Recent Progress in Brain Tumors

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Juvenile Pilocytic Astrocytoma
Glioblastoma Multiforme
Desmoplastic Infantile Ganglioglioma
Desmoplastic Variant Astrocytoma
Medulloblastoma
Atypical Teratoid Rhabdoid Tumor
Diffuse Intrinsic Pontine Glioma

-Mutational analysis, microarray expression, epigenetic phenomenology

-Age-specific biology of brain cancer

-Is there an overlap? Neuroimmunology Stem cell hypothesis

Late Effects

Long term effect of chemotherapy and radiation on neurocognition
Risks of secondary malignancy secondary to chemotherapy and/or radiation
Neurovascular long term effects: stroke, moya moya

Courtesy of Dr. John Crawford
**Importance**

- Increase in aging population with increased incidence of cancer
- Patients with cancer living longer and developing neurologic disorders due to nervous system relapse or toxicity from treatments

**Overview**

- Introduction
- Clinical Presentation
- Primary Brain Tumors
- Metastatic Brain Tumors
- Leptomeningeal Metastases
- Primary CNS Lymphoma
- Paraneoplastic Syndromes
Classification of Brain Tumors

- **Tumors of Neuroepithelial Tissue**
  - Glial tumors (astrocytic, oligodendroglial, mixed)
  - Neuronal and mixed neuronal-glial tumors
  - Neuroblastic tumors
  - Pineal parenchymal tumors
  - Embryonal tumors

- **Tumors of Peripheral Nerves**
  - Shwannoma
  - Neurofibroma
  - Perineurioma
  - Malignant peripheral nerve sheath tumor

Classification of Brain Tumors

- **Tumors of the meninges**
  - Tumors of meningothelial cells
  - Mesenchymal, non-meningothelial tumors
  - Primary melanocytic tumors
  - Tumors of uncertain histogenesis

- Lymphomas and hematopoetic neoplasms
- Germ cell tumors
- Tumors of Sella region
- Metastatic tumors
### Brain Cancer Incidence

<table>
<thead>
<tr>
<th>Site</th>
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<th>Deaths</th>
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### Incidence Increases with Age

**Brain and CNS Tumors by Selected Histologies**

Adult Primary Brain Tumors

- Gliomas
- Meningiomas
- Pituitary Adenoma
- Neurinoma
- Medulloblastoma
- Craniopharyngioma
- Hemangioma
- Sarcoma
- Others

- 55% Malignant Gliomas
- 10% Low Grade Gliomas
- 20% Meningiomas
- 5% Vestibular Schwanommas
- 5% Pituitary Tumors
- 5% Miscellaneous

Impact on Morbidity and Mortality

- Primary Brain Tumors (PBT) account for only 2% of all cancers but a disproportionate share of morbidity and mortality
  - CBTRUS: Incidence of 14 per 100,000 person-years benign and malignant brain tumors
  - SEER: Incidence 6.4 cases per 100,000 person-years malignant brain tumors
  - CBTRUS: 39,550 new cases per year benign and malignant brain tumors
  - ACS: 17,000 new cases year of malignant brain tumors
  - Prevalence: PBT is 130 per 100,000 (359,000 persons living)
Impact on Morbidity and Mortality-2

- 13,100 deaths in 2002 attributed to primary malignant brain tumors
- 2\textsuperscript{nd} leading cause of cancer-related death <34 yrs
- 4\textsuperscript{th} leading cause of cancer-related death 35-54 yrs
- Loss of productive work years
- Loss of independence
- Progressive physical and cognitive impairment

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Clinical Presentation

- For tumors within the brain parenchyma there are two classes of symptoms:
  - Increased intracranial pressure
  - Focal cerebral syndromes
- For leptomeningeal disease or spinal metastases, back or radicular pain is the usual presenting symptom.

Symptoms/Signs

- Headache 60% (early morning 15%)
  - Lifetime prevalence 90%
- Seizures 33%
- Visual disturbance/papilledema 10-20%
- Nausea/vomiting
- Focal neurologic signs
Non-acute Headache and Imaging

- 435 patients with migraine with aura (age 17-52) with normal neurologic exam:
  - CT + contrast normal in all but 1 (incidental choroid plexus papilloma) (Cuetter and Aita, Headache 1983, 23: 195)

- Meta-analysis of 2,377 patients (17 studies) with normal neurologic exam with CT or MRI
  - 897 patients with migraine:
    - 3 brain tumors (1 associated with seizure), 1 AVM (associated with seizure) (Yield 0.4%)
  - 1825 patients with unspecified headache:
    - 21 brain tumors, 6 AVM, 3 aneurysms, 5 SDH, 8 hydrocephalus (Yield 2.4%) (AAN Practice parameter Neurology 1994, 44:1353 & Frishberg Neurology 1994, 44:1191)

Recommendations

- Neuroimaging warranted in:
  - New-onset headache
  - Change in pattern of headache
  - Headache with progressive course
  - Abnormal neurologic exam
  - History of seizures
  - Known malignancy

(Frishberg, Semin Neurol. 1997;17(4):373-82)
Increased Intracranial Pressure

- **Early:**
  - Headache, nausea, vomiting, change in mental status

- **Late:**
  - Coma from uncal or cerebellar-foramen magnum herniation

Cerebral Syndromes

- **Hemispheric Specialization**
  - Dominant (left for 90%)
    - Language
    - Speech
    - Calculation
  - Non-Dominant (right)
    - Spatial perception
Frontal Lobe

- Inappropriate social behavior
- Cognitive deficits
- Contralateral Weakness
- Abulia/aphasia (Broca’s)
- Frontal release signs
- Seizures
- “Depression”

Temporal Lobe

- Fluent aphasia (Wernicke’s)
- Homonymous superior quadrantianopsia
- Short term memory loss
- Irritability/Limbic system – judgment, emotion
- Seizures (olfactory, gustatory hallucinations)
- Hemiparesis (mass effect)
Parietal Lobe

- Sensory deficit
- Contralateral neglect, R/L confusion (tumor in non-dominant hemisphere)
- Dyslexia
- Dysgraphia
- Homonymous inferior quadrantanopsia

Occipital Lobe

- Loss of visual acuity
- Visual hallucinations
- Prosopagnosia – inability to recognize familiar/famous faces
- Seizures
Cerebellum

- Gait ataxia with or without truncal ataxia
- Dysarthria
- Dysmetria
- Nystagmus
- May have obstructive symptoms related to 4th ventricle compression

Corpus Callosum

- “Butterfly glioma”
- Progressive severe dementia
- Incontinence
- Bilateral pyramidal symptoms
**Imaging: CT scan**

- **Primary screen for:**
  - Mass effect
  - Hemorrhage
  - Edema
  - Calcification

- **Advantages:**
  - Rapid emergency access

**Imaging: MRI**

- T1 no contrast
- T1 with contrast
- FLAIR

- **Advantages:** Multiplanar imaging, superior sensitivity
  - Offers physiological information
MRI as primary diagnostic tool?

Glioblastoma

Breast cancer

MR Spectroscopy

Low grade glioma

Choline>CRE | Choline>Creatine
• increase reflects tumor cellularity (turnover)
N-acetyl aspartate (NAA)
• neuronal marker depicts normal functional neurons

High grade glioma

Choline>>>CRE | Choline>>Creatine
• reflects high cellularity
N-acetyl aspartate
• loss of peak reflects tumor replacing normal brain
PET Scan

Indications:

1. Evaluate enhancement
   - Tumor
   - FDG

2. Document disease progression

Biopsy and CSF Analysis

- Stereotactic Biopsy
  - CT or MRI guided biopsy
  - Low risk, high yield although sample variability is a problem in gliomas

- Open Biopsy: Craniotomy
  - Mortality <5% in major centers
  - If localized tumor and likely will need resection, often maximal tumor removal at time of initial craniotomy

- CSF Analysis
  - Not part of the workup of primary malignant tumor or solid tumor metastases (except medulloblastoma)
  - Used to diagnose leptomeningeal metastases
  - Usually contraindicated when large cerebral masses present
Primary Brain Tumors: Etiology

- Challenges to epidemiological study
  - Uncommon form of cancer
  - Diversity of histologic brain tumor types
  - Lack of uniformly accepted classification system
  - Variable reliability of exposure assessment (cognitive impairment of subjects and remote exposures)
Primary Brain Tumors: Etiology

- Genetic Syndromes: 1-5% of brain tumors
  - NFI and NFII
  - Li-Fraumeni syndrome (P53 mutation)
- Radiation
  - Ionizing radiation: meningiomas, nerve sheath
  - Electromagnetic radiation?
  - Radiofrequency radiation: ? Cellular telephones
- Head trauma, Environmental toxins, Infections

Malignant Gliomas

- Glioblastoma
  - 10-14 months
- Anaplastic Astrocytoma
  - 2-3 yrs
- Low grade astrocytoma
  - 5-8 yrs
- Ependymoma
- Oligodendroglioma
Two pathways to Glioblastoma

Clinical Features
- Low mitotic index
- Diffuse invasion
- High rate of transformation

Primary Glioblastoma
- Rapid proliferation
- Diffuse invasion
- Angiogenesis
- Cellular necrosis

Low grade Astrocytoma
Secondary Glioblastoma
5-10 years

Low grade glioma (II)

Non-enhancing mass
- High cellularity
- Cellular pleomorphism
- Infiltrative

H&E
Anaplastic Astrocytoma (III)

- Non-enhancing mass, heterogeneous
- High cellularity
- Pleomorphism
- Mitosis

Glioblastoma (IV)

- Enhancing mass, cystic components, variable necrosis
- High cellularity
- Pleomorphism
- Microvascular proliferation
- Necrosis
Oligodendroglioma

Low grade (II)  Anaplastic (III)

High cellularity, classic “fried egg” appearance of cells

Increased cellularity, mitosis, Microvascular prolif, necrosis

Treatment of Malignant Gliomas

- Surgery and Radiation, although standard treatments, are not curative because of the infiltrative nature of gliomas.
- Chemotherapy extends survival but there are no curative regimens.
- No significant change in overall survival for any stage glioma in the past 20 years, until recently with the use of Temodar.
Surgery

Goals:
- Accurate diagnosis
- Maximum tumor debulking
- Preserve neurologic function
- Increases survival by 2-3 months

New techniques:
- Intraoperative MRI
- Functional mapping

Intraoperative MRI

GE Medical Systems
Radiation Therapy

- Prolongs overall survival for anaplastic gliomas and glioblastomas.
- Unclear benefit for low-grade astrocytomas where median survival may be 10 years.
- Radiation to tumor and adjacent field (T2 areas + 2 cm margin) as effective as WBRT
- Dose 54-60 Gy in 180-200 cGy fractions
  - no benefit from hyperfractionation
- No agent with documented radiosensitization
- Brachytherapy
  - possibly prolong survival but increased risk of radiation necrosis

Brachytherapy

- Stereotactic radiosurgery
  - used primarily for recurrent disease – good local control
- 80-90% patients recur within primary site

Adjuvant Chemotherapy

- Low grade astrocytoma
  - Likely role for chemotherapy but used in progressive cases
- Anaplastic glioma (astrocytoma, oligo-astro, oligodendroglioma)
  - Procarbazine, CCNU and vincristine
  - BCNU
  - Temozolamide (Temodar)
- Glioblastoma
  - Temozolamide recently shown to be beneficial.
Oligodendrogliomas are a chemosensitive subset of gliomas

- Characteristic genetic profile includes loss of 1p and 19q
- Example: “GBM” reclassified as Anaplastic Oligo
  - rapid and durable response to chemo/XRT

Jan 1999 | May 2002
---|---
PCV + XRT

Temozolomide (Temodar)

- 2nd generation alkylating agent, bioavailable, crosses BBB
- Side effects profile
  - 10-20% severe nausea and vomiting
  - 3% myelosuppression
    - Profound thrombocytopenia
- Single agent therapy
  - Recurrent anaplastic glioma – 35% objective response rate, 27% stable disease, 46% 6 month PFS.
  - Recurrent glioblastoma – reported response rate initial studies 5% and therefore is not initially approved for this indication.
Maximal surgical resection

Involved-field RT

Concurrent temozolomide 75 mg/m²

6-12 cycles of temozolomide 150-200 mg/m²

Recent Progress:
New Standard of Care for Glioblastoma

*2005: Temodar: 1st new drug for brain tumor in decades
Chemotherapy for Low-grade Gliomas

Oligodendroglioma PR after cycle 10

Oligodendroglioma MR after cycle 12

Astrocytoma PR after cycle 12

Astrocytoma PR 7 months after cycle 12

New Targets

<table>
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<tr>
<th>Survival</th>
<th>Low-grade Astrocytoma</th>
<th>Anaplastic Astrocytoma</th>
<th>Glioblastoma</th>
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<td>++</td>
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</tr>
<tr>
<td>Necrosis</td>
<td>-</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Rx Responsive</td>
<td>-</td>
<td>++</td>
<td>-</td>
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Thalidomide  
Anti-VEGF

- p53 mutations
- PDGF/R overexpression
- RB mutation
- CDK4 amplification
- INK4a/ARF loss
- PTEN loss
- DMBT1/mxd loss
- 19q loss
- 11p loss

EGFR amplification
- EGFR mutation
- INK4a/ARF loss
- PTEN loss
- RB mutation
Targeting specific genetic pathways

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<tr>
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<td>Invasion</td>
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<tr>
<td>Rx Responsive</td>
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</table>

EGFR antagonists (Iressa, Tarceva)

Mode of Action of Tyrosine Kinase Inhibitors

EGF, PDGF, IGF

Extracellular

Membrane

Intracellular

Zarnestra SCH66336

Bay 43-9006

PI3K

PTEN

Cell survival (anti-apoptosis)

Angiogenesis

DNA

Chemotherapy/radiotherapy resistance

Proliferation

Ras

Raf

Mek

Erk

PI3K

mTOR

mTOR Inhibitor

CCI-779, RAD001, AP23573

EGFR Iressa, Tarceva

PDGFR Gleevec

VEGFR PTK787

Antibody

mTOR Inhibitor

CDK4 amplification

INK4a/ARF loss

PTEN loss

DMBT1/mxi loss

19q loss

11p loss

Gleevec

EGFR amplification

EGFR mutation

p53 mutations

PDGF/R overexpression

Membrane

Ras

Raf

Mek

Erk

PI3K

mTOR

PTEN

Cell survival (anti-apoptosis)

Angiogenesis

DNA

Chemotherapy/ radiotherapy resistance

Proliferation

Ras

Raf

Mek

Erk

PI3K

mTOR

mTOR Inhibitor

CCI-779, RAD001, AP23573

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Membrane

Ras

Raf

Mek

Erk

PI3K

mTOR

PTEN

Cell survival (anti-apoptosis)

Angiogenesis

DNA

Chemotherapy/ radiotherapy resistance

Proliferation
Adult Brain Tumor: Targeted Therapeutics Responders

Erlotinib/rapamycin  
Bevacizumab/CPT-11

*2009: Avastin 2nd new drug for brain tumor

Pediatric Brain Tumors: Everolimus for Subependymal Giant Cell Astrocytomas

*2012: Affinitor: 3rd new drug for brain tumors
Novocure device approval

NovocureTM Establishes Initial Clinical Centers of Excellence for Treatment of Recurrent Glioblastoma Multiforme with Tumor Treating Fields (TTFields)TM Therapy

*2011: Novocure: 1st new device for brain tumors

MRI-Guided injection allowed accurate delivery of Toca 511 to multiple locations within the tumor

- Injection is started in the superior region of the tumor
- Injection is completed in the inferior region of the tumor

Tocagen Patient 171
Tumor regression after Toca 511 & Toca FC

Before Toca 511 & Toca FC After Toca 511 and 1st cycle of Toca FC

July, 2013 September, 2013
Tocagen patient 177

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- Leptomeningeal Metastases
- Primary CNS Lymphoma
- Paraneoplastic Syndromes
Brain Metastases: A Growing Problem

- Incidence: 25-40% of all cancer patients
  - Symptomatic in 14% (~170,000 per year)
  - Increasing as patients live longer with systemic disease
- Most common: lung (40%), breast (20%), melanoma (10%), renal (4%), unknown primary (1%)
- Melanoma and renal cell have high predilection for the brain
- 80% of metastases are supratentorial
- Median survival 2 – 9 months with aggressive treatment

Brain Metastases of Unknown Primary

- **Lung Cancer** most common (>70-80%), especially adenocarcinoma and SCLC
- Less Common: GI, melanoma, lymphoma, breast
- Physical examination, stool guaic, urinalysis, CBC, tumor markers eg CEA, CXR, chest, abdomen, pelvic CT, bone scan, PET
Chest CT and brain MRI alone identified a biopsy site in 97% of patients with a newly detected brain mass.

Treatment of Brain Metastases

Factors central to decision making:
- Status of systemic disease – prognosis without brain metastases
- Overall neurologic function
- Number of metastases
- Size of each lesion
- Location of each lesion
Whole Brain Radiation

Indications:
- Previously, standard Rx for all cases
- Multifocal disease (>3 lesions)
- Symptomatic
- Not amenable to surgery or radiosurgery

Breast cancer – 10 mets

Surgery for Metastases

- Solitary or <3 metastases
  - Surgery + WBRT vs. WBRT alone
  - 2 randomized trials demonstrated survival benefit for addition of surgery, 1 did not
  - Accepted “standard” therapy
- Multiple metastases
  - Remove largest/symptomatic lesions
Stereotactic Radiosurgery

- Delivery of single fraction, high dose (15 Gy) radiation to a mass of <3 cm.

- Options for use:
  - WBRT + Radiosurgery to 1-3 metastases
    - ~ Equivalent to Surgery + WBRT
  - Radiosurgery to control recurrent disease
  - Radiosurgery as primary management without WBRT

- Survival data: wide variation depends on specifics of case.

Chemotherapy

- Surgery, radiosurgery, radiation therapy do not result in cure

- Systemic therapy is treatment of choice but no active agents currently available
  - Disease resistance to potentially active agents
  - Inability to cross blood brain barrier
  - Lack tumor-specific therapies
  - Pts heavily pretreated with cytotoxic agents limits choice of drugs

- Desperate need for new therapies
  - Need cooperative group input/planning
Case: Metastatic Breast Cancer

- 48yo female with breast cancer pre-treatment (A, B) and after treatment with whole-brain radiation and capecitabine chemotherapy (C, D). The enhancing lesions are markedly decreased in size. Because the patient had multiple, surgically inaccessible lesions, resection was not an option in this case.

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Leptomeningeal Metastases

- **Increasing**
- 5-8% of patients with solid tumors
  - Lung, breast, melanoma, prostate, renal cell, lymphoma (NHL) and myeloma
- SCLC: 9-18% of patients with prior cranial radiation; 20-25% without prior radiation
- NHL: 5-29%
- 1%-2% of primary brain tumors
- Most patients (70%) have progressive systemic disease at presentation
- 1/3 of patients have concurrent epidural spinal or brain metastases
- Median survival 2-4 months

Mechanism of Tumor Spread to Meninges

- Hematogenous spread to meninges
- Spread from brain metastases
- Invasion of meninges from vertebral metastases
- Spread via nerve sheath
- Hematogenous spread to choroid plexus
- Spread via Batson’s plexus
- Iatrogenic
Clinical Diagnosis

- LM should always be considered in a cancer patient with neurologic symptoms and signs involving several different sites in the neuroaxis
- Usually occurs in the setting of disseminated systemic disease

Radiologic Diagnosis

76% sensitivity
77% specificity
Leptomeningeal Metastases

- Median survival 2-4 months
- Intrathecal chemotherapy is standard treatment
  - Methotrexate, Thiotepa, Cytarabine
- Craniospinal radiation too toxic
- Radiation to localized sites of symptomatic disease
- Need for new systemic therapy – same issues as chemotherapy for brain metastases

Achieving adequate CSF levels of drugs

Response and Resistance in a Non–Small-Cell Lung Cancer Patient With an Epidermal Growth Factor Receptor Mutation and Leptomeningeal Metastases Treated With High-Dose Gefitinib

<table>
<thead>
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<th>Date</th>
<th>Gefitinib Dose (mg)</th>
<th>CSF Site</th>
<th>Gefitinib Concentration, CSF (mg/mL)</th>
<th>CSF Cytology Result</th>
<th>ALVAST (mg/mL)</th>
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*On September 6, 2004, the patient’s treatment was changed from pheyn/loin (an enzyme-inducing antiepileptic drug) to lassatracatam (a nonenzyme-inducing antiepileptic drug).
Primary CNS Lymphoma

- 2% of all intracranial tumors
- Increasing incidence over past 10 years
- HIV-related
- EBV-related
- Median survival >40 months
Primary CNS Lymphoma

- 25-50% are multifocal
- Cells can infiltrate spinal cord, CSF (~30%) uvea or vitreous of the eye (~10%)
- Histology: most are diffuse B cell
- Staging: must exclude systemic disease
  - CT chest, abdomen, pelvis
  - CSF analysis (minimum 10 cc)
  - Slit lamp eye examination

Primary CNS Lymphoma - Treatment

- Surgery: Biopsy only
- Radiation therapy: Whole brain radiation is not standard for patients anymore
- Chemotherapy: High-dose methotrexate improves long-term survival
  - 3.5 g/m² is standard - ? Benefit from higher dose
  - Unclear added benefit from other cytotoxic agents
- Intrathecal therapy if CSF is positive – treat twice weekly until CSF clear x 3
  - Methotrexate
  - Ara-C
  - Thiotepa
PCNSL: Chemosensitive tumors

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Paraneoplastic Syndromes

- Group of neurologic disorders in cancer patients
  - Not caused by direct effects of the cancer itself or its metastases
  - Not caused by non-metastatic effects of the cancer such as:
    - Opportunistic infections
    - Side effects of therapy
    - Nutritional deficiency
    - Metabolic abnormalities
    - Cerebrovascular disorders

Incidence

- Many cancer patients have mild neurologic findings such as neuropathies and myopathies (5-10%)
- Clearly defined paraneoplastic syndromes are rare (<1%)
- Increasingly diagnosed as recognition of clinical syndromes improve and specific antibody tests become widely available
Significance

- Accounts for a high percentage of patients with particular syndromes (e.g. > 60% LEMS, >50% PCD, opsoclonus-myoclonus)
- Produce significant disability
- Frequently precede diagnosis of cancer
- May be mistaken for metastatic disease
- Provides information regarding autoimmunity and tumor immunology

Pathogenesis

- Unresolved but probably autoimmune in most cases
- Antibodies against tumor antigens cross-react with neuronal antigens producing paraneoplastic syndrome
- Cellular immunity probably also plays an important role
Clinical Features of Paraneoplastic Syndrome

- Characteristic clinical syndrome
- Predominantly affecting one area of the nervous system
- Acute or subacute onset
- Results in severe neurologic disability
- Often precedes diagnosis of cancer
- CSF pleocytosis, elevated protein, oligoclonal bands

Figure 3. Spontaneous Regression of Lung Lesions in a Patient with Encephalomyelitis and Anti-Hu Antibodies.

The computed tomographic (CT) scan in Panel A shows a lung mass with hilar and mediastinal adenopathy. During the course of the workup, sensory loss and cerebellar signs developed and anti-Hu antibodies were found in the serum. A second CT scan, obtained before any treatment was administered (Panel B), shows partial resolution of the lung lesion and the adenopathy. A right-upper-lobe lobectomy yielded only fibrous tissue and inflammation. The adenopathy then resolved without further treatment (Panel C). The patient’s clinical symptoms also began to improve, and she was left with only mild cerebellar signs. This case is described as Case 1 in Byrne et al. Scans courtesy of Dr. Thorn as Byrne.
Therapy For Paraneoplastic Cerebellar Degeneration

- **Prognosis:** Generally poor
  - Especially with anti-Yo positive patients
  - Yo negative patients have slightly better prognosis

- **Therapy:**
  - Treatment of underlying cancer
  - Immunosuppression
    - IVIG
    - Steroids
    - Cellcept, cytoxan
    - Plasmapheresis (usually ineffective)
NPH-Hydrocephalus

60yo female with history of recurrent NHL treated 15 years ago s/p auto stem cell transplant 12 months ago, now with 6 months of progressive decline in gait and now wheelchair bound.

After VP-Shunt
Acknowledgments

- NIH
- McDonnell Foundation
- American Brain Tumor Association
- Sontag Foundation
- National Brain Tumor Foundation
- Accelerate Brain Cancer Cure (ABC²)
- Boston Fire Department/John Kenney Foundation
- Florence Family Fund
- Patients and families

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The Hospital Physician Oncology Board Review Manual is a study guide for fellows and practicing physicians preparing for board examinations in oncology. Each manual reviews a topic essential to the current practice of oncology.

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This publication has been developed without involvement of or review by the American Board of Internal Medicine.

Metastatic Brain Tumors

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INTRODUCTION

Systemic cancer can affect the central nervous system in several different ways, including direct tumor metastasis and indirect remote effects. Intracranial metastasis can involve the skull, dura, and leptomeninges (arachnoid and pia mater), as well as the brain parenchyma. Of these, parenchymal brain metastases are the most common and have been found in as many as 24% of cancer patients in autopsy studies. It has been reported that metastatic brain tumors outnumber primary brain tumors 10 to 1.

Metastasis to the brain generally occurs by hematogenous dissemination, with tumor cells having a propensity to lodge and grow at the gray-white junction. The distribution of brain metastases is proportionate to the cerebral blood flow, with 80% occurring in the supratentorial region, 15% in the cerebellum, and 5% in the brainstem. Unlike primary brain tumors, such as glioblastoma, brain metastases do not typically involve the corpus callosum or infiltrate across the midline. The most common primary histologies include lung, breast, melanoma, renal, and colon cancer, and tumors of unknown primary.

Brain metastases can present with a variety of symptoms, including focal neurological deficits, headache, and seizures. The sudden onset of symptoms may be related to intracranial hemorrhage associated with brain metastases. Given its relatively high incidence, lung cancer is the most common type of brain metastases to result in intracranial hemorrhage. However, other cancer primaries have, relative to their incidence, a very high propensity to spontaneously develop tumor-associated intracranial hemorrhage; they are melanoma, renal cell carcinoma, choriocarcinoma, thyroid, and germ cell. Ultimately, any brain metastasis has the potential for spontaneous hemorrhage.

Often, the presentation of brain metastasis occurs in a patient with established malignancy, in which case a clinical and radiological diagnosis is usually sufficient. Magnetic resonance imaging (MRI) with gadolinium contrast is preferred over computed tomography (CT) alone due to greater sensitivity in identifying additional lesions. For example, in approximately one-third of cases presenting with a single metastasis on CT, MRI will lead to the discovery of additional metastases.

Occasionally, brain metastasis can occur as the presenting feature in a patient not known to have...
A thorough assessment is essential in identifying the associated systemic malignancy and in determining which site of disease is safest for tissue diagnosis. In the differential diagnosis, conditions apart from metastatic disease need to be considered (Table 1).

**CASE PRESENTATION**

**INITIAL PRESENTATION AND EVALUATION**

A 54-year-old woman presents with a left breast mass and is treated with a lumpectomy and axillary lymph node dissection. Her tumor is negative for hormonal receptors (estrogen receptor, progesterone receptor) and is also negative for HER2/neu (human epidermal growth factor receptor 2). She has positive lymph nodes and receives local radiation therapy and 8 cycles of adjuvant cyclophosphamide, methotrexate, and 5-fluorouracil. There are no other sites of metastatic disease at diagnosis.

Eight months after her diagnosis, she develops right-sided headaches. She has an excellent performance status. CT of the brain without contrast reveals a right parietal hypodensity with significant mass effect. MRI with gadolinium contrast does not reveal any additional lesions (Figure 4). There is no evidence of any active extracranial disease.

- **What are important prognostic factors in brain metastasis?**

**PROGNOSIS**

Several factors have been validated as important prognostic factors in patients with brain metastasis. These include age, performance status, and extent of extracranial disease. These factors have been used to stratify patients into several prognostic...
categories, known as RPA (recursive partitioning analysis) classes. Discrete differences in survival have been demonstrated based upon this classification (Table 2). Poor performance status suggests a poor outcome (RPA class 3) regardless of the other factors. The patient in this case is in the most favorable group, RPA class 1.

Recently these prognostic categories were updated and a fourth prognostic element was incorporated: number of brain metastases. Known as graded prognostic assessment (GPA), this system scores patients from 0 to 4, with 4 corresponding to the most favorable prognosis. The most recent update found that significant prognostic factors differed for each of the following tumor types: non-small cell lung cancer (NSCLC), breast cancer, melanoma, renal cell carcinoma, and gastrointestinal cancers. In this analysis, patients with a low GPA score (0 to 1) tended to have a poor survival (of approximately 3 months) in all histologies examined. In addition, performance status was found to be an important prognostic factor in all groups.

With regard to breast cancer, there is emerging data that patients with hormone receptor-negative breast cancer may have increased risk of brain metastasis. Elevated serum lactate dehydrogenase (LDH) also has been suggested as a predictor for developing brain metastasis. The role of HER2/neu receptor status is unclear, but the prognosis of patients with brain metastasis in the setting of HER2-positive disease may be more favorable due to better control of extracranial disease with trastuzumab. Features of breast cancer which may increase risk for developing brain metastasis

![Figure 2](image-url) Common presenting symptoms of brain metastasis. (Data from Posner.)

![Figure 3](image-url) (A) Computed tomography of the brain reveals a single brain metastasis (arrow). (B) Magnetic resonance imaging with contrast reveals a second small site of metastasis in the contralateral hemisphere (arrow).
include age less than 50 years, high-grade histology, expression of basal cytokeratin CK5/6, overexpression of HER2 or epidermal growth factor receptor (EGFR), and the lack of estrogen receptors. Stratification of breast cancer with gene expression arrays has identified subsets of breast cancer with varying prognoses. Ongoing research is exploring the implications of these categories with regard to brain metastasis.

- What treatment options are available for brain metastasis?

**TREATMENT**

**Surgery**

Surgical resection is an important consideration for a patient with favorable prognostic factors (RPA class 1 or 2) and a single brain metastasis in a surgically accessible area. Several studies suggest improved functional independence and overall survival if surgical resection is performed in addition to whole brain radiation therapy (WBRT), although one randomized study and a subsequent meta-analysis dispute this benefit. Resection for several metastases is less well-established than resection for single lesions, although it appears that resection of all intracranial metastases confers an outcome similar to resection of a single brain metastasis. Resection of recurrent brain metastasis after initial treatment has also been shown to be feasible in retrospective analyses. Large tumor size, significant mass effect, noneloquent tumor location, and the need for diagnostic tissue are also considerations in making a decision to perform an operation.

**Whole Brain Radiation Therapy**

WBRT for brain metastases was described over 50 years ago by Chao and colleagues. This modality, in contrast to the other local therapies, may address microscopic metastatic disease in the brain that is not yet clinically or radiographically evident. There is only one randomized study comparing WBRT and supportive care (with corticosteroids). In this study, 46 patients were randomized to either WBRT or supportive care; median survival was slightly longer in the group receiving WBRT (14 weeks versus 10 weeks). However, neither brain imaging with CT or MRI nor statistical analysis was performed. Rates of local recurrence are significantly higher in patients who have WBRT withheld and only receive local therapy (either sur-
Metastatic Brain Tumors

A trial of PCI for locally advanced NSCLC revealed a decreased risk of brain metastasis with increased neurocognitive toxicity. This trial was closed prematurely due to poor accrual.

Stereotactic Radiosurgery

Stereotactic radiosurgery (SRS) involves techniques to precisely deliver high-dose radiation to a small area of brain in a single or small number of fractions. Theoretically, the surrounding tissue is spared most of the dose. Small spherical brain tumors are the ideal target for SRS. SRS has indications outside the cancer setting, such as trigeminal neuralgia and arteriovenous malformation. Depending on the technology, the dose is given either as a single fraction (most commonly) or over a small number of fractions. Use of a head-frame may be a necessary part of the technique (e.g., Gamma knife). A late and serious complication of SRS is radionecrosis. Multiple studies have confirmed the ability of SRS to achieve local tumor control, even in radioresistant malignancies. SRS offers less morbidity than surgical resection in treating patients with multiple brain metastases, and it may be more cost effective. Whether there is an upper limit to the number of brain metastases that can be treated with SRS is unclear; it appears feasible to treat patients with more than 10 metastases. Randomized clinical trials evaluating surgical resection, WBRT and SRS for brain metastasis are summarized in Table 3.

Pharmacologic Therapy

In randomized trials, traditional chemotherapy has demonstrated limited benefit in controlling metastatic brain tumors. There may be several reasons for this. Most important, the blood-brain barrier limits the penetration of chemotherapy into brain and brain tumor tissue. Additionally, because
### Table 3. Summary of Randomized Clinical Trials Regarding Treatments for Parenchymal Brain Metastases

<table>
<thead>
<tr>
<th>Study</th>
<th>Clinical Situation</th>
<th>All Received</th>
<th>Randomized Intervention</th>
<th>N</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patchell et al (1990)</td>
<td>Single brain</td>
<td>WBRT</td>
<td>Surgical resection</td>
<td>48</td>
<td>Undergoing surgical resection prior to WBRT improved local control at original site of metastasis, overall survival, and functional independence</td>
</tr>
<tr>
<td>Vecht et al (1993)</td>
<td>Single brain</td>
<td>WBRT</td>
<td>Surgical resection</td>
<td>63</td>
<td>Undergoing surgical resection prior to WBRT improved local control at original site of metastasis, overall survival, and functional independence,* particularly in patients with well-controlled extracranial disease</td>
</tr>
<tr>
<td>Mintz et al (1996)</td>
<td>Single brain</td>
<td>WBRT</td>
<td>Surgical resection</td>
<td>84</td>
<td>Undergoing surgical resection prior to WBRT failed to demonstrate an improvement in overall survival or functional independence</td>
</tr>
<tr>
<td>Patchell et al (1998)</td>
<td>Single brain</td>
<td>Surgical</td>
<td>WBRT</td>
<td>95</td>
<td>The addition of WBRT following surgical resection decreased the risk of intracranial relapse and risk of neurologic death, but did not improve overall survival or functional independence.</td>
</tr>
<tr>
<td>Kondziolka et al (1999)</td>
<td>2–4 brain</td>
<td>WBRT</td>
<td>SRS</td>
<td>27†</td>
<td>Adding SRS to WBRT was well tolerated and improved local control, but did not improve overall survival</td>
</tr>
<tr>
<td>Andrews et al (2004)</td>
<td>Unresectable</td>
<td>WBRT</td>
<td>SRS</td>
<td>333</td>
<td>In patients with a single unresectable brain metastasis, adding SRS to WBRT led to improved overall survival. The SRS group experienced improved performance status. In subset analysis, patients with favorable histology (NSCLC), RPA class I, and age &lt;50 also experienced a survival advantage with the addition of SRS to WBRT.</td>
</tr>
<tr>
<td>Aoyama et al (2006)</td>
<td>1–4 small (&lt;3 cm)</td>
<td>SRS</td>
<td>WBRT</td>
<td>132</td>
<td>Omitting WBRT after SRS increased the risk of local recurrence, but did not change overall survival. There were no significant differences in neurological function and toxicity between the 2 groups.</td>
</tr>
<tr>
<td>Muacevic et al (2008)</td>
<td>Single resectable</td>
<td>-</td>
<td>Resection + WBRT</td>
<td>33†</td>
<td>The group treated with SRS alone experienced an increased rate of distant intracranial relapse, although these distant sites could be salvaged with additional SRS. Other conclusions are difficult to make due to limited accrual to the study.</td>
</tr>
<tr>
<td>Kocher et al (2011)</td>
<td>1–3 brain</td>
<td>Either</td>
<td>WBRT</td>
<td>359</td>
<td>Omitting WBRT after local therapy (with either surgery or SRS) led to increased risk of intracranial relapse and neurologic death; however, there were no significant differences in overall survival or functional independence. Separately published analysis demonstrated improved QOL in the group that did not receive WBRT.‡</td>
</tr>
<tr>
<td>Sperduto et al (2013)</td>
<td>1–3 brain</td>
<td>WBRT and</td>
<td>3-arm study of concurrent/adjuvant temozolomide versus erlotinib versus none</td>
<td>126†</td>
<td>The study was underpowered to derive conclusions; however, there was a suggestion of improved survival and improved time to CNS progression in the control group,* that is, the group that received radiotherapy without drug.</td>
</tr>
</tbody>
</table>

CNS = central nervous system; NSCLC = non–small cell lung cancer; QOL = quality of life; RPA = reverse partitioning analysis; SRS = stereotactic radiosurgery; WBRT = whole-brain radiation therapy.

*Trend, but not statistically significant.

†Study terminated early.

brain metastasis can develop as a late feature in the course of cancer, the tumor may have already been treated with several chemotherapy regimens, leading to some degree of chemoresistance in the metastatic tissue.

However, systemic chemotherapy does play an important role in controlling extracranial disease. For example, patients with brain metastasis from HER2-positive breast cancer may have improved survival compared to patients with brain metastasis associated with HER2-negative disease due to the efficacy of agents such as trastuzumab in controlling extracranial disease. Trastuzumab itself has no significant penetration across the blood-brain barrier.

Newer agents with better penetration into the central nervous system, such as temozolomide, capecitabine, lapatinib, and erlotinib, have been investigated as treatment options for brain metastasis, and as potential radiosensitizers. Many such agents are small-molecule compounds with relatively favorable toxicity profiles. The optimal role of chemotherapy in the treatment of brain metastasis is still evolving.

The histology of the primary tumor is an important consideration when selecting drug therapies. In patients with metastatic melanoma and brain metastasis, ipilimumab does not appear to contribute to toxicity and may warrant further exploration. Sorafenib may decrease the incidence of brain metastasis in patients with renal cell carcinoma.

EGFR mutations predict response to therapy with anti-EFGR agents such as erlotinib. Systemic resistance may occur while the metastatic disease in the central nervous system remains sensitive; higher concentration of drug might be achievable in the central nervous system via weekly “pulsatile” dosing of erlotinib. Finally, in HER2-positive breast cancer, responses are observed (objective response rate of 38%) with the combination of lapatinib plus capecitabine. Experimental therapies for brain metastasis include the placement of BCNU (bis-chloroethylnitrosourea)-impregnated wafers into the resection cavity at the time of surgery for single metastasis.

**Radiation Sensitizers**

Another approach in treating brain metastasis is to utilize agents that may serve as a radiosensitizer. Agents tested in a randomized controlled fashion include lonidamine, metronidazole, thalidomide, misonidazole, bromodeoxyuridine, gefitinib, and motexafin gadolinium. None of these agents has been shown to prolong overall survival in brain metastases, but motexafin gadolinium has been shown to improve time to neurological progression as well as neurocognitive function in the subset of patients with NSCLC. Based on the success of the concurrent use of temozolomide with radiation therapy in glioblastoma, temozolomide and erlotinib were separately tested as radiosensitizers in a randomized controlled trial (RTOG-0320) for patients with 3 or fewer brain metastases from NSCLC. All arms of the study included SRS and WBRT. Patients were randomized to either temozolomide, erlotinib, or no chemotherapy during the period of radiotherapy and were allowed to continue the drug as adjuvant therapy. Unfortunately, the study was terminated early due to poor accrual, and it appeared that overall survival was in fact worsened by adding 1 of the 2 agents compared with SRS/WBRT alone, although the study was underpowered to confirm this trend.

Efaproxiral, an allosteric modifier of hemoglobin, demonstrated improved survival and quality of life when randomly assigned to 106 patients with breast cancer receiving WBRT and supplemental oxygen.
Supportive Care

In addition to selecting definitive treatment of the central nervous system neoplasm, managing neurological symptoms is an important aspect of care of patients with metastatic brain tumors. There are several measures which can be taken to improve quality of life.

Cerebral edema and mass effect from the tumor may result in many neurological symptoms. Surgical resection of tumor, when feasible, is the most direct way of ameliorating this problem. Corticosteroids improve vasogenic edema and are a mainstay in treating cerebral edema from primary or metastatic brain tumors. A typical dose of dexamethasone consists of an intravenous bolus of 10 to 20 mg followed by 4 to 24 mg/day in divided doses. Vigilance is needed for side effects including hyperglycemia, peptic ulcer disease, weight gain, edema, psychosis, immunosuppression, and proximal weakness due to steroid myopathy. Corticosteroids are often continued until tumor control is achieved with definitive treatment (eg, surgery or WBRT) and should then be tapered.

Seizures can occur in patients with brain metastasis. However, anticonvulsants should be reserved for patients who have actually experienced a seizure. Anticonvulsants that do not induce hepatic enzymes, such as levetiracetam, valproate, gabapentin, and pregabalin, are less likely to interact with chemotherapy and are preferred.

CASE 1 CONTINUED

The single metastasis is surgically resected without significant neurological sequelae (Figure 4). The pathological review is consistent with metastatic breast cancer. The patient then receives WBRT to a total dose of 30 Gy in 15 fractions. She receives surveillance brain MRI with gadolinium every 3 months. She remains clinically and radiologically stable 6 months after the completion of WBRT. After the eighth month, she reports impaired balance and urinary incontinence. Contrast MRI of the brain reveals sulcal enhancement within the cerebellum. MRI of the spine shows leptomeningeal enhancement near the conus medullaris (Figure 5). Lumbar puncture is performed; cerebrospinal fluid (CSF) analysis reveals elevated protein (121 mg/dL) and the presence of malignant cells on CSF cytology. These cells are consistent with the primary cancer cells.

What is the significance of these findings?

LEPTOMENINGEAL METASTASIS

The clinical, radiological, and laboratory findings are suggestive of leptomeningeal metastasis (LM). LM refers to infiltration of the leptomeninges (arachnoid and pia mater) with neoplastic cells. Synonyms for this condition include neoplastic
Meningitis, meningeal carcinomatosis, and leptomeningeal disease. The presence of malignant cells on CSF cytology is considered the diagnostic gold standard for this condition and is highly specific; however, a single negative cytology does not necessarily exclude the diagnosis. Three serial lumbar punctures for CSF analysis has a sensitivity of approximately 90%. CSF protein is commonly elevated. When unequivocal evidence of LM is noted on MRI, a radiographic diagnosis of LM may be made without CSF.

Simultaneous involvement of multiple levels of the neuroaxis is a clinical hallmark of LM. Cerebral, cranial nerve, and spine involvement are common and each may be associated with a specific set of signs and symptoms (Table 4). Elevated intracranial pressure may result in headache, nausea, vomiting, and confusion. Hematological malignancies are frequently associated with LM, as are many types of solid malignancies and primary brain tumors (Table 5).

The disease process may be diffuse or nodular. Diffuse LM may be difficult to detect on MRI. Nodular LM can cause symptoms due to mass effect and can result in spinal cord compression. Use of intra-CSF chemotherapy may have limited benefit for bulky leptomeningeal tumors greater than 2 mm in size due to limited penetration of drug. MRI findings in LM are noted in Table 6.

### Table 4. Signs and Symptoms of Leptomeningeal Metastasis at Initial Presentation

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Percentage</th>
<th>Signs</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cerebral</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>38</td>
<td>Papilledema</td>
<td>12</td>
</tr>
<tr>
<td>Mental change</td>
<td>25</td>
<td>Abnormal mental state</td>
<td>50</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>12</td>
<td>Seizures</td>
<td>14</td>
</tr>
<tr>
<td>Gait difficulty</td>
<td>46</td>
<td>Extensor plantar response</td>
<td>50</td>
</tr>
<tr>
<td>Dysarthria/dysphagia</td>
<td>4</td>
<td>Diabetes insipidus</td>
<td>1</td>
</tr>
<tr>
<td>Loss of consciousness</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cranial nerve</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual loss</td>
<td>8</td>
<td>Optic neuropathy</td>
<td>2</td>
</tr>
<tr>
<td>Diplopia</td>
<td>8</td>
<td>Ocular motor paresis</td>
<td>30</td>
</tr>
<tr>
<td>Facial numbness</td>
<td>0</td>
<td>Trigeminal neuropathy</td>
<td>12</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>6</td>
<td>Facial weakness</td>
<td>25</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>2</td>
<td>Hearing loss</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypoglossal neuropathy</td>
<td>8</td>
</tr>
<tr>
<td><strong>Spinal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>25</td>
<td>Nuchal rigidity</td>
<td>16</td>
</tr>
<tr>
<td>Back</td>
<td>18</td>
<td>Straight leg raising</td>
<td>12</td>
</tr>
<tr>
<td>Radicular</td>
<td>12</td>
<td>Absent reflex</td>
<td>60</td>
</tr>
<tr>
<td>Paresthesias</td>
<td>10</td>
<td>Dermatomal sensory loss</td>
<td>50</td>
</tr>
<tr>
<td>Weakness</td>
<td>22</td>
<td>Lower motor neuron weakness</td>
<td>78</td>
</tr>
<tr>
<td>Bladder/bowel dysfunction</td>
<td>2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The prognosis of LM is poor and survival is typically less than 6 months. However, a small subset of patients with LM (including those with breast cancer) may experience prolonged survival of 1 year or greater.

- **What treatment options are available for patients with LM?**

Treatment options for patients with LM are palliative and include intrathecal chemotherapy, systemic chemotherapy, and radiotherapy.

### Chemotherapy

Intra-CSF chemotherapy can be delivered via lumbar puncture (intrathecal) or via a ventricular catheter connected to a reservoir placed under the scalp (Ommaya reservoir). While complications are possible from an Ommaya reservoir, it offers a means of delivering intra-CSF chemotherapy as well as obtaining CSF sampling with greater convenience than serial lumbar puncture. A radionuclide CSF flow study (cisternogram) may be performed prior to delivering intrathecal chemotherapy to identify any sites of obstruction to CSF flow; these areas may be treated with focal radiotherapy to restore normal flow patterns. Agents which may be administered into CSF for LM are listed in Table 7.

### Arachnoiditis

Arachnoiditis, a common acute complication of intra-CSF chemotherapy, may present within 72 hours of drug administration as headache, nausea, and vomiting, and is treated with systemic cortico-steroids.

### Systemic Chemotherapy

Systemic chemotherapy may play a role in treating LM as well as managing the extracranial malignancy (Table 8). Supportive care for patients with LM includes CSF shunting, corticosteroids, and anticonvulsants.

### Radiation Therapy

Radiation therapy can also be used to palliate LM. The extent of the central nervous system...
Metastatic Brain Tumors

**CASE CONTINUED**

Treatment consisted of radiation therapy to the caudal equina area with improvement in urinary incontinence. Following radiation therapy, intrathecal liposomal cytarabine was administered via an Ommaya reservoir with clearing of CSF cytology after 3 doses. The patient remained neurologically stable, but developed new lung metastases which were unresponsive to salvage treatment and resulted in significant functional impairment. She decided to pursue comfort care and died shortly thereafter.

**CONCLUSION**

Metastatic disease to the central nervous system is an issue that has become more significant as patients survive longer with cancer. Brain metastases and leptomeningeal metastases are 2 types of central nervous system metastases which require careful selection of treatment modalities for each individual patient. The prognosis is generally poor for both conditions, but prognostic factors have been identified which help to stratify patients and determine the appropriateness of available therapies. In addition to treatment of malignancy, management of neurological complications is important in managing these patients. More effective therapies for these conditions are essential, as they represent a critical obstacle to the overall progress of cancer treatment.

**Table 7. Agents That Have Been Administered into Cerebrospinal Fluid for Leptomeningeal Metastasis**

<table>
<thead>
<tr>
<th>Drug</th>
<th>CSF–Plasma Ratio (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>3</td>
</tr>
<tr>
<td>Cytarabine (ara-C)</td>
<td>25</td>
</tr>
<tr>
<td>Liposomal cytarabine (DepoCyt)</td>
<td>20</td>
</tr>
<tr>
<td>Thiotepa</td>
<td>25</td>
</tr>
<tr>
<td>Topotecan</td>
<td>20</td>
</tr>
<tr>
<td>Trastuzumab*</td>
<td>Unknown</td>
</tr>
<tr>
<td>Rituximab*</td>
<td>&gt;90</td>
</tr>
<tr>
<td>Interleukin-2</td>
<td>20</td>
</tr>
</tbody>
</table>


**Table 8. Chemotherapy Options in Leptomeningeal Metastasis.**

<table>
<thead>
<tr>
<th>Drug</th>
<th>CSF–Plasma Ratio (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimetabolites</td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>3</td>
</tr>
<tr>
<td>6-Mercaptopurine</td>
<td>25</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>20</td>
</tr>
<tr>
<td>Capecitabine*</td>
<td>Unknown</td>
</tr>
<tr>
<td>Alkylating agents</td>
<td></td>
</tr>
<tr>
<td>Thiotepa</td>
<td>&gt;90</td>
</tr>
<tr>
<td>Temozolomide†</td>
<td>20</td>
</tr>
</tbody>
</table>


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Malignant Gliomas in Adults

Patrick Y. Wen, M.D., and Santosh Kesari, M.D., Ph.D.

MALIGNANT GLIOMAS ACCOUNT FOR APPROXIMATELY 70% OF THE 22,500 new cases of malignant primary brain tumors that are diagnosed in adults in the United States each year.\(^1\,^2\) Although relatively uncommon, malignant gliomas are associated with disproportionately high morbidity and mortality. Despite optimal treatment, the median survival is only 12 to 15 months for patients with glioblastomas and 2 to 5 years for patients with anaplastic gliomas. Recently, there have been important advances in our understanding of the molecular pathogenesis of malignant gliomas and progress in treating them. This review summarizes the diagnosis and management of these tumors in adults and highlights some areas under investigation.

EPIDEMIOLOGIC FEATURES

The annual incidence of malignant gliomas is approximately 5 cases per 100,000 people.\(^1\,^2\) Each year, more than 14,000 new cases are diagnosed in the United States.\(^1\,^2\) Glioblastomas account for approximately 60 to 70% of malignant gliomas, anaplastic astrocytomas for 10 to 15%, and anaplastic oligodendrogliomas and anaplastic oligoastrocytomas for 10%; less common tumors such as anaplastic ependymomas and anaplastic gangliogliomas account for the rest.\(^1\,^2\) The incidence of these tumors has increased slightly over the past two decades, especially in the elderly,\(^4\) primarily as a result of improved diagnostic imaging. Malignant gliomas are 40% more common in men than in women and twice as common in whites as in blacks.\(^2\) The median age of patients at the time of diagnosis is 64 years in the case of glioblastomas and 45 years in the case of anaplastic gliomas.\(^2\,^4\)

No underlying cause has been identified for the majority of malignant gliomas. The only established risk factor is exposure to ionizing radiation.\(^4\) Evidence for an association with head injury, foods containing N-nitroso compounds, occupational risk factors, and exposure to electromagnetic fields is inconclusive.\(^4\) Although there has been some concern about an increased risk of gliomas in association with the use of cellular telephones,\(^5\) the largest studies have not demonstrated this.\(^4\,^6\,^7\) There is suggestive evidence of an association between immunologic factors and gliomas. Patients with atopy have a reduced risk of gliomas,\(^8\) and patients with glioblastoma who have elevated IgE levels appear to live longer than those with normal levels.\(^9\) The importance of these associations is unclear. Gene polymorphisms that affect detoxification, DNA repair, and cell-cycle regulation have also been implicated in the development of gliomas.\(^4\)

Approximately 5% of patients with malignant gliomas have a family history of gliomas. Some of these familial cases are associated with rare genetic syndromes, such as neurofibromatosis types 1 and 2, the Li–Fraumeni syndrome (germ-line p53 mutations associated with an increased risk of several cancers), and Turcot's syndrome (intestinal polyposis and brain tumors).\(^10\) However, most familial cases have
Malignant gliomas are histologically heterogeneous and invasive tumors that are derived from glia. The World Health Organization (WHO) classifies astrocytomas on the basis of histologic features into four prognostic grades: grade I (pilocytic astrocytoma), grade II (diffuse astrocytoma), grade III (anaplastic astrocytoma), and grade IV (glioblastoma). Grade III and IV tumors are considered malignant gliomas. Anaplastic astrocytomas are characterized by increased cellularity, nuclear atypia, and mitotic activity. Glioblastomas also contain areas of microvascular proliferation, necrosis, or both (Fig. 1 and 2). Uncommon glioblastoma variants include gliosarcomas, which contain a prominent sarcomatous element; giant-cell glioblastomas, which have multinucleated giant cells; small-cell glioblastomas, which are associated with amplification of the epidermal growth factor receptor (EGFR); and glioblastomas with oligodendrogial features, which may be associated with a better prognosis than standard glioblastomas. Oligodendrogliomas are divided by the WHO into two grades: well-differentiated oligodendrogliomas and oligoastrocytomas (WHO grade II), and anaplastic oligodendrogliomas and anaplastic oligoastrocytomas (WHO grade III) (Fig. 1). All of these tumors may contain perinuclear halos (Fig. 2C) and a delicate network of branching blood vessels (chicken-wire pattern).

Malignant gliomas typically contain both neoplastic and stromal tissues, which contribute to their histologic heterogeneity and variable outcome. Molecular studies such as gene-expression profiling potentially allow for better classification of these tumors and separation of the tumors into different prognostic groups.

**MOLECULAR PATHOGENESIS**

Recently, there has been important progress in our understanding of the molecular pathogenesis of malignant gliomas, and especially the importance of cancer stem cells. Malignant transformation in gliomas results from the sequential accumulation of genetic aberrations and the deregulation of growth-factor signaling pathways (Fig. 1 and 3). Glioblastomas can be separated into two main subtypes on the basis of biologic and genetic differences. Primary glioblastomas typically occur in patients older than 50 years of age and are characterized by EGFR amplification and mutations, loss of heterozygosity of chromosome 10q, deletion of the phosphatase and tensin homologue on chromosome 10 (PTEN), and p16 deletion. Secondary glioblastomas are manifested in younger patients as low-grade or anaplastic astrocytomas and transform over a period of several years into glioblastomas. These tumors, which are much less common than primary glioblastomas, are characterized by mutations in the p53 tumor-suppressor gene, overexpression of the platelet-derived growth factor receptor (PDGFR), abnormalities in the p16 and retinoblastoma (Rb) pathways, and loss of heterozygosity of chromosome 10q. Secondary glioblastomas have transcriptional patterns and aberrations in the DNA copy number that differ markedly from those of primary glioblastomas. Despite their genetic differences, primary and secondary glioblastomas are morphologically indistinguishable and respond similarly to conventional therapy, but they may respond differently to targeted molecular therapies.

High-grade oligodendrogliomas are characterized by the loss of chromosomes 1p and 19q (in 50 to 90% of patients). Progression from low-grade to anaplastic oligodendroglioma is associated with defects in PTEN, Rb, p53, and cell-cycle pathways.

**DEREGULATED GROWTH FACTOR SIGNALING**

The most common defects in growth-factor signaling involve EGFR and PDGFR (Fig. 3). Amplification of EGFR occurs almost exclusively in primary glioblastomas and is seen in approximately 40 to 50% of patients with that type of tumor. About half of the tumors with EGFR amplification express a constitutively autophosphorylated variant of EGFR, known as EGFRvIII, that lacks the extracellular ligand-binding domain (exons 2 through 7). This characteristic variant has become an important therapeutic target for kinase inhibitors, immunotoxins, and peptide vaccines. Recently, activating mutations in the extracellular domain of EGFR have been identified. PDGF signaling is a key regulator of glial development, and both ligand and receptors are frequently expressed in gliomas, creating an autocrine loop that stimulates proliferation of the
Olig2 expression (100%)
PS3 mutated (~65%)
PDGFA/PDGFR-α overexpressed (~60%)

Low-Grade Astrocytoma (5–10 yr)*
(WHO Grade II)
- LOH 19q (~50%)
- RB mutated (~25%)
- CDK4 amplified (15%)
- MDM2 overexpressed (10%)
- PI6ink4a/P14ARF loss (4%)
- LOH 11p (~30%)

Anaplastic Astrocytoma (2–3 yr)*
(WHO Grade III)
- LOH 10q (~70%)
- DCC loss (~50%)
- PDGFR-α amplified (~10%)
- PI3K mutated (~10%)
- P13K mutated/amplified (~10%)
- VEGF overexpressed

Secondary Glioblastoma (12–15 mo)*
(WHO Grade IV)

Primary Glioblastoma (12–15 mo)*
(WHO Grade IV)

Olig2 expression (100%)
EGFR amplified (~40%)
EGFR overexpressed (~60%)
EGFR mutated (~20–30%)
MDM2 amplified (~10%)
MDM2 overexpressed (~50%)
LOH 10q (~70%)
PI6ink4a/P14ARF loss (~30%)
PTEN mutated (~40%)
P13K mutated/amplified (~20%)
RB mutated
- VEGF overexpressed

Low-Grade Oligodendroglioma (5–10 yr)*
(WHO Grade II)
- PI6ink4a/P14ARF loss
- RB mutated (~65%)
- p53 mutated
- PTEN loss
- LOH 9p, 10q
- CDK4/EGFR/MYC amplified
- VEGF overexpressed

Anaplastic Oligodendroglioma (3–5 yr)*
(WHO Grade III)

**Figure 1. Pathways in the Development of Malignant Gliomas.**

Genetic and chromosomal alterations involved in the development of the three main types of malignant gliomas (primary and secondary glioblastomas and anaplastic oligodendroglialoma) are shown. Oligodendrocyte transcription factor 2 (Olig2) (blue) and vascular endothelial growth factor (VEGF) (red) are expressed in all high-grade gliomas. Median lengths of survival (asterisks) are shown. A slash denotes deleted in colorectal carcinoma, EGFR epidermal growth factor receptor, LOH loss of heterozygosity, MDM2 murine double minute 2, CDK4/EGFR/MYC amplified, VEGF overexpressed.

**Role of Stem Cells in Pathogenesis and Resistance to Therapy.**

Although the genetic and signaling pathways involved in the development of malignant gliomas...
have been relatively well characterized, the cellular origins of these tumors are unknown. The adult nervous system harbors neural stem cells that are capable of self-renewal, proliferation, and differentiation into distinctive mature cell types. There is increasing evidence that neural stem cells, or related progenitor cells, can be transformed into cancer stem cells and give rise to malignant gliomas.
by escaping the mechanisms that control proliferation and programmed differentiation (Fig. 4).32-36 These stem cells are identified by several immunocytochemical markers, such as CD133, a glycoprotein also known as prominin 1,26,32,35,37 Although stem cells account for only a minority of the cells within malignant gliomas, they appear to be critical for generating these tumors.36,38 Recent studies suggest that glioma stem cells produce VEGF and promote angiogenesis in the tumor microenvironment.39 In addition, tumor stem cells appear to require a vascular niche for optimal function.40 These observations raise the possibility that antiangiogenic therapy may inhibit the functioning of glioma stem cells.

There is growing evidence that glioma stem cells may contribute to the resistance of malignant gliomas to standard treatments (Fig. 4). Radioresistance in stem cells generally results from the preferential activation of DNA-damage-response pathways,44 whereas chemoresistance results partly from the overexpression of O6-methylguanine–DNA methyltransferase (MGMT), the up-regulation of multidrug resistance genes, and the inhibition of apoptosis.42-44 Therapeutic strategies that effectively target stem cells and overcome their resistance to treatment will be necessary if malignant gliomas are to be completely eradicated (Fig. 4). A better understanding of the biologic differences between normal and cancer stem cells will be required to develop selective therapies that spare normal brain cells.

**DIAGNOSIS**

**CLINICAL PRESENTATION**

Patients with malignant gliomas may present with a variety of symptoms, including headaches, seizures, focal neurologic deficits, confusion, memory loss, and personality changes. Although the classic headaches that are suggestive of increased intracranial pressure are most severe in the morning and may wake the patient from sleep, many patients experience headaches that are indistinguishable from tension headaches. When severe, the headaches may be associated with nausea and vomiting.

**IMAGING**

The diagnosis of malignant gliomas is usually suggested by magnetic resonance imaging (MRI) or computed tomography. These imaging studies typically show a heterogeneously enhancing mass with surrounding edema. Glioblastomas frequently have central areas of necrosis and more extensive peritumoral edema than that associated with anaplastic gliomas.45 Functional MRI may help define the relationship of speech and motor areas to the tumor and aid in the planning of surgery. Diffusion-weighted imaging, diffusion tensor imaging, dynamic contrast-enhanced MRI to measure vessel permeability, and perfusion imaging to measure relative cerebral blood volume are increasingly used as diagnostic aids and as a means of monitoring the response to therapy.46

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**Figure 3 (facing page). Major Signaling Pathways in Malignant Gliomas and the Corresponding Targeted Agents in Development for Glioblastoma.**

RTK inhibitors that target epidermal growth factor (EGF) receptor include gefitinib, erlotinib, lapatinib, BIBW2992, and vandetanib; those that target platelet-derived growth factor (PDGF) receptor include imatinib, dasatinib, and tandutinib; those that target vascular endothelial growth factor (VEGF) receptor include cediranib, pazopanib, sorafenib, sunitinib, vatalanib, vandetanib, and XL184. EGF receptor antibodies include cetuximab and panitumumab. Farnesyl transferase inhibitors include lonafarnib and tipifarnib; HDAC inhibitors include depsipeptide, vorinostat, and LBHS589; PI3K inhibitors include BEZ235 and XL765; mTOR inhibitors include sirolimus, temsirolimus, everolimus, and deforolimus; and VEGF receptor inhibitors include bevacizumab, afibercept (VEGTrap), and CT-322. Growth factor ligands include EGF, PDGF, IGf, TGF, HGF/SF, VEGF, and FGF. Stem-cell pathways include SHH, wingless family, and Notch. Akt denotes murine thymoma viral oncogene homolog (also known as protein kinase B), CDK cyclin-dependent kinase, ERK extracellular signal-regulated kinase, FGf fibroblast growth factor, Fgf2 farnesyltransferase inhibitors, GDP guanine diphosphate, Grb2 growth factor receptor-bound protein 2, GTP guanine triphosphate, HDAC histone deacetylase, HGF/SF Hepatocyte growth factor/scatter factor, IGF insulin-like growth factor, MEK mitogen-activated protein kinase kinase, mTOR mammalian target of rapamycin, NF1 neurofibromin 1, PIP2 phosphatidylinositol (4,5) biphosphate, PIP3 phosphatidylinositol 3-kinase, PKC protein kinase C, PLC phosphatidylinositol 3-kinase, PI3K phosphatidylinositol 3-kinase, PLD phospholipase D, PTEN phosphatase and tensin homologue, RAF v-raf 1 murine leukemia viral oncogene homologue, Ras ras oncogene, RAS rat sarcoma viral oncogene homologue, RTK receptor tyrosine kinase inhibitor, SHH sonic hedgehog, SOS son of sevenless, Srrc sarcoma (Schmidt-Ruppin A-2) viral oncogene homologue, TGF transforming growth factor family, and TSC1 and 2 tuberous sclerosis gene 1 and 2. Red text denotes inhibitors. Data are from Sathornsumetee et al., Furnari et al.,39 Chi and Wen, Chi et al., and Sathornsumetee et al.21

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Proton magnetic resonance spectroscopy detects the levels of metabolites and may help differentiate a tumor from necrosis or benign lesions. In patients with malignant gliomas, this imaging technique typically shows an increase in the choline peak (reflecting increased membrane turnover) and a decrease in the N-acetyl aspartate peak (reflecting decreased neuronal cellularity), as compared with the findings in unaffected areas of the brain.\textsuperscript{45,46} Positron-emission tomography that uses
isotopes such as $^{18}$F-fluorodeoxyglucose, $^{18}$F-fluoro-L-thymidine, $^{11}$C-methionine, and 3,4-dihydroxy-6-$^{18}$F-fluoro-L-phenylalanine is being evaluated for its usefulness in diagnosis and in monitoring the response to therapy.\textsuperscript{47}

In up to 40% of cases, the MRI studies that are performed in the first month after radiotherapy show increased enhancement.\textsuperscript{48} In 50% of these cases, the increased enhancement reflects a transient increase in vessel permeability as a result of radiotherapy, a phenomenon termed “pseudoprogression,” which improves with time.\textsuperscript{48} Different
tiating this transient effect from true progression of the cancer can be challenging initially, even with advanced imaging techniques.

### TREATMENT

#### GENERAL MEDICAL MANAGEMENT

Much of the care of patients with malignant gliomas involves general medical management. The most common problems include seizures, peritumoral edema, venous thromboembolism, fatigue, and cognitive dysfunction. Patients who present with seizures should be treated with antiepileptic drugs. Since antiepileptic drugs that induce hepatic cytochrome P-450 enzymes, such as phenytoin and carbamazepine, increase the metabolism of many chemotherapeutic agents, antiepileptic drugs that do not induce these enzymes, such as levetiracetam, are generally preferred. The use of prophylactic antiepileptic drugs in patients with malignant gliomas who have never had a seizure is controversial. The American Academy of Neurology issued a practice guideline indicating that there is no evidence that prophylactic antiepileptic drugs are beneficial and advises against their routine use in patients with brain tumors who have not had seizures.

Antiepileptic drugs such as levetiracetam are generally preferred. The standard therapy for newly diagnosed malignant gliomas involves surgical resection when feasible, radiotherapy, and chemotherapy (Table 1). Malignant gliomas cannot be completely eliminated surgically because of their infiltrative nature, but patients should undergo maximal surgical resection whenever possible. Surgical debulking reduces the symptoms from mass effect and provides tissue for histologic diagnosis and molecular studies. Advances such as MRI-guided neuronavigation, intraoperative MRI, functional MRI, intraoperative mapping, and fluorescence-guided surgery have improved the safety of surgery and increased the extent of resection that can be achieved. The value of surgery in prolonging survival is controversial, but patients who undergo extensive resection probably have a modest survival advantage.

Radiotherapy is the mainstay of treatment for malignant gliomas. The addition of radiotherapy to surgery increases survival among patients with glioblastomas from a range of 3 to 4 months to a range of 7 to 12 months. Conventional radiotherapy consists of 60 Gy of partial-field external-beam irradiation delivered 5 days per week in fractions of 1.8 to 2.0 Gy. After standard radio-

The risk of intratumoral hemorrhage associated with anticoagulation therapy in patients with gliomas who have venous thromboembolism is low, whereas inferior vena cava filters are associated with high complication rates. Unless a patient with malignant glioma and venous thromboembolism has an intracerebral hemorrhage or other contraindications, it is generally safe to provide anticoagulation therapy for the venous thromboembolism. Low-molecular-weight heparin may be more effective and safer than warfarin.

Patients with malignant gliomas frequently experience fatigue and may benefit from treatment with modafinil or methylphenidate. Methylphenidate may also help abulia, and donepezil and memantine may reduce memory loss, although evidence supporting these approaches remains limited. Depression is underdiagnosed in patients with malignant gliomas, and antidepressants and psychiatric support are often invaluable.

### SPECIFIC THERAPY FOR NEWLY DIAGNOSED MALIGNANT GLIOMAS

The standard therapy for newly diagnosed malignant gliomas involves surgical resection when feasible, radiotherapy, and chemotherapy (Table 1). Malignant gliomas cannot be completely eliminated surgically because of their infiltrative nature, but patients should undergo maximal surgical resection whenever possible. Surgical debulking reduces the symptoms from mass effect and provides tissue for histologic diagnosis and molecular studies. Advances such as MRI-guided neuronavigation, intraoperative MRI, functional MRI, intraoperative mapping, and fluorescence-guided surgery have improved the safety of surgery and increased the extent of resection that can be achieved. The value of surgery in prolonging survival is controversial, but patients who undergo extensive resection probably have a modest survival advantage. Stereotactic biopsies should be performed only in patients who have inoperable tumors that are located in critical areas.

Radiotherapy is the mainstay of treatment for malignant gliomas. The addition of radiotherapy to surgery increases survival among patients with glioblastomas from a range of 3 to 4 months to a range of 7 to 12 months. Conventional radiotherapy consists of 60 Gy of partial-field external-beam irradiation delivered 5 days per week in fractions of 1.8 to 2.0 Gy. After standard radio-
therapy, 90% of the tumors recur at the original site.\textsuperscript{65} Strategies to increase the radiation dose to the tumor with the use of brachytherapy\textsuperscript{66} and stereotactic radiosurgery\textsuperscript{67,68} have failed to improve survival. Newer chemotherapeutic agents,\textsuperscript{69} targeted molecular agents,\textsuperscript{20} and antiangiogenic agents\textsuperscript{70} may enhance the effectiveness of radiotherapy.

Patients who are older than 70 years of age have a worse prognosis than younger patients and represent a particular challenge. Among these patients, radiotherapy produces a modest benefit in median survival (29.1 weeks) as compared with supportive care (16.9 weeks).\textsuperscript{71} Since older patients often tolerate radiotherapy less well than younger patients, an abbreviated course of radiotherapy (40 Gy in 15 fractions over a period of 3 weeks)\textsuperscript{72} or chemotherapy with temozolomide (an oral alkylating agent with good penetration of the blood–brain barrier) alone\textsuperscript{73} may be considered, since the outcomes with these approaches are similar to the outcomes with conventional radiotherapy regimens.

Chemotherapy is assuming an increasingly important role in the treatment of malignant gliomas. Although early studies of adjuvant chemotherapy for malignant gliomas with the use of nitrosoureas failed to show a benefit,\textsuperscript{63,74} two meta-analyses have suggested that adjuvant chemotherapy results in a modest increase in survival (a 6 to 10% increase in the 1-year survival rate).\textsuperscript{75,76}

The European Organisation for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCIC) conducted a phase III trial comparing radiotherapy alone (60 Gy over a period of 6 weeks) with radiotherapy and concomitant treatment with temozolomide (75 mg per square meter of body-surface area per day for 5 days every 28 days for 6 cycles), in patients with newly diagnosed glioblastomas.\textsuperscript{64} As reported by Stupp et al., the combination of radiotherapy and temozolomide had an acceptable side-effect profile and, as compared with radiotherapy alone, increased the median survival (14.6 months vs. 12.1 months, P<0.001).\textsuperscript{64} In addition, the survival rate at 2 years among the patients who received radiotherapy and temozolomide was significantly greater than the rate among the patients who received radiotherapy alone (26.5% vs. 10.4%).\textsuperscript{64} Establishing radiotherapy with concomitant and adjuvant temozolomide as a useful combination for newly diagnosed glioblastomas.

MGMT is an important repair enzyme that contributes to resistance to temozolomide. In a companion study to the EORTC–NCIC study reported by Stupp et al., tumor specimens from the pa-
patients were examined for epigenetic silencing of the MGMT gene. MGMT promoter methylation silences the gene, thus decreasing DNA repair activity and increasing the susceptibility of the tumor cells to temozolomide. Patients with glioblastoma and MGMT promoter methylation (45% of the total) who were treated with temozolomide had a median survival of 21.7 months and a 2-year survival rate of 46%. In contrast, patients without MGMT promoter methylation who were treated with temozolomide had a significantly shorter median survival of only 12.7 months and a 2-year survival rate of 13.8%. Currently, temozolomide is used in the treatment of glioblastomas regardless of MGMT promoter methylation status. However, if the importance of MGMT promoter methylation is confirmed by the results of an ongoing study by the Radiation Therapy Oncology Group (RTOG 0525), patients with unfavorable MGMT methylation status may be selected for other treatments in future investigations. Studies of dose-intensive temozolomide regimens to deplete MGMT and of combinations of temozolomide with inhibitors of MGMT, such as O6-benzylguanine, and inhibitors of other repair enzymes, such as poly-(ADP-ribose)-polymerase, are in progress.

Another chemotherapeutic approach involves the implantation of biodegradable polymers containing carmustine (Gliadel Wafers, MGI Pharma) into the tumor bed after resection of the tumor. The aim of treatment with these polymers, which release carmustine gradually over the course of several weeks, is to kill residual tumor cells. In a randomized, placebo-controlled trial that investigated the use of these polymers in patients with newly diagnosed malignant gliomas, median survival increased from 11.6 months to 13.9 months (P=0.03). This survival advantage was maintained at 2 and 3 years.

Therapy for Anaplastic Gliomas

Anaplastic astrocytomas are treated with radiotherapy and either concurrent and adjuvant temozolomide (as for glioblastomas) or adjuvant temozolomide alone. Currently, there are no findings from controlled trials that support the use of concurrent temozolomide in patients with anaplastic astrocytomas.

Anaplastic oligodendrogliomas and anaplastic oligoastrocytomas are an important subgroup of malignant gliomas that are generally more responsive to therapy than are pure astrocytic tumors. A codeletion of chromosomes 1p and 19q, mediated by an unbalanced translocation of 19p to 1q, occurs in 61 to 89% of patients with anaplastic oligodendrogliomas and 14 to 20% of patients with anaplastic oligoastrocytomas. Tumors in patients with the 1p and 19q codeletion are particularly sensitive to chemotherapy with PCV — procarbazine, lomustine (CCNU), and vincristine — with response rates of up to 100%, as compared with response rates of 23 to 31% among patients without the deletion of chromosomes 1p and 19q. The reason for the increased chemosensitivity of tumors in patients with the 1p and 19q codeletion is unclear. One study suggested that 1p loss is associated with decreased levels of stathmin and an increased sensitivity to nitrosoureas. The status of chromosomes 1p and 19q, rather than standard histologic assessment, is now used as an eligibility criterion in studies involving patients with anaplastic oligodendrogliomas and anaplastic oligoastrocytomas, reflecting a paradigm shift in the design of clinical trials for patients with these tumors.

Two large phase III studies of PCV chemotherapy with radiotherapy, as compared with radiotherapy alone, in patients with newly diagnosed anaplastic oligodendrogliomas or anaplastic oligoastrocytomas, have been reported. In both studies, the addition of chemotherapy to radiotherapy increased the time to tumor progression by 10 to 12 months but did not improve overall survival (median, 3.4 and 4.9 years). The failure of chemotherapy to increase survival may be partly explained by the fact that patients who initially received radiotherapy alone subsequently received chemotherapy when they had a relapse, so that most patients in both groups eventually received chemotherapy. In both studies, patients with the codeletion of 1p and 19q had improved survival as compared with those without the codeletion of 1p and 19q. Although most studies involving patients with anaplastic oligodendrogliomas or anaplastic oligoastrocytomas were conducted with PCV chemotherapy, temozolomide is likely to have similar activity and less toxicity; however, studies directly comparing the two regimens have not been performed.

Therapy for Recurrent Malignant Gliomas

Despite optimal treatment, nearly all malignant gliomas eventually recur. For glioblastomas, the median time to progression after treatment with radiotherapy and temozolomide is 6.9 months. If the tumor is symptomatic from mass effect, re-
operation may be indicated (Table 1). However, surgery performed in selected patients results in only limited prolongation of survival.86

The usefulness of radiotherapy for recurrent malignant gliomas is controversial.87 Although some reports have suggested that fractionated stereotactic reirradiation88 and stereotactic radiosurgery89 may be beneficial, selection bias may have influenced these results.

The value of conventional chemotherapy for recurrent malignant gliomas is modest. In general, chemotherapy is more effective for anaplastic gliomas than for glioblastomas.79,87 Temozolomide was evaluated in a phase II study involving patients with recurrent anaplastic gliomas who had previously been treated with nitrosoureas; the study showed a 35% response rate. The 6-month rate of progression-free survival was 46%,89 comparing favorably with the 31% rate of progression-free survival at 6 months for therapies that were reported to be ineffective.90 In contrast, temozolomide has only limited activity in patients with recurrent glioblastomas (response rate, 5.4%; 6-month rate of progression-free survival, 21%).91 Other chemotherapeutic agents that are used for recurrent gliomas include nitrosoureas, carboplatin, procarbazine, irinotecan, and etoposide. Carmustine wafers have modest activity, increasing the median survival by approximately 8 weeks in patients with recurrent glioblastomas.92

INVESTIGATIONAL THERAPIES

TARGETED MOLECULAR THERAPIES

The improved understanding of the molecular pathogenesis of malignant gliomas has allowed a more rational use of targeted molecular therapies (Fig. 3).18,20,21 Particular interest has focused on inhibitors that target receptor tyrosine kinases such as EGFR,93 PDGFR,94 and VEGFR,52 as well as on signal-transduction inhibitors targeting mTOR,95 farnesyltransferase,97 and PI3K (Table 2). Single agents have only modest activity, with response rates of 0 to 15% and no prolongation of 6-month progression-free survival.3,20,21 These disappointing results are due to several factors. Most malignant gliomas have coactivation of multiple tyrosine kinases,98 as well as redundant signaling pathways, thus limiting the activity of single agents. In addition, many of these agents have poor penetration across the blood–tumor barrier. There has been considerable interest in identifying molecular features of the tumor that predict a response, so that patients who are most likely to benefit can be selected for a particular treatment. EGFR inhibitors appear to be more effective in patients who have tumors with EGFRvIII mutations and intact PTEN than in patients who do not have these molecular changes99; patients who have tumors with increased activity of the PI3K–Akt pathway, as indicated by an increase in phosphorylated Akt, generally do not have a response.100 Current experimental strategies to increase the effectiveness of targeted molecular therapies include the use of a single agent targeted against several kinases, combinations of agents that inhibit complementary targets such as EGFR and mTOR (Table 2 and Fig. 5A through 5D), and targeted agents combined with radiotherapy and chemotherapy.3,18,20,21

ANTIANGIOGENIC AGENTS

Malignant gliomas are among the most vascular of human tumors,18 making them especially attractive targets for angiogenesis inhibitors.29 Although older antiangiogenic agents such as thalidomide had only modest activity,101 newer and more potent angiogenesis inhibitors show promising activity. In preliminary studies, treatment with the combination of bevacizumab and irinotecan was associated with a low incidence of hemorrhage and response rates of 57 to 63% among patients with malignant gliomas (Fig. 5E through 5H).102,103 Some of the improvement that is seen on radiographic images may be artifactual, caused by reduced vascular permeability and decreased contrast enhancement as a result of the inhibition of VEGF. However, this regimen also has antitumor activity, as evidenced by the fact that it increased the 6-month rate of progression-free survival to 46% among patients with recurrent glioblastomas,102,103 as compared with a 6-month rate of progression-free survival of 21% for patients who were receiving treatment with temozolomide.91 Recently, a large, randomized phase II trial of bevacizumab alone and bevacizumab with irinotecan was completed. Preliminary results confirmed the safety of bevacizumab and showed an increase in the 6-month rate of progression-free survival to 35.1% for patients receiving bevacizu-
### Table 2. Selected Investigational Treatments for Malignant Gliomas.

<table>
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<tr>
<th>Type of Treatment</th>
<th>Example</th>
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<tbody>
<tr>
<td>Convection-enhanced surgical delivery of pharmacologic agent</td>
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<td>Drugs to overcome resistance to TMZ</td>
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<tr>
<td>PKCβ</td>
<td>Enzastaurin</td>
</tr>
<tr>
<td>PDGFR inhibitors</td>
<td>Dasatinib, imatinib, tandutinib</td>
</tr>
<tr>
<td>Proteasome</td>
<td>Bortezomib</td>
</tr>
<tr>
<td>Raf</td>
<td>Sorafenib</td>
</tr>
<tr>
<td>Src</td>
<td>Dasatinib</td>
</tr>
<tr>
<td>TGF-β</td>
<td>AP12009</td>
</tr>
<tr>
<td>Combination therapies</td>
<td>Erlotinib plus temsirolimus, gefitinib plus everolimus, gefitinib plus temsirolimus, erlotinib, or tipifarnib, pazopanib plus lapatinib</td>
</tr>
</tbody>
</table>

#### Immunotherapies

- **Dendritic cell and EGFRVIII peptide vaccines**: DCVax, CDX-110
- **Monoclonal antibodies**: 131I-anti-tenascin antibody
- **Gene therapy**: 131I-TM-601
- **Other therapies**: 131I-TM-601

---

* Data are from Sathornsumetee et al.,¹³ Furnari et al.,¹⁸ Chi and Wen,²⁰ and Sathornsumetee et al.²¹ EGFR denotes epidermal growth factor receptor, FTI farnesyltransferase, HDAC histone deacetylase, HSP90 heat-shock protein 90, MGMT O6-methylguanine–DNA methyltransferase, mTOR mammalian target of rapamycin, PARP poly (ADP-ribose) polymerase, PDGFR platelet-derived growth factor receptor, PI3K phosphatidylinositol 3-kinase, PKCβ protein kinase Cβ, TGF transforming growth factor, TMZ temozolomide, and VEGFR vascular endothelial growth factor receptor.
mab alone and 50.2% for patients receiving the combination of bevacizumab and irinotecan. A phase II trial of the pan-VEGFR inhibitor cediranib in patients with recurrent glioblastomas showed response rates in excess of 50% and prolongation of the 6-month rate of progression-free survival to approximately 26%. These agents also decrease peritumoral edema, potentially allowing for a reduction in corticosteroid requirements. Since antiangiogenic agents may have synergistic activity with radiotherapy, there is increasing interest in combining them with radiotherapy and temozolomide in patients with newly diagnosed glioblastomas. As noted previously, glioma stem cells produce VEGF and require a vascular niche for optimal function. Antiangiogenic agents may therefore also target glioma stem cells.

**OTHER THERAPIES**

Other investigational therapies for malignant gliomas include chemotherapeutic agents that cross the blood–tumor barrier more effectively, gene therapy, peptide and dendritic-cell vaccines, radiolabeled monoclonal antibodies against the extracellular matrix protein tenascin, synthetic chlorotoxins, and infusion of radiolabeled drugs and targeted toxins into the tumor and surrounding brain by means of convection-enhanced delivery (Table 2).

**PROGNOSTIC FACTORS**

The most important adverse prognostic factors in patients with malignant gliomas are advanced age, histologic features of glioblastoma, poor Karnofsky performance status, and unresectable tumor. There are ongoing efforts to identify biologic and genetic alterations in the tumors that may provide additional prognostic information, as well as guidance in making decisions about optimal therapy.

---

**Figure 5. MRI Scans Showing Responses to Targeted Agents.**

Panels A through D show MRI scans in a patient with a recurrent malignant glioma who was treated with a combination of erlotinib (an inhibitor of epidermal growth factor receptor [EGFR]) and sirolimus (an inhibitor of the mammalian target of rapamycin [mTOR]). T1-weighted images obtained after the administration of gadolinium show a reduction in the size of the enhancing tumor from the pretreatment image (Panel A) to the image obtained 2 months after treatment (Panel B), with fluid-attenuated inversion recovery (FLAIR) studies showing a reduction of edema from the pretreatment image (Panel C) to the post-treatment image (Panel D). Panels E through H show MRI scans of a recurrent glioblastoma in a patient who was treated with a combination of bevacizumab and irinotecan. T1-weighted images obtained after the administration of gadolinium show a reduction in the size of the enhancing tumor from the image obtained before treatment (Panel E) to the image obtained 7 months after treatment (Panel F) and an associated reduction of edema from the pretreatment FLAIR image (Panel G) to the post-treatment FLAIR image (Panel H).
Recently, there has been important progress in the treatment of malignant gliomas\footnote{\textsuperscript{111}} and in our understanding of the molecular pathogenesis of these tumors and the critical role that stem cells play in their development and resistance to treatment. As our understanding of the molecular correlates of response improves, it may be possible to select the most appropriate therapies on the basis of the patient’s tumor genotype. These advances provide real opportunities for the development of effective therapies for malignant gliomas.

\section*{References}


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This article is dedicated to the memories of Elizabeth Atkins, Will Kraft, and John Kenney.

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Primary Brain Tumors

Jai Grewal, MD, Harpreet Kaur Grewal, MD, and Santosh Kesari, MD, PhD

INTRODUCTION

Primary central nervous system tumors are relatively rare, but they can cause significant morbidity. They are also among the most lethal of all neoplasms. Brain tumors are the second most common cause of death due to intracranial disease, second only to stroke. The estimated annual incidence of primary brain tumors is approximately 21 per 100,000 individuals in the United States. The incidence of brain tumors varies by gender, age, race, ethnicity, and geography and has increased over time. Gliomas and germ cell tumors are more common in men, whereas meningiomas are twice as common in women. The only validated environmental risk factor for primary brain tumors is exposure to ionizing radiation. Other etiologies include inherited cancer syndromes and primary central nervous system lymphoma associated with AIDS. Approximately 5% to 10% of gliomas are associated with a family history. Inherited cancer syndromes involving brain tumors are listed in Table 1.

Primary brain tumors are classified according to the World Health Organization 2007 classification, as shown in Table 2. The TNM staging system is not used for primary brain tumors. Primary brain tumors are rarely metastatic outside the central nervous system, with some exceptions (embryonal tumors, malignant meningiomas). Tumors are graded from I to IV based on histological grading and prognosis, with grade IV being the most aggressive. Notable features of selected nervous system tumors are shown in Table 3. Gliomas account for 78% of all primary malignant central nervous system tumors, and glioblastoma (WHO grade IV) is the most common malignant primary brain tumor in adults. Despite advances in the field of oncology, the prognosis of these aggressive tumors remains poor.

This review focuses on the evaluation and management of primary brain tumors, in particular glioblastoma (the most common malignant brain tumor in adults), and highlights new advances in treatment options. Management of common complications associated with brain tumors will also be discussed.

CASE PRESENTATION

A 40-year-old right-handed nonsmoking man presents to the emergency department (ED) with the sudden onset of right-sided weakness. His family reports that he has had
progressive difficulty speaking over the last 3 to 4 weeks. He has had particular trouble with finding the right word. One hour prior to presentation to the ED, he had been preparing lunch when he noticed that his right arm was shaking. After about 30 seconds, the shaking stopped but he could not hold anything in his right hand. Examination reveals an alert man with expressive aphasia, who is otherwise cognitively intact and follows commands. He is noted to make frequent paraphasic errors. Nam-

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Nervous System</th>
<th>Skin</th>
<th>Other</th>
<th>Locus</th>
<th>Gene</th>
<th>Protein</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurofibromatosis type 1</td>
<td>Neurofibroma, MPNST, optic nerve glioma, astrocytoma</td>
<td>Café-au-lait, axillary freckling</td>
<td>Iris hamartomas, osseous lesions, pheochromocytoma, leukemia</td>
<td>17q11</td>
<td>NF1</td>
<td>Neurofibromin</td>
<td>Tumor suppressor gene, ras GTPase-activating protein regulates cell proliferation and differentiation</td>
</tr>
<tr>
<td>Neurofibromatosis type 2</td>
<td>Bilateral vestibular schwannomas, peripheral schwannomas, meningiomas, meningioangiomatosis, spinal ependymoma, astrocytoma, glial hamartins, cerebral calcifications</td>
<td>None</td>
<td>Posterior lens opacities, retinal hamartoma</td>
<td>22q12</td>
<td>NF2</td>
<td>Merlin or schwannomin</td>
<td>Tumor suppressor gene, binds to actin, regulating membrane cytoskeleton</td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td>Subependymal giant cell astrocytoma, cortical glioneuronal hamartomas (tubers), ependymal hamartomas (candle gutterings)</td>
<td>Angiofibroma (adenoma sebaceum), subungual fibromas</td>
<td>Cardiac rhabdomyoma, renal angiomyolipoma, pulmonary lymphangiomatosis</td>
<td>9q34 (TSC1), 16p13 (TSC2)</td>
<td>TSC1, TSC2</td>
<td>Hamartin (TSC1), tuberin (TSC2)</td>
<td>Tumor suppressor genes, tuberin-hamartin complex suppresses activation of the mTOR pathway (which increases proliferation and cell growth)</td>
</tr>
<tr>
<td>von Hippel-Lindau</td>
<td>Cerebrellar and spinal cord hemangioblastoma</td>
<td>None</td>
<td>Renal cell carcinoma, pheochromocytoma, renal angiomyolipoma, cysts of kidney and pancreas, cyst adenoma of epididymis</td>
<td>3p25</td>
<td>VHL</td>
<td>pVHL</td>
<td>Tumor suppressor gene, role in protein degradation and angiogenesis</td>
</tr>
<tr>
<td>Li-Fraumeni</td>
<td>Diffuse astrocytoma, medulloblastoma, supratentorial PNET</td>
<td>None</td>
<td>Bone and soft tissue sarcoma, breast cancer</td>
<td>17p13</td>
<td>TP53</td>
<td>p53</td>
<td>Tumor suppressor gene, promotes apoptosis in cells with DNA damage (continued on page 4)</td>
</tr>
</tbody>
</table>
ing and repetition are impaired. Motor examination reveals significant weakness in his right hand. Deep tendon reflexes are more brisk on the entire right side. The right plantar response is upgoing. Coordination testing on the right side is hampered by weakness, but is intact on the left side. The remainder of the examination is unremarkable.

- **What are the common presenting features of a brain tumor?**

## CLINICAL FEATURES OF BRAIN TUMORS

Symptoms from a brain tumor can be focal or generalized. The most common presenting symptoms in patients with brain tumor include headaches, seizures, cognitive impairment, personality changes, and focal neurological deficits. Focal signs and symptoms reflect the location of the tumor within the central nervous system.

Headache is a presenting symptom in approximately 48\% of newly diagnosed brain tumors. It is often dull, non-throbbing, and intermittent. Supratentorial masses can result in frontal headache. Posterior fossa masses cause headache in occipital and cervical areas. Early morning headache is considered a classic presentation because of increased intracranial pressure (ICP) in the recumbent position. However, this classic presentation occurs in a minority of patients.

Seizures are the presenting feature of brain tumors in approximately one-third of cases. They occur due to irritation of the brain parenchyma. There is evidence that blood–brain-barrier failure may be an etiological factor contributing to the development of seizures.

Low-grade tumors, particularly oligodendrogliomas, have a relatively greater tendency to present with seizures (over 70\% in some series). Even if seizures do not occur at presentation, they may

### Table 1. Genetic Syndromes Associated with Nervous System Tumors (continued)

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Nervous System</th>
<th>Skin</th>
<th>Other</th>
<th>Locus</th>
<th>Gene</th>
<th>Protein</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cowden</td>
<td>Dysplastic gangliocytoma of the cerebellum (Lhermitte-Duclos)</td>
<td>Multiple trichilemmoma, fibroma</td>
<td>Oral mucosa fibroma, hamartomatous colon polyps, thyroid tumors, breast cancer</td>
<td>10q23</td>
<td>PTEN</td>
<td>PTEN</td>
<td>Tumor suppressor gene, expression causes cell cycle arrest and apoptosis, regulates PI3K/Akt pathway</td>
</tr>
<tr>
<td>Turcot</td>
<td>Medulloblastoma, glioblastoma</td>
<td>Café-au-lait</td>
<td>Colorectal polyps or carcinoma</td>
<td>5q21, 3p21, 7p22w</td>
<td>APC, hMLH1, hPMS2</td>
<td>APC, hMLH1, hPMS2</td>
<td>APC-tumor suppressor gene regulating β-catenin, hMLH1, hPMS2 mismatch repair proteins</td>
</tr>
<tr>
<td>Gorlin</td>
<td>Medulloblastoma (desmoplastic)</td>
<td>Nevoid basal cell carcinoma, palmar and plantar pits</td>
<td>Jaw kerato cysts, ovarian fibroma</td>
<td>9q22</td>
<td>PTCH1</td>
<td>Ptc1</td>
<td>Tumor suppressor, suppresses smoothen-mediated cell proliferation</td>
</tr>
</tbody>
</table>

APC = adenomatous polyposis coli; hMLH1 = human MutL homolog; hPMS2 = human postmeiotic segregation increased 2; MPNST = malignant peripheral nerve sheath tumor; mTOR = mammalian target of rapamycin; PI3K = phosphoinositide-3-kinase, PTCH = Drosophila patched homolog 1; PTEN = phosphatase and tensin homolog.
occur later in 40% to 60% of patients with brain tumors. Seizures tend to be partial with possible secondary generalization; seizure semiology will correlate with the tumor location within the brain. Seizure frequency varies among patients. In patients who have experienced an extensive surgical resection, there may be a marked improvement in seizure frequency (or even complete seizure resolution) if the active seizure focus has been removed. Conversely, worsening of seizure type or seizure frequency (or even status epilepticus) may herald radiologic tumor progression.10

### Table 2. Abbreviated 2007 World Health Organization Classification of Brain Tumors

<table>
<thead>
<tr>
<th>Tumors of neuroepithelial tissue</th>
<th>Tumors of the pineal region</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astrocytic tumors</td>
<td>Pineocytoma</td>
</tr>
<tr>
<td>Pilocytic astrocytoma</td>
<td>Pineal parenchymal tumor of intermediate differentiation</td>
</tr>
<tr>
<td>Subependymal giant cell astrocytoma</td>
<td>Pineoblastoma</td>
</tr>
<tr>
<td>Pleomorphic xanthoastrocytoma</td>
<td>Embryonal tumors</td>
</tr>
<tr>
<td>Diffuse astrocytoma</td>
<td>Medulloblastoma</td>
</tr>
<tr>
<td>Anaplastic astrocytoma</td>
<td>CNS primitive neuroectodermal tumor</td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>CNS neuroblastoma</td>
</tr>
<tr>
<td>Gliomatosis cerebri</td>
<td>Atypical teratoid/rhabdoid tumor</td>
</tr>
<tr>
<td>Oligodendrogial tumors</td>
<td>Tumors of cranial and paraspinal nerves</td>
</tr>
<tr>
<td>Oligodendroglioma</td>
<td>Schwannoma</td>
</tr>
<tr>
<td>Anaplastic oligodendroglioma</td>
<td>Neurofibroma</td>
</tr>
<tr>
<td>Oligoastrocytic (mixed) tumors</td>
<td>Malignant peripheral nerve sheath tumor</td>
</tr>
<tr>
<td>Oligoastrocytoma</td>
<td></td>
</tr>
<tr>
<td>Anaplastic oligoastrocytoma</td>
<td></td>
</tr>
<tr>
<td>Ependymal tumors</td>
<td>Tumors of the meninges</td>
</tr>
<tr>
<td>Subependymoma</td>
<td>Meningioma (15 variants)</td>
</tr>
<tr>
<td>Myxopapillary ependymoma</td>
<td>Hemangioblastoma</td>
</tr>
<tr>
<td>Ependymoma</td>
<td>Hemangiopericytoma</td>
</tr>
<tr>
<td>Anaplastic ependymoma</td>
<td></td>
</tr>
<tr>
<td>Choroid plexus tumors</td>
<td>Germ cell tumors</td>
</tr>
<tr>
<td>Choroid plexus papilloma</td>
<td>Germinoma</td>
</tr>
<tr>
<td>Choroid plexus carcinoma</td>
<td>Embryonal carcinoma</td>
</tr>
<tr>
<td>Neuronal and mixed neuronal-gial tumors</td>
<td>Yolk-sac tumor</td>
</tr>
<tr>
<td>Dysplastic gangliocytoma of cerebellum</td>
<td>Choriocarcinoma</td>
</tr>
<tr>
<td>Dysembryoplastic neuroepithelial tumor</td>
<td>Teratoma</td>
</tr>
<tr>
<td>Gangliocytoma</td>
<td>Mixed germ cell tumor</td>
</tr>
<tr>
<td>Ganglioglioma</td>
<td></td>
</tr>
<tr>
<td>Anaplastic ganglioglioma</td>
<td></td>
</tr>
<tr>
<td>Central neurocytoma</td>
<td></td>
</tr>
<tr>
<td>Paraganglioma</td>
<td></td>
</tr>
</tbody>
</table>

CNS = central nervous system.

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Clinical</th>
<th>Radiologic</th>
<th>Pathologic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Central Nervous System</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oligodendroglioma</td>
<td>Often present with seizures</td>
<td>Calcifications</td>
<td>“Fried egg” appearance 1p and 19q chromosomal deletions</td>
</tr>
<tr>
<td>Diffuse low-grade astrocytoma</td>
<td>May present with seizures or subtle symptoms</td>
<td>Nonenhancing diffuse area of T2 signal Gyral expansion</td>
<td>Low mitotic activity Positive for p53, associated with IDH1/2 mutations</td>
</tr>
<tr>
<td>Ependymoma</td>
<td>Peak age 15 yr</td>
<td>Majority are in fourth ventricle or spinal cord Enhancing May spread via CSF pathways</td>
<td>Perivascular pseudorosettes</td>
</tr>
<tr>
<td>Meningioma</td>
<td>Most common primary CNS tumor (40%) More common in women Pregnancy may promote growth</td>
<td>Diffuse contrast enhancement Dural tail sign Locations: convexity, parasagittal, sphenoid wing, spinal, cavernous sinus</td>
<td>EMA-positive Desmosomes Progesterone receptors Many variants</td>
</tr>
<tr>
<td>Primary CNS lymphoma</td>
<td>May shrink or disappear (transiently) with corticosteroids May be associated with HIV</td>
<td>Diffuse contrast enhancement Periventricular lesions Restricted diffusion on DWI</td>
<td>Most B-cell Perivascular cuffing CD20+ (B-cell type)</td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>Most common adult malignant primary tumor Peak age 55, median survival 14.6 mo Chemotherapy shown to prolong survival in RCT</td>
<td>Ring-enhancing, irregular, necrotic-appearing mass(es)</td>
<td>Vascular proliferation Necrosis Pseudopalisadating arrangement of tumor cells</td>
</tr>
<tr>
<td>Medulloblastoma</td>
<td>Peaks in first and third decades of life May present with obstructive hydrocephalus or cerebellar signs</td>
<td>Posterior fossa enhancing mass May seed via CSF pathways (“drop metastases”)</td>
<td>Small, round blue cells (on H&amp;E stain) Homer-Wright rosettes (characteristic of all PNETs)</td>
</tr>
<tr>
<td>Ependymoblastoma</td>
<td>First 5 years of life Prognosis poor</td>
<td>Supratentorial enhancing mass with possible CSF seeding</td>
<td>True rosettes</td>
</tr>
<tr>
<td>Gangliocytoma/ganglioglioma</td>
<td>First 2 decades of life Intractable complex-partial seizures</td>
<td>Temporal lobe mass</td>
<td>Gangliocytoma: only neoplastic neuronal cells Ganglioglioma: mixed neoplastic neuronal and glial cells; eosinophilic granular bodies</td>
</tr>
<tr>
<td>Dysembryoplastic neuroepithelial Tumor</td>
<td>Second and third decades of life Rarely regrows after surgical resection</td>
<td>Medial temporal lobe</td>
<td>Neuronal and glial elements</td>
</tr>
<tr>
<td>Choroid plexus papilloma</td>
<td>In adults tumor of choroid plexus more likely to be metastatic</td>
<td>Children: lateral ventricle Adults: fourth ventricle</td>
<td>(continued on page 7)</td>
</tr>
</tbody>
</table>
Altered mental status is a presenting feature in 15% to 20% of cases. Tumors associated with elevated ICP, gliomatosis cerebri, and those located in the frontal lobes are more likely to be associated with altered mental status at presentation. The severity can range from mild inattention to deep coma.

Focal neurological deficits such as aphasia, hemiparesis, sensory loss, and visual field loss may also occur at presentation and correlate with tumor location. Aphasia is associated with involvement of the dominant hemisphere (usually the left), while sensorimotor and visual deficits can occur if the tumor affects the corresponding pathways within the central nervous system.

The time course of symptoms often correlates with the growth rate of the neoplasm. Symptoms may gradually progress over time. In the case presented, the patient comes to medical attention after an acute event. Careful history taking revealed that neurological symptoms had been apparent for several weeks before this. Patients with slow-growing tumors may have less pronounced symptoms than patients with fast growing masses of similar size and location.

Table 3. Notable Features of Selected Central and Peripheral Nervous System Tumors (continued)

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Clinical</th>
<th>Radiologic</th>
<th>Pathologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral Nervous System</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>First decade of life</td>
<td>Sympathetic chain in chest or abdomen</td>
<td>Similar to medulloblastomas</td>
</tr>
<tr>
<td></td>
<td>May present with “dancing eyes” (opsoclonus-myoclonus)</td>
<td></td>
<td>May form “flourettes”</td>
</tr>
<tr>
<td>Neurofibromas</td>
<td>Associated with NF1</td>
<td>Dorsal spinal nerve roots</td>
<td>Hyperplasia of Schwann cells</td>
</tr>
<tr>
<td>Schwannomas</td>
<td>Tinnitus, hearing loss</td>
<td>Cerebropontine angle mass</td>
<td>Antoni A and B Verocay bodies</td>
</tr>
<tr>
<td></td>
<td>Bilateral schwannomas</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>May be associated with NF2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CNS = central nervous system; CSF = cerebrospinal fluid; DWI = diffusion-weighted imaging; EMA = epithelial membrane antigen; H&E = hematoxylin and eosin; RCT = randomized controlled trial; NF1 = neurofibromatosis 1; NF2 = neurofibromatosis 2; PNET = primitive neuroectodermal tumor.

CASE CONTINUED

Computed tomography (CT) of the brain shows a left frontal hypodensity with surrounding mass effect. This is followed by magnetic resonance imaging (MRI) of the brain, which reveals a heterogeneous mass in the left frontal lobe. The lesion is hypointense on T1-weighted imaging and hyperintense on T2-weighted imaging with extensive surrounding edema. There is associated mass effect. Post-gadolinium T1-weighted imaging reveals an irregularly shaped ring-enhancing mass with necrosis (see Figure 1 for imaging findings from a similar case). Due to the patient’s recent seizure and evidence of mass effect, intravenous levetiracetam and dexamethasone are initiated.

- What is the work-up of a patient with a possible brain tumor?

NARROWING THE DIFFERENTIAL DIAGNOSIS

A patient suspected of possibly having a brain tumor should undergo a thorough general and neurological evaluation. Often, a noncontrast head CT is the initial imaging study. It is favored due to its wide availability and short imaging time. It is helpful in the rapid diagnosis of intracranial
herniation, in identifying mass effect, and for visualization of calcifications and bony destruction. Patients with contraindication to MRI may benefit from a subsequent contrast-enhanced head CT evaluation.

An MRI of the brain with gadolinium contrast is usually the test of choice, and often follows a head CT scan. An MRI provides greater anatomic and pathologic detail than a CT scan. On MRI, tumors generally appear as a hypointense area on T1-weighted imaging with corresponding hyperintensity on T2-weighted imaging (Figure 1). The presence of enhancement on administration of gadolinium indicates the breakdown of the blood-brain barrier and suggests a high-grade neoplasm. Low- and high-grade gliomas usually show poorly defined margins, heterogeneous areas of hemorrhage and necrosis, and significant surrounding vasogenic edema. These findings are usually less prominent in low-grade lesions. Calcifications within the mass (better seen on CT) are generally suggestive of a more indolent (lower grade) neoplasm, such as an oligodendroglioma and craniopharyngioma.

Figure 1. Magnetic resonance imaging (MRI) and pathologic features of an anaplastic glioma (A–D) and glioblastoma (E–H). Axial T1-weighted images (A, E) show no definite abnormality in the case of low-grade glioma and marked hypodensity in the case of glioblastoma; axial T1-weighted post-gadolinium images (B, F) show no enhancement in the case of low-grade glioma and marked heterogeneous enhancement in the case of glioblastoma; axial fluid-attenuated inversion recovery MRI images (C, G) show T2 hyperintensity within and surrounding the tumor, more so in glioblastoma; and pathologic specimens from low-grade glioma (D) and glioblastoma (H) show characteristic features. Low-grade tumors are moderately hypercellular and composed of well-differentiated astrocytes that infiltrate into normal brain. Modest nuclear atypia is present, but mitoses, necrosis, and vascular proliferation are absent. Glioblastoma shows very high cellularity, marked nuclear atypia, vascular proliferation, many mitoses, and geographic necrosis with pseudopalisading. (Adapted with permission from Norden AD, Kesari S. Cancer neurology: Primary and metastatic brain tumors. Hospital Physician Neurology Board Review Manual. Wayne [PA]: Turner White Communications; 2006:10[Pt 3]:1–16).
With certain tumors (eg, medulloblastoma), imaging of the spine is required to exclude drop metastases. Leptomeningeal metastasis may be evident on MRI as abnormal meningeal enhancement or tumor nodules within the cerebrospinal fluid (CSF) flow pathways. CSF cytology is considered the gold standard for this diagnosis; however, lumbar puncture may be contraindicated if there is significant mass effect on imaging. A systemic evaluation should be considered to exclude metastatic cancer presenting as brain metastasis. This includes testicular, breast, and prostate exams, and imaging of the chest, abdomen and pelvis. Of these, CT of the chest has the highest yield. A lesion that is more accessible to biopsy than the CNS mass may become evident. Additional diagnostic studies, such as bone marrow biopsy, positron emission tomography (PET), or tumor markers, may be useful if brain metastasis or lymphoma is suspected. An abscess or demyelinating lesion might be distinguished based on clinical and imaging features. For most primary central nervous system neoplasms, tissue diagnosis with biopsy or resection is necessary. Occasionally, such as in the case of diffuse intrinsic brainstem gliomas, a presumptive diagnosis is made based on imaging and clinical findings, as biopsy in this area carries significant risk.

Newer imaging techniques provide additional information about a suspicious mass. Magnetic resonance spectroscopy (MRS) may demonstrate an elevated ratio of choline to creatine in tumors due to increased cell membrane turnover (Figure 2). Neuronal loss due to infiltration of tumor results in decreased levels of N-acetylaspartate (NAA). Multi-voxel technique can evaluate different regions of the tumor to determine where high-grade features are more likely to be found on biopsy; this can be helpful in surgical planning. Other MR techniques with potential utility include tractography (diffusion tensor imaging), in which illustration of the white matter tracts associated with a tumor may be helpful in surgical planning. Also, MR perfusion is an evolving technique which may help differentiate between tumor recurrence and treatment effects (eg, radiation necrosis).

- What is the initial management of a patient found to have a mass lesion?

**INITIAL MANAGEMENT**

**Seizures**

The patient’s symptoms of shaking of the right arm followed by hand weakness are suggestive
**Figure 3.** An approach to seizures in patients with brain tumors. AEDs = antiepileptic drugs; CSF = cerebrospinal fluid; EEG = electroencephalography. (Adapted with permission from Grewal J, Grewal HK, Forman AD. Seizures and epilepsy in cancer: etiologies, evaluation, and management. Curr Onc Rep 2008;10:64–72.)

of a seizure and Todd’s paralysis. An approach to management of the patient with seizures is outlined in **Figure 3.** Because the patient experienced a seizure, initiation of an antiepileptic drug (AED) for secondary prophylaxis of seizures is warranted. Although AEDs may not completely prevent all
seizures, data show that they can reduce seizure generalization.\textsuperscript{14} Traditionally, anticonvulsants such as phenytoin, phenobarbital, and valproic acid have been used as first-line agents, particularly in the acute setting. A major drawback of using these older AEDs is the relative frequency of interactions with chemotherapeutic agents that are used in the treatment of brain tumors.\textsuperscript{15,16} Enzyme-inducing AEDs such as phenytoin, phenobarbital, and carbamazepine may increase the clearance and reduce the clinical efficacy of corticosteroids and antineoplastic agents that are metabolized by the cytochrome P450 system.

Newer AEDs such as levetiracetam, lacosamide, and pregabalin have fewer adverse effects and do not have significant interactions with chemotherapeutic agents. Therefore, they are preferred over older AEDs in the brain tumor (and systemic cancer) population. Intravenous formulations of levetiracetam and lacosamide are available. In the setting of refractory seizures or status epilepticus, acute treatment with classical AEDs should be strongly considered.

Primary prophylaxis of seizures is not recommended by the American Academy of Neurology guidelines for brain tumor patients who have never had a seizure.\textsuperscript{17} Clinical trials to determine the efficacy of prophylactic anticonvulsants in this situation have not yet demonstrated a benefit that outweighs the risks.\textsuperscript{18,19} Therefore, anticonvulsants should be reserved for brain tumor patients who have demonstrated a tendency to have seizures. It should be mentioned that many of these newer anticonvulsants are not FDA-approved for use as monotherapy or treatment of status epilepticus.

Cerebral Edema

Cerebral edema in the setting of brain tumors is vasogenic, and vasogenic edema increases the ICP. Corticosteroids are the mainstay for management of cerebral edema. The most commonly used corticosteroid is dexamethasone. It has high potency, a long half-life, and minimal mineralocorticoid effect. A typical regimen consists of an initial dose of 10 mg intravenously followed by 4 mg every 6 hours; however, a lower dose may produce similar benefit.\textsuperscript{20} Once definitive therapy has been delivered and clinical improvement is seen, the dose is gradually tapered to avoid serious long-term side effects such as gastric ulcers, cataracts, osteoporosis, hyperglycemia, adrenal suppression, muscle wasting, weight gain, and Cushing’s syndrome.

**CASE CONTINUED**

The patient undergoes a CT scan of the chest, abdomen, and pelvis, which does not reveal a systemic malignancy. A neurosurgical consultation is obtained and the patient receives a subtotal resection. The pathology is consistent with glioblastoma, exhibiting a pseudopalisading pattern, microvascular proliferation, and necrosis (Figure 1). The patient is counseled regarding his diagnosis and treatment options. A plan is made to administer outpatient external-beam radiation therapy (EBRT) with concurrent chemotherapy. The radiation therapy consists of a total dose of 59.4 Gy delivered in 33 fractions of 1.8 Gy each. Oral concurrent temozolomide (TMZ) is administered daily at 75 mg/m\textsuperscript{2} for 42 consecutive doses (over 6 weeks).

- What treatment options are recommended for a patient with newly diagnosed glioblastoma?

**TREATMENT OF GLIOBLASTOMA**

Based on the results of a phase III randomized, controlled trial,\textsuperscript{21} the standard of care for a patient
with newly diagnosed glioblastoma involves maximal safe surgical resection followed by the combination of EBRT and concurrent chemotherapy with daily TMZ. The patient is then assessed clinically and by MRI approximately 3 to 4 weeks following the completion of this treatment. If the tumor does not progress, chemoradiation is followed by at least 6 cycles of adjuvant TMZ on days 1 through 5 of a 28-day cycle.

Surgery

The extent of tumor removal by surgery depends on tumor location (especially proximity to eloquent brain), general health of the patient, and the presence of mass effect. While a biopsy poses minimal risk to the patient and is well tolerated, it allows for pathological evaluation of only a small portion of the tumor. The pathological grade may change nearly half the time if resection is performed after biopsy.22 Class I data do not exist regarding the issue of whether extensive surgical debulking provides a survival benefit. One small randomized study23 did find a small but statistically significant benefit of craniotomy and resection over biopsy alone. A number of larger retrospective studies do suggest a survival benefit for initial,24-26 recurrent,27 and multiple28 resections for glioblastoma. At the time of initial resection, the data suggest a possible survival benefit for patients with an extent of resection of 78% or greater.26 In one study, the morbidity from gross total resection was not significantly increased over biopsy or subtotal resection, and the risk at the time of initial surgery did not differ from the risk at reoperation.29 Carmustine (BCNU)-impregnated wafers can be placed into a tumor resection cavity at the time of operation. They are FDA-approved for newly diagnosed malignant glioma, although in the associated clinical trial, statistical significance was not achieved in the glioblastoma subgroup.30

A prospective, randomized, phase III clinical trial utilizing 5-aminolevulinic acid for intraoperative visualization of tumor under fluoroscopic light was completed.31 Improved progression-free survival was seen in the group in which this technique was utilized. Preoperative imaging (such as functional MRI), intraoperative MRI, and other techniques (such as awake surgery) may help safely increase the extent of resection.32,33 A list of primary brain tumors potentially curable by surgical resection is outlined in Table 4.

Radiation Therapy

EBRT is the most important type of radiation therapy used in treating infiltrating tumors such as glioblastoma.34 While whole brain radiation therapy (WBRT) has been used in the past, data show that a more focused approach spares some of the toxicity of WBRT without a loss of efficacy.35,36 A typical dose would be approximately 60 Gy to the tumor evident on imaging with a 2-cm margin. Clear survival advantages have been demonstrated in several studies at 50 to 60 Gy, but above 60 Gy there is a marked increase in toxicity.37,38 It is unknown whether the benefit observed with TMZ

<table>
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<th>Table 4. Tumors Treated by Surgical Resection</th>
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<tr>
<td>Pilocytic astrocytoma</td>
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<td>Pleomorphic xanthoastrocytoma</td>
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<td>Subependymal giant cell astrocytoma</td>
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<td>Subependymoma</td>
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<td>Myxopapillary ependymoma</td>
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<td>Paraganglioma of the filum terminale</td>
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<td>Dysplastic gangliocytoma of the cerebellum</td>
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<td>Dysembryoplastic neuroepithelial tumor</td>
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<td>Ganglioglioma</td>
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<td>Central neurocytoma</td>
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<td>Meningioma</td>
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<td>Hemangioblastoma</td>
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in glioblastoma is predominantly due to a radiosensitization effect, from the use of an effective alkylating agent, or both.\(^{39}\)

**Chemotherapy**

Temozolomide is a member of the class of drugs known as imidotetrazines. It was developed as a less toxic alternative to precursor compounds and exhibited excellent penetration into the central nervous system.\(^{40,41}\) In 1999, it was first approved in the United States for recurrent anaplastic astrocytoma.\(^{42}\) Following the positive results of an international phase III trial for glioblastoma,\(^{21}\) concurrent TMZ and radiation therapy has become the standard of care for patients with newly diagnosed glioblastoma. This multicenter, randomized, controlled trial compared the efficacy and safety of TMZ administered concurrently and following radiation therapy (RT) with RT alone in patients with newly diagnosed glioblastoma. TMZ combined with RT was more effective than RT alone, and the combined treatment was well tolerated. Median overall survival time (OS) was 14.6 months in the TMZ plus RT group as compared to 12.1 months in the RT alone group. Based on the results of this study, the FDA approved TMZ in 2005 for the treatment of adult patients with newly diagnosed glioblastoma. TMZ has 100% oral bioavailability and readily crosses the blood-brain barrier. It acts by methylating the O\(^6\) position of guanine in DNA. Mispairing of thymidine with the O\(^6\)-methylguanine results in DNA strand breakage and cell death.

TMZ is given orally at a daily dose of 75 mg/m\(^2\) for 6 weeks along with radiation therapy. Patients completing chemoradiation without disease progression may proceed to receive adjuvant TMZ at 150 to 200 mg/m\(^2\) on days 1 through 5 of a 28-day cycle. Although the trial limited adjuvant TMZ to 6 cycles,\(^{21}\) in clinical practice patients have been treated longer if there is no disease progression. Patients may receive Pneumocystis carinii prophylaxis during the concurrent phase of treatment. Adverse effects include myelosuppression, nausea, vomiting, anorexia, constipation, and fatigue. Hepatitis B reactivation has also been reported with the use of TMZ.\(^{43,44}\)

Bevacizumab is a novel humanized monoclonal antibody targeting vascular endothelial growth factor (VEGF). This pathway is important for tumor angiogenesis. The use of bevacizumab for newly diagnosed disease is being evaluated in clinical trials and therefore is not considered standard of care at present.

**What are the most important molecular markers in brain tumors?**

**MOLECULAR MARKERS IN BRAIN TUMORS**

Identifying subsets of patients who may be more likely to respond to a particular therapy is an important focus of brain tumor research. This is commonly done in the case of many other malignancies, such as testing for estrogen, progesterone, and HER2/neu receptors in breast cancer.

Anaplastic oligodendrogliomas have been reported to have a favorable response to chemotherapy (and radiation) if they are associated with 1p and 19q chromosomal co-deletions.\(^{45}\) Two prospective, randomized, controlled trials evaluated the potential benefit of adding PCV chemotherapy (procarbazine, lomustine, vincristine) to radiation therapy alone as initial therapy.\(^{46,47}\) The long-term analysis for both studies confirmed the importance of 1p and 19q co-deletions as favorable independent prognostic factors.\(^{48,49}\)

Patients with glioblastoma associated with O\(^6\)-methylguanine-DNA-methyltransferase (MGMT) promoter methylation experienced greater ben-
efit from TMZ.\textsuperscript{50} The MGMT repair enzyme is one mechanism by which tumor cells repair DNA damage from alkylating agents such as TMZ. MGMT promoter methylation suggests decreased availability of this enzyme and alkylating chemotherapy may be more likely to lead to cell death.

Overexpression, amplification, or mutations of the epidermal growth factor receptor (EGFR) are common in glioblastoma.\textsuperscript{51} Several EGFR inhibitors have been approved for other malignancies, but unfortunately clinical trials have failed to demonstrate a benefit in malignant glioma.\textsuperscript{52} One interesting mutation results in a constitutively active receptor, the EGFR\textsubscript{vIII}. The co-expression of EGFR\textsubscript{vIII} and phosphatase and tensin homolog (PTEN) seems to predict sensitivity of recurrent GBM to EGFR inhibitors.\textsuperscript{53} While found in other cancers, EGFR\textsubscript{vIII} is not found in normal human tissue. The unique protein structure is the target of a cancer vaccine in clinical trials for glioblastoma.\textsuperscript{54} Other novel experimental therapies include small-molecule targeted agents, oncolytic viruses,\textsuperscript{55,56} and dendritic-cell immunotherapies.\textsuperscript{57}

Discovered in 2008, mutations of the isocitrate dehydrogenase glycolytic enzyme (IDH1 and IDH2) are commonly found in low-grade and secondary high-grade gliomas.\textsuperscript{58} These mutations appear to occur early in the development of gliomas and change the function of IDH to produce 2-hydroxyglutarate, a potential oncometabolite. When compared with wild-type IDH, the presence of IDH1 and IDH2 mutations is associated with improved prognosis in glioma.

Significant work is being performed using microarray technology and sophisticated analysis to identify gene expression patterns that may have prognostic significance.\textsuperscript{59,60} One such analysis stratified tumors into 3 groups: proneural, mesenchymal, and proliferative,\textsuperscript{59} with tumors exhibiting the proneural signature correlated with improved prognosis. It was noted that at recurrence, tumors tended to exhibit more of the mesenchymal pattern, which was correlated with a poorer prognosis.

**CASE CONTINUED**

Four weeks after the patient completed concurrent chemoradiation, an MRI of the brain was obtained. This revealed increased contrast enhancement and surrounding edema. The patient was clinically unchanged. Surgical re-operation was deemed risky. The patient was continued on adjuvant TMZ with a shorter interval of MRI tumor surveillance (4-week intervals). By the third scan following chemoradiation, there was marked reduction in the size of the contrast-enhancing lesion, measuring approximately 50% of the pre-radiation size. The early MRI changes were attributed to a transient post-treatment phenomenon known as pseudoprogression. MRI surveillance was changed to 8-week intervals (after every 2 cycles of TMZ).

- **What is the significance of transient radiological worsening after concurrent radiation and chemotherapy?**

**PSEUDOPROGRESSION**

It is becoming increasingly evident that patients may experience transient radiological “progression” early after the completion of chemoradiation with TMZ. This phenomenon has been labeled pseudoprogression.\textsuperscript{61-63} Patients may remain clinically stable in many of these cases. Up to half of all radiologic progression following chemoradiation may in fact fall under this category. The most significant consideration in a patient with possible pseudoprogression is whether to continue adjuvant TMZ, as a proportion of such patients have
been reported to experience an eventual response to therapy. Early radiation necrosis was found when these patients underwent re-operation. Close imaging surveillance is warranted if a patient with suspected pseudoprogression is continued on adjuvant TMZ. Patients who do not exhibit an improvement on follow-up imaging may have true progression and should be switched to alternate therapy. Pseudoprogression appears to be more common in glioblastoma patients expressing MGMT promoter methylation.

- What are the neurologic complications of radiation therapy?

Toxicity from RT can be divided into 3 types based on the amount of time that has elapsed since the completion of RT. Acute toxicity manifests as encephalopathy within days to weeks of therapy. The risk increases with higher dose, larger volume of brain irradiated, and poorer baseline cognitive status. The pathogenesis may involve breakdown of the blood-brain barrier, leading to cerebral edema. Corticosteroids may be used to prevent and manage acute toxicity. Early delayed toxicity usually occurs within a few weeks of treatment and is usually reversible. It may present as somnolence and neurologic deterioration. It usually resolves spontaneously and may be managed with corticosteroids. Late radiation injury occurs months to years following therapy and is often irreversible. Radiation necrosis may be difficult to distinguish from tumor progression on imaging and can change similarly over time. If corticosteroids fail to control the necrotic process, surgical resection may be warranted. Bevacizumab has been reported to be beneficial for radiation necrosis in a prospective randomized clinical trial. Cognitive impairment is one of the most frequent complications in long-term survivors (more problematic in patients with low-grade tumors due to longer survival), and can range in severity. Deficits may involve attention, learning, memory, processing speed, ability to multitask, and word-finding. Psychostimulants (eg, methylphenidate) in conjunction with serial neuropsychological evaluations have been used to help patients remain functionally active.

CASE CONTINUED

The patient remains clinically stable after 5 cycles of TMZ. Prior to completing his sixth adjuvant cycle, he experiences the sudden onset of shortness of breath, tachycardia, and chest pain. Examination reveals a swollen and tender right calf. The patient is given 100% oxygen by mask and receives an emergent spiral CT arteriogram of the chest, which confirms extensive bilateral pulmonary embolism. A lower extremity Doppler ultrasound reveals deep vein thrombosis. The patient is admitted to the hospital and is initiated on low-molecular-weight heparin (LMWH). An inferior vena cava filter is not placed. Over the next 4 days, his symptoms improve and he is discharged home on the same anticoagulant. His wife is trained to subcutaneously administer the LMWH daily at home.

- What is the incidence and management of venous thromboembolism (VTE) in patients with brain tumors?

Thromboembolic complications are very common, occurring in 30% to 60% of malignant glioma patients. VTE is a frequent complication following craniotomy for brain tumors. This increased risk is shared with other cancers, in particular, multiple myeloma. However, the pathogenesis of VTE in glioblastoma is not completely understood. In
addition to typical risk factors such as immobility, it is possible that circulating factors produced by the tumor may be contributory, as these patients have altered hematologic profiles.\(^{72,73}\)

Surveillance of thromboembolic complications is important. Intermittent pneumatic compression of the calf reduces the incidence of VTE during the perioperative period. A randomized, prospective, double-blind clinical trial showed that a multimodality approach with enoxaparin or unfractionated heparin in combination with graduated compression stockings, intermittent pneumatic compression, and surveillance venous ultrasonography of the legs was safe and effective in the primary prevention of VTE.\(^{74}\) Patients should be counseled regarding the risk of VTE and the importance of notifying their physician of appropriate symptoms.

LMWH may be the therapy of choice for secondary prevention of VTE. A randomized, controlled trial of LMWH versus warfarin reported a survival advantage for LMWH in patients with cancer.\(^{75}\) Inferior vena cava interruption by a filter is indicated when oral anticoagulation is contraindicated or ineffective. Although filters are convenient for patients at a high risk for bleeding, thrombosis may occur at or above the filter site and lead to pulmonary embolism or complete obstruction of venous return below the placement site.

**CASE CONTINUED**

The patient obtains a brain MRI after his sixth cycle of adjuvant TMZ and is found to have tumor progression. On examination, his aphasia appears to be worse. He is still ambulatory and is able to perform his own activities of daily living. He is offered participation in a clinical trial for recurrent glioblastoma and receives an experimental therapy along with bevacizumab. He continues to have neurologic deterioration and has radiologic progression. He does not wish to pursue additional therapy and is referred to hospice. He dies shortly thereafter, 10 months after his diagnosis.

- **What is the management of tumor recurrence?**

The majority of glioblastoma recurrences occur within 2 cm of the primary tumor site. Treatment options for recurrent glioblastoma include re-operation, additional radiation, and additional chemotherapy. Referral for a clinical trial should also be a consideration in patients with adequate functional status. Surgical re-resection offers the opportunity to remove a significant tumor burden in selected patients. Carmustine (BCNU)-impregnated wafers may be placed into the surgical cavity and have shown benefit in recurrent high-grade glioma.\(^{76}\)

Additional radiation may be delivered in several ways. Additional EBRT may be delivered but may cause significant toxicity from overlapping fields unless several years have elapsed from the initial radiation.\(^{77}\) Stereotactic radiosurgery (SRS) may be considered as a salvage option for a subgroup of patients with smaller lesions of recurrent glioblastoma, and is well tolerated.\(^{78}\) Other radiotherapy options include brachytherapy with an implanted (GliaSite) balloon system.\(^{79}\)

Standard recurrent high-grade glioma chemotherapy options include nitrosoureas (carbmustine, lomustine), irinotecan, carboplatin, cisplatin, and etoposide, often in combination. Bevacizumab is a humanized monoclonal antibody targeting VEGF. When compared with other agents, significant response rates have been reported both as monotherapy and in combination with other cytotoxic agents.\(^{80}\) Based on this data, bevacizumab has received FDA approval as monotherapy for recurrent glioblastoma. However, the use of beva-
Cizumab and its effect upon neuroimaging has led to the development of new imaging criteria to assess response to treatment, particularly in the setting of anti-angiogenic agents. Recently, a device utilizing alternating electrical fields (NovoTTF, Novocure, Portsmouth, NH) worn on the head was approved by the FDA as monotherapy for recurrent glioblastoma.

- What is the prognosis of glioblastoma?

The likelihood of a patient becoming a 2-year survivor increased from 10% with RT alone to 26% with the combination of radiation and TMZ. In subsequent long-term analysis, the likelihood of becoming a 5-year survivor after initial treatment with radiation and concurrent TMZ was 9.8% versus 1.9% with radiation alone. Validated prognostic factors which influence survival in glioblastoma include age, performance status, extent of resection, and neurologic function. Other factors which might affect prognosis include mental status and tumor size. The role of molecular markers beyond MGMT and IDH1 in stratifying patients into prognostic categories is an important subject of research.

CONCLUSION

Glioblastoma represents one of the most aggressive central nervous system neoplasms in adults. Unfortunately, it is also the most common malignant primary central nervous system tumor. The advent of TMZ has increased survival and solidified the role of chemotherapy in treating this neoplasm. However, even with current standards of care, more research is needed to stratify patients into prognostic categories and guide therapy. Novel therapies are on the horizon for this and other cancers; patients and their caregivers should remain hopeful that research will lead to more effective and less toxic therapies in the near future.

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