2005. I strive to continue to set an example to my son, my family, my peers, and my community, in hopes that I can create even a small amount of impact while I am here.

KEY TAKEAWAYS TO REMEMBER



Both the tumor and its treatment can produce a range of frustrating even frightening side effects. Not everyone will have all the side effects described here and some may have side effects not discussed here. It's a good idea to have a candid discussion with your doctor about what you can expect and what you can do about them should they arise.

If you are in your child-bearing years, talk to your doctors about using birth control and consider using sperm banks or egg harvesting.

Chemo treatment can produce birth defects. Use contraceptive protection.





Eighteen

Survivorship
Living Meaningfully in the Midst of Uncertainty

Introduction: Survivorship When the Diagnosis Is Serious

For people diagnosed with a high-grade brain tumor, the word survivorship may sound confusing or even insensitive and inappropriate. These tumors are often described as life-threatening, or incurable; the tumor and its treatment are often referred to as aggressive. From the beginning, the conversation may focus on prognosis and timelines rather than living.

And yet, people do survive—sometimes for months, sometimes for years, sometimes far longer than expected. There are more long term (greater than 5 years) survivors for glioblastoma, the worst of these tumors, than in the past. Although it is uncommon, some patients do live many years after diagnosis. Large registry data suggest roughly 5–7 % of people diagnosed with glioblastoma are alive at five years, and some individuals live far longer than this.

While high-grade brain tumors like glioblastoma remain very serious diagnoses, encouraging trends are emerging, especially with innovative treatments and advances in medical care. Meaningful increases in progression-free survival (PFS) and overall survival (OS) are being achieved in multiple studies of advanced treatments, like DCVax.

Emerging therapies like tumor-treating fields (TTFields), immunotherapies (including CAR-T and vaccines), and precision medicine approaches are actively being studied and have shown tumor shrinkage or extended survival in some trial participants. While these are not yet standard for all patients, ongoing research continues to push survival boundaries.

Individual case reports and community experiences also describe survivors living eight, ten, or more in rare situations, particularly when tumors have favorable molecular features that are treated at specialized centers.

Survivorship in high-grade brain cancer is not defined by cure. It is defined by living meaningfully in the midst of uncertainty.

This chapter is written for people living with high-grade brain tumors and for those who love and care for them. It names realities honestly while affirming that your life, now and going forward, deserves attention, care, and respect.

Survivorship Programs

Exactly because of improvements being made in survival, survivorship programs are being initiated at multiple major cancer centers to assist patients in navigating the challenges. Examples of programs include these:

- Dana-Farber Cancer Institute (Harvard/Brigham)– Survivorship care integrated into comprehensive oncology care.
- Johns Hopkins Sidney Kimmel Comprehensive Cancer Center– Survivorship programs across specialties.
- Mass General Brigham Cancer Institute (Massachusetts General Hospital)
- Mayo Clinic Comprehensive Cancer Center Personalized survivorship care plans and follow-up services across locations (Rochester, Scottsdale, Jacksonville).
- MD Anderson Cancer Center– Long-term survivorship clinics across multiple cancer types (pediatric & adult) and structured survivorship care.
- Memorial Sloan Kettering Cancer Center– Survivorship clinics for adult and pediatric survivors with follow-up planning and late effect monitoring.
- Moffitt Cancer Center- Total Cancer Care® (TCC). This protocol, which forms a lifetime partnership with cancer patients and includes survivorship, has been adopted by numerous leading cancer centers through a consortium called Oncology Research Information Exchange Network® (ORIEN).
- Penn Medicine / Abramson Cancer Center– One of the first adult survivorship programs in the U.S. with extensive follow-up services. See https://www.pennmedicine.org/specialties/cancer/survivorship-care



Drawing by Sarah Gimigliano

- Robert H. Lurie Comprehensive Cancer Center (Northwestern)– Survivorship institute with adult and youth programs.
- UCLA Jonsson Comprehensive Cancer Center– Survivorship support, integrative oncology resources, and long-term care planning.
- UCSF Cancer Survivorship & Wellness Institute– Holistic post-treatment care at UCSF's model Sheri Sobrato Survivorship Program. See https://braintumorcenter.ucsf.edu/support/survivorship
- University of Kansas Cancer Center– Survivorship clinics covering multiple cancer types.
- Wake Forest Baptist Health Survivorship Clinic– Regional formal clinic for post-treatment care.

Many other hospitals have survivorship services available, though they may be more regional or smaller than the national centers above.

Experts at these facilities can answer your questions, suggest appropriate lifestyle changes, and outline a care plan that focuses on improving your quality of life and staying as healthy as possible.

When Does Survivorship Begin in High-Grade Brain Cancer?

In high-grade brain tumors, survivorship begins at diagnosis. You do not need to finish treatment, achieve remission, or "beat" cancer to be considered a survivor. From the moment of diagnosis, you are navigating life alongside a serious illness. That is survivorship.

Some people reject the notion because it feels misleading or minimizing. Others embrace it as an act of defiance or truth. Both responses are valid. What matters is recognizing that your life and human needs continue, even when the future feels fragile. So, the best time to enroll in your hospital's survivorship program is as soon as possible.

Understanding The Prognosis Without Letting It Define You

High-grade brain tumors carry real risks, including a high likelihood of recurrence.

Survival statistics are often shared early and can feel overwhelming.

It is important to know:

- Statistics apply to populations, large numbers of patients, but each patient has their own trajectory, and there are an increasing number of long-term survivors. Do not be discouraged by "averages". Given the advances in the field and your own unique biology, it is very possible that you will be successful and have a much better prognosis than predicted by mere statistics.
- Statistics showing PFS or OS may be the "gold standard" endpoints in oncology, but they describe populations, not individuals
- PFS and OS statistics are based on past data, not your specific future
- These statistics cannot measure your personal resilience or response to treatment

Many survivors of high-grade tumors are living longer than expected and they are living more fully.

Others live for shorter periods but with depth, connection, and dignity. Survivorship is not about denying prognosis. It is about not allowing statistics to erase your personhood.

Handling the Fear of Recurrence

Illustration Credit Stuart Volkow



Fear of recurrence after a brain cancer diagnosis is not a sign of weakness or pessimism—it is a normal human response to having lived through uncertainty, loss of control, and real threat. For many people, this fear comes and goes in waves, often intensifying around scans, anniversaries, or new symptoms. While it may never disappear entirely, it can be handled in ways that keep it from dominating daily life.

One of the most important steps is naming the fear rather than fighting it. Trying to suppress

fear of recurrence often makes it louder. Acknowledging—"This fear makes sense given what I've been through"—can allow the emotion to pass more quickly. Many survivors find it helpful to distinguish between possibility and probability: recurrence is possible, but that does not mean it is happening now.

Structure and predictability can also reduce anxiety. Clear follow-up plans, written surveillance schedules, and knowing who to call with concerns help contain fear so it does not spill into every thought. Some people intentionally "contain" worry by setting aside a brief, regular time to write or think about fears, rather than letting them intrude all day.

Learning to interpret bodily sensations realistically is another key skill. Brain tumor survivors are understandably hyper-attuned to headaches, fatigue, or cognitive slips. Working with a clinician to understand which symptoms are expected, which warrant monitoring, and which truly require urgent attention can prevent fear from escalating with every sensation.

Psychological tools are often very effective. Cognitive behavioral therapy (CBT) can help interrupt catastrophic thinking ("This headache means the tumor is back"), while acceptance-based therapies teach people to live meaningfully even with uncertainty. Mindfulness practices, especially those focused on grounding in the present moment, can reduce the mental spiraling that often accompanies scan anxiety.

Equally important is reclaiming your identity beyond the illness. Fear of recurrence tends to shrink life; intentionally expanding your life through relationships, purpose, creativity, spiritual practices, or service can restore a sense of agency. Many survivors find that meaning-making, rather than reassurance, is what most weakens fear over time.

For some, peer connection is essential. Speaking with others who live with the same uncertainty can normalize fears in a way that clinicians alone cannot. Hearing how others cope and how life continues despite uncertainty often brings quiet relief.

Finally, it is important to recognize when fear becomes overwhelming. If anxiety interferes with sleep, decision-making, relationships, or joy, obtaining professional support is not a failure, it is an appropriate response to a profound life experience. In some cases, medication may be helpful, particularly when fear is accompanied by

depression or panic.

Living with the fear of recurrence means learning to carry uncertainty without letting it define your future. Over time, many survivors discover that while fear may still visit, it no longer rules their house, and that is a meaningful and hard-won form of survivorship.

The Physical Reality of Survivorship With a High-Grade Tumor

Ongoing Neurological Effects

High-grade brain tumors and their treatments often cause lasting neurological changes, such as:

- Cognitive slowing or memory loss
- Difficulty with speech or word-finding
- Weakness, balance problems, or coordination issues
- Seizures
- Visual or sensory changes

These effects may fluctuate and can worsen temporarily with treatment or recurrence. Survivorship often involves learning how to live with instability rather than steady improvement.

Seizure Control

Seizures may remain a long-term issue, even in stable disease. Seizures can occur because of residual tumor, scar tissue from surgery, radiation effects, or ongoing irritation of brain tissue. Importantly, a seizure does not always mean tumor progression. Many patients experience well-controlled disease yet still require long-term antiseizure medication.

Many brain tumor patients remain on antiseizure drugs indefinitely, especially if they have had one or more seizures. When a doctor prescribes an antiseizure medication for someone with a brain tumor, their objective extends well beyond simply "stopping seizures." Their overarching goal is to achieve the best possible balance

between seizure control, safety, and quality of life over the long term, because seizures can cause injury, loss of independence, hospitalization, and significant emotional distress. However, doctors are also well aware that effective seizure control supports daily functioning such as driving eligibility, employment, social participation, and a reduced fear of seizures occurring unexpectedly. These quality-of-life considerations are a core objective of treatment.

Seizure Medications

The "right" medication balances seizure control with cognitive clarity, mood stability, and fatigue. Doctors aim to choose a medication that controls seizures without unnecessarily impairing thinking, memory, speech, or attention. This is especially critical in brain cancer, where cognition may already be affected by the tumor, surgery, radiation, or chemotherapy. Newer drugs (such as levetiracetam, lacosamide, or brivaracetam) are often preferred because they have fewer drug interactions, particularly with chemotherapy and steroids—but no single drug works best for everyone.

Cognitive slowing, irritability, mood changes, fatigue, or balance problems from seizure medications are not "just something to live with." Many of these effects can be improved by dose adjustments or medication changes. Because brain cancer patients already face cognitive challenges, seizure management should aim not only for seizure freedom but also for quality of life. If you are experiencing unwelcome or intolerable problems, you should have a frank discussion with your doctor.

Seizure Triggers

Common seizure triggers include sleep deprivation, illness, dehydration, missed medication, alcohol, and severe stress. Keeping a seizure diary, even noting near-misses or auras, can help your doctor fine-tune your treatment and may reassure you by revealing patterns rather than randomness.

Responding to Seizures

Patients and caregivers should know what to do if a seizure occurs: when to wait, when to give rescue medication (if prescribed), and when to call emergency services. Having a written seizure action plan reduces panic and improves safety, especially

in the home.

Driving restrictions vary by state and depend on seizure control. Patients should also consider practical safety adaptations, such as showering instead of bathing, avoiding ladders, and using caution around open flames, while recognizing that safety planning is meant to preserve independence, not eliminate it.

A new seizure type, increased frequency, or change in recovery time warrants prompt medical evaluation. While seizures do not automatically mean recurrence, changes may signal medication issues, metabolic changes, or treatment effects.

Long Term Seizure Management

The fear of having a seizure in public or while alone can be as limiting as the seizures themselves. Addressing this fear through education, counseling, and reassurance is a vital part of care. Many patients benefit from knowing that seizure control often improves over time, and that breakthroughs can usually be managed.

Ultimately, long-term seizure management in brain cancer is not just about preventing events; it is about protecting cognition, dignity, independence, and peace of mind. With attentive care and open communication with your doctor, most patients can achieve meaningful stability and confidence in their daily lives.

Living Well With Long-Term Optune Gio® Use

Using the Optune Gio® device over many months is not simply a treatment, it becomes part of daily life. While the therapy works quietly beneath the surface to disrupt tumor cell division, the day-to-day experience of wearing the cap, caring for the scalp, and maintaining routines can feel demanding. Learning how to manage Optune Gio® over the long term can make a meaningful difference in comfort, confidence, and adherence to therapy.

Consistency is essential to Optune Gio®'s effectiveness, but sustainability matters just as much. Most patients find that building a predictable daily rhythm, such as set times for array changes, scalp checks, and device care, reduces stress and prevents lapses. Over time, these routines become second nature, much like brushing teeth or

taking medication. Planning ahead for travel, appointments, or special events helps maintain treatment continuity without feeling constrained.

Maintaining Healthy Skin

Healthy skin is the cornerstone of long-term Optune use. The scalp is under constant contact, heat, and mild pressure, so proactive care is critical. Gentle cleansing, careful drying, and regular inspection help prevent irritation before it escalates. Small changes, such as rotating array placement slightly, ensuring the scalp is completely dry before applying arrays, and avoiding harsh products, can significantly reduce discomfort.

If redness, itching, or tenderness appears, addressing it early is far easier than managing advanced skin breakdown. Patients should never feel hesitant to report skin changes to their care team; these issues are common, manageable, and not a sign of failure.

Long-term Optune use teaches patients to become skilled observers of their own bodies. Tingling, warmth, or mild sensitivity may occur, especially during the early months, but persistent pain or open skin should always prompt evaluation. Adjustments, whether in array placement, wear schedule, or topical treatments, are often enough to restore comfort without interrupting therapy.

Use Fatigue/Maintaining Independence

Fatigue, frustration, or emotional weariness can also emerge over time. These responses are normal. Acknowledging them, rather than pushing through silently, allows patients and caregivers to find practical and emotional supports.

One of Optune Gio®'s strengths is that it allows patients to remain active and engaged in life. Thoughtful clothing choices, secure device placement, and confidence with battery management make it easier to move freely through the day. Many patients discover that once initial self-consciousness fades, the device becomes simply another part of their medical landscape - not their identity.

Maintaining independence includes learning how to troubleshoot alarms, manage supplies, and advocate for one's needs. Over time, patients often become experts in

their own care, which fosters confidence and autonomy.

Successful Long-Term Use

Successful long-term Optune use is a partnership. Regular communication with neuro-oncology providers, nurses, and device support specialists ensures that problems are addressed early and adjustments are personalized. No two scalps, schedules, or lifestyles are identical, and care plans should reflect that reality.

Patients are encouraged to ask questions, request demonstrations, and share honest feedback. The goal is not perfection, but steady, supported adherence.

Wearing Optune Gio® day after day can serve as a constant reminder of illness, which may stir anxiety, sadness, or fear of recurrence. Building emotional resilience through counseling, peer support, faith, mindfulness, or trusted relationships can be as important as managing the physical aspects of treatment. Many patients find strength in reframing the device not as a burden, but as an active form of protection they are giving themselves.

Long-term Optune use is a commitment to possibility. While it requires patience and adaptation, many patients find that with time, the challenges become manageable and the routines familiar. With attentive care, open communication, and self-compassion, patients can use Optune Gio® not just effectively, but sustainably, preserving comfort and dignity throughout treatment.

Summary of actions for successful long-term Optune Gio® use:

GOAL	KEY ACTIONS
Prevent irritation	Clean, shave gently, alcohol prep, regular array changes
Protect skin	Gentle removal, moisturize between changes
Manage irritation	Corticosteroids/antibiotics as needed, reposition arrays
Treating Issues	Prompt treatment of issues + clinician support

Reducing Your Risk of Stroke with Brain Cancer

Living with brain cancer can bring many challenges, and one of the less obvious risks is stroke. Certain tumors, treatments, and medications can increase the likelihood of changes in your blood vessels or blood flow, which may trigger a stroke. The good news is that there are many steps you can take to reduce your risk and protect your brain and heart.

There are several factors that may increase your risk of stroke. Brain tumors and their treatment can affect your blood vessels and blood flow in several ways:

- Tumors can press on or involve blood vessels.
- Cancer can make your blood more prone to clotting.
- Some treatments, like certain chemotherapy drugs or radiation, may impact your blood vessels over time.
- Steroid medications can raise blood pressure or blood sugar.
- Reduced activity or dehydration can increase clot risk.

Understanding these risks helps you and your care team take steps to protect yourself.
Even small improvements in everyday habits can make a difference:

- Blood Pressure: Keep your blood pressure under control. Monitor it at home, if possible, and discuss any changes with your doctor.
- Blood Sugar: Steroids and stress can raise blood sugar, which can increase stroke risk. Follow your diet and medication plan closely.
- Cholesterol: Your doctor may recommend medications to keep cholesterol in a healthy range.
- Smoking: If you smoke, quitting is one of the most powerful ways to protect your blood vessels.

Cancer can make your blood "stickier," increasing the chance of clots. Some patients may be advised to take medications like aspirin or other blood thinners, but these must always be prescribed and monitored by your doctor, especially with brain tumors, due to bleeding risk.

Important ways of reducing stroke risk are adhering to these lifestyle fundamentals:

- Drink enough water each day to stay hydrated.
- Move gently and regularly, even short walks or stretches.
- Avoid long periods of inactivity.
- Get adequate sleep.
- Practice stress reduction, such as mindfulness, meditation, or counseling.
- Eat a balanced, anti-inflammatory diet, whenever possible.
- Treat depression or anxiety—they can independently affect blood vessel health.

If you've had radiation, your blood vessels may be more vulnerable over time. Regular follow-up imaging and prompt attention to any new neurological symptoms are important as is proper seizure control and having your care team review your medications to ensure they are not adding extra risk to your heart or blood vessels.

Even with prevention, strokes can still happen. Knowing the warning signs can save precious time. Remember FAST:

- **F**ace drooping
- **A**rm weakness
- **S**peech difficulty
- **T**ime to call emergency services

Do not assume new symptoms are "just the tumor." Call (or have your caregiver call) for help immediately.

Stroke prevention works best when your care is coordinated. Your oncology team, neurologist, and primary care provider can work together to monitor your risk and keep you safe. Don't hesitate to ask: "Given my tumor and treatments, what is my specific stroke risk—and what steps are we taking to reduce it?"

While the stroke risk is higher for people with brain cancer, many strokes can be prevented. By managing blood pressure, blood sugar, cholesterol, staying active, taking medications as prescribed, and knowing the warning signs, you are actively protecting your brain and long-term health.

Mitigating Long-Term Cognitive Effects of Radiation & Other Brain Cancer Treatments

For many people living with or beyond a brain cancer diagnosis, treatment does not end when radiation, chemotherapy, or surgery is completed. One of the most common and challenging tell-tale effects of treatment involves changes in thinking, memory, attention, and processing speed. These cognitive changes can emerge gradually over months or even years, and they are influenced by the tumor itself, radiation exposure, chemotherapy, seizures, fatigue, emotional stress, and aging. While these effects can feel discouraging, there are many ways patients and care teams can work together to protect brain health and maximize cognitive function over the long term.

These changes can challenge your sense of self. Grieving who you were, and who you expected to be, is a normal part of survivorship. You are not failing at survivorship because you feel altered. You are responding to a neurological illness.

Understanding What Is Happening

Radiation therapy, while essential for controlling tumor growth, can affect healthy brain tissue. Over time, this may lead to slowed information processing, difficulty finding words, short-term memory challenges, or reduced multitasking ability. Chemotherapy, immunotherapy, antiseizure medications, steroids, and even chronic inflammation can further contribute to what many patients describe as "brain fog."

Recognizing that these changes are biological, not a personal failure, is an important first step toward effective management. Naming these changes openly allows patients and families to shift from frustration to problem-solving and self-compassion.

Survivorship begins with replacing the question "What's wrong with me?" with "What has my brain been through, and how can I support it now?"

Protecting the Brain During and After Treatment

Modern radiation techniques are designed to minimize cognitive harm whenever possible. Approaches such as targeted radiation, fractionated dosing, hippocampal

avoidance, and proton therapy may reduce exposure to critical memory centers. Patients should feel empowered to ask their care team how cognitive preservation was considered in treatment planning and whether follow-up imaging or neurocognitive monitoring is appropriate.

Ask for Formal Cognitive Evaluation

A neuropsychological evaluation can:

- Identify specific strengths and vulnerabilities
- Distinguish tumor-related changes from fatigue, mood, or medication effects
- Provide concrete recommendations for work, daily life, and rehabilitation

This evaluation is not about labeling deficits; it is about creating a roadmap for functioning in the real world.

Cognitive Rehabilitation and Mental Exercise:

Just as physical therapy helps restore movement, cognitive rehabilitation can help retrain the brain. Neuropsychologists and speech-language therapists can assess strengths and weaknesses and provide personalized strategies to improve attention, memory, organization, and word retrieval. Structured cognitive exercises, whether therapist-guided or computer-based, can help maintain mental flexibility and slow decline. Activities such as reading, puzzles, learning new skills, music, or languages also support neuroplasticity and brain resilience.

Cognitive rehabilitation can help patients:

- Learn compensatory strategies (lists, routines, alarms, visual cues)
- Improve attention, memory, and executive functioning where possible
- Reduce cognitive fatigue

Rehabilitation focuses less on "fixing" the brain and more on helping the person function successfully with the brain they have now.

Simplifying Life Without Shrinking It

Survivorship often means embracing a different rhythm of life. Instead of juggling multiple responsibilities at once, a person may choose to focus on fewer tasks, giving each one the time it truly needs. By letting go of nonessential obligations, you can create more room for what really matters. This mindful approach helps conserve cognitive energy, making it possible to dedicate attention to priorities even if those pursuits must now fit within new limitations.

Protecting Against Cognitive Fatigue

For many survivors, cognitive fatigue can be even more challenging than memory loss itself. It often interferes with daily life, making it difficult to concentrate, remember details, or sustain mental effort over time. To help manage this, survivors have found that scheduling demanding tasks earlier in the day, when their energy is highest, can make a significant difference. It's also important to build in periods of rest before exhaustion sets in, rather than waiting until fatigue becomes overwhelming. Limiting overstimulation, such as reducing noise, avoiding multitasking, and keeping conversations short, can further help preserve mental energy throughout the day.

Adopting a proactive approach to rest, rather than waiting until fatigue hits, is a core skill for survivorship. By learning to recognize personal limits and plan for breaks, you can better protect your cognitive health and maintain a higher quality of life.

Managing Physical Fatigue and Sleep

Following treatment for brain cancer, many people experience ongoing fatigue that can impact memory and thinking skills. If you have trouble focusing or feel mentally foggy, you're not alone; these symptoms often relate to tiredness and sleep patterns. Establishing consistent sleep habits, addressing sleep issues like apnea or insomnia, and learning practical ways to manage your energy during the day may help improve how you feel. Any changes in alertness or cognition are worth discussing with your healthcare providers.

Fatigue from high-grade brain cancer goes far beyond everyday tiredness; it is a profound exhaustion affecting the entire body and can make daily tasks daunting.

While you might want to maximize your time, your body now needs more rest. This struggle between activity and rest is valid and deserves recognition. There's no expectation to be constantly productive during recovery; rest is not only acceptable but vital for self-care.

Physical Activity and Brain Health

Regular physical activity is one of the most effective, evidence-based ways to support cognitive function. Even gentle exercise improves blood flow to the brain, reduces inflammation, supports mood, and enhances memory. Walking, stretching, yoga, swimming, or strength training—adapted to individual ability—can all be beneficial. Consistency matters more than intensity.

Nutrition and Vascular Health

The brain depends on healthy blood vessels and metabolic support. Managing cardiovascular risk factors such as high blood pressure, diabetes, cholesterol, and smoking is especially important after radiation, which can increase stroke risk over time. A balanced diet rich in fruits, vegetables, whole grains, healthy fats, and adequate protein supports brain health and energy levels. Staying well hydrated also helps reduce cognitive fatigue.



Photo/Styling Credit Andy Singer

Emotional and Psychological Support

Cognitive changes can threaten a person's sense of self, especially for those whose identity was tied to intellect, work, or independence. Survivorship includes grieving these losses while also remaining open to new ways of being.

Anxiety, depression, grief, and fear of recurrence are common and can significantly worsen cognitive symptoms. Emotional distress consumes mental energy and impairs concentration and memory. Counseling, mindfulness practices, support groups, and—when appropriate—medication can help reduce this burden. Addressing mental health is not separate from cognitive care; it is central to it.

Holding Space for Realistic Hope

Hope, in the context of survivorship, does not mean pretending that cognitive changes haven't happened. Instead, it is about allowing hope and uncertainty to exist side by side—acknowledging loss while still searching for meaning. For many, hope becomes a quieter presence, woven throughout daily life in subtle but significant ways. It might be the hope for a good day, a genuine connection with another person, or the discovery of peace, insight, or a renewed sense of purpose.

Survivors often find that although their cognitive abilities may have shifted, other qualities can deepen. Wisdom, empathy, and a sense of depth are not necessarily diminished by illness; in fact, these strengths sometimes grow stronger, offering new perspectives and ways of relating to the world.

Adapting the Environment and Daily Expectations

Many survivors benefit from practical strategies that reduce cognitive strain. Using calendars, reminders, written notes, routines, and simplified schedules can conserve mental energy. Allowing extra time for tasks, minimizing multitasking, and planning cognitively demanding activities during times of peak alertness can improve daily functioning. Acceptance of "new limits" often brings relief and enables patients to focus on what matters most.

Long-Term Monitoring and Advocacy

Cognitive changes may evolve over time, making long-term follow-up essential. Periodic neurocognitive testing can track changes, guide interventions, and provide documentation for workplace accommodations or disability support when needed. Patients and caregivers should feel encouraged to raise cognitive concerns early and often; these symptoms are common, valid, and worthy of care.

Living Fully With a Changed Brain

For someone with a high-grade brain tumor, success may no longer mean returning to a previous baseline. While some cognitive changes may be permanent, many patients find that with support, adaptation, and time, they can live meaningful, engaged, and intellectually rich lives. The goal is not simply to preserve cognition as it once was, but to help each person function as well as possible in the present—honoring resilience, redefining productivity, and sustaining quality of life.

Cognitive survivorship is an ongoing process, not a failure of treatment. With thoughtful care, compassionate support, and proactive strategies, patients can continue to learn, connect, and contribute long after brain cancer treatment ends.

Emotional Survivorship Under a Shadow of Recurrence

For those living after a diagnosis of a high-grade brain tumor, the emotional landscape is often shaped by the persistent awareness that the risk of recurrence is never far away. The fear isn't vague or imagined; it's a reality survivors come to expect.

Routine follow-up scans become more than medical appointments; they take on the weight of momentous decisions, sometimes feeling as if each scan delivers a verdict on the future. Life is lived from one scan to the next, and time itself is measured in intervals, making long-term plans feel nearly impossible and draining the emotional reserves of even the most resilient individuals.

The psychological impact of this ongoing uncertainty can be profound. Anxiety, depression, and post-traumatic stress are common among people with high-grade brain tumors. These emotions aren't signs of weakness or negative thinking; rather, they are deeply human responses to the experience of living with constant threat.

The journey of survivorship is not just physical, but also an ongoing emotional struggle to manage fear and maintain hope.

Seeking mental health support as a survivor is not a sign of surrender, but a vital part of caring for oneself. It is a way to acknowledge the burdens carried and to ensure that emotional well-being is not overlooked. In this context, survivors learn that asking for help is an act of strength, and that tending to mental health is just as essential as any other aspect of survivorship.

Relationships Under Pressure

Survivorship after a high-grade brain tumor diagnosis is rarely a solitary experience. Relationships, which once felt steady and predictable, can be shaken by the challenges that come with the illness.

Caregivers often find themselves stepping into new roles, perhaps managing medications, appointments, or daily tasks that the survivor used to handle with ease. For the survivor, the loss of independence is a profound adjustment, sometimes leaving them feeling exposed or vulnerable. Both the survivor and the caregiver live under a constant cloud of fear and fatigue, each carrying worries about the future and responsibilities that can seem overwhelming. In truth, survivorship is not the journey of one person—it belongs to both. And both deserve compassion, support, and care along the way.

Intimacy and partnership can also change in unexpected ways. The fatigue and emotional ups and downs that come with brain tumors may alter how couples connect. Things that once felt simple—communication, physical closeness, shared plans—might require new language and new rituals. Many couples discover that love can adapt, becoming quieter, softer, or more practical, but remaining deeply genuine even in its new form.

Social isolation is another, more subtle, challenge. Because the effects of high-grade tumors aren't always visible, survivors can encounter misunderstanding or insensitivity from others. Well-meaning comments, meant to motivate or reassure, may unintentionally dismiss the survivor's real risks or struggles. In these moments, finding relationships—whether with friends, support groups, or professionals—where one is understood and accepted without judgment or exaggeration, can be

profoundly healing. For many, these authentic connections are as essential to survival as any medical treatment.

Work, Finances, and the Meaning of Contribution

For many individuals who have survived high-grade brain tumors, the journey back to the workplace is not always possible. The lingering effects of cognitive fatigue, the unpredictability of symptoms, and the demands of ongoing treatment frequently make traditional employment unattainable. Instead of returning to a routine or career that once defined them, survivors often find themselves navigating a world with new limitations and unexpected detours.

This shift can deeply shake one's sense of identity and self-worth. Without the familiar markers of productivity, many survivors are compelled to reconsider what it means to contribute. Over time, contribution may come to mean something different—being present for loved ones, nurturing connections, or simply enduring each day with honesty and resilience. In this new reality, value is no longer measured by output or a paycheck, but by the quiet strength it takes to keep going.

No disability can erase your worth. Even when work and finances change, your value remains intact—rooted not in what you do, but in who you are, and in the courage it takes to face each new day. Your value is not diminished by any disability.



Photo Credit Linda Singer

Medical Care as a Lifelong Companion

Ongoing Treatment and Monitoring

Survivorship with a high-grade tumor often includes:

- Regular imaging
- Maintenance or repeat treatments
- Symptom management
- Palliative care alongside active treatment

Palliative care does not mean giving up. It means prioritizing comfort, clarity, and quality of life at every stage.

Monitoring for late effects related to cancer treatment

Overview

The impact of treatment often extends far beyond the initial years of survivorship. For about two-thirds of survivors, late effects stemming from chemotherapy, radiation, or other diagnostic interventions can surface more than five years after diagnosis. These challenges may affect the body, mind, or behavior, sometimes in subtle ways. Understanding these risks empowers survivors and their health-care teams to remain proactive, monitoring health with an eye toward early detection and intervention.

Skin Cancer Risk

Radiation therapy is a powerful and often life-saving treatment, but it can have long-term effects on the skin that are important for survivors to understand. One of these potential late effects is an increased risk of developing skin cancer in areas that were previously irradiated.

Why radiation can increase skin cancer risk

Radiation works by damaging the DNA of cancer cells so they can no longer grow and divide. However, nearby healthy skin cells can also be affected. Over time—often many years or even decades later—this DNA damage can accumulate and, in some cases, lead to the development of skin cancers. The risk is generally confined to the specific area that received radiation, rather than the entire body.

Types of skin cancer most commonly seen

The skin cancers most often associated with prior radiation exposure are:

- Basal cell carcinoma (BCC) – the most common and usually slow-growing
- Squamous cell carcinoma (SCC) – which can be more aggressive than BCC if not treated

Melanoma is less commonly linked to radiation, but it can still occur and should always be taken seriously.

Timing and magnitude of risk

Radiation-associated skin cancers typically do not appear soon after treatment. The increased risk may begin 5–10 years after radiation and can persist for a lifetime. While the absolute risk for any one person is still relatively low, it is clearly higher than for skin that was never irradiated. Higher radiation doses, treatment at a younger age, and additional risk factors (such as fair skin or significant sun exposure) can further increase risk.

How irradiated skin may behave differently

Skin that has been irradiated often remains more fragile and biologically altered. It may:

- Heal more slowly
- Be more sensitive to sun exposure
- Develop cancers that look atypical or arise in scarred or fibrotic tissue

Because of this, changes in irradiated skin can be harder to recognize and deserve careful attention.

Prevention and monitoring

Long-term skin surveillance is an important part of survivorship care:

- Regular self-exams: Watch for new growths, non-healing sores, scaly patches, or changes in existing spots within the radiation field.
- Dermatologic follow-up: Periodic skin exams by a dermatologist are especially important for people who received radiation, particularly to the head, neck, or scalp.

- Sun protection: Irradiated skin should be carefully protected from ultraviolet (UV) exposure using broad-spectrum sunscreen, hats, protective clothing, and avoidance of peak sun hours.
- Prompt evaluation: Any suspicious change in irradiated skin should be evaluated early, as treatment is most effective when skin cancers are detected at an early stage.

A survivorship perspective

For many cancer survivors, radiation therapy makes long-term survival possible. Awareness of late effects such as secondary skin cancers is not meant to cause alarm, but to empower patients with knowledge. With vigilance, sun protection, and regular follow-up, radiation-associated skin cancers are often detected early and treated successfully.

Medical Care as a Lifelong Companion

Ongoing Treatment and Monitoring

For those living with a high-grade tumor, medical care becomes an enduring presence, shaping daily routines and long-term outlooks. Survivorship is not a static phase, but a journey that requires continuous vigilance and adaptation. Regular imaging appointments serve as milestones, each scan a moment of hope and anxiety, charting the progress of treatment and the status of one's health. Treatments may be ongoing or revisited, as the body and mind respond in unpredictable ways.

Managing symptoms becomes a central part of life, with every new ache or change in ability prompting careful attention. Palliative care is woven into the fabric of active treatment, offering relief and comfort, not as a sign of defeat, but as a commitment to living as well as possible. The focus shifts to clarity and quality of life, ensuring that each day is approached with intention and compassion.

Living Fully Without False Promises

To live with high-grade brain cancer is to redefine hope in profound and meaningful ways. For many survivors, hope is not tied to the certainty of a cure. Instead, it becomes a companion in daily life—a quiet force that shapes each moment and helps

navigate an uncertain future.

Hope shows up in a variety of forms. There are days when waking up and finding more good days than bad is a victory in itself. Relief from stubborn symptoms can bring a sense of peace, a small but significant reprieve from discomfort. Time spent with loved ones gains a new depth and importance, as ordinary moments become extraordinary simply because they are shared. Even in the midst of illness, meaningful experiences—whether a heartfelt conversation, the beauty of nature, or laughter around the dinner table—carry weight and purpose.

Most importantly, holding onto one's dignity and agency, choosing how to respond to each challenge, embodies the essence of living fully despite the circumstances. Hope, then, is honest and rooted in reality. It does not promise what cannot be delivered, but it makes space for joy, meaning, and self-worth, no matter what lies ahead. It is possible to hope honestly without denying reality.

The Power and Limits of Survivor Stories

For many, hearing stories about those who have survived cancer for years brings a sense of hope and possibility. These tales of resilience can light a path forward, suggesting that life after diagnosis can be rich and meaningful.

Yet, woven into this inspiration is another thread—one that can tug uncomfortably at those whose own journey looks different. Sometimes, these survivor stories create an unspoken pressure to measure up, to feel as if your experience should mirror theirs. It's easy to fall into comparison, wondering why your path might be less smooth, or why your milestones might not match those celebrated by others.

Survivorship is not a competition, nor is it a one-size-fits-all journey. There is no right or wrong way to walk this road. If your story is shorter, if the challenges seem

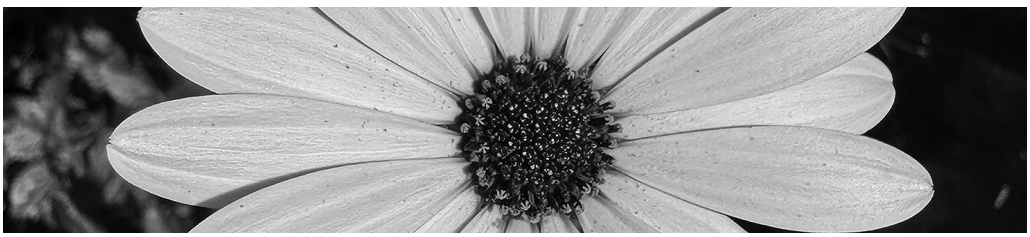


Photo Credit Stuart Volkow

steeper, or if your days unfold differently, you are not failing at survivorship. Your experience is valid, and your way of navigating it is uniquely your own.

Conclusion: Survivorship as Courage, Not Outcome

Survivorship with a high-grade brain tumor is not simply a matter of counting time. Instead, it is defined by how one chooses to live when the future feels fragile. Each day brings its own challenges, and sometimes, the act of enduring is itself an act of courage. On some days, just making it through is a triumph. On others, finding moments of meaning or connection can feel like a small victory. These experiences, whether quiet or profound, all matter—they are all part of the journey.

What truly gives life meaning is not the diagnosis itself, nor the time that has passed, but the fact that you remain present; you are still human, still deserving of care, honesty, and compassion. Survivorship, then, is not measured by milestones or comparisons, but by the courage and determination to live each day as fully and authentically as possible.





Nineteen

Caregiving and Support Groups

It is all too common: You enter your doctor's office with a list of questions, but as soon as your physician has finished his or her comments, you forget your own questions, or worse, forget or misunderstand the answers you receive. Emotions, not your brain tumor, are typically responsible. Emotional support and a second pair of ears can be of tremendous help while you navigate through a new world of tumor terminology.

Even for seemingly routine appointments, whenever possible, take a friend, loved one, or caregiver with you. Aside from taking notes of your session, if you become overwhelmed at any time during your physician's explanation of a particular treatment, necessary tests, or expected results, another person will be at hand to hear (or interpret) the details and will be able to ask questions that you might not think of at that moment.

Encourage your companion to make frequent notations or observations in your personal treatment binder and take an active role in discussing your care options. If your physician will allow recorded sessions, have your companion manage a small hand-held recording device and review the discussion afterwards with you.

In Table 1 (below) there is a list of organizations that can help provide support for caregivers, families, and loved ones.

Caregiving

Certain types of brain tumors, particularly the malignant ones, require the support of a caregiver. In the final stages of the disease, because the effects can encompass every aspect of how being human is defined, the challenge can be significant.

Because of its impact on personality, mobility, and cognitive abilities, not to mention the crucial treatment decisions, second opinions, and appointments you probably are having to make, high-grade brain cancer caregiving is considered by many to be the #1 caregiving challenge of all cancers. You should accept that this health challenge may be the hardest thing - physically and emotionally - that you may ever do.

The reason for that unwelcome distinction is simple: The brain is the Master Switch that determines how a person expresses themselves, how they think, how they dream; and it controls virtually all bodily functions. When the brain is compromised by the disease and the effects of treatment (which can leave their mark, too), many abilities are put at risk. Mental and physical decline is a distinct potential, but the one with the disease might not even realize there is anything wrong. Your loved one may exhibit personality and emotional changes that can take a real toll on you.

Caregiver's Fatigue

At times this 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.

Table 1: Organizations that provide support for caregivers

Organization	Website	Description
American Brain Tumor Association (ABTA)	https://www.abta.org	Offers a Peer-to-Peer Mentor Program that pairs caregivers with mentors who have shared similar experience. They also provide a free Caregiver Handbook and a dedicated CareLine (800-886-2282).
Cancer Care	www.cancercare.org	Stories and podcasts on subjects ranging from financial assistance to stress management
Cancer Compass	www.cancercompass.com	Discussion groups and resources
Caregiver Action Network	www.caregiveraction.org	Wealth of informative tips and tools about financial and medical benefits, support groups, respite care, newsletters, and publications
Caring.Com	www.caring.com	Articles about caregiver wellness and money and legal matters, and a directory of reviewed and rated home healthcare agencies, nursing homes, and hospice facilities
End Brain Cancer Initiative (EBCI)	www.endbraincancer.org	Provides education, advocacy, and personalized navigation support for patients and caregivers. Through its "Direct Connect" program, EBCI links families to specialists, clinical trials, and advanced treatment options, while also offering resources for financial, legal, and mental health challenges.
Family Caregiver Alliance National Center on Caregiving	www.caregiver.org	Helps provide long-term care at home by offering national, state, and local programs to support caregivers
Glioblastoma Foundation	www.glioblastomafoundation.org	Facilitates the Glioblastoma Support Circle, a professionally led virtual support group for patients and their families.

Organization	Website	Description
Lotsa Helping Hands	www.lotsahelpinghands.com	Allows you to organize family and friends for needed tasks via electronic calendars and announcements and provides resources for caregivers
The Musella Foundation for Brain Tumor Research & Information, Inc.	www.virtualtrials.org	Supports brain tumor patients and their caregivers with emotional and financial assistance, education, advocacy, and access to clinical trial information. It also awards grants to innovative brain tumor research, runs a drug copayment assistance program, and through a patient navigation program helps treatment option identification.
National Brain Tumor Society (NBTS)	www.braintumor.org	Hosts Caregiver Support Conversations, a monthly virtual group specifically for those currently caring for a patient. Their Patient & Care Partner Toolkit includes personalized navigation services.
National Hospice & Palliative Care Organization	www.nhpco.org/	Resources for caregivers including checklists advance directives
Pediatric Brain Tumor Foundation (PBTF)	https://curethekids.org	Focuses on families of children with brain tumors, offering online support groups for parents and caregivers of the newly diagnosed.

Palliative Care

Palliative care is medical care that is focused on relieving pain, symptoms, and stress. Unlike hospice which is conducted when all treatment of the disease has stopped, palliative care takes place during treatment. It can be a support mechanism for you, your caregiver, and your family.

It is not new, having come on the scene for patients around the 1970s. However, today it has evolved into so much more and is provided to patients for any diagnosis, at any stage of the condition and/or treatment plan. With palliative care, you, your caregiver, and your family receive emotional support, knowledge, and resources associated with your illness to ensure that your concerns about treatment, medications, side effects,

and symptoms are addressed and to enable you to make the most knowledgeable decisions about your care. The first step in seeking palliative care is to ask your doctor or cancer center. Your goals will be to reestablish the quality of your life, to ease stress, and to be more in control. It will take time and patience, but you will find your comfort zone.

At some point, you may want to transition to hospice care, which can be given at home, in hospitals, nursing homes, or inpatient hospice facilities. This highly specialized concept of care — given by a partnership of family members, caregivers, and medical professionals — focuses on providing ongoing comfort, emotional support, and pain management 24 hours a day. It may also include spiritual counseling for the patient and family members. Hospice care will provide medications, equipment, and any medical supplies needed, as well as physical, speech, and occupational therapies to make you feel as comfortable as possible. You will work with an interdisciplinary team including medical professionals, social workers, home health aides, clergy members, and trained volunteers. Because most people see hospice care as marking an end of life, it is often not started soon enough. You can always opt out of hospice care if you wish to re-enter appropriate treatment or if you experience remission. Like palliative care, the main focus of hospice care is to bring quality-of-life and support services to the patient, caregivers, and family members. While palliative care may be given at any time and even through treatment, hospice care is appropriate when life expectancy is six months or less and treatments are no longer an option.

"A Joyful Moment" by Hana Brem



Impairments And Strategies For Coping

Now that you have been diagnosed with a brain tumor, you may start to experience a variety of impaired functional abilities depending on the size and location of your brain tumor and your treatment plan. You may experience depression, memory and concentration lapses, personality and mood shifts, anxiety, insomnia, difficulties with self-care, poor balance, bowel and bladder incontinence, and conversational speech and word-finding problems. Healing and recovery from surgery and treatment are very important. When you are discharged from the hospital, make sure you are given clear instructions for caring for the surgical site, for what activities you can and can't do for a period of time, for medications and dosages, and for what to do if problems develop. Arrange your ride home from the hospital and have someone at home to help you until you feel well enough to manage on your own.

Each brain reacts differently to treatment, but you can find a way to adjust and compensate. There are strategies you can use that will help you to function and feel better and, in some cases, regain lost functional ability.

First and foremost, speak with your medical team about your difficulties before they become more complicated. They may prescribe some medications to ease your symptoms or refer you for physical, speech, occupational, or hyperbaric therapy sessions. Physical therapists will provide exercises that strengthen your muscles, increase your flexibility and mobility, and help you regain balance. Occupational therapists will work to strengthen small muscle control and gain functionality with self-help daily activities. Speech therapists will help in developing communication skills, vocabulary, and swallowing. Neuropsychologists will help you cope with and assess cognitive and emotional changes, as well as memory, thinking skills, problem- solving and reasoning, and perception. Hyperbaric oxygen therapy sessions may be recommended to aid in healing damaged tissue. Each of the therapists may also recommend adaptive devices to help you regain some degree of functional independence.

Second, speak with your partner or family members and explain how and what you are feeling. It is important to bring people on as part of your team to support you and help make things a little easier for you. However, they need to understand what you are experiencing before they can help. The more informed they are, the better they will be able to cope, understand you, and help you set goals.

The following coping strategies have been used successfully by people in our online support group to regain quality of life. But first you must understand your strengths and weaknesses, identify, or know the problems, and be willing to try a solution. At this point you may be feeling overwhelmed and confused about the changes you are experiencing. You may also feel some grief or denial for the loss of functioning. These strategies will provide the tools you and your loved ones need to help you rebuild your life.

Sometimes, the simplest solutions for what you are experiencing are organization and altering the environment. For cognitive difficulties, making notations on a legal pad, calendar, or day planner will aid memory. Include a check-off sheet or page as needed for each task completed. It will be helpful to use an alarm watch or kitchen timer to alert you of time sensitive activities. You may wish to use a weekly medicine dispenser with slots for am and pm medications. For better concentration, you may need to minimize or avoid distractions such as loud noises. Stay focused on one task at a time or alter a task by breaking it down into smaller parts. Sometimes a daily activity or time-management chart may help organize your day. Set limits and don't schedule too many activities in one day. Rest when you need to. You may find it helpful to follow a routine by keeping a consistent schedule. Keeping daily items in predetermined designated places will make them easy to find and save time locating them.

For physical safety and comfort, be aware of potential dangers in and outside of the home such as clutter, fire hazards, sharp objects, hazardous household products, scatter rugs, inadequate lighting, water heater temperature, and outside hoses. Don't forget to declutter drawers and closets. Switch to plastic cups and plates when needed. You may need to install additional handrails or place brightly colored tape across steps. You may need to conserve your energy or find it safer to use assistive aids such as canes, walkers, or wheelchairs. You may also need to install grab bars in bathroom/shower areas, use a shower seat while bathing, or purchase disposable underwear. Daily movement, which may be as simple as stretching, no matter how limited your ability, will help with improving your night's sleep, reducing negative emotions, and reducing stress, and will also help you focus.

You and your family may find it helpful to communicate with the use of word cues, picture flash cards, simple language, and sentence structure, or by asking only one question at a time and repeating back information to ensure understanding. But

first, make sure you are looking at the person speaking to you, so that you can focus and pick up visual cues. You may also find it helpful to play word games and puzzles.

It is important to recognize that there is no one way of doing things. You will learn to compensate for your deficits by learning new ways. Sometimes, you may feel that you have reached a plateau, but that doesn't mean that you will not progress again. You may continue to experience progress and setbacks in functioning. However, it is important to realize that when one way of doing things may no longer work for you, the strategy needs to be changed. Having patience and flexibility will be essential to your recovery. Your life will feel more normal and on track by using coping strategies that work for you.

Support Groups

Support groups found on the Internet, or a local support group sponsored by your hospital/regional cancer organization can often assist with nonmedical issues — such as nutrition, relationships, and/or financial concerns.

Most people are shy about joining a support group, but don't be. You will be amazed at how quickly you feel at ease, because the members know and understand what you are going through, something (hopefully) nobody else in your circle of friends knows about.

"Real-World" Support Groups

We urge all brain tumor patients to try out one or several support groups, whether online or "real world." It is a very powerful experience to speak directly with people who have undergone the same passage. Real-world and even online support groups are typically facilitated by nurses or other caregivers.

If you live near a metropolitan area, you can attend a support group in person. These support groups provide community, and they can be safe places to open up and share both positive and negative emotions.

Some cancer and dedicated brain tumor organizations provide search engines on their websites that can help you find nearby real-world support groups in your area. These organizations include:

Organization	Website
American Brain Tumor Association	https://www.abta.org/support-groups/
American Cancer Society Cancer Survivors Network (for Brain Cancer)	https://csn.cancer.org/forum/165
Clinical Trials & Noteworthy Treatments For Brain Tumors	https://www.facebook.com/groups/13657508258
Glioblastoma - GBM SURVIVORS TO THRIVERS!	https://www.facebook.com/groups/197153540892173
National Brain Tumor Society	https://braintumor.org/support-services/support-groups/brain-tumor-support-conversations/
Novocure, Optune Support For Glioblastoma	https://www.facebook.com/groups/347097922150691
Smart Patients Brain Tumor Community	https://www.smartpatients.com/communities/brain-tumor
Surviving Glioblastoma (GBM)	https://www.facebook.com/groups/35382736500

The Musella Foundation also maintains a comprehensive list of "real-world" face-to- face support groups, with contact numbers and email addresses, and with meeting locations and schedules. To access that list to find a support group near where you live, go to: https://virtualtrials.org/support.cfm**.**

Online Support Groups

The Internet and social media sites offer nearly an unlimited resource for brain tumor patients, including online support groups, sometimes called "mailing lists" or "listservs," chat groups, and message boards for sharing experiences and treatment options with others who understand what you're going through. Although social media sites like Facebook are a good way to keep in touch with family and friends, and some brain-tumor groups are active there, be aware that Facebook is very public. So be cautious, and be sure to activate privacy settings, if you do not want information about yourself or your medical condition to be available for years to people who do not know you.

Common Sense Cautions about Support Groups

A word of caution: Support groups (both online and "real world") play an important and, in many cases, vital role in helping participants maintain a positive outlook during treatment and stay up to date on the latest brain tumor issues.

However, you have to be cautious and evaluate how much you can trust anything you find. There are people out there who are simply looking to make money off of your misfortune, and even people who are trying to help might inadvertently supply you with misleading information. NOTHING on the Internet or at a support group meeting should be taken as real medical advice. It is important to research anything you find and discuss it with your medical team.

Chat rooms are especially susceptible to problems because they may have few participants and an insufficient number of other people with whom you can discuss the pros and cons of a treatment. On the other hand, in an online support group you can ask for the experiences of many people with a specific treatment and get a broader view of it.

When using the Internet, exercise common sense and discuss information with your medical team to help you make the best possible decisions about your care. To evaluate information found on a website, consider the credentials of the person posting the information, how up to date the site is, whether any contact information is posted on the site, and whether the claims on the site are too good to be true or sound as if something is being sold to you.

SURVIVOR STORY #11: YARON BUTTERFIELD

Vancouver, Canada

The beginning of 2004 kicked off as a new stage in my life. I had survived the breakup of a 4-year relationship and was ready to move forward. Work was going well and I hoped to move up in my career as a cancer genomics scientist; just 10 months earlier in April 2003, I played a large role in the analysis of the SARS coronavirus genome that made world-wide headlines after we announced our accomplishment. Life was busy with my work and I balanced it out with taekwondo, yoga, art, and my love of ice hockey.

On a Monday morning, February 23, 2004, a day and a half after I had scored 5 goals in the best hockey game of my life, I collapsed in a grand-mal seizure and was subsequently diagnosed with glioblastoma and was given a prognosis of living 12 to 18 months. Analysis also showed that I had the IDH1 mutation of interest and that MGMT was methylated—both good in my case. I decided to follow any treatment plan that was laid before me. The tumour was deemed to be too deep for surgery, so I went ahead with chemotherapy (temozolomide or "TMZ") and radiation.

I focused my emotions and energy on the events of the day without really looking forward. I absorbed the beauty around me, the flowers and trees, the fresh air, even the grocery cashier lady. Friends and family, including my twin brother were there for me 24/7. Rather than rushing to work in the morning and then in the evening to do whatever I had planned, I had a lot of time to think. All my thoughts were directed towards my healing.

Unfortunately, in my third week of treatment, my white blood cells count dropped dramatically so I had to stop chemo and get blood transfusions. I continued with radiation and a couple weeks after it was done, we tried to see if I could handle the chemo but it immediately had an effect on my blood count so treatment was over.

It was time to wait, to see the results of treatment which would be a few months as they wanted to avoid any misinterpretation from possible pseudoprogression. I decided I wasn't going to let my cancer diagnosis and devastating prognosis rule my life. I also realized that life was too short, whether with cancer or not. And so I signed up on a dating website and soon after met someone. We went on a date a week after my

birthday in July when I turned 30. I warned her about my recent diagnosis and that I hadn't even got results of treatment at that point. She said she wanted to stick around and see how things go, that she saw a fighting spirit in me. We started to date and with her being a big part of my thoughts and energy, I had little time to worry about the cancer. A few months later, the MRI results indicated that the tumour had shrunk.

It felt like a new future was unfolding in front of me. My girlfriend moved in with me, I started fundraising and training for a run, and I became a student again registering for courses in immunology and in bioethics at the local university. My fundraising led to the opportunity to do a marathon in Iceland. I used to be quite a runner and had done many half-marathons but I thought I'd see if I could do a full one.

That August of 2005, I completed the 42km run on the volcanic island and then traveled inland with friends. One night we sat in the hills of Vik, taking in the beautiful Northern Lights, and I felt that I was as far away as can be from the cancer and all that came with it. I had left the tumour behind; I imagined hoping it would never return. But it did. An MRI a couple months after I got back home showed that the tumour increased to double the size. I had to consider further treatment. TMZ is often less successful after recurrence as the new tumour is usually genetically very different form the first tumour. Any cells resistant to TMZ in the first treatment have now multiplied into a new mass. Given that, I was offered a clinical trial drug in November.

Once again, while I subjected my brain to more drugs, I was excited, preparing to getting married at the end of the year. During the ceremony my alarm went to reminded me to take the chemo. That night, I got sick which was a common thing for me since starting the new medication. An MRI in early 2006 showed the tumour had not shrunk. A decision was made to attempt TMZ again. Keeping in mind that I had showed much sensitivity to the drug when I took it before, the thought was that taking it one week per month would be tolerated. Also, I had not initially completed a full round treatment of the chemo; there could still be cancer cells sensitive to the drug.

This was my treatment for first 8 months of 2006 and thankfully by the Fall of that year, the MRI showed that the tumour has shrunk significantly. Around that time, I returned to my hockey team but now, instead of being one of the best players on the team, I was the worst. I also went back to my job at BC Cancer, thrilled to be back to the research, working with colleagues and making discoveries to help lead to more understanding on how to treat cancer. I managed to get involved in various research studies about brain

cancer. One such project I was heavily involved in was the analysis of tumour profiles from patients with oligodendroglioma where we identified key interactions with a couple genes of interest and chromosomal alterations (e.g., CIC, IDH, 1p/19q). I also contributed to one of the first research projects https://
/?client=safari demonstrating the benefits of personalized oncogenomics.

In 2008, my daughter was born and she gave me even more motivation to stay healthy and strong. I wanted to give back to the brain cancer community and became coordinator of Canada's Brain Tumour foundation (BTFC) walk/run in Vancouver which I did for 7 years. In 2015 BTFC handed me the David Kelley Award for Community Service. At the ceremony after the award was presented, my daughter came to me and quietly asked, "You had cancer daddy?" I gave her a big hug, held back tears, and told her yes, but not to worry, it was gone.

With my knees a little compromised with all my running, I started to get involved in biking. In 2009, three other brain cancer survivors and I created a team we called the Brainiacs to help fundraise for cancer research leading to a 200km ride over two days every August. Over the years, our team has recruited many each with their own story, and we have raised millions of dollars.

I had graduated over the years from MRIs every three months, to every six and then once a year. Time was moving farther and farther away from my personal cancer experience. Perhaps it was gone but the side effects lingered. In 2014, during a hockey game, I sensed something strange. By the third period, I seemed to be seeing double and my brother drove me home. We were worried that I had experienced a seizure, but it was found that I was getting double vision because of damage to an optical nerve. This wasn't the first long term effect of radiation I experienced; my hearing on the left side of my brain around where the tumour had been, was also compromised. I attempted to continue to play but problems with my vision led to a few bad falls and a couple concussions as a result.

In the Spring of 2016, one morning with my daughter, I had trouble with my balance while walking and fell into the wall. I knew something was wrong and tried to call my brother but couldn't hit the right numbers. My daughter, now 8, called him and then 911 and before I knew it, I was at the hospital and by evening my voice was gradually returning. The next day, I felt much better and was told that I had a seizure. Thankfully, the incident was not a sign that the cancer was back but that my anti-seizure medication

was too low. I recovered fairly quickly physically, but cognitively; the seizure affected me such that I had trouble doing the detailed tasks of analyzing sequenced cancer genomes. In January 2017, I had to take a break from work.

A couple eye surgeries to try and fix the double video were not very successful but over time, things improved slightly. After a 2-week trip to Peru with other cancer survivors in November 2019, which included a great day on Machu Picchu, I felt ready to consider returning to work. However, in the Spring of 2020, I had another seizure. Staff at the hospital initially thought I had a stroke but soon realized that there was a blood leak between my brain and the skull: a subdural hematoma. This was another long-term effect of the radiation I had in 2004. One night at the hospital, I woke up and realized I could not move the right side of my body at all. After a surgery, I spent most of the rest of the year in physical and cognitive rehab. Since then, I have been trying to heal in various ways: continuing to exercise with biking and hiking, exploring yoga, tai chi, and qi gong, reading, writing and doing my art. I hope soon I will be ready to return to work and contribute to continued cancer research.

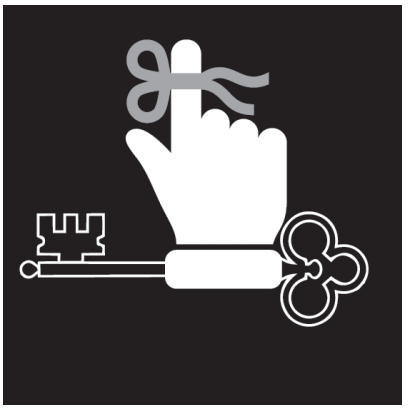
At this point in 2022, it's been over 18 years since my diagnosis of GBM. MRI's have been clear since the Fall of 2006. I am slowly getting my memoir together with the hope readers will be inspired and see that you can move forward past a devastating diagnosis and enjoy the world in your own way. I intend to continue doing that.

http://yaronbutterfield.com

Photo Credit Andy Singer



KEY TAKEAWAYS TO REMEMBER



Whenever possible, go to all appointments with a friend, loved one, or caregiver to help you understand what the doctors are saying to you.

Do not neglect the rest of your body. Do not neglect your emotional health.

Caregivers also need to take extra care for themselves. Caregiver's fatigue is very real.

Support groups can educate you, lift you up, be a place to express both positive and negative emotions, and provide a strong sense of community.

Many cancer organizations and local hospitals offer support groups.

Online support groups can cover a wide variety of topics and issues. To find a support group near where you live, go to: https://virtualtrials.org/support.cfm.

Nothing on the Internet or at a support group meeting should be taken as medical advice. If you have any questions, discuss them with your medical team.



Twenty

Late Stage

Intubation and Ethical Considerations

In certain cases, a loved one becomes critically ill, but owing to their expressed wishes or the wishes of family members, the cessation of treatment and enrollment in hospice is not yet acceptable. However, they are too ill to eat and in order for life to be sustained so that treatment may possibly be continued, the doctor raises the concept of intubation - the insertion of a tube, sometimes a PEG (percutaneous endoscopic gastrostomy), for the purposes of delivering food.

This decision is not to be entered into lightly and without a conscious understanding of the potential consequences. Doctors must be able to provide assurances that the current symptoms are reasonably reversible within the next 2-4 weeks. The issue is that in a few weeks if your loved one does not rebound, you are going to be faced with an even more horrid decision. If the PEG is installed and your loved one does not rebound, the hospital will come to you in a few weeks and discuss its removal. At that point, you will essentially be removing your loved one's life support. No spouse, no parent, no child, no one should ever have to make that kind of a decision on behalf of their loved one.

Unless the doctors can say with assurance there is a reasonable chance your loved one will turn around before they decide it is time to stop the PEG, it is not advisable to agree to its installation, but rather would continue to provide nourishment as best as possible using thickened foods. It's not ideal, but people who are bedridden/asleep can live for a long time without any food.

If you are faced with this decision, you may wish to ask for a meeting with the

doctor, a palliative care counselor and if you have a religious tradition, a clergy member to help guide you.

Just as a data point, the intubation of a patient with a terminal illness like GBM is rarely done because of the ethical dilemma that it could cause.

Hospice

Deciding When To Start

The decision to begin hospice can be a very painful one. For some people, just the word "hospice" evokes a great deal of anguish. Starting hospice is a very common source of reluctance for those facing the latter stages of this disease and for that reason, most people enroll so late that they are not able to receive the benefit of the comforts and support that hospice can provide.

The people at Massachusetts General Hospital found in one of their studies that:

- 37% of people with terminal brain cancer fail to receive any hospice care at all prior to their passing thereby depriving them and their loves ones of the numerous benefits available from hospice.

- 60% enroll in hospice with an average length of stay of 21 days. (Typically, the length of time a person with GBM is in hospice prior to passing is 6 to 8 weeks once treatment has stopped.)

- 23% of patients enrolled within a week before their death, and 11 % were enrolled less than three days before their death, which is considered too late to do much good for the patient or their loves ones, according to authors of the study.

The issue we all struggle with is, of course, Hope. But it is essential that our hope is realistic and not unrealistic. If we labor under an unrealistic hope, then we may be depriving our loved ones and ourselves of the compassionate support that is available through hospice.

On the other hand, if there is some turnaround, for instance, if a loved one receives what is thought to be a final infusion, enrolls in hospice, but then rebounds to the point where further medical treatment makes sense, he or she can be un-enrolled from hospice. Hospice is not a one-way street nor is it necessarily giving up; it is simply applying the right support when and how it is most needed.

For more information about hospice care, go to the following websites:

The Hospice Foundation of America: https://hospicefoundation.org

National Association for Home Care & Hospice: https://www.nahc.org

The brain-tumor help site for hospice care, Seeking Peace: Brain Tumor Hospice Care: https://www.brainhospice.org

American Brain Tumor Association (ABTA) offers a comprehensive End-of-Life Care guide, detailing hospice services such as pain management and spiritual support at https://www.abta.org/about-brain-tumors/treatments-side-effects/end-of-life-care/. **ABTA also hosts webinars on Facing End of Life Together. A video of a past Facing End of Life Together webinar is available at** https://www.youtube.com/watch?v=o-2IVCZ7ErE

National Brain Tumor Society Patient & Cargeiver Toolkit is available at https://braintumor.org/support-services/toolkit/

The Publication "Medicare & Hospice Benefits" is available at https://www.medicare.gov/coverage/hospice-care

Practical Tips

Emotional Support

Although there are plenty of them, don't get caught up doing tasks. There are only two things a person with a brain cancer (of any Grade) really most wants: to know that they love and to know that they are loved. Make saying kind and loving things a priority every day.

Pain/Discomfort Control

Most GBM patients have a low degree of pain, but plenty have an overabundance of sensitivity to stimulation. Consider putting a sign near where your loved one is resting that says " Don't Touch Me! Air Hugs only!" (Obviously, touching your loved one for necessary care purposes or when he/she asks for a hand is excluded.)

If your loved one is uncomfortable in any way, breathing hard, not drinking, or eating, running a fever, or experiencing any other symptoms, tell hospice right away – no matter what time it is - and request their assistance to manage the symptom. That's what they are there for.

When your loved one becomes more and more bed bound, it will probably mess with his/her lung function. Your loved one may need to have a condenser and be on low level oxygen just to ease their breathing as a comfort measure. Having the O2 available is important if he/she starts breathing rapidly. When your loved one starts breathing hard, don't assume it will get better later. Just ask for the condenser.

At some point, your loved one will not be drinking as many fluids as he/she needs, and he/she will become disoriented and confused just from being dehydrated. It is suggested you having an electrolyte replacement available (like Pedialyte) to put into your loved one's water, which he/she is more likely to sip on through a bendable straw (so you'll need that kind of a straw, too, if you don't already have it).

At some point, your loved one will just stop eating and drinking. Forcing water or food when the swallowing function has ceased may cause your loved one to aspirate the liquids or food into his/her lungs which may give your loved one aspiration pneumonia. Pneumonia can be a lethal complication at this point, so everyone needs to know that stopping the food and drink is just part of the natural process and not to force him/her. That said, some (but not all) hospice organizations will agree to provide liquids via IV when a person can no longer drink/swallow. If you opt for this, it may give your loved one a few additional days, but then your loved one might not want the discomfort of the IV. Something to think about.

At some point, your loved one's ability to speak may falter, but he/she still wants to communicate. Try and make some kind of sign with little pictures to avoid a lot of frustration for your loved one. For example. I'm cold, I'm thirsty. Try and plan some

basic signals.

Mobility Management

If you are unable to move or properly clean or feed your loved one, tell hospice and request their assistance and/or equipment. Take no chances that your loved one might fall or be dropped or get hurt or that you might be hurt.
One person is usually not enough for handling someone who is bedridden; trying to do so can be inventory for back surgeons. There is a patient hoist (called various things but Hoyer Lift is a common name) that can be provided and used for moving your loved one around in the bed so that your loved one can be cleaned. As with all pieces of equipment, you want this hoist available immediately when the need is recognized.

If your loved one is well enough to use a wheelchair, be aware that your loved one can fall forward out of the chair in the blink of an eye. Watch your loved one as you would a baby.

Keep your cell phone on you (e.g., like in a pocket) at all times. You could end up in an emergency situation (e.g., your loved one falls, no one is around to help and you don't want to have to leave him/her, unless it is to let medical personnel in the door.)

Hospice can provide all the equipment you will need, for instance a hospital-like bed which is essential for lower/raising your loved one so that you can best care for your loved one. That hospital-like bed requires an extra-long twin fitted sheet that no one really has, but twin flat sheets will be fine. You can tuck these. Make sure you have several (4 to 6) sheets and pillowcases. You'll need several to be able to keep your loved one in clean linens.

Hospital beds are designed to be waterproof, not comfortable. The super soft quilt-like bed coverings with waterproof liner will need to be washed, so you might need three or four, used with large, soft, waterproof bed pad (washable or throwaway) on top. That can make all the difference in final comfort.

If your loved one can't turn in bed on their own, consider getting a bed that automatically turns the patient to reduce chance of bed sores.

If your loved one is in a bed in one location of the house and you would just like to go the kitchen or laundry room but still want to keep an eye on your loved one, baby monitors work would great.

It is possible to get a kind of frame around the toilet which provides arm handles for your loved one to lean on for as long as he/she is mobile.

Managing Hospice

If you don't like your lead nurse, say something to hospice about changing him/her out with another. No medals are available for being long-suffering or more discontented than you otherwise need to be during this highly critical time. You won't "hurt their feelings"; hospice knows that not every nurse works with every family.

Especially during weekends and holidays, hospice can get overwhelmed so if you aren't getting the help you think you need, pester. Be nice but pester. Call at any time of the day or night, but best time to call and alert them to a priority need is early in the morning before shift change (usually 7am).

If you have competent family or a close friend helping you, get them to call hospice for what you need.

Keep hospice phone numbers nearby and easy to locate. Know the name of your assigned nurse's head nurse or team lead just in case you need to escalate a requirement. Do not be shy about your real concerns.

All concerned family members should have the most critical phone numbers on the refrigerator door (or other location) since GBM is famous for creating emergencies at the drop of a hat. Family members that are not in your same location need to keep an overnight bag packed and under the bed/in a closet to be ready to move at a moment's notice.

Miscellaneous Topics

For ease of clothing your loved one when he/she is very bed bound, you may wish to use soft, cotton t-shirts. If you slit the back of the t-shirt (right in the middle) from the bottom hem of the shirt to the hem of the neckline (but not through the neckline

hem), you'll have a shirt you can easily slip on and off to keep your loved one covered and clean. You may need to have a pile of them ready (like 10 or so).

Keep a good, reliable thermometer handy and take your loved one's temperature regularly. If you notice any fever spikes beyond 100.4 (Fahrenheit – 38 degrees Celsius) [or whatever the medical team tells you the magic number is], call them immediately. They will probably suggest you treat your loved one with acetaminophen (aka Tylenol). You should consider tracking your loved one's temperature. The higher the fever and the more constant that fever (absent some underlying reason like an infection) may be indicative of how close your loved one is getting to passing.

Assuming you are caring for your loved one at home, make sure you have plenty of fresh (not expired) acetaminophen and ibuprofen available. Keep all your loved one's meds in the refrigerator (in a place where children cannot get at them) unless the hospice nurse tells you otherwise. Later, when your loved one can no longer swallow, suppositories of many of these meds can be provided from hospice.

For sponge baths and clean-ups after bowel movements when your loved one is largely bed bound, it is handy to assemble a kit in a small plastic tub of essentials like these:

- Nitrile exam gloves (for you)
- a roll of toilet paper
- pre-moistened disposable wipes*
- baby powder
- diaper rash ointment or another perineal skin protector
- a spray which is a no-rinse perineal & skin cleanser and/or no rinse body wash/incontinent cleanser
- 1 or 2 replacement pull ups or adult diapers
- 1 or 2 replacement bed pads - nicknamed "chucks"
- Cloth washcloths
- Small cloth towels

* It is a good idea to put 4 or 5 wipes in a small baggie and then when needed, toss the baggie into the microwave for about 10 seconds to warm them up. You should consider having several of these baggies ready to go at any moment.

Most of these items can be provided by hospice on your request.

Whatever mattress your loved one is on needs to have a WATERPROOF mattress pad.

At some point, the natural saliva flow in your loved one's mouth will decrease and so his/her mouth will get rather sticky/muddy. They make a special mouth cleanser to use for cleaning the mouths of individuals in this situation. Hospice should be able to provide. These cleansers come with a brush, but it is better to just use a damp wash cloth with some of this cleanser in order to really clean the mouth and in particular the cheeks. (GBM patients are famous for storing medications in their cheeks and not swallowing them; if this happens, this mouth cleaning with a washcloth will pick them up and get them out of the mouth.)

Your loved one's lips are likely to become very dry. You'll probably need to moisten his/her lips frequently with a lip balm or a bit of Vaseline.

It is useful to have a little white board for writing down what medicines your loved one has taken that day and which he/she still needs to take and when. There are usually lots of medicines each with their own schedule and it can get confusing without writing them down.

Don't be surprised if you have to do several loads of laundry a day. Pull ups (while your loved one is still mobile enough) and incontinence pads on every seat help cut down on laundry. Once mobility has ceased, then you'll need to use adult diapers.



Twenty-One

Passing

If you are reading this, we understand that you are facing a very significant loss and for that we extend our deepest condolences. We hope that this description of what you might expect and when will be of help to you for planning, but most of all for diminishing the amount of suffering and heartache that is normally associated with the departure of a loved one from this life.

The following is a summary of the major symptoms you can expect and within roughly what time period. Not everyone will experience all of this, so you should read this as a sort of general idea of what may happen and when.



Photo Credit Linda Singer

Few Months Before Passing

- May have or continue to have crises that precipitate panicky visits to the hospital. Examples of issues that may arise that may cause one to scurry to the hospital are:
    - Seizures ranging from all out generalized grand mal type to absence seizures where your loved one just sits and stares for some minutes.
    - Brain bleeds which might be minor or serious enough to produce stroke-like symptoms.
    - Sudden weakness in a limb, facial palsy (drooping), eyesight or hearing issues.
    - Infections ranging from pneumonia to urinary tract infections.
    - Uncontrollable nausea/vomiting or even persistent hiccoughs.
    - May have severe headaches from an increase in intracranial pressure.
    - Deep fatigue/ inability to be fully awakened.
- Mounting issues may precipitate a "decision MRI" which, if results are poor, initiates discussion leading to hospice enrollment.
- Likely to display a decrease in facial expressions and verbal expressiveness; may have more trouble finding words.
- May display obsession/compulsive behaviors (e.g., may turn light switches on and off repetitively).
- Sleeping more (e.g., 10+ hours each night, with daytime naps).
- Increased in confusion and memory lapses (may forget how to operate a TV remote control or what toilet paper is for; may change passwords on

accounts and forget those passwords; may put dirty clothes in the refrigerator).

- May start falling with recurring frequency; may need to use a walker/wheelchair; stairs in home become safety concern.

- Likely will need help at home for most if not all waking hours each day; may need to be watched carefully.

6-8 Weeks Before Passing

- Likely needs care 24/7 (Should be enrolled in hospice at this point; early hospice enrollment is best).

- Headaches from increase in intracranial pressure may increase.

- Increasing weakness on the affected side.

- Becomes a fall risk and may have periodic falls due to resistance to accept help.

- May have a need for more assistance with walking and transfers (e.g., from bed to toilet).

- Sleeping much more (e.g., 12+ hours each night, with daytime naps). May also be more likely to just nap or phase in and out of sleep. Sleep disturbances are common at this point.

- Elevated heart rate (e.g., in the 90s) and possibly shortness of breath.

- Increased memory issues and confusion; may not recognize own spouse/children; may not know what month it is.

- May start to become expressionless facially and verbally. (While a few people retain the ability to communicate until very near the end, most do not.)

- Harder to sustain a conversation. May make strange statements.
- Needs more medications to control symptoms.
- Start of loss of bladder and/or bowel control; may experience reluctance to wear protective pants due to loss of ability to understand future consequences.
- May exhibit less tolerance for/interest in food.
- May start to exhibit problems swallowing food.

About A Month Before Passing

- Should be enrolled in hospice and needs 24/7 care.
- Will feel safest/less anxious at home on one area of the couch or on one certain recliner.
- Even the side of the body not previously affected is now showing signs of weakness.
- Has likely become a true fall risk and must have support. Legs may just buckle at some point, and they will not be able to support their own weight.
- If still able to walk, may wander around the house. You may find them standing, staring blankly in some room in the middle of the night. May have some level of restlessness/agitation.
- May sleep 18-20 hours a day, but not continuously. Will wake, be alert for a while, potentially will have something to eat, then drift back to sleep. May have sundowner's syndrome - a condition where there is confusion over what time of day it is.
- Memory continues to lag; displays less interest in anything having to do with normal life (e.g., seems detached from family, friends, interests.) No longer interested in activities that require an attention span (e.g., will not

care to watch a TV show, play a video game, or read a book.)

- Conversations become even more difficult to sustain. Word finding may be very slow or be frustrating with words ending up on the "tip of the tongue".
- Speech may become slurred; sentences may be unfinished.
- May make statements indicating they are aware of their impending passing. May describe visions involving deceased relatives or angels.
- May become childlike. Questions only needing a yes/no response work best.
- Urine becomes orange or dark (can be described as "tea-colored").
- May experience less warning before needing to urinate. May have "accidents". May saturate the bed with urine at night and will need an external catheter to control.
- Appetite may start to be sporadic.
- Swallowing problems may increase. (It is important to not force food or drink at this point because they could aspirate the food or drink causing aspiration pneumonia.)

Days Before Passing

- Totally bed ridden and sleeping all the time.
- Decreased food and drink intake (most will stop entirely; swallowing problems will make any efforts to feed downright dangerous). It is important not to force food or water to avoid aspiration pneumonia. Sometimes when/if requested, hospice will start a saline drip for fluids which may provide another extra day or so.
- Dry mouth (will need to keep Vaseline or other softener on their lips).

- Restlessness (if too much, get with hospice to help with this; they can provide a medication).

- Labored breathing (get with hospice to help with this; they can provide oxygen which can help).

- Fever (will probably need to use Tylenol or other med to control fever, but the fever will just go up again when the med wears off).

- Dark orange/brown urine; reduced output.

- Heart Rate: Near the end, heart rate can become very elevated. It is not unusual for someone to have a beats per minute of 140, 150 160 (or more). As the heart rate increases, so may breathing for which they could use some oxygen support. When you see the heart rate start to come down from these peaks (if you are monitoring the heart rate), then you know they are getting ready to pass.

- Communication: Most individuals have not communicated for a long while at this point, but a few may suddenly, a day or so before they pass, awaken, may even sit up, ask for food, tell a few stories, say that they love you, then fall back to sleep and never again wake up.

- Pain and Awareness: Awareness of what is happening, including any pain, is ending. Normally, people who pass from brain cancer do so with very limited amounts of pain. The only real way you may have of knowing they are in some level of discomfort and needs a bit of medicine to alleviate that discomfort will be some very subtle facial expression (e.g., furrows the eyebrows) or maybe some soft groaning.

Hours Before Passing

- Purple spots on skin start appearing (usually starting around the feet and knees).

- Twitching.

- "Urine dump" (the body could release a large amount of fluid in a short amount of time).

- Perspiration (you'll want to just clean their face, arms, and legs with a clean, cool, moist wash cloth).

- Often in a coma or deep sleep.

- Breathing changes (if there was labored breathing before, it could suddenly calm down before stopping).

- It is recommended that you do not engage in disconcerting conversations around your loved one when he/she is "sleeping" (even if the hospice nurse says he/she is in a coma/ semi-coma). Hearing is the last sense to go, so assume that he/she can hear and possibly even understand everything said in her earshot.

    - One study by a neuroscientist says that the brains of 15-20% of people in a deep coma/vegetative state still show conscious and responsive activity under an MRI. So, if you need to tell your loved one something important, do that; it is possible he/she hears you on some level and understands. Similarly, if someone has something tough to say, it should be taken outside or into another room.

- Keep regular track of your loved one's heart rate. In the beginning of the transition process, the heart rate may be high, sometimes going very high (like into the 140's, 150's, 160's) and then as the process concludes, your loved one's heart rate will start to taper. Once it starts, this tapering can go fairly quickly with his/her passing following in a short time.

- Be ready with family, friends, and any clergy you might want to have present.

- It is suggested that you plan your last religious readings and prayers sooner rather than later and have the materials nearby. Be careful not to use your very favorite prayer at the very end because you may not be able to recite that prayer again for a very long time without breaking down emotionally.

Where Has My Loved One Gone?

The answer to this question is intimately tied to and is best addressed by one's own religious views on the topic. However, for those with a spiritual nature who are craving answers but are not affiliated religiously may find it consoling and useful to review the reports of individuals who have experienced a near death experience. The largest collection of these experiences has been assembled by a radiation oncologist named Dr. Jeffrey Long and is available online at this link:

https://www.nderf.org



Photo of Gorgeous Gal

Disposal of Unused Medications

Disposal of Federally Controlled Substances

If hospice has been conducted at home and the loved one passes in the home, there is often the question of how to dispose of the unused medications. The question of how to dispose of unused medications should be referred to the hospice doctor, physician's assistant, or nurse.

Some of the medications used during hospice are considered controlled substances (as that term is defined under the US Controlled Substances Act and equivalent laws if hospice occurs in another country), which if not properly disposed of, can be diverted and misused by others.

The most commonly misused controlled substances include opioids (such as oxycodone) which is used to treat pain and central nervous system depressants (such as diazepam), which are used to treat anxiety and sleep disorders. These and similar types of drugs are commonly prescribed for patients in hospice care.

In 2018, an amendment to the US Controlled Substances Act allows employees of "qualified hospices" to dispose of a patient's unused controlled substances onsite and in accordance with all applicable laws after the patient's death or the controlled substance expires. The employee must be a physician, physician assistant, nurse, or other person who is:

- employed by a qualified hospice (i.e., a business set up to provide hospice services that has written procedures and procedures, and properly documents the disposal of the substances); and
- licensed to perform medical or nursing services by the jurisdiction in which the patient has received hospice care; and
- acting within the scope of their employment in accordance with applicable state law; and
- trained on the disposal of controlled substances by the qualified hospice.

Disposal of Medications NOT a Federally Controlled Substance

Once qualified hospice personnel have identified to you medications that are NOT federally controlled substances, then you may dispose of the medications following the instructions from the US Food and Drug Administration (FDA) on their website:
https://www.fda.gov/drugs/safe-disposal-medicines/disposal-unused-medicines-what-you-should-know

Identify Theft of Deceased

Regrettably, some individuals will attempt to steal the identities of individuals who are deceased. They review obituaries and may try but using these guidelines should help you prevent an attempt, recognize an attempt, and know how to react if an attempt at identity theft is being made.

What To Look For

Watch for a letter from the post office saying that your loved one's mail is being forwarded or letters from a bank or banks requesting additional information for the credit applications. These are likely to arrive on or about the time.

What To Do If You Suspect Identify Theft Of A Deceased Person

Request a copy of the decedent's credit report. Then, place a flag on the account stating "deceased alert" on the report, as described below.

Notify the police in the decedent's jurisdiction if you have evidence of fraud (collection notice, bills, credit report). A suspicion of identity theft is best when backed with concrete evidence.

Notify any creditor, collection agency, credit issuer and utility company that the person is deceased. Be sure to include a copy of the death certificate. Request an immediate investigation and that they contact you with the results of the investigation. Insist on letters of clearance, which you should keep with the other estate papers.

In the event that the thief is a family member or relative (which unfortunately does happen), seek the advice of an attorney that specializes in estate or family law.

How to Prevent Identity Theft Of A Deceased Person

In obituaries, list the age but don't include birth date, mother's maiden name or other personal identifiers that could be useful to identity thieves. Omitting the person's address also reduces the likelihood of a home burglary during the funeral (sadly, this also does happen).

Using certified mail with return receipt, send a copy of the death certificate to each credit-reporting bureau — Equifax, Experian, and TransUnion. Make sure that your letter and/or the death certificate includes the following and any other data needed by the particular bureau:

- Name and Social Security Number of deceased
- Last known address
- Last 5 years of addresses
- Date of birth
- Date of death

In your letter, ask them to place a "deceased alert" on the credit report and mark the file as follows:

> "Deceased. Do not issue credit. If an application is made for credit, notify the following person(s) immediately: (list the next surviving relative, executor/ trustee of the estate and/or local law enforcement agency- noting the relationship)."

Mail a copy of the death certificate to banks, insurance companies (auto, health, life, etc.), Veteran's Administration (if person was a former member of the military), brokerages, credit card and mortgage companies where the deceased held accounts, membership programs (video rentals, fitness clubs, etc.)

If you're closing an individual account, make sure the institution lists "Closed: Account Holder Is Deceased" as the reason. For joint accounts, remove the deceased's name.

Report the death to Social Security by calling 800-772-1213.

Contact the department of motor vehicles to cancel the deceased's driver's license, to prevent duplicates from being issued to fraudsters.

Keep copies of all correspondence, noting date sent and any response(s) you receive.

Brain Donation

While considerable progress can be made through the current medical research methods, there is so much more neuroscientists can make given the advantage of working with donated brain tissue. From one brain, dozens if not hundreds of studies can be made.

Brain donation makes it possible to advance research into brain cancer that can provide a lasting and significant legacy for your loved one, and families may derive a sense of comfort from contributing to the eradication of this disease with the goal that other families will not have to endure such a loss.

There is no cost to the families for the steps involved in making this donation.

For those interested in making this extremely precious gift, you may find more information at this website:

https://braindonorproject.org





Twenty-Two

Grieving

Overview

Even though we know that everyone will die, each death can still have a huge impact those of us who are left behind. Experiencing grief is natural and necessary, and the vast majority of people suffering the loss of a loved one will experience it.

We have neuroimaging studies basically of grief, of the momentary reaction where you have that emotional yearning experience. One thing that we know is that grief is tied to all sorts of different brain functions, from being able to recall memories to taking the perspective of another person, to even things like regulating our heart rate and the experience of pain and suffering. This is why we have a large variety of emotions and why they can be quite intense.

In this section we discuss the three main categories of grief that individuals who have lost or expect to lose a loved one to brain cancer may experience:

- Anticipatory Grief
- Grief after the Passing
- Prolonged Grief Disorder



Photo Credit Linda Singer

Anticipatory Grief

Unlike the grief that happens after a loved one has passed away, "anticipatory grief" is a distinct kind of grief that begins once we realize our loved one is in danger of passing away within the foreseeable future. For caregivers and family members who closely step through the brain cancer diagnosis and treatment journey with a loved one, the growing reality of the impending loss can be all the more intense and real.

Many of the emotions experienced by someone grieving after the loss will be experienced by someone in anticipatory grief. Differing levels of a wide variety of thoughts and emotions like sadness, anger, frustration, denial, guilt, and a clinging to every hope however valid or flimsy can be experienced. Sometimes the experience of anticipatory grief lessens the post-loss grief, but not always. By the time the loved one does pass, a person experiencing anticipatory grief can be very entrenched in the variety of painful emotions that characterize grief after passing.

Anticipatory grief is quite real and should not be ignored. It can sap the energy you want and need to care for your loved one and spend very precious time together making important memories.

You should endeavor to spend time in your normal activities. Staying grounded in your life with your activities and your friends can help. Reaching out to trusted and caring confidants and telling them how you feel can help to "vent" some of the painful emotions you are experiencing. Taking time for yourself is not being selfish; it is recharging your batteries to enable you to be a better caregiver through a very difficult time in your life.

Grief After the Passing

No matter how long you knew, no matter how much you accepted the loss, nothing can prepare you fully for the reality of the loss.

Grieving is a process that involves your mind, your emotions as well as your body. Many people are surprised to understand that grief is also physical. Here are some practical ideas to help you with this challenging period of your life:

- **Unique**. Your grief will be unique to you, so no one can or should tell you what is right or wrong for you to be experiencing.

- **Find Those Who Understand**. You should find others who understand. Some people cannot relate to anyone who has gone through the brain cancer journey with all its intense complexities, so it is helpful to seek out those who have gone before you.

- **Talk About It**. People who have not gone through such an intense loss will tolerate hearing about it once or twice, but that might not be enough venting for you. Ideally, you should find those who will let you talk about what you have experienced as much as you want.

- **Emotions**. Expect that your emotions will be a stew that will change day by day, even hour by hour. You may visit every emotion like sadness, fear, confusion, depression, guilt, anger, even relief (and then guilt from feeling relieved.)

Others may tell you that something you are feeling is wrong. Do not accept their judgment; accept your emotions unconditionally and seek out individuals who can do the same.

- **Guilt**. Almost everyone who goes through this journey ends up feeling guilty about something they think they could have done or should have done to extend the life of their loved one or to make them more comfortable. This is an unfair and bottomless pit. Accept that you did the very best you could under the circumstances, which were extreme. Caring for someone with brain cancer is the #1 caregiving challenge given all the complexities of the disease.

- **Hindsight Inflation.** In the aftermath of loss, memories become more vivid and regrets can intensify—a phenomenon called hindsight inflation. Grief magnifies past moments and prompts self-doubt, not due to a lack of care or judgment, but because the mind seeks meaning and control where none exists.

When we are grieving, our brains struggle to reconcile an irreversible loss with our ideas of how things should work. This can leave us feeling responsible for things beyond our knowledge or power and cause us to believe we missed signs, wasted time, or failed to say or do enough. This pattern of thinking can produce doubts about one's competence, character, or capacity for love, which transforms normal uncertainty into painful feelings of negligence or inadequacy.

The key for someone going through grief is to recognize that grief, which is like going through an emotional tsunami, temporarily biases normal brain functioning as it relates to our confidence, sense of blame and certainty – all of which take a beating during grief. The resulting biases and doubts that go through our minds are best understood as a misfiring of brain systems that under normal circumstances would protect us. But during grief, our brain is searching for control, meaning, or reversal, but because reversal is out of reach, doubts spring up like mushrooms. Recognizing these reactions as natural effects of grief can help ease feelings of inadequacy.

With time, grief and its cognitive effects usually lessen. It can help to remember that choices were made with the best intentions and the best understandings at the moment.

● **Extreme Emotions**. Some people have difficult reigning in their behavior after a loss. They may be overly angry and engage in road rage. They may experience intense sadness for more than 2 weeks which then migrates into depression. If you experience any long-lasting extremes of emotion that can compromise your normal behaviors in unhealthy ways, please reach out for help to a responsible friend or doctor.

● **Exhaustion**. Grief is hard work and can leave you sapped of strength. Expect fatigue and expect to need to baby yourself with rest. If others want you to do things to take your mind off the loss, do not feel you must go. Maybe a nap will be the best for you at that time.

● **Diet**. It may be hard, but you need to eat, and you may find you have to force yourself a bit to not just eat but to eat healthy foods.

● **Grief Ambushes**. Grief can ambush you when you least expect it. You may have strung 2 good days together and then the third day hits you like a truck and you are overwhelmed again. Or you are holding your own at the grocery store and then you see a food your loved one really liked, and you break down right there in the bread aisle. These ambushes are a normal experience. Over time they should subside in frequency.

● **Funerals**. The funeral is not just to celebrate and honor the life that has just been lost but is intended to support you in mourning. If someone suggests not to have a funeral, talking to a trusted friend or clergy may ease your questions.

● **Relying On Faith**. If you have religious tradition, make use of it to the maximum extent you want. Faith at a time of grief can be a significant help, so seek out people who share your faith convictions.

● **Anger/Questions For God**. If you have been left with questions or anger at God about why this all happened, please talk to a friend or clergy who will understand and not condemn your feelings. Also, when someone tells you that your loved one is in a better place, no matter what your views are of Heaven, you may recoil from that well-meaning but insensitive comment. You don't have to accept any comments like that.

- **Rebuilding Meaning**. When a diagnosis like brain cancer happens and certainly if a loss happens because of it, it can take a person's sense of meaning and ruin it. As a mourner, you are grieving not just the loss of your loved one, but all the meanings you had in life associate with that person. You task now is to rebuild your sense of meaning - figuring out why you are getting out of bed in the morning. This is not an easy task, so lean into your support group to help you.

- **Treasuring The Past**. Your memories of your loved one are precious. If you have items of theirs you want to keep, keep them. If you want to put up more pictures of them, do that. This is your loss and your way of treasuring what has been lost. Ideally, you will find people who can share your memories with you.

- **Learning To Bear The Loss**. Grieving is a process of self-paced learning. It takes time and patience to learn how to bear the loss of a loved one and then balance it with the continuation of your life. Your life has been deeply changed by your loss, but with the help and support of those who understand what you have gone through, you will come through and one day the sun will shine again in your life.



Prolonged Grief Disorder

When a loved one dies, those left behind naturally feel various levels of sadness, anger, guilt, fear, and loneliness. These are the hallmarks of normal grief.
The initial period is intense and for the majority if people (about 93%) is limited to a predictable period of time—about six to twelve months. The exact time will vary from person to person and from culture to culture.

Eventually, the initial grief will slip to the background of the survivor's life and will be integrated into their thoughts and emotions in a way that enables a balancing of the loss with the ongoing life. The mind and heart adapt. The grief does not end, but its sting will lessen and how it is experienced will change.

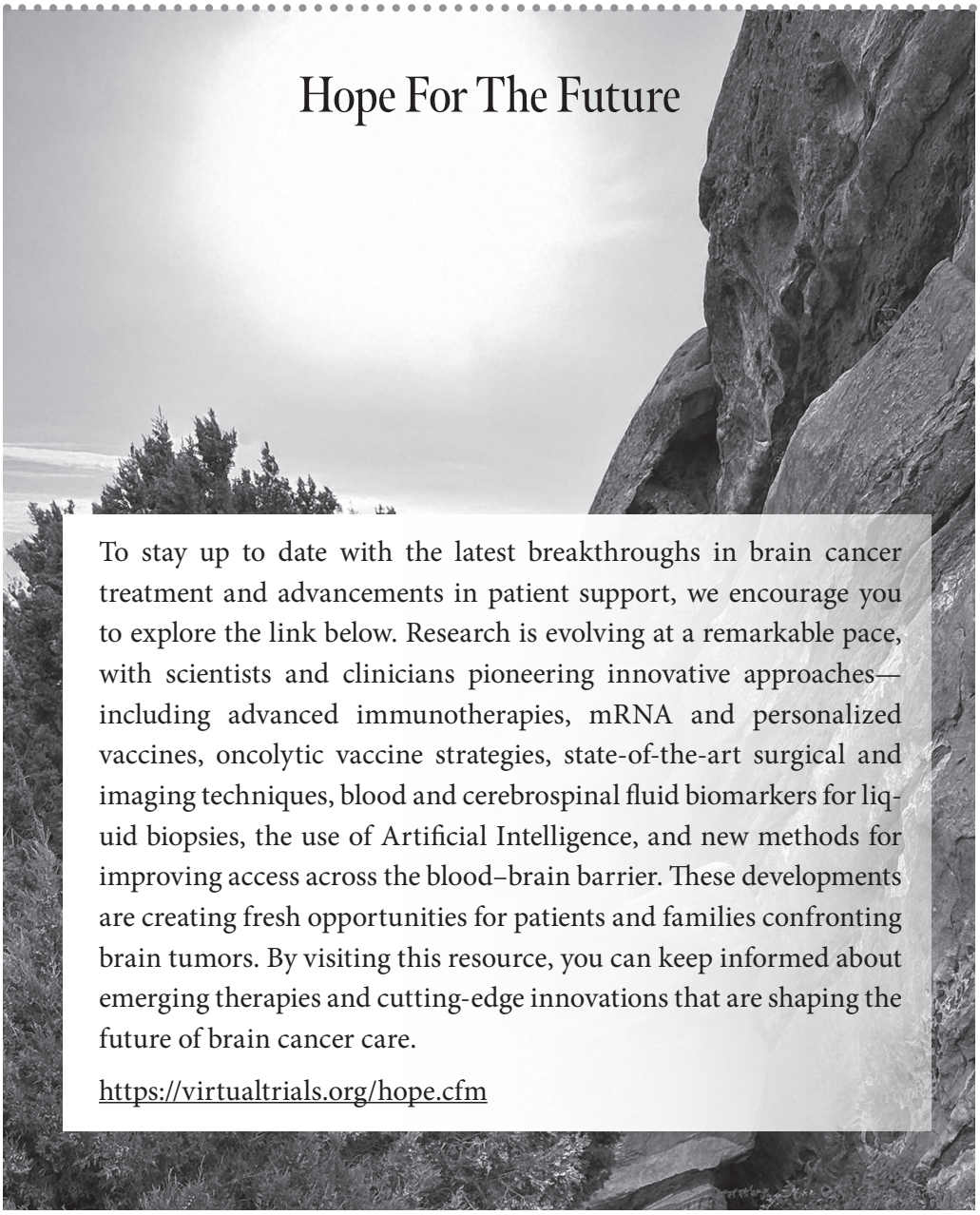
For about 7 percent of those who are bereaved, however, grief ensnares people, which can prevent them from restoring their capacity to experience life in a healthy fashion. In 2018, the American Psychiatric Association, in the fifth edition update of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), added Prolonged Grief Disorder as a disorder, describing it as grief that persists for one year or more.

Those who lose a central relationship like a parent, child or spouse are more susceptible to Prolonged Grief Disorder.

If you feel you may be caught in Prolonged Grief Disorder, please reach out to a counselor with experience in grief.



Twenty-Three



Hope For The Future

To stay up to date with the latest breakthroughs in brain cancer treatment and advancements in patient support, we encourage you to explore the link below. Research is evolving at a remarkable pace, with scientists and clinicians pioneering innovative approaches—including advanced immunotherapies, mRNA and personalized vaccines, oncolytic vaccine strategies, state-of-the-art surgical and imaging techniques, blood and cerebrospinal fluid biomarkers for liquid biopsies, the use of Artificial Intelligence, and new methods for improving access across the blood–brain barrier. These developments are creating fresh opportunities for patients and families confronting brain tumors. By visiting this resource, you can keep informed about emerging therapies and cutting-edge innovations that are shaping the future of brain cancer care.

https://virtualtrials.org/hope.cfm





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.

Antagonist: A substance that acts against or blocks an action.

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

Antigen: Any substance that causes the body to make an immune response against that substance. Antigens include toxins, chemicals, bacteria, viruses, or other substances from outside the body. Cancer cells also have antigens on them that can cause an immune response.

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

Astrocytic: Refers to the large, star shaped cells in the brain that form connective tissue between the nerve cells and the blood vessels.

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

Autologous: Cells obtained from the patient themselves.

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: An abbreviation for the drug, bischlorethyl nitrosourea. The generic name is “carmustine” and the brand name is BiCNU®. Since carmustine is the active molecule in the slow-release, biodegradable, FDA-approved “chemowafer” with the brand name Gliadel®, implanted in the surgical site to prevent progression / recurrence of a malignant glioma.

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.

Calcification: A buildup of calcium in a tissue causing the tissue to harden.

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

CCNU: An abbreviation, a chemical shorthand, for the drug, Chloroethyl-Cylohexyl-Nitrosourea. Lomustine is the generic name (the official international non-proprietary name). Gleostine is the brand name, currently used by the manufacturer. All three terms (CCNU, Lomustine, Gleostine) describe a single drug that is in the nitrosourea family and acts as an alkylating agent.

Centimeter or "cm": A unit of measure. There are 2.54 centimeters in one inch; said another way, 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 carefully controlled research study designed to determine whether a new treatment (such as a drug or medical device) is safe and effective for use in people. Every clinical trial follows a detailed, protocol-driven plan that clearly defines participant eligibility criteria, the schedule of tests and procedures, and the specific objectives and endpoints of the study.

Unlike observational studies, in which researchers monitor participants without intervening, clinical trials involve one or more specific interventions, such as surgery, radiation therapy, tumor treating fields, chemotherapy, or other therapeutic approaches.

Each clinical trial must be reviewed and approved by an Institutional Review Board (IRB) and/or an ethics or scientific review committee to ensure that patient safety and rights are protected, and that participants receive at least the current standard of care (SOC).

The primary objective of a clinical trial is to improve upon the current SOC by evaluating new drugs, devices, or treatment strategies (including novel combinations). The resulting data are rigorously analyzed, and if the new

approach demonstrates benefit over the existing SOC, it may lead to approval by the U.S. Food and Drug Administration (FDA).

In essence, clinical trials represent "tomorrow's medicine, today."

Organizations such as the Musella Foundation, National Comprehensive Cancer Network (NCCN), and the American Brain Tumor Association (ABTA) encourage eligible patients to consider participating in clinical trials whenever appropriate. There is also an ongoing effort across the medical community to expand access to clinical trials.

Research suggests that patients enrolled in clinical trials often experience improved outcomes—even when the investigational treatment ultimately proves ineffective—likely due to closer monitoring, structured follow-up, and care delivered at specialized centers of excellence.

CMV: Cytomegalovirus. A virus that infects most adults in the US by the age of 40. CMV is from the herpes family and may cause disease in individuals whose immune systems are compromised.

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.

Dendritic cell: A special type of immune cell that is found in body tissues and that enhances an immune response by showing antigens on its surface to other cells of the immune system. A dendritic cell is a type of phagocyte and a type of antigen-presenting cell (APC).

DIPG: Diffuse Intrinsic Pontine Glioma. A rare, fast-growing, histone-driven tumor that forms in cells called glial cells in a part of the brain stem called the pons. They usually occur in children.

Diffuse: Widely spread; not localized or confined.

DMG: Diffuse Midline Glioma is a type of brain tumor that is a clarified diagnosis of a DIPG. It is a histone-driven astrocytoma located along the midline of the brain but can also be found in midline structures like the spinal cord or thalamus. Often these tumors start as an “atypical” DIPG and are later formally diagnosed as DMG

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.

GBM: Glioblastoma Multiforme, which is a Grade 4 tumor. See also Glioblastoma.

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.

Glioblastoma: A fast-growing type of brain tumor that forms from glial (supportive) tissue of the brain and spinal cord and has cells that look very different from normal cells. Glioblastoma usually occurs in adults and affects the

brain more often than the spinal cord. Also called GBM, glioblastoma multiforme, and grade IV astrocytoma.

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.

Hyperbaric Oxygen: Oxygen that is given at a pressure that is higher than the pressure of the atmosphere at sea level. In medicine, breathing hyperbaric oxygen increases the amount of oxygen in the body. It is used in treating certain kinds of wounds, injuries, and infections (e.g., is sometimes used to treat necrosis). It is being studied in the treatment of some types of cancer. Hyperbaric oxygen may increase the amount of oxygen in cancer cells, which may make them easier to kill with radiation therapy and chemotherapy.

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.

Mesenchymal: Brain cancer that are developed from soft or connective tissues. They are one of four (4) subtypes of GBMs and is one of the most aggressive types.

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.

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.

Multicentric glioma: Multiple, widely separated brain tumor masses in different lobes or different hemispheres. These masses arise completely separately from one another; they do not spread by means of any common pathways or cerebrospinal fluid channels or any local metastases via satellite formation

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. The goal of palliative care is to prevent or treat as early as possible the symptoms of a disease, side effects caused by treatment of a disease, and psychological, social, and spiritual problems related to a disease or its treatment. 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.

PEG: Percutaneous endoscopic gastrostomy. A tube inserted through the skin and the stomach wall for the purpose of providing food.

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 (PET) scan is a nuclear medicine imaging technique that uses small amounts of radioactive substances, called tracers, to visualize brain tumors based on their metabolic activity. Unlike MRI, which primarily reveals brain anatomy and structural characteristics, PET imaging highlights functional and biochemical changes within tissues.

The procedure involves injecting a tracer into a vein. In FDG-PET imaging, the tracer is linked to glucose (FDG), while other PET tracers use radiolabeled amino acids such as [18F]FET, [18F]fluciclovine, or [18F]FDOPA. These tracers help define the full extent of a tumor's borders, which may extend beyond what is visible on MRI.

Because PET identifies areas of highest metabolic activity ("hot spots") within a heterogeneous tumor, it can assist surgeons in targeting the most aggressive regions for biopsy, improving diagnostic accuracy. Malignant cells typically consume more glucose and amino acids than normal cells, and this increased metabolic activity produces images that reveal cancerous tissue that might otherwise go undetected.

Furthermore, newer tracers with improved sensitivity and specificity can help distinguish true tumor progression from treatment-related changes such as

pseudoprogression.

Petechiae: Small red spots that may form on the arms and legs as a result of a drop in platelets.

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.

Primary endpoint: With reference to a clinical trial, means the result of a trial measured at the end to see if the treatment being tested worked, i.e., that there was a positive and clinically significant difference in survival between the group of patients getting the treatment and a control group of patients who did not.

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; this is often observed in patients receiving immunotherapy but can lead to premature discontinuation of treatment owing to the false judgment of actual progression. Patients with a methylated MGMT promoter are significantly more likely to experience pseudoprogression following chemotherapy (Temodar) and radiation therapy. Plus, in approximately 20% to 30% of GBM cases, the first MRI(s) obtained after radiation therapy and concurrent Temodar meets the criteria for progressive disease, but subsequent follow-up scans show lesion shrinkage or stability, demonstrating pseudo-progression in those cases. Pseudo-progression is among the most common causes of misdiagnosed tumor recurrence.

Randomized Clinical Trial: A study in which the participants are assigned by chance to separate groups that compare different treatments; neither the researchers nor the participants can choose which group. Using chance to assign people to groups means that the groups will be similar and that the treatments they receive can be compared objectively. At the time of the trial, it is not known which treatment is best. It is the patient's choice to be in a randomized trial.

Recur, Recurrence: The return of a tumor after a period of stability or remission.

Refractory: When the disease becomes non-responsive to treatment of any kind.

Resectable: Able to be removed by surgery.

Resection: Surgical removal of a tumor. A resection may be partial (also called "subtotal") or total.

RNA (ribonucleic acid): A vital molecule that carries genetic instructions used to make proteins. If DNA is the master blueprint stored safely in the cell's nucleus, RNA is the working copy that delivers those instructions to the rest of the cell. Because of its versatility, RNA has become central to advances in virology, vaccine development, and emerging brain tumor therapies.

One promising approach involves designing RNA molecules that can "silence" specific genes that drive cancer growth—essentially locating a tumor's "on" switch and turning it off. Researchers are also analyzing individual patients' brain tumors to identify their unique genetic signatures and then creating personalized messenger RNA (mRNA) vaccines. These vaccines train the immune system to recognize and attack cancer cells while sparing healthy brain tissue. Early clinical trial results suggest that mRNA vaccines can effectively "prime" the immune system to detect and destroy residual cancer cells that surgery may have missed.

In addition, some viruses use RNA as their genetic material. Scientists are

harnessing this property to develop innovative cancer treatments. For example, the Poliovirus has been genetically modified so it no longer causes disease but can selectively infect glioblastoma (GBM) cells, making them more visible to the immune system. The Measles virus has been explored in a similar way. Researchers are also working to re-engineer the Zika virus so that it targets brain tumor cells instead of healthy tissue.

SEER: National Cancer Institute's Surveillance, Epidemiology and End Results Program, a national cancer registry that covers more than a quarter of the U.S. population and represents the extensive diversity of the country.

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. Those with GBM are susceptible to having TIAs.

If you or someone close to you experiences sudden paralysis, blindness, or loss of speech, then seek emergency care immediately by calling 911 or visiting the closest Emergency Room as only medical evaluation and imaging can differentiate between a TIA, seizure, stroke or other causes.

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.





"Fishing with Aba" by Hana Brem

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 also told her there were no clinical trials that would take her because of the size of her tumor. In fact, 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 there was no treatment options for her other than a standard course of BCNU, which had no chance to help her for more than 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 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!

Al found a few clinical trials that would accept Lana, after being told by a few major brain tumor centers that there were none (because her tumor was too large and multifocal). 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, with her 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 Foundation 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 has helped convince Medicare to pay for Temodar, Gliadel, Avastin and Optune. It has helped accelerate FDA approval of Temodar, Avastin, Gleolan and Optune for brain tumor patients.

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. But although the government now funds brain tumor research at an unprecedented level, many promising projects remain unfunded.

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 its support for brain tumor research

or its co-payment assistance program. For more details on how you can help us speed up the search for the cure, please visit the virtualtrials.org website.



Photo credit: 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

Below is a listing of recent research grants made since 2020 by the Musella Foundation. The Musella Foundation has awarded investigators with over $4 million in 126 grants since 2003. We have helped fund the early work on some of the most promising therapies in the pipeline.

Interested investigators should call the Musella Foundation directly to discuss the project(s) for which they seek funding before submitting the formal grant application. To see a list of all grants awarded by the Musella Foundation, please go to the grants page at the virtualtrials.org website: https://virtualtrials.org/grants.cfm.

2026 (year to date) Grant Awards

$33,750 grant to Cancer Commons for the **"Brain Cancer Support and Solutions Alliance"**(BCSSA) patient navigation program

$50,000 to CV Bio to support the project titled: **"DNX 2401Oncolytic Virus for DIPG / DMG"** This is in partnership with DDRFA as part of a million dollar grant from DDRFA to CV Bio!

$50,000 to KiraGen Bio, Inc to support the project titled: **"Validating TME-Resistant CAR-T in Patient-Derived GBM Tumoroids"**

$50,000 to AVIL Therapeutics, Coop to support the project titled: **"Lead optimization of first-in-class small molecule inhibitors targeting AVIL in glioblastoma"**

$100,000 to Zenagem to support the project titled: **"Advancing a first-in-class novel therapeutic for recurrent glioblastoma"**

$75,000 to the DIPG/DMG Collaborative as a general grant to support the expenses of running the DIPG/DMG Collaborative

$55,000 to the NETA Foundation to support the project titled: **"Development of Flag-003 for pediatric brain tumors"**

$50,000 to Cypris Therapeutics to support the project titled: **"Development of novel small molecule therapeutics for the treatment of gliomas, including glioblastoma"**

$40,000 to Dr. Michael Lim to support the project titled: **"Defining interferon signaling dependence in dual PD-1/LAG-3 checkpoint immunotherapy for glioblastoma"**

$35,000 to Dr. Haack to support the project titled: **"Computer modeling of tumor treating fields"**

$25,000 to Dr. John Prensner to support the project titled: **"RNA liquid biopsy for DMG/DIPG"**

$25,000 to Dr. James Ross to support the project titled: **"Defining and targeting lipid metabolism in DMG-associated macrophages and microglia"**

$10,000 to Dr. Vivekanand Yadav to support the project titled: **"Preclinical evaluation of a non-psychoactive cannabinoid combined with an imipridone-class small molecule in DMG"**

$8,500 to Dr. Jasia Mahdi to support the project titled: **"Real-time cytokine sampling for inflammation-associated neurotoxicity following CAR T cell treatment for DIPG/DMG"**

$6,500 to Nicole Lions / Tough Together to support the project titled: **"Qualitative and safety analysis of patient-reported data, decision making, and clinical outcomes in DMG"**

$4,000 to Imaging Biometrics to help patients pay for participation in the project titled: **"Expanded Access Program for Oral Gallium Maltolate"**

Total for 2026 (to date): $617,750.00

2025 Grant Awards

$6,000 grant to DDARFA (DIPG/DMG Research Funding Alliance) to help fund the DIPG National Tumor Board project

$20,000 grant to the CHOP Foundation for the **"Children's Brain Tumor Network"**

$25,000 grant to DIPG Collaborative to help fund research into pediatric DIPGs/ DMGs

$35,000 grant to Targeputics, Inc to fund the project: GB-13 (Glioblast-13) for DIPG. This grant was as part of a collaborative grant through DDARFA.

$22,000 grant to Dr. Danielle A. Bazer at Cooper University, to fund the project: Pre-Radiation Chemotherapy for Newly Diagnosed High Grade Glioma: An Approach to Drug Screening that Requires Confirmation.

$16,500 add on grant to Imaging Biometrics for Dr. Danielle A. Bazer at Cooper University, to fund the creation of Fractional Tumor Burden Maps (FTB Maps) for her project: Pre-Radiation Chemotherapy for Newly Diagnosed High Grade Glioma: An Approach to Drug Screening that Requires Confirmation.

$198,500 grant to Neta Foundation to support the project: Development of Flag-003 for pediatric brain tumors. This is in collaboration with DDARFA (DIPG/ DMG Research Funding Alliance) , The Tough2Gether Foundation and the AYJ Fund.

$25,000 grant to Dr. Brice Martin at Weill Cornell Medicine, to fund the project: Low-intensity focused ultrasound for spatially controlled release of ThermoDox® in diffuse midline glioma.

$52,235 grant to Dr. Kathy Warren at Dana-Farber Cancer Institute, to fund the project: Preclinical (in vivo) studies of FLAG-003 to inform the first-in-human study in children with DIPG. This grant is from our DIPG All-In-Initiative fund.

$15,000 grant to Dr. Chritopher Chitambar at The Medical College of Wisconsin to fund the project: Mechanistic- and biomarker-based approach to enhance clinical translation of gallium maltolate for treatment of glioblastoma

$20,000 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. We only partially funded the grant which requested $322,000 and are saving up for the rest. This is the second payment.

$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 our annual grant to help support this important ongoing project.

$40,000 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"**

$5,500 to DDRFA (DIPG / DMG Research Funding Alliance) to fund DIPG / DMG Virtual Tumor Boards!

$12,349 grant to Dr. Macarena de la Fuente at Sylvester Comprehensive Cancer Center for the project **"Gallium Maltolate Expanded Access Program"**

$50,000 grant to Dr. Haack at Beth Israel Deaconess Medical Center to fund the project: Computer modeling of tumor treating fields

$12,500 grant to the CHOP Foundation for the **"Children's Brain Tumor Network"**

$77,925 grant to Cancer Commons for the **"Brain Cancer Support and Solutions Alliance"**(BCSSA) patient navigation program

Total for Year 2025: $638,509.00



Photo Credit Andy Singer



APPENDIX A: MOLECULAR CHARACTERISTICS OF A GBM

Subtypes of GBMs

In modern neuro-oncology, the World Health Organization (WHO) no longer emphasizes the older "proneural, classical, mesenchymal" subtypes for diagnosis. Instead, it defines glioblastoma more precisely through a small set of core molecular (genetic) features that together characterize what is now called glioblastoma, IDH-wildtype.

Within this framework, three hallmark genetic alterations function almost like defining "molecular subtypes," because the presence of any one of them—along with appropriate histology—can establish the diagnosis. Glioblastoma, therefore, is fundamentally a tumor driven by IDH-wildtype biology, meaning it lacks mutations in the IDH1 or IDH2 genes that are seen in lower-grade gliomas. Instead, it is marked by one or more of three defining genetic features.

The first is TERT promoter mutation, involving the TERT gene. This alteration leads to reactivation of telomerase, an enzyme that maintains chromosome ends (telomeres), effectively allowing tumor cells to divide indefinitely. It is one of the most common events in glioblastoma and reflects the tumor's capacity for cellular "immortality."

A second defining pathway involves amplification of the epidermal growth factor receptor, or EGFR. In many glioblastomas, this gene is not only amplified (present in many extra copies) but also mutated into constitutively active forms such as EGFR-vIII. These changes drive continuous growth signaling, pushing cells to proliferate even in the absence of normal external cues. Tumors with EGFR alterations often also show broader chromosomal instability, including gain of chromosome 7 where EGFR resides.

The third major genetic signature is a combined chromosomal pattern known as +7/–10, meaning gain of an entire copy of chromosome 7 and loss of chromosome 10. This pattern reflects widespread genomic imbalance. The loss of chromosome 10

is particularly important because it often includes deletion or inactivation of tumor suppressor genes such as PTEN, which normally restrains cell growth through the PI3K/AKT pathway. Together, chromosome 7 gain and chromosome 10 loss create a powerful combination of increased oncogenic signaling and reduced tumor suppression.

Although these three genetic patterns—TERT promoter mutation, EGFR amplification, and +7/–10 chromosomal change—can occur together, the WHO framework treats each as sufficient evidence of glioblastoma biology when paired with the appropriate clinical and histologic context. In this way, they function as three molecular "entry points" into the same aggressive disease entity rather than completely separate diseases.

This approach reflects a shift away from broad expression-based subtypes toward genetically defined mechanisms of tumor behavior, aligning diagnosis more closely with prognosis and, increasingly, with targeted therapeutic strategies.

Immunosuppressive Environment Differences in GBMs

In addition to the molecular variables identified by Dr. Verhaak's group, studies over the last few years demonstrate that GBMs can be expected to respond differently to treatment because of differences in their immune landscape.
The latest studies identify four distinct immune landscapes in GBMs:

- Type 1 tumors with a high number of macrophages and a few T cells.
- Type 2 tumors with a moderate number of macrophages.
- Type 3 tumors with high numbers of T cells and a few macrophages.
- Type 4 tumors that the researchers call an immune desert, because they have few or no immune cells of any type.

What is emerging from the latest study is that GBMs subtypes vary significantly in the percentage of immune cells in their microenvironment.

APPENDIX B:

Brain Functions and Dysfunctions by Location

To understand what symptoms you may experience as a result of the tumor and its treatment, it is helpful to specifically understand the tumor's location. Symptoms depend on the tumor's location, the amount of edema (swelling) it produces and also its size and development rate. Tumors that are less than 2 centimeters in diameter or that develop very slowly may be asymptomatic. Larger tumors, those that rapidly develop (over weeks or months rather than years), and tumors that simultaneously affect both hemispheres are more likely to become symptomatic.

Your neurosurgeon or neuro-oncologist would be able to help you identify the tumor location. The doctor may provide you with a diagram of the brain with a penciled-in identification of your tumor site. Alternatively, you may use the images of the brain provided below in discussions with your doctor.

The top part of the figure (1A) shows the major parts of the brain. The bottom part of the figure (1B) shows some of the functions associated with each of the brain parts.

Figure 1A: Major parts of the brain

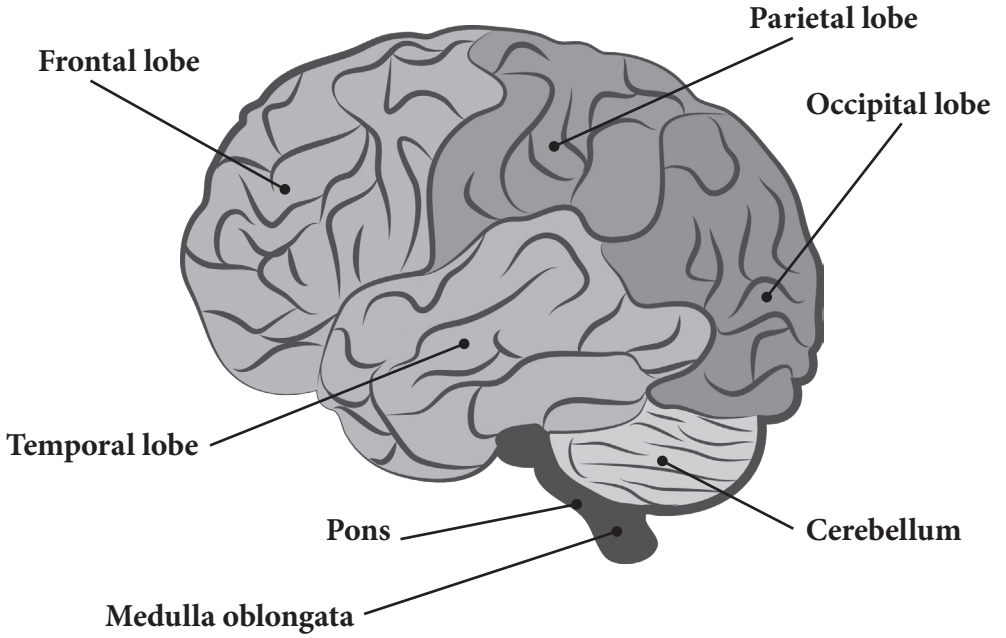
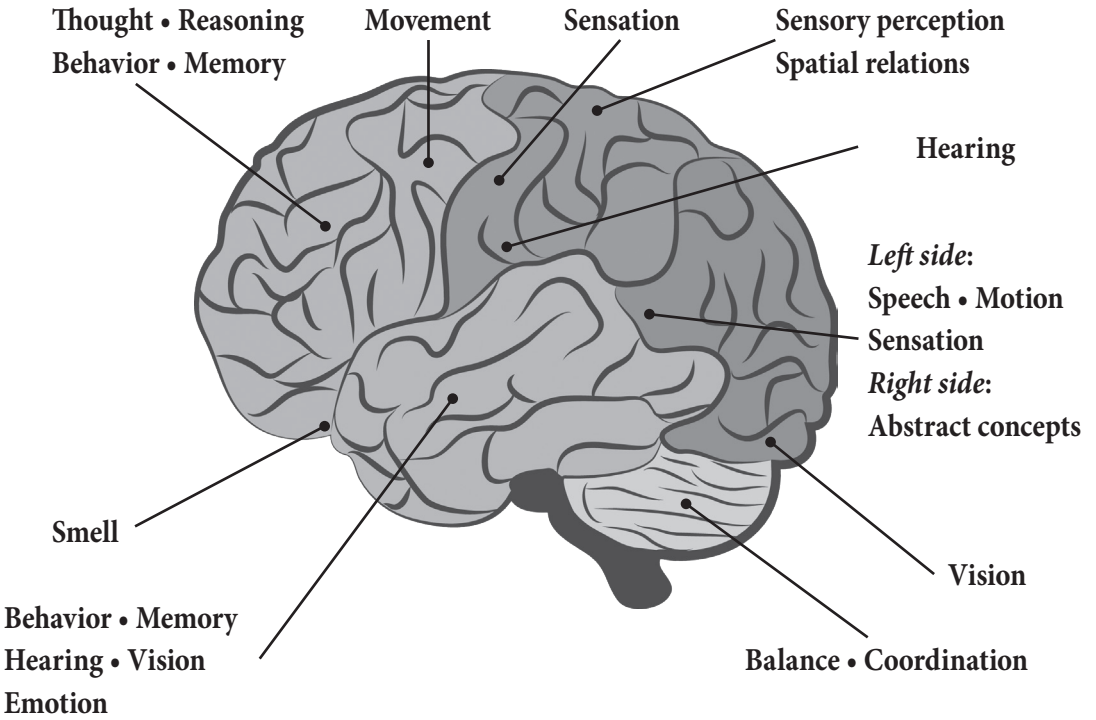


Figure 1B: Associated functions of the parts of the brain



Hemispheres Of The Brain

The brain is divided into two halves called hemispheres. The hemisphere affected by the disease is important because the functions of the two halves of the brain are not identical. Some functions are performed exclusively by one hemisphere. For example, movement and sensation on one side of the body are controlled by the hemisphere on the opposite side. Other functions are performed mainly by one, dominant hemisphere. In those cases, damage to the single, dominant hemisphere may cause complete loss of a function.

However, most functions, like memory, require the cooperation of areas in both hemispheres. For such functions to be completely lost, both hemispheres must be damaged or the connection between the hemispheres (usually through a connecting point like the Corpus Callosum) is damaged.

The most classic symptoms occurring when the connection between the hemispheres is disrupted are:

- left hand anomia (unable to recall names of everyday objects)
- left upper limb ideomotor dyspraxia (problems with gross and fine motor skills; affects coordination, playing sports or driving a car)
- left visual field dyslexia (making the person easily frustrated, angered, or annoyed) and
- dysnomia (inability to recall words, names, or numbers; they may be "just on the tip of the tongue").

Diagnosing Dysfunctions

Specific dysfunctions are usually related to an area of the brain that has been damaged. In many cases, doctors can diagnose the dysfunction in conjunction with, and using the same techniques as needed in diagnosing brain cancer (e.g., MRI and interview questions).

Frontal Lobe Damage

The frontal lobes are responsible for a multitude of functions such as:

- Initiating many actions,
- Controlling learned motor skills, such as writing, playing musical instruments, and tying shoelaces,
- Controlling complex intellectual processes, such as speech, thought, concentration, problem-solving, and planning for the future,
- Controlling facial expressions and hand and arm gestures, and
- Coordinating expressions and gestures with mood and feelings.

Often, damage to the frontal lobes causes loss of the ability to solve problems and to plan and initiate actions, such as crossing the street or answering a complex question (sometimes called "executive functions"). Some specific impairments can occur depending on which part of the frontal lobe is damaged.

If the back part of the frontal lobe (which controls voluntary movements) is damaged, weakness or paralysis can result. Because each side of the brain controls movement of the opposite side of the body, damage to the left hemisphere causes weakness on the right side of the body, and vice versa.

If the middle part of the frontal lobe is damaged, people may become apathetic, inattentive, and unmotivated. Their thinking becomes slow, and their responses to questions are very slow.

If the middle back part of the left frontal lobe (Broca area) is damaged, people may have difficulty expressing themselves in words—an impairment called Broca (expressive aphasia).

If the front part of the frontal lobe is damaged, any of the following may result:

- Difficulty temporarily holding information available for processing (called working memory),

- Reduced fluency of speech,
- Apathy (lack of emotion, interest, and concern),
- Inattentiveness, and
- Delayed responses to questions.

A striking lack of inhibition, including socially inappropriate behavior. People who lose their inhibitions may be inappropriately elated (euphoric) or depressed, excessively argumentative, or passive, and vulgar. They may show no regard for the consequences of their behavior. They may also repeat what they say, not unlike individuals with dementia.

Parietal Lobe Damage

The parietal lobes have the following functions:

- Interpreting sensory information from the rest of the body,
- Combining impressions of form, texture, and weight into general perceptions,
- Influencing mathematical skills and language comprehension,
- Storing spatial memories that enable people to orient themselves in space (know where they are) and to maintain a sense of direction (know where they are going), and
- Processing information that helps people know the position of their body parts.

Certain functions tend to be controlled more by one of the parietal lobes (usually the left). The left is considered the dominant lobe. The right lobe (nondominant) has other functions, such as enabling people to be aware of how the body relates to the space around it.

Damage to the front part of the parietal lobe on one side causes numbness and impairs sensation on the opposite side of the body. Affected people have difficulty identifying a sensation's location and type (pain, heat, cold, or vibration). People may have difficulty recognizing objects by touch (that is, by their texture and shape).

If the middle part is damaged, people cannot tell the right from the left side (called right-left disorientation) and have problems with calculations and writing. They may have problems sensing where parts of their body are (a sense called "proprioception").

If the nondominant (usually right) parietal lobe is damaged, people may be unable to do simple skilled tasks, such as combing their hair or dressing—called apraxia. They may also have trouble understanding how objects relate to each other in space. As a result, they may have trouble drawing and constructing things, and they may get lost in their own neighborhood. These people may also ignore the serious nature of their disorder or deny its existence, a condition called "anosognosia". They may neglect the side of the body opposite the brain damage (usually the left side).

Temporal Lobe Damage

The temporal lobes have the following functions:

- Generating memory and emotions,
- Processing immediate events into recent and long-term memory,
- Storing and retrieving long-term memories, and
- Comprehending sounds and images, enabling people to recognize other people and objects and to integrate hearing and speech.

In most people, part of the left temporal lobe controls language comprehension. If that part is damaged, memory for words can be drastically impaired, as can the ability to understand language—an impairment called Wernicke receptive aphasia.

If certain areas of the right temporal lobe are damaged, memory for sounds and music may be impaired. As a result, people may have trouble singing.

Occipital Lobe Damage

The occipital lobe contains the main center for processing visual information and have the following functions:

- Processing and interpreting vision,
- Enabling people to form visual memories, and
- Integrating visual perceptions with the spatial information provided by the adjacent parietal lobes.

If both sides of the occipital lobe are damaged, people cannot recognize objects by sight, even though the eyes themselves are functioning normally. This disorder is called cortical blindness. Some people with cortical blindness are unaware that they cannot see. Instead, they often make up descriptions of what they see (called confabulation).

Seizures that involve the occipital lobe can cause hallucinations involving vision. For example, people may see lines of color when they look in a certain direction.

Limbic Lobe (Limbic System)

The limbic lobe includes structures located deep within the cerebrum and some parts of the adjacent lobes, such as the temporal lobe. These structures have the following functions:

- Receiving and integrating information from many areas of the brain, enabling people to experience and express emotions,
- Helping form and retrieve memories, and
- Helping people connect memories to the emotions experienced when the memories form.

Damage that affects the limbic lobe usually results in a variety of problems. If seizures result from damage to the temporal lobe area in the limbic lobe, people may not be able to control their feelings or to think clearly. They may smell bad odors that are not there (a type of hallucination). Occasionally, these seizures cause personality changes such as humorlessness, extreme religiosity, and obsessiveness. People may also have an overwhelming urge to write.

Other Locations

Many functions of the brain are performed by several areas of the brain working together (networks), not by a single area in the brain. Damage to these networks can cause the following:

- Agnosia (loss of the ability to identify objects using one or more of the senses)
- Amnesia (total or partial loss of the ability to recall experiences or events)
- Aphasia (partial or complete loss of the ability to express or understand spoken or written language)
- Apraxia (loss of the ability to do tasks that require remembering patterns or sequences of movements)
- Dysarthria (loss of the ability to articulate words normally) may be caused by damage to areas of the brain or cranial nerves that control the muscles involved in producing speech or by damage to the nerve fibers that connect these areas.

Rehabilitation

Recovery of some portion of an impaired function may be possible through the action of neuroplasticity. Neuroplasticity is the ability of the neural networks in the brain to change as a result of their biological, chemical, and physical capacities.

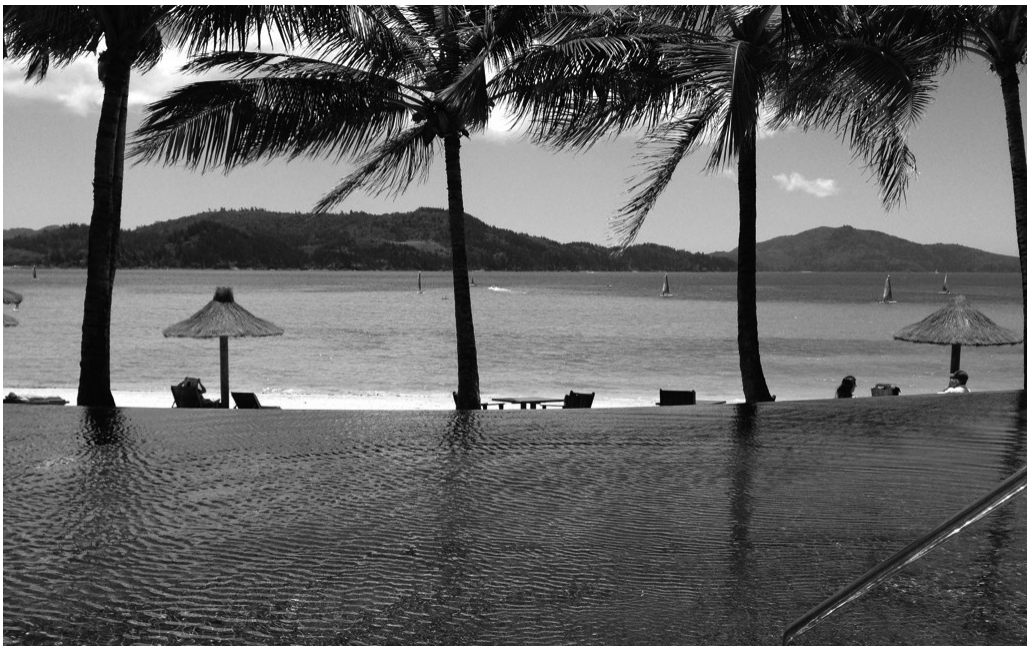
When certain neural networks in the brain are damaged by disease, those networks may be encouraged by experience or learning to rearrange themselves to adapt to the changed situation as they continue to try to function normally.

After a brain injury such as damage from a tumor, the unaffected brain areas may adapt and take over the functions of the affected parts. This can enable individuals with brain damage to regain some of the past capabilities. For example, case studies of stroke victims who have experienced brain damage and lost some brain functions have shown that the brain has an ability to re-wire itself with undamaged brain sites taking over the functions of damaged brain sites.

This potential for neuroplasticity declines with age, however, efforts like rehabilitation ("rehab"), which is intended to encourage the brain to re-wire itself, can help to regain lost or degraded functions. In order to take advantage of this capacity of the brain, a person should begin rehab as soon after the loss of a function as advised by the doctor.

In addition, studies have found that Gamma waves are associated with enhancing the coordination of neural activity in the brain. Levels of gamma brain waves are far higher than normal in individuals who practice meditation, suggesting that daily meditation for 15-20 minutes may be a helpful routine.

Photo Credit Linda Singer



APPENDIX C: CAUSES OF BRAIN TUMORS

Overview

One of the most troubling issues faced by anyone diagnosed with a brain tumor is: where did it come from? This question is even more urgent and frustrating for those who are otherwise healthy, have led a relatively healthy lifestyle for a long time, are youthful and have no such cancer in their familial bloodline. The disease just seems to have come out of nowhere.

So, where does a brain tumor, especially a cancerous one, come from?

In most cases, the cause of an individuals' brain tumor is never determined.

As it relates to GBMs, about 90% of them will go through a lengthy multistep development process. Researchers theorize that a cancerous kernel may take up to seven (7) years to develop into a GBM before it becomes symptomatic and requiring medical attention. The other 10% of GBMs develop from a pre-existing tumor of a lower grade (e.g., an AA3).

The factors that contribute to the development of brain cancers are described below.

Immune System Escape

Our bodies are guarded from microbials that causes disease and flawed cells that could become a problem by a complex immune system that includes powerful defenders like lymphocytes, macrophages, mast cells, dendritic cells (DCs), and natural killer (NK) cells. These components are ever vigilant and eliminate the risks to the preservation of our well-being.

Sometimes, however, our immune systems become tired or lazy due to us being overstressed and instead of eliminating risky intruders, our immune system no longer see when the intruders loiter around. One of the strategies for brain cancer treatment is to re-train the immune system into being able to recognize intruder cells again so that the immune system can function properly again.

When the immune system is unable to see intruder cells, eventually they break down the powerful defensive line of all the earlier mentioned components of our immune system. Brain cancer is, first and foremost, a breakdown of the immune system. The intruder cells develop genetic and epigenetic changes to camouflage themselves, which misleads all the defender cells we have, and an invasion of intruder cells starts. Once that invasion is large enough, we will call it a tumor.

When the intruder cells reach enough critical mass, they begin sending out chemical signals that convince some of the defending components of our immune system to join their ranks. Because the intruder cells have been entrenched for a long time and have hijacked some of our best defenders, the battle is fierce, employing a multitude of therapies: surgery, radiation, chemo and more.

Our growing understandings of how our immune system falters, allowing the breakdown and how cancer cells co-opt parts of our immune system for their own purposes provides considerable research opportunities for eventually reversing the process that started the cancer in the first place, and is encouraging the development of combination therapies such as CAR T-cell plus oncolytic virus treatment to attack the tumor in different ways.

Triggers that May Lead to Immune System Escape

A brain tumor is a perfect storm of a variety of factors. Below are listed some of the factors that are believed to be contributors:

- Size - the bigger the brain, the greater the risk. (This is why a slightly greater percentage of men will get this disease.)

- Overweight - Doctors don't know exactly why being overweight may help trigger this disease, but the evidence it does is piling up. Some guesses are things like hormones and inflammation. What is known at the DNA level is that a cancerous gene (c-Myc) is present in visceral fat, which is found around the inner organs of the body as opposed to subcutaneous fat, which is located under the skin.

    - Additionally, it appears that there is a deep connection between our

metabolism and fat and how our brains regulate our immune systems. Brain cancer is, fundamentally, a failure of the body's immune system. For an interesting description of what we know of the connection between visceral fat and cancer, please see this article:

https://www.inverse.com/mind-body/visceral-fat-study

- Viruses - There may be links between certain viruses (e.g., Cytomegalovirus). Plus, there is an apparent association between having an Epstein-Barr virus infection or mononucleosis in the case of gliomas and an associated between the human papilloma virus (HPV) and head and neck squamous cell carcinoma (HNSCC).

- Oxidative Stress - When our oxidative stress exceeds our defense system, cellular stress occurs and that can lead to the development of a tumor. Excessive oxidative stress can result from a variety of sources: metabolic complications, ionizing radiation from being a pilot, ionizing radiation due to being a frequent passenger on airplanes, heavy metals exposure as a machinist might experience, food or water with triggering substances, cigarette smoking, or other environmental exposures.

Autoimmune Conditions - Autoimmune conditions, such as Rheumatoid Arthritis, Lupus, Type 1 Diabetes, and Multiple Sclerosis, do not directly cause an increased risk of developing brain cancer. However, these diseases can influence the risk and development of brain cancer through mechanisms like chronic inflammation and dysregulation of the immune system. In autoimmune diseases, the immune system mistakenly attacks the body's healthy tissues, which can damage the protective blood-brain barrier and foster a pro-inflammatory environment within the brain.

Persistent inflammation resulting from these conditions may contribute to cellular stress, DNA damage, and impaired immune surveillance—factors that could increase the risk of malignant transformation in brain cells. In addition, some immunosuppressive treatments used to manage autoimmune diseases might decrease the body's capacity to detect and eliminate emerging cancer cells, which could further increase the risk of brain tumors. Recent evidence in the field of cancer neuroscience also indicates that injury to white matter and

fiber tracts may promote the growth and progression of gliomas.

The relationship between autoimmune conditions and brain cancer is complex. There is a delicate "yin-yang" balance between a hyperactive immune system, which can promote tumor progression through chronic inflammation, and a paradoxical benefit, where heightened immune surveillance may help in identifying and destroying malignant cells.

The available data for specific autoimmune diseases remain inconclusive:

- **Multiple Sclerosis (MS):** Some studies indicate an increased risk of brain tumors, possibly due to chronic inflammation or shared genetic factors, while other studies do not find a predisposing effect.
- **Type 1 Diabetes (T1D):** Long-term diabetes is generally associated with a reduced risk of glioma, potentially due to lower levels of insulin-like growth factor (IGF-1).
- **Lupus (Systemic Lupus Erythematosus, SLE):** Meta-analyses show no significant link between SLE and brain cancer risk.
- **Rheumatoid Arthritis (RA):** There is an increased risk of other cancers such as lung cancer and lymphoma, but no direct link to brain cancer has been established. Some studies even suggest a protective effect or no significant change in risk for primary brain tumors.

The pathophysiology of glioma formation in the context of autoimmune disease is multifaceted. Chronic inflammation driven by autoimmune processes can secrete factors such as IL-6 and TGF-β, which support tumor survival and help cancer cells evade the immune system. On the other hand, an overactive immune response, as seen in conditions like RA or MS, may recognize and destroy early-stage or premalignant cells, potentially delaying tumor development. Certain medications, such as cyclophosphamide—used to treat lupus or RA—can impair natural antitumor defenses, possibly accelerating brain tumor progression. In diabetic patients, the medication metformin has been studied for its potential to reduce brain tumor risk and progression, depending on dosage.

The immune system's complexity, with its simultaneous stimulatory and suppressive effects, creates challenges in both understanding and treating brain cancer in patients with autoimmune diseases. Because of these complexities,

individuals with pre-existing autoimmune conditions are frequently excluded from immunomodulatory clinical trials, such as those involving immune checkpoint inhibitors (ICIs), due to concerns that these therapies may exacerbate underlying autoimmune diseases.

- Carcinogens - Exposure to pesticides and herbicides (like RoundUp that was recently featured in a $2 Billion award to a couple who claimed their cancer was caused by that product) and fertilizers are believed to make a person susceptible.

- Working with elements such as lead, certain plastics, rubber, petroleum, and some textiles can add to the equation that produces cancer. Inhaling the smoke from these materials (such as when working as a firefighter or first responder) is a brain cancer risk. Many firefighters and first responders pay for their selfless service by getting brain cancer.

- The Department of Defense estimates that roughly 3.5 million military members could have been exposed to burn pits (excavations filled with any and all waste from a deployment and set aflame with jet fuel or diesel) during wars in the Middle East and Afghanistan, and it is believed that some of them have or may develop brain cancer from those burn pit exposures.

- Pollution - Researchers in the UK concluded that there is a growing body of evidence that exposure to air pollution, notably arising from the carcinogenic components of vehicle exhausts, such as PAHs, 1,3-butadiene, and diesel particulate matter generally, may be associated with increased risk of brain tumors in both children and adults.

- Environmental- Currently, there is only one (1) established brain tumor environmental risk factor: exposure to ionizing radiation. This association is strongest for meningioma and glioma in younger patients. Patients who also received cranial radiation as treatment for acute lymphocytic leukemia in youth are also at a higher risk for subsequent brain tumors.

- Genetics - Even if a person has exposures to one or more of the factors above, the right genetics eventually need to be present for brain cancer to

develop. Genes either "break" because of an exposure or were always in a condition that could develop into cancer.

More than 50 genes have been identified and associated with increasing an individual's lifetime risk of developing some form of cancer. We do know that about 5% of brain cancers occur in people with certain inherited genetic syndromes such as neurofibromatosis type 1, Turcot syndrome and Li Fraumeni syndrome.

Some of the genes noted for causing brain cancer that are thought to be passed from generation to generation are these:

Gene	Syndrome	Features	Brain Tumor Type
CDKN2A	Melanoma-neural system tumor syndrome	Predisposition to malignant melanoma and malignant brain tumors	Glioma
MSH2, MLH1, MSH6, PMS2	Contributes 40-50% of all cases of Lynch syndrome	Elevated risk of cancers of the brain, as well as colon, endometrium, ovaries, upper urinary tract, stomach, and small intestine	GBM and other gliomas
NF1	Neurofibromatosis 1	Neurofibromas, schwannomas, café-au-lait macules	Astrocytoma, optic nerve glioma
NF2	Neurofibromatosis 2	Acoustic neuromas, meningiomas, neurofibromas, eye lesions	Ependymoma

Gene	Syndrome	Features	Brain Tumor Type
PMS2	2% of Lynch Syndrome Cases	Elevated risk of cancers of the brain, as well as colon, endometrium, ovaries, upper urinary tract, stomach, and small intestine	GBM and other gliomas
POT1	Predisposition syndrome	Associated with longer telomeres in familial melanoma	Glioma
SMARCA4/ Brg1	Atypical teratoid/ rhabdoid tumors (ATRTs) predisposition syndrome	Increased risk of developing cancerous tumors in many parts of the body.	Medulloblastoma
TP53	Li-Fraumeni syndrome	Predisposition to numerous cancers, especially breast, brain, and soft-tissue sarcoma	GBM and other gliomas
TSC1, TSC2	Tuberous sclerosis	Development of multisystem nonmalignant tumors	Giant cell astrocytoma

An organization called Gliogene, which is located within the Department of Epidemiology and Population Health at the Stanford School of Medicine, is engaged in a study of familial brain tumors. A link to their site is:

https://med.stanford.edu/content/sm/bondylab/projects/gliogene-project.html/

We also know that a high percentage of those with GBM have an extra Chromosome 7, but we cannot say from that, that everyone with a pair of Chromosome 7s gets GBM.

Add to all those external factors and those genetic factors, the following:

- Chronic Inflammation. Can be caused by virtually anything. One major thing that causes it is chronic stress and the typical American diet: too much red meat, too many sugar/glucose laced foods, too many grain-based products with gluten. Chronic inflammation can also be caused by harboring certain viruses or parasites (e.g., toxoplasmosis).

AND

- Cancer Cell Survival. Cancers cells, like all normal cells, have a shelf life. The process by which cells remove themselves is called apoptosis. Apoptosis is a highly regulated mechanism of cell death for the removal of unnecessary, surplus, aged or damaged cells. Dysregulation of the process of apoptosis can result in the persistence of mutated cells, leading to cancer. This dysregulation can occur as a result of an over or under expression of required proteins, peptides, hormones, or the presence of other body chemicals that have become out of balance owing to the factors described above.

AND

- Proliferative Factors. There are several factors that collaborate with the cancerous cells to proliferate and coalesce into a tumor. For example, in GBMs, approximately 45% of adult human cases harbor amplifications or activating mutations in the epidermal growth factor receptor (EGFR). Approximately 29% and 21% of pediatric and adult high-grade gliomas, respectively, harbor Platelet-derived growth factor A (PDGFRA) amplifications. Approximately 18% of adult GBMs show mutations or homozygous deletions of the NF1 gene. These and other factors help the cancerous cells to survive and proliferate into tumors.

In summary, the development of a brain tumor is not the result of bad luck or something that you or your loved one did or did not do. A brain tumor is the result of often continuing external assaults on the body which the body could no longer defend against and/or a significant misstep in the body's formidable ability to suppress the formation of a tumor. It is the intent of research for tumor treatments to understand how to un-do the effects of these assaults and missteps.



ACKNOWLEDGMENTS

The Brain Tumor Guide for the Newly Diagnosed is based on an original concept by Al Musella. This Edition 13 was produced collaboratively by the following individuals who contributed to its research and writing:

Al Musella, DPM: Chief Author
Steven Brem, MD: Chief Scientific Advisor and Scientific Author
Channah Piscioneri, Patient Advocate: Editor and Author
Linda Singer: Graphics Designer and Contributing Photographer
Vanessa Hugo, Patient Advocate: Contributing Author

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 make a donation, please go to: https://virtualtrials.org/donate.cfm

All proceeds from the sale of Brain Tumor Guide for the Newly Diagnosed are used to fund brain tumor research.

IF YOU HAVE TIME TO READ ANYTHING IN THIS BOOK, PLEASE READ THE MUSELLA FOUNDATION NEED-TO-KNOW CHECKLIST, STARTING ON PAGE 92.

Al Musella, DPM



The diagnosis of brain tumor is a life-shaking event, compounded by the need to make crucial immediate decisions. What doctors to choose, where to be treated, what treatments are available, what clinical trials can be entered — to make the most rational decisions for yourself or for a loved one, you need to become as informed as possible as soon as possible.

The goal of ***Brain Tumor Guide for the Newly Diagnosed*** is to provide a vital first resource with tools for organizing and engaging with a medical team and the complex array of treatment options.

Represented here in readily actionable form is the wealth of helpful and hopeful information accumulated over the past two decades by the Musella Foundation for Brain Tumor Research & Information, an organization dedicated to the cure of brain tumors.

Brain Tumor Guide for the Newly Diagnosed was written with explicit reference to the Musella Foundation's influential virtualtrials.org website that since the 1990s has served as a clearinghouse for information related to brain tumor clinical trials and treatments while hosting multiple online support groups. The Musella Foundation also awards investigators with research grants to study brain tumor treatments.

$29.95
ISBN 978-0-9899740-6-6
52995>
9 780989 974066

MUSELLA
FOUNDATION FOR BRAIN TUMOR RESEARCH & INFORMATION, INC.
www.VirtualTrials.org

Brain Tumor Guide for the Newly Diagnosed • 13th edition • Musella Foundation for Brain Tumor Research & Information