SYSTEMIC MANAGEMENT OF PEDIATRIC PRIMARY BRAIN TUMORS

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University of Puerto Rico Medical Sciences Campus
DISCLOSURES

- No disclosures
INTRODUCTION

- Pediatric CNS tumors
  - most common solid tumor
  - 2\textsuperscript{nd} most common malignancy in children after leukemia, representing about 20-25% of all childhood cancer
  - 4,300 new cases per year in USA
FIGURA 82: PRIMEROS 5 TIPOS DE CÁNCER INFANTIL MÁS DIAGNOSTICADOS EN PUERTO RICO, 2008-2012

Figure 82: Top five incidence childhood cancer sites in Puerto Rico, 2008-2012

<table>
<thead>
<tr>
<th>Niños / Boys (N = 389)</th>
<th>%</th>
<th>Niñas / Girls (N = 369)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leucemias/Leukemias</td>
<td>30.3</td>
<td>Leucemias/Leukemias</td>
<td>25.7</td>
</tr>
<tr>
<td>Linfomas/Lymphomas</td>
<td>22.4</td>
<td>Carcinomas/Carcinomas</td>
<td>19.5</td>
</tr>
<tr>
<td>Neoplasmas del SNC/CNS</td>
<td>17.7</td>
<td>Linfomas/Lymphomas</td>
<td>13.0</td>
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<tr>
<td>Neoplasmas</td>
<td>6.2</td>
<td>Neoplasmas del SNC/CNS</td>
<td>12.2</td>
</tr>
<tr>
<td>Carcinomas/Carcinomas</td>
<td></td>
<td>Sarcomas de tejidos blandos/Soft tissue sarcomas</td>
<td>8.1</td>
</tr>
<tr>
<td>Neoplasia de células germinales/Germ cell neoplasm</td>
<td>5.7</td>
<td>Otros sitios/Other sites</td>
<td>21.4</td>
</tr>
<tr>
<td>Otros sitios/Other sites</td>
<td>17.7</td>
<td></td>
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</tbody>
</table>

Fuente de Datos: Archivo de Incidencia del Registro Central de Cáncer de Puerto Rico, 6 de julio de 2015.
• Leading cause of death related to cancer in pediatric population
• More than 70% of children diagnosed with brain tumors will survive for more than 5 years after diagnosis
  ○ But survival rates are wide-ranging depending on tumor type and stage.
• Long-term sequelae related to the initial presence of the tumor and subsequent treatment are common.
The evaluation and treatment of CNS tumors are complex due to:

- challenge for complete surgical removal
- complications related to treatment
- poor response to therapy in certain situations

Treatment requires coordinated multimodal pediatric specialists
Neuro-oncology has emerged as a separate subspecialty in the past 20-30 years

- Since then, significant advances in treatment and overall survivals have been achieved in some CNS tumors (ex. MB)
  - Others continued to be a challenge (ex. HGG, BSG)
  - Improvements in cure rates since then are largely as a result of technologic advances in imaging, neurosurgery, and radiation oncology and the introduction of combination chemotherapy
Challenges may be overcome by new technologies that facilitate our understanding of the genomic landscape of pediatric brain tumors, international cooperation among leading laboratory and clinical investigators

- COG, PBTC, CERN, European Groups

All patients should be considered for enrollment in a clinical trial when an appropriate study is available

- Multi-institutional, cooperative studies
New WHO Classification in 2016

Genetic and epigenetic profiling of tumors has impacted their diagnosis, allowing for the subgrouping of heterogeneous tumor groups and leading to the complete renaming of some tumor types

- New entities
- New subtypes
- Removals

Uses

- Risk stratification and staging
- Treatment planning
The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary

David N. Louis1 · Arie Perry2 · Guido Reifenberger3,4 · Andreas von Deimling4,5 · Dominique Figarella-Branger6 · Webster K. Cavenee7 · Hiroko Ohgaki8 · Otmar D. Wiestler9 · Paul Kleihues10 · David W. Ellison11
<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>World Health Organization (WHO) Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse astrocytic and oligodendrogial tumors</td>
<td></td>
</tr>
<tr>
<td>Diffuse astrocytoma</td>
<td>WHO grade II</td>
</tr>
<tr>
<td>Anaplastic astrocytoma</td>
<td>WHO grade III</td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>WHO grade IV</td>
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<tr>
<td>Diffuse midline glioma</td>
<td>WHO grade IV</td>
</tr>
<tr>
<td>Oligodendroglioma</td>
<td>WHO grade II</td>
</tr>
<tr>
<td>Other astrocytic tumors</td>
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<tr>
<td>Pilocytic astrocytoma</td>
<td>WHO grade I</td>
</tr>
<tr>
<td>Subependymal giant cell astrocytoma</td>
<td>WHO grade I</td>
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<tr>
<td>Pleomorphic santoastrocytoma</td>
<td>WHO grade II</td>
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<tr>
<td>Ependymal tumors</td>
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<tr>
<td>Ependymoma</td>
<td>WHO grades II or III</td>
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<tr>
<td>Ependymoma, RELA fusion-positive</td>
<td>WHO grades II or III</td>
</tr>
<tr>
<td>Choroid plexus tumors</td>
<td></td>
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<tr>
<td>Choroid plexus papilloma</td>
<td>WHO grade I</td>
</tr>
<tr>
<td>Atypical choroid plexus papilloma</td>
<td>WHO grade II</td>
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<tr>
<td>Choroid plexus carcinoma</td>
<td>WHO grade III</td>
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<tr>
<td>Neuronal and mixed neuronal-glial tumors</td>
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<tr>
<td>Dysembryoplastic neuroepithelial tumor</td>
<td>WHO grade I</td>
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<tr>
<td>Ganglioglioma</td>
<td>WHO grade I</td>
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<tr>
<td>Desmoplastic infantile astrocytoma and ganglioglioma</td>
<td>WHO grade I</td>
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<tr>
<td>Tumors of the pineal region</td>
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<tr>
<td>Pineoblastoma</td>
<td>WHO grade IV</td>
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<tr>
<td>Embryonal tumors</td>
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<tr>
<td>Medulloblastoma</td>
<td>WHO grade IV</td>
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<tr>
<td>Medulloblastoma, genetically defined</td>
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<tr>
<td>Medulloblastoma, WNT-activated</td>
<td></td>
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<tr>
<td>Medulloblastoma, SHH-activated and TP53 mutant</td>
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<tr>
<td>Medulloblastoma, SHH-activated and TP53-wildtype</td>
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<tr>
<td>Medulloblastoma, non-WNT/non-SHH</td>
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<tr>
<td>Medulloblastoma, group 3</td>
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<tr>
<td>Medulloblastoma, group 4</td>
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<td>Medulloblastomas, histologically defined</td>
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<tr>
<td>Medulloblastoma, classic</td>
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<tr>
<td>Medulloblastoma, desmoplastic/nodular</td>
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<tr>
<td>Medulloblastoma with extensive nodularity</td>
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<tr>
<td>Medulloblastoma, large cell/neoplastic</td>
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<tr>
<td>Atypical teratoid/thaboid tumor</td>
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<tr>
<td>Germ cell tumors</td>
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<td>Germinoma</td>
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<tr>
<td>Embryonal carcinoma</td>
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<td>Yolk sac tumor</td>
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<td>Choriocarcinoma</td>
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<tr>
<td>Teratoma</td>
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<tr>
<td>Mature teratoma</td>
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<tr>
<td>Immature teratoma</td>
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<tr>
<td>Mixed germ cell tumor</td>
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<tr>
<td>Tumors of the sellar region</td>
<td></td>
</tr>
<tr>
<td>Craniopharyngioma</td>
<td>WHO grade I</td>
</tr>
</tbody>
</table>

Pediatric Brain Tumors.
Dang, Mai; MD, PhD; Phillips, Peter

CONTINUUM: Lifelong Learning in Neurology. 23(6, Neuro-oncology):1727-1757, December 2017. DOI: 10.1212/CON.0000000000000545
Molecular features commonly seen or characteristic of specific pediatric brain tumors

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Genetic Alterations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medulloblastoma</td>
<td><strong>CTNNB1, DDX3X, TP53 mutation</strong></td>
</tr>
<tr>
<td>WNT</td>
<td><strong>PTCH1, SUFU, SMO, TP53, TERT mutations, GLI2 amplification</strong></td>
</tr>
<tr>
<td>SHH</td>
<td><strong>MYC amplification</strong></td>
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<tr>
<td>Group 3</td>
<td>17p deletion, 17q gain</td>
</tr>
<tr>
<td>Group 4</td>
<td></td>
</tr>
<tr>
<td>Atypical teratoid/rhabdoid tumor</td>
<td><strong>INI1/SNF5, BRG mutations</strong></td>
</tr>
<tr>
<td>Low-grade glioma</td>
<td>Mitogen-activated protein kinase (MAPK) pathway <strong>(BRAF fusions, V600E), NTRK2, FGFR1 mutations</strong></td>
</tr>
<tr>
<td>High-grade diffuse glioma</td>
<td><strong>H3.3G34RIV, TP53, ATRX, BRAF (V600E), PDGFRA, KRAS mutations; NTRK fusions</strong></td>
</tr>
<tr>
<td>Diffuse midline astrocytoma</td>
<td><strong>H3.3K27M, ACVR1 mutations</strong></td>
</tr>
<tr>
<td>Ependymoma</td>
<td><strong>RELA fusions, YAP1 fusions</strong></td>
</tr>
<tr>
<td>Dysembryoplastic neuroepithelial tumor</td>
<td><strong>FGFR1, BRAF mutations</strong></td>
</tr>
<tr>
<td>Ganglioglioma</td>
<td><strong>BRAF (V600E) mutation</strong></td>
</tr>
</tbody>
</table>

SHH = sonic hedgehog; WNT = wingless.

Data from International Agency for Research on Cancer, World Health Organization.1
EMBRYONAL TUMORS

- Medulloblastoma
  - Most common malignant brain tumor in pediatrics
- Atypical Teratoid Rhabdoid tumor
- PNET were removed
  - Now classified as other types
**Medulloblastoma**

- Most common embryonal tumor
- Most common malignant CNS tumor in pediatrics
- Current classification of medulloblastomas is based on molecular characterization; histopathologic criteria are retained when molecular analysis is not feasible or molecular results are not diagnostic
The molecular subgrouping of medulloblastomas arose from large-scale genetic profiling studies that identified four subgroups:

- WNT-activated (10%)
- Sonic hedgehog (SHH)-activated (30%)
- Group 3 (20%)
- Group 4 (40%)
Molecular subgroups of medulloblastoma: the current consensus.

WNT subgroup is characterized by activation of the WNT pathway
- commonly harbors mutations in exon 3 of CTNNB1 and monosomy chromosome 6
- Otherwise, WNT tumors harbor remarkably few genomic alterations
- Patients under the age of 16 with WNT tumors have an excellent prognosis when treated with surgery and craniospinal irradiation

SHH subgroup is characterized by activation of the SHH pathway
- A proportion of SHH tumors exhibit amplification of MYCN and GLI2, and mutations in TP53, frequently associated with anaplastic morphology
SHH tumors arise across all age groups and constitute the predominant tumor type in young children (<3 years of age) and adults, however, TP53 mutations are highly enriched in children aged 3–17 constituting a higher risk group with significantly worse outcomes.

Group 3 is characterized by recurrent MYC amplifications.

Group 3 are frequently metastatic, and overall outcome, particularly for those harboring MYC amplifications, is worse compared to the other subgroups.
Group 4 is the most common subgroup, but remains the least well biologically characterized

- the most common aberration is isochromosome 17q, followed by MYCN amplification
- Group 4 medulloblastomas occur most frequently in children and teenagers and approximately 30% are metastatic at diagnosis
## Novel molecular subgroups for clinical classification and outcome prediction in childhood medulloblastoma: a cohort study

Schwalbe, Edward C et al.
The Lancet Oncology, Volume 18, Issue 7, 958 - 971
Histopathologic sub-classification

- Classic
- Desmoplastic/nodular
- Extensive nodularity
- Large cell/anaplastic

Patients with nodular tumors tend to have good outcomes, while those with large cell/anaplastic tumors have poorer outcomes.
Management

- Treatment strategy has been based on clinical criteria: age, presence of metastasis, extent of resection, pathology
  - Average risk vs High risk
- Full metastatic work-up is essential because of increased tendency to spread outside the CNS.
  - Complete Spine MRI and CSF cytology by LP
- Maximal surgical resection was key (key in the future??)
- Combination of surgery, radiation and chemotherapy
- In younger children (particularly < 3 y/o) there is an attempt to avoid and delay radiation.
A recent international consensus report proposed a new stratification system based on molecular subgrouping.
- **Low-risk** (greater than 90% survival)
  - WNT-mediated tumors and non-metastatic group 4 tumors with whole chromosome 11 loss or whole chromosome 17 gain
  - May qualify for reduced therapy

- **Average (standard) risk** (75% to 90% survival)

- **High-risk** (50% to 75% survival)
  - metastatic SHH or group 4 tumors or *MYCN*-amplified SHH medulloblastomas

- **Very high-risk** (50% survival)
  - group 3 tumors with metastases or SHH tumors with *TP53* mutation
Identification of activating pathways in some subgroups has provided an opportunity for the development of small molecule inhibitors as molecular-targeted therapy.

- Ex: vismodegib, an SMO inhibitor that inhibits the SHH pathway
  - Phase I and II clinical trials for relapsed medulloblastoma and have shown some response, although loss of sensitivity after initial response was frequently observed.
The newest generation of biologically-informed clinical trials, specifically PNET5, SJMB12 and the planned COG study, are evaluating therapy de-escalation for patients with WNT tumors, and excluding MYC and MYCN amplified tumors from the average risk strata.
Atypical teratoid / rhabdoid tumors are very aggressive tumors mainly seen in children younger than 3 years of age and can occur in all brain locations.

- Associated with inactivation of INI1
  - Now required for diagnosis

- Prognosis for patients is very poor even with high-dose chemotherapy and intrathecal chemotherapy followed by autologous stem cell rescue and radiation therapy
Variable tumor responses to treatment of ATRTs led researchers to question the molecular heterogeneity within this tumor group

- New sub groups
  - highly expresses tyrosinase along with transcription factor OTX2
  - highly expresses MYC
  - overexpression of either NOTCH in one study and proteins in the SHH pathway in the other

- Torchia and colleagues additionally showed that two groups share an overexpression pattern of PDGFRB, which makes ATRT tumor cells sensitive to dasatinib and nilotinib, tyrosine kinase inhibitors
Future clinical studies and preclinical experiments will undoubtedly benefit from this new subgrouping of ATRTs as well as the molecular findings of potential drug targets.
Gliomas

- Astrocytic tumors are a type of glioma that arise from astrocytes.
- The 2016 WHO classification system organizes these tumors as either diffuse, including diffuse astrocytoma, or “other astrocytic” tumors.
  - **Diffuse astrocytic and oligodendroglial** tumors include diffuse astrocytoma grade II, anaplastic astrocytoma (III), glioblastoma (IV), oligodendroglioma, and high-grade brainstem glioma.
  - Those with more circumscribed growth patterns grouped as “**other astrocytic**” tumors include pilocytic astrocytoma, subependymal giant cell astrocytoma (SEGA), and pleomorphic xanthoastrocytoma.
LGG

- Multiple subtypes
- MC pediatric brain tumor
- BRAF oncogene mutations are the most frequent genomic alteration
  - KIAA1549-BRAF: associated with cerebellar pilocytic astrocytomas
  - BRAF V600E: associated with pleomorphic xanthoastrocytomas, gangliogliomas, subset of extracerebellar pylocytic astrocytomas
  - Unlike LGGs among older adolescents and adults, childhood LGGs almost never express IDH1 or IDH2 mutations and rarely undergo malignant transformation into higher-grade neoplasms
Current therapy:

- Surgery followed by observation
- Carbo-containing chemotherapy or cRT reserved for recurrent or progressive tumors
- Treatment decisions largely are based on the tumor’s location and the patient’s age at diagnosis rather than on the glioma histologic subtype or tumor biology
- With such strategies, the 10- to 20-year OS for children with LGGs is 83% to 94%
Future therapy:

- Targeted therapy
  - BRAF duplication/MAPK pathway–targeting agents
    - Selumetinib under study by PBTC
  - BRAFV600E–targeting agents
    - Dabrafenib is being studied in pediatric LGG
  - mTOR inhibitors
    - Everolimus approved for SEGA
    - Studies have shown activity in progressive pediatric LGG
      - (Yalon et al, Kieran et al)
        - These responses justify additional exploration of mTOR inhibitors against pediatric LGG
HGG

- Pediatric high-grade glioma (HGG) and diffuse intrinsic pontine glioma (DIPG) are diffusely infiltrative, malignant glial neoplasms that comprise a spectrum of histologies, and the vast majority anaplastic astrocytoma (WHO III) or glioblastoma (WHO IV)
- Subgroups have been distinguished on the basis of recurrent combinations of genomic and/or epigenomic features with distinct biologic and clinical characteristics
  - Oncogenic driver mutations in histones H3.1 (position K27) and H3.3 (positions K27 and G34) as well as in the activin A receptor, type I (ACVR1)
  - Rare *IDH1* and *IDH2* mutations in < 15 years old in GBM
HGG Subgroups

Fig 2. Subgroups of pediatric high-grade glioma that are based on German Cancer Research Center (DKFZ) methylation, age at onset, tumor location, oncogenic drivers, gene expression, and median survival. IDH, isocitrate dehydrogenase; PXA, pleomorphic xanthoastrocytoma; RTK-I, receptor tyrosine kinase (subgroup 1).
Current therapies: unfortunately continues to be very poor despite other advances

Surgery: extent of resection extremely important

There is a need for more effective regimens.......

- Temozolomide
  - Oral alkylating agent
  - Initially demonstrated antitumor activity as a single agent in the treatment of recurrent gliomas

- MGMT (O-6-Methylguanine-DNA methyltransferase)
  - DNA repair pathway functions to counteract the cytotoxic effects of alkylating agents, such as nitrosoureas and TMZ
Stupp et al, 2005

- The addition of TMZ to RT on newly diagnosed GBM resulted in a statistically significant survival benefit (12.2 months in RT alone vs. 14.6 months RT/TMZ) in adults
- Minimal additional toxicity (MC: hematological)
• TMZ has been well tolerated in children, but improvement in survival has not been seen as expected

  - COG phase II trial (ACNS-0126)
    - For newly diagnosed patients with HGGs and DIPG
    - TMZ/RT followed by TMZ maint.
EXPERIMENTAL DESIGN SCHEMA

SURGERY
(HGG ONLY)

ON STUDY

CHEMORADIOThERAPY
Radiation Therapy Dose: 54.0 Gy
with a Boost of 5.4 Gy
Temozolomide 90mg/m²/day
Daily for 42 Days

4 WEEK REST

MAINTENANCE
Temozolomide 200mg/m²/day
Days 1-5 Given Every 28 Days
Total = 10 Cycles

FOLLOW-UP

July 6, 2004
4-year EFS not significantly different between groups

Table 9 shows the distribution by pathology for both cohorts. The ACNS0126 diagnosis was based on the reviewer diagnosis, if available, and the institutional diagnosis, if the
4 year EFS is affected by present or increased MGMT status.

EFS comparison as a function of MGMT expression (no overexpression: 0, 1, and 2; overexpression: 3 and 4).
COG ACNS 0423 – closed August 2008

- For symptomatic newly diagnosed patients > 3 y/o
- XRT/TMZ followed by TMZ/CCNU maintenance
  - Synergistic effect combining TMZ/CCNU
  - Comparability with ACNS0126 results
EXPERIMENTAL DESIGN SCHEMA

SURGERY

ON STUDY

CHEMORADIOThERAPY
Radiation Therapy Dose: 54.0 Gy
with a Boost of 5.4 Gy
Temozolomide 90mg/m^2/day
Daily for 42 Days

4 WEEK REST

MAINTENANCE
CCNU 90 mg/m^2
Temozolomide 160mg/m^2/day x 5
Every 42 Days
Total = 6 Cycles

FOLLOW-UP
Phase 2 study of concurrent radiotherapy and temozolomide followed by temozolomide and lomustine in the treatment of children with high-grade glioma: a report of the Children's Oncology Group ACNS0423 study
Regina I. Jakacki  Kenneth J. Cohen  Allen Buxton  Mark D. Krailo  Peter C. Burger  Marc K. Rosenblum  Daniel J. Brat  Ronald L. Hamilton  Sandra P. Eckel  Tianni Zhou  ... Show more
Neuro Oncol (2016) 18 (10): 1442-1450
- Improved OS/EFS as compared to Maintenance TMZ alone
- Suggested benefit in MGMT overexpression, less than GTR and GBM!
  - Limitations: Unknown influence of IDH status and other molecular characteristics
Future therapies:

- the identification of multiple epigenetic regulatory processes provide a foundation for the development of novel treatments that target the genetic and epigenetic drivers of pediatric HGG initiation and progression
**Ependymoma**

- Second most common malignant pediatric brain tumor.
- Composed predominantly of neoplastic ependymal cells.
- Account for about 9% of all childhood brain tumors.
- Supratentorial
  - Posterior Fossa
- Spinal tumors
Molecular Subgrouping of Ependymal Tumors is Superior to Histopathological Grading for Risk Stratification

- **ST-SE** (Subependymoma with Balanced Genome)
- **ST-EPN-YAP1** (Anaplastic Ependymoma with YAP1-fusion)
- **ST-EPN-RELA** (Anaplastic Ependymoma with RELA-fusion)
- **PF-SE** (Subependymoma with Balanced Genome)
- **PF-EPN-A** (Anaplastic Ependymoma with Balanced Genome)
- **PF-EPN-B** (Anaplastic Ependymoma with Chromosomal Instability)
- **SP-SE** (Subependymoma with 6q deletion)
- **SP-MPE** (Myxopapillary Ependymoma with Chromosomal Instability)
- **SP-EPN** (Anaplastic Ependymoma with NF2 mutation)

**WHO grade** | **Age Group** | **Outcome**
--- | --- | ---
I | I | I
II / III | II / III | II / III
II / III | II / III | II / III
I | I | I
II / III | II / III | II / III
II / III | II / III | II / III
I | I | I
II / III | II / III | II / III
II / III | II / III | II / III
The integration of molecular subtypes and clinical follow-up data revealed a strong association with poor OS of patients with ST-EPN-RELA and PF-EPN-A tumors, who are usually children.
TREATMENT

- Surgery!!
- Adjuvant radiation therapy is often utilized, especially in PF lesions.
  - CS irradiation is no longer utilized because it does not significantly improve outcomes.
- Chemotherapy, in general, previously thought not to be effective impacting OS
ACNS0121: concluded that adjuvant cRT after surgical resection showed no improvement in outcome versus historical data, though the subset of patients with gross-total resection had an improved EFS

ACNS0831: Ongoing study investigating benefit of addition of adjuvant chemotherapy to surgical resection and RT
Targeted therapy
LONG TERM CARE

Many children with long-term sequelae 2ry to treatment:

- Neurologic: from surgery and tumor itself
- Endocrine: from tumor and post-radiation therapy
- Neurocognitive: from radiation therapy
- Secondary malignancies: from radiation, chemotherapy and associated syndromes
- Infertility: from some chemotherapy agents
- Hearing and vision loss
Multi-institutional trials are being conducted in an attempt to:

- improve EFS and OS
- decrease toxicities associated to chemotherapy agents
- try new agents, new combinations and modalities
- decrease total RT doses as much as possible in an attempt to diminish long-term side effects without compromising patient’s survival
APEC1621 (Pediatric MATCH: Targeted Therapy Directed by Genetic Testing in Treating Pediatric Patients with Relapsed or Refractory Advanced Solid Tumors, Non-Hodgkin Lymphomas, or Histiocytic Disorders):

- NCI-COG: will match targeted agents with specific molecular changes identified using a next-generation sequencing targeted assay of more than 3,000 different mutations across more than 160 genes in refractory and recurrent solid tumors
- Patients with tumors that have molecular variants addressed by treatment arms included in the trial will be offered treatment on Pediatric MATCH
THE GOAL

BRAIN TUMOR MAN

MY EXPERIENCE AS A PATIENT & SURVIVOR!
CONCLUSIONS

- Rapidly evolving field
- New classification integrating molecular profile
- Major advances in genomics and epigenomics that should impact targeted therapy
- All patients should be considered for enrollment in a clinical trial when an appropriate study is available
  - 2 COG affiliated centers in PR
  - 2 pediatric Neuro-Oncologist
¡Gracias!