Pediatric Brain Tumors Update

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Disclosures

• None
This lecture will discuss:

- Imaging findings in a group of pediatric supratentorial and posterior fossa tumors with multiparametric imaging approaches
Pediatric Brain Tumors

• In 2017, there will be an estimated 4830 new cases
  • Incidence rate: 5.47 per 100,000 person-years
  • Prevalence rate: 35.4 per 100,000
  • >28,000 children living with this diagnosis
• Leading cause of death from solid tumors
Comparison: Primary Brain & CNS Tumors to Other Common Cancers in Childhood
Pediatric Brain Tumor Imaging

• **Goal of imaging**
  • *Define and diagnose* extent of disease
  • *Guide treatment planning* and intraoperative image-guided therapies: surgery, radiotherapy, chemotherapy
  • Morphometry and volumetrics
  • *Longitudinal quantitation* of tumor growth and volume
  • *Tissue characterization* with physiological specificity
    • Monitor response to local and systemic therapies in longitudinal studies
Neuroimaging Techniques

- Cellularity – diffusion weighted imaging
- White matter fiber tracts – diffusion tensor imaging
- Perfusion and vascularity – dynamic contrast enhanced MR perfusion
- Angiogenesis – Microvascular Permeability
- Metabolism – MR spectroscopy
- Biochemical pathways – molecular imaging (PET)
- Eloquent cortex – fMRI and MEG/MSI
Imaging Protocol

• Brain
  • Standard: Sagittal T1, axial T2, axial FLAIR, postcontrast multiplanar T1 images
  • Diffusion
  • Multivoxel Spectroscopy
  • T1 permeability perfusion

• Spine:
  • Postcontrast multiplanar T1
  • Optional: sagittal T2 SPACE and sagittal diffusion
Pediatric Brain Tumors:

• **Supratentorial tumors**
  • Most common in first 3 years of life
• **Infratentorial tumors**
  • Most common from age 4-10 years
• **Equal frequency of supratentorial and infratentorial tumors**
  • > 10 years of age
Pilocytic Astrocytoma

- WHO Grade 1
- Most common glioma in children
- Males > females
- Occur primarily in children
  - Peak age 0-9 years and then incidence decreases
  - Cerebellum, optic pathway, diencephalon and temporal lobe
- Older children
  - Cerebral hemisphere
- Best outcome with complete resection
- Genetics
  - Tandem duplication at 7q34 leading to fusion between KIAA and BRAF
  - Increased incidence in NF-1 and Noonan syndrome
Duplication of 7q32 in Pediatric Low-Grade Astrocytomas

Deregulated BRAF kinase activity leads to high levels of MEK/ERK and mTOR activity and increased cell growth. Chen Y-H, Gutmann DH. The molecular and cell biology of pediatric low-grade gliomas. Oncogene, 33(16):2019-26, 2014
Low Grade Glioma Management

Pediatric Low Grade Astrocytoma

• Long survival but high morbidity for unresected disease
• NF-1 association
• BRAF alterations are frequent
PBTC 029: AZD644 MEK inhibitor

Diagnosis

4 months later

5 months after treatment
Suprasellar Low Grade Glioma
Diencephalic Syndrome

- Rare cause of failure to thrive
- Emaciation with normal caloric intake, absent fat, alertness, hyperactivity
- Association with chiasmatic/hypothalamic glioma
- Astrocytomas often larger and occur at younger age than other astrocytomas in this region
- Low grade histology but can seed and have aggressive behavior
- Model of partial growth hormone resistance

New WHO Classification: Embryonal Tumors

- Embryonal tumour with multilayered rosettes, C19MC altered
- Embryonal tumour with multilayered rosettes, NOS
- Medulloepithelioma
- CNS neuroblastoma
- CNS ganglioneuroblastoma
- CNS embryonal tumour, NOS
- Atypical teratoid/rhabdoid tumour
- CNS embryonal tumour with rhabdoid features
- Medulloblastoma
ATRT

• Most common malignant CNS tumor < 6 months of age
• Median age 2-4 years
• Poor prognosis
  • CSF dissemination common (20-30% at diagnosis)
• Infratentorial location < age 3 years
• Heterogeneous on CT and MR
  • Cysts, hemorrhage, necrosis
• Mutation in SMARCB1 tumor suppressor gene on chromosome 22q which codes for a subunit(INI1) of the SWI/SNF chromatin remodeling protein complex
Atypical Teratoid Rhabdoid Tumor

Genetic hallmark of ATRT is loss of or mutation of the INI1 locus at 22q11.2.
T1 Permeability and Pediatric Brain Tumors

- 38 children with brain tumors
- Determination of high grade vs low grade
  - Statistically significant for $K_{\text{trans}}$, $V_e$ and $K_{\text{ep}}$
    - $K_{\text{trans}}$ (transfer rate constant from blood to EES)
      - Higher for high grade tumors: p-value <0.001
    - $V_e$ (extracellular, extravascular volume fraction)
      - Lower for high grade tumors: p-value <0.001
      - Different from adults
    - $K_{\text{ep}}$ (rate constant from EES back to blood)
      - Higher for high grade tumors: p-value <0.001

Vajapeyam S, Stamoulis C, Ricci K, Kieran M, Poussaint TY. Automated Processing of DCE MRI: Correlation of Advanced Pharmacokinetic Metrics with Tumor Grade in Pediatric Brain Tumors. AJNR 2016 In press
17 year old girl with Anaplastic Ependymoma
3 year old boy with Pilocytic Astrocytoma
Posterior Fossa Tumors of Childhood

- Medulloblastoma
- Cerebellar pilocytic astrocytoma
- Ependymoma
- Brainstem glioma
- Rare:
  - Rhabdoid tumors, hemangioblastoma, dermoid-epidermoid tumors, acoustic schwannomas, meningioma, teratoma and skull base tumors
Medulloblastoma

- Incidence: peaks at age 9 years and younger
- Treatment based on risk stratification
  - Age of presentation
  - Presence of residual disease
  - Presence of disseminated disease
- Average risk
  - > 3 years
  - Rx: Craniospinal radiation and adjuvant chemotherapy
  - 80-85% 5 year survival
- High risk
  - < 3 years, subtotal resection (>1.5 cm³), metastatic disease at diagnosis; 60-70% 5 year survival
Medulloblastoma

Molecular subtypes

Group 4  Group 3  WNT  SHH

Tumor

Normal
Vomiting and altered gait
Metastatic Medulloblastoma
MRI of the Spine

Questionable drop metastases at dorsal aspect of cord at C2 and T4

Axial T1 C+ at levels of questionable abnormalities

Courtesy of Laura Hayes
DTI

Nodular foci of restricted diffusion consistent with metastases
Postop medulloblastoma resection
PBTC-025B Response to Smoothened Inhibitor: Vismodegib which targets SHH pathway.

Baseline

4 months later
MRI Surrogates for Molecular Subgroups of Medulloblastoma

## MRI characteristics

<table>
<thead>
<tr>
<th>Location</th>
<th>WNT N=4</th>
<th>SHH N=13</th>
<th>3 N=13</th>
<th>4 N=17</th>
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<tbody>
<tr>
<td>Peduncle</td>
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<td>L Hemisphere</td>
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<td>Fourth V</td>
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### Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>WNT N=4</th>
<th>SHH N=13</th>
<th>3 N=13</th>
<th>4 N=17</th>
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<tbody>
<tr>
<td>Blood product</td>
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<tr>
<td>Poorly defined</td>
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<tr>
<td>T1+Gad</td>
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<tr>
<td>Minimal enh.</td>
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<td>Uniform enh.</td>
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<td>Ring-like enh.</td>
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Radiogenomic Mapping for Medulloblastoma

• Collaborative Project with Stanford, Toronto and Boston Children’s Hospital
• Correlation of oncogenomic data with imaging features to create radiogenomic maps for medulloblastoma
• RSNA 2016 Abstract:
  • A Pilot Study of Integrating Computational Image Features and Molecular Subtypes in Medulloblastoma
    • 249-dimensional image features capturing a variety of tumor phenotypic characteristics including tumor intensity, histogram, gabor filters, shape, and edge sharpness features correlate with molecular subtypes
Radiogenomics: Linking Genomics and Imaging Data

- Understand biological process reflected in clinical imaging
- Create imaging biomarkers that identify the genomic characteristics
Study Design

Medulloblastoma database

29 patients
Risk assessment
Physiological condition

Molecular subgroups

4 identified molecular subtypes with Wnt (n=4), Shh (n=11), Group 3 (n=6), and Group 4 (n=8)

Preoperative T2-w MRI
Quantitative cancer imaging feature pipeline

Tumor phenotypic characteristics including tumor intensity, histogram, gabor filters, shape, and edge sharpness features correlate with molecular subtypes.
Image feature visualization by unsupervised hierarchical clustering

Edge features

Shape features

Texture features

Gabor features

Histogram features
• MRI-defined computational image features can be used to associate with molecularly-defined subtypes of medulloblastoma.

• Tumor edge and histogram-based features reflected strong associations with molecular subgroups (p-value = 0.036 and 0.032 respectively)

• Extensions:
  - access other imaging modalities
  - evaluate inter-reader variability
  - validation with external clinical cohorts
Ependymoma

- Fourth most common posterior fossa tumor
- 8-12% of CNS tumors
- Infratentorial location in 70% of cases
- Arise from radial glial cells which are candidate stem cells
- 50% with calcification; 20% with cysts
- Slightly more frequent in males
- 60% of pediatric ependymomas rely on telomerase activity, a ribonucleoprotein permitting limitless replication
  - Children with telomerase-active tumors have reduced survival*

**Molecular Classification of Ependymal Tumors across All CNS Compartments, Histopathological Grades, and Age Groups**

<table>
<thead>
<tr>
<th>Anatomic Compartment</th>
<th>SPINE (SP-)</th>
<th>Posterior Fossa (PF-)</th>
<th>Supratentorial (ST-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular Subgroup</td>
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<tr>
<td>Histopathology</td>
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<td></td>
<td></td>
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<tr>
<td>Genetics</td>
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<tr>
<td>Oncogenic Driver</td>
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<tr>
<td>Tumor Location</td>
<td></td>
<td></td>
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<tr>
<td>Age Distribution (years)</td>
<td>4 18 60</td>
<td>4 18 60</td>
<td>4 18 60</td>
</tr>
<tr>
<td>Gender Distribution</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Patient Survival (OS; months)</td>
<td>120</td>
<td>120</td>
<td>120</td>
</tr>
</tbody>
</table>


Cancer Cell, 27:728-43, 2015
Ependymoma
NAA/Cr void
Cho/cr 1.33
ml/Cr 2.67
Diffuse Midline Glioma

- Infiltrative midline glioma
  - Astrocytic differentiation
  - K27M mutation in H3F3A or HIST1H3B/C
  - Location: brainstem, thalamus and spinal cord
  - WHO grade IV
  - Age at presentation: 5-11 years
- Brainstem:
  - Poor prognosis
  - < 10% 2 year survival despite therapies
Diffuse Midline Glioma

- Thalamic glioma
- Cervical spinal cord astrocytoma
- Brainstem glioma
Pontine Gliogenesis and DIPG Tumorigenesis

- **Initiating event (H3F3A, P53 mutations, etc)**
- **Olig2+ Pontine Precursor Cell**
- **Unregulated Hedgehog Pathway**
- **Hedgehog Pathway**
- **PDGFRa+ Cell**
- **Additional dysregulation (MET, PI3K, etc)**
- **Normal glial cells**
- **Diffuse intrinsic pontine glioma**

*Courtesy of Dr. Michelle Monje*
Diffuse Intrinsic Brainstem Glioma:  
6 year old girl with cranial nerve palsies

Diagnosis made on MR without biopsy
- Limited tumor samples
- Lack of knowledge of molecular targets
- Limited therapeutic stratification
DTI Brainstem Glioma:
Before and After Radiation

At diagnosis

5 months after XRT
### One-Year PFS and OS by $^{18}$F-FDG Uptake

<table>
<thead>
<tr>
<th>Baseline $^{18}$F-FDG uptake</th>
<th>n</th>
<th>1-y PFS ± SE</th>
<th>1-y OS ± SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;White matter (no further data)</td>
<td>6</td>
<td>15.2% ± 5.7%</td>
<td>53.4% ± 8.6%</td>
</tr>
<tr>
<td>=White matter</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;White matter</td>
<td>23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;gray matter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>=Gray matter</td>
<td>1</td>
<td>14.3% ± 9.4%</td>
<td>28.6% ± 13.9%</td>
</tr>
<tr>
<td>&gt;Gray matter</td>
<td>6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

12 year old girl with DIPG where intensity of $^{18}$F-FDG uptake between white and gray matter <25% of tumor

PFS = 258 days
OS = 348 days
7 year old boy with DIPG with high intensity and > 75% tumor $^{18}$F-FDG uptake

PFS=169 days; OS= 196 days
Apparent Diffusion Coefficient (ADC)
Brownian Motion (mm²/s)

High Diffusion
Low Cellularity

Low Diffusion
High Cellularity
Making the Histogram

1. FLAIR (or T2) Images
2. Used to Generate 3D ROI for Multiple Image Series
3. Volumetric 3D ROI Isolated
4. Volumetric 3D ROI Thresholded
5. Mapped to ADC, PET & Contrast Enhanced Images
6. Histogram of All Voxels in 3D ROI Generated
Diffusion Histogram Number of Peaks at Baseline with PFS and OS

Poussaint TY, Vajapeyam S, Ricci KI et al. Neuro Oncol. 2016 18(5), 725-34
PFS 40 days; OS 52 days

PFS 455 days; OS 997 days
Change in Number of Peaks Post-RT

- No change in peaks (0), Peaks from 1 → 2 (1) have worse PFS compared to number of peaks decreased from 2 → 1 (-1)
No change in ADC peaks, PFS 60 days and OS 137 days
Bimodal peak of enhancement, PFS 98 days

Unimodal peak of enhancement, PFS 218 days
ADC Histogram in Molecular Subgroups of DIPG

Zukotynski KA, Vajapeyam S, Fahey FH, Kocak M, Brown D, Ricci KI, Onar-Thomas A, Fouladi M, Poussaint TY. Correlation of 18F-FDG PET and MR Apparent Diffusion Coefficient (ADC) Histogram Metrics with Survival in Diffuse Intrinsic Pontine Glioma: A Report from the Pediatric Brain Tumor Consortium. JNM Accepted
Patients with more negative correlation coefficients have lower PFS, (HR of 0.17, (95% CI: 0.03-0.89, p=0.036)).
Summary

• Overview of imaging features of a subset of pediatric brain tumors
• Thank you for your attention!
Acknowledgments

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• PBTC Site Principal Investigators
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