Brain Tumors in Children

Michael A. Grotzer

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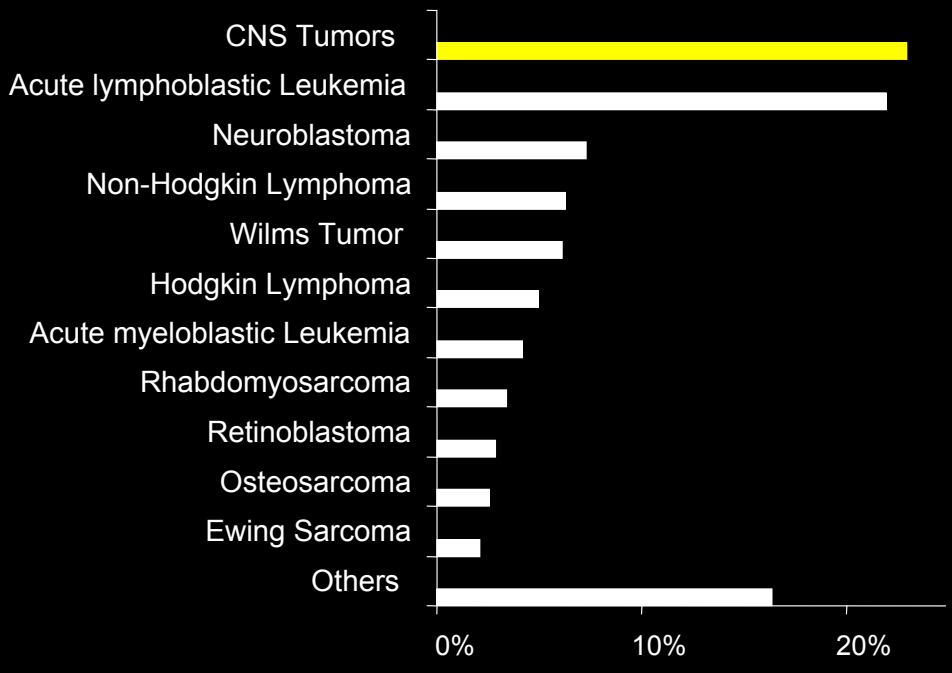
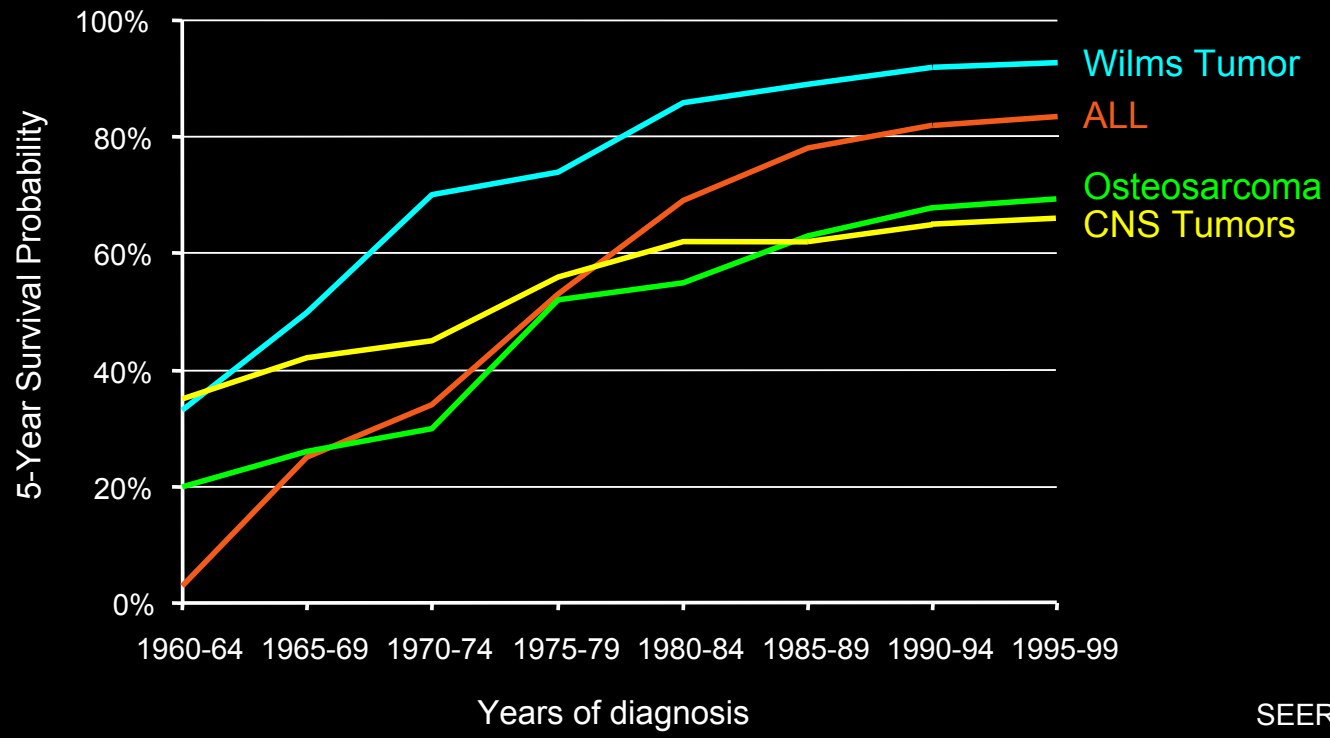
Incidence of Childhood Cancer



Prognosis of Pediatric Cancer



SEER (USA)

Etiology of Childhood CNS Tumors: Hereditary Factors

NF-1	astrocytomas (optic pathways)
NF-2	schwannomas (vestibular, trigeminal), ependymomas, meningiomas
Tuberous sclerosis	cortical dysplasia (cortical tubers), subependymal nodules, subependymal giant cell astrocytomas
Von Hippel-Lindau disease	hemangioblastomas (cerebellar,…)
Turcot syndrome	medulloblastoma
NBCC syndrome	medulloblastoma
Li-Fraumeni syndrome	choroid plexus carcinoma, astrocytomas, medulloblastoma, ependymoma

Etiology of Childhood CNS Tumors: Ionizing Radiation

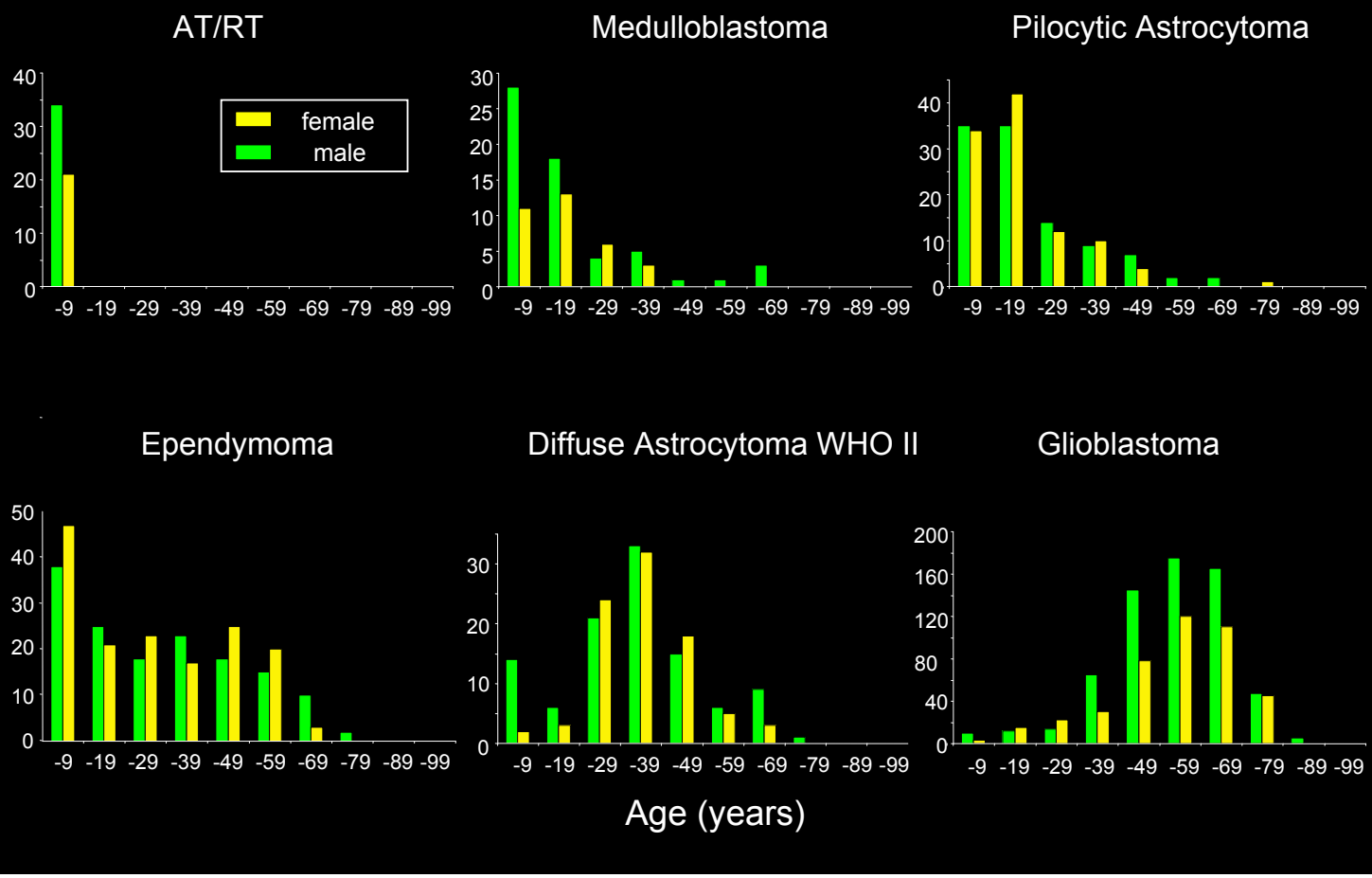
- Cranial irradiation for treatment of tinea capitis, leukemia, CNS tumors
- Radiation doses as low as 3 Gy
- Latency usually 5-25 years
- Most of these secondary CNS tumors classified as astrocytomas and meningiomas

Etiology of Childhood CNS Tumors: Other Factors

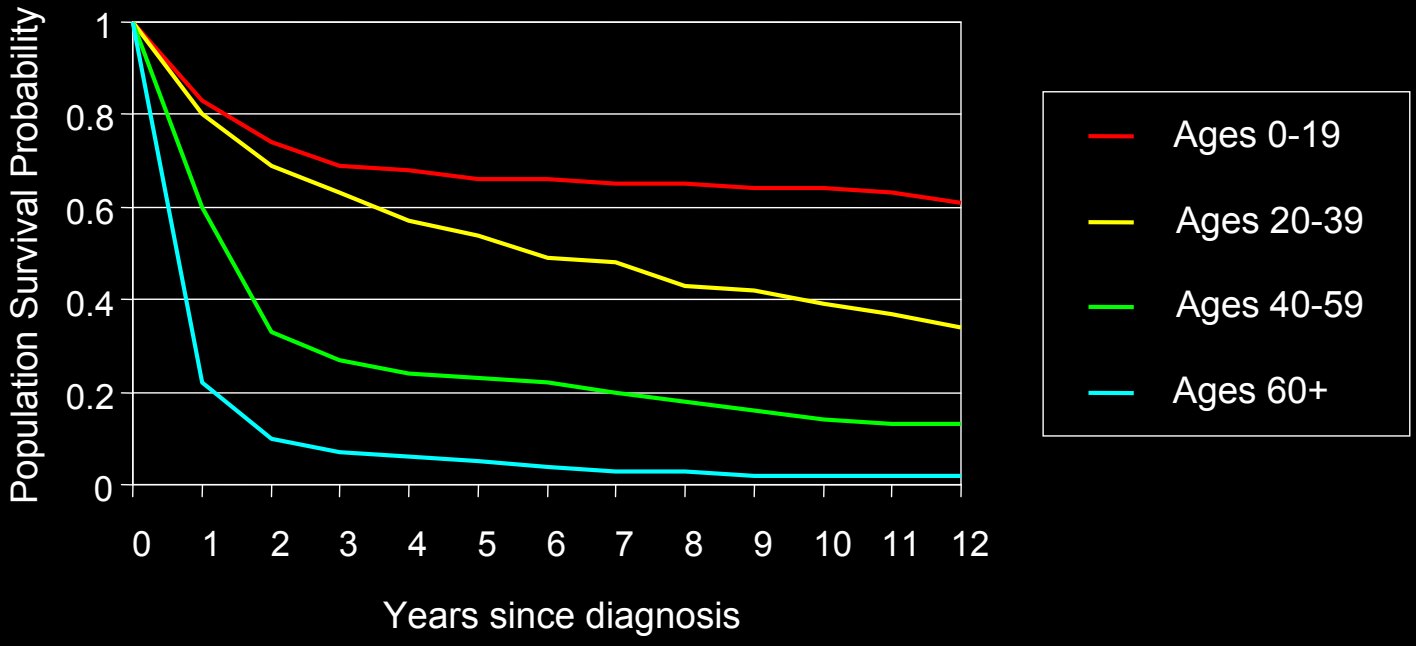
- Endogenous immunosuppression
  - Wiskott-Aldrich syndrome
  - Ataxia teleangiektasia
- Exogenous immunosuppression
  - Organ-transplant recipients
  - HIV infection
- ~~Polyomaviruses ?~~
  - ~~SV40, JC, BK~~

Pediatric Brain Tumors Differ From Adult Brain Tumors

- Histology:
  - The types of tumors encountered in children are uncommon in adults, and vice versa
- Localization:
  - infratentorial > supratentorial
- Surgery:
  - The value of extensive tumor resection has been confirmed for a variaty of childhood brain tumors
- Chemotherapy:
  - has been shown to be effective in improving overall outcome in several childhood brain tumors
  - is increasingly used to delay or avoid using radiotherapy in children younger than 3 years of age

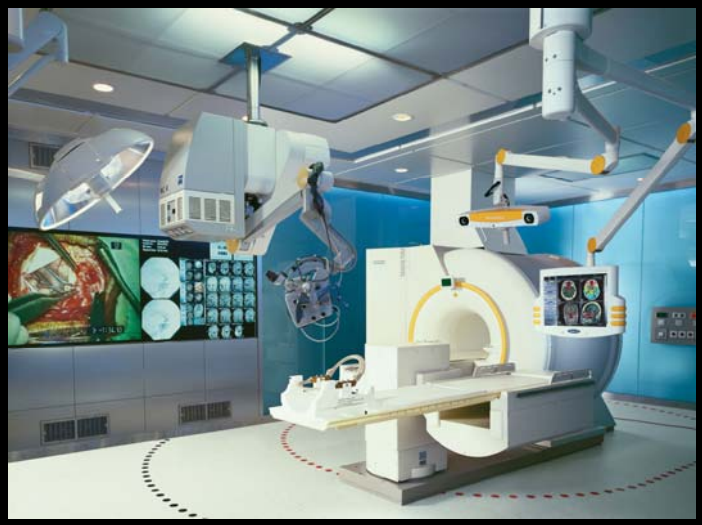


Survival by Age for Malignant Brain Tumors

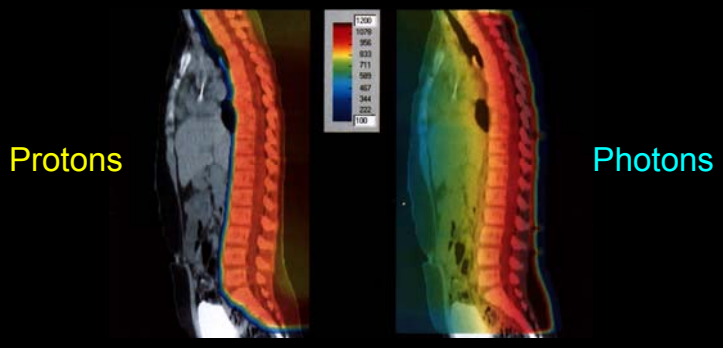


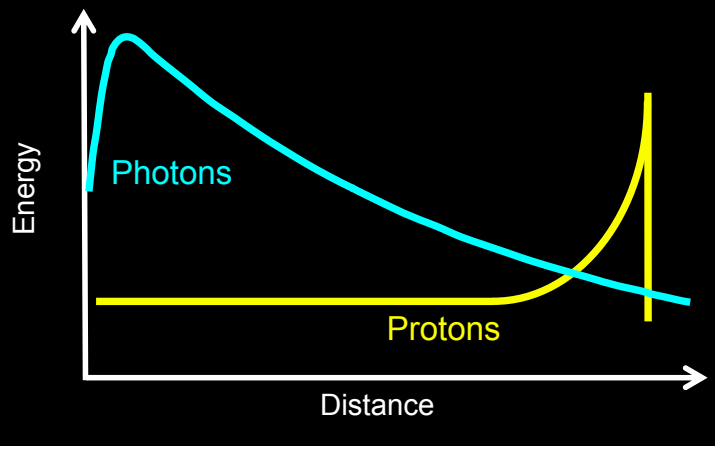
SEER (USA)

Technical Advances in Imaging and Neurosurgery



Irradiation Using Protons





Ependymoma: Incidence and Epidemiology

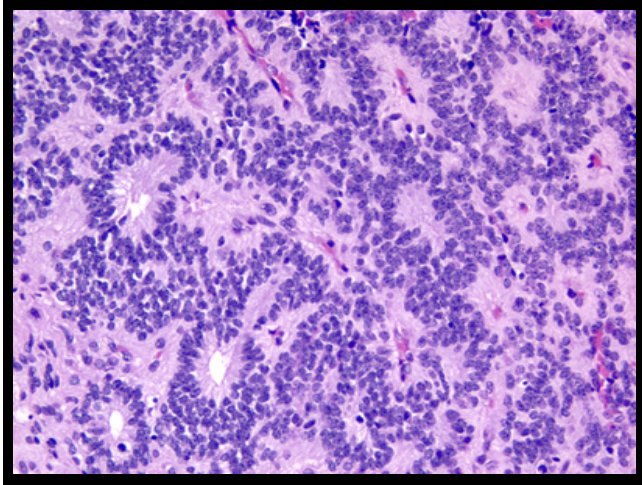
- Frequency: 10-15% of all childhood CNS cancers
- Prevalence: 1 in 28,000 live birth (USA)
- Median age: 6 years
- No known predisposing exposures

Ependymoma: Localization

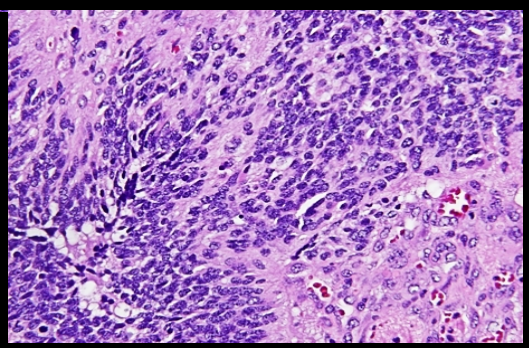
- Posterior fossa > supratentorial extraventricular > lateral ventricles > spinal
- The majority of tumors are localized at the time of diagnosis
- The primary tumor site remains the most likely area of disease relapse

Pathology and Grading

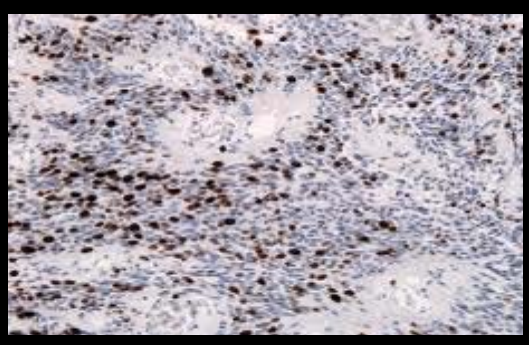
Ependymoma WHO II



Anaplastic Ependymoma WHO III



microvascular proliferation



high mitotic activity

Ependymoma: Prognostic Factors

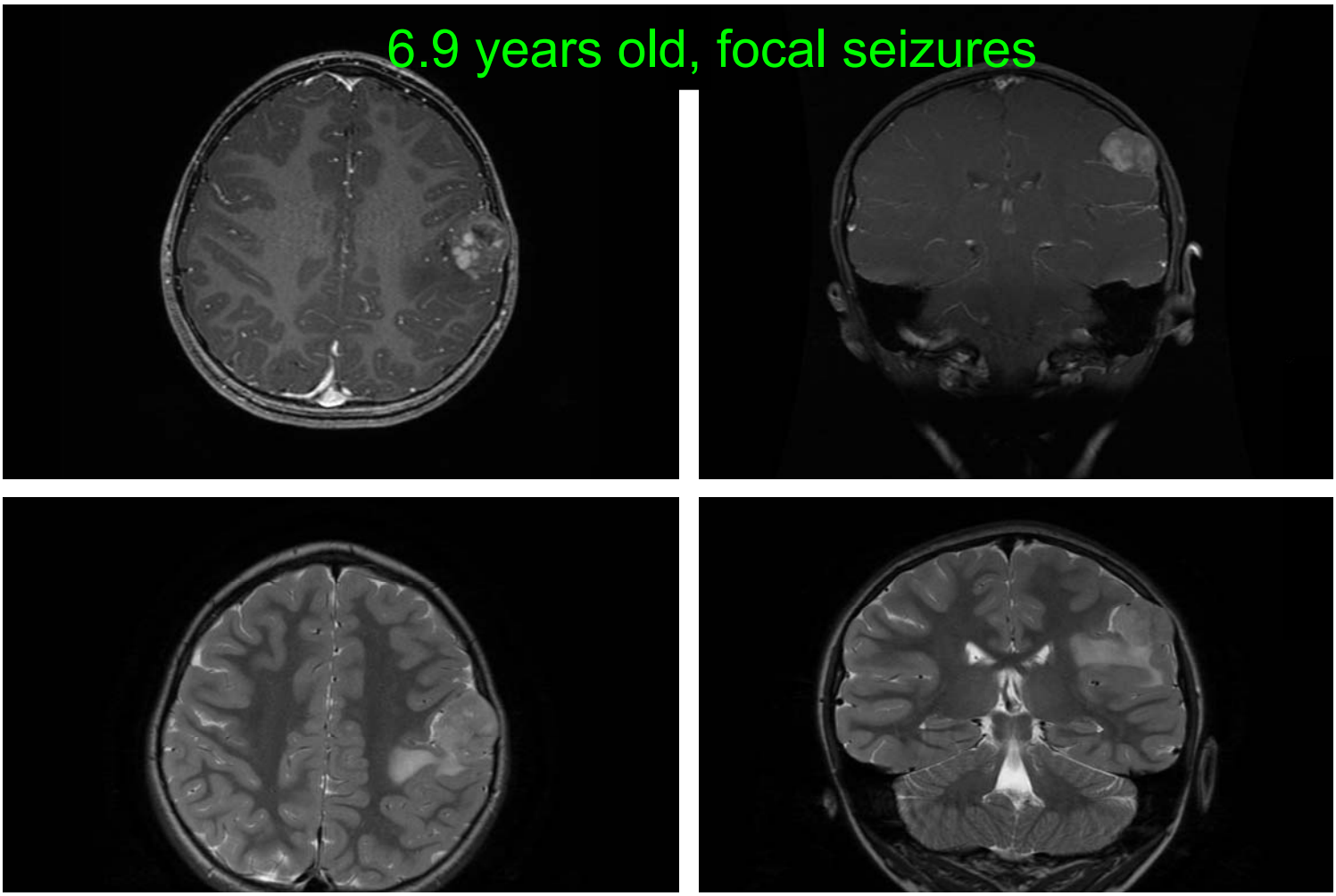
positive

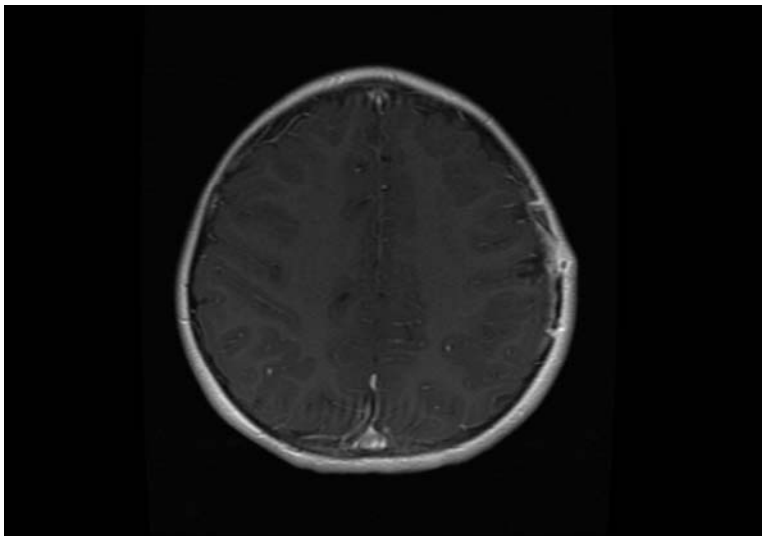
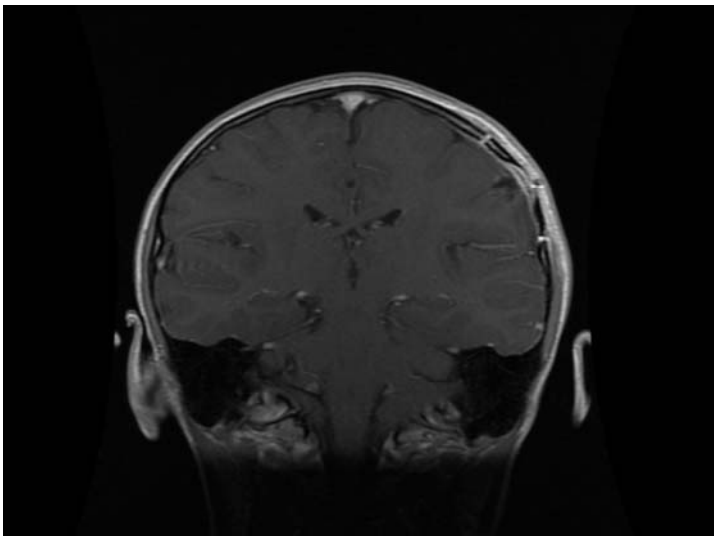
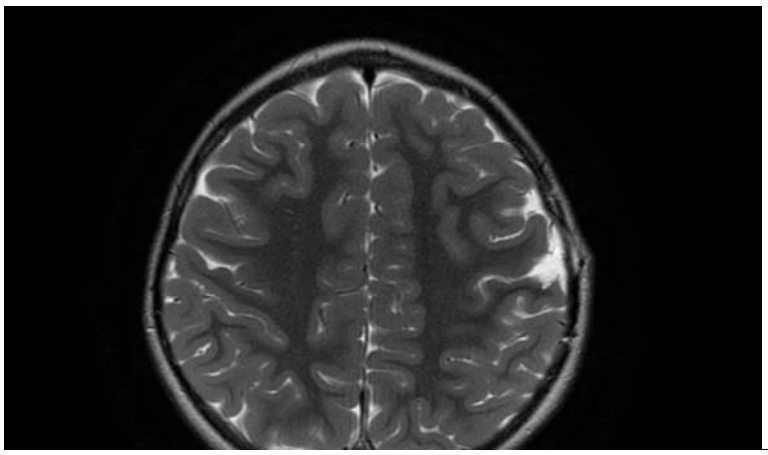
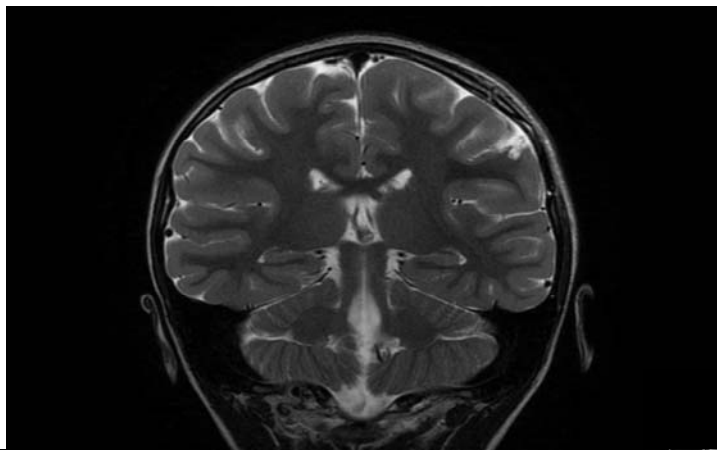
- Total resection
- Age over 4 - 6 years
- Local XRT > 45 Gy
- Differentiated (WHO II)

negative

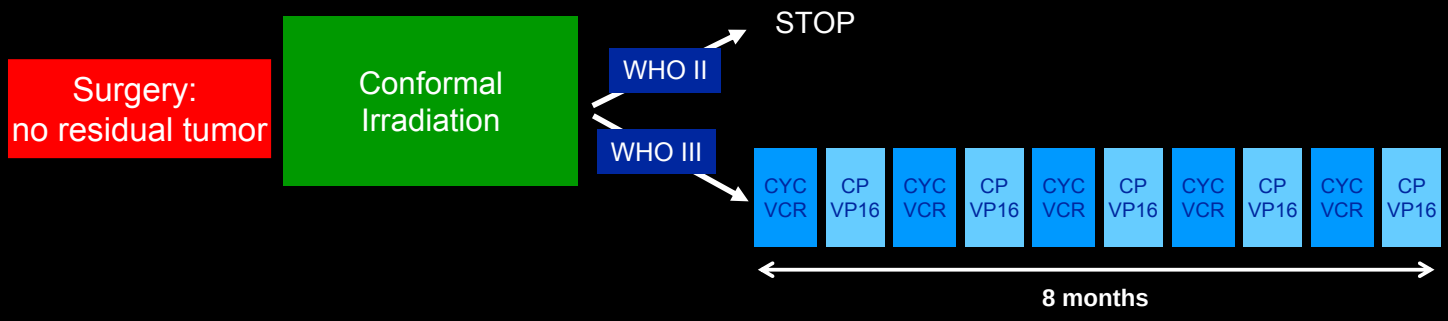
- Less than total resection
- Age under 4 - 6 years
- Local XRT < 45 Gy
- Anaplastic (WHO III)

6.9 years old, focal seizures

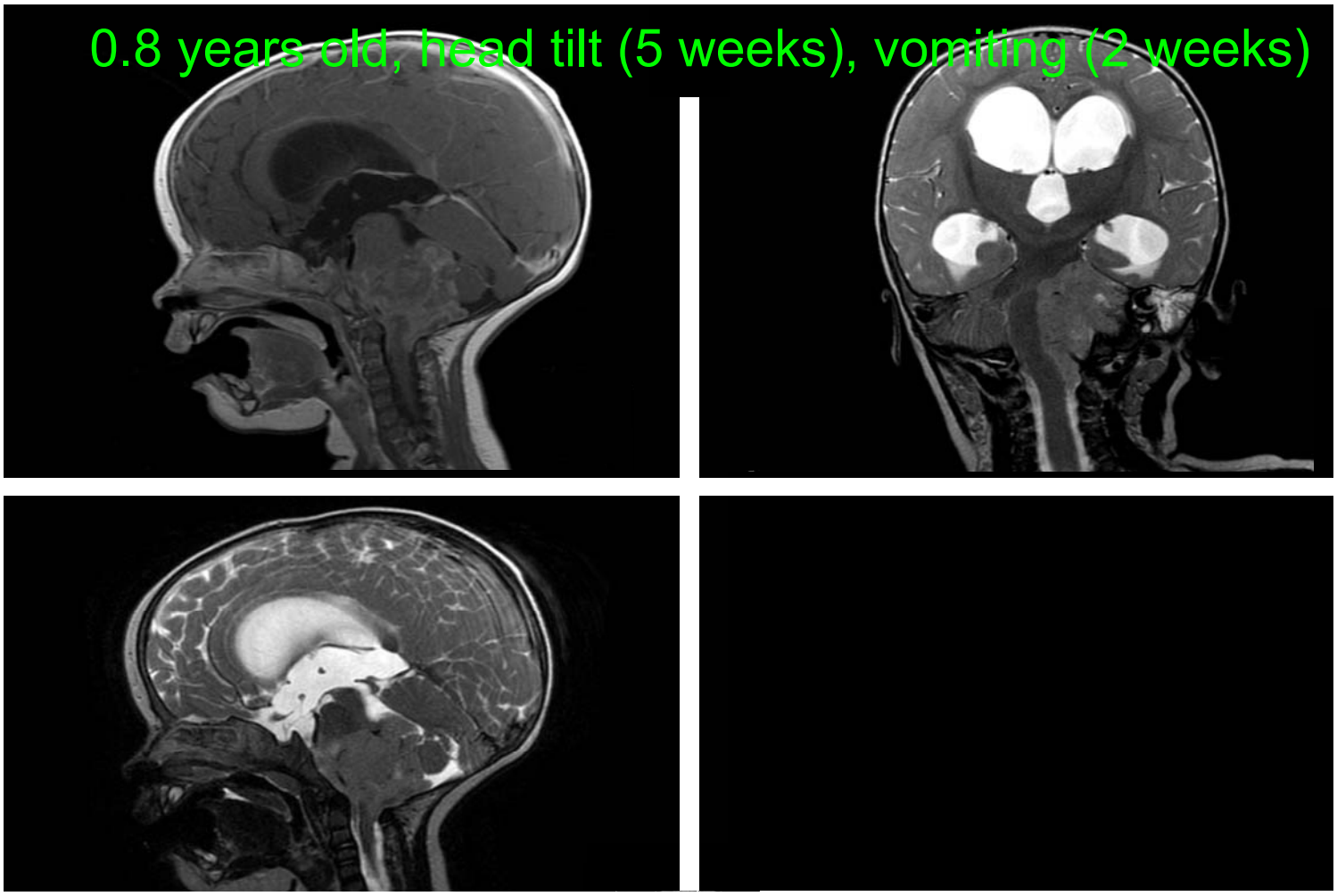


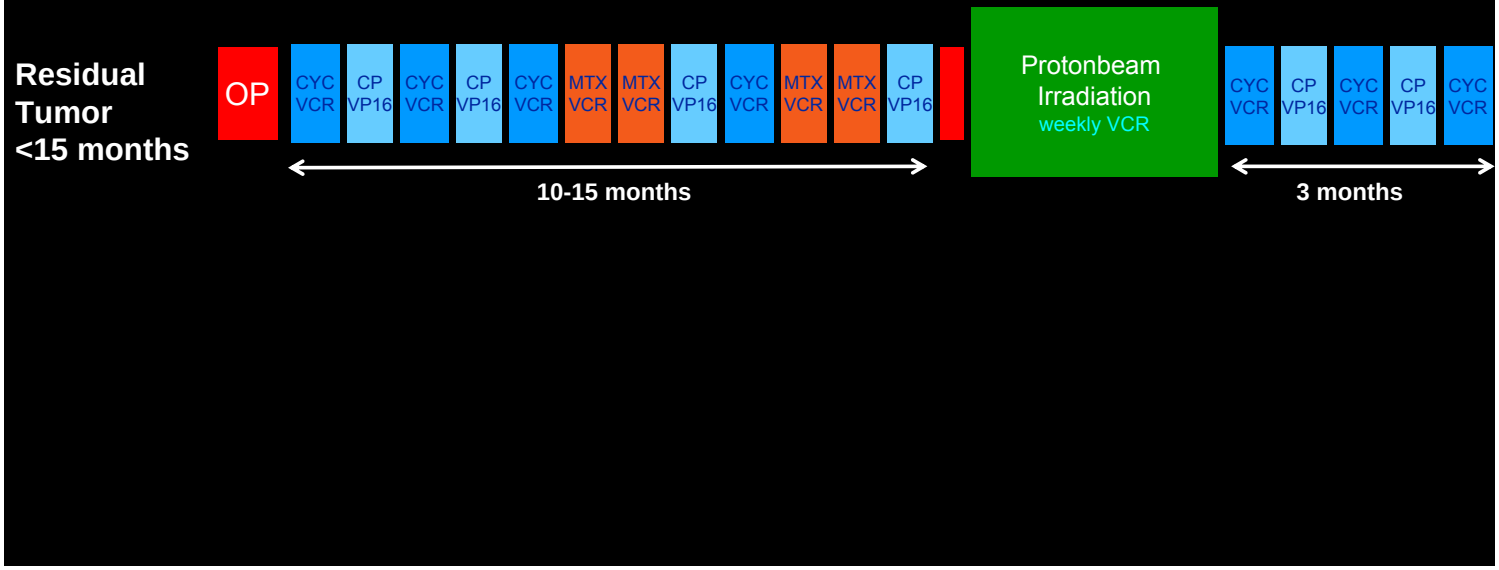
Localized Ependymoma >4 Years of Age

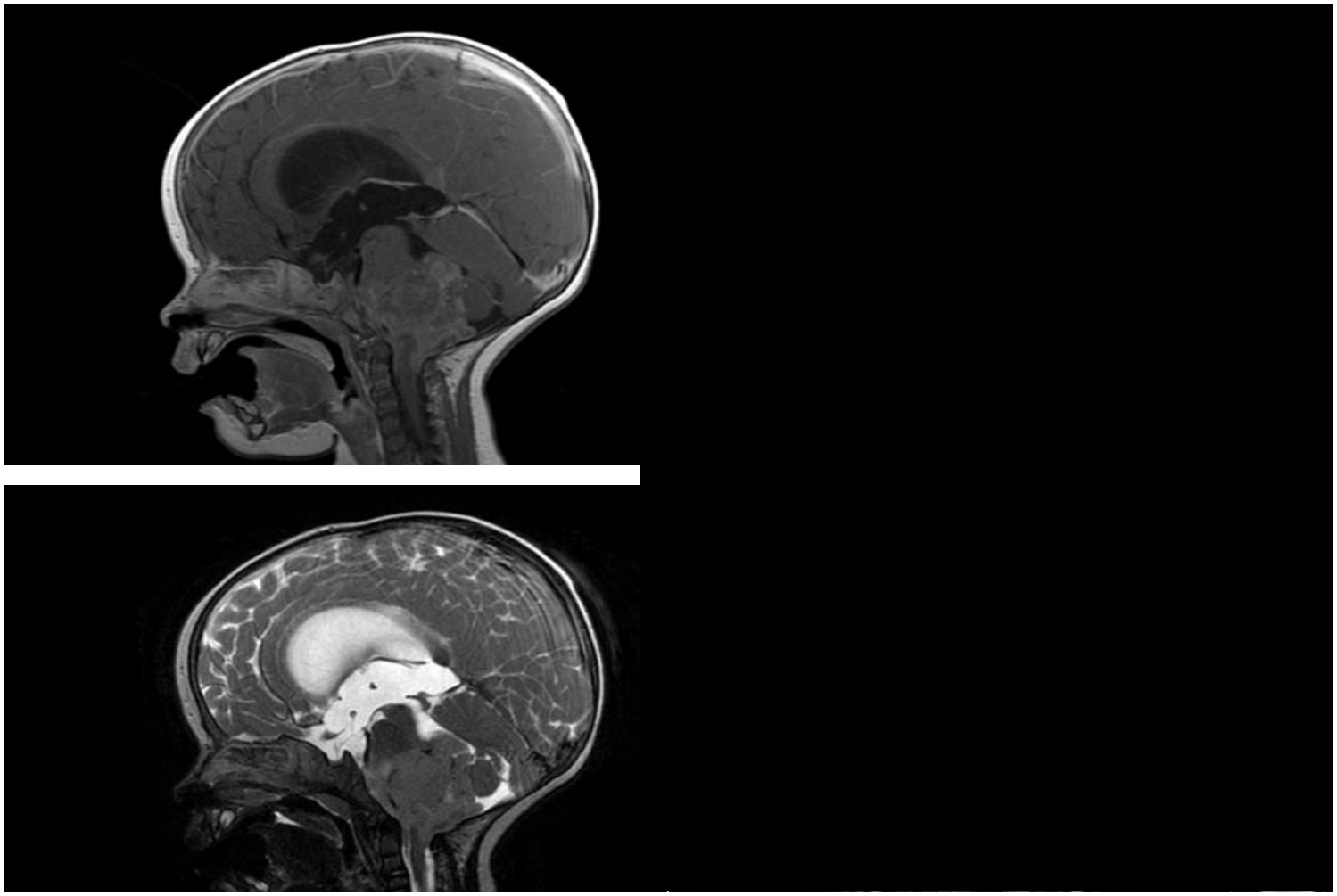


0.8 years old, head tilt (5 weeks), vomiting (2 weeks)

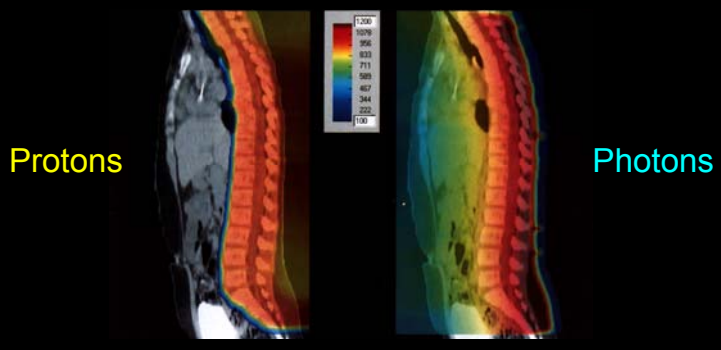


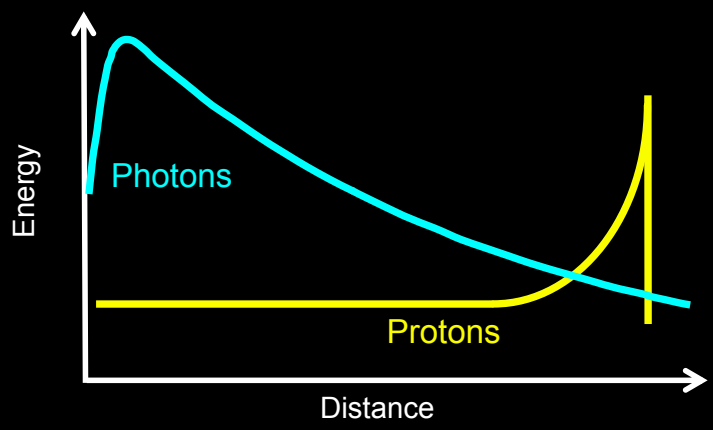
Localized Ependymoma <4 Years of Age



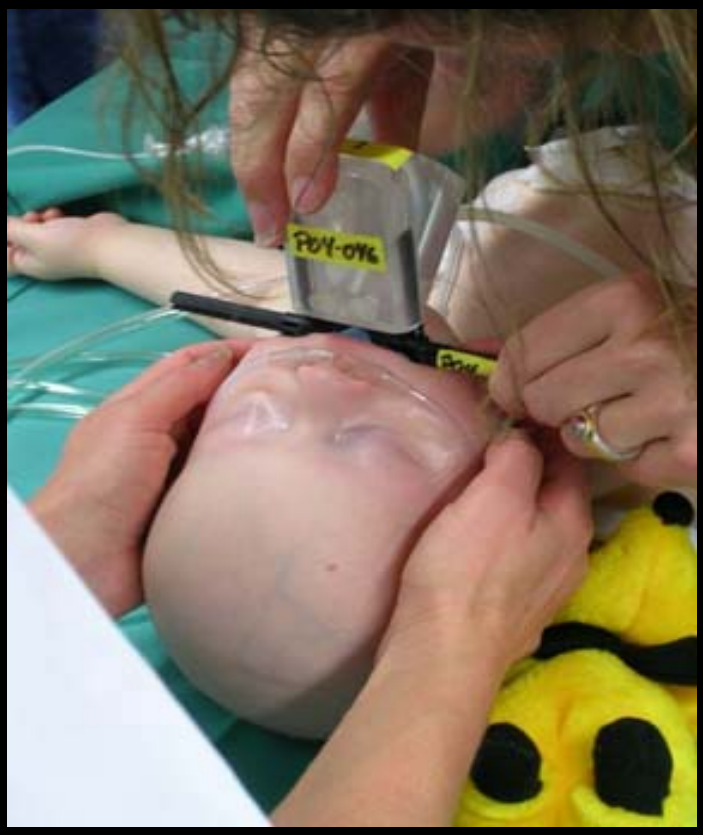


Irradiation Using Protons





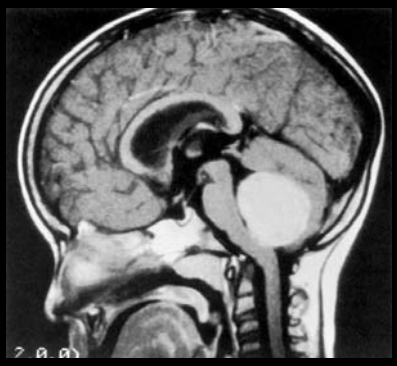
Anesthesia



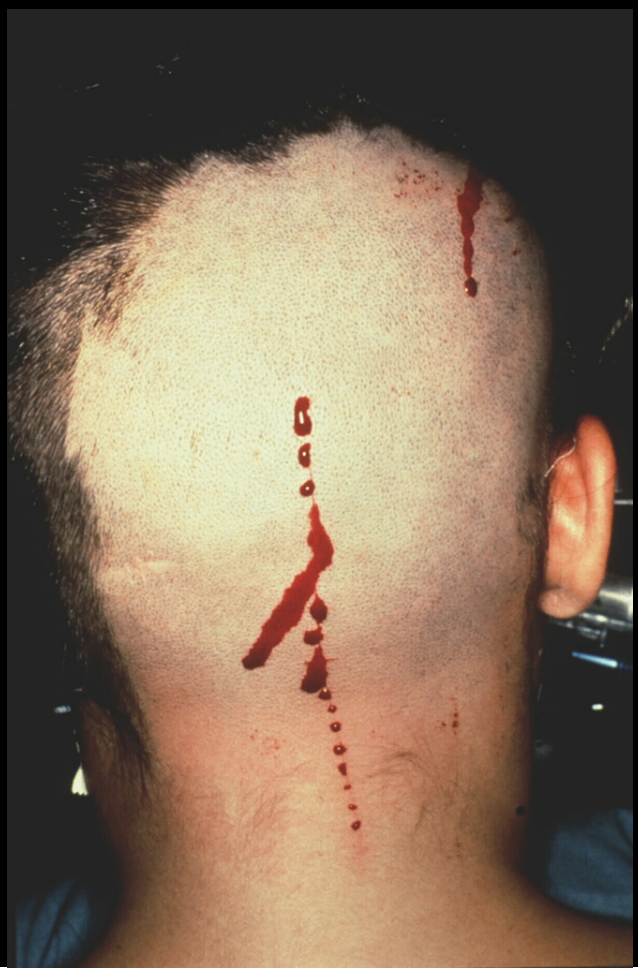
Patient immobilization

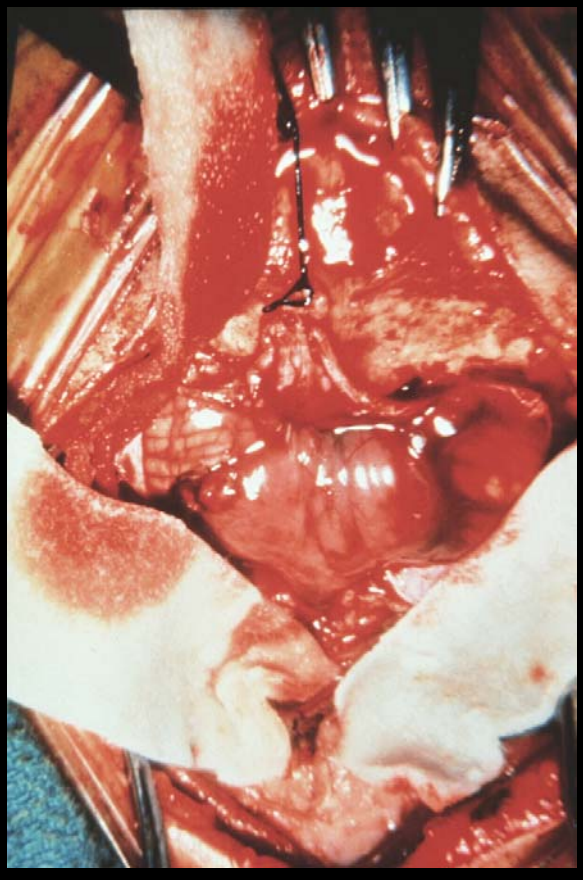
Appropriate patient safety system

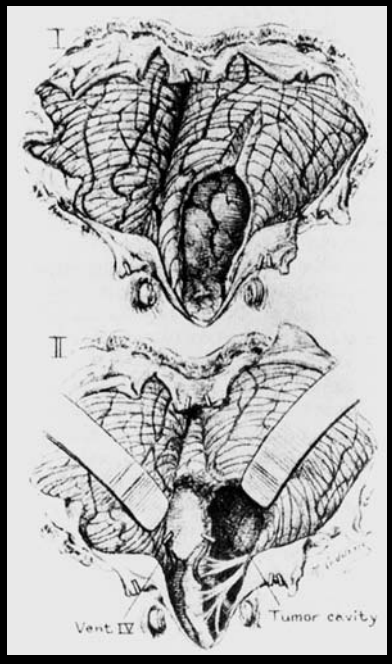
Medulloblastoma

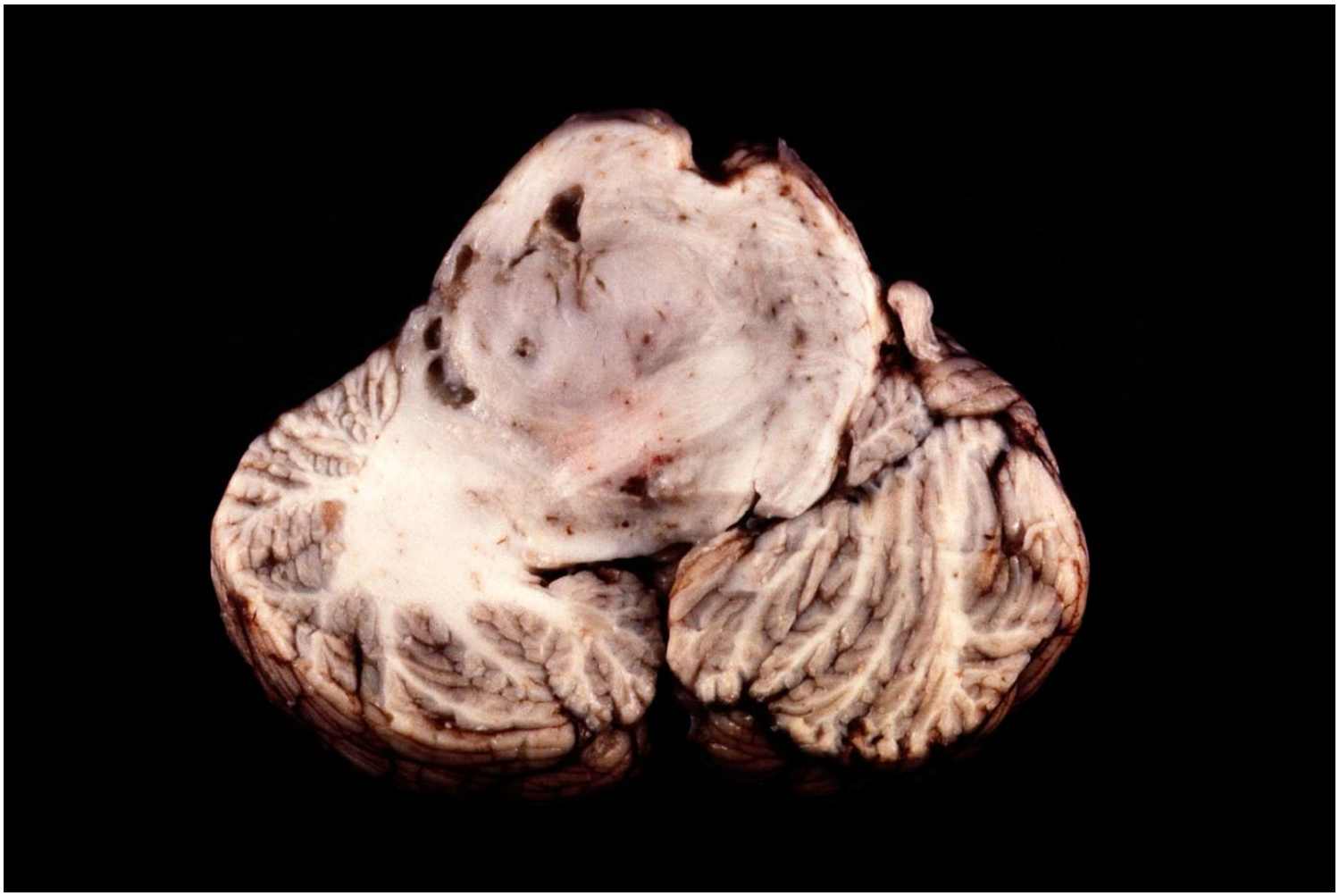


	Surgery	Radio	Chemo	5-Year Survival
Before 1930				0%
1930-40		local		0%
Since 1940		local + cs		50%
Since 1975				65%
1995				80%

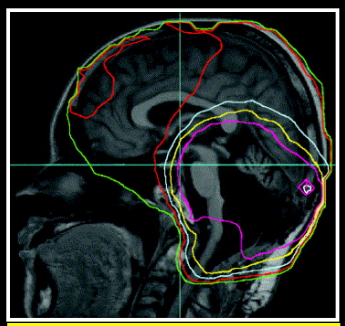





I
II
Vent IV
Tumor cavity



Medulloblastoma: Treatment for Children > 3 Years (Packer RJ, 1994)



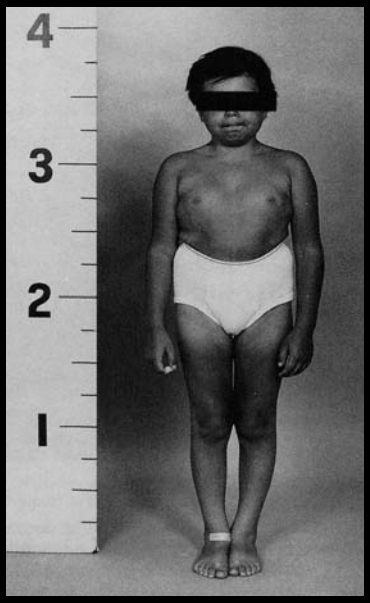
SURGERY

RADIATION
Posterior fossa 54 Gy
Craniospinal 36 Gy

Cisplatin
Lomustine
Vincristin

week 1 2 3 4 5 6 7 8 10 16 22 28 34 40 46 52

Longterm Effects of Current Medulloblastoma Therapy



- Growth dysfunction
- Endocrine dysfunction
- Hearing loss
- Alopecia
- Risk for second malignancies
- Social and emotional problems
- Intellectual deficits

Late Effects in Pediatric Brain Tumor Survivors: Interplay of Different Factors

Therapy	Tumor	Patient
RT total dose	direct tissue effects	development status
RT dose rate	indirect mechanical effects	genetic predisposition
RT treatment volume		tissue sensitivities
RT dose distribution		compensating mechanisms
other therapy		

HIT-SKK`92
Medulloblastoma Age <3 years

CYC/VCR hdMTX Carbo/VP MTX i. ventr.

CYC/VCR hdMTX Carbo/VP MTX i. ventr.

CYC/VCR hdMTX Carbo/VP MTX i. ventr.

CCR → End of Therapy

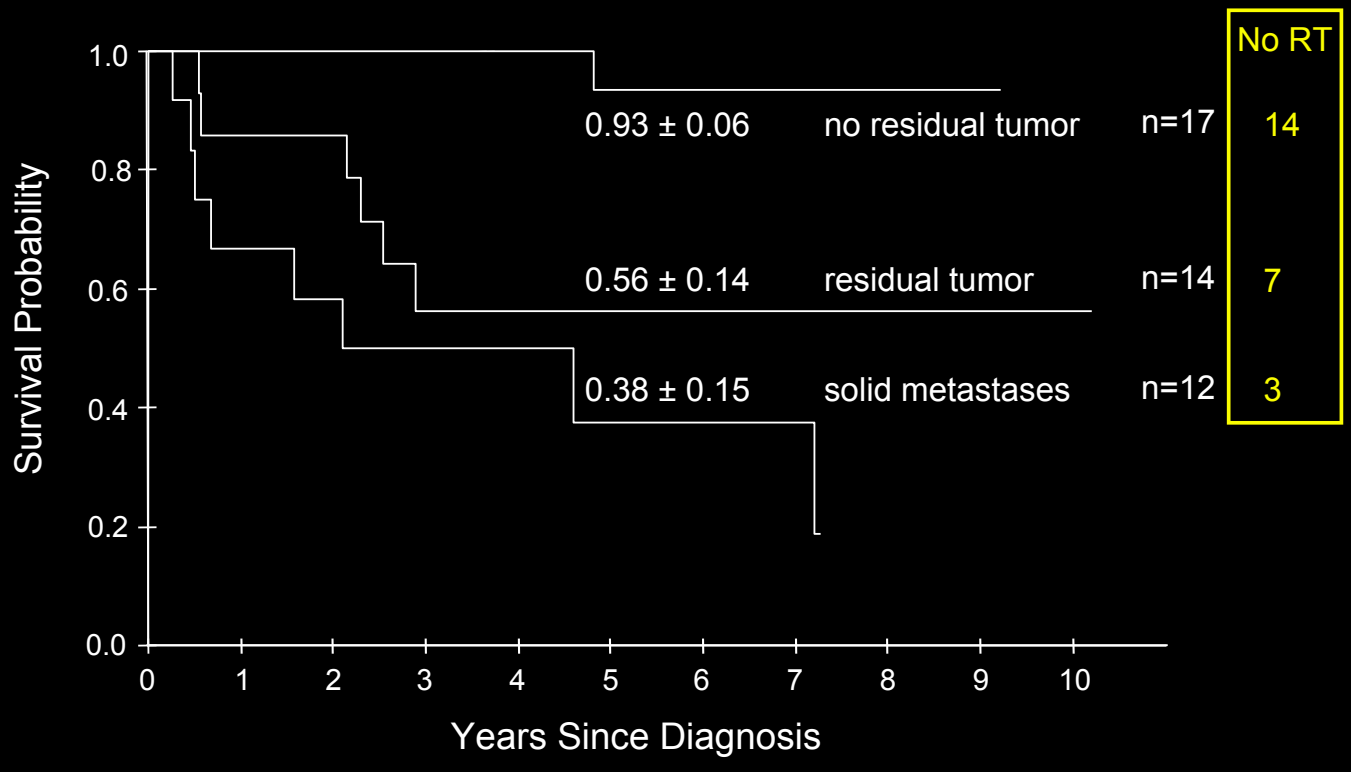
no CCR

<18 Months → experimental Chemo

>18 Months → craniospinal Radiation

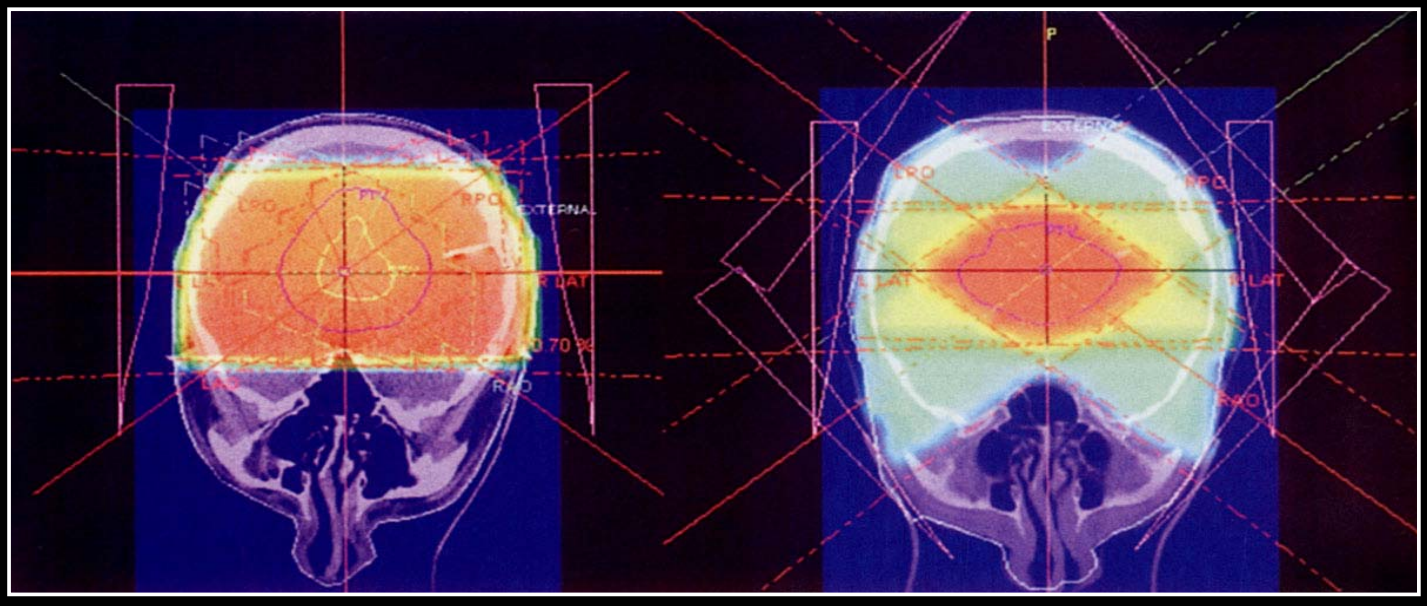
Rutkowski S et al. N Engl J Med 2005

HIT-SKK`92



Rutkowski S et al. N Engl J Med 2005

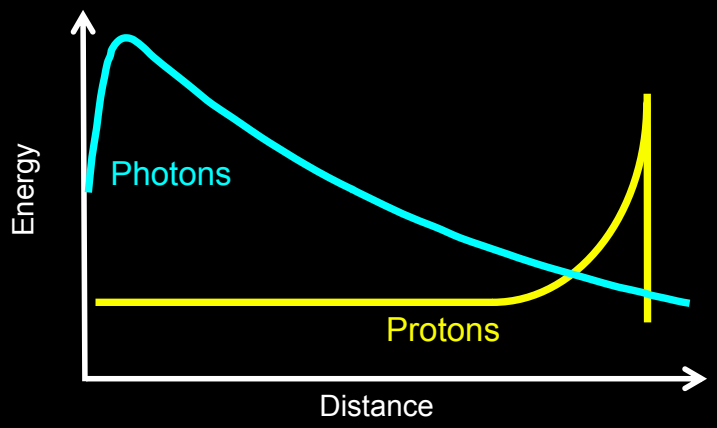
Intensity-Modulated Radiotherapy (IMRT)

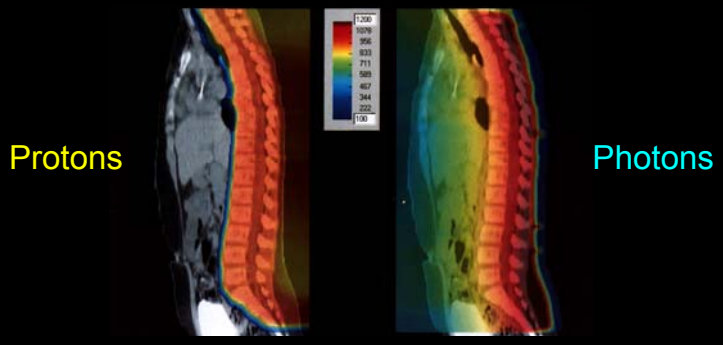


54.2 Gy 64 %	auditory apparatus radiation WHO grade 3/4 hearing loss (n = 26 medulloblastoma)	36.7 Gy (-32%) 13 %

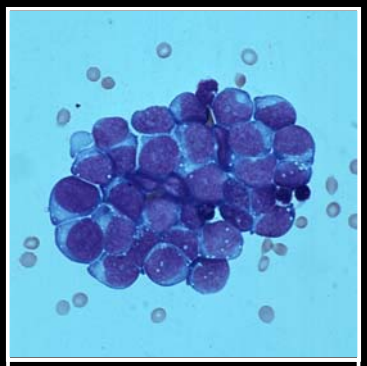
Huang E et al. Int J Radiat Oncol Biol Phys 2002

Irradiation Using Protons

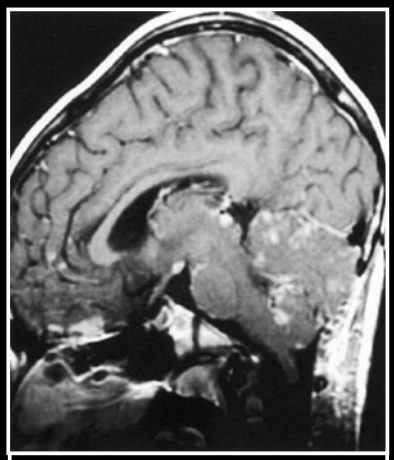




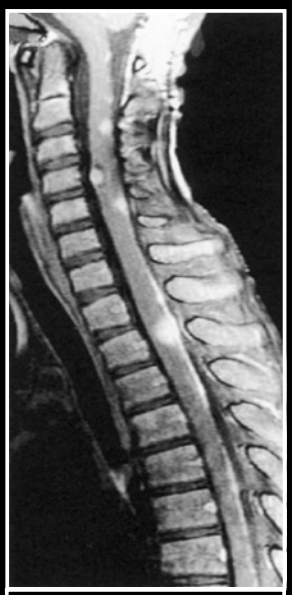
Medulloblastoma Staging: Modified Chang Classification System



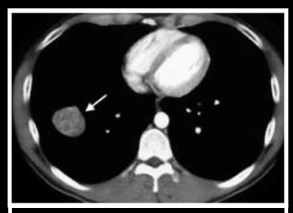
M1
Tumor cells in CSF



M2
Nodular seeding in cerebellum, cerebral subarachnoid space, or in 3rd or 4th ventricles



M3
Nodular seeding in spinal subarachnoid space



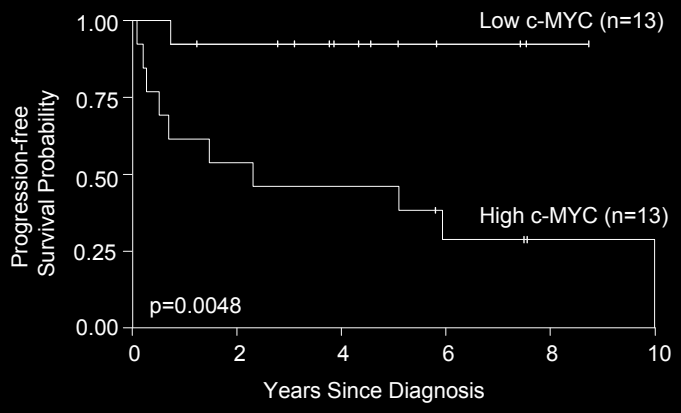
M4
Extraneuraxial metastasis

Patient Stratification

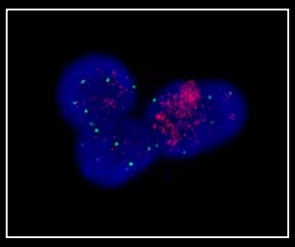
SURGERY → Clinical Factors + Molecular Phenotype

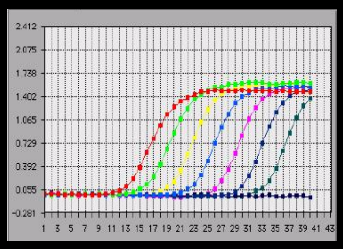
- Low Risk: Minimal Therapy
- Standard Risk: Maximal Therapy
- High Risk: Novel Therapies

c-MYC

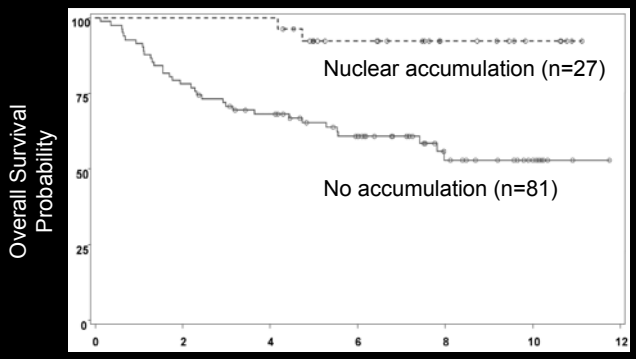


Grotzer, Clin Cancer Res 2001

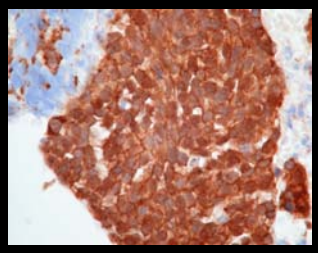


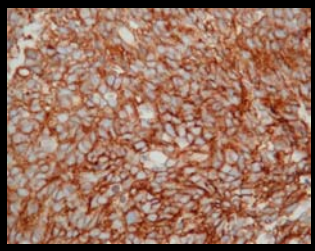


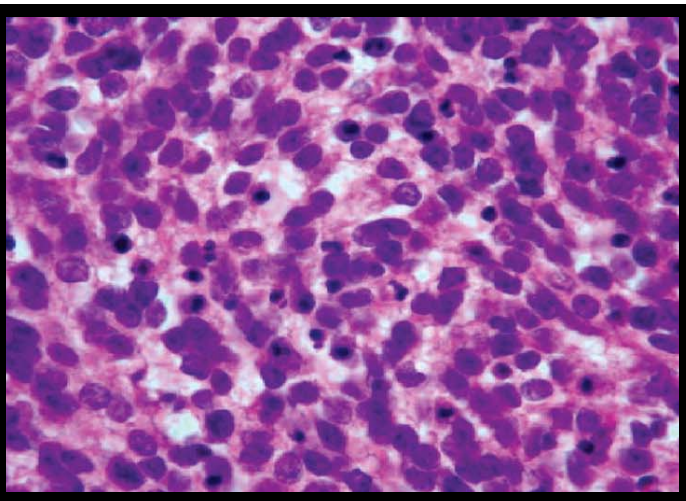
β-catenin

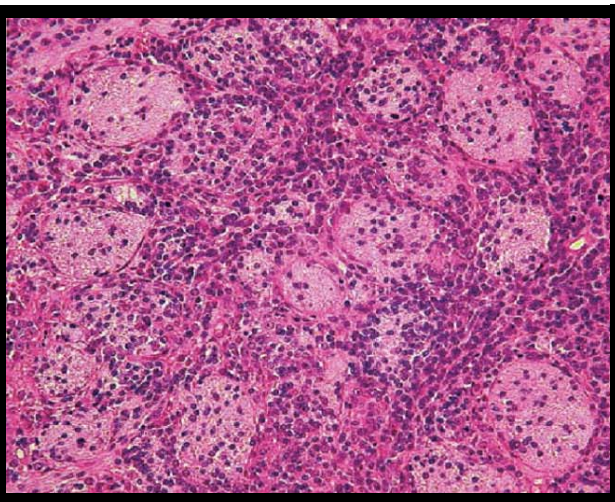


Ellison, J Clin Oncol 2005









Classic MB (64-83%)

composed of sheets of small uniform cells with a high nuclear-to cytoplasmatic ratio

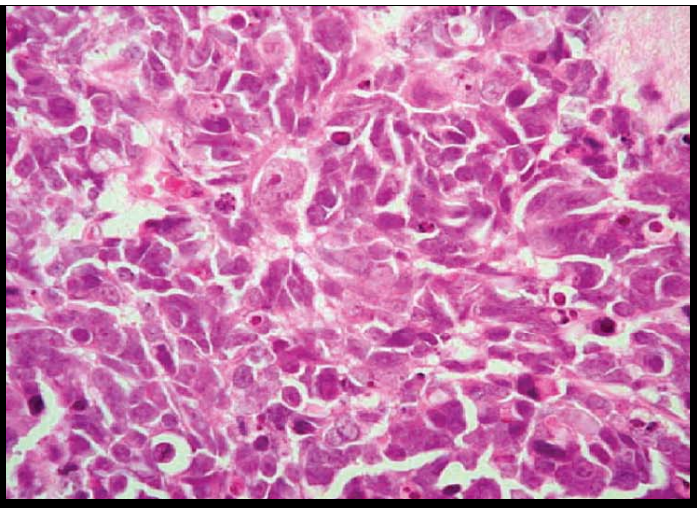
MB with extensive nodularity (3%)

Desmoplastic MB (7%)

combines nodules of differentiated neurocytic cells with a low growth fraction and desmoplastic internodular zones of moderately pleomorphic cells with a high growth fraction

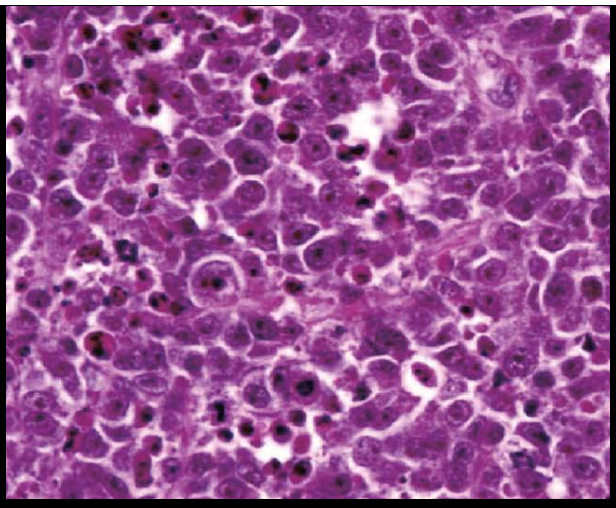
Infants (favourable prognosis) and adults

Gilbertson & Ellison Annu Rev Pathol Mech Dis 2008



Anaplastic MB (10-22%)

contains pleomorphic cells with polyhedral forms and a high growth fraction. Abundant apoptosis and examples of cell wrapping are evident

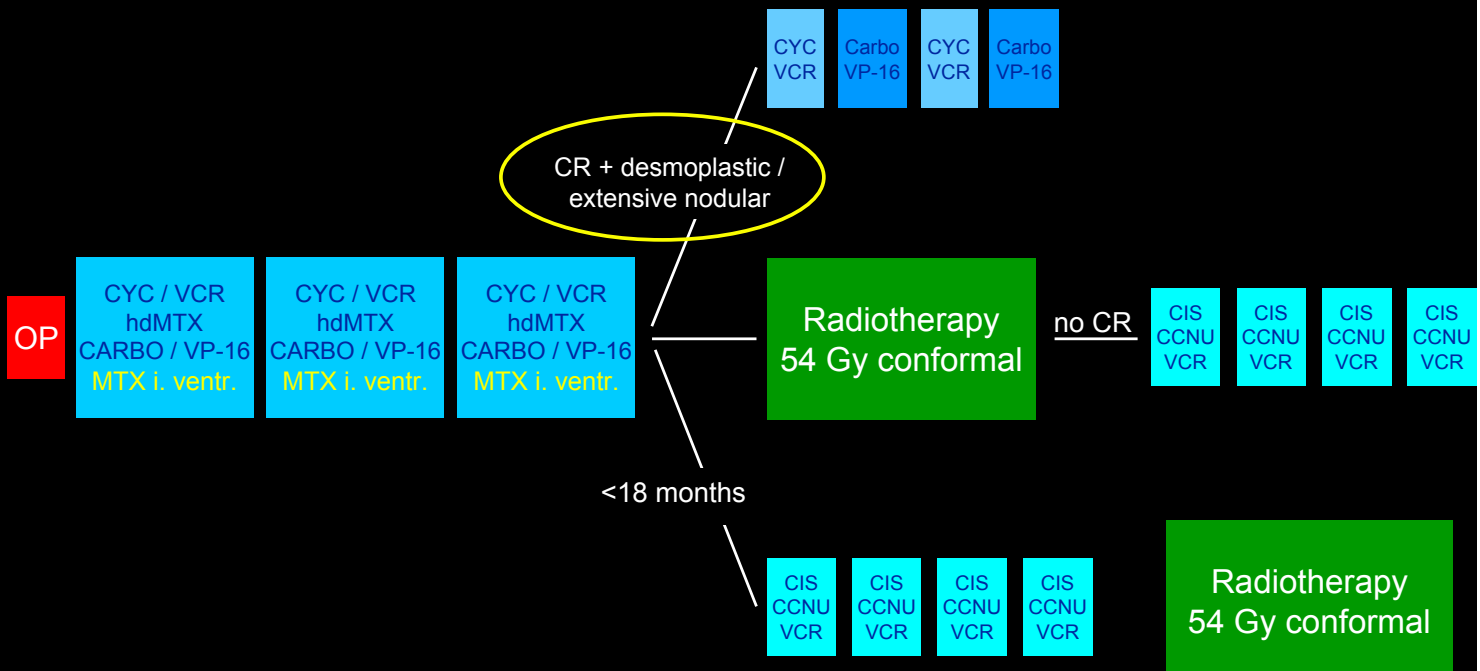


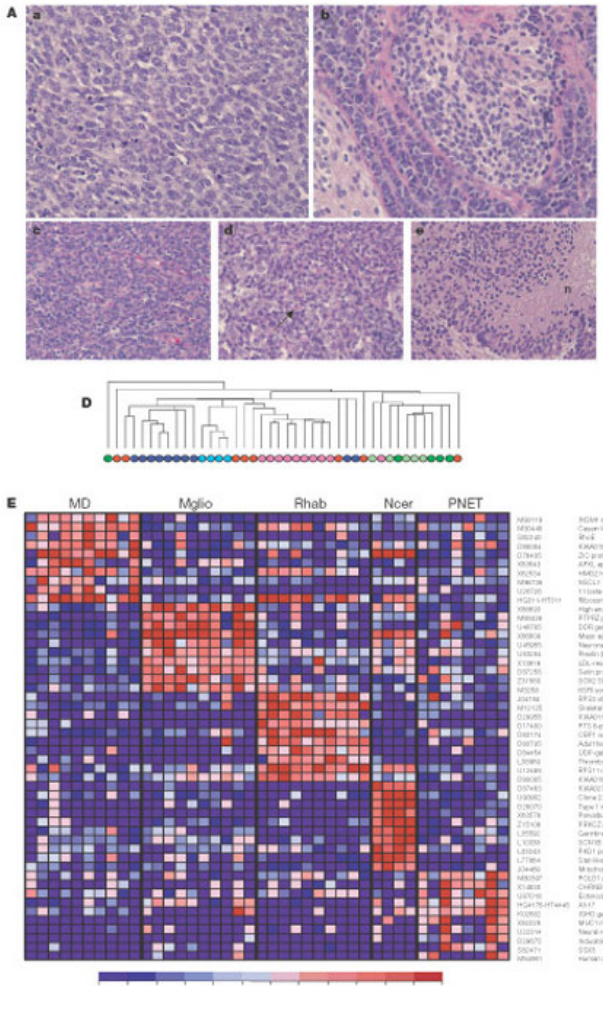
Large-cell MB (2-4%)

contains groups of large uniform cells with vesicular nuclei and a single nucleolus. Anaplasia characterizes other regions of this variant

Gilbertson & Ellison Annu Rev Pathol Mech Dis 2008

Localized Medulloblastoma <4 Years of Age HIT 2000

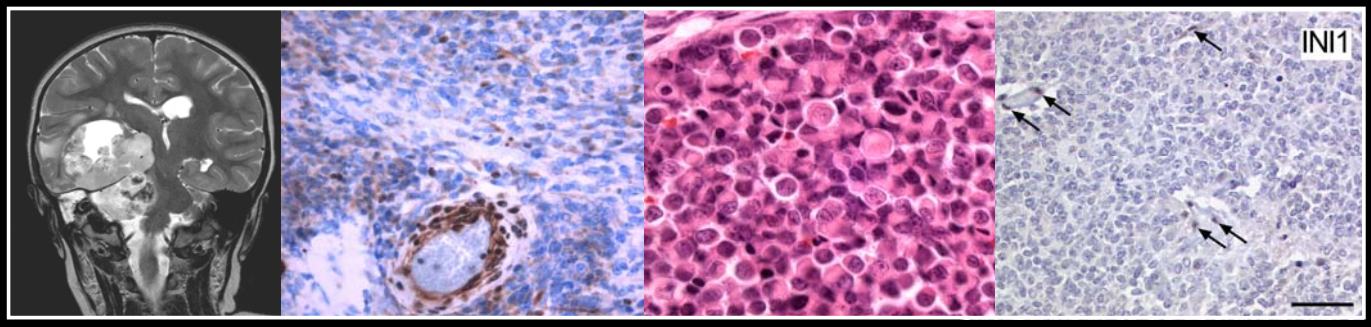




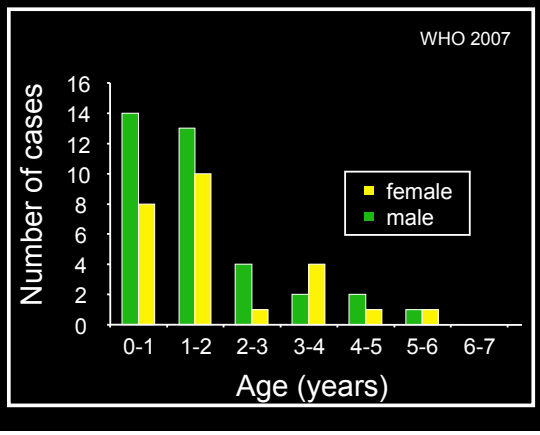
Medulloblastoma are molecularly distinct from sPNET and AT/RT

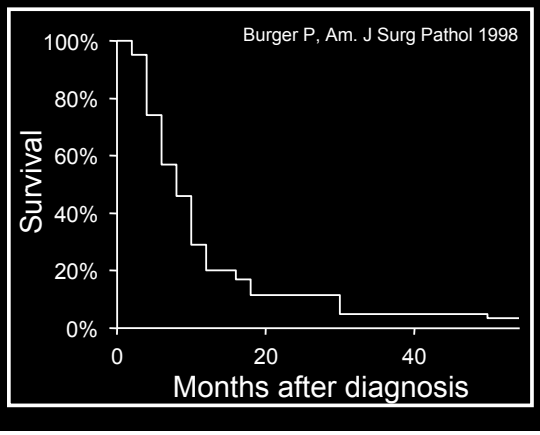
Pomeroy SL et al. Nature 2002

Atypical Teratoid/Rhabdoid CNS Tumor (AT/RT)



Mutation/deletion of the tumor suppressor SMARCB1 (INI1)





PRE-IRRADIATION/CHEMO-RADIATION/POST RADIATION INDUCTION CHEMOTHERAPY

1	2	3	4	5	6	EVALUATION	7	8	9	10	11	12	13	14	15	16	17	18	EVALUATION
V	V	V	V	V	V		V	V	V	V	V	V	V			V			
P			P				P			P									
D			D										D						
C							C*			C*			C			C			
			E				E			E									
							RADIATION									A			
I	I		I				I						I						
L	L		L				L						L						

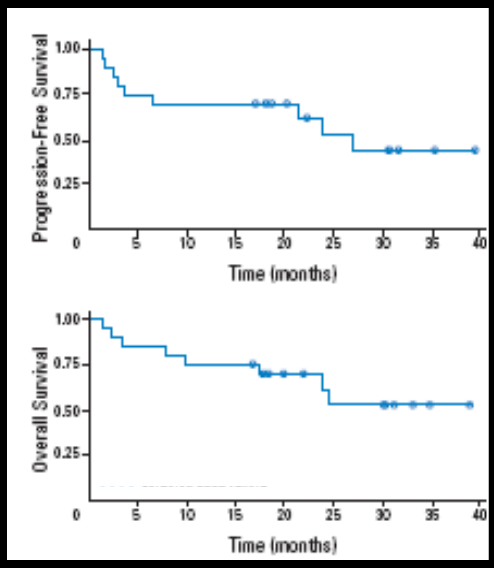
MAINTENANCE CHEMOTHERAPY

19	23	27	30	EVALUATION	33	36	39	42	EVALUATION
T	T								
A*	A*								
		V	V*		V	V*	V	V*	
		D			D		D*		
		C	C		C	C	C	C	
			A			A		A	
							DX		
I		I			I		I		
L		L			L		L		

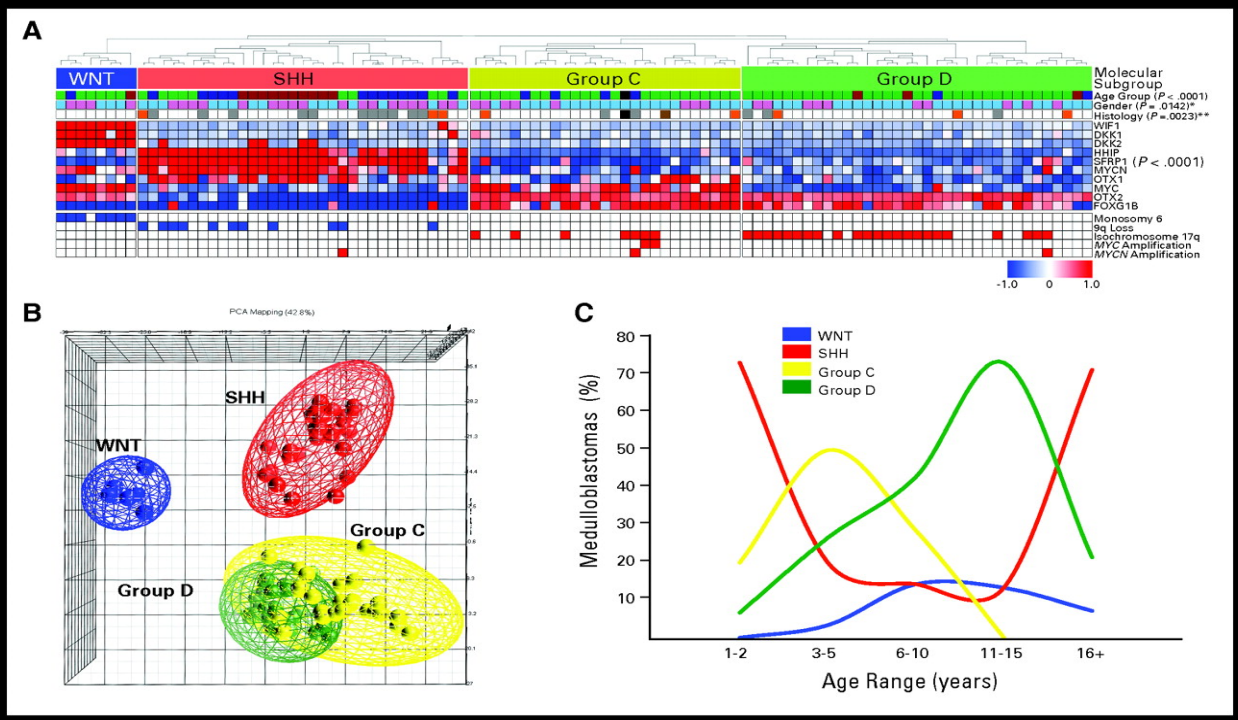
DOXORUBICIN CONTINUATION THERAPY

45	48	51	EVALUATION
V	V*	V	
C	C	C	
DX	A	DX	
D*		D*	
I		I	
L		L	

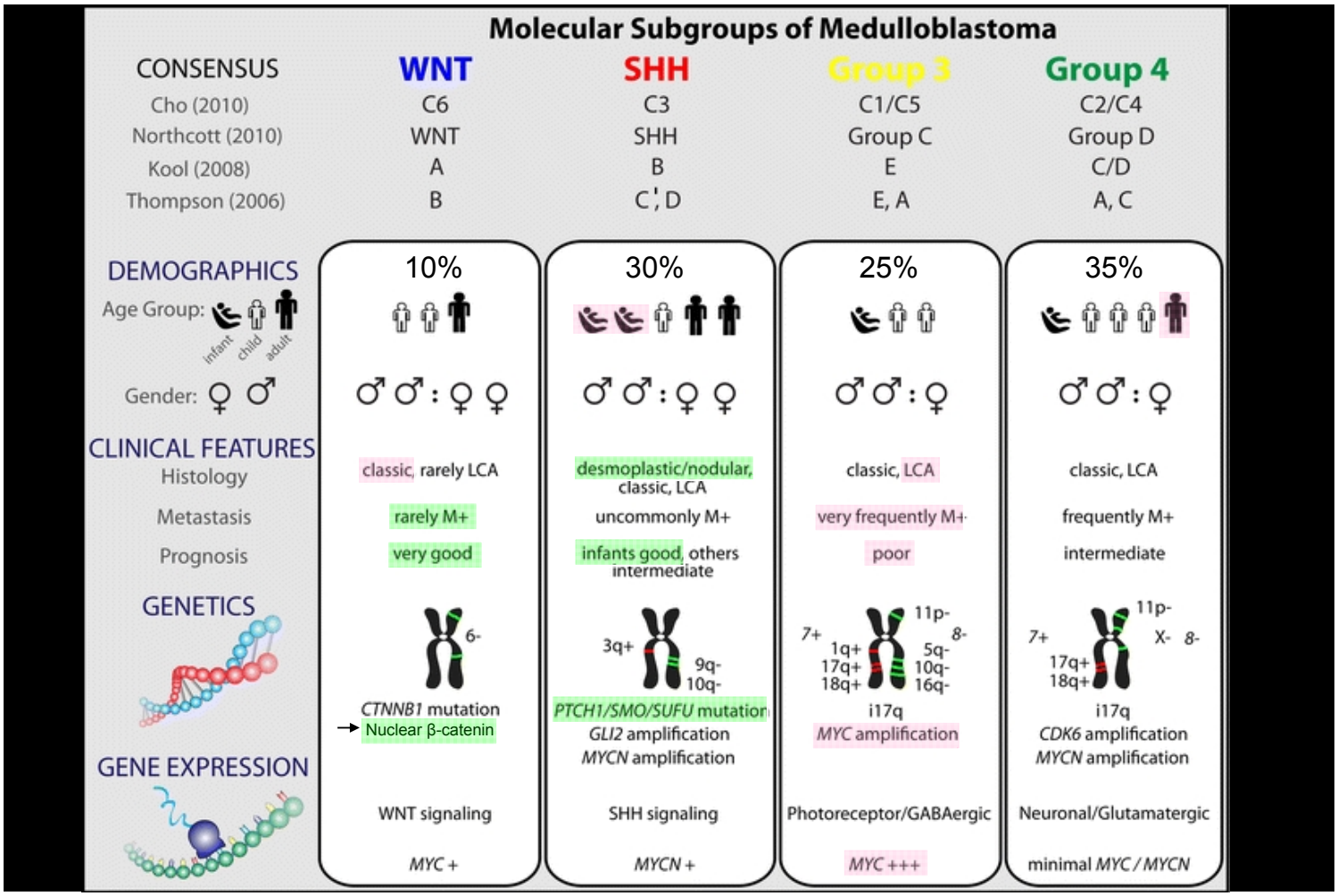
V: Vincristine
P: Cisplatin
D: **Doxorubicin**
C: Cyclophosphamide
E: Etoposide
A: **Dactinomycin**
i.th.: MTX, Cytarabin, Hydrocortisone



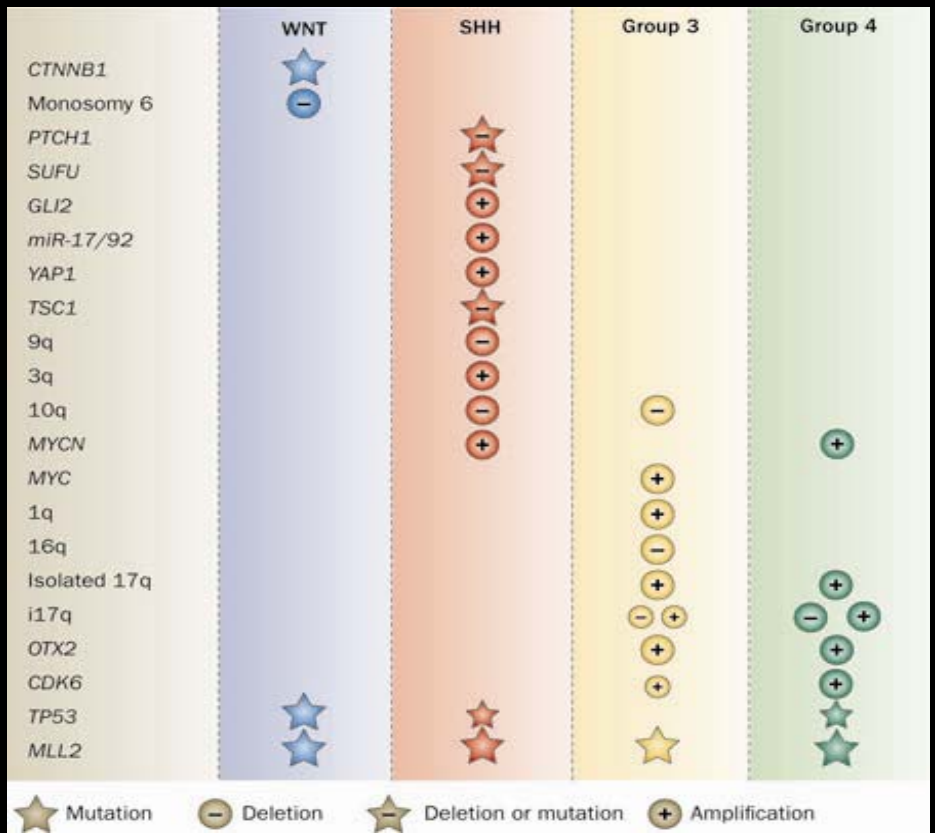
2-year Overall Survival: 70 ± 10%



Northcott P A et al. JCO 2010



Oncogenes, Tumor Suppressors, and Key Cytogenetics

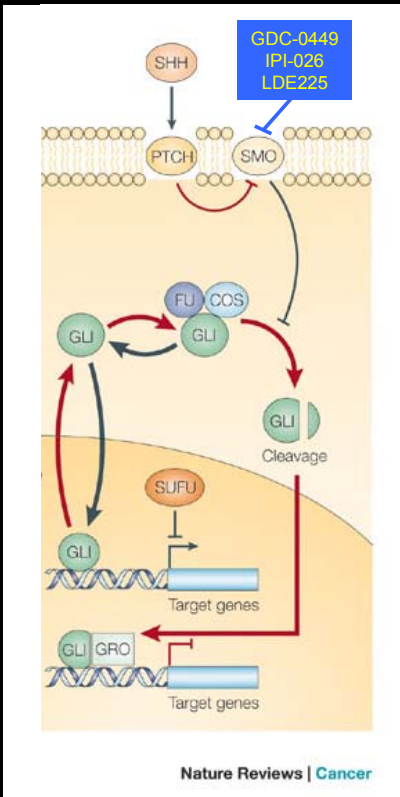


Northcott PA et al. (2012) Nat. Rev. Neurol.

Therapeutic Targets of WNT Medulloblastomas

- None of the WNT targeted therapies have shown benefits in MB
- Therapies that target mutated TP53 are not in regular use for MB therapy
- Mouse model of WNT MB developed
- Current strategy: de-escalation

Therapeutic Targets of SHH Medulloblastomas

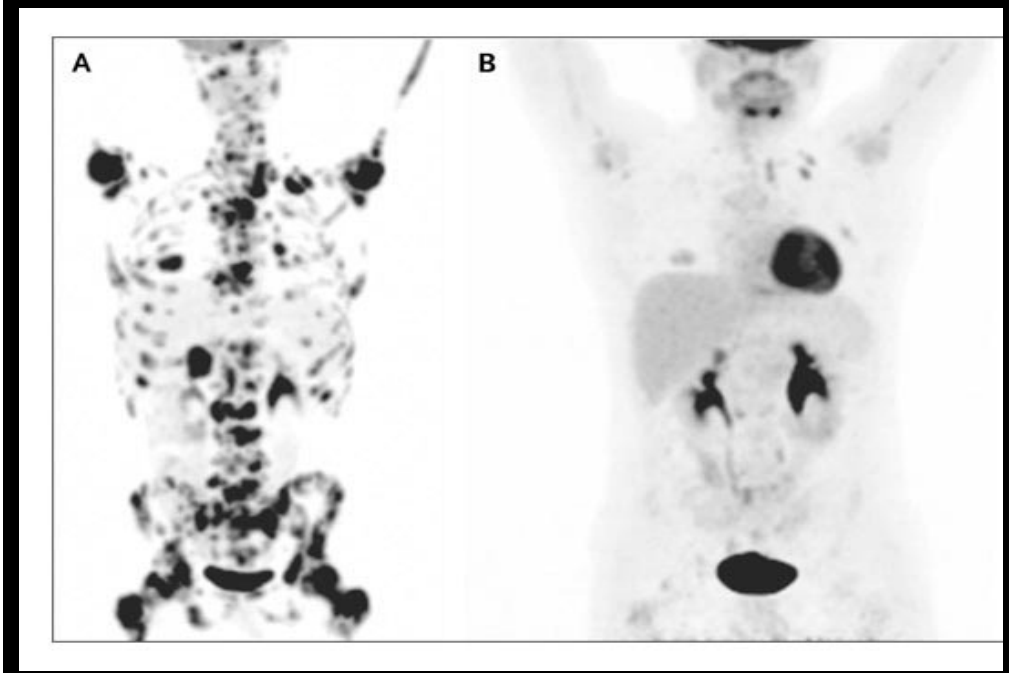


- <3 years + >14 years of age
- Desmoplastic / nodular subtype
- Somatic mutations in PTCH1/2, SMO, or SUFU
- High-level amplification of the SHH effectors, GLI1/2
- Germline mutations of SUFU (young children), PTCH1 (Gorlin syndrome)
- SMO antagonists GDC-0449, IPI-926, LDE225,…

SMO Inhibitor Treatment in an Adult with Metastatic MB

Rudin CM et al. N Engl J Med 2009

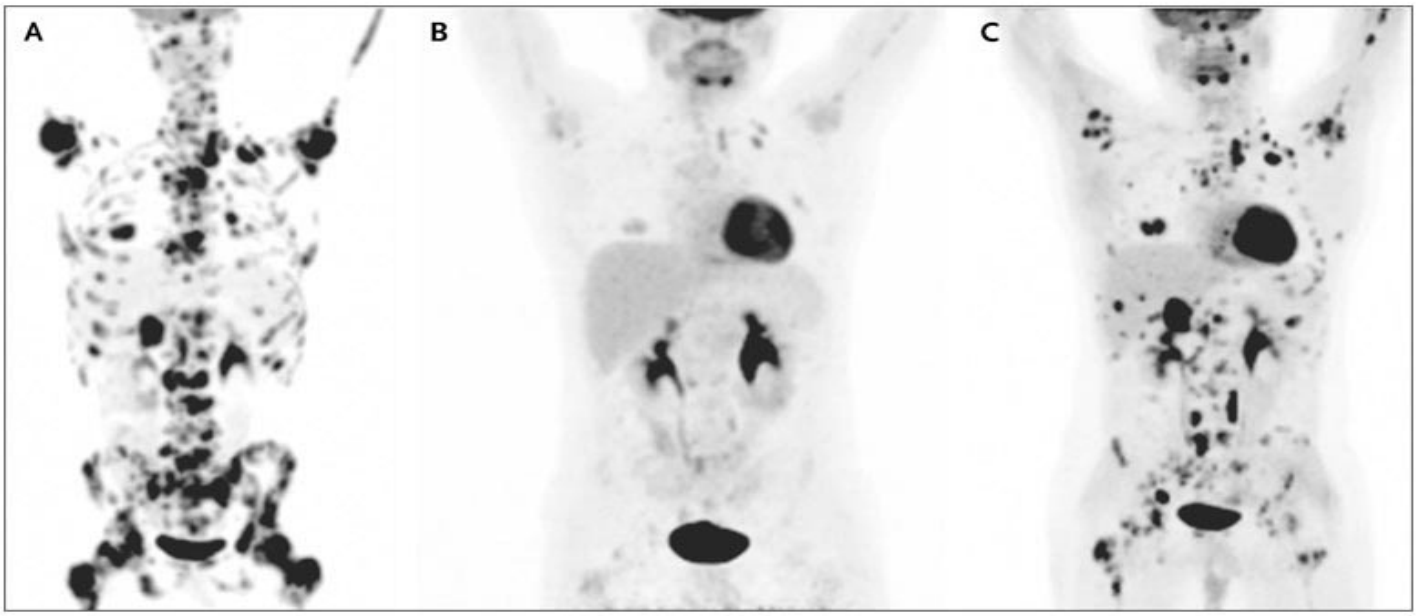
SMO Inhibitor Treatment in an Adult with Metastatic MB



after 2 months of therapy
with GDC-0449

Rudin CM et al. N Engl J Med 2009

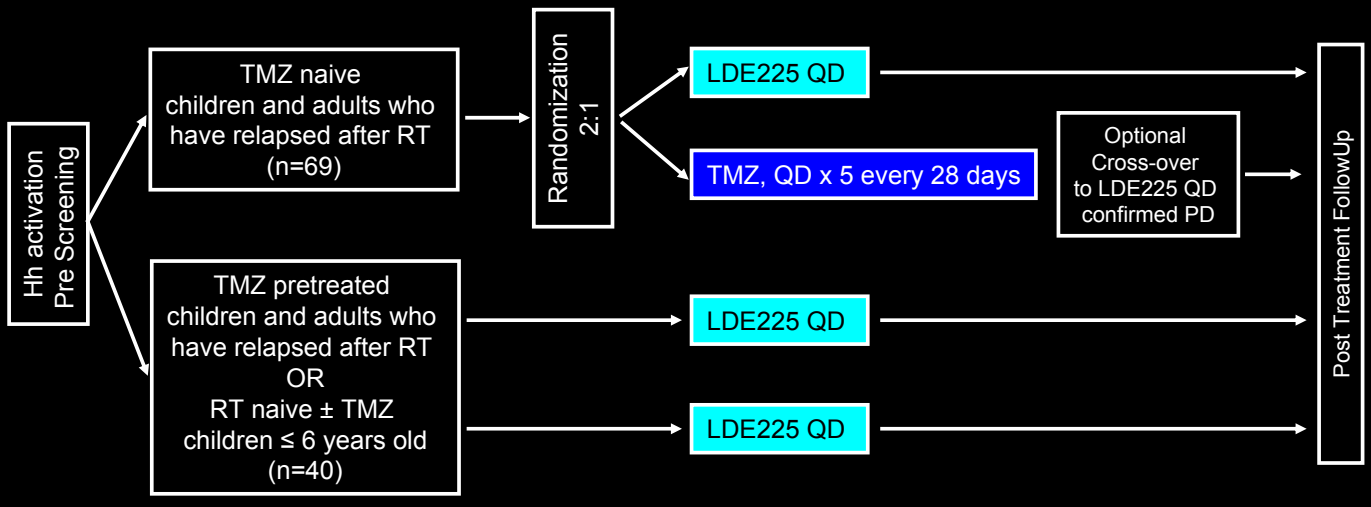
SMO Inhibitor Treatment in an Adult with Metastatic MB



after 2 months of therapy with GDC-0449

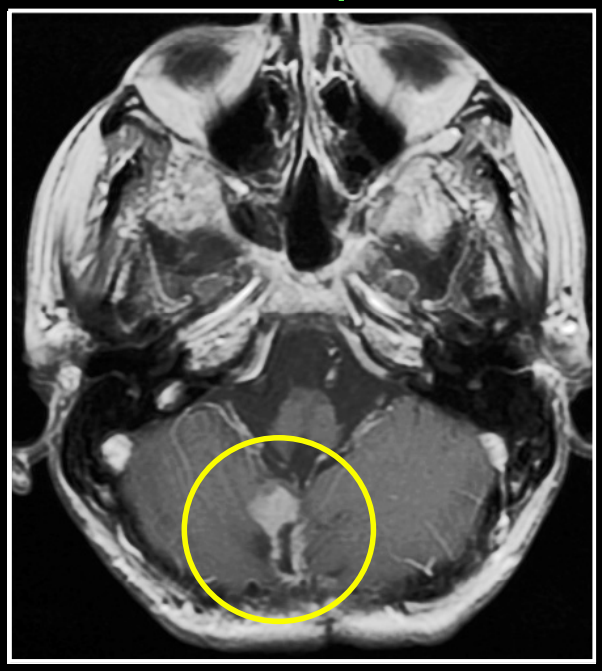
after 5 months of therapy with GCD-0449

Rudin CM et al. N Engl J Med 2009

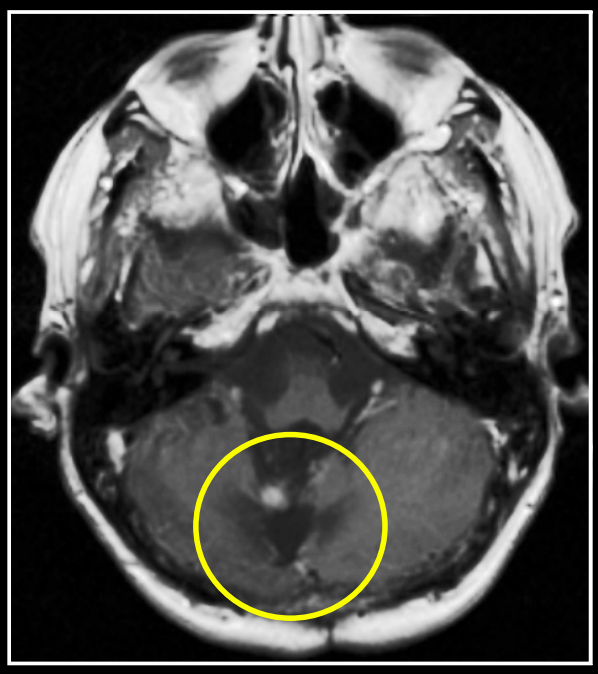


Primary endpoints: ORR
Secondary endpoints: DoR, PFS, safety, OS, QoL

LDE225 (200 mg QD): Responses in Medulloblastoma



Pre-treatment: surgery, irradiation, 4 chemotherapy regimens and HDCT

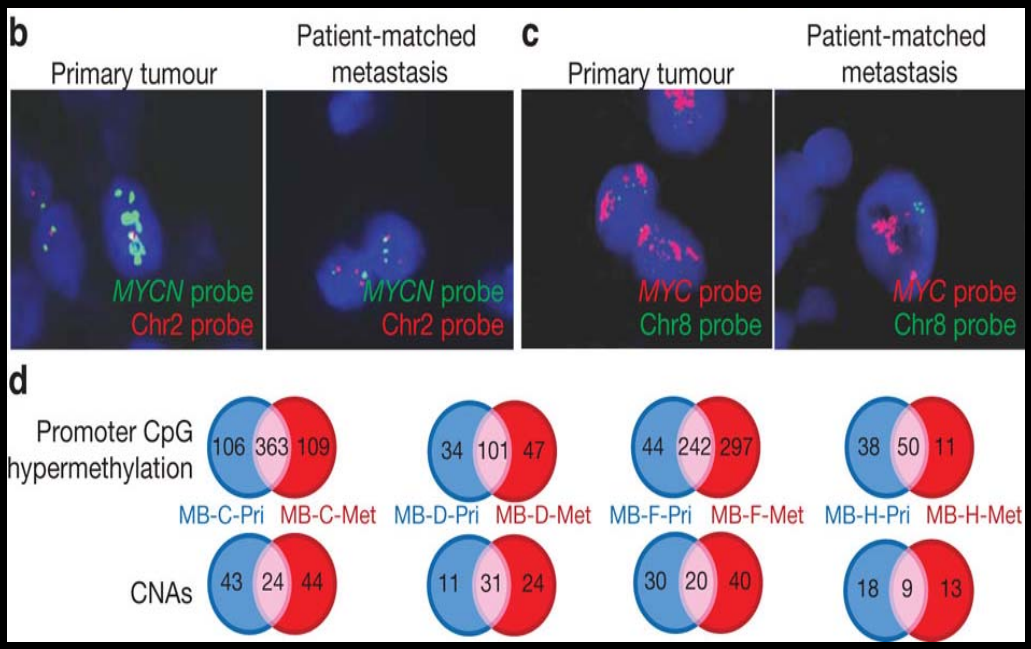


Partial response maintained for 4 months

Therapeutic Targets of Group 3 Medulloblastomas

- Owing the pharmacological difficulty of targeting a a transcription factor, small molecule inhibitors of MYC have not yet achieved wide success or acceptance in the clinic
- Studies on other rationally chosen targets for Group 3 have not yet been described
- Mouse model available
- Current strategy: intensification

MB Metastases and Primary Tumors are Distinct



XH Wu et al. Nature 2012

Conclusions

- Patient subgroup status will become an integral component of prospective clinical trials
- This will enable the use of treatment protocols that are rationally tailored towards each subgroup of the disease
- Methods to verify patient subgroup affiliation will continue to evolve
- Targeting primary tumor ≠ targeting metastasis