RADIOTHERAPY IN MEDULLOBLASTOMA

RATIONALE & RESULTS

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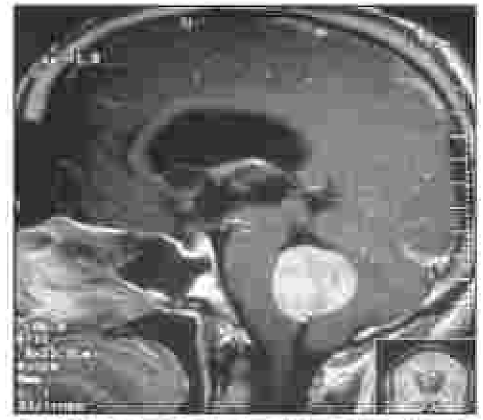
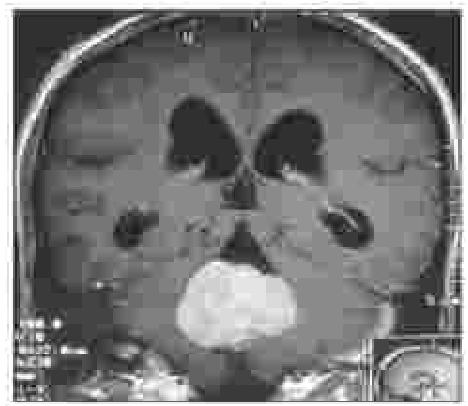
Introduction

- Commonest malignant brain tumor in children
- 20-25% of all childhood brain tumors
- Belongs to family of small blue RCT
- Median age at presentation: 5-8 years
- High propensity of CSF dissemination (20-30%)
- Current standard of care: Maximal safe resection followed by adjuvant radiation therapy +/- chemotherapy



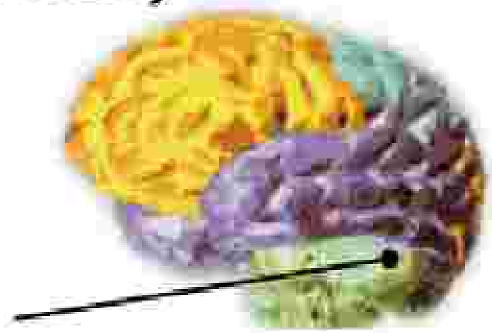


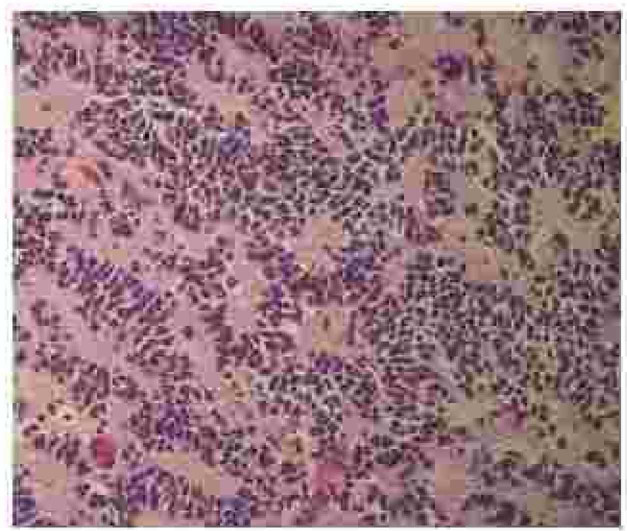
Role of Radiotherapy

"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"

Harvey Cushing, 1930

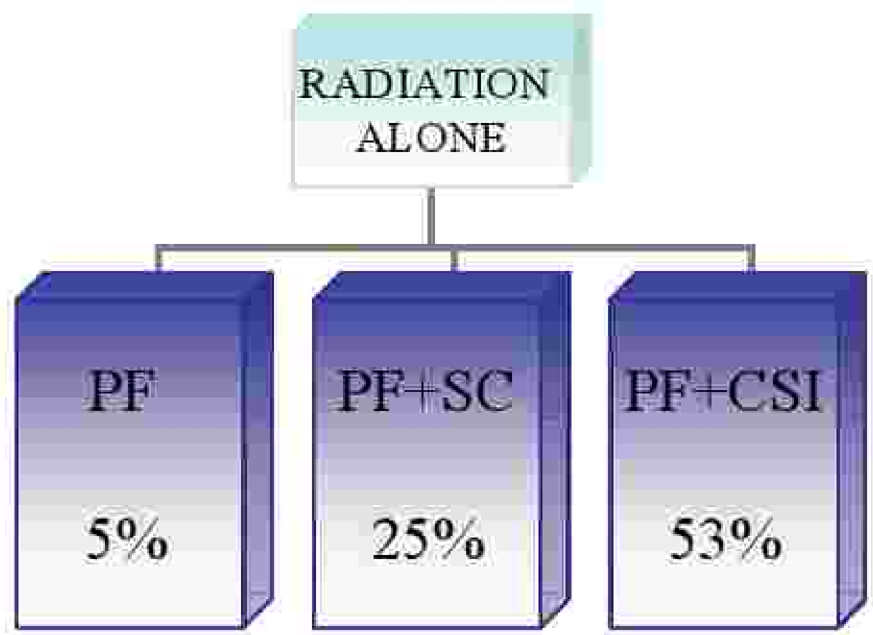
Medulloblastoma (PNET)





Rationale

- Generally a radiosensitive disease
- Historical controls: No long term survivors without RT
- High recurrence rates with focal (posterior fossa only) RT
- High recurrence rates for reduced dose CSI without CT



Landberg 1953

Cranio-spinal Irradiation (CSI)

- Cornerstone of adjuvant treatment
- Most challenging planning in RT

Issues in RT for Medulloblastoma

- Positioning and Immobilization
- Planning and Verification
- Pertinent Questions for RT
- Newer perspectives in RT
- Clinical Trials

Positioning & Immobilization for CSI

Prone vs Supine

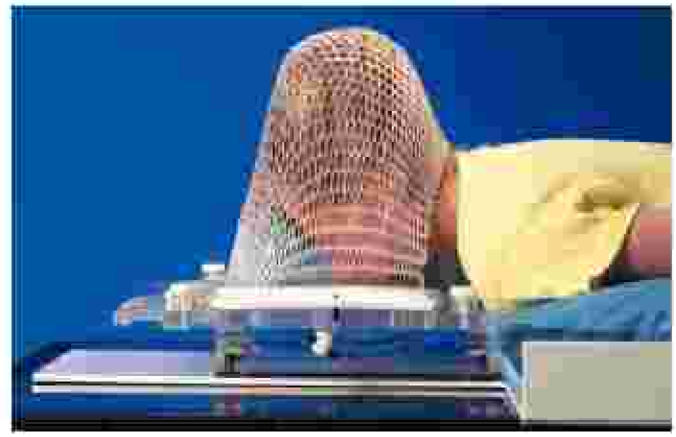
Prone preferred due to direct verification

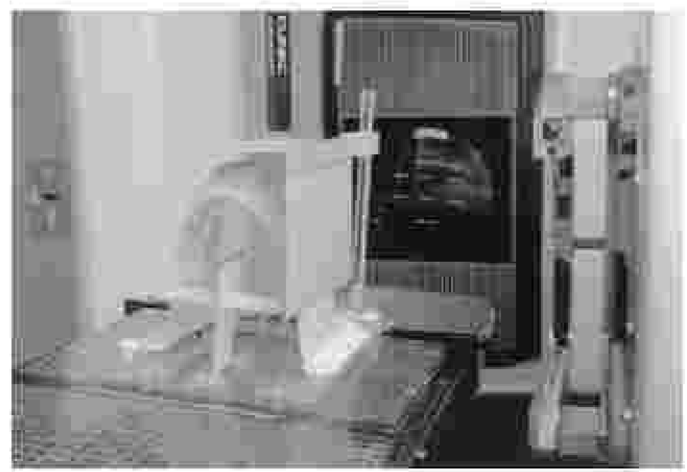
Disadvantages

- Relatively poor reproducibility
- Larger scope for patient movement
- Discomfort to the patient
- Difficult anesthesia if needed

Customized immobilization

- Customized immobilization with use of commercially available prone head rests integrated with vacuum bags achieves maximum set up accuracy
- Alternatively CT-based planning and/or virtual simulation and verification needed for supine position

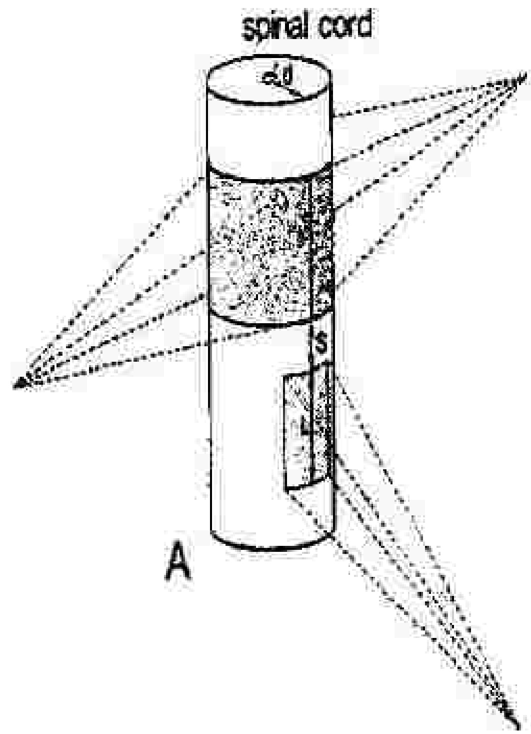




Field matching in CSI

- **A geometrical method of orthogonal field separation (Werner et al.)**

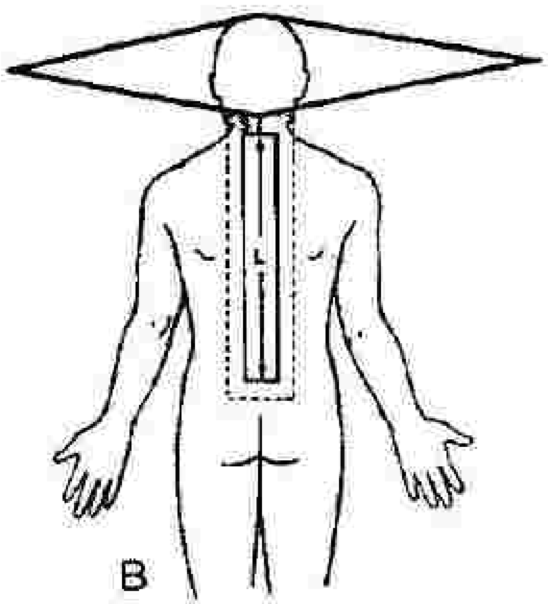
$$S = \frac{1}{2} \bullet L \bullet \frac{d}{SSD}$$



d **→ depth at which the orthogonal fields are allowed to join**

Matching Craniospinal Fields

- ***Techinque A***
  - **Bilateral cranial fields adjacent to a spinal field**
  - **The inferior border of cranial field meet at a point midway on the posterior neck surface**



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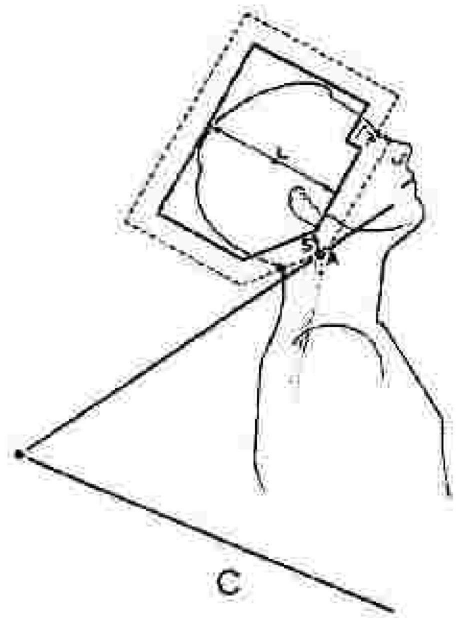
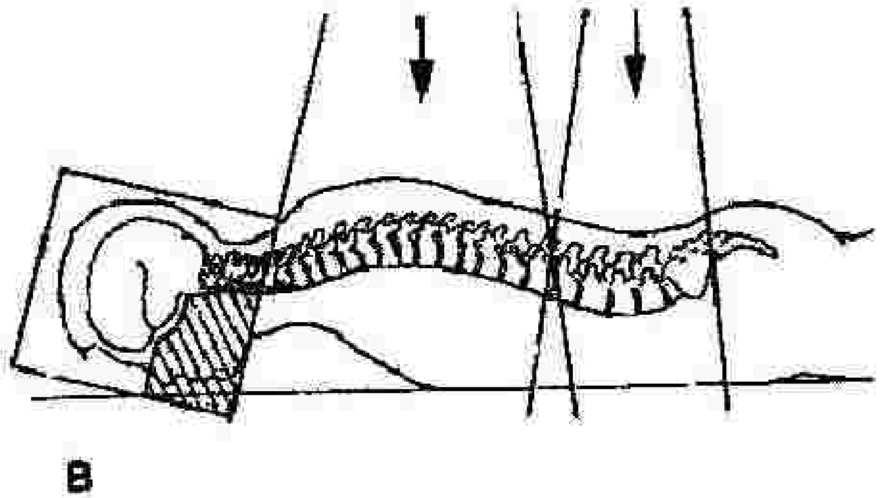
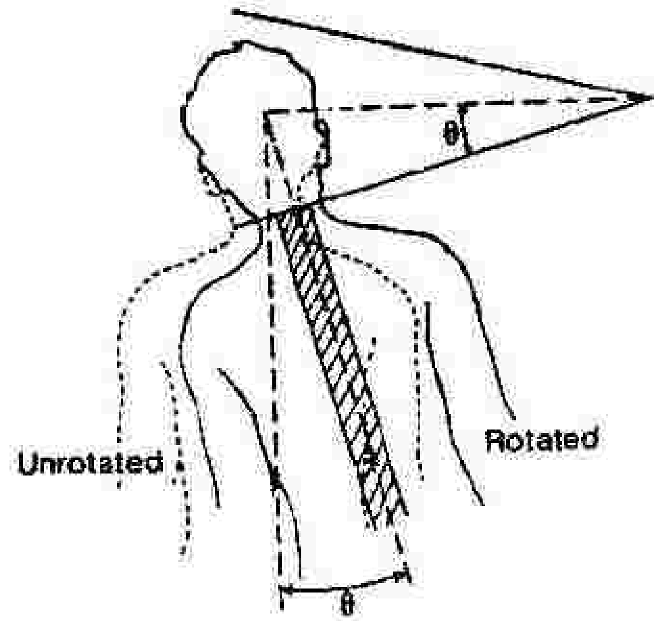


C

- ***Technique B***
  - **Rotation the couch and collimator**

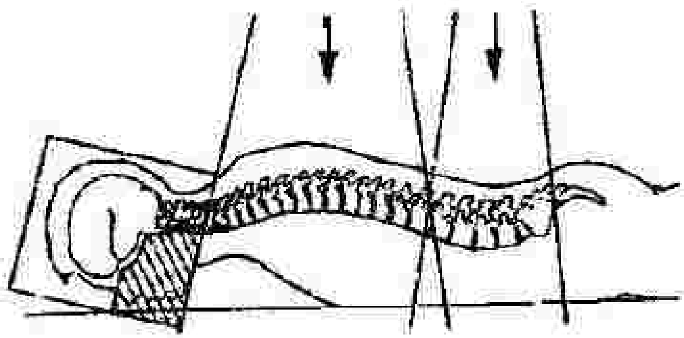




  - **Calculation of the two angles θ_{coll} and θ_{couch}**

$$\theta_{coll} = \arctan\left(\frac{1}{2} \bullet L_1 \bullet \frac{1}{SSD}\right) \qquad \theta_{couch} = \arctan\left(\frac{1}{2} \bullet L_1 \bullet \frac{1}{SAD}\right)$$

- ***Technique C***
  - **Rotation of the collimator only with using hemiblock of the cranial fields**



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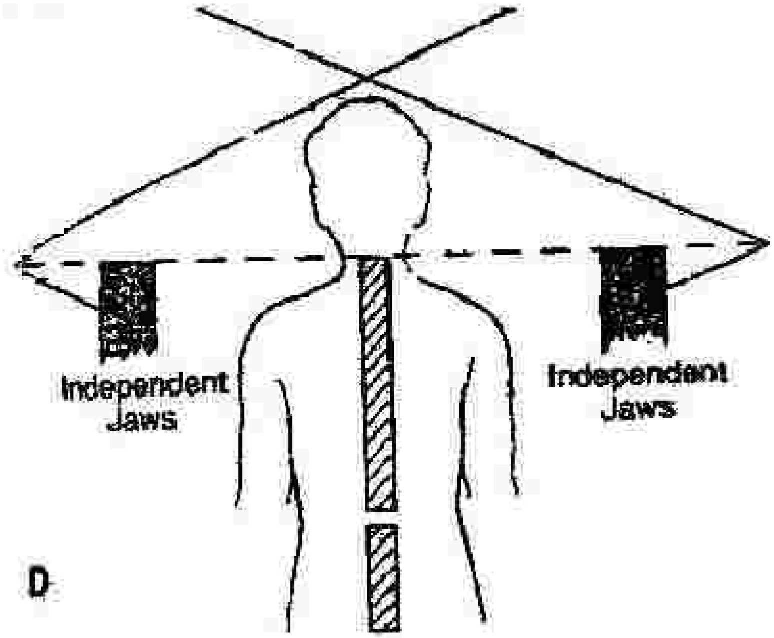
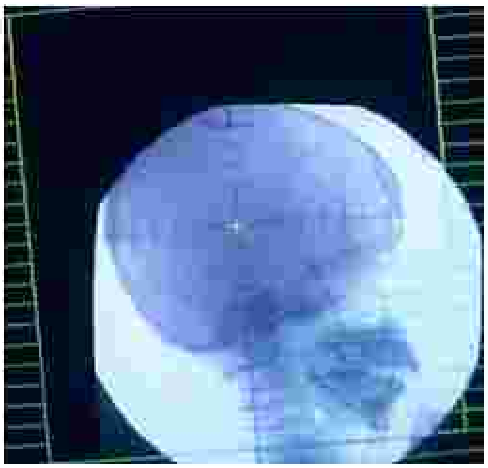


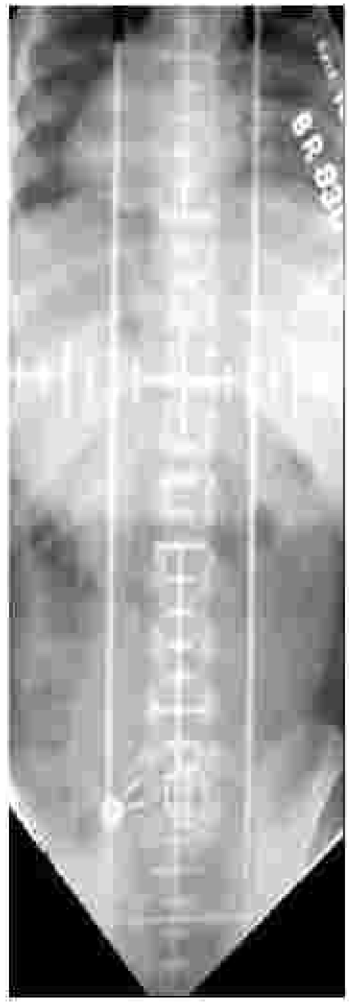
D

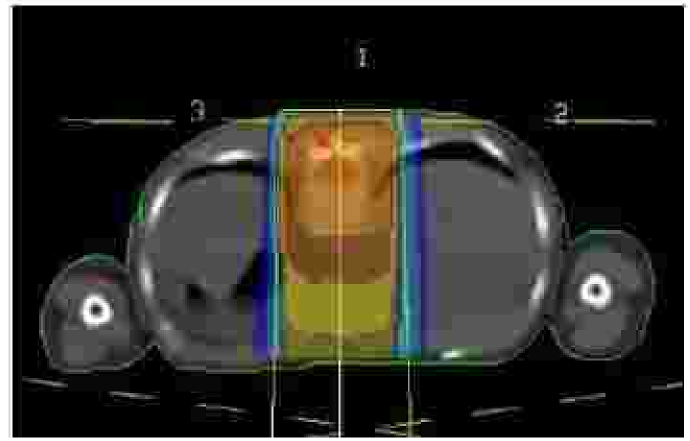
$$\theta_{coll} = \arctan\left(\frac{1}{2} \bullet L_1 \bullet \frac{1}{SSD}\right)$$

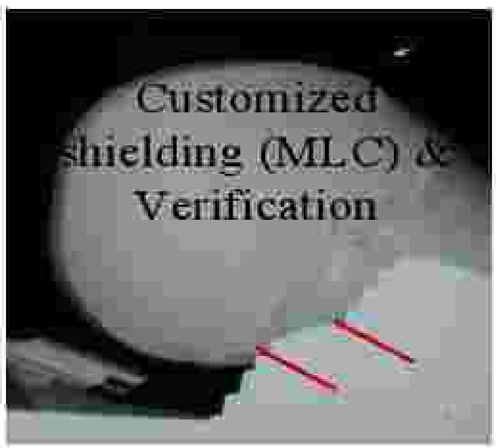
  - **Calculation of the collimator angles θ_{coll} only**

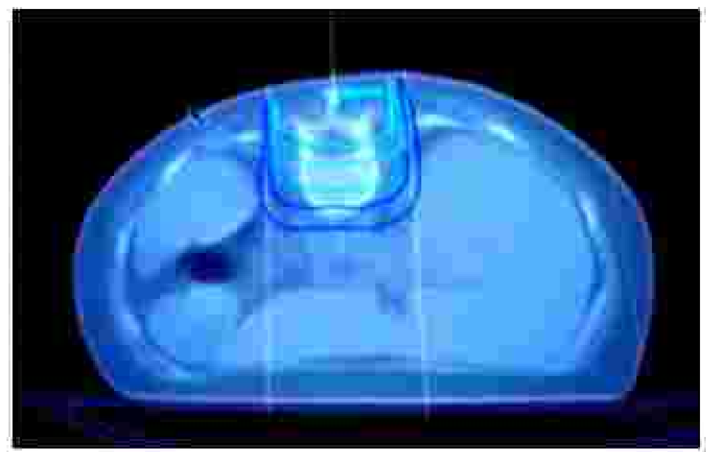
Field shaping & Dose distribution



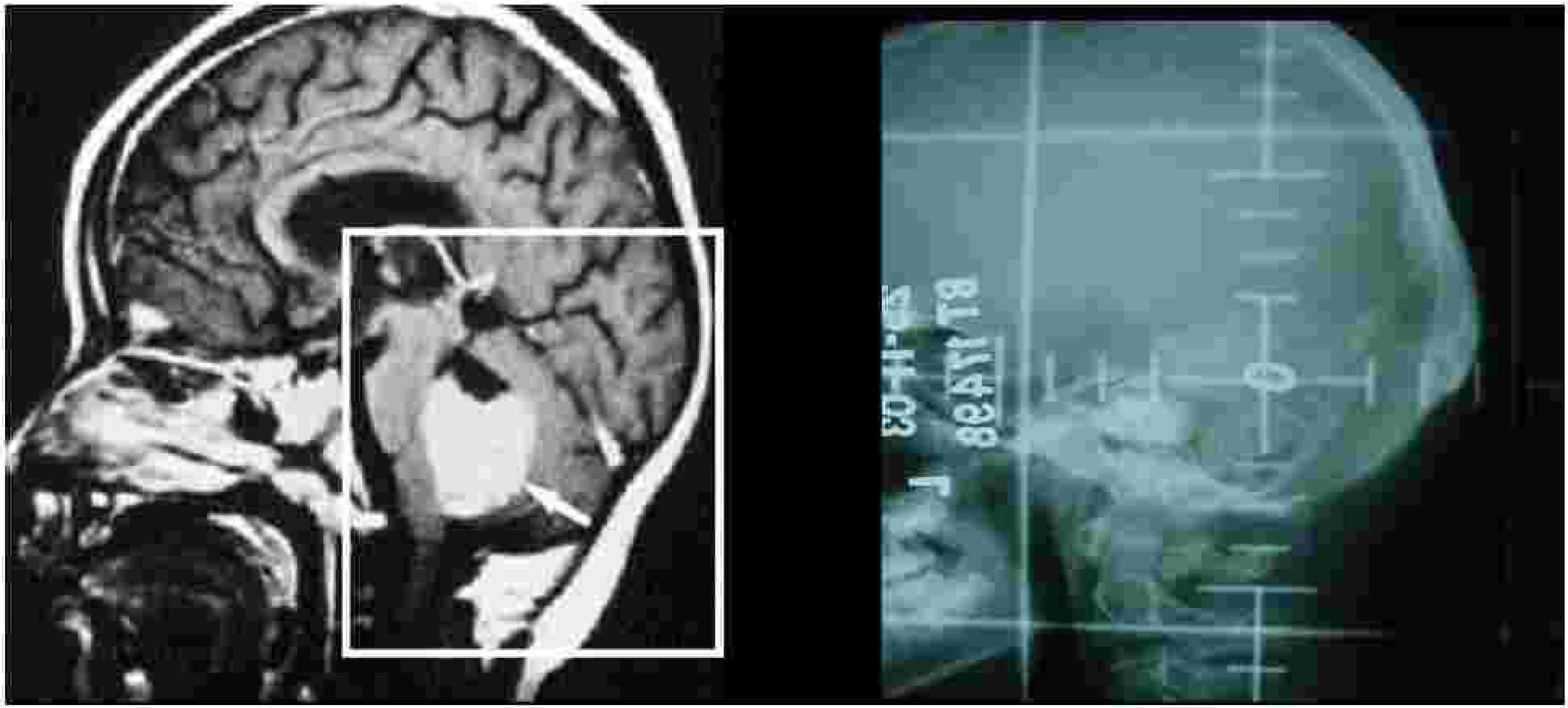








Posterior Fossa Boost : Conventional Simulation



Current Risk Stratification for Medulloblastoma

	Average	*High*
Clinical Age	**≥ 3 Yrs**	**< 3 Yrs**
Residual Tumor	**⩽ 1.5 cm2**	**> 1.5 cm2**
Metastases	**M0**	**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

Doses and volumes as per risk stratification

CSI for average-risk disease

(age >3 yrs, M0 status, and residual <1.5 cm2)

- 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)
- Very reduced dose CSI: 18 Gy/10#/2 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
- *If very reduced dose CSI:* Tumour bed boost: 39.6 Gy/22#/4.5 weeks

Total tumour bed dose: 54-56 Gy/ 30-33#/ 6.6.5 weeks

(conventional #)

High-risk medulloblastoma

CSI for high-risk disease

(age <3 yrs, M+ status, and residual >1.5 cm2)

- 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: 7.2-9 Gy/4-5#/1 week

Can the dose of CSI be reduced

Average-risk disease :

Definitely NOT without CT

Probably YES with CT

High-risk disease

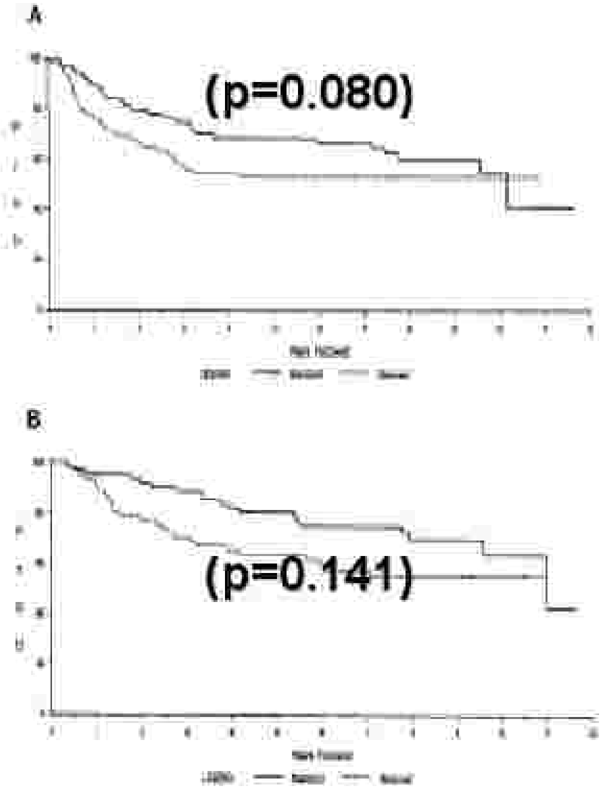
Definitely NOT

Long-term survival with full dose CSI

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

Low-Stage Medulloblastoma: Final Analysis of Trial Comparing Standard-Dose With Reduced-Dose Neuraxis Irradiation



Standard dose (36 Gy CSI; 54 GyPF)

5 yr- 67±7.4%
8 yr- 67±8.8%

Reduced dose (23.4Gy CSI; 54 Gy PF)

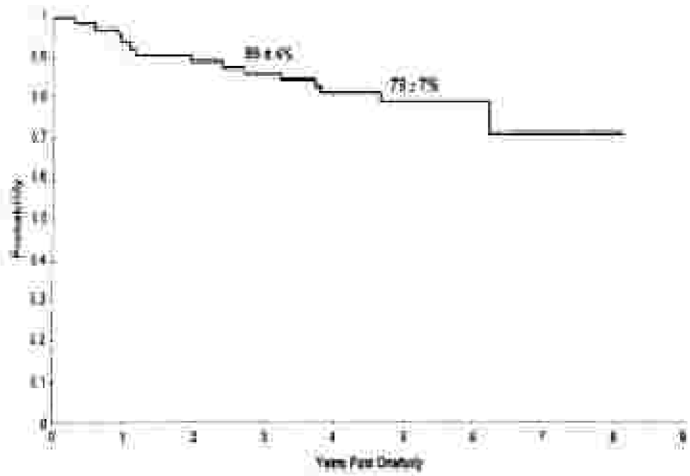
5 yr- 52±7.7%
8 yr- 52±11%

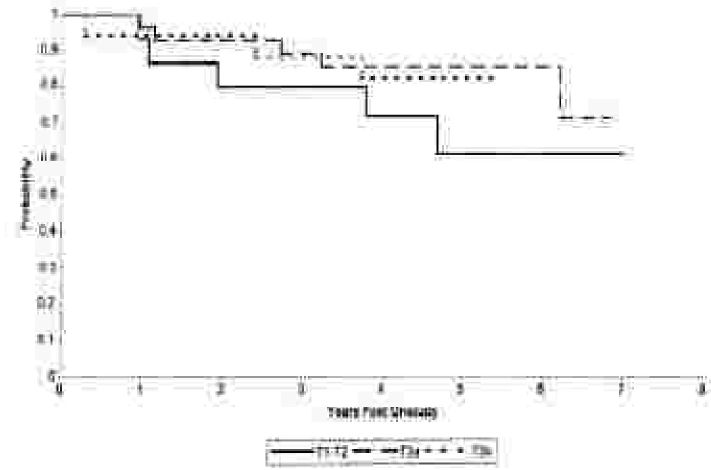
Trial closed prematurely at N=126

Reduced dose CSI negatively impacts EFS

Thomas JCO 2000

Treatment of Children With Medulloblastomas With Reduced-Dose Craniospinal Radiation Therapy and Adjuvant Chemotherapy: A Children's Cancer Group Study





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 JCO 1999

How much can the CSI dose be reduced

23.4 Gy : Probably YES

18 Gy : Immediately NOT

0 Gy : MUST BE KIDDING

Ongoing CCG trial randomizing to 23.4 Gy CSI vs 18 Gy CSI in average-risk MB followed by same CT

UPDATED RESULTS OF A PILOT STUDY OF LOW DOSE CRANIOSPINAL IRRADIATION PLUS CHEMOTHERAPY FOR CHILDREN UNDER FIVE WITH CEREBELLAR PRIMITIVE NEUROECTODERMAL TUMORS (MEDULLOBLASTOMA)

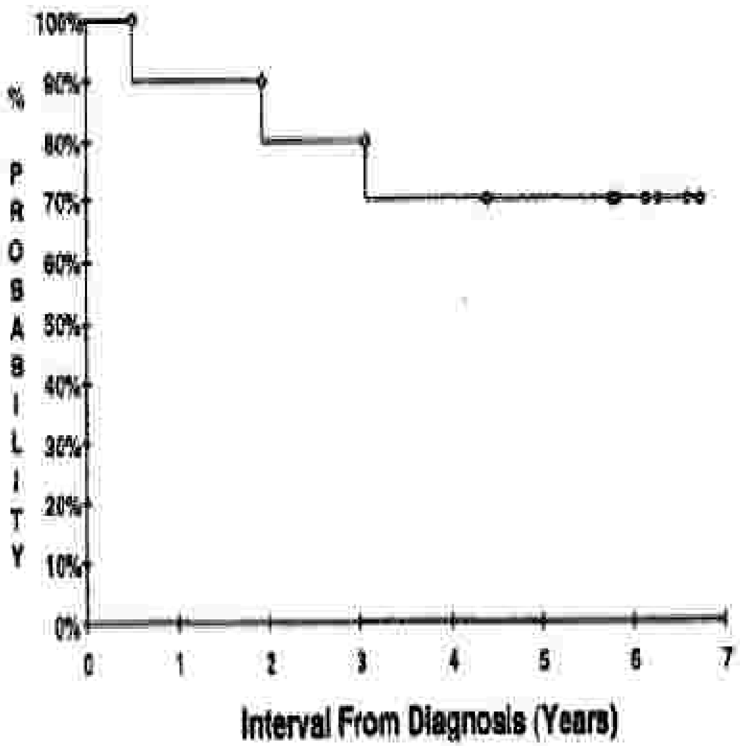


Fig. 1. Actuarial surivival of 10 children treated with 18 Gy CSRT.

- 10 Pts (1988 – 1990)
- < 5 Yrs age, median f/u = 6.3 yrs
- < 1.5 cm2 RD, No SAS spread.
- Total / Near total resection – 8 pts
Sub total resection - 2
- 18 Gy CSI + PF Boost upto 55.8 Gy
- Concurrent VCR → Maintenance
VCR + Cisplatin + CCNU
- Trial stopped when 3rd patient
presented with relapse
- 7/10 patients = long term DFS
- Minimal neurocognitive damage

Goldwein IJROBP 1996

Is it necessary to treat the entire posterior fossa

Average-risk disease

Probably NOT

High-risk disease

Probably YES

PATTERNS OF FAILURE FOLLOWING TREATMENT FOR MEDULLOBLASTOMA: IS IT NECESSARY TO TREAT THE 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 IJROBP 1998

Patterns of Failure Using a Conformal Radiation Therapy Tumor Bed Boost for Medulloblastoma

- N = 32 (Standard risk -27, High risk -5)
- CT + RT – 28 Pts, RT Alone- 4 Pts
- Recc = 6
  - 4 = extensive leptomeningeal inv with out significant post fossa component
  - 1 = supratentorial only
  - 1 = post fossa
- DFS at 5 yrs – 84% and OAS at 5 yrs – 85%
- Freedom from distant failure
  - Std dose – 100% at 10 yrs and Low dose – 63% (P = 0.06, trend.)
- Freedom from posterior fossa failure was 100% and 86% at 5 and 10 years

Conformal treatment to the tumor bed allows for significant sparing of critical structures. The posterior fossa failure rate in this series is similar to that reported when the entire posterior fossa is treated. This approach should be investigated further in a phase III trial

Wolden JCO 2003

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

Does reduction in dose and volume impact upon long-term outcomes

- Neuro-cognitive dysfunction: YES (Reduced)
- Neuro-physiologic dysfunction: YES (Reduced)
- Endocrine dysfunction: YES (Lesser)
- Oto-toxicity: EQUIVOCAL (Reduced cochlear dose offset by addition of platinum
- Hematologic: YES (Significantly incresed with CT)
- GI toxicity: YES (Significantly increased with CT)
- Second malignant neoplasms: EQUIVOCAL (conflicting data)

Benefit of reducing CSI dose and boost volumes

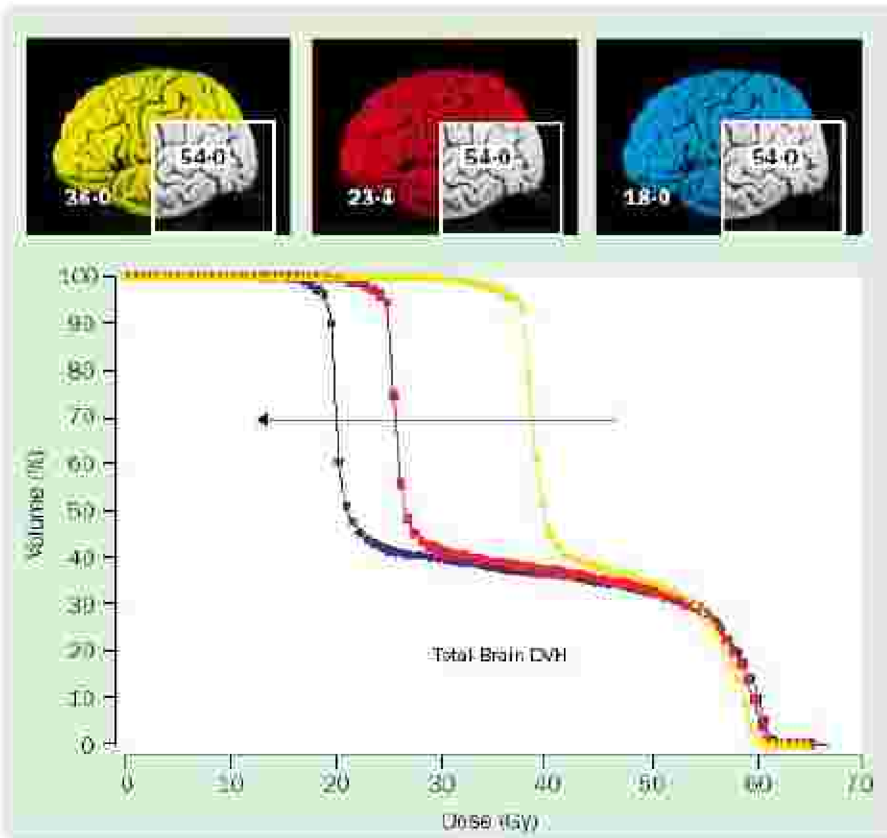


Figure 3. Benefits of dose decreases in planning of craniospinal radiotherapy shown with total-brain dose-volume histograms (DVH), comparison of 36·0 Gy (yellow), 23·4 Gy (red), and 18·0 Gy (blue).

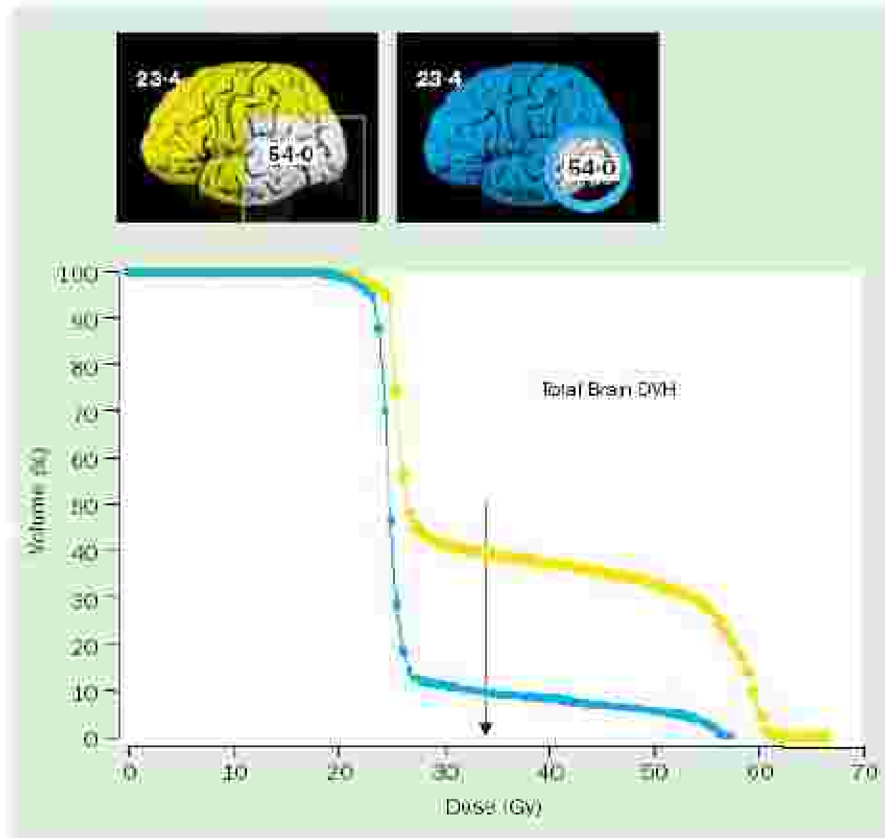
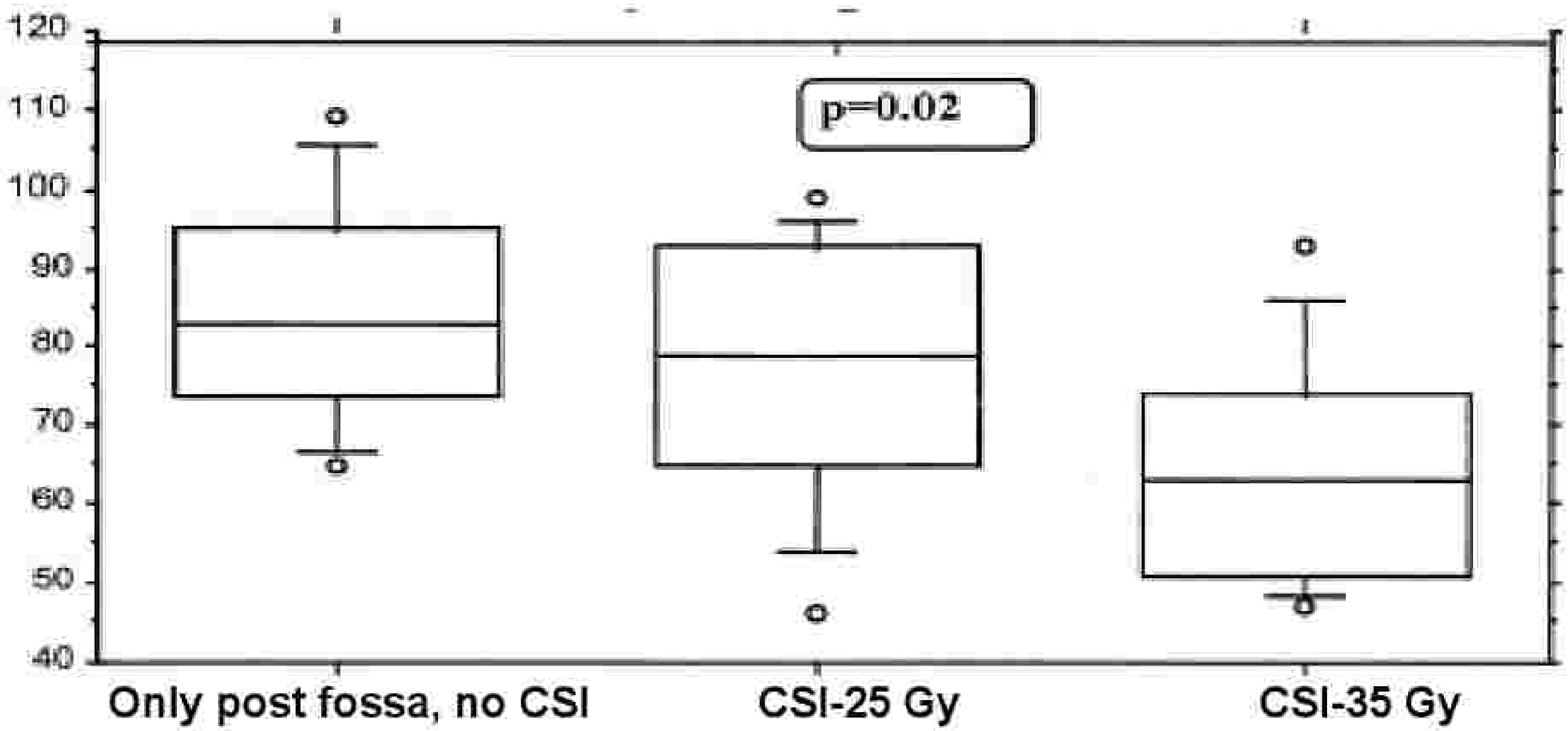


Figure 4. Benefits of dose decreases in planning of radiotherapy to posterior fossa shown with total-brain dose-volume histograms (DVH), comparison of conventional boost (blue) to posterior fossa with conformal boost (yellow) to the primary site after 23·4 Gy craniospinal irradiation.

Mulhern R: Lancet Oncol 2004;5:399-408

Long Term Intellectual Outcome with Different volume & dose of radiation

31 Children with various post fossa tumours irradiated at the mean age of 6 years assessed after a mean period of 5 years Post RT



Grill IJROBP 1999

Neurocognitive Consequences of Risk-Adapted Therapy for Childhood Medulloblastoma

- 111 patients, 3 – 20 yrs of age
- 37 High risk (CSI std dose 36 – 40 Gy + conf boost + 4# CT)
- 74 Avg. Risk (Low dose CSI 23.4 Gy + conformal boost + 4# CT)
- Greatest declines in HR patients who were < 7 yrs of age.
- No significant diff between low dose Vs high dose CSI

	AR	HR
IQ	- 0.99 (NS)	- 3.0
Reading	- 2.9	- 3.08
Spelling	- 2.7	- 3.4
Math	- 1.57	- 2.4

Mulhern JCO 2001

Is there a role for modified fractionation

Maybe YES

Strong radio-biologic rationale

Average-risk disease

Hyper-fractionated Radiation Therapy (HFRT):

CSI: 36 Gy/36#/4 wks, 1 Gy BID, 6 hrs apart, 5 days/wk

Boost: 32 Gy/32#/2.5 wks, 1 Gy BID, 6 hrs apart, 5 days/wk

High-risk disease

Hyper-fractionated Accelerated Radiation Therapy (HART):

CSI: 36 Gy/36#/3 wks, 1 Gy BID, 6 hrs apart, 6 days/wk

Boost: 24 Gy/20#/2 wks, 1.2 Gy BID, 6 hrs apart, 6 days/wk

Ongoing HFRT/HART trials : SIOP PNET IV, HIT 2000 and CNS 2001

CONFORMAL RADIOTHERAPY, REDUCED BOOST VOLUME, HYPERFRACTIONATED RADIOTHERAPY, AND ONLINE QUALITY CONTROL IN STANDARD-RISK MEDULLOBLASTOMA WITHOUT CHEMOTHERAPY: RESULTS OF THE FRENCH M-SFOP 98 PROTOCOL

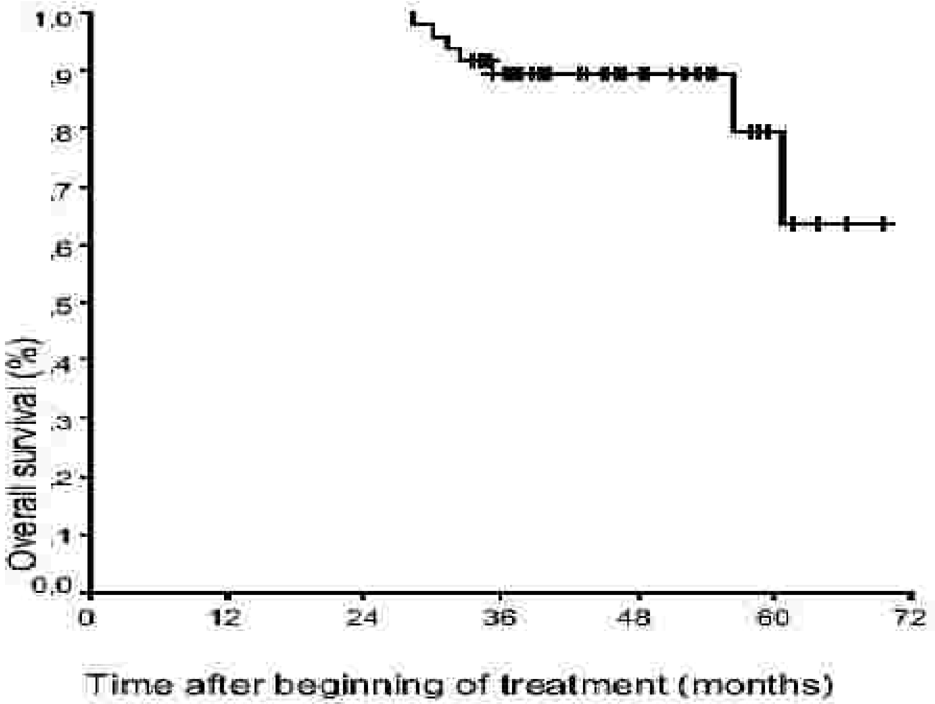


Fig. 1. Overall survival distribution (Kaplan-Meier method, 48 patients).

Table 2. Acute toxicities observed during radiotherapy

Toxicity	Grade II	Grade III	Total (%)
Platelets	1	1	2 (4)
Neutrophils	11	3	14 (29)
Hemoglobin	2	0	2 (4)
Skin	3	3	6 (12.5)
Mucosa	0	0	0 (0)

Carrie C: IJROBP 2005

Decline in IQ with HFRT

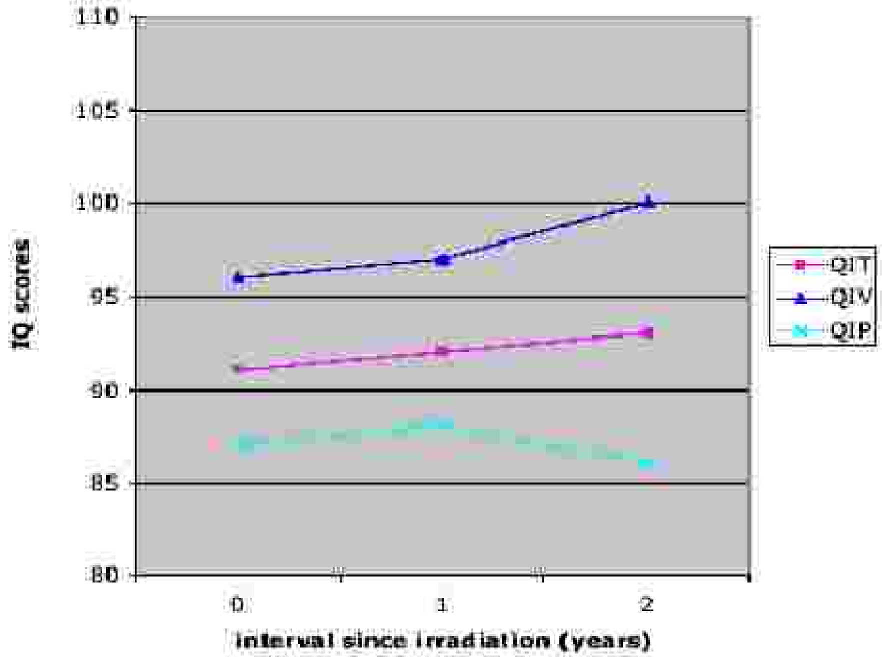


Fig. 3. Intelligence quotient (IQ) changes during early post-radi therapy M-SFOP98 period—Wechsler scales (22 patients).

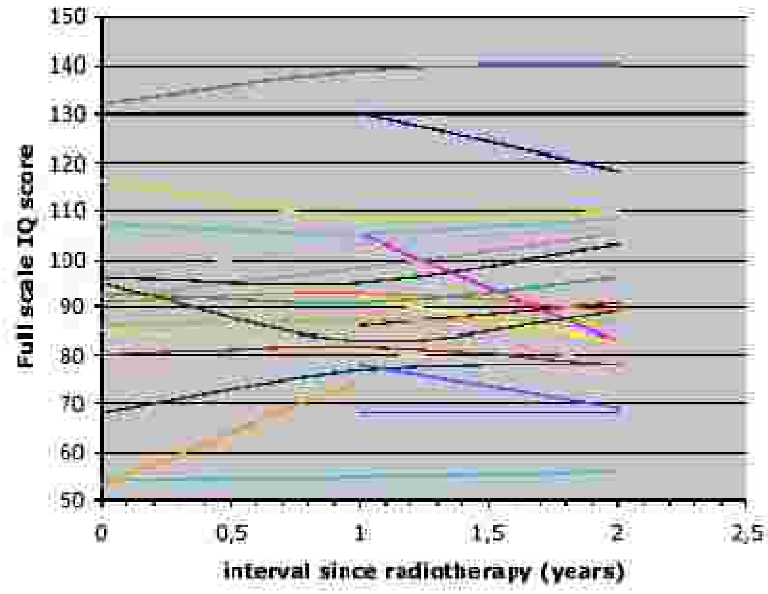


Fig. 4. Full-scale intelligence quotient (IQ) (individual patient data)—No significant full-scale IQ variation.

Is there an impact of RT deviations on outcome

A RESOUNDING YES

GOOD RADIOTHERAPY

- **CRUCIAL**
- **CRITICAL**
- **CENTRAL**

FOR SUCCESSFUL OUTCOME

IMPACT OF TARGETING DEVIATIONS ON OUTCOME IN MEDULLOBLASTOMA: STUDY OF THE FRENCH SOCIETY OF PEDIATRIC ONCOLOGY (SFOP)

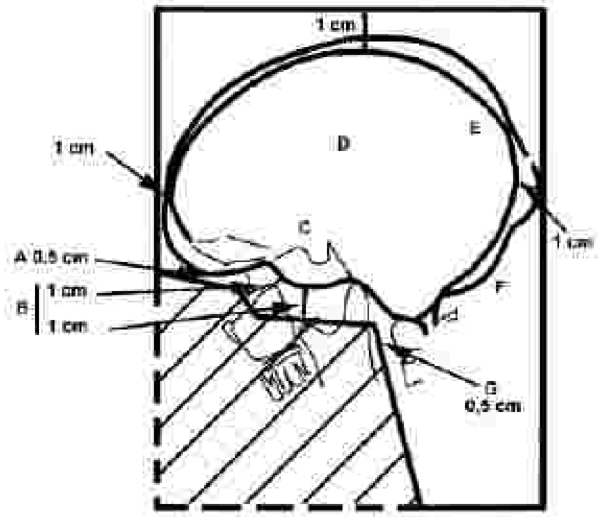


Table 1. Summary of site of targeting deviations*

	A	B	C	D	E	F	H	I
Minor deviation	40	53	9	19	11	34	19	16
%	24%	31%	5%	11%	7%	20%	11%	9.5%
Major deviation	28	18	6	3	5	8	3	5
%	17%	11%	4%	2%	3%	5%	2%	3%
Total *n*	68	71	15	22	16	42	22	21
%	40%	42%	9%	13%	10%	25%	13%	13%

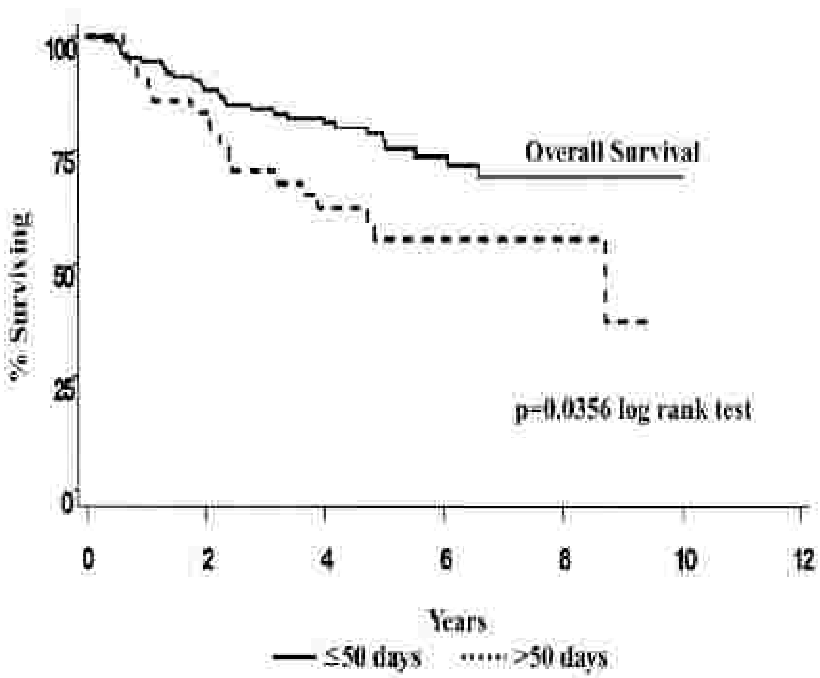
67% risk of tumour relapse at 3 years with 2 major deviations

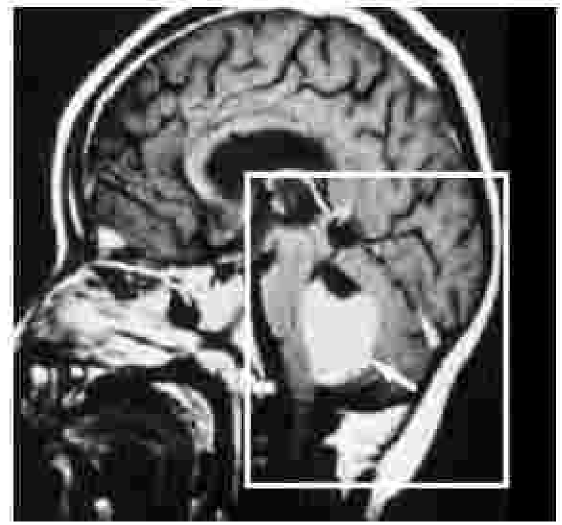
78% risk of tumour relapse at 3 years with 3 major deviations

Insignificantly increased risk of relapse with minor deviations

Carrie C: IJROBP 1999

Radiotherapy Parameters Affecting Outcome
UKCCSG PNET-3 study
217 children: chemo + RT vs RT alone. 176 analyzable





131 RT Planning films reviewed PF recurrence in 34% with deviations vs 16% if no deviation in PF fields (P=0.04)

Taylor: IJROBP 2004

RADIOTHERAPY IN PEDIATRIC MEDULLOBLASTOMA: QUALITY ASSESSMENT OF PEDIATRIC ONCOLOGY GROUP TRIAL 9031

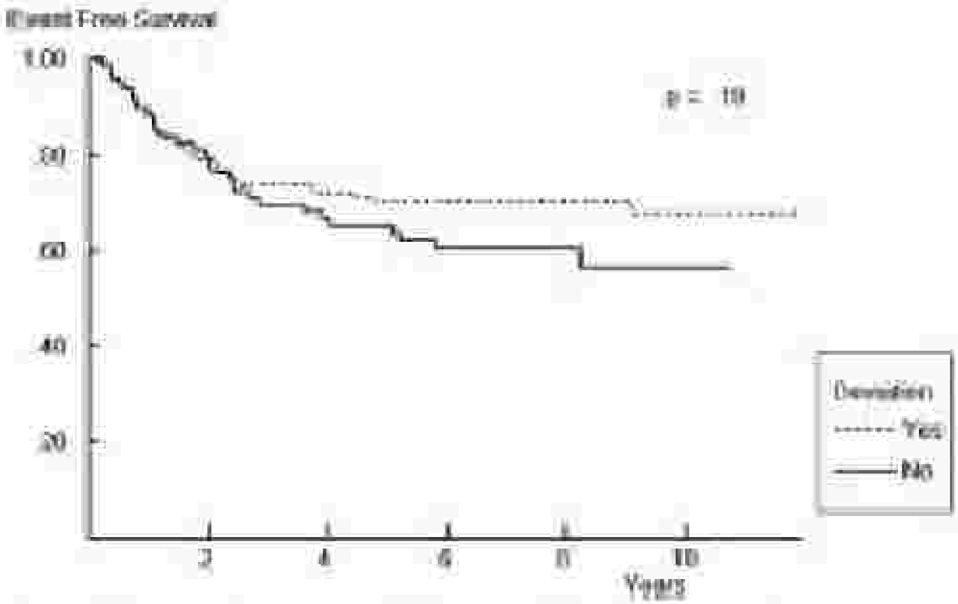


Fig. 1. Event-free survival of 188 eligible patients by treatment deviation.

Table 1. Summary on treatment deviations of 160 patients fully evaluable for all treatment parameters

Type	Deviation	Number of patients (percent)
All treatments	0	69 (43%)
	1	50 (31%)
	2	31 (19%)
	3	9 (6%)
	4	1 (1%)
Brain	No	119 (74%)
	Yes	41 (26%)
Posterior fossa	No	96 (60%)
	Yes	64 (40%)
Spine*	No	149 (93%)
	Yes	11 (7%)
Primary tumor	No	133 (83%)
	Yes	27 (17%)

Miralbell IJROBP 2006

How best to integrate CT with RT

- Delay in starting RT results in inferior outcome: Halperin
- Prolongation of RT duration negatively impacts upon survival: Del Charco & SIOP PNET 3
- Pre RT CT inferior to post RT CT: CCG 921 and HIT 91
- Pre RT CT does not improve survival compared to RT alone: SIOP II & SIOP PNET 3
- Pre RT CT followed by reduced dose CSI inferior: SIOP II

Does adjuvant CT improve survival

Average-risk disease

Definitely NOT

CCG 942 & SIOP I

High-risk disease

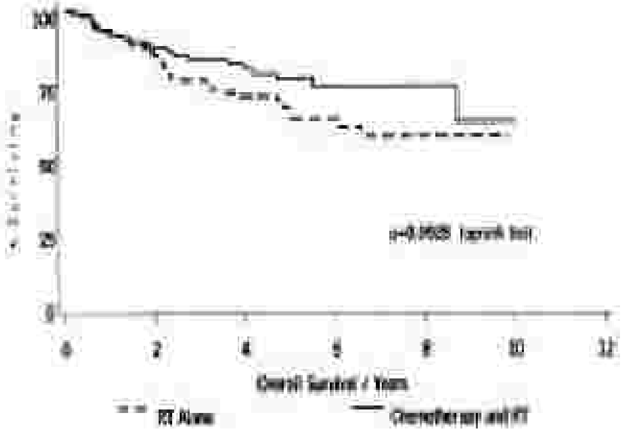
Definitely YES

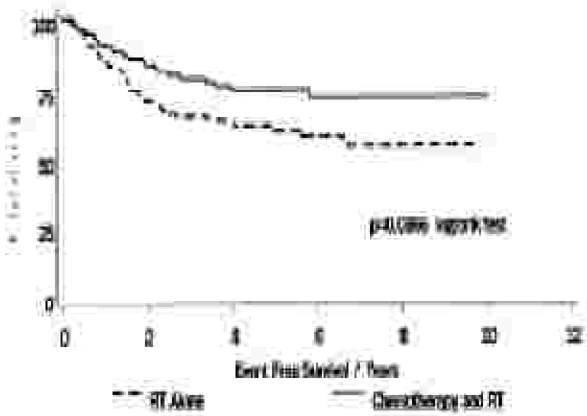
Evans, Tait et al

HIT 91, CCG 942 & SIOP I

POG 9031 & SIOP PNET 3

Results of a Randomized Study of Preradiation Chemotherapy Versus Radiotherapy Alone for Nonmetastatic Medulloblastoma: The International Society of Paediatric Oncology/United Kingdom Children's Cancer Study Group PNET-3 Study





- 1st large multicentre RCT to show better EFS with CT (74.2% vs 59.8%; *p*=0.0366)
- M0-M1 PreRT CT Vs RT alone
- VCR + Eto + Carbo/Cyclo → CSI
- 217 pts (179 analyzable), 5 year f/u
- Overall survival – not different
- Significant impact of RT duration on EFS

Taylor JCO 2003

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

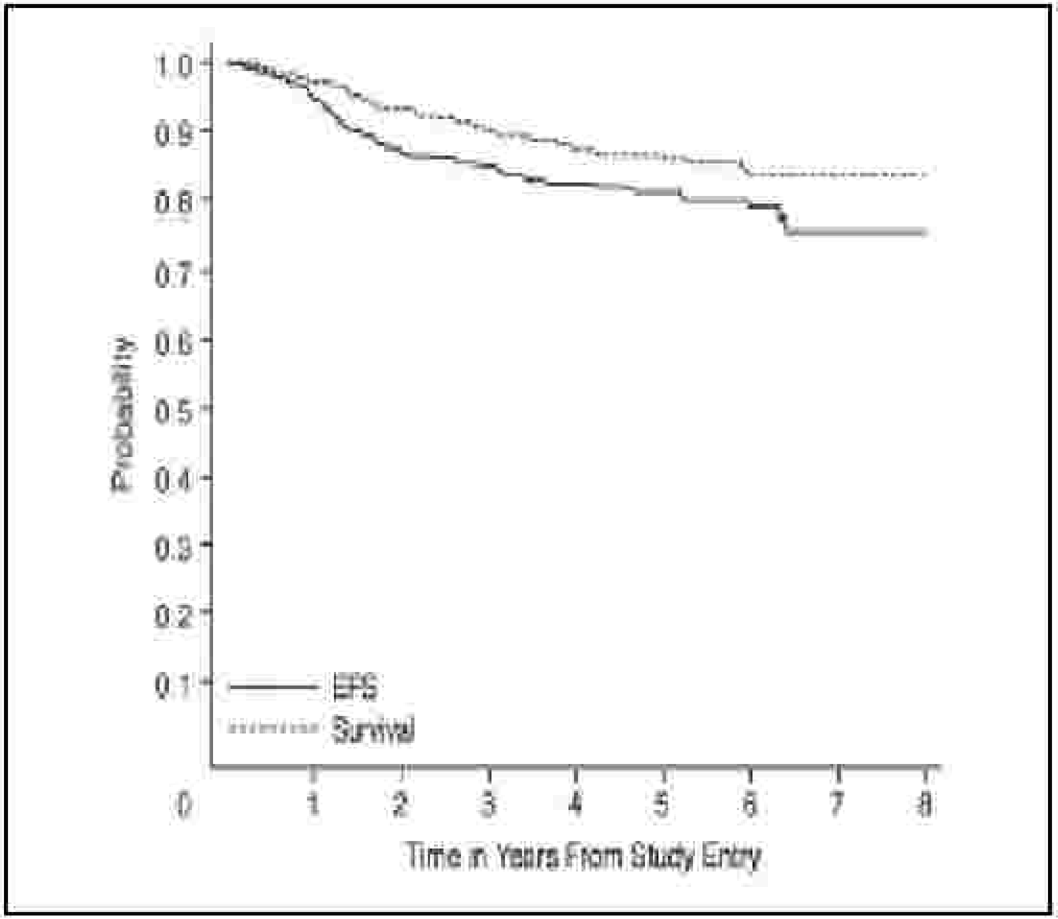


Fig 1. Event-free survival (EFS) and survival from study entry.

Packer: JCO 2006

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	

Randomized Controlled Trial

Least Toxic Standard Dose RT alone schedule

Vs

Reduced dose CSI + CT

(average-risk disease)

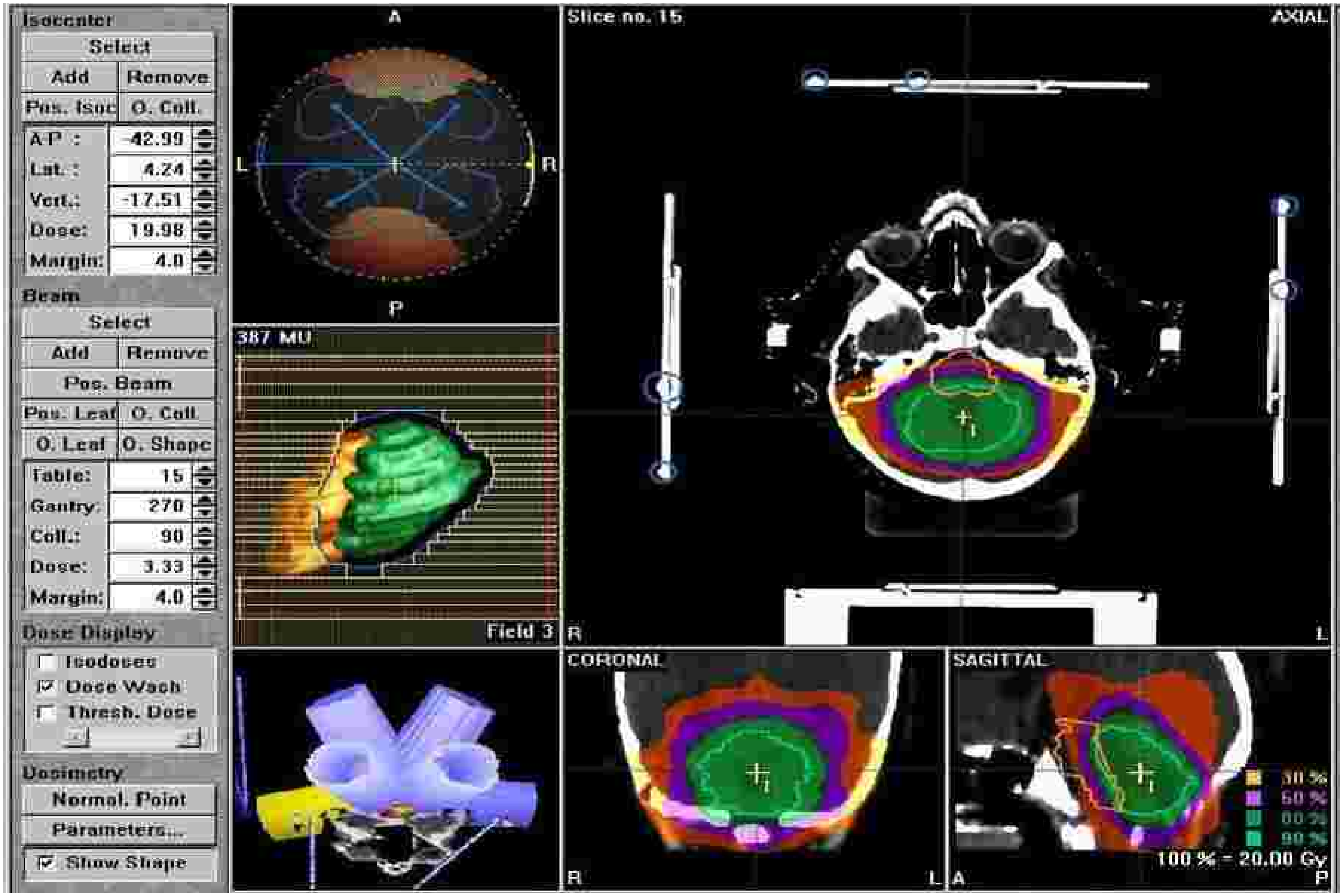
OVERKILL or OVERDUE

Maximizing Cure

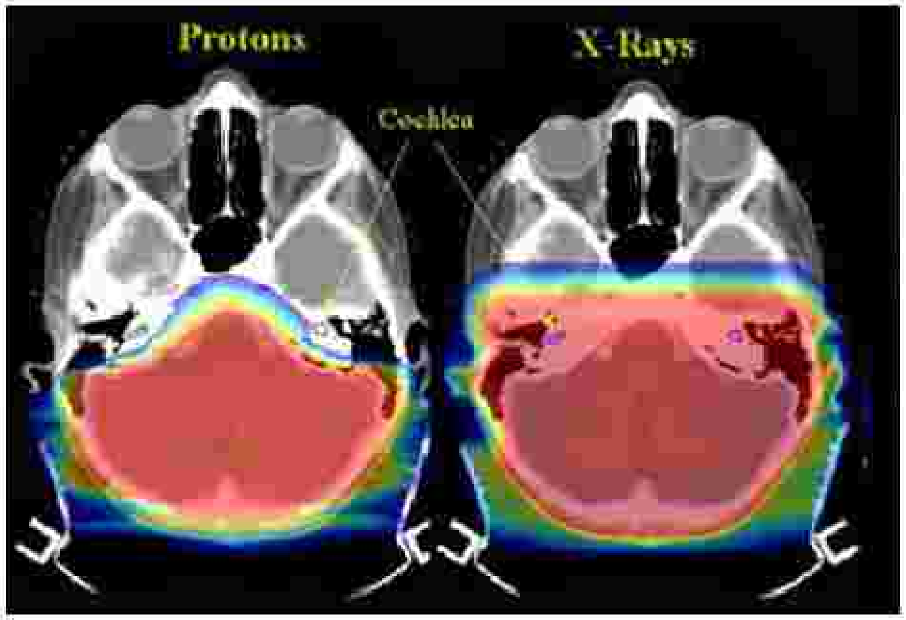
Minimizing Sequelae

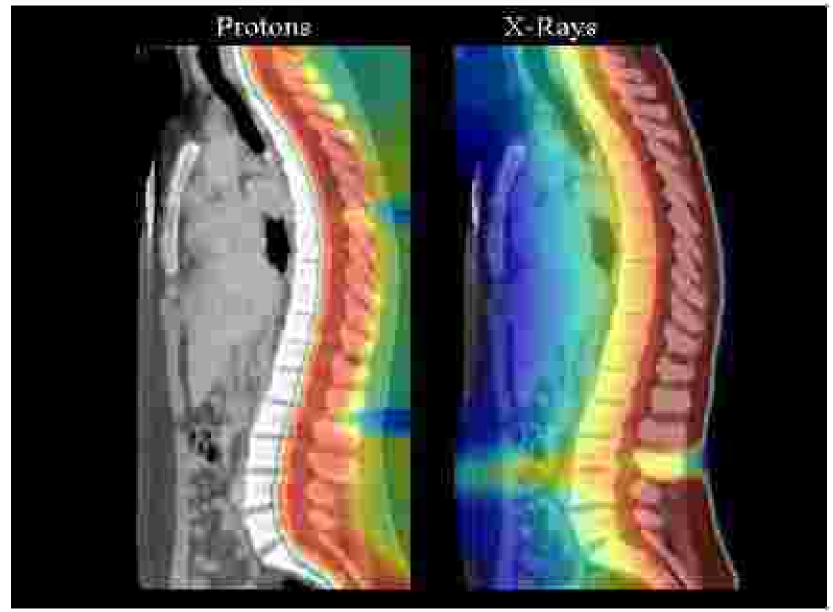
Newer perspectives in RT for Medulloblastoma

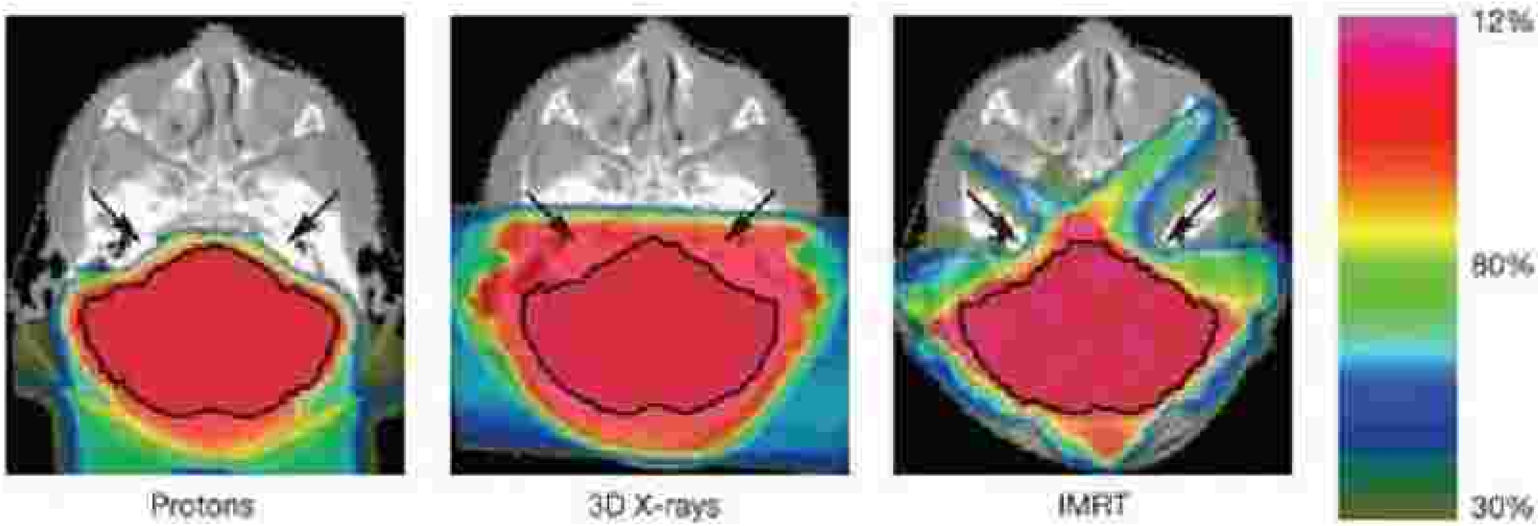
Stereotactic Conformal Radiation Therapy for Tumour Bed Boost



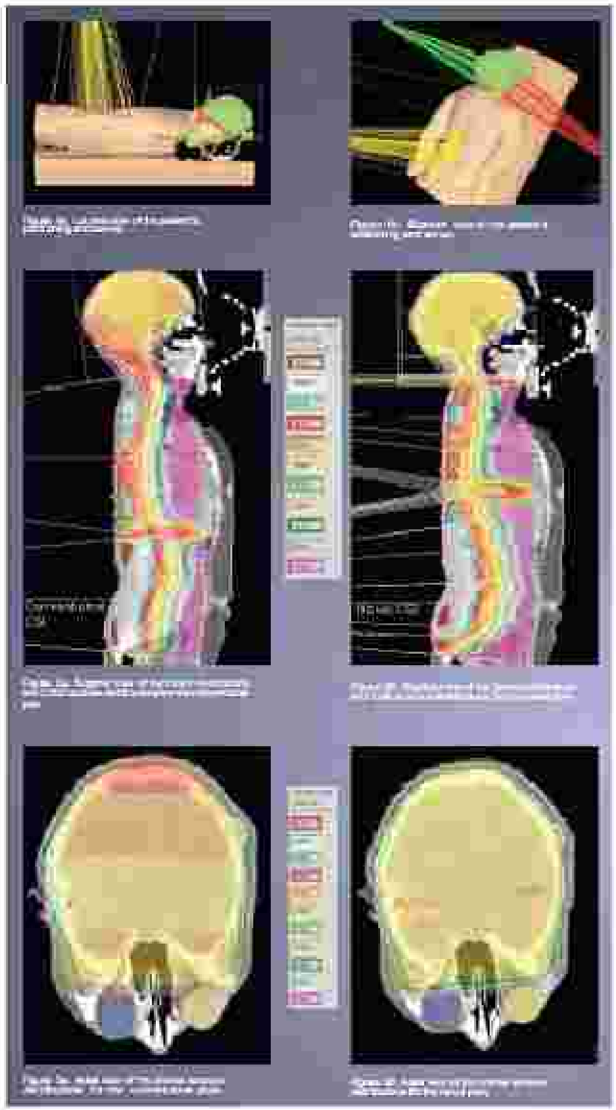
Protons vs photons for Medulloblastoma

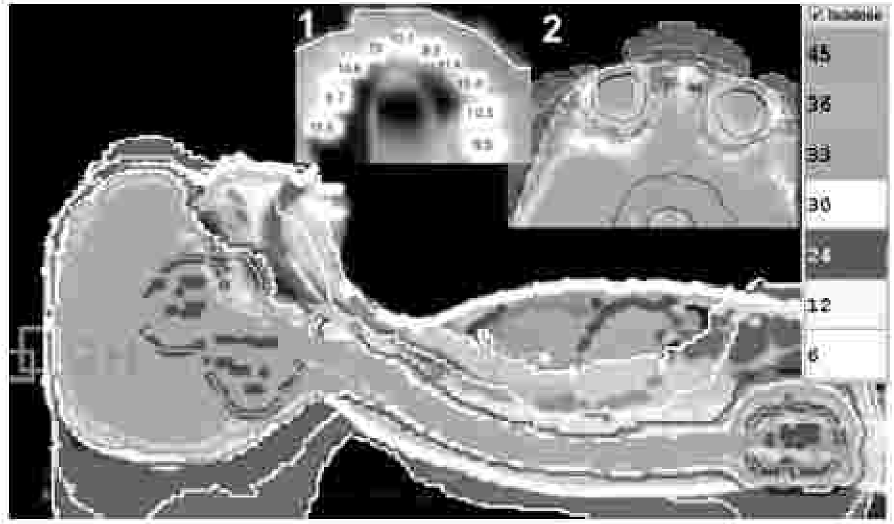


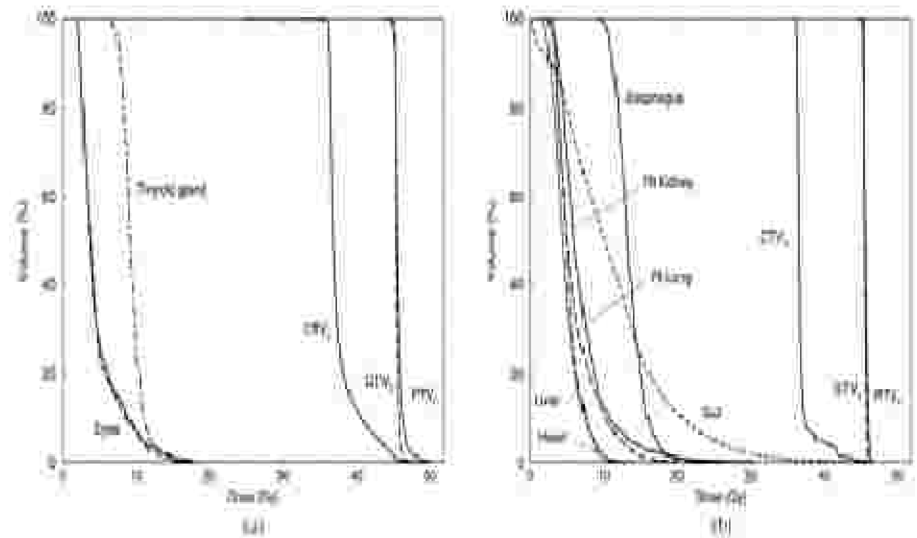




IMRT for CSI




1
2
45
36
33
30
24
12
6


Thyroid gland
Eyes
Esophagus
Rt Kidney
Rt Lung
Liver
Heart
(a)
(b)