

# Low grade and high grade gliomas: contemporary management

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# Overview

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

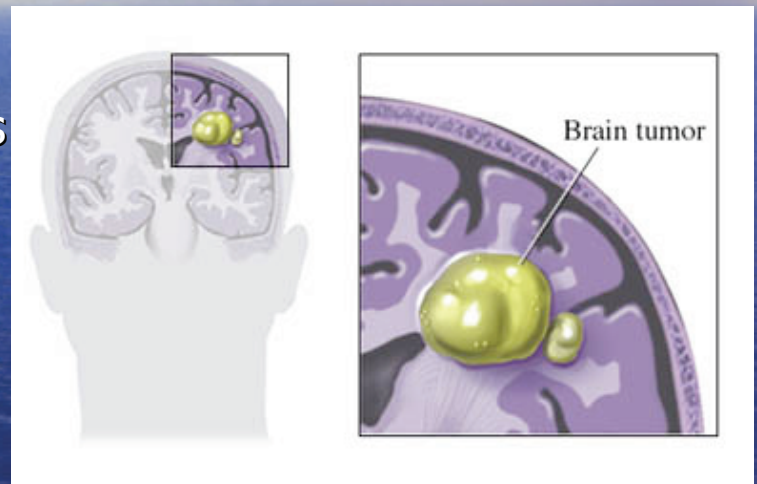






# Introduction Brain Tumors

- **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





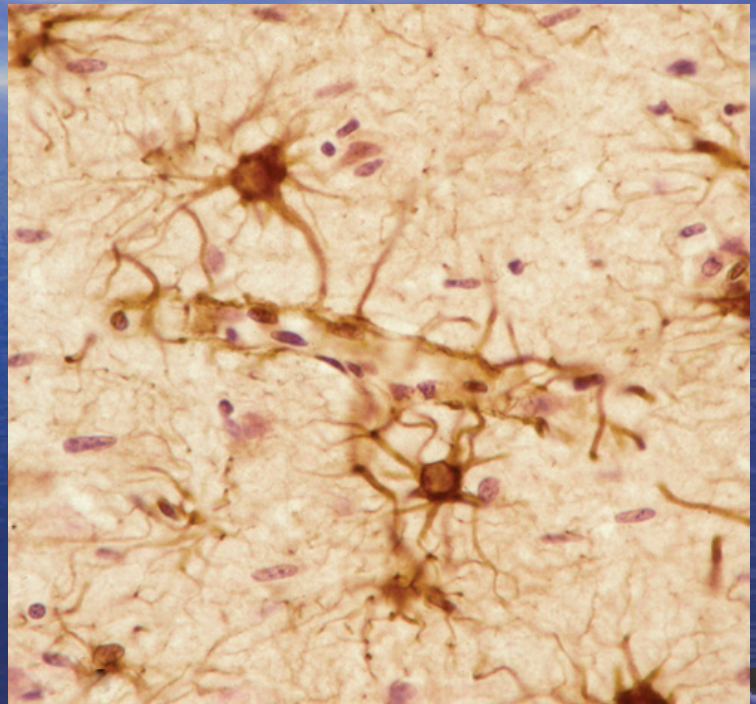
# Introduction

- 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

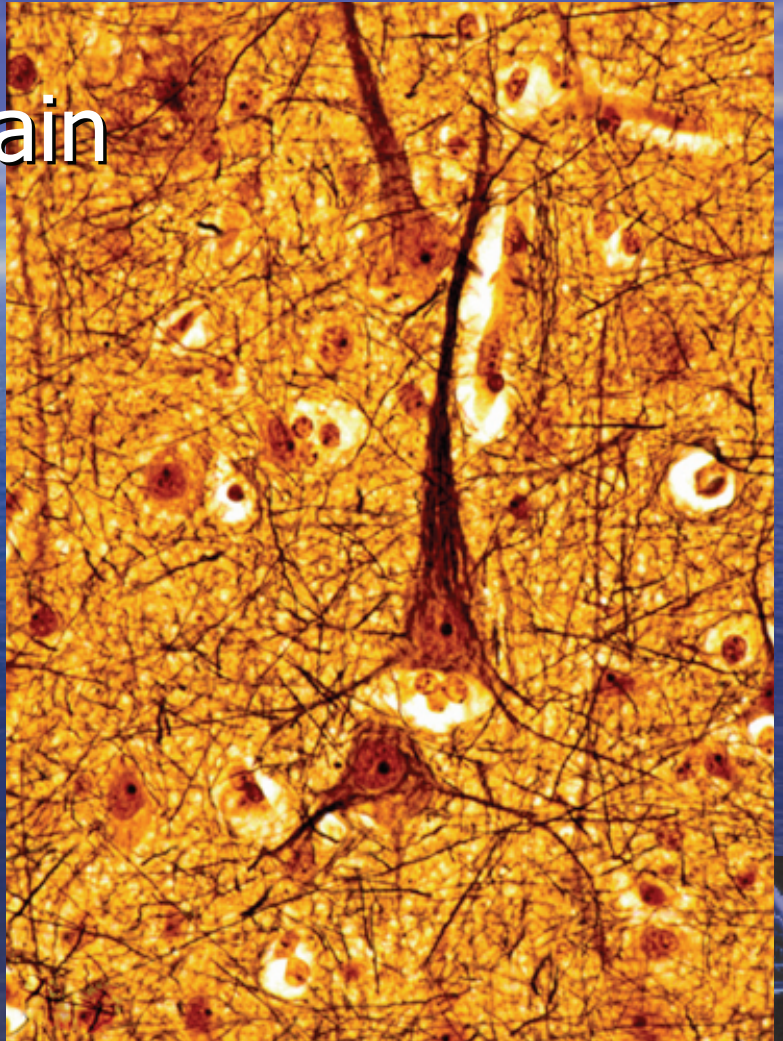
- Astrocytes
- Neurons
- Oligodendrocytes
  
- Ependymal cells
- Choroid plexus
- Pineal cells
- Pituitary gland
- Schwann cells
- Lymphocytes





# Cells of the Brain

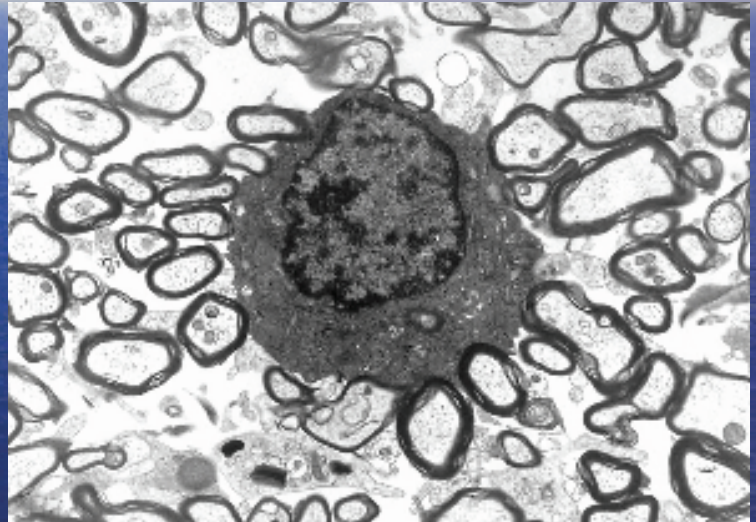
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# Introduction

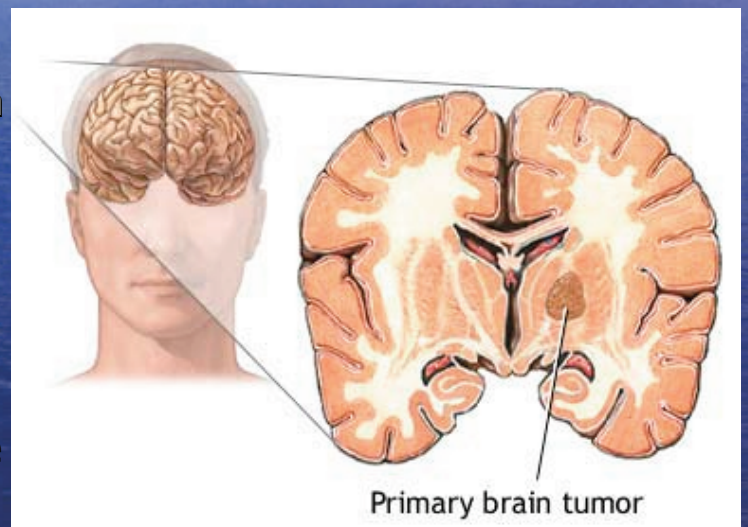
- **Metastatic** brain tumors
  - By definition, malignant
  - Formed by cancer cells that originate elsewhere in the body then travel to the brain, usually by hematogenous spread
  - Common cancers that metastasize to the brain:
    - lung, breast, colon, and melanoma





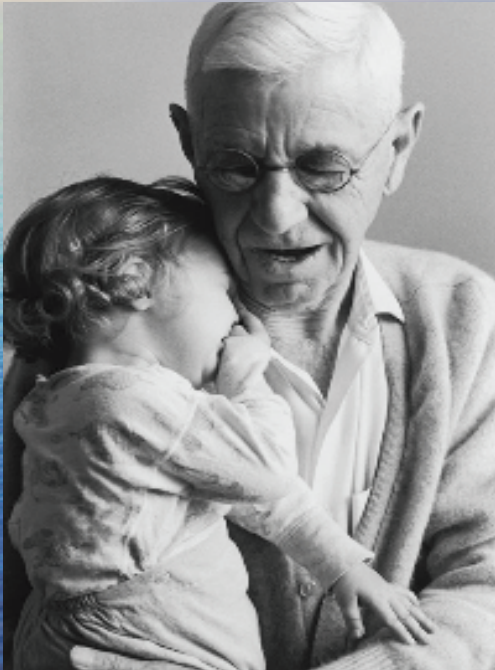
# Incidence of Brain Tumors

- 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 <sup>(NIH)</sup>
- ~190,000 people in the US are diagnosed with a metastatic brain tumor each year <sup>(NBTf)</sup>





# 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 6. Distribution of All Primary Brain and CNS Tumors by Histology  
CBTRUS 2000-2004 (n=73,583)

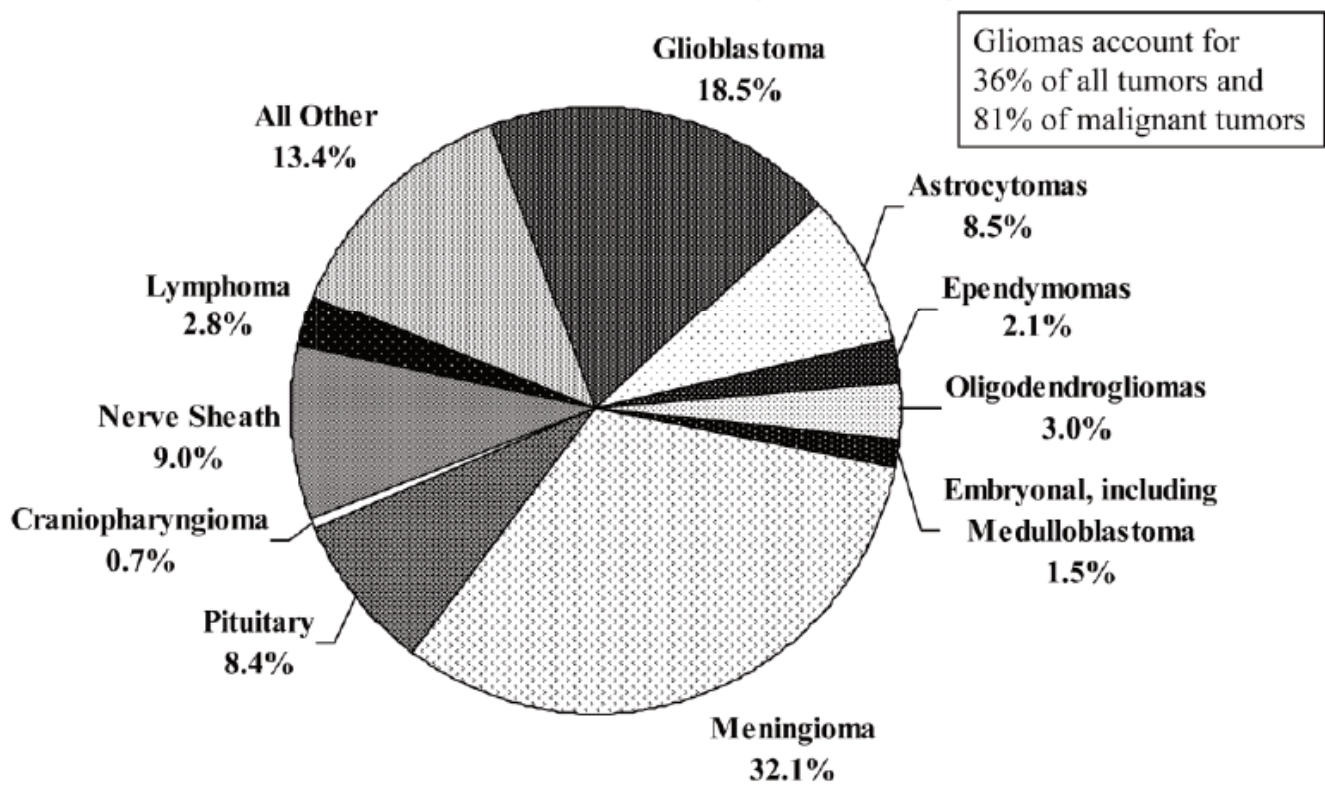
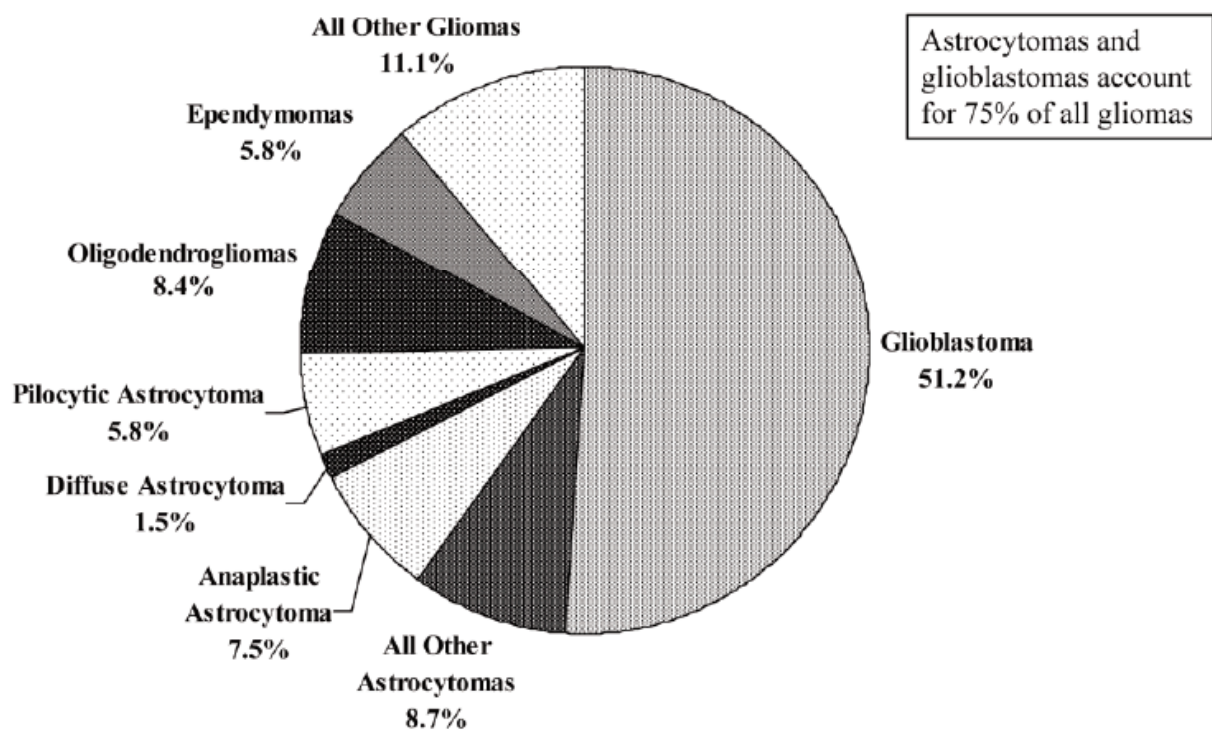
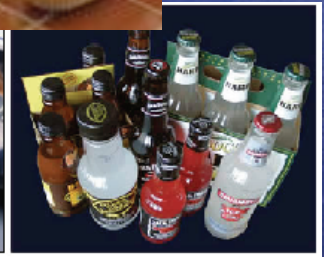


Figure 8. Distribution of All Primary Brain and CNS Gliomas by Histology Subtypes  
CBTRUS 2000-2004 (n=26,630)



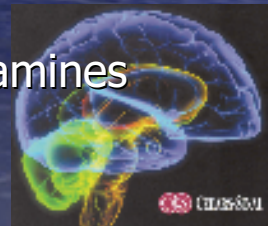


# Possible Causes of Brain Tumors and Risk Factors - Environmental



# 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



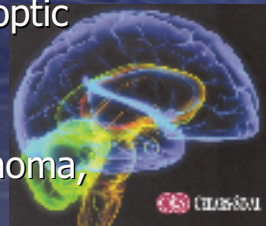


# Possible Causes-Genetic Syndromes



– Approximately 1-5% of brain tumors are due to genetic syndromes that confer an increased risk of tumors of the CNS.

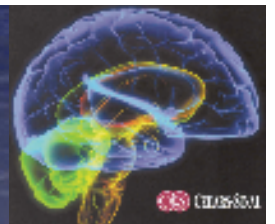
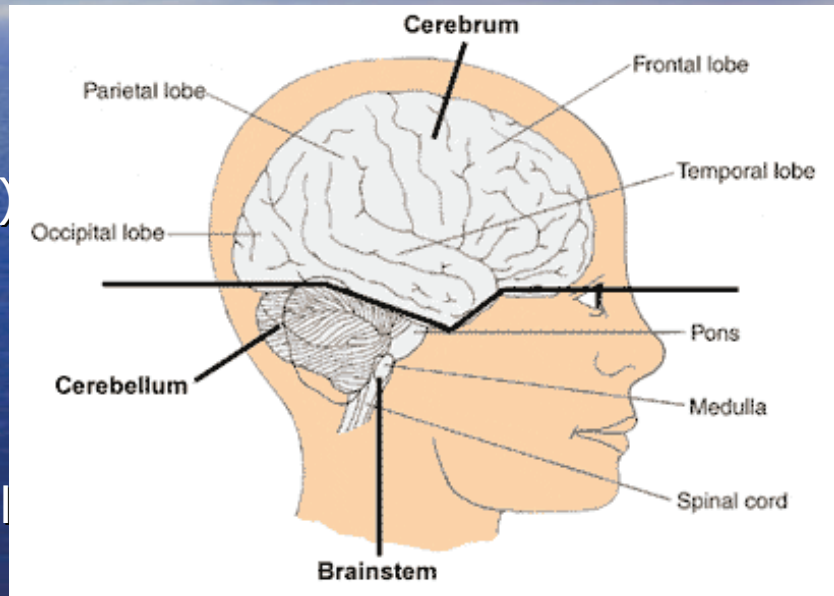
- Mutations in a specific gene is passed from one generation to the next:
  - Neurofibromatosis 1 (NF1 gene) – Glioma, meningiomas
  - Neurofibromatosis 2 (NF2 gene) – Acoustic neuroma, optic neuroma, meningioma
  - Gorlin syndrome (PTCH gene) – Medulloblastoma
  - Tuberous sclerosis (TSC1 and TSC2 genes) – Ependymoma, astrocytoma, ganglioneuroma





# 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



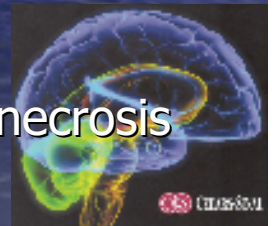
# Tumor Grading

- **Low Grade**
- Few dividing cells (mitoses)
- May have bizarre nuclei
- No vascular proliferation
- No necrosis
- **High Grade**
- Many dividing cells (mitoses)
- Bizarre nuclei
- Vascular proliferation
- Necrosis

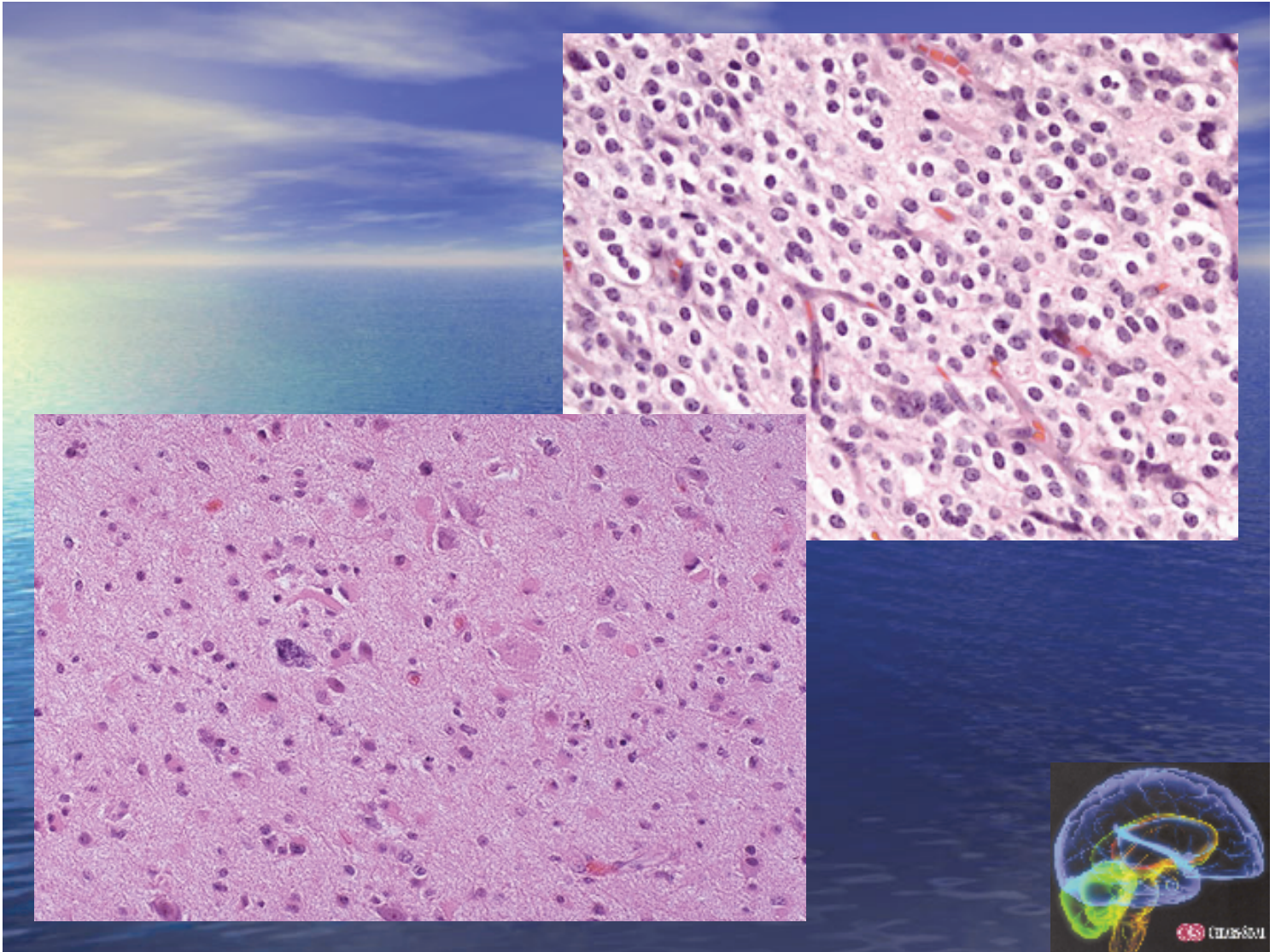


# Grading Scheme

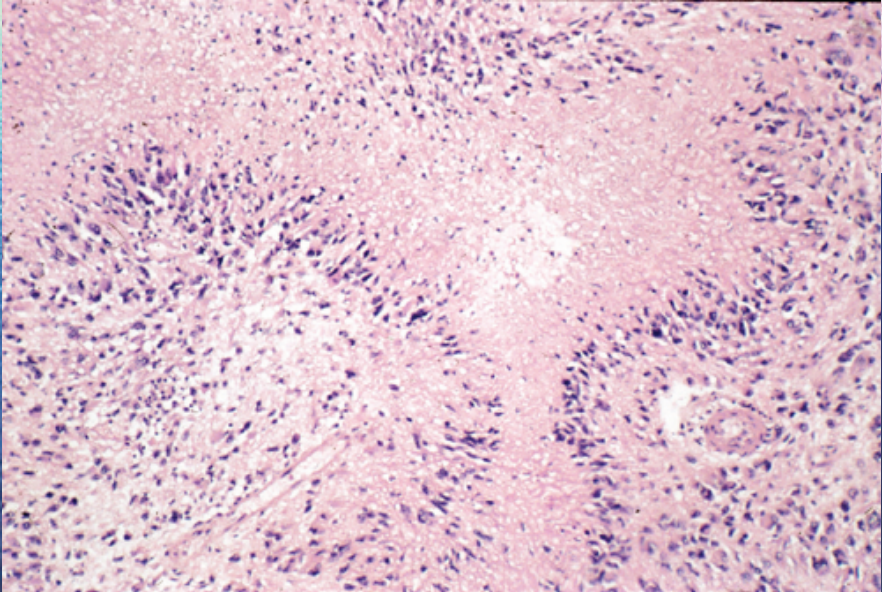
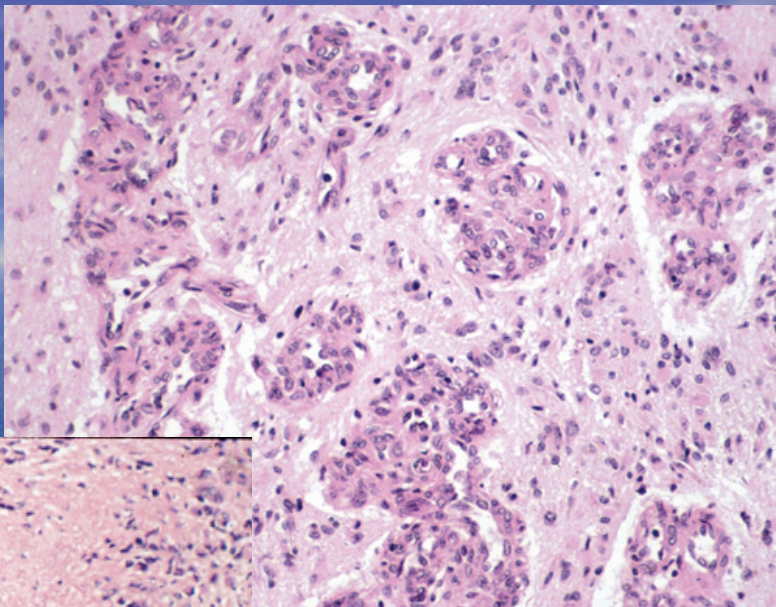
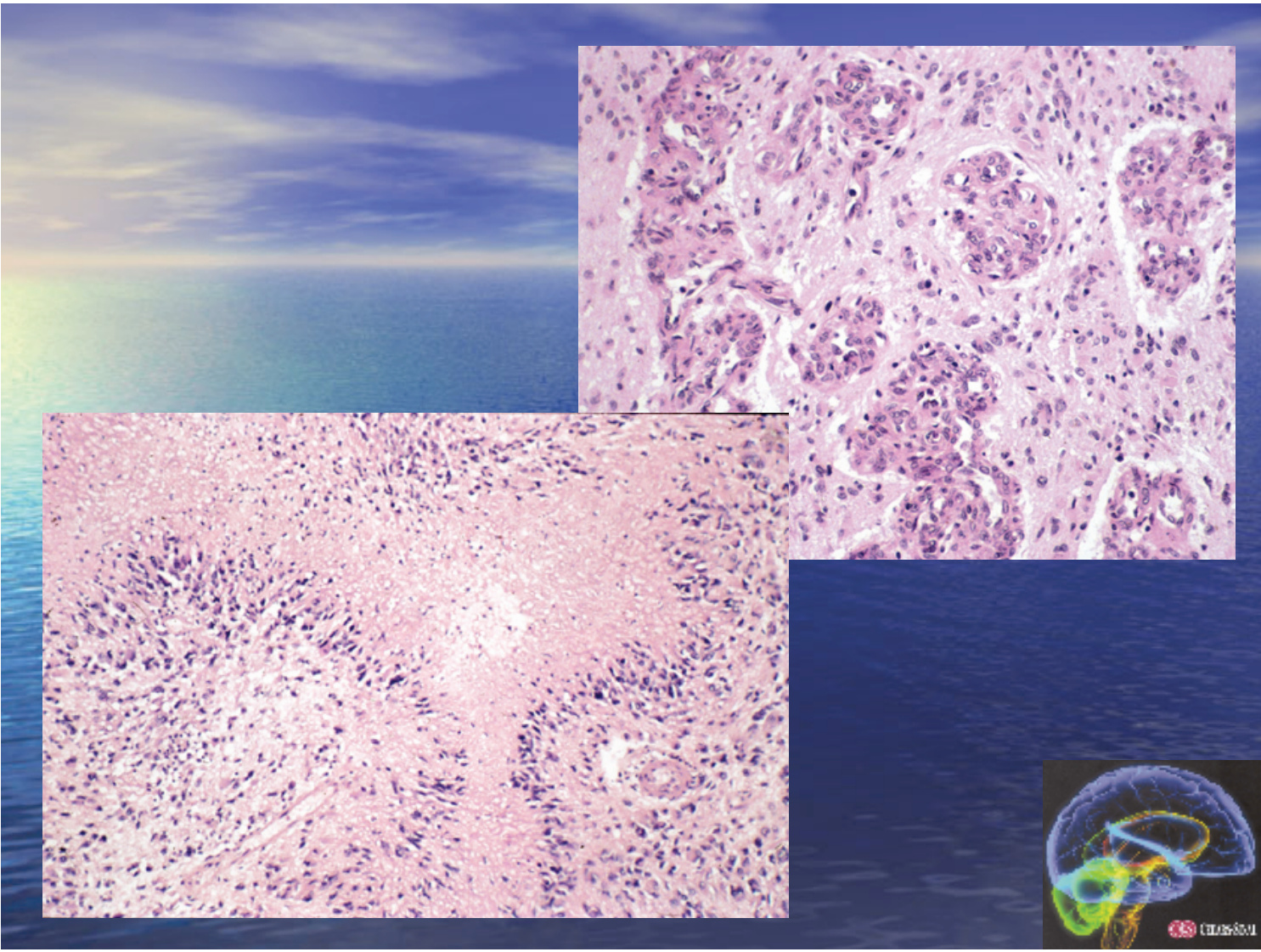
- Grade I
  - Well-circumscribed
  - Rosenthal fibers, eosinophilic granular bodies, calcification
- Grade II
  - Infiltrating, bizarre nuclei
  - Can progress to malignant
- Grade III (anaplastic astrocytoma, AA)
  - Mitoses, bizarre nuclei, vascular proliferation
  - Increasing DNA abnormalities
-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





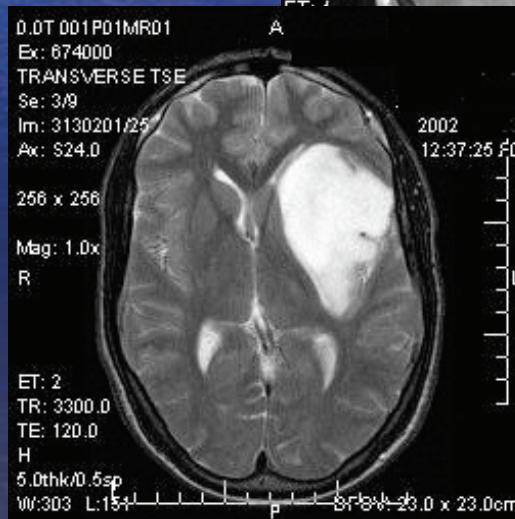
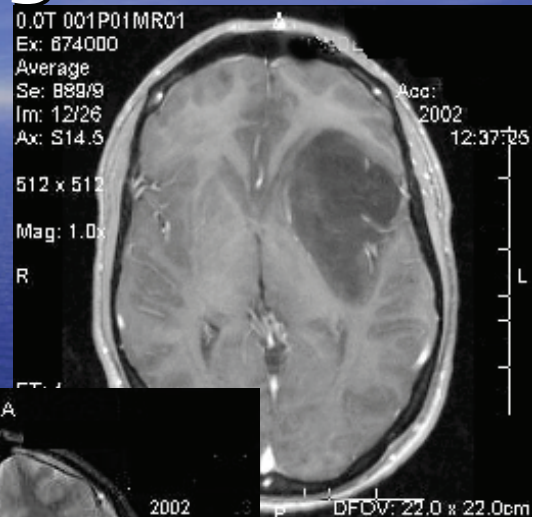






# Common Brain Tumors – *Astrocytomas* - Imaging

- 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



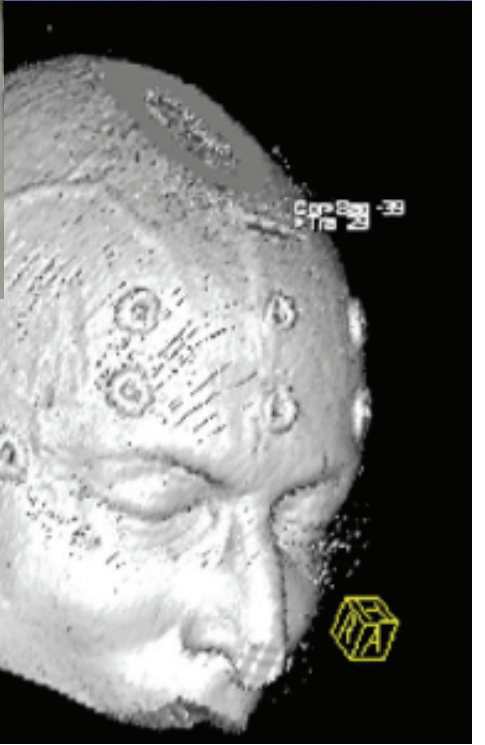


# Low Grade Gliomas

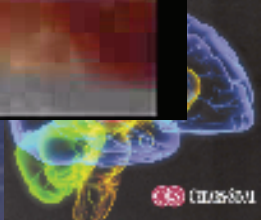
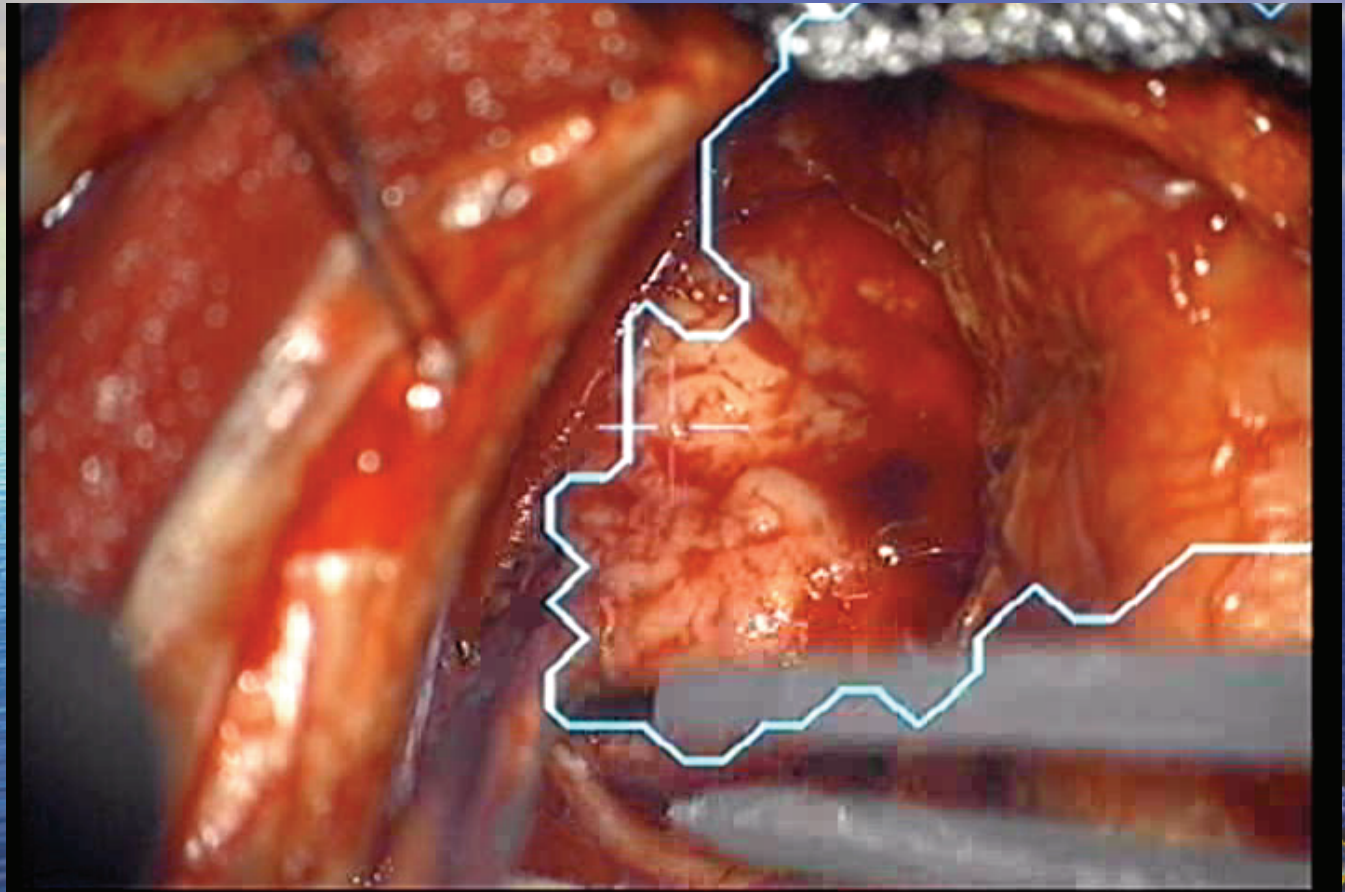
- Grade I and Grade II
  - Surgery
    - Complete surgical resection if possible
    - Biopsy or partial resection is recommended in almost all cases to determine pathology

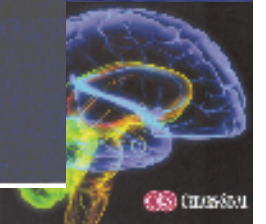








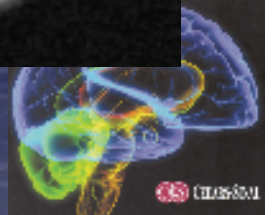
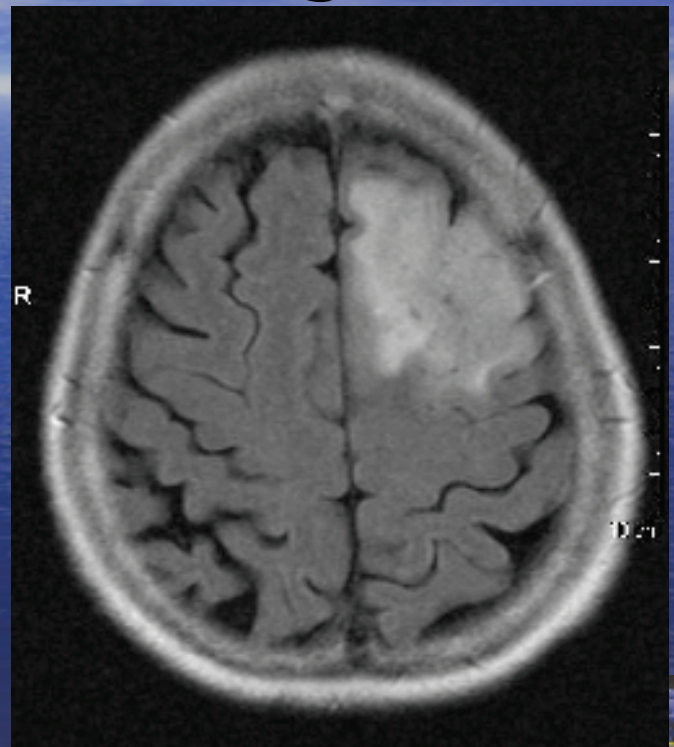






# Surgical decision-making

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

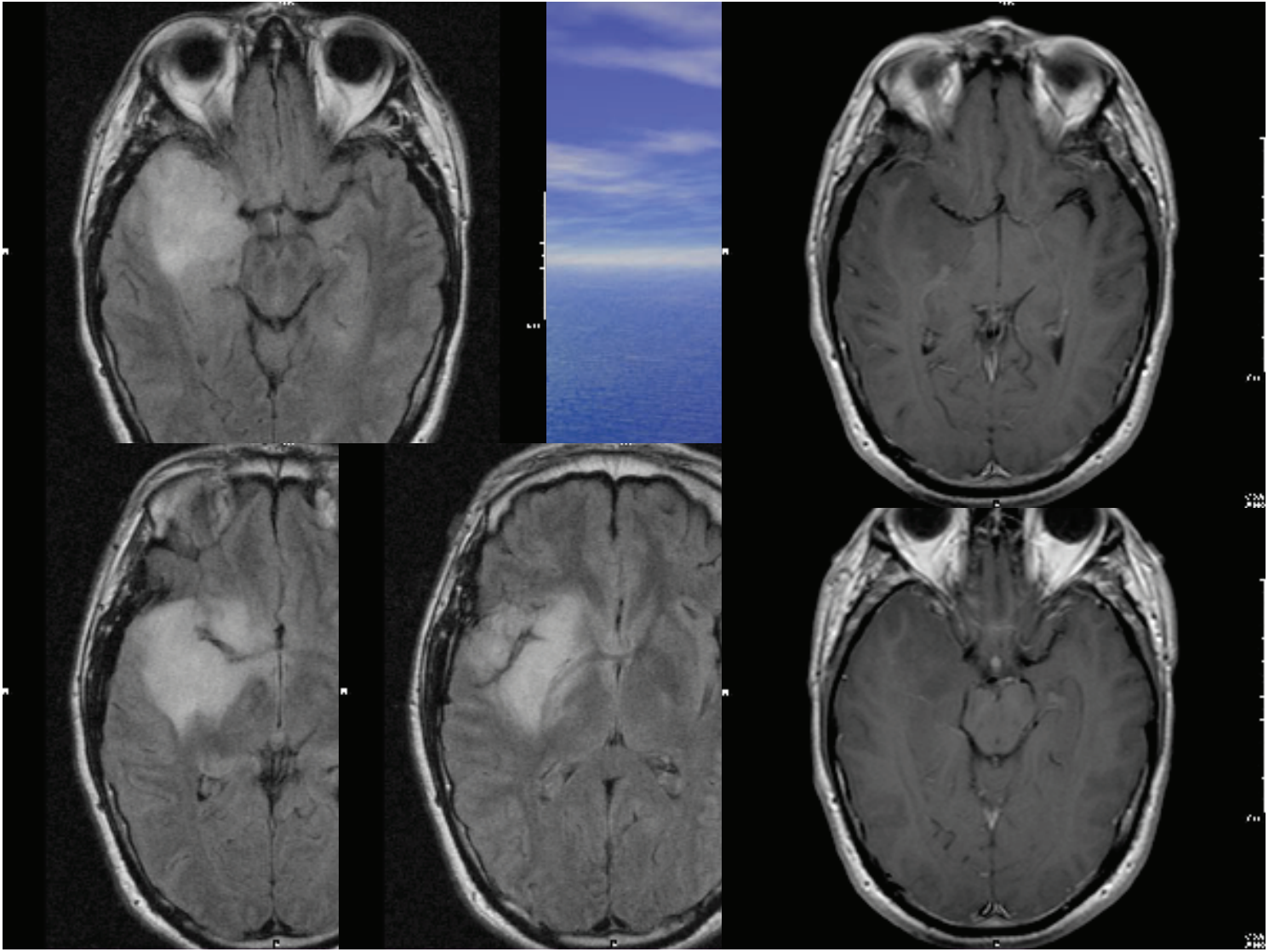


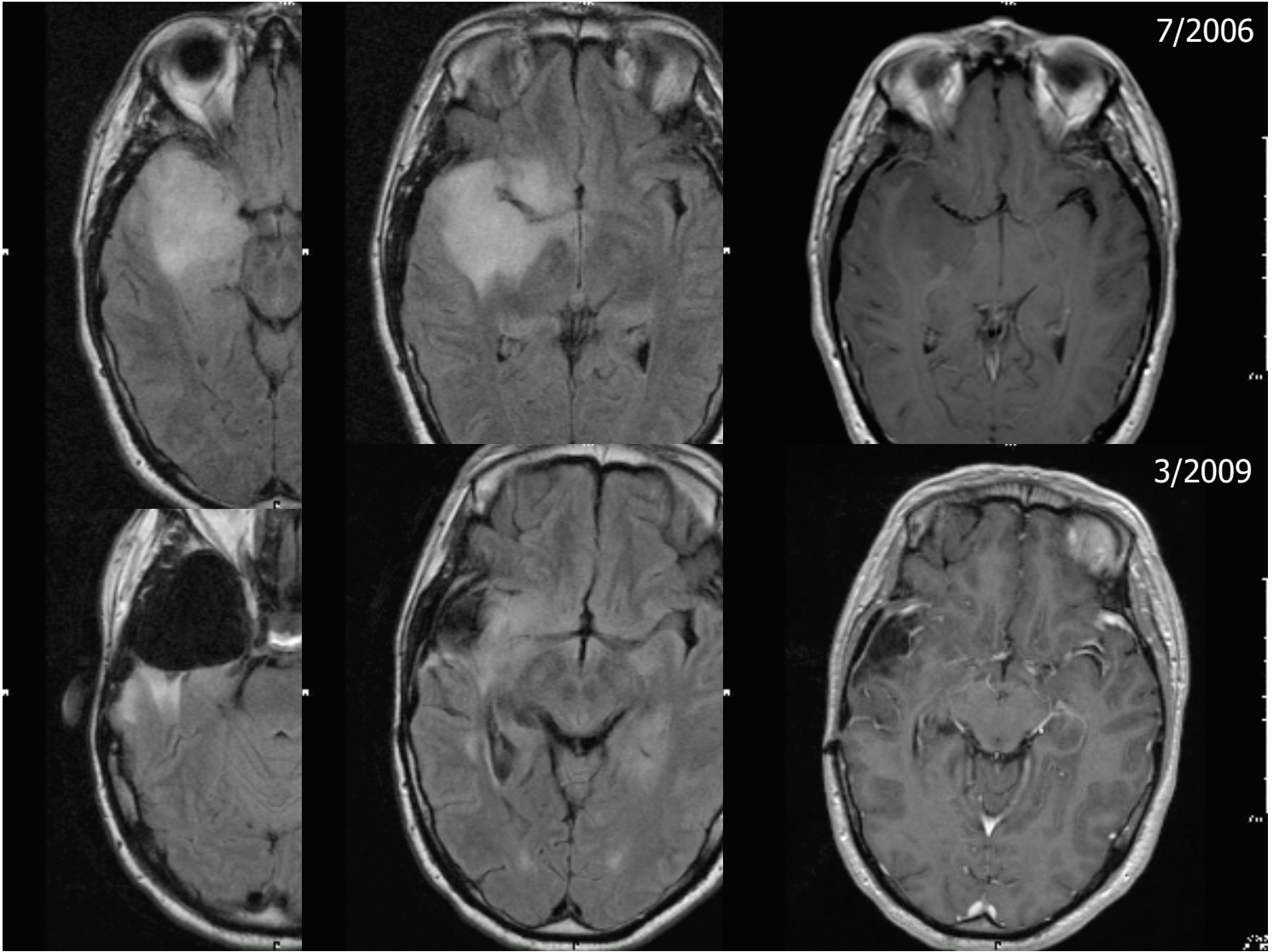


# Low Grade Glioma Treatment

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









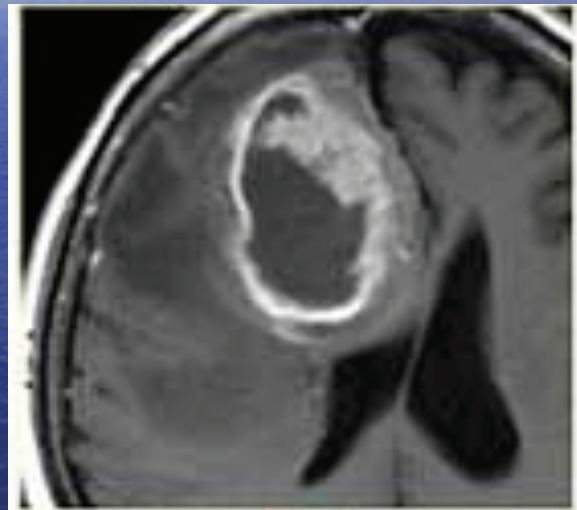
# Common Brain Tumors – *Astrocytomas*

- 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



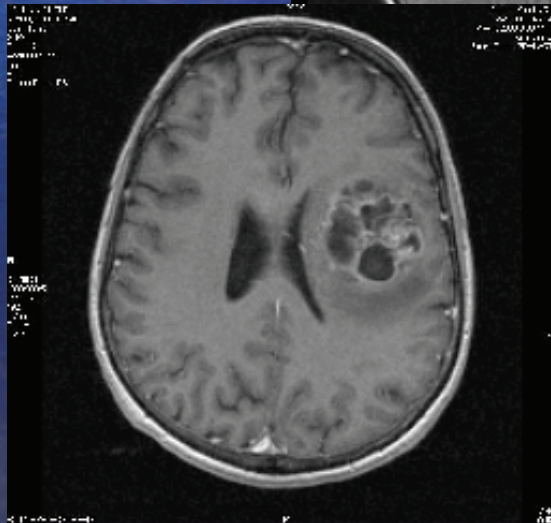
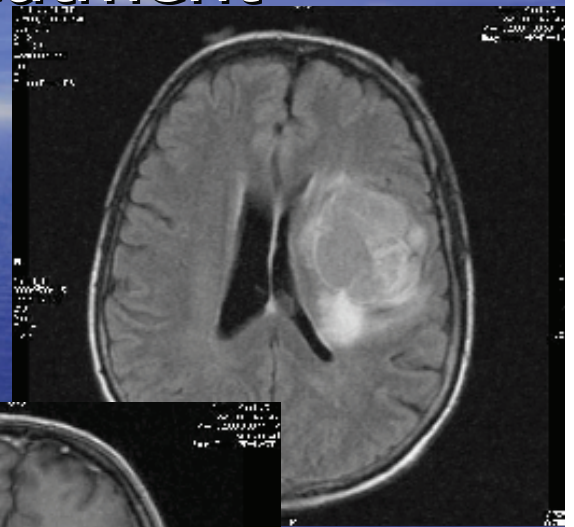
GBM





# 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

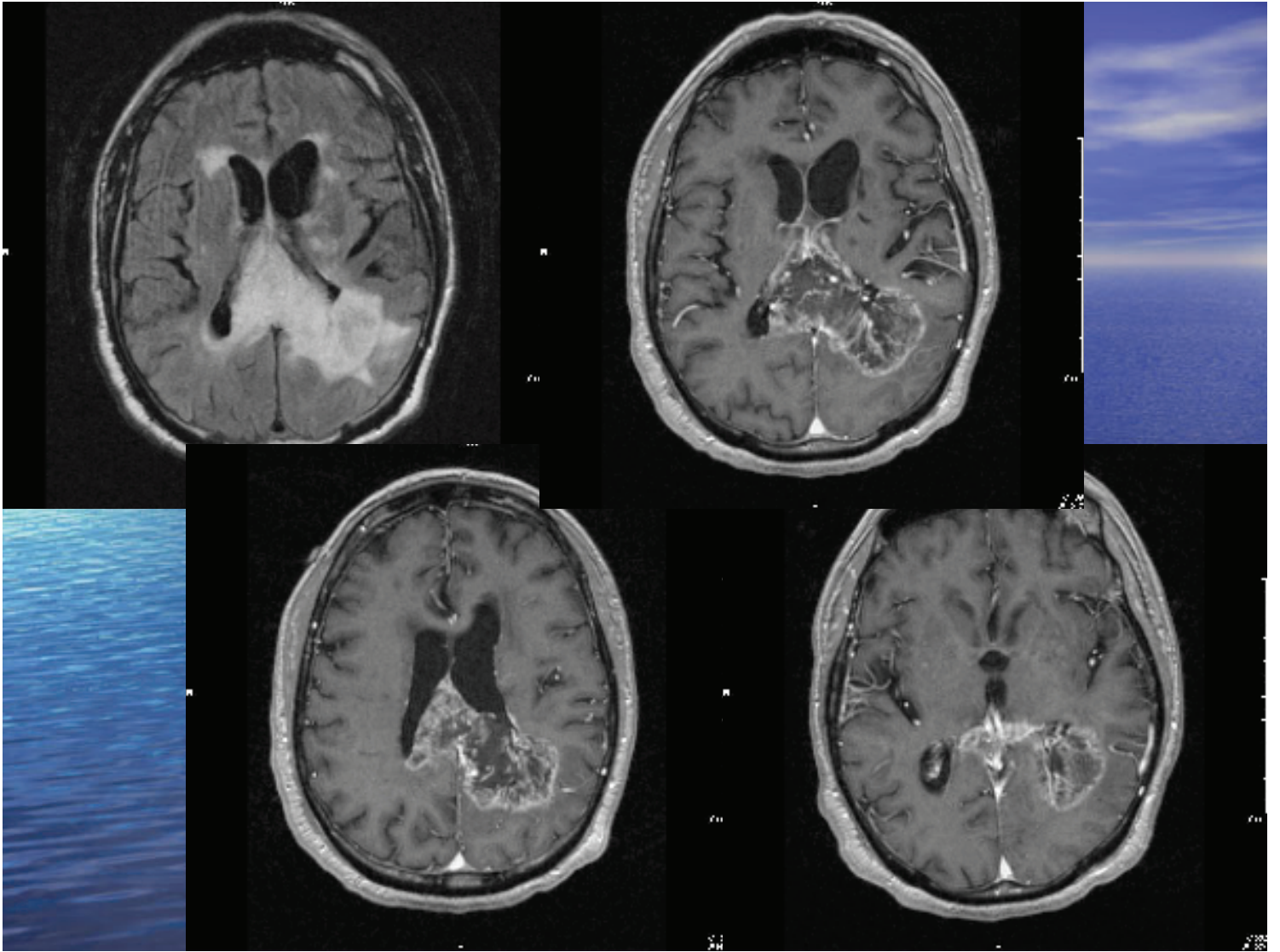


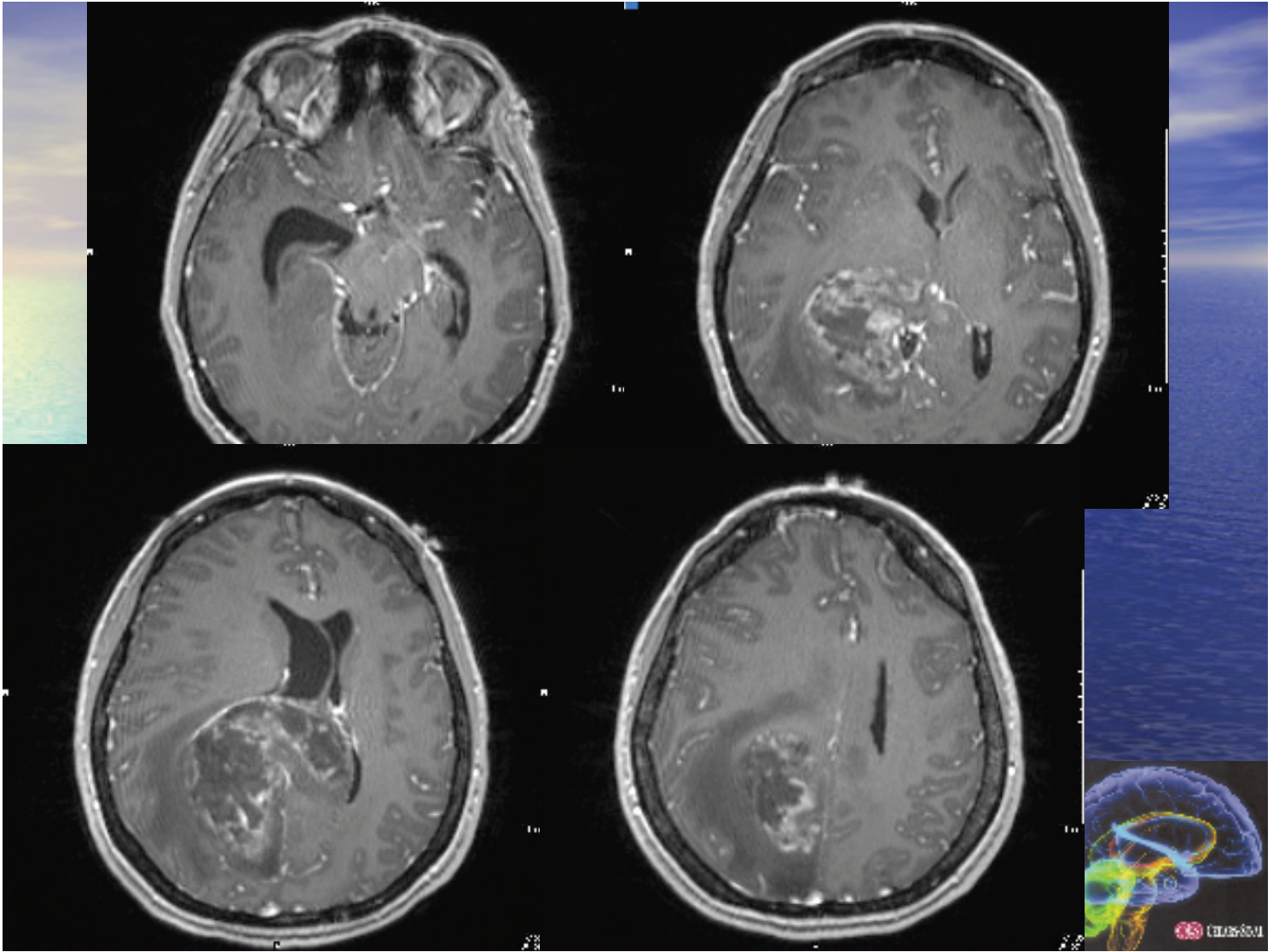
# Principles of Medical Management for Brain Tumors

- **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





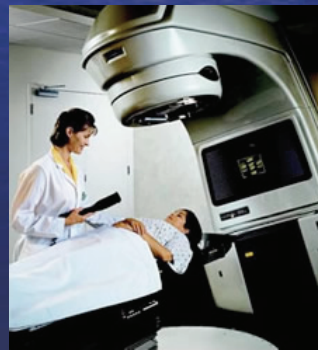






# Malignant Glioma Treatment

- 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

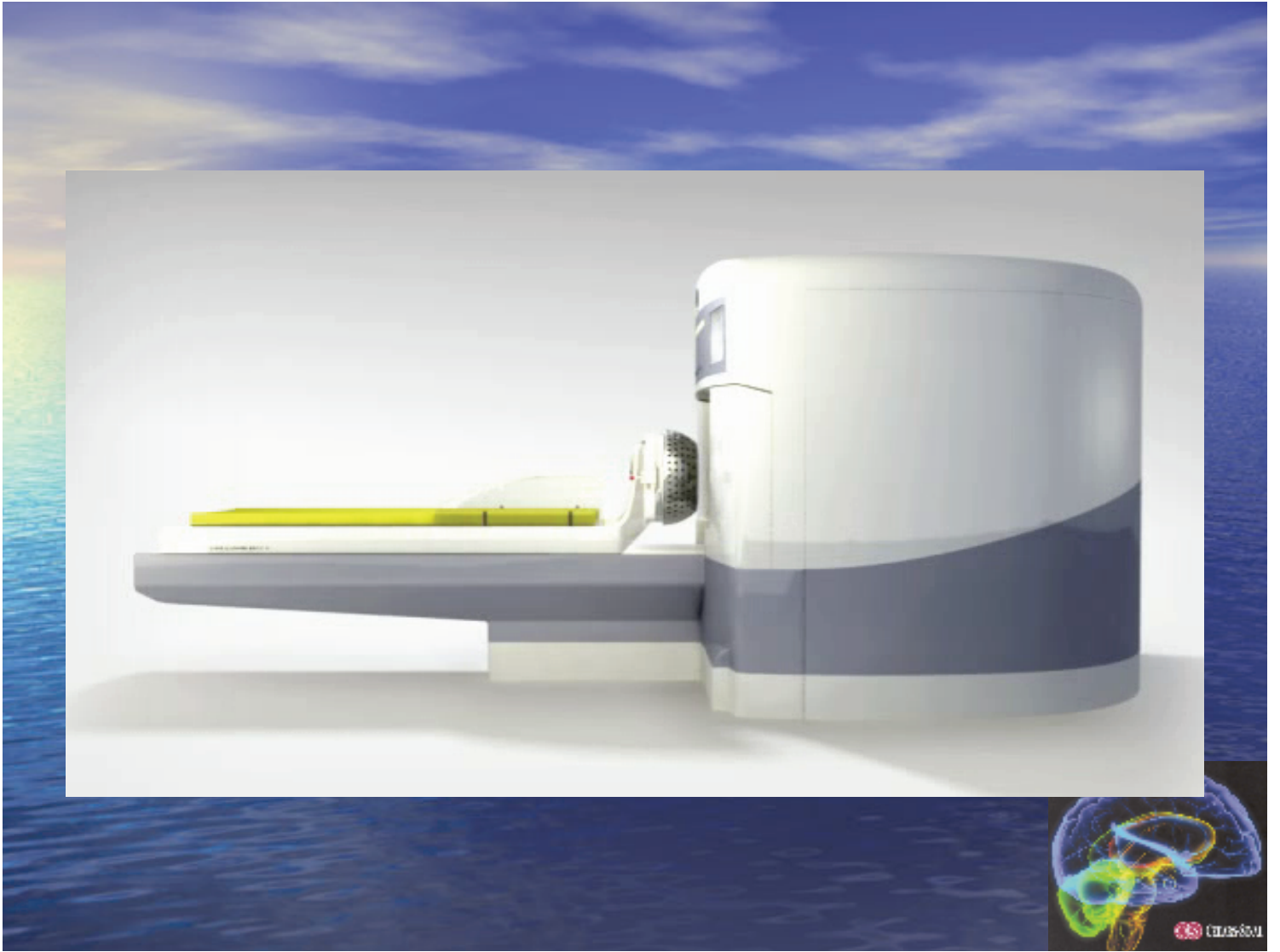


# Principles of Medical Management for Brain Tumors

- **Radiation therapy**
  - (WBRT)
  - Focal radiation
  - SRS
    - Xknife – 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)
  - Cisplatinum (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 (polifeprosen 20 with carboxine implant)**

As a randomized, controlled, multicenter trial of patients with histologic malignant gliomas (LGG/AG), Wafers (polifeprosen 20 with carboxine implant) extended the six-month survival over 5% greater than 20% compared with placebo. Median survival increased for high grade (HGG) series for 13.2(95% CI) Wafers compared 10.2(95% CI) for placebo.

**GLIADEL® Wafers** Administer chemotherapy directly to residual tumor cells, while avoiding systemic effects. It also acts locally above the site of effect of 13.2(95% CI) Wafers and provides long-term and continuous drug release for up to 6 weeks (LGG/AG). Wafers are placed directly into the tumor, allowing drug release in the proximity.

**GLIADEL® Wafers** are recommended as an option for treatment in the National Comprehensive Cancer Network.

After you (the surgeon) **GLIADEL WAFER** (polifeprosen 20 with carboxine implant)

An illustration of a hand holding a Gliadel wafer. The wafer is a small, white, circular disc. A syringe is shown injecting a substance into the wafer. The background is dark with white dots, suggesting a surgical or medical setting.



# Common Brain Tumors – *Astrocytoma* - **Survival**

- Approximate survival for astrocytomas after receiving “optimal treatment”:

<b>WHO Grade</b>	<b>Median Survival</b>
I	?
II	7-8 years?
III	≈ 3 years
IV	≈ 1 year



# 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)





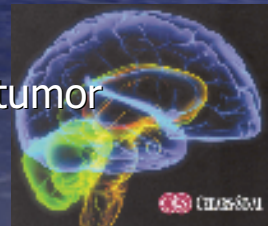
# Mixed tumors

- 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



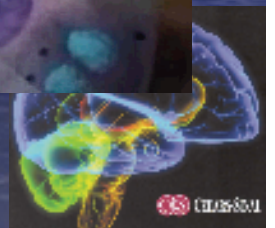
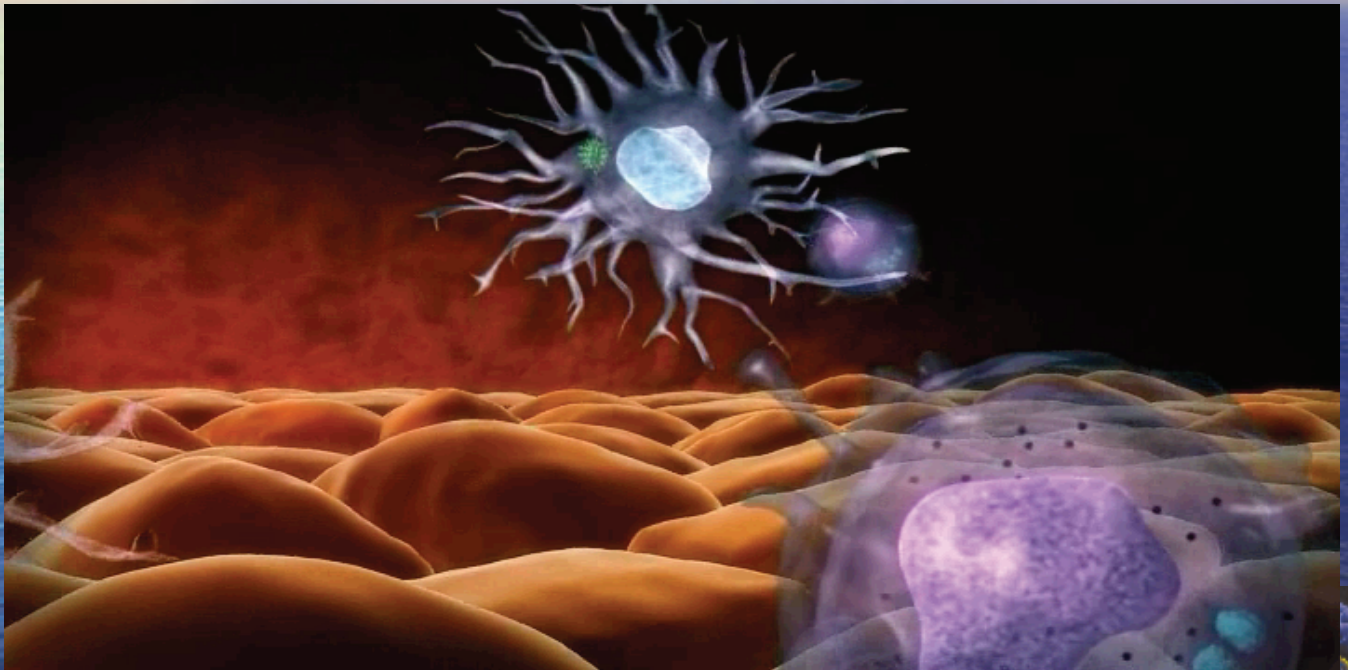
# Clinical Trials

- **Blood brain barrier disruption**
  - Requires intraarterial infusion of mannitol (osmotic diuretic) to open barrier, then infusion of chemotherapy
  - Appears to double median survival time for pts with malignant gliomas
- **Stem cell rescue/bone marrow transplant**
  - Prior to chemo, peripheral blood stem cells harvested by apheresis
  - Very high dose of chemotherapy delivered
  - After chemo, harvested stem cells given back to patient peripherally
- **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.

