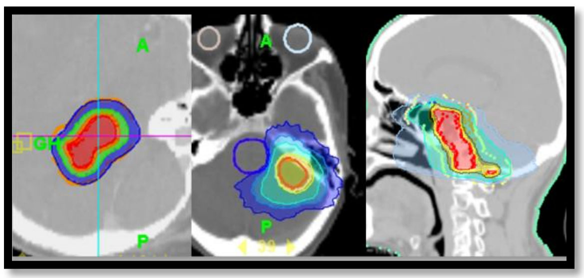
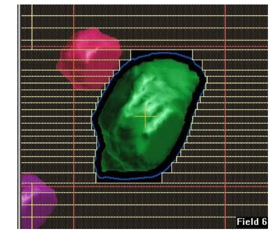
Novel tools in radiation oncology: is there any impact?





Brain Tumour Foundation of India

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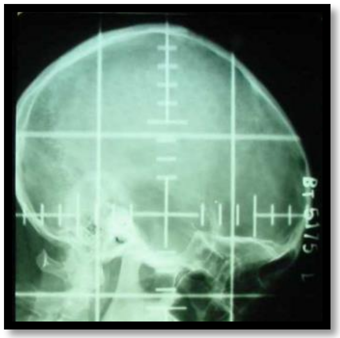
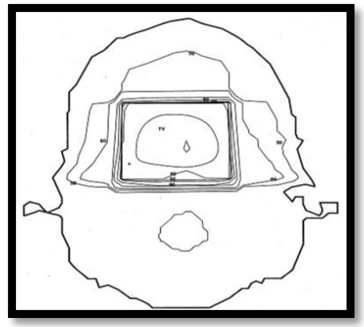
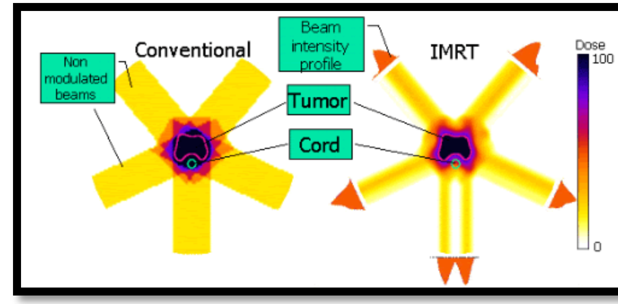
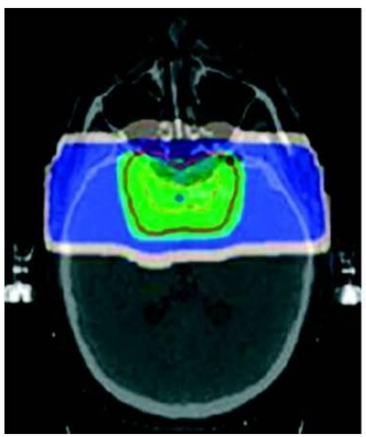
TATA MEMORIAL CENTRE
टाटा स्मारक केंद्र
SERVICE RESEARCH EDUCATION

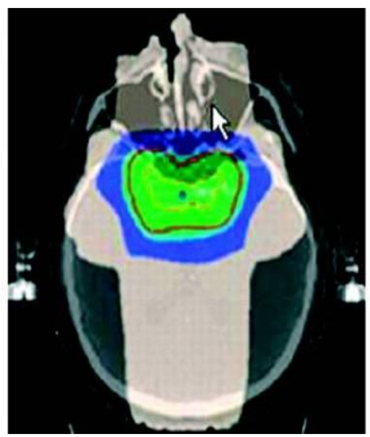
Era of high-precision conformal radiation therapy

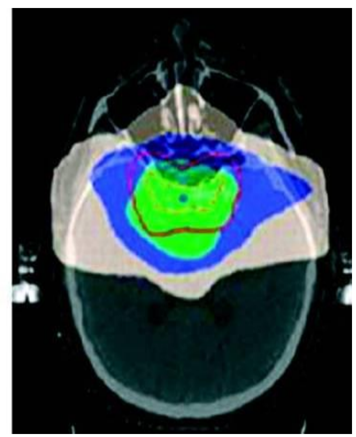


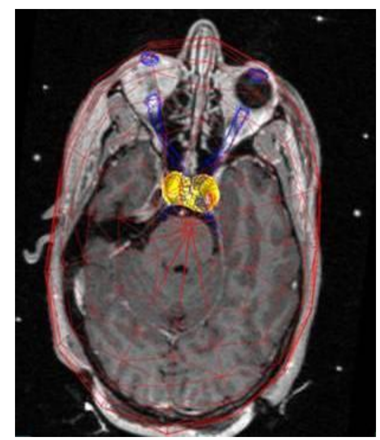




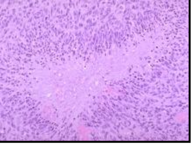


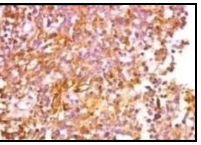






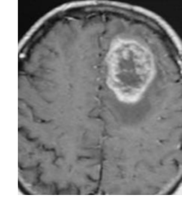
Larger number of beams & intensity modulation (IMRT) result in better high-dose conformality and improved organ-at-risk sparing; precisely delivered

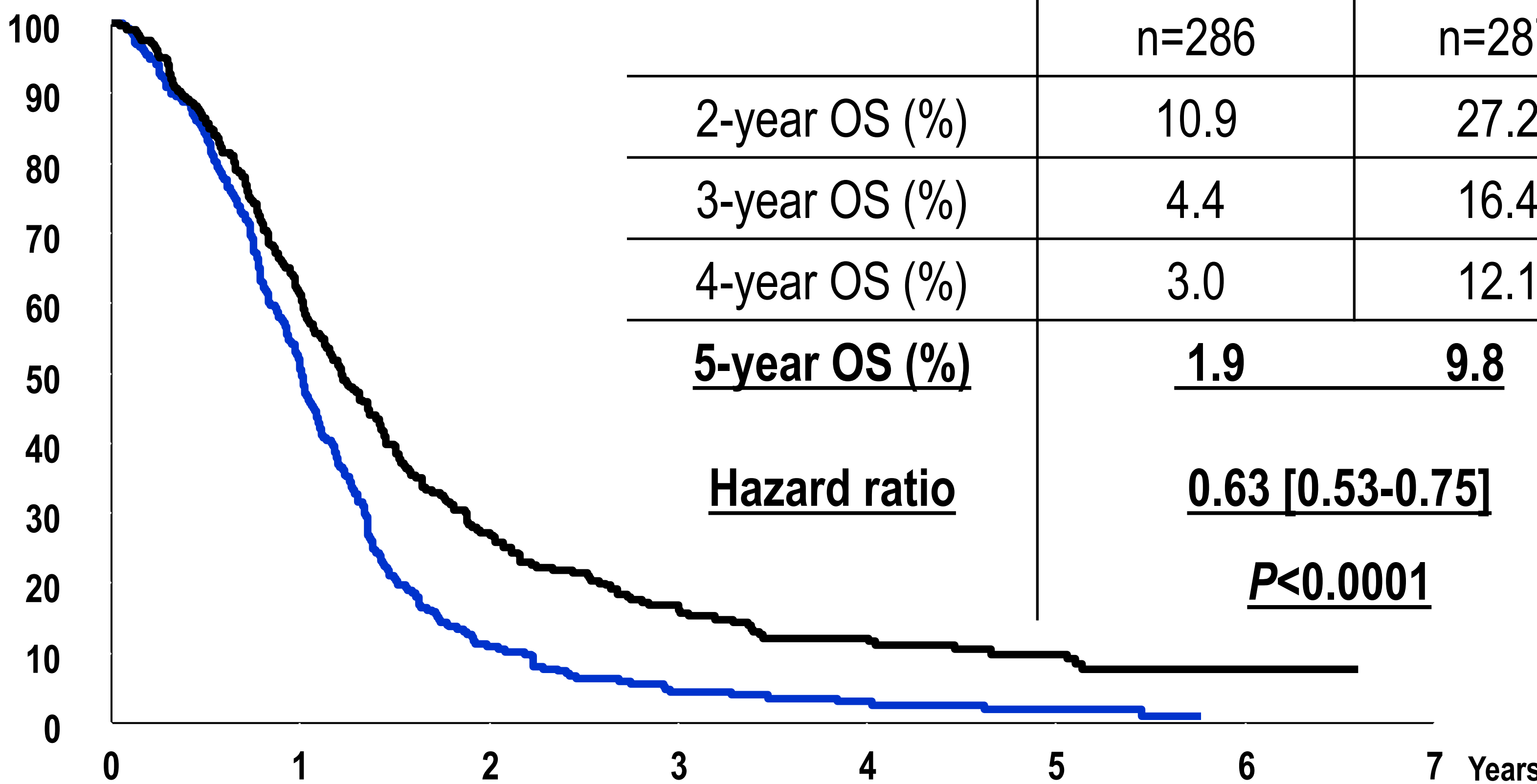




RT+TMZ still the standard of care

Landmark EORTC/NCI study





Treatment	RT n=286	RT+TMZ n=287
2-year OS (%)	10.9	27.2
3-year OS (%)	4.4	16.4
4-year OS (%)	3.0	12.1
5-year OS (%)	**1.9**	**9.8**
Hazard ratio	**0.63 [0.53-0.75]**	
	***P*<0.0001**	

Focal conformal radiotherapy (Gross tumour+ 2-3 cm margin covering all T2 weighted abnormality) with 2-4 fields;
Dose: 59.4-60 Gy/30-33#/6+ weeks

0

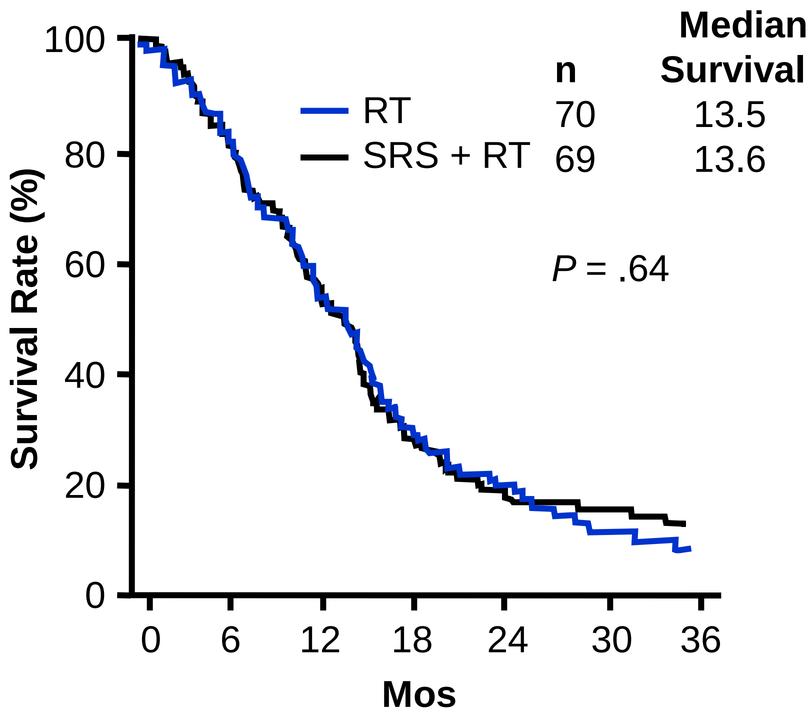
Stupp et al NEJM 2005
Stupp et al Lancet Oncol 2009

Phase III trials of dose escalation in high grade gliomas

Stereotactic radiosurgery (Gama Knife) or Brachytherapy

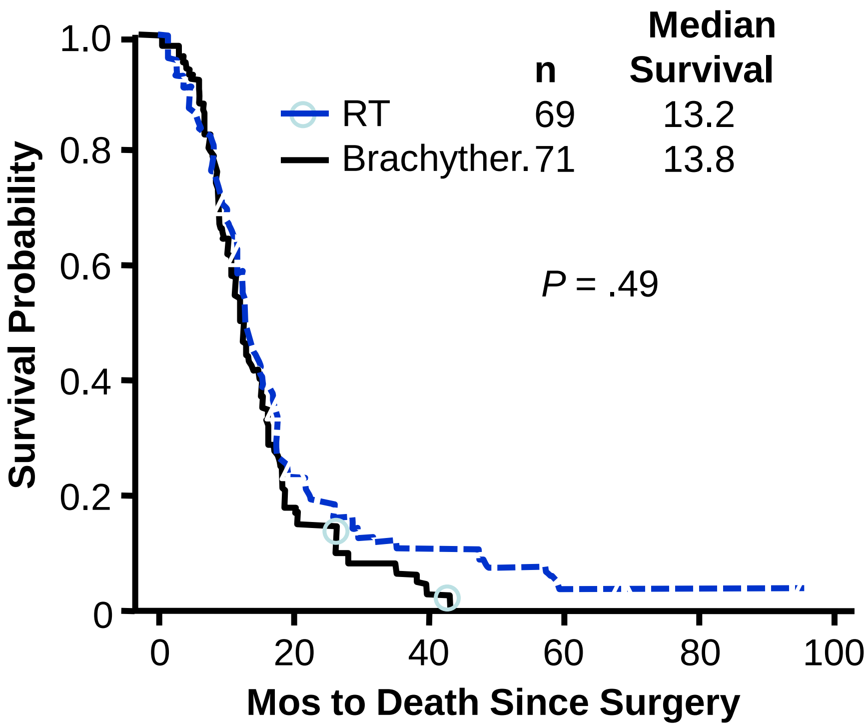
Souhami L et al IJROBP 2004

SRS ± RT



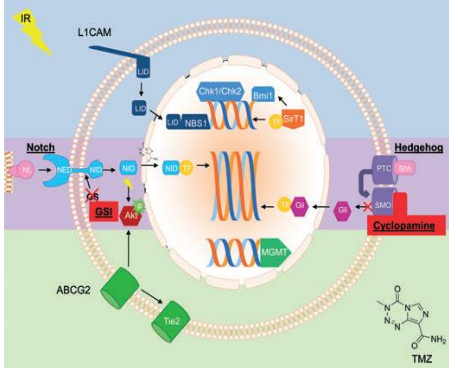
Laperriere NJ et al IJROBP 1998

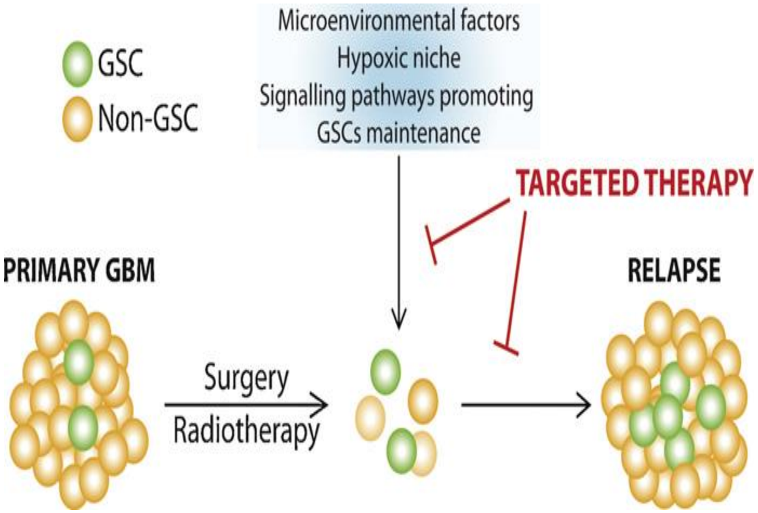
Brachytherapy ± RT



Level 1 evidence : higher doses nor better

Targeting glioma stem cells

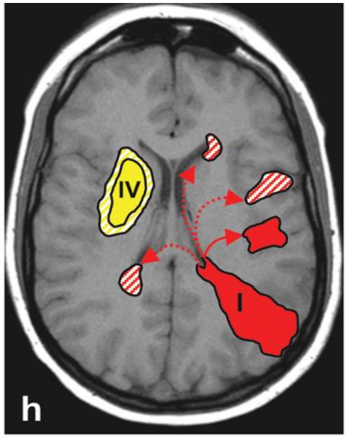




Understanding the Origins of Gliomas and Developing Novel Therapies: Cerebrospinal Fluid and Subventricular Zone Interplay

Michael Glantz[a], Santosh Kesari[b], Lawrence Recht[c], Gudrun Fleischhack[d], Alexis Van Horn[e]

- By inducing differentiation (BMP, Wnt/Akt pathways)
- Glioma stem cell (GSC) signalling pathways
- GSC microenvironment (Perivascular and hypoxic niche)

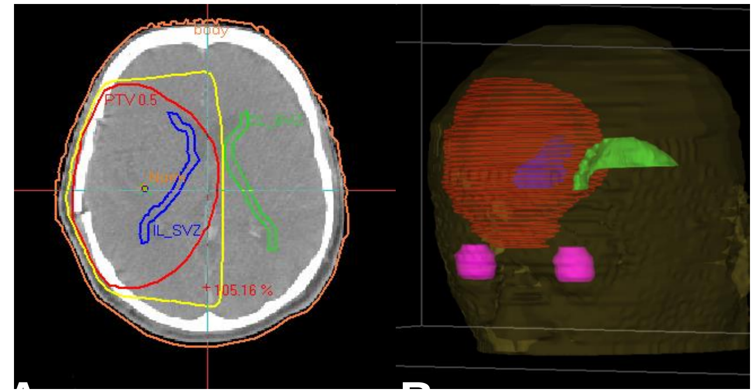


J Neurooncol
DOI 10.1007/s11060-012-0887-3

CLINICAL STUDY

Can irradiation of potential cancer stem-cell niche in the subventricular zone influence survival in patients with newly diagnosed glioblastoma?

Tejpal Gupta · Vimoj Nair · Siji Nojin Paul · Sadhana Kannan · Aliasgar Moiyadi · Sridhar Epari · Rakesh Jalali

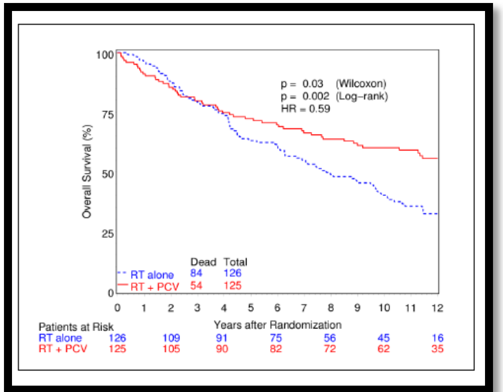


Prognostic factor	*HR (95%CI) for PFS*	*p-value*	*HR (95%CI) for OAS*	*p-value*
Age	1.00 (0.94-1.07)	0.931	1.02 (0.94-1.11)	0.660
KPS (low vs high)	0.32 (0.11-0.92)	**0.035**	0.24 (0.08-0.73)	**0.012**
RPA class (good vs poor)	2.04 (1.05-5.55)	**0.016**	6.76 (1.62-28.7)	**0.009**
Mean ipsilateral SVZ dose	0.91 (0.80-1.03)	0.116	0.87 (0.77-0.98)	**0.025**
Mean contralateral SVZ dose	0.96 (0.71-1.30)	0.797	0.95 (0.71-1.25)	0.695

A prospective study ongoing to evaluate the pattern of relapses wrt SVZ locations (n=100); accrual so far: 71

Low-grade gliomas (LGGs) : Changing landscape

Diffuse grade II astrocytomas, oligodendrogliomas, and mixed oligo-astrocytomas are **infiltrative**, less likely to be completely resected and frequently need adjuvant Rx.



Mature results of RTOG 9802 - Overall Survival

	RT ALONE [%]	RT + PCV [%]
MEDIAN OS	**7.8 YEARS**	**13.3 YEARS**
5-YEAR	63.1	72.3
10- YEAR	40.1	60.1

Focal conformal RT (all T2 tumour) and spare as much normal brain as possible

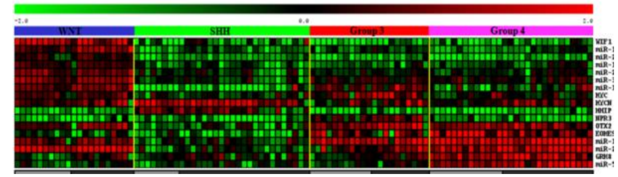
Histologic classification

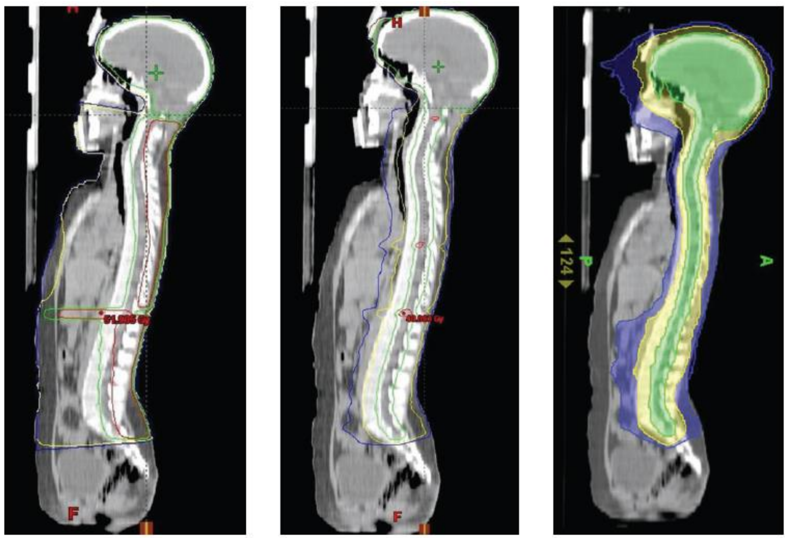
Molecular information	Diffuse astrocytoma	Oligodendroglioma	"Oligoastrocytoma" or ambiguous histology
IDH-mut, 1p/19q-nondel, ATRX loss	*Diffuse astrocytoma, ATRX loss of expression*	*Diffuse glioma* (oligodendroglioma phenotype), 1p/19q non-deleted, ATRX loss of expression*	*Diffuse astrocytoma, ATRX loss of expression*
IDH-mut, 1p/19q-codel, ATRX intact	*Diffuse glioma (astrocytoma phenotype), 1p/19q-codeleted*	*Oligodendroglioma, 1p/19q-codeleted*	*Oligodendroglioma, 1p/19q-codeleted*
IDH wild type	*Diffuse astrocytoma, IDH wild type**	*Diffuse glioma* (oligodendroglioma phenotype), IDH wild type**	*Diffuse astrocytoma, IDH wild type**
Testing not performed	*Diffuse astrocytoma, NOS*	*Oligodendroglioma, NOS*	*"Diffuse glioma, NOS"*

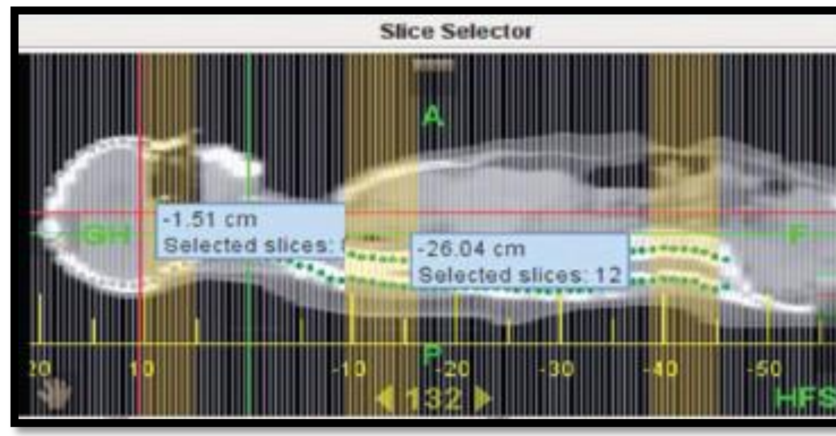
The British Journal of Radiology

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





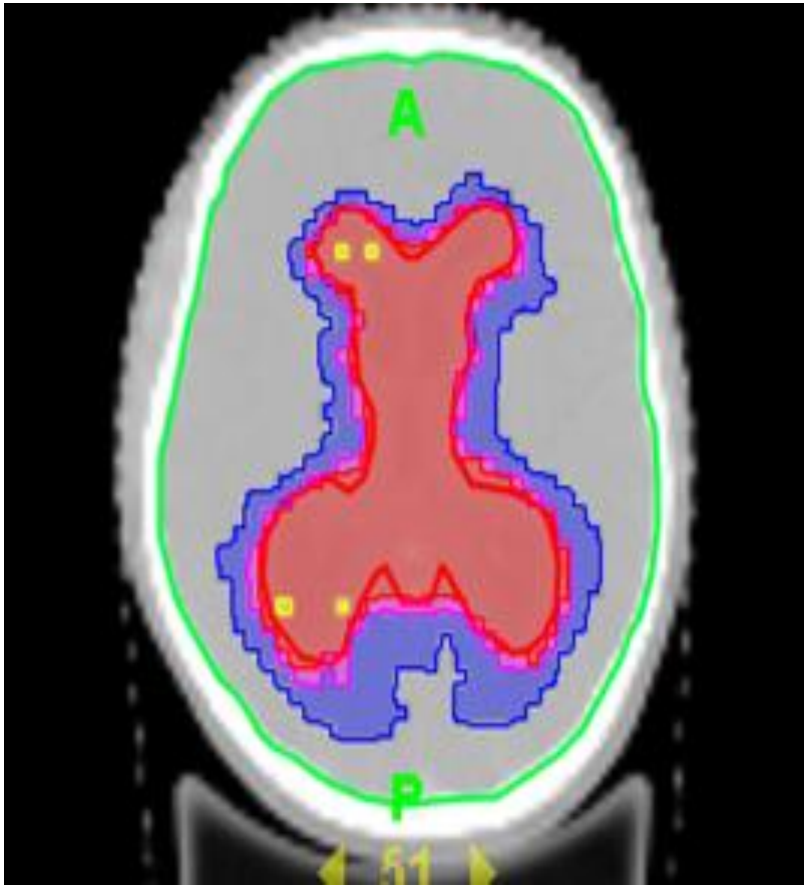


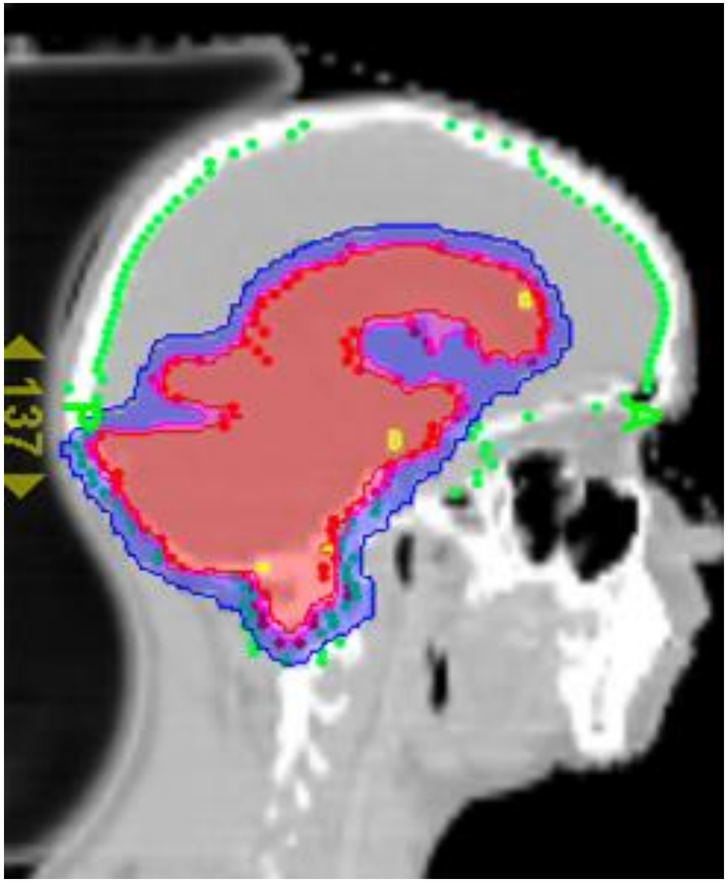
Craniospinal axis RT: critical in medulloblastoma: needs meticulous planning & execution

Potential suggested trials in WNT / SHH (favourable) pathway tumours

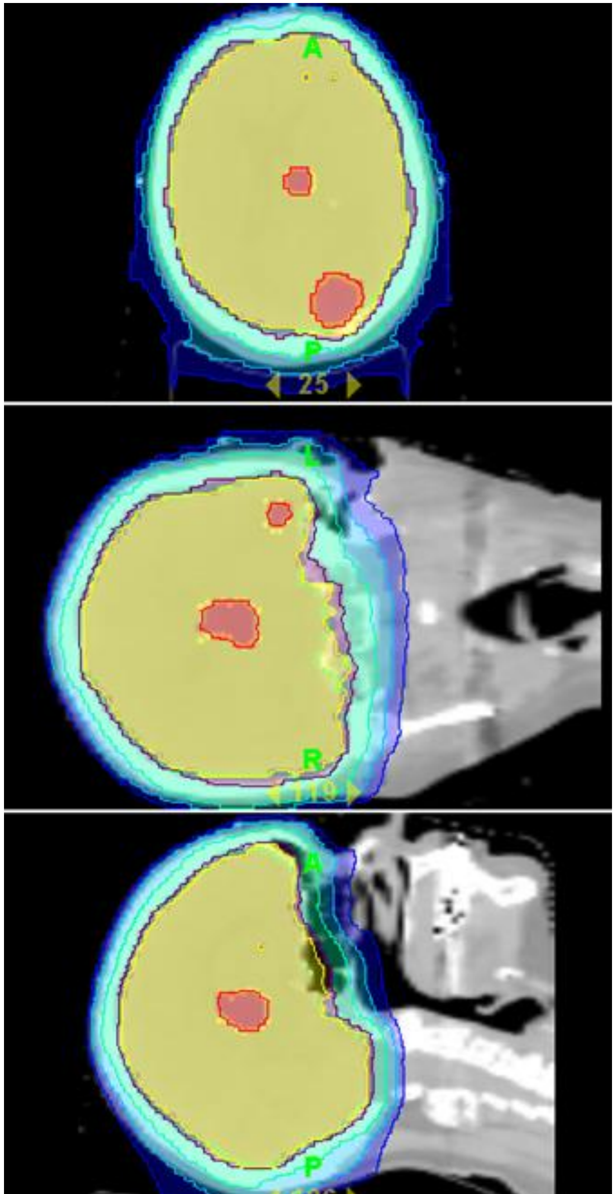
- De-escalate therapy; RT dose and chemotherapy, explore targeted therapies etc
- Delay RT as much as possible (? 5 years)T
- Localised RT only/ No CSI

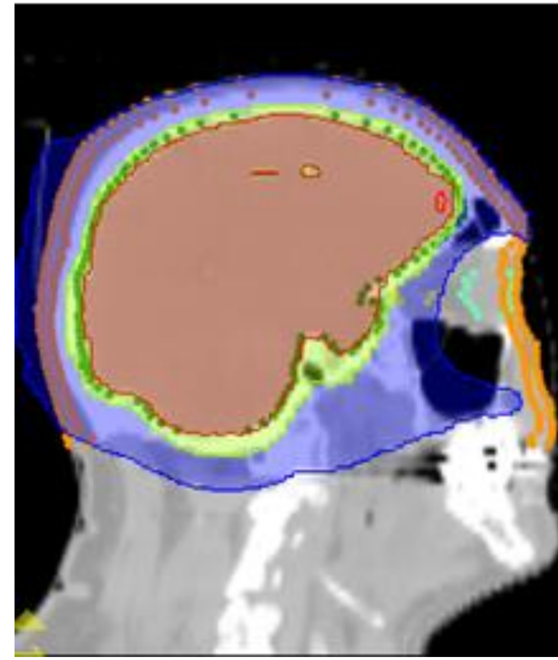
Highly conformal whole ventricular irradiation in germ cell tumours





Scalp-sparing WBRT in brain metastases: SIB



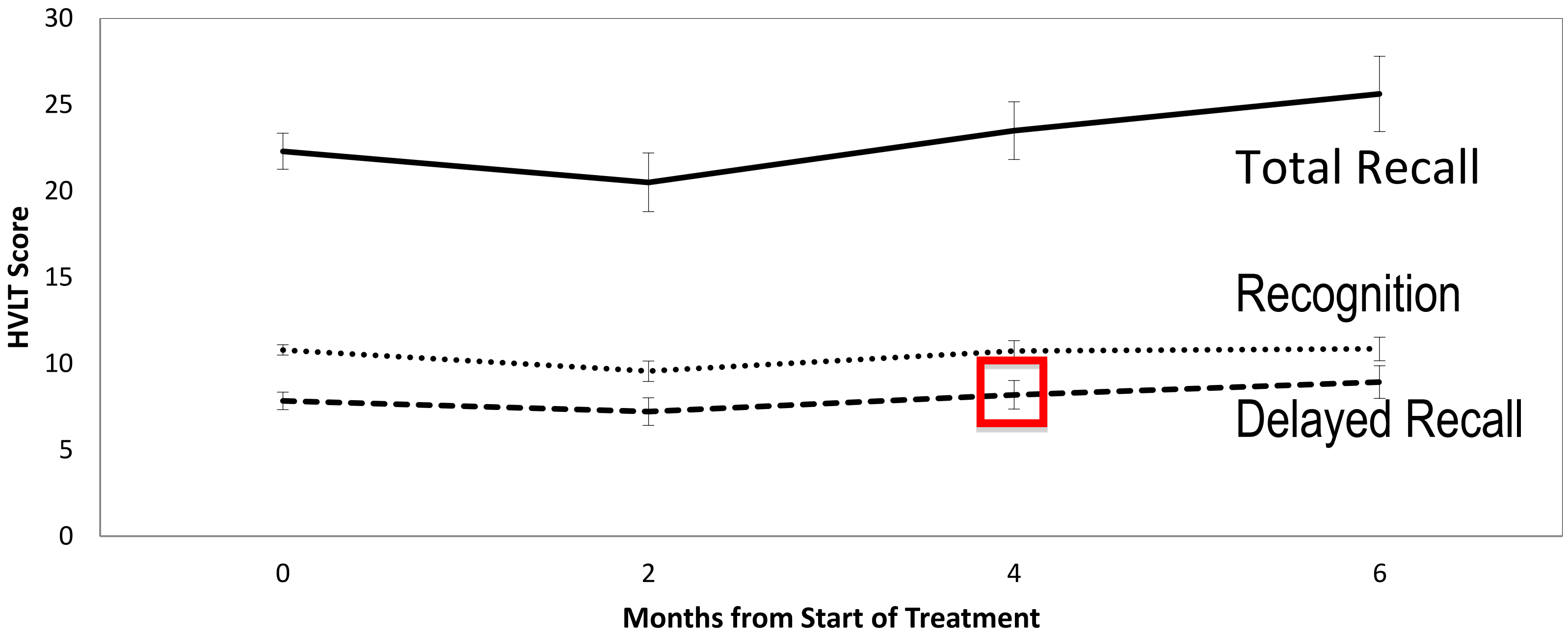


Whole Brain Dose = 30 Gy
Scalp Dose = ~15 Gy

Whole Brain Dose = 30 Gy
Metastatic boosts = 45 Gy
Scalp Dose = ~18 Gy

Hippocampal sparing trial in brain metastasis

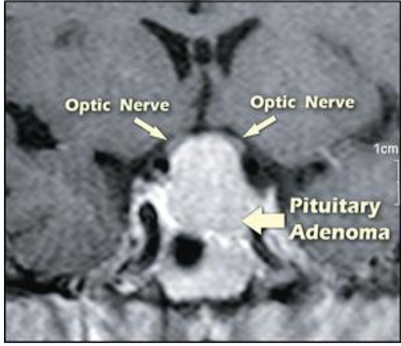
RTOG 0933 (n=100)



- Mean relative decline in HVLT-Delayed Recall from baseline to 4 months: **7.0%** (95% CI: 4.7 to 18.7%)
- Significant less than historical control: **30%** (*p*=0.0003)
- 42 patients had assessment at 4 months

Gondi JCO 2014

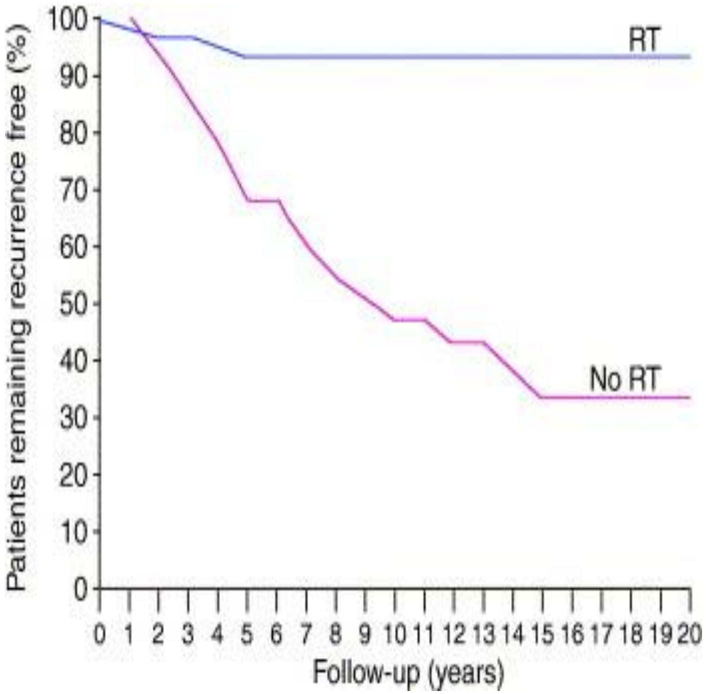
Benign brain tumours - Pituitary adenomas
residuals/progressive/functioning



Comparative study of 2 surgical institutions; same RT set up

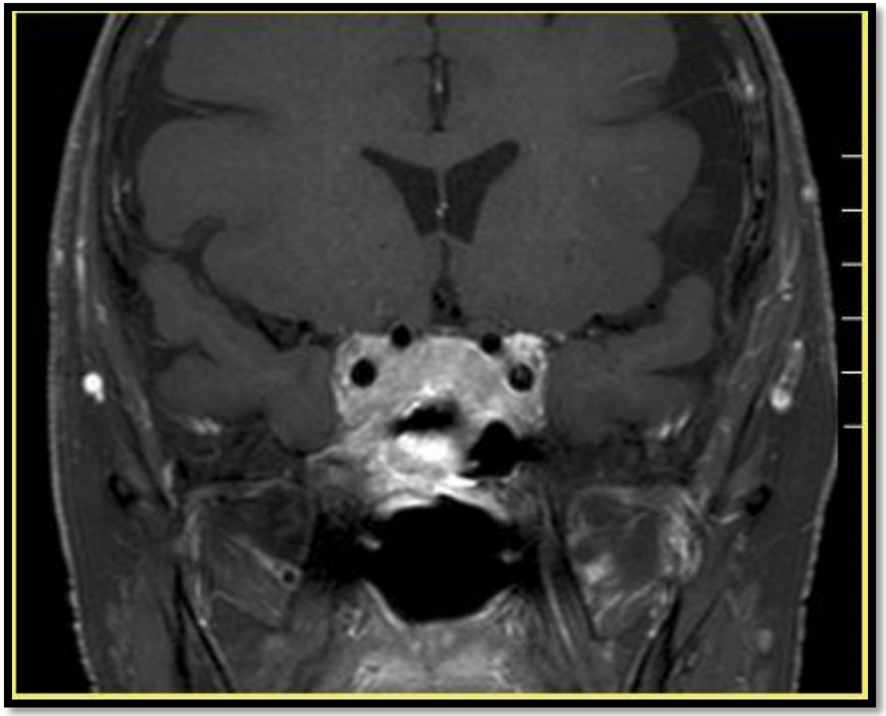
PFS	RT *n=63*	No RT *n=63*
5 yr	93%	68%
10 yr	93%	47%
15 yr	93%	33%

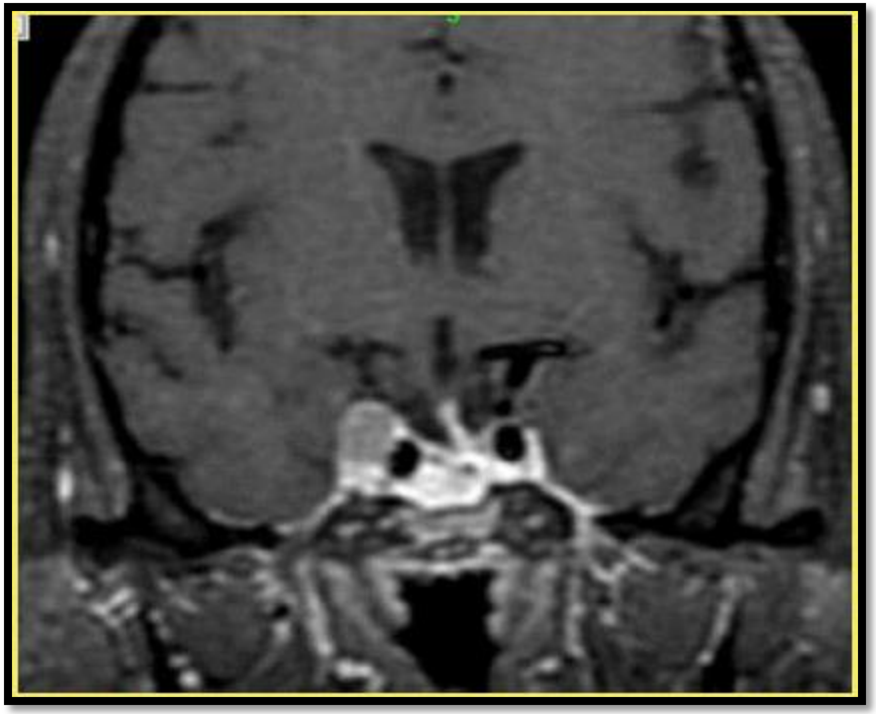
Administration of RT was the only significant factor



Gittoes Clin Endocrinol 1998

Radiotherapy Vs. Radiosurgery (SRS)

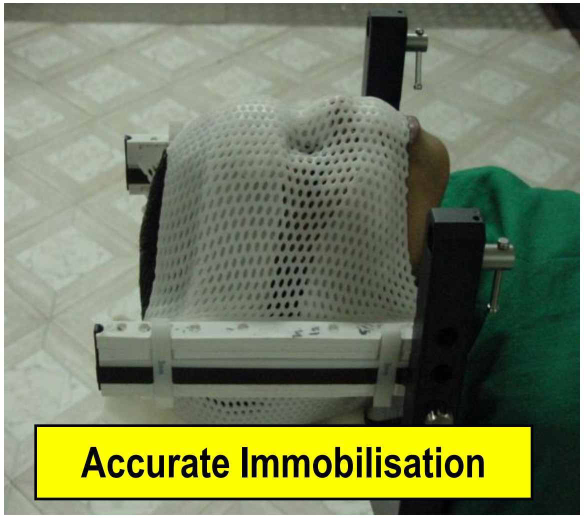


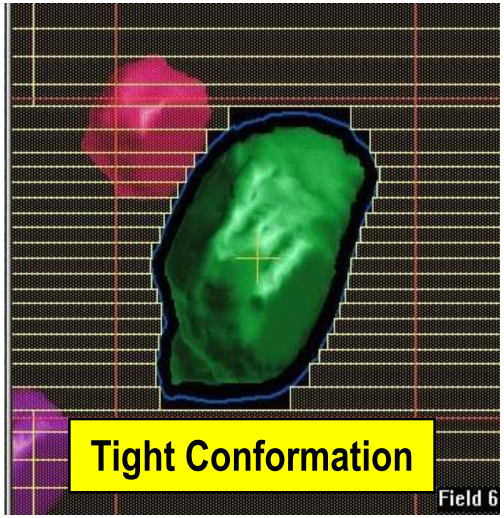


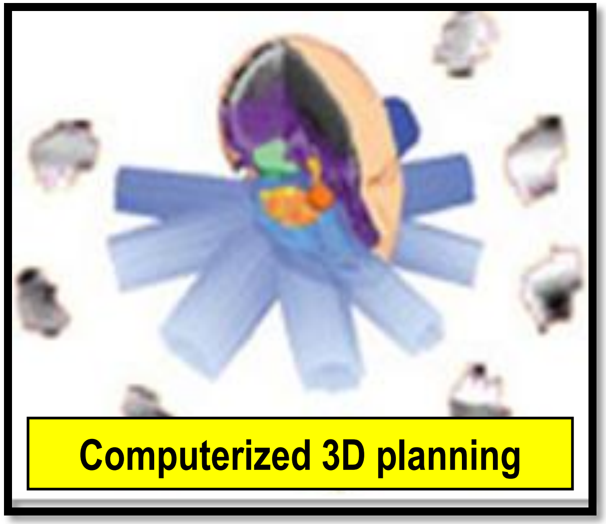
- Large OR
- Touching optic nerves / chiasm

- Small AND
- ≥2-3 mm from optic n / chiasm
- AND well-defined

Modern Conformal RT process and workflow

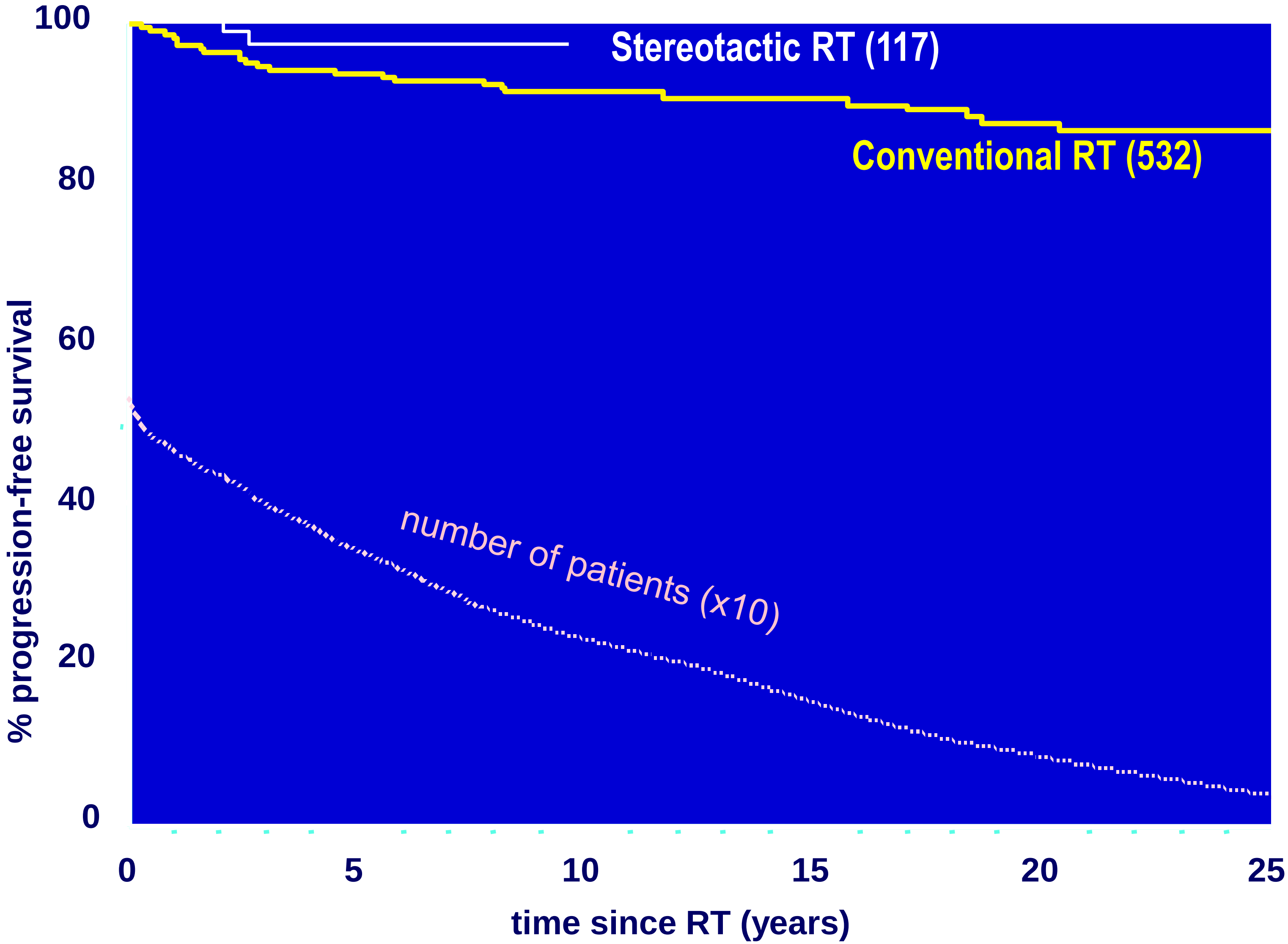






Jalali et al, Clin Endocrinol 2000

Long term tumour control after RT



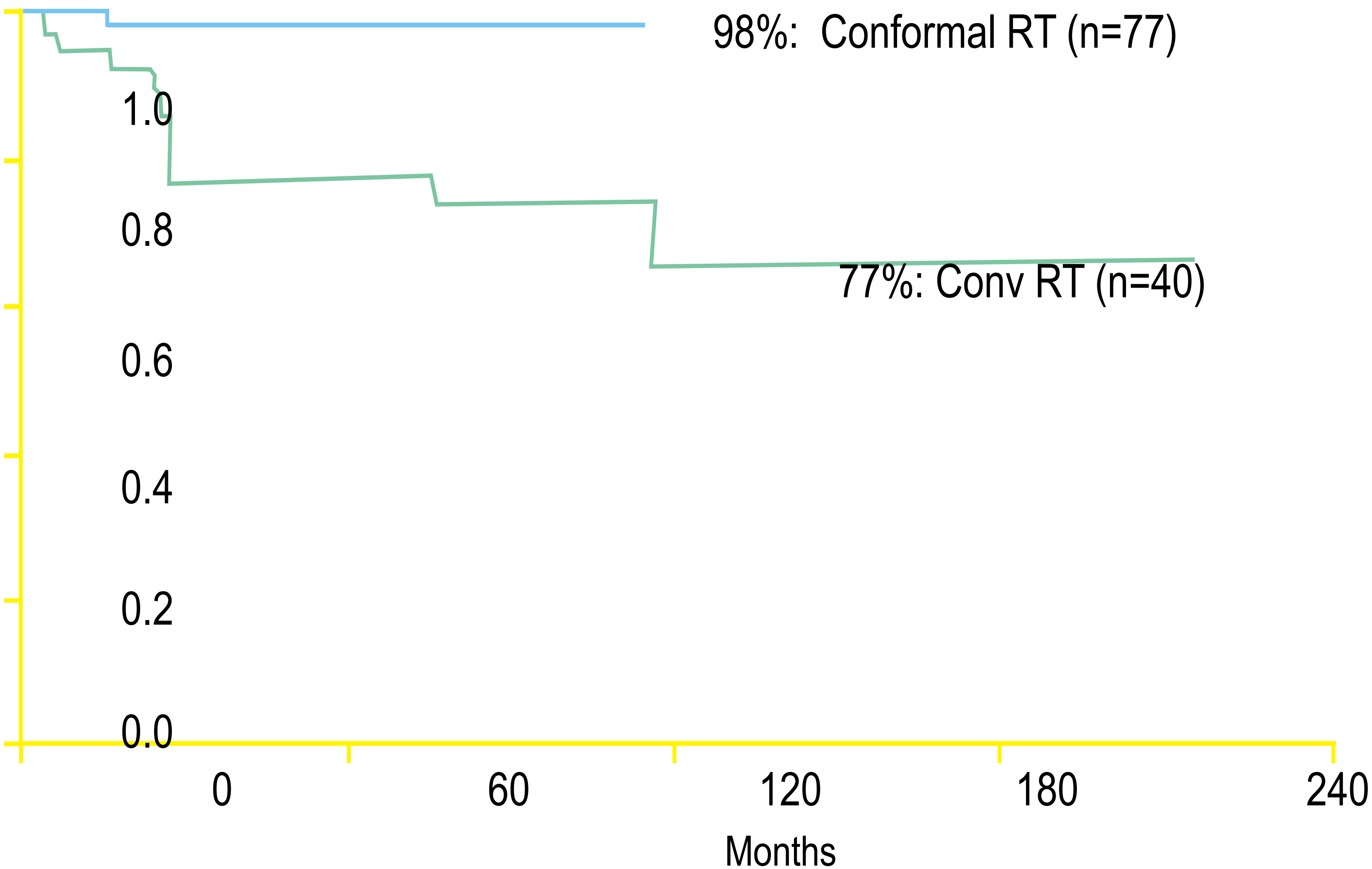
Meningioma- long term results

[a] 16 atypical

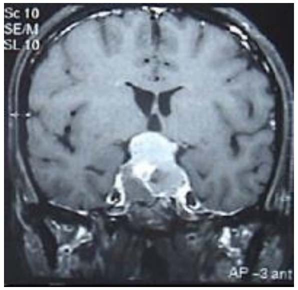
Author (year)	n	GTR	STR	STR+ RT
Mirimanoff (1985)	225	93% (n=145)	63% (n=80)	
Taylor (1988)	132	96% (n=90)	43% (n=42)	85% (n=13)
Glaholm (1990)	117			84%
Miralbell (1992)	115		48% (n=79)	88% (n=17, 8yPFS)
Mahmood (1994)	254	98% (n=183)	54% (n=65)	4/6 stable disease
Goldsmith (1994)	117			89% (98% p1980, n=77)
Condra (1997)	246[a]	95% (n=174)	83% (n=55)	86% (n=17, 5 atypical)
Stafford (1998)	581	88% (n=465)[b]	61% (n=116)[c]	
Nutting (1999)	82			92%
Vendrely (1999)	156			89% (12 >WHO grade 1)
Debus J (2005)	153			90.5%
	2389	**88-98%**	**43-83%**	**84-98%**

Impact of modern RT planning

Progression-Free Survival
STR + postop RT; p=0.002

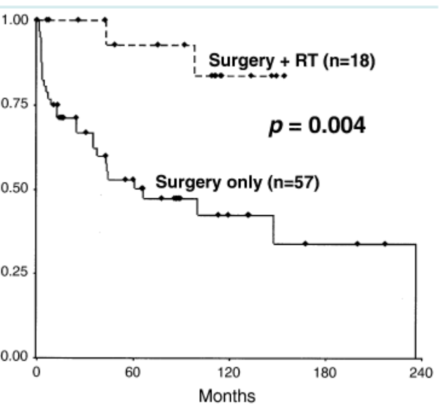


Craniopharyngioma



- 2-5% of all primary intracranial tumours
- Radical surgery: high incidence of hypothalamic damage
- Increasingly treated with conservative surgery + RT
- Good results with RT; 70-85% long term control

Review of 144 published data; Adamson & Yasargil 2008



Fractionated stereotactic conformal radiotherapy following conservative surgery in the control of craniopharyngiomas

Giuseppe Minniti[a,1], Frank Saran[a,b], Daphne Traish[a,e], Rubin Soomal[b], Susan Sardell[a], Adam Gonsalves[a], Susan Ashley[c], Jim Warrington[d], Kevin Burke[d], Amin Mosleh-Shirazi[b,d], Michael Brada[a,e,*]

CLINICAL INVESTIGATION Brain

FRACTIONATED STEREOTACTIC RADIOTHERAPY FOR CRANIOPHARYNGIOMAS

Daniela Schulz-Ertner, M.D.,* Claudia Frank, M.D.,† Klaus K. Herfarth, M.D.,* Bernhard Rhein, M.Sc.,‡ Michael Wannenmacher, M.D., D.D.S.,* and Jürgen Debus, M.D., Ph.D.*‡

Prospective data with conformal RT

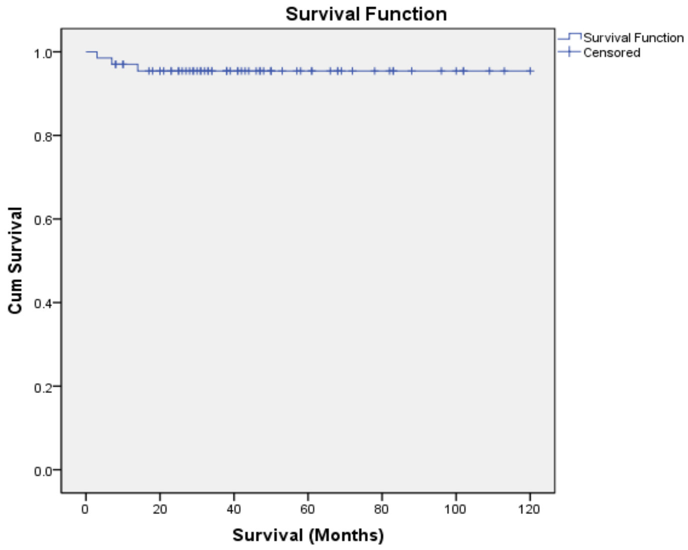
Total no. of patients with **craniopharyngioma** accrued (**2001-2011)**	73
Patients completed Rx as per trial protocol	70
Patients with detailed outcome analysis (at least 1 post RT 6 month evaluation)	66

Follow up period

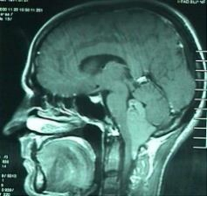
Median (months)	41
Mean (months)	44
Range (months)	3-120

Survival at last follow up

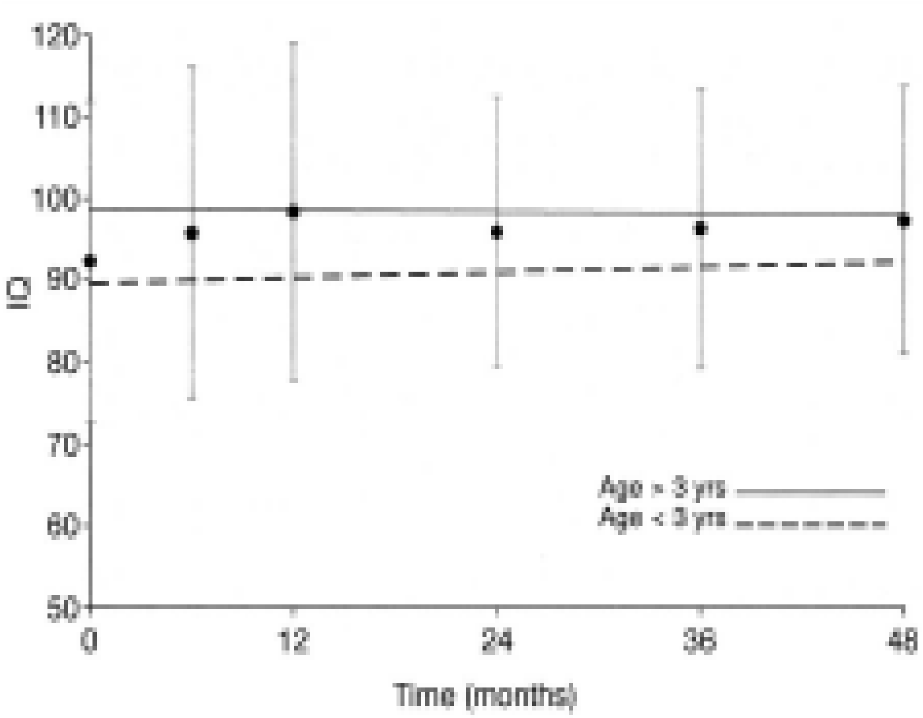
Deaths	3
Cause of death (electrolyte imbalance, repeated infections/septicemia/vascular events)	

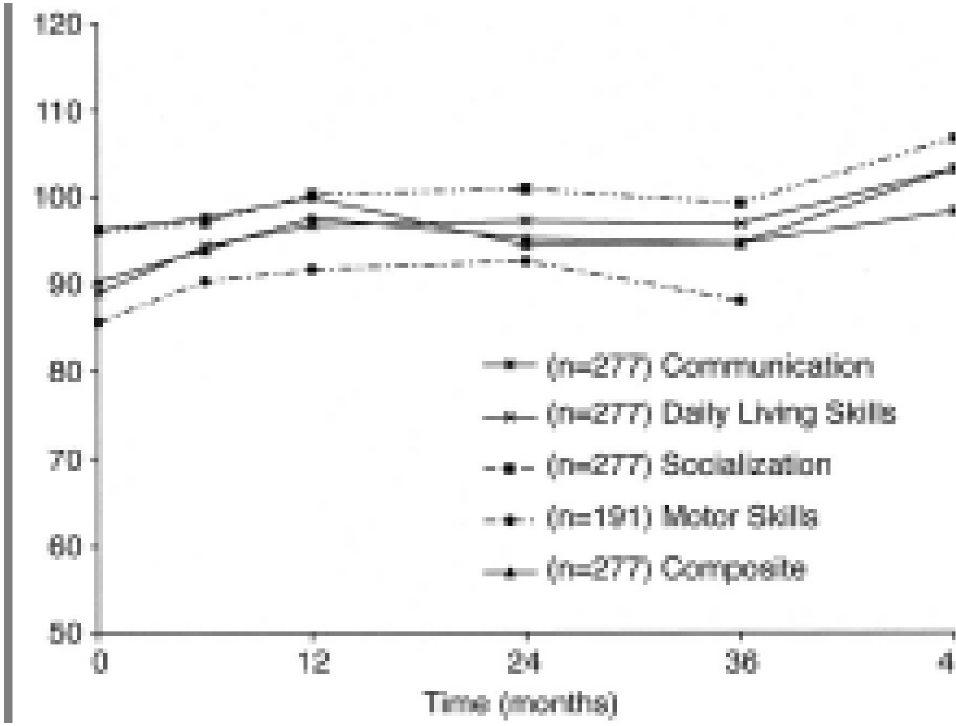


7 year Overall Survival: 95.0%



Prospective trial of conformal RT in children less than 3 years of age (ependymoma)

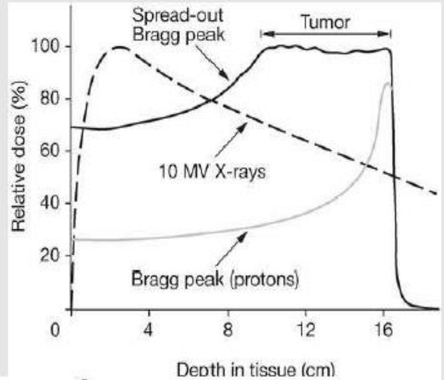


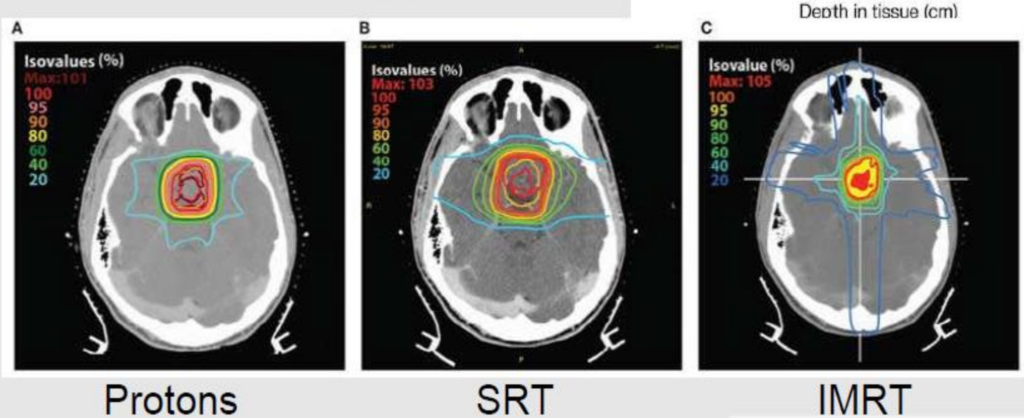


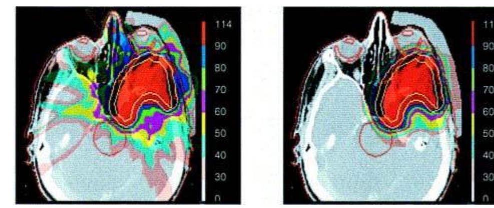
Merchant JCO 2004;22:3156-62

Protons

- Steep dose fall-off at distal edge
- Less dose to normal tissues
- Becoming more available

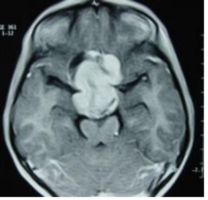




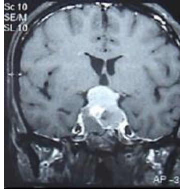


- Unequivocal clinical superiority yet to be demonstrated
- May be beneficial in benign tumours, ? recurrent tumours
- Potentially counter productive in infiltrating tumours as gliomas
- QA, cost
- Just not ***A Proton*** facility; should be spot scanning, with image guidance
- Collaborative data needed

Yock & Tarbell, NCPO 2009

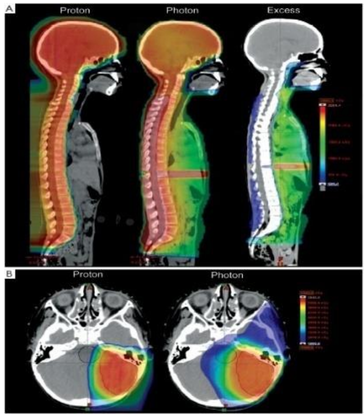


High-precision radiotherapy for progressive/residual low grade/benign brain tumours



- Excellent long term control
- Advances in technology and increasing use of high precision techniques (Stereotactic RT, IMRT, Proton beam therapy, Tomotherapy, Cyber knife, etc)

Evaluation of efficacy of modern high-precision RT



- *Physics / dosimeteric*

  Dose distributions, dose volume histograms, indices
- *Clinical*

  Reduction of RT induced toxicity

  Survival

Clinical evidence is based on retrospective or relatively few prospective studies

Stereotactic **Conformal RT Vs Conventional RT** in Children and Young Adults With Low Grade and Benign Brain Tumours

Sponsor:	Tata Memorial Hospital
Collaborator:	Terry Fox Foundation
Information provided by:	Tata Memorial Hospital
ClinicalTrials.gov :	**NCT00517959**

Primary endpoint

Incidence and magnitude of neuropsychological, cognitive, neuroendocrine and neurological dysfunction in the two arms

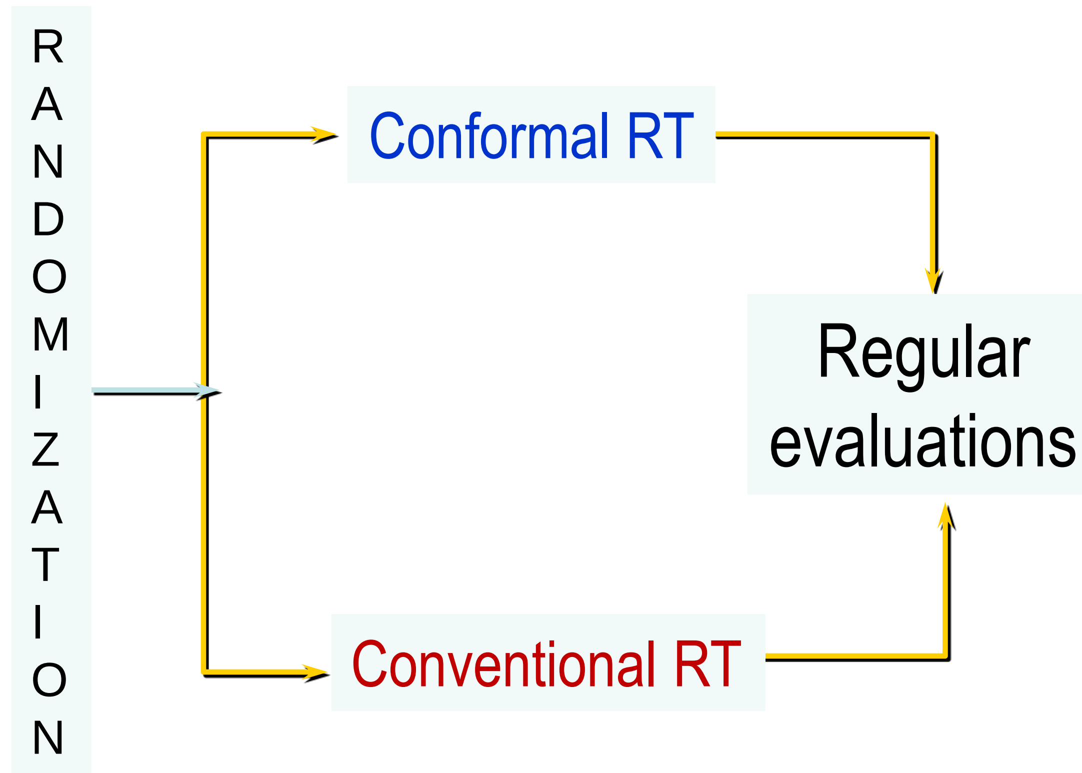
Secondary endpoint

Survival

- **Sample size**: N=200; 80% power to detect a 15-20% reduction in primary endpoints in Conformal RT arm compared to conventional RT arm at a significant level of $p<0.05$
- **Informed consent** (English, Hindi, Marathi)

Trial schema

- Age 3-25 years
- Residual/progressive low grade and benign tumours needing RT
- Informed consent
- Detailed neurological endocrine and neuropsychological evaluation



Stratification

- Pre vs. post pubertal
- NPS 0-1 vs. 2-3
- Hydrocephalus nil/mild vs. moderate/severe

IRB Clearance: May 2001
Accrual: 2001 - 2011

RT techniques in the two arms

	High precision Conformal RT	Conventional RT
Immobilisation	**BrainLAB stereotactic mask**	Thermoplastic mask
Imaging datasets	CT **+ MRI** (3D-FSPGR/T2 FLAIR)	CT simulation
Volume delineation	CTV= Residual tumour/ tumour bed GTV+3-5mm	CTV=Residual tumour/ tumour bed GTV+3-5mm
Safety margin or Planning target volume (PTV)	**2mm**; RT delivery under stereotactic guidance	**5 mm**
Beam planning	**microMLC based Conformal, non coplanar 6-9 beams**	2-3 coplanar beams, appropriate wedges and shielding
Dose/fractionation	**54 Gy/ 30 #/ 6 weeks**	**54 Gy/ 30 #/ 6 weeks**

Jalali *et al,* Radiotherapy and Oncology 2005

Patient demographic profile (n=200)

Characteristics		CRT	Conv RT
Age median (IQR)		13yr (8-17.5)	12yr (9-17)
Gender	Male	69	64
	Female	36	31
Pathology	Cranio	39	44
	Astrocytoma	34	29
	OPG	22	15
	Ependymoma	6	6
	Others	4	1
Location	Supratentorial	82	81
	Infratentorial	23	14
Vision	Normal	98	88
	Impaired	7	7
Hydrocephalus	Mild	34	29
	Mod/Severe	71	66
NPS	0/1	79	73
	2/3	26	22
Pubertal status	Prepubertal	65	61
	Postpubertal	40	34

IQ before starting adj *Rx* in benign/low grade tumours

45% of pediatric patients with low grade and benign tumours in a prospective study (n=103) at had low IQ (performance IQ) baseline before starting SRT

Carpentieri *et al* Neurosurg 2003

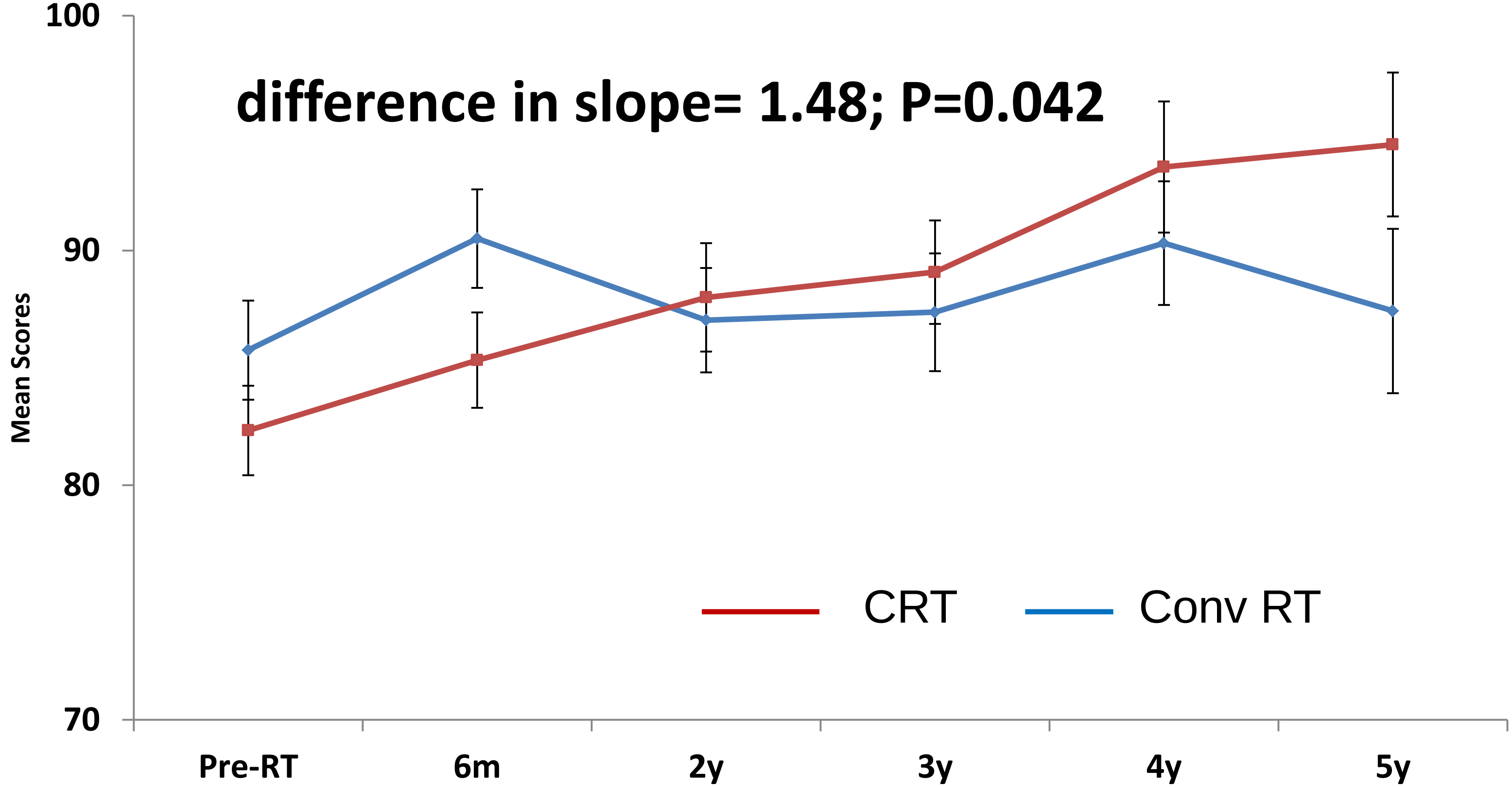
60.4% patients at pre RT baseline had below normal values (n=78)

	IQ	patients
Defective	<69	12 (15.4%)
Borderline	70-79	23 (29.5%)
Dull Normal	80-89	17 (21.8%)
Average	90-109	22 (28.2%)
Bright Normal	110-119	4 (5.1%)
Superior	120-129	0 (0%)
Very Superior	>130	0 (0%)

Jalali *et al* IJROBP 2006, 2010

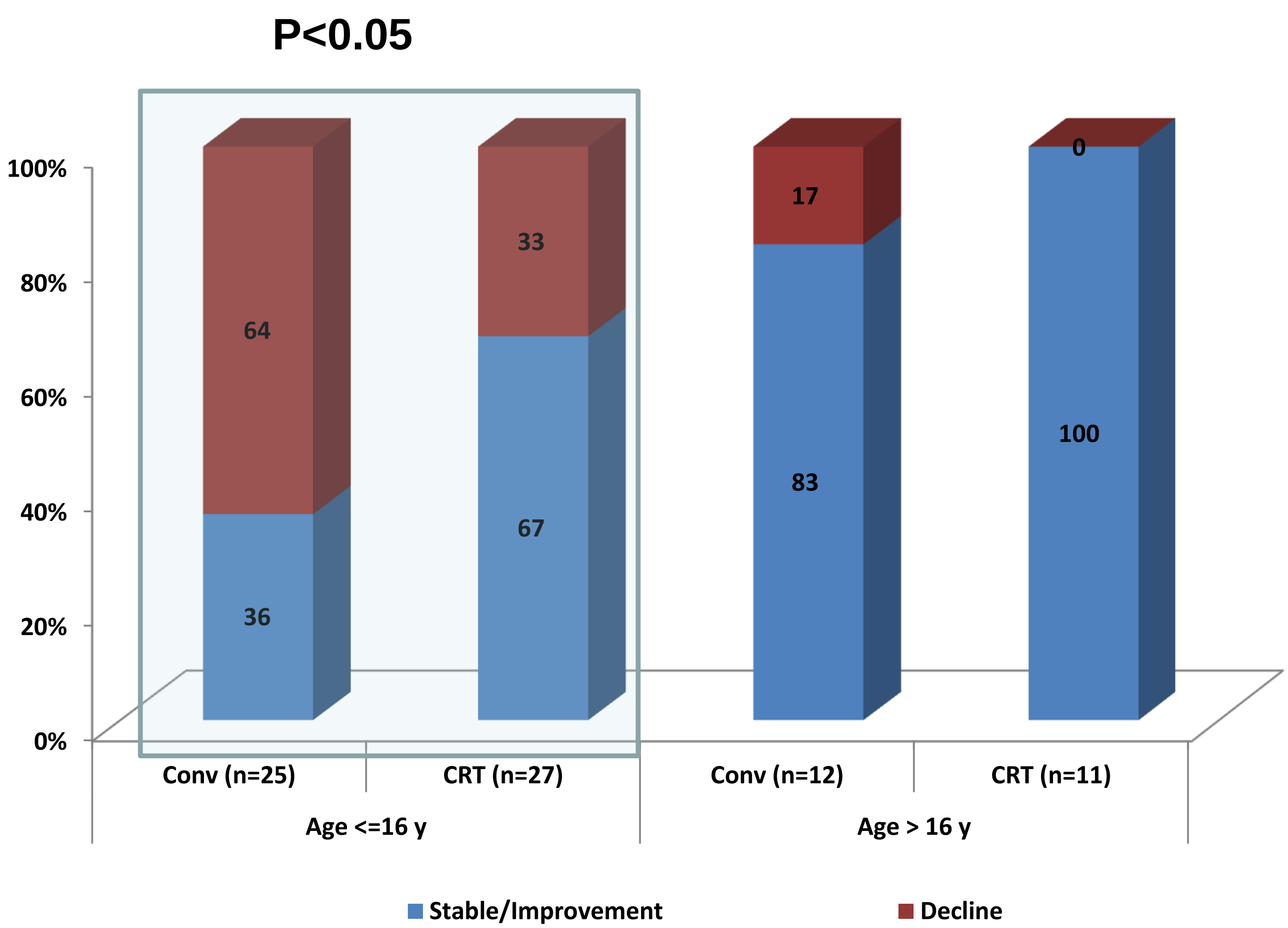
Time trends in Full scale IQ (FSIQ)

Linear mixed model



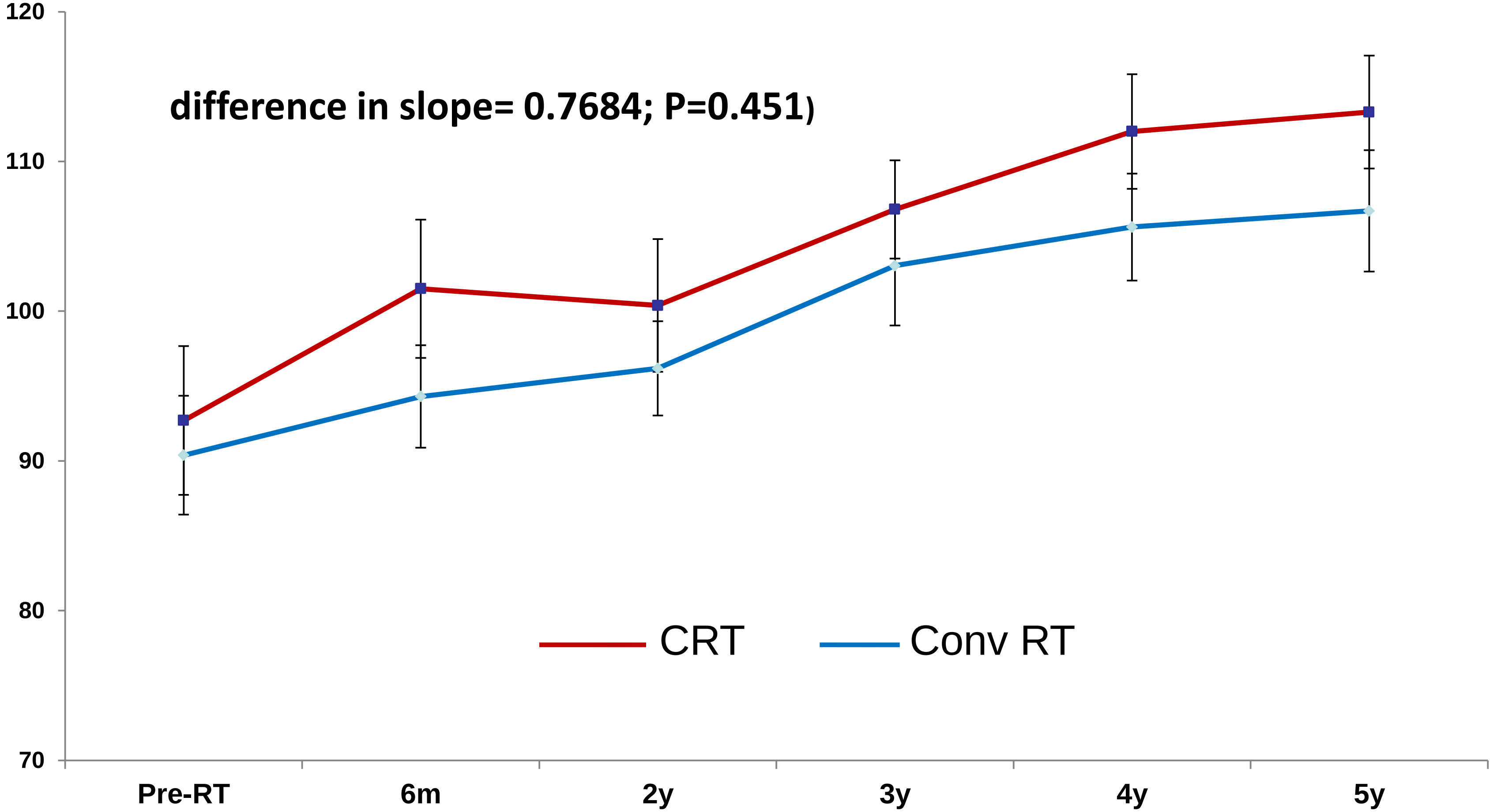
	Pre-RT	06	2	3	4	5
CRT	97	72	61	43	39	29
Conv	83	69	63	51	38	22

Distribution of clinically significant FSIQ wrt to age



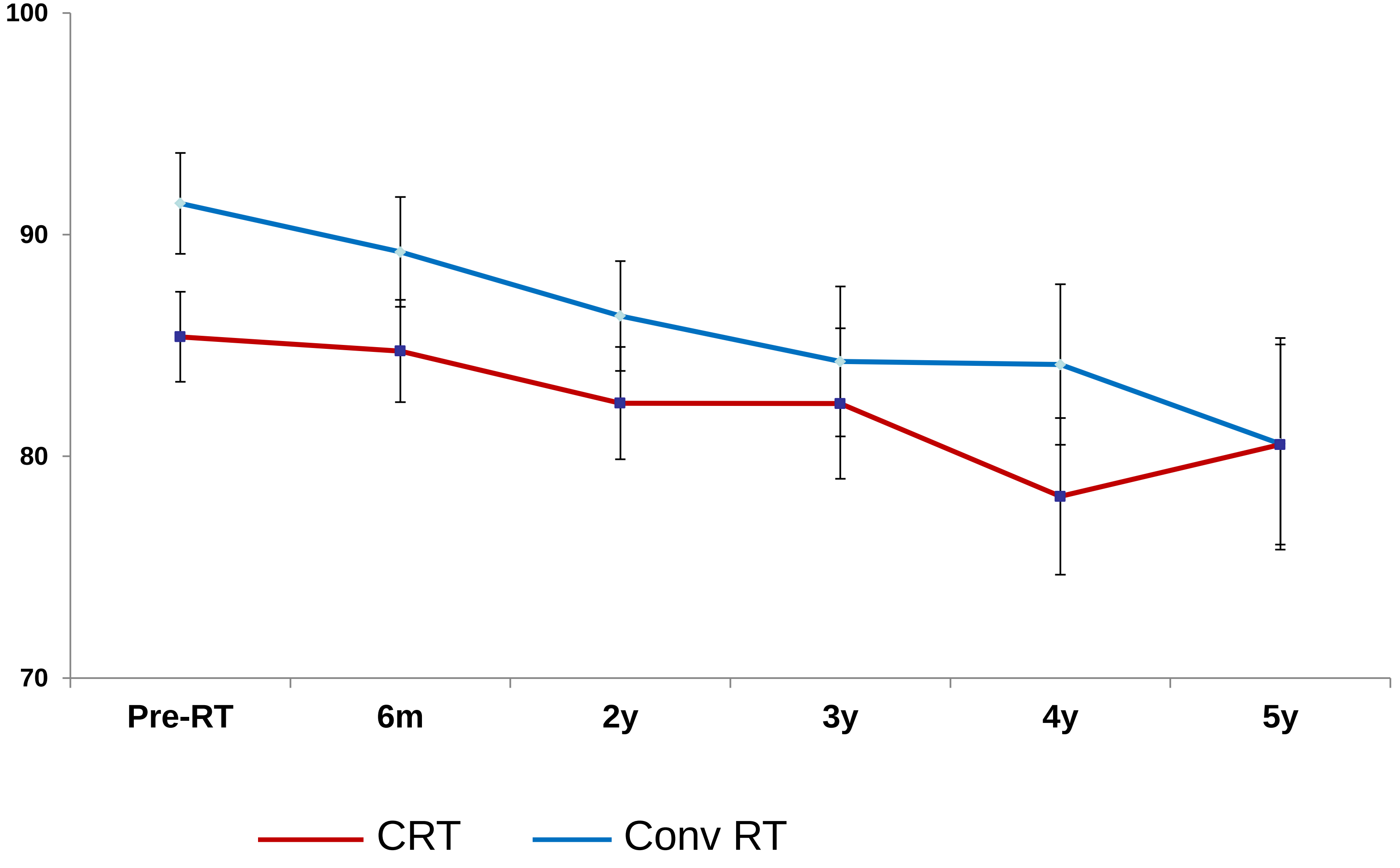
Reference value for clinically significant change was taken as 5 point decline/improvement (3%)

Time trends in MQ
Linear mixed model



Time trends in VQ

Linear mixed model(LMM)



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doi:10.1016/j.ijrobp.2009.06.025

CLINICAL INVESTIGATION — **Brain**

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

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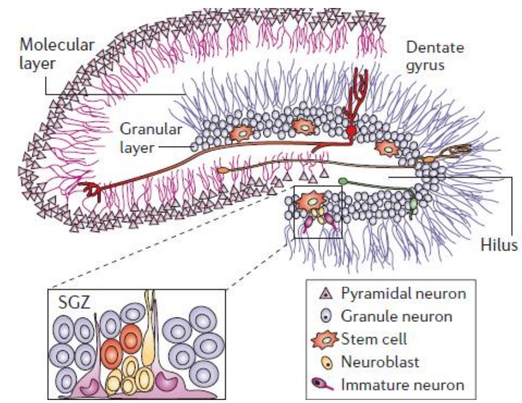
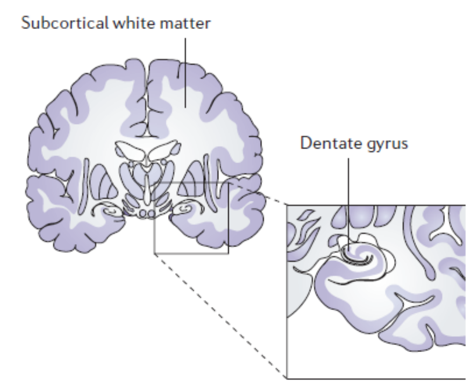


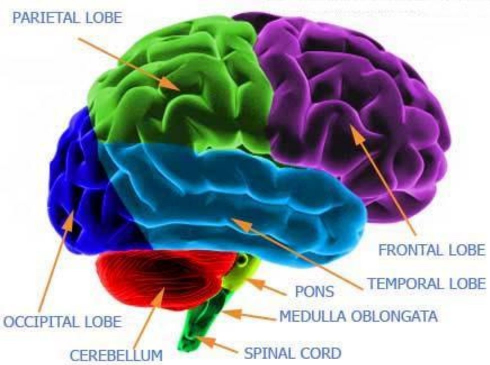


Possible dose constraint model

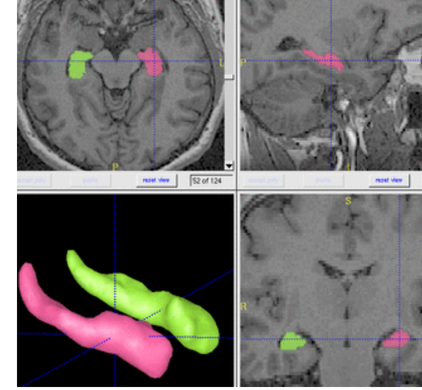
No IQ decline

Left temporal lobe

- < 13% volume receiving > 43 Gy



Left Hippocampus RT dose & IQ preservation at 5 years

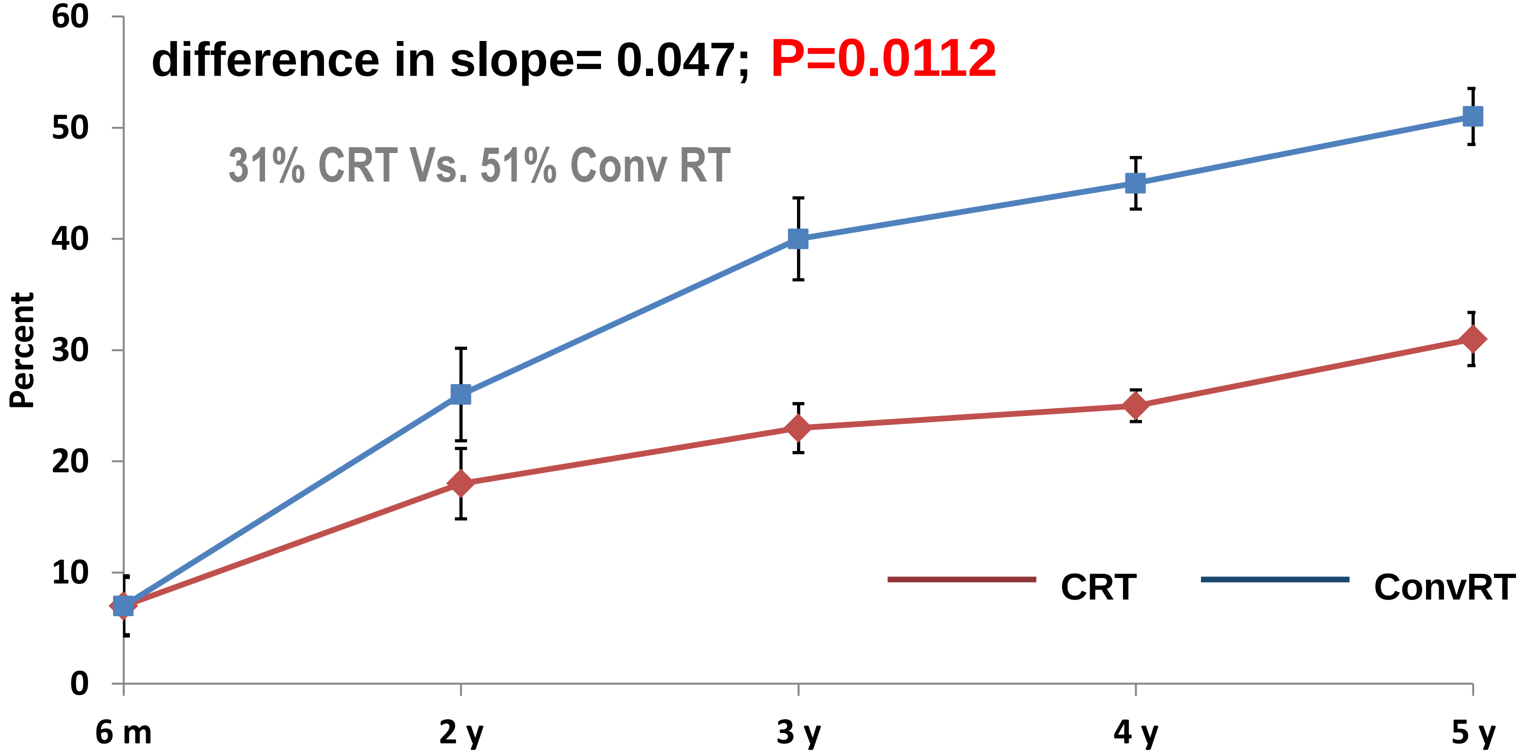


Logistic regression analysis, model fit

		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	

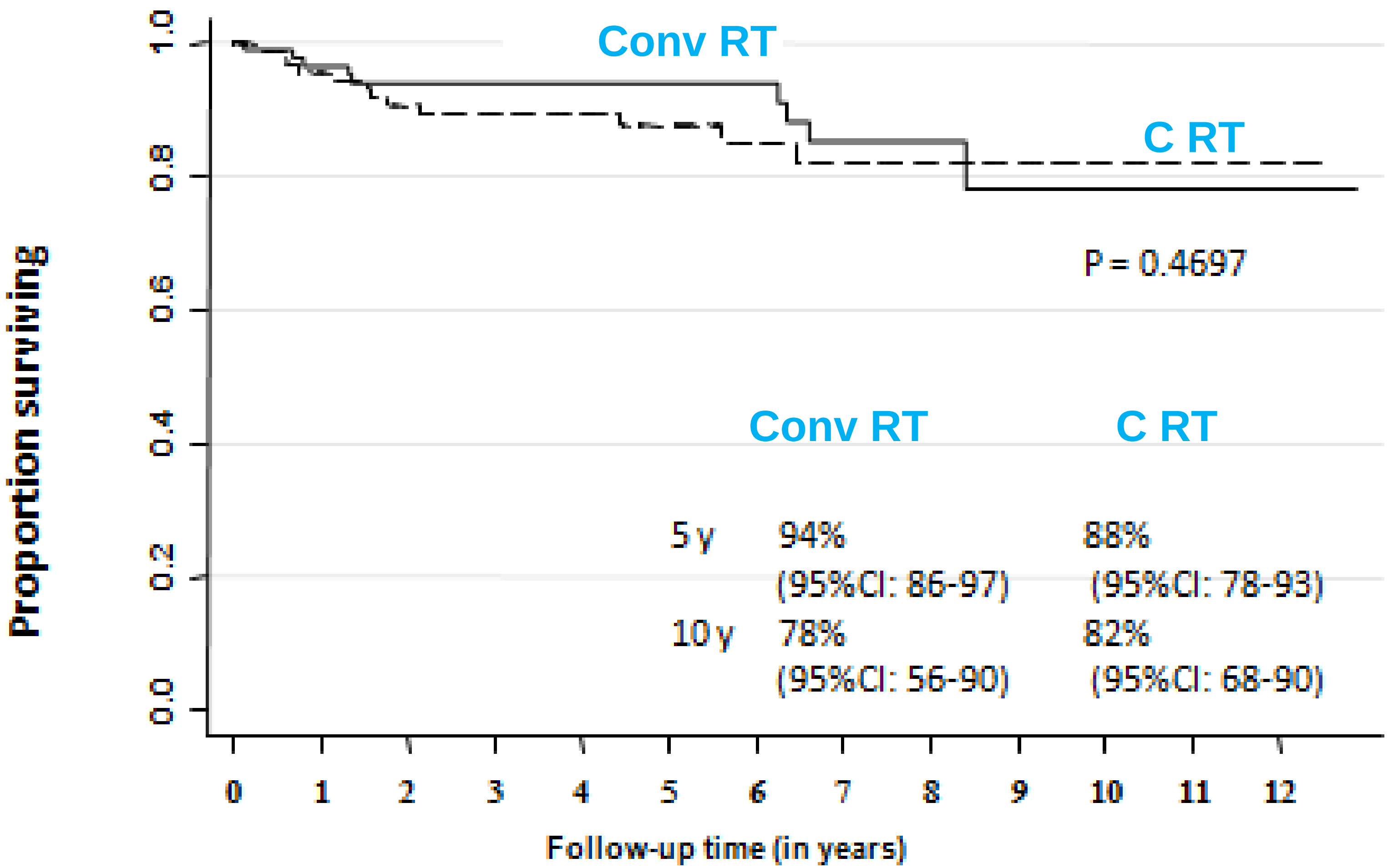
Mean doses ≤30 Gy as a possible dose constraint cut off for IQ decline

Cumulative incidence of new endocrine dysfunction



Patients at risk	6 months	2 yr	3 yr	4 yr	5 yr
CRT	91	66	56	49	33
Conv RT	82	68	56	46	39

Overall Survival



Conclusions

- RT indicated and vital in optimal management of many CNS tumours

- Modern conformal RT spares critical areas safely

- Efficacy of conformal RT proven in a randomised controlled trial in terms of preservation of neurocognition and significantly less endocrine dysfunctions at 5 years follow up following radiotherapy; all meaningful and clinically relevant late endpoints

- Could be used as a template/corroboration for other modern evolving high precision RT techniques (including possibly particle therapy)

*"Therapy should be **permanently** backed up by **scientific research** without which no progress is possible. Moreover the search for pure knowledge is one of the most important needs for mankind…"*