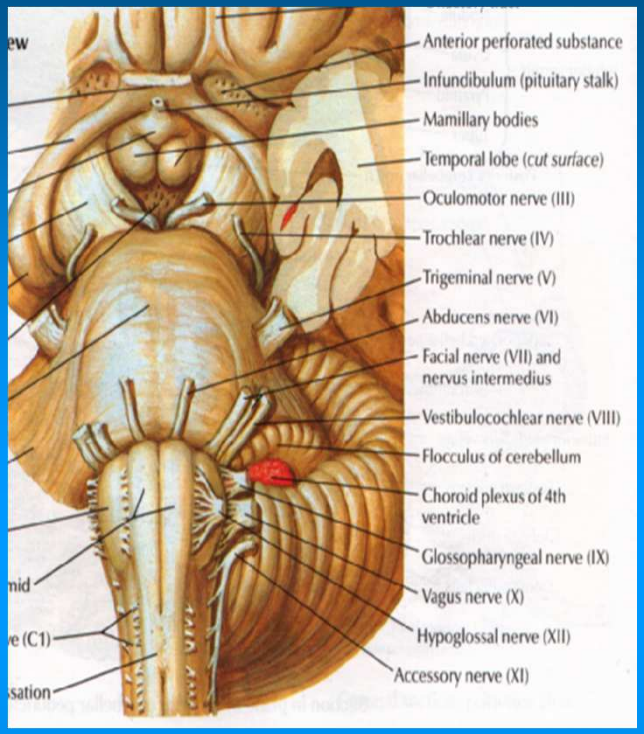
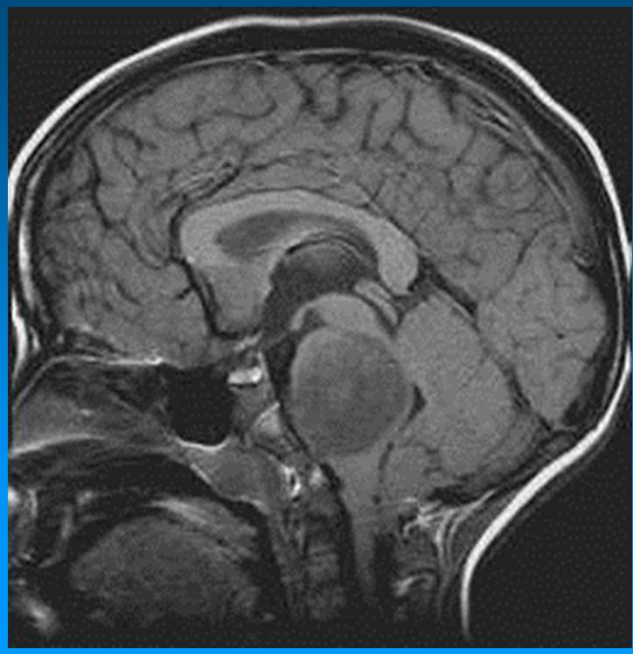
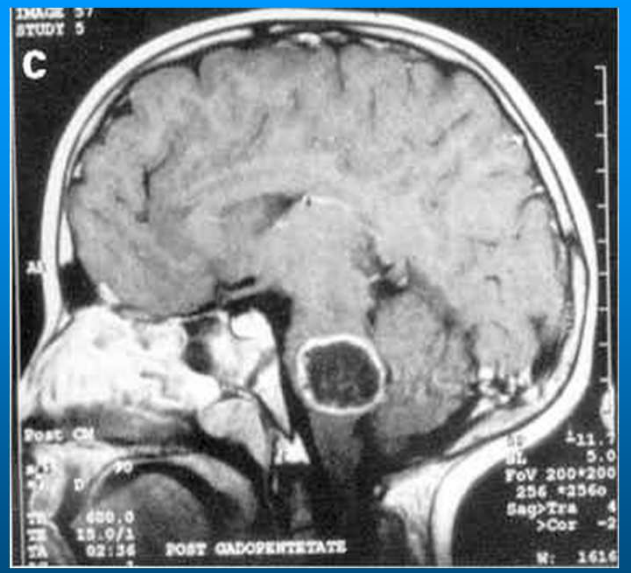
Brain stem glioma





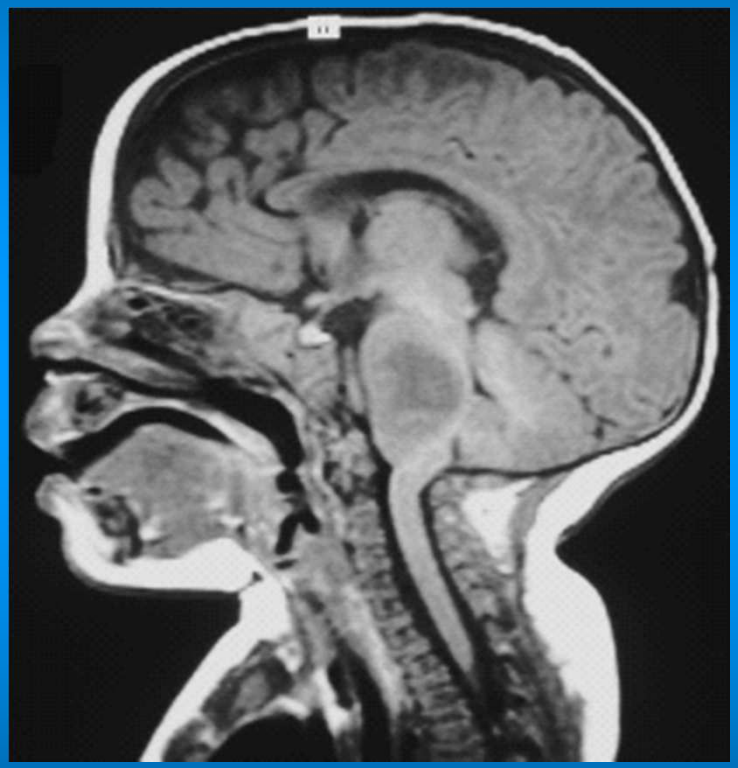


Insidious/sudden onset
Cranial nerve palsies
Long tract signs (hemiparesis)
Cerebellar signs (ataxia)

Long history – better prognosis

Diffuse pontine tumours

Major therapeutic challenge



- Typically present with short history
- Surgery (including biopsy) not feasible
- Most are fibrillary, but on autopsy high-grade
- Direct RT in view of typical clinico-radiological picture
- MRS/perfusion/PET could be complementary

Hyperfractionated RT

POG #9239:

132 pts between 6/92 and 3/96

randomized

Arm 1: 66 pts

54Gy/1.8

+

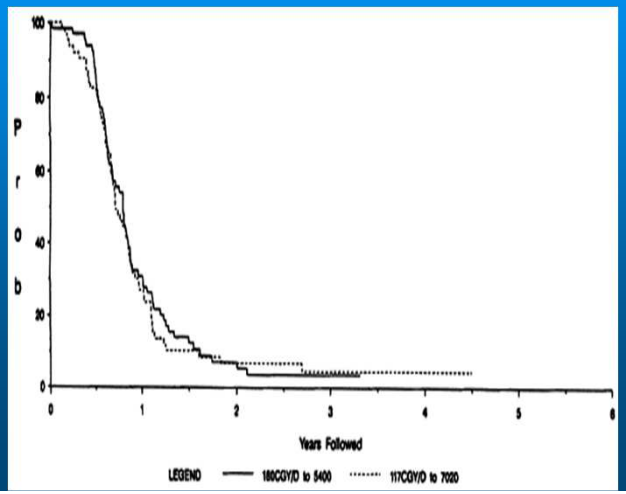
Cisplatin 100mg/m2 (120hr cont. infusion)

Arm 2: 64 pts

HFT: 70.2Gy/1.17Gy BID

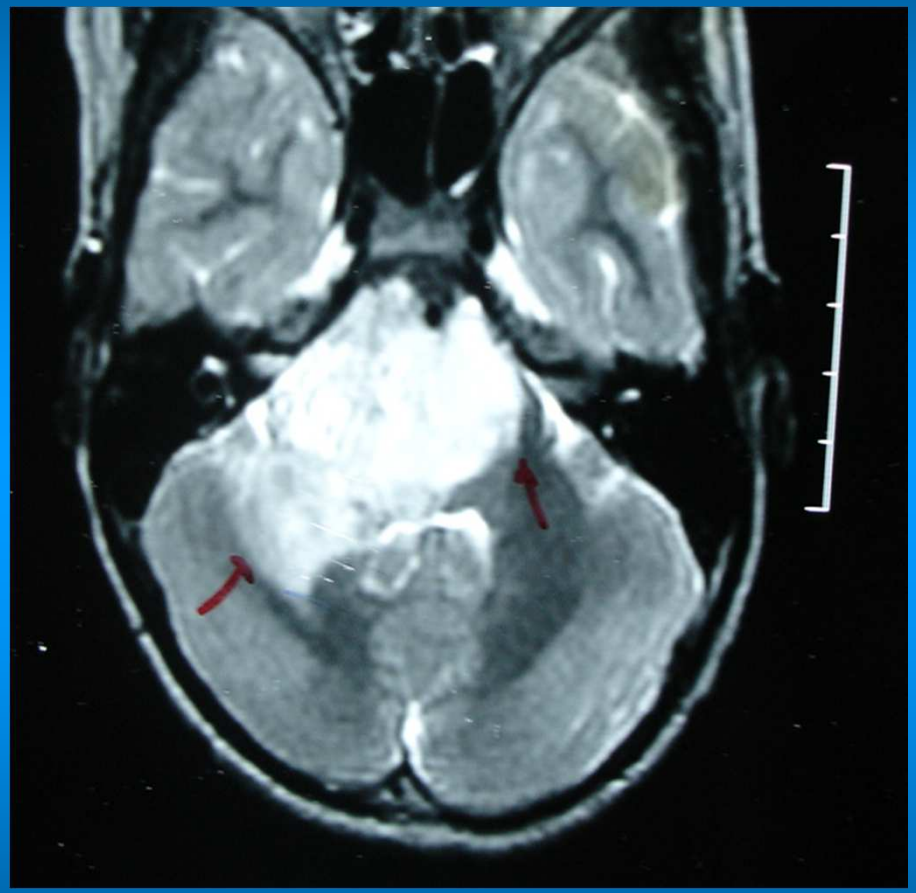
+

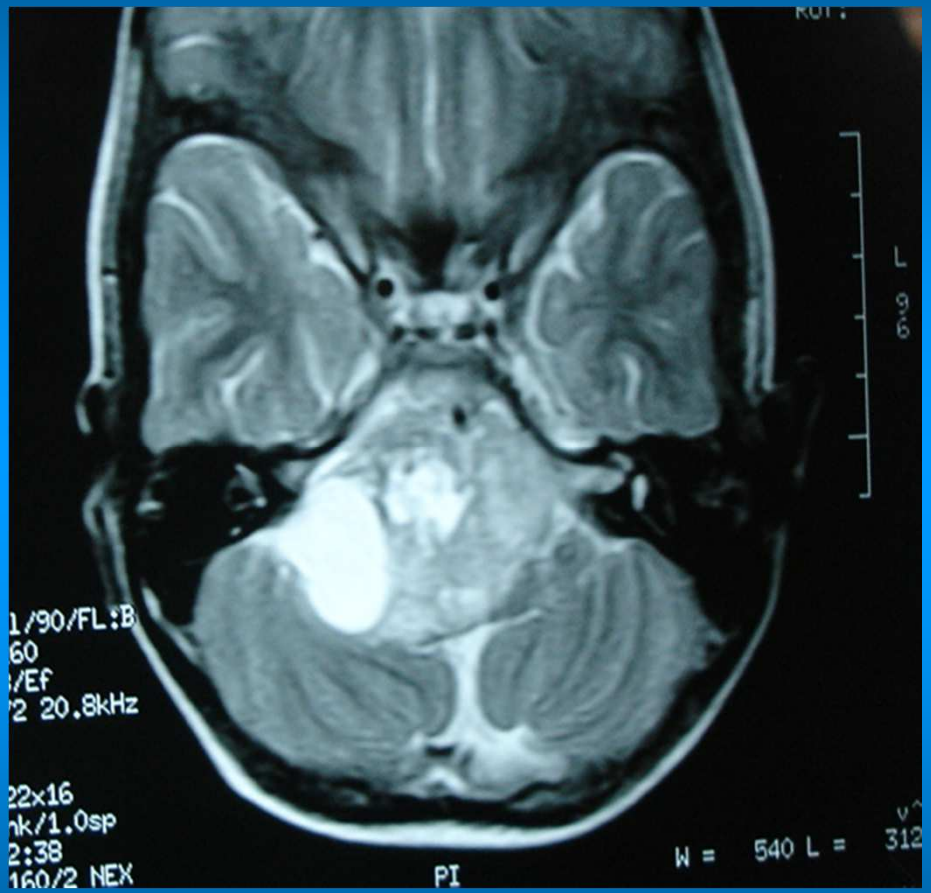
Cisplatin 100mg/m2 (120hr cont. infusion)



Mandell IJORBP; 1999: 43(5)

TMH RT + TMZ study; phase II design





Little encouraging; await final results

Jalali NeuroOncology 2006; 2007;9 (2):189

Study design

Phase II Study; TMC IRB Cleared
Investigator initiated

Clinicoradiologically consistent diffuse intrinsic pontine glioma
Biopsy wherever possible but not mandatory

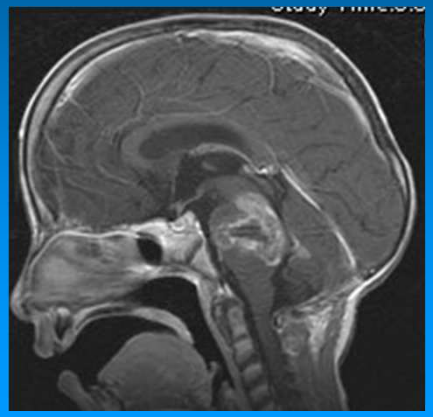
RT dose: 54 Gy/30#/6weeks

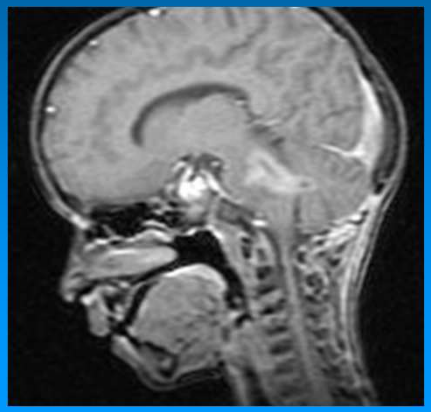
Concurrent TMZ with RT: 75mg/m^2; Day 1 - Day 42

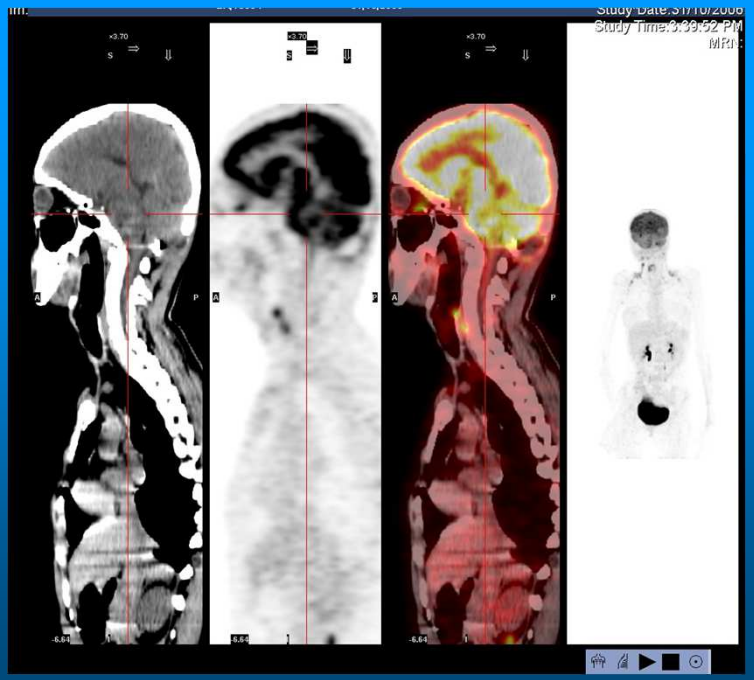
Adjuvant TMZ: 200 mg/m^2 Day 1- 5; 4 weekly

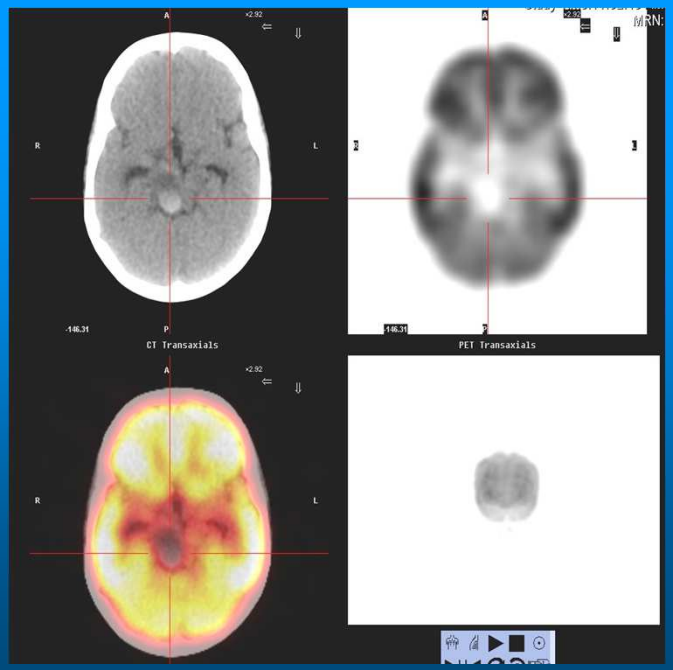
Max: **12 cycles of adjuvant TMZ**

Detailed Imaging Protocol





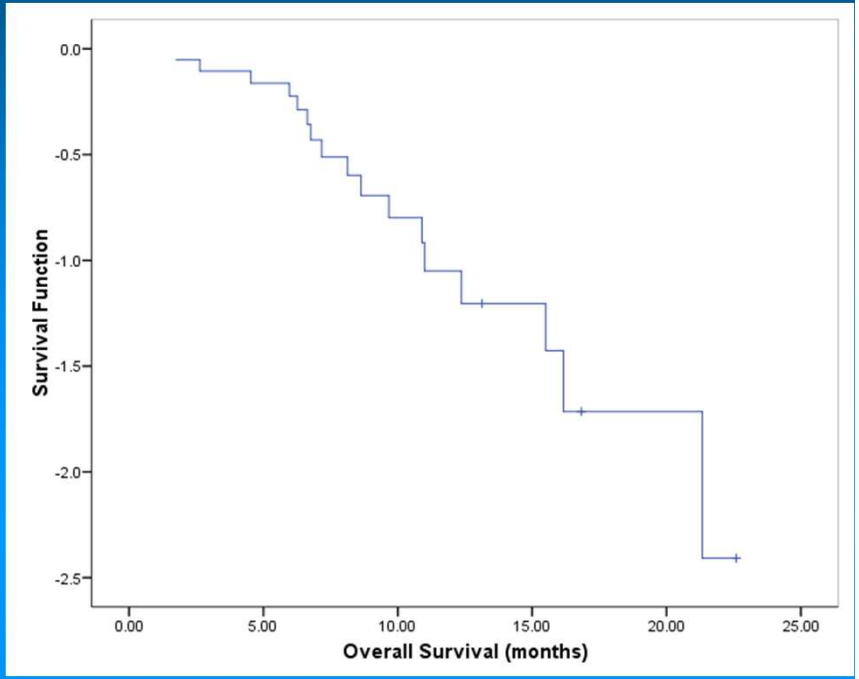




- MRI Brain plain+contrast
- MRI Spine
- MR Spectroscopy
- MR Perfusion
- FDG PET Scan

Survival and events

Mean overall Survival	11.87 mo
Median	9.15 mo
> 6 months Survival	16 (80%)
> 9 months Survival	10 (50%)
> 1 year Survival	07 (35%)
>18 months Survival	02 (20%)
Alive	01 (5%)
Death	19 (95%)
Death due to progression	19 (100%)
Death with spinal metastasis	03 (15%)



Thrombocytopenia Gr-III/IV	03
Vomiting, Grade-III	03
Hospitalization	06

Jalali et al EANO 2008

RT+TMZ in DIPG

Int. J. Radiation Oncology Biol. Phys., Vol. ■, No. ■, pp. 1–6, 2009

0360-3016/09/$–see front matter

ELSEVIER

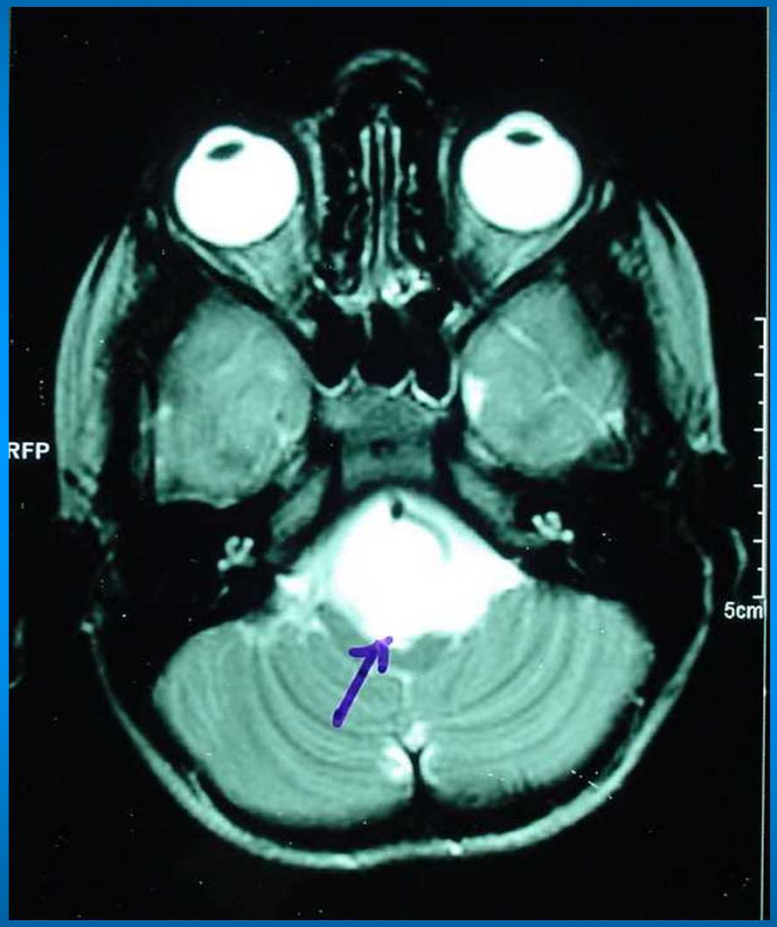
doi:10.1016/j.ijrobp.2009.04.031

CLINICAL INVESTIGATION

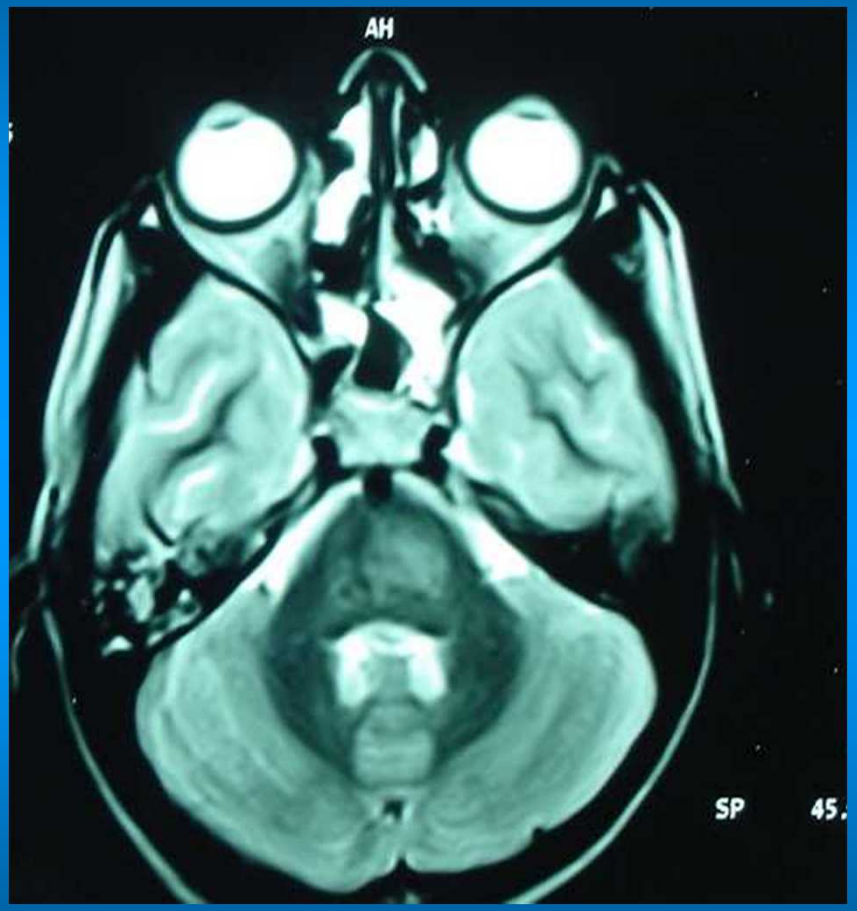
PROSPECTIVE EVALUATION OF RADIOTHERAPY WITH CONCURRENT AND ADJUVANT TEMOZOLOMIDE IN CHILDREN WITH NEWLY DIAGNOSED DIFFUSE INTRINSIC PONTINE GLIOMA

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.†

*Department of Radiation Oncology; and †Medical Oncology, Division of Pediatric Oncology, Tata Memorial Centre, Mumbai, India



Pre Treatment

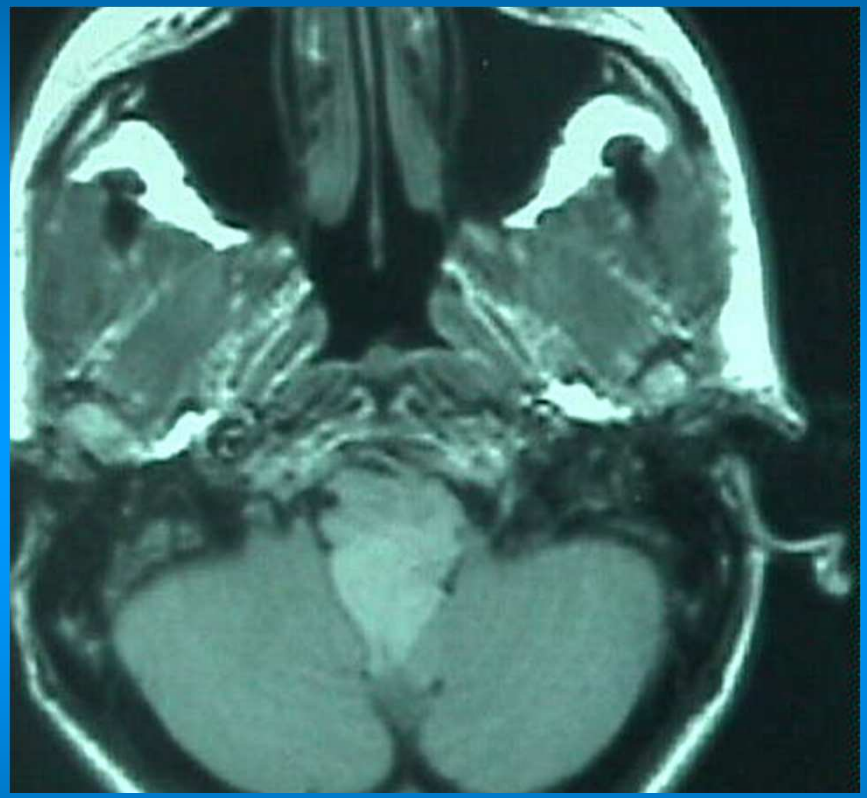


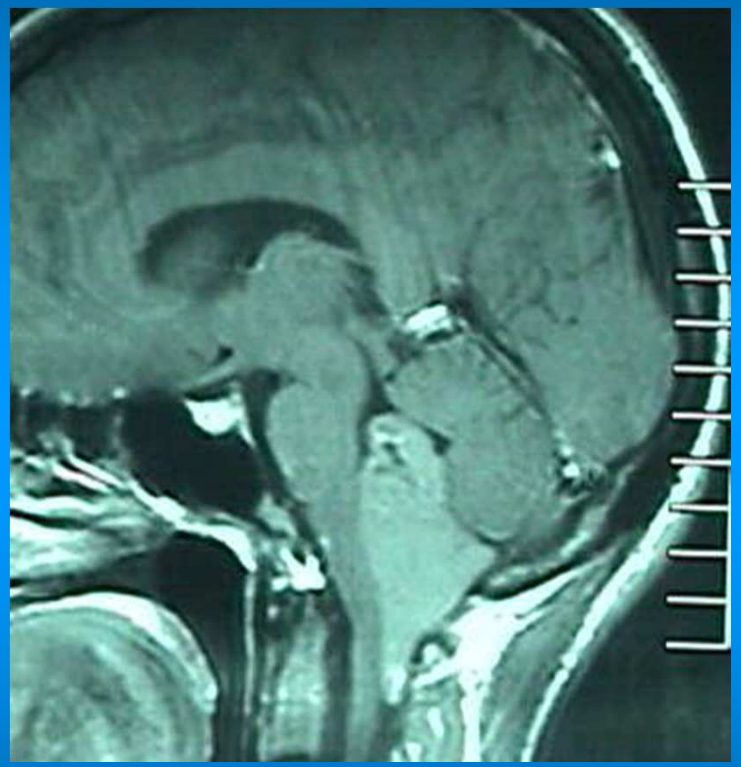
Post RT+TMZ

Prognostic factors

Variables	*Parameters*	*Mean OS (mo)*	*p-value*
MR Perfusion	Hyperperfusion	8.87	*0.043*
	Hypoperfusion	15.10	
Diagnosis with MRI, MRS & Perfusion scan	High grade	6.8	*0.001*
	Low grade	15.14	
Histopathological diagnosis	Grade-III	7.05	0.112
	Grade I/II	14.19	
Clinical Response	Partial / No response	8.23	*0.048*
	Significant response	13.31	
MRI Response	No / minimal response	11.63	0.236
	Partial response	7.21	
PET Response	No/ partial response	14.59	0.966
	Complete response	13.1	

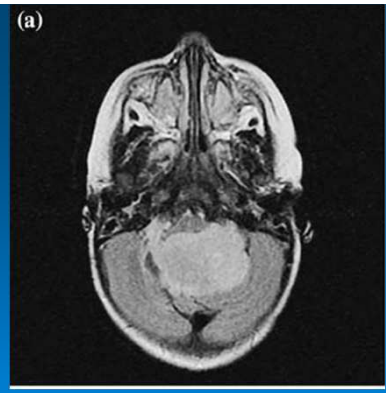
Ependymoma





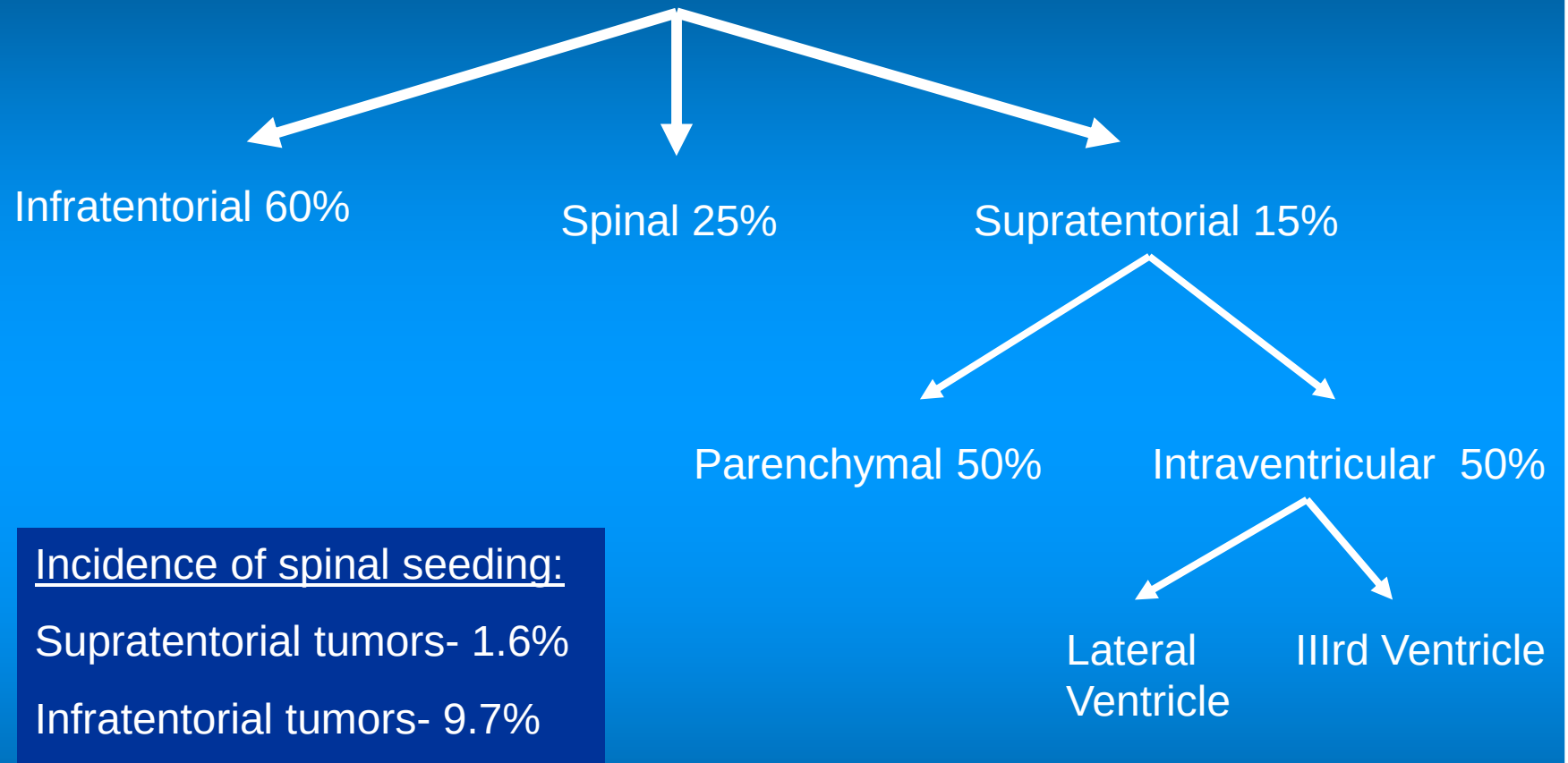
- 10% of all childhood CNS tumours
- 90% are intracranial; 2/3 within the posterior fossa
- 50% of pts are < 5yrs old, 25% are less than 2
- Difficult to treat, perplexing tumours

Epidemiology



- Third most common CNS tumor in children
- 12% of childhood brain tumours
- Annual Incidence rates vary between 2-4 per million.
- Asia: <2 per million
- Scandinavian countries: >4 per million
- TMH Data 2006: 2.4% of all CNS tumors.
- 46 patients were registered with median age of 18.5 yrs.

Localization



Incidence of spinal seeding:

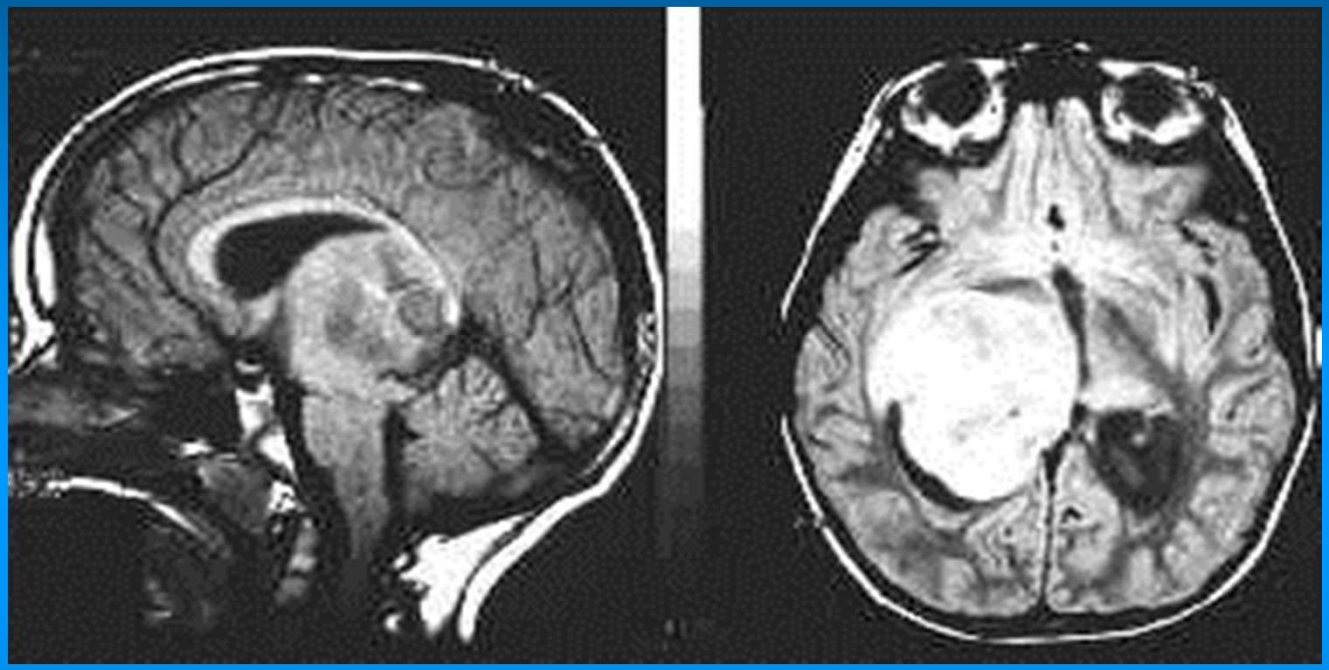
Supratentorial tumors- 1.6%

Infratentorial tumors- 9.7%

High grade tumors- 8.4- 20%

Low grade tumors- 2-4.5%

Surgery



Surgery treatment of choice and the most important prognostic factor

Gross tumour resection (GTR) - 50-75% long term control

Usually grow in highly specialized areas of CNS.

Van Veelan JNS 2002

Schild IJROBP 1998

Surgery

Frequency of complete resections higher in surgical series than in RT series

25-93% -Supratentorial.
35-72% for Infratentorial

- Need to classify patients on the basis of residual tumour as in medulloblastoma.
- Need for second surgery if gross total resection not performed at the first attempt.
- Although gross resection is the most important prognostic factor, cranial nerves should not be sacrificed and caution exercised near the brainstem
- Newer approaches being tried
- Preoperative chemotherapy being evaluated in current Children Oncology group study.

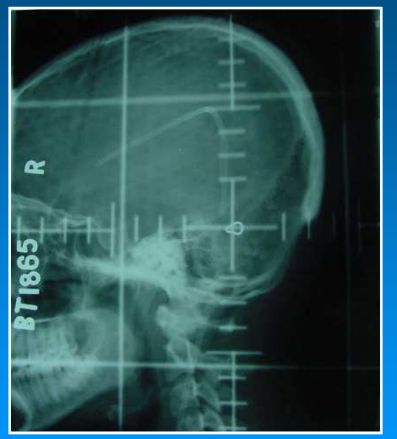
Radiotherapy

- No randomised trial of RT vs. no RT, but large data about efficacy of RT
- Craniospinal RT (CSI) - in 1970's and 80's, but does not influence local control/survival.
- Present recommendations- local RT (even in anaplastic)
- CSI – if spinal mets (CSF or MRI)
- Unresolved questions – a) RT in completely resected tumours
  b) can we avoid RT in very young children

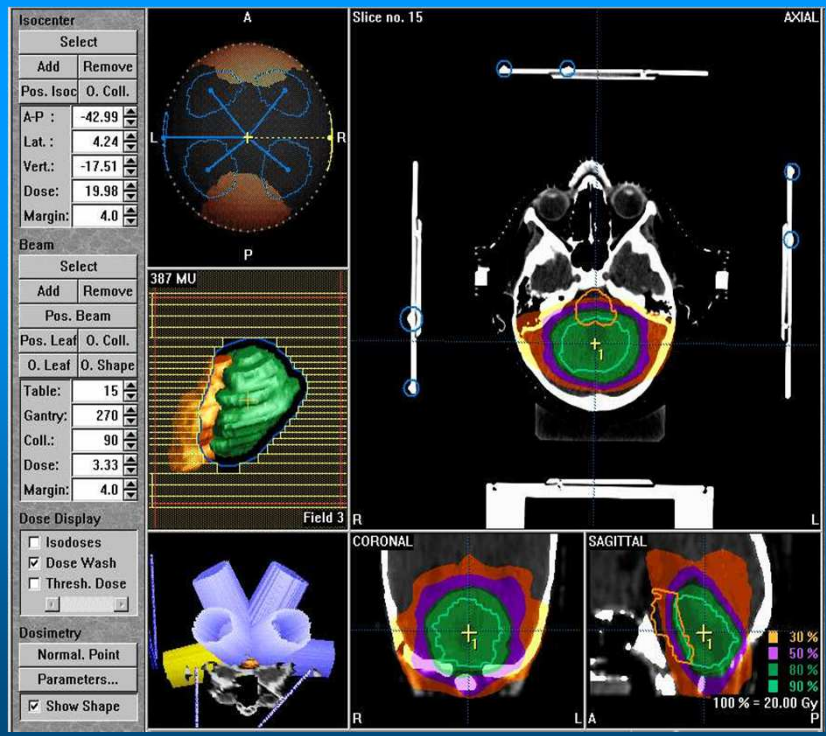
Merchant IJROBP 2002;53:51-7

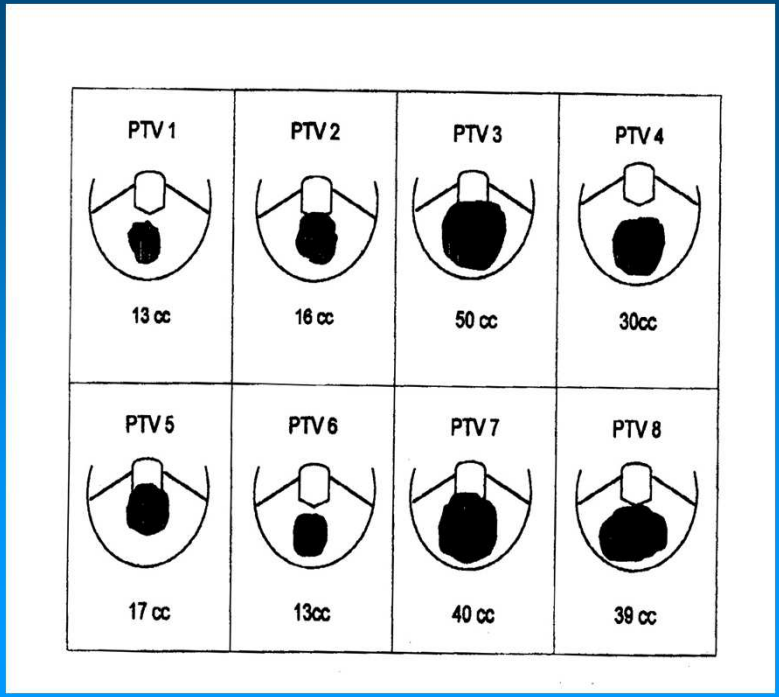
Vanuytsel IJROBP 1992;23:313-9

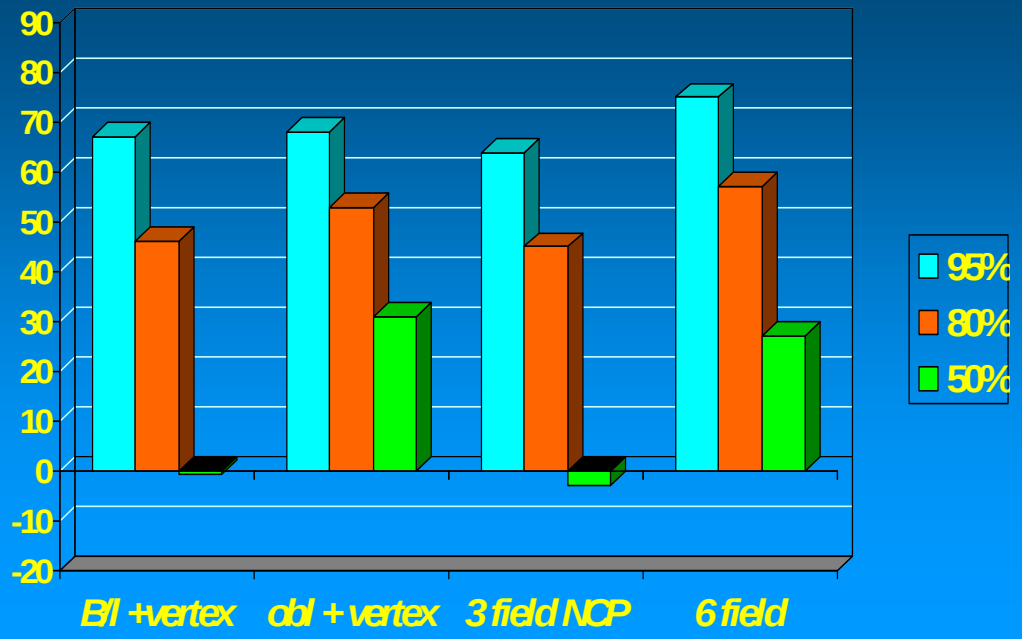
Radiotherapy



- Traditionally post fossa irradiation, cover inferiorly upto C3-C4
- Local RT= GTV + margin (2 cms)
- Conformal (3D CRT, Stereotactic RT with lesser margins)







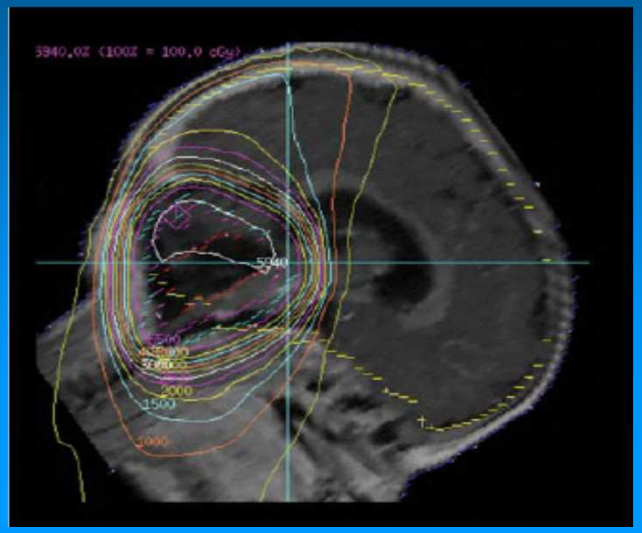
Stereotactic conformal RT attractive option

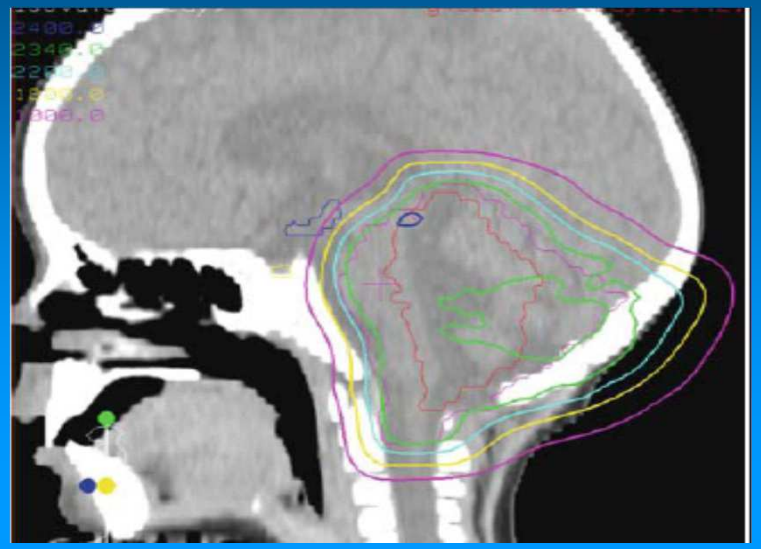
minimise treatment related toxicity; dose escalation

6 field noncoplanar technique the most optimal

Murthy Radioth.& Oncol 2003;67:191-8

RT1 (St Jude's) Study





- Majority of the patients were younger- >60%
- No difference in PFS between younger than 3 yrs and older patients
- No difference between Infratentorial and supratentorial lesions
- PFS better among patients without chemotherapy than with chemotherapy.
- Excellent functional outcomes for the patients younger than 3 years.
- Efficacy of Conformal techniques

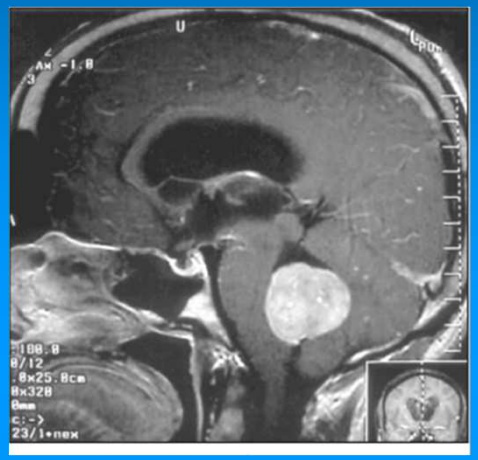
Chemotherapy

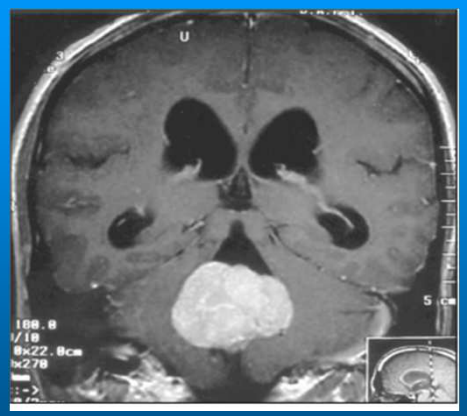
- Role unknown
  - 95% of pediatric ependymomas express P glycoprotein.
  - 75% of them express MDR1 transcripts
- Several disappointing phase II studies
- Randomised trial of RT Vs RT + adj V, CCNU & P – no benefit (MPO 1996;27:8-14)
- CCG trial – V, CCNU, P Vs 8-in-1 chemo: no difference (JNS 1999;88:695-03)
- FSOP study- dismal 22% 4 yr PFS with chemo alone

All radiotherapy deferral strategies have been more or less abandoned in North America after RT-1 study

Medulloblastoma

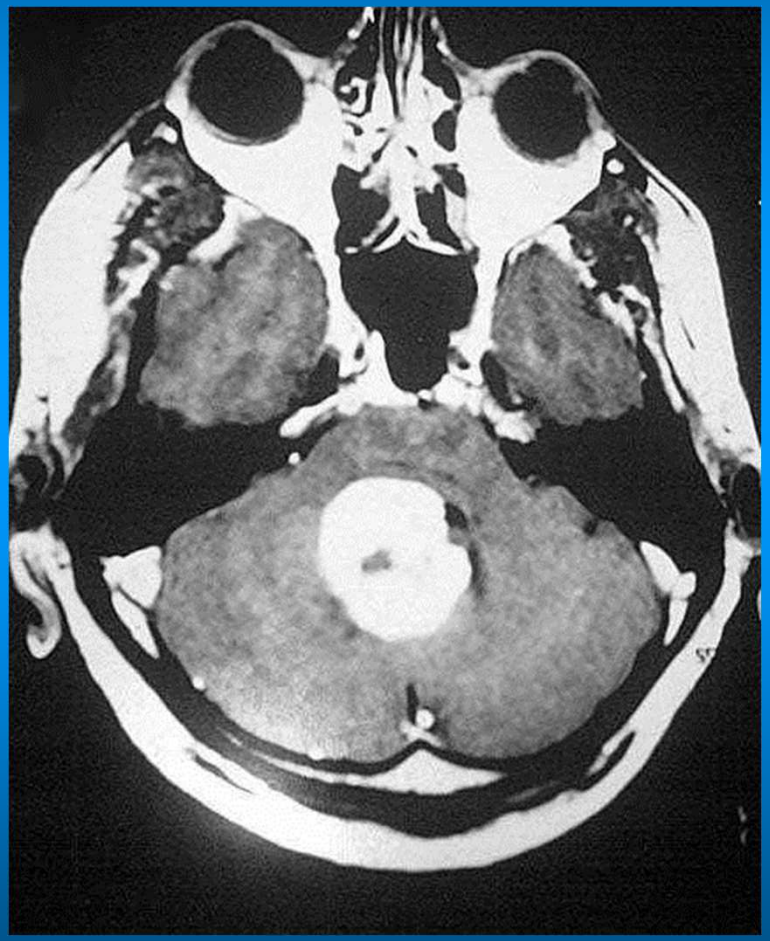
- Commonest malignant brain tumor in children
- 20-25% of all childhood brain tumors
- Belongs to family of small blue RCT
- Median age at presentation: 5-8 years
- High propensity of CSF dissemination (20-30%)
- Current standard of care: Maximal safe resection followed by adjuvant radiation therapy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





Medulloblastoma

Risk categorisation



Low/average risk

- no/minimal residual
  - post op scan <1.5 cc
- M0 disease

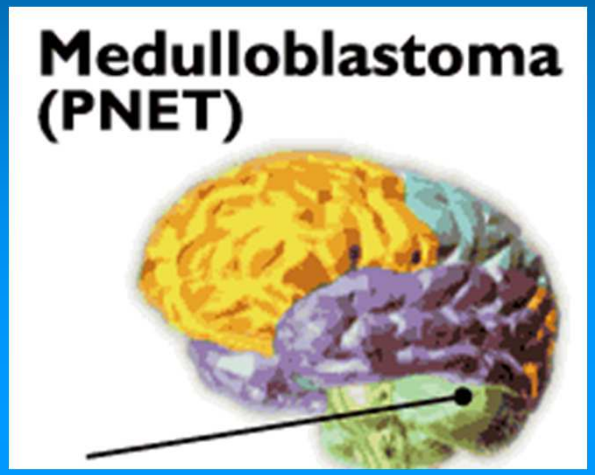
  spinal MR/CSF
- age > 3 years

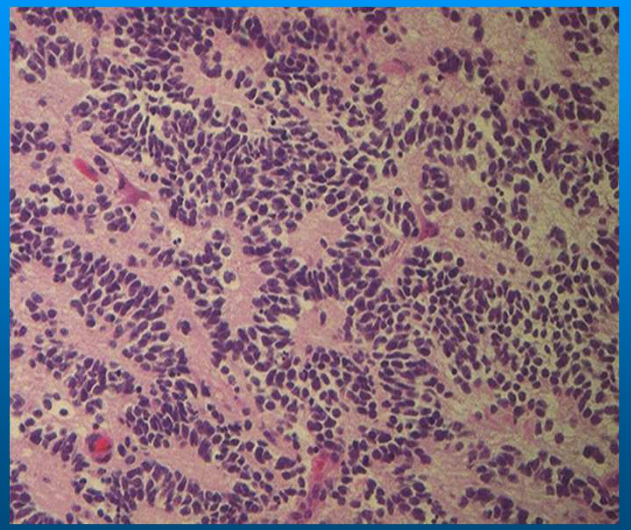
High risk (RT + CT)

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

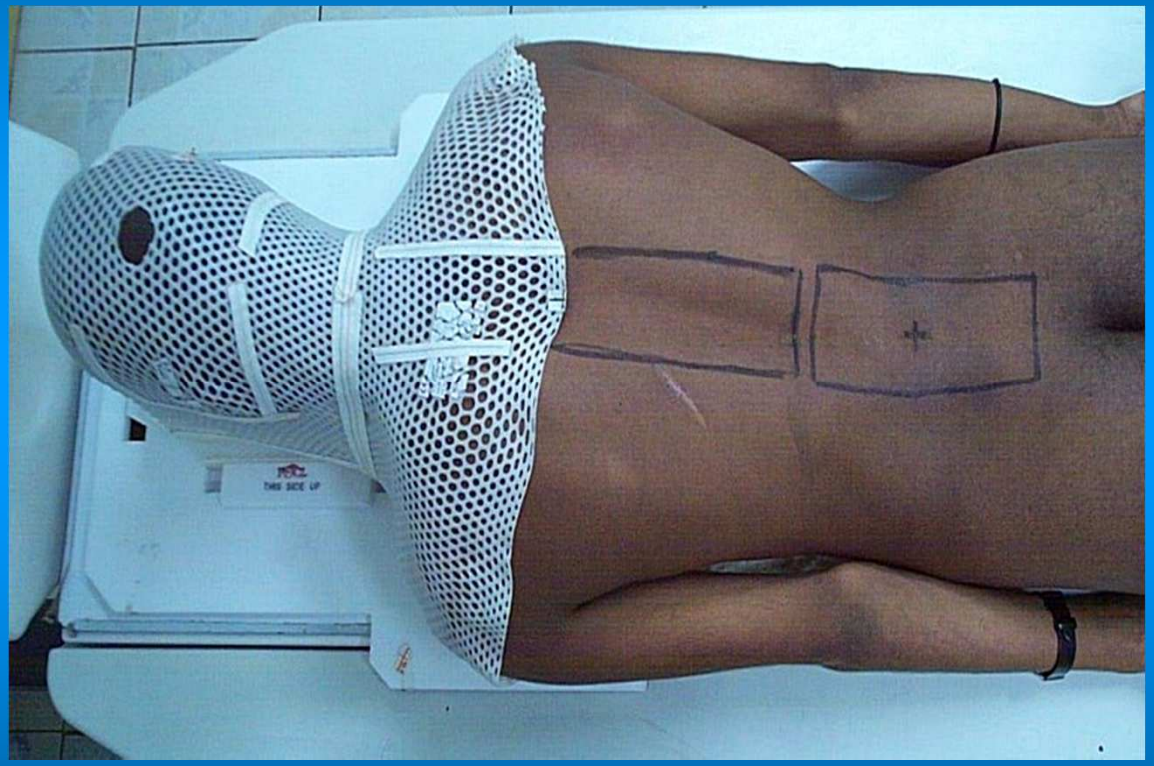


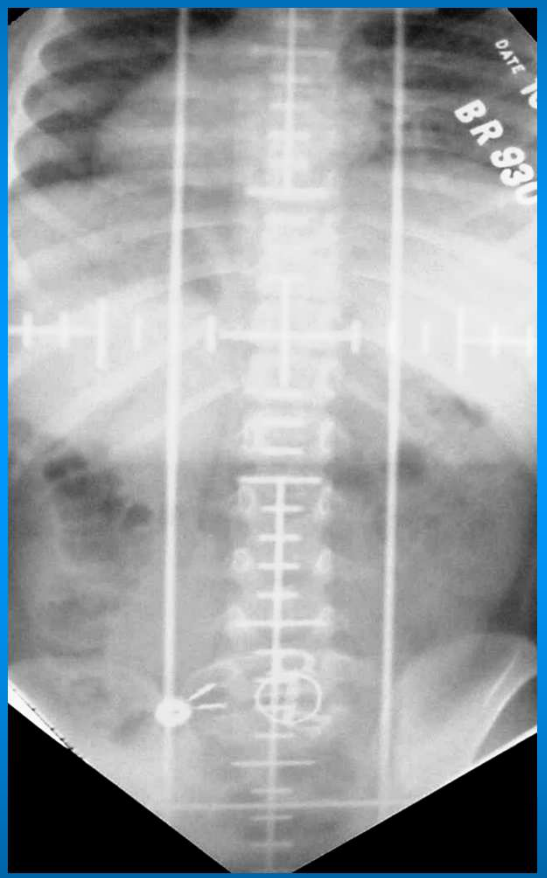


Radiation therapy in medulloblastoma

- central in the management
- relatively radiosensitive tumours
- volume of RT important- entire leptomeningeal axis
- planning of RT very careful and meticulous
- timing of RT- early imp.

CRANIOSPINAL IRRADIATION (CSI) - phase I



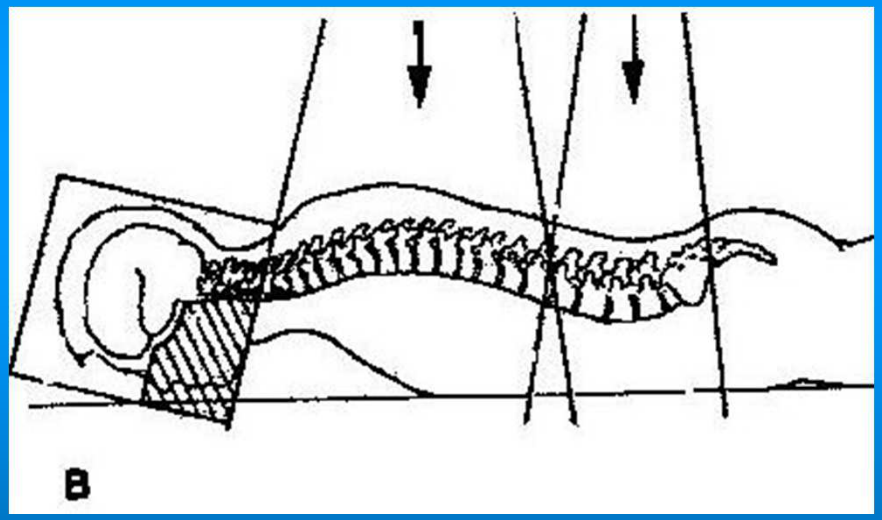


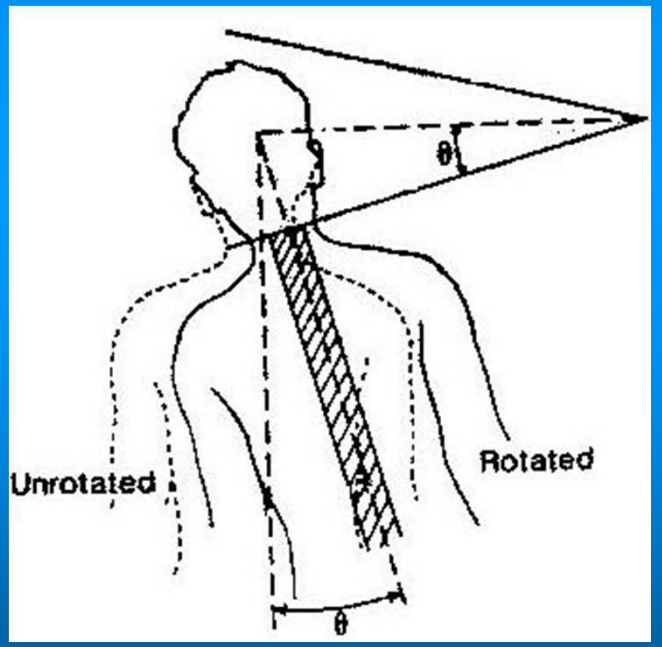
Dose: 35 Gy/21 fractions/4 weeks

23.4 Gy CSI plus chemo in avg risk

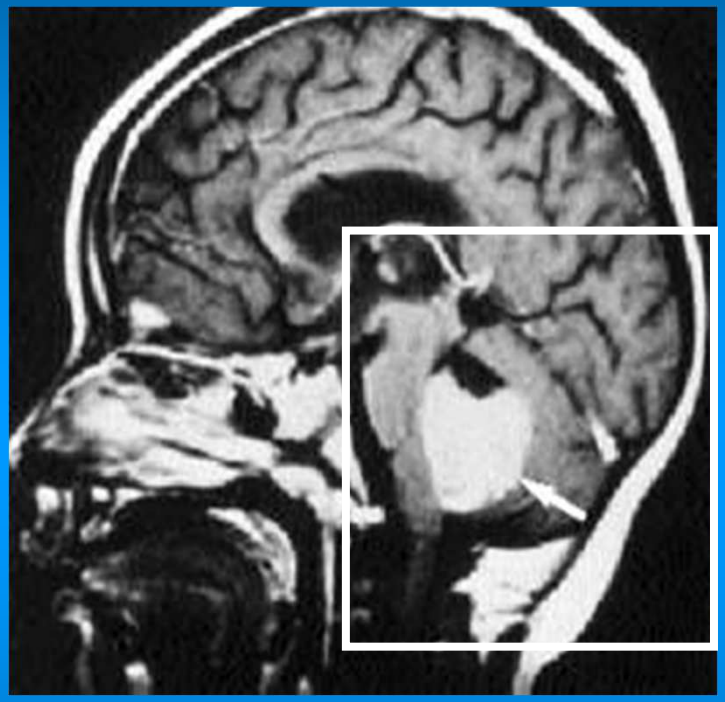
CSI Technique

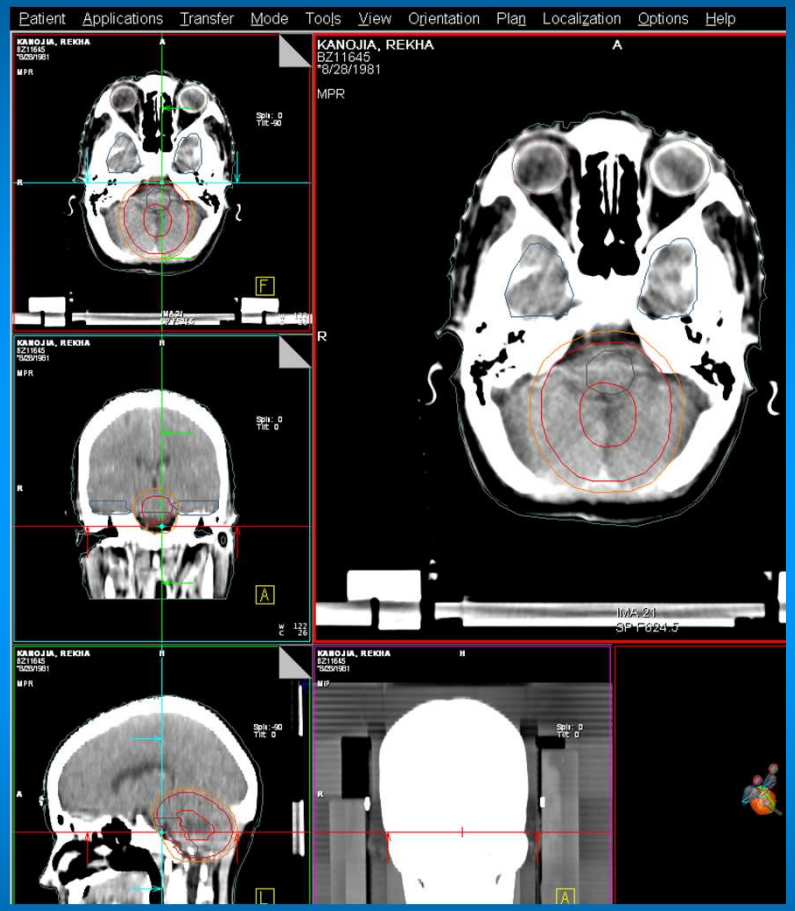
Rotate the couch (around 6° and collimator to match spinal field)





Posterior fossa boost - phase II

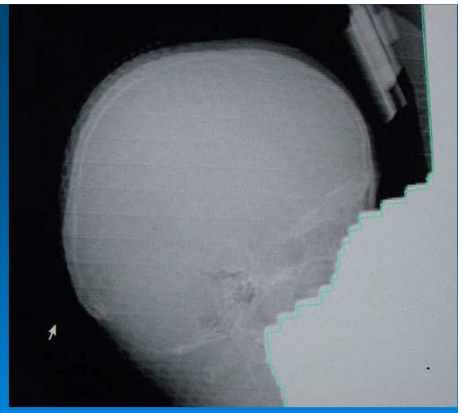




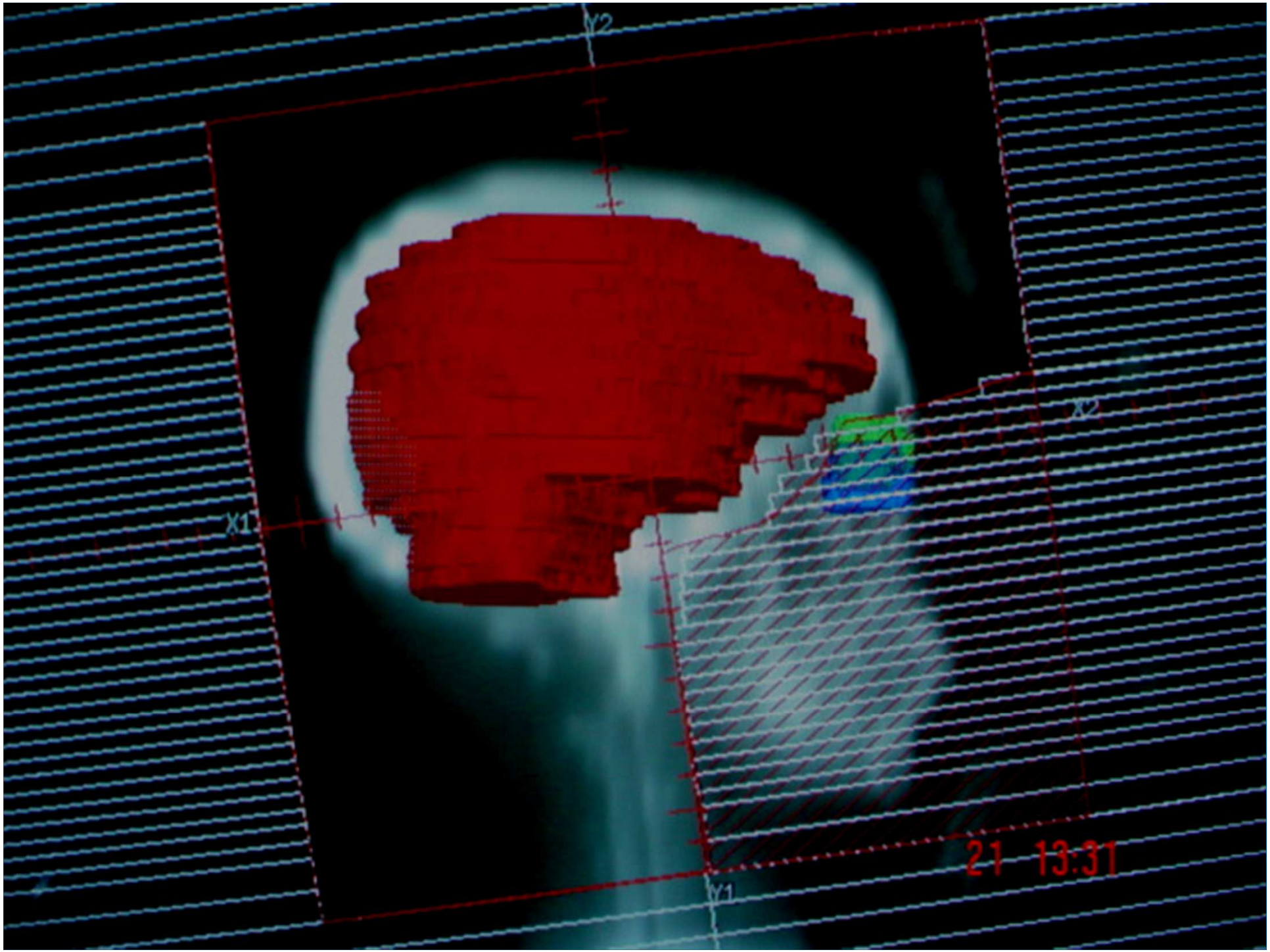
Dose: 20 Gy/10-12 fractions

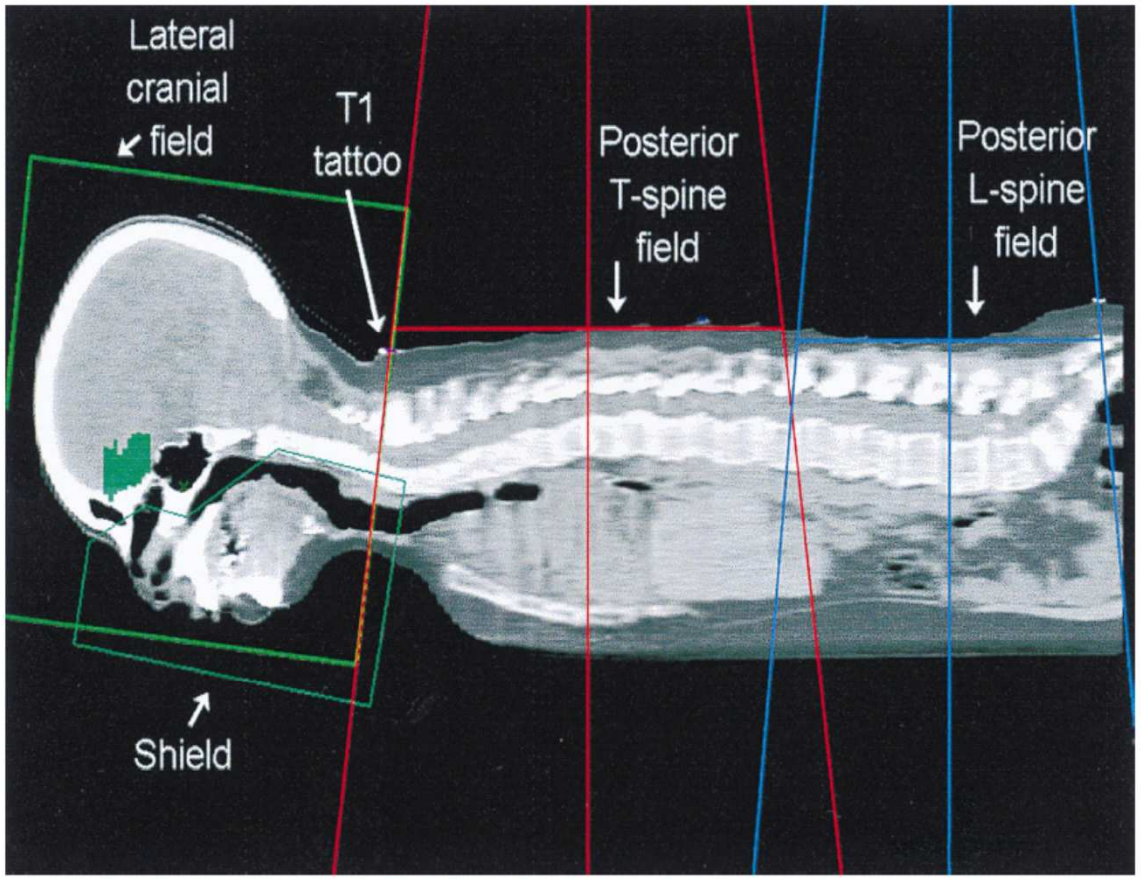
total dose to the primary site: 55 Gy

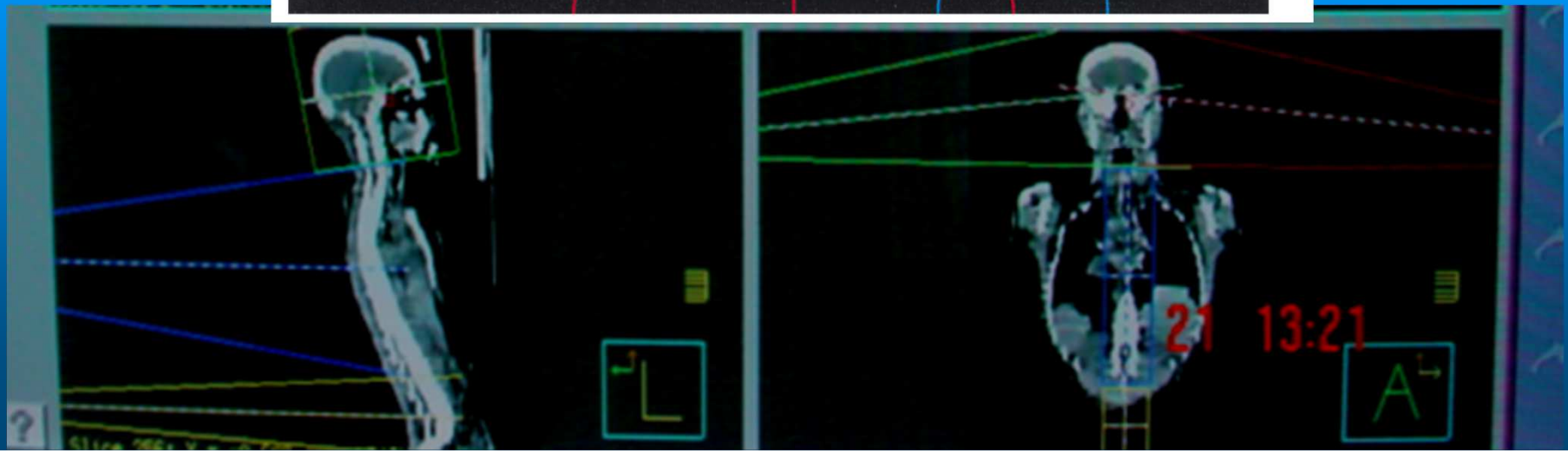
RT planning



- Direct impact on disease control and toxicity
- 20-45% failures inadequate subarachnoid (cribriform plate) coverage in subfrontal/temporal regions (*Miralbell IJROBP 1997*)
- prospective series under QA programme shows 10-12% inadequate irradiation (*Kortmann IJROBP 1997*)


Y2
X2
X1
Y1
21 13:31


Lateral
cranial
field
T1
tattoo
Posterior
T-spine
field
Posterior
L-spine
field
Shield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21
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A

Long term results

Avg/low risk

disease free survival: 50% to 90%

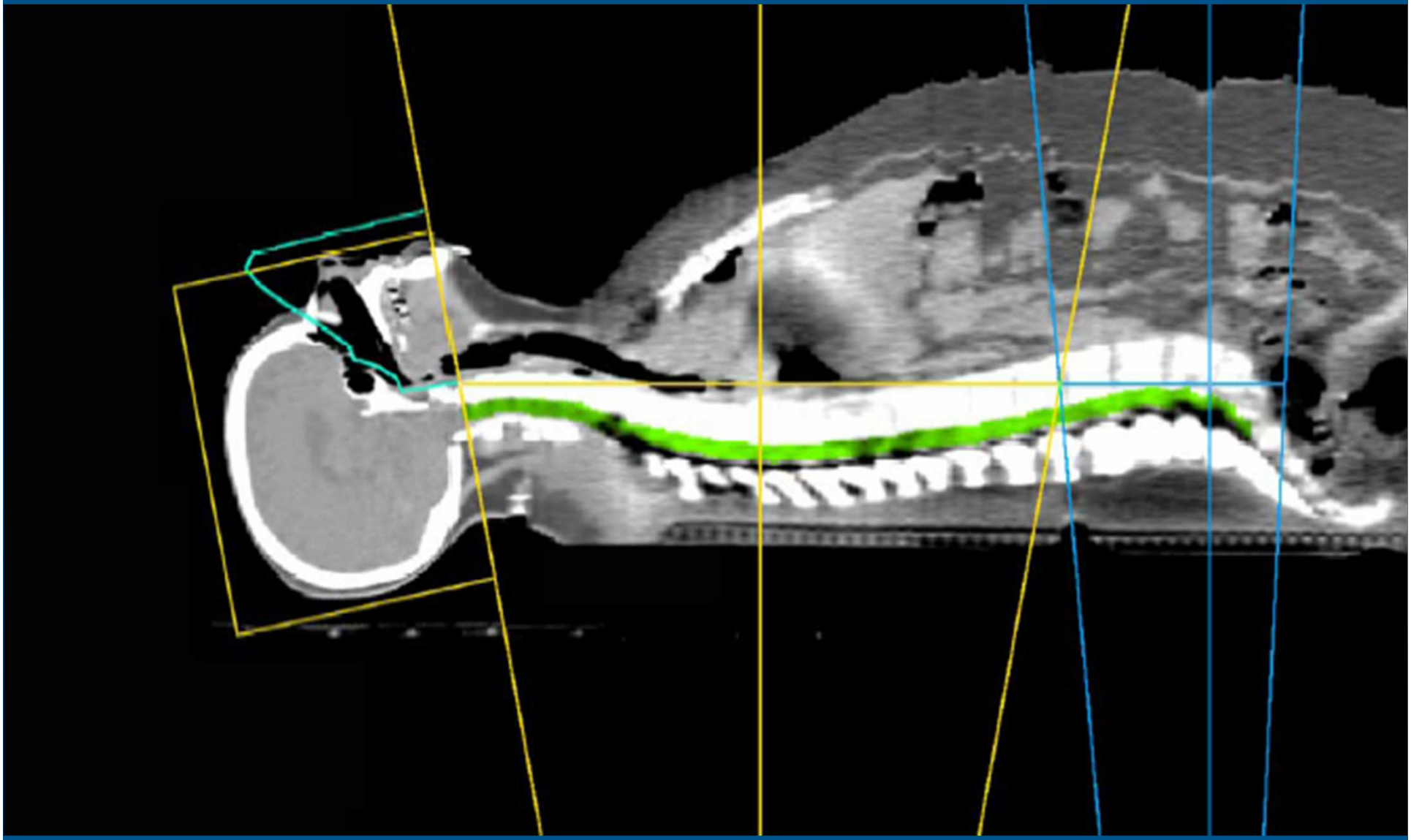
overall survival: 50% to 80% (~ 70%)

high risk

disease free survival: 20% to 80%

overall survival: 20% to 60% (~ 50%)

Supine CSI



Munshi and Jalali Med Dosimetry 2008

Data with reduced dose CSI (23.4 Gy+boost) plus Chemo

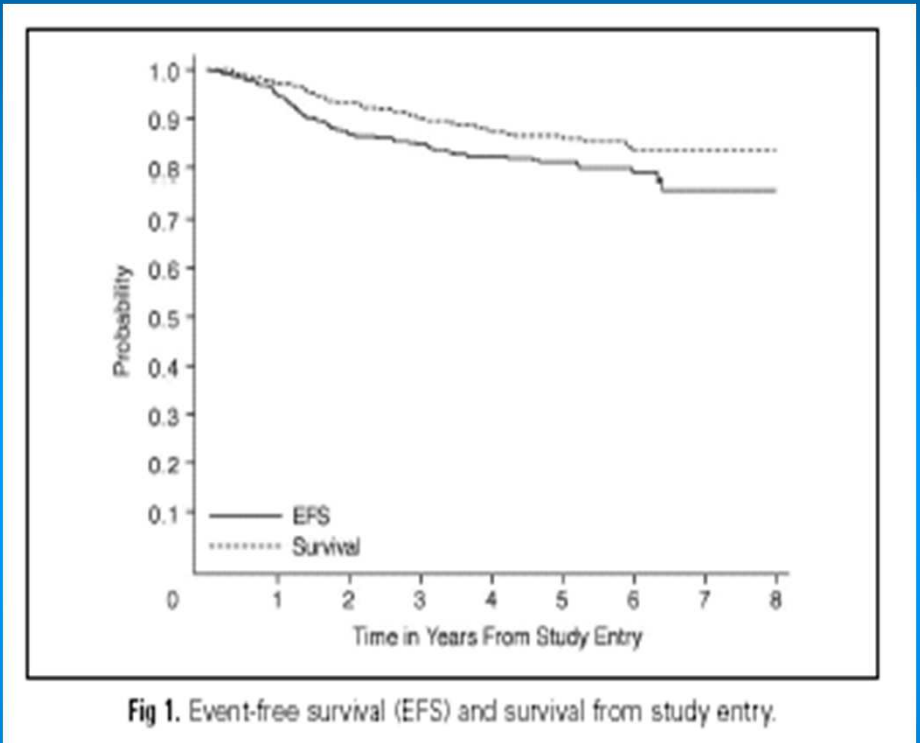
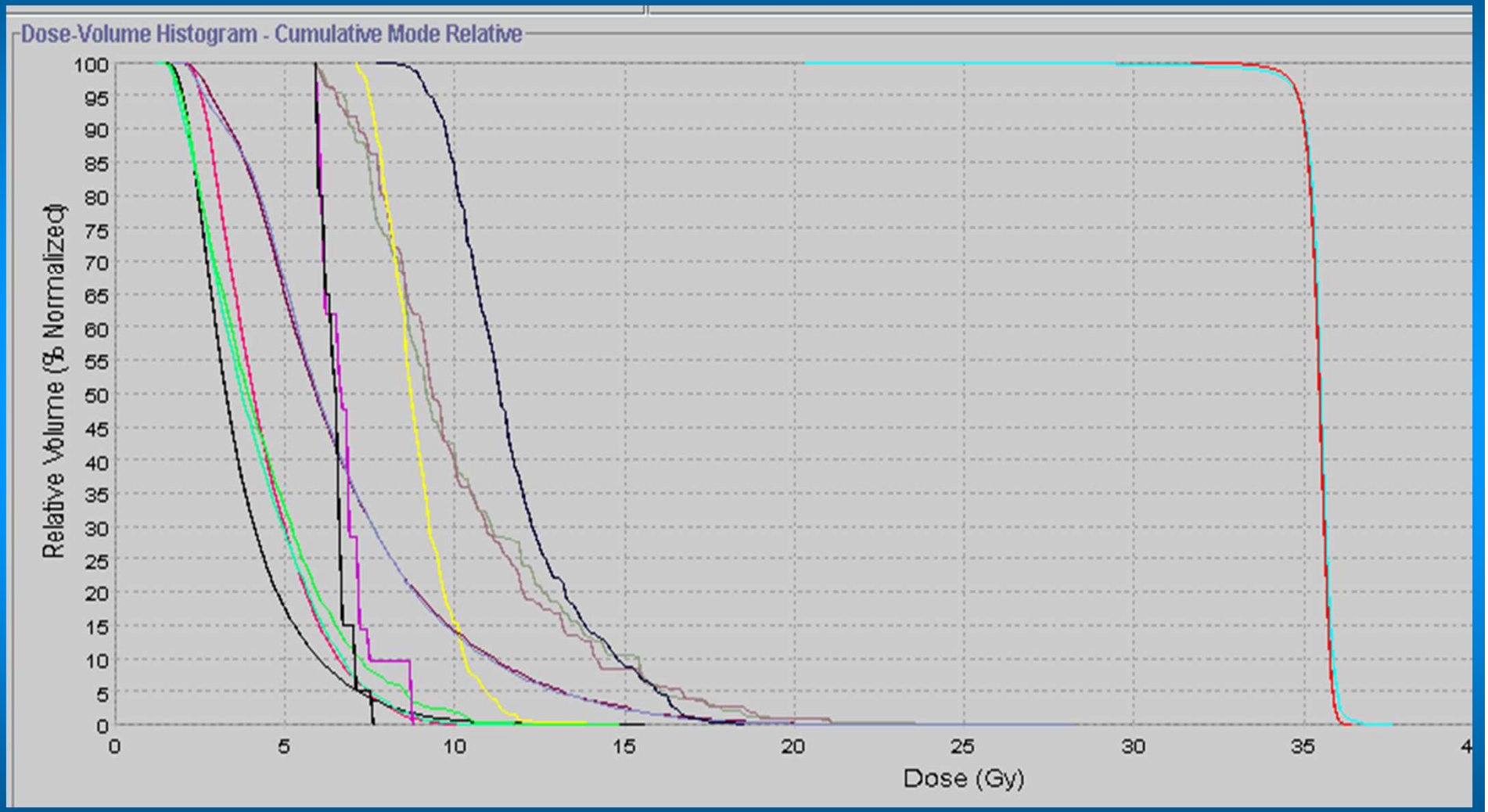


Fig 1. Event-free survival (EFS) and survival from study entry.

Cognitive function may be better but not proven conclusively

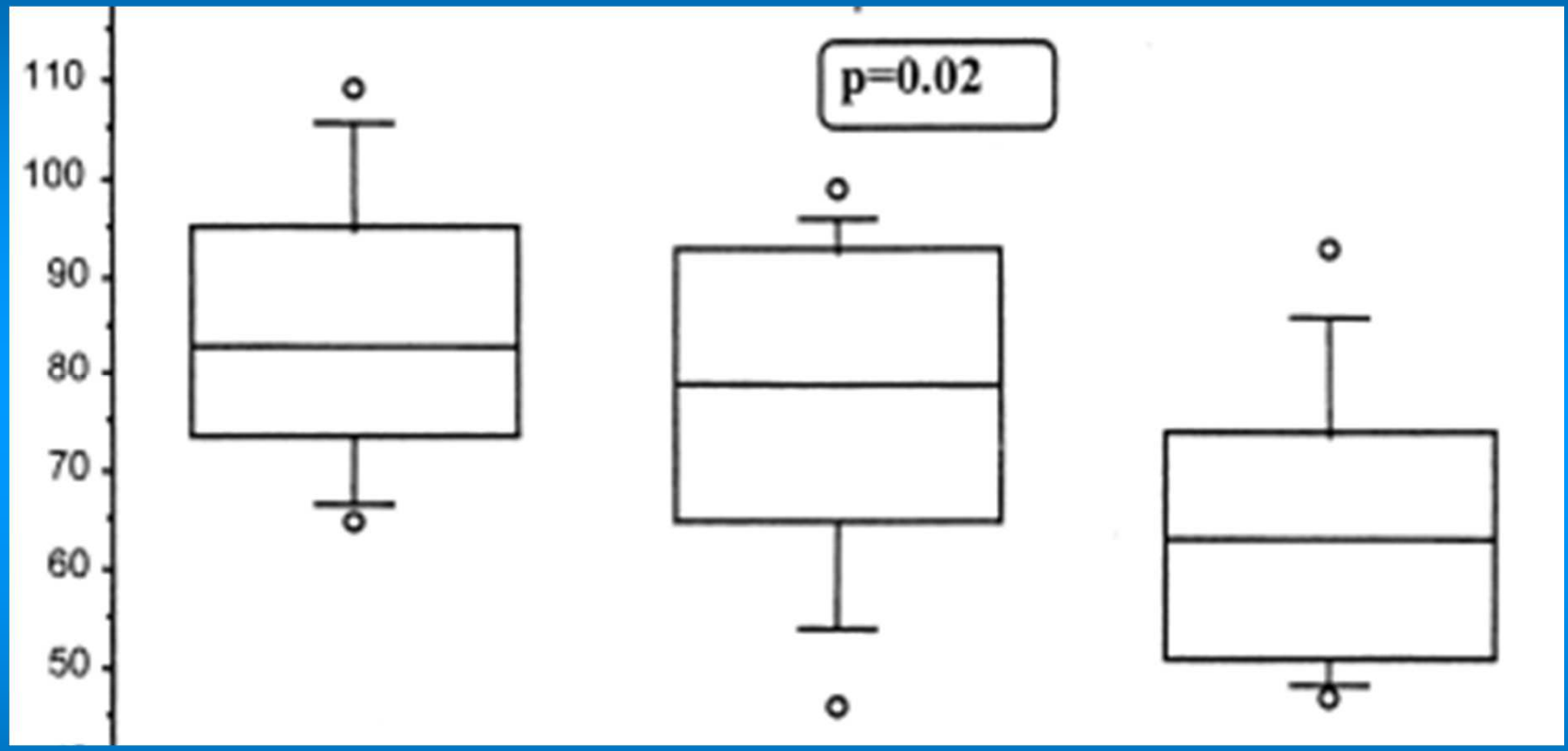
Packer: JCO 2006

IMRT _TOMO for CSI_ investigational



Zade *et al* Poster P-08-86 AROICON 2008

Long Term IQ with different volume & dose of RT



Only post fossa, no CSI CSI-25 Gy CSI-35 Gy

Grill IJROBP 1999

Hyperfractionated CSI/RT

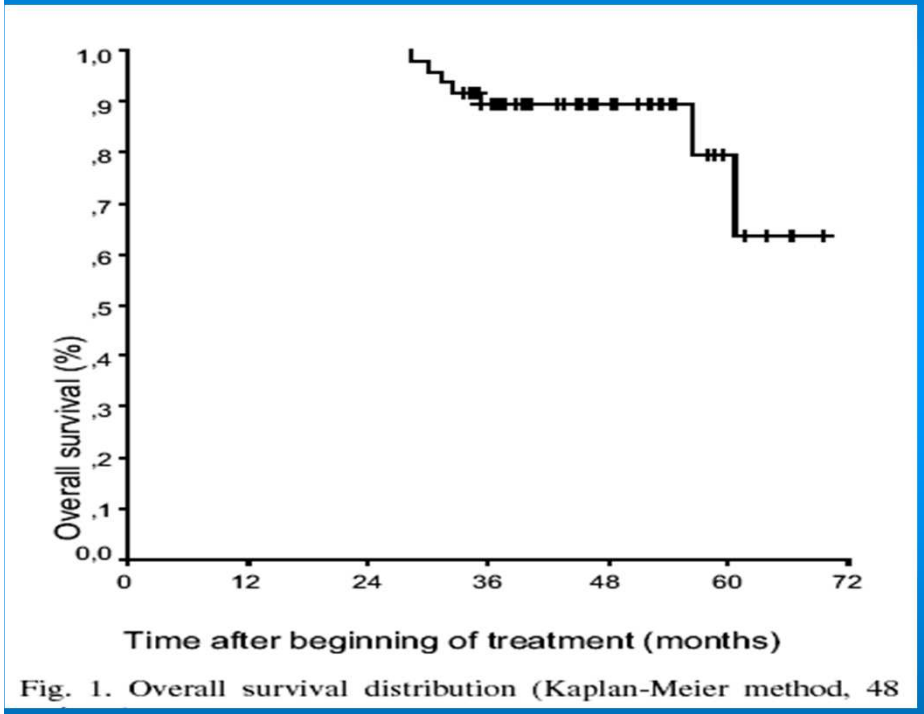
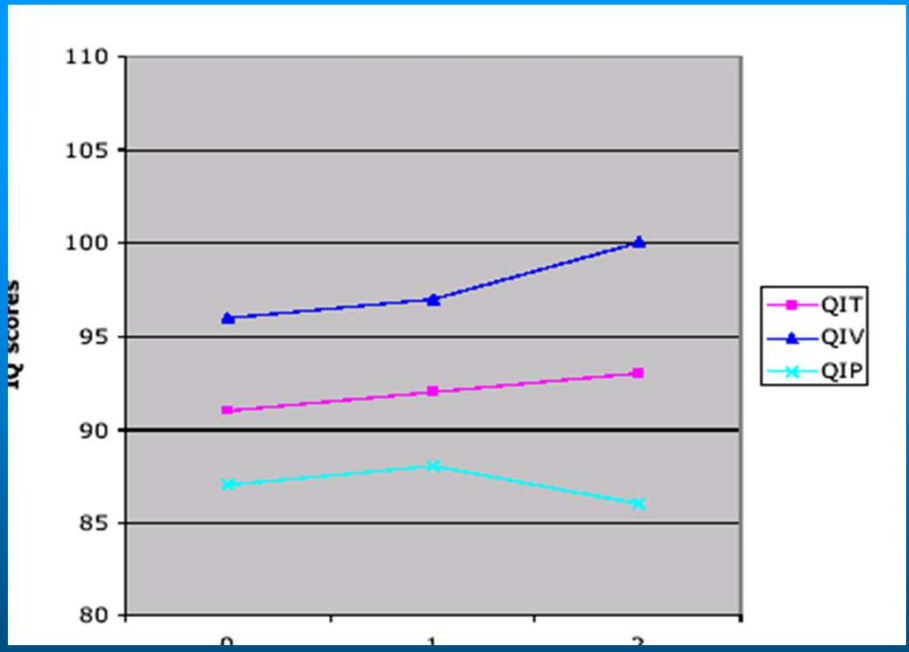


Fig. 1. Overall survival distribution (Kaplan-Meier method, 48

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

Hyperfractionated RT for CSI

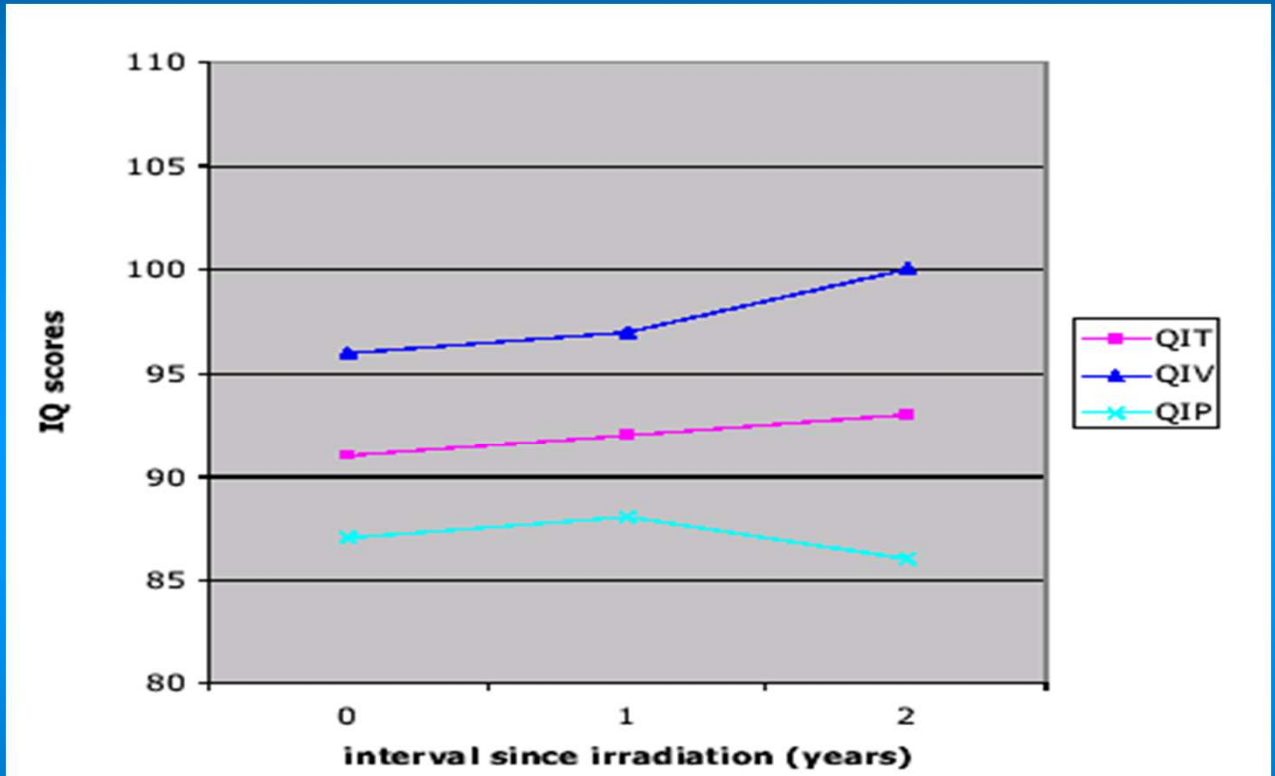


Fig. 3. Intelligence quotient (IQ) changes during early post-radiotherapy M-SFOP98 period—Wechsler scales (22 patients).

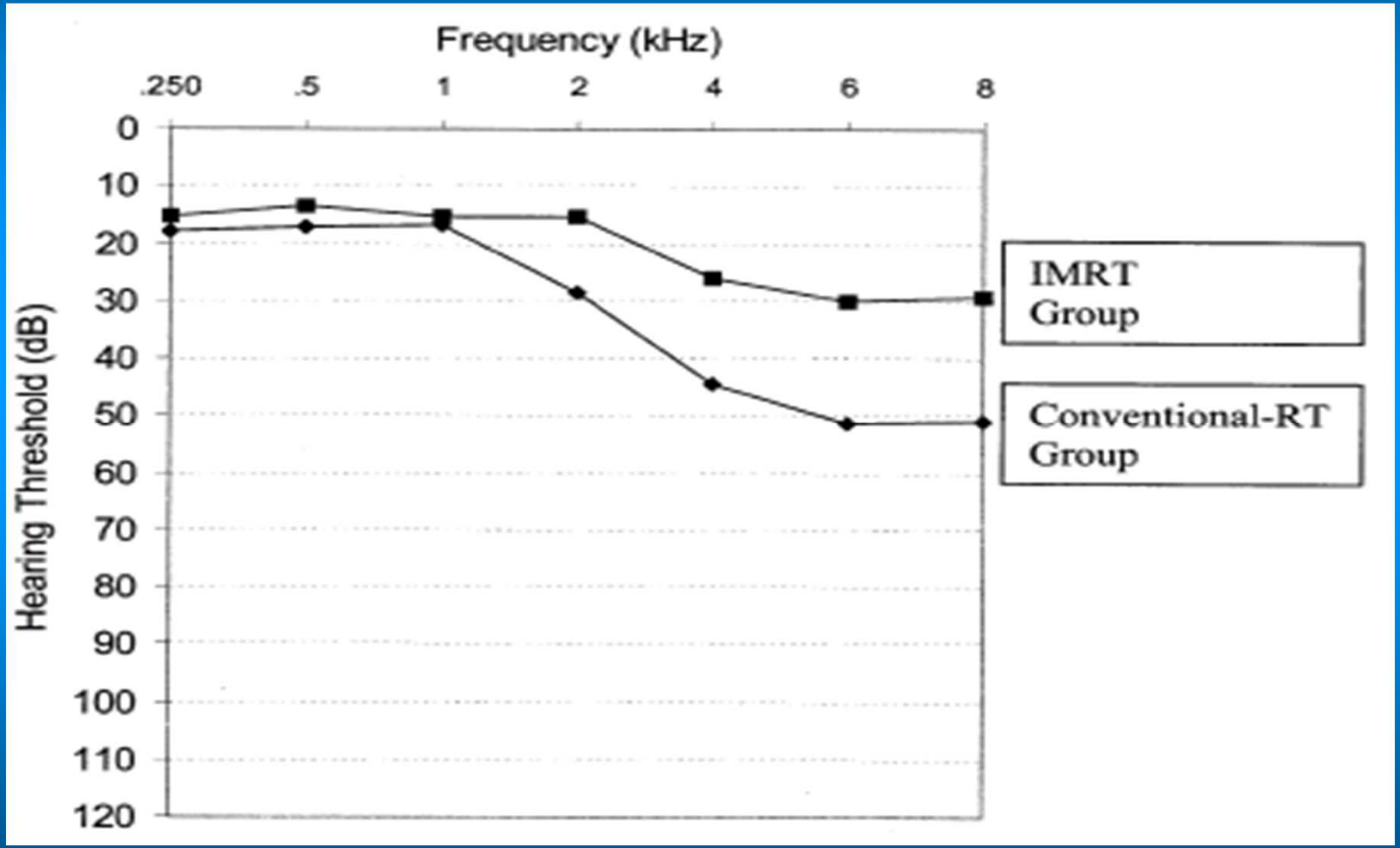
Ongoing trial in TMC: data accrual including cognition

PI: T Gupta

Carrie C IJROBP 2005

Ototoxicity: Platinum + RT

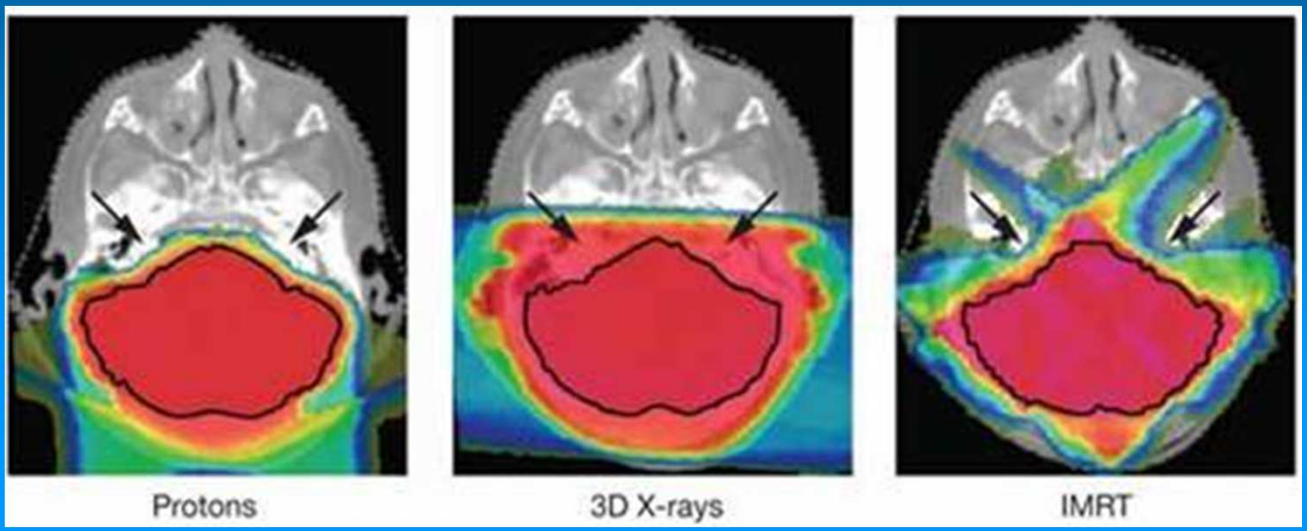
Modern RT minimises the effect of Chemotherapy

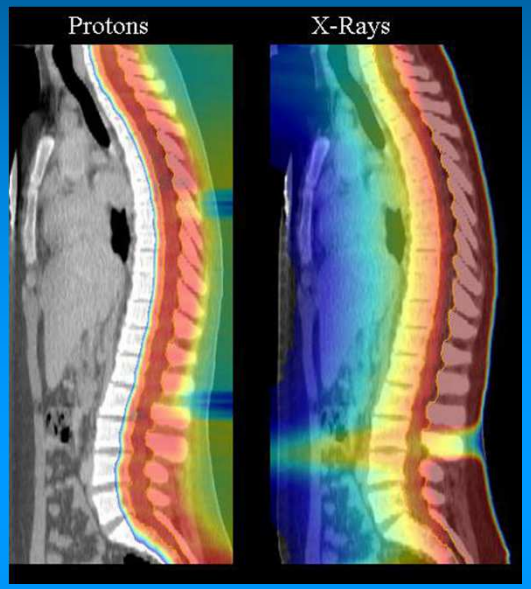


Huang IJROBP 2004

Huang IJROBP 2002

Protons/IMRT for CSI





- Be cautious about protons
- Risk of partial vertebra irradiation
- Cardiac, gut, lungs etc not an issue
- Real issue: cognition and endocrine- no effect with protons
- Neutrons, low dose bath with IMRT, Tomotherapy: to be careful

High-risk medulloblastoma

CSI for high-risk disease

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

CHEMOTHERAPY essential

- 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

Concurrent chemo+RT (CRT)

- Treatment naïve patients with confirmed diagnoses of high risk PCET, > 3 yrs & < 22 yrs accrued since July 2004
- Surgery is followed by CRT within 6 wks of surgery. The CRT includes craniospinal radiation (35Gy/21#) with local tumor bed boost 19.8 Gy/11# along with carboplatin 35mg/m2/day given 5 days a week for 15 doses (during first 3 wks.)
- CRT followed by 6 cycles of maintenance chemotherapy at 4 weekly interval beginning 4 to 6 wks post CRT using Vincristine, Carboplatin and Cyclophosphamide.

Results

- 38 patients have completed the CRT
- Medulloblastoma (63%) and Supratentorial PNET (37%); M Stage M0 (53%) , M1 (6%) , M2 (6%), M3 (35%)
- All patients completed CRT as per schedule except interruption for 1 week in one patient due to facial cellulitis and another due to malaria.

Hematological Toxicity

Toxicity	Total (%)	Grade III/IV(%)
Anaemia	78	14
Neutropenia	86	58
Thombocytopenia	74	22

Supportive care in CTRT phase

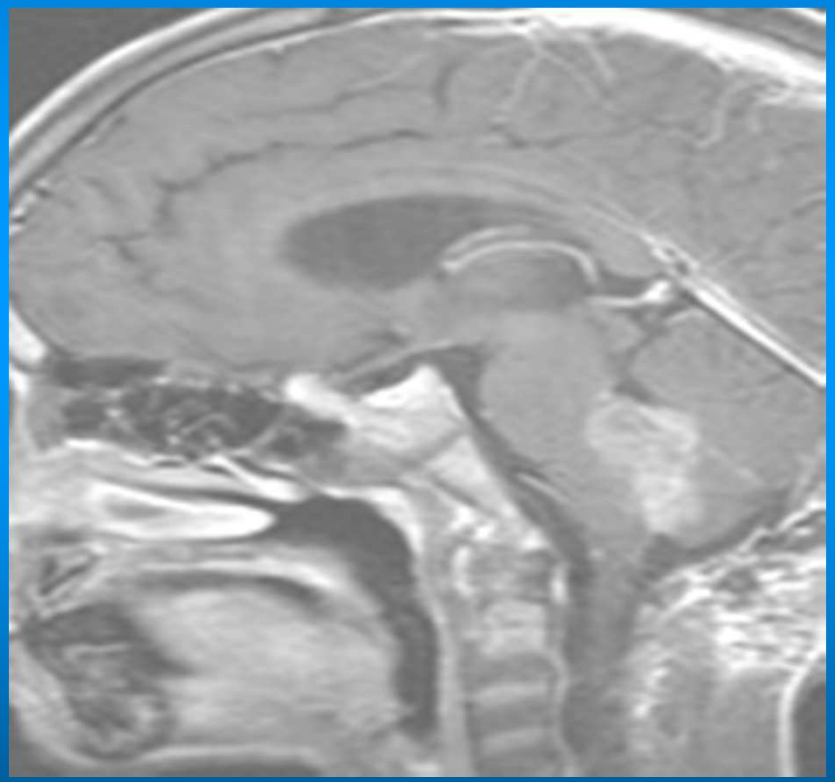
- A total of 58% patients required GCSF for > grade II neutropenia.
- 4 (18%) patients required RBC transfusion
- One patient needed platelet support.

- **None of the patients died of treatment related toxicity**

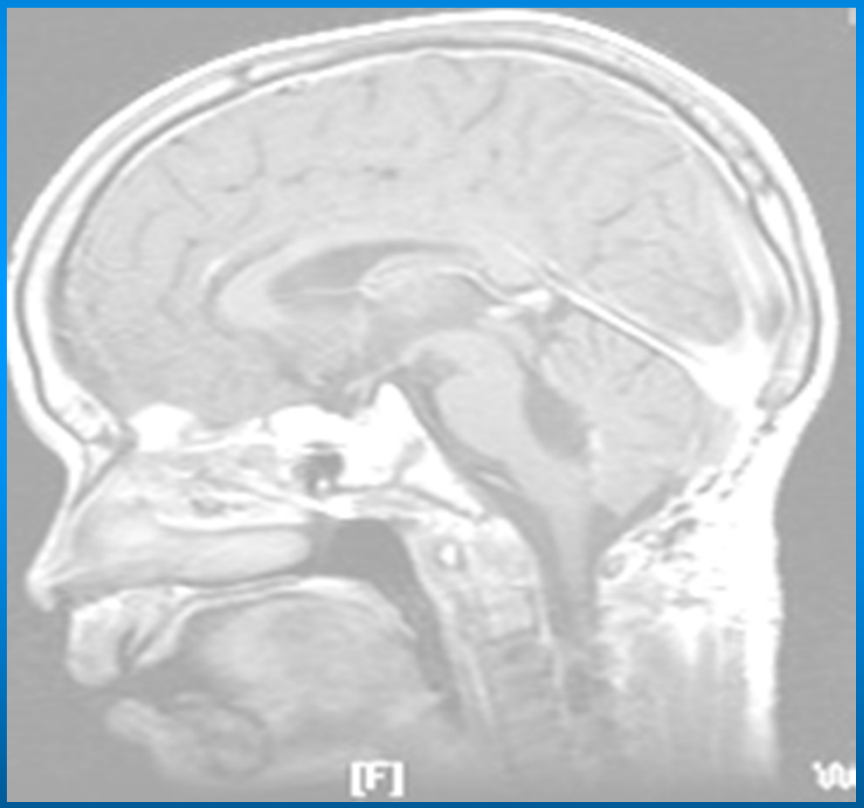
Response

Response	Percentage
complete remission	59
good partial remission	31
stable disease	10

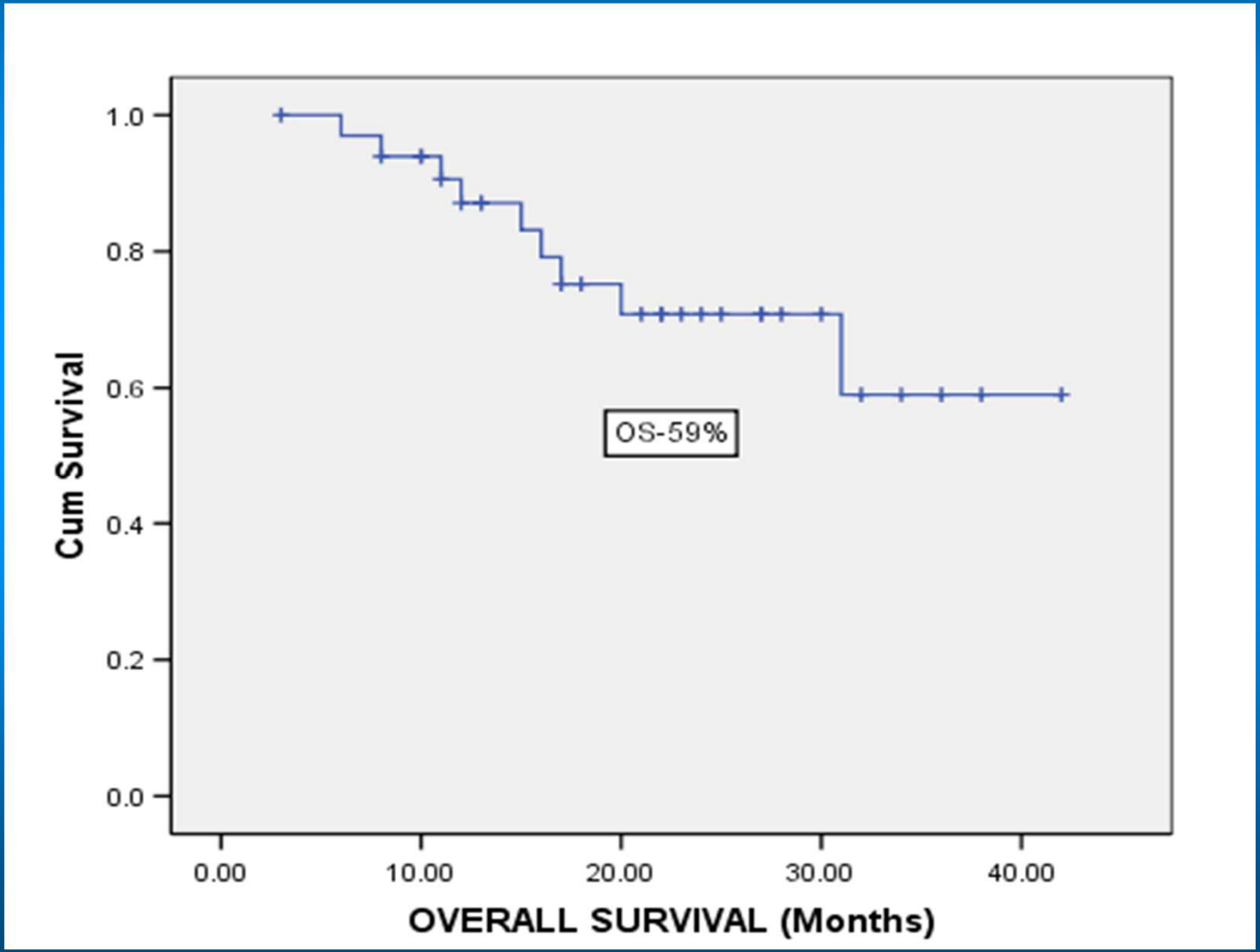
Pre-Treatment



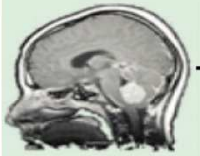
Post-Treatment



Overall Survival (N-38)



Role of biology in future important

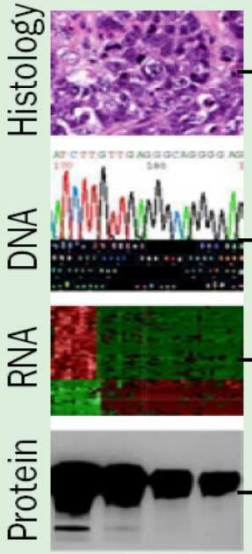


Surgery

Neuraxis imaging and cerebrospinal fluid

Tumour

Molecular and histopathological studies



Comprehensive clinical, histopathological, and molecular staging

Low risk → Chemotherapy and 55/18 Gy

Moderate risk → Chemotherapy and 55/35 Gy

High risk → High-dose chemotherapy with or without experimental treatment and 55/36 Gy