An Introduction to Brain Tumors

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Disclosures

None
The evolving philosophy of brain tumor surgery
Common brain and skull base tumors
  Essentials of preoperative workup
  What is urgent, what can wait?
  Case Illustrations
  Postoperative expectations, management and potential complications
Technology and Research at the PBSI
Historical Difficulties in Brain Tumor Surgery

- Localization
- Visualization
- Hemorrhage control
- Brain swelling

Guido da Vigevano, c. 1345.
The Old Dogma

- Localization
- Visualization
- Hemorrhage control
- Brain swelling

→ Large exposures lead to safer operations

Guido da Vigevano, c. 1345.
Neurosurgical innovations

- Operating Microscope and Microsurgical techniques
- Neuroimaging Techniques
  - CT and MRI
  - fMRI, DTI
- Neuroanesthesia
  - Non volatile anesthetics
  - Electrophysiological monitoring
  - Brain relaxation
  - Awake craniotomy
- Intraoperative Neuronavigation
- Intraoperative MRI
- Fluorescence-guided tumor resection
- Minimally invasive laser ablation
The “Keyhole” Philosophy

- A limited, directed cranial opening tailored to address the relevant intracranial pathology via anatomic corridors
- **Principles**
  - Elimination of brain retraction
  - Improved visualization
  - Minimization of tissue disruption
- **Without sacrifice of operative efficacy or safety**
Keyhole is a concept, not a size
Keyhole concept
Small keyhole example
Brain Tumor Presentation

- Location, Location, Location...
- Size
- Rate of growth
- Endocrine effects
When to scan

- Sudden onset severe headache → ED
- New, persisting or dramatically changed headache
- Any neurological deficit (motor, sensory, visual, cognitive or cranial nerve)
- New seizure
- HA with history of cancer

- Looked at 5 trials with newly dx intrinsic or extrinsic brain tumors
- Phenytoin, VPA, Phenobarbital
- No benefit for sz prevention at 1 week or 1 year
- CONCLUSIONS: No evidence supports AED prophylaxis with phenobarbital, phenytoin, or valproic acid in patients with brain tumors and no history of seizures, regardless of neoplastic type.
**AED prophylaxis**

- **Antiepileptic drugs for preventing seizures in people with brain tumors.**
  - Tremont-Lukats IW¹, Ratilal BO, Armstrong T, Gilbert MR.
- **Author information**
- **MAIN RESULTS:**
  - There was no difference between the treatment interventions and the control groups in preventing a first seizure in participants with brain tumors. The risk of an adverse event was higher for those on antiepileptic drugs than for participants not on antiepileptic drugs (NNH 3; RR 6.10, 95% CI 1.10 to 34.63; P = 0.046).
- **AUTHORS' CONCLUSIONS:**
  - The evidence is neutral, neither for nor against seizure prophylaxis, in people with brain tumors. These conclusions apply only for the antiepileptic drugs phenytoin, phenobarbital, and divalproex sodium. The decision to start an antiepileptic drug for seizure prophylaxis is ultimately guided by assessment of individual risk factors and careful discussion with patients.
Guidelines for Urgent Referral

- Subacute progressive neurological deficit developing over days to weeks (e.g., weakness, sensory loss, dysphasia and ataxia)

- New onset seizures

- Patients with headache, vomiting and papilledema

- Cranial nerve palsy (e.g., diplopia, visual loss, unilateral sensorineural deafness)

- Referral guidelines for suspected central nervous system or brain tumours (J Neurol Neurosurg Psychiatry. 2006)
Common Brain and Skull Base Tumors

- Meningioma
- Low-grade Glioma
- Malignant Glioma
- Acoustic Neuroma
- Pituitary Tumor
- Metastatic Lesions
Meningioma

- Tumors that arise from the arachnoid cap cells of the meninges
- Most common benign brain tumor
- 20% of all intracranial neoplasms
- Incidence
  - 2/100,000 in general pop.
  - Increases with age 13/100,000, age 65-74 years
  - F:M = 3:1
Meningioma Grading

- Grade 1 – Benign – 91%
- Grade 2 – Atypical – 7%
- Grade 3 – Malignant – 2%
Meningioma Natural History

- Average growth rate is 1-2 mm/year
- HOWEVER
  - 63% remain stable in 4 year follow up
  - 37% grew 2-4 mm
- < 2 cm in size usually asymptomatic
- > 2.5 cm will typically develop new or worsened symptoms
Meningioma Presentation

- Headaches
- Seizures
- Cranial Neuropathy
- Cognitive Changes
- Gait Alteration

PRESENTATION is completely dictated by location
Meningioma Treatment

- Observation
  - Stable asymptomatic lesions
  - Age > 70 with slow growth
- Gamma Knife
  - Tumors smaller than 10 cm³
  - High surgical morbidity
    - Older patients or
    - Difficult to reach areas
    - Postop Residual
- External Beam radiation
  - Larger tumors
  - Unresectable or Postop Residual
- Surgery
### Meningioma Prognosis - Extent of Resection

<table>
<thead>
<tr>
<th>Simpson Grade</th>
<th>Completeness of Resection</th>
<th>10-year Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>complete removal including resection of underlying bone and associated dura</td>
<td>9%</td>
</tr>
<tr>
<td>Grade II</td>
<td>complete removal + coagulation of dural attachment</td>
<td>19%</td>
</tr>
<tr>
<td>Grade III</td>
<td>complete removal w/o resection of dura or coagulation</td>
<td>29%</td>
</tr>
<tr>
<td>Grade IV</td>
<td>subtotal resection</td>
<td>40%</td>
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</tbody>
</table>
Meningioma Prognosis - Radiation

- Gamma Knife and External Beam techniques have ~ 90% control rates in mid-term (4-5 year) follow up.
Case: Meningioma

57 y/o F dx with fibromyalgia and headaches.
Case: Meningioma

- Embolization
Case: Meningioma
Case: Meningioma (postop)
Meningioma Receptor Expression

- 70-80% have progesterone receptor
- ~8% have estrogen receptor
- HRT doubles risk of developing meningioma
- Avoid OCPs and HRT in pt’s with known meningiomas
Case 2

40 y/o F on longstanding OCP
Glioma (Low Grade)

Heterogeneous group of tumors that arise from the glia - “support” cells of the brain
Glioma Grading

- **Grade I**
  - Pilocytic astrocytoma
  - Dysembryoplastic neuroepithelial tumor (DNET)
  - Pleomorphic xanthoastrocytoma (PXA)
  - Ganglioglioma

- **Grade II**
  - Astrocytoma
  - Oligodendroglioma
  - Ependymoma
Glioma Grading

× Grade I
- Pilocytic astrocytoma
- Dysembryoplastic neuroepithelial tumor (DNET)
- Pleomorphic xanthoastrocytoma (PXA)
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× Grade II
- Astrocytoma
- Oligodendroglioma
- Ependymoma
Grade II Glioma Epidemiology

- 45% of CNS tumors in Ages 20-34
- 0.9 per 100,000 incidence (Grade I and II)
Low Grade Glioma Presentation

✗ Seizure (~80%)
✗ Headache
✗ Neurological deficit
✗ Cognitive changes
Grade II Glioma Prognosis

- Variable course ranging from 2 to 20 years before malignant degeneration
- 50-75% eventual mortality from tumor progression or malignant degeneration
Low Grade Glioma Treatment

- Surgery
- Chemo
- Radiation
Grade II Glioma: Surgery

- 1st line treatment with goal of maximal safe resection
- Multiple studies indicate extent of resection correlates strongly with survival (Keles, JNS 2001)
Grade II Glioma: Radiation

- EORTC (European Organization for the Research and Treatment of Cancer) 22845
  - 311 pts randomized post-surgery to radiation vs observation
  - OS - no difference
  - PFS 2 years longer (5 vs 3) with RT
  - Better seizure control with RT

- Radiation in young patients usually reserved for tumor progression or recurrence because of neurotoxic side effects
Grade II Glioma: Chemotherapy

- 1p19q deletions
  - Increased chemosensitivity
  - Longer recurrence-free survival
- IDH-1 mutation

- RTOG 9802 (2014)
  - High risk grade II pts (age > 40 or < 40 with subtotal resection)
  - RT vs PCV+RT
  - OS 7.8 vs 13 years
Grade II Glioma Prognostic Factors

× Positive

✦ Oligodendroglioma
✦ Age < 40
✦ Higher Karnofsky score
✦ Gross total Resection

× Negative

✦ Astrocytoma
✦ > 3cm tumor size
✦ Presentation with neurological deficit

Chaichana, JNS 2012
Technology: fMRI and tractography

- Functional MRI
  - Uses blood flow alterations to identify areas of brain activity during tasks
Technology: fMRI and tractography

Tractography

- 3D modelling technique used to delineate white matter tracts using diffusion tensor imaging
Technology: Intraoperative MRI
Case: Grade II Glioma

36 y/o Intel engineer with new onset seizure
Case: Grade II Glioma

- Functional MRI and tractography
Case: Grade II Glioma

- Intraop MR Images
Case: Grade II Glioma

- Postop course
- 1 week of left leg > arm hemiplegia (expected)
- Subsequent full recovery by 6 weeks.
Case: Left insular glioma

- 33 y/o RH M with new onset seizure
Case: Grade II Glioma

- Postop course
- Dysphasia for several weeks
- High irritability due to Keppra
- Subsequent full recovery by 6 weeks.
- Neurologically normal
- Undergoing chemo/rad
Malignant Glioma (Grade III and IV)

- 5/100,000
- 14,000 new cases per year
- 70% GBM (Grade IV)
- 10-15% Anaplastic Astrocytoma
- ~15% other
GBM (Grade IV Glioma)

- Median age = 64
- 90% de novo
- Most common malignant brain tumor
GBM presentation

- Short course – sx < 3 months
- HA
- Seizure
- Location related neuro deficits
GBM Treatment

- Maximum safe surgical resection
  - Goal 95-98%

- Radiation
  - Increases survival from 3-4 to 7-12 months

- Chemo
  - Temozolomide (TMZ)
    - 14.6 mo median survival (vs 12 months with RT)

- +/- Immunotherapy
- +/- Genetic profiling
- Avastin (bevacizumab)
  - Not indicated in new dx GBM (AVAglio, RTOG 0825, NEJM 2014)
Fluorescein-guided resection
GBM Treatment

- Stupp protocol (Stupp et al. NEJM, 2005)
  - Concurrent RT and chemo initiated 3 weeks after surgery
  - RT: 60 Gy over 6 weeks
  - Daily TMZ for 49 days
  - 5 days/month maintenance TMZ x 6 – 12 months
Tumor Treatment Fields (Optune)

- Electric field generated to interfere with mitotic spindle formation
- First new FDA approval for GBM treatment in 10 years
- Stupp et al, JAMA Dec 2015
- 700 pts, completed standard chemo/rad with no evidence of progression
- Increases median PFS from 4 to 7 months vs TMZ chemo alone
- Increases OS from 16.6 to 19.4 months
GBM Prognostic Factors

- Positive
  - 95-98% resection
  - Age < 60
  - KPS > 70
  - MGMT promoter methylation
  - Cell proliferation Index (MIB-1) < 20%

Chaichana, JNS 2012
**GBM Genetics**

- **MGMT promoter methylation**
  - Increases susceptibility to TMZ
  - 21.7 mo median survival
  - 46% 2-year survival rate (vs 13.8%)

- **EGFRvIII**
  - Mutant EGFR receptor not found in normal tissues
  - 30% of GBM
Phase I Study of Safety and Immunogenicity of ADU-623, a live-attenuated *Listeria monocytogenes* vaccine (\(\Delta actA/\Delta inlB\)) expressing EGFRvIII and NY-ESO-1, in Patients with Treated and Recurrent WHO Grade III/IV Astrocytomas

- **PI:** Marka Crittenden
- **CI:** Brendan Curti, Walter Urba, Keith Bahjat and Pankaj Gore

Attenuated Listeria strain is used to generate a heightened immune response to the novel EGFRvIII peptide sequence
Acoustic Neuroma

- Benign tumors that arise from the vestibular nerves
- 1/100,000 pt
- Mean age 53
- 5% have NF2
- No clear relationship to environmental exposures other than high-dose ionizing radiation as a child
Acoustic Neuroma Presentation

- Hearing loss
  - Acute
  - Slowly progressive
- Tinnitus
- Vertigo/Disequilibrium
- Trigeminal nerve symptoms
- Mass effect on brain stem
Acoustic Neuroma Natural History

- Mean growth rate 1-1.5 mm/year
- Significant variation can exist
- ~40% may remain stable over short term follow up (~4 years)
Acoustic Neuroma Treatment

- Observation
  - Small tumors

- Radiosurgery
  - Older patients
  - < 2 cm tumors

- Surgery
  - Younger patients
  - Larger tumors
  - Hearing preservation (60% successful)
Case Example: Large AN

52 y/o with hearing loss, imbalance and headaches
Hearing Preservation Surgery

43 y/o with disequilibrium
Hearing Preservation Surgery
Acoustic Neuroma Postop Course

- Typical hospital stay is 3 - 5 days
- Significant initial disequilibrium
  - Usually resolves over several days
- Transient facial weakness is possible
  - Recovery can take 6-12 months
  - 90-95% of patients will achieve HB Grade 1 or 2 function
Pituitary Tumors

- 3rd most common intracranial tumor
- 90% are adenomas
Pituitary Tumor Presentation

- **Nonfunctioning**
  - Present by mass effect
  - On gland → hormonal deficiencies, inc Prolactin
    - Low Testosterone, Amenorrhea
    - Secondary hypothyroidism
    - Adrenal Insufficiency
  - On optic chiasm → bitemporal hemianopsia
  - On cavernous sinus → diplopia

- **Functioning**
  - Prolactinoma
Pituitary Tumor Presentation

- Functioning adenomas
  - Prolactinoma → amenorrhea, galactorrhea, low T
  - Somatotroph → acromegaly/gigantism
  - Corticotroph → Cushing’s disease

- Gonadotroph and thyrotroph are rare
Pituitary apoplexy

- Ischemic or hemorrhagic infarction of pituitary gland

- Sx
  - Severe HA
  - IIIrd or VIth nv paresis
  - Chiasmopathy

- Can be a surgical emergency
- Pt should go to ED
- Start stress dose steroids
Pituitary labs

- 8 am cortisol
- Thyroid panel
- Prolactin
- ACTH
- GH
- IGF-1
- FSH, LH
- Estrogen or Testosterone
Pituitary Tumor Treatment

- Prolactinoma
  - >200 ng/mL
  - Medical therapy with dopamine agonist

- All other secreting tumors
  - Surgery is first-line
  - 80+% cure rate for microadenomas
  - 50% for macroadenomas

- Smaller non-secreting tumors can be followed

- Larger tumors/suprasellar extension → Surgery
Case: Pituitary Adenoma

- 61 y/o with 3 years of progressive fatigue
- Dx with depression and fibromyalgia
Case: Pituitary Adenoma
• Stage I: Expanded Endonasal Approach to
  – Nasal-Septal flap and abdominal fat graft

• Stage II: Right Modified orbitozygomatic craniotomy
  – Right Middle Fossa Component

  – Stage III: Gamma Knife to right cavernous sinus
Endoscopy has revolutionized pituitary and midline skull base surgery

- Larger tumors → increased risk of CSF leak
  - Lumbar drain
  - Abdominal fat graft
  - Vascularized nasal-septal flap

- Transient postop DI is not uncommon
- Long term DI is very rare
- Sinus infections are not unusual
- Endocrinology follow up is necessary
Case: Endoscopic Skull Base Approach

× 57 y/o with left eye visual loss
Case: Endoscopic Skull Base Approach
25 y/o M with left 6th nerve palsy
25 y M, left sixth nerve palsy
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