Pediatric Brain Tumors: Updates in Treatment and Care

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Objectives

• Introduce the common pediatric brain tumors

• Discuss current treatment strategies for pediatric brain tumors

• Answer your questions
Epidemiology

- Brain tumors are the most common solid tumor among children under 15 years of age.
- Pediatric brain tumors represent about 20% of all childhood cancers.
- Childhood brain tumors account for a small percentage of all primary brain tumors (adults + children).
- Brain tumors account for a high percentage of morbidity and mortality in children with cancer.
Incidence

- Overall incidence of brain tumors in the United States is approximately 6.3 primary malignant brain tumors per 100,000 individuals
- In children < 15 years old, incidence is 2.8 per 100,000
- Overall, appears to be a slight increased incidence in males
Location and Metastases

• Most tumors in children are located in the infratentorium or the bottom and back part of the brain
• Primary brain tumors are more common than brain metastases in pediatrics
• In pediatrics metastatic tumors to the brain are generally from other solid tumors or leukemia/lymphoma
Four Brain Tumors in Childhood

- Astrocytoma or Glioma
- Diffuse Intrinsic Pontine Glioma (DIPG)
- Medulloblastoma
- Ependymoma
Astrocytomas/Gliomas

- The most common type of pediatric brain tumor

- Divided into two major categories:
  - Low grade
  - High Grade
Low Grade Gliomas

- Comprise about 35-50% of all childhood brain tumors
- Heterogeneous group of tumors
- Diverse clinical behavior from spontaneous regression to progressive and metastatic disease
Causes

• The cause of most pediatric brain tumors is unknown
• Rare inherited syndromes:
  • Neurofibromatosis Type-1, NF-2, Tuberous Sclerosis
Low Grade Glioma Presentation

- Specific symptoms depend upon tumor location and patient’s age
- Cerebral hemispheric lesions (in the front and top of the brain) may present with headaches, seizures and occasionally focal neurologic deficits.
- Posterior fossa (in the back and lower part of the brain) lesions present with hydrocephalus, weakness and imbalance.
MRI Appearance of a Low Grade Astrocytoma
Treatment of Low Grade Glioma

• Close observation alone in patients in some patients (especially NF-1)
  • Tumors may regress on their own
• Surgical resection is mainstay of treatment
  • A complete surgical resection leads to 80-100% long-term disease-free and overall survival
Treatment of Low Grade Glioma

- Chemotherapy has been used since the 1980’s and continued to improve
  - Combination of oral and IV medications
  - Newer targeted therapies
- Radiation therapy is generally reserved for older children with progressive disease that is unresectable and if chemotherapy is failing
Targeted therapy

Figure 2. Activation of a receptor tyrosine kinase leads to converting RAS from the inactive GDP-bound form to the active GTP-bound form, which localizes to the cellular membrane. The activation of RAS starts a cascade via the RAF/MEK/ERK or PI3K/AKT/mTOR pathways. Many tumor suppressors affect different steps in the cascade, and their loss leads to hyperactivation of the pathway. First, neurofibromin converts the GTP-bound active RAS into the GDP-bound inactive form. Second, PTEN is a lipid phosphatase that counteracts PI3K by dephosphorylating its second messengers. Third, the hamartin/tuberin complex, which is a GTP-activating protein, inhibits mTOR by inactivating Rheb. Different small molecules and compounds are being studied as potential targeted therapies by blocking different steps in both pathways.
Outcomes

• Depends upon age, tumor location, ability to perform surgery and responses to therapy.
  • With a complete surgical resection, may be close to 90% long term cure
  • Some tumors in difficult locations or resistant to chemotherapy and radiation can have much worse outcomes even though they are technically “Low Grade”
High Grade Astrocytomas

- Highly malignant and infiltrative tumors
  - Anaplastic Astrocytoma and Glioblastoma Multiforme (GBM) are most common types
- More common in adults than children
- The presentation is similar to the symptoms of low grade astrocytomas, but often there is a much shorter duration
MRI Images of an Anaplastic Astrocytoma of the right temporal lobe.
Treatment

• Maximal surgical resection if possible
• Many strategies employed:
  • Radiation therapy
  • Intensive chemotherapy
  • Biologically targeted agents
Outcomes

• Very difficult tumor to cure, but with a complete surgical resection followed by focal radiotherapy, some children can and do survive this tumor
Diffuse Intrinsic Pontine Glioma

- Unique tumor of the brainstem that is very aggressive
- Surgical resection of this tumor is not possible
- Unfortunately, no long term effective treatment strategy has been realized
- Focal radiation therapy usually provides some stability of the tumor for 6 months to 18 months.
Normal Brainstem  Diffuse Intrinsic Pontine Glioma
Medulloblastoma

- Most common “malignant” brain tumor of childhood (~20% of all brain tumors in kids)
- Has a tendency to spread to the other parts of the CNS
- Peak incidence is at age 5-7 years old
- Often presents with a wobbly gait, vomiting and headaches
MRI of a medulloblastoma located in the cerebellum.
Evaluation and Treatment

• Full metastatic work-up is essential
  • Spine MRI and spinal tap looking for bulky tumor or floating tumor cells

• Maximal surgical resection is key
  • Patients who undergo a complete surgical resection have a better prognosis compared to those who do not
Treatments

- Treatment strategy often based on age
- Combination of surgery, chemotherapy, radiation and intense chemotherapy with hematopoietic cell rescue
- In younger children we make every attempt to avoid or delay radiation
Outcomes

• Depending on patient’s age, metastatic work-up, type of tumor and extent of surgical resection, there is approximately 50-85% 5-year overall survival

• Highest risk of recurrence in 1st year post-therapy

• The future is again trying to harness tumor-directed therapy that specifically targets the tumor in an effort to improve outcomes and decrease toxic side effects
# Big News in Medulloblastoma

## Molecular Subgroups of Medulloblastoma

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<th>Consensus</th>
<th>WNT</th>
<th>SHH</th>
<th>Group 3</th>
<th>Group 4</th>
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<td>Cho (2010)</td>
<td>C6</td>
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<td>C2/C4</td>
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<td>Group C</td>
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<td>Thompson (2006)</td>
<td>B</td>
<td>C',D</td>
<td>E, A</td>
<td>A, C</td>
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### Demographics
- **Age Group:** Infant, Child, Adult
- **Gender:** Male, Female

### Clinical Features
- **Histology:**
  - Classic, rarely LCA
  - Desmoplastic/nodular, classic, LCA
  - Uncommonly M+
  - Infants good, others intermediate

- **Metastasis:**
  - Rarely M+
  - Very good

- **Prognosis:**
  - Very frequently M+
  - Poor

- **Gender:**
  - Male
  - Female

### Genetics
- **CTNNB1 Mutation:**
  - 6-

- **FET1/SMO/SUFU Mutation:**
  - 9q-, 10q-

- **GLI2 Amplification:**
  - 3q+, 17q+

- **MYCN Amplification:**
  - 11p-, 17q+

- **MYC Amplification:**
  - 5q-, 10q-

- **Neuronal/Glutamatergic:**
  - Neuronal/Glutamatergic

### Gene Expression
- **WNT Signaling:**
  - MYC+

- **SHH Signaling:**
  - MYCN+

- **Photoreceptor/GABAergic:**
  - MYC+++
Ependymoma

- Third most common pediatric brain tumor
  - 8-10% of all childhood brain tumors
- Can occur anywhere in the central nervous system, but usually associated with a ventricular surface (ependymal lining)
- Most common symptoms include nausea, vomiting and headache
0.0T MRC22422
Ex: 1
AXIAL SE T1 POST GAD
Se: 7/18
Im: 9/24
Ax: 127.7

512 x 448
Mag: 1.1x

ET: 1
TR: 663.0
TE: 17.0

5.0thk/1.0sp
W: 758 I: 536

PENOV 15.9 x 18.9cm
Treatments

• Surgery is the most important part of therapy
• Focal radiation therapy improves outcomes after tumor resection
• Chemotherapy, in general, is not effective in improving survival
  New combinations are under investigation
Outcomes

• 5-year survivals range from 60-80%.
• Higher in completely removed lesions with modern surgical technique and improved radiotherapy strategies
Late Effects and Quality of Life

- Neurocognitive deficits
  - Learning difficulties and memory problems

- Endocrine dysfunction
  - Thyroid problems, growth delay, weak bones, abnormal puberty and inability to have children

- Secondary malignancies
  - Development of different aggressive tumors 10-20 years after initial treatment
Where are We Headed?

- Improved Survival and More Research
- Best Quality of Life
The Future

• New biologic targeted therapies
  • Medulloblastoma
  • Gliomas
• Immunotherapy - Vaccine based strategies to stimulate the body’s natural anti-tumor activity
• Improved radiation techniques
  • Proton beam
How?

- Collaboration
- Awareness
- Hard Work
- Commitment
Collaborative Group Efforts

- Institutional and multi-institutional studies
- Collaboration with industry and drug manufacturers
Thank You

• Our patients and their families
• My colleagues dedicated to improving the lives of children with brain tumors
• American Brain Tumor Association
Like us to follow our program, hear about our research, share your stories and most importantly – support our courageous patients!

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