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
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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

- Glioblastoma: 17.1%
- Astrocytomas: 6.8%
- Epidermoid tumors: 1.9%
- Oligodendroglia: 2.1%
- Embryonal, including Medulloblastoma: 1.8%
- All Other: 12.7%
- Lymphomas: 2.4%
- Nerve Sheath: 8.7%
- Craniopharyngiomas: 0.7%
- Pituitary: 12.7%
- Meningiomas: 33.8%

Gliomas (ICD-O-3: 9380-9384, 9391-9440, 9480) account for 32% of all tumors and 80% of malignant tumors.
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, ganglieneuroma
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
    - 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
- Eloquent
  - 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 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

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)
  - 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)

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

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

<table>
<thead>
<tr>
<th>WHO Grade</th>
<th>Median Survival</th>
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<tbody>
<tr>
<td>I</td>
<td>?</td>
</tr>
<tr>
<td>II</td>
<td>7-8 years?</td>
</tr>
<tr>
<td>III</td>
<td>≈ 3-4 years</td>
</tr>
<tr>
<td>IV</td>
<td>≈ 14 months</td>
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</tbody>
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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

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, diptheria 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.