Systemic Management of Pediatric Primary Brain Tumors

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Disclosures

- No disclosures

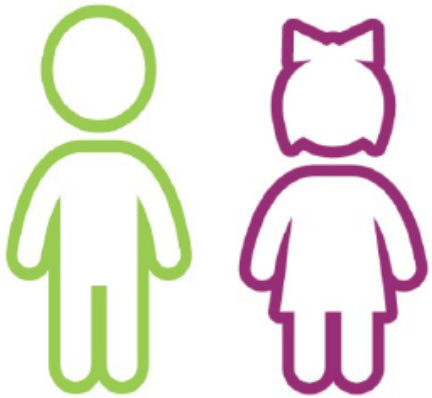
Introduction

- Pediatric CNS tumors
  - most common solid tumor
  - 2nd most common malignancy in children after leukemia, representing about 20-25% of all childhood cancer
  - 4,300 new cases per year in USA

Puerto Rico: 2008-2012

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

Niños / Boys (N = 389)	%
Leucemias/Leukemias	30.3
Linfomas/Lymphomas	22.4
Neoplasmas del SNC/CNS Neoplasms	17.7
Carcinomas/Carcinomas	6.2
Neoplasia de células germinales/Germ cell neoplasm	5.7
Otros sitios/Other sites	17.7



Niñas / Girls (N = 369)	%
Leucemias/Leukemias	25.7
Carcinomas/Carcinomas	19.5
Linfomas/Lymphomas	13.0
Neoplasmas del SNC/CNS Neoplasms	12.2
Sarcomas de tejidos blandos/ Soft tissue sarcomas	8.1
Otros sitios/Other sites	21.4

Fuente de Datos: Archivo de Incidencia del Registro Central de Cáncer de Puerto Rico, 6 de julio de 2015.
Data Source: Incidence Case File of Puerto Rico from the Puerto Rico Central Cancer Registry, July 6, 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 sub-specialty 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

Classification

- 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

Acta Neuropathol (2016) 131:803–820
DOI 10.1007/s00401-016-1545-1

REVIEW

The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary

David N. Louis[1] · Arie Perry[2] · Guido Reifenberger[3,4] · Andreas von Deimling[4,5] · Dominique Figarella-Branger[6] · Webster K. Cavenee[7] · Hiroko Ohgaki[8] · Otmar D. Wiestler[9] · Paul Kleihues[10] · David W. Ellison[11]

Tumor Type	World Health Organization (WHO) Grade
Diffuse astrocytic and oligodendroglial tumors	
Diffuse astrocytoma	WHO grade II
Anaplastic astrocytoma	WHO grade III
Glioblastoma	WHO grade IV
Diffuse midline glioma	WHO grade IV
Oligodendroglioma	WHO grade II
Other astrocytic tumors	
Pilocytic astrocytoma	WHO grade I
Subependymal giant cell astrocytoma	WHO grade I
Pleomorphic xanthoastrocytoma	WHO grade II
Ependymal tumors	
Ependymoma	WHO grades II or III
Ependymoma, *RELA* fusion-positive	WHO grades II or III
Choroid plexus tumors	
Choroid plexus papilloma	WHO grade I
Atypical choroid plexus papilloma	WHO grade II
Choroid plexus carcinoma	WHO grade III
Neuronal and mixed neuronal-glial tumors	
Dysembryoplastic neuroepithelial tumor	WHO grade I
Ganglioglioma	WHO grade I
Desmoplastic infantile astrocytoma and gangliglioma	WHO grade I
Tumors of the pineal region	
Pineoblastoma	WHO grade IV
Embryonal tumors	
Medulloblastoma	WHO grade IV
Medulloblastoma, genetically defined	
Medulloblastoma, WNT-activated	
Medulloblastoma, SHH-activated and *TP53* mutant	
Medulloblastoma, SHH-activated and *TP53*-wildtype	
Medulloblastoma, non-WNT/non-SHH	
Medulloblastoma, group 3	
Medulloblastoma, group 4	
Medulloblastomas, histologically defined	
Medulloblastoma, classic	
Medulloblastoma, desmoplastic/nodular	
Medulloblastoma with extensive nodularity	
Medulloblastoma, large cell/anaplastic	
Atypical teratoid/rhabdoid tumor	
Germ cell tumors	
Germinoma	
Embryonal carcinoma	
Yolk sac tumor	
Choriocarcinoma	
Teratoma	
Mature teratoma	
Immature teratoma	
Mixed germ cell tumor	
Tumors of the sellar region	
Craniopharyngioma	WHO grade I

SHH = sonic hedgehog; WNT = wingless.

[a] Data from International Agency for Research on Cancer, World Health Organization.[1]

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

Tumor	Genetic Alterations
Medulloblastoma	
WNT	*CTNNB1, DDX3X, TP53* mutation
SHH	*PTCH1, SUFU, SMO, TP53, TERT* mutations, *GLI2* amplification
Group 3	*MYC* amplification
Group 4	17p deletion, 17q gain
Atypical teratoid/rhabdoid tumor	*INI1/SNF5, BRG* mutations
Low-grade glioma	Mitogen-activated protein kinase (MAPK) pathway (*BRAF* fusions, V600E), *NTRK2, FGFR1* mutations
High-grade diffuse glioma	*H3.3G34R/V, TP53, ATRX, BRAF* (V600E), *PDGFRA, KRAS* mutations; *NTRK* fusions
Diffuse midline astrocytoma	*H3.3K27M, ACVR1* mutations
Ependymoma	*RELA* fusions, *YAP1* fusions
Dysembryoplastic neuroepithelial tumor	*FGFR1, BRAF* mutations
Ganglioglioma	*BRAF* (V600E) mutation

SHH = sonic hedgehog; WNT = wingless.

[a] Data from International Agency for Research on Cancer, World Health Organization.[1]

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

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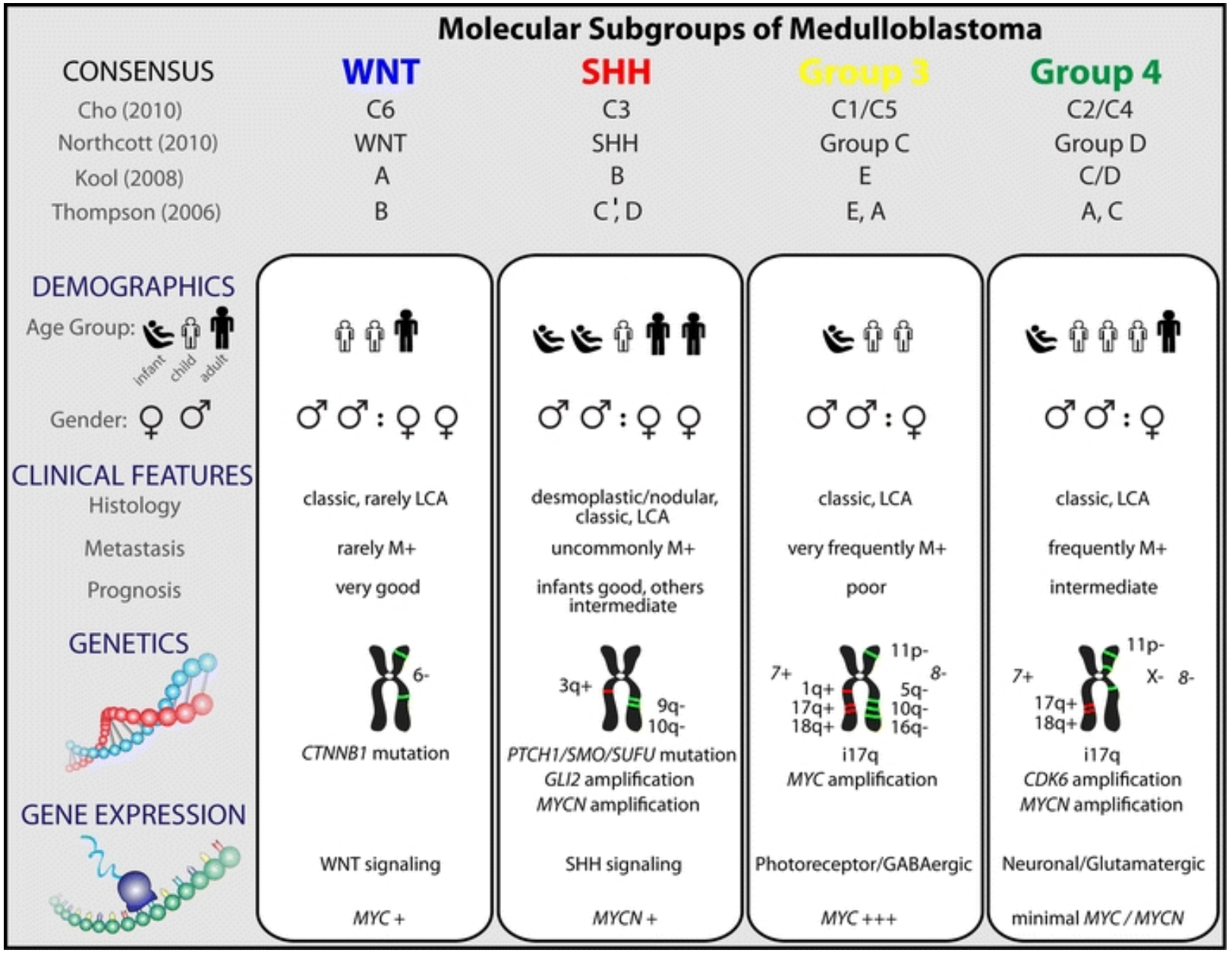
Embryonal tumors

- 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%)



Taylor MD, Northcott PA, Korshunov A, et al. Molecular subgroups of medulloblastoma: the current consensus. Acta Neuropathologica. 2012

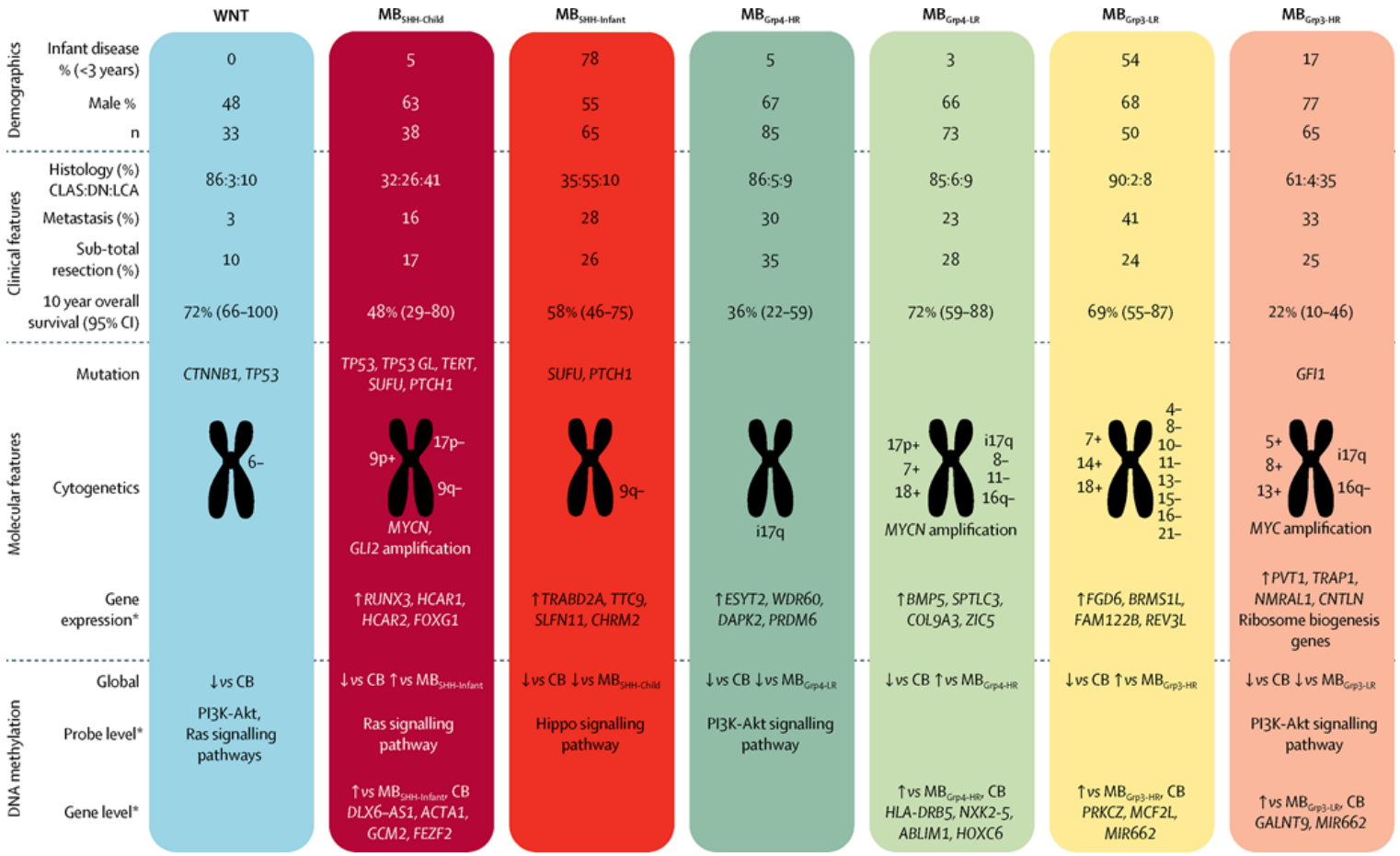
- WNT subgroup is characterized by activation of the WNT pathway
  - commonly harbors mutations in exon 3 of *CTNNB1* and monosomy chromosome 6
  - Otherwise, WNT tumors harbor remarkably few genomic alterations
  - Patients under the age of 16 with WNT tumors have an excellent prognosis when treated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

2017: 6 SUBGROUPS



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

Acta Neuropathol. 2016 June ; 131(6): 821–831. doi:10.1007/s00401-016-1569-6.

Risk stratification of childhood medulloblastoma in the molecular era: The Current Consensus

Vijay Ramaswamy[1,*], Marc Remke[2,3,*], Eric Bouffet[1], Simon Bailey[4], Steven C. Clifford[4], Francois Doz[5], Marcel Kool[6], Christelle Dufour[7], Gilles Vassal[7], Till Milde[8,9], Olaf Witt[8,9], Katja von Hoff[10], Torsten Pietsch[11], Paul A. Northcott[12], Amar Gajjar[12], Giles W. Robinson[12], Laetitia Padovani[13], Nicolas André[14], Maura Massimino[15], Barry Pizer[16], Roger Packer[17], Stefan Rutkowski[10], Stefan M. Pfister[6,8], Michael D. Taylor[18], and Scott L. Pomeroy[19]

- 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

Management

- 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.

Future

- 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

ATRT

- 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

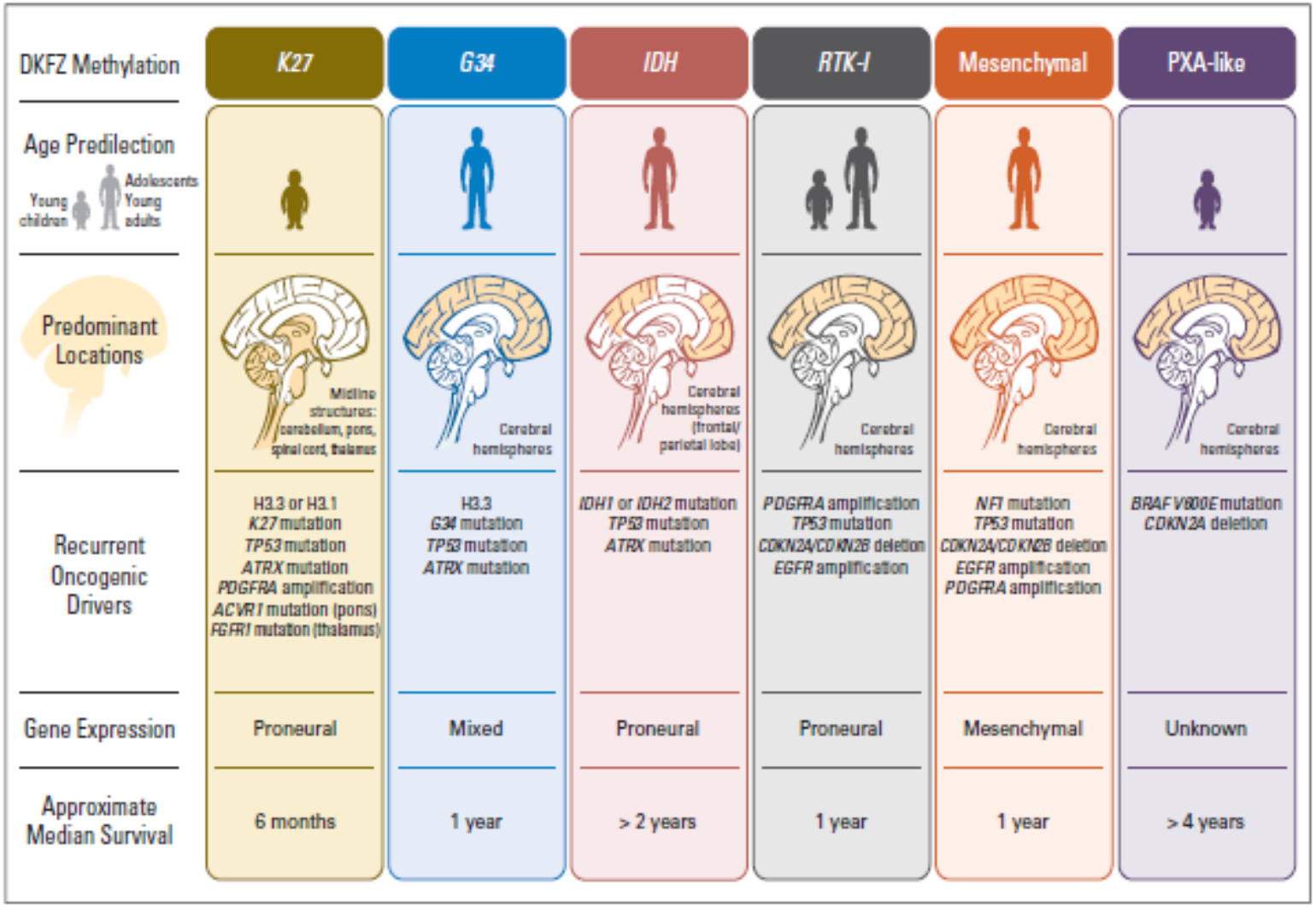


Fig 2. Subgroups of pediatric high-grade glioma that are based on German Cancer Research Center (DKFZ) methylation, age at onset, tumor location, oncogenic drives, gene expression, and median survival. IDH, isocitrate dehydrogenase; PXA, pleomorphic xanthoastrocytoma; RTK-I, receptor tyrosine kinase (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)

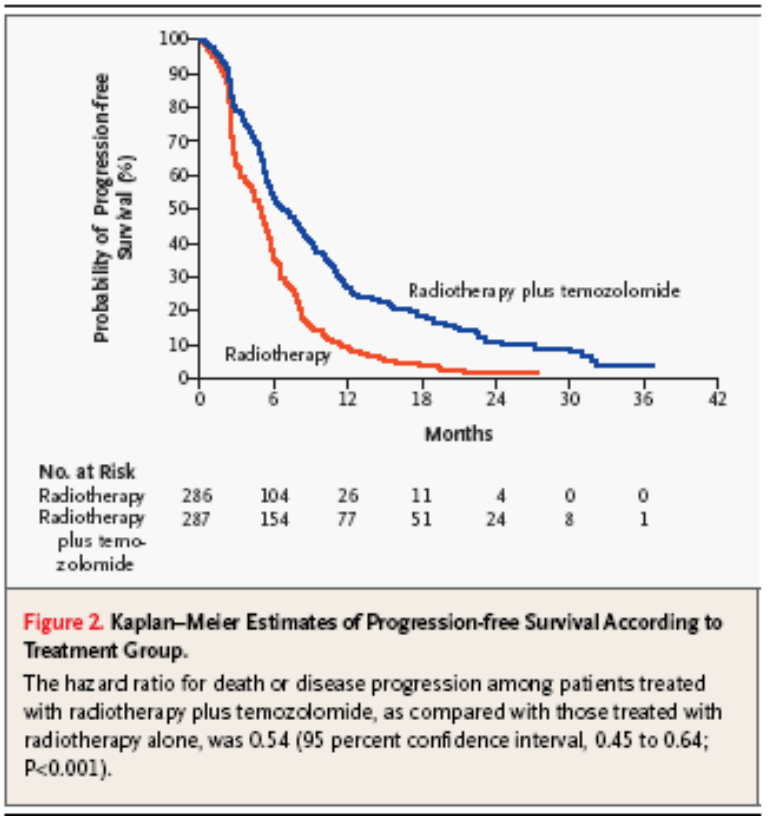


Figure 2. Kaplan–Meier Estimates of Progression-free Survival According to Treatment Group.

The hazard ratio for death or disease progression among patients treated with radiotherapy plus temozolomide, as compared with those treated with radiotherapy alone, was 0.54 (95 percent confidence interval, 0.45 to 0.64; P<0.001).

- 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

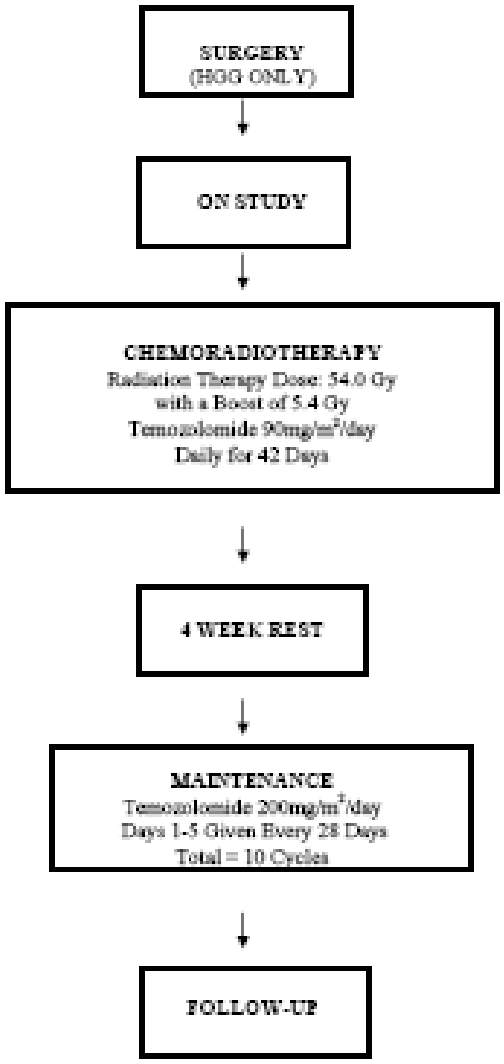


Figure 1. Event-Free Survival for HGG

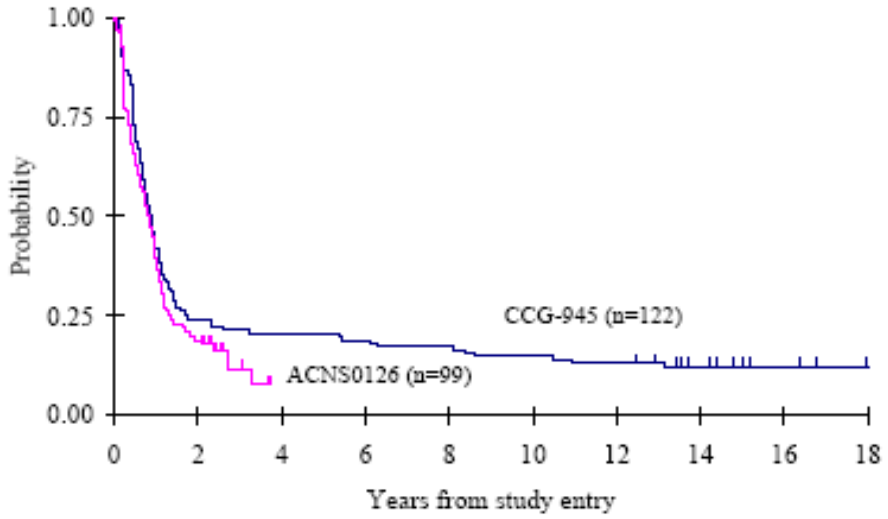
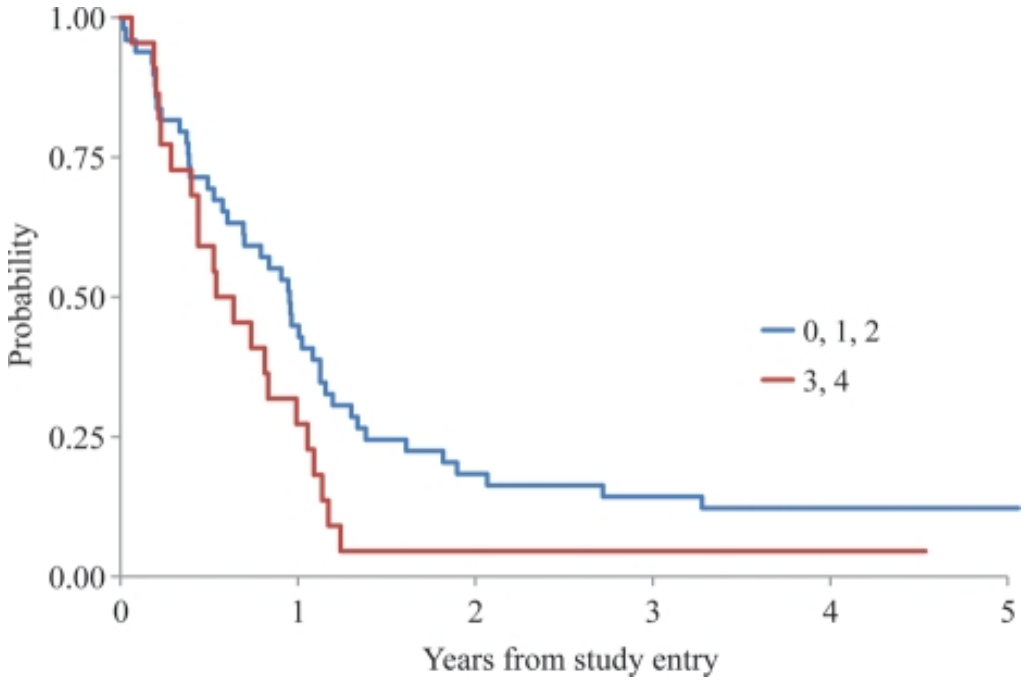


Table 9 shows the distribution by pathology for both cohorts. The ACNS0126 diagnosis was based on the reviewer diagnosis, if available, and the institutional diagnosis, if the

- 4-year EFS not significantly different between groups

Temozolomide in the treatment of high-grade gliomas in children: a report from the Children's Oncology Group
Kenneth J. Cohen Ian F. Pollack Tianni Zhou Allen Buxton Emiko J. Holmes Peter C. Burger Daniel J. Brat Marc K. Rosenblum Ronald L. Hamilton Robert S. Lavey ... Show more
Neuro Oncol (2011) 13 (3): 317-323



EFS comparison as a function of MGMT expression
(no overexpression: 0, 1, and 2; overexpression: 3 and 4).

- 4 year EFS is affected by present or increased MGMT status

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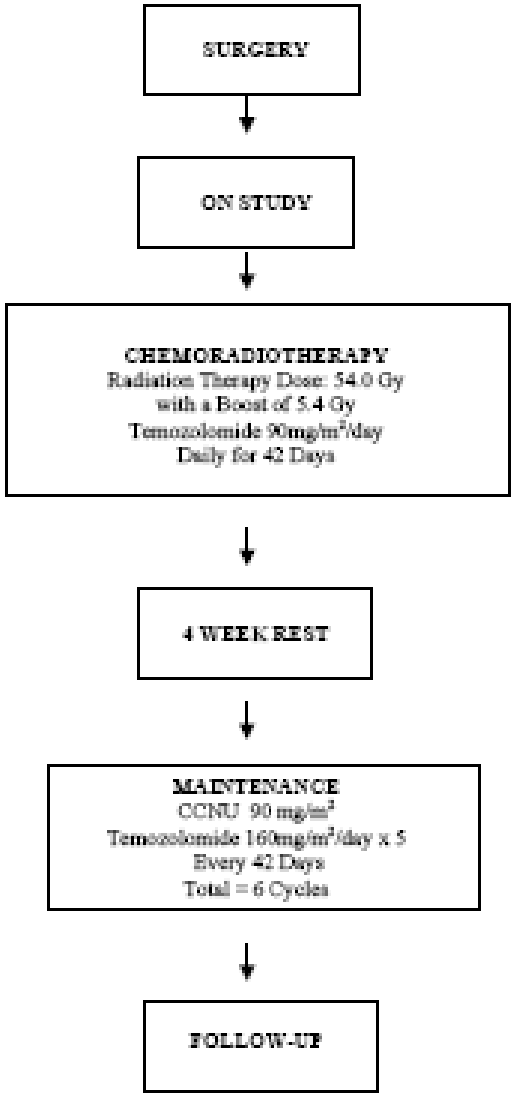
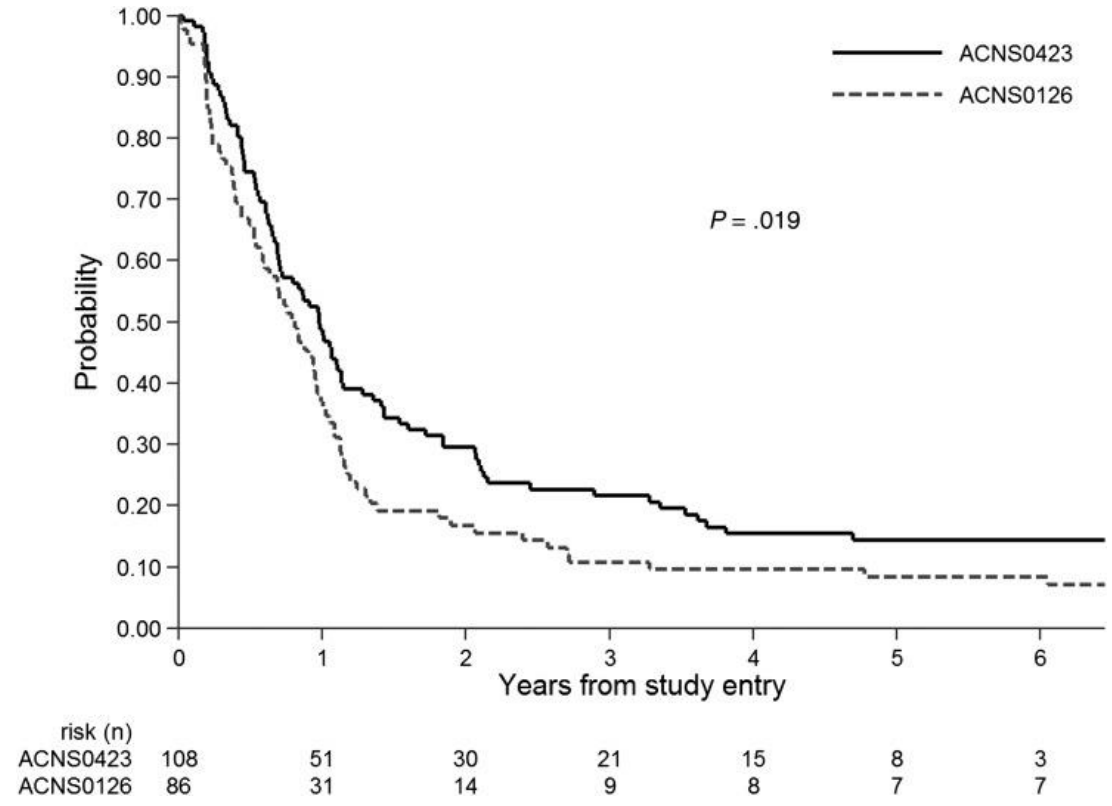
Neuro Oncol (2011) 13 (3): 317-323

- 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



HGG EFS



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 Sandrah 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

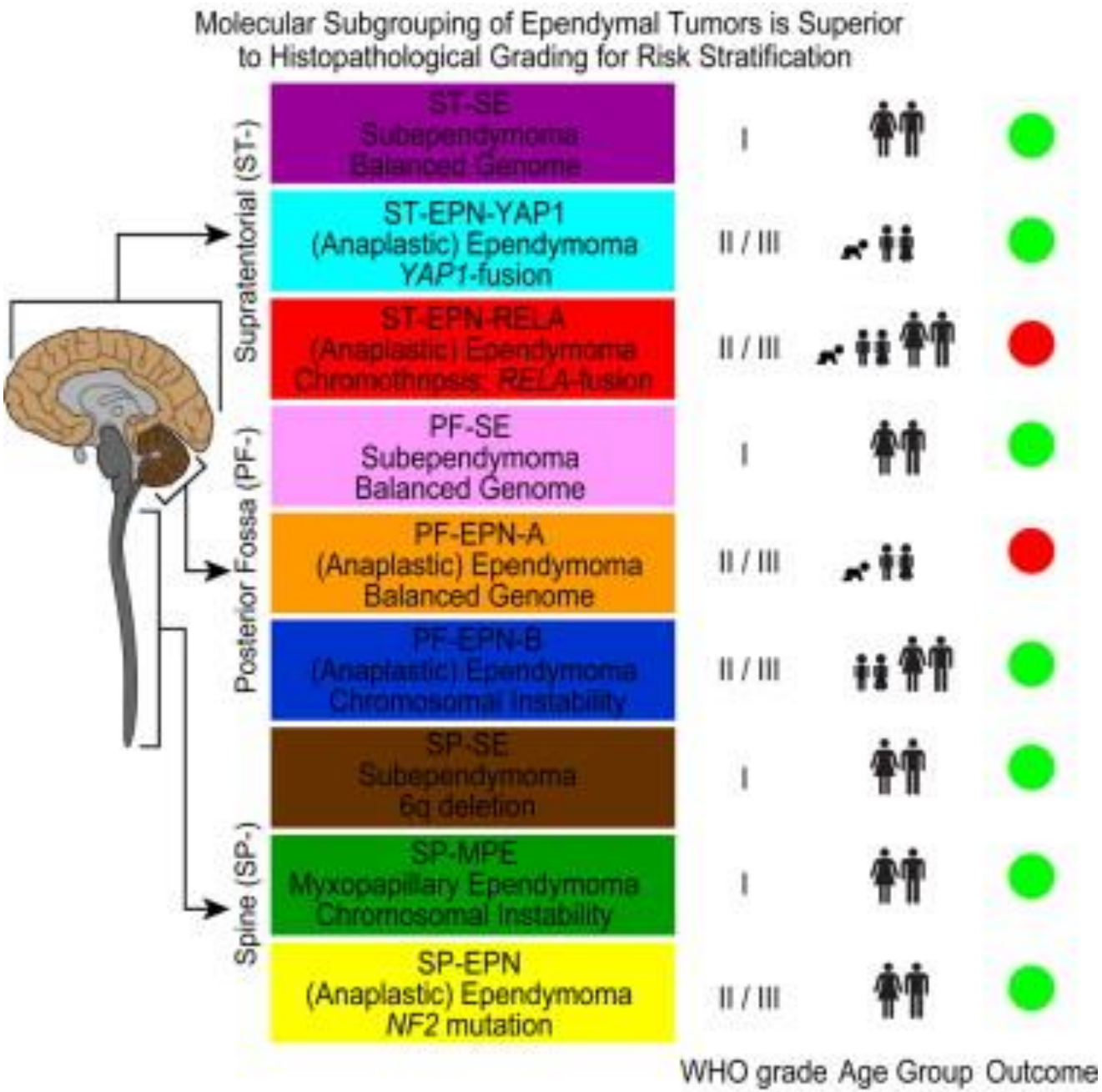
- Future therapies:
  - the identification of multiple epigenetic regulatory processes provide a foundation for the development of novel treatments that target the genetic and epigenetic drivers of pediatric HGG initiation and progression

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
Supratentorial (ST-)
Posterior Fossa (PF-)
Spine (SP-)
ST-SE
Subependymoma
Balanced Genome
ST-EPN-YAP1
(Anaplastic) Ependymoma
YAP1-fusion
ST-EPN-RELA
(Anaplastic) Ependymoma
Chromothripsis; RELA-fusion
PF-SE
Subependymoma
Balanced Genome
PF-EPN-A
(Anaplastic) Ependymoma
Balanced Genome
PF-EPN-B
(Anaplastic) Ependymoma
Chromosomal Instability
SP-SE
Subependymoma
6q deletion
SP-MPE
Myxopapillary Ependymoma
Chromosomal Instability
SP-EPN
(Anaplastic) Ependymoma
NF2 mutation
I
II / III
I
II / III
I
I
II / III
WHO grade
Age Group
Outcome

- 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

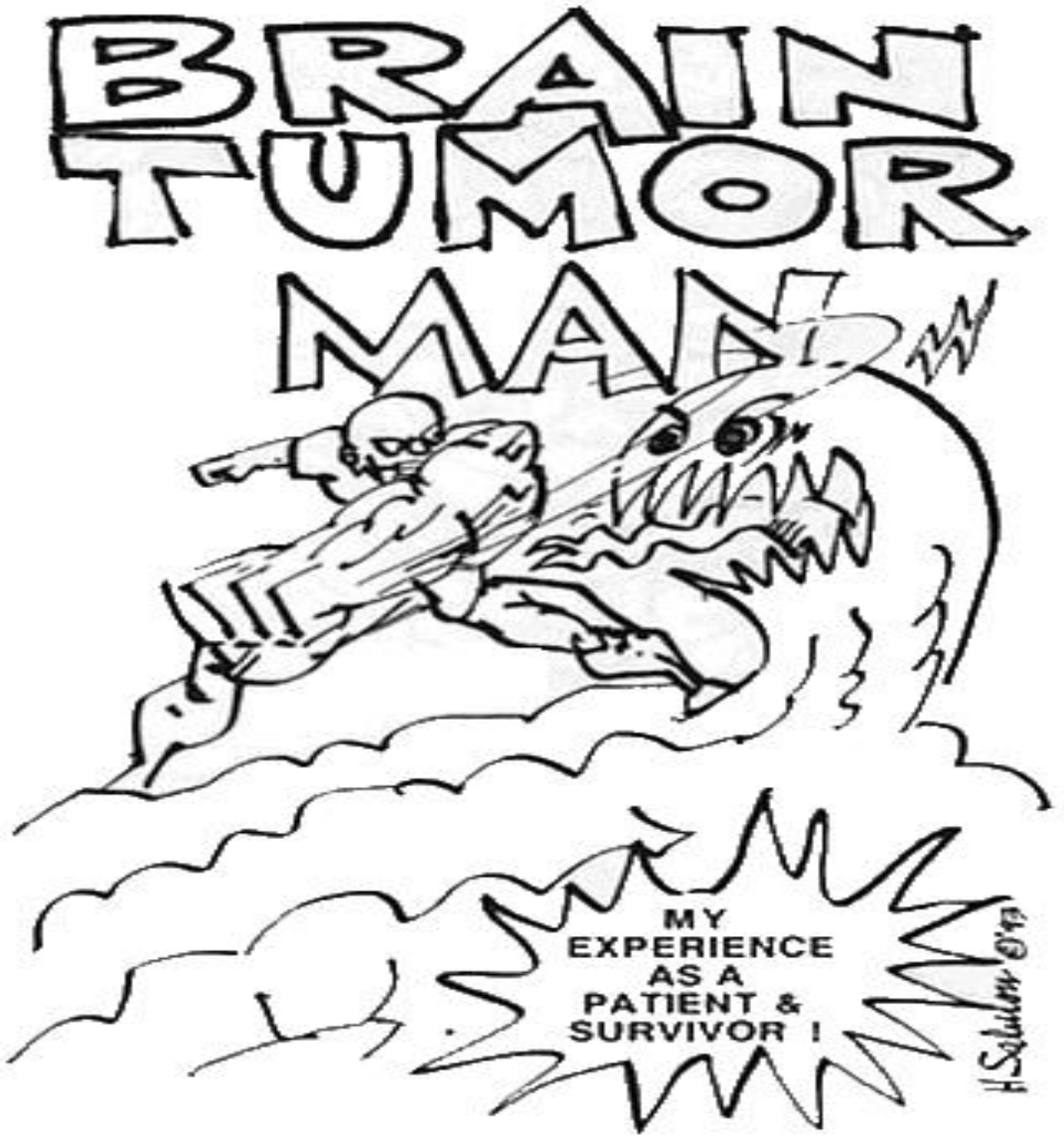
- Many children with long-term sequelae 2ry to treatment:
  - Neurologic: from surgery and tumor itself
  - Endocrine: from tumor and post-radiation therapy
  - Neurocognitive: from radiation therapy
  - Secondary malignancies: from radiation, chemotherapy and associated syndromes
  - Infertility: from some chemotherapy agents
  - Hearing and vision loss

Future

- 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



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!