The Abdus Salam International Centre for Theoretical Physics

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Workshop on Biomedical Applications of High Energy Ion Beams

Co-sponsored by: ICGEB and University of Surrey

12-16 February 2007

Venue:
Adriatico Guest House Giambiagi Lecture Hall
ICTP, Trieste, Italy

Tumour Response To Radiotherapy

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Optimising tumour response to radiotherapy

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Clinician Scientist

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CNIG

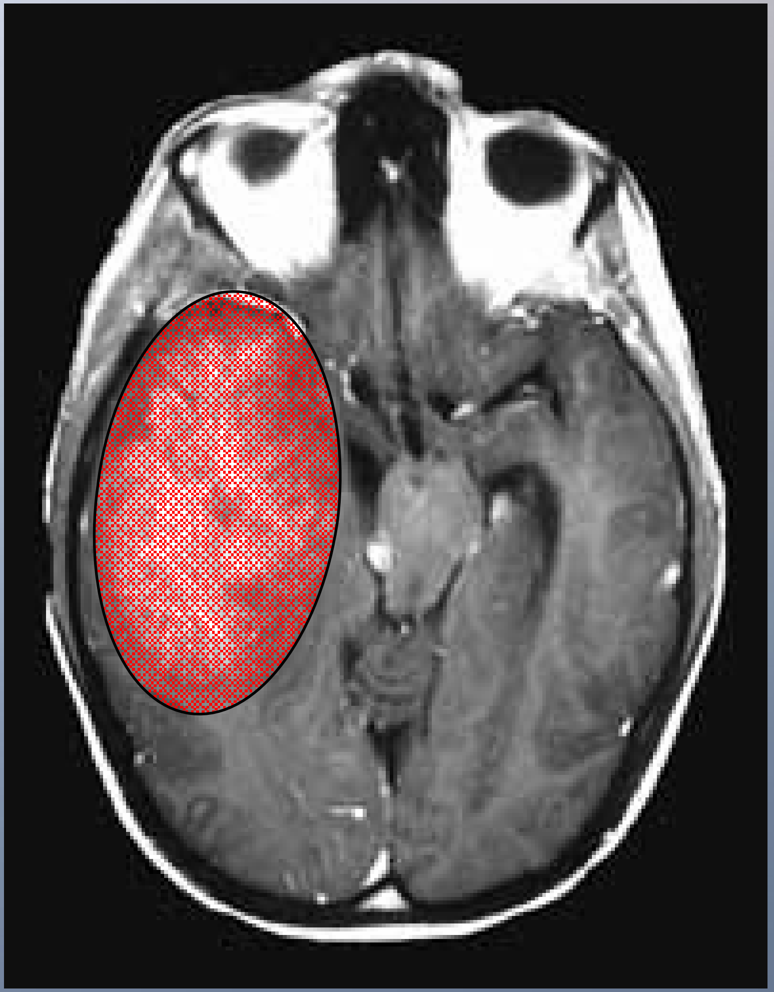
Cambridge Neuro-oncology Imaging Group

Overview of talk

- Homogeneous & inhomogenous dose distributions
- Novel imaging for delineation of target and dose
- Clinical application : High Grade Gliomas
- IMRT and Bioeffect planning
- New models of normal tissue response
- Improved precision – protons & bioeffect planning

Homogeneous dose

- Traditional goal of RT planning is to deliver homogeneous dose distribution to the entire target, and minimal dose to adjacent structures



Homogeneous dose

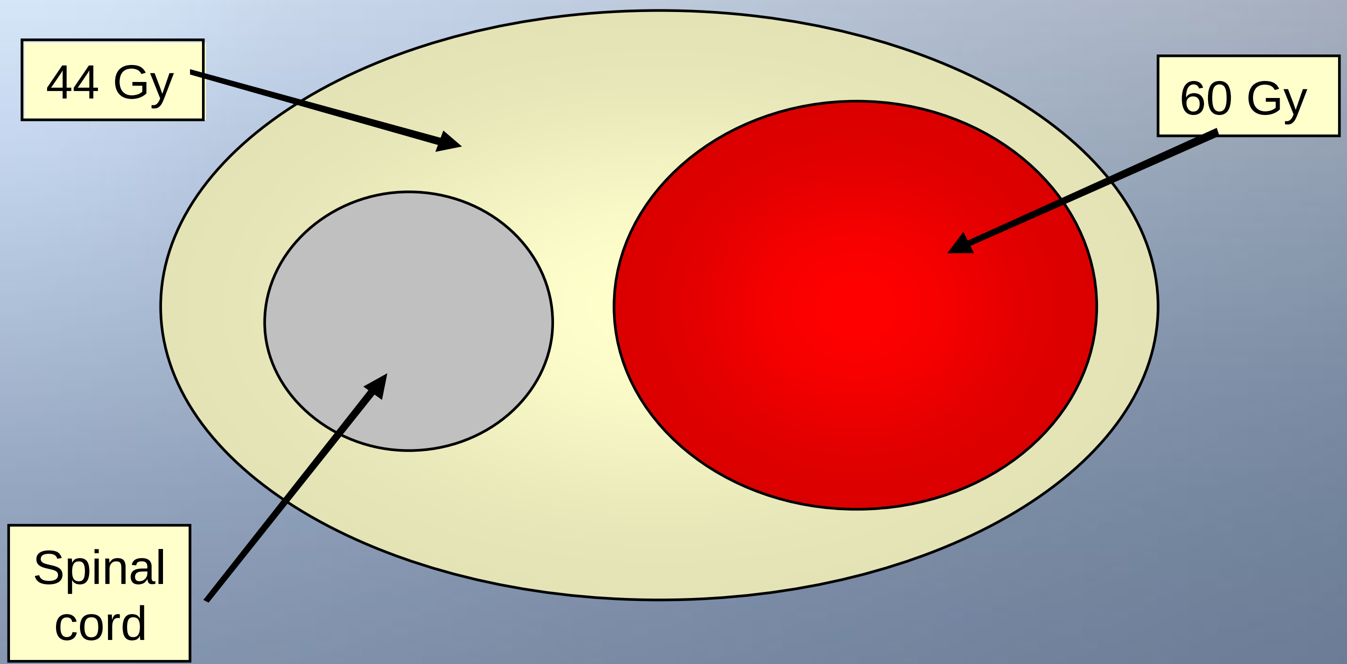
- Tumour is biologically homogeneous
- Binary nature of tumour control
- Simple tolerance dose models for effect on normal tissues
- Computationally straightforward

Clinical challenges

- Pancoast tumour
- Tumour intimately related to spinal cord
- Limit dose to tolerance dose of critical normal structure?
- Use additional phase of treatment, sparing critical normal structure

Dose inhomogeneity

- This form of planning starts to introduce dose inhomogeneity



Change in paradigm

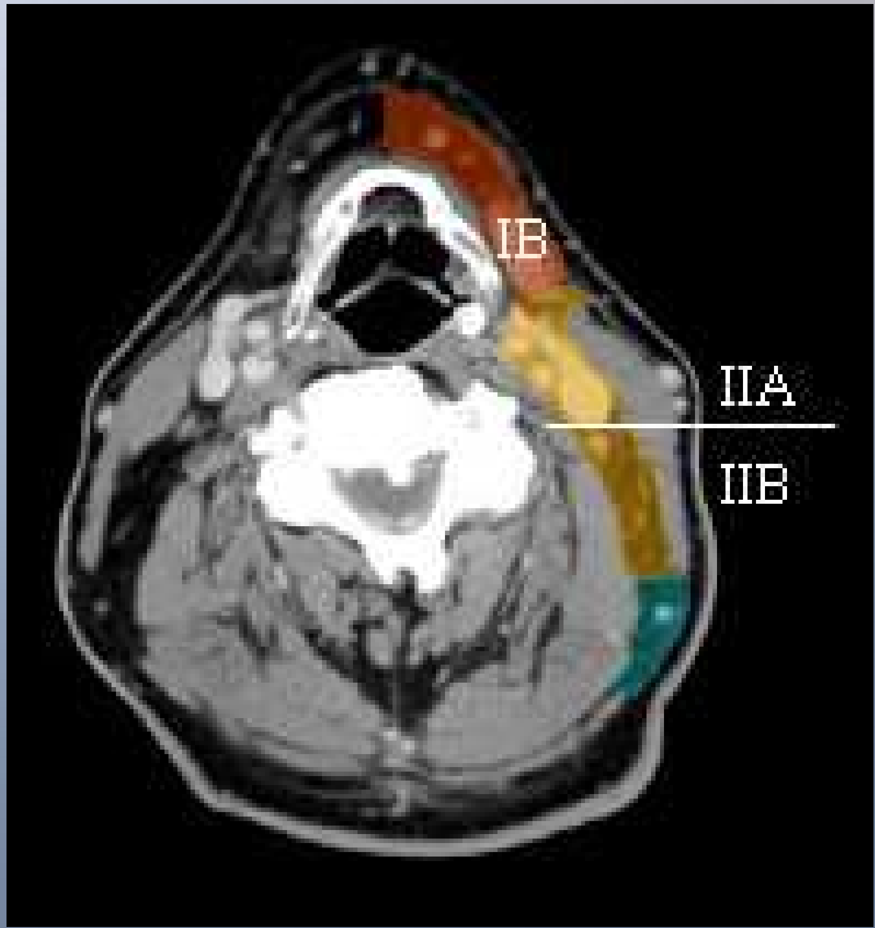
- Traditional paradigm
  - Rely on longitudinal clinical data and experience
  - Prescribe to accepted dose values for target and tolerance doses for normal tissues
- Modern paradigm (Imaging Era)
  - Start considering tumours as heterogeneous
  - Gather biological data on tumour inhomogeneity
  - Consider non-binary outcomes for tumour control
  - Specify inhomogenous target dose distributions
  - Model effect of dose distribution on tumour control

Dose painting

- Coined by Clifton Ling
- Idea of conforming dose to biological heterogeneity of the tumour
- Remove dose constraint to regions containing no normal tissue

Where do I paint the dose?

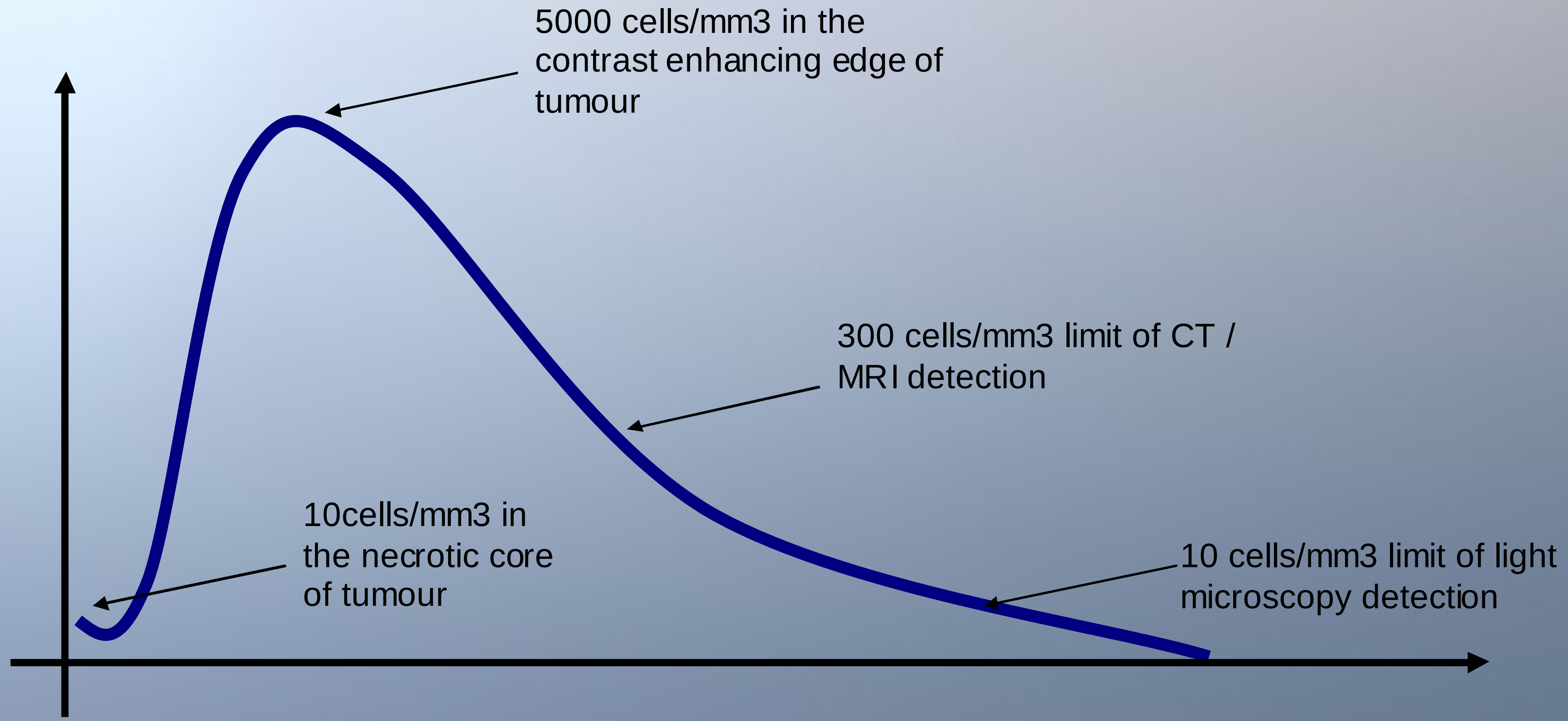
- Direct visualisation & palpation of tumour
- Knowledge of anatomy, nodal basins etc
- **Imaging**



Application of imaging

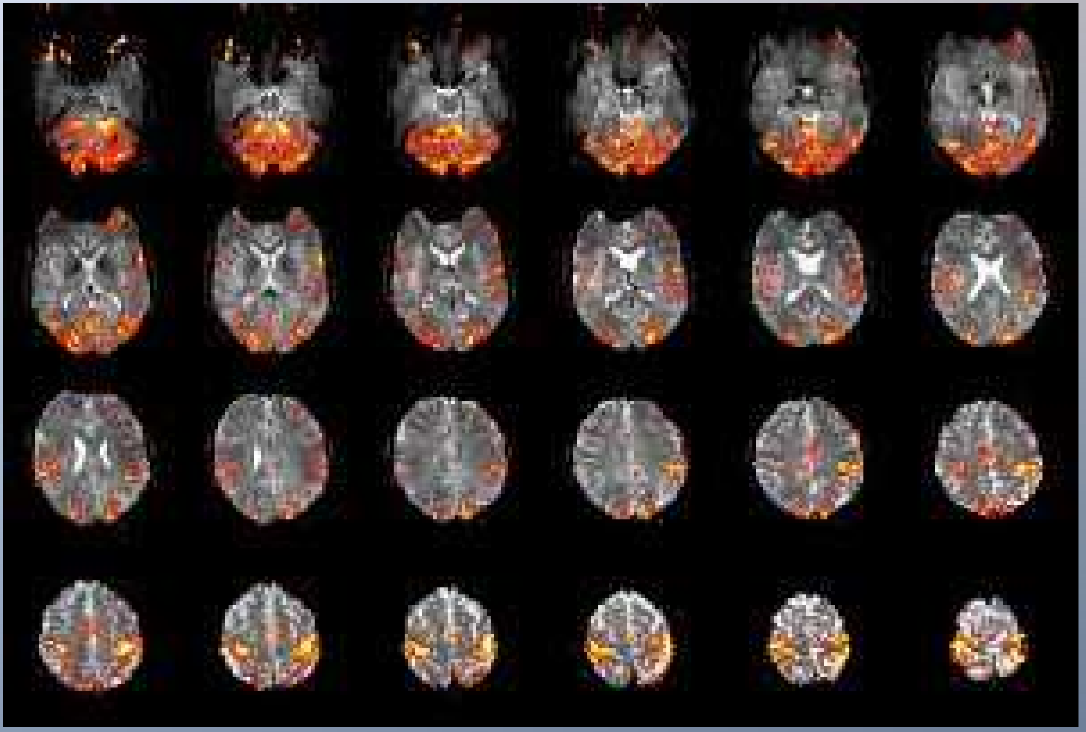
- Traditional cross sectional imaging aids location of the tumour
- Improved soft tissue imaging and spatial resolution, 100 microns with MRI
- But we can do better than this …

Clonogen density



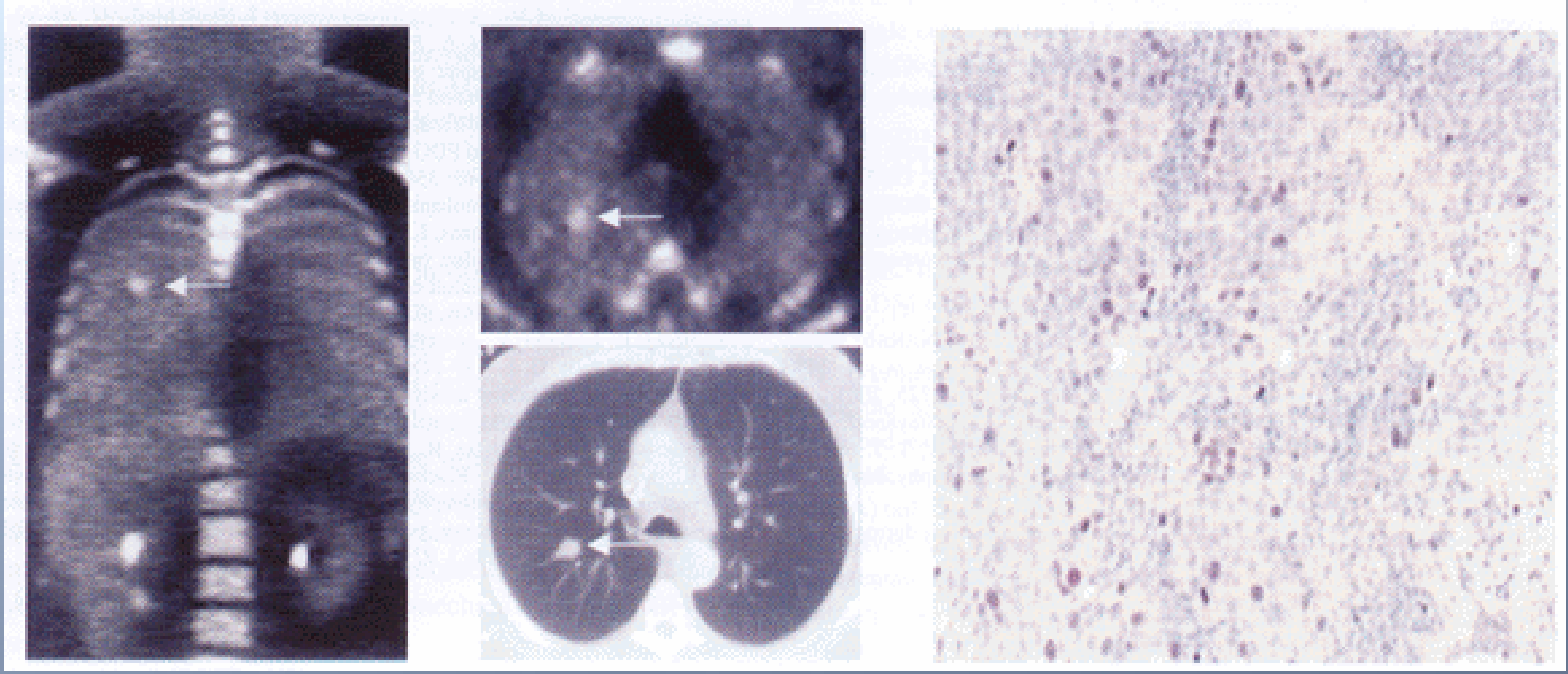
Tumour Oxygenation

- BOLD MR Oximetry (Oxygen extraction)
- 18F Misonidazole PET



Labelling index

- 18-FLT PET correlates with Ki-67 proliferation marker in lung cancers



“Theragnostic imaging”

- Using imaging to assist in treatment planning for targeting of dose
- Deriving prognostic information from imaging to assist with management
- Individualisation of therapy

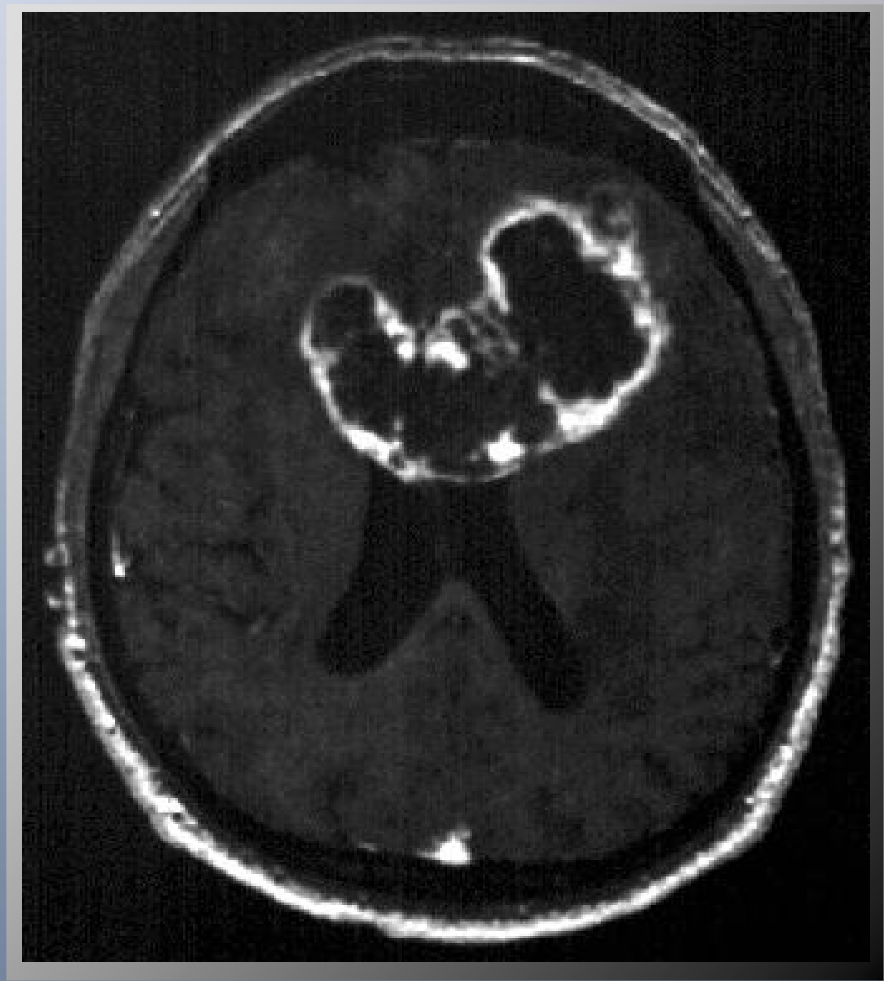
High grade gliomas

Dr Robert Moog

George Gershwin

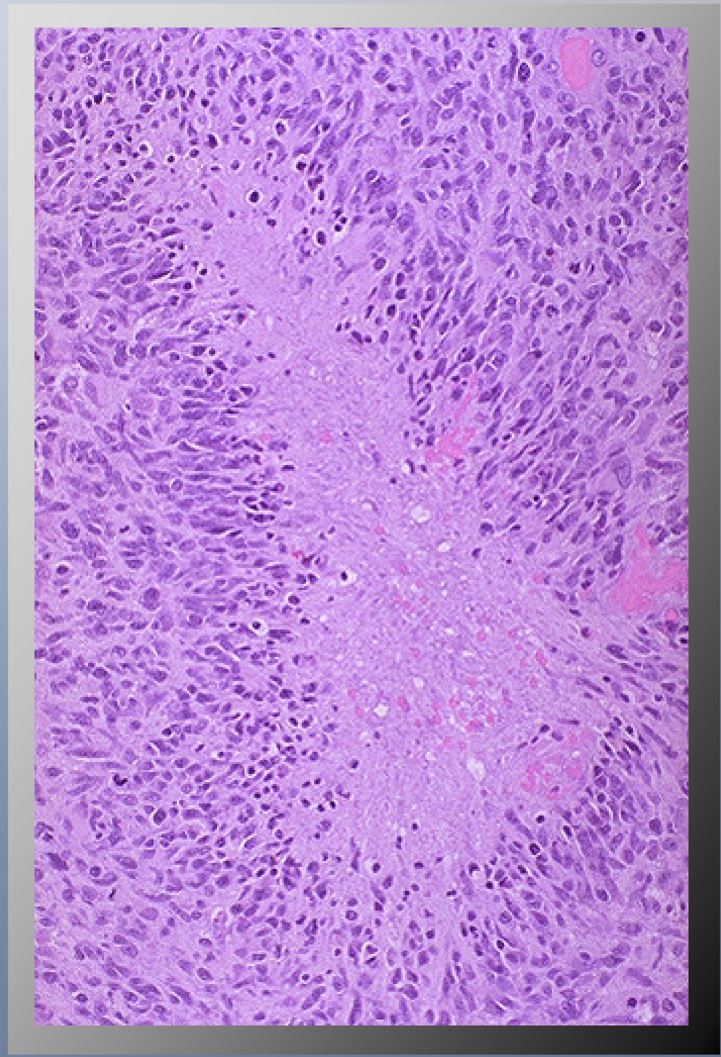
High grade gliomas (HGG)

- Tumour arising from the supporting cells (glial cells) of the brain
- Commonest brain tumour in adults
- Median survival is only 10 months
- 5% of patients sustain long term cure



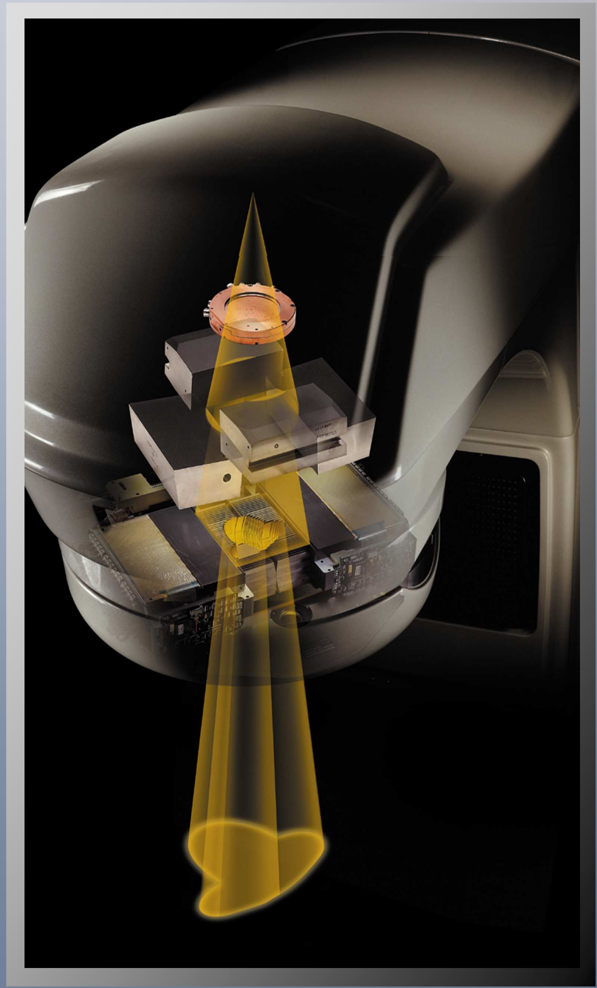
HGG Tumour Biology

- Rapid proliferation
- Cellular heterogeneity
- Areas of hypoxia : growth arrest, radioresistance
- Insidious white matter tract infiltration



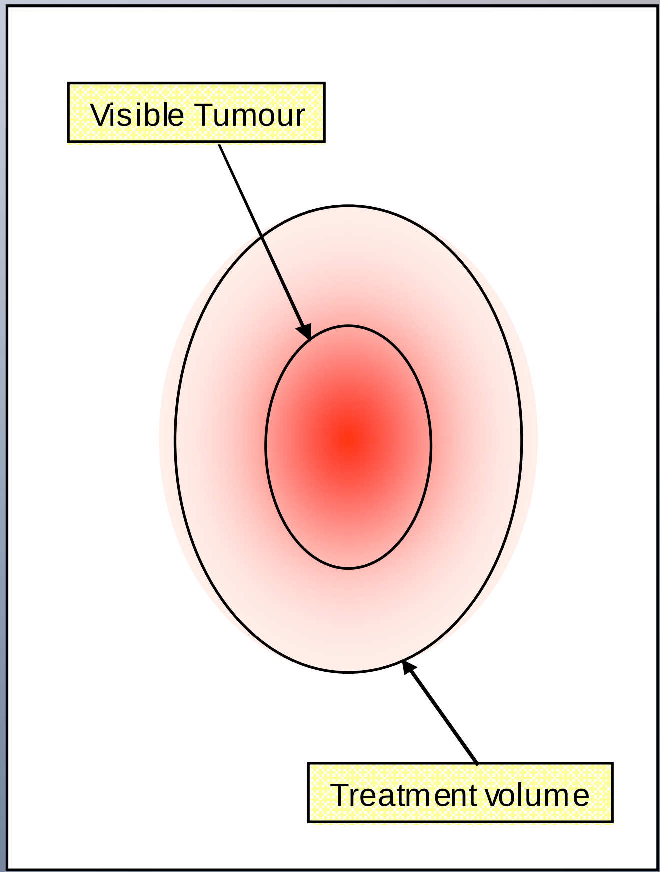
Conventional radiotherapy

- Improves survival from 4 months to 9-10 months
- Improves symptoms (less headache and neurological dysfunction)
- Early studies of higher doses of RT failed to show survival benefit



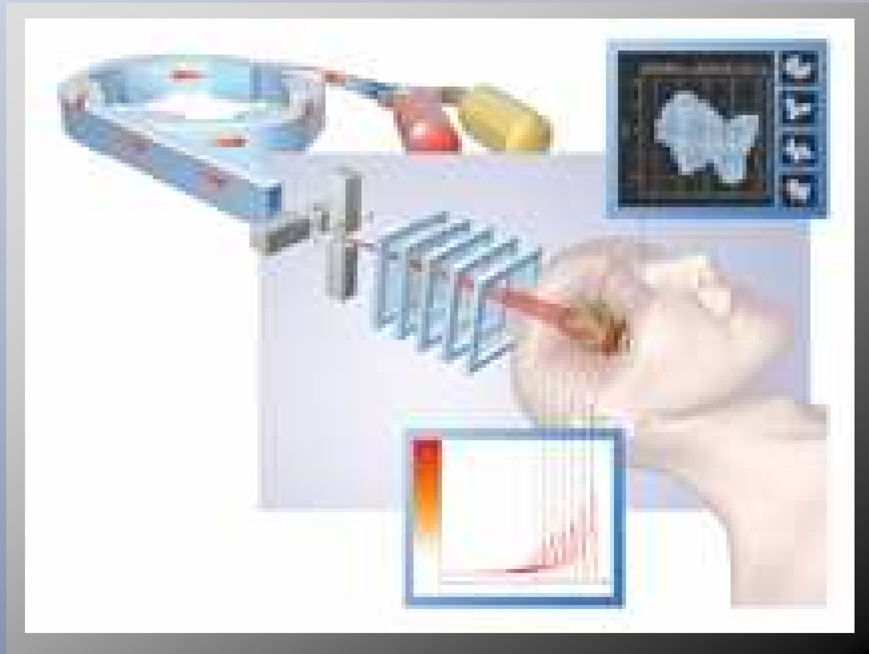
Radiotherapy Planning problems

- Can't accurately visualise tumour invading into white matter
- Oncologist must add generous margins to visible tumour
- Large volume of normal brain tissue is treated



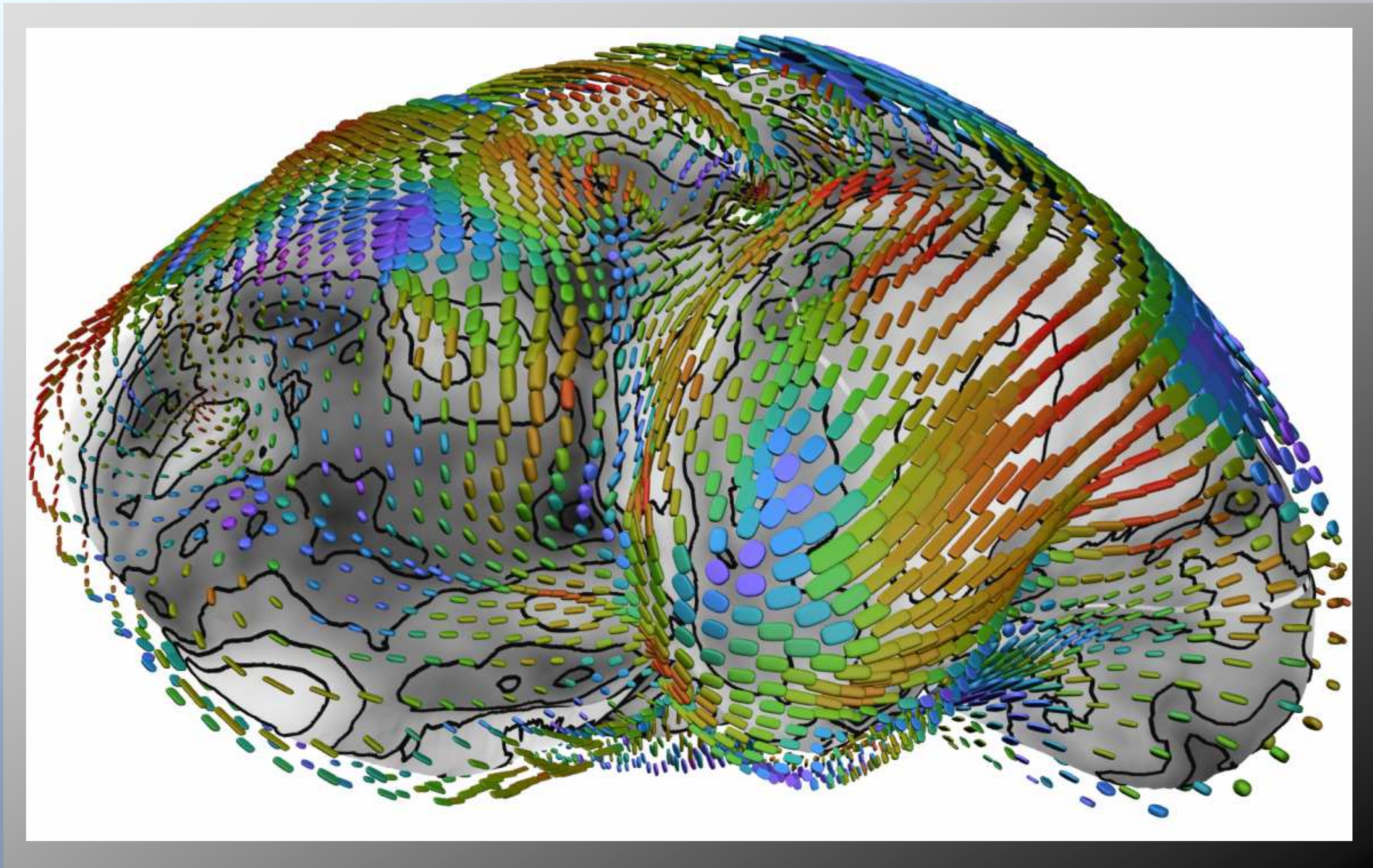
HGG and Protons

- MGH group*
  - Accelerated RT
  - Doses of 90Gy to central core of tumour
  - Significant toxicity to treatment but
  - 30% of patients had complete sterilisation of their tumours



*Fitzek MM, Thornton AF, Rabinov JD, Lev MH, Pardo FS, Munzenrider JE, Okunieff P, Bussiere M, Braun I, Hochberg FH, Hedley-Whyte ET, Liebsch NJ, Harsh GR 4th. Accelerated fractionated proton/photon irradiation to 90 cobalt gray equivalent for glioblastoma multiforme: results of a phase II prospective trial. J Neurosurg. 1999 Aug;91(2):251-60.

Imaging Technology



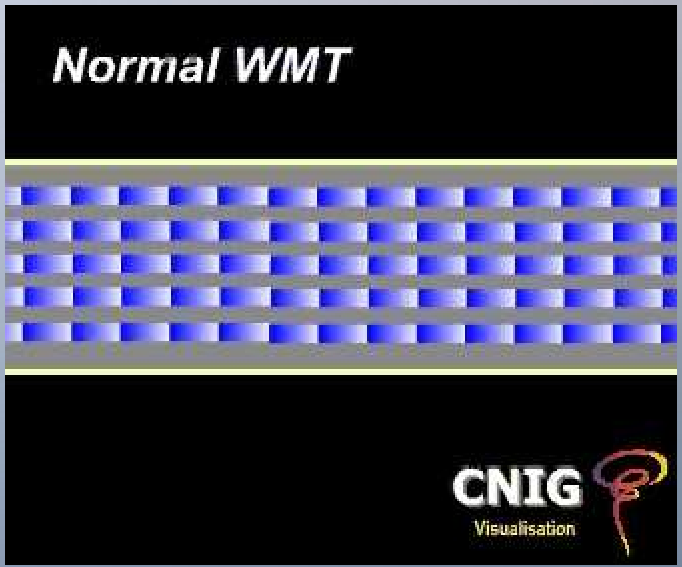
Diffusion Tensor Imaging (DTI)

- Recent development of diffusion MR imaging
- Sensitive to water diffusion along white matter tracts
- Used in assessment of white matter injury, stroke, demyelinating disease
- Our group applied DTI to tumour invasion

Diffusion Tensor Imaging

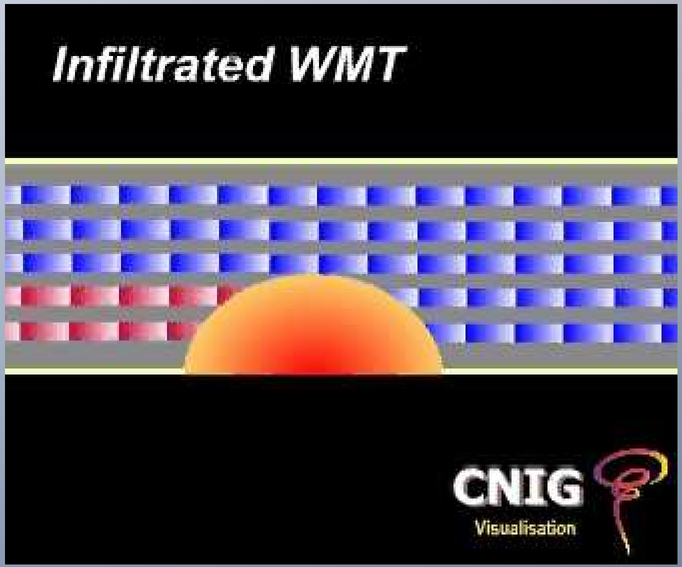
White matter tract architecture

- Highly ordered water diffusion pattern parallel to direction of white matter tract



White matter tract architecture

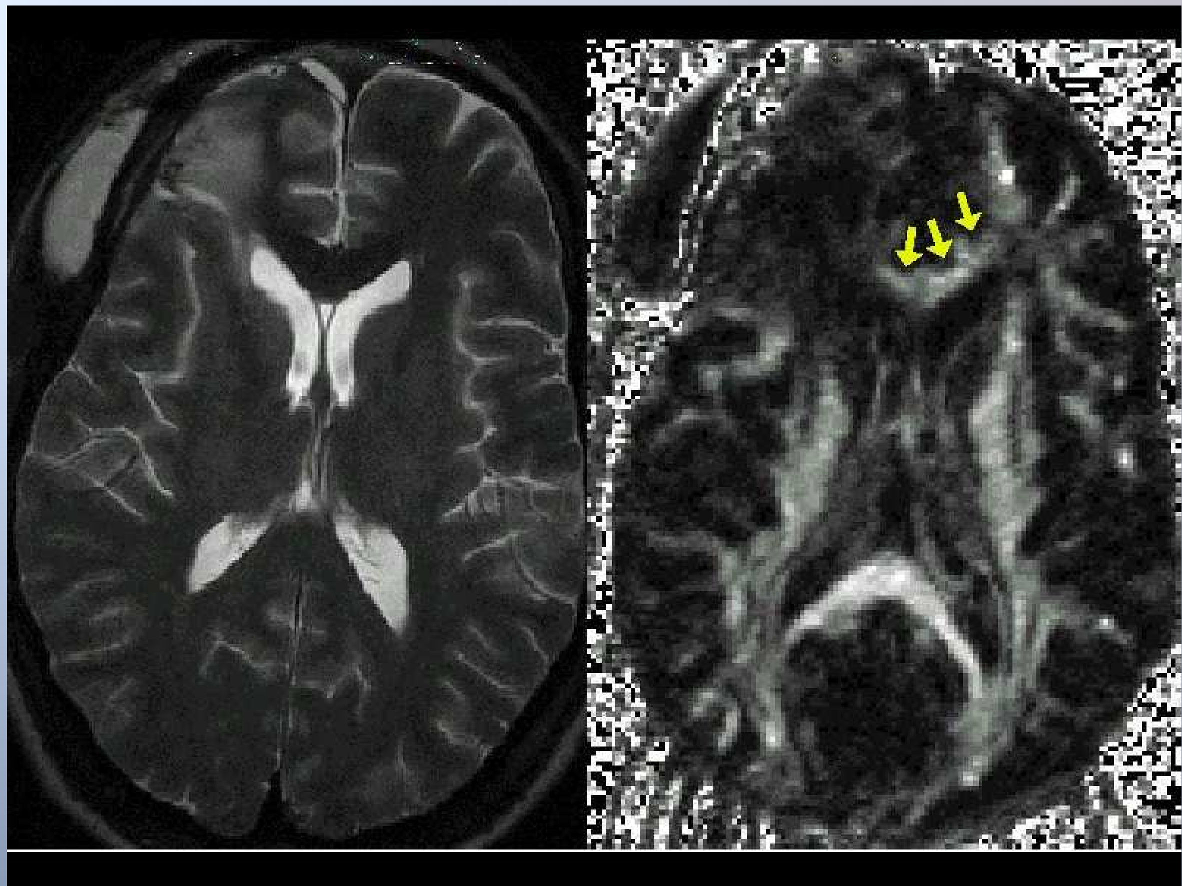
- Effect of tumour infiltration into white matter tract



WMT invasion on DTI

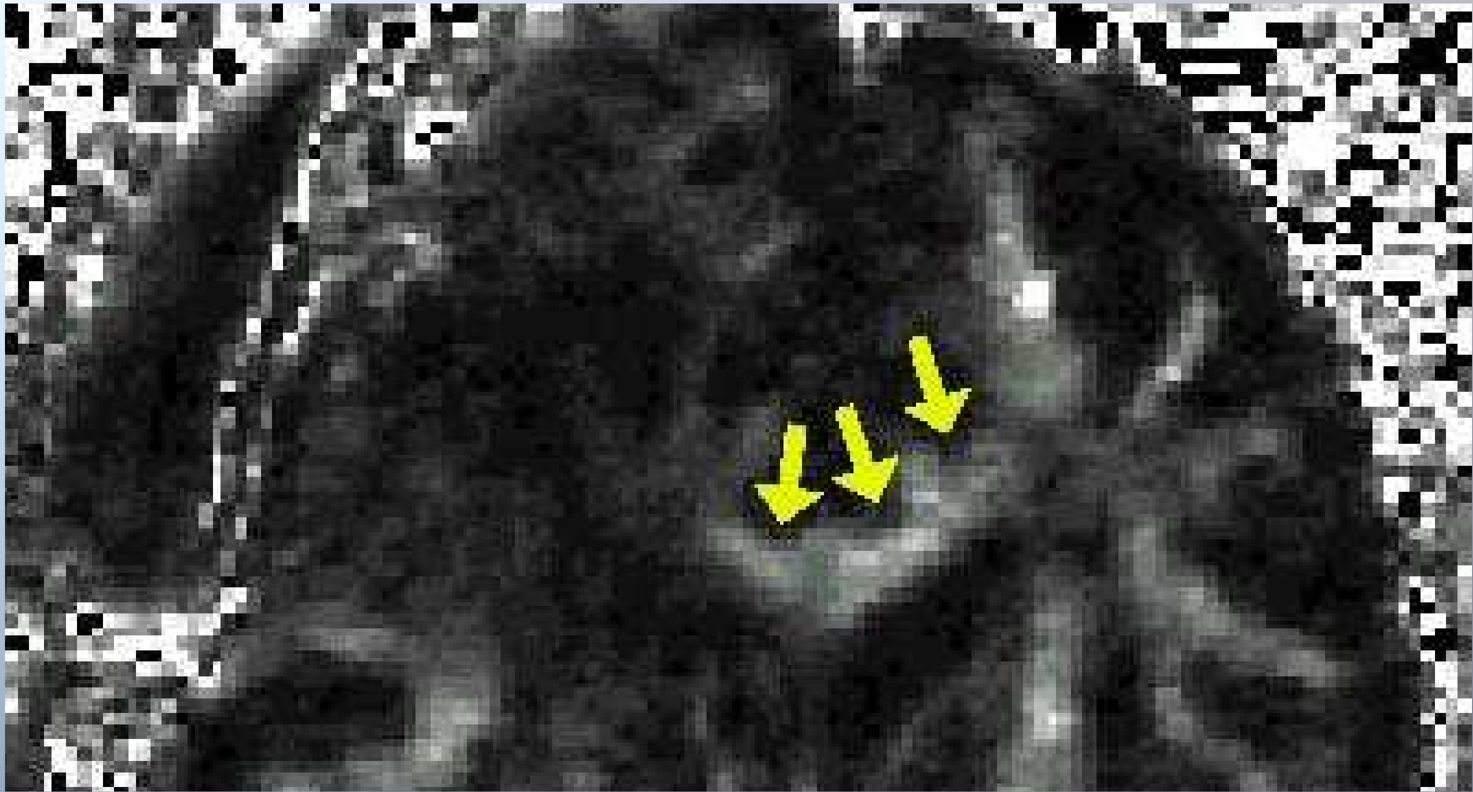
T2W MRI

(Post op)



DTI

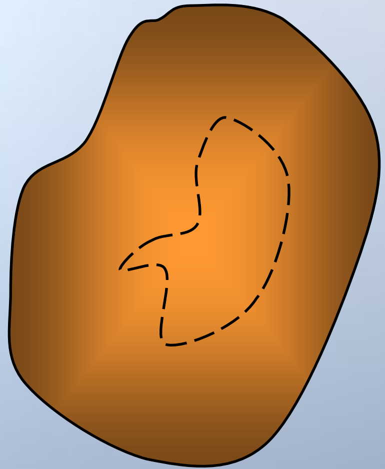
White matter invasion



Individualised Therapy

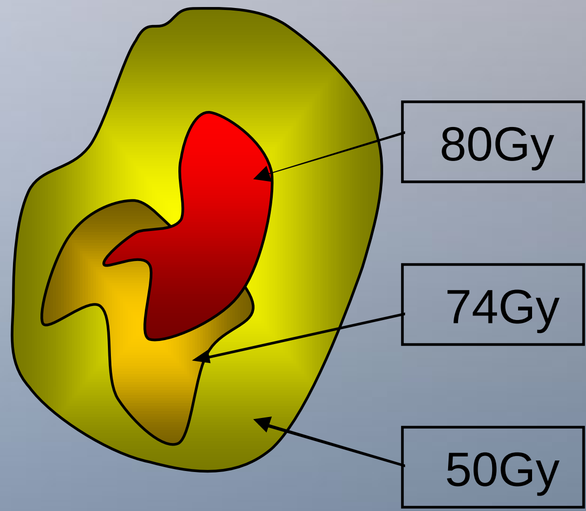
Individualising therapy

Conformal RT



Treat tumour and surrounding brain tissue to uniform dose of 60Gy

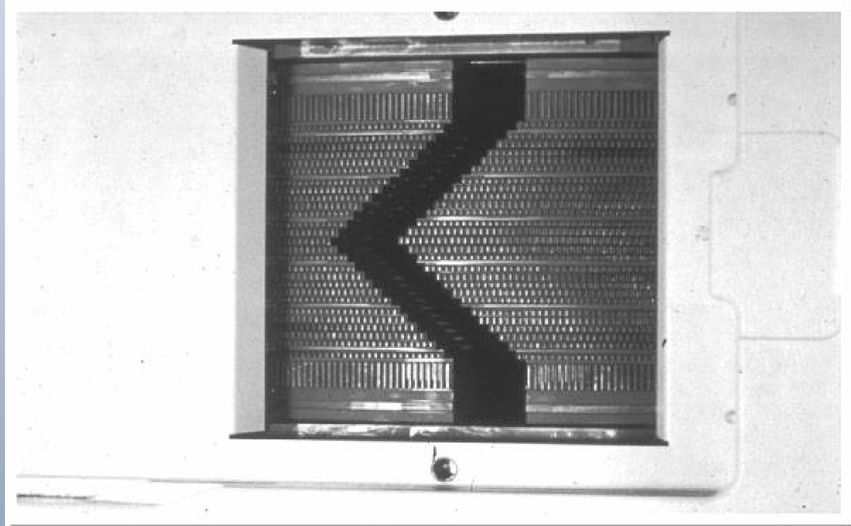
Photon IMRT



Boost tumour core and suspicious white matter areas to higher doses than standard plan.

Photon IMRT

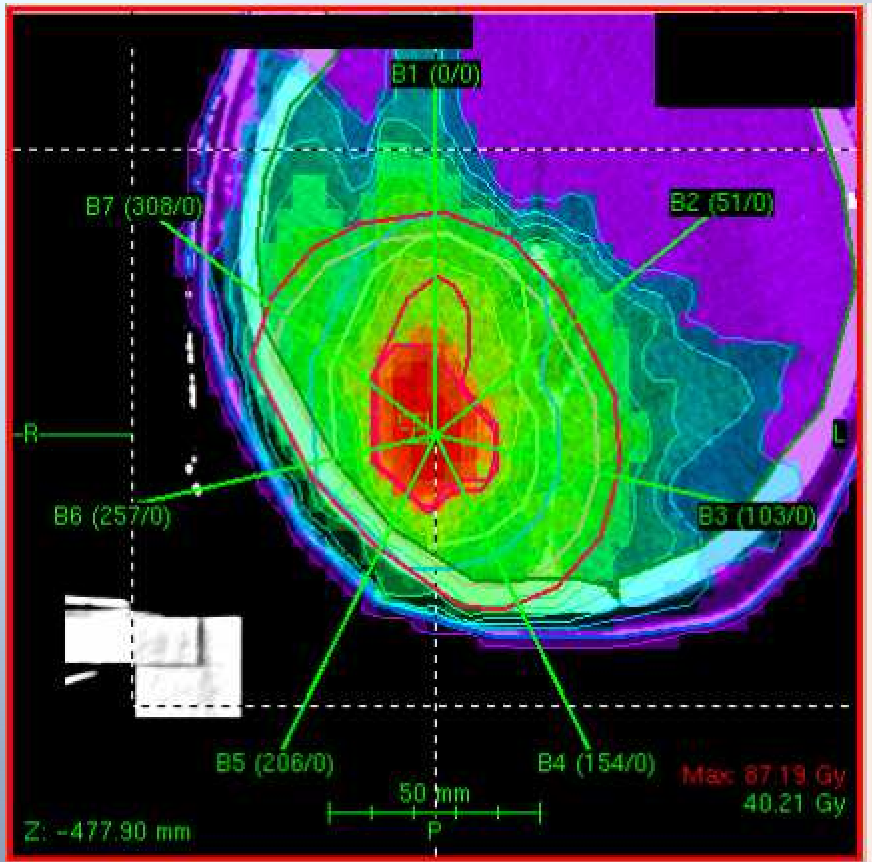
- Construct a complex fluence profile by advanced beam collimation techniques
- Multiple leaves within collimator move to predefined positions during the course of radiotherapy treatment
- Complex process
  - Computation & sequencing of leaf movements
  - Engineering & Quality Assurance

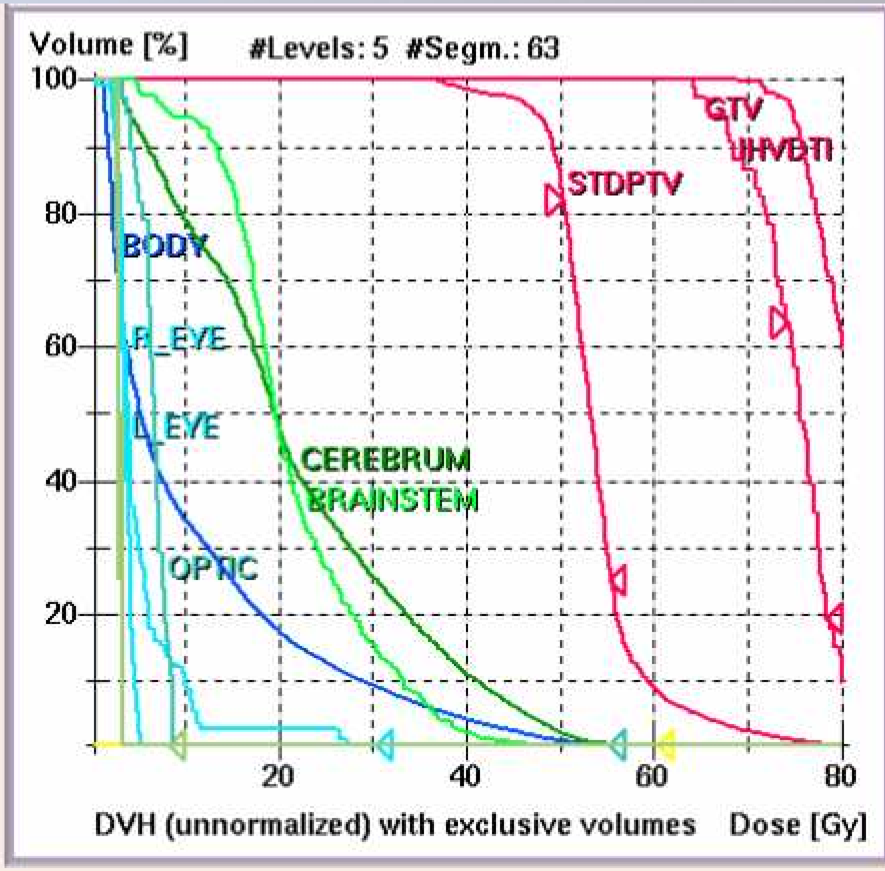


Photon IMRT

- Photon IMRT : Small tumour

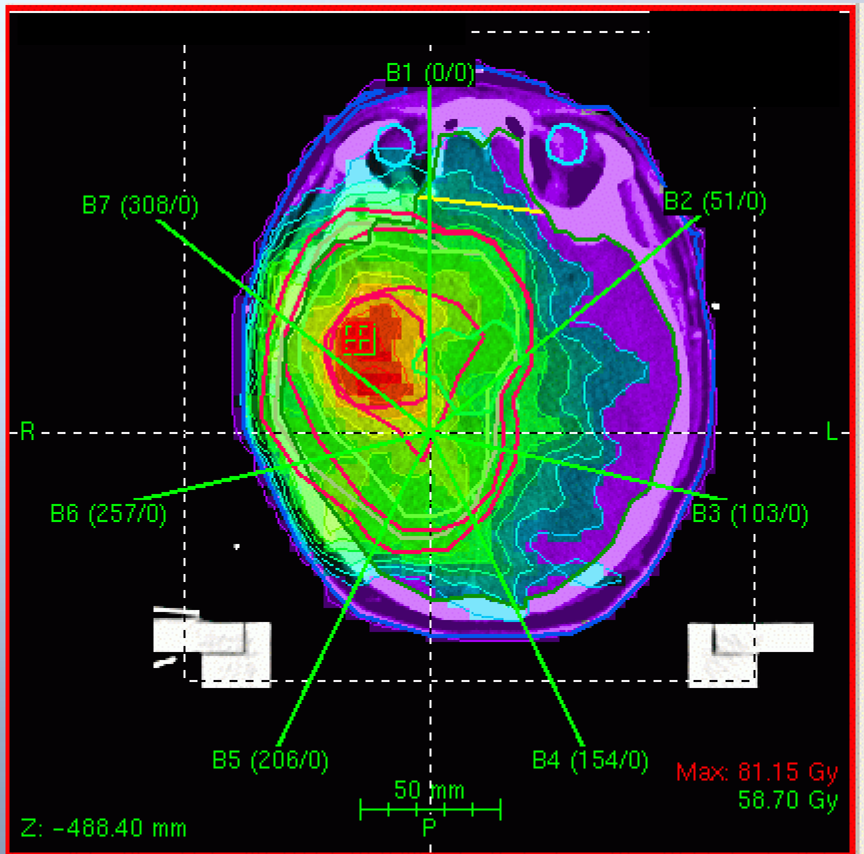
Look at areas of low dose outside target

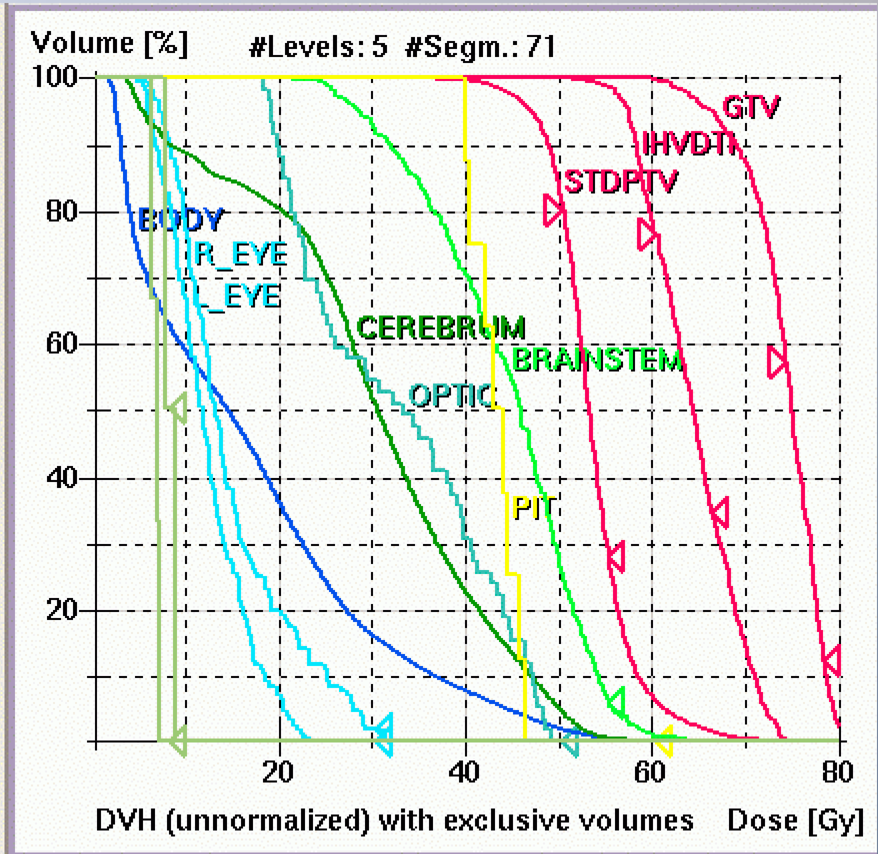




Konrad IMRT planning system provided by Siemens Oncology Care Systems

- Photon IMRT : Medium sized tumour

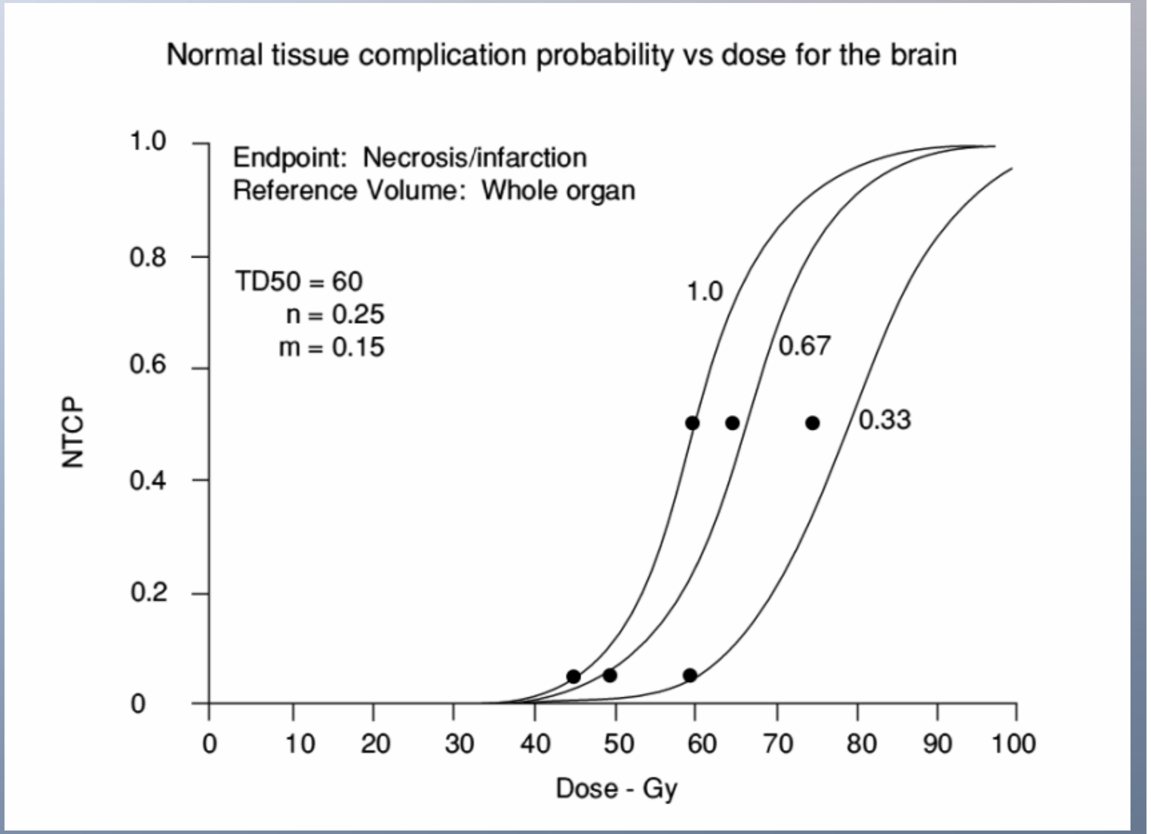




Konrad IMRT planning system provided by Siemens Oncology Care Systems

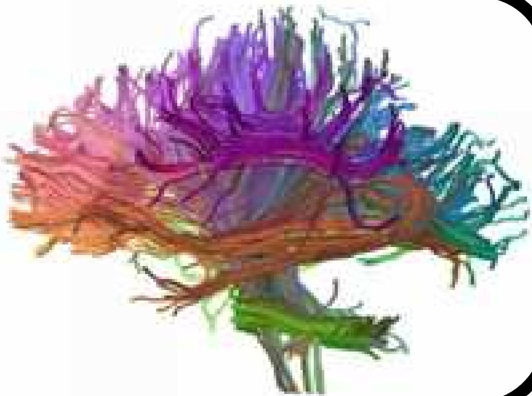
Individualisation of dose

- NTCP models try to estimate risk of normal tissue injury for a given dose distribution
- Optimise treatment to deliver as high a dose as possible for fixed risk of normal tissue complication

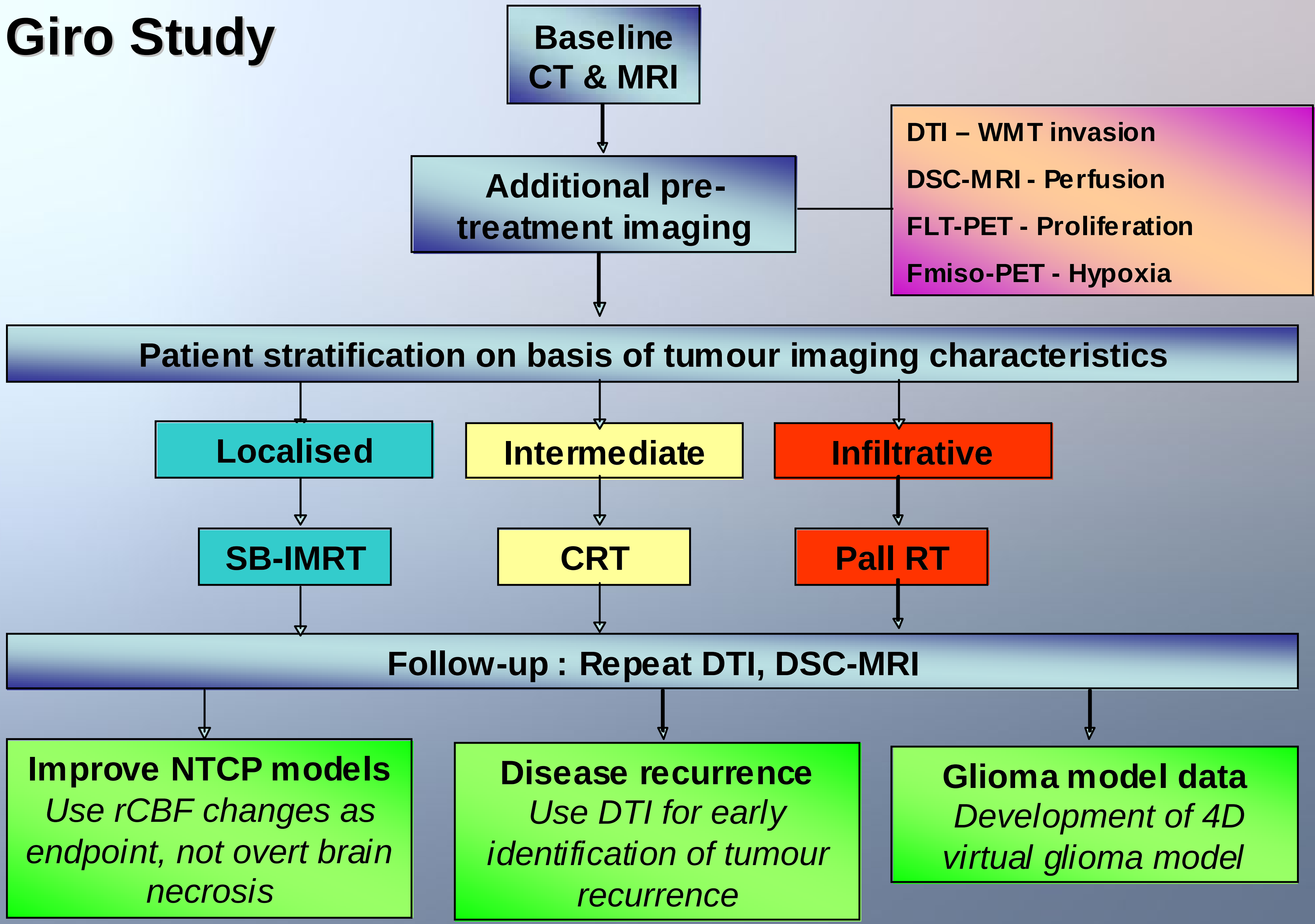


Giro

Glioma Imaging & Radiotherapy Optimisation



Giro Study



Baseline CT & MRI
Additional pre-treatment imaging
DTI – WMT invasion
DSC-MRI - Perfusion
FLT-PET - Proliferation
Fmiso-PET - Hypoxia
Patient stratification on basis of tumour imaging characteristics
Localised
Intermediate
Infiltrative
SB-IMRT
CRT
Pall RT
Follow-up : Repeat DTI, DSC-MRI
Improve NTCP models
Use rCBF changes as endpoint, not overt brain necrosis
Disease recurrence
Use DTI for early identification of tumour recurrence
Glioma model data
Development of 4D virtual glioma model

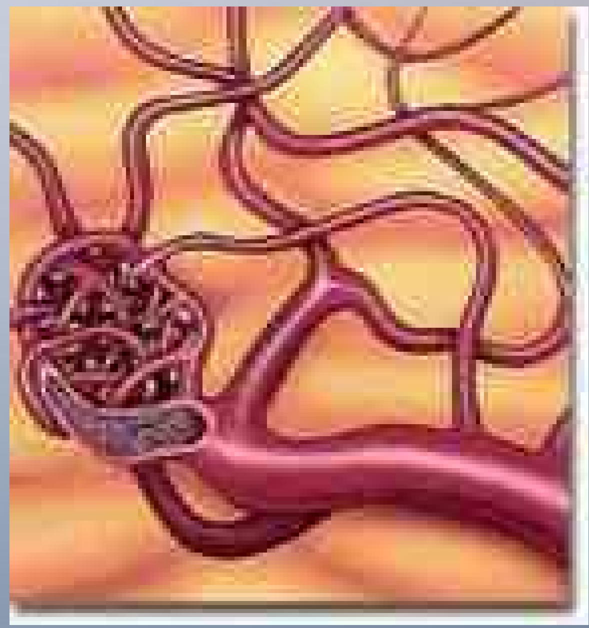
Assessing response to RT

Assessing response

- Tumour response
  - Quantitative assessment of CT / MRI
  - Diffusion Tensor Imaging – resolution of whiter matter changes
- Normal tissue response
  - Standard MRI (T2 weighting)
  - MR Perfusion imaging …

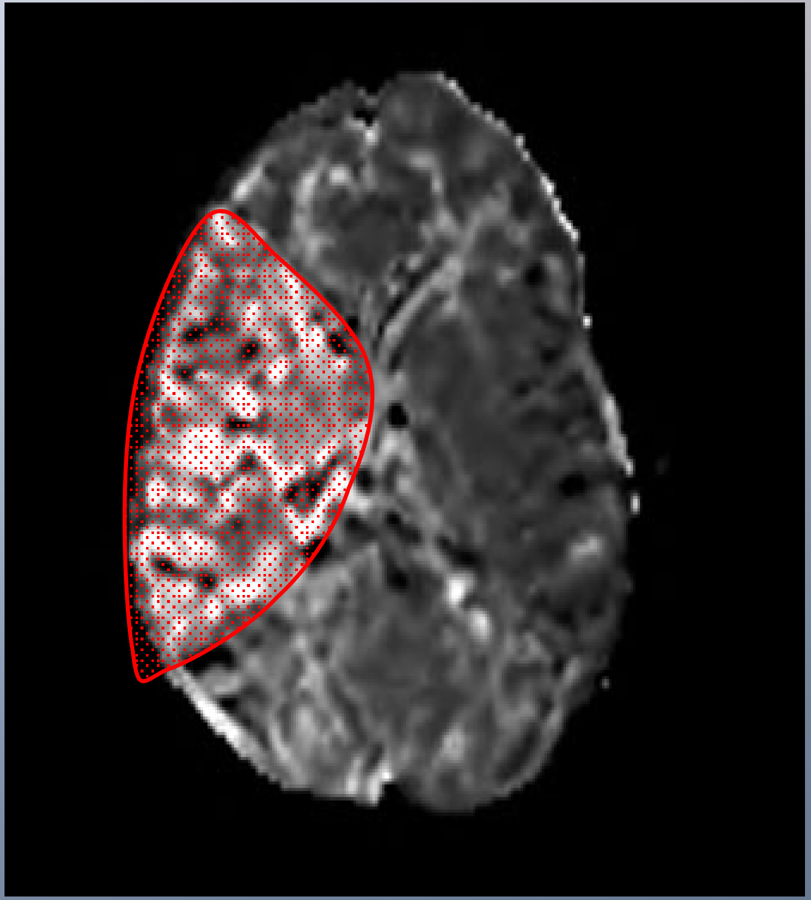
MR based perfusion imaging

- Injury to small blood vessels is an important factor radiation injury of healthy brain tissue
- Dynamic contrast enhancement MR imaging of cerebral perfusion (DCE-MRI) allows quantitative volumetric assessment of microvascular cerebral blood flow

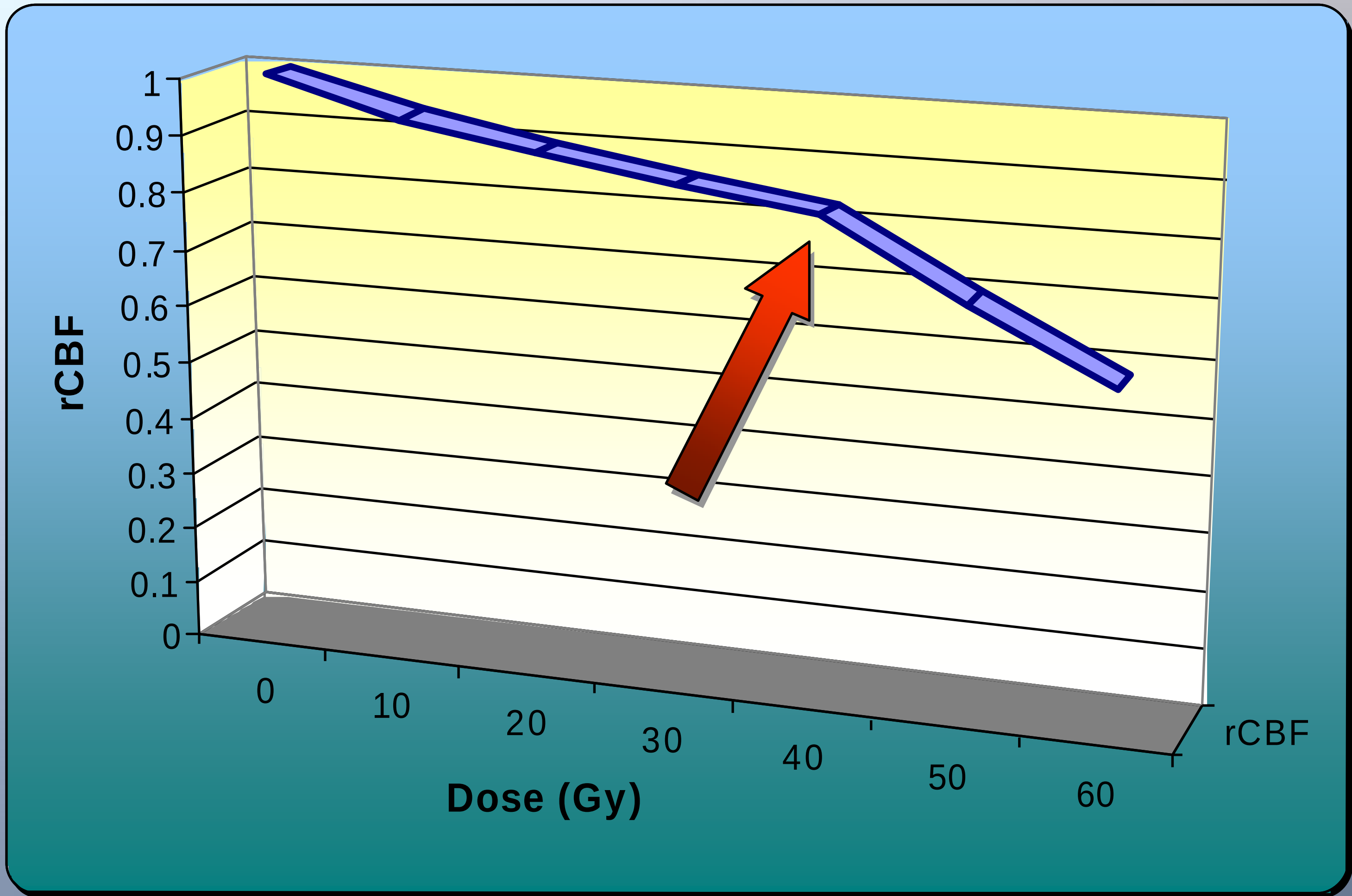


DCE-MRI Perfusion imaging

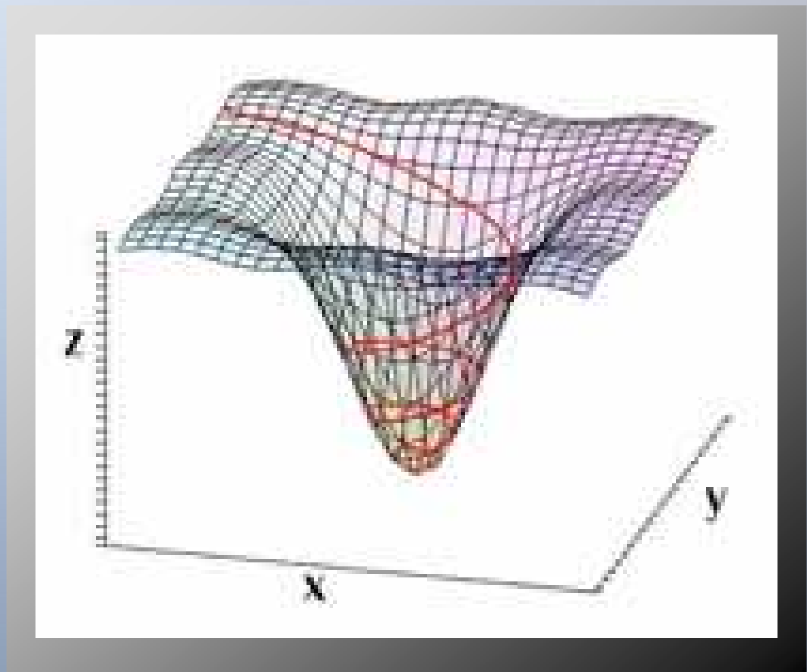
- Perfusion map showing mean transit time for contrast to move through tissue bed
- Demonstrates area in which small vessel perfusion has been reduced



Cerebral perfusion and RT

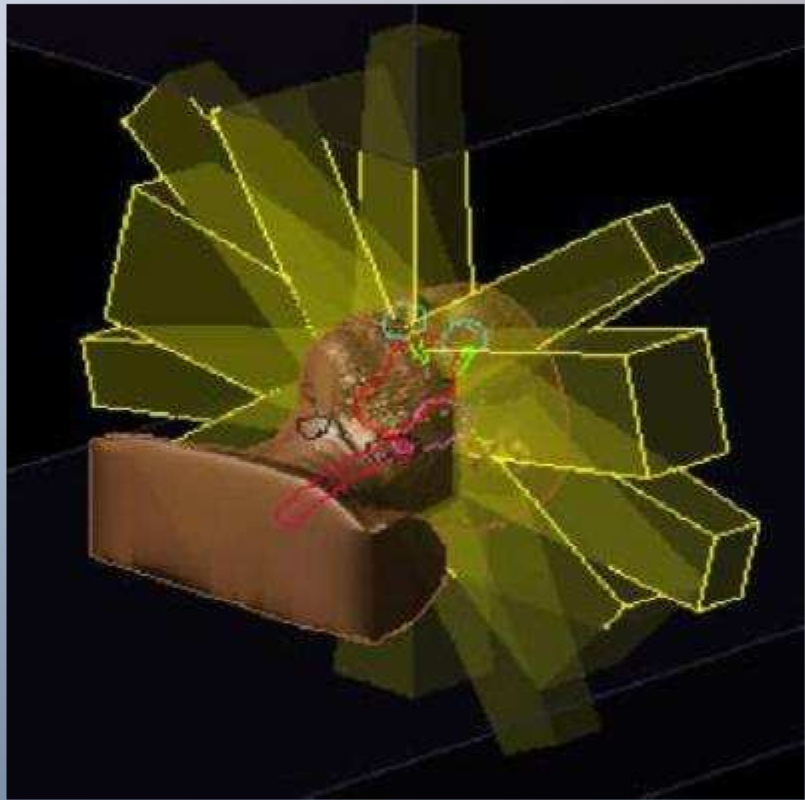


Bio-effect planning

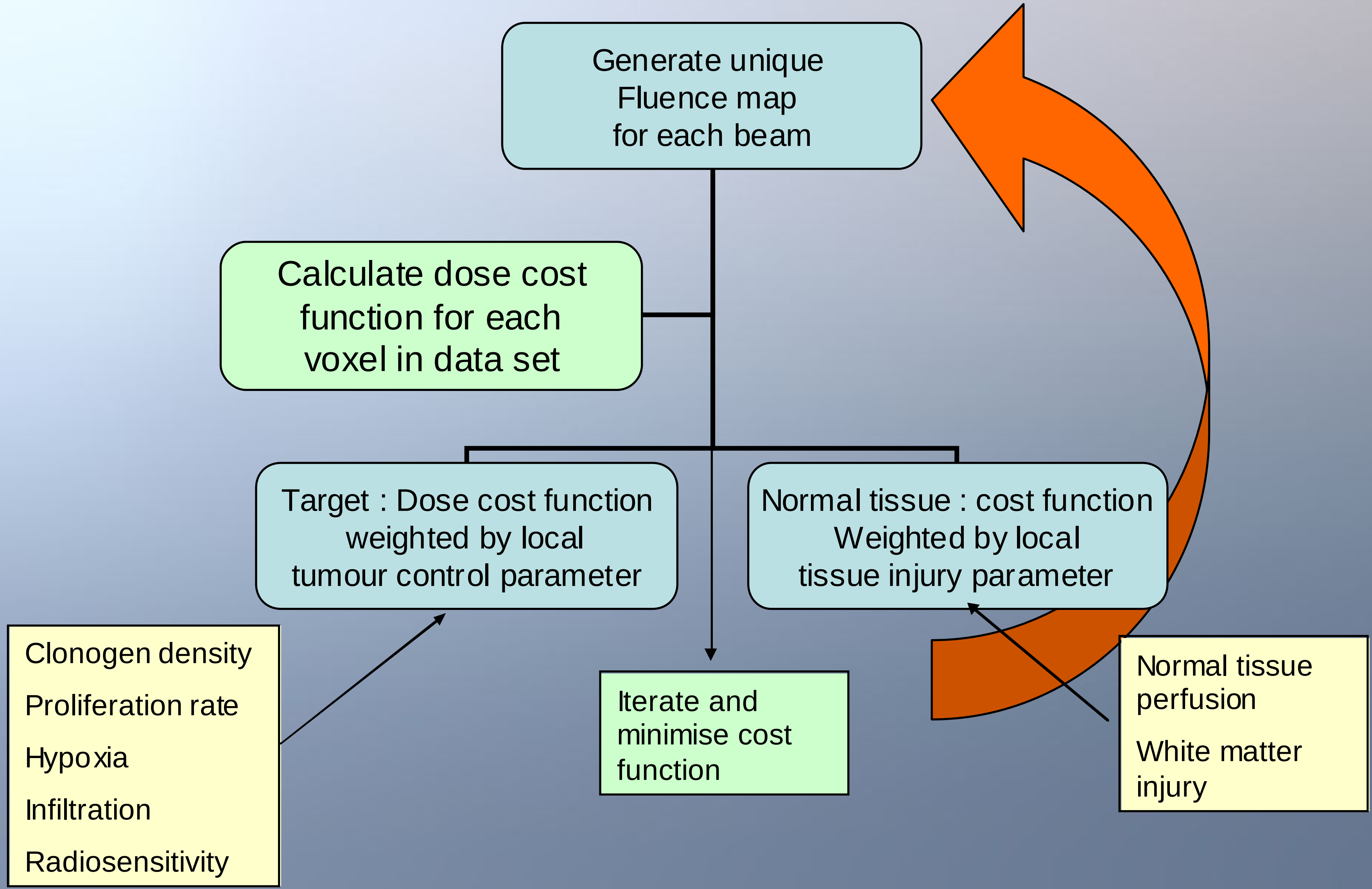


Inverse-planned IMRT

- Classical optimisation problem
  - Variation of beam profile and fluence generates a dose distribution
  - Cost function quantifies difference between test dose distribution and desired dose distribution
  - Iterate through thousands of possible plans, and accept plan with lowest cost function

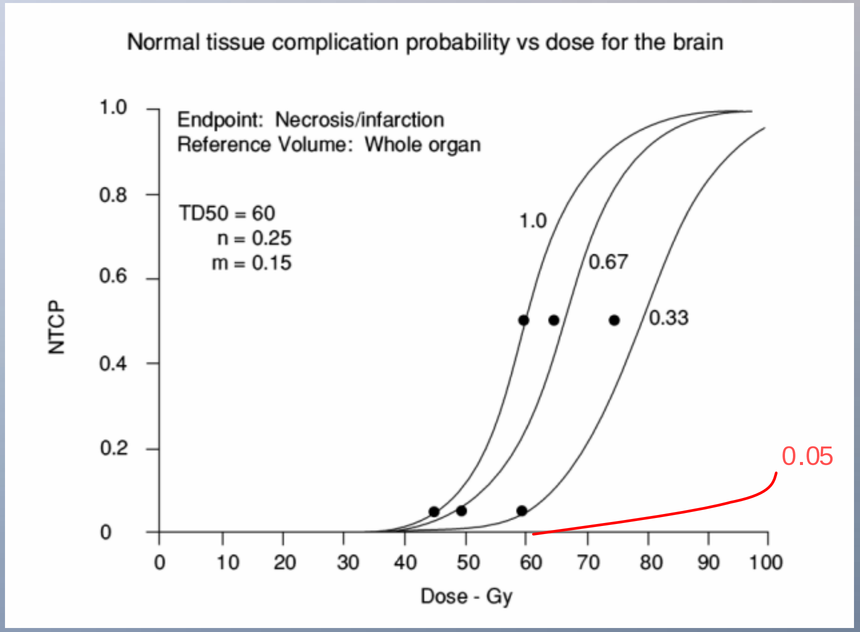


Bio-effect IP-IMRT



New clinical endpoints needed

- Brain necrosis NTCP model
- Endpoint is avoided in clinical practice
- No data for extrapolation to high doses and small partial volumes
- Perfusion changes are a better normal tissue endpoint

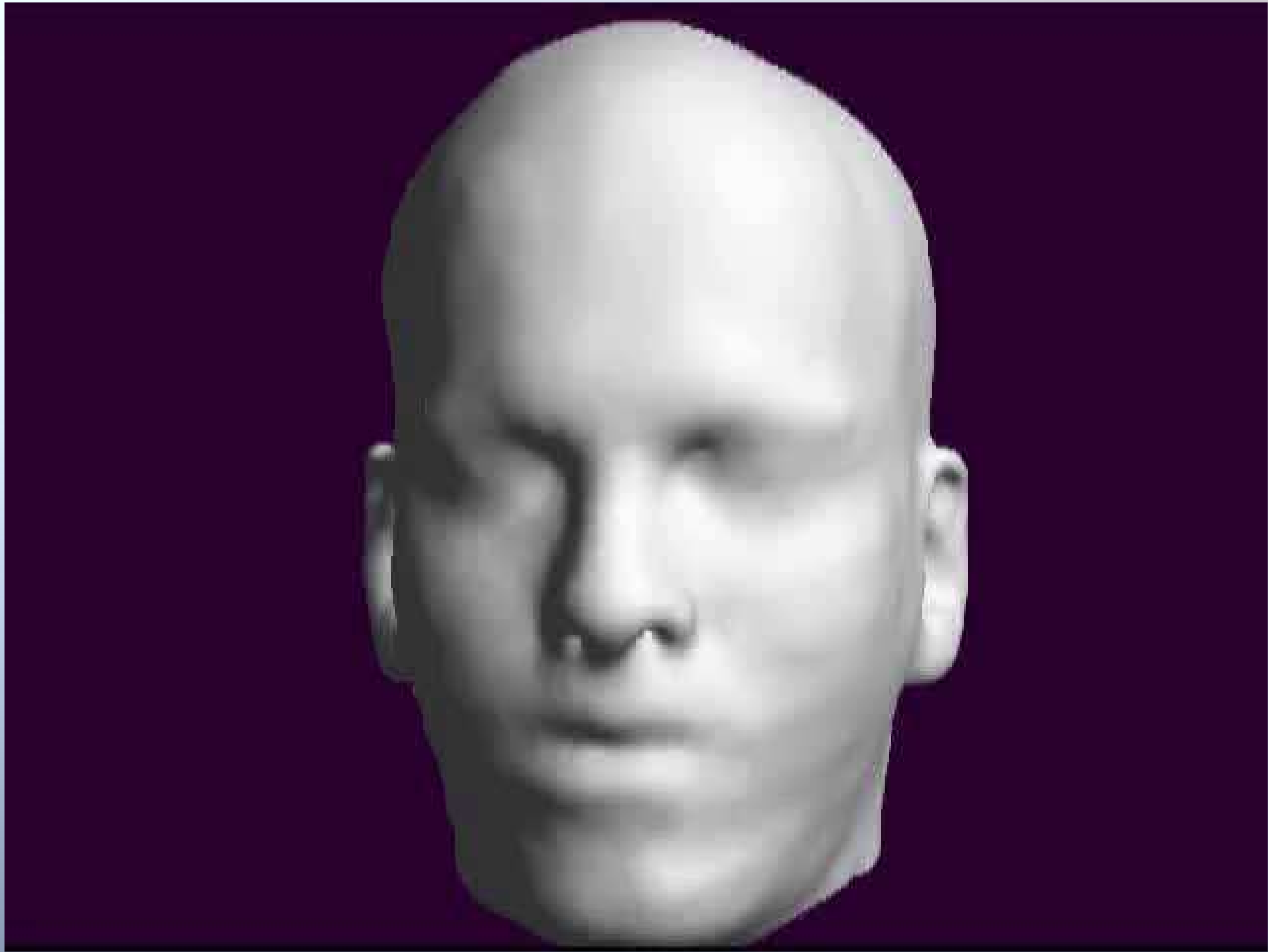


Parameter optimisation for MCO

- Need to determine what the weighting factors for each parameter
  - Clonogen density (MRI, Biopsy)
  - Proliferation rate (FLT PET)
  - Hypoxia (Fmiso PET, BOLD MRI)
  - Infiltration (DTI)
- Models extremely useful in studying these indices and deriving weighting factors for MCO algorithms

Image based tissue models

- Tissue level models based on
  - auto-segmentation
  - automated extraction of physiological parameters
- Data within image sets



With permission from Dr Gordon Kindlmann, University of Utah

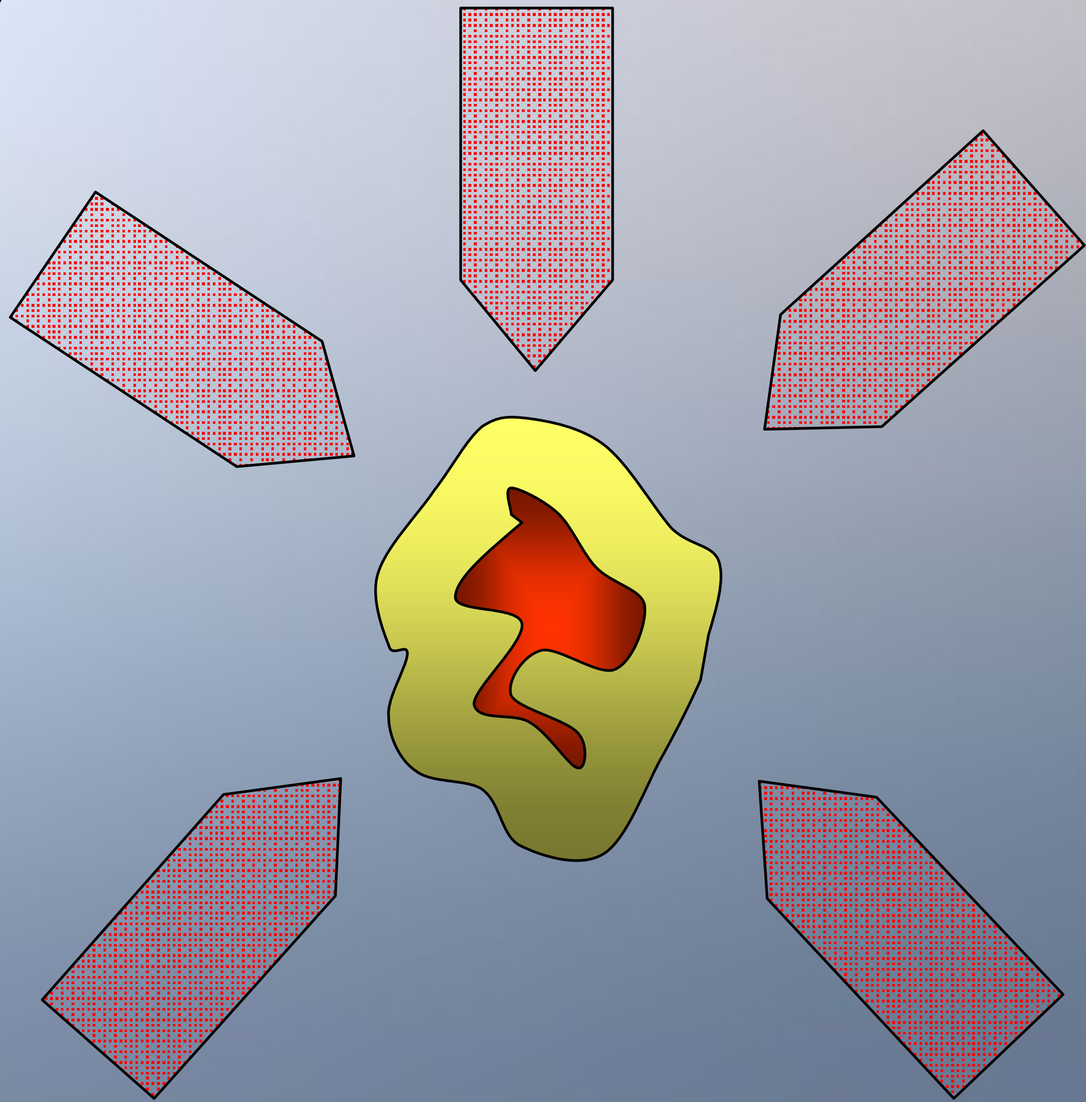
Improved Precision with Protons

Advantages of protons

- High LET radiation
  - overcoming hypoxic radioresistance
  - No cell cycle dependent radiosensitivity
- Steep dose gradient
  - Skull base / paraspinal tumours
- Exit dose
  - Paediatrics
- **Integral dose and NTCP**

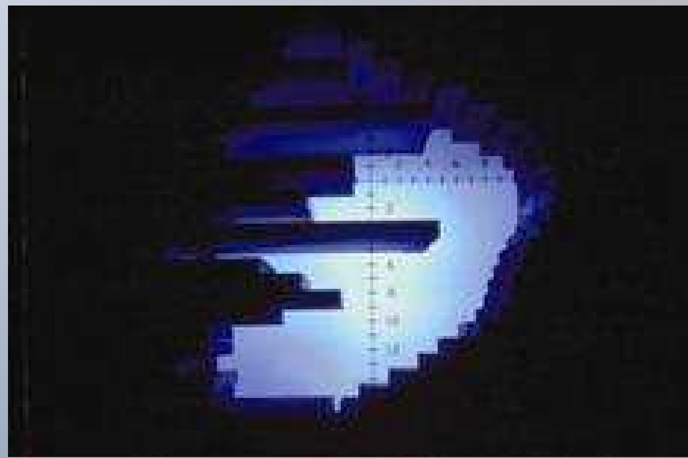
Integral dose & IMRT

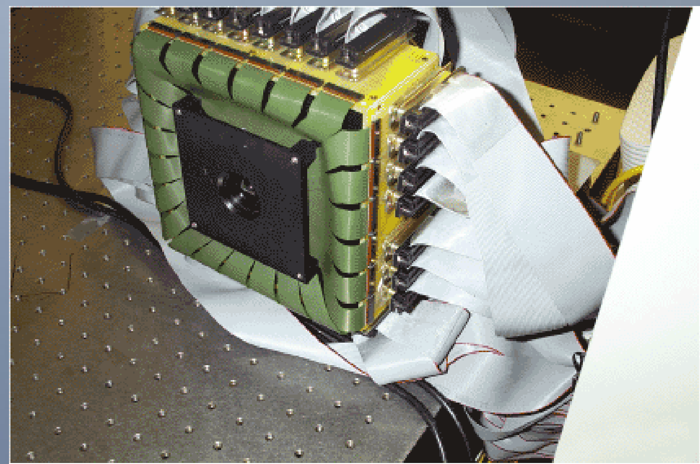
- Conformation to complex shapes requires multiple beams with complex fluences
- Large volume of irradiated normal tissue, higher integral dose



Intensity Modulated Proton Therapy

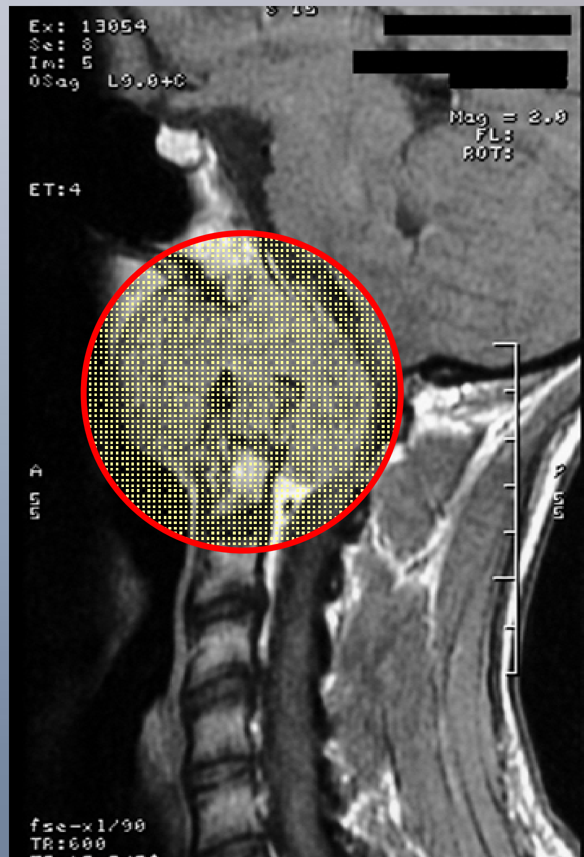
- IMPT can produce similar dose conformation with lower dose to normal tissues
- This is of critical importance in bioeffect planning, where maximum dose is limited by normal tissue effects





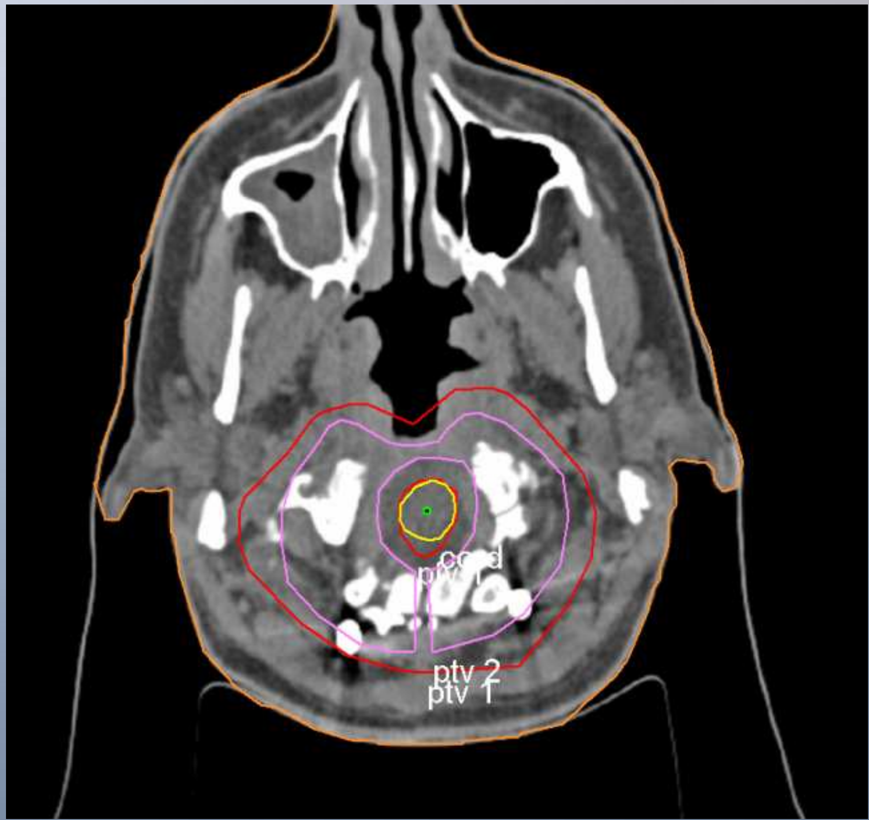
An example case

- 17 year old with learning difficulties develops chordoma of skull base
- Incomplete resection, referred for post-operative radiotherapy
- High doses (65-70Gy) required to control tumour
- Target dose exceeds the tolerance dose of the spinal cord
- Comparative dosimetry of CRT, IMRT, IMPT



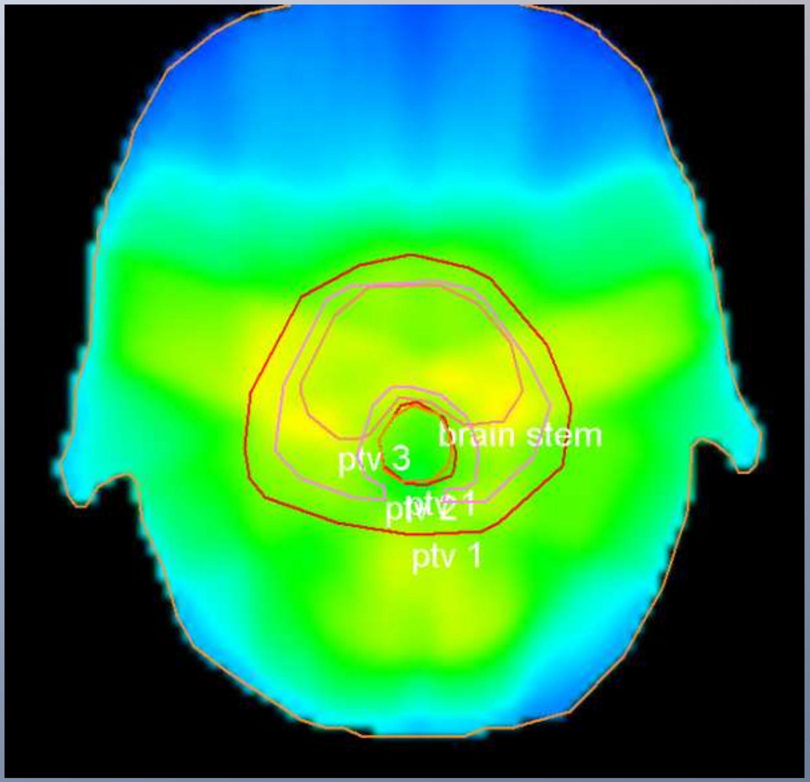
Target volume

- Spinal cord dose limit = 50Gy in 30#
- PTV3 = 65Gy
- PTV2 = 60Gy
- PTV1 = 55Gy



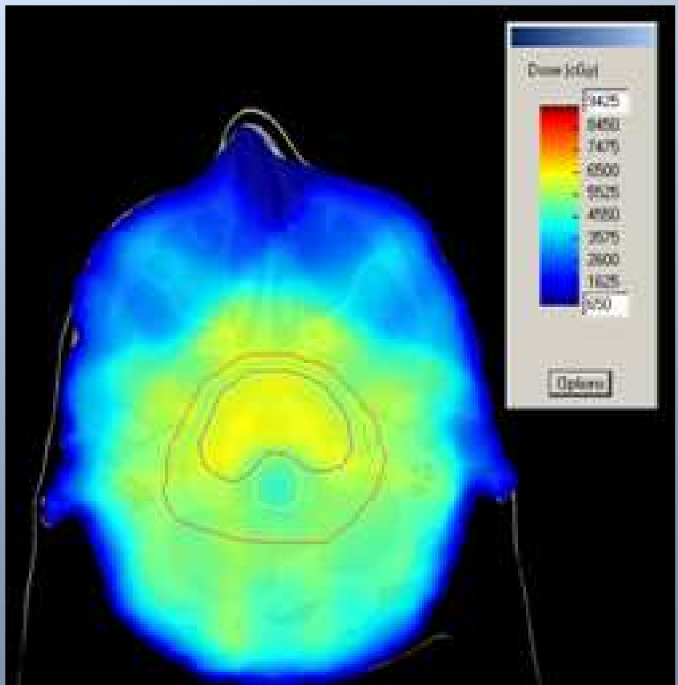
Conformal photon therapy

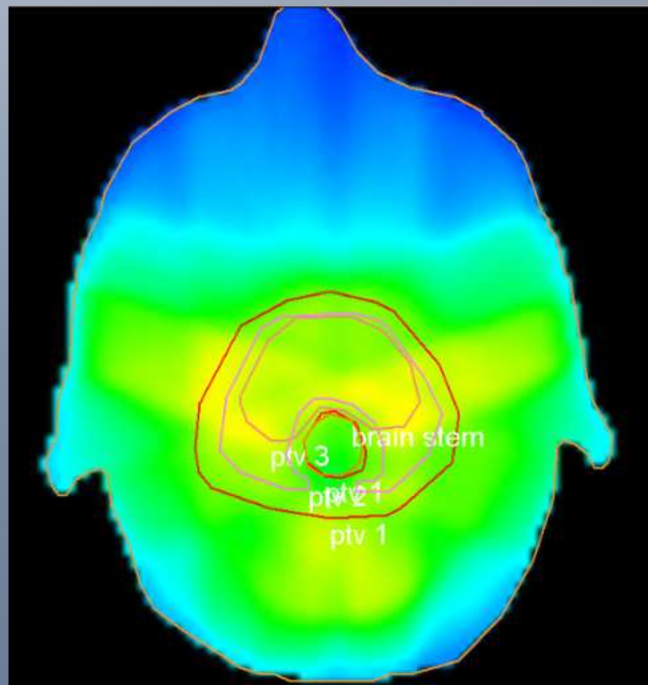
- Complex plan with 6 fixed beam directions and 12 arcs
- Achieves target dose but note how dose is scattered outside target



IMRT (Photons)

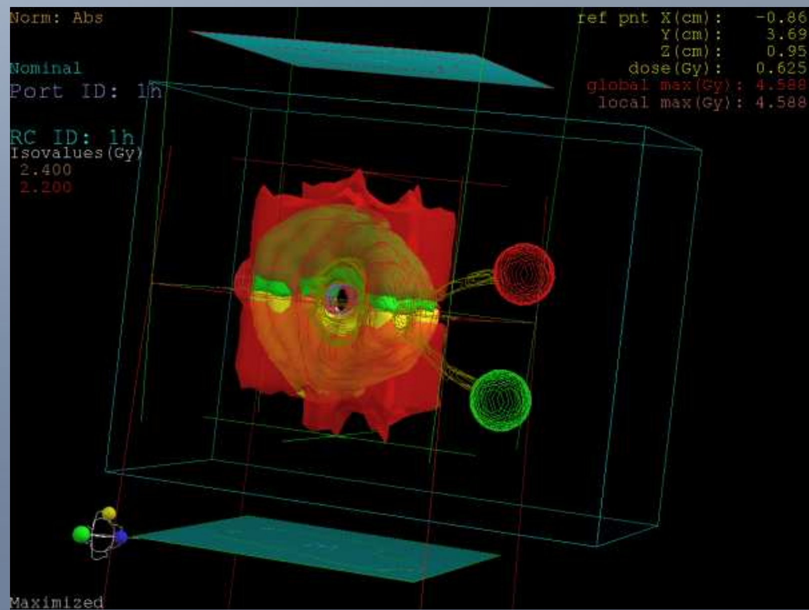
- Better conformation of dose
- Still get significant dose outside the target volume



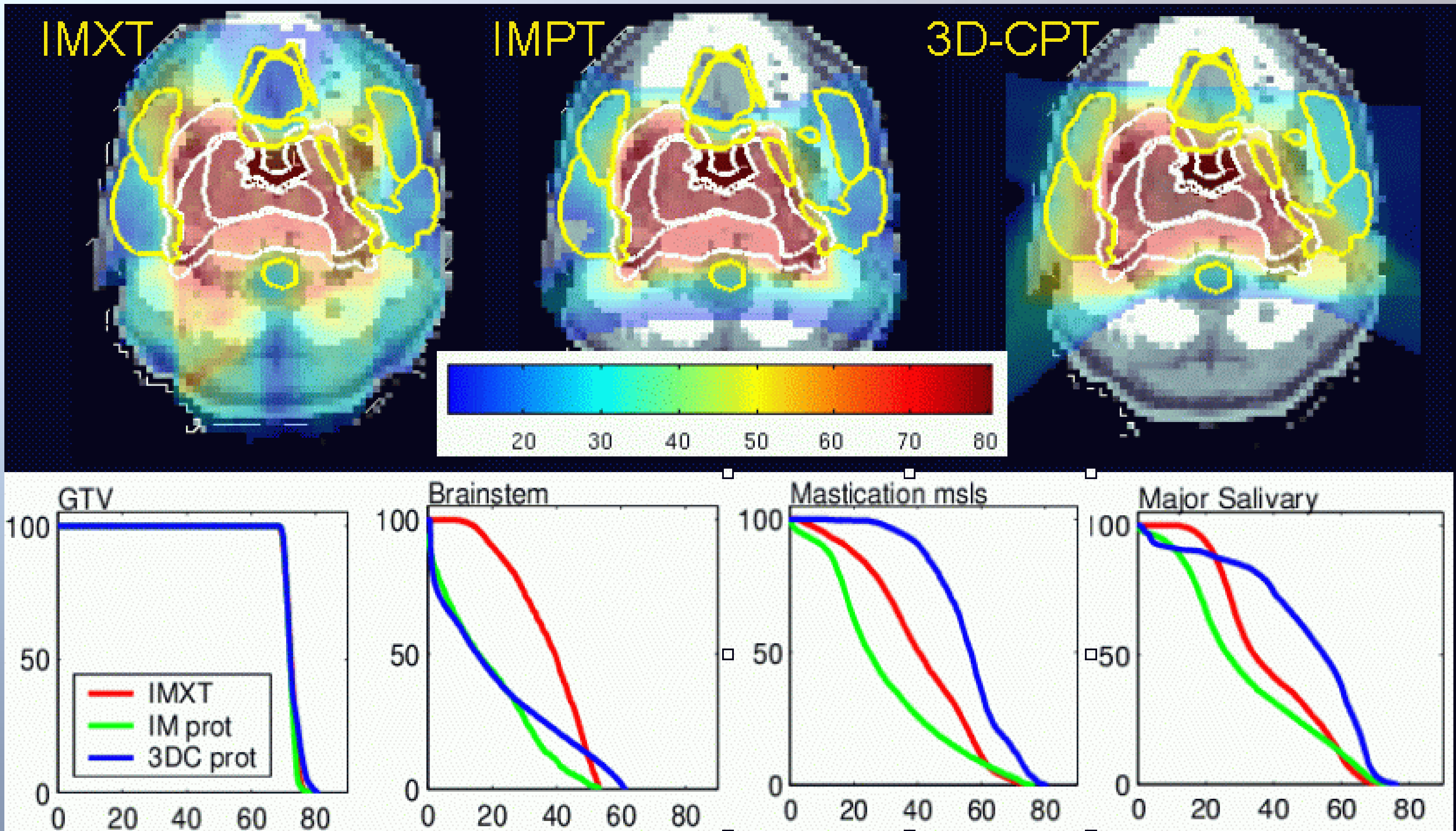


IMPT (Protons)

- Parallel pair beam arrangement spares significant amount of normal tissue



IMRT vs IMPT

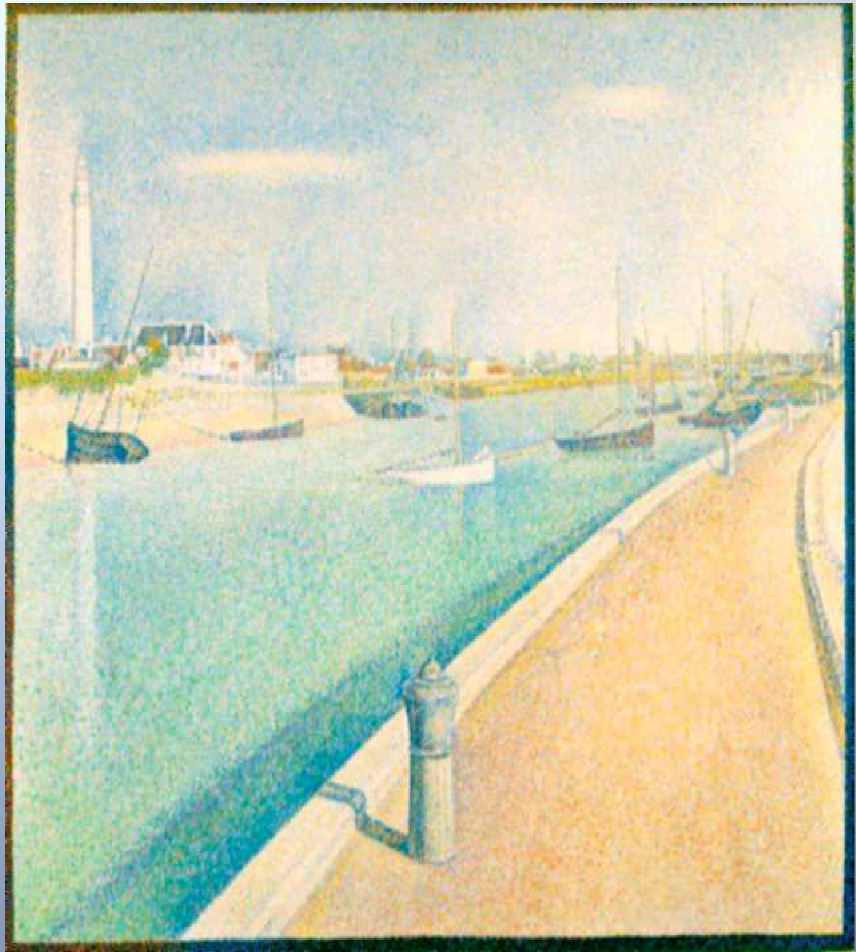


IMXT
IMPT
3D-CPT
20 30 40 50 60 70 80
GTV
Brainstem
Mastication msls
Major Salivary
100
50
0
0 20 40 60 80
IMXT
IM prot
3DC prot

Conclusion

- Radiotherapy treatment needs to be individualised, to target dose precisely to the most biologically aggressive regions of the tumour
- Photon IMRT can achieve this, at the expense of irradiating larger volumes of normal tissue to low dose
- Proton IMRT can achieve similar or better target dose distributions, with lower dose to normal tissue
- Proton IMRT is therefore a better tool for bioeffect planning

Precision is the key



Le port de Gravelines, Seurat

Acknowledgements

UNIVERSITY OF CAMBRIDGE

- Neil Burnet
- Simon Thomas
- Andrew Hoole

UniS University of Surrey Guildford

- Norman Kirkby
- Karen Kirkby

THE UNIVERSITY OF BIRMINGHAM

- Bleddyn Jones
- Stuart Green

SIEMENS

- Ajit Singh
- Chris Amies
- Dimitre Hristov

The Health Foundation

- Jan Walmsley
- Raheel Anwar