Management of pediatric brain tumors

- In the contemporary era

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ACTREC

TATA MEMORIAL CENTRE
SERVICE RESEARCH EDUCATION

Outline

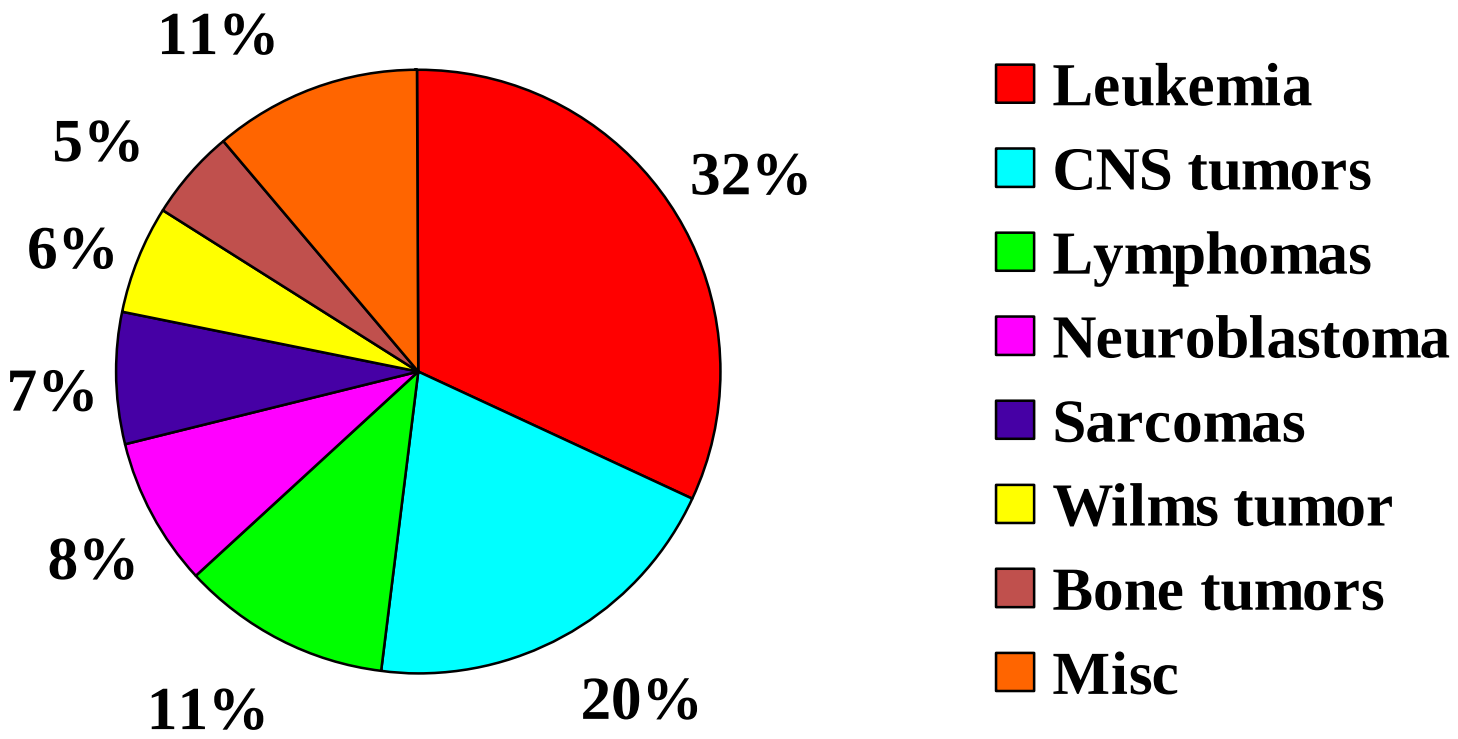
1. Statistics & epidemiology

2. Management of common pediatric brain tumors

3. High-precision radiotherapy techniques

4. Newer & future perspectives

Common Childhood Cancers



What about the spectrum in India?

Tumor	AIIMS	NIMHANS	GB Pant	TMH	CSMMU	CMC Vellore	PGIMER	Average
Astrocytoma	33.7	44.1	22.3	28.6	30.6	46.7	37	34.7
MB and PNETs	16.8	19.7	32	29	27.7	10.3	21.6	22.4
Craniopharyngioma	12.7	7.7	13.5	4.5	13.1	8.5	11.5	10.2
Ependymal	8.5	8.5	12.2	19.1	9.4	4.8	6.3	9.8
Nerve sheath	7	4.3	1.3	2.4	2.2	4.6	NA	3.6
Meningeal	5.6	4.3	0.3	3.4	2.2	3.5	NA	3.2
Neuronal and mixed neuronal glial	4.1	2.8	5.2	2.1	0	NA	NA	2.4
Germ cell tumors	2.2	2.2	3.3	1.7	2.2	NA	NA	2
Choroid plexus tumors	1.5	2.6	1.6	1.7	1.5	NA	3.5	1.8
Pineal tumors	0.7	1.4	1.3	1	3	NA	NA	1.3
Oligodendroglioma	0.7	0.9	2.9	1.4	1.5	0	0	1.1
Lymphoma	1	0.5	0.3	0	0	1.1	NA	0.5

MB and PNET - Medulloblastomas and supratentorial PNETs, includes other rare embryonal tumors; AIIMS - All India Institute of Medical Sciences, New Delhi; NIMHANS - National Institute of Mental Health and Neuro Sciences, Bangalore; TMH - Tata Memorial Hospital, Mumbai; CSMMU - Chhatrapati Shahuji Maharaj Medical University, Lucknow; PGIMER - Post Graduate Institute of Medical Education and Research, Chandigarh; CMC - Christian Medical College, Vellore; GB Pant - Govind Ballabh Pant Hospital, New Delhi; NA - Data not available

Generally consistent with CBTRUS as well as other international registry data

Jain A et al, Neurol Ind 2011

Comparison with published Western data

* SEER Cancer Registry and CBTRUS Cancer Registry

	Median age of presentation	
	TMH data	**Western data***
Medulloblastoma	10 yrs	9 yrs
Ependymoma	18.5 yrs	19 yrs
Brain stem glioma	11.5 yrs	11 yrs
Supratentorial PNET	15 yrs	9 yrs
Pineal tumour	18.5 yrs	18 yrs
Craniopharyngioma	*20 yrs*	*28 yrs*
Pilocytic Astrocytoma	*16 yrs*	*23 yrs*

Jalali and Datta J NeuroOncol 2008

Location of primary

Infra versus supra-tentorial

Supratentorial	**25-40%**
Low grade astro	8-20%
High grade astro	6-12%
Ependymoma	2-5%
Mixed glioma	1-5%
Ganglioglioma	1-5%
Oligodendroglioma	1-2%
PNET	1-2%
Choroid plexus tumor	1-2%
Meningioma	1-2%
Germ Cell Tumors	1-2%
Others	1-3%

Infratentorial	**45-60%**
Medulloblastoma (PNET)	20-25%
Astrocytoma, low grade	12-18%
Ependymoma	4-8%
Brain stem glioma, high grade	3-9%
Brain stem glioma, low grade	3-6%
Others	2-5%

Spinal tumors	**2-4%**
Ependymoma	1-3%
Astrocytoma	1%

Juvenile Pilocytic Astrocytoma

Most common astrocytic tumor in children

WHO Grade I (with low metastatic potential)

Commonly arises from cerebellum (posterior fossa)

Other common sites: optic pathway, thalamus, tectum, cerebral

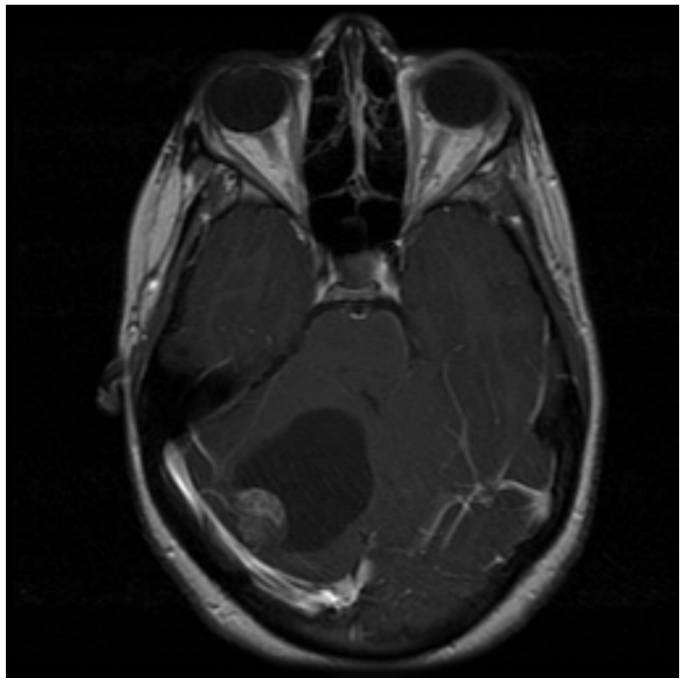
Peak incidence is between 6-8 years of age

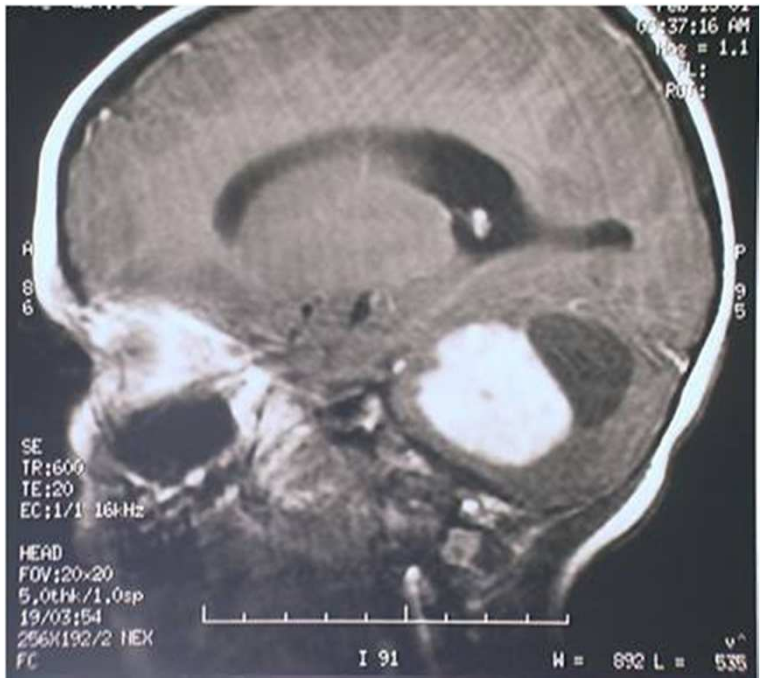
Discrete, well circumscribed cystic SOL with contrast enhancing mural nodule

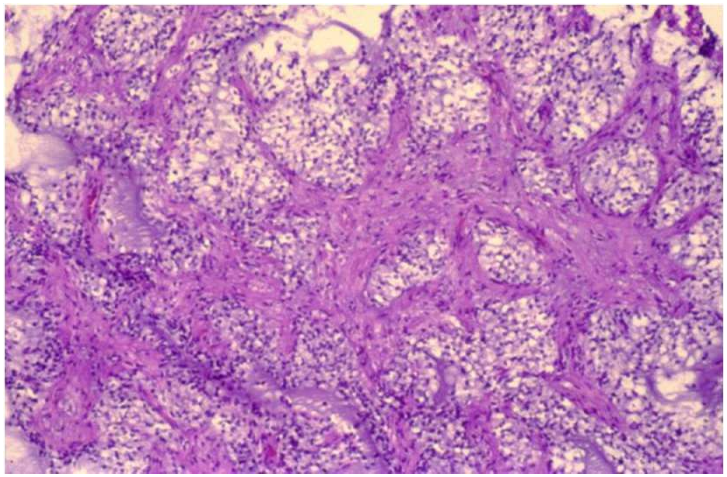
Sometime larger solid component, occasionally completely solid tumors

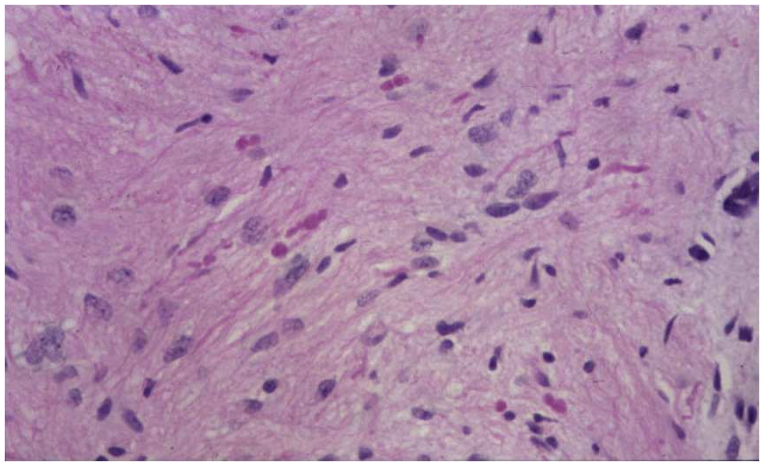
Histologic appearance: Biphasic with compact & spongy areas
Piloid cells & microcystic areas, Rosenthal fibers
No mitoses, no anaplasia, no necrosis

Classical Radiology & Pathology









Management of cerebellar pilocytic astocytoma

Surgery is the treatment of choice

Gross total resection (GTR) is generally curative

Pre-operative and per-operative considerations

- Midline vs lateralized
- Mainly cystic vs solid
- Relationship to vermis and IV th ventricle
- Drain the cyst early, respect boundaries, & preserve the vermis

In experienced hands, GTR achieved in >90% patients

What are the long-term outcomes in cerebellar JPA?

Tonnessen et al, Pediatr Neurosurg, 2002

Large series of 110 consecutive patients (0-19 years) from 1960-2001

97 of 110 children alive at last follow-up

10-year and 25-year survival 89% and 85% respectively

5-year survival improved from 76% (before 1988) to 100% (after 1988)

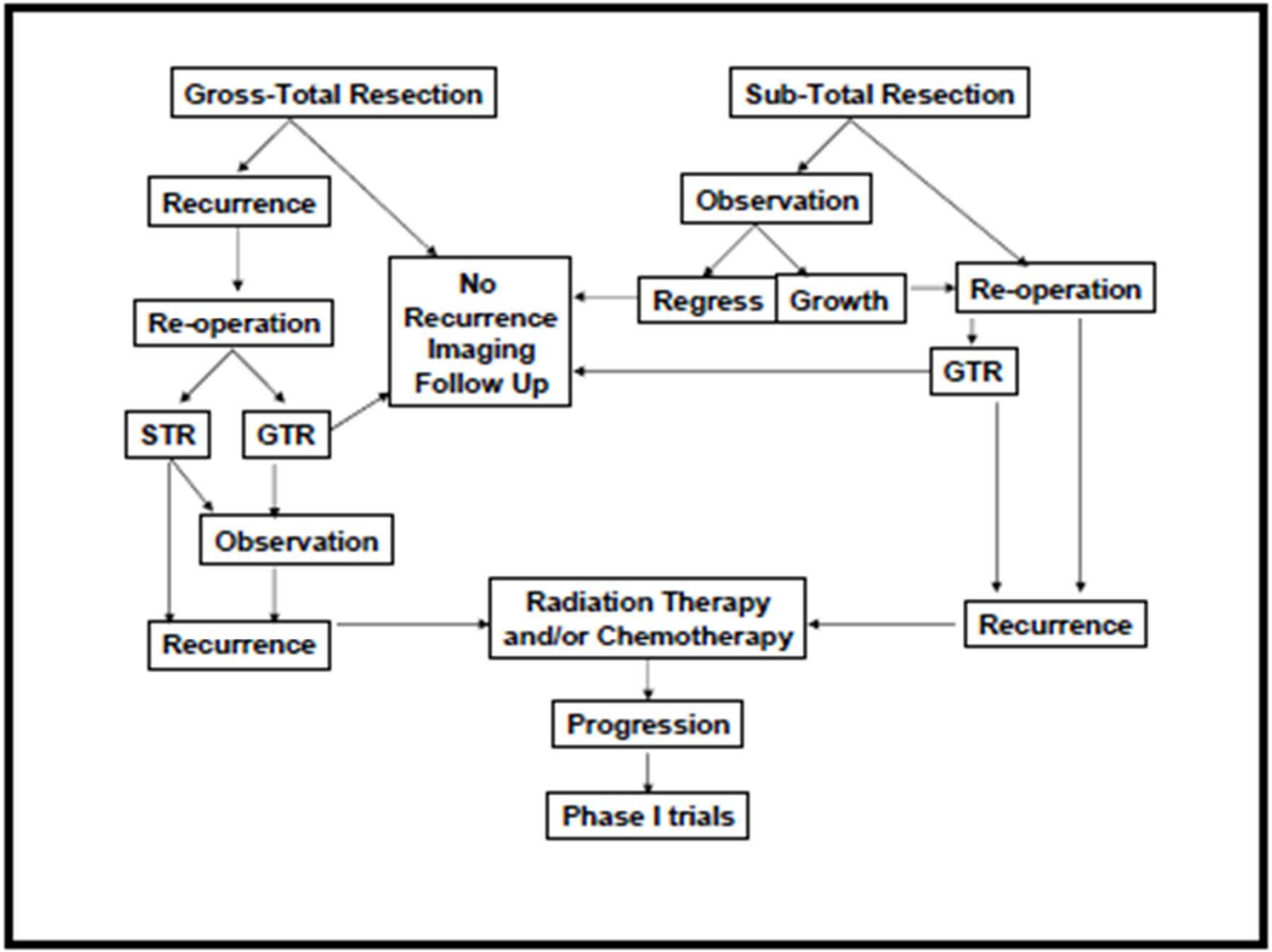
Recurrence after GTR seen in only 5 of 76 patients

Growth of residual tumor seen in 7 of 26 patients after STR

Only 5 of these patients received radiotherapy.

Preserved or favorable function outcomes seen in 82% patients

Suggested algorithm for cerebellar pilocytic astrocytomas



Non-cerebellar pilocytic astrocytomas

(Optico-chiasmatic-hypothalamic (visual pathway) tumors)

Mostly predominantly solid pilocytic tumors

Difficult to resect, may precipitate unwarranted morbidity

Safe decompression (generally biospy) recommended

NF-1 ASSOCIATED

-15% of patients

- very indolent, biopsy not necessary

-safely OBSERVED clinico-radiologically

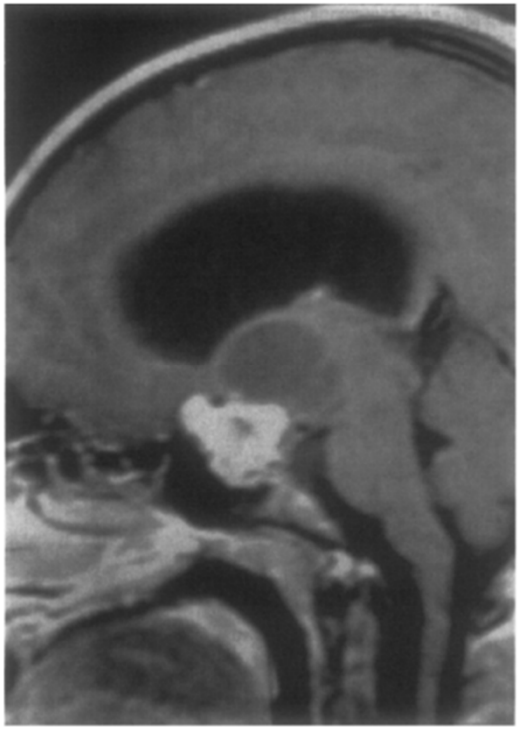
SPORADIC

-Sporadic and progressive optic pathway gliomas need intervention

-Treated with definitive radiotherapy for preservation of useful vision

-Chemotherapy (VCR + Carboplatin): Allows deferral of RT in young children

CHILDHOOD OPTIC CHIASM GLIOMAS: RADIOGRAPHIC RESPONSE FOLLOWING RADIOTHERAPY AND LONG-TERM CLINICAL OUTCOME



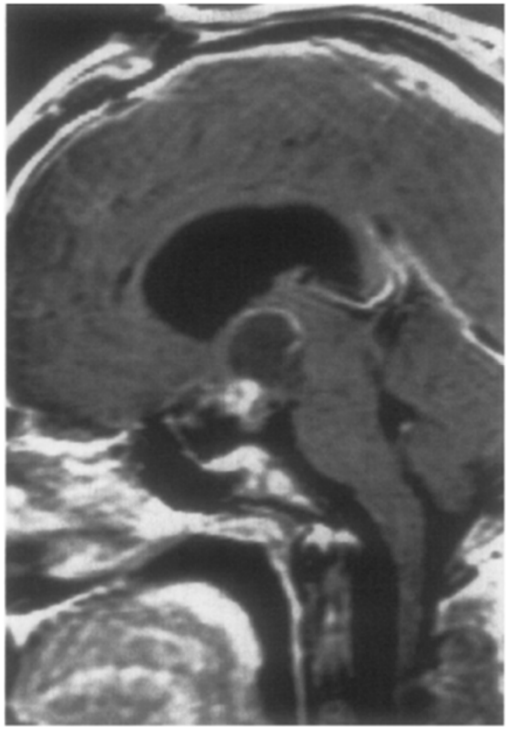
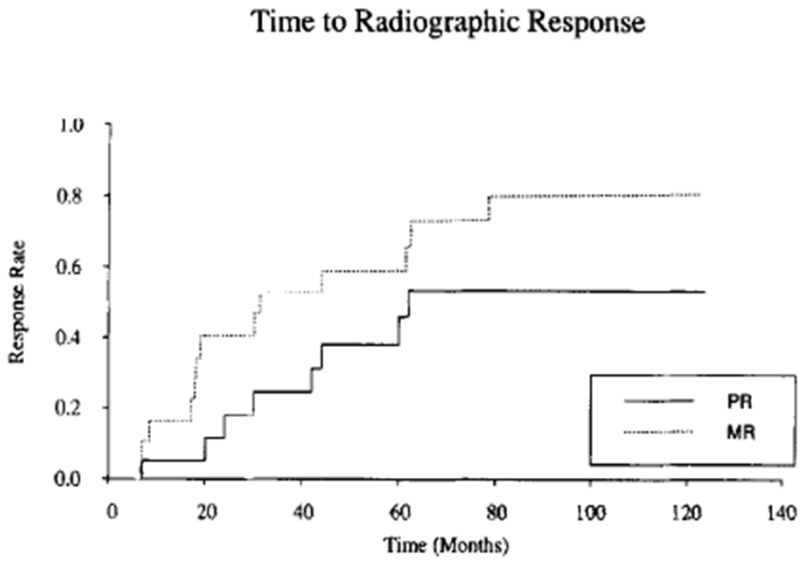
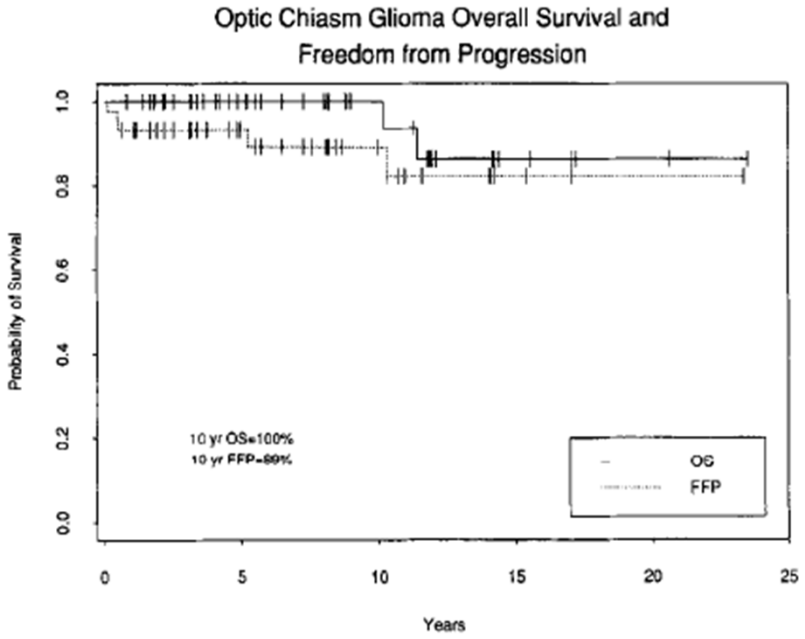


Table 3. Best radiographic response to RT

Best response	*n*	%
Stable or <MR	9	36
MR	5	20
PR	6	24
CR	4	16
Progression*	1	4

May L Tao, IJROBP 1997





Vision improved in 34%, stabilized in 49% & worsened in 17% only establishing RT as the mainstay of treatment in OPGs

Conclusions: Notable radiographic response may be observed years after irradiation. Radiation therapy provides excellent long-term tumor control and vision preservation or improvement in the majority of patients with progressive chiasmal gliomas.

Does chemotherapy affect the visual outcome in children with optic pathway glioma? A systematic review of the evidence

Lucas Moreno [a,*], *Francisco Bautista* [a], *Sue Ashley* [b], *Catriona Duncan* [a], *Stergios Zacharoulis* [a]

Eur J Cancer 2010

Table 2 – Responses to chemotherapy.

Reference	Schedule	Objective radiological responses (%)	Improving vision (%)	Stable vision	Deteriorating vision	Total
Massimino et al.[16]	Cisplatin–etoposide	24 (82.8)	10 (45.5)	7	5	22
Laithier et al.[17]	BabyBrain SFOP	51 (60)	2 (3.5)	16	39	57
Petronio et al.[11]	Nitrosurea based/TPCV	10 (52.6)	2 (10.5)	14	3	19
Chamberlain and Grafe[12]	Oral etoposide	6 (42.8)	0	14	0	14
Janss et al.[13]	Vincristine–actinomycinD	11 (23.9)	5 (18.5)	14	8	27
Silva et al.[14]	Carboplatin–vincristine	8 (57.1)	2 (14.3)	12	0	14
Mitchell et al.[15]	Carboplatin monthly	1 (8.3)	4 (40)	3	3	11
Dalla Via et al.[3]	Carboplatin–vincristine	ND	0	2	9	11
Total			25 (14.4)	82 **(47.1%)**	67 **(38.5%)**	174

Discussion: Published studies on childhood low grade gliomas have not shown satisfactorily whether chemotherapy improves outcome of vision in children with OPG. Based on our systematic review it appears that treatment with chemotherapy does not improve resulting vision in the majority of children with OPG. The data available does not allow us to assess whether vision is stabilised sufficiently prior to treatment with radiotherapy.

Non-pilocytic low grade (grade II) astrocytoma

Not commonly seen in cerebellum

More common in supratentorial location

Some are pilomyxoid astrocytoma

Some are diffuse fibrillary astrocytoma

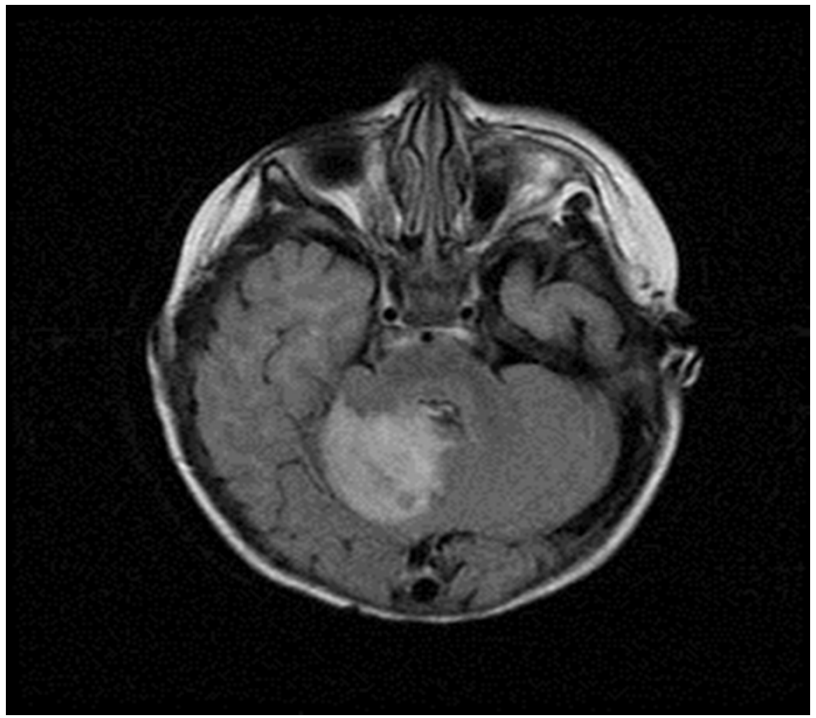
Others may be PXA or Ganglioglioma

Gross total resection is the goal

Can be observed if no atypical features

Adjuvant RT indicated for large residual

RT dose :54 Gy/30#/6 weeks

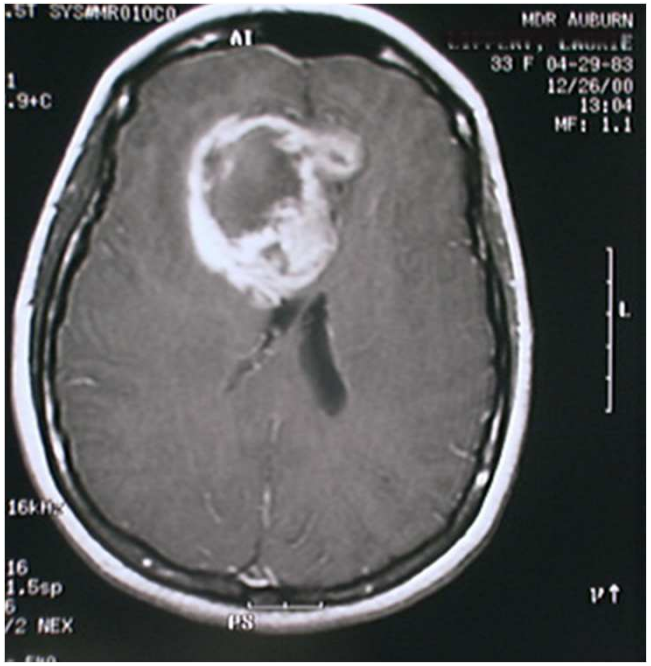


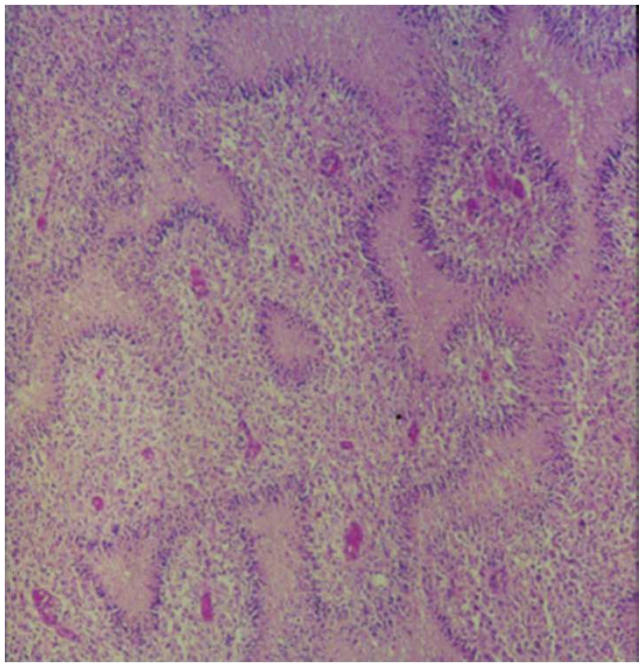
High-grade astrocytoma (WHO grade III-IV)

Rare brain tumors of childhood (<5% of all astrocytomas)

Being increasingly diagnosed in contemporary practice

Different molecular biology and pathology





Management of childhood high-grade astrocytomas

No established standard of care due to lack of high quality evidence

Maximal safe resection and decompression recommended

Generally treated as per Stupp's protocol post-operatively

Focal conformal radiation (59.4-60Gy in 30-33#s)

Concurrent daily temozolomide (75mg/m2) during RT

6-12 cycles of adjuvant temozolomide (150-200mg/m2) post RT

Chemotherapy in childhood high-grade astrocytoma

CCG 943 (Sposto et al, J Neurooncol 1989):

Randomized trial of adding chemotherapy (CCNU, VCR, PRED) to RT

58 patients with histologically proven high-grade astrocytoma

5-year EFS significantly better (46% vs 18%, p=0.026) with chemoRx

5-year overall survival marginally better (p=0.067) with chemoRx

CCG 945 (Finlay et al, J Clin Oncol 1995):

Randomized trial involving 172 pts comparing 2 chemoRx regimens

8-in-1 drug regimen (experimental) compared to standard CCNU/VCR/PRED

PFS & OAS at 5-years was 33% + 5% and 36% + 6% respectively

No significant difference in efficacy between the two regimens

Chemotherapy in childhood high-grade Astrocytoma

(COG ACNS0126 study (Cohen et al. Neuro Oncology 2011)

107 patients with a diagnosis of high grade gliomas were enrolled

concomitant RT with TMZ, followed by adjuvant TMZ

outcomes compared with CCG-945

The 3 year-EFS and OS rates were 11+3% and 22+5%

The 3 year –EFS and OS when compared with CCG 945 not significant

There was no evidence that RT+ TMZ and as adjuvant resulted in improved EFS compared with that found in CCG-945

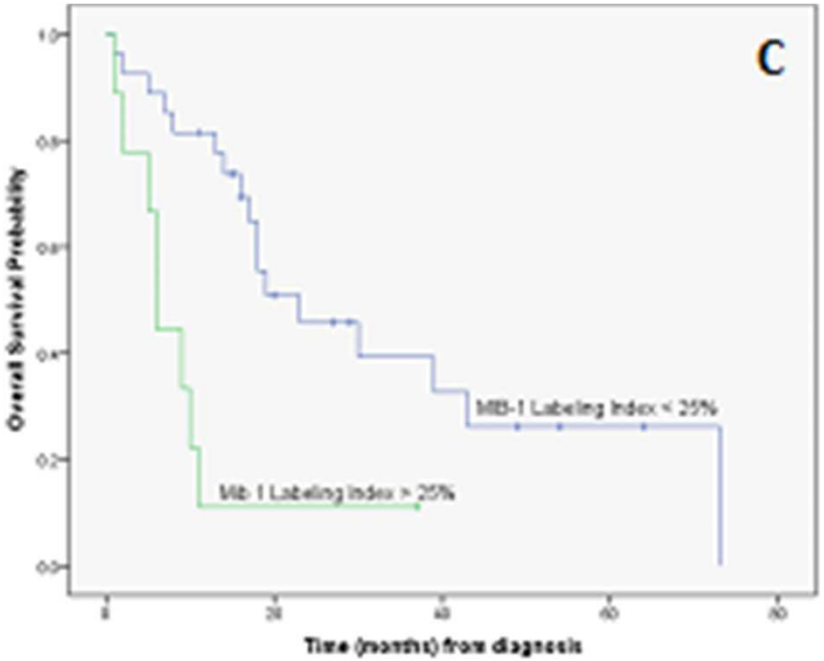
TMH Experience of Pediatric GBM

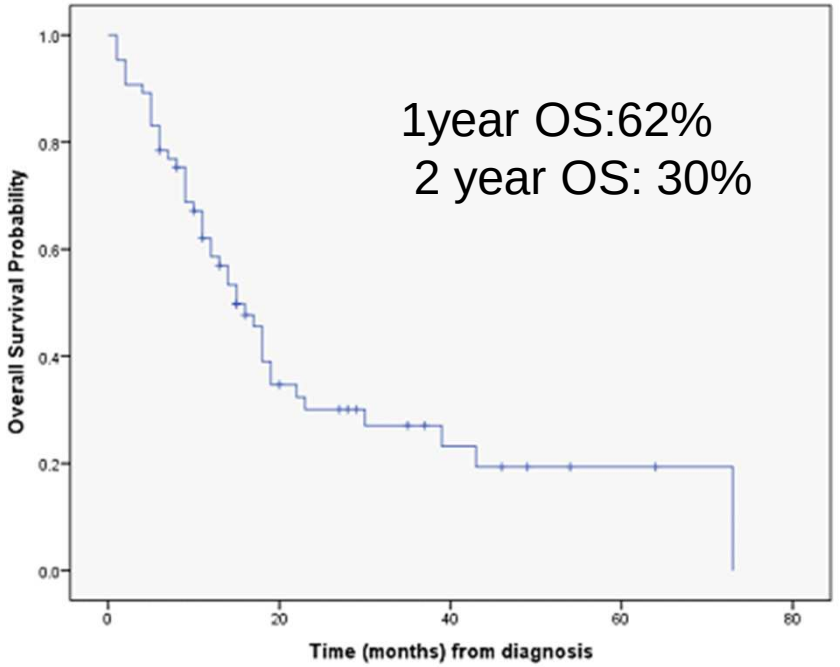
N= 66 children (2004-2013)

Treated uniformly with post of RT+TMZ

Median OS: 15months

Tumors with MIB-1 labeling index >25% (p<0.002) had poor OS





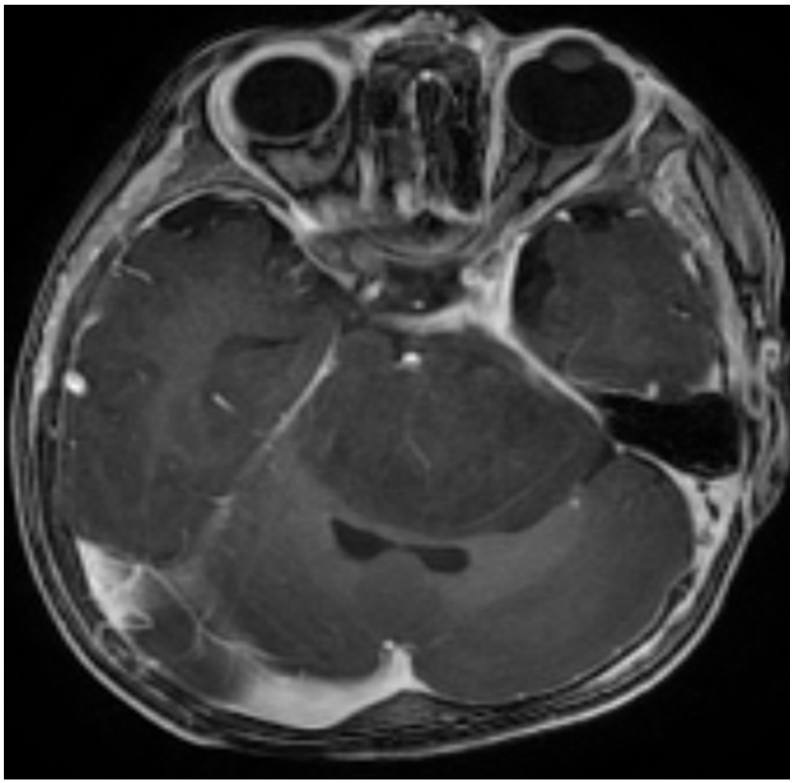
Submitted in Neuro Oncology practise

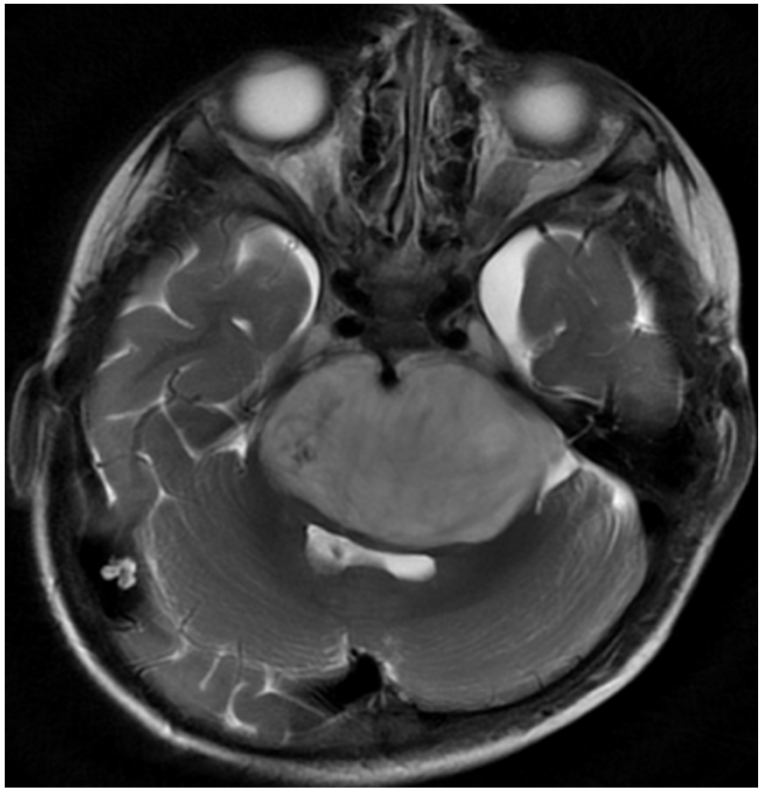
Brain stem gliomas

Heterogenous group of tumors with varying biological behavior & outcome

Most common and challenging type is Diffuse Intrinsic Pontine Glioma (DIPG)

Less common and rather indolent types are Focal & Dorsal Exophytic Tumors





Diffuse Intrinsic Pontine Glioma

Most frustrating and challenging childhood brain tumor

Most common type of brainstem glioma (>80%)

No role of biopsy (open or stereotactic)

Propensity for leptomeningeal dissemination at relapse

Definitive radiotherapy (54Gy in 30#s) is the treatment of choice

RT provides early and durable symptomatic relief

No benefit of adding chemotherapy to RT

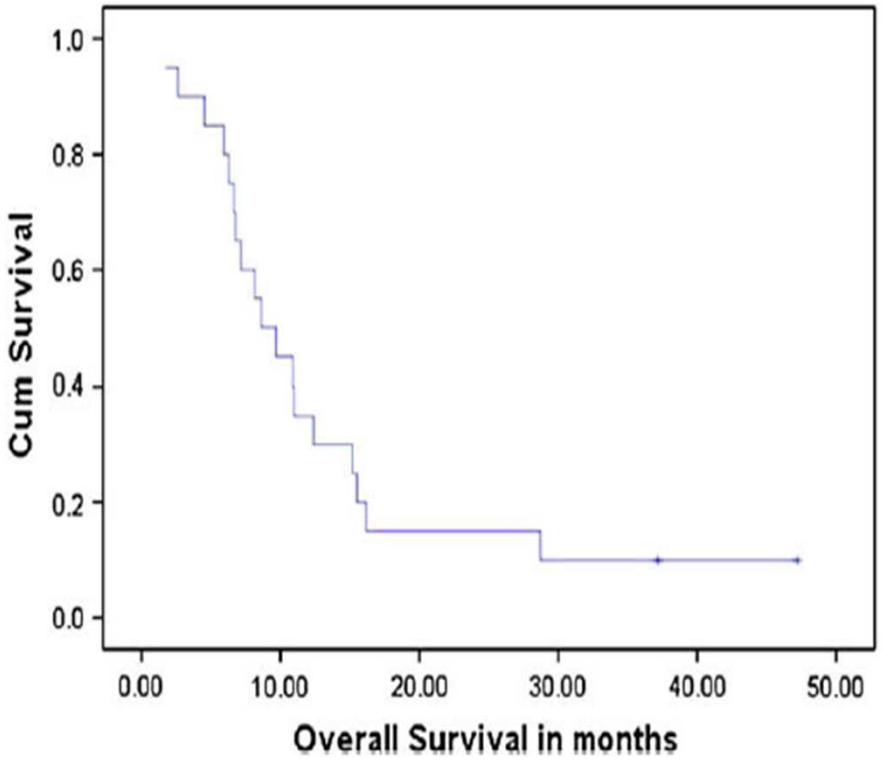
Median survival 10-12 months; 2-year survival around 5-8%

Lack of tissue samples hinders further progress

PROSPECTIVE EVALUATION OF RADIOTHERAPY WITH CONCURRENT AND ADJUVANT TEMOZOLOMIDE IN CHILDREN WITH NEWLY DIAGNOSED DIFFUSE INTRINSIC PONTINE GLIOMA

RAKESH JALALI, M.D.,* NIRMAL RAUT, M.D.,* BRIJESH ARORA, D.M.,† TEJPAL GUPTA, M.D.,* DEBNARAYAN DUTTA, M.D.,* ANUSHEEL MUNSHI, M.D.,* RAJIV SARIN, F.R.C.R.,* AND PURNA KURKURE, M.D.†

MRI contrast enhancement	Non-enhancing	13.98	0.166
	Enhancing	9.63	
MRI grade	High grade	8.87	0.043
	Low grade	15.10	
MRS grade	High grade	8.79	0.258
	Low grade	12.99	
Magnetic resonance perfusion	Hyperperfusion	8.87	0.043
	Hypoperfusion	15.10	
PET scan	No uptake	14.28	0.911
	Uptake present	13.78	
MRI + MRS + perfusion diagnosis	High grade	6.8	0.001

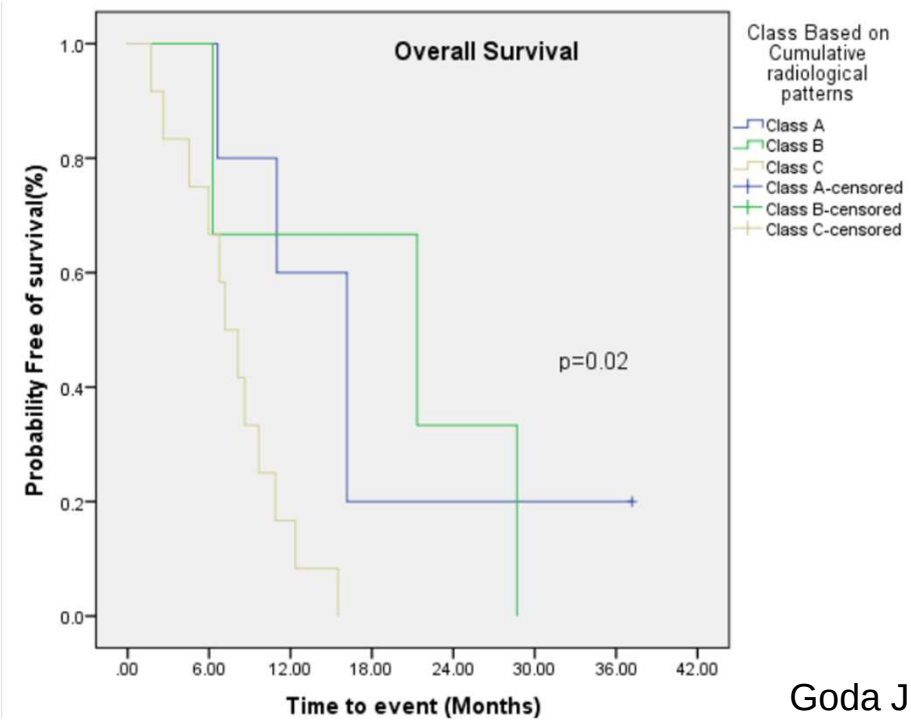


IJROBP 2010

Multiparametric MRI Predicts Outcome in Diffuse Brainstem Glioma – A Report from a Prospective Phase-II Study

MR Parameters*	Adverse Pattern	General index
Contrast enhancement	yes	1
Pattern of contrast enhancement	Heterogeneous	1
MR perfusion	Hyper perfusion	1
MR spectroscopy	High Choline: NAA ratio; High Choline : Cr ratio; Presence of lipid lactate peaks	1
	Maximum score	**4**

No of adverse parameters	RPI Grade of tumour	Class of tumour	1year OS	P - value
0-1	Low Grade	A	60%	0.02
2	Intermediate Grade	B	66%	
3-4	High Grade	C	8.3%	



Goda JS, Ped Neuro Surg,2014

Focal Brainstem Gliomas

Most commonly arise from midbrain (tectum or tegmentum)

Less commonly arise from medulla oblongata

Most are low-grade (generally pilocytic), occasionally higher grade gliomas

Treatment is controversial and not standardized

Focal tectal plate gliomas can be followed clinico-radiologically

Resection/Biospy of dorsal exophytic tumors is possible

Some focal brainstem gliomas may just need CSF diversion

Progressive lesions benefit from radiotherapy

No established role of chemotherapy as yet

SEER database analysis of over 6000 pediatric glioma patients

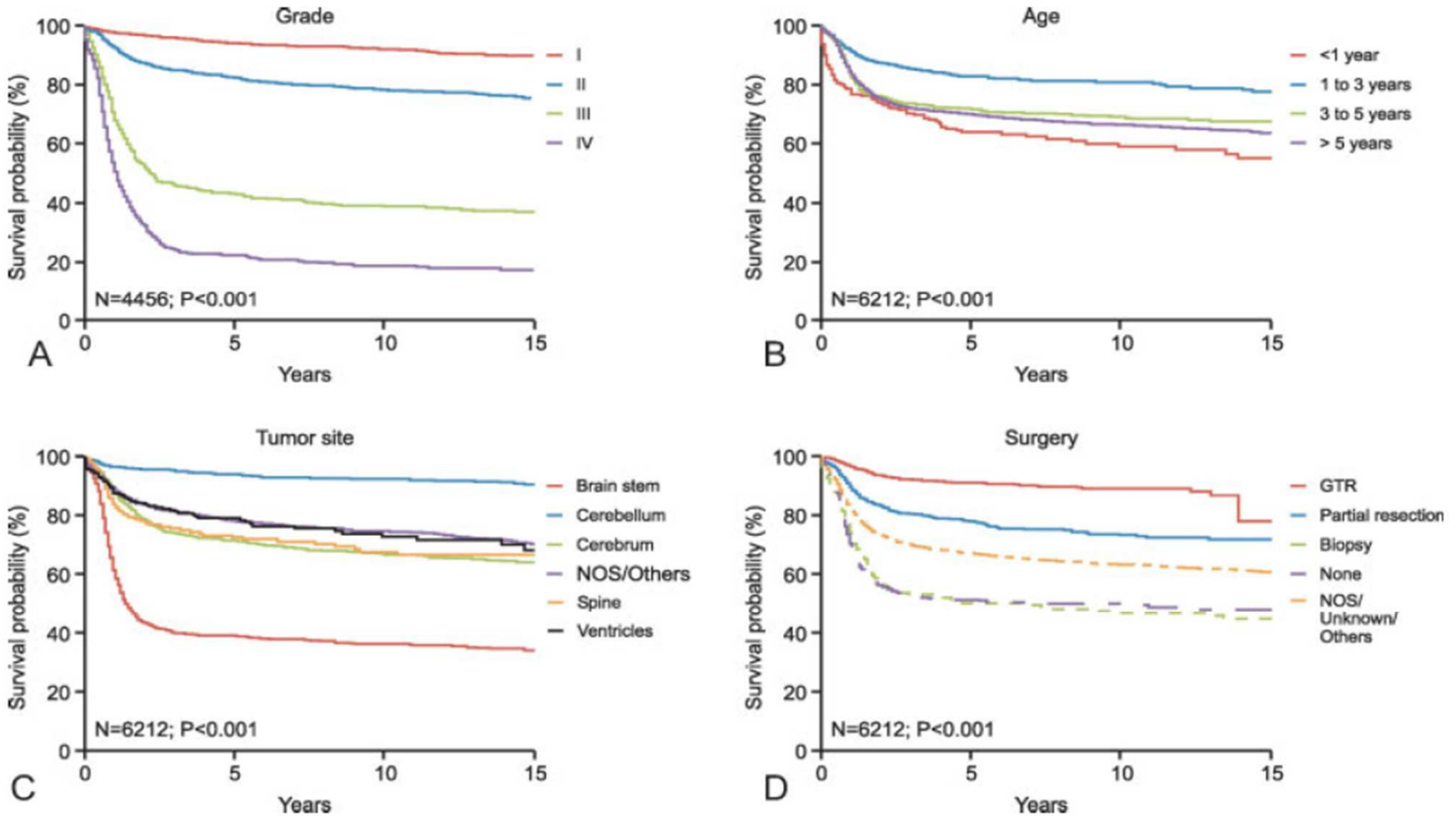


FIGURE 3. Survival of pediatric patients with gliomas is shown according to (A) tumor grade (n = 4456), (B) age (n = 6212), (C) tumor site (n = 6212), and (D) extent of surgery (n = 6212). The log-rank test was used to compare survival curves. NOS indicates not otherwise specified; GTR, gross total resection.

Quadoomi et al, Cancer 2009

Pediatric Ependymomas

3rd most common primary brain tumor of childhood

Peak age of incidence between birth to 4 years

70% arise in the IVth ventricle in posterior fossa

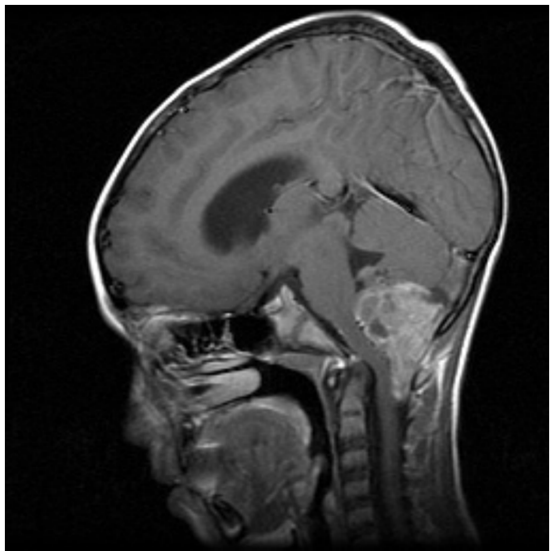
Large majority (>70%) are WHO grade II

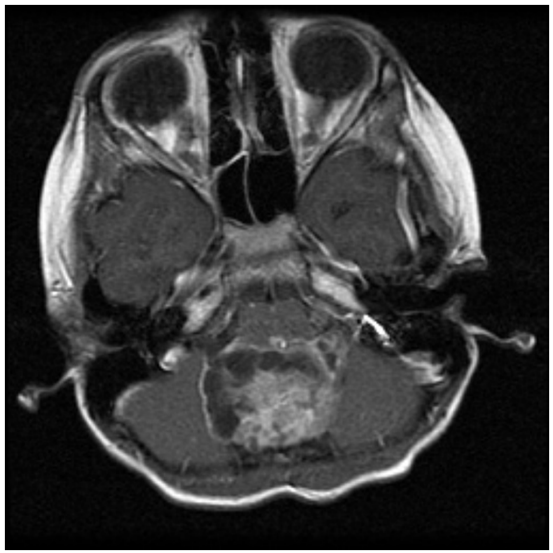
Frequently extend outside the foramina & into upper spine

Locally invasive and difficult to resect completely

Small but definite propensity for CSF dissemination (5-7%)

Adjuvant therapy with RT; CT is not effective





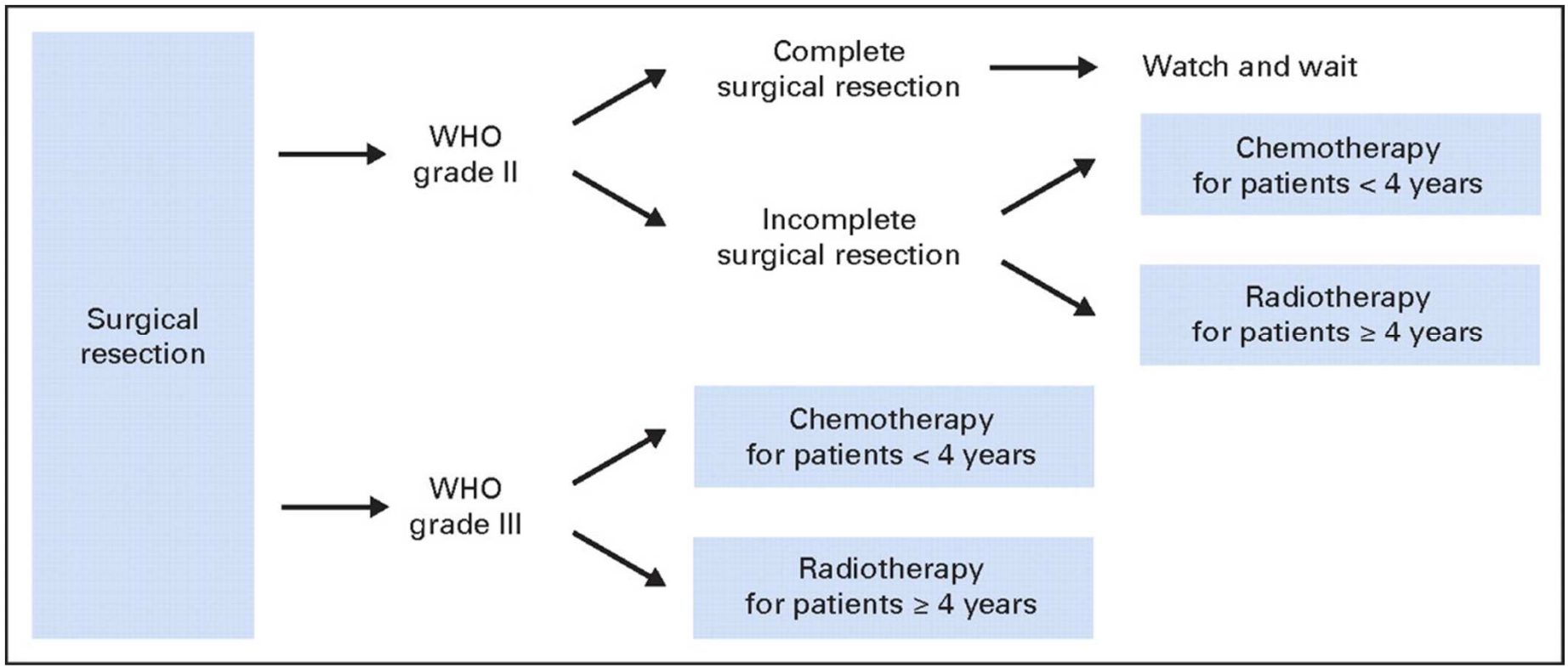
Largely considered a surgical disease

Surgeons have the highest impact on prognosis

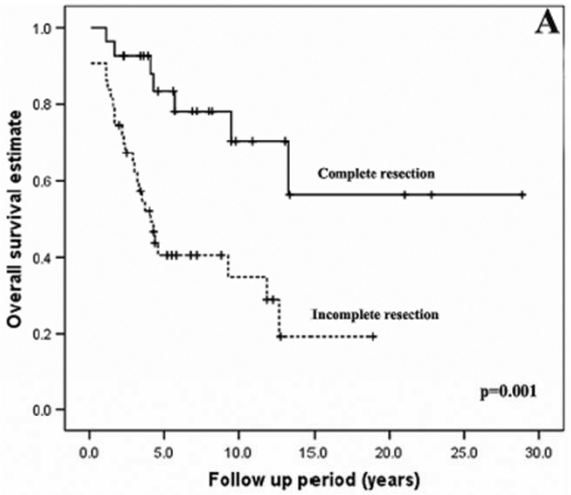
Aggressive resection (GTR) recommended to achieve long term control

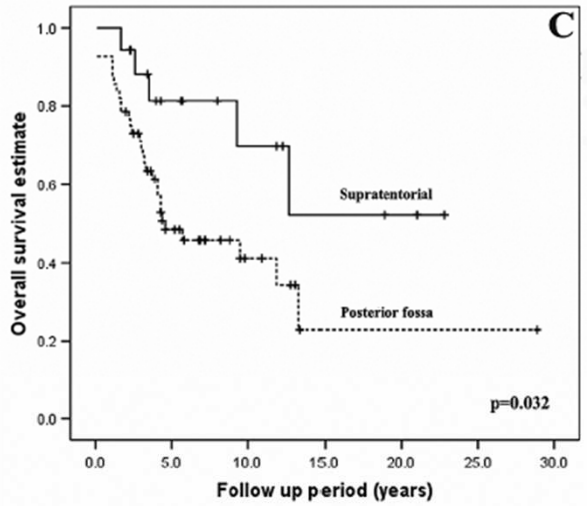
Most surgeons don't chase the tumor in the floor of the IVth ventricle

Delicate balance between morbidity and control



Prognostic factors in pediatric intracranial ependymomas (N=97)





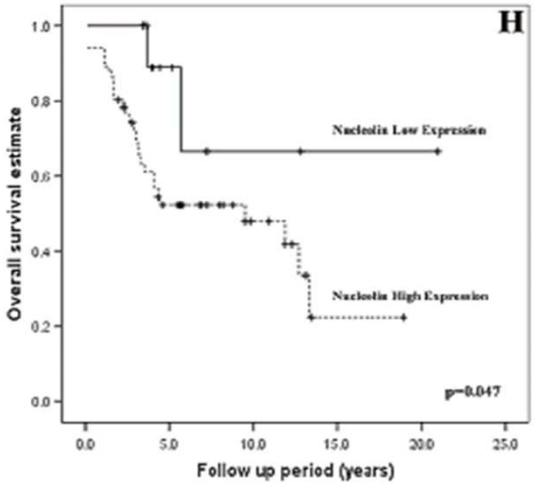


Table 2. Cox regression multivariate analysis of clinical and biological factors

	Event-Free Survival		
Factor	HR	95% CI	*p*-Value
Histology (II vs. III)	1.237	0.449–3.406	0.680
Tumor location (ST vs. PF)	0.392	0.120–1.280	0.222
Surgical resection (complete vs. incomplete)	4.736	1.819–12.330	0.001
Age at diagnosis (<3 vs. >3 years)	0.430	0.134–1.382	0.156
Ki-67 LI (low vs. intermediate/high)	0.792	0.227–2.769	0.715
Survivin LI (low vs. intermediate/high)	0.722	0.189–2.753	0.633
Nucleolin LI (low vs. high)	6.252	1.614–24.210	0.008
Radiation[a] (yes vs. no)	0.511	0.206–1.267	0.148

Ridley et al, Neuro-Oncol 2008

Conformal radiotherapy after surgery for paediatric ependymoma: a prospective study

	Patients (N=153)
Age at CRT (years)	
Mean (SD)	4·9 (4·4)
Median (range)	2·9 (0·9–22·9)
Age at diagnosis (years)	
Mean (SD)	2·9 (4·4)
Median (range)	2·4 (0·0–22·7)
Elapsed days of CRT	
Mean (SD)	44 (2·5)
Median (range)	44 (37–56)
Age (years), n (%)	
<3	78 (51·0)
≥3	75 (49·0)
Tumour grade, n (%)	
Differentiated	68 (44·4)
Anaplastic	85 (55·6)
Tumour location, n (%)	
Infratentorial	122 (79·7)
Supratentorial	31 (20·3)

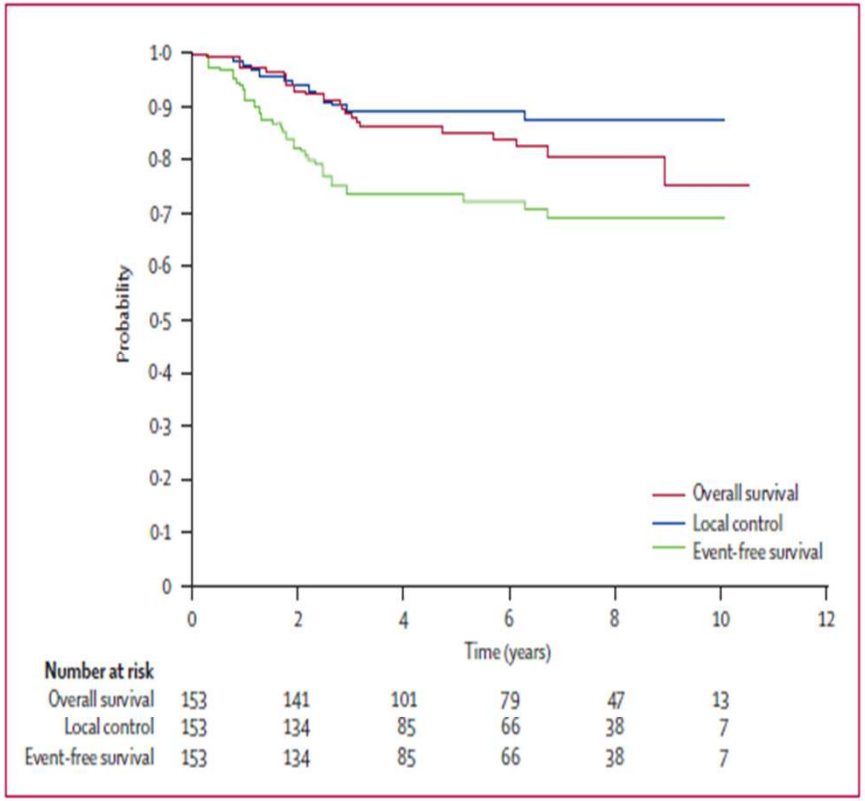


Figure 2: Event-free survival, overall survival, and local control for 153 patients with localised ependymoma treated with conformal radiotherapy

Interpretation Treatment of ependymoma should include surgery with the aim of gross-total resection and conformal, high-dose, postoperative irradiation. Future trials might consider treatment stratification based on sex and age.

Merchant et al, Lancet Oncol, 2009

	Time period	Patients, n	5-year EFS	10-year EFS	5-year OS	10-year OS
Merchant (present)	1997–2007	153	74%	69%	85%	75%
Akyuz[18]	1972–91	62	..	36%	..	50%
Perilongo[19]	1977–93	92	..	35%	..	56%
Shu[20]	1980–2000	49	41%	31%	66%	56%
Oya[21]	1961–99	48	42%	42%	62%	47%
Pollack[22]	1975–93	40	46%	36%	57%	45%
Jaing[23]	1985–2002	43	46%	..	54%	..
Van Veelan-Vincent[24]	1980–99	83	48%	46%	73%	51%
Robertson[25]	1986–92	32	50%	..	64%	..
Mansur[26]	1964–2000	60	58%	46%	71%	55%

EFS=event-free survival. OS=overall survival.

Table 3: **Event-free survival and overall survival estimates from selected radiotherapy series reporting 5-year and 10-year outcomes**

Post-operative radiotherapy improves outcomes in ependymoma

Primary postoperative chemotherapy without radiotherapy for intracranial ependymoma in children: the UKCCSG/SIOP prospective study

	Number of relapses (n=59)	5-year overall survival from the date of relapse (95% CI)
Relapse site		
Local relapse site	47	26 (13-41)
Local and metastatic relapse	6	Too early to tell
Metastatic relapse only	4	Too early to tell
Unknown	1	0
Perioperative death	1	0
WHO grade		
WHO primary tumour grade II	37	30 (13-48)
WHO primary tumour grade III	22	25 (8-47)
Surgery		
No surgery after relapse	28	24 (8-44)
Surgery after relapse	30	31 (13-51)
Perioperative death	1	0
Radiotherapy		
No radiotherapy after relapse	18	Too early to tell
Radiotherapy without surgery	17	20 (5-43)
Radiotherapy with surgery	23	32 (11-55)
Perioperative death	1	0

Table 4: Outcome in patients with a first relapse after primary treatment

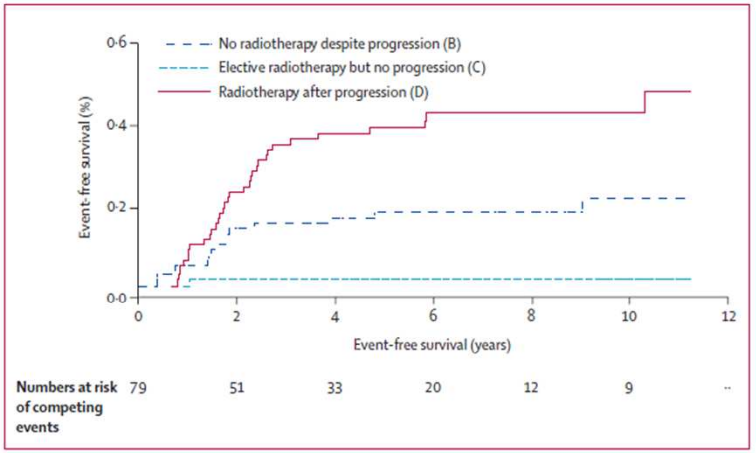
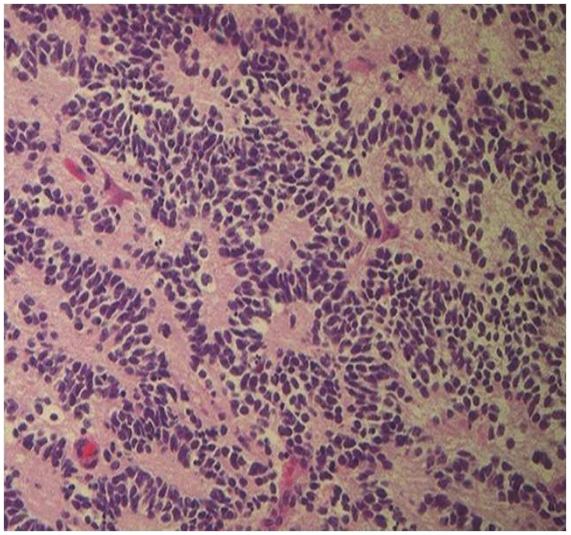


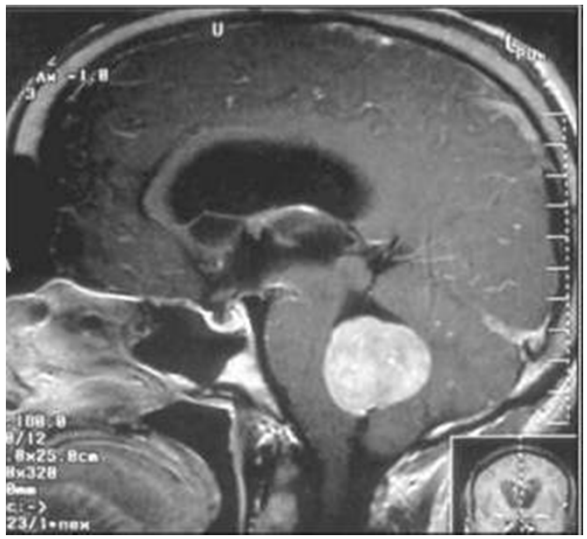
Figure 2: Competing risks analysis for patients with non-metastatic ependymoma

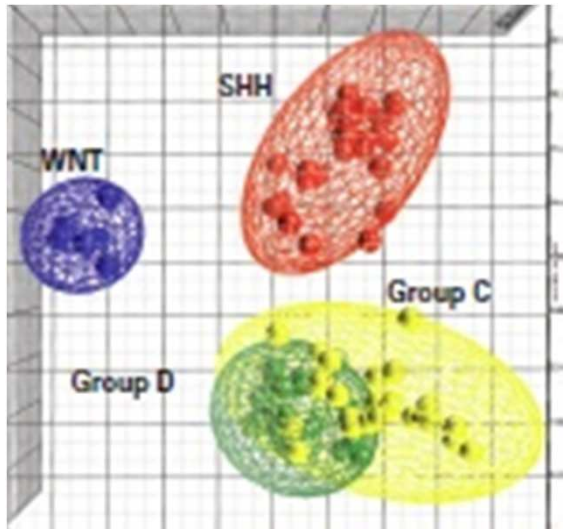
- **This protocol avoided or delayed radiotherapy in a substantial proportion of children younger than 3 years without compromising survival.**
- **Primary chemotherapy strategies have an important role in the treatment of very young children with intracranial ependymoma**

Grundy et al, Lancet Oncol, 2007

Medulloblastoma: enigmatic small blue round cell tumor





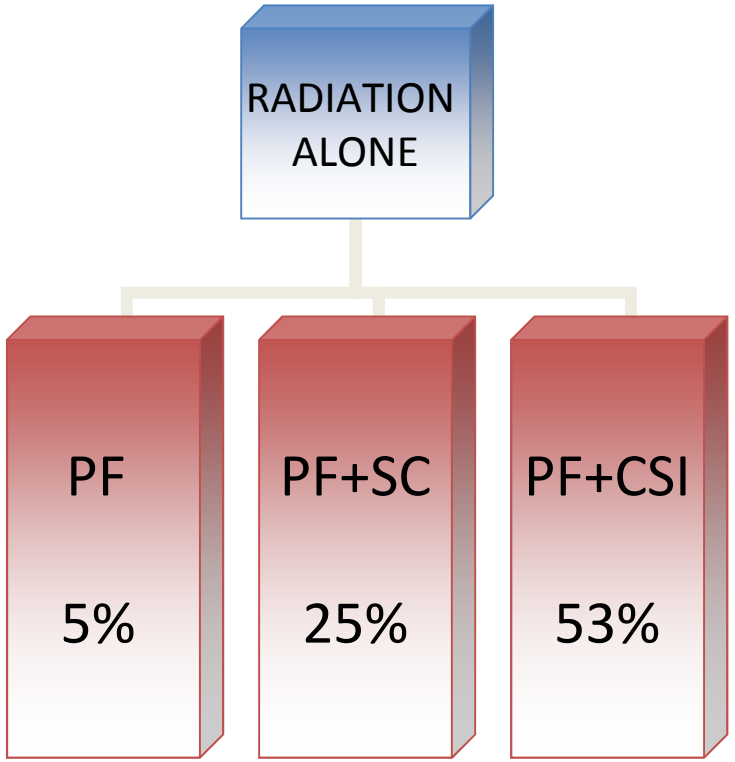


"In the course of our growing acquaintance with these baffling tumours, we suspected from their peculiar cytology that they might be susceptible to radiation and the first of the cases so treated both by the X-rays and radium was in December, 1919. Here at least was a new therapeutic recourse and we began with renewed encouragement to attack them with renewed vigour"

Cushing, 1930

Rationale of radiotherapy in medulloblastoma

- Generally a radiosensitive & chemosensitive tumour
- Historical controls: No long-term survivors without RT
- High recurrence rates with focal posterior fossa (PF) RT
- High recurrence rates for reduced dose craniospinal irradiation (CSI) without chemotherapy (CT)



Landberg, 1953

Current clinical risk-stratification for medulloblastoma

	Average-risk	*High-risk*
Age	**≥3 yrs**	**<3 yrs**
Residual Tumor	**≤1.5 x 1.5 cm^2**	**>1.5 cm^2**
Metastases	**No metastases (M0)**	**Metastases (M1 – M4)**
Pathology	Desmoplastic	Anaplastic
Brain Stem invasion	None	Present
Mitotic index	Low	High
Trk-C protein mRNA	High	Low
C-myc & ERBB2	Low	Amplified
Tumor DNA Content	Diploid	Aneuploid
Apoptotic Index	High	Low

Long-term survival with full-dose radiotherapy

Table 4. Results from large, contemporary series or series with 10-year survival data employing full-dose radiation therapy

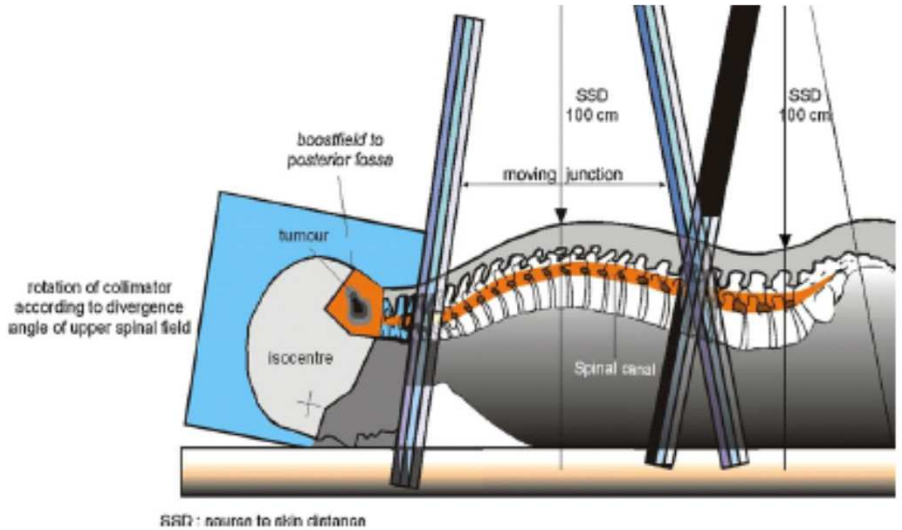
Series (date) details	Reference	Study (5 yr)	*n* (10 yr)	RT follow-up	Chemotherapy	Entire group	Median	Dates
Evans *et al.* (1990)	6	1975–1981	88	*	Adjuvant (*n* = 88)	65%		5 yr
			91		Adjuvant (*n* = 0)			
Hershatter *et al.* (1986)	7	1940–1983	127	†	Adjuvant (4/127)	33%	21%	26 yr
Jenkin *et al.* (1990)	8	1977–1987	72 (v)	‡	Adjuvant (3%)	71%	63%	7 yr
Stiller and Lennox (1983)	14	1971–1977	304	§	Adjuvant (94/304)	35%	30%	9 yr
Tait *et al.* (1990)	15	1975–1979	141	¶	Adjuvant (*n* = 141)	53%	45%	12 yr
			145		Adjuvant (*n* = 0)			
Tarbell *et al* (1991)	16	1970–1989	89	**	Pre-RT (*n* = 39)	65%	48%	9 yr
Merchant *et al.* (1995)		1979–1994	100		Adjuvant (49%)	50%	25%	8 yr

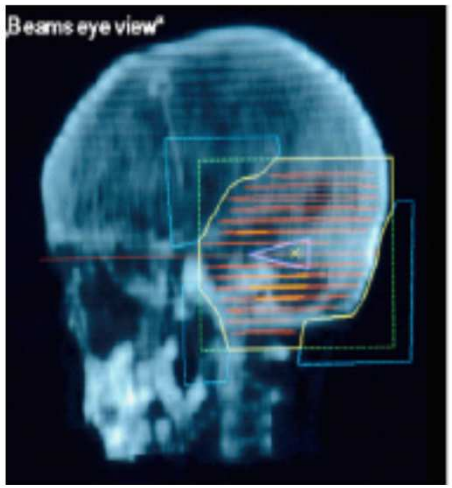
Full-dose radiation therapy is defined as 30–35 Gy to the craniospinal axis and 50–56 Gy to the posterior fossa.

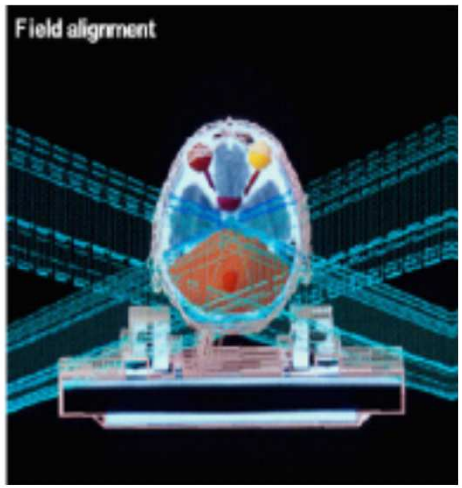
Merchant et al, IJROBP 1996

Long-term sequelae of RT in medulloblastoma

- Neurocognitive & neurophysiological dysfunction
- Endocrine abnormalities & hormonal imbalance
- Growth retardation - spinal component
- Ototoxicity- particularly with platinum based adj CT
- Cerebrovascular accidents
- Gonadal toxicity & reduced feritility
- Second malignant neoplasms







Radiotherapy Toxicity: Dose-Volume Related

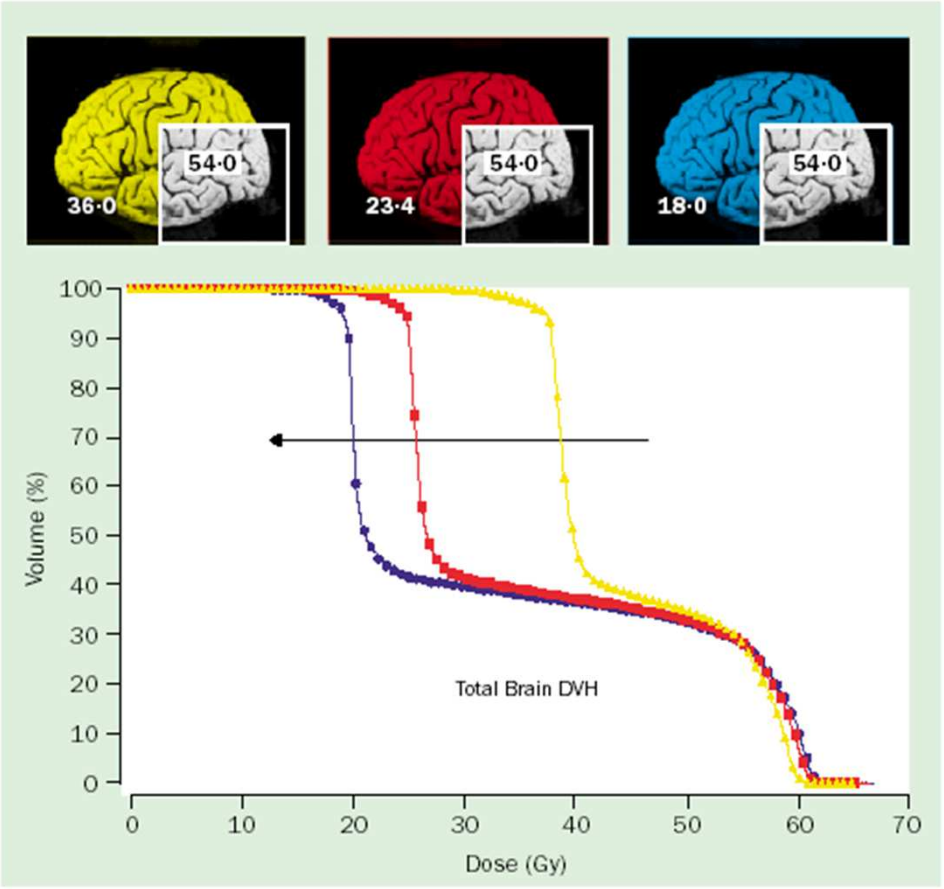


Figure 3. Benefits of dose decreases in planning of craniospinal radiotherapy shown with total-brain dose-volume histograms (DVH), comparison of 36·0 Gy (yellow), 23·4 Gy (red), and 18 Gy (blue).

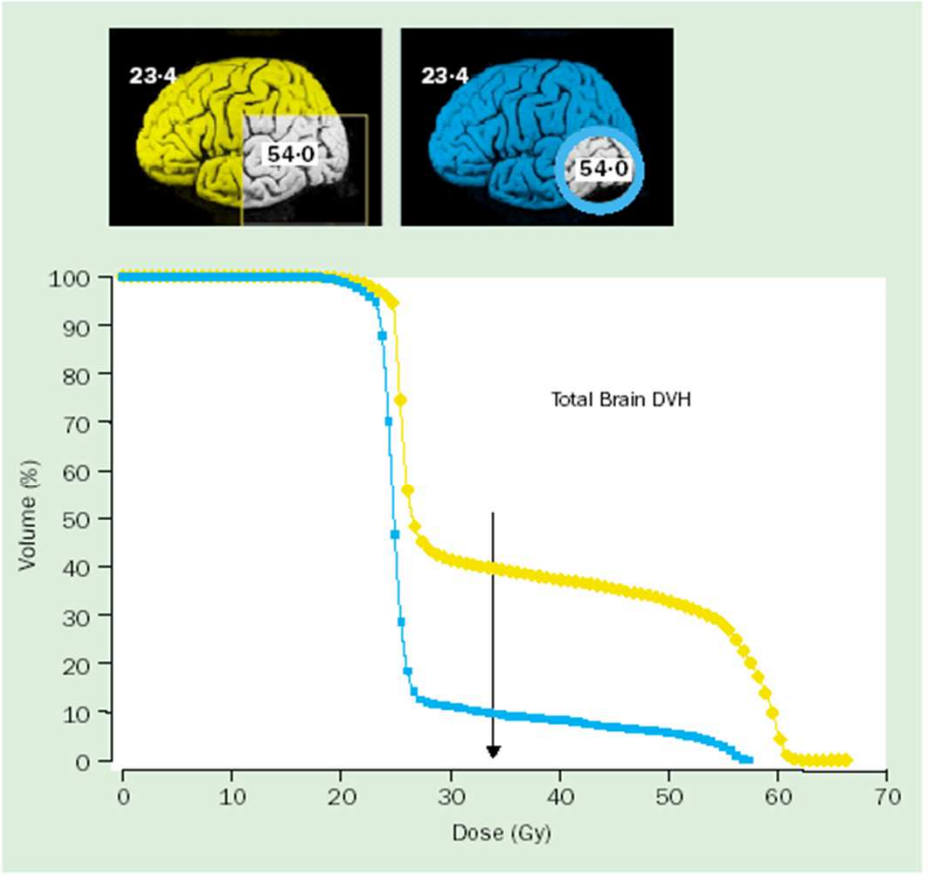


Figure 4. Benefits of dose decreases in planning of radiotherapy to posterior fossa shown with total-brain dose-volume histograms (DVH), comparison of conventional boost (blue) to posterior fossa with conformal boost (yellow) to the primary site after 23·4 Gy craniospinal irradiation.

Mulhern et al: Lancet Oncol 2004

Doses & volumes as per risk-stratification

CSI for average-risk disease

Standard dose CSI: 35-36 Gy/21-20#/4 weeks @ 1.67-1.8 Gy/#

Reduced dose CSI: 23.4 Gy/13#/2.5 weeks @1.8 Gy/# (+ adj CT)

Boost for average-risk disease

If Standard dose CSI : PF or TB boost: 19.8 Gy/11#/2 weeks

If reduced dose CSI: Tumour bed boost: 32.4 Gy/18#/3.5 weeks

CSI for high-risk disease

Standard dose CSI: 35-36 Gy/21-20#/4 weeks @ 1.67-1.8 Gy/#

Higher dose spinal RT: 39.6 Gy/22#/4.5 weeks @1.8 Gy/#

Boost for high-risk disease

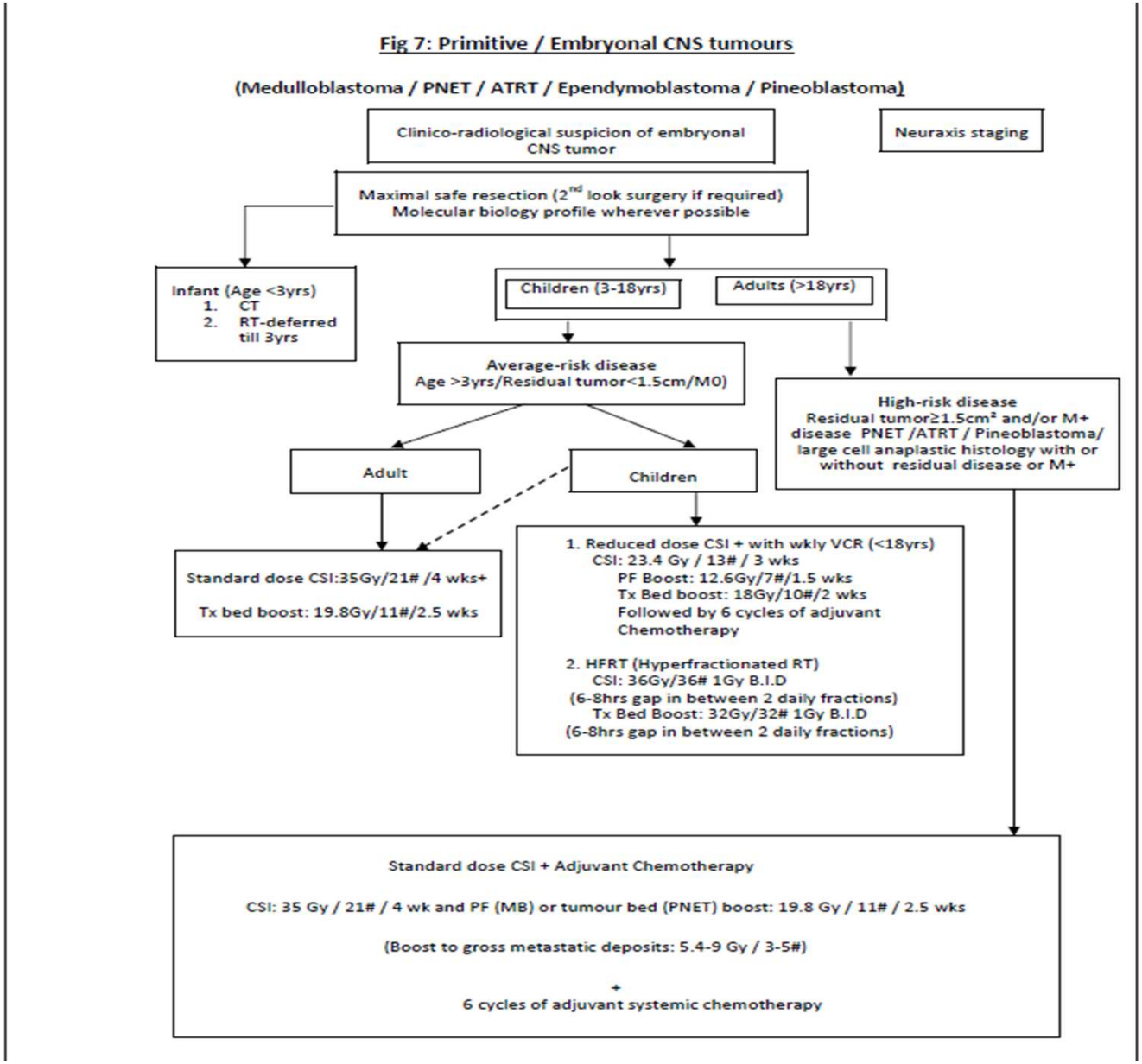
Whole posterior fossa boost: 19.8 Gy/11#/2 weeks

Boost for gross focal spinal deposit: 5.4-9 Gy/3-5#/1 week

Total tumor bed dose: 54-56 Gy/30-33#/ 6.5 weeks (conventional #)

TMH Protocol for Medulloblastomas /PNET

https://tmc.gov.in/SBF/Nouro/flowcharts_final.pdf



Methods to improve outcomes in medulloblastoma

Reduce toxicity of radiotherapy

1. Reduce the dose & volume of RT:

a) Reduction in CSI dose

CSI dose to 23.4 Gy (with chemotherapy)

CSI dose 18 Gy: Investigational (ongoing randomized trial)

b) Reduction in primary site dose

Total tumor dose <54 Gy: Increased incidence of local failures

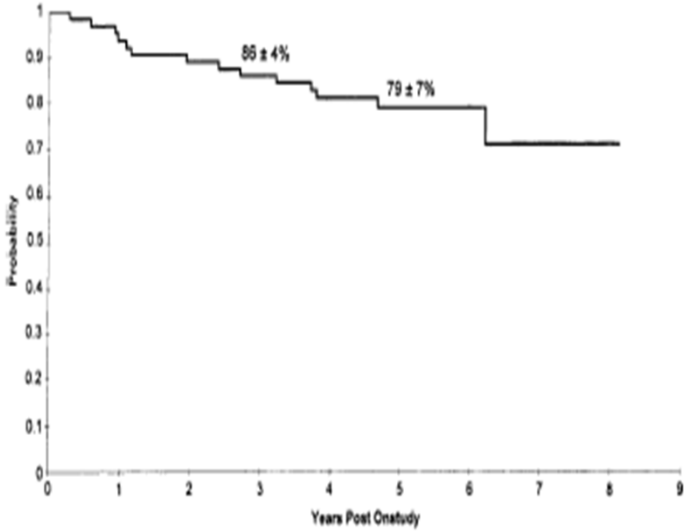
c) Reduction in volume

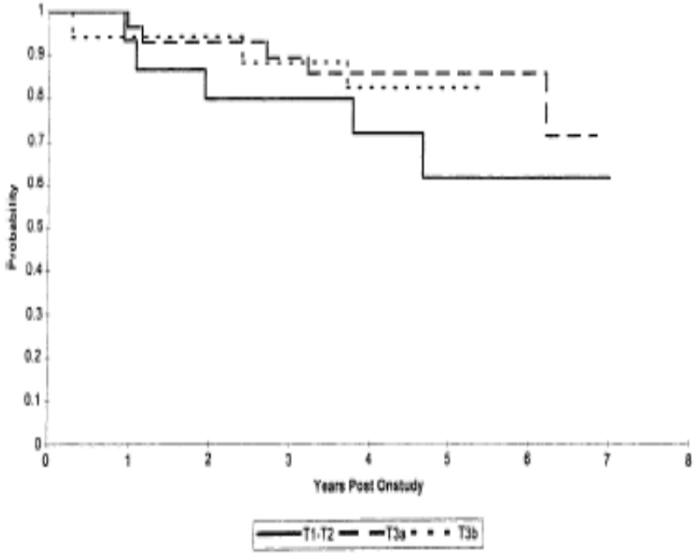
Boost tumor bed with margins (1-1.5 cm): Acceptable

d) *Radiation avoidance strategies*

Avoiding RT in <3 (sometimes 5) year old children

Reduced dose CSI plus adjuvant chemotherapy





N=65 patients

Conc wkly VCR followed by 8 cycles of CCNU, CDDP and VCR

PFS- 86 ± 4% at 3 years , 79 ± 7% at 5 years.

Results better than earlier study using reduced dose CSI alone

Positive impact of adjuvant chemotherapy on EFS

Packer et al, JCO 1999

Phase III Study of Craniospinal Radiation Therapy Followed by Adjuvant Chemotherapy for Newly Diagnosed Average-Risk Medulloblastoma

Table 4. Cumulative Toxicity Rate

Toxicity	Grade 3 or 4 Regimen A/B %	*P*	Grade 4 Regimen A/B %	*P*
Hematologic	97/98		82/90	< .01
Hepatic	12/11		1.7/2.2	
Renal	9.0/5.0		1.1/0.0	
Pulmonary	3.4/2.2		1.6/1.6	
Nervous system	51/46		5.4/3.8	
Hearing	28/23		5.8/6.7	
Electrolytes	6.2/12	< .10	1.7/3.9	
Infection	18/30	< .01	1.6/6.9	< .05
Performance	21/14	< .10	4.9/4.8	

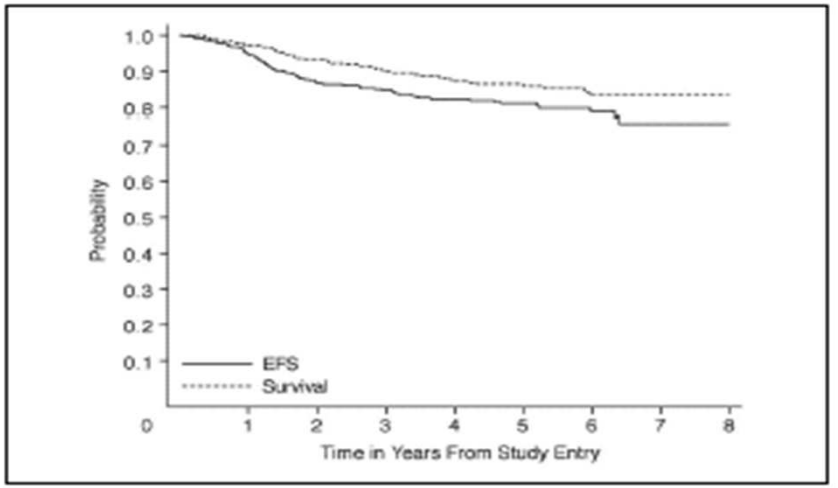


Fig 1. Event-free survival (EFS) and survival from study entry.

Results

Forty-two of 421 patients enrolled were excluded from analysis. Sixty-six of the remaining 379 patients had incompletely assessable postoperative studies. Five-year EFS and survival for the cohort of 379 patients was 81% ± 2.1% and 86% ± 9%, respectively (median follow-up over 5 years). EFS was unaffected by sex, race, age, treatment regimen, brainstem involvement, or excessive anaplasia. EFS was detrimentally affected by neuroradiographic unassessability. Patients with areas of frank dissemination had a 5-year EFS of 36% ± 15%. Sixty-seven percent of progressions had some component of dissemination. There were seven second malignancies. Infections occurred more frequently on the cyclophosphamide arm and electrolyte abnormalities were more common on the CCNU regimen.

Conclusion

This study discloses an encouraging EFS rate for children with nondisseminated MB treated with reduced-dose craniospinal radiation and chemotherapy. Additional, careful, step-wise reductions in CSRT in adequately staged patients may be possible.

Packer et al, JCO 2006

Patterns of failure following treatment for Medulloblastoma

Do we need to treat entire posterior fossa

- **N = 114 Patients, 27 Recurrence (Median Age 8.6 Yrs, Median time to recurrence 19.5 Mths.)**
- **Failure was defined as MRI or CT evidence of recurrence or positive cerebrospinal fluid cytology.**
  - **Local Relapse = within the original tumor bed**
  - **Regional = Outside of the tumor bed but still within the PF.**

Table 3. Patterns of failure

Site of first failure	Only site of failure	Any component of failure
Tumor bed	2 (7%)	14 (52%)
PF outside TB	1 (3%)	11 (41%)
Spine	5 (19%)	19 (70%)
Supratentorial	2 (7%)	7 (26%)
Extraneural	2 (7%)	3 (11%)

Table 4. Sites of failure

Site of failure	Only site of failure	Any component of failure
TB + PF outside TB	0	8
TB + spine	2	11
PF outside TB + spine	1	9
PF outside TB + supratentorial	0	2
Spine + supratentorium	1	5
TB + PF outside TB + spine	5	7

Fukunaga et al, IJROBP 1998

Patterns of failure following treatment for medulloblastoma

Do we need to treat entire posterior fossa

Patterns of Failure Using a Conformal Radiation Therapy Tumor Bed Boost for Medulloblastoma (Wolden et al JCO 2003)

Median follow-up of 56 months.

32 consecutive patients.

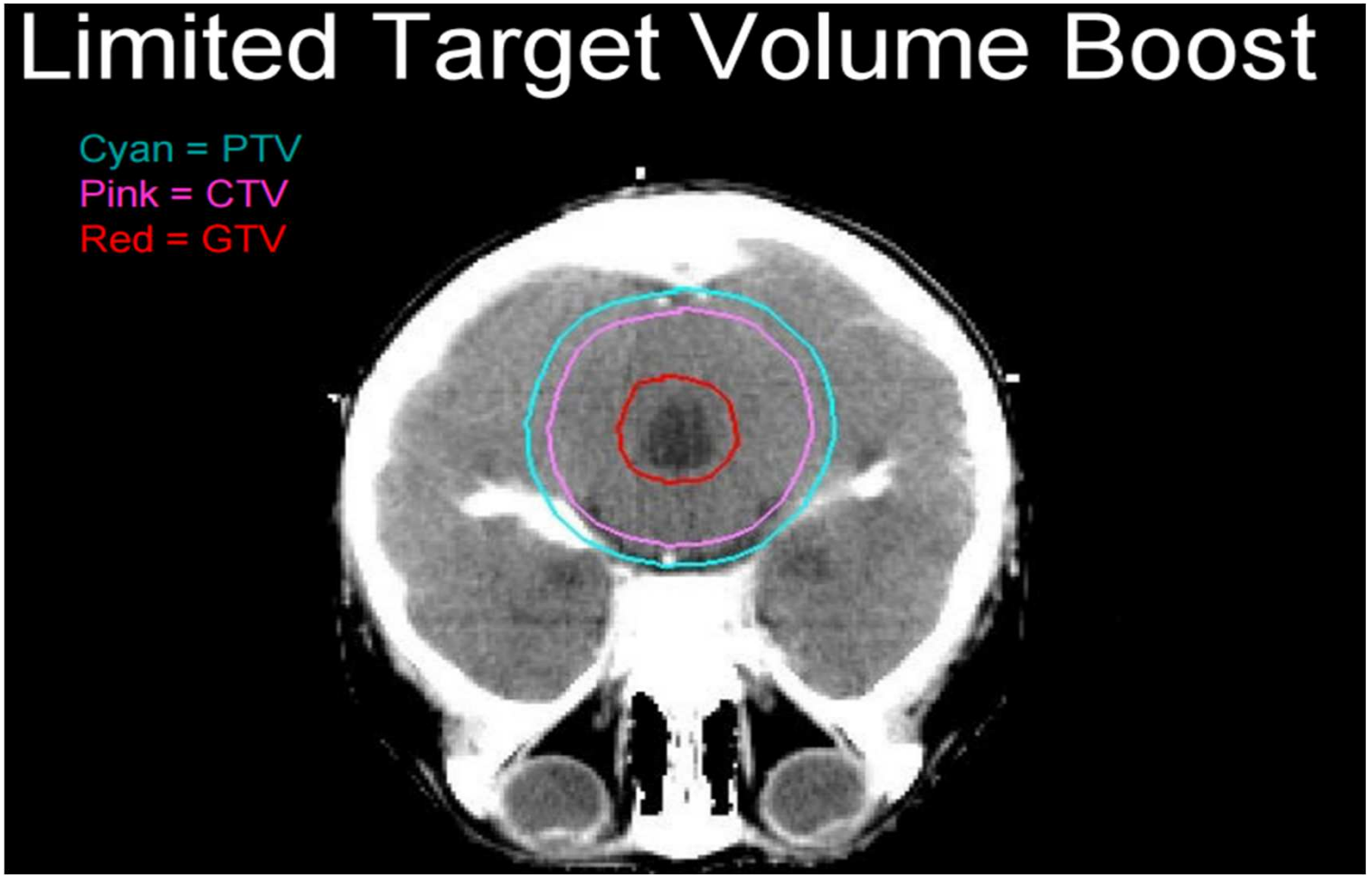
6 patients have relapsed

- 5 outside PF
- only 1 in the PF

Freedom from posterior fossa failure was 100% and 86% at 5 and 10 years

Five-year actuarial disease-free and overall survival rates were 84% and 85%

COG_ACNS_0331 study



Jeff Michalski

Methods to improves outcomes in medulloblastoma

Reduce toxicity and/or improve efficacy

1. **Maintain good quality of radiotherapy**
   - *a) Minimize deviations & comply to protocol specifications*
2. **Modify the fractionation schedule**
   - *a) Hyperfractionated Radiotherapy (HFRT)*
   - *b) Hyperfractionated-Accelerated RT (HART)*
3. **Add concurrent chemotherapy to RT**
4. **Integrate newer/novel technology**
   - *a) IMRT/IGRT: Helical TomoTherapy*
   - *b) Proton beam therapy*

Does minimizing RT deviations help?

Impact of quality of radiotherapy on outcome in childhood medulloblastoma.

Author/study	Patients	"Low quality"	"High quality"	Survival	Significance
Packer et al. (1991)	108	RT 1975–1982 $n=67$	RT 1983-89 $n=41$	49% vs. 82% 5-year PFS	Significant $p=0.004$
Graben bauer et al. (1996)	40	RT before 1980	RT after 1980	5-year overall survival 64% vs. 80%	Significant $p=0.02$
Miralbell et al. (1997)	77	36 inadequate "helmet-technique"	41 adequate « "helmet-technique"	5-year PFS 94% vs. 72%	Significant $p=0.016$
Carrie et al. (1999)	169	Min. viol.: 67 (40%) Maj. viol.: 53 (31%), Of these: 36 one maj. viol. 11 two maj. viol. 6 three maj. Viol.	49 (29%)	3-year relapse rate 33%: all patients 23%: corr. treatment 17%: one maj. viol. 67%: two maj. viol. 78%: three maj. viol.	Significant $p=0.04$
Packer et al. (1999)	63	Violations: 20	No viol.: 43	5-year PFS 81% vs. 70%	Not significant $p=0.42$

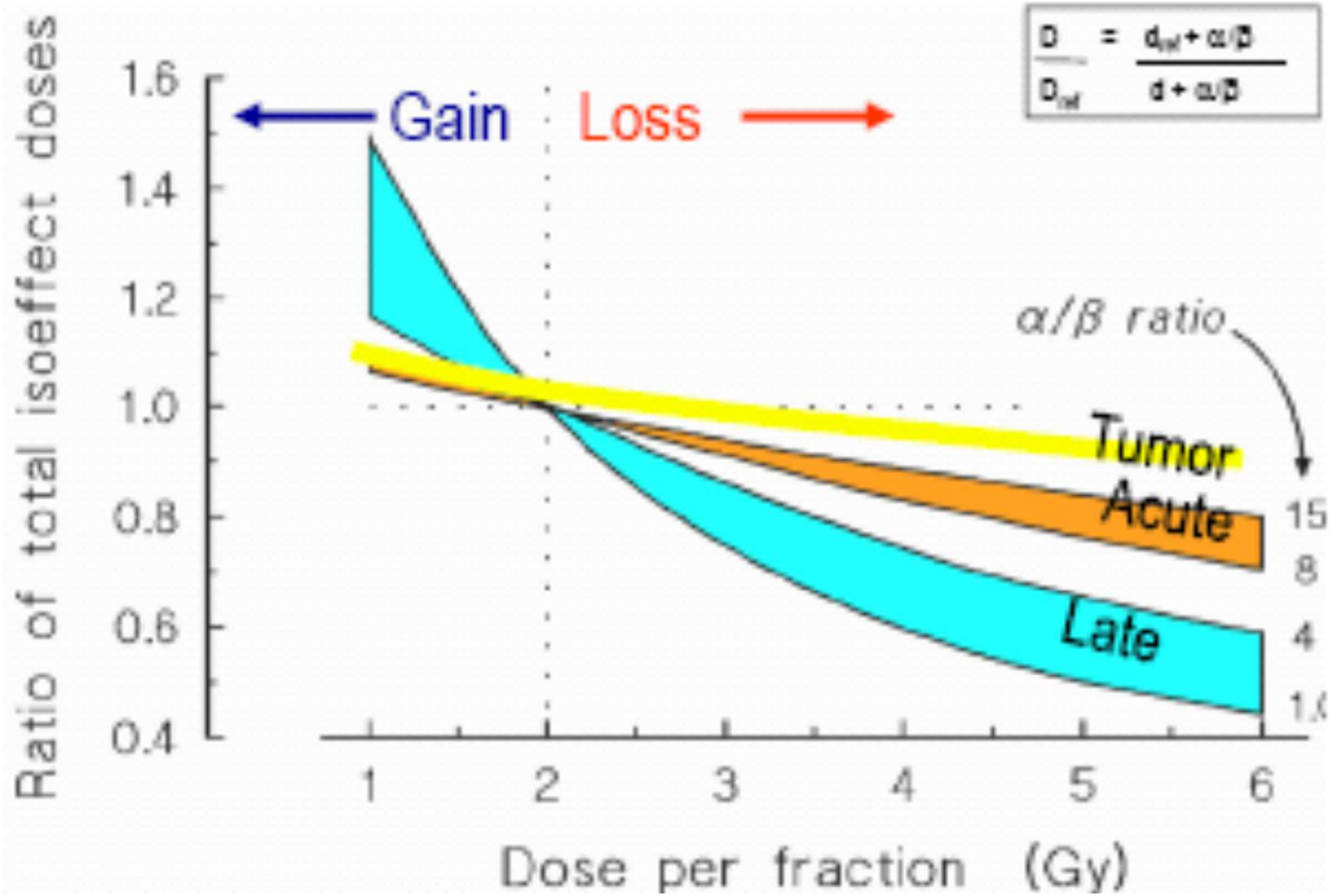
GOOD QUALITY RADIOTHERAPY

CRUCIAL CRITICAL CENTRAL

Is there a role for modified fractionation?

HFRT & HART

Strong radio-biologic rationale



HFRT in Medullblastoma: Tata Memorial Experience

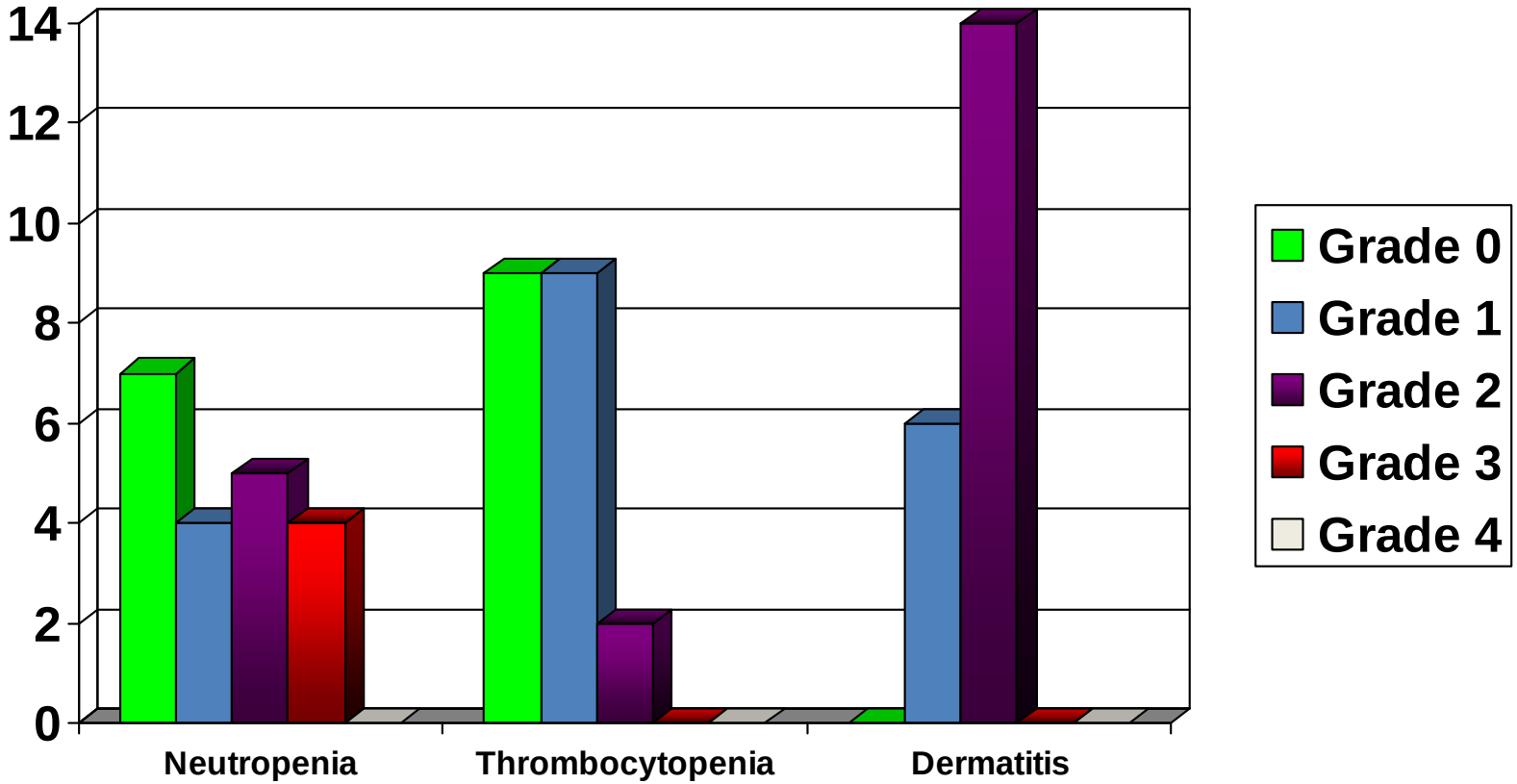
Dr T Gupta (Principal Investigator)

Clinical, demographic & treatment characteristics

- **Study accrual period: 2006 – 2010**
- **Patients completed treatment: All 20 patients**
- **Median age: 8 years (range 5-14 years)**
- **Risk-stratification: Average-risk disease (all patients)**
- **CSI dose: 36 Gy/36 fx, 1 Gy BID, 6 hrs apart over 3.5 wks**
- **Tumor bed boost: 32 Gy/32 fx, 1 Gy BID, 6 hrs apart over 3 wks**
- **Total tumor bed dose: 68 Gy /68 fx, 1 Gy BID, 6 hrs apart over 6.5 wks**
- **Adjuvant chemotherapy: Not initially (offered only at progression)**
- **Median follow-up: 27 months (range 13-54 months)**

Gupta T,IJROBP 2012

Acute toxicity of HFRT: Mild & self-limiting



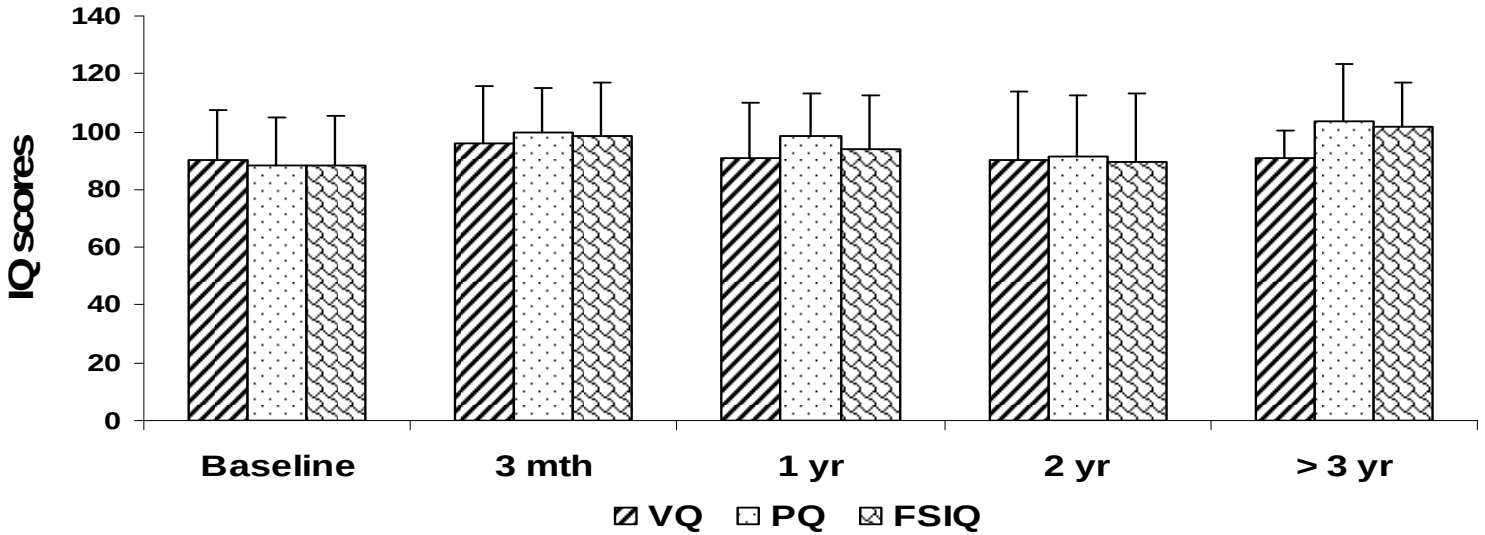
Hematologic toxicity very very acceptable (mild & self-limiting)

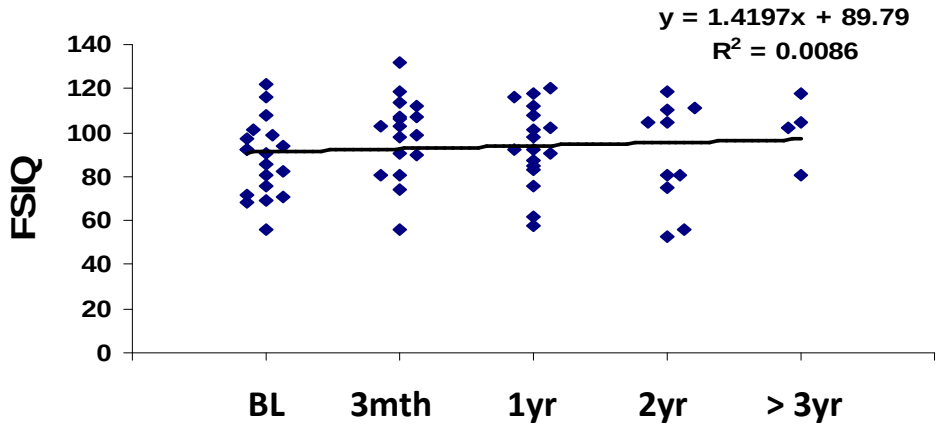
No episodes of febrile neutropenia, only 1 patient given G-CSF x 3 days

No patients required blood or blood-product transfusion

No interruptions of treatment due to toxicity

Neuro-cognitive outcomes





8 (40%) children had subnormal intelligence even before RT (FSIQ<85)

Cognitive function preserved on all tested domains over time

Patterns of relapse and survival outcomes

Two patients relapsed at 18 and 21 months respectively from initial diagnosis

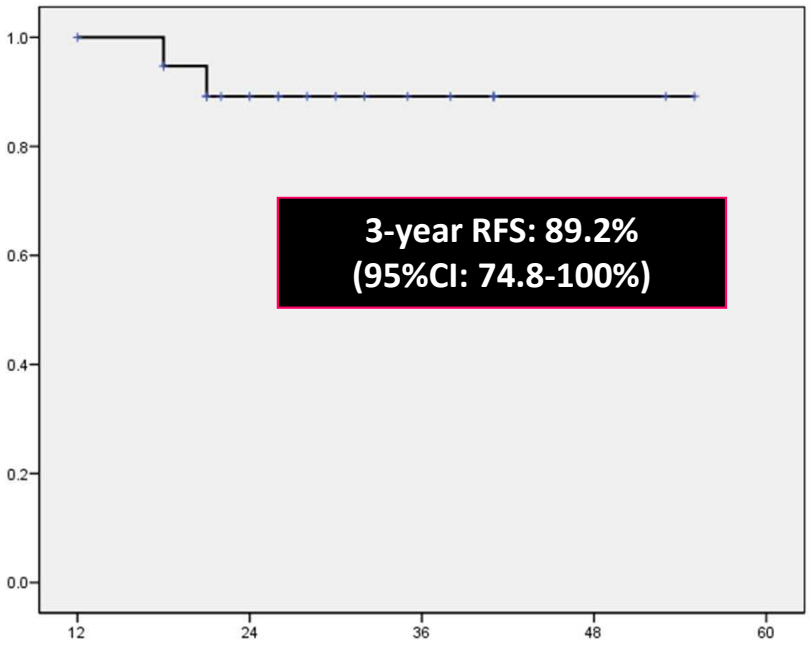
One had leptomeningeal disease and local failure within tumor bed

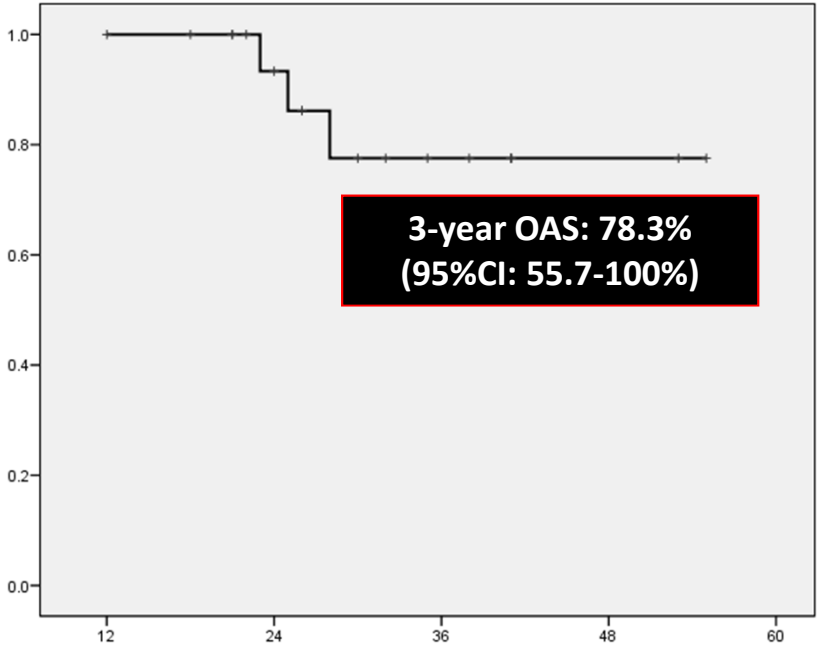
Second had supratentorial frontal relapse (away from cribriform plate)

One child received salvage chemotherapy; the other refused salvage

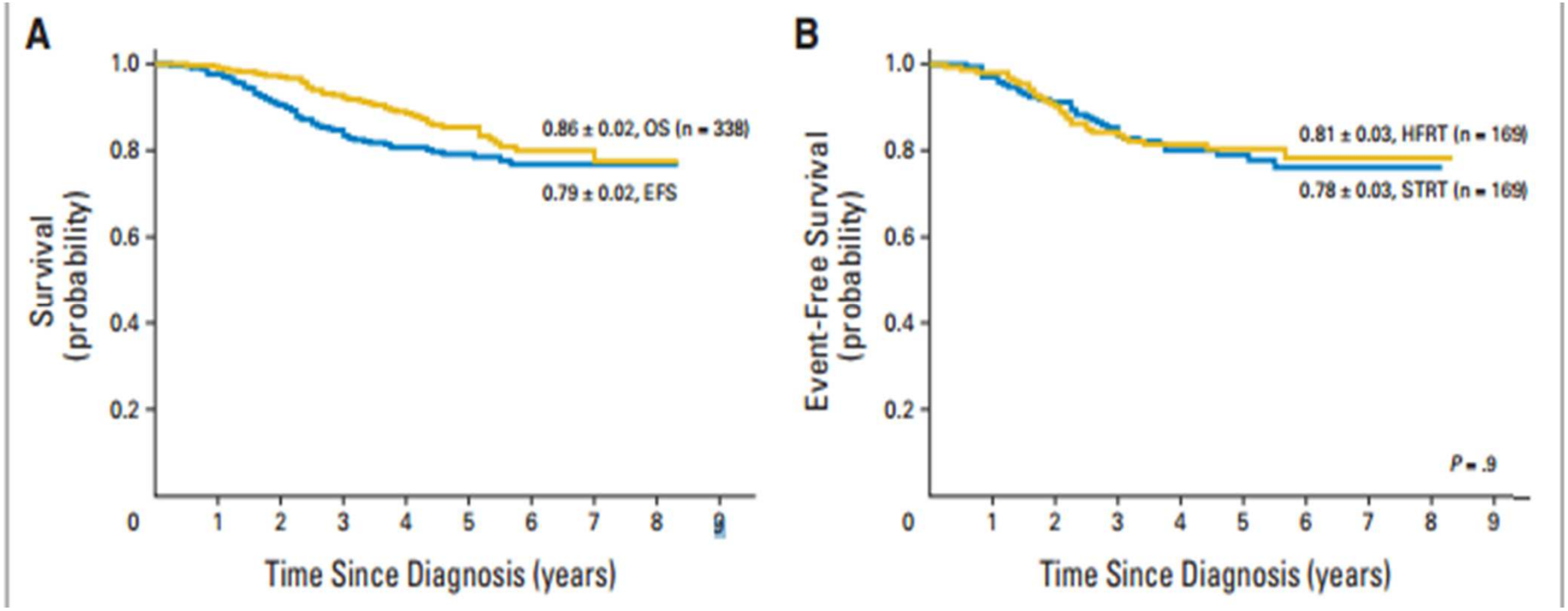
Both children succumbed to disease at 21 and 27 months respectively

One child died on accidental burn injuries (unrelated cause)





Is Hyperfractionated RT better than Standard fractionation in Avg risk Medulloblastoma..... SIOP PNET 4 Randomised trial



- 322 Children with avg risk medulloblastoma across 122 european centres.
- Standard fraction:23.4 Gy to the CS axis and 54 Gy to whole posterior fossa
- HFRT: 36Gy CS and 60 Gy to Posterior fossa in 68Fractions,1Gy/# twice daily
- Chemotherapy regimen consisting of eight cycles of cisplatin, lomustine, and vincristine.

Lannering, JCO 2012

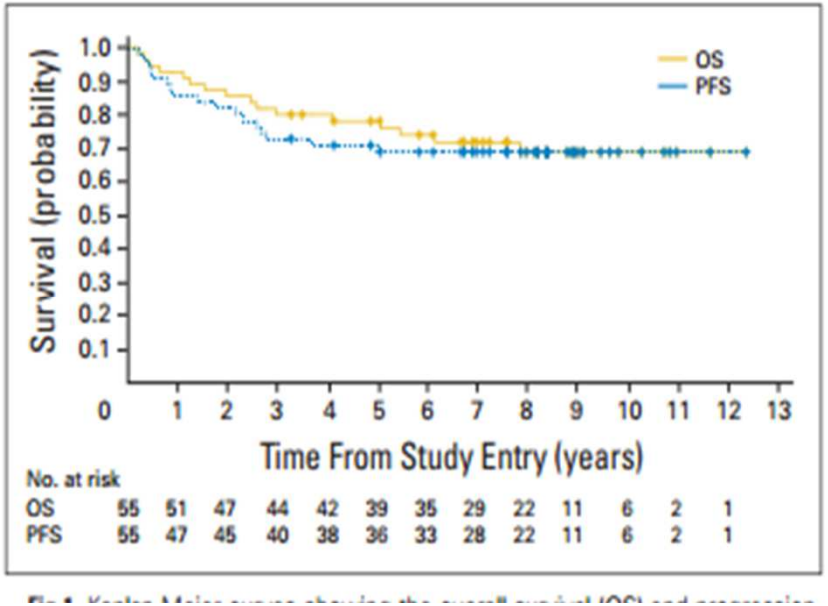
Table 2. Hearing Loss at Latest Follow-Up in Treatment Arms

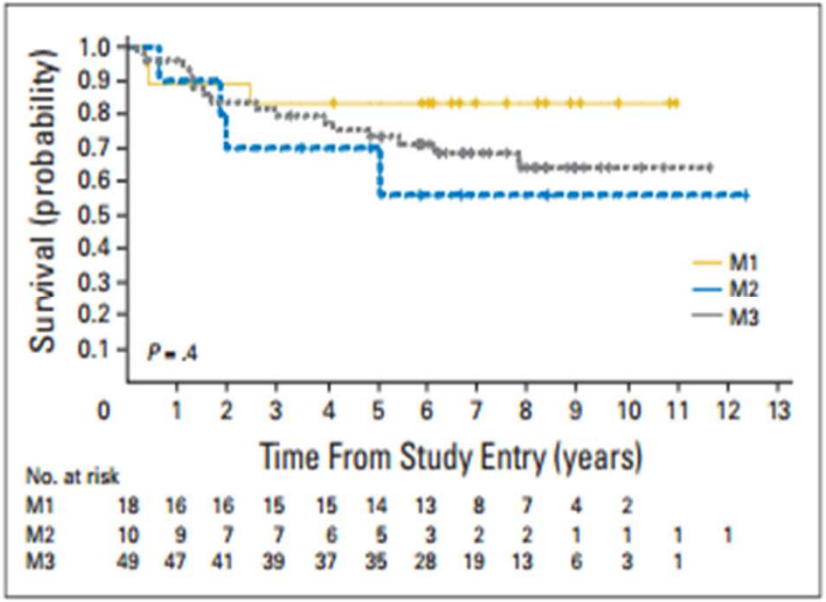
Grading System	Hearing Thresholds	STRT (n = 78; %)	HFRT (n = 68; %)
HIT*			
Grade 0 to 1	≤ 15 dB at 2 kHz	62	65
Grade 2	16-30 dB at 2 kHz	23	18
Grade 3 to 4	≥ 31 dB at 2 kHz	15	17
Brock†			
Grade 0 to 1	< 40 dB on all frequencies or ≥ 40 dB at 8 kHz	78	75
Grade 2	≥ 40 dB at 4 kHz	18	21
Grade 3 to 4	≥ 40 dB at 2-1 kHz	4	4
Mean time from diagnosis, months		45	44
Median time from diagnosis, months		45	44

Conclusion of the study:

Excellent survival rates were achieved in patients with Avg risk Medulloblastoma wiithout RT treatment delays. EFS and OS for HFRT was not superior to STRT, which therefore remains standard of care in this disease.

High Risk Medulloblastoma: Using carboplatin as a radiosensitizer COG Phase studyI-II.





- ❑ 161 children with M + medulloblastoma
- ❑ carboplatin 35mg/m2 given with CSI

Conclusion: Carboplatin as a radiosensitizer in M+ Medulloblastoma is a promising strategy

Regina Jackaki, JCO 2012

Our own encouraging experiencing of adding concurrent carboplatin

OT-17. A PROSPECTIVE STUDY OF CONCURRENT CARBOPLATIN AND RADIATION THERAPY (CTRT) FOLLOWED BY ADJUVANT CHEMOTHERAPY IN PATIENTS WITH HIGH-RISK MEDULLOBLASTOMA

Tushar Vora, Purna Kurkure, Brijesh Arora, Tejpal Gupta, Vandana Dhamankar, Shripad Banavali, Aliasgar Moiyadi, Shridhar Epari, Nikhil Merchant and Rakesh Jalali

+ Author Affiliations

Abstract

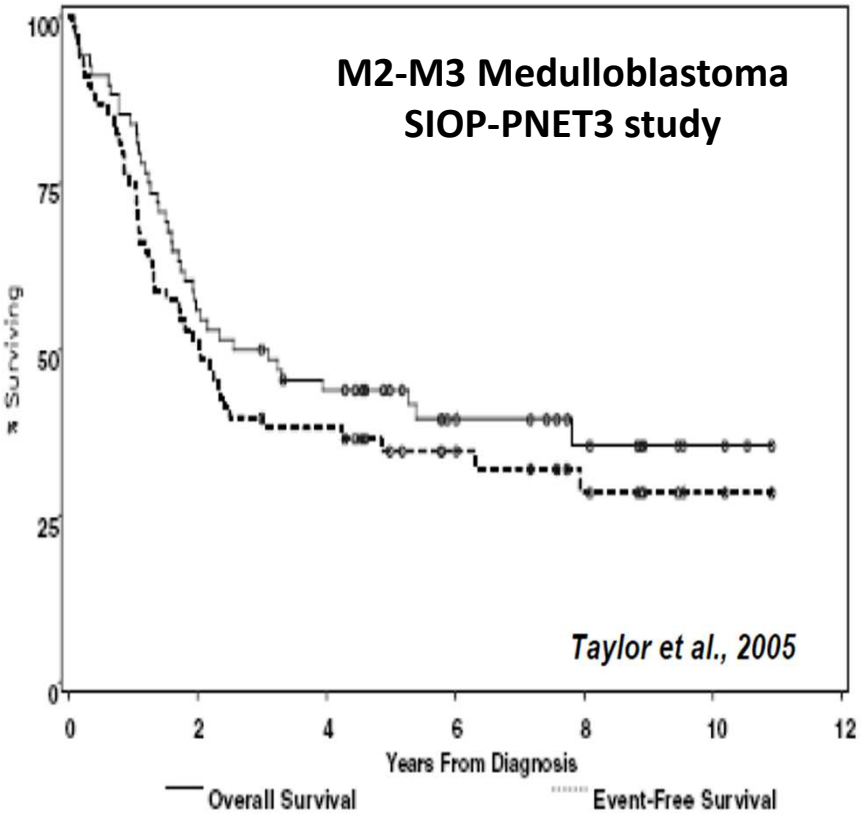
AIM: To assess the role of concurrent carboplatin and radiation therapy (CTRT) followed by adjuvant chemotherapy (AC) in patients with high-risk medulloblastoma (HRM) for improving event-free survival (EFS). METHODOLOGY: Newly-diagnosed 3- to 21-year-old HRM patients have been prospectively accrued since July 2004. Within 6 weeks of surgery, all patients underwent CTRT, including craniospinal radiation (CSI; 35 Gy/21#) with tumor bed boost (19.8 Gy/11#) with 35-mg/m^2/day carboplatin 5 days a week for 15 doses (during 3 weeks of CSI), followed by 6 cycles of 4-weekly adjuvant chemotherapy (using vincristine, cisplatinum, and cyclophosphamide) beginning 4 weeks post-CTRT.

RESULTS: 26 patients have been accrued. Median age was 8.5 years (range, 4-17 yrs). M:F ratio was 3.1:1. M stage: 62% were M0, 3.8% each were M1 and M2, and 30.8% were M3. At the end of CTRT, 23 (88.5%) are in complete response (CR), 2 (7.7%) are in partial response (PR), 1 (3.8%) has radiologic stable disease, and none of the patients has had progression on CTRT. 26 patients were started on AC, 19 of whom have completed treatment. Two patients are still on AC, 2 (7.7%) had progressive disease, 2 (7.7%) died from toxicity, and in 1 (3.8%), treatment was discontinued because of toxicity. At a median follow-up duration of 30 months (range, 2-51 months), 17/26 are in CR (EFS - 65%) and 5/26 (19.2%) patients have relapsed/progressive disease. During treatment, grade III-IV anemia was observed in 17%, neutropenia in 54%, and thrombocytopenia in 26%. 92% of patients had anorexia, 100% had nausea/vomiting, 71% developed mucositis, 70% had grade II-III radiation dermatitis, and 94% had alopecia. 21% of patients had febrile neutropenia and 57% required G-CSF support. During adjuvant chemotherapy, hematologic toxicity (grade III-IV) was observed in 85%

Presented at SNO 2010

Metastatic medulloblastoma?

SIOP PNET 3 STUDY



Metastatic Medulloblastoma

Full dose craniospinal RT and chemotherapy

Authors & Year (study group)	Dates of Enrollment	M Stage (no. of patients)	PFS Rate (%)†	PFS (yrs)
Packer, et al., 1994	1983–1991	M+ (15)	67 ± 15	5
Bouffet, et al., 1994 (French M7)	1985–1988	M+ (23)	43	7
Yao, et al., 1997 (CCG 921)	1986–1992	M+ (90)	43 ± 7	5
Tarbell (POG 9031)	1990–1996	M+ (102)	61 ± 6	5
Kortmann, et al., 2000 (HIT 91)	1991–1997	M2/3 (46)	41 ± 7	5

From: Jakacki R. et al., JNS 2005

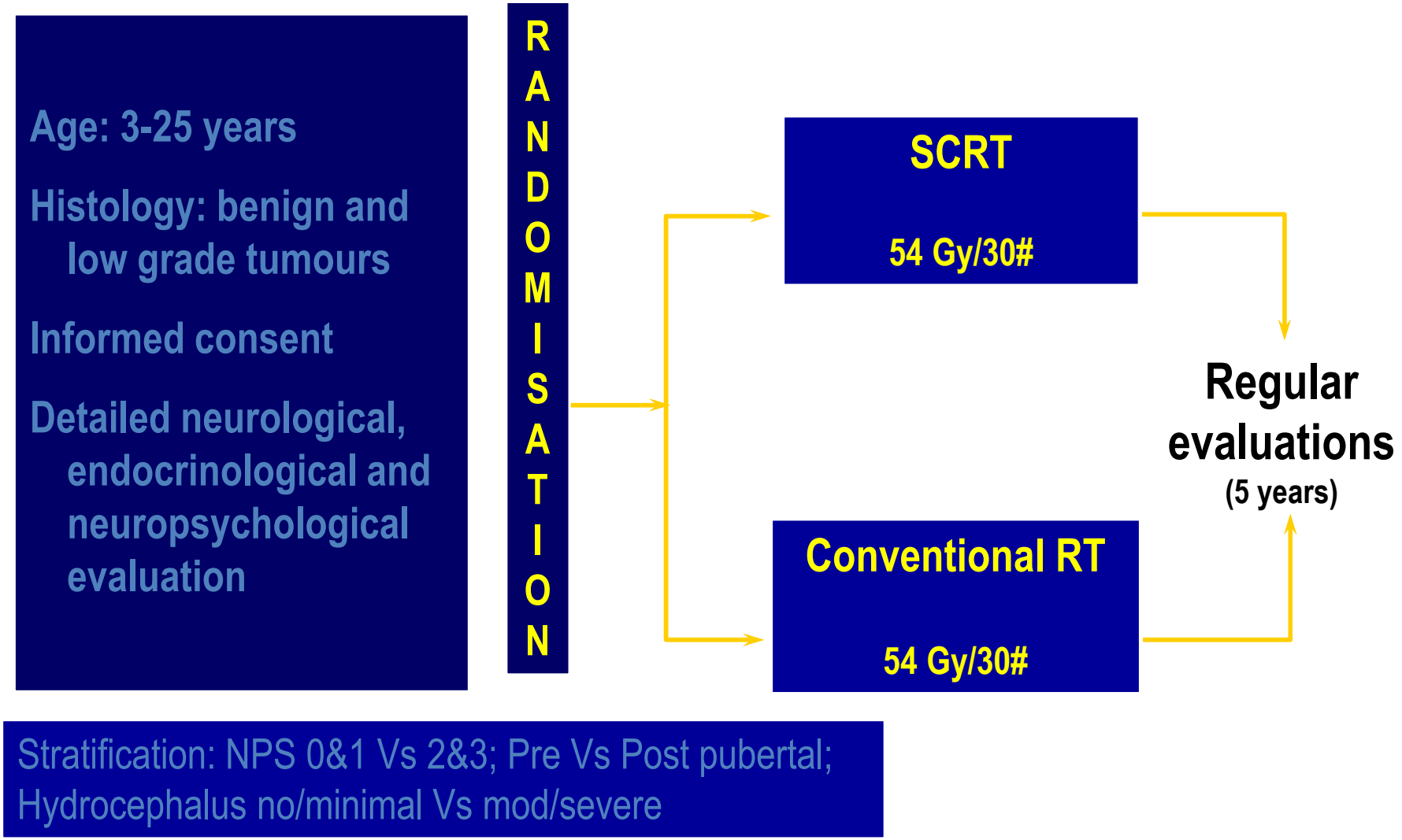
1 in 2 children likely to survive for 5 years even with metastatic disease

Medulloblastoma: in summary

- Common & radiosensitive childhood brain tumor
- Radiotherapy: An integral component of multi-modality management
- Significant long-term sequelae in survivors (dose & volume related)
- Favorable impact of reduction in radiotherapy dose & volume
- Quality of radiotherapy significantly impacts upon outcome
- Modifying fractionation provides a therapeutic window of gain
- Adding chemotherapy improves outcomes
- Combining these approaches may yield the most optimal therapy

SCRT trial: Schema & Design

Dr R Jalali (Principal Investigator)



FACTORS INFLUENCING NEUROCOGNITIVE OUTCOMES IN YOUNG PATIENTS WITH BENIGN AND LOW-GRADE BRAIN TUMORS TREATED WITH STEREOTACTIC CONFORMAL RADIOTHERAPY

RAKESH JALALI, M.D.,* INDRANIL MALLICK, M.D.,* DEBNARAYAN DUTTA, M.D.,* SAVITA GOSWAMI, M.SC.,† TEJPAL GUPTA, M.D.,* ANUSHEEL MUNSHI, M.D.,* DEEPAK DESHPANDE, PH.D.,‡ AND RAJIV SARIN, F.R.C.R.*

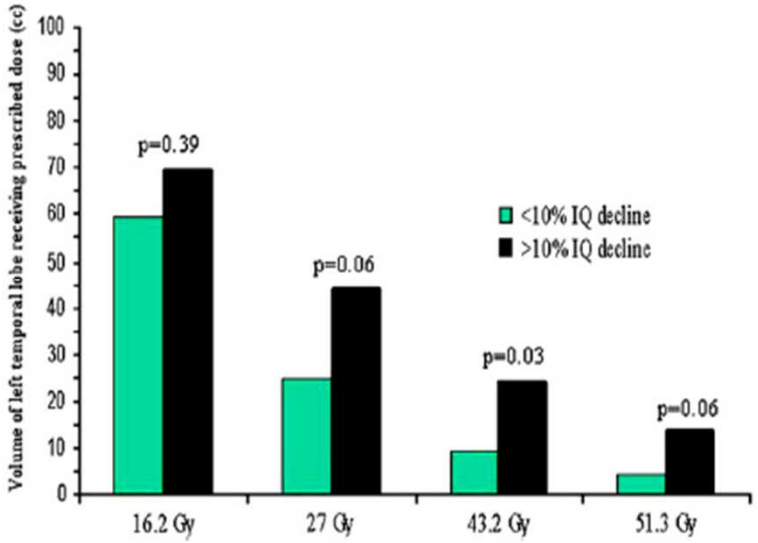


Fig. 1. Intelligence quotient (IQ) decline with respect to radiotherapy doses to left temporal lobe.

Table 4. Logistic regression using age and doses to different volumes of left temporal lobe in the causation of IQ decline in patients

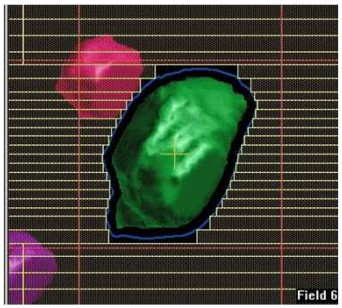
Variable	Odds ratio	*p* (95% confidence interval)
Age <15 y	13.58	0.041 (1.1–166.42)
13% temporal lobe receiving >43.2 Gy (80% of the prescribed dose)	7.57	0.048 (1.02–56.16)

Conclusion: Our prospectively collected dosimetric data show younger age and radiotherapy doses to left temporal lobe to be predictors of neurocognitive decline, and may well be used as possible dose constraints for high-precision radiotherapy planning.

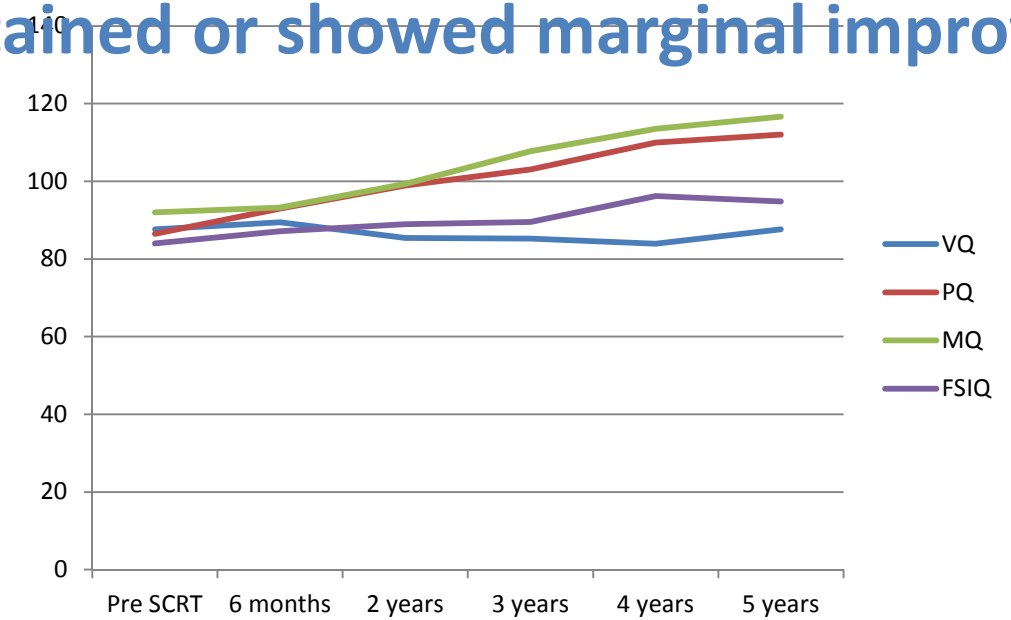
IJROBP, 2010

TMH Experience With Hippocamapal Dose And Effect On Neurocognition

- Hippcampus contouring done retrospectively in 50 patients accrued in the prospective TMH Stereotactic Conformal radiotherapy(SCRT) trial.
- Low grade gliomas and benign tumours in pediatric and young adults
- Carefully laid out RT protocol with image fusion of CT images with MRI images.
- RT dose of 54Gy/30Fractions given with very conservative margins(CTV to PTV = 2mm).
- Detailed Neurocognitive assessment done.
- No attempt had been made to give any dose constraints to the hippocampi during SCRT treatment.
- Correlation of various Hippocampal dosimetric parameters on neurocognition



IQ parameters over 5 year follow-up were maintained or showed marginal improvement



Normal value: 90-109

	Mean IQ level after SCRT					
IQ Parameters	**Baseline**	**6 months**	**2 year**	**3 year**	**4 year**	**5 year**
Verbal IQ	87.59	89.43	85.39	85.22	83.94	87.62
Performance IQ	86.53	93.00	98.89	102.50	109.50	112.28
Memory IQ	92.00	93.16	99.29	107.75	113.56	116.61
Global/Full-scale IQ	83.96	87.1	88.98	89.49	96.19	94.81

Left Hippocampus dose & percentage change in IQ at 5 years

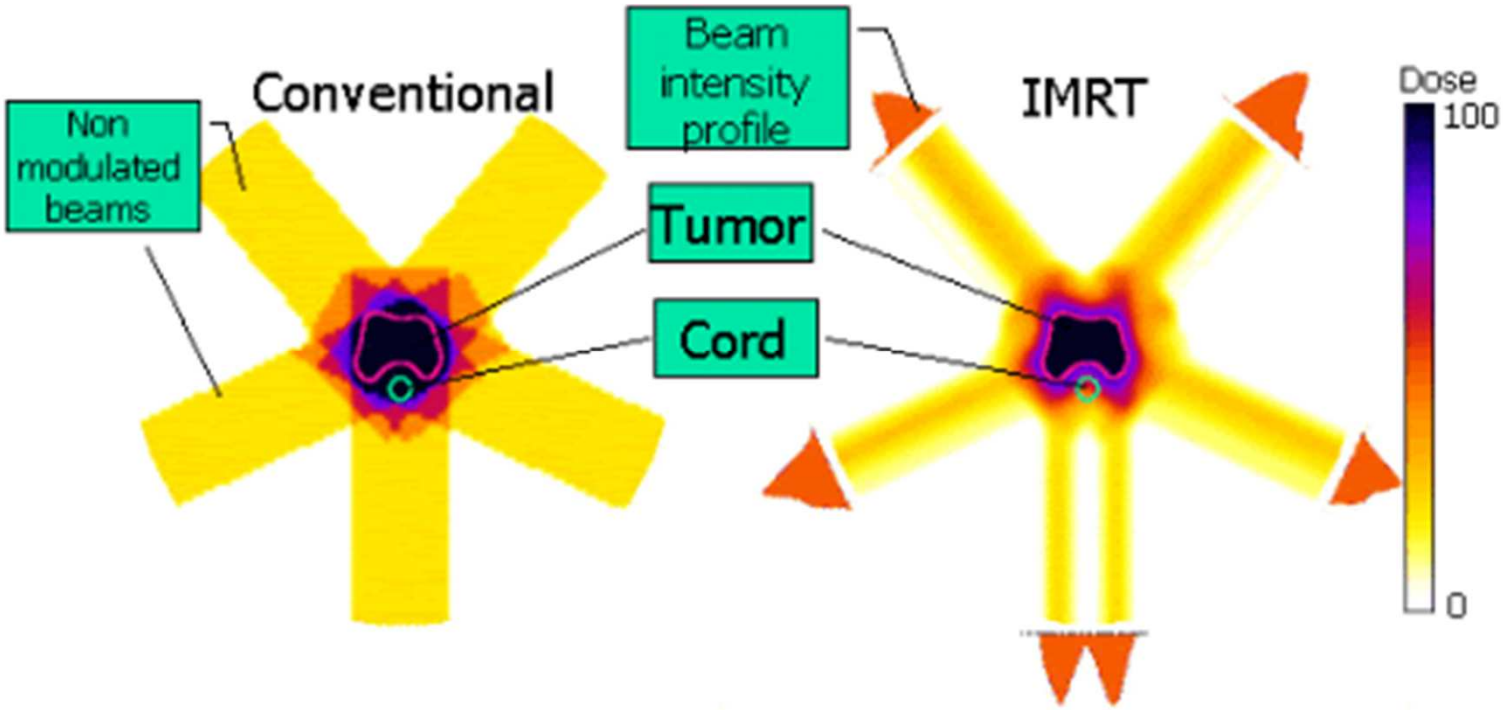
Logistic regression analysis, model fit

		5 year evaluation	
		Mean dose (Gy)	p-value*
FSIQ	>10%drop	31.0	**0.040***
	<10% drop	26.5	
VQ	>10%drop	32.0	1.00
	<10% drop	25.6	
PQ	>10%drop	32.0	**0.037***
	<10% drop	26.0	

Mean doses ≤30 Gy as a possible dose constraint cut off for IQ decline

IMRT: Really exciting technology

An advanced form of high-precision radiotherapy wherein the beam intensity is modulated to produce highly conformal dose distributions around target volumes with maximal avoidance of surrounding normal structures



High-precision radiotherapy for craniospinal irradiation: evaluation of three-dimensional conformal radiotherapy, intensity-modulated radiation therapy and helical TomoTherapy

[1]D S SHARMA, MSc, DipRP, [2]T GUPTA, MD, [3]R JALALI, MD, [2]Z MASTER, MS, [2]R D PHURAILATPAM, MSc, DipRP and [2]R SARIN, MD, FRCR

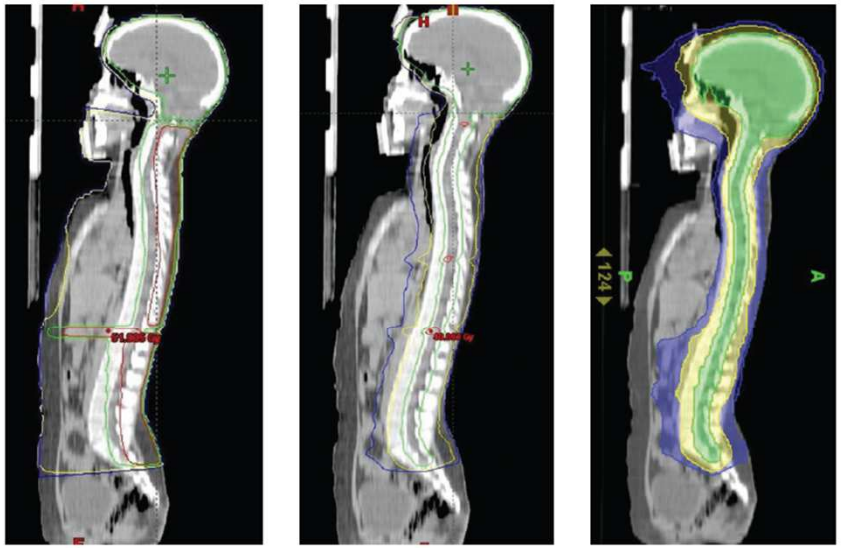


Table 2. Maximum (D_{max}) and mean (D_{mean}) doses to various organs at risk when prescribing 35 Gy to the whole craniospinal axis in the three different treatment techniques. All values are the mean of four patients

	D_{max} in Gy (SD)			D_{mean} in Gy (SD)		
Organs at risk	3DCRT	IMRT_LA	IMRT_Tomo	3DCRT	IMRT_LA	IMRT_Tomo
Left eye	36.3 (0.5)	36.3 (0.5)	18.9 (2.5)	21.3 (4.9)	21.3 (4.9)	8.1 (0.7)
Right eye	36.3 (1.7)	36.3 (1.7)	19.1 (1.3)	19.4 (6.7)	19.4 (6.7)	8.2 (0.6)
Heart	33.1 (1.8)	17.1 (4.2)	11.9 (1.8)	17.8 (2.1)	7.5 (1.0)	5.0 (1.0)
Right lung	35.7 (2.5)	24.5 (3.4)	27.5 (2.5)	4.8 (2.2)	5.2 (1.4)	6.7 (7.3)
Left lung	32.2 (3.2)	26.7 (1.6)	27.0 (3.2)	5.3 (2.4)	5.7 (0.9)	6.7 (3.8)
Thyroid	32.9 (1.9)	17.4 (6.3)	12.0 (1.9)	30.5 (2.5)	12.2 (4.8)	8.3 (2.9)
Right kidney	28.1 (5.9)	17.7 (2.4)	12.2 (5.9)	3.1 (1.7)	5.3 (1.7)	4.5 (0.6)
Left kidney	29.2 (10.8)	19.2 (2.9)	13.7 (10.8)	3.2 (1.5)	5.7 (1.1)	4.5 (0.5)
Liver	31.0 (1.4)	17.9 (2.2)	14.8 (1.4)	7.2 (1.4)	5.3 (0.6)	3.9 (0.6)
Oesophagus	33.1 (2.2)	27.9 (1.5)	17.1 (2.2)	32.7 (2.3)	18.7 (1.8)	9.1 (0.3)

Table 1. Dose–volume indices for the three different treatment techniques. All values represent the mean of four patients

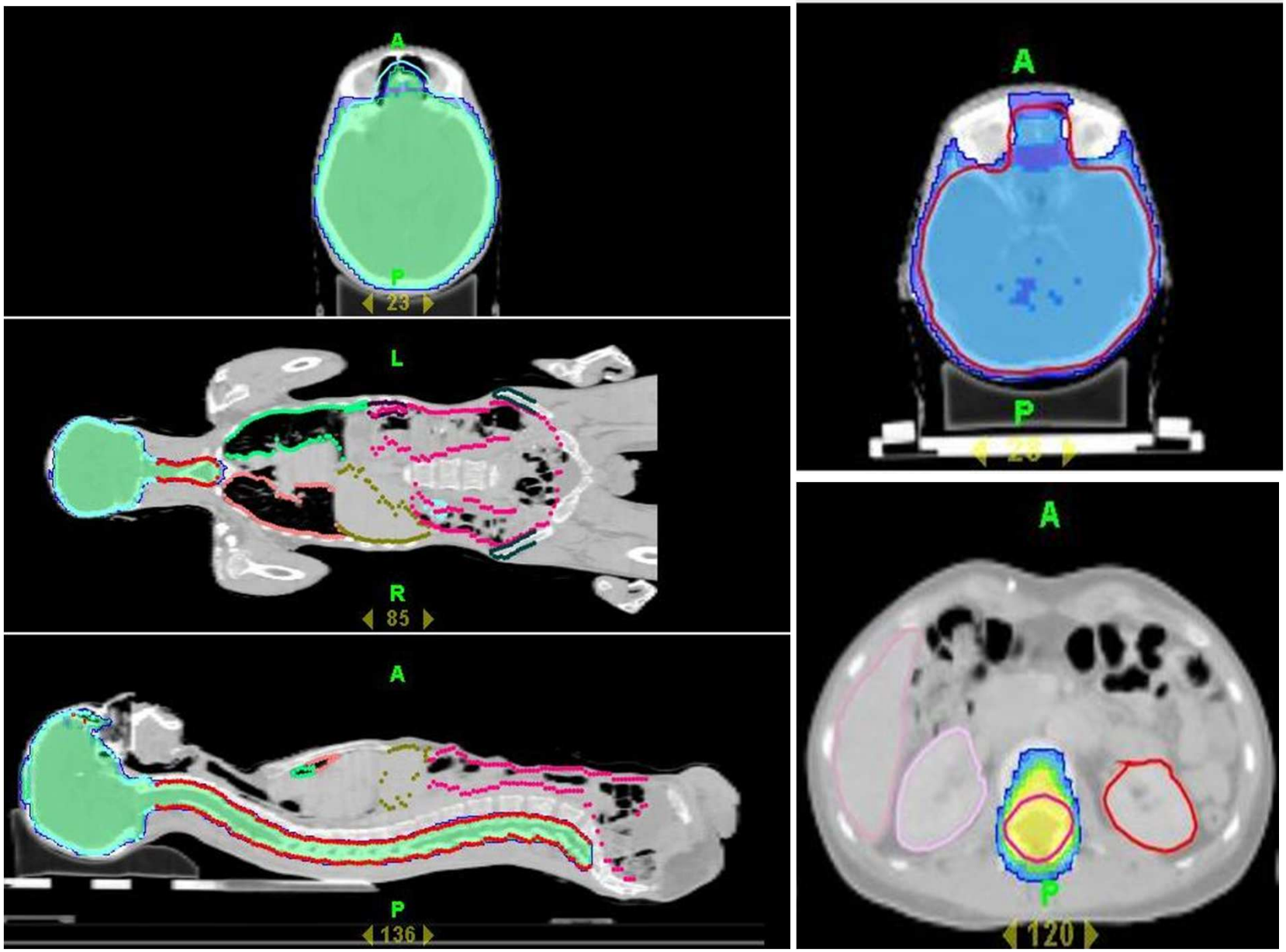
	PTV_Brain			PTV_Spine		
Parameters	3DCRT	IMRT_LA	IMRT_Tomo	3DCRT	IMRT_LA	IMRT_Tomo
D_{max} (SD)	37.4 (0.2)	38.6 (1.3)	38.5 (0.5)	42.3 (1.5)	39.2 (1.2)	36.9 (0.3)
D_{min} (SD)	18.5 (6.5)	22.6 (2.0)	18.5 (5.3)	31.8 (1.7)	30.0 (3.4)	31.1 (2.3)
D_{mean} (SD)	35.5 (0.1)	35.5 (0.1)	35.9 (0.2)	37.0 (0.8)	36.3 (0.8)	35.9 (0.2)
$V_{95\%}$ (SD)	98.2 (0.6)	98.3 (0.7)	99.3 (0.4)	99.5 (0.2)	98.8 (1.1)	99.9 (0.2)
$V_{107\%}$ (SD)	0.0 (0.0)	0.1 (0.1)	0.3 (0.1)	34.6 (16.4)	3.0 (1.4)	0.2 (0.5)
DHI (SD)	0.9 (0.0)	0.9 (0.0)	1.0 (0.0)	0.8 (0.0)	0.9 (0.0)	1.0 (0.0)
V_{pi} (SD)	1713 (79)	1715 (89)	1664 (200)	630 (231)	171 (52)	233 (74)
CI (SD)	0.9 (0.1)	0.9 (0.1)	0.9 (0.0)	0.2 (0.0)	0.8 (0.1)	0.6 (0.1)

Br J Radiol 2009

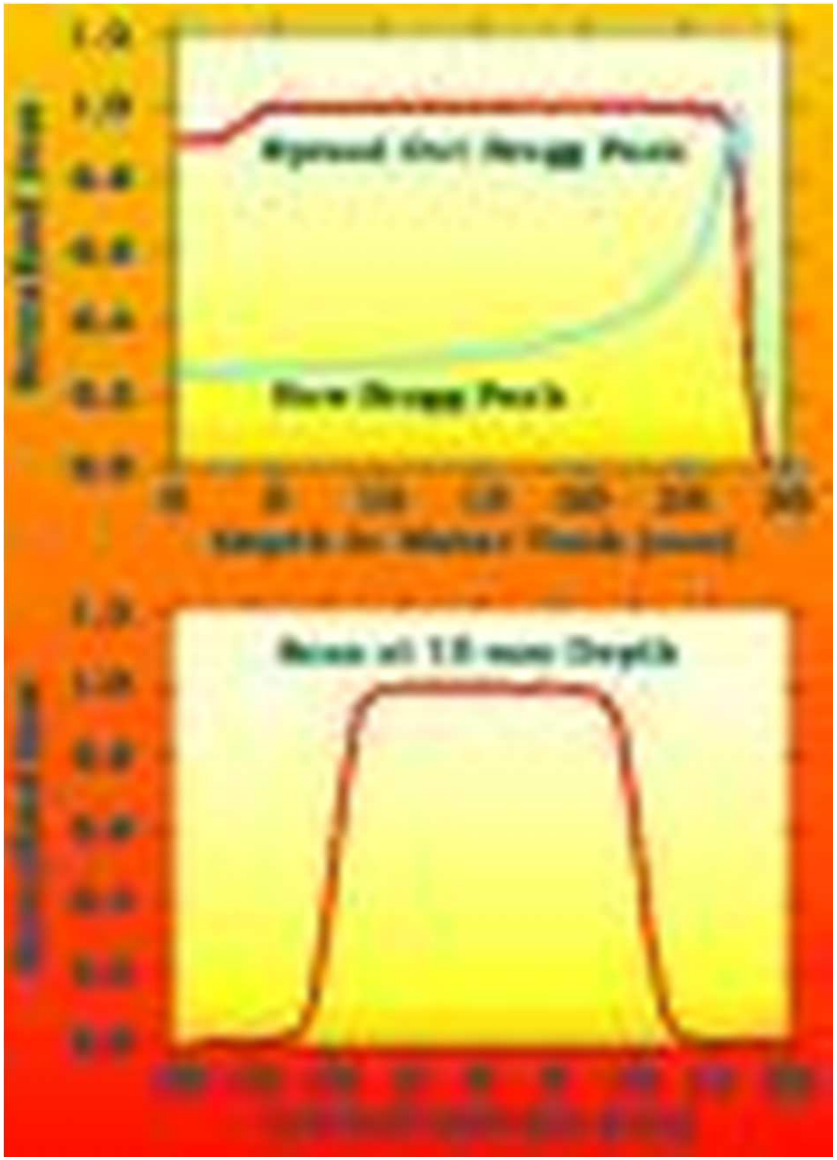
Challenges in immobilization and CT-simulation

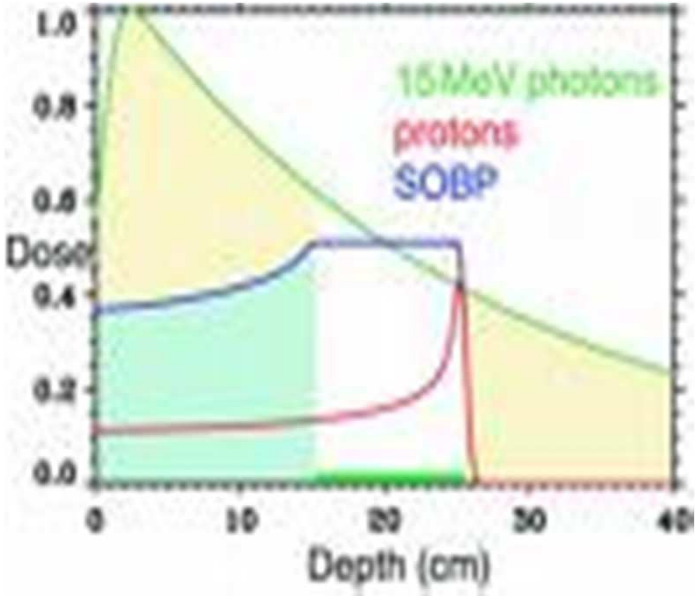
- Difficulty in having reproducible whole-body immobolization & alignment
- Long vacuum-cradle with base-plate, thermoplastic mask, & knee rest
- Leakage of the vacuum-cradle (necessitating repeat CT-simulation)
- Restricted gantry bore (60 cm) of CT-simulator
- Contouring almost every organ in the body

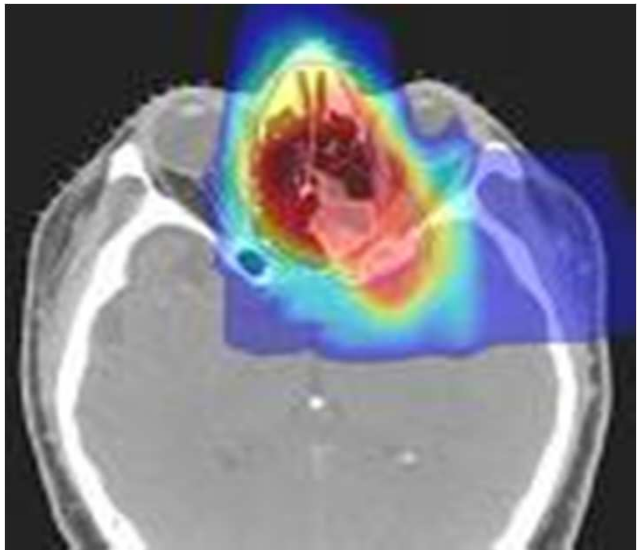
Excellent PTV coverage & conformal avoidance of OARs



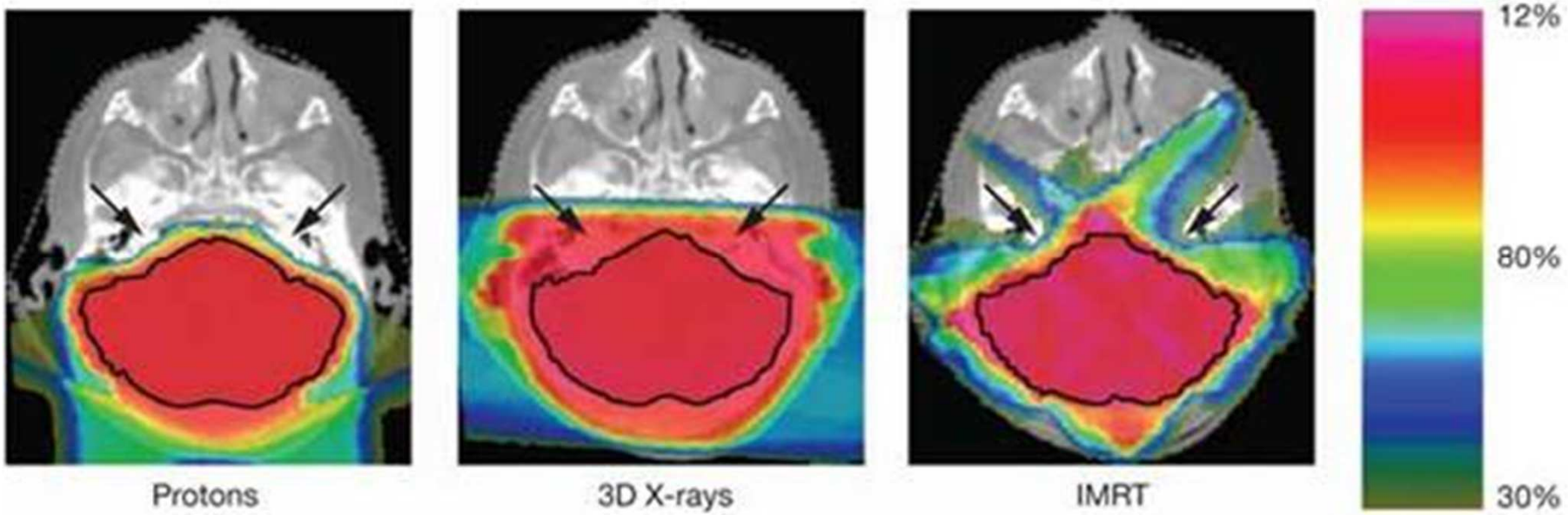
Proton beam radiotherapy for pediatric brain tumors

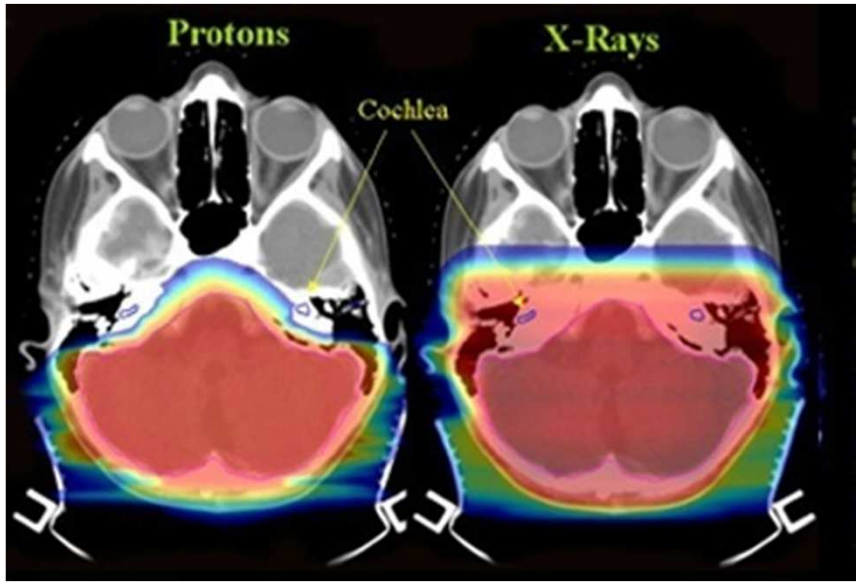


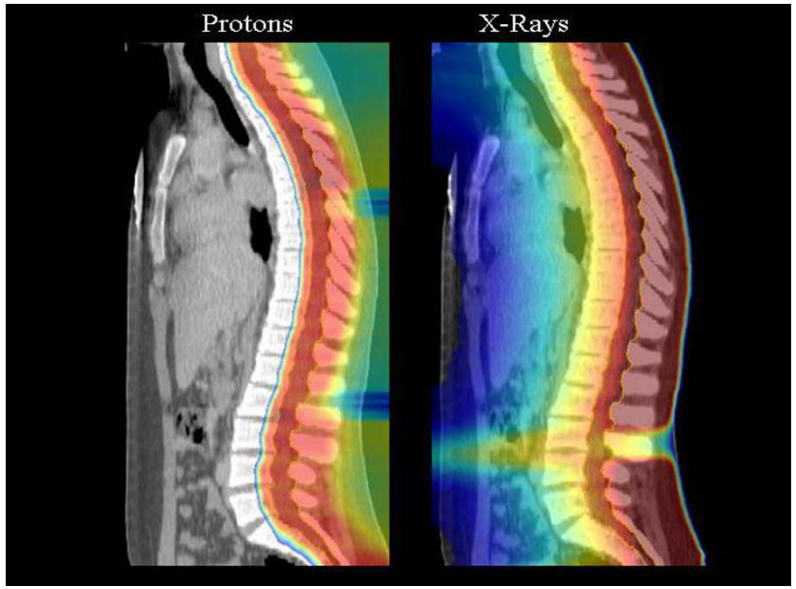




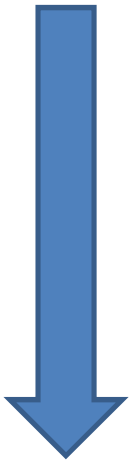
Proton-beam radiotherapy in medulloblastoma







What next in childhood brain tumours



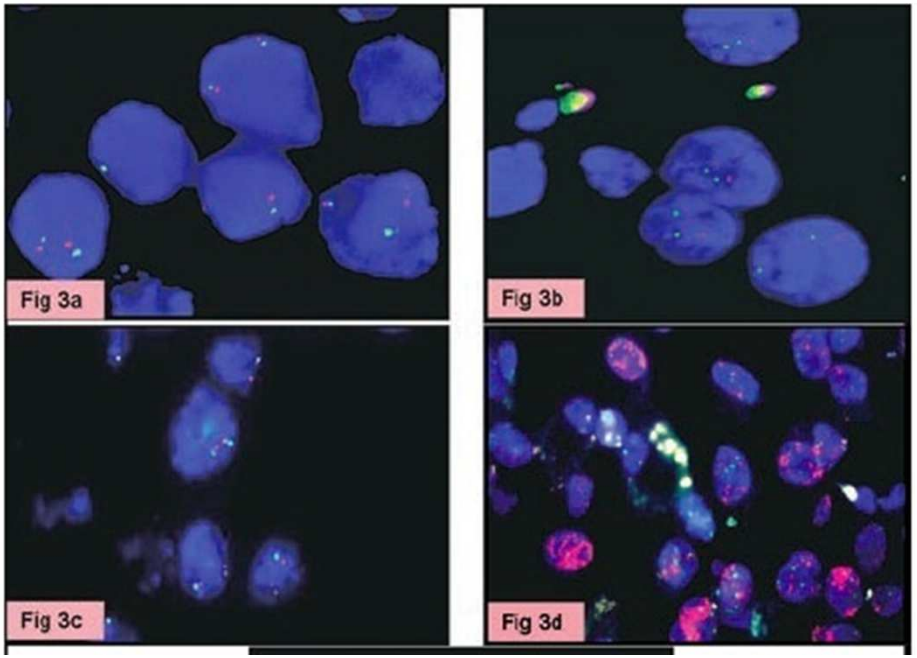
Back to Biology:

Newer and future perspectives

Pediatric glioblastomas: A histopathological and molecular genetic study

Vaishali Suri, Prasenjit Das, Ayushi Jain, Mehar Chand Sharma, Sachin Anil Borkar, Ashish Suri, Deepak Gupta, and Chitra Sarkar

Departments of Pathology and Neurosurgery, All India Institute of Medical Sciences, New Delhi, India



30 pts with pediatric GBM analysed

p53 overexpression: Common: 63%

EGFR protein overexpression: 23%

EGFR gene amplification: Rare (5.5%)

PTEN gene deletion: Rare (5.5%)

Pediatric glioblastomas are different from adult counterparts?

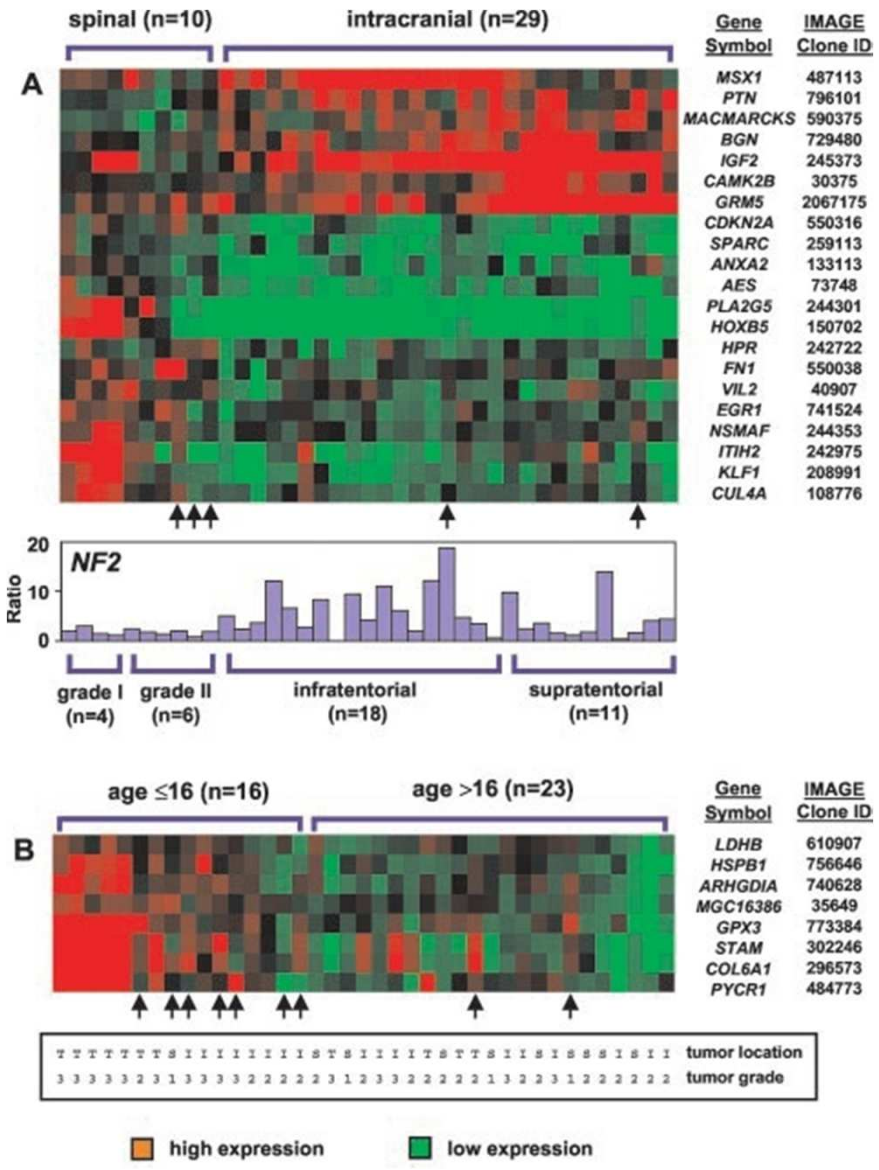
Neuro-Oncol 2009

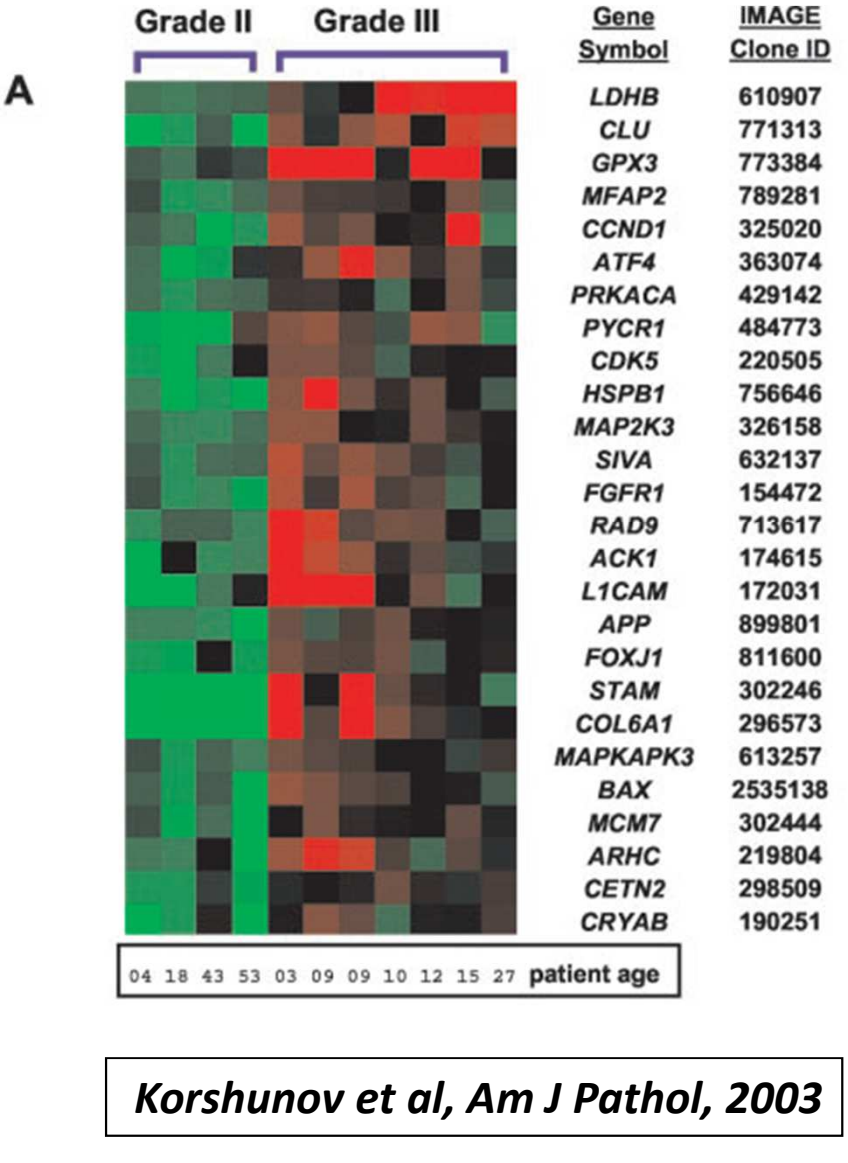
Key molecular differences between childhood GBM and adult GBM

Characteristic	Pediatric GBM (TMH)	Adult primary GBM	Adult secondary GBM
P53 mutation	74 %	25 - 30 %	60 - 65%
MGMT methylation	37 %	36%	75%
EGFR amplification	0%	35 - 50%	8%
IDH-1 mutation	4 %	10%	85%

Under revisions in neuro Oncology Practise

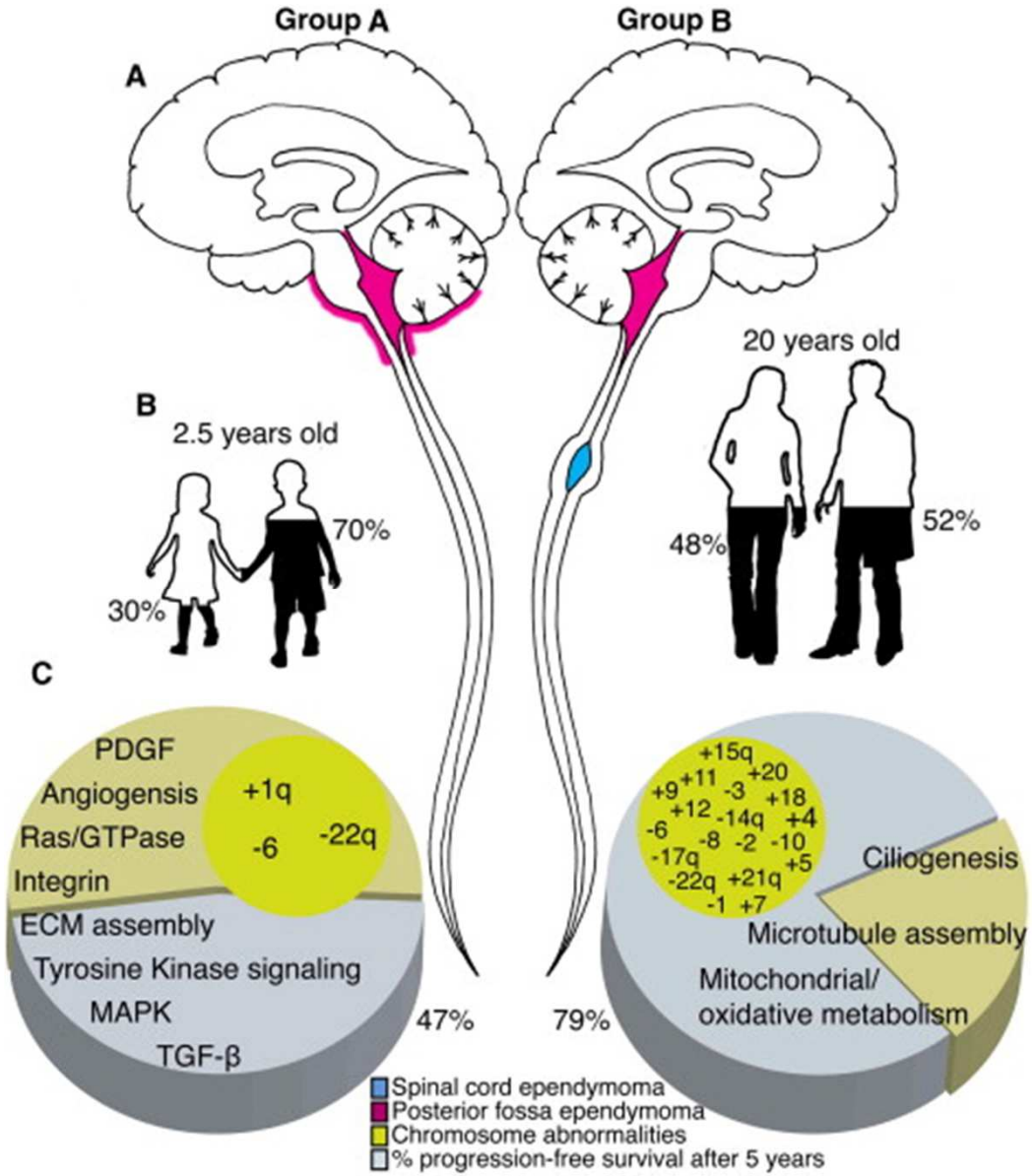
Gene expression patterns in ependymomas correlate with location, age, and grade





Korshunov et al, Am J Pathol, 2003

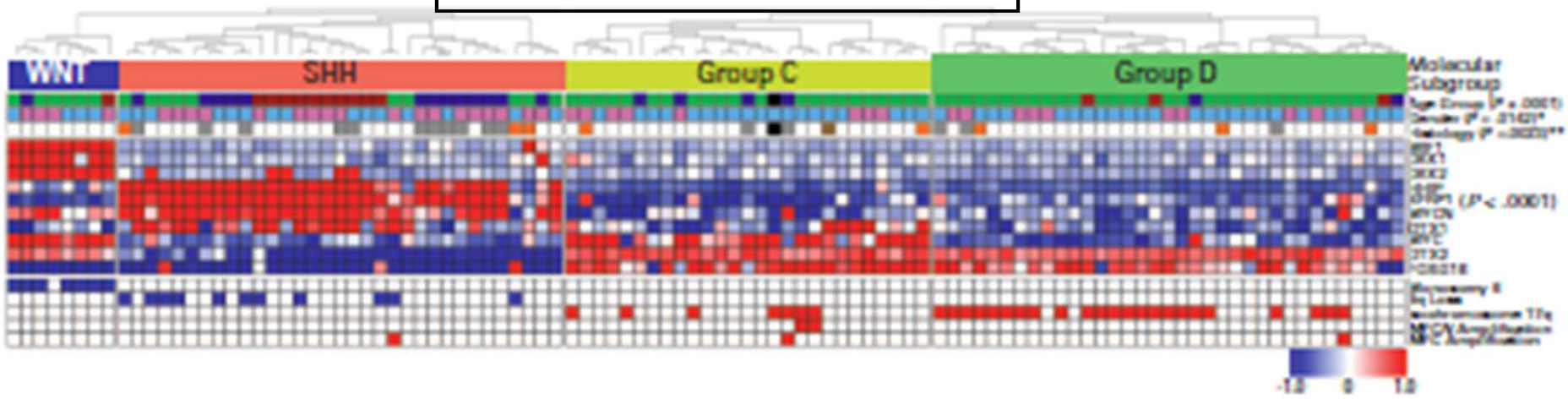
Molecular subclassification of Ependymomas

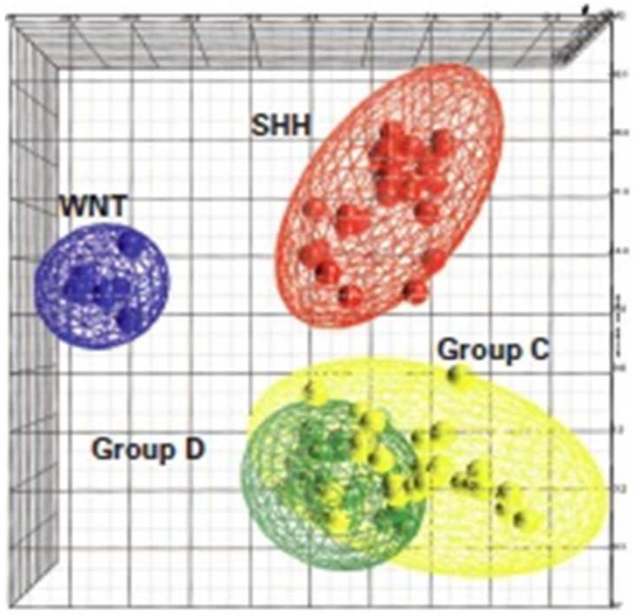


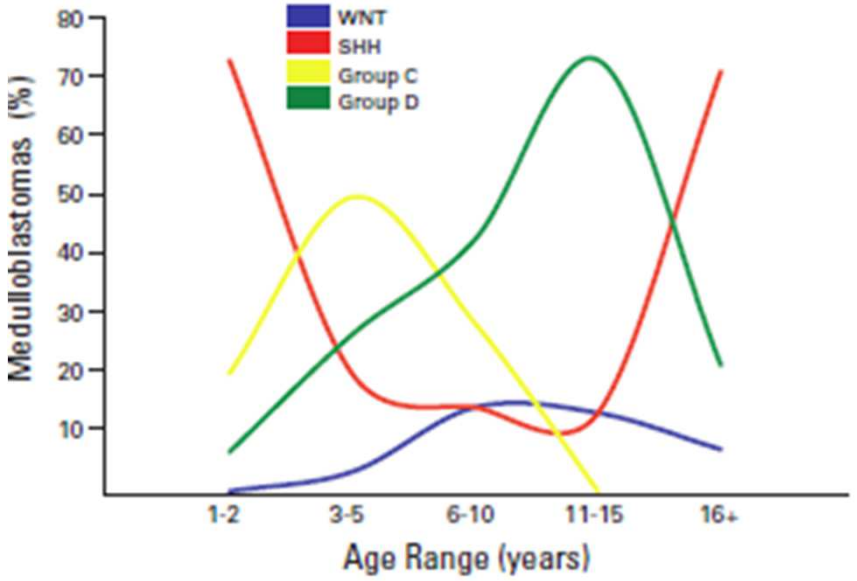
Tenley C. Archer, Scott L. Pomeroy,cell 2011

Medulloblastoma comprises four distinct molecular variants

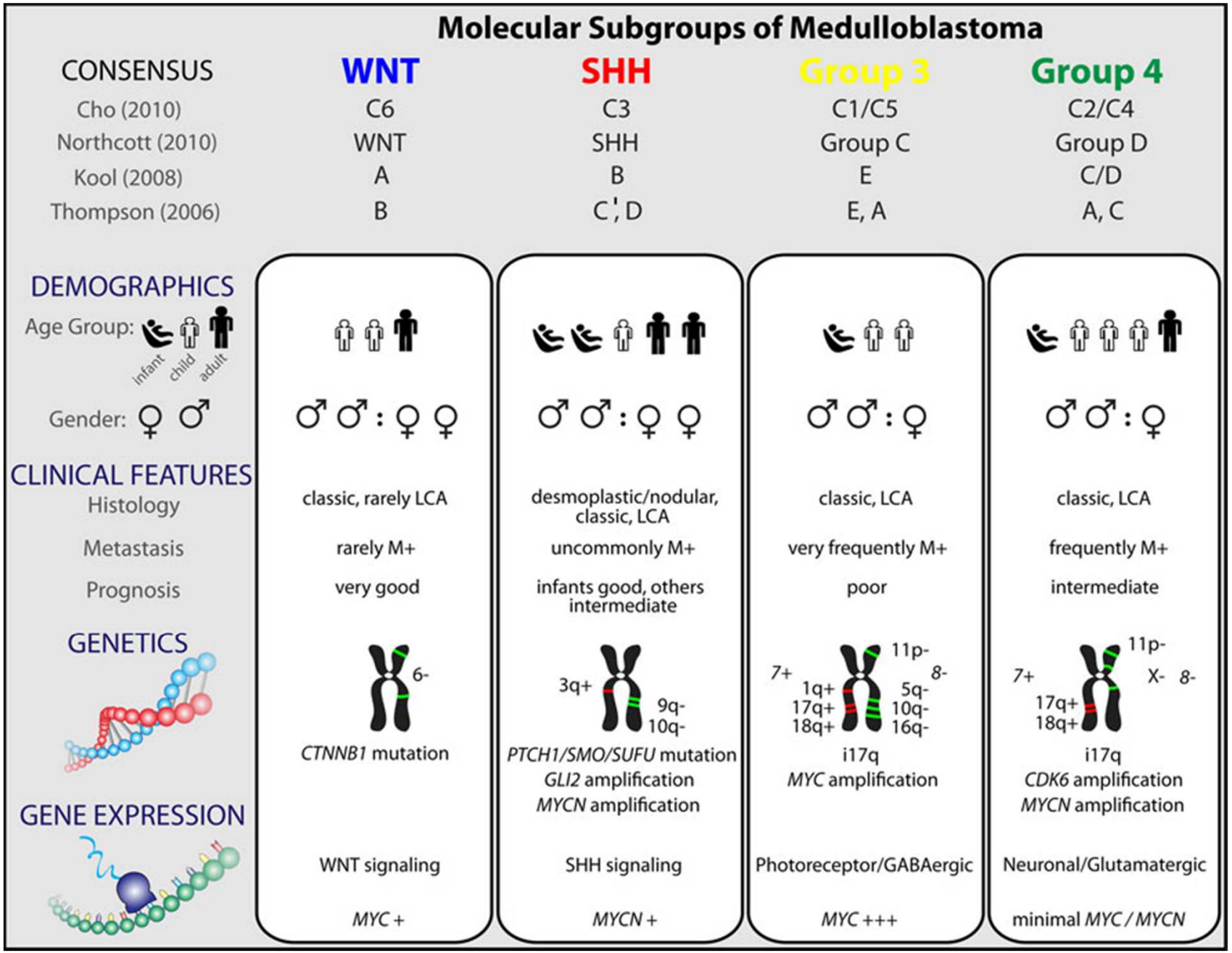
Northcott et al, JCO 2010







Time for molecular classification & biological risk-stratification



Taylor M, Acta Neuropathologica,2012

Clinical trials in Medulloblastomas incorporating the molecular subtypes

A Clinical and Molecular Risk-Directed Therapy for Newly Diagnosed Medulloblastoma

This study is currently recruiting participants. (see Contacts and Locations)

Verified March 2015 by St. Jude Children's Research Hospital

Sponsor:
St. Jude Children's Research Hospital

ClinicalTrials.gov Identifier:
NCT01878617

First received: June 10, 2013
Last updated: April 6, 2015
Last verified: March 2015

HART with concurrent carboplatin in high risk Medulloblastomas

TMH Protocol
PI: Dr Tejpal Gupta

Awaiting IRB approval

Thank You