Primary Brain Tumors: Grading, Prognosis and Treatment

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Adult Primary Brain Tumors

• Many different types of primary CNS tumors.
• Greatly varied in cells of origin, histological characteristics, biologic behavior, and prognosis.
Incidence of Gliomas

- 5-10 new cases per 100,000 general population per year.
  - 21,690 newly diagnosed cases in US (2005).
- 42% of all primary CNS tumors.
- 77% of all malignant primary CNS tumors.
- Three basic types based on histological criteria: astrocytomas, oligodendrogliomas, and mixed oligoastrocytomas.
Incidence and Relative Risk

- Age specific incidence is bimodal.
- Small peak in early childhood, pronounced peak in the elderly.
- Men are slightly more prone than women.
- Caucasians greater than African-Americans.
- Metropolitan residents slightly more prone than those living in the country.
Increasing Incidence?

- Incidence of primary CNS tumors increased until 1987.
  - Elderly with largest increase.
  - Increased across all groups.
- Increase in diagnosis roughly corresponds to widespread availability of CT and MRI.
- Has declined modestly since that time.
- Cell phones do not cause brain tumors.
Circumstances of Diagnosis

• Partial or generalized seizures.
  – More frequent when cortical and slow growing (80% low grade vs. 30% high grade)

• Increased intracranial pressure.
  – Due to tumor mass effect, breakdown of blood brain barrier with vasogenic edema and/or hydrocephalus.
  – Headache, nausea, vomiting, drowsiness and visual abnormalities.

• Progressive focal neurological deficit.
  – Motor or sensory deficits, hemianopsia, aphasia etc.

• Cognitive Dysfunction.
Location and Symptoms

- **Frontal:** motor, motor planning, speech expression (dominant).
- **Parietal:** sensory, spatial relationships, speech understanding (dominant).
- **Occipital:** vision.
- **Temporal:** hearing, memory, vision, speech word finding and understanding (mixed).
- **Insular:** autonomic.
**Karnofsky Performance Scale**

- **100**  Normal, no complaints, no evidence of disease
- **90**  Able to carry on normal activity: minor symptoms of disease
- **80**  Normal activity with effort: some symptoms of disease
- **70**  Cares for self: unable to carry on normal activity or active work
- **60**  Requires occasional assistance but is able to care for needs
- **50**  Requires considerable assistance and frequent medical care
- **40**  Disabled: requires special care and assistance
- **30**  Severely disabled: hospitalization is indicated, death not imminent
- **20**  Very sick, hospitalization necessary: active treatment necessary
- **10**  Moribund, fatal processes progressing rapidly
- **0**  Dead
MRI Characteristics

- MRI with contrast has revolutionized detection and diagnosis.
- Low Grade (WHO I&II): mild expansion of affected brain, no enhancement and minimal to no edema.
- Anaplastic (WHO III): nodular enhancement, moderate expansion with some edema.
- GBM (WHO IV): heterogeneous enhancement with central clearing, pronounced mass effect and edema.
Histological Grading of Gliomas

- WHO Criteria.
- Scale of malignancy reflecting the biological behavior and average clinical prognosis.
- Grade I: well circumscribed.
- Grade II: infiltrative.
- Grade III: anaplastic foci.
- Grade IV: marked anaplasia with rapid growth.
- Histologically: cellular atypia, mitosis, microvascular proliferation, and necrosis.
- Poor reproducibility.
Primary and Secondary Malignancy

- **Secondary GBM:**
  - Adolescents and young adults.
  - Arise from step wise accumulation of genetic errors over period of years.
  - Arise from low grade tumors.
  - 50% degeneration rate.
  - 5-10 year period of time.

- **Primary GBM:**
  - Elderly.
  - Short period of symptoms.

- Express different surface markers.
Beware

- Tumor heterogeneity can lead to sampling errors and result in misdiagnosis.
- Poor reproducibility within and between observers.
- Tumors showing a common morphology can be genetically different.
  - Different clinical courses and prognosis.
Genetic Changes and Malignancy

- Need molecular/genetic analysis for tumor classification.
- Oncogenes and tumor suppressor genes involved are not specific but the accumulation is characteristic.
- Gliomagenesis and tumor progression closely associated with.
  - Loss of cell cycle control.
  - Increased tyrosine-kinase signaling.
Prognosis

• Patient age.
  – Younger patients do better than old.

• Tumor histology (WHO Grade).
  – Lower grade tumors do better than higher grade tumors.

• Karnofsky performance Scale.
  – Highly functional patients do better than poorly functioning patients.
  – Are the deficits reversible?
Pilocytic Astrocytoma

- Peak incidence in children and young adults.
- Low cell density, fibrillary texture and Rosenthal fibers, may be vascular.
- Well circumscribed enhancing tumors.
- Slow growth, rare regression (may degenerate).
- Surgical resection indicated when possible (80% 5yr survival).
Diffuse Astrocytoma

- Young adults (35 yrs).
- Different histological subtypes.
  - Increased cellularity.
- Hypointense T1 and hyperintense on T2.
- Usually do not enhance.
- Infiltrate beyond apparent margin.
- Role of surgery is unknown (diagnosis).
- Radiation and chemotherapy without effect.
- 5 to 8 yr median survival.
Anaplastic Astrocytoma

- Adults (40 yrs).
- Hypercellularity, atypical nuclei, numerous mitosis.
- Hypointense on T1 and hyperintense on T2 with patchy enhancement and marked edema.
- Incurable.
- Local and leptomeningeal spread (through CSF).
- Surgery, radiation and chemotherapy.
- 6-8 mo median survival.
Oligodendroglioma

- Adults (40 yrs) with small peak in childhood.
- Frequently present with seizures.
- Fried egg or chicken wire appearance.
- Delicate capillary web.
- Hypointense to mixed on T1 and hyperintense on T2, minimal to no enhancement.
- May have calcifications and mixed age hemorrhage.
- 1p/19q deletions very sensitive to radiation and chemotherapy.
- 12-16 yr survival.
Anaplastic Oligodendroglioma

- Adults (40 yrs).
- Increased cellularity, atypical mitosis, neovascularization.
- Hypointense on T1, hyperintense on T2 with heterogeneous enhancement.
- May have calcifications and mixed age hemorrhage.
- Still remain chemotherapy and radiation sensitive (1p/19q).
- Prognosis variable.
Mixed Oligoastrocytoma

- Adults (40yrs).
- Distinct oligodendroglial and astocyteic components to the tumor.
- Difficult diagnosis dependent on tumor sampling.
- Imaging appearance variable.
- Intermediate prognosis.
- Surgery, radiation and chemotherapy.
Glioblastoma Multiforme

• Adults (53 yrs).
• Most common glioma.
• Hypercellularity, atypical nuclei, mitosis, neovascularization and necrosis.
• Incurable.
• Local and leptomeningeal spread (through CSF).
• Surgery, radiation and chemotherapy.
• 4-6 mo median survival.
Treatment and Survival in GBM

- Supportive Care: <14 wks.
- Surgical Resection: <20 wks.
- Resection with radiotherapy: <35 wks.
- Resection, radiotherapy and chemotherapy: <45 wks.
Gliadel Wafers

- BCNU impregnated polymer wafers.
- Attempt to circumvent BBB by local administration of chemotherapeutic agent.
- Minimal systemic effects.
- Implanted at time of original surgery or with recurrence.
- Median increase in lifespan approximately 2 months.
Temozolomide (Temozolomide)

- Oral alkylating agent.
- Minimal systemic side effects: minimal myelosuppression and GI upset.
- Increased median lifespan from 12.1 to 14.6 months
- More than doubled 2 yr survival to 27% and quintupled 5 year survival to 10%
- Some tumors may be more sensitive than others depending on degree of MGMT expression.
Avastin (bevacizumab)

- Humanized antivascular endothelial growth factor antibody.
- Antiangiogenic properties.
- No phase 3 clinical data.
- Appears to have a role in the treatment of recurrent high grade gliomas.
- May significantly decrease associated brain edema allowing for an overall decrease in the maintenance steroid doses used.
- Withdrawal or failure of therapy associated with rapid progression and decline.