

CHOC

Pediatric Brain Tumor: A Molecular Era

Mariko Sato, MD, PhD

Program Director, Neuro-Oncology

09.14.2022



Disclosure Statement

- I have no financial relationships with any commercial interest related to the content of this presentation.


SEPTEMBER
IS National
CHILDHOOD CANCER
Awareness Month
COURAGE
HOPE
LOVE
FAITH
EDUCATE
STRENGTH

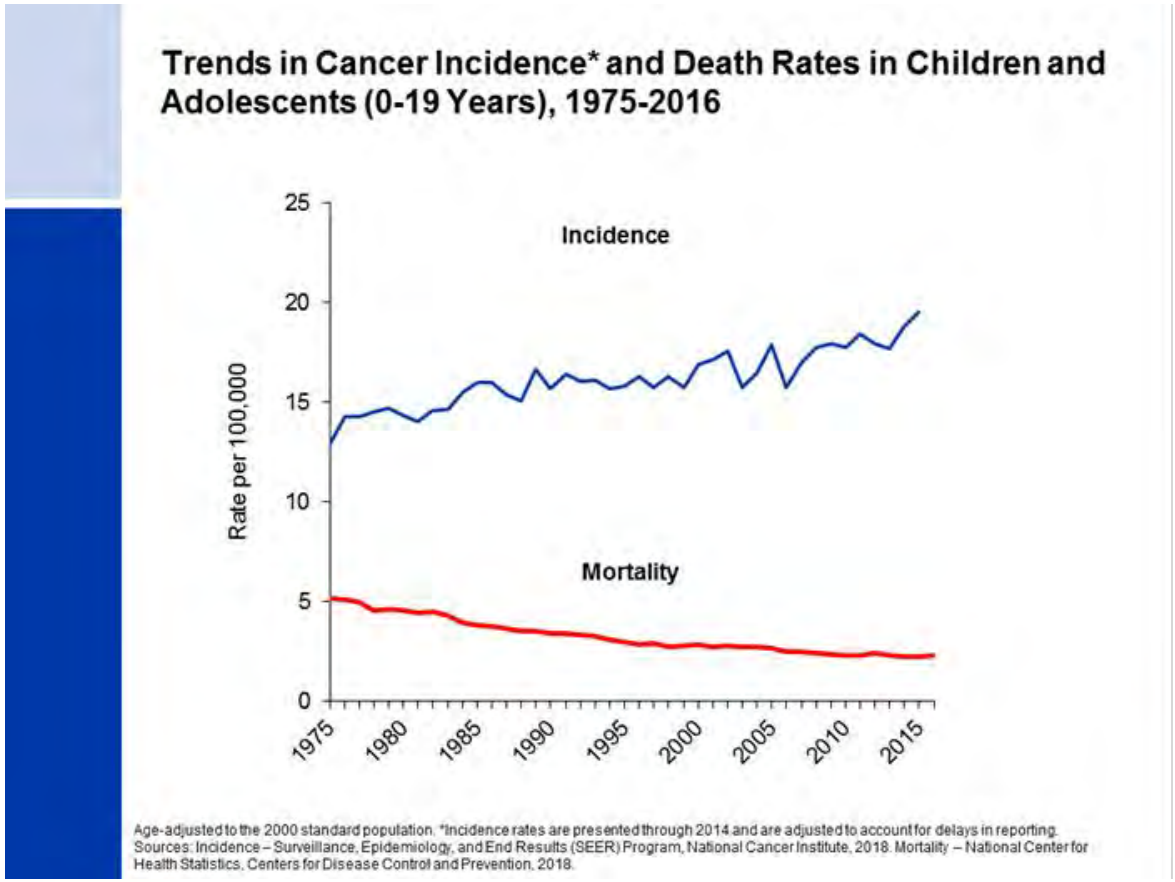
CHOC

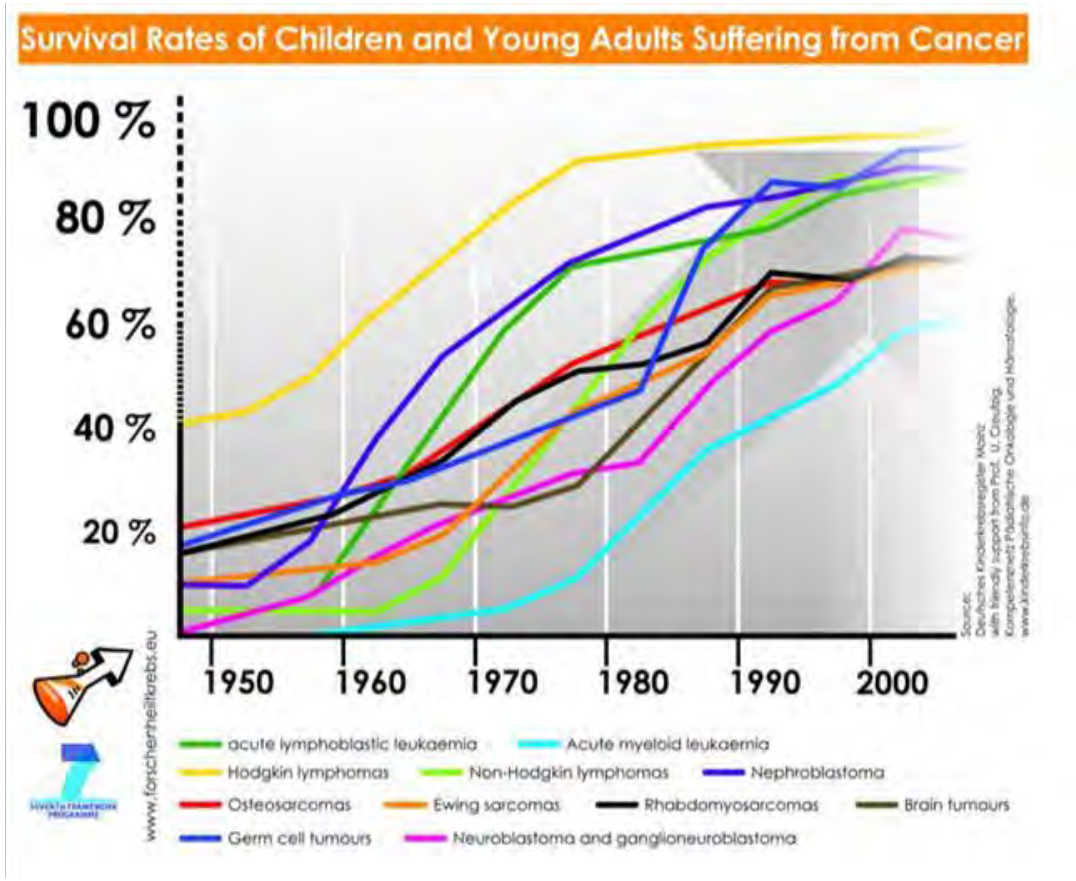
Outline

1. Epidemiology of brain tumors
2. Three cases
    1. Three common diagnosis of brain tumors
    2. Evolving diagnosis-New WHO classification
    3. New therapeutic approach
3. Questions

CHOC

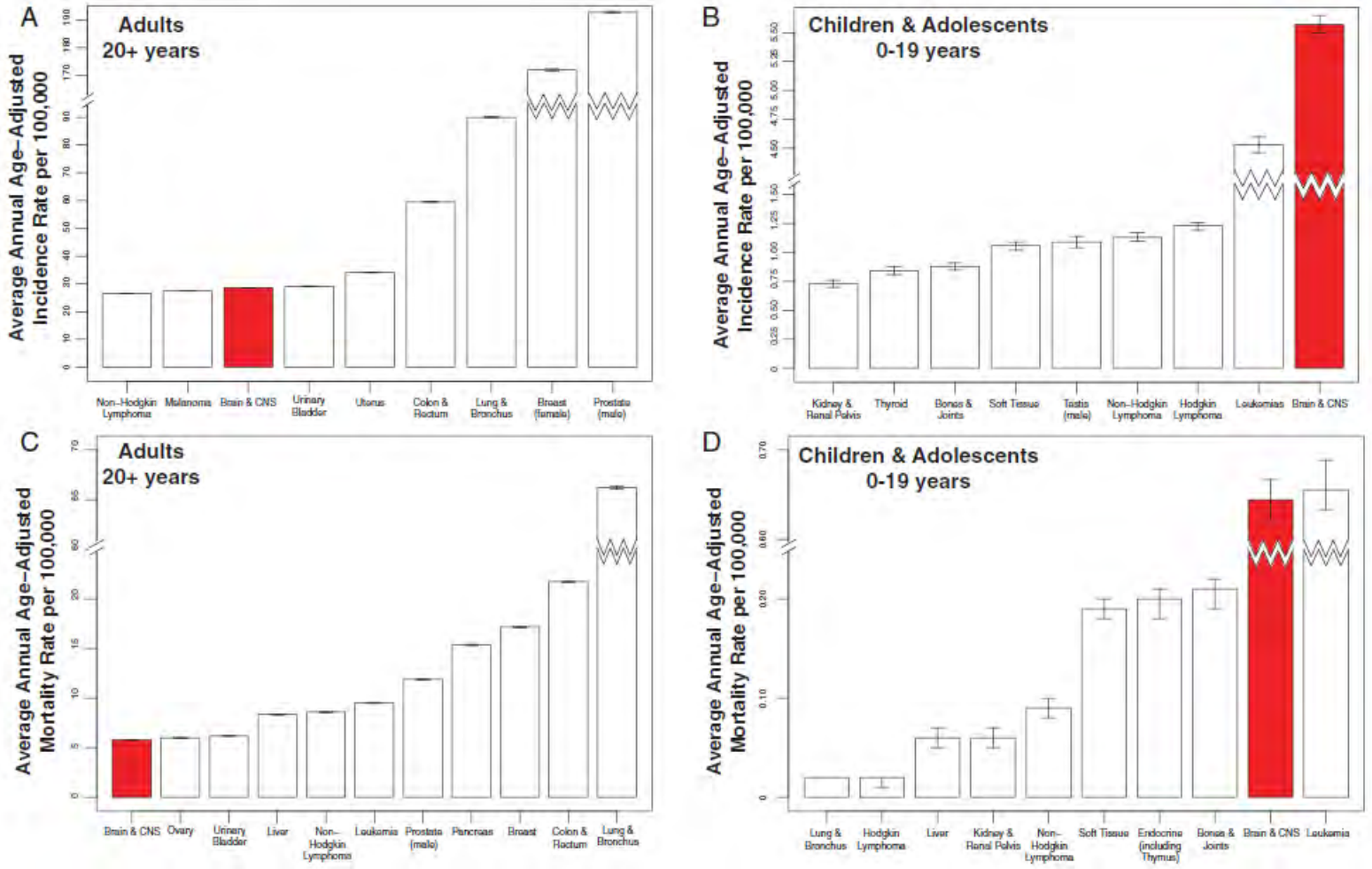
Pediatric cancer incidence is increasing, and/but death rate is decreasing





CHOC

Children and Adolescents (0-19 years) vs Adults (20+ years)



1. From #2 to #1 diagnosis
2. # 1 cancer mortality
3. 0.7% yearly increase from 2008 to 2017

CHOC

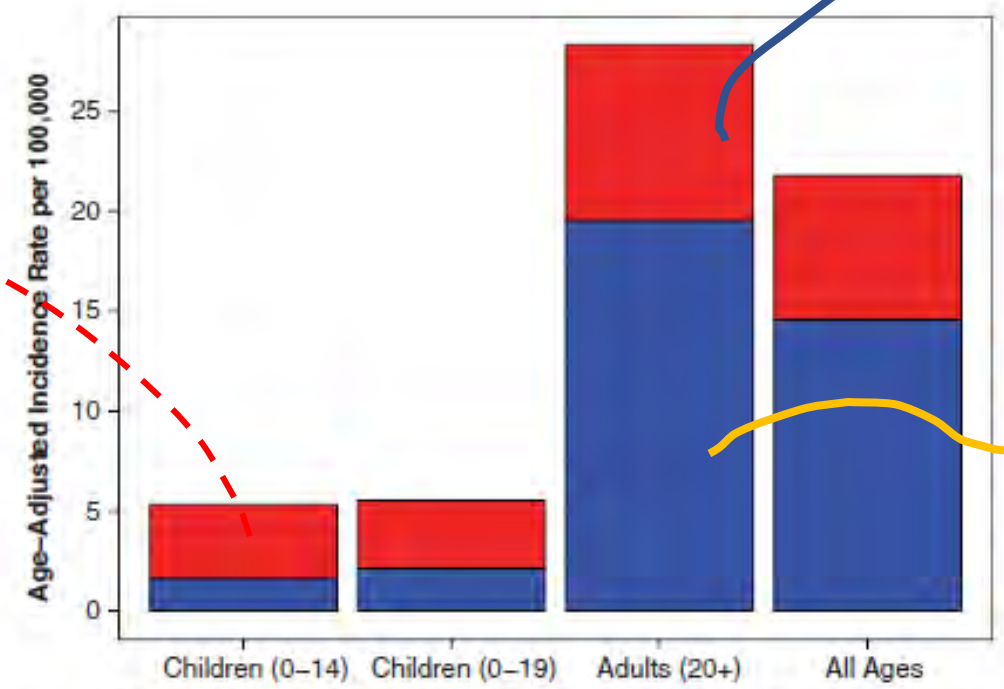
CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2008-2012, 2015 Neuro-oncology

Average Annual Age-Adjusted Incidence Rate

Over 100 different diagnosis

Glioblastoma

Meningioma



	Children (0–14)	Children (0–19)	Adults (20+)	All Ages
Non-Malignant	1.64	2.15	19.82	14.75
Malignant	3.73	3.42	8.76	7.23
Total	5.37	5.57	28.58	21.98

a. Rates per 100,000 and age-adjusted to the 2000 United States standard population.

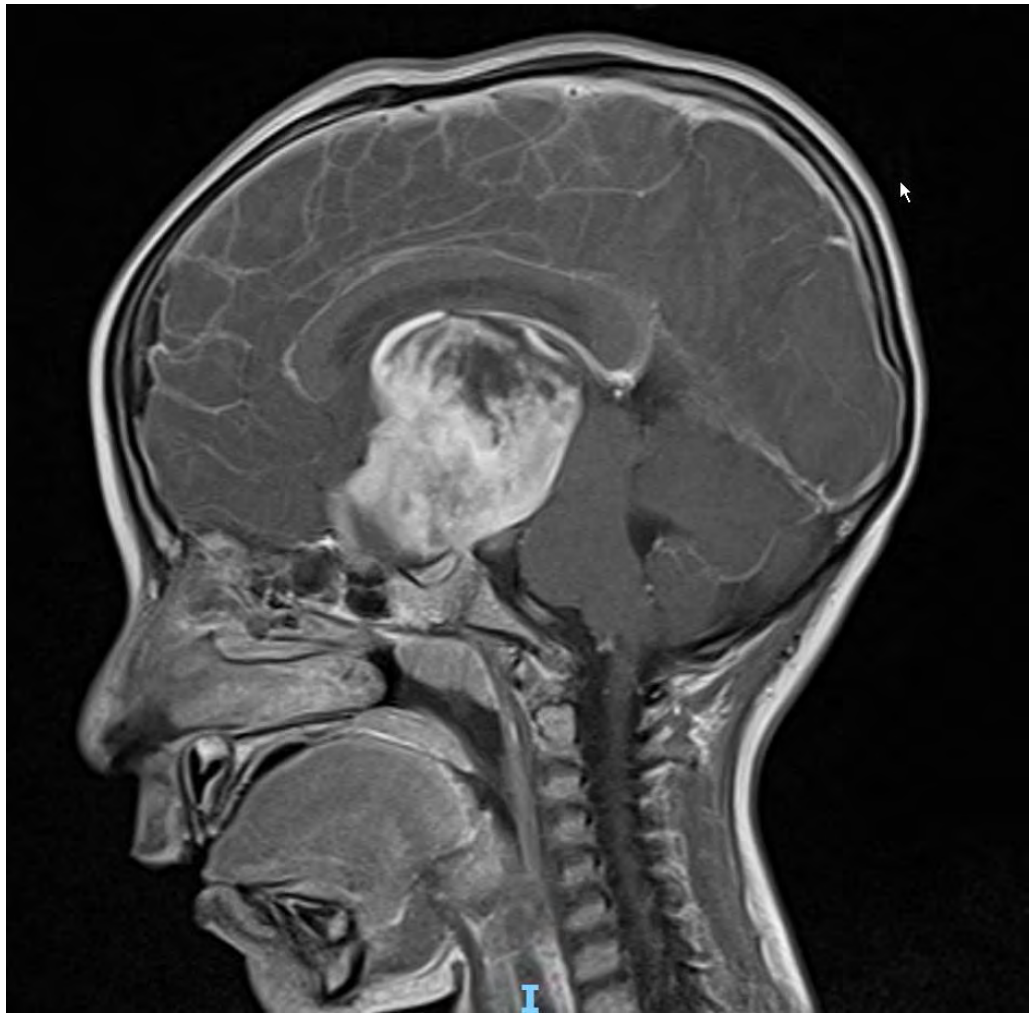
CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2008-2012, 2015 Neuro-oncology

Case 1

CHOC

Case 1

- 4 years old male with known NF1
  - Diagnosed as NF1 at 14 mo of age with café au lait spots and axillary freckling
  - Followed by ophthalmology once a year, last seen 3 month ago, with WNL findings
- CC: 3 month history of headache, nausea vomiting



Challenges in Treatment of pediatric brain tumor

SURGERY

RADIATION

CHEMOTHERAPY

1. Location of the tumor does not allow gross total resection
   - optic nerves, brain stem, hypothalamic and chiasmatic location
2. Children's brain is developing
3. Toxicity of chemotherapy in long surviving patient – late effect

We need different treatment!

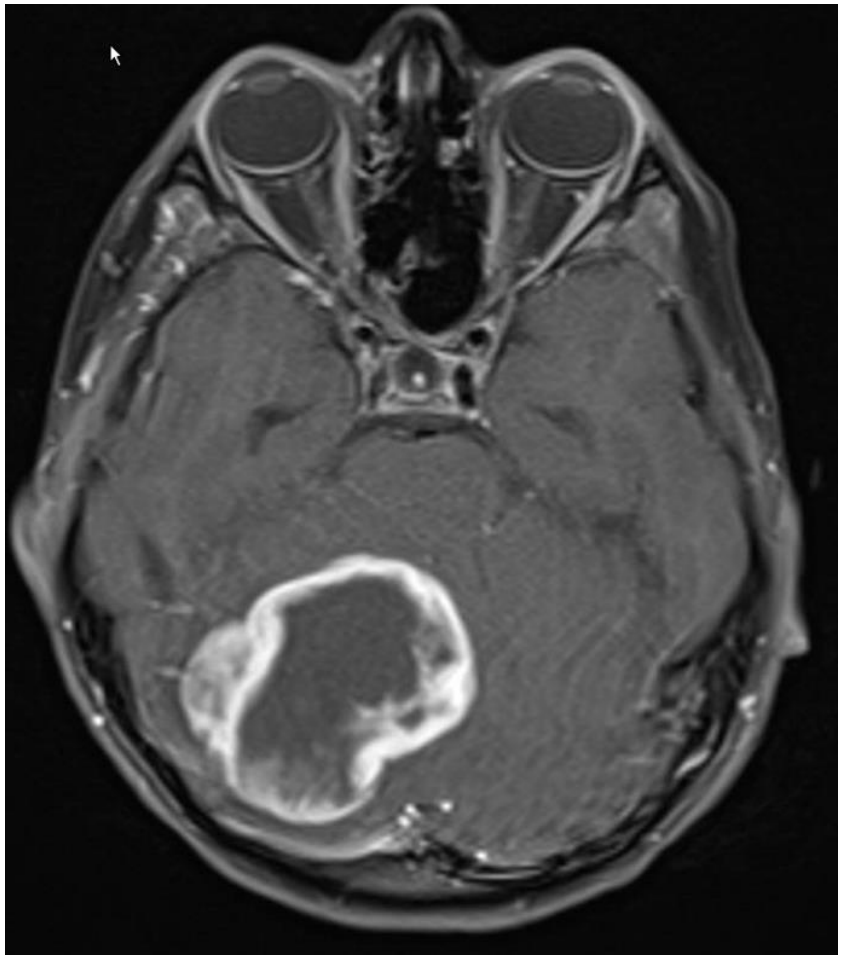
CHOC

Diagnosis

- Pilocytic astrocytoma, STR, treated with chemotherapy

Pilocytic astrocytoma

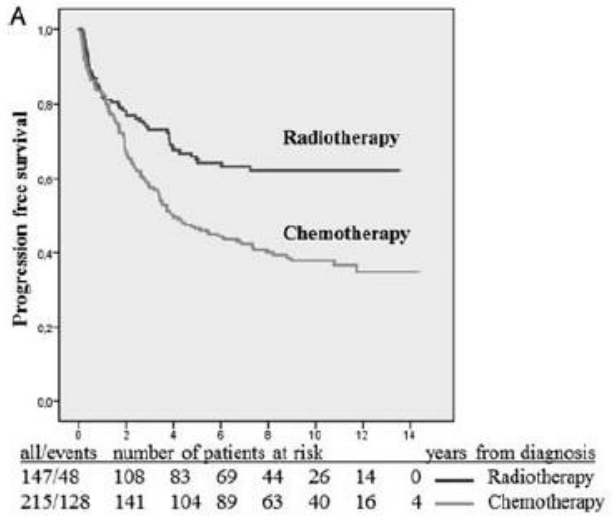
- Most common brain tumor
- Benign – slow glowing
- Founds in Cerebellum or midline structure
  - OPG with NF1
  - hypothalamic chiasmatic tumor
  - brain stem
- Surgery is curative
  - If not resectable, radiation and/or chemotherapy
- Mutations in MAPK pathway
  - BRAF KIAA 1544 fusion, or BRAF V600E mutation

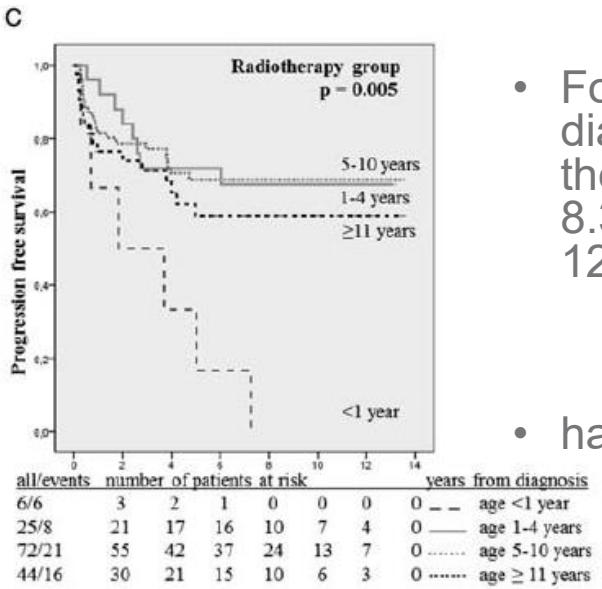


CHOC

Goal of pLGG therapy

1. To achieve a long quality of life
2. Postpone or avoid radiation





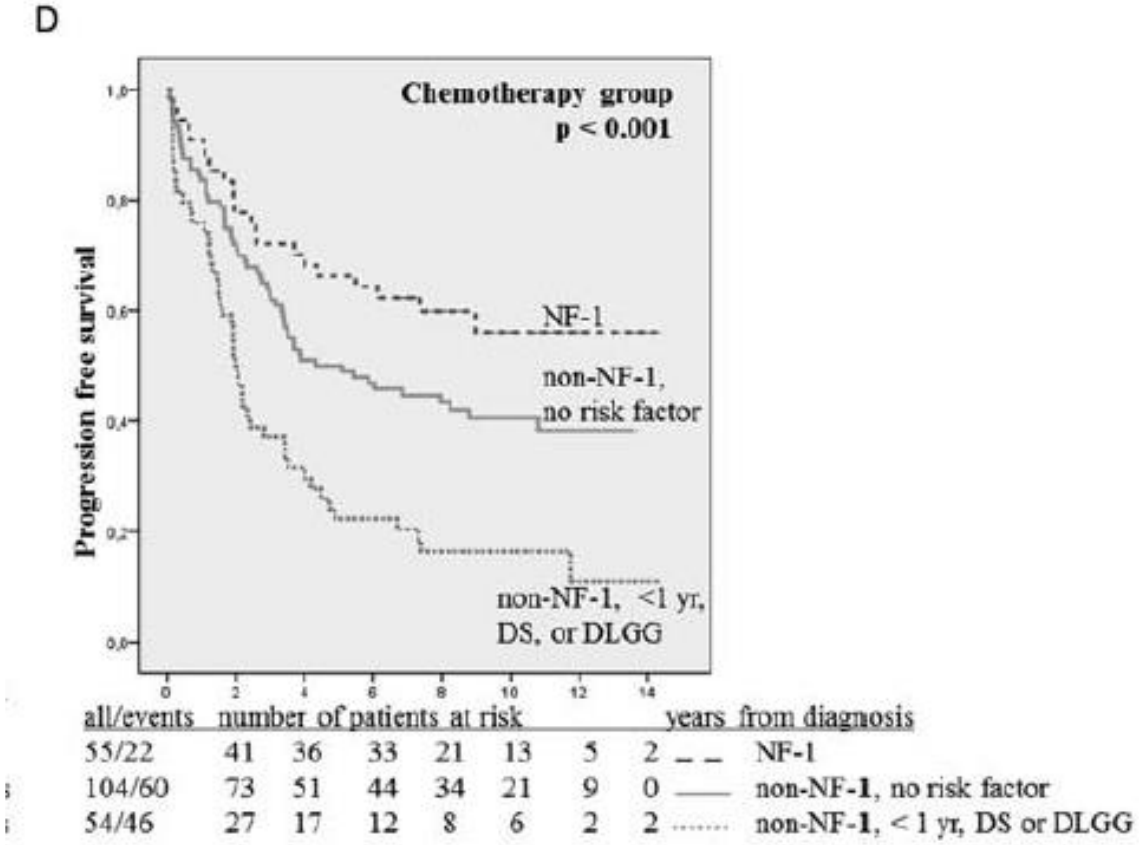
- Risk of secondary neoplasms after external-beam radiation therapy treatment of pediatric low-grade gliomas: a SEER analysis, 1973–2015 Adrian J. Rodrigues, BA, Michael C. Jin, BS, Adela Wu, MD, Hriday P. Bhambhvani, BS, Gordon Li, MD, and Gerald A. Grant, MD, J Neurosurg Pediatr 28:306–314, 2021
- For patients alive 30 years from the initial LGG diagnosis, the absolute risk of SN development in the EBRT-treated cohort was 12.61% (95% CI 8.31–13.00) compared with 4.99% (95% CI 4.38–12.23) in the non–EBRT-treated cohort (p = 0.013).
- hazard ratio 2.26

CHOC

Goal of pLGG therapy

Chemotherapy

- Carboplatin + vincristine
- Carboplatin only
- Vinblastine
- Temozolomide
- Irinotecan + bevacizumab

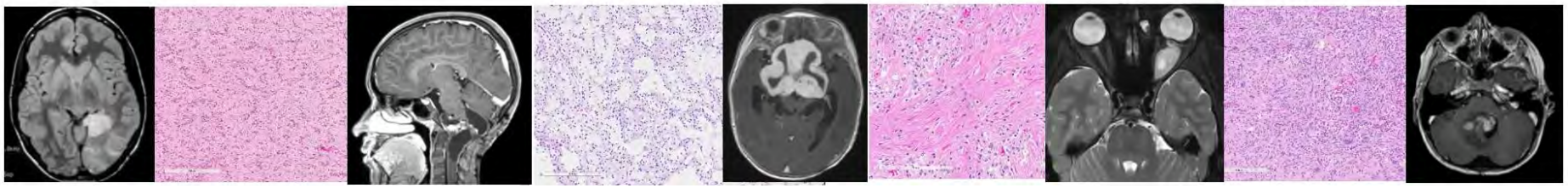


Neuro-oncology 14(10): 1265-1284,2012

CHOC

Pediatric Low Grade Glioma

- Histologically diverse group of tumors arising throughout CNS
- Now categorized under
  1. Pediatric-type diffuse low-grade gliomas
  2. Circumscribed astrocytic gliomas
  3. Glioneuronal and neuronal tumors
- Distinct from adult LGG



CHOC

Pediatr Blood Cancer 2014;61:1173–1179

Long-Term Outcome of 4,040 Children Diagnosed With Pediatric Low-Grade Gliomas: An Analysis of the Surveillance Epidemiology and End Results (SEER) Database

Pratiti Bandopadhayay, MBBS, PhD,[1,2] Guillaume Bergthold, MD,[2] Wendy B. London, PhD,[3] Liliana C. Goumnerova, MD,[1,4] Andres Morales La Madrid, MD,[1] Karen J. Marcus, MD,[5] Dongjing Guo, MPH,[3] Nicole J. Ullrich, MD, PhD,[1,6] Nathan J. Robison, MD,[8] Susan N. Chi, MD,[1] Rameen Beroukhim, MD, PhD,[2,7] Mark W. Kieran, MD, PhD,[1] and Peter E. Manley, MD[1]*

At least 15 y FU

22th birthday and up

Tumor specific death

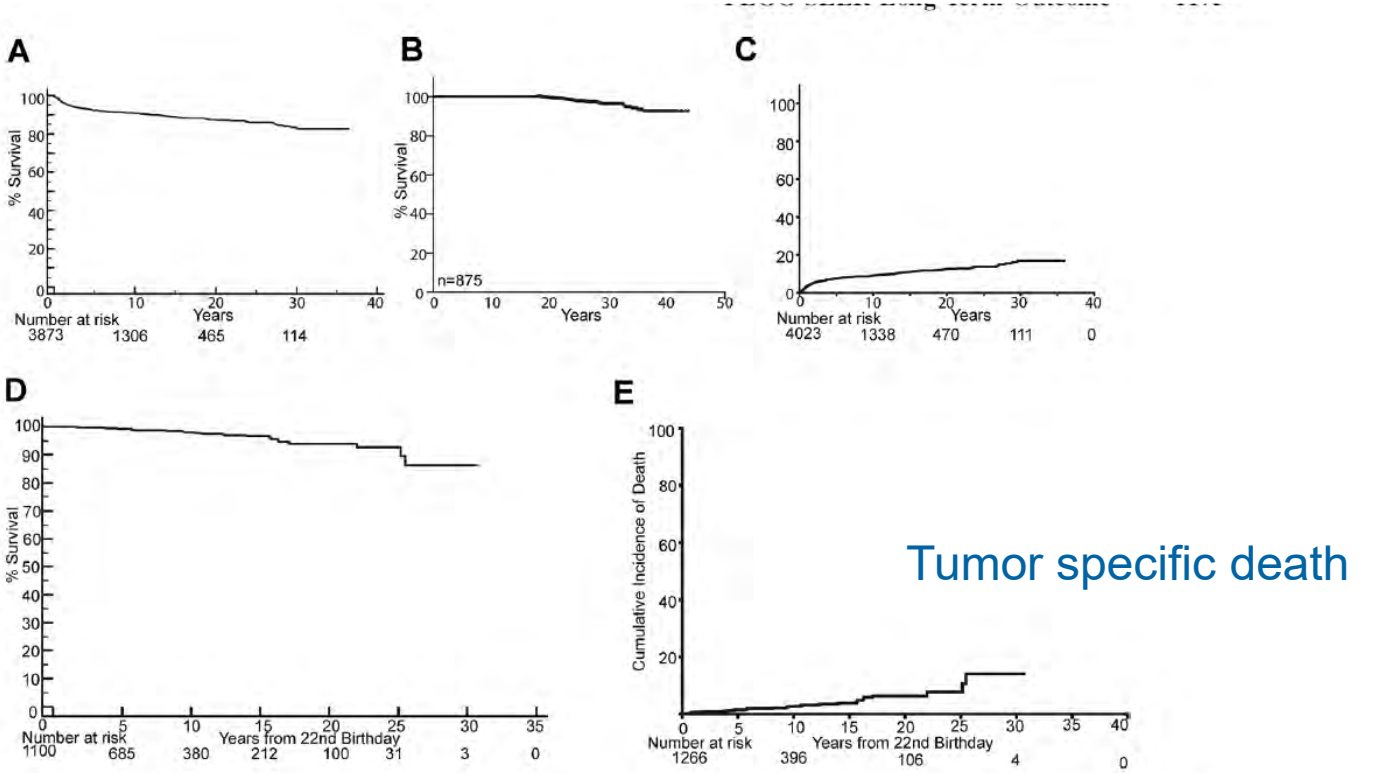
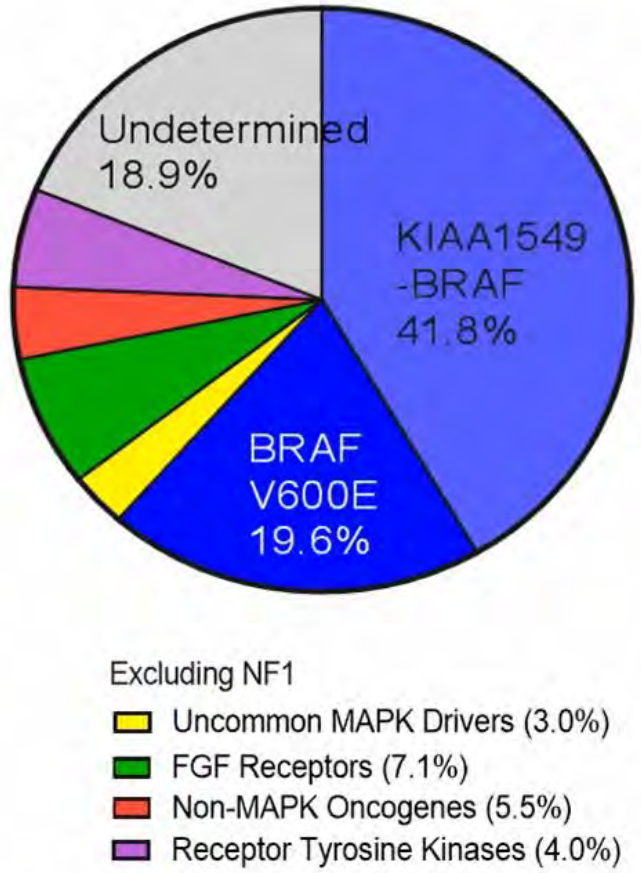


Fig. 1. Adult survivors of pediatric low-grade gliomas have excellent overall survival with low rates of mortality after patients transition into adulthood. **A**: Kaplan–Meier overall survival curve of patients with PLGG including only tumor related deaths. **B**: Kaplan–Meier overall survival curve of patients for which there is at least 15 years of follow-up. **C**: Pepe–Mori cumulative incidence of tumor specific death curve of patients diagnosed with PLGG. **D**, **A**: Kaplan–Meier overall survival curve of patients with PLGG showing survival starting from the patient's 22nd birthday. **E**: Pepe–Mori cumulative incidence of tumor specific death curves of patients starting from patient's 22nd birthday.

CHOC

Approach to molecular testing for pLGG

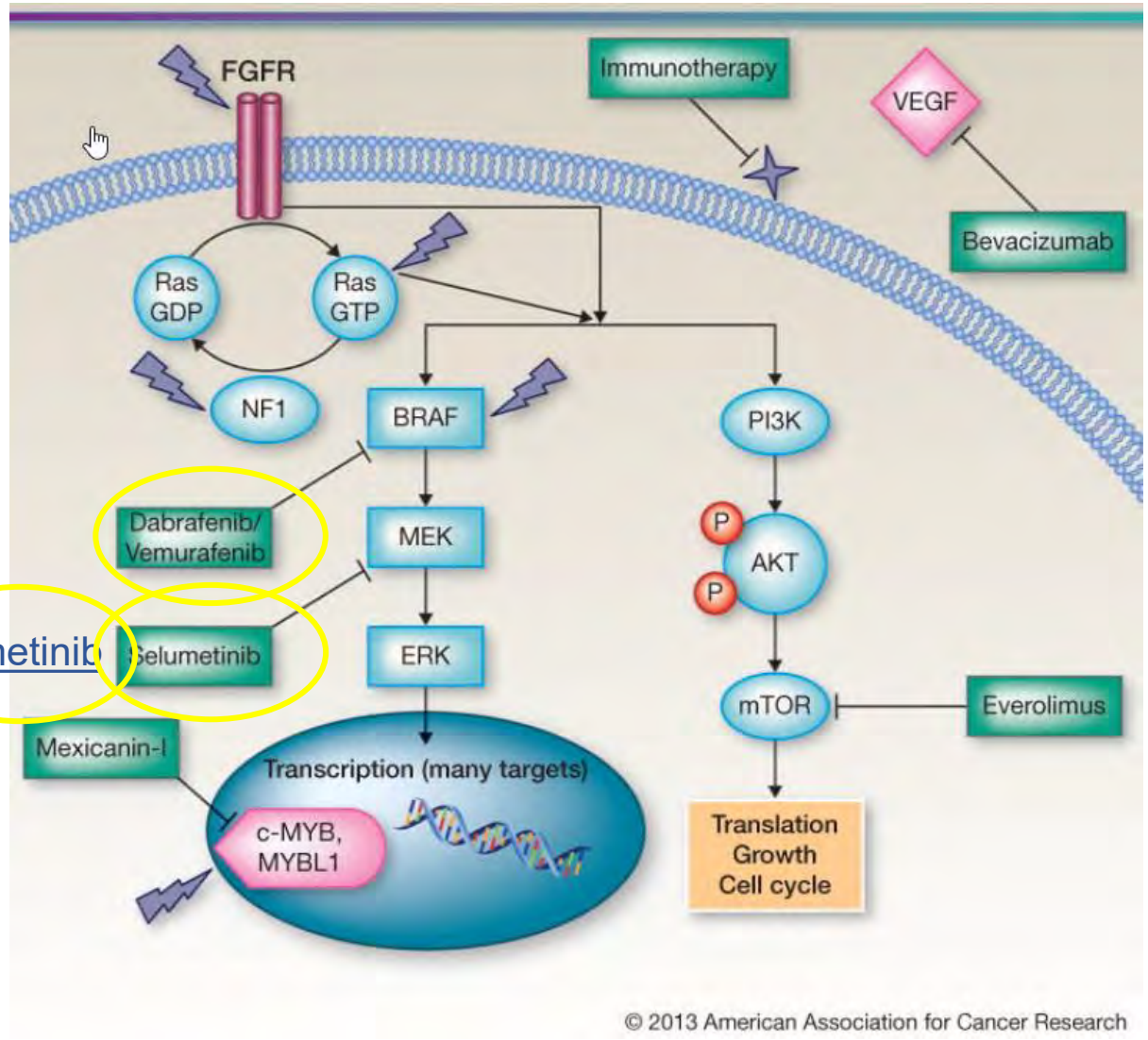
- Many can be identified with IHC or FISH
- 2/3 of alterations in pLGG are either BRAF fusion or BRAF V600E



Ryall et al. Cancer cell, 2020

Targeting MAPK pathway

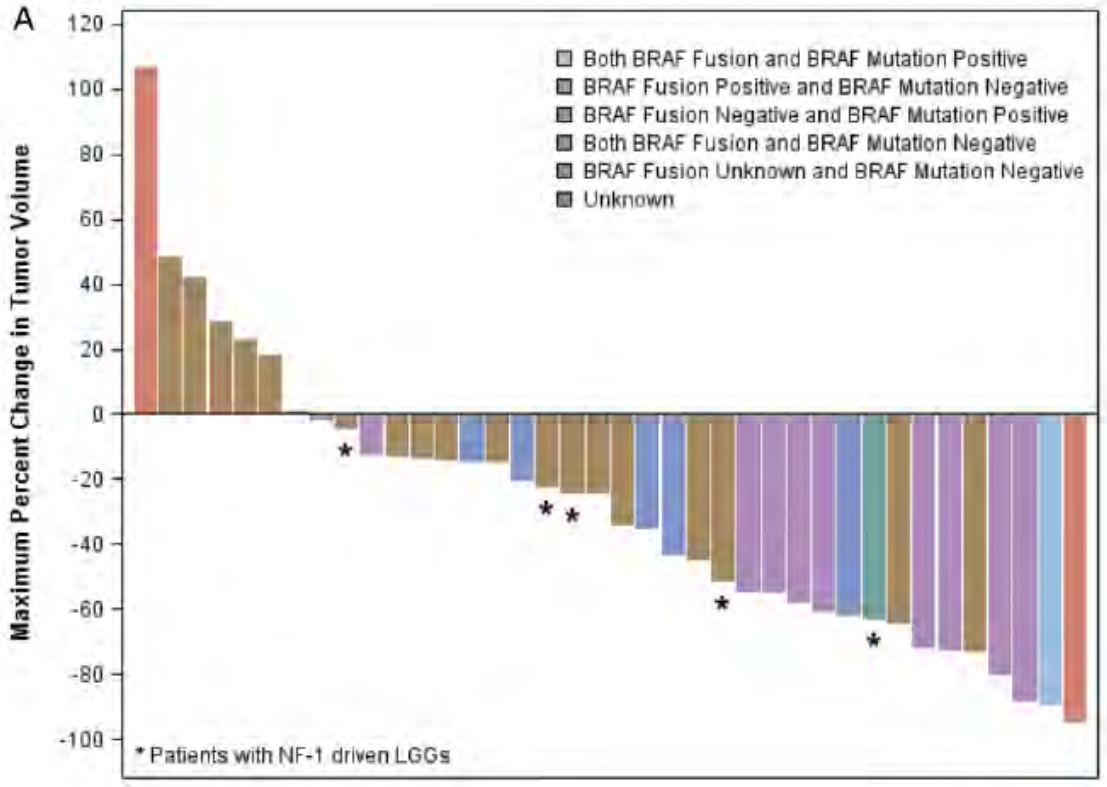
DAY101
type II pan-RAF
kinase inhibitor



Selumetinib

2y PFS 75% with selumetinib for both BRAF fusion or mutation

39% is currently Progression free



Current ongoing study

A Phase 3 Randomized Non-Inferiority Study of Carboplatin and Vincristine vs Selumetinib in Newly Diagnosed or Previously Untreated LGG not associated with BRAFV600E Mutations or systemic NF1

A Phase 3 Randomized Study of Selumetinib vs Carboplatin/Vincristine in Newly Diagnosed or Previously Untreated NF1 Associated LGG

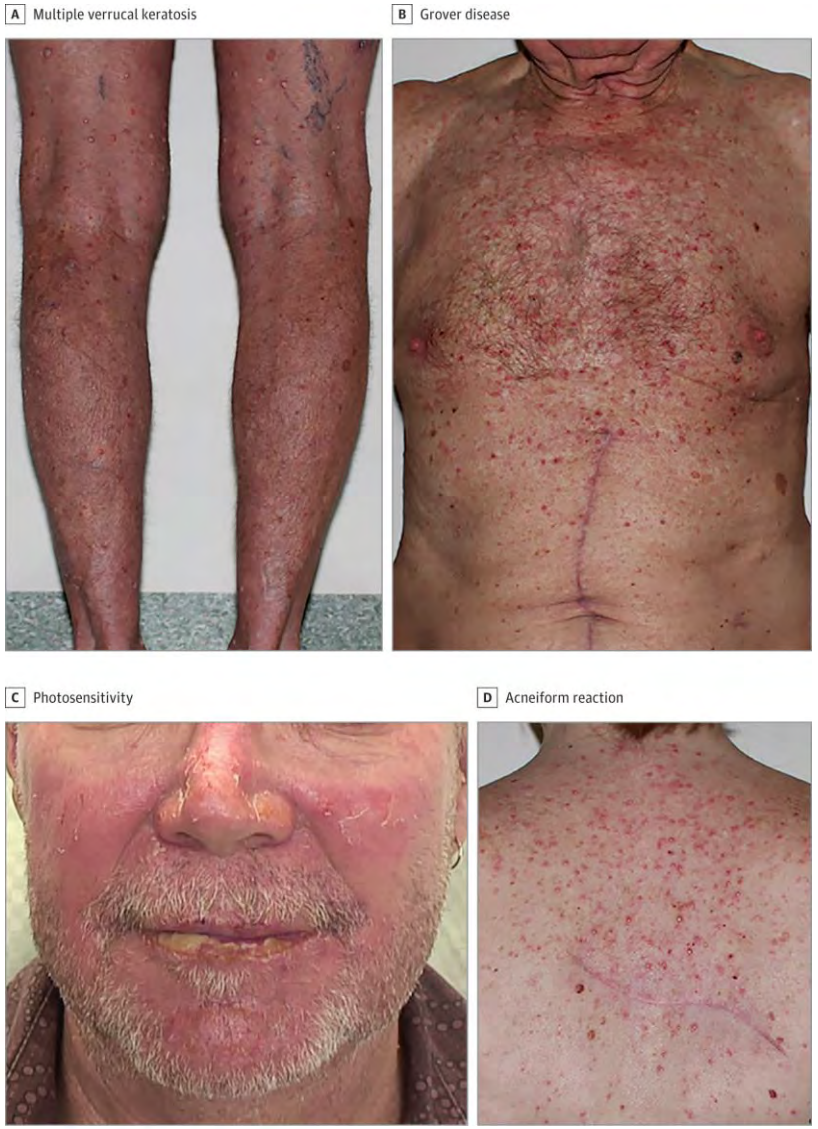
A Phase 3 Study of Selumetinib or Selumetinib in Combination with Vinblastine for non-NF1, non-TSC Patients with Recurrent or Progressive LGGs Lacking *BRAFV600E* or *IDH1* Mutations

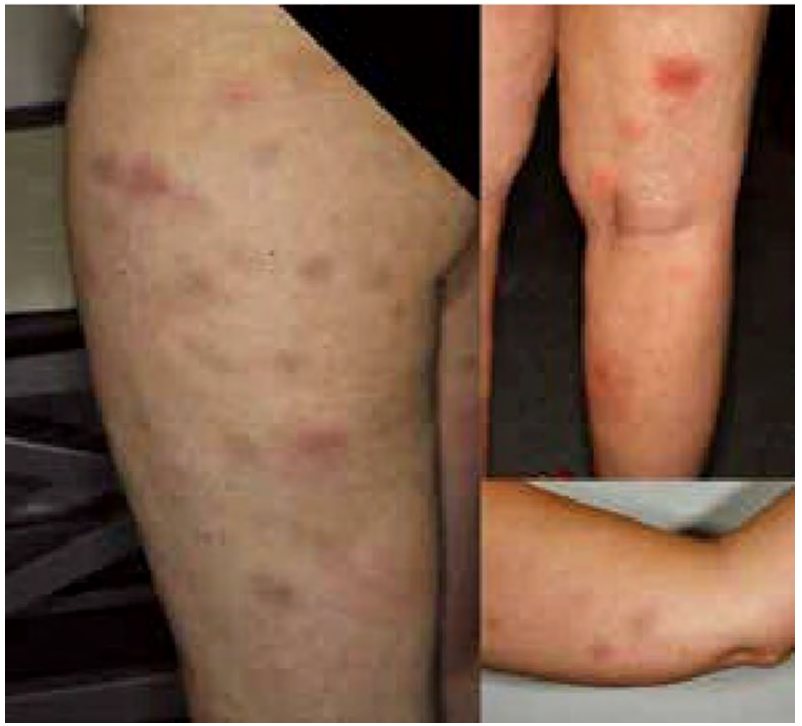
FIREFLY-1: A Phase 2, Oral Pan-RAF Inhibitor DAY101 in Pediatric Patients with BRAF-Altered, Recurrent or Progressive Low-Grade Glioma

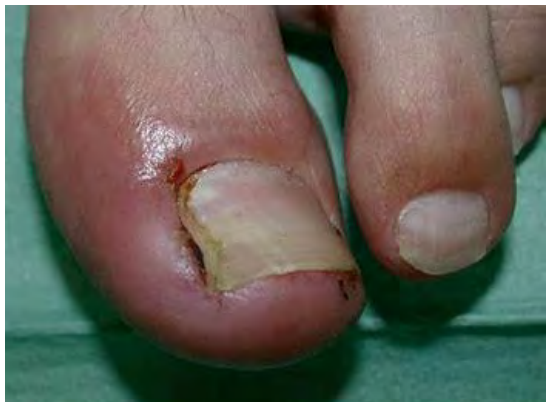
- 25 pt >60% response

CHOC

Side effect and management

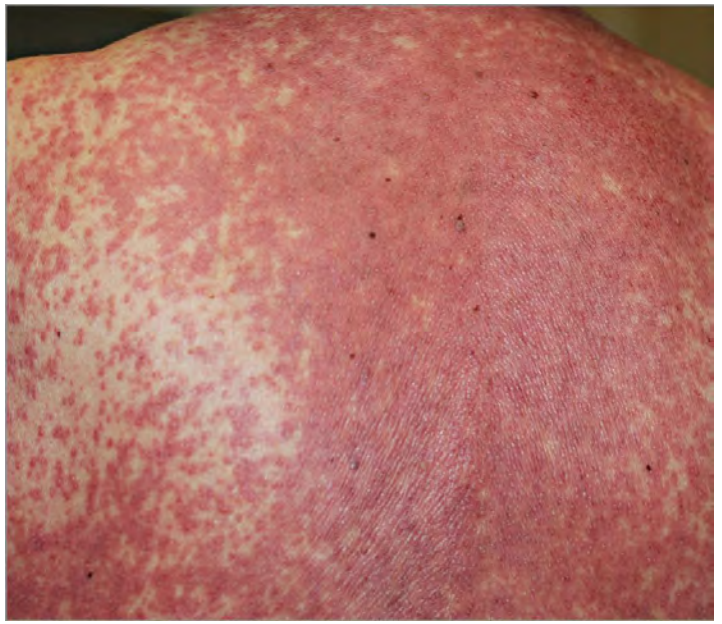






Paronychia

DRESS syndrome:**early-onset drug reaction with eosinophilia and systemic symptoms**



Case 2

Case 2 : 6 year-old Hispanic male

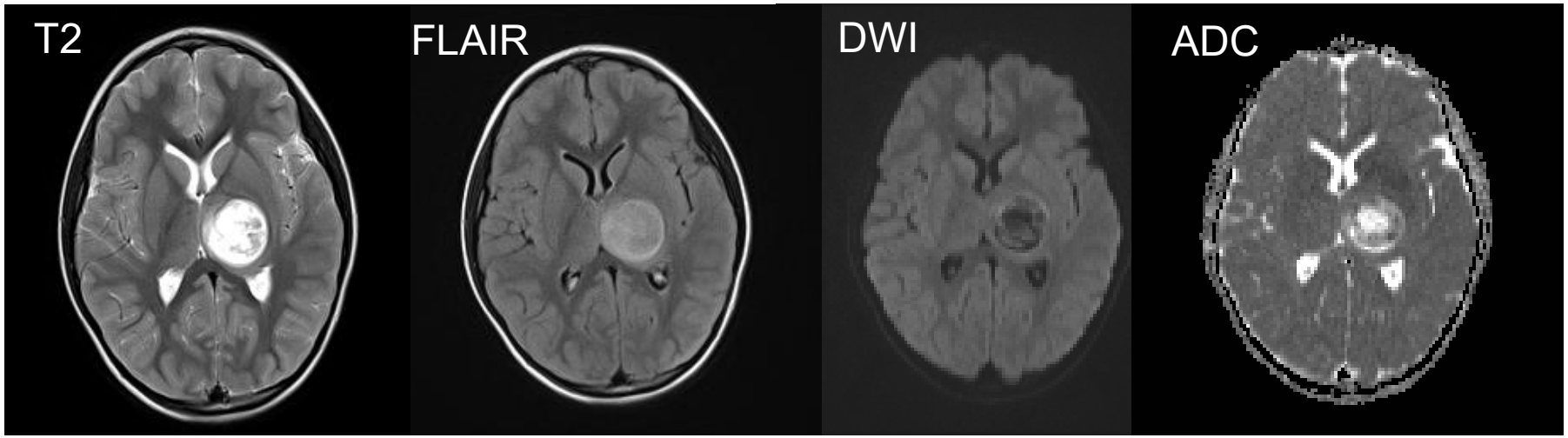
- **History of present illness (HPI):**
  - He was previously healthy. When he was playing with his tablet, his right arm suddenly dropped. The next day, he complained of headache. Shortly after, he developed right sided weakness and no longer able to walk.

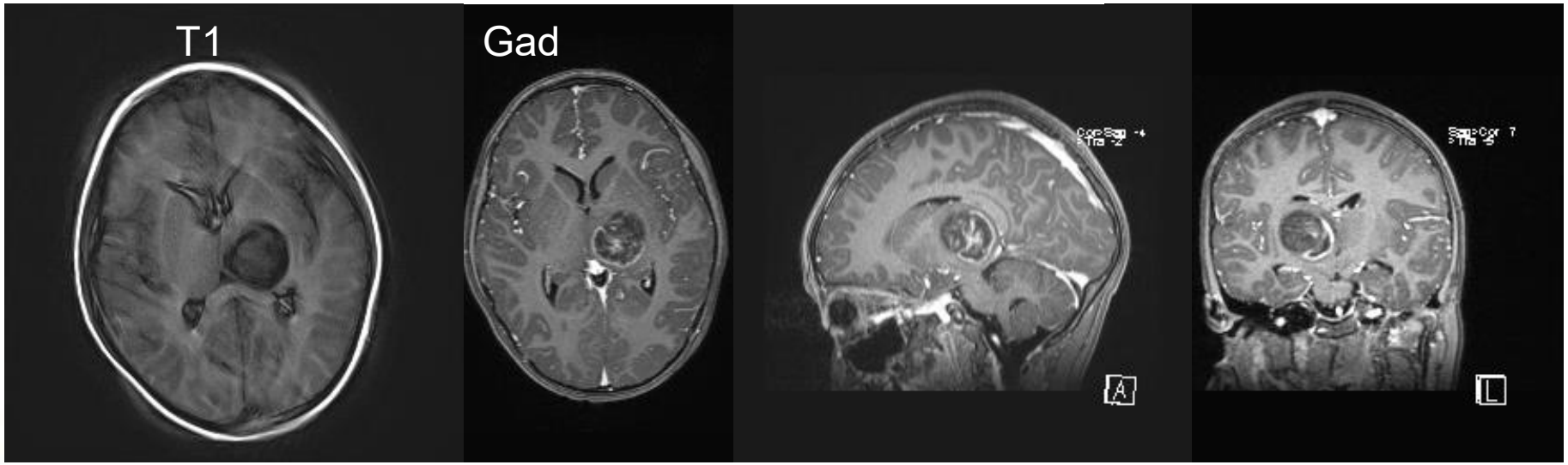
- **Past medical history (PMH):** none

- **Physical Exam (PE) :**
  - Right facial droop, right UE and LE weakness, decreased sensation on the right side

CHOC

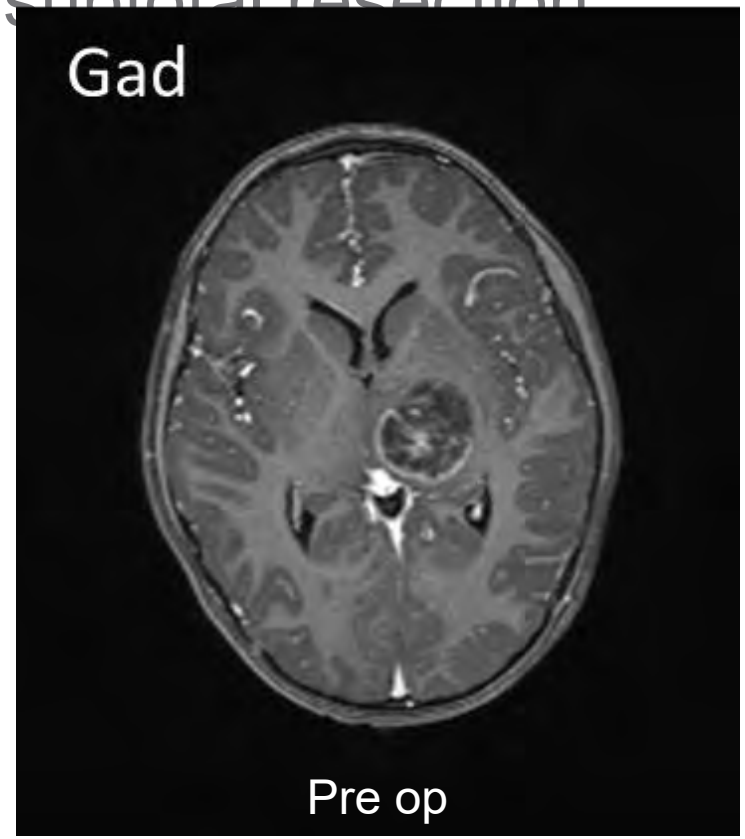
Case 1 MRI

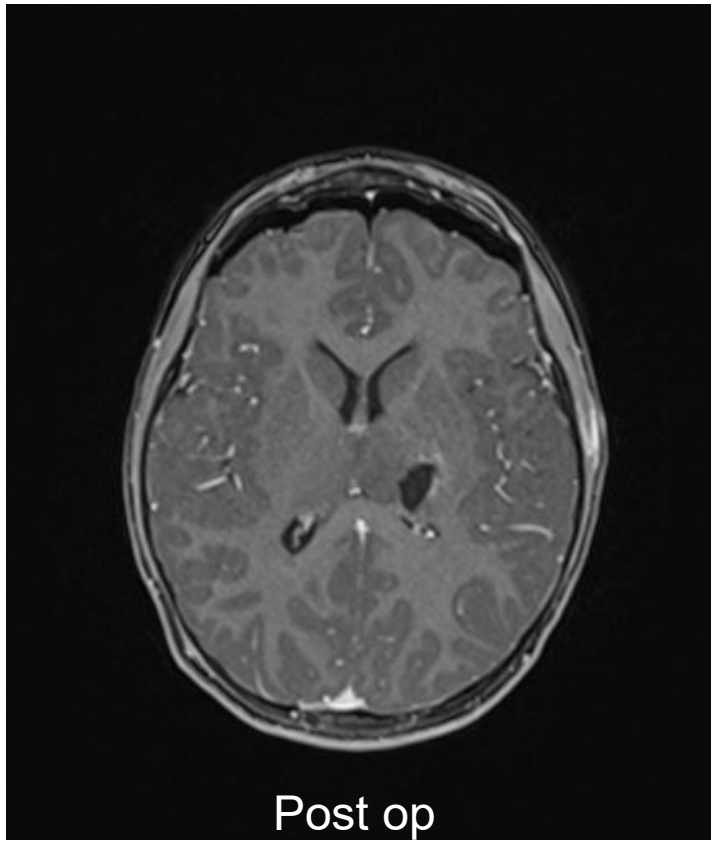




Case 1 Surgery

- Taken to subtotal resection





CHOC

Histopathology: “Glioblastoma"

- The sample showed predominantly necrotic and hemorrhagic, cellular neoplasm composed of atypical cells in a fibrillary background. The tumor has many mitoses and microvascular proliferation. Thrombosed vessels are noted.
- Immunostaining showed strong widespread nuclear immunoreactivity for p53 and the mutant (K27M) H3 gene product. There is concomitant loss of immunoreactivity for the H3 K27-trimethylation marker. This suggests there is a mutation at this codon in one of the H3.3 or H3.1 genes. ATRX is retained. Ki67 immunolabeling is high. (tested at St. Jude)

CHOC

New diagnostic name
“Diffuse midline glioma, H3K27M mutation”

- Histologically “glioblastoma”
- Primarily occurring in children
- K27M mutation in the histone H3 gene H3F3A
  - Or less commonly in the HIST1H3B gene
- Midline location – thalamus, brainstem, spinal cord, and diffuse intrinsic pontine glioma
- 1/3 of children’s glioblastoma carries H3K27M mutation

CHOC

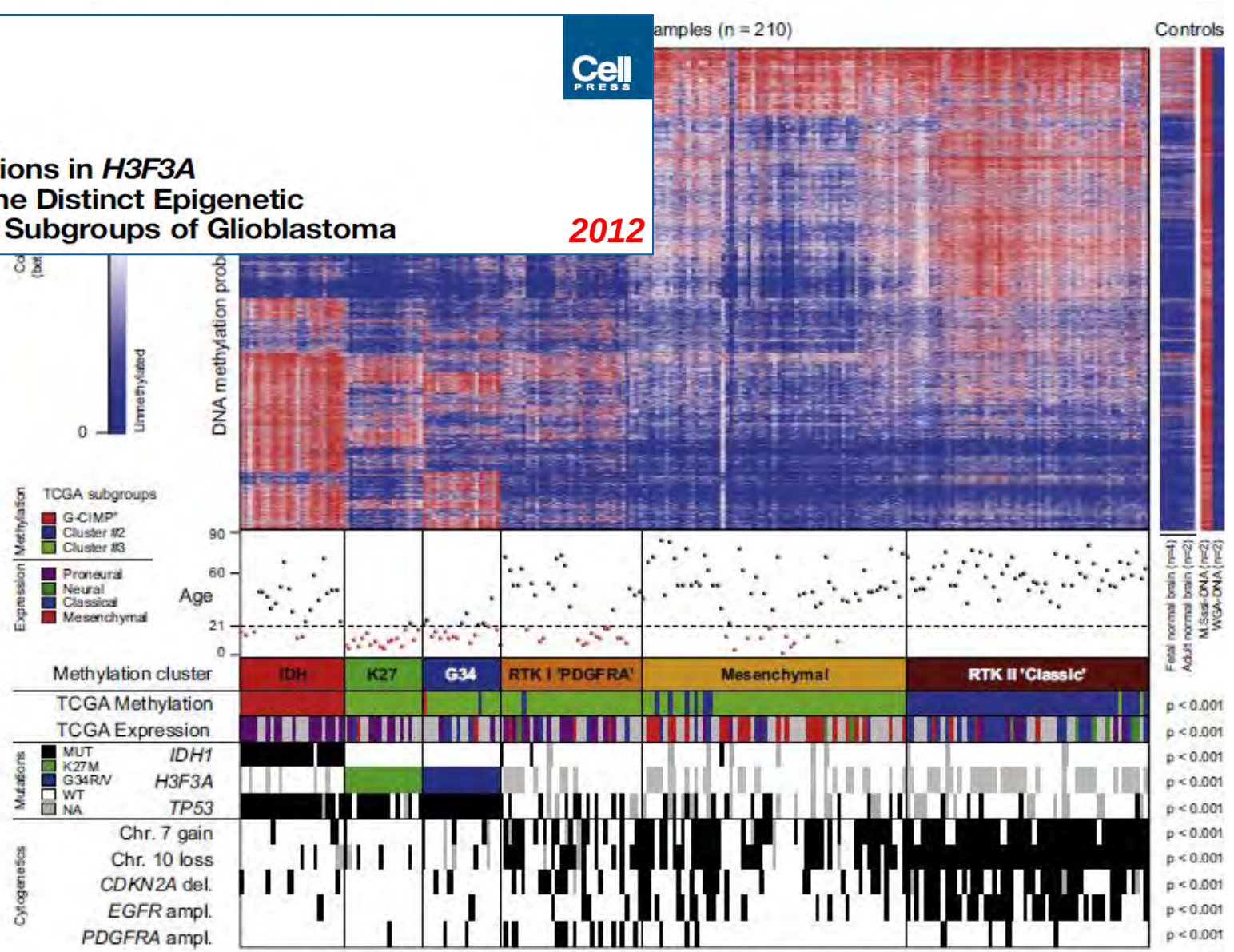
Glioblastoma
Dif n

Cancer Cell
Article

Hotspot Mutations in *H3F3A* and *IDH1* Define Distinct Epigenetic and Biological Subgroups of Glioblastoma

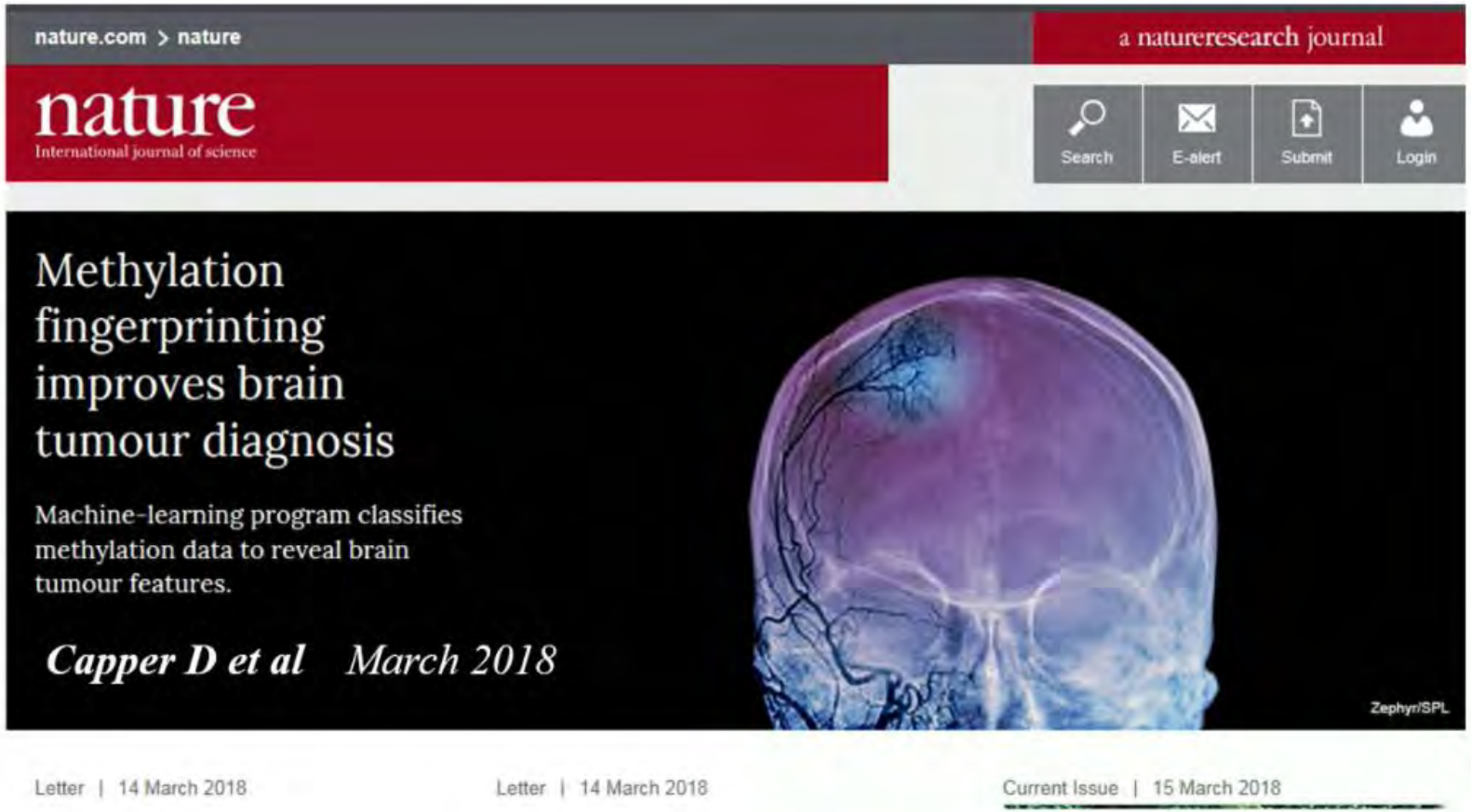
Cell PRESS

2012



CHOC

March 2018


nature.com > nature
a natureresearch journal
nature
International journal of science
Search
E-alert
Submit
Login
Methylation fingerprinting improves brain tumour diagnosis
Machine-learning program classifies methylation data to reveal brain tumour features.
Capper D et al March 2018
Zephyr/SPL
Letter | 14 March 2018
Letter | 14 March 2018
Current Issue | 15 March 2018

DNA methylation is an example of one of the many mechanisms of epigenetics.

NEWS & VIEWS

MEDICAL RESEARCH

Machine learning classifies cancer

Brain tumours are often classified by visual assessment of tumour cells, yet such diagnoses can vary depending on the observer. Machine-learning methods to spot molecular patterns could improve cancer diagnosis. SEE ARTICLE P.469

DEREK WONG & STEPHEN YIP

Accurate diagnosis is essential for appropriate disease treatment. A core technique used to diagnose brain cancer today is the microscope-based analysis of tumour samples on glass slides, termed histology. However, this requires the appraisal of subtle cellular alterations, which in some cases may lead to different classifications for a given sample by different individuals. Nowadays, technological developments enable vast amounts of molecular data to be obtained and assessed for a tumour without the need for such subjective diagnostics. Machine-based-learning approaches are being developed to aid the diagnosis of clinical samples, and on page 469, Capper *et al.*[1] report such a method for classifying brain tumours on the basis of molecular patterns.

In 1926, a publication entitled *A Classification of the Tumors of the Glioma Group on a Histo-Genetic Basis with a Correlated Study of Prognosis*[2] by neurosurgeons Percival Bailey and Harvey Cushing provided early insight into the development, cellular characteristics and clinical consequences of glioma, a type of cancer of the central nervous system (CNS). The book's title was prophetic and ambitious

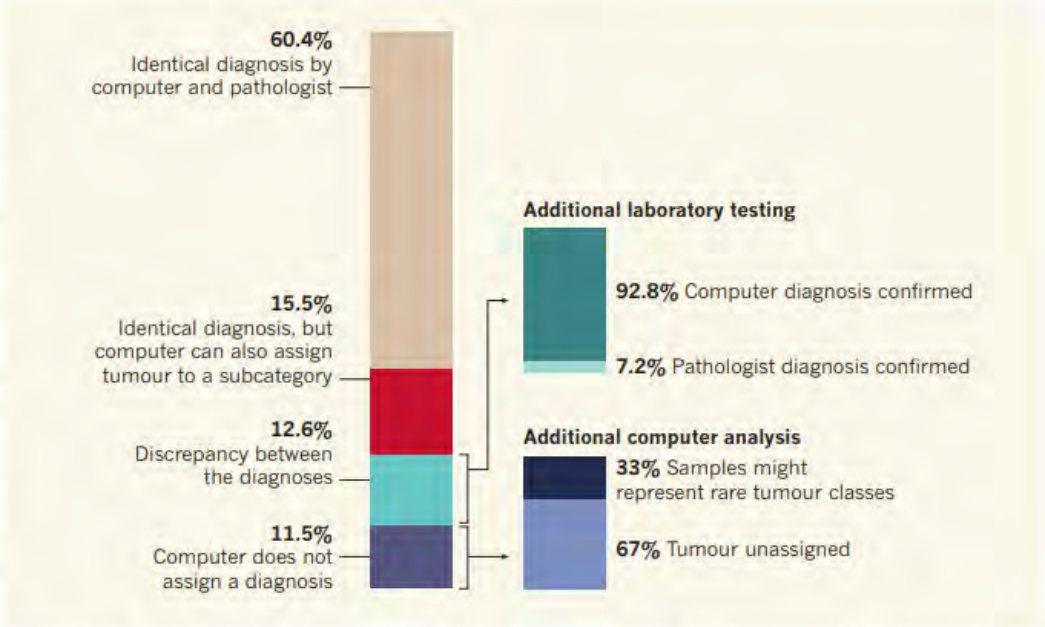
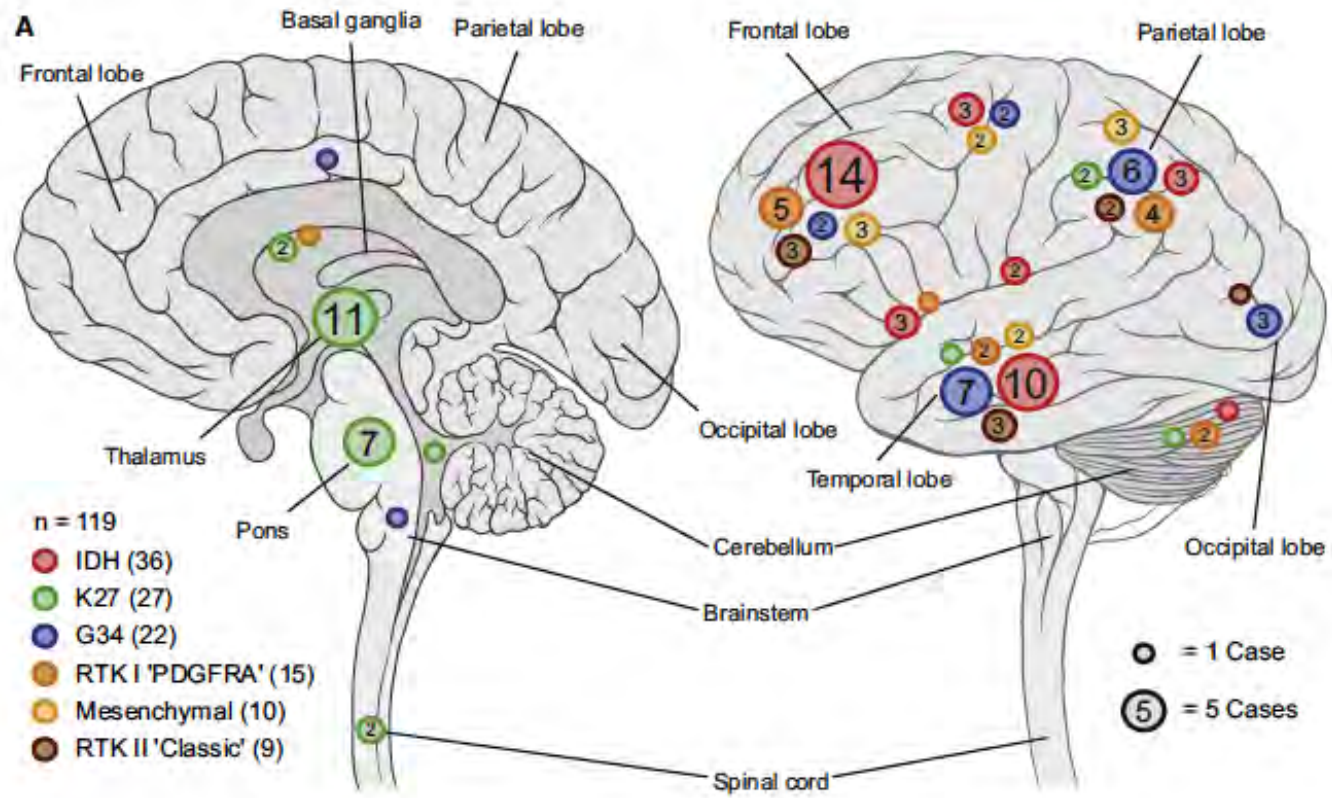


Figure 1 | Tumour classification using a machine-learning approach. Capper *et al.*[1] used a machine-learning approach to classify brain tumours on the basis of genome-wide patterns of a type of DNA alteration called methylation. The computer was trained using methylation data for tumour samples that had been diagnosed by pathologists using standard microscopy-based analysis or analysis of selected genes. After training, the computer was given 1,104 test cases. The authors compared the diagnoses made by the computer and by the pathologists. Although the machine was unable to diagnose all specimens, of the specimens that it classified, the machine-based diagnosis was more accurate or could assign tumours to more-specific subcategories than the classifications made by the pathologists.

CHOC

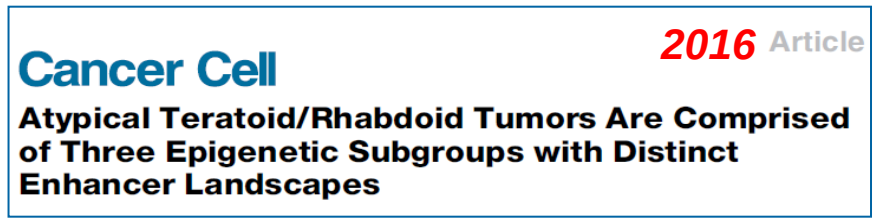
Location of 111 GBM grouped by methylation clusters



Genotype of pediatric brain tumor is being revealed

An Integrated Genomic Analysis of Human Glioblastoma Multiforme

2008 Science



CHOC

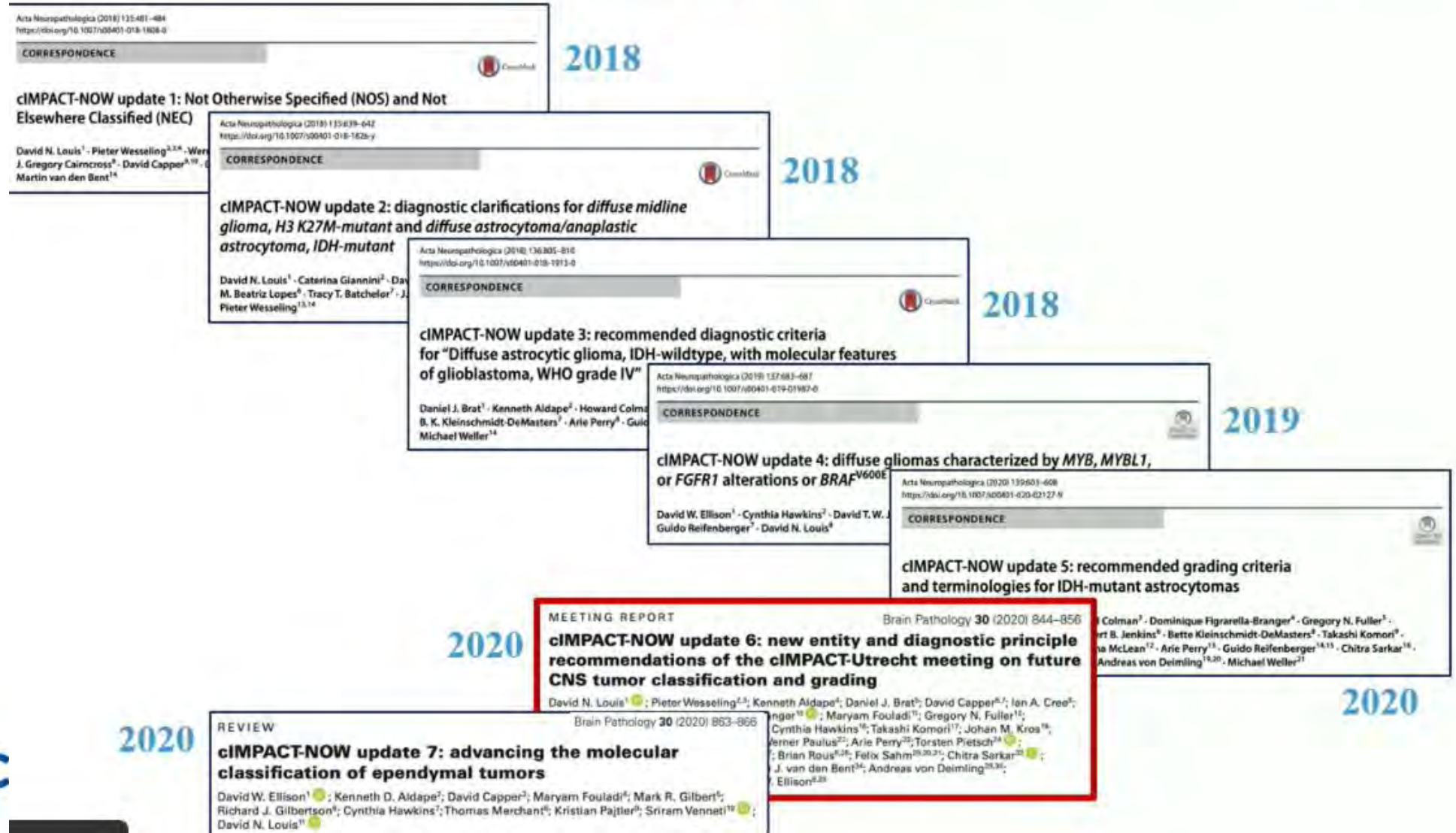
Fall of the Optical Wall: Freedom from the Tyranny of the Microscope Improves Glioma Risk Stratification

Cancer Cell Previews

Vijay Ramaswamy[1] and Michael D. Taylor[2,*] Cancer Cell 29, February 8, 2016

cIMPACT-NOW

Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy

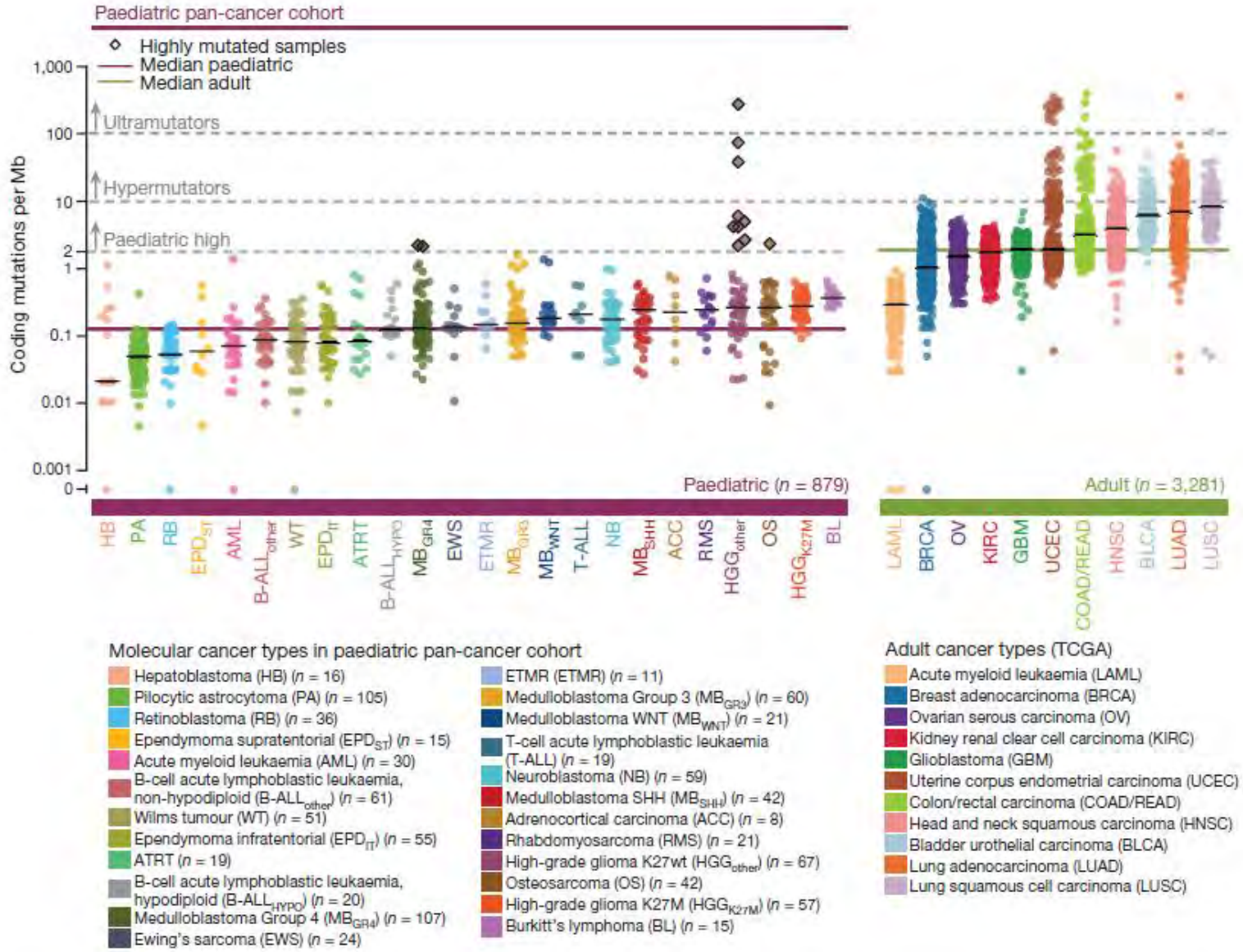


WHO Classification of CNS tumors throughout the years

Integrated molecular diagnosis

Diagnosis : DMG H3K27M mutation

- With CDK4 amplification, KIT amplification, PDGFRA amplification, deletion exons 8-9,TP53 G279E,H3F3A K28M by Foundationone



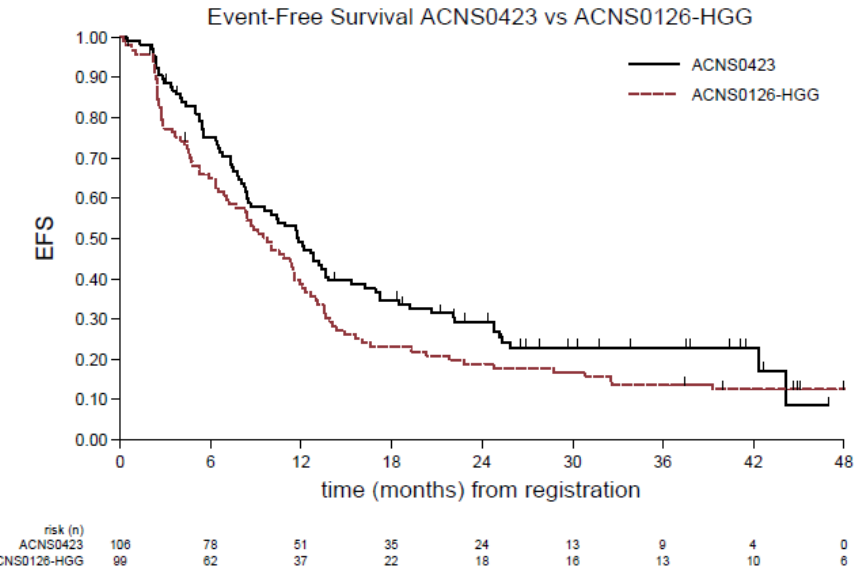
Grobner S et al. The landscape of genomic alterations across childhood cancers. *Nature* **volume555**, pages321–327 (15 March 2018)

How did I treat this patient?

- There is no specific treatment for Diffuse midline glioma.
- Utilizing the same approach as glioblastoma

CHOC

How are we treating glioblastoma?



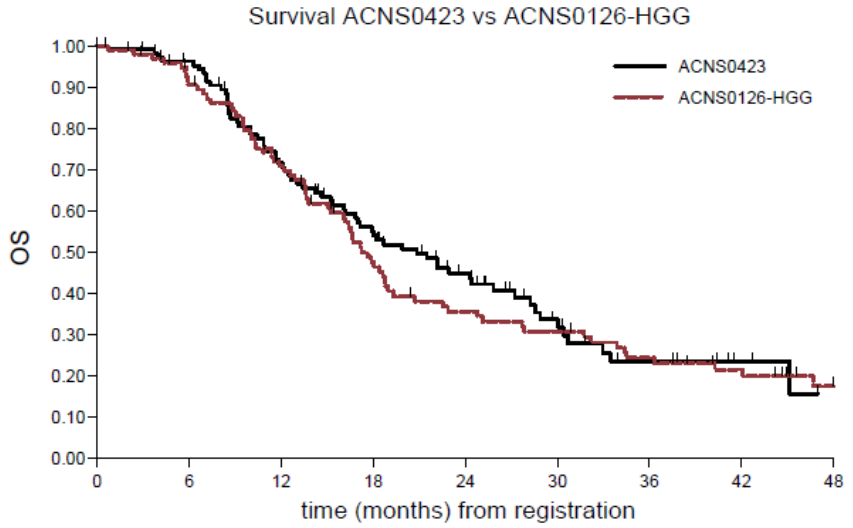
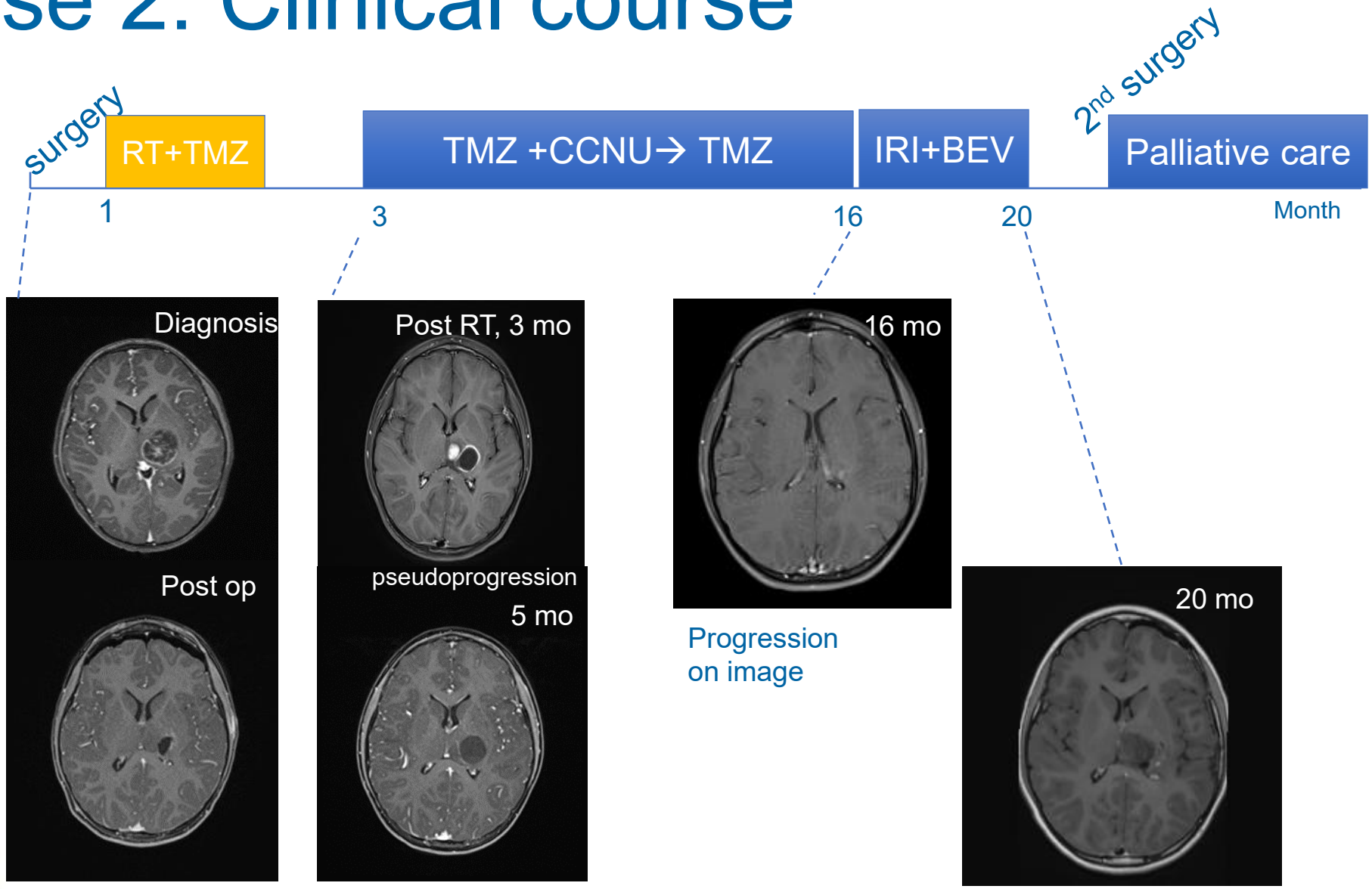


Figure 1: Event-free survival comparison between HGG patients on ACNS0423 and ACNS0126

---- Temozolomide + CCNU vs ----Temozolomide

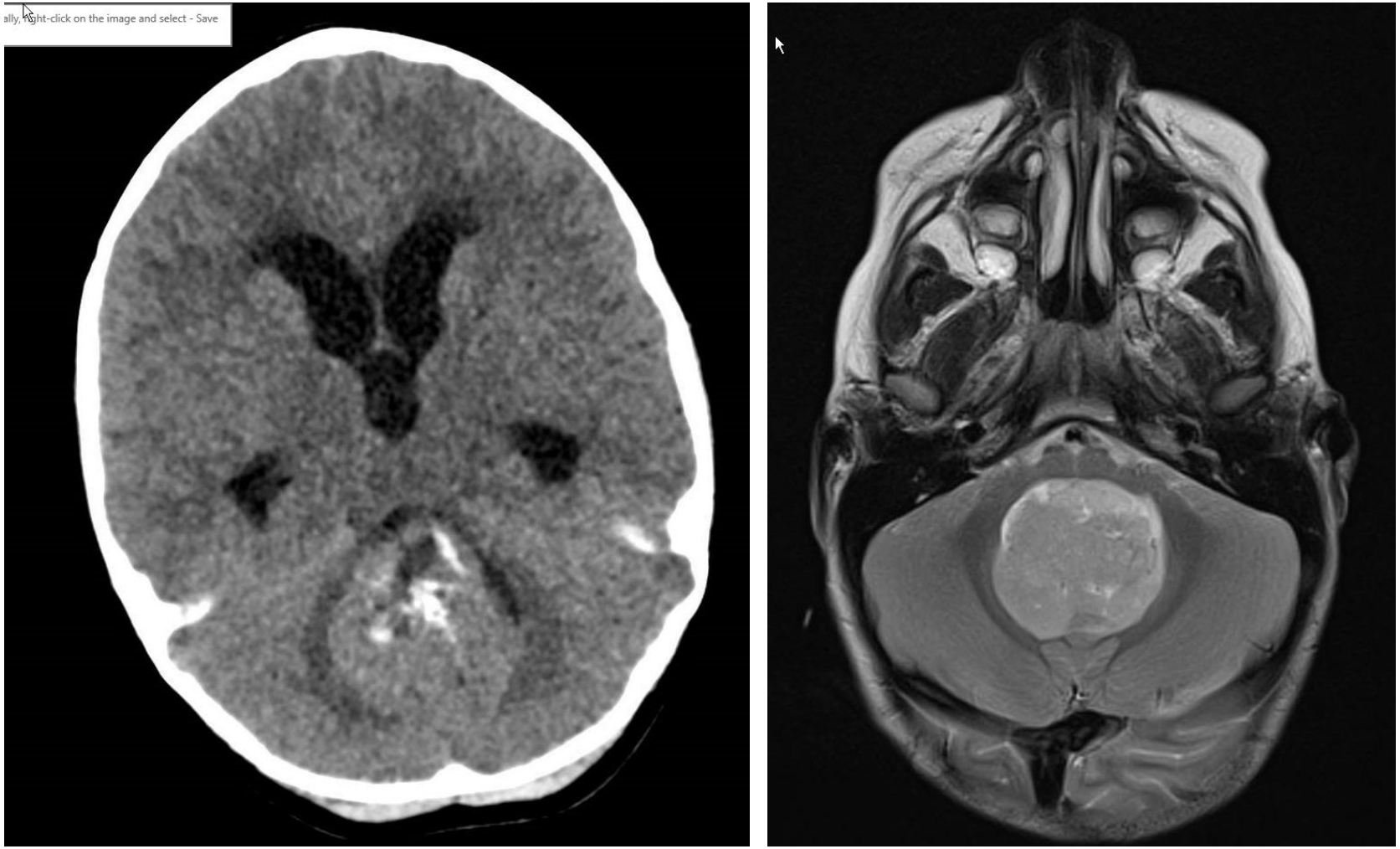
Reference from COG final report of ACNS0423

Case 2: Clinical course



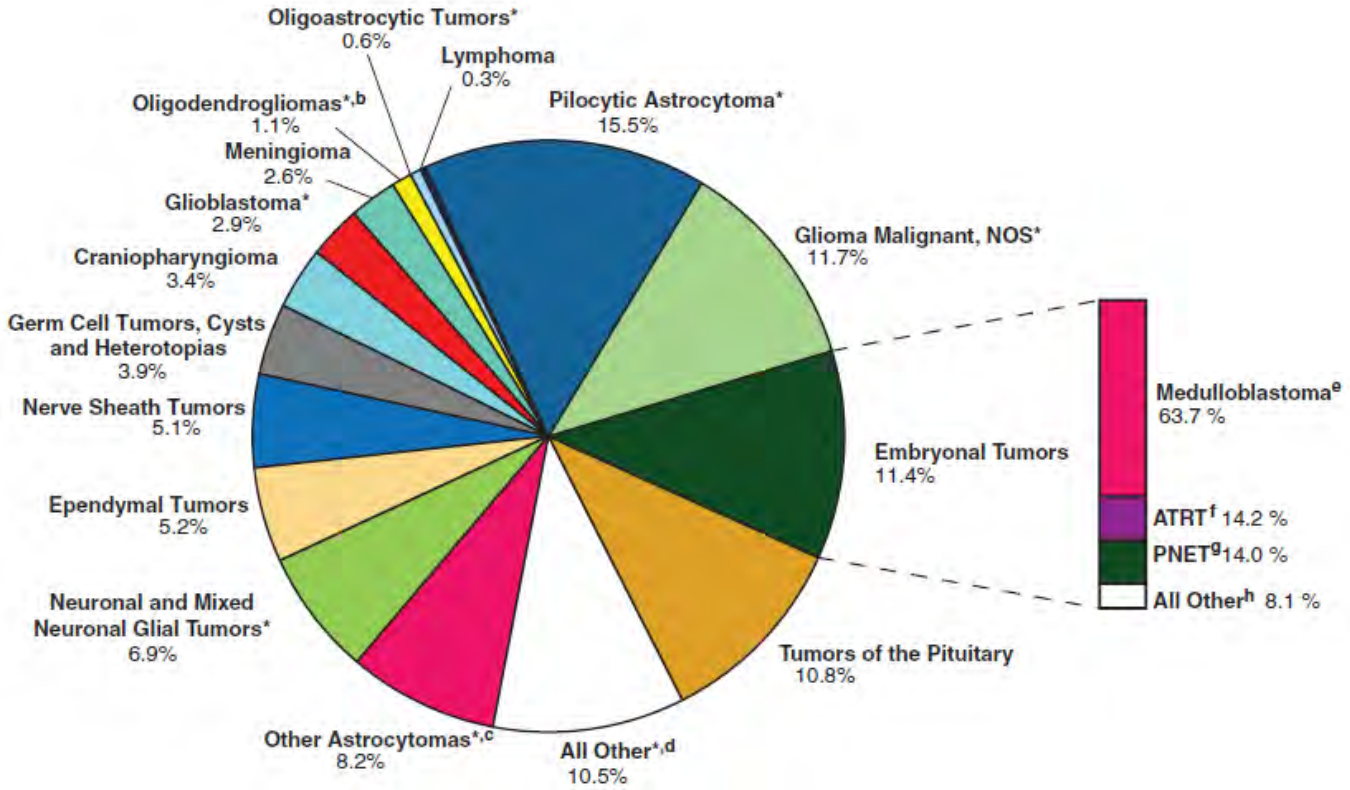
Case 3

3 yo M with HA, N, V, ataxia



Medulloblastoma, GTR, treated with radiation and chemotherapy

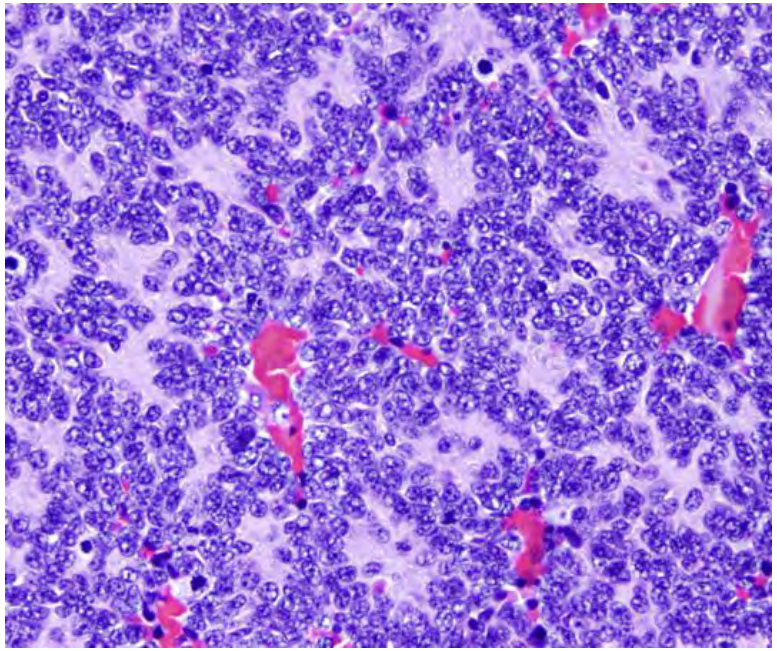
Distribution in Children and Adolescents (Age 0-19 years) of Primary Brain and CNS Tumors

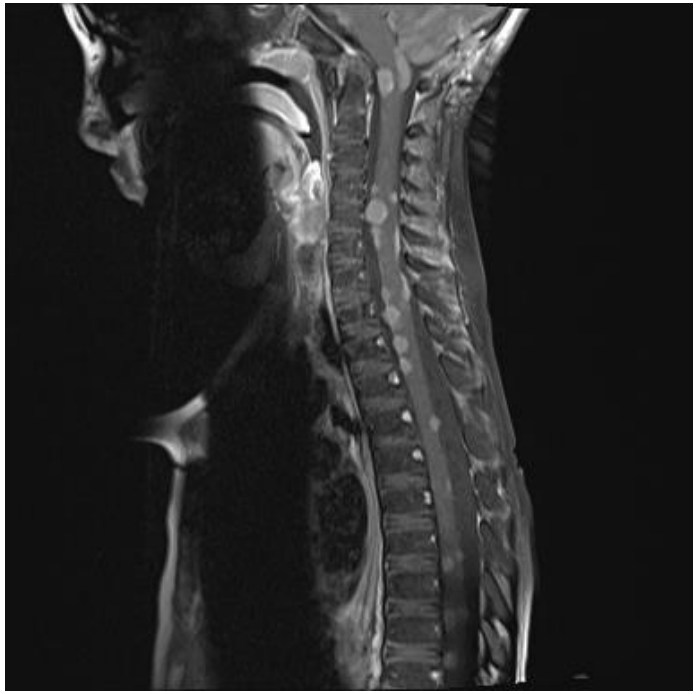


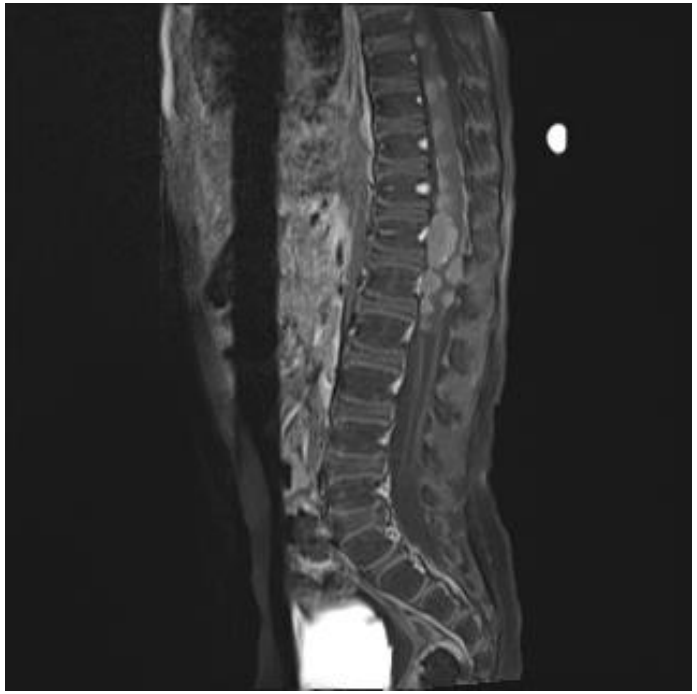
Embryonal tumor=small blue round cell tumor

Medulloblastoma

- Most common malignant tumor
  - 15-40% leptomeningeal infiltration at diagnosis
  - 5-35% of extraneural spread, bone, bone marrow, liver, lung, LNs

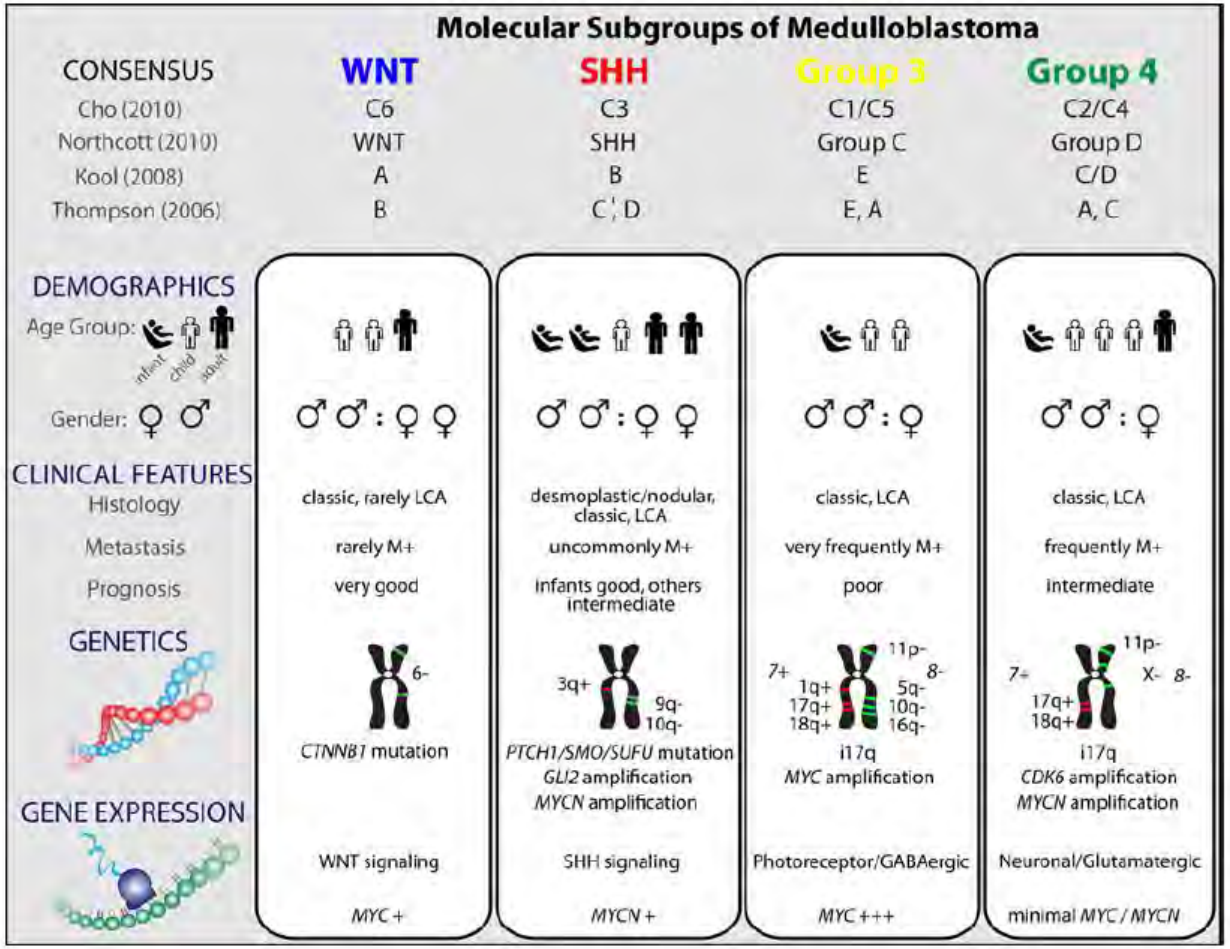




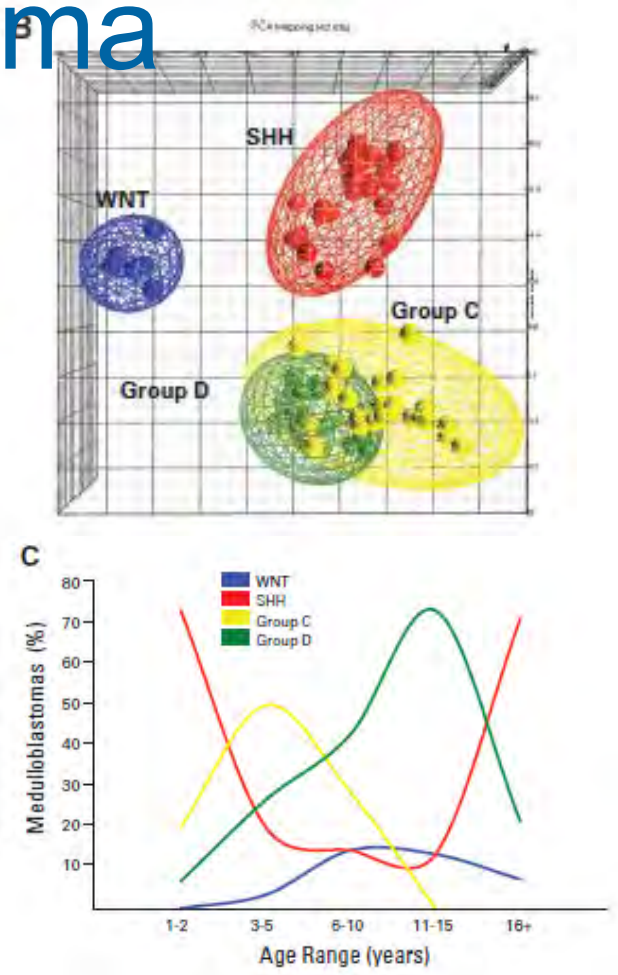


CHOC

Subgroup of medulloblastoma



Molecular subgroups of medulloblastoma: The current consensus, Acta Neuropathol 2012



Medulloblastoma comprises four distinct molecular variants, JCO 2011

Outcome of patient with high risk vs average risk

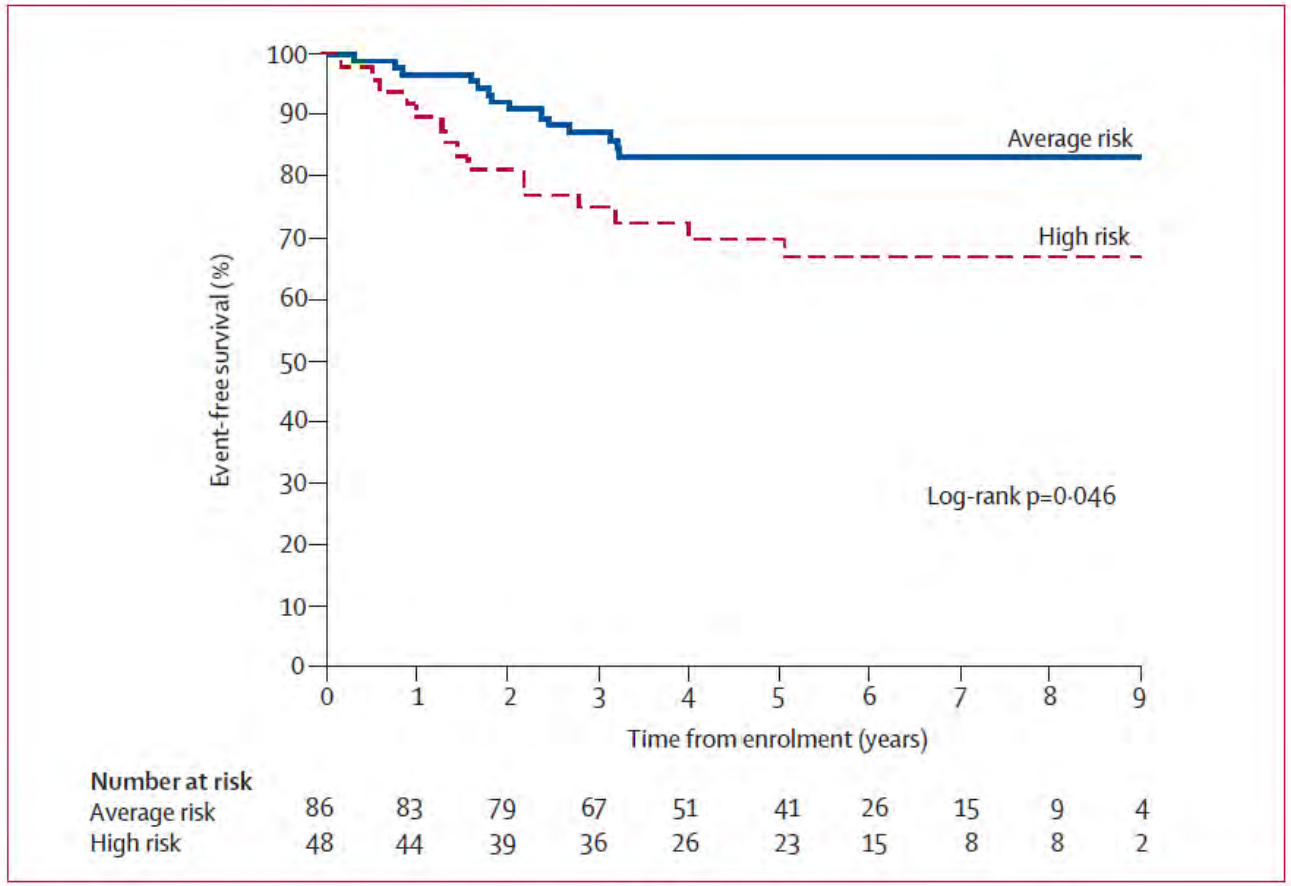
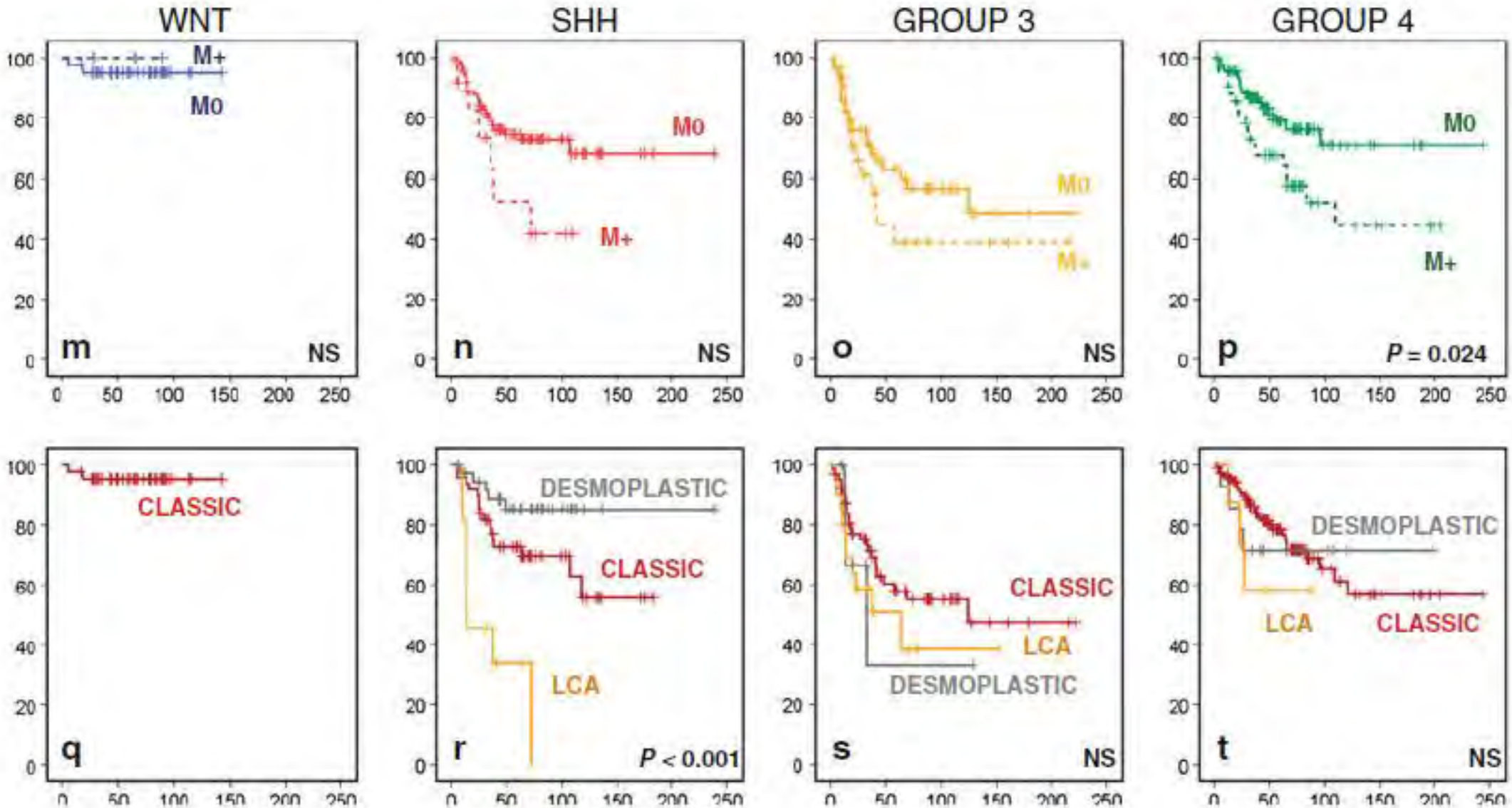
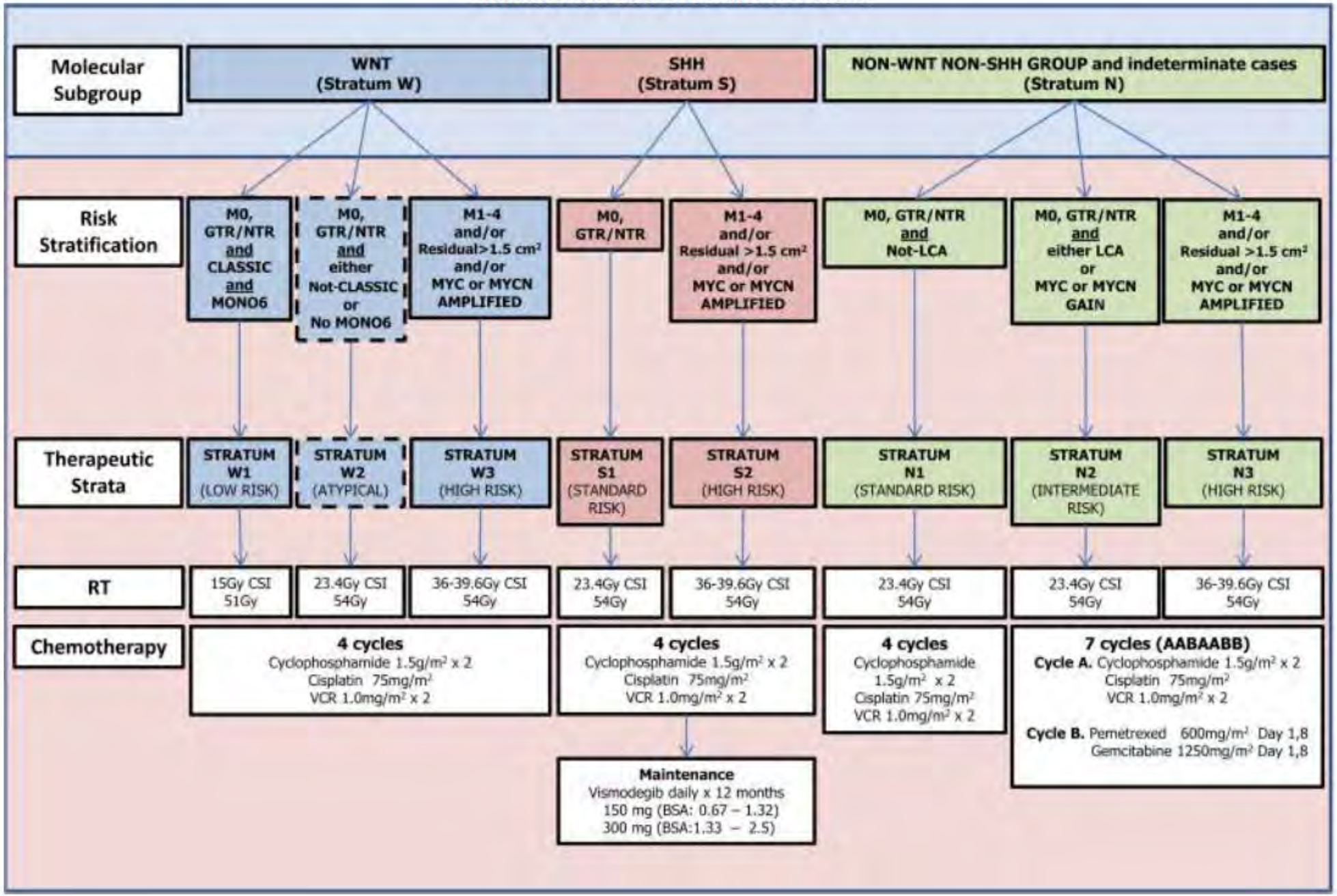


Figure 1: Event-free survival for average-risk and high-risk patients

Gajjar et al. Lancet Oncology 2006;7;813-20


WNT
SHH
GROUP 3
GROUP 4
M+
M0
m
NS
n
NS
o
NS
p
P = 0.024
CLASSIC
q
DESMOPLASTIC
CLASSIC
LCA
r
P < 0.001
s
NS
t
NS

Stratification and Treatment Schema



CHOC

Management of Medulloblastoma

- Accurate staging
- Maximum surgery
  - Goal: residual <1.5cm^2
- Craniospinal RT + Chemotherapy
- Chemotherapy to all
  - to reduce radiation dose
  - reduce risk of development of extra-CNS metastases

CHOC

Medulloblastoma

- Treatment
  1. Craniospinal radiation
  2. Adjuvant chemotherapy
- Outcome
  - Standard risk – 5y PFS 80%
  - High risk 5y PFS 50%
- Late effect
  - Neurological deficit
  - Hearing loss
  - Endocrinopathy
  - Secondary malignancy
  - Cognitive effect

CHOC

Questions

Question 1:

11 yo female presented with morning emesis and lethargy

1. Is this an emergent condition?
2. What exam gives you an informative information?
3. What image would you obtain first? What would we see?
4. What would neurosurgery do first?

1. Yes
2. Neurological exam and or fundoscopic exam- looking for papilledema.
3. CT head, obstructive hydrocephalous
4. Extraventricular drain placement

CHOC

Question 2
Radiation is one of weapons in treatment of brain tumors.

1. What do we consider when we decide the use of radiation therapy?

2. Is it OK to treat a child with low grade glioma with radiation?

1. Tumor grade. Radiation field and side effect, such as hormone effect and neurocognitive effect. Secondary malignancy risk

2. No and Yes

CHOC

Question 3:

A 7-year-old female presents to the ED, complaining of progressively worsening headache and clumsiness. Her mother states that she has been more lethargic lately. She has been nauseous and has been vomiting, more so in the mornings.

- What should we consider differentials?

- Gastroenteritis
- Hydrocephalus
- Allergies
- Viral meningitis
- intracranial bleed
- Accidental ingestion
- Childhood migraine
- Brain tumor

CHOC

Question 4:
What are type of new treatment in cancer?

- Target therapy
- Immunotherapy – vaccines or immune recruitment type
- CBDs as supplement

CHOC

Question 5: How should we deliver a bad news to the patient and parents in different culture ?

- There are challenges in change in health care system.
  - Integrated molecular diagnosis
  - There may be treatment options
  - Interpreter limitation
  - Time limitation

- Use language which is simple and precise
- Ask understanding, teach-back system
- Use professionally trained interpreter
- Understand cultural background, such as Jehovah's witness

CHOC

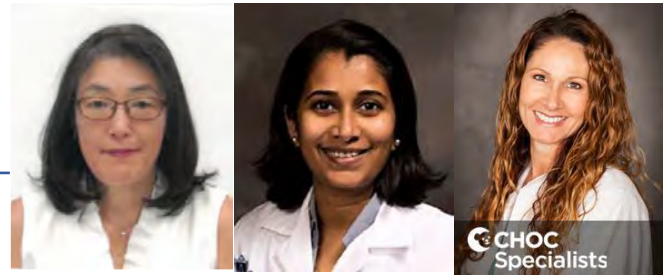
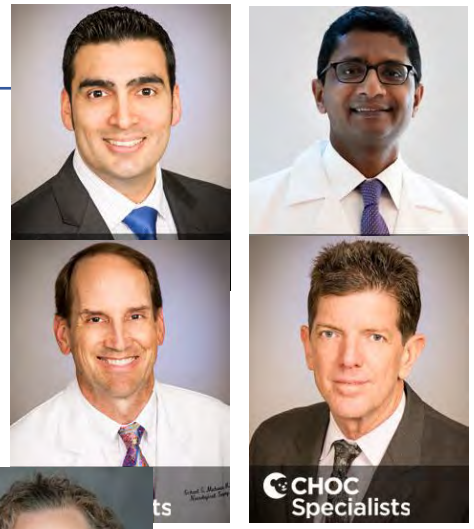
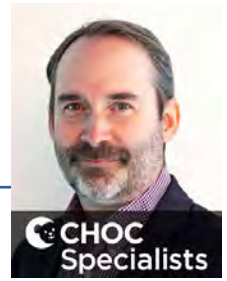
Summery

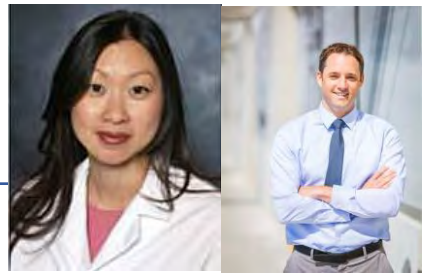
1. Histopathologic diagnosis is increasingly being supplemented with gene alterations. These data subsequently inform treatment decision making.
2. In pediatric brain tumor, risk stratification and modification of therapy based on genotype has not completely established.
3. Challenges continue due to heterogeneity of tumor, vulnerable population, and drug companies, as well as biological hurdles such as blood brain barrier or microenvironment

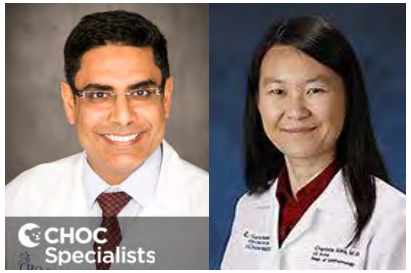
CHOC

Brain and spinal cord tumor program

- Neuro-oncology
- Neurosurgery
- Neurology
- Neuroradiology
- Neuropathology
- Radiation oncology
- Endocrine
- Ophthalmology
- Neuropsychology




Social worker
Case manager
Child life
Palliative care team
Administrative staff

CHOC

When you suspect your patient may have a brain tumor, call us.

Pediatric Neuro-Oncology

714-509-4348 or msato@choc.org

Thank you

LONG LIVE CHILDHOOD

Contact: Name / msato@choc.org

CHOC

PRACTICE CONTACT INFORMATION

Hyundai Cancer Institute Clinic

CHOC Clinic

1201 W. La Veta Ave., 2nd Floor

Orange, CA 92868

Phone: 714-509-8636

Fax: 714-509-4748

choc.org/cancer

Physicians available via telehealth and pingmd ®

CHOC

LONG LIVE CHILDHOOD

THANK YOU!

Contact: bdinfo@choc.org

CHOC