Pediatric gliomas with special emphasis on RT

Durable local control
Survival

Quality of life

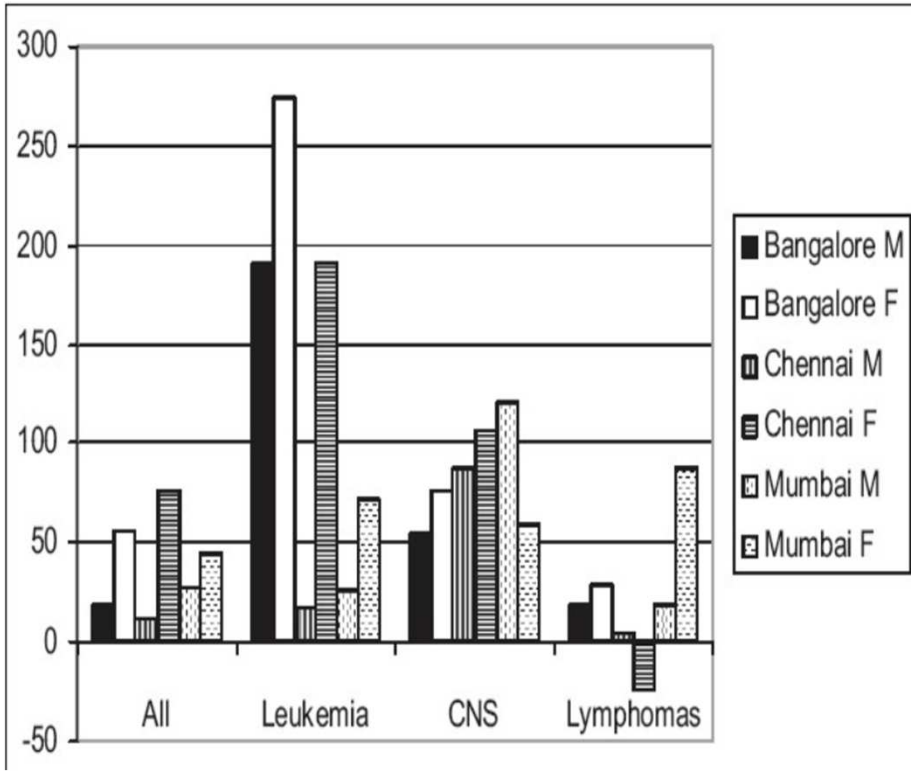
Multidisciplinary approach

Challenges in children….

- Broad spectrum of complex diseases
  - Own biology
  - Own natural history
- Optimal and ‘creative’ integration
  - Understanding disease
  - Understanding adverse consequences
- Not only to enter the realm
  - But also be successful

Incidence

Cancer	Incidence
Leukemias	32%
CNS Tumors	18%
Astrocytoma	10%
Medulloblastomas	4%
Ependymomas	2%
Others	2%
Lymphoma	13%
BST	12%
Neuroblastoma	8%
Wilms	6%
Retinoblastomas	3%
Hepatic	1%
Germ cell + others	7%



Rare compared to adult cancers

Nearly 1 in 5 located in the CNS

Common brain tumors in children
Relative Incidence

Supratentorial	50 – 55%
Astrocytoma	23%
Malignant gliomas	6%
Craniopharyngioma	6%
PNET & others	4%
Pineal/GCT	4%
Ependymoma	3%
Oligodendroglioma	2%
Others [CPCs, gangliogliomas, etc]	2%

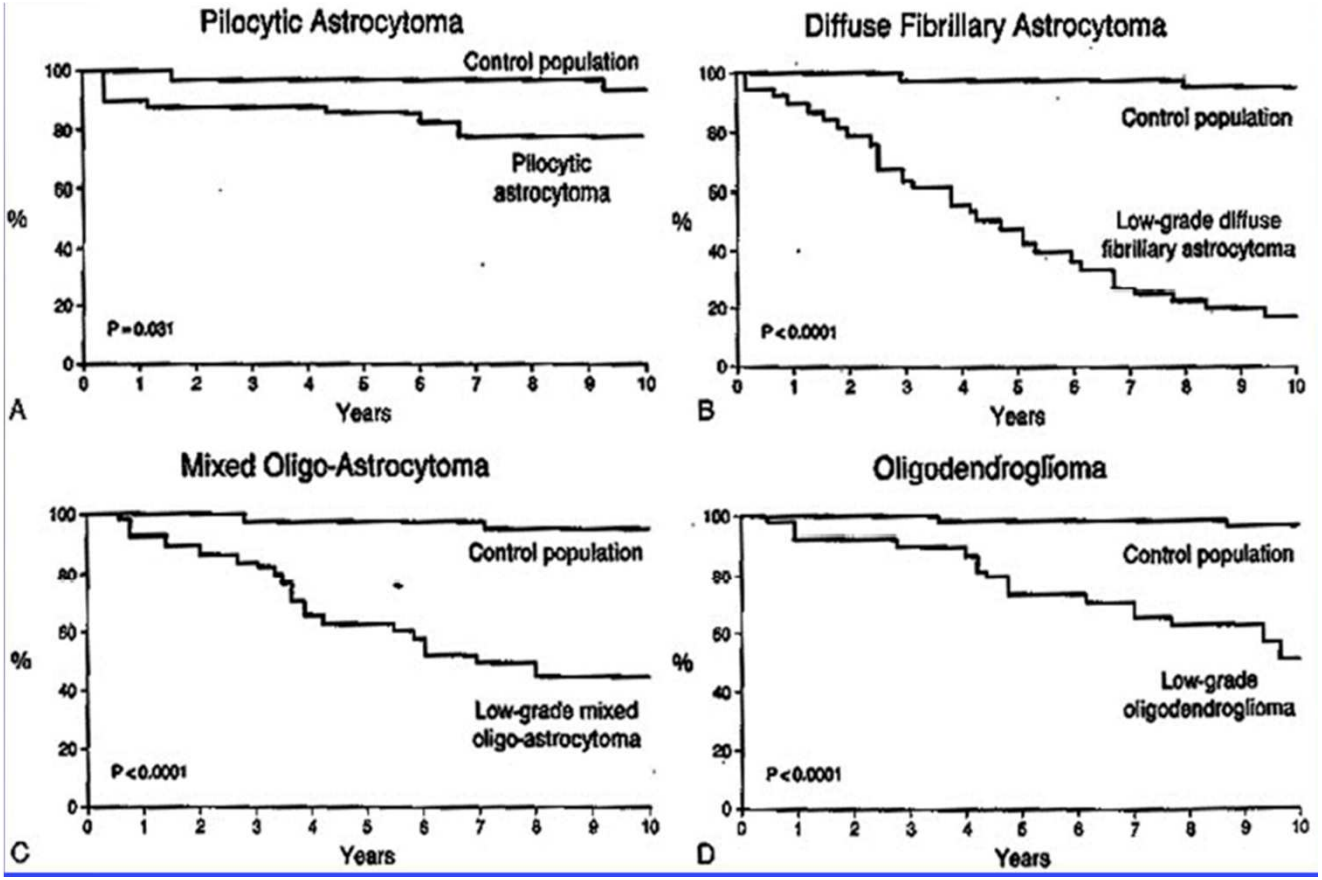
Syndrome	Location	Histiotype
NF 1	NF1 (17q11)	Gliomas
NF 2	NF2 (22q12)	AN, meningiomas
Tuberous sclerosis	TSC1 (9q34) TSC2 (16p13)	SEGA
Li-Fraumeni	TP53 (17p13)	Medulloblastoma Astrocytoma
Turcot	APC hMSH2 Others	Medulloblastoma High grade glioma
Retinoblastoma I	RB1 (13q14)	Pineoblastoma

Etiology
Mostly sporadic
Neurocutaneous and other genetic syndromes
Radiation induced meningiomas in later life

Louis et al. WHO classification 2007
Mulvihill et al. NEJM 1985; 312:1569-1570

Pediatric low grade gliomas
Diverse range

- Largely 3 groups
  - Pilocytic astrocytomas
  - DNET, PXA, SEGA, gangliogliomas
  - Astrocytoma, ODG (WHO Grade II), mixed



Clinical presentation

- Symptoms over extended time intervals
- Seizures
- Lateralizing neurologic signs
  - thalamic region tumors
  - increased intracranial pressure (i.e., headaches, vomiting)
- Suprasellar tumors typically occlude the foramen of Monro
  - Visual signs
  - Endocrine abnormalities
    - Midline suprasellar lesions
    - Diencephalic syndrome
- Pineal region tumors
  - Hydrocephalus by compressing the aqueduct of Sylvius
  - Parinaud syndrome

Low grade supratentorial astrocytomas

- Diverse group
- Diencephalon
  - Commonest site
- Management
  - variable and depends on
  - tumor location
  - patient age
  - presence of a genetic mutation
  - physician and parental preference
- Outcomes favorable

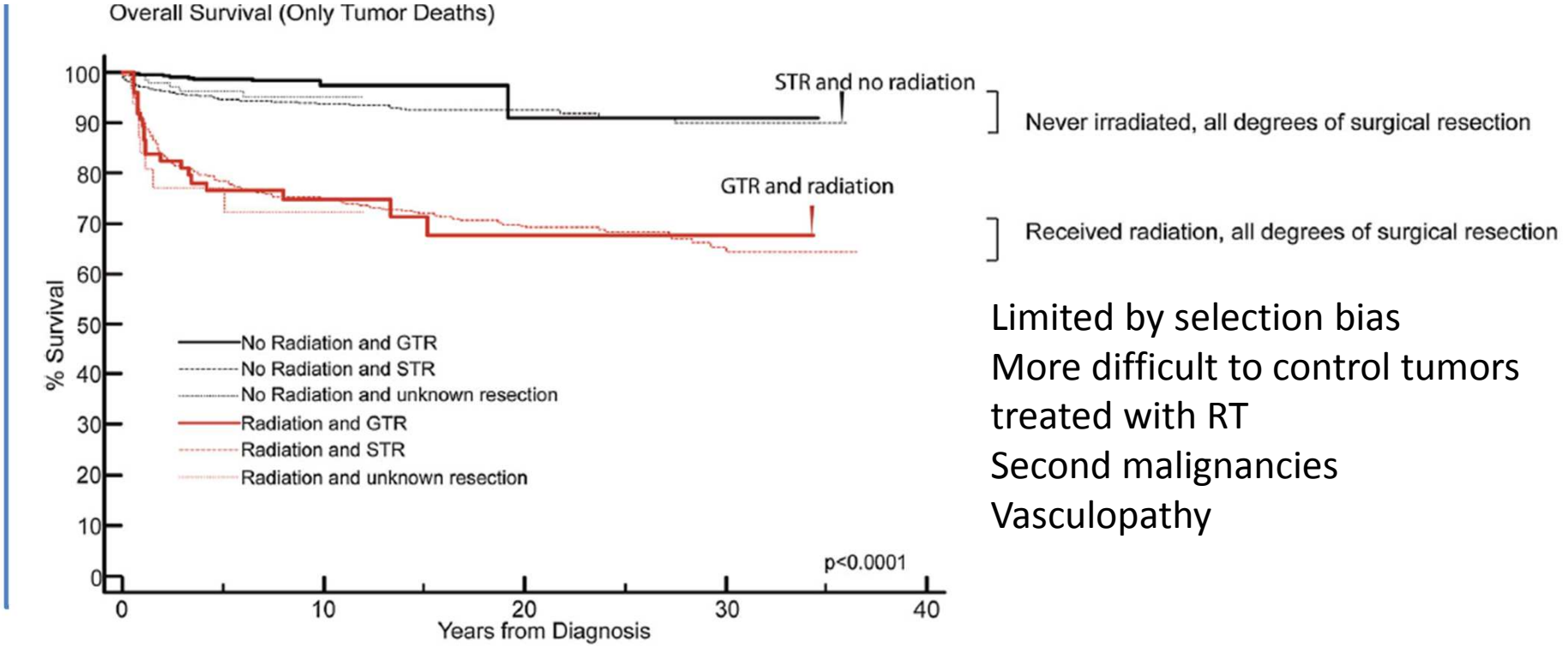
- Baseline examination
- Bloods
- Diagnostic imaging
  - Isodense on CT
  - Isointense on T1 MR
  - Hyperintense on T2 MR
  - JPAs enhance briskly, others do not
  - Scattered calcifications
  - Tumor cysts may be seen
- Post gadolinium T2 FLAIR most optimal sequence for voluming
- Ophthalmic/ endocrine/neuropsychiatric evaluations
- Any other

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

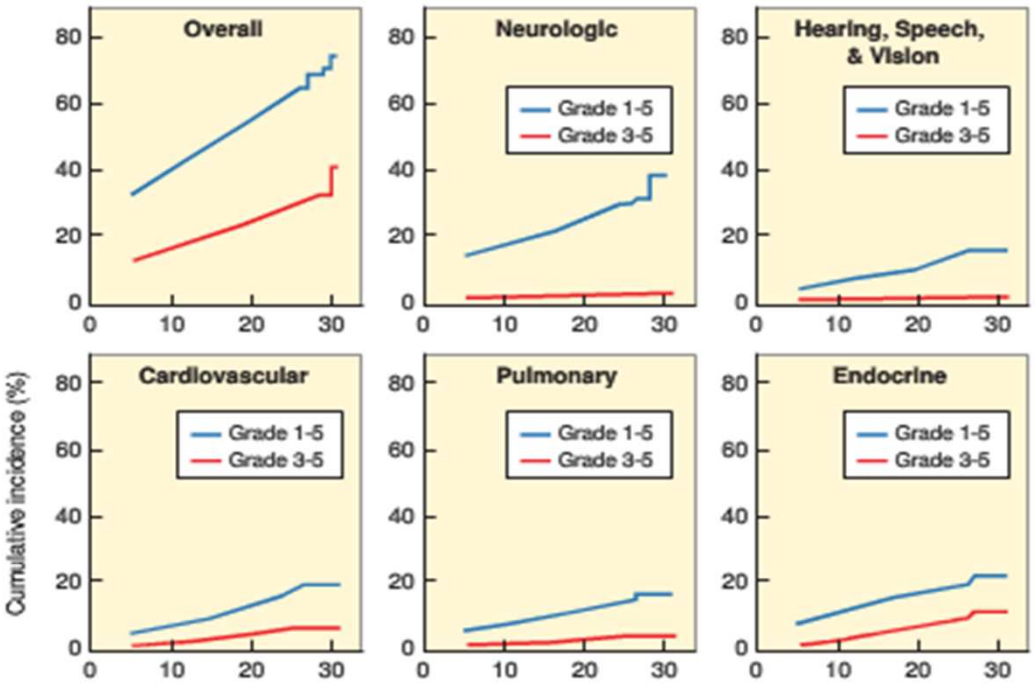
Outcomes

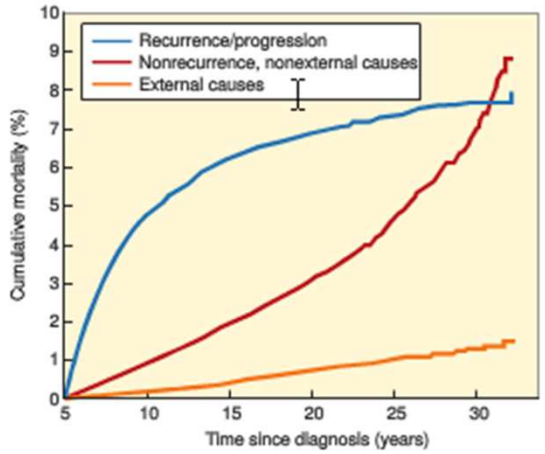
	Death due to disease		Death from non-disease causes	
Factor (reference level)	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Beam radiation, with or without implants or isotopes (no radiation)	3.9 (3.0, 4.9)	<0.0001	2.4 (1.4, 3.9)	0.0006
Degree of radiation unknown (no radiation)	3.1 (1.7, 5.8)	0.0003	NA	1.0
Primary site (cerebellum)	2.3 (1.6, 3.2)	<0.0001	NA	1.0
Histology group (pilocytic astrocytoma)	2.2 (1.7, 2.8)	<0.0001	NA	0.05
Age of diagnosis (≥2 years old)	2.0 (1.5, 2.8)	<0.0001	2.2 (1.1, 4.5)	0.03
Subtotal resection, biopsy or no resection (total resection)	1.5 (1.01, 2.1)	0.04	3.0 (1.1, 8.6)	0.04

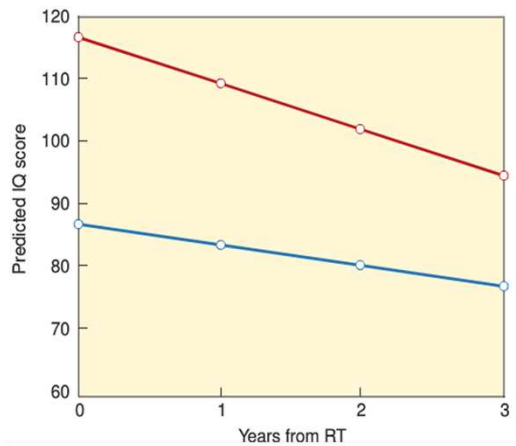


Limited by selection bias
More difficult to control tumors treated with RT
Second malignancies
Vasculopathy

Issues in survivors…





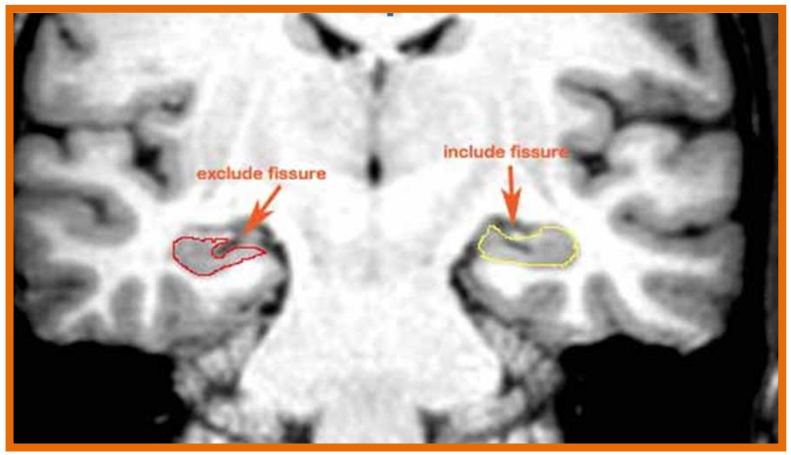


A growing population

CURE = Not merely absence of disease

Provide 'functional cure'

Minimize need for support



Treatment[s] and the Team

- Surgery – Frequently cannot be entirely removed
- Radiation – Frequently employed alone or in combination
  - Late effects may be limited by conformity
- Chemotherapy – Cannot eliminate all tumor cells

  when used alone and sensitivity varies

Therapy
Surgery

- Amenable to resection
- Surgery – first & sole treatment
- Incidence of GTR – 90%
- Low recurrence rates
- CCG and POG
- 5 yr PFS after primary surgery - 92%
  - 95-100% for JPAs and gangliogliomas
  - 80% for grade II diffuse astrocytomas
- Eloquent cortex: decompression
- Location in diencephalon
  - Technically limited by deep location
  - Eloquent area
- Contemporary series
  - Reporting successful resection
- Occasional resection of diencephalic JPA
- CCG-POG study
  - PFS after surgery alone 50-60%
  - Wisoff et al. *Neurosurgery,2009*

Chemotherapy

- Been used with increasing frequency as a strategy to delay or avoid RT
  - Studied primarily in centrally located tumors in younger patients not amenable to resection
  - Ideal age – controversial
- COG looks at 10 years for trial eligibility for initial chemo
- Carboplatin and vincristine
  - First line therapy
  - Favorable control rates
  - Absence of serious toxicity
- Decision to proceed with chemotherapy or irradiation
  - Patient age
  - Clinical presentation
  - Multidisciplinary decision
  - Weighing risks and benefits with the family
- Possible radiation volumes versus chemotherapy as initial treatment
  - No confirmation that rate and durabilty of disease control following RT are independent of prior chemotherapy

Chemotherapy

- Chemotherapy - Carboplatin + VCR
  - for very young children to avoid/defer RT
  - Objective response rate (CR+PR): 42%
  - 5Yr PFS: 34%; OS: 89%
  - 5Yr RT free survival rate: 61% (French prospective study)
- RT – large residual, and/or progressive tumors

Radiation Therapy

- Established and effective
- Durable tumor response and disease control
- Pollack et al
  - 10 years after RT for incompletely resected hemispheric astrocytomas
  - PFS: 82% with RT vs 42% with surgery alone
  - No difference in OS
- Merchant et al, Phase II
  - EFS: 87% and 74% at 5y and 10y for 3DCRT with MR defined volumes
  - 90% OS at 10y

- Decreased volume of normal brain exposed to moderate or high doses of RT may help decrease serious late effects
- Accurate delineation
  - Addressing white matter tracts
  - Standard margin 10 mm
  - **Suggestion** that 5 mm margin in well demarcated lesions should be accurate when multimodality imaging is incorporated

Current indications for RT after near total excision

- Symptoms or signs that might improve with RT
- Postsurgical progression in a location not amenable to definitive second resection

Radiation Therapy

- Large CCG-POG low grade trial suggest that a significant number remain indolent for 3-5 years
  - PFS at 5 years: 55% after near total resection
  - Decision to observe children with residual astrocytoma should involve all specialties indicating the obligation to follow up and imaging
- RT can be initiated at progression
- Balances efficacy versus potential toxicity

- JPAs predominate in hypothalamic and OPT
  - Prolonged PFS after RT alone – reflects both indolence and efficacy
  - Survival > 80% at 10 y after RT are common
- In thalamic astrocytomas, pilocytic histology is less prevalent
  - 10 y survivals: 33-60%
- Gliomatosis cerebri or bithalamic astrocytomas
  - May represent supratentorial counterparts of infiltrating pontine astrocytomas
  - Progression often apparent after 1 year

Radiation Therapy

Volume

- Fusion of MRI with CT
- Define CTV as 1 cm anatomic expansion
  - Prospective study at St Jude's dearth of marginal recurrences with this expansion
  - Additional 3-5mm for PTV
  - Careful review of all neuroimaging
  - Shrinking fields not typically used
- Assess cyst changes during treatment
- Tumors with subarachnoid seeding need craniospinal irradiation

Dosage

- Little definitive dose-response data specific for pediatric low grade gliomas
- Shaw et al
  - Advantage at doses > 53gy in conventional fractionation
  - Ironic that doses have been tested in adult low grade gliomas [EORTC,NCCTG,RTOG,ECOG]
- 50 – 54 Gy, conventional fractionation, optimal conformality
- Same dose level recommended throughout the pediatric age range

Radiation Therapy

Technique

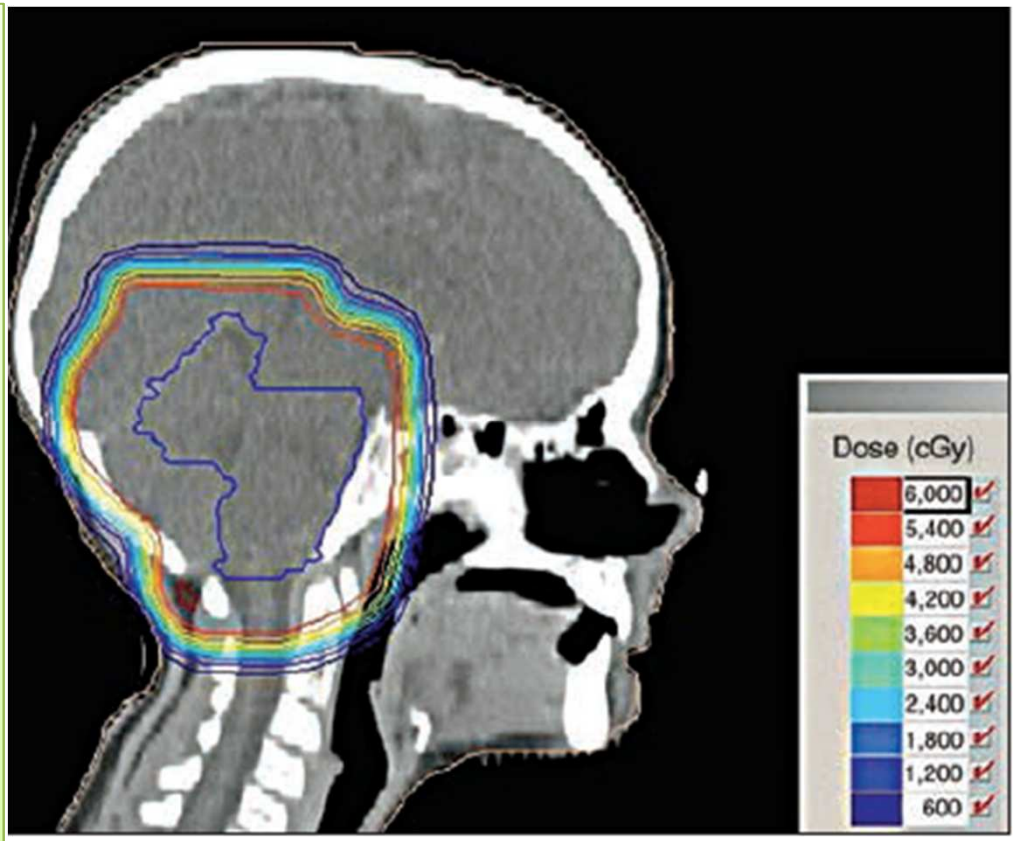
- 3 D conformal RT remains maximally used
- Intensity modulated radiotherapy
- Stereotactic treatments

Results

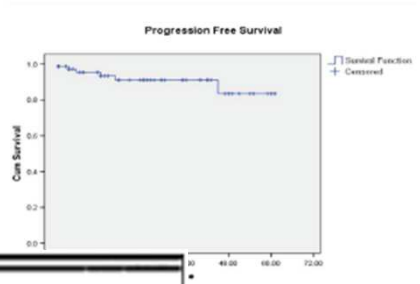
- Quite favorable
  - Older children enjoy more favorable outcome
  - GTR consistently linked to better PFS
- Diverse histiotypes
  - Molecular and genetic classification near
- Addition of therapeutic radiation when indicated
  - 80% PFS at 10y

Conformal Radiation Therapy

- Any technique where dose conforms to target
- Limits dose to non target tissues
- May decrease late morbidity
- Incorporates imaging modalities
  - Accurate definition of targets and critical normal structures



Optimal conformality
Impacts morbidity



ELSEVIER

Radiotherapy and Oncology 74 (2005) 37–44

RADIOTHERAPY & ONCOLOGY

www.elsevier.com/locate/radonline

High precision conformal radiotherapy employing conservative margins in childhood benign and low-grade brain tumours

Rakesh Jalali[a,*], Ashwini Budrukkar[a], Rajiv Sarin[a], Dayananda S. Sharma[b]

CLINICAL INVESTIGATION

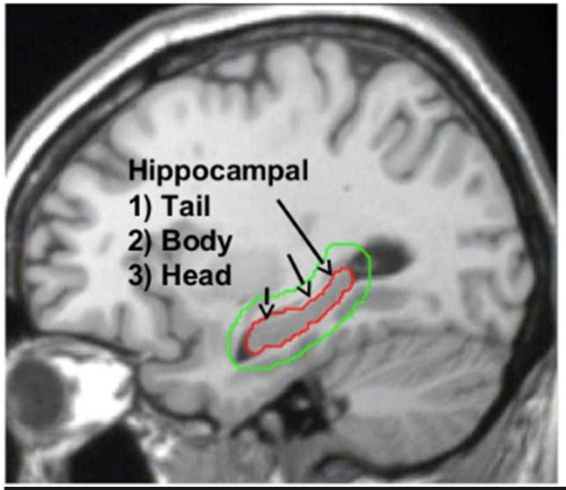
FACTORS INFLUENCING NEUROCOGNITIVE OUTCOMES IN YOUNG PATIENTS WITH BENIGN AND LOW-GRADE BRAIN TUMORS TREATED WITH STEREOTACTIC CONFORMAL RADIOTHERAPY

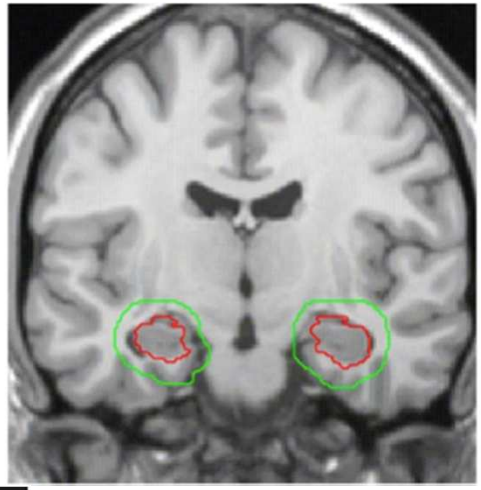
RAKESH JALALI, M.D.,* INDRANIL MALLICK, M.D.,* DEBNARAYAN DUTTA, M.D.,* SAVITA GOSWAMI, M.SC.,† TEJPAL GUPTA, M.D.,* ANUSHEEL MUNSHI, M.D.,* DEEPAK DESHPANDE, PH.D.,‡ AND RAJIV SARIN, F.R.C.R.*

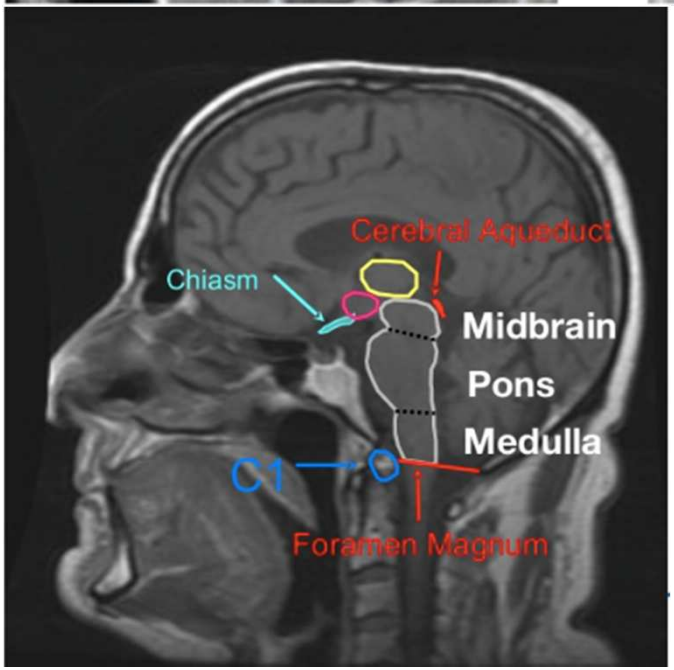
Departments of *Radiation Oncology, †Clinical Psychology, and ‡Medical Physics, Tata Memorial Centre, Mumbai, India

Optimal conformality
Impacts morbidity

- Left temporal lobe
- >13% volume receiving > 80% dose (43 Gy)
- >24% volume receiving > 50% dose (27 Gy)
- Right temporal lobe
  - No significant correlation between dose and drop in IQ
- Normal brain
  - No correlation
- ? Hippocampus







- RTOG Atlas
- Fuse the 3D-SPGR MRI and the treatment-planning CT
- 5 mm expansion zone

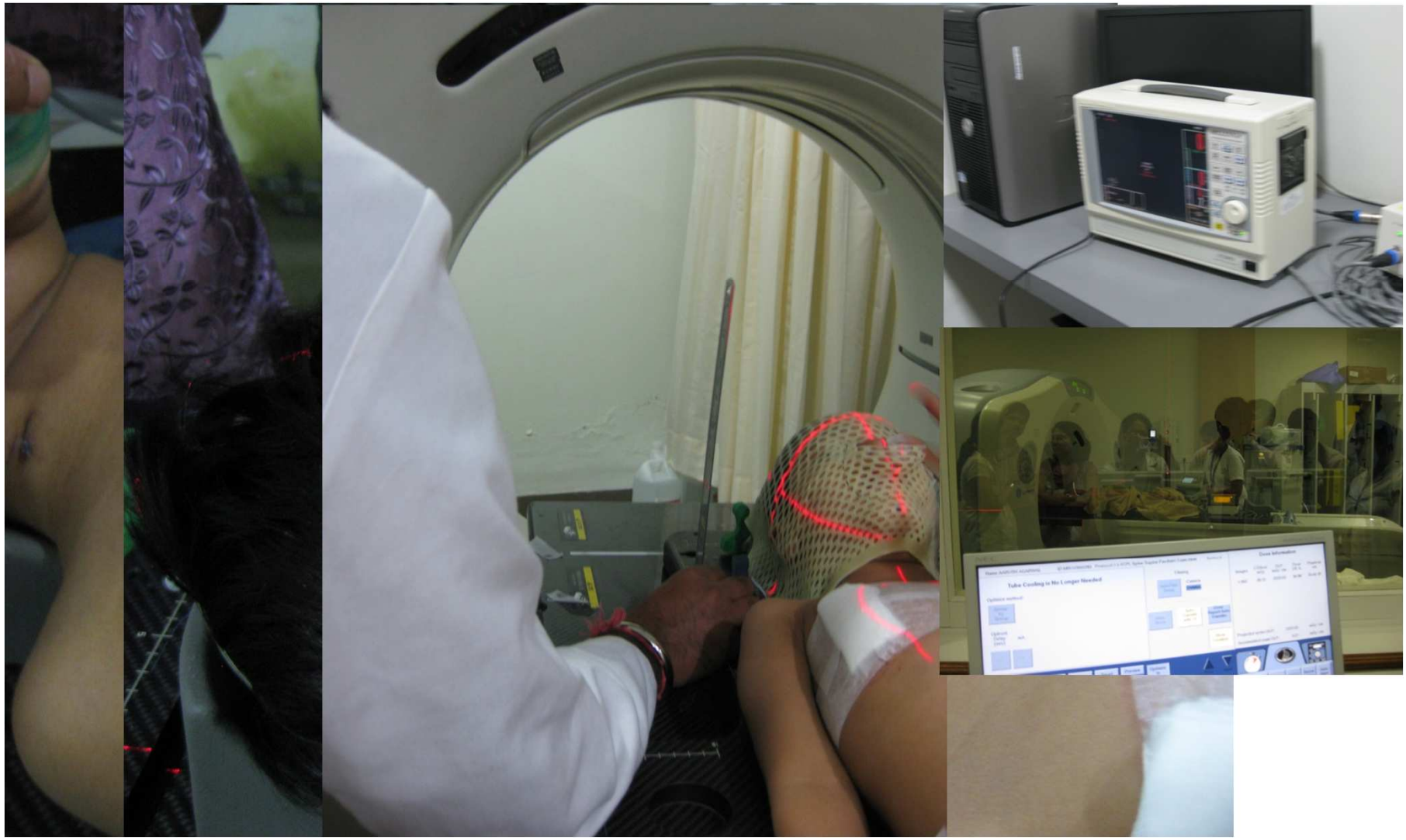
Conformal Radiation Therapy

Technique	Advantages	Disadvantages
3 D conformal RT	Widely available, limits dose	Exit dose treats normal tissues
IMRT	High dose region follows the tumor closely	Considerable low dose to normal brain tissue
SRT with arc photons	High dose region follows the tumor closely	Exit dose treats normal tissues
Radiosurgery	Precise delivery	Limitation: single #
Brachytherapy	Sources inside cavity	Dosimetry less certain
Proton RT	Holds promise No exit dose issues	Expensive Limited availability

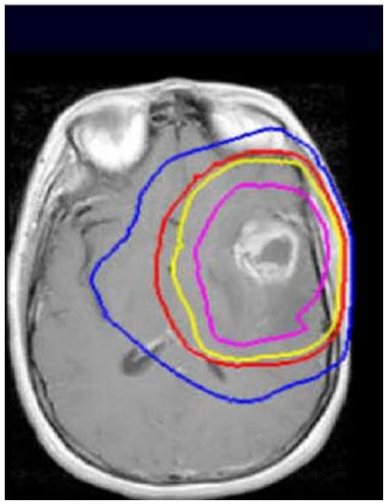
Conformal radiotherapy
Pre treatment Simulation

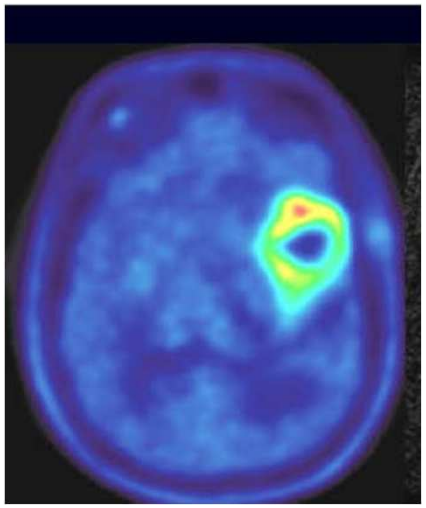
Conformal Radiation
Child care…

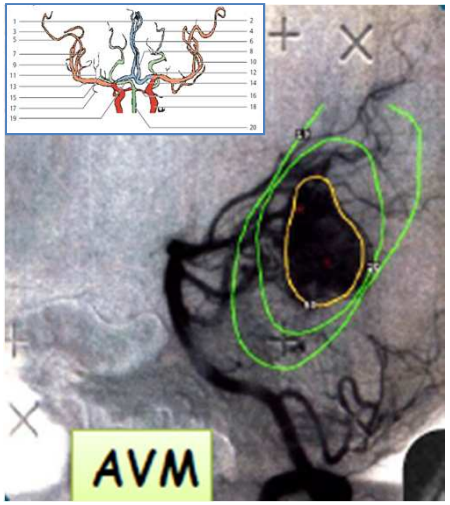
Conformal Radiation Radiotherapy Chain…



Conformal Radiotherapy
Modalities of Image Fusion







CT	MRI	PET/ SPECT	Angiography
•Bone information •Limited soft tissue information •Crux for calculations	•Soft tissue •Limited bone information •Multiplanar •CBV/ Spectroscopy •Diffusion/ Perfusion •Sequences	•Functional •Response •Hypoxia marker •Prognostication	•DSA •CT angio •MR angio •Vascular anatomy

Conformal Radiotherapy - Chain

PHYSICAL PATIENT →

PATIENT

- CT Room
- Lasers
- Skin markers
- Images
- Bone
- Tumor
- Delineation
- Margin
- Planned beam

- Treatment room
- Lasers
- Skin markers
- Bone
- Tumor

- Beam
- Accelerator
- Treatment room

TREATMENT

TREATMENT PLAN →

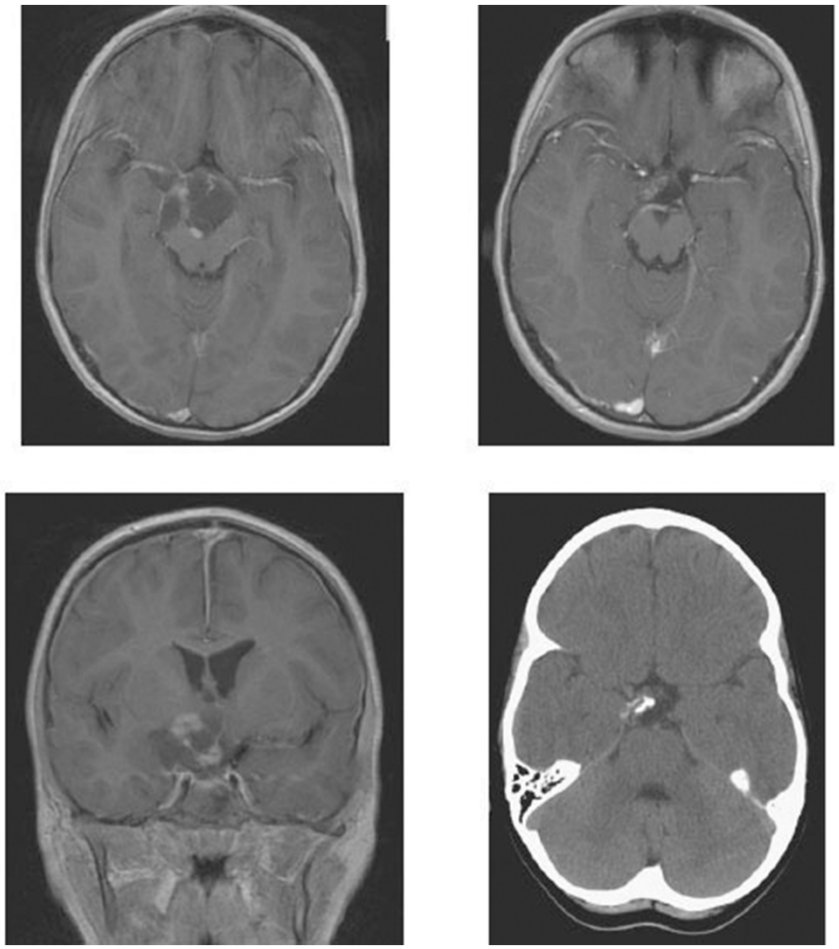
Checked by imaging

Newer Technology
Impact and need

- While much has changed in technology
  - Certain principles remain unchanged
  - Excellent functional outcomes and QOL
  - IQ, Endocrine sparing, Vision, Hearing*
- Pay respect to historical information
- Due deference to controversies
  - Margins can possibly be reduced in certain tumors**
- Cancers are curable, stakes are high
  - Blend of technology and emerging knowledge
  - Improve quality and quantity of the life saved

* Merchant et al IJROBP 2006, 210 - 221
** Merchant et al JCO 2009, 3598 - 3604

Craniopharyngioma

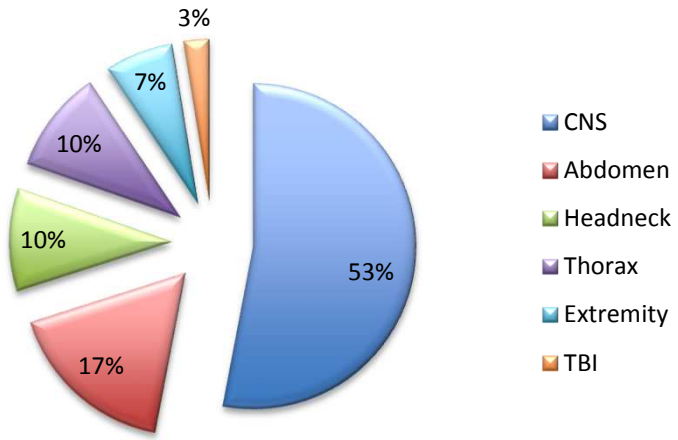


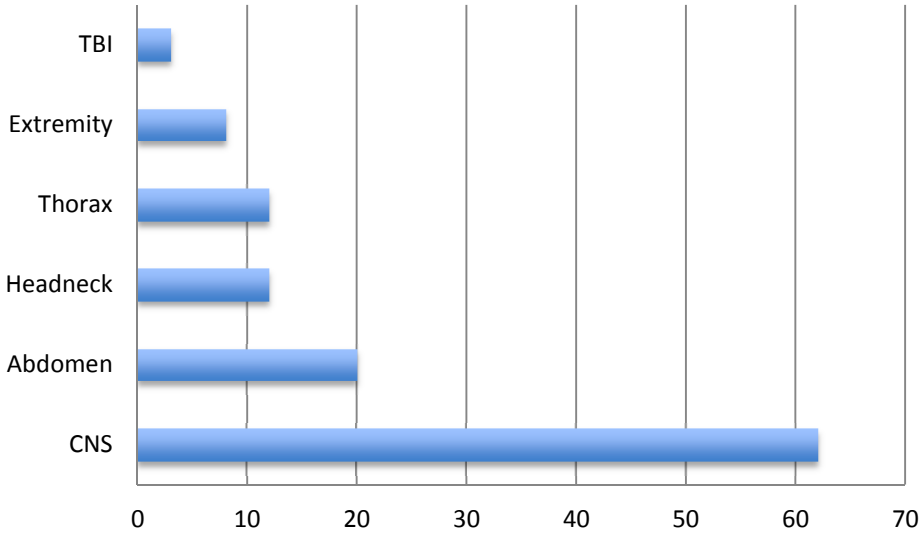
- Benign tumors of epithelial origin
  - Believed to arise from remnants of the Rathke pouch in the suprasellar region
  - <20 yrs
  - 5-15% of primary tumors in children
  - Almost always adamantinomatous
- Treatment
  - one of the most controversial issues in pediatric neuro-oncology
  - Matson's classic 1969 neurosurgical text
  - complete resection in 44 of 57 children
  - 10 of the 44 required more than one surgical procedure to achieve GTR
  - 60% local failure after resections
- Similar numbers were reported in Yasargil's series published two decades ago
- Partial excision+RT: 10 – 33% local failure
- Volume
  - Both cystic and solid component + 5 mm margin
  - 50 – 54 gy @1.8 gy per fractions over 5.5 weeks

Important to monitor the cyst during image guided treatment delivery

Pediatric Image Guided Conformal Radiotherapy

TMC_Overview_demography

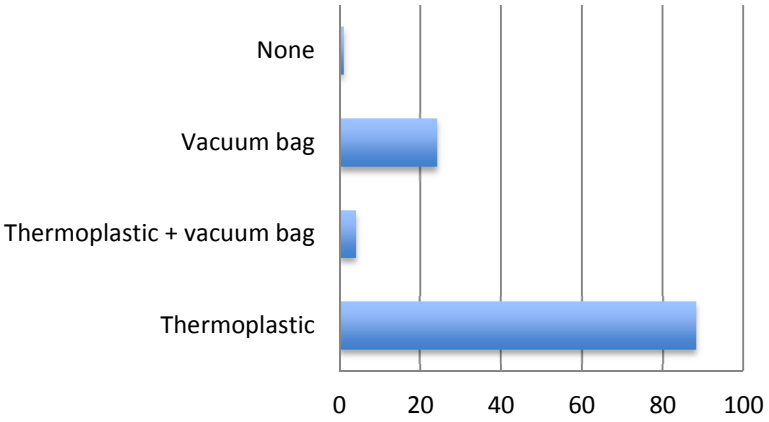


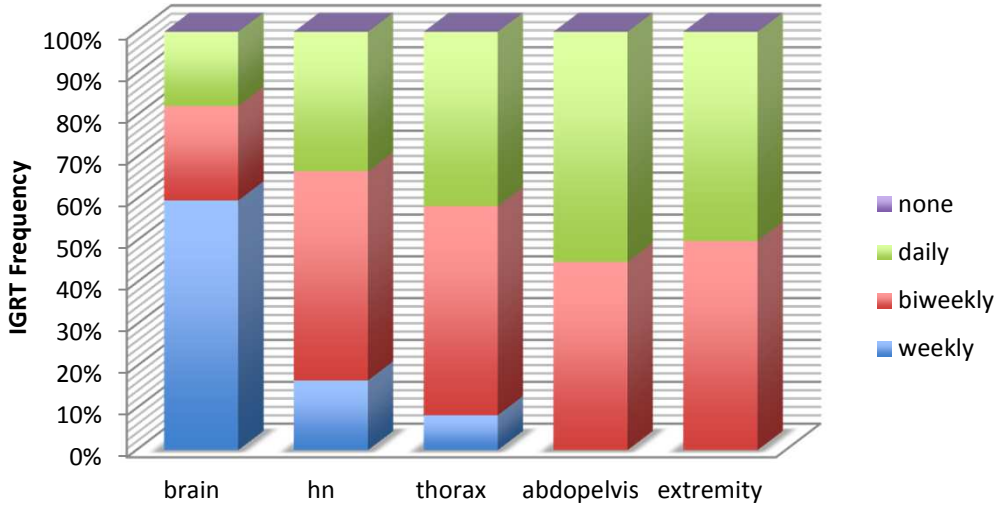


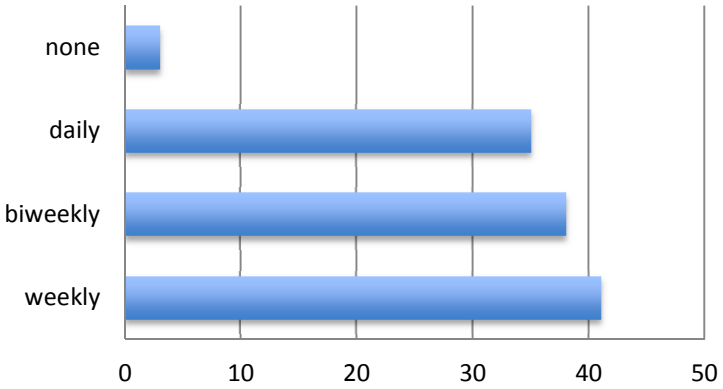
- May 2011 – October 2014
  - 135 patients treated
  - 117 evaluable
  - Analyzed: November 2014
- CNS
  - Commonest 53%
- Age
  - 0.5 – 18 years
  - Median: 8 years
- Gender
  - Male: 65% (76)
  - Female: 35% (41)

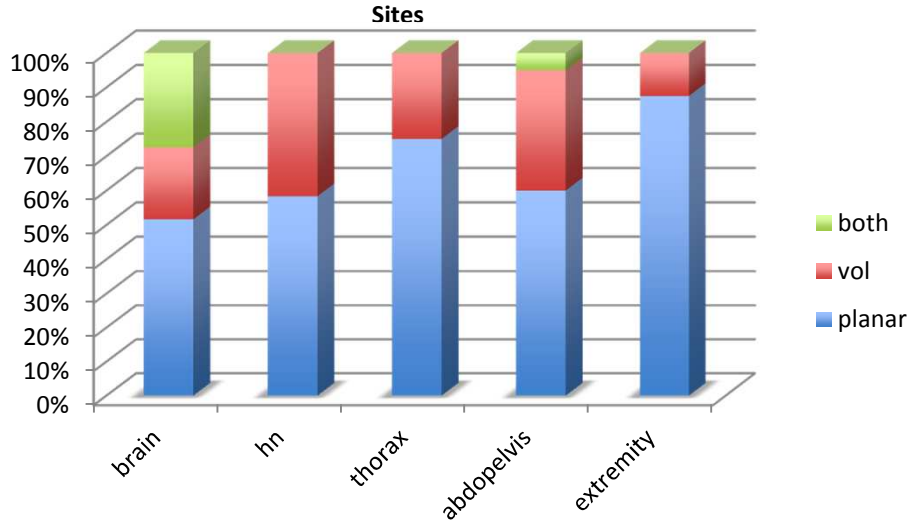
Pediatric Image Guided Radiotherapy at TMC

Imaging frequency across 117 patients









Pediatric Image Guidance

Before we begin

- Concerns?
- Image gently
- Image wisely

The management of imaging dose during image-guided radiotherapy: Report of the AAPM Task Group 75

Martin J. Murphy
Department of Radiation Oncology, Virginia Commonwealth University, Richmond, Virginia 23298

HOUNSFIELD REVIEW SERIES

Cancer risks from diagnostic radiology

E J HALL, DPhil, DSc, FACR, FRCR and D J BRENNER, PhD, DSc

PHYSICS CONTRIBUTION

KILOVOLTAGE IMAGING DOSES IN THE RADIOTHERAPY OF PEDIATRIC CANCER PATIENTS

JUN DENG, PH.D., ZHE CHEN, PH.D., KENNETH B. ROBERTS, M.D., AND RAVINDER NATH, PH.D.

Department of Therapeutic Radiology, Yale University, New Haven, CT

- Read the manual
- Closed circuit monitoring
- Planned treatment setup fields and corresponding reference images
  - Image verification system
  - 4D Console running
- Vendor software
  - 2D/2D or
  - 3D/3D matching
- OBI must be calibrated
- ALARA

Current status of pediatric image guidance

Practice patterns of photon and proton pediatric image guided radiation treatment: Results from an International Pediatric Research Consortium

Sara R. Alcorn MD, MPH [a], Michael J. Chen MD [b], Line Claude MD [c], Karin Dieckmann MD [d], Ralph P. Ermoian MD [e], Eric C. Ford PhD [a,e], Claude Malet MD [c], Shannon M. MacDonald MD [f], Alexey V. Nechesnyuk MD [g], Kristina Nilsson MD, PhD [h], Rosangela C. Villar MD [i], Brian A. Winey PhD [f], Erik J. Tryggestad PhD [a,j], Stephanie A. Terezakis MD [a,*]

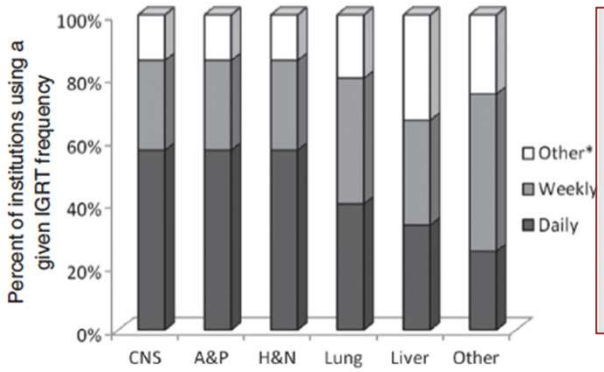


Table 2 Mean and standard deviation of maximum PTV expansions used with and without image guided radiation therapy (IGRT) by treatment site for photon therapy

Treatment site	PTV expansion used without IGRT			PTV expansion used with IGRT		
	No.	Mean	Standard deviation	No.	Mean	Standard deviation
CNS	6	0.48	0.04	6	0.38	0.10
A&P	5	0.84	0.23	5	0.72	0.26
H&N	6	0.53	0.08	6	0.45	0.08
Lung	5	1.24	0.51	5	1.08	0.54
Liver	2	0.85	0.21	2	0.85	0.21
Other	2	0.85	0.21	2	0.85	0.21

PTV expansions not very different

Prevalent, site specific variability, limited reporting of imaging dose, warrants attention…

Plan your imaging please
Correlation between Previous and New CBCT Modes

Previous Mode Name [OBI 1.3]	Present Mode Name [OBI 1.4]
n/a	Low dose head ✔
Low dose 150 cm Bow tie [Head]	Standard dose head
Standard dose 150 cm Bow tie [Head]	High quality head
Standard dose 150 cm Bow tie [Body]	Pelvis
n/a	Pelvis spot light
Low dose 150 cm Bow tie [Body]	Low dose thorax ✔

- New CBCT modes ***only*** calibrated for ***either*** full fan or half fan acquisition
- All head and pelvis in low dose modes
  - 200 degree gantry rotation [half scan acquisition]
  - Reduces dose
  - Reduces scan acquisition time

Current status of pediatric image guidance

Author	Site	Equipment	Imaging	Errors	Remarks
Zhu, 1999	Brain (22)	-	Daily port	Head frame < 4mm Vacuum bag < 4mm	? Imaging dose
Beltran, 2010	Brain (15)	Siemens M Vision IBL-MVCBCT 1cGy/scan	MVCBCT Daily pre and post treatment	Intrafraction 0.04mm Interfraction 0.12mm	Interfraction motion resulted in 0.4% of TCP loss NTCP change: < 5%
Panandikar 2012	Abdomen (20)	4DCT	33mGy/scan 400 mA 120KV 0.5-1s	<9 years 5-25mm >9 years 5-52mm	age, height diaphragmatic motion

12 studies, reporting use, some comment on imaging dose, most on margins

Pediatric Image Guided Radiotherapy at TMC
Brain as a sub site (n = 45)

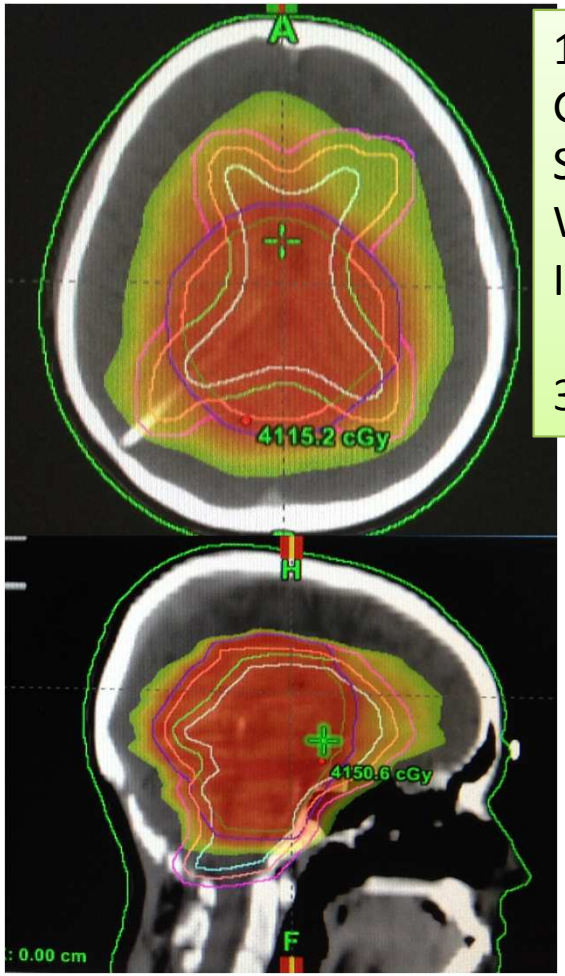
Direction	Mean	Systematic Error (Σ)	Random Error (σ)	PTV margin
Lateral (mm)	1.18	1.49	0.78	4.29
Longitudinal (mm)	0.34	0.96	0.76	2.94
Vertical (mm)	1.14	1.52	0.76	4.34
Rotation (^{0})	0.11	0.42	0.77	1.58

Departmental policy: 5mm PTV*, reposition if rotation > 3 degrees and patience

Shifts	Daily Imaging				Intermittent Imaging			
	Mean	SE (Σ)	RE (σ)	PTV margin	Mean	SE (Σ)	RE (σ)	PTV margin
Lateral (mm)	0.88	1.33	0.82	3.91	1.76	1.29	1.11	4.01
Longitudinal (mm)	0.42	0.76	0.96	2.57	0.79	0.74	0.91	2.49
Vertical (mm)	0.89	1.33	0.82	3.92	1.76	1.29	0.75	3.75
Rotation (^{0})	0.12	0.28	0.56	1.07	0.22	0.26	0.61	1.08

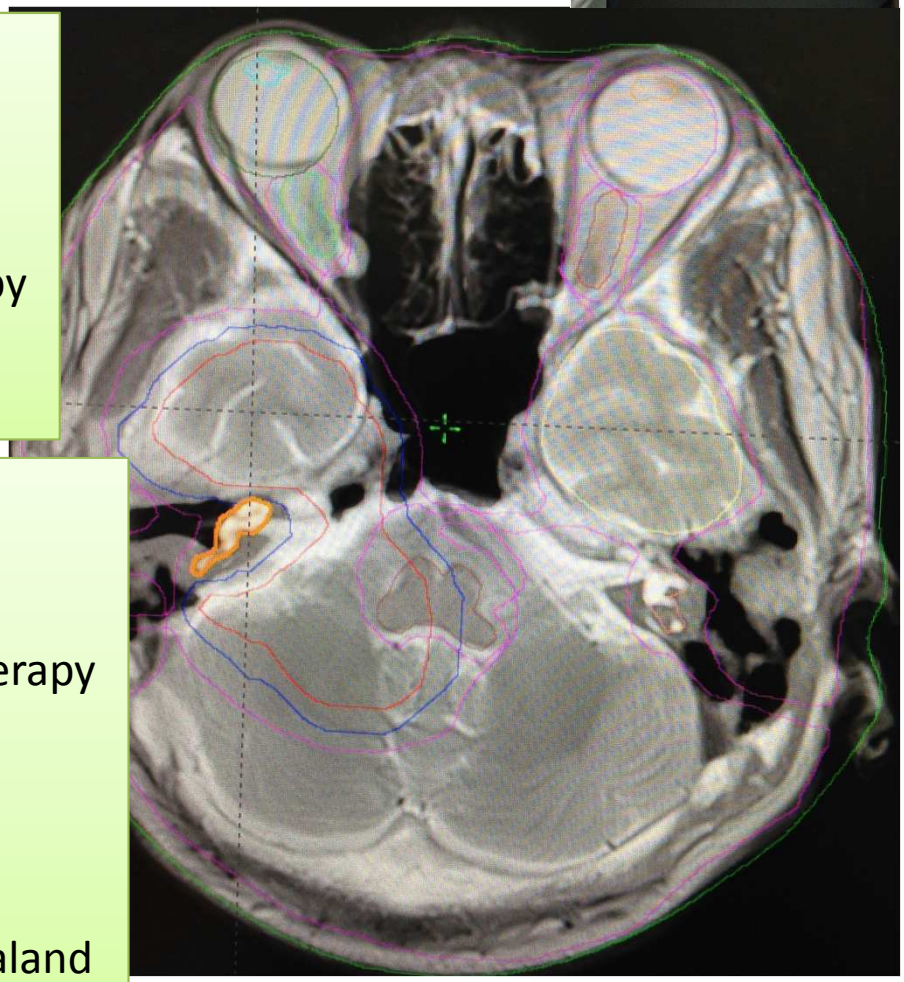
No significant difference; lesser imaging dose; better optimization of machine time
Remember…. A finite percentage need anesthesia

Conformal Radiation
Clinical examples



12 Y F
Germinoma
Surgery
WVI after CT
IMRT: Tomotherapy

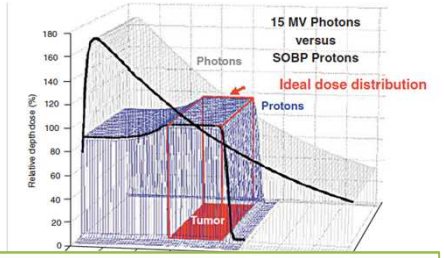
36 mo NED



18 Y M
LGG II
Contra: deaf
IMRT: Tomotherapy
IPSI cochlear sparing

42 mo VGPR
Job in SBI Nagaland

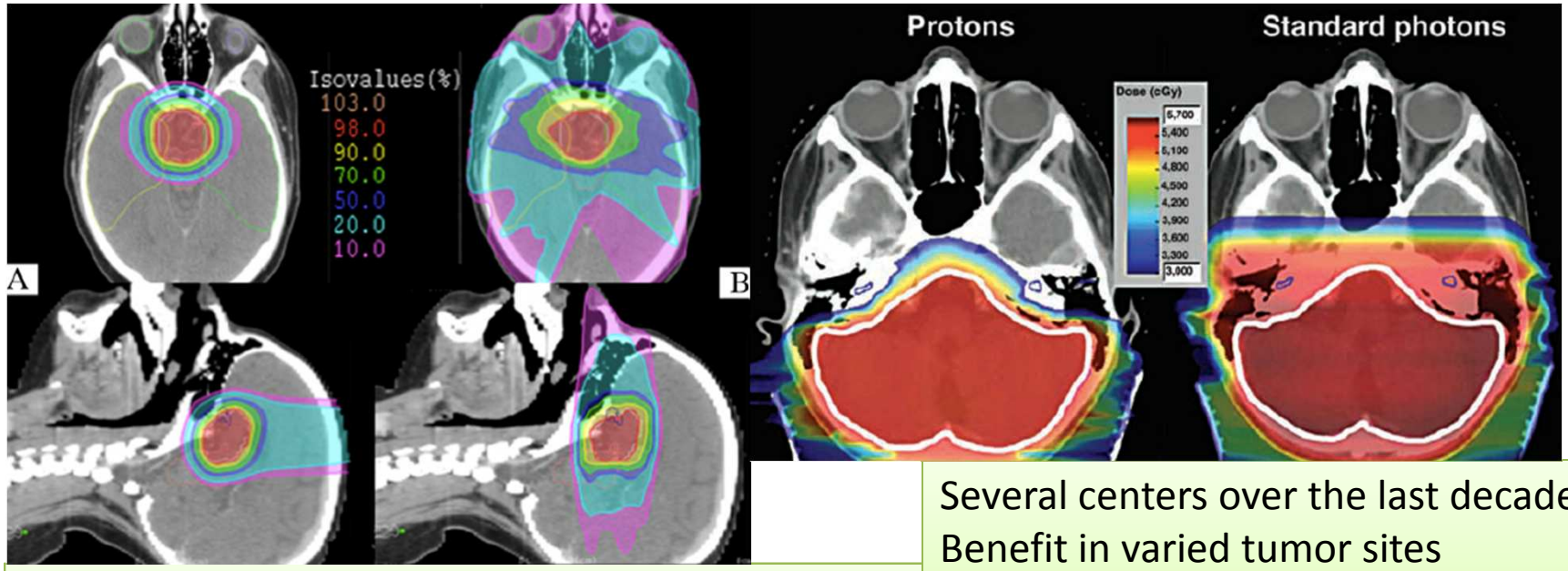
Emerging technology with promise



REVIEW Open Access

Proton radiotherapy for pediatric tumors: review of first clinical results

Barbara Rombi[1*], Sabina Vennarini[1†], Lorenzo Vinante[1,2†], Daniele Ravanelli[1] and Maurizio Amichetti[1]



Main advantage
Spare intermediate to low dose to healthy tissues

Several centers over the last decade
Benefit in varied tumor sites
Evidence gradually becoming more robust
Expensive, limited availabilty

When used judiciously
Optimal technology offers more than just treatment
It optimally rehabilitates a child to society

Cognitive Appraisal of childhood cancER and adherence to health advice: A mixed methods prospective study on the interaction of child-parent-doctor triad (CARE study)

Investigators: **Dr. Soumitra Shankar Datta**, Consultant Child & Adolescent Psychiatrist, Dept of Palliative Care & Psycho-oncology ; **Dr. Arpita Bhattacharyya**, Consultant Paediatric Haemato-oncologist; **Dr. Rimpa Achari**, Consultant Radiation Oncologist; **Dr. Mammen Chandy**, Consultant Haemologist and Director, *Tata Medical Centre, Kolkata*