Clinical Requirements

Dr Paul Sanghera

Oncologist

Radiotherapy / Stereotactic Radiosurgery Lead

QEHBirmingham

Conflicts

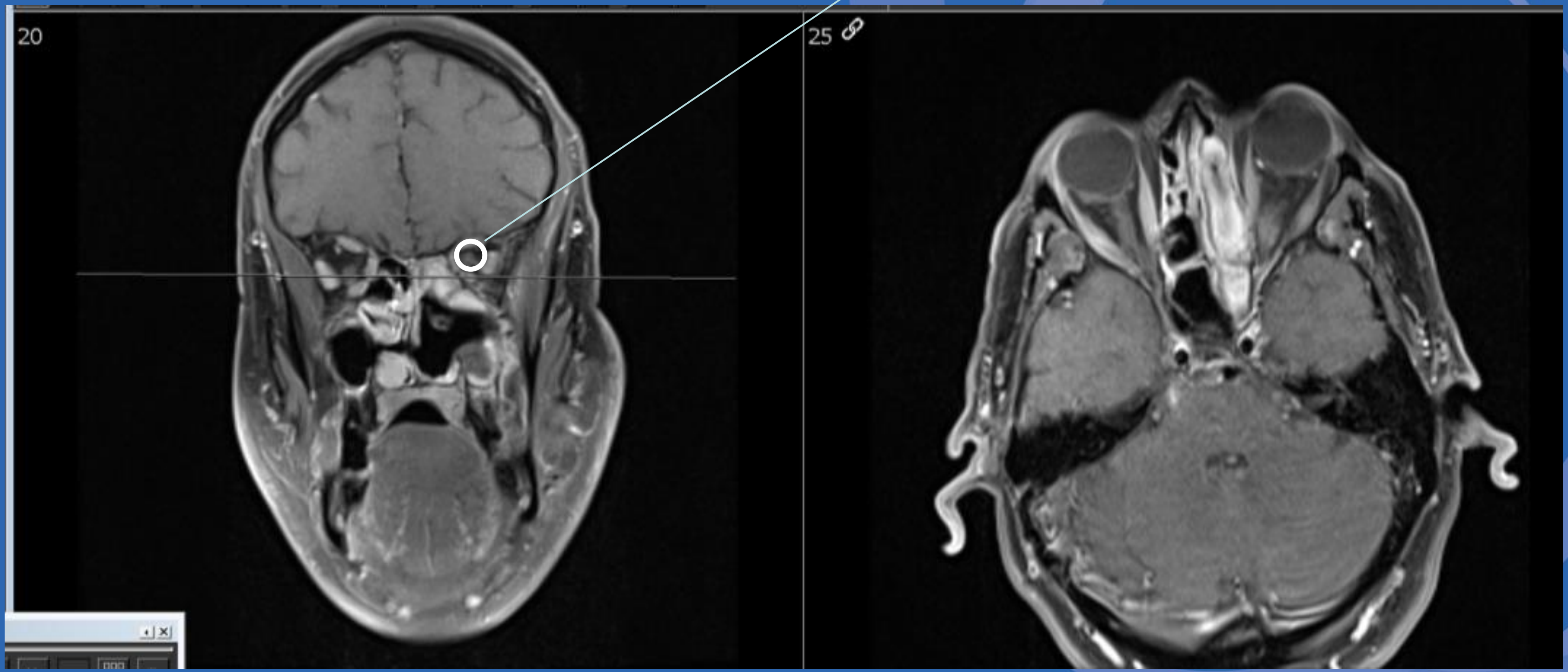
- No financial disclosures
- Photon based experienced
  - SRS/T (range of platforms)
  - IG IMRT (led implementation at UHB)
- Member of the Adult UK Proton Clinical Referral Group

NHS overseas programme for PBT

- Children
  - Chordoma & Chondrosarcoma
  - Ependymoma
  - Selected Rhabdomyosarcomas
  - Ewings Sarcoma
  - Retinoblastoma
  - Pelvic Sarcoma
  - **Optic pathway and other selected low grade gliomas**
  - **Craniopharyngioma**
  - Pineal Parenchymal Tumours (not Pineoblastoma)
- Adults
  - Base of skull and spinal Chordoma
  - Base of skull Chondrosarcoma
  - Spinal and paraspinal soft tissue sarcomas
  - **Complex skull base cancers (sinonasal ACC/melanoma)**
  - **“TYA” extension to age 25 years**

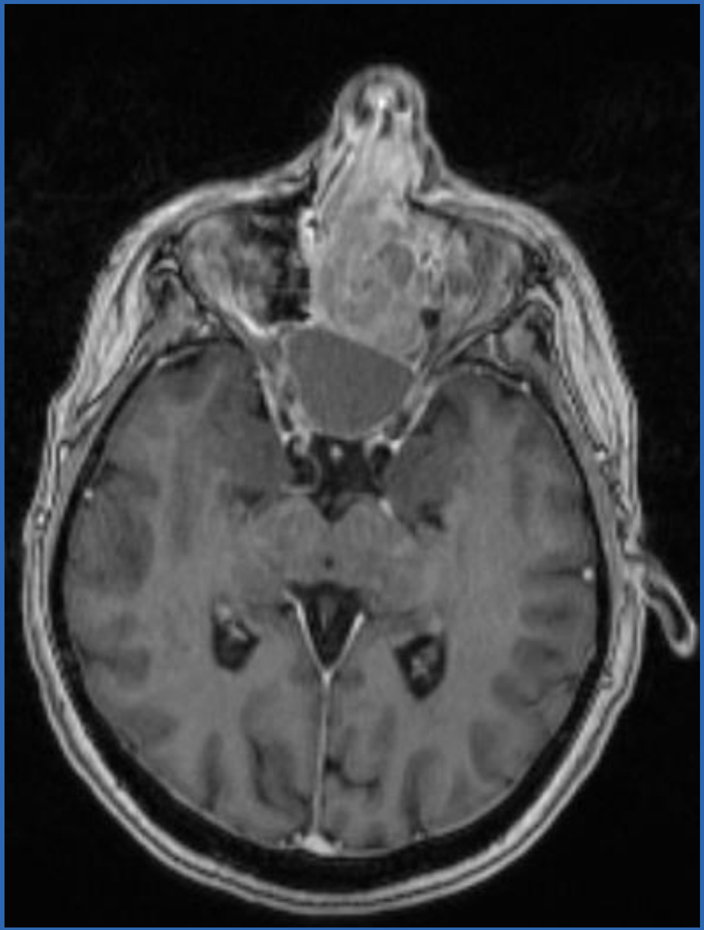
Steep dose gradient to respect critical OAR tolerance? Improved therapeutic ratio?

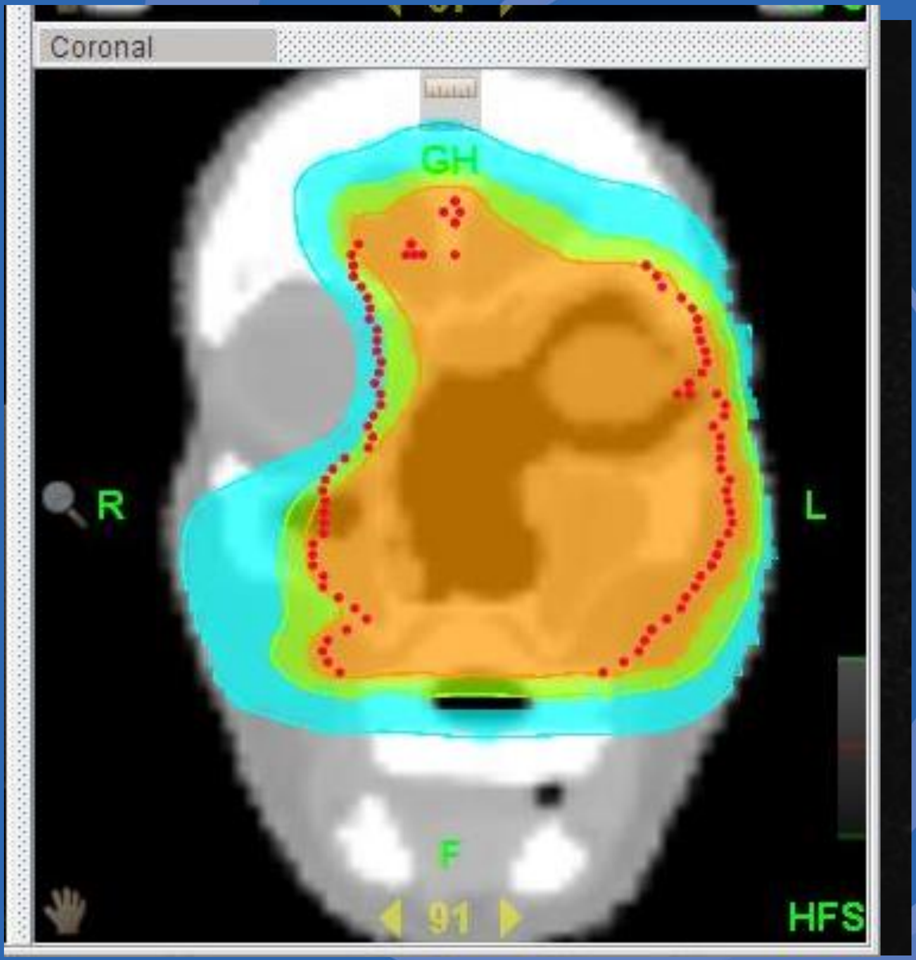
Optic nerve close to target volume (Dose <55Gy)



Sino-nasal Melanoma

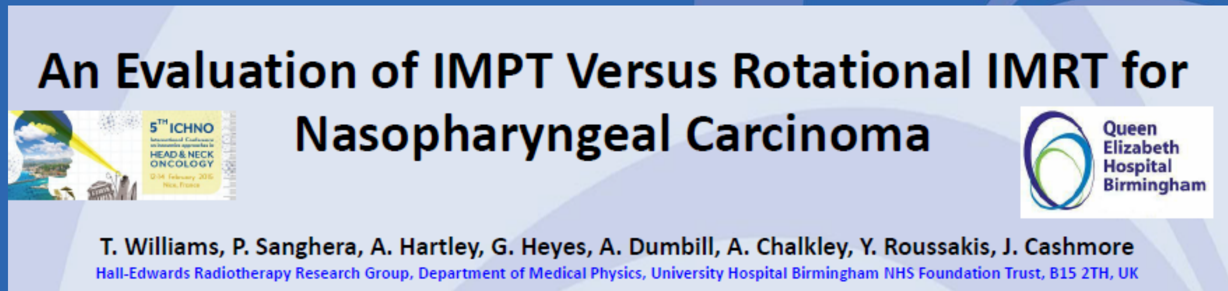
Preserve Function?



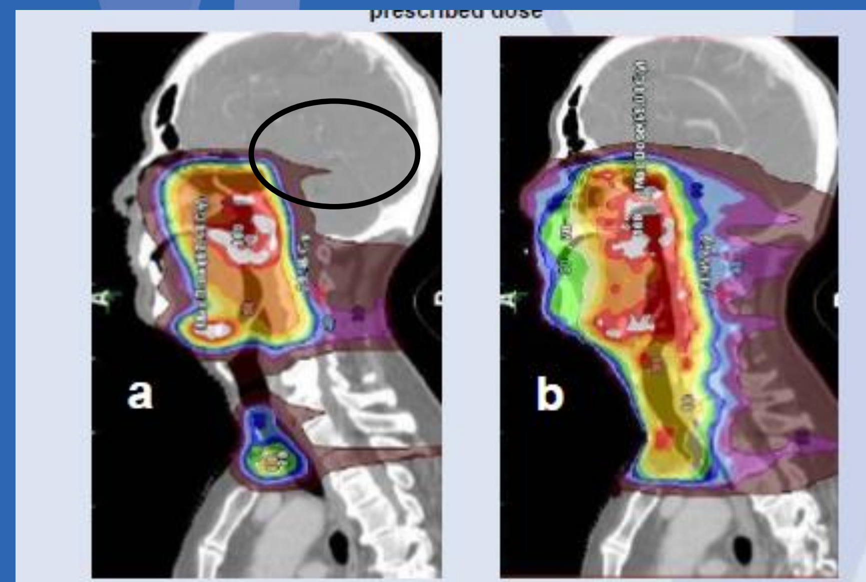


Skull base invasion / peri-orbital disease managed with surgery (morbid)

Improve Quality of Life through less peripheral dose



- Mean dose reduction to posterior fossa (p=0.004) and oral mucosa (p=0.004)
- Greatest dose advantage to distal structures



Study lead : Jason Cashmore (UHB Physics)

Endocrine late-effects of cancer treatment 3

Effect of cancer treatment on hypothalamic–pituitary function

Elizabeth Crowne, Helena Gleeson, Helen Benghiat, Paul Sanghera, Andrew Toogood

The Lancet Diabetes and Endocrinology 2015

- GH most sensitive to RT
- Common > 40Gy
- Pituitary dysfunction expected >60Gy
- Point prevalence post Brain/Nasopharyngeal RT 66%
  - GH 45%l LH/FSH 30%; TSH25%; ACTH22%

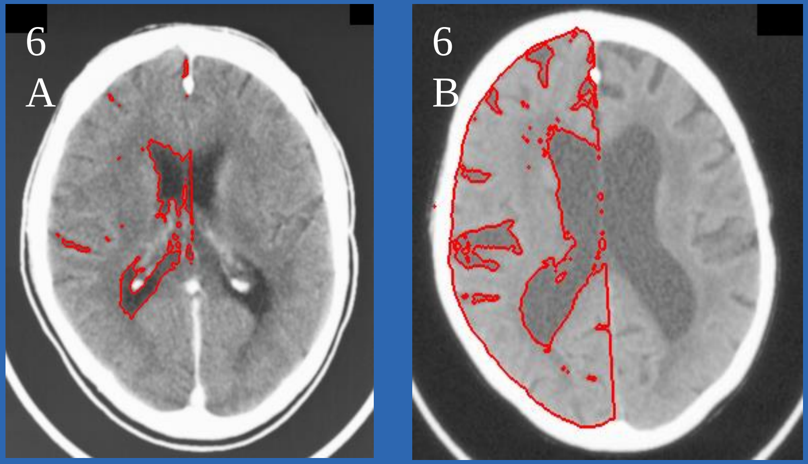
- Lifelong pituitary function follow up
- Ion therapy could improve QoL?

PBT: Head and Neck benefits : less dose to normal tissue ? (DARS Study launched by RMH)

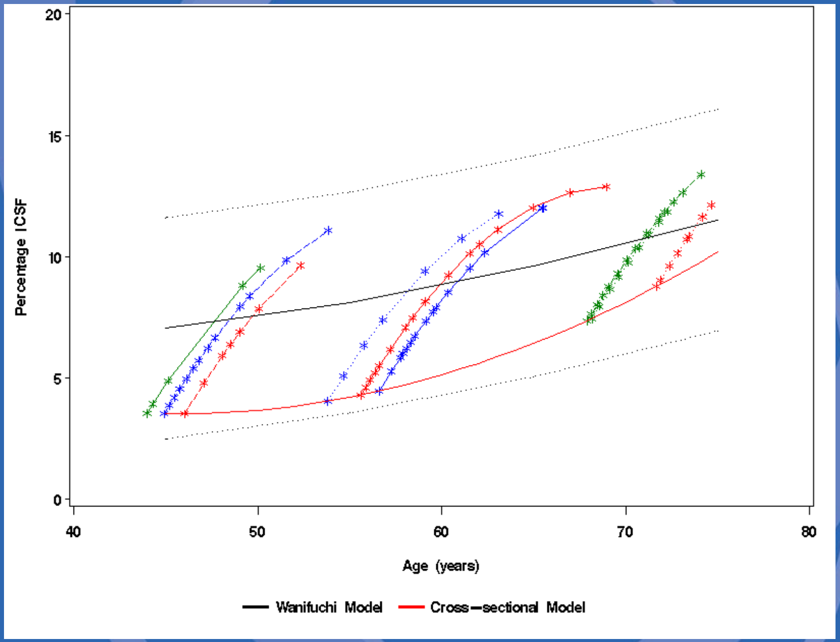
- Studies show that risks for late swallowing dysfunction include
  - Dose to pharyngeal constrictors + supraglottic larynx
- Better sparing of swallowing structure possible with PBT

Dirix et al IJROBP 09

Radiotherapy causes neurocognitive decline

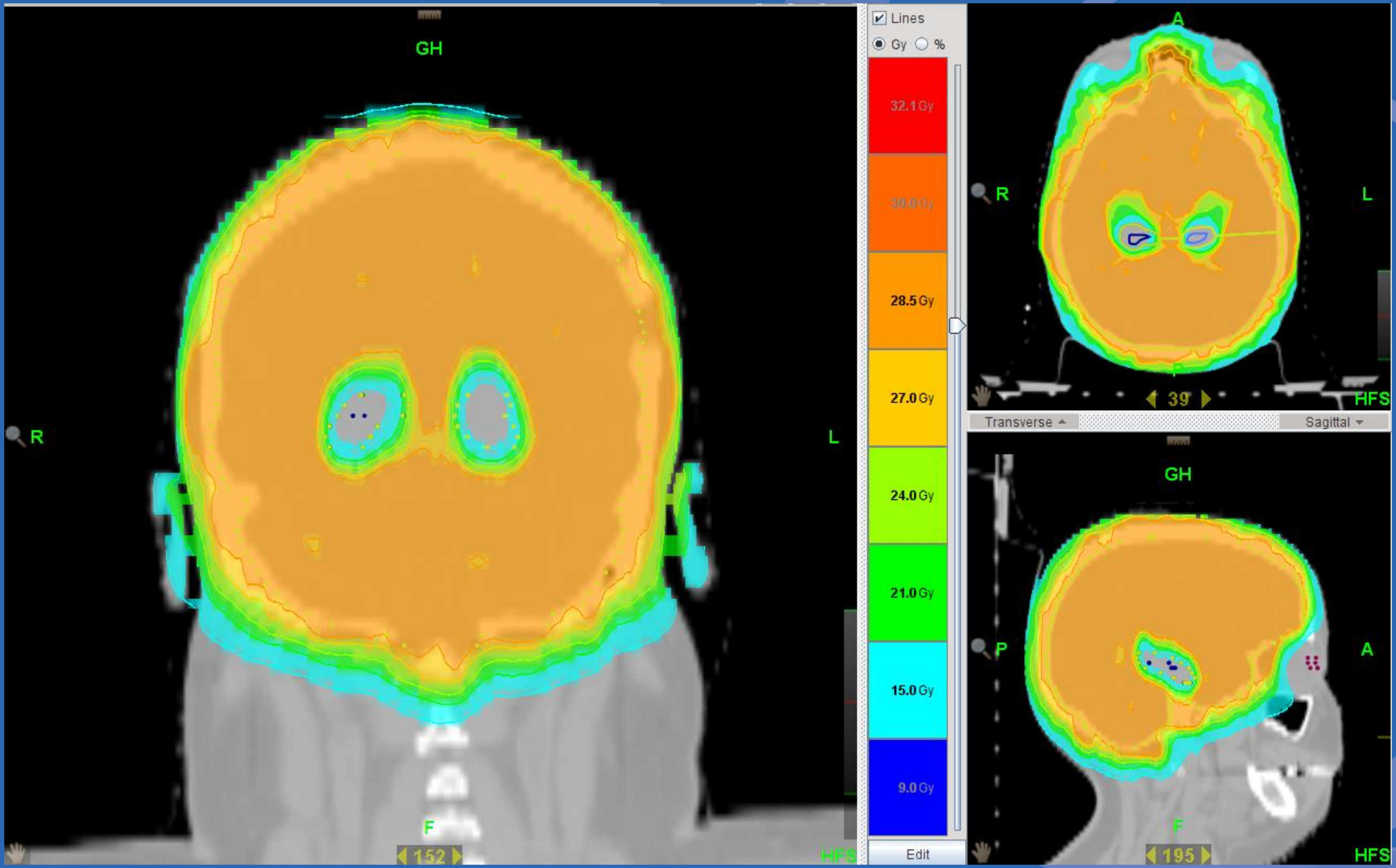


1992 2005



Sanghera et al, IJROBP 2010

Hippocampal sparing (region of neurogenesis)



Jason Cashmore Physics UHB

HIPPO Study

Gill Whitfield Lead (Christie) / UHB Co application

Radiosurgery or surgical resection of 1-4 brain metastasis(es)

Randomised
ph II – 84 pts

Whole brain radiotherapy: 30Gy in 10 fractions with hippocampal sparing

Whole brain radiotherapy: 30Gy in 10 fractions

- Primary End point NCF measured using HVLT-R at 4 months
- Secondary includes cognitive battery (Prof Lambon Ralp Cognitive Neuroscientist Manchester)
- MRI scans at 3 months and to continue at 3monthly intervals up to 24months

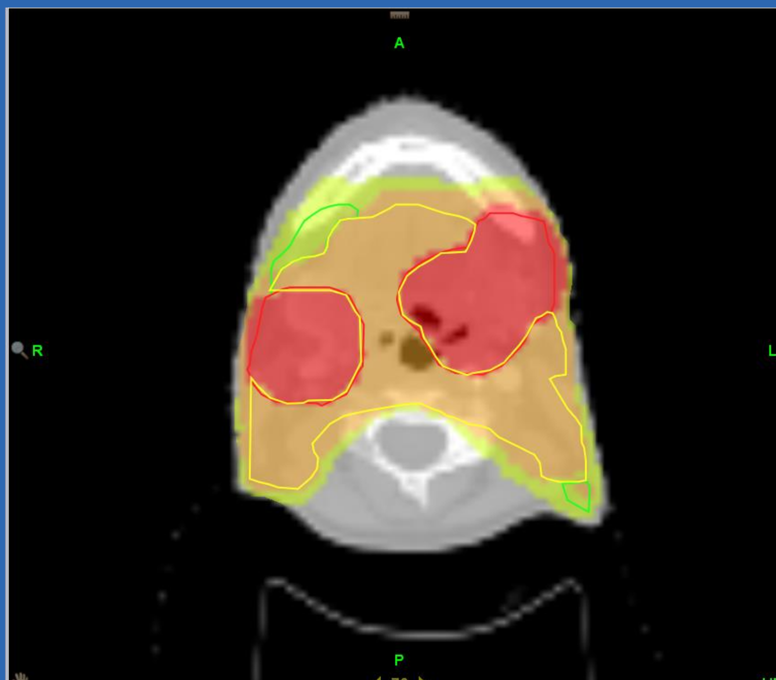
Requirement : Select endpoints for trials to reflect gains from intermediate / low dose related morbidity?

- Quality of Life
- Cognition (e.g. short term memory measured using HVLT)
- Ocular (dry eye, vision, cataracts..)
- Cardiac events (explore early surrogates)
- Lung function (exercise ability..)
- Pelvis – bladder /bowel function low grade morbidity
- 2^{nd} cancers (challenging)
- USE EARLY SURROGATES WHERE POSSIBLE

University Hospitals Birmingham NHS
NHS Foundation Trust

Chemoradiotherapy for poor/intermediate risk oropharyngeal carcinoma: First results of the ArChIMEDEs-Op study

Harrop V[1,2], Meade S[1], Gaunt P[3], Babrah J[3], Wagstaff L[2], Robinson M[4], Cashmore J[1], Mehanna H[2], Hartley A[1,2], Sanghera P[1,2]
1 Hall-Edwards Radiotherapy Research Group, Queen Elizabeth Hospital, Birmingham, UK, 2 Institute of Head and Neck Studies and Education (InHANSE) University of Birmingham, Birmingham, UK, 3 CRUK Clinical Trials Unit, University of Birmingham, Birmingham, UK, 4 Centre for Oral Health Research, Newcastle University, Newcastle-upon-Tyne, UK



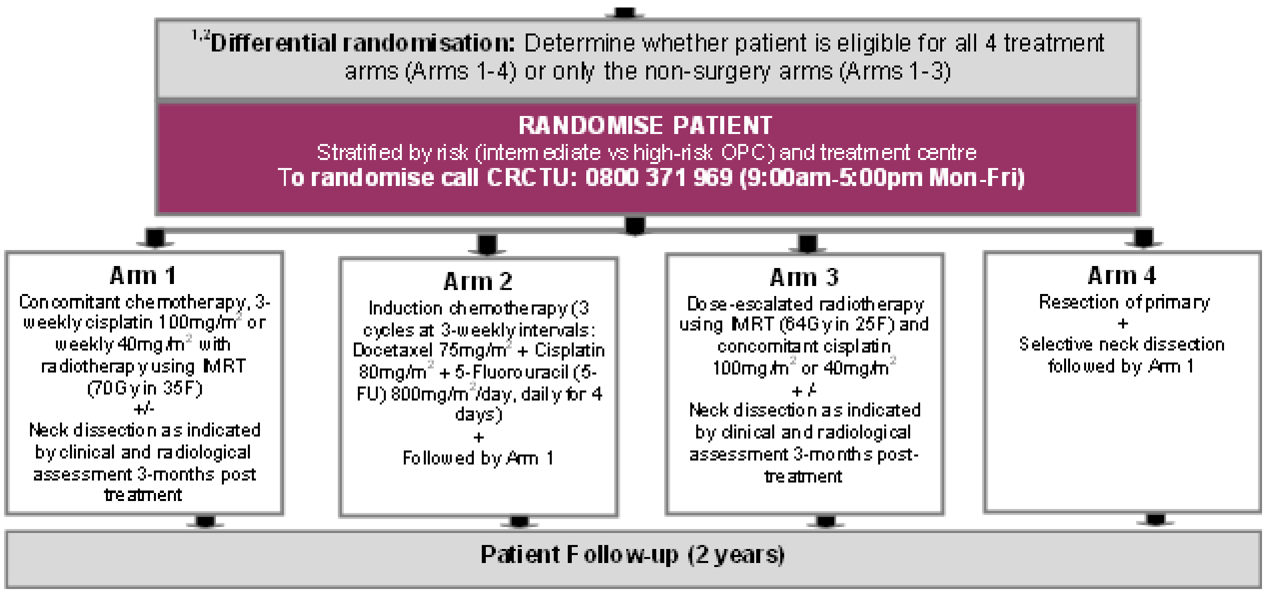
Pilot Study Completed

- Primary toxicity endpt met
- 100% LR / 93% Nodal at 3months
- 1/15 patients required supplementary tube feeding at 3 months (metastatic disease)
- 14/15 tube independent (includes any use)
- 9/15 Normal diet

Ability to dose escalate with less morbidity (dose response)?

COMPARE TRIAL (CI : H Mehanna)

Standard care
International gold standard



Systematic Review of Particle Therapy for Paranasal Sinus and Nasal Cavity Malignancy

(Patel et al, Lancet Oncol 2014)

- 43 non-comparative observation cohorts
- Pooled 5Y OS significantly higher for particle therapy vs photons (RR 1.51, p=0.0038)
- Subgroup of PBT v IMRT : Higher 5Y DFS (p=0.045) but not 5 year LRC
- Higher neurological toxicity with particle therapy (p=0.0002)

- Multiple confounding factors including surgery / dose objectives / histology....

Photon technical developments: Conform + accurate delivery + adapt

- Accuracy: Stereotactic techniques + Image guided radiotherapy routine practice
- Conformality : IMRT routine practice (software improving + reliable distributions + arcs help dose fall off)
- Adaptive capability: evaluate dose during treatment and change the plan to maintain therapeutic ratio

Radiotherapy for skull base tumours : pathology highly variable

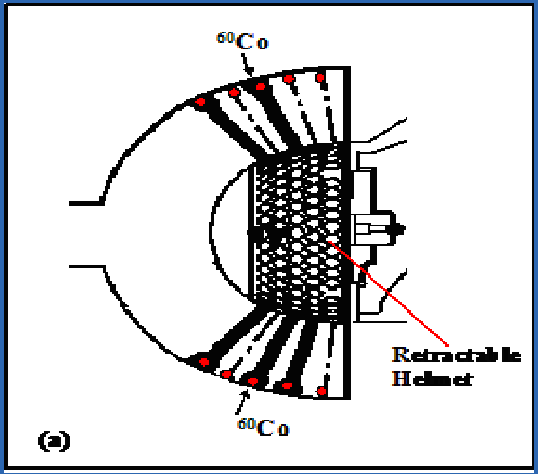
Malignant		Benign
Paranasal Sinus	Adenocarcinoma	Vestibular schwannomas
	SCC	Meningiomas
	Adenosquamous	Pituitary Adeneomas
	Adenoid cystic	Paragangliomas
	Olfactory Neuroblastoma	Hemangiopericytomas
	Neuroendocrine carcinomas	Craniopharyngiomas
	Sinonasal undifferentiated	
	Carcinosarcoma	
	Mucosal Melanoma	
	Other salivary gland	
	Sarcoma (various)	
Nasopharyngeal Carcinoma		
Oropharynx SCC		
Chondrosarcoma		
Chordoma		

Fractionated ⟷ SRS+ Fractionated

Some overlap

Not a comprehensive list

Accuracy: Gamma Knife: >40 years



Accurate and conformal

Linear Accelerator SRS (Birmingham)

- 6MV standard linear accelerator
- -adapted for stereotactic use using externally mounted circular collimator

- Machine set-up for SRS took ~1hr (additional QA to ensure accuracy)

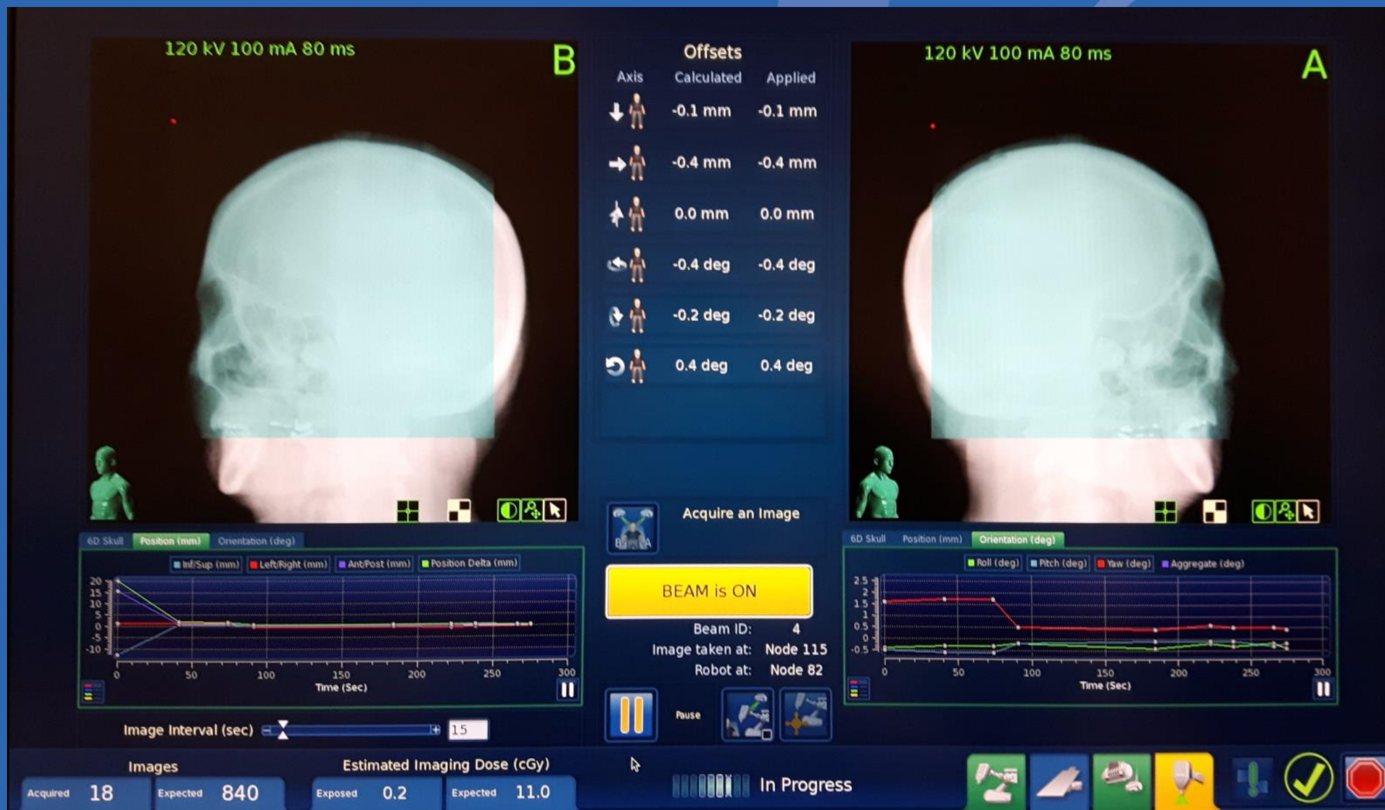
- Surgical frame attached to couch

Move to Cyberknife 2013

- 100’s of beams
- Small collimators
- Monitor target during treatment delivery

Aim to provide sub-mm precision and steep dose gradient required for SRS

Intra-fractional imaging



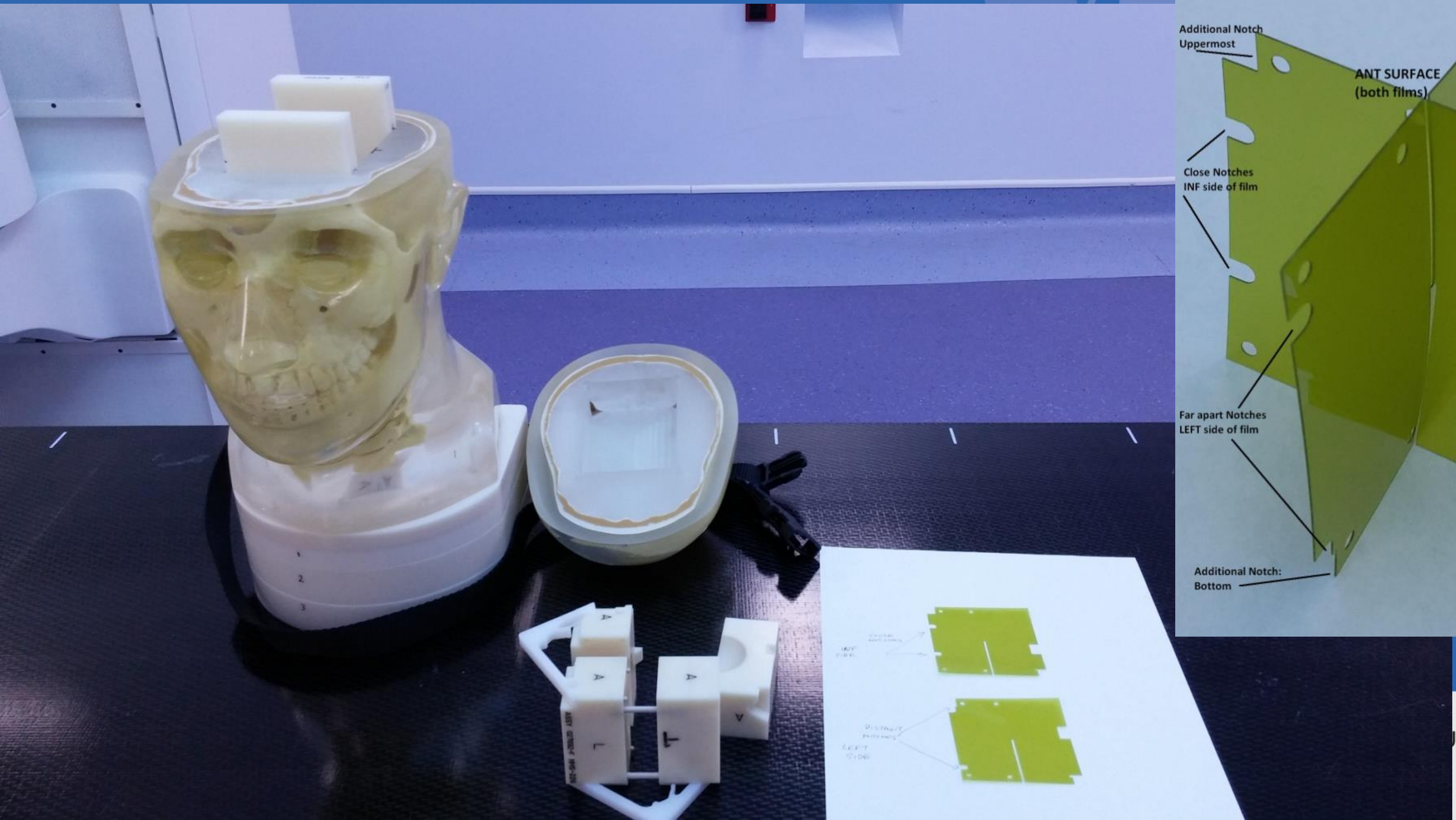
- Patients skull anatomy used to correct- patient remains static- robot path is adjusted
- Corrections >0.1mm are applied

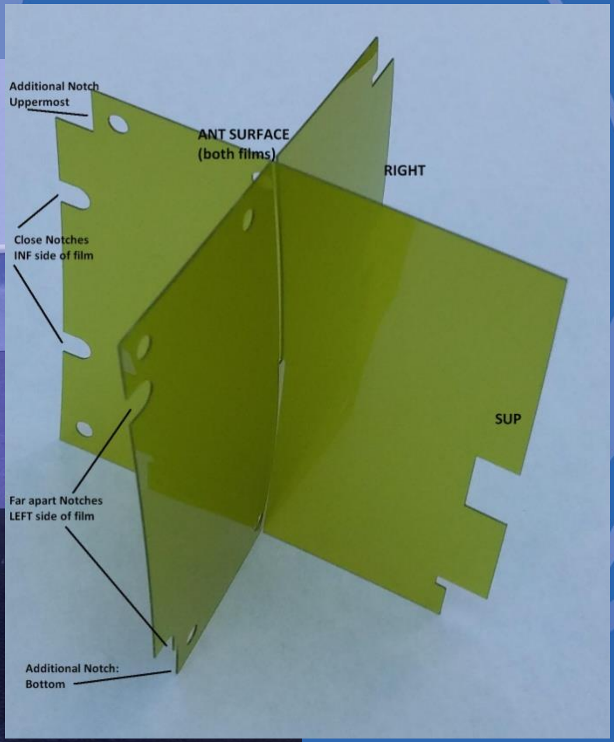
Motion tracking during delivery

- Motion corrected 'on-line' by machine
- Imaging dose over 60 mins ≈ Dose from CT scan
- Imaging frequency can be increased /reduced depending on patient compliance

End-to-End Precision

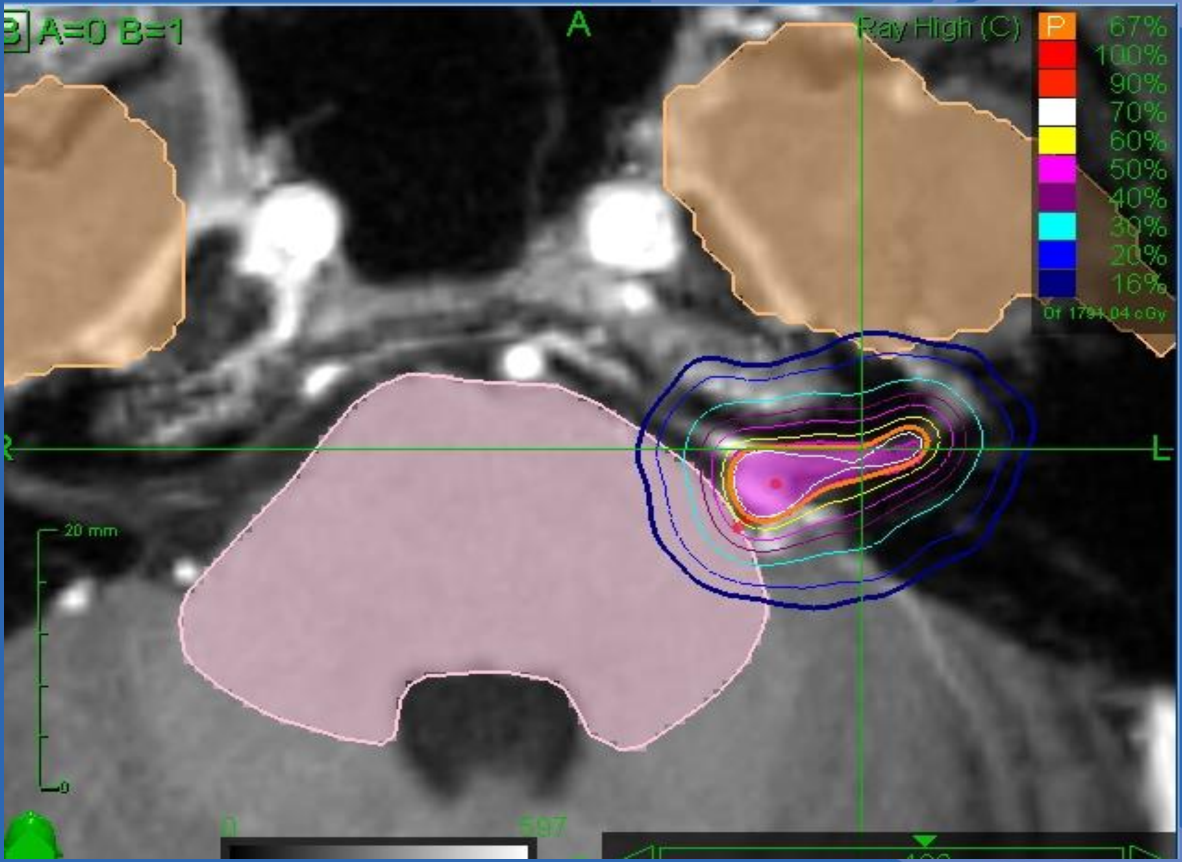
- Anthropomorphic Phantoms containing film
- Tracking accuracy 0.35mm





University Hospitals Birmingham NHS Foundation Trust

Vestibular Schwannoma– GTV to PTV 0mm



No additional margin for inaccuracies including set up/motion during treatment/mechanical/co-registration…………

Do we believe that no uncertainty margins are required?

SRS LACKS PROSPECTIVE DATA
HOWEVER LOTS OF DATA FROM SERIES

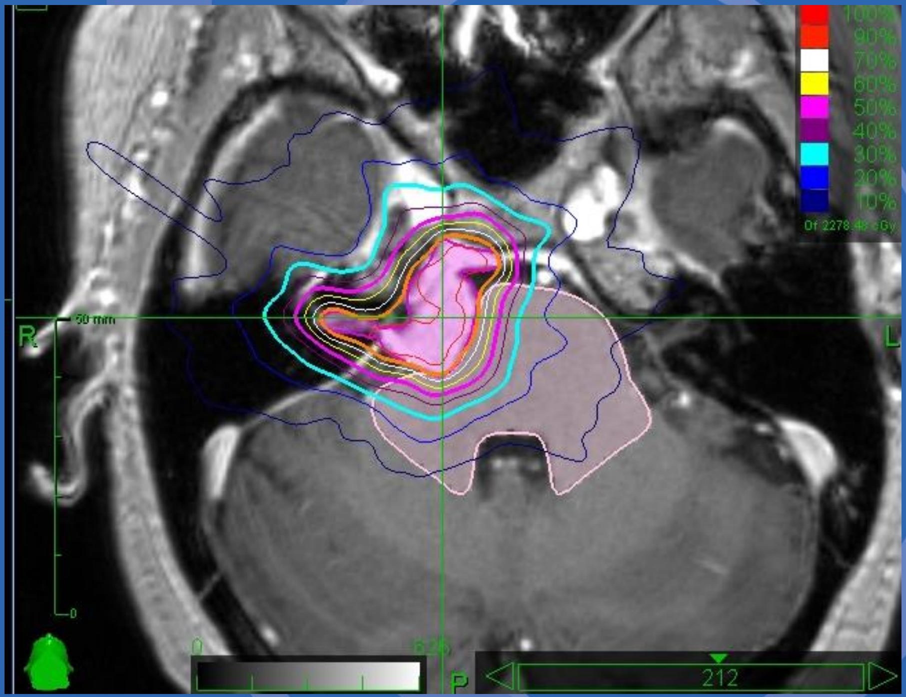
Outcomes Vestibular Schwannomas

Institution & Modality	Authors	N=	Follow up (yrs)	Median dose (Gy)	Median tumour vol (cm^3)	Tumour control rate (%)	CN VII preservation (%)	CN V preservation (%)
Florida (Linac)	Friedman (2006)	296	3.3	12.5	2.2	98 (2yrs)	99.3	99.3
Heidelburg (Linac)	Combs (2006)	26	9	13	n/a	91 (5yrs)	95	92
Pittsburgh (GK)	Chopra (2007)	216	5.7	13	1.1	98.6	100	94.9
Toronto (GK)	Hayhurst (2012)	73	2.4	12	1.95	91 (5yrs)	96.3	78.7
Birmingham (Linac)	**Benghiat (2014)**	**97**	**2.4**	**12**	**1.65**	***100**	**98**	**91.8**

*** 2 patients suspected of radiological progression**

Meningioma SRS

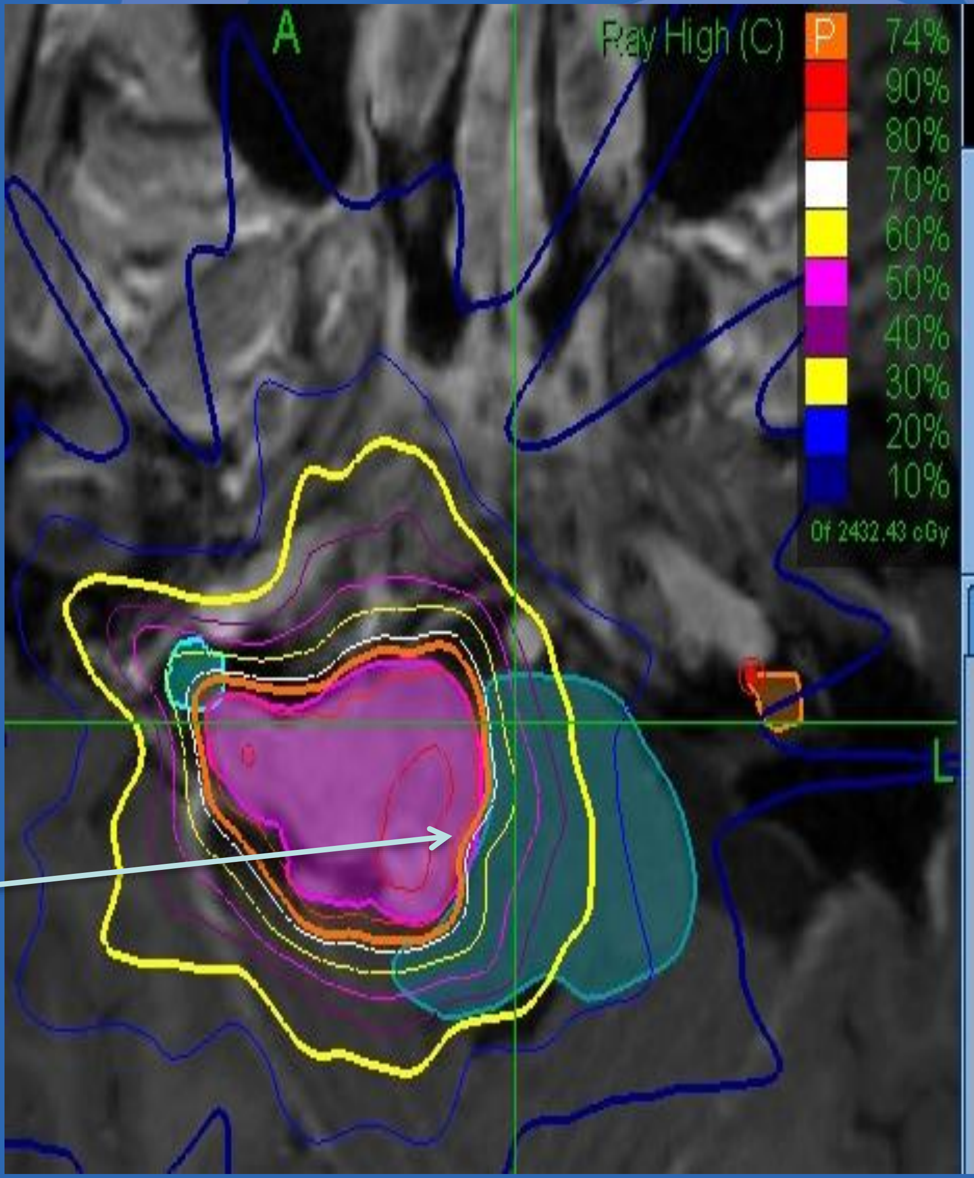
- 5 year LC > 90%
- Prolonged fractionation required if
  - Close to optic pathways
  - Atypical
  - Larger volume

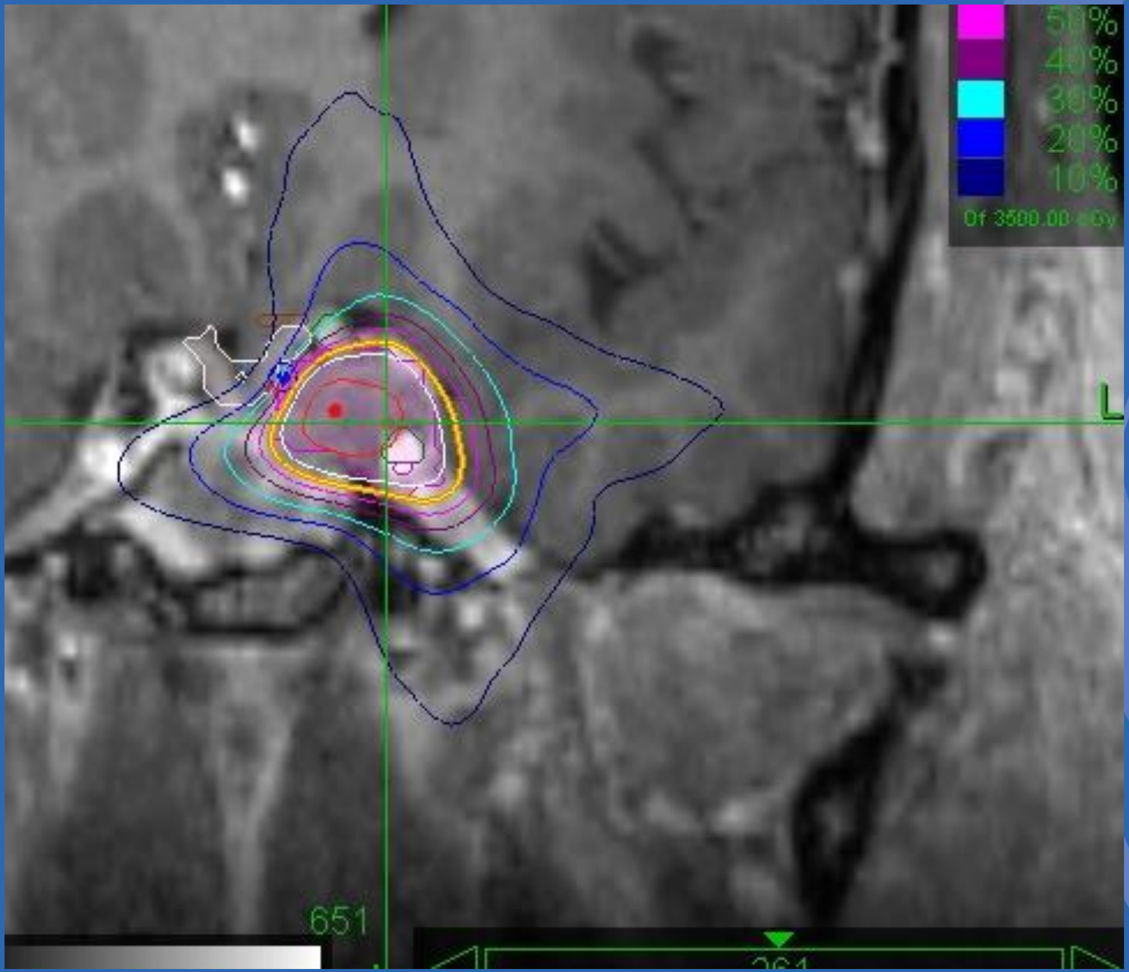


- Medically inoperable acoustic neuroma (KOOS 4)

- 18Gy in 3 fractions
  - (74% isodose)

18GY highly conformal at brainstem with steep dose graident





Functional and growing pituitary tumour in 35 year old man

Repeated surgery (life threatening bleed on last attempt)

No medical options

Previous external beam

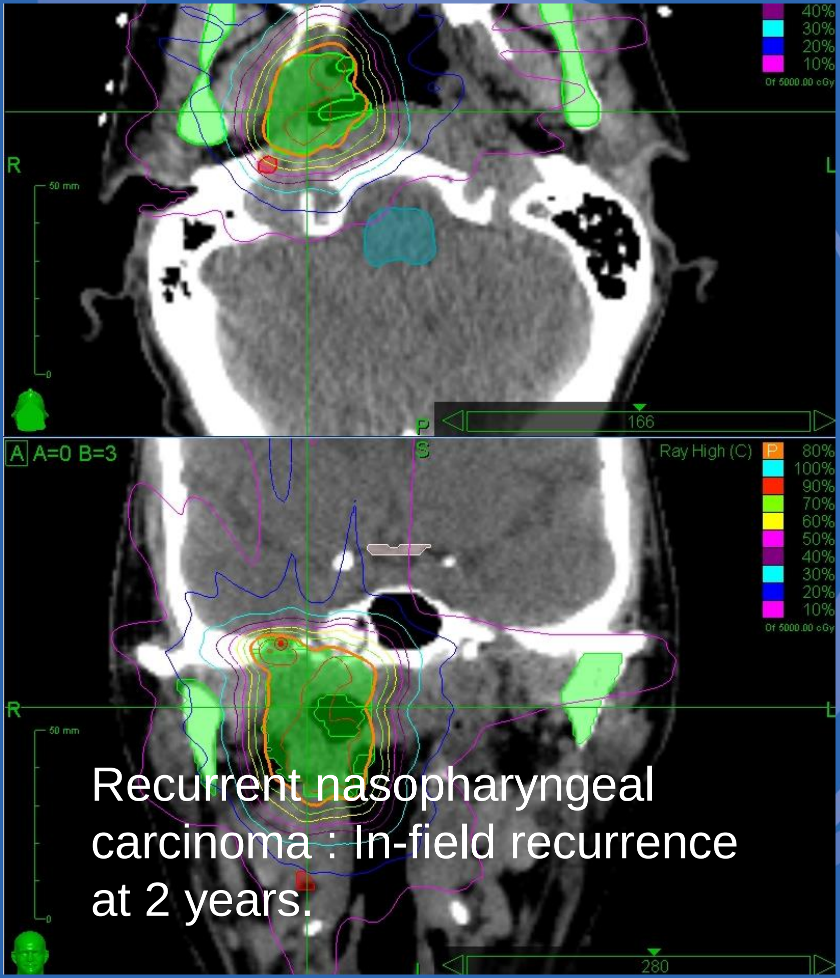
Recommended dose: 21 -24GY

Chiasm pulled down (<8Gy achieved)

Need a high degree of confidence in accuracy being maintained through treatment

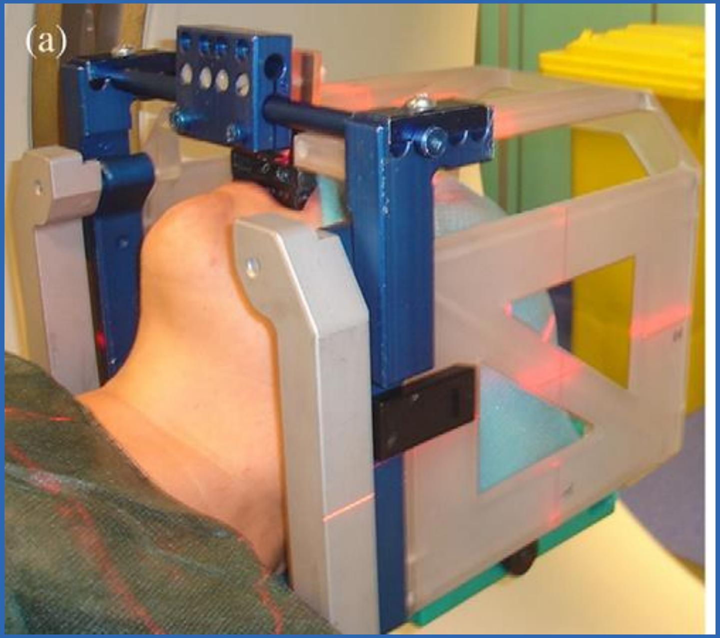
Stereotactic photon techniques for malignant disease - limited

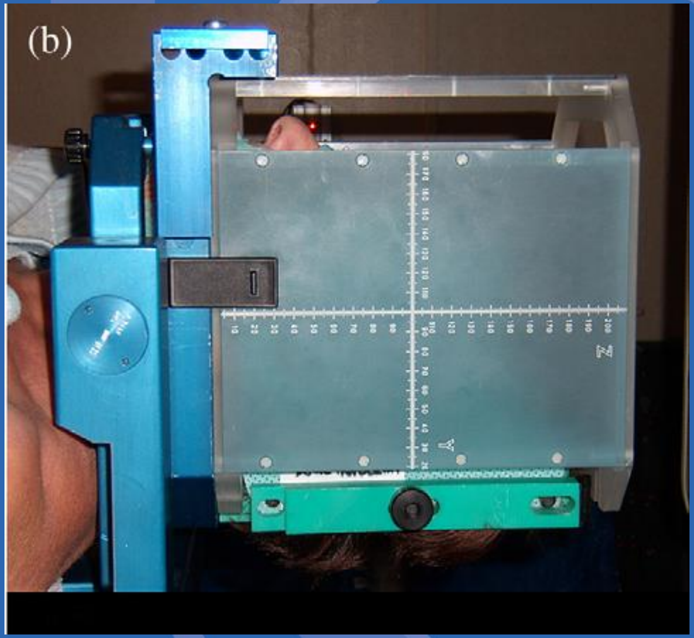
- **Limited role :**
  - Infiltrating margins
  - Need to cover microscopic spread / surgical bed
  - Judicial use for recurrence (Rule out surgery 1st)



Recurrent nasopharyngeal carcinoma : In-field recurrence at 2 years.

Fractionated Stereotactic
accuracy + steep dose gradients for small targets





Bite Block relocatable immobilisation devices

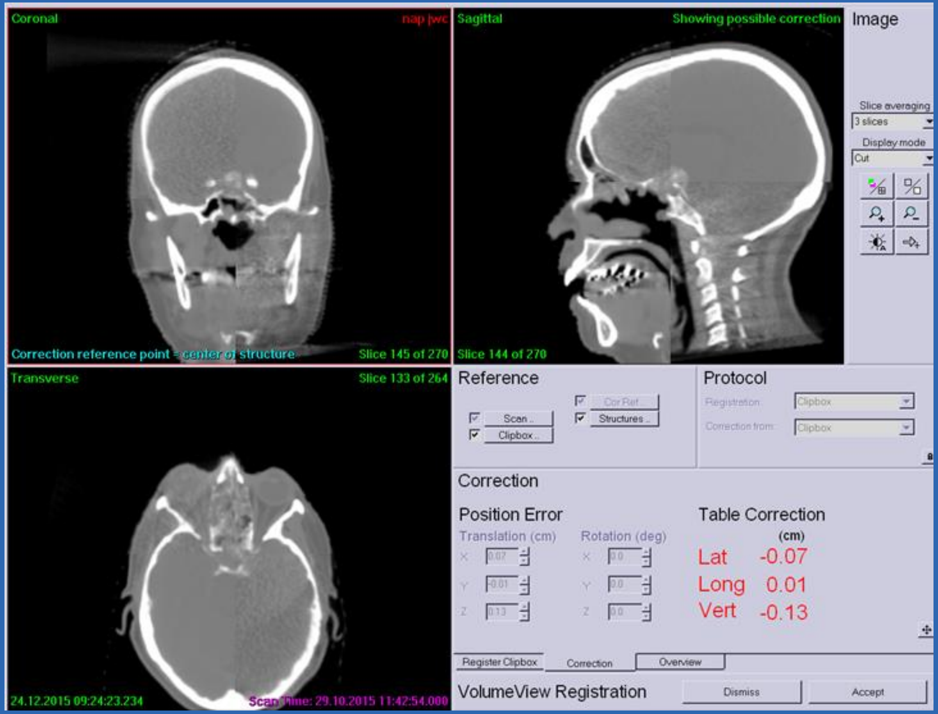
+

Co-ordinate based stereotactic positioning

PTV ~2mm

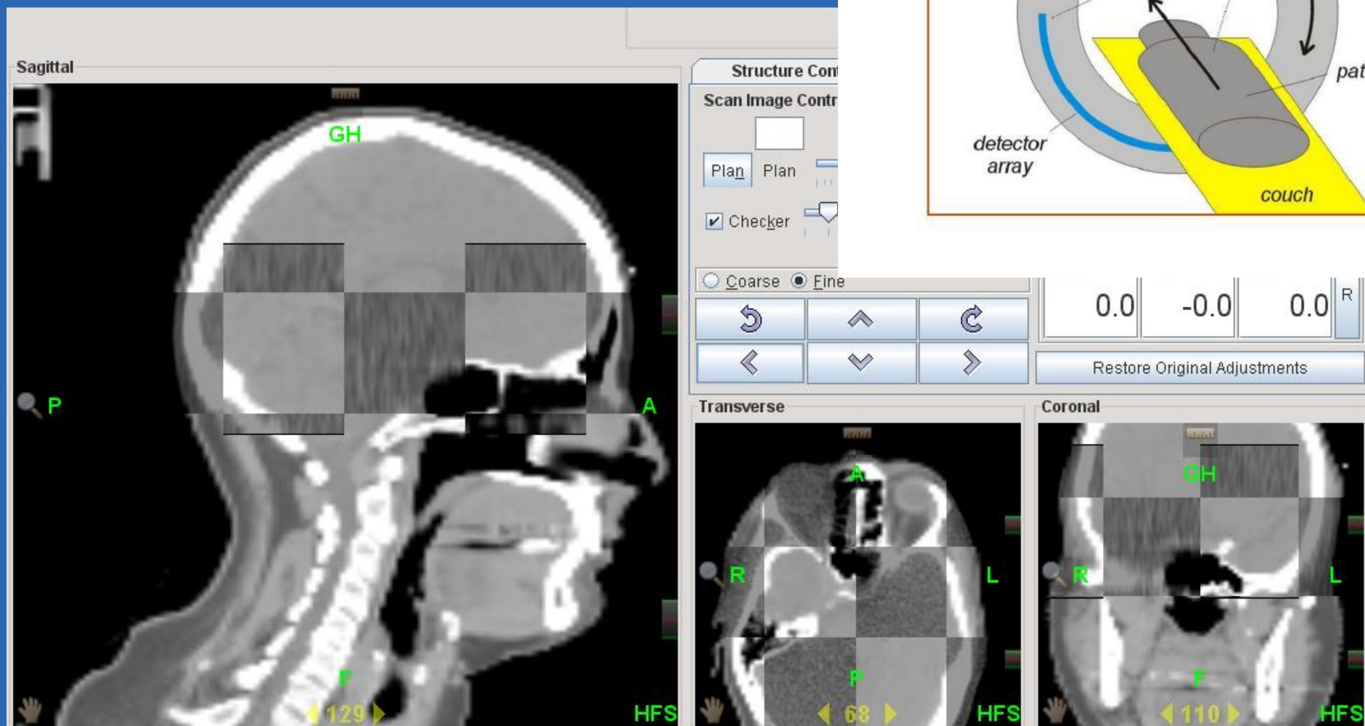
Volumetric Image Guidance

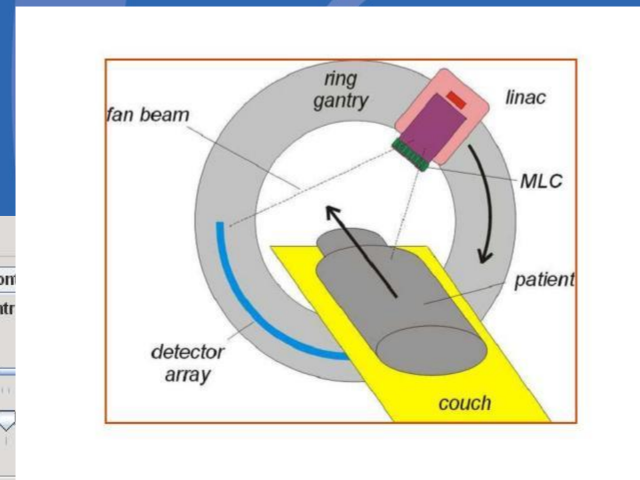
- Image guidance (IG-)
  - Hit the target more precisely + explore anatomy changes
  - Daily volumetric IGRT is common practice



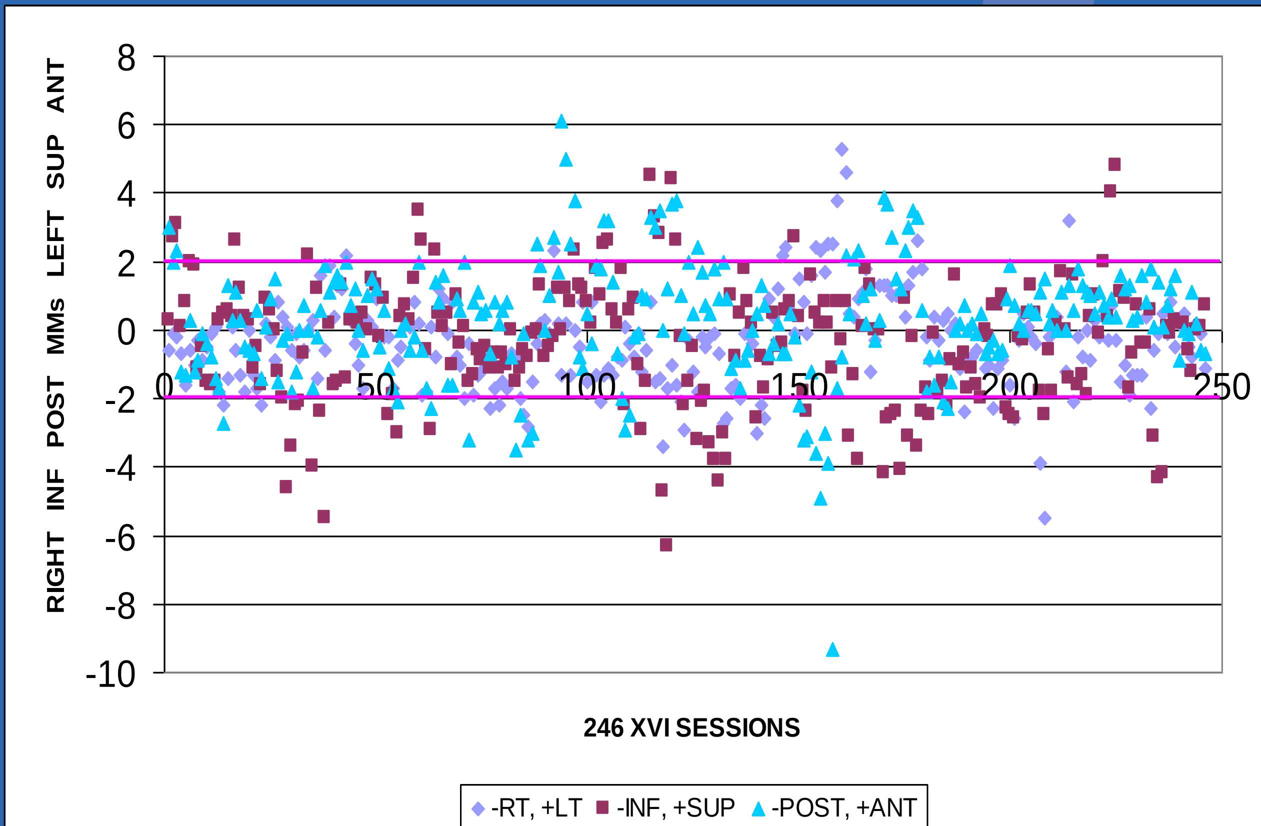
MV CT (TomoTherapy)

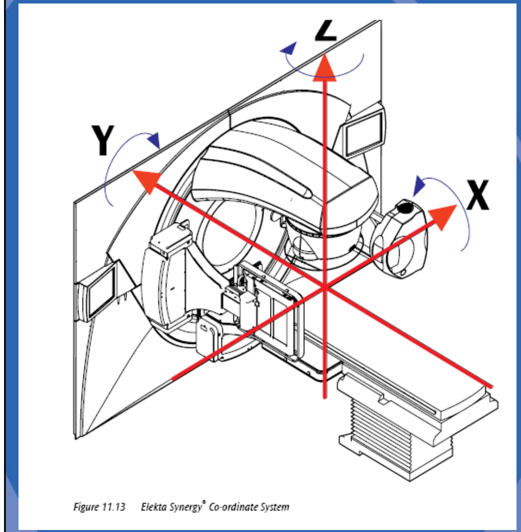
MV CT (3.5MV) acquired imaging/treatment isocentres the same





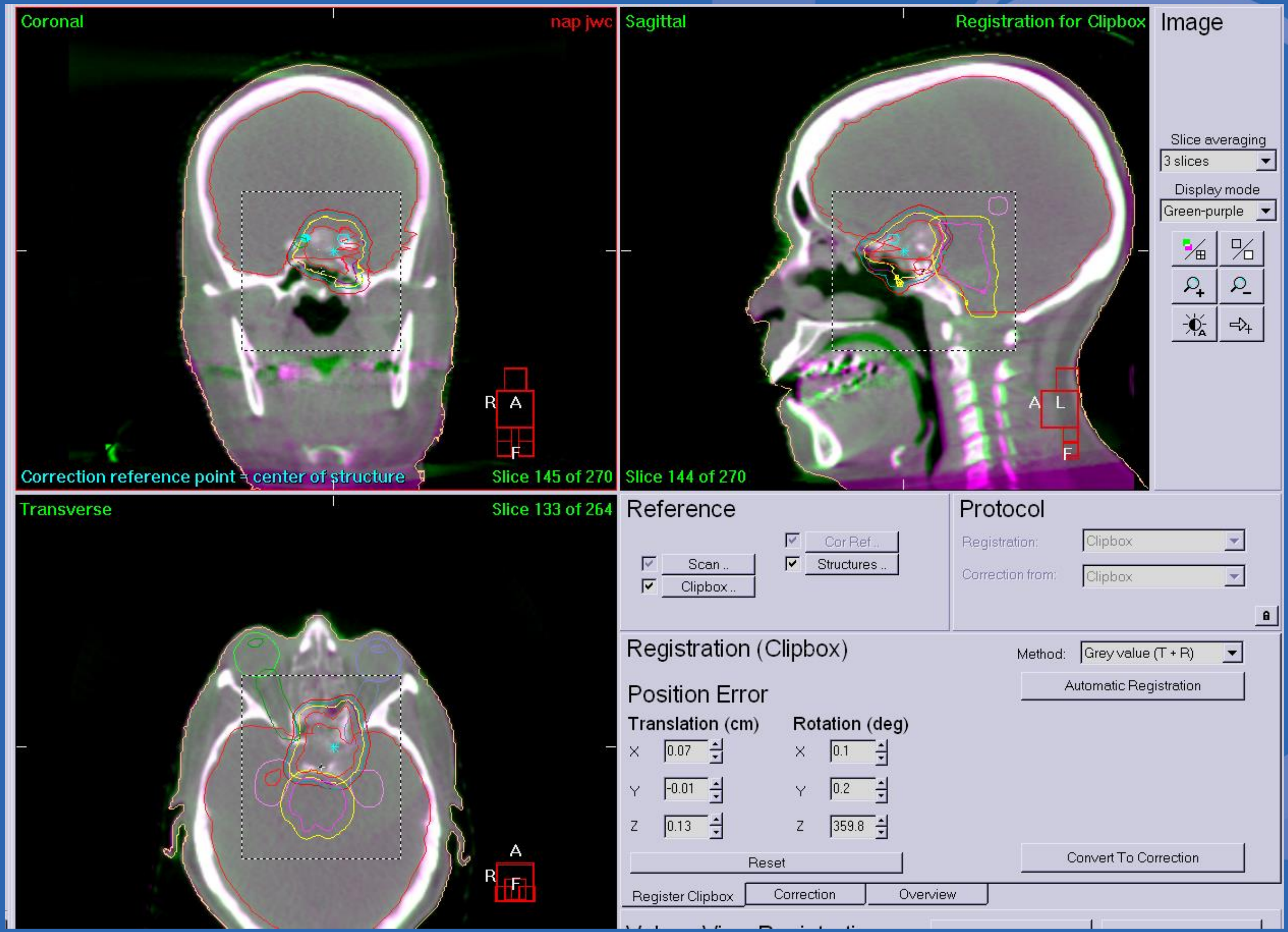
26 PATIENTS: LINEAR SETTING UP DISPLACEMENTS using KV CT with 9 point Kevlar Shell





Daily online imaging and correction justifiable and ?essential

On Line KV CT to helps to reduce margins for small volume tumours



Post treatment imaging evaluation : 9 point immobilisation shell KVCT

- 41 post correction CBCTs in 27 patients
- All residual displacements within 2mm
  - 4/41 <1.5-2mm
- (SD : L/R 0.7mm, Sup/Inf 0.9 Ant/Post 0.77mm)

Additional sources of error remain significant

- PTV remains minimum 3mm despite high quality IGRT
- Calculation below for TomoTherapy

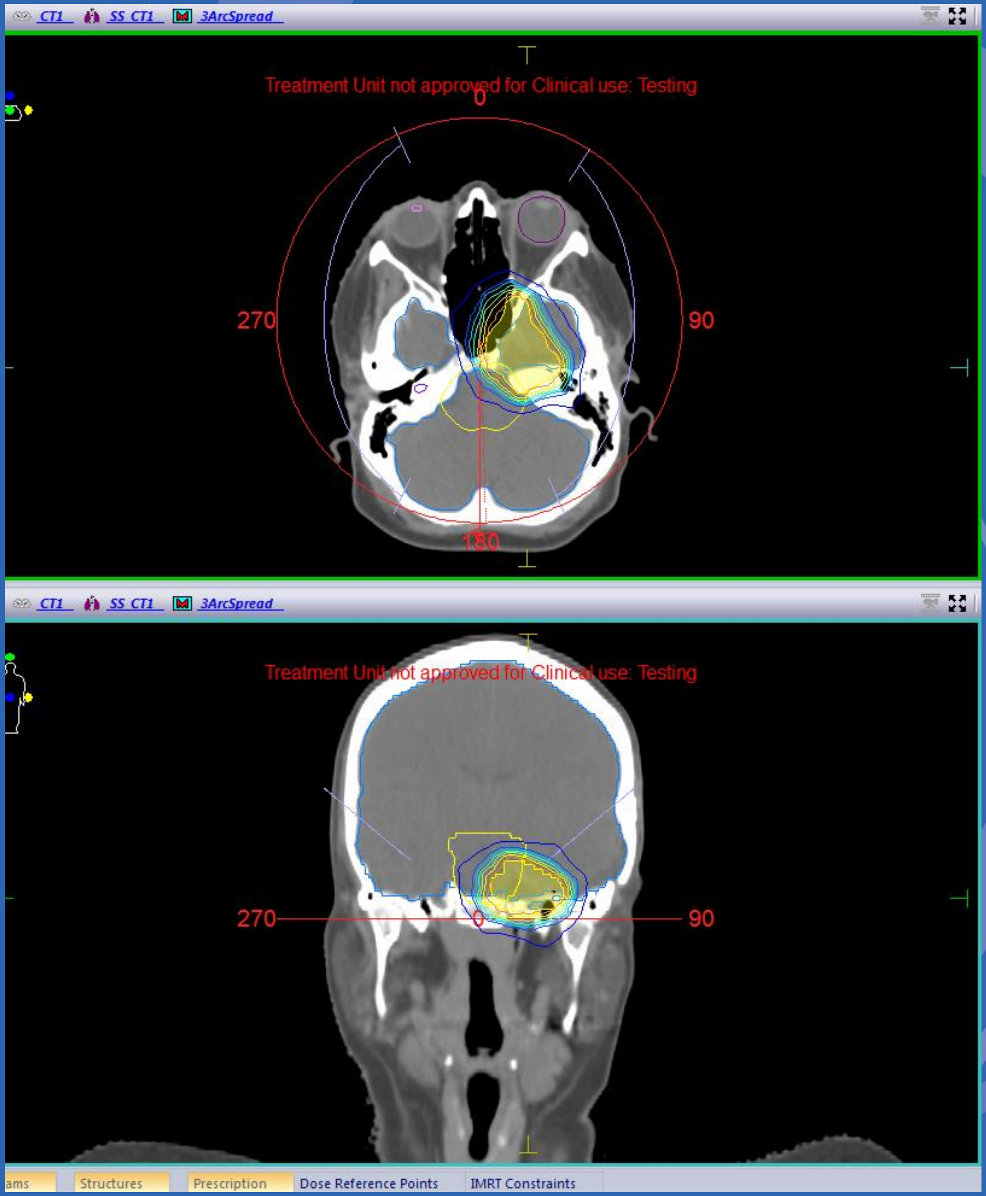
(using method by van Herk M, IJROBP 2000)

	Systematic error (cm)			Random error (cm)		
	X	**Y**	**Z**	**X**	**Y**	**Z**
Inter-fractional rotation	0.02	0.03	0.05	0.02	0.02	0.04
Intra-fractional setup	0.00	0.07	0.01	0.02	0.10	0.06
Inter-observer setup	0.03	0.03	0.02	0.05	0.07	0.06
Mechanical uncertainty	0.05	0.05	0.05	0.00	0.00	0.00
Inter-observer delineation	0.00	0.00	0.00			
Combined error	0.06	0.09	0.07	0.06	0.12	0.09
Margin	**0.16**	**0.27**	**0.21**			

Multiple Arcs for skull base meningioma gives rapid dose fall off / high conformality

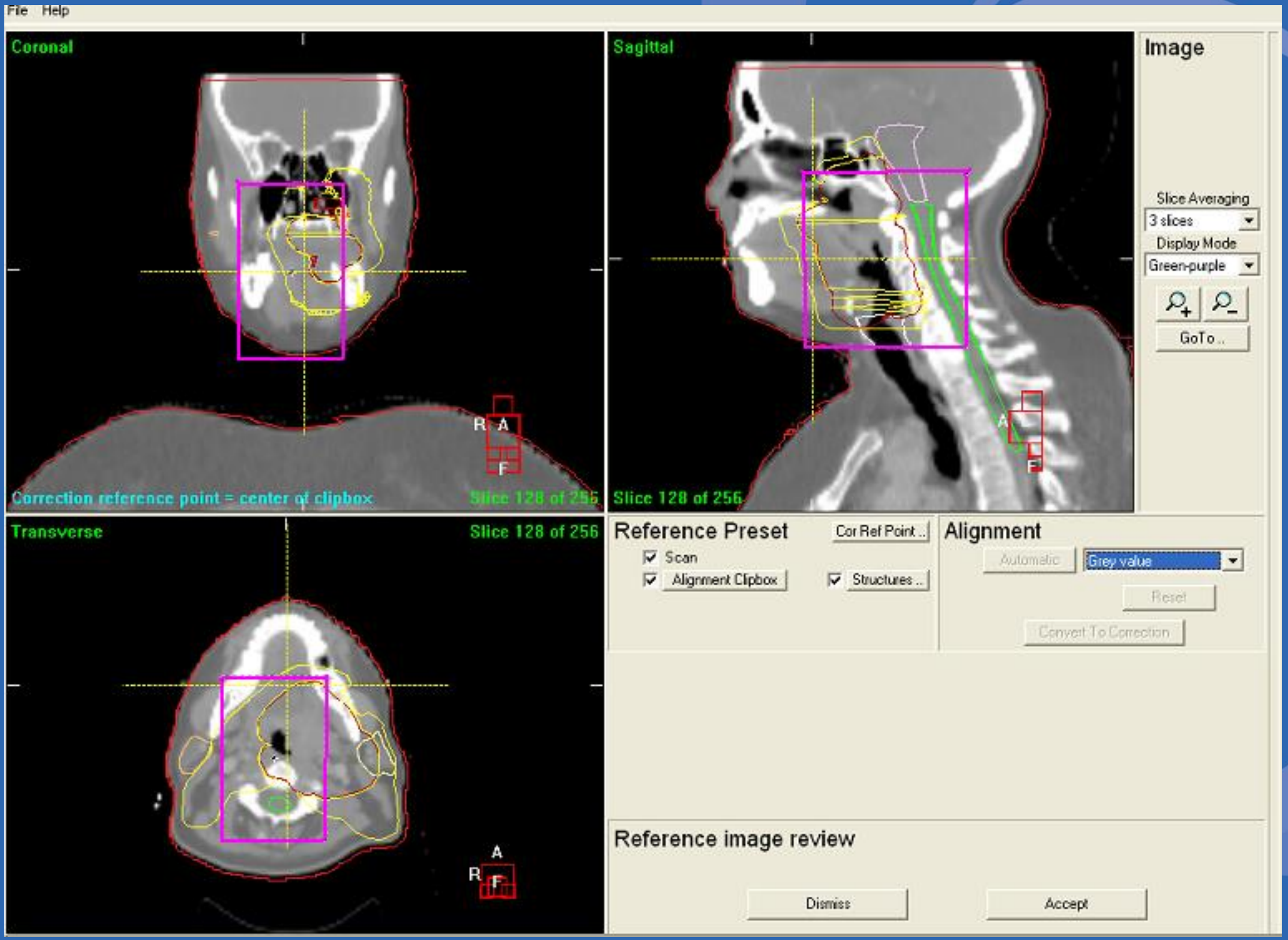
Daily IG IMRT with 9 point shell (3mm PTV)

?Greater caution required with steeper dose gradients

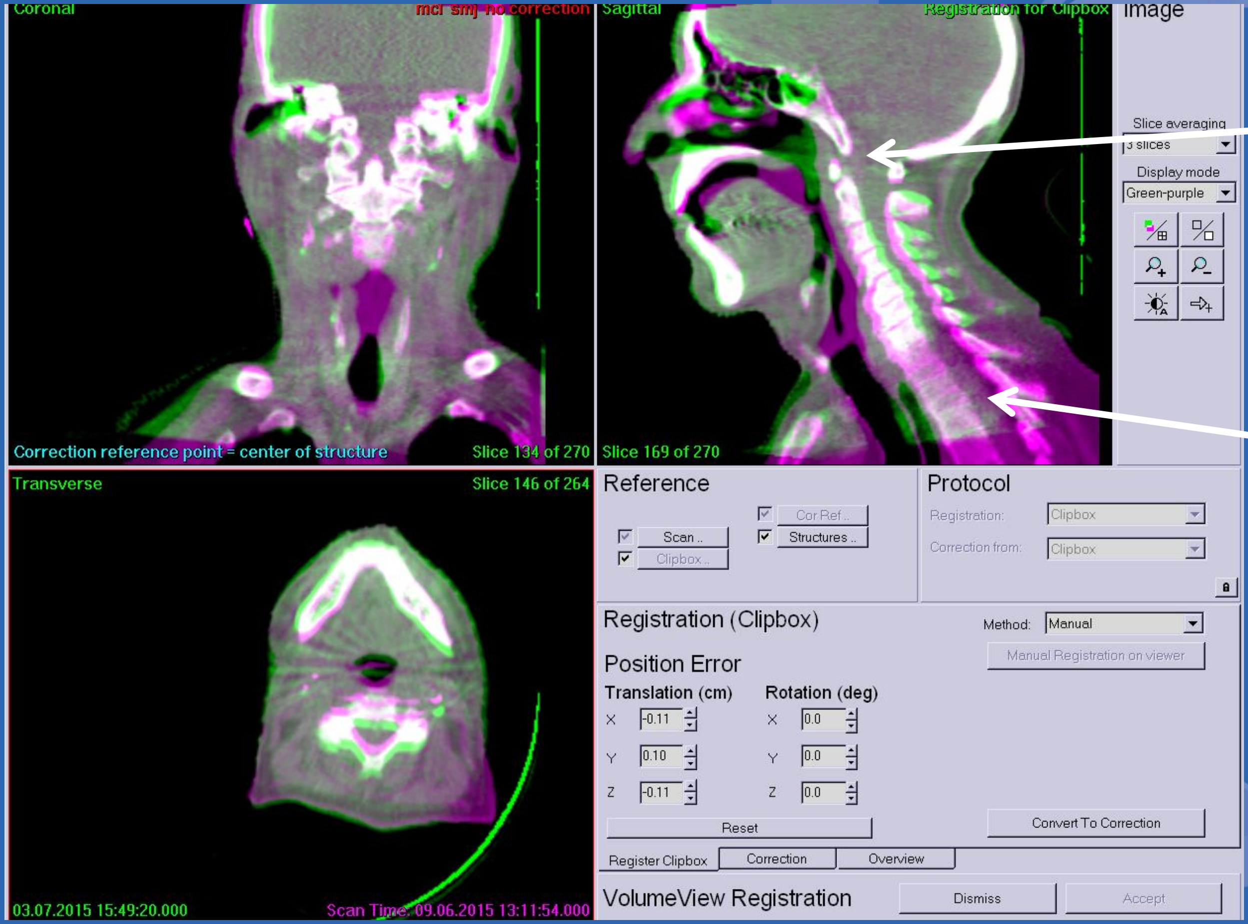


KV Volumetric Image Guidance

More challenging to reduce margins when treated outside skull – soft tissue matching / changes in anatomy



Matching across longer volumes challenging



Match here

Greater uncertainty here

Cheo et al, Radiotherapy and Oncology *in press*

- Evaluated errors at three 3 anatomical levels of the neck in Nasopharyngeal Carcinoma
- 36 pts (9 CBCTs per pt)
- Variable PTV recommended
  - (van Herk formula using imaging data $2.5\Sigma + 0.7\sigma$)

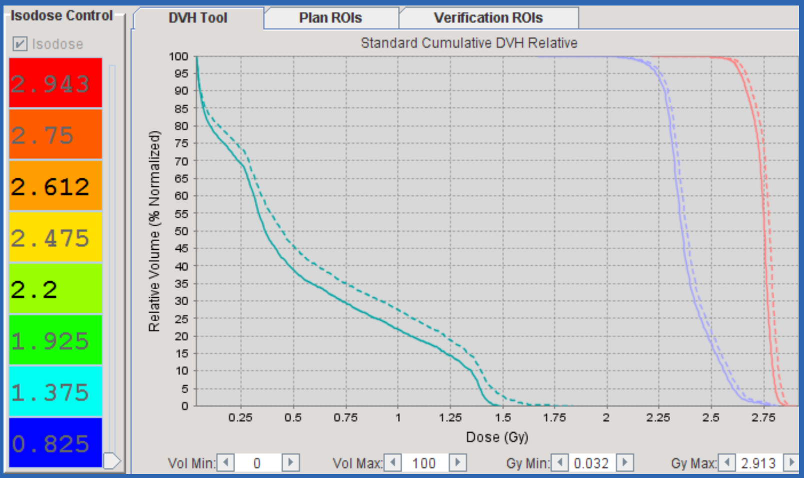
PTV Margin (mm)

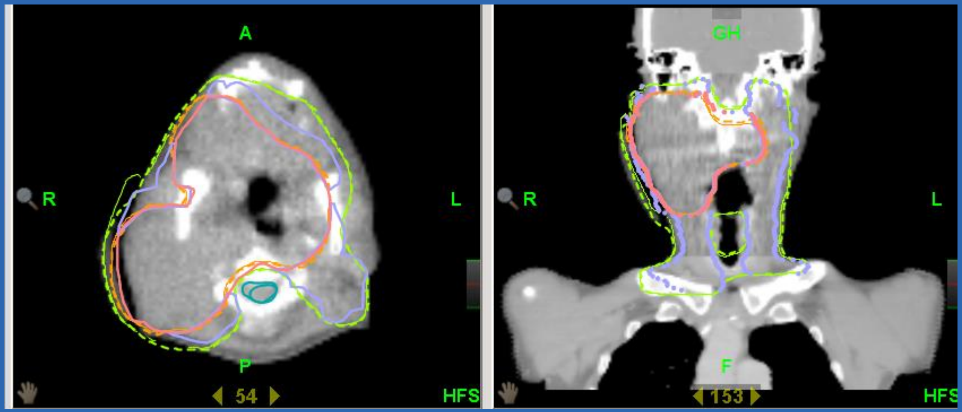
	Pre CBCT (uncorrected)			Post CBCT (corrected)		
	Left/right	Sup/inf	Ant/post	Left/right	Sup/inf	Ant/post
Clivus	1.75	2.33	2.19	0.59	0.51	1.2
C4	4.33	2.61	3.63	3.72	0.97	2.77
C7	**6.52**	2.72	**4.7**	**6.08**	1.2	4.01

Clinical requirement

Evaluation of uncertainty margins
+ use of high quality image
guidance (volumetric)

Does evaluation and adaptive capability





TomoHD example UHB

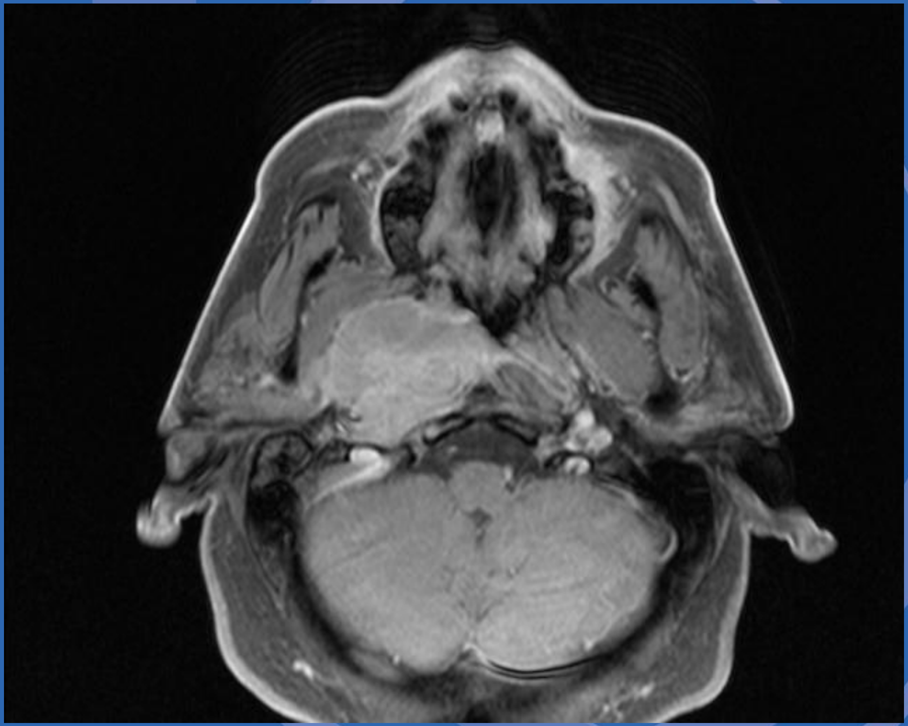
- Dose can change due to weight loss / changes in anatomy / fluid in sinuses
- Evaluate dose during treatment to tumour and OARs
- Re-plan if required
- (reduce margins/reduce morbidity)

Nasopharynx Carcinoma :Chemo IG IMRT

Boon C, Hartley A, Sanghera P Clinical Oncology 2015

Since 2011 (Tomo)

- N=14 : 10 with locally advanced or metastatic disease (TPF used)
- 65Gy/30 (3 dose level)
- 2 year LC = 100%, 2 year OS = 86%
- (1 death with systemic disease / No LR)



Plan robustness to anatomical changes:

Protons (IMPT) vs photons (VMAT, TomoTherapy)

Y. Roussakis[1,2], T. Williams[1], P. Sanghera[1], A. Hartley[1], G. Heyes[1], A. Dumbill[1], A. Chalkey[1], S. Green[1], G. Webster[1], J. Cashmore[1]

[1]Hall-Edwards Radiotherapy Research Group, Queen Elizabeth Hospital, Birmingham, UK

[2]PSIBS Doctoral Training Centre, University of Birmingham, Birmingham, UK

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EPSRC
Engineering and Physical Sciences Research Council

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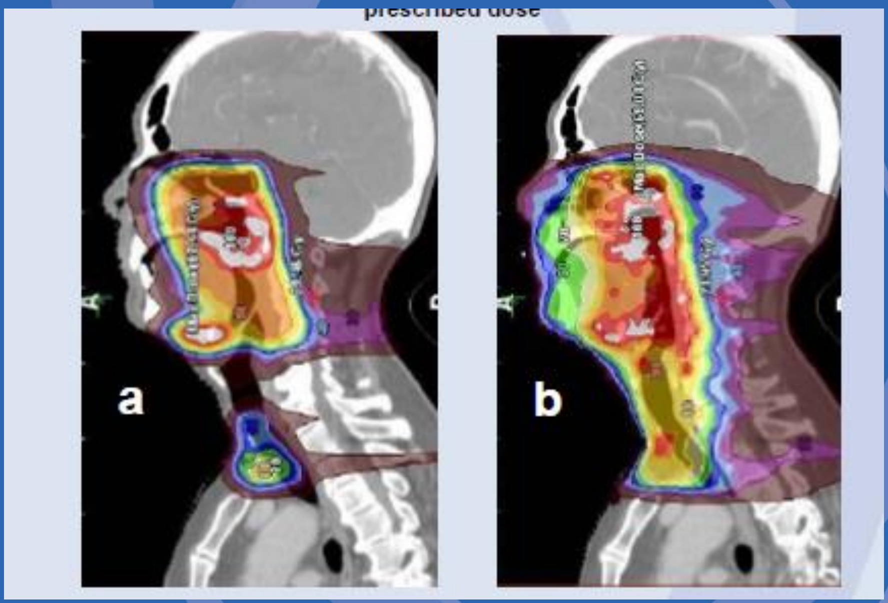
Planning Study

- 10 Nasopharyngeal Carcinoma
- 5 mm PTV margins
- 65 Gray RBE Equivalent (GyE) to primary PTV (PTV1)
- 60 GyE to intermediate risk nodal regions (PTV2)
- 54 GyE to low risk nodal regions (PTV3)

IMPT v VMAT v Tomo (NPC)

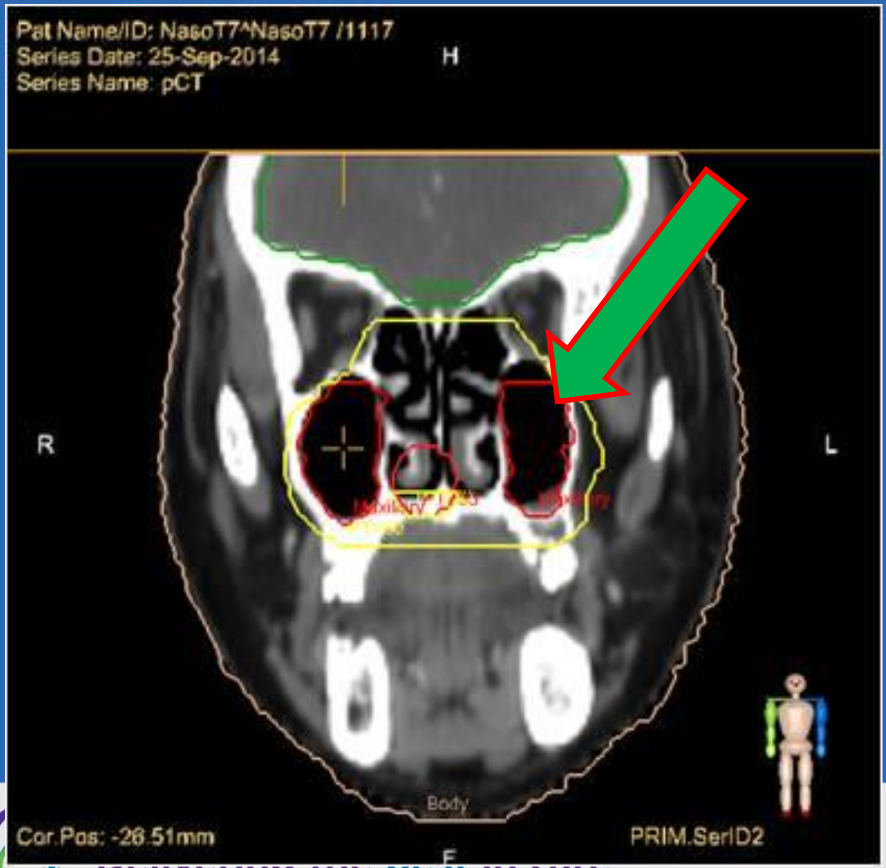
- Better PTV conformity (Wilcoxon test, p=0.008)
- Reductions in mean dose :
  - larynx (p=0.002)
  - brain (p=0.006)
  - oral cavity (p=0.004)
- (No diff Tomo /VMAT)



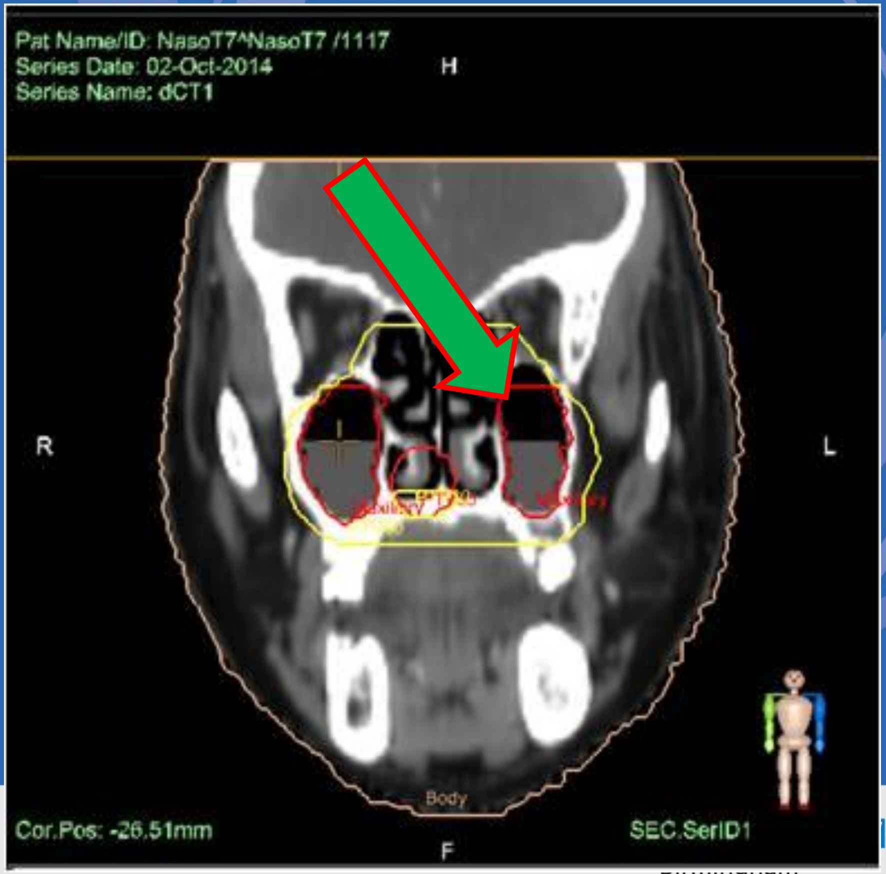
Anatomical changes introduced

- Partial nasal cavity filling (50% of empty volume)

Pre

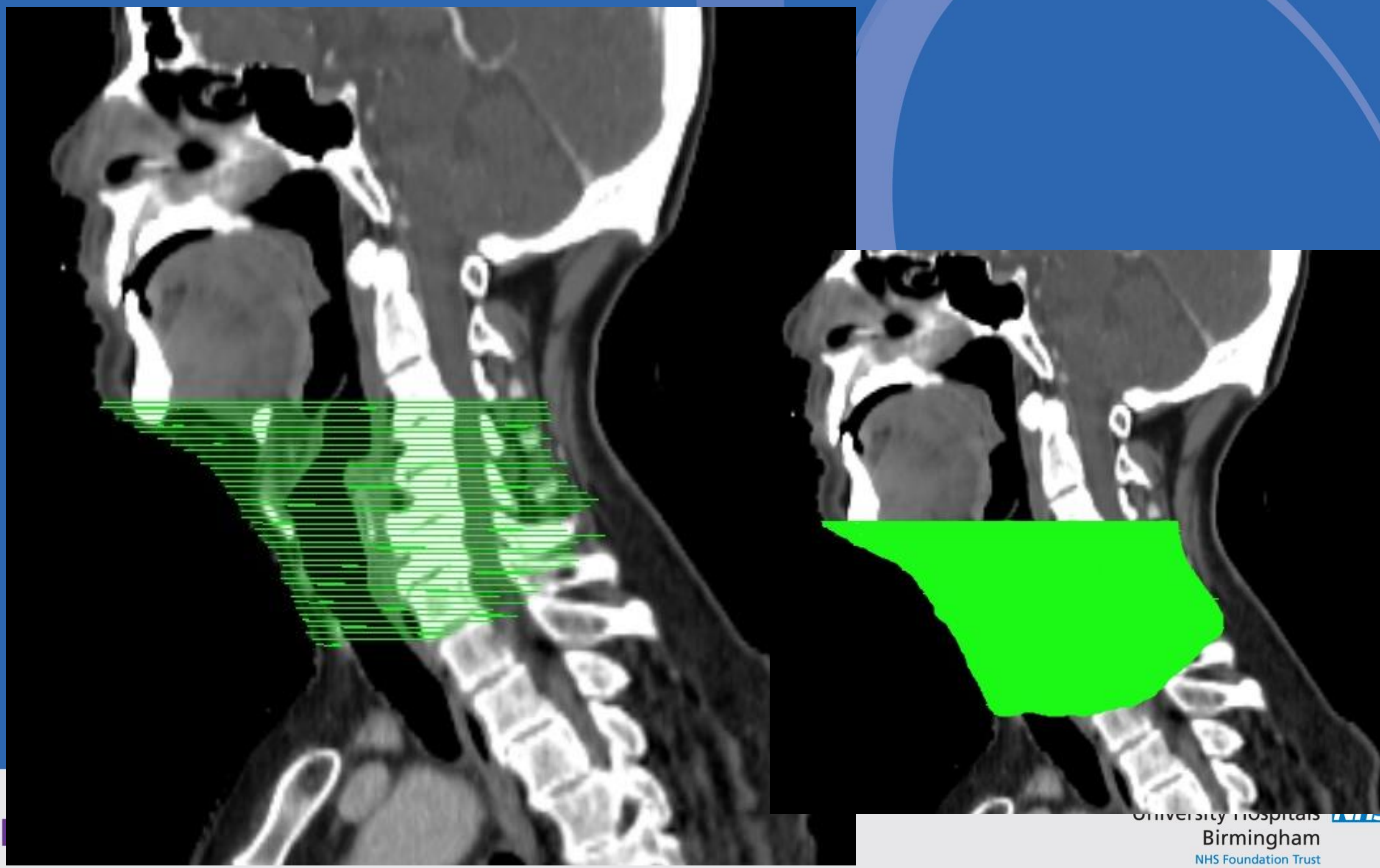


Post

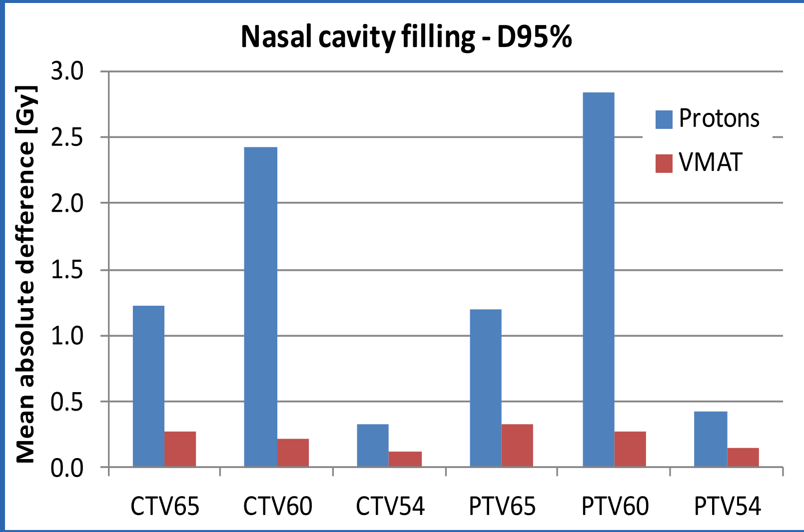


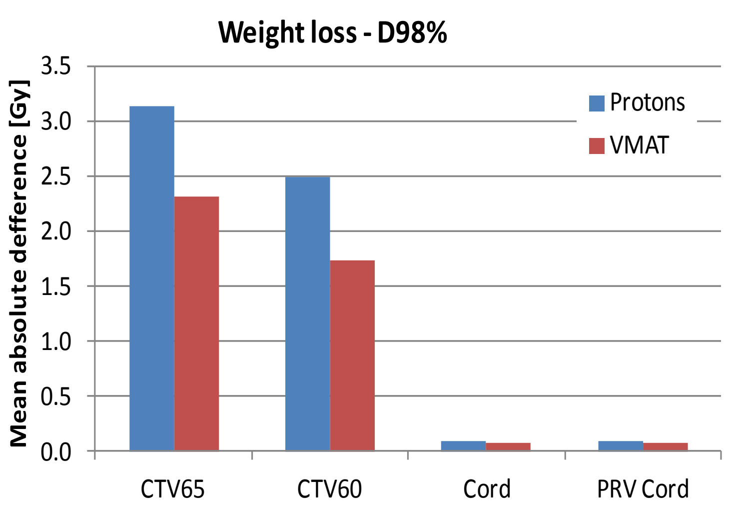
Anatomical changes introduced

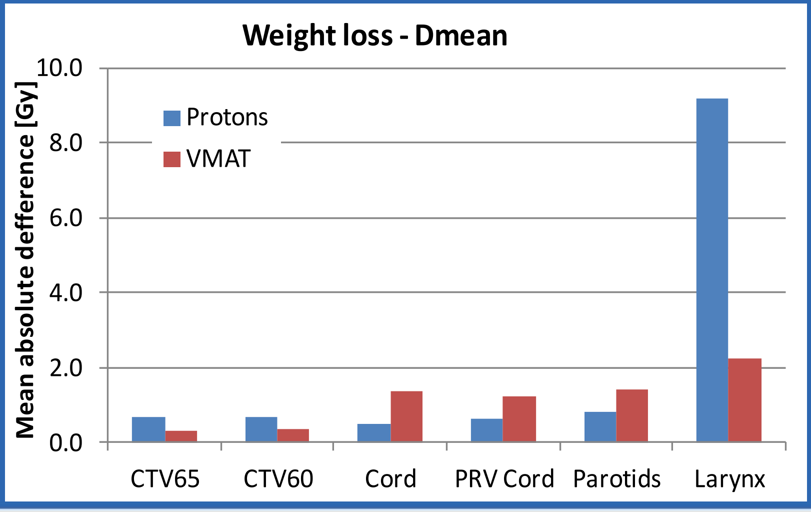
- Weight loss (5 mm of tissue in neck region)

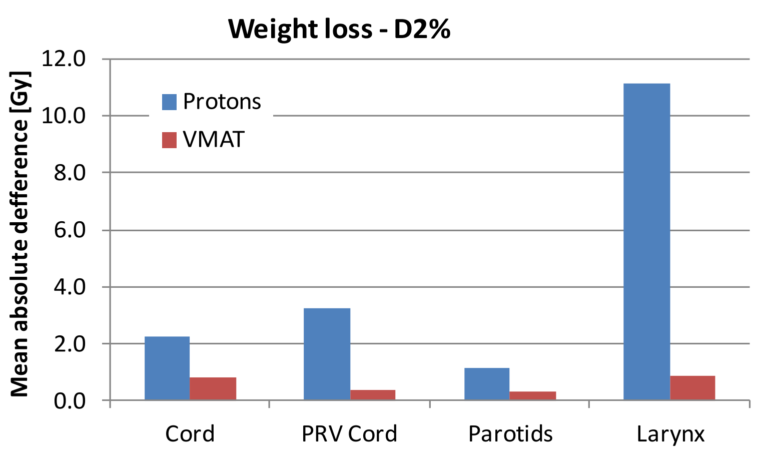


IMPT : Greater vulnerability to change







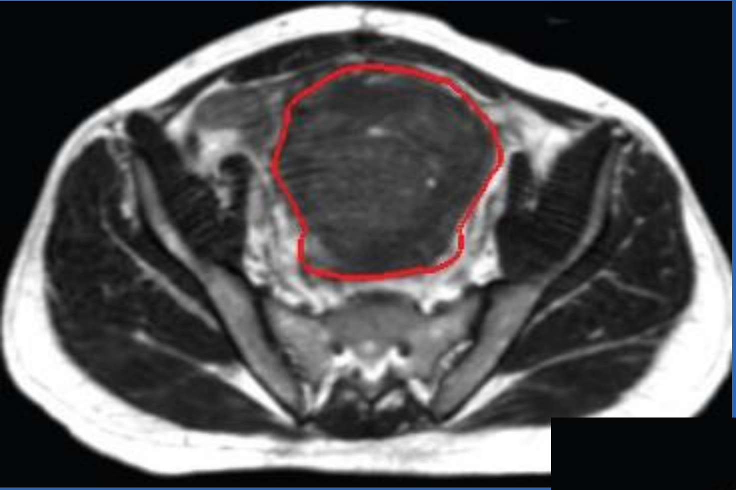


Clinical requirement?

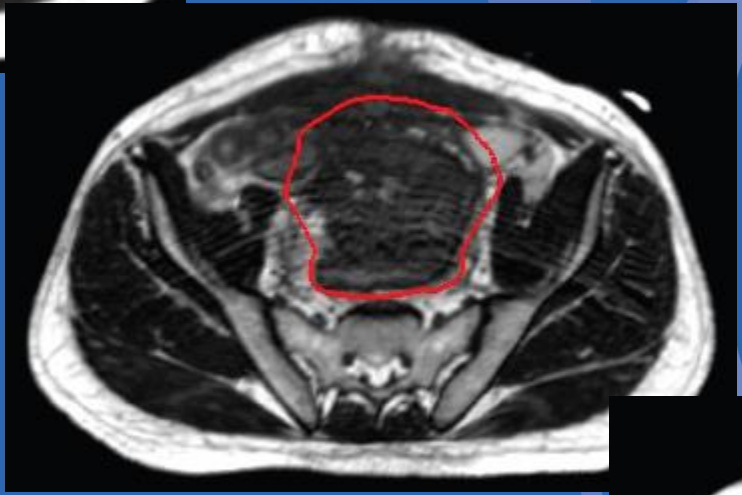
Dose evaluation during treatment

MR Linac – better soft tissue visualisation

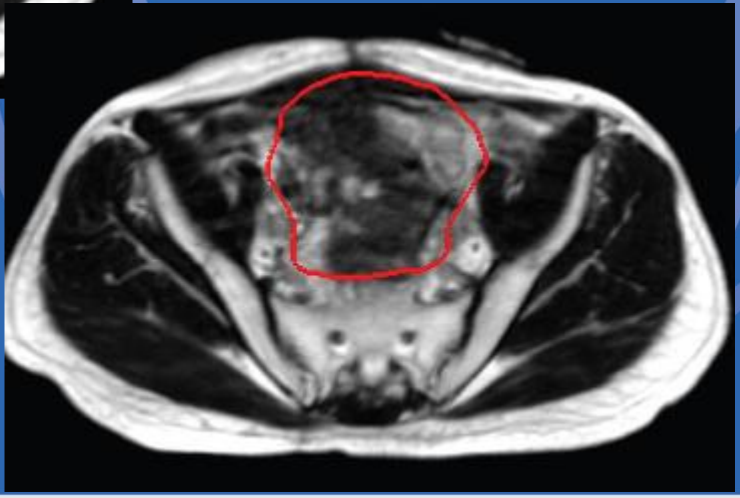
Images courtesy Imaging Equipment Limited (UK partners for Viewray)



- Higher quality soft tissue resolution (assess anatomy changes)
- On table dose distributions evaluation to guide adaptation
- Real time imaging for tracking + gating



Changes through treatment lead to changes in dose to OARs / PTV



MR Linac Abstracts emerging

Confirming ability to integrate MR based adaptation /gating into workflow

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Implementation of Real-Time, Real-Anatomy Tracking and Radiation Beam Control on the First MR-IGRT Clinical System

O.L. Green, L.J. Rankine, B. Cai, R. Kashani, L. Santanam, S.M. Goddu, C.G. Robinson, P.J. Parikh, J.R. Olsen, J.D. Bradley, and S. Mutic; *Washington University School of Medicine, St. Louis, MO*

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Year One of the First Ever MR-IGRT Program: System Practicality and Future Implications

S. Mutic,[1] J.R. Olsen,[1] O.L. Green,[1] R. Kashani,[1] H. Li,[1] V.L. Rodriguez,[1] H. Wooten,[1] T. Zhao,[1] D. Yang,[1] J.D. Bradley,[1] I. Zoberi,[2] M.A. Thomas,[2] C.G. Robinson,[1] P.J. Parikh,[1] I. Kawrakow,[3] J.R. Victoria,[3] T. Hand,[3] J.F. Dempsey,[3] and J.M. Michalski[1]; [1]*Washington University School of Medicine, St. Louis, MO,* [2]*Washington University School of Medicine, Department of Radiation Oncology, St. Louis, MO,* [3]*ViewRay Inc., Cleveland, OH*

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Summary

- Clinical trials to confirm QoL benefits taking into account intermediate / low dose benefits
- Investigate improved local control in photon resistant tumours with high LET radiation / Improve therapeutic ratio in tumours adjacent to critical OARs
- Evaluate and manage uncertainties through treatment (Volumetric imaging essential + ability to adapt)

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THANK YOU