

Low grade and high grade gliomas: contemporary management

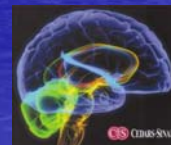
Ray M Chu, MD, Neurosurgeon
Anne Luptrawan MSN, FNP

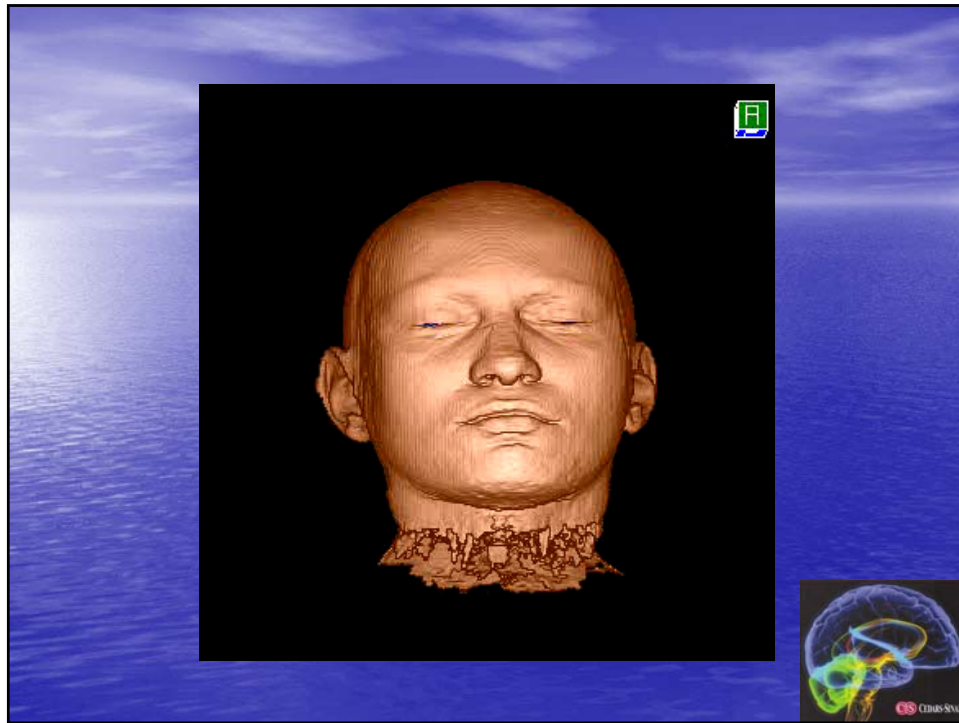
Maxine Dunitz Neurosurgical Institute
Department of Neurosurgery
Cedars Sinai Medical Center



Overview

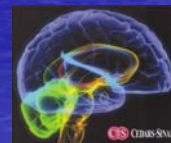
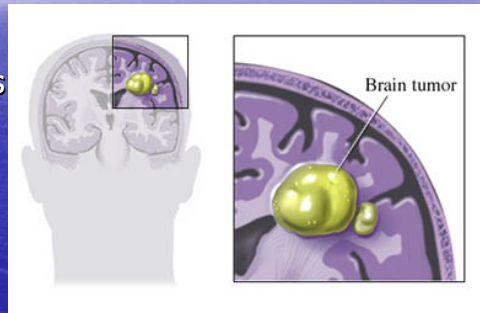
- Definitions
- Epidemiology
- Classification of brain tumors
- Diagnosis
- Treatment





Introduction Brain Tumors

- **Brain tumors**
 - Abnormal mass of cells that grow uncontrollably in the brain
 - Can grow slowly or quickly
 - Can invade critical parts of the brain
 - Can cause life-threatening damage



Introduction

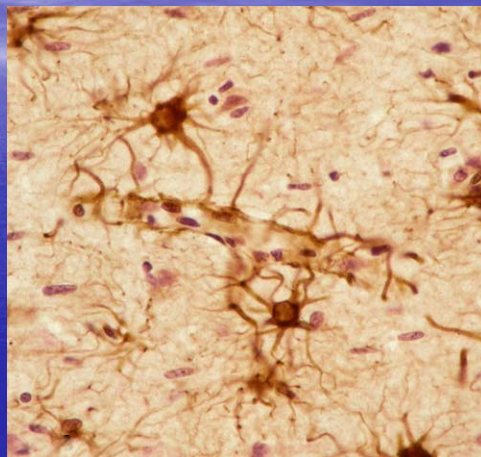
- Two types of brain tumors: *Primary and Metastatic*
 - Primary brain tumors
 - Tumors start in the brain
 - Most commonly arise from the brain's support cells, aka glial cells
 - Astrocytes - astrocytomas
 - Oligodendrocytes - oligodendrogliomas
 - Ependymal cells - ependymomas
 - Some tumors, more commonly seen in children, arise from primitive neuroectodermal cells
 - Primitive neuroectodermal cell tumors (PNETs)



Cells of the Brain

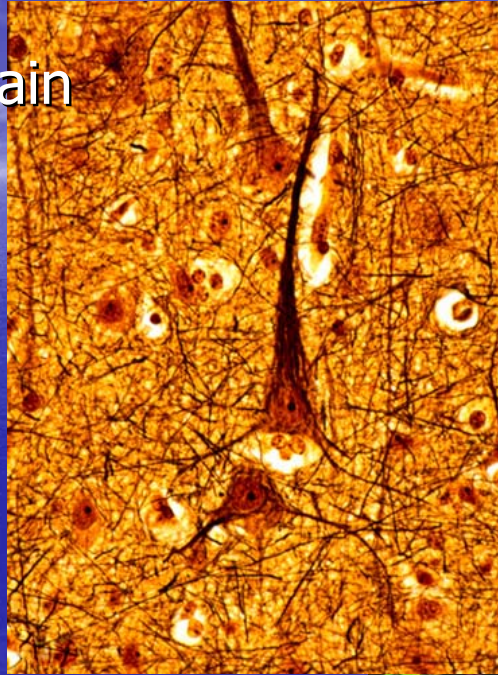
- Astrocytes
- Neurons
- Oligodendrocytes

- Ependymal cells
- Choroid plexus
- Pineal cells
- Pituitary gland
- Schwann cells
- Lymphocytes



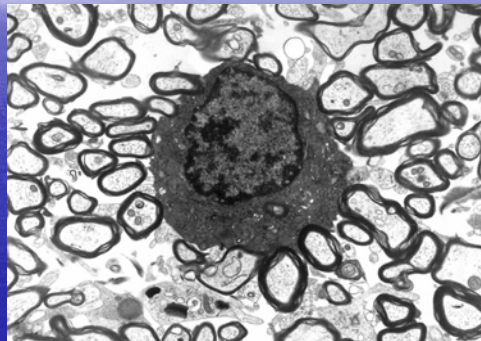
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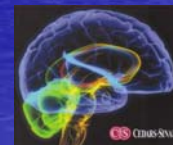
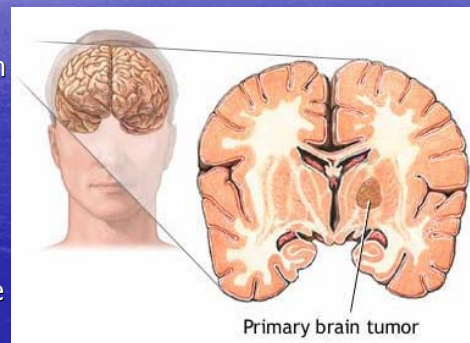
Introduction

- **Metastatic brain tumors**
 - By definition, malignant
 - Formed by cancer cells that originate elsewhere in the body then travel to the brain, usually by hematogenous spread
 - Common cancers that metastasize to the brain:
 - lung, breast, colon, and melanoma

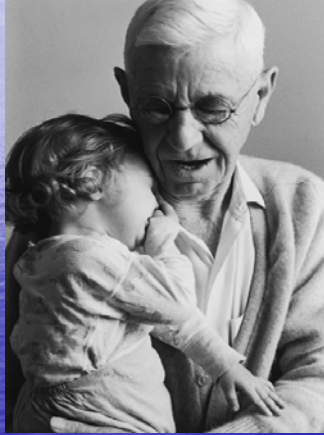


Incidence of Brain Tumors

- Brain tumors account for 2% of all cancers.
- Incidence rate of primary brain tumors
 - 14 per 100,000 persons (malignant and benign)
- ~40,000 people are diagnosed with a new primary brain tumor each year ^(NIH)
- ~190,000 people in the US are diagnosed with a metastatic brain tumor each year ^(NBTf)



Incidence of Brain Tumors



- Primary brain tumors occur in all ages
 - Statistically more frequent in two age groups
 - Children under age 15
 - Older adults
- Incidence rate of primary brain tumors per year (CBTRUS)
 - 15.1 per 100,000 for females
 - 14.5 per 100,000 for males



Figure 5. Distribution of All Primary Brain and CNS Tumors by Histology (N=158,088)

CBTRUS Statistical Report: NPCR and SEER Data from 2004-2006

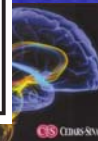
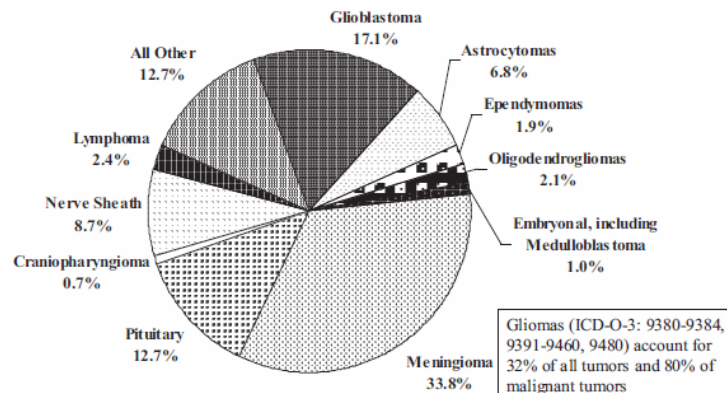
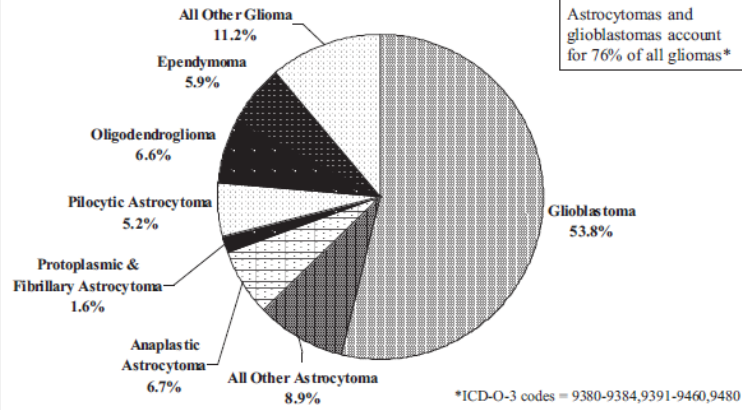


Figure 7. Distribution of All Primary Brain and CNS Gliomas* by Histology Subtypes (N=50,240)

CBTRUS Statistical Report: NPCR and SEER Data from 2004-2006



Possible Causes of Brain Tumors and Risk Factors - Environmental



Possible Causes of Brain Tumors and Risk Factors- Environmental

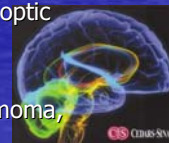
- Consistent Environmental Factors:
 - Exposure to ionizing radiation (x-ray and gamma rays) has consistently been shown in studies to increase the risk for developing brain tumors
- Inconsistent:
 - Occupational Exposure
 - Electromagnetic fields (EMF)
 - Pesticides, herbicides, fungicides
 - Working in an Oil refinery
 - Working in vinyl chloride, petrochemical, and rubber industries
 - History of head trauma
 - Consumption of nitrites
 - Viruses and common infections
 - Intake of Nitrosamines
 - Cigarettes
 - Alcohol



Possible Causes-Genetic Syndromes

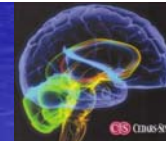
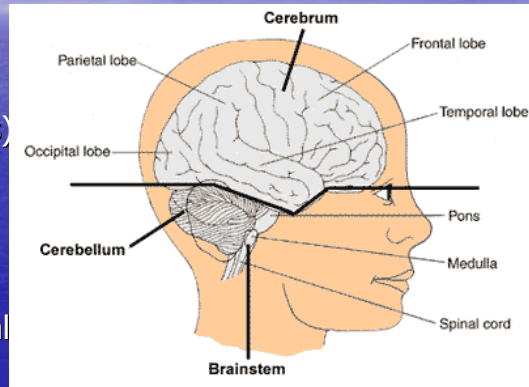


- Approximately 1-5% of brain tumors are due to genetic syndromes that confer an increased risk of tumors of the CNS.
 - Mutations in a specific gene is passed from one generation to the next:
 - Neurofibromatosis 1 (NF1 gene) – Glioma, meningiomas
 - Neurofibromatosis 2 (NF2 gene) – Acoustic neuroma, optic neuroma, meningioma
 - Gorlin syndrome (PTCH gene) – Medulloblastoma
 - Tuberous sclerosis (TSC1 and TSC2 genes) – Ependymoma, astrocytoma, ganglioglioma



Location of Tumors

- 70% of all brain tumors occur **supratentorially** (within the cerebral hemisphere or coverings)
- 70% of childhood brain tumors are **infratentorial** (e.g. cerebellum, brainstem) and are neuroectodermal in origin



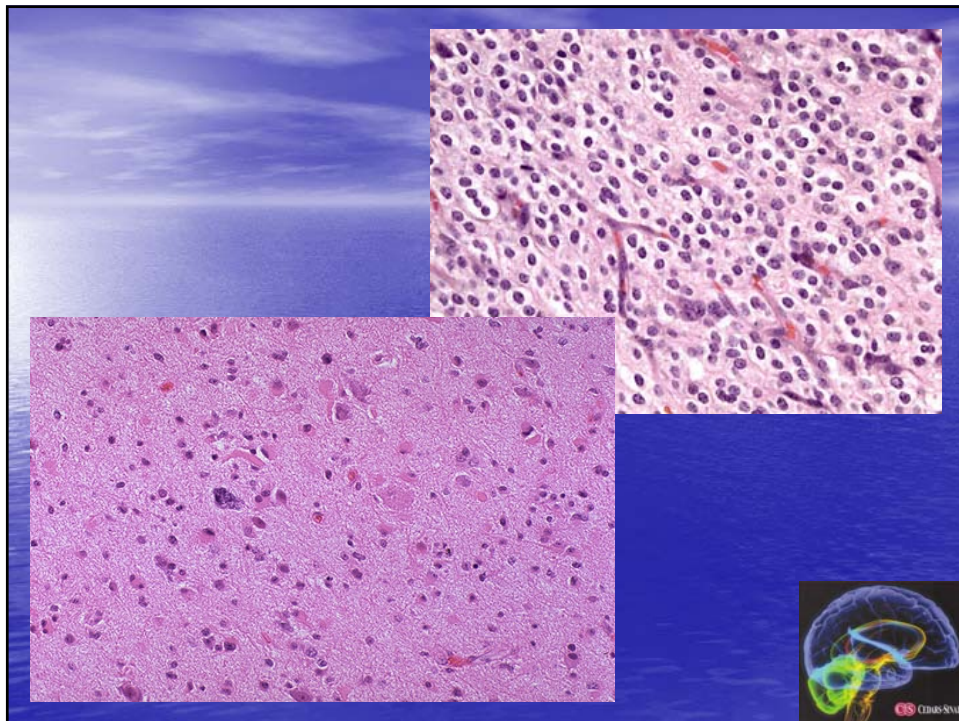
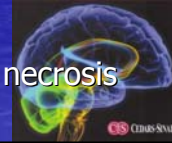
Tumor Grading

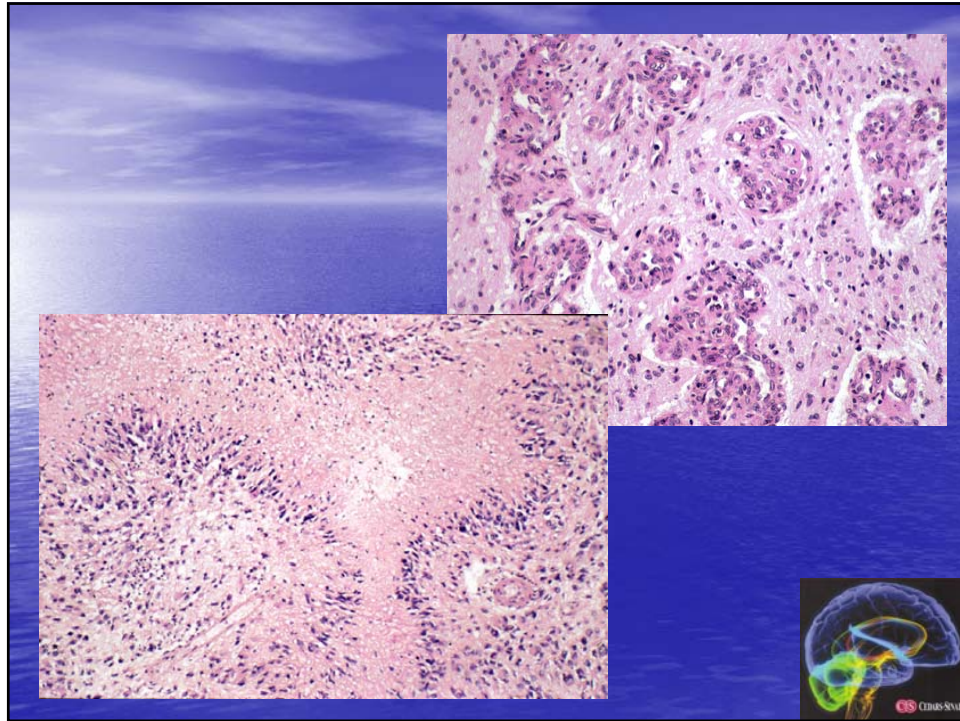
- | | |
|---|--|
| <ul style="list-style-type: none">• Low Grade• Few dividing cells (mitoses)• May have bizarre nuclei• No vascular proliferation• No necrosis | <ul style="list-style-type: none">• High Grade• Many dividing cells (mitoses)• Bizarre nuclei• Vascular proliferation• Necrosis |
|---|--|



Grading Scheme

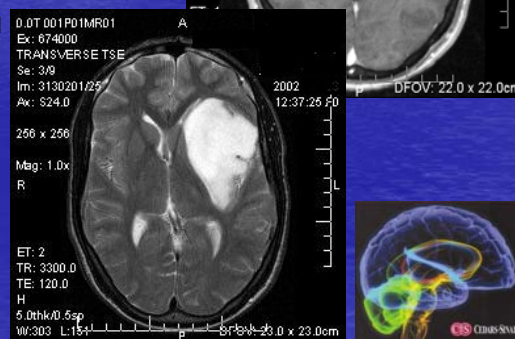
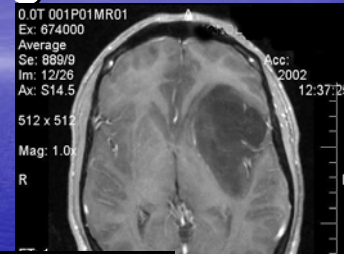
- Grade I
 - Well-circumscribed
 - Rosenthal fibers, eosinophilic granular bodies, calcification
- Grade II
 - Infiltrating, bizarre nuclei
 - Can progress to malignant
- Grade III (anaplastic astrocytoma, AA)
 - Mitoses, bizarre nuclei, vascular proliferation
 - Increasing DNA abnormalities
- Grade IV (glioblastoma, GBM)
 - Mitoses, bizarre nuclei, vascular proliferation, necrosis





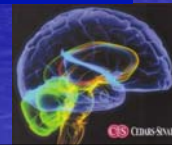
Common Brain Tumors – *Astrocytomas - Imaging*

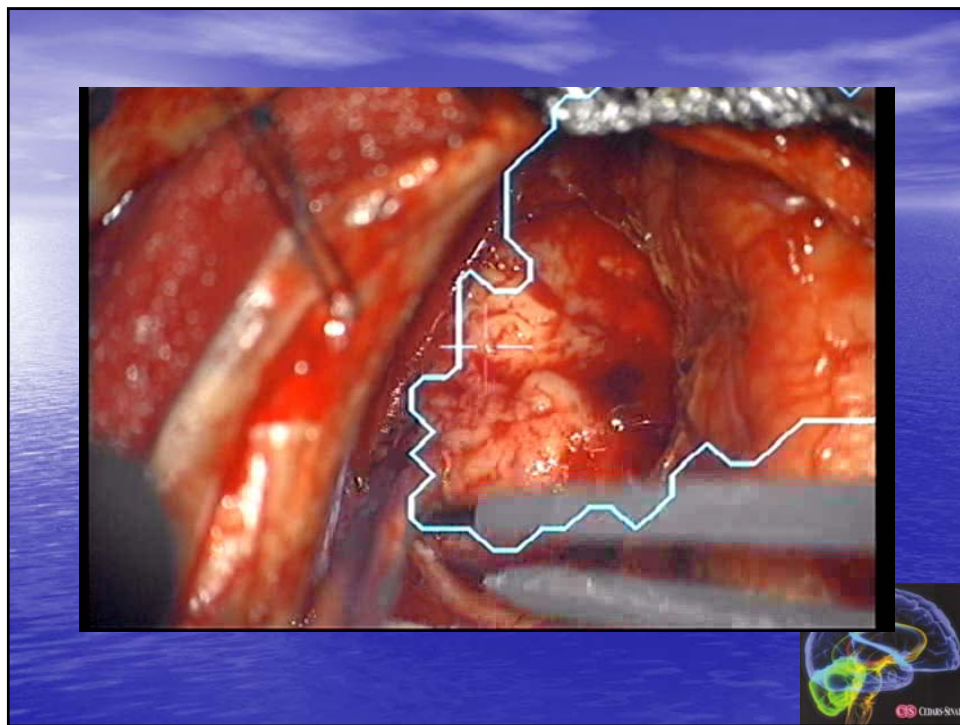
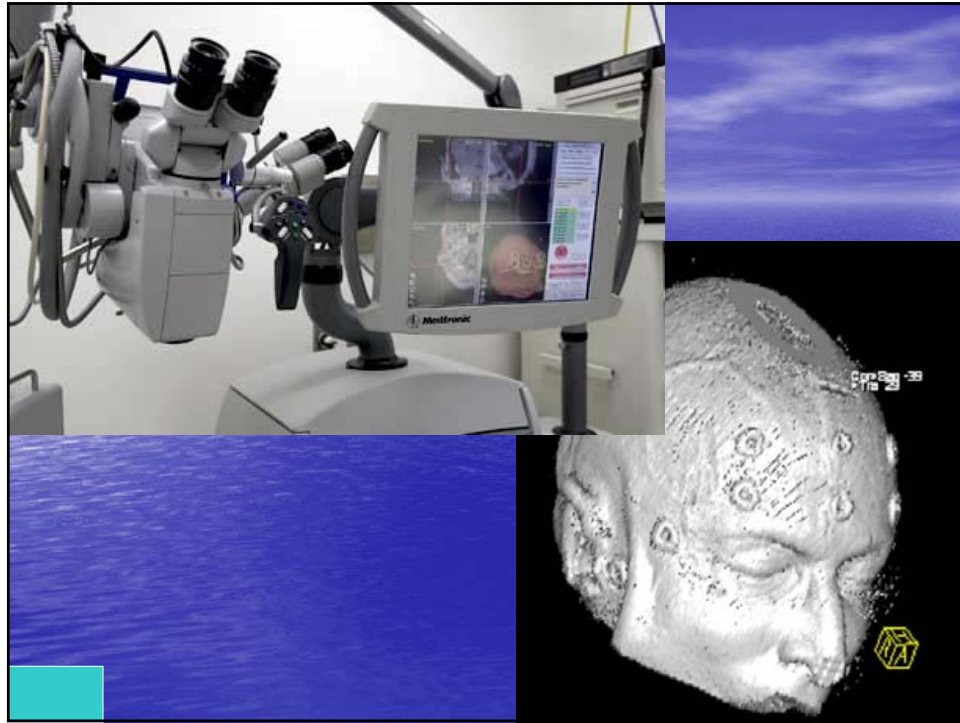
- Low grade astrocytoma grade I/grade II
 - Little, or no enhancement
 - Pilocytic astrocytomas –
 - Contrast enhancing often cystic with mural nodule
 - Little, if any edema
 - Little, or no mass effect

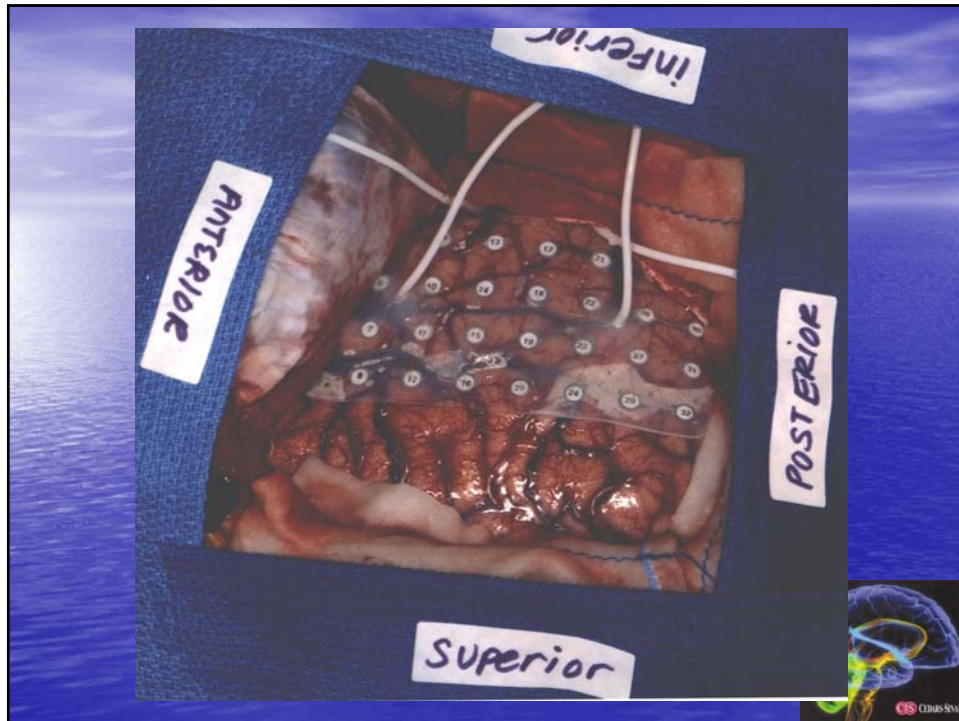


Low Grade Gliomas

- Grade I and Grade II
 - Surgery
 - Complete surgical resection if possible
 - At least biopsy or partial resection is recommended in almost all cases to determine pathology

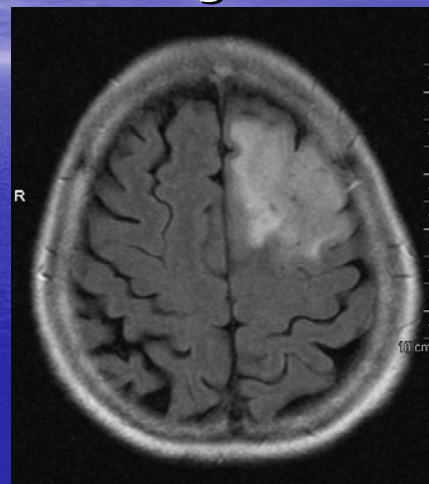






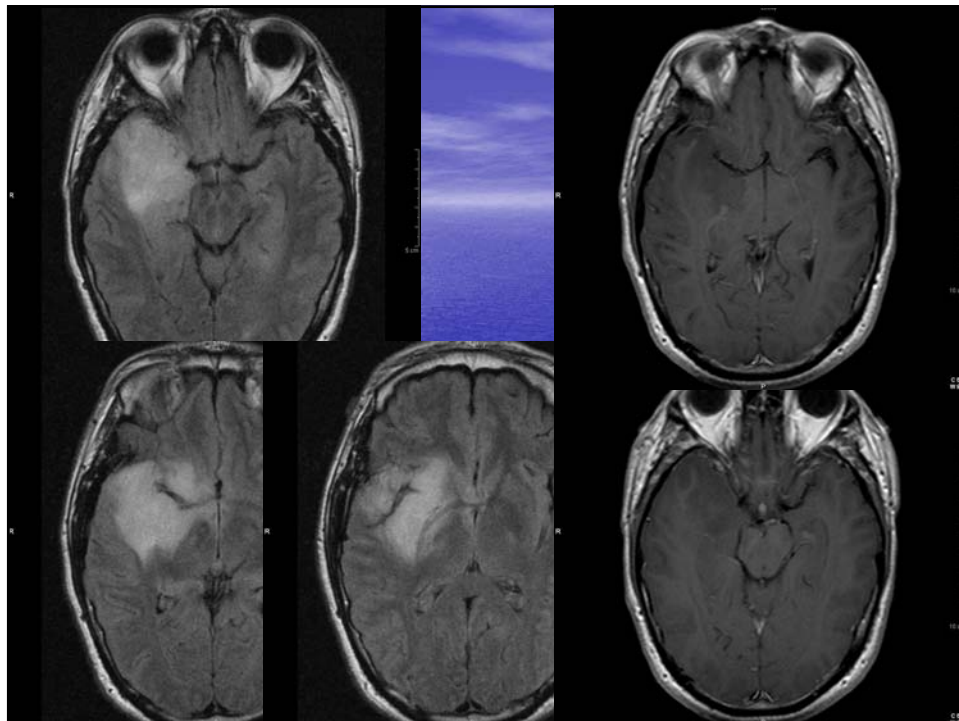
Surgical decision-making

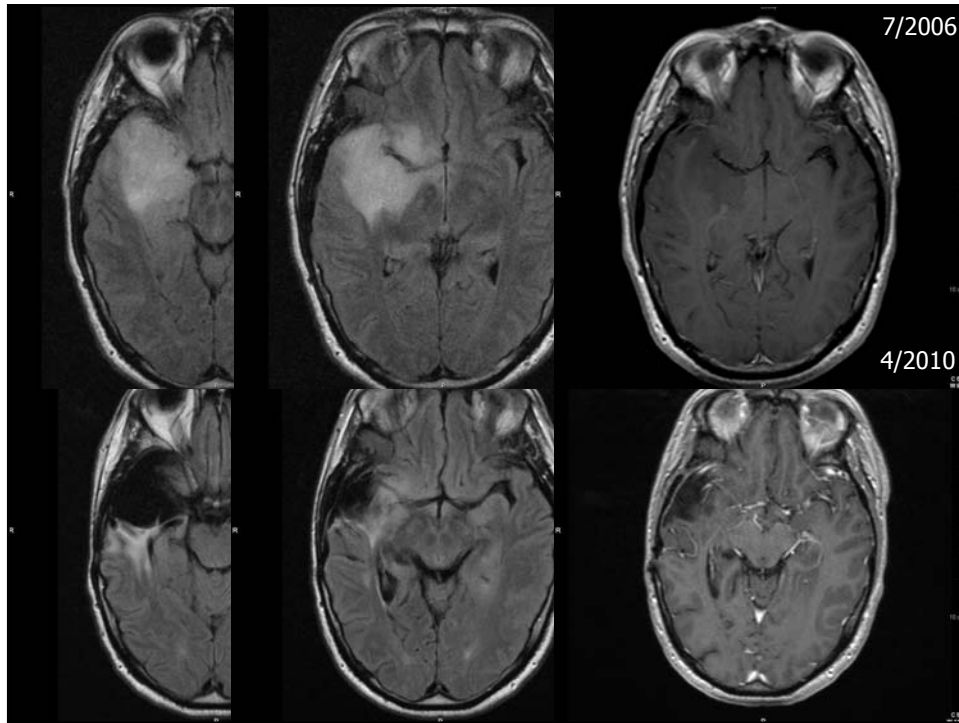
- If tumor is localized
- If no major medical problems which make surgery risky
- Eloquence
 - Motor
 - Language
 - Vision
- Deep vs superficial



Low Grade Glioma Treatment

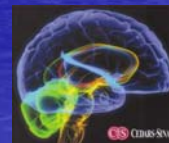
- Grade I and Grade II
 - Surgical resection
 - Radiation Therapy
 - ?Fractionated XRT to residual tumor postop
 - Chemotherapy
 - Usually with tumor progression or if significant residual tumor/ biopsy only
 - Often Temodar





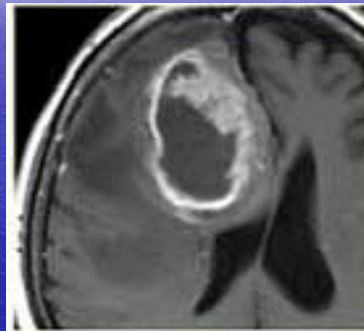
Common Brain Tumors – *Astrocytomas*

- Malignant Astrocytomas
 - Constitute over 40% of all primary intracranial tumors
 - Widely infiltrate adjacent brain
 - Growth is rapid
- Anaplastic astrocytoma (Grade III)
- Glioblastoma Multiforme (Grade IV)

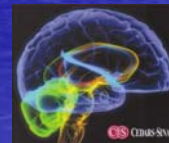


Imaging

- Anaplastic astrocytoma grade III/GBM grade IV
 - Complex enhancement on contrast imaging
 - Areas of hemorrhage
 - Mass effect
 - Irregular ring enhancement with hypointense center represents necrosis
 - GBM
 - Cerebral edema

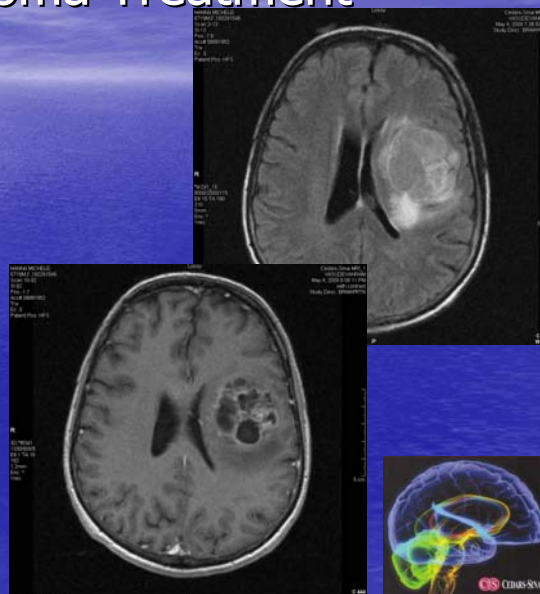


GBM



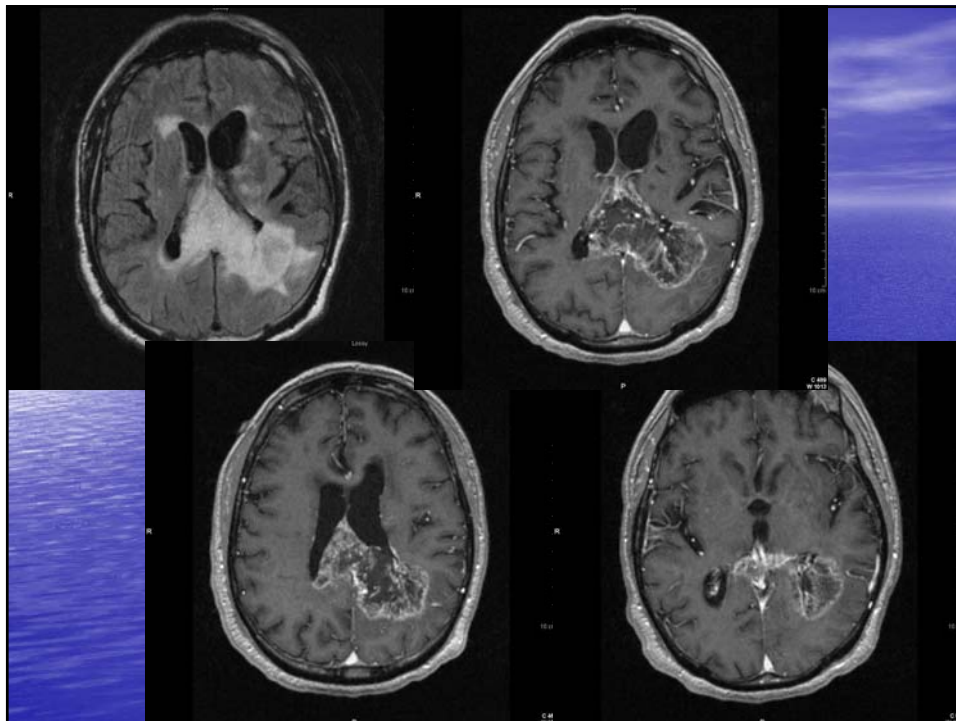
High Grade Glioma Treatment

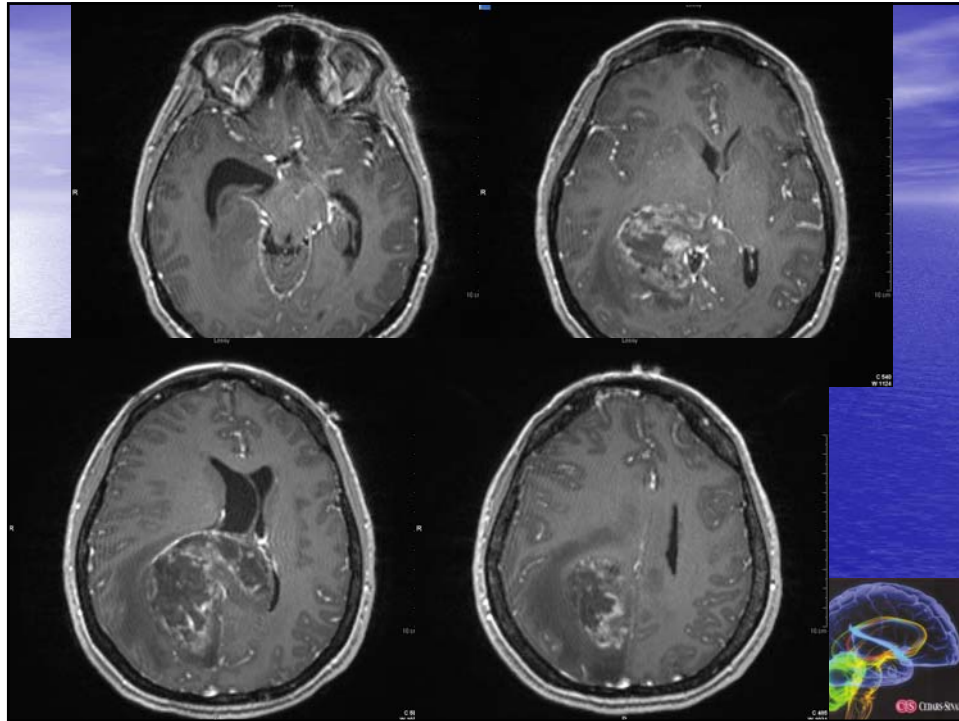
- Depends on a number of factors:
 - Site of lesion
 - Degree of malignancy
 - +/- Elevated ICP
 - Degree of disability and effect of steroid therapy
 - Suspected nature of tumor on imaging
 - Patient's age
 - Patient's wishes



Principles of Medical Management for Brain Tumors

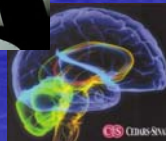
- **Surgery**
 - Craniotomy for tumor resection
 - To reduce mass effect/decrease tumor burden
 - Diagnostic tissue sampling
 - Stereotactic biopsy
 - Tissue sampling to make a diagnosis
 - When removal of tumor unsafe
 - Requires head frame or frameless navigation
 - Burr hole





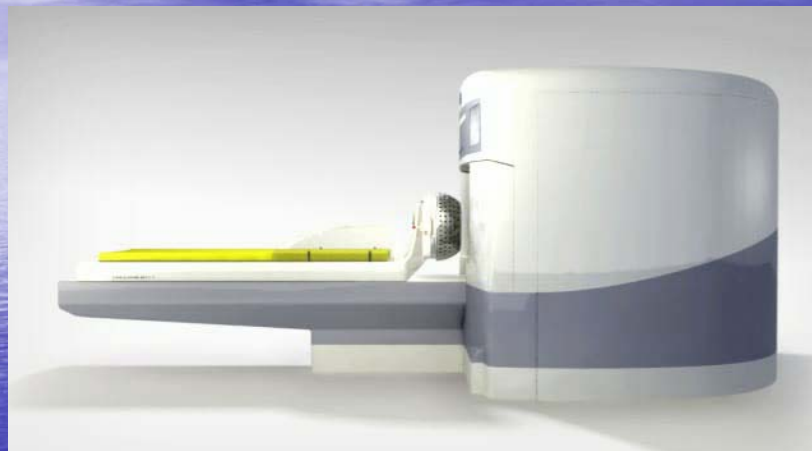
Malignant Glioma Treatment

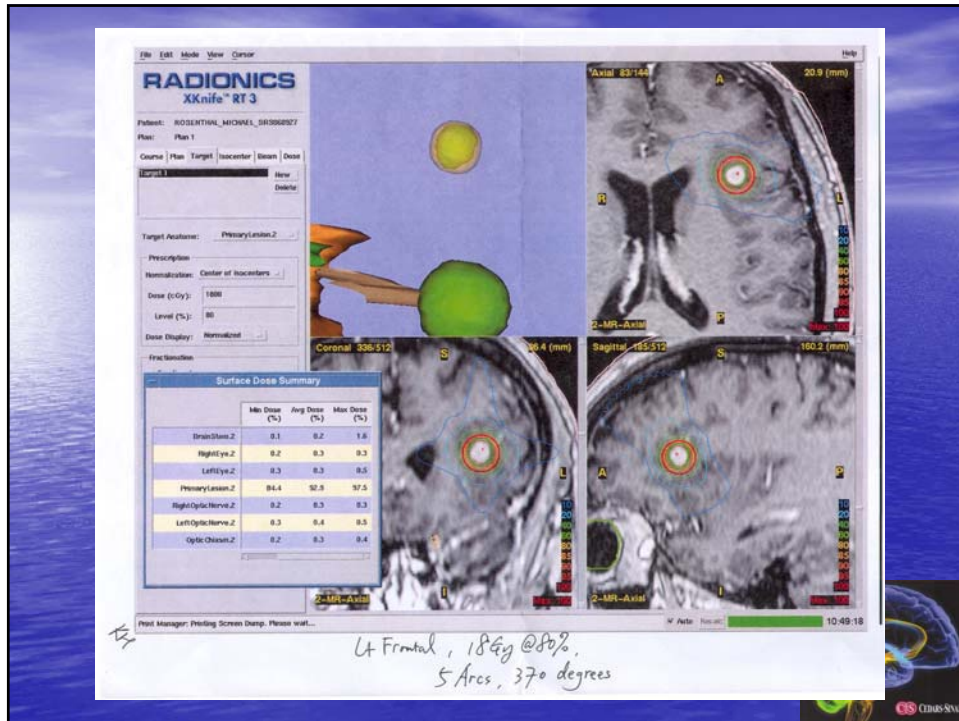
- Grade III and Grade IV
- Surgical resection vs biopsy
- Followed by external beam radiation (EBRT)
 - 40 Gy whole brain + 15-20 Gy to tumor bed =60 Gy
- GBM- Median survival of
 - One month w/o treatment
 - 12-14 mos w/ surgery, xrt, chemo



Principles of Medical Management for Brain Tumors

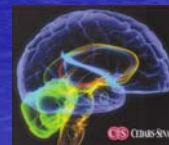
- **Radiation therapy**
 - (WBRT)
 - Focal radiation
 - SRS (stereotactic radiosurgery)
 - Focused radiation as if to replace surgery
 - X-knife – linear accelerator
 - Gamma Knife – cobalt 60
 - (Proton beam)
- **(Brachytherapy)**
 - Implantation of radioactive seeds
 - 125-Iodine
 - Gliasite





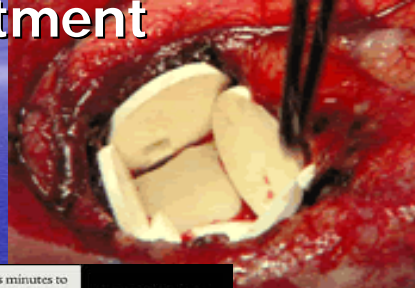
Common Brain Tumors – *Astrocytoma* - Treatment

- Chemotherapy
 - Alkylating agent
 - Temozolomide (Temodar)
 - FDA approved for treatment of initial relapse of AA and progression
 - Used (off label) for newly dx'd GBM and AA
 - Carmustine (BCNU)
 - Cisplatin (Cisplatin)



Common Brain Tumors – *Astrocytoma* - Treatment

- Gliadel wafers
 - Impregnated with BCNU
 - Up to 8 wafers at time of SX.
 - Drug released over 6 weeks
 - 113 x the concentration of BCNU than IV
 - Lg series from Mass Gen-resection + TMZ
 - Median survival 20.6 mos w/ Gliadel vs 14.7 mos (but diffuse dz, subtotal resection)



It adds minutes to your surgery.

It may add months to your patient's life.

GLIADEL WAFER
Impregnated with BCNU

CS CDUS-SNU

Common Brain Tumors – *Astrocytoma* - Survival

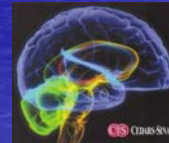
- Approximate survival for astrocytomas after receiving "optimal treatment":

WHO Grade	Median Survival
I	?
II	7-8 years?
III	≈ 3-4 years
IV	≈ 14 months



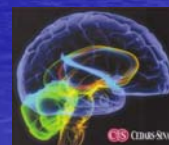
Prognostic Factors

- **Prognosis is based on:**
 - Type of tumor
 - Tumor grade
 - Location
 - Spread (if any)
 - Age of the patient
 - How long the patient had symptoms before it was diagnosed
 - How much the tumor has affected the patient's ability to function
 - Extent of surgery if surgery was performed
 - Type of therapy
- **Favorable prognostic factors**
 - Lower pathologic grade
 - Young age (<60)
 - High Karnofsky performance status (standard way of measuring the ability of cancer patients to perform ordinary tasks/ADLs)



Mixed tumors

- Oligoastrocytomas
- More oligodendroglial component
 - Better prognosis
- Oligoastro Gr III > oligoastro Gr IV > AA > GBM
- J Neurooncol. 2007 Sep;84(3):279-86. Epub 2007 Apr 13. Mayo clinic. 1368 pts



Clinical Trials

- **Blood brain barrier disruption**
 - Formerly requires intraarterial infusion of mannitol (osmotic diuretic) to open barrier, then infusion of chemotherapy
 - Appears to improve median survival time for pts with malignant gliomas
 - Possibly oral medication (Levitra)
- **Gene therapy**
 - Primarily for malignant gliomas
 - Delivery of viral vectors carrying therapeutic gene into tumor cells
 - Herpes simplex virus, diphtheria toxin



Antigen presentation from tumor cells



Immunotherapy/ Vaccine

- T-cell mediated antitumor immunity
- Pt's with gliomas demonstrate impaired immune function.
- Glioma cells down regulate surface expression of MHC molecules, depriving infiltrating immune cells of signals needed to recognize and clear tumor cells.
- Dendritic cells (antigen presenting cells) are pulsed with tumor protein to make a vaccine.
- DC introduces tumor associated antigen (TAA) to T-cells.
- Activation of T-cells to eliminate tumor cells.

