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Broadening the therapeutic band width

Neil Burnet

University of Cambridge Department of Oncology,
Oncology Centre, Addenbrooke's Hospital,
Cambridge, UK

ATP Cambridge 2016

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TomoTherapy
HI·ART

Introduction

Radiotherapy (RT) is a hugely important cancer treatment

- Improvements will have a major effect to benefit society

- Small improvements in dosimetry translate into significant improvements in outcome for individual patients

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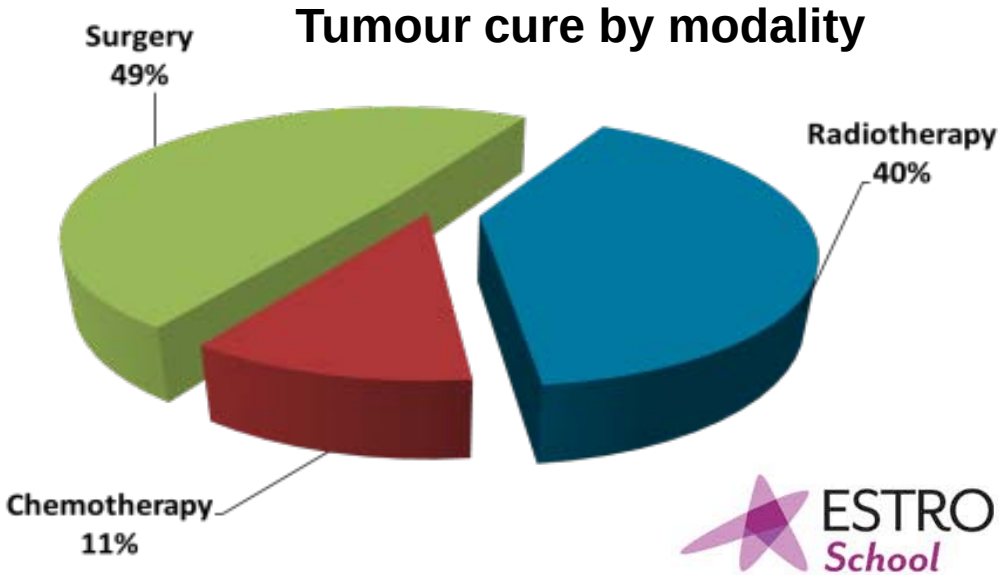
Introduction

RT is potent and cost-effective

- 50% of cancer patients require RT
- 60% treated with curative intent

- UK 66M population
- ~ 100,000 patients receive RT with curative intent in each year

Treatment modality	Annual spend
Surgery	£2.1 billion
Chemotherapy	£1.7 billion
Radiotherapy	£0.5 billion



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Introduction

- Broadening the therapeutic bandwidth = Improving the therapeutic ratio
- Equivalent to the therapeutic window for drugs

- TCP = Tumour control probability = local control
- NTCP = Normal tissue complication probability = toxicity

- RT is always a balance

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Quality of RT affects outcome

Quality of RT affects outcome

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(2010; 28(18): 2996-3001)

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

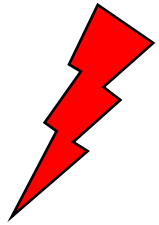
Critical Impact of Radiotherapy Protocol Compliance and Quality in the Treatment of Advanced Head and Neck Cancer: Results From TROG 02.02

Lester J. Peters, Brian O'Sullivan, Jordi Giralt, Thomas J. Fitzgerald, Andy Trotti, Jacques Bernier, Jean Bourhis, Kally Yuen, Richard Fisher, and Danny Rischin

- Very scary results
- Poor radiotherapy

20% ↓ in OS

24% ↓ in DFS



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Quality of RT affects outcome

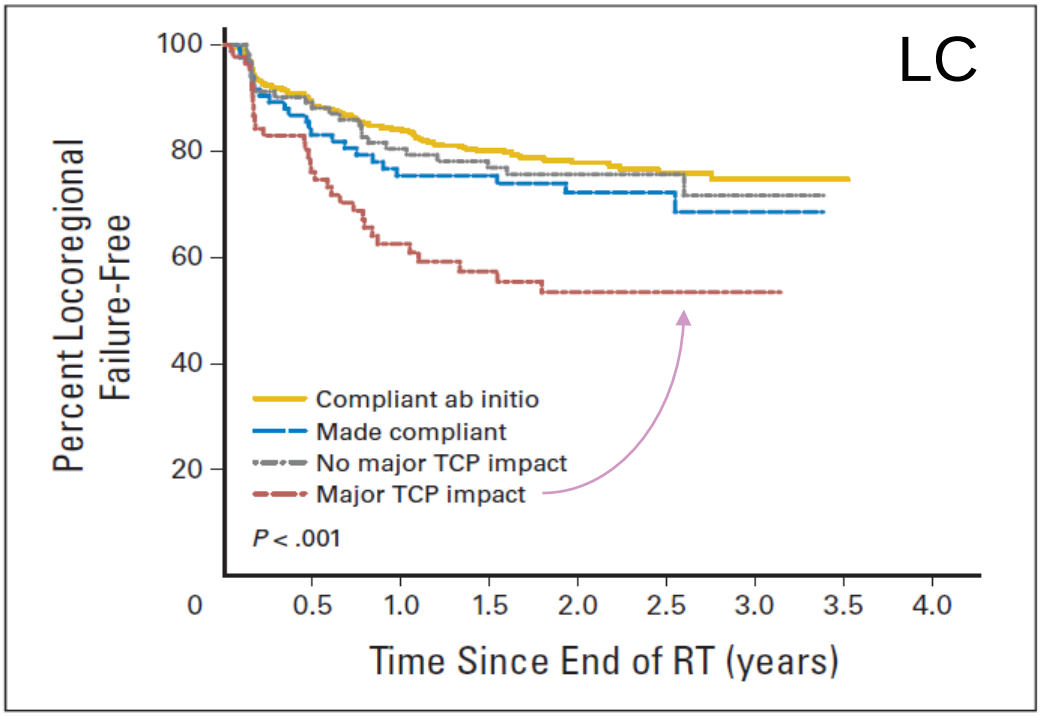

Fig 3. Time to locoregional failure by deviation status

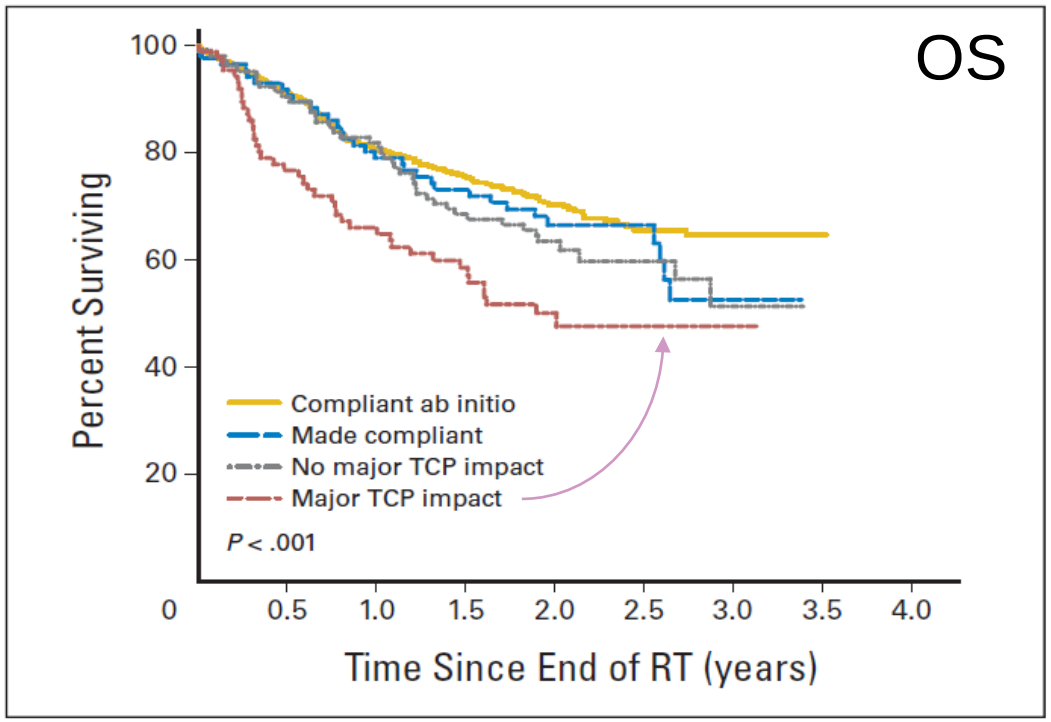

Fig 2. Overall survival by deviation status:

- Poor radiotherapy in 12% of patients in study
  - ➢ Considered likely to have a major impact on outcome

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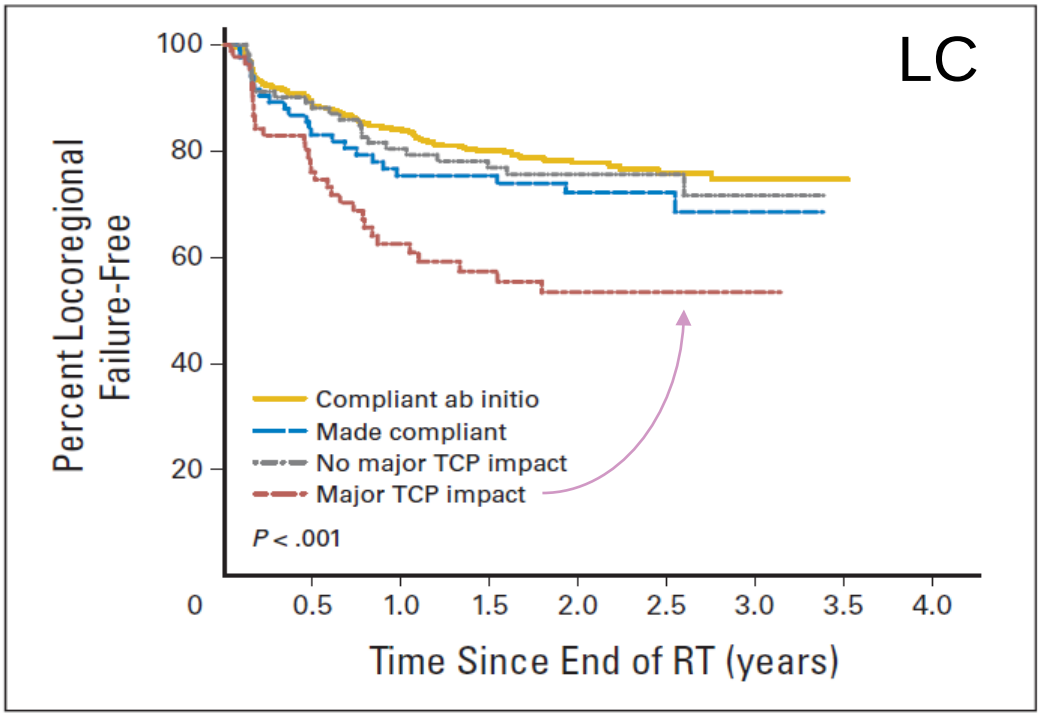
Quality of RT affects outcome



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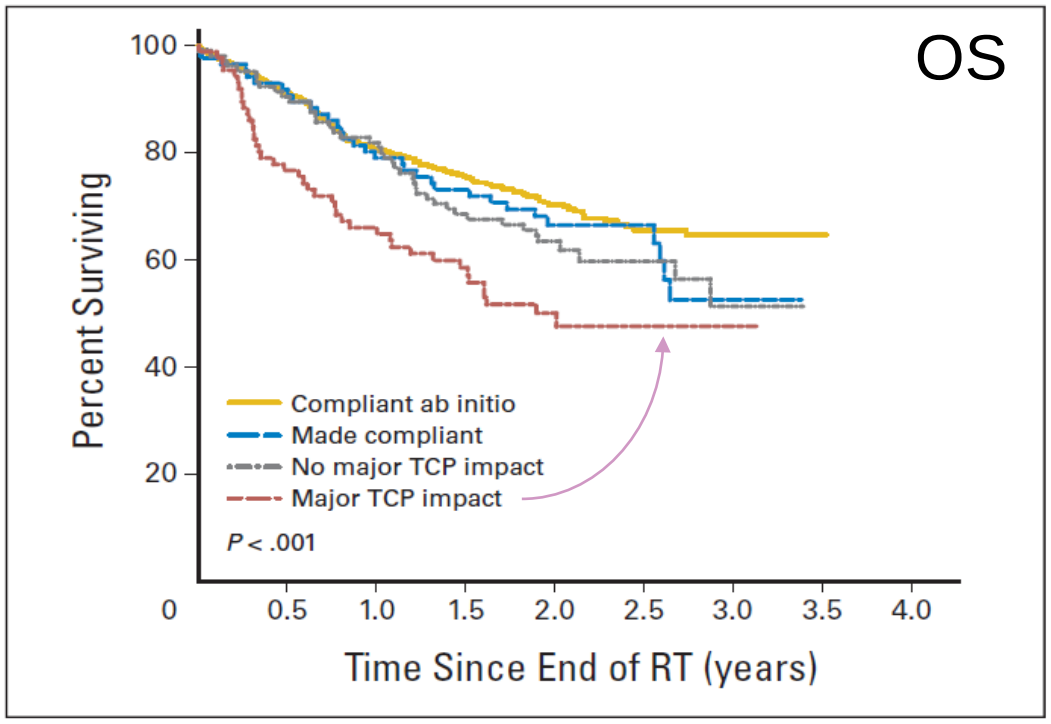

Fig 2. Overall survival by deviation status:

- Poor radiotherapy in 12% of patients in study
  - Considered likely to have a major impact on outcome
    - 3% poor contouring
    - 5% poor plan preparation

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Broadening RT band width

Broadening RT band width

- Physical – dose distributions - individualising treatment
  - IMRT
  - IGRT
  - Adaptive RT
  - Imaging including for target volume delineation
  - Proton beam therapy – PBT

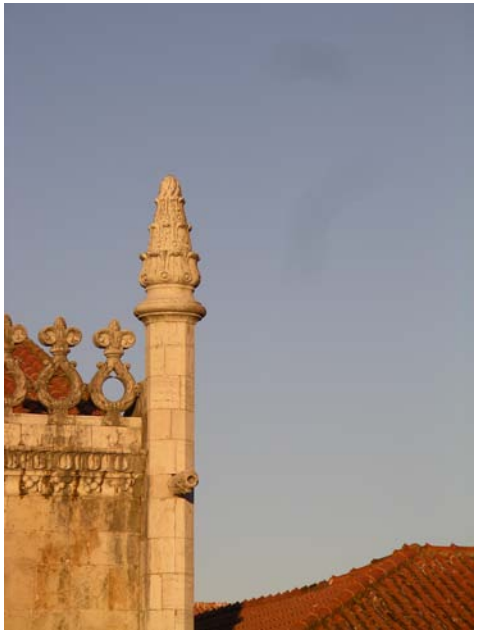
- Biological strategies
  - Fractionation
  - Exploiting individual variation in normal tissue toxicity
  - Drugs – sensitise tumours & protect normal tissues

Broadening RT band width

- Improving the therapeutic ratio is based on ***individualisation***

- Focus on physical dose individualisation
  - Integral part of RT for many years – actually > 100 years!

  - IMRT is main component of course
  - Accurate delivery essential, so IGRT relevant
  - Proton beam therapy becoming avaialble



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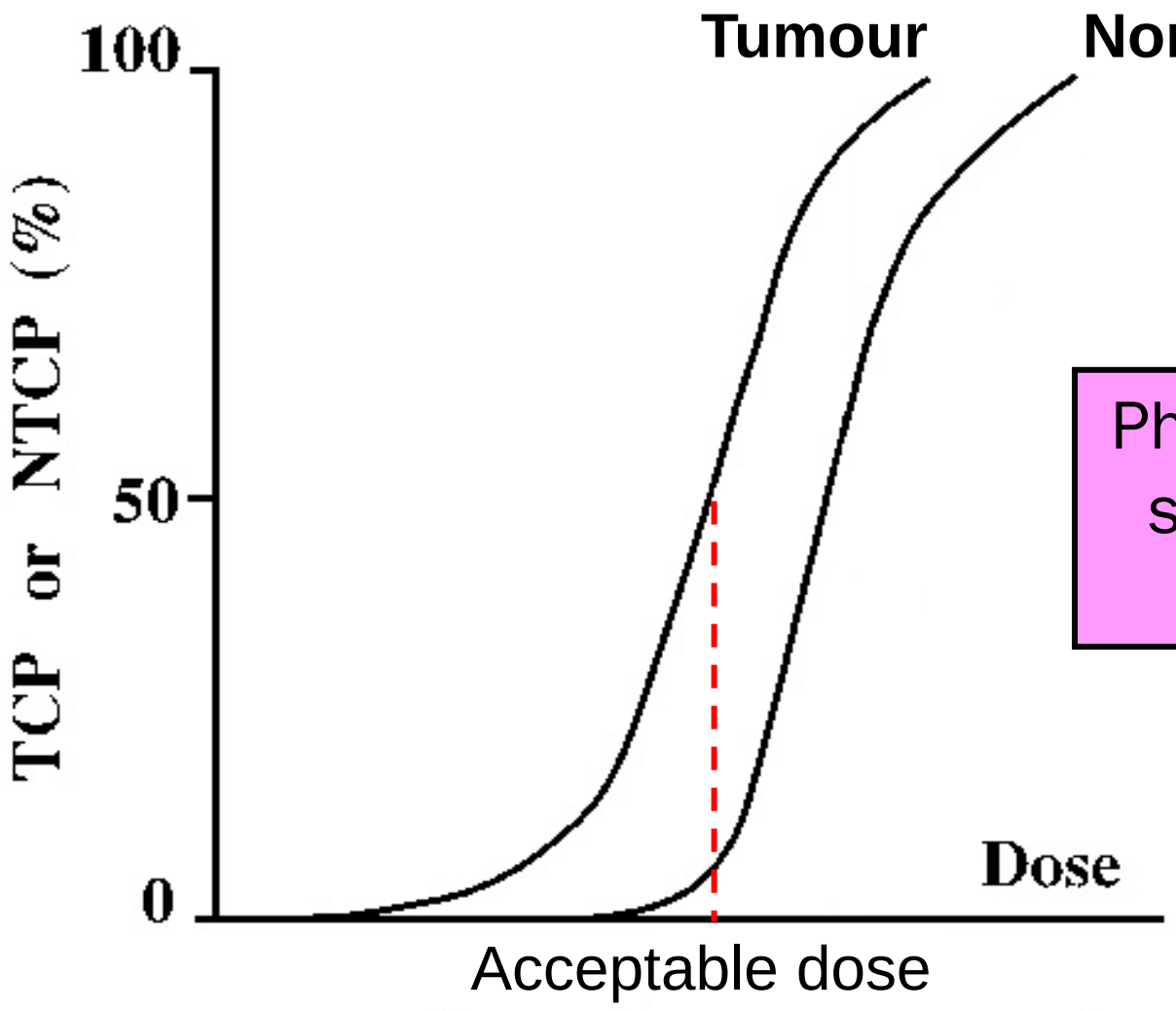
Broadening RT band width

- Local control will translate into overall cure in many patients
  - For breast –1 life saved for every 4 recurrences prevented

- Three variations on improved therapeutic ratio
  - Same cure, lower toxicity
  - Higher cure, same toxicity
  - Higher cure, lower toxicity (if we can !)

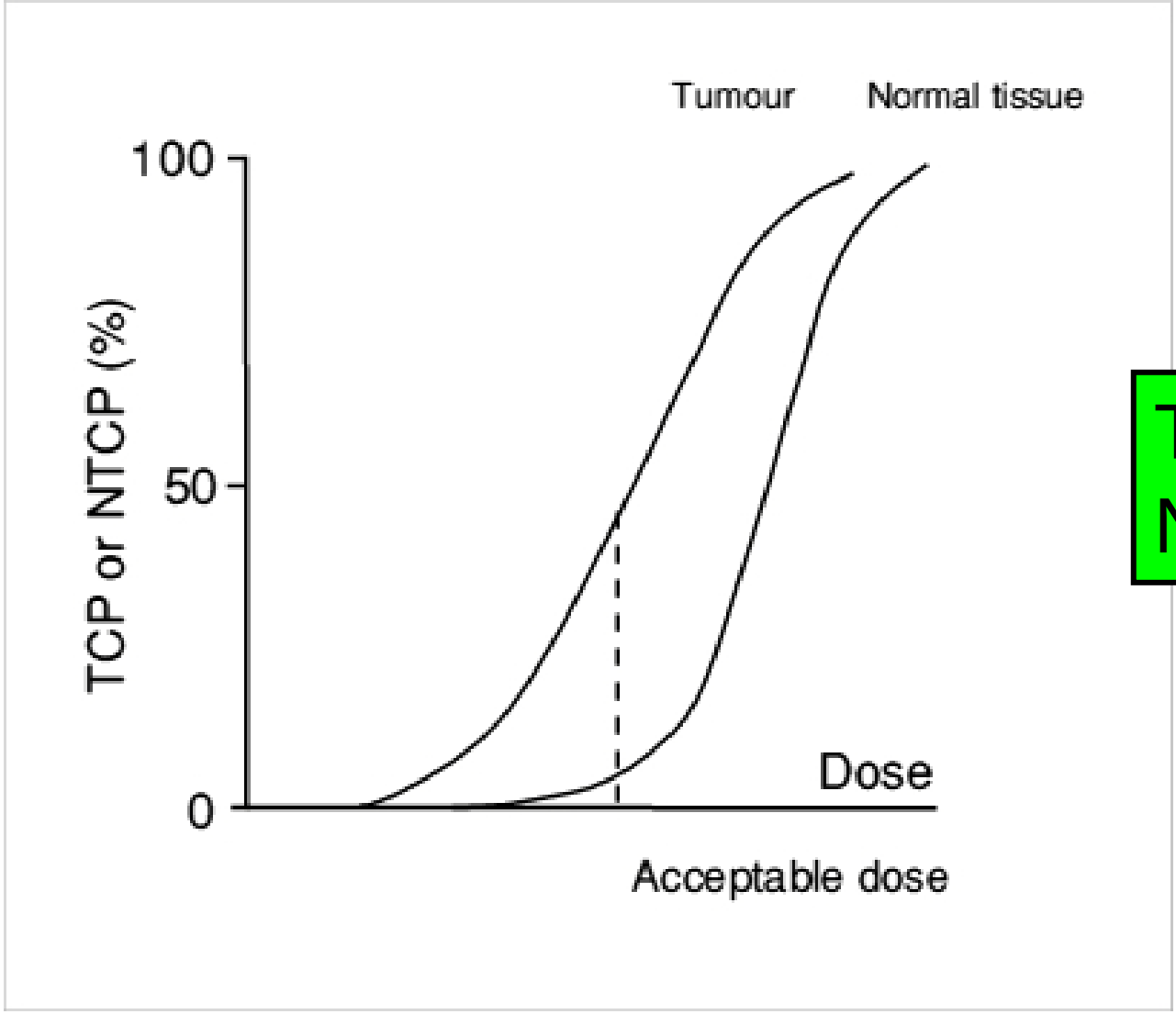
- Visually described by dose-response curves (population curves)

Increase the therapeutic ratio



Physical *and* biological strategies can move the curves apart

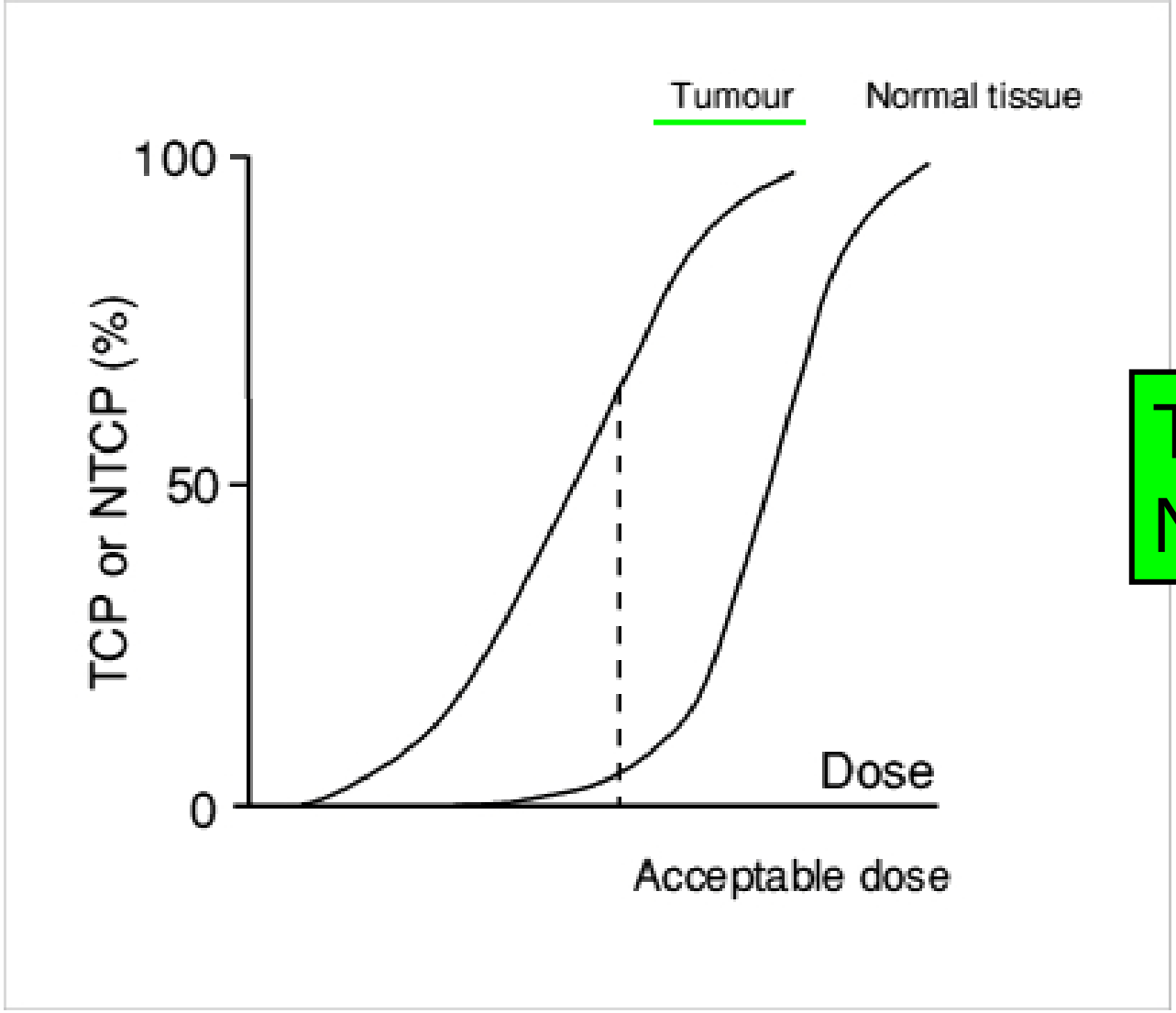
Increase the therapeutic ratio



TCP 50%
NTCP 5%

(a)

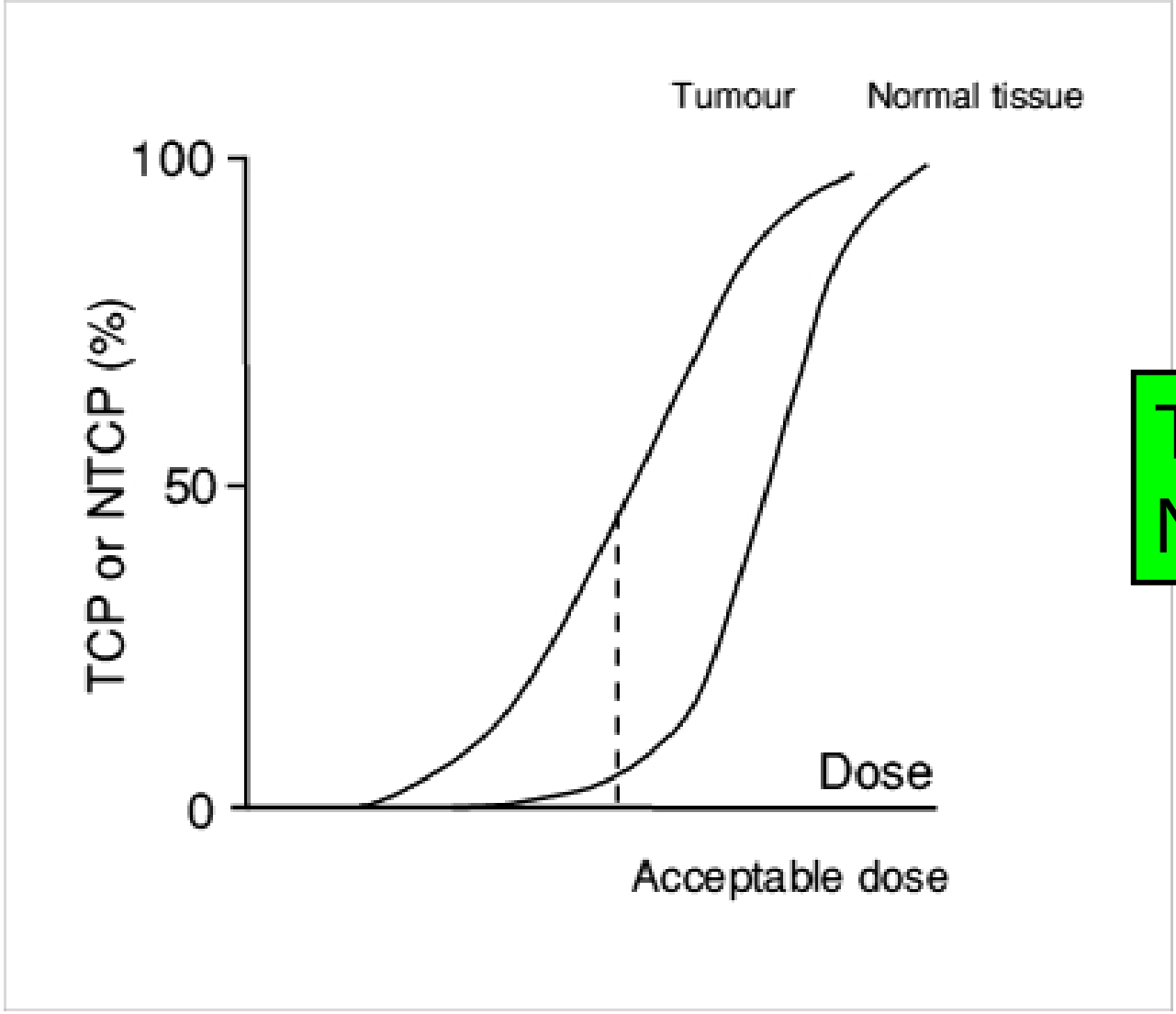
Increase the therapeutic ratio



TCP 70%
NTCP 5%

(b)

Increase the therapeutic ratio



TCP 50%
NTCP 5%

(a)

Back to the beginning

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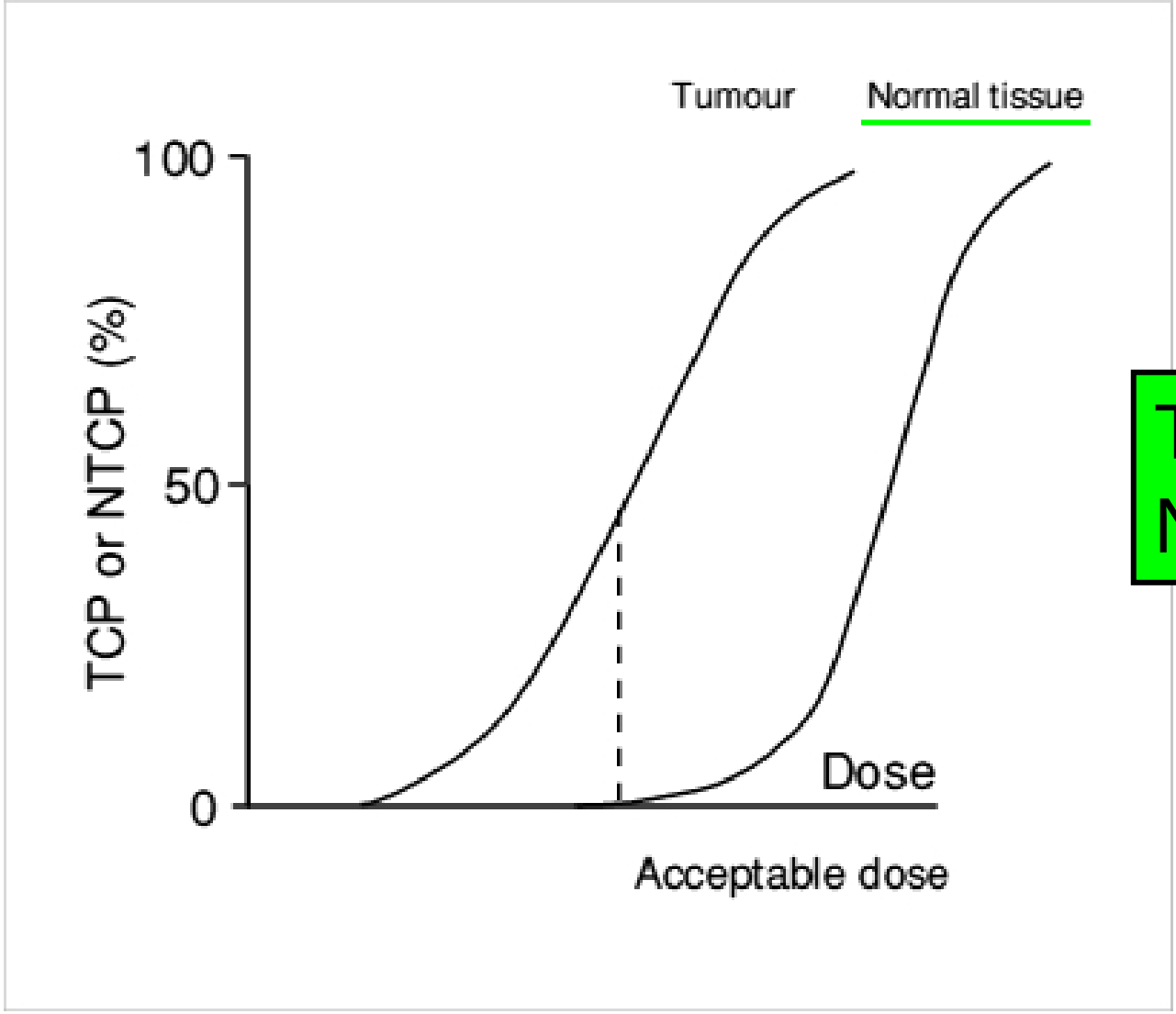
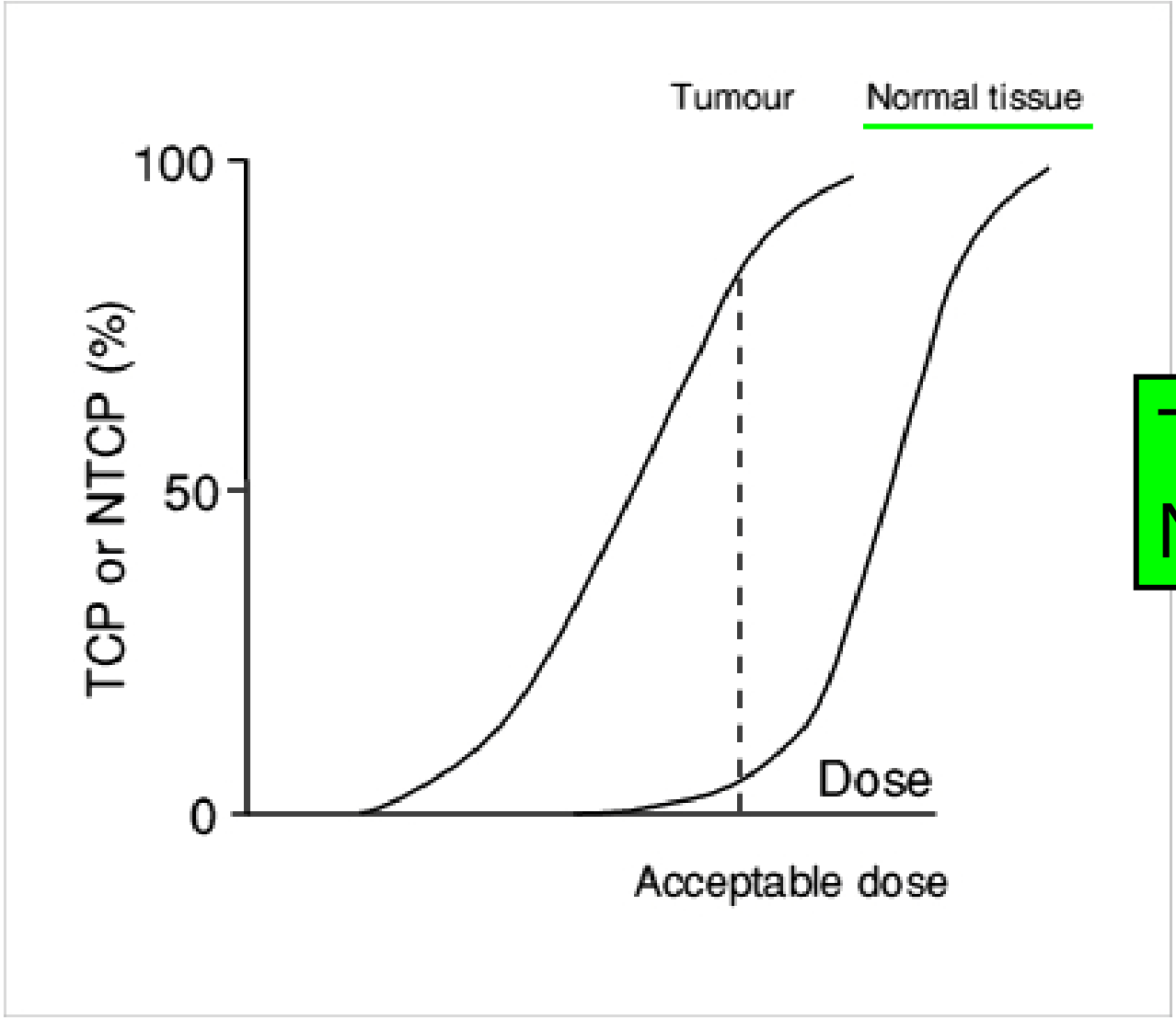
Increase the therapeutic ratio



TCP 50%
NTCP ~0%

(c)

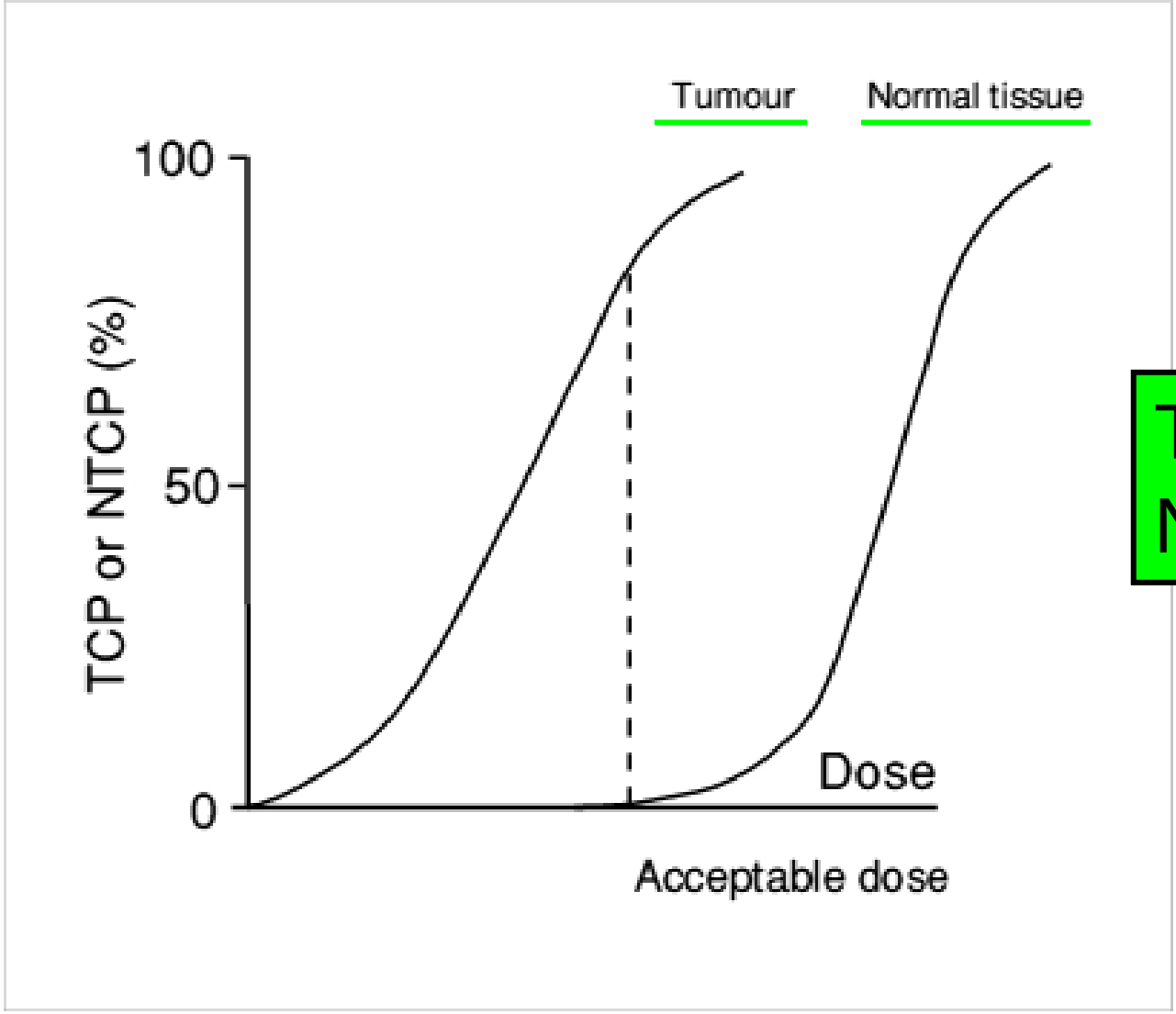
Increase the therapeutic ratio



TCP 80%
NTCP 5%

(d)

Increase the therapeutic ratio



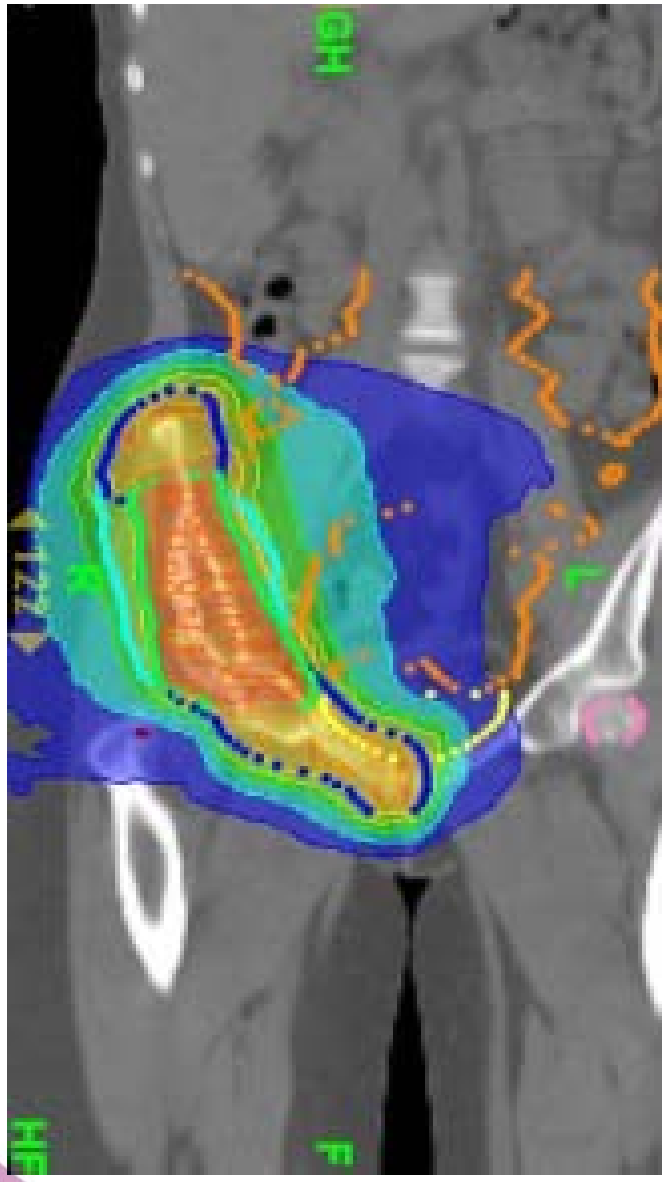
TCP 80%
NTCP ~0%

(e)

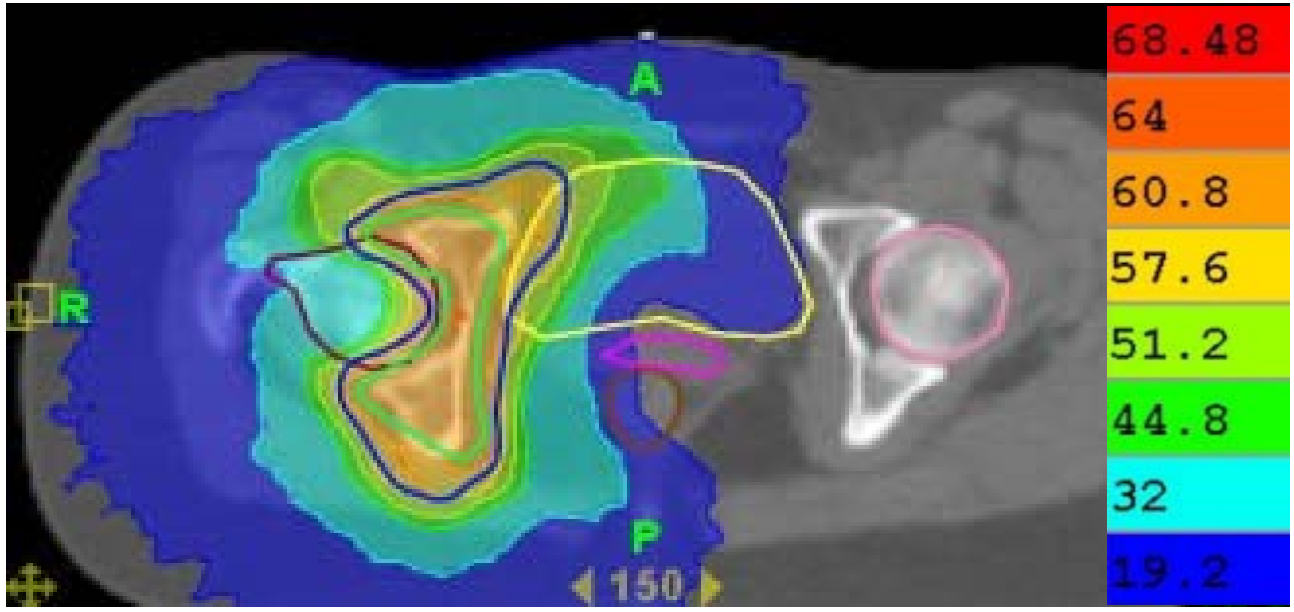
Normal tissue toxicities

- Toxicity largely relates to **late normal tissue effects**
  - Tissue specific
- Some **acute toxicities** also important
  - Especially applies to concurrent chemo-RT
- **Very late effects** of second malignancy
  - Difficult to estimate reliably
  - For IMRT, need to balance risk from larger irradiated volume against lower risk of organ damage
  - Role for PBT in children

Pelvic Ewing's sarcoma



- Age 15. Female. Dose 64/60 Gy
- Sparing of central pelvic organs
  - Reduced acute & late toxicities



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Normal tissue response

- Toxicity is related to dose
- Volume effect seen in many tissues/organs
- Tissue architecture also relevant
  - Serial organs - eg ...
  - Parallel organs - eg ...

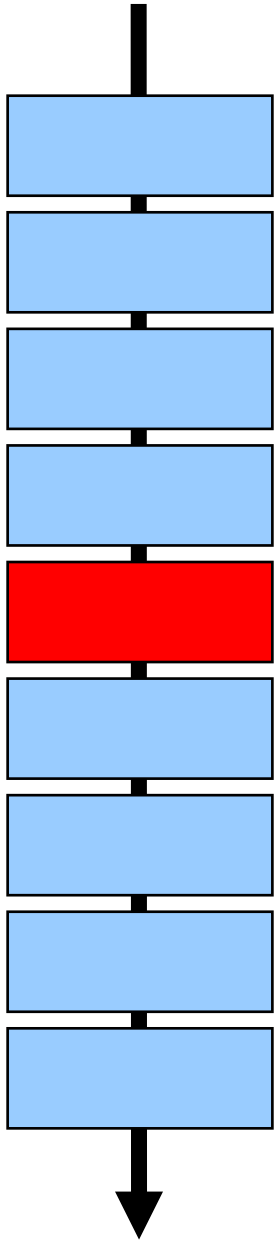
Normal tissue response

- Serial organ

- Damage to 1 part causes failure
- Serious clinical consequence

- High dose most important

- For example ... ?



Normal tissue response

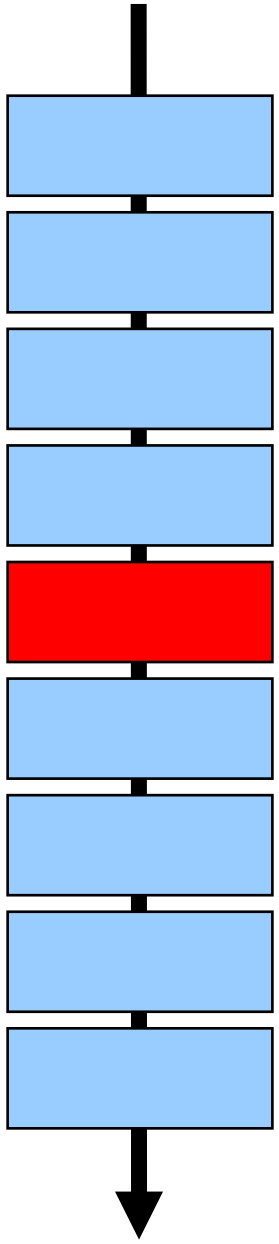
- Serial organ

- Damage to 1 part causes failure
- Serious clinical consequence

- High dose most important

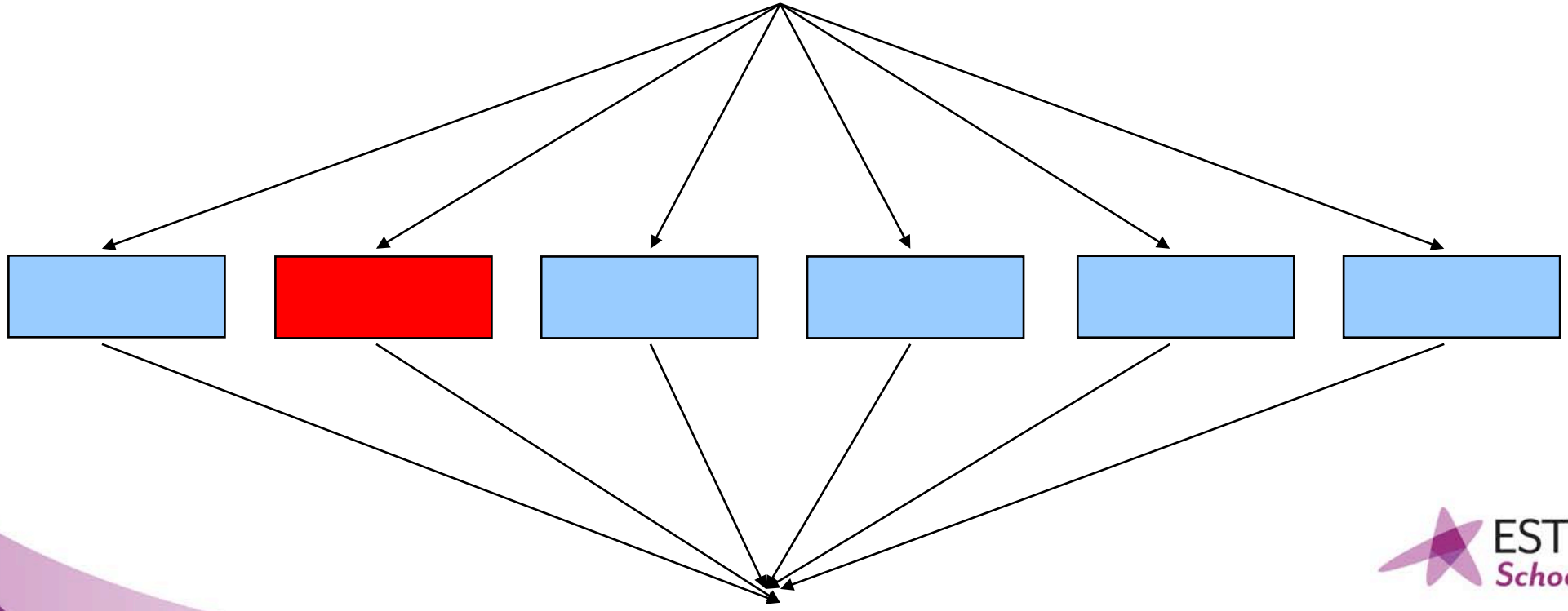
- For example ...

... spinal cord



Normal tissue response

- Parallel organ
- Damage to 1 part does not compromise function
- Low dose (and volume) usually most important
- For example ... ?



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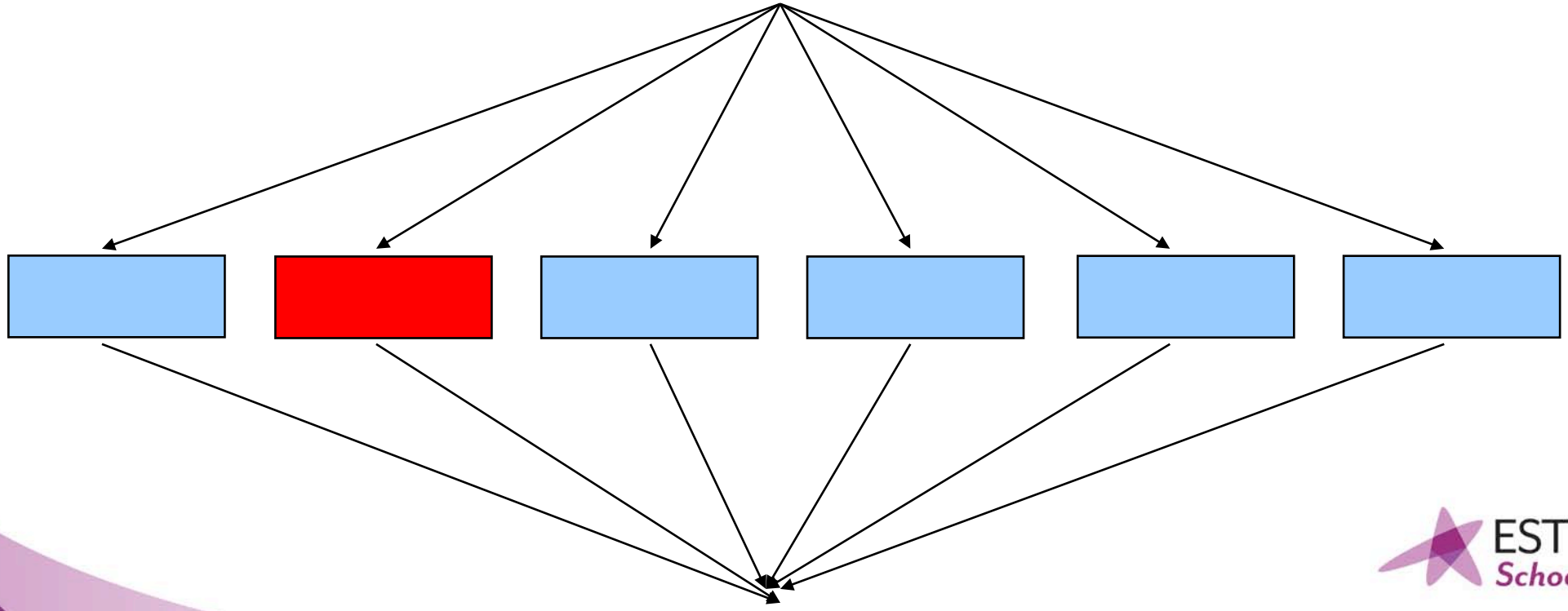
Normal tissue response

- Parallel organ
- Damage to 1 part does not compromise function
- Low dose (and volume) usually most important
- For example ...

... lung, liver, salivary glands, skin ...



Normal tissue response

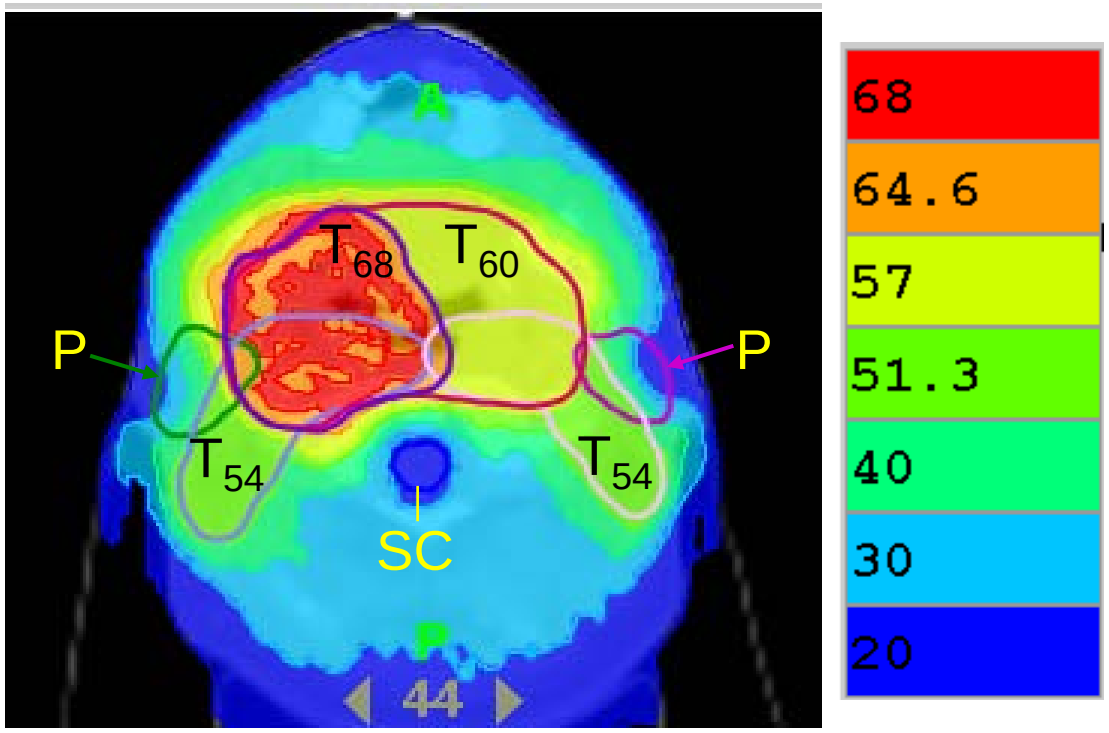
- Volume and architecture important

- If medium dose destroys function, then:
  - Must irradiate only small volume
  - No penalty from higher dose

- If high dose destroys function, then:
  - Avoid high dose
  - Can accept larger volume of irradiation

Broadening the band width

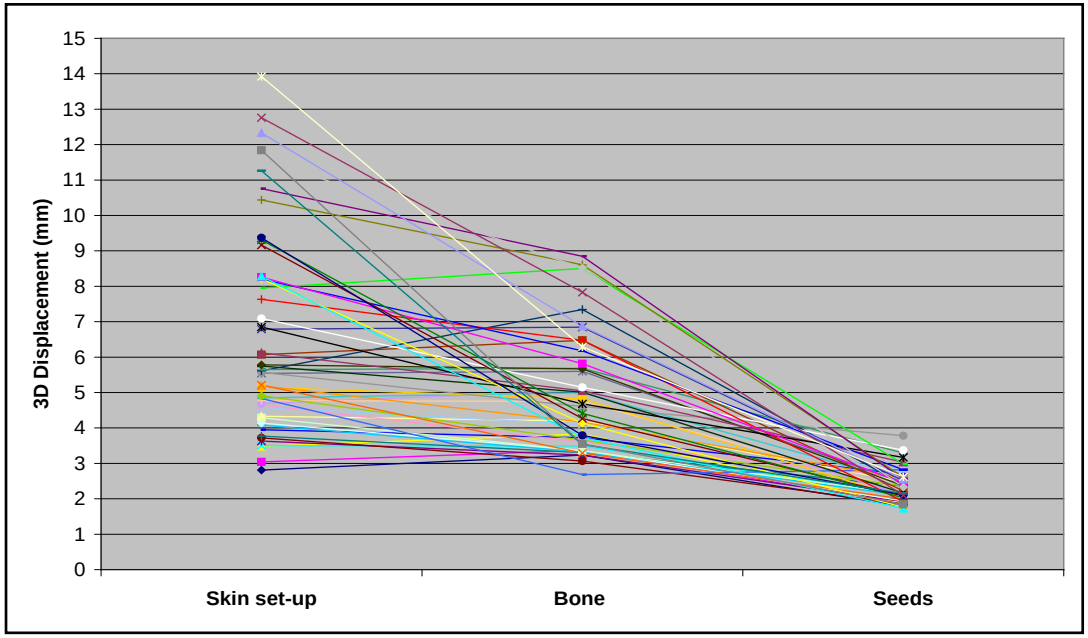
- IMRT for Head and neck cancer
- Sparing parotids reduces toxicity ¶
- Restricting dose to spinal cord allows high dose



¶ Nutting et al Lancet Oncol. 2011; 12(2): 127-36

Image guidance

- Patients position less well than we think
- IGRT allows more accurate delivery of dose
  - ➢ Deliver the dose to where you planned
  - ➢ ? Reduce PTV margins (don't over-reduce)
  - ➢ If no reduction of margin, delivers dose more precisely to target and (probably) normal tissue
  - ➢ Especially important with steep dose gradients



- ➢ Prostate
- ➢ Skin set up
- ➢ Pelvic bone EPID
- ➢ Seed IGRT
- ➢ (Dr Yvonne Rimmer)

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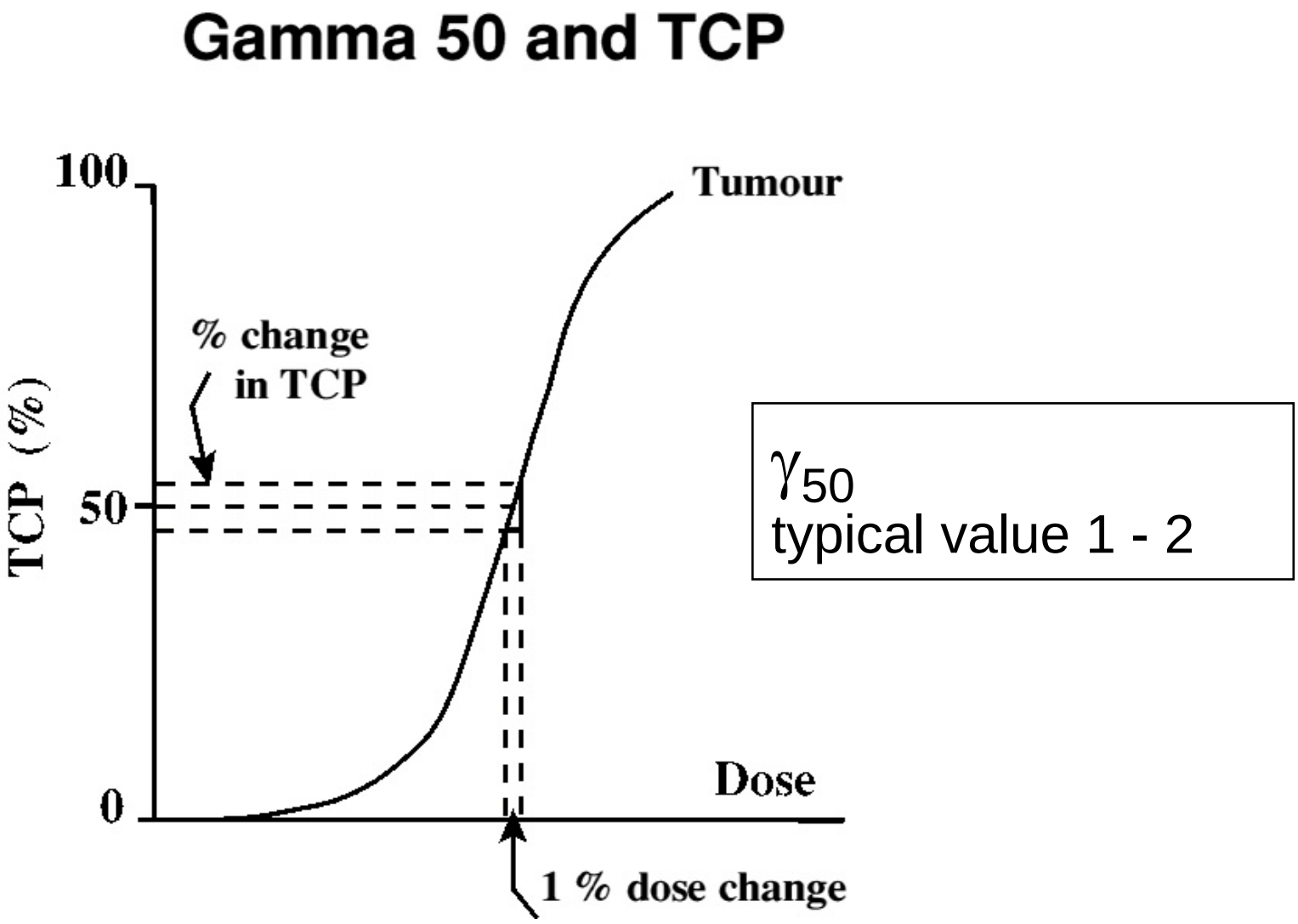
Broadening the band width

- Dose response curves are ***steep*** for both tumour and normal tissue

- Therefore a ***small*** dose difference can produce a ***large*** difference in outcome

- This applies to
  - individual patients
  - populations

Broadening the band width



γ_{50}
typical value 1 - 2

Broadening the band width

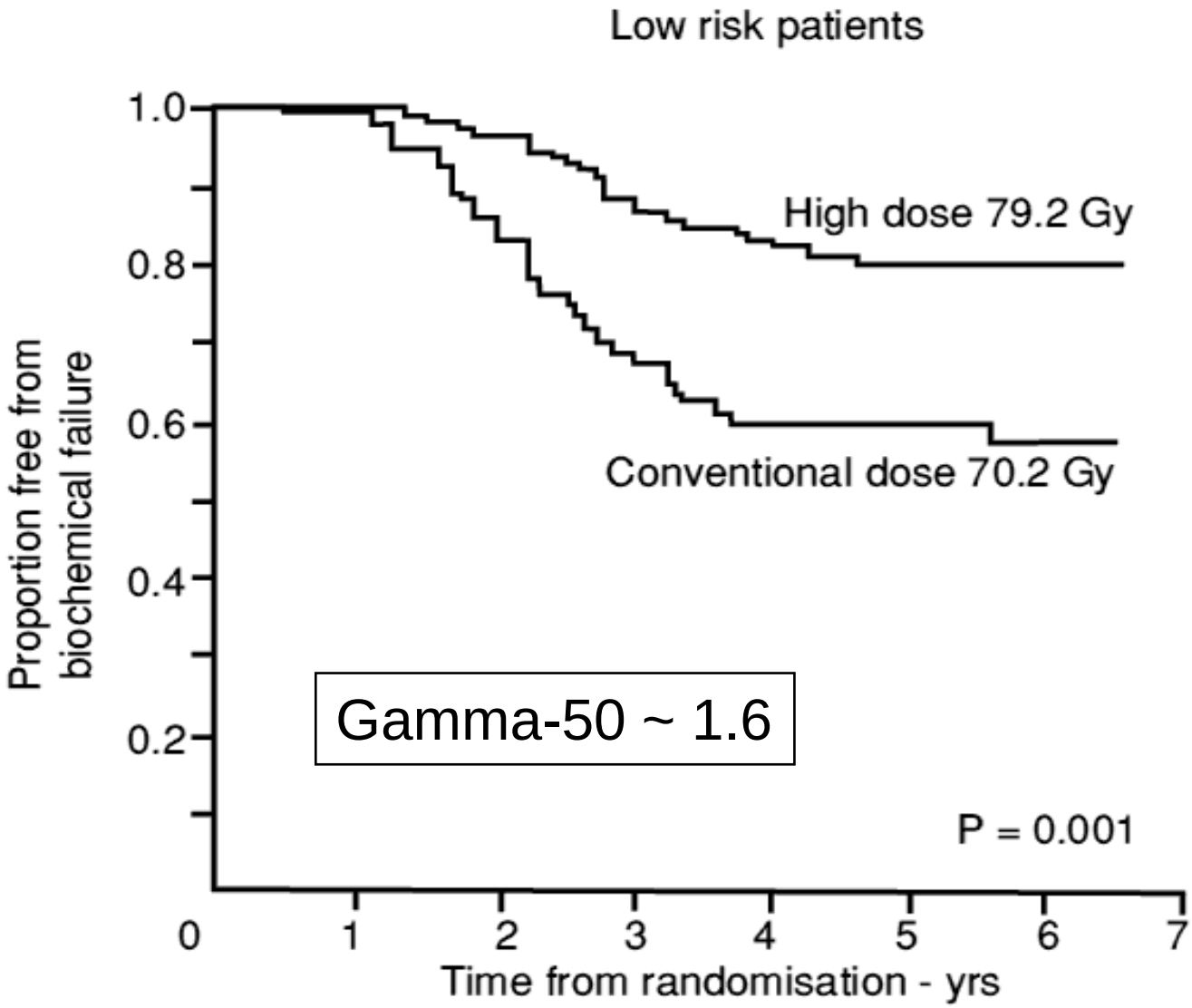
- A 5% dose increase will achieve a 5 – 10% improvement in tumour control
- Toxicity – normal tissue complications – show the same effect
- Small steps of improvement are very worthwhile
- Attention to detail will pay dividends

Broadening the band width

- Prostate cancer, randomised trial
- 70.2 : 79.2 Gy
- 12% dose diff

- Zietman et al
- JAMA 2005; 294(10): 1233-9

- (Used protons in both arms)



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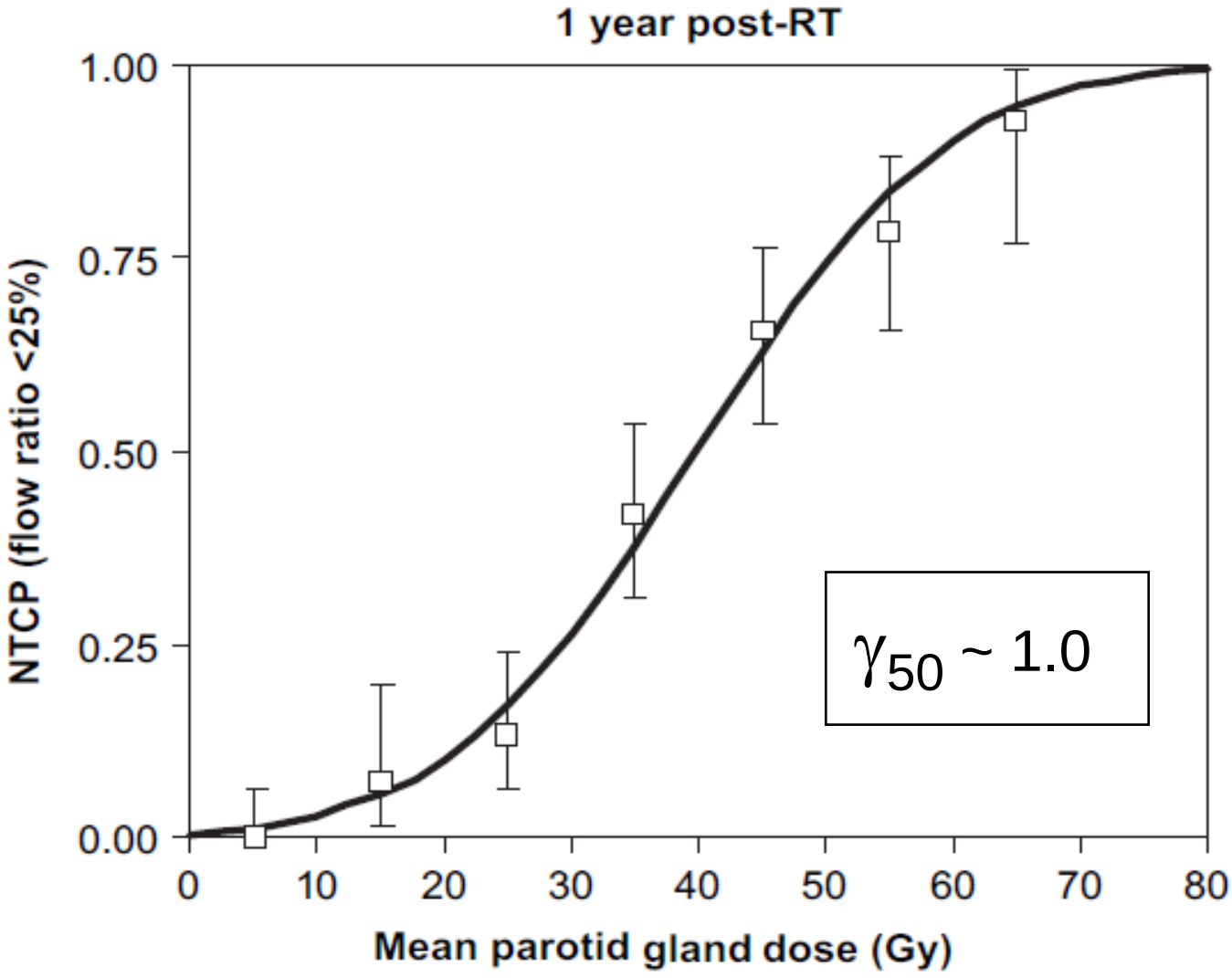
Broadening the band width

Parotid toxicity



Dijkema et al IJROBP 2010; 78(2): 449-453

Combined Michigan & Utrecht data

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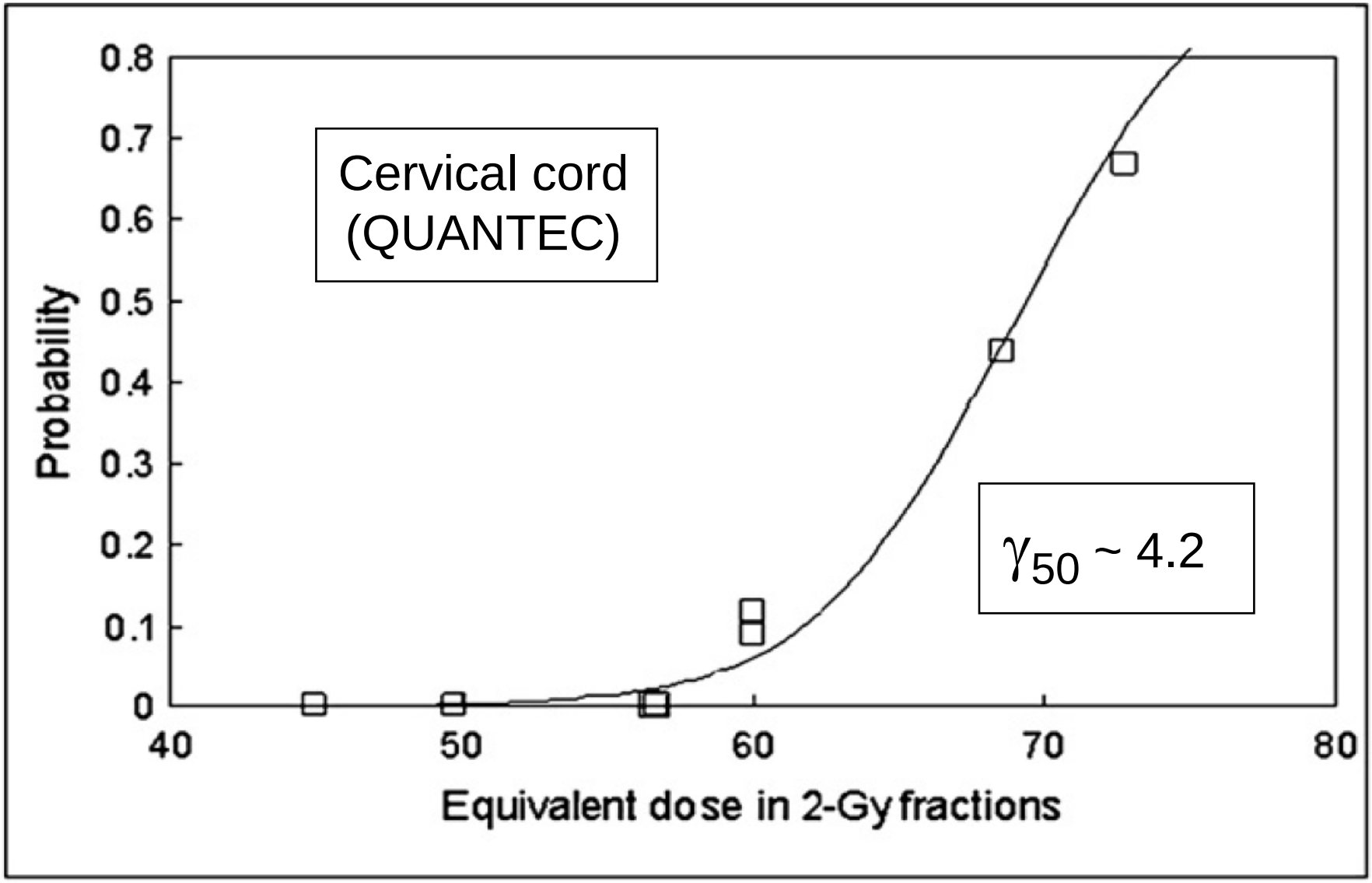
Broadening the band width



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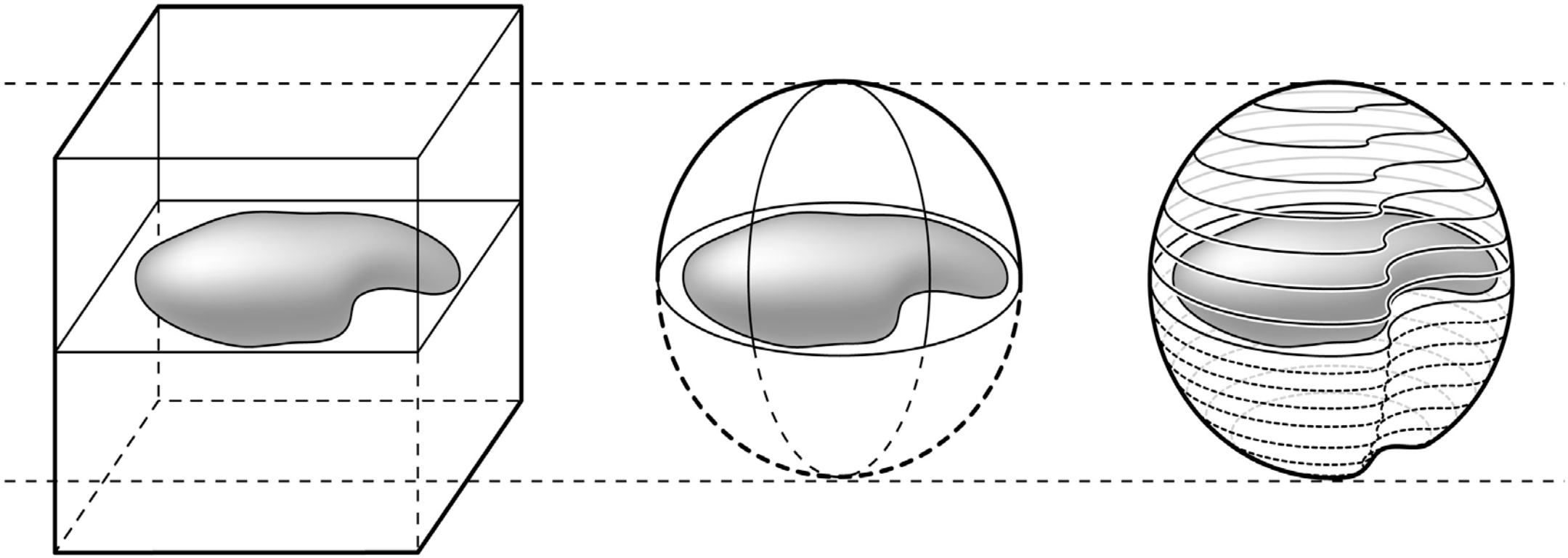
Treatment volumes compared



Conventional ‘square’ plan

3D CRT plan

IMRT plan

Use the best equipment you can!

- Old equipment
- Poor maintenance
- Bad choice!

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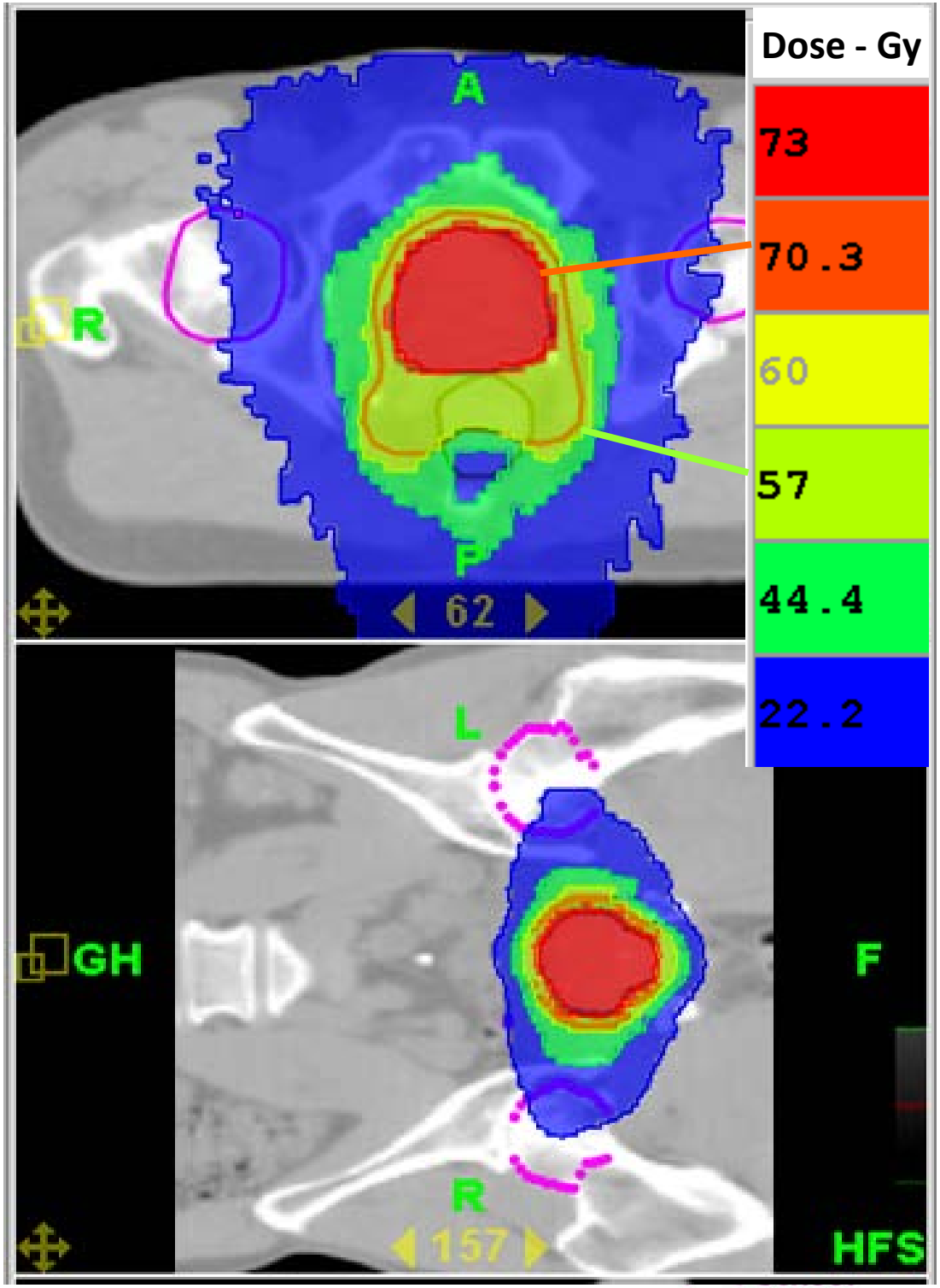
Ca prostate

- Ca prostate

- 74 Gy to primary (37#)
- 60 Gy to seminal vesicles

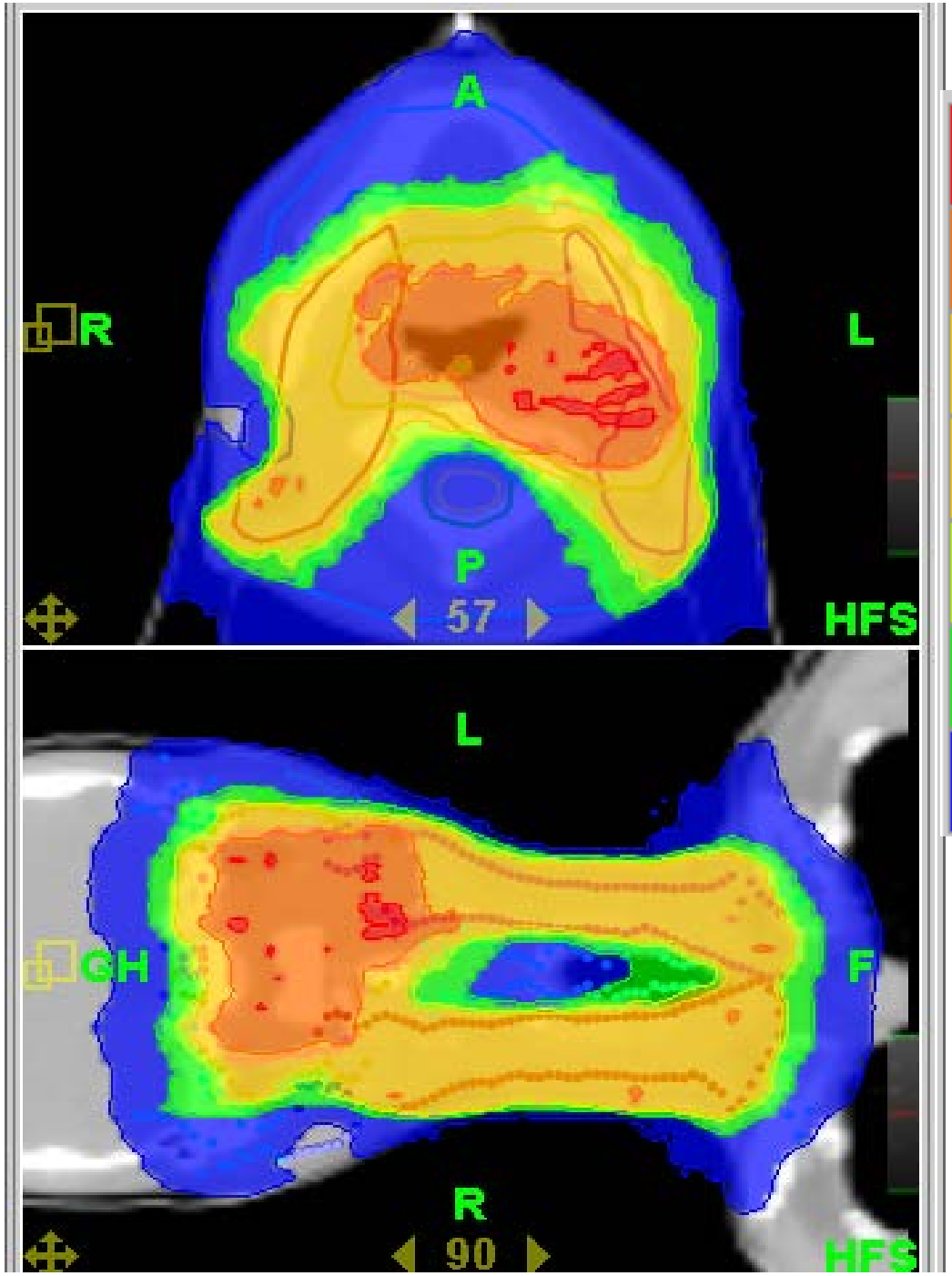
- Rectal sparing behind PTV



Ca nasopharynx

- 68 Gy to primary (34#)
- 60 Gy to nodes

- Cord dose < 45 Gy
- *No* field junctions
- *No* electrons



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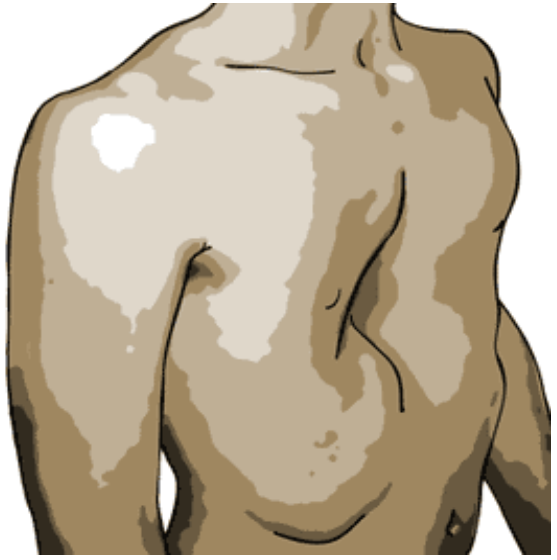
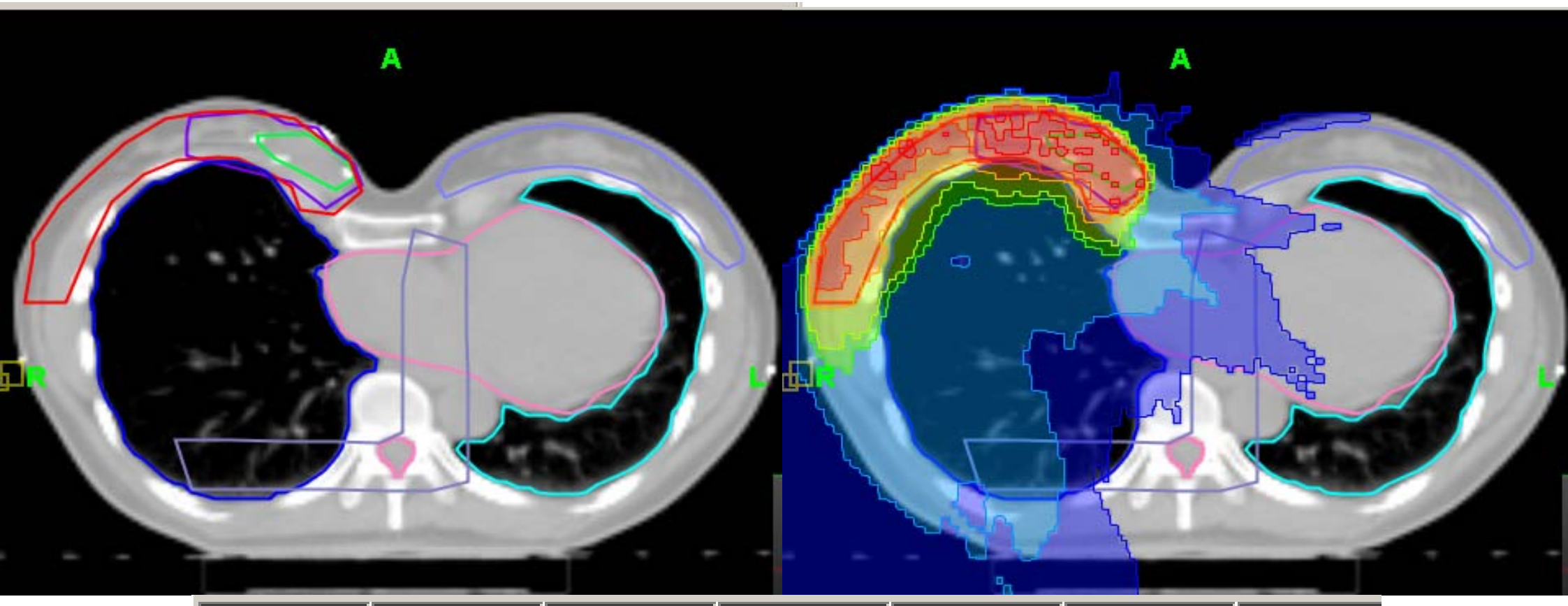
Ca breast

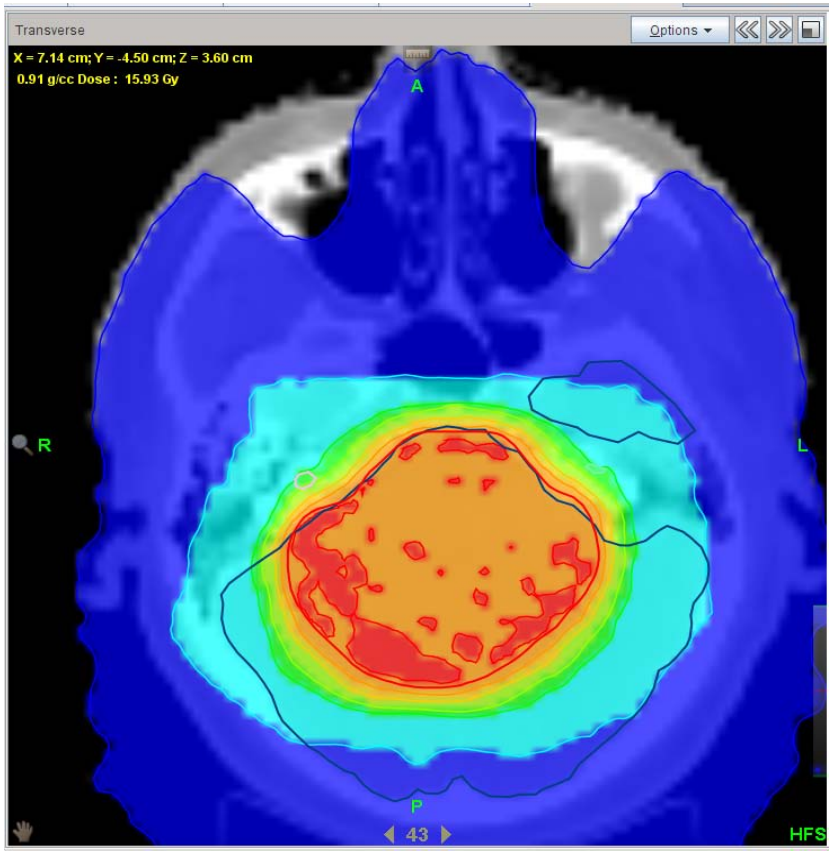
- Ca breast
- Pectus excavatum
- 40 Gy / 15 #

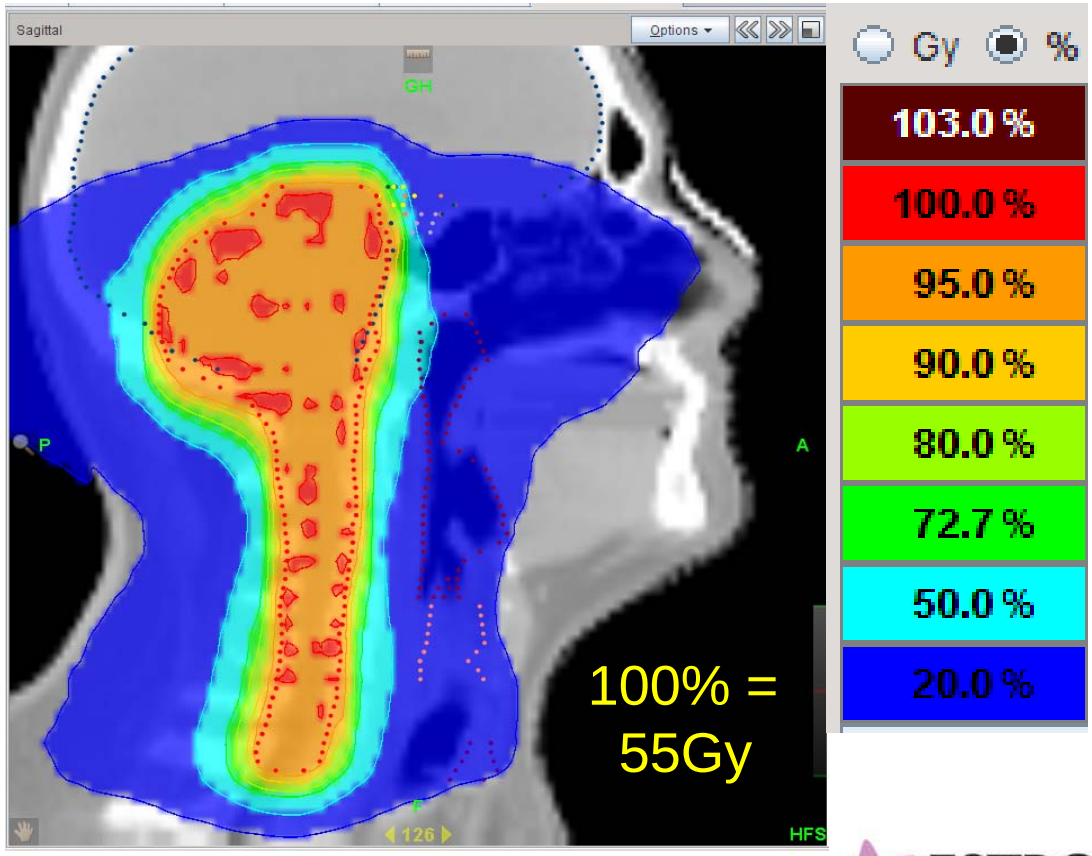




Brainstem + upper cord glioma

- Low grade glioma (clinical and radiological diagnosis)
- Huge volume, variable body contour
- 55 Gy / 33 #





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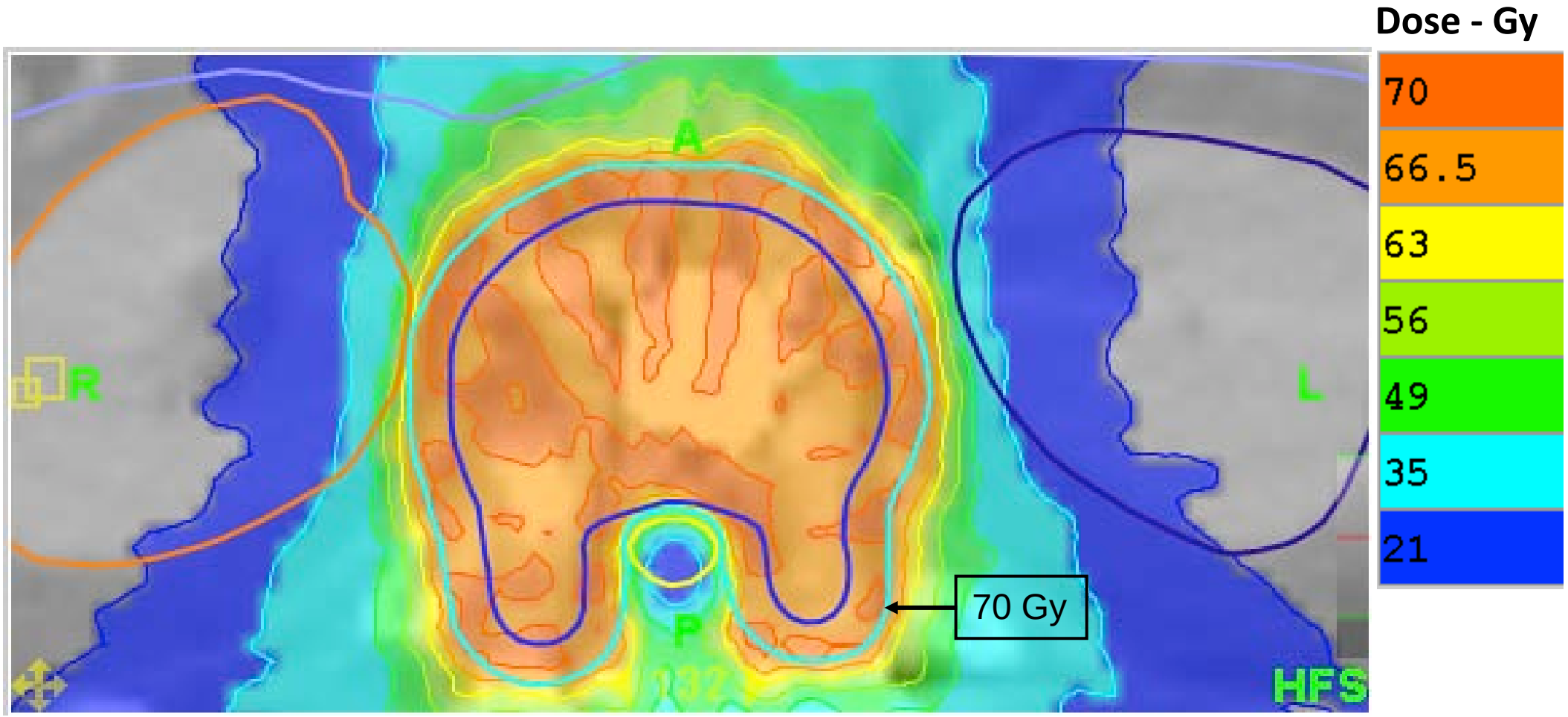
IMRT for chordoma



CTV

PTV-PRV

PRV cord

70 Gy / 39#

(+ IGRT)

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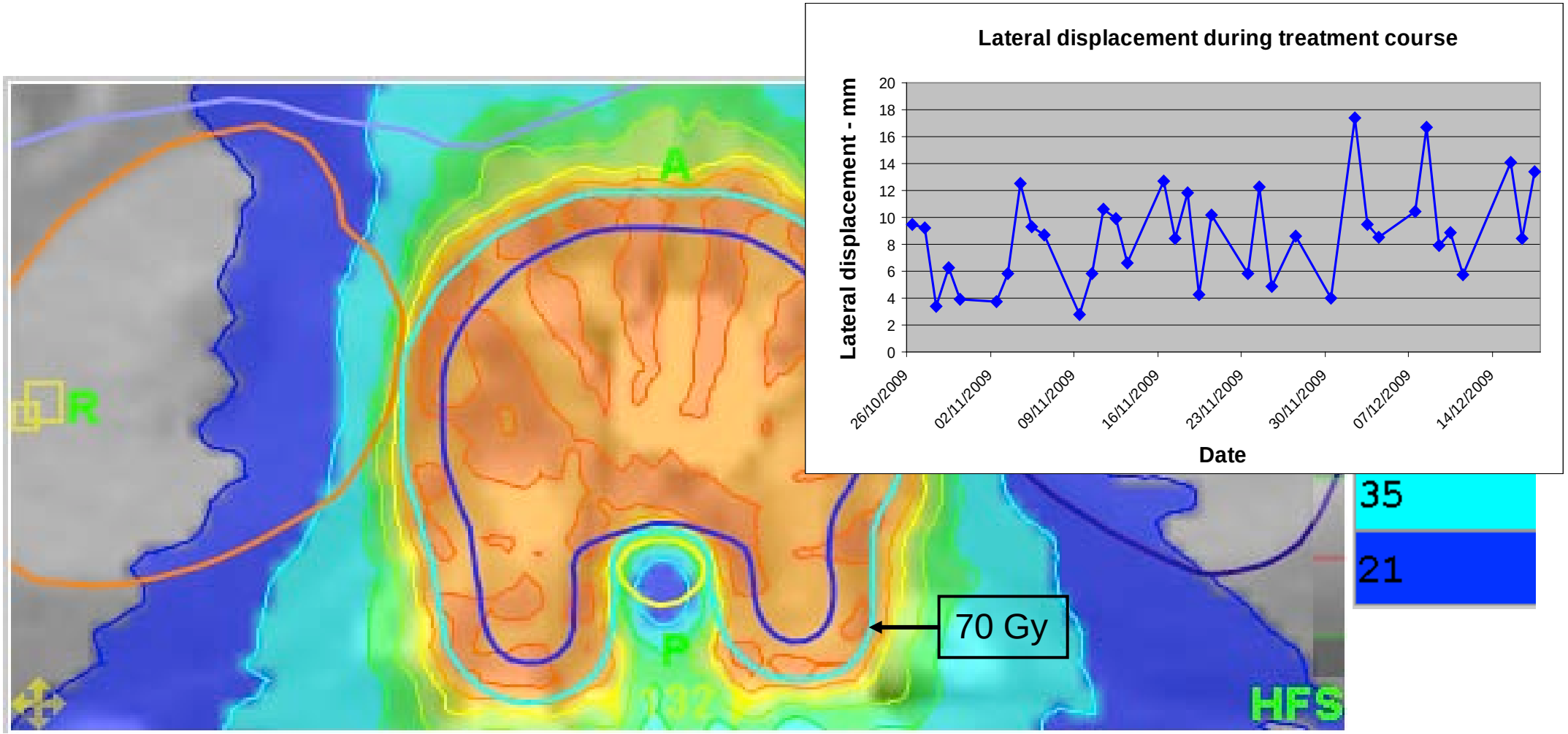
IMRT for chordoma



CTV

PTV-PRV

PRV cord

70 Gy / 39#

(+ IGRT)

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Bandwidth

- Advanced technology is for patient benefit
- Tumour control with minimal toxicity

Conclusions

- Small steps of dose improvement are worthwhile
- Increasing radiotherapy band width requires modern treatment approaches
- Attention to detail translates into clinical advantage for patients
- Lots more to do ...

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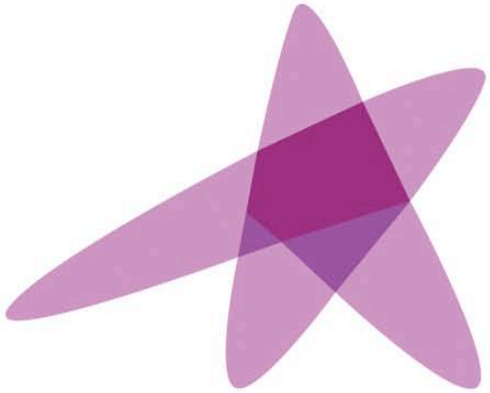

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Dose calculation algorithms & their differrences in clinical impact

Advanced Treatment Planning Course
14-18 September 2016 – Cambridge, UK

Markus Stock
(slide courtesy Michael Sharpe, Dietmar Georg)

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MedAustron

Acknowledgements

- Michael Sharpe
- Dietmar Georg
- Marika Enmark
- Jake Van Dyk
- Jerry Battista
- Anders Ahnesjö

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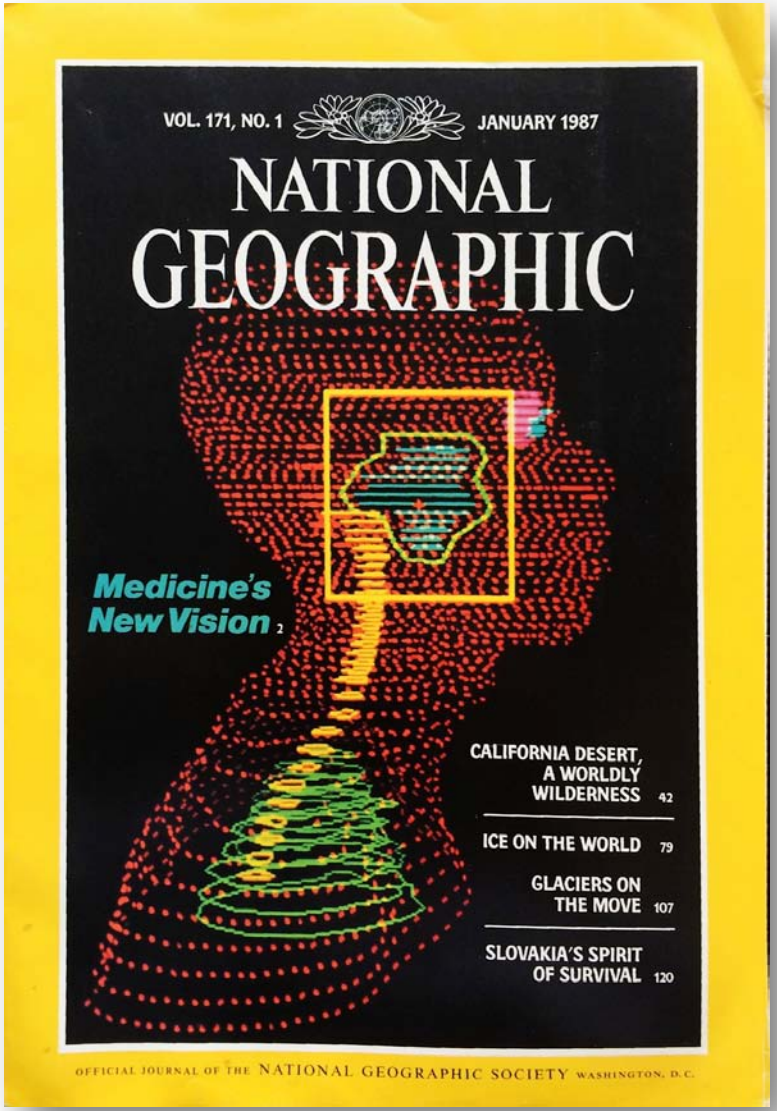
Computer-Aided Treatment Planning

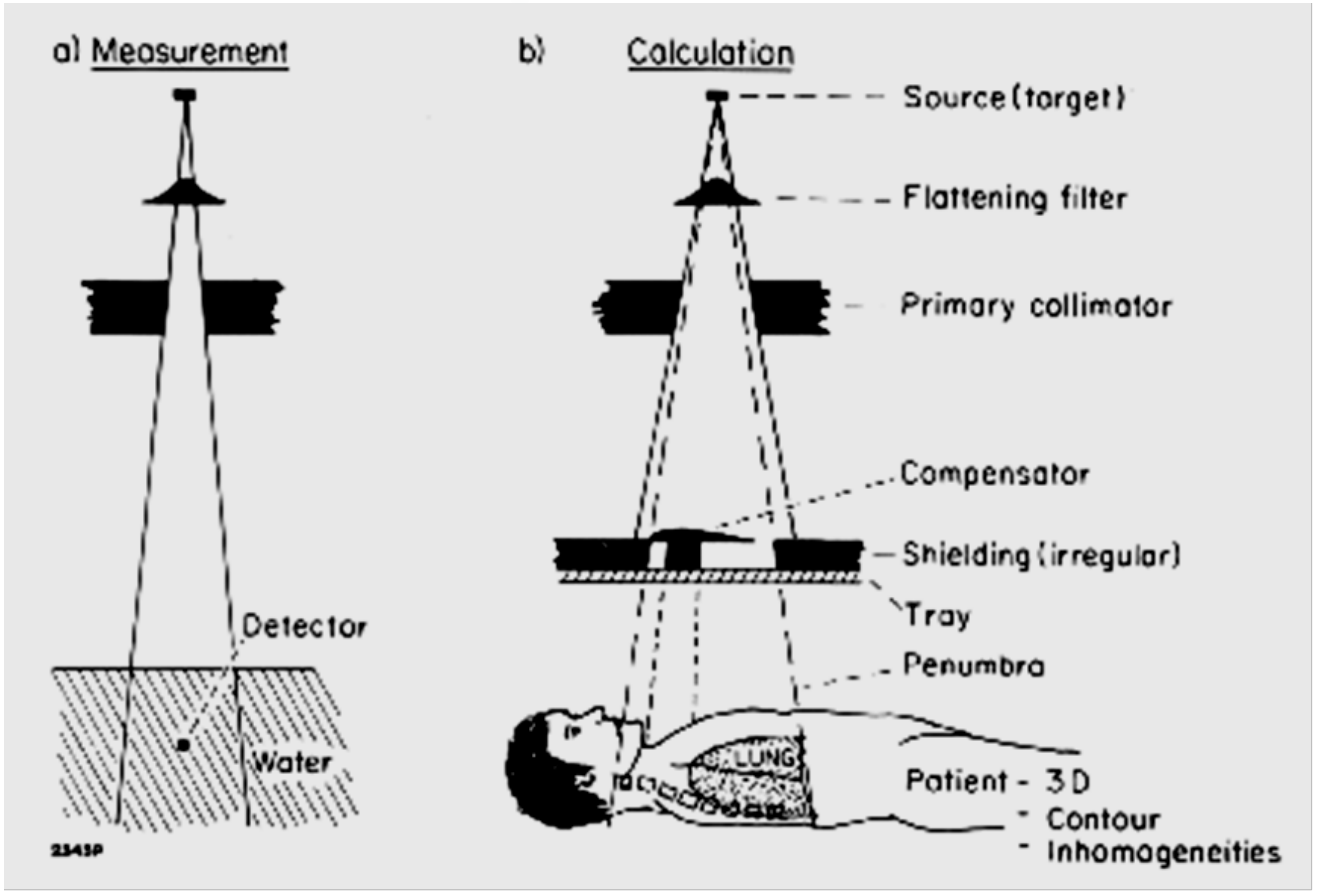
- Patient-specific
  - Delineation of disease
  - Treatment optimization
- Requirements:
  - Anatomical information
  - Simulate treatment approach
  - Estimate dose in vivo under all treatment conditions

- TPS has a long-established role in image interpretation, segmentation, beam placement and shaping.



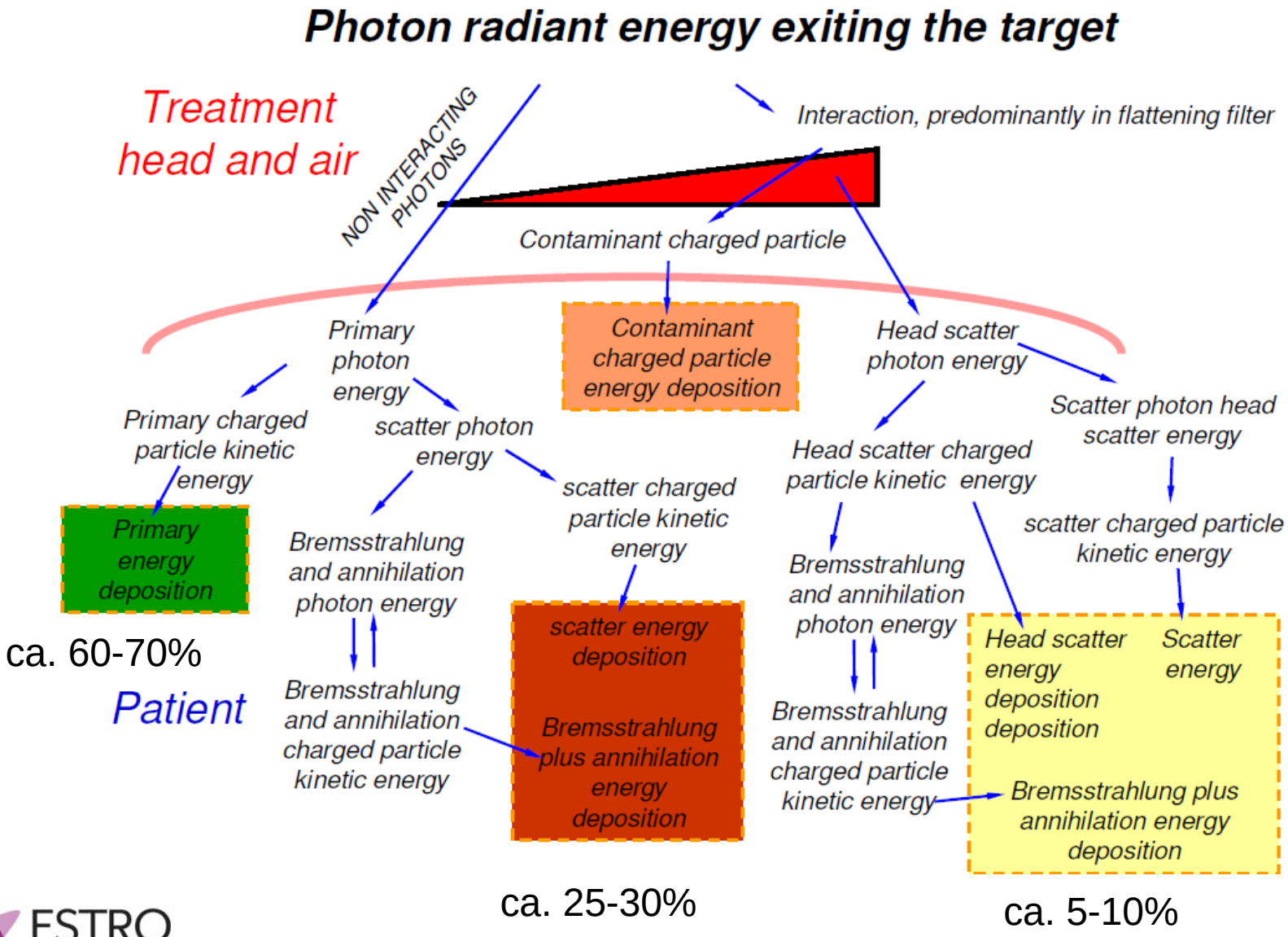
Dose Calculation Problem

Relate dose calculation in patient to beam calibration conditions



- Papanikolaou, et al- 2004 - AAPM Task Group 65

Complexity of dose calculation



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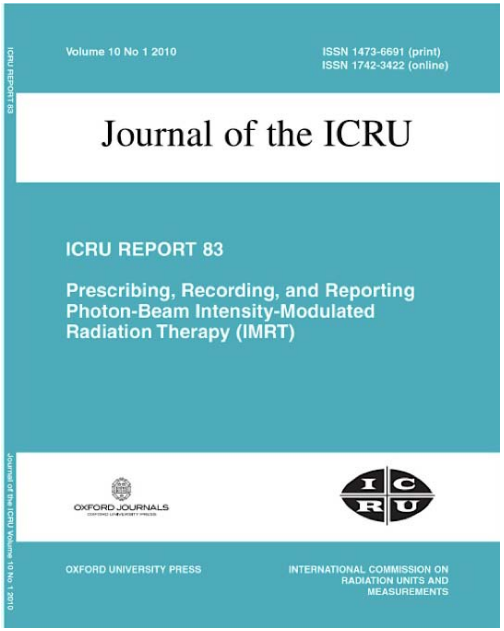
Expectations

- *More demanding treatment techniques require more accurate and predictive dose calculations.*

- ICRU 83 recommendation:
  - RTP systems must estimate absorbed dose accurately for:
    - Small fields
    - Tissue heterogeneities
    - Regions with disequilibrium
      - especially high energy photons



Dose Calculation Methods

Absolute Calibration in water

Relative Distribution in water

Tabulate & Interpolate	Model & fit parameters to emulate measurements
Reconstitute distribution in water by distance, depth, & field size	Compute dose directly from beam geometry & CT images
Apply correction factors (inhomogeneity, contour)	

"Correction" based methods ***"Model" based methods***

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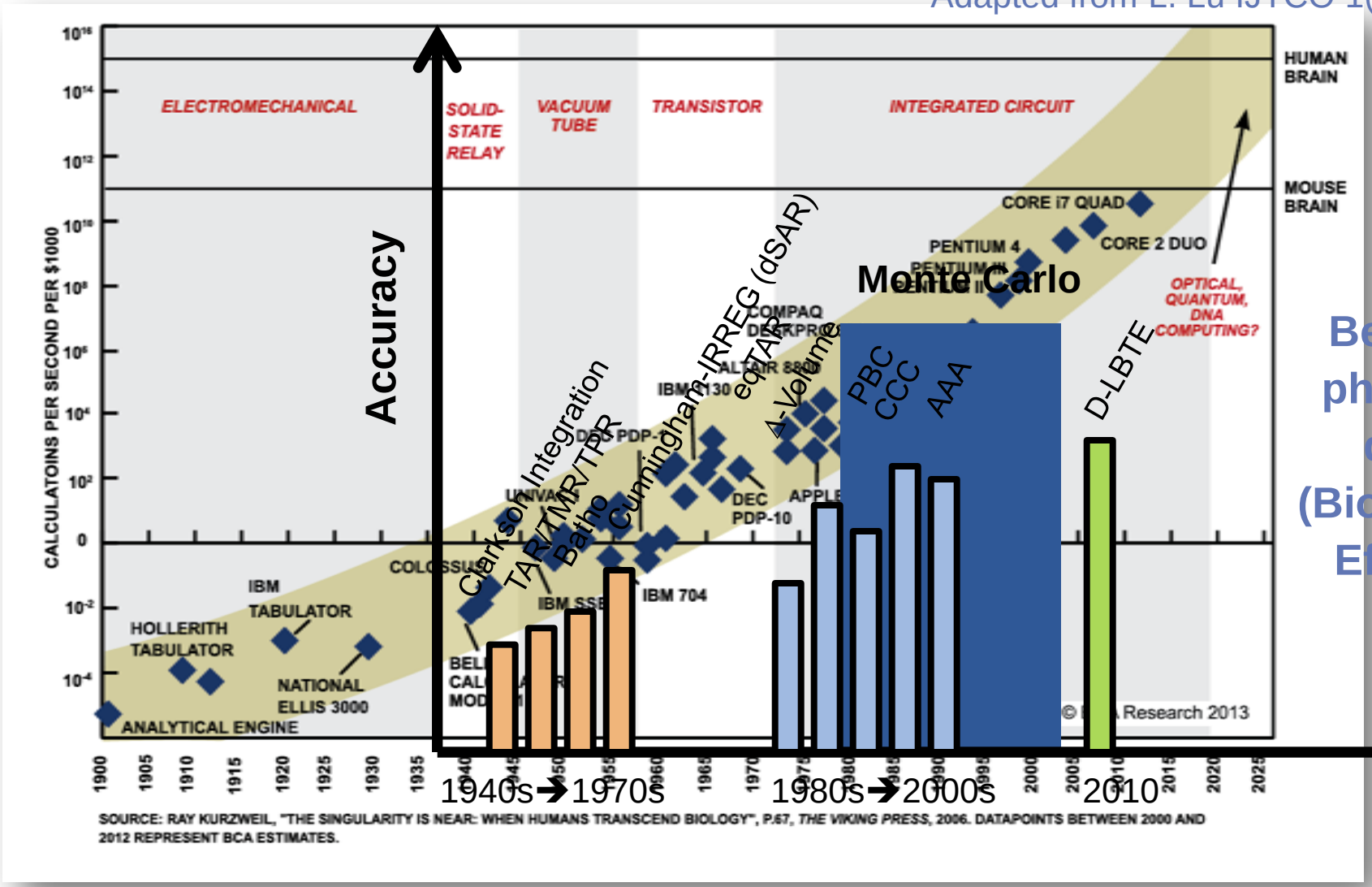
Evolution of Photon Beam Dose Algorithms

Adapted from L. Lu IJTCO 1(2) 1 (2013).



Beyond physical dose (Biological Effects)

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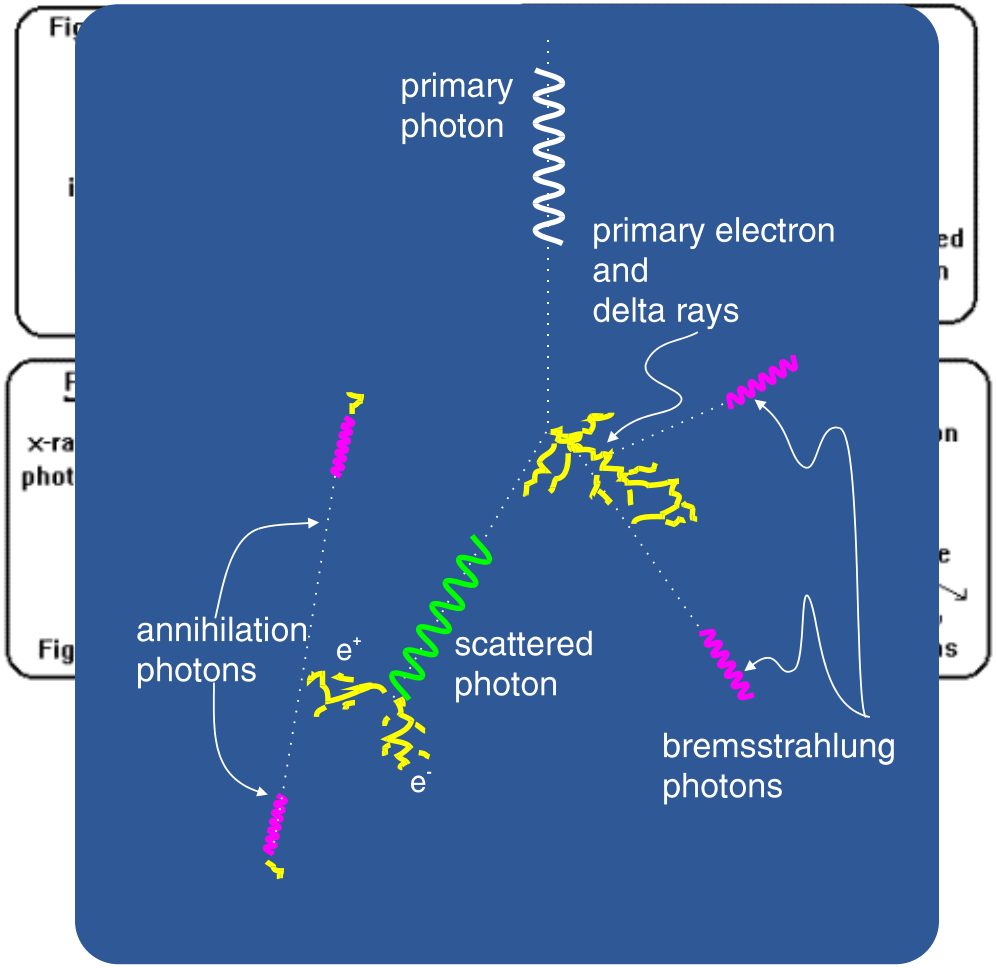
X-Rays: Energy Deposition in a Nutshell

- X rays are ionize *indirectly.*
- On interaction, energy is scattered or transferred to electrons, then absorbed.
- Biological effect depends on the amount of energy absorbed (*dose*).
- Tracking electrons is highly important for accurate dose calculations.
- One treatment (2Gy) requires ~$10^{8\text{-}9}$ incident x rays per mm^{2}.



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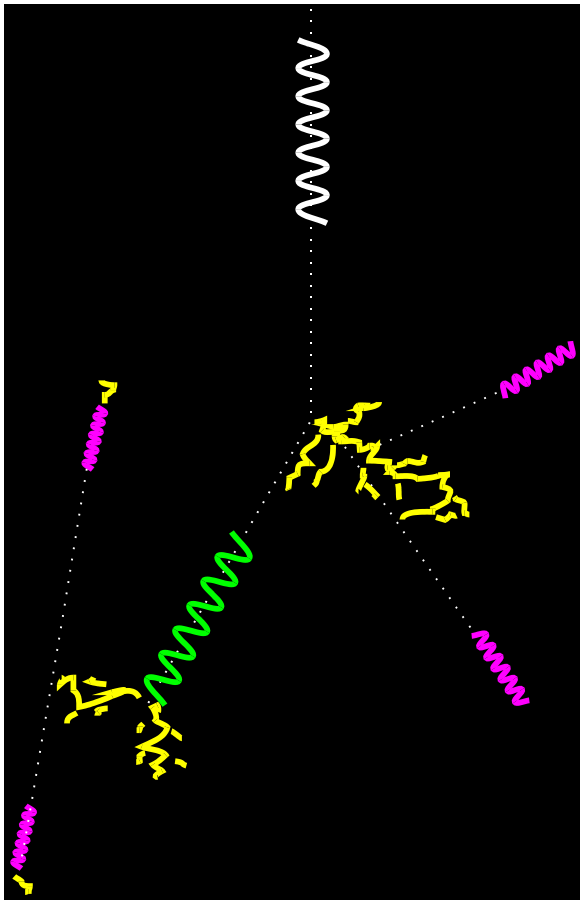
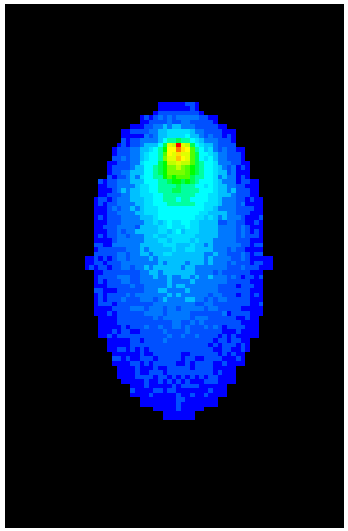
Dose Spread Kernel

- Mackie *et al*, PMB **33**(1) (1988).



Average energy deposition pattern (10^6 interacting photons)



One incident photon interacts at a point

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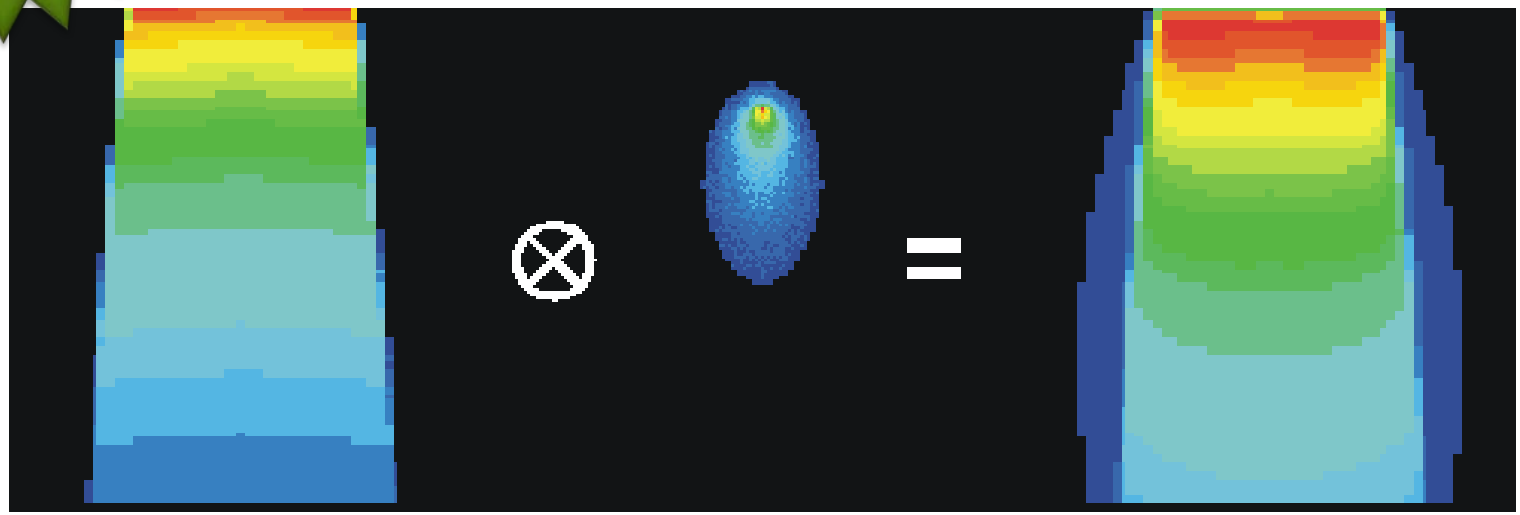
Method: Convolution/Superposition

$$D(\vec{r}) = \iiint \phi(\vec{r}')K_{3D}(\vec{r}', \vec{r})d^3r$$

Ideal Conditions Only



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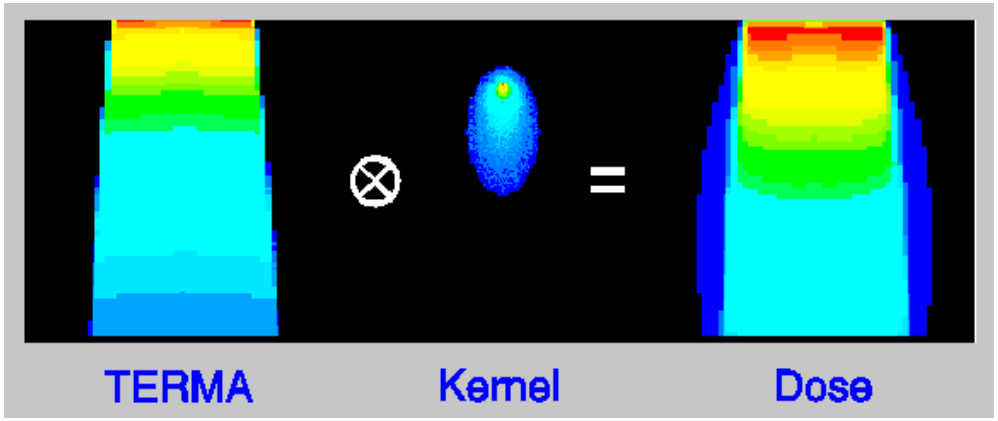
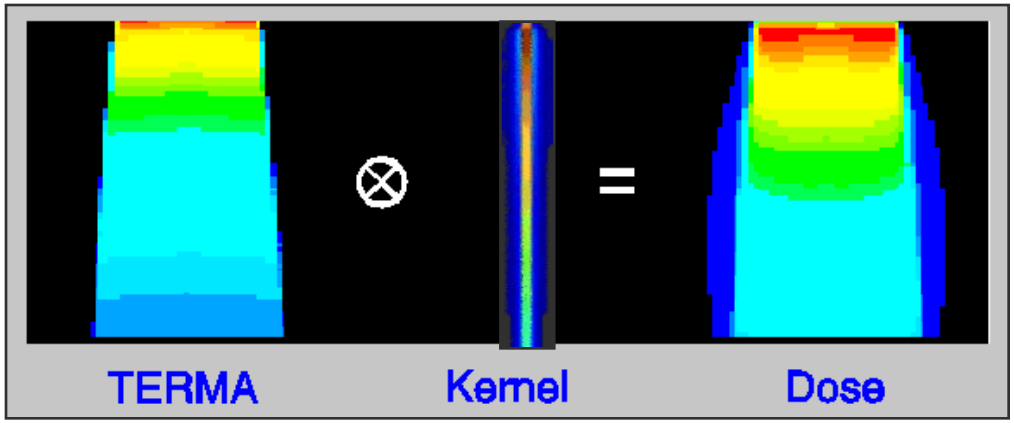
Convolution - Point Kernel

$$D(x,y,z) = \iiint \Phi(x',y',z')K(x-x',y-y',z-z')dxdydz$$



$$D(x,y,z) = \int\int \Phi(x',y',z)K_z(x-x',y-y')\,dx\,dy$$



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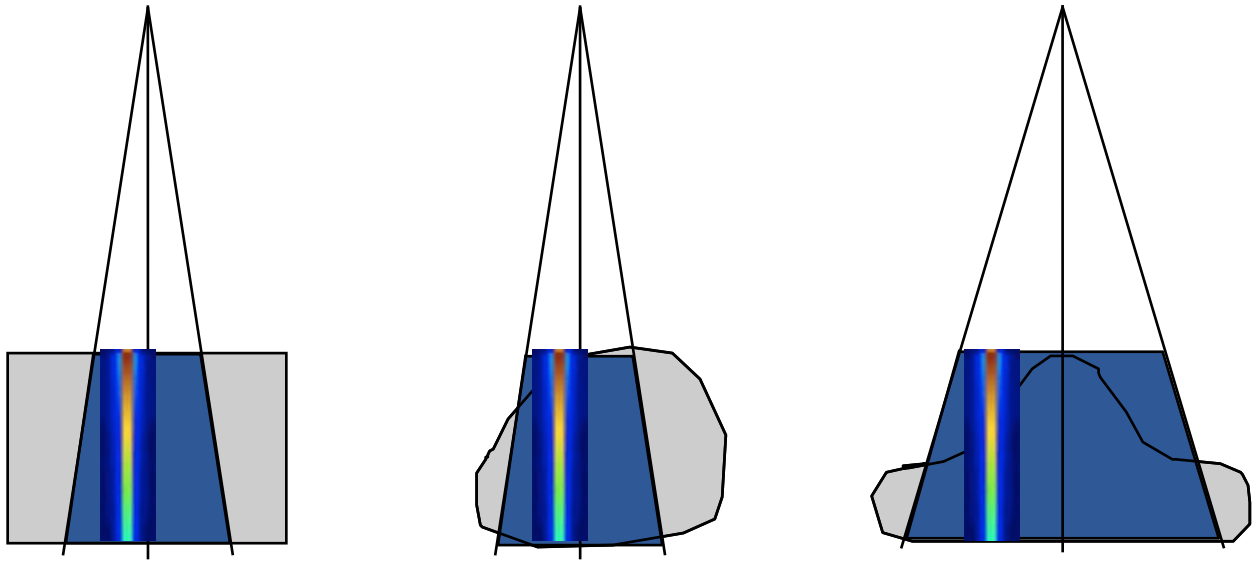
Pencil Kernel Integration

- Pencil kernel methods account for heterogeneity effects along the beam direction but not for lateral effects (penumbra broadening in lungs not modeled).



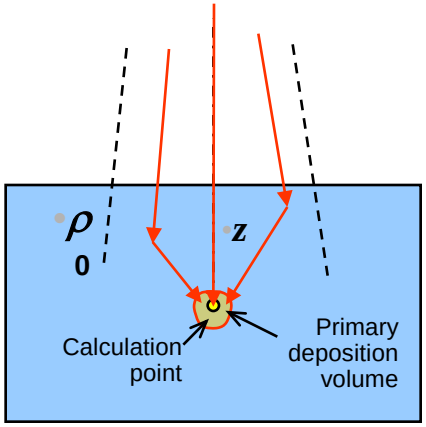
Correct

Approximately correct
(error cancels)

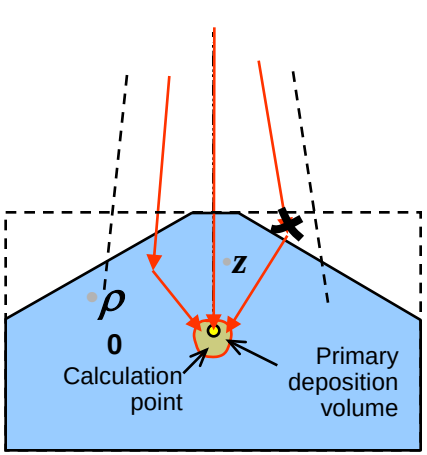
Scatter is
overestimated

Pencil beam kernel

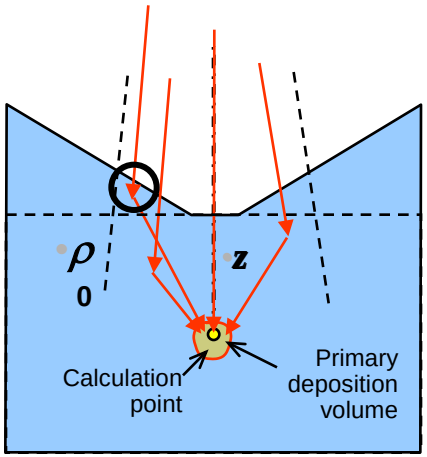
- Calculation object approximations



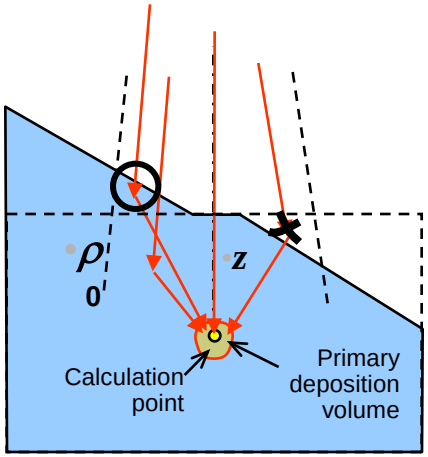
The depth (z) is generally assumed to be constant within the lateral integration plane during calculation of the scatter dose to a point.



Scatter overestimated



Scatter underestimated



Errors cancel (roughly)

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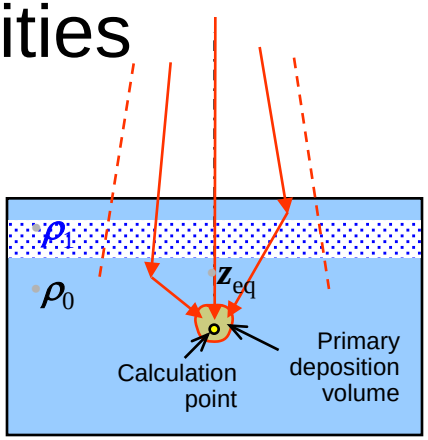
Pencil beam kernel

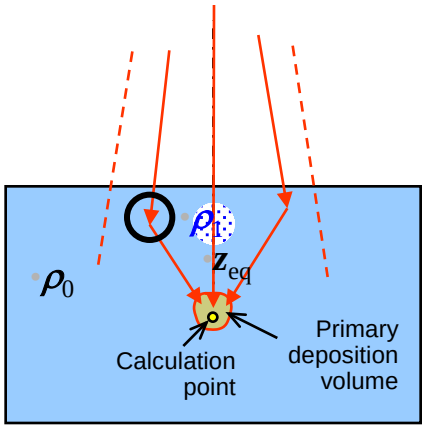
- Calculation object approximations with heterogeneities



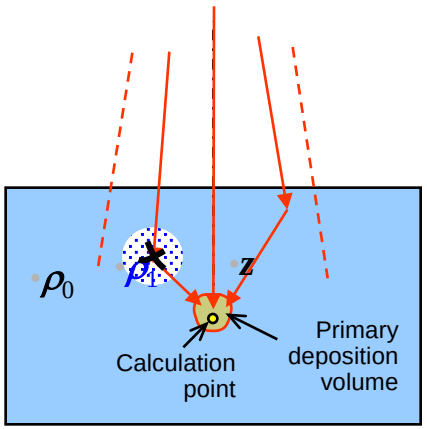
Heterogeneous slab phantom

- ρ_1 illustrates a low density region, e.g. lung tissue.

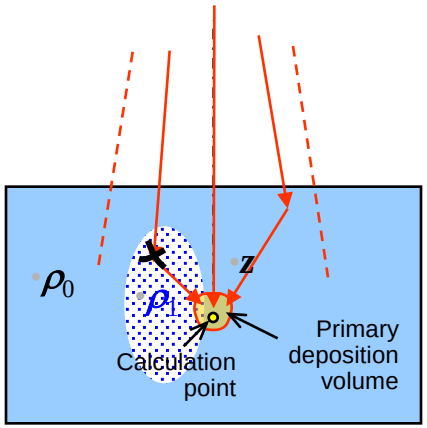
- Effects of heterogeneities are generally modelled in pencil kernel algorithms through depth scaling along rayline (and no lateral scaling). Correct handling of heterogeneities requires proper 3D modelling of the secondary particle transport.



Scatter underestimated



Scatter overestimated



Scatter and primary overestimated

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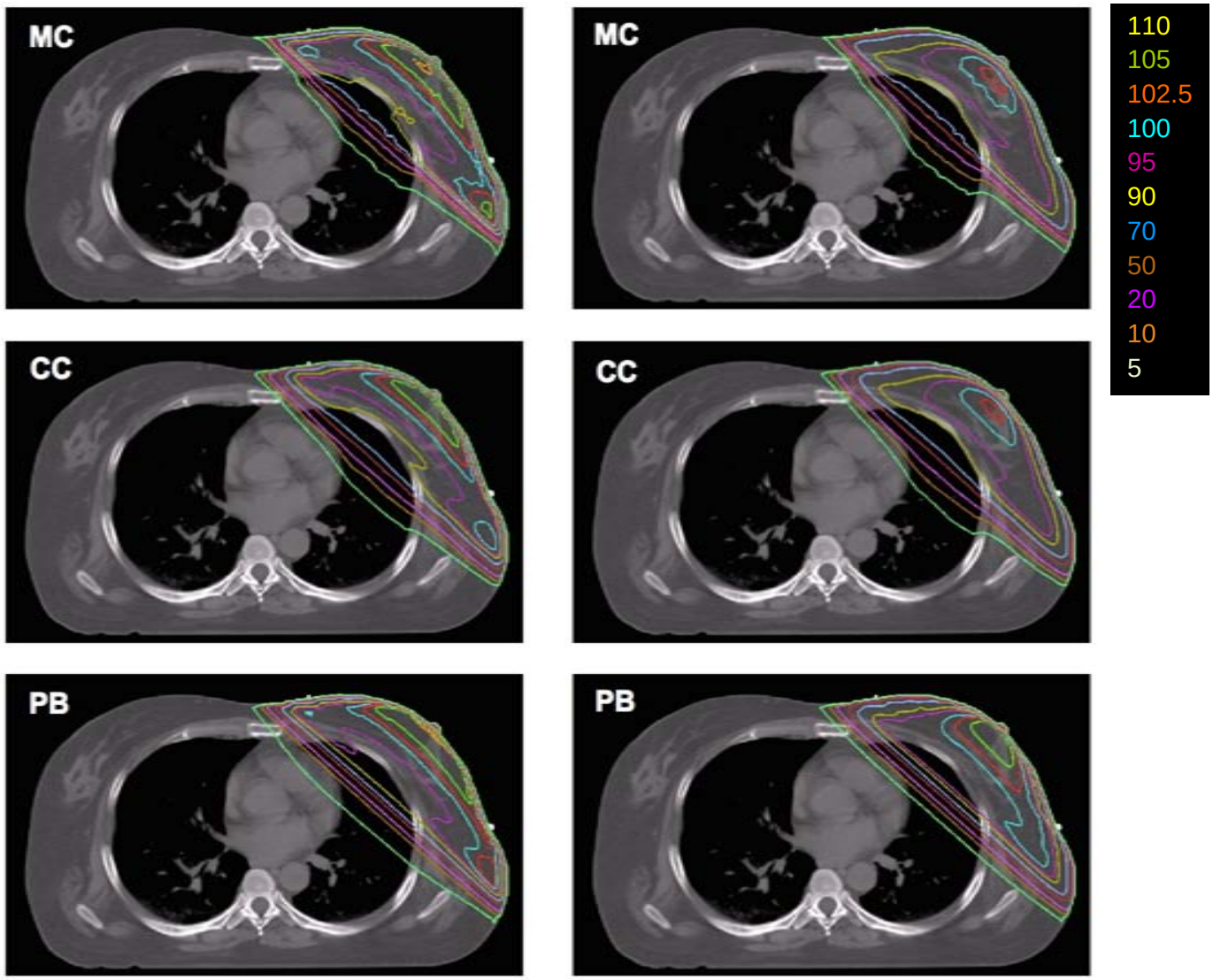
Breast Tangent Example



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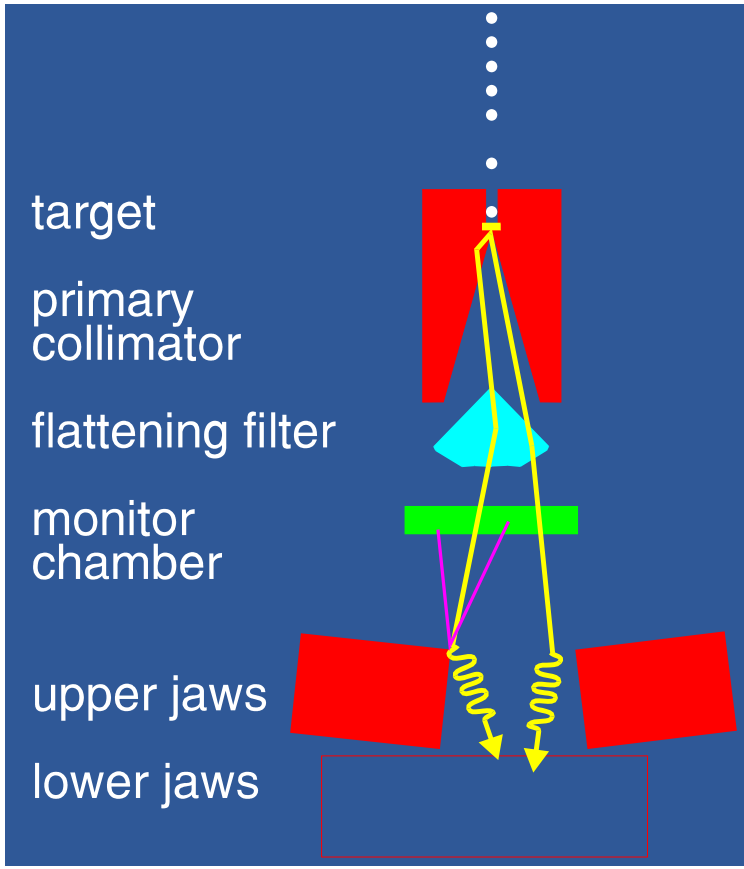
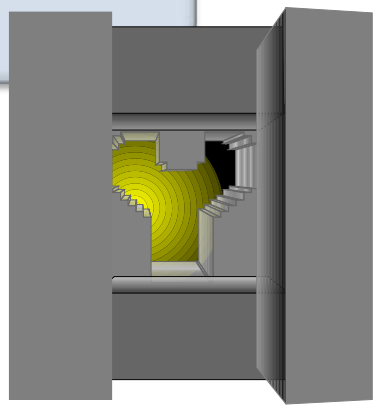
Total Energy Released per MAss (TERMA)

- Radiation is scattered within the treatment head of the accelerator.
- Dose rate “in-air” depends on field size.

$$T(r') = \frac{\mu}{\rho}(\vec{r}')\Psi(\vec{r}')$$



Extra-focal radiation
(head scatter)
Secondary source



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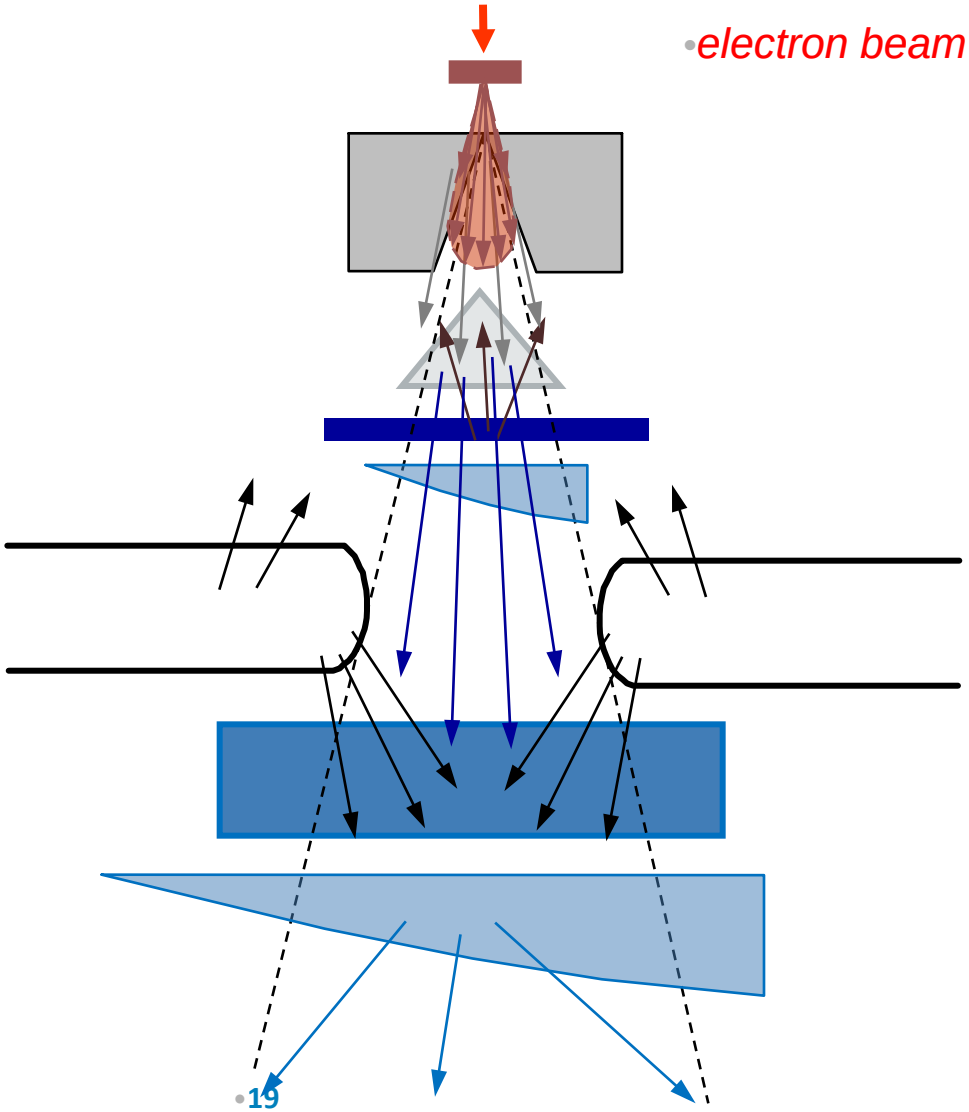
Physics considerations

SCATTER SOURCES

- primary collimator
- flattening filter
- collimator scatter (secondary coll., blocks, MLC)
- backscatter into monitor chamber
- wedges, compensators
- blocks, trays, ...

➔ **all effects together determine the incident energy fluence Ψ_0 !!!**



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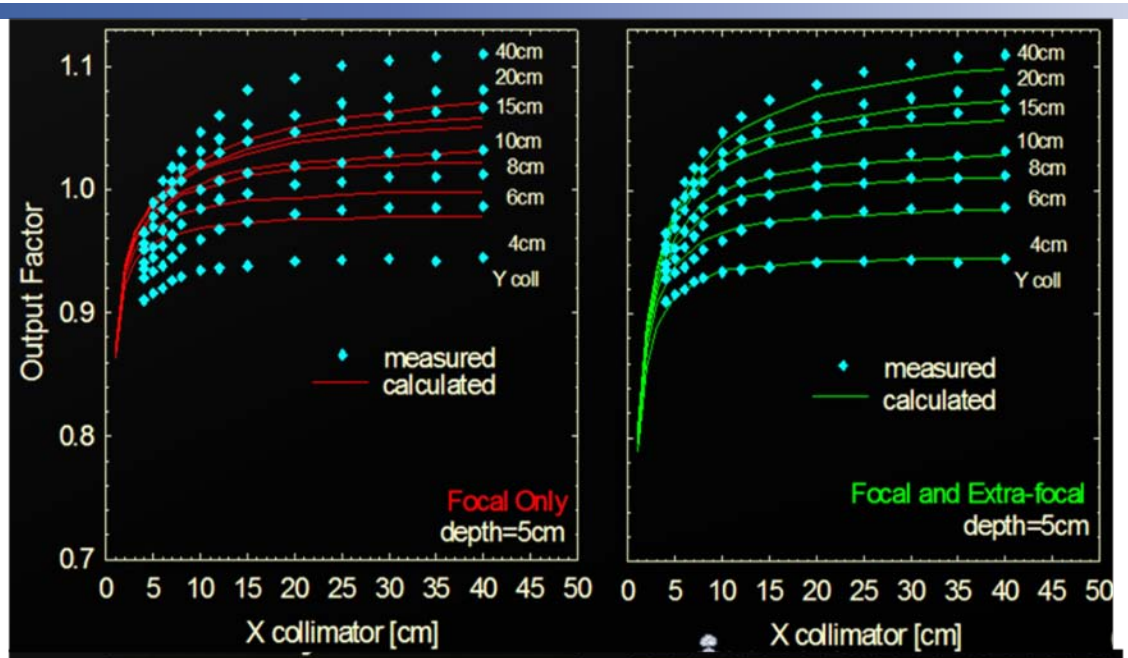
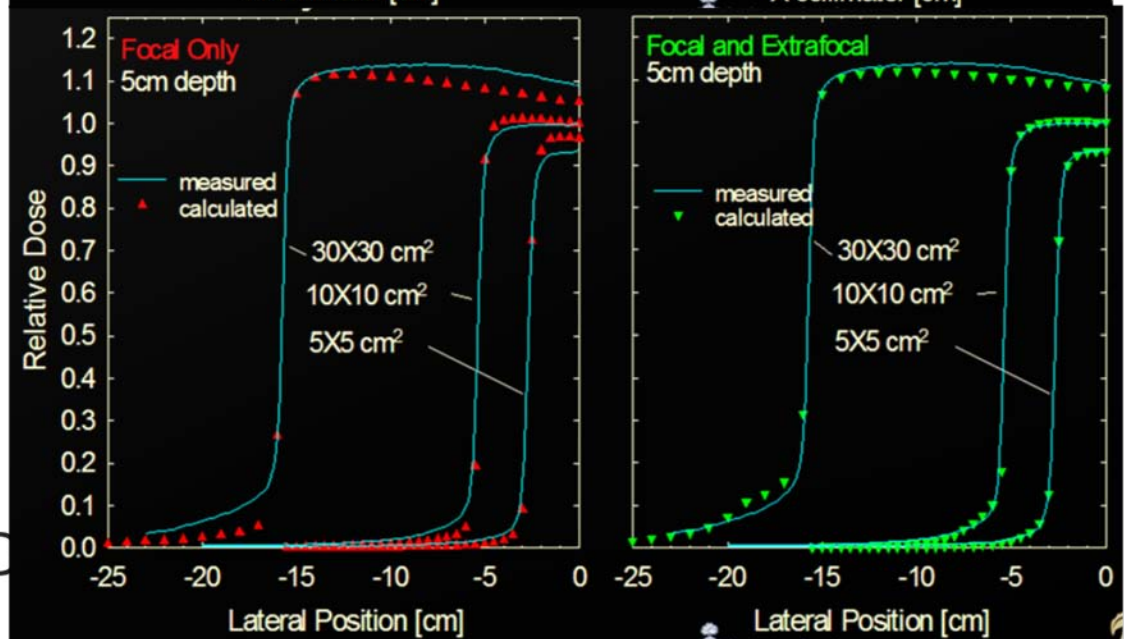
Influence of Head Scatter



Dose Rate



Dose Profile

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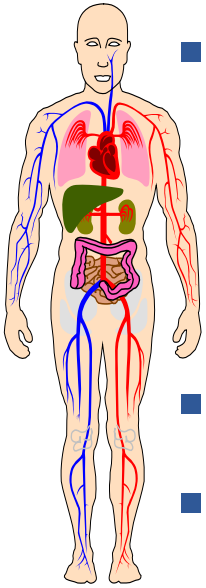
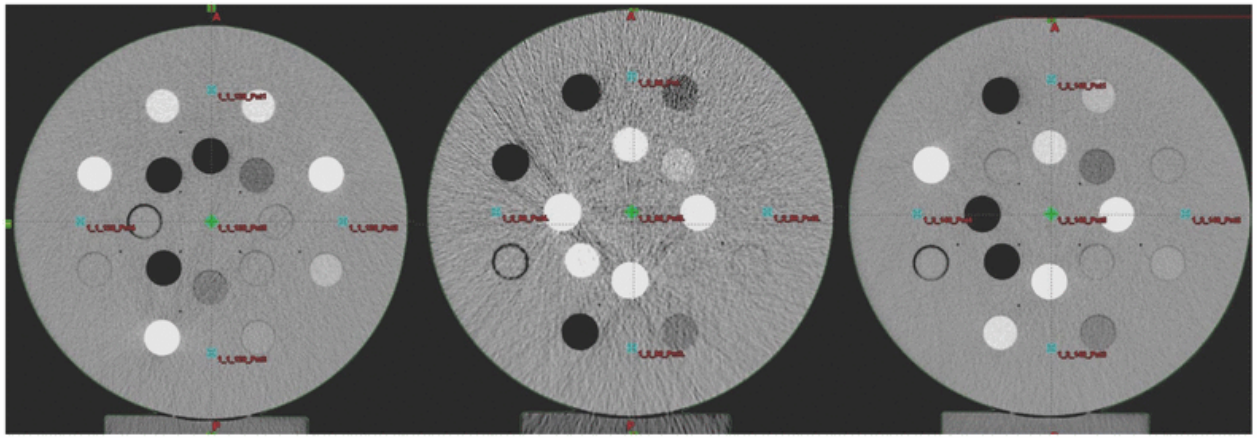
CT Data to Tissue Properties



- Human body: many tissues/cavities
  - Muscle, fat, lungs
  - Bones, teeth
  - cavities (nasal, oral, sinus, trachea)
- Prosthetic devices: metal, plastics
- Different radiological properties.

$$\mathrm{HU} = 1000\left(\frac{\mu - \mu_{\mathrm{w}}}{\mu_{\mathrm{w}}}\right)$$



Nohbah A *et al,* JACMP, 12(3) (2011)

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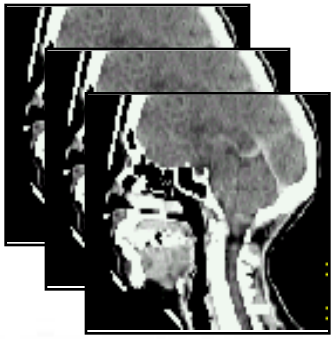
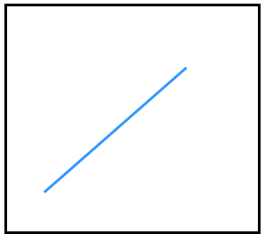
Images Support Dose Calculations



CT



density

μ/ρ lookup table

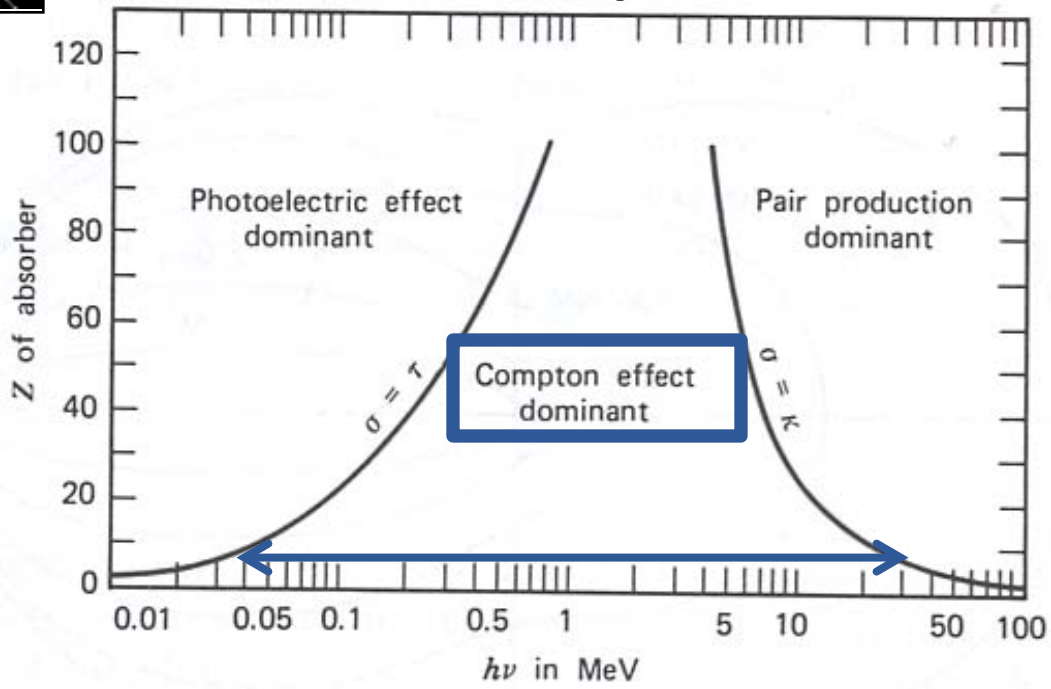
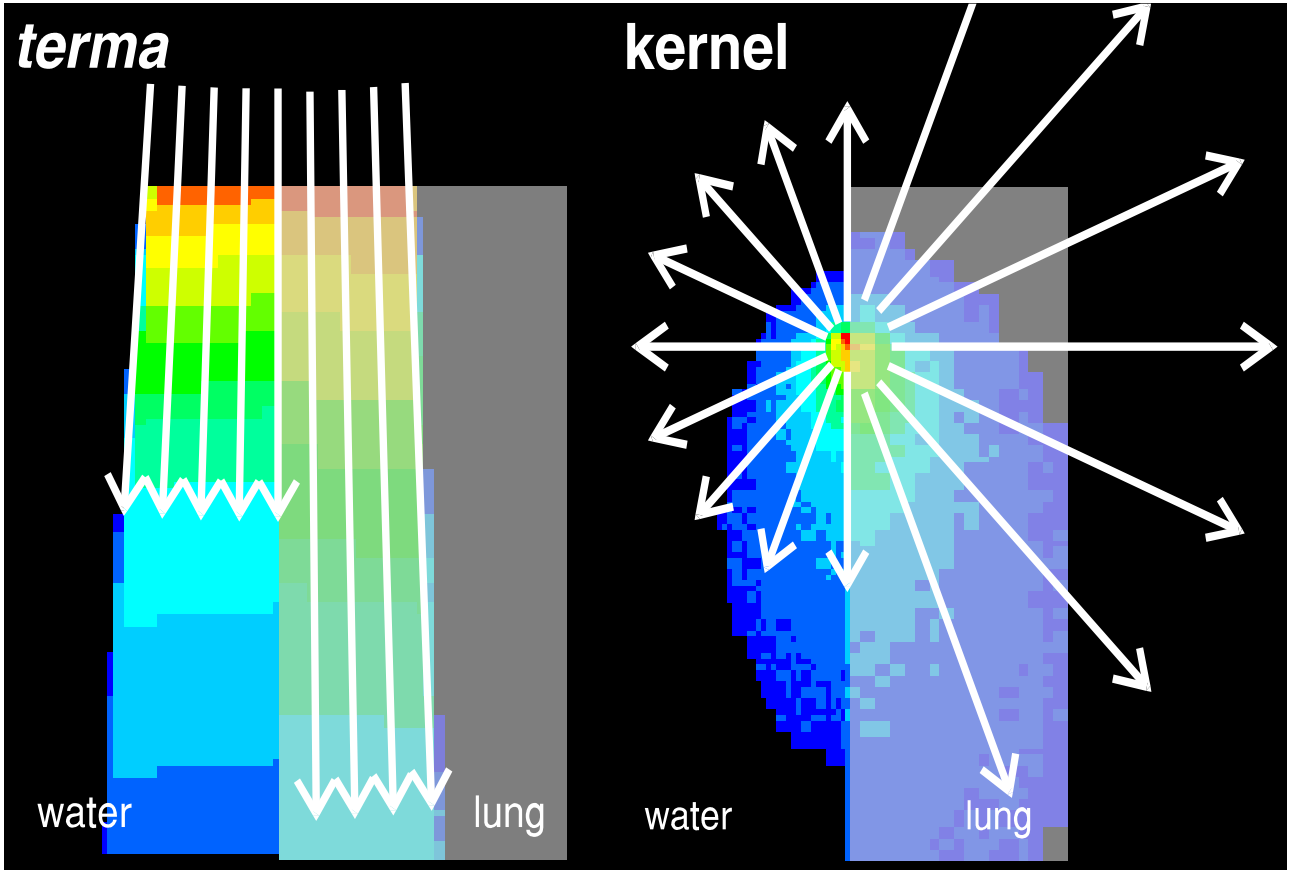


Figure 2-20 The relative importance of the three major types of gamma-ray interaction. The lines show the values of Z and $h\nu$ for which the two neighboring effects are just equal. (From *The Atomic Nucleus* by R. D. Evans. Copyright 1955 by the McGraw-Hill Book Company. Used with permission.)

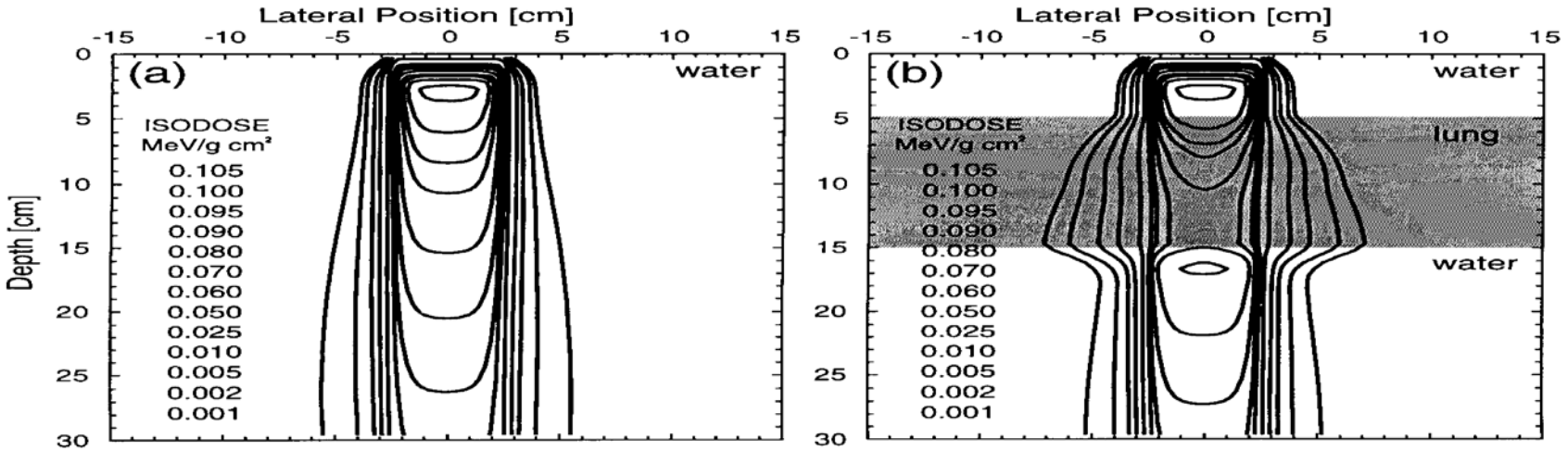
Density Scaling Approximation

- *terma* and kernel are computed for water and scaled by the average density computed along raylines.



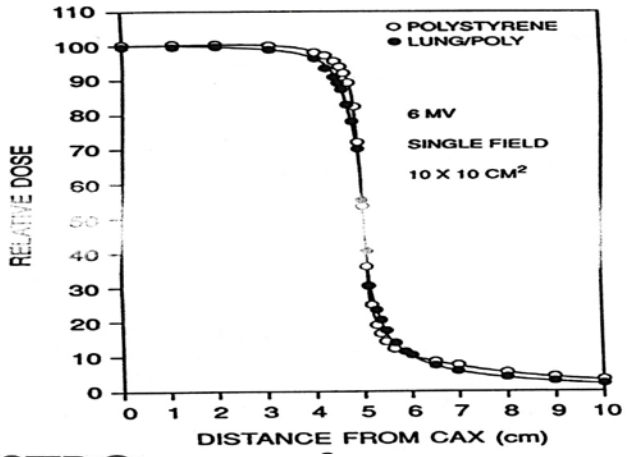
Calculated Data

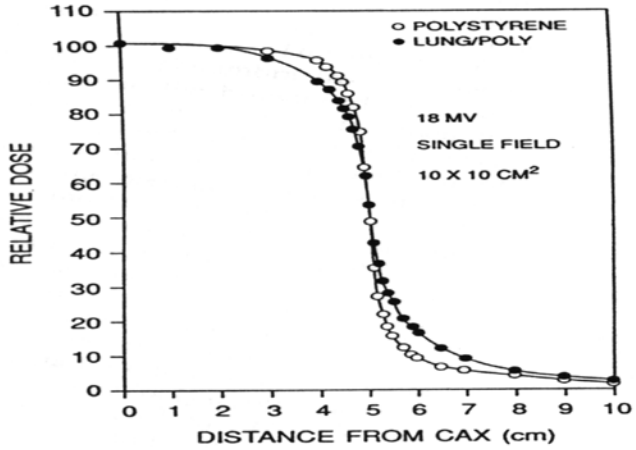
- Papanikolaou et al, AAPM Report 85 (2004)



Measured Data

- White *et al* IJROBP 34(5) 1141 (1996)





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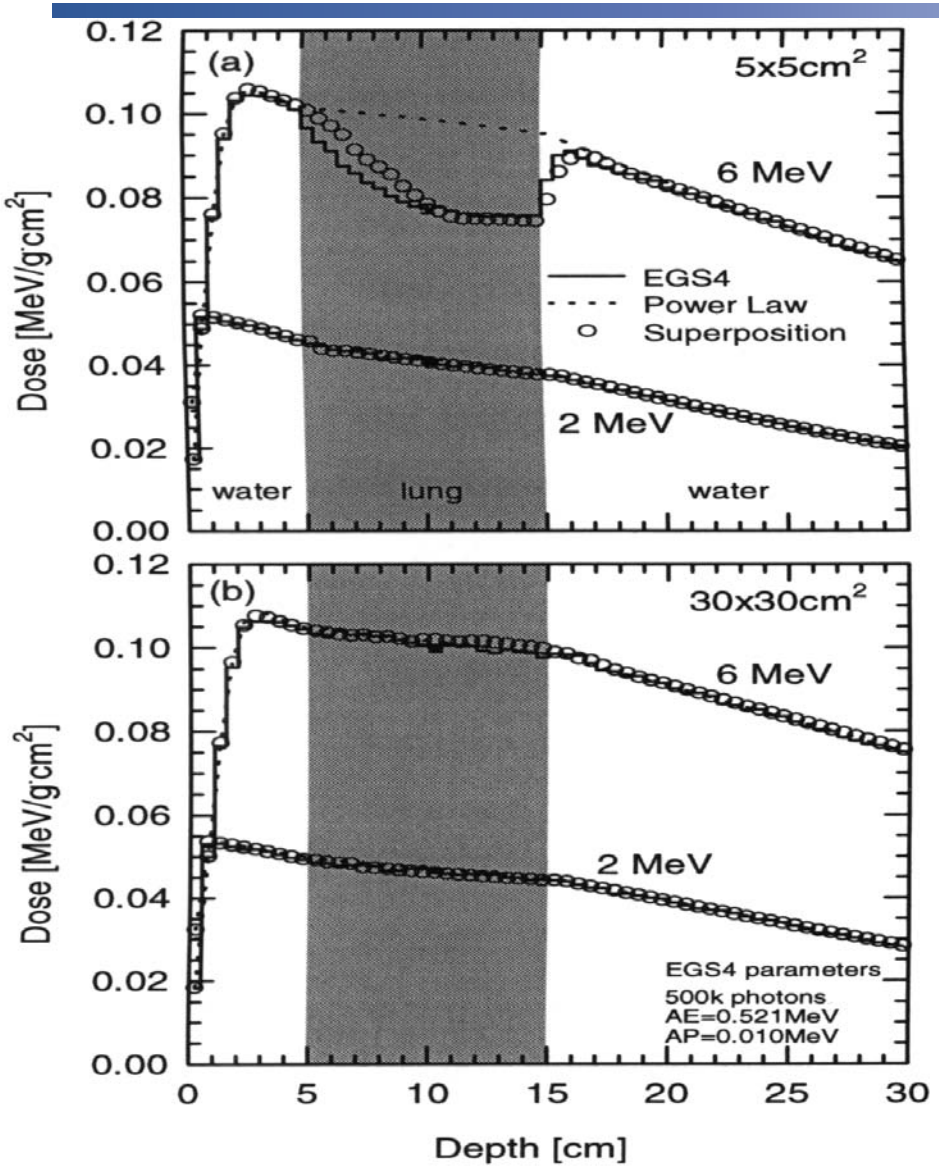
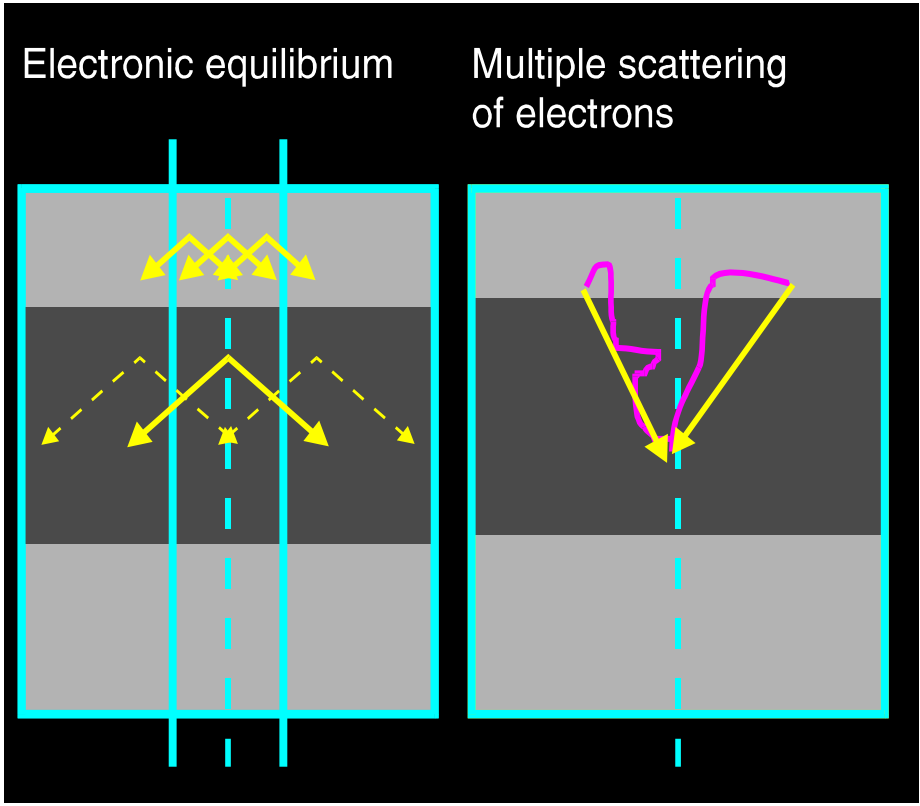
Electronic Disequilibrium





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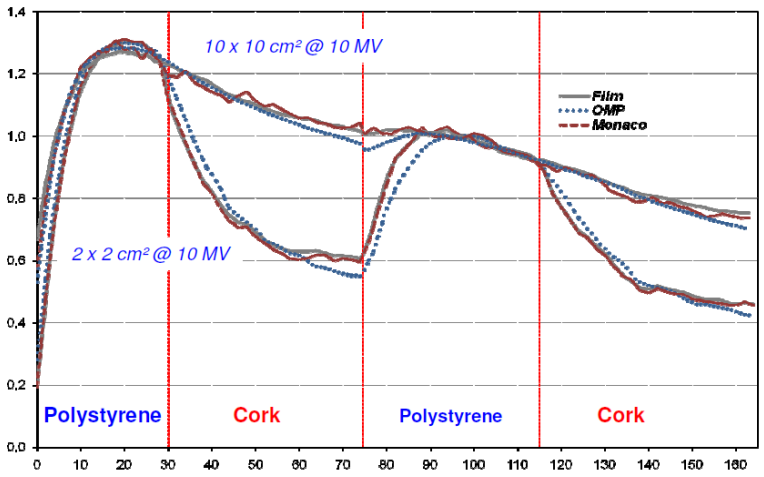
Summary model based & MC approaches

- Point Kernel algorithms much more accurate than Pencil Kernel models - minor deviations versus MC for clinical cases
  - for low density material MC slightly higher accuracy compared to advanced kernel methods
- PK implementations faster than MC
- PK can efficiently use GPU for dose calculations literally in seconds
- MC based dose calculation for high energy photon beams is clinically used



Fotina et al R&O 2009

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Advanced Kernel Methods

- Collapsed-Cone Convolution, AAA, etc. perform well
  - But Monte Carlo methods are becoming available more widely.

T Knöös et al, Phys. Med. Biol. 51 (2006) 5785–5807

E Gershkevitsh et al, Radio & Oncol 89 (2009) 338–346

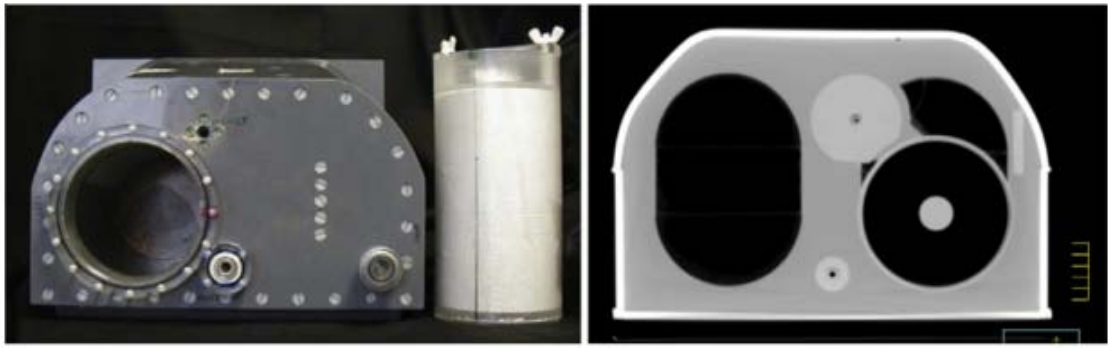
I Fontina et al, Radio & Oncol 93 (2009) 645–653

- Except…

S Kry et al, IJROBP 85(1) e95-e100, 2013 (RPC/RTOG)

RPC/RTOG phantom for SBRT

- S Kry et al, IJROBP 85(1) e95-e100 (2013) – Compares 304 institutions



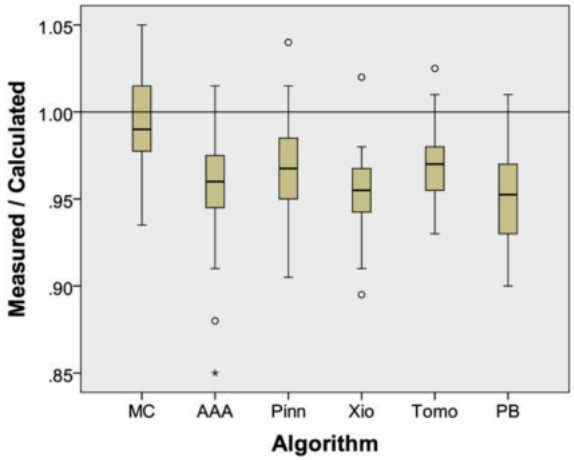


Fig. 2. Ratio of the in-phantom-measured dose to the planning system-calculated dose to the center of the lung target by treatment planning algorithm. Algorithms are Monte Carlo (MC), Eclipse AAA (AAA), Pinnacle CS (Pinn), CMS Xio CS (Xio), Hi-ART Tomotherapy CS (Tomo), and pencil beam (PB).

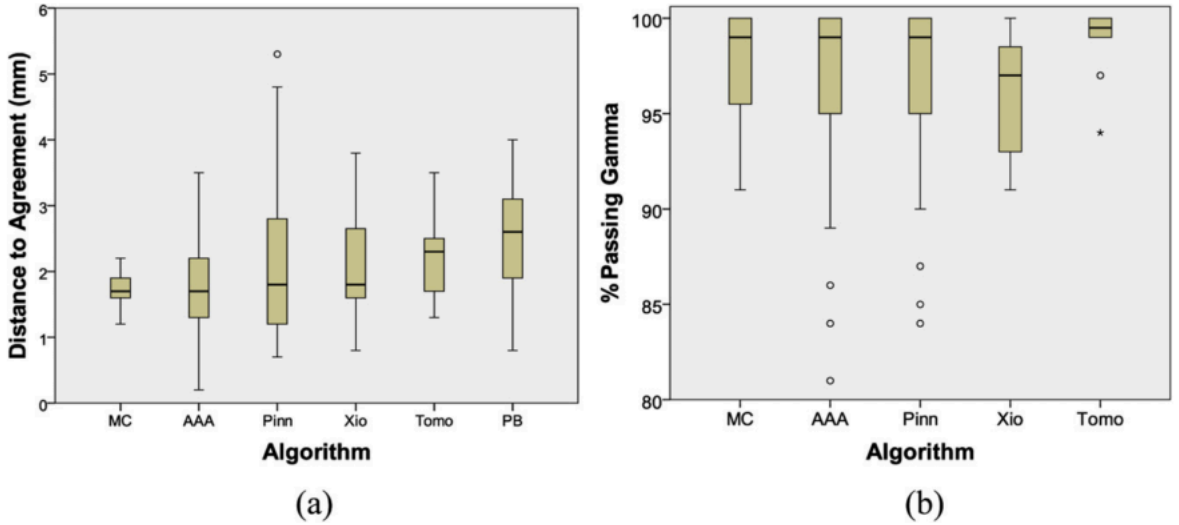
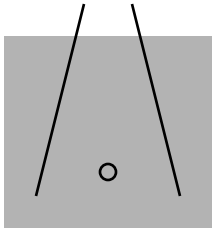


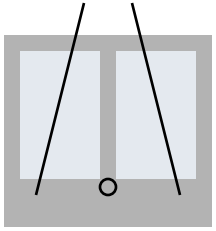
Fig. 3. Two-dimensional agreement between the in-phantom-measured dose and the planning system-calculated dose, based on distance-to-agreement criteria (a) or the percentage of pixels passing the gamma criterion (b). Algorithms are Monte Carlo (MC), Eclipse AAA (AAA), Pinnacle CS (Pinn), CMS Xio CS (Xio), Hi-ART Tomotherapy CS (Tomo), and pencil beam (PB).

A Simple Algorithm Check

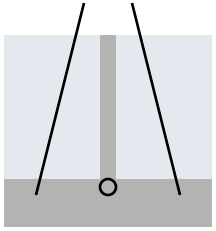
- IMRT: the State of the Art, AAPM Monograph 29 pg 449-473 (2003)



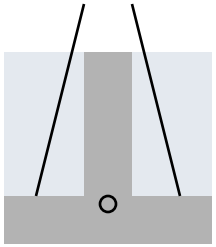
- 20 X 20 cm^2 field, 18MV
- 50 X 50 X 50cm^3 water phantom
- 200cGy to 22cm depth



- Introduce air inhomogeneities,
- 1cm wide mediastinum, 2cm surface layer



- Contour correction: 1cm^2 wide “spike”



- Contour correction: 25cm^2 wide “spike”

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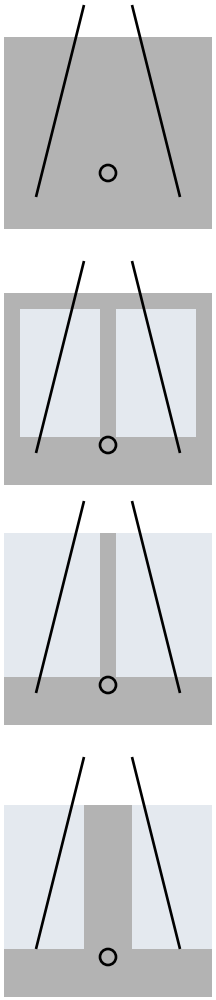
A Simple Algorithm Check: MU's

- IMRT: the State of the Art, AAPM Monograph 29 pg 449-473 (2003)



System A homo/hetero	System B homo/hetero
242.7 / 242.0	244 / 244
246.8 / 260.7	244 / 244
321.7 / 321.0	244 / 244
279.7 / 278.8	244 / 244

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Energy Absorbed by an Inhomogeneity

- The absorbed dose within an inhomogeneity, or in adjacent soft tissue is strongly affected by perturbations of the secondary electron fluence generated by the photon beam.
- The absorbed dose in tissue is related to the absorbed dose in water:

$$\frac{f_{med}}{f_{water}} = \left(\frac{\mu_{en}}{\rho} \right)_{water}^{med}$$

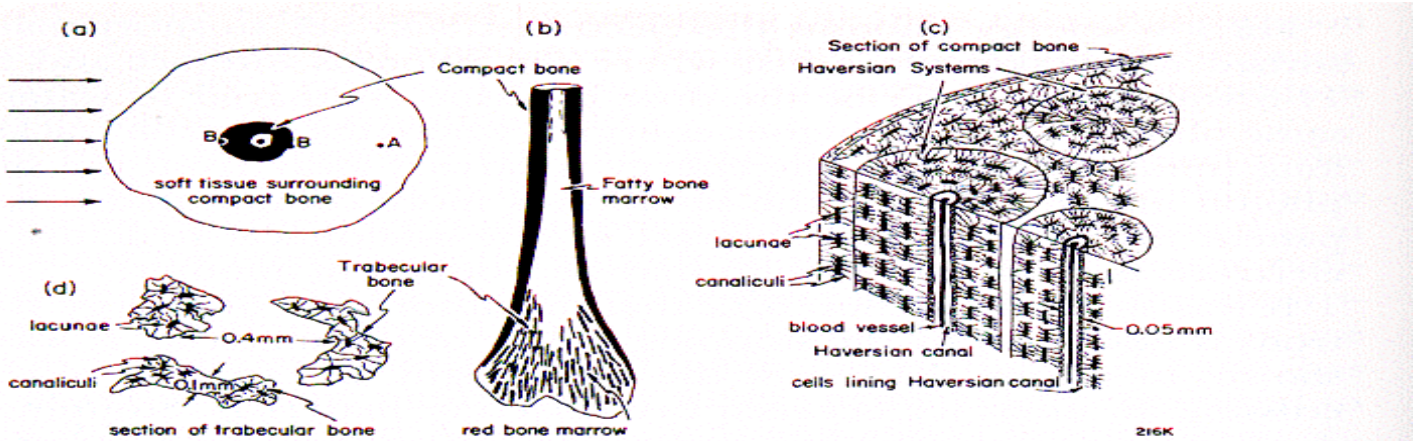

Figure 11-10. (a) Cross section of long bone imbedded in soft tissue. (b) Longitudinal view of lower end of femur. (c) Schematic diagram of Haversian system adapted from Ham (H13). (d) Cross section of trabecular bone.

Energy Absorbed by an Inhomogeneity

BONE

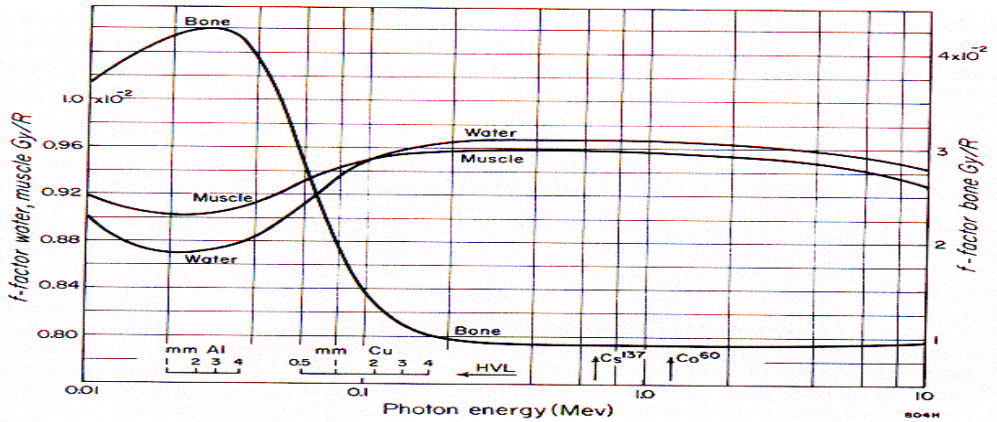

Figure 8-10. The f-factor as a function of photon energy for water, muscle, and bone taken from data in Table A-7. The auxiliary scale relates the HVL in Al and Cu to the energy scale.

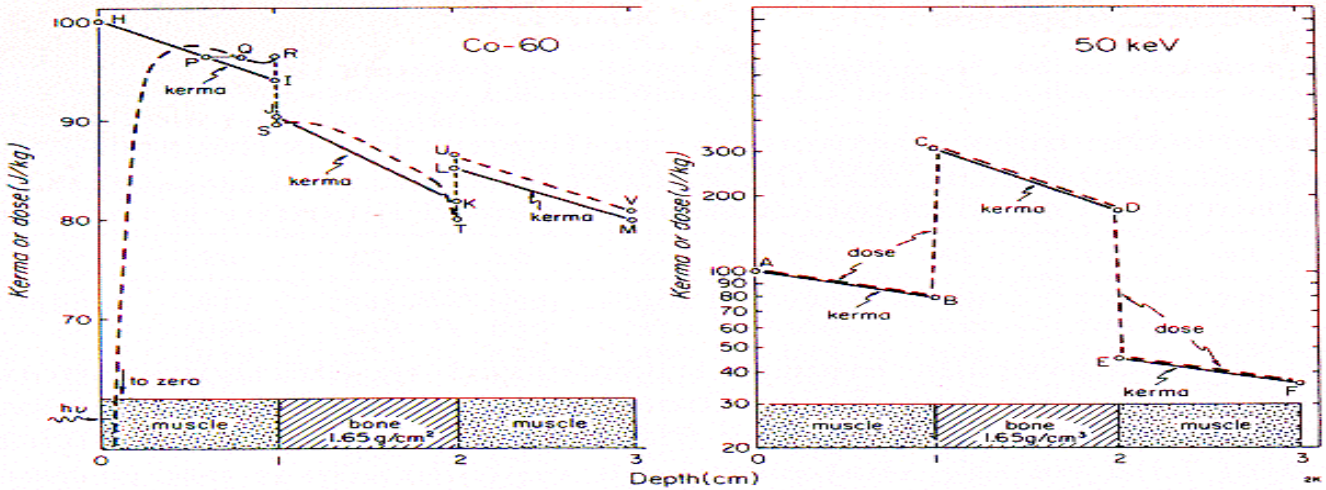

Figure 7-13. Diagram showing kerma and dose in a composite phantom irradiated from the left by cobalt 60 radiation and 50 keV radiation.

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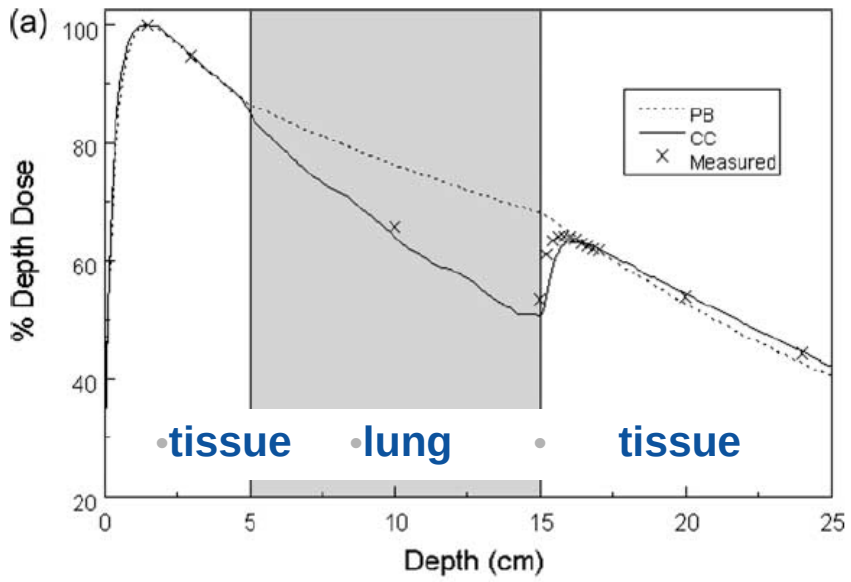
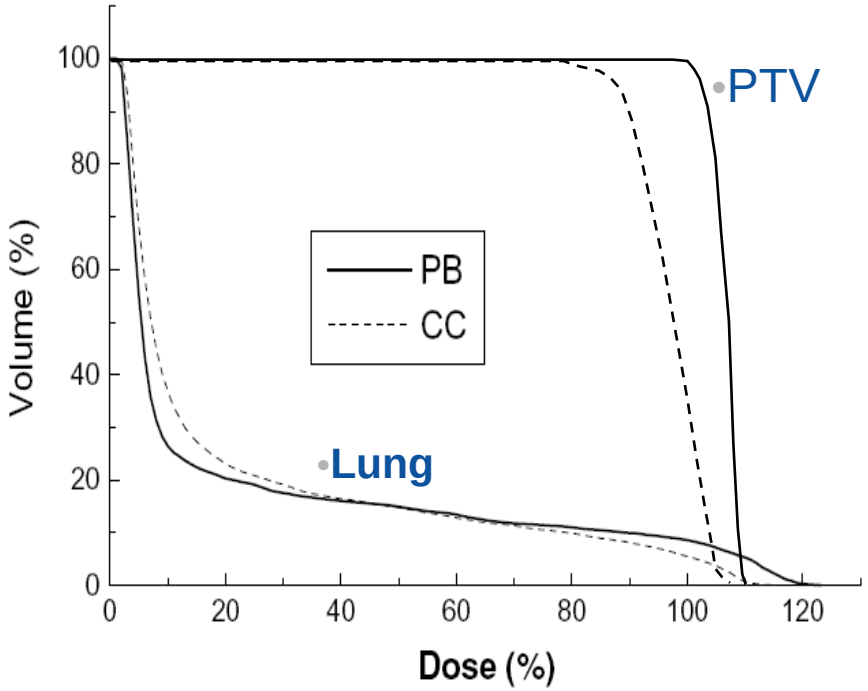
Clinical impact of dose calculation

- E.g. inaccurate dose calculation in low density regions (lung)



Nisbet *et al* RadOnc 73 (2004) p79

TMS



Irvine *et al* ClinOnc 16 (2004) p148

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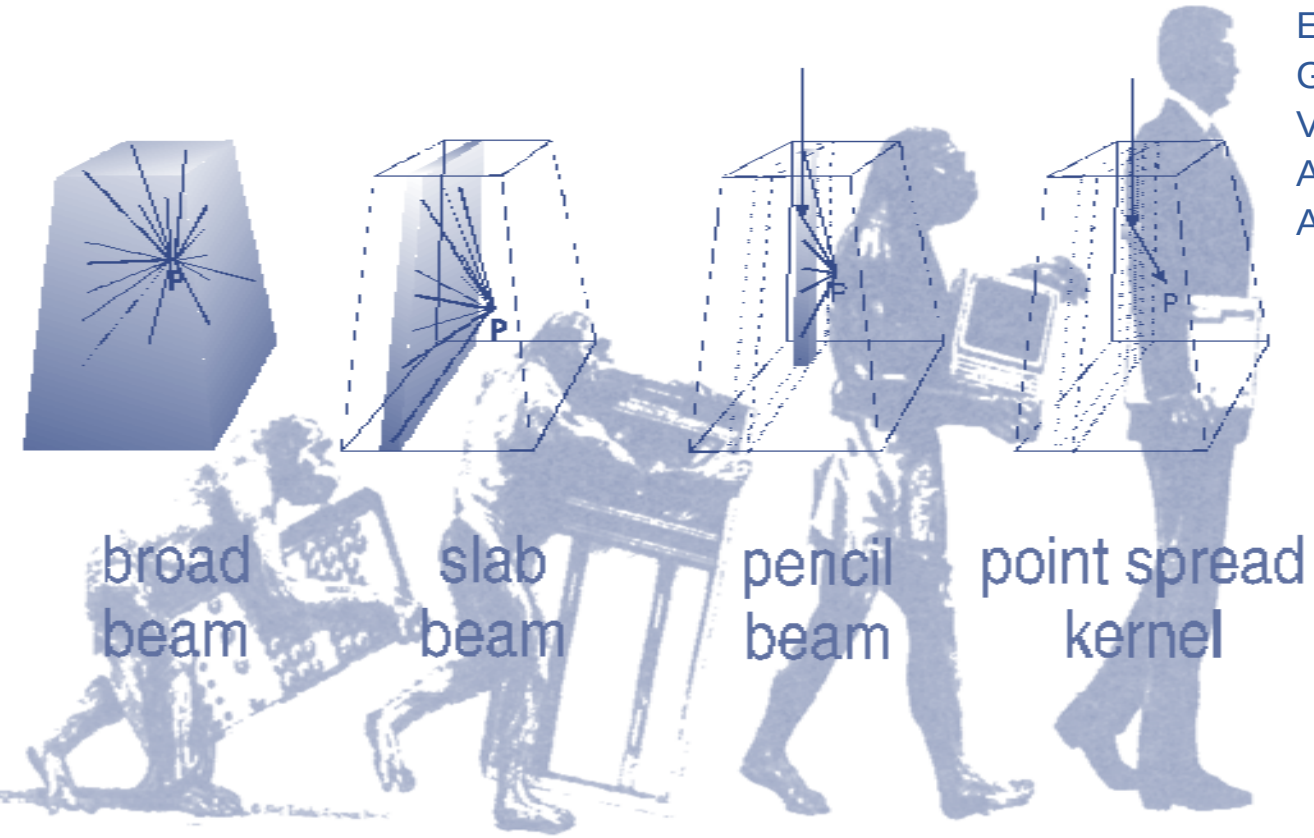
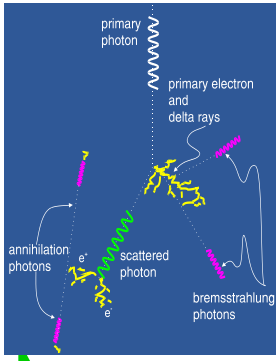
Summary – Evolution, not Revolution

Modern algorithms are hybrids of deterministic numerical and Monte Carlo methods. They can be expected to predict dose in heterogeneous tissues more accurately



EGSnrc
Geant
VMC
Attila
Acuros



Monte Carlo

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ICRU guidance on planning and prescribing

Neil Burnet

University of Cambridge Department of Oncology,
Oncology Centre, Addenbrooke's Hospital,
Cambridge, UK

ATP Cambridge 2016

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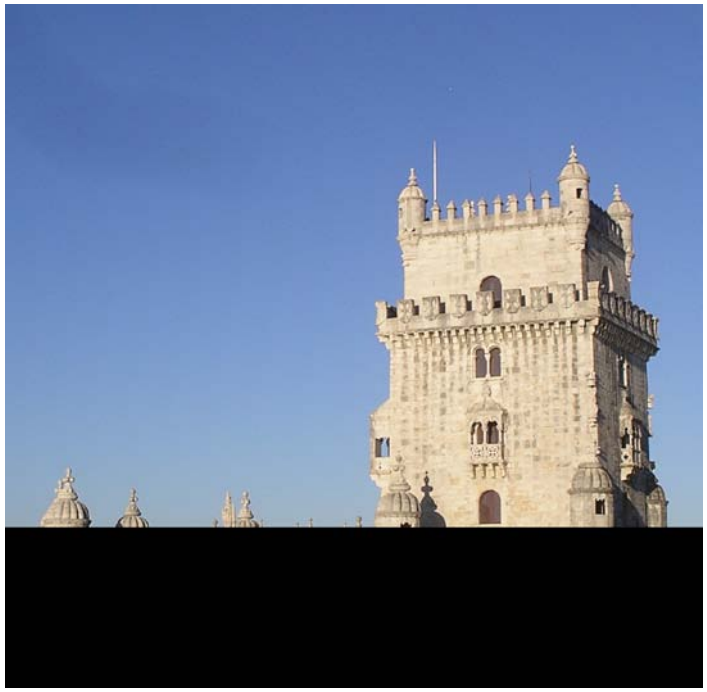
Summary

- Prescribing
- Definition of planning volumes
  - GTV, CTV, PTV
  - Other volumes
  - Organs at Risk (OARs)
  - Planning organ at Risk Volume (PRV)
- Optimising volumes
- Overlapping volumes
- Questions



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The history of radiotherapy

- 1895 - Röntgen discovered X-rays
- 1896 - first treatment of cancer with X-rays

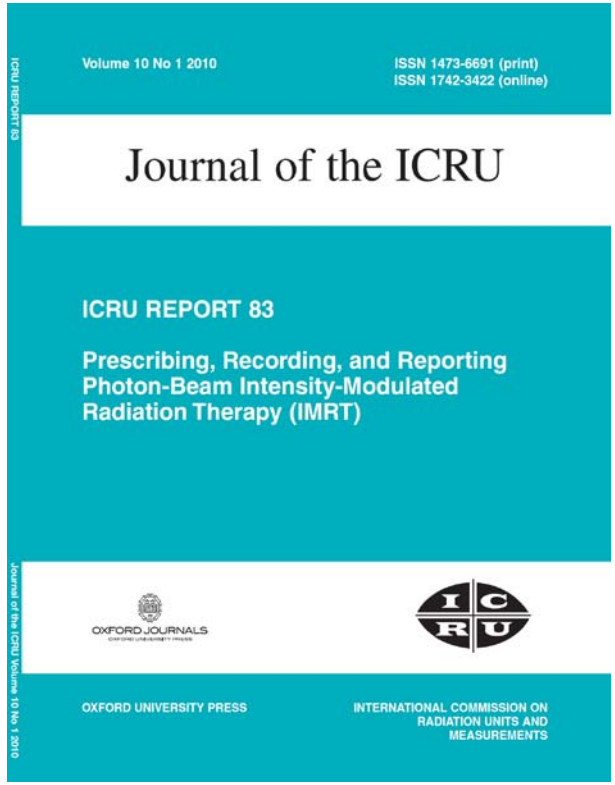
- 100+ years later the technology has changed!
- ICRU reports are here to help us

- Series began with Report 50 and Supplement 62 (1993 + 1999)
- ICRU 71 (2004) added a few details

- ICRU 83 is designed for IMRT

ICRU guidance

- ICRU 83 specifically dedicated to IMRT
- Recommendations for prescribing changed
- Emphasises need for clear nomenclature for different targets, both GTV and CTV
- Introduces some specific aspects of reporting of dose to normal tissues



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ICRU guidance

- Advice on dose planning in the build up region or if PTV extends outside the body contour is given

- Concept of adaptive review introduced
  - Possible to review dose and dose change during treatment

- Comments on QA given
  - ***Not*** discussed here

Prescribing

- Key changes in prescribing

  - Prescribe to ***median dose*** rather than ICRU reference point (≈ isocentre dose)
    - median dose = $D_{50\,\%}$
    - = dose to 50% of the volume

  - Report ***near-maximum*** and ***near-minimum***, rather than actual max & min

  - Still need to be aware of target coverage

Prescribing

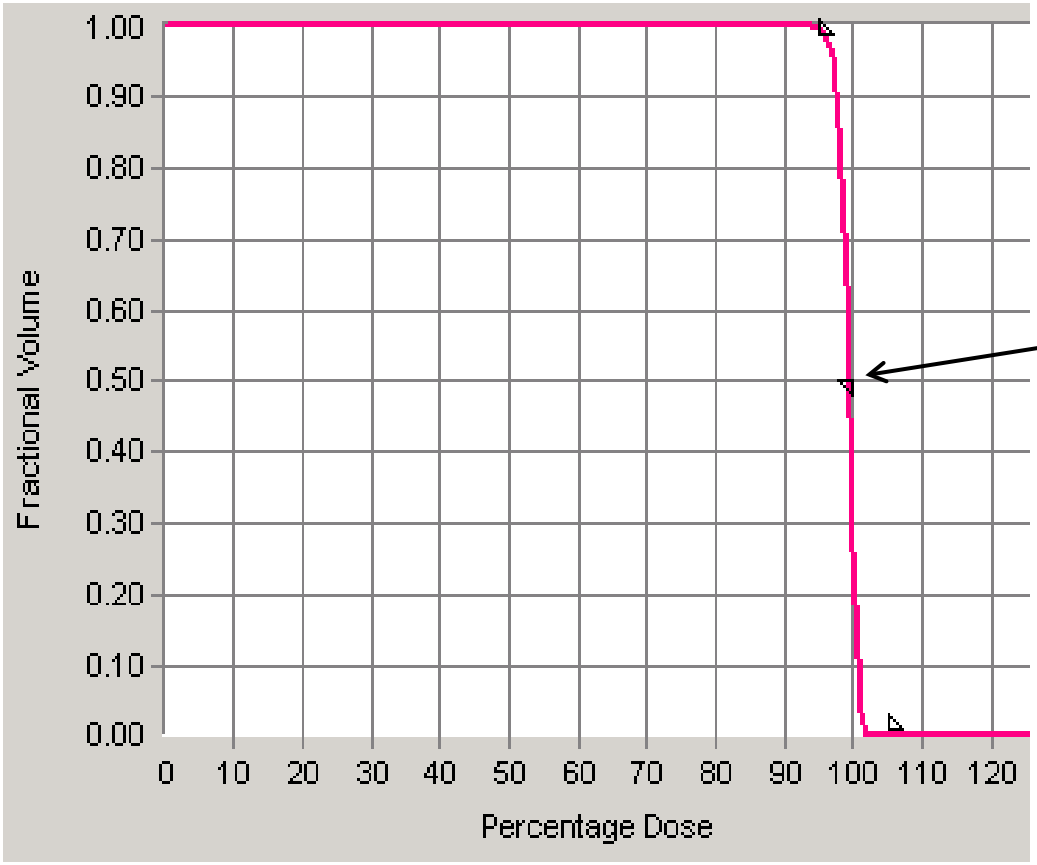
- Specify median dose - $D_{median} = D_{50\ \%}$
  - Corresponds best to previous ICRU reference point dose (≈ isocentre dose)
  - Often close to mean dose
  - Not influenced by 'tails' on the DVH
  - Accurately calculated in TPSs

  - Possible to move from isocentre dose (CRT) to median dose (IMRT) with confidence

- NB useful to add units e.g $D_{50\ \%}$ or $V_{20\ Gy}$

Prescribing

- Median dose = D_{median} = $D_{50\ \%}$



Median dose = $D_{50\ \%}$

Prescribing

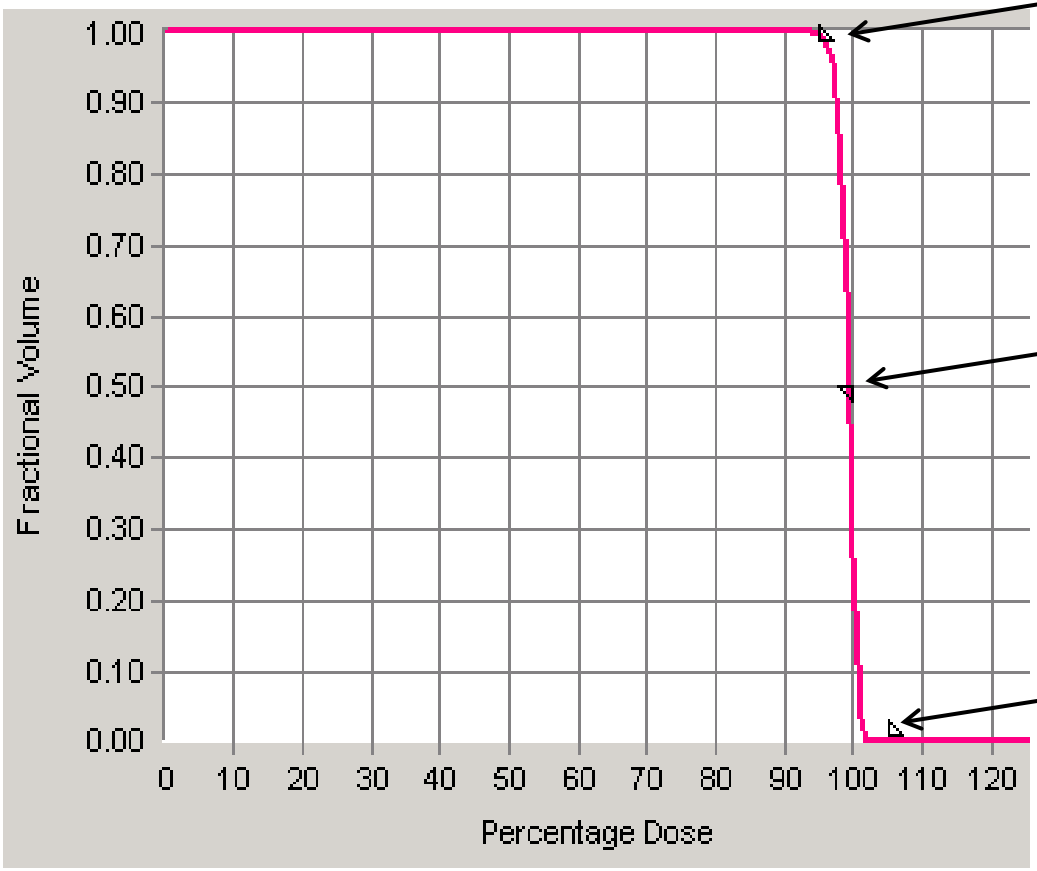
- Prescribing to median dose without some restriction on the slope of the target DVH could allow a shallow slope and low target minimum dose

- Need some agreement on minimum acceptable
  - At least 99% of the volume ($D_{99\,\%}$) to receive>95% of dose
  - At least 98% of the volume ($D_{98\,\%}$) to receive>95% of dose

- Limit on maximum also needed, for example
  - Less than 1% of the volume >105% of dose

Prescribing

- Dose constraints (objectives) for min & max included (and median)



$V_{95\ \%}$

Median dose = $D_{50\ \%}$

$V_{105\ \%}$

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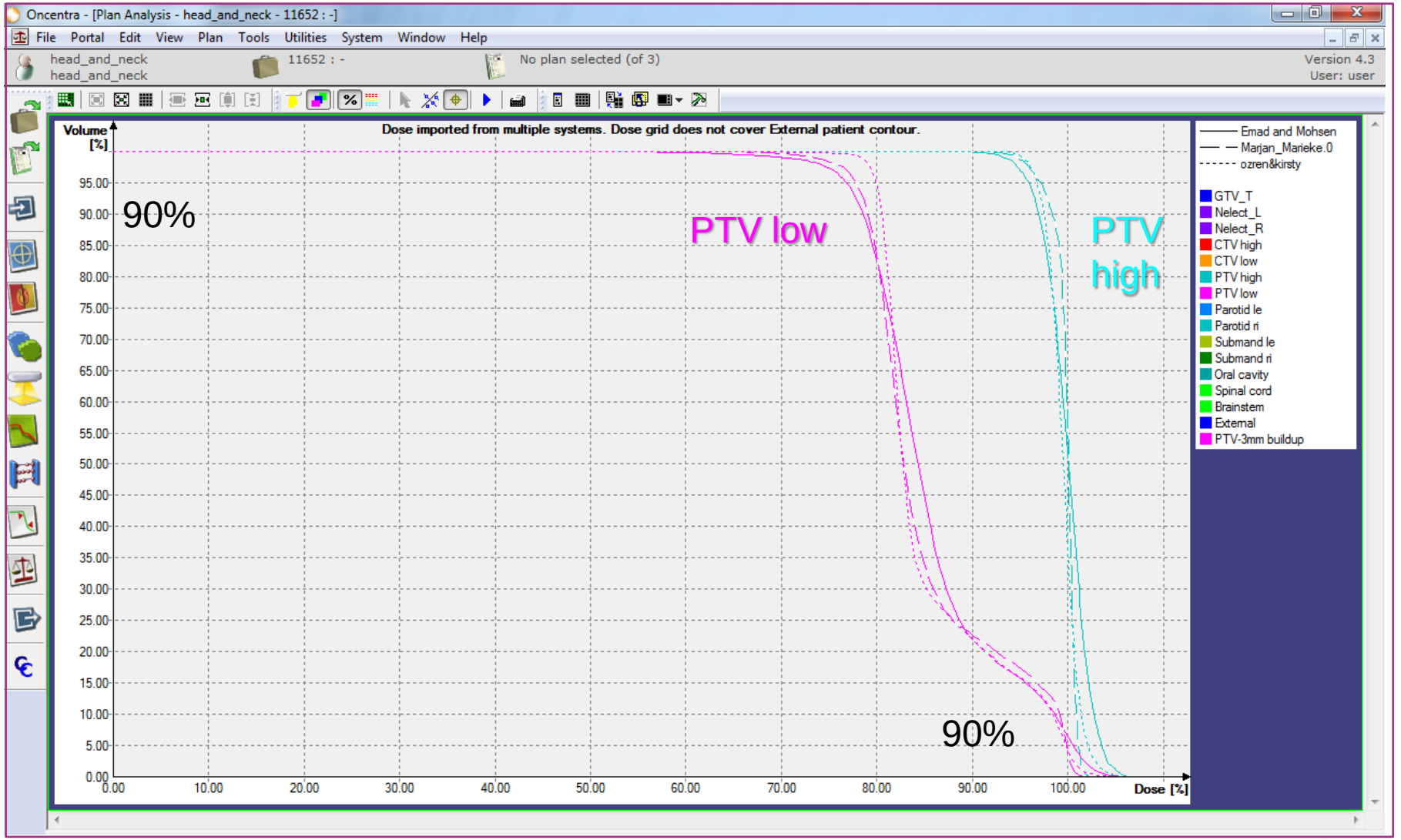
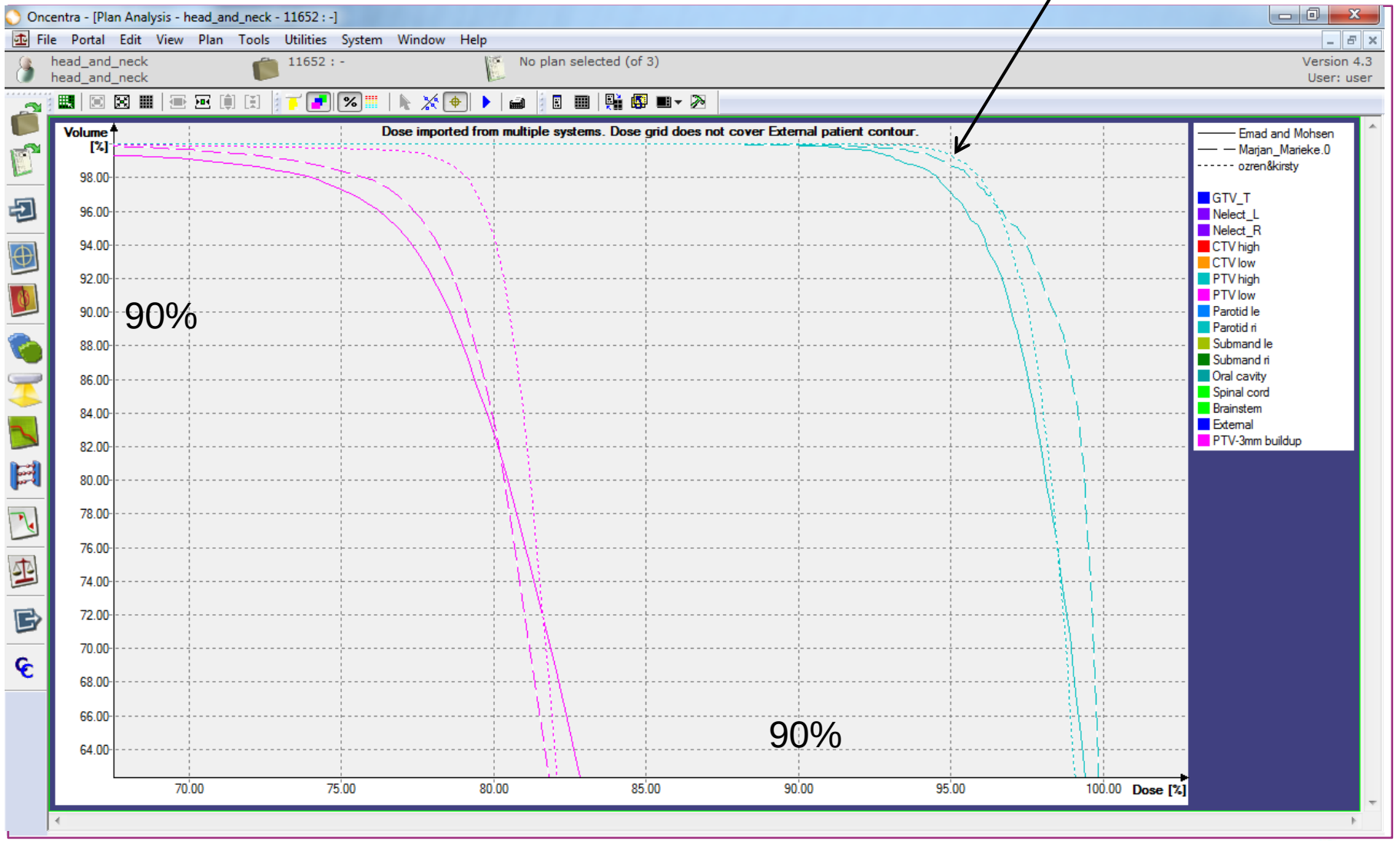
Prescribing



Prescribing

$D_{99\ \%}$ >95%
(of prescription dose)



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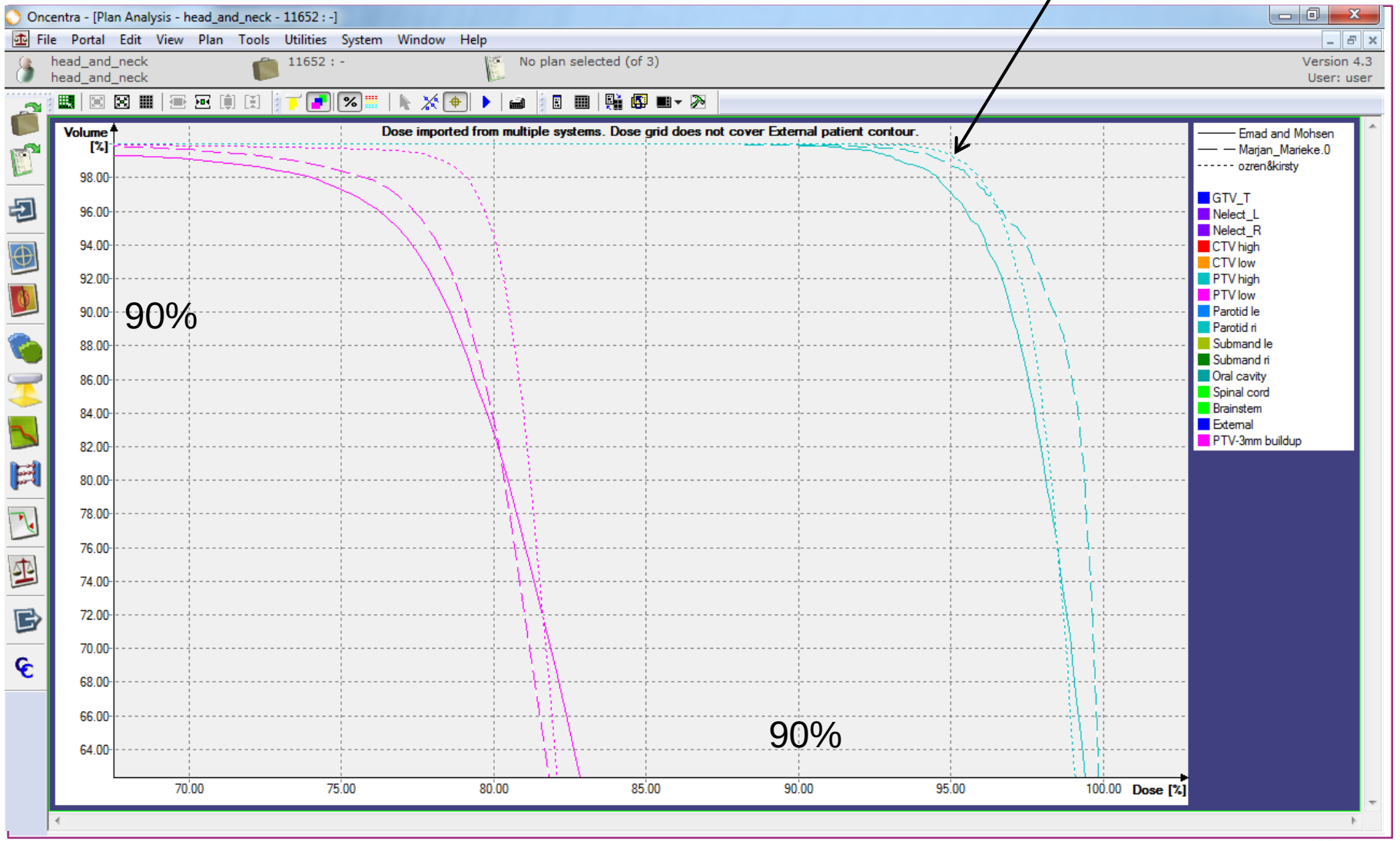
Prescribing

$D_{99\ \%}$ >95%
(of prescription dose)

$V_{95\ \%}$ >99%
(of target volume)



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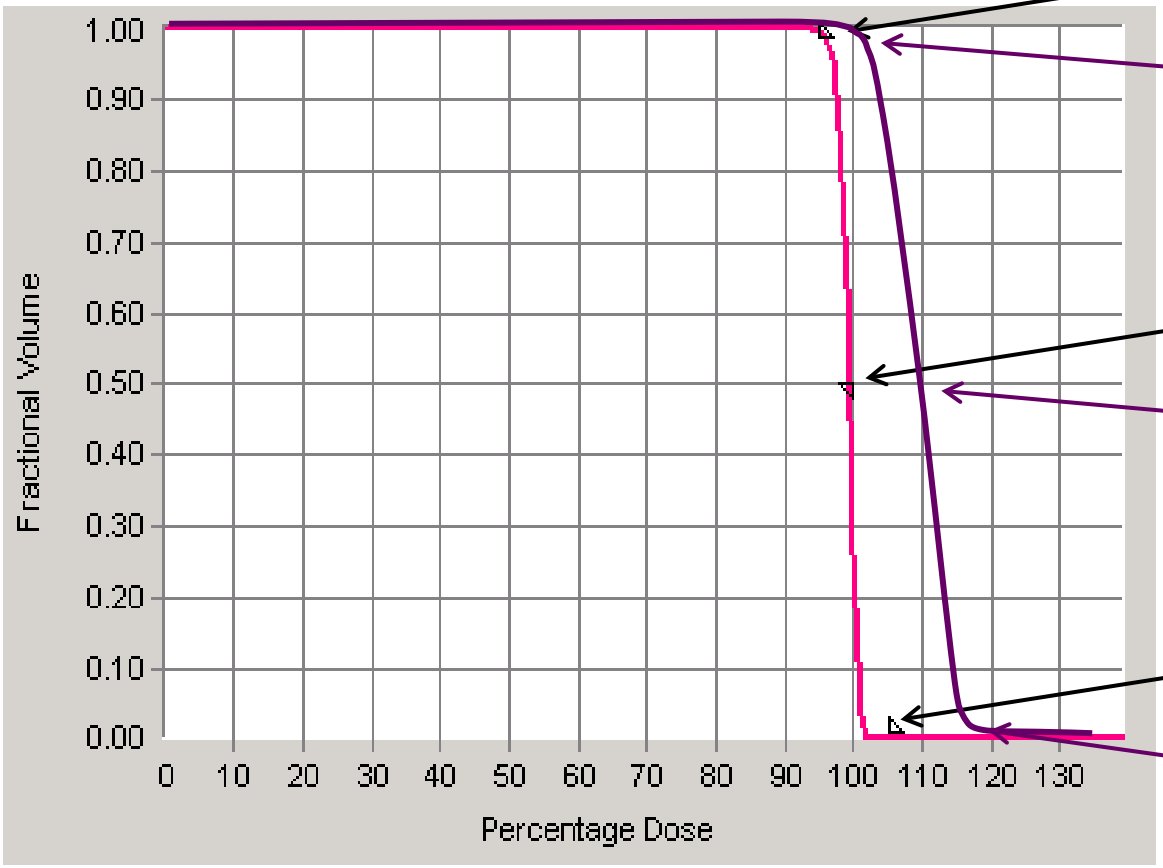
Prescribing

- Dose constraints (objectives) for min & max included (and median)



$V_{95\ \%}$

(Near) min dose increased

Median dose = $D_{50\ \%}$

Median now too high

$V_{105\ \%}$

(Near) max very high

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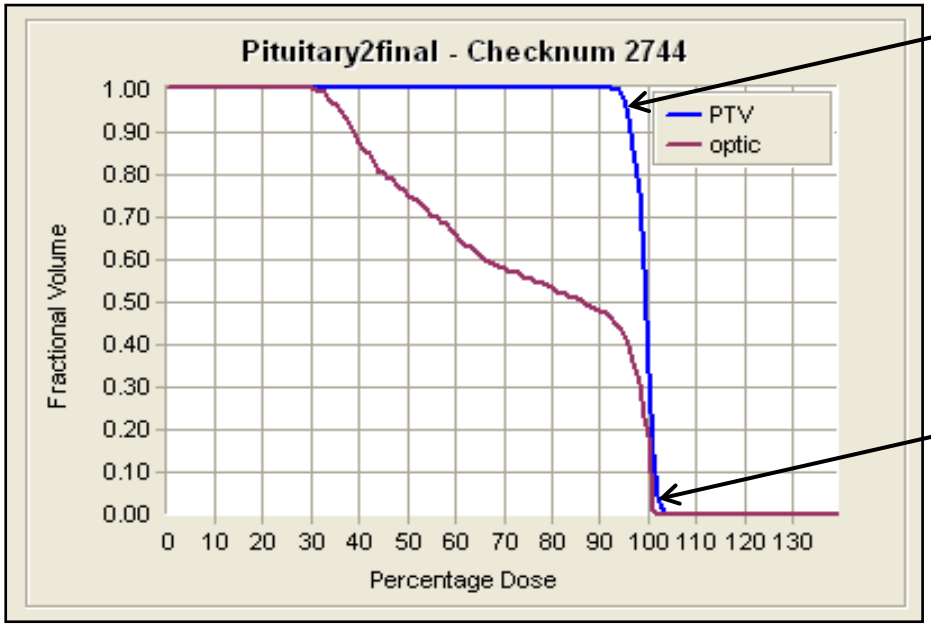
Prescribing

- Report near-maximum and near-minimum in target volume, rather than actual max & min
  - $D_{2\ \%}$ for near-max, $D_{98\ \%}$ for near-min

Prescribing

- Report near-maximum and near-minimum in target volume, rather than actual max & min
  - $D_{2\ \%}$ for near-max, $D_{98\ \%}$ for near-min



$D_{98\ \%}$ = target near-min (dose covering 98% of target volume)

$D_{2\ \%}$ = target near-max (dose covering 2% of target volume)

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Prescribing

- Clinical relevance of minimum (near-min) dose point may depend on its position within the PTV
  - Minimum dose in edge of PTV may be of marginal significance
  - Minimum dose in centre (in GTV) may be rather important

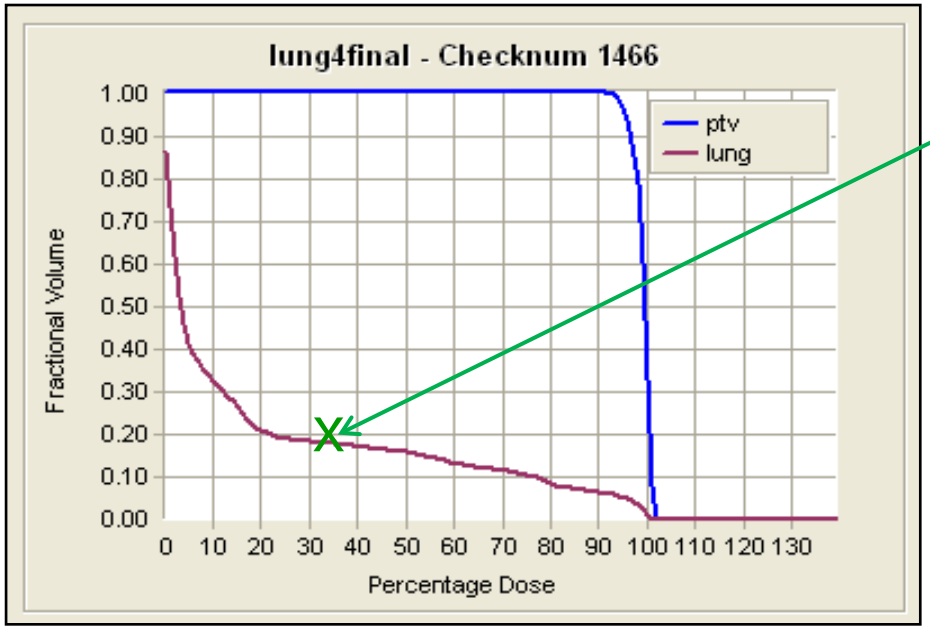
Prescribing

- Concept of using dose volume histograms for dose specification is introduced in ICRU 83
  - Dose-volume prescribing in place of dose
  - Dose-at-a-point specification is retained for purposes of comparison

- Contains worked examples, which may be helpful

Prescribing

- Add volume parameters where relevant
  - e.g. $V_{20\ Gy}$ for lung



$V_{20\ Gy}$

Relates to clinical outcome

NB $V_{20\ Gy} = V_{33\ \%}$ (for 60 Gy)

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Prescribing

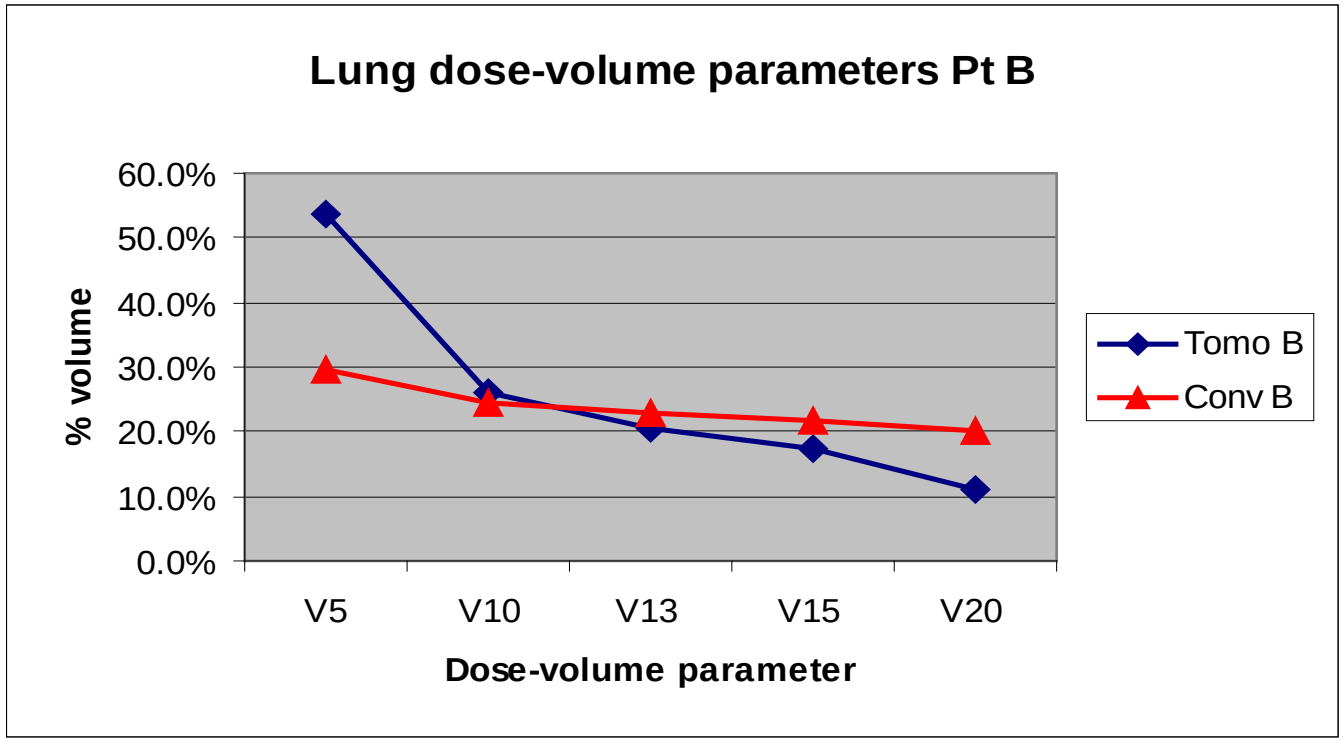
- Add volume parameters where relevant
  - e.g. $V_{20\ Gy}$ for lung

- For parallel structures, worth reporting more than 1 dose point
  - i.e. moving towards dose-volume reporting

- Essential to add units e.g $D_{50\ \%}$ or $V_{20\ Gy}$
  - $D_{50\ \%}$ = dose covering 50% of the target volume
  - $V_{20\ Gy}$ = volume receiving 20 Gy (or less)

Lung doses

- 2 plans compared
  - IMRT : 'CRT'
- Mean lung dose same = 9 Gy
- DVH different
- In reporting, the DVH (or some points on it) may be useful



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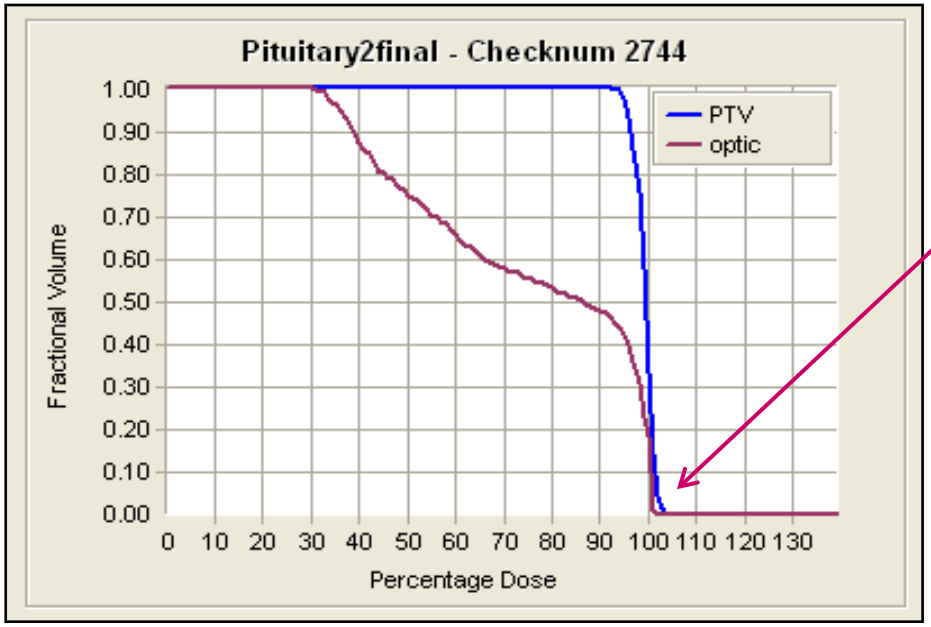
Prescribing

- For serial organs, maximum (near-max) dose is relevant parameter
  - ICRU recommends $D_{2\,\%}$ rather than D_{Max} ($D_{0\,\%}$)
  - Overcomes problem of defining (knowing!) what volume of the structure is important
  - Note that $D_{2\,\%}$ not validated (yet); caution given !
  - But ... it is logical
  - However, effect will depend on total volume of structure
  - In gynae brachtherapy often use $D_{2\,cm^3}$

Prescribing

- Report near-maximum
  - $D_{2\ \%}$ for near-max



$D_{2\ \%}$ = OAR near-max (dose covering 2% of target volume)

No PRV used here because
- OAR enclosed within PTV
- dose < OAR tolerance

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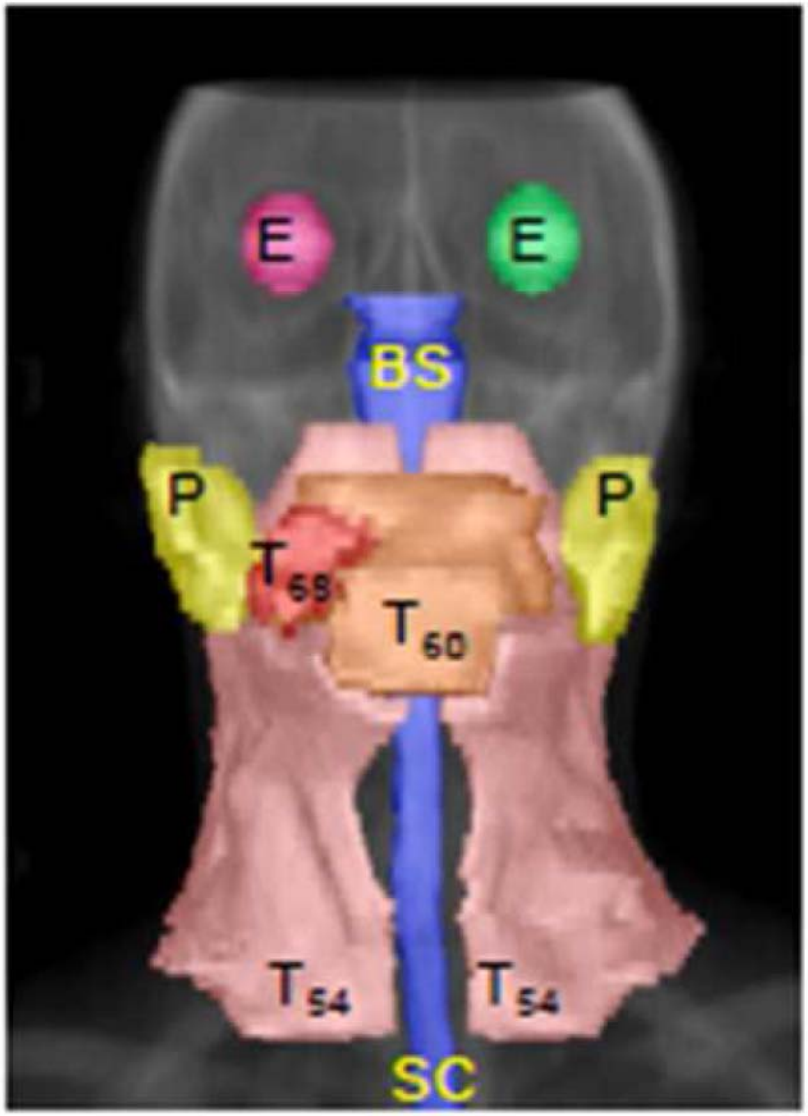
ICRU guidance

- ICRU 83 mentions the possibility of adding some additional parameters relating to dose
- Optional, but may become interesting

  - Homogeneity Index & Conformity Index
  - EUD – Equivalent Uniform Dose
  - TCP, NTCP
  - Probability of uncomplicated tumour control (PUC)

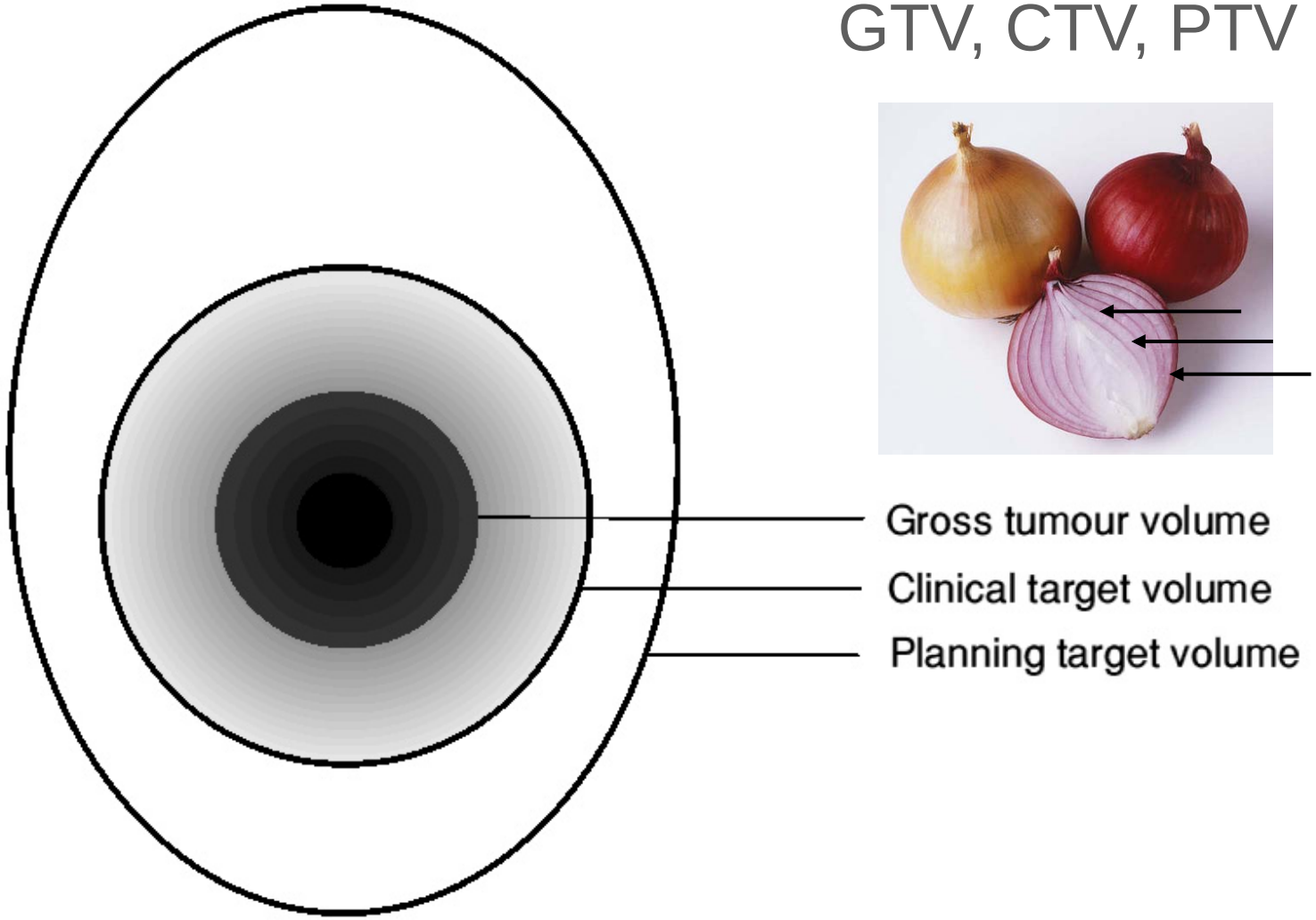
- Some details at end of lecture notes

Target volumes



Target volumes

- ICRU 50 target volumes
- The PTV can be eccentric



Summary

- GTV is tumour you can ***See - Feel – Image***
  - Outline what you see !

- CTV - contains GTV and/or sub-clinical disease
  - Tumour ***cannot*** be seen or imaged
  - Can be individualised to anatomy

- PTV is a geometric volume
  - Ensures prescription dose is delivered to the CTV
  - Includes systematic + random error components

Target volumes - PTV

- PTV is a geometric concept designed to ensure that the prescription dose is actually delivered to the CTV

- In a sense, it is a volume in space, rather than in the patient
- PTV may extend beyond bony margins, and even outside the patient

- ***Systematic*** and ***random*** errors need to be quantified to produce the PTV margin

    - **PTV = 2.5Σ + 0.7σ**

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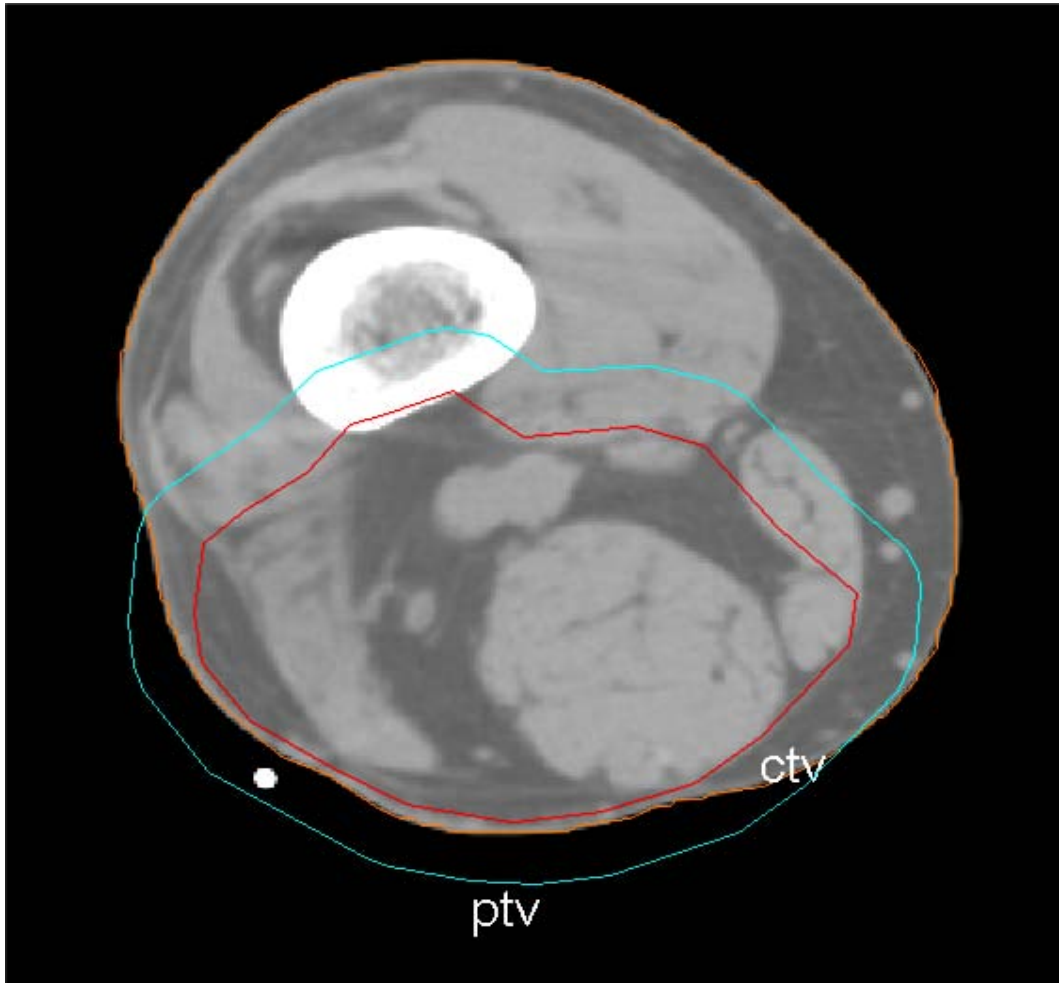
Target volumes - PTV

- PTV extends outside the patient
- NB problem of IMRT optimisation
  - in the PTV outside the patient
  - in the build up region



Other volumes - TD

- **Treated volume – TD**

- Recognises that specified isodose does not conform perfectly to the PTV
  - Can be larger or smaller

- $D_{98\%}$ could be used

- Needs to report size, shape & position relative to PTV
  - Can help evaluation of causes for local recurrences

Other volumes - RVR

- **Remaining Volume at Risk – RVR**

- Volume of the patient excluding the CTV and OARs

- Relevant because unexpected high dose can occur within it
- Can be useful for IMRT optimisation

- Might be useful for estimating risks of late carcinogenesis

Target volumes – OARs

- Organs at Risk are normal tissues whose radiation tolerance influences
  - treatment planning, and /or
  - prescribed dose
- Now know as OARs (not ORs)
- Could be any normal tissue

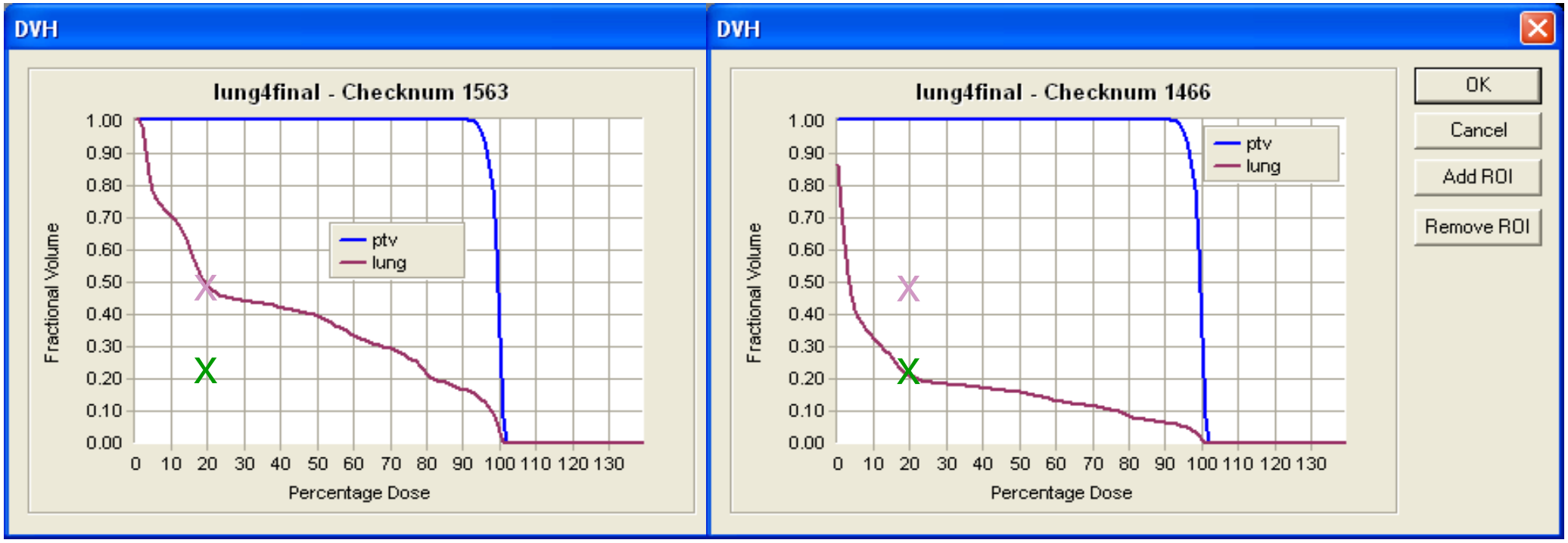
Target volumes – OARs

- Best available data is given in the QUANTEC review

- Marks LB, Ten Kaken R, and guest editors
  Int. J. Radiat Oncol Biol. Phys. 2010; 76; 3 (Suppl): S1 - 159

Target volumes – OARs

- For parallel organs, comparison between plans, patients or centres requires the ***whole*** organ to be delineated, according to an agreed ***protocol***



- Whole lung not outlined
- Better !

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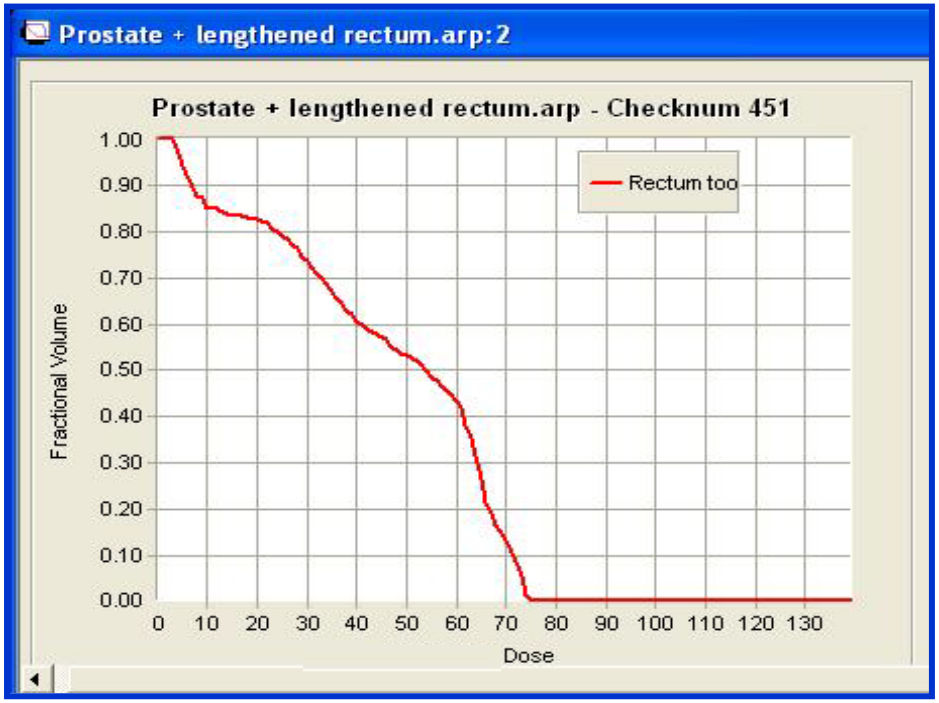
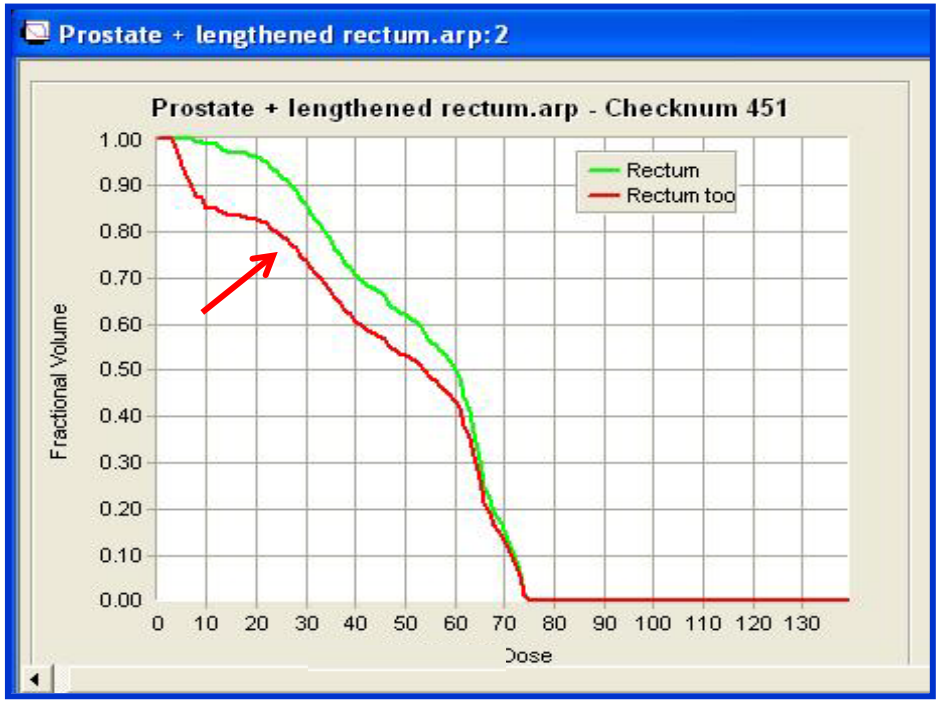
Target volumes – OARs

- For other parallel organs, over-contouring may lead to DVHs which appear better but are incorrect
- Rectum– needs clear delineated, according to an agreed protocol



- Rectum 'over-contoured'



- 'Better' DVH is incorrect

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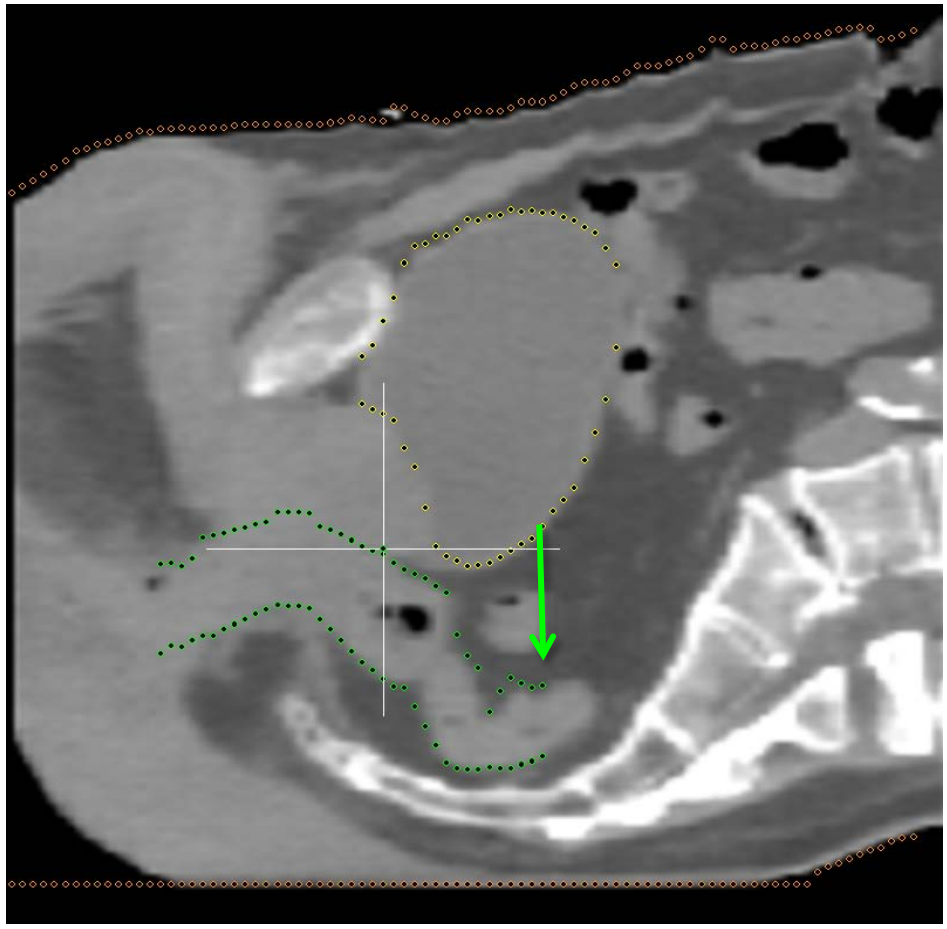
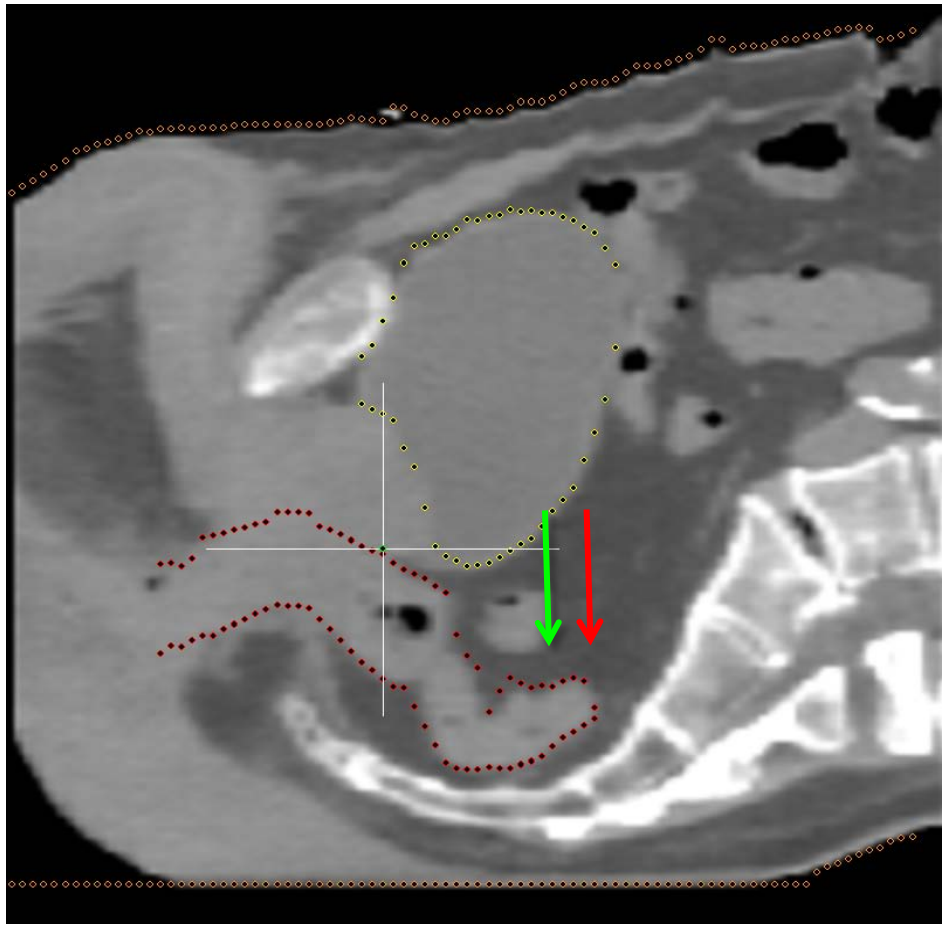
Target volumes – OARs

- Rectum–clear delineation, according to an agreed protocol



- Rectum correct



- Rectum on 4 slices more

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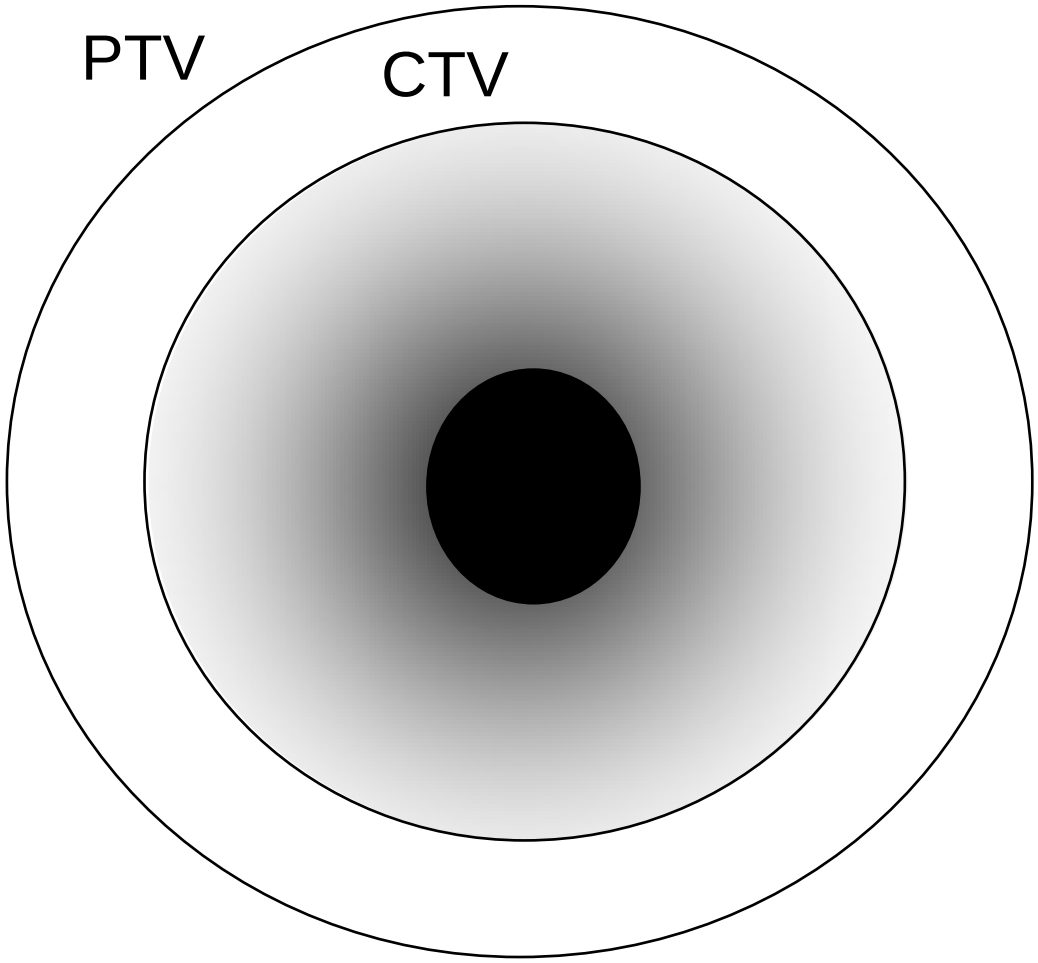
Target volumes – OARs + PRVs

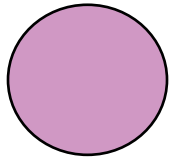
- Uncertainties apply to the OAR … so a 'PTV margin' can be added around it - to give the Planning organ at Risk Volume (PRV)

- But … the use of this technique will substantially increase the volume of normal structures

- May be smaller than PTV margin
  - Component for systematic error can often be smaller

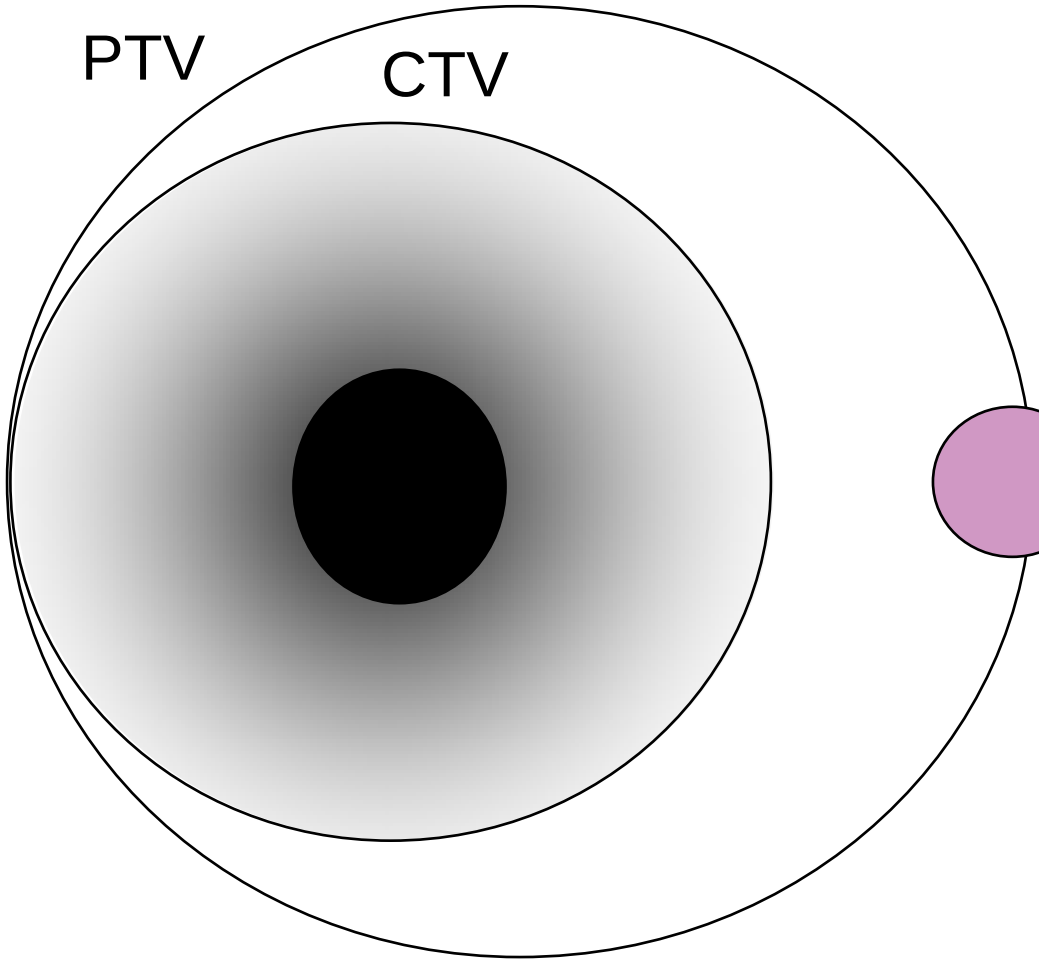
Target volumes – OARs + PRVs





- OAR clear of PTV
- OAR safe …

Target volumes – OARs + PRVs



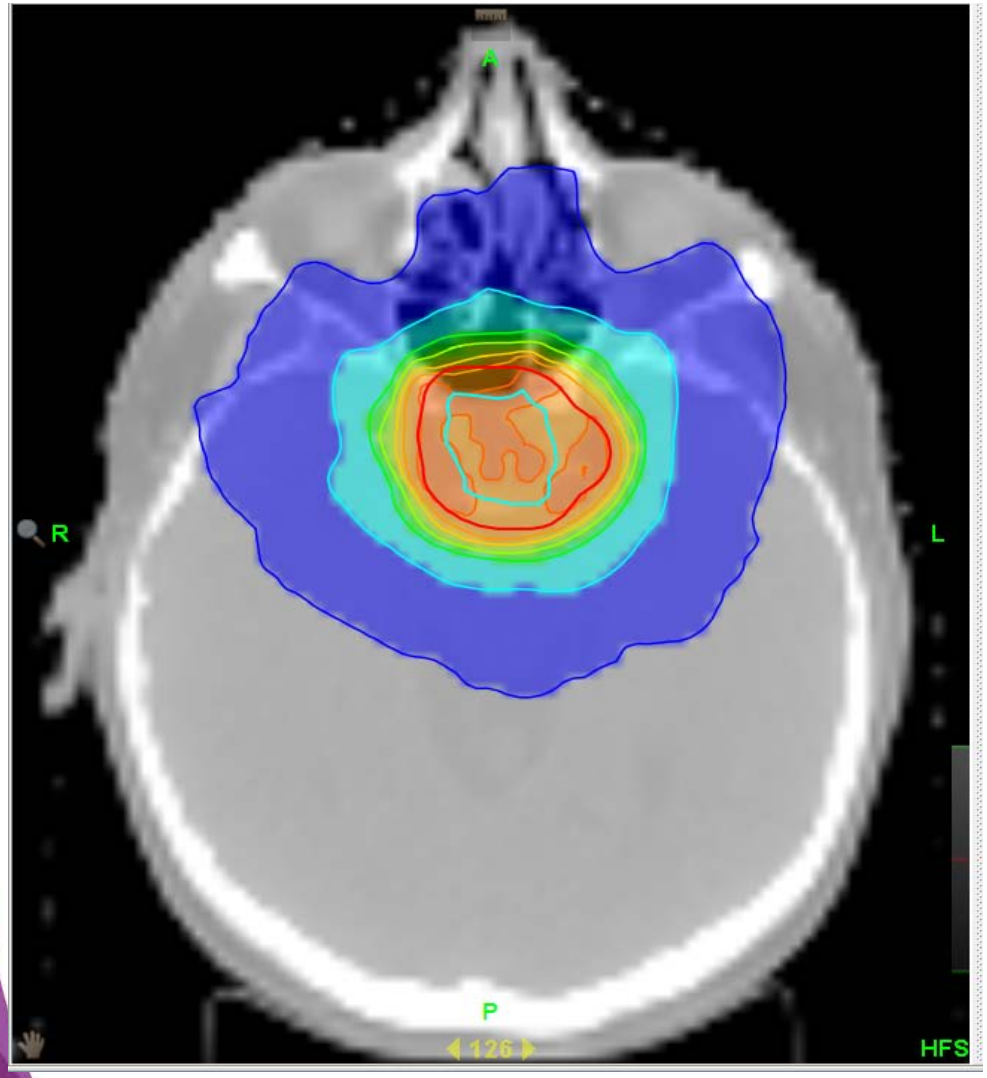
- OAR moves with CTV
- OAR not so safe ...

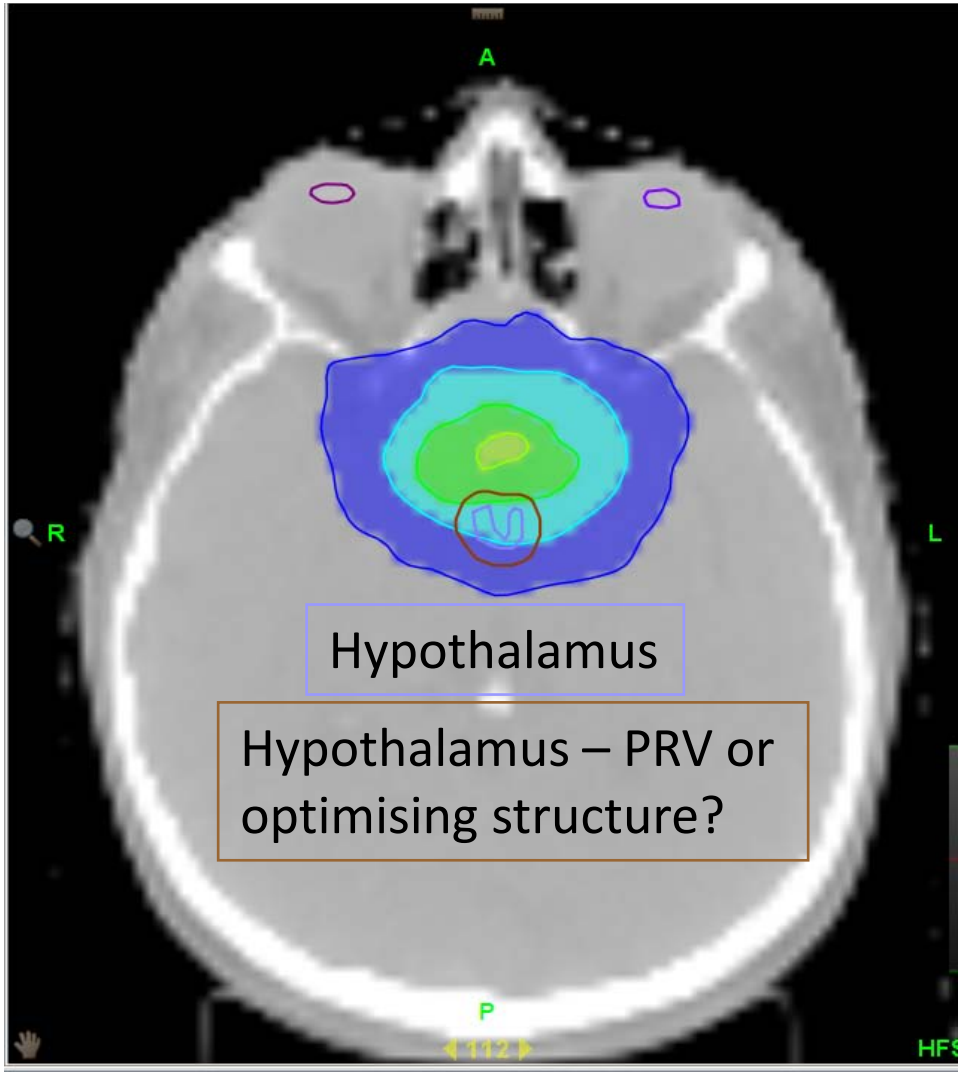
Target volumes – PRV

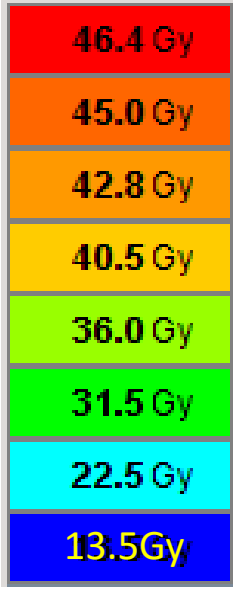
- The use of a PRV around an Organ at Risk is relevant for OARs whose damage is especially dangerous
- This applies to organs where loss of a ***small*** amount of tissue would produce a ***severe*** clinical manifestation
- A PRV is relevant for an OAR with serial organisation (almost exclusively)
  - Spinal cord
  - Brain stem
  - Optic pathway
- A PRV is ***not*** the same as a plan optimising volume

Target volumes – PRV or optimising structure?

Hypothalamus DVHs







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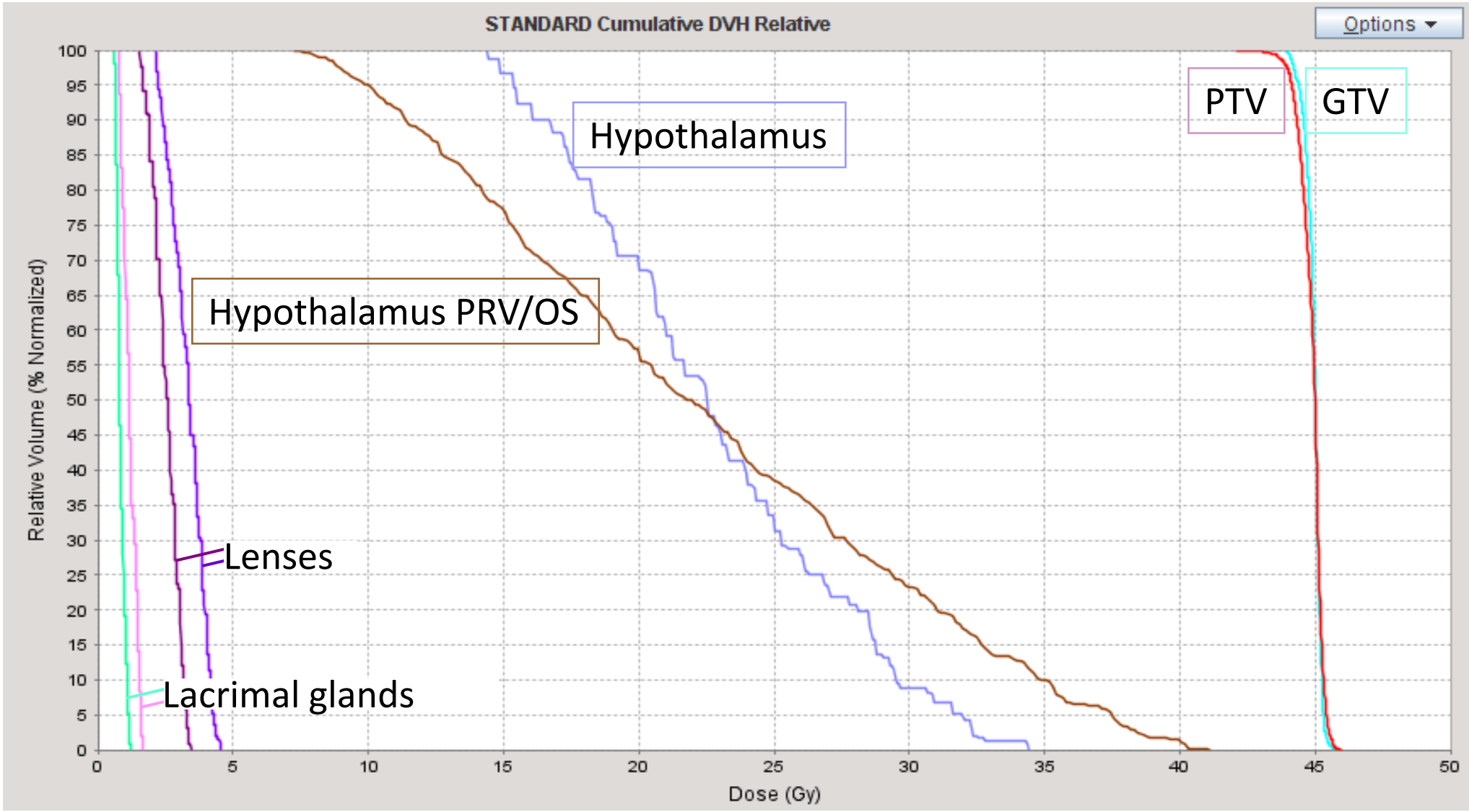
Hypothalamus DVHs



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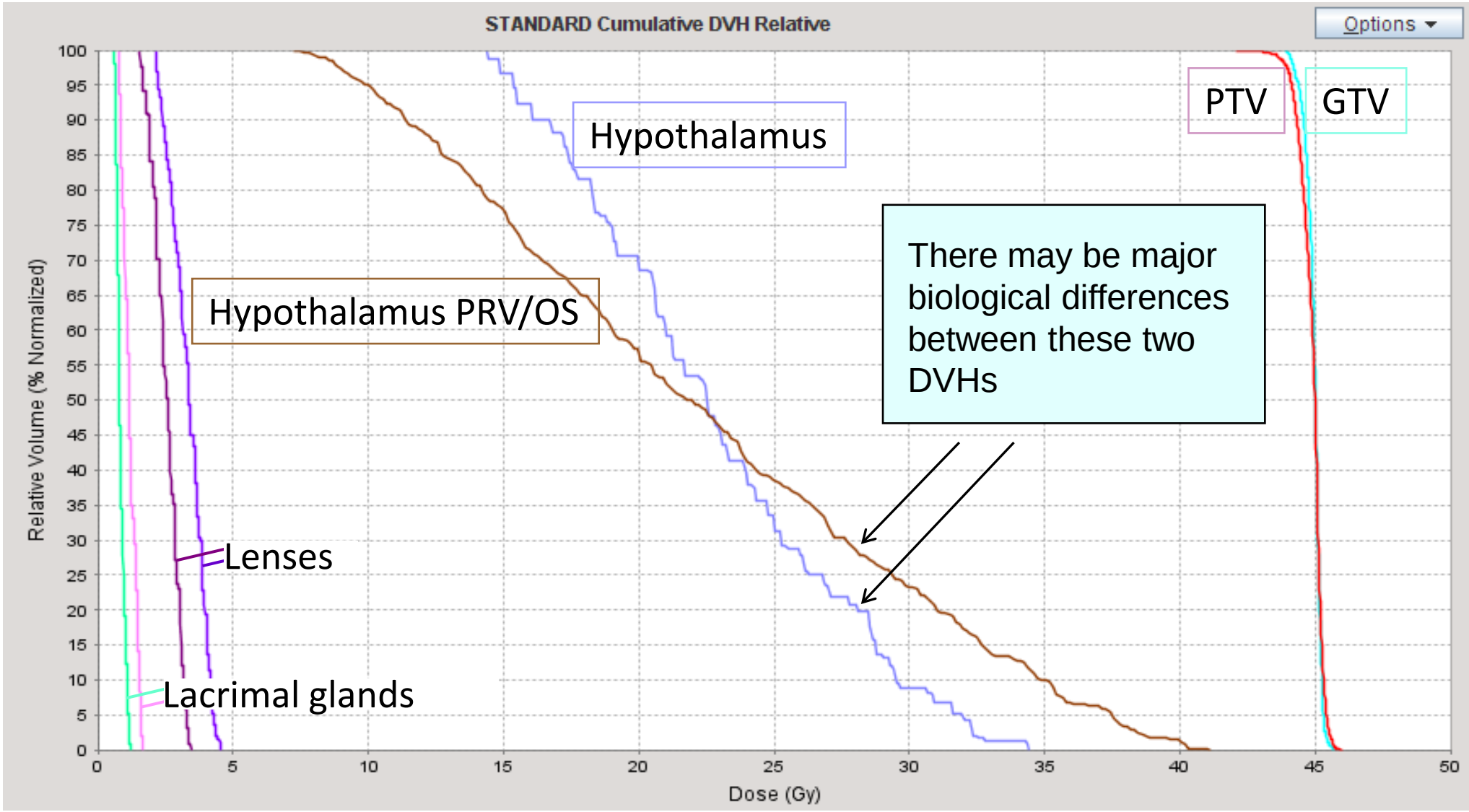
Hypothalamus DVHs



Planning dose limits

Planning limits

- Planning dose limits are either
  - Objectives
  - Constraints = absolute

- Important to consider dose limits as one or other type

- Not quite as easy as it seems to set values for them

Planning constraints

- Objectives
  - What we would *like* to achieve
  - We should try to meet them
  - Allow greater dose (or volume) if no alternative

- Constraints
  - What we *must* achieve
  - These are like a ‘wall’
  - We must meet them
  - Absolute limits (e.g. no areas of higher dose)

Planning constraints

- For a ‘class solution’ it should be possible to set good values
  - Values are based on experience from other cases
  - Typically apply to most of the patients
  - Not fully individualised

Planning constraints

- For an uncommon (challenging) case, there may be no experience
  - Objective
    - If set too low allows computer (planner) to accept plan less good than is really possible
    - If set too high then effectively fail to guide the plan
  - Constraint
    - If set too low, then drives the plan away from optimal solution
    - If this is a normal tissue constraint then typically drives down dose in PTV
    - If too high then may not protect normal tissue

Prioritising

- Constraints also need to be *prioritised*
  - Primary constraint = PTV dose
  - Primary constraint = normal tissue absolute constraint
  - Balance of prioritisation for different normal tissues may be needed
  - Different solutions may be possible

Planning sheet

- Pre-printed sheet for CNS cases
- 2 clear columns
- Absolute = constraint

Radiotherapy Physics
Cancer Division & Haematology Directorate

CT Volume Definition – CNS Standard

Diagnosis			
Planning Date		Radical ☐	
		Palliative ☐	
Volume	**PTV1**	**PTV2**	**PTV3**
Dose			
Fractions			

Hospital no: {Ident.IDA@U}
Surname: {Patient.Last_Name@U}
First names: {Patient.First_Name@U}
Date of birth: {Admin.Birth_Date@d6b}
NHS No: {Ident.IDB@U}

Volumes defined in Prosoma

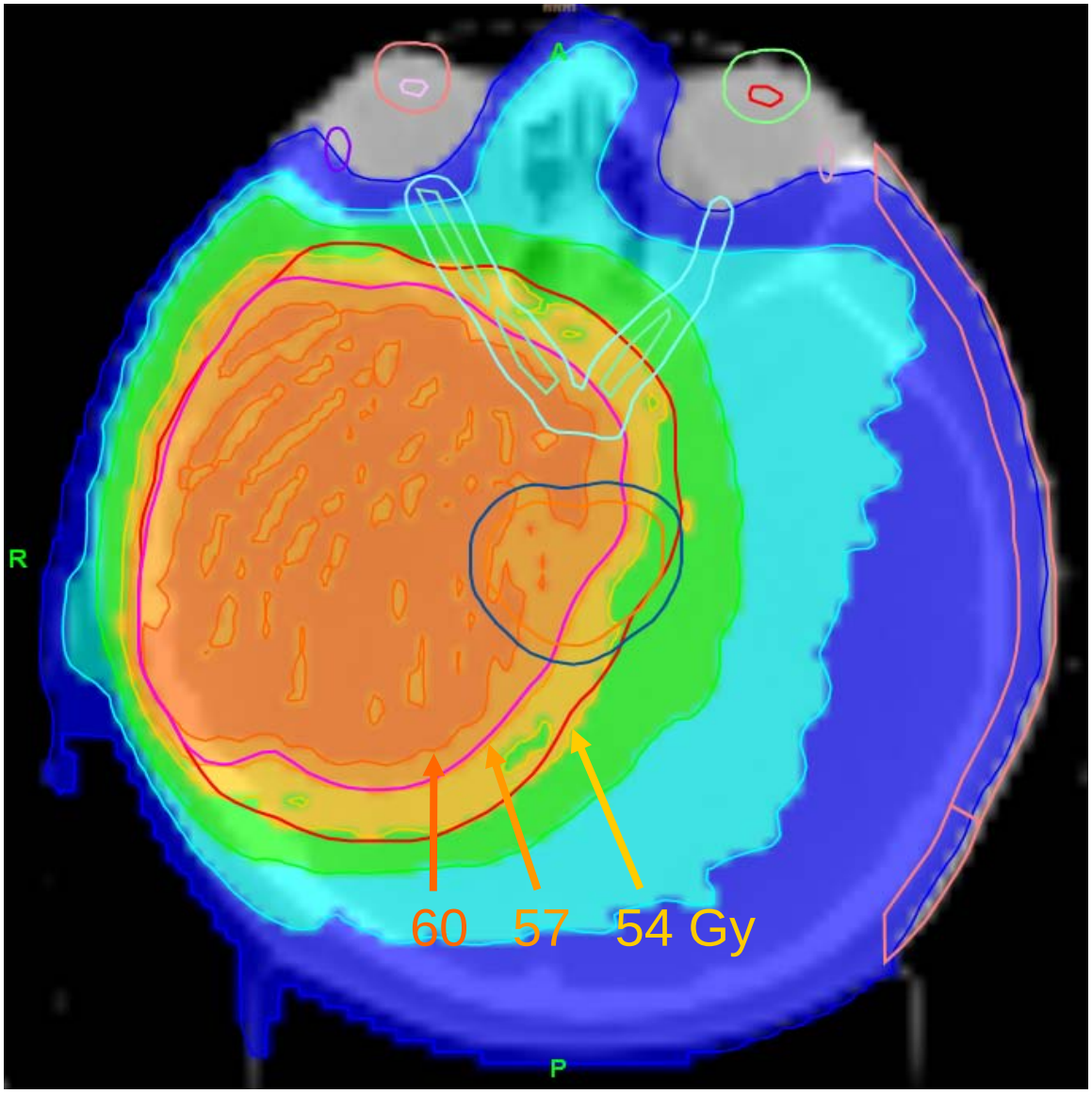
SP		ProSoma Comment	

Margins to be used (cm)	All	*AP*	*Lateral*	*Sup-Inf*
CTV1 – PTV1	cm	cm	cm	cm
CTV2 – PTV2	cm	cm	cm	cm
CTV3 – PTV3	cm	cm	cm	cm

All dose constraints are maximum point dose unless otherwise specified

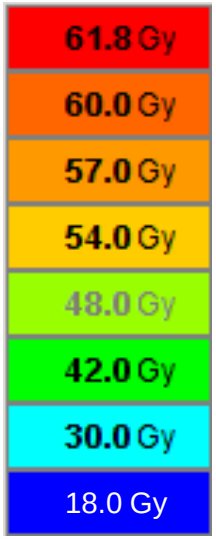
Use?	Organ	Objective (Gy)	Absolute (Gy)
☐	PRV Spinal Cord	48	50
☐	PRV Brainstem	50	52
☐	PRV –Optic Chiasm	50	54
☐	PRV Lt Optic Nerve	50	54
☐	PRV Rt Optic Nerve	50	54
☐	Hippocampus / Eloquent cortex (1cc)		
☐	Pituitary		
☐	Lt Globe	40	45
☐	Rt Globe	40	45
☐	Lt Lens	6	
☐	Rt Lens	6	
☐	Lt Cornea	30	
☐	Rt Cornea	30	
☐	Lt parotid (mean)	20	-
☐	Rt parotid (mean)	20	-
☐	PRV Lt Cochlea (mean)	35	45
☐	PRV Rt Cochlea (mean)	35	45
☐	Mandible	60	-
☐	Lt Lacrimal gland (mean)	26	-
☐	Rt Lacrimal gland (mean)	26	-
☐	Skin		

Objectives and Priorities



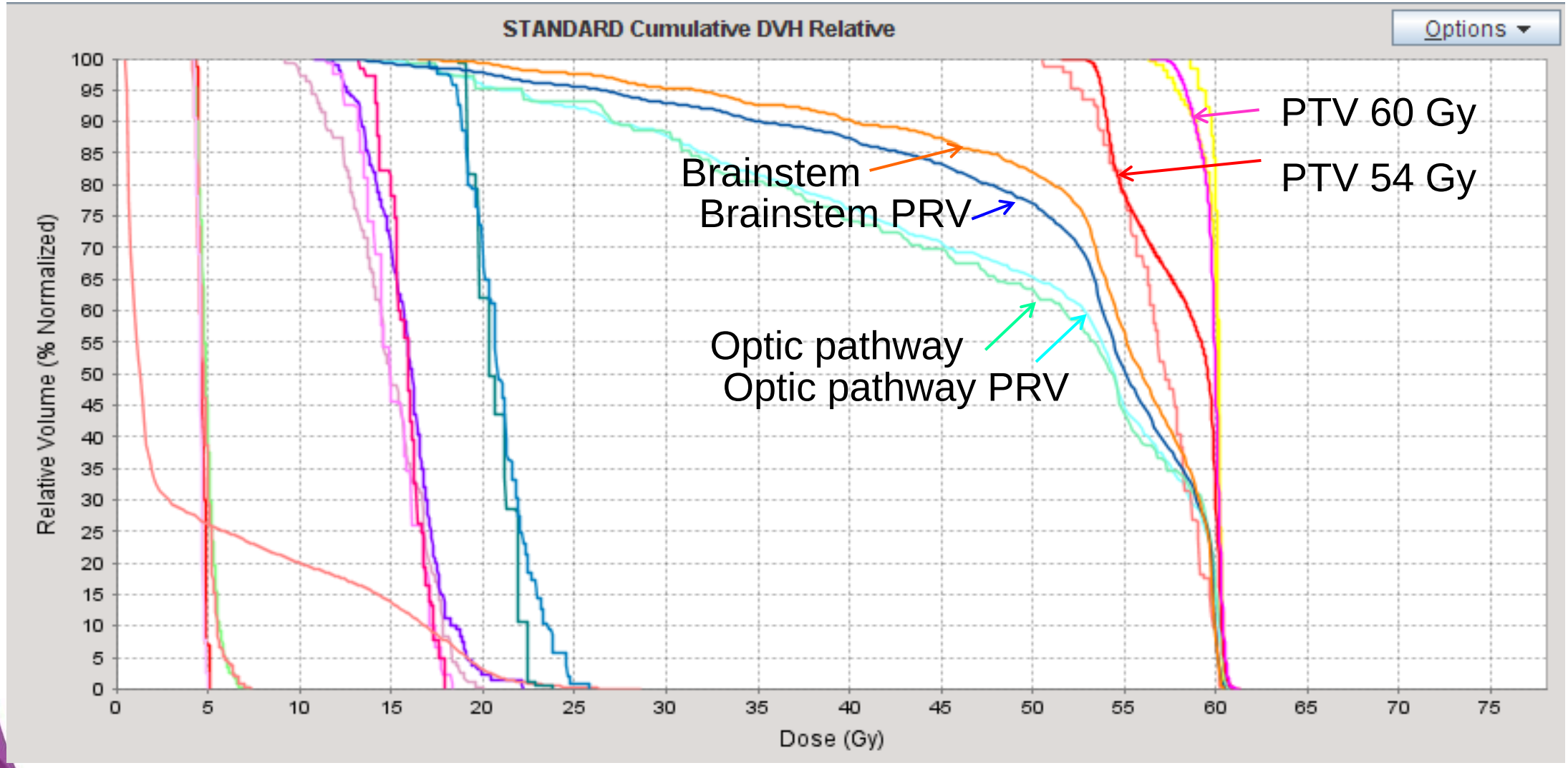
Glioblastoma

Dose - Gy



- Objectives for PTV doses
- Constraint for max dose in optic nerves
- Prioritise PTV > PRV

GBM - IMRT plan DVHs



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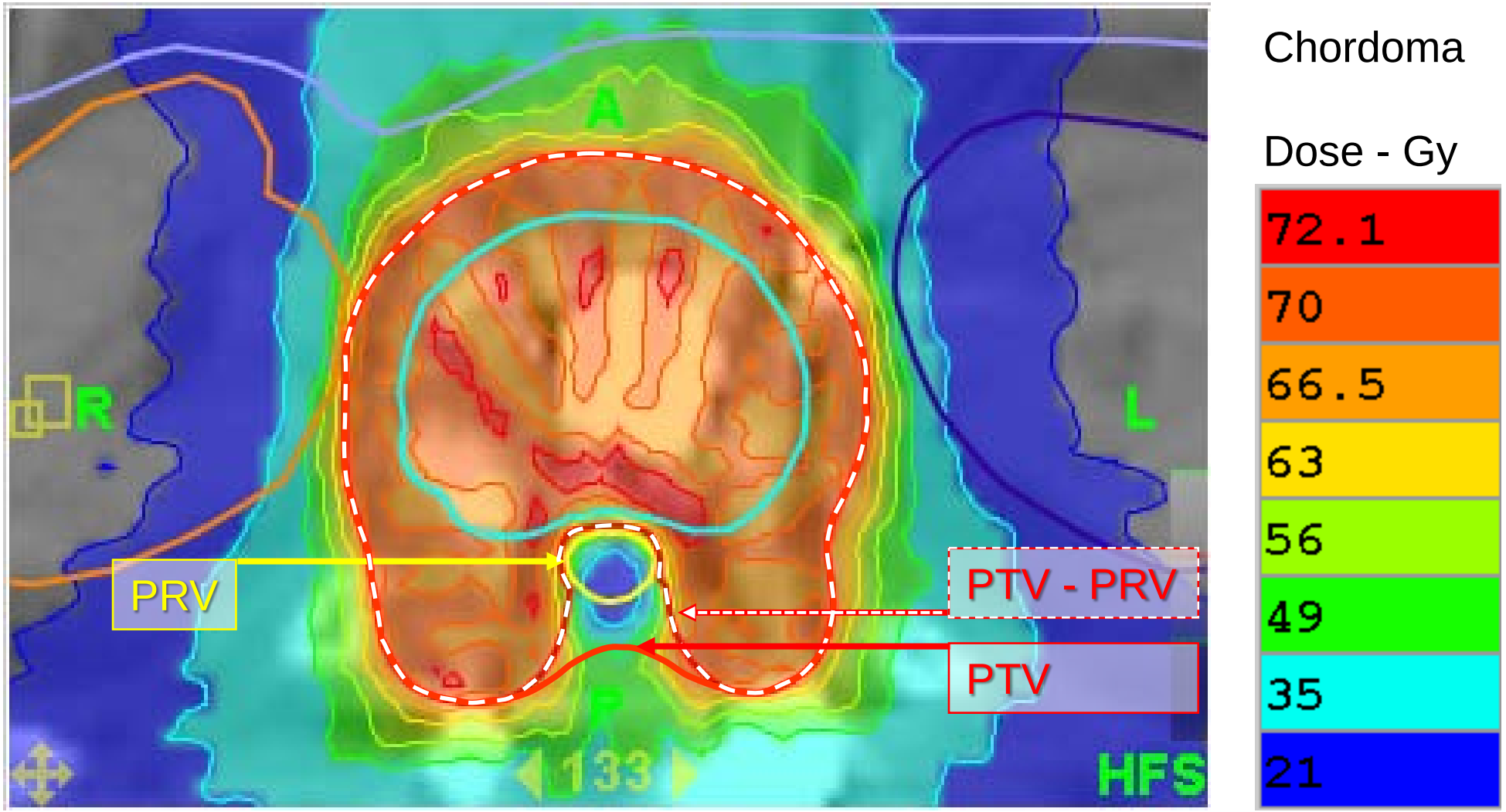
Constraints and Priorities



- Absolute dose constraint for cord PRV (58.6 Gy for 70 Gy/39#)
- Priority PRV > PTV

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Target volumes – overlaps

Target volumes – overlaps

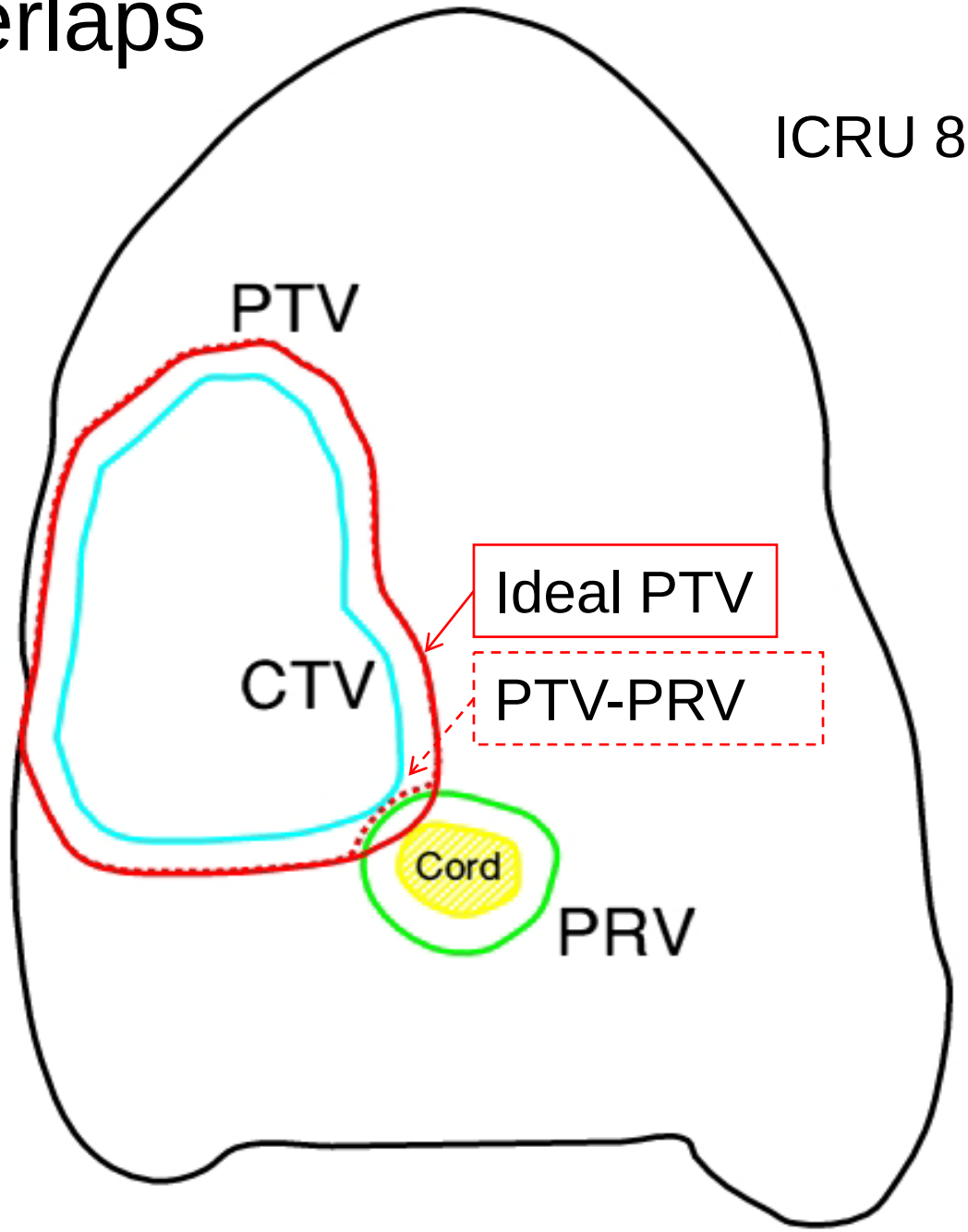
- There are always occasions when the PTV and OARs/PRVs overlap
- What is the best strategy?

- The planning concept has changed between ICRU 62 and 83
- In fact it changed completely in ICRU 83

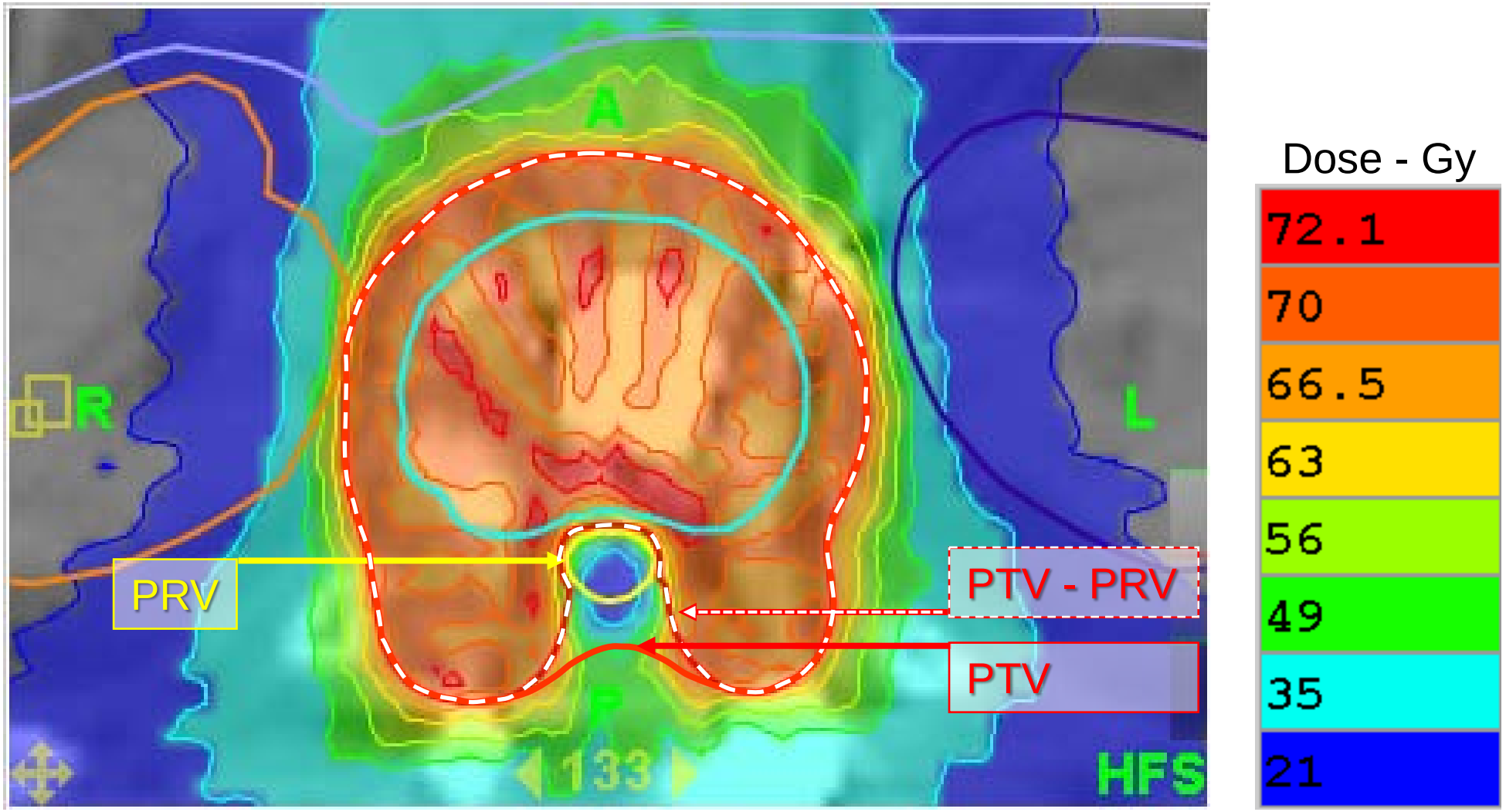
- ICRU 62 – edit PTV (even CTV) – fine for CRT
- ICRU 83 – ***do not*** edit – better for IMRT

Target volumes – overlaps

- ICRU 83 approach for IMRT
- Add 2nd volume avoiding overlap
- Specify priorities and doses



Target volumes – overlaps



- PRV essential here to protect cord (so is IGRT)
- Priority PRV > PTV

Target volumes – overlaps

- Advantages of not editing PTV (ICRU 83)
  - Clear to planner what is required
  - Clear on subsequent review what target was intended
  - Doses can be adjusted by dose constraints
  - More clearly matches the real clinical objectives
  - Ideal for IMRT delivery

Target volumes – overlaps

- Overlapping volumes requires:
  - Very clear objective setting
  - Good communication between clinician & planner

    Dialogue (i.e. 2 way communication) is recommended !

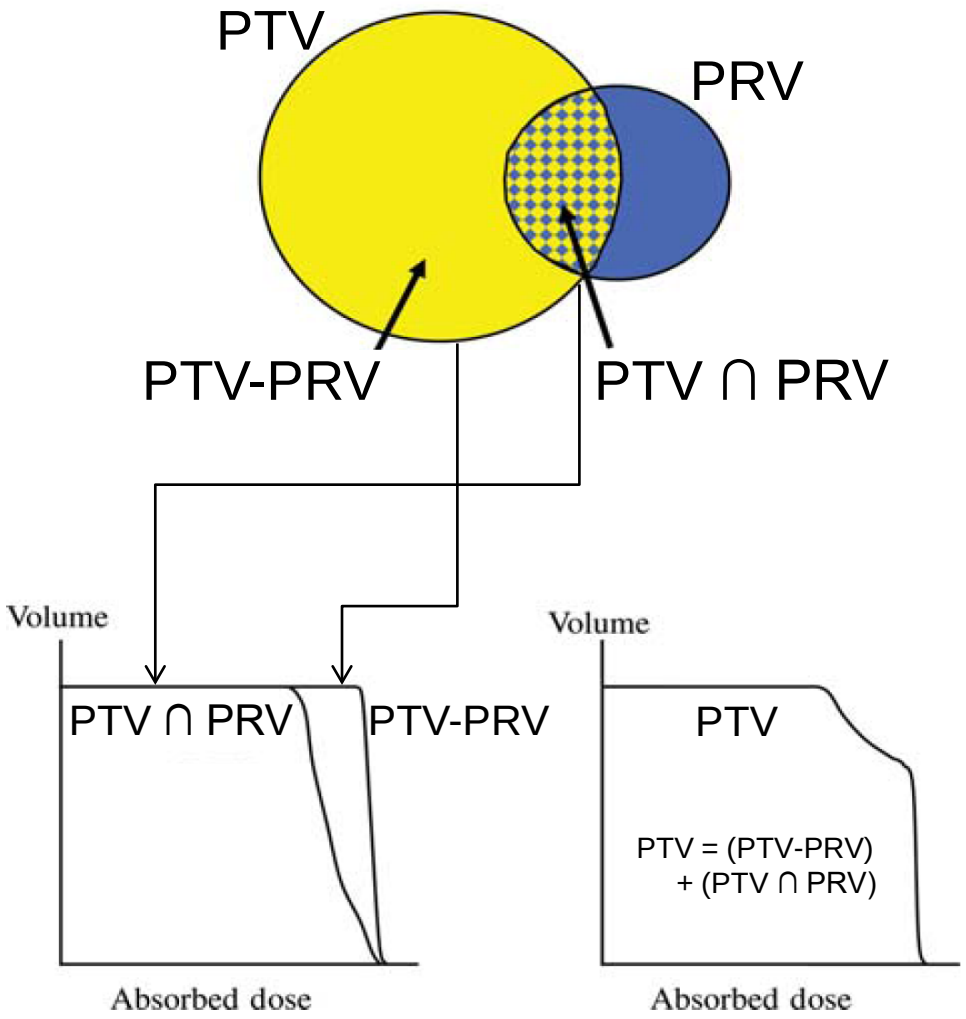
  - Use of optimiser to deliver different doses to different parts of the target

  - May make assessment of plan using DVH for the PTV more difficult

Target volumes – overlaps

From ICRU 83

- Review DVHs carefully
- Overall, more robust method



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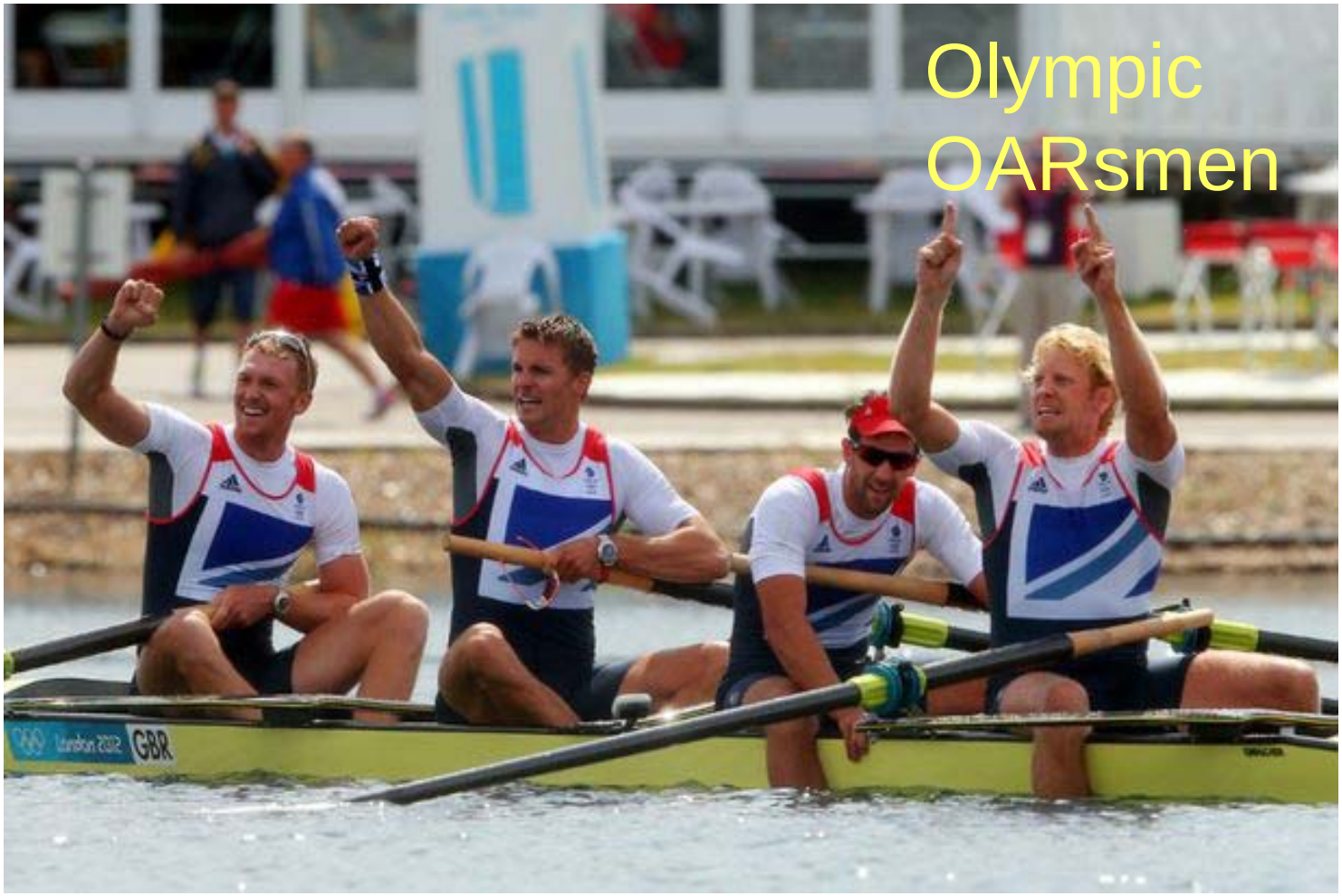
Take home messages

- Median dose closest to ‘old’ ICRU isocentre prescription point
- Contour OARs carefully with protocol
- Add PRV around CNS structures if giving high doses
- Overlaps can occur between PTV and OAR (or PRV)
  - Do not edit
  - Construct additional exclusion volumes
  - Use IMRT

Radiation oncology - a team effort



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Additional resources

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ICRU guidance

- ICRU 83 mentions the possibility of adding some additional parameters relating to dose
- Optional, but may become interesting

  - Homogeneity Index & Conformity Index
  - EUD – Equivalent Uniform Dose
  - TCP, NTCP
  - Probability of uncomplicated tumour control (PUC)

Homogeneity Index

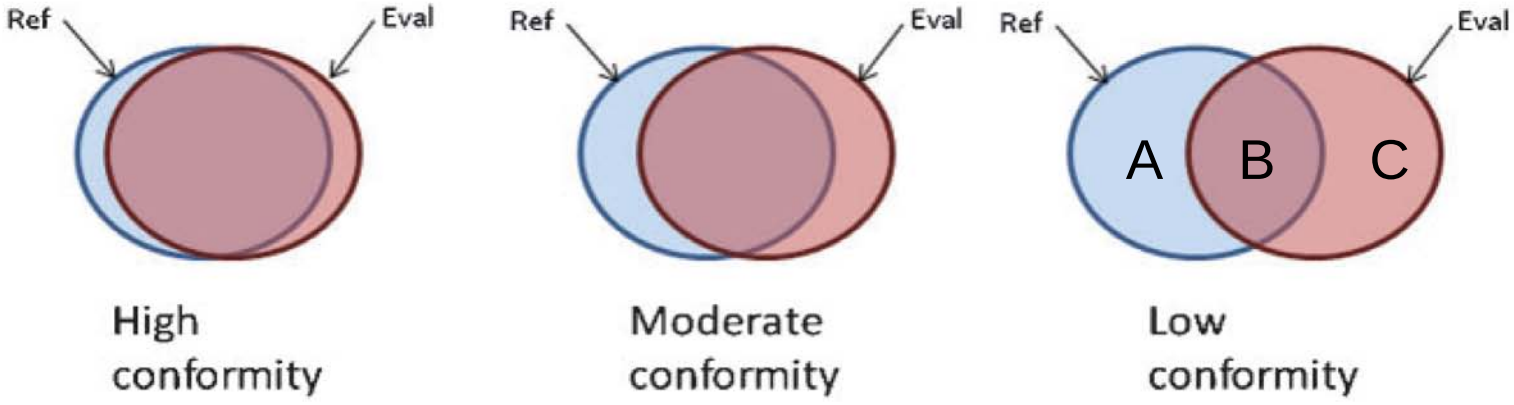
- Designed to show level of homogeneity

$$HI = \frac{D_{2\,\%} - D_{98\,\%}}{D_{50\,\%}}.$$

- Difficult to relate to experience (for me)
- Requires further investigation

Conformity Index

- Conformity index
  - Describes how well high dose isodoses ‘conform’ to the PTV
  - Compares specified isodose to PTV



$$\text{Conformity Index} = \frac{B}{(A+B+C)}$$

Equivalent Uniform Dose - EUD

- Reduces an inhomogeneous dose distribution to an equivalent homogeneous dose
- Can then be described by a single dose parameter

- Useful and worth understanding

- Gay HA, Niemierko A. A free program for calculating EUD-based NTCP and TCP in external beam radiotherapy. Phys Med. 2007; 23(3-4): 115-25
- Niemierko A. Reporting and analyzing dose distributions: a concept of equivalent uniform dose. Med Phys. 1997; 24(1): 103-10.

Equivalent Uniform Dose - EUD

- Depends on ‘knowing’ the value of the exponent ‘a’

$$EUD = \left(\sum_i v_i D_i^a \right)^{1/a}$$

  - v_i = volume of the dose-volume bin D_i
  - ‘a’ = response-specific parameter

Equivalent Uniform Dose - EUD

- For tumours ‘a’ is negative
  - Typical range -5 (‘less malignant’) – meningioma
  - to -15 (‘more malignant’) - chordoma

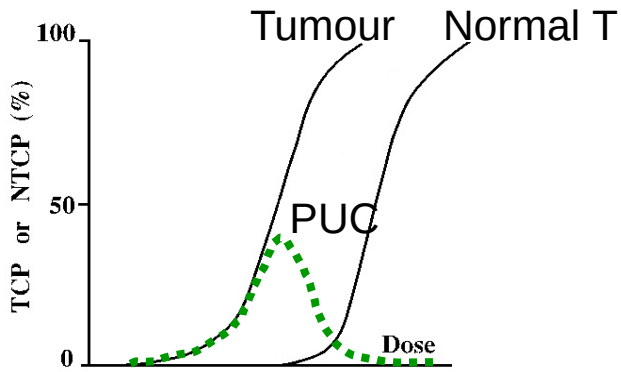
- For normal tissues ‘a’ is positive
  - Parallel - near 1
  - Serial – larger e.g. up to 20 for spinal cord

  - ‘a’ = 1/n in the LKB formulation

TCP, NTCP, PUC

- TCP, NTCP
  - Require assumptions and estimates in models
  - An obvious development
  - Requires more hard dose-volume response data

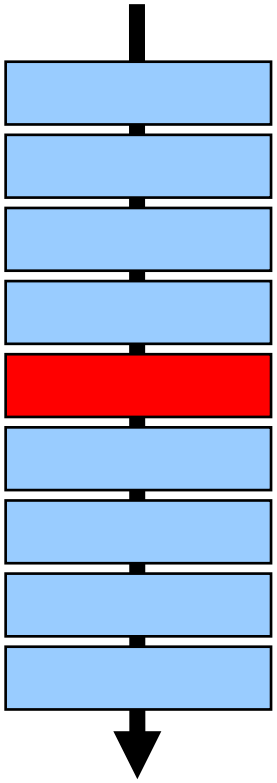
- Probability of uncomplicated tumour control (PUC)
  - ‘ideal’ parameter ?
  - May suggest lower doses



Extra slides

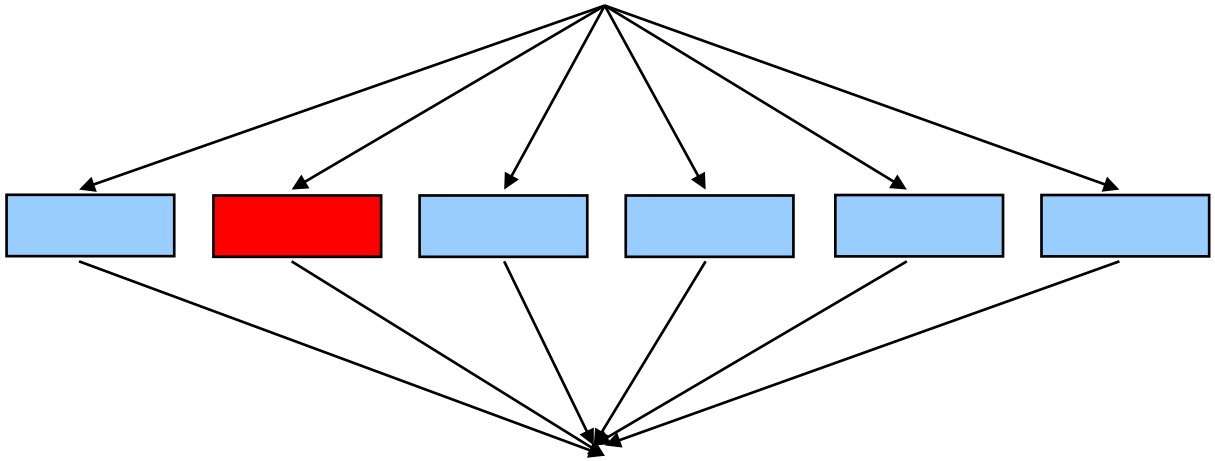
Tissue architecture

- Serial organ



- Damage to 1 part causes failure – eg spinal cord
- Severe clinical consequence

- Parallel organ



- Damage to 1 part (only) does not compromise function
- Examples ...

Target volumes – PRV

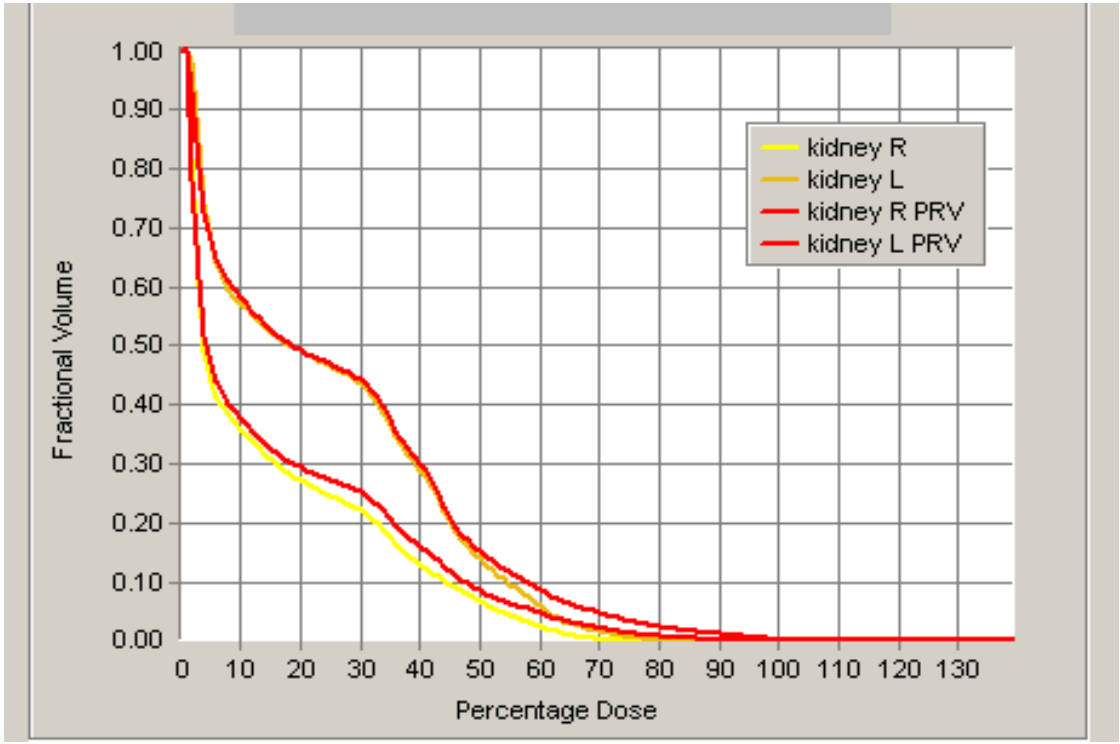
- Spinal cord & optic nerves/chiasm are perfect examples where a PRV may be helpful
  - serial tissue organisation
  - damage is clinically catastrophic
  - Add a PRV, especially if high doses are planned

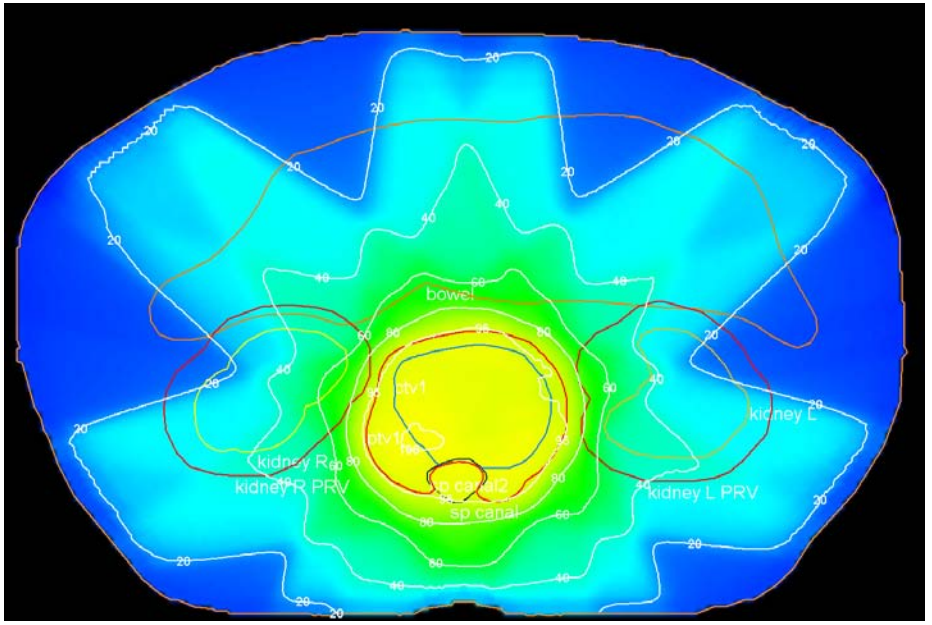
- Almost no other OARs where a PRV is needed
- PRV may be misleading for parallel organs

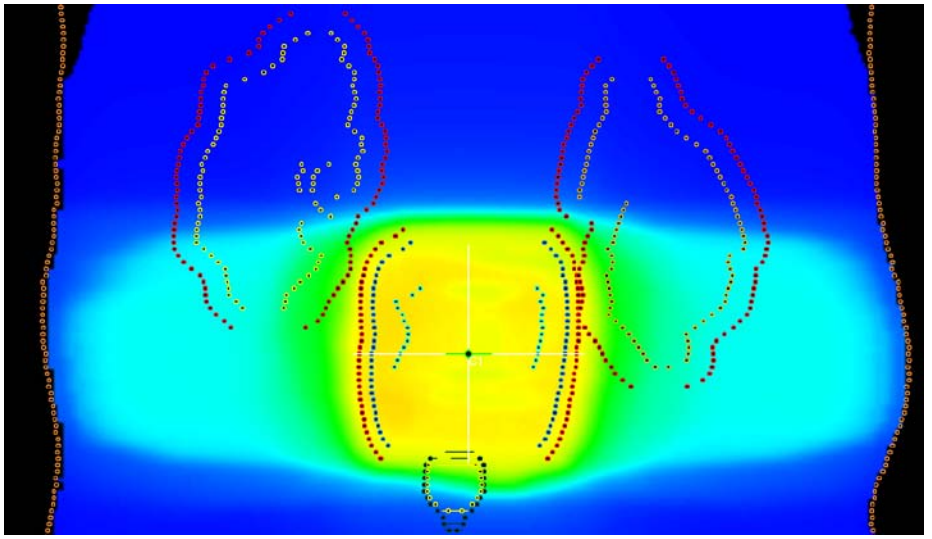
- Question of PRV for mixed parallel-serial structures

Target volumes – PRV

- Kidney PRV 10mm
- DVH for PTVs ≈ PRVs
- PRV often not of particular value

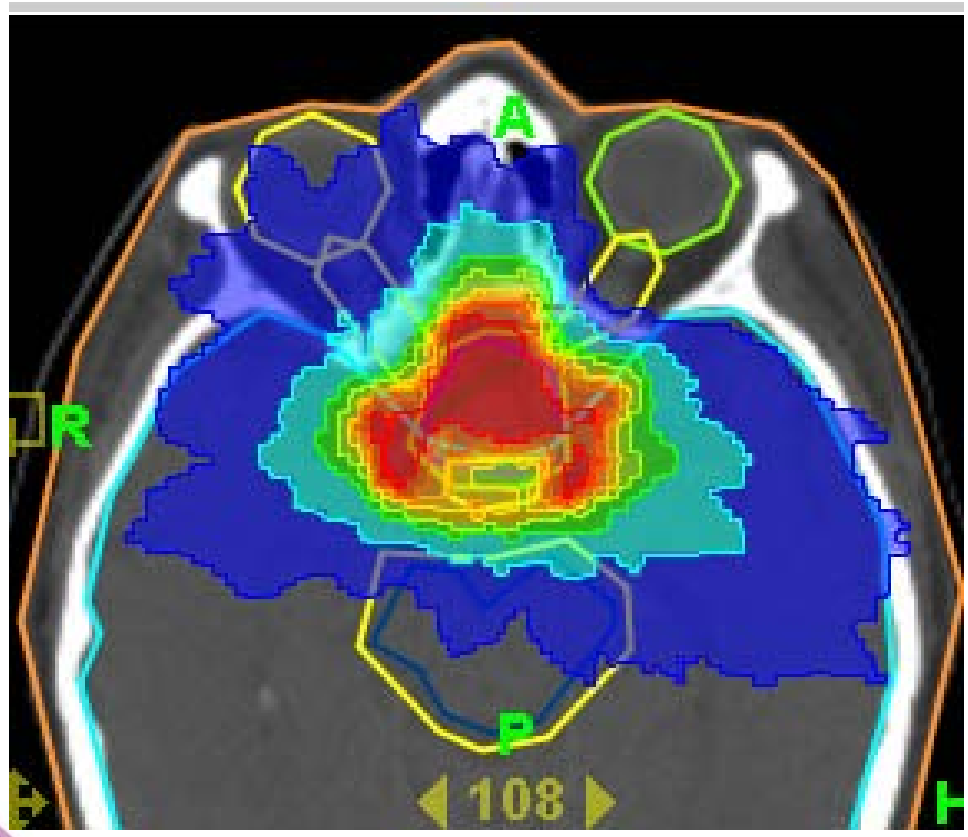


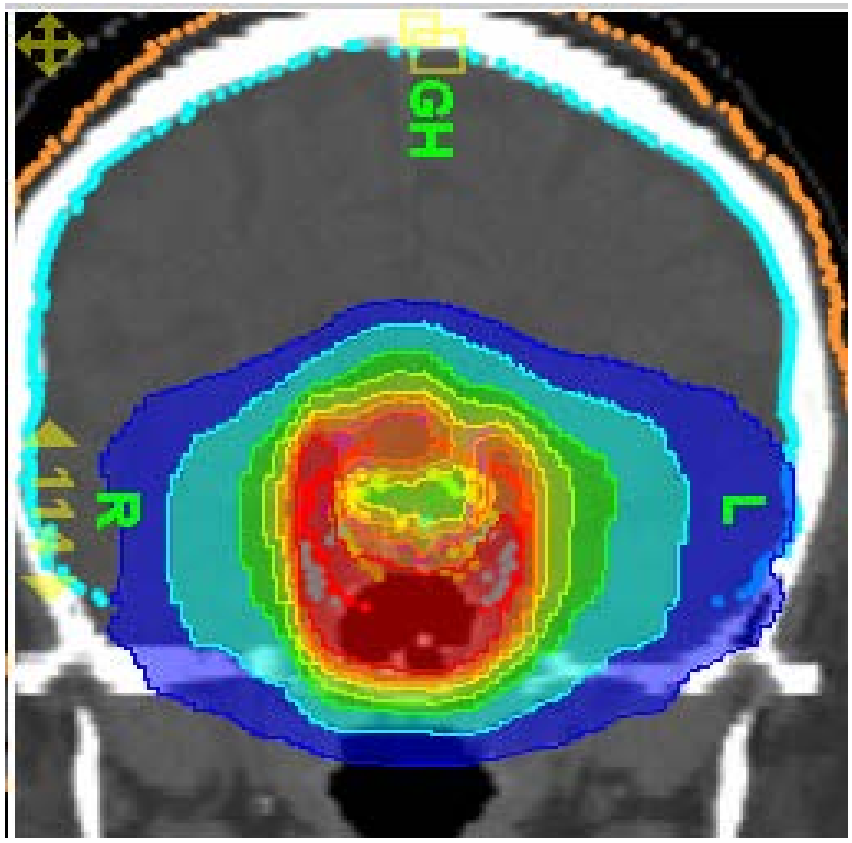




Target volumes – PRV

- PRV around optic nerves and chiasm
- Allows dose escalation - not needed for 50 Gy dose





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Non-IMRT planning
from simple to complex

Advanced Treatment Planning Course
14-18 September 2016 – Cambridge, UK

Markus Stock

MedAustron

ESTRO School

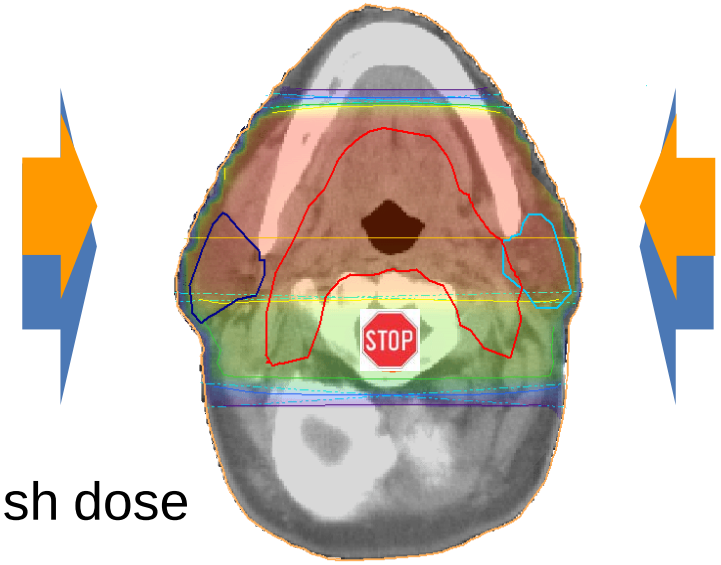
Content

- Basics 3D-CRT and IMRT
- General planning aspects
- Clinical examples
    - head and neck:
        - 3D conformal
    - cranio-spinal lesions:
        - beam set-up non-IMRT
        - challenges in planning

- advanced treatment planning – how to do it?

Basics and general planning aspects

Limitations of 3DCRT



- Hard to get acceptable plans for concave targets
- One needs a large number of beams to accomplish dose coverage for complicated target volumes
- limited possible beam directions in regions with large number of critical structures
- optimal beam angles often non- coplanar and can be difficult to apply without collisions, and moreover: *difficult to find*

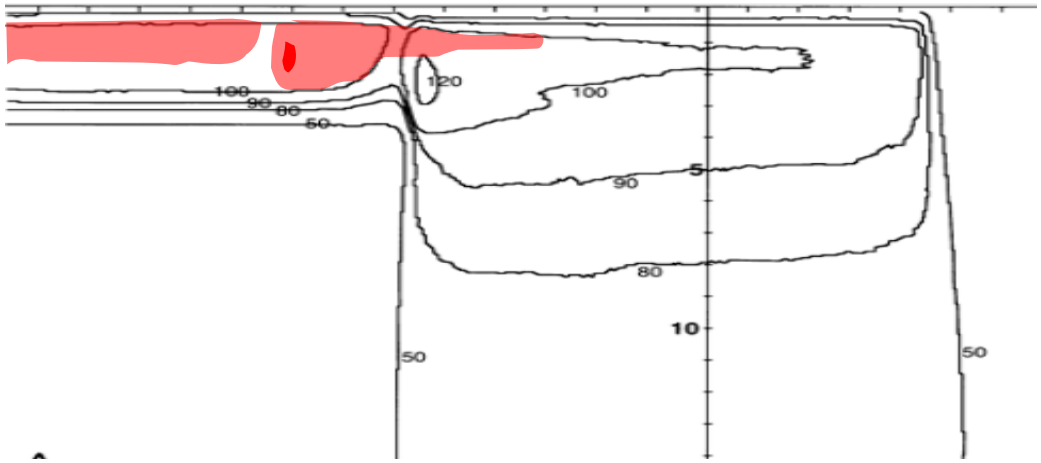
Courtesy Marika Enmark

Use of abutting beams

- Electron - electron beam matching
  - difficult to match without hot- or cold-spots due to influence on isodose lines of patient curvature

- Electron – photon beam matching
  - beams abutted on the surface gives a hot spot on the photon side and a cold spot on the electron side
  - caused by out-scattering of electrons from the electron fields

electron **photon**



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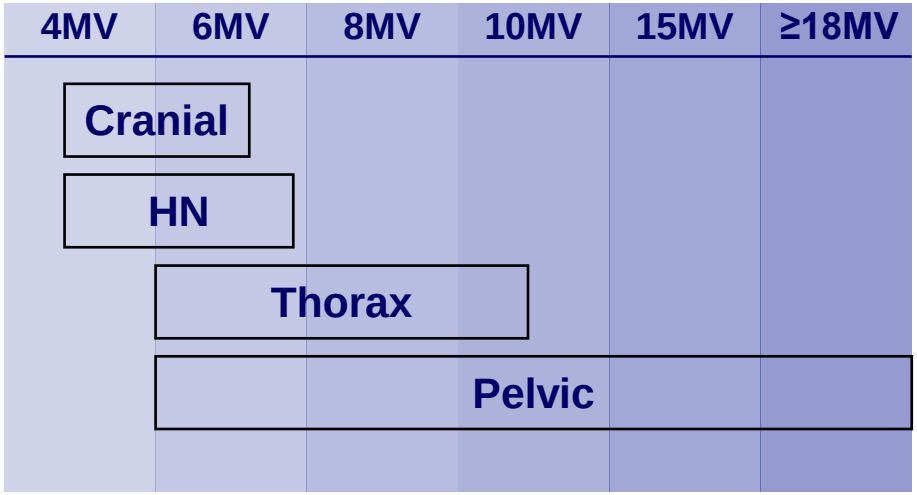
Choice of optimal beam energy

Aspects

- penetration depth
- dose delivered to normal tissue
- penumbra broadening



Higher energy in low density regions

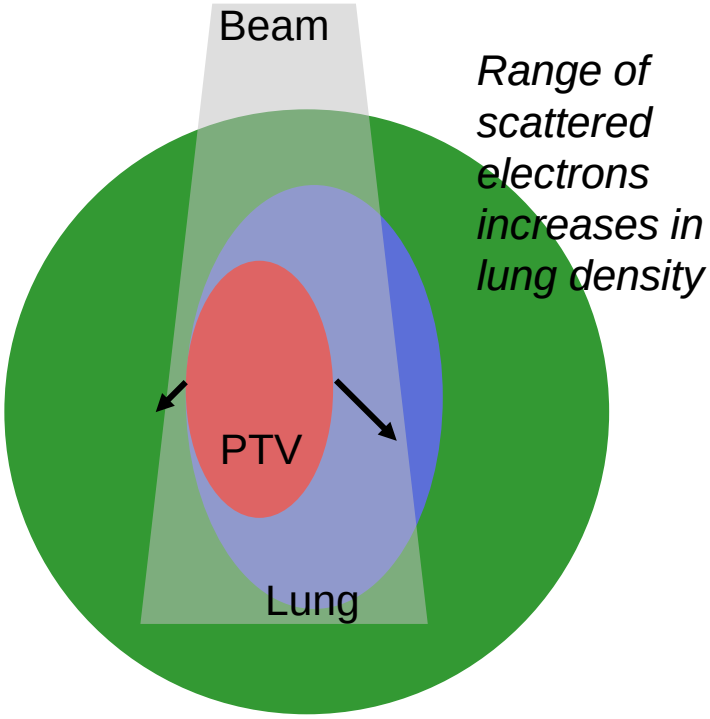
- higher energies means larger penumbra due to increase in lateral electron transport (≥10MV)
- sufficiently accurate planning calculation algorithms are required for decisions on optimal beam energy

Choice of optimal beam energy in the thorax region

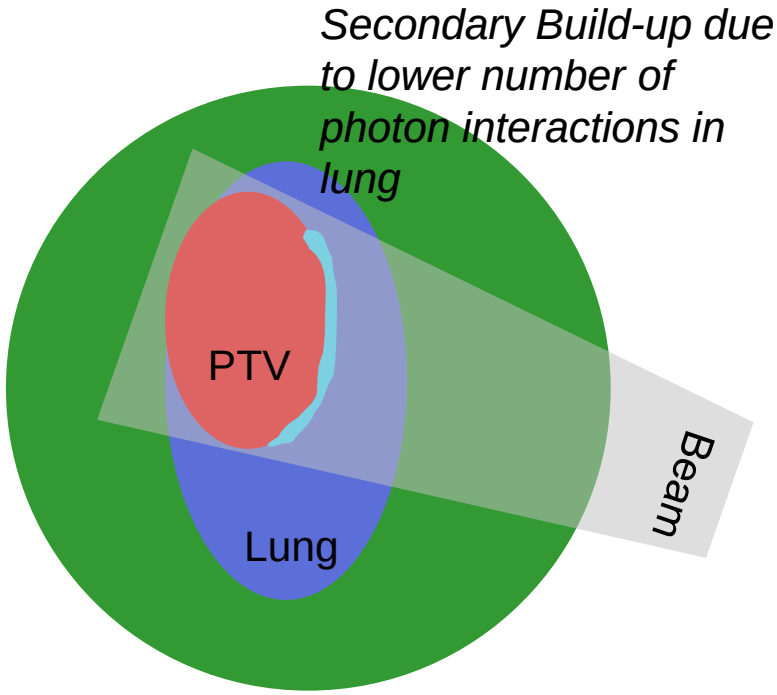
- Low energy beam is preferable
  - tighter margins, sharp dose gradient
  - no significant difference between 6 and 18MV treatment plan (# beams!)
- High energy may be used
  - central tumor location or consolidated lung

Interface effects

- Broadening penumbra in low density area



- Build-up and build-down in low density area



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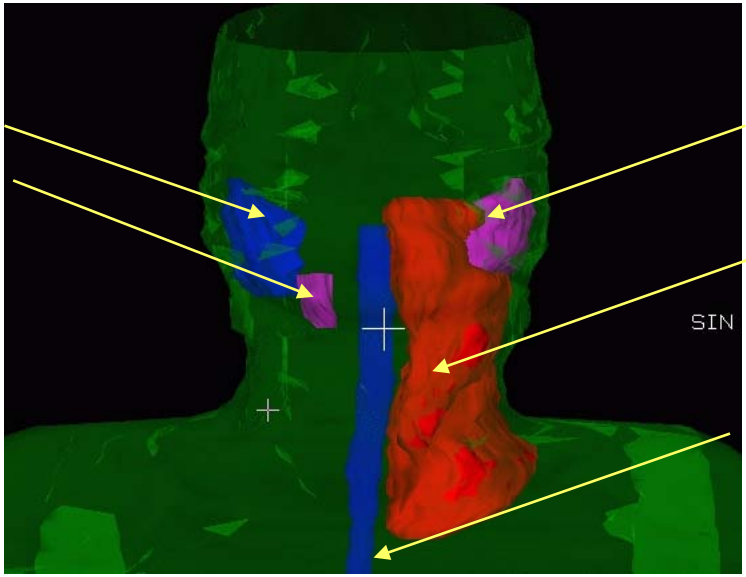
Head & Neck 3D

Head and neck 3D-CRT example: Tonsillar fossa Ca.

- T1-T3, N0
- CTV = primary tumor + uni-lateral neck (level II-IV)
- 46 Gy 3D-CRT
- BT boost

right parotid gland

right SMG



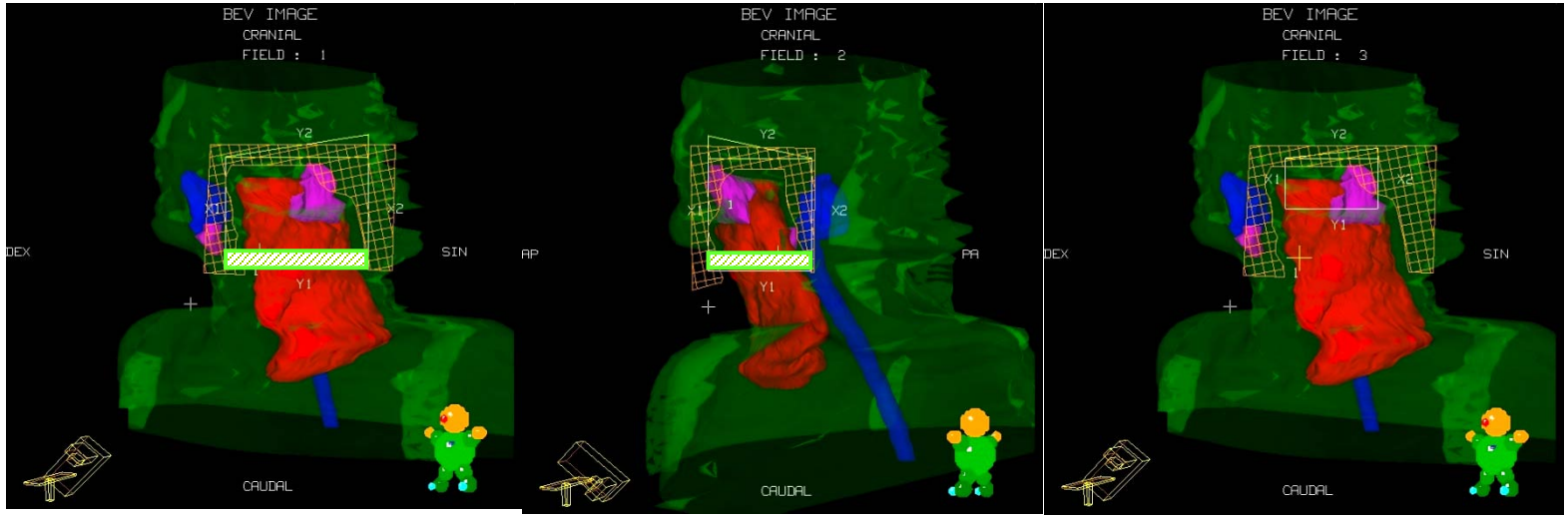
left parotid gland

PTV 0-46 Gy

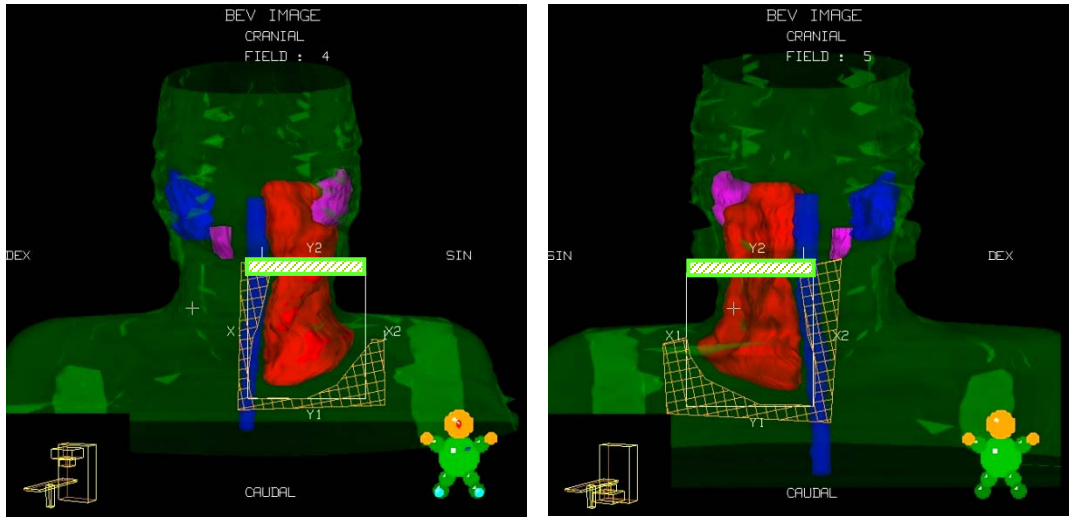
spinal cord

‘simple’ 3D CRT plan

Head and neck: Tonsillar fossa Ca.



5 fields:
3 cranial fields
2 caudal fields } *
sliding junction



* total: 9 fields

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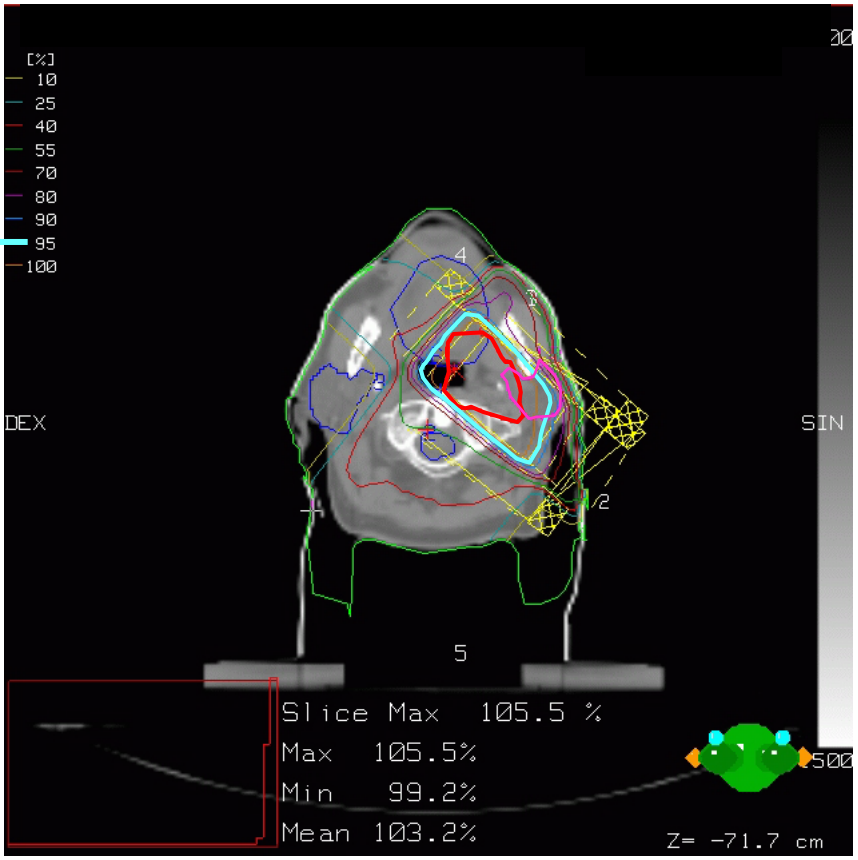
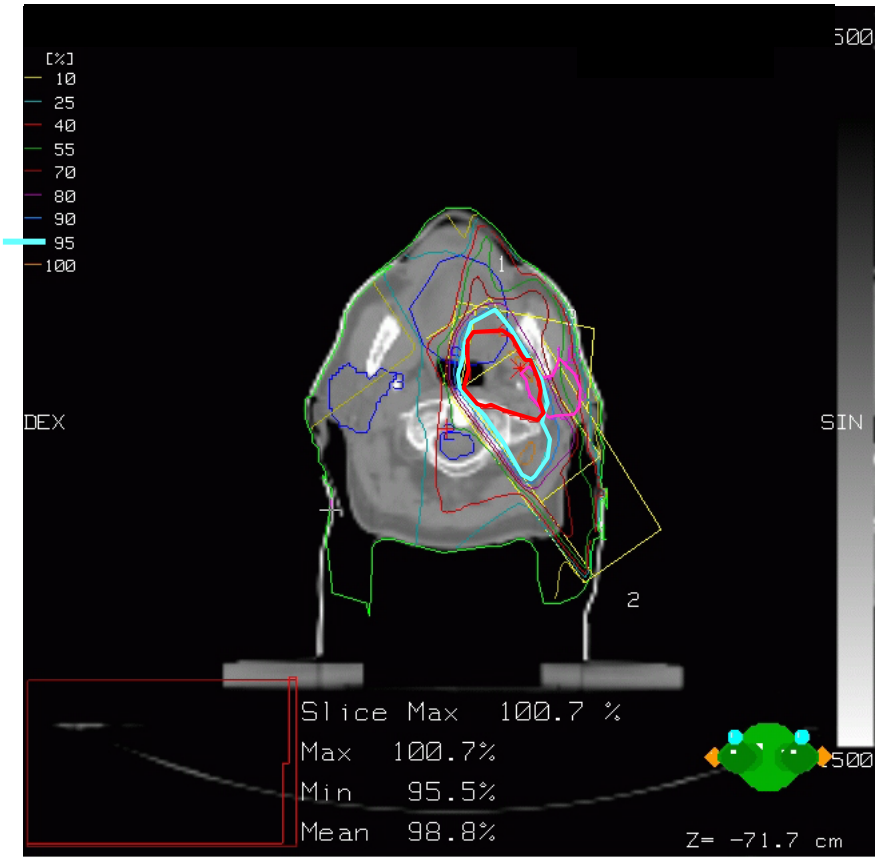
Head and neck: Tonsillar fossa Ca.

9-field 3D-CRT



4-field IMRT



Head and neck: Tonsillar fossa Ca.

mean dose (Gy)	3D-CRT	4 field IMRT
right parotid gland	2.6 Gy	4.0 Gy
left parotid gland	40 Gy	27 Gy
ri SMG	18 Gy	10 Gy
oral cavity	24 Gy	24 Gy

Head and neck: Tonsillar fossa Ca.

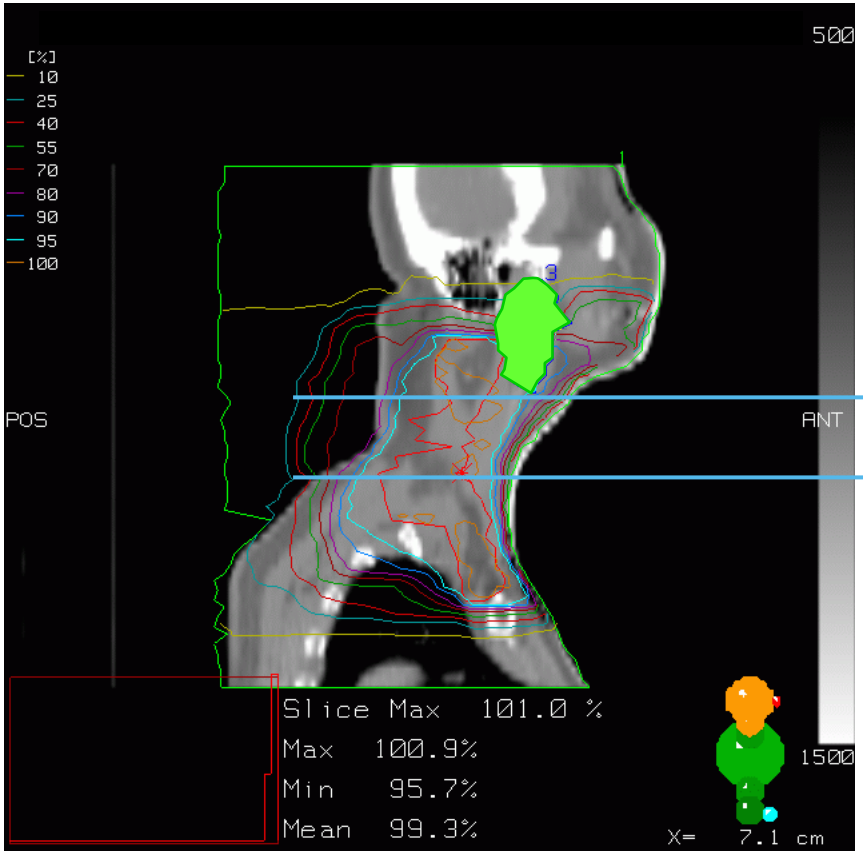
do we <u>really</u> need IMRT for this case?

no we don’t, but application of IMRT results in:

- more OAR sparing
- less treatment planning time
- less delivery time
- no use of a sliding junction, so less risk

Head and neck: Tonsillar fossa Ca.

position of the isocenter



2 identical IMRT plans except for the isocenter position

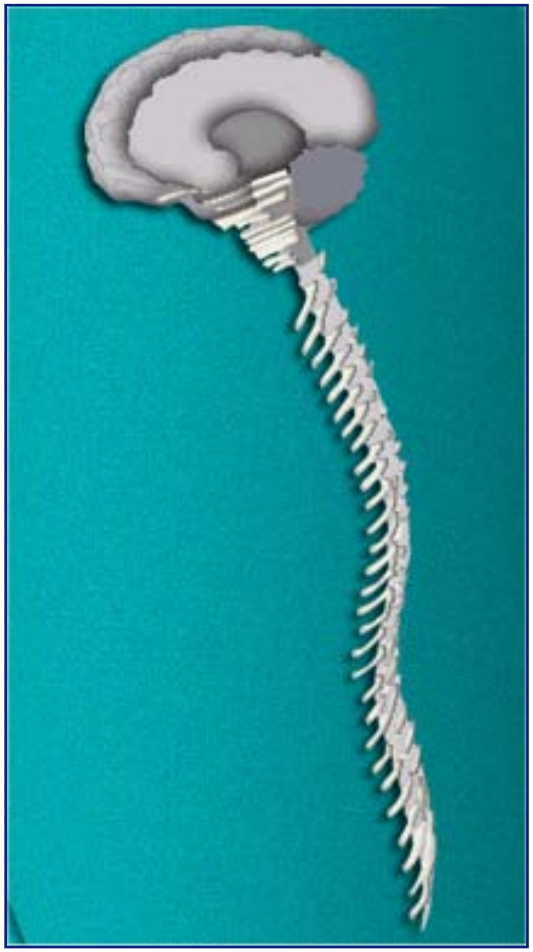
mean dose parotid 27 Gy

mean dose parotid 30 Gy

divergence of the beam in OAR direction

Cranio-spinal lesions

Cranio-spinal lesions



clinical target volume for cranio-spinal irradiation:

- meningeal surfaces of the brain
- spinal cord

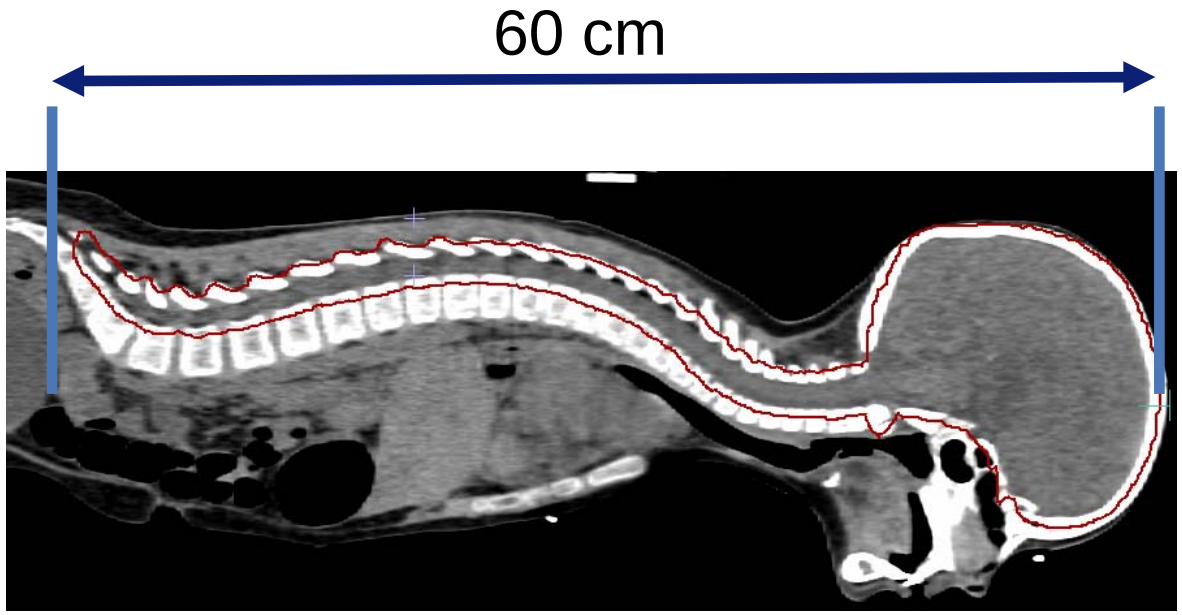
Cranio-spinal lesions

- small number of patients, lack of planning experience
- hardware limitations of TPS?
  - max number of CT slices ? (300+)
  - calculation time / grid size
- beam set-up cranio-spinal treatment
  - need for IMRT? combination 3D-CRT + IMRT?
    - multiple energy, sliding junction etc.

Cranio-spinal lesions

Challenges:

- limitation in maximum field size
- junction area lateral cranial fields – posterior spinal field
- dose distribution spinal field?



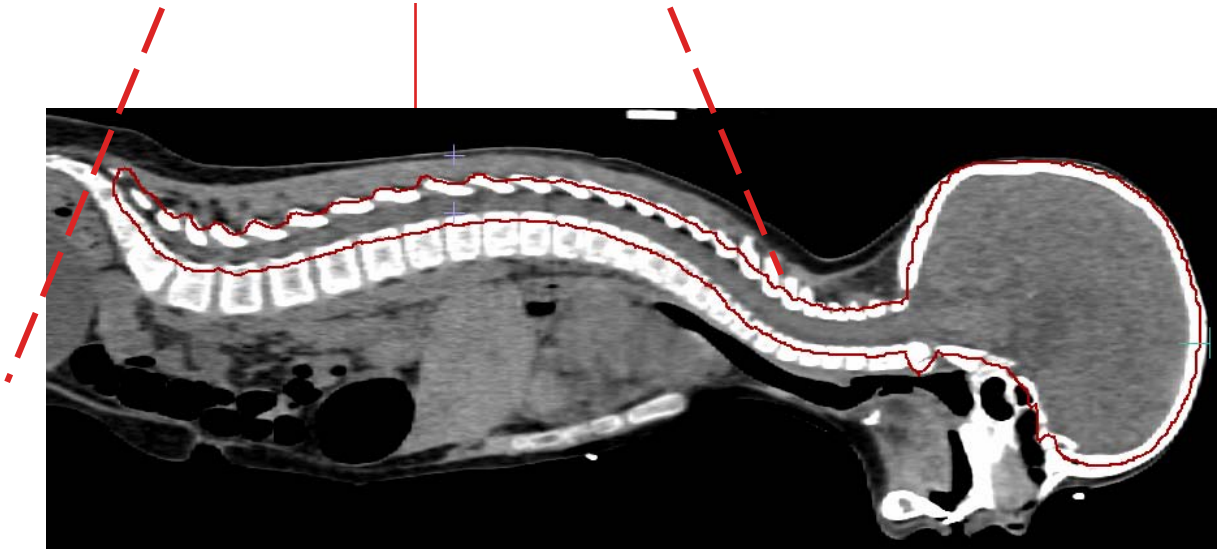
Cranio-spinal lesions

Challenges spinal field:

maximum field size:

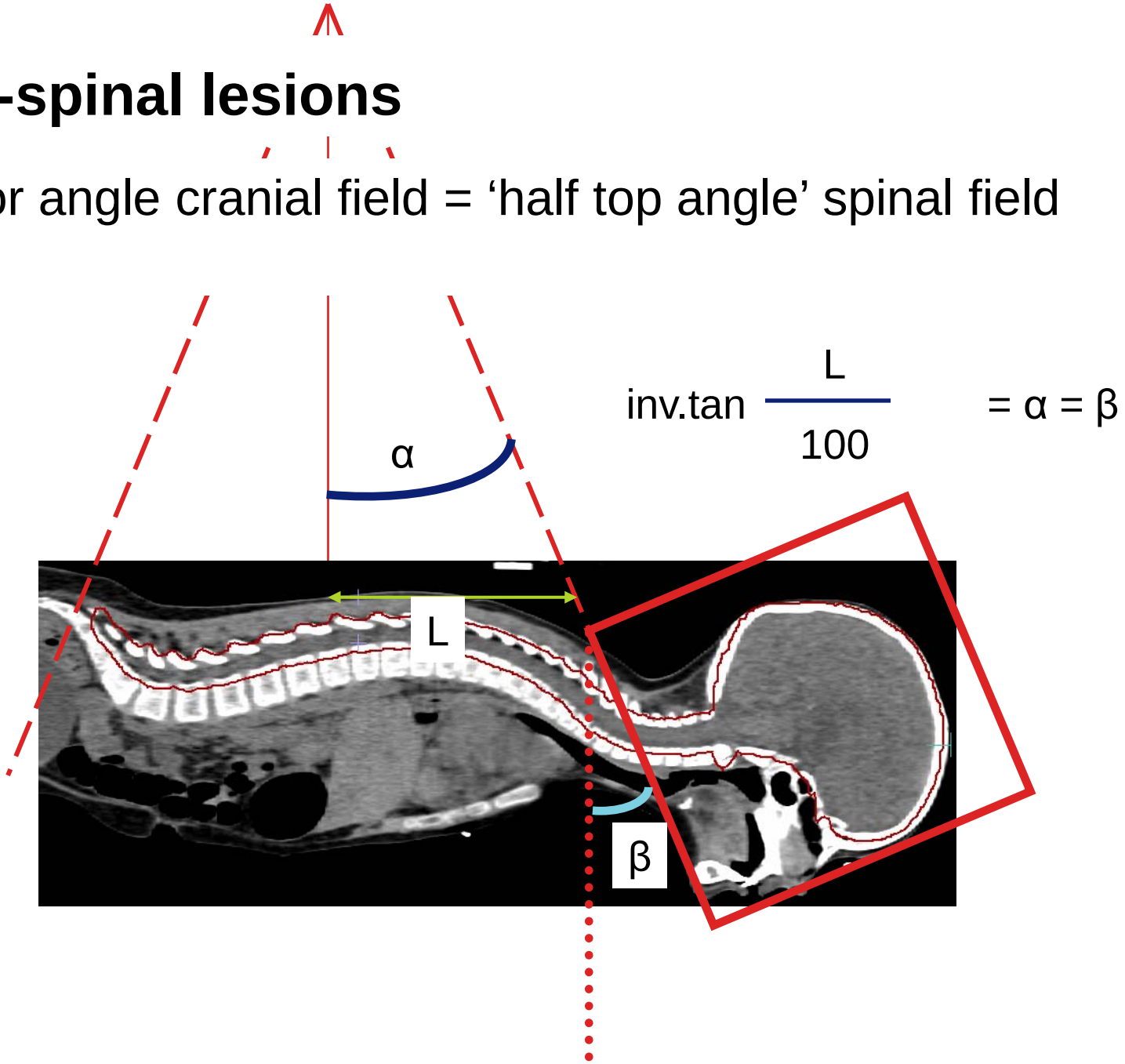
40 cm at focus isocenter distance 100 cm

1 or 2 spinal fields (1=supine, 2= prone)



Cranio-spinal lesions

collimator angle cranial field = ‘half top angle’ spinal field

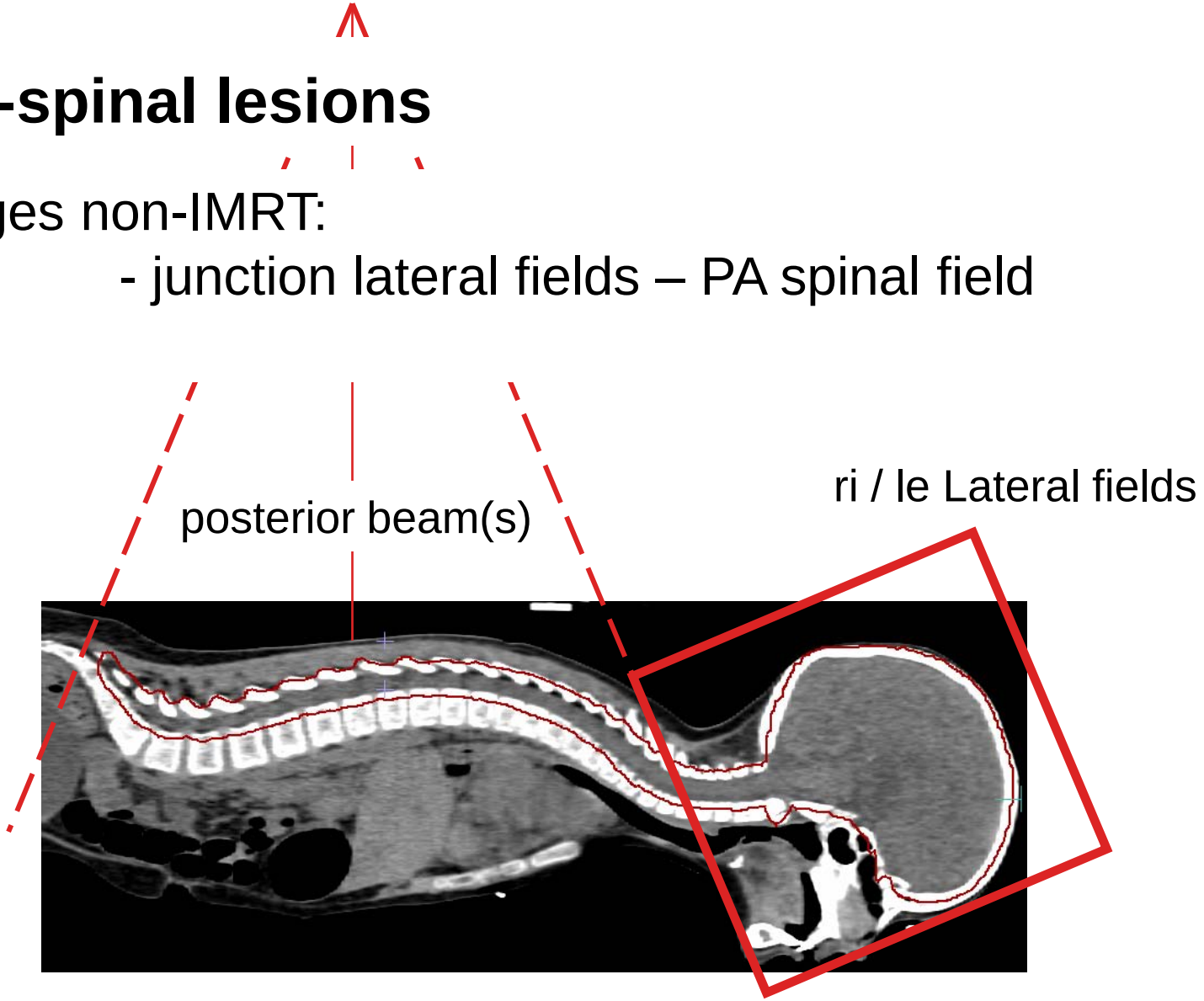


$$\text{inv.tan}\ \frac{L}{100} = \alpha = \beta$$

Cranio-spinal lesions

Challenges non-IMRT:

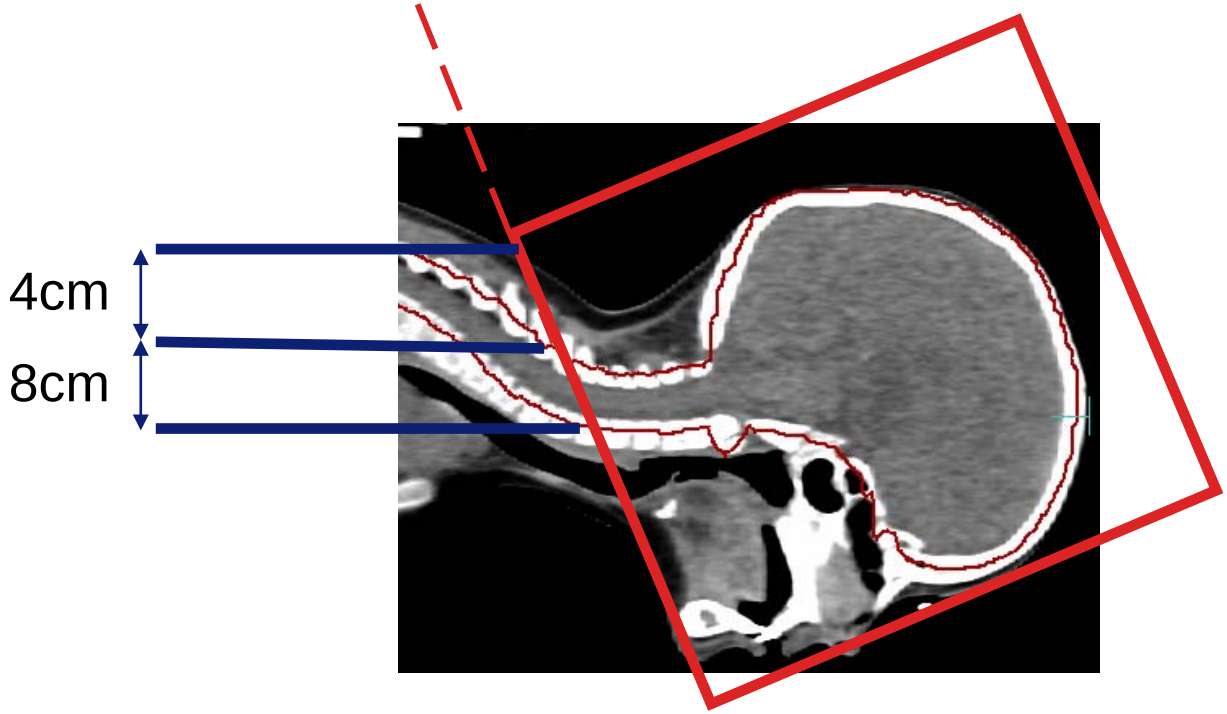
- junction lateral fields – PA spinal field



Cranio-spinal lesions

Challenges non-IMRT:

- junction lateral fields – PA spinal field
  difficult due to differences in depth in junction area

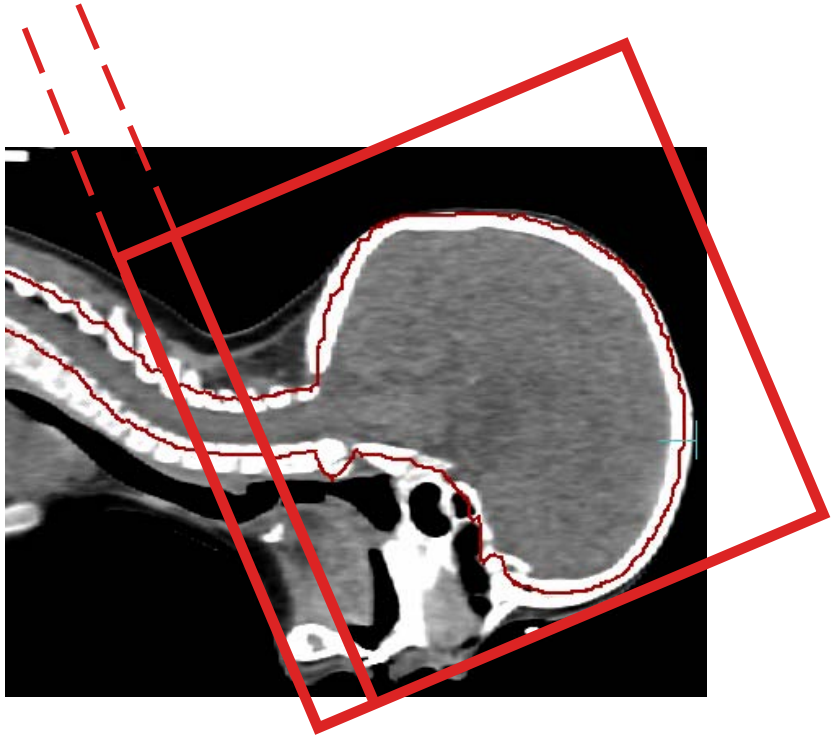


additional sub-fields , multiple energies?

Cranio-spinal lesions: cranial fields

Challenges non-IMRT:

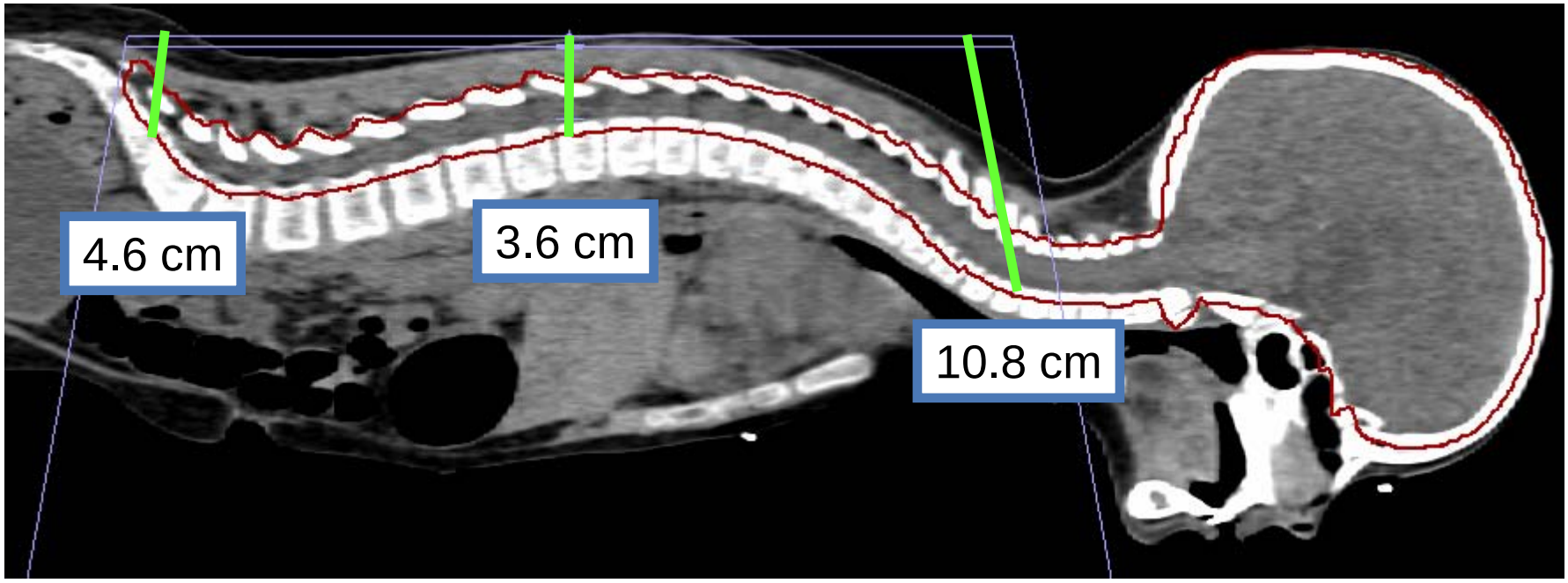
- junction lateral fields – PA spinal field
  better dose-distribution in junction, broader penumbra
  → sliding junction



Cranio-spinal lesions: spinal field

Challenges Non-IMRT:

- differences in depth of spinal PTV
- different focus skin distances

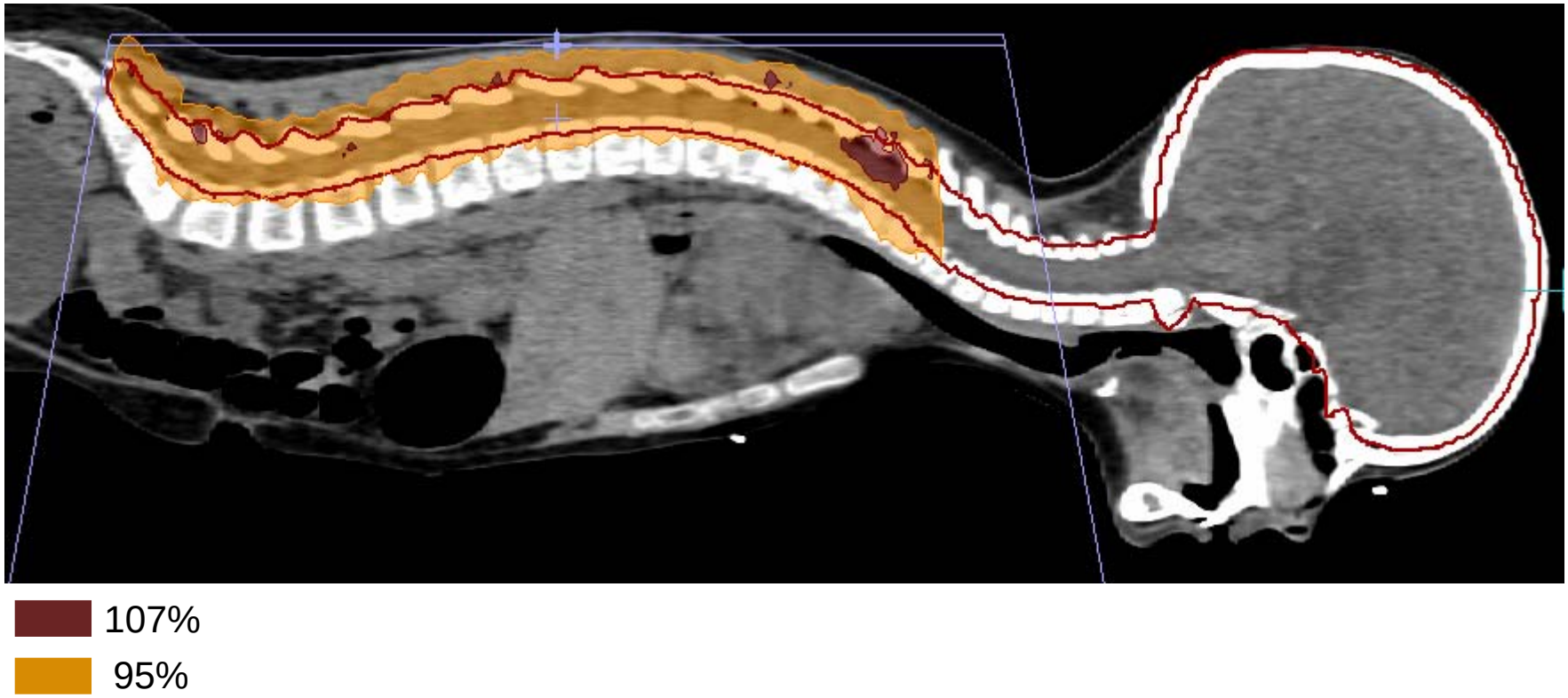


prescribing dose at mean depth, or additional sub-fields needed
multiple energy fields

Cranio-spinal lesions: need for IMRT??

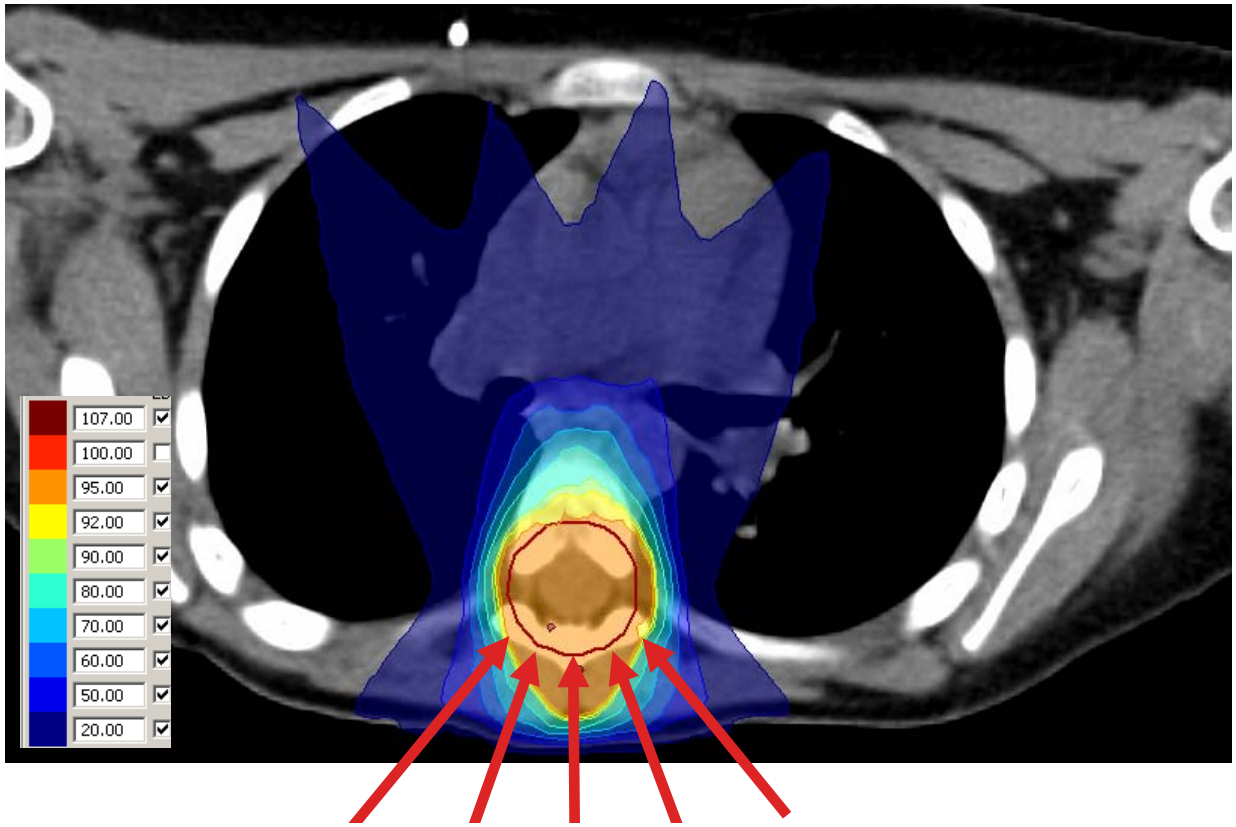
IMRT planning:

- differences in depth of spinal PTV
- differences in focus skin distances



Cranio-spinal lesions: 3D-CRT or IMRT for spinal fields

5 field IMRT / 3D-CRT spinal fields



- lower dose in superficial area
- lower dose ‘behind’ the PTV

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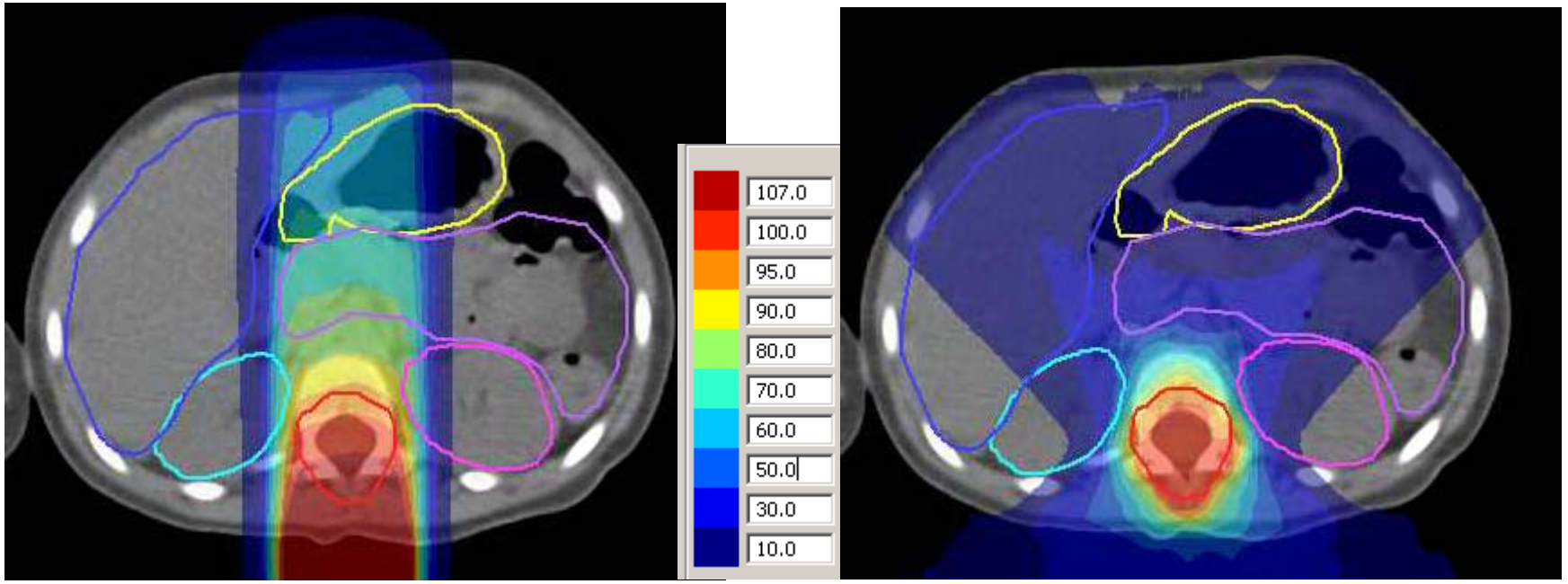
Cranio-spinal lesions: 3D-CRT vs IMRT

‘simple’ 3D-CRT

5 field IMRT / 3D-CRT



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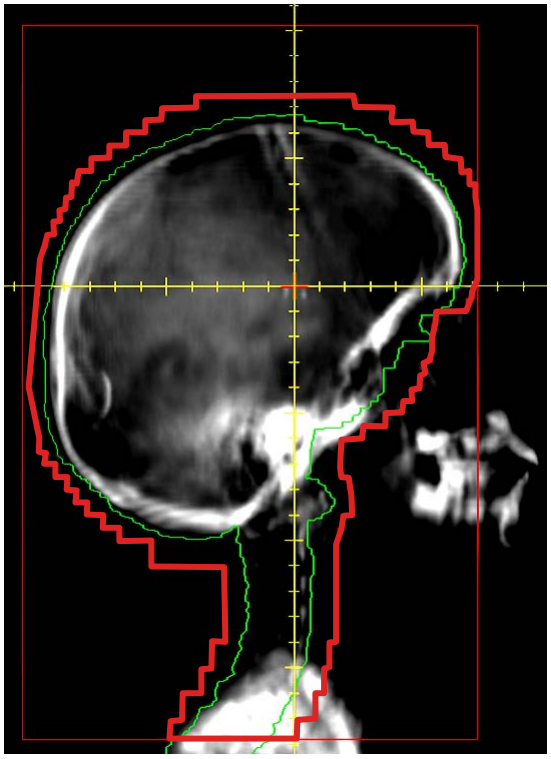
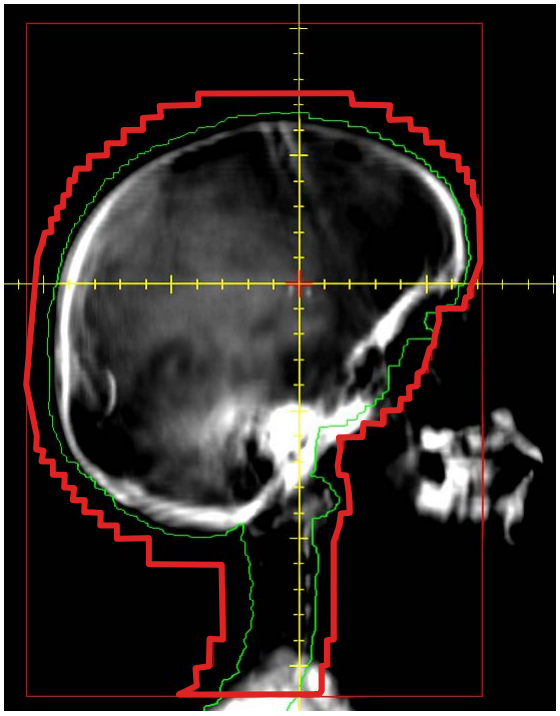
Cranio-spinal lesions: junction with lateral cranial beams

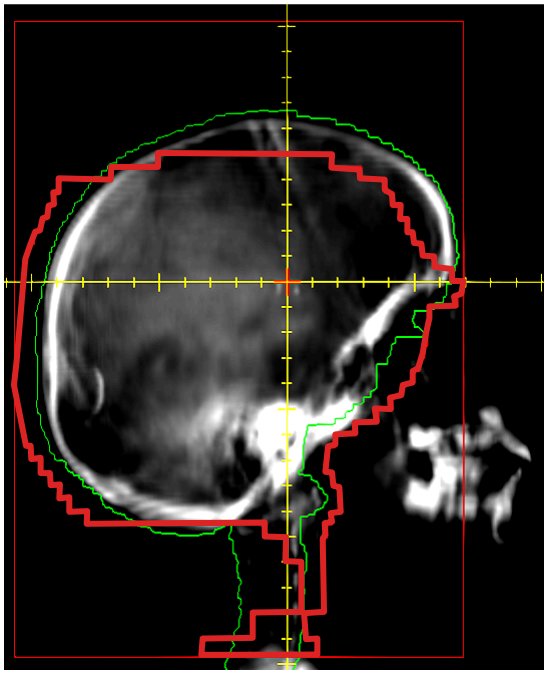
3D-CRT cranial plan with a broad caudal penumbra



ri lat: 1a

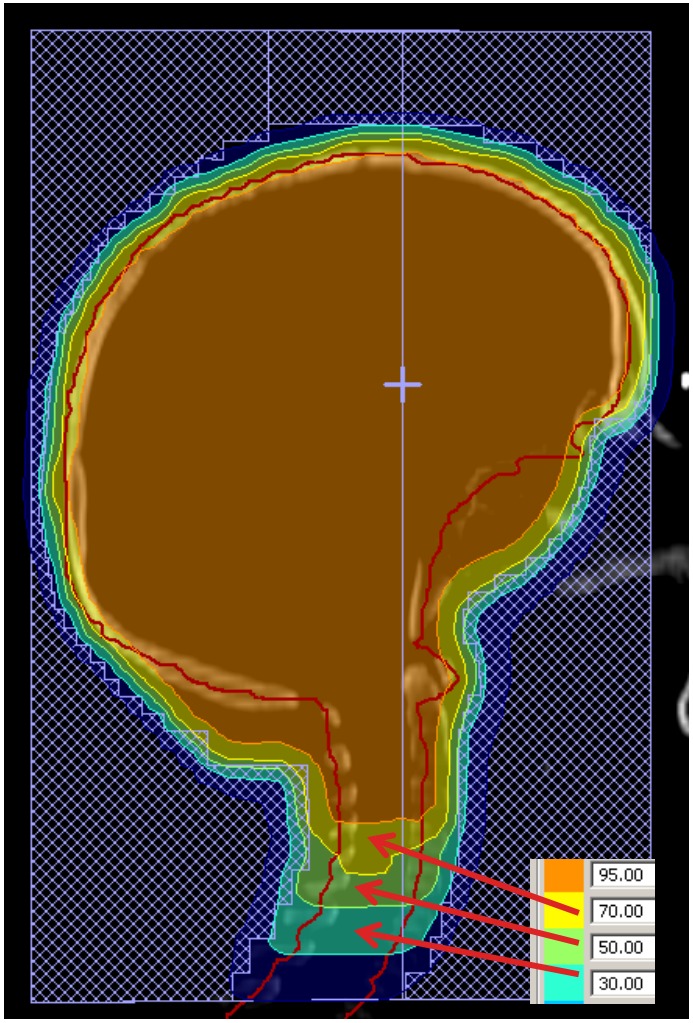


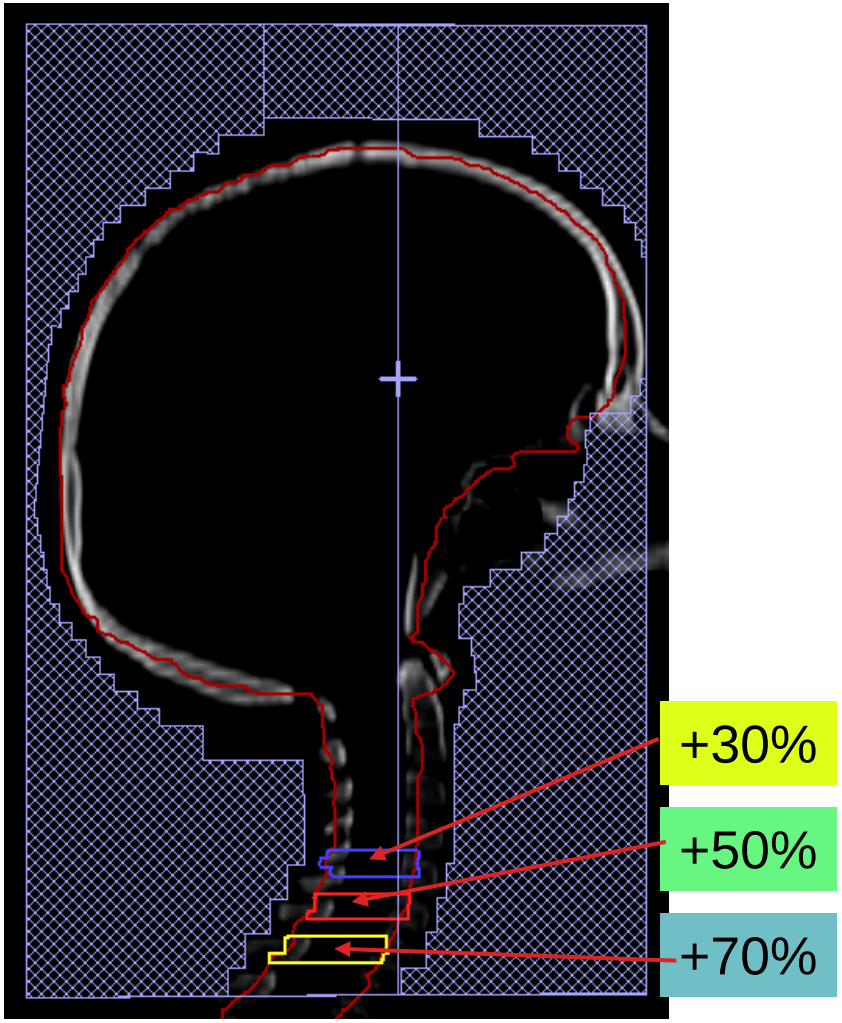
ri lat: 1b



ri lat: 1c

Cranio-spinal lesions: junction with lateral cranial beams





‘dose modulation volumes’

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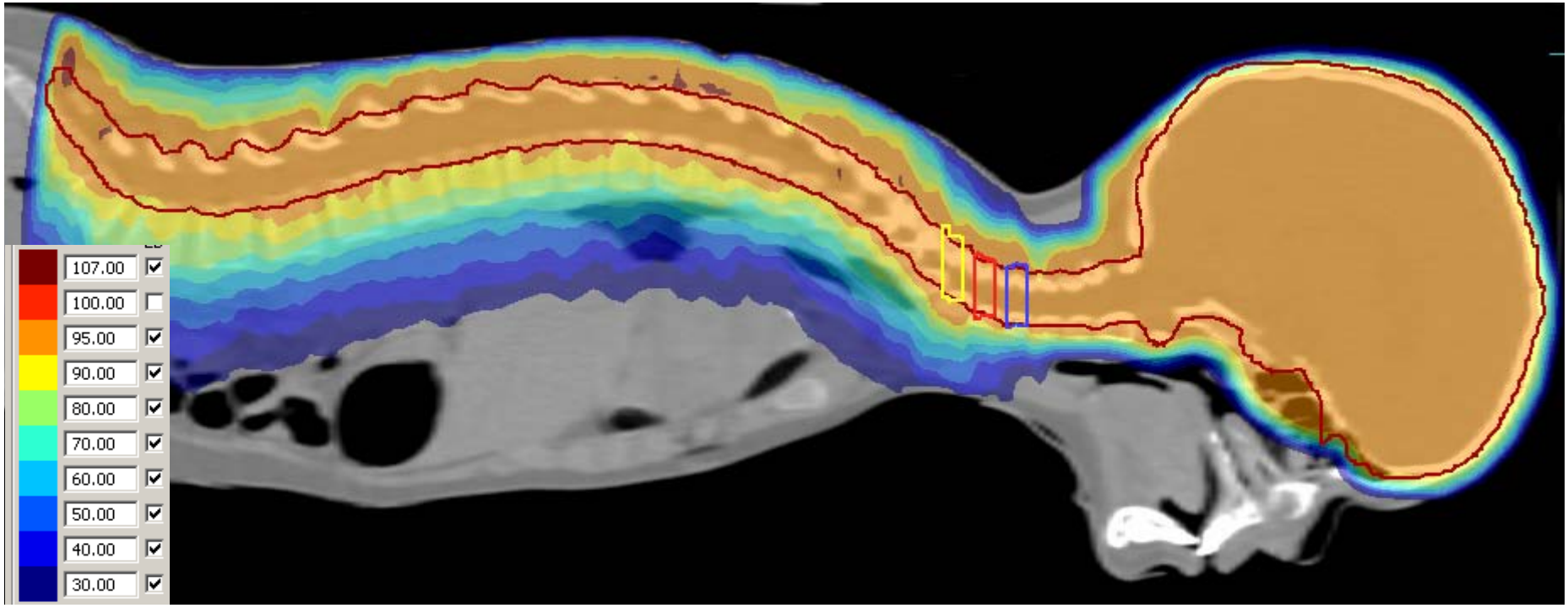
Cranio-spinal lesions: 3D-CRT solution

6 3D-CRT cranial beams (start planning)
5 3D-CRT spinal fields (x 3 for broad penumbra)
⟶ so … 21 fields



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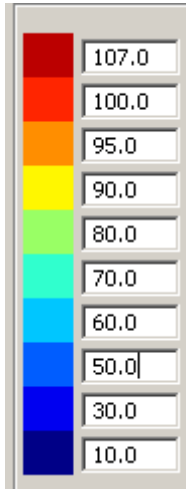
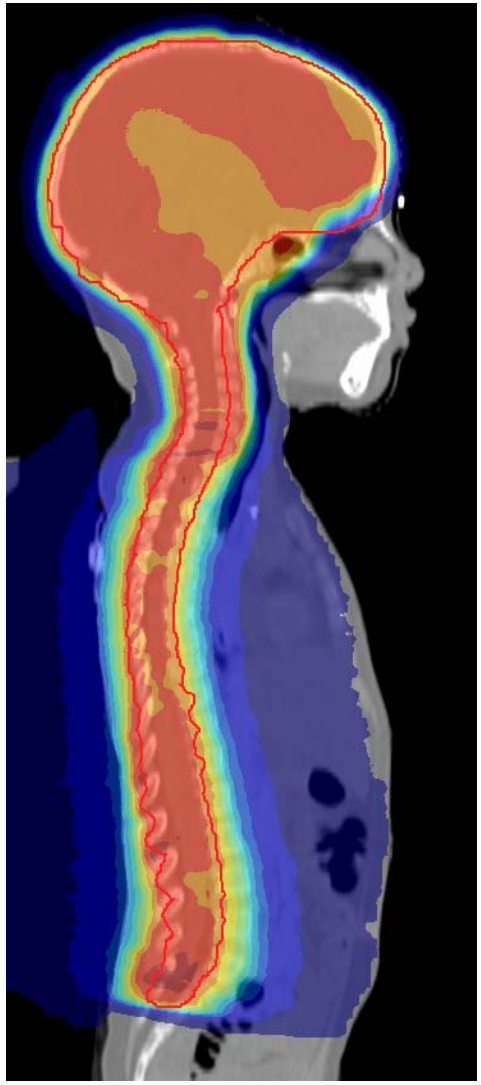
Cranio-spinal lesions: 3D-CRT old vs new

3D-CRT old (single PA)



3D-CRT new



Cranio-spinal lesions: 3D-CRT old vs new

mean dose (Gy)	old	new
thyroid gland	19.1	11.4
heart	7.8	4.4
lungs	3.5	4.7
small bowel	8.1	5.7
liver	4.6	3.8
le kidney	3.2	4.1
stomach	8.1	5.7

General start of a treatment plan

General start of a treatment plan

- where to place the isocenter?
- how to select the proper beam angles?
- how many fields?
- cerrobend blocks or MLC?

Where to place the isocenter?

- high dose region is the most favorite place for the physicist ☺

  (and normally it is a very good choice!)

  - find the best isocenter location with respect to:
    - MLC limits
    - use of wedges
    - build up area, air cavities, bone

  - isocenter position outside the high dose region often results in a more complicated plan

  - apply a-priori patient set-up translations if necessary

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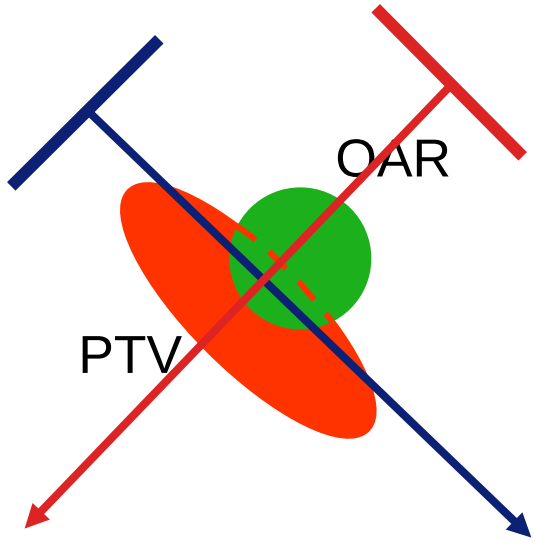
How to select the proper beam angles?

- think about the dose distribution you want to achieve

- geometrical avoidance



steep dose gradients can only be made using a beam penumbra !

How to select the proper beam angles? Single lung:

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Curative radiotherapy for a second primary lung cancer arising after pneumonectomy — techniques and results☆

Frank J. Lagerwaard, Peter W.J. Voet, Jan P. van Meerbeeck, Sjaak A. Burgers, Suresh Senan*

University Hospital Rotterdam, Groene Hilledijk 301, 3075 EA Rotterdam, The Netherlands

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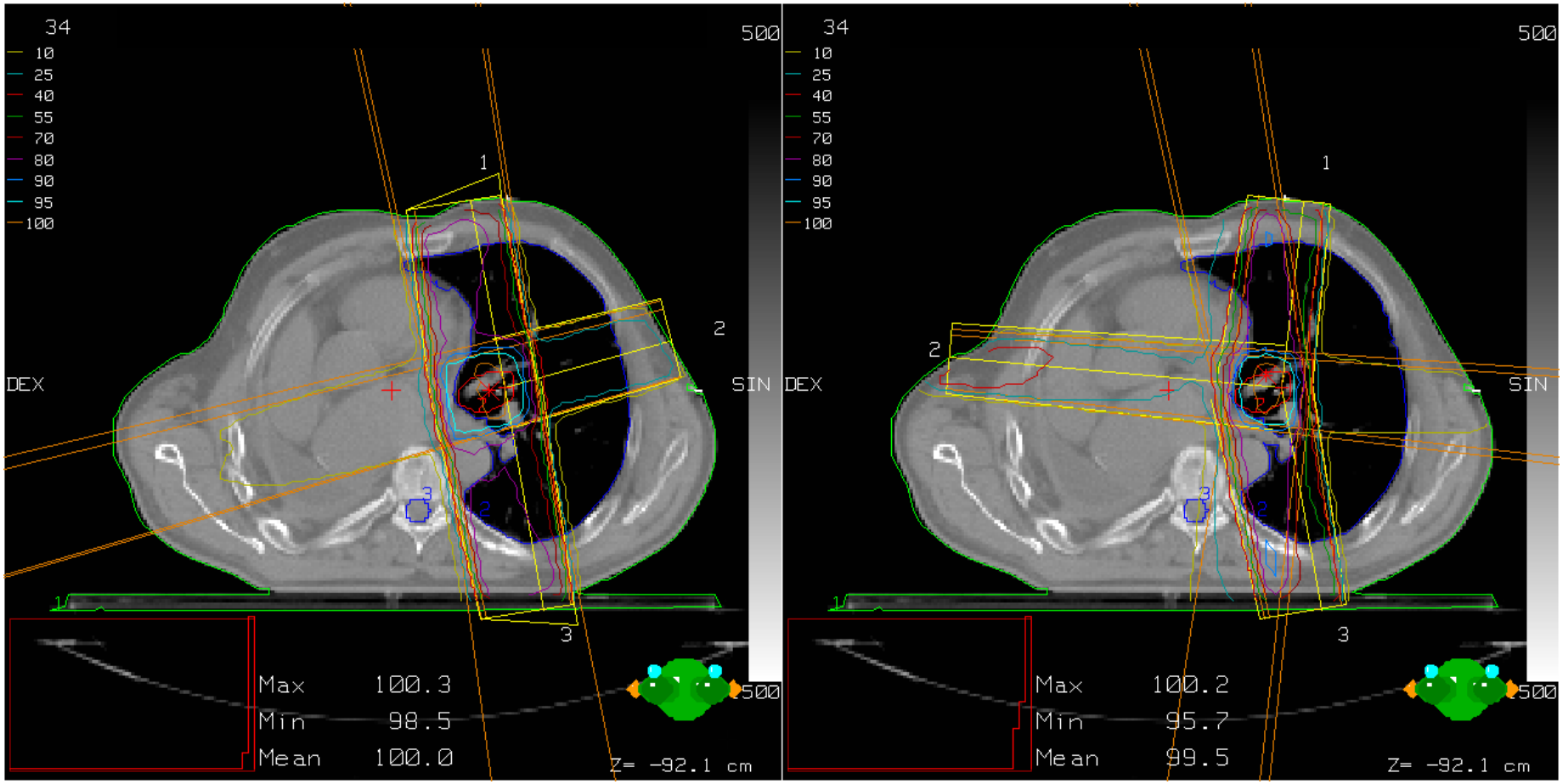
How to select the proper beam angles? Single lung:



V_{20} = 25 %

V_{20} = 19 %

Lagerwaard et al: R&O, 2001

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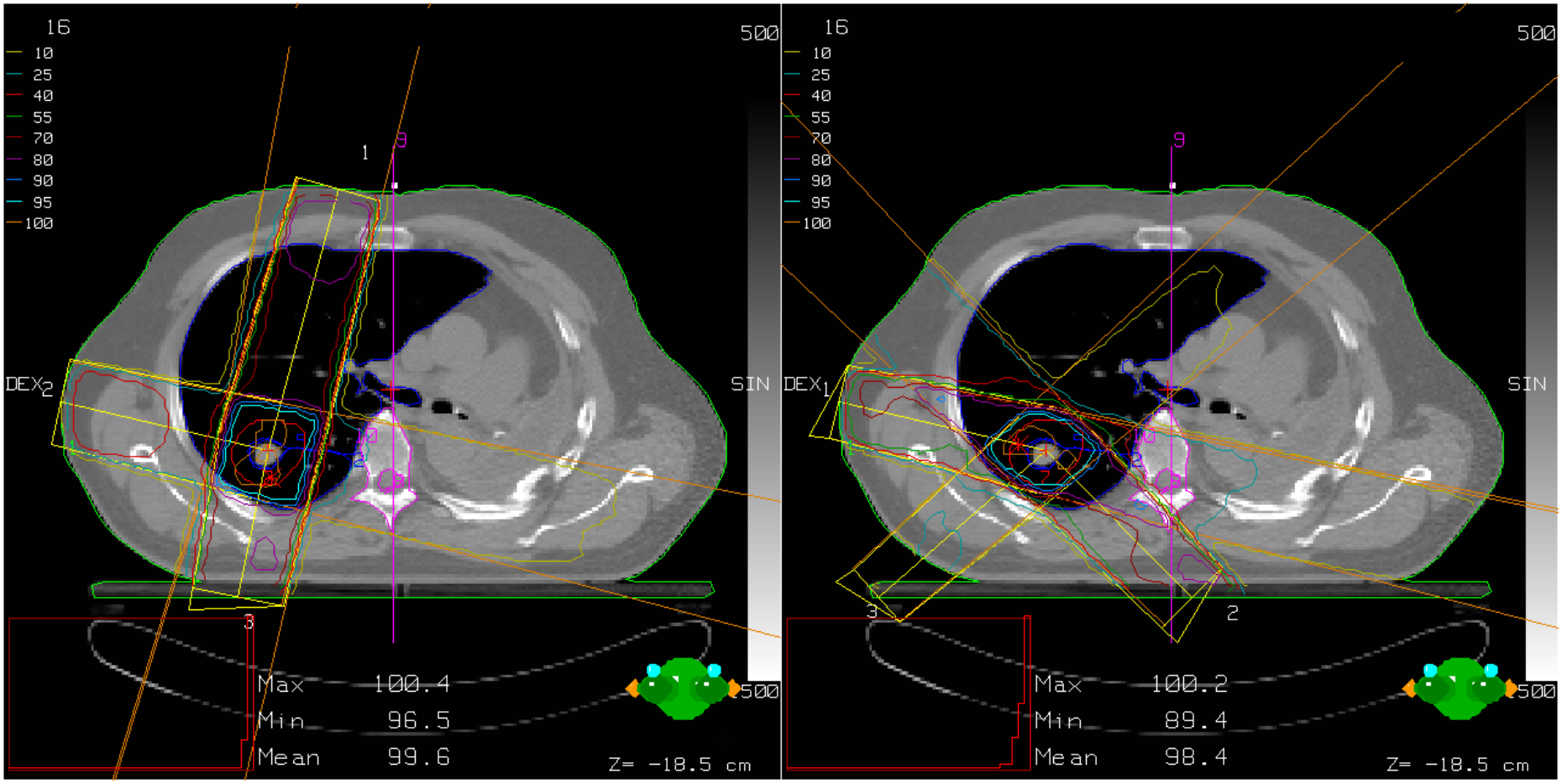
How to select the proper beam angles? Single Lung:



V_{20} = 27 %

V_{20} = 15 %

Lagerwaard et al: R&O, 2001

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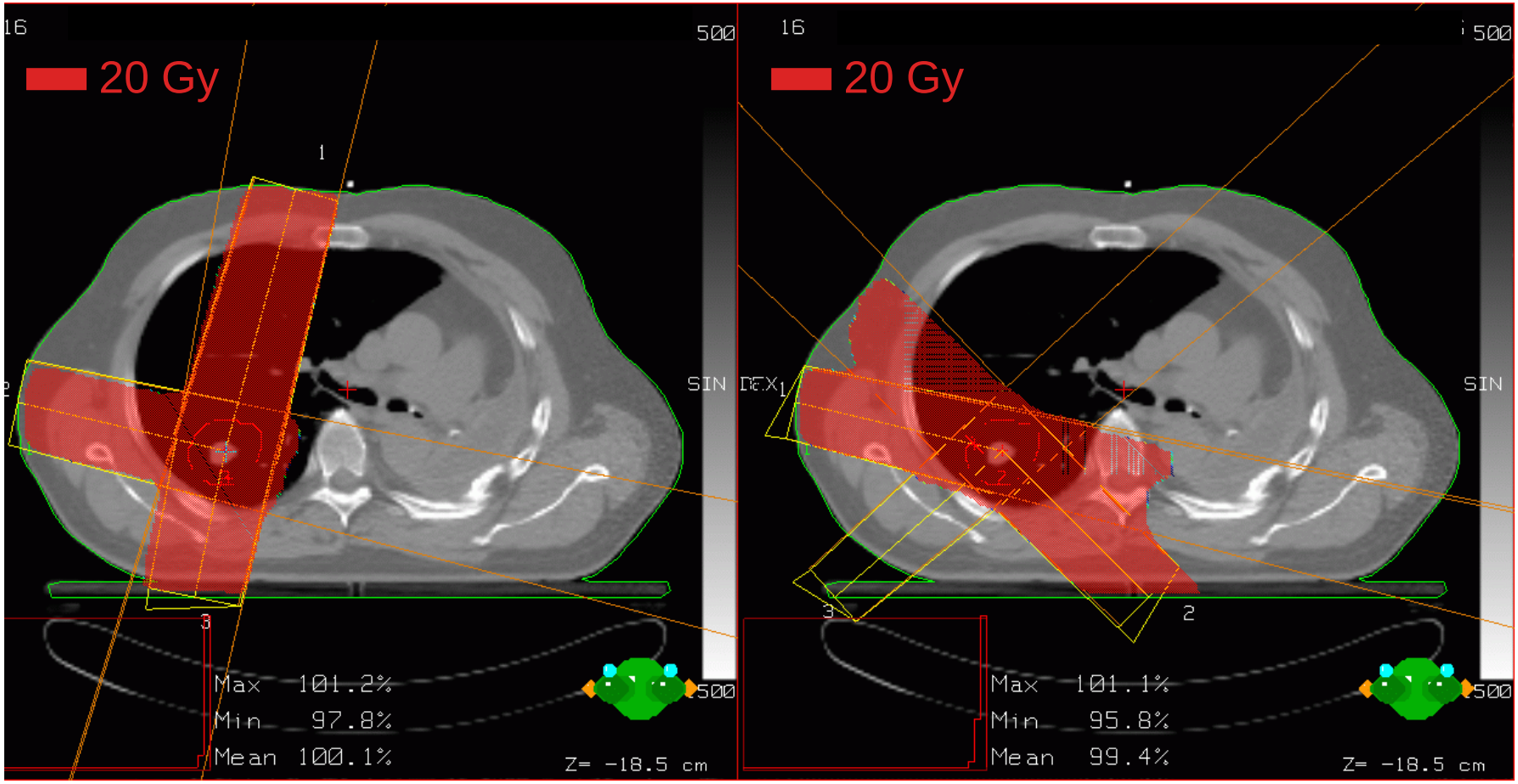
How to select the proper beam angles? Single Lung:



$V_{20} = 27\ \%$

$V_{20} = 15\ \%$

Lagerwaard et al: R&O, 2001

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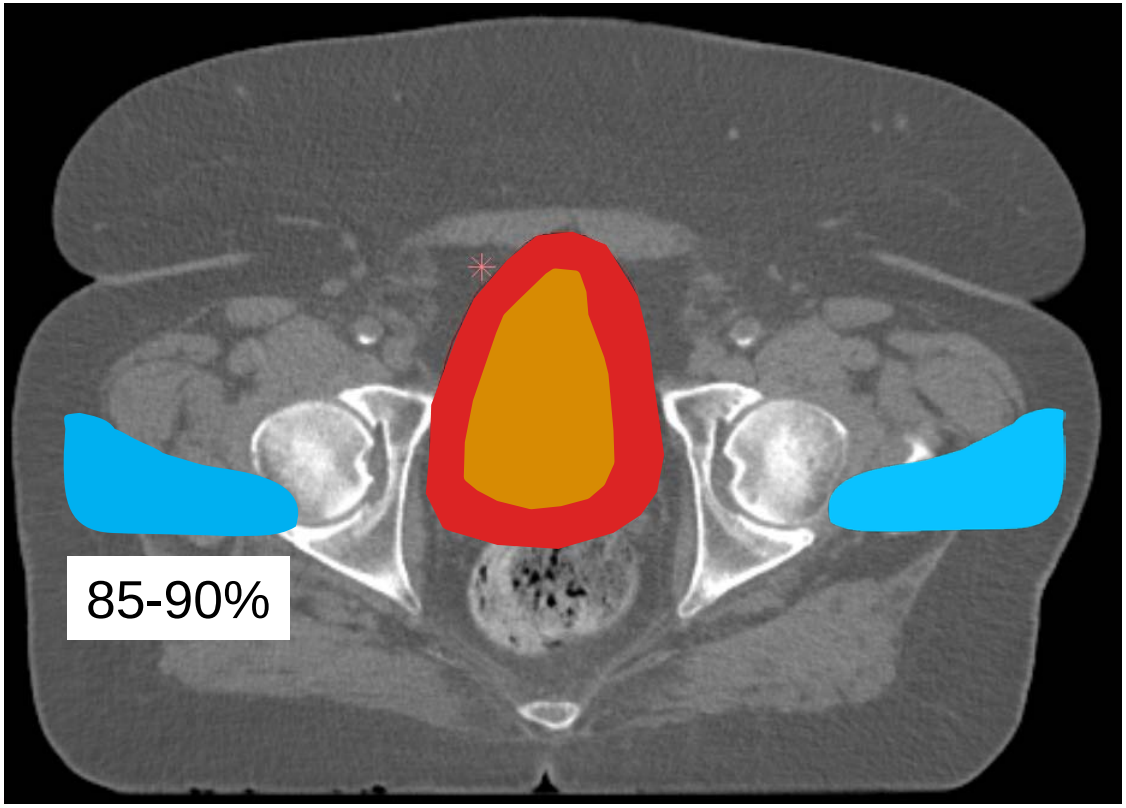
How many fields?

- depends on the complexity of the case
- size of the PTV, size of the patient

‘Standard’ 3D-CRT bladder treatment : 33 x 2.0 Gy:
- 3 field (18MV) 3D CRT: CTV bladder + 15mm = PTV



4-5 field technique reduces high dose areas…..
but increases low dose areas
do not be afraid of adding beams

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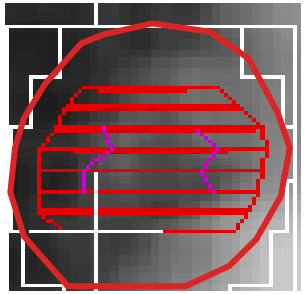
MLC versus Cerrobend blocking

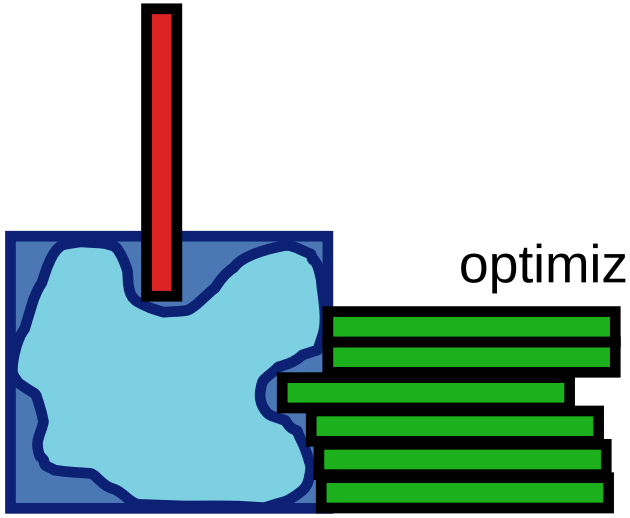


shielding by using cerrobend blocks is always the best

Δ quality with MLC shielding depends on :

- MLC geometry (1cm, 0.5cm, 0.2cm, ..cm)
- size of PTV
- shape of PTV

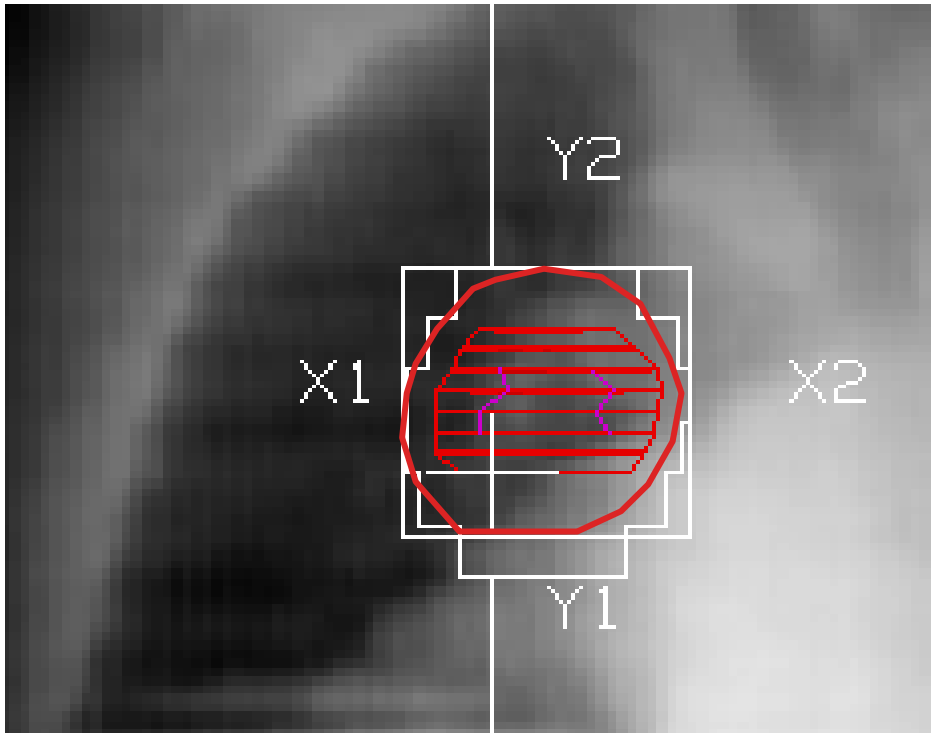
'normally' MLC will do just fine, but be aware of it's limitations



optimize on collimator rotation

MLC versus Cerrobend blocking:

example early stage lung cancer : field size appr. 5 x 5 cm



Lagerwaard et al: R&O, 2001

MLC versus Cerrobend blocking:

		MLC	Cerrobend
1	V20 (%)	15	12
	Mean lungdose (Gy)	10.3	8.9
	Conformity-index	0.54	0.56
2	V20 (%)	18	16
	Mean lungdose (Gy)	10.1	9.2
	Conformity-index	0.46	0.57
3	V20 (%)	16	12
	Mean lungdose (Gy)	10.3	8.6
	Conformity-index	0.55	0.62
4	V20 (%)	27	23
	Mean lungdose (Gy)	18.8	16.9
	Conformity-index	0.58	0.63
5	V20 (%)	21	19
	Mean lungdose (Gy)	14.8	13.9
	Conformity-index	0,58 - 0,66	0,63 - 0,71

Lagerwaard et al: R&O, 2001

MLC versus Cerrobend blocking:

N=8

Mean (1SD)	**mlc**	**cerrobend**
V20 (%)	19.9(5.0)	17.3(5.1)
mean lung (Gy)	14.8(3.1)	12.0(3.3)
CI	0.46(0.1)	0.60(0.0)

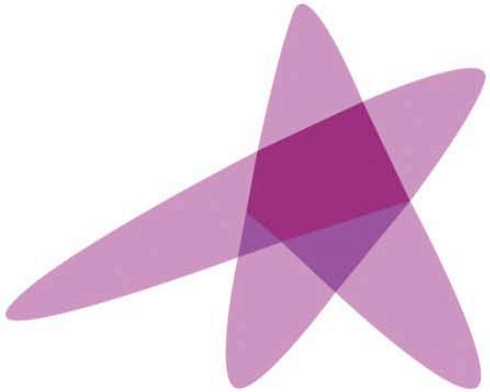
V_{20}	Actuarial incidence ≥ grade 2 pneumonitis at 24 months
<22%	0 %
22-31%	7 %
32-40%	13 %
>40%	36 %

Ref: Graham MV et al. IJROBP 45, 323-329, 1999

Lagerwaard et al: R&O, 2001

Making the ‘best plan’

- finding ‘*optimal*’ plans is time consuming
  - plan approach is based on ‘common sense’ and experience,
    and allotted time
  - class solutions may generally result into good plans, however,
    specific patients may benefit from an individual approach
  - do not be afraid of additional beams



ESTRO School

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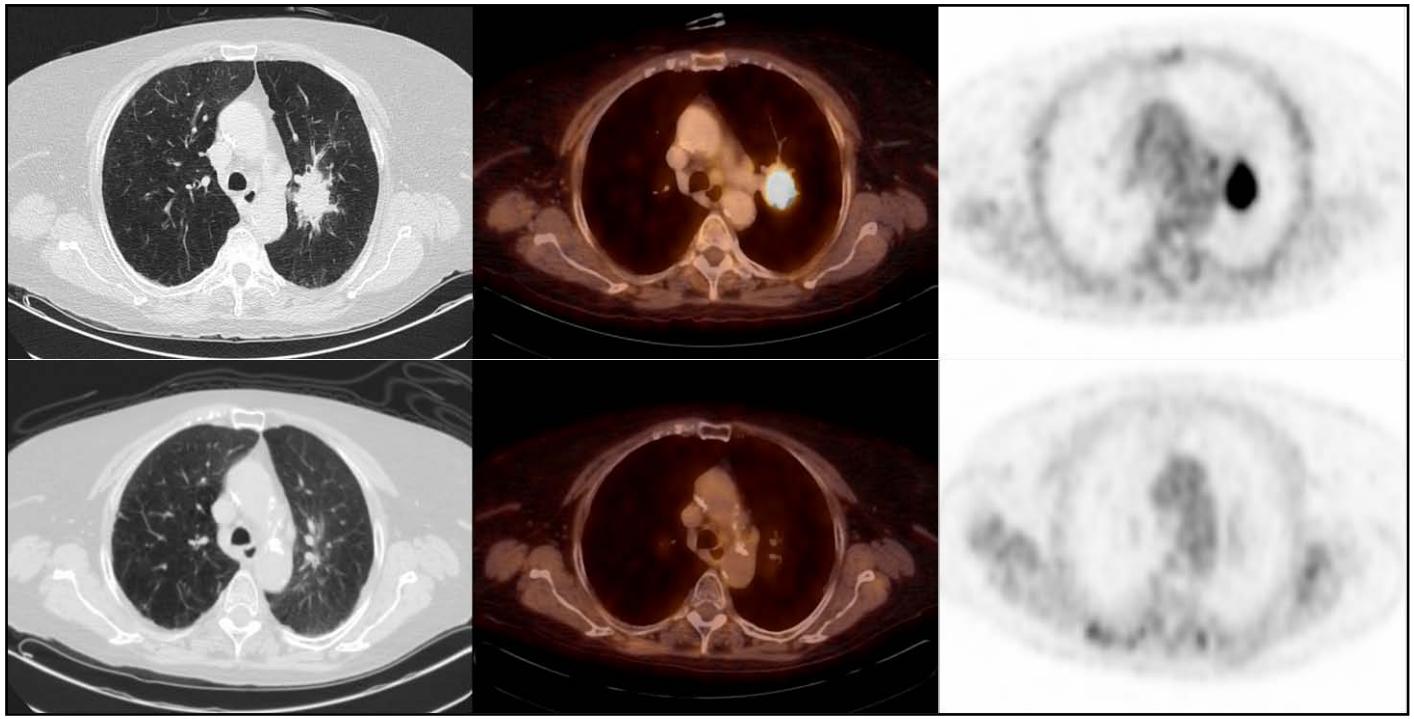
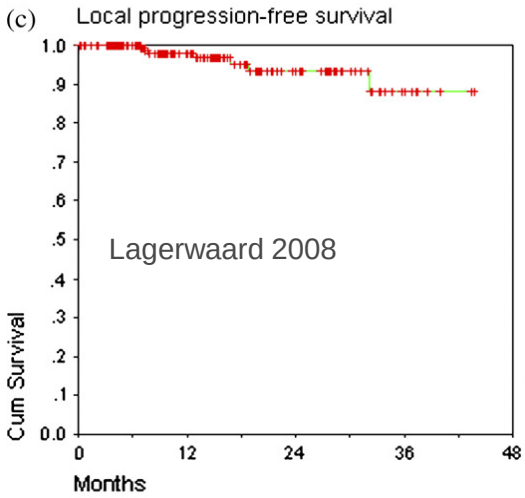


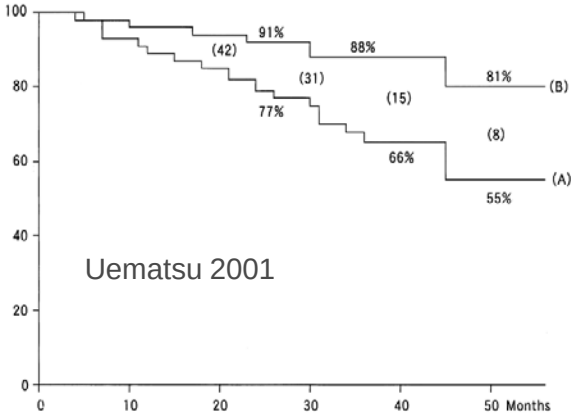
Relationships between 3D dose distributions and clinical toxicities - Chest

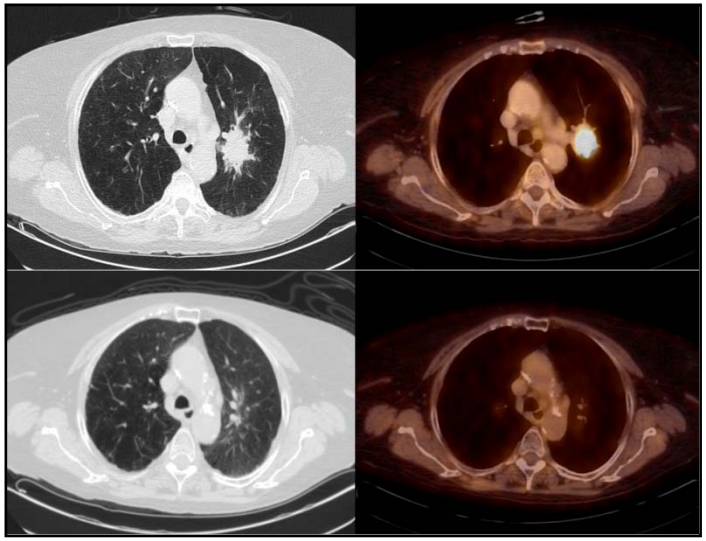
Example: SBRT for lung tumors

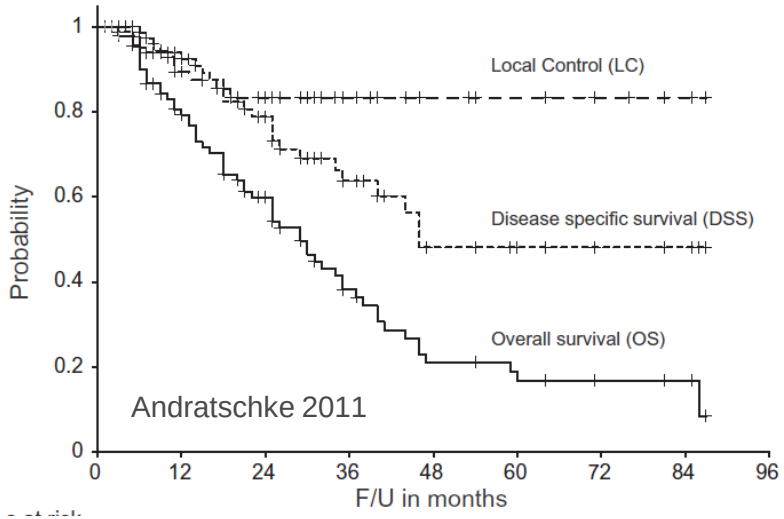
Ursula Nestle

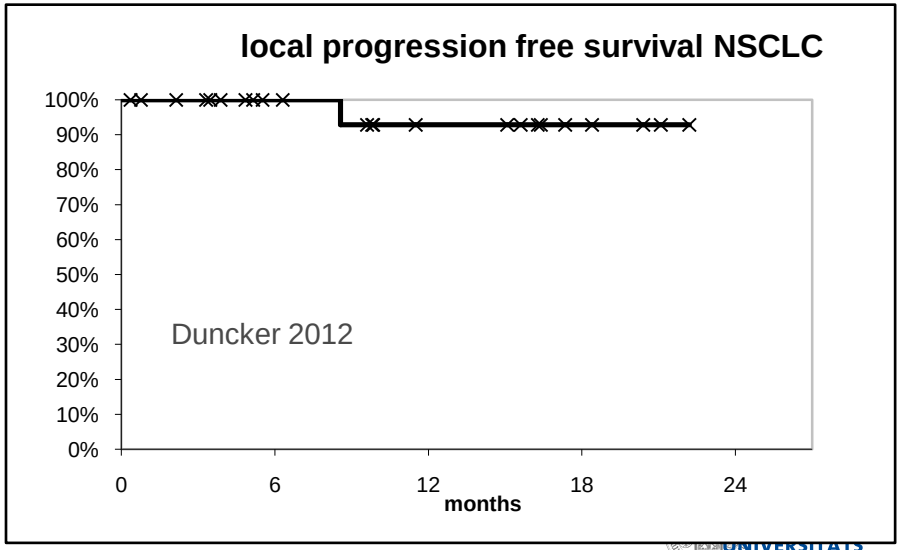
SBRT: success story





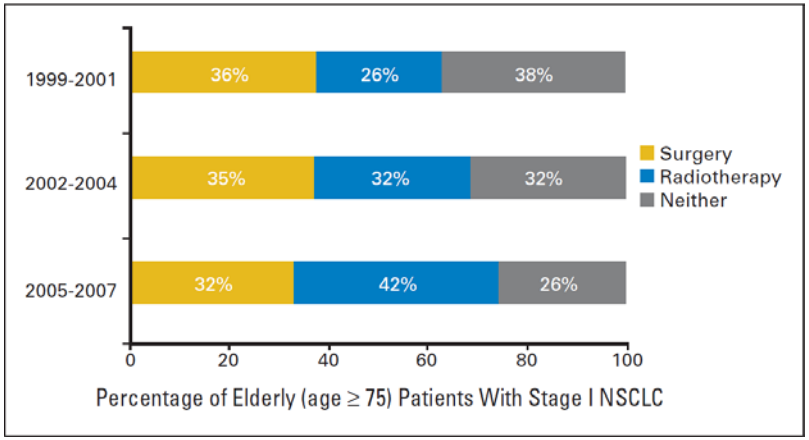




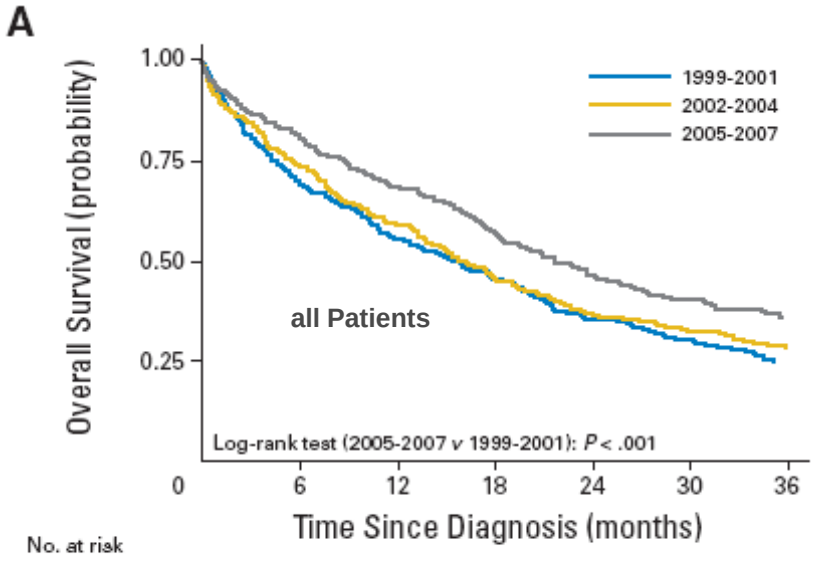


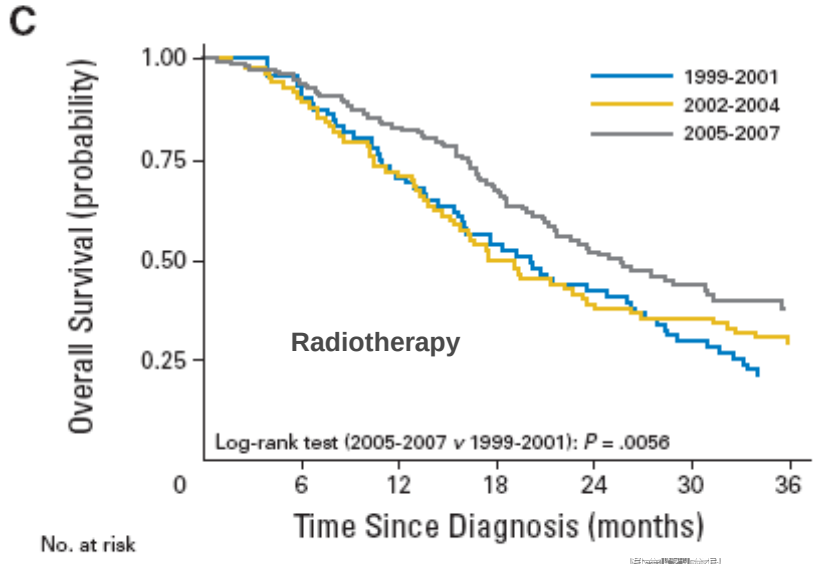
SBRT: improving outcomes stage I LC

Palma D, 2010
Population registry –North Holland



N = 843 stage I patients ≥75 years
SBRT introduction associated with
- 16% increase in RT utilization
- improved survival for whole cohort
- improved survival for RT patients





„Standards“ for dose/prescription to PTV?

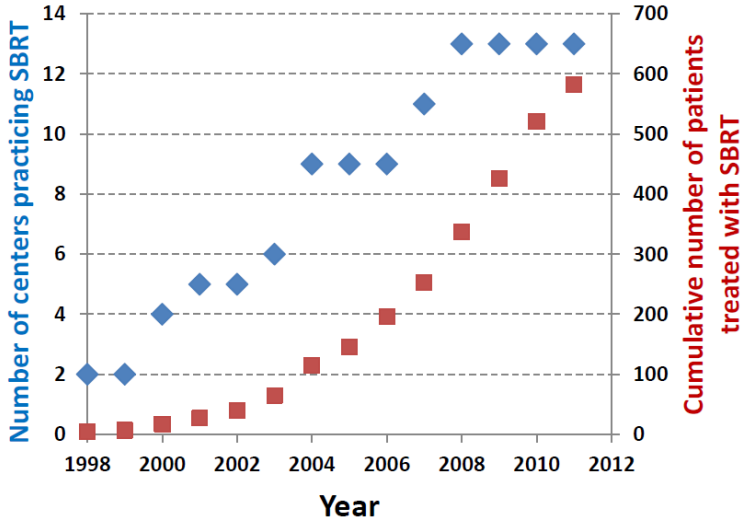
Author	fractionation	dose prescription on % isodose	dose encompassing the PTV	BED for tumor (prescribed dose)	BED on 100%
van Baardwijk [22]	10 x 6 Gy	100%	60 Gy	96 Gy	
Haasbeek [45]	8 x 7.5 Gy	100%	60 Gy	105 Gy	
Mc Garry [16]	3 x 8 Gy	80%	24 Gy	43 Gy	
Mc Garry [16]	3 x 20 Gy	80%	60 Gy		262 Gy
Mc Garry [16]	3 x 22 Gy	80%	66 Gy		309 Gy
Bradley [32]	3 x 18 Gy	80%		151 Gy	219 Gy
Wulf [29]	3 x 12.5 Gy		37.5 Gy	84 Gy	
Wulf [29]	1		26 Gy	94 Gy	138 Gy
Zimmermann [21]		60%	37.5 Gy	84 Gy	192 Gy
Zimm	5 x 7 Gy	60%	35 Gy	60 Gy	126 Gy
own dat	3 x 12.5 Gy	60%	37.5 Gy	84 Gy	192 Gy
own data	5 x 7 Gy	60%	35 Gy	60 Gy	126 Gy

Van Baardwijk, DeRuysscher 2012: Overkill?

Duncker 2012

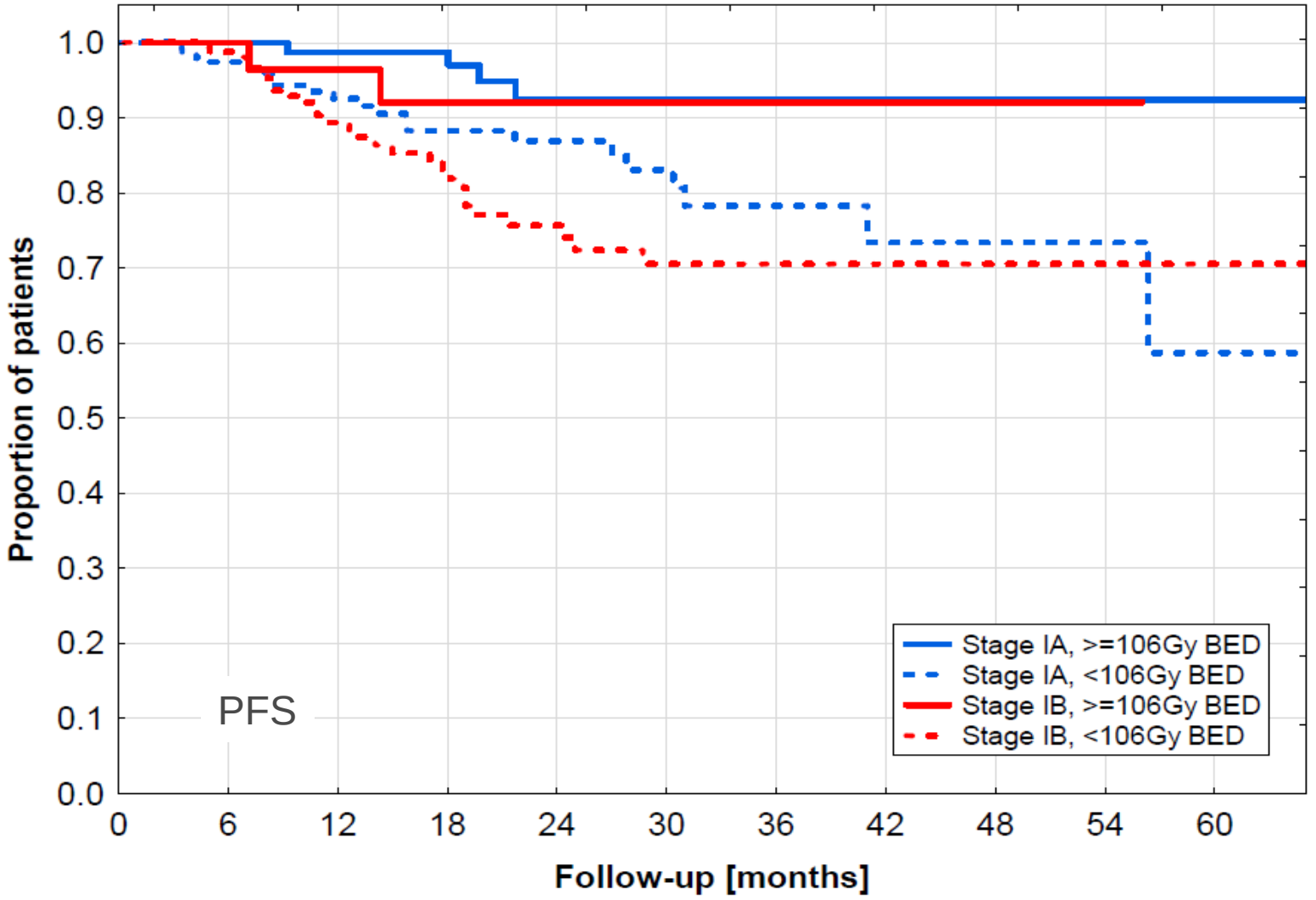
SBRT: wide use, high heterogeneity

M. Guckenberger et al. JTO 2013:
n=582, 13 institutions, SBRT 1998 - 2011



	Number of patients	Percentage	Median	Minimum	Maximum	Time-trend	Inter-institutional variability
Dose calculation algorithm						p<0.001	p<0.001
Type A	265	45.5					
Type B	249	42.8					
unknown	68	11.7					
Number of SBRT fractions	582		3	1	20	0.02	p<0.001
Single fraction dose PTV encomassing (Gy)	582		12.5	2.9	33.0	NS	p<0.001
Total dose PTV encompassing (Gy)	582		37.5	12.0	64.0	p<0.001	p<0.001
Dose inhomogeneity (PTV encompasing dose / Maximum PTV dose) (%)	582		65	60	100	NS	p<0.001
Total BED dose PTV encompassing (Gy)	582		84.4	38.3	180.0	p<0.001	p<0.001

SBRT: „magic BED_{10}“ of 100 Gy?



M. Guckenberger et al. JTO 2013

Radiotherapy and Oncology 110 (2014) 499–504

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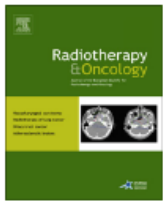


SBRT of lung cancer

Dose–response relationship with clinical outcome for lung stereotactic body radiotherapy (SBRT) delivered via online image guidance ☆

Larry Kestin [a,*], Inga Grills [b], Matthias Guckenberger [c], Jose Belderbos [d], Andrew J. Hope [e], Maria Werner-Wasik [f], Jan-Jakob Sonke [d], Jean-Pierre Bissonnette [e], Ying Xiao [f], Di Yan [b], on behalf of the Elekta Lung Research Group

[a] 21st Century Oncology/Michigan Healthcare Professionals, Farmington Hills, USA; [b] Department of Radiation Oncology, William Beaumont Hospital, Royal Oak, USA; [c] Department of Radiation Oncology, University of Wuerzburg, Germany; [d] Department of Radiation Oncology, Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands; [e] Princess Margaret Hospital, University of Toronto, Canada; [f] Department of Radiation Oncology, Thomas Jefferson University Hospital, Philadelphia, USA

5 institutions, 505 tumors (483 pts.), T1/2 N0 M0

5% local recurrences

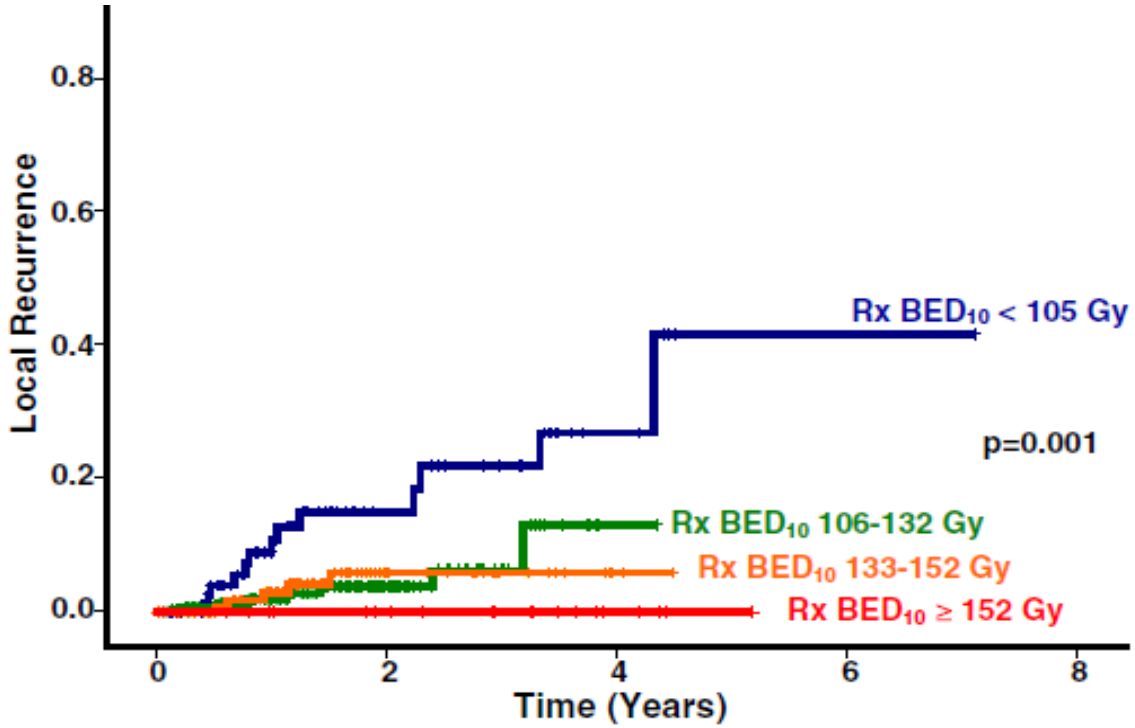
prescriptions (median: 54 Gy/3 fx):

- 3x18-20 (54-60) Gy, 3x12.5 (37.5) Gy
- 4x12 (48) Gy, 5x12 (60) Gy
- 8x7.5 (60) Gy

Elekta group: Doses vs. outcome

Table 1
ROC curves for factors predicting for local control.

Parameter	Area under curve	*p*-Value	Optimal cut point	Sensitivity (%)	Specificity (%)	2-Year local control (%)
Prescription BED_{10}	0.693	0.001	105.3 Gy	81	50	96 vs. 85
PTV_{mean} BED_{10}	0.654	0.02	125.8 Gy	84	57	96 vs. 83
GTV_{mean} BED_{10}	0.654	0.02	147.1 Gy	81	52	97 vs. 83
PTV_{max} BED_{10}	0.650	0.02	175.3 Gy	68	62	97 vs. 87
GTV_{max} BED_{10}	0.650	0.02	175.3 Gy	68	62	97 vs. 88
PTV_{min} BED_{10}	0.638	0.03	110.1 Gy	53	77	97 vs. 90
PTV D99 BED_{10}	0.637	0.03	92.6 Gy	87	62	95 vs. 83
GTV_{min} BED_{10}	0.632	0.04	149.8 Gy	57	72	98 vs. 89
PTV D1 BED_{10}	0.627	0.05	163.5 Gy	68	57	96 vs. 87
Treatment duration	0.644	0.01	11 days	50	82	96 vs. 86
GTV_{max} dimension	0.614	0.05	2.7 cm	65	55	97 vs. 91



Cox regression analysis:

independent parameters
- Dose (prescription BED_{10})
- treatment duration

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bonus slide

SPACE - A randomized study of SBRT vs conventional fractionated radiotherapy in medically inoperable stage I NSCLC

J. Nyman et al. world lung 2015

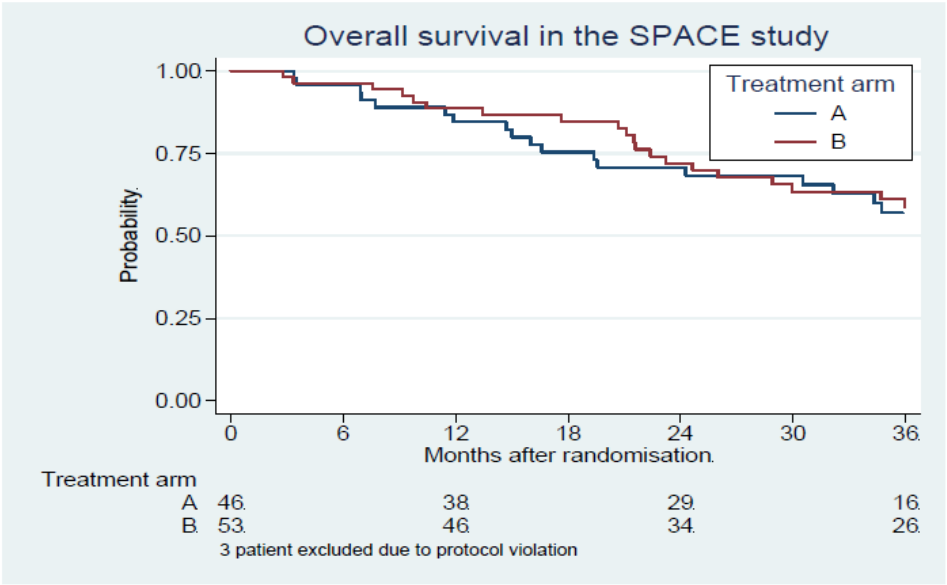
102 patients,
- (T1-2N0M0) NSCLC,
- significant comorbidity

9 Scandinavian centers

rando:
- SBRT 3x 22 Gy;
- CFRT 35x 2 Gy

primary endpoint:
- freedom from progression at 3 years

Per protocol



IASLC
INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER
16TH WORLD CONFERENCE ON LUNG CANCER
SEPTEMBER 6–9, 2015 • DENVER, COLORADO, USA

Conclusions

1. In this randomized phase II trial stage I patients treated with SBRT had the same PFS and OS as the 3DCRT patients despite an imbalance in prognostic factors (T2 tumors and male gender)
2. There was a tendency to improved disease control rate at the end of study in the SBRT patients
3. SBRT patients experienced better QoL values regarding dyspnea, cough and chest pain as well as numerically less toxicity (CTC 3.0)
4. Shortcomings: PET and 4DCT was not mandatory

→ 5. SBRT should probably be considered standard therapy for this patient group

IASLC 40 YEARS

Abstract 923: The SPACE study: A. Hallqvist

Central tumors: outcome from expert treatment

bonus slide

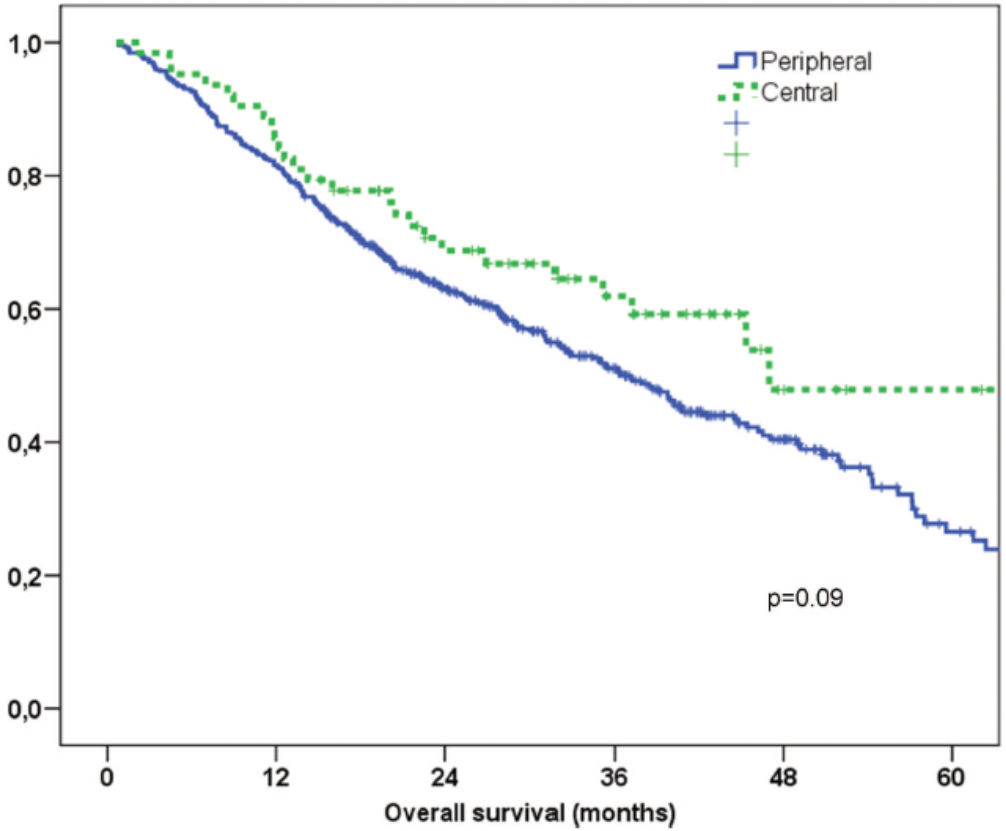
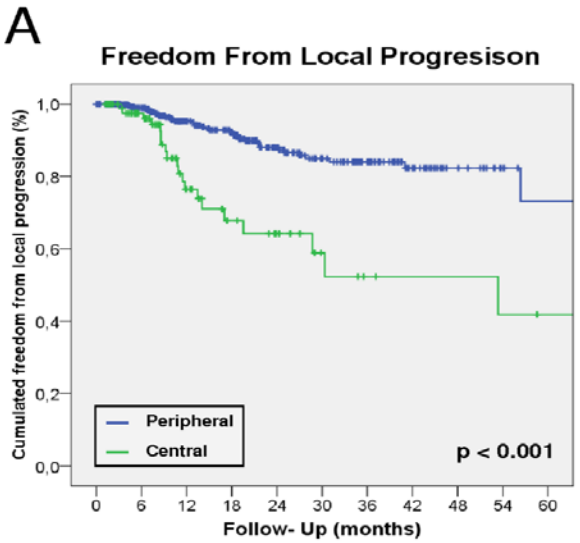
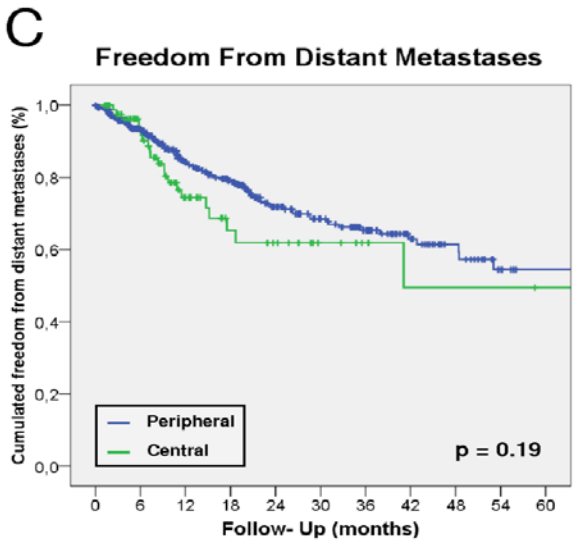


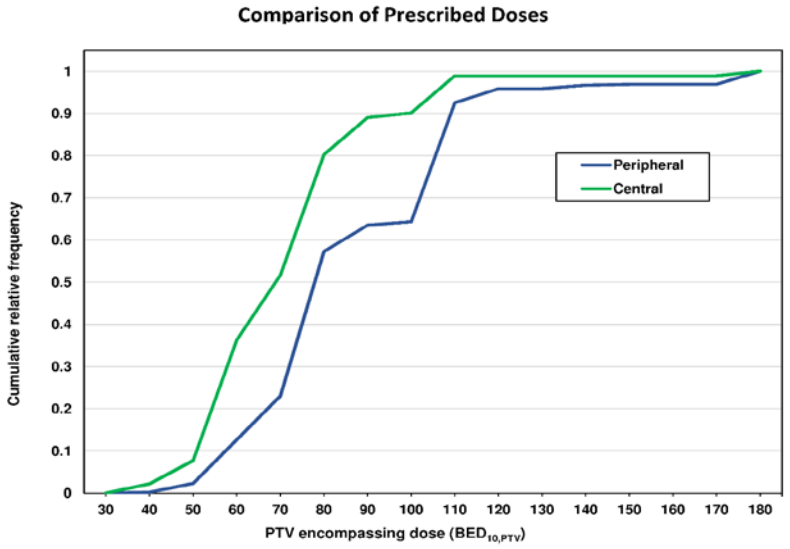
FIGURE 3. Overall survival for central and peripheral early-stage lung tumors after stereotactic ablative radiotherapy (SABR).

Haasbeek JTO 2011, BED_{10}=105 Gy

Central tumors







"Local tumor control in patients treated with SBRT for centrally located, early-stage NSCLC was favorable, provided ablative radiation doses were prescribed."

This was, however, not the case in the majority of patients!

Schanne, D. et al. S&O 2013

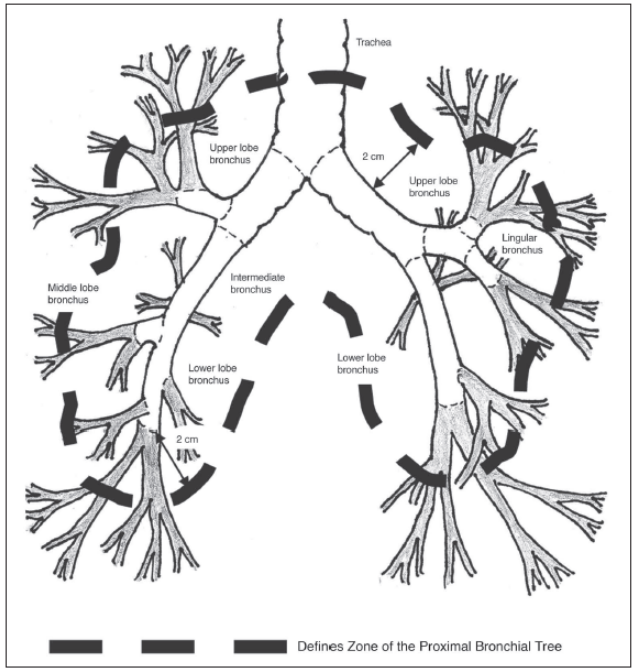
Toxicity!

VOLUME 24 · NUMBER 30 · OCTOBER 20 2006

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

70 pts.,
T1/T2 NSCLC
3x20Gy; 3x22 Gy
prescription to 80%
Type A
no density corrections



Excessive Toxicity When Treating Central Tumors in a Phase II Study of Stereotactic Body Radiation Therapy for Medically Inoperable Early-Stage Lung Cancer

Robert Timmerman, Ronald McGarry, Constantin Yiannoutsos, Lech Papiez, Kathy Tudor, Jill DeLuca, Marvene Ewing, Ramzi Abdulrahman, Colleen DesRosiers, Mark Williams, and James Fletcher

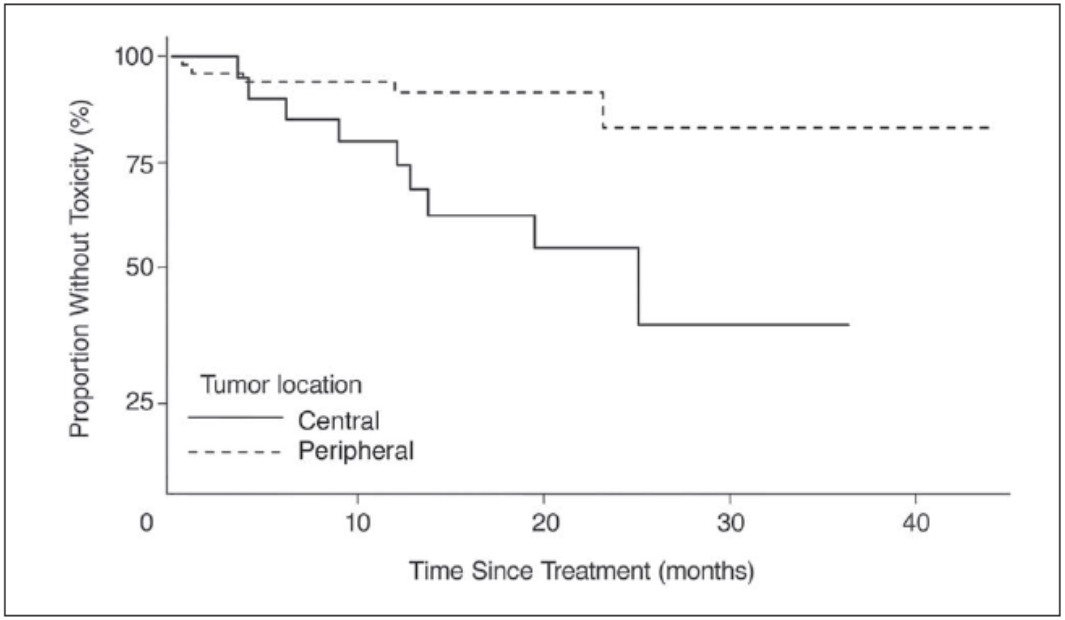
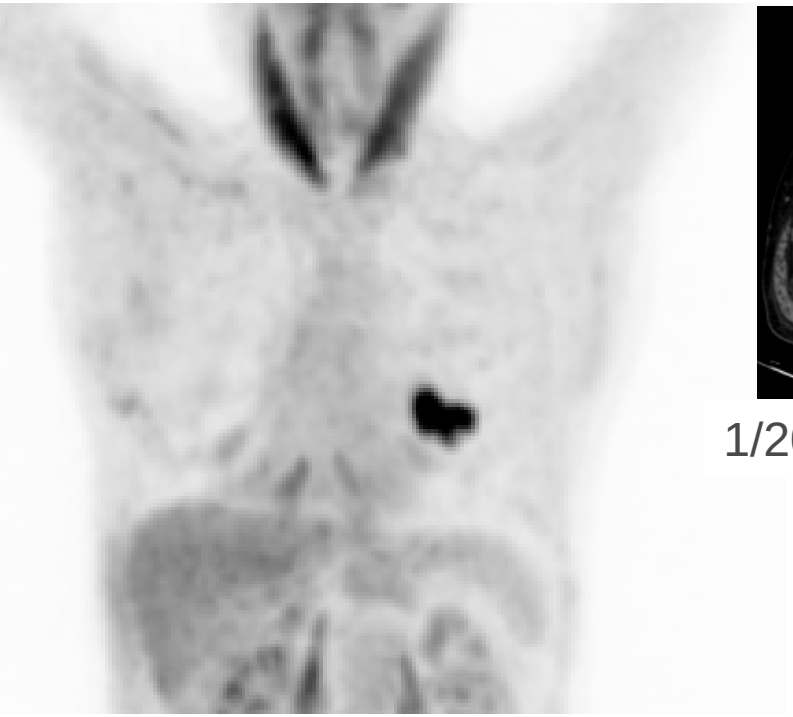
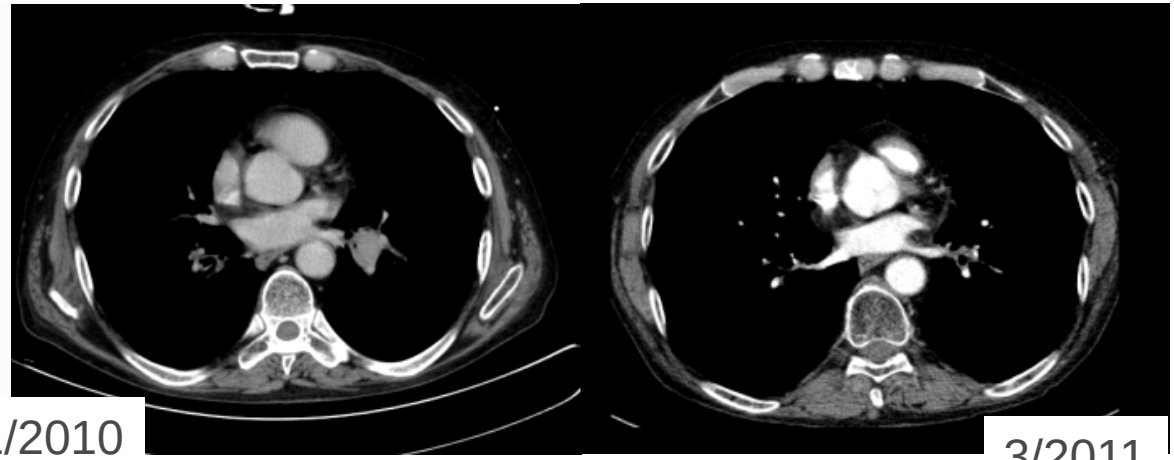


Fig 4. Kaplan-Meier plot of time from treatment until grade 3 to 5 treatment related toxicity comparing patients with tumors in the central (perihilar and central mediastinal) regions from those with more peripheral tumors.

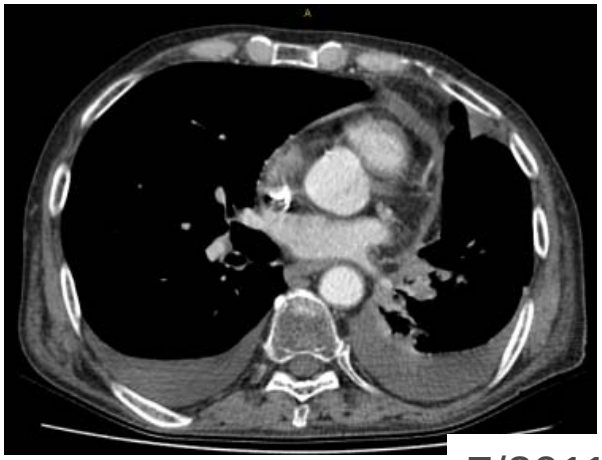
Pat. S.D. *1943, SCC



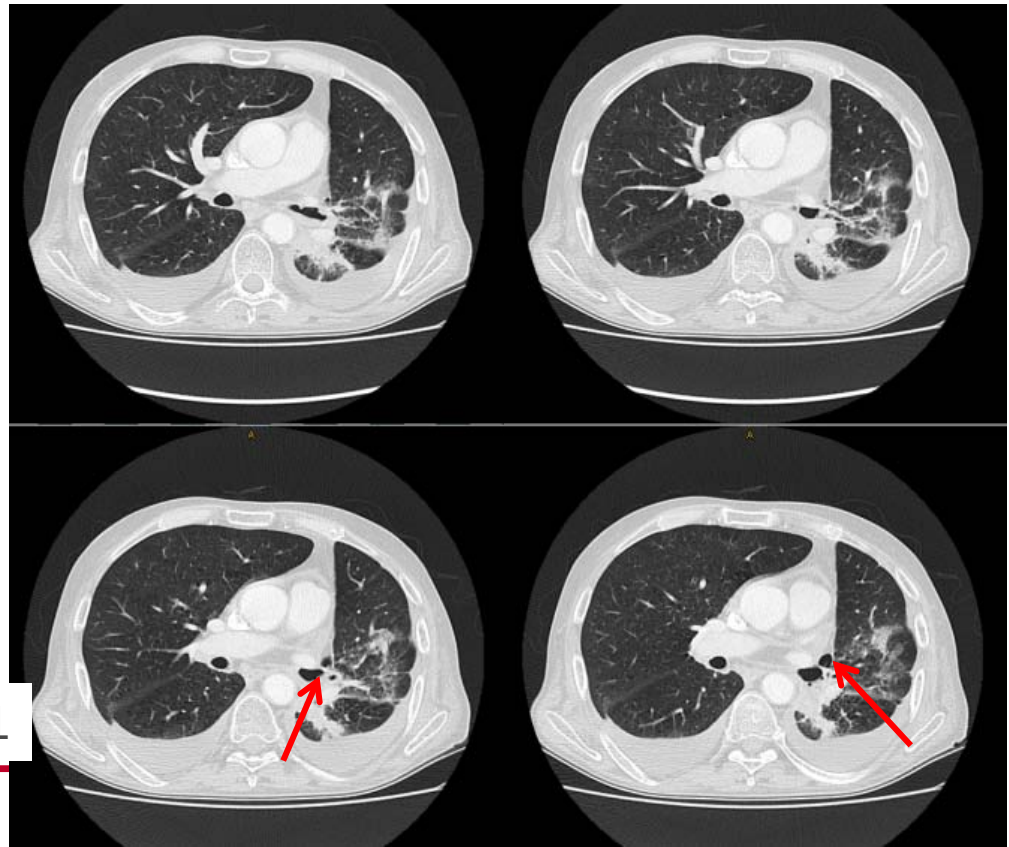


1/2010

3/2011



7/2011

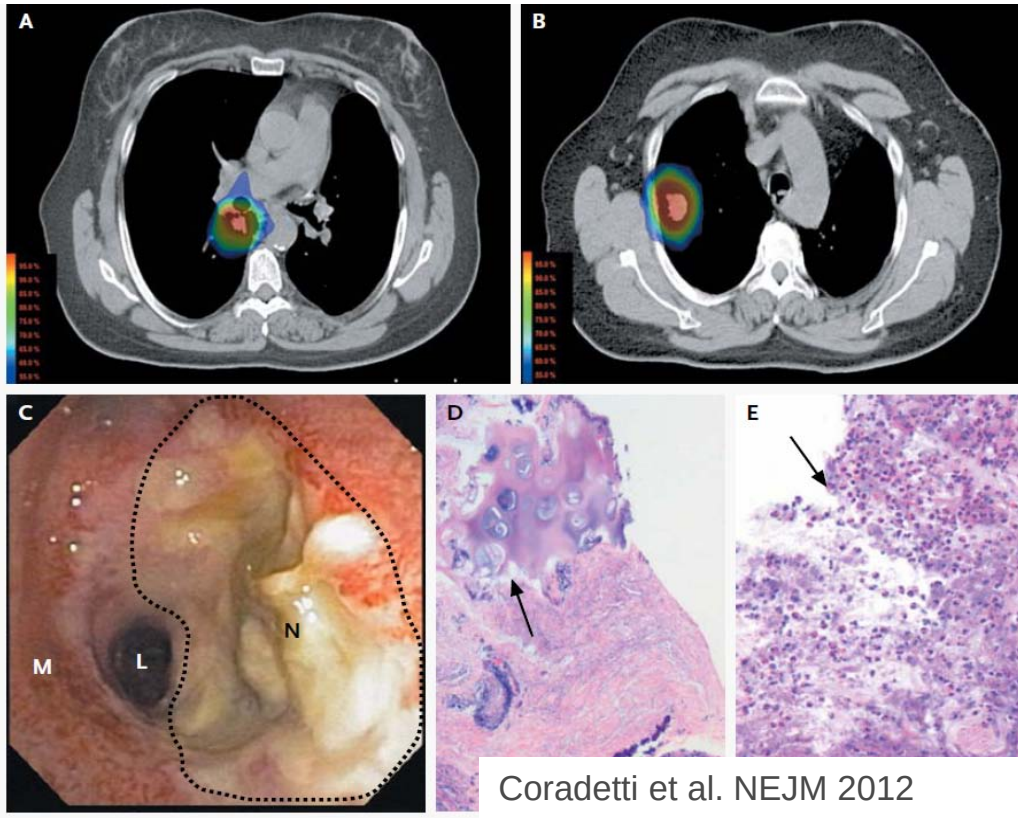


Another fatal necrosis after central SBRT…

bonus slide

Case report: Central Airway Necrosis after SBRT

- SBRT to two NSCLC,
  one of them centrally located
- 8 months later:
  mediastinal LN recurrence,
  extensive changes within
  irradiated bronchus
  (**biopsy**: fibrosis)
- **Chemo** / hemoptysis / intubation
- Died 11 months after SBRT



Coradetti et al. NEJM 2012

Dose-Limiting Toxicity After Hypofractionated Dose-Escalated Radiotherapy in Non–Small-Cell Lung Cancer

Donald M. Cannon, Minesh P. Mehta, Jarrod B. Adkison, Deepak Khuntia, Anne M. Traynor, Wolfgang A. Tomé, Richard J. Chappell, Ranjini Tolakanahalli, Pranshu Mohindra, Søren M. Bentzen, and George M. Cannon

J Clin Oncol 31:4343-4348.

Conclusion

Although this dose-escalation model limited the rates of clinically significant pneumonitis, dose-limiting toxicity occurred and was dominated by late radiation toxicity involving central and perihilar structures. The identified dose-response for damage to the proximal bronchial tree warrants caution in future dose-intensification protocols, especially when using hypofractionation.

57 Gy – 85.5 Gy in 25 fractions
EQD2 predicting 5% complication rate @2y:
75-83 Gy

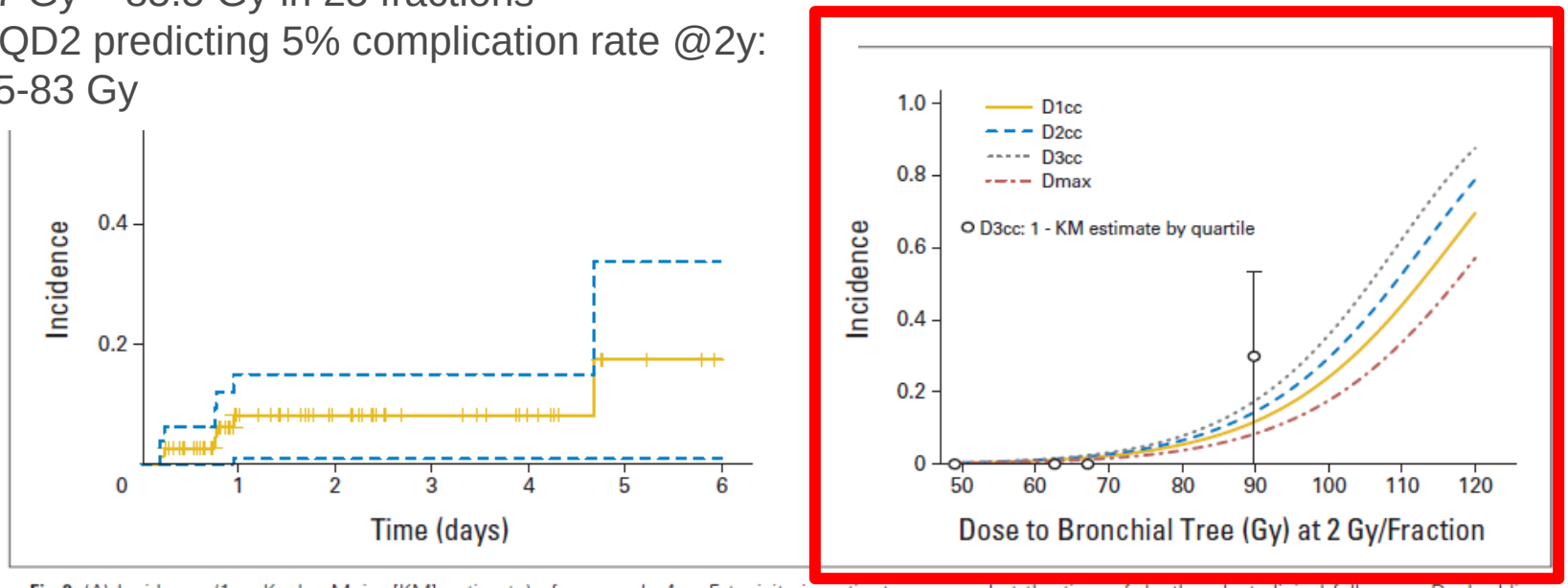
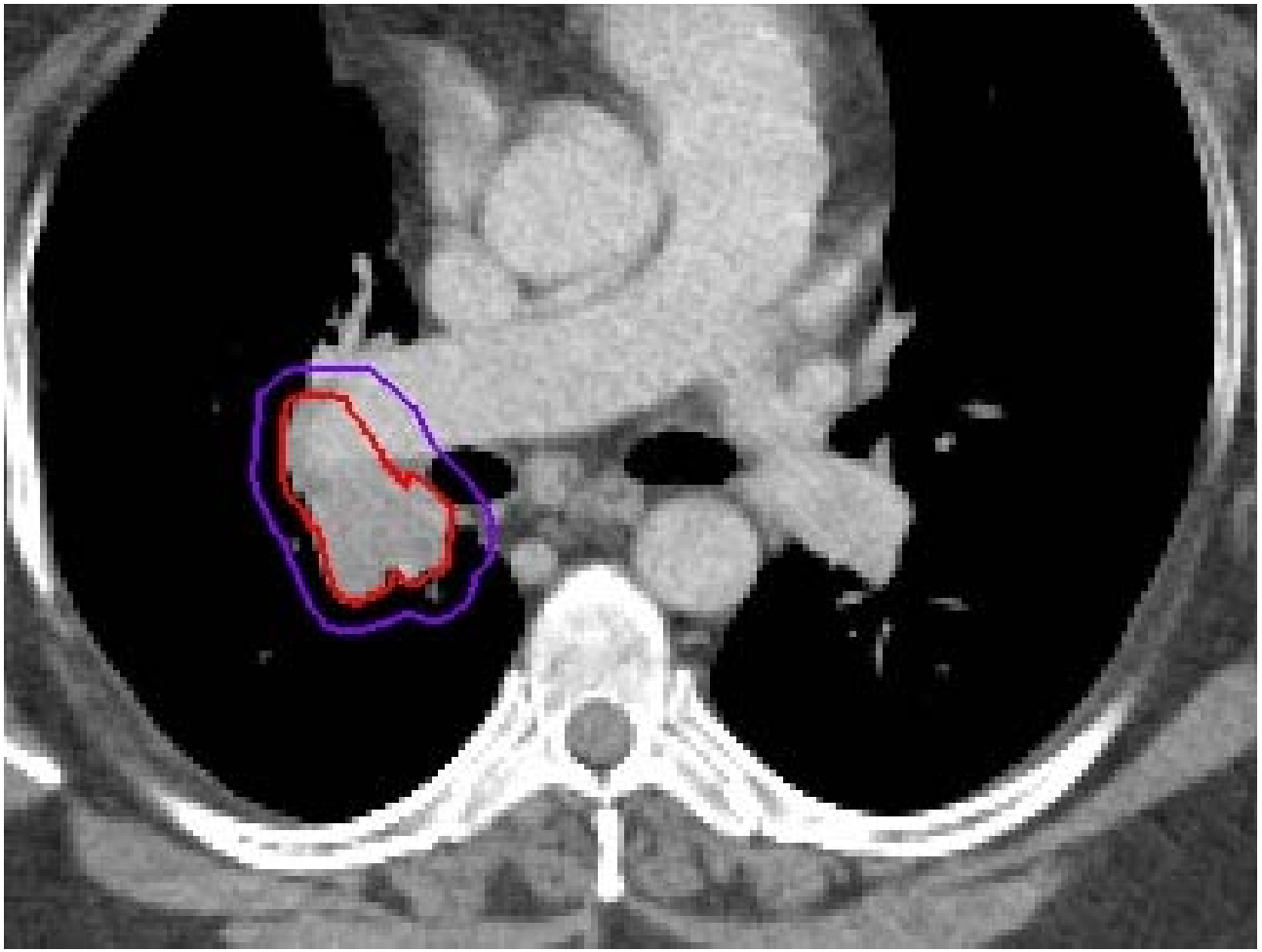


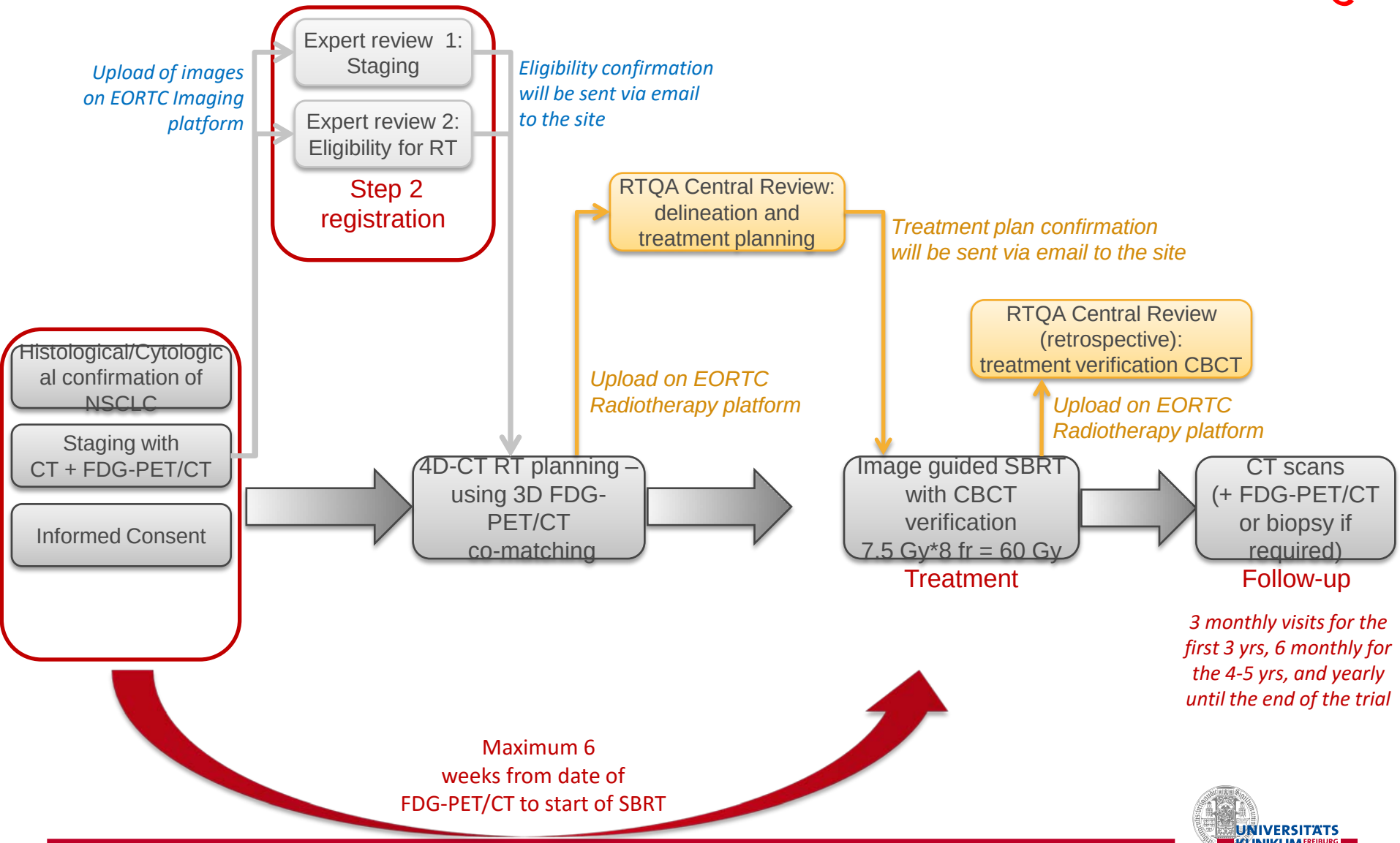
Fig 2. (A) Incidence (1 − Kaplan-Meier [KM] estimate) of any grade 4 or 5 toxicity in patients censored at the time of death or last clinical follow-up. Dashed lines represent the 95% CI. (B) Two-year probabilities of late grade 4 or 5 toxicity according to dose-per-fraction normalized dose (EQD2) to the proximal bronchial tree and estimated using a Cox proportional hazards model. Open circles represent the 1 − KM estimate (± 95% CI) for quartiles of EQD2 D3cc (centered at the quartile mean). DXcc, maximum dose D such that X cm^3 of the structure received a dose ≥ D; Dmax, maximum dose to any voxel within structure.

“competing risk”:
Tumor invasion of bronchus and vessel



22113 – 08113 Trial design

bonus slide



Adebahr et al ,BJR /2015

EORTC 22113-08113: LUNGTECH

- VU monocenter experience: Data with risk-adapted doses show good local control rates and moderate toxicity [Haasbeek, J Thor Oncol 2009] :

- SBRT: 60 Gy in 8 fractions of 7.5 Gy will be given alternate days, i.e. over a total treatment time of 2.5 weeks

EORTC 22113-08113: LungTech

Stereotactic Body Radiotherapy (SBRT) of medically inoperable patients with centrally located NSCLC

Study Coordinator: Ursula Nestle

A study of the EORTC Radiation Oncology and Lung Cancer Groups

EORTC The future of cancer therapy

CANCER RESEARCH UK

Deutsche Krebshilfe HELFEN. FORSCHEN. INFORMIEREN.

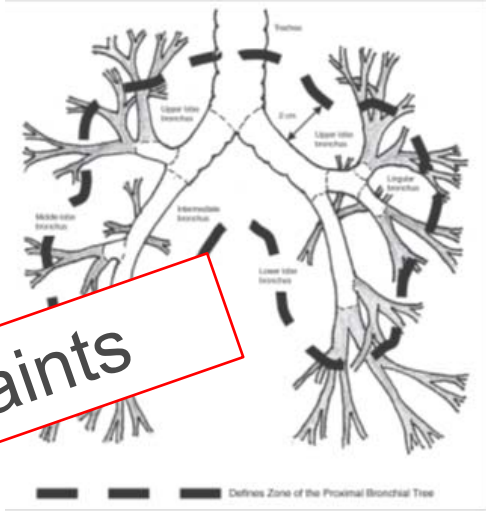
LUNGTECH – KEY NOTES

- *Study treatment:*
  - SBRT of centrally located NSCLC (T1-T3 N0)
  - 8 X 7.5 Gy, GD 60Gy, ICRU 83

- *Primary endpoint:*
  to evaluate the freedom of local progression ra
  at 3 years

- *Secondary endpoints:*
  - acute and la pping rules)
  - patt d distant recurrence
  - over ival and causes of death

… need to define NT constraints



Timmerman et al , JCO 2006

- *Sites:*
  - 23 Participating sites have been selected from 7 European countries

DOSE CONSTRAINTS

- Maximum tolerated doses and optimum fractionation for mediastinal structures is currently unknown
- Toxicity for SBRT delivered to central tumors is not well documented
- Serious doubts in the validity of available data, mostly coming from retrospective series with small sample sizes
- Lacking, incomplete or inconsistent reporting on dose specification
- Questionable use of EqD2, α/ß-ratios, LQM estimates

→ Summary of current experiences in dose/ fraction - toxicity coherences after SBRT to the mediastinal structures that lead to LungTech normal tissue constraints

Critical Review

The Tumor Radiobiology of SRS and SBRT: Are More Than the 5 Rs Involved?

J. Martin Brown, PhD,* David J. Carlson, PhD,† and David J. Brenner, PhD‡

*Department of Radiation Oncology, Stanford University School of Medicine, Stanford, California; †Department of Therapeutic Radiology, Yale University School of Medicine, New Haven, Connecticut, and ‡Center for Radiological Research, Columbia University Medical Center, New York, New York

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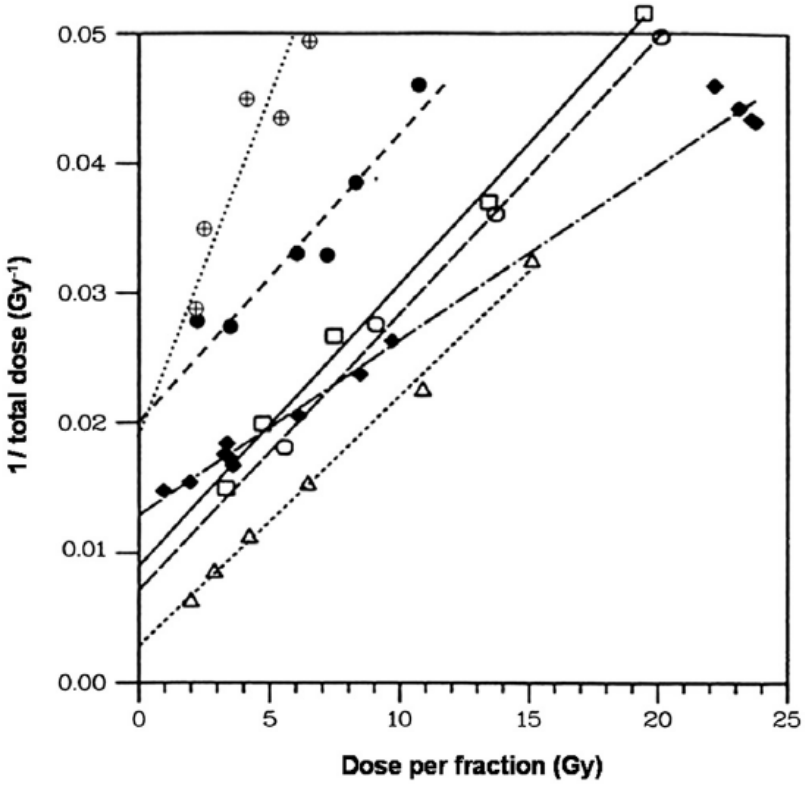


"Thus, we suggest that for most tumors, the standard radiobiology concepts of the 5 Rs are sufficient to explain the clinical data …"

"There is compelling in vitro and in vivo normal tissue evidence that the LQ model provides reasonable results at high doses …"

Fig. 2. Isoeffect data for response in normal tissues fit the linear quadratic model. Data for different regions (□, O, Δ) of the rat spinal cord (24), for acute skin reactions (◆) in mice (25), and for early (●) and late (O+) murine intestinal damage (26). The LQ model predicts straight lines for these plots. From (15) with permission.

DOSE CONSTRAINTS: OAR IN MORE „CENTRAL“ SBRT

- bronchial tree
- heart
- large vessels
- esophagus

problem:

life threatening toxicities possible;
only case reports and small mainly retrospective series available

DOSE CONSTRAINTS: **PROX BRONCHIAL TREE**

Bronchial tree / trachea
(α/ß 3 Gy), potential side effects: fatal hemoptysis, fistula, stenosis, necrosis, atelectasis, pneumonia and abscess

Reference	*Number of reported patients (treated tumours)*	*Number of centres*	*Pro (p)-/ retro(r)-spective*	*Results (max. point dose or dose/fractionatio*
Timmerman (50)	70	1		with 19.5
Fakiris				ns),
M				
O				
Br				
Ung				1 x bronchial fistula, mainstem bronchus received a maximum point dose of 49 Gy (**EqD2 not applicable**)
Canc		1	p	CFRT: **EqD2 of 75-83 Gy** predicting a 5% complication rate, 3 x fatal hemoptysis, 85 and 75 Gy, 25 fractions (**EqD2 118 and 90, respectively**), tumors encasing or abutting a mainstem or proximal lobar bronchus and partially local invasion of adjacent normal structures

Recommendations/NT constraints

Timmerman (66) — maximum point dose: 20.2 Gy (1 fraction regime – **EqD2: 93.7 Gy**) 40 Gy (5 fraction regime – **EqD2: 88 Gy**)

RTOG 0813 (56) — >105% PTV, **EqD2 not applicable**

Haasbeek (53) — maximum dose restriction (0.5 cc): 8 x 5,5 = 44 Gy (**EqD2: 74.8Gy**)

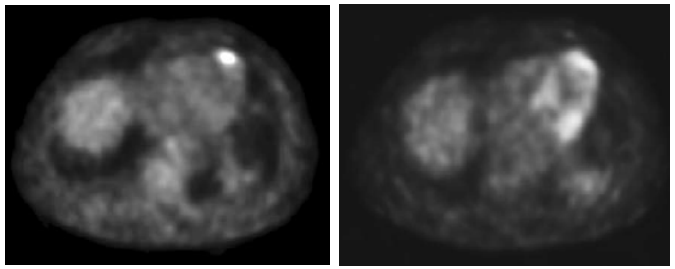
Nuyttens (67) — maximum dose restriction (0.5 cc): 6 x 8 = 48 Gy (**EqD2: 105.6Gy**)

EORTC 22113-08113 — dose constraint: 8 x 5.5 Gy = 44Gy, **(EqD2 74.8Gy)**

Adebahr et al , BJR 2015, in press

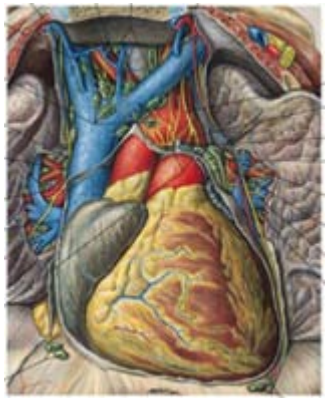
DOSE CONSTRAINTS: **HEART**

Heart
(α/ß 3 Gy), potential side effects: Congestive heart failure, pericarditis, pericardial effusion and arrhythmia



Bonomo et al. Radiol med 2013

- 16 pts with paracardiac and cardiac lesions
- 30-36 Gy, 3# (70%)
- D100%: 51.4 Gy
- EQD2 (αβ3):108-204 Gy
- BED3: 240 Gy



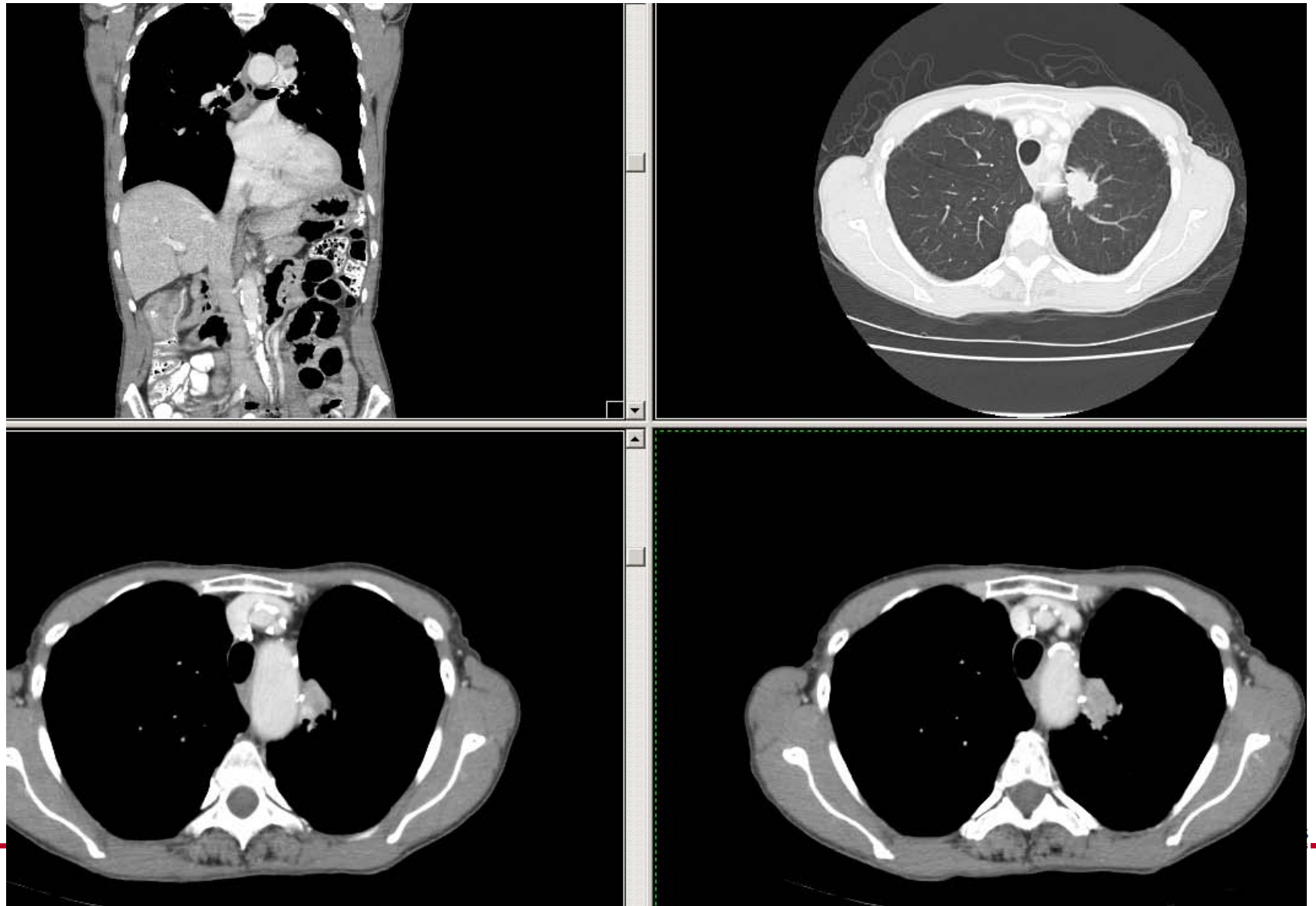
- no cardiological symptoms or electrocardiographic abnormalities, even months after SBRT
- 1 clinically irrelevant, pericardial effusion (PCE) at 3 months, disappeared at follow-up

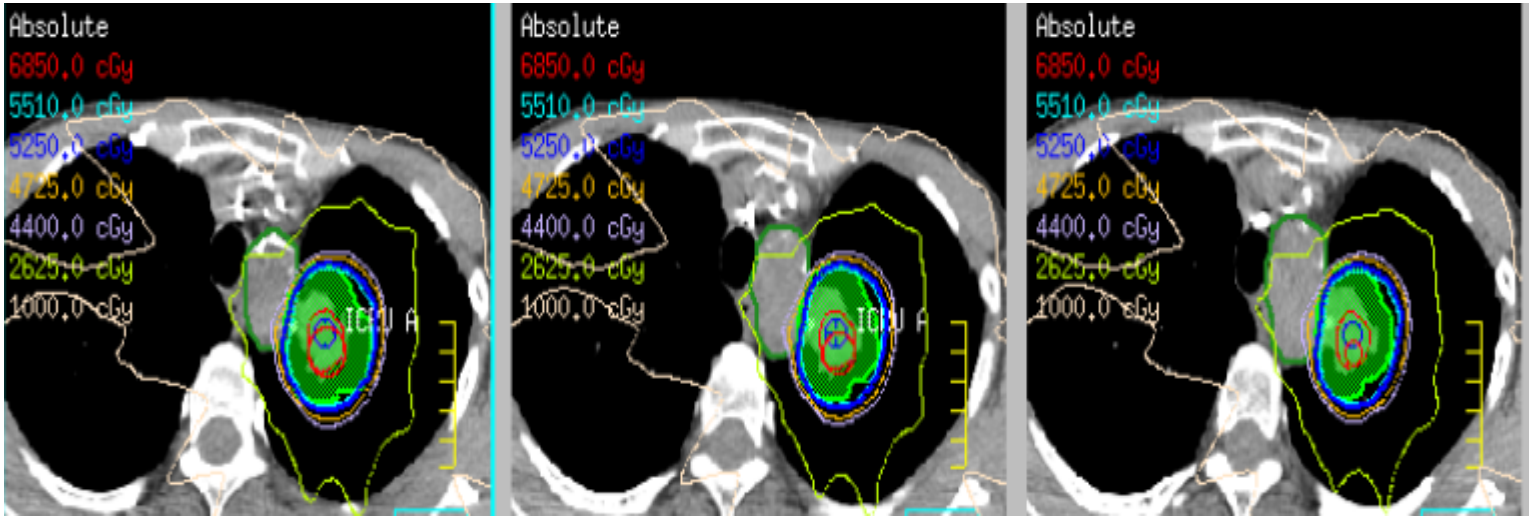
Recommendations/NT constraints	
Timmerman (66)	maximum point dose: 22 Gy (1 fraction regime – **EqD2: 110 Gy**) 38 Gy (5 fraction regime – **EqD2: 80.6 Gy**)
RTOG 0813 (56)	maximum point dose: 63 Gy (5 fractions regime - **EqD2: 196 Gy**) 60 Gy (10 fractions regime - **EqD2: 108 Gy**)
EORTC 22113-08113	no restrictions, but recording of DVH data for toxicity

Adebahr et al ,BJR, accepted 04/2015

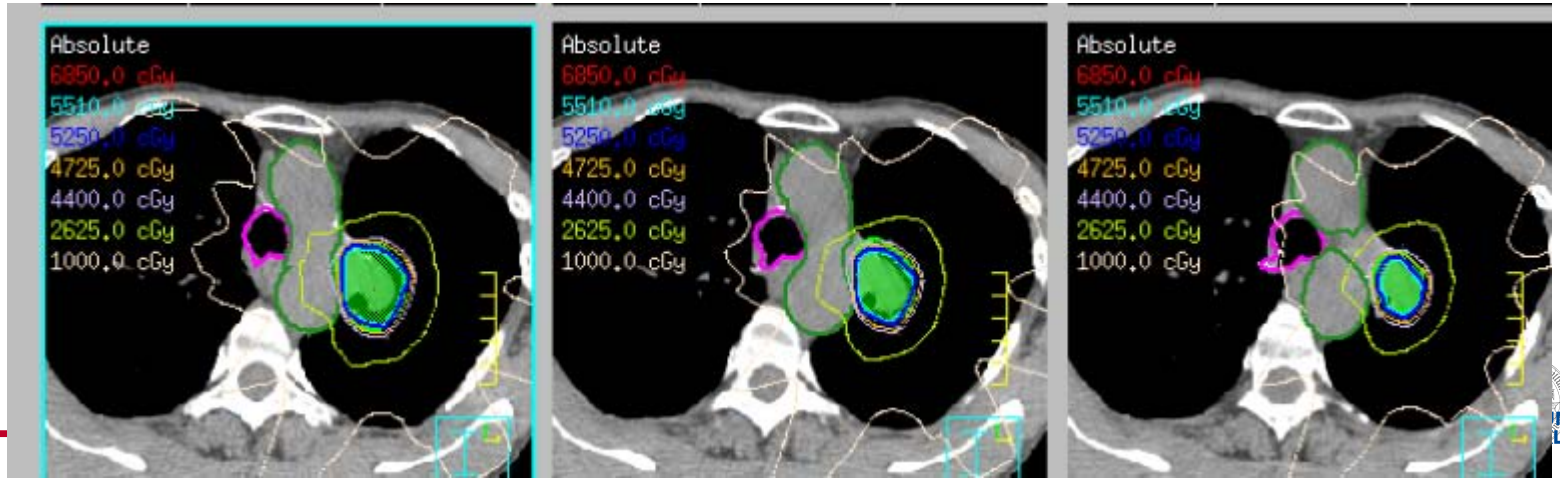
Great vessels: a case from A. Bezjak

59 yr old lady, 2.2 cm adenoca, SUV 8
previous RUL and LUL lobectomies 4 and 6 yrs prior





Treated on RTOG 0813 phase I study - 52.5Gy/5 fr
Great Vessel (Aorta) max=5507.7cGy (Limit=55.1Gy)
10cc=3368cGy



Course post SBRT

6 w and 3 mo f/u - well, response on CXR

5.7 mo post SBRT– sudden onset of feeling unwell, looked pale, refused to go to MD

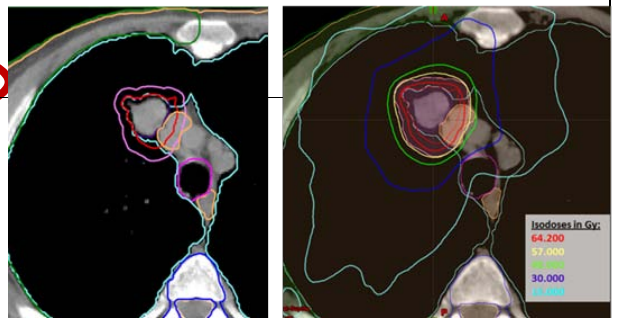
Next day blood - ? coughed or vomited – called ambulance – pt arrested within minutes of ambulance arrival –resuscitation attempts unsuccessful

Autopsy not performed

DOSE CONSTRAINTS: **GREAT VESSLES**

Great vessels (aorta, vena cava sup. and inf., brachiocephalic veins) (α/ß 3 Gy), potential side effects: hemoptysis and fatal bleeding				
Reference	*Number of reported patients (treated tumours)*	*Number of centres*	*Pro (p)-/ retro(r)-spective*	*Results (max. point dose or dose/fractionation and EqD2 in Gy provided if possible)*
Timmerman (50)	70	1	p	Single cases of hemoptysis and fatal bleeding with varying SBRT regimens (s. bronchus)
Senthi (9)	(563)	20°	r/p(4)	Single cases of hemoptysis and fatal bleeding with varying SBRT regimens (s. bronchus: Song (51), Milano(62), Oshiro (63), Bral (36))
Canon et al. (65)	75*	1	p	(s. bronchus)

Recommendations/NT constraints	
Timmerman (66)	maximum point dose: 37 Gy (1 fraction regime – **EqD2: 296 Gy**) 53 Gy (5 fraction regime – **EqD2: 144.2Gy**)
RTOG 0813 (56)	maximum point dose: 63 Gy (5 fraction regime - **EqD2: 196,6Gy**) 75 Gy (10 fractions regime - **EqD2: 157.5Gy**)
EORTC 22113-08113	no restrictions, but recording of DVH data for toxicity



Adebahr et al , BJR 2015, in press

Esophageal toxicity

bonus slide

Grade 1 radiation-induced esophagitis was observed 1 week after the start of IGRT in 1 patient with metastatic lung cancer who received 48 Gy/8 Fr to the 3.5-cm tumor located posterior to the right main bronchus. The pain resulting from acute radiation esophagitis was relieved at 1 month after IGRT ended. However, this patient suffered from swallowing pain again 3 months after IGRT ended and died as a result of bleeding from an esophageal ulcer 5 months after IGRT ended.

Onimaru IJROBP 2003

- Very few reports of significant esophagitis
- most centers exclude pts with PTV touching the esophagus from SBRT:

⇨ few cases @ risk

DOSE CONSTRAINTS: **OESOPHAGUS**

Oesophagus (α/ß 3 Gy), potential side effects: fistula, stenosis, perforation, oesophagitis, ulcer, hemorrhage)				
Reference	*Number of reported patients (treated tumours)*	*Number of centres*	*Pro (p)-/ retro(r)-spective*	*Results (max. point dose or dose/fractionation and EqD2 in Gy provided if possible)*
Onimaru (69)	45(57)*	1	p	1 death due to radiation-induced ulcer in the oesphagus 5 months after SBRT, 48 Gy, 8 fractions **(EqD2 86.4 Gy)#**, maximum dose of 50.5 Gy at the oesphagus (**EqD2 =93.7Gy**)
Stephans (70)	52	1	r	2 cases of oesophageal fistula, when the oesophageal point dose> 51 Gy and 1-cc doses > 48 Gy, **EqD2 not applicable**
Modh (57)	91	1	r	1 fistula with an oesophageal Dmax of 46Gy in 5 fractions (**EqD2 =112Gy**). Oesophageal toxicity ≥ G2 2: 12.8% (median Dmax of 29.5Gy for those patients with oesophageal toxicity), **EqD2 could not be derived from those data.**

Recommendations/NT constraints	
Timmerman (66)	maximum point dose: 15.4 Gy (1 fraction regime – EqD2: 56.7Gy) 35 Gy (5 fraction regime – EqD2: 70 Gy)
RTOG 0813 (56)	maximum point dose: 63Gy (5 fraction regime – EqD2: 196Gy) 50 Gy (10 fraction regime – EqD2: 80Gy)
Nuyttens (67)	maximum dose restriction (0.5 cc): 6 x 6 = 36 Gy (EqD2: 64.8Gy)
EORTC 22113-08113	dose constraint: 8 x 5 Gy= 40Gy, (EqD2: 64Gy)

Adebahr et al ,BJR, accepted 04/2015

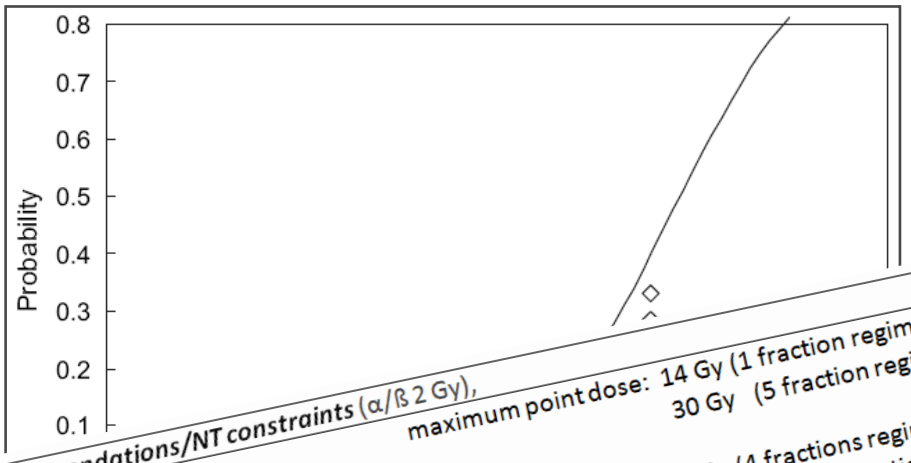
DOSE CONSTRAINTS: OAR IN „PERIPHERAL“ SBRT

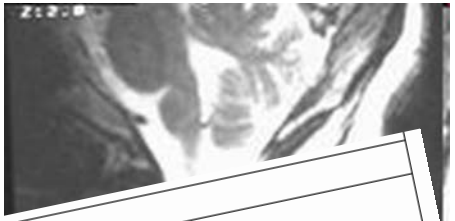
- spinal cord
- brachial plexus
- lung
- chest wall

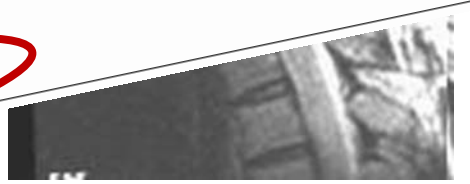
advantage: some larger series available

DOSE CONSTRAINTS: **SPINAL CORD**

QUANTEC (Kirkpatrick 2010):







Recommendations/NT constraints (α/ß 2 Gy),	
Timmerman (66)	maximum point dose: 14 Gy (1 fraction regime – EqD2: 56 Gy) 30 Gy (5 fraction regime – EqD2: 60Gy)
RTOG 0813 (56)	maximum point dose: 25Gy (4 fractions regime- EqD2: 51,6 Gy) 30/40Gy (5/10 fractions regime- EqD2: 60Gy)
Haasbeek (53)	maximum dose restriction (0.5 cc): 8 x 3,5 = 28 Gy (EqD2: 36 Gy)
Nuyttens (67)	maximum dose restriction (0.5 cc): 6 x 4.5 = 27Gy (EqD2: 43.9 Gy)
EORTC 22113-1081[13]	dose constraint: 8x 4 Gy= 32Gy, (EqD2: 48 Gy)

For partial cord irradiation as part of spine radiosurgery, maximum cord dose of 13 Gy in 1 fraction (**EqD2: 48.8**) or 20 Gy in 3 fractions (**EqD2: 110 Gy**) appear associated with a **<1% risk of injury**

DOSE CONSTRAINTS: **BRACHIAL PLEXUS**

Radiotherapy and Oncology 93 (2009) 408–413

Contents lists available at ScienceDirect

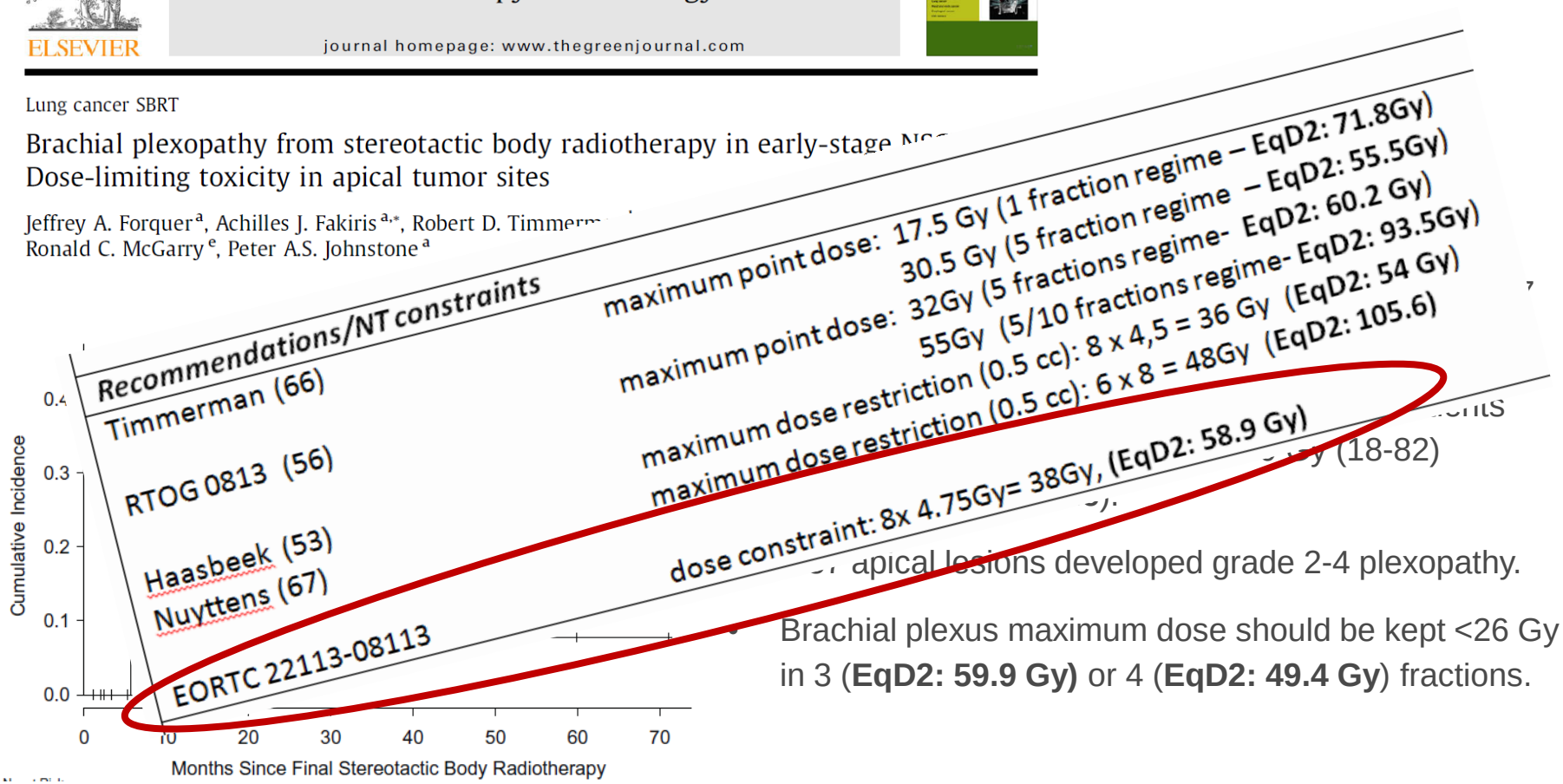
Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Lung cancer SBRT

Brachial plexopathy from stereotactic body radiotherapy in early-stage NS
Dose-limiting toxicity in apical tumor sites

Jeffrey A. Forquer [a], Achilles J. Fakiris [a,*], Robert D. Timmerm
Ronald C. McGarry [e], Peter A.S. Johnstone [a]



(18-82)

apical lesions developed grade 2-4 plexopathy.

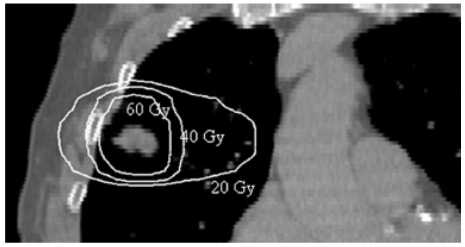
Brachial plexus maximum dose should be kept <26 Gy in 3 (**EqD2: 59.9 Gy)** or 4 (**EqD2: 49.4 Gy**) fractions.

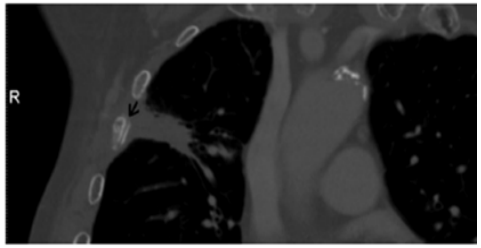
DOSE CONSTRAINTS: LUNGS

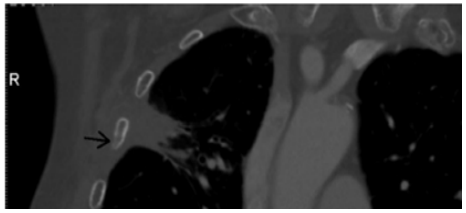
Lungs (α/ß 3 Gy), potential side effects: radiation induced pneumonitis, fibrosis and decrease in lung function, atelectasis, pneumonia (s. bronchus) and abscess				
Reference	*Number of reported patients (treated tumours)*	*Number of centres*	*Pro (p)-/ retro(r)-spective*	*Results (max. point dose or dose/fractionation and EqD2 in Gy provided if possible)*
Borst (73)	128*	1	r	No difference between SBRT and CFRT for the relationship between the lung dose and the incidence of radiation induced pneumonitis
Stanic / RTOG0236 (74)	55	43	p	No clinically significant changes in pulmonary function following SBRT for early- stage peripheral NSCLC
Unger (64)	17	1	r	1 x G III radiation pneumonitis (**EqD2 not applicable**)
Recommendations/NT constraints				
RTOG 0813 (56)		V12.5 >1500cc and V 13.5 Gy < 1000cc, **EqD2 not applicable**		
EORTC 22113-08113		no restrictions, but recording of DVH data for toxicity		

Adebahr et al , BJR 2015, in press

DOSE CONSTRAINTS: **CHEST WALL**







Taremi et al , Radiat Oncol. 2012

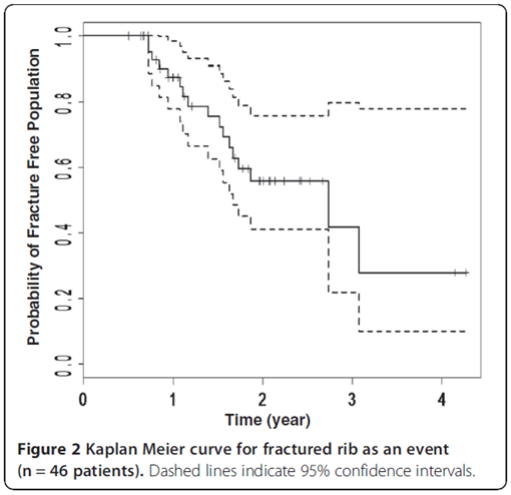


Figure 2 Kaplan Meier curve for fractured rib as an event (n = 46 patients). Dashed lines indicate 95% confidence intervals.

Chest wall (α/ß 3 Gy), potential side effects: Chest wall pain and rib fractures				
Reference	*Number of reported patients (treated tumours)*	*Number of centres*	*Pro (p)-/ retro(r)-spective*	*Results (max. point dose or dose/fractionation and EqD2 in Gy provided if possible)*
Taremi (75)	46 (49*)	1	r	Description of risk factors for radiation induced bone injury after SBRT: increasing age, female gender and high RT dose to 0.5 cc of nearby ribs
Recommendations/NT constraints				
Timmerman (66)		maximum point dose:		30 Gy (1 fraction regime – EqD2: 198Gy) 43 Gy (5 fraction regime – EqD2: 99.8Gy)
RTOG 0813 (56)		maximum point dose:		32Gy (5 fractions regime- EqD2: 60.2 Gy) 82Gy (10 fractions regime- EqD2: 183Gy)
EORTC 22113-08113		no restrictions, but recording of DVH data for toxicity		

Adebahr et al , BJR 2015, in press

DOSE CONSTRAINTS: SUMMARY

OAR	αβ in Gy	D_{max} in Gy	EqD2 in Gy	Acceptable variation in Gy	Acceptable variation EqD2 in Gy	Unacceptable variation in Gy	Unaccep- table variation EqD2 in Gy
Trachea/ Main bronchus	3	8*5.5= 44	74.8	<8*5.81=46.68	< 81.9	≥8*5.81=46.68	>81.9
Heart§	3						
Great vessels§	3						
Oesphagus	3	8*5 = 40	64	<8*5.44=43.52	<73.6	≥8*5.44=43.52	≥73.6
Spinal cord&	2	8*4 = 32	48			>8*4=32	>48
Brachial plexus&	3	8*4.75=38	58.9	<8*5.17=41.36	< 67.7	≥8*5.17=41.36	≥67.7
Body-PTV&	3	8*7.5= 60	126	<8*7.785=62.28	<134.2	≥8*7.785=62.28	≥134.2
Lung-CTV§	3						
Chest wall§	3						

& for <0.5 cc

§ no restrictions are provided but recording of DVH data for toxicity evaluation is required

EORTC 22113-0813-LungTech RTQA Guidelines

Adebahr et al , BJR 2015, in press

There is more than dose and fractionation…

Beyond prescribed dose, multiple factors influence local control and toxicity after SBRT:

- Imaging in staging and treatment planning (PET-staging? 4D-imaging for TV-delineation?)

- Treatment planning (NT-compromising? PTV-concept? dose calculation algorithms? allowed min/max doses? prescription point …)

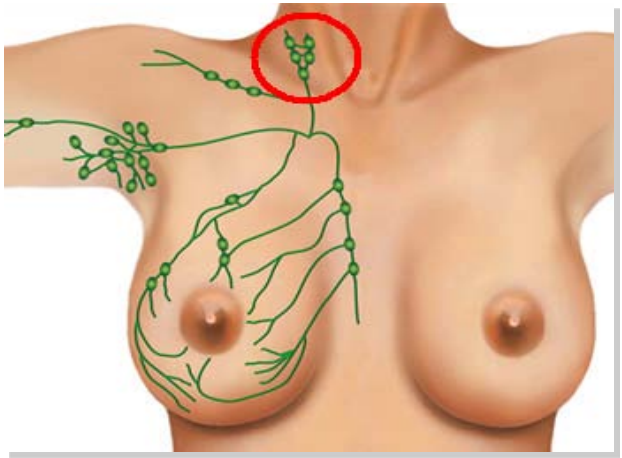
- Immobilisation and image guidance (cbct? 4D-cbct? post treatment scan?

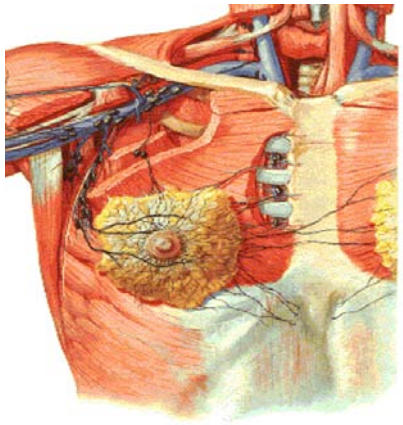
…

ESTRO School

WWW.ESTRO.ORG/SCHOOL

Planning aspects in breast irradiation





Desirée van den Bongard
Radiation Oncologist, MD PhD
UMC Utrecht, the Netherlands

ESTRO School

Planning aspects in breast RT

- Breast cancer treatment and toxicity
- Hypofractionation
- Accelerated partial breast irradiation
- Cardiac sparing – Breath hold technique
- Optimization of breast RT planning techniques

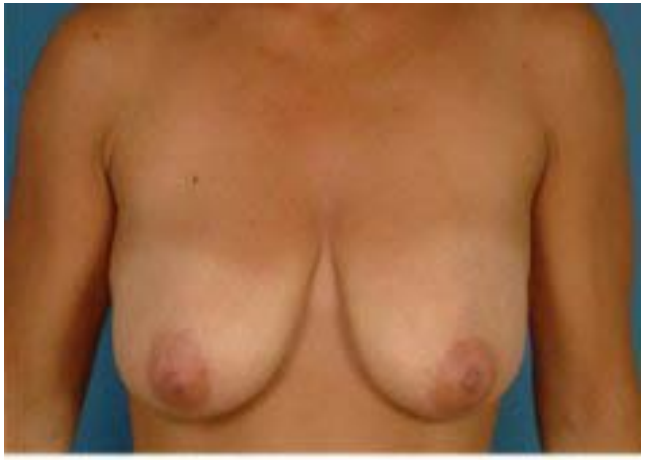
Breast cancer treatment

Local treatment:

- Breast-conserving therapy:

  Breast-conserving surgery →

  Whole breast irradiation +/- boost tumor bed



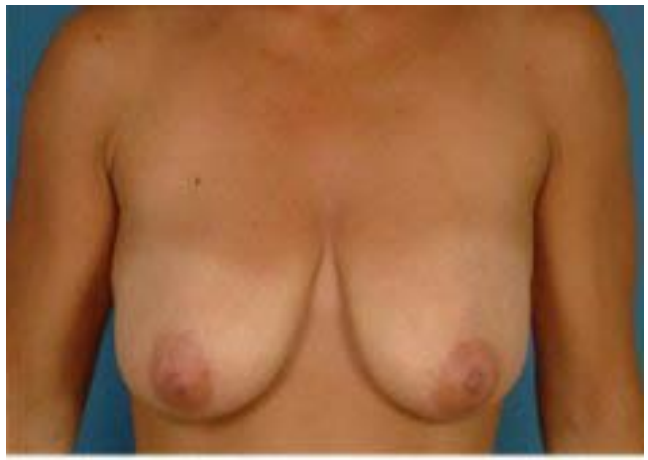
Breast cancer treatment

Local treatment:

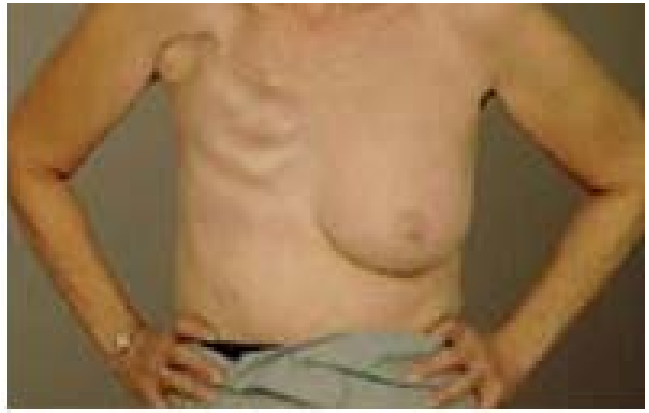
- Breast-conserving therapy:

  Breast-conserving surgery →

  Whole breast irradiation +/- boost tumor bed



- Mastectomy +/- Radiotherapy Chest wall



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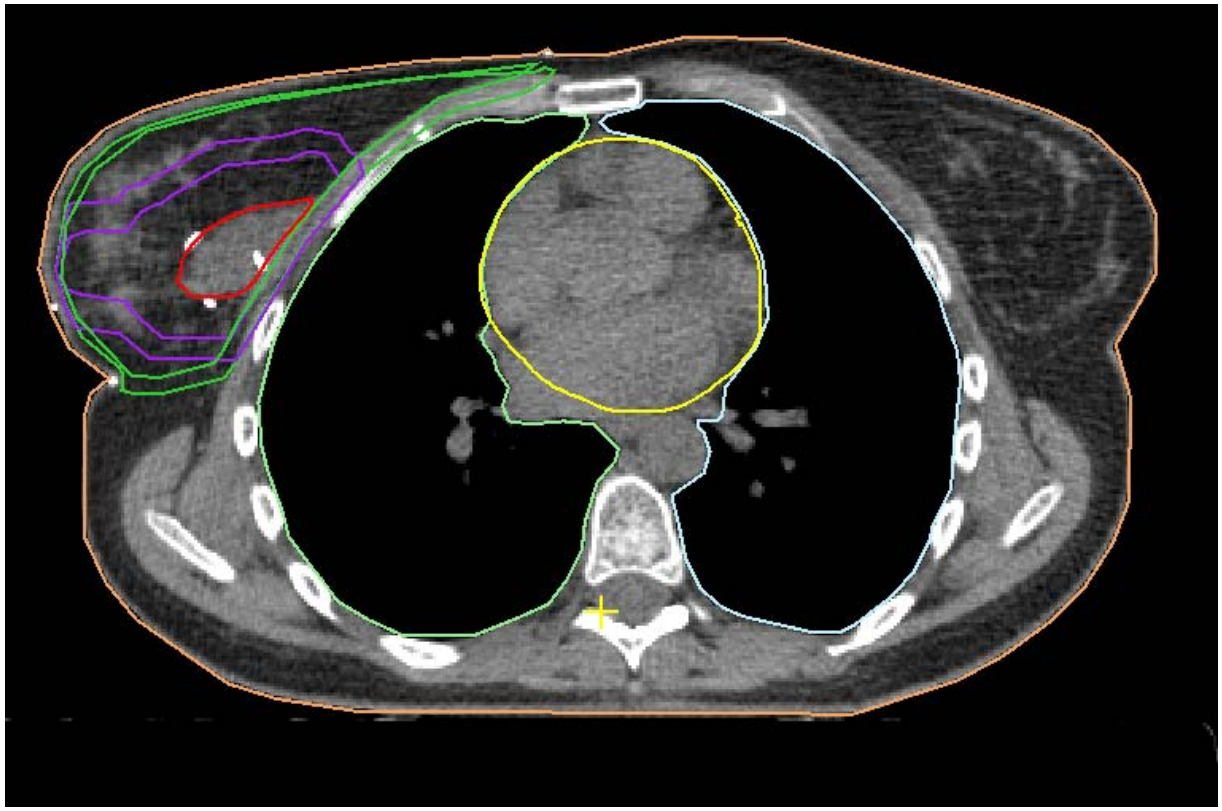
Breast cancer treatment

- **Local treatment:**

  Breast-conserving therapy:

  Breast-conserving surgery →

  Whole breast irradiation +/- boost tumor bed



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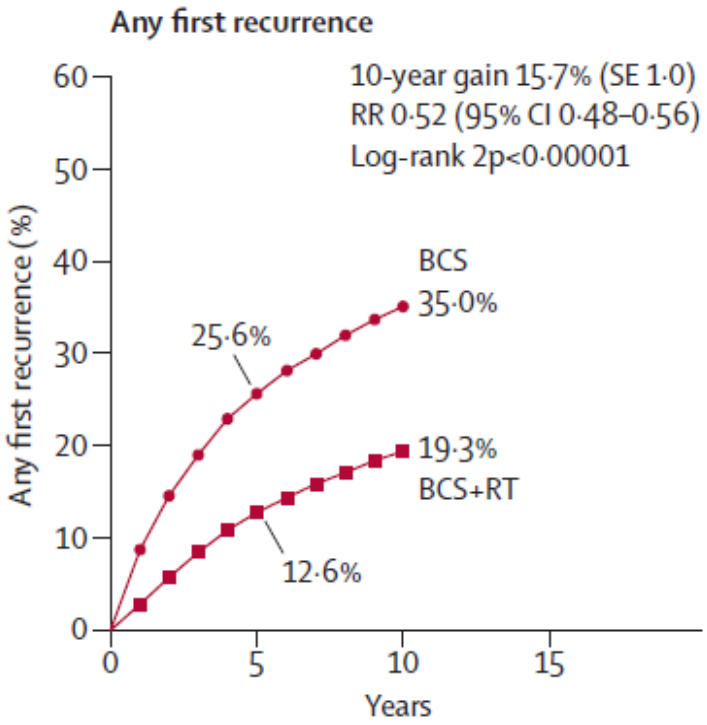
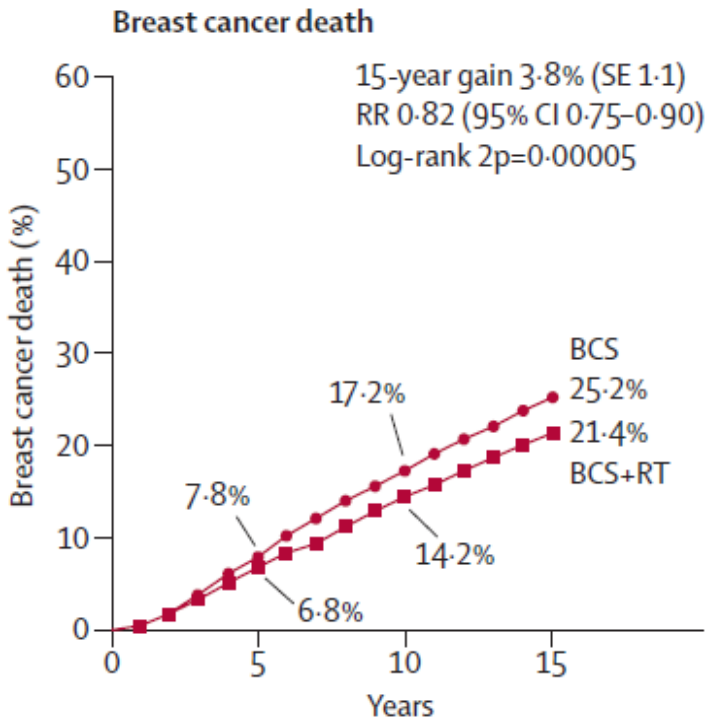
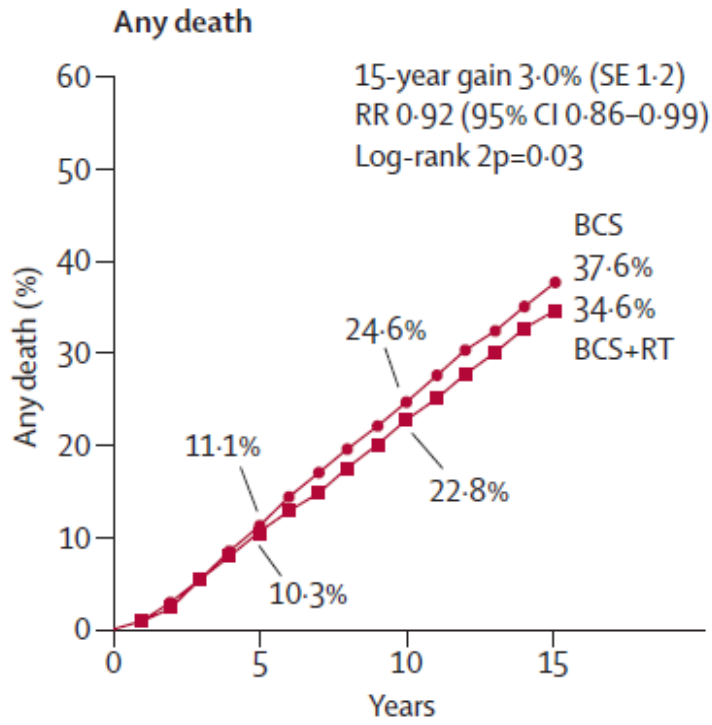
Breast-conserving surgery +/- whole breast RT







EBCTCG Lancet 2011

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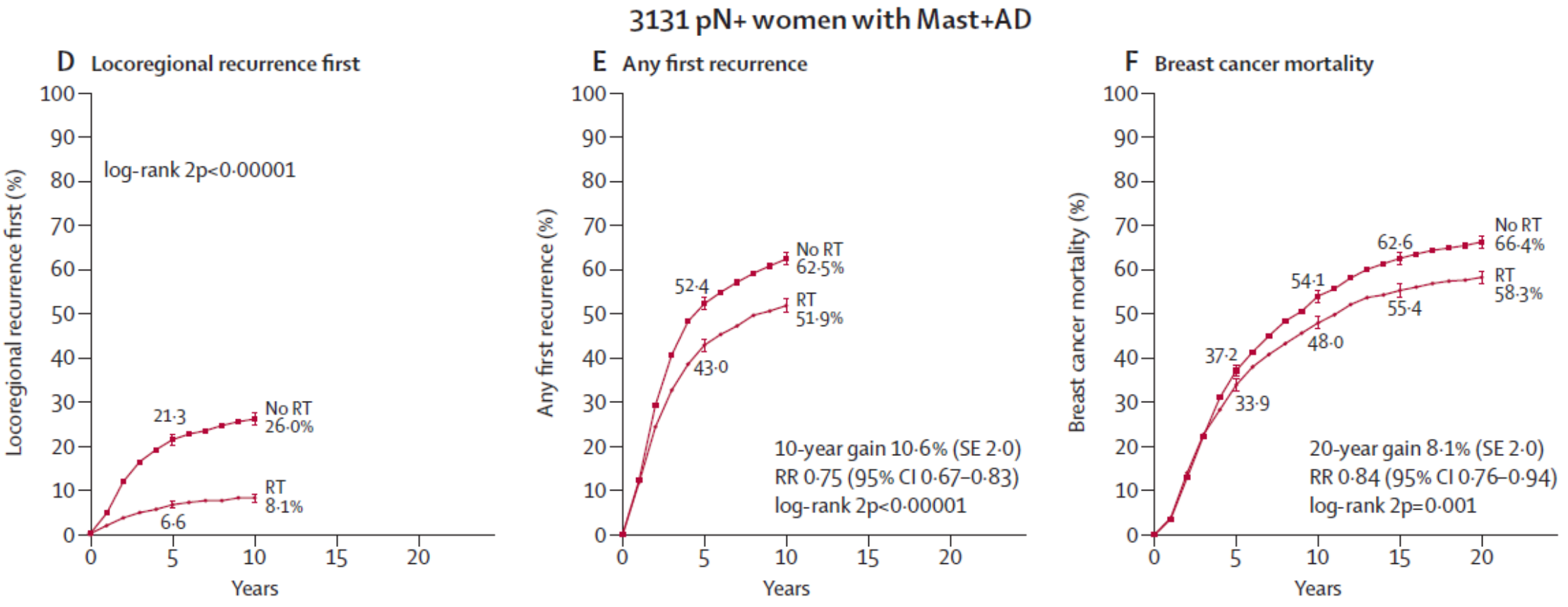
RT after mastectomy and axillary lymph node dissection



EBCTCG Lancet 2014

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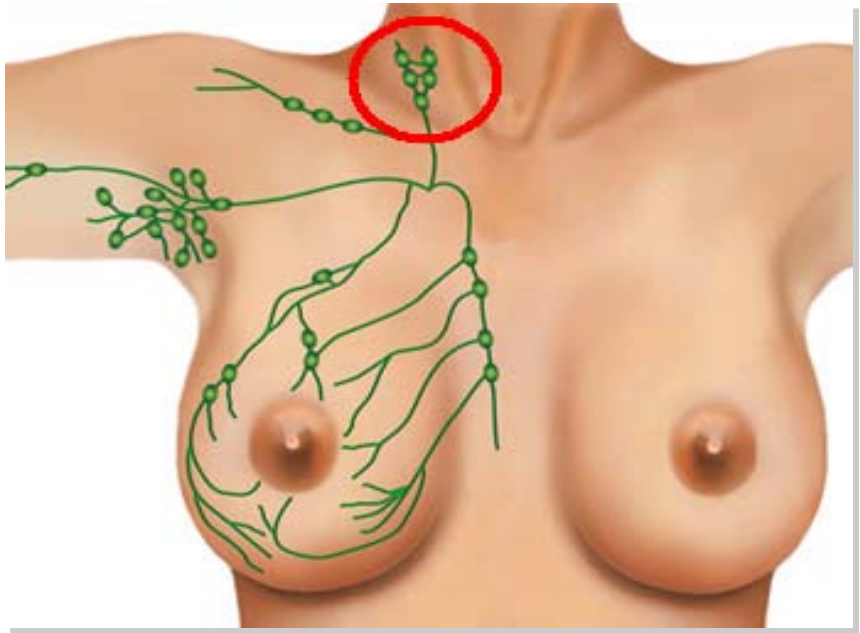
Breast cancer treatment

- **Local treatment:**
  - Breast-conserving therapy
  - Mastectomy +/- Radiotherapy chest wall

- **Regional lymph node treatment:**
  - Axillary lymph node dissection
  - Lymph node irradiation:
    - axilla
    - periclavicular region
    - internal mammary nodes



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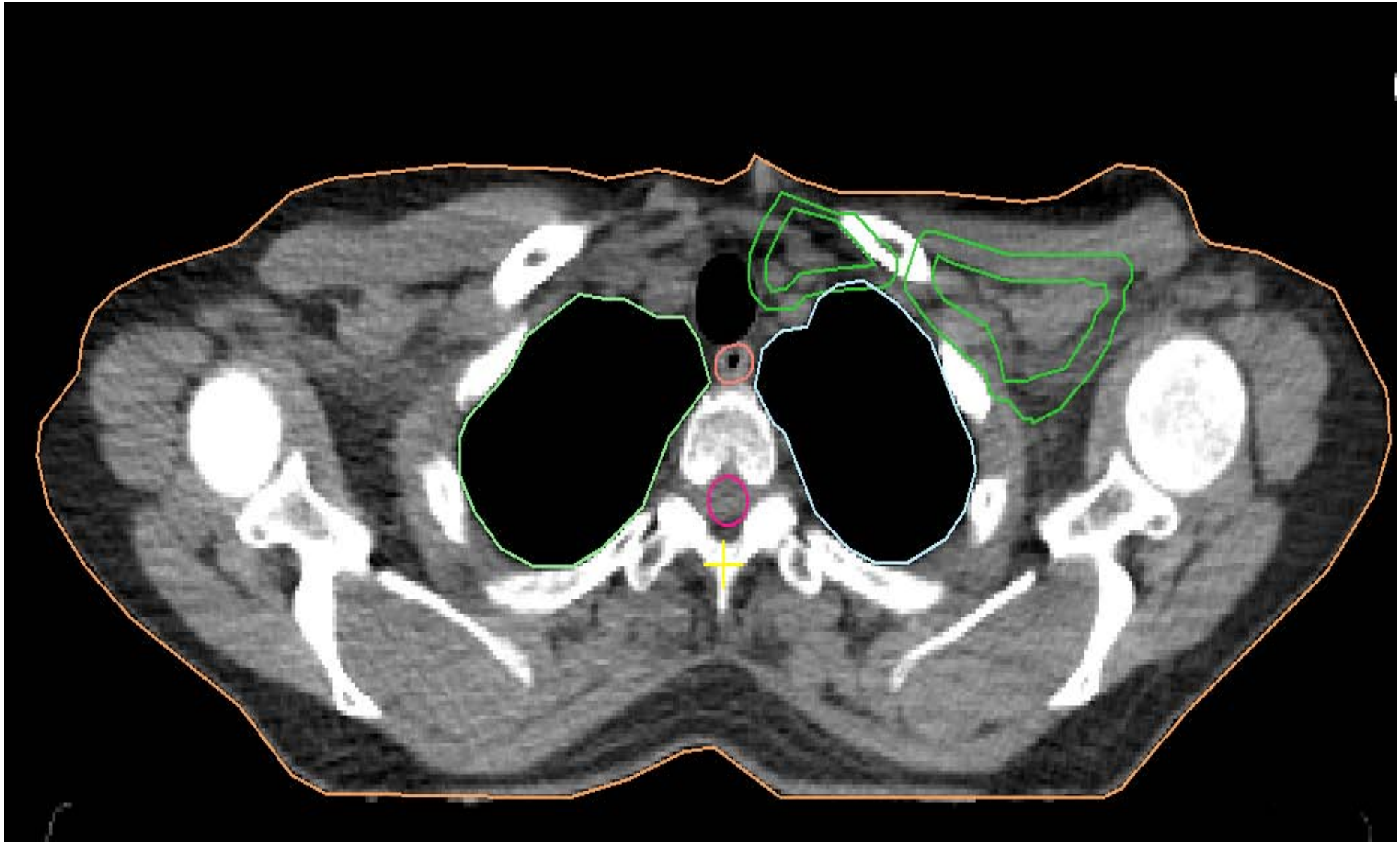
Regional lymph node irradiation – delineation on planning CT



Survival and Toxicity – Breast cancer

During the last decades **survival** has increased due to:

- breast cancer screening
- improved imaging
- improved surgical and radiotherapeutic techniques
- increased use of and more effective systemic treatment

Treatment-induced **toxicity** can cause:

- non-breast cancer mortality
- decreased quality of life

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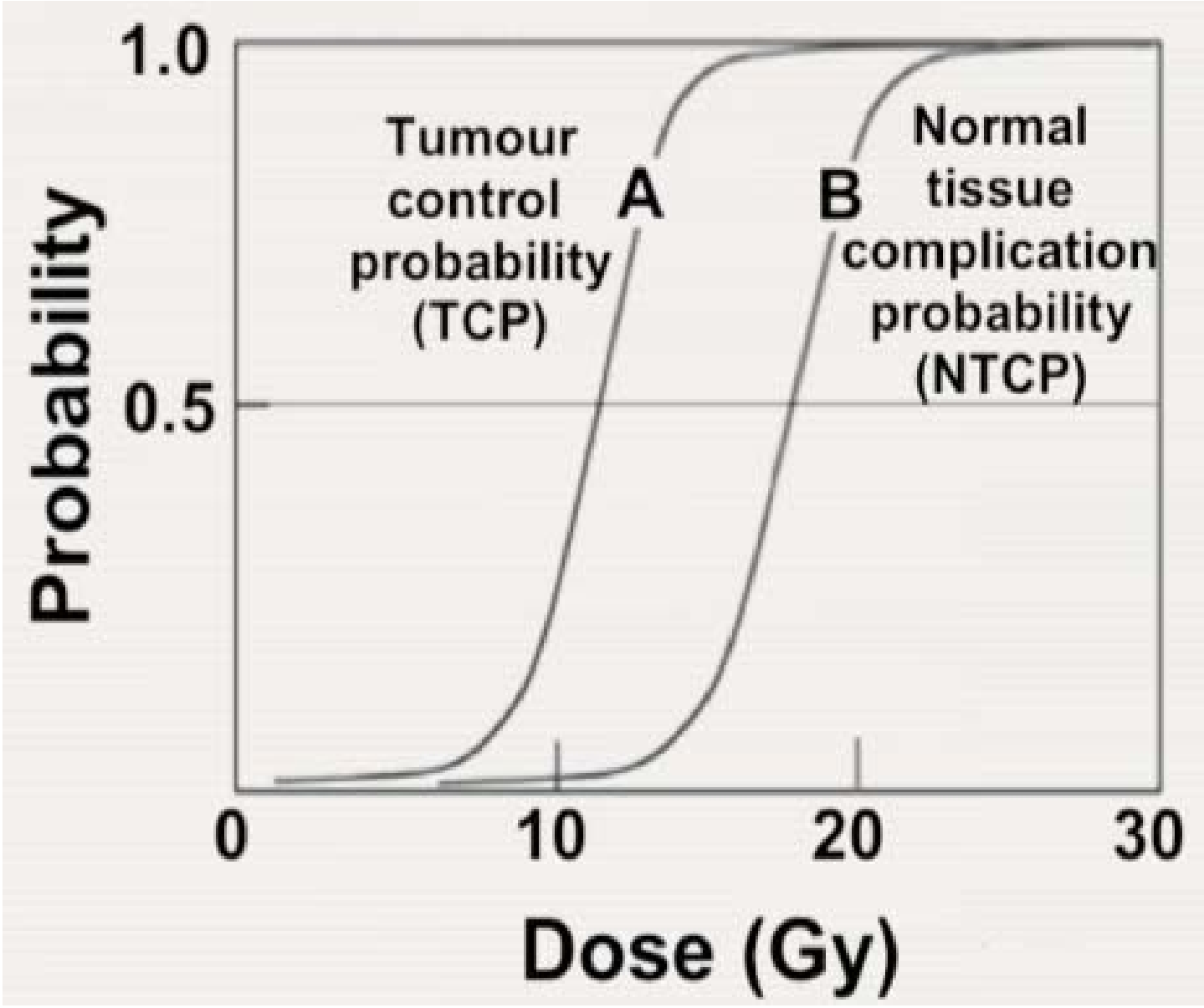
Therapeutic window: principle of radiotherapy



To maximize Tumor control **and** minimize toxicity

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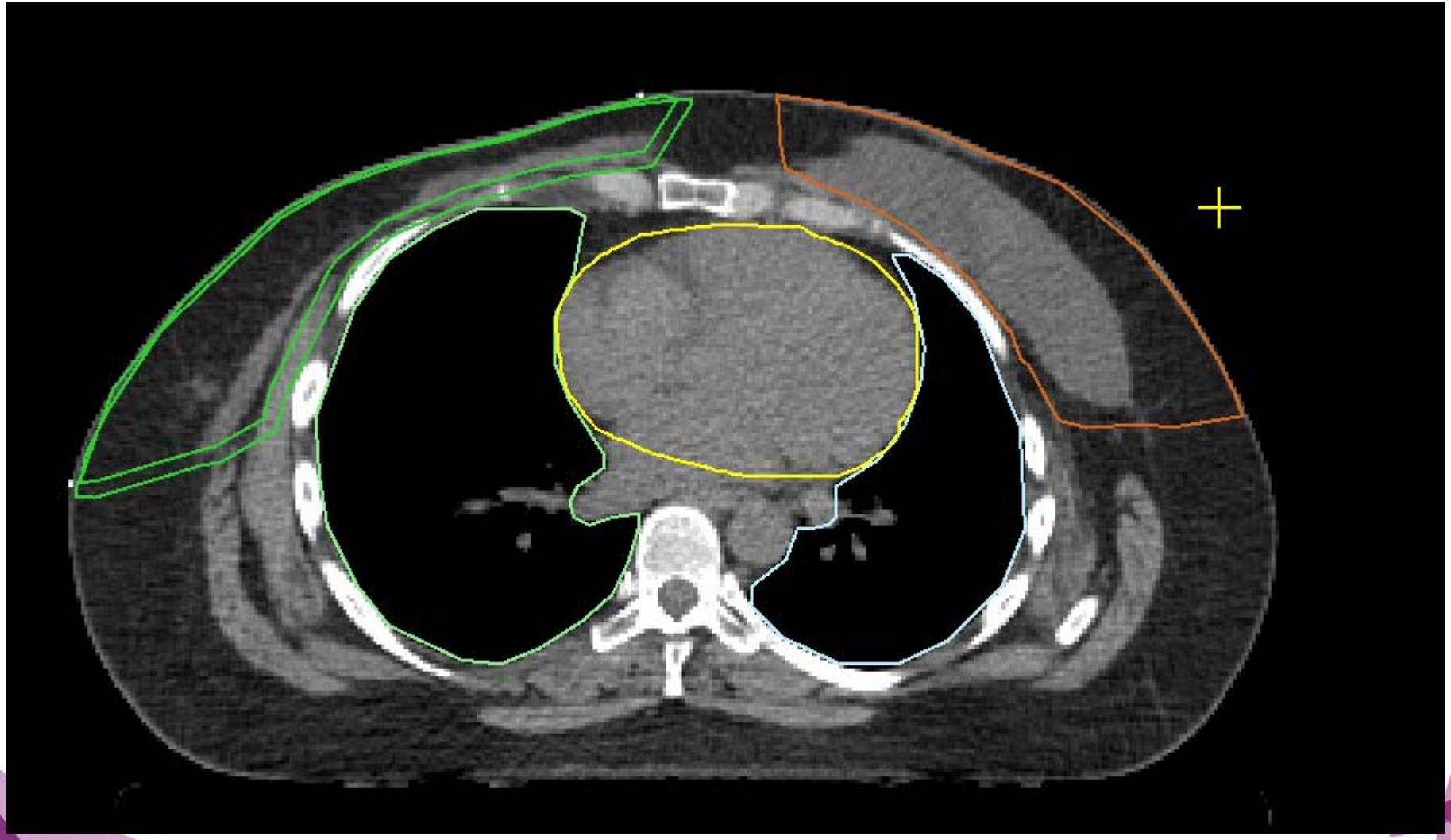
Radiotherapy-induced toxicity

Local radiotherapy (Breast/Chest wall)

- Organs at risk: skin, lung, heart, contralateral breast



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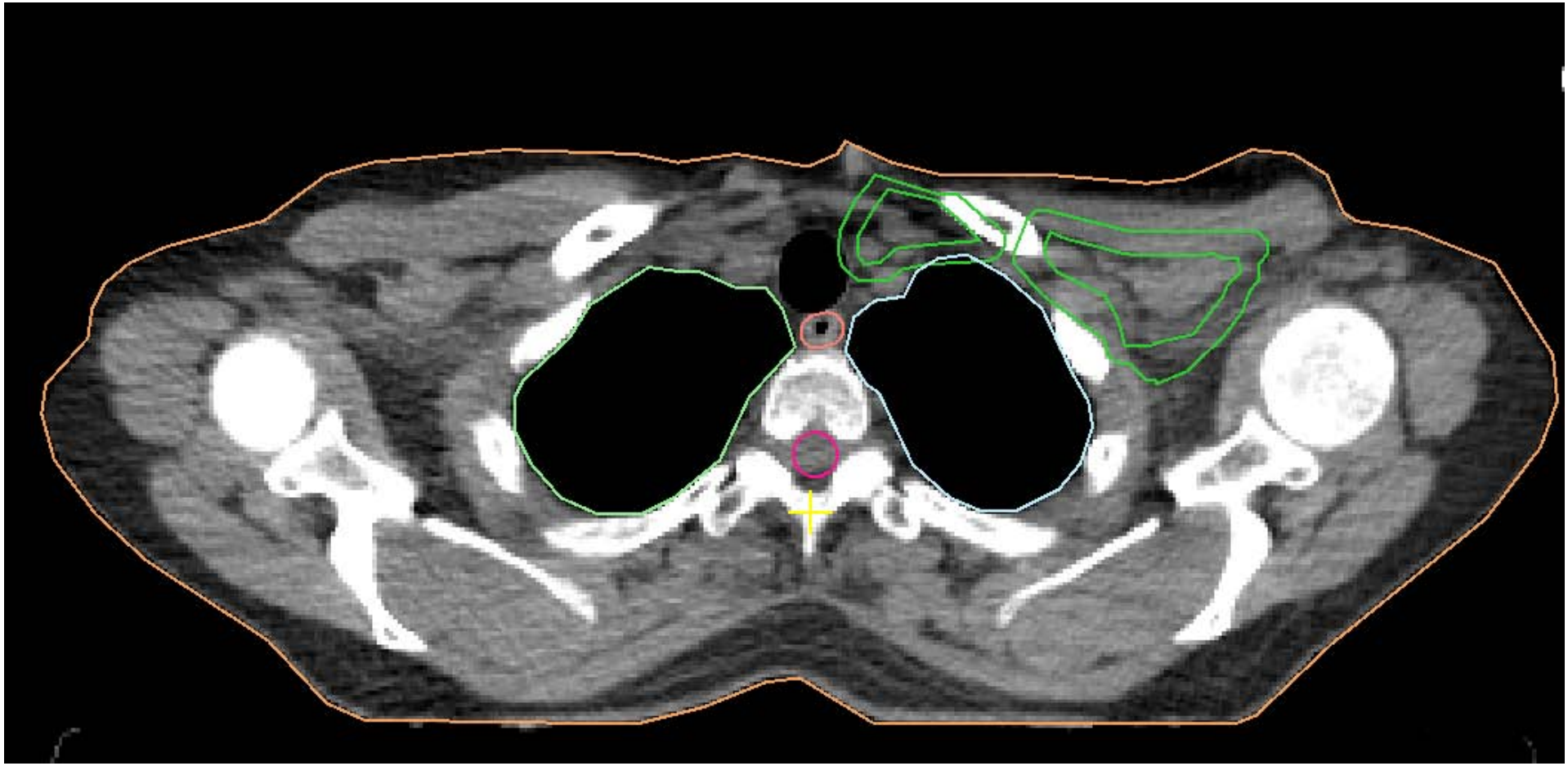
Radiotherapy-induced toxicity
Regional radiotherapy

- Organs at risk: lung, spinal cord, esophagus, trachea



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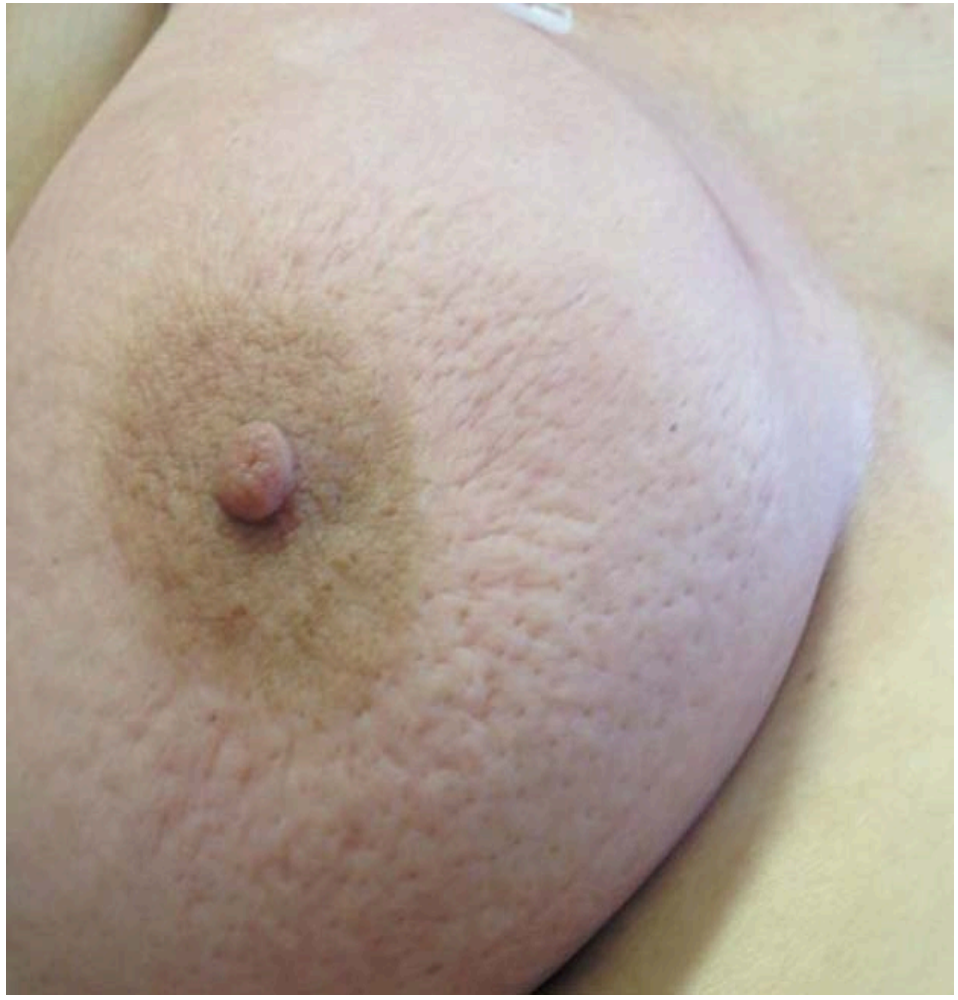
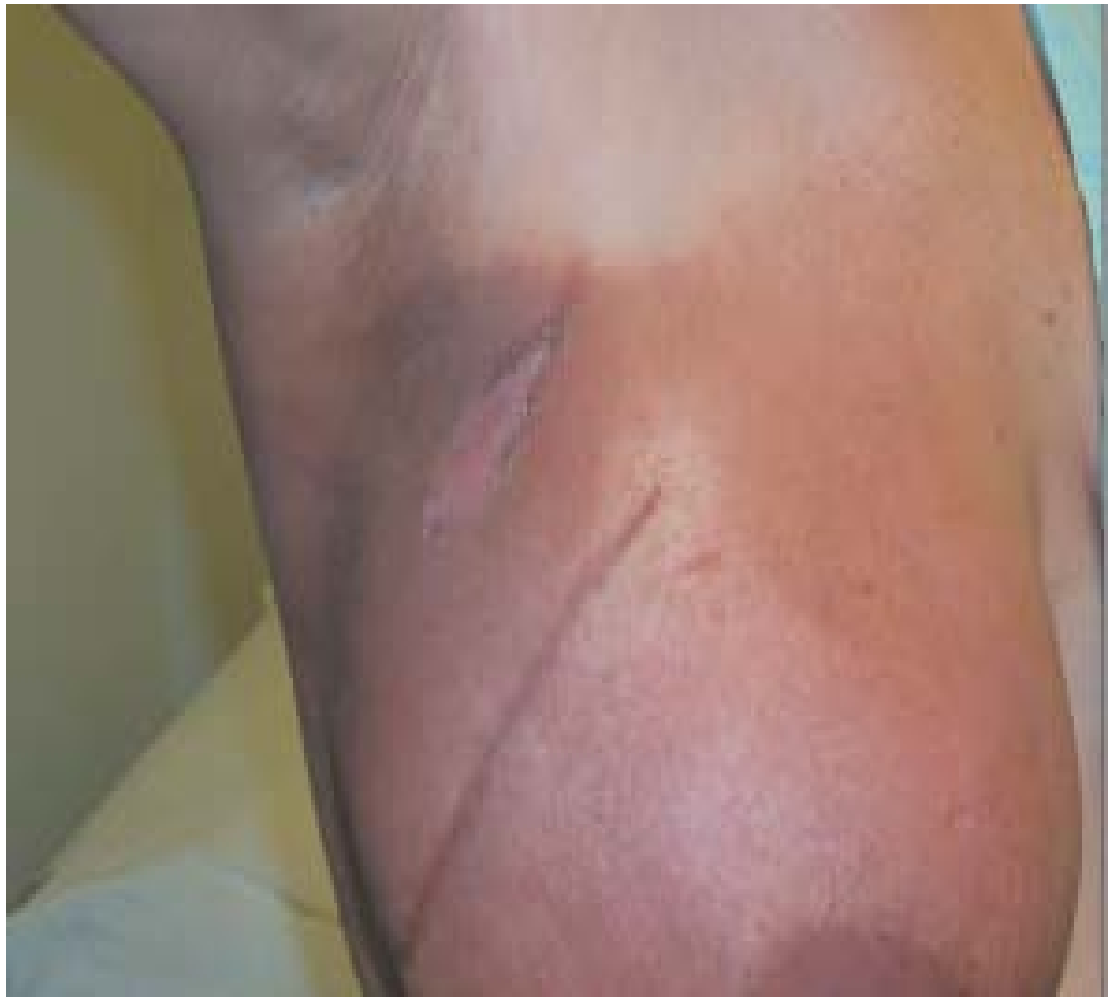
Acute toxicity skin - Radiation dermatitis





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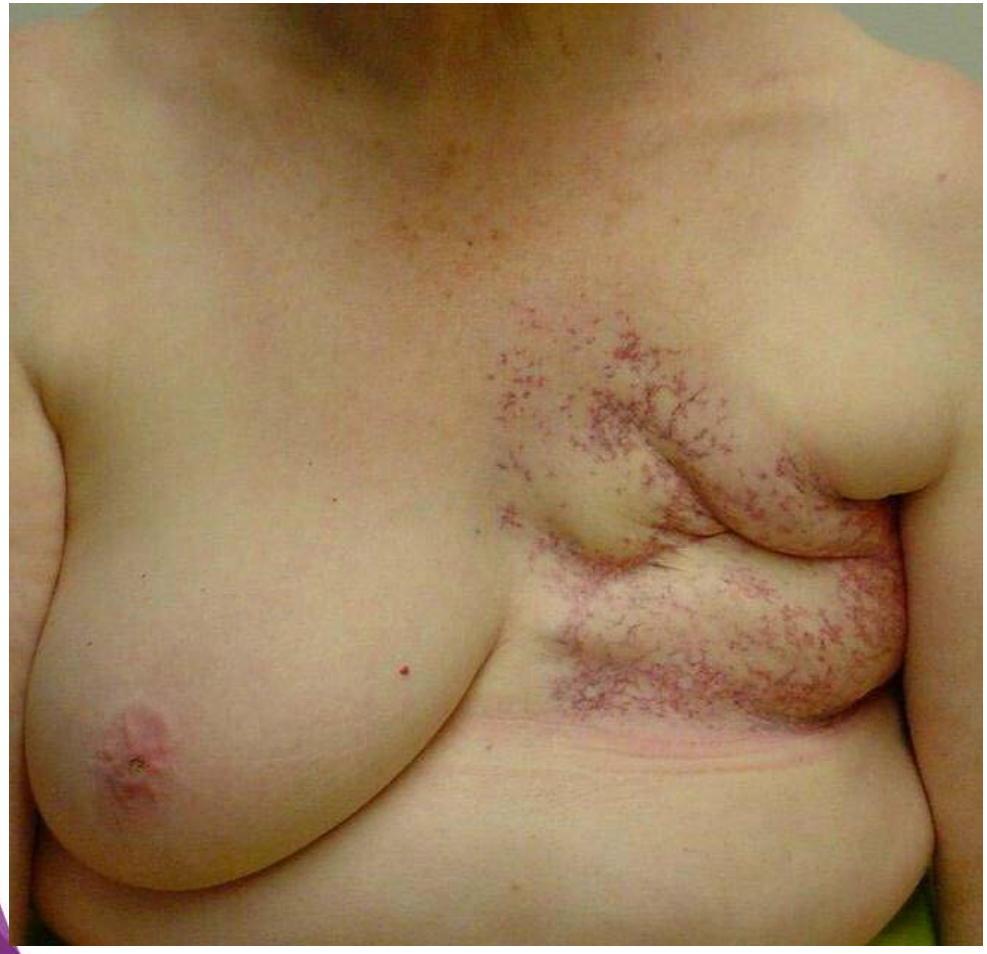
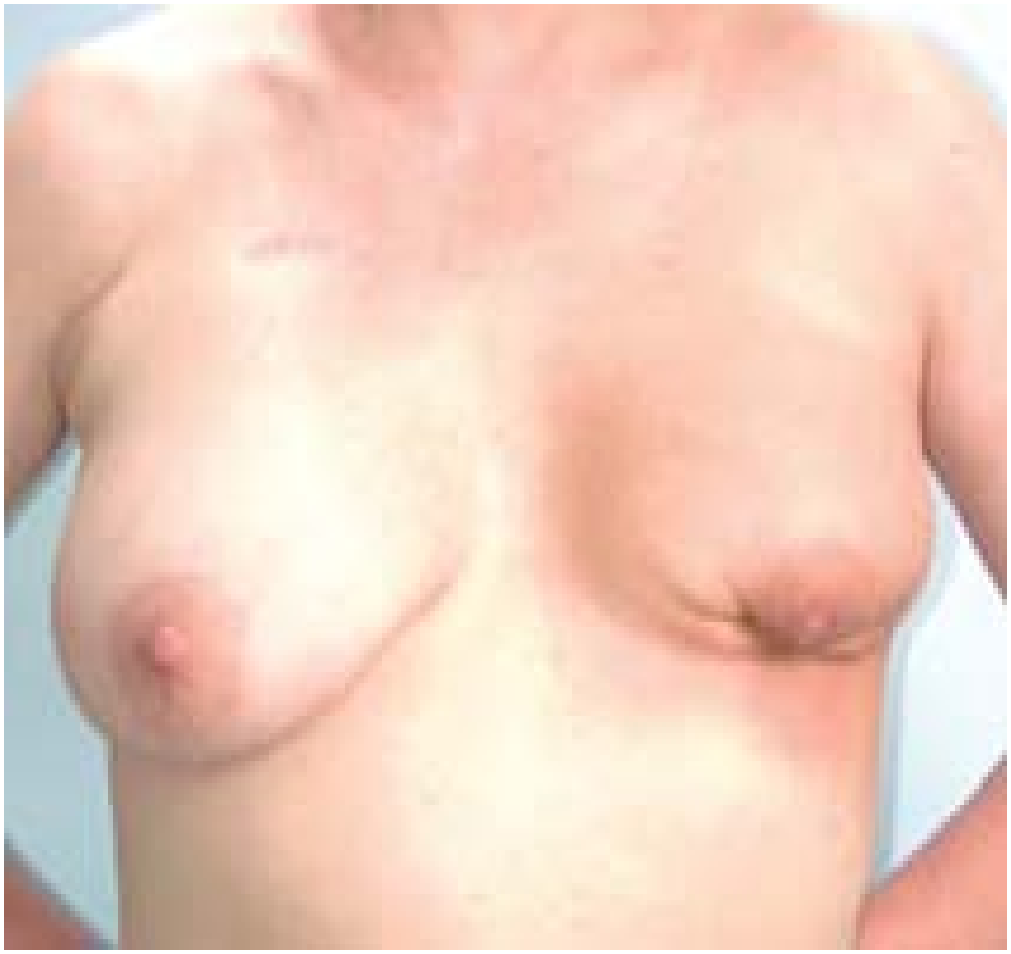
Late skin / breast toxicity

Telangiectasia



Breast fibrosis:



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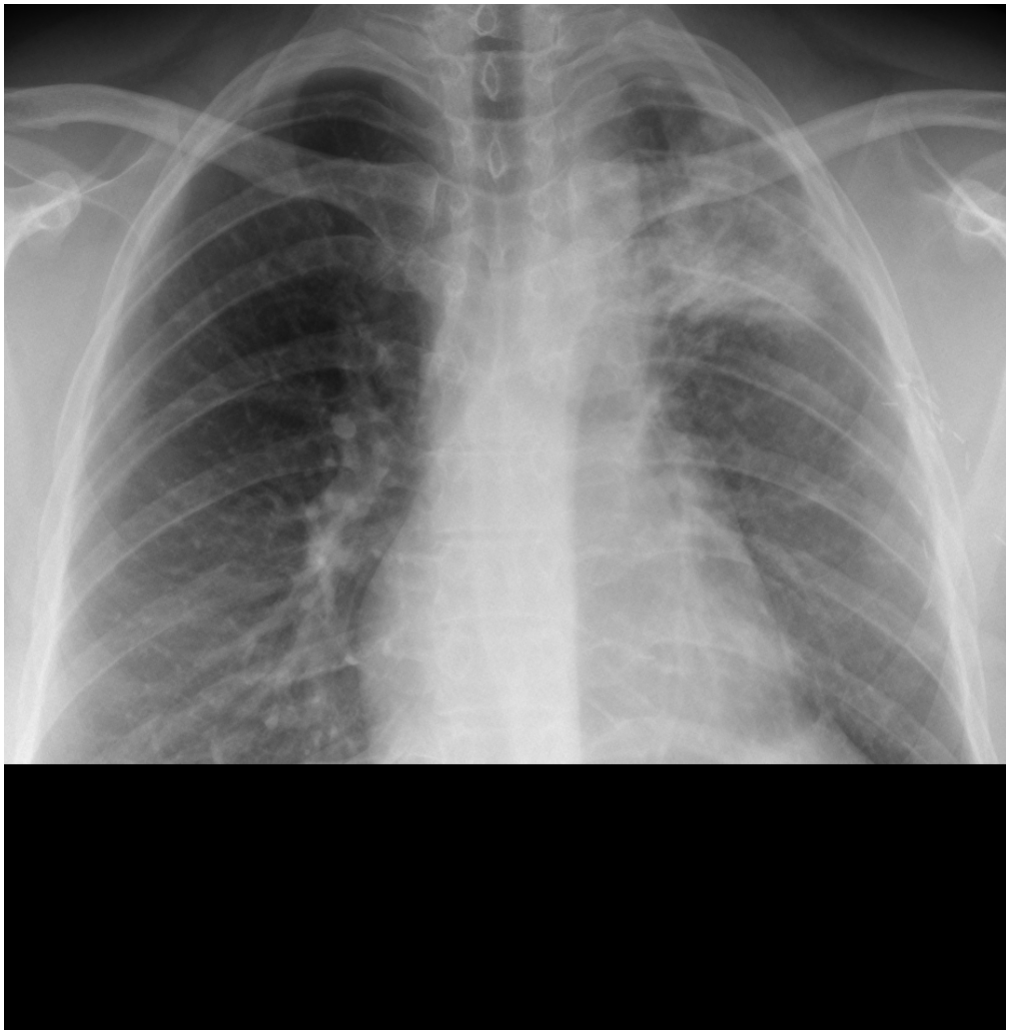
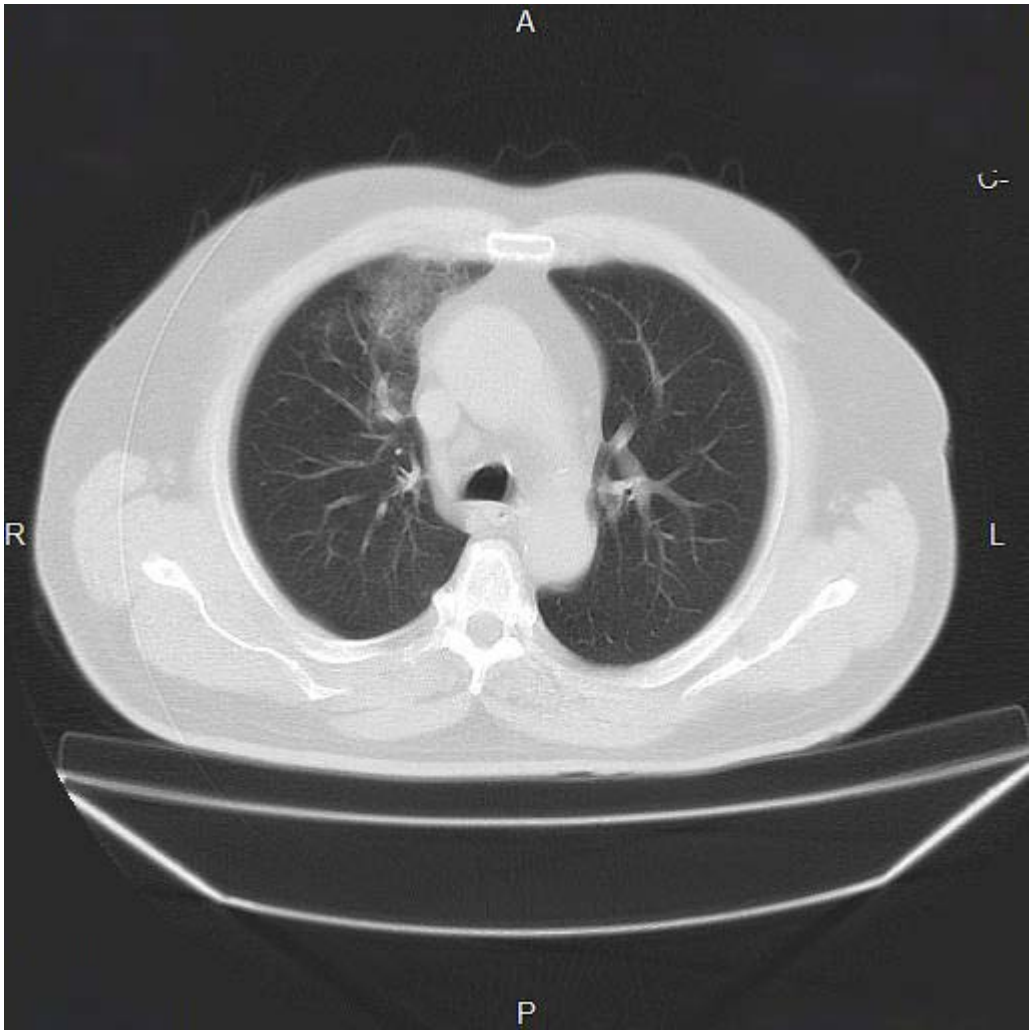
Lung - Radiation pneumonitis (subacute toxicity)





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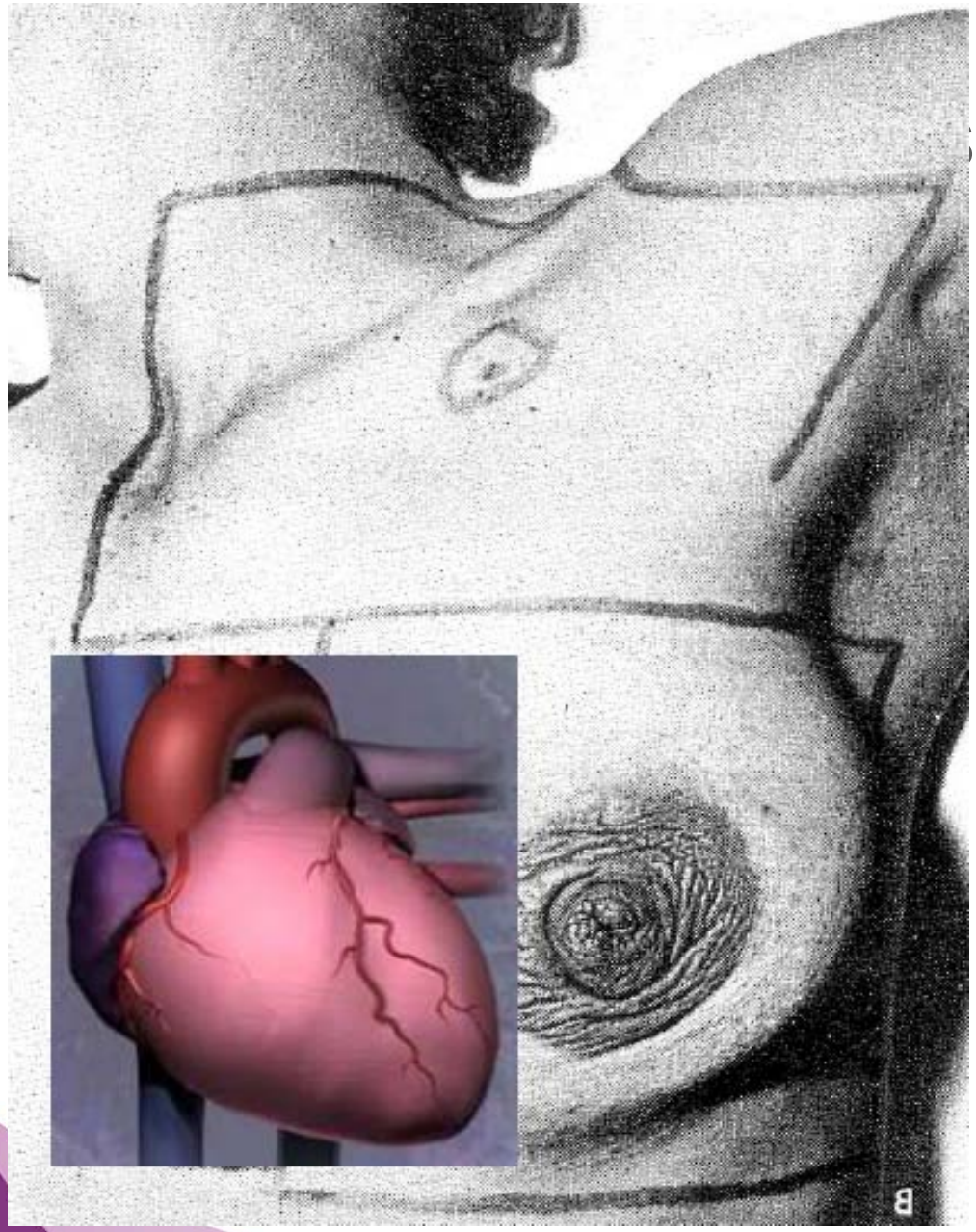
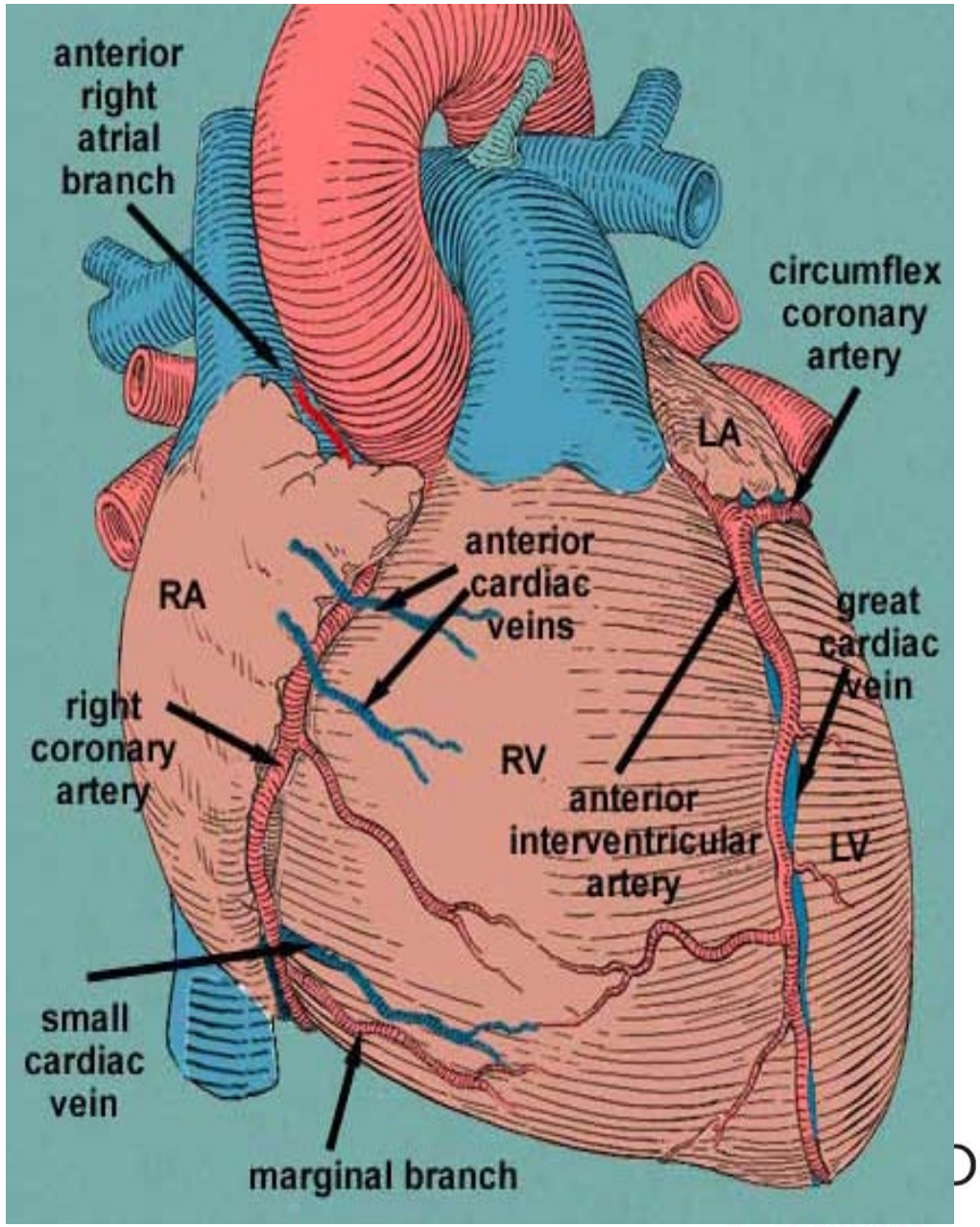
Heart - Left-sided breast radiotherapy

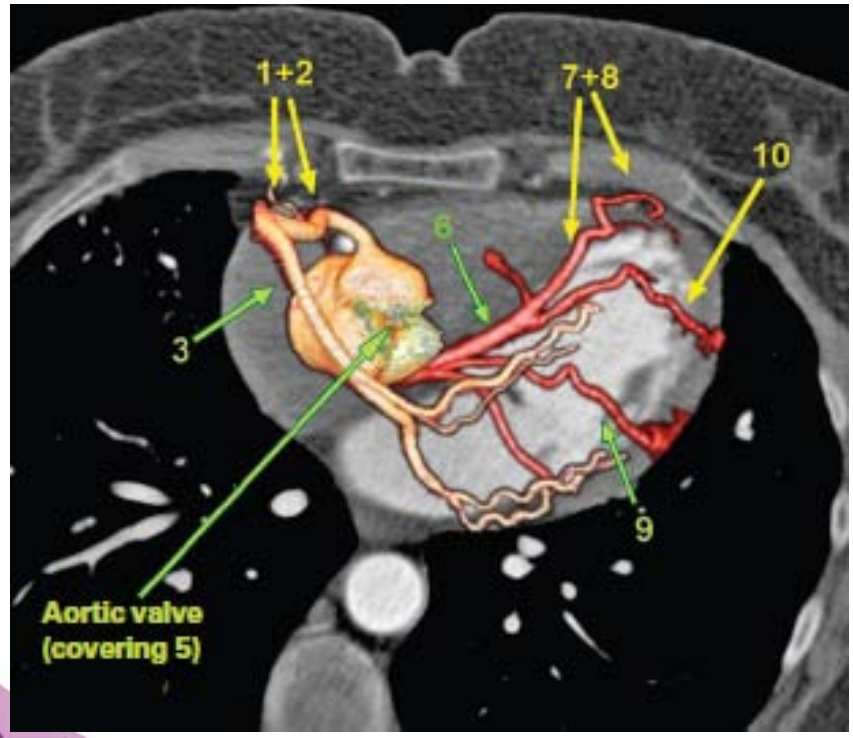


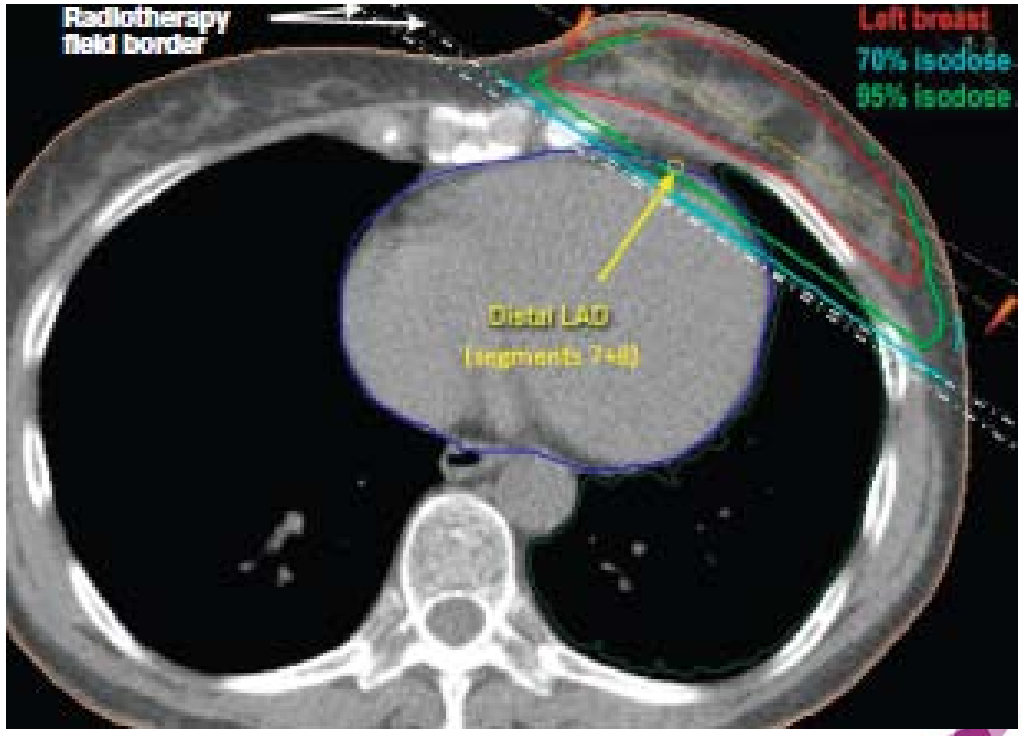


Radiation-induced heart disease

Late toxicity: up to 20 years after RT

- Coronary artery disease (most common)
- Cardiac valve dysfunction
- Myocardial fibrosis, conduction defects





Nilsson JCO 2012, Senkus-Konefka Cancer Treatment Rev 2007, Adams Crit Rev Oncol/Hematol 2003

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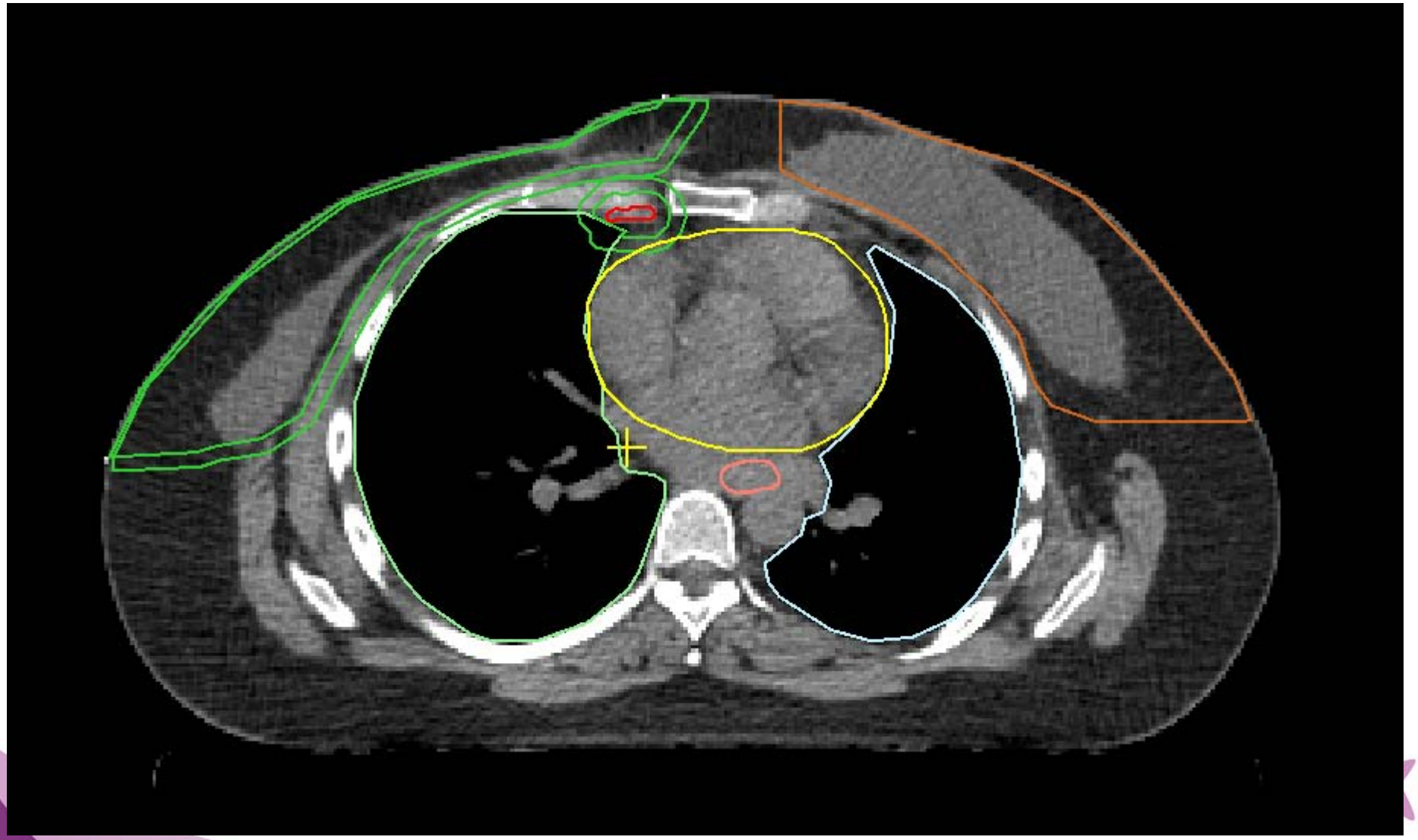
Radiation-induced heart disease
Regional radiotherapy

Internal mammary nodes – RT dose heart



Cardiac toxicity and mortality due to RT

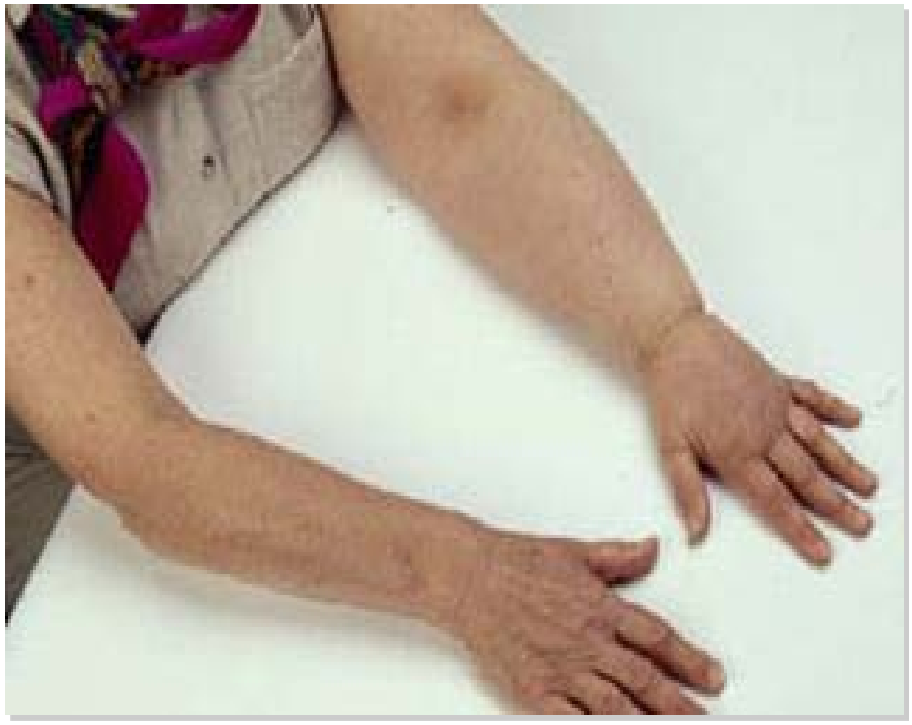
- No threshold dose for cardiac morbidity and mortality

- 7% increased risk on cardiac toxicity per 1 Gy increase in mean heart dose
  →**ALARA (As Low As Reasonably Achievable)!**

- Cardiac risks can differ due to pre-existing cardiac risks:
  - pre-existing cardiac disease
  - lifestyle (smoking, obesity)
  - comorbidity (diabetes, hypertension, hypercholesterolaemia)
  - older age
  - family history of cardiac disease

Darby NEJM 2013, Taylor Clinical Oncol 2015, Barlett Clin Oncol 2013

Arm oedema -
After axillary surgery and/or regional radiotherapy



Regional radiotherapy instead of axillary surgery

AMAROS trial (EORTC): Radiotherapy or Surgery of the axilla
Donkers et al. Lancet Oncol 2015

- 4,806 BC patients (cN0) → sentinel node procedure

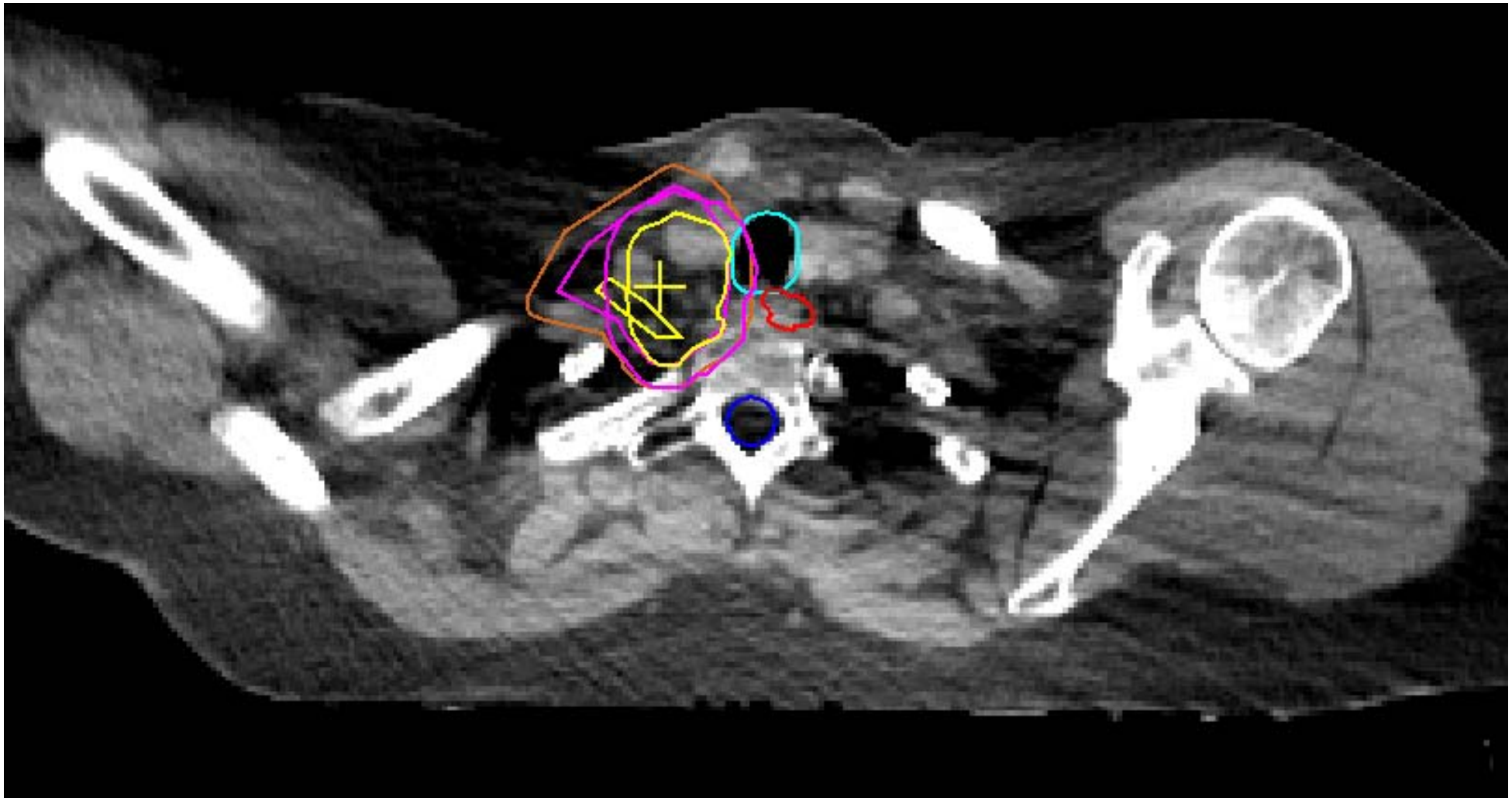
- Tumorpositive sentinel node(s):
  Axillary RT (n=681) *vs.* Axillary surgery (n=744)

Median follow-up 6.1 years:
Regional recurrence rate at 5 years: 0.54% ALND vs. 1.03% ART (NS)
Toxicity i.e. arm oedema at 5 years: 23% ALND vs. 11% ART

→ Clinical practice: Increased use of regional RT

Donker Lancet Oncol 2014

Brachial plexus
Regional radiotherapy boost



- Plexopathy: paresthesias, decreased muscular strength, paralysis

Radiation-induced secondary cancer after breast radiotherapy

- Most second cancers after radiotherapy are attributed to other factors, e.g. lifestyle and genetics

  Berrington de Gonzales Lancet Oncol 2011

- Contralateral breast cancer:

  In patients < 40 years: if mean dose > 1 Gy (dose-dependent)

  Stovall IJROBP 2008

- Induction of non-breast cancer, e.g. lung, esophagus

  Grantzau RO 2015

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Planning aspects in breast RT

- Introduction in breast RT
- **Hypofractionation**
- Accelerated partial breast RT
- Cardiac sparing – Breath hold technique
- Optimization of breast RT planning techniques

Hypofractionation – breast Radiotherapy

- Adjusted α/β 4.6

  Breast cancer is more sensitive to fraction size:

  No advantage in using $\leq$ 2 Gy fractions

- 4 phase III studies whole breast irradiation:

  Standard fractionation (25 x 2 Gy) **vs.** Hypofractionation

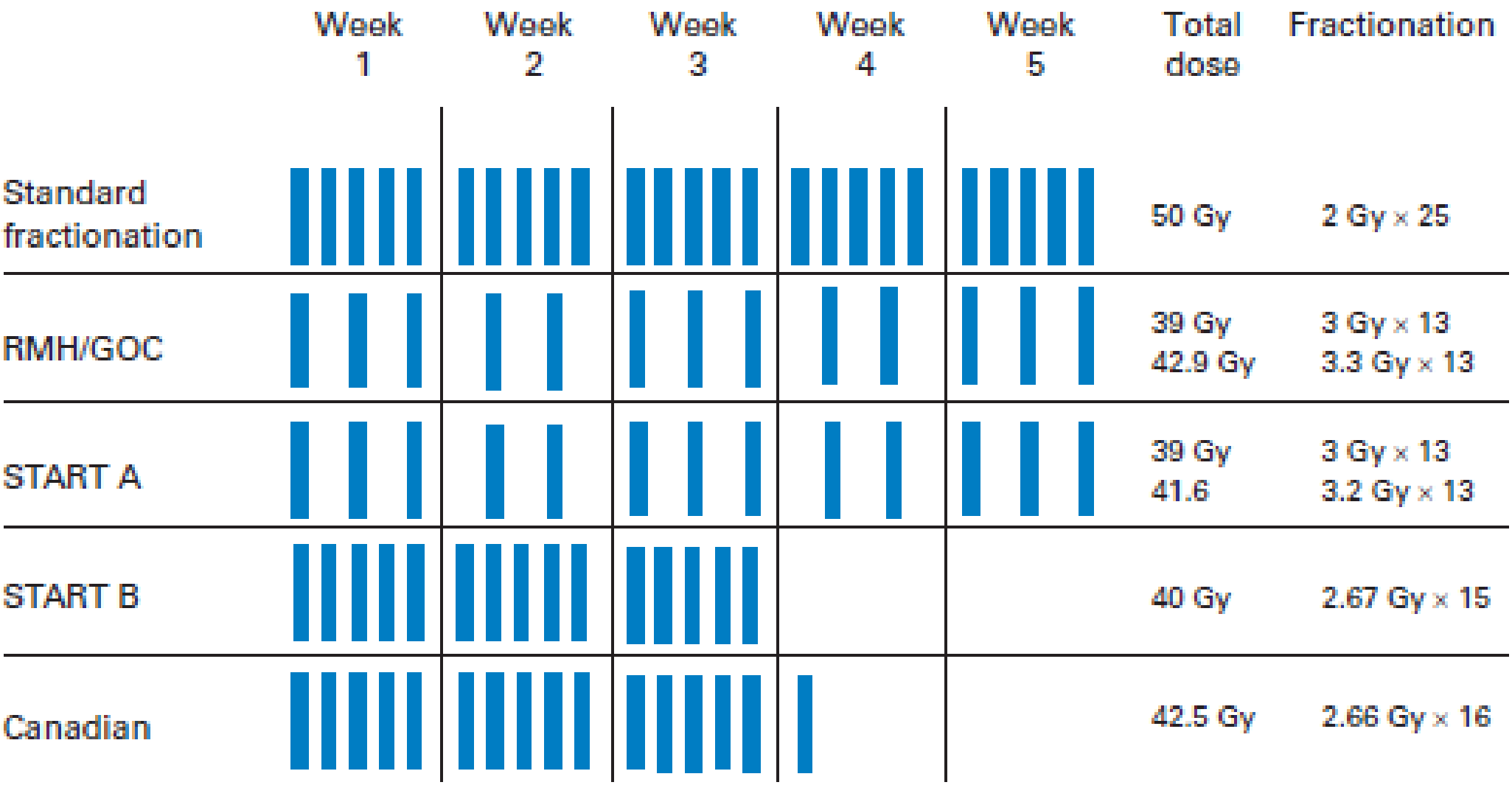
  Canada: 16x 2.66 Gy

  UK: 15x 2.67 Gy / 13x 3 / 13x 3.2 / 13x 3.3 Gy

- n = 7,000 patients; median follow-up 10 years

Haviland Lancet Oncol 2013, Yarnold RO 2005, Whelan NEJM 2010, START B Lancet 2008, START A Lancet Oncol 2008, Owen Lancet Oncol 2006

Hypofractionation – whole breast irradiation



Fisher JCO 2014, Haviland Lancet Oncol 2013, Yarnold RO 2005, Whelan NEJM 2010, START B Lancet 2008, START A Lancet Oncol 2008, Owen Lancet Oncol 2006

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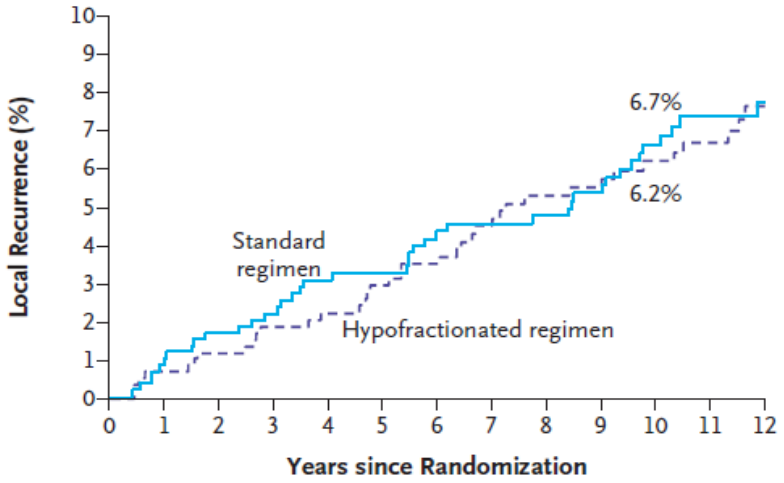
Canadian study

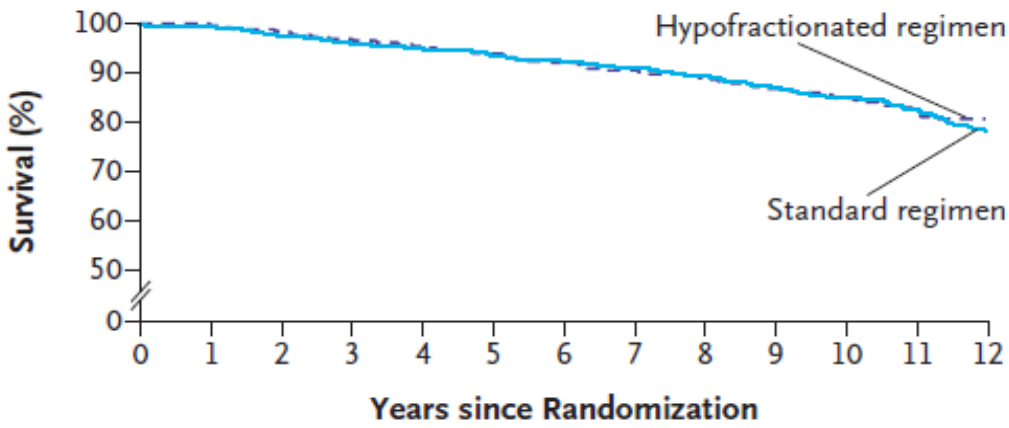
Local recurrence



No. at Risk

Standard regimen	612	597	578	562	550	553	499	485	470	449	410	317	218
Hypofractionated regimen	622	609	592	569	548	524	500	472	447	430	406	330	214

Overall survival



No. at Risk

Standard regimen	612	606	594	583	573	559	535	519	505	487	453	355	242
Hypofractionated regimen	622	617	605	592	576	562	539	517	495	482	455	369	241

Whelan et al. NEJM 2010

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Toxicity – hypofractionated and conventional scheme

- No significant difference in toxicity

  lung, cardiac, rib fractures, shoulder movement

- 40 Gy-arm: Less common normal tissue effects (START B trial)

  breast oedema, breast shrinkage, telangiectasia

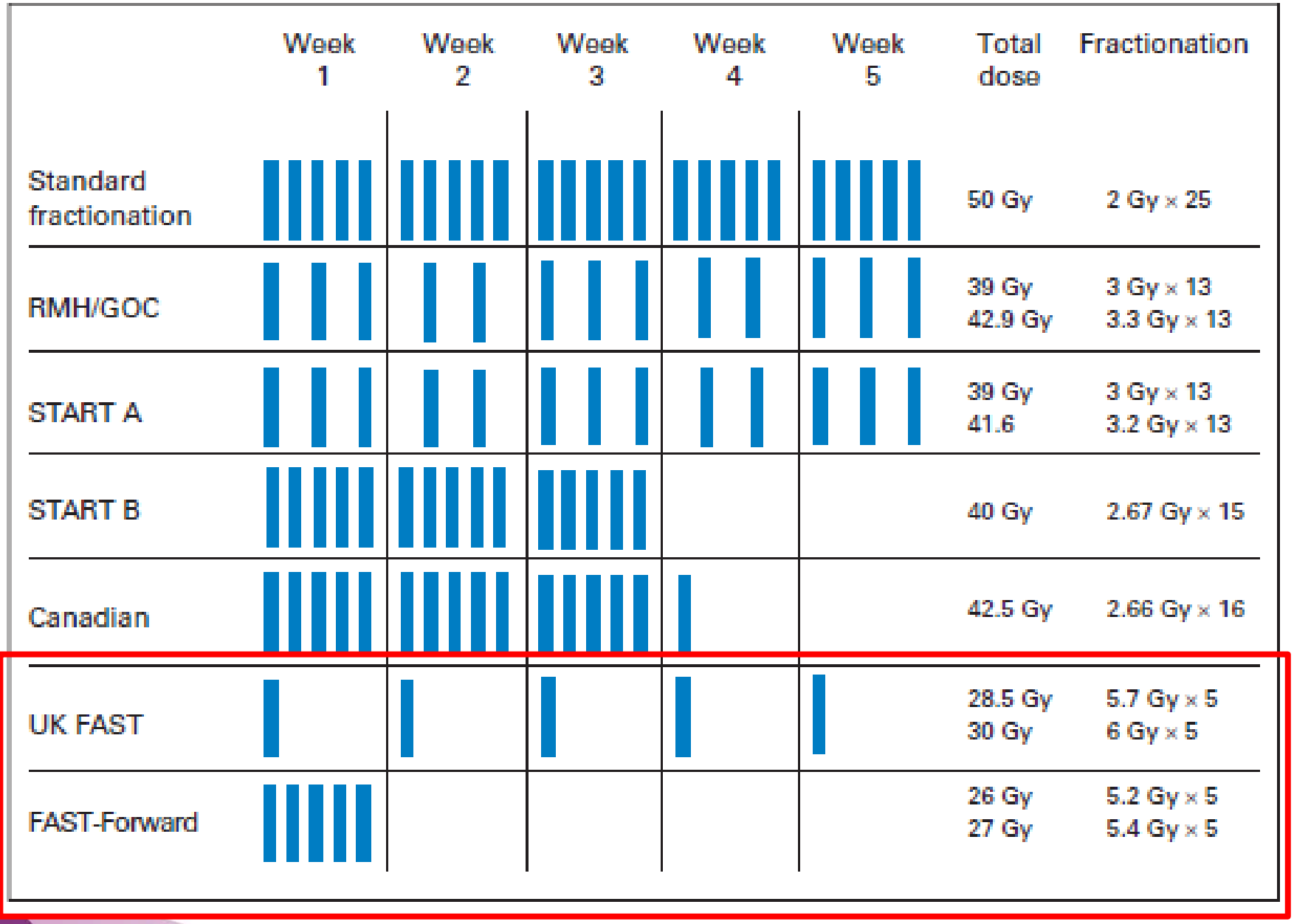
Haviland Lancet Oncol 2013, Haviland NEJM 2010, Whelan NEJM 2010, START B Lancet 2008, START A Lancet Oncol 2008, Owen Lancet Oncol 2006

Hypofractionation – Clinical practice

Since 2010 in the Netherlands: 16 x 2.66 Gy (5x/week)

Canadian scheme: longest follow-up

Hypofractionation – FAST (FORWARD)



	Week 1	Week 2	Week 3	Week 4	Week 5	Total dose	Fractionation
Standard fractionation						50 Gy	2 Gy × 25
RMH/GOC						39 Gy 42.9 Gy	3 Gy × 13 3.3 Gy × 13
START A						39 Gy 41.6	3 Gy × 13 3.2 Gy × 13
START B						40 Gy	2.67 Gy × 15
Canadian						42.5 Gy	2.66 Gy × 16
UK FAST						28.5 Gy 30 Gy	5.7 Gy × 5 6 Gy × 5
FAST-Forward						26 Gy 27 Gy	5.2 Gy × 5 5.4 Gy × 5

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Planning aspects in breast RT

- Introduction in breast RT
- Hypofractionation
- **Accelerated partial breast RT**
- Cardiac sparing – Breath hold technique
- Optimization of breast RT planning techniques

Partial breast RT - Rationale

- Recurrences occur mainly in or near excision cavity
- Occurrence of ‘elsewhere recurrences’ is equal after Breast-conserving surgery +/- whole breast irradiation (WBI)

Fisher NEJM 2002, Veronesi Ann Oncol 2001, Liljegren JCO 1999

Accelerated partial breast RT - Advantages

- Smaller RT volume:
  Less fibrosis, fat necrosis → *Better cosmetic outcome?*
  Lower RT dose in organs at risk, i.e. heart, lungs, contralateral breast

- Shorter overall treatment time (higher dose per fraction)

- Cheaper?
  → *depends on technique*

Offersen RO 2009, Njeh RO 2010, Theberge Sem Rad Oncol 2011

Accelerated Partial breast RT (APBI) - guidelines

Organization	Patient Age (y)	Tumor Size (cm)	Histology	Lymph Node Status	Margin Status
ABS	≥50	≤3	Infiltrating ductal carcinoma	Negative (by sentinel lymph node or axillary dissection)	Negative (at inked margin)
American Society of Breast Surgeons	≥45	≤2	Invasive ductal carcinoma or ductal carcinoma in situ	Negative (by sentinel lymph node or axillary dissection)	Negative (>2 mm)
NSABP B-39/RTOG- 0413	≥18	≤3	Invasive ductal carcinoma and ductal carcinoma in situ	Allows for 0-3 nodes involved (with negative sentinel lymph node or >6 nodes sampled)	Negative (at inked margin)
ASTRO ("suitable" patients outside of a clinical trial)	≥60	≤2	Invasive ductal carcinoma or other favorable subtypes (mucinous, tubular, and colloid)	Negative (by sentinel lymph node or axillary dissection)	Negative (>2 mm)
GEC-ESTRO ("low risk" patients outside of a clinical trial)	≥50	≤3	Invasive ductal carcinoma or other favorable subtypes (mucinous, tubular, and colloid)	Negative (by sentinel lymph node or axillary dissection)	Negative (>2 mm)

Abbreviations: ABS, American Brachytherapy Society; ASBS, American Society of Breast Surgeons; NSABP, National Surgical Adjuvant Breast and Bowel Project; ASTRO, American Society for Radiation Oncology; GEC-ESTRO, Groupe Européen de Curiethérapie—European Society for Therapeutic Radiology and Oncology.

Theberge Sem Rad Oncol 2011

APBI – low-risk patients

Organization	Patient Age (y)	Tumor Size (cm)	Histology	Lymph Node Status	Margin Status
ABS	≥50	≤3	Infiltrating ductal carcinoma	Negative (by sentinel lymph node or axillary dissection)	Negative (at inked margin)
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Theberge Sem Rad Oncol 2011

APBI - Methods

1. Brachytherapy (postoperative)
   - Interstitial: multiple needles of catheters
   - Balloon-catheter: Mammosite®

2. Intraoperative RT (postoperative)

3. External Beam RT

Offersen et al. RO 2009, Njeh et al. RO 2010, Thebergen Sem Rad Oncol 2011

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APBI - Methods

1. Brachytherapy (postoperative)
   - Interstitial: multiple needles of catheters
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2. Intraoperative RT (postoperative)

3. **External Beam RT**

Offersen et al. RO 2009, Njeh et al. RO 2010, Thebergen Sem Rad Oncol 2011

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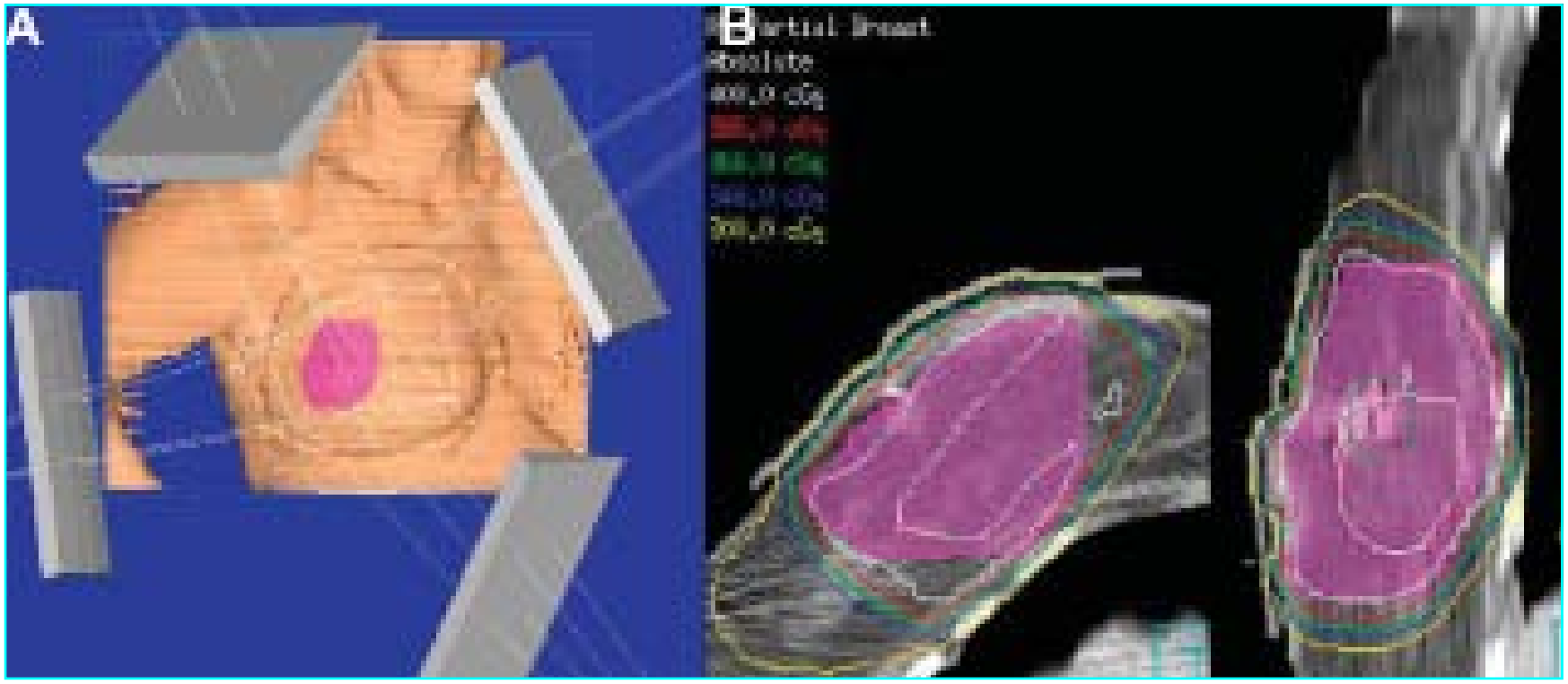
APBI - External Beam RT



Courtesy of
P. Elkhuizen

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Whole *vs.* Partial breast irradiation – phase III studies

Table 2
Randomised trials comparing hypofractionated accelerated partial breast irradiation (PBI) with whole breast irradiation (WBI)

Trial/institute	Control arm (WBI)	Test arms (PBI)	Target accrual	Median follow-up (months)
Hungarian National Institute of Oncology [33]	50 Gy in 25 fractions	HDR Ir-192 (85 patients) to a dose of 36.4 Gy in seven fractions over 4 days or electrons (40 patients) to a dose of 50 Gy in 25 fractions prescribed to the 80% isodose	258	66
GEC-ESTRO [34]	50–50.4 Gy in 25–28 fractions ± 10 Gy boost	32 Gy in eight fractions or 30.3 Gy in seven fractions HDR or 50 Gy PDR	1170	6.6 years
NSABP-39 [35]	50–50.4 Gy in 25–28 fractions ± 10–16 Gy boost	34 Gy in 10 fractions over 5 days using single/multi-source brachytherapy or 38.5 Gy in 10 fractions over 5 days using 3D-CRT	4300	Not reported
RAPID [36]	42.5 Gy in 16 fractions ± 10 Gy boost	38.5 Gy in 10 fractions BD over 5–8 days using 3D-CRT	2128	Not reported
IRMA [37]	45 Gy in 18 fractions or 50 Gy in 25 fractions or 50.4 Gy in 28 fractions ± 10–16 Gy boost	38.5 Gy in 10 fractions BD over 5 days using 3D-CRT	3302	Not reported
SHARE [38]	50 Gy in 25 fractions + 16 Gy boost or 40–42.5 Gy in 15–16 fractions without boost	40 Gy in 10 fractions BD over 5–7 days using 3D-CRT	2796	Not reported

HDR, high dose rate; PDR, pulsed dose rate; 3D-CRT, three-dimensional conformal radiotherapy.

Coles Clin Oncol 2013, Strnad Lancet 2016

Whole *vs.* Partial breast irradiation – phase III studies

Table 2
Randomised trials comparing hypofractionated accelerated partial breast irradiation (PBI) with whole breast irradiation (WBI)

Partial breast irradiation:

- *Intensively studied in (ongoing) phase III trials*
- *No differences in local recurrence rate in low-risk patients*
- *Toxicity and cosmetic outcome: favorable (in most published trials)*
- *Additional data will be reported in the coming years*

Extreme breast hypofractionation – preoperative single-dose PBI

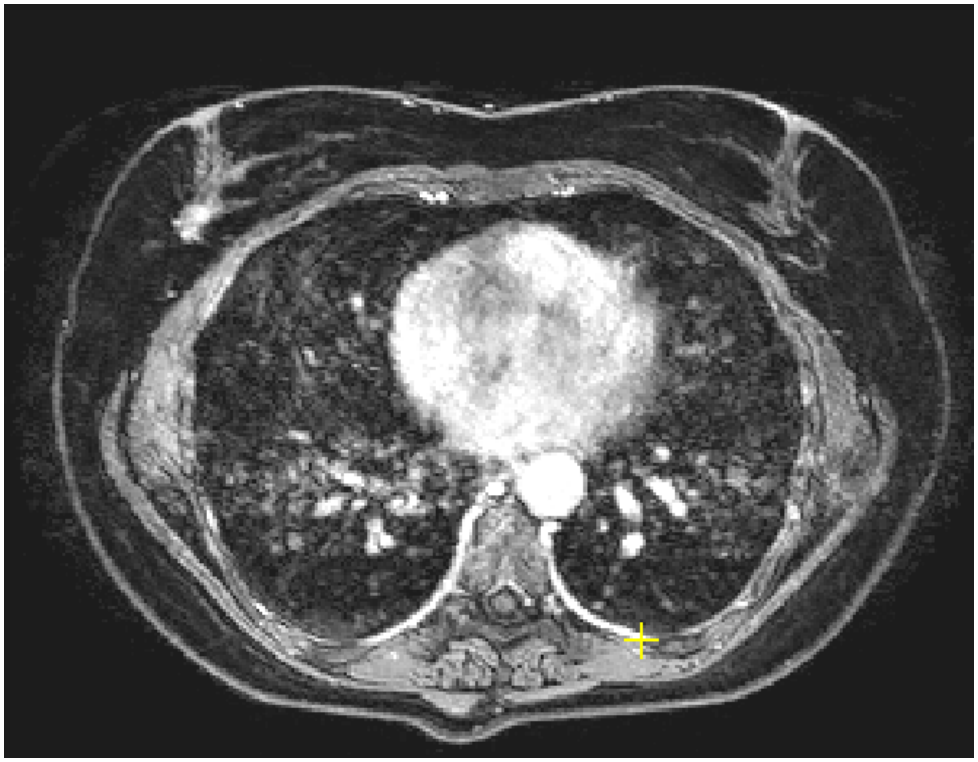
Ongoing Phase II studies

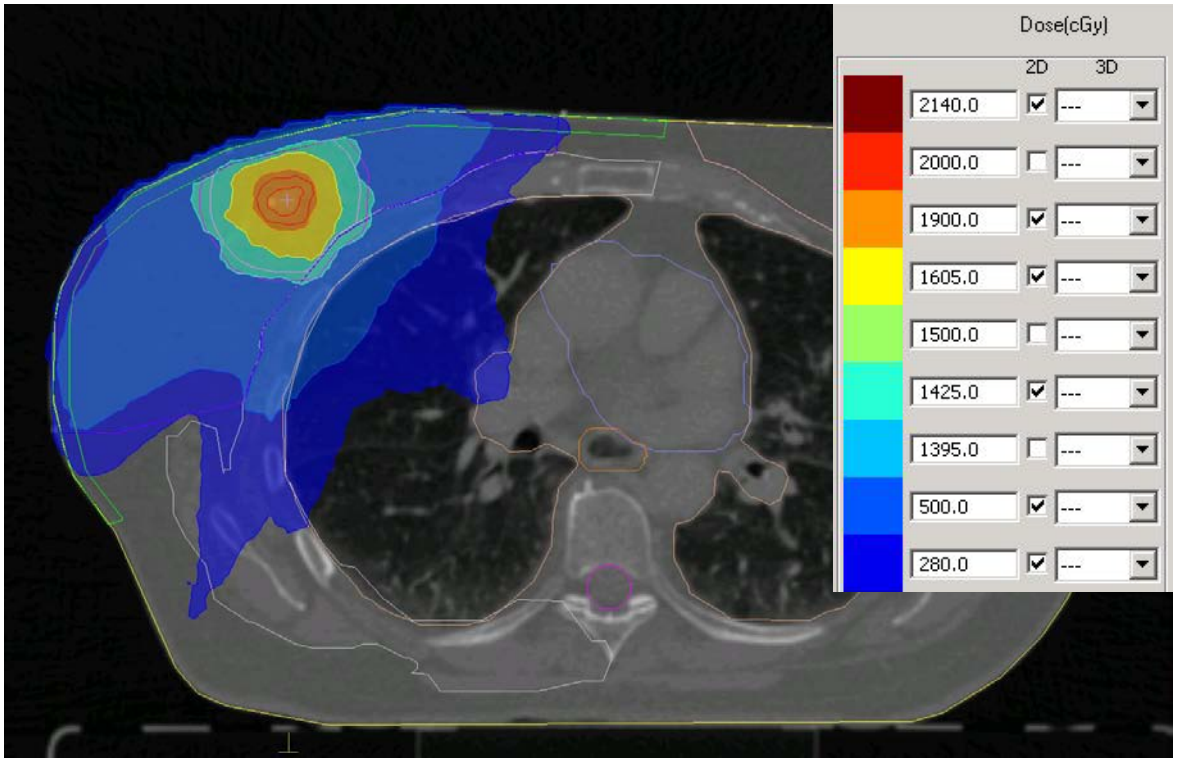
1. Duke University 1x21 Gy
   - in prone position
   - breast-conserving surgery at 6 weeks after RT

2. UMC Utrecht 1x20 / 15 Gy
   - in supine position
   - breast-conserving surgery at 6 months after RT
   - Primary endpoint: pathological complete response

Horton IJROBP 2015, Charaghvandi RO 2015

Preoperative single dose Radiotherapy supine position – UMC Utrecht





- Feasibility study
- 1x20 Gy tumor, 1x15 Gy tumor bed
- At 6 months after RT: lumpectomy

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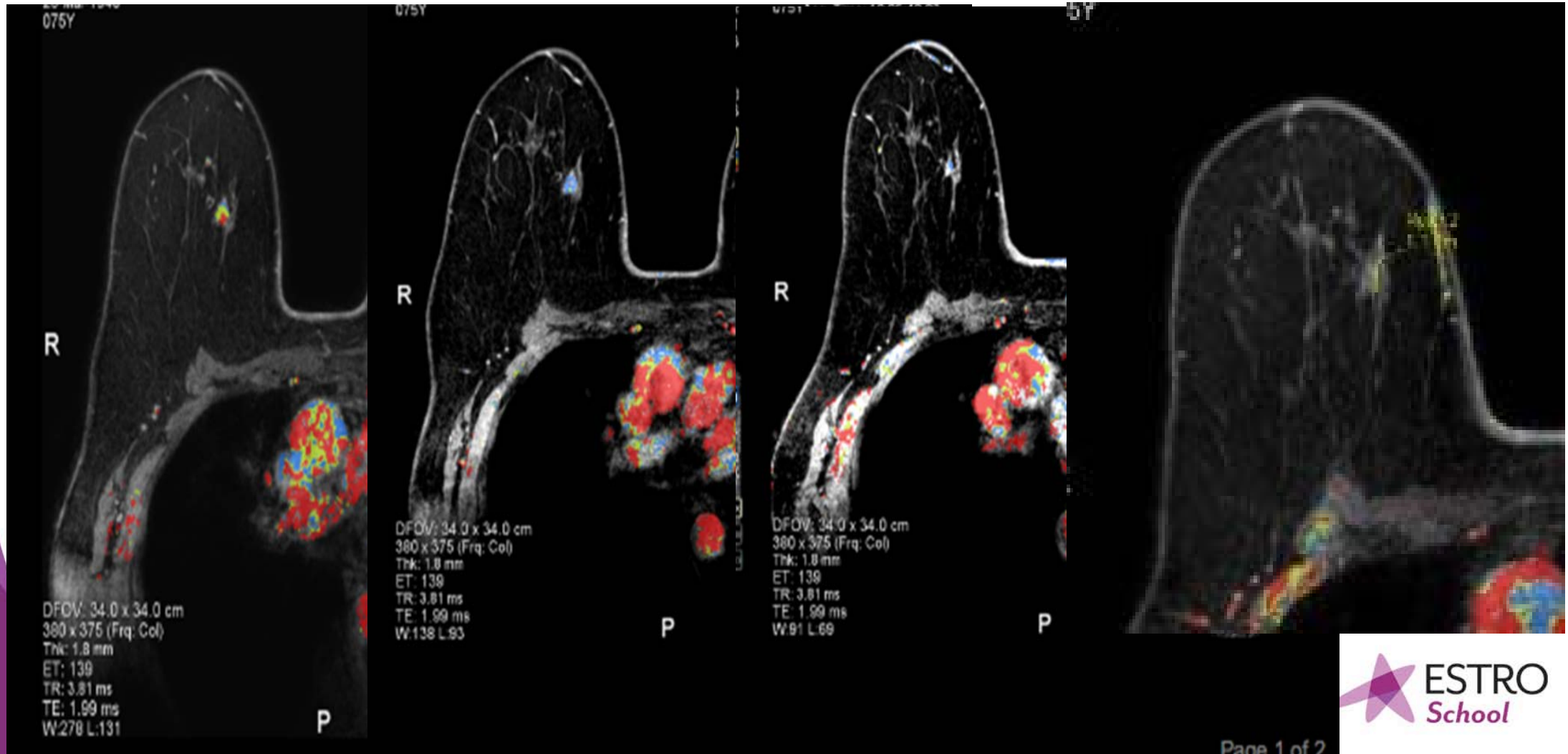
MRI – complete response

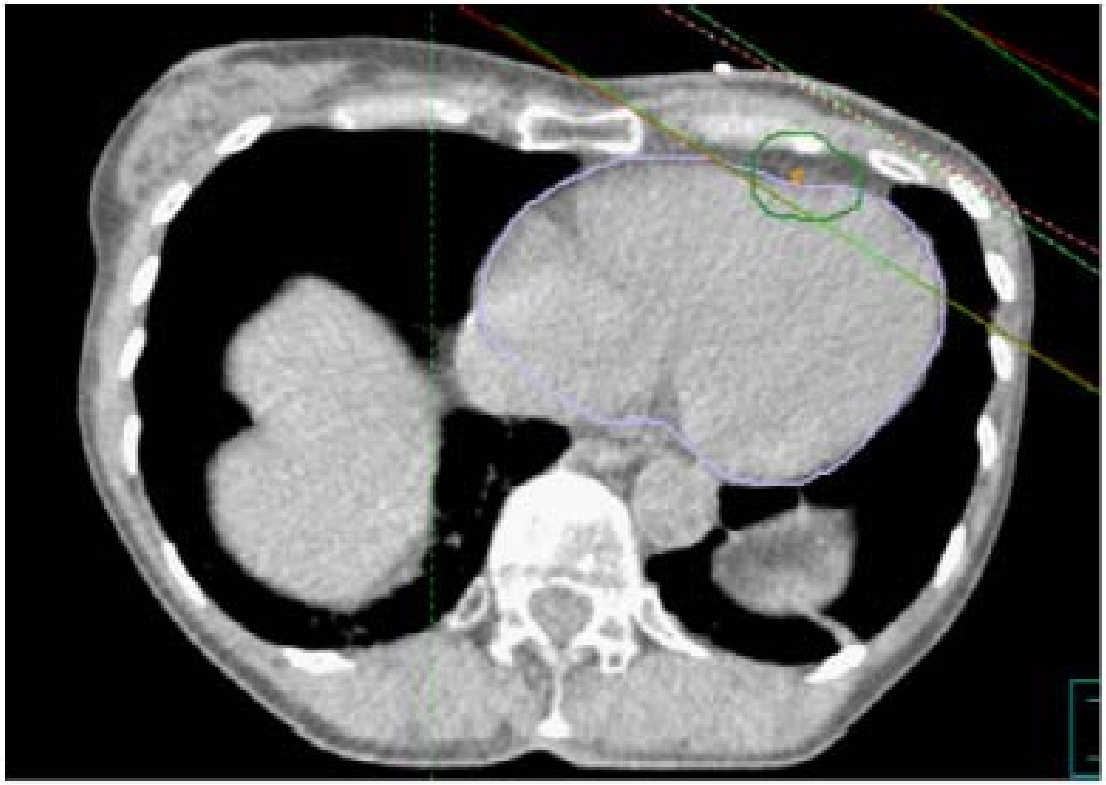
baseline 2 months 4 months 6 months



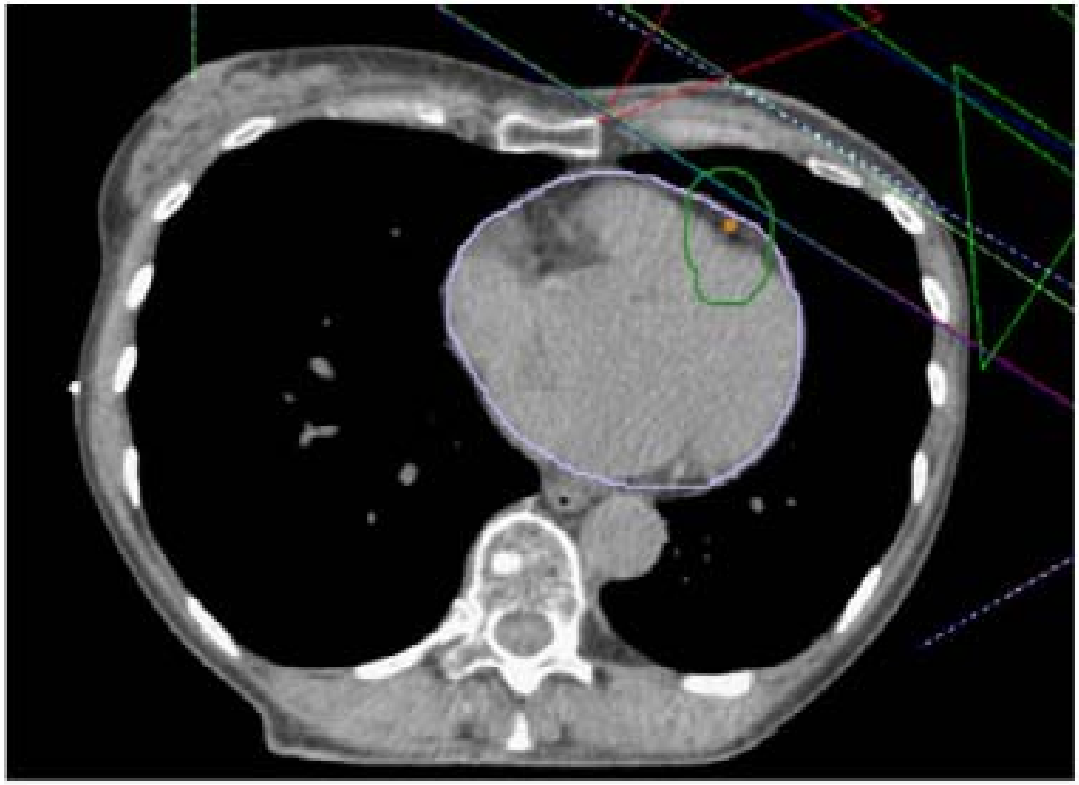
Planning aspects in breast RT

- Introduction in breast RT
- Hypofractionation
- Accelerated partial breast RT
- **Cardiac sparing – Breath hold technique**
- Optimization of breast RT planning techniques

Optimal cardiac sparing – Breath-hold technique



Free breathing



v_DIBH

Bartlett Radiother Oncol 2013

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Breath hold techniques

- ABC-technique: Active breathing coordinator™

Spirometry trace is visualized on a monitor and inspiration is held at a predetermined lung volume

- Gating:

RT is delivered only when patient is in inspiratory phase of breathing cycle

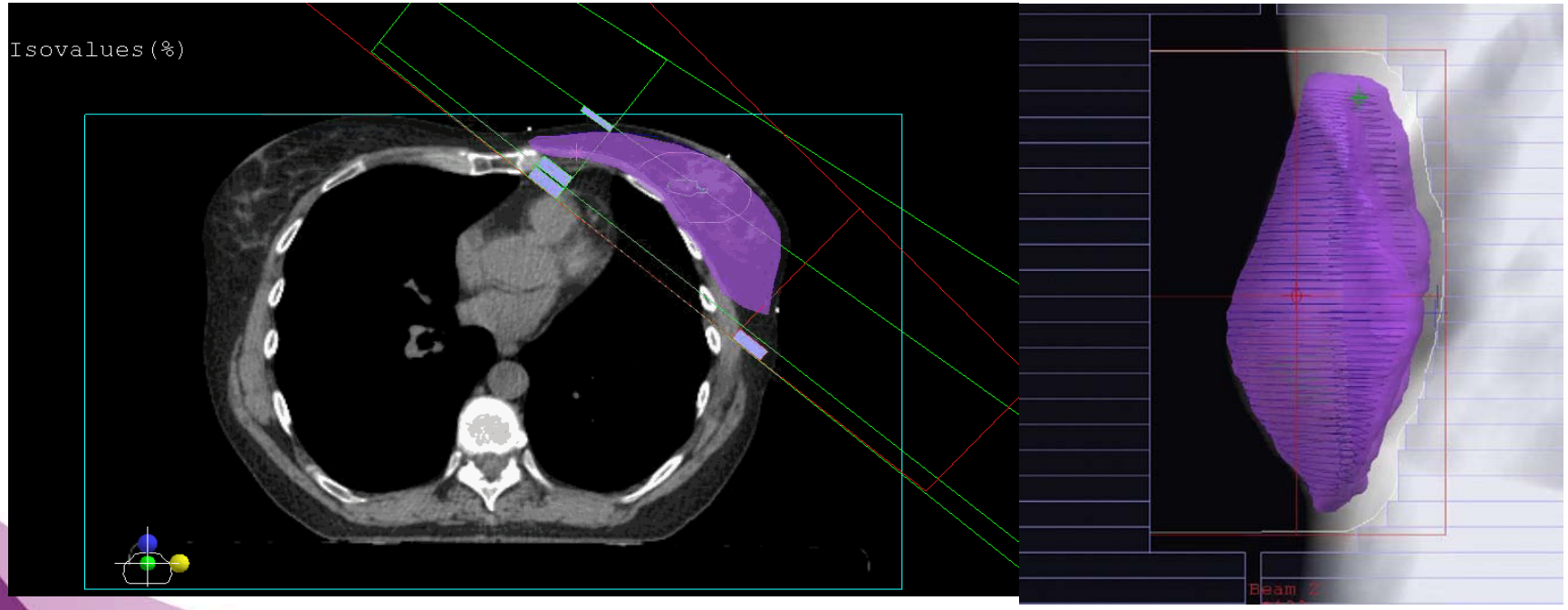
- Voluntary breath-hold technique: standard linear accelerator

Bartlett Radiother Oncol 2013

UMC Utrecht – voluntary deep inspiration breath hold technique

local +/- regional lymph nodes

- Instruction: session + home training + DVD
- 2 days later: planning CT-scan (Free breathing and Breath hold)
- Delineation: target volumes and organs at risk
- RT Planning on Breath hold CT (XiO), 4-10 fields
- Audio coaching during irradiation



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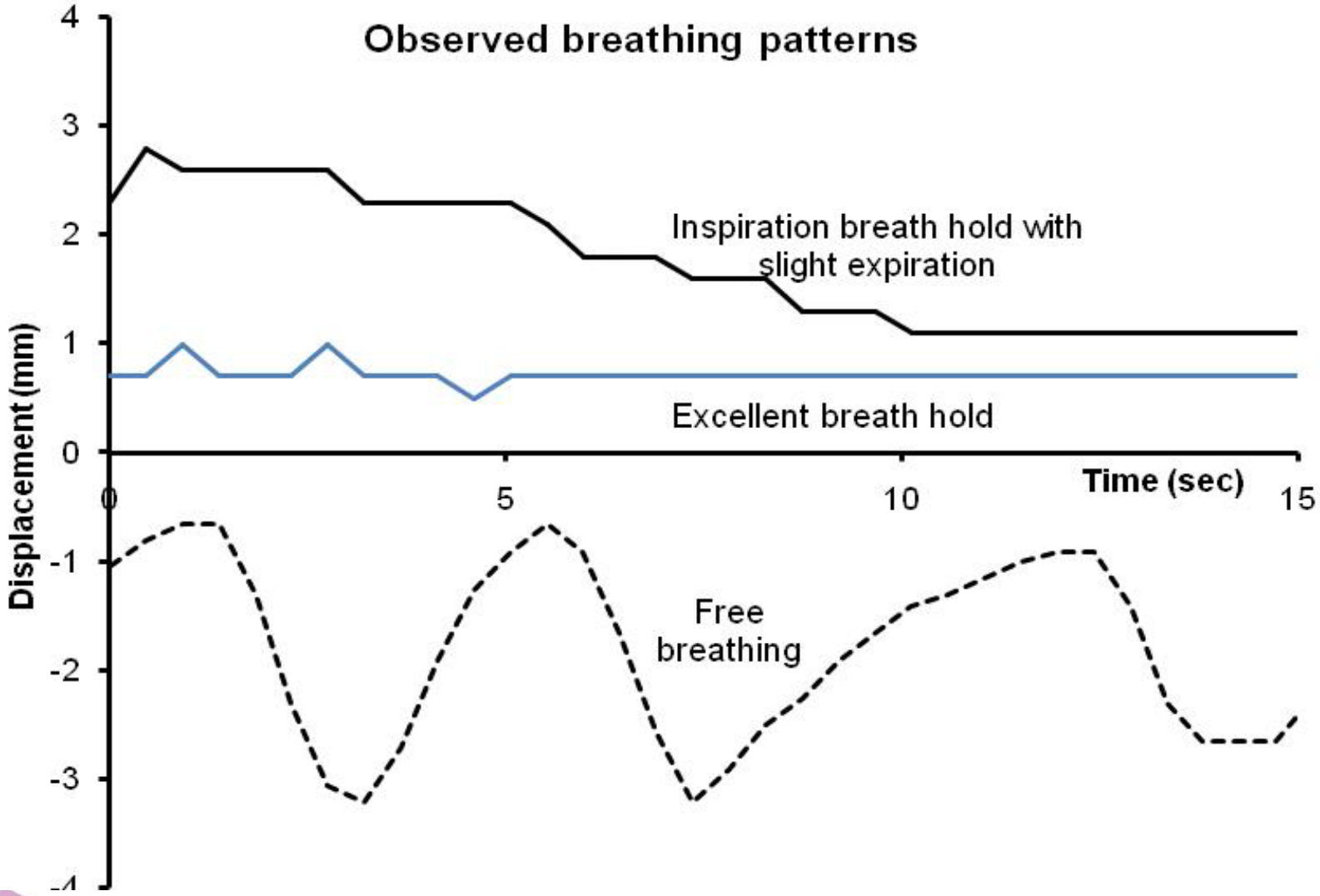
Breath hold analysis



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Breath hold technique

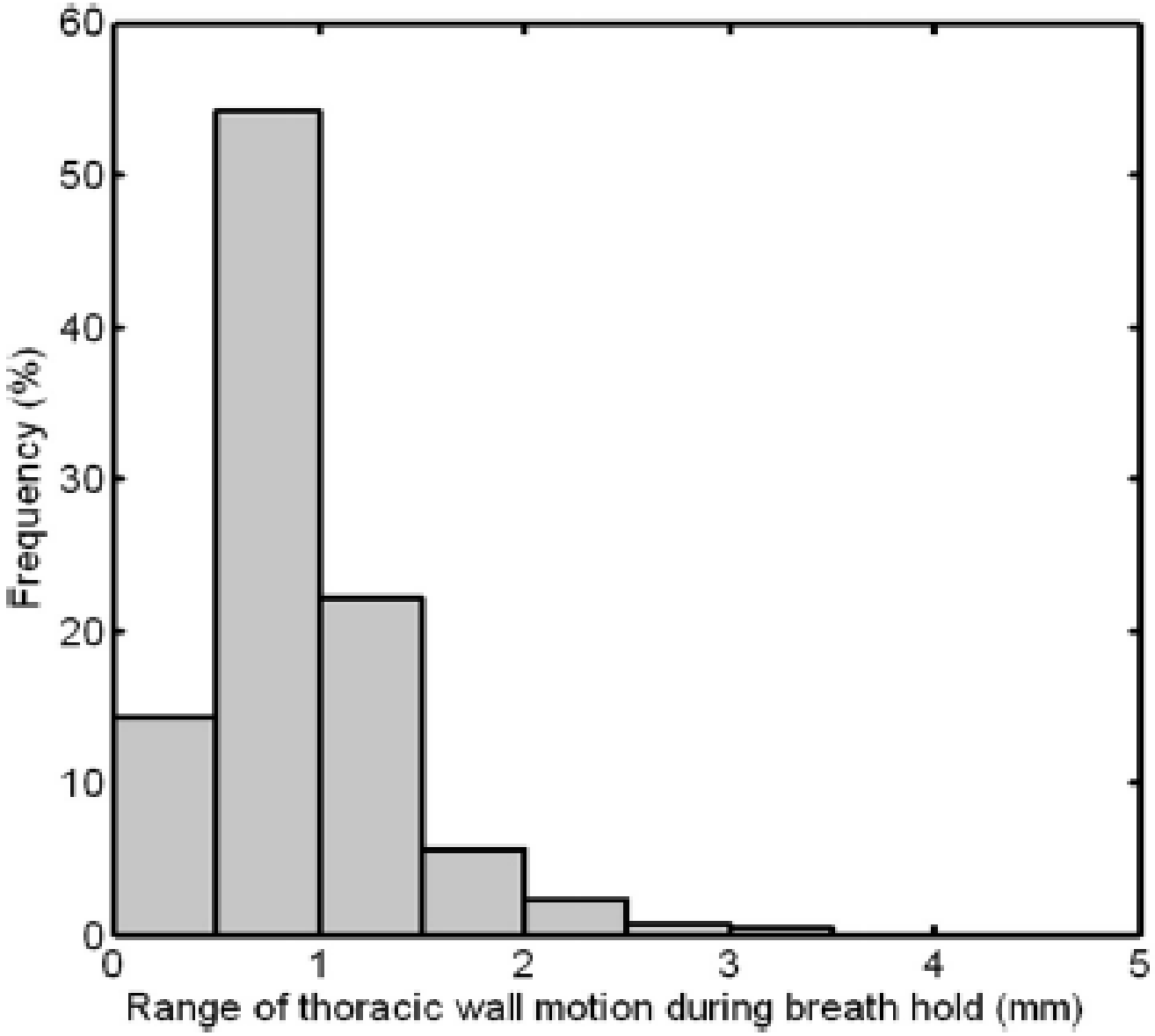


Fig. 1. Frequency distribution of the full ranges of thoracic wall motion (RTWM) in the 490 patients with stable BH.

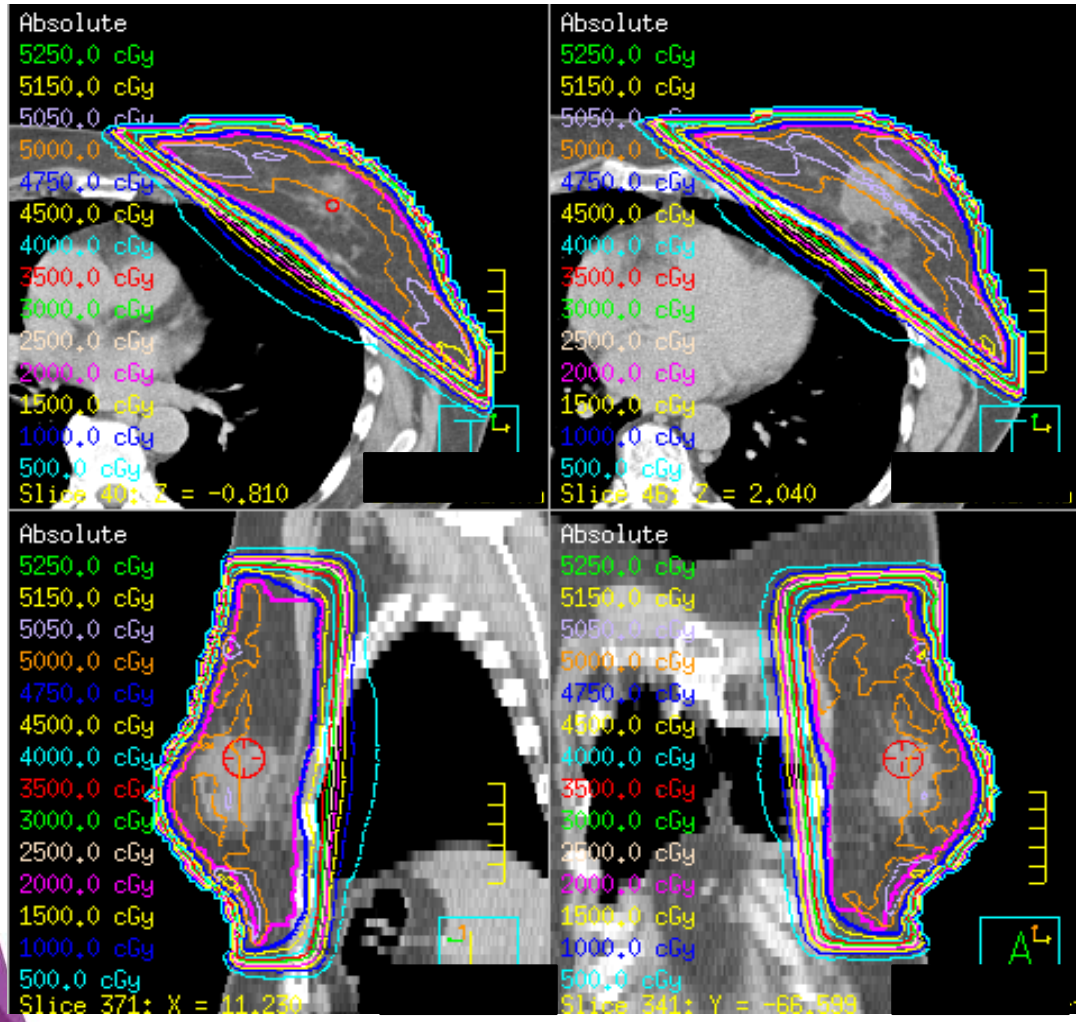
Compliance Breath hold technique

- Pulmonary disease, e.g. COPD
- Unable to follow breathing instructions, e.g. language barrier

Planning aspects in breast RT

- Introduction in RT breast cancer
- Hypofractionation
- Accelerated partial breast RT
- Cardiac sparing – Breath hold technique
- **Optimization of breast RT planning techniques**

Forward IMRT / 3DCRT



Field-in-field technique / forward IMRT:

- 2 Tangential mediolateral and lateromedial fields
- Small segments are added to achieve a more homogeneous dose distribution instead of wedges
- Mixture of 6 and 10 MV photon beams

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More advanced planning techniques in breast cancer patients

Aim: Reduction of RT-induced toxicity

- Forward-MRT *vs.* 2D planning: less acute toxicity (dermatitis, oedema)

  Pignol JCO 2008

- 2D planning *vs.* forward-IMRT: 1.7 times more likely to have change in breast appearance (after follow-up of 5 years)

  Donovan Radiother Oncol 2007

- Forward-IMRT *vs.* 3DCRT planning: superior cosmesis and reduction in telangiectasia (after follow-up of 5 years)

  Mukesh JCO 2015

Comparison of 3D-CRT, IMRT, VMAT in locoregional RT

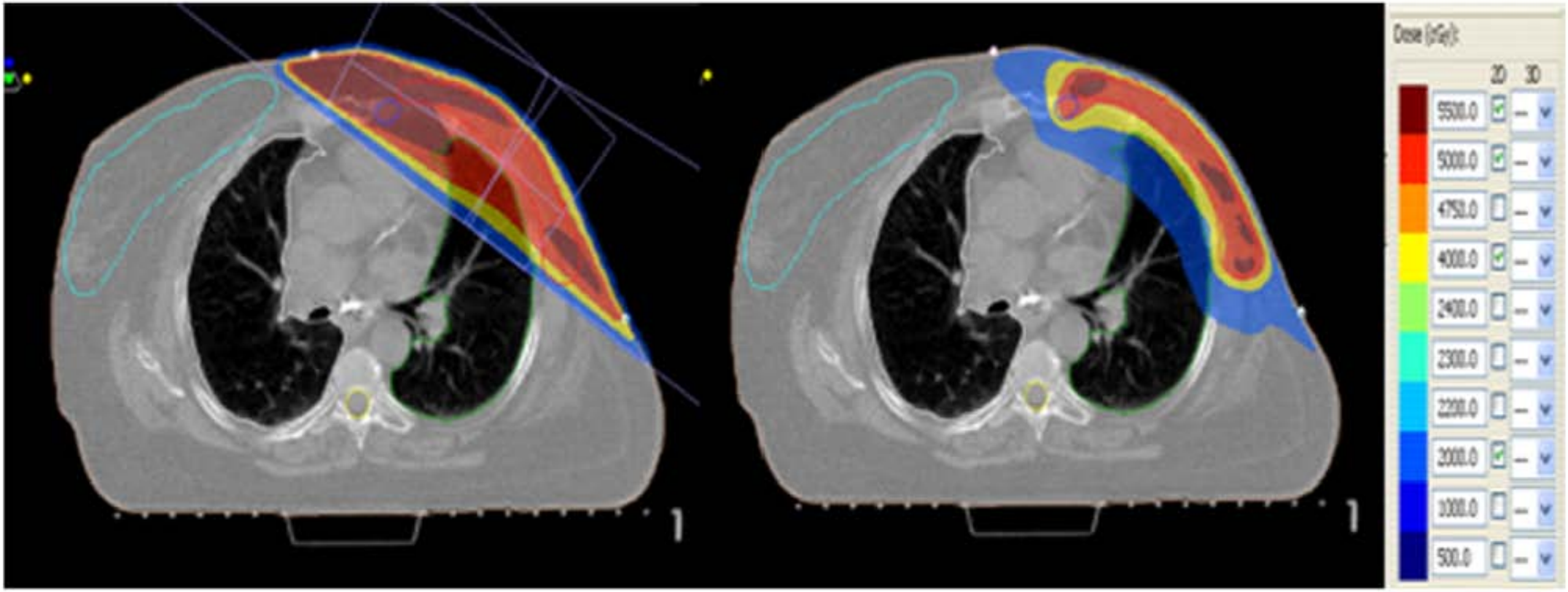
(including internal mammary nodes)

Multibeam-IMRT, VMAT:

- Improved dose conformity compared with 3D-CRT or forward-IMRT

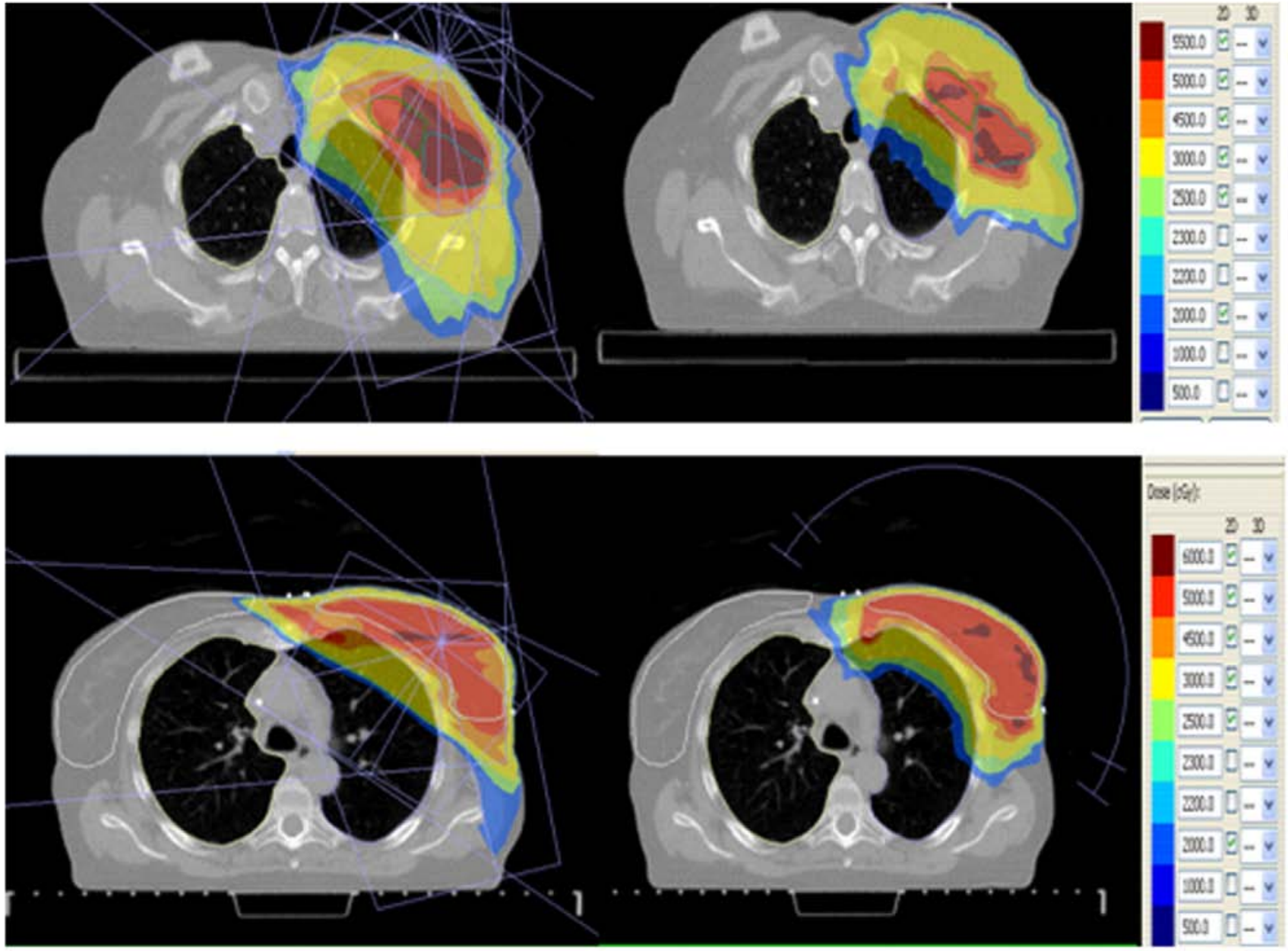
Osman RO 2014, Popescu IJROBP 2010, Qi Med Dosimetry 2014

3D-CRT compared with VMAT



3D-CRT VMAT

Multibeam-IMRT compared with VMAT



Qi Med Dosimetry 2014

Comparison of 3D-CRT, IMRT, VMAT
locoregional RT including IMN

VMAT:

- Improved / similar dose conformity
- Reduction in mean heart and ipsilateral lung dose
- Shorter delivery time
- Reduced number of monitor units
- However,
  - Slight increase in mean contralateral lung and breast dose
  - Higher volume of the heart receiving low dose

Osman RO 2014, Popescu IJROBP 2010, Qi Med Dosimetry 2014

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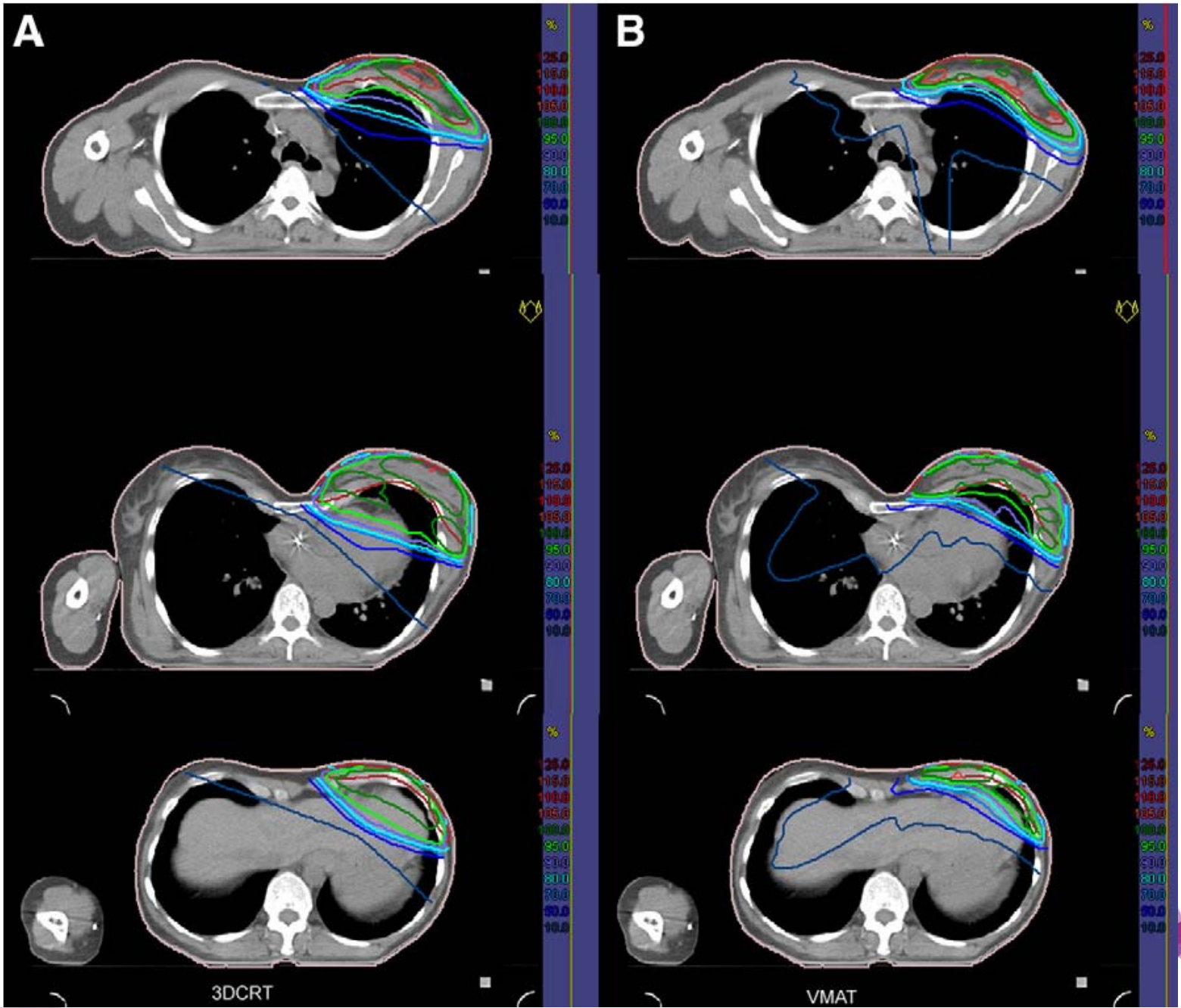
Other indications VMAT - Funnel chest

Heartl 2014



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What about second cancer risk?

VMAT and multibeam-IMRT vs. 3D-CRT and forward-IMRT:

- More beams → larger volume of normal tissue is exposed to a 'low-dose-bath'
- Require a longer beam-on time

  → *integral dose can increase because of head leakage and collimator scatter*

- Second cancer risk can increase

  however, absolute risk on second cancer risk is low

Abo Madyan RO 2014, Ibrahim BMC Cancer 2012, Boyce NEJM 2002

Recommendations VMAT and m-IMRT

Valid treatment option for breast cancer patients:

- with high heart dose using 3DCRT or forward-IMRT or
- when irradiation of the internal mammary lymph-node chain is indicated

In these ‘special cases’ the risk of late cardiac complications with a tangential technique might outweigh the increased second cancer risk with a multibeam IMRT technique

Abo Madyan RO 2014, Ibrahim BMC Cancer 2012, Boyce NEJM 2002

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Take home messages – innovations in RT breast cancer

- Shorter duration of overall treatment time:
  - Hypofractionation
  - Accelerated Partial breast irradiation

- Reduced toxicity:
  - Optimal cardiac sparing with Breath hold technique
  - APBI
  - Less arm morbidty: Regional RT instead of axillary lymph node dissection
  - VMAT in breast radiotherapy in ‘special cases’ to reduce cardiac / lung dose

    e.g regional RT including internal mammary nodes, funnel chest

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Thank you for your attention!

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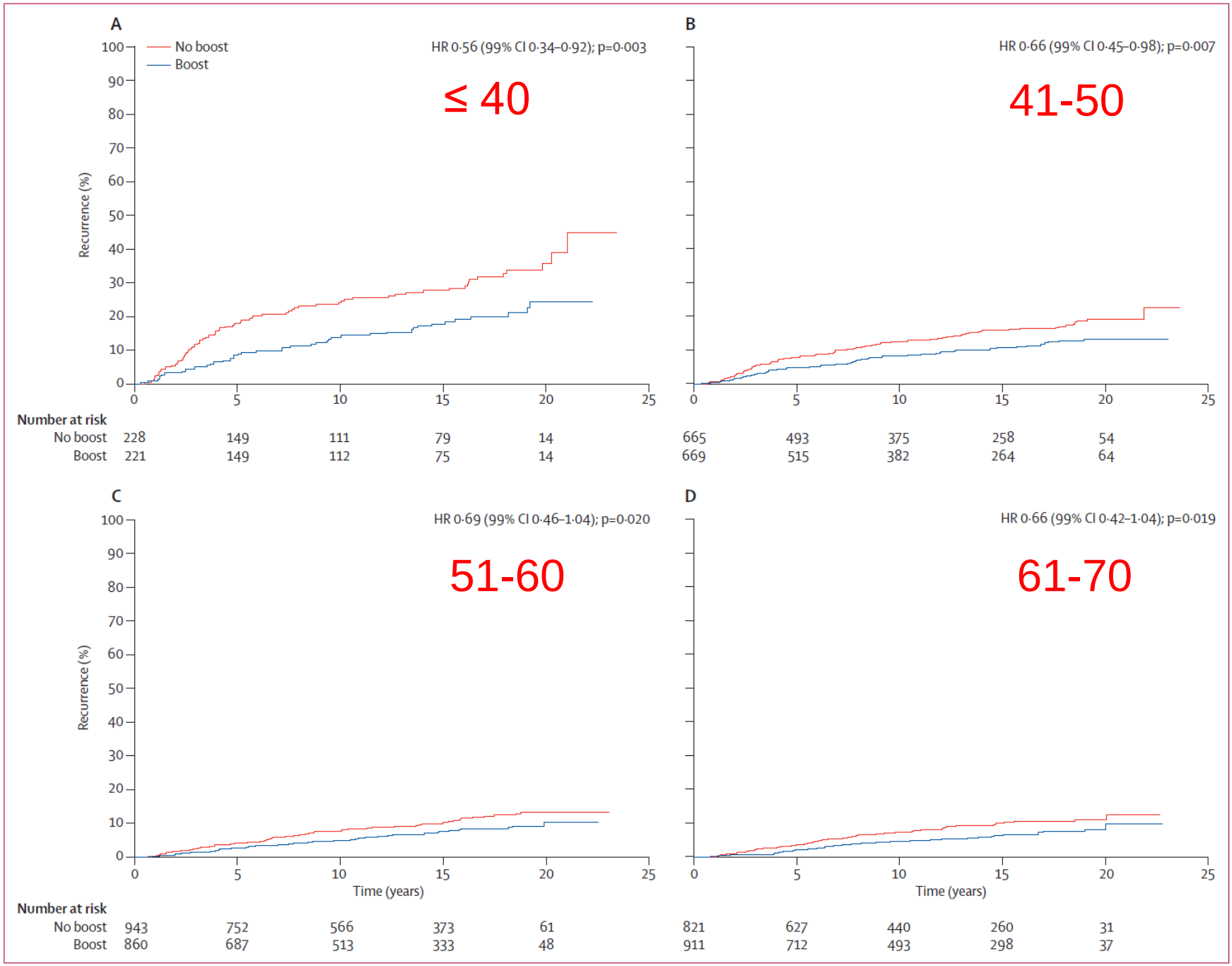
Planning aspects in breast RT

- Introduction in breast RT
- Hypofractionation
- Accelerated partial breast RT
- **Simultaneously integrated boost (SIB)**
- Cardiac sparing – Breath hold technique
- Optimization of breast RT planning techniques

Boost on tumor bed: decreased local recurrence



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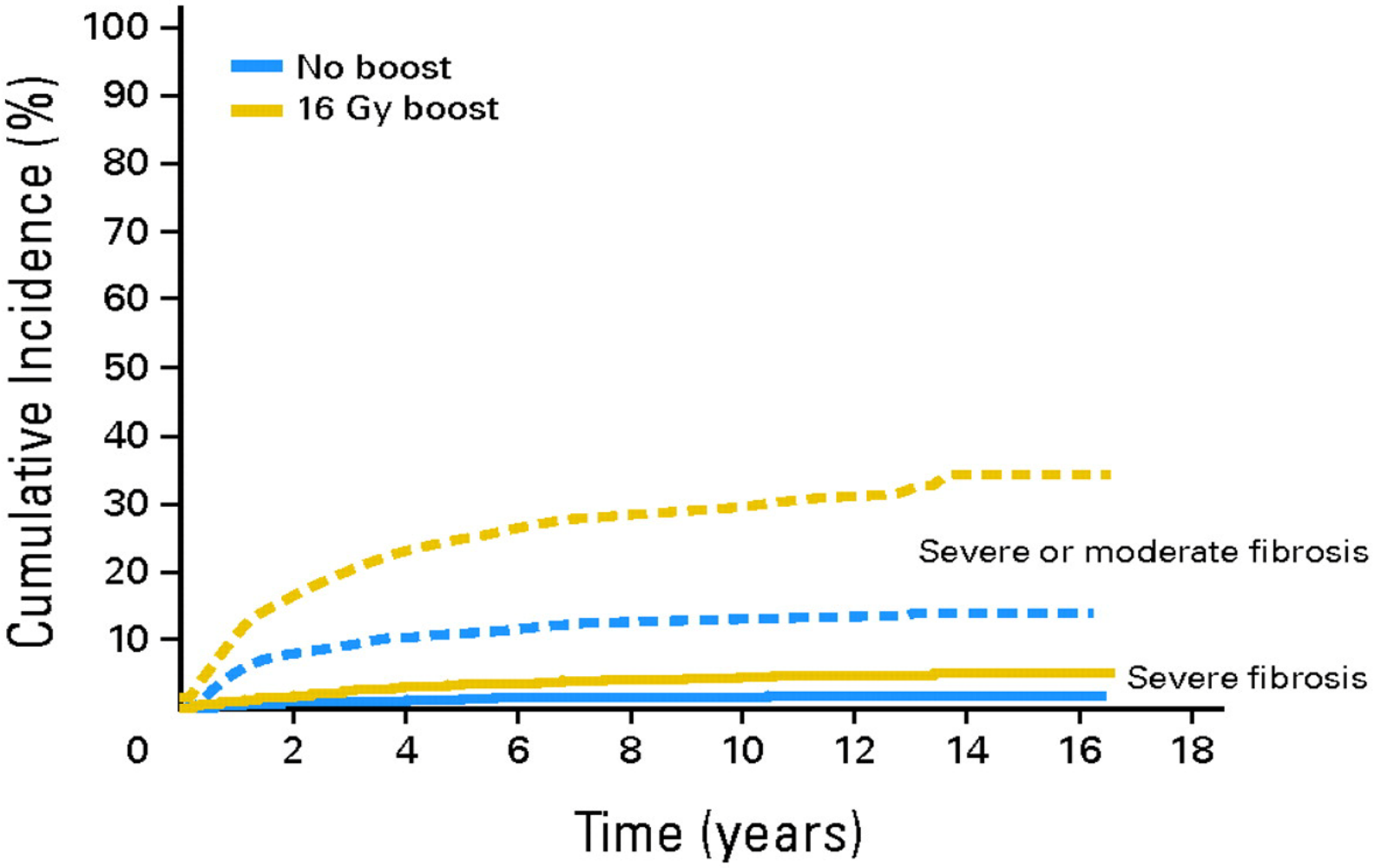
Bartelink Lancet Oncol 2015

Boost on tumor bed – breast fibrosis



Boost tumor bed (mainly direct electron field):
increased rates of moderate-severe breast fibrosis by 15% at 10 years

Bartelink JCO 2007

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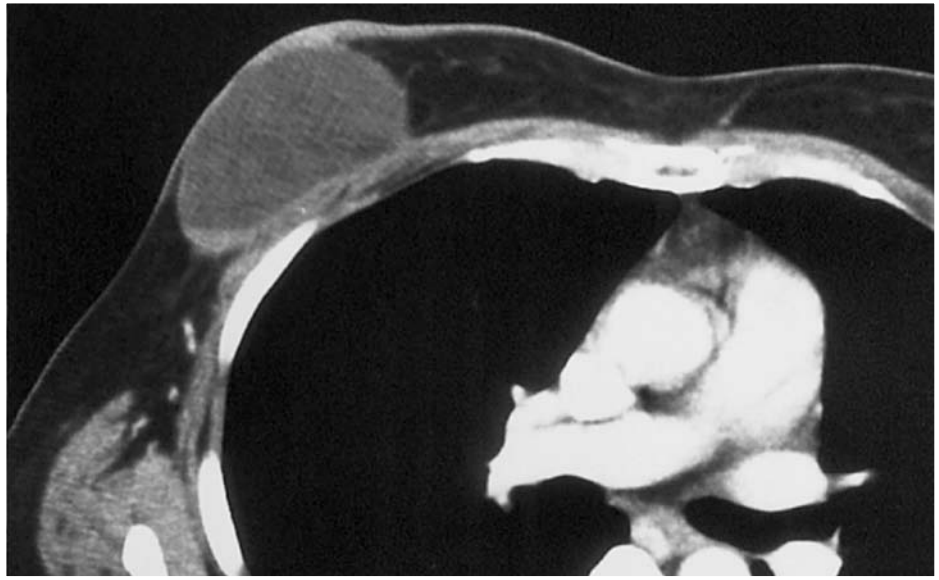
Breast fibrosis – Increased risk of

Risk is increased:

- Higher RT dose
- RT boost on tumor bed
- Postoperative breast oedema or hematoma
- Seroma in tumor bed



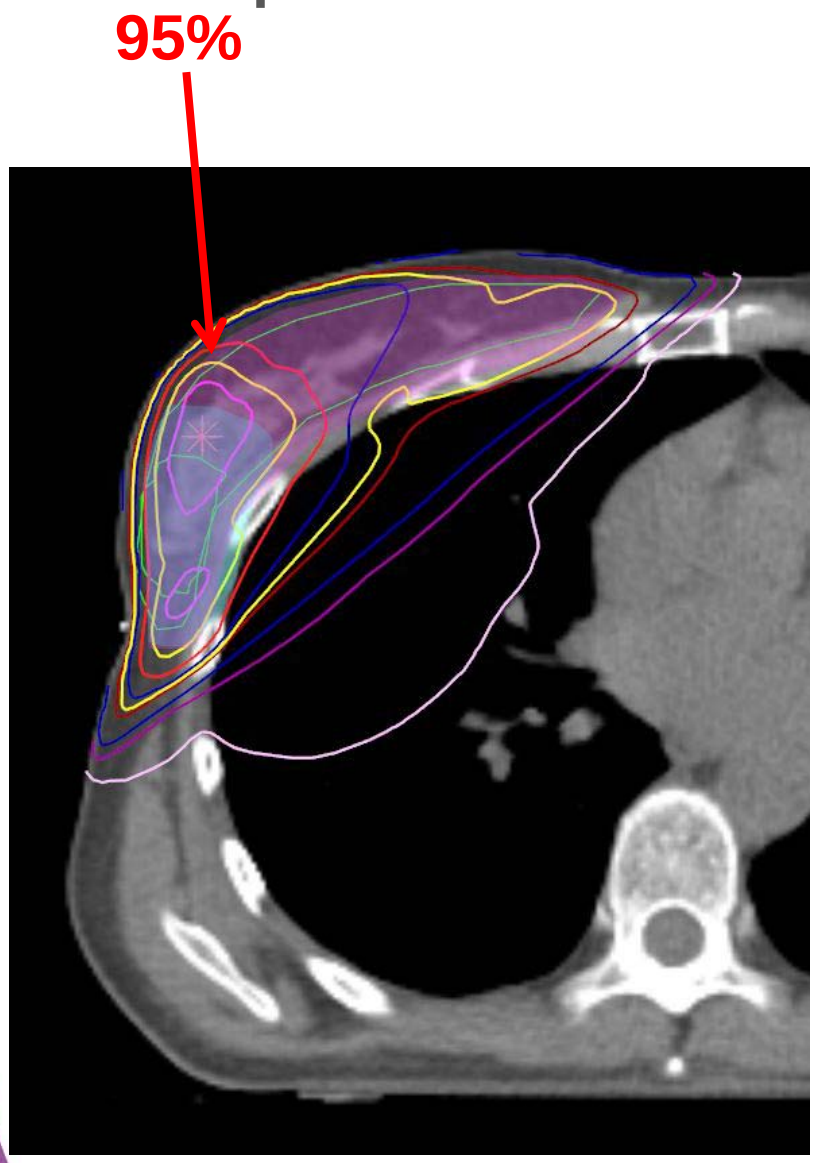
Bartelink Lancet Oncol 2015, Collette Eur J Cancer 2008, Mukesh Radiother Oncol 2012

Simultaneously integrated boost (SIB) instead of sequential boost

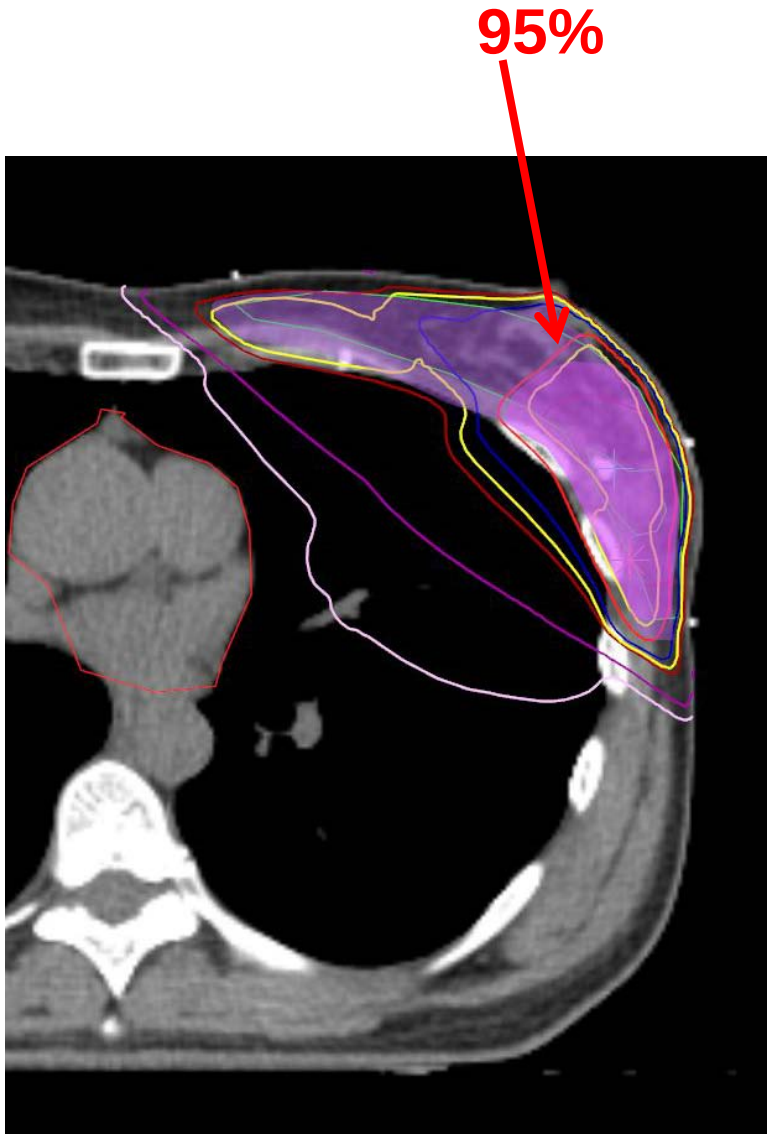
SIB:

- Increased dose homogeneity
- Less unintended excessive dose outside tumorbed

Sequential boost *vs.* SIB



Sequential boost



SIB

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Simultaneously integrated boost (SIB)

Results SIB tumor bed (stage I-III breast cancer patients):

- Excellent 5-year control (99%)

  Bantema-Joppe RO 2013

- Higher dose per fraction to tumor bed →

  Equal toxicity and cosmetic result

  Bantema-Joppe IJROBP 2012

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Preoperative external beam Radiotherapy prone position

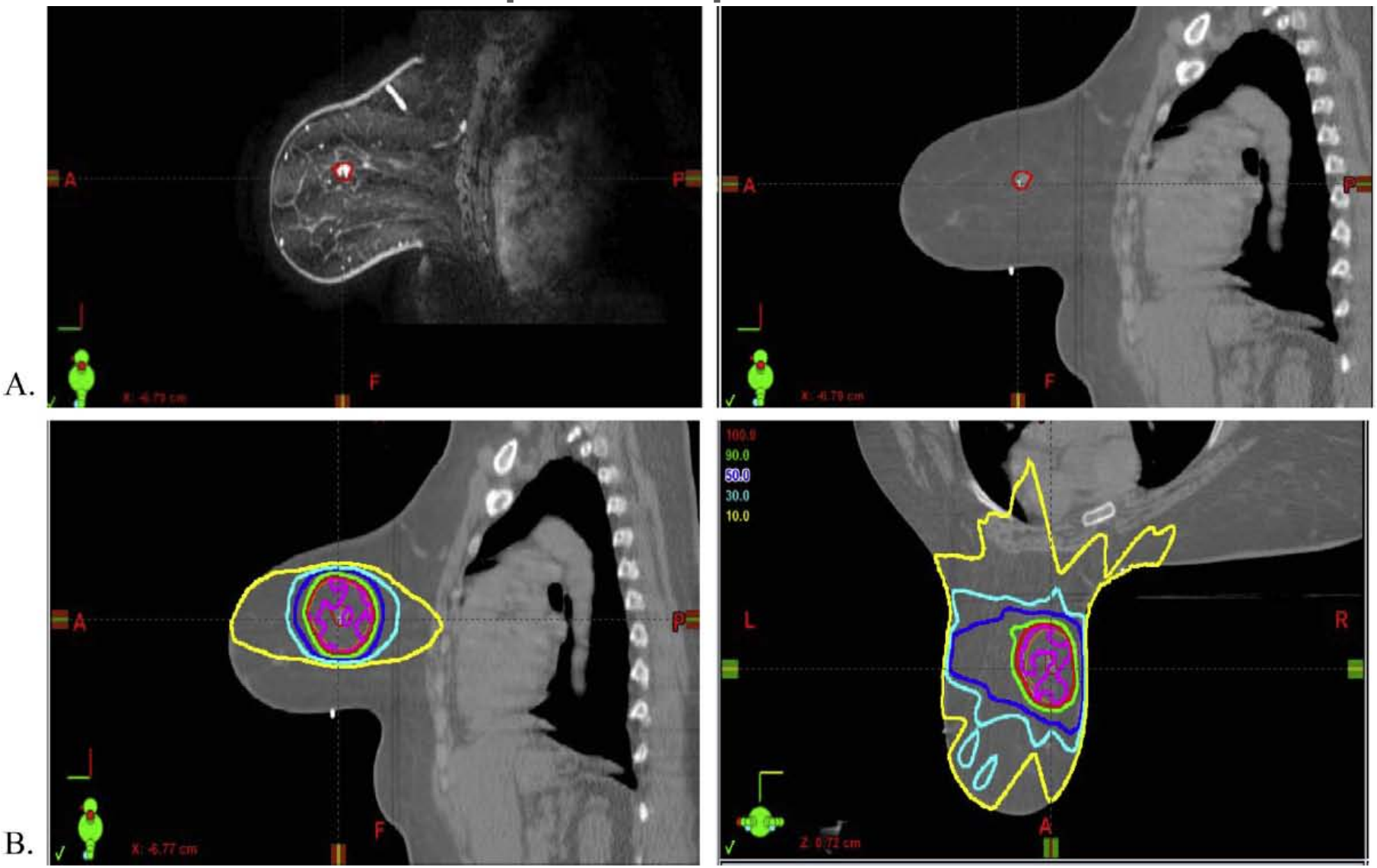

Fig. 1. Preoperative radiation to the intact tumor. (A) Sagittal view of a prone treatment planning magnetic resonance imaging scan (left) and computed tomography scan (right). (B) Sagittal (left) and axial (right) treatment planning images with dose distribution in the same patient.

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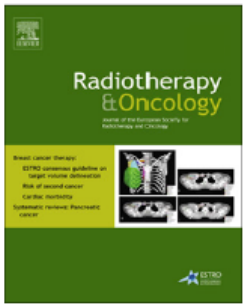

Systematic review

Risk of second non-breast cancer after radiotherapy for breast cancer: A systematic review and meta-analysis of 762,468 patients

Trine Grantzau *, Jens Overgaard

Department of Experimental Clinical Oncology, Aarhus University Hospital, Denmark

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Risk of second non-breast cancer after radiotherapy for breast cancer: A systematic review and meta-analysis of 762,468 patients

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Relative risk	Lung cancer n=631,021	Esophageal cancer n=413,650	Thyroid cancer n=322,461
≥ 5 years	1.39 (1.28-1.51)	1.53 (1.01-2.31)	0.96 (0.59-1.57)
≥ 10 years	1.59 (1.39-1.81)	1.56 (1.03-2.38)	1.53 (0.69-3.39)
≥ 15 years	1.66 (1.36-2.01)	2.17 (1.11-4.25)	2.21 (0.64-7.61)

40%: treated with radiotherapy

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≥ 15 years	1.66 (1.36-2.01)	2.17 (1.11-4.25)	2.21 (0.64-7.61)

Risk of lung and esophageal cancer:

- increased after breast radiotherapy
- increased by time following breast cancer diagnosis
- Increased with delivered Gy

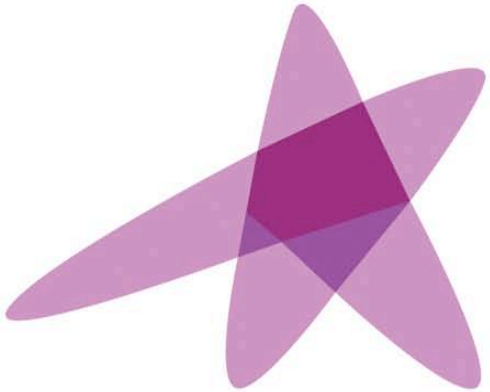
However,
no information about age, smoking, chemotherapy, irradiated volumes
older radiotherapy techniques

Treatment and Toxicity - Conclusions

- Adjuvant radiotherapy is essential part of breast cancer treatment → improves locoregional tumor control and survival

- Risk of radiation-induced second cancer is increased, but low compared to benefit of radiotherapy

- Any dose reduction in organs at risk →
  risk reduction of lung and esophageal cancer
  contralateral breast cancer in young patients



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Case 1: Breast

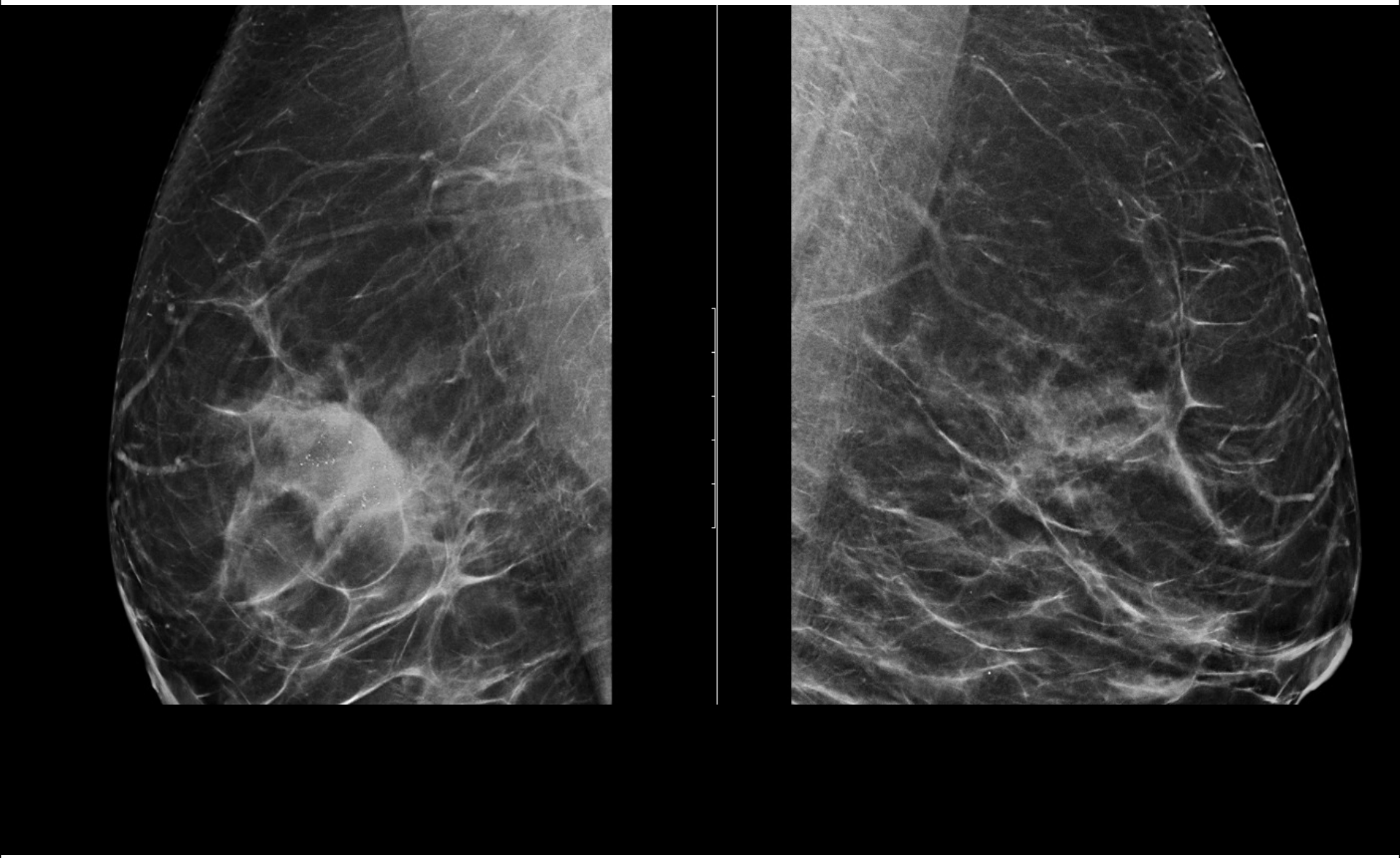
ESTRO Cambridge
September 2016

Introduction case 1:
Breast and regional lymph nodes (i.e. axillary, supraclavicular and internal mammary nodes)

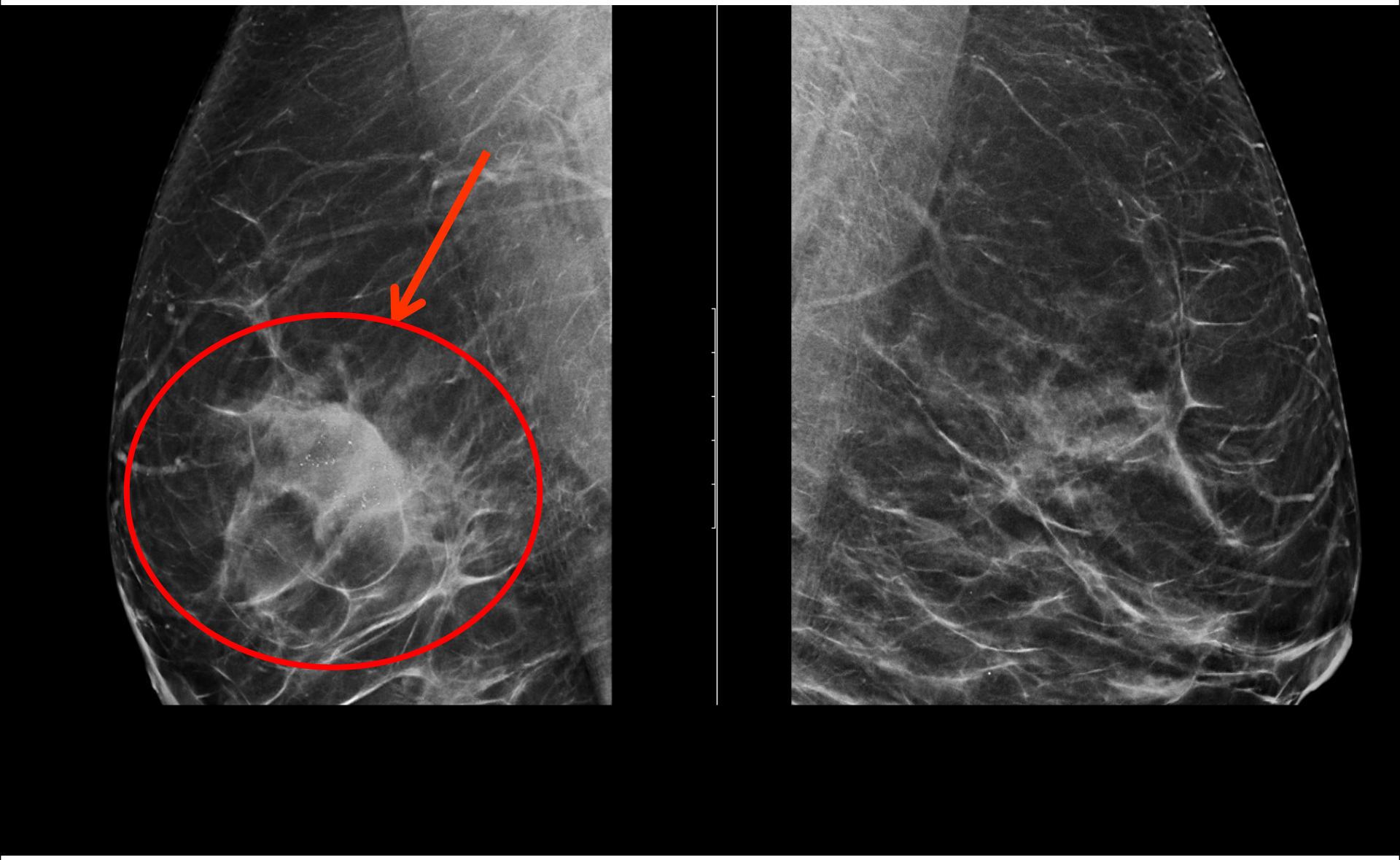
Mrs H, 54 years old

- Medical history: Obesity, Thrombosis left leg (postoperatively)
- July 2015: Palpable lump in right breast
- Physical examination:
  - Right breast: tumor 4x4 cm
  - Right axilla: pathologically enlarged lymph nodes
- Mammography:
  - Lesion in right breast, Upper-outer quadrant, 5 cm
  - 2nd lesion in upper outer quadrant, 1 cm
  - Birads-IV

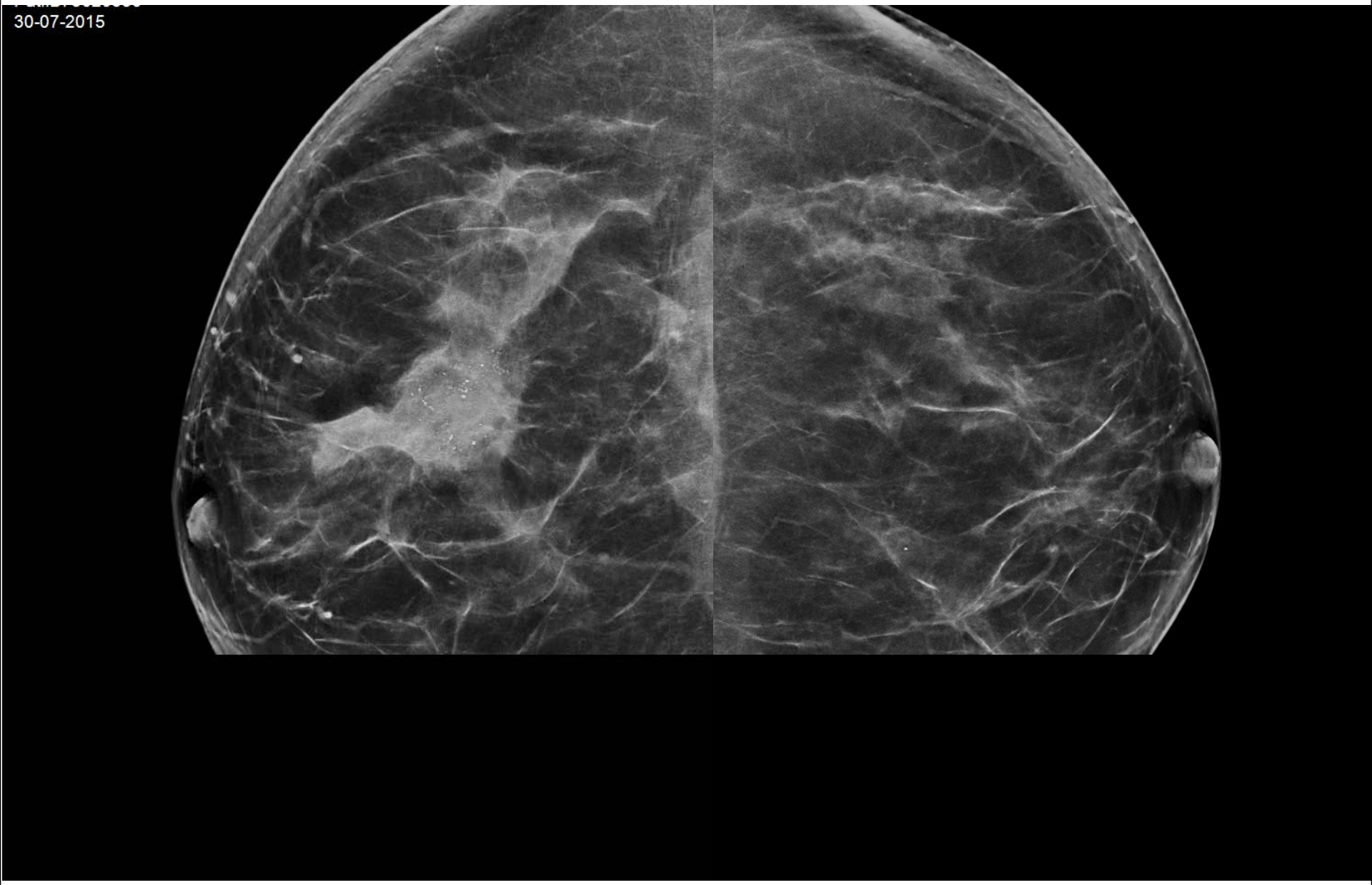
Mammography - Mediolateral view



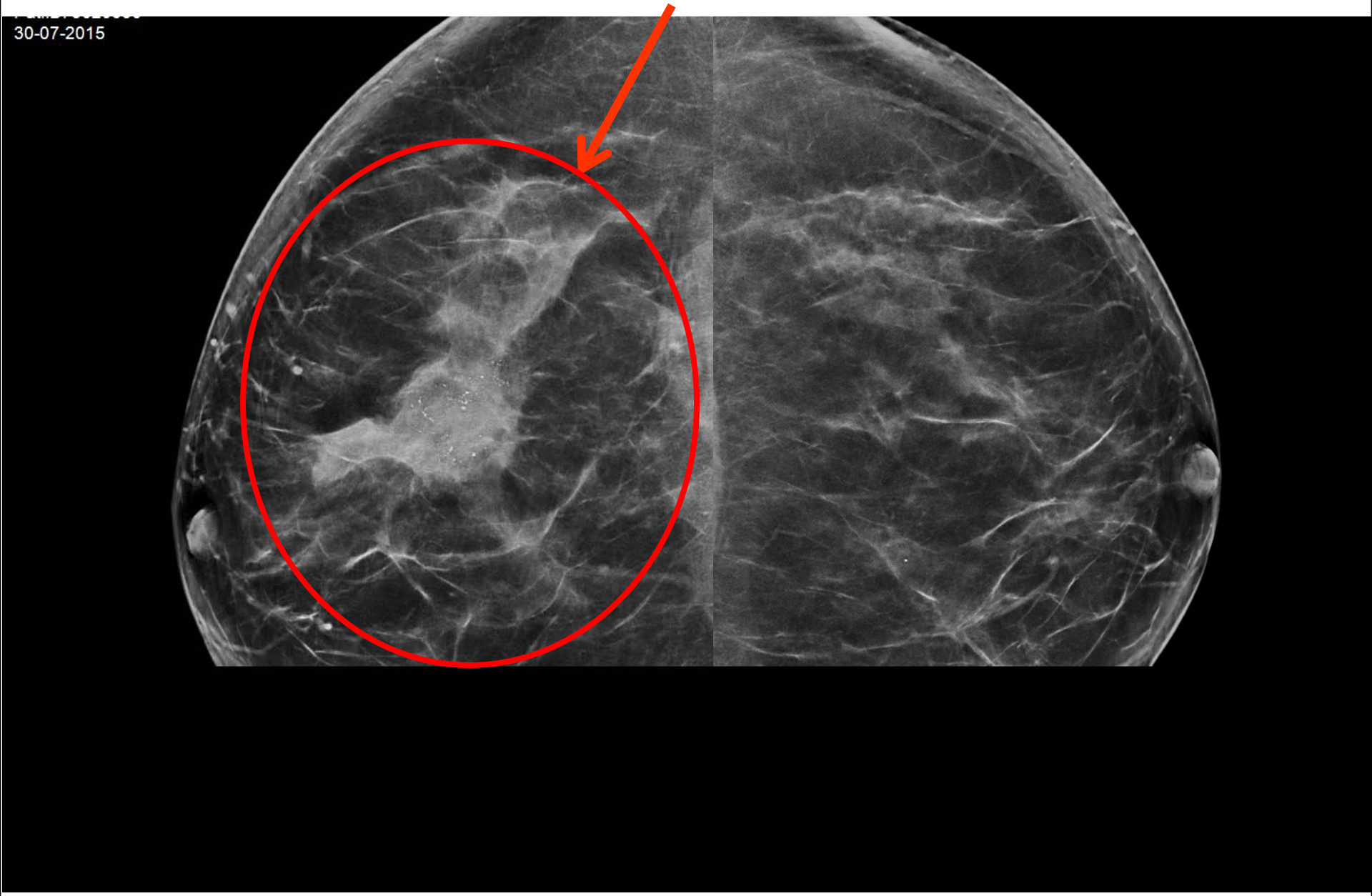
Mammography - Mediolateral view



Mammography- Craniocaudal view



Mammography- Craniocaudal view



BI-RADS: Breast Imaging-reporting and data system

Final Assessment Categories			
Category		Management	Likelihood of cancer
0	Need additional imaging or prior examinations	Recall for additional imaging and/or await prior examinations	n/a
1	Negative	Routine screening	Essentially 0%
2	Benign	Routine screening	Essentially 0%
3	Probably Benign	Short interval-follow-up (6 month) or continued	>0 % but ≤ 2%
4	Suspicious	Tissue diagnosis	4a. low suspicion for malignancy (>2% to ≤ 10%) 4b. moderate suspicion for malignancy (>10% to ≤ 50%) 4c. high suspicion for malignancy (>50% to <95%)
5	Highly suggestive of malignancy	Tissue diagnosis	≥95%
6	Known biopsy-proven	Surgical excision when clinical appropriate	n/a

BI-RADS classification

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  - Right axilla: pathologically enlarged lymph nodes → cN1
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  - 2nd lesion in upper outer quadrant, 1 cm
  - Birads-IV

Mrs H, 54 years old

- Ultrasound: 2 pathologically enlarged lymph nodes in right axilla
- Ultrasound-guided biopsy right breast and fine needle aspiration (FNA) right axilla

- Histology right breast: infiltrating ductal carcinoma, grade 3, ER1%, PR1%, HER2 positive
- FNA right axilla: metastases

- MRI:
    1. tumor in right breast, 4 cm
    2. 2nd tumor in right breast, 18 mm, BIRADS-6.

MRI - BI-RADS classification

Final Assessment Categories			
Category		Management	Likelihood of cancer
0	Need additional imaging or prior examinations	Recall for additional imaging and/or await prior examinations	n/a
1	Negative	Routine screening	Essentially 0%
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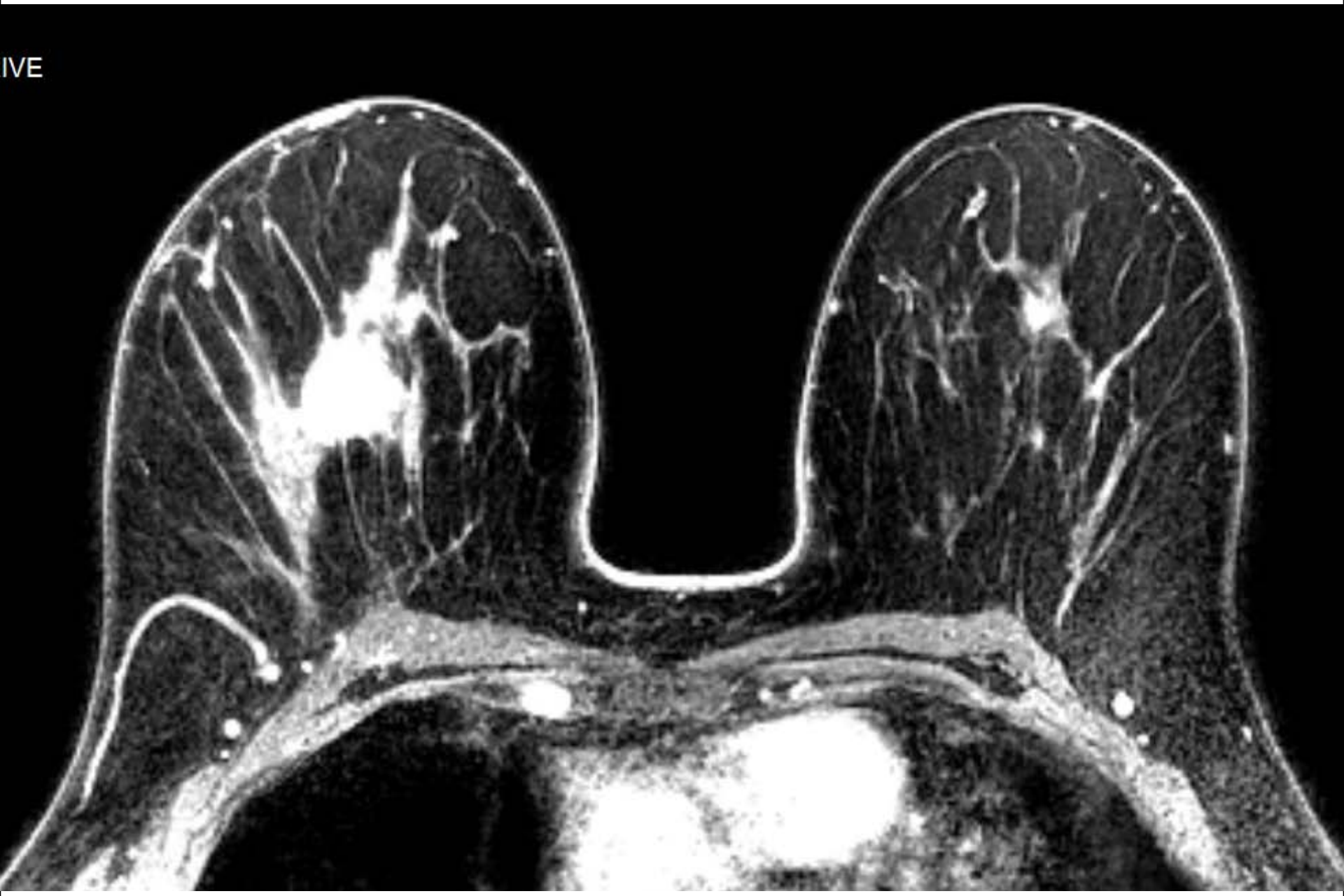
MRI



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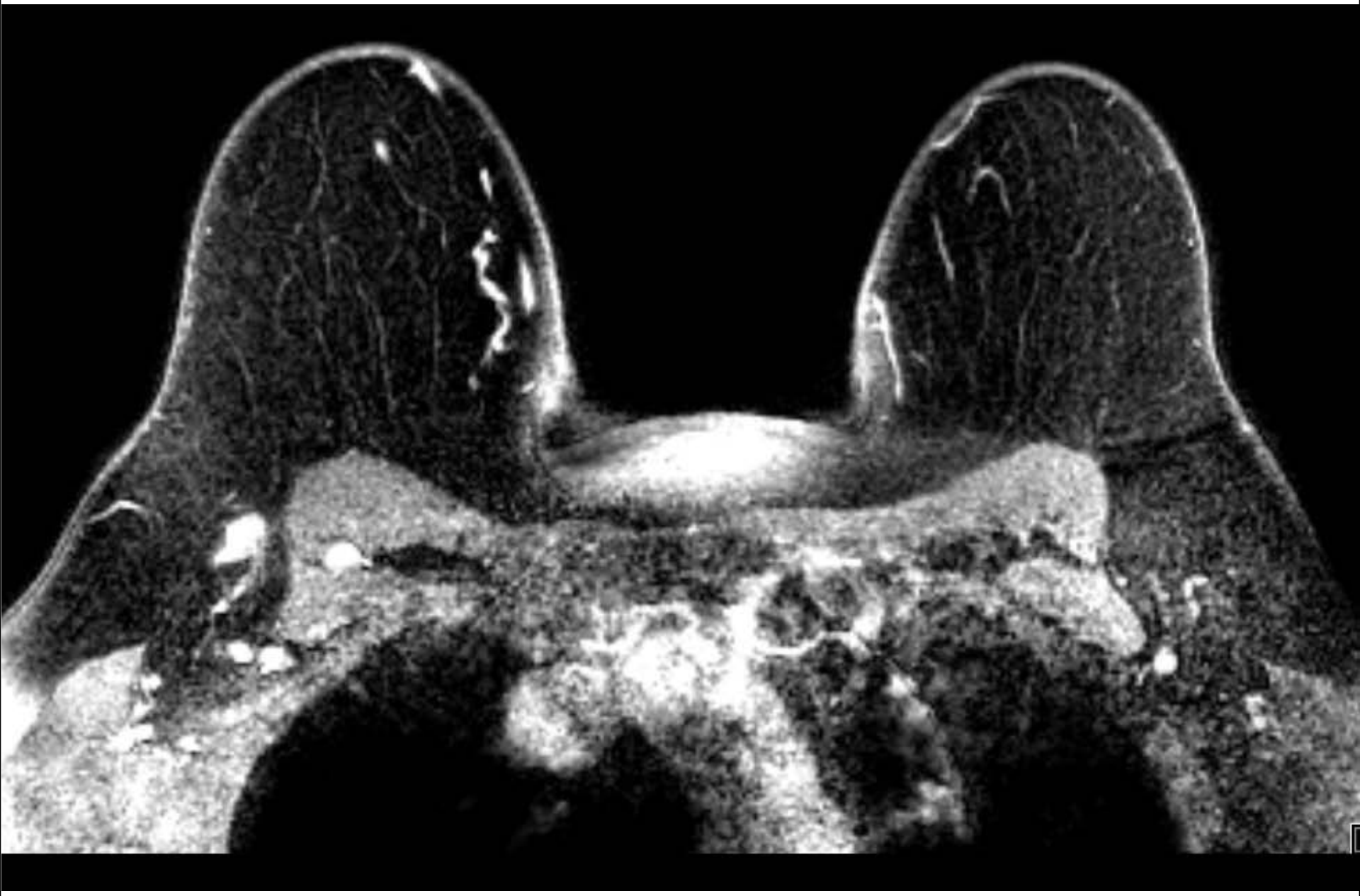
- Histology right breast: infiltrating ductal carcinoma, grade 3, ER10%, PR1%, HER2 positive
- FNA right axilla: metastases

- MRI:

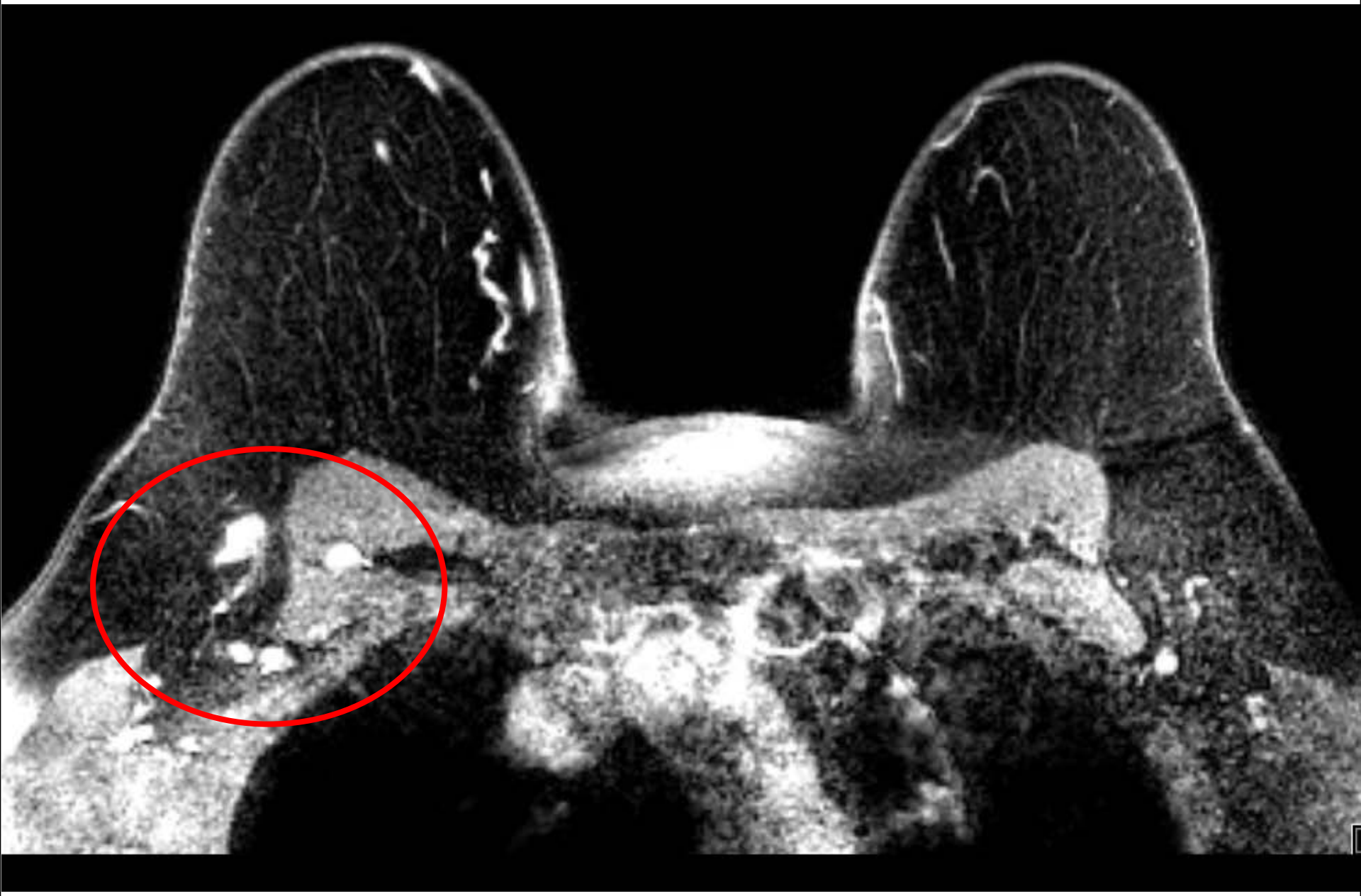
  1. tumor in right breast, 4 cm
  2. 2nd tumor in right breast, 18 mm, BIRADS-6.

  2 pathologically enlarged lymph nodes in right axilla
  interpectoral region: 2 enlarged lymph nodes
  internal mammary nodes: 1 enlarged lymph node

MRI



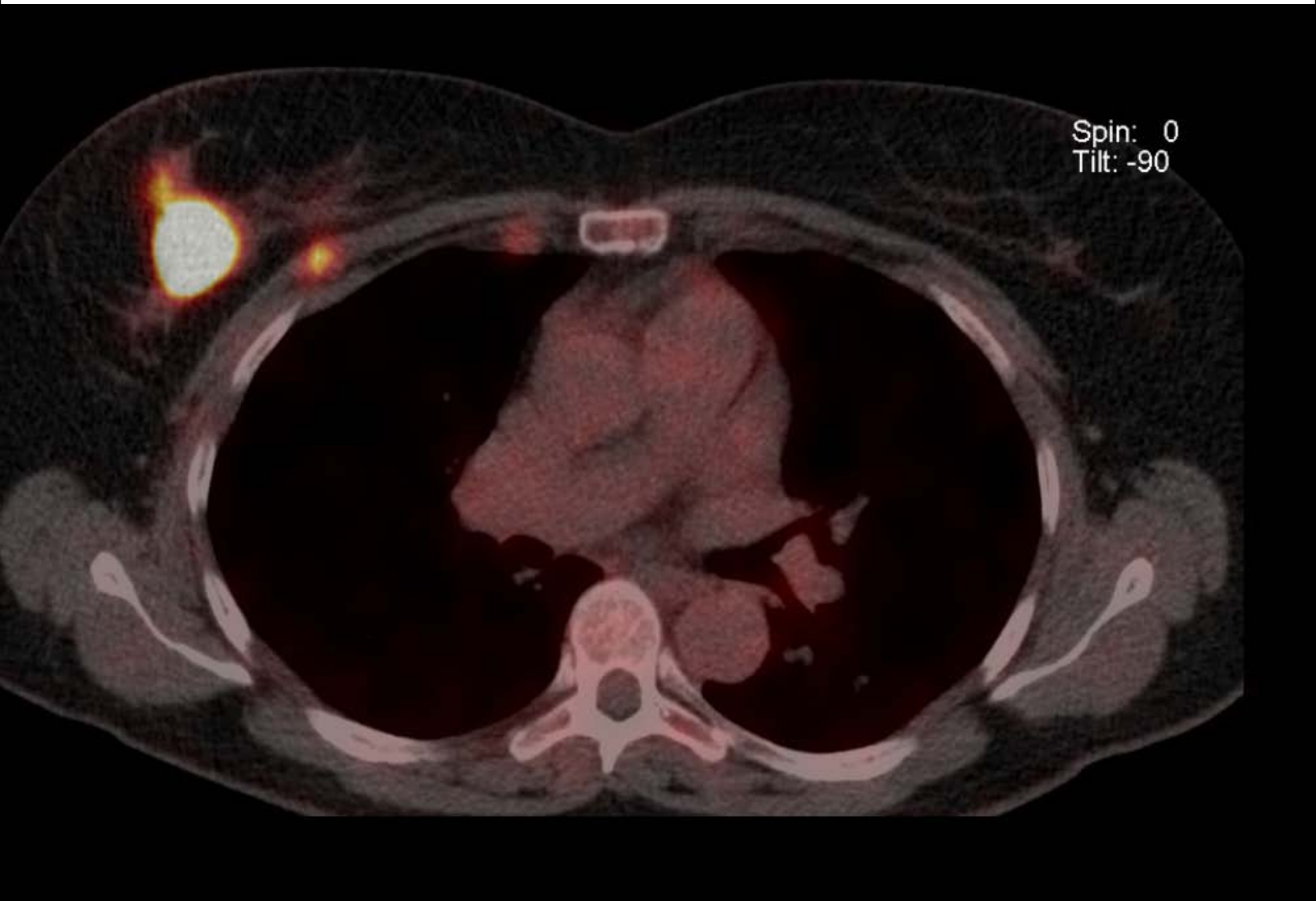
MRI



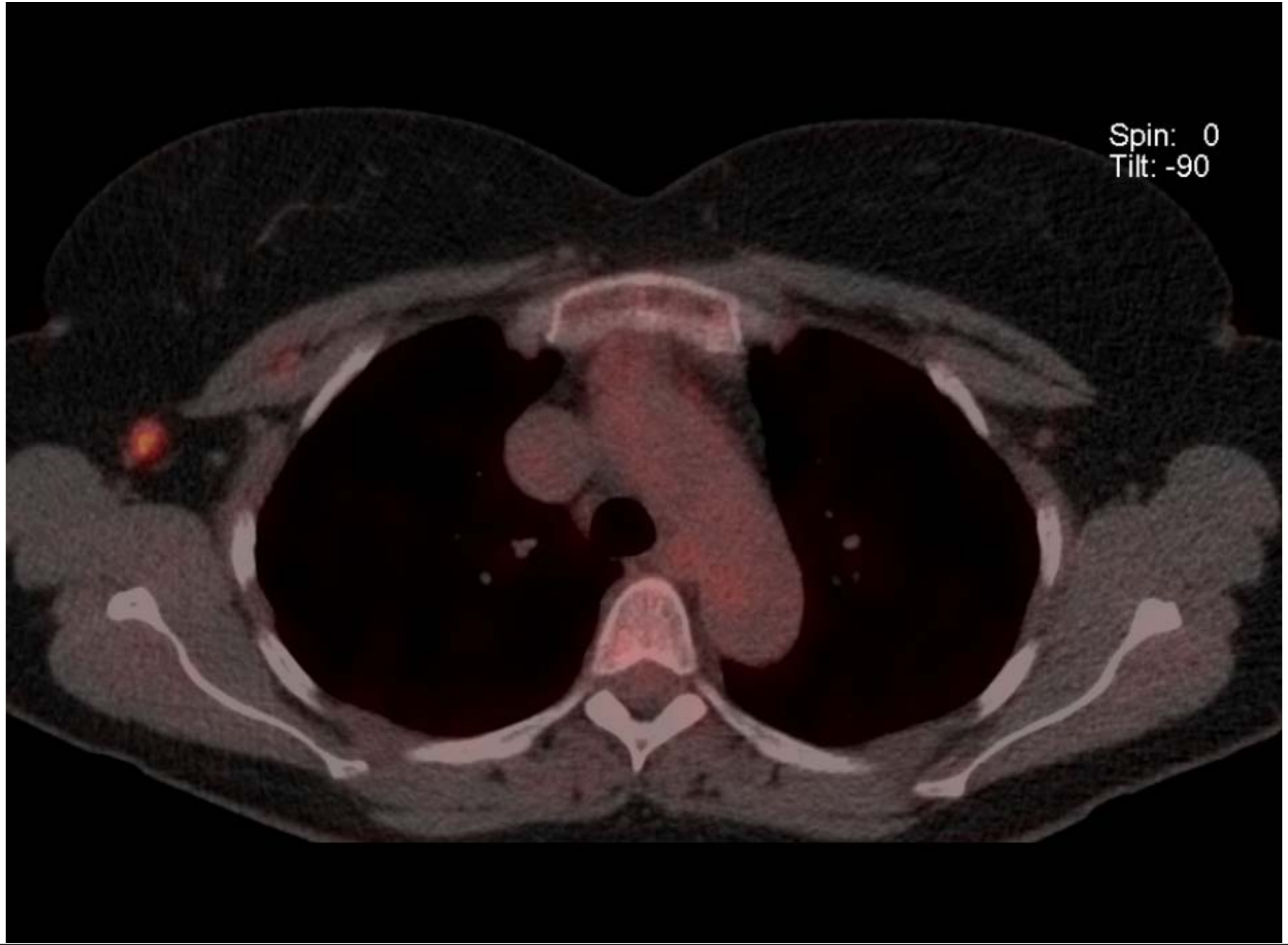
Mrs H, 54 years old

- ^{18}FDG-PET-CT, uptake:
  - in tumor right breast
  - in 2 lymph nodes in axillary region
  - in interpectoral region
  - in internal mammary nodes

^{18}FDG-PET-CT



^{18}FDG-PET-CT



Mrs H, 54 years old

- 18FDG-PET-CT, uptake:
  in tumor right breast
  in 2 lymph nodes in axillary region
  In interpectoral region
  In internal mammary nodes

Clinical stage: cT3N3bM0 right breast

Mrs H - Treatment

- **Neo-adjuvant systemic therapy**

  until January 2016 (chemotherapy and immunotherapy)

- Imaging after neo-adjuvant systemic therapy:

  MRI: complete response

  ^{18}FDG-PET-CT: complete response

Mrs H - Treatment

- **Neo-adjuvant chemotherapy** until January 2016

- **Breast-conserving surgery including MARI-procedure and sentinel node procedure**

  Microscopy: no vital tumor cells

  4 lymph nodes: tumornegative

→ Pathologically complete respons: ypT0N0

- Locoregional RT 16x2.66 Gy:

  Breast

  Axilla level I –IV (Level IV: supraclavicular region)

  internal mammary nodes

Locoregional RT – Organs at risk

Organ at risk	Acute toxicity	Late toxicity	Dose constraint
Skin	radiation dermatitis	Teleangiectasia	ALARA*
(Contralateral) breast	oedema	tumor induction, teleangiectasia, fibrosis	ALARA* *< 1 Gy if age ≤ 40 year* *< 5 Gy if age > 40 year*
Heart	pericarditis	valvular dysfunction cardiomyopathy atherosclerosis	V10Gy < 5%, V5Gy < 10%, mean heart dose < 3 Gy (V25 < 10%)
Lungs	radiation pneumonitis	lung fibrosis	Mean lung dose < 7 Gy
Esophagus	radiation esophagitis	stenosis, fistula	ALARA* (Dmean < 45 Gy)
Spinal cord		myelopathy	Dmax 50 Gy (α/β 2)
Brachial plexus		plexopathy (paralysis)	Dmax 66 Gy (α/β 2)
Upper extremity (musculature)	Pain, limited mobility, oedema		ALARA*

*ALARA: As Low As Reasonably Achievable

Breast planning – session objectives

- Target volumes
  - Breast
  - Axillary levels I-IV
  - Internal mammary lymph nodes
- Dose: 42.56 Gy in 16 fractions
- V95% PTV's > 99%
- Techniques:
  - 3D CRT /
  - Forward IMRT /
  - VMAT /
  - Tomotherapy /
  - Hybrid technique

IMRT treatment planning parameters

or

20 tips and tricks for happy IMRT planning

Gert Meijer

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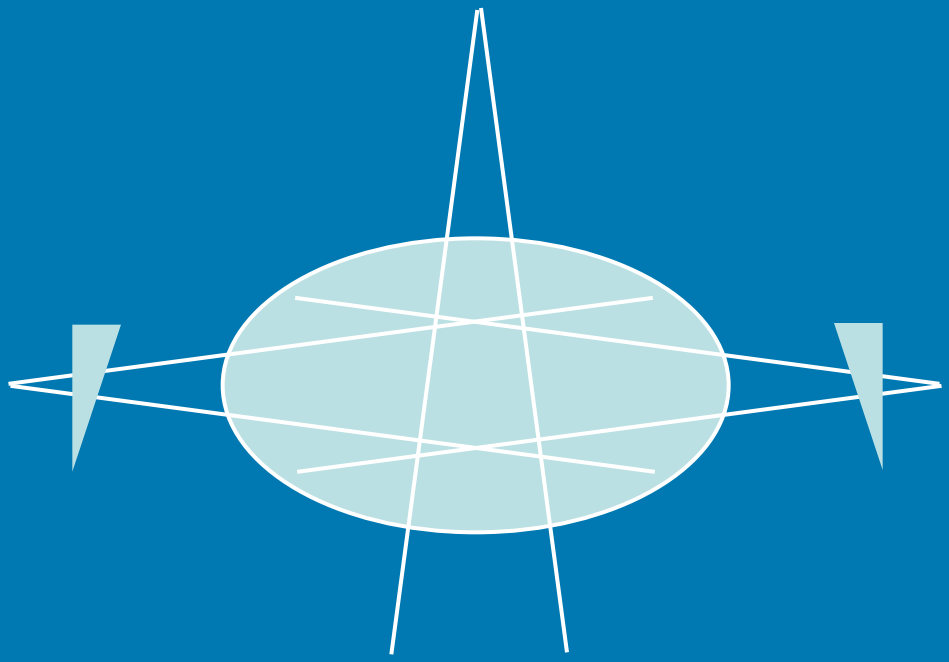
Optimalisation 3DCRT

- gantry angle
- beam weight
- wedge
- collimator angle
- beam energy



5 degrees of freedom

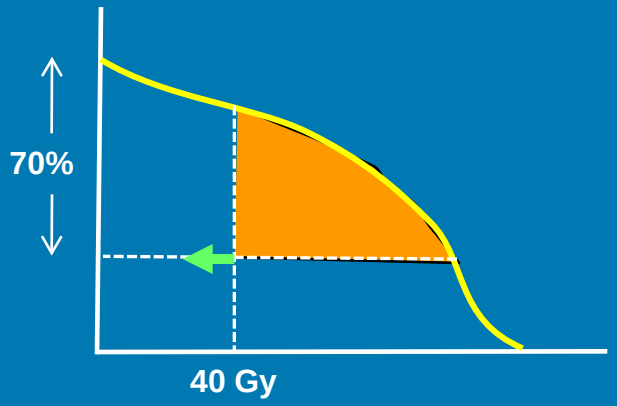
Optimalisatie IMRT

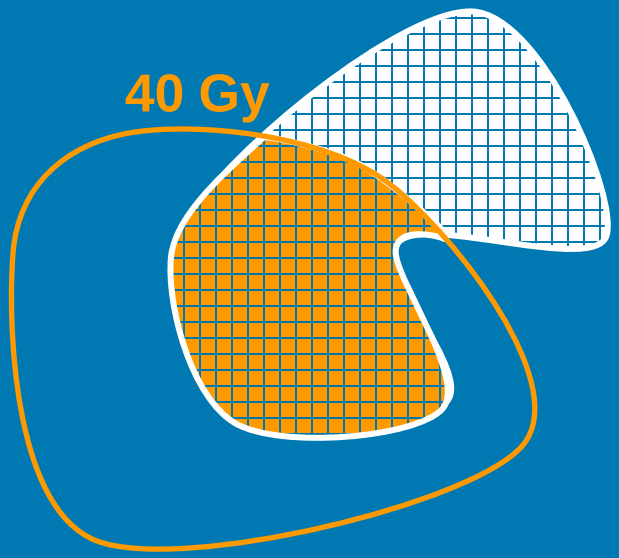
- ~~gantry angle~~
- beam weight
- ~~wedge~~
- ~~collimator angle~~
- ~~beam energie~~

- fluence profile

2000 degrees of freedom

Eclipse	iPlan	OnCentra	Pinnacle	RayStation	Tomotherapy	XiO	Monaco
physical dose volume parameters quadratic cost functions	physical dose volume parameters quadratic cost functions	physical dose volume parameters quadratic cost functions	physical dose volume parameters quadratic cost functions	physical dose volume parameters quadratic cost functions	physical dose volume parameters quadratic cost functions	physical dose volume parameters quadratic cost functions	physical dose volume parameters
dose conformality shaping functions	dose conformality shaping functions	dose conformality shaping functions					dose conformality shaping functions
biological cost functions		mean dose	equivalent uniform dose	equivalent uniform dose			biological cost functions





70% should receive 40 Gy or less

70%

30%

33	0
35	0
36	0
38	0
39	0
41	$1/7\times(1/40)^2$
42	$1/7\times(2/40)^2$
43	**1/7×5/1600**
49	

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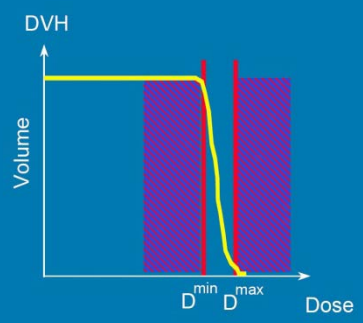
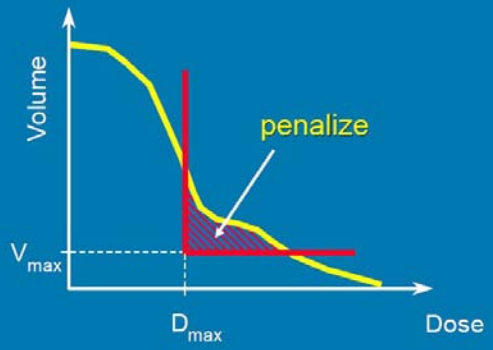
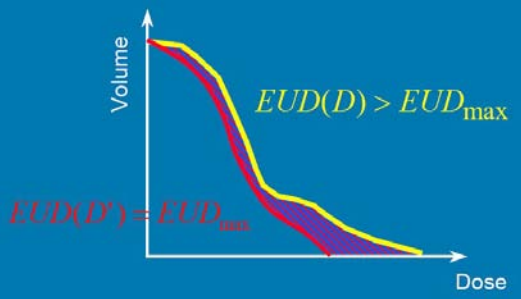
Optimization

$$F = w_{\text{Target}} F_{\text{Target}} + w_{\text{Risk1}} F_{\text{Risk1}} + w_{\text{Risk2}} F_{\text{Risk2}} + \cdots$$







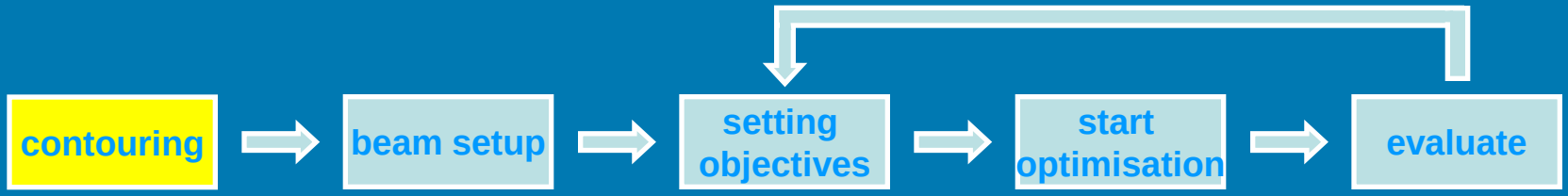
20 tips and tricks for happy IMRT planning

1

make sure your delineations are accurate

your plan outcome directly relates to DVHs and therefore to your volumes

Be careful when creating the CTV using automatic expansion tools that you do not extend into regions that are not clinically appropriate, such as bony compartments. The CTV should be trimmed to avoid targeting tissues unnecessarily



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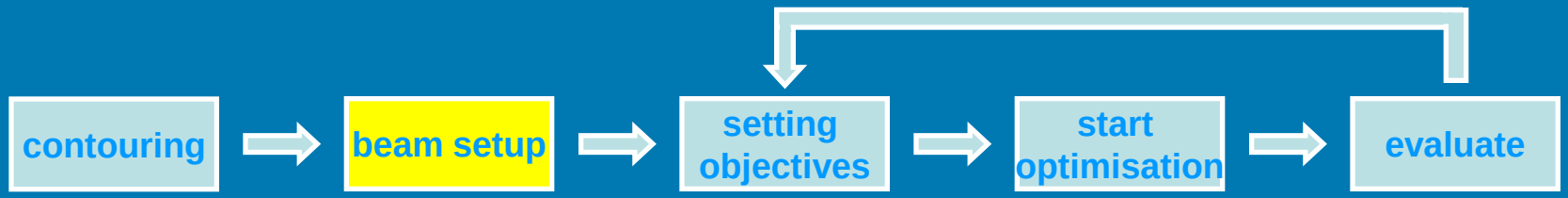
2

place your isocenter in the center of all PTVs

this is not that critical but this generally narrows the amount of a-symmetry for your segments and you may end up with more reliable dose calculations



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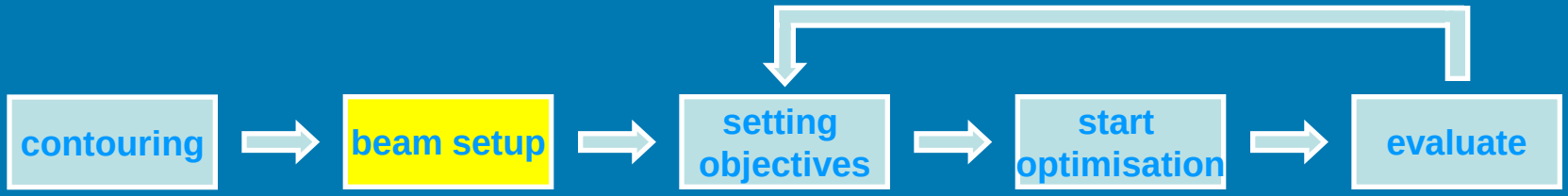
3

start with an odd number of equidistant beams

but always remember that steep dose gradients can **ONLY** be obtained perpendicular to beam axes just like in 3DCRT

IMRT is not some magic tool, there is still always physics, photons are uncharged particles and they just don't bend around corners no matter what



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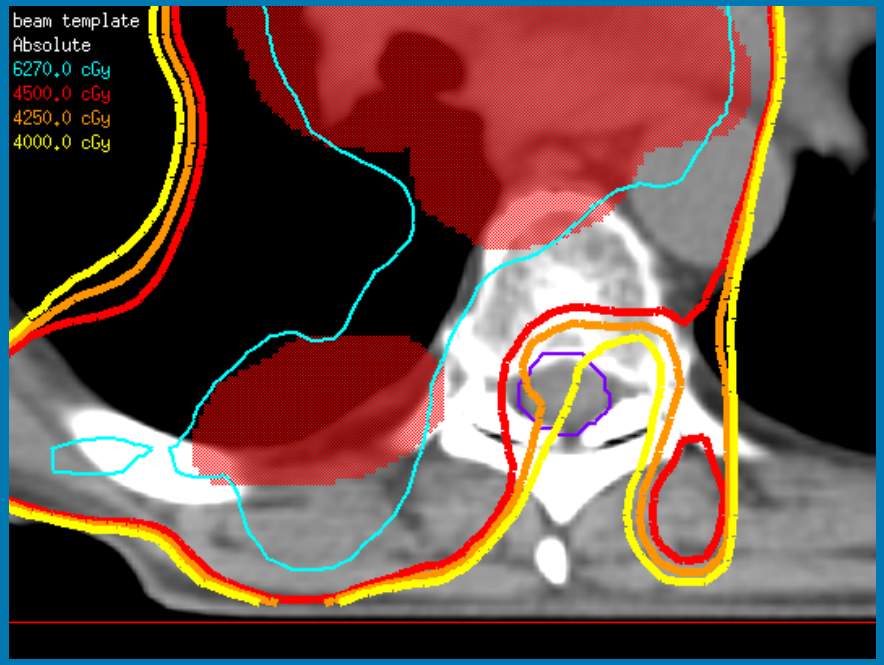

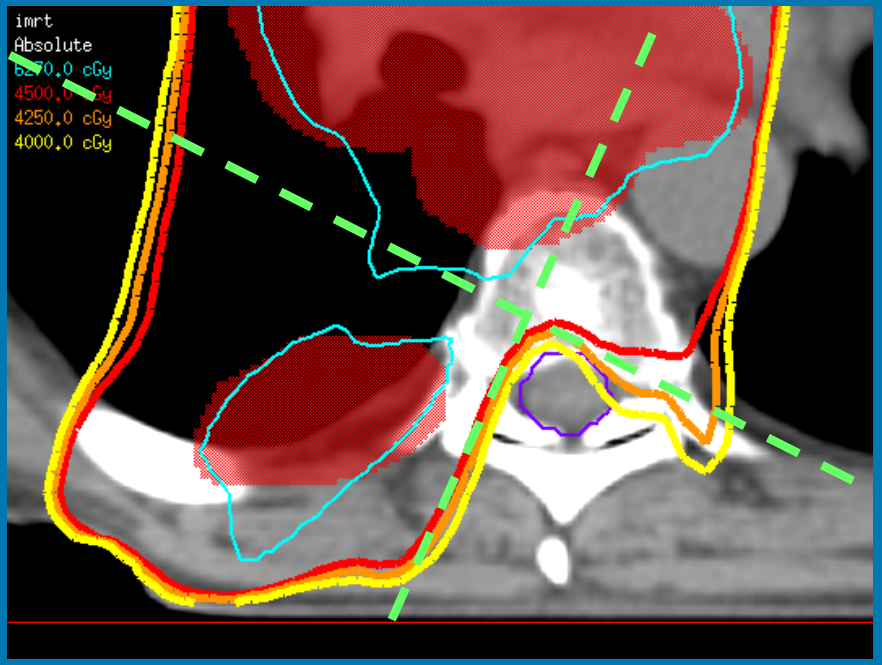

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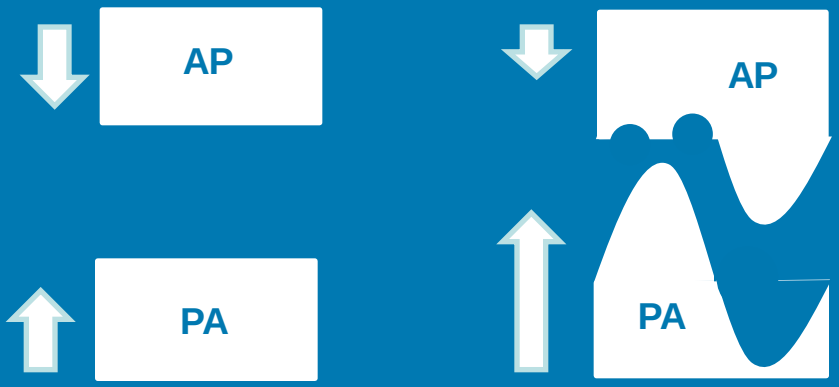
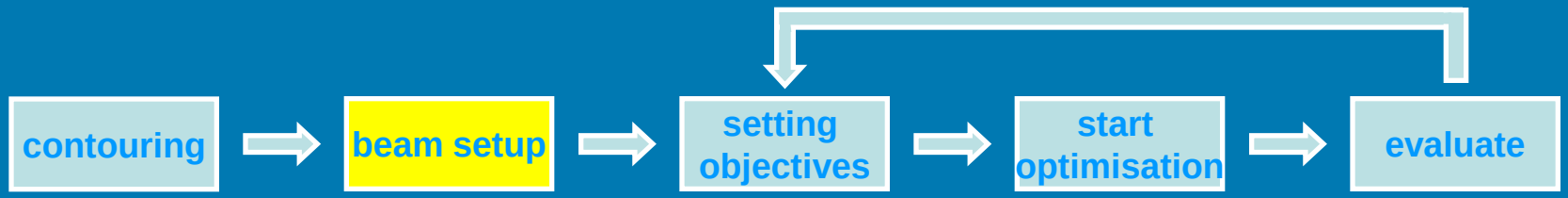
4

avoid opposing beams is this will not optimally increase your solution space





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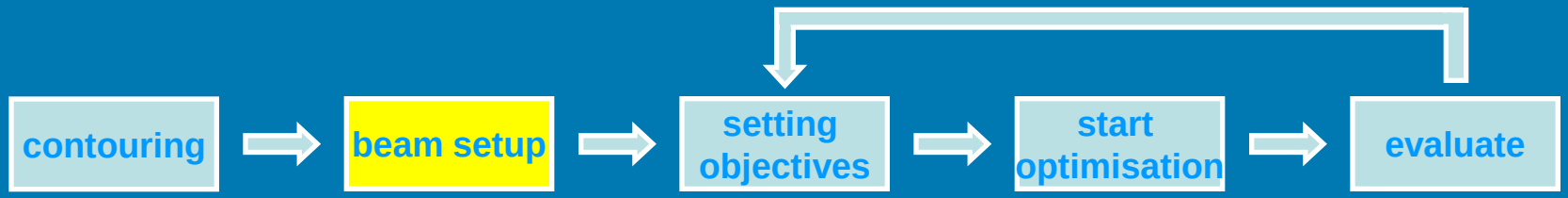
5

adding beams increases solution space, optimization time but not necessarily treatment time

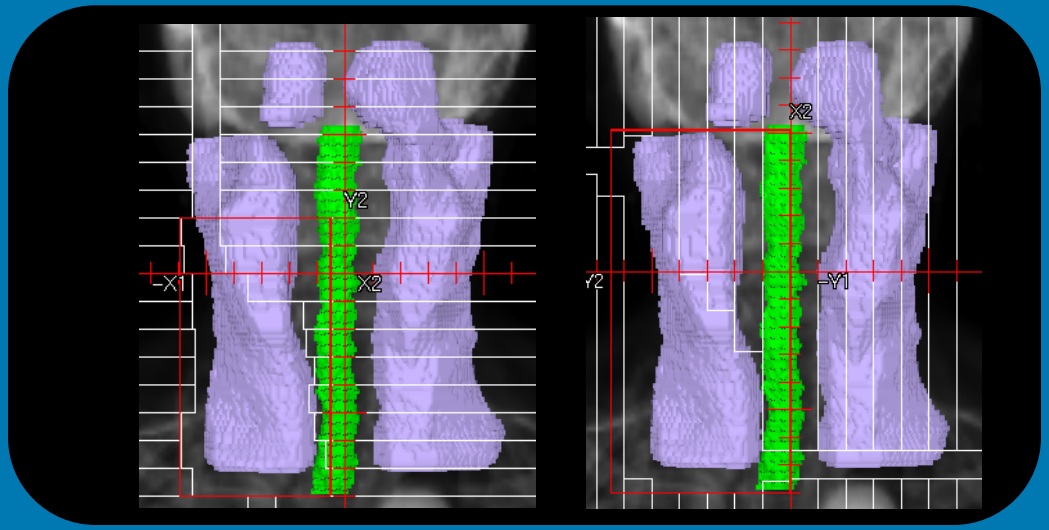
typical numbers:
- **5 beams: prostate, bladder**
- **7 beams: lung, head and neck**
- **9 beams: complex cases**

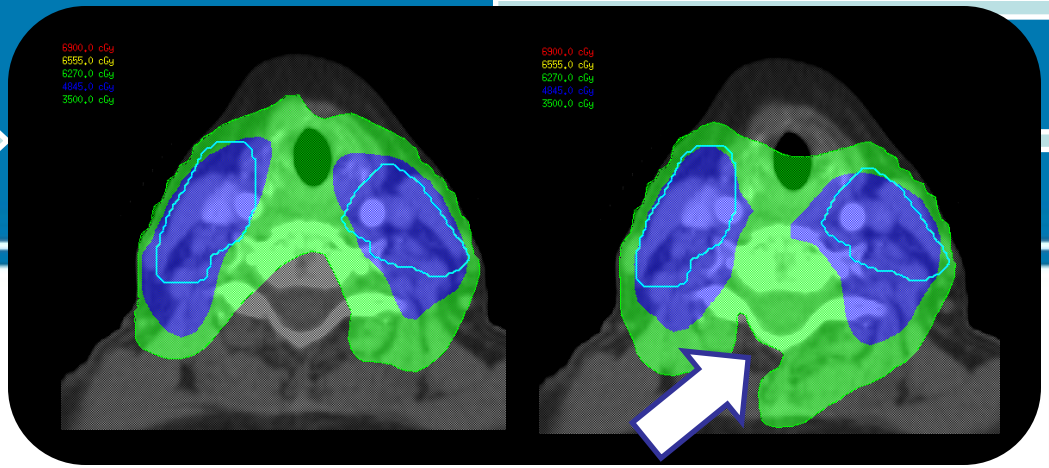


20 tips and tricks for happy IMRT planning

6

collimator angle: generally have your leaves run perpendicular to the outlines of your PTVs and OARs



contouring →  → evaluate

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7

create optimisation structures next to evaluation structures

Avoid (optimisation) PTVs that extend into the buildup region unless it is clinically appropriate. This prevents the optimizer from creating very high intensities to account for the low dose region. If the target does extend close to the skin surface, then bolus should be used in that area.

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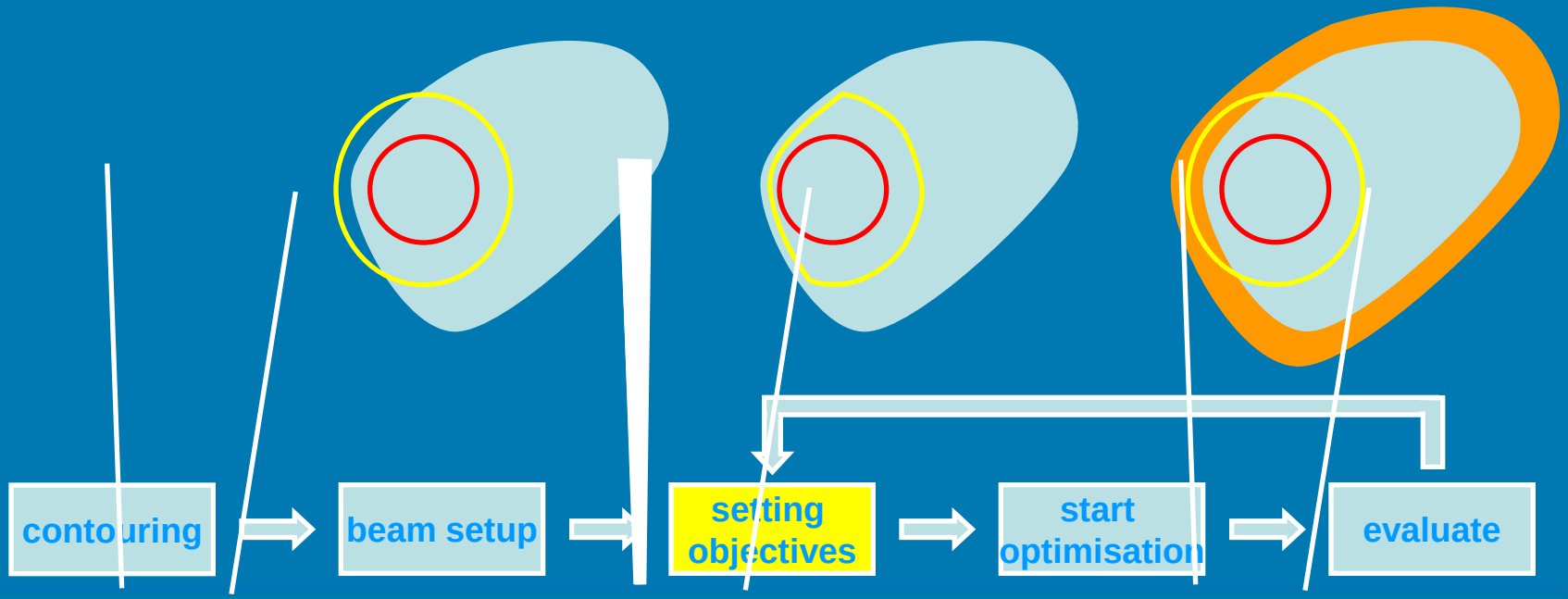
8

create optimisation structures next to evaluation structures



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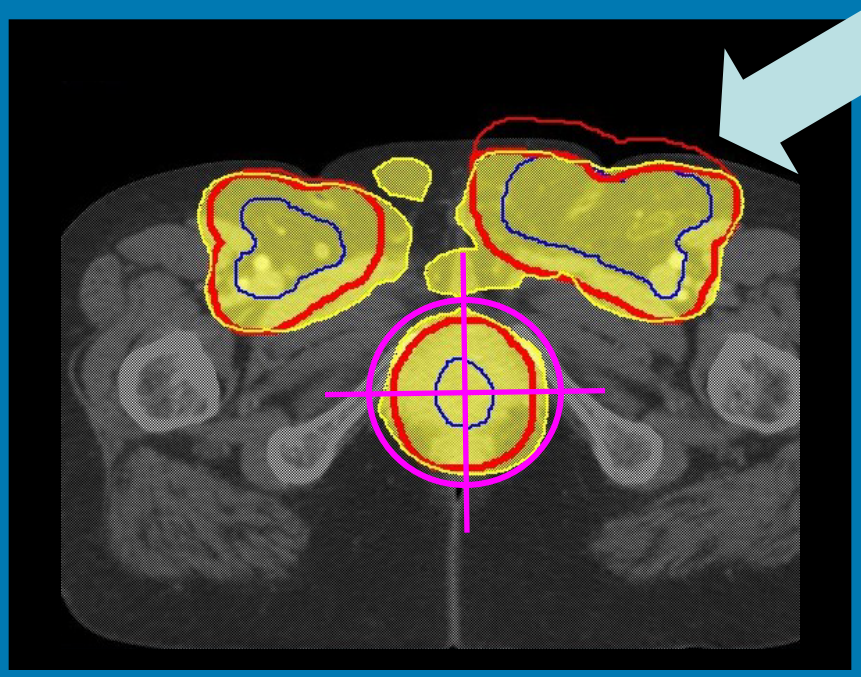
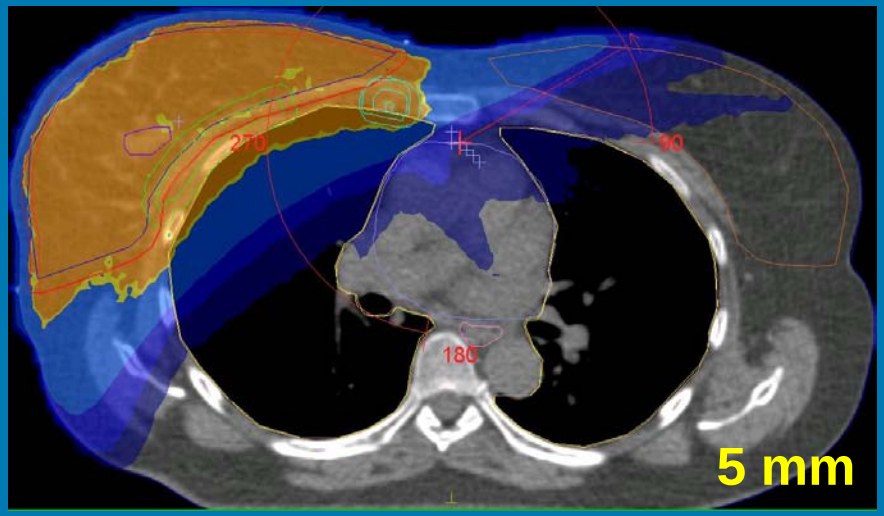
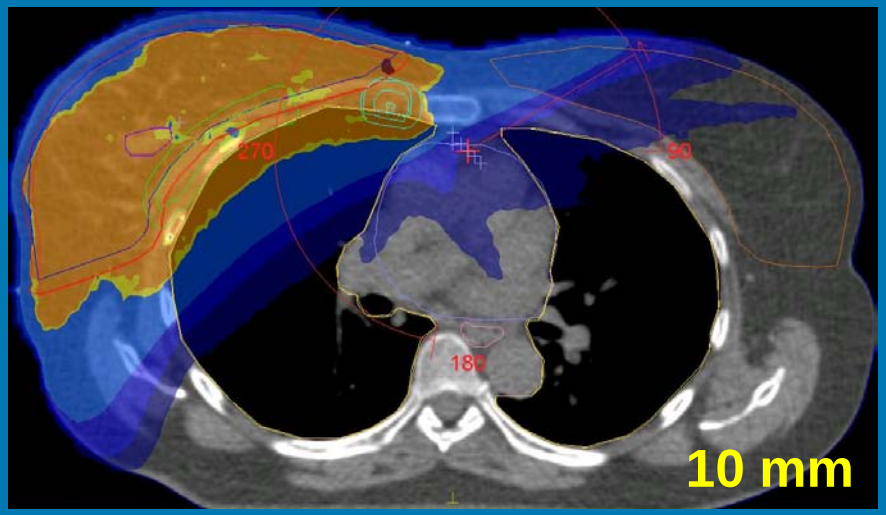
9

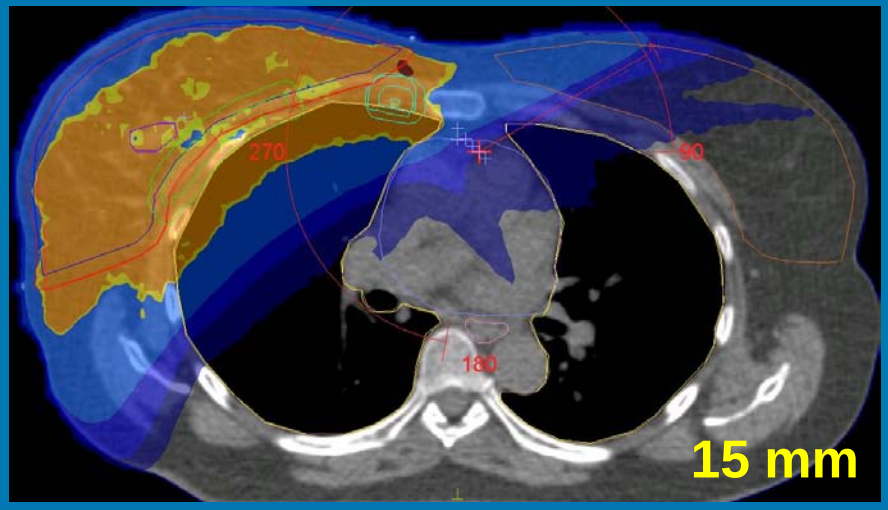


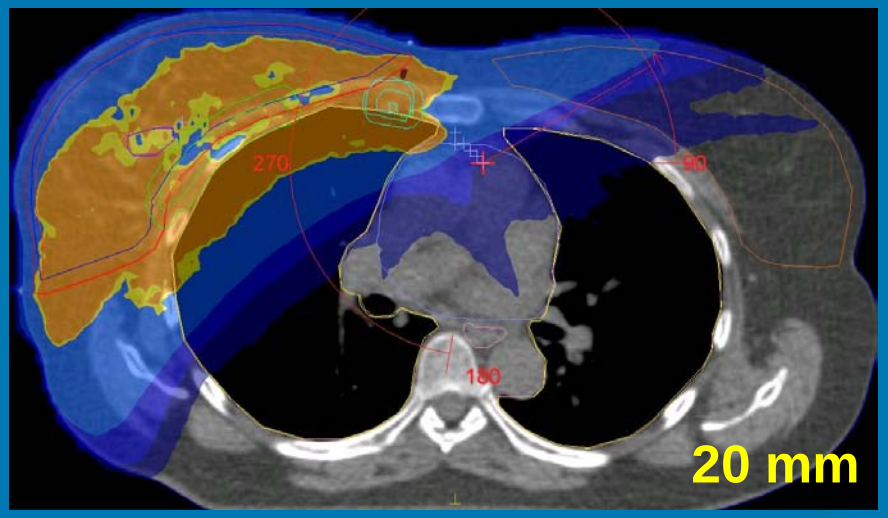
target near skin moves up to 2cm but is still reasonably well covered

contouring → beam setup → setting objectives → start optimisation → evaluate









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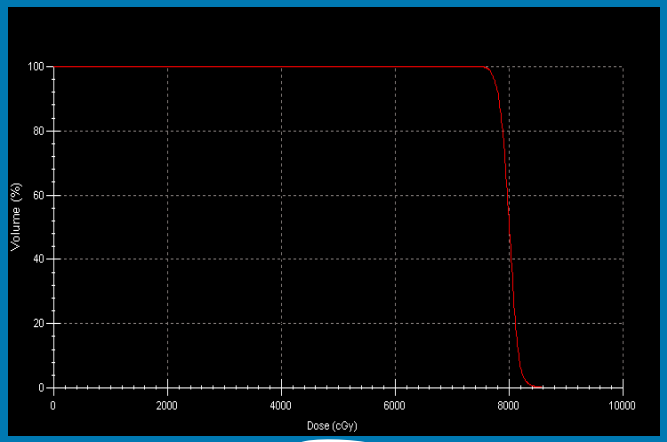
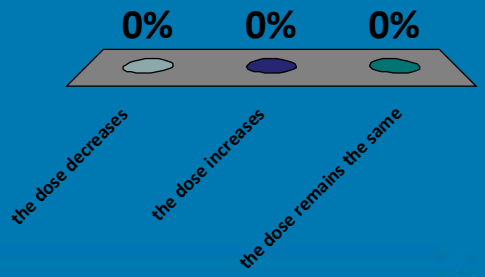
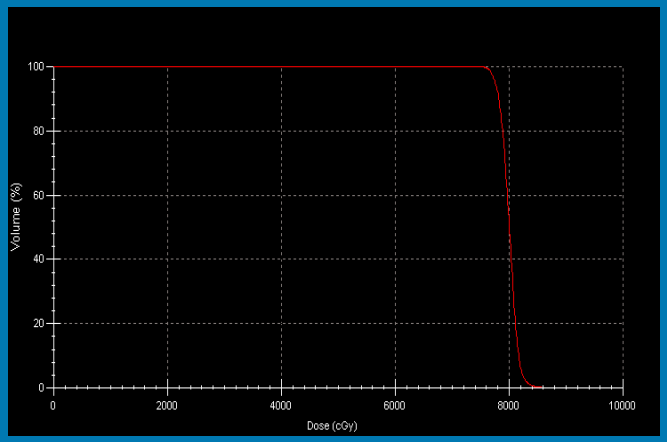
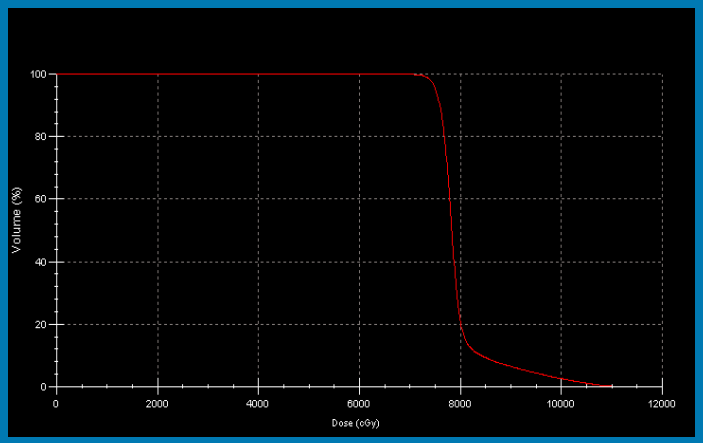


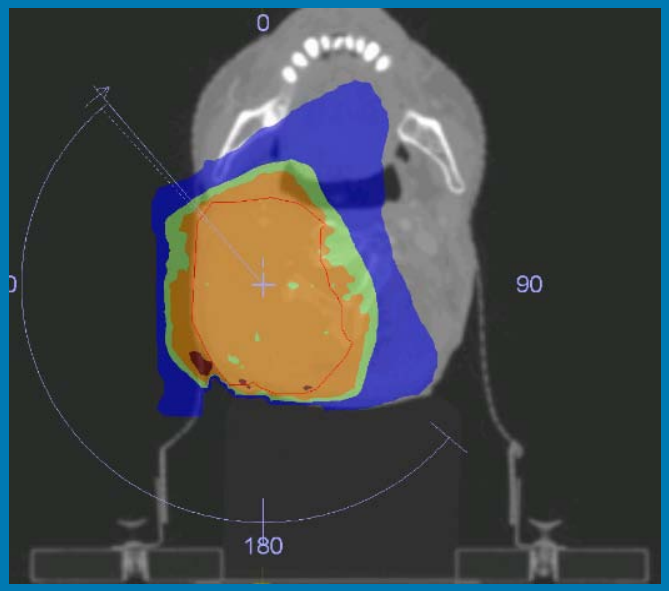
what happens to the dose in the posterior part of PTV when the patient is shifted 1 cm dorsally?

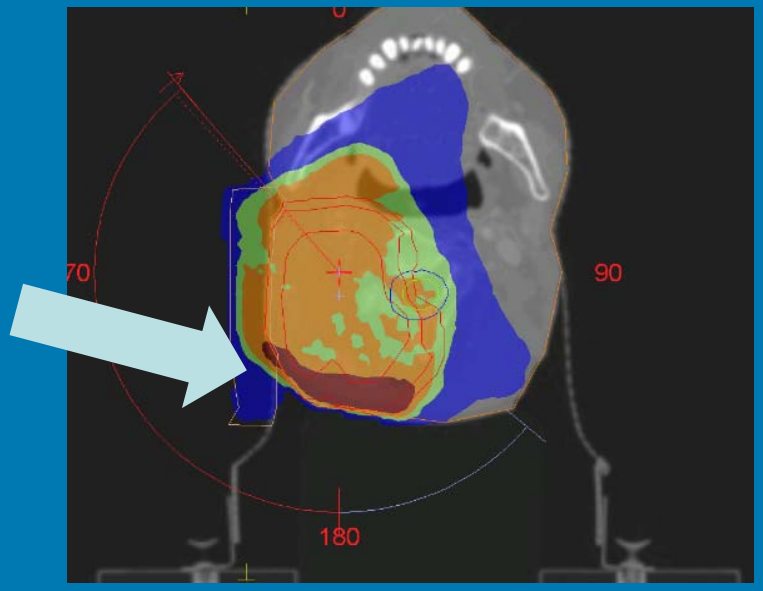
A. the dose decreases
B. the dose increases
C. the dose remains the same











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20 tips and tricks for happy IMRT planning

10

avoid voxels with conflicting objectives

create some hierarchy in your objectives in case a organ at risk has an overlap with your target volume. (some TPSs intrinsically rank the objectives)

conflicting objectives to the same voxels will increase to total cost and distract the optimiser from real optimisation problems

carefully chosen objectives will always yield a low total cost in the end of the optimisation

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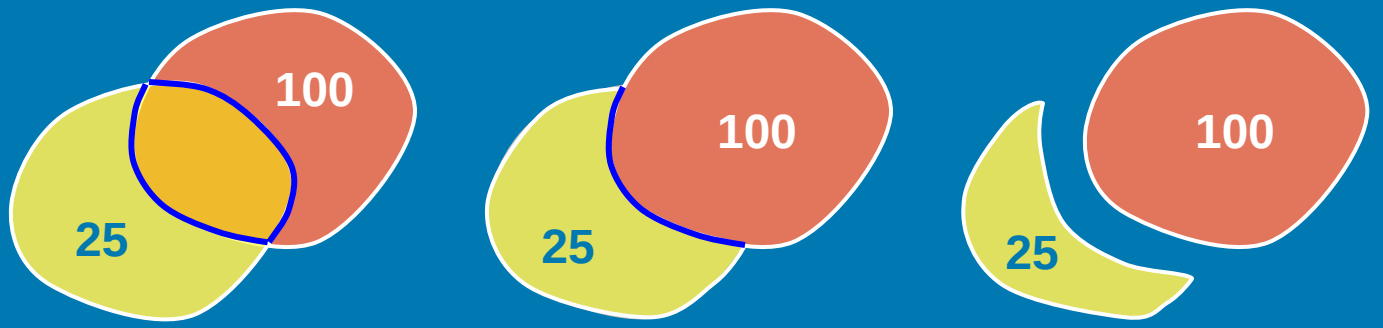
10

when target coverage has a higher priority than organ sparing



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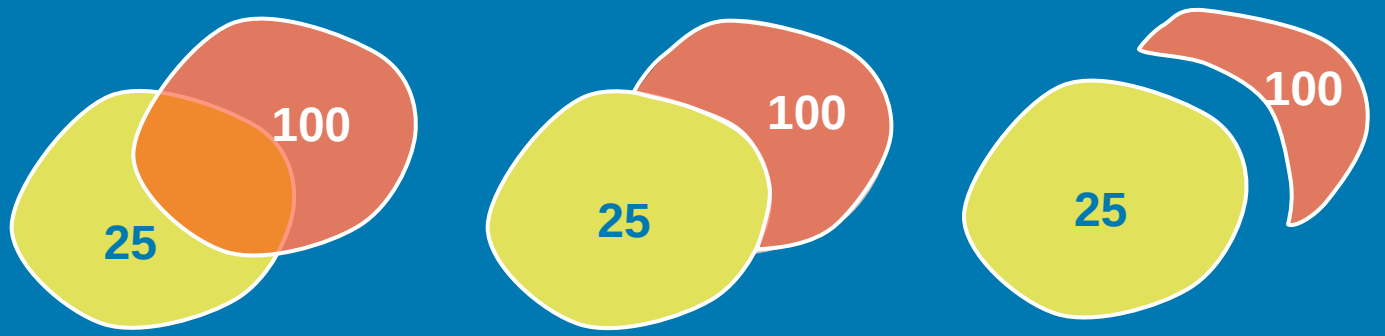
10

when organ function preservation has a higher priority than target coverage



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11

start of with high-weighted objectives at your targets and low-weighted objectives at your OARs

once your going downhill on the steep slope of organ a sparing you might get trapped into a local minimum and never reach your target dose

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20 tips and tricks for happy IMRT planning

12

try to minimise the use of constraints and rather use objectives with high weights

- from a radiobiology perspective there is no such thing a hard constraint
- hard constraints will generally slow down the optimization process and sometimes makes it instable
- hard constraints bias the total cost making it more difficult to judge your final result

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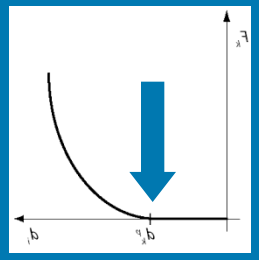
13

always set your IMRT objectives more stringent than your clinical objectives

for instance, if you require a mimimum dose to the PTV of 95% of the prescription dose than set an objective hat will penalise all PTV voxels that have dose lower than 98%



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14

use safety margins for critical OARs (e.g. spinal cord) to partially account for organ motion, patient movement and setup uncertainties

it is generally not recommended that you add margins around every critical structure

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try using ring structures to increase the conformality of the 95% isodose to your target

typically use a 7-mm to 10-mm margin between your PTVs and ring

(some TPSs have dose conformality tools that don't require extra ring structures)

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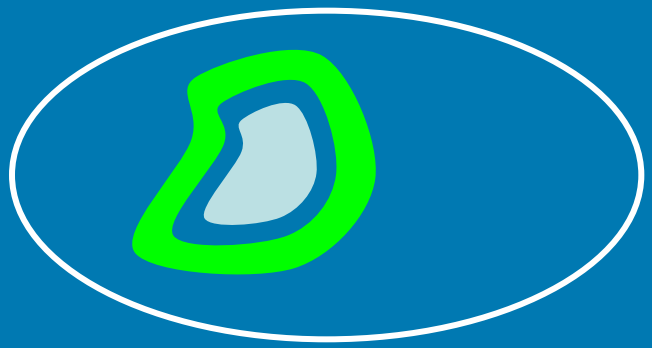

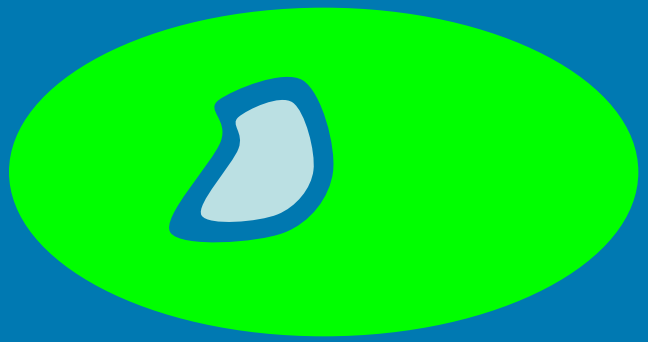

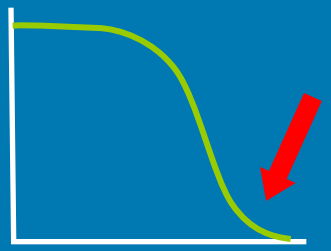

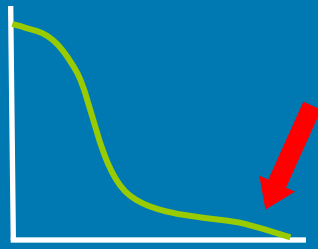

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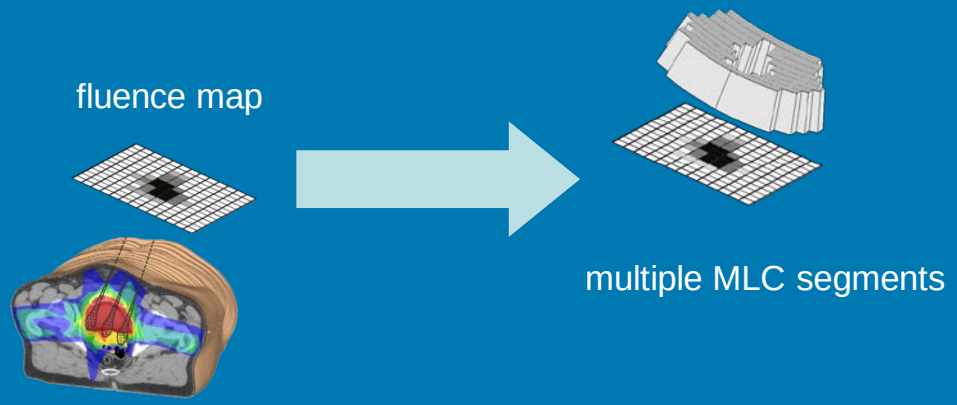
20 tips and tricks for happy IMRT planning



… and then at some point in our journey we need to convert the fluence map into MLC segments

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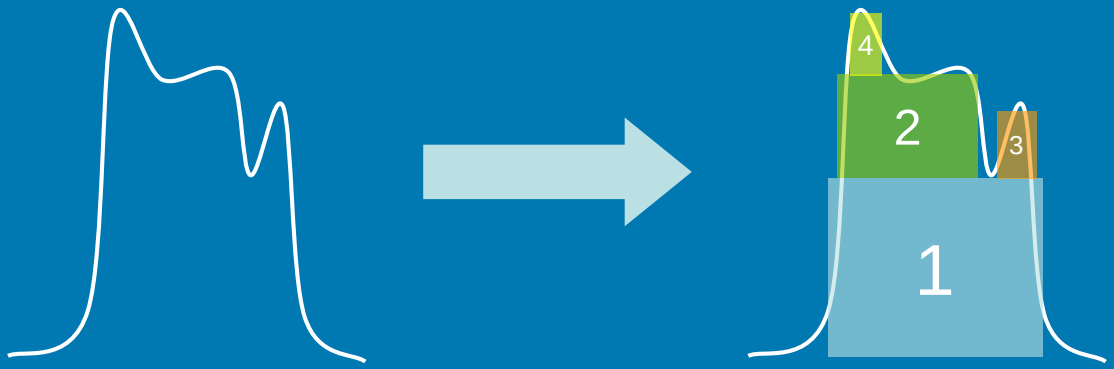
20 tips and tricks for happy IMRT planning



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20 tips and tricks for happy IMRT planning

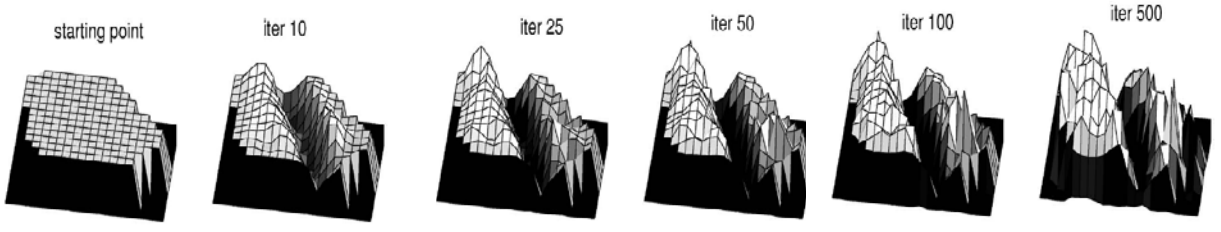
close in

sliding window

20 tips and tricks for happy IMRT planning

16

there is an optimum number of iterations for the point of segmentation (typically 8-20)



Carlsson and Forsgren, Med. Phys. 33(1) 225-234

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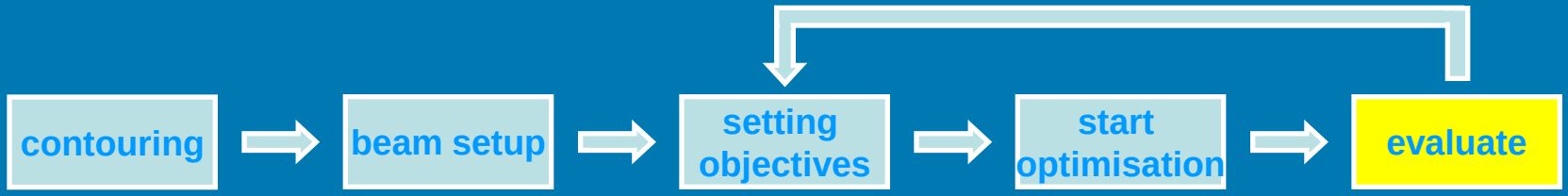
20 tips and tricks for happy IMRT planning

17

be critical towards objectives that do not contribute to the total cost after the optimisation

it is the task of the optimiser to minimise the total cost (not yours!)

objectives with zero contribution to the total cost could as well been left out since they have no influence on the final result



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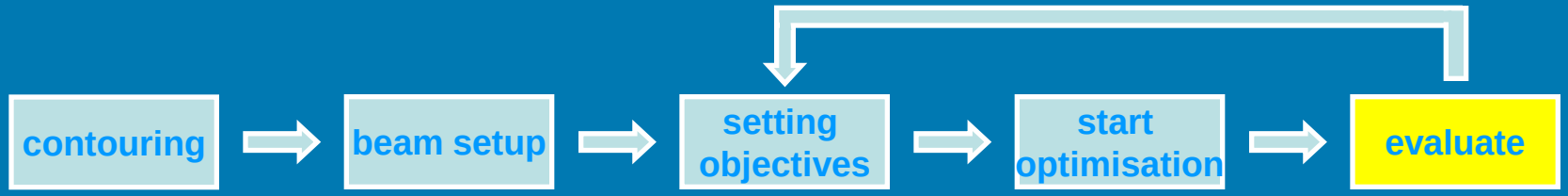
20 tips and tricks for happy IMRT planning

18

be critical towards objectives that highly contribute to the total cost after the optimisation

it is likely that the overall result of your optimization predominantly determined by these objectives

(for instance if you have a min dose objective to a structure in the build-up region, a high cost might alarm you)



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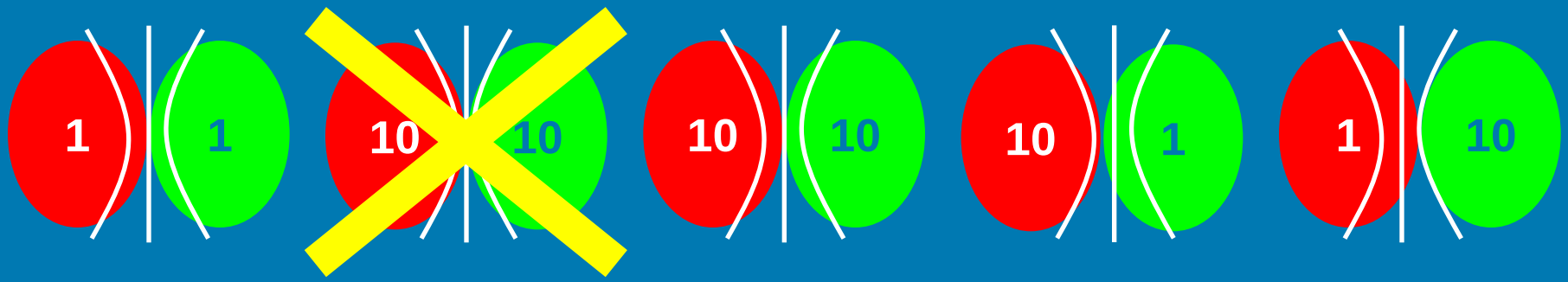
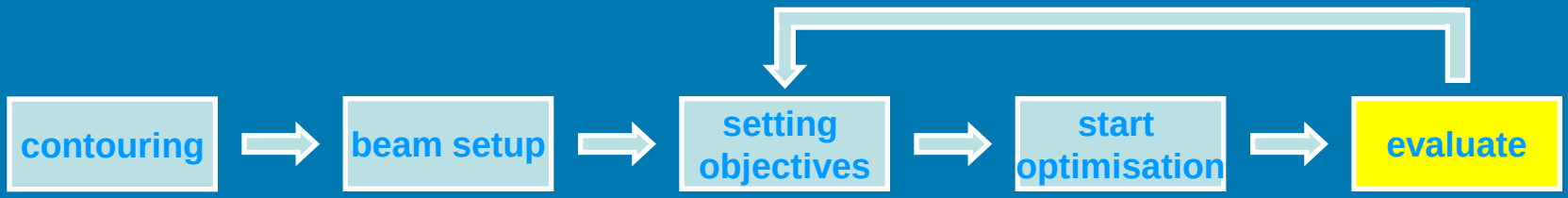
20 tips and tricks for happy IMRT planning

19

adjusting weights generally causes a shift of the dose gradient between the target and organ at risk rather than an increase of the dose gradient





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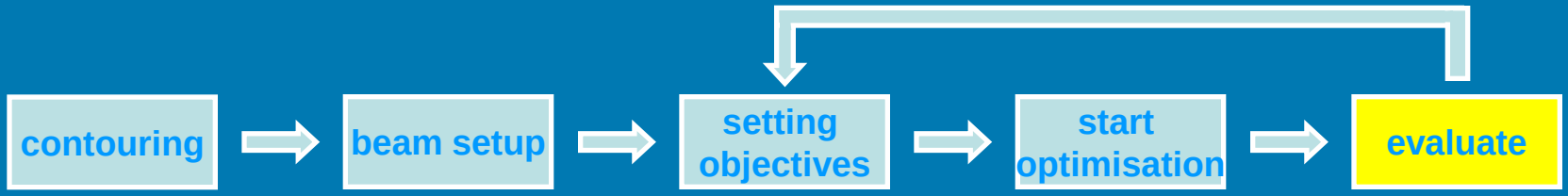
20 tips and tricks for happy IMRT planning

20

you may try defining small dummy structures at small persistent high or low dose regions

but most likely you will move the problem to another area;
sometimes you feel like playing with balloon with water;



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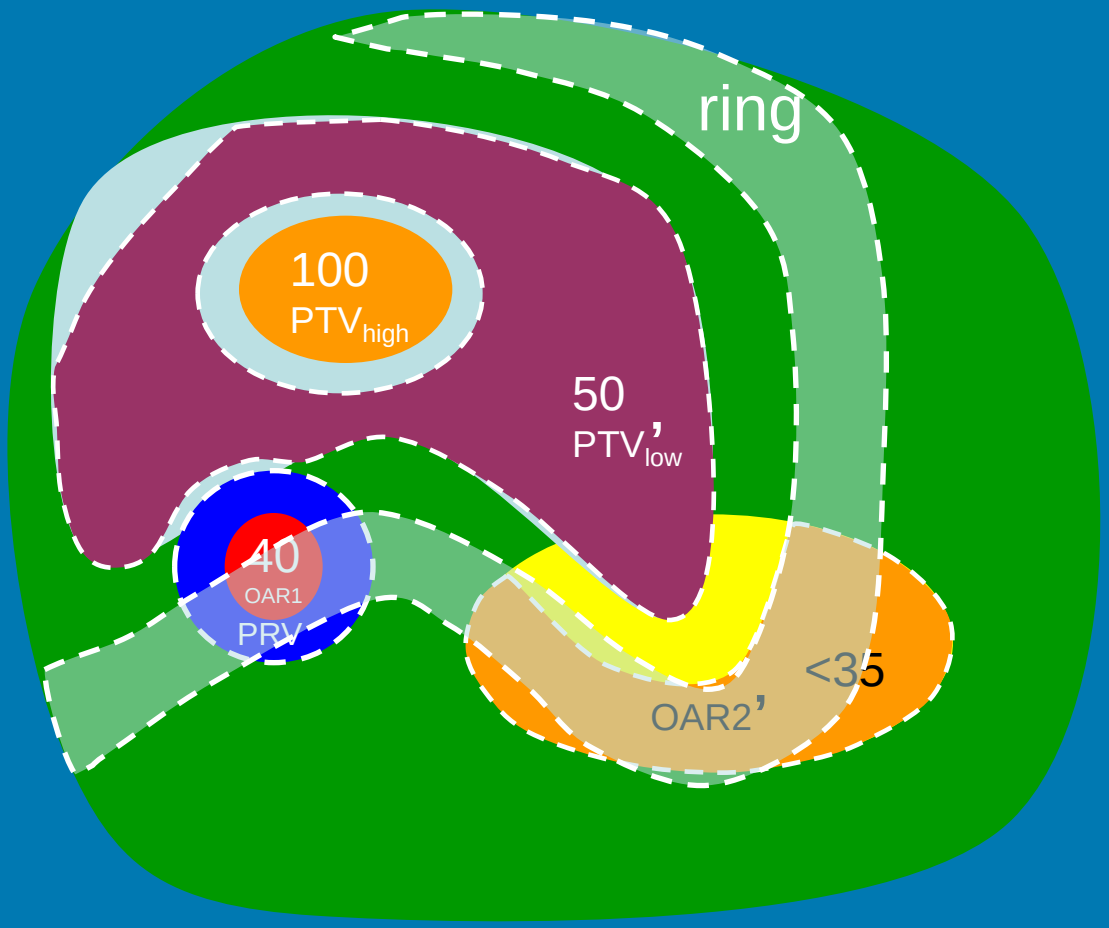

high priority

low priority

PRV	max dose	39
PTV$_{high}$	min dose	97
PTV$_{high}$	max dose	105
PTV'$_{low}$	min dose	49
PTV'$_{low}$	max dose	57
OAR2'	max dose	35
ring	max dose	30

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Conclusions

- try thinking how the optimiser thinks, imagine you descending in the multidimensional world
- developing good objectives and constraints is an iterative process.

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Practical aspects of IMRT planning part 2

Advanced Treatment Planning Course
14-18 September 2016 – Cambridge, UK

Markus Stock

MedAustron ESTRO School

Content

- number of beams, class solutions
- beam angle optimization
- energy
- MLC geometry, limitations
- collimator angle
- leaf width
- # of MU in IMRT planning
- isocenter position
- IMRT as efficiency tool for ‘simple 3D-CRT’

Number of beams, class solutions

standard number of beams is often applied to specific treatment sites:

- 3,5 or 7 beams in prostate treatment
- 5,7,9 beams in head and neck treatment

class solution = ‘group average’ set of constraints, number of beams and beam angles (for an ‘average’ patient!?)

→ consider class solutions a good starting point
look at differences between this patient and the group
(different shape, rotations, etc.)

Number of beams, class solutions

- when an IMRT plan is getting complicated: try to add a beam!

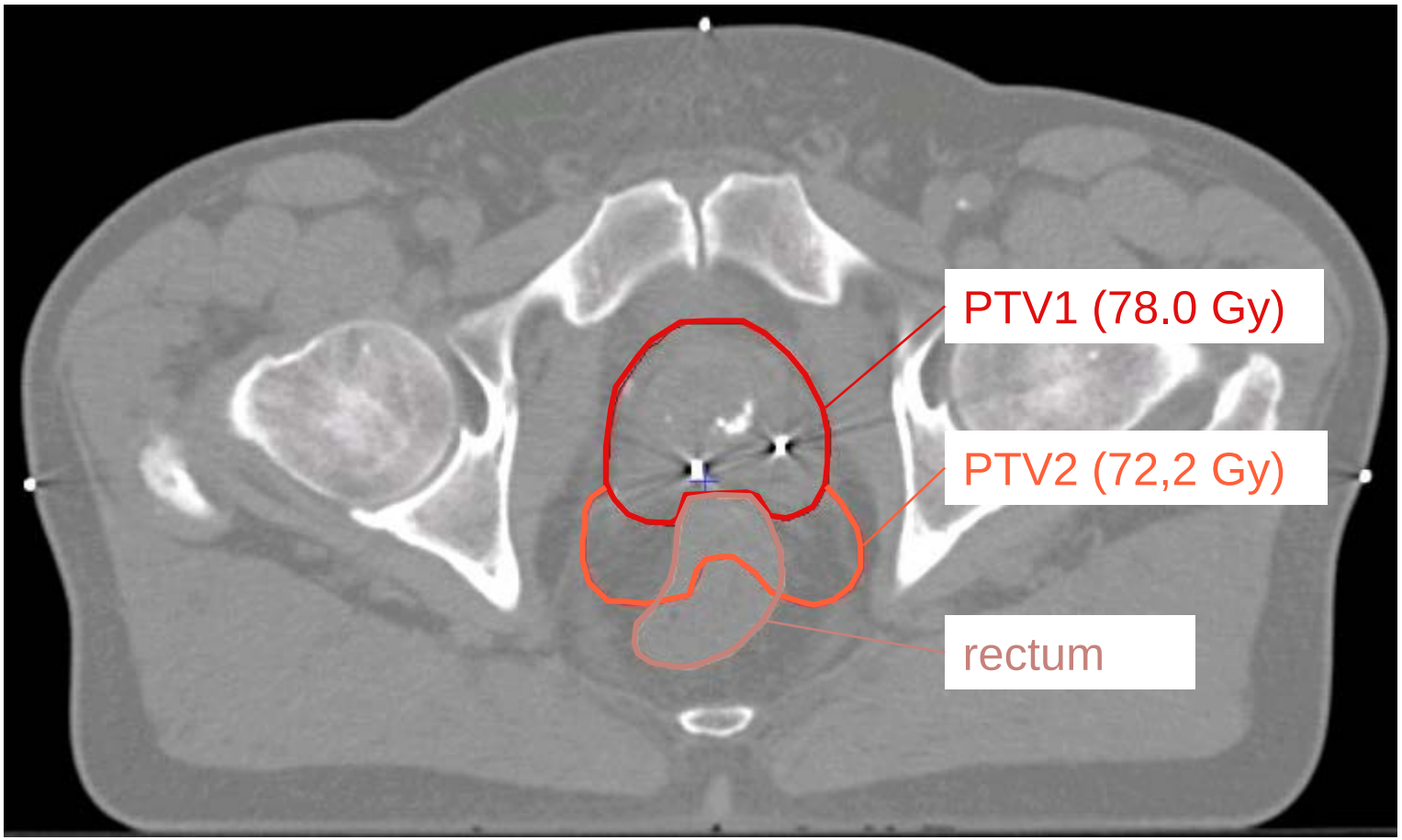
  more beams results in:

  - more degrees of freedom for the optimizer
  - (often) less modulation per field, so easier to segment

more beams will not automatically result in more treatment time!

prostate planning: 5 vs 7 beams

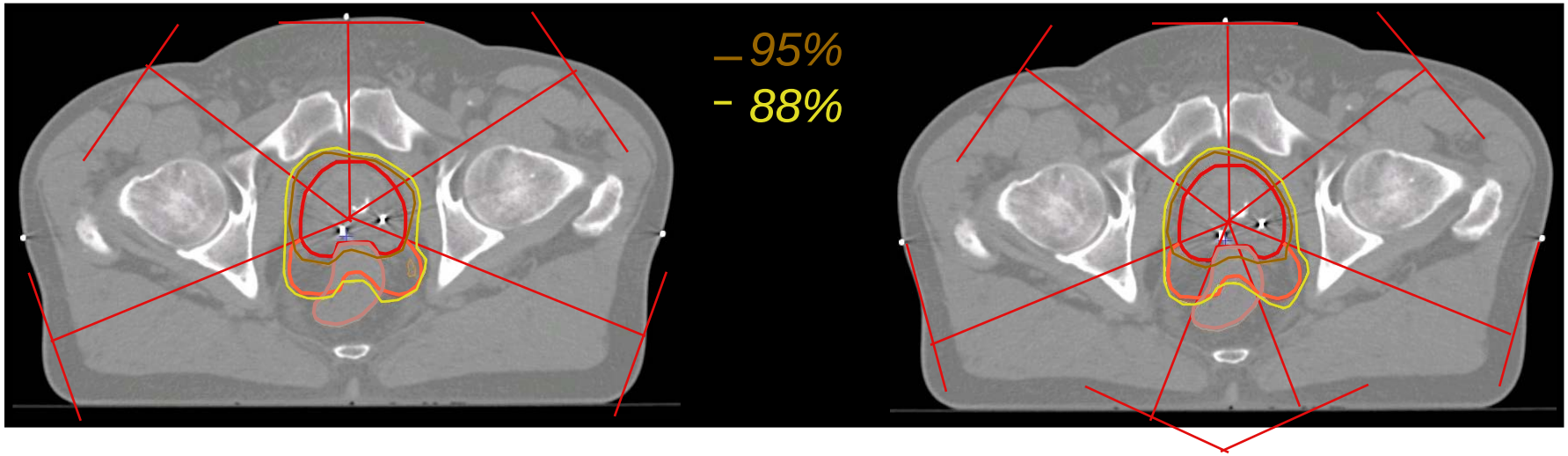
- SIB planning



prostate planning: 5 vs 7 beams

5 beams

7 beams



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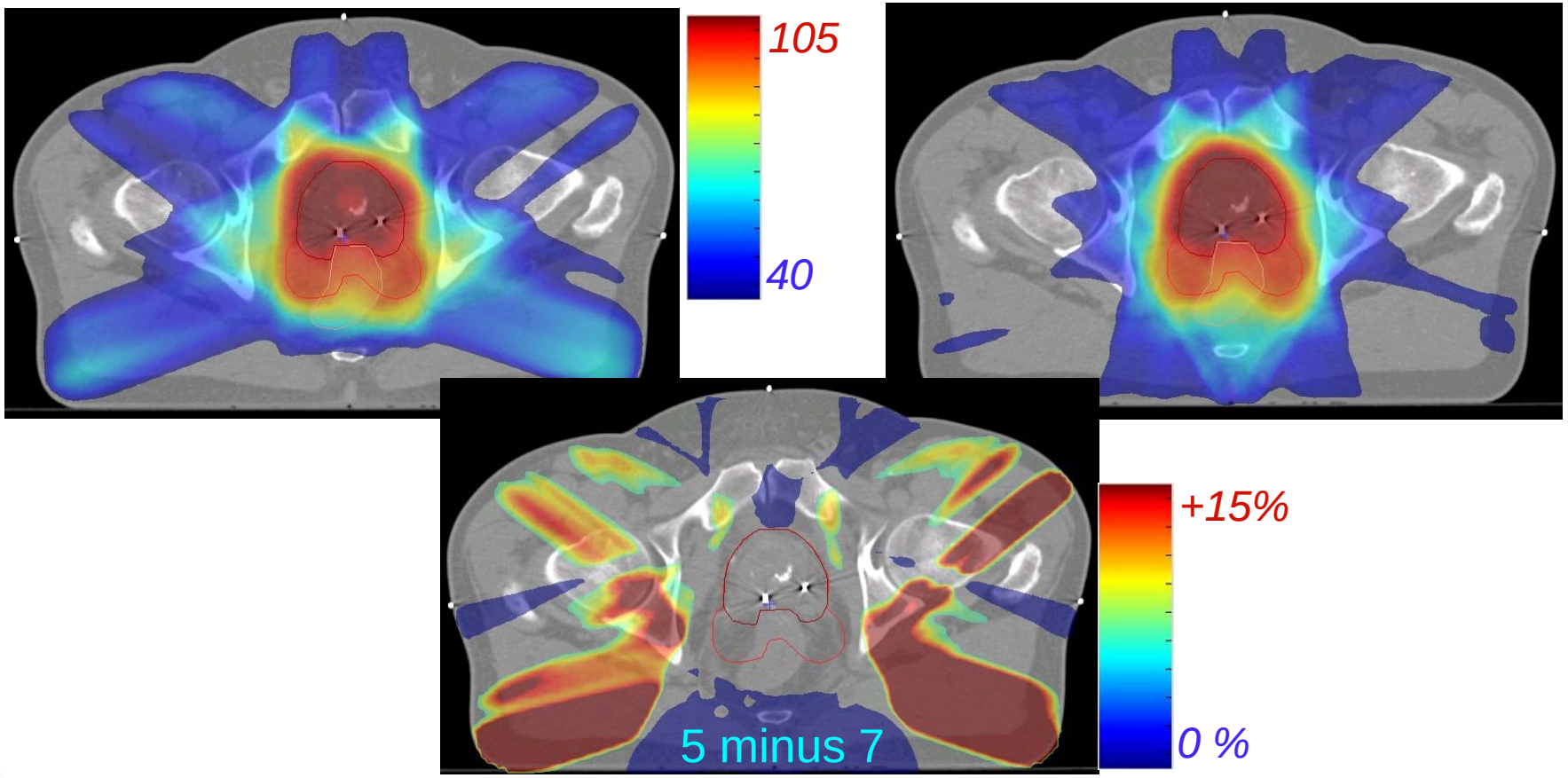
prostate planning: 5 vs 7 beams

5 beams

7 beams



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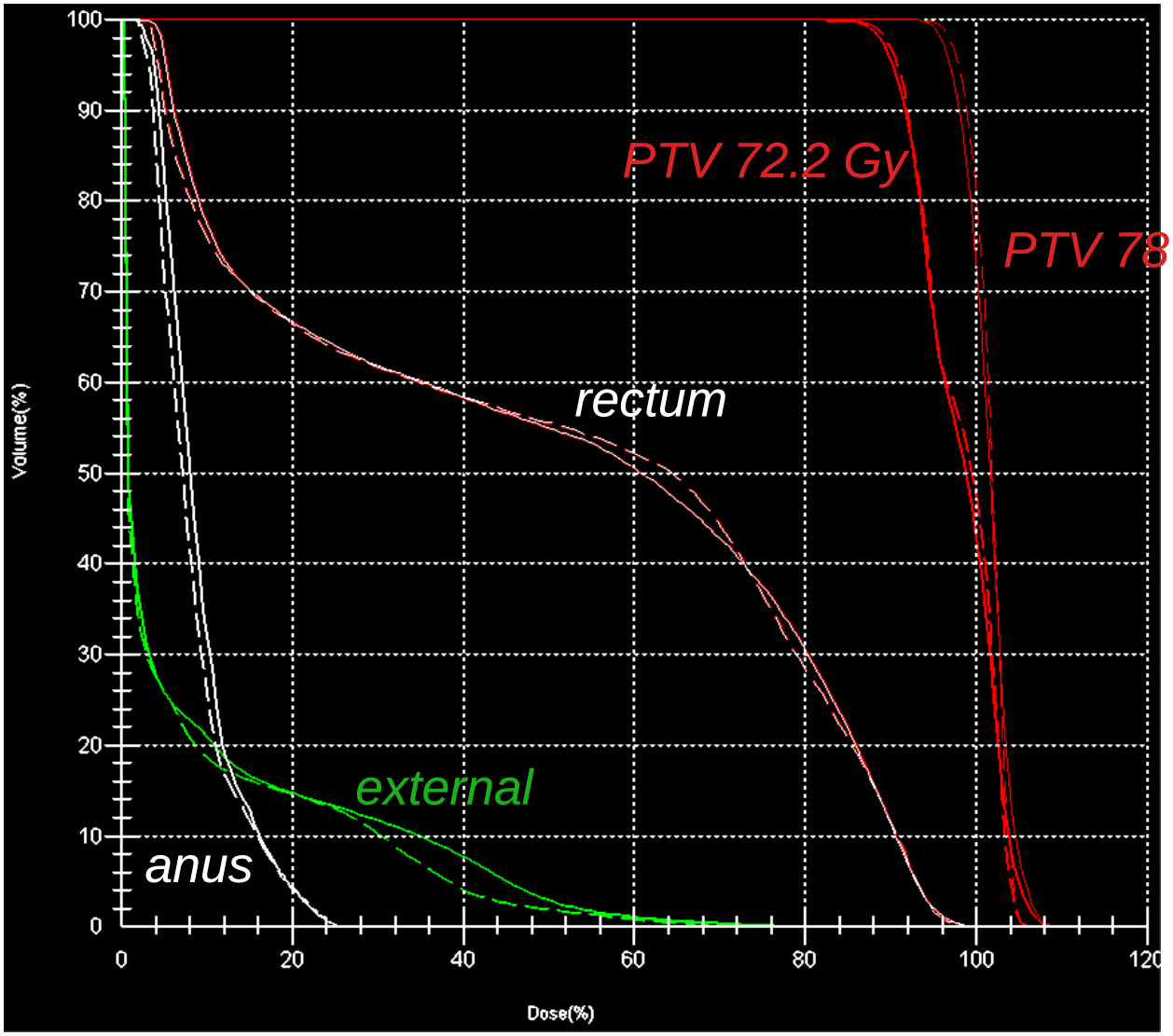
prostate planning: 5 vs 7 beams



5 beams

7 beams

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prostate planning: 5 vs 7 beams

Monaco		
Mean Dose (Gy)	*5 beams*	*7 beams*
External	6.0	5.3
Rectum	39.3	39.2
Anus	6.9	6.3

Monaco		
	5 beams	*7 beams*
# segments	37	32
# MU's	465	438

beam angle optimization

Beam angle optimization

current status of the clinical use of non-coplanar (nCP) beams and of

beam angle optimization (BAO):

- nCP beams used a lot in cranial SRT and SBRT (liver, lung), generally without IMRT
- Gantry-based units: nCP beams requires couch rotations ➡ time consuming, so preferentially avoided
- (Commercial) TPS for BAO + IMRT are generally not available

➡ little is (and can be) known on the added value of BAO + IMRT and non-coplanar beams

Beam angle optimization

Rotterdam:

- 14 years ago start of a program focused on building inverse planning systems for BAO to investigate optimization of both co-planar
  and non-coplanar beam setups (initial main focus: liver SBRT)
- new data with strong evidence that both BAO and nCP beams can significantly contribute to treatment plan quality

→ ***Erasmus- iCycle***

Med Phys. 2012 Feb;39(2):951-63.

iCycle: Integrated, multicriterial beam angle, and profile optimization for generation of coplanar and noncoplanar IMRT plans.

Breedveld S, Storchi PR, Voet PW, Heijmen BJ.

Department of Radiation Oncology, Erasmus MC Rotterdam, Groene Hilledijk 301, 3075 EA Rotterdam, The Netherlands. s.breedveld@erasmusmc.nl

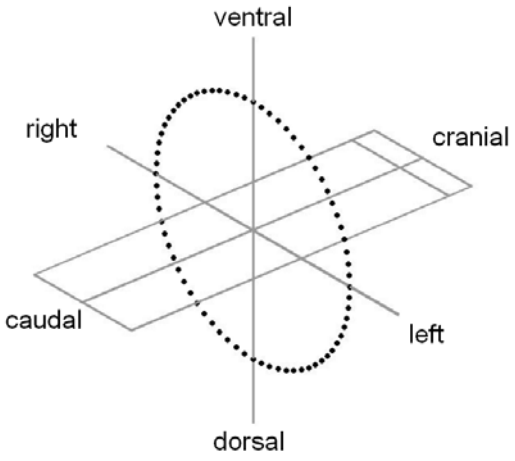
Erasmus-iCycle: main features

- in-house developed algorithm for integrated beam intensity optimization and BAO
- core is 2pεc[1]:
  - beam intensity optimization
  - multi-criteria optimization
  - 1 pareto optimal plan is generated based on a 'wishlist' with prioritized objectives and hard constraints
  - wishlists can be used for broad ranges of patients, e.g. all head and neck patients that need sparing of salivary glands
  - planning is automated ('*push button system*'), excellent plans without 'tweaking' of parameters, the result is operator independent

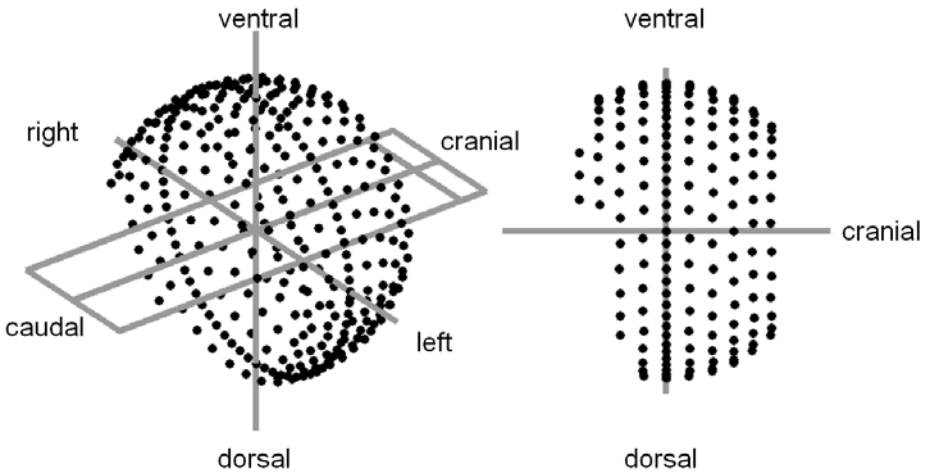
(1): Breedveld et al

Erasmus-iCycle: main features

- beams are sequentially added to the plan in an iterative procedure
- coplanar beam set-ups: selection from 72 directions (5°)
- non-coplanar set-ups: extend input beam set with non-coplanar beams that avoid collisions (every 10°, ~300)



coplanar



non-coplanar

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Example iCycle output

Non coplanar

Nr of beams	9	8	7	6
Constraints and objectives:				
PTV-bu	49.2	49.2	49.2	49.2
Cord	38.0	38.0	38.0	38.0
ExternalRing	46.7	46.2	46.1	46.8
Unspecified 1	49.2	49.2	49.2	49.2
PTV-bu	0.5	0.5	0.5	0.5
PTVring1cm	47.3	47.6	47.5	48.3
PTVring2cm	41.0	41.8	42.1	43.0
PTVring3cm	35.8	36.8	38.9	37.9
PTVring4cm	33.0	34.1	37.3	35.2
PTVring5cm	30.7	33.6	34.4	32.2
parotis_re	20.0	20.3	20.3	20.4
parotis_li	18.5	19.3	19.8	20.0
SMG_re	26.8	28.8	32.1	36.7
SMG_li	39.9	40.1	40.5	40.7
Unspecified 1	12.7	11.9	11.8	12.3

gain per added beam →

Angles:

(Gantry, Cou	(59, -56, 6)	(59, -56, 6)	(59, -56, 6)	(59, -56, 6)
	(309, -36, 6)	(309, -36, 6)	(309, -36, 6)	(309, -36, 6)
	(68, 39, 6)	(68, 39, 6)	(68, 39, 6)	(68, 39, 6)
	(292, 50, 6)	(292, 50, 6)	(292, 50, 6)	(292, 50, 6)
	(313, -76, 6)	(313, -76, 6)	(313, -76, 6)	(313, -76, 6)
	(38, -74, 6)	(38, -74, 6)	(38, -74, 6)	(38, -74, 6)
	(270, -27, 6)	(270, -27, 6)	(270, -27, 6)	
	(43, 60, 6)	(43, 60, 6)		
	(308, 11, 6)			

Optimality when using small number of beams?

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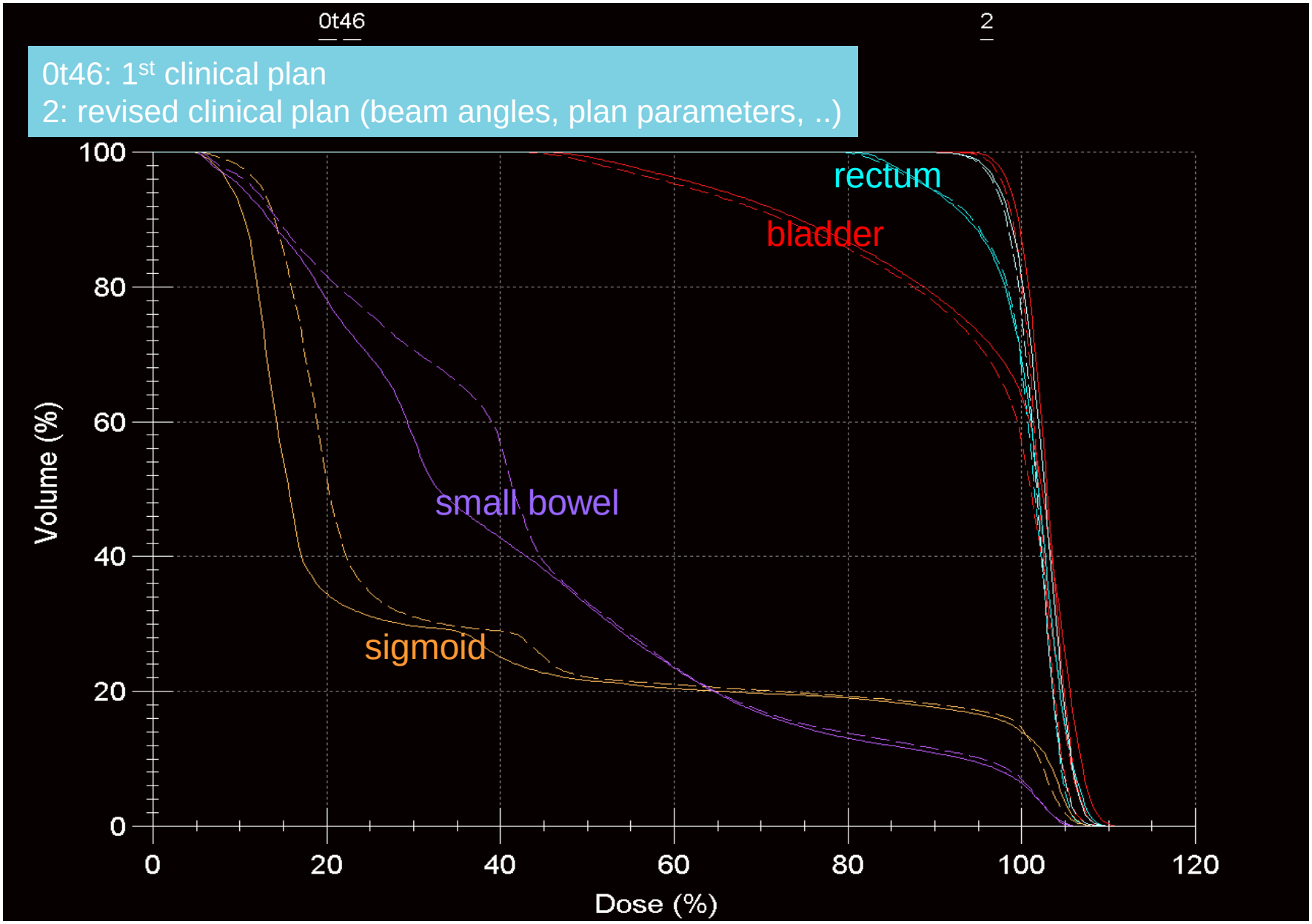
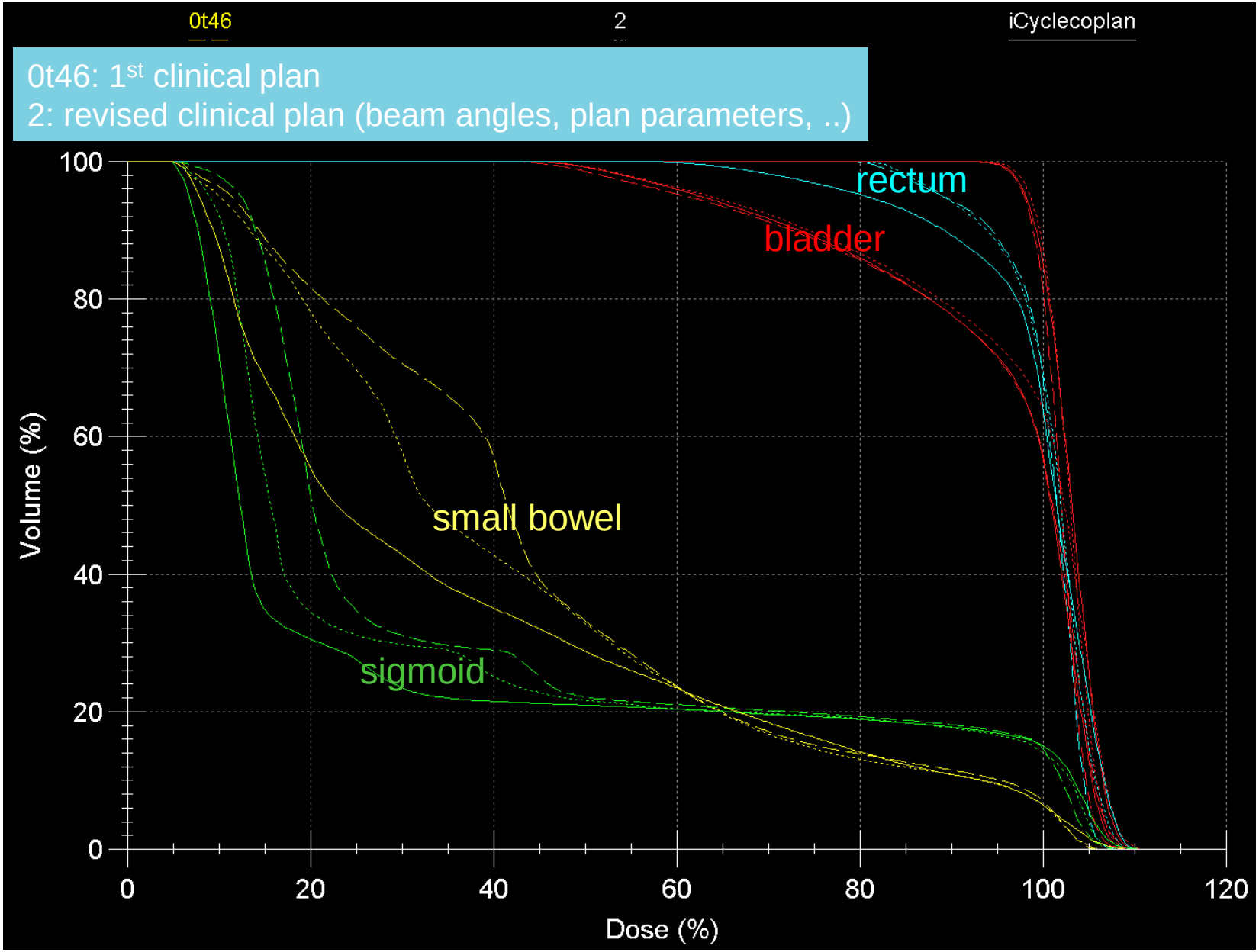
Example: Cervix IMRT Monaco patient



Example: Cervix IMRT Monaco patient



Effect of energy in IMRT planning

- 6 MV, 10MV, 18MV
  - sharp gradients can only be created using the beam penumbra

    so, 6 MV often results in the best plan, in terms of OAR sparing

  - however, the volume treated with low dose differs a lot between different energies

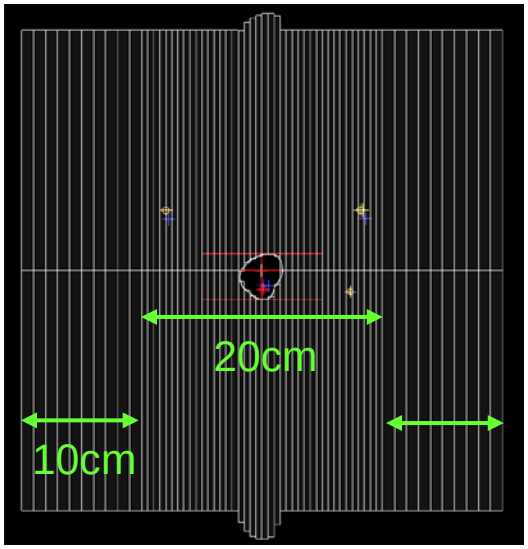
  - 6 MV in pelvic region??

  - combination of different energies is a good option

    (computer based choice?)

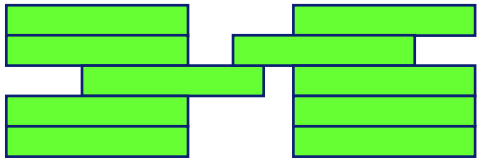
MLC geometry: Varian (millenium MLC)

- 120 MLC
- max field size : 40 x 40 cm
  - 20 cm : leaf width = 5mm, outside, 1 cm



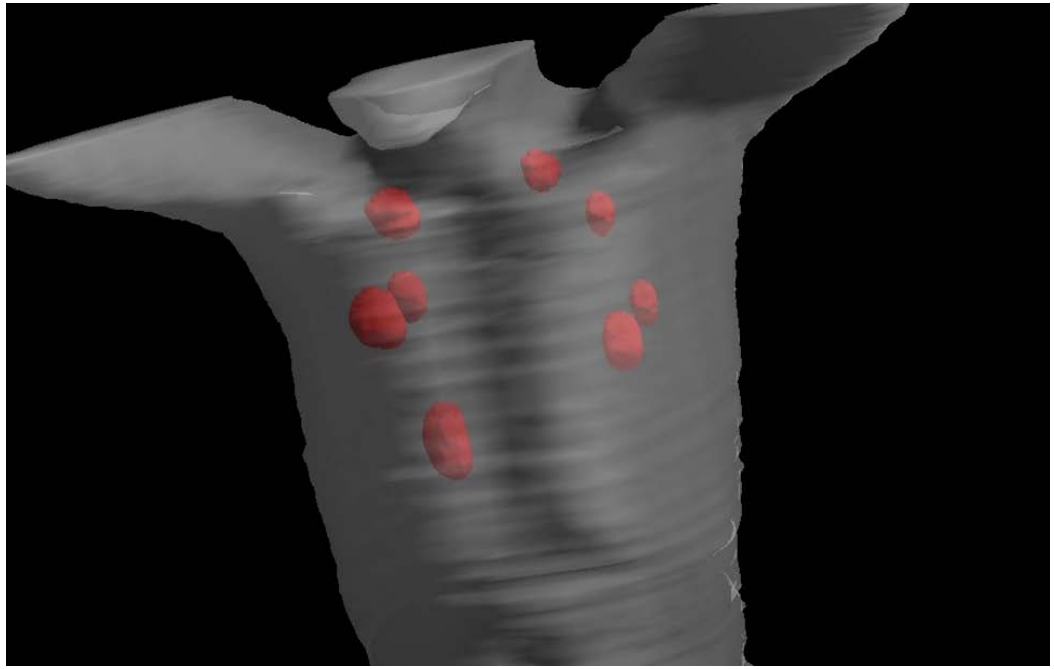
- maximum overtravel in (IMRT) fields is 14.3 cm:
  - so, if an IMRT field width ≥ 14.3 cm ⟶ splitting beam
  - field width ≈ 28 cm ⟶ splitting again (‘*carriage positions*’)

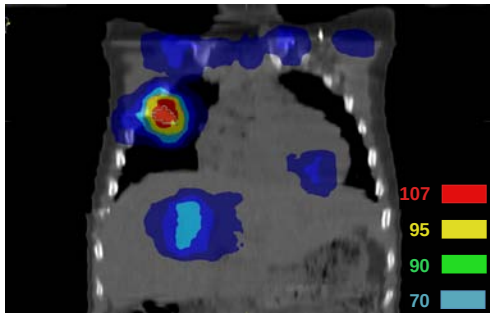
- inter-digitating MLC’s
- closing opposing leaf-pairs

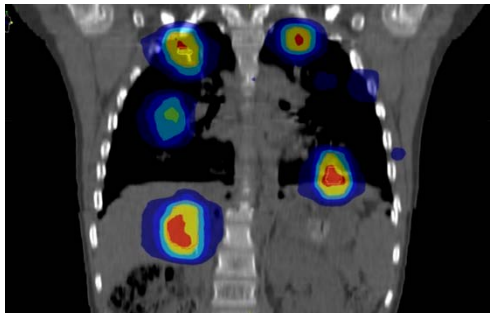


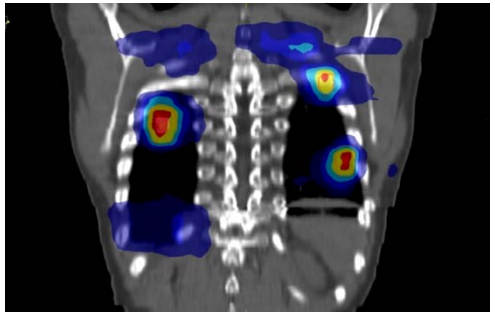
Clinical example multiple PTV case

- 6 year old boy, nefroblastoma, ri.kidney
- boost on multiple metastases (8 in total!)
- 1 isocenter, 6 x 1.8 Gy

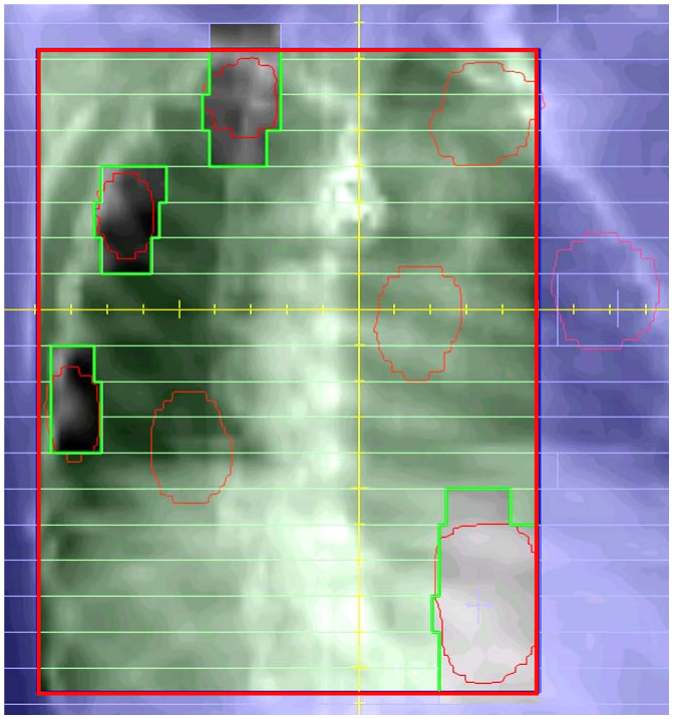








Example multiple PTV (8!) IMRT plan: Varian



segment 1

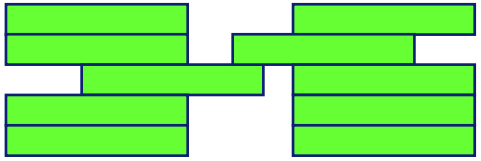
segment x

1.8 Gy / fraction
8 fields
38 segments, 555 MU

MLC geometry: Elekta (MLCi, MLCi2)

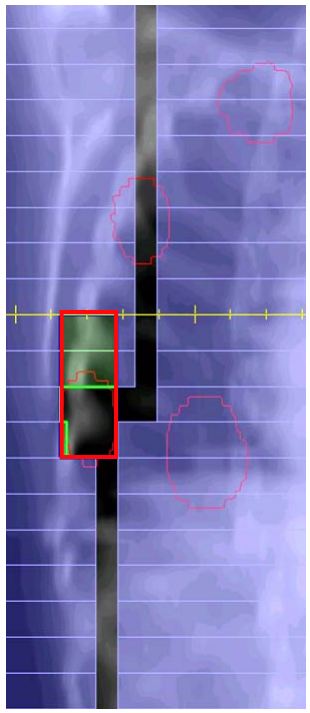
- no splitting of beams

- MLCi : no interdigitating leafs
- MLCi2 : interdigitating leafs



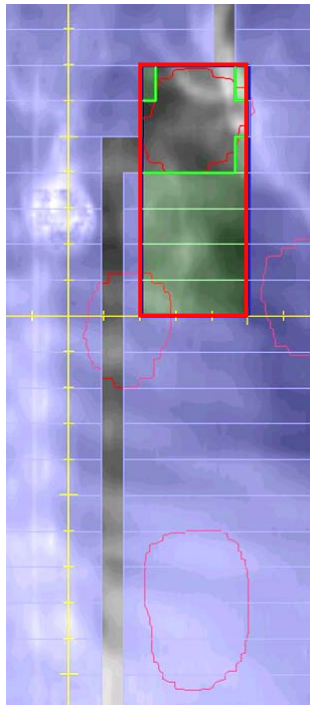
- minimum gap for opposing leaf pairs : 5 mm (MLCi , MLCi2)
- No overtravel on Y-jaws (MLCi , MLCi2)

Example multiple PTV IMRT plan: Elekta , MLCi

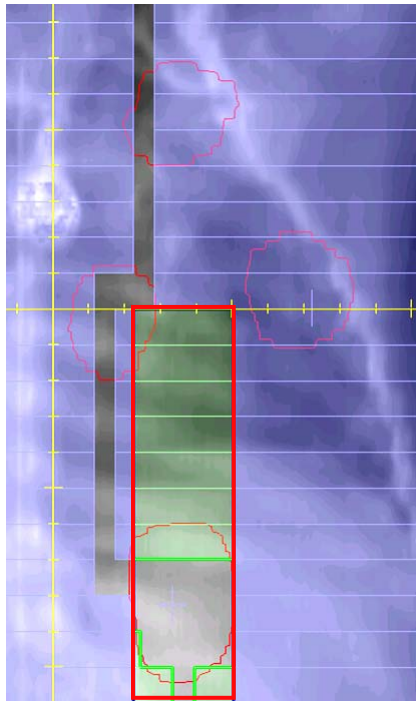


segment 1

segment 2



segment 3



segment x

1.8 Gy / fraction
8 fields
131 segments, 2239 MU

similar DVH's Varian - Elekta

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Example multiple PTV IMRT plan: Elekta versus Varian

- 3.4 x more # segments
- 4 x more # MU

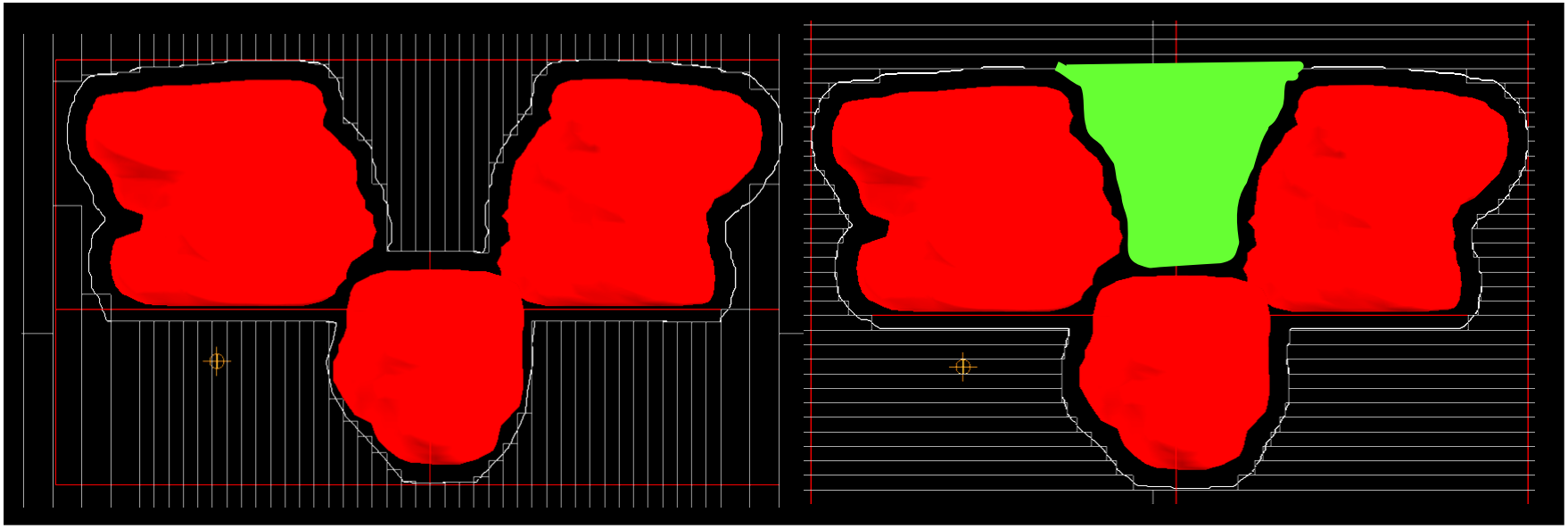
- in this example the MLC limitations resulted in large differences.

  Step&Shoot IMRT segmentation might not be the best approach on an Elekta linac equiped with MLCi in **this specific** case

in ‘normal’ cases not much difference between Varian and Elekta MLCi
MLCi2: improved segmentation, similar to Varian MLC

Collimator angle

- effect of collimator angle depends on the IMRT restrictions

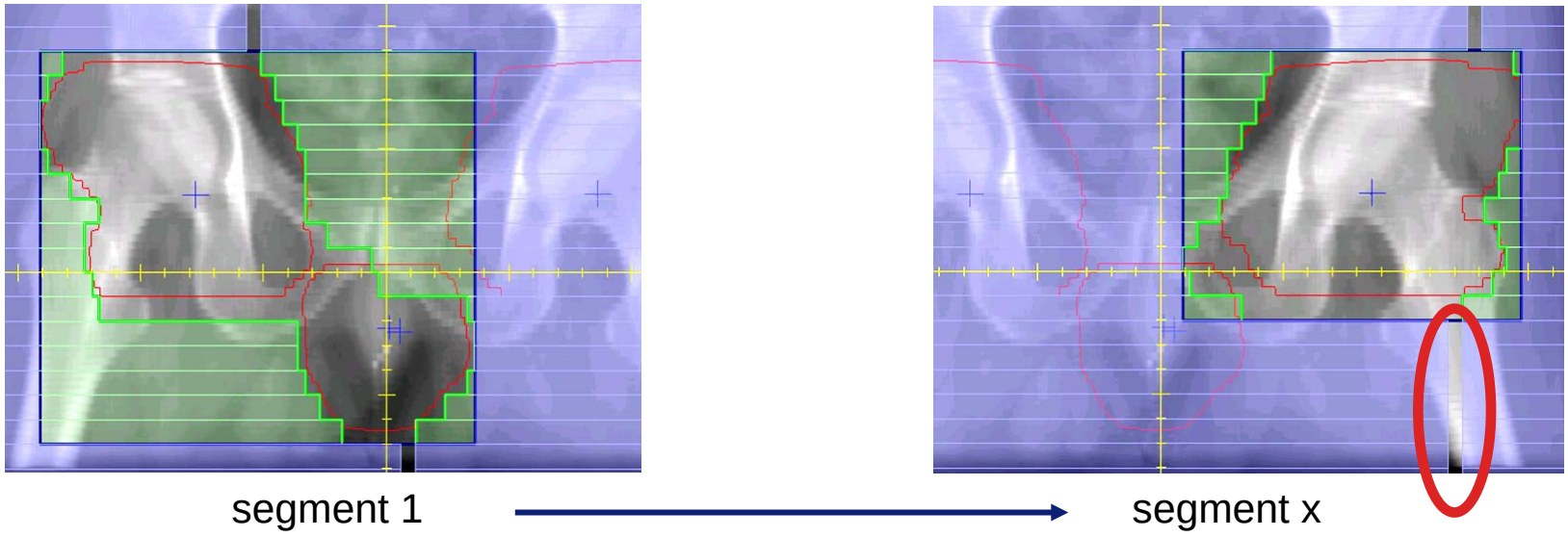


Collimator 90º

Collimator 0º

Effect of collimator angle depends on the IMRT delivery

- In step&shoot delivery: block the ‘central area’



- in d-MLC delivery:

  leafs should be closed when travelling ‘across’ the central area

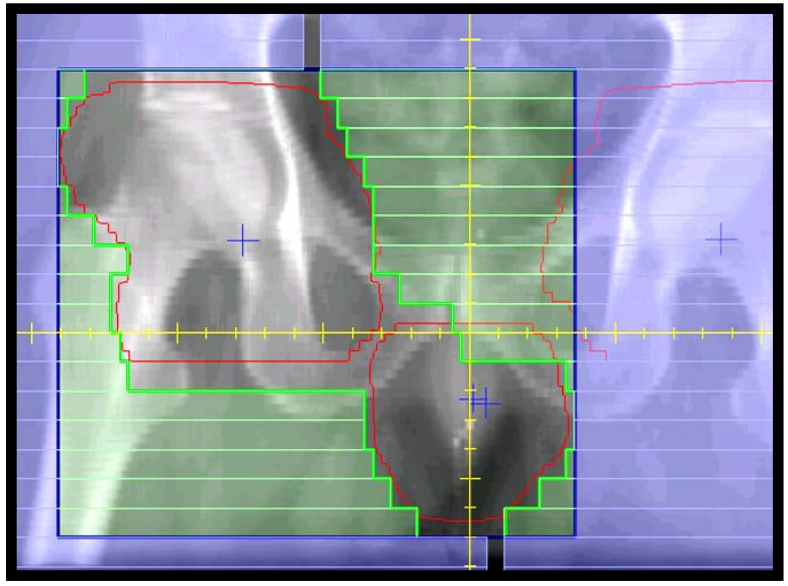
  Elekta MLCi 90º versus Varian / Elekta MLCi2: 0º / 90º

  or allow for ‘*move only segments*’

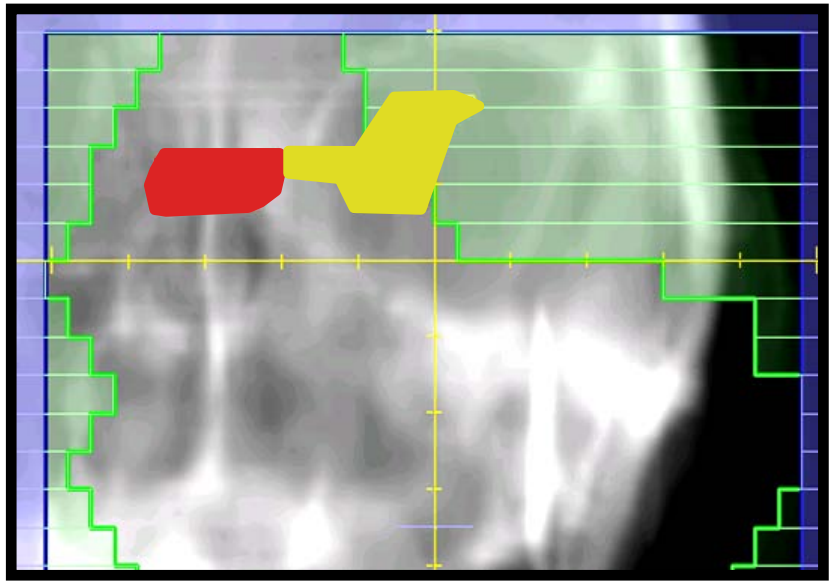
Leaf width

- '*The smaller the leaf width, the better the plan*' …..

  however …. the effect of leaf width is relative!



1 cm width will do fine in most cases (anal case)



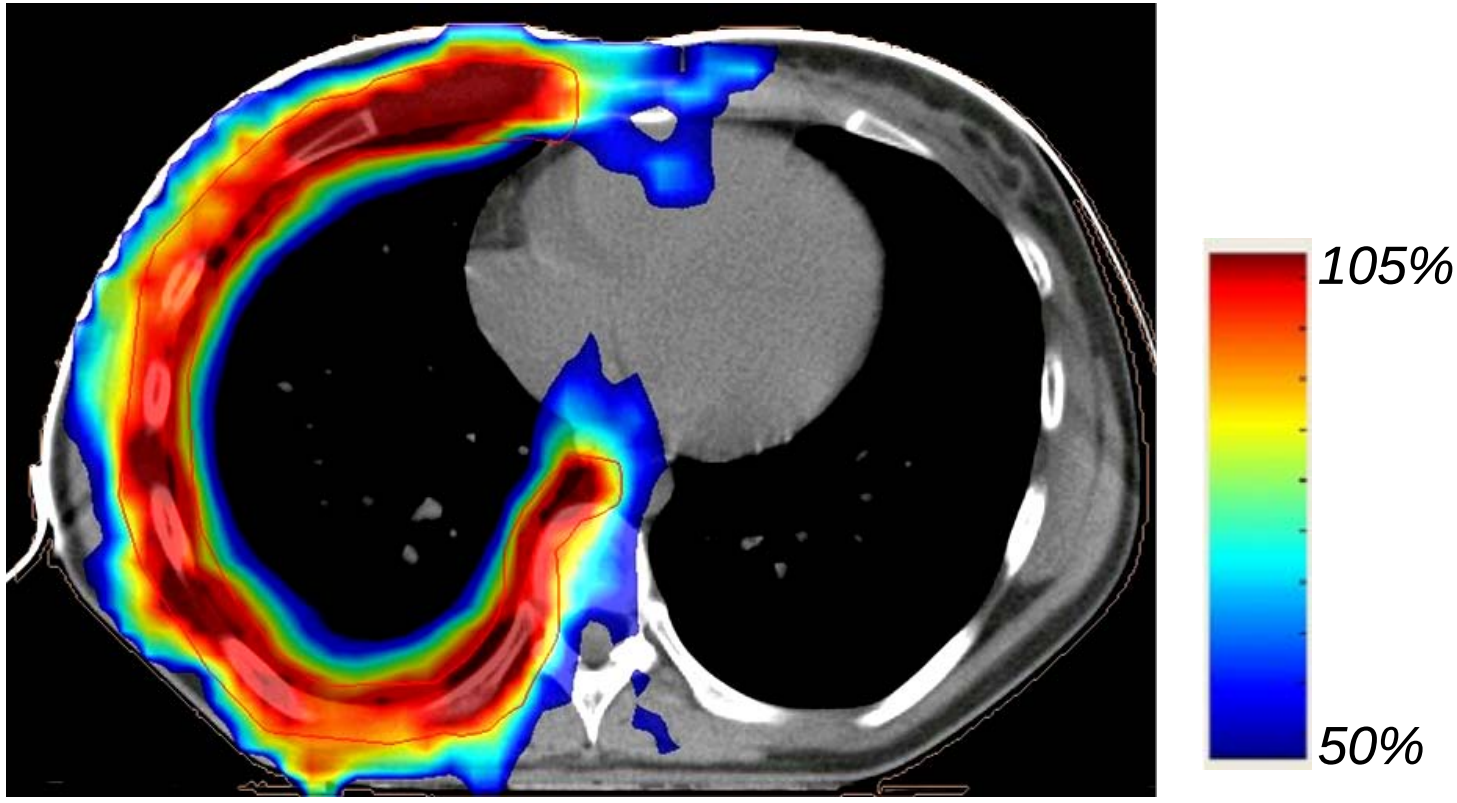
0.5 cm width might be too coarse for small OARs

optimize collimator rotation and isocenter position

Number of MU in IMRT planning

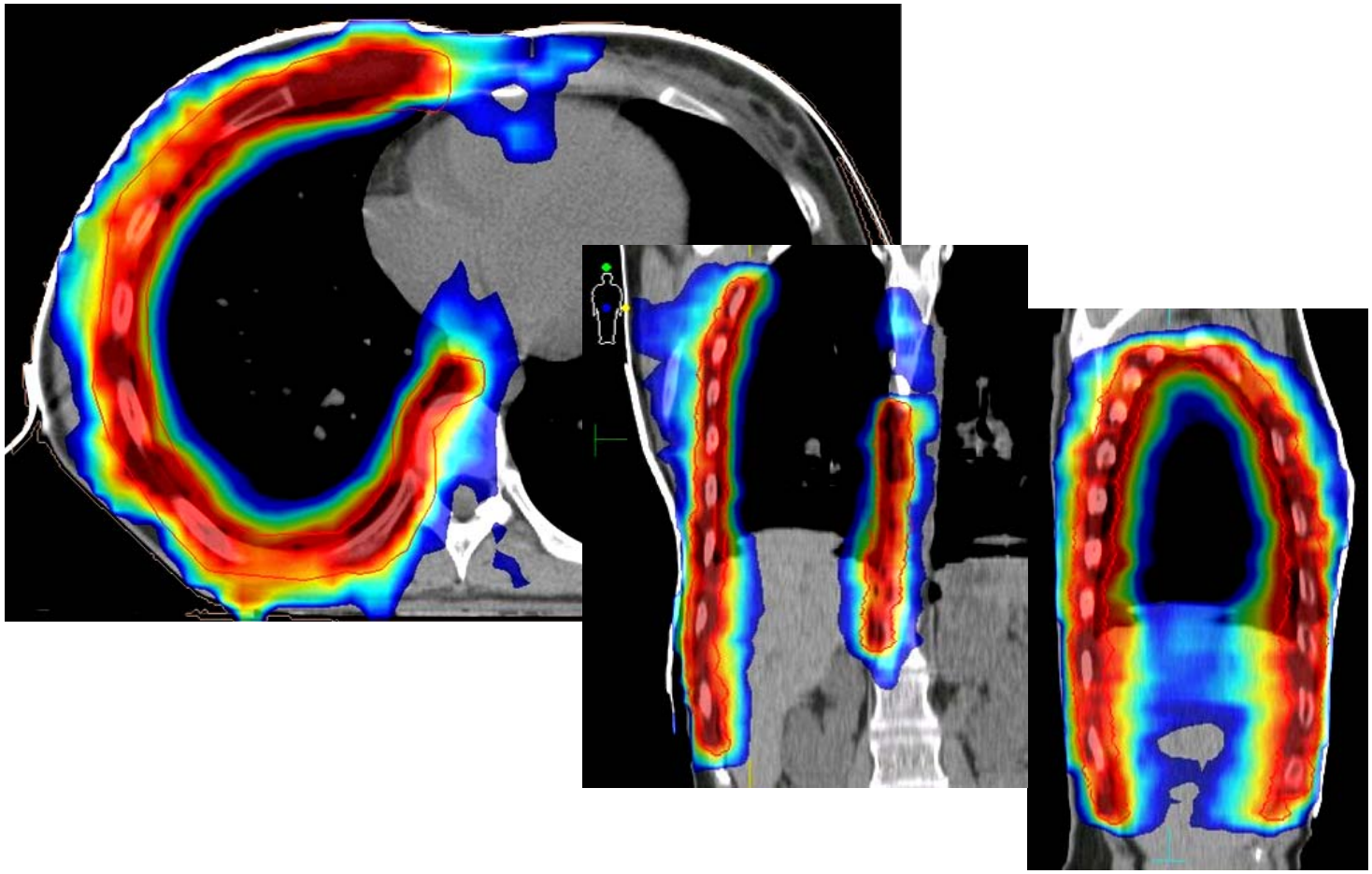
- is there a maximum in the number of MU to be delivered?

  how many MU/Gy do we accept?



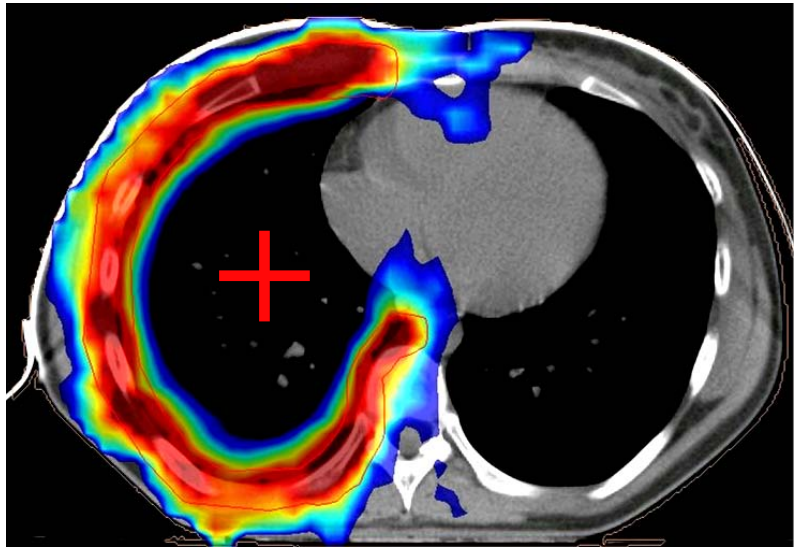
Number of MU in IMRT planning

- around 2200 MU / 2 Gy ⟶ is there an alternative??



Isocenter position

- like in non-IMRT:
  - try to place the isocenter in the high-dose region
  - in some cases this is not possible



-isocenter dose = 35%
-additional points per beam to check the dose

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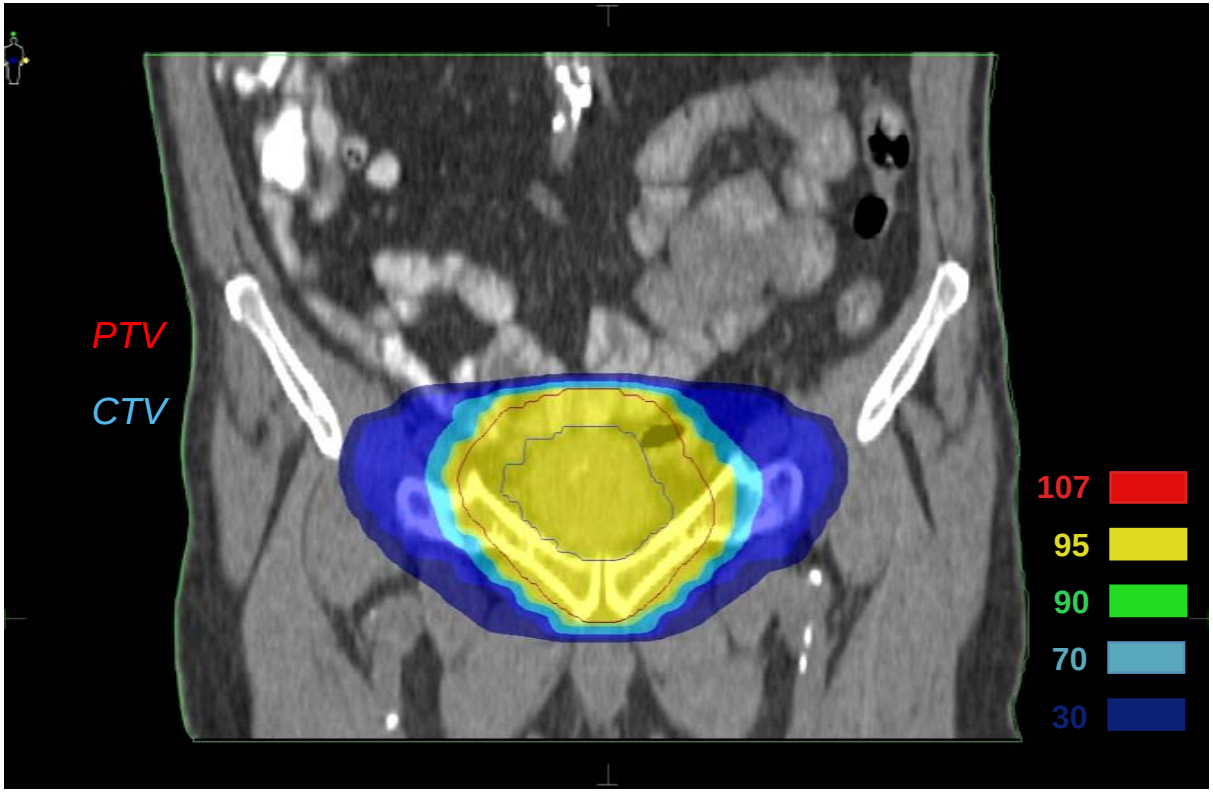
IMRT as efficiency tool for ‘simple 3D-CRT’

- IMRT is often used as technique for the most difficult cases

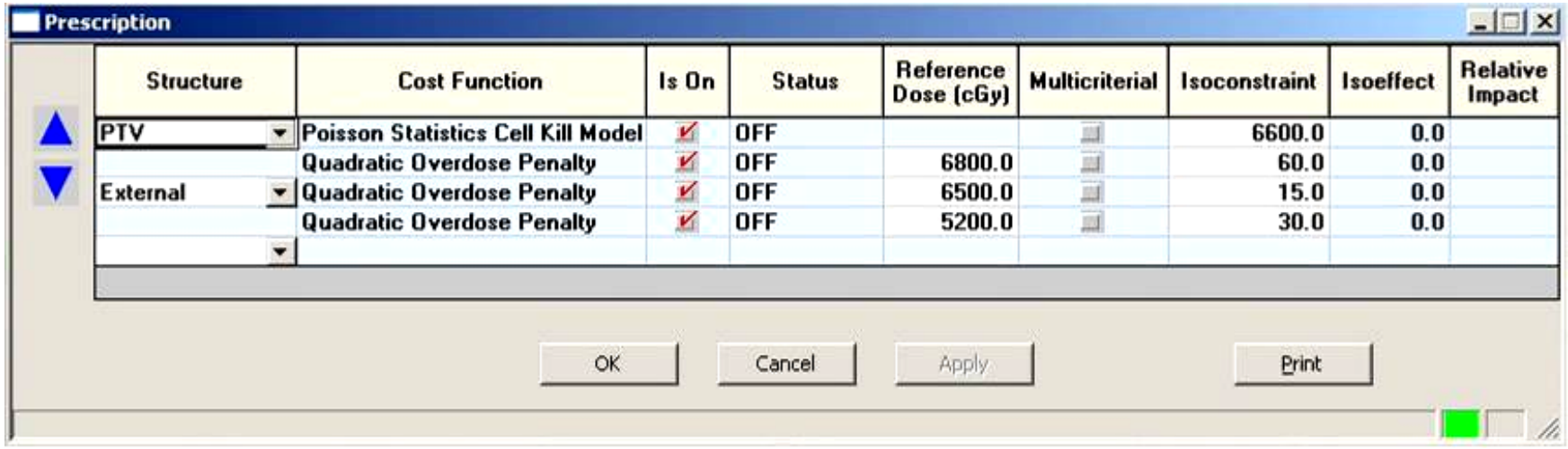
  - what about using it for ‘simple’ 3D conformal plans?

IMRT as efficiency tool for ‘simple 3D-CRT’

- bladder : 33 x 2.0 Gy



IMRT as efficiency tool for ‘simple 3D-CRT’ : Bladder



challenges:

- coverage at least similar to 3DCRT
- reduction of planning time
- no increase in treatment time

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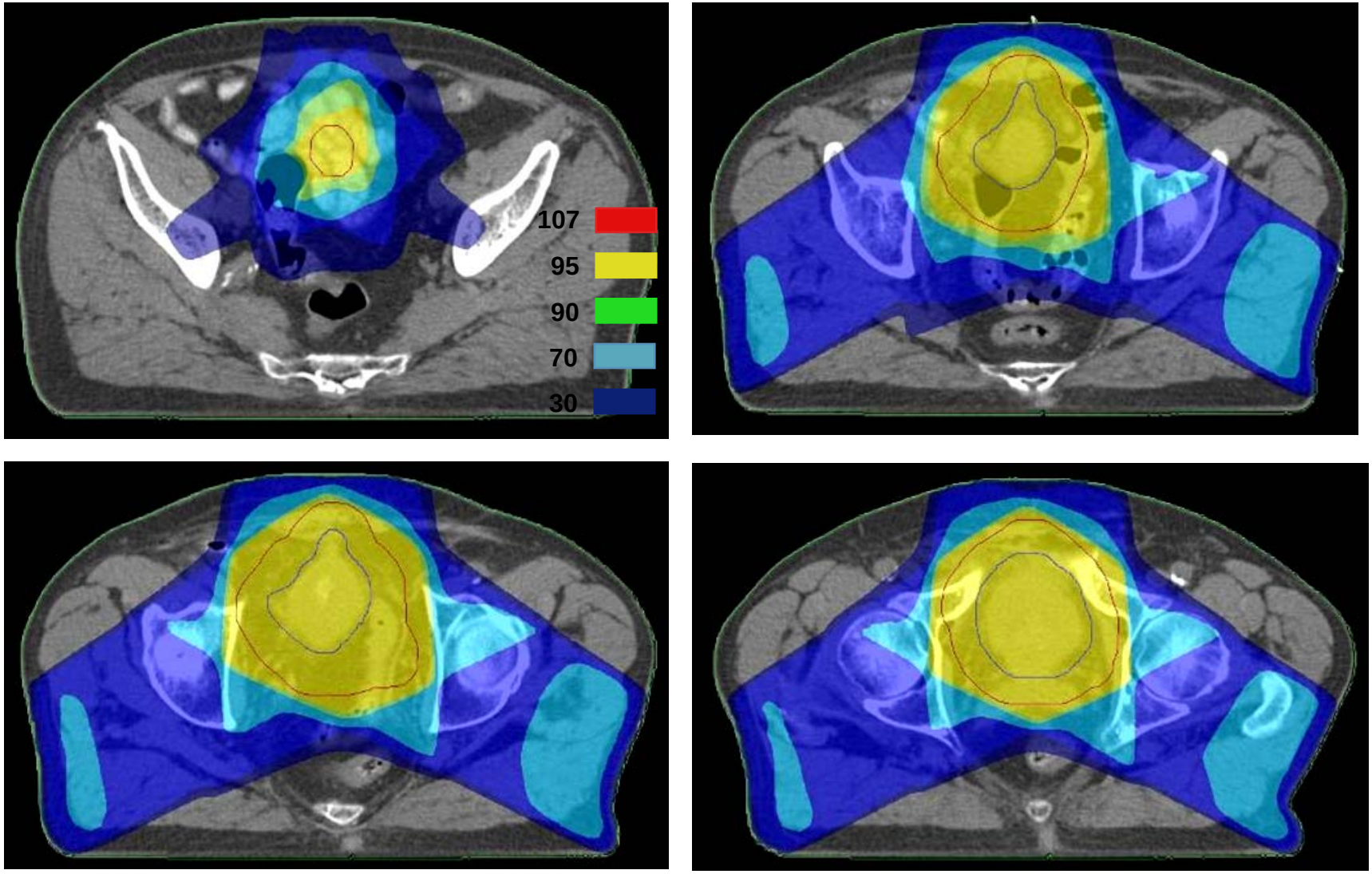
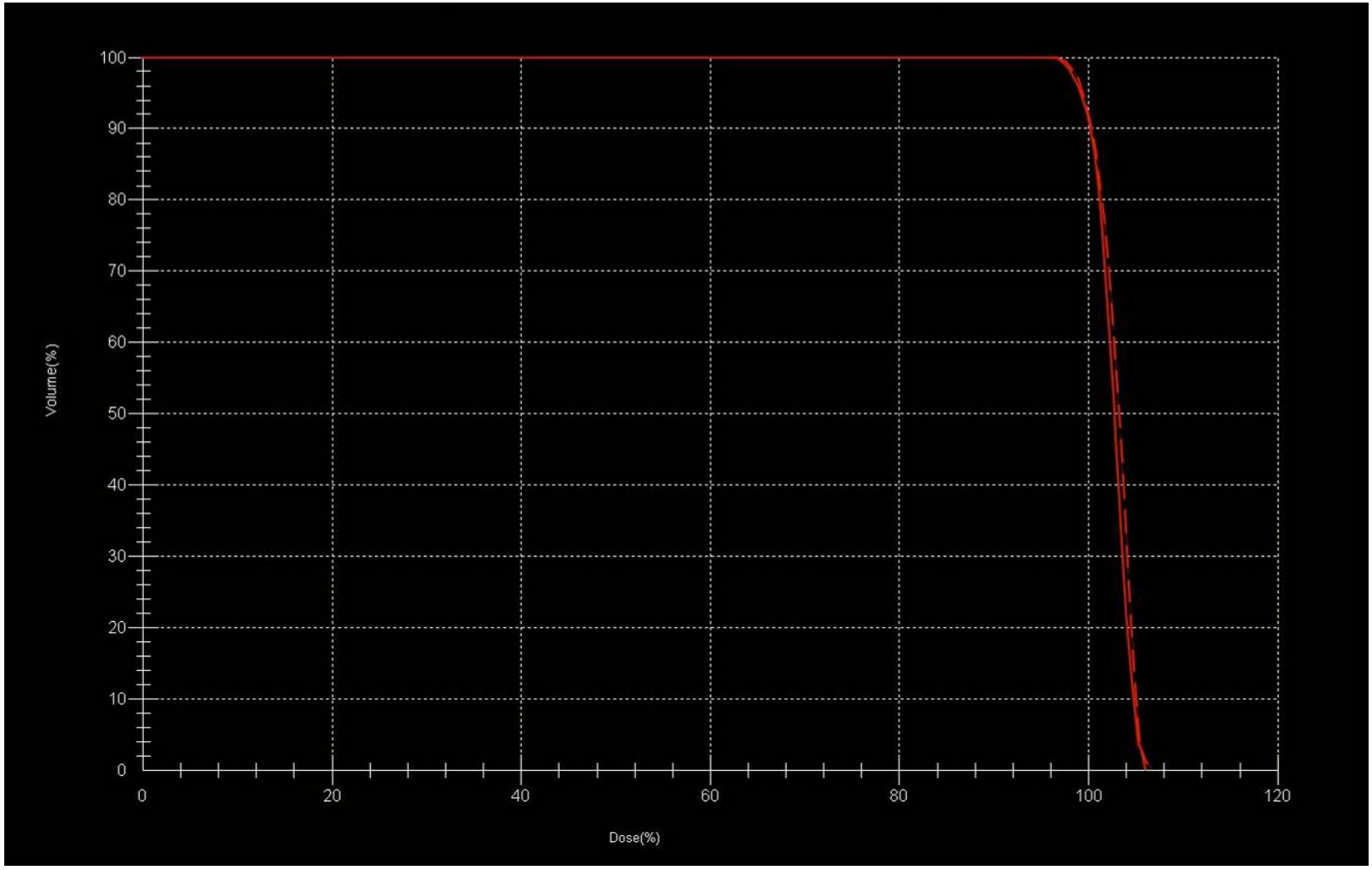
IMRT as efficiency tool for ‘simple 3D-CRT’ : bladder



IMRT as efficiency tool for ‘simple 3D-CRT’ : Bladder



IMRT

3DCRT

IMRT as efficiency tool for ‘simple 3D-CRT’ : Bladder

- IMRT
- Plan time 6 min.
- 3 beams
- 312 MU
- 5 segments

- 3DCRT
- Plan time 30 min. (hands on!)
- 3 beams
- 468 MU (wedges)

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Physical and biological optimisation

Gert Meijer

ESTRO
European Society for Therapeutic Radiology and Oncology

Physical optimisations

- **Input**: prescribed dose distribution
- **Goal**: maximise agreement between prescribed and resulting dose distribution
- **Example**: minimise quadratic difference between

  prescribed and calculated dose distribution

Advantages

Physical optimisations

- Use of dose and dose-volume objectives is easy and intuitive
- Clinical knowledge is expressed in dose-volume endpoints and can easily be incorporated in the treatment planning recipe
- Objectives are easily and efficiently implemented in computer algorithms

Limitations

Physical optimisations

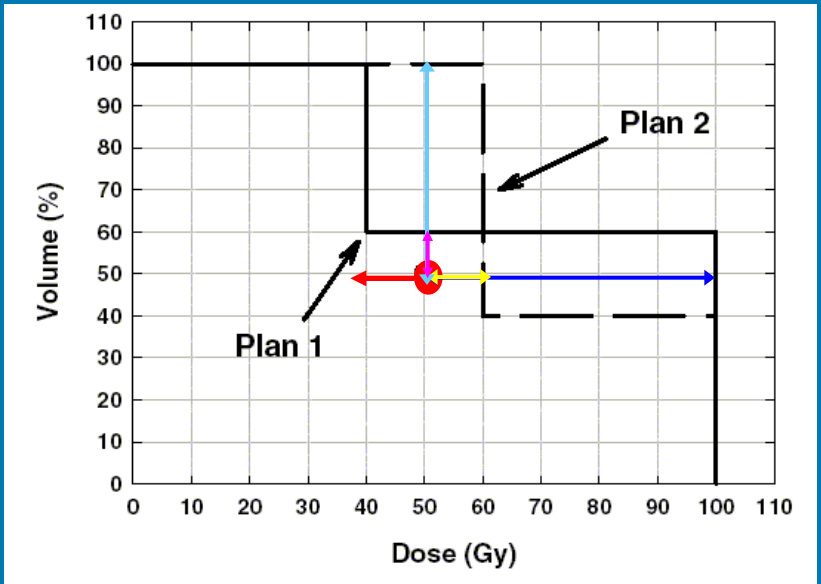
- Quadratic dose difference may not reflect clinical objective
- Properly ranking plans based on dose-volume objectives may fail

Objective: 50% of volume is to receive <50 Gy

Score: Plan 1: $10/100 \times (100 - 50)^2 = 250$

Plan 2: $50/100 \times (60 - 50)^2 = 50$

Result: Plan 1 is rejected!



Courtesy of Aswin Hoffmann

Limitations

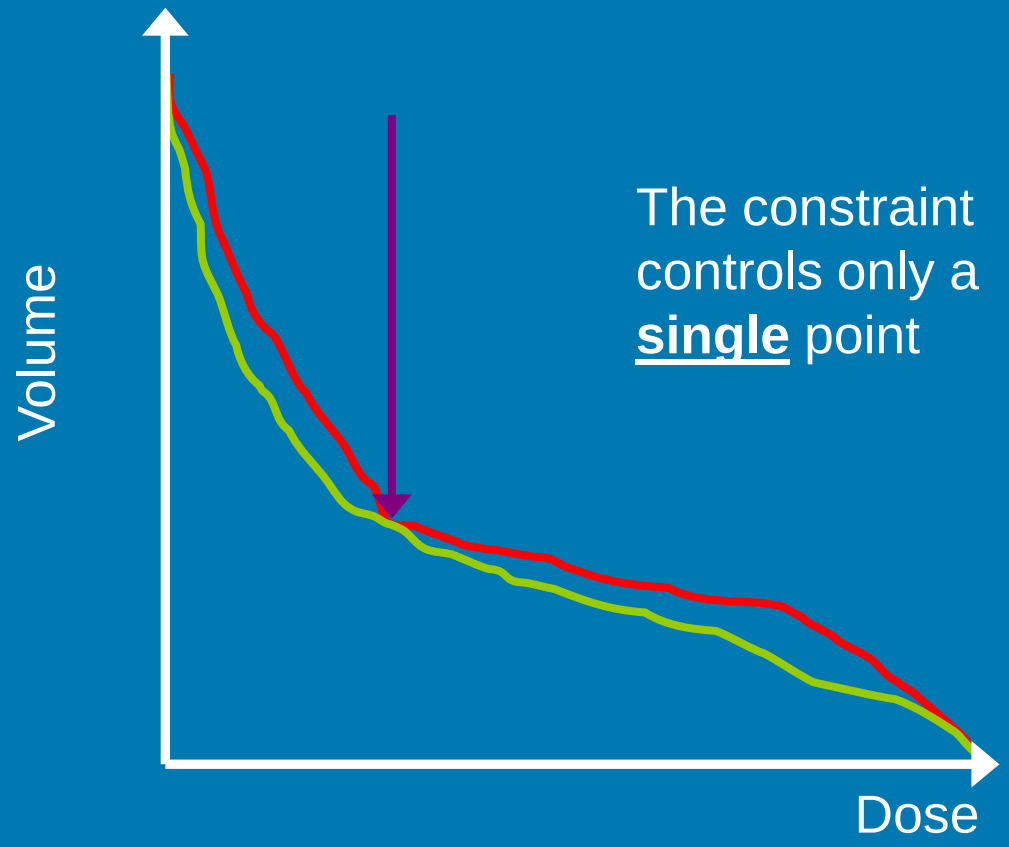
Physical optimisations

- Objectives do not reflect non-linear dose-response relationship
  - Resulting treatment plan is therefore usually not clinically optimal

- Planning efficiency
  - For each objective a triplet (dose, volume, weight) has to be specified
  - Multiple objectives are needed for the same organ to define a DVH

Limitations

Physical optimisations



The constraint controls only a **single** point

Optimization in the biology domain

- **Rationale:** The aim of RT is not to give a required dose to the target, but to accomplish a clinical effect

- **Idea:** Incorporate radiosensitivity of a tumor and normal tissues in the optimization process

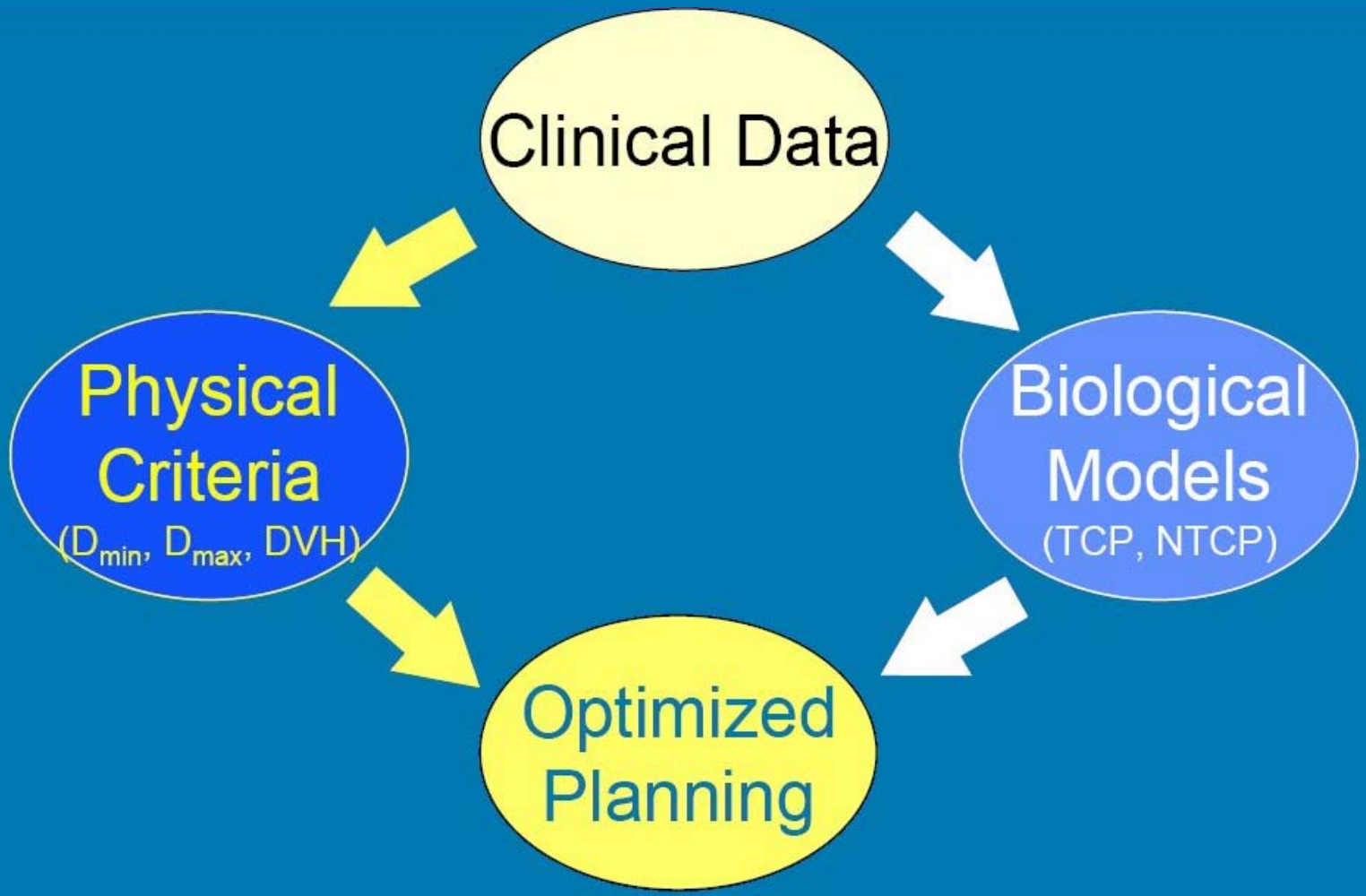
- **Method:** Use an adequate model to quantify the biological effect of dose deposition

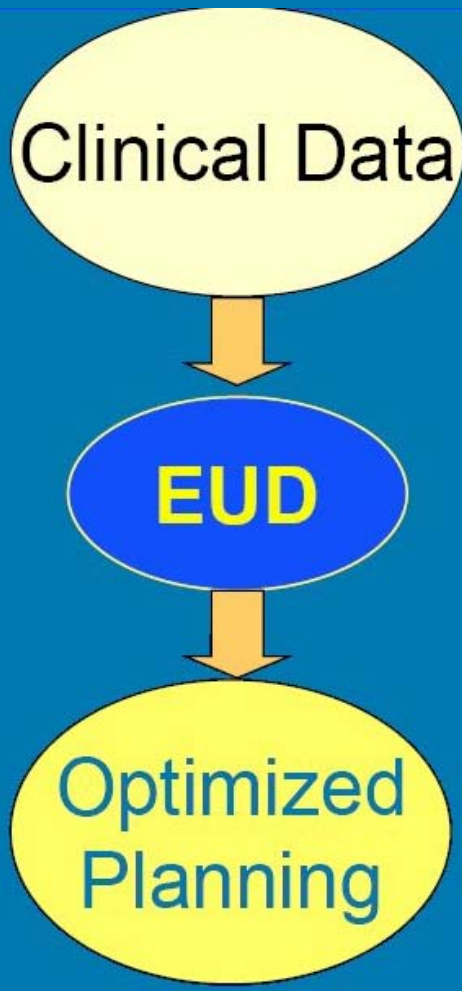
Radiobiological dose-response models

- **Mechanistic models**: radiobiological basis
  - energy deposition in tissue → clinical/biologi…
  - adequate mechanistic model…

this is merely a dream

- **Empirical/phenomenological models**
  - describe observed clinical effect as dose-response relationship
  - find a way to substitute lack of biological knowledge with clinical experience: “let the data speak”

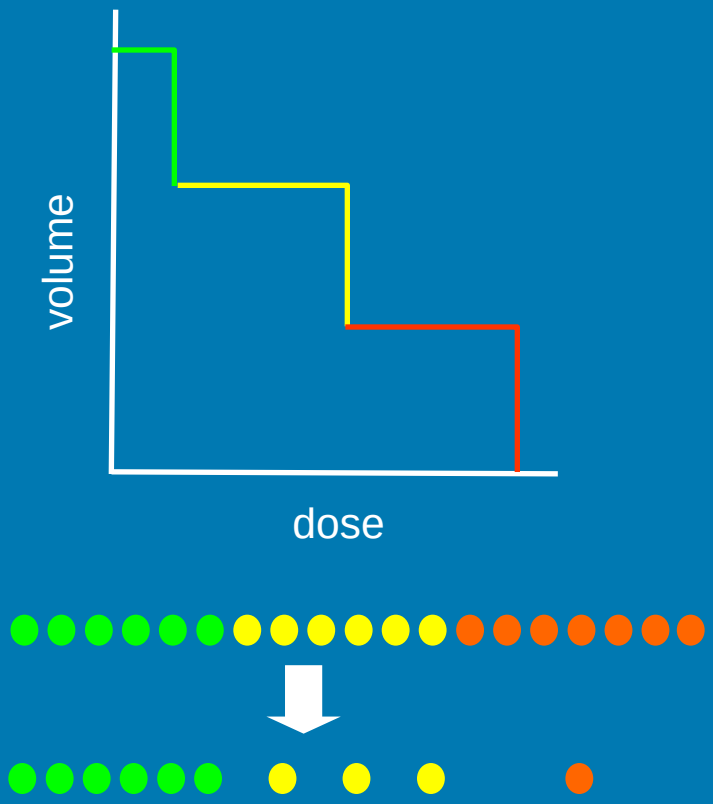


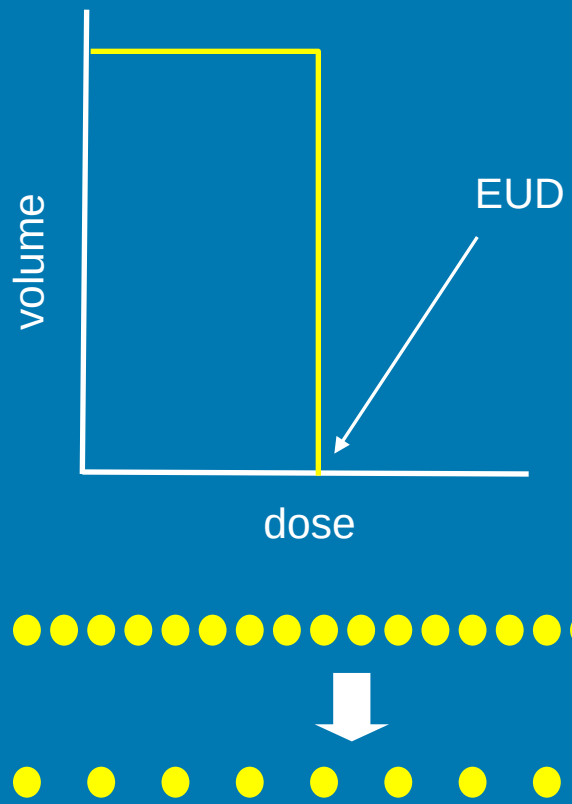


Equivalent uniform dose

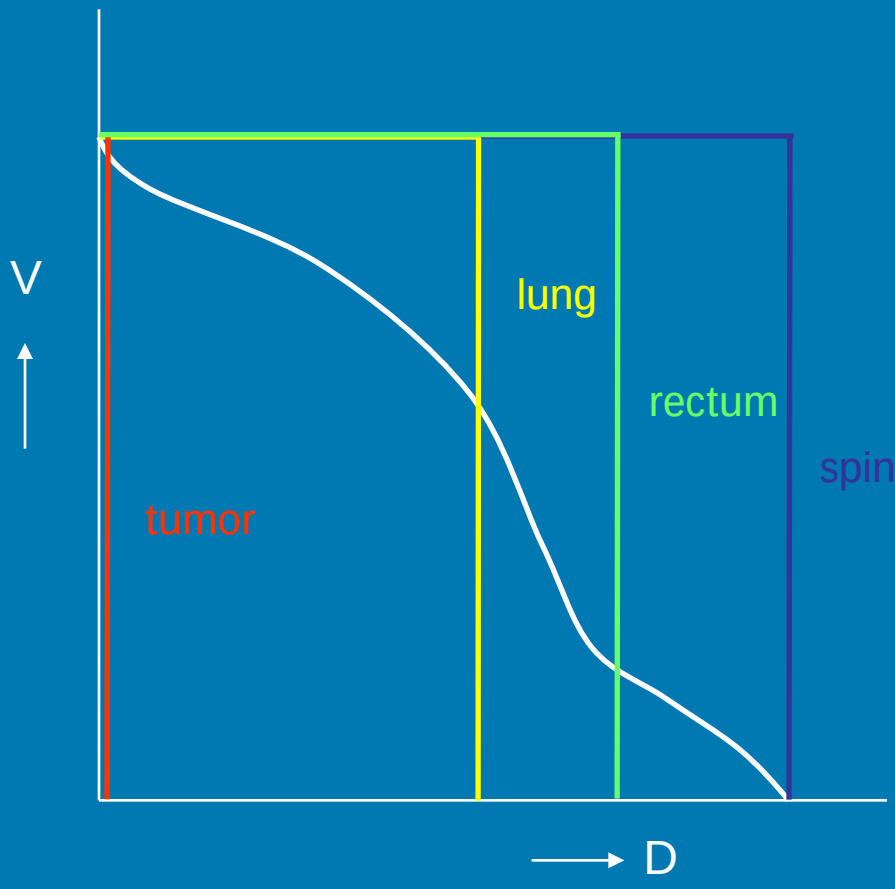
the EUD represents a uniform dose,
which leads to the same probability
of a radiobiological effect as
the corresponding inhomogeneous dose

Equivalent uniform dose





Equivalent uniform dose



Question:

What homogenous dose results in an identical probability of an radiobiological effect?

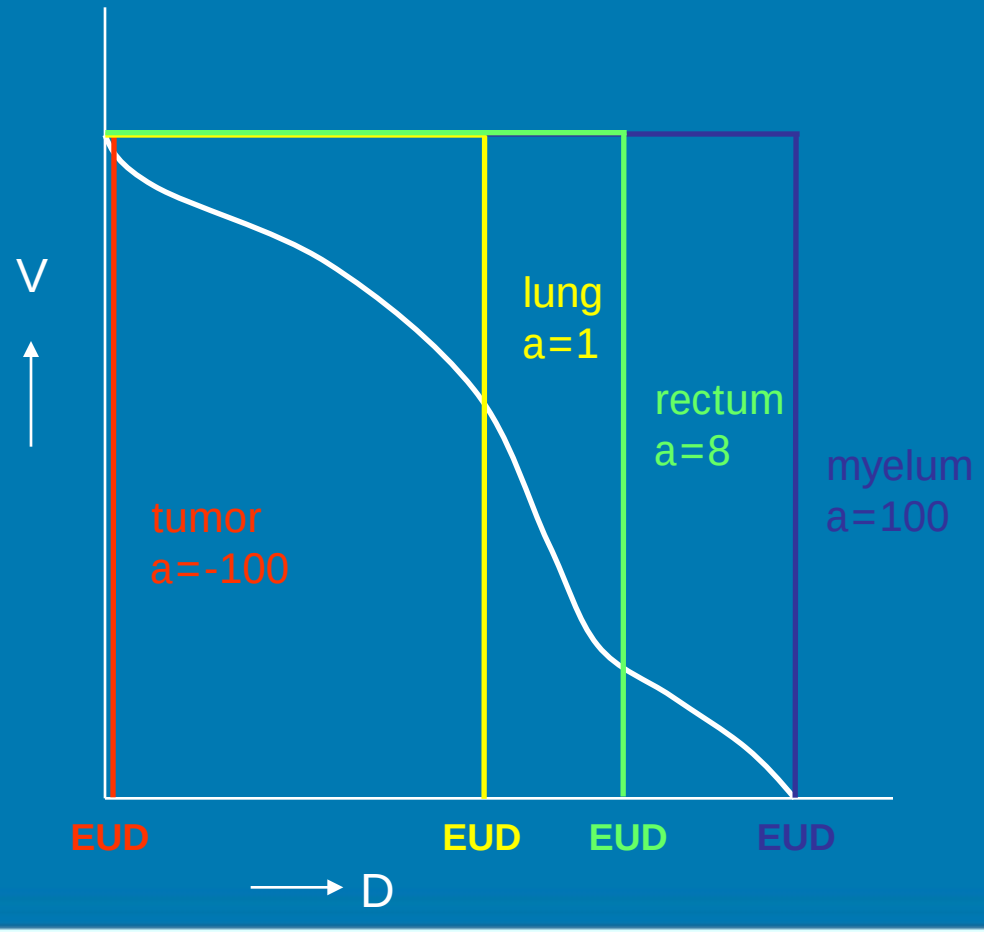
Equivalent uniform dose

$$\mathrm{EUD} = \left(\frac{1}{N} \sum_{i=1}^{N} d_i^{\,a} \right)^{1/a}$$

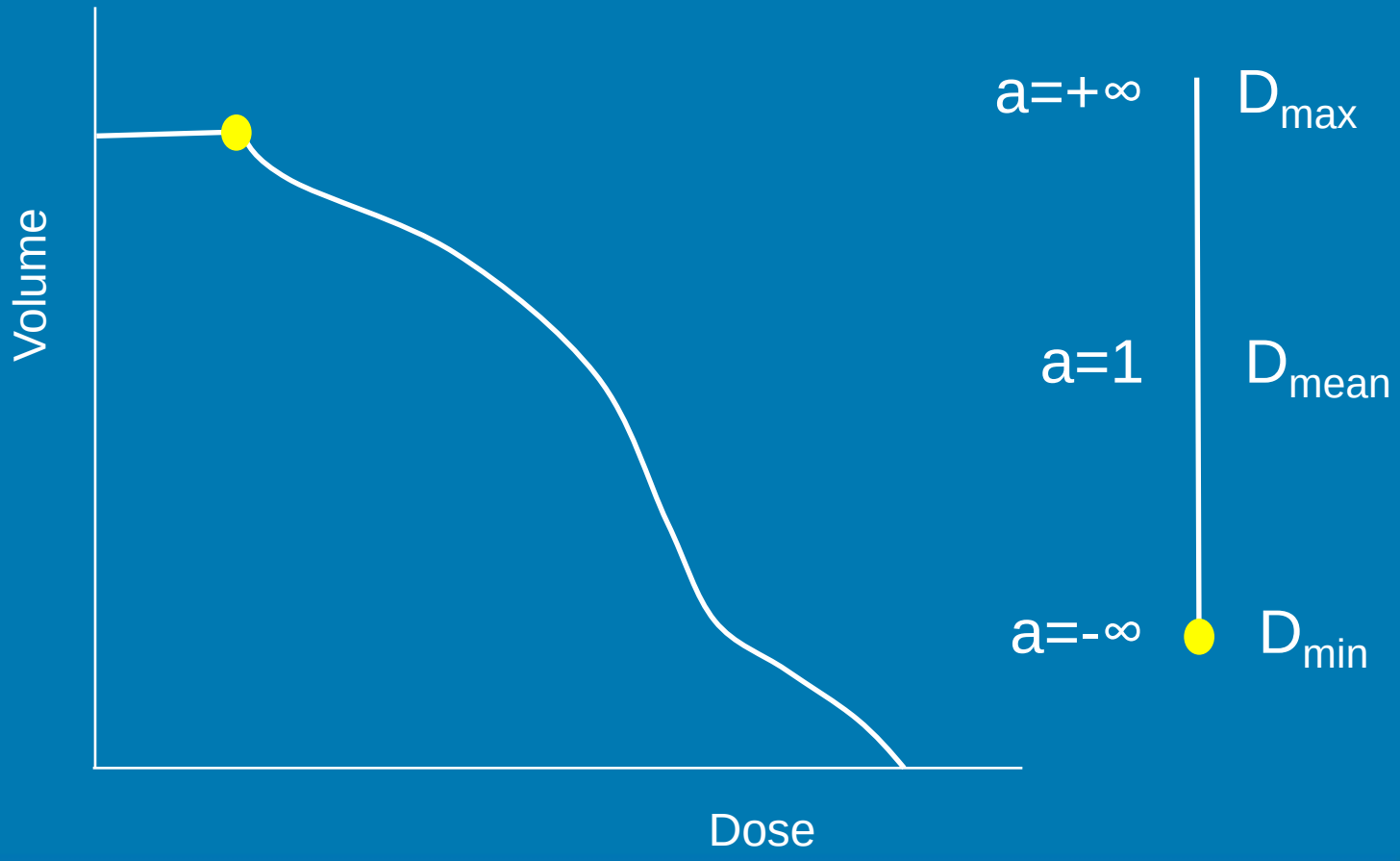
$$\mathrm{EUD} = \frac{1}{N} \sum_{i=1}^{N} d_i$$

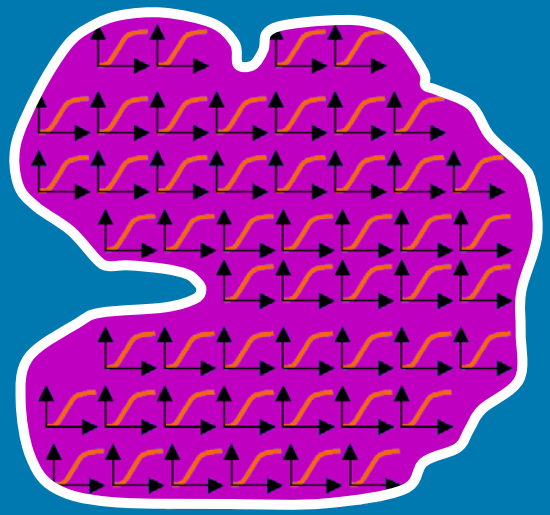
	Effect	Suitable organs
$a < 1$	Lower doses are given higher weight, so that cold spots affect the EUD to a large extent.	Targets.
$a = 1$	This corresponds to the mean dose. Cold and hot spots are given equal weight.	Parallel organized normal tissue, such as lung and liver.
$a > 1$	Larger doses are given higher weight, so that hot spots affect the EUD to a large extent	Serial tissue, such as the spinal cord.

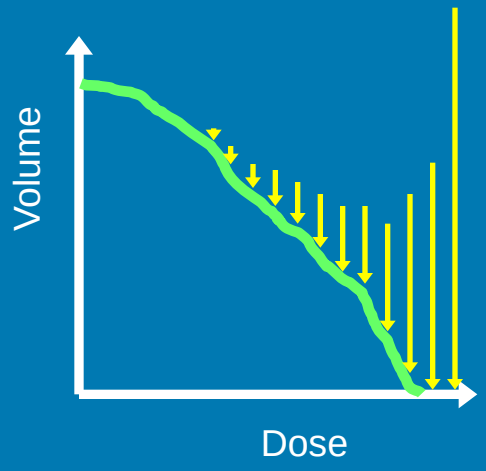
Equivalent uniform dose



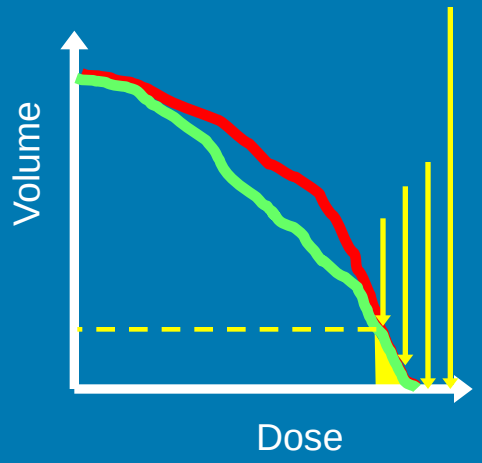
Equivalent uniform dose



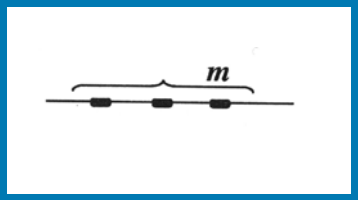


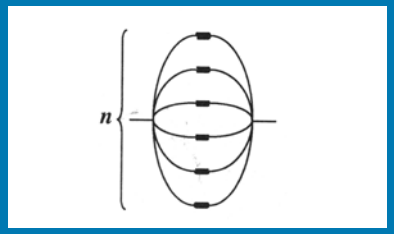


in contrast
d_{max}

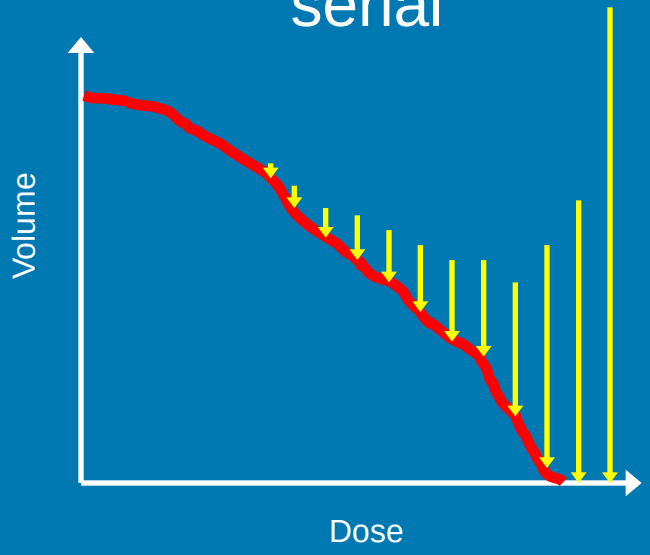


Essentially, a biological cost function is applied to each volume element of a structure
The total effect is described in the resulting DVH

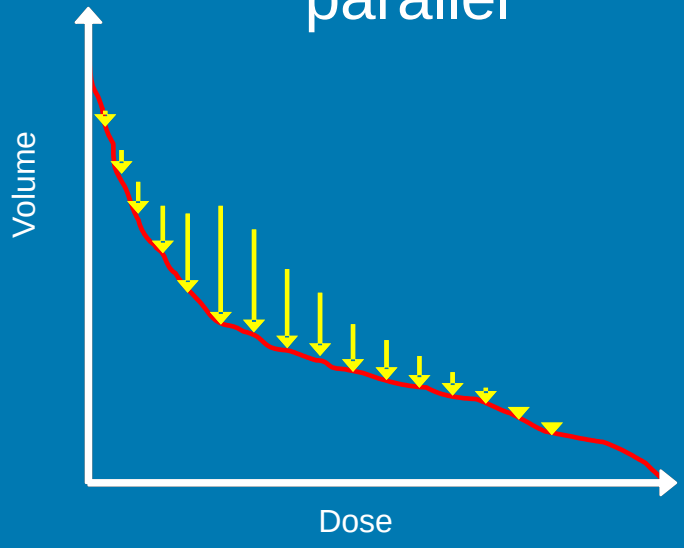




serial

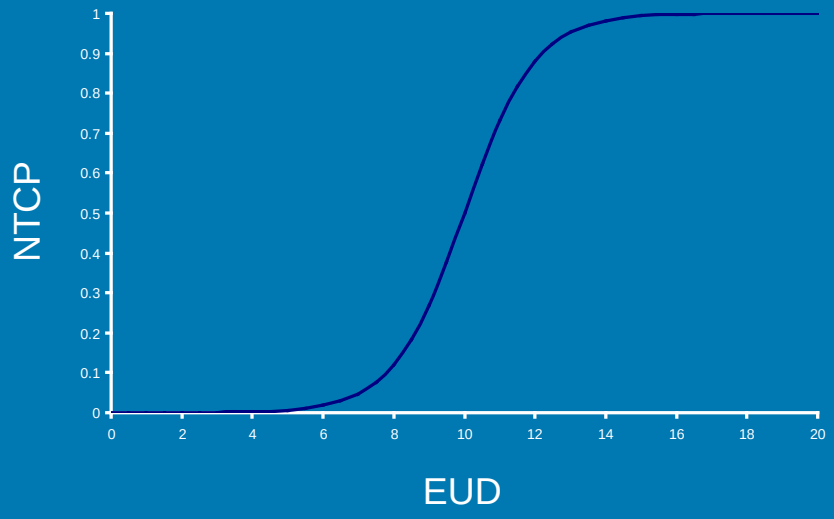


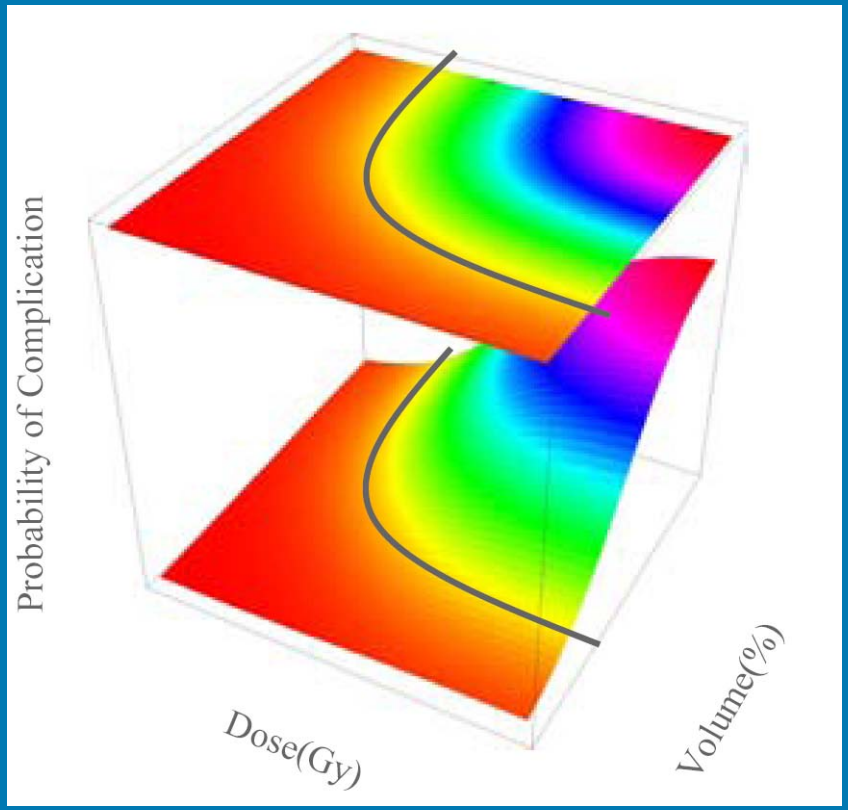
parallel



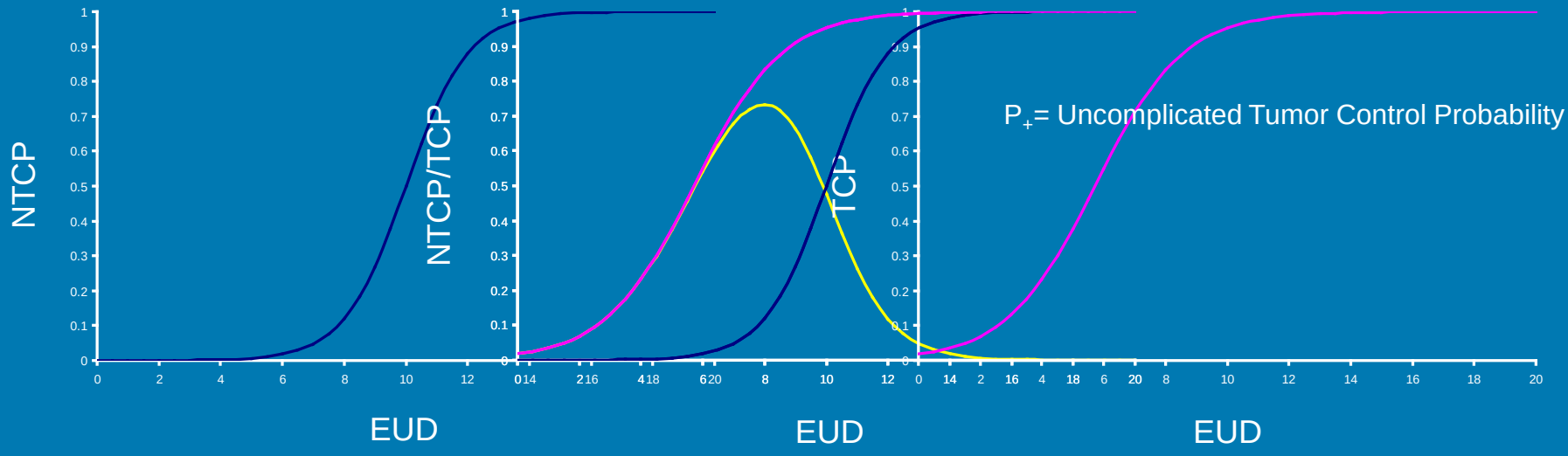
Can we go beyond EUD?

NTCP =
normal tissue complication probability





Can we go beyond EUD?



Limitations

Biological optimisations

- Knowledge about biological effects and clinical data is scarce and incomplete
- The models are insufficient and the parameters are uncertain
- Models are not self-limiting: dose distributions can be generated beyond the model's range of validity

Advantages

Biological optimisations

- Both tissue architecture and radiation response are taken into account
- The volume effect is explicitly discounted for in the models used for optimisation
- Sigmoidal models seem to be more clinically relevant than a quadratically scored deviation from the prescribed dose

Conclusions

- **Physical optimisation** using quadratic cost functions to penalize the dose deviations seems practical, but may be too optimistic in meeting the clinical objective

- **Radiobiological optimisation** will become more trustworthy by judicious use of more accurate dose-response models

- **Physico-biological optimisation** can generate plans that are clinically recognized and fulfill the dose and dose-volume constraints based on clinical practice, while outperforming physically optimised plans

Special acknowledgements to Aswin Hoffmann who kindly provided many slides

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Particle therapy planning

Advanced Treatment Planning Course
14-18 September 2016 – Cambridge, UK

Markus Stock

(slide courtesy Gabriele Kragl, Till Böhlen, Barbara Knäusl)

MedAustron

ESTRO School

Content

- Photon vs. Protons
- Plan comparisons
- Particle therapy and uncertainties
- Other particle therapy planning specificities
- Short intro to carbon planning

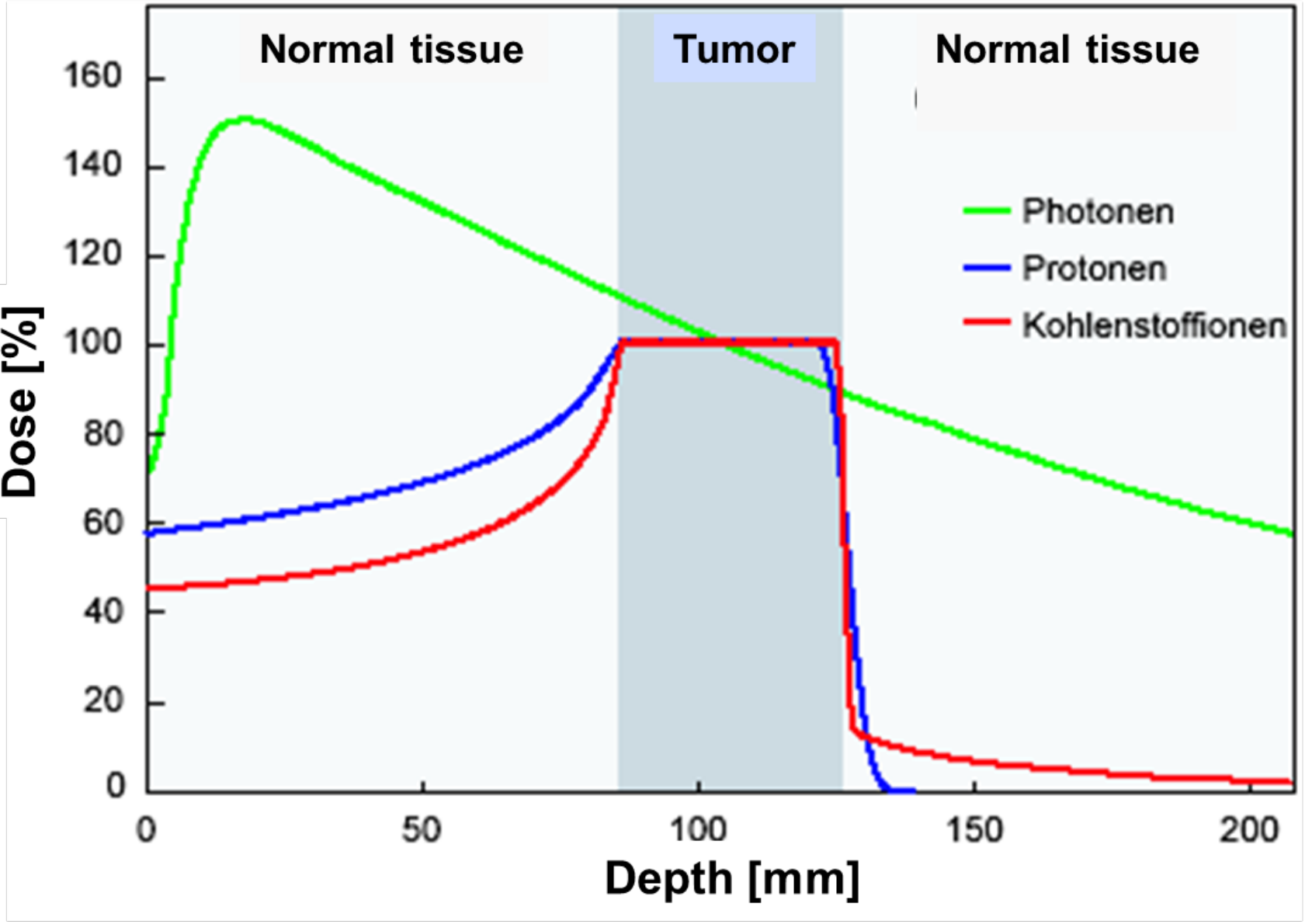
Differences between proton and photon planning

Differences derived from differences in physics

- Finite and controllable depth of penetration
- Penetration of protons strongly affected by the nature of the tissue (e.g. density)
- Proton therapy very sensitive to tissue heterogeneities
- Apparatus for proton-beam delivery is different
- For intensity modulated spot scanning proton therapy the „segments“ are defined by the spots and not by mechanical devices
- Intensity varied by number of particles in a spot (photon therapy: fluence modulation by using small segments)

ICRU 78: Prescribing, Recording and Reporting Proton beam Therapy

Unfair comparison



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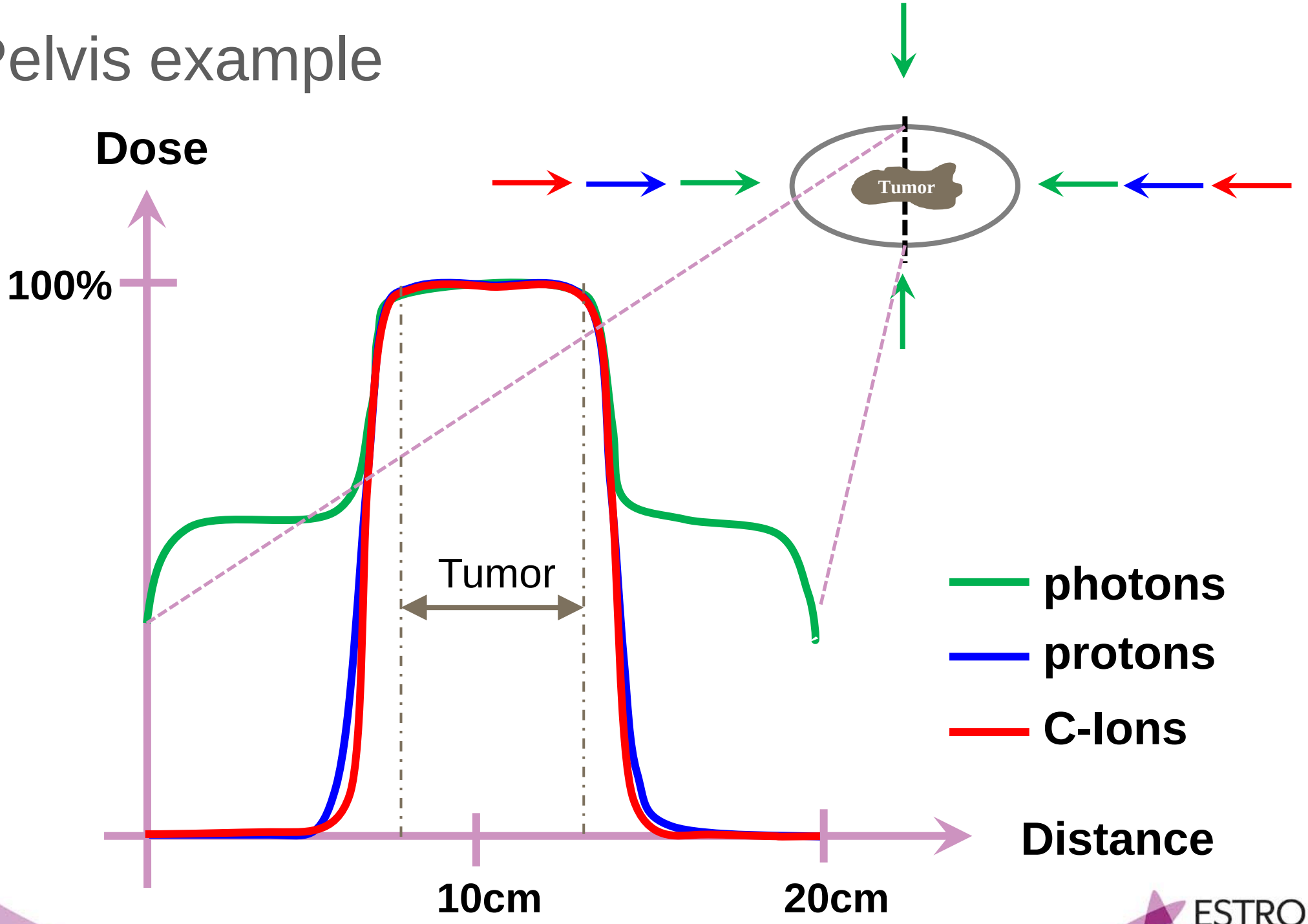
Pelvis example



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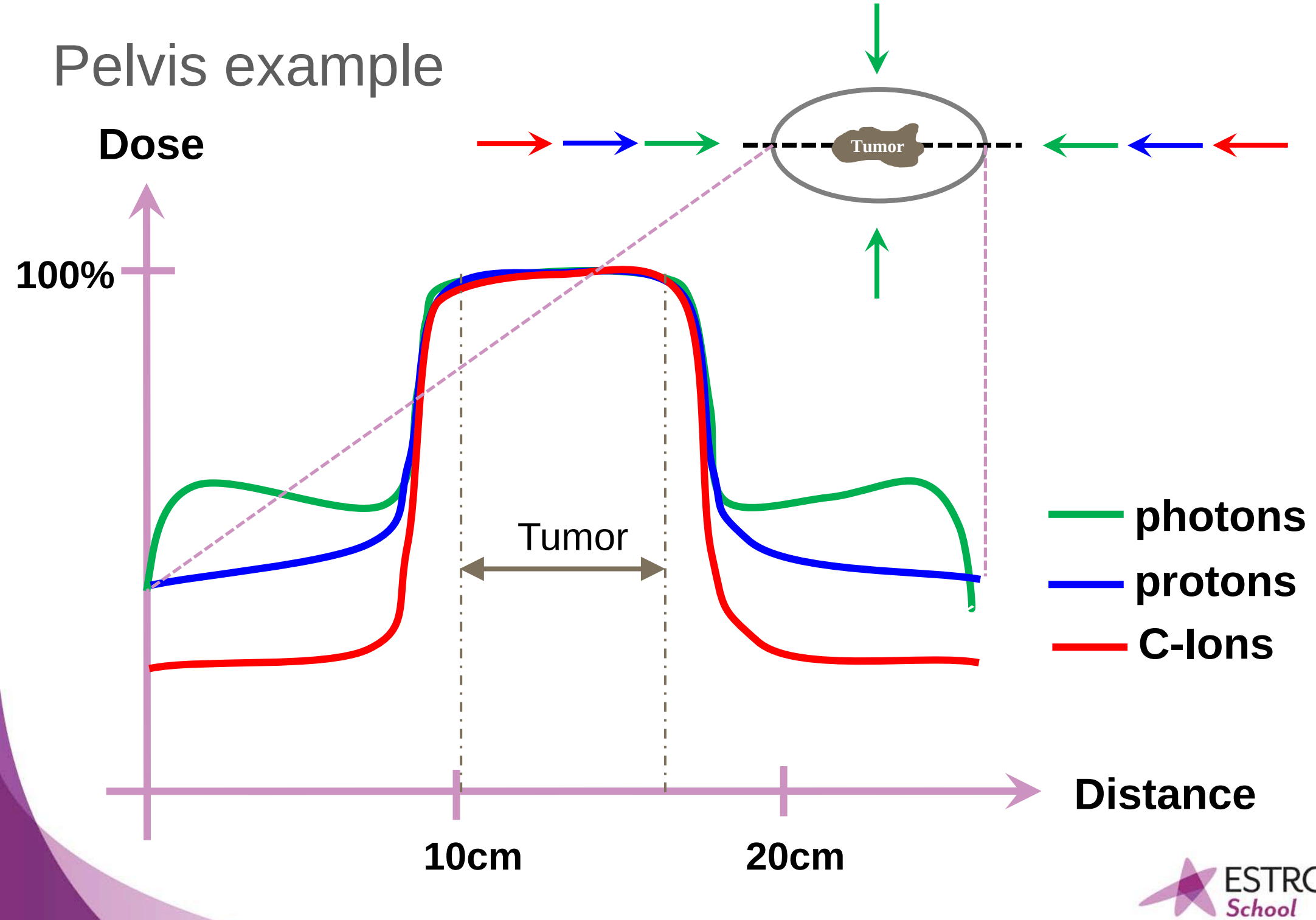
Pelvis example



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Radiation Production

LINAC vs. Cyclotron/Synchrotron

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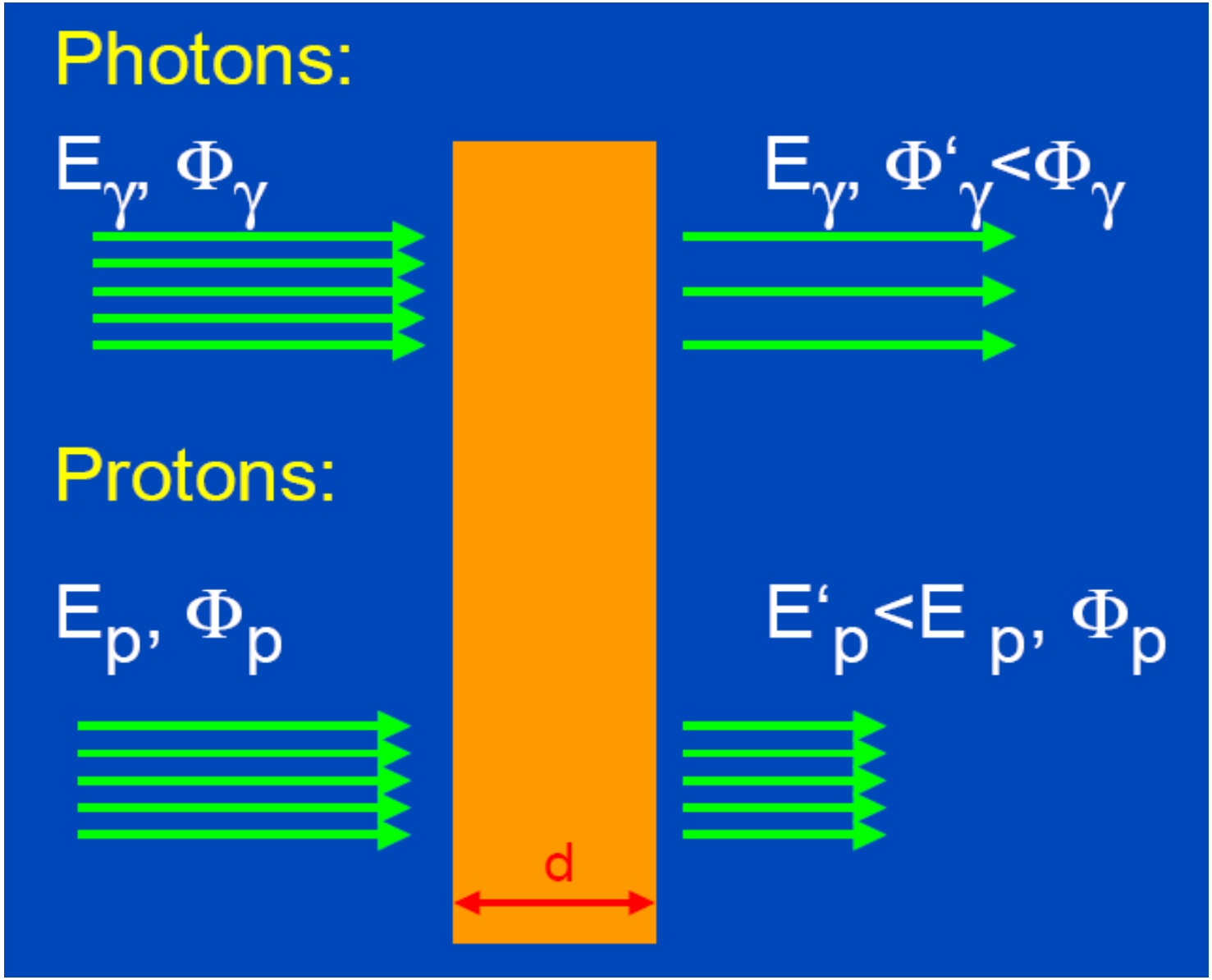
Fundamental Difference in Penetration



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Energy lost = Dose deposition

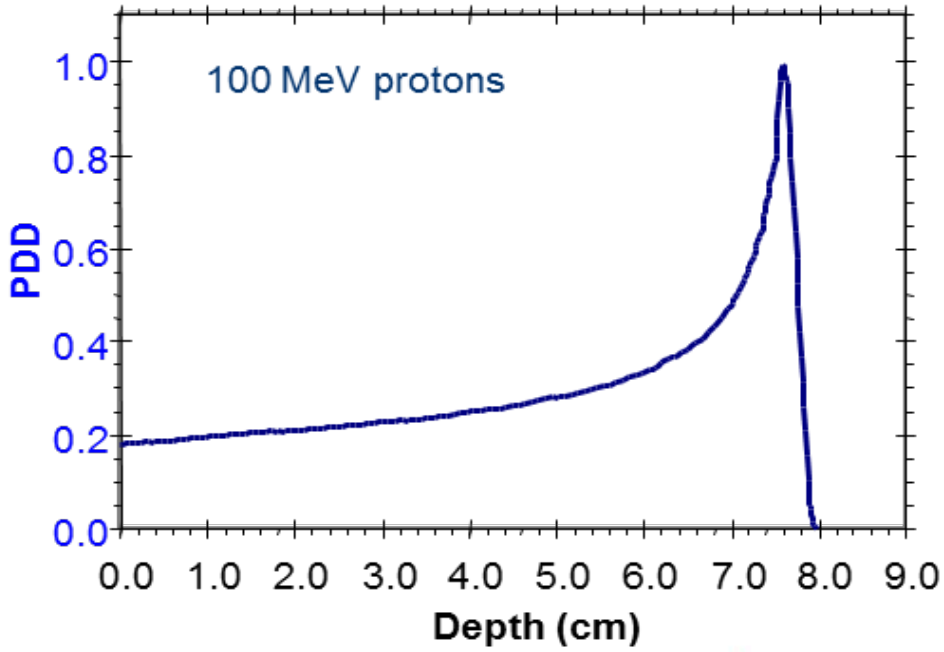
H. Bethe: Annalen der Physik. 397, Nr. 3, 1930

- Heavy charged particle follow the Bethe-Bloch formula:

$$-\frac{1}{\rho}\frac{dE}{ds} = \frac{K}{\beta^2}\cdot z^2 \cdot \frac{Z}{A}\left[\frac{1}{2}\ln\left(\frac{2m_e c^2\cdot\beta^2\cdot W_{\max}}{\left(1-\beta^2\right)\cdot I^2}\right) - \beta^2 + SDBB\right]$$

- First approximation:

  $1/v^2$ → Bragg peak



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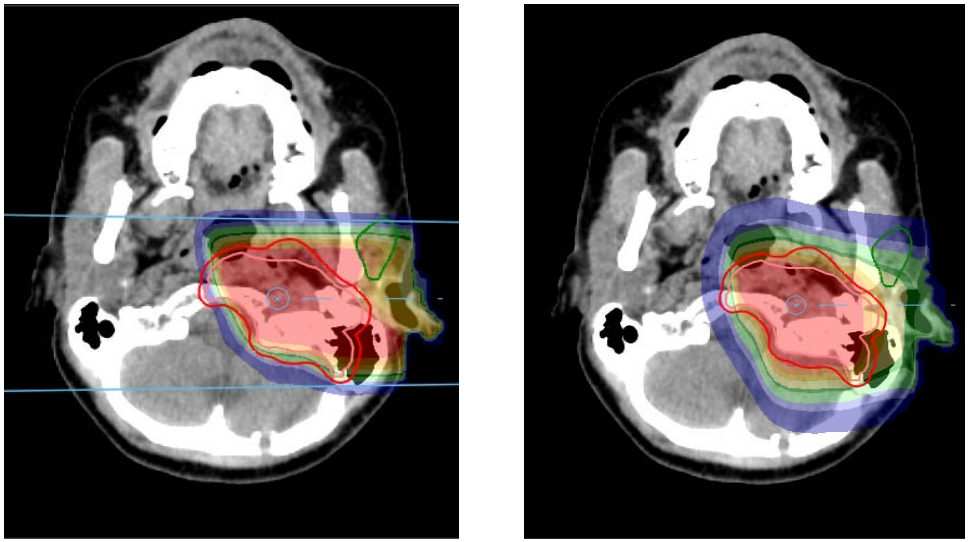
Passive vs. active particle beam delivery

- Mono-energetic pencil beam scanning (PBS) is widely considered superior to passive techniques.

PBS - PROs	PBS - CONs
• less passive elements in the beam line	• penumbra
• no patient customized passive elements	• (without mitigation strategies) less robust to organ motion
• reduced neutron dose	
• superior dose distribution	
• less fields required	

Planning exercise (single field):

double scattering vs. IMPT



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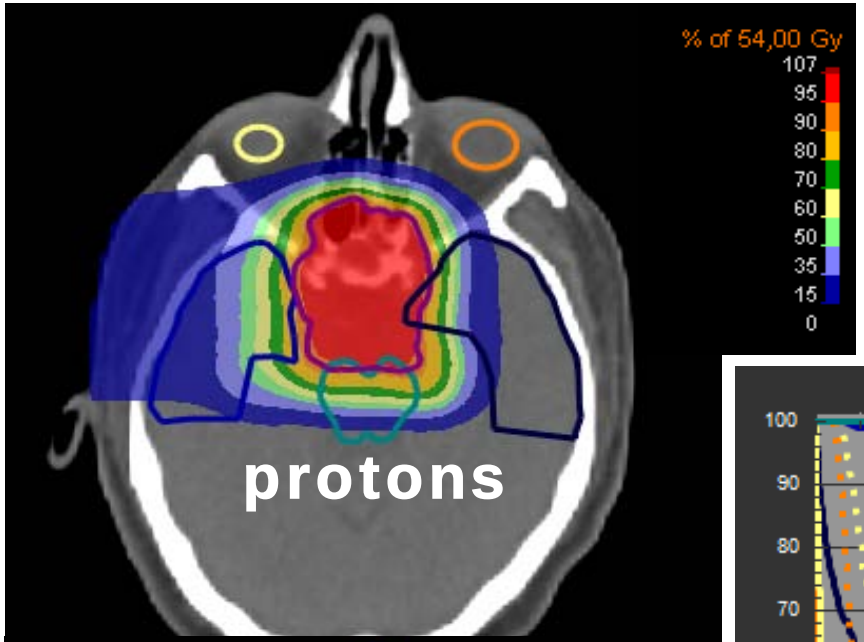
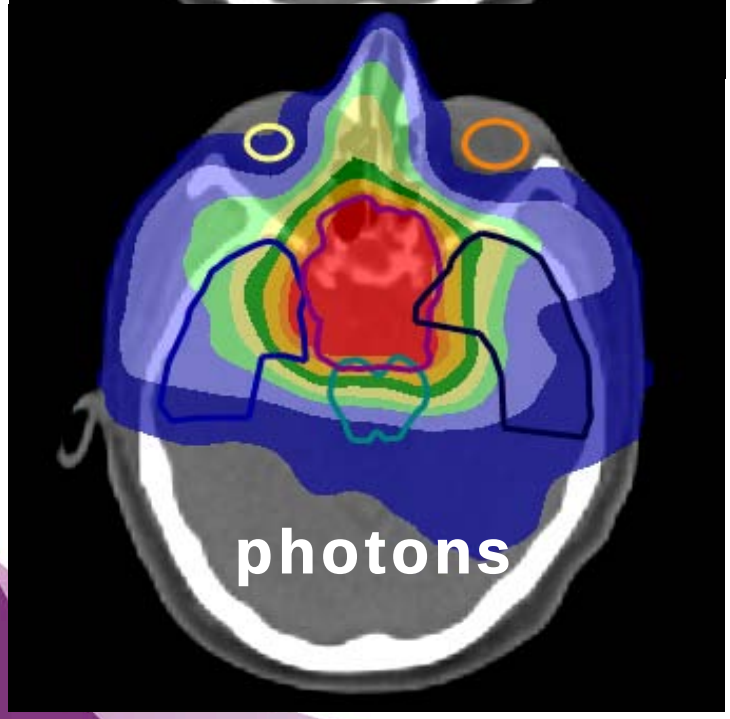
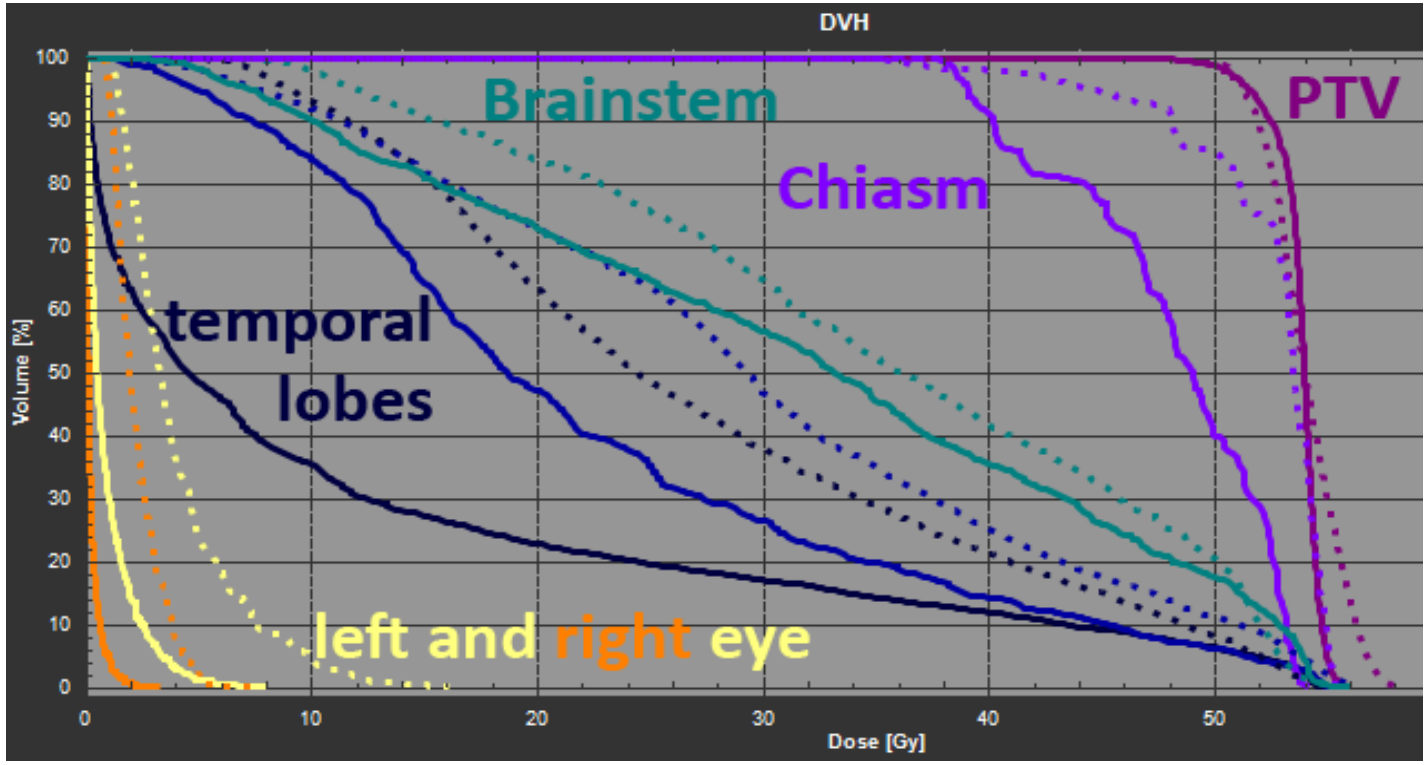
Skull base chordoma





Solid: protons (IMPT)

Dotted: photons (VMAT)



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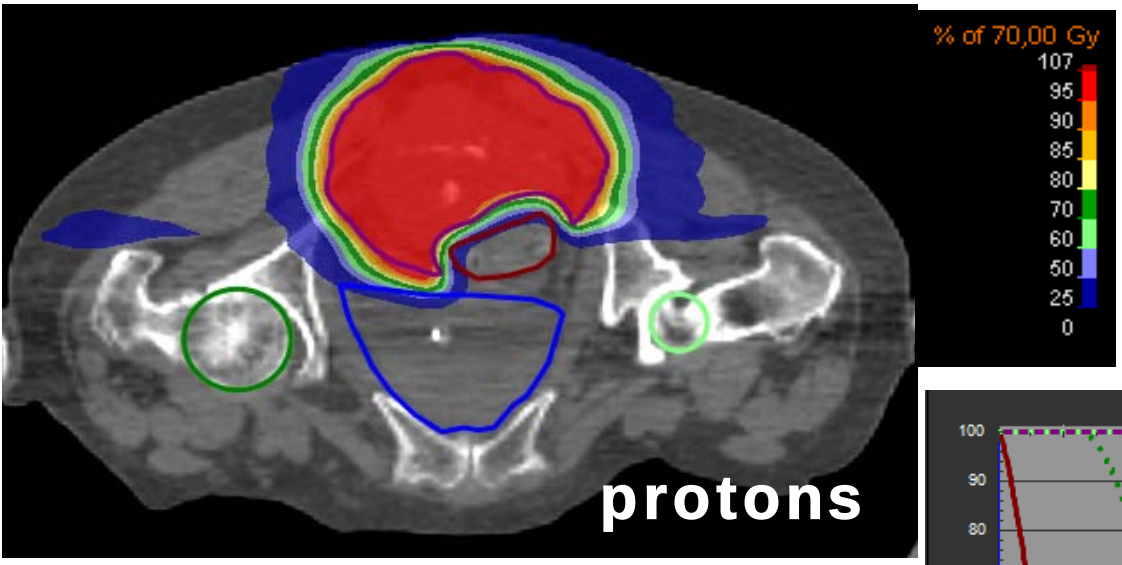
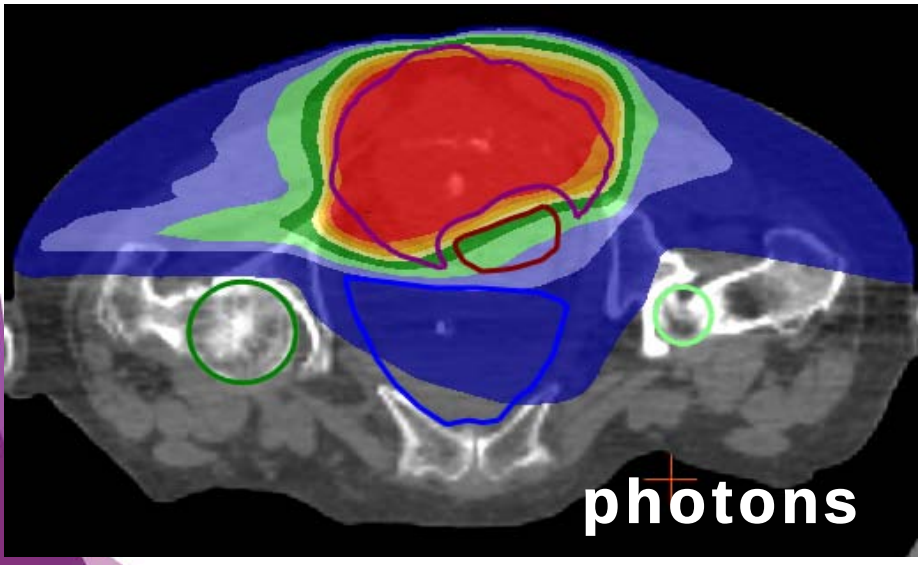
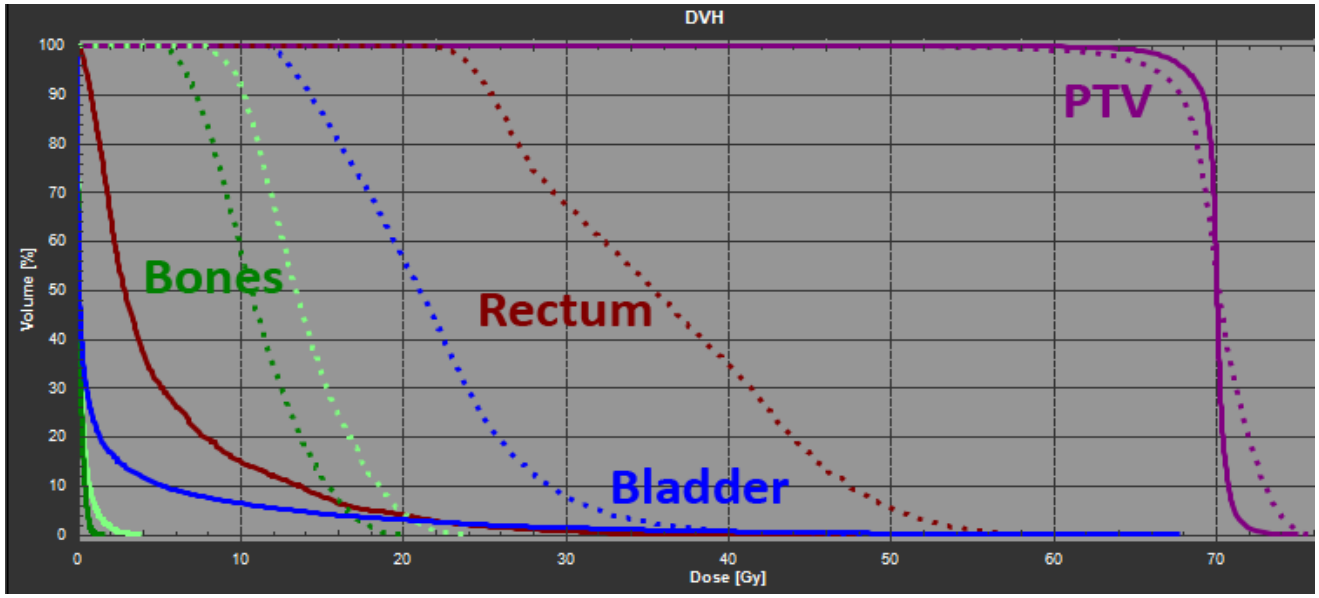
Sacrum chordoma





Solid: protons (IMPT)

Dotted: photons (VMAT)



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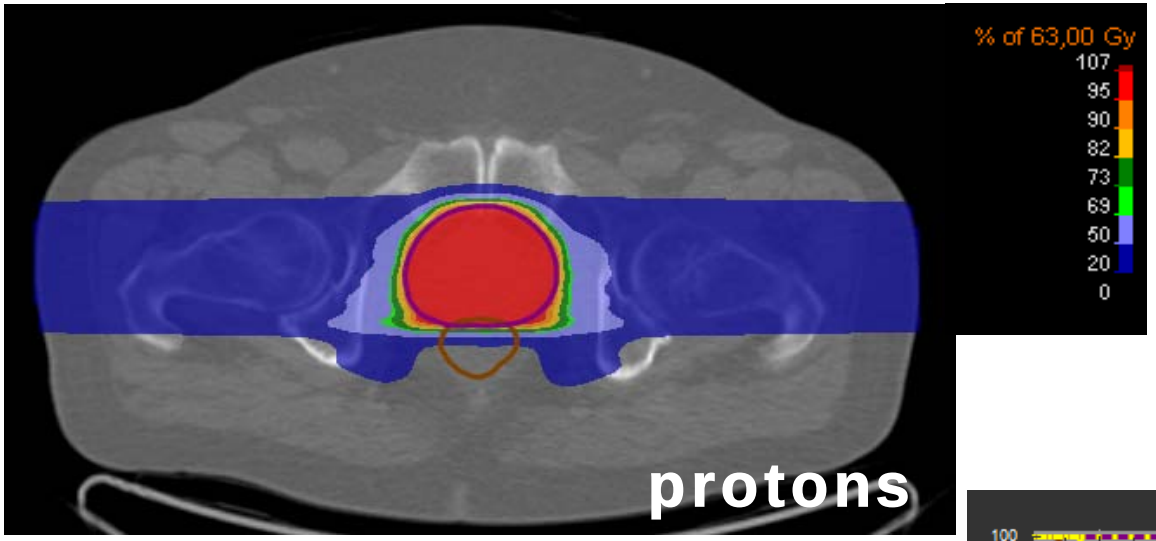
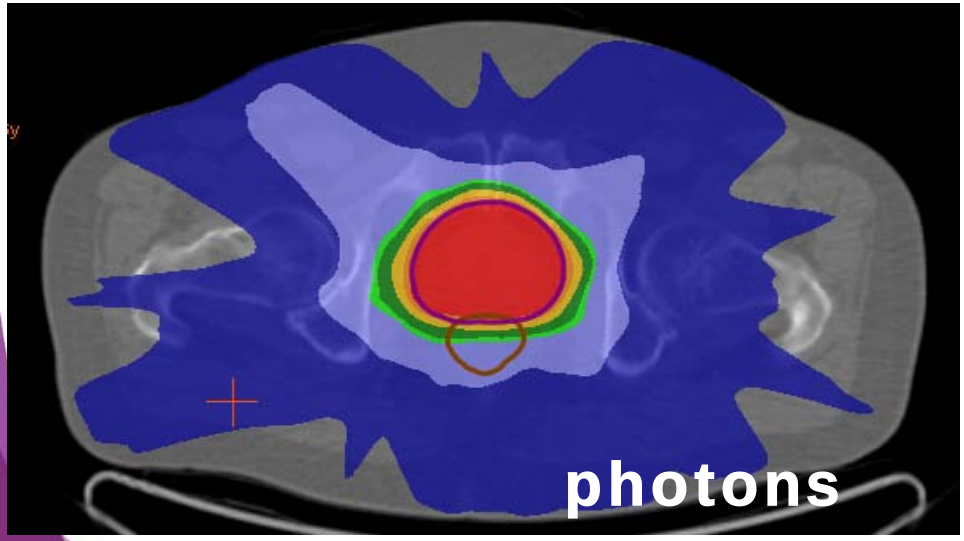
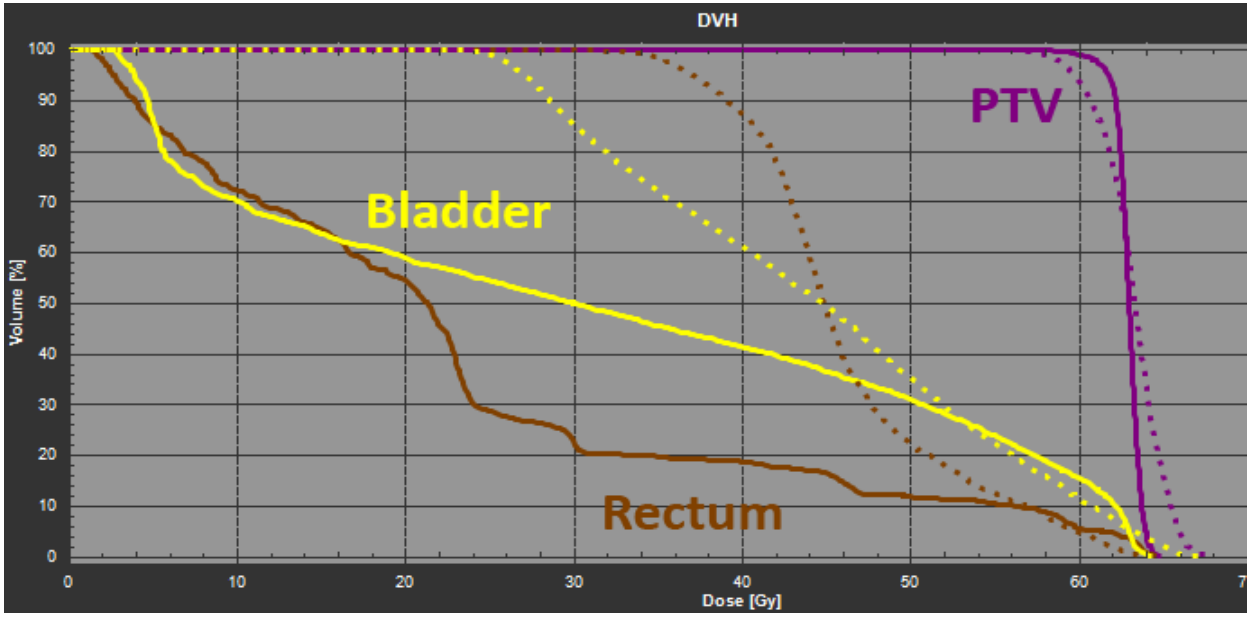
Prostate





Solid: protons (IMPT)

Dotted: photons (VMAT)



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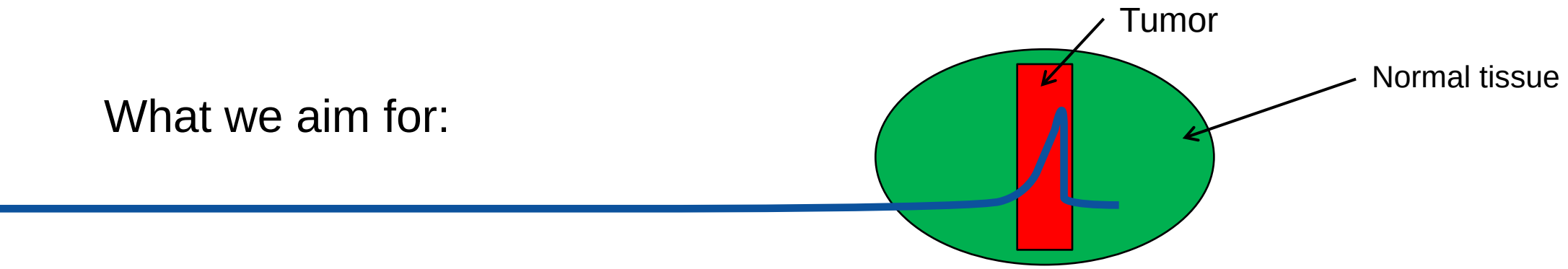
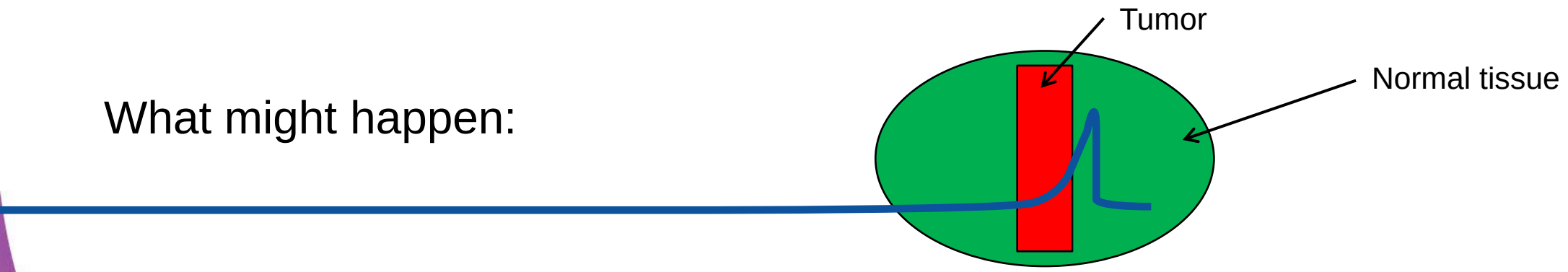
Effect of range uncertainties

What we aim for:

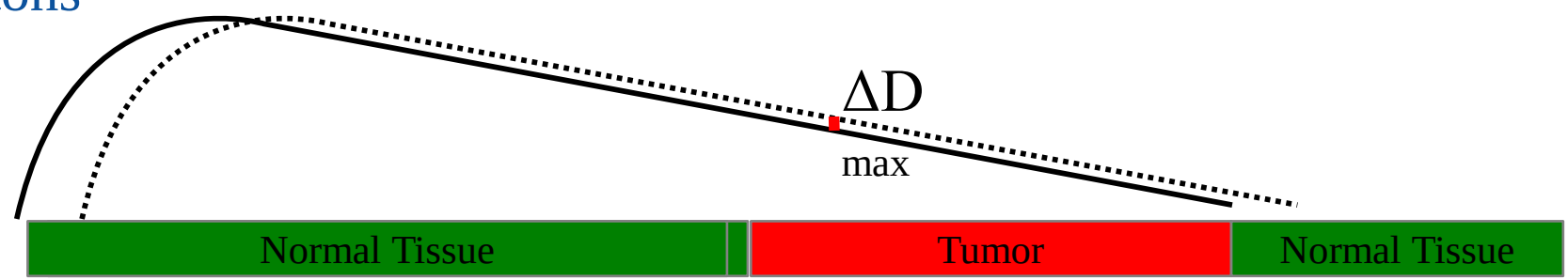


What might happen:

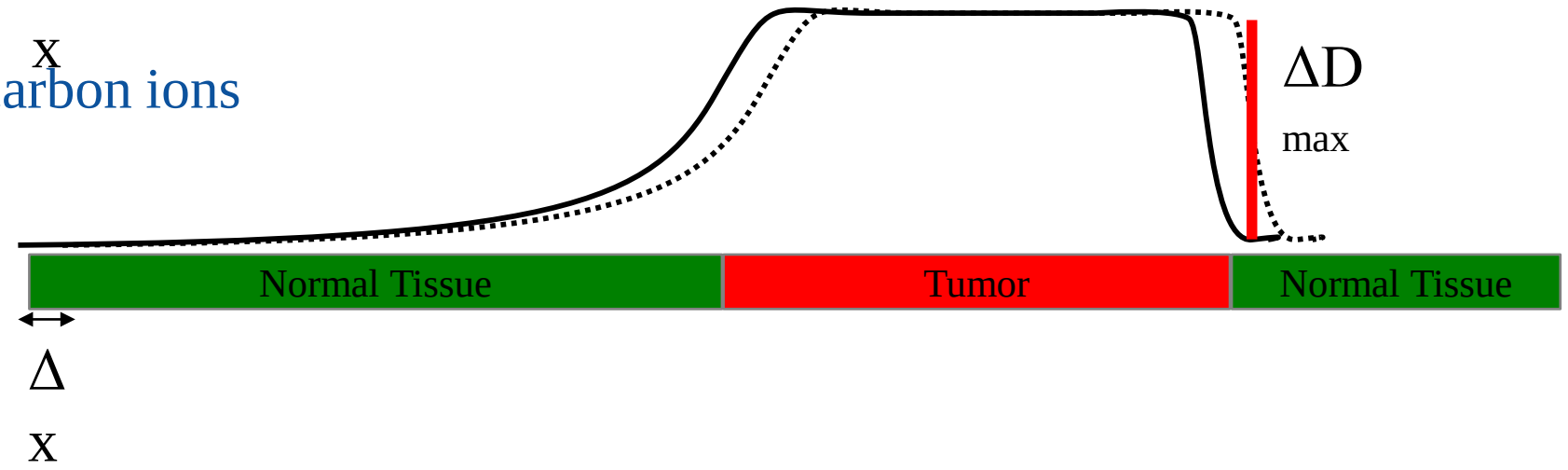


Effect of range uncertainties

MV photons



Protons/carbon ions



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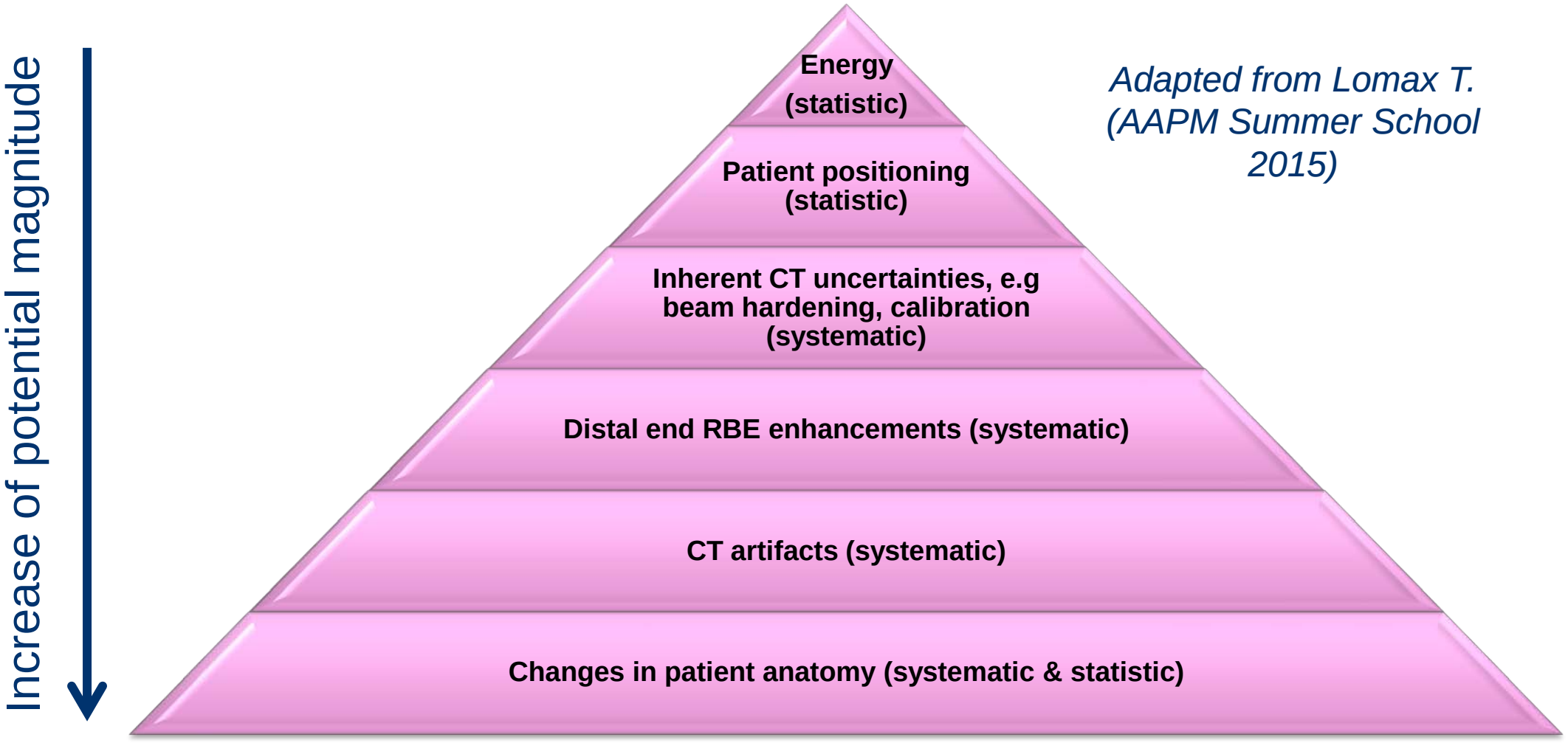
Range uncertainty



Adapted from Lomax T. (AAPM Summer School 2015)

- Estimated sum of range uncertainties: ~3 - 5%
- Range uncertainties are likely to be systematic.

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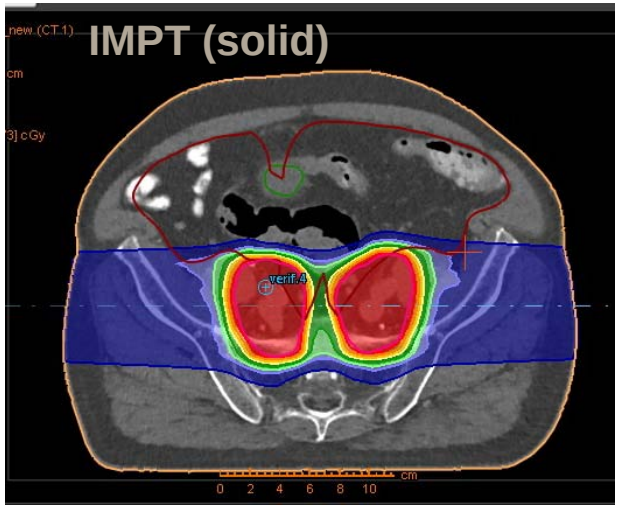
Dealing with uncertainties in TP

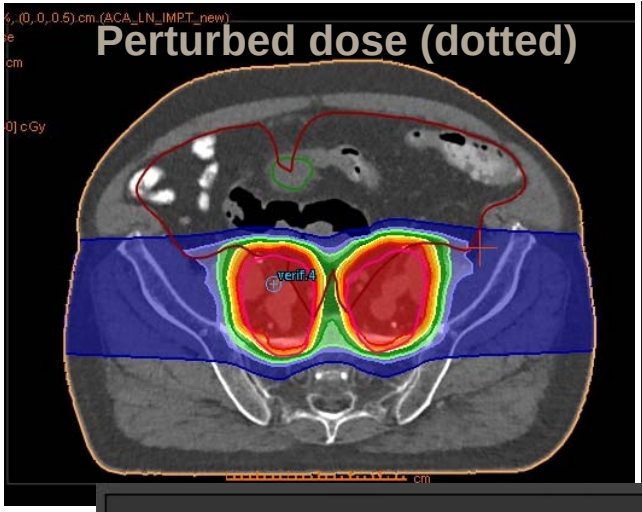
- Robust beam arrangement
- Use of PRVs
- Beam specific PTV margins
- Use single beam optimization
- Robust optimization

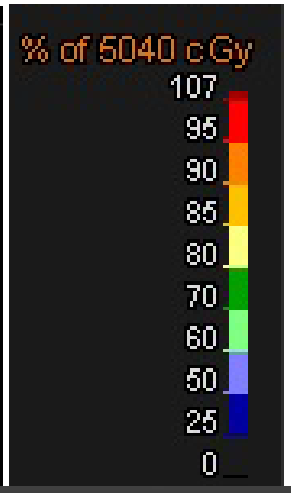
Evaluation of robustness

(Advanced tools in commercial TPSs required!)

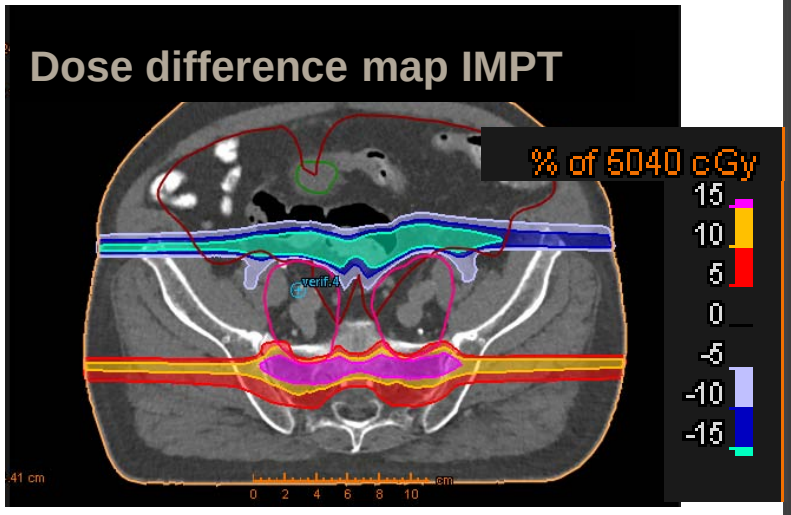
Clinical example for dose distortion

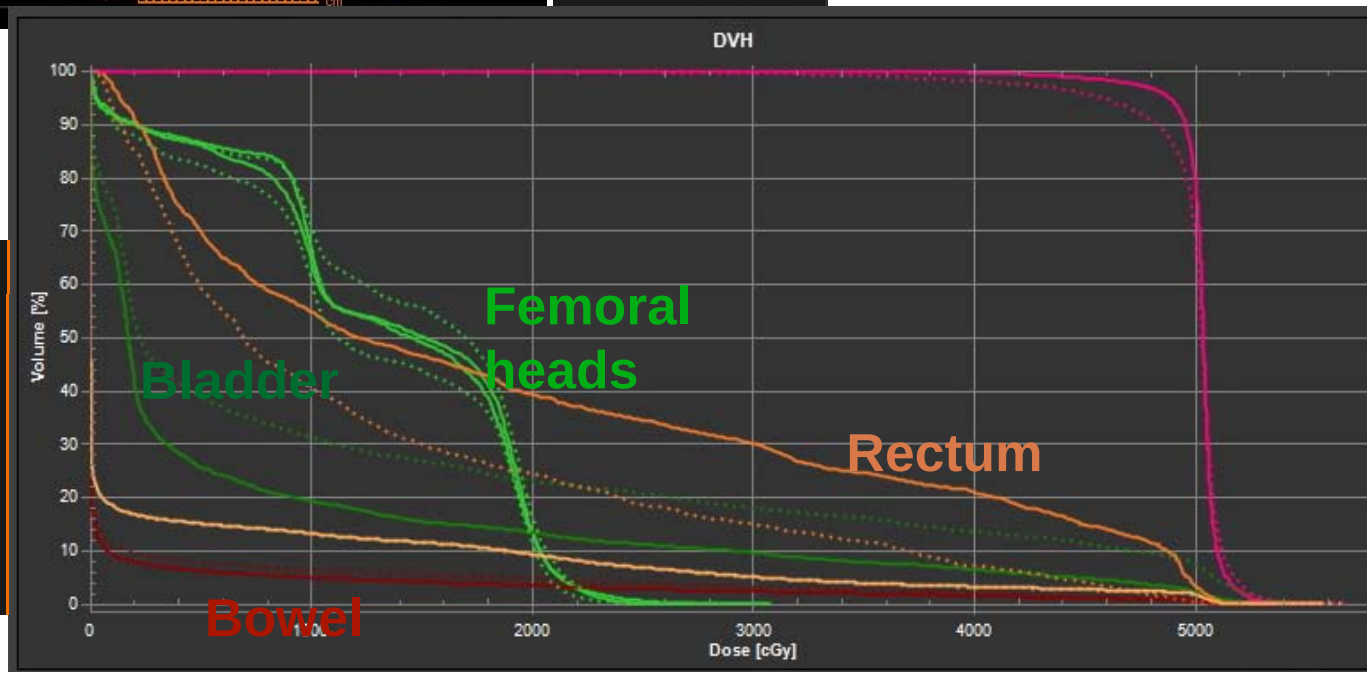






shift Patient 5 mm posterior





Treatment plan robustness

Robustness of a treatment plan is one of the most important criteria in the plan assessment – complex treatment plans are susceptible to errors

Major uncertainties:

- Ion range
- RBE (fragementation tail of carbon ions)

Possibilities to achieve a good robustness

- Beam through most homogenous tissue (avoid areas with larger movement)
- Avoiding beam angles perpendicular to organ motion

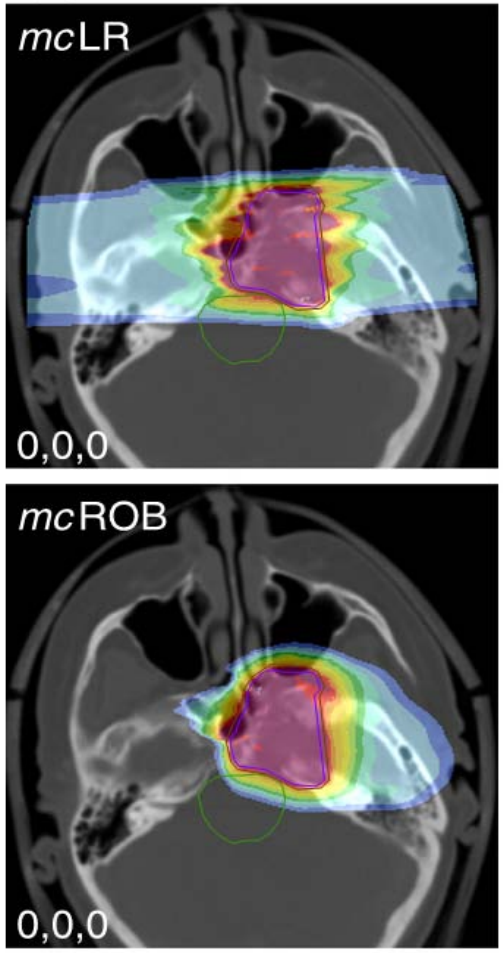
Assessing robustness against set-up errors and patient or organ motion by simulating these variation and their influence on dose distribution

Opposing field arrangement is very robust with regard to range uncertainties

PTV margins can be optimised in order to maximise the robustness

Robust beam arrangement

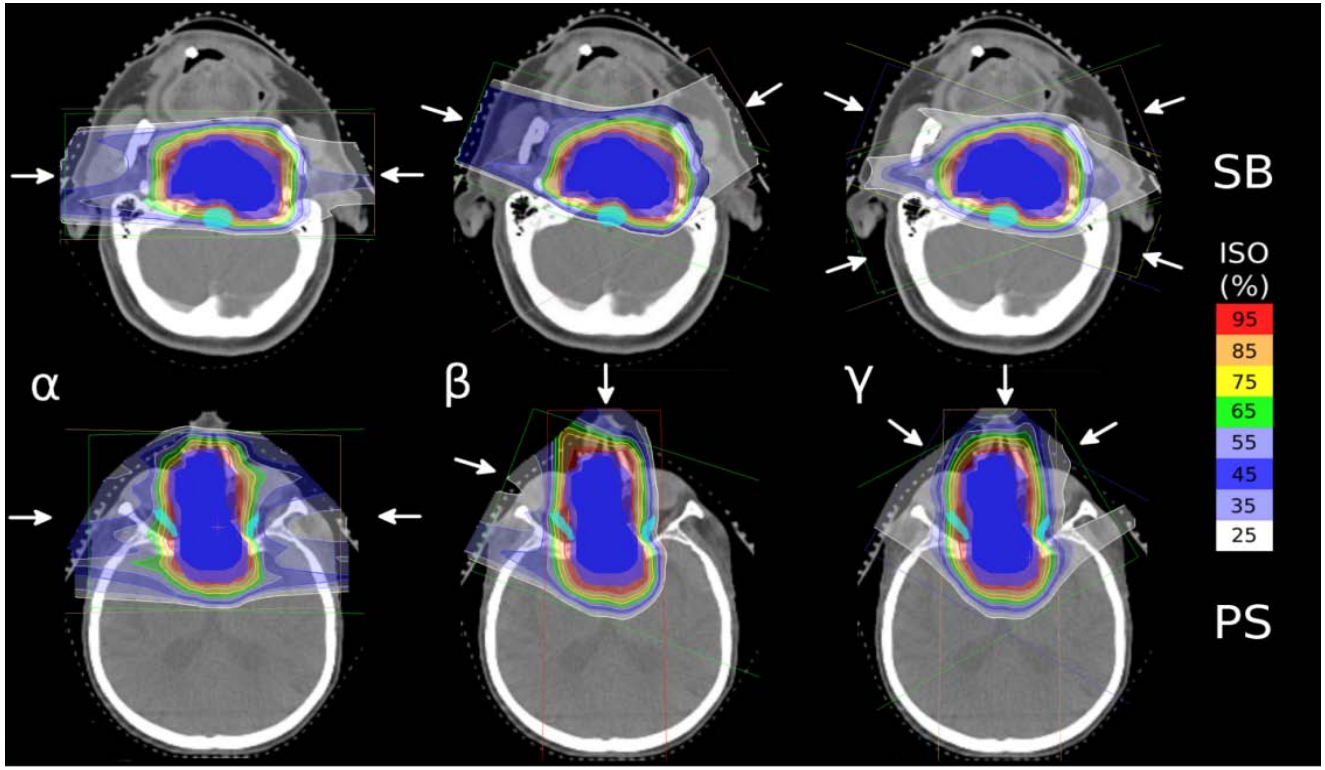
- dose homogeneity: ***choose beam angles avoiding*** large ***density interfaces*** along the beam axis
- range uncertainty: ***avoid*** placing ***Bragg peaks proximal to*** critical ***OARs***
  - beam incidence parallel to OARs
  - spot positioning margins/restrictions around OARs

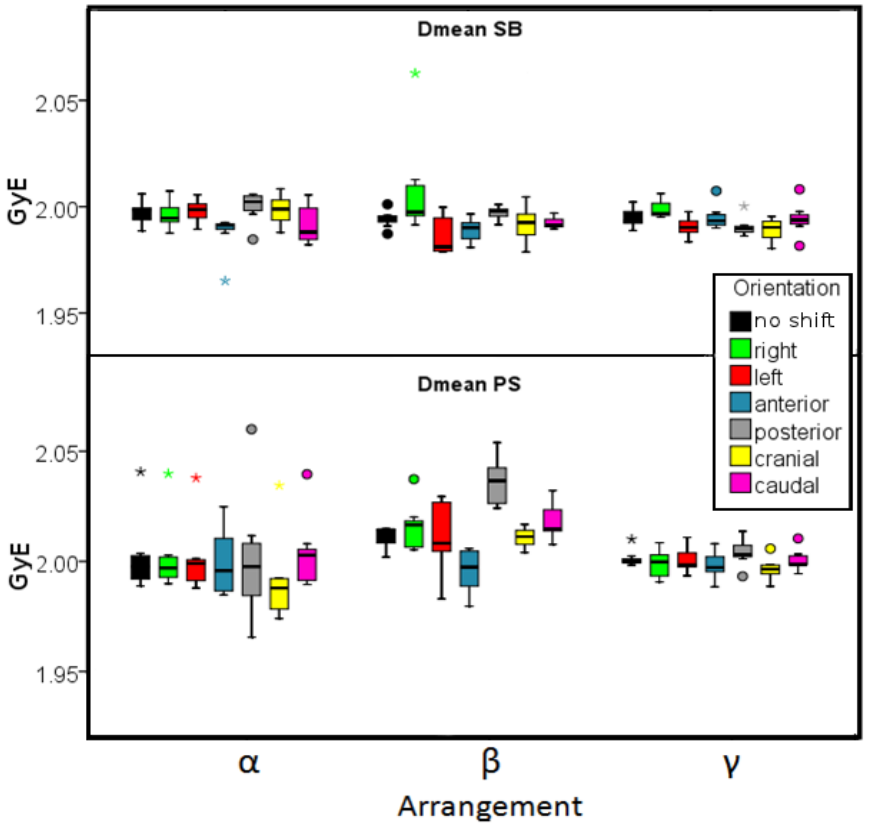


Ammazalorso et al. Radiat Oncol 9 (2014)

Robust beam arrangement

- use multiple beams





Hopfgartner & Stock et al (2013) Acta Oncol 52:570-79

No gantry approach α: lateral opposed beams (2 fields)

Gantry approach β: individually optimized beam angles (2 fields)

Gantry approach γ: multi-beam approach (3 or 4 fields)

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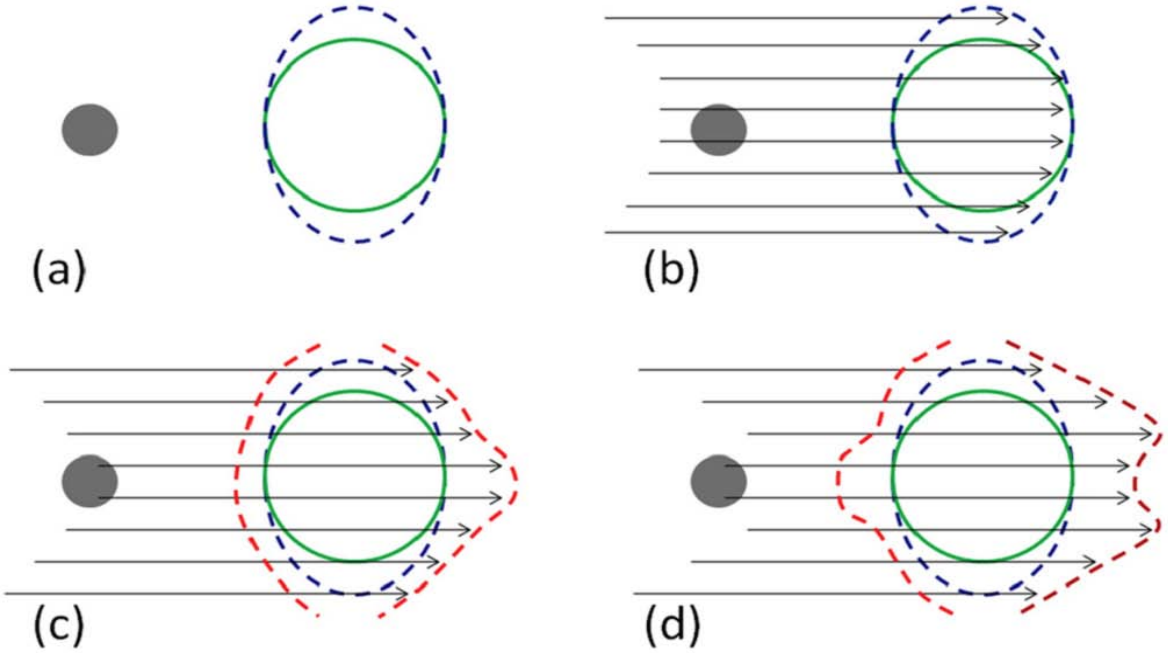
Beam specific margins

- Dealing with the range uncertainty separately by ***applying*** additional ***beam specific margin*** on top of positioning uncertainty.



Park et al (2012) IJROBP 82(2):e329-36

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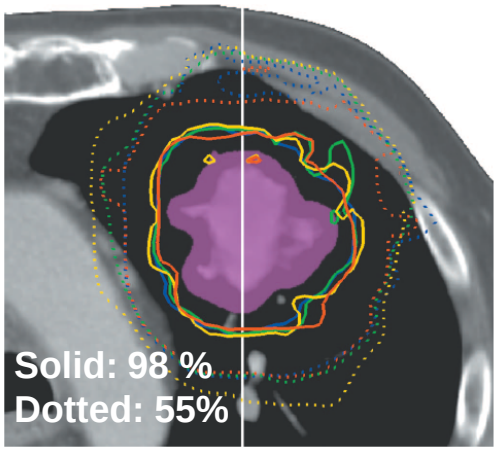
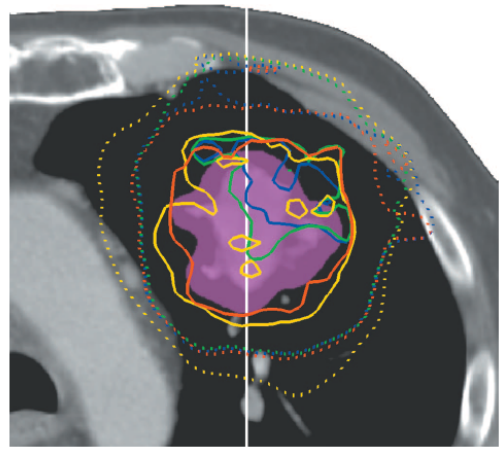
Robust optimisation

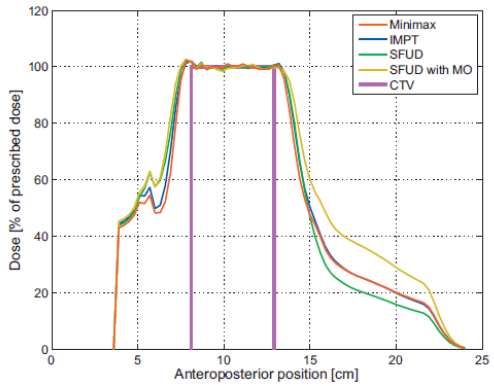
MinMax Optimization

- Minimizing the penalty of the worst case scenario
- Considers only scenarios that are physically realizable
- Accounts for uncertainties in the probability distribution of errors

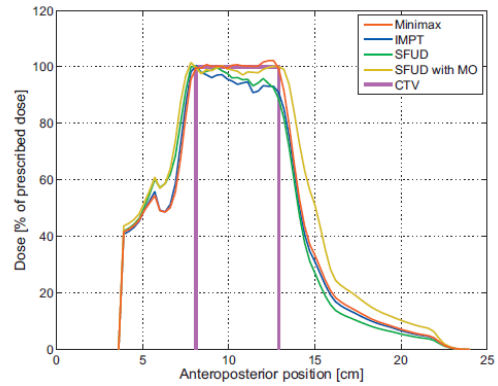


(a) Nominal scenario isodose curves


(b) Perturbed scenario isodose curves



(c) Nominal scenario line doses



(d) Perturbed scenario line doses

With robust optimization the traditional margin concepts becomes unsuitable

Robust methods are discretized into scenarios (choice of scenarios has high impact on the quality)

Up to … scenarios have to be calculated in case …is taken into account

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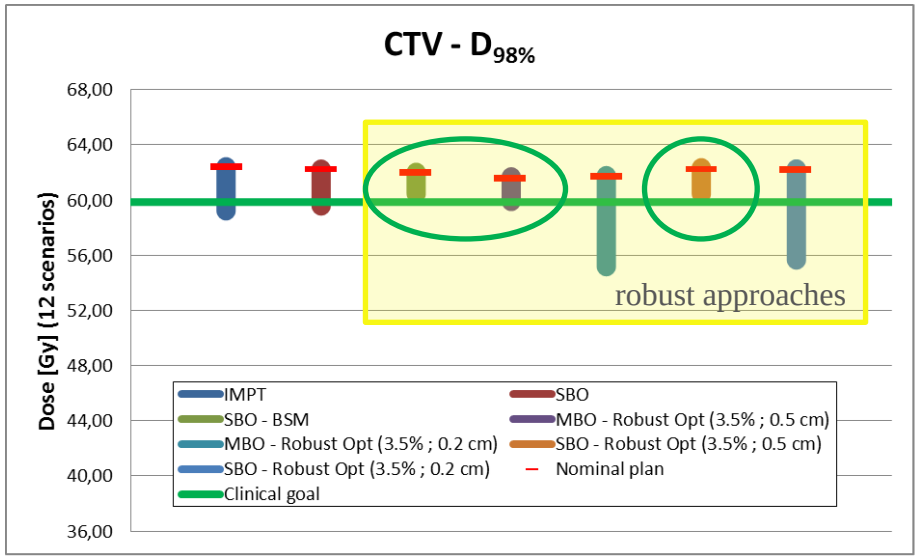
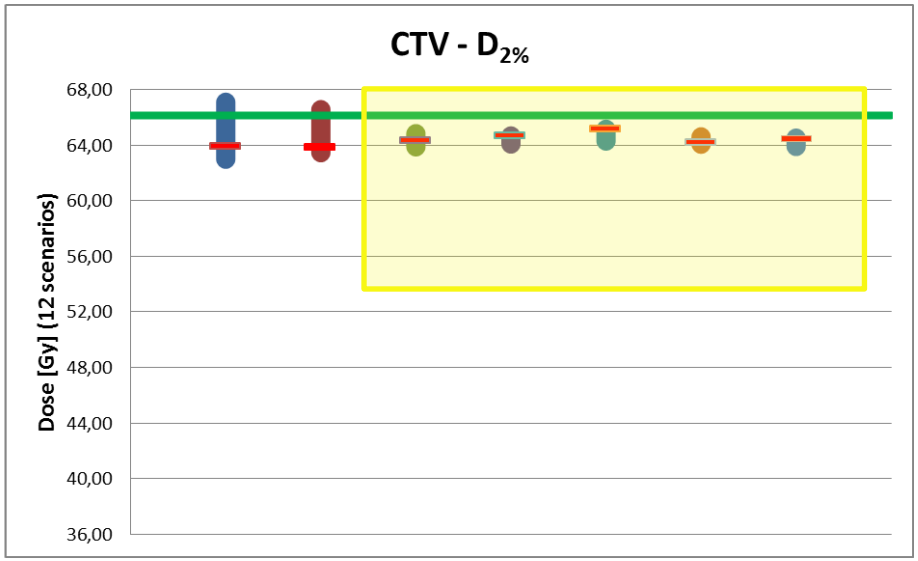
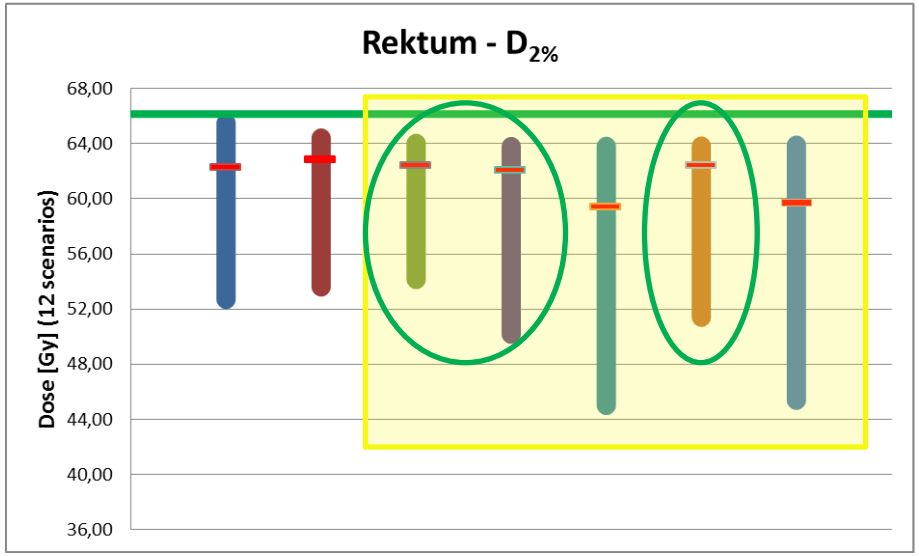
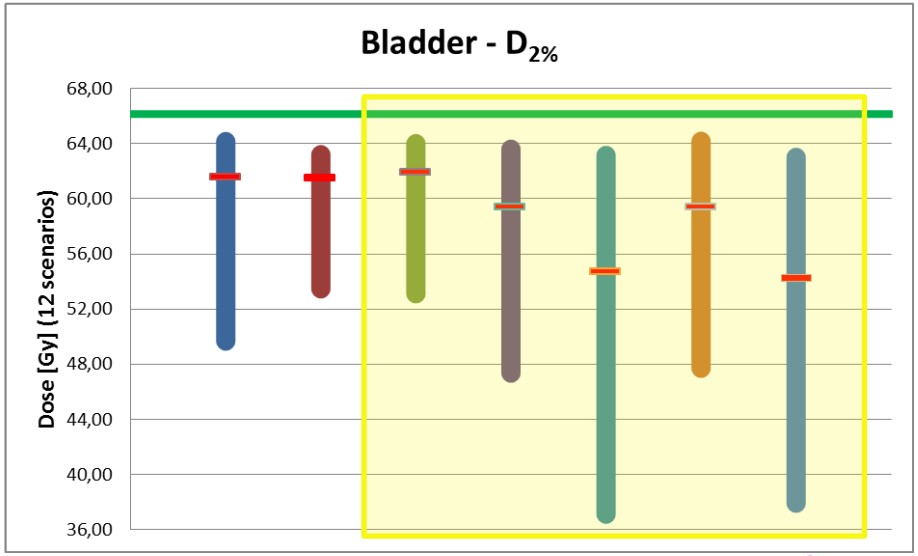
Robustness considerations e.g. Prostate









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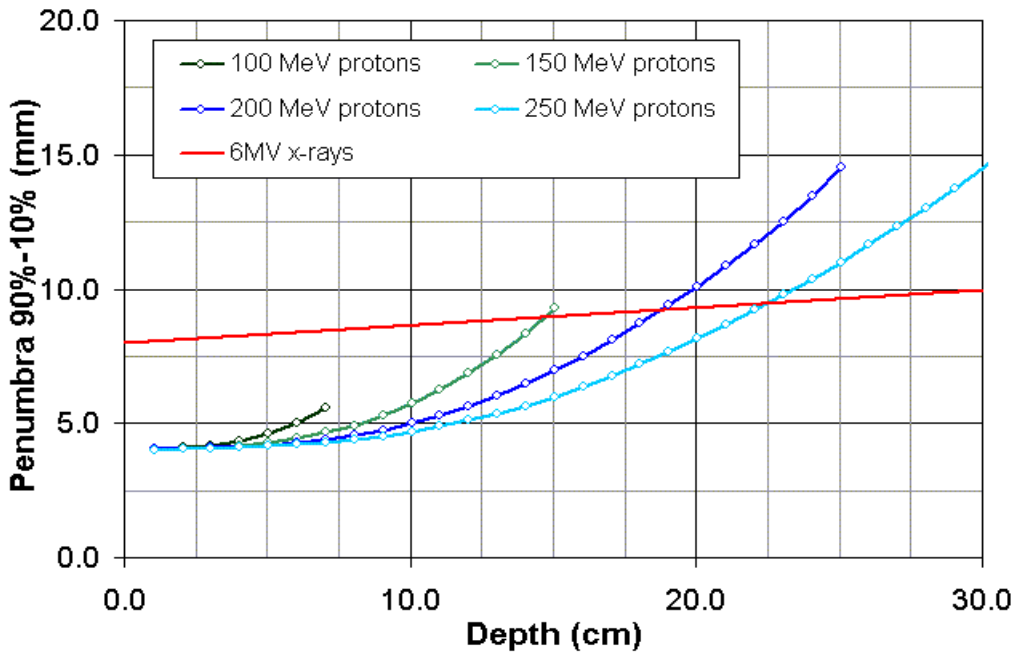
Penumbra

Lateral scattering:

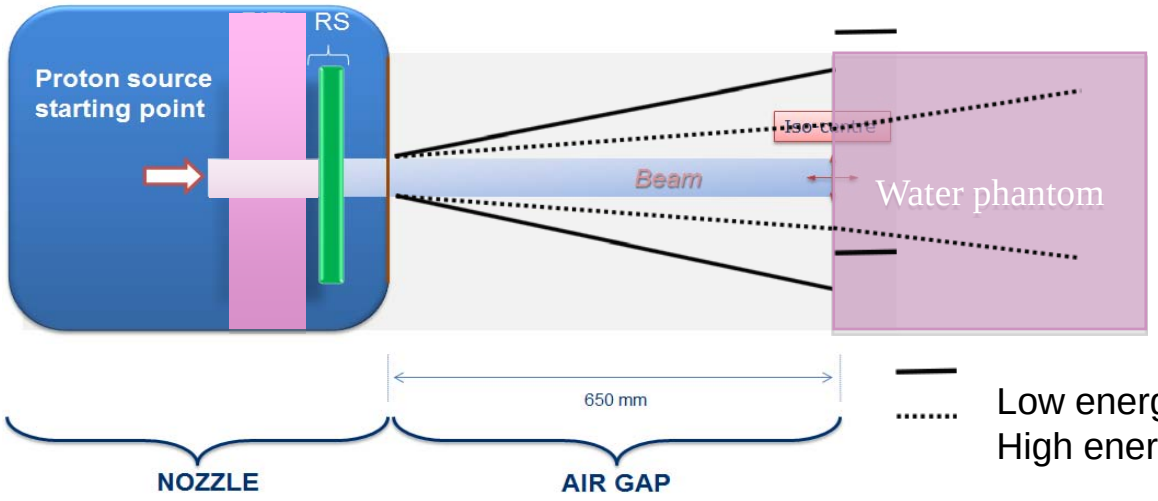
- MCS: penumbra increases with increasing penetration depth.
- Exceeds penumbra of photons at some point.



Courtesy Palmans 2006

Presence of range shifter (combined with low energies):

- Substantial increase of spot size.
- Dose calculation accuracy for PB algorithm impaired.
- ***Reduce air gap.***



Courtesy Grevillot 2014

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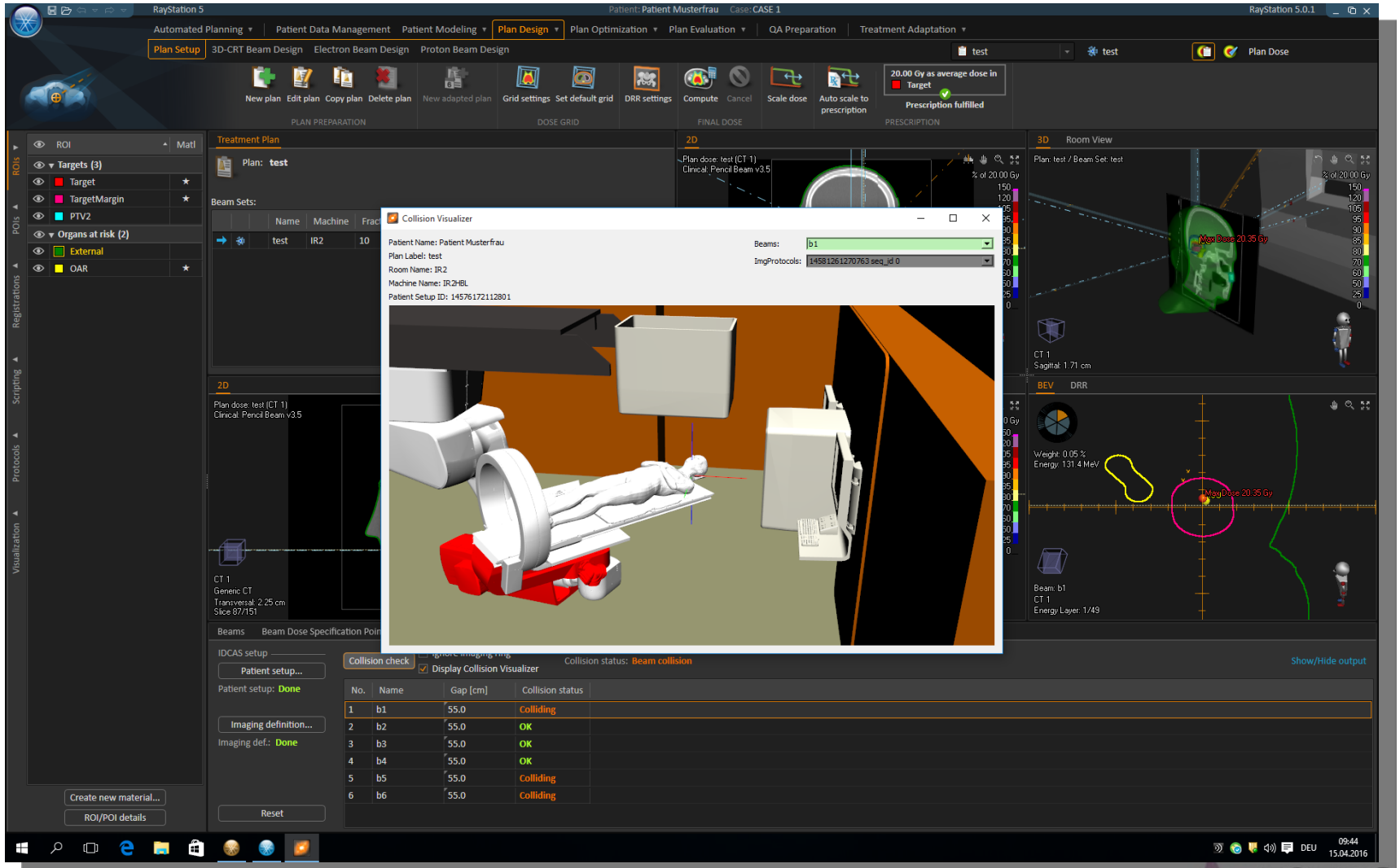
Penumbra

- Reduction of air gap

efficient workflow may be supported by TPS based modelling of room geometries

also check

Imaging protocols



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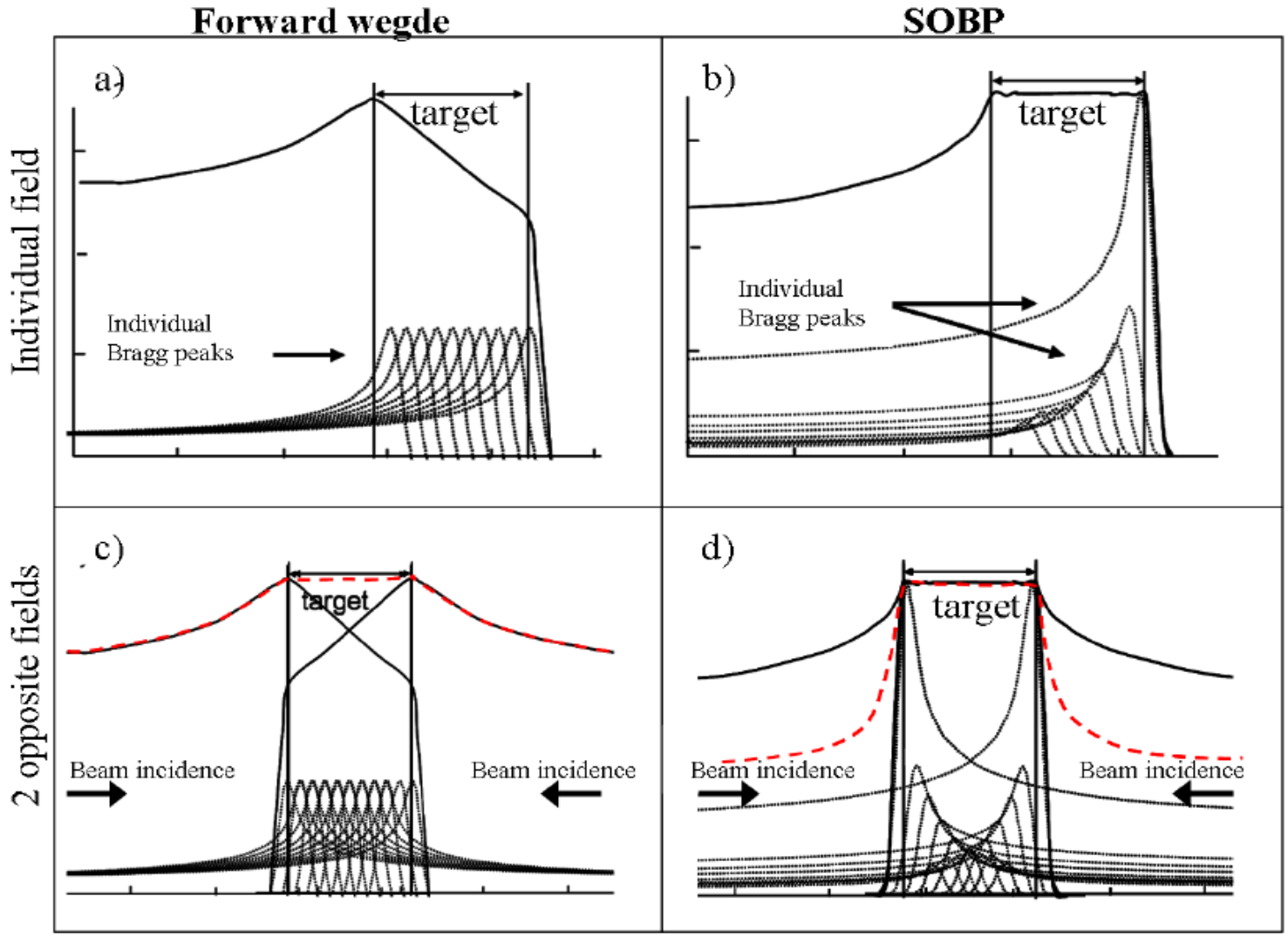
Integral dose



Dissertation, F. Albertini 2011, PSI Villigen

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CT artefacts due to metallic implants

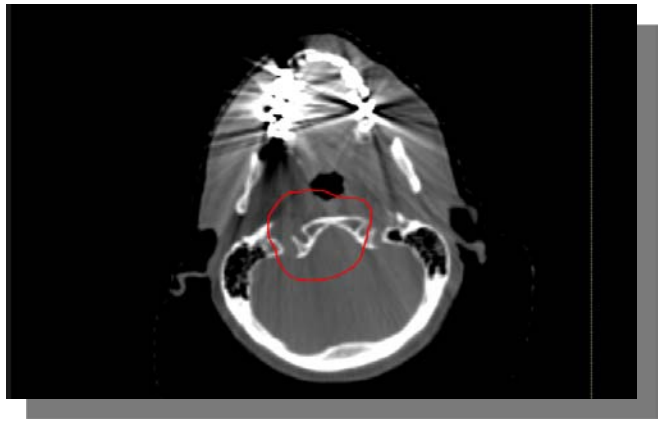
Jäkel et al, PMB 2007 reported <5% of patients with neither fillings nor prosthesis

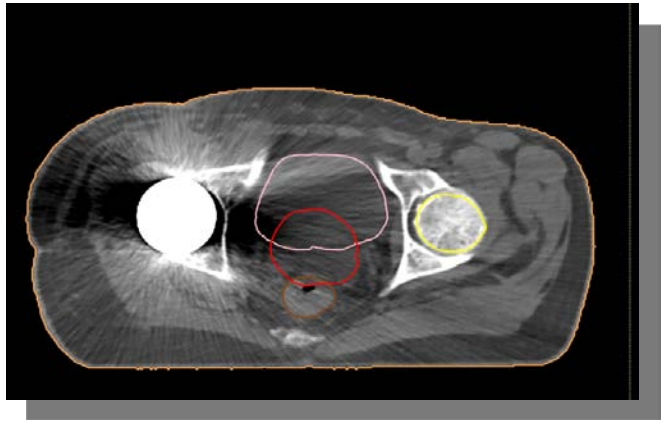
There is no method at the stage of TP which will solve the problem for protons. Try to diminish the effect:

- artefact reduction algorithms (HUs are influenced)
- delineation of artefacts (and implants) and HU override
- estimation of related uncertainties required for clinical decisions

In case of less pronounced artefacts:

- avoid parallel incidence to streak artefacts
- increase margins or use increased uncertainty in robust optimization
- use multiple beams





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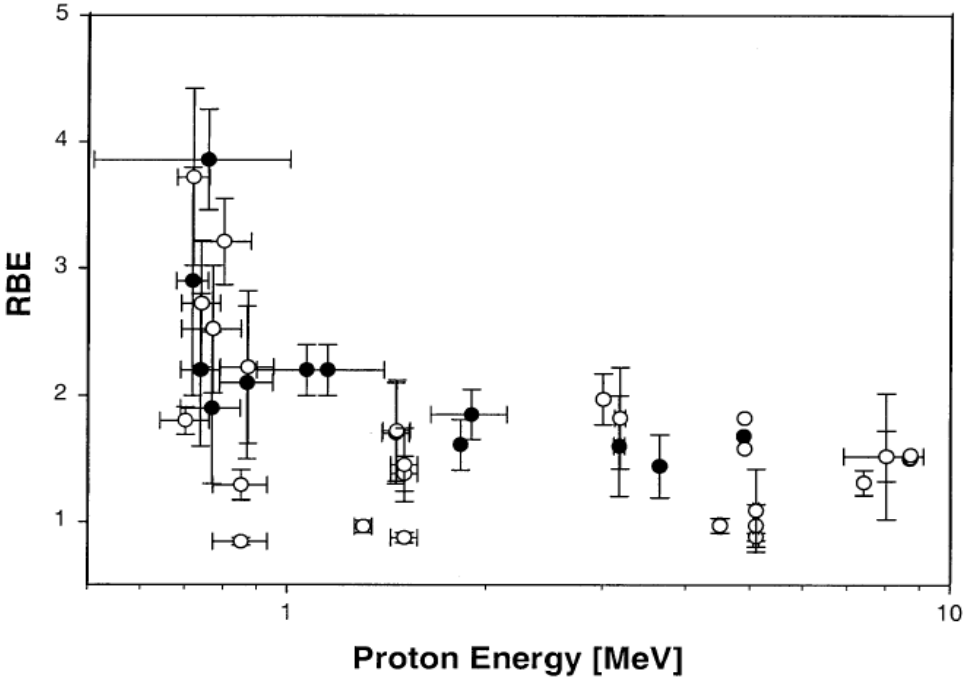
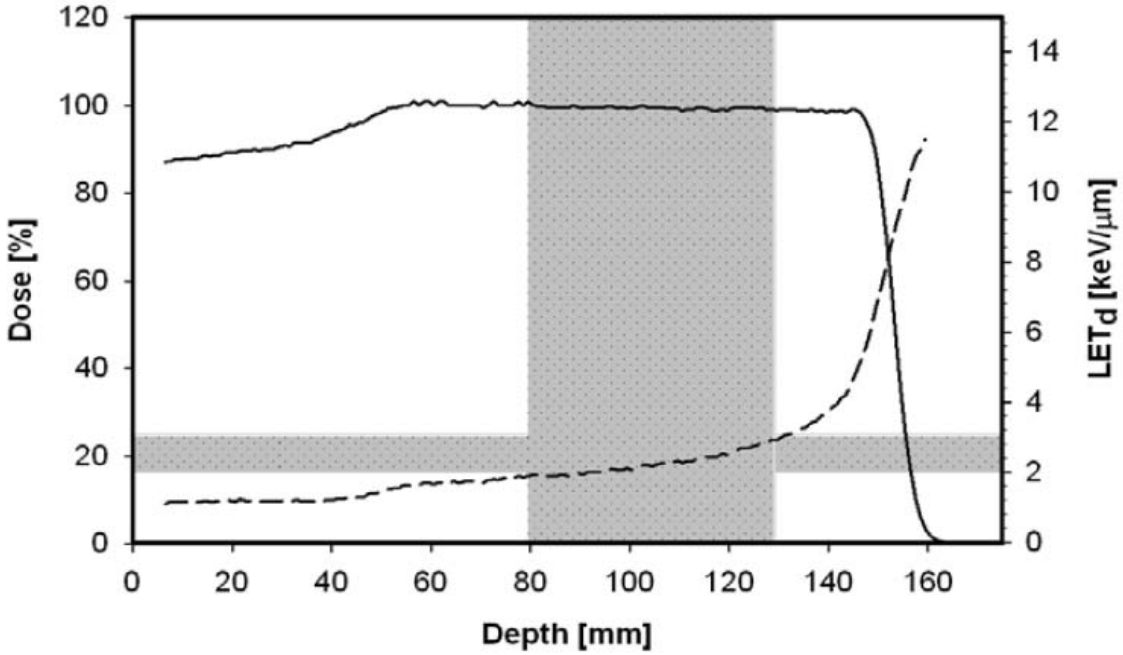
RBE protons

- constant RBE of 1.1 commonly used in clinical routine
- RBE increases at the end of the range



Paganetti et al. IJROBP 53 (2002)



Paganetti. PMB 59 (2014)

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SBO (SFUD) and MBO (IMPT)

SBO: Single beam optimization

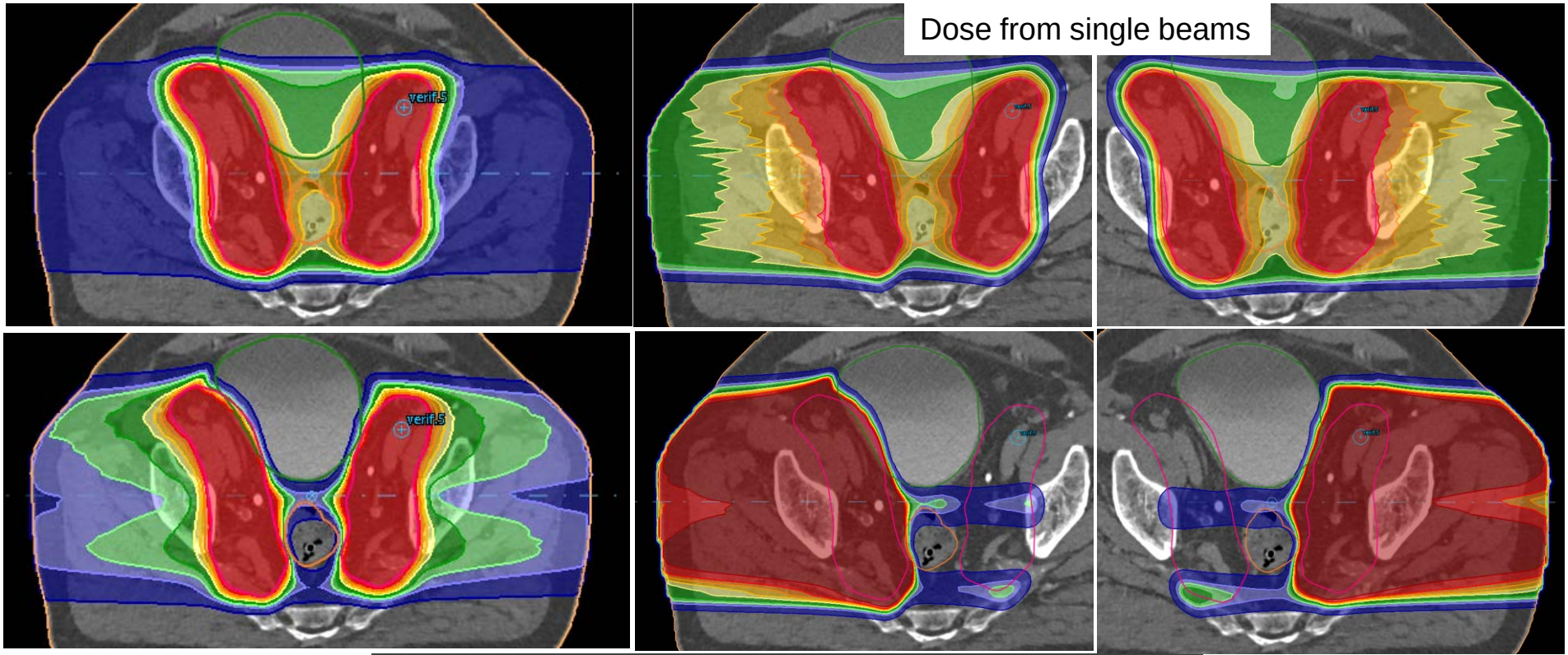
- Possible with passive scattering and active scanning technology
- Spots are weighted in order to achieve a homogenous target dose for every single beam
- OAR sparing only possible by using help structures
- More robust treatment plans

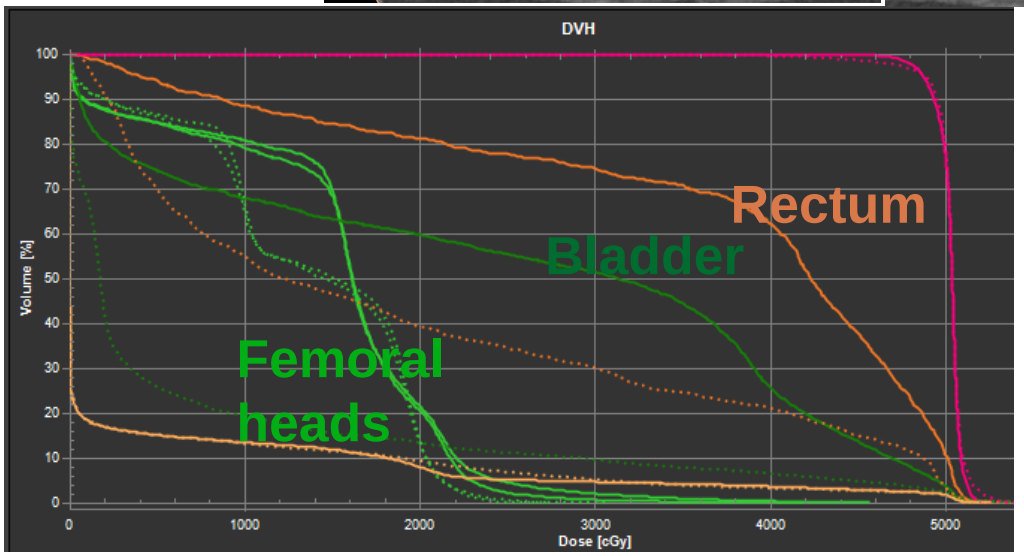
MBO: Multi Beam Optimization

- Active scanning required
- Single beam target doses are not homogenous
- Better OAR sparing possible

SBO vs MBO example prostate case

MBO (dotted) SBO (solid)





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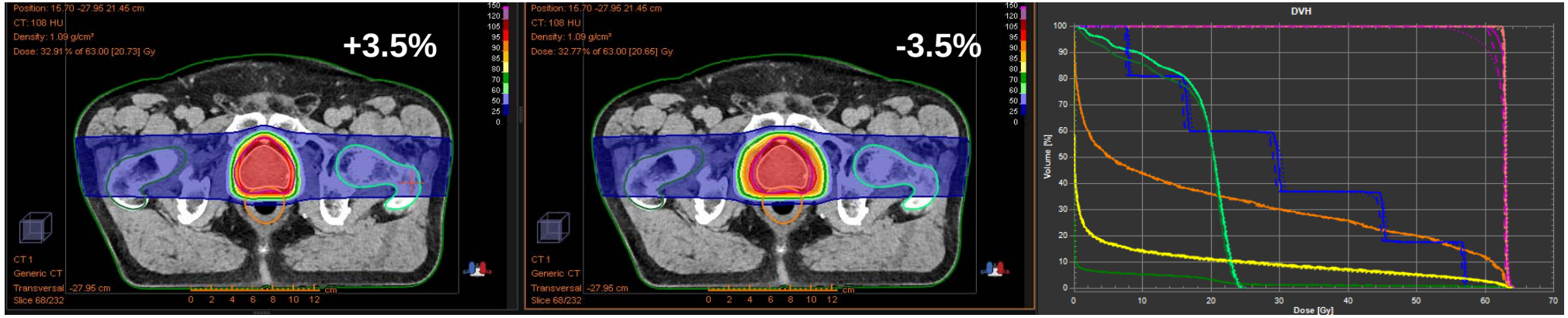
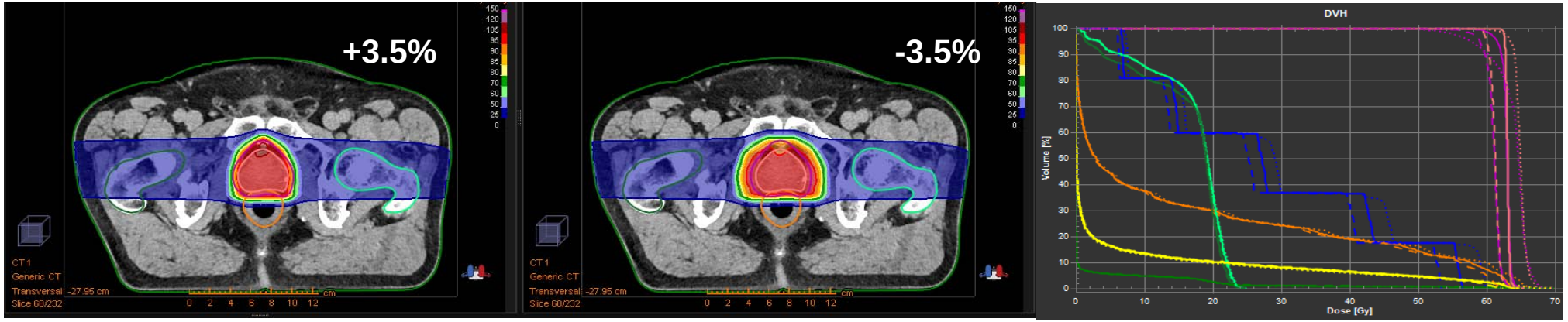
Optimization strategy

Simulation of range uncertainty by HU scaling

SBO



MBO



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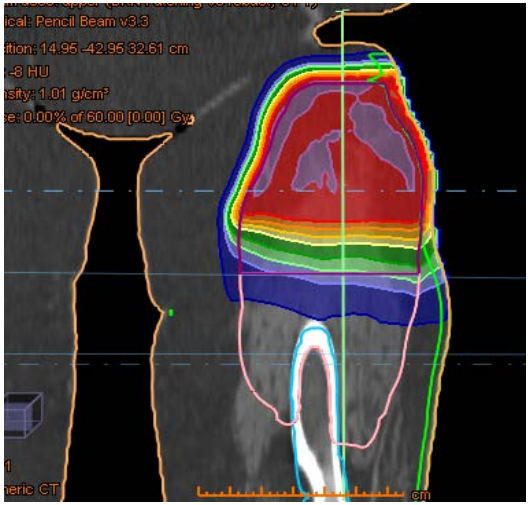
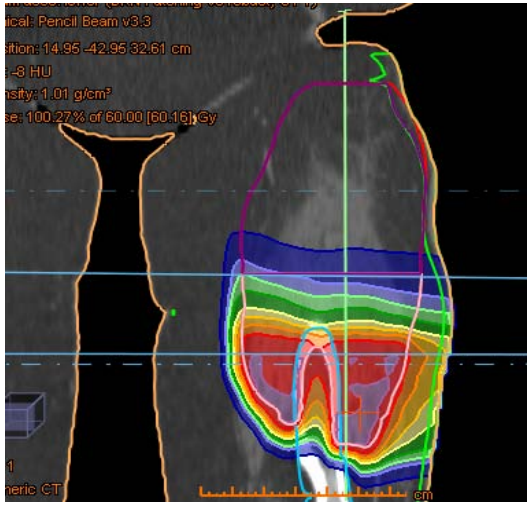
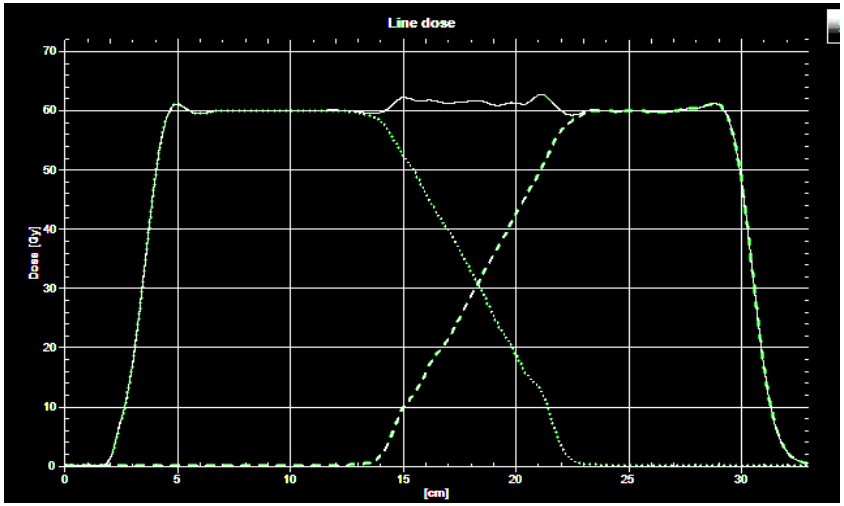
Field matching

- robust optimization for independent beams

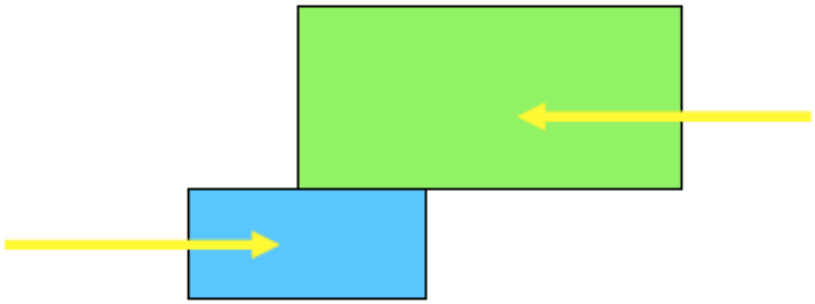






Particle planning basics

Abbuting fields

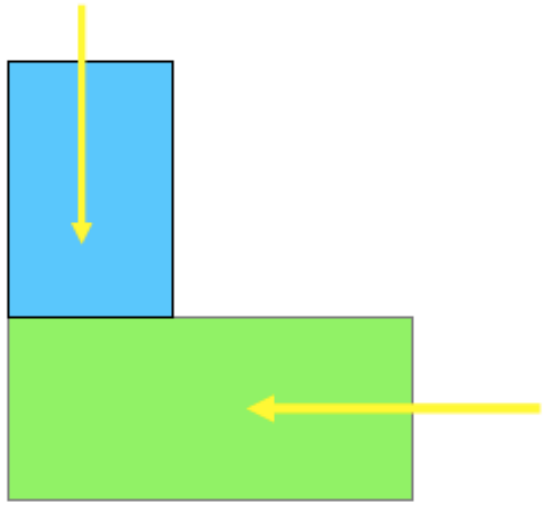


Lateral penumbra

+

Lateral penumbra

Patch fields



Distal penumbra

+

Lateral/distal penumbra

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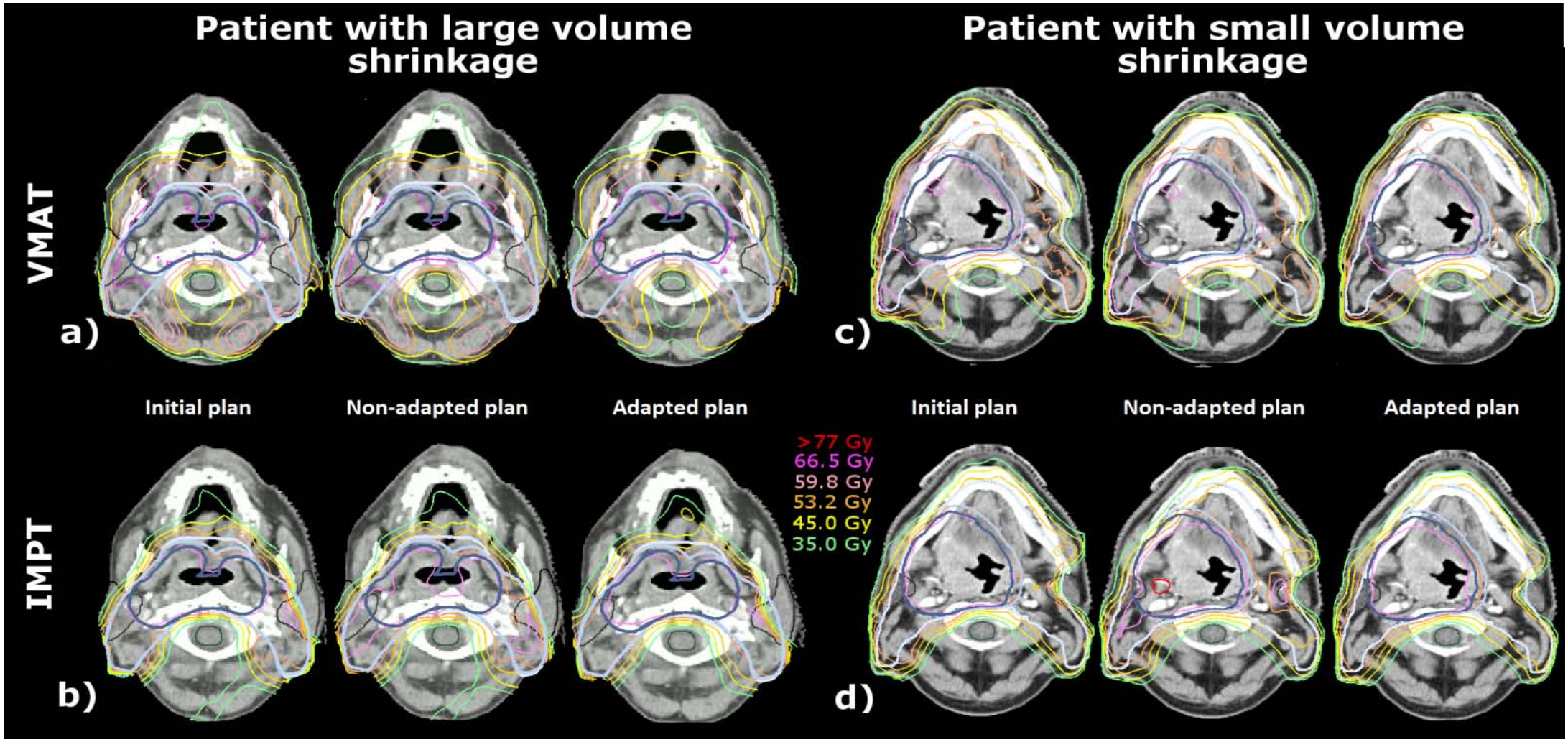
Potential of ART



Gora&Stock et al. Acta Oncol 2015 54(8):1166-74

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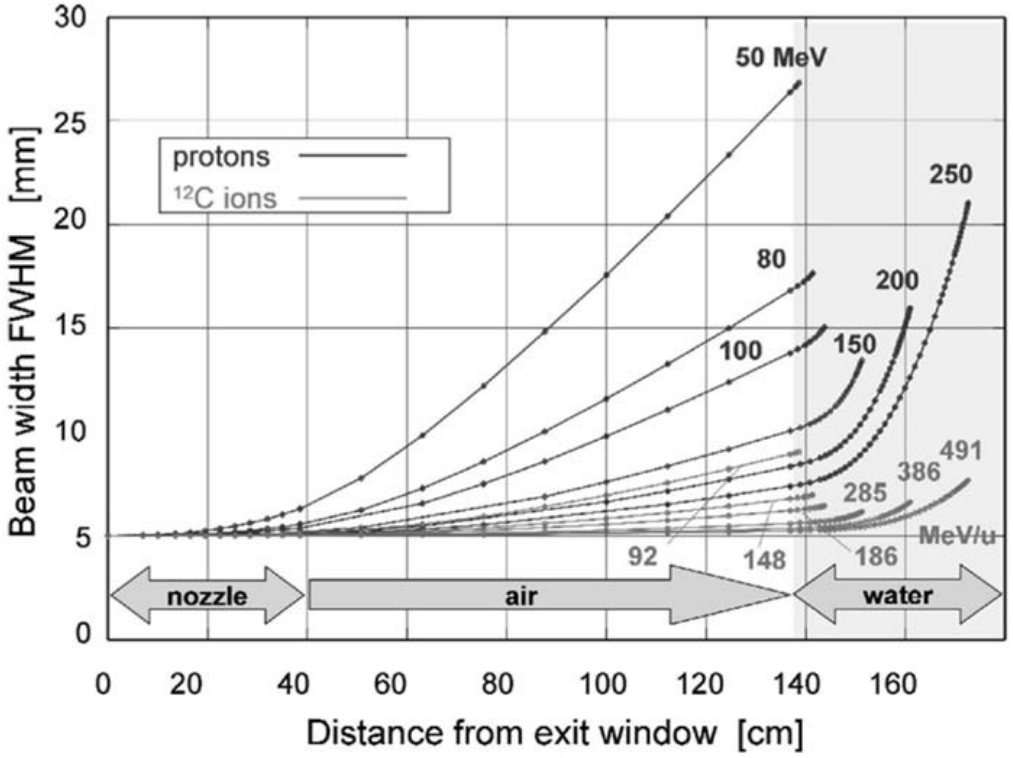
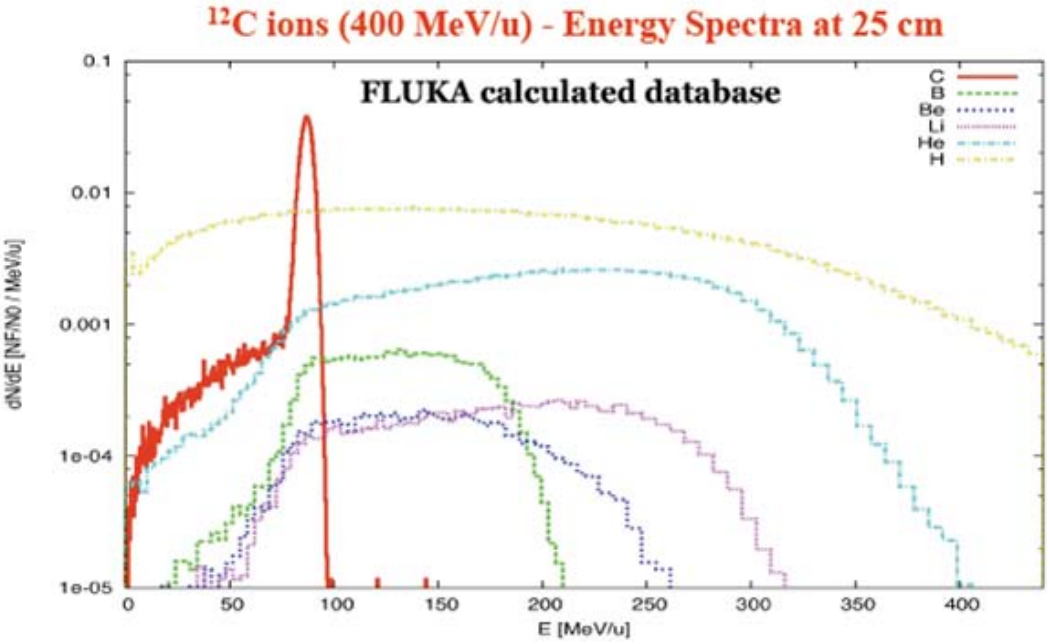
CIBT wrt PT: Some important differences for TP

- Sharper lateral penumbra but tail
- Fragment fluences/LET to be modelled
- No influence of air gap



Weber and Kraft, *Cancer J* (2009) **15**(4):325–32



Mairani et al., PMB

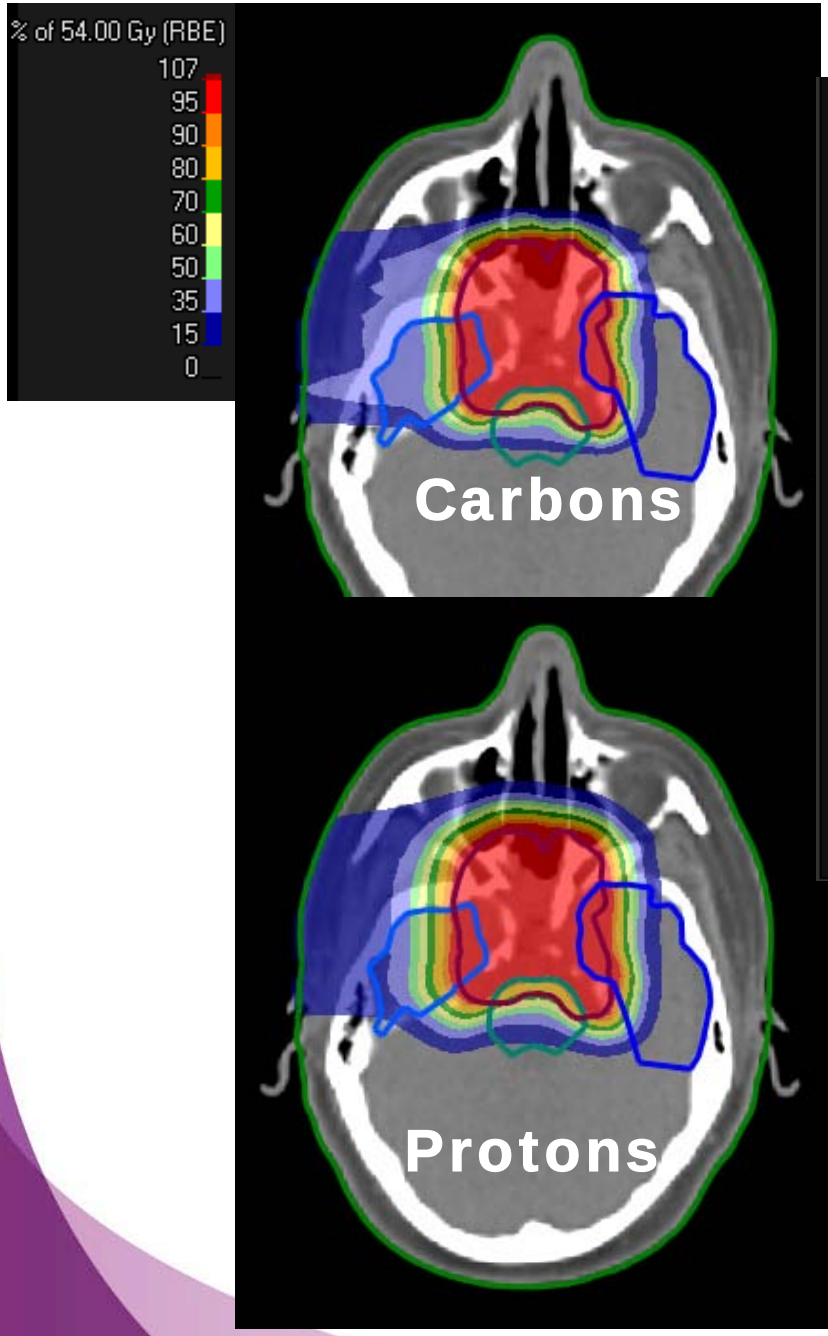
CIBT wrt PT: Some important differences for TP

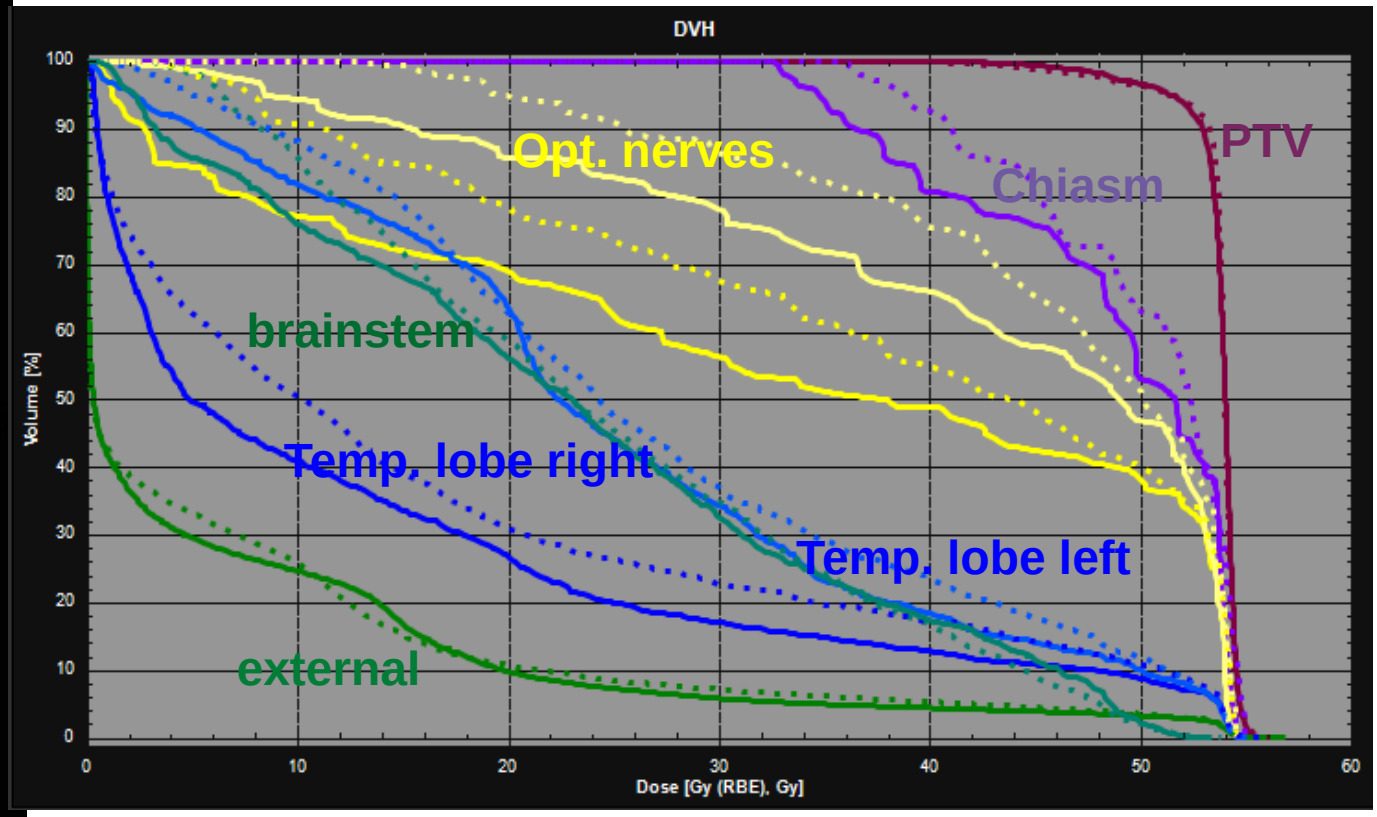
Peculiarities of carbon ion RBE and implications

- RBE-dependence on dose
  - Plan MUs not scalable any longer!
- RBE not constant: How to come up with a robust multi-beam plan?
  - SFU(B)D only applicable for single beam per fraction (NIRS)!
- $D_{RBE,LEM-I} \neq D_{RBE,NIRS}$, conversion of treatment protocols needed! Is always approximate!
- Approximations and shortcomings in clinical RBE-models

Fossati et al. (2012), PMB

C vs p: Skull base

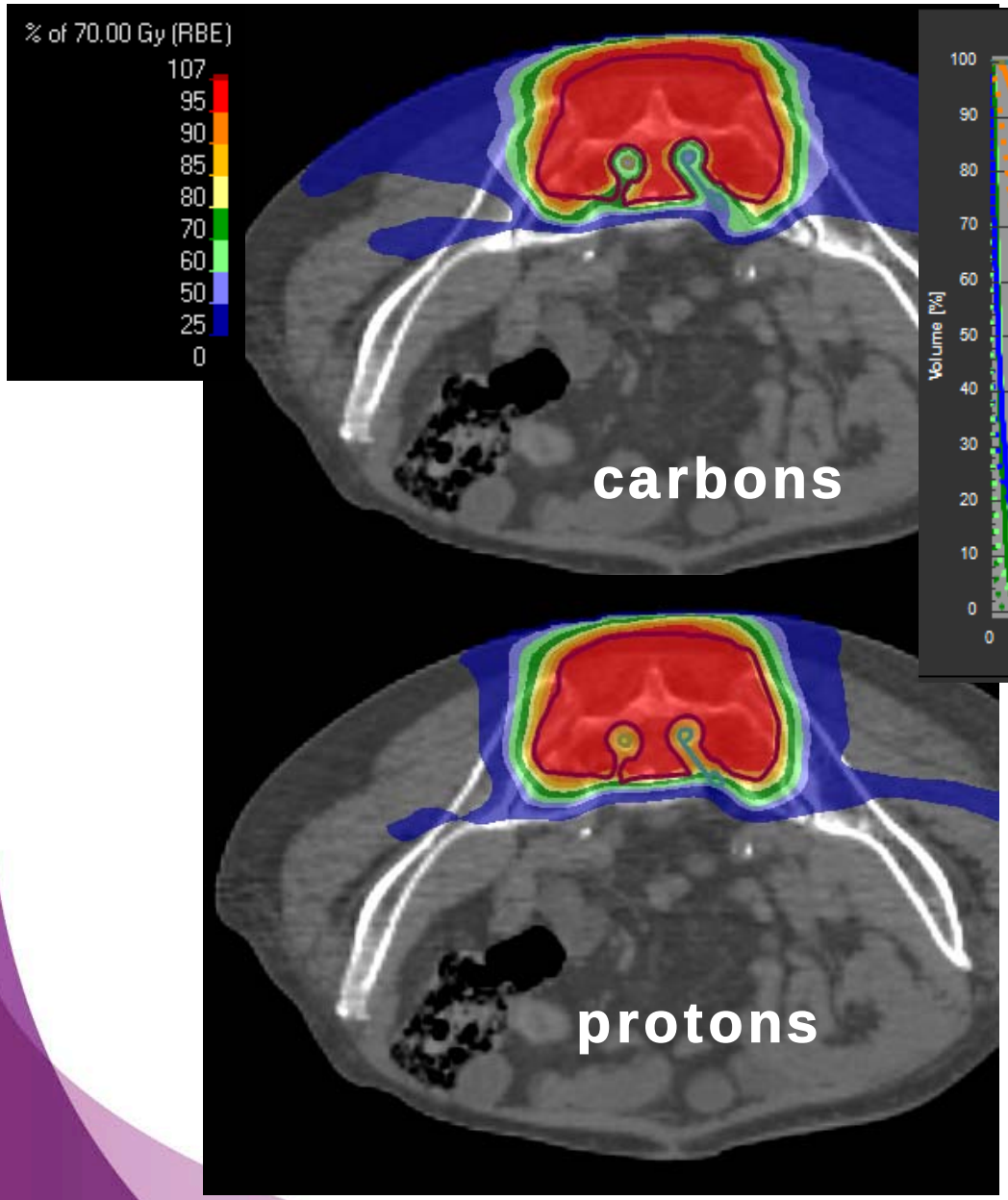


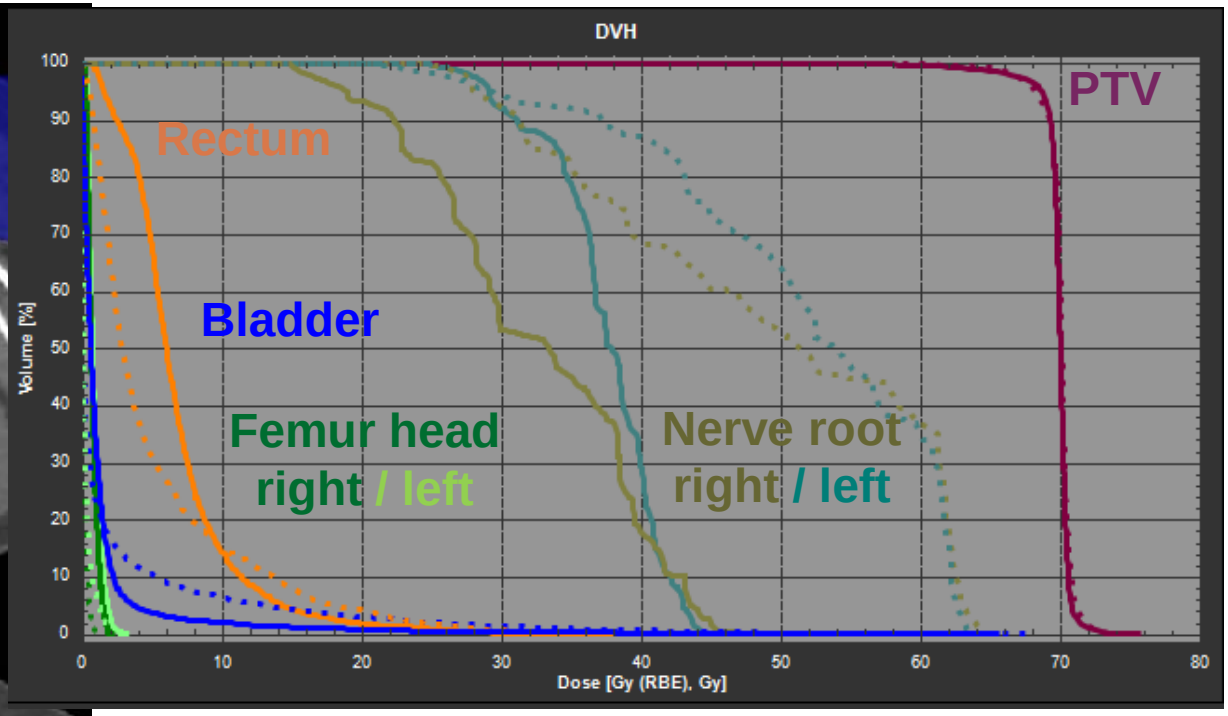


Solid: C

Dotted: p

C vs p: Sacrum





Solid: C

Dotted: p

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Some practical aspect in ion beam planning

General aspects

- SFUD might be a good treatment technique for many indications
- Combination of SFUD and IMPT might be helpful to assure robustness in target coverage and OARs sparing within one treatment
- Range shifter in the beam path degrade beam quality
- Non isocentric treatments to improve beam characteristics
- HU to ED conversion sensitive to errors

Some practical aspect in ion beam planning

For plan creation:

- Limited number of beams should be chosen
- Beam path optimization: Picking “good” beam directions to avoid to pass through heterogeneities or lie tangent to a tissue air-interface
- Intelligent creation of planning help structures for PTV and targets
- Visualization of spot distribution and weighting
- Avoiding corners and edges from positioning devices/ no beam path through shoulders

For plan quality assessment:

- Robust evaluation and optimisation
- Surface dose!
- Hot spots within OARs (position of high dose areas)

Conclusion

- Fundamental difference in beam penetration
- Less beams used in particle therapy
- PBS vs Scattering technique experience
- Robustness optimization major concern
- Limited field size and incidence angles

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Introduction Case 2: Prostate

Mr R, 80 years old

History: Mitralic valve surgery

•2008: PSA (=prostate specific antigen): 3.3 µg/L

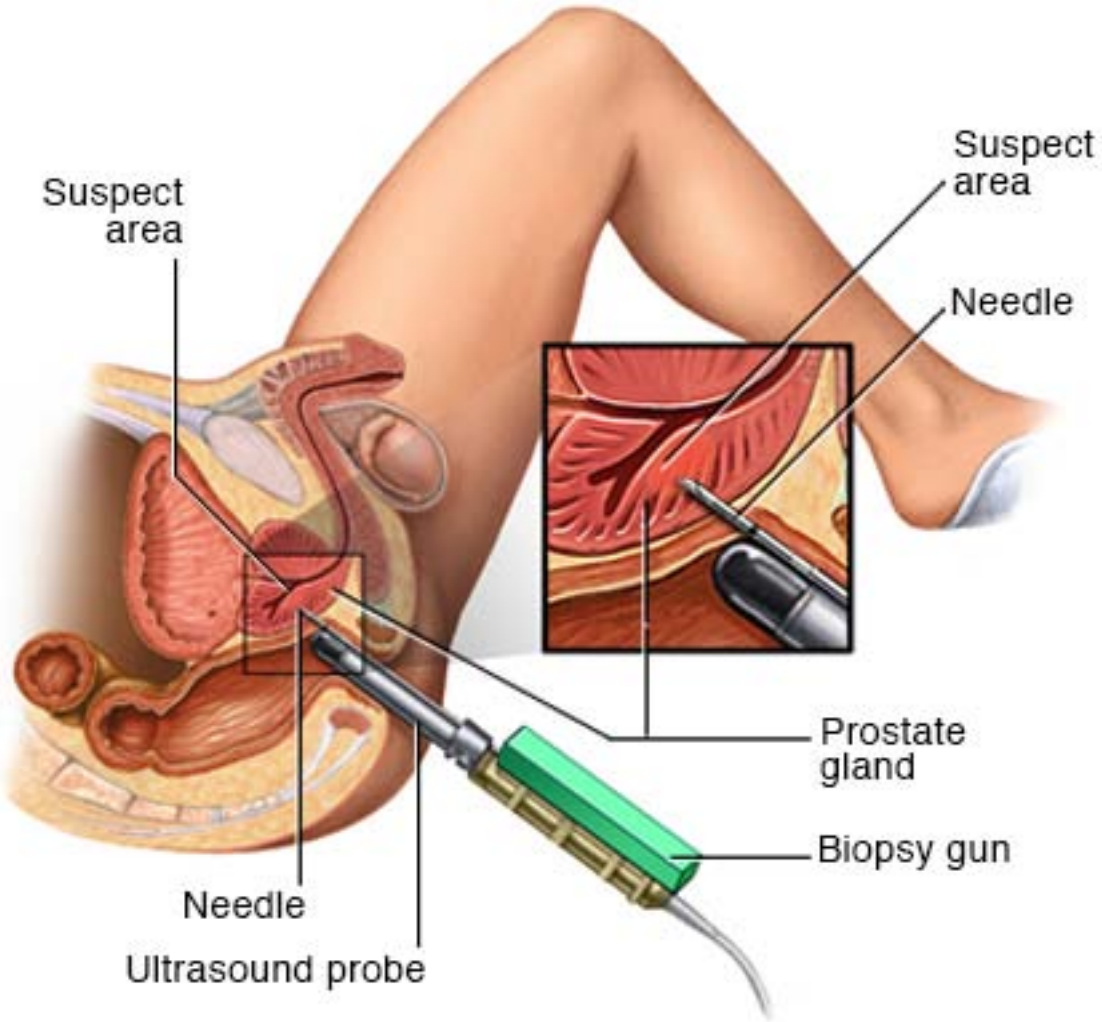
•April 2011: PSA: 5.2 µg/L

•September 2011: PSA 11.6 µg/L

No urinary symptoms

→ Prostate biopsy

Prostate biopsy



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Mr R, 80 years old

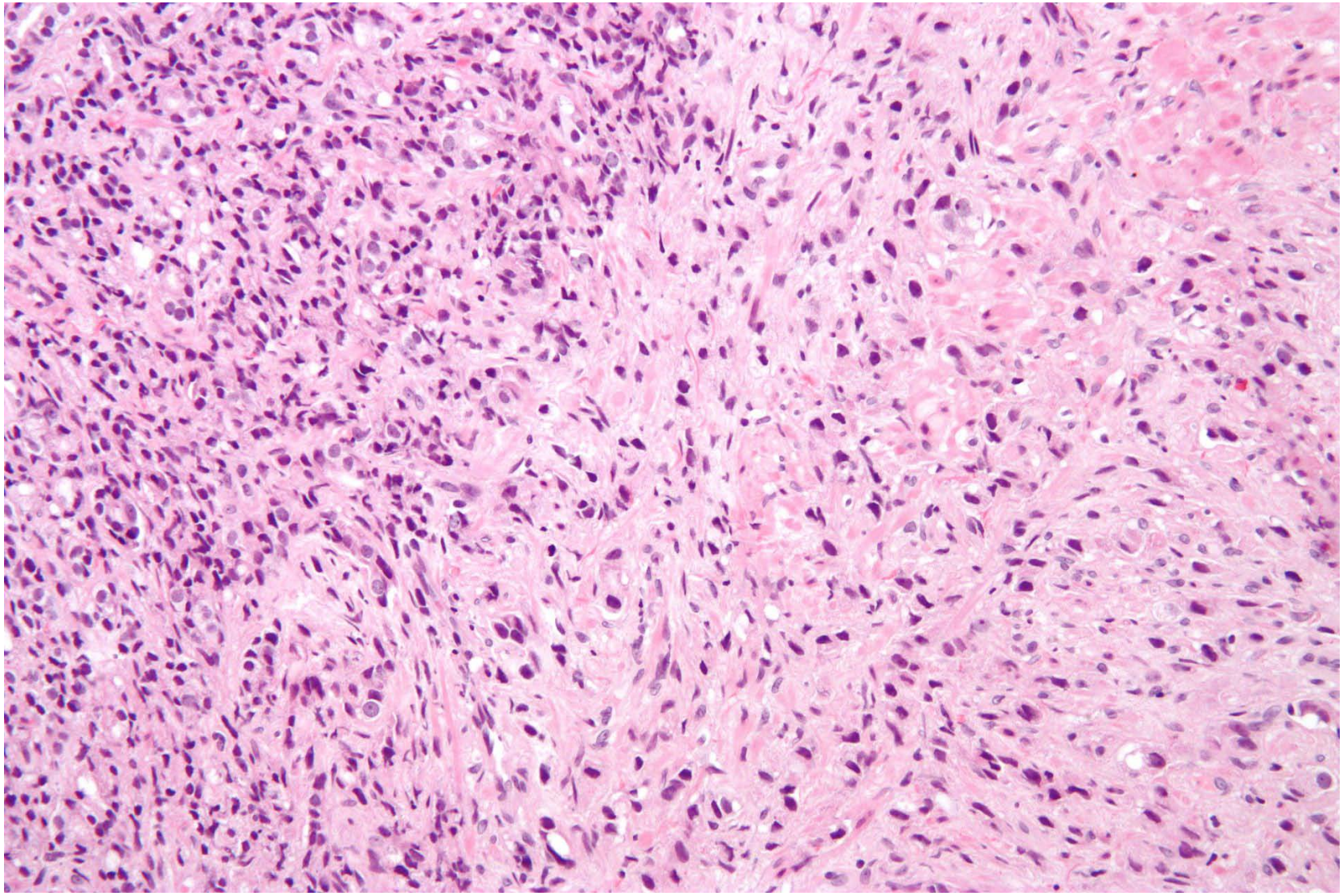
Prostate biopsy: Prostate cancer in right prostate lobe, Gleason score 6

Gleason score is based on patterns:

Pattern 1:
normal prostate with small, well-formed glands
corresponds to a well differentiated carcinoma

Pattern 5:
tissue does not have any or only a few prostate glands
corresponds to a poorly differentiated carcinoma

Gleason score



Gleason 4

Gleason 5

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Mr R, 80 years old

Prostate biopsy: Prostate cancer in right prostate lobe, Gleason score 6

Gleason score:

- based on patterns:

  Pattern 1: normal prostate with small, well-formed glands corresponds to a well differentiated carcinoma

  Pattern 5: tissue does not have any or only a few prostate glands corresponds to a poorly differentiated carcinoma

- grading: sum of dominant pattern and next-most frequent pattern

  e.g. 3 + 4 = 7

→ Low-risk: Gleason score ≤ 6, High-risk: Gleason ≥ 8

Mr R, 80 years old

- November 2011: PSA 13 µg/L
- No urinary symptoms

Diagnosis: Prostate cancer
Gleason score: 3+3

Referred for radiation therapy:
Volume prostate > 80 cc (too high for brachytherapy)

→ External beam radiotherapy (FLAME trial)

FLAME trial

Focal **L**esion **A**blative **M**icroboost in prostat**E** cancer

Multicenter randomized controlled trial

Randomization:

1. Standard arm:

   77 Gy in 35 fractions whole prostate (2.2 Gy per fraction)

2. Study arm:

   Additional integrated boost to macroscopic tumor to 95 Gy tumor (2.7 Gy per fraction)

Patients were blinded to the actual treatment given

Lips et al. Trials 2011

FLAME trial

Focal **L**esion **A**blative **M**icroboost in prostat**E** cancer

Can dose escalation to the macroscopic tumor increase freedom from biochemical relapse rate?

Current five-year biochemical relapse rate: 35%

- For patients with intermediate or high risk prostate cancer

  PSA ≥ 10 ng/mL / Stage ≥ T2b / Gleason score ≥ 7

- Endpoints:

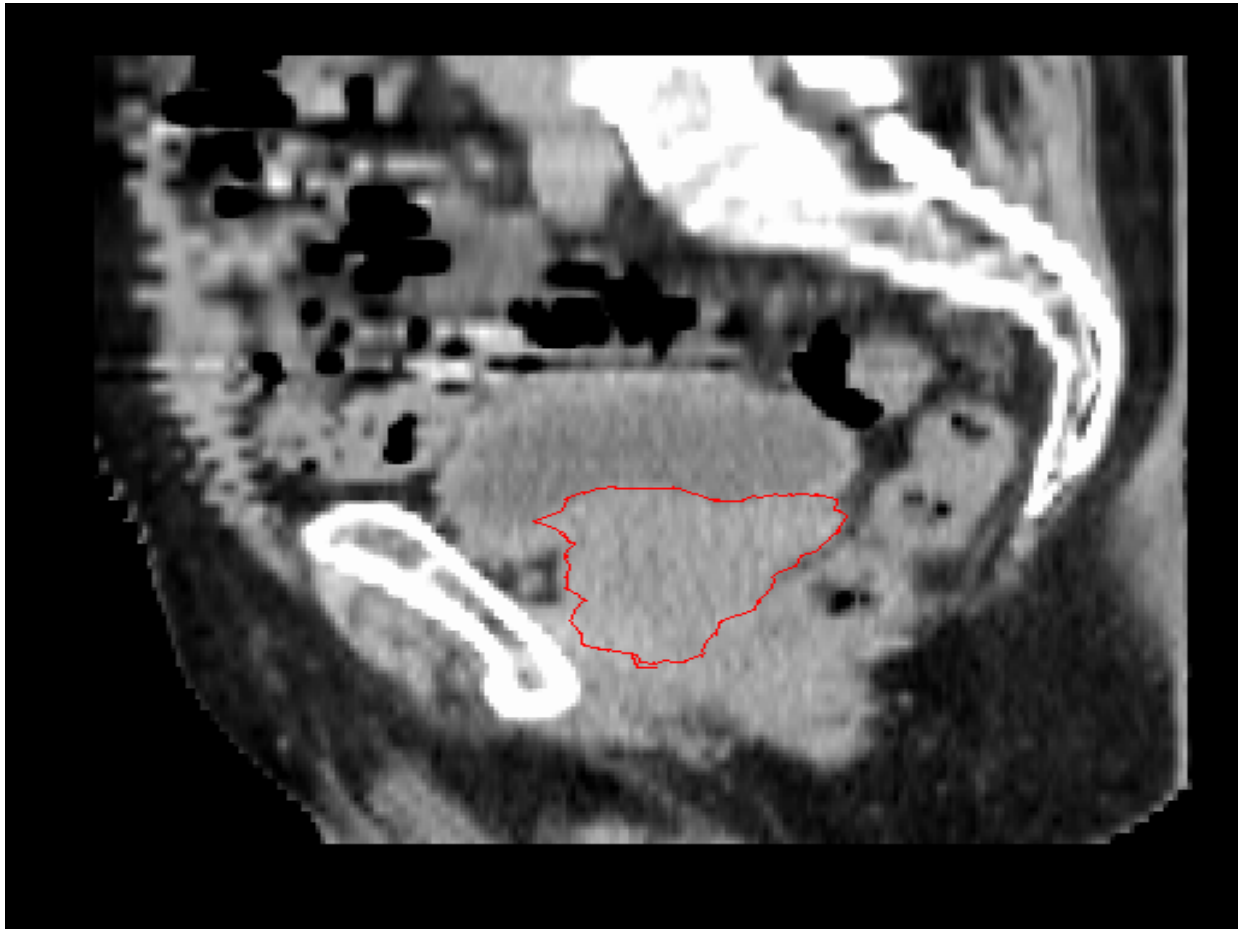
  Primary: 5-year freedom from biochemical relapse rate

  Secondary: Toxicity, quality of life and disease-specific survival

Lips et al. Trials 2011

Prostate - RT planning and position verification

Prostate is moving due to changes in rectal and bladder filling



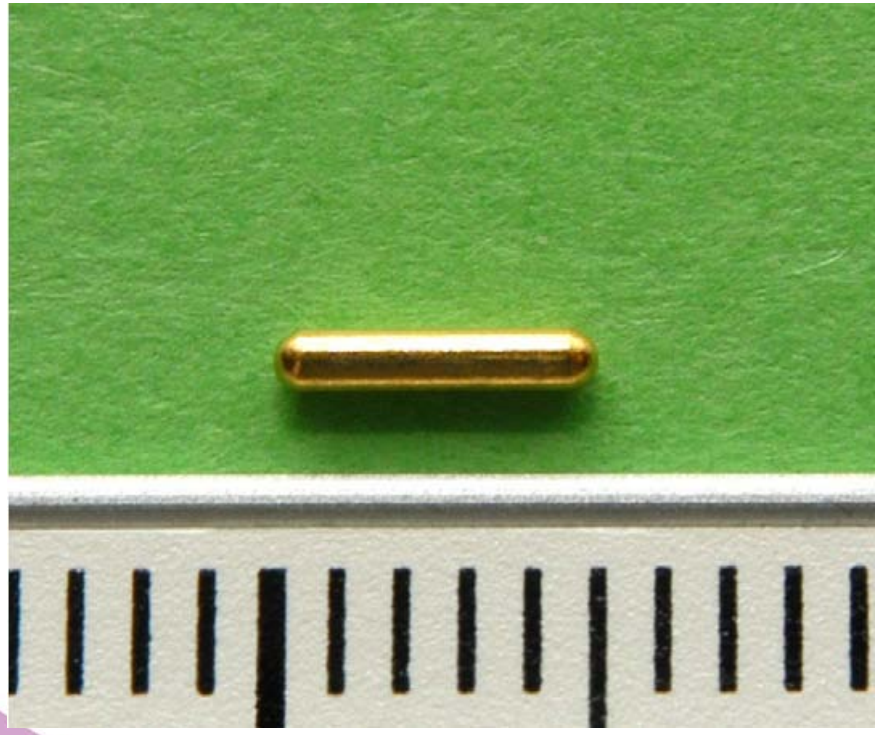
Courtesy of M van Herk

RT planning

Insertion of fiducial gold markers in prostate (ultrasound-guided)

- daily prostate localization during IGRT instead of bony anatomy
- daily assessment of set-up and physiological motion errors

  → smaller margins



Moman RO 2010

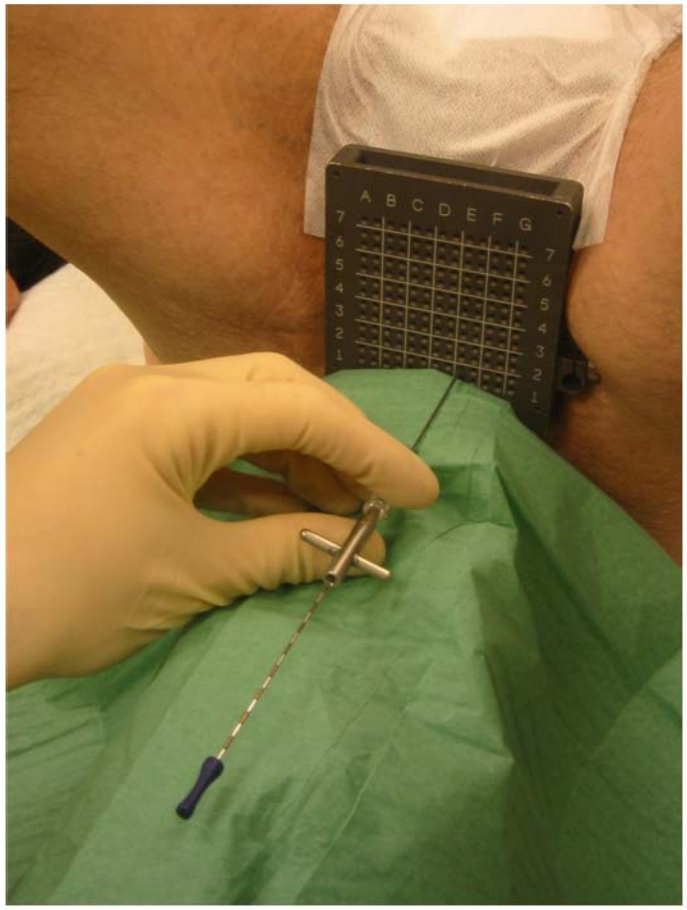
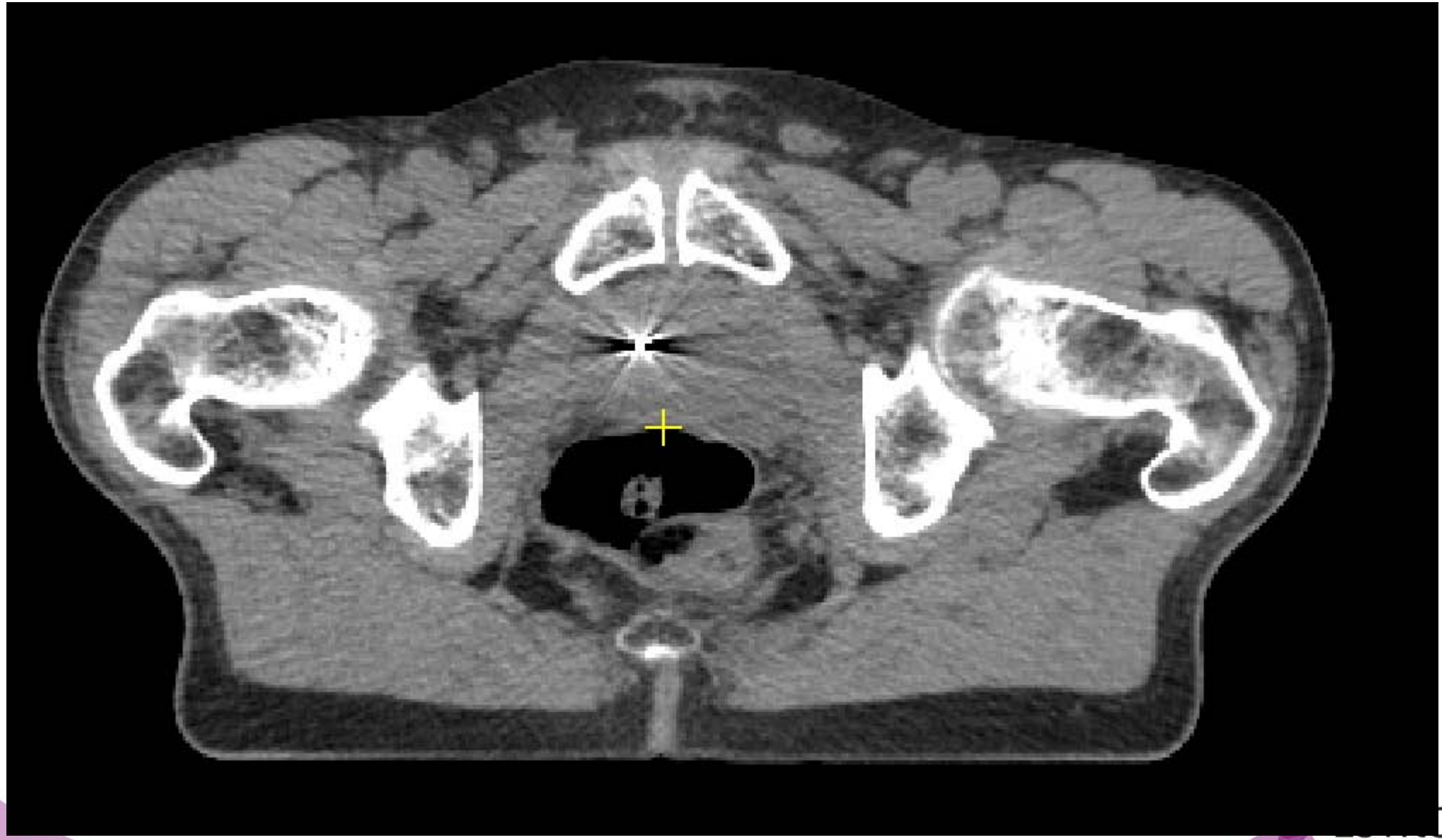


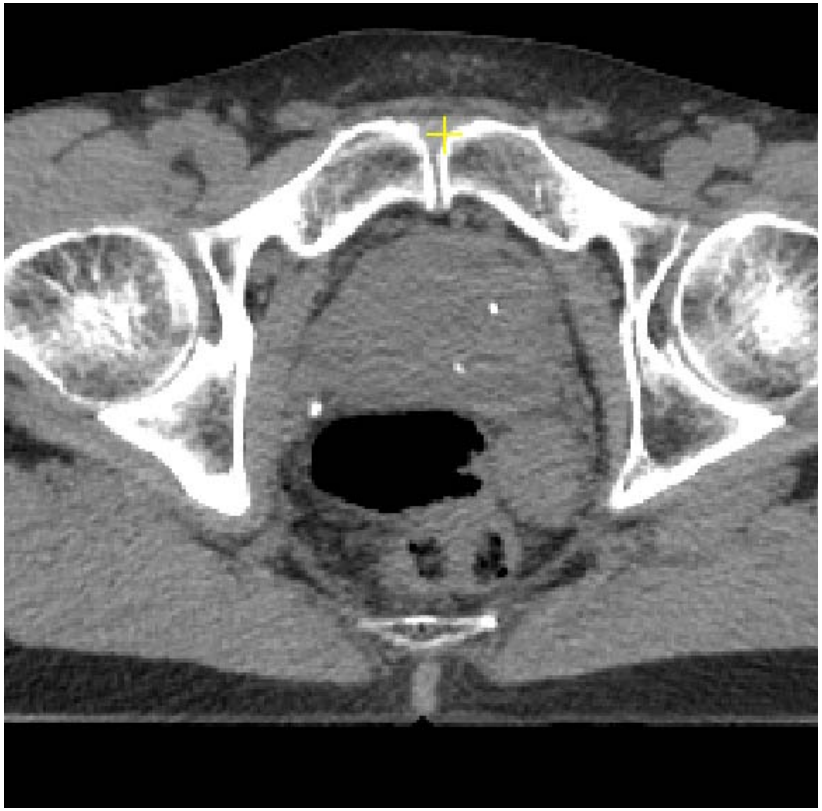
Figure 2. Implantation is facilitated by a template that is positioned against the perineum, placed on the transrectal ultrasound probe.

Planning-CT – fiducial gold marker

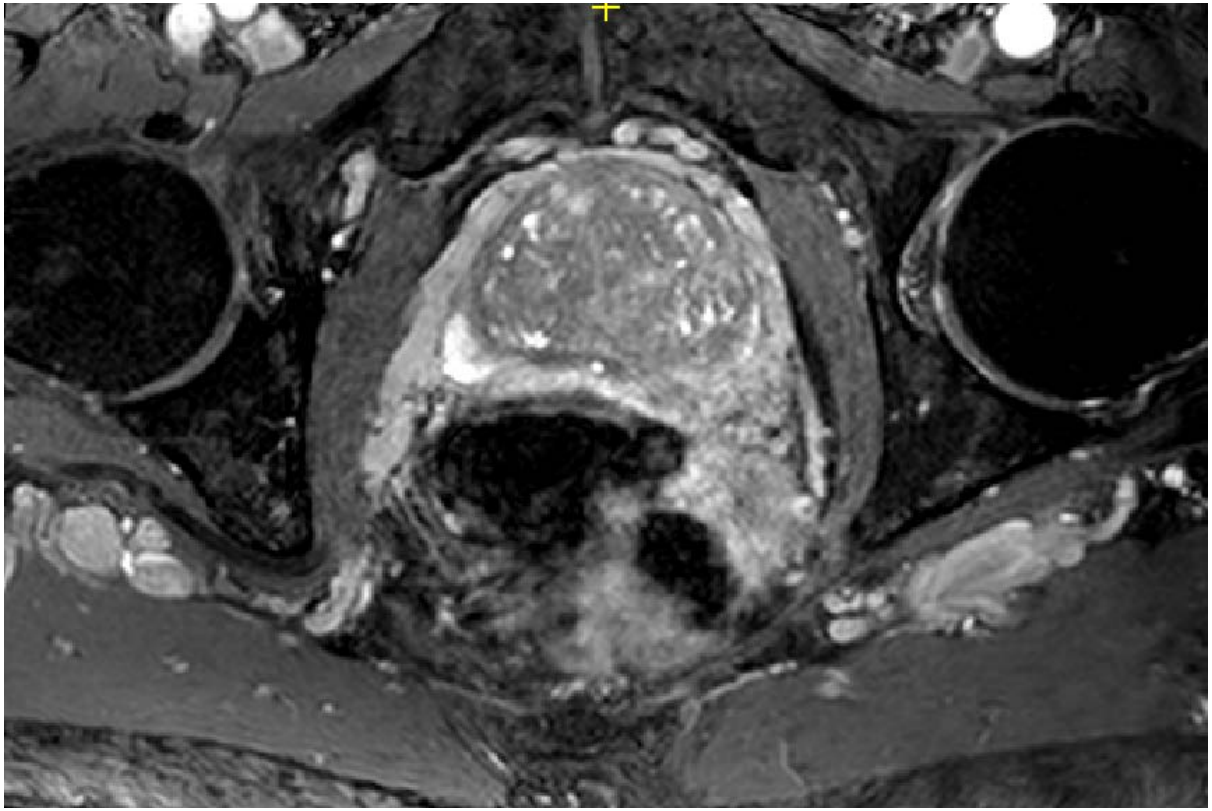


Planning-CT and -MRI

CT



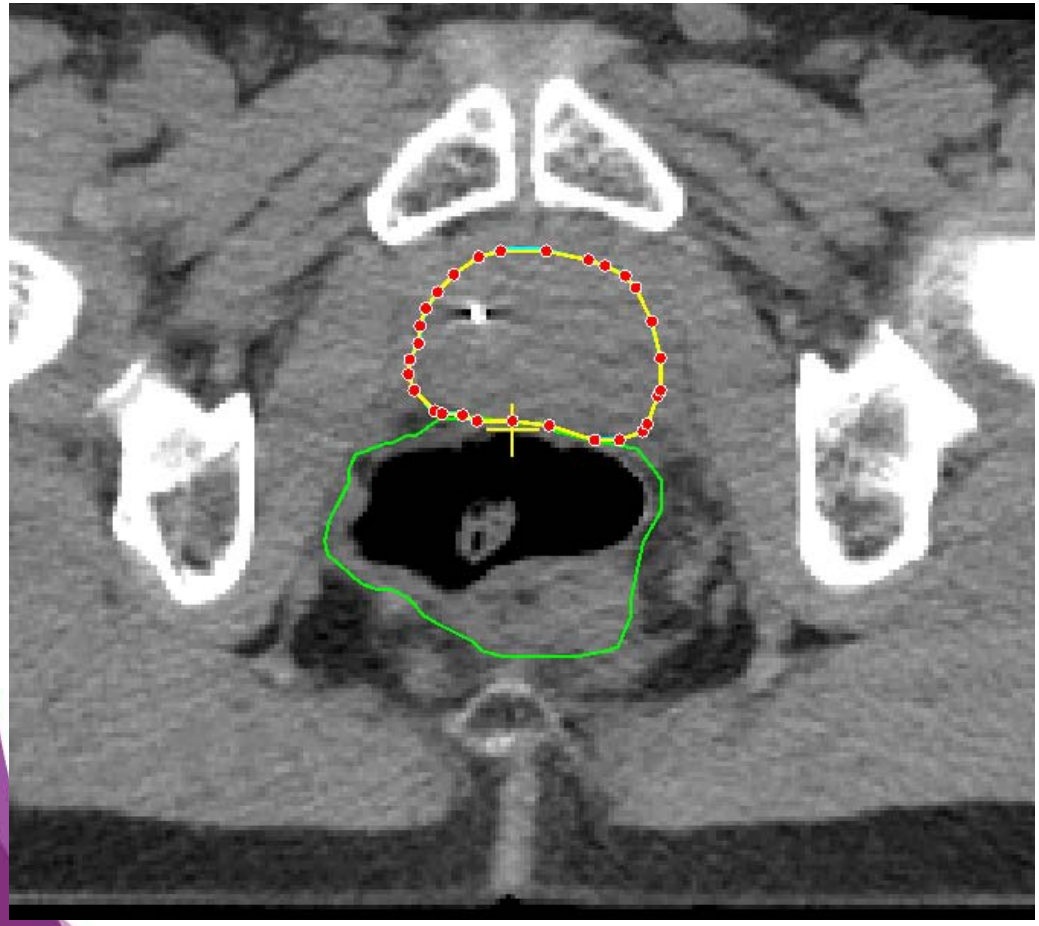
MRI



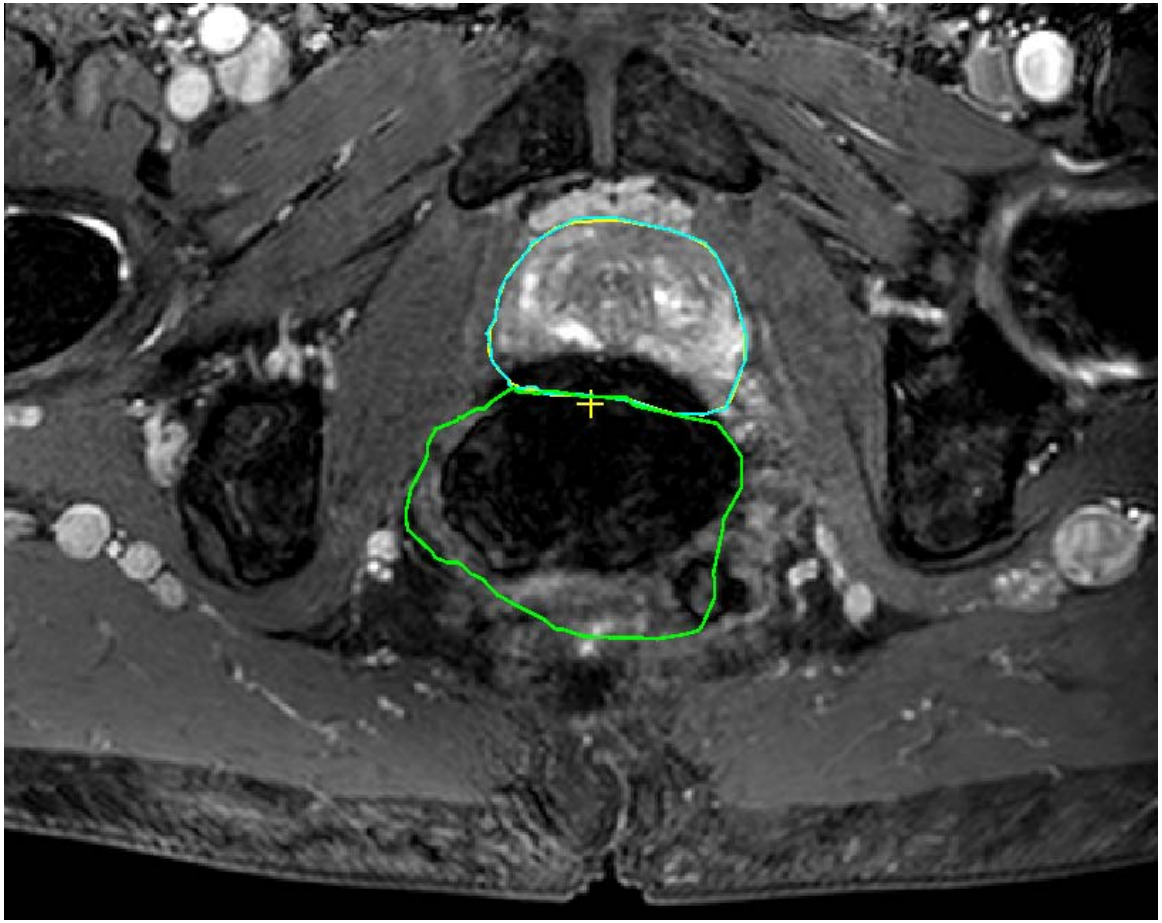
Planning-CT and –MRI

Changes in rectal and bladder filling

CT

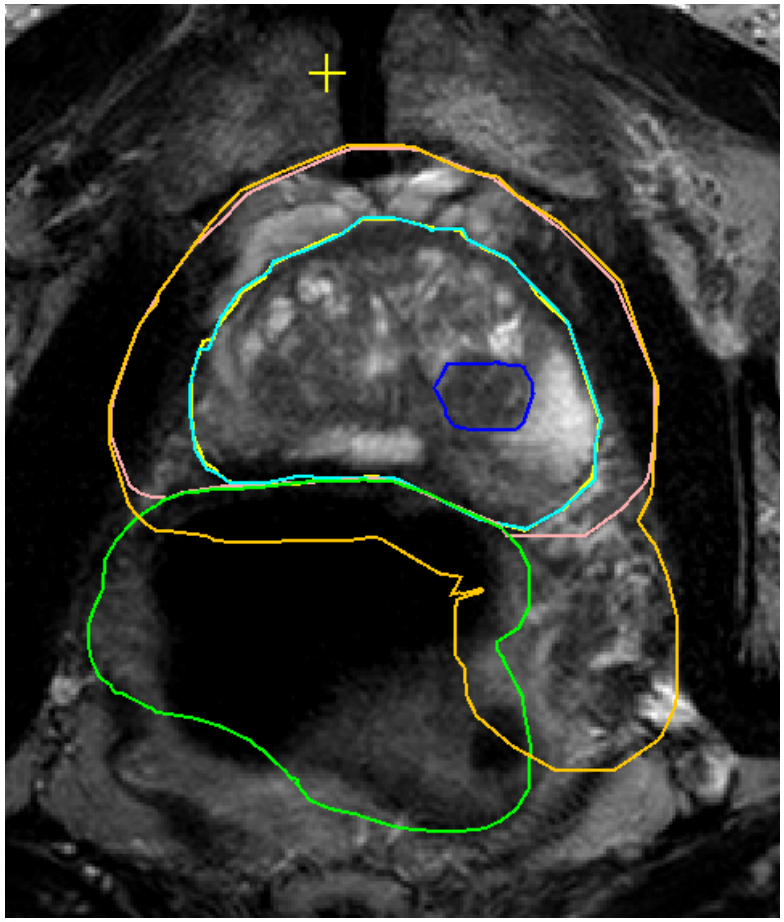


MRI



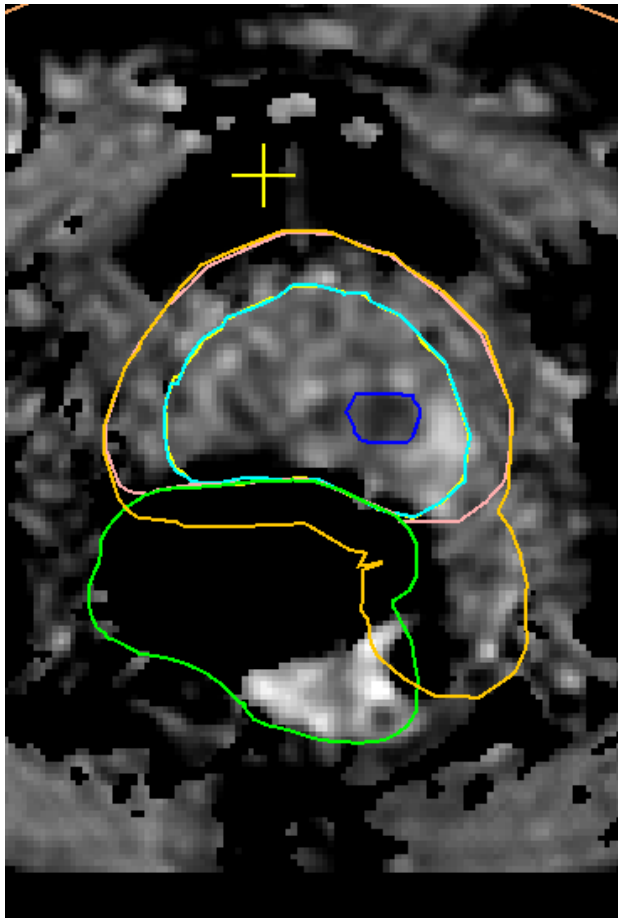
Functional MRI – prostate tumor (GTV2: 95 Gy)

T2



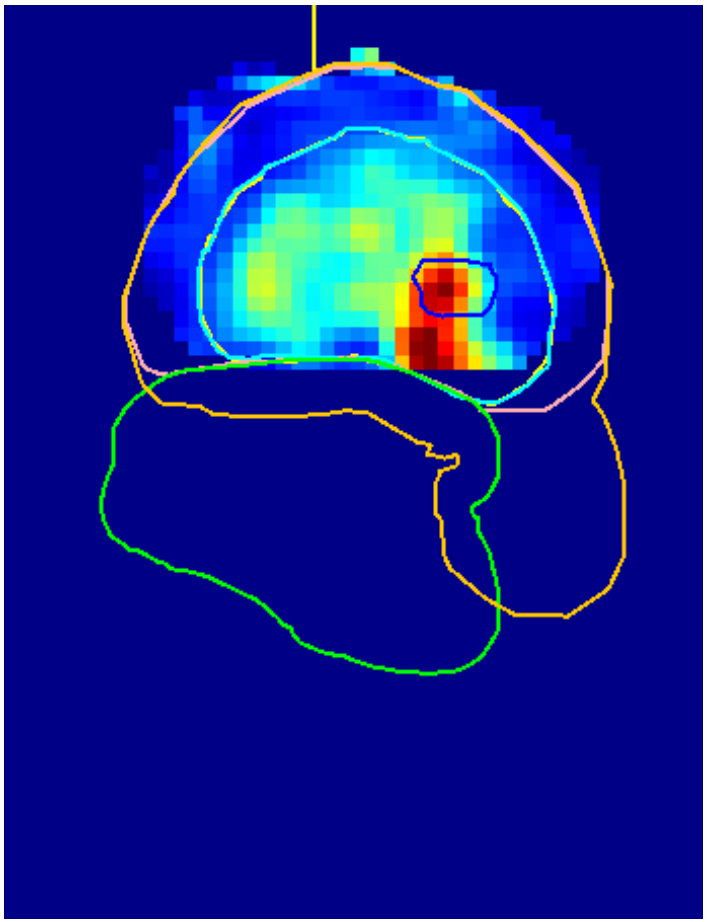
Tumor: Hypo-intense signal

ADC



In tumor: Mobility of water molecules is reduced

Ktrans



Contrast-enhanced-MRI; Tumor contain higher density of leaky blood vessels

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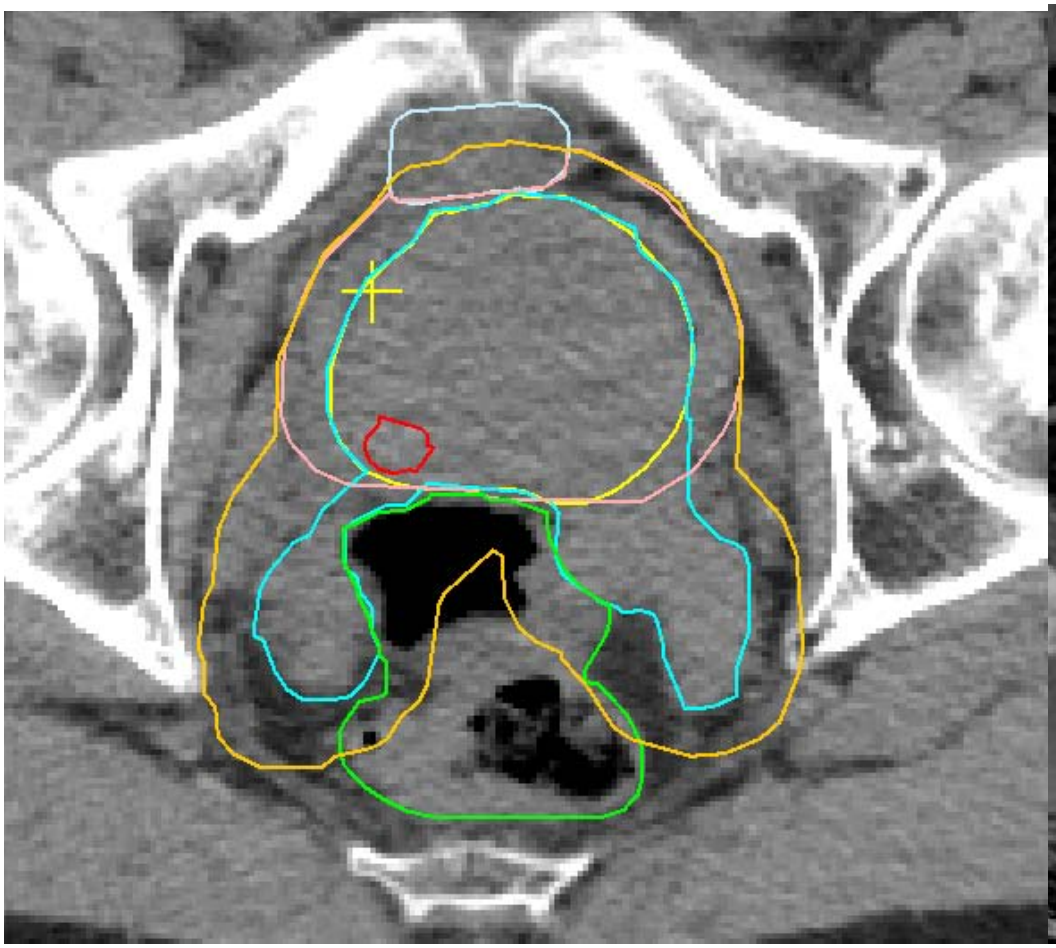
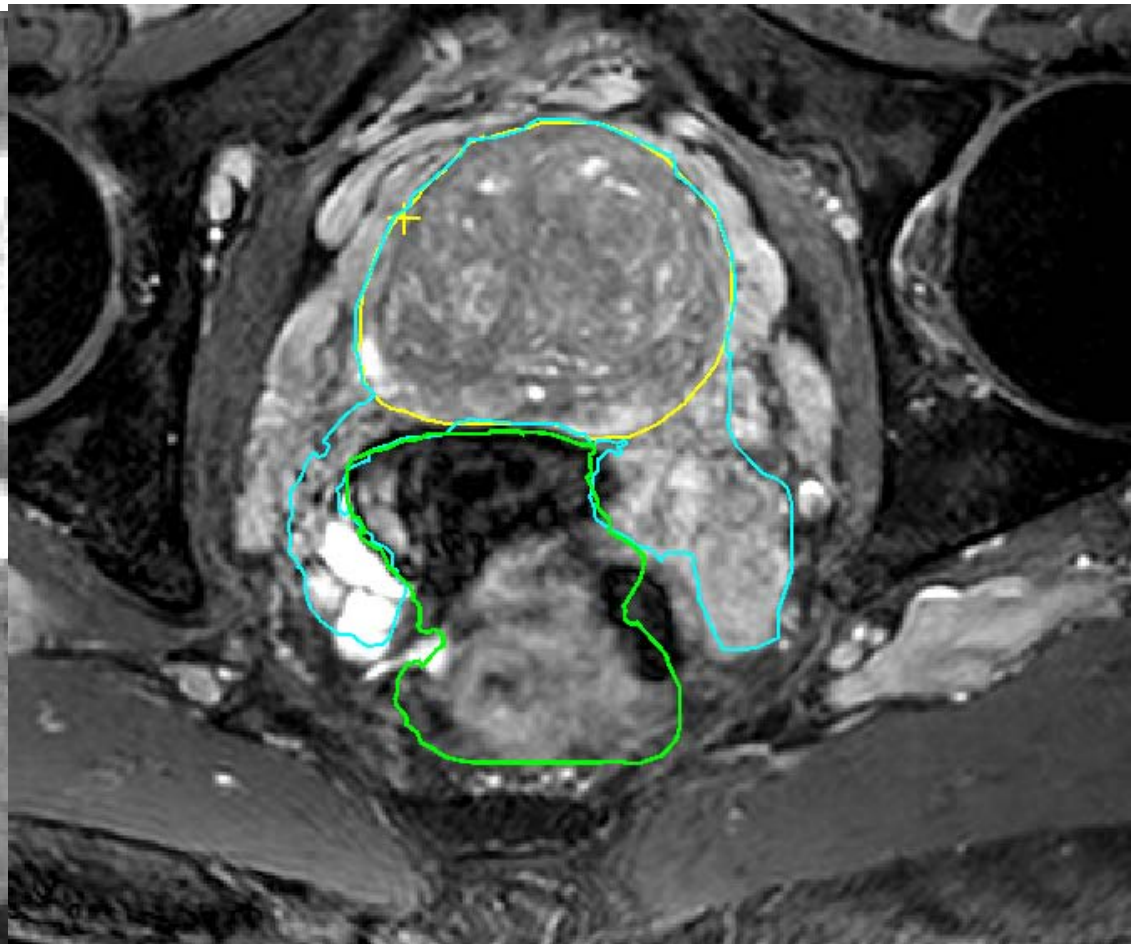
MRI – special case





high volume seminal vesicles
bladder around cranial border prostate

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Prostate RT – Organs at risk + FLAME constraints

Organ at risk	Toxicity	Dose constraint
Rectum	Radiation proctitis, e.g. increased bowel frequention, cramps, blood / mucus discharge, diarrhea, use of pads	V72 Gy < 5% V50 Gy < 50%
Bladder, urethra	Radiation cystitis, e.g. increase in urinary frequency, nocturia, dysuria, hematuria	V80 Gy < cc V72 Gy < 10% V50 Gy < 50%
Anal sphincter	Pain, incontinence	Dmean < 37 Gy
Skin	Radiation dermatitis	ALARA

Prostate planning – session objectives

- Targets:
  - PTVprostate_77

    i.e. prostate + 8 mm excluding cranial and dorsal direction, rectum and bladder: 77 Gy
  - PTVprostate including seminal vesicles_70

    i.e. Prostate including seminal vesicles + 8 mm margin: 70 Gy
  - GTV1_95 and GTV2_95

    i.e. GTV1 and GTV 2: 95 Gy

- Technique:
  - (3D-CRT)
  - IMRT
  - VMAT
  - Tomo
  - Protons

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Prostate case

Advanced Treatment Planning Course

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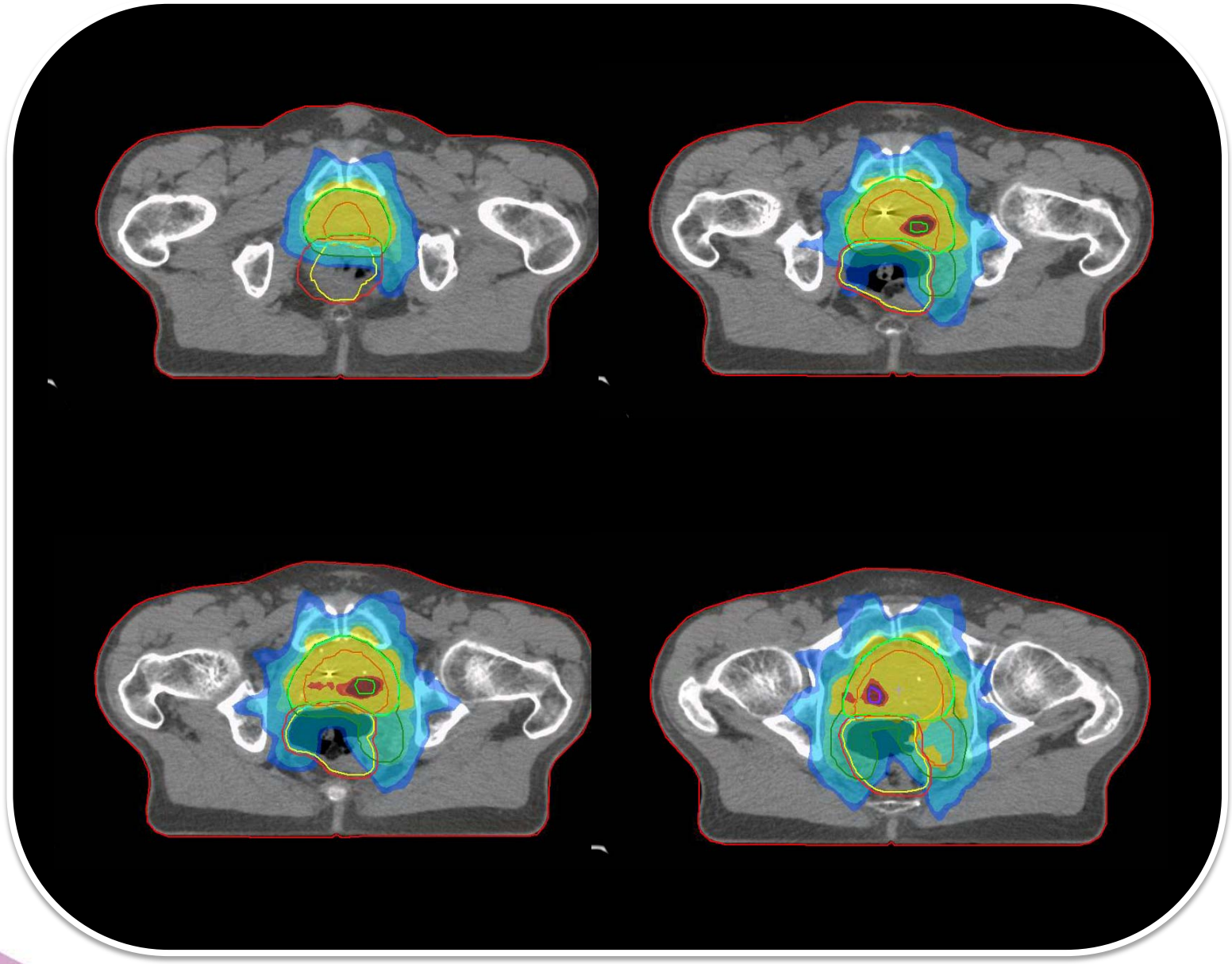
Clinical case 2: Prostate



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- GTV: Try to achieve 95Gy
- PTV_7700: D99% > 7315cGy
- PTV_7000: D99% > 6650cGy
- Rectum_02: D2cc < 7700cGy / V77Gy < 2cc
- Rectum: D5% < 7200cGy / V72Gy < 5%
  D50% < 5000cGy / V50Gy < 50%
- Bladder: D1cc < 8000cGy / V80Gy < 1cc
  D10% < 7200cGy / V72Gy < 10%
  D50% < 5000cGy / V50Gy < 50%
- Rectum sparing has a higher priority the bladder sparing.
- Anus sphincter: Dmean < 3700cGy
- Avoid high spots (>50Gy) in the lateral parts

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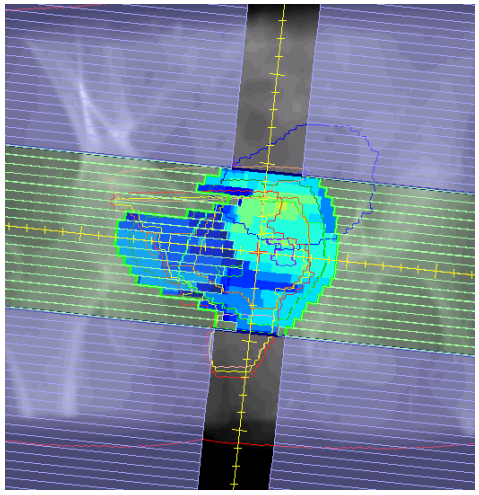
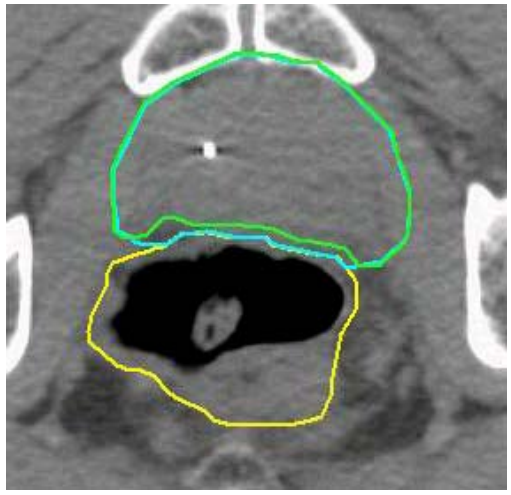
some suggestions

- S&S IMRT : 7 beams
- VMAT: 2 arcs
- slightly turn collimator (10-15 degrees)





- use aiding structures for getting the dose gradients exactly where you want them to

- Good luck!

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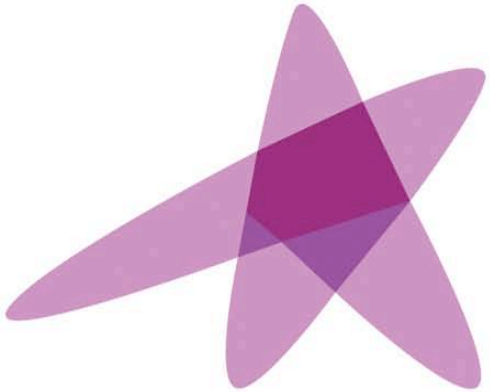

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Prostate case discussion

ESTRO Cambridge
September 2016

Clinical details

- Mr R – 80 years old
- Prostate cancer, PSA 13 µg/L, Gleason score: 3+3

- External beam radiation (according to FLAME trial)

- Objectives

  Dose 95 Gy GTV, 77 Gy Prostate, 70 Gy seminal vesicles 35#

  - (rotational) IMRT, Tomo

Switch to Oncentra revue

Which is the ‘best’ plan?

Individual planning session

Well done everybody !

Which is the ‘best’ plan?

- Consider PTV
  - What is most important part of the PTV?
- Consider organs at risk
  - Which organ at risk is most important in this patient?
- Consider other factors
  - Planning & delivery issues
  - Treatment time
- Beam arrangement

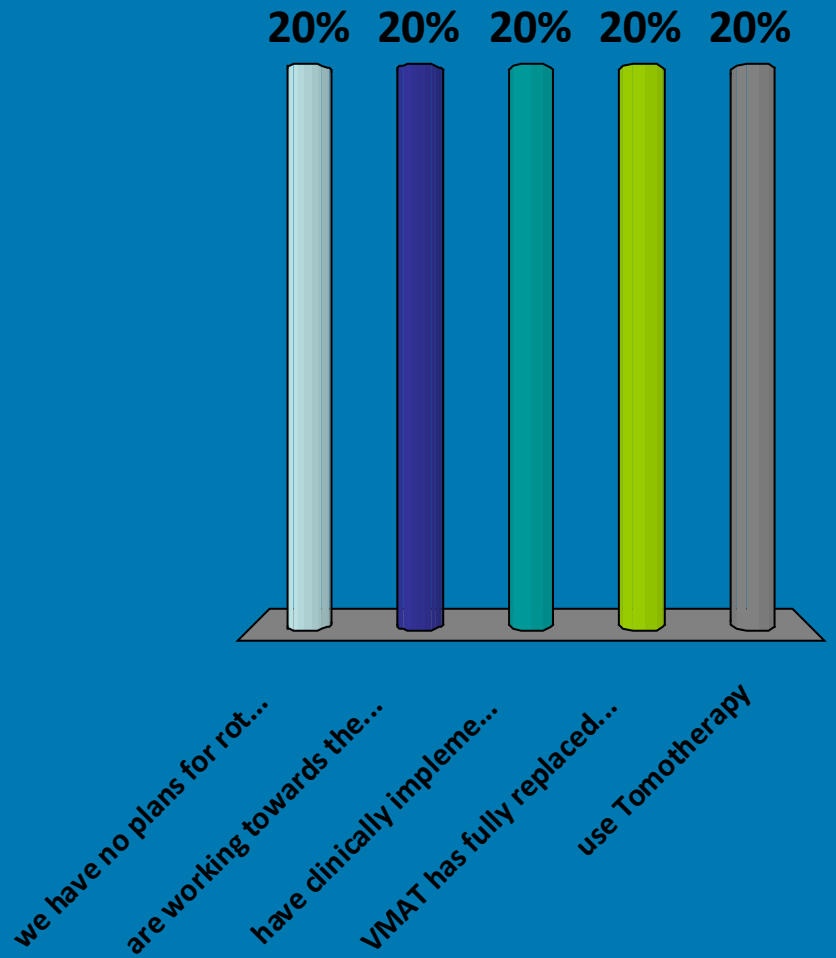
Basic principles of rotational IMRT planning

Gert Meijer

ESTRO
European Society for Therapeutic Radiology and Oncology

In my institute

a. we have no plans for rotational IMRT
b. are working towards the implementation of rotational IMRT
c. have clinically implemented VMAT
d. VMAT has fully replaced S&S IMRT
e. use Tomotherapy



Rotational IMRT not really new

- “A logical extension of multiple beam therapy is to use 1 beam, have it directed towards the tumour, and cause the machine to rotate about an axis through the tumour, or keep the machine fixed and rotate the patient about this axis …”

- When the radiotherapist was limited to the use of 250 kV X-rays, it was very difficult to get enough radiation into an internal tumour … As a result many workers developed rotation techniques

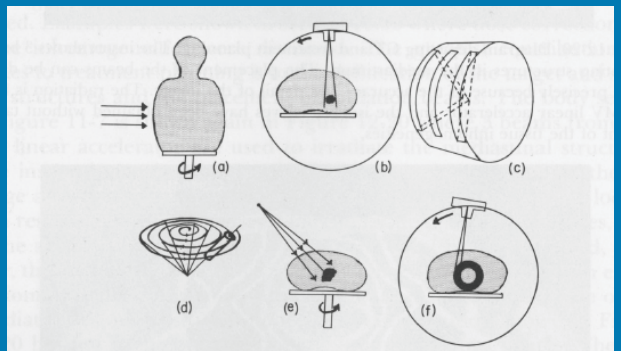


Figure 12-22. Diagrams illustrating the various types of rotation therapy.

Courstesy of Dirk Verellen

AUTOMATIC CONTROL OF THE TUBE CURRENT AS A MEANS OF DOSE REGULATION IN TANGENTIAL ROTATION

By PROFESSOR H. HOLTHUSEN, M.D., F. GAUWERKY, M.D., and F. HEINZEL, M.D.

From the Radiotherapy Department, St. George's General Hospital, Hamburg, Germany

(An invited contribution for the Diamond Jubilee Number)

SINCE the introduction of tangential pendulum irradiation or tangential rotation for post-operative X-ray treatment of cancer of the breast by Hare, Trump and Webster in 1952, a lively interest has arisen in Germany, particularly as the result of the publications by Rossmann (1954 and 1955), and Becker, Werner and Kuttig (1954), in this efficient method of irradiation. Tangential rotation offers excellent possibilities for optimum sparing of the

of the usual commercial moving-beam therapy appliances on a recumbent patient. In this case, according to the design of the pendulum apparatus, either the central ray is set eccentrically by tilting the tube out of the pendulum axis (Rossmann, 1954) or an eccentric tangential X-ray beam is diaphragmed from a tube unaltered in position. For this purpose, using the universal irradiation apparatus TU I of Messrs. C. H. F. Müller, Hamburg, which we have at our disposal, a continuously adjustable tangential slot diaphragm is used with whose aid tumour field

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radiated
-lateral
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art near

Of the two possibilities available in principle to carry out the desired compensation, namely variable speed of the X-ray tube movement during irradiation on the one hand and variation of dose output on the other, the latter was chosen since a regulation of the tube current in accordance with a predetermined scheme could be achieved with less constructional difficulties. Thus the tube current will have to be reduced in the higher dosed skin areas, and increased in the positions of the tube in which the surface areas are lower dosed. For this purpose, distribution schemes for the tube current

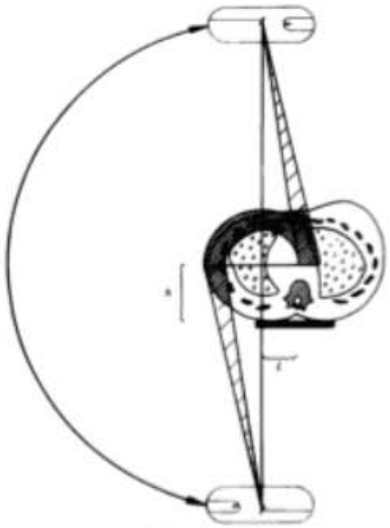


FIG. 1.

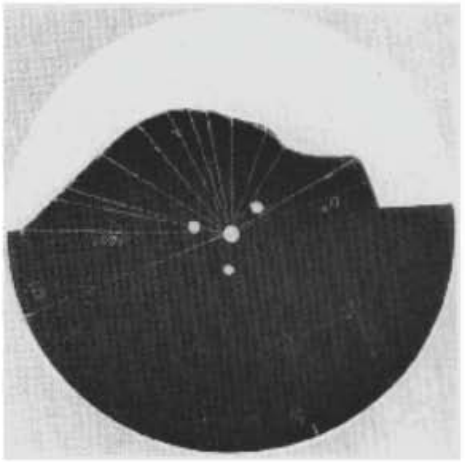


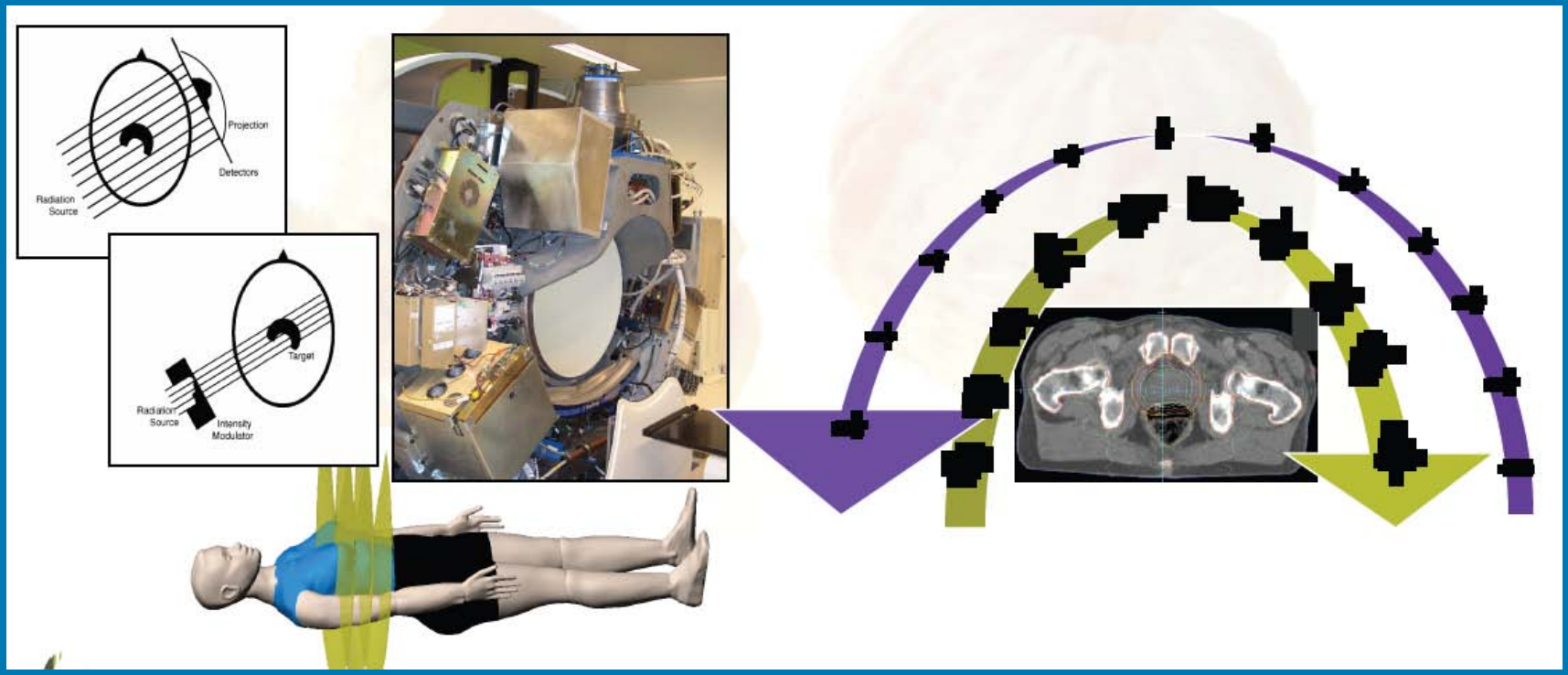
FIG. 2.

British Journal of Radiology, 1956

(1944, Wachsmann, Pendulum unit)

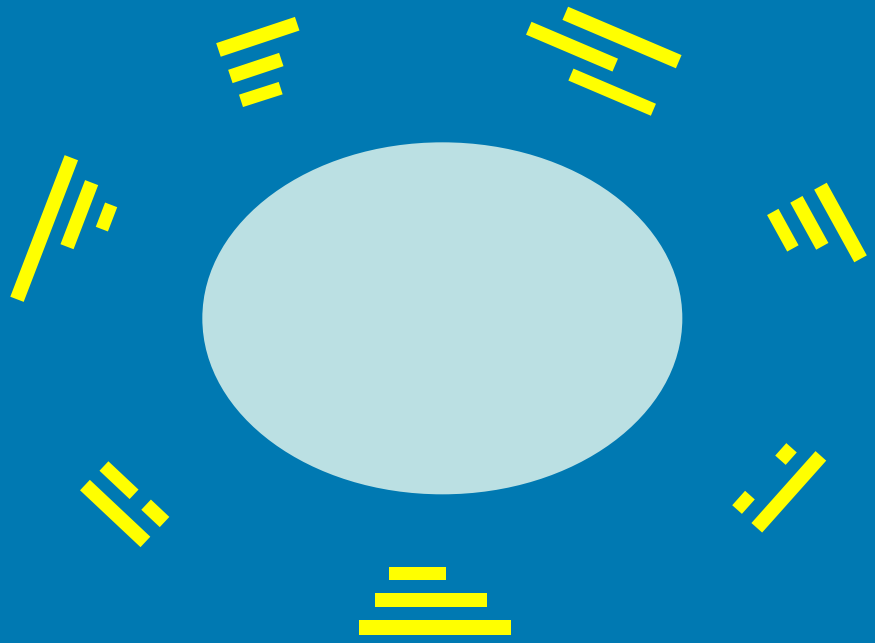
Courstesy of Dirk Verellen

fan beam vs cone beam

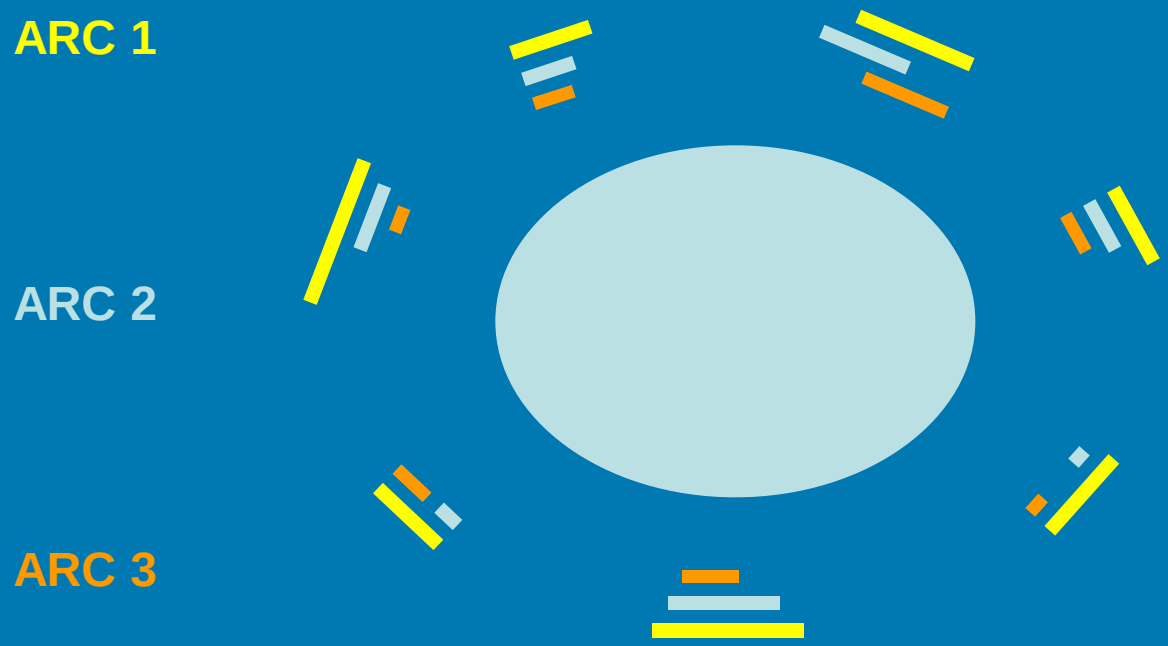


Courstesy of Dirk Verellen

IMRT

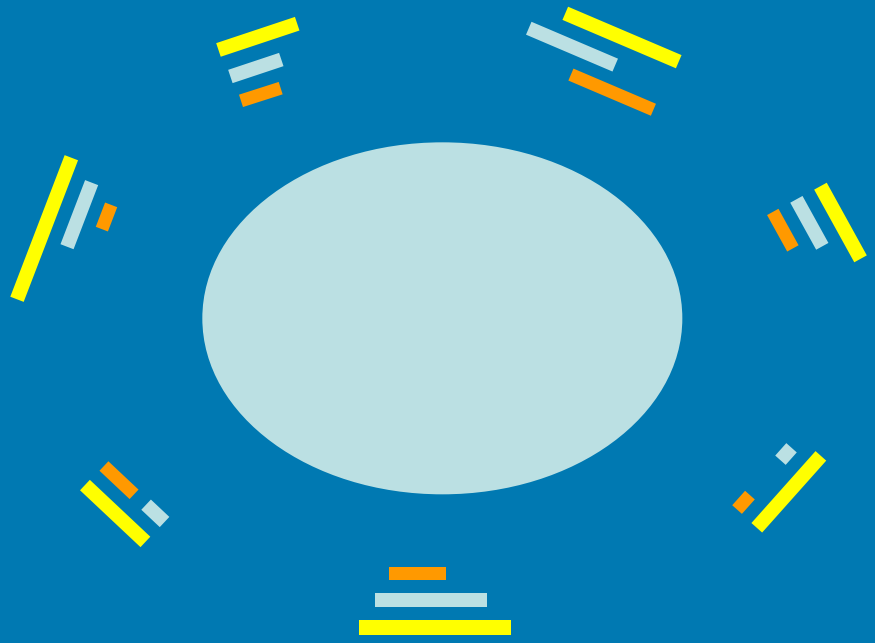


IMAT



from 3 arcs to a single arc

moving from stacked to spaced



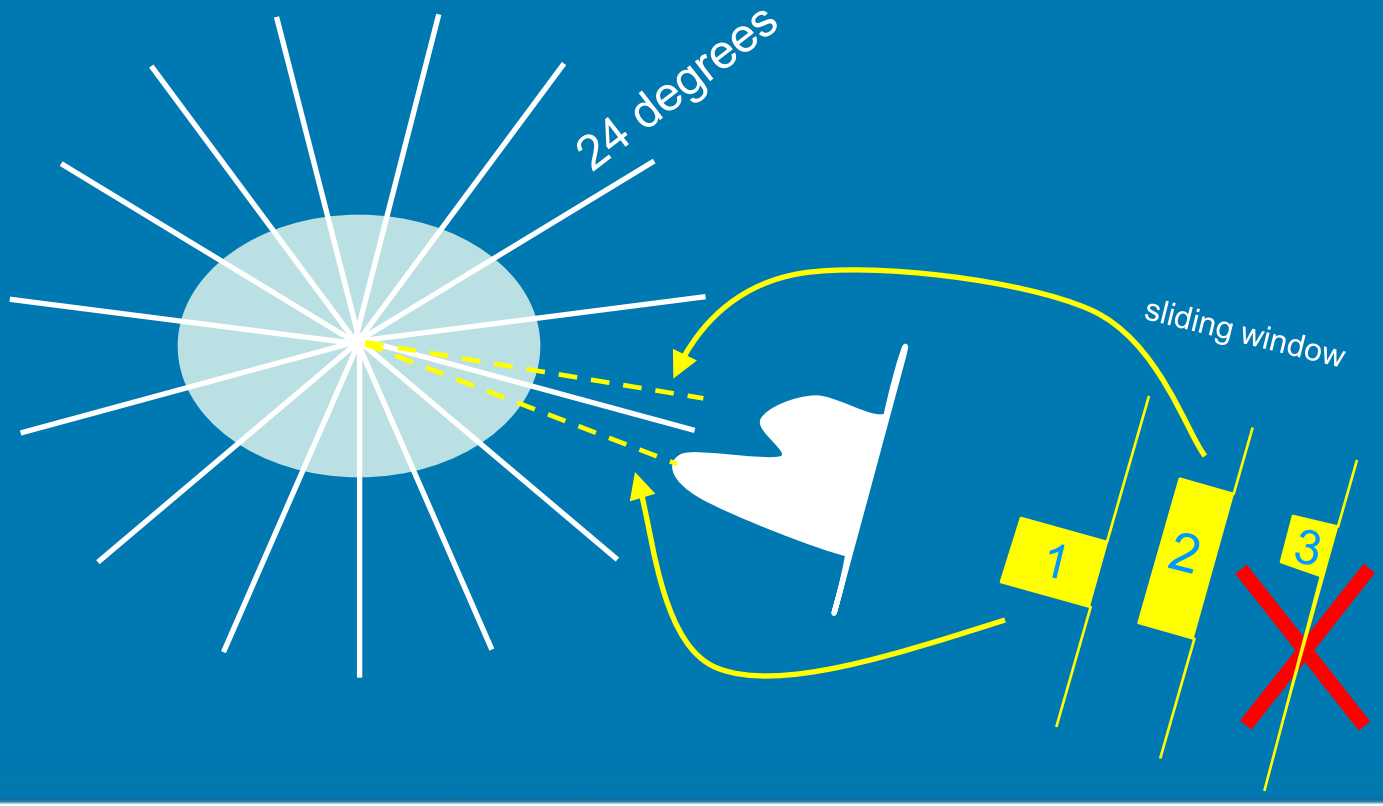
Tang *et al.* (IJROBP 2007)

So….

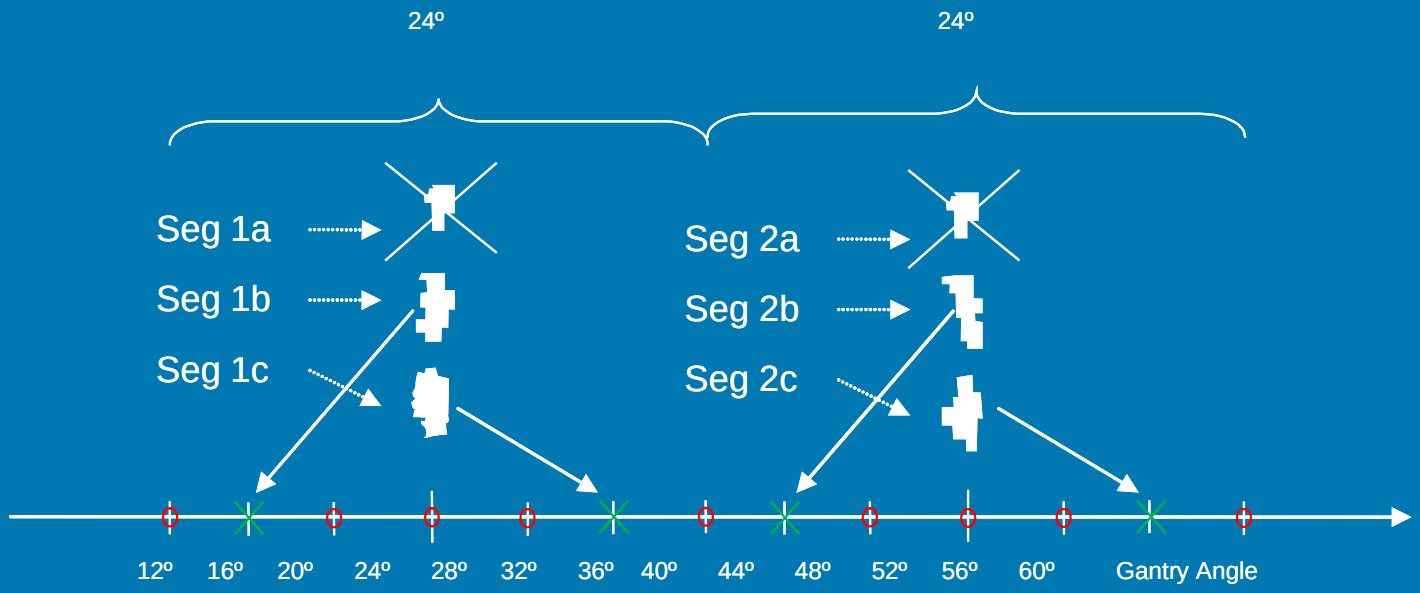
rotational therapy is rather insensitive to angle deviations

but also that cone beam rotational IMRT is not that different from static IMRT

So how does is work in practise?



Segmentation



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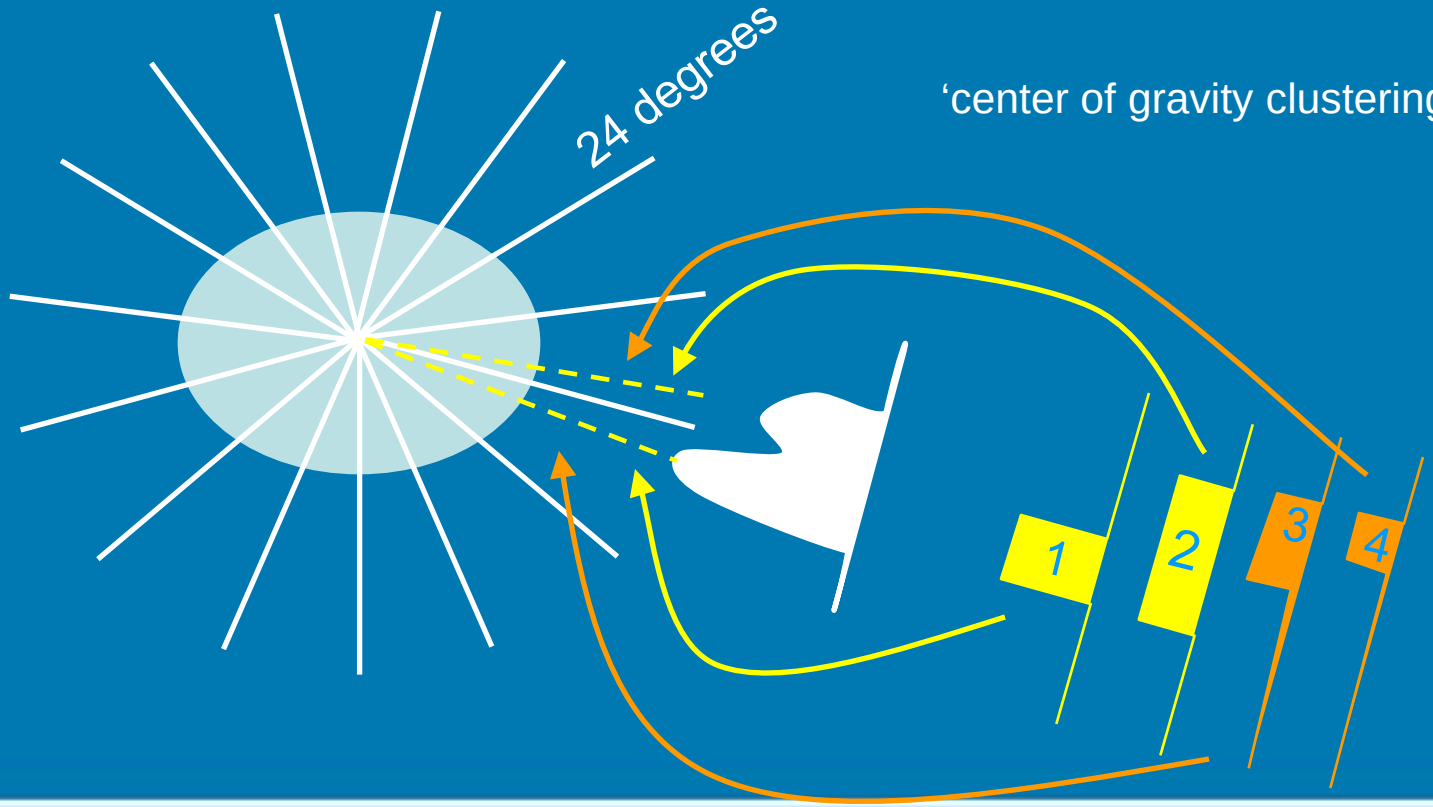
How about dual arcs?




IMRT
VMAT

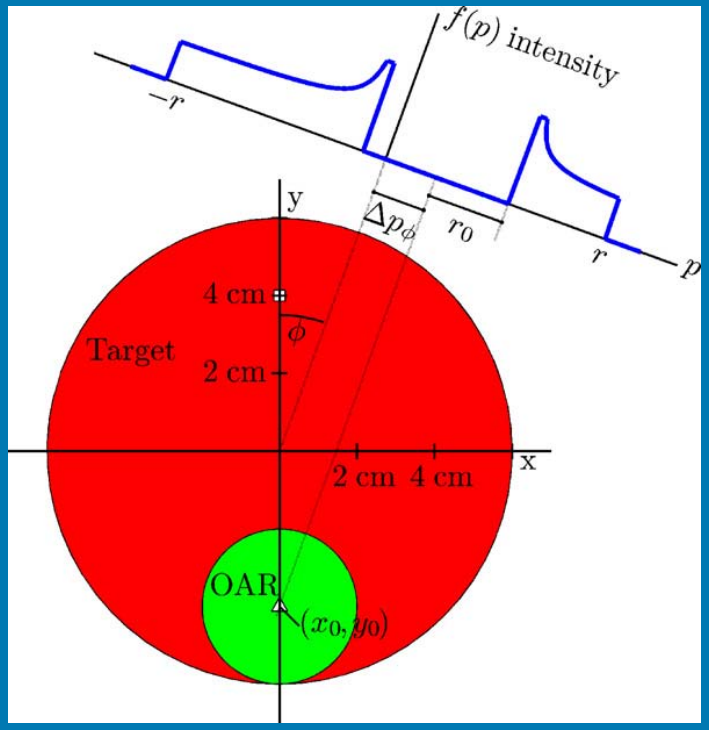
Static IMRT vs VMAT - Conceptual issues

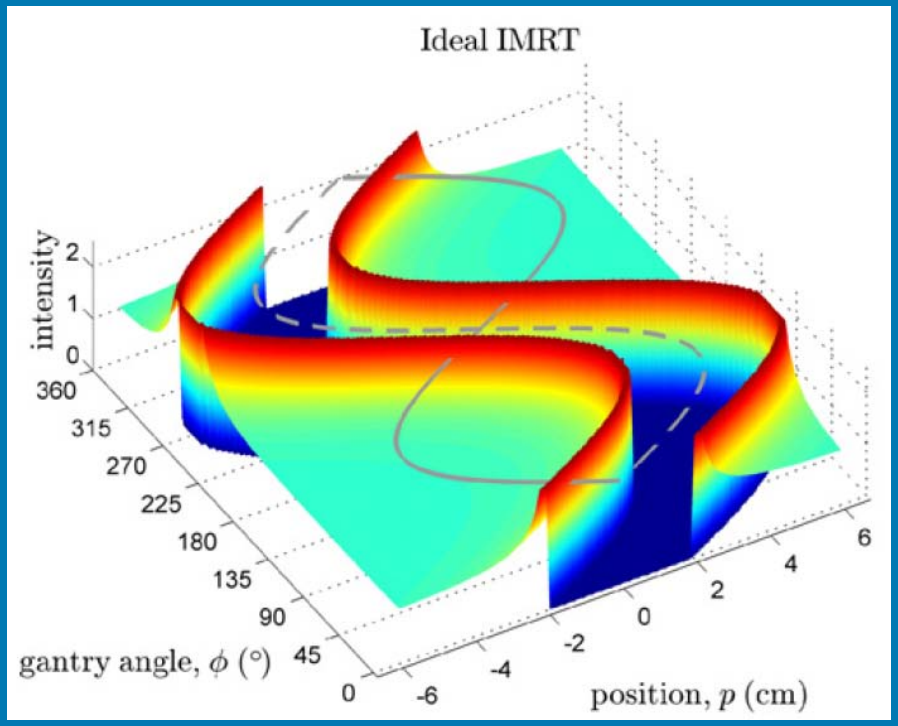
Is there any difference between static IMRT and VMAT?

- Use the same hardware
- Can be virtually ‘mapped’ onto each other:
  - S-IMRT with infinite number of beams → VMAT
  - **VMAT with** infinitely small gantry speeds (quasi static) → S-IMRT

Courstesy of Jochem Wolthaus

IMRT vs. VMAT - Conceptual differences

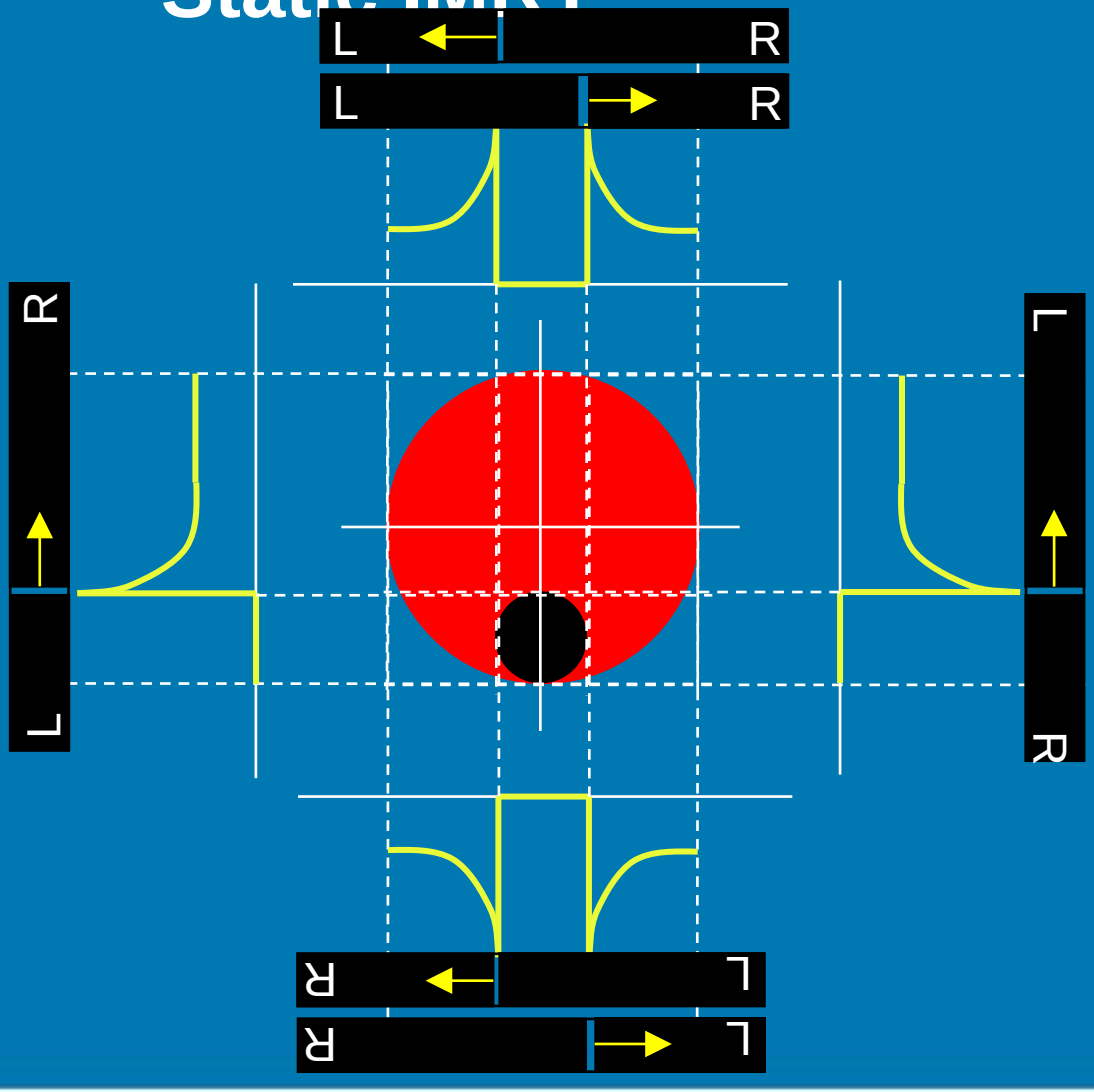


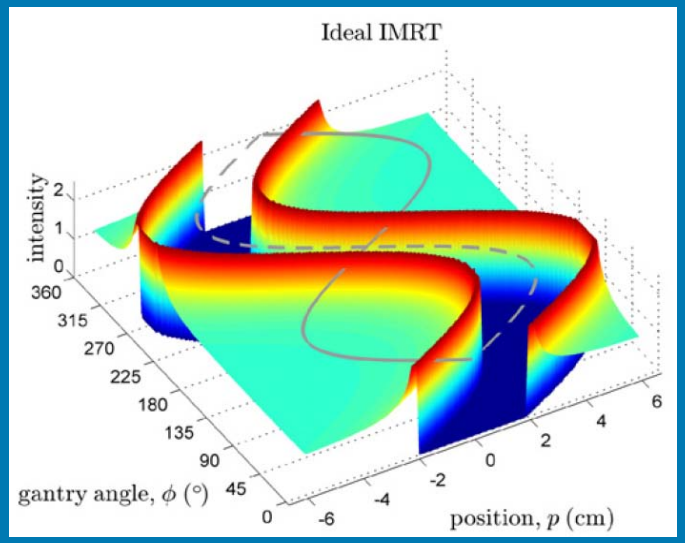


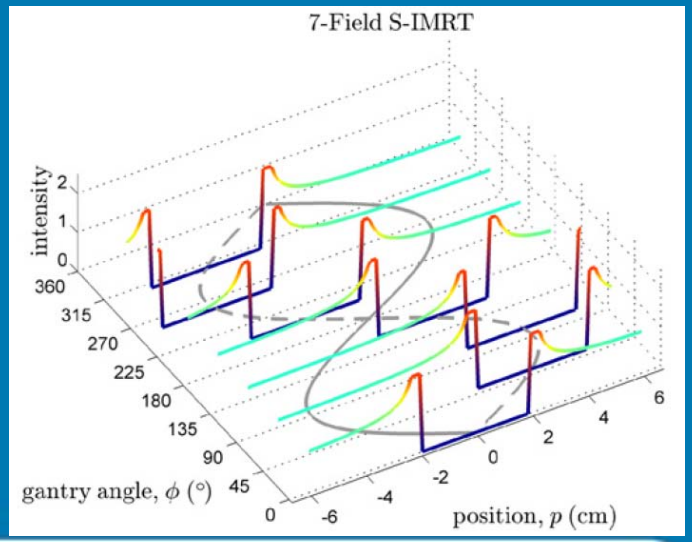
Bortfeld and Webb (2009) explaining VMAT by Brahme's IMRT case (1982). Target volume is wrapped around an OAR. Analytical solution is known

Courstesy of Jochem Wolthaus

Static IMRT







Courstesy of Jochem Wolthaus

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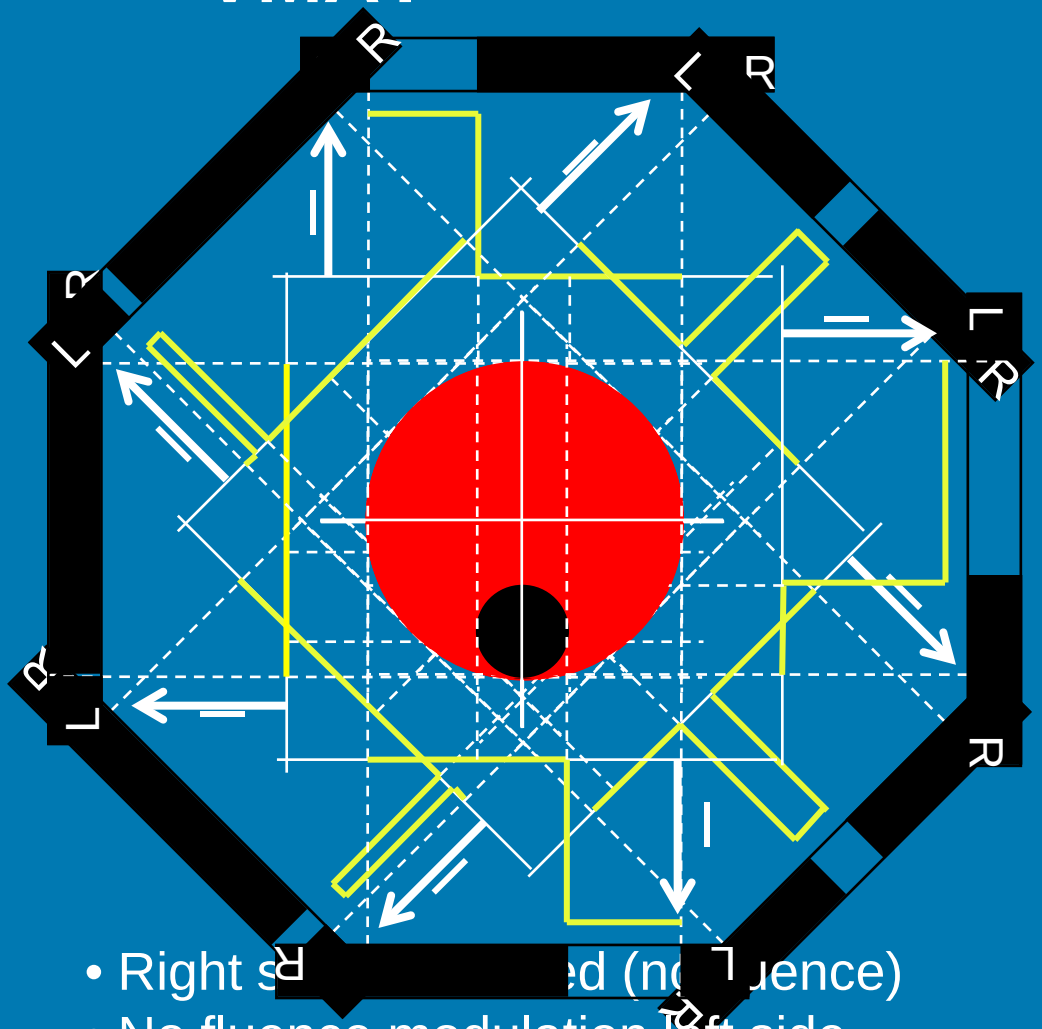
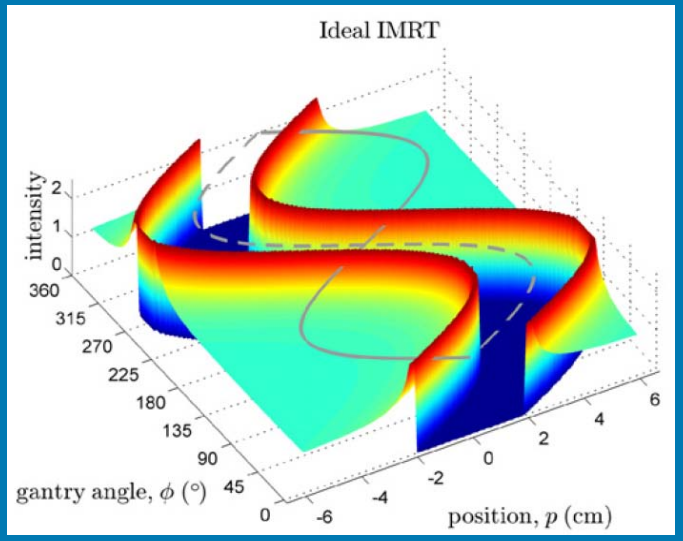
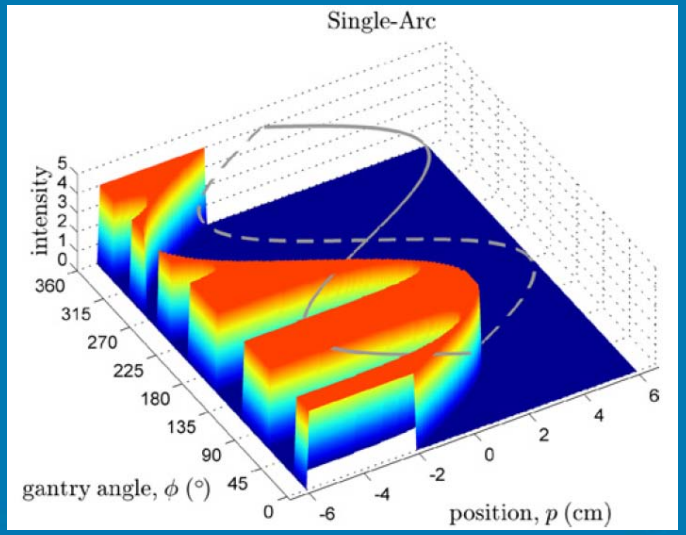
VMAT



- Right s ed (n uence)
- No fluence modulation left side





Courstesy of Jochem Wolthaus

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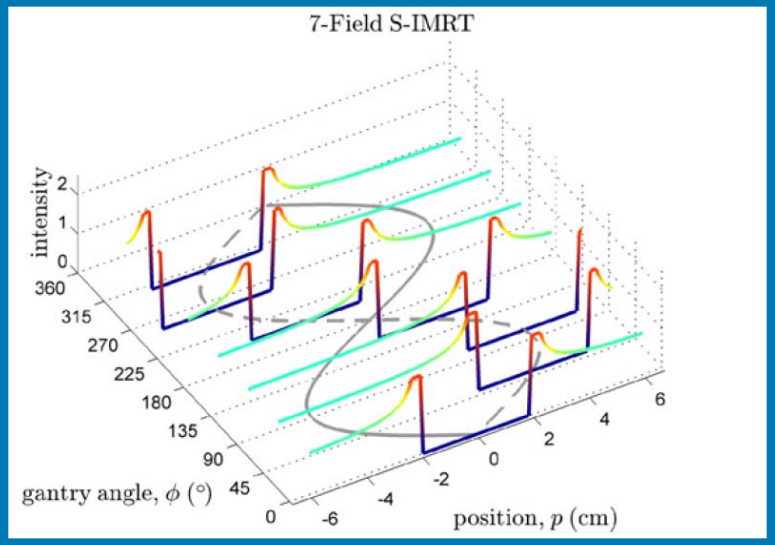
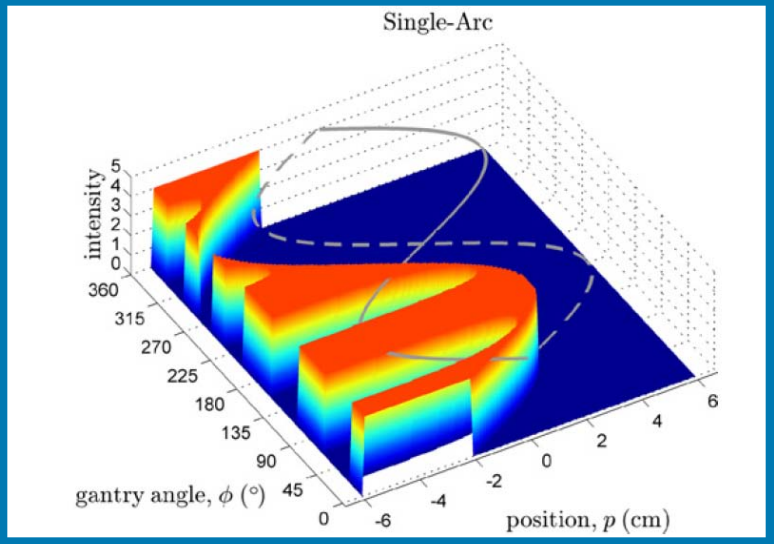
IMRT vs. VMAT - Conceptual differences



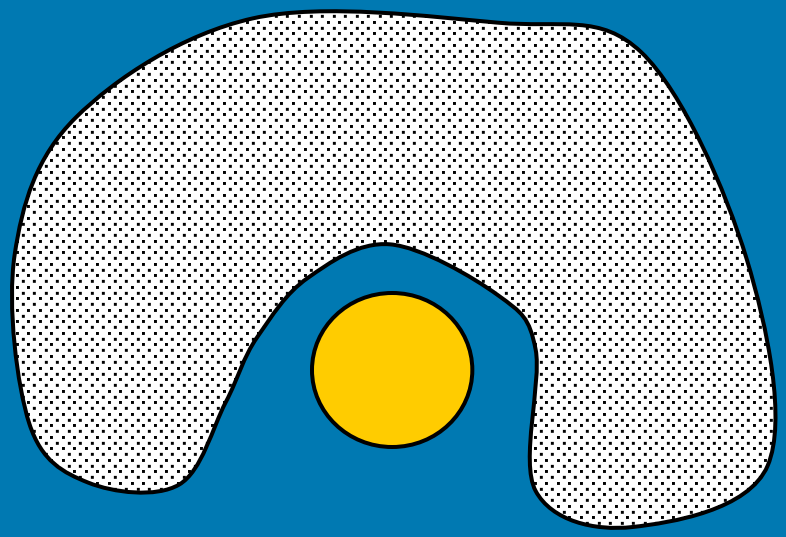


Compromises in different areas:

Static IMRT uses a very coarse sampling of the gantry angle but with full intensity modulation
VMAT uses all angles but without intensity modulation (per gantry angle)

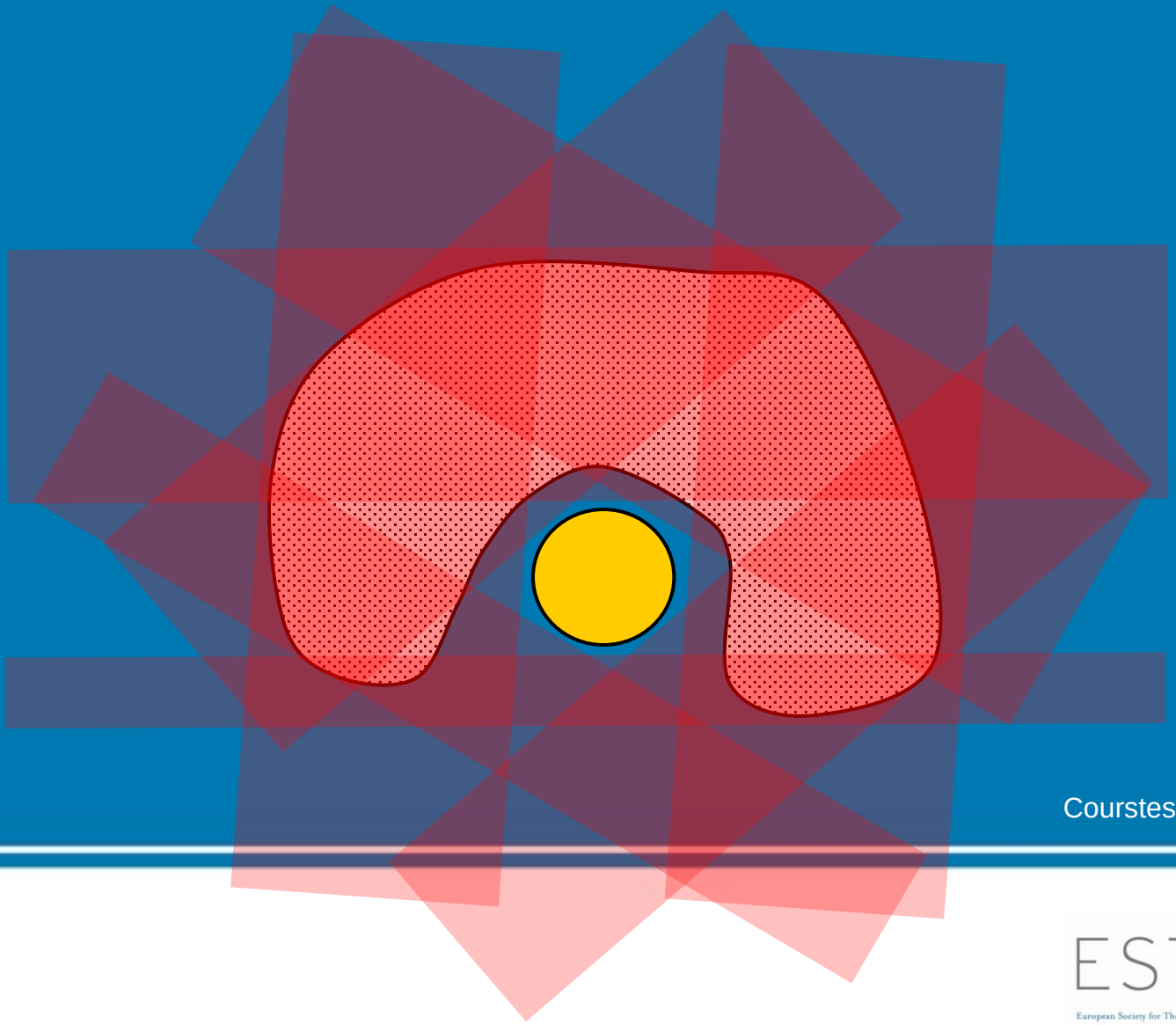
Courstesy of Jochem Wolthaus

Why need multiple arcs??



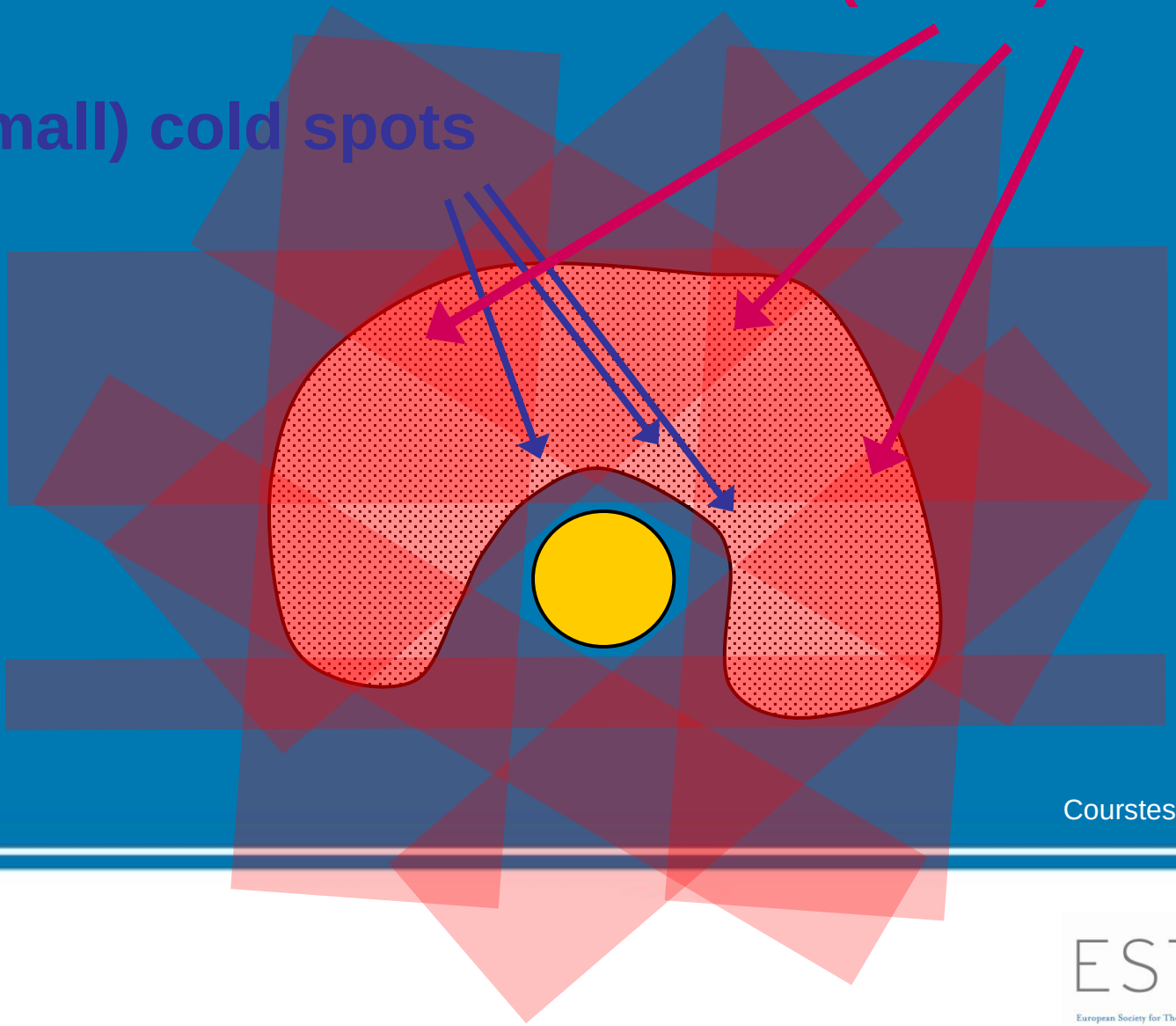
Courstesy of Markus Alber

Start with 4 beam angles



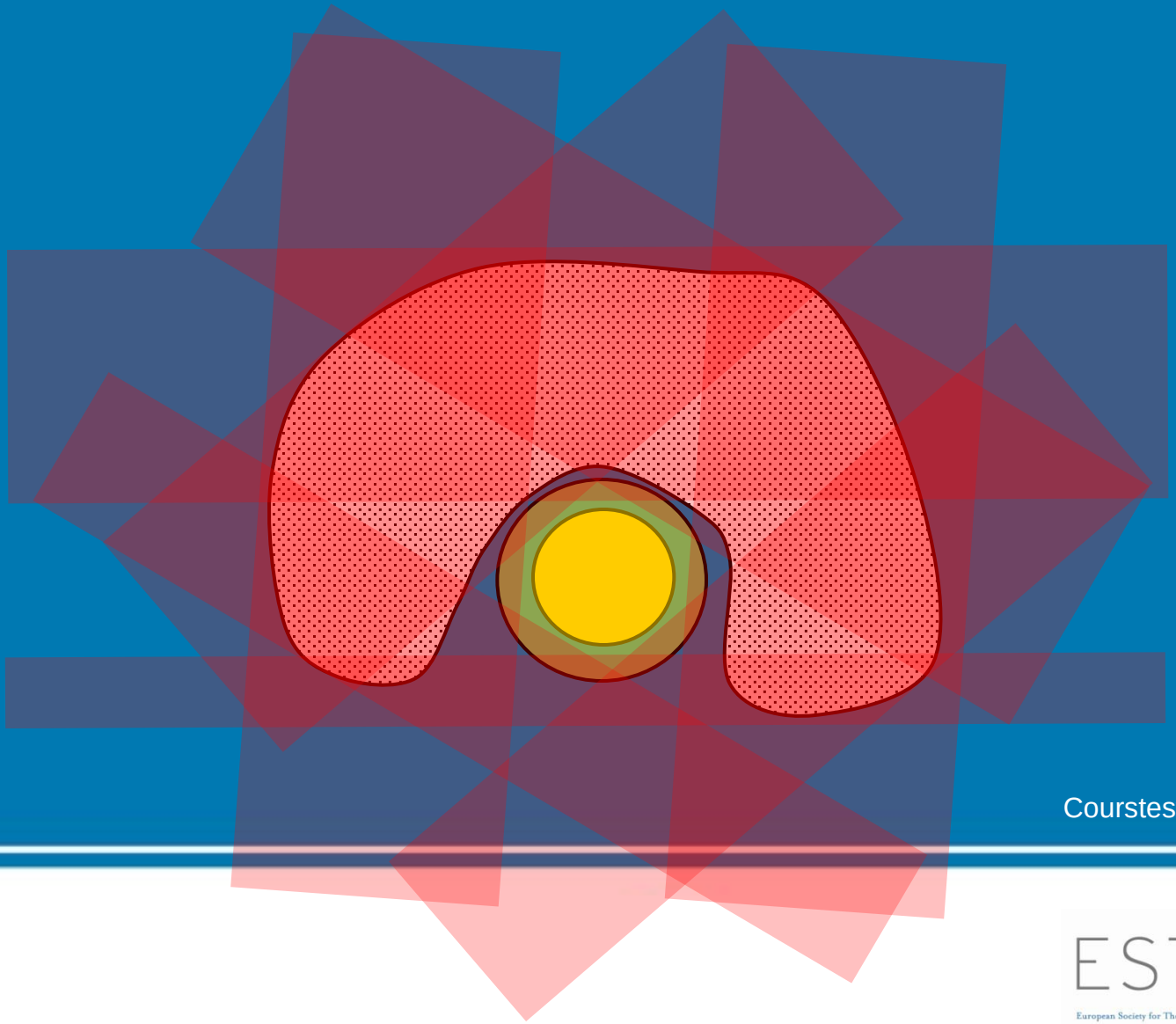
Courstesy of Markus Alber

Start with 4 beam angles



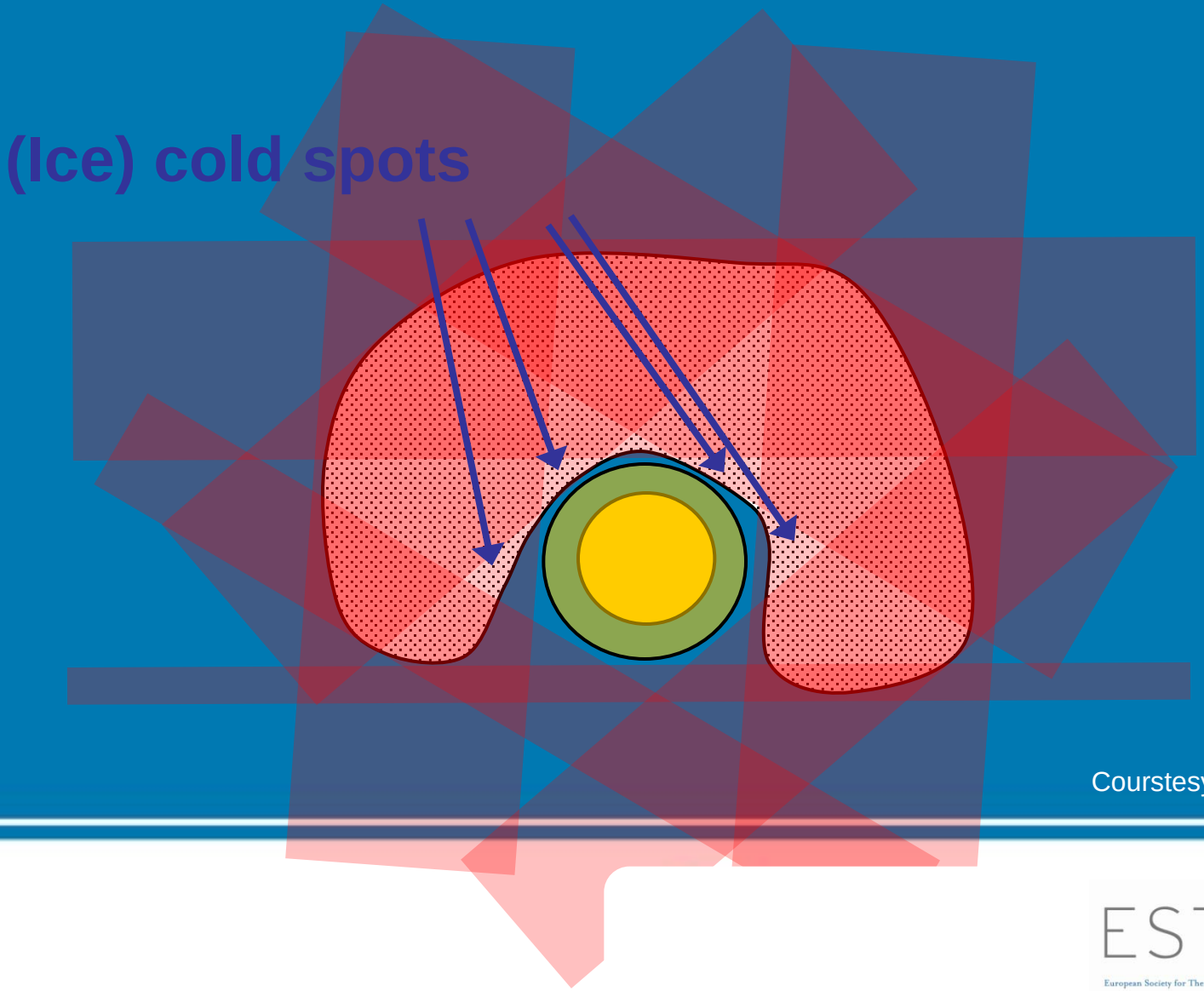
Courstesy of Markus Alber

What if the gradient has to be tighter?



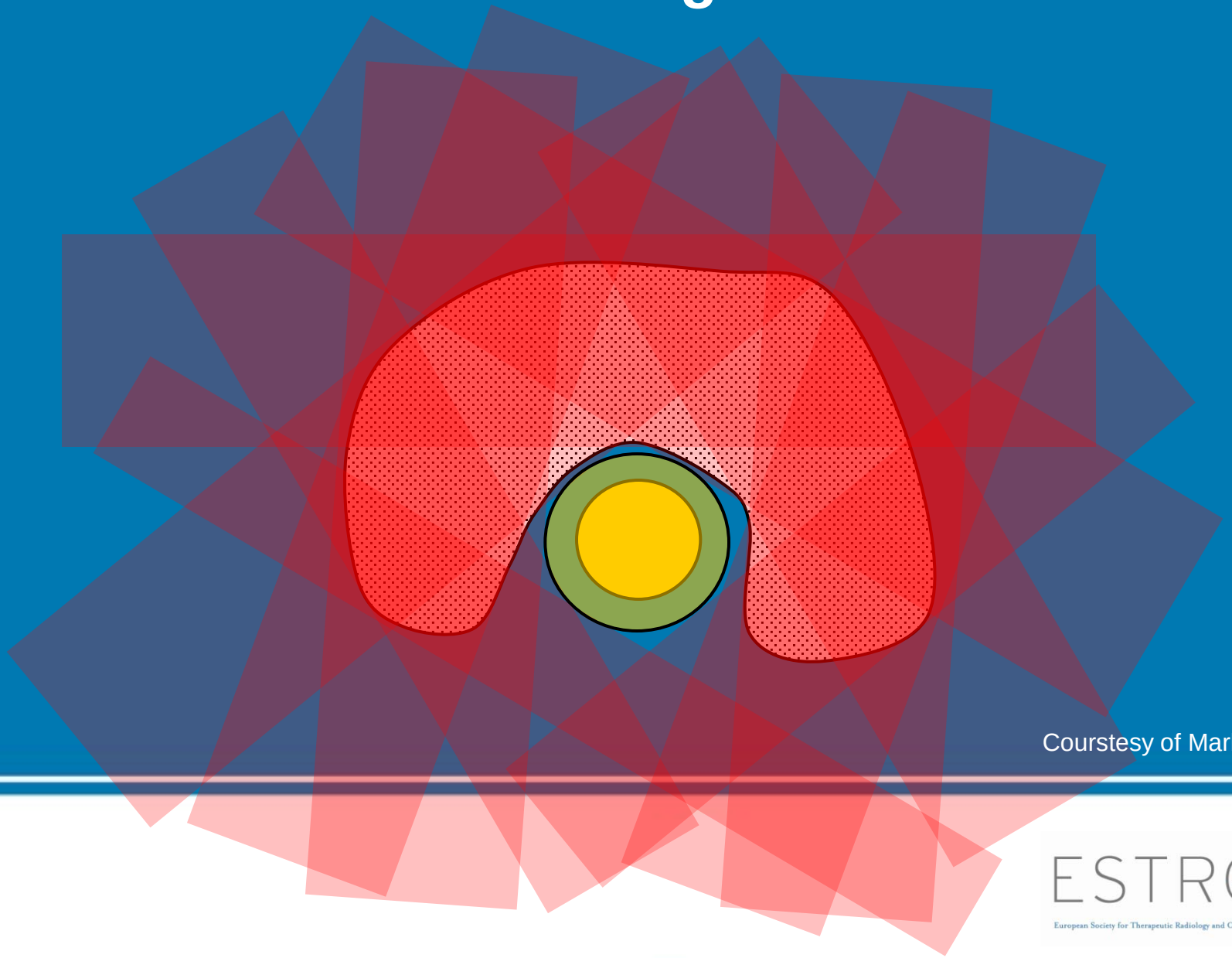
Courstesy of Markus Alber

What if the gradient has to be tighter?



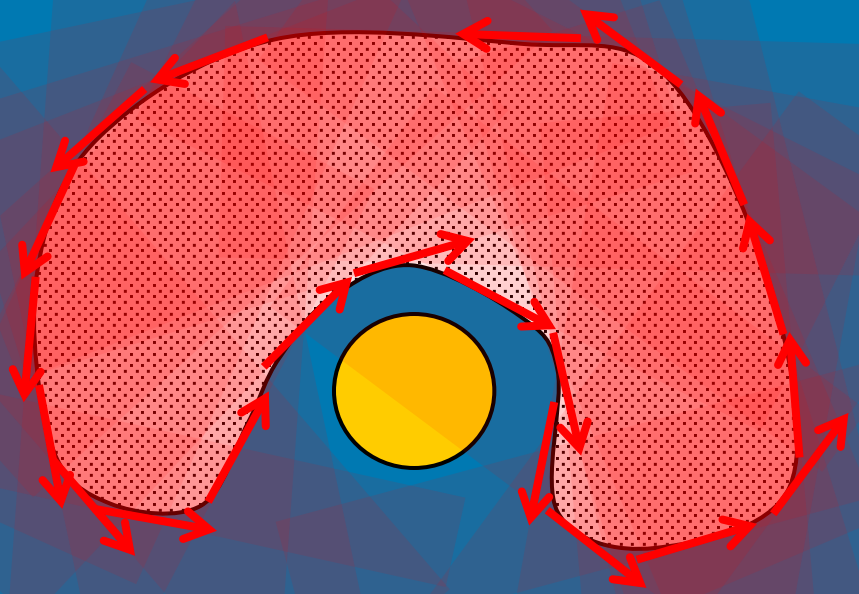
Courstesy of Markus Alber

Use more beam angles!



Courstesy of Markus Alber

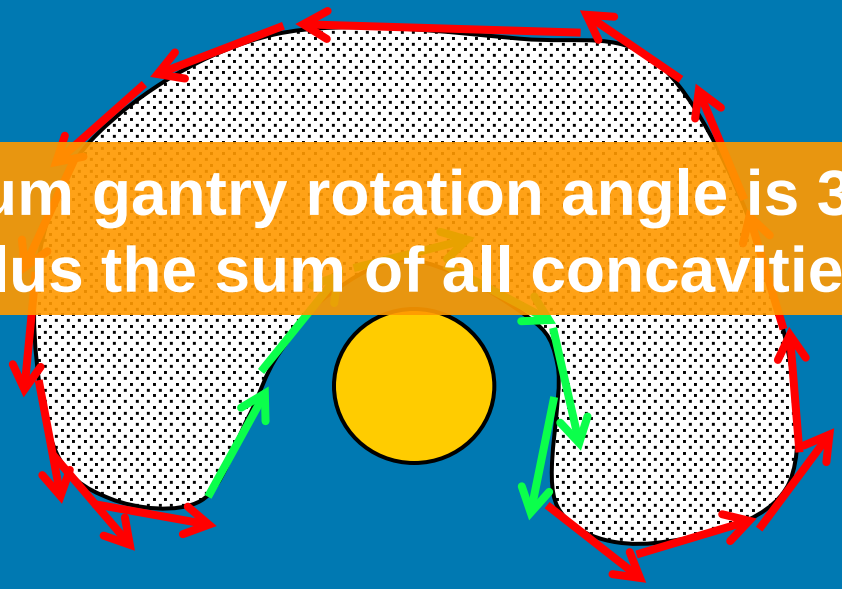
What is the maximum gantry rotation angle needed to paint all gradients for this target??



Courstesy of Markus Alber

What is the maximum gantry rotation angle needed to paint all gradients for this target??

The total gantry rotation is the sum of all red angles (counter-clockwise) and all green angles (clockwise).

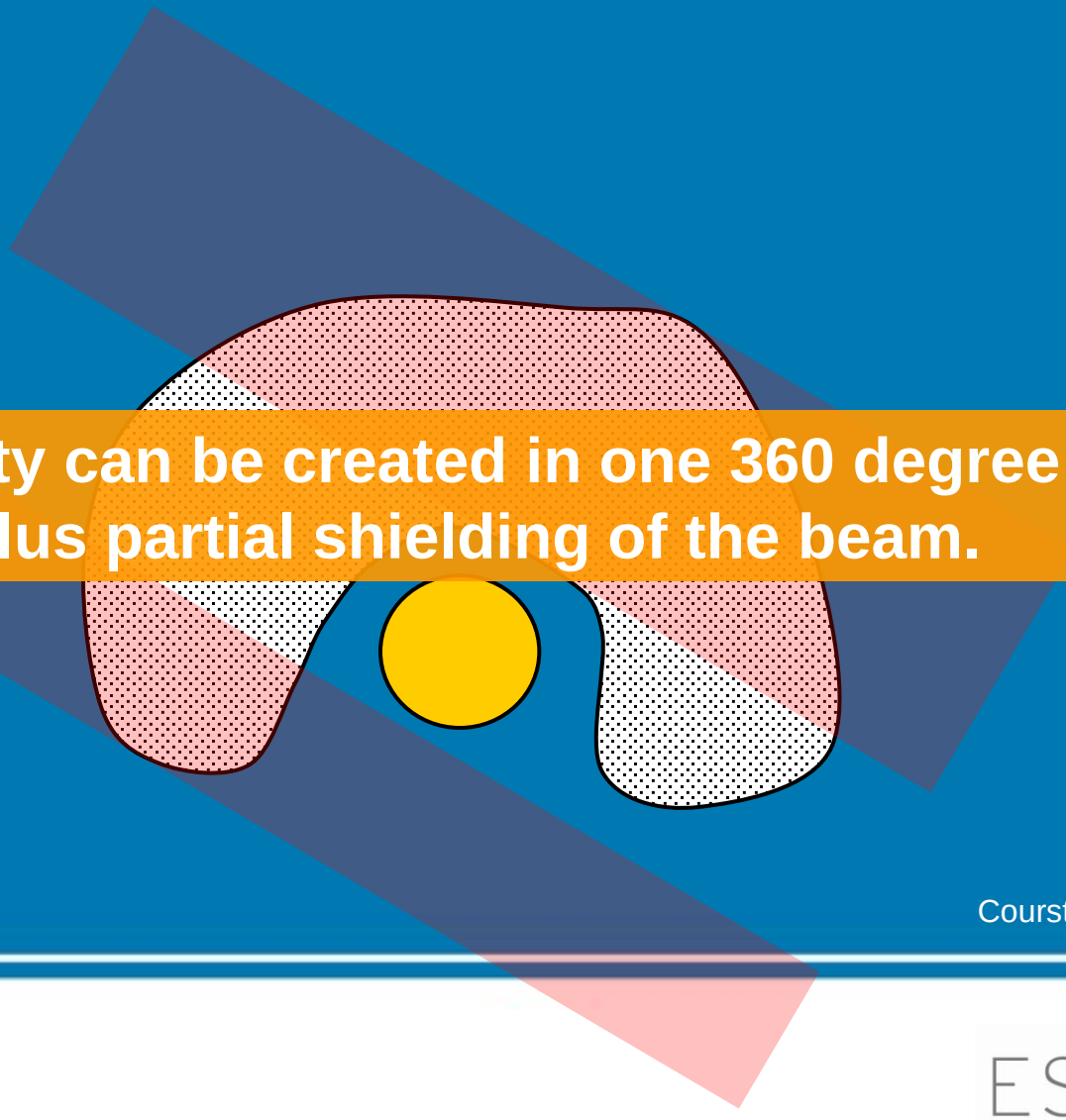


The maximum gantry rotation angle is 360 degrees plus the sum of all concavities

The sum of all red angles is 360 degrees.

Courstesy of Markus Alber

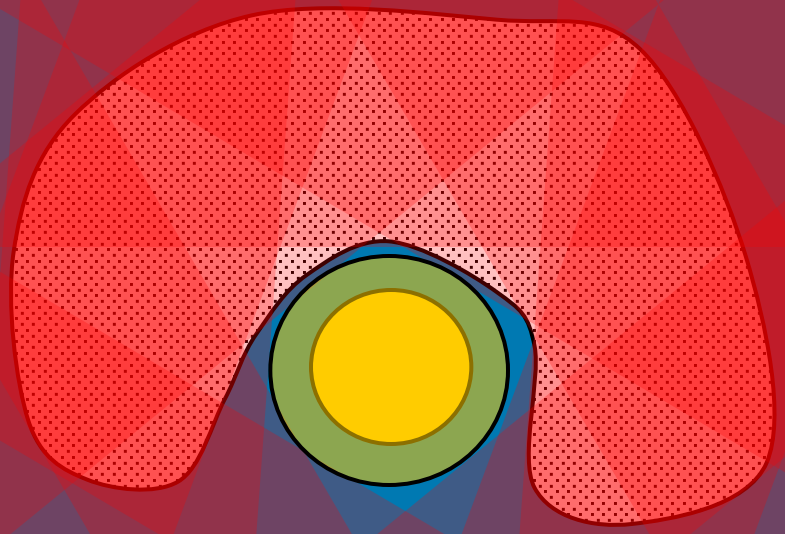
Alternatively:



The concavity can be created in one 360 degree rotation plus partial shielding of the beam.

Courstesy of Markus Alber

Alternatively:



Courstesy of Markus Alber

So .....

The maximum gantry rotation angle is 360 degrees plus the sum of all concavities

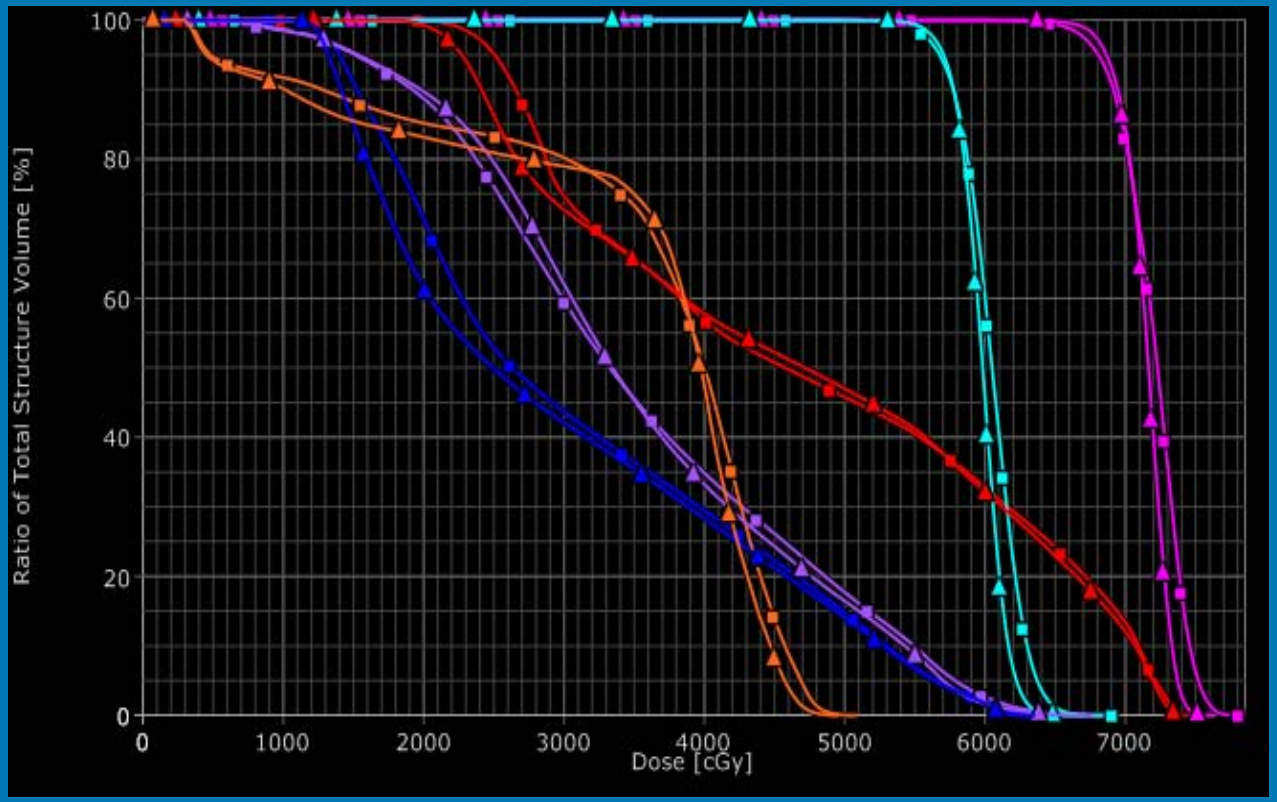
This is the *dynamic conformal arc* way. It is analogous to the step and shoot technique in static gantry IMRT.

The concavity can be created in one 360 degree rotation plus partial shielding of the beam.

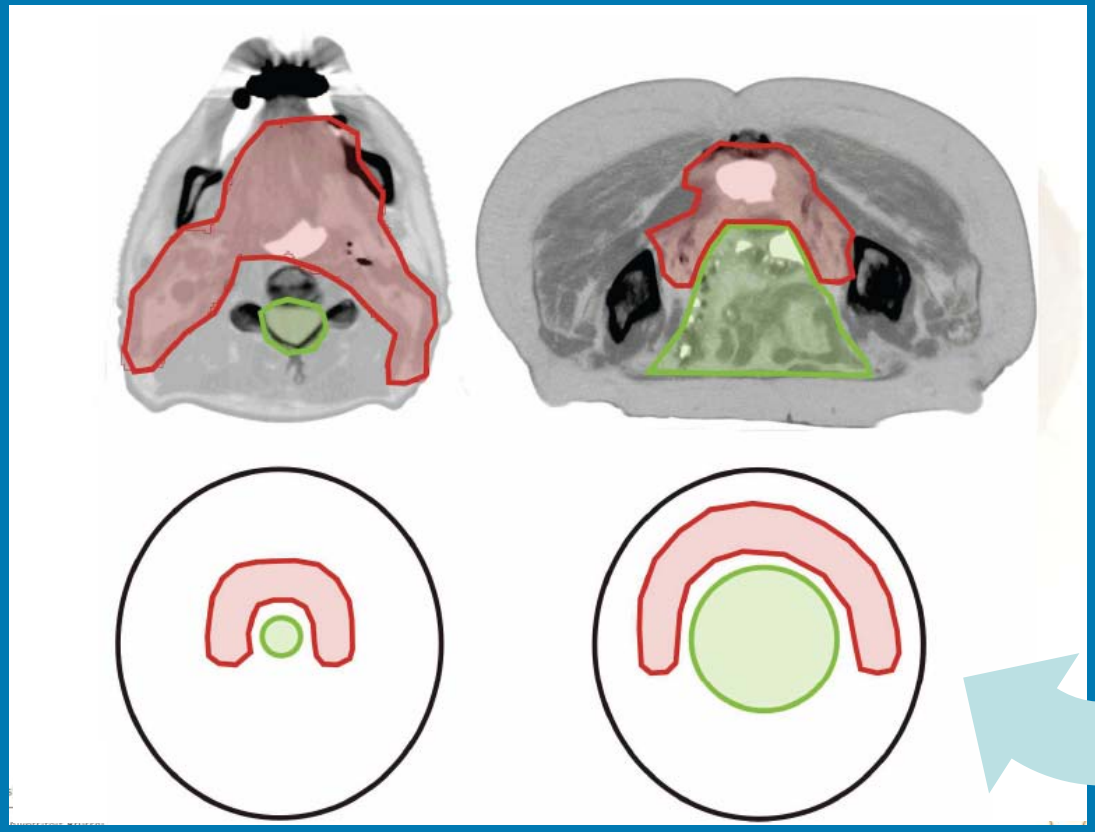
This is the *tomotherapy way*. Emulating it with a cone-beam MLC means large leaf travel and is wasteful in terms of primary radiation. (Notice, tomotherapy is also wasteful for narrow fan-beams and long target volumes)

Courstesy of Markus Alber

RapidArc single arc versus double arc

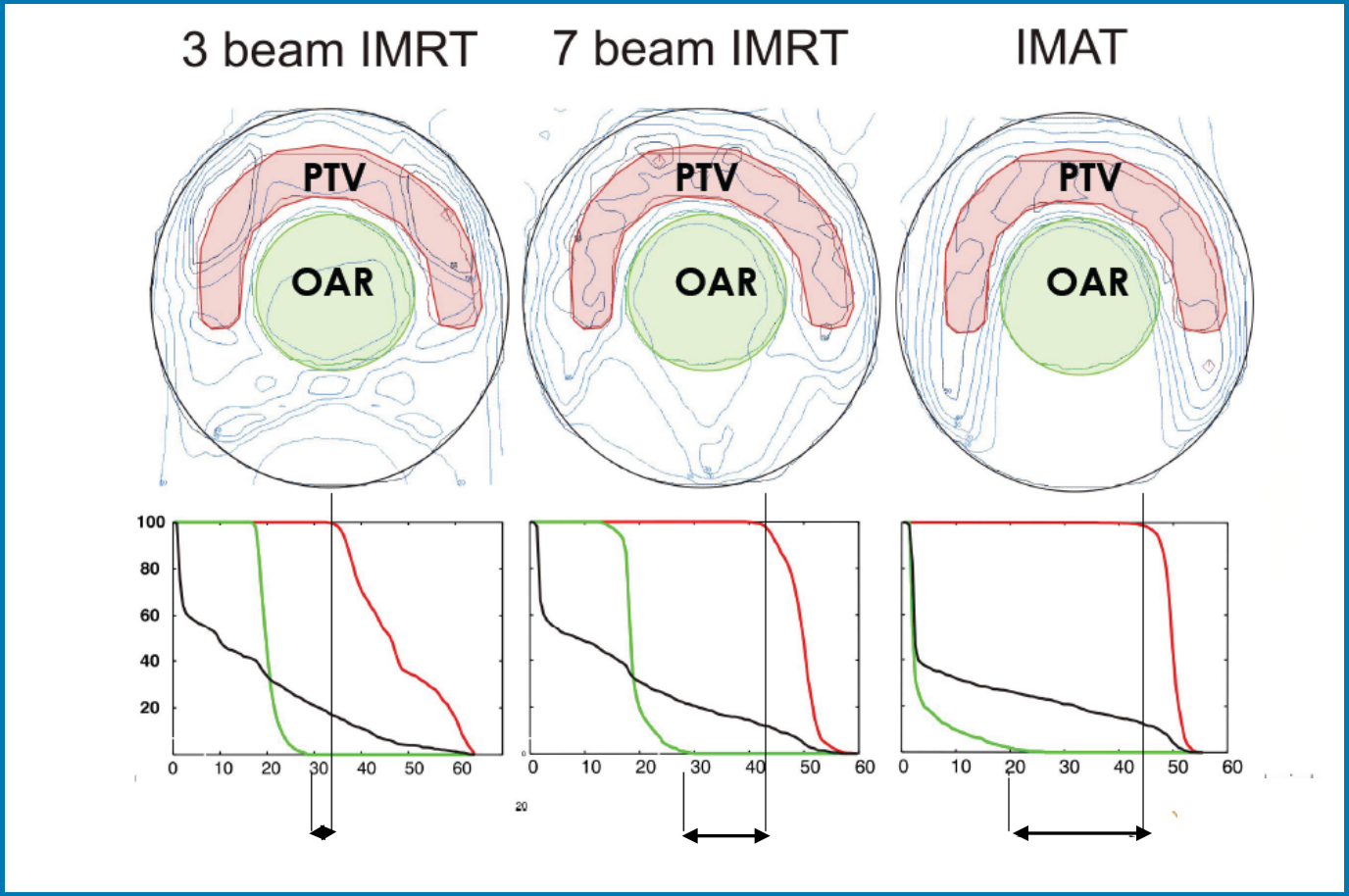


Courtesy of Wilko Verbakel



rotational IMRT generally does a better job at large concavities

De Meerleer *et al.*



De Meerleer *et al.*

rotational cone beam IMRT vs static IMRT

- faster delivery
- comparable plan quality

fan beam

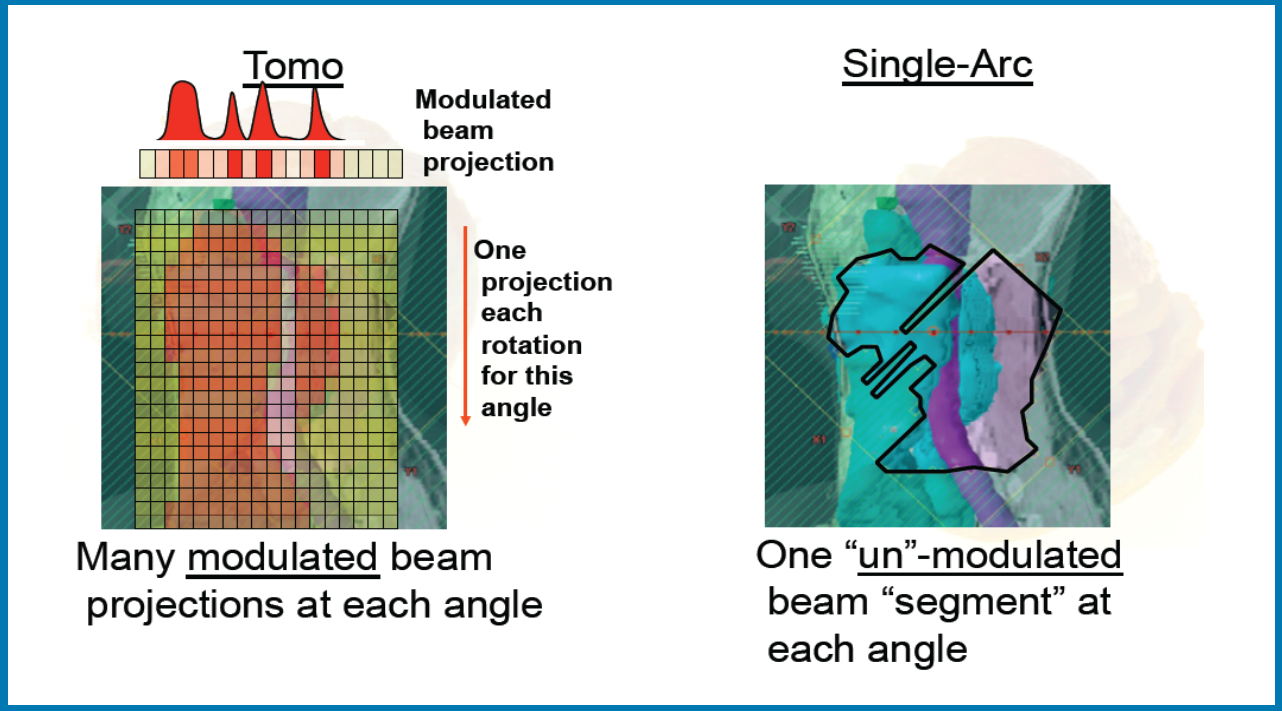
binary leaves

cone beam

sliding leaves

fan beam IMRT offers more modulation than cone beam IMRT

(but comes at cost of longer irradiation time?)



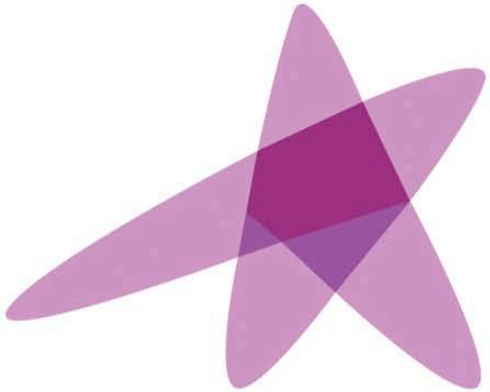
Courstesy of Dirk Verellen

Conclusions

- cone beam rotational IMRT just another flavour but faster because of continuous irradiation but not better (more gantry angles but unmodulated fluence per angle)

- fan beam rotational IMRT (Tomo) offers independent bixel optimisation and therefore more dose shaping functionality

- in both cases fluence enters the patient from all (gantry) angles sometimes requiring different optimisation strategies



ESTRO School

Geometric uncertainties and how to deal with them

Marcel van Herk

Institute of Cancer Sciences
Manchester University
The Christie NHS Trust

(Formerly at the Netherlands Cancer Institute)

MANCHESTER 1824
The University of Manchester
Manchester Cancer Research Centre

The Christie NHS
NHS Foundation Trust

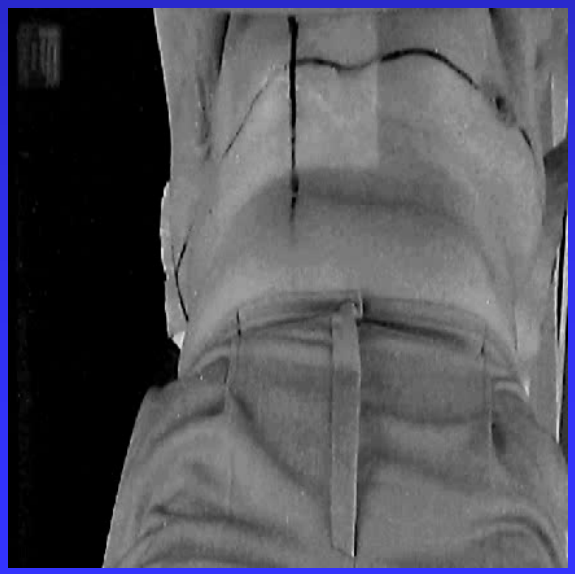
Problems in radiotherapy:

The patient is nervous, did not sleep the night before and lay wriggling on the CT scanner

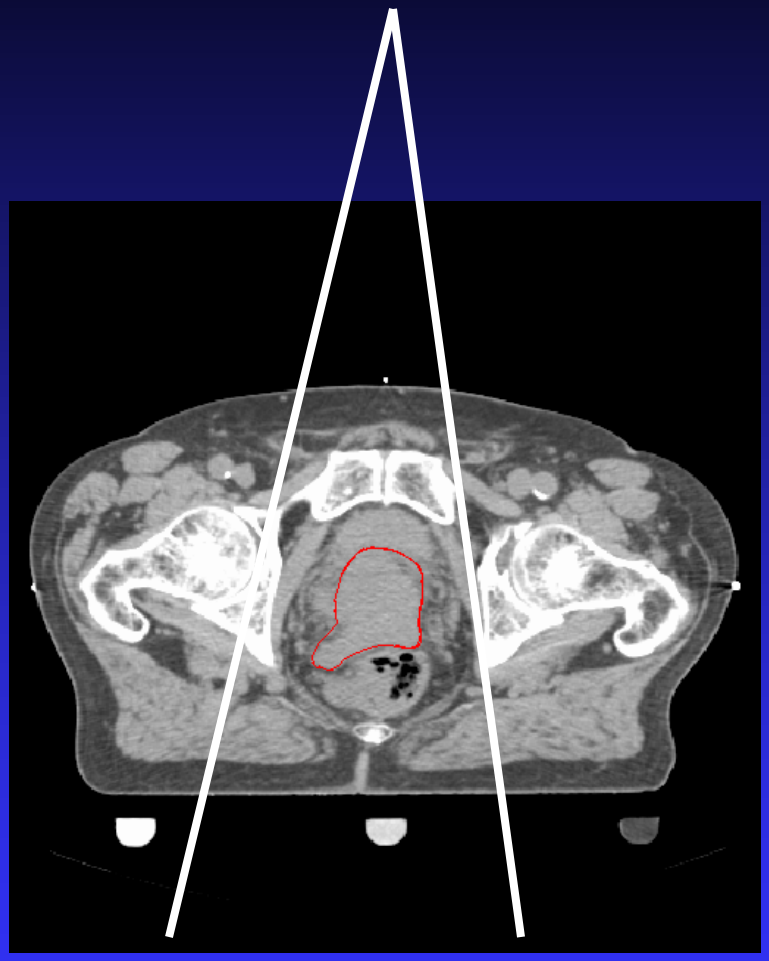
The physician was in a rush when drawing the target volume

The patients belly flopped from day to day, letting the skin marks move all over the place

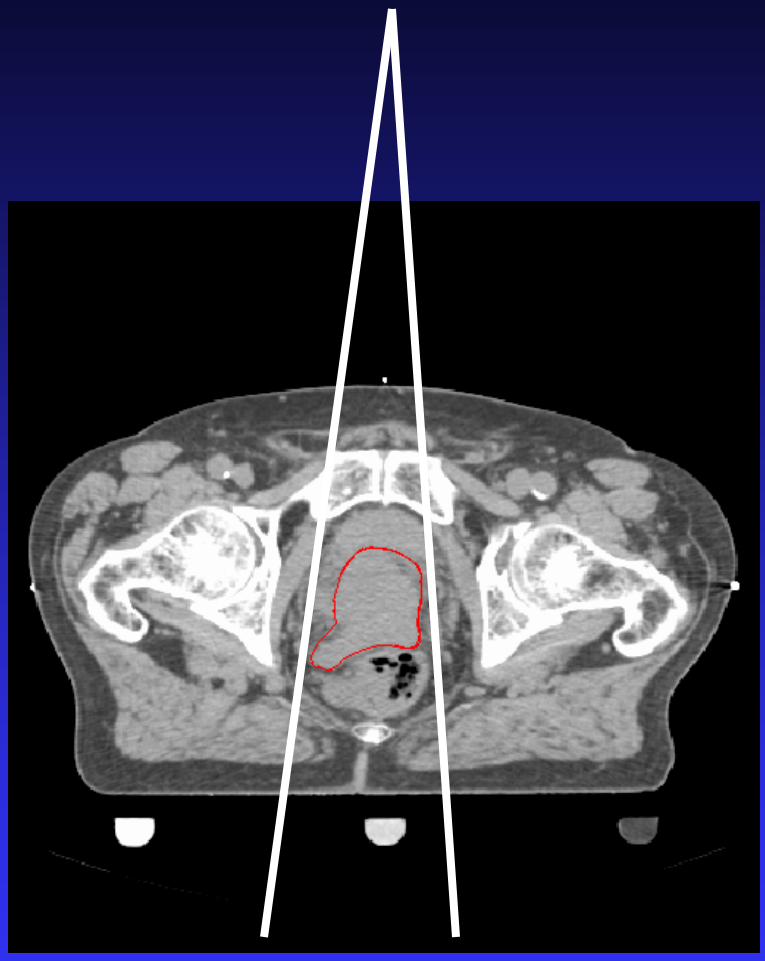
The patient was breathing



How can we solve this problem ?



1. Use large margins, irradiating too much healthy tissues



2. Use small margins, and risk missing the target

3. Or: use image guided radiotherapy

Image Guided Radiotherapy

Increase precision by imaging target and/or healthy tissues just prior to treatment

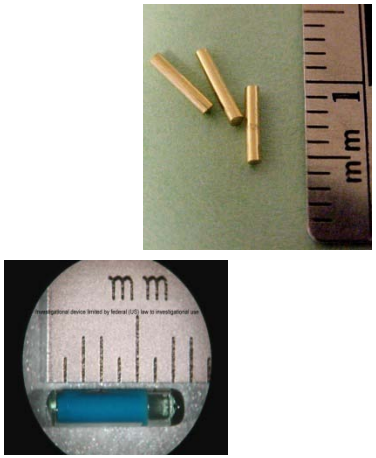
Image guidance does not solve all geometrical uncertainties and variations *and introduces new ones*

IGRT Technologies

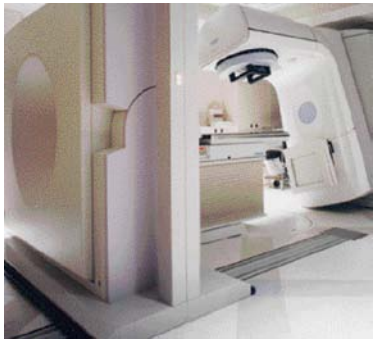
Ultrasound

kV Radiographic

Portal Imaging



Markers
(Active and Passive)



Siemens
PRIMATOM™

TomoTherapy
Hi-Art™

Elekta Synergy

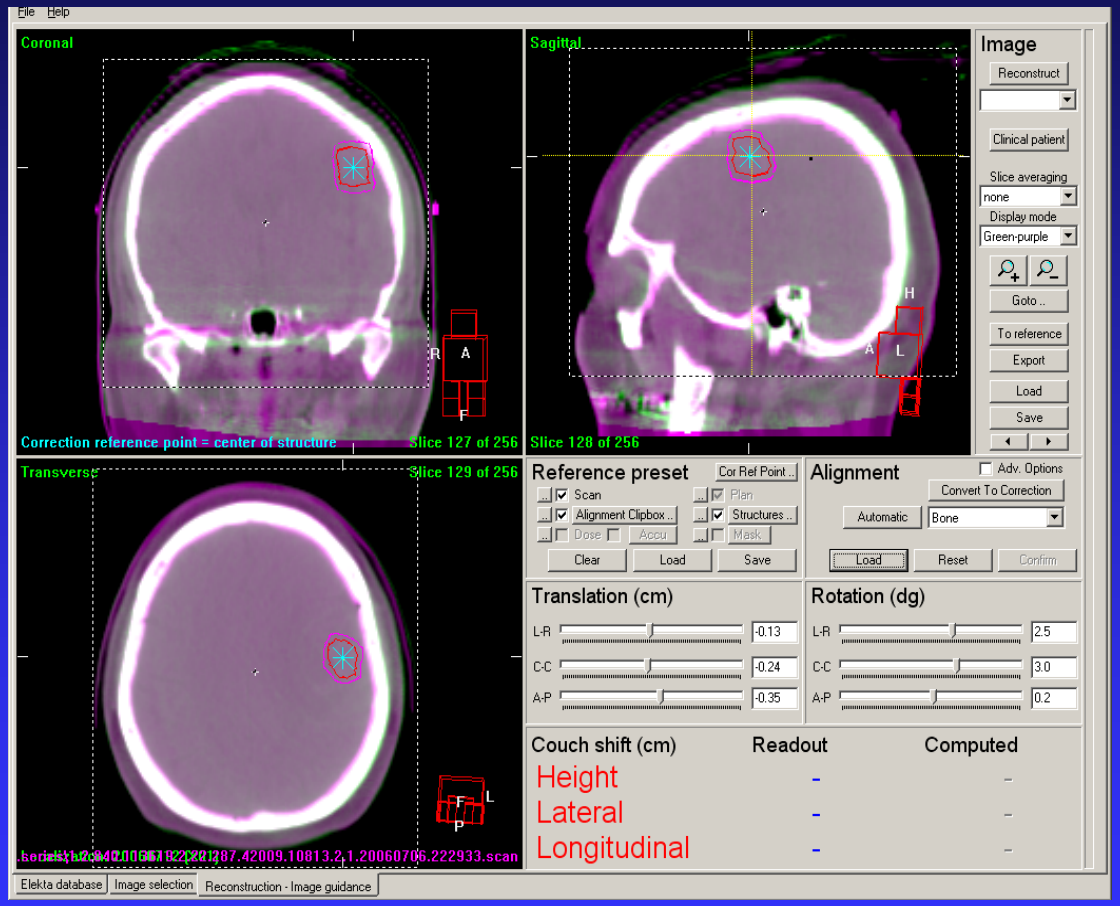
Varian OBI™

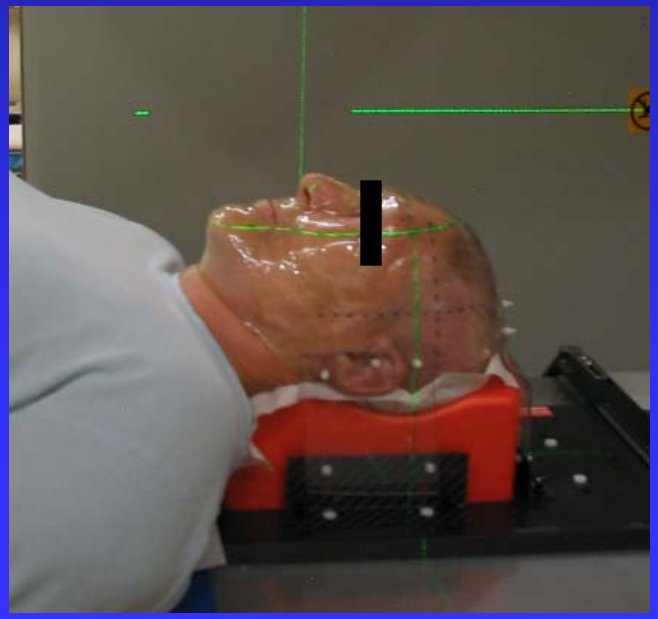
kV CT

MV CT

kV and MV Cone-beam CT

IGRT is brilliant !





Accuracy registration: 0.1 mm SD
Accuracy table: 0.5 mm {x, y, z}
Intra-fraction motion: 0.3 mm SD

Nomenclature

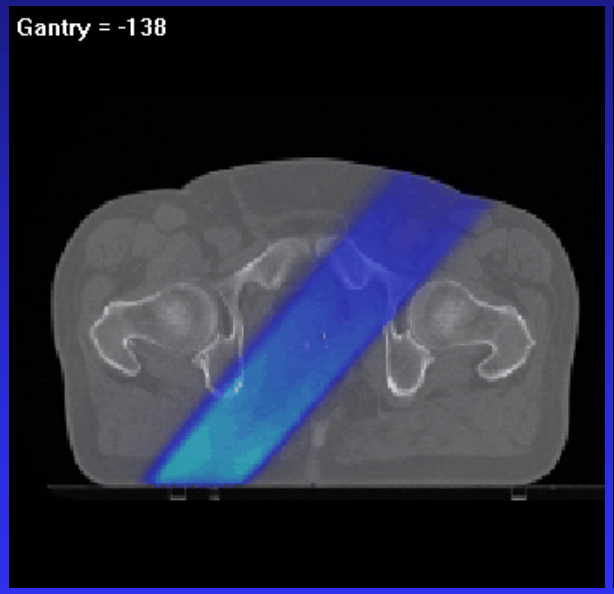
- Gross error: mistakes, transcription errors, software faults:
  - must be caught by QA
- Error: difference between planned value and its true value during treatment, however small
- Uncertainty: the fact that unpredictable errors occur – quantified by standard deviations
- Variation: the fact that predictable or periodic errors occur

EPID dosimetry QA to catch gross errors: used for all curative patients at NKI

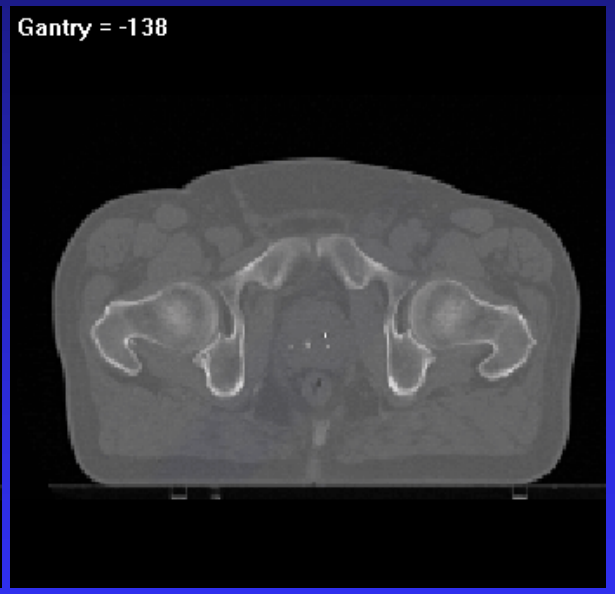
EPID movie

-140° 140°

Reconstructed EPID dose (VMAT case)



per frame



cumulative

Precision: within few %, enough to catch gross errors

Mans et al, 2010

Gross errors detected in NKI

TABLE I. Errors detected by means of EPID dosimetry from the clinical introduction to July 2009, grouped by (a) treatment site and (b) error type.

(a) Site	Clinical introduction	No. of patients	No. of errors
Prostate	02–2005	1018	2
Rectum	07–2006	602	4
Head-and-neck	06–2007	543	4
Breast	01–2008	1319	2
Lung	01–2008	454	2
Others	01–2008	401	3
	Total	**4337**	**17**

(b) Error type	No. of errors
Patient anatomy	7
Plan transfer	4
Suboptimally tuned TPS parameter	2
Accidental plan modification	2
Failed delivery	1
Dosimetrically undeliverable plan	1
Total	**17**

0.4% of treatments show a gross error (>10% dose)

9 out of 17 errors would not have been detected pre-treatment !!

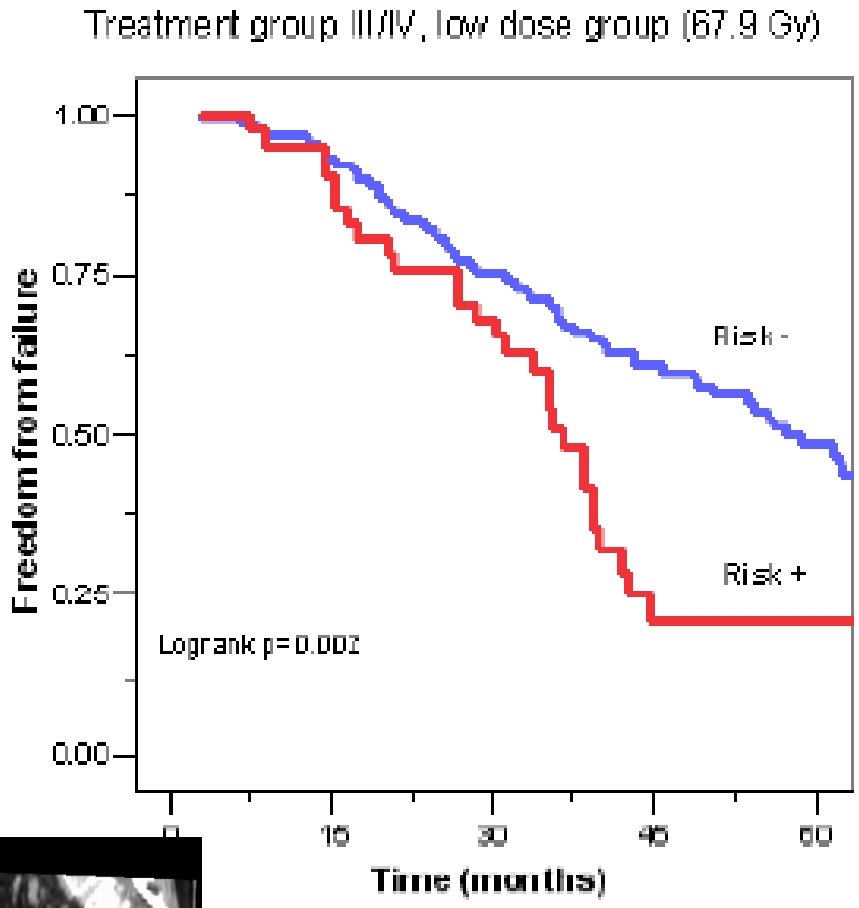
Mans et al, 2010

What happens in the other 99.6% ?

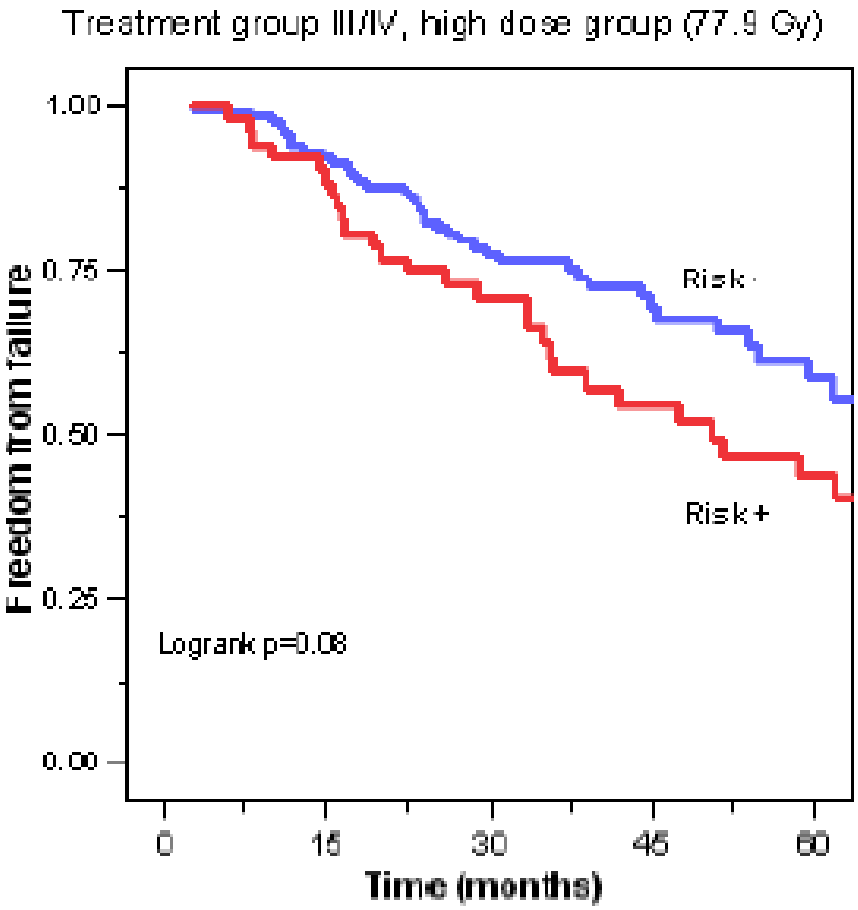
- There are many small unavoidable errors (mm size) in all steps of radiotherapy
  - In some cases many of these small errors point in the same direction
  - I.e., in some patients large (cm) errors occur(ed)
- This is not a fault, this is purely statistics
- What effect does this have on treatment?
  - We do not really know!

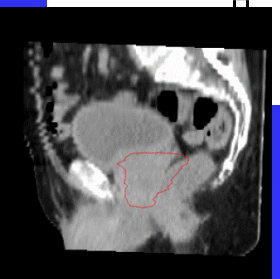
Motion counts? Prostate trial data (1996)

N=185 (42 risk+)



N=168 (52 risk+)





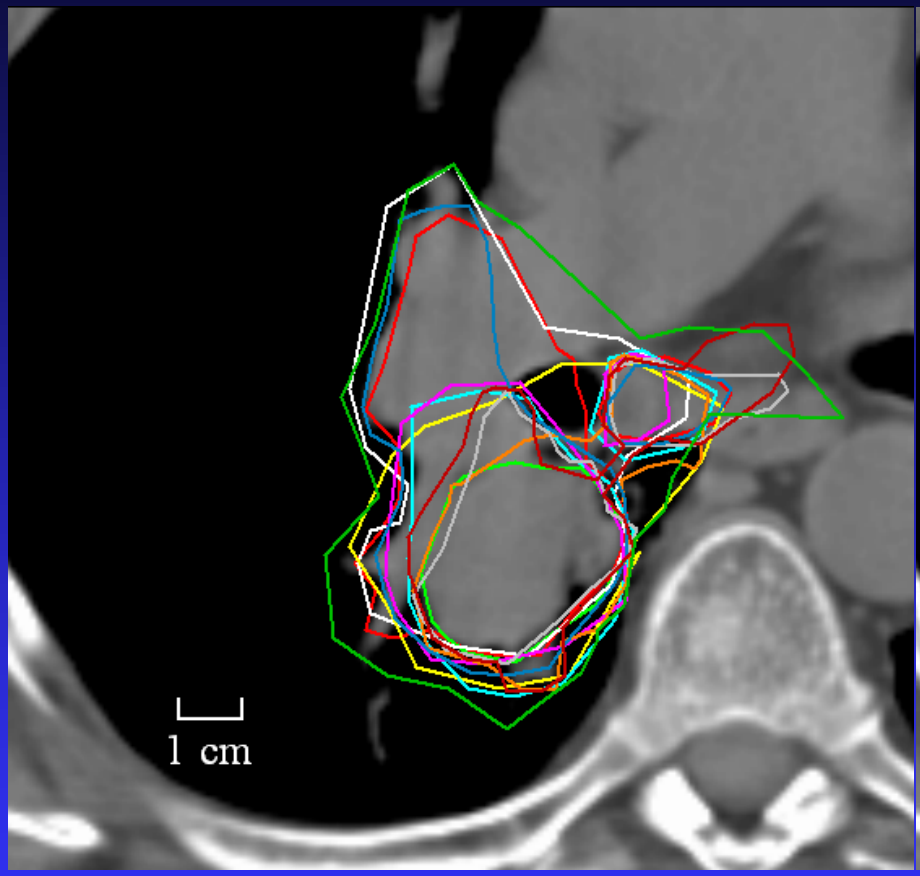
Risk+: initial full rectum, later diarrhea

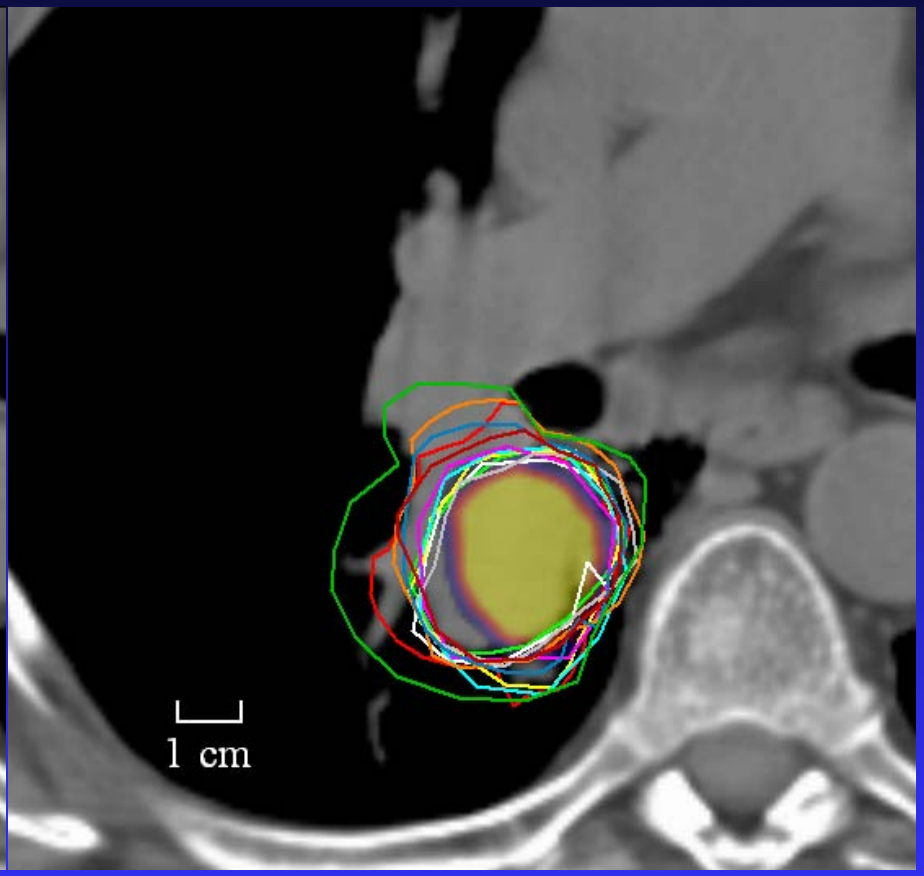
Heemsbergen et al, IJROBP 2007

The major uncertainties not solved by IGRT

- Target volume definition
  - GTV consistency
  - GTV accuracy
- Inadequacy of surrogate used for IGRT
- Motion that cannot be corrected
  - Too fast
  - Too complex

Delineation variation: CT versus CT + PET





CT (T_2N_2)

SD 7.5 mm

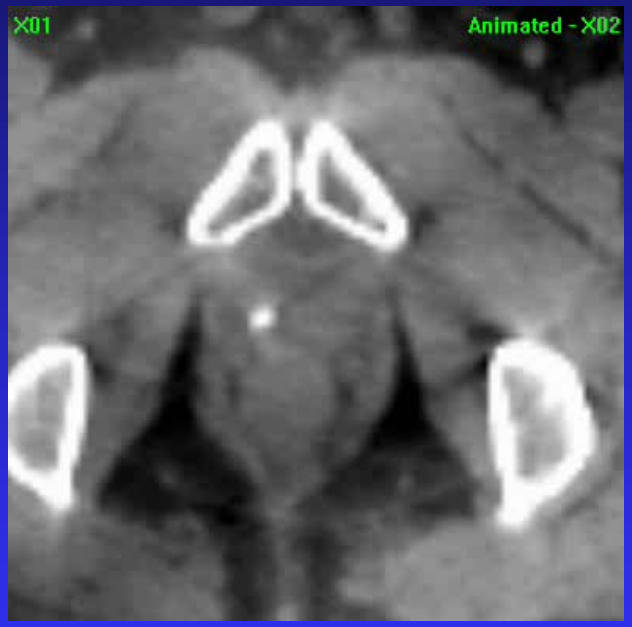
CT + PET (T_2N_1)

SD 3.5 mm

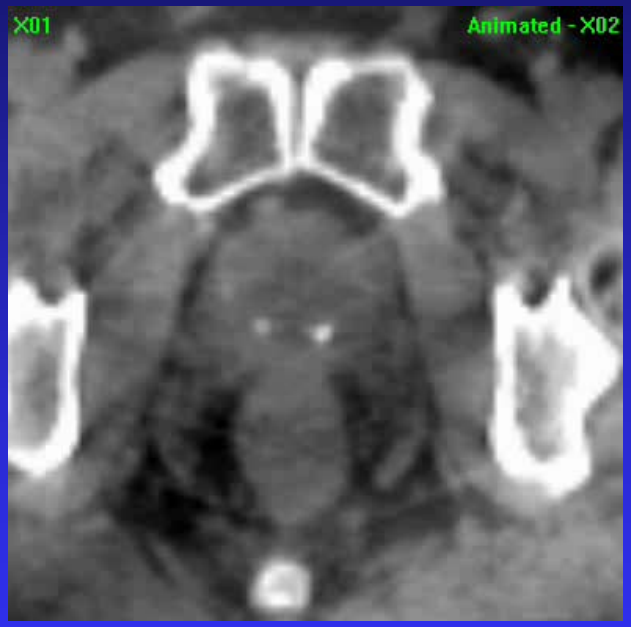
Consistency is imperative to gather clinical evidence!

Steenbakkers et al, IJROBP 2005

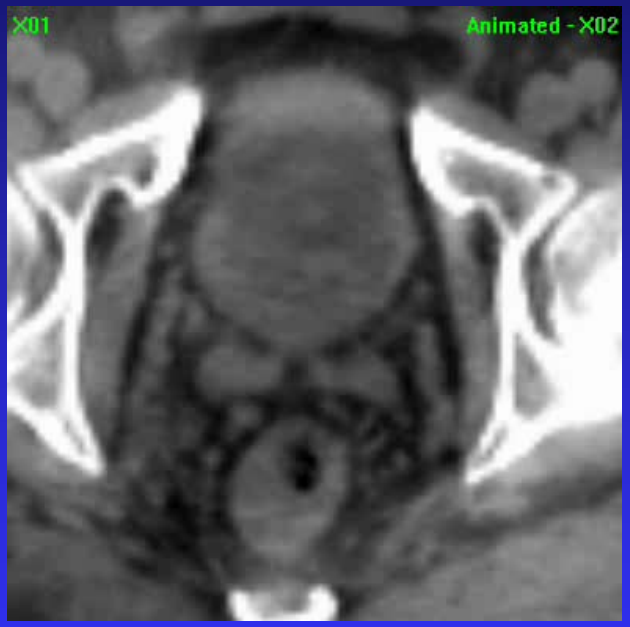
Are prostate markers perfect ?



Apex



Base



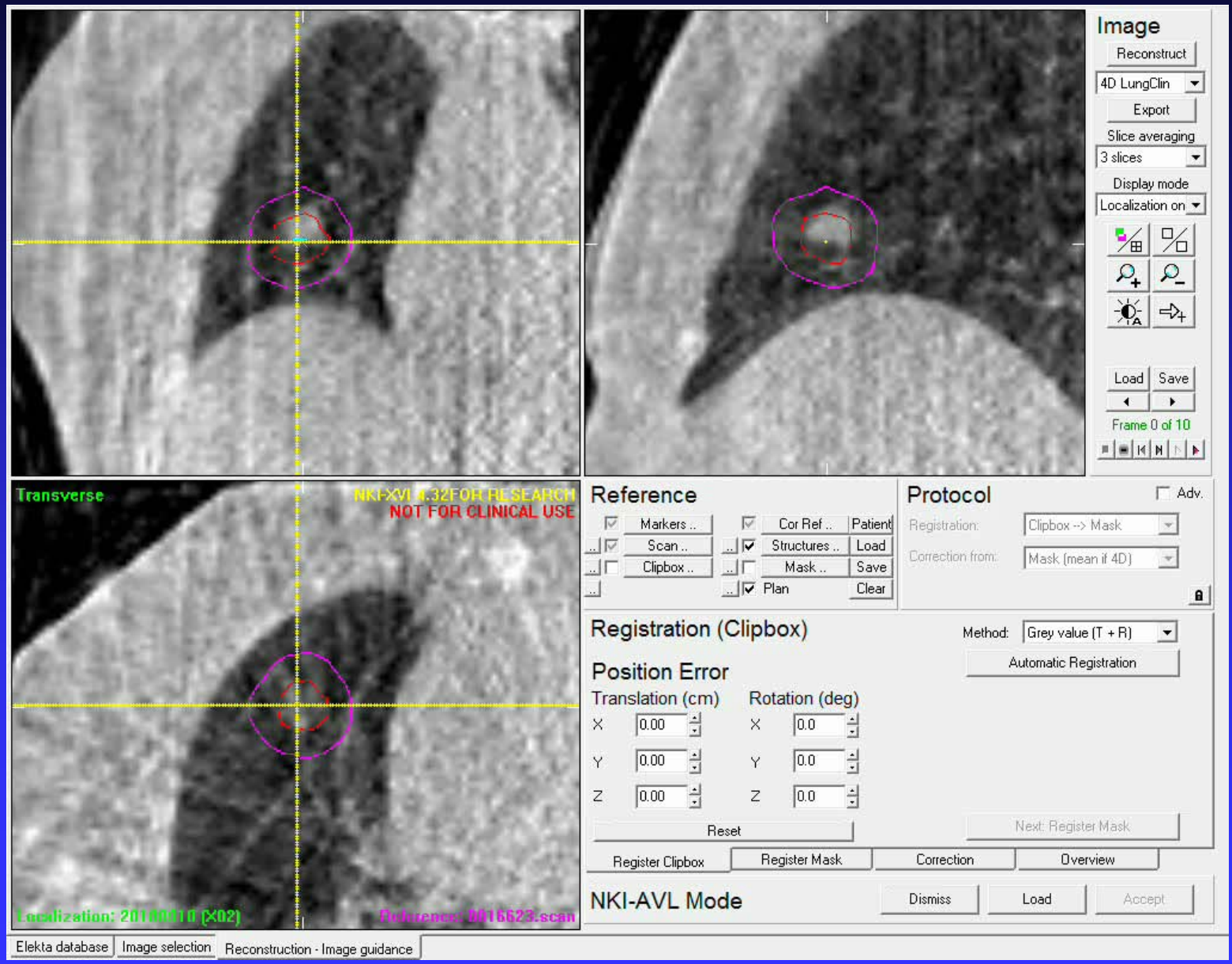
Sem. Vesicles

→ +/-1 cm margin required

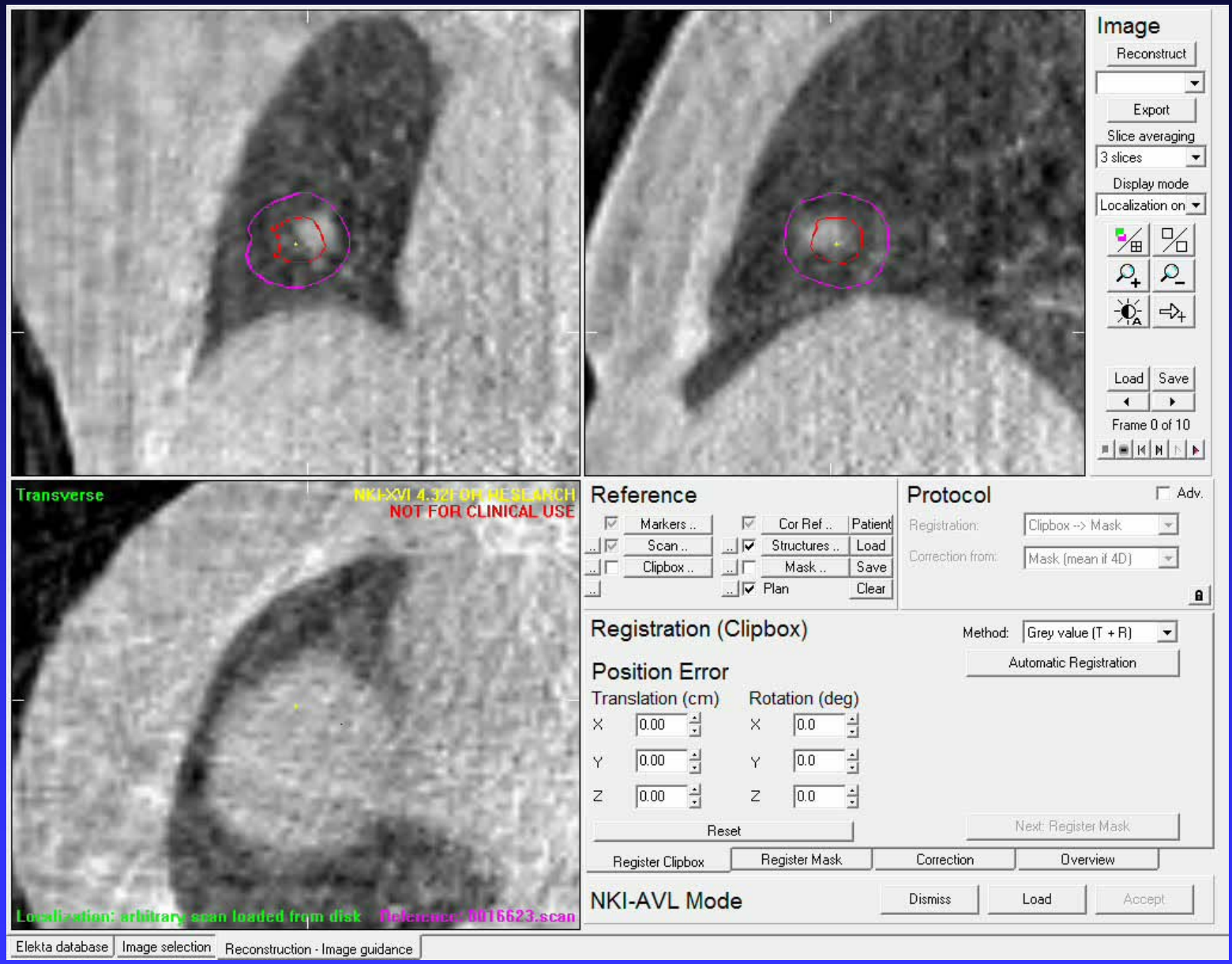
Best: combine markers with low dose CBCT

van der Wielen, IJROBP 2008
Smitsmans, IJROBP 2010

Intra-fraction motion: CBCT during VMAT



Intra-fraction motion: CBCT during VMAT



This amount of intra-fraction motion is rare for lung SBRT

Definitions (sloppy)

- CTV: Clinical Target Volume
  The region that needs to be treated (visible plus suspected tumor)

- PTV: Planning Target Volume
  The region that is given a high dose to allow for errors in the position of the CTV

- PTV margin: distance between CTV and PTV

- *ITV not optimal for external beam! (SD add quadratically)*

Analysis of uncertainties
Keep the measurement sign!

	patient 1	patient 2	patient 3	patient 4
fraction 1	0.5	0.0	0.2	0.7
fraction 2	0.6	-0.5	0.3	0.2
fraction 3	0.9	0.2	0.2	-0.4
fraction 4	1.3	-1.1	0.3	-0.1
mean	0.8	-0.4	0.3	0.1
sd	0.3	0.6	0.1	0.5

mean =M
SD = Σ
RMS = σ

Intra-fraction

0.0

0.3

0.4

0.1

0.3

Mean = 0.2

RMS of SD = σ_f

M = mean group error (equipment)

Σ = standard deviation of the inter-patient error

σ = standard deviation of the inter-fraction error

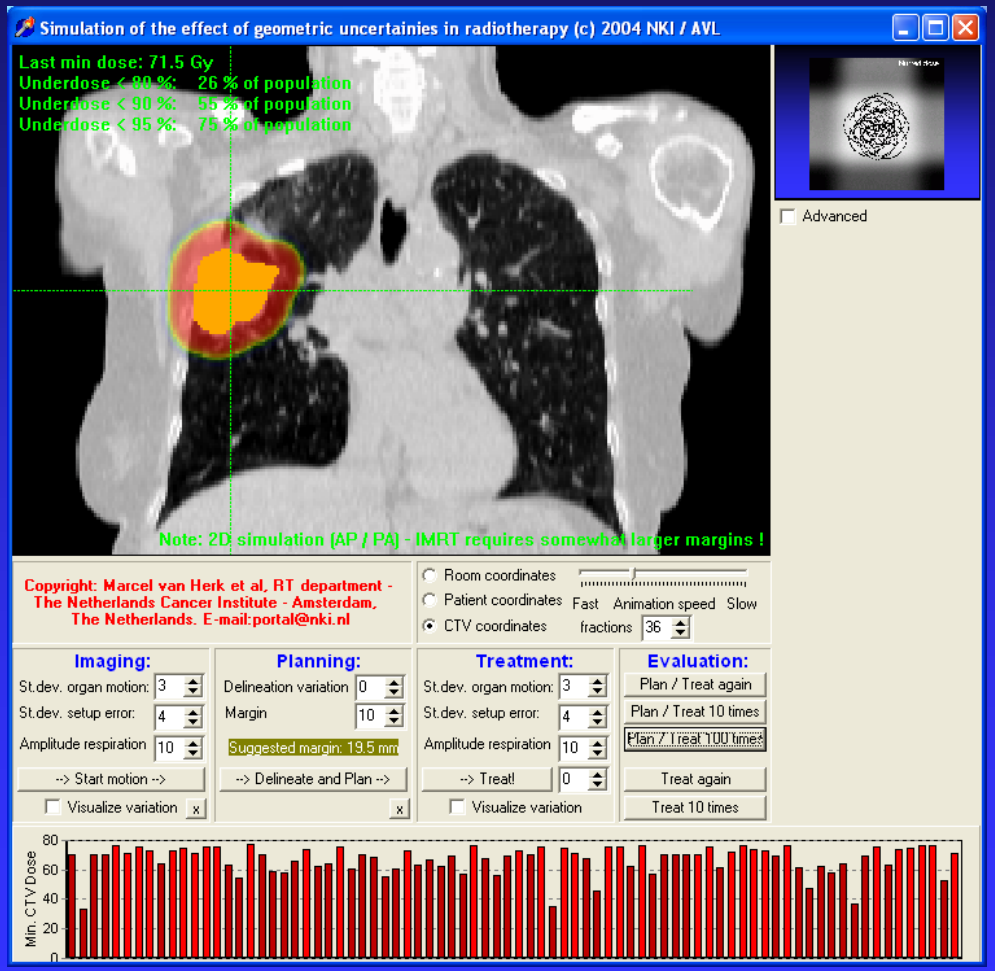
σf = standard deviation of the intra-fraction motion

van Herk et al, Sem Rad Onc 2004

Demonstration – errors in RT

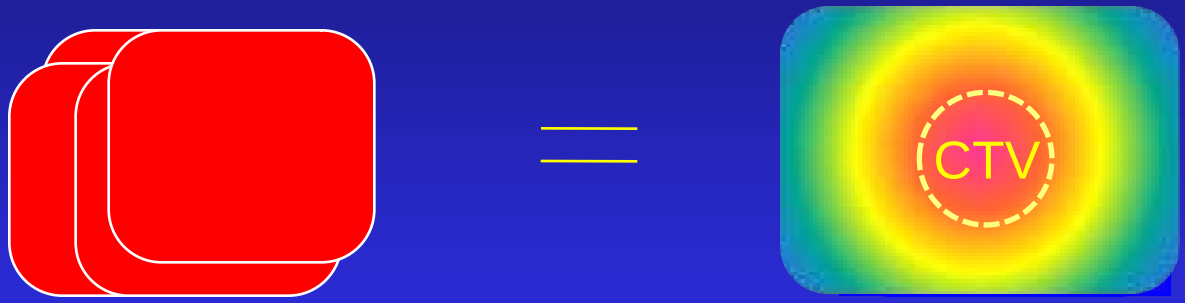
- Margin between CTV and PTV: 10 mm

- Errors:
  - Setup error:
    - 4 mm SD (x, y)
  - Organ motion:
    - 3 mm SD (x, y)
    - 10 mm respiration
  - Delineation error: optional

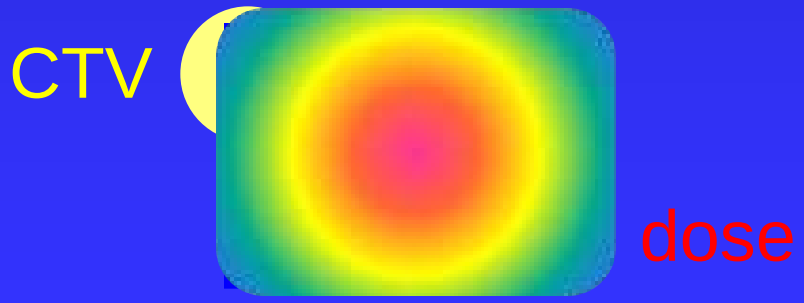


What is the effect of geometrical errors on the CTV dose ?

Random: Breathing, intrafraction motion, IGRT inaccuracy



Systematic: delineation, intrafraction motion, IGRT inaccuracy



Analysis of CTV dose probability

- Blur planned dose distribution *with all execution (random) errors* to estimate the cumulative dose distribution

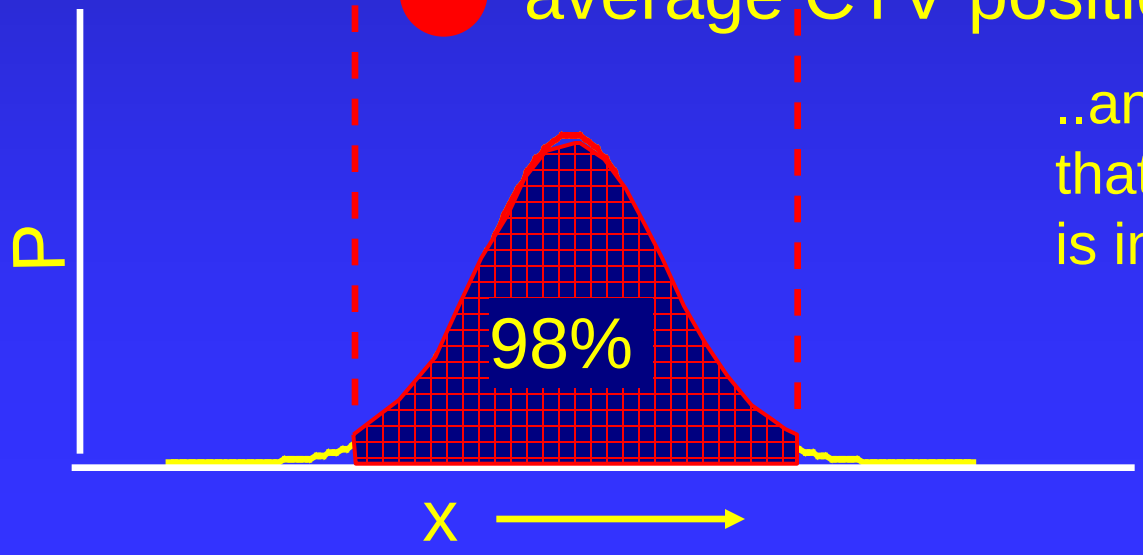
- For a given *dose* level:
  - Find region of space where the cumulative dose exceeds the given level
  - Compute *probability* that the CTV is in this region

Computation of the dose probability for a small CTV in 1D

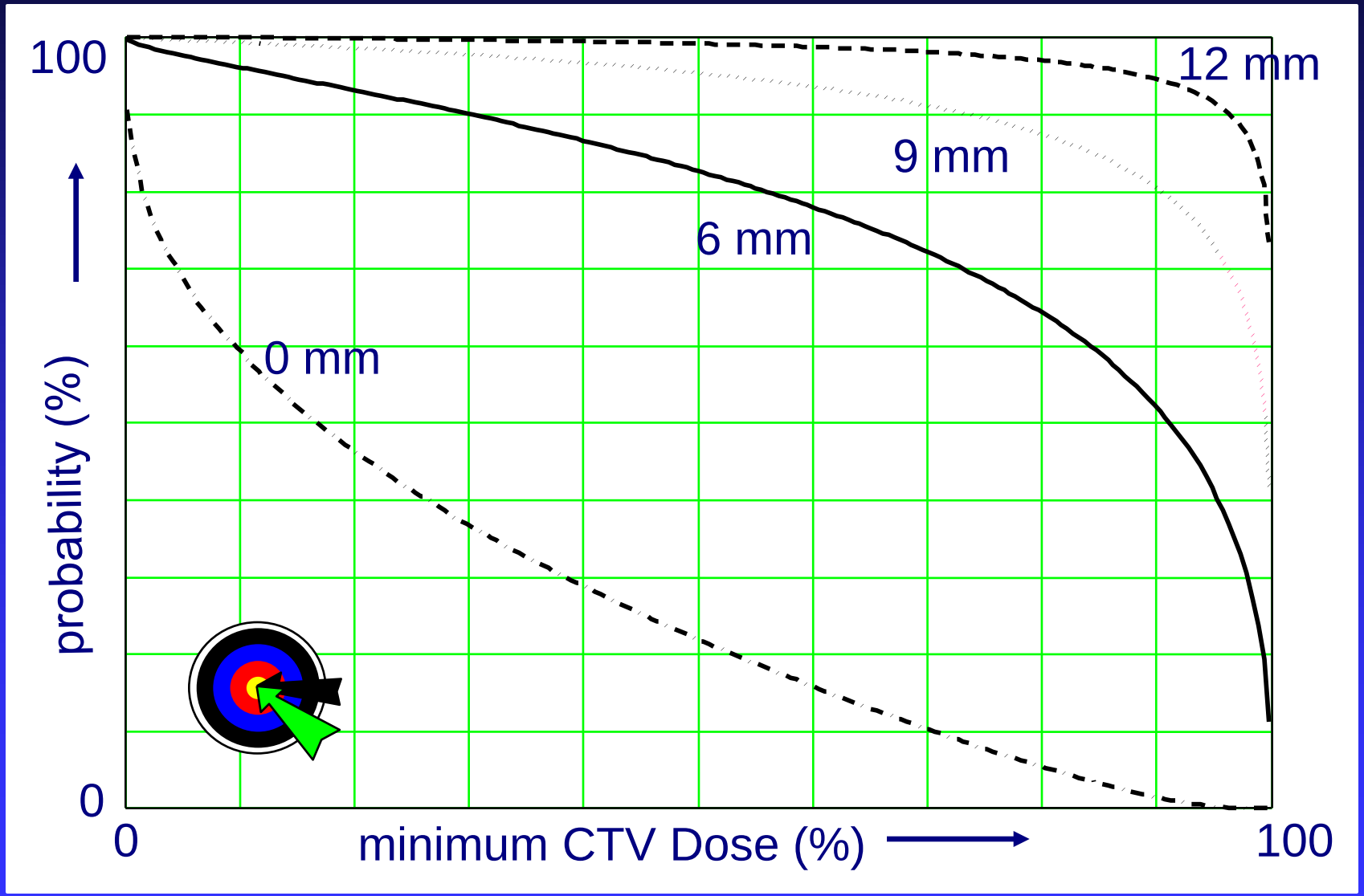
In the cumulative (blurred) dose, find where the dose > 95%

average CTV position

..and compute the probability that the average CTV position is in this area



What should the margin be ?



Typical prostate uncertainties with bone-based setup verification

Simplified PTV margin recipe for dose - probability

To cover the CTV for 90% of the patients with the 95% isodose (analytical solution) :

PTV margin = 2.5 Σ + 0.7 σ

Σ = quadratic sum of SD of all preparation (systematic) errors
σ = quadratic sum of SD of all execution (random) errors

(van Herk et al, IJROBP 47: 1121-1135, 2000)

*For a big CTV with smooth shape, penumbra 5 mm

$2.5\Sigma + 0.7\sigma$ is a simplification

- Dose gradients ('penumbra' = σ_p) very shallow in lung → smaller margins for random errors

$$M = 2.5\Sigma + 1.64\sqrt{(\sigma_p^2 + \sigma^2)} - 1.64\sigma_p$$

- Number of fractions is small in hypofractionation
  - Residual mean of random error gives systematic error
  - Beam on time long → respiration causes dose blurring

- If dose prescription is at 80% instead of 95%:

$$M = 2.5\Sigma + 0.84\sqrt{(\sigma_p^2 + \sigma^2)} - 0.84\sigma_p$$

(van Herk et al, IJROBP 47: 1121-1135, 2000)

Practical examples

Prostate: 2.5 Σ + 0.7 σ

all in cm	systematic errors	squared	random errors	squared	
delineation	**0.25**	0.0625	**0**	0	Rasch et al, Sem. RO 2005
organ motion	**0.3**	0.09	**0.3**	0.09	van Herk et al, IJROBP 1995
setup error	**0.1**	0.01	**0.2**	0.04	Bel et al,IJROBP 1995
intrafraction motion			**0.1**	0.01	
total error	**0.40**	0.16	**0.37**	0.14	
	times 2.5		**times 0.7**		
error margin	**1.01**		**0.26**		
total error margin		**1.27**			

Prostate: 2.5 Σ + 0.7 σ
Now add IGRT

all in cm	systematic errors	squared	random errors	squared			
delineation	**0.25**	0.0625	**0**	0	Rasch et al, Sem. RO 2005		
organ motion	**0**	0	**0**	0	van Herk et al, IJROBP 1995		
setup error	**0**	0	**0**	0	Bel et al,IJROBP 1995		
intrafraction motion			**0.1**	0.01			
total error	**0.25**	0.06	**0.10**	0.01			
	times 2.5		**times 0.7**				
error margin	**0.63**		**0.07**				
total error margin		**0.70**					

Engels et al (Brussels, 2010) found 50% recurrences using 3 mm margin with marker IGRT

Lung planning target volume concepts

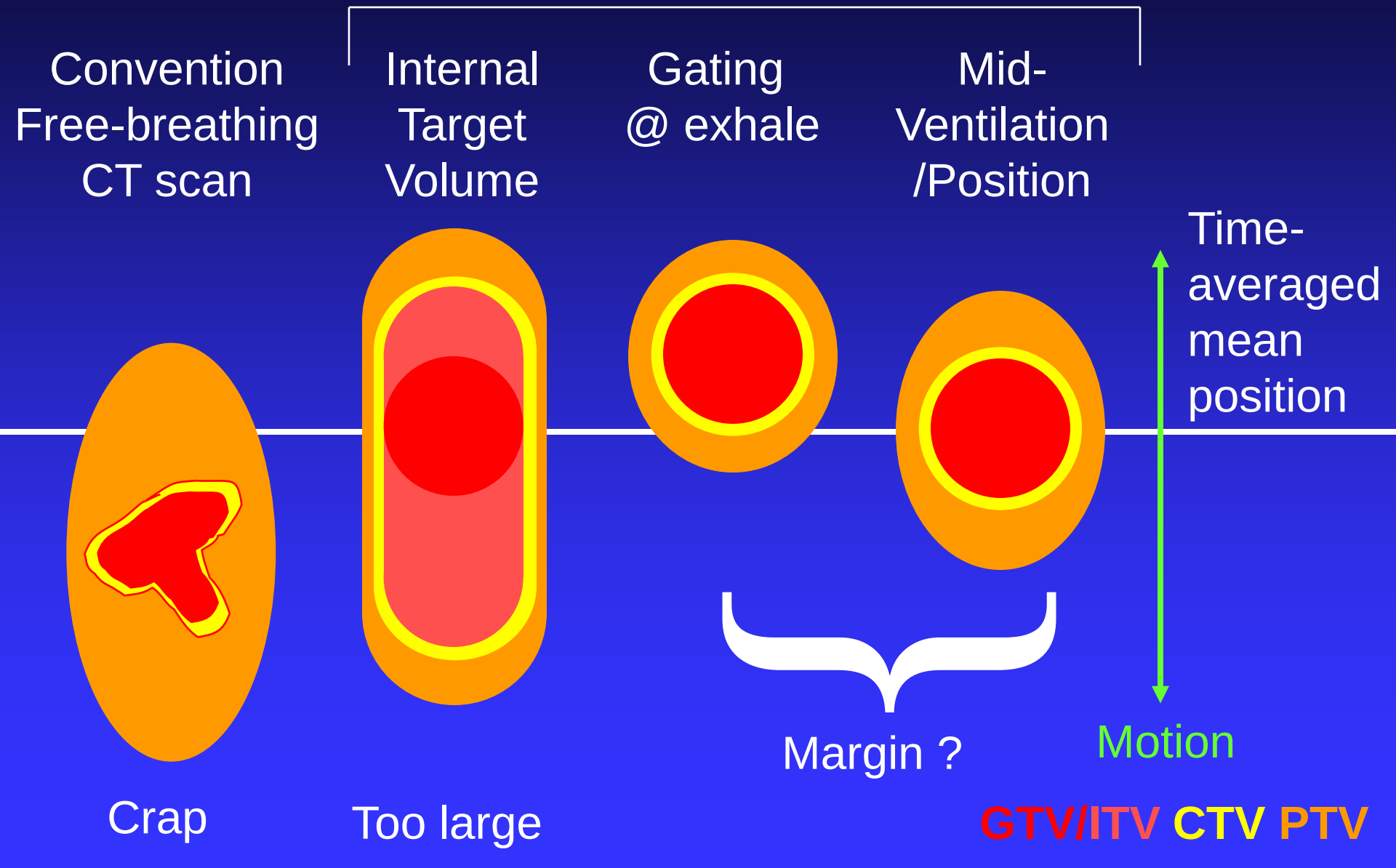
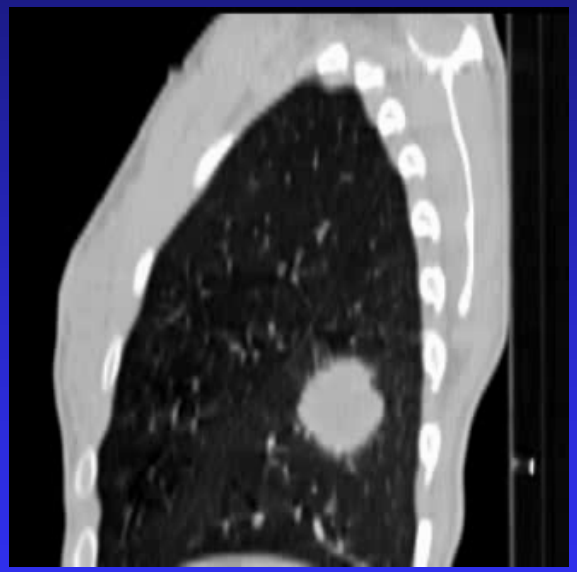
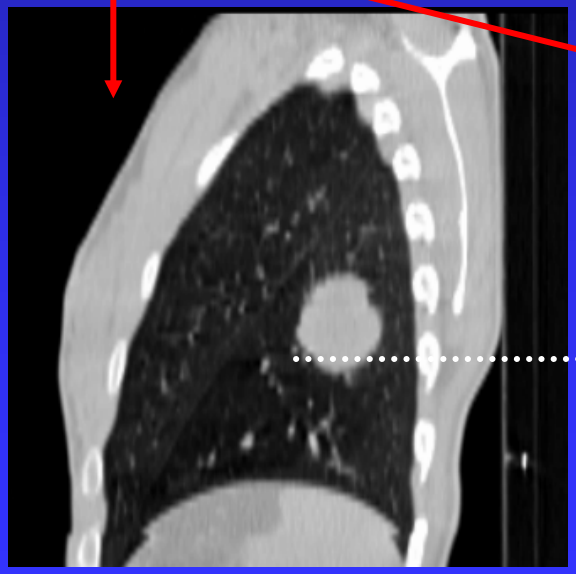


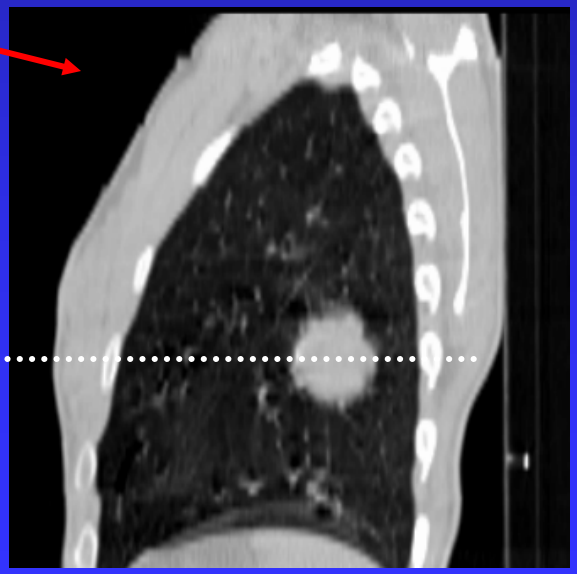
Image *selection* approaches to derive representative 3D data



4D CT



Exhale (for gating)



Mid-ventilation

Very clear lung tumor: classic RT

all in cm	**systematic errors**	squared	**random errors**	squared	
delineation	**0.2**	0.04		0	
organ motion	**0.3**	0.09	**0.3**	0.09	
setup error	**0.2**	0.04	**0.4**	0.16	
Intra-fraction motion		0		0	
respiration motion	**0.1**	0.01	**0.3**	0.111111	**1**
(0.33A)					
total error	**0.42**	0.18	**0.60**	0.361111	
	times 2.5		**difficult equation**		
			(almost times 0.7)		
error margin	**1.06**		**0.41**		
total error margin		**1.47**			

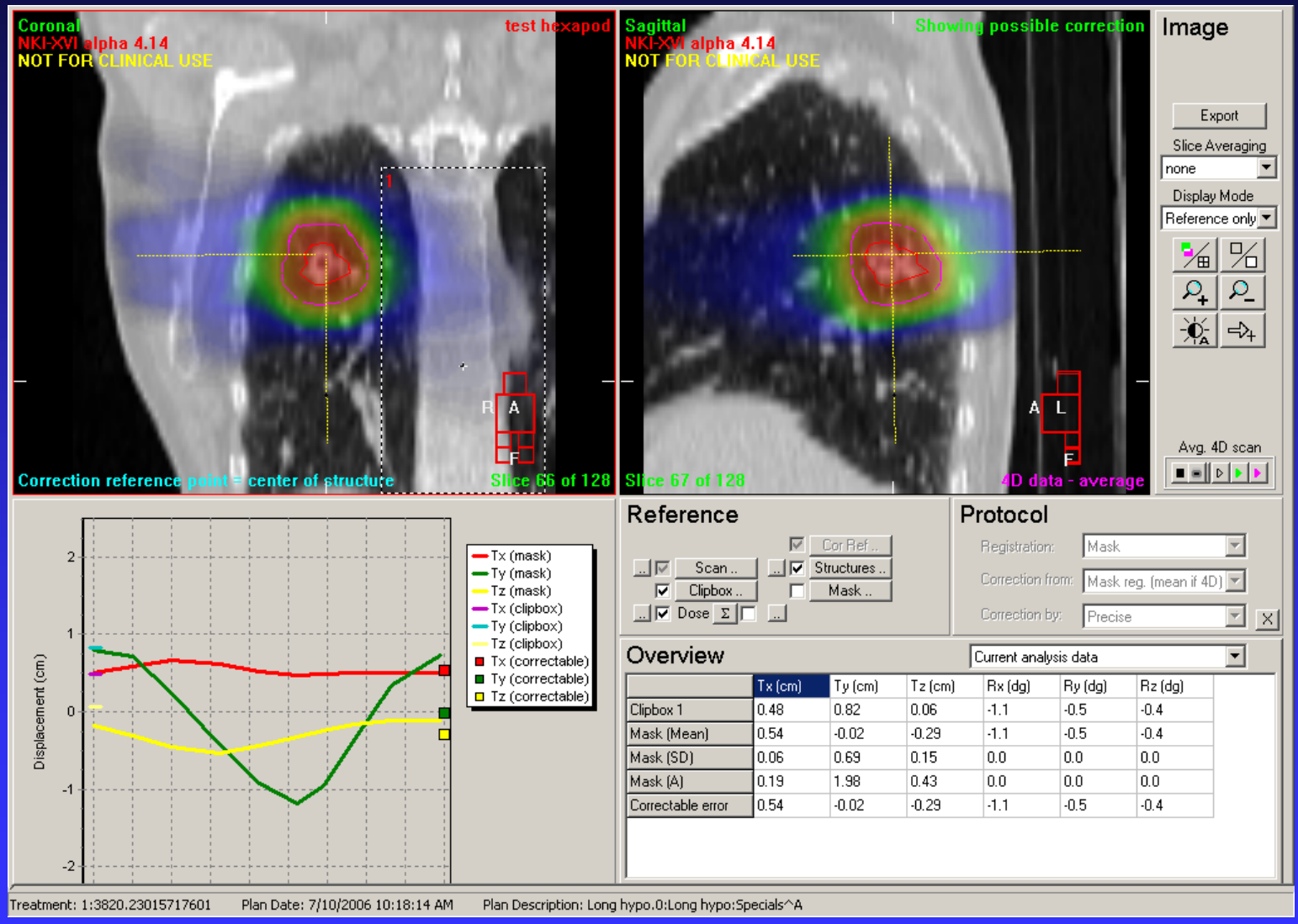
Using conventional fractionation, prescription at 95% isodose line in lung

Very clear lung tumor: IGRT hypo

all in cm	**systematic errors**	squared	**random errors**	squared	
delineation	**0.17**	0.0289		0	
organ motion	**0.1**	0.01	**0.1**	0.01	
setup error	**0.03**	0.0009	**0.03**	0.0009	
Intra-fraction motion	**0.1**	0.01	**0.1**	0.01	
respiration motion		0	0.3	0.111111	**1**
(0.33A)					
total error	**0.22**	0.05	**0.36**	0.132011	
	times 2.5		**difficult equation**		
			non-linear		
error margin	**0.56**		**0.07**		
total error margin		**0.63**			

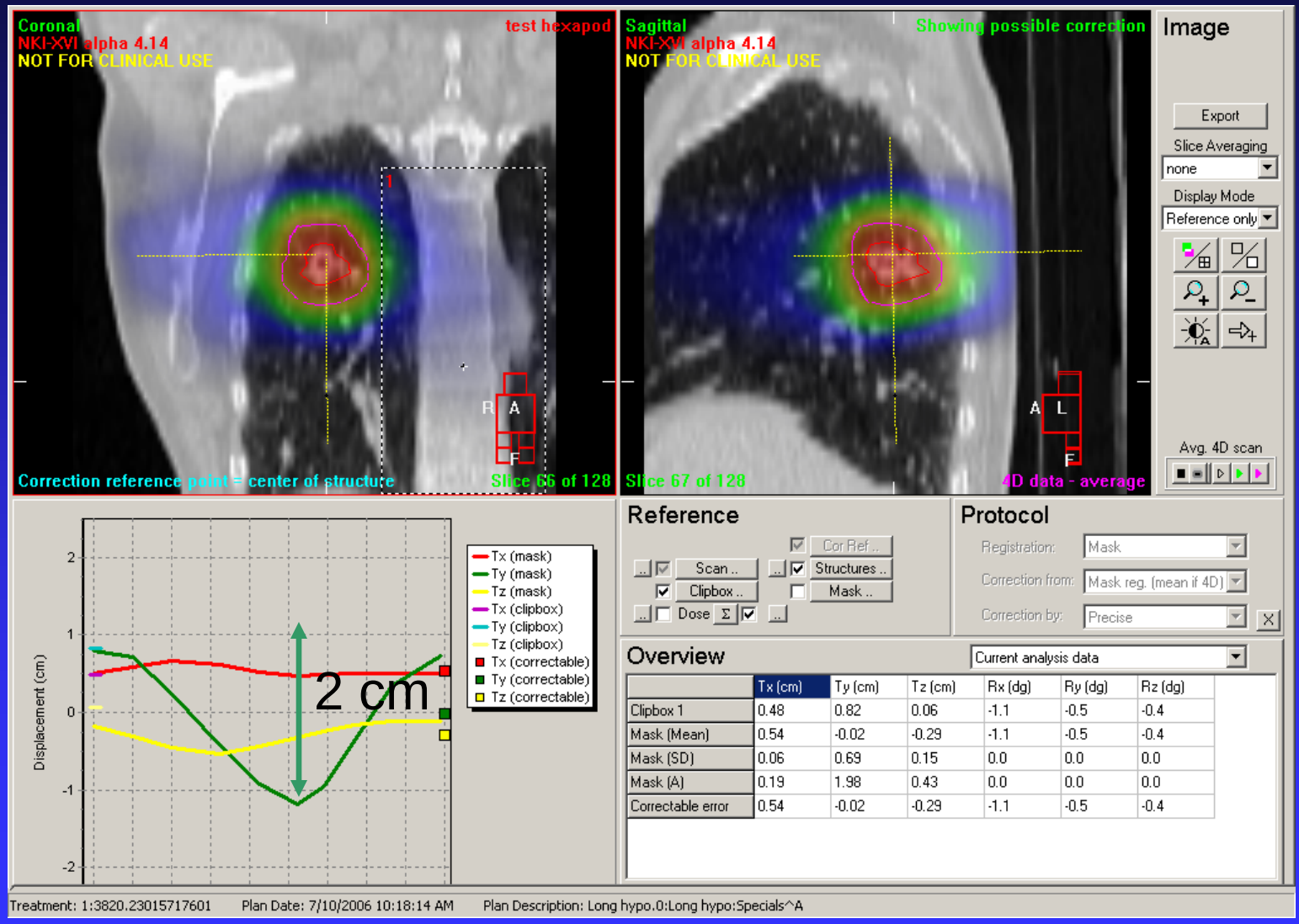
Using hypo-fractionation, prescription at 80% isodose line in lung

Planned dose distribution: hypofractionated lung treatment 3x18 Gy



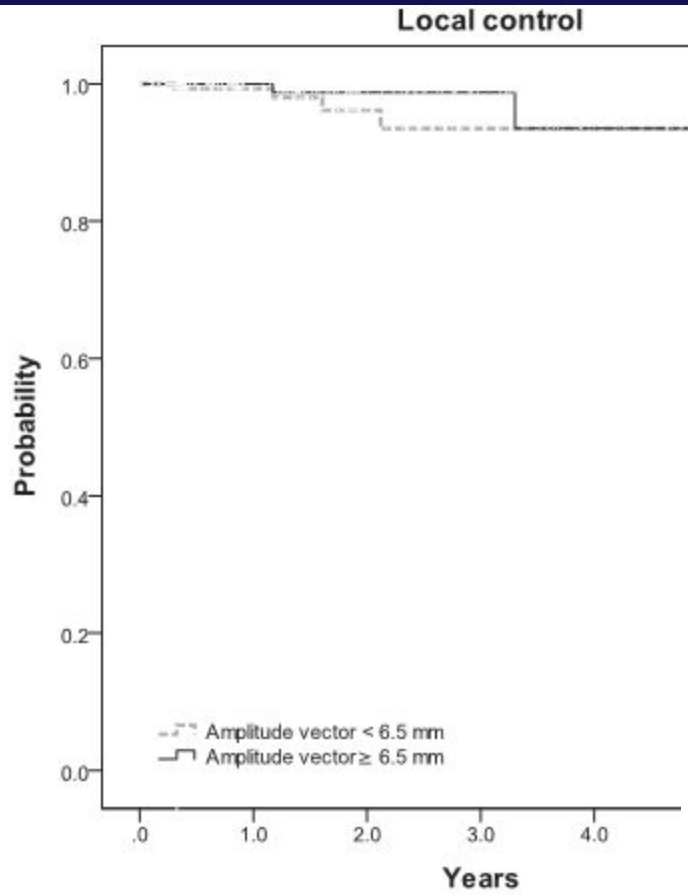
	Tx (cm)	Ty (cm)	Tz (cm)	Rx (dg)	Ry (dg)	Rz (dg)
Clipbox 1	0.48	0.82	0.06	-1.1	-0.5	-0.4
Mask (Mean)	0.54	-0.02	-0.29	-1.1	-0.5	-0.4
Mask (SD)	0.06	0.69	0.15	0.0	0.0	0.0
Mask (A)	0.19	1.98	0.43	0.0	0.0	0.0
Correctable error	0.54	-0.02	-0.29	-1.1	-0.5	-0.4

Realized dose distribution with daily IGRT on tumor (no gating)



9 mm margin is adequate even with 2 cm intrafraction motion

Clinical results with mid-V



No at risk < 6.5 mm	160	80	36	14	4
No at risk ≥ 6.5 mm	154	82	43	24	12

Fig. 3. Local control analyzed per tumor according to respiratory tumor ar

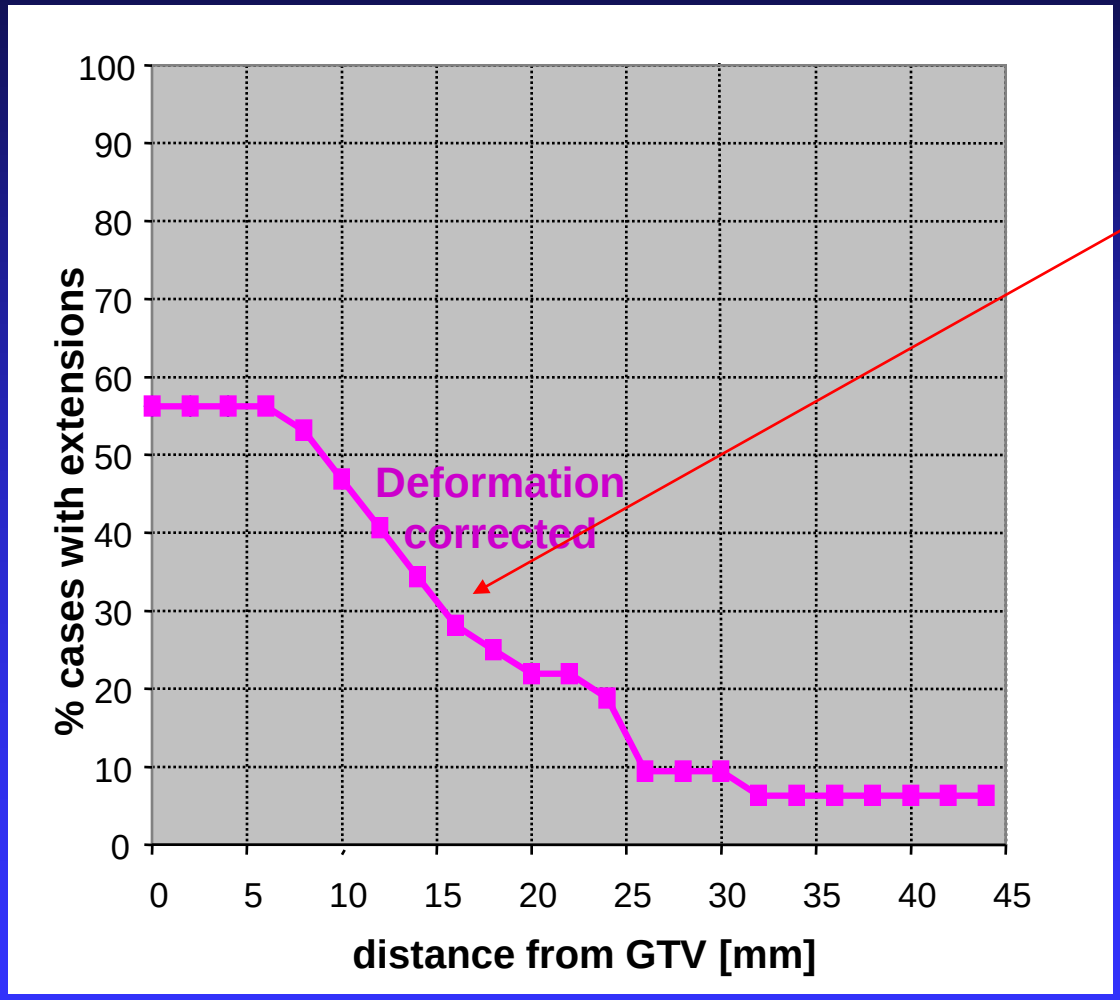
and 3 mm (range 0–18 mm), respectively. The median amplitude vector was 6.5 mm (range 0–39 mm) for all tumors as well as for the locally controlled tumors. In case of local recurrence, the median amplitude vector was significantly *smaller*: 3.0 mm (range 1–8.1 mm) ($p = 0.04$). In patients with a local recurrence the median GTV was significantly larger with a volume of 16.0 cm^3 (range 2.1–57.6 cm^3) ($p = 0.04$). In univariate continuous Cox-regression analysis GTV was predictive for local recurrence ($p < 0.001$ and HR = 1.08). Amplitude vector was borderline significant ($p = 0.08$ and HR = 0.77). ROC analysis revealed an optimal cut-off for amplitude vector of 3.5 mm. Additional Cox-regression was significant for LR ($p = 0.02$, HR = 0.13)

Peulen et al, R&O 2014

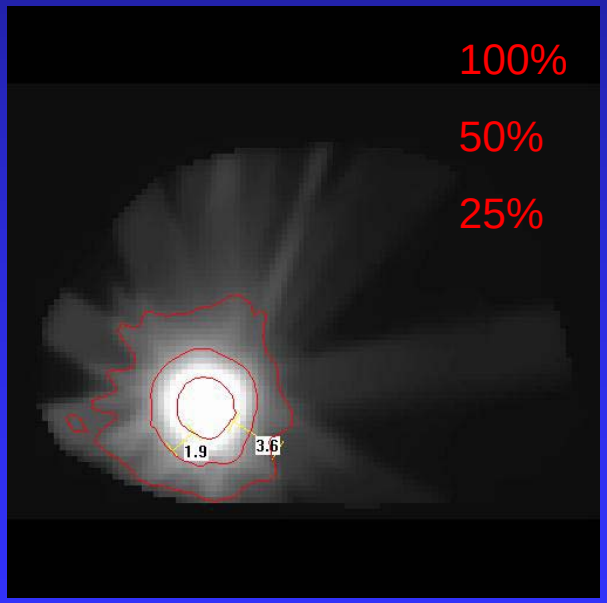
But what about the CTV ?

- By definition disease between the GTV and the CTV cannot be detected
- Instead, the CTV is defined by means of margin expansion of the GTV and/or anatomical boundaries
- Very little is known of margins in relation to the CTV
  - Very little clinical / pathology data
  - Models to be developed

Hard data: microscopic extensions in lung cancer



30% patients with low grade tumors (now treated with SBRT with few mm margins), have spread at 15 mm distance

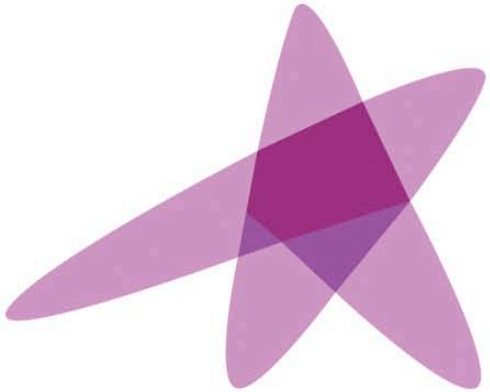


Having dose there may be essential!

Slide courtesy of Gilhuijs and Stroom, NKI

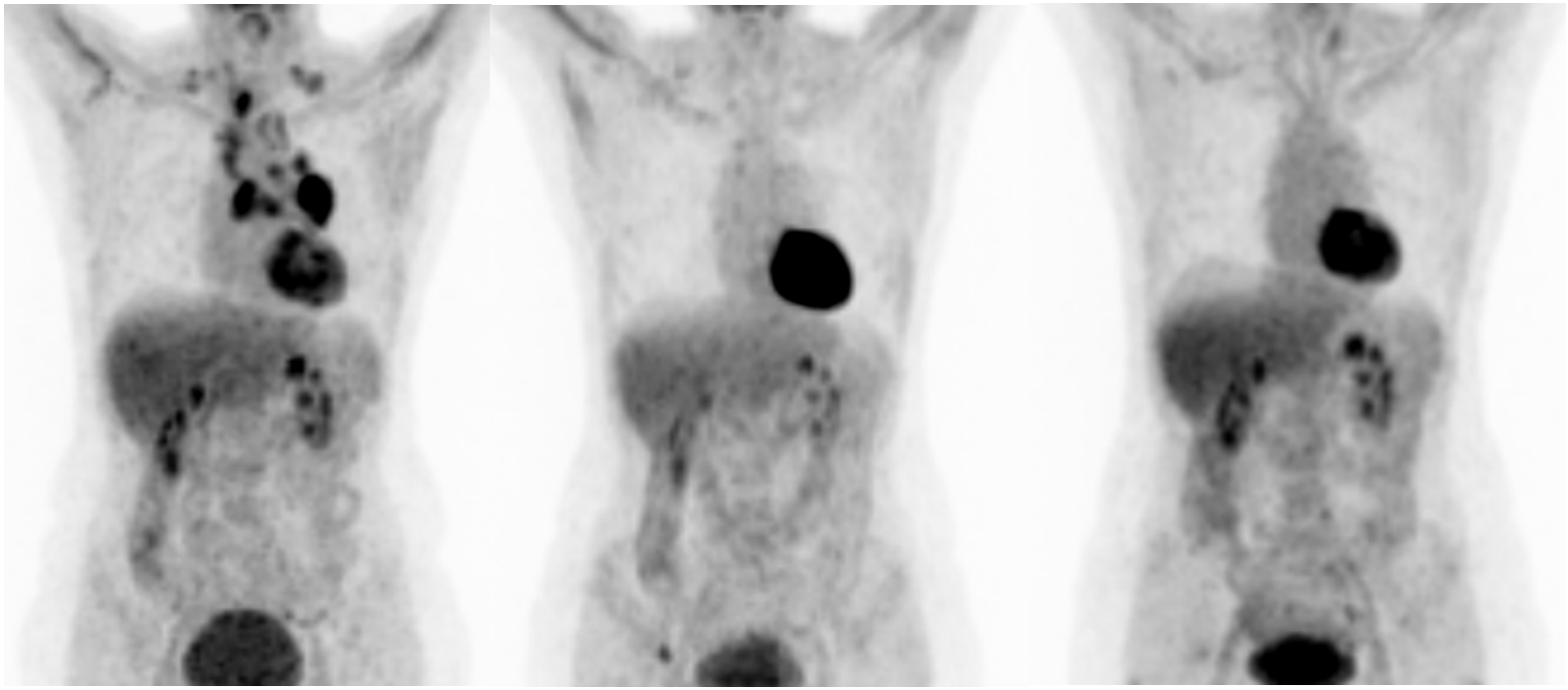
Conclusions

- In spite of IGRT there are still uncertainties that need to be covered by safety margins
- Margins for random uncertainties and respiratory motion in lung can be very small because of the shallow dose falloff in the original plans
- Important uncertainties relate to imaging and biology that are not corrected by IGRT: The margin with IGRT is dominated by delineation uncertainties
- Even though PTV margins are designed to cover geometrical uncertainties, they also cover microscopic disease
- Reducing margins after introducing IGRT should therefore be done with utmost care (especially in higher stage disease)



ESTRO School

UNIVERSITÄTS KLINIKUM FREIBURG



Molecular imaging in radiotherapy

Ursula Nestle

Freiburg, Germany

Medical imaging in radiation oncology

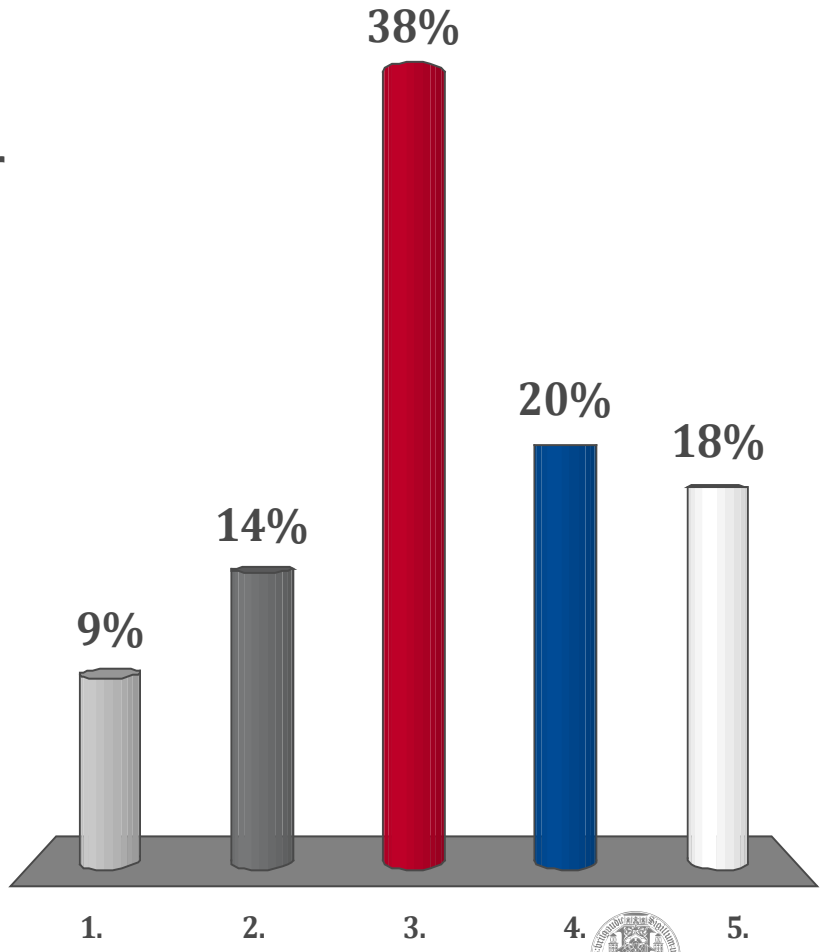
- Imaging for diagnosis and staging:
  - treatment indication
- imaging for radiotherapy planning
  - target (GTV – CTV – PTV)
  - normal tissues
  - movements
- Imaging during RT application
  - repositioning
  - adaptive radiotherapy
  - normal tissue reactions
- imaging during follow up
  - response
  - recurrence
  - normal tissue injury

Types of medical imaging

	Morphological imaging	**Functional imaging**
Methods	CT, morph. MRI	PET, SPECT, MRS, DWI
imaged aspect	Morphology	Biological process
imaged detail	physical density magnetic properties	positron anihilation metabolism
example	(Pathologic) anatomy	Tumor metabolism Perfusion Organ function

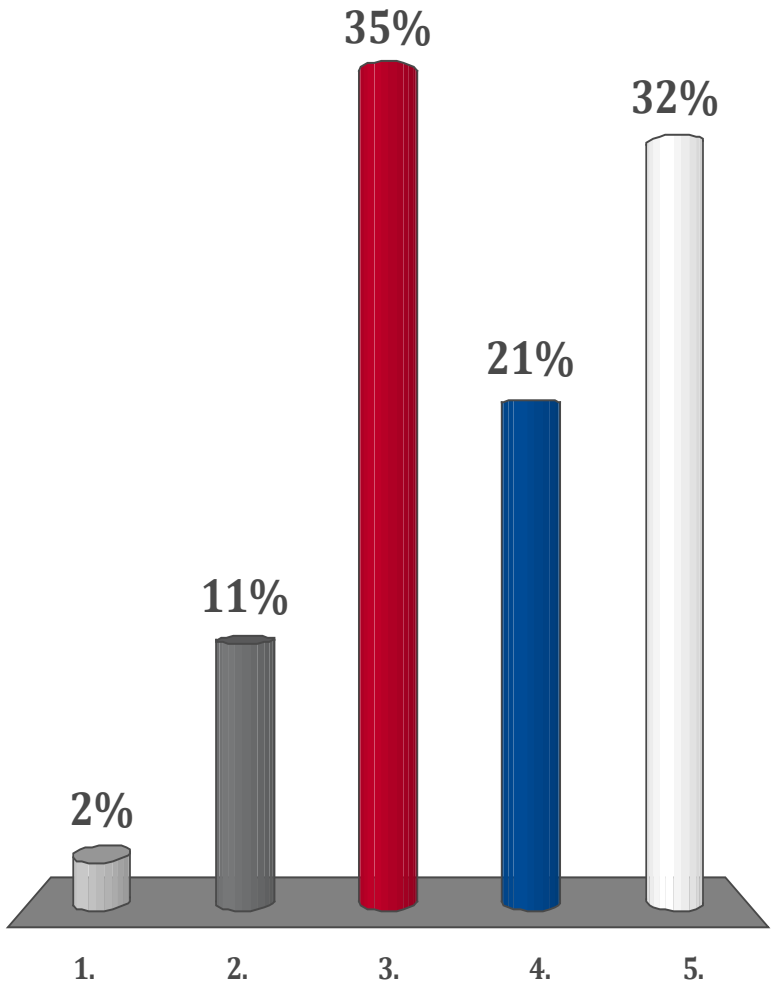
Q1: In your center, do you use functional imaging for radiotherapy planning?

1. never
2. FDG-PET for lung cancer
3. FDG-PET for lung and other types of cancer
4. FDG and other tracers in many types of cancer
5. PET and other molecular imaging spectroscopy



Q2: How do you / would you use functional imaging for radiotherapy planning?

1. never
2. side by side viewing
3. coregistered in TPS
4. coregistered in treatment position @diagnostic acquisition (no RTT involved)
5. coregistered in treatment position @planning acquisition (RTT involved)



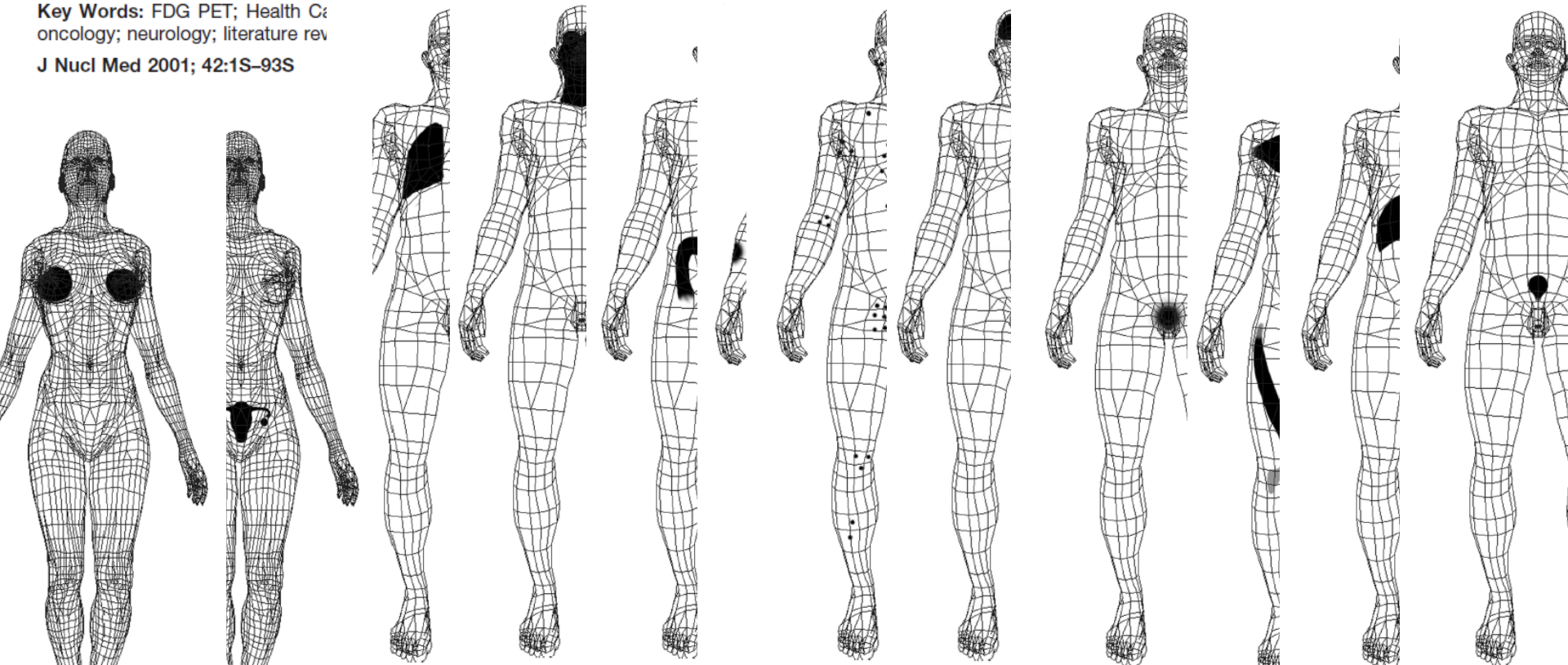
Imaging literature, example PET

A Tabulated Summary of the FDG PET Literature

Sanjiv S. Gambhir, Johannes Czernin, Judy Schwimmer, Daniel H. S. Silverman, R. Edward Coleman, and Michael E. Phelps

The Crump Institute for Molecular Imaging, The Ahmanson Biological Imaging Center, Department of Molecular and Medical Pharmacology, University of California Los Angeles School of Medicine, Los Angeles, California; Duke University School of Medicine, Durham, North Carolina

Key Words: FDG PET; Health Ca
oncology; neurology; literature rev
J Nucl Med 2001; 42:1S–93S

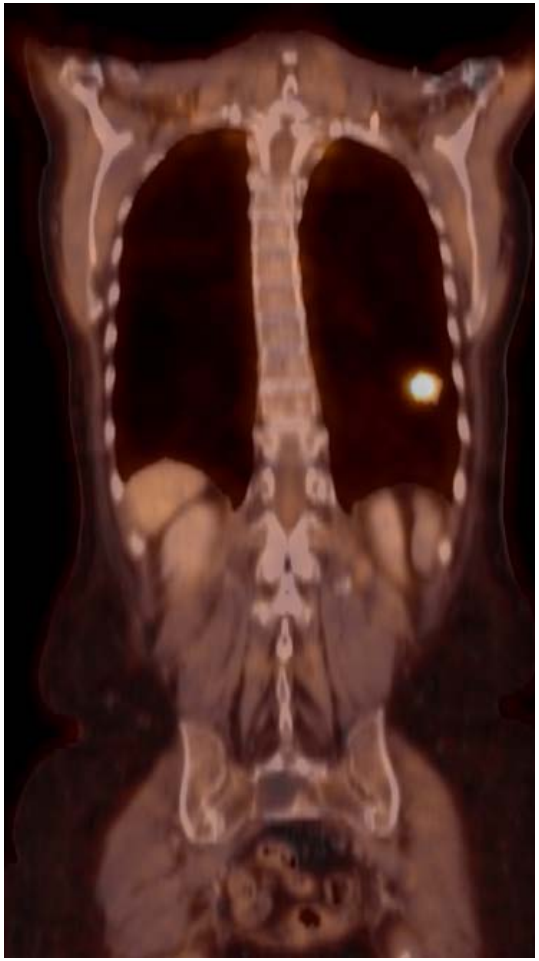


Imaging literature, example PET

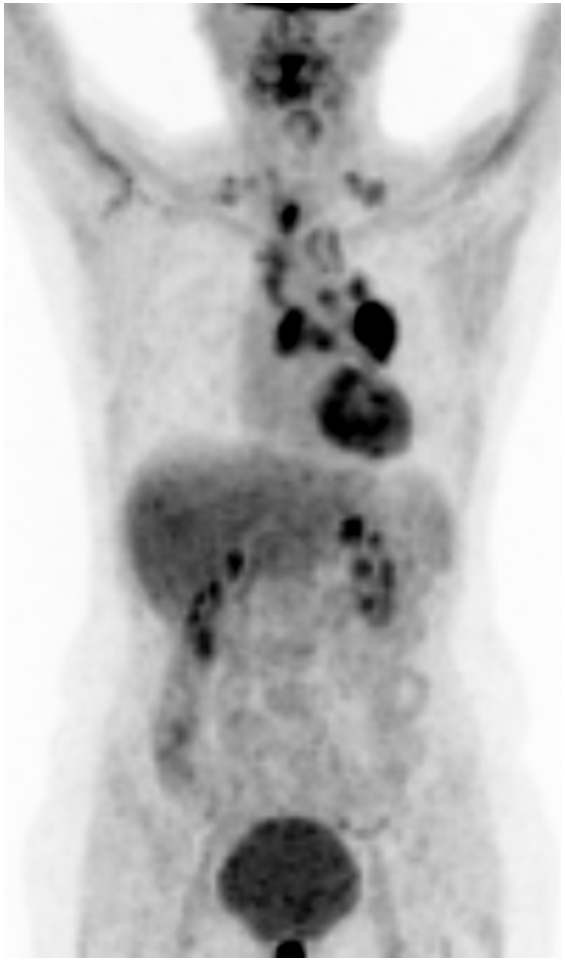
TABLE 2
FDG PET in Colorectal Cancer: Results of Literature Search

COLORECTAL CANCER	ARTICLE TYPE	PURPOSE	Total No. Patients	Total Pt. Studies	Total Lesions	Non-Ded PET	SENS PET (%)	SENS CT (%)	SPEC PET (%)	SPEC CT (%)	PPV PET (%)	PPV CT (%)	NPV PET (%)	NPV CT (%)	ACC PET (%)	ACC CT (%)	GOLD STD	MGMT(%) EFFECT
Diagnosis																		
No Articles																		
Staging																		
Arnthauer, 2000	A	management	49	49													biop/surg/follow-up	42
Oyen, 2000	A	management	48	48													histopath/follow-up	15
Seltzer, 2000[1]	A	management	53	53													follow-up	42
Meta, 2000[2]	A	management	51	51													clin follow-up	40
Baehre, 2000	A	dual head coincidence	18		24	yes	96										immunoscintigraphy	
Beets, 1994	RA	management	35	35													histol/serial radiol follow-up	40
	Summary	.	**254**	**236**														**36**
		by lesions			**24**		**96**											
Dx/Staging																		
Abdel-Nabi, 1998[3]	RA	dx prim	48	44			100		43		90		100		91		CT/surg/histopath	
		staging LN mets		14			29											
				33				29		85								
		staging liver mets		43			88	38	100	97	100	50	97	86	98	81		
	Summary	**by patients**	**48**	**134**			**85**	**34**	**71**	**92**	**95**	**50**	**99**	**86**	**94**	**81**		
Recurrence																		
Whiteford, 2000[4]	RA	susp met or recur colorectal adenocarc																
		overall	105	105			87	66	68	59							histopath/clin follow-up	26
		detecting mucinous cancer		16			58											
		detecting nonmucinous cancer		93			92											
		locoregional recurrence		70			90	71										
		hepatic metastasis		101			89	71										
		extrahepatic metastases		101			94	67										
Zhuang, 2000	A	hepatic	72	72			100	76									surg/clin follow-up	
Lang, 2000	A	whole body/overall	156	156			88	80									CT/MRI	24
		whole body/local recurrence					73	61										
		whole body/distant mets					93	92										
Baehre, 2000	A	dual head coincidence	18		24	yes	96										immunoscintigraphy	
Montravers, 2000[5]	A	dx/recurr	53		85	yes									71	48	post surg histol	
Schirrmeister, 2000[6]	A	recurr/mgmt	100	100			98	91	90	72							histopath/clin follow-up	61
Peterson, 2000[7]	A	resid/recurr/post local ablation to liver mets	7		9		89	44									serial CT/CEA/biopsy	
Gamez, 2000[8]	A	whole body	18	18			100										histol/clin follow-up	

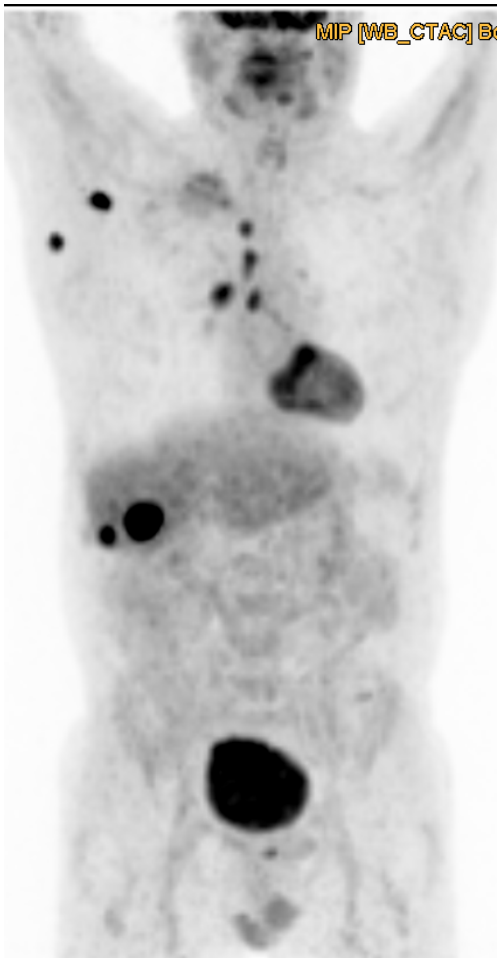
FDG-PET/CT in diagnosis of solid tumors



SPN

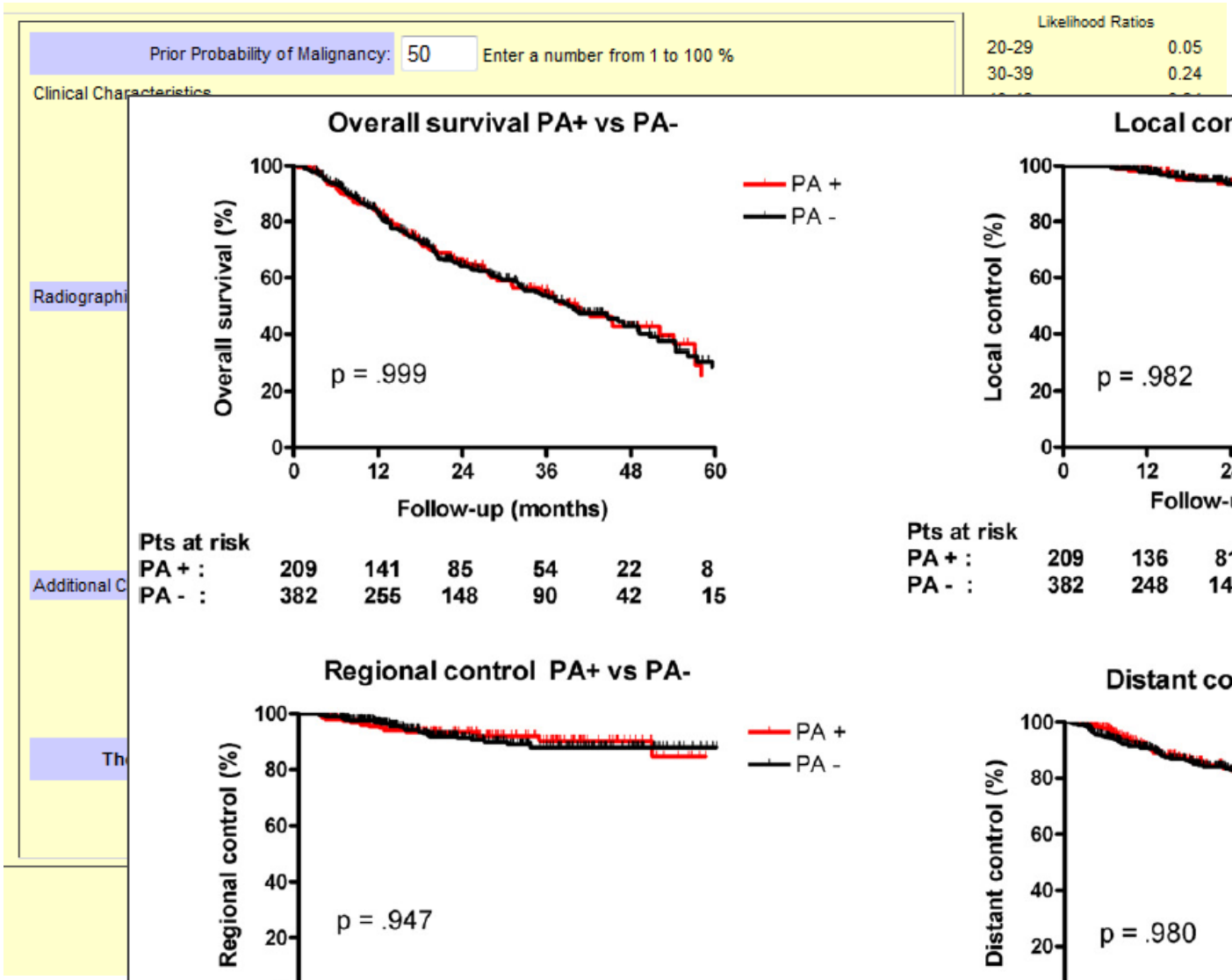


N-Staging



M-Staging

SPN: probability of malignancy

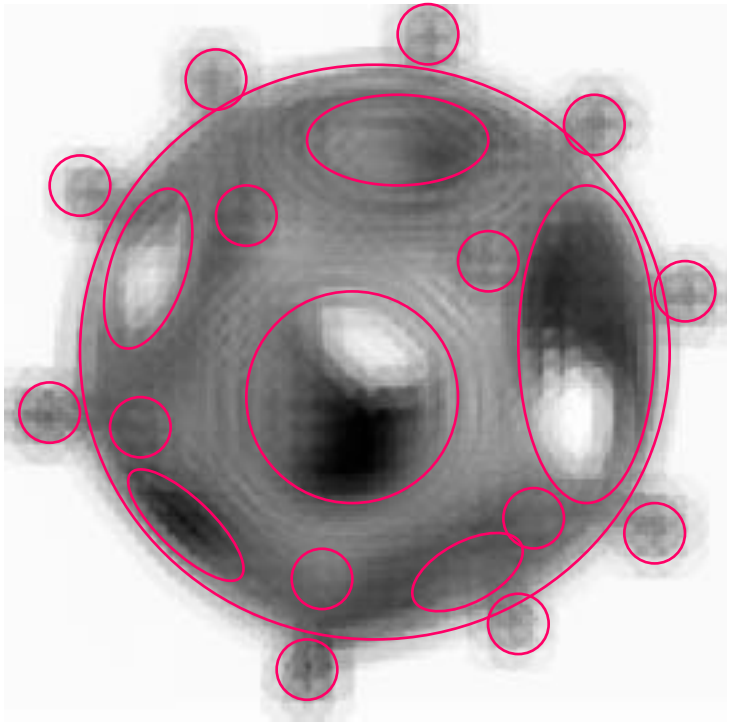


Verstegen, N. et al. R&O 2011

Medical imaging in radiation oncology

- Imaging for diagnosis and staging:
  - treatment indication
- imaging for radiotherapy planning
  - target (GTV – CTV – PTV)
  - normal tissues
  - movements
- Imaging during RT application
  - repositioning
  - adaptive radiotherapy
  - normal tissue reactions
- imaging during follow up
  - response
  - recurrence
  - normal tissue injury

Questions to medical images



diagnostic imaging:

What is this?

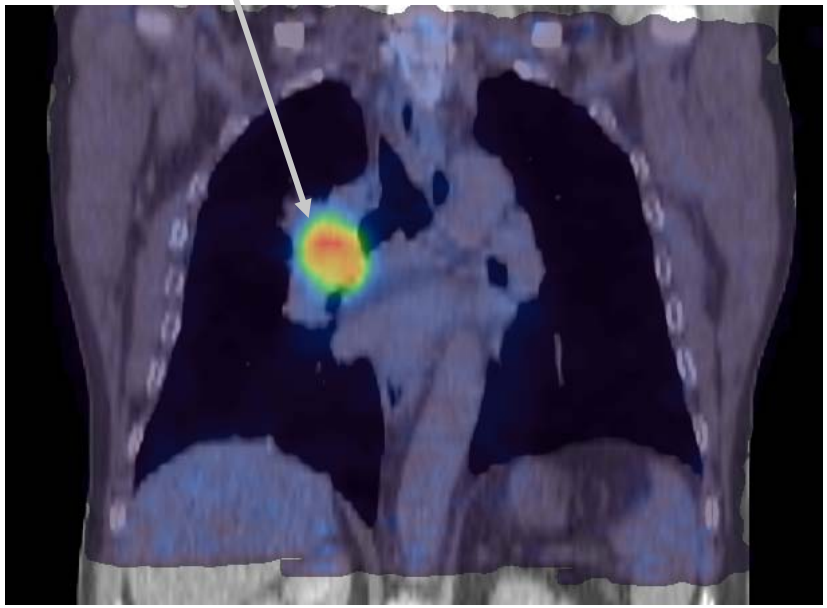
treatment planning:

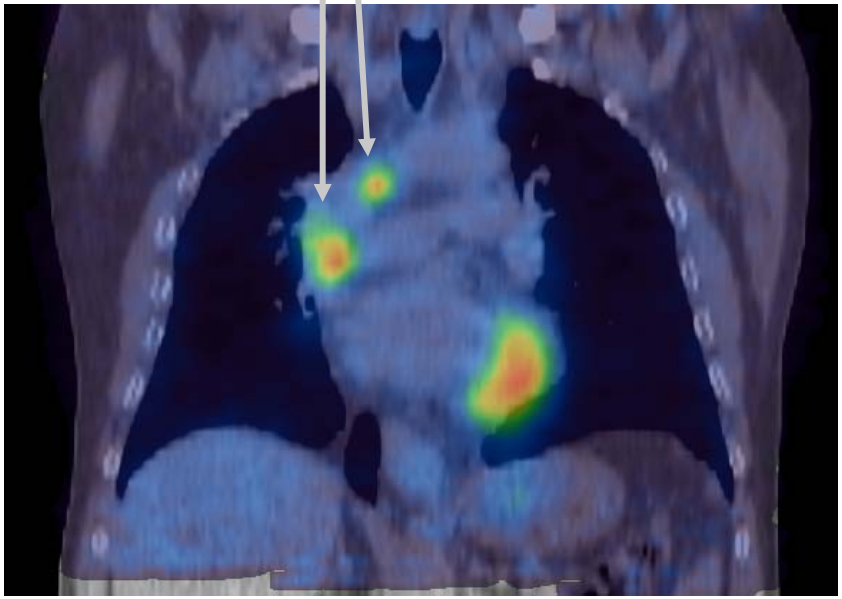
Where is this?
what exactly is around it?

Imaging for GTV delineation

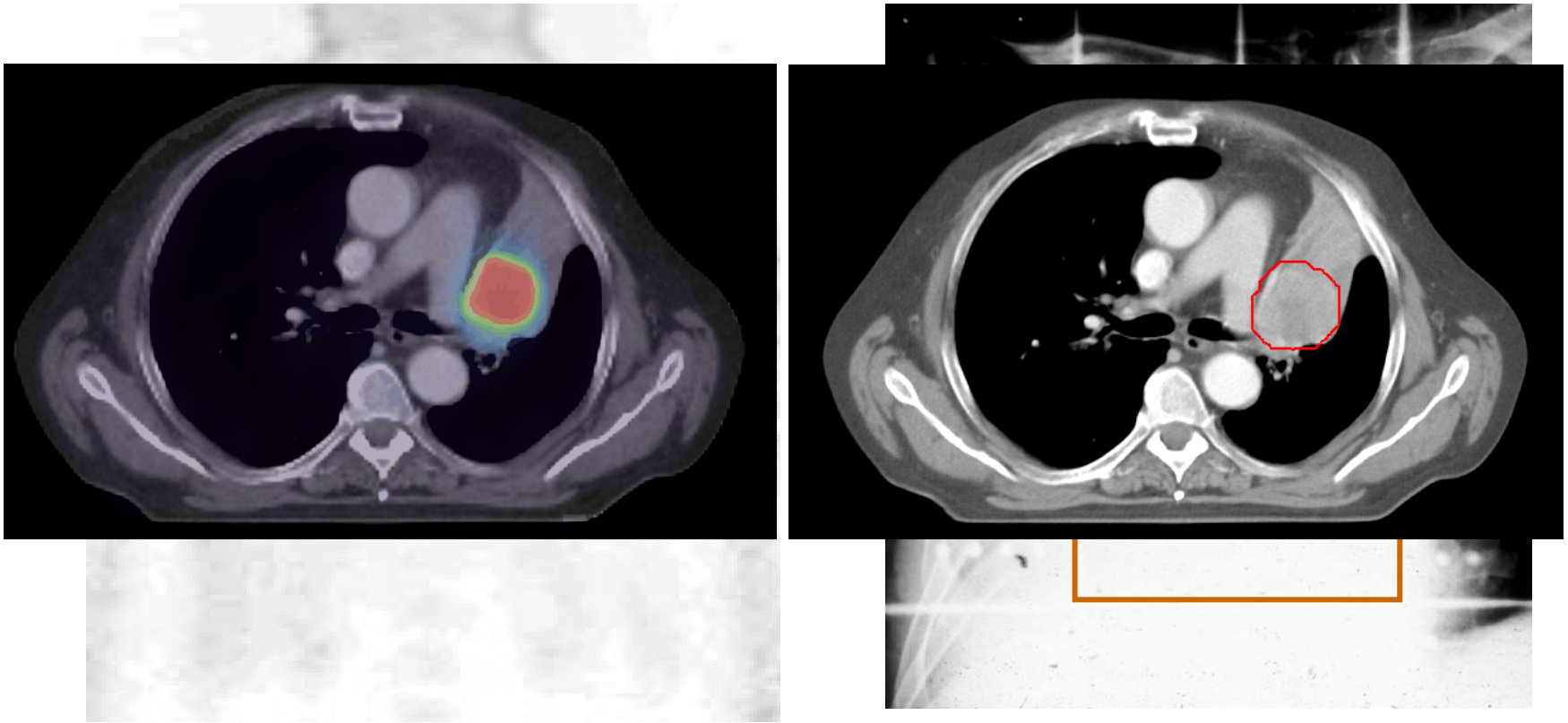
primary tumor

lymph nodes





Molecular imaging for GTV delineation



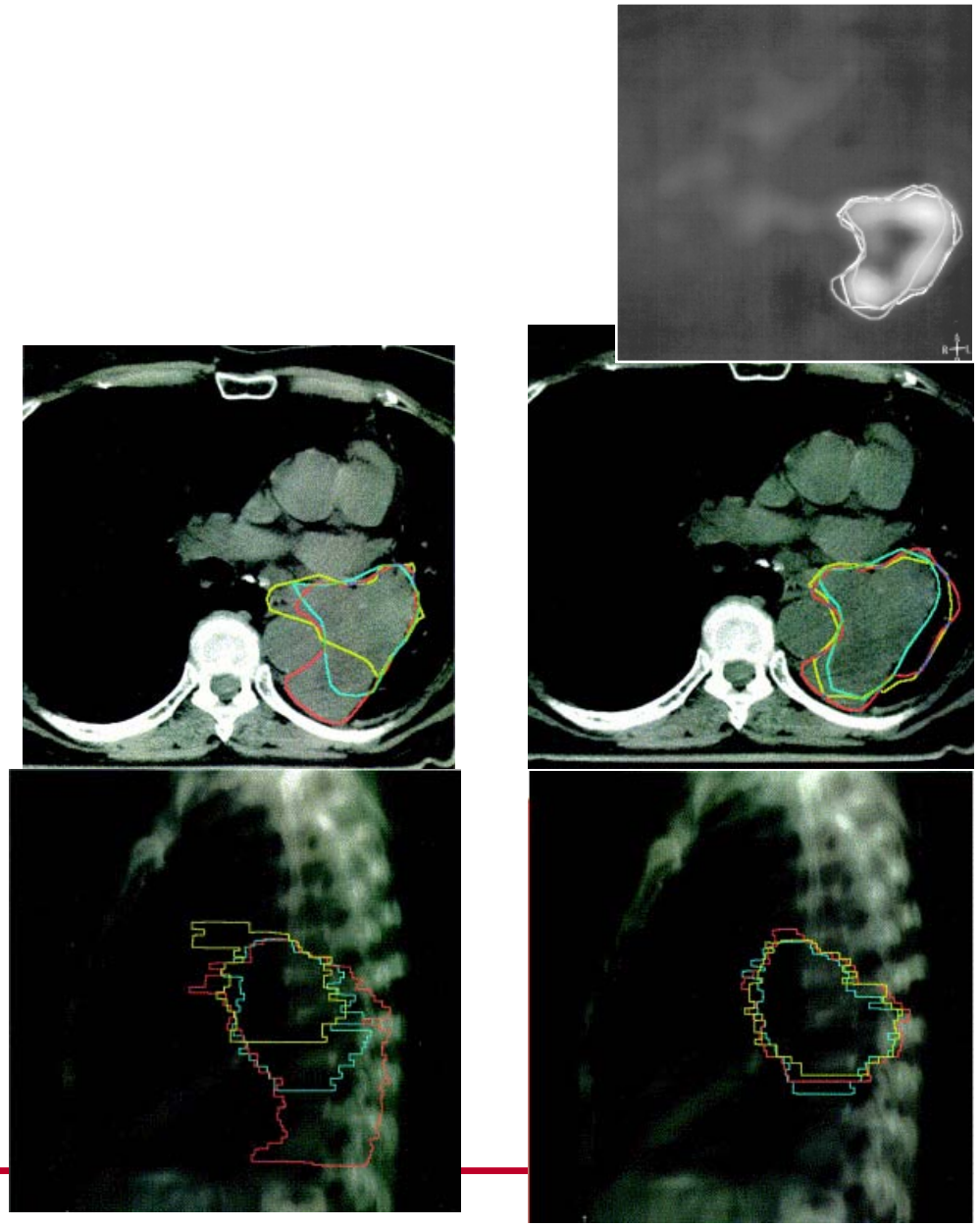
Reduction of IOV by new imaging methods

GTV-Definition (3 RO)

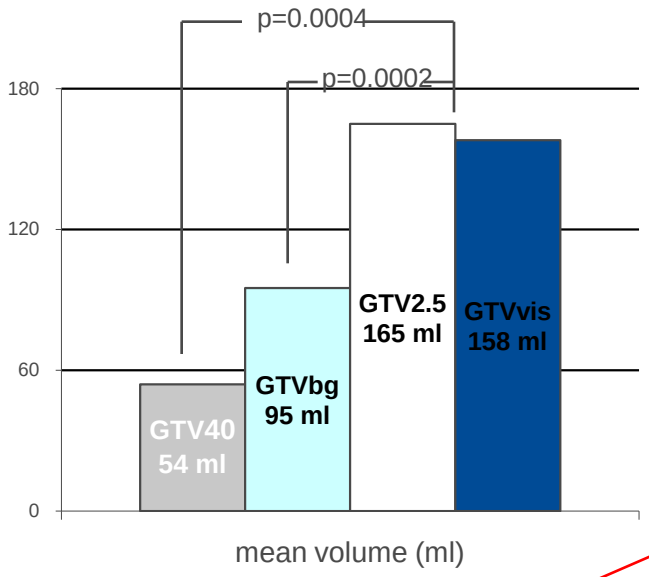
large interindividual differences in GTV-Definition

Use of FDG-PET: significant improvement

Caldwell IJROBP 2001



Molecular imaging in GTV contouring: how?

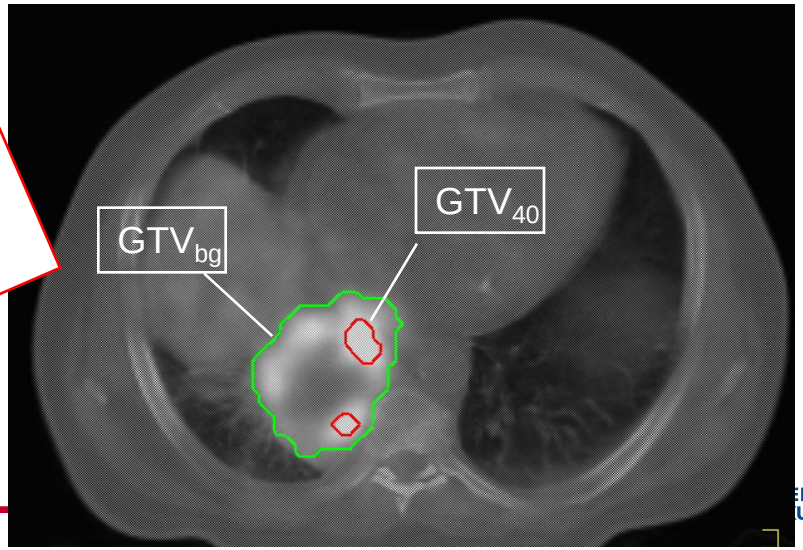


25 primary NSCLC ,
4 conturing methods:
1 visual, 3 thresholding

correlation of differences with
- SUV_{max}
- size of lesion
- FDG-inhomogeneity

Nestle JNM 200

today: YAPETISM…
no standard method



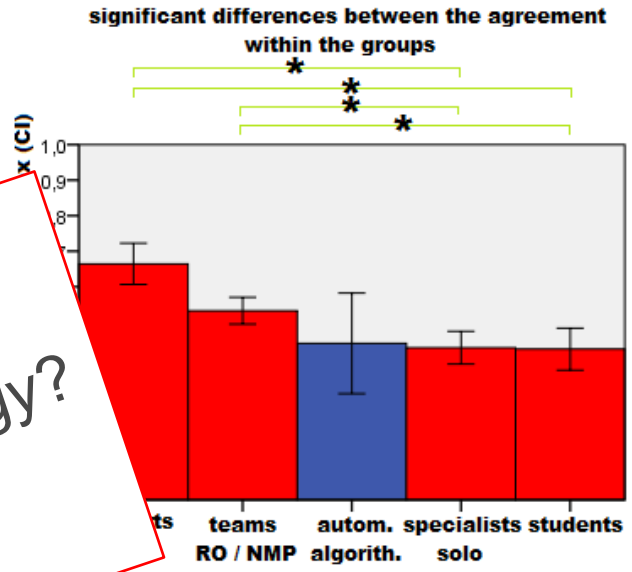
Visual contouring

- 1 case, 40 contours
- Experts(**A**) and teams RO & NM (**B**)
  → Significantly higher IOV (**C**)

- IOV Specialists (**C**) vs. st
- „PET-years“ n.s.

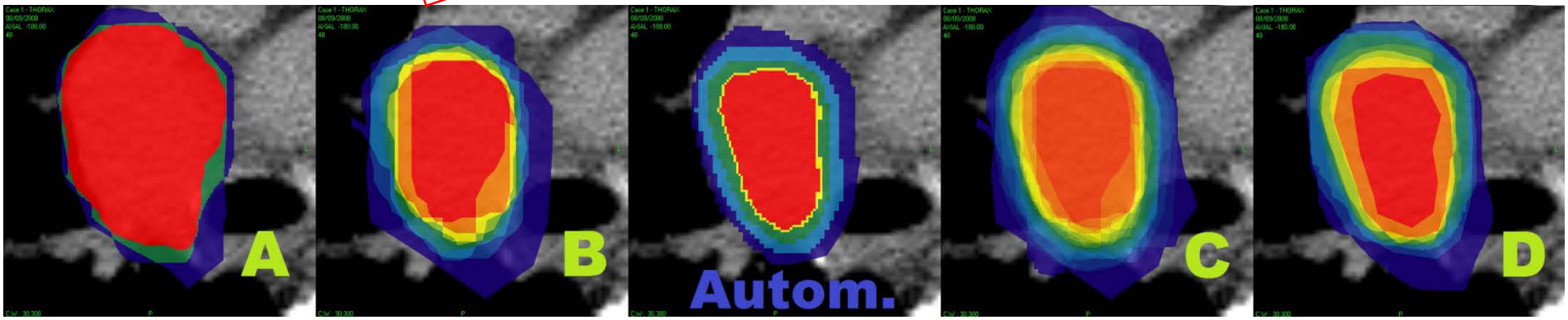
- IMV of autom.

What is the gold standard:
- size of tumor in CT?
- size of tumor by pathology?
- ITV?
- expert delineation?



	A	B	C	D
C I	0,67	0,53	0,44	0,43	0,42
Kappa Index	0,80	0,69	0,59	0,57	0,57

C. Doll et al. 2013



The „Turku PET contouring challenge“

label	team	type	median rank	
			phant.	patient
A	01	PL	17	19
B	02	WS	1.5	1.5
C	03	PL	24	31.5
D			23.5	27
E			10.5	12.5
F		T2	4	7
G	04	MD	28.5	23
H		T4	6	9
I			18.5	15.5
J			17.5	20.5
K_1	05	MD	13.5	25.5
K_2			20.5	31.5
L		RG	14.5	17
M	06	HB	n/a	12
N	07	WS	8.5	26
O	08	T1	3	23
P			28.5	11
Q		T2	13.5	14
R			11.5	16.5

label	team	type	median rank	
			phant.	patient
S_1	09	RG	31	7
S_2			31.5	8
T_1			20	20.5
T_2			25	22.5
U	10	PL	20	12
V			27.5	14
W	11	GR	25	23
X	12	MD	28.5	32.5
Y		T1	3	3.5
Z		T3	10.5	2
Γ			4.5	3.5
Λ		T2	7	7.5
Ω			18.5	
Φ	13	PL		

”accuracy metrics”
combines DSC
with Hausdorff distance

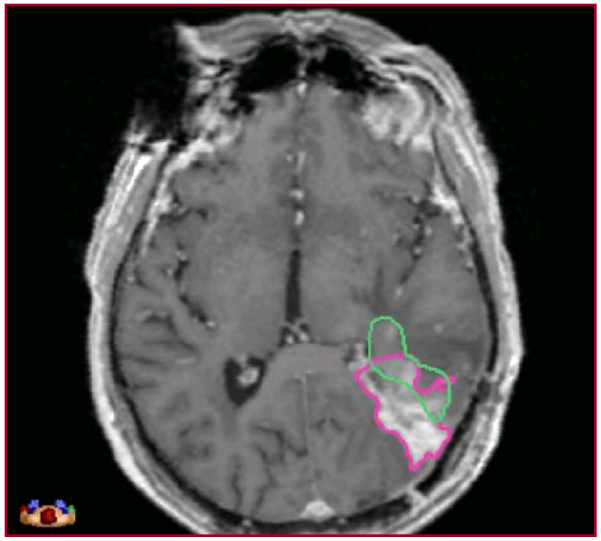
„**Winner**“:
visually adapted
thresholding method

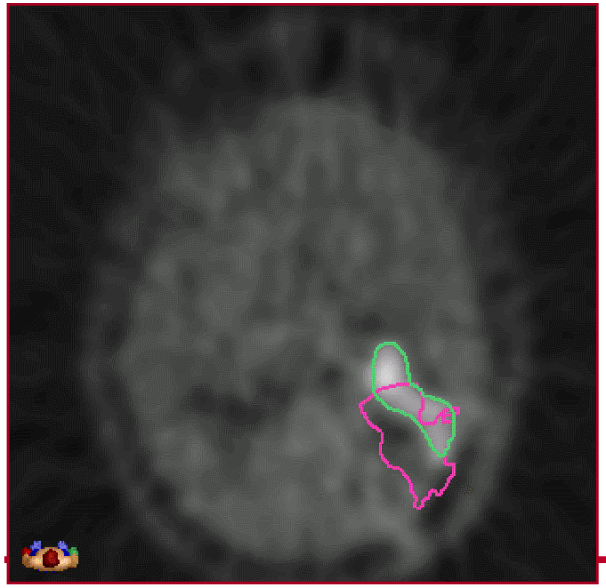
Under development:
AAPM-standard evaluation tool

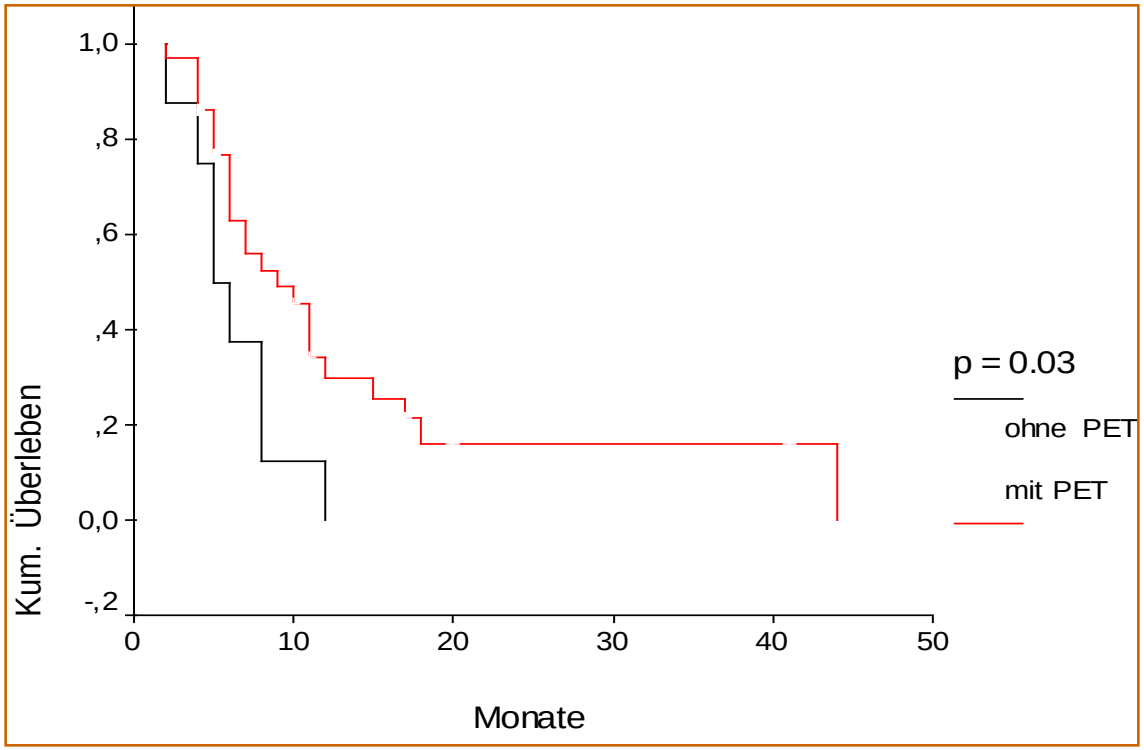
	algorithm type	description
MD	manual delineation	slice-by-slice outlining of PET VOIs using a computer mouse
RG	region growing	variants of the classical algorithm
WS	watershed	variants of the classical algorithm
PL	pipeline	multi-step algorithms that combine established image processing methods
GR	gradient-based	novel edge-finding method
HB	hybrid	novel segmentation algorithm for multi- spectral images, adapted for PET/CT

Shepherd, T. et al. IEEE 2012

PET and SPECT in RT-TP for glioma

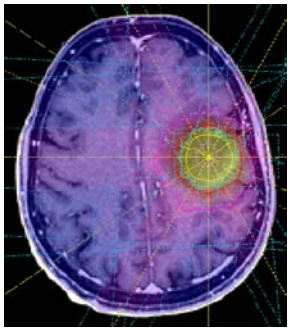






survival benefit by addition of AA-PET in TP for glioma

Amino-acid PET versus MRI guided re-irradiation in patients with recurrent glioblastoma multiforme - A randomised phase II trial

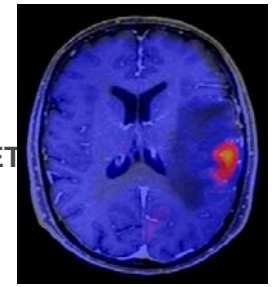


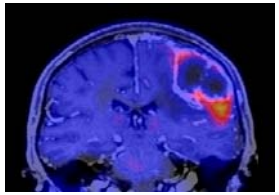
GLIAA

Arm A (experimental Intervention)

Target volume definition based on **FET-PET**

GTV = AA uptake PET

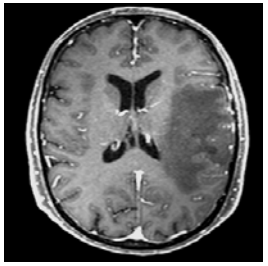


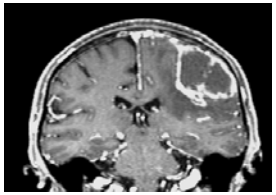


Arm B (Control Intervention)

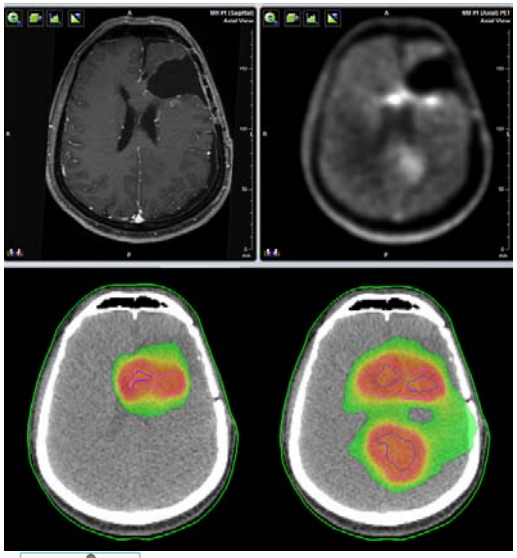
Target volume definition based on **T1Gd-MRI**:

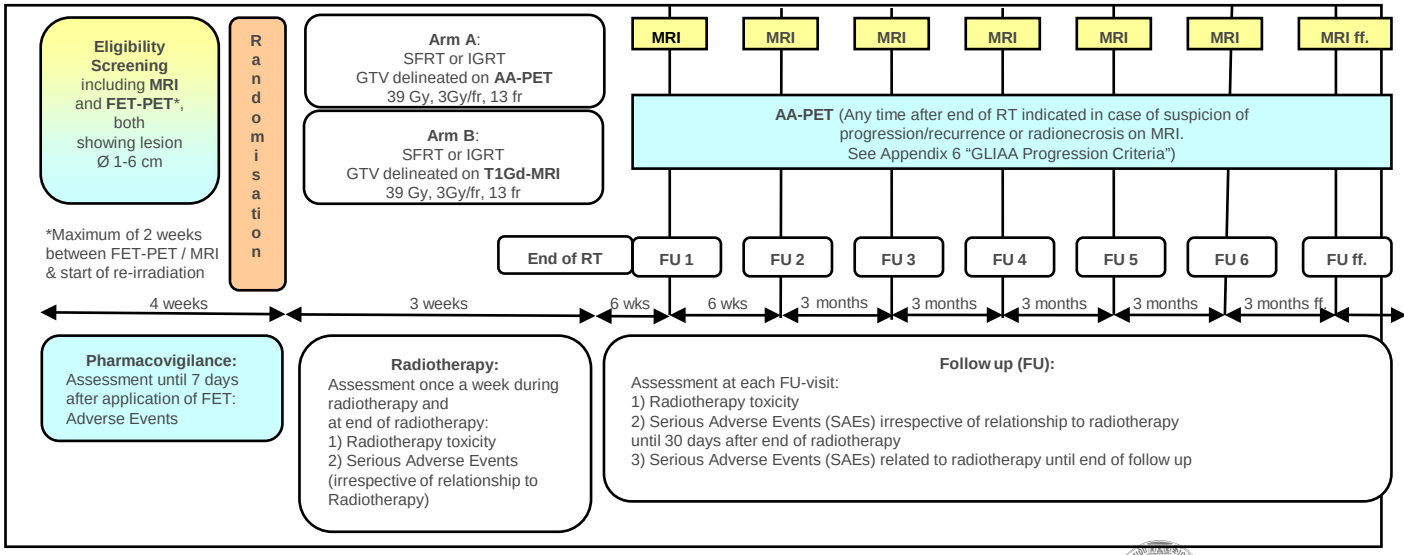
GTV = Contrast enhancement on MRI





PI: A.-L. Grosu, Freiburg, Germany





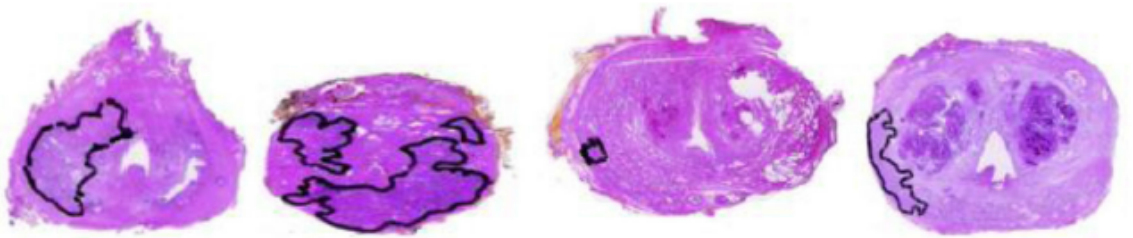
DEGRO Deutsche Gesellschaft für Radioonkologie e.V. | DGN | ARO Arbeitsgemeinschaft Radiologische Onkologie | Deutsche Krebshilfe HELFEN. FORSCHEN. INFORMIEREN. | Universitätsklinikum Freiburg CCCF Comprehensive Cancer Center Freiburg | dkfz. German Cancer Consortium Partner site Freiburg

Eur J Nucl Med Mol Imaging (2014) 41:2242–2248
DOI 10.1007/s00259-014-2861-0

ORIGINAL ARTICLE

^{11}C-Choline PET/pathology image coregistration in primary localized prostate cancer

Anca-Ligia Grosu · Gregor Weirich · Christina Wendl · Vesna Prokic · Simon Kirste · Hans Geinitz · Michael Souvatzoglou · Juergen E. Gschwend · Markus Schwaiger · Michael Molls · Wolfgang A. Weber · Uwe Treiber · Bernd Joachim Krause



unifocal multifocal microcarcinoma peripheral carcinoma

Tumor configuration	Patients (total=28)	Patients with SUVmax in TVP
unifocal	8 patients	
multifocal	6 patients	
microcarcinoma	13 patients	
peripheral carcinoma	1 patient	

Patient	TVP	GTV-PET
1	Right	Left
2	Right	Right
3	Left	Left and right
4	Left	Left
5	Left	Left
6	Left	Left
7	Left and right	Right
8	Left and right	Right
9	Left and right	Right
10	Left and right	Right
11	Left and right	Left
12	Left and right	Right
13	Right	Right
14		Right
		Left and right
		Right
		Left and right
	Left and right	Left and right
25	Left	Left and right
26	Right	Left
27	Left and right	Left
28	Left	Left

Conclusion

We developed a new method of imaging/pathology coregistration in primary localized PC. Our data do not support the concept of using ^{11}C-choline for GTV delineation in patients with primary PC.

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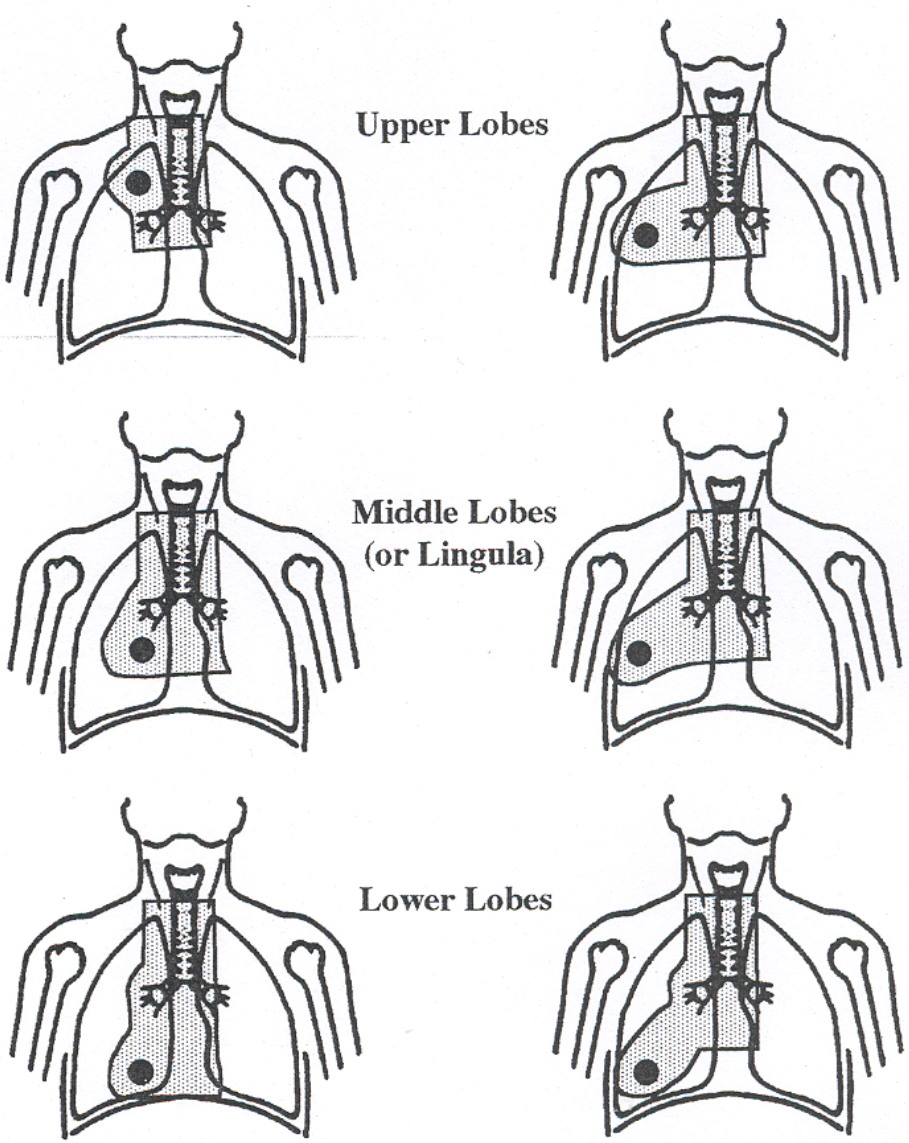
Conclusion

We developed a new method of imaging/pathology coregistration in primary localized PC. Our data do not support the concept of using ^{11}C-choline for GTV delineation in patients with primary PC.

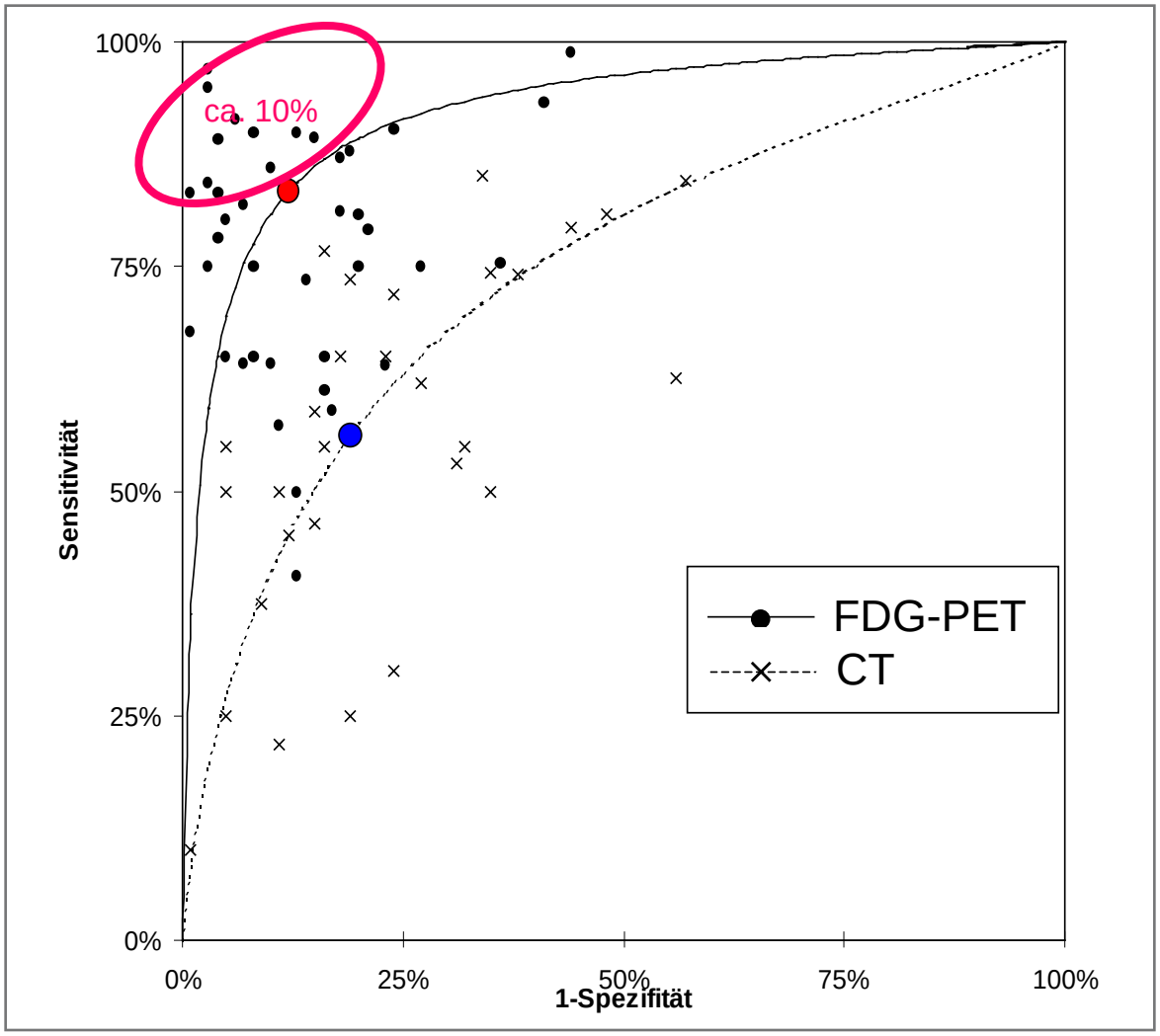
Patient	TVP	GTV-PET
1	Right	Left
2	Right	Right
3	Left	Left and right
4	Left	Left
5	Left	Left
6	Left	Left
7	Left and right	Right
8	Left and right	Right
9	Left and right	Right
10	Left and right	Right
11	Left and right	Left
12	Left and right	Right
13	Right	Right
14	Left and right	Right
15	Left and right	Left and right
16	Left	Left
17	Left and right	Right
18	Left	Left and right
19	Left and right	Left
20	Left and right	Left
21	Left and right	Right
22	Right	Right
23	Left	Left and right
24	Left and right	Left and right
25	Left	Left and right
26	Right	Left
27	Left and right	Left
28	Left	Left

CTV: nodal spread



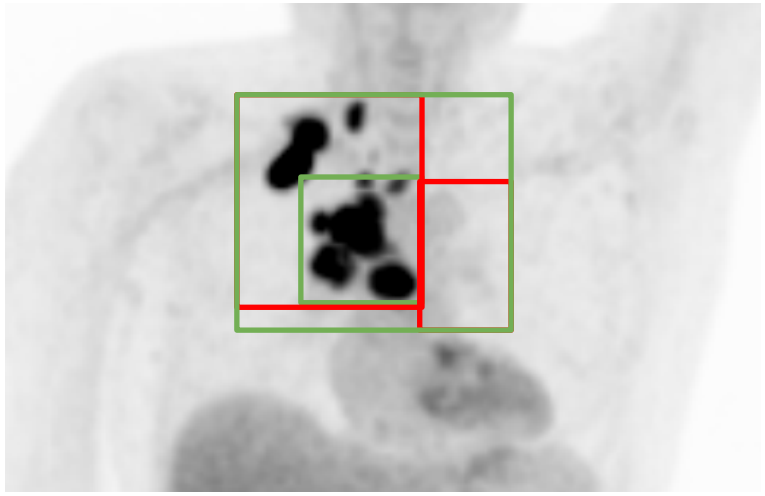
Perez/Brady 1991

Diagnostic accuracy of FDG-PET/CT in N-staging of NSCLC



Hellwig 2009: Metaanalysis
21 studies, 691 patients

CTV: where are the nodes?



diagnostic imaging:

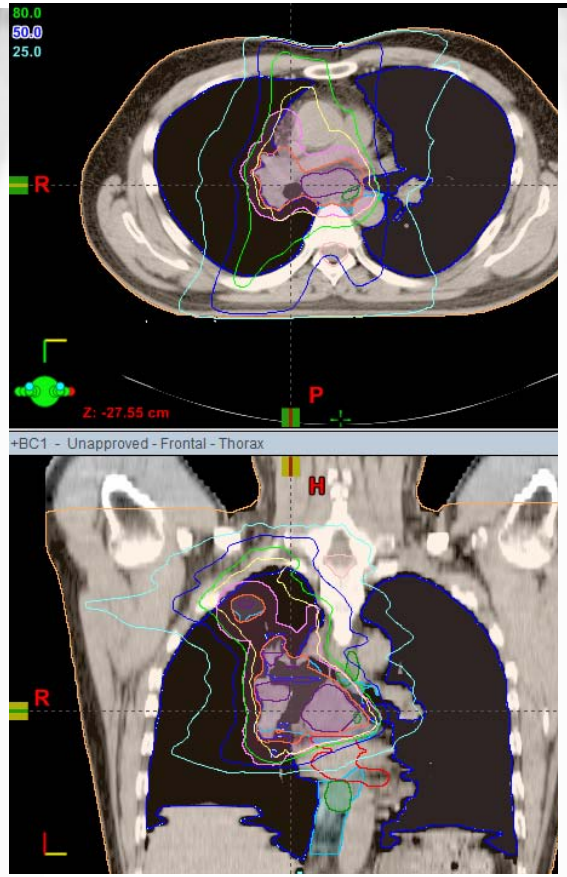
N2

RT treatment planning:

Treat what?

19.4.2012

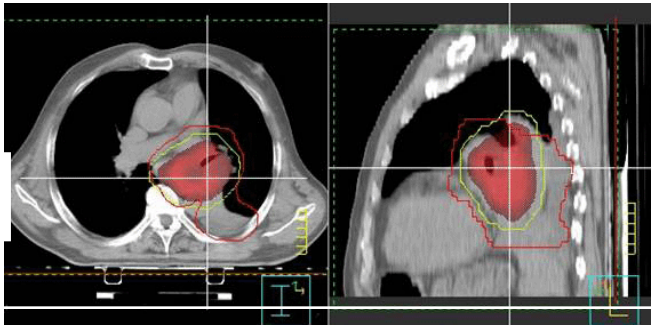
14.12.2012



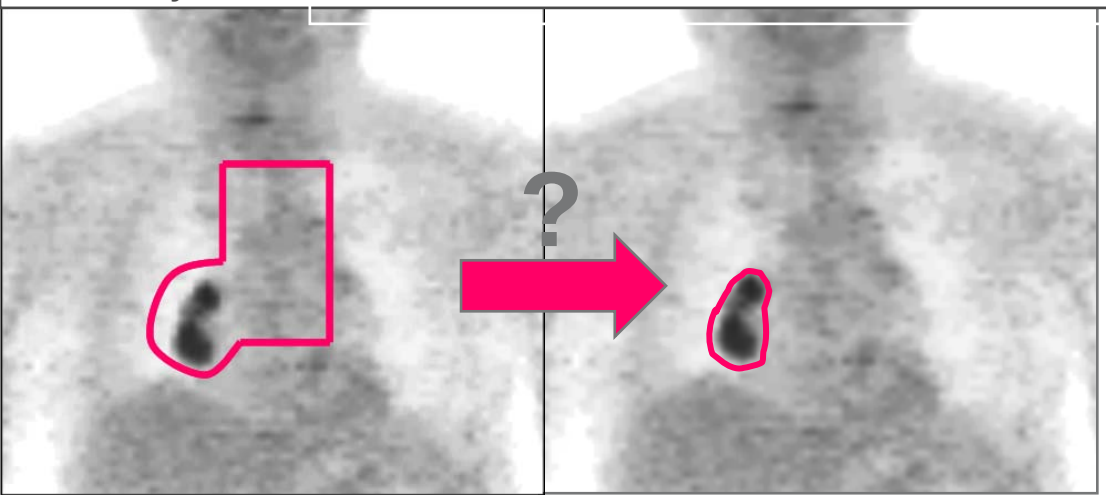
NSCLC (SCC) IIIb;
RCT 07/2012; Platin,
66 Gy/2 Gy

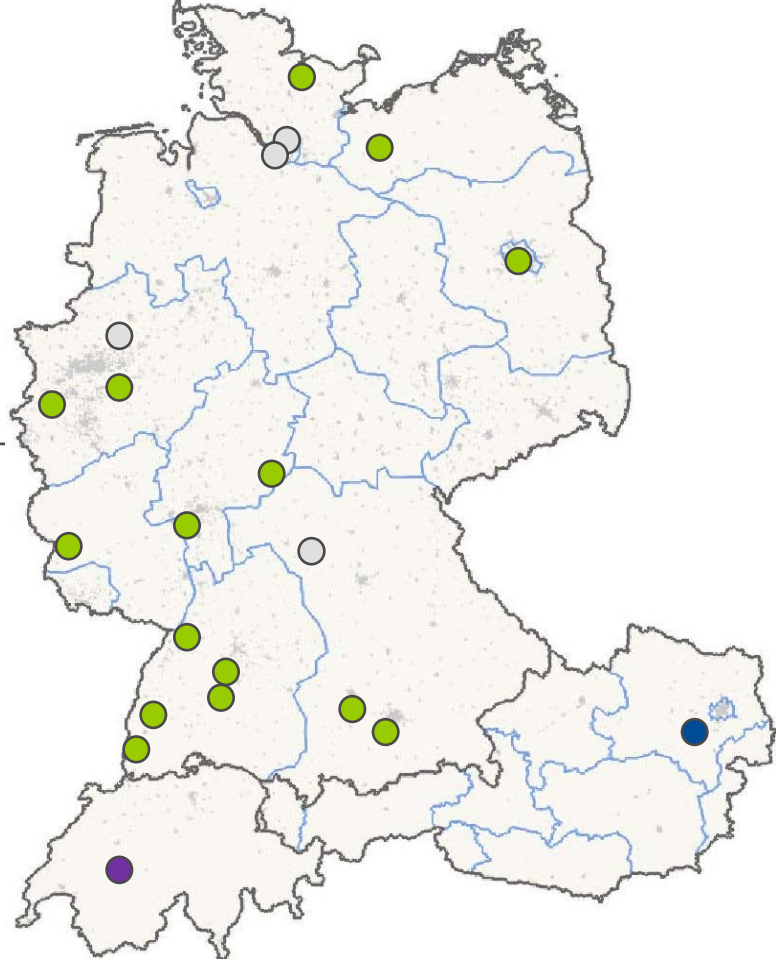
gefördert durch die Deutsche Krebshilfe

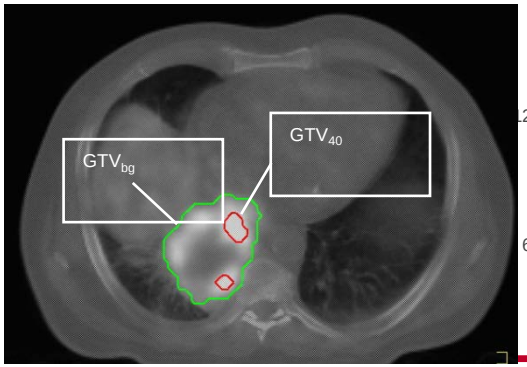
PI: U. Nestle, Freiburg, Germany

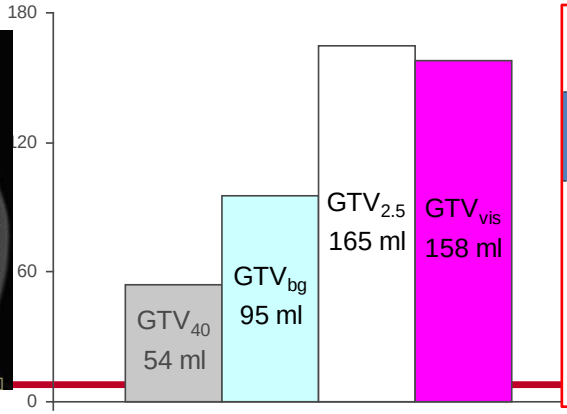


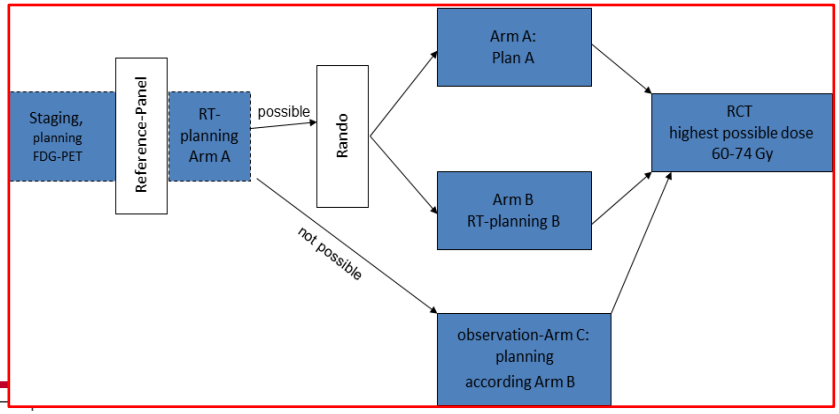
PET - Plan



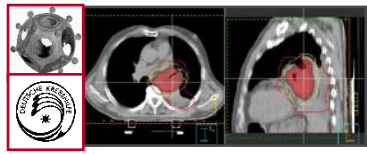


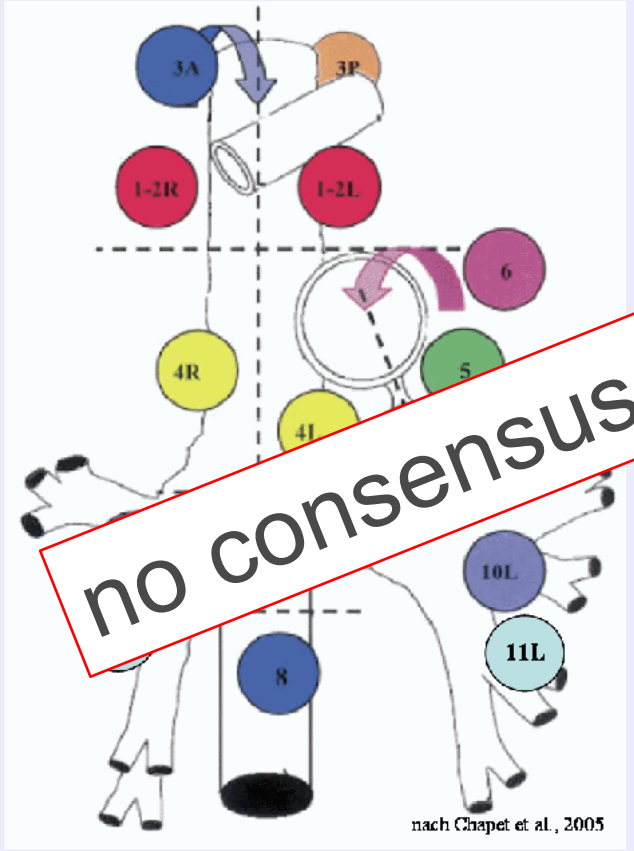






PET-Plan Study: diagnostic expert-panel



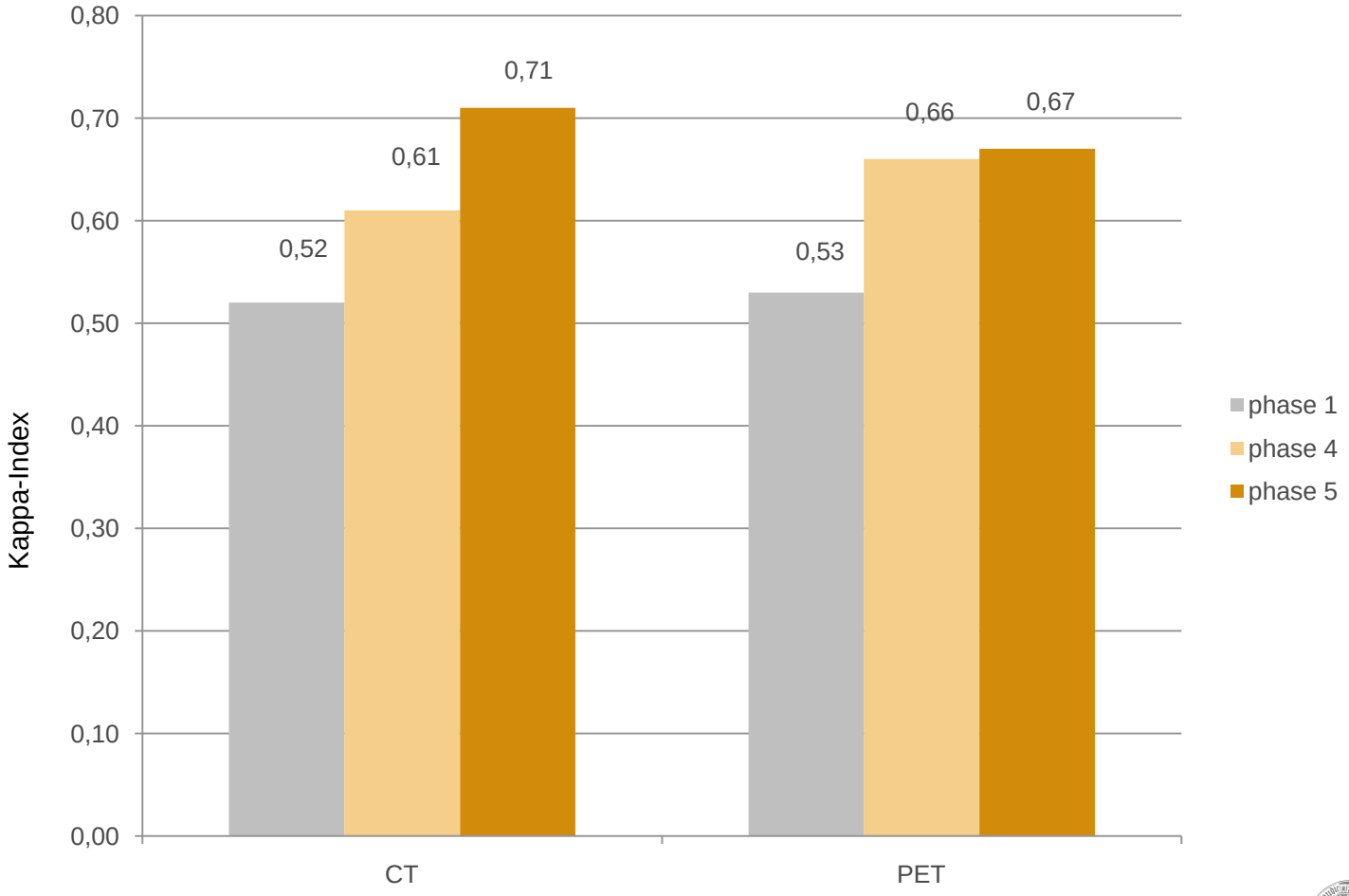


Station	Findings study center 29.04.2010	Findings Review 1 05.05.2010	Findings Review 2 05.05.2010	Consensus Reviewer 3
1R*	neg	neg	pos	
1L*	neg	neg	neg	
2R*	pos	pos		
2L*	neg			pos
3A*	neg		neg	neg
3P*			neg	neg
		pos	pos	pos
		pos	neg	pos
5*	neg	neg	pos	neg
6*	neg	neg	neg	neg
7*	pos	pos	pos	pos
8*	neg	neg	neg	neg
10R*	neg	pos	pos	neg
10L*	pos	pos	pos	pos
11R*	neg	neg	neg	neg
11L*	neg	pos	neg	neg

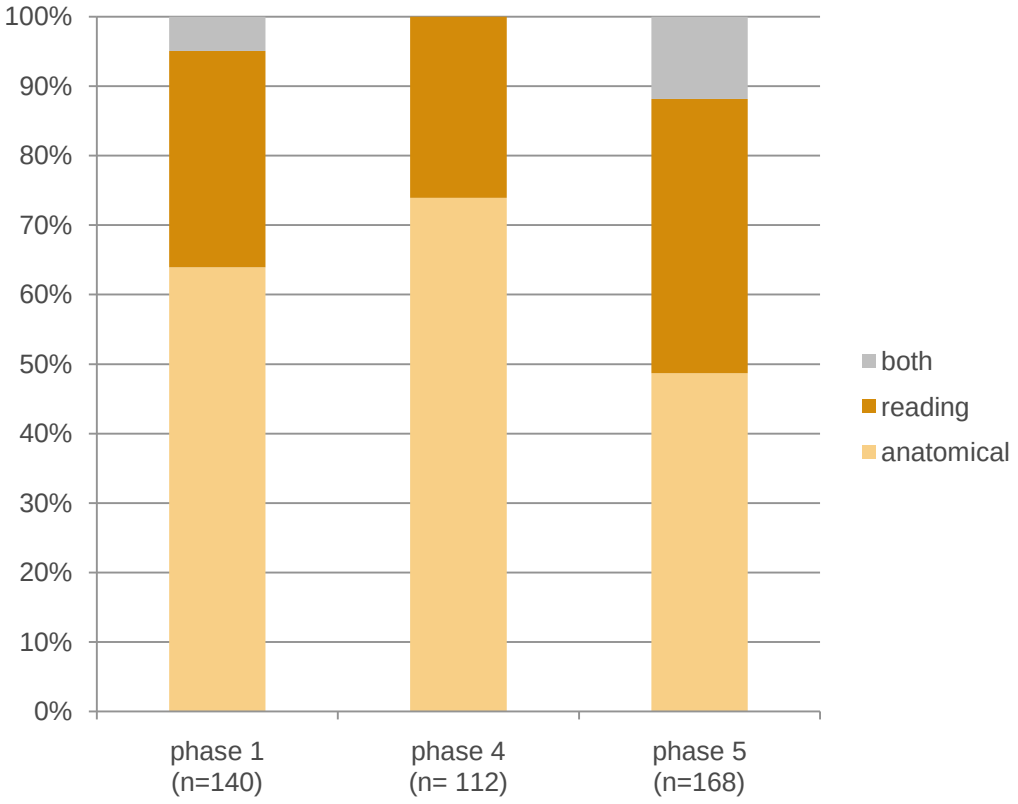
no consensus in first 10 cases ...

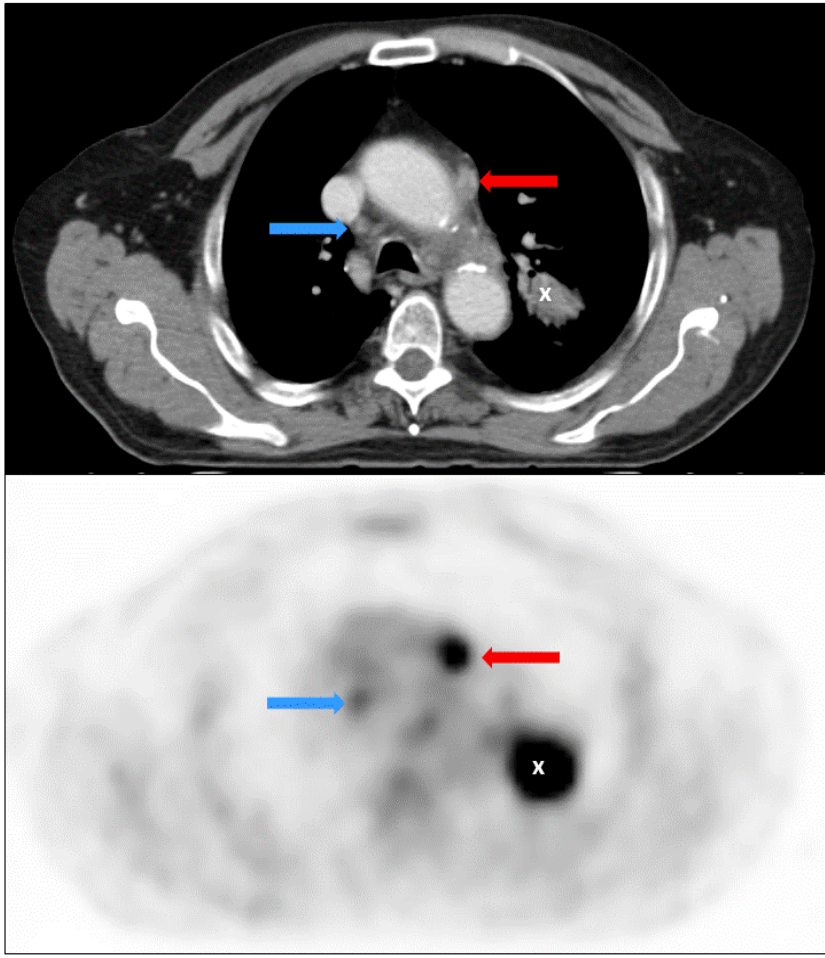
32 LN-reports for PET (16) and CT (16) to be entered at each review step

PET-Plan Panel: overall observer agreement by phase

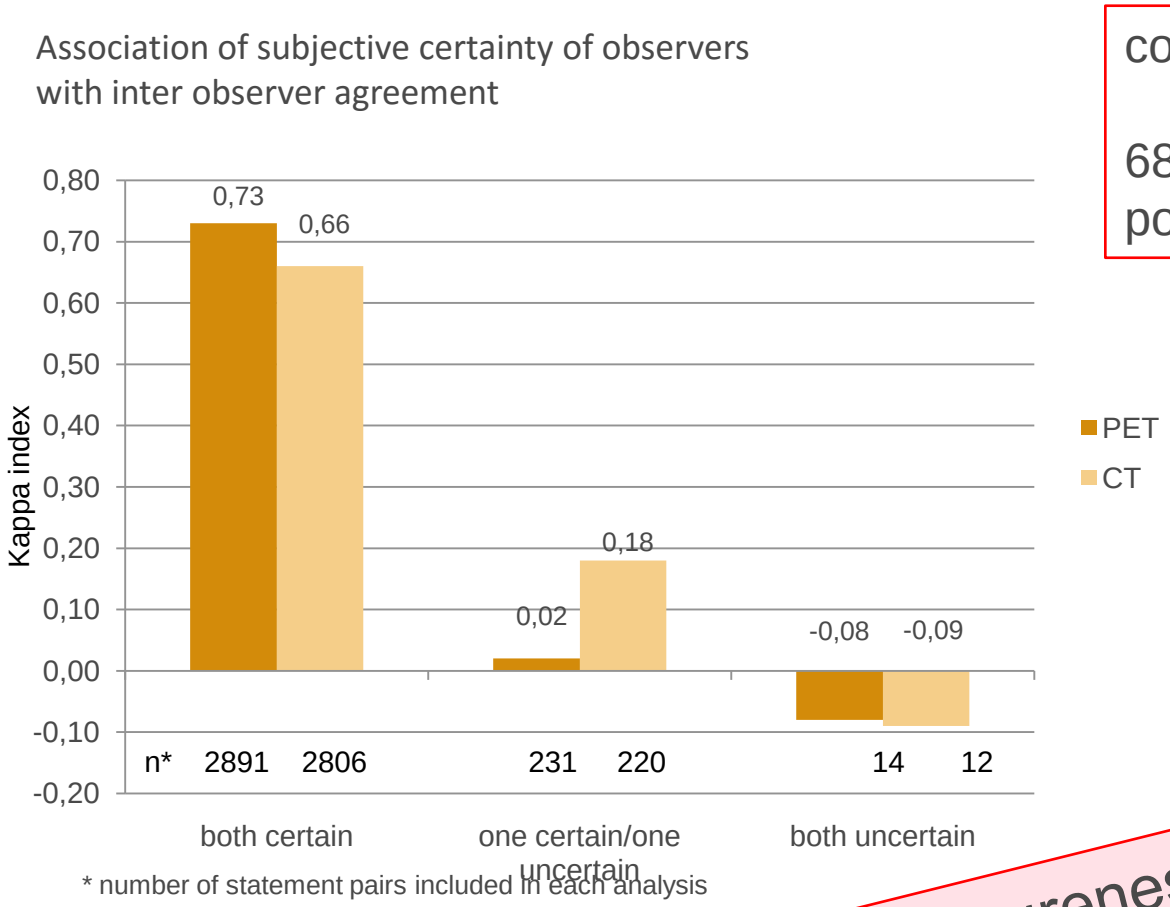


What are the reasons for reporting disagreements?





Are you sure about your finding?



comparison with biopsy:

68% (FP) vs. 90% (RP) pos LN-reports

reporting the „sureness“ of findings may ease further treatment decisions

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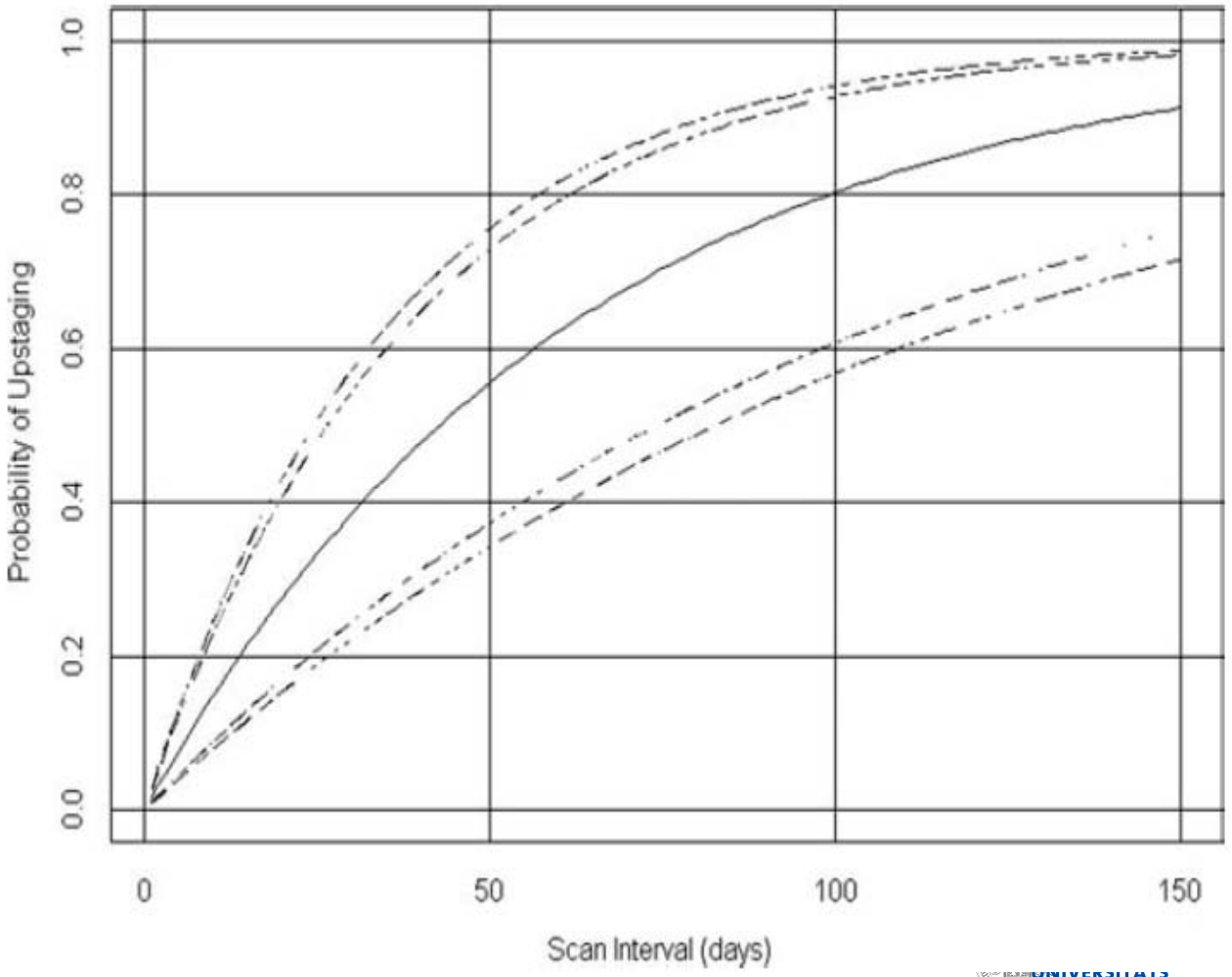
Imaging for RT-planning: soon before treatment!

82 pts, NSCLC
before radical RT
2 FDG-PET scans
median interval 24 days

progression in 39%

upstaging probability
within 24 days: **32%**

Everitt, S. et al.
Cancer 2010



Medical imaging in radiation oncology

- Imaging for diagnosis and staging:
  - treatment indication

- imaging for radiotherapy planning
  - target (GTV – CTV – PTV)
  - normal tissues
  - movements

- Imaging during RT application
  - repositioning
  - adaptive radiotherapy
  - normal tissue reactions

- imaging during follow up
  - response
  - recurrence
  - normal tissue injury

Cone-Beam CT


Varian Medical Systems
Lung, ROBERT
3D / 3D Match
Transversal - CT_Lung - CBCT 2006/10/16 08:50 - 1/1/0001 - 12:00 AM
Head First-Supine
Z: 1.75 cm
Transversal - CT_Lung
Z: 1.75 cm
Frontal - CT_Lung - CBCT 2006/10/16 08:50 - 1/1/0001 - 12:00 AM
Y: -0.05 cm
CBCT 2006/10/16 08:50 - 1/1/0001 - 12:00 AM
X: -0.76 cm
Auto Match Control
Progress
Preparing multiresolution image 2
Stop
Reset
Close
Couch Shift (VAR_IEC Scale, All units in cm and degrees)
Raw Shift Values
SHIFT
Couch Lat 0.0
Couch Lng 0.0
Couch Vrt 0.0
Couch Pitch 0.0
Couch Roll 0.0
Couch Rtn 0.0
Couch Proj Rtn 0.0
Machine Values
TARGET
ACTUAL
SHIFT
Couch Lat 0.00 0.0 0.0 Include
Couch Lng 0.00 0.0 0.0 Include
Couch Vrt 0.00 0.0 0.0 Include
Couch Rtn 0.00 0.0 0.0 Include
Reset Shift
Apply Shift
Perform the anatomy match
1. Acquire
2. Analyze
Cancel
Start
Clinac Console
Varian Medical Systems -...
OBI Server
Varian Medical Syste..
Removable Disk (E:)
Lung_Before_Match.bmp...
8:52 AM

Imaging for adaptive radiotherapy

Imaging of tumor during treatment
- size
- biology

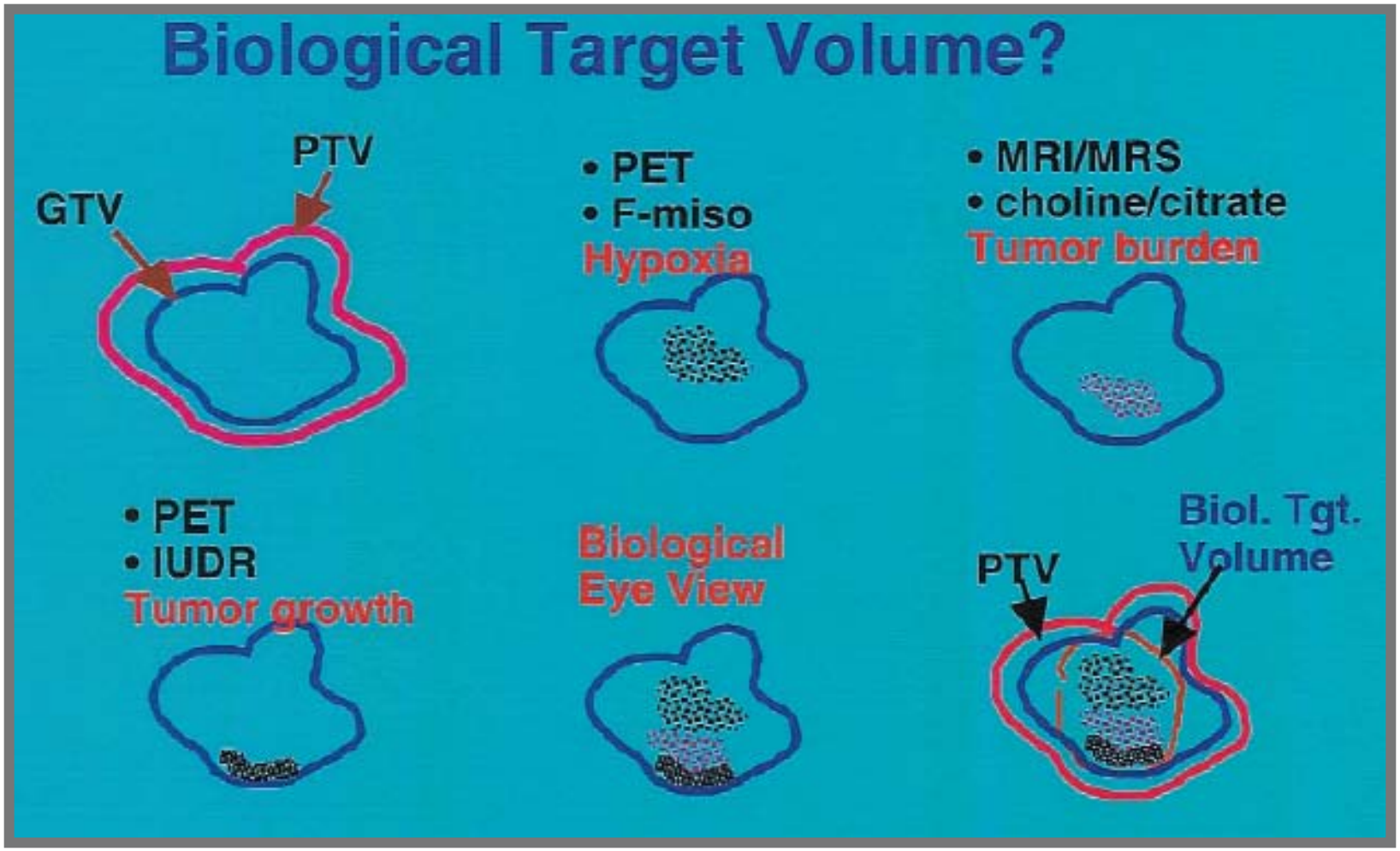
imaging of normal tissues
- filling (bladder/bowel)
- changing anatomy (h&n; lung)

perspectives …

Further questions to imaging during radiotherapy

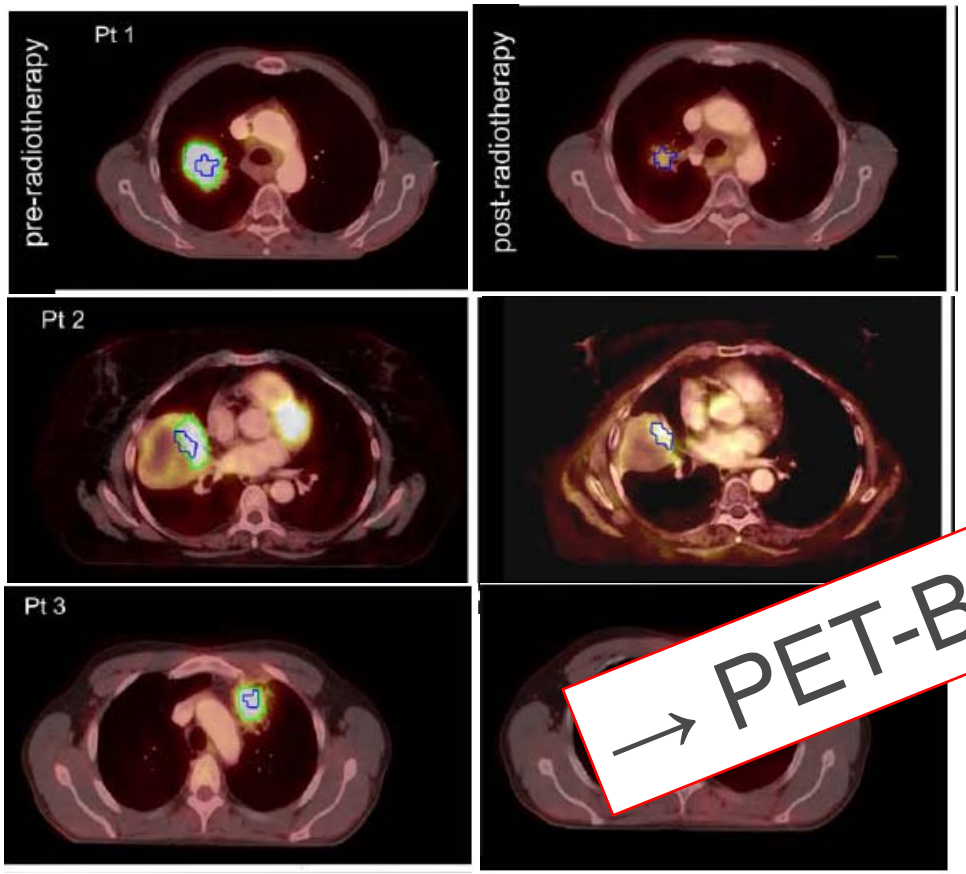
clinical situation	question to imaging	consequence
neoadjuvant R(C)T		
during	response prediction	early resection? change of CHT?
end	response y/n?	resection y/n further RT
radical R(C)T		
during	response prediction topography of response prediction of NT-reactions	modify RT/CHT? modify dose distribution? modify dose to NT?
end	residual disease	additional dose? „adjuvant“ CHT?
follow up after RT	recurrence vs. side effects	treatment y/n

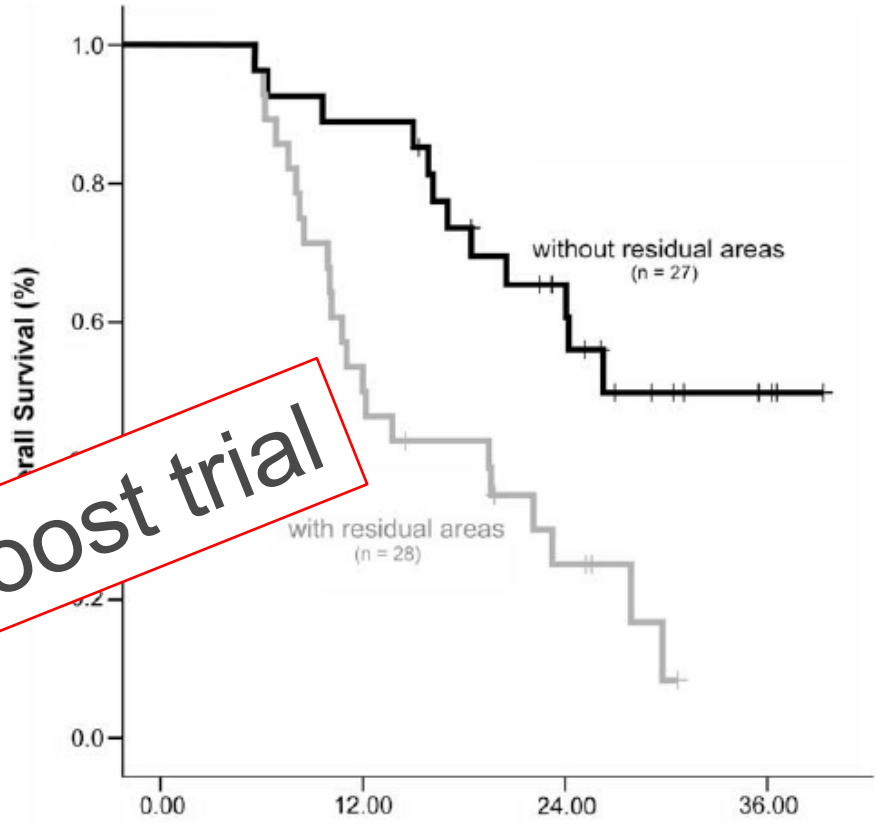
... dose painting



Ling 2000

PET in RT planning: beyond GTV





→ PET-Boost trial

55 pts., FDG-PET pre/post RT

Aerts, R&O 2009

Radiotherapy and Oncology xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Radiotherapy and Oncology

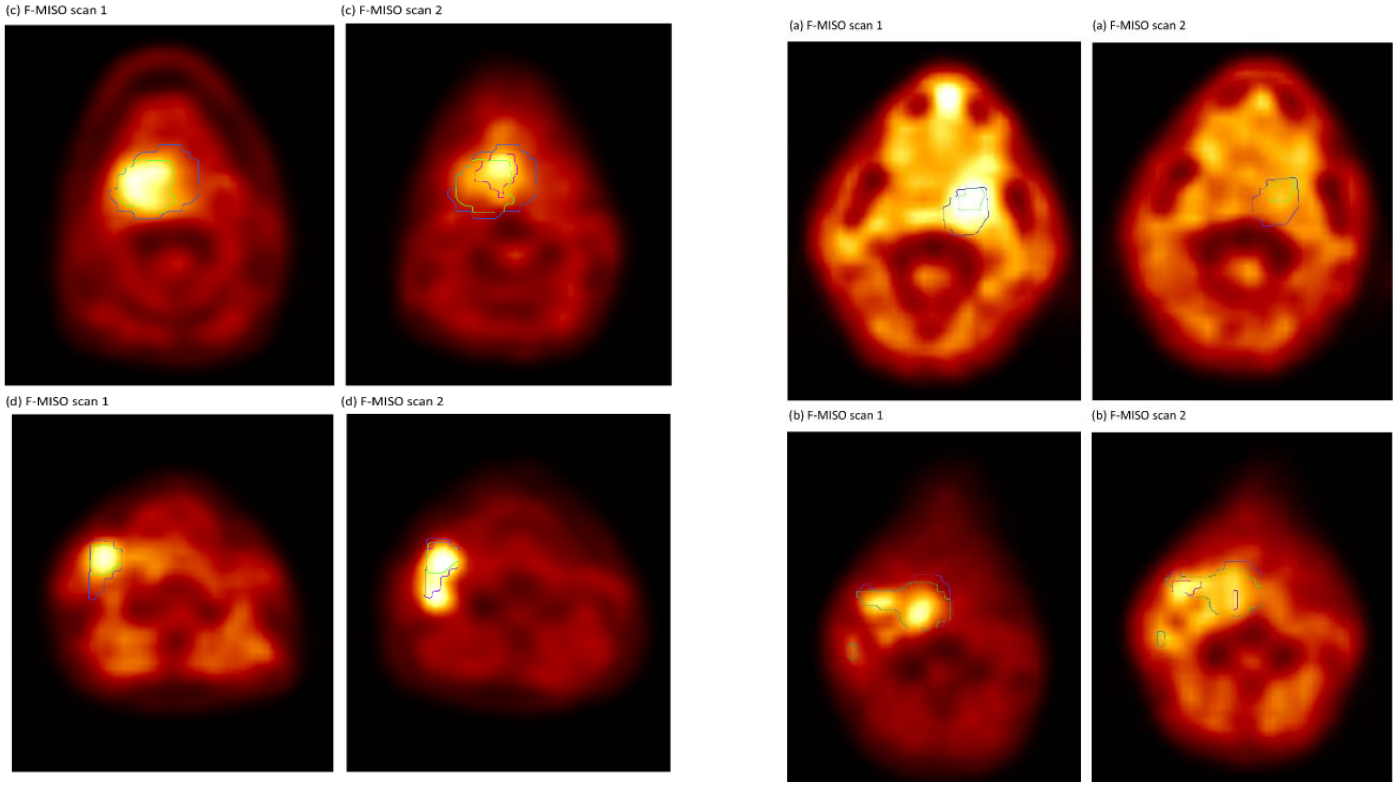
journal homepage: www.thegreenjournal.com

Original article

Exploratory geographical analysis of hypoxic subvolumes using ^{18}F-MISO-PET imaging in patients with head and neck cancer in the course of primary chemoradiotherapy

Martin-Immanuel Bittner [a,*], Nicole Wiedenmann [a], Sabine Bucher [a], Michael Hentschel [a,c], Michael Mix [b], Wolfgang A. Weber [b,d,1], Anca-Ligia Grosu [a,1]

[a] Department of Radiation Oncology; [b] Department of Nuclear Medicine, University Medical Center Freiburg, Germany; [c] Department of Nuclear Medicine, Inselspital Bern, Switzerland; [d] Molecular Imaging and Therapy Service, Memorial Sloan-Kettering Cancer Center, New York, USA



Conclusion: In patients with persistent hypoxia after 2 weeks of treatment, the hypoxic subvolumes showed mostly a geographically relatively stable conformation.

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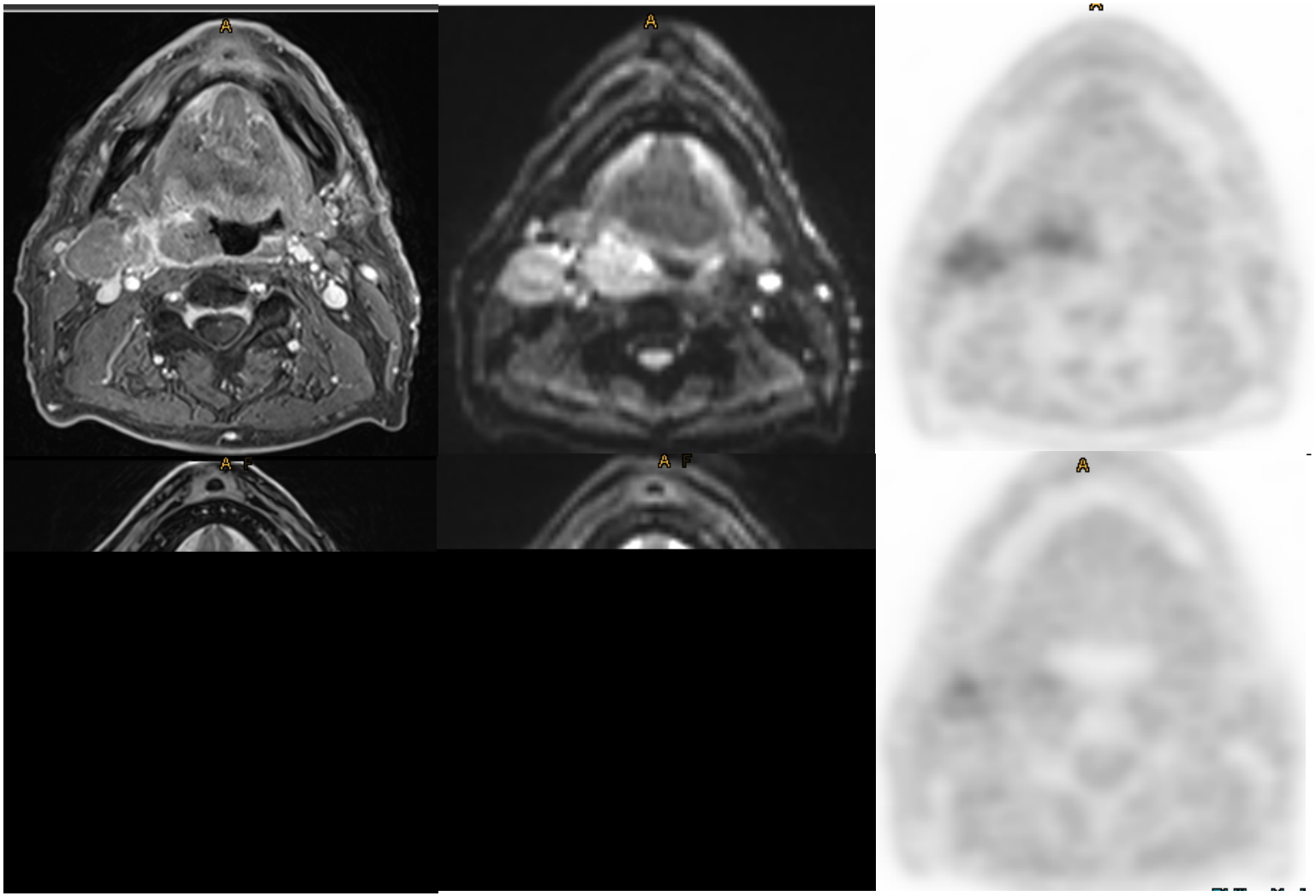
Dose painting: Which timepoint?



before RCT

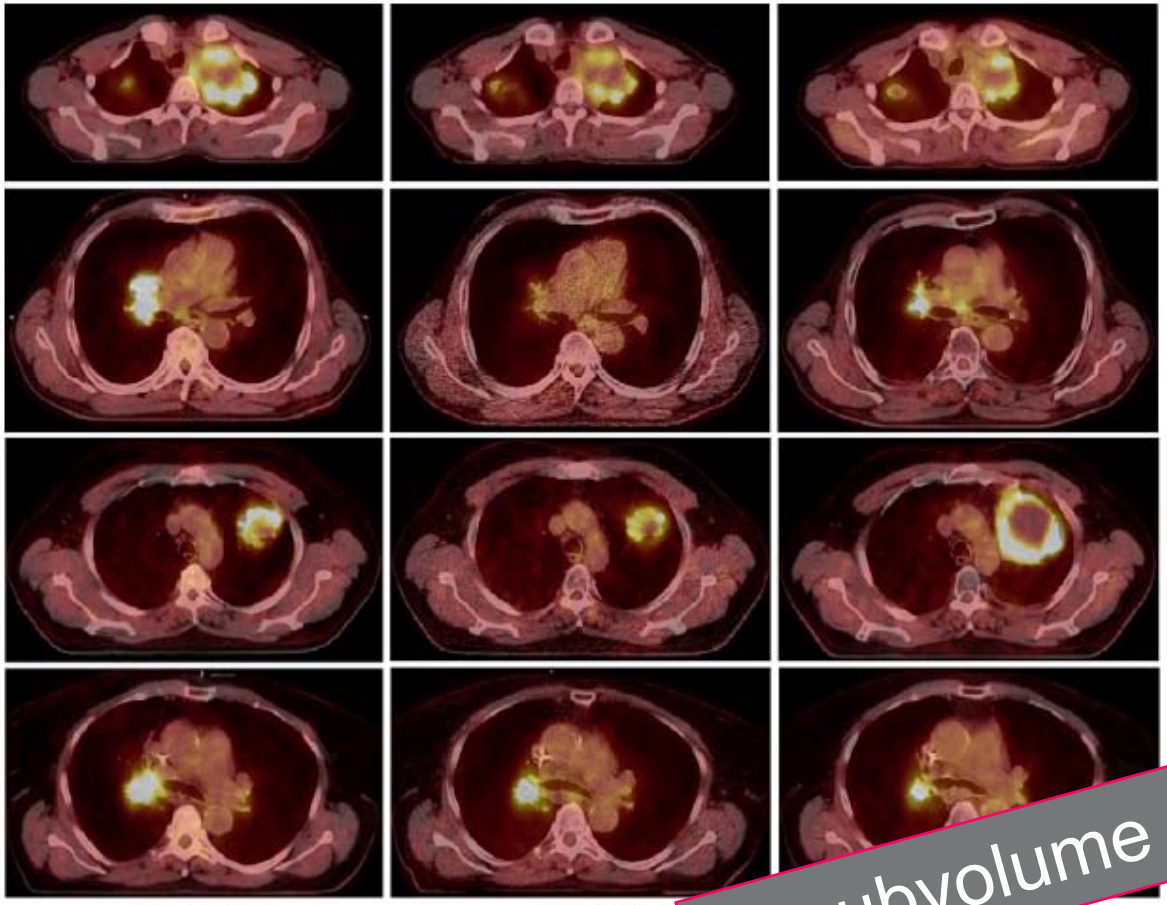
4th week of RCT

T1 + Gd

DWI

F-MISO PET/CT

Prediction of local recurrence



→ subvolume dose escalation?

10 pts with NSCLC relapse after RT
6/10 relapses in pre RT- PET high uptake areas

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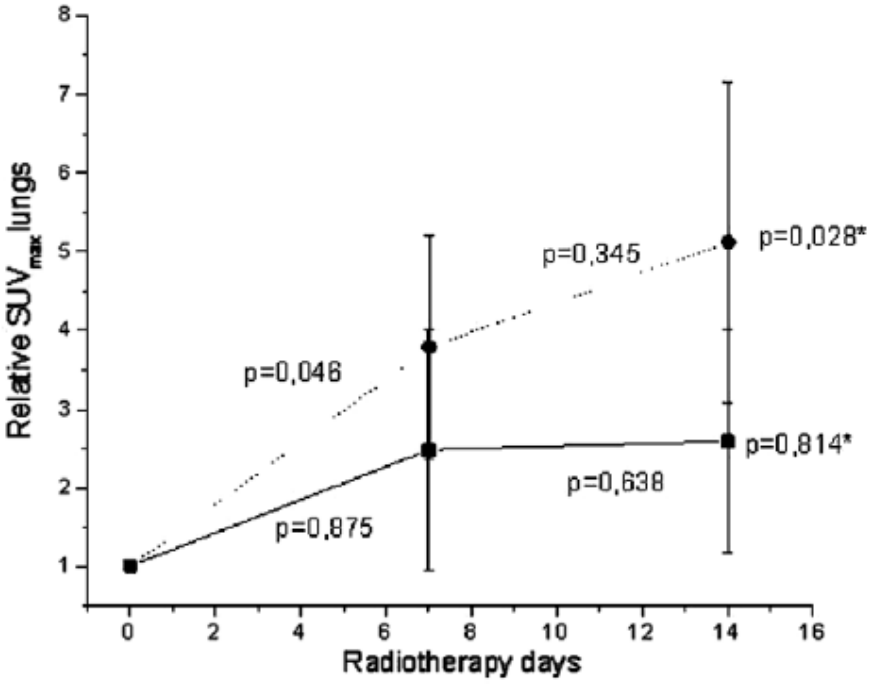
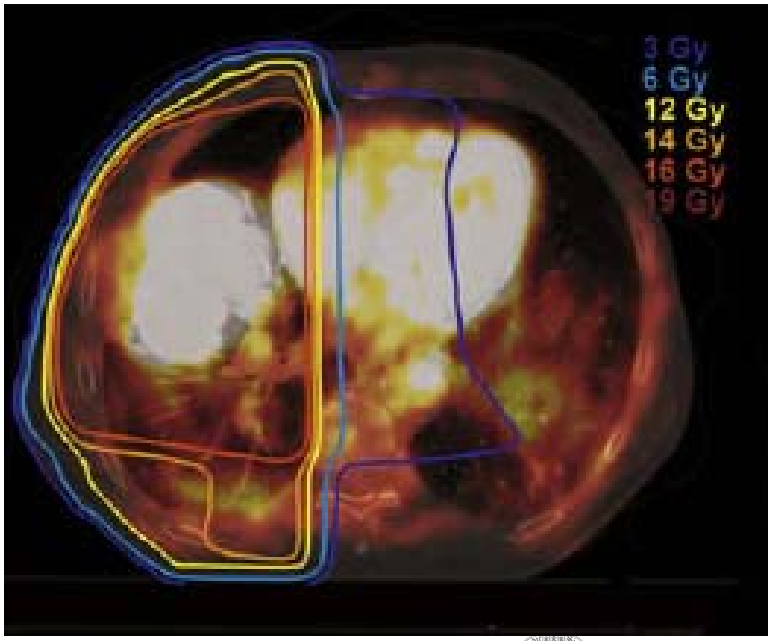
Abramyuk, R+O 2009

Prediction of NT-reactions?

Time	SUV_{max} of the lungs				
	No RILT	*p*-Value no RILT	RILT	*p*-Value RILT	*p*-Value no RILT vs. RILT
Day 0	3.40 ± 1.04	Day 0 vs. 7 = 0.39	2.09 ± 0.87	Day 0 vs. 7 = 0.17	Day 0 = 0.345
Day 7	2.69 ± 0.39	Day 7 vs. 14 = 0.75	3.74 ± 0.99	Day 7 vs. 14 = 0.25	Day 7 = 0.053
Day 14	2.88 ± 0.74	Day 0 vs. 14 = 0.48	**5.20 ± 1.41**	**Day 0 vs. 14 = 0.03**	**Day 14 = 0.032**





day 8 of RT

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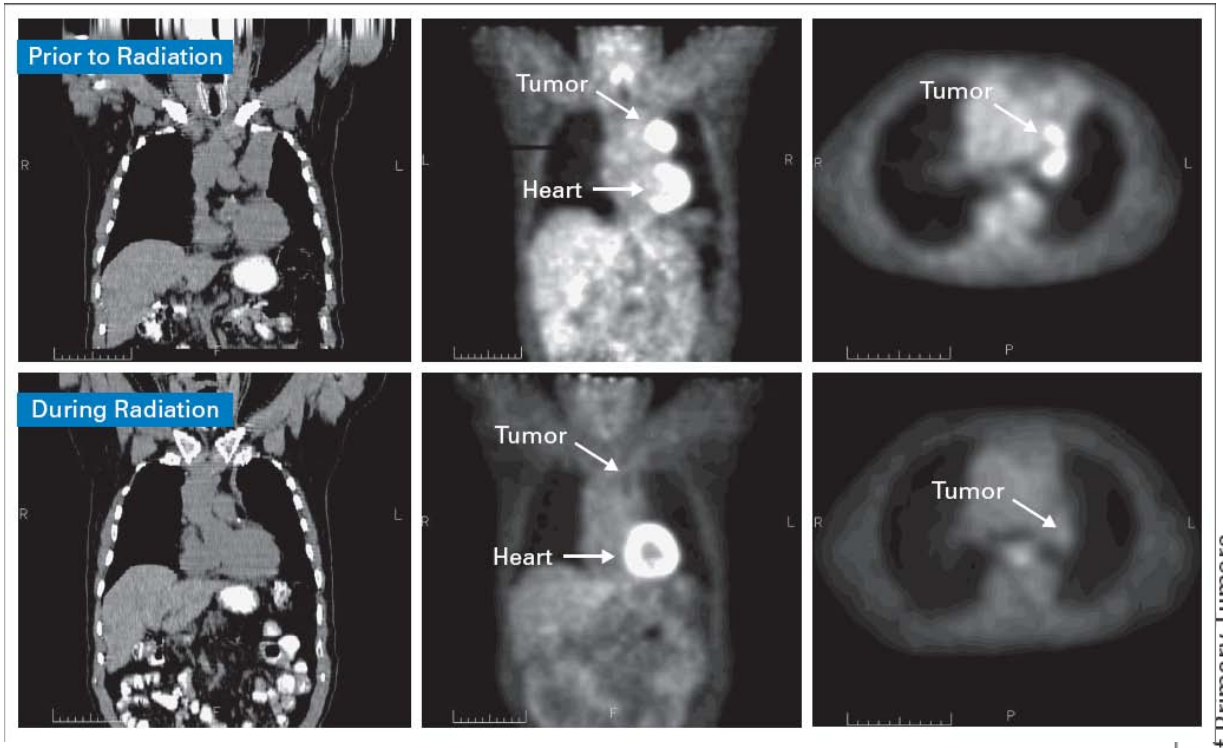
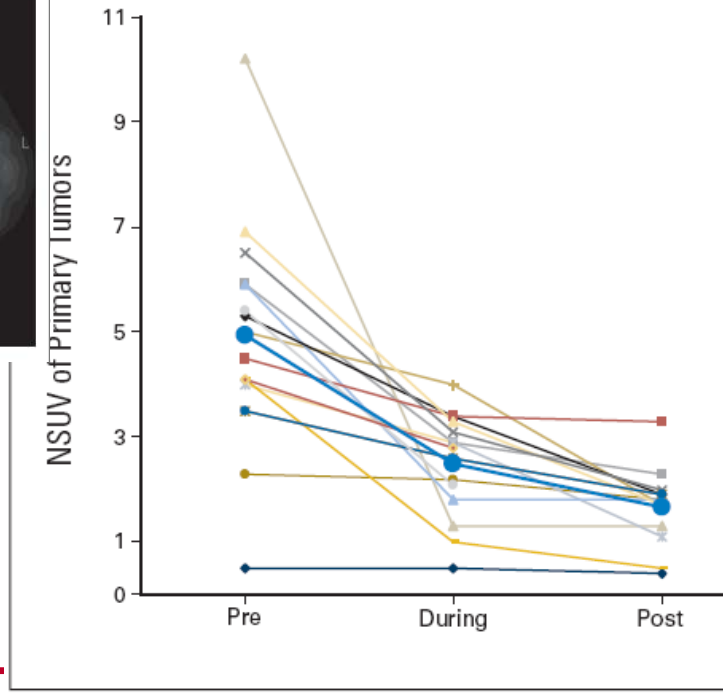
De Ruysscher 2009

Response prediction during RT?





significant correlation
PET-response during vs. after RT

Kong, JCO 2007

„cooking recipe“ for the translation of new imaging modalities in radiation oncology

Ingredients:

diagnostic data (topography, biology)

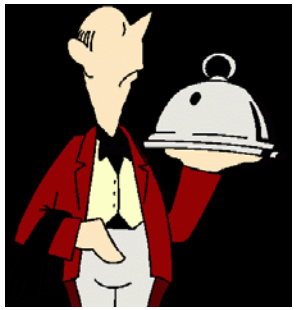
clinical problem („unmet need“)

Preparation:

analyse current treatment concepts:
chance for optimisation by better imaging?

establish methods to use new imaging for new concept:
technical implementation, workflow …

clinical trials (feasibility? effectivity?)



Serve:

Establish new standards for safe routine use

Medical imaging in radiation oncology

- Imaging for diagnosis and staging:
  - treatment indication

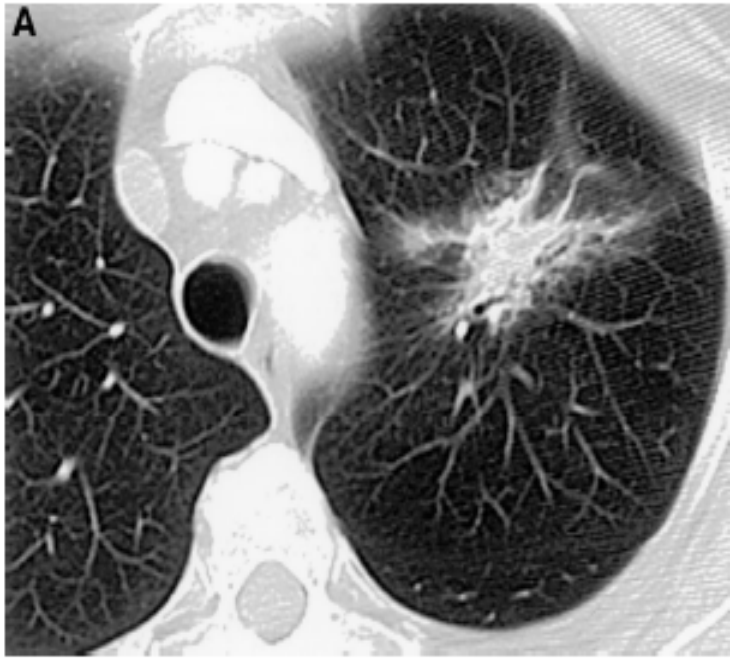
- imaging for radiotherapy planning
  - target (GTV – CTV – PTV)
  - normal tissues
  - movements

- Imaging during RT application
  - repositioning
  - adaptive radiotherapy
  - normal tissue reactions

- imaging during follow up
  - response
  - recurrence
  - normal tissue injury

Morphological assessment of response

How large is this tumor?



40 tumors, 5 radiologists
Interobserver variability: 140%
Intraobserver variability: 37%

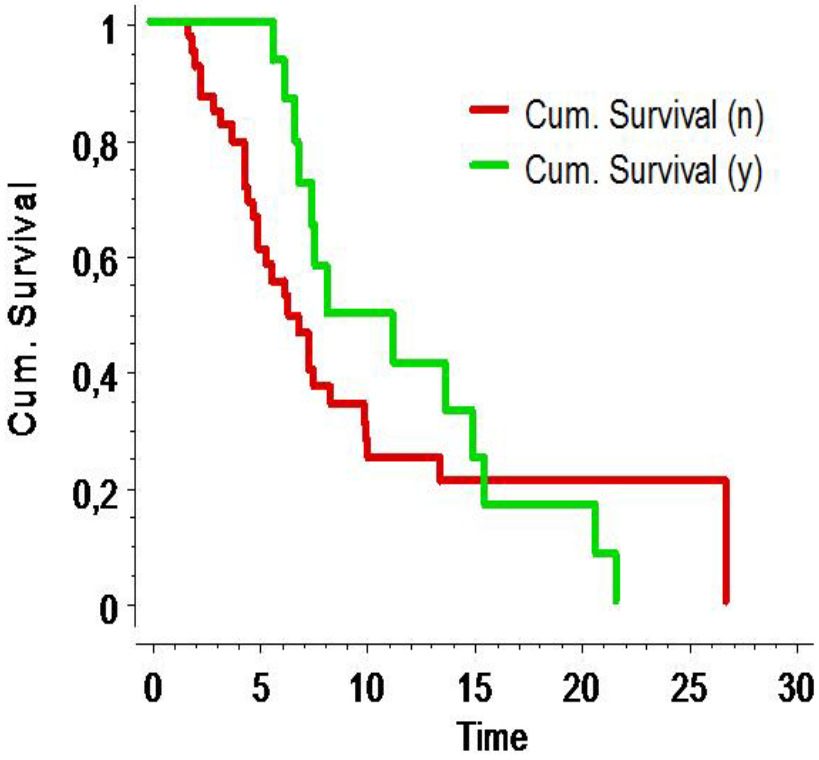
Assessment of PD in CT

Unidimensional	
Minimum RD, %	0.00
Maximum RD, %	50.00
Median RD, %	5.20
No. of misclassifications	7
% of tumors	17.50
Bidimensional	
Minimum RD, %	0.00
Maximum RD, %	183.33
Median RD, %	8.74
No. of misclassifications	9
% of tumors	22.50

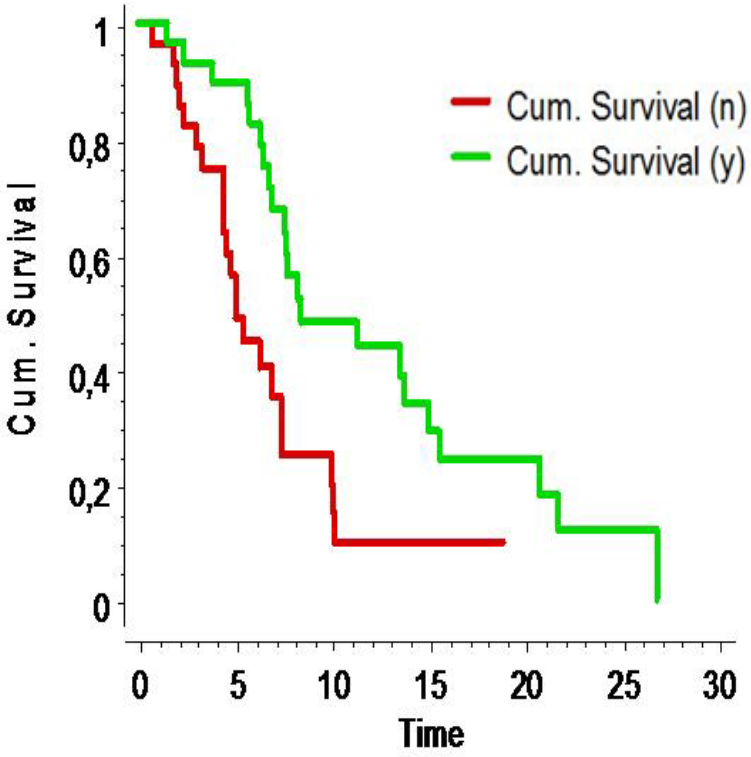
Erasmus, JCO 2003

“Functional” response assessment

CT response after 2 cycles



PET response after 1 cycle



Data from Weber, JCO 2003

Thanks to

A.L. Grosu, Freiburg
W. Weber, Freiburg
M. Mix, Freiburg
G. Bruggmoser, Freiburg
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L. Kuder, Freiburg
K. Schumm, Freiburg
C. Doll, Erlangen

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R. Kluge, Leipzig
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A. Schaefer, Homburg
S. Kremp, Homburg
D. Hellwig, Homburg
A. Grgic, Homburg

B. Reymen, Maastricht
D. DeRuysscher, Leuven
W. Vogel, Amsterdam
N. Picchio, Milano

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Università Cattolica del Sacro Cuore

Gemelli ART
Advanced Radiation Therapy

UNIVERSITÀ CATTOLICA del Sacro Cuore

MRI in treatment planning

N. Dinapoli

ESTRO School

Introduction:
MRI – why, where, when?

- Traditional planning procedures use CT images to calculate dose distribution.
- This is because extraction images process of CT is based on X-rays interaction with matter
- The **informations** that CT can give for planning are of **three types:**
  - **Geometry**
  - **Density**
  - **Atomic number**

Electron density maps

Dose distribution calculation

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Introduction:
MRI – why, where, when?

- **Advantages of MRI:**
  - Better contrast definition
  - Better “chemical” description of the matter structure
  - Better definition of **functional** aspects of the tissues (tumor and OAR) that is **physiology** of the tissues

Introduction:
MRI – why, where, when?

- **MRI sequences**
  - **Traditional** (relaxation time)**:**
    - **T1w**
    - **T2w**
  - **Functional** (post-processing)**:**
    - **DWI**
    - **DTI**
    - **PWI**
    - **SMR**

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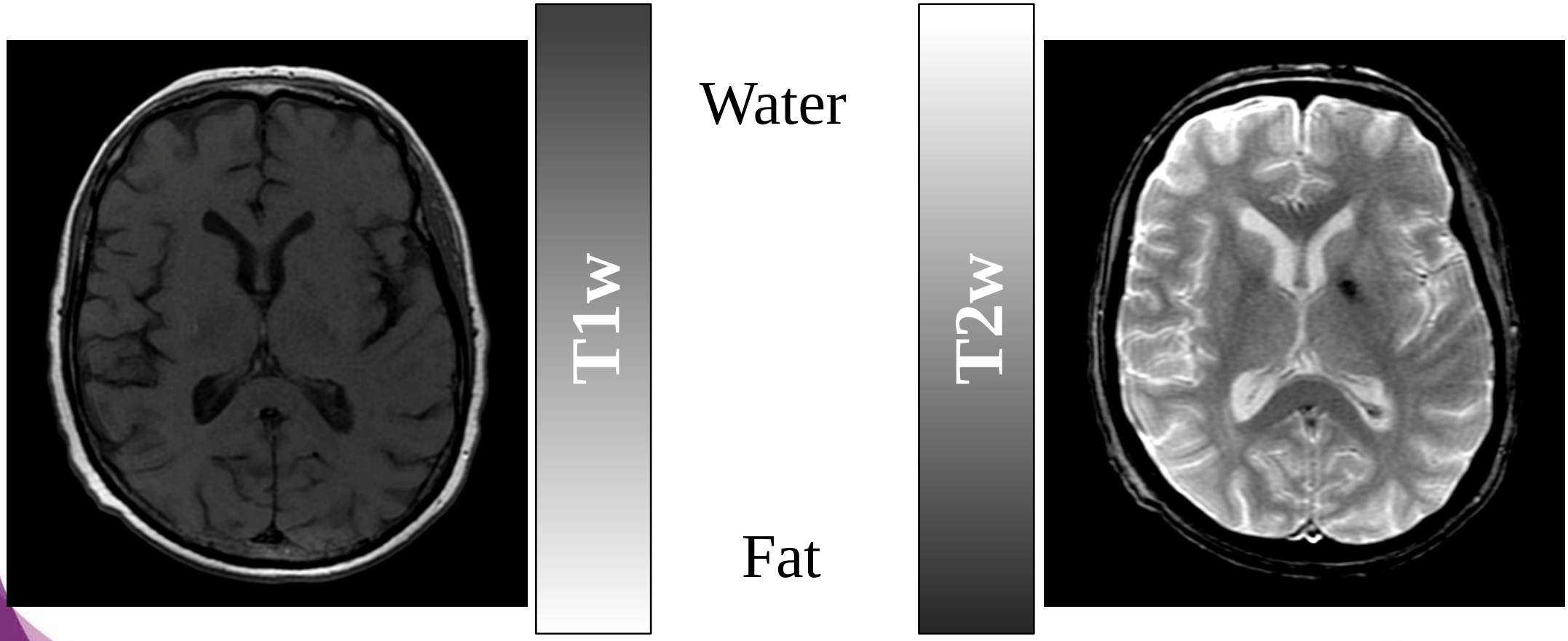
Introduction:
MRI – why, where, when?

- MRI T1w T2w images:



No signal: air, cortical bone

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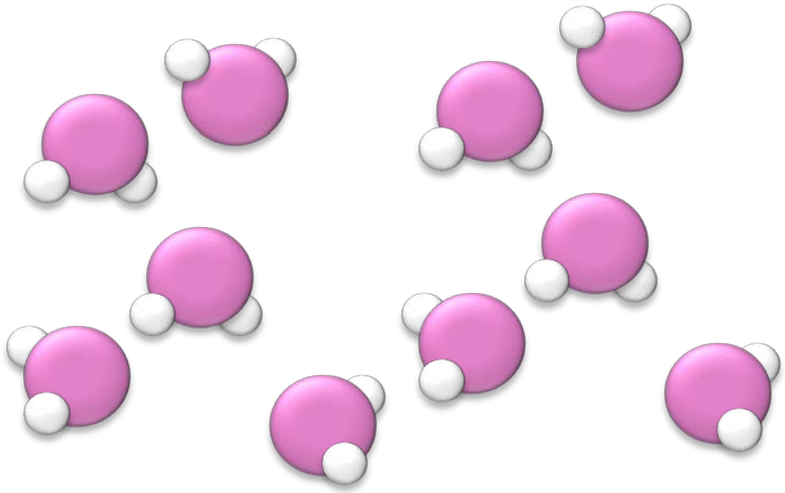
Functional imaging modalities in MRI

- Functional MRI: imaging modalities that focus on physiological/chemical features of tissues and vascularization, rather than morphology
  - Diffusion weighted MRI **DWI**
  - Diffusion tensor imaging **DTI**
  - Perfusion MRI **PWI**
  - Spectroscopy MRI **SMR**

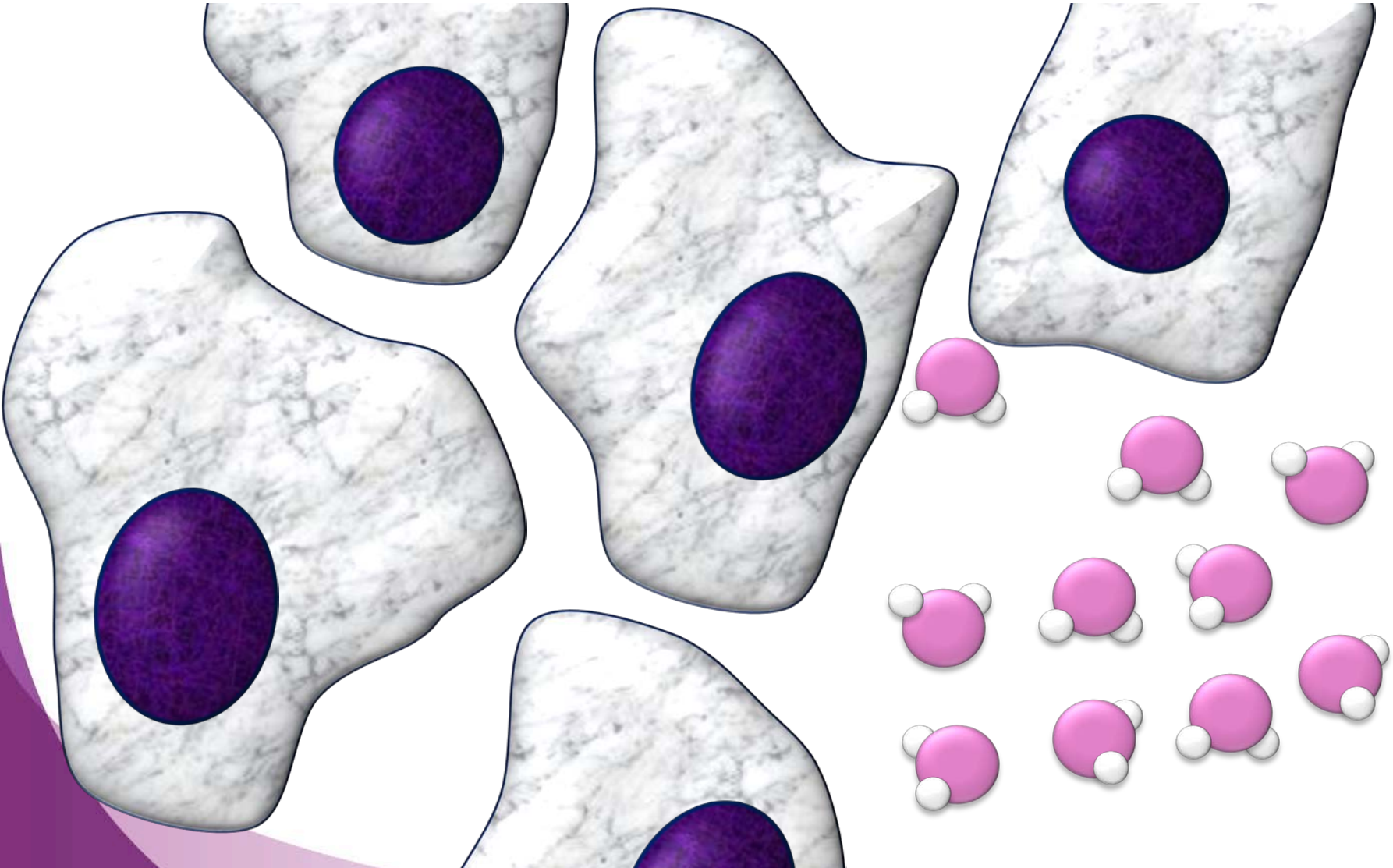
DWI images

- Rationale
  - In biological tissues H2O molecules produce random micro-movements due to the thermal energy (Brownian movements)
  - In DWI images can be obtained by analyzing this kind of movements
  - The micro-diffusion of water molecules gives informations about the normal and pathologic tissues structure



DWI images – ADC maps

- High cellularity – Lower Apparent Diffusion Coefficient (ADC)



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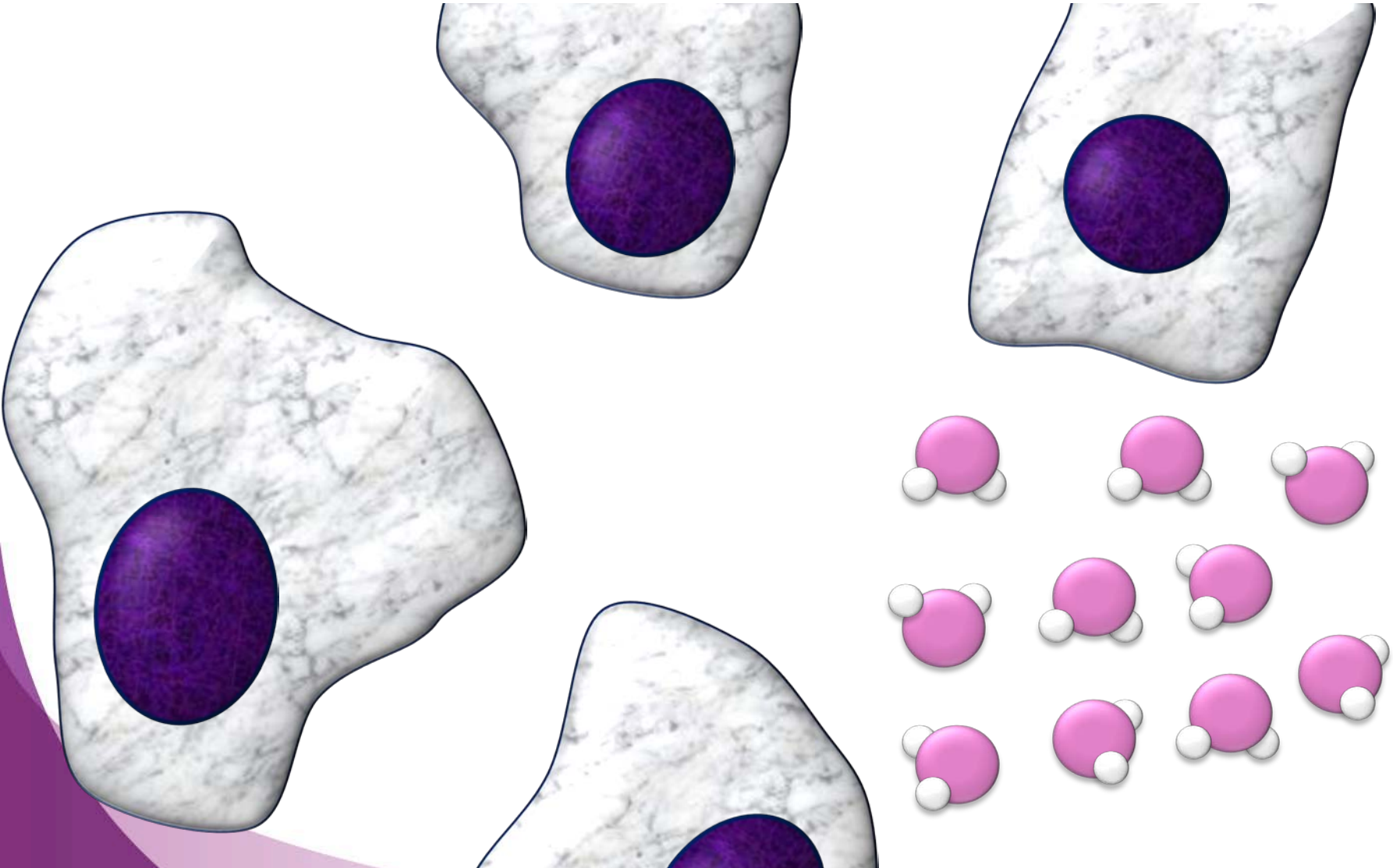
DWI images – ADC maps

- Low cellularity – Higher Apparent Diffusion Coefficient (ADC)



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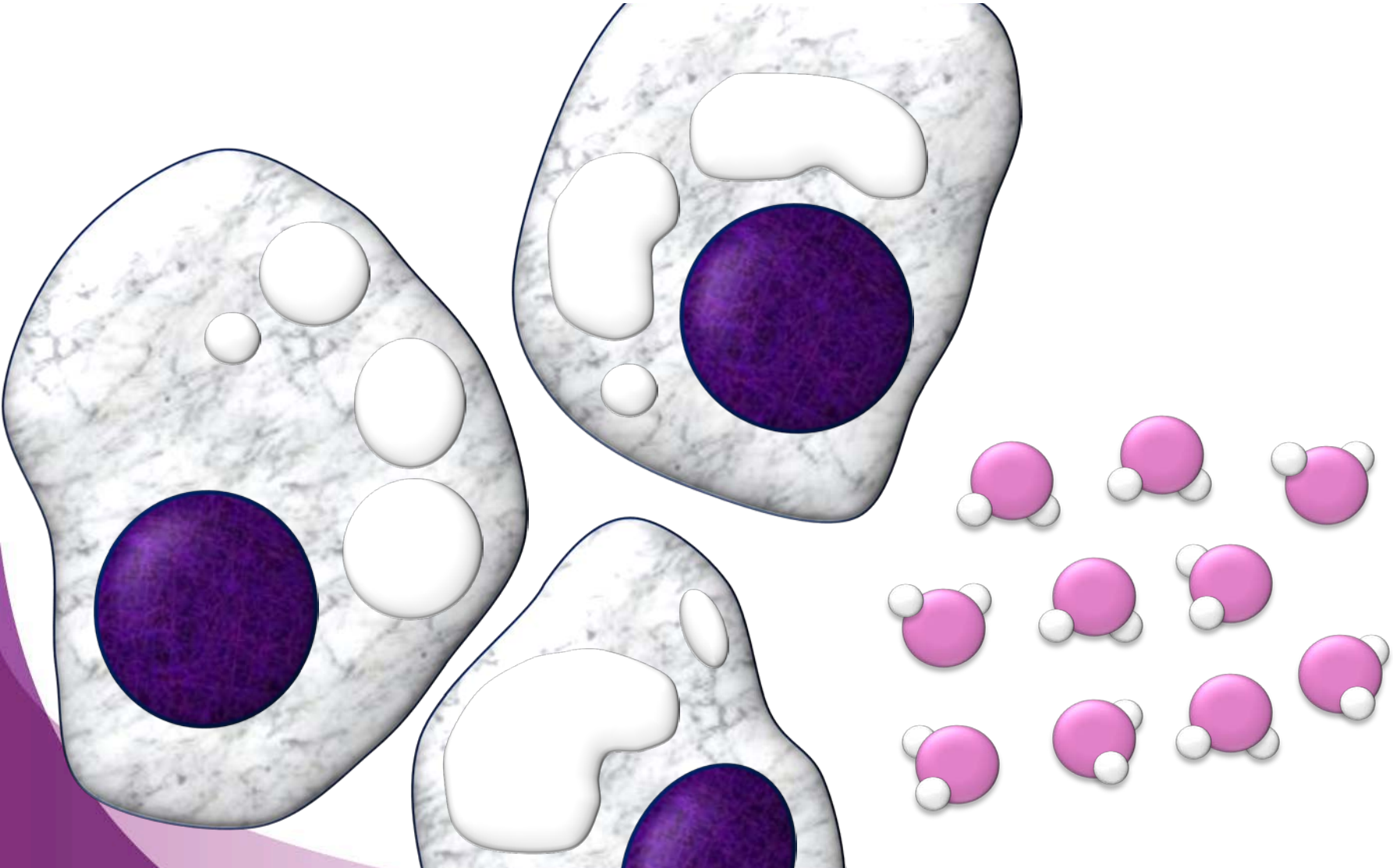
DWI images – ADC maps

- Intracellular edema – Lower Apparent Diffusion Coefficient (ADC)



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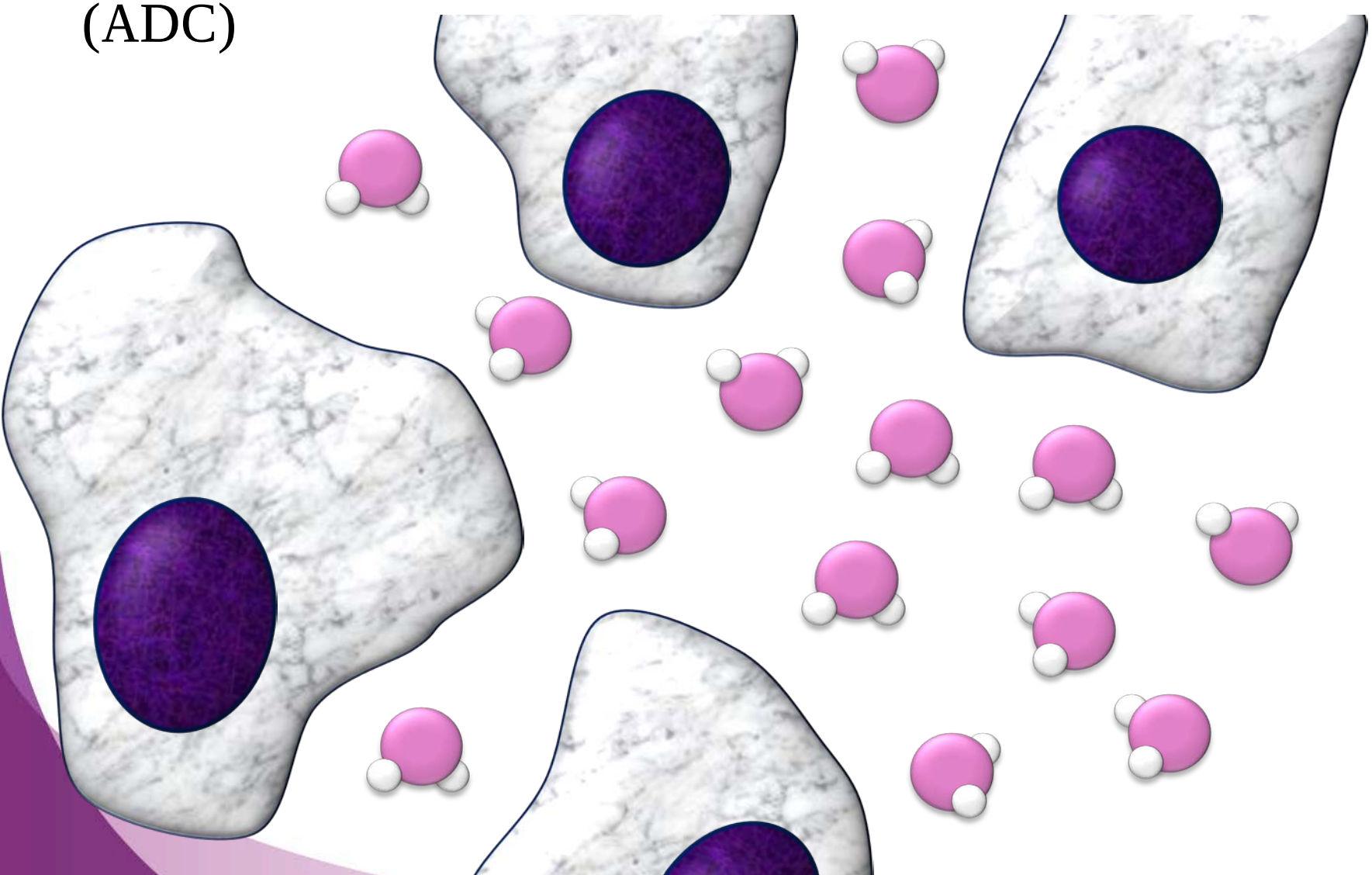
DWI images – ADC maps

- Extracellular edema – Higher Apparent Diffusion Coefficient (ADC)



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DWI images – ADC maps

- ADC mapping allows to obtain more informations on the biological "nature" of the tissues
  - Acute lesion (ischemic) ➡ oedema ➡ ▼ ADC
  - Chronic lesion (post-ischemic) ➡ relaxing tissues ➡ ▲ ADC
  - Neoplastic lesions ➡ high cellularity ➡ ▼ ADC
  - Neoplastic lesions ➡ necrosis ➡ ▲ ADC

I Berry. Imagerie par résonance magnétique. 2004; Masson Editeur, Paris.

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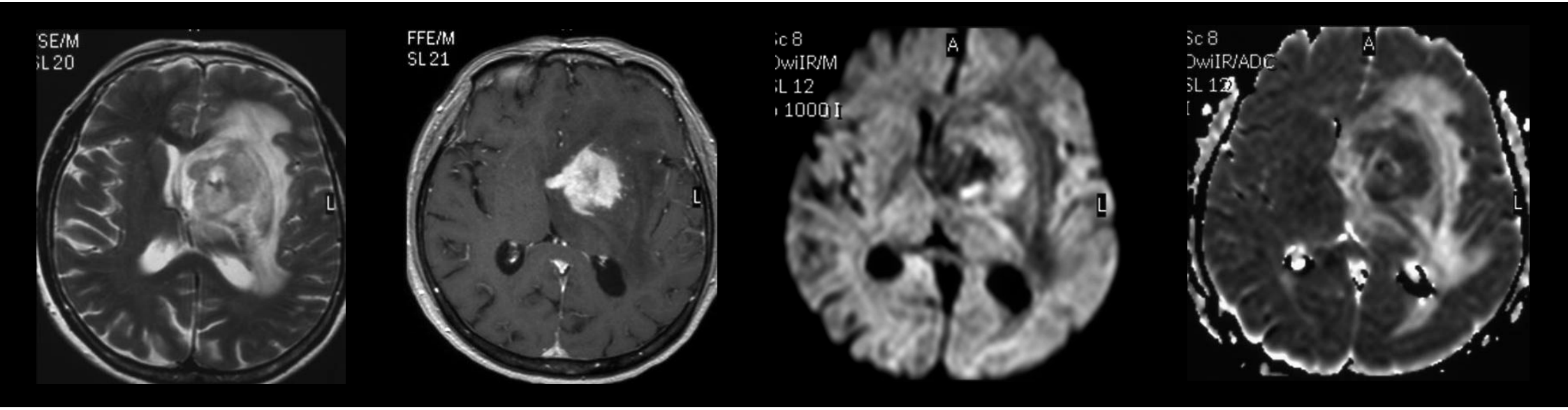
DWI images – ADC maps

T2 low signal CE DWI ▼ADC



High cellularity ➡ Primary Brain Lymphoma

Courtesy of C. Colosimo. Inst. of Radiology/Neuroradiology. UCSC - Rome

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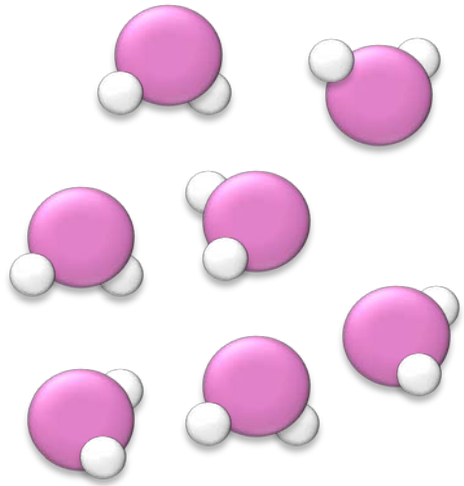
Diffusion tensor imaging - DTI

- Rationale: anisotropic DWI
  - Random movements of H2O molecules can be “driven” by anatomical structures in a subcellular scale



Axon or **Myocite**

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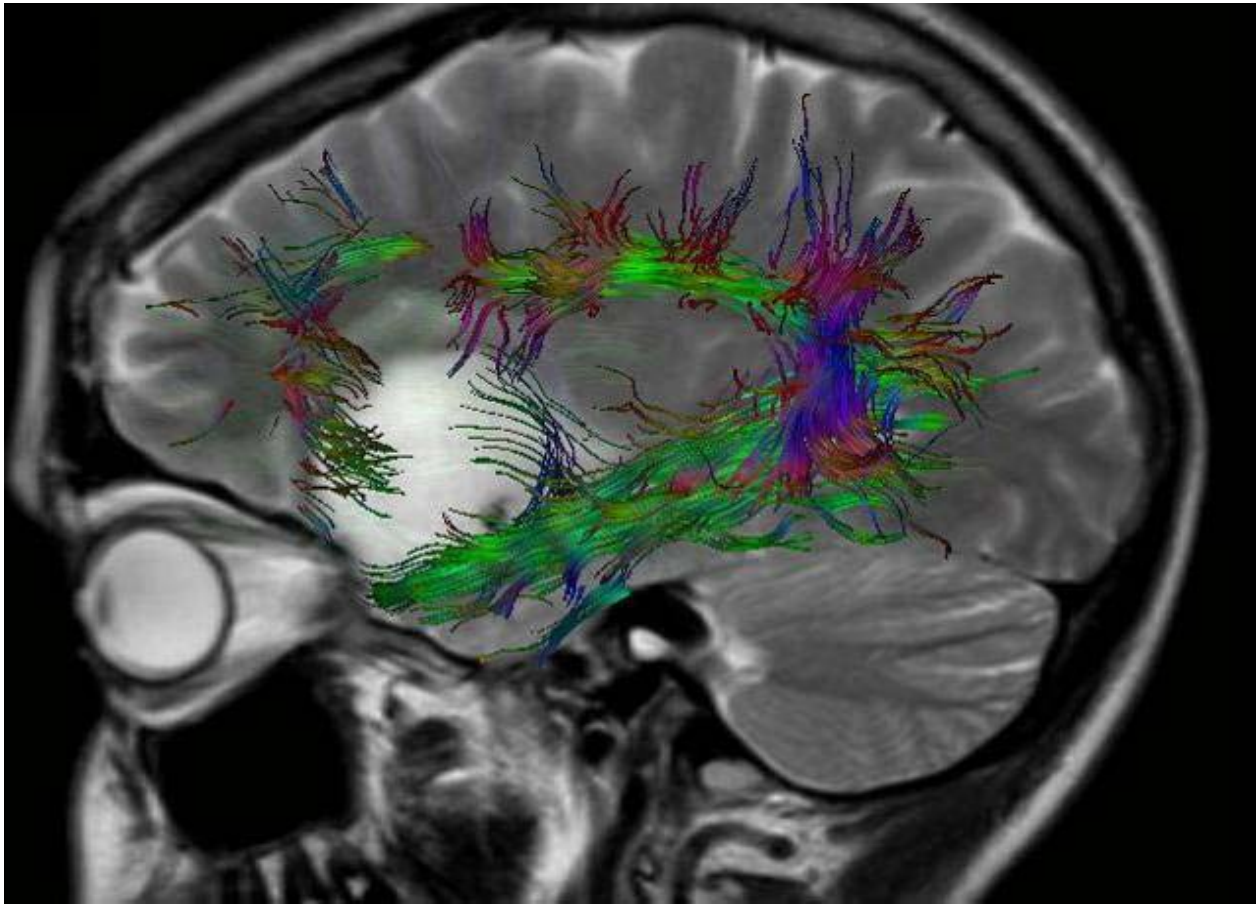
Diffusion tensor imaging - DTI

- Fibers pathway reconstruction around a tumor



Courtesy of C. Colosimo. Inst. of Radiology/Neuroradiology. UCSC - Rome

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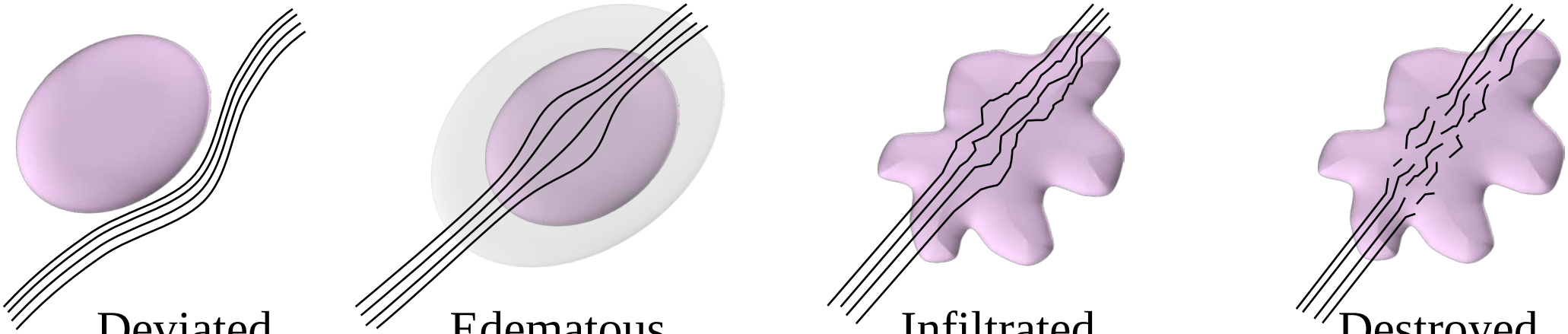
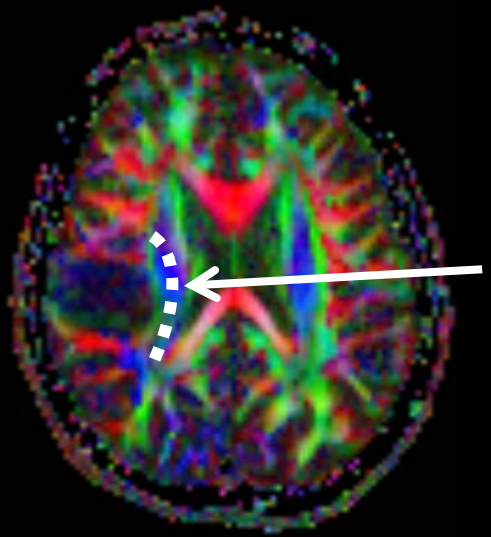
Diffusion tensor imaging - DTI

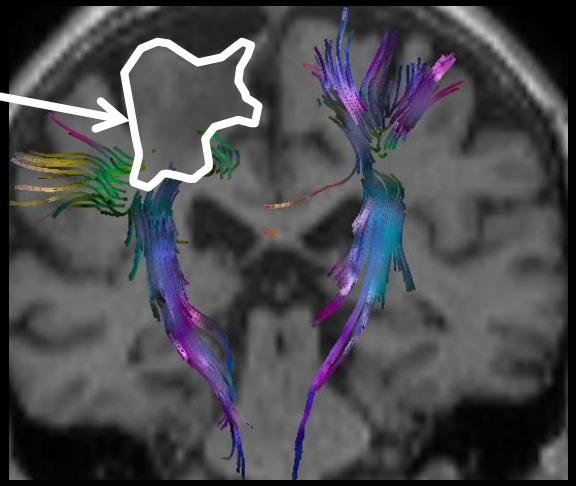
- Relationship among tumor and fibers





Deviation:
ODG

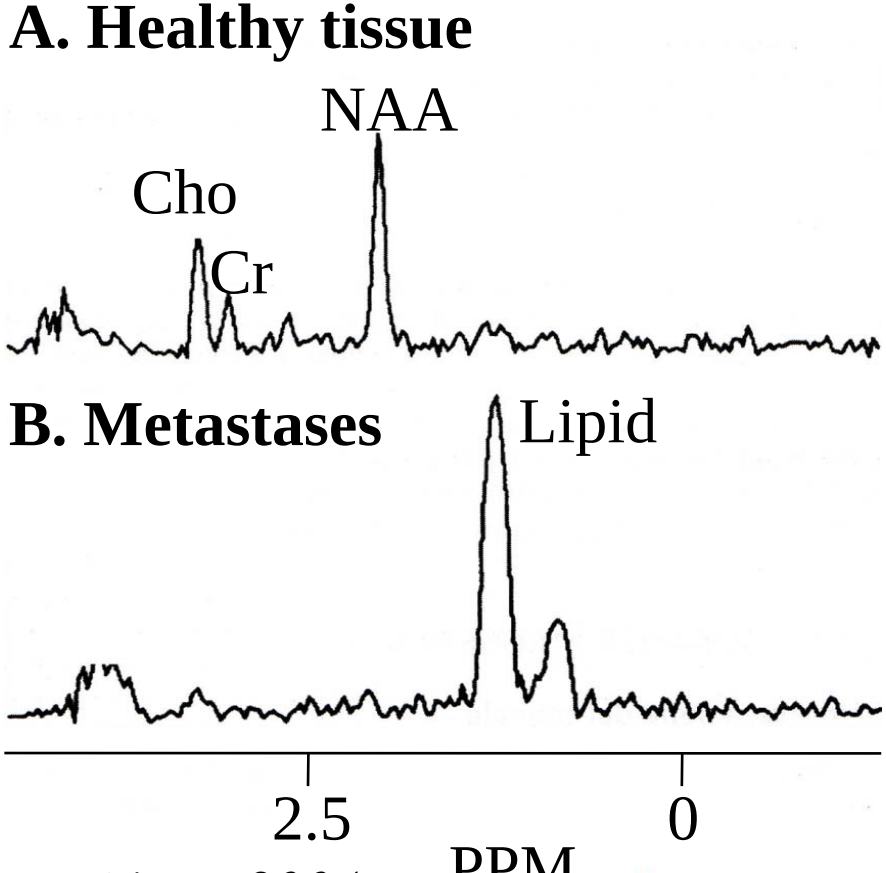
Infiltration –
destruction:
ALL localization



Modified from C. Colosimo. Inst. of Radiology/Neuroradiology. UCSC - Rome

Spectroscopic Magnetic Resonance

- Rationale
  - Chemical analysis of voxels focusing some metabolites
  - Distinction between fatty molecules, choline and aminoacid derived metabolites



I Berry. Imagerie par résonance magnétique. 2004; Masson Editeur, Paris.

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Perfusion weighted images - PWI

- Rationale
  - Brain perfusion represents the steady state blood delivery (i.e. nutrients and oxygen) through capillary bed (GM= 60 ml/100g/min)
  - Post-contrast enhancement on T1-WI depicts only disruption/absence of BBB
  - PWI (P-CT) can truly assess brain perfusion and relies on "central volume theory", depending on multiple factors and reflecting the capillary density/richness

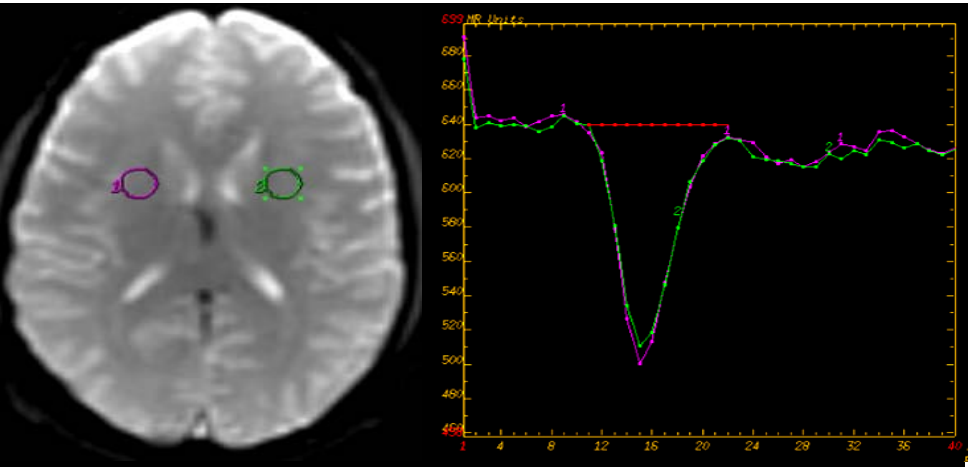
Courtesy of C. Colosimo. Inst. of Radiology/Neuroradiology. UCSC - Rome

Perfusion weighted images - PWI

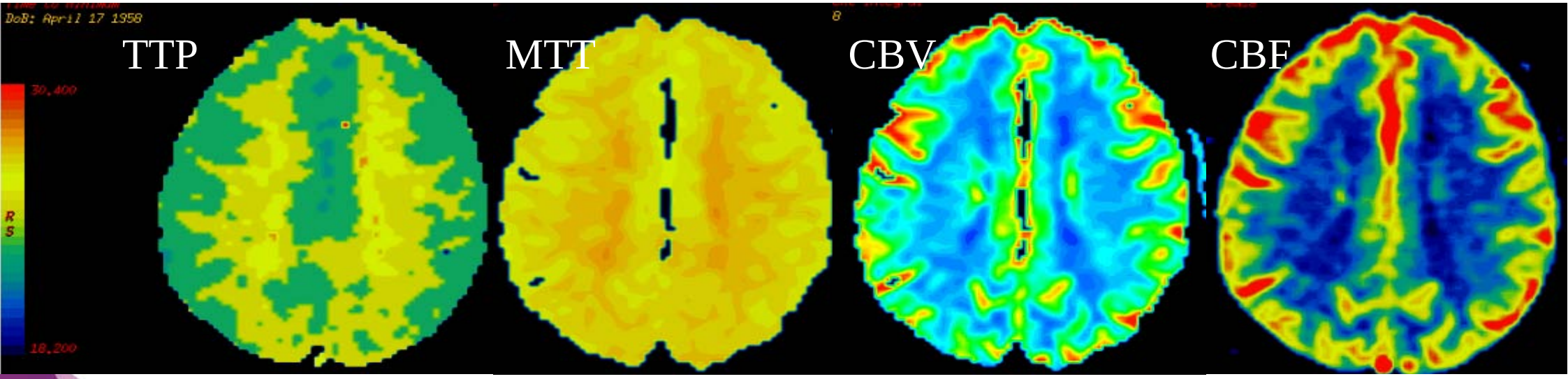
- Rationale
  - The most accepted method is based on the so-called Dynamic Susceptibility Contrast Technique (**DSCT**)
  - DSCT is performed by bolus injection of Gd chelate, assessing the first pass of CM through the brain, but obtaining also data regarding permeability ("leakage")
  - CM must be injected at 5-6 ml/sec rate in order to obtain a compact bolus and generate valuable **color maps** of cerebral blood volume (**CBV**), time to peak (**TTP**), mean transit time (**MTT**) and **CBF** (cerebral blood flow = CBV/MTT)

Courtesy of C. Colosimo. Inst. of Radiology/Neuroradiology. UCSC - Rome

Perfusion weighted images - PWI



Based on the curve and the analysis method,the software generates color maps:



Courtesy of C. Colosimo. Inst. of Radiology/Neuroradiology. UCSC - Rome

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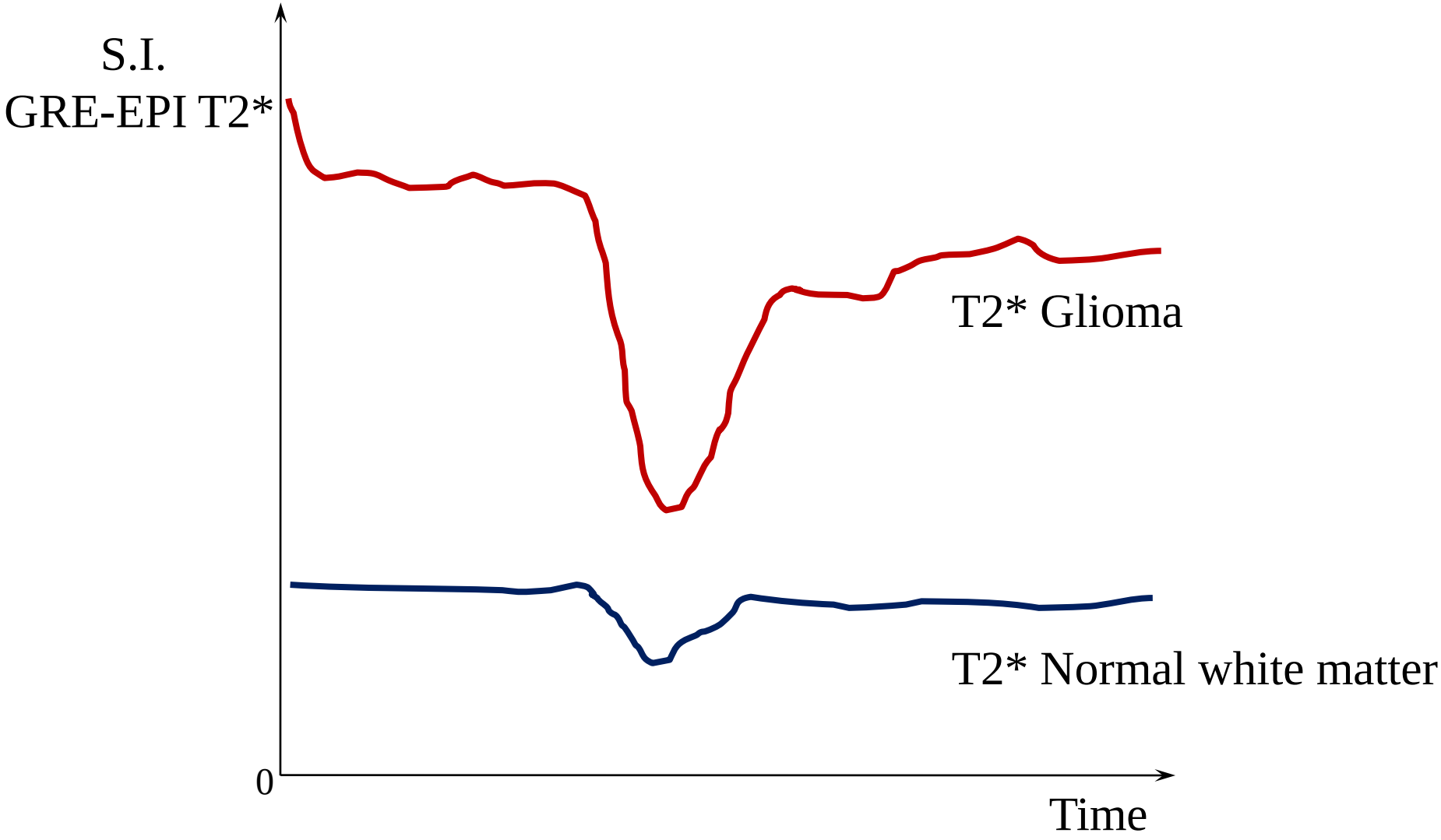
Perfusion weighted images - PWI



Courtesy of C. Colosimo. Inst. of Radiology/Neuroradiology. UCSC - Rome

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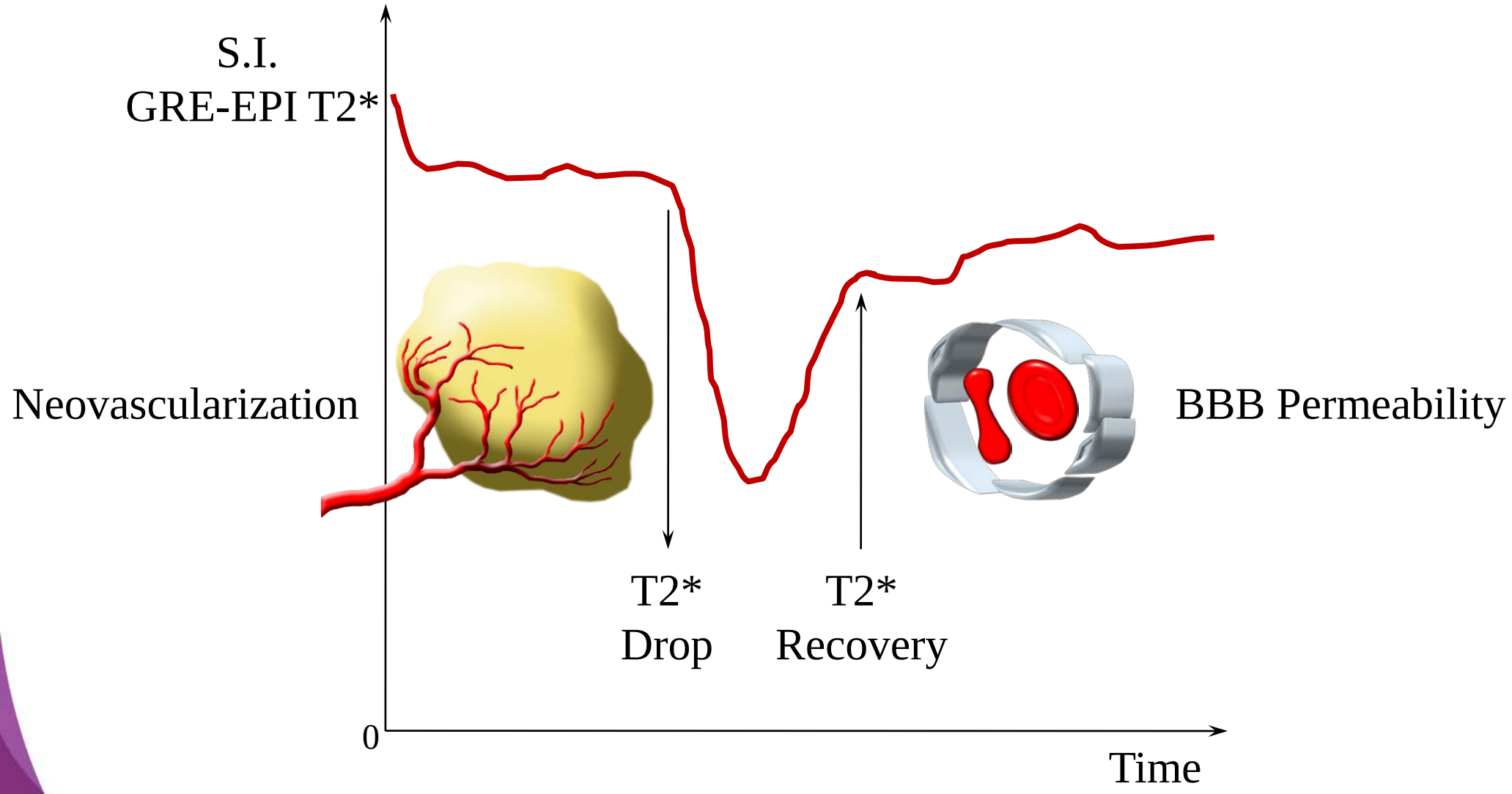
Perfusion weighted images - PWI



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New MRI imaging modalities and radiotherapy planning

- When using new MRI imaging modalities?
  1. Refining the GTV (**targeting**)

     ⇩

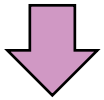
     - Dose escalation protocols

     ⇩

     - Dose distribution-imaging adaptation for simultaneous or sequential boost treatments
  2. Direct **planning** on MRI images
  3. Hybrid machines

New MRI imaging modalities and radiotherapy planning

- When using new MRI imaging modalities?
  1. Refining the GTV (**targeting**)



     - Dose escalation protocols

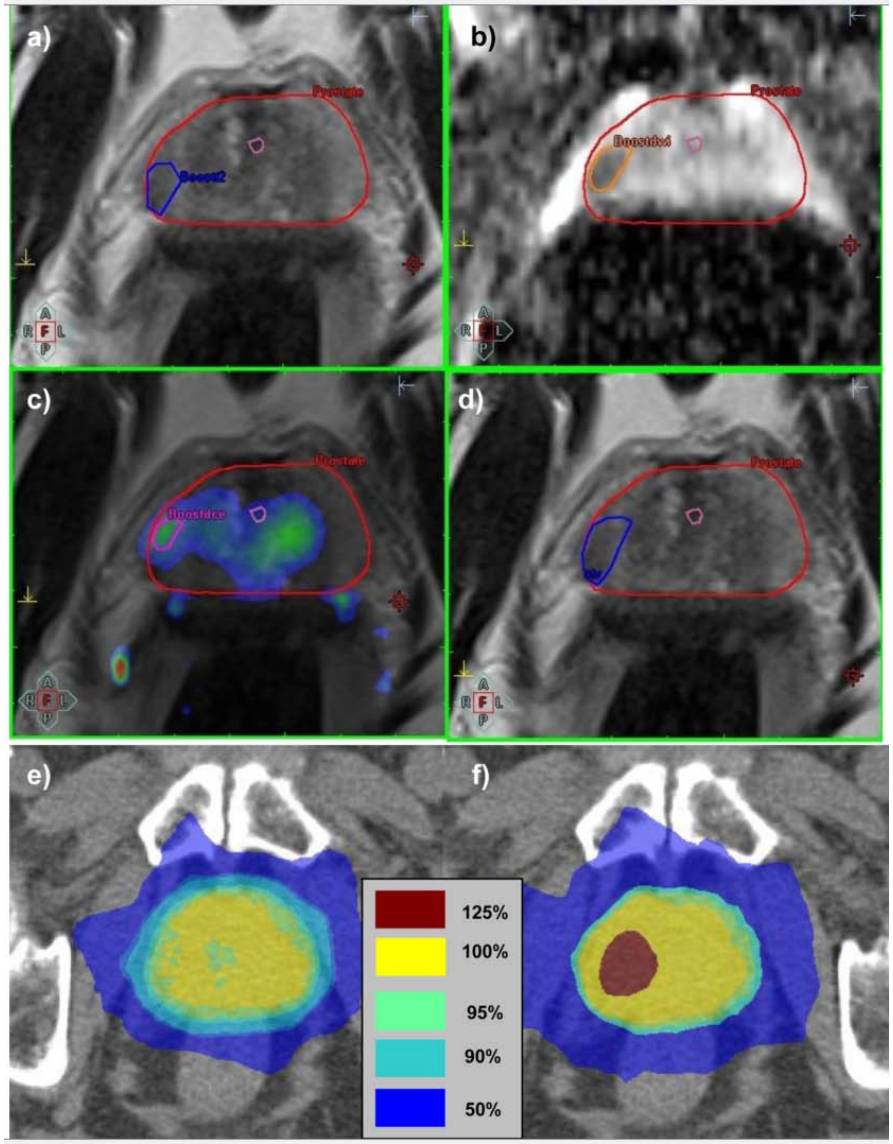
     - Dose distribution-imaging adaptation for simultaneous or sequential boost treatments
  2. Direct **planning** on MRI images
  3. Hybrid machines

1. MRI for targeting: prostate

- Prostate cancer treatment
  - Boosting dominant intraprostatic lesions (DILs) in the context of stereotactic ablative radiation therapy (SABR)
  - T2-weighted, dynamic contrast-enhanced and diffusion-weighted magnetic resonance imaging
  - Prostate planning target volume (PTV) prescription: 42.7 Gy in 7 fractions (6.1 Gy/fr)
  - Median PTV_{DIL} prescription: 125% (range: 110%-140%)

LJ Murray et al. Prostate Stereotactic Ablative Radiation Therapy Using Volumetric Modulated Arc Therapy to Dominant Intraprostatic Lesions. Int J Radiation Oncol Biol Phys, Vol. 89, No. 2, pp. 406e415, 2014

1. MRI for targeting: prostate



(a) T2w CTV
(b) DWI CTV
(c) DCE CTV
} (d) Combined CTV

(e) Planning without PTV_{DIL}

(f) Planning with PTV_{DIL}

Technically feasible

Uncertainties due to image registration and positioning

LJ Murray et al. Prostate Stereotactic Ablative Radiation Therapy Using Volumetric Modulated Arc Therapy to Dominant Intraprostatic Lesions. Int J Radiation Oncol Biol Phys, Vol. 89, No. 2, pp. 406e415, 2014

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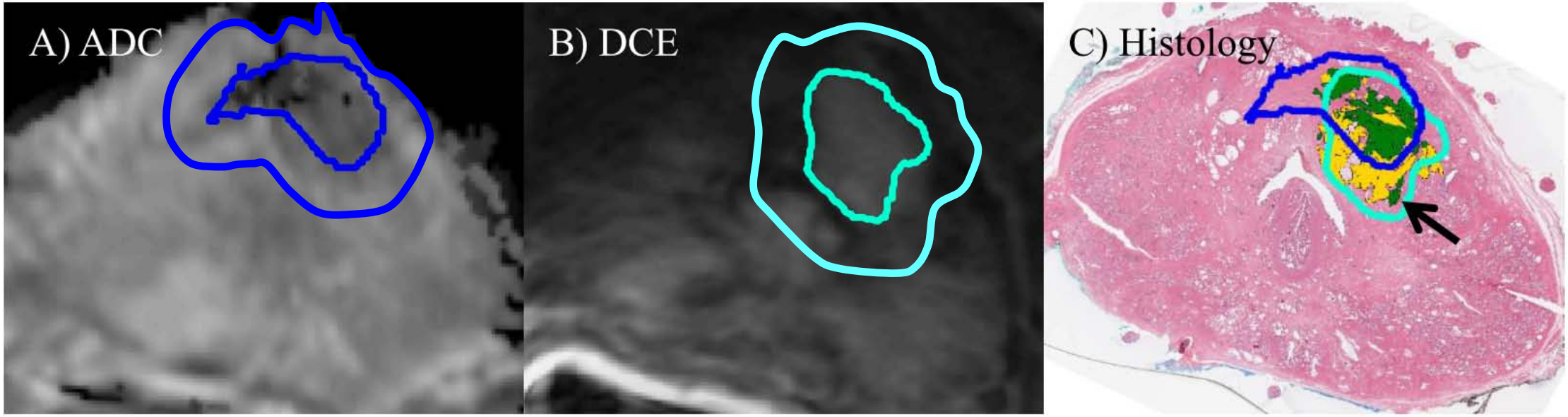
1. MRI for targeting: prostate



A. ADC GTV

B. DCE GTV

C. Histology reference GTV: Gleason 7, Gleason 6

Gibson E, Bauman GS, Romagnoli C, et al. Toward Prostate Cancer Contouring Guidelines on Magnetic Resonance Imaging: Dominant Lesion Gross and Clinical Target Volume Coverage Via Accurate Histology Fusion. Int J Radiat Oncol. 2016;96:188–196.

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1. MRI for targeting: prostate

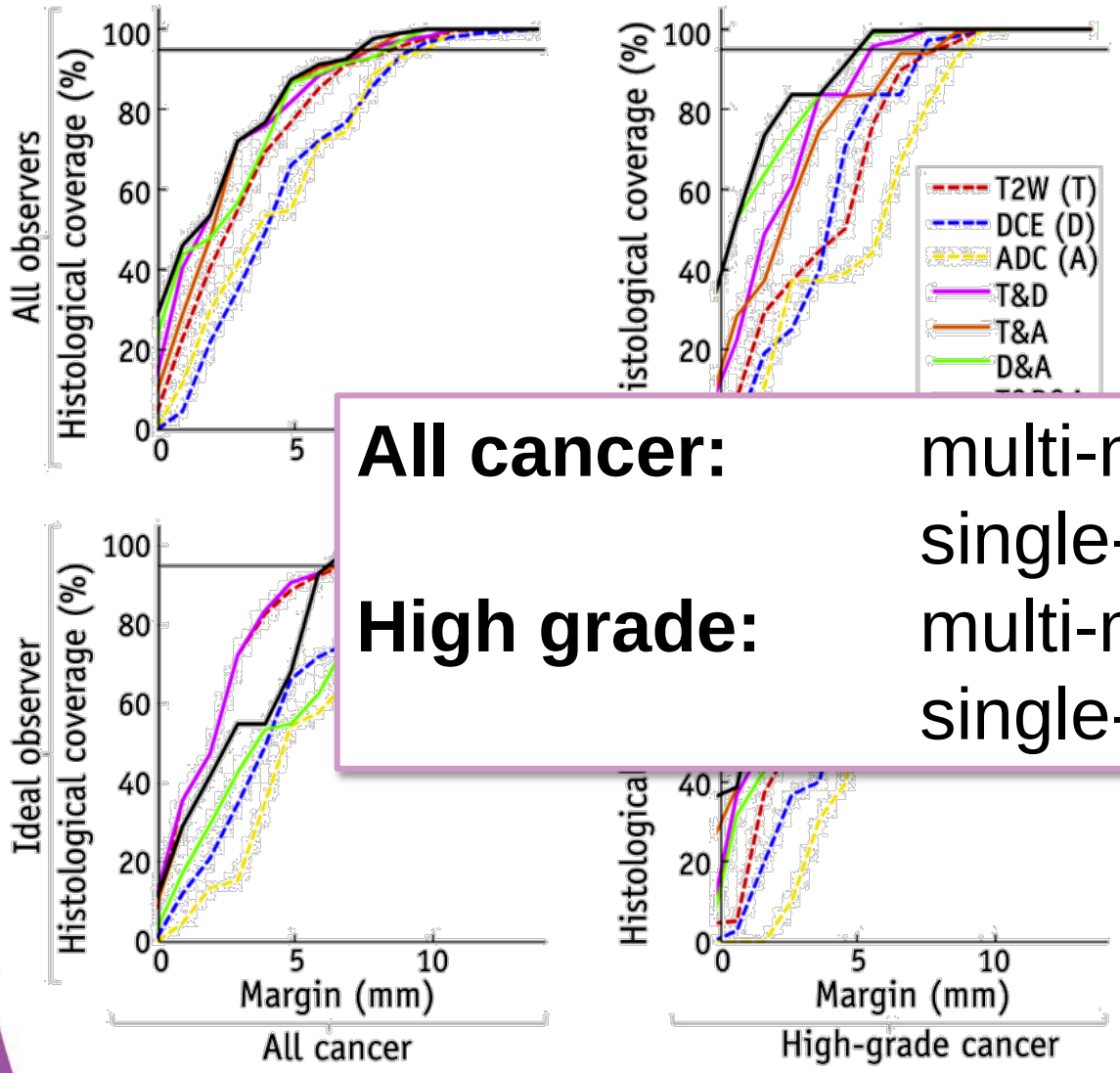

Table 2 Isotropic margins to cover 95% of histologic cancer for prospective case and proportion of prostate tissue spared by CTVs with such margins

	All cancer		High-grade cancer	
CTV type	95% Coverage margin, mm	Median spared tissue, %	95% Coverage margin, mm	Median spared tissue, %
T, A, and D	8	58-69	6	68-79
				55-68
				71-81
				70-80
				60-71
				53-67
				64-77

t; CTV = clinical
= T2 weighted.

Spared tissue is reported as the range (across observers) of the median proportion of prostate tissue not covered by CTVs. These 95% coverage margins account for interobserver and intertumor variability in the required boundary expansions, as necessary for development of guidelines to be used for future patients in prospective studies. CTV types are denoted by magnetic resonance imaging sequence (combinations of T, A, and D).

All cancer: multi-modality **8 mm**
single-modality **9-10 mm**

High grade: multi-modality **6-9 mm**
single-modality **9-10 mm**

Gibson E, Bauman GS, Romagnoli C, et al. Toward Prostate Cancer Contouring Guidelines on Magnetic Resonance Imaging: Dominant Lesion Gross and Clinical Target Volume Coverage Via Accurate Histology Fusion. Int J Radiat Oncol. 2016;96:188–196.

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1. MRI for targeting: cervix

- Planning Intensity Modulated Arc-Therapy in cervical cancer
- MRI is optimal imaging for GTV (T + N) detection in cervix cancer
- Combination with PET-CT can increase targeting accuracy (sens. + spec.)

K Vandecasteele et al. Intensity-Modulated Arc Therapy with Simultaneous Integrated Boost in the Treatment of Primary Irresectable Cervical Cancer. Strahlenther Onkol 2009;185:799–807

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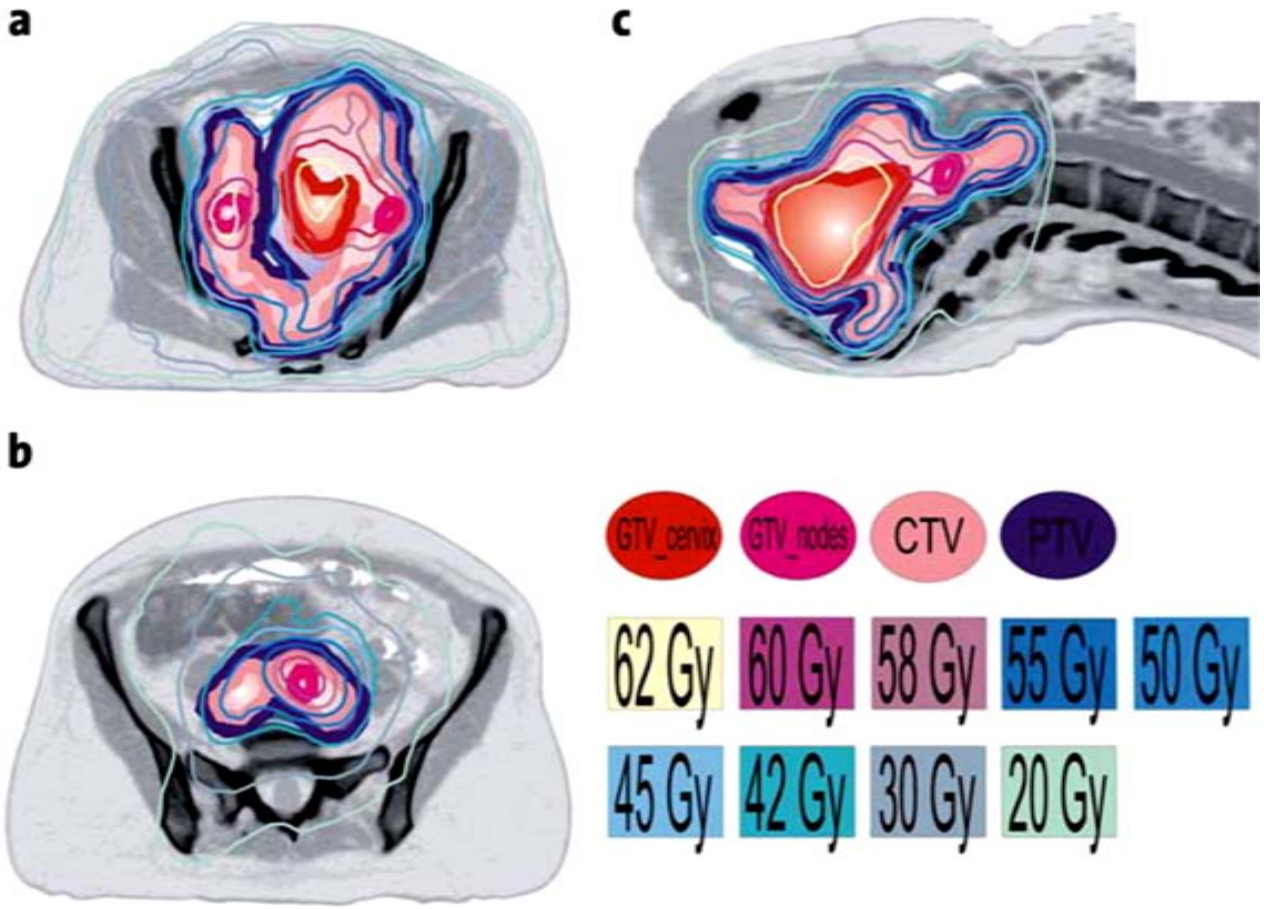
1. MRI for targeting: cervix

- Dose limiting structures: small bowel, bladder, rectum



K Vandecasteele et al. Intensity-Modulated Arc Therapy with Simultaneous Integrated Boost in the Treatment of Primary Irresectable Cervical Cancer. Strahlenther Onkol 2009;185:799–807

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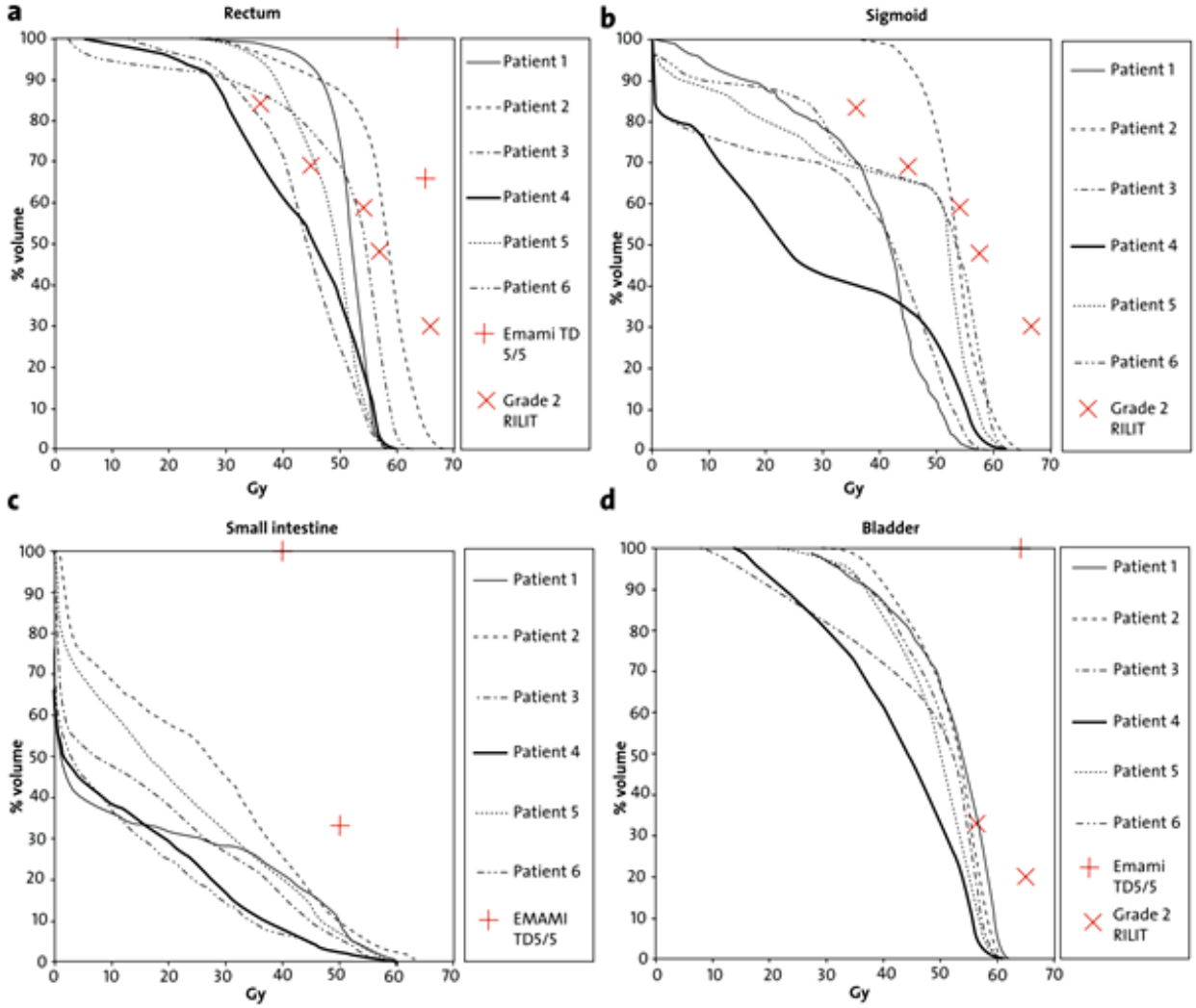
1. MRI for targeting: cervix

- Better sparing of OAR



K Vandecasteele et al. Intensity-Modulated Arc Therapy with Simultaneous Integrated Boost in the Treatment of Primary Irresectable Cervical Cancer. Strahlenther Onkol 2009;185:799–807

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1. MRI for targeting: brain

- Brain tumors (Low grade or High grade astrocitomas)
- 10 patients
- Comparison of 3D-CRT, 3D-CRT fMRI based, **IMRT** fMRI based
- Evaluation of **dosimetric** and **radiobiological** endpoints

A Kovacs et al. Simultaneous MRI Integrating functional MRI information into conventional 3D radiotherapy planning of CNS tumors. Is it worth it? J Neurooncol (2011) 105:629–637.

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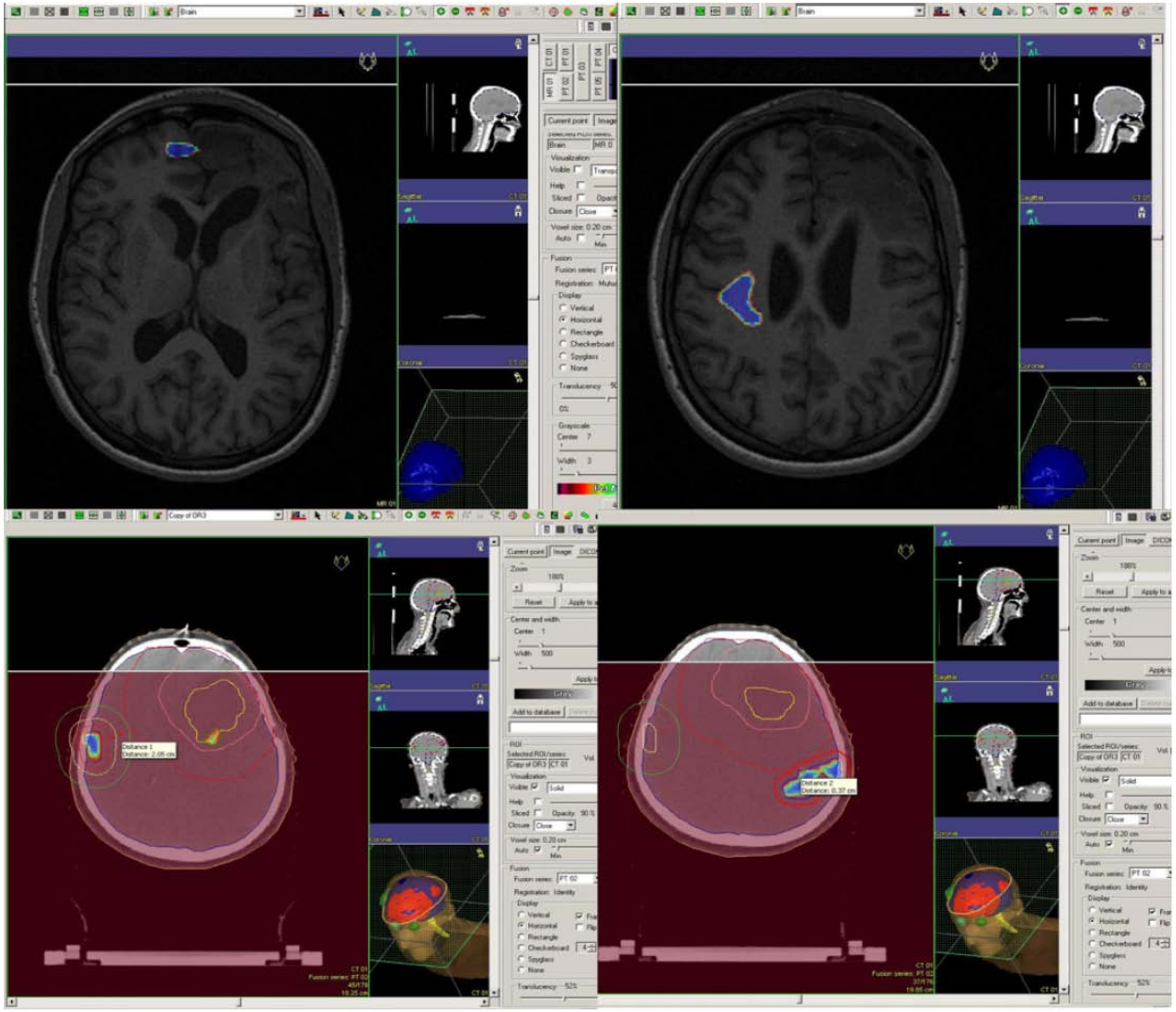
1. MRI for targeting: brain



1. MRI for targeting: brain

OR mean doses based on PR-PTV distance grouping

	3D without fMRI	3D with fMRI	Wilcoxon matched pairs test	3D without fMRI	IMRT with fMRI	Wilcoxon matched pairs test	3D with fMRI	IMRT with fMRI	Wilcoxon matched pairs test
OR–PTV distance less than 1 cm ($n = 10$)									
Mean	40.23	27.71	**0.016605**	40.23	21.91	**0.006911**	27.71	21.91	**0.005062**
Median	44.15	23.49		44.15	19.29		23.49	19.29	
SD	18.25	15.14		18.25	14.88		15.14	14.88	
OR–PTV distance 1–2 cm ($n = 7$)									
Mean	29.77	22.23	0.398025	29.77	12.97	**0.017961**	22.23	12.97	**0.062980**
Median	30.42	20.23		30.42	10.90		20.23	10.90	
SD	7.19	15.04		7.19	6.47		15.04	6.47	
OR–PTV distance greater than 2 cm ($n = 21$)									
Mean	18.72	8.64	**0.001021**	18.72	9.19	**0.000069**	8.64	9.19	**0.663947**
Median	19.76	10.43		19.76	8.41		10.43	8.41	
SD	8.14	6.16		8.14	4.70		6.16	4.70	

The use of fMRI information resulted in a better sparing effect on ORs in all subgroups. When the conventional 3D-based method was compared with IMRT, only the OR–PTV distance less than 1 cm (red zone) was significantly superior in favour of IMRT

Bold values indicate highly significant differences

1. MRI for targeting: brain

- Better results of IMRT fMRI based when PTV-OAR distance < 1 cm
- Better results of IMRT fMRI based in sparing optic tract or brainstem

1. MRI for targeting: brain

- fMRI tractography used to optimize CyberKnife SRS on brain lesions
- 4 patients: arteriovenous malformation (AVM), astrocytoma, brain metastasis, hemangioma
- Tractography used to identify critical brain sites as 17 Brodmann area (visual cortex), motor cortex, pyramidal tracts or optic tract

E Pantelis et al. Integration of functional MRI and white matter tractography in stereotactic radiosurgery clinical practice. Int J Radiat Oncol Biol Phys. 2010 Sep 1;78(1):257-67

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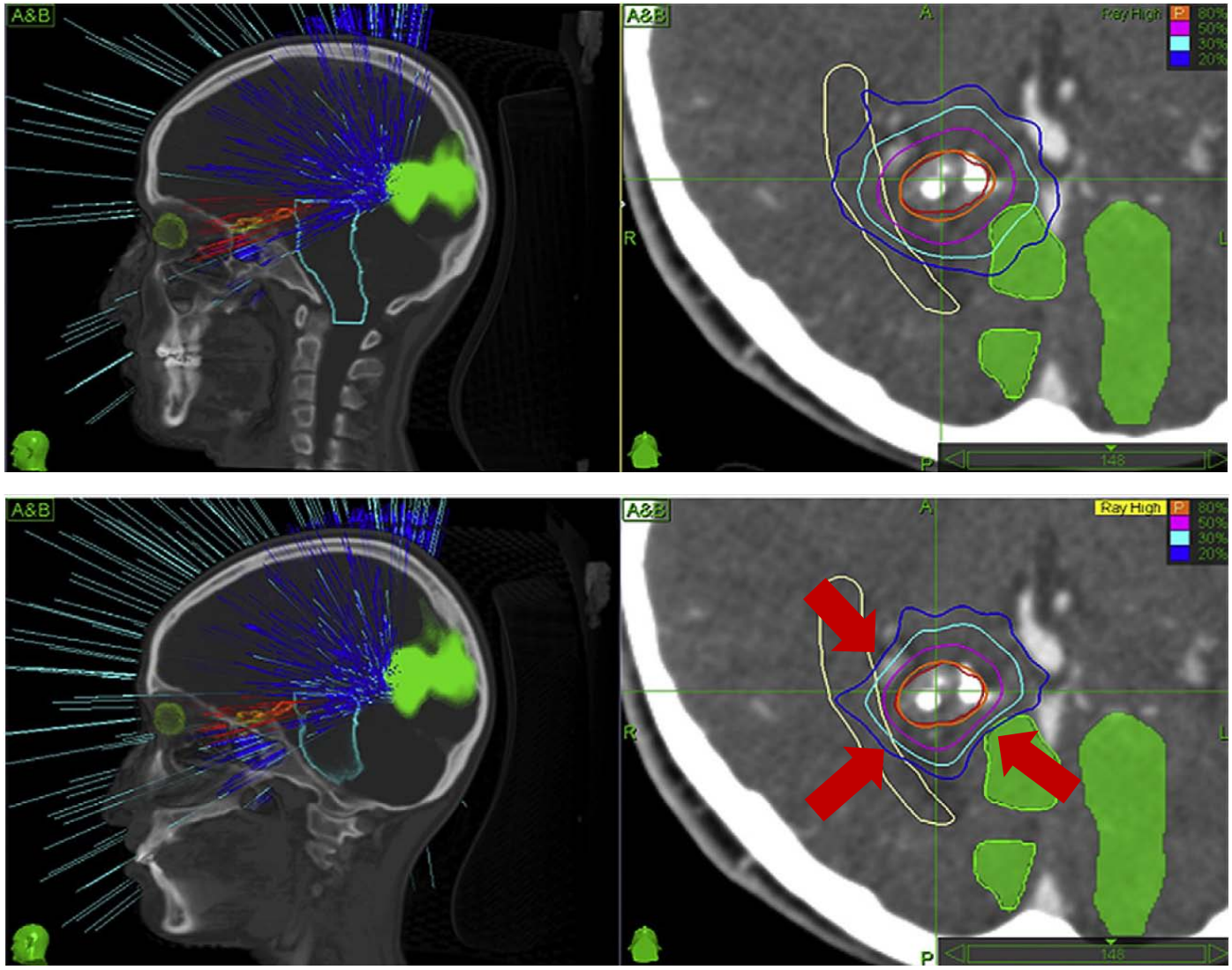
1. MRI for targeting: brain

Without opt.

With opt.



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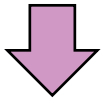
New MRI imaging modalities and radiotherapy planning

- When using new MRI imaging modalities?
  1. Refining the GTV (**targeting**)



     - Dose escalation protocols

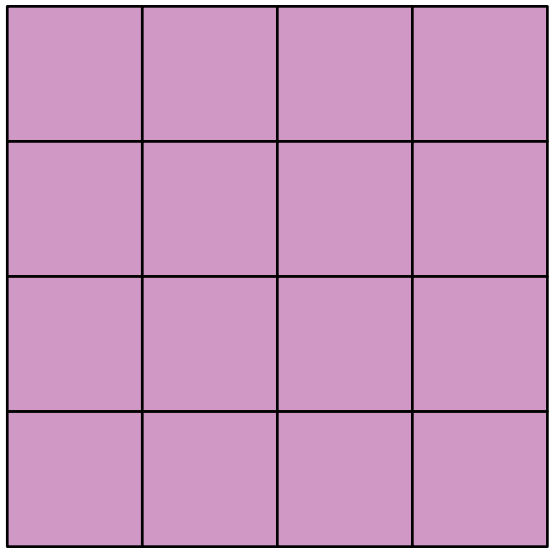
     - Dose distribution-imaging adaptation for simultaneous or sequential boost treatments
  2. Direct **planning** on MRI images
  3. Hybrid machines

2. Direct planning on MRI images

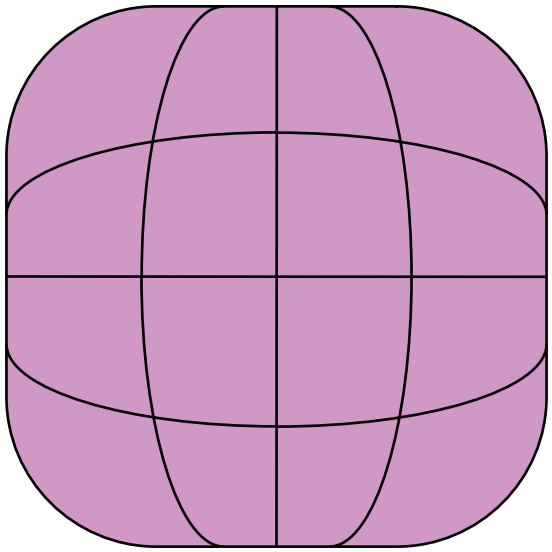
- Problems in using only MRI for planning
  1. Image **distortion**
  2. Dose calculation (lacking informations needed to recontruct **electron density maps**)

2. Direct planning on MRI images

- Strategies for reduce geometry artifact due MRI images acquisition process



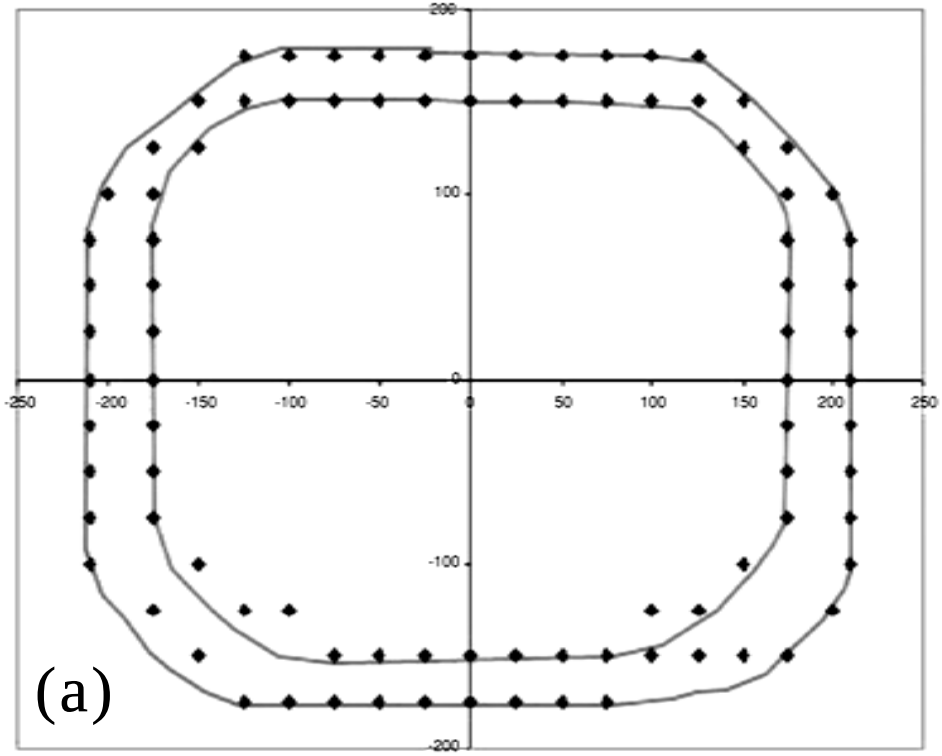
CT

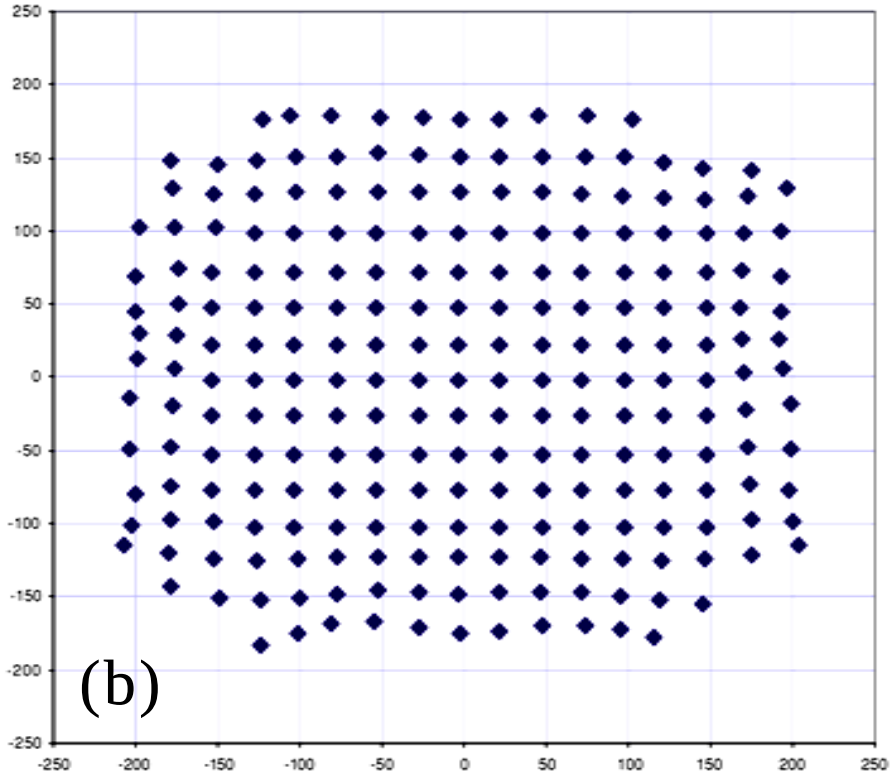


MRI

2. Direct planning on MRI images

- Definition of viewable area of the scanner (a) and creation of a distortion map (b)





Z Chen et al. Investigation ofMR image distortion for radiotherapy treatment planning of prostate cancer. Phys.Med. Biol. 51 (2006) 1393–1403

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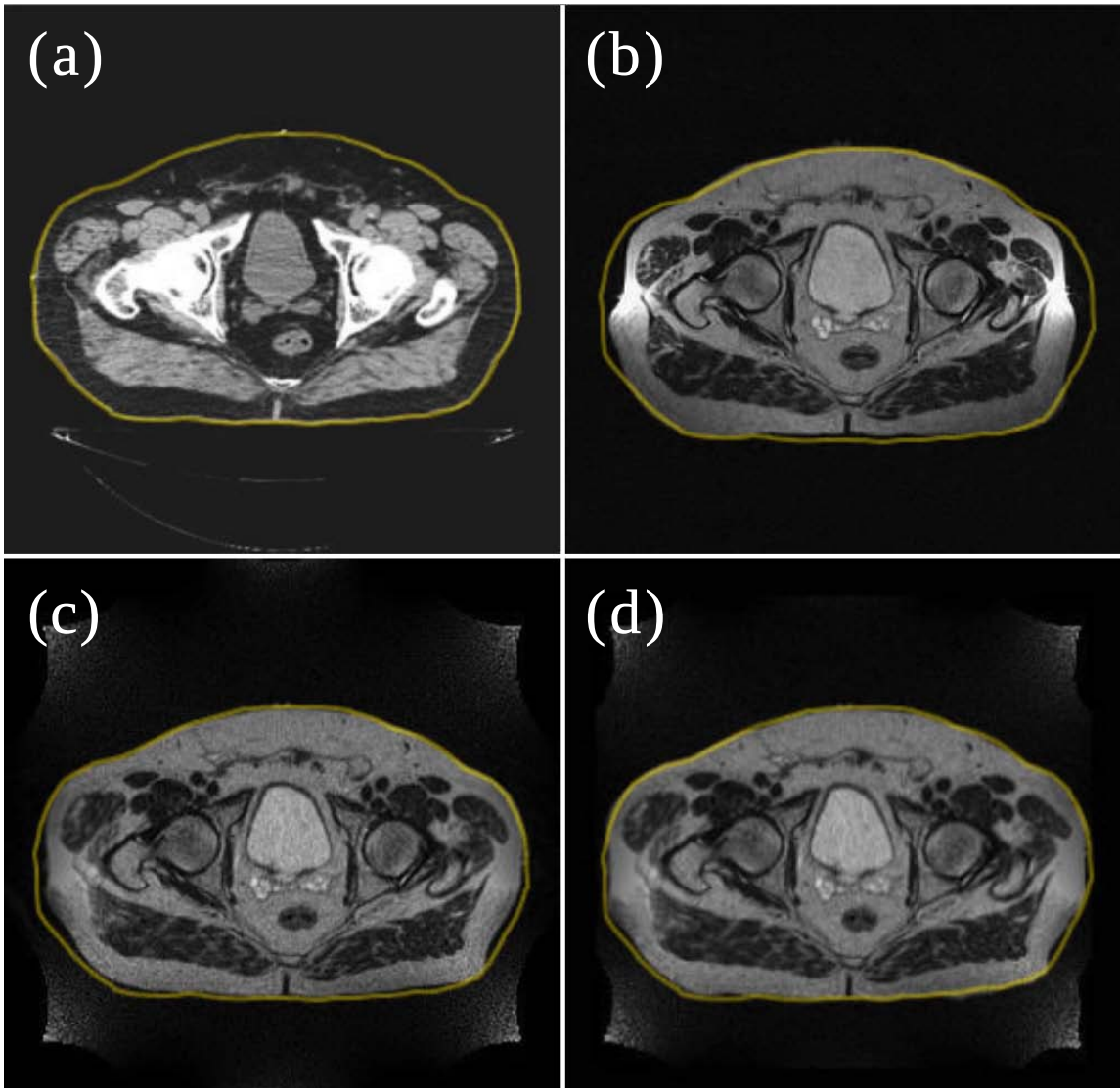
2. Direct planning on MRI images

- Use of scanner software and correction map for image correction
  a) CT scan
  b) MRI uncorrected
  c) On-scanner correction
  d) Distortion map correction



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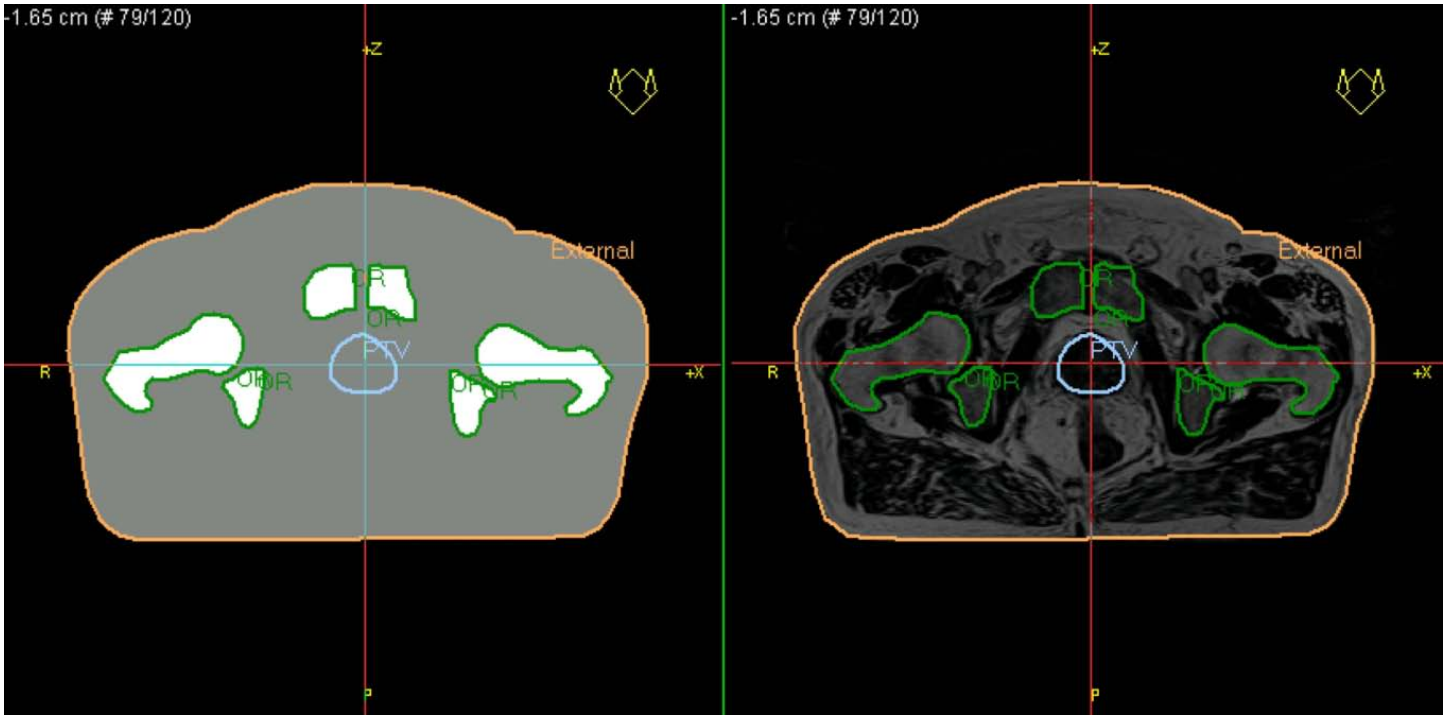
2. Direct planning on MRI images

- Strategies for adding informations to allow calculation of dose distribution
  - Image registration
  - Creation of **bulk-density CT images**
  - Creation of **simulated CT-images** (**s-CT**)

2. Direct planning on MRI images

- **Bulk-density images** are synthetic CT images where the HU are simulated in a simplified way, using the anatomy in MRI to create regions to be assigned with a specific HU value



JH Jonsson et al. Treatment planning using MRI data: an analysis of the dose calculation accuracy for different treatment regions. Radiation Oncology 2010, 5:62

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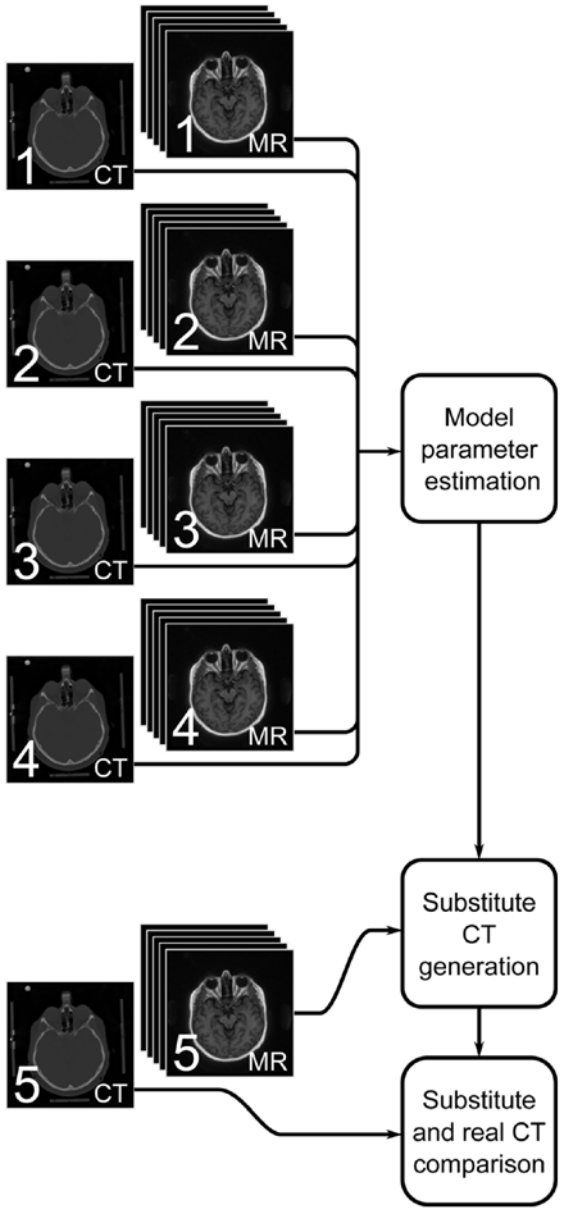
2. Direct planning on MRI images

Model definition for creating simulated CT images:
Gaussian mixture regression (**GMR**) model

Model optimization and parameters estimation

s-CT generation and model results verification



A Johansson et al. CT substitute derived from MRI sequences with ultrashort echo time. Med. Phys. 38 (5), 2011

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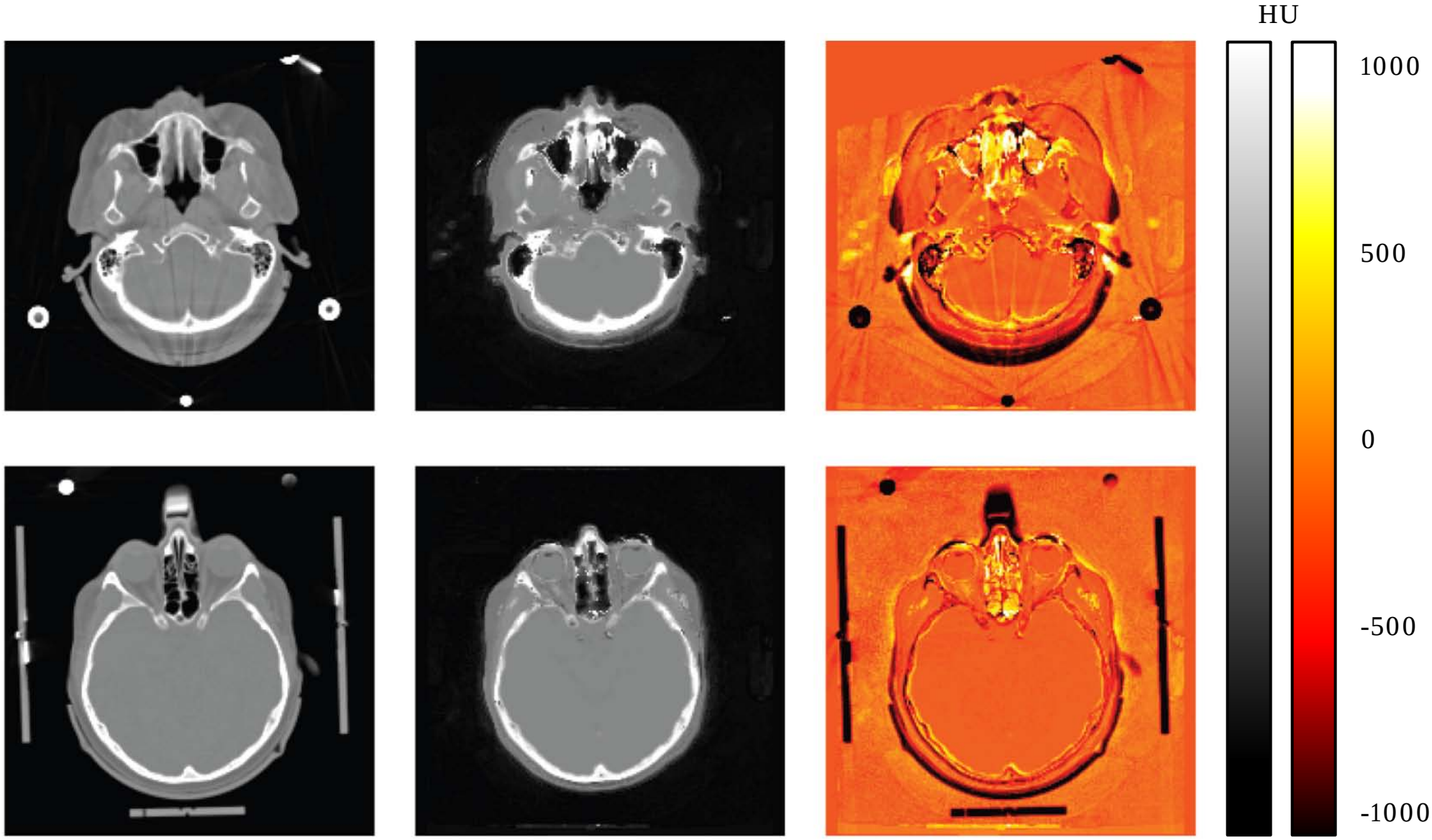
2. Direct planning on MRI images



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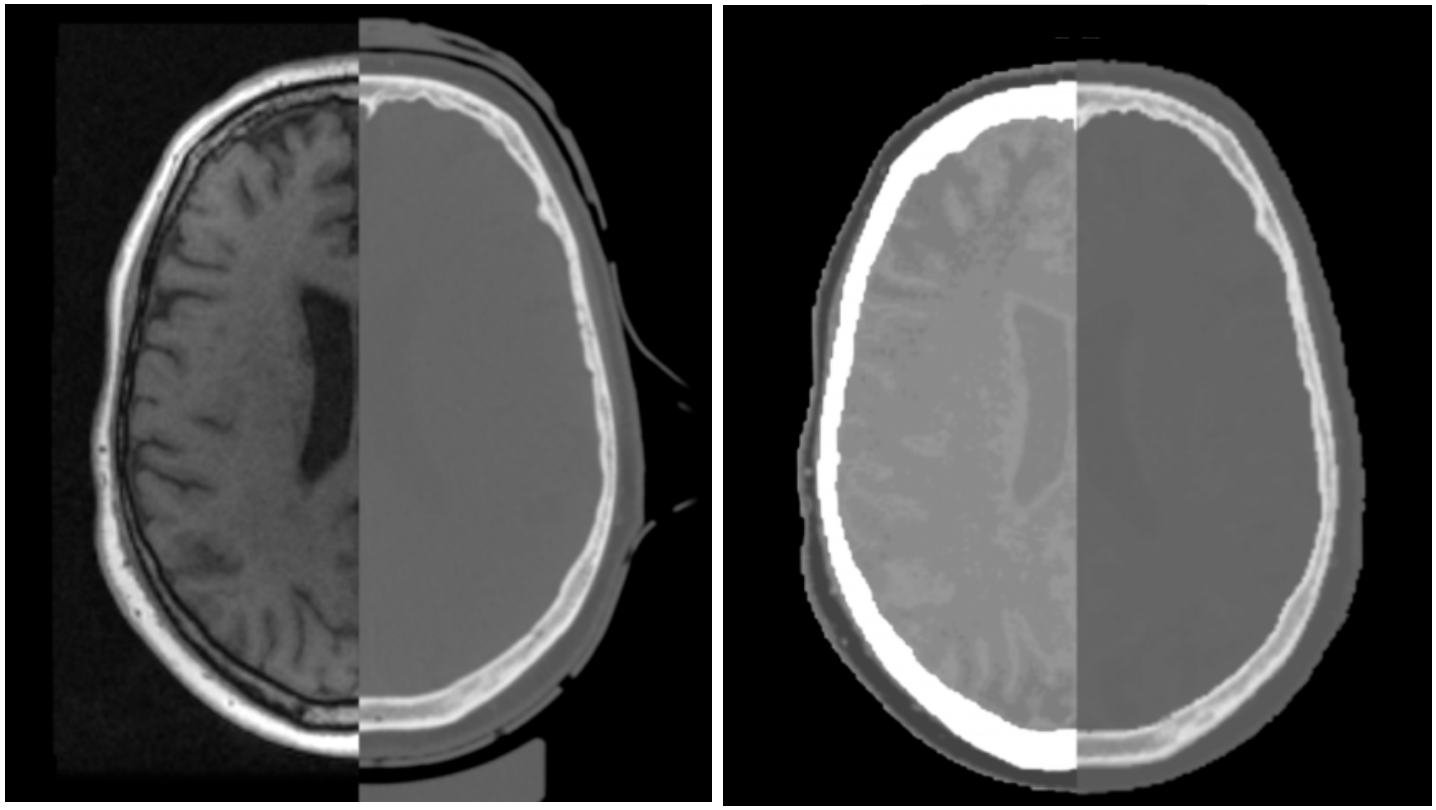
2. Direct planning on MRI images



Koivula L et al. Feasibility of MRI-only treatment planning for proton therapy in brain and prostate cancers: Dose calculation accuracy in substitute CT images. Med Phys. 2016;43:4634–4642.

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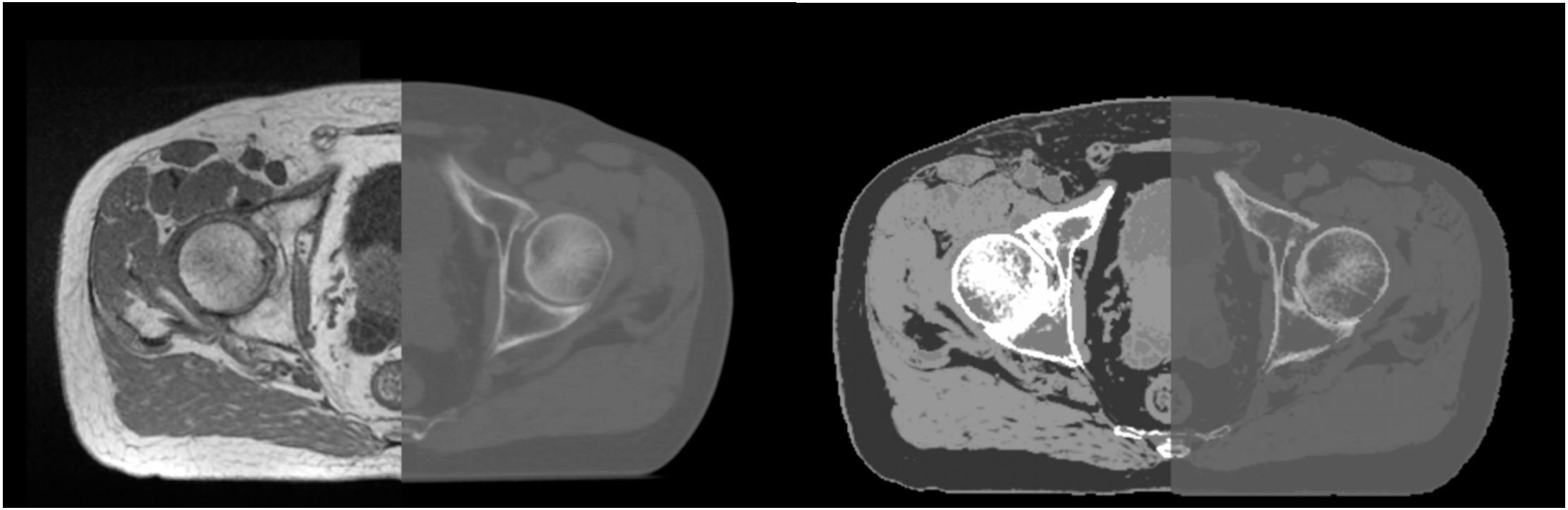
2. Direct planning on MRI images



Koivula L et al. Feasibility of MRI-only treatment planning for proton therapy in brain and prostate cancers: Dose calculation accuracy in substitute CT images. Med Phys. 2016;43:4634–4642.

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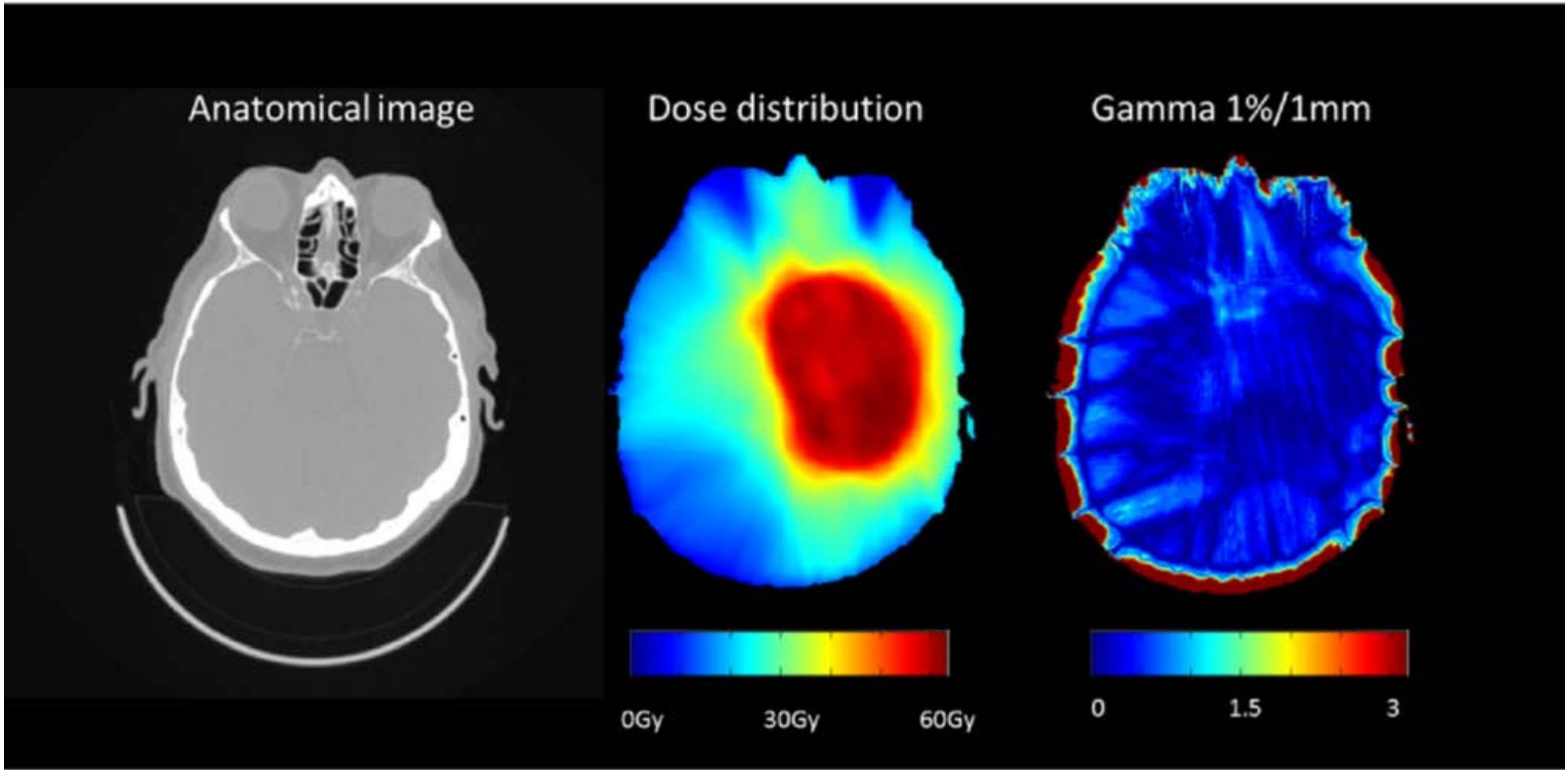
2. Direct planning on MRI images



Jonsson JH et al. Accuracy of inverse treatment planning on substitute CT images derived from MR data for brain lesions. Radiat Oncol. 2015;10:13.

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2. Direct planning on MRI images

Table 2 Dose comparison results

	Diff.D_{min}(%)	Diff.D_{max}(%)	Diff.D_{median}(%)	Diff.D_{mean}(%)
PTV	0.3 (1.6)	−0.3 (0.6)	−0.1 (0.1)	0.0 (0.0)
GTV	0.8 (1.0)	0.5 (0.6)	0.3 (0.8)	0.3 (0.7)
Brainstem	−5.9 (7.9)	−0.4 (4.0)	1.6 (3.7)	−0.4 (1.9)
Pituitary gland	−0.9 (4.0)	0.9 (3.5)	0.7 (3.5)	0.1 (3.4)
Right lens	4.8 (8.6)	0.4 (6.4)	2.3 (7.8)	2.3 (7.7)
Left lens	4.6 (2.0)	−5.0 (24.8)	5.2 (4.4)	5.1 (4.0)
Right opticus	1.2 (5.6)	0.6 (4.7)	1.6 (4.0)	2.3 (5.0)
Left opticus	4.2 (4.3)	5.1 (11.6)	−2.2 (11.6)	5.0 (6.3)
Chiasma	−2.1 (3.1)	−0.7 (3.5)	−0.7 (3.3)	−1.0 (3.6)

Legend: Average differences between D_{max}, D_{min}, D_{median} and D_{mean} dose for plans optimized on CT and s-CT. The standard deviation calculated based on the five patients are presented within brackets.

Jonsson JH et al. Accuracy of inverse treatment planning on substitute CT images derived from MR data for brain lesions. Radiat Oncol. 2015;10:13.

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2. Direct planning on MRI images

- The method of **generating s-CT images** using UTE MRI sequences together with Gaussian regression models is very **fast and accurate**.
- The results from the treatment planning study demonstrate that it produces **dose calculation results** that are close to traditional CT scan planning results.
- In contrast to manual bulk density assignments, the **s-CT method is automatic**.

New MRI imaging modalities and radiotherapy planning

- When using new MRI imaging modalities?
  1. Refining the GTV (**targeting**)

     ⇩

     - Dose escalation protocols

     ⇩

     - Dose distribution-imaging adaptation for simultaneous or sequential boost treatments
  2. Direct **planning** on MRI images
  3. Hybrid machines

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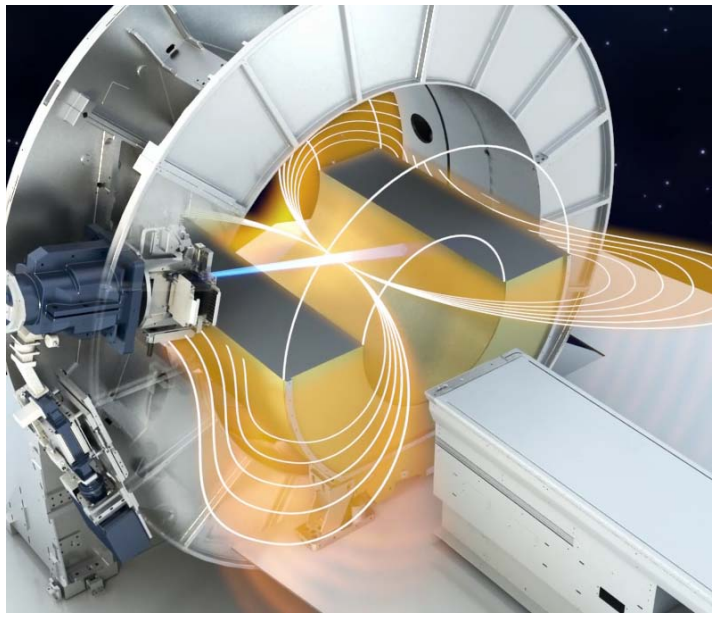
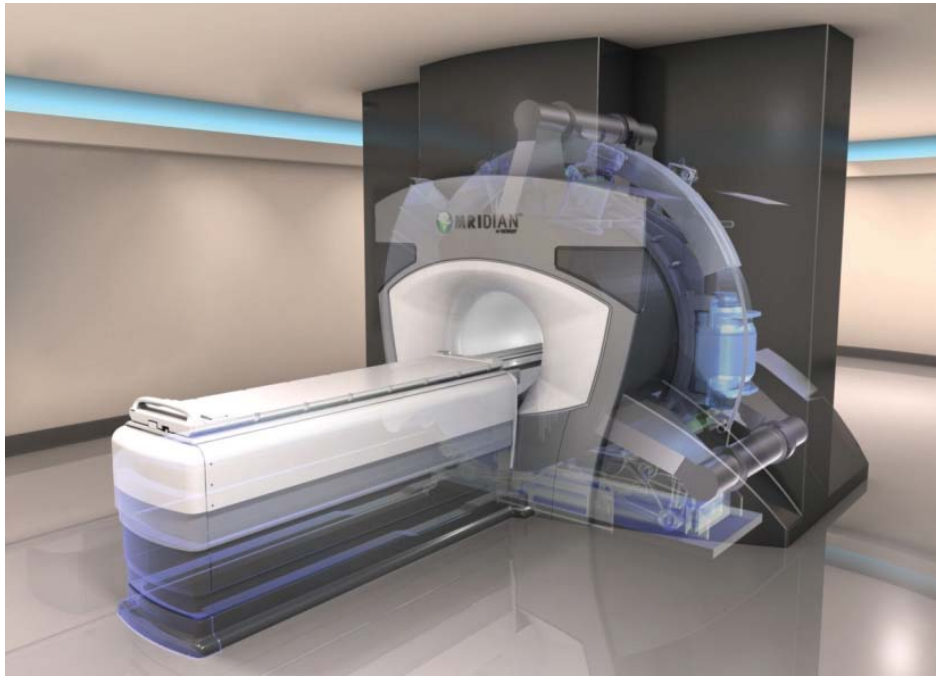
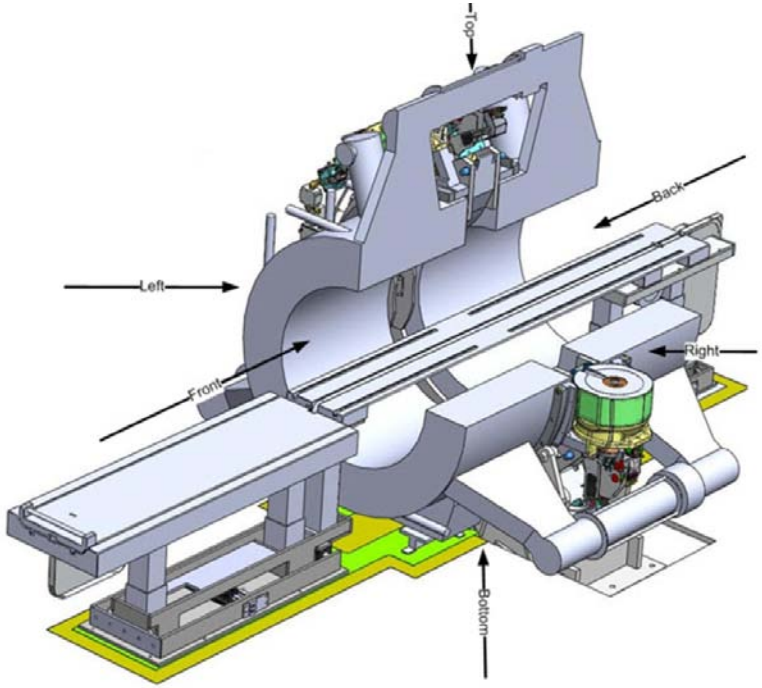
MR-Linac



- 8 MV accelerator, FFF
- Modified 1.5 T Philips Ingenia MRI scanner
- Linac mounted in ring around MRI

MR-^{60}Co





split 0,35T/ 3 ^{60}Co heads on a ring gantry
first commercially available

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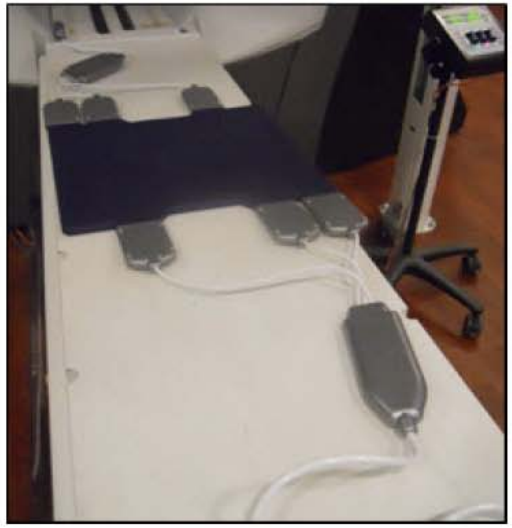
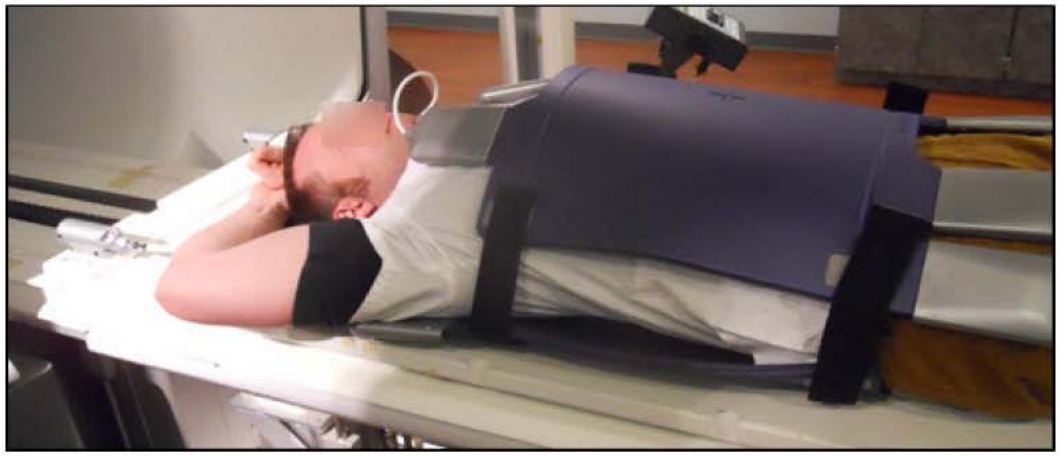
MRI – ^{60}Co: imaging features

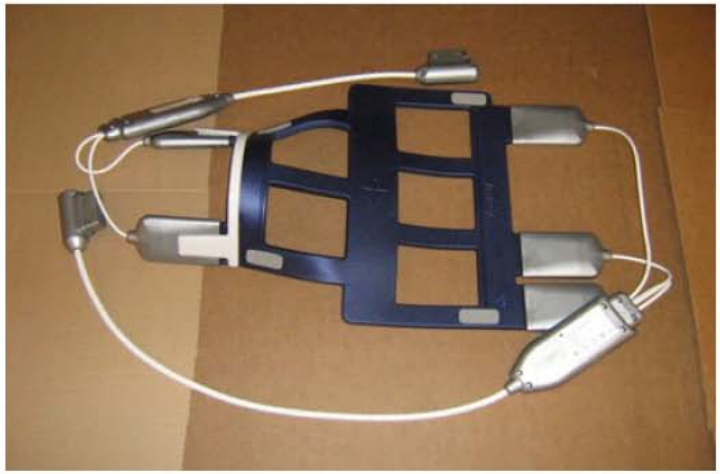
Torso Coil half



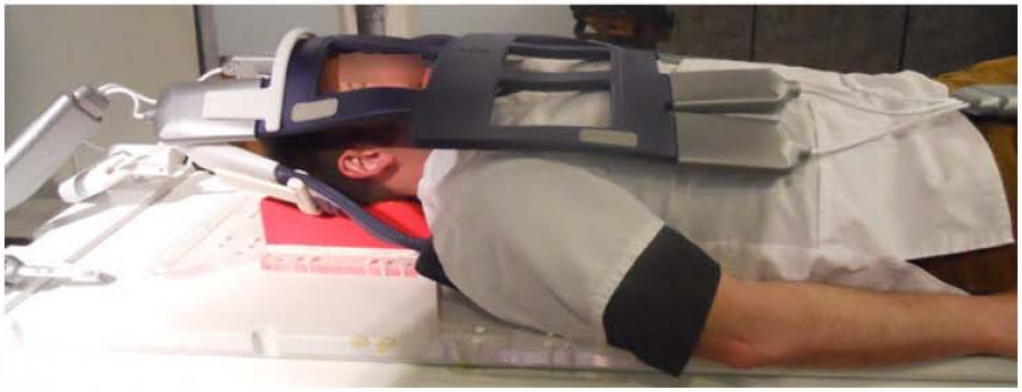
Torso Coils in place



Head and Neck Coil half



Head and Neck coils in place



Courtesy of VIewRay: 00016 technical manual revG

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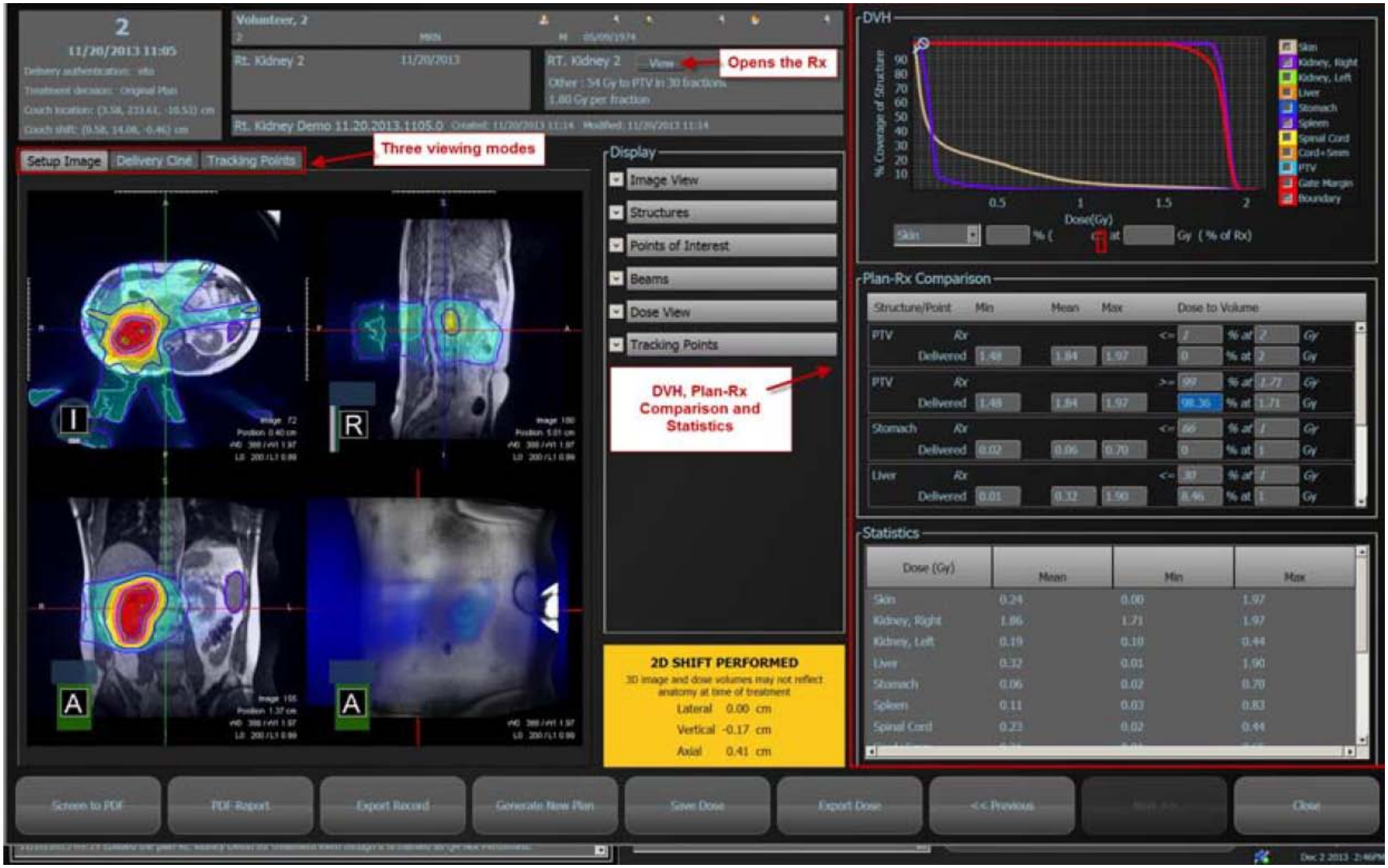
MRI – ^{60}Co: imaging features

Scan Name	Sequence Types	Function
Pilot Scan	GRE (3D) TRUFI (3D)	Localization of anatomy and patient positioning
Planning Scan	GRE (3D) TRUFI (3D) TFL (3D)	Treatment Planning
Treatment Scan	EPI (2D) GRE (2D) TRUFI (2D)	MRIS monitoring during treatment delivery
QA	SE (2D)	SNR, uniformity, contrast, and other QA functions

GRE: Gradient Echo - Proton density, T1, T2 - 2D GRE is 25 seconds per image
TRUFI: TRUe Fast Imaging with steady state free precession – T1, T2 – 25 sec 3D planning/pilot, 0.25 sec treatment scan
TFL: Turbo Flash – T1, mix T1/T2 – 3 min
EPI: Echo Planar Imaging – T2, mix T1/T2 – 0.25 sec per frame
SE: Spin Echo

Courtesy of VIewRay: 00016 technical manual revG

MRI – ^{60}Co: imaging features



Courtesy of VIewRay: 00016 technical manual revG

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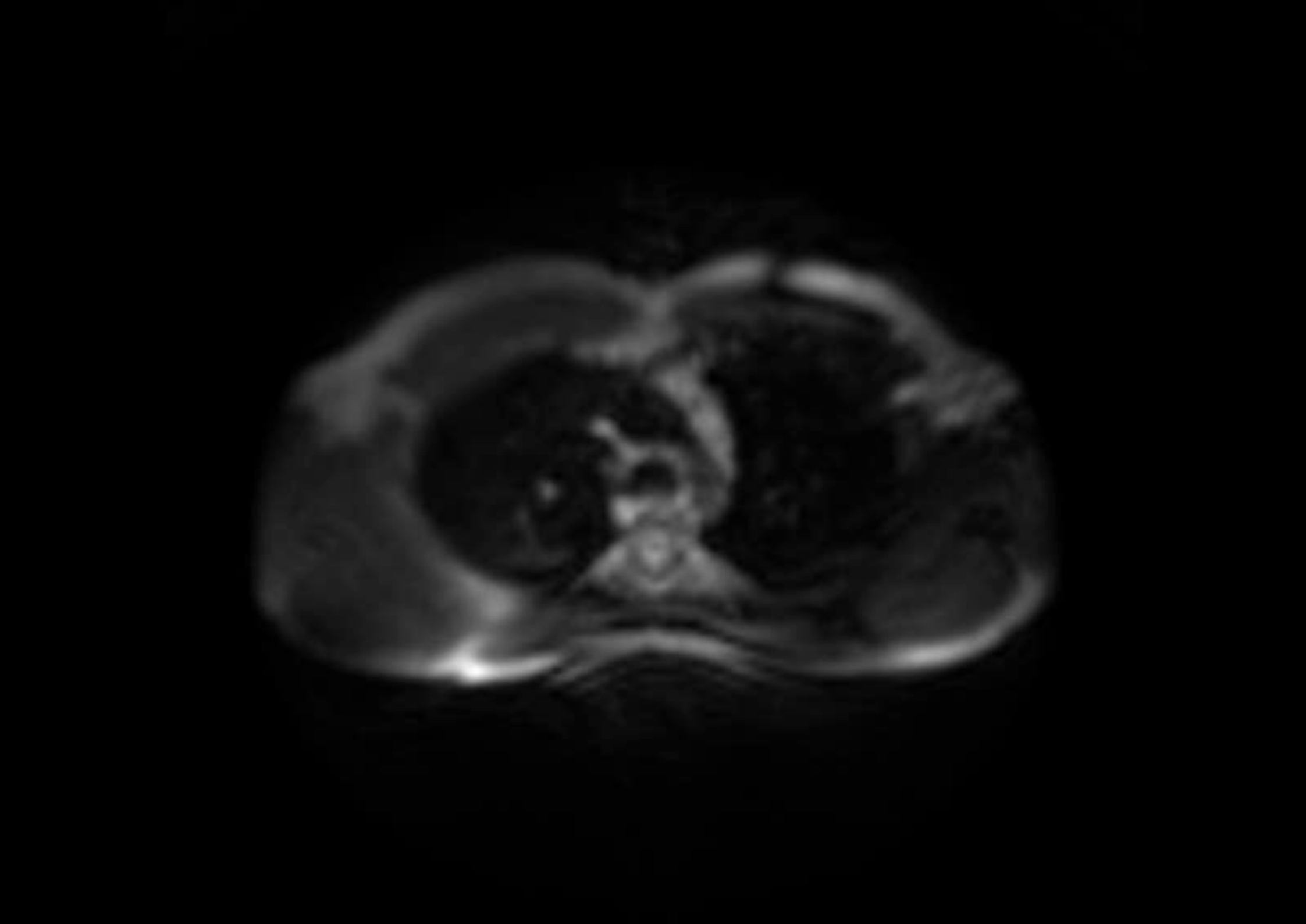

New MRI imaging modalities and radiotherapy planning: conclusions

- Introduction of new MR imaging techniques in radiotherapy treatment planning is still pioneering
- The multiparametric features of MRI need to be **clinically and perspectively verified** in order to provide affordable thresholds and cutoff values to gain the useful informations
- Further developments waited for **better volume delineation and characterization** (even biologically) and for decision making protocols in order to modify the treatment course of patients

New MRI imaging modalities and radiotherapy planning: conclusions

- Using **MRI in planning procedures** without registration is feasible. Actually there are not shared and diffused standards to perform it on commercial planning platforms yet
- The introduction of **hybrid machines** will increase the speed of MR adoption in clinical routine, both for planning and treatment verification

Thank you!

Grazie!

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Advanced planning strategies for lung tumours

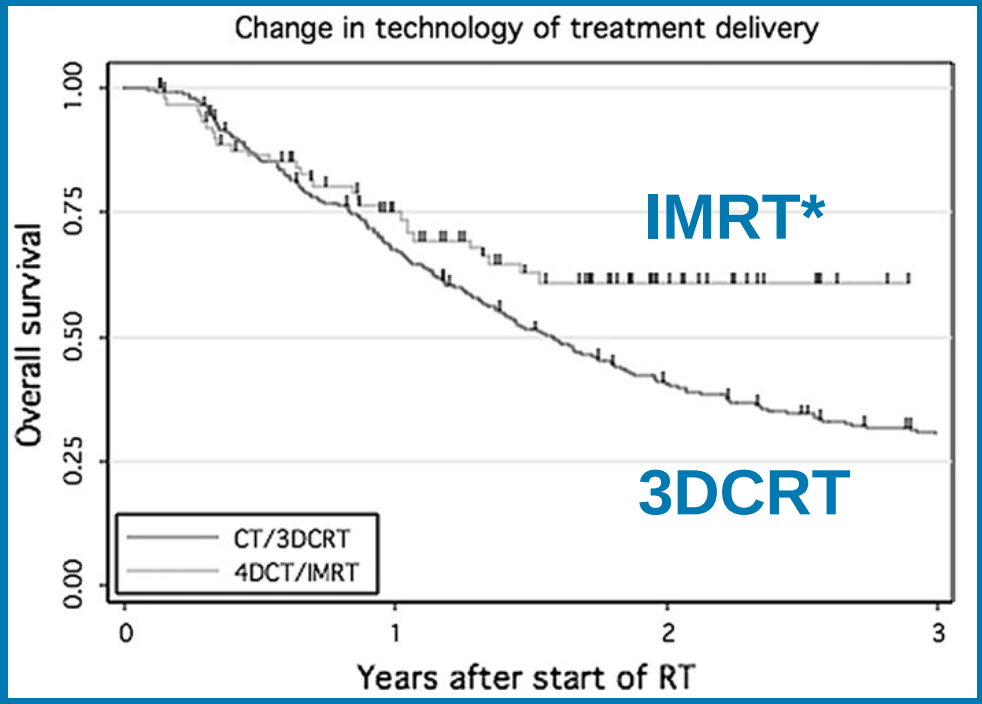
physical aspects

Gert Meijer

ESTRO
European Society for Therapeutic Radiology and Oncology

Why use IMRT in lung

- better survival
- better local control
- less pneumonitis



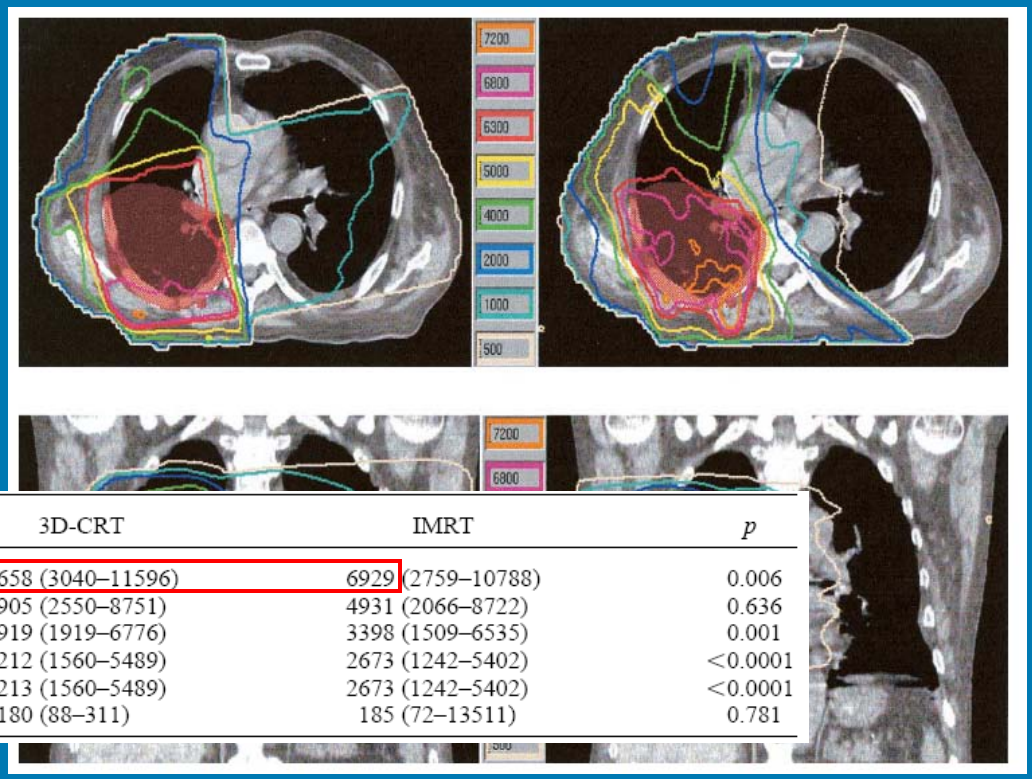
* in combination with IGRT and 4DCT

Liao *et al.* (IJROBP 2010)

Why use IMRT in lung

43 patients

- more conformal
- better sparing OARs
- lower dose to all lung parameters except V5

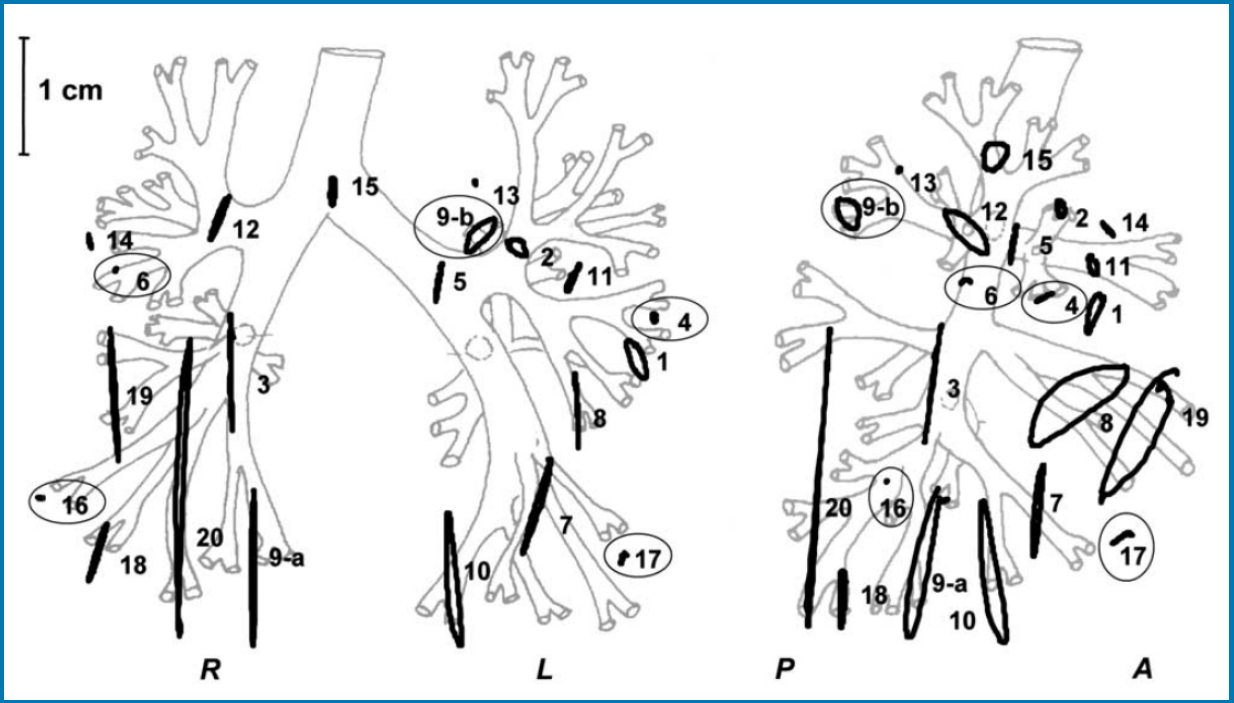


Parameter	3D-CRT	IMRT	*p*
Thoracic normal tissue V_5 (cm^3)	5658 (3040–11596)	6929 (2759–10788)	0.006
Thoracic Normal Tissue V_{10} (cm^3)	4905 (2550–8751)	4931 (2066–8722)	0.636
Thoracic Normal Tissue V_{20} (cm^3)	3919 (1919–6776)	3398 (1509–6535)	0.001
Thoracic Normal Tissue V_{30} (cm^3)	3212 (1560–5489)	2673 (1242–5402)	<0.0001
Thoracic normal tissue V_{40} (cm^3)	3213 (1560–5489)	2673 (1242–5402)	<0.0001
Thoracic normal tissue integral dose (J)	180 (88–311)	185 (72–13511)	0.781

3DCRT **IMRT**

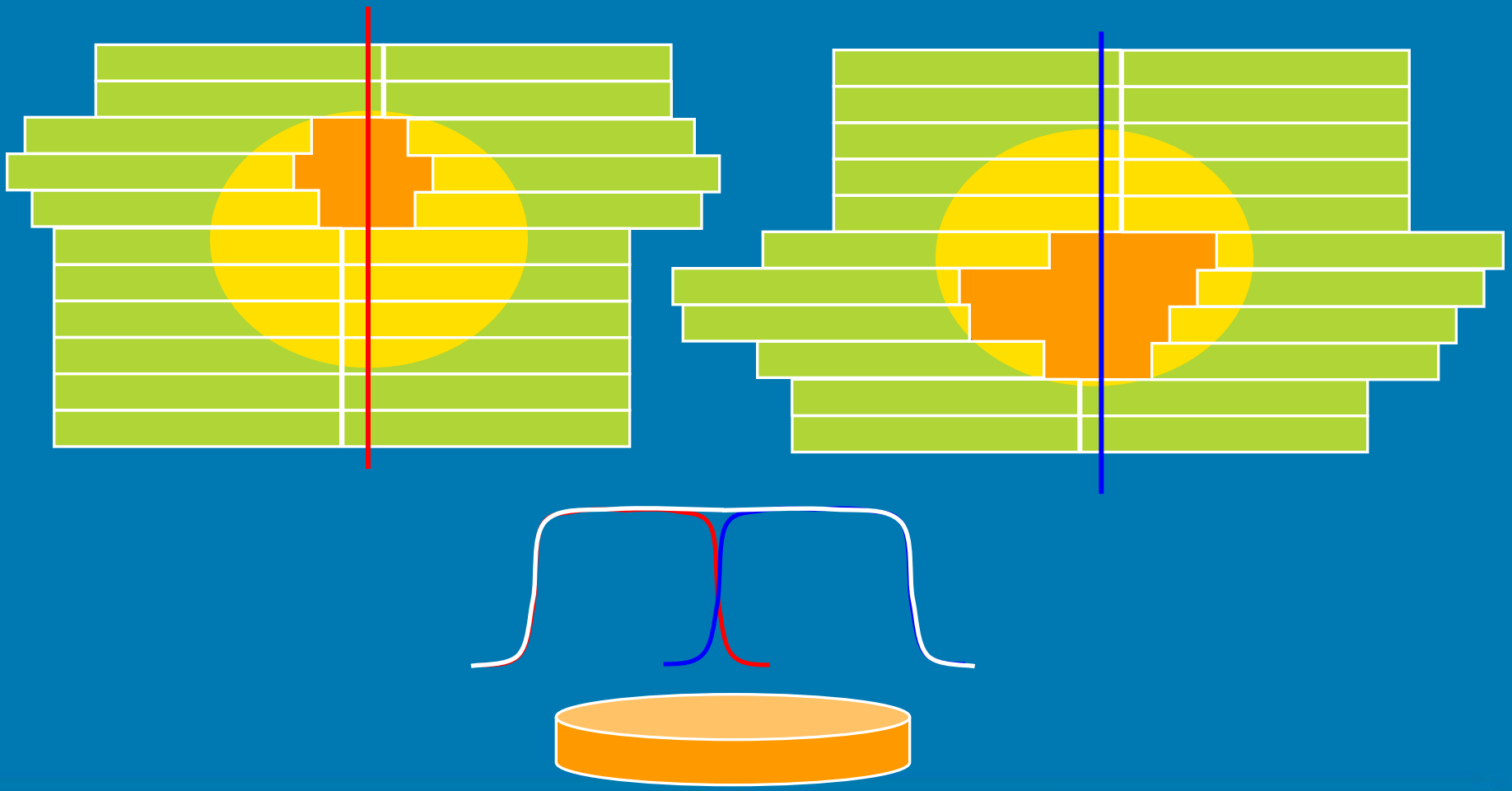
Murshed *et al.* (IJROBP 2004)

Why not use IMRT in lung

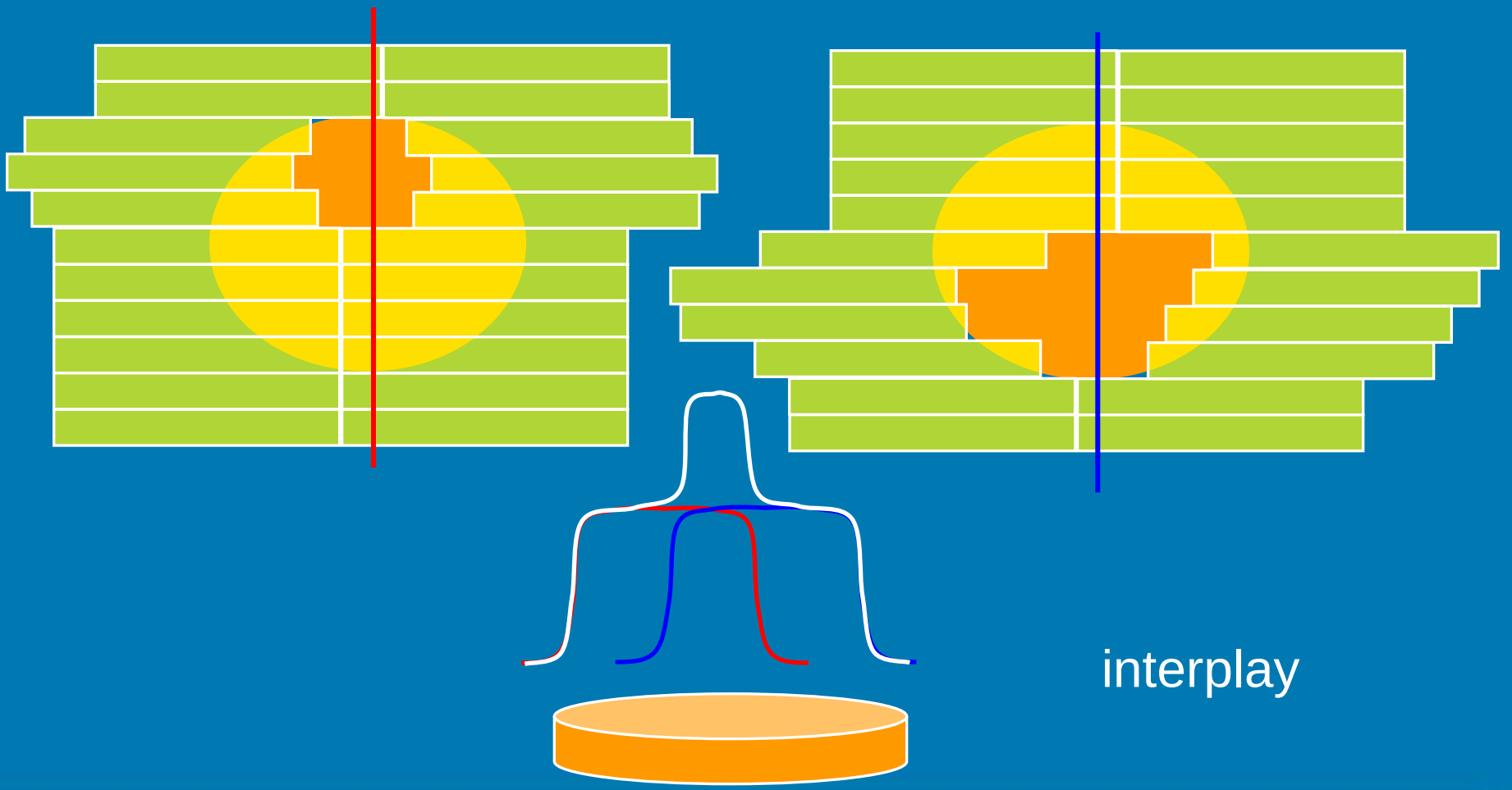


Seppenwoolde *et al.* (IJROBP 2002)

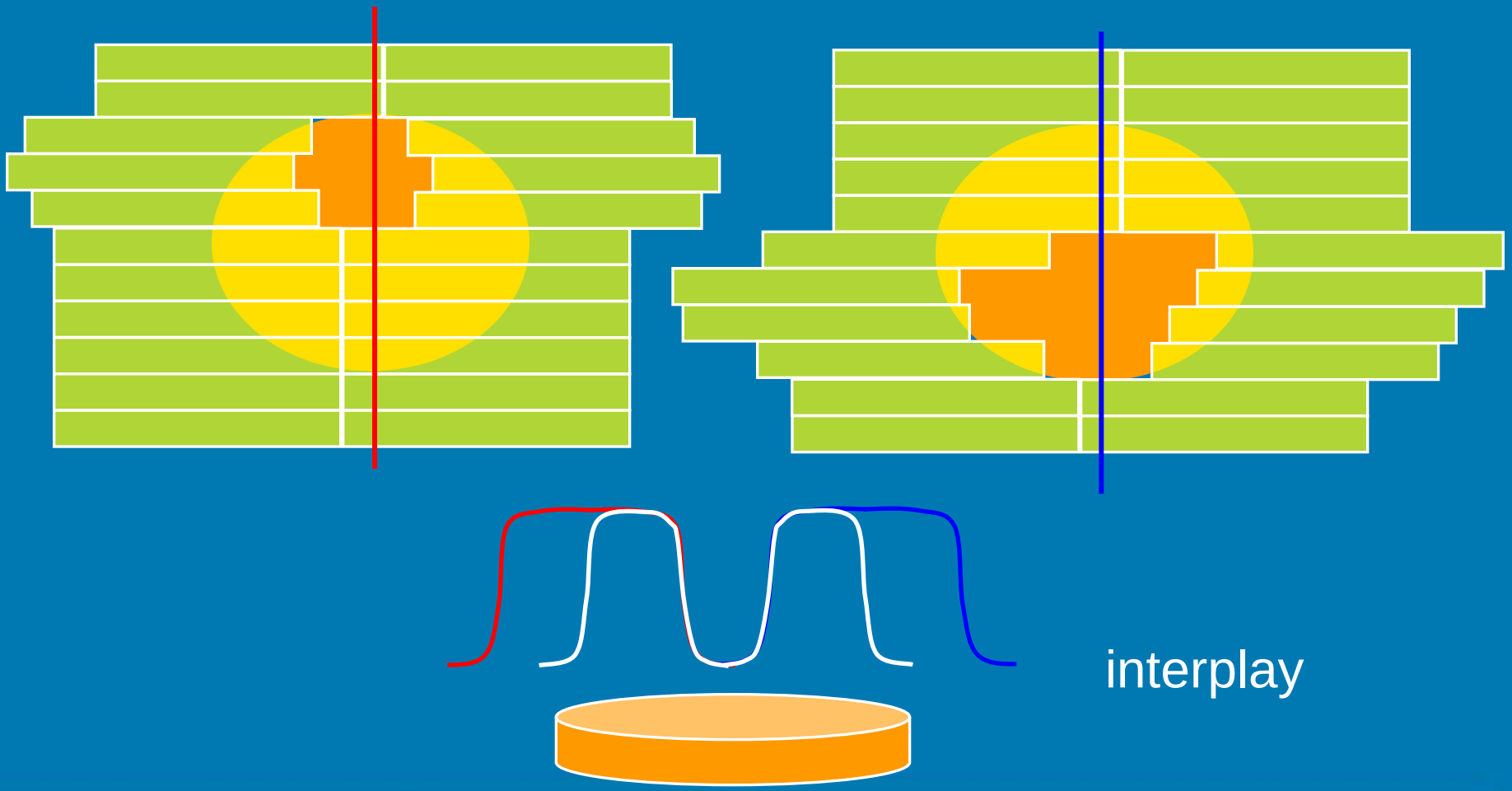
Why not use IMRT in lung

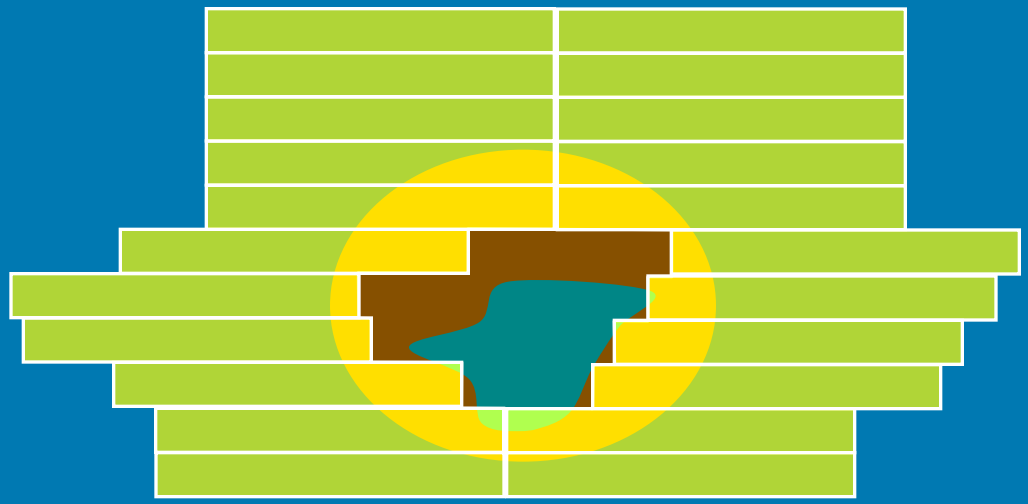


Why not use IMRT in lung



Why not use IMRT in lung

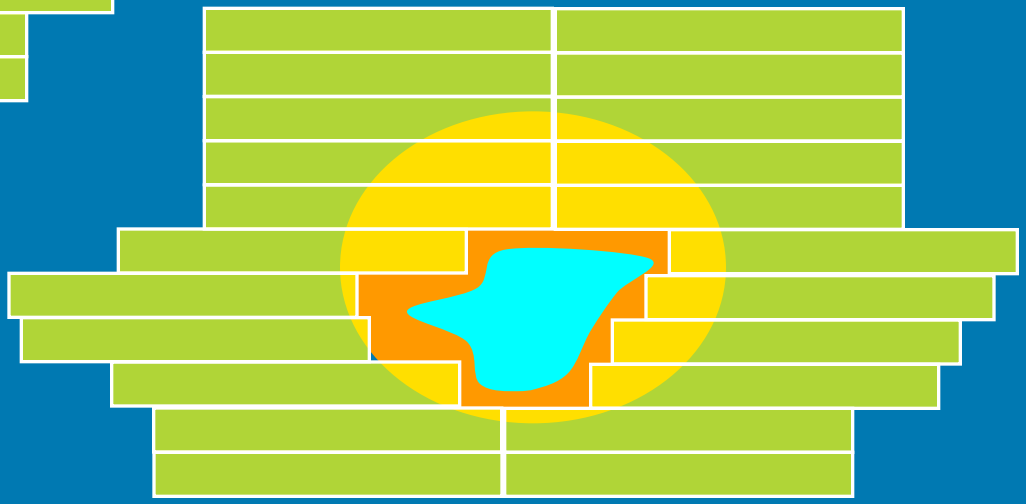


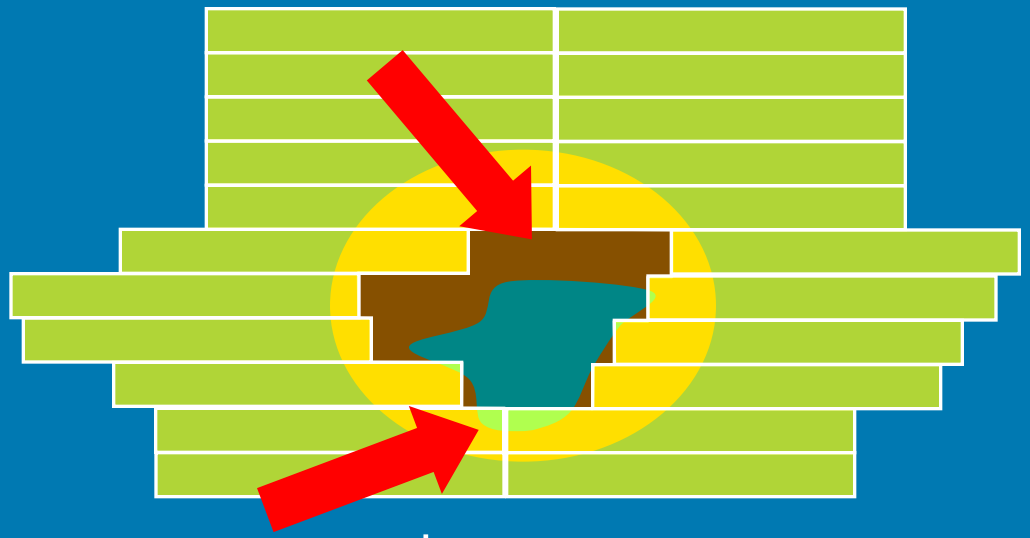


beam on
beam off

gating

‘breathing leaves’



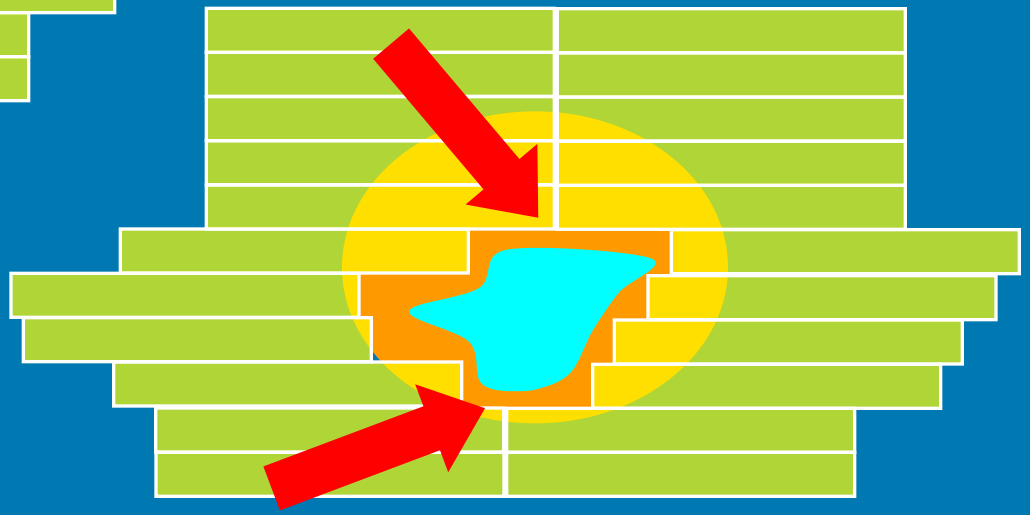


beam on
beam off

gating

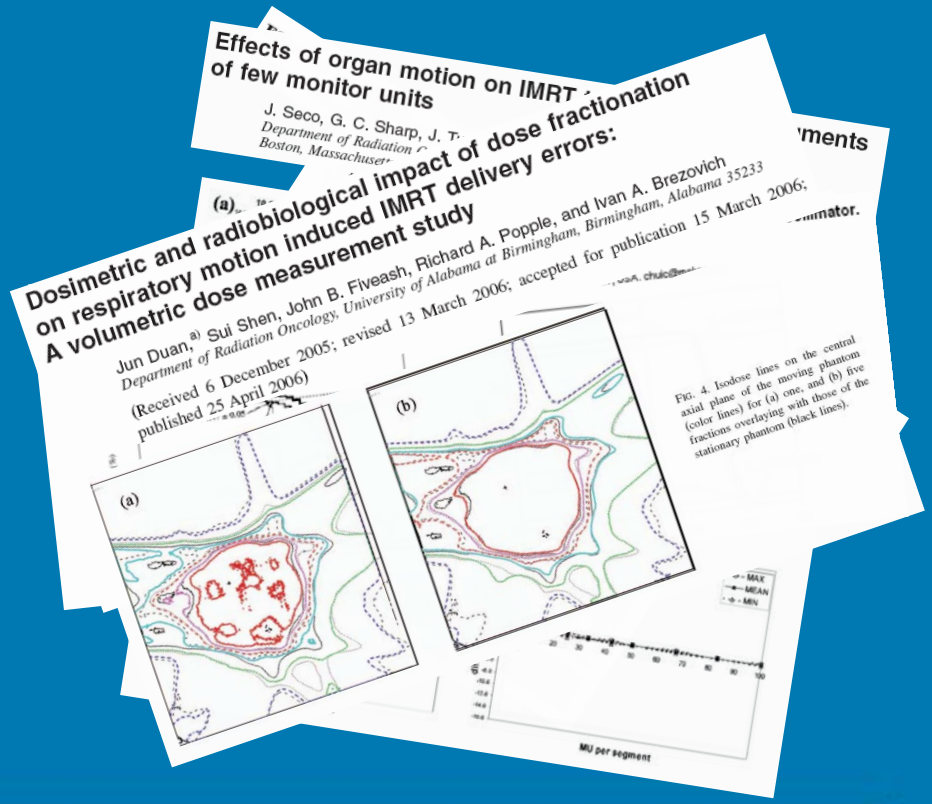
bad synchronisation

‘breathing leaves’



So forget about IMRT for lung if you don't have these fancy tools?

Many studies investigated this phenomenon and ……..



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Key findings:

- large potential for interplay effects per fraction
- but cancel out for large fractions or large # MUs
- stability in TCP at 5 fractions
- IMRT for SBRT may even be acceptable

- **appropriate margins more important than respiratory control**

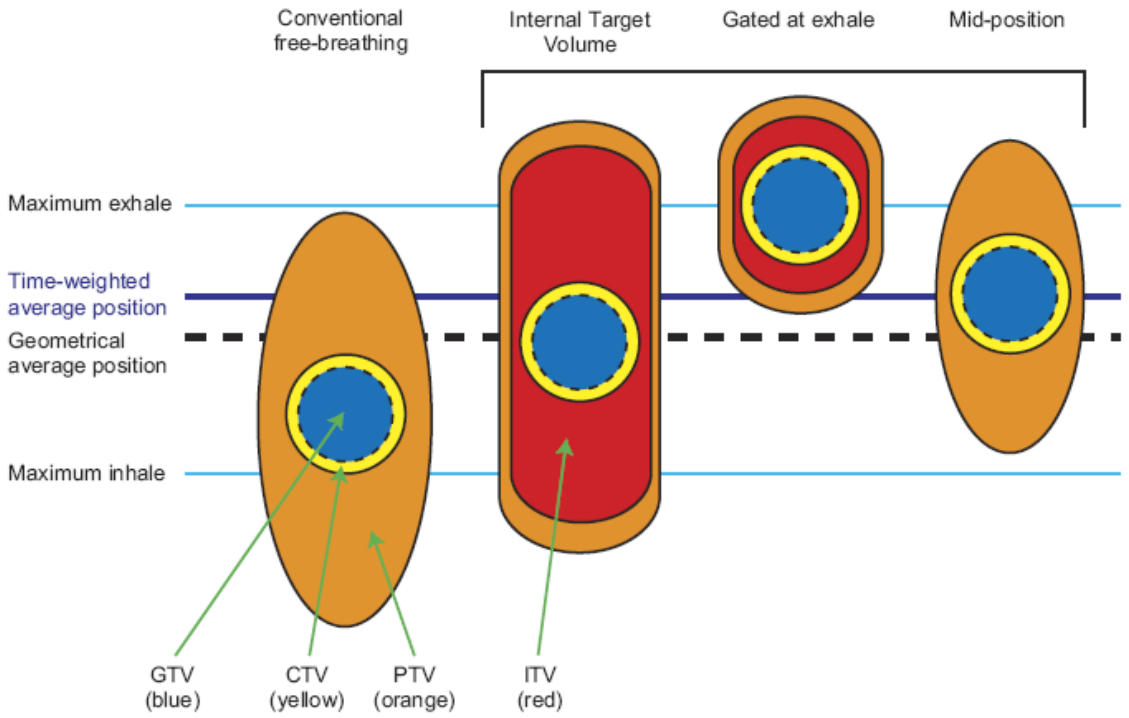
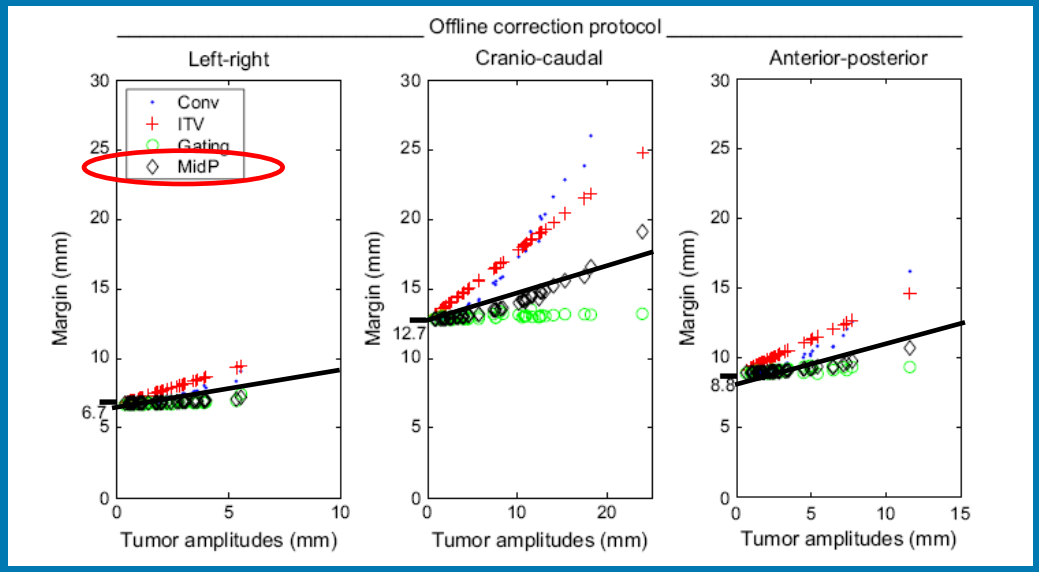


Fig. 1. Schematic overview of different treatment-planning concepts: conventional free-breathing, internal target volume (ITV), gating (at exhale), and mid-position. GTV = gross tumor volume; CTV = clinical target volume; PTV = planning target volume.

Wolthaus *et al.* (IJROBP 2008)



$\Delta M = 1/4\ A$

Wolthaus *et al.* (IJROBP 2008)

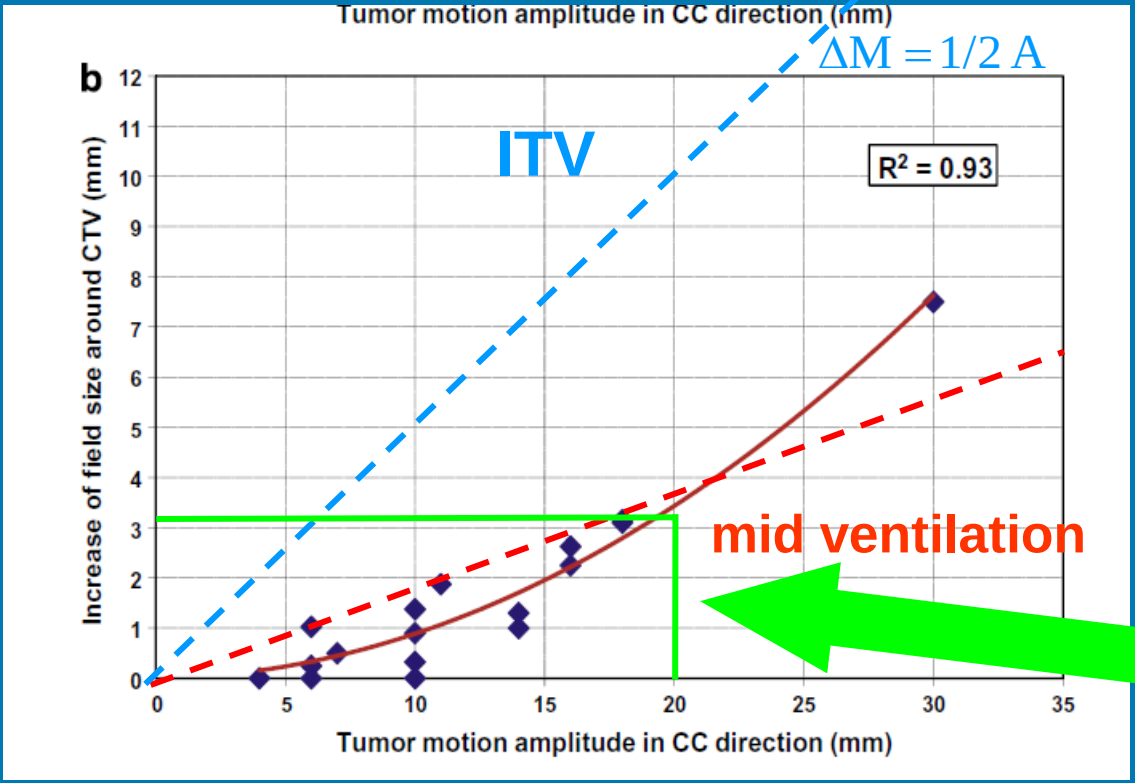
$$M = 2.5\Sigma + 1.64\sqrt{\sigma^2 + \sigma_p^2} - 1.64\sigma_p$$

0.7σ

breathing

broad penumbra

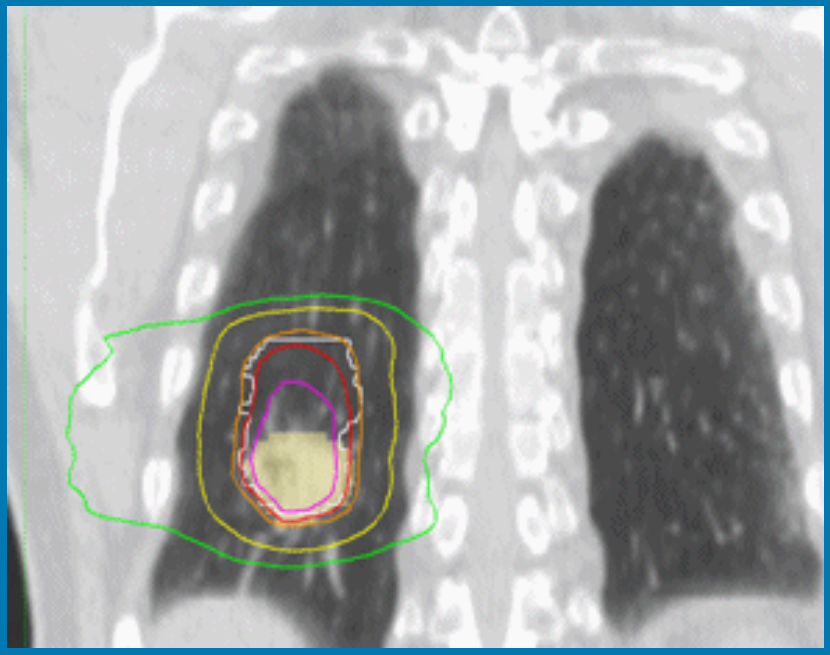
SBRT



Guckenberger *et al*. (R&O 2009)

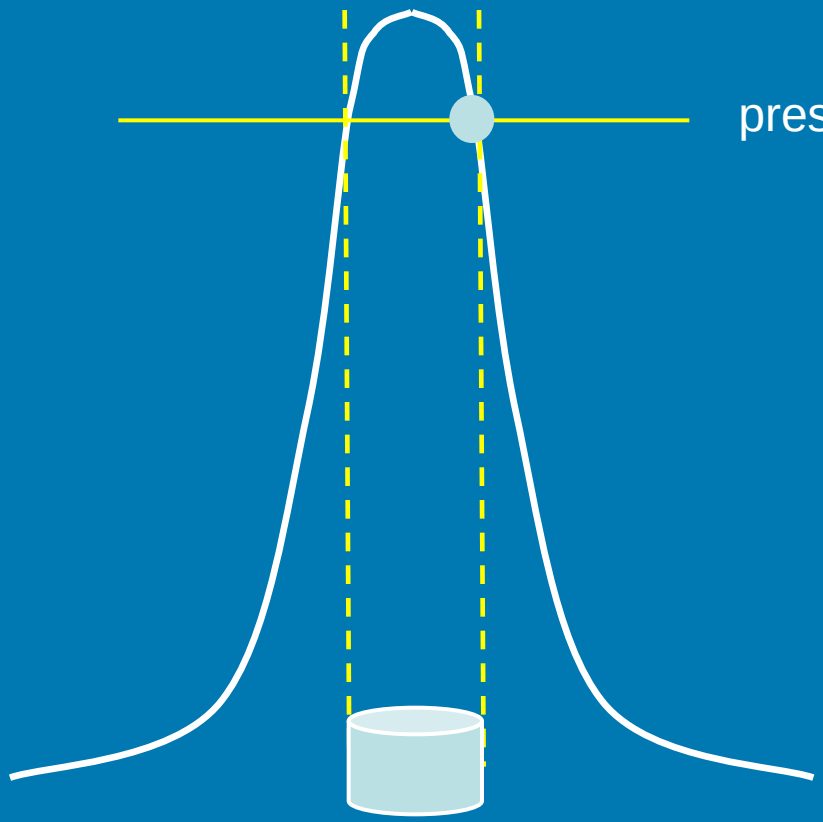
Why? 1

Admiraal *et al*. (R&O 2008)



because high dose regions move along with the tumour

Why? 2



So …….

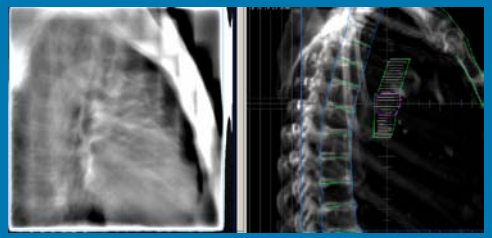
- extra margin for respiration is about ¼ of the breathing amplitude

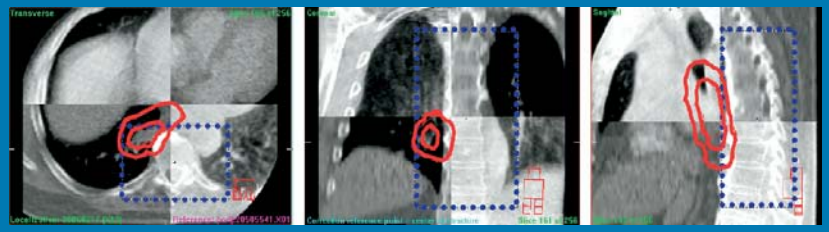
- how about the other uncertainties?

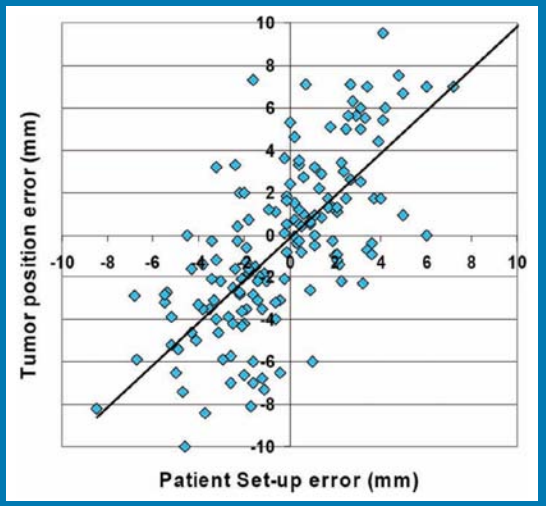
IGRT (not addressed in this course) is key here

- 4DCT
  - unblurred target delineation
  - tumour movement

- CBCT
  - 3D soft tissue matching superior to regular 2D bony anatomy matching

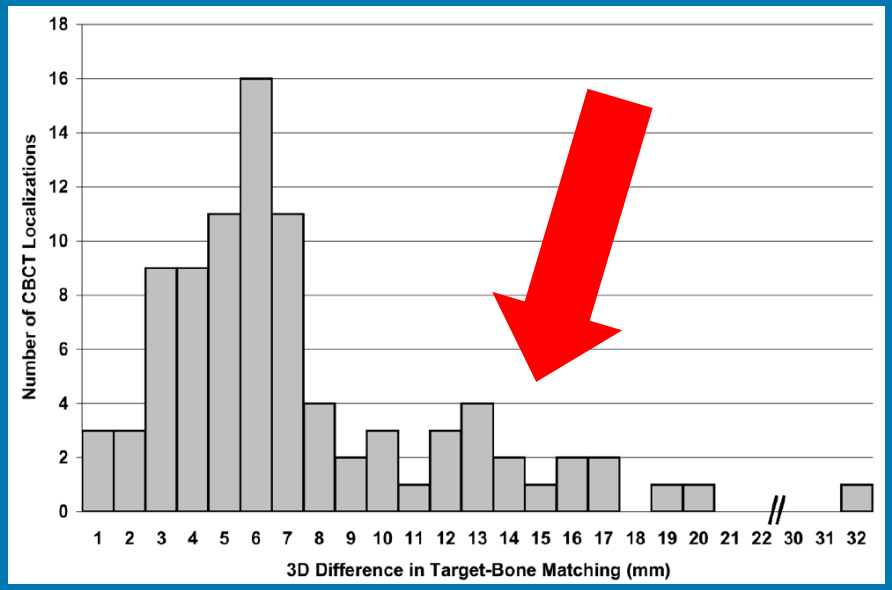






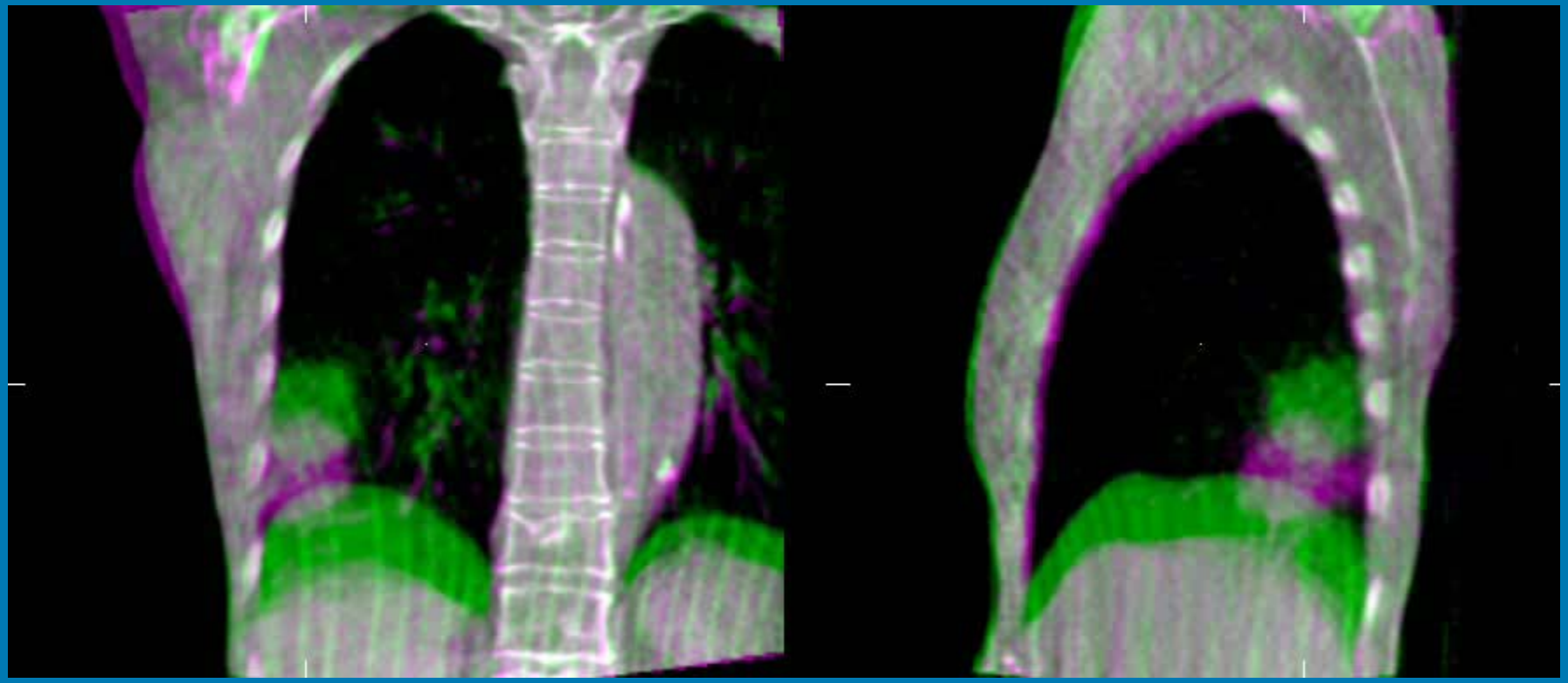
	Sys. ± rand. error	Group mean error	Max. error
SI	2.1 ± 1.1	0.3 (superior)	8.2
AP	3.3 ± 1.3	1.7 (posterior)	9.1
LR	2.2 ± 1.1	0.7 (left)	6.4

Guckenberger *et al.* (ActaOncol 2006)



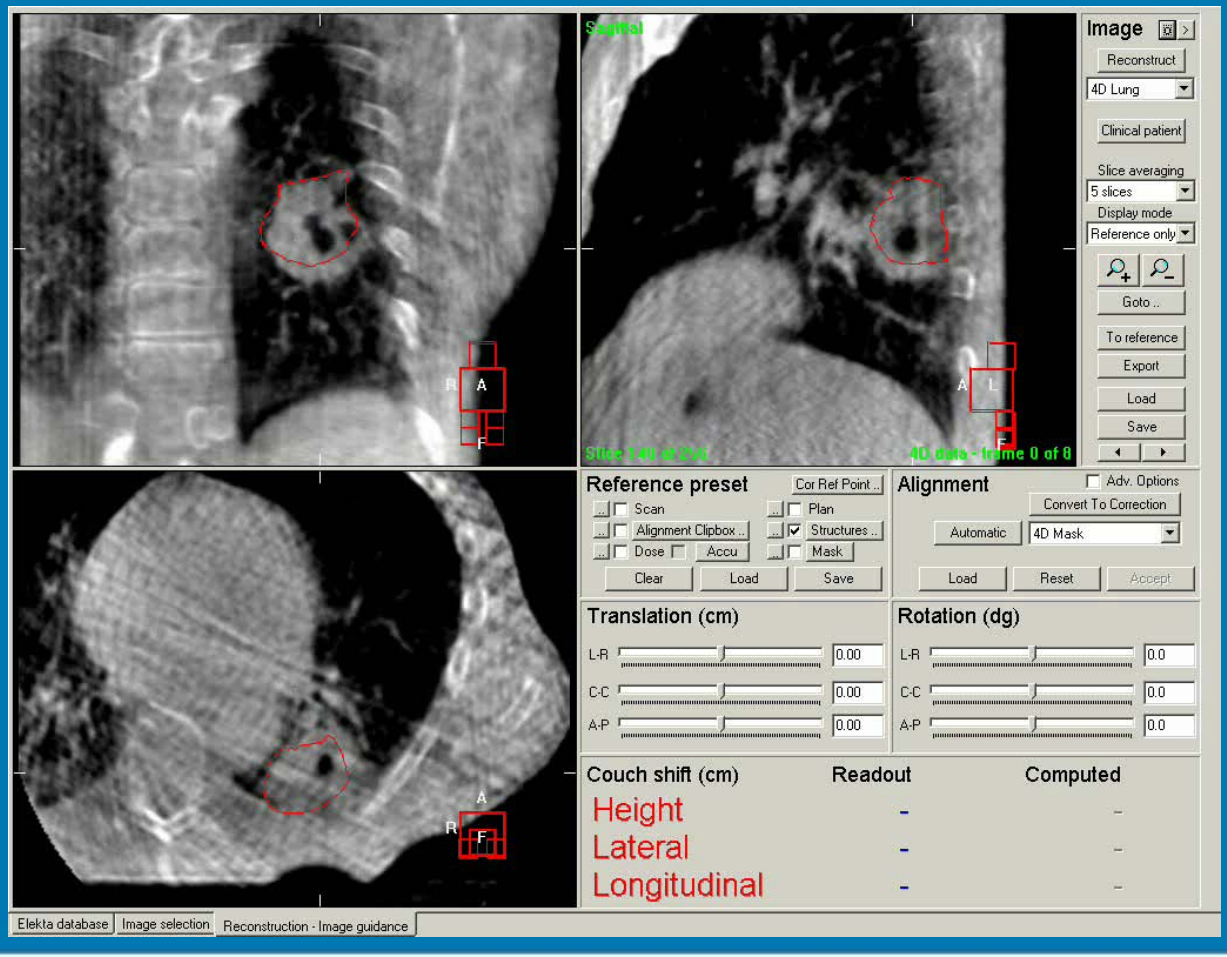
Purdie *et al.* (IJROBP2007)

Baseline shifts



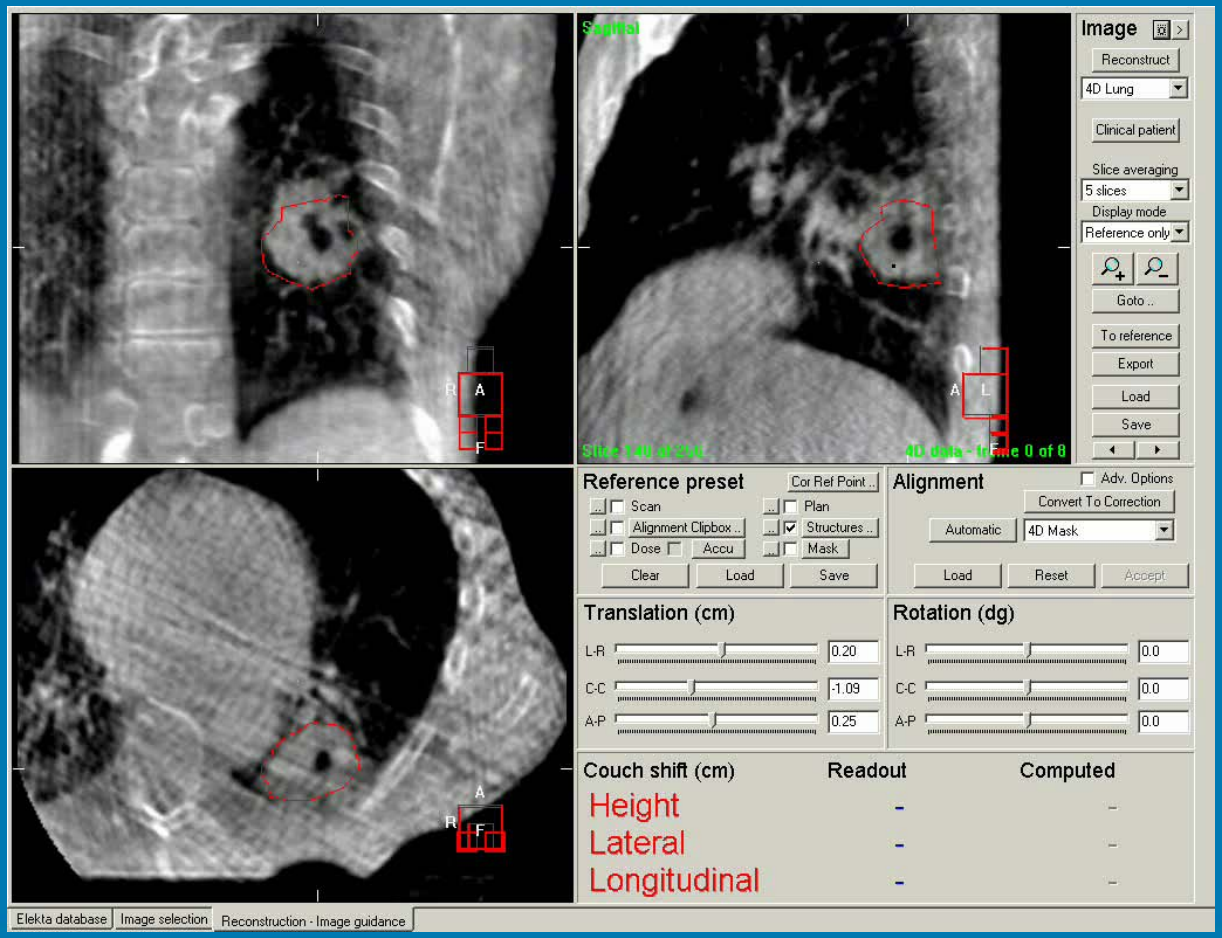
Sonke *et al.* IJROBP 2008

4D CBCT + GTV Contour



ESTRO
European Society for Therapeutic Radiology and Oncology

Apply Correction

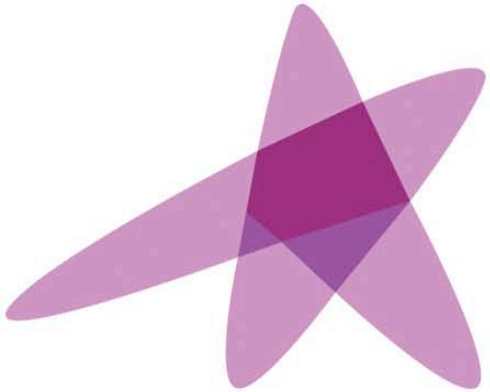


Conclusions

- IMRT superior to 3DCRT for locally advanced NSCLC
  - lower dose to all risk organs except low dose to lungs

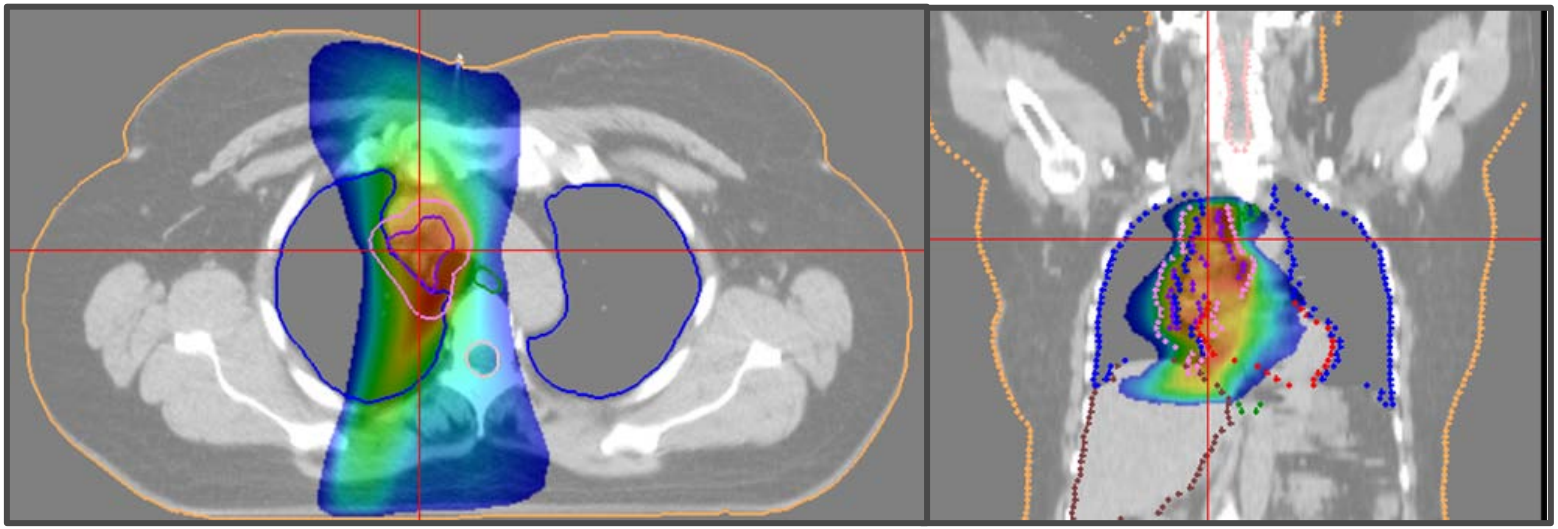
- Interplay effects not really critical in IMRT
  - gated delivery not crucial for IMRT
  - but start off with ‘simple’ plans with large segment shapes
  - additional respiration margin of about ¼ amplitude (if GTV is delineated at mid-vent CT)

- Start working on a sound IGRT protocol before going into optimizing your planning procedures



ESTRO School

UNIVERSITÄTS KLINIKUM FREIBURG

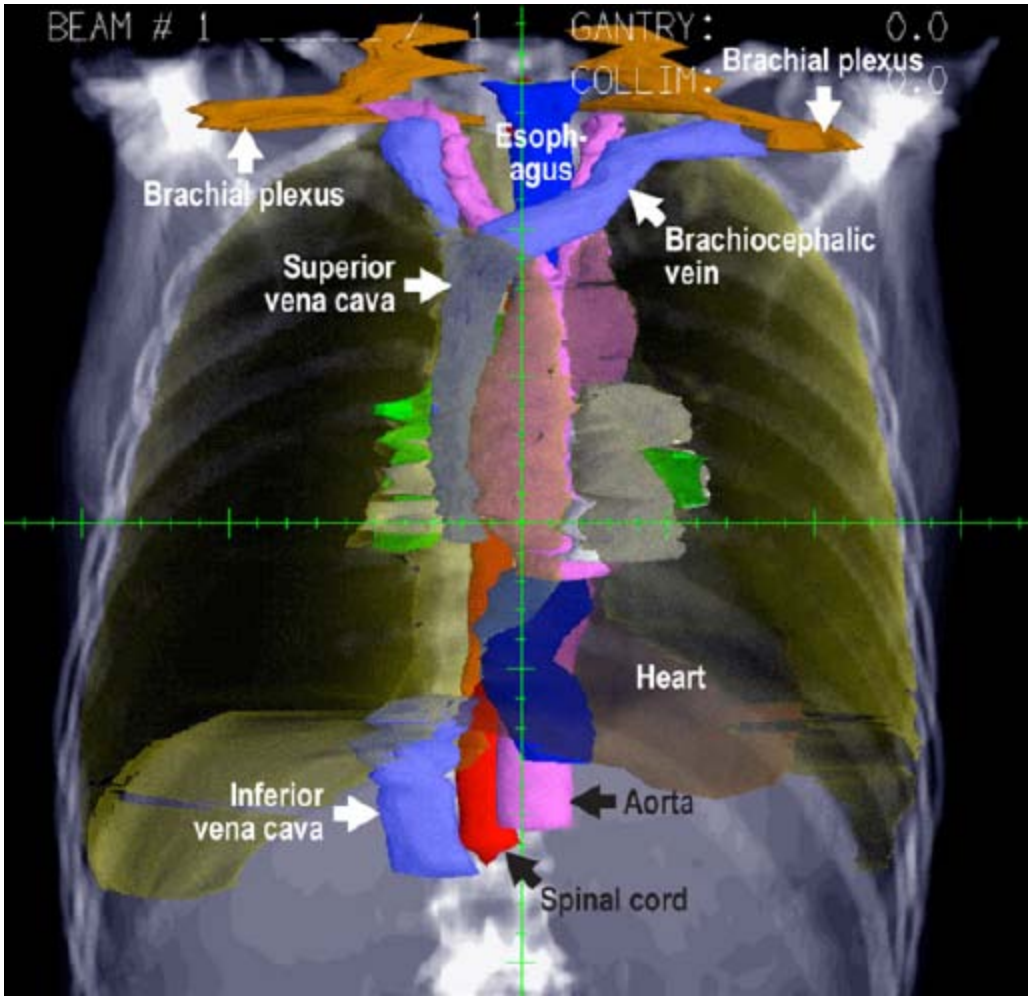


Relationships between 3D dose distributions and clinical toxicities - Chest

Ursula Nestle

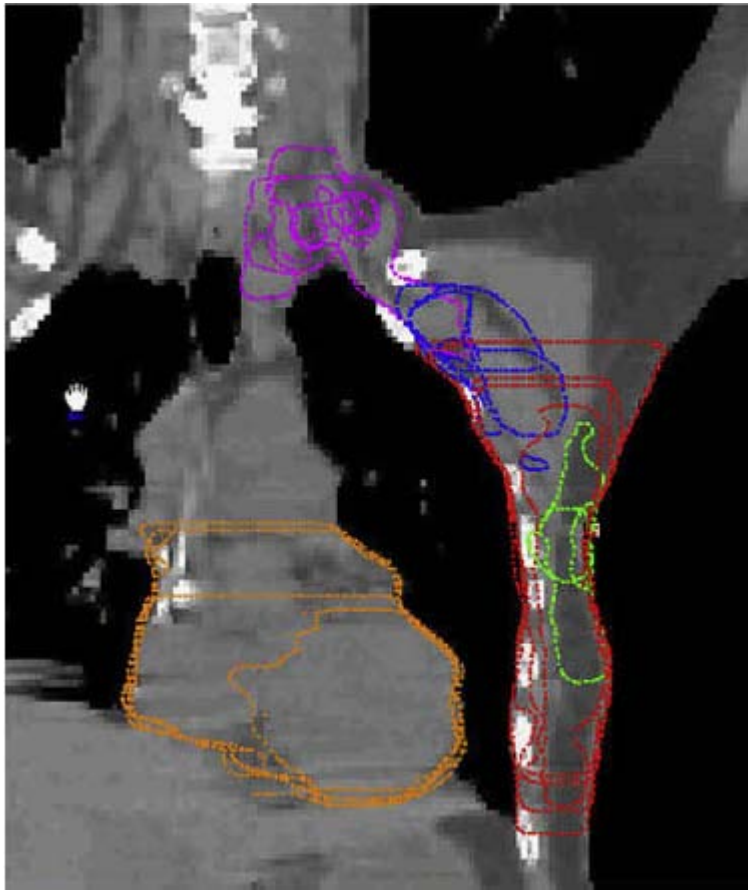
Freiburg, Germany

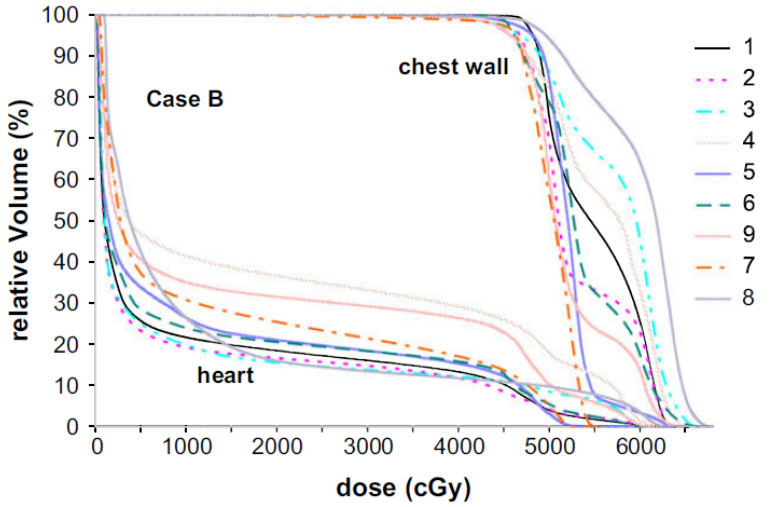
Normal tissues in the chest

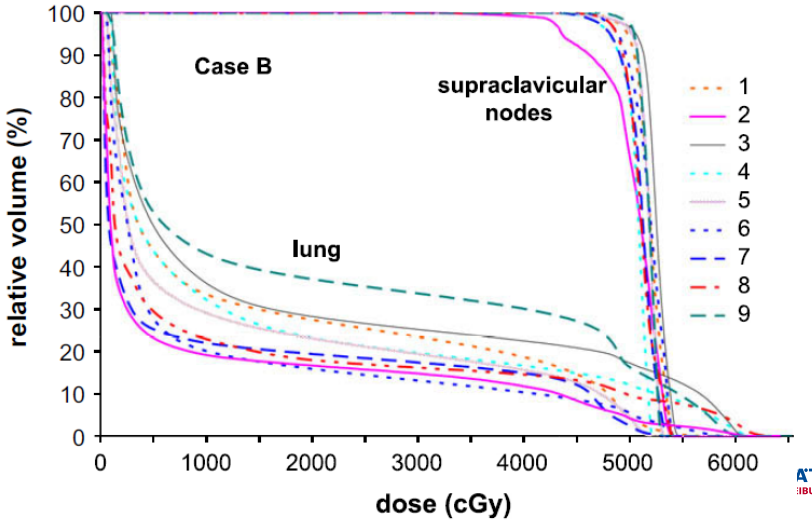


Kong, IJROBP 2011; 81(5); 1442-57

IOV in NT contouring: impact on dose calculation and plan optimisation







Li, IJROBP 2009; 73(3); 944-51

Dose limits for normal tissues in the chest

Table 1. Dosimetric limits for thoracic organs at risk

Dose limits for OARs	3D-CRT (RTOG 0617)	3D-CRT (RTOG 0972/CALGB 36050)	SBRT (RTOG 0618, 3 fx)	SBRT (ROSEL European trial, 3 or 5 fx)
Spinal cord (point dose)	Point dose ≤50.5 Gy	Any portion ≤50 Gy	≤18 Gy (6 Gy/fx)	18 Gy (3 fx) 25 Gy (5fx)
Lung	Mean lung dose ≤20 Gy, V_{20} ≤37%	V_{20} ≤35%	V_{20} ≤10%*	V_{20} <5–10%†
Esophagus	Mean dose ≤34 Gy	Not limited	≤27 Gy (9 Gy/fx)	24 Gy (3 fx) 27 Gy (5 fx)
Brachial plexus (point dose)	≤66 Gy	Not limited	≤24 Gy (8 Gy/fx)	24 Gy (3 fx) 27 Gy (5 fx)
Heart‡	≤60, ≤45, ≤40 Gy for 1/3, 2/3, 3/3 of heart	≤60, ≤45, ≤40 Gy for 1/3, 2/3, 3/3 of heart	≤30 Gy (10 Gy/fx)	24 Gy (3 fx) 27 Gy (5 fx)
Trachea, bronchus	Not limited	Not limited	≤30 Gy (10 Gy/fx)	30 Gy (3 fx) 32 Gy (5 fx)
Ribs	Not limited	Not limited	Not limited§	Not limited
Skin	Not limited	Not limited	≤24 Gy (8 Gy/fx)	Not limited

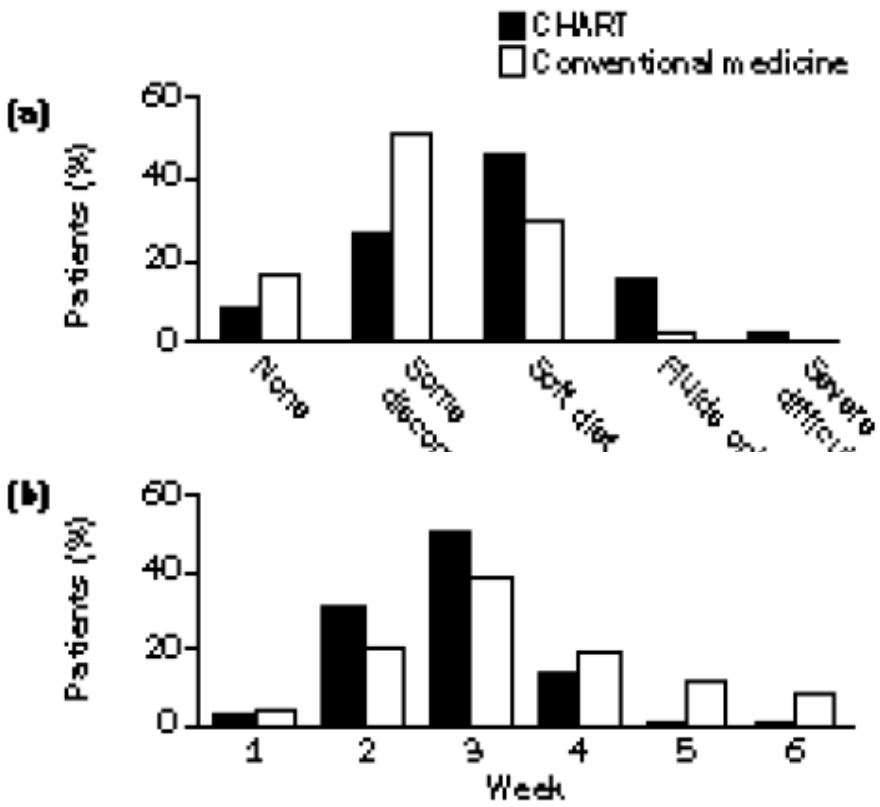
Kong, IJROBP 2011; 81(5); 1442-57

Esophagus: acute reactions

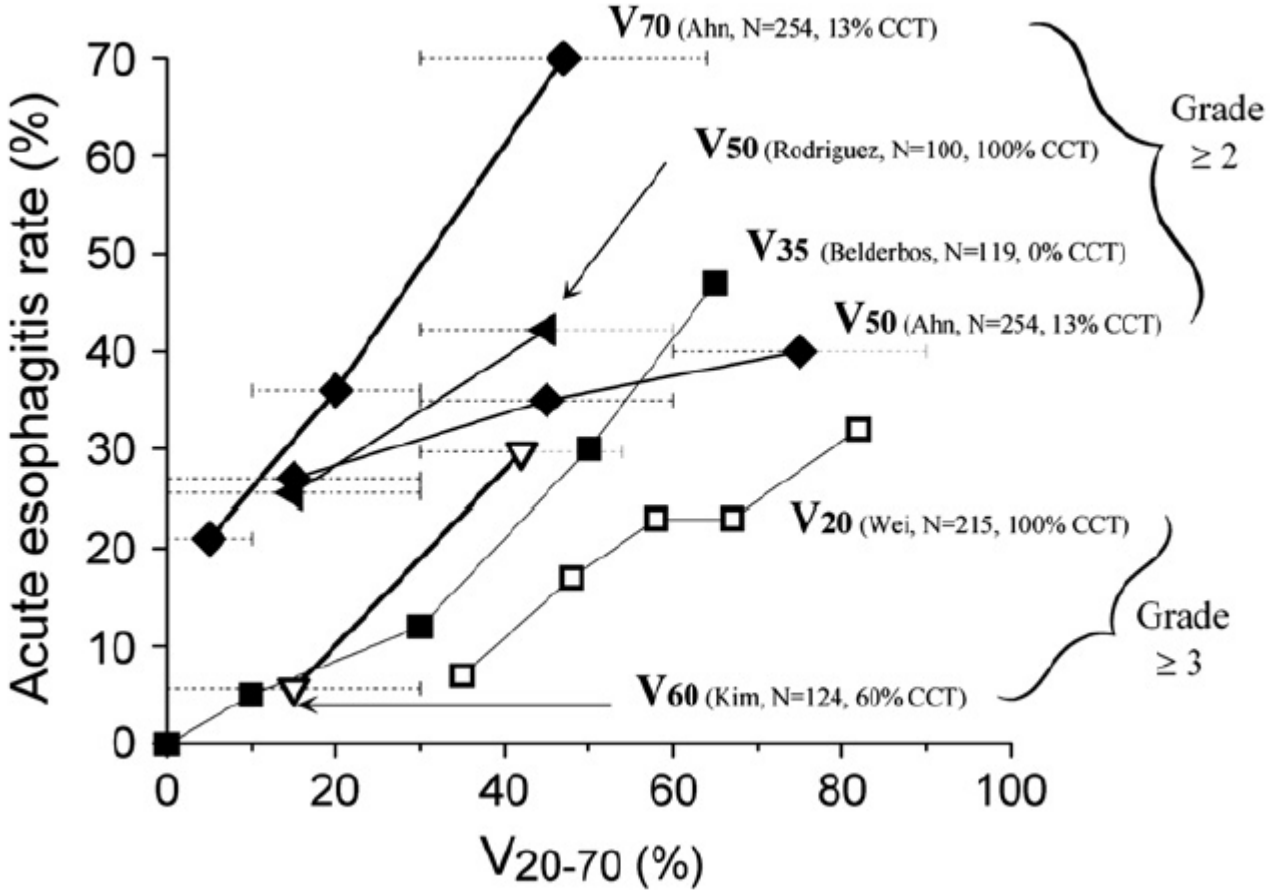
Acute esophagitis
- from ca. 30 Gy/2 Gy
- ca. 3%/ 60 Gy fluid only

Influencing factors:
- Dose
- Fractionation
- Chemotherapy

Therapy:
- symptomatic



Acute esophagitis: dose/volume effects



Werner-Wasik IRJOBP 2010 76(3) Suppl., S86-S93

Esophagus: late reactions

Fibrosis

Stricture < 2% < 60 Gy

Influence factors:

- Dose
- Fractionation
- Volume

Therapy:

symptomatic

Grade 1 radiation-induced esophagitis was observed 1 week after the start of IGRT in 1 patient with metastatic lung cancer who received 48 Gy/8 Fr to the 3.5-cm tumor located posterior to the right main bronchus. The pain resulting from acute radiation esophagitis was relieved at 1 month after IGRT ended. However, this patient suffered from swallowing pain again 3 months after IGRT ended and died as a result of bleeding from an esophageal ulcer 5 months after IGRT ended.

Onimaru IJROBP 2003

Esophagus: planning constraints

conventional fractionation

RTOG 0117:

- V55 < 30%; mean dose < 34Gy

QUANTEC (Werner-Wasik 2010):

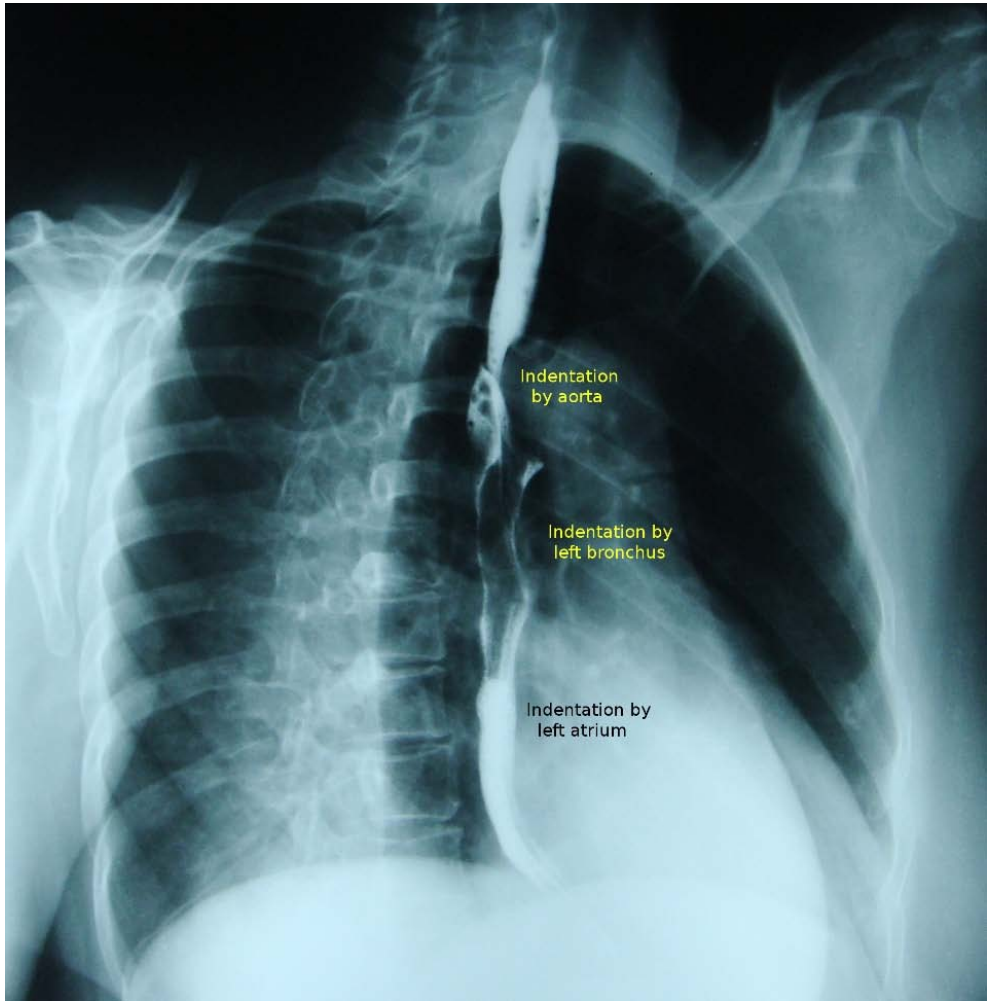
- esophagus dose should not exceed prescription dose
- mean dose < 34 Gy
- max dose up to 74 Gy/ 2Gy + CHT

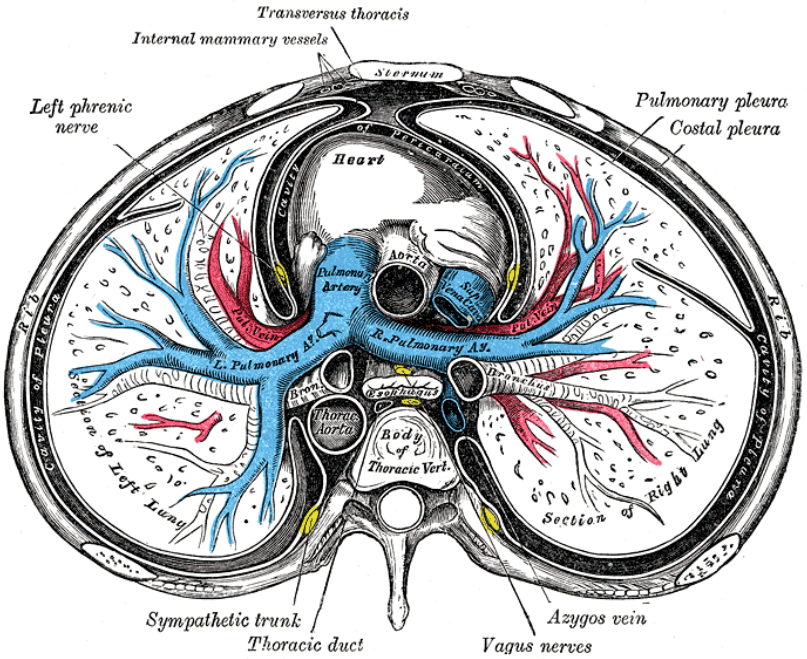
SBRT

Rosel-trial:

maximum dose: 24Gy/3fr or 27Gy/5fr

Esophagus: anatomy





Wikipedia

Esophagus: contouring

- contour whole organ including its filling from cricoid cartilage to gastroesophageal junction

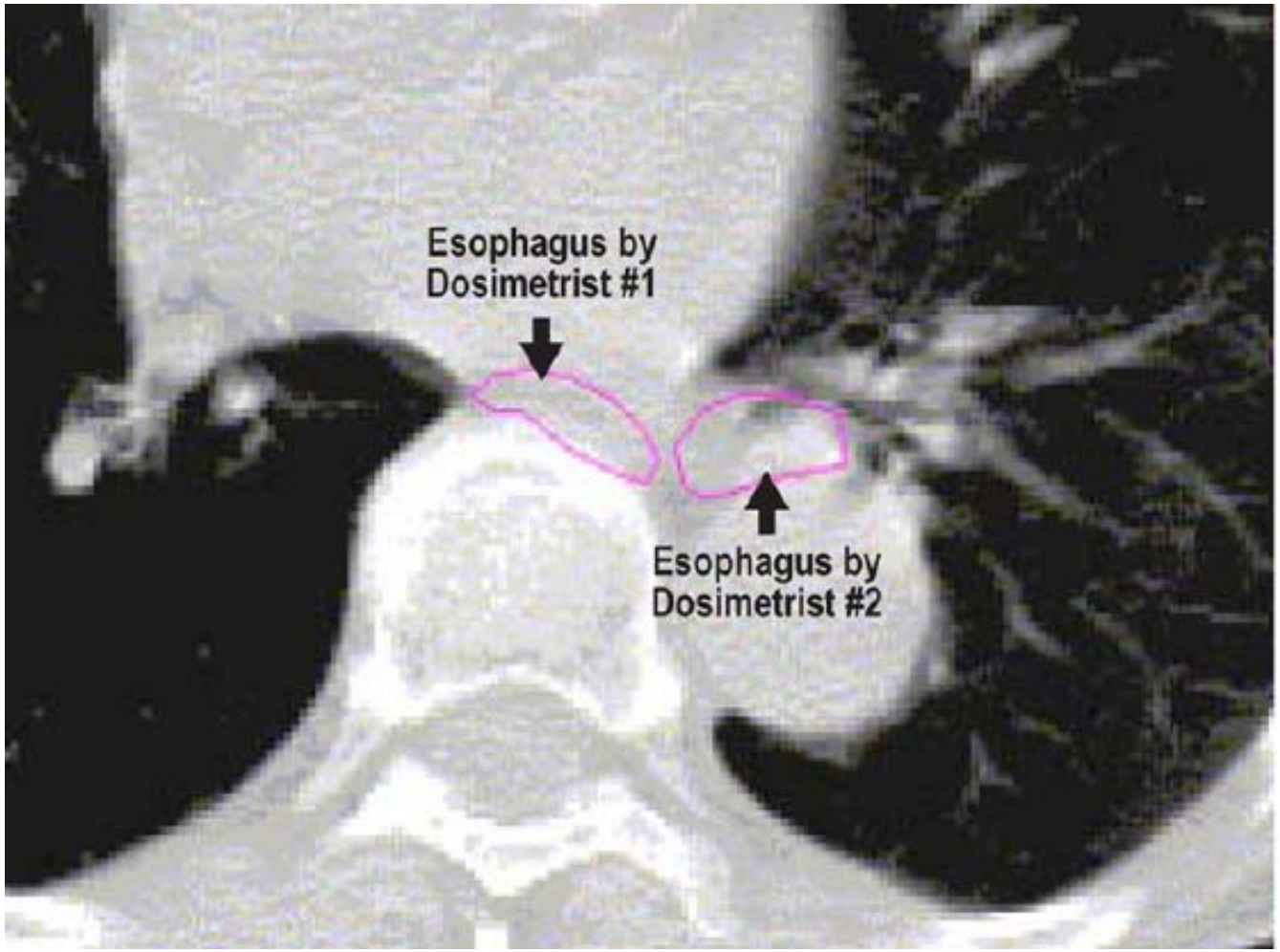
Challenges:

may be difficult to find (search for air)

varying filling

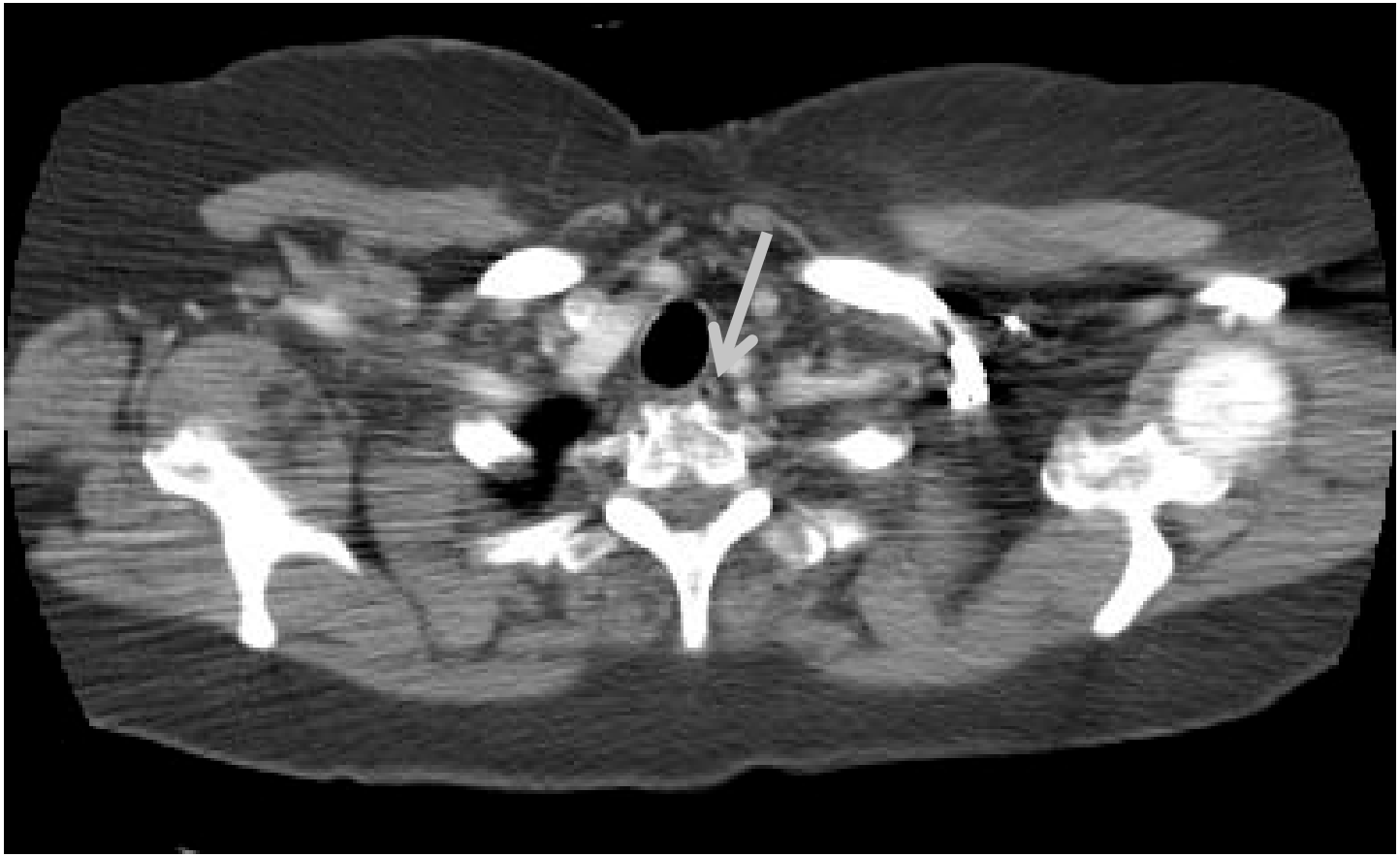
often collapsed (barium swallow or interpolation may help)

Esophagus: geographic miss

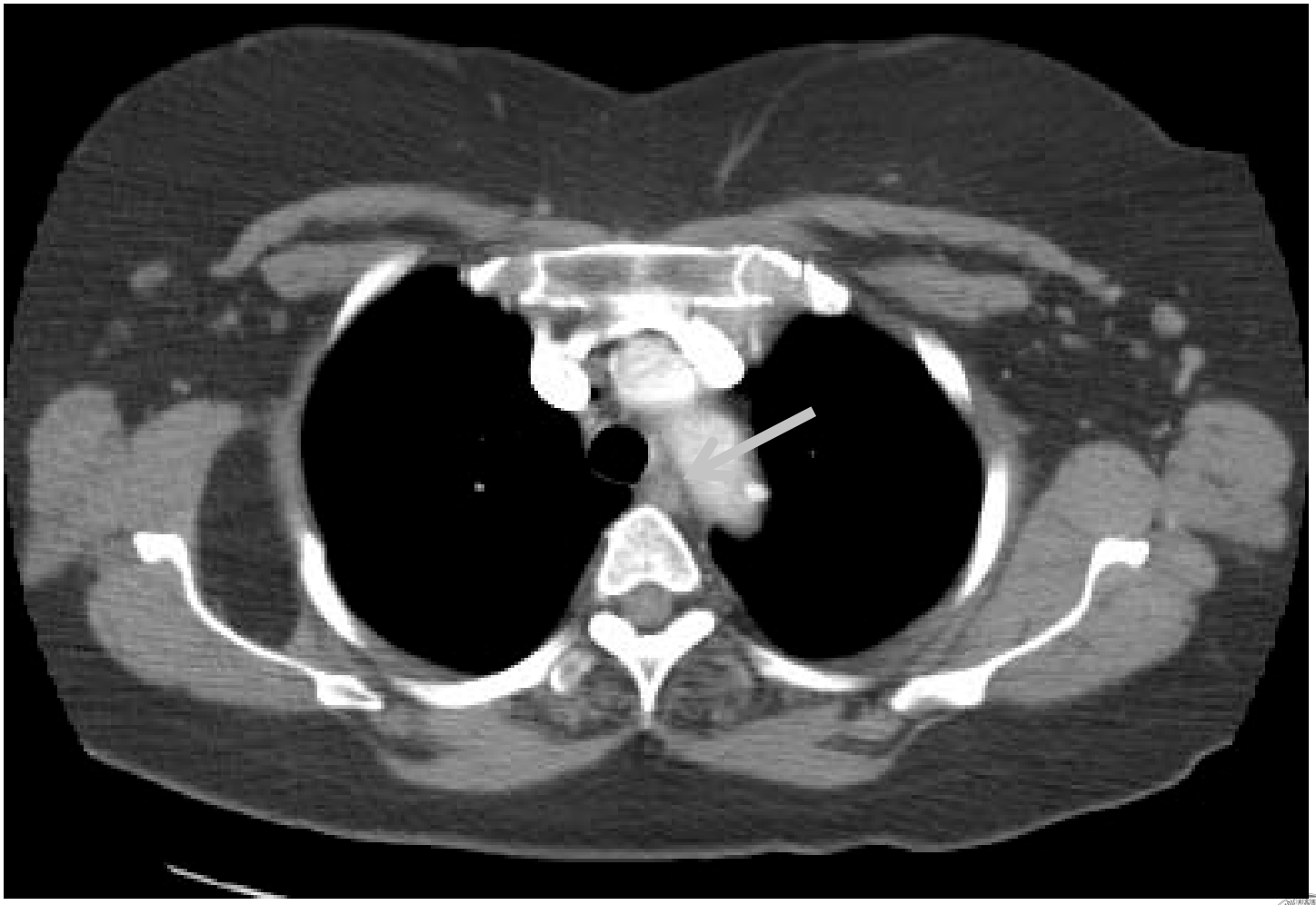


Collier 2003 JACMP 4; 17-24

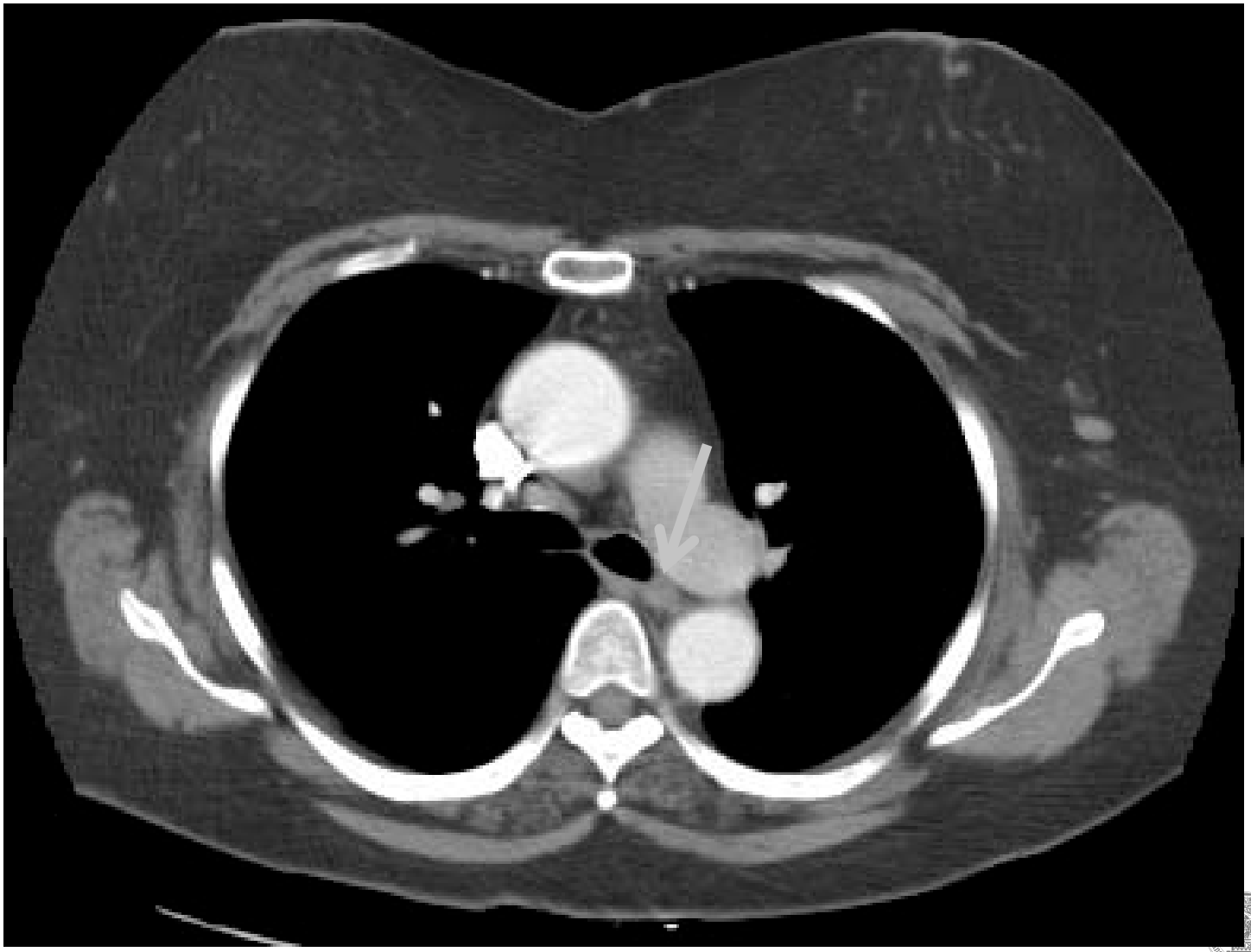
Find the esophagus



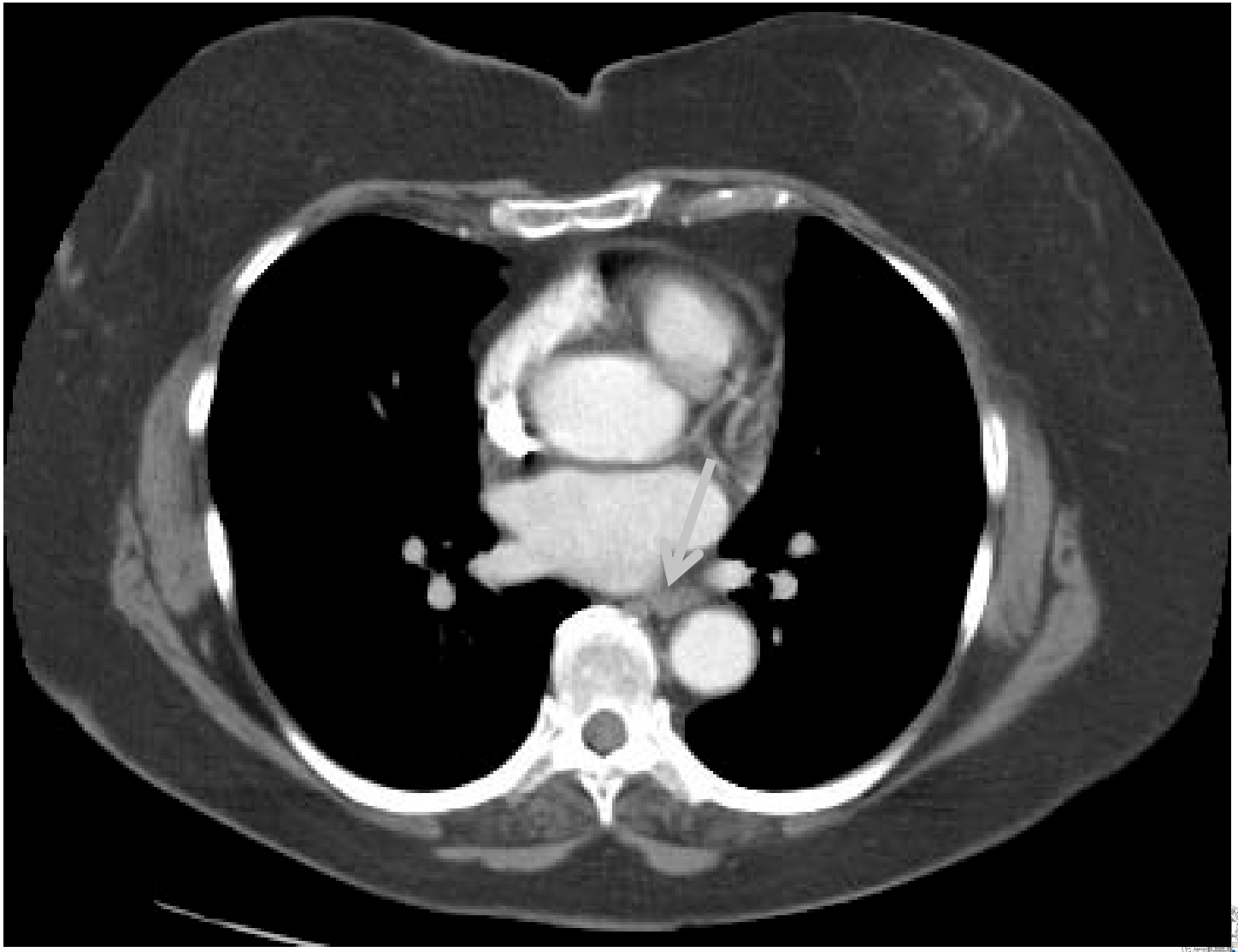
Find the esophagus



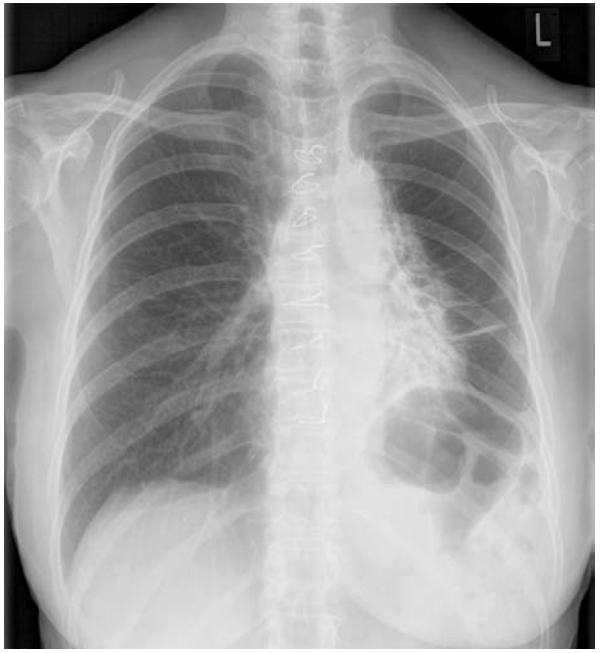
Find the esophagus



Find the esophagus

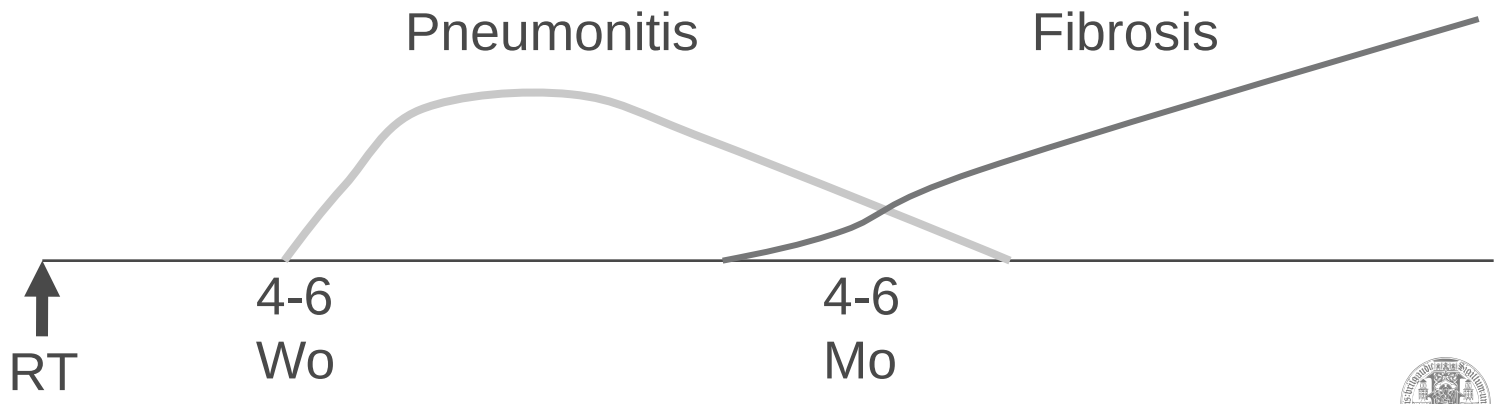


Lung (RILD)



1. acute radiogenous Pneumonitis
   (cough, fever, dyspnea)
   Treatment: Corticoids

2. focal radiogenous fibrosis
   symptoms depending on volume involved
   treatment: none
   prophylaxis: treatment planning



RILD: influence factors

Total dose: clear dose-response relation; tolerance < 25 Gy/2 Gy

clear fractionation effect

Influence factors: old age, smoking, chemotherapy

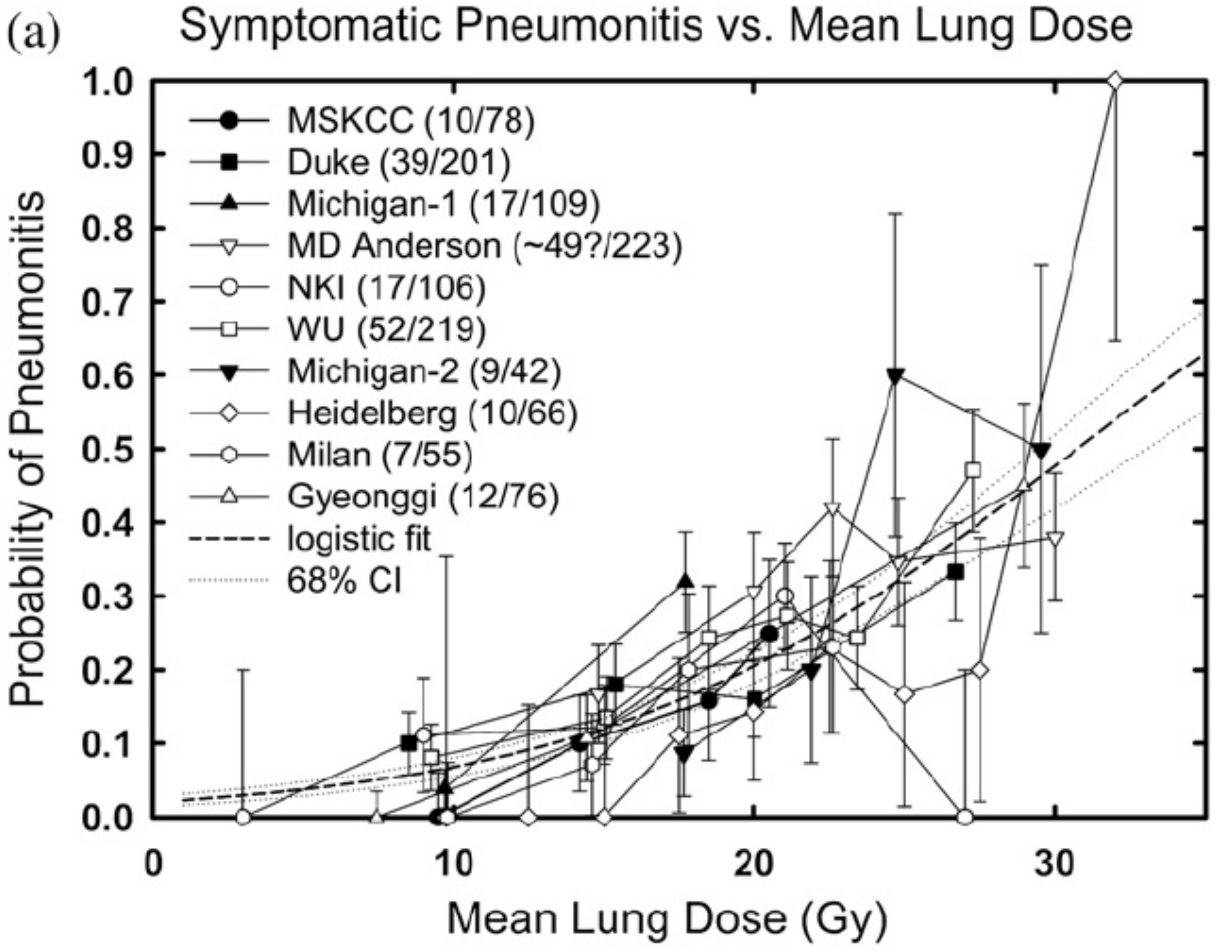
Graham et al. IJROBP1999:

V20 single best predictor of acute pneumonitis (cave: 3D-CRT)

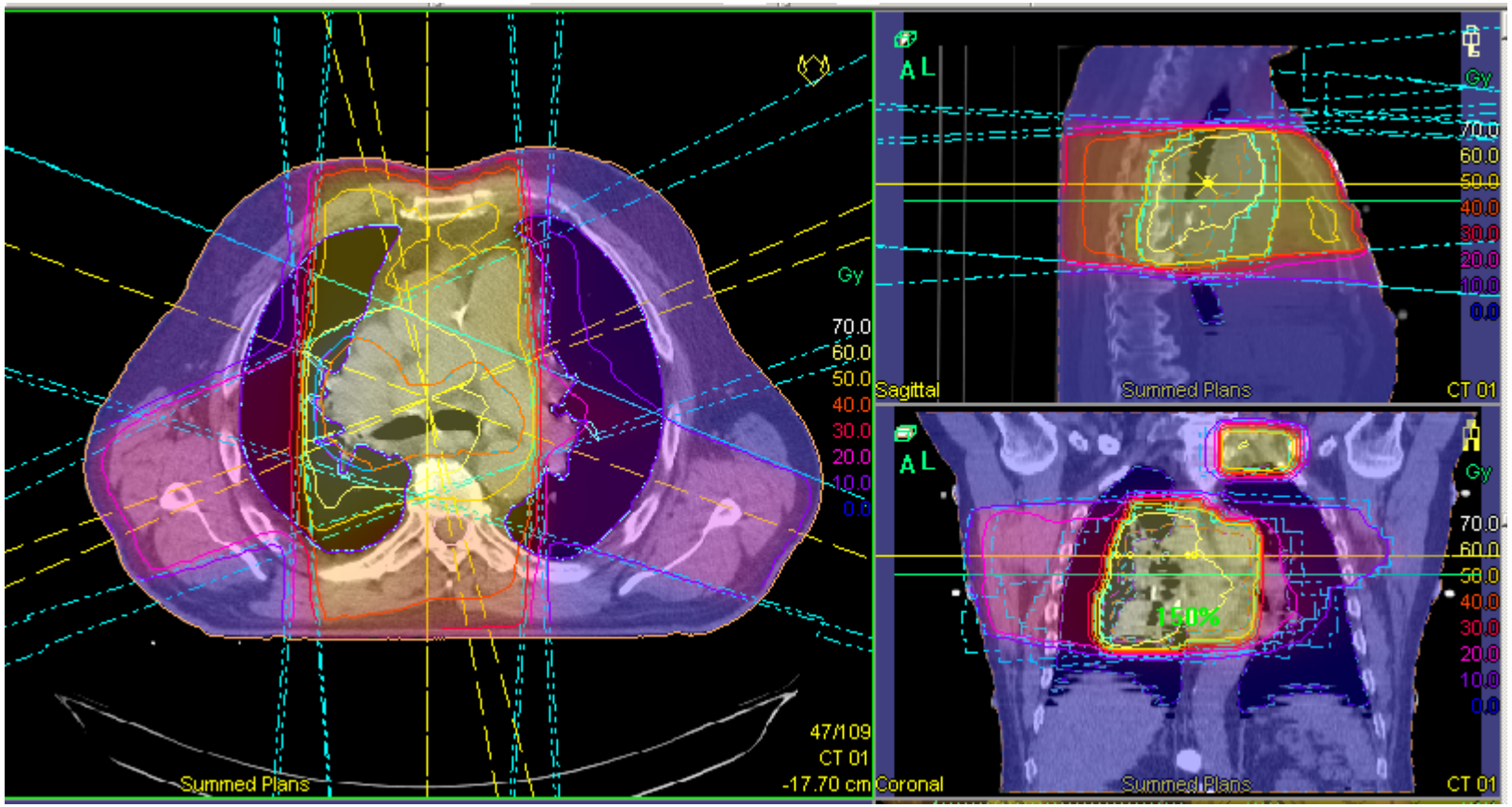
Table 6. Correlation between V_{20} and severity of pneumonitis

V_{20} (%)	Grade 2 (%)	Grade 3–5 (%)
<22	0	0
22–31	8	8
32–40	13	5 (1 fatal)
>40	19	23 (3 fatal)

RILD: corelation between MLD and probability of symptomatic pneumonitis

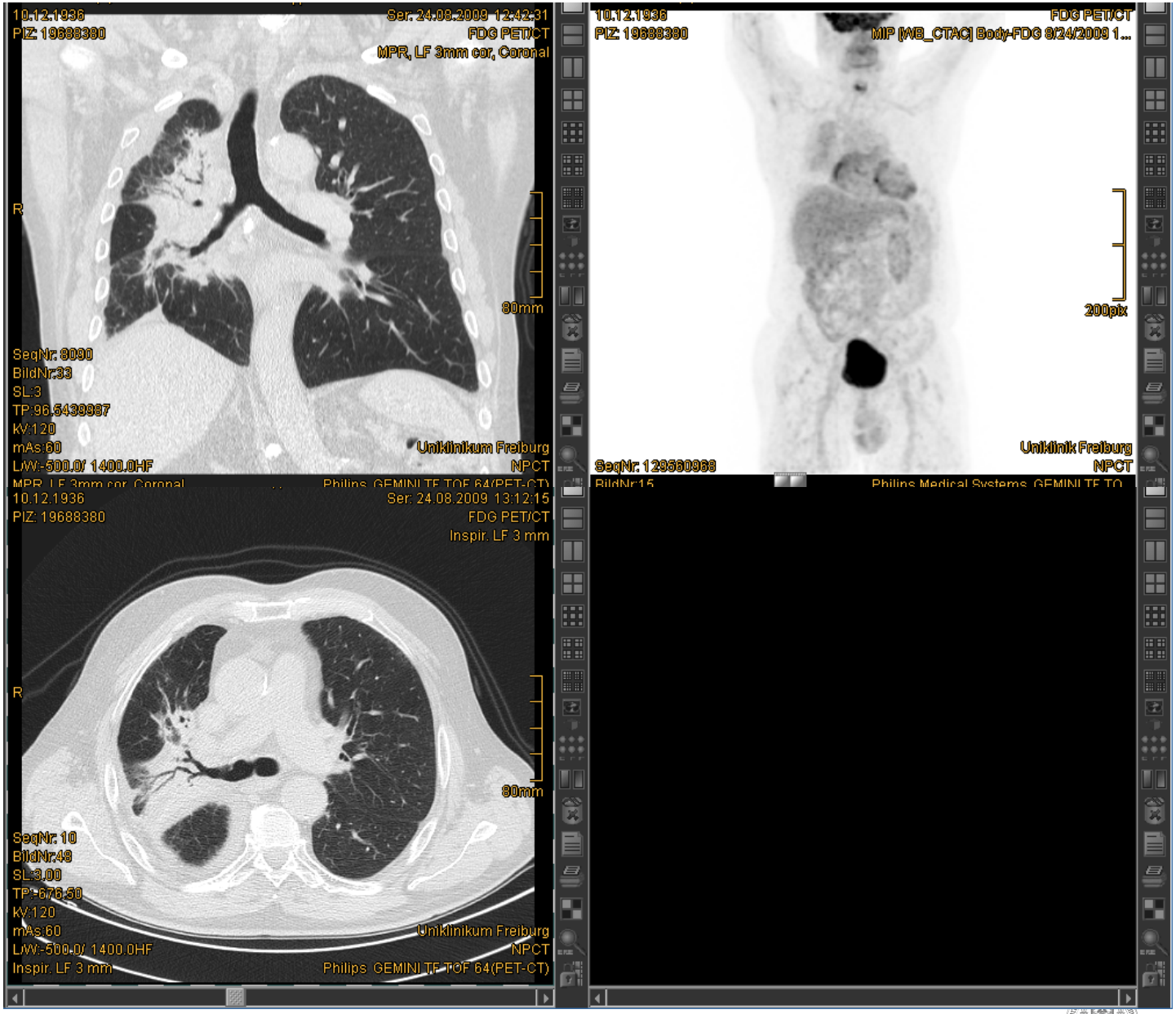


Marks, IJRBOP 76(3) S70-S76 2010



NSCLC IIIb, chemo-radiotherapy; 60 Gy/2 Gy + 2 cycles Cisplatinum
V20: 36%; MLD: 20 Gy

PET/CT
11 mths
after RT



Lung: planning constraints I

Conventional RT

V20:

< 30% (RTOG 0117)
< 35% (PET-Plan; Convert)
< 31% (LungART, after lobectomy)
< 22% (LungART, after pneumonecomy)

mean lung dose

< 20 Gy (PET-Plan)
to be recorded (Convert, LungART)

QUANTEC:

> Despite these caveats, it is prudent to limit V20 to ≤30–35 % and MLD to ≤20–23 Gy (with conventional fractionation) if one wants to limit the risk of RP to ≤20% in definitively treated patients with non–small-cell lung cancer.

Lung: what about low doses?

Shi *et al. Radiation Oncology* 2010, **5**:35
http://www.ro-journal.com/content/5/1/35

RESEARCH Open Access

Analysis of clinical and dosimetric factors associated with severe acute radiation pneumonitis in patients with locally advanced non-small cell lung cancer treated with concurrent chemotherapy and intensity-modulated radiotherapy

Anhui Shi, Guangying Zhu*, Hao Wu, Rong Yu, Fuhai Li and Bo Xu

94 pts, LANSCLC

RCT + IMRT

CTC 3.0

Table 4: Observed rates of SARP as a function of dosimetric parameters (NTCP/V10)

Varibale	Median(Range)	Group	No. of patients	No. of RP	*p* value*
NTCP	2.33%	≤4.20%	71	1(1.4%)	0.001
	(0.51-9.68%)	>4.20%	23	10(43.5%)	
V10	42.16%	≤50%	70	4(5.7%)	0.005
	(9.91-83.34%)	>50%	24	7(29.2%)	

Abbreviation: NTCP = normal tissue complication probability; SARP = severe acute radiation pneumonitis; * Multivariate logistic regression analysis.

Conclusions: NTCP value and V10 are the useful indicators for predicting SARP in NSCLC patients treated with concurrent chemotherapy and IMRT.

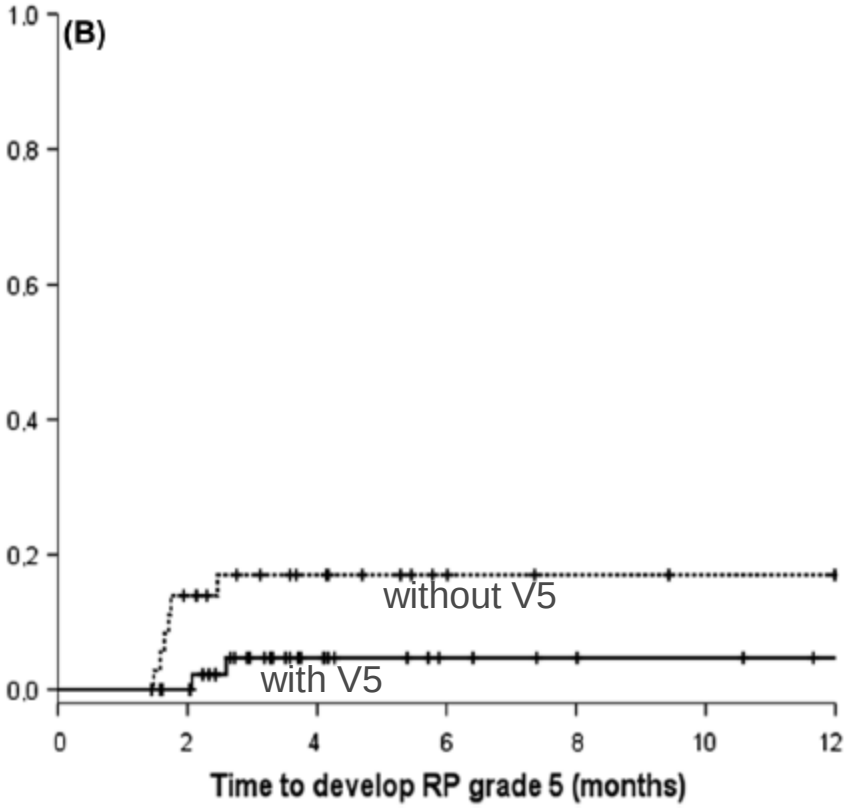
Lung: what about low doses?

Khalil et al. Acta Oncol 2015: IMRT, LANSCLC, 87 cases

phase I (n=12)
- only V20 < 40%

phase II (n=25)
- V20 < 40%
- and MLD ≤ 20 Gy.

phase III (n=50)
- V20 < 40%
- and MLD ≤ 20 Gy
- and V5 ≤ 60%



In conclusion, introducing IMRT combined with chemotherapy for the treatment of NSCLC resulted in higher incidence of RP grade 3 or more in comparison to 3D-CRT. Prospectively monitoring patients and introduction of new dose constraints, especially for volume receiving low doses could reduce the incidence of lethal RP in patients treated with IMRT.

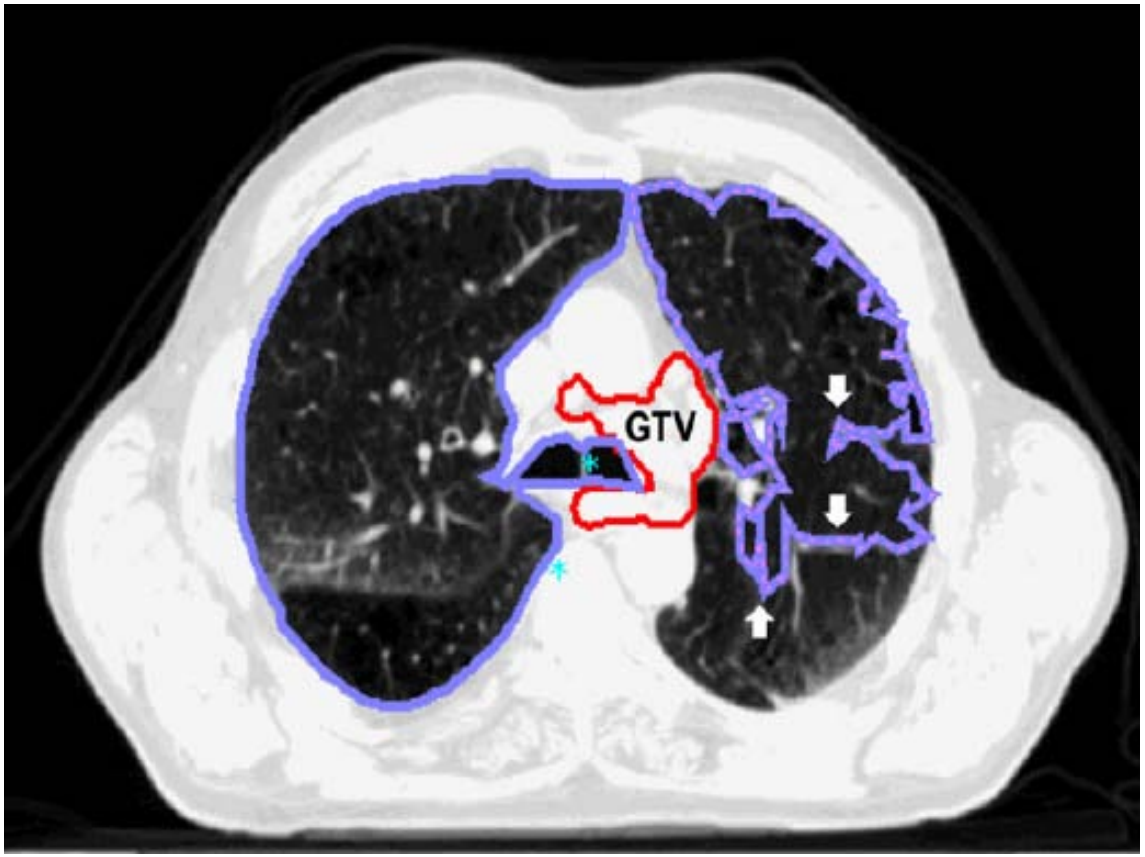
Lung: planning constraints II

SBRT (RTOG 0813)

Lung (Right & Left)	1500 cc	12.5 Gy (2.5 Gy/fx)		Basic Lung Function
Lung (Right & Left)	1000 cc	13.5 Gy (2.7 Gy/fx)		Pneumonitis

… if any !

Lung: contouring

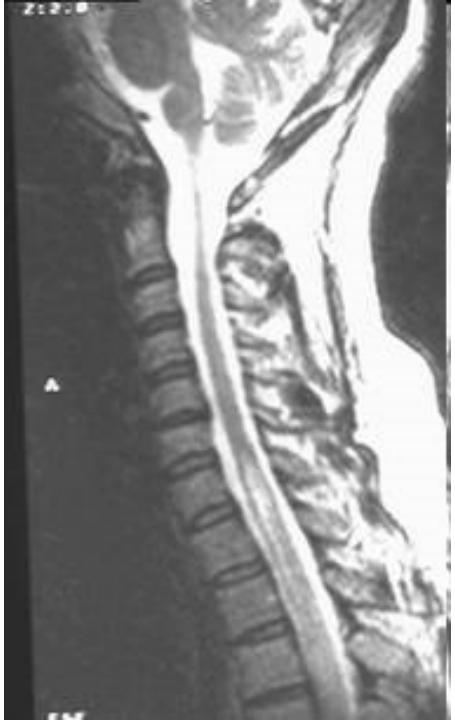


Check complete volume after automatic contouring!

exclude bronchi, bullae, non-lung air

Kong, IJROBP 2011; 81(5); 1442-57

Spinal cord



Tersteeg, Cancer Therapy 2004

Late effect: Myelitis

Incidence:

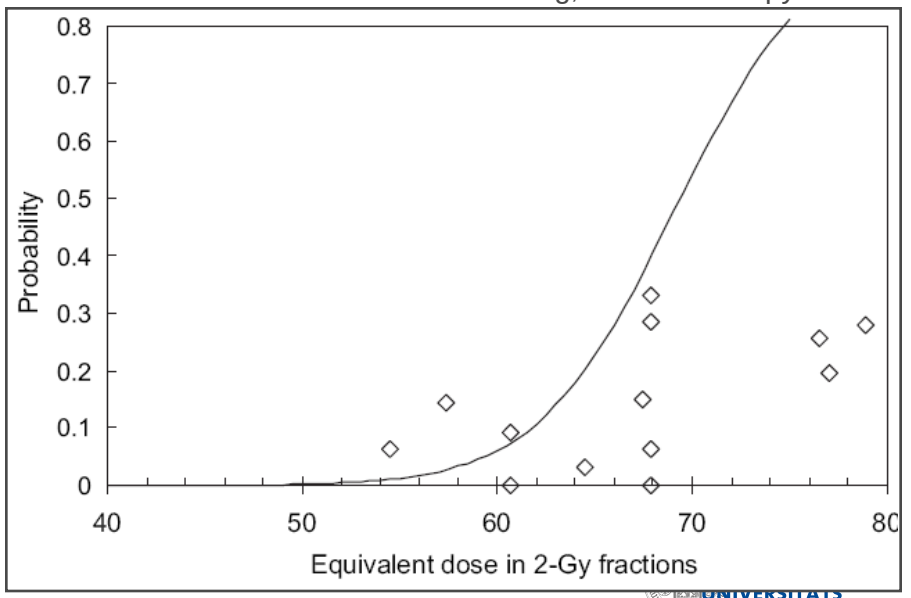
1% @ 2 years after 50-55 Gy/2

Influence factors

- Dose
- Fractionation
- Volume

Therapy: symptomatic

Prophylaxis: RT-Planning



Spinal cord: planning constraints

conventional RT

maximum dose

<= 45 Gy (RTOG 0117, LungART)

<= 48 Gy (Convert, PET-Plan)

SBRT

maximum dose

18 Gy/ 3 fr or 25 Gy / 5 fr (ROSEL)

30 Gy / 5 fr < 0.25 cc (RTOG 0813)

QUANTEC:

> With conventional fractionation of 2 Gy per day including the full cord cross-section, a total dose of 50 Gy, 60 Gy, and ~69 Gy are associated with a 0.2, 6, and 50% rate of myelopathy.

Spinal cord: contouring

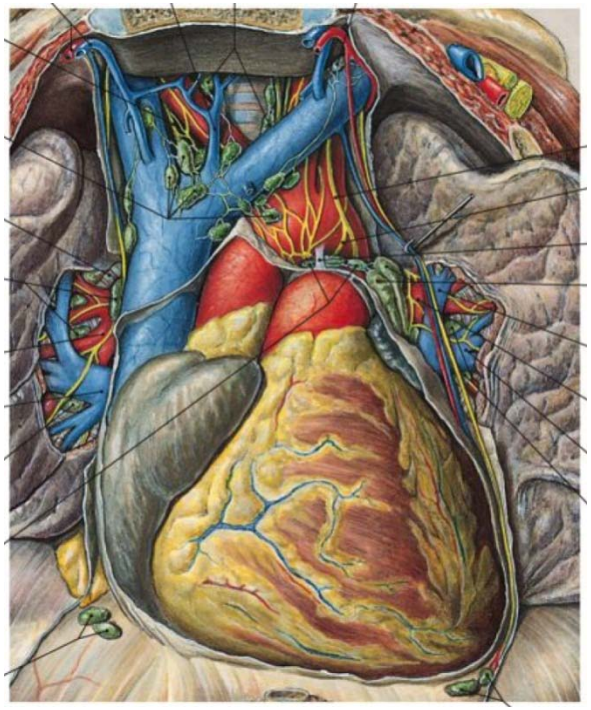
For the purpose of treating lung tumors, we would recommend that the spinal cord be contoured according to the bony limits of the spinal canal. The contour of the spinal cord can start at the same cranial level as the esophagus to the bottom of L2, or the level at which the cord ends.

Kong, IJROBP 2011; 81(5); 1442-57

Heart

acute reactions
- arrhythmias

late reactions:
- coronary artery disease
- cardiomyopathia
- valvular disease



Tolerance dose for clinically relevant endpoints
40 Gy/ 2 Gy ?

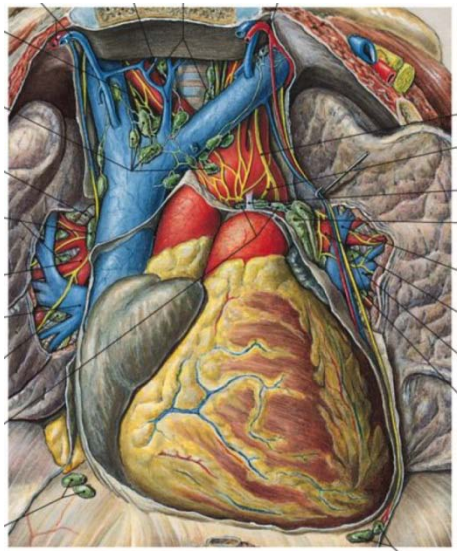
Treatment: symptomatic

Heart

Table 1. Endpoints related to radiation-induced heart disease

	Regional endpoints
Subclinical	Localized imaging abnormality (*e.g.*, perfusion defect or regional wall motion abnormality)
	Myocardial fibrosis
Clinical	Coronary artery disease
	Myocardial infarction
	Valvular disease

Global endpoints
Global imaging abnormality (*e.g.*, diffuse hypocontractility)
Asymptomatic decline in ejection fraction
Congestive heart failure
Pericarditis/pericardial effusion
Arrhythmia
Autonomic dysfunction (monotonous heart beat responding to changes in hemodynamic requirements)



OAR: whole myocardium, coronary arteries, Pericardium

Gagliardi, IJROBP 2010

Heart: planning constraints

conventional RT

as low as possible, whole heart < 40 Gy (RTOG 0117)

V30 < 35 Gy (LungART)

V50 < 33 Gy (Convert)

SBRT

maximum dose

- 24 Gy/ 3 fr or 27 Gy / 5 fr (ROSEL)
- 32 Gy / 5 fr < 15 cc (RTOG 0813)

QUANTEC:

For partial irradiation, conservative (NTCP) model-based estimates predict that a $V_{25Gy} < 10\%$ (in 2 Gy per fraction) will be associated with a <1% probability of cardiac mortality ~15 years after RT. For this a conservative (*i.e.*, overly safe) model was

Heart: Delineation

there is no present standard for contouring heart

Options:

1. contour relevant structures (CAs, valves, myocardium)
problem: movements; no restrictions available due to lack of data

2. contour left ventricle only
problem: dose to other relevant cardiac structures not documented

3. contour whole organ

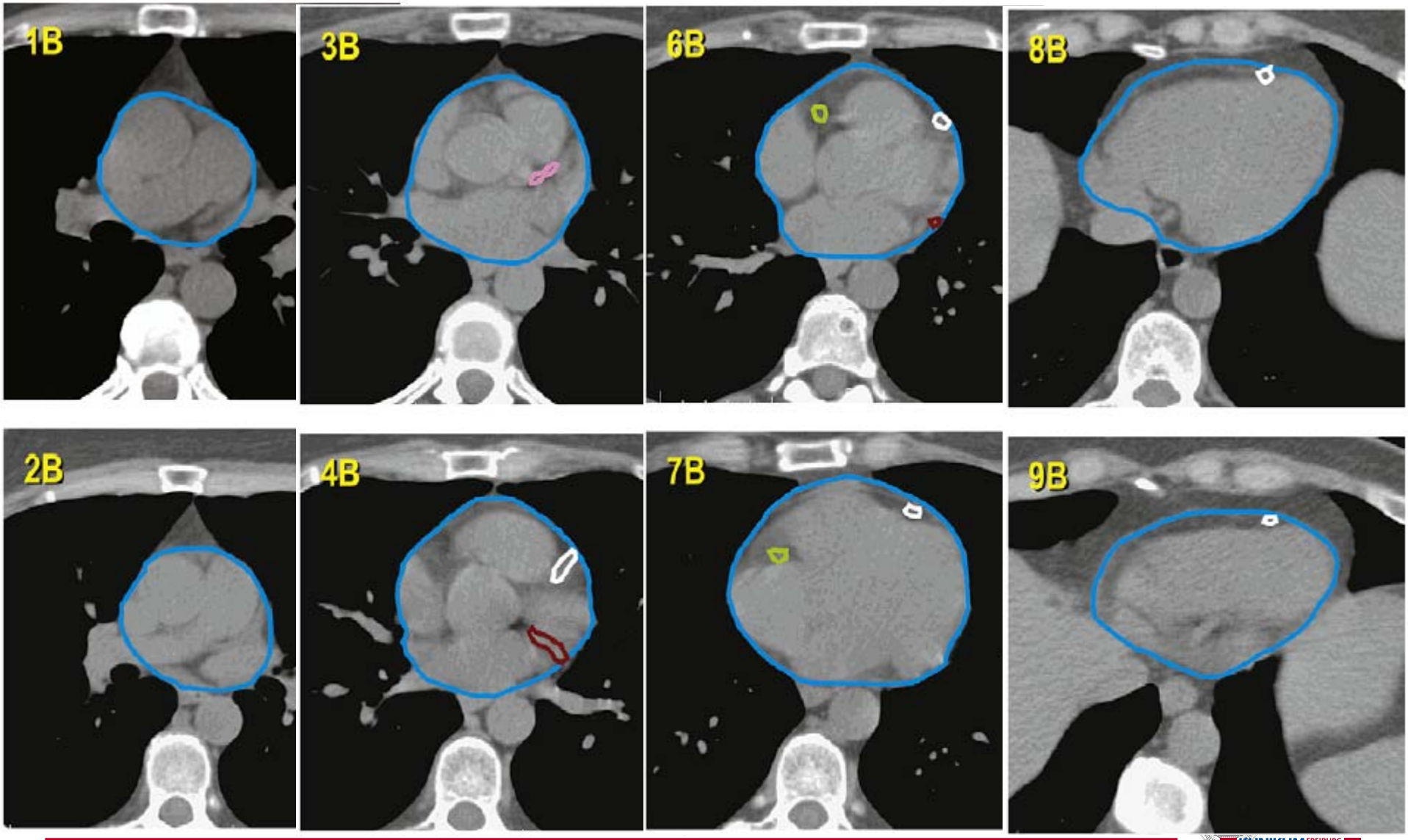
problem: no subvolumes available for further optimisation

Heart: contouring

Whole Heart and pericardium. Superiorly, the WH starts just inferior to the left pulmonary artery. For simplification, a round structure to include the great vessels as well can be contoured. Inferiorly, the heart blends with the diaphragm. Since cardiac vessels run in the fatty tissue within the pericardium, they should be included in the contours, even if there is no heart muscle visible in that area. If contrast is administered, the superior vena cava (SVC) can generally be contoured separately from the WH. If this is not possible, or when working with a noncontrast scan, the superior vena cava can be included for simplification and consistency.

Feng IJRBOP 2011 79(1) 10-18

Heart: contouring



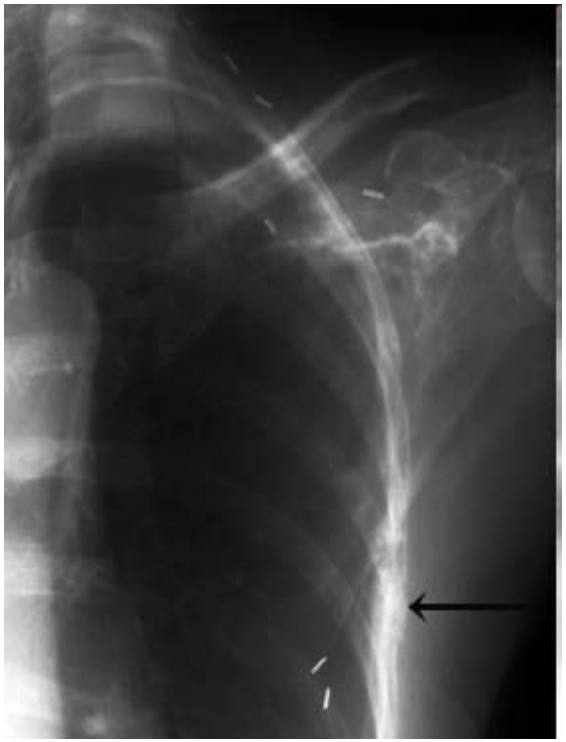
Feng IJRBOP 2011 79(1) 10-18

Bone

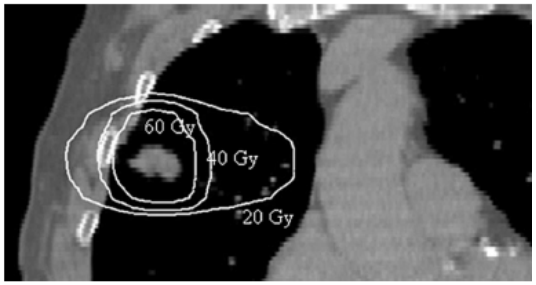
late effect
    Osteoradionecrosis

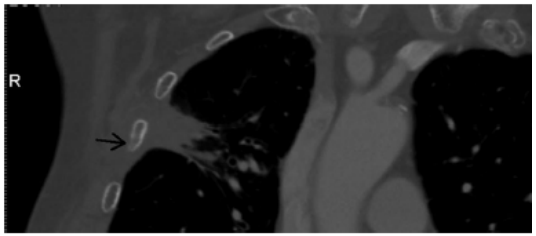
Tolerance dose
    ca. 60 Gy/2 Gy

treatment:
    symptomatic



Predictors of Radiotherapy Induced Bone Injury (RIBI) after stereotactic lung radiotherapy





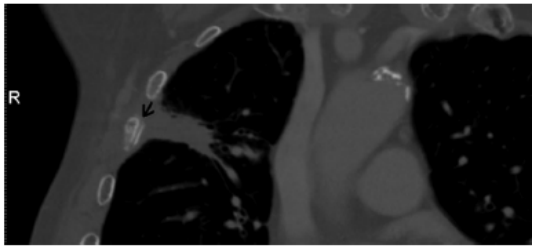


Table 5 Univariate and multivariate analysis on predictors for rib fractures (repeated measures have been taken into consideration)

Univariate analysis			
Predictor	**Odds Ratio**	**95% CI**	**p-value**
Age (years)	1.083	1.002 - 1.172	0.045
Gender-F	2.256	0.656 - 7.756	0.2
Diabetes Mellitus-yes	0.51	0.091 - 2.876	0.45
COPD-yes	0.97	0.275 – 3.386	0.96
Tumor size	1.037	0.982 -1.095	0.19
Smallest 3D distance between the tumor and closest rib	0.408	0.152 – 10.970	0.07
Multivariate analysis			
Age (year)	1.121	1.04 – 1.21	0.003
Gender-F	4.43	1.68 – 11.68	0.003
$D_{0.5}$	1.0009	1.0007 - 1.0011	<0.0001

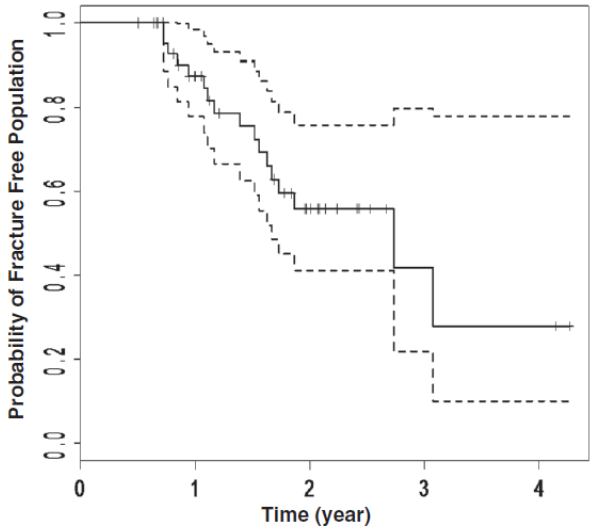


Figure 2 Kaplan Meier curve for fractured rib as an event (n = 46 patients). Dashed lines indicate 95% confidence intervals.

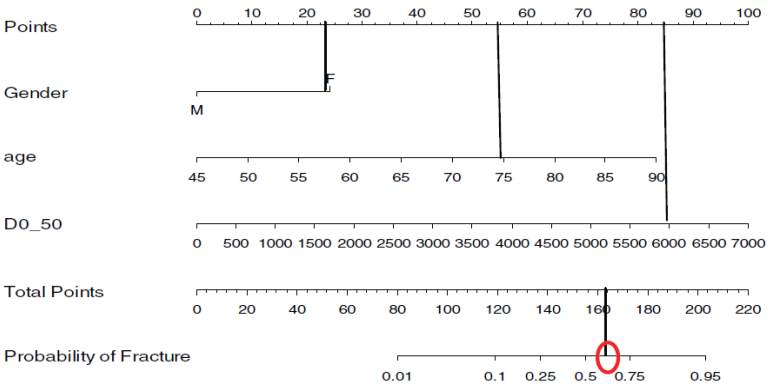
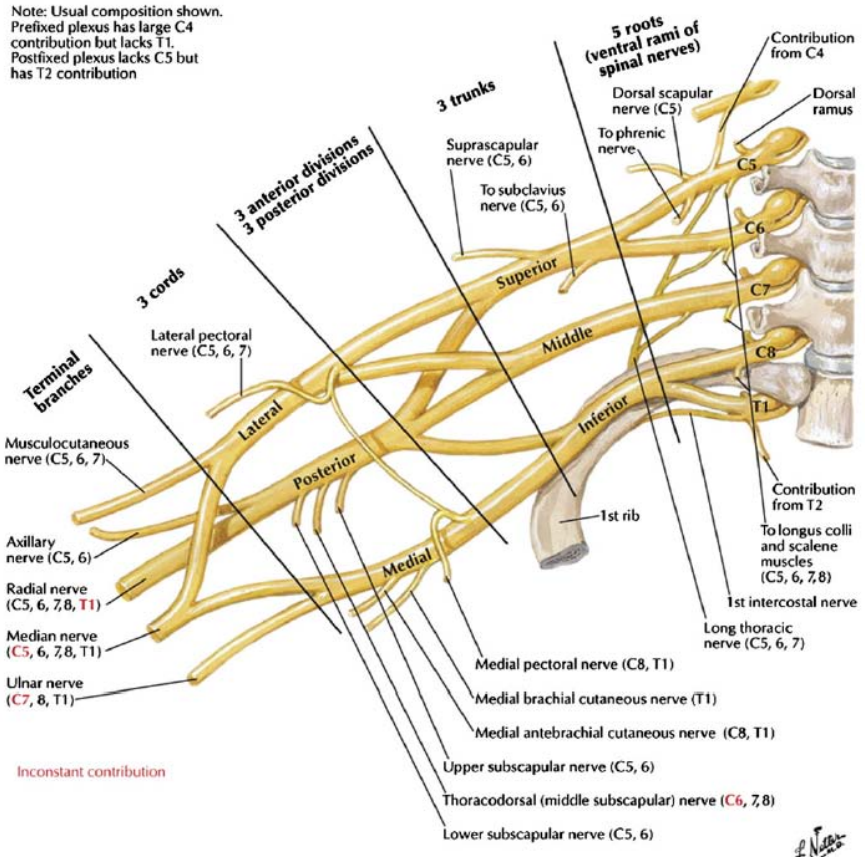
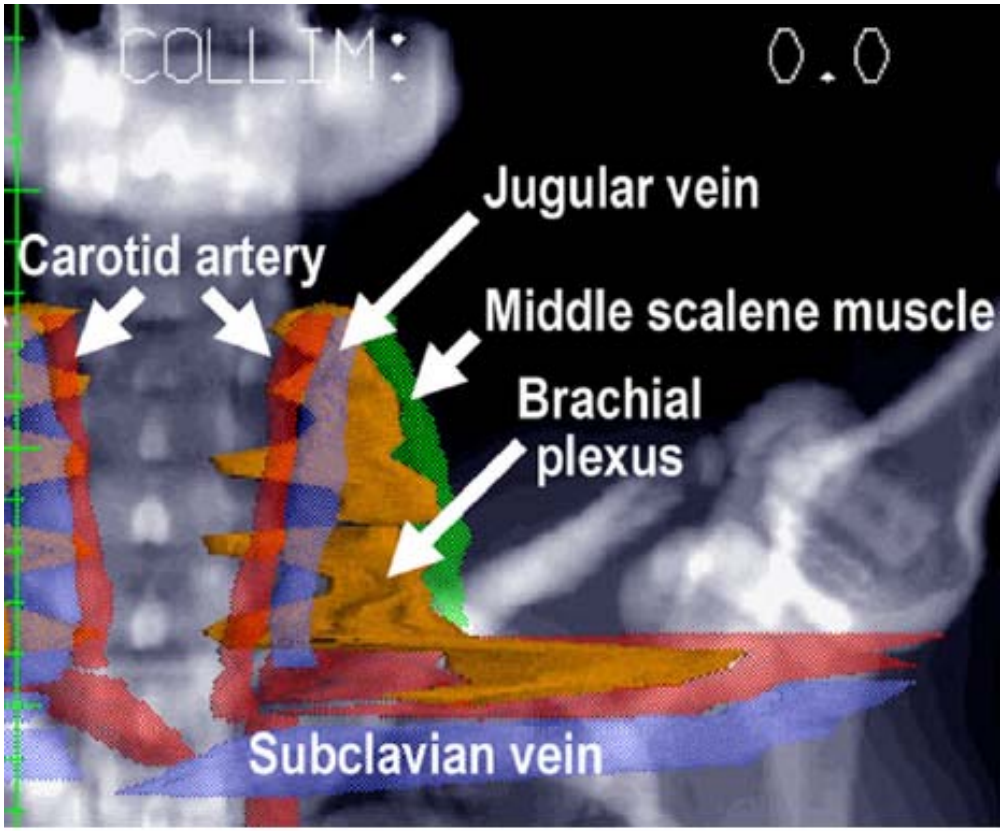


Figure 6 RIBI nomogram based on gender, age and $D_{0.5}$ in 46 patients treated with SBRT at Princess Margaret Hospital (Estimating risk of rib fracture at median follow up of 25 month). Risk of rib fracture in a 75 year old lady treated with 54 Gy in 3 fractions and D0.5 of 60 Gy (within a median FU of 2 years)is about 65%.

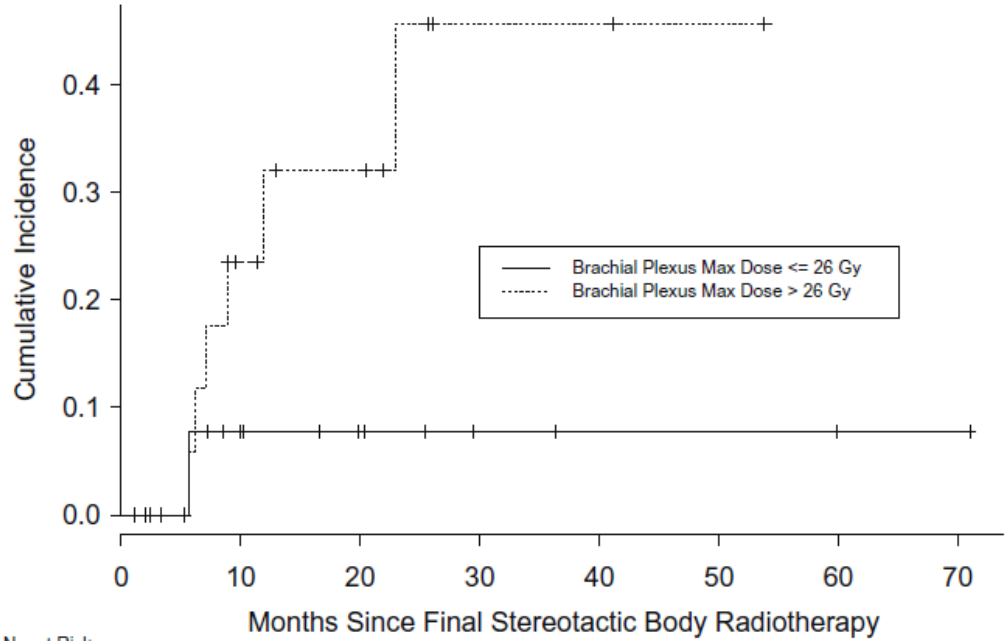
Brachial plexus

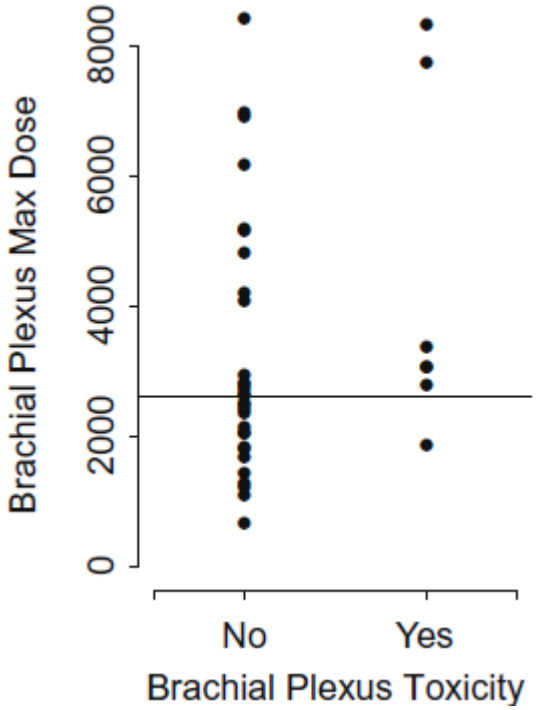




Kong, IJROBP 2011; 81(5); 1442-57

Brachial plexus: toxicity





Forquer, R&O 2009; 93; 408-412

Brachial plexus: planning constraints

Table 2
Maximum point dose constraints for various dose fractionation schemes used for conventional radiotherapy (30 fractions) and SBRT (1–6 fractions).

Daily dose (Gy)	No. of fractions	Total dose (Gy)	BED-3 (Gy3)	SFED-4 (Gy)
15	1	15	NA	15.0
9.5	2	19	NA	15.0
7.65	3	22.95	NA	15.0
6.75	4	27	NA	15.0
6.2	5	31	95	15.0
5.55	6	33.3	95	NA
2	30	60	100	NA

NA, not applicable.

Forquer, R&O 2009; 93; 408-412

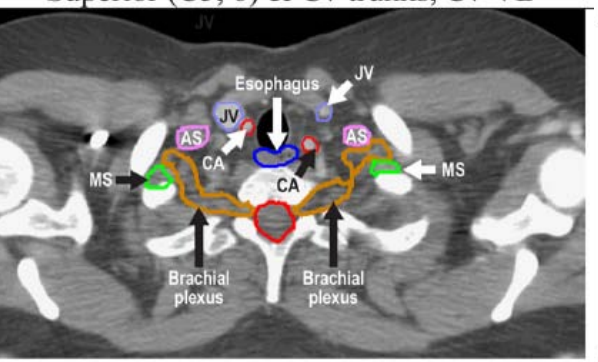
Contouring the brachial plexus

1. Locate the neural foramina at the C4-C5 and T1-T2 levels to identify the C5 and T1 roots, respectively
2. Locate the subclavian and axillary neurovascular bundle to identify the lateral aspect of the brachial plexus inferiorly
3. Locate the anterior and middle scalene muscles from the C5 vertebral level to their respective insertions on the first rib
4. Start at the neural foramina at the C4-C5 level and moving caudally; contour the region from the lateral aspect of the spinal canal laterally to the small space between the anterior and middle scalene muscles. At levels at which no neural foramina are present, contour the space or soft tissue between the anterior and middle scalene muscles
5. Continue to contour the space between the anterior and middle scalene muscles; eventually, the middle scalene muscle will terminate in the region of the subclavian neurovascular bundle
6. Contour the brachial plexus structures inferiorly until the region of the subclavian vascular bundle is identified, the second rib should serve as the medial limit

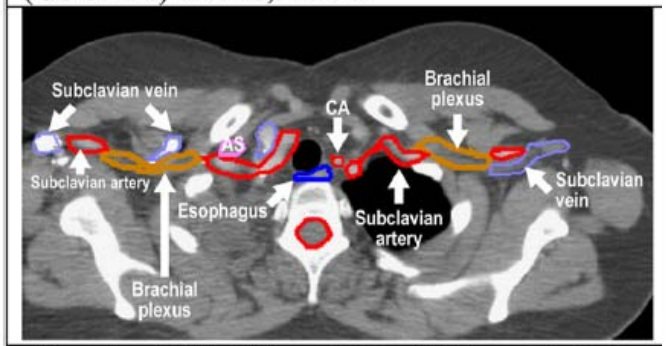
Kong, IJROBP 2011; 81(5); 1442-57

Contouring the brachial plexus

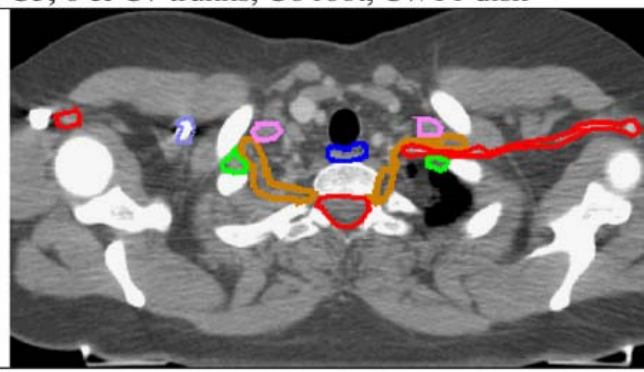
Superior (C5, 6) & C7 trunks, C7 VB



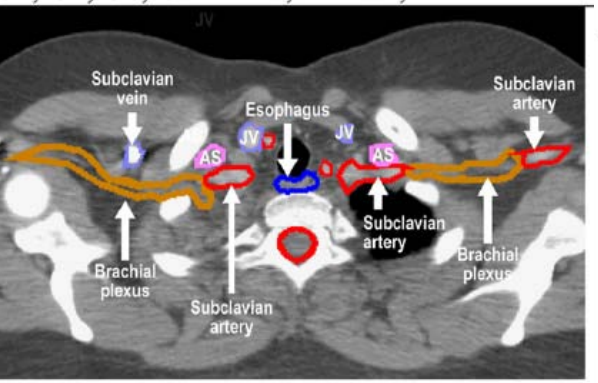
Superior (C5, C6), middle (C7), and inferior (C8 & T1) trunks, T2VB



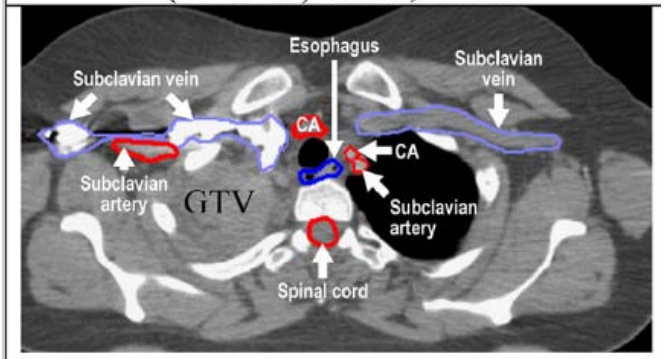
C5, 6 & C7 trunks, C8 root, C7/T1 disk



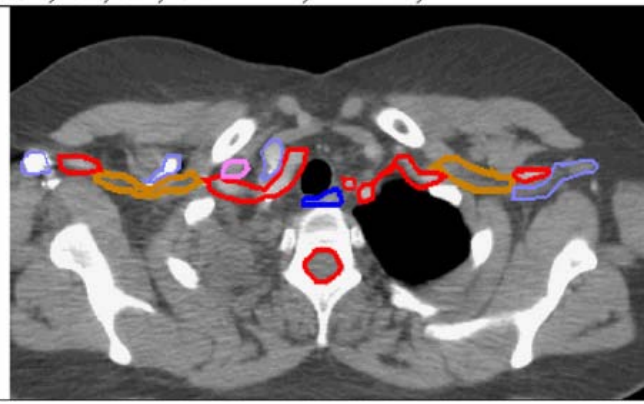
C5, C6, C7, C8 trunks, T1 root, T1VB



Superior (C5, C6), middle (C7), and inferior (C8 & T1) trunks, T2VB



C5, C6, C7, C8 trunks, T1 root, T1/T2 disk



Kong, IJROBP 2011; 81(5); 1442-57

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Vesna Prokic
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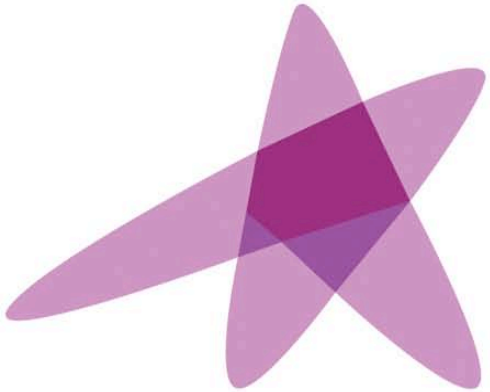
Andreas Thomsen

other places …
Michael Baumann
Matthias Guckenberger
Branislav Jeremic



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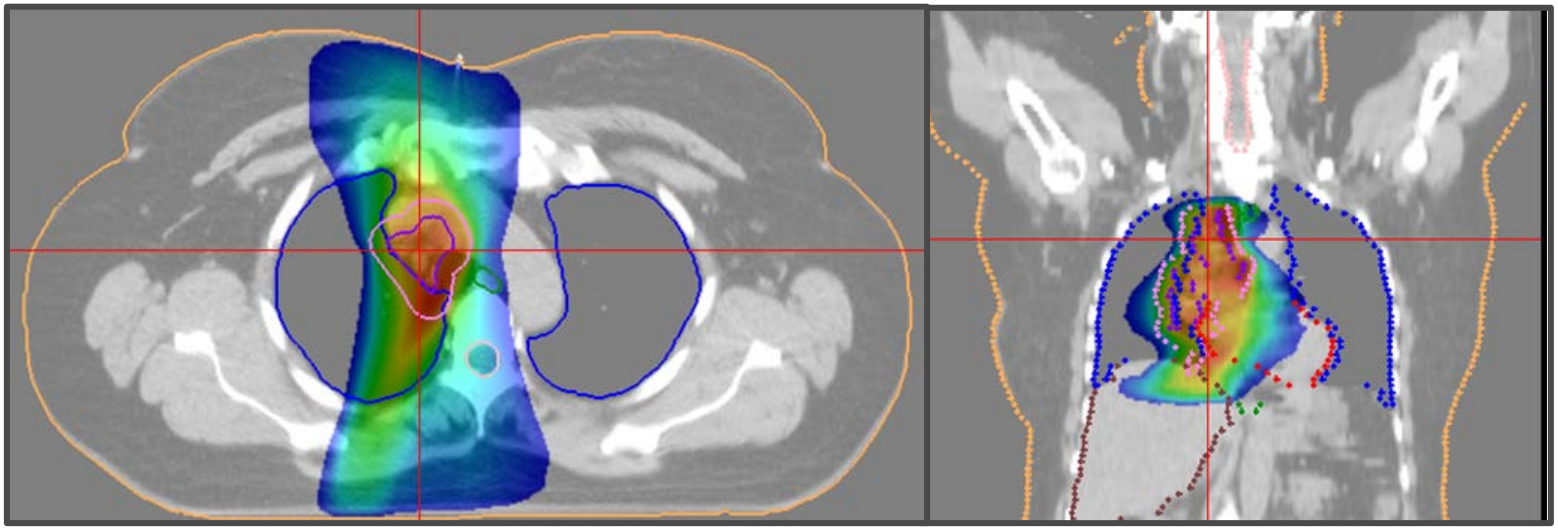
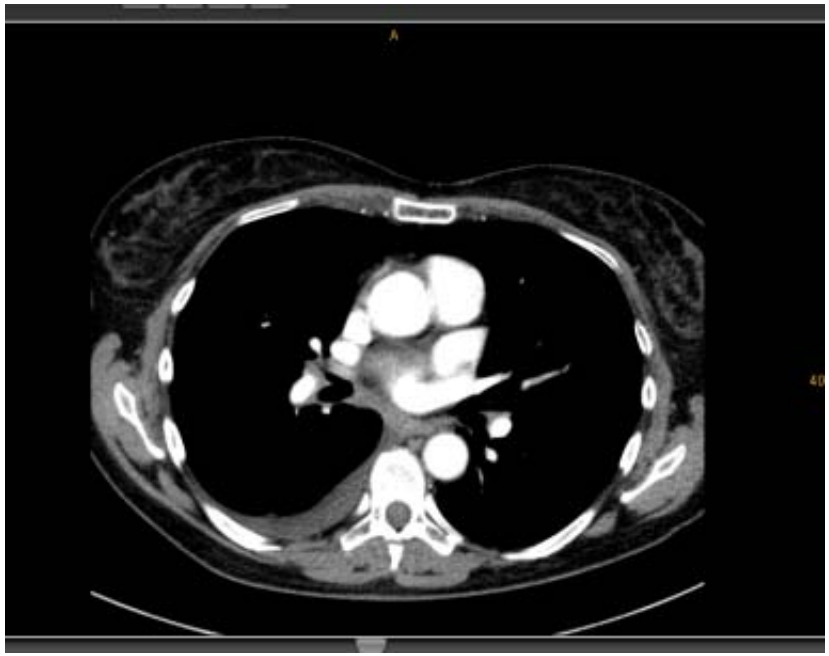


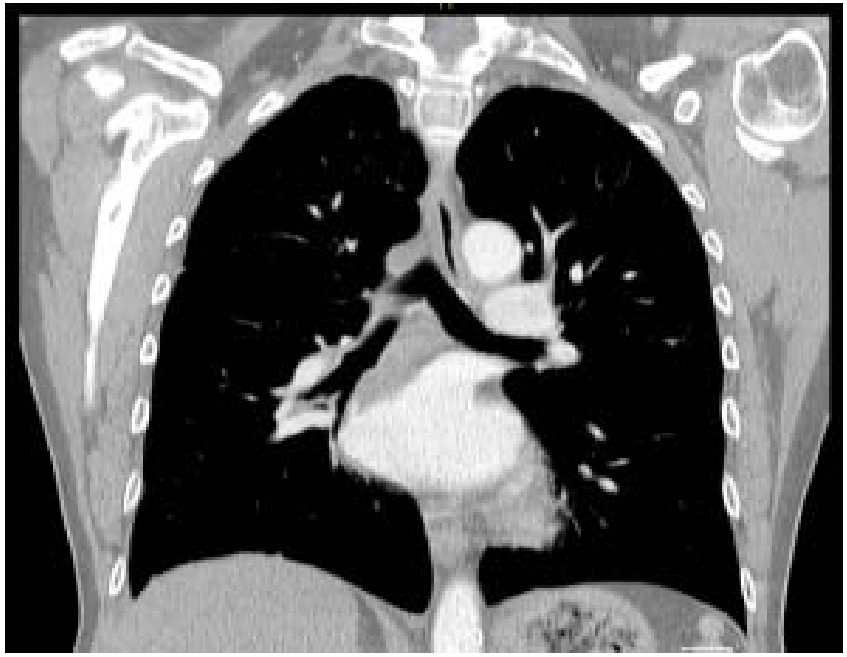
Case 3 (lung)

Ursula Nestle

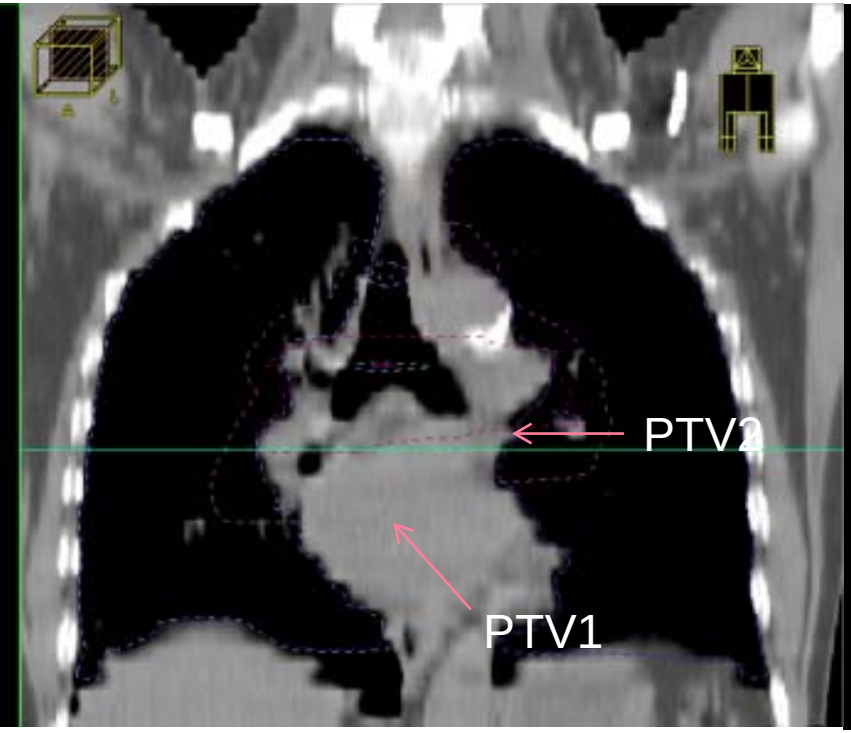
Freiburg, Germany

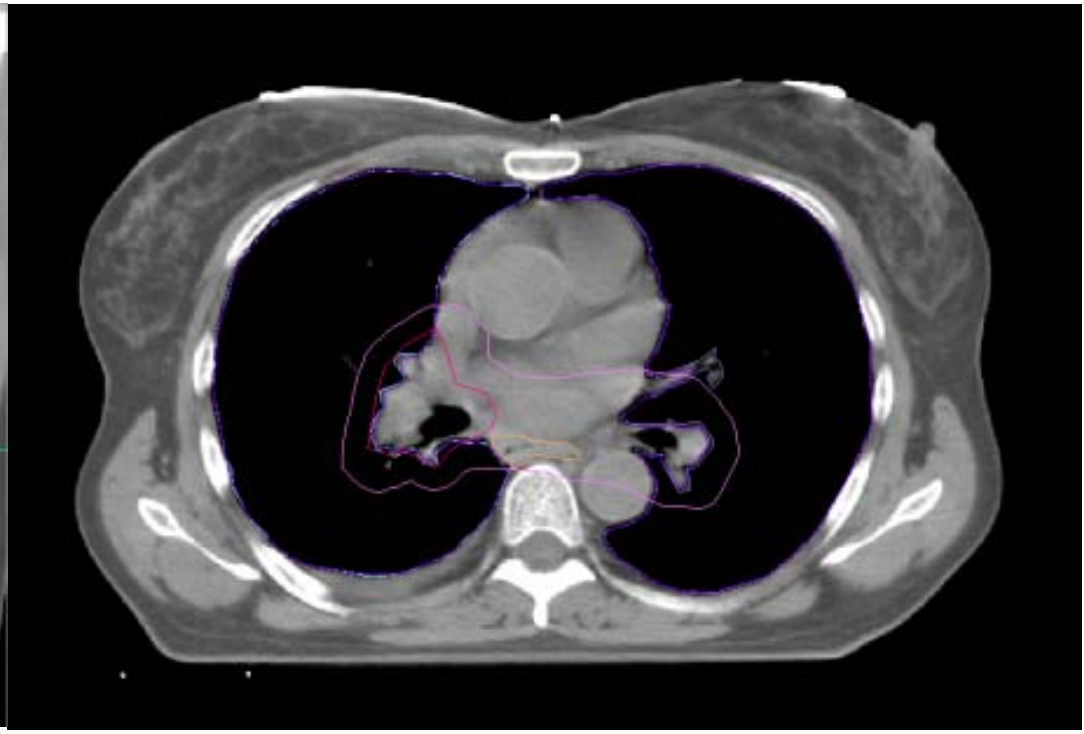
Case 3 (lung)

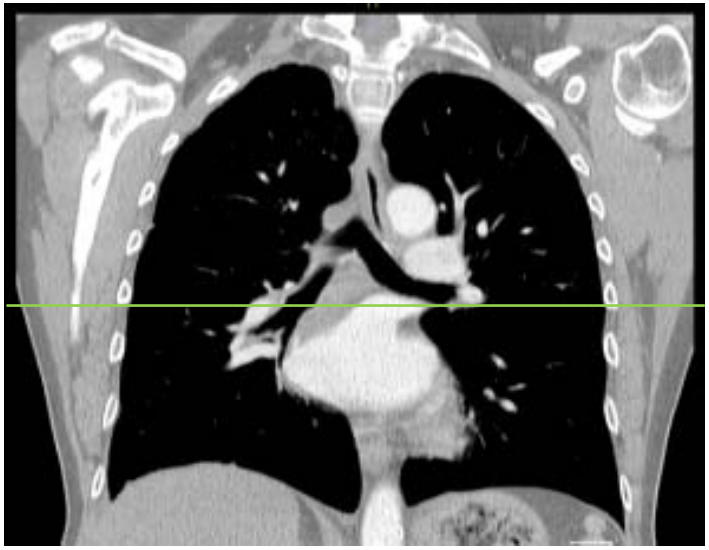




Female pt. *1952;
SCLC diagnosed in 2009
cT4 cN3 Mx
(suspected liver metastasis, lateron excluded)
finally: M0 = limited disease
before 08/2009 6 x CE, partial remission
referred for consolidating radiotherapy of mediastinum







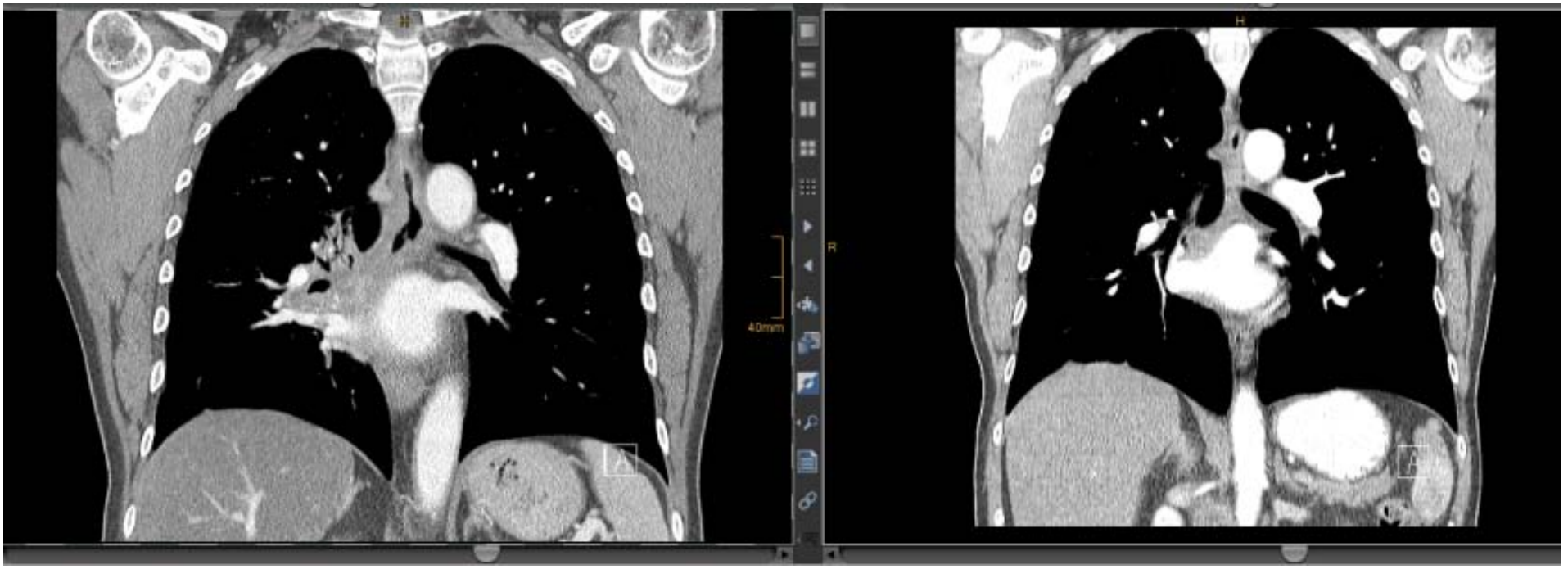
RT planning and administration:

initial PTV and dose prescription:
PTV1, 59.4/1.8 Gy

„not possible“

final PTV and dose prescription:
PTV2, 45/1.8 Gy

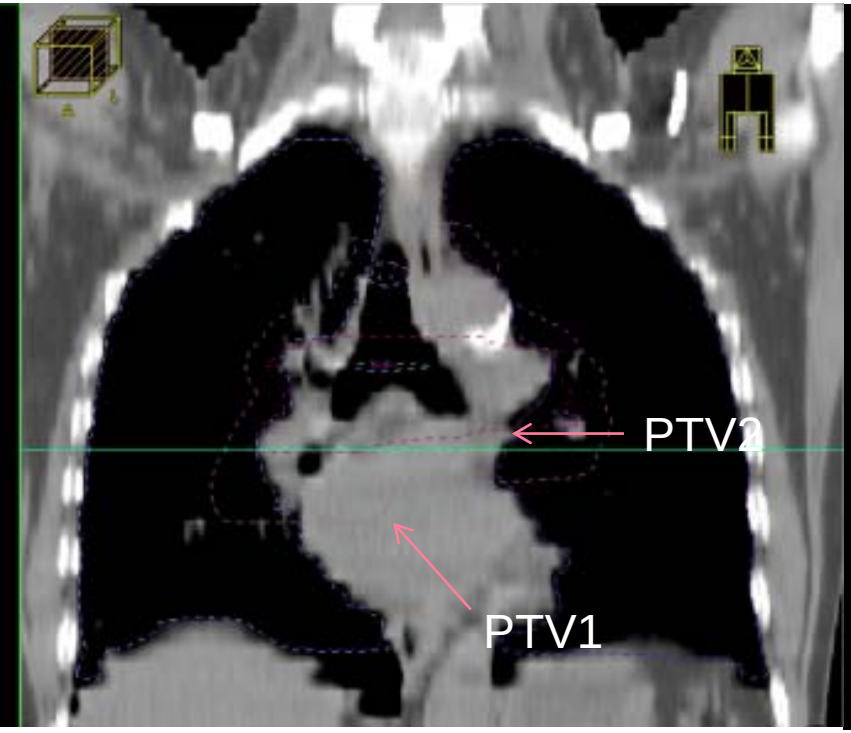
Case 3 (lung): further development of disease

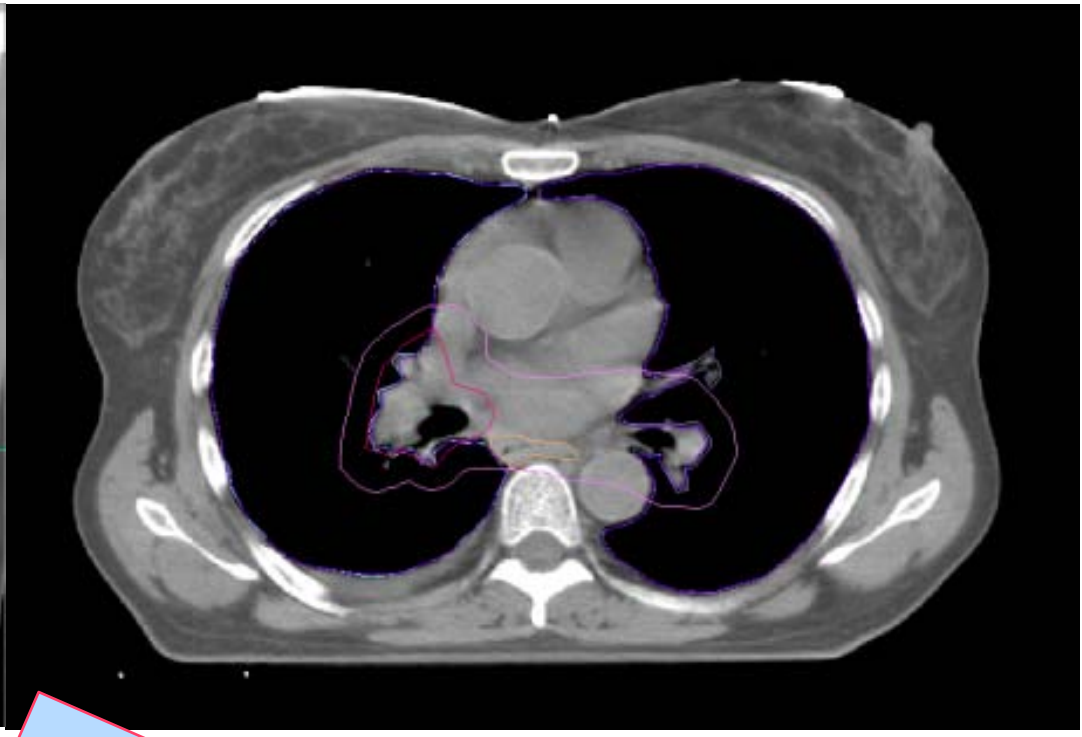


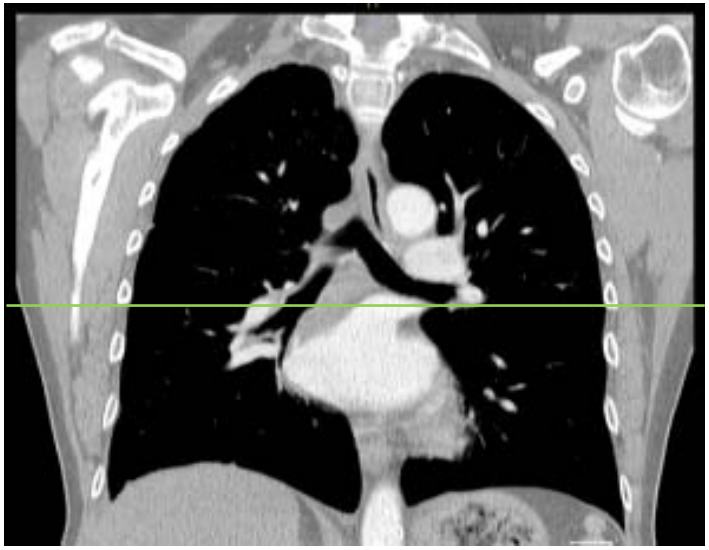
01/2010: local recurrence right hilum, brain metastasis

brain radiotherapy, chemotherapy

pat. died in 2010







Your challenge!

ing and administration:

initi… …escription:

„not possible“

final PTV and dose prescription:
PTV2, 45/1.8 Gy

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Case 3 (lung): your planning task

Please try to design a RT treatment plan for
59.4 Gy 1.8 Gy to the whole PTV1 (ICRU)

NT restrictions

- *lung* — V20% < 35%
  and MLD < 18 Gy
  V5 of both lungs < 60%
- *spinal cord (PRV)* — D_{max} < 48 Gy
- *esophagus* — V55Gy < 35 %
  or D_{mean} < 35 Gy

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Lung Locally advanced

Advanced Treatment Planning Course

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Clinical case 2: Lung Locally advanced

- Central PTV 33 x 2.0 Gy

  Almost 600 cc

- Constraints:
  - Max dose spinal cord < 48 Gy
  - Lungs:
    - Mean lung dose < 18 Gy
    - V_{20Gy} < 35%
    - V_{5Gy} < 60% (VMAT?!?)
  - Esophagus:
    - V_{55} < 35%
    - Mean dose <35 Gy

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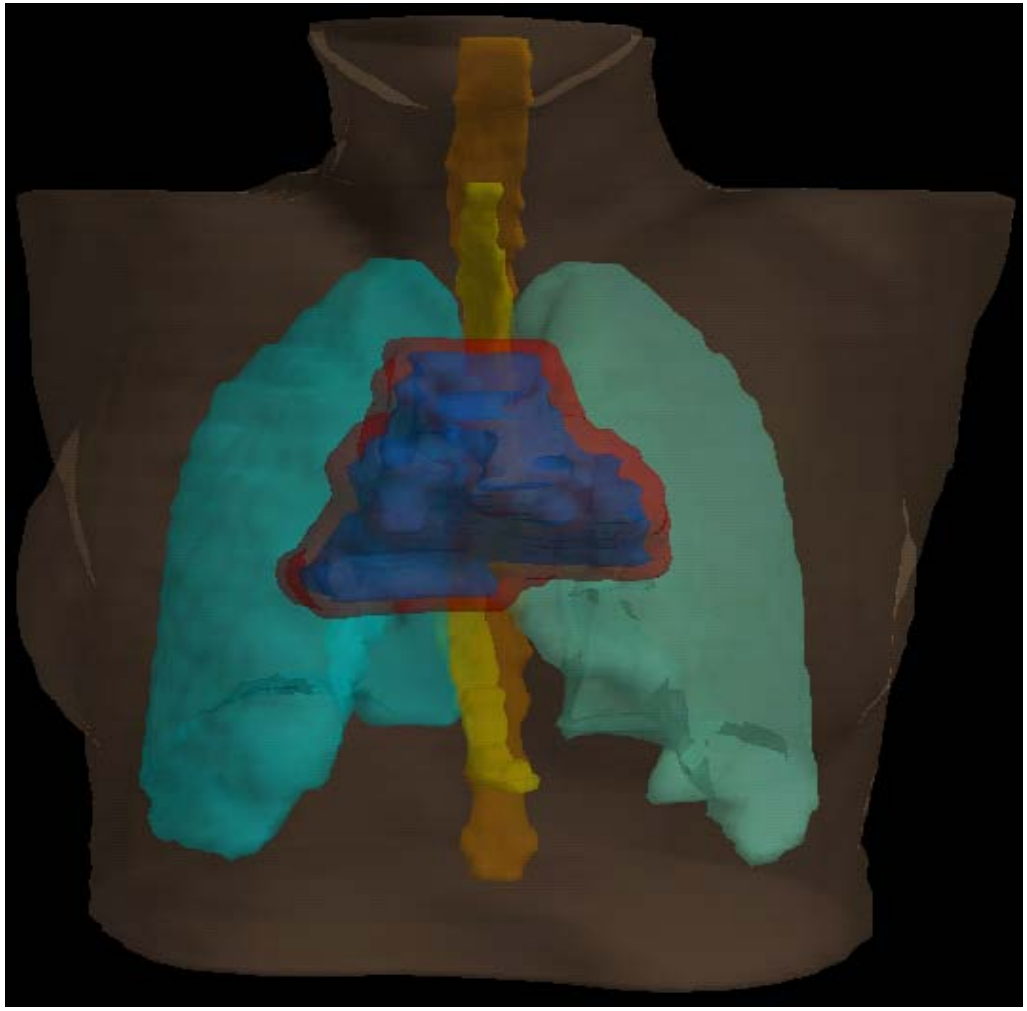
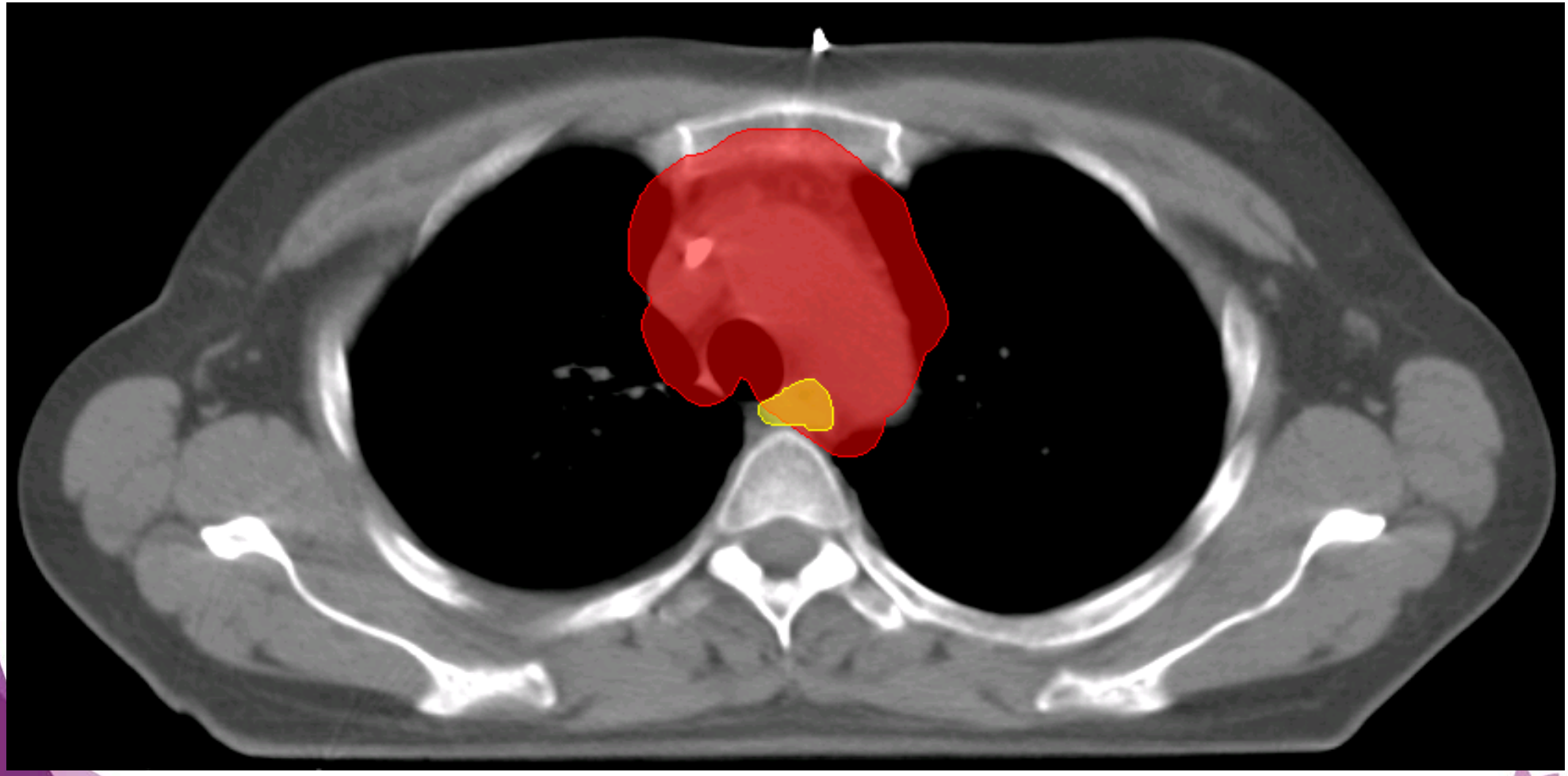
Clinical case 2: Lung Locally advanced

- Overview PTV / OARs



Clinical case 2: Lung Locally advanced

- PTV overlapping esophagus
- Planning trade off : conformality vs V_{20Gy} ??



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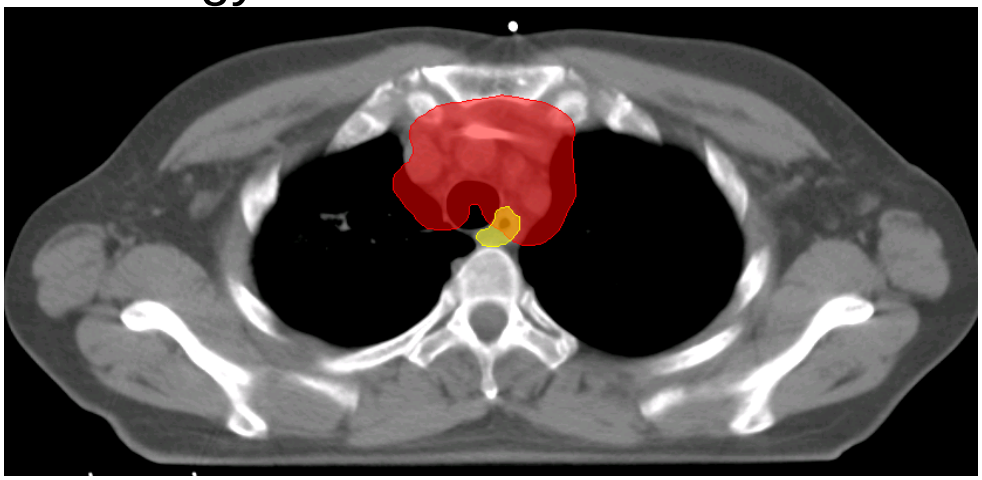
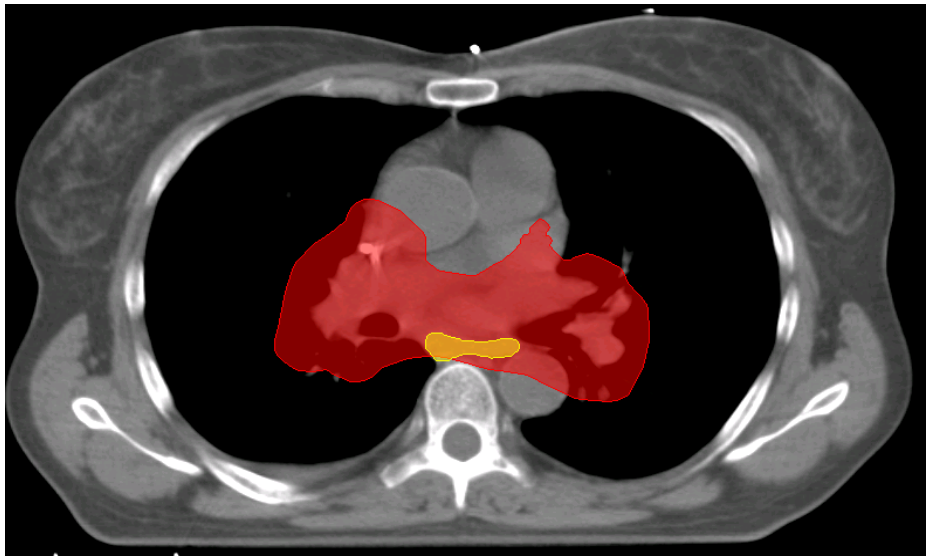
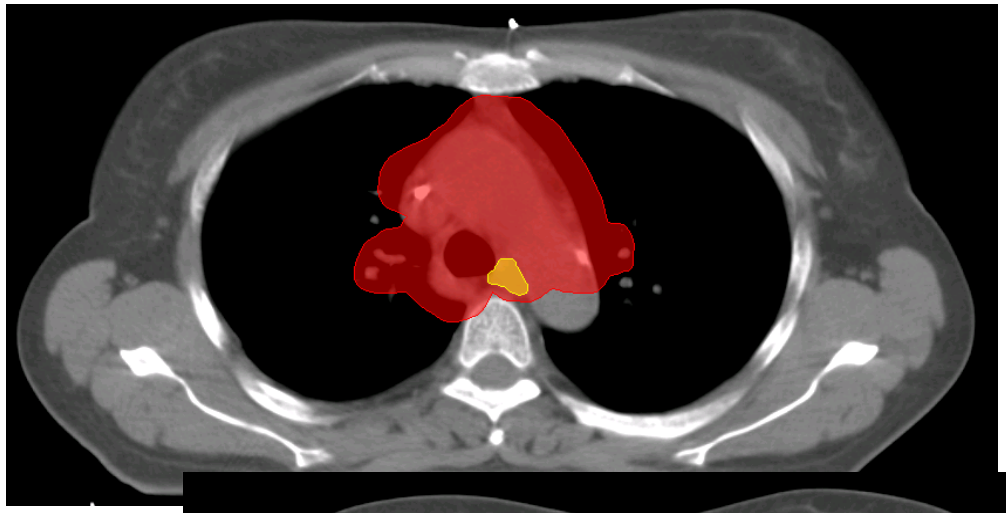
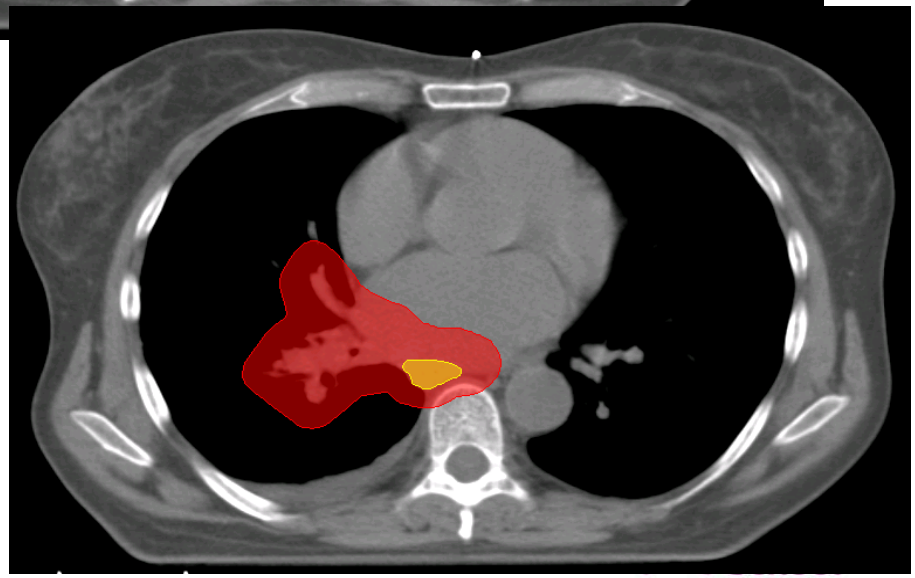
Clinical case 2: Lung Locally advanced

- Beam arrangement? VMAT?
- Energy 6 / 10 MV?









Clinical case 2: Lung Locally advanced

- 11 beams : S&S IMRT : 794 MU (10 min delivery time)
- 1 single arc dual rotation VMAT : 800-1500 MU (2.5 -5 min delivery time)

V_{5Gy} in VMAT / RapidArc !!

Clinical case 2: Lung Locally advanced

- Max dose spinal cord = 47.52 Gy (= < 48 Gy)
  - Lung:
    - Mean lung dose = 22.55 Gy (= < 18 Gy)
    - V_{20Gy} = 36.8% (= < 35 %)
  - Esophagus:
    - V_{55Gy} = 46% (= < 35 %)
    - Mean dose = 34.26 Gy (= < 35 Gy)

not OK ☹

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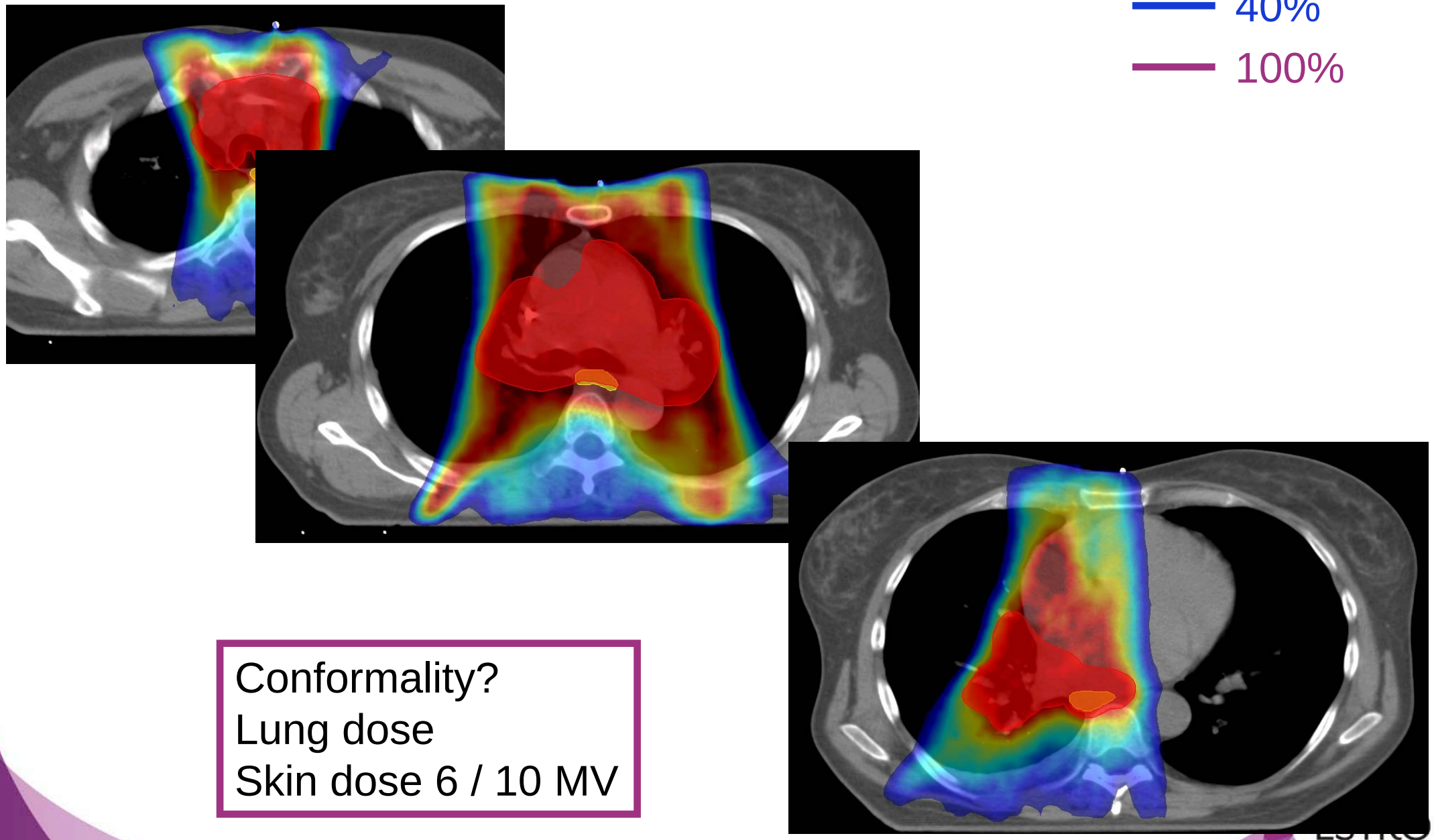
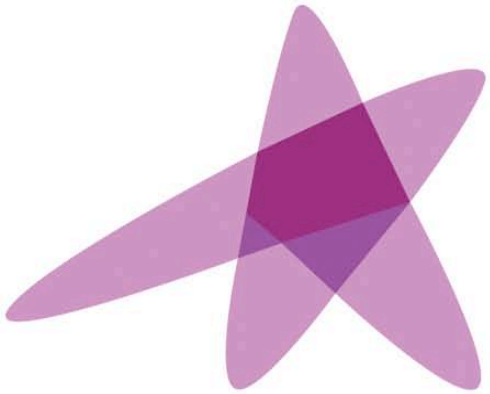
Clinical case 2: Lung Locally advanced



Conformality?
Lung dose
Skin dose 6 / 10 MV



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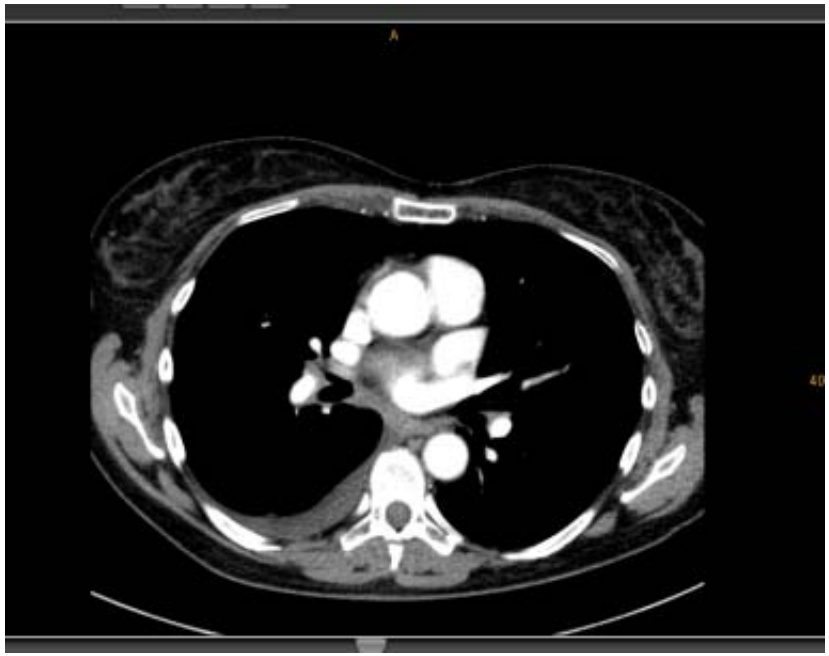
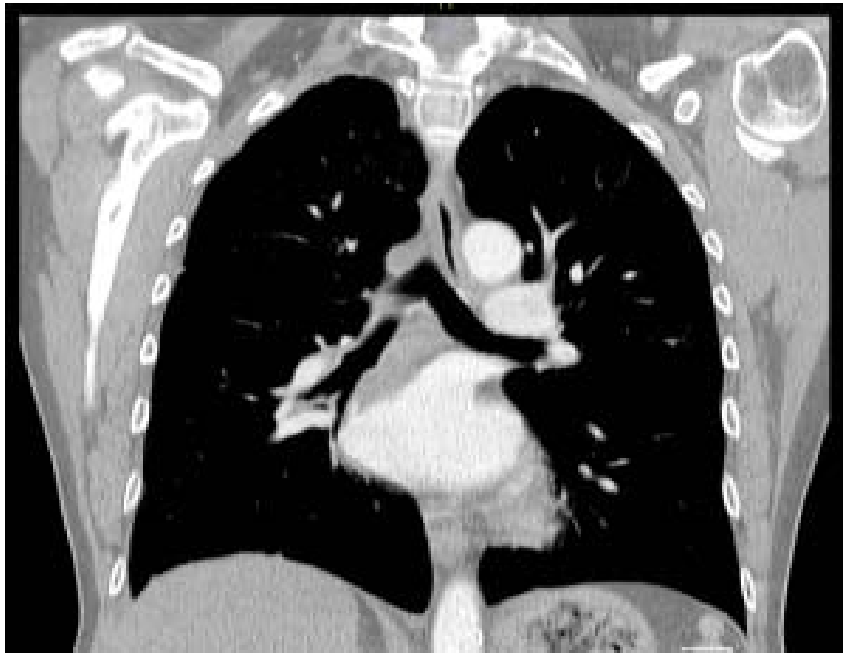
Lung case discussion

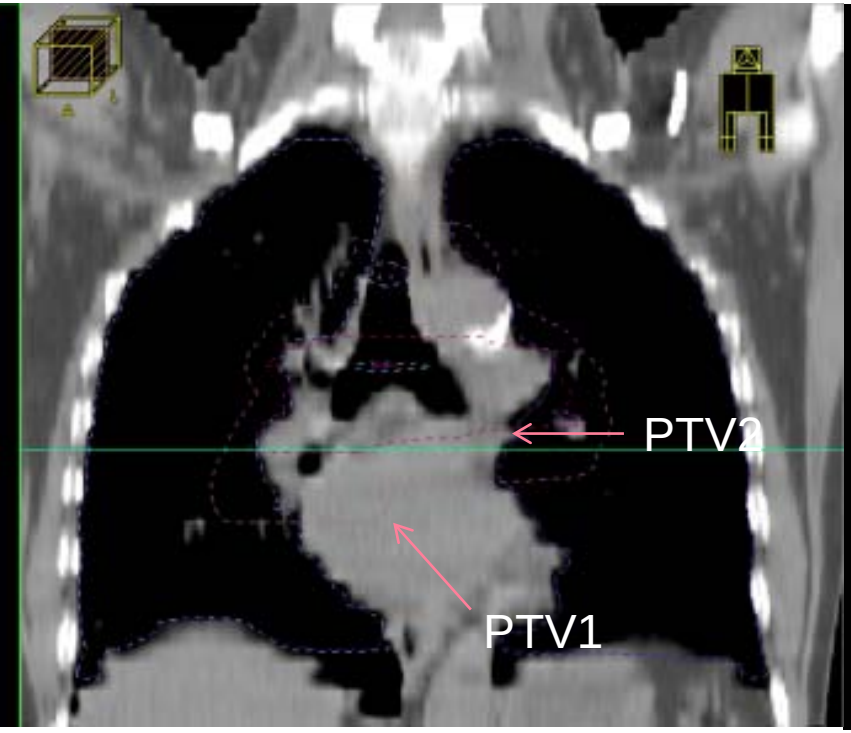
ESTRO ATP Cambridge
September 2016

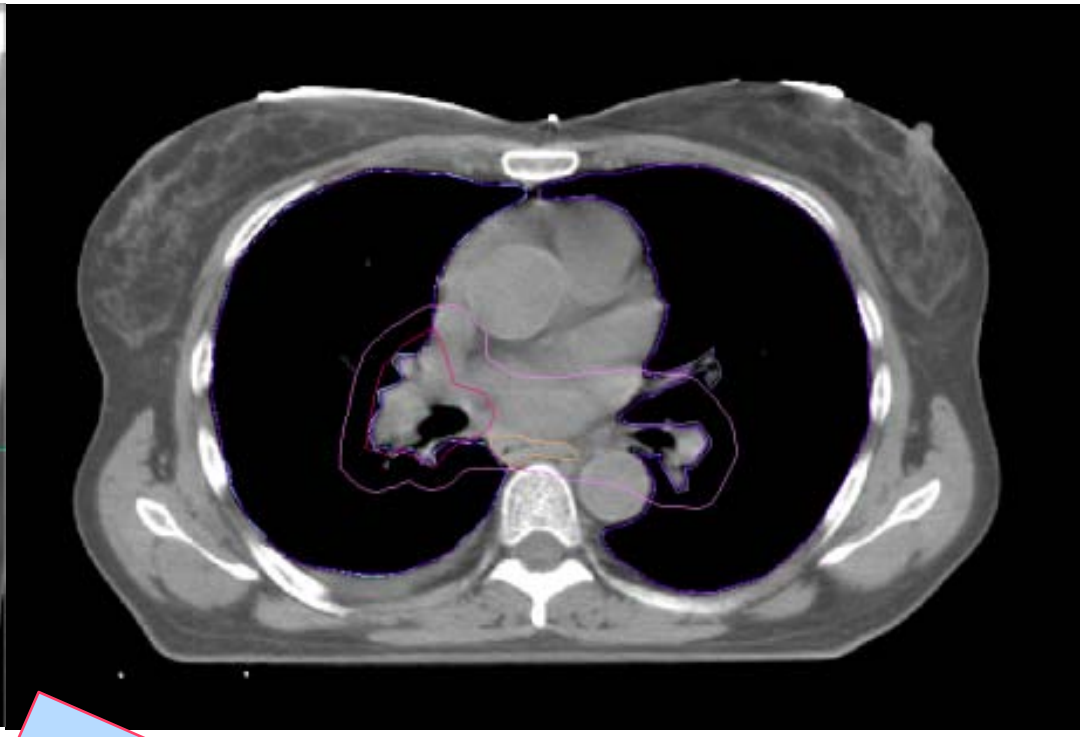
Case 3 (lung)

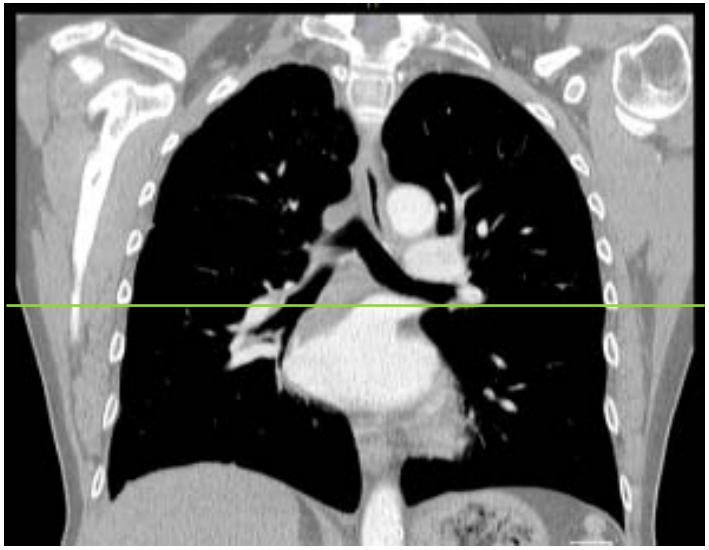




Female pt. *1952;
SCLC diagnosed in 2009
cT4 cN3 Mx
(suspected liver metastasis, lateron excluded)
finally: M0 = limited disease
before 08/2009 6 x CE, partial remission
referred for consolidating radiotherapy of mediastinum







Your challenge!

ing and administration:

initi… …escription:

„not possible“

final PTV and dose prescription:
PTV2, 45/1.8 Gy

UNIVERSITÄTS KLINIKUM FREIBURG

Case 3 (lung): your planning task

Please try to design a RT treatment plan for
59.4 Gy 1.8 Gy to the whole PTV1 (ICRU)

NT restrictions

- *lung* — V20% < 35%
  and MLD < 18 Gy
  V5 of both lungs < 60%
- *spinal cord (PRV)* D_{max} — < 48 Gy
- *esophagus* — V55Gy < 35 %
  or D_{mean} < 35 Gy

Which is the ‘best’ plan?

- Consider PTV
- Consider normal tissues
  - Which normal tissue is most important?
- Consider other factors
  - Planning & delivery issues
  - Patient comfort

- Beam arrangement?

Further considerations:

f the constraints cannot be reached, a **compromise** may be needed.

Possible trade-offs for compromise:

- discuss to **loosen PTV coverage** from lower constraint 99% receiving 95% of the prescribed dose to 95%

- as pneumonitis may kill the patient soon, try to keep the **lung** constraints without compromise

- allow up to 50 Gy point dose to the **spinal cord** and/or steep dose gradients near to the spine, if IGRT is available

- allow more dose to the **esophagus**, as this will affect acute toxicity, which can be monitored and treated clinically

Which is the ‘best’ plan?

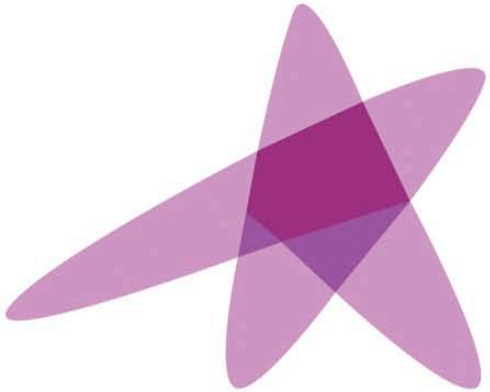
- Which is the most important part of the PTV in this patient?
- Which is the most important normal tissue in this patient?

Switch to Oncentra revue

Which is the ‘best’ plan?

Individual planning session

- Well done everybody !



ESTRO School

Adaptive radiotherapy

Marcel van Herk
Includes slides by Michael Sharpe

Institute of Cancer Sciences
Manchester University
The Christie NHS Trust

(Formerly at the Netherlands Cancer Institute)

What is ART?

What is Adaptive Radiation Therapy?

"4D"

dose reconstruction

target du jour

dose painting

gating & tracking

replan per fraction

FDG PET

mid-course

biological targeting

feedback

replan

dynamic

patient-specific PTV

on-line correction

Two-phase replan

geometry-based replan

Scholar

About 92,800 results (0.05 sec)

Articles

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Adaptive radiation therapy
D Yan, F Vicini, J Wong, A Martinez - Physics in medicine and ..., 1997 - iopscience.iop.org
Abstract. **Adaptive radiation therapy** is a closed-loop **radiation** treatment process where the treatment plan can be modified using a systematic feedback of measurements. **Adaptive radiation therapy** intends to improve **radiation** treatment by systematically monitoring ...
Cited by 260 Related articles All 7 versions Cite

[BOOK] **Adaptive radiation therapy**
XA Li - 2011 - books.google.com
Modern medical imaging and **radiation therapy** technologies are so complex and computer driven that it is difficult for physicians and technologists to know exactly what is happening at the point-of-care. Medical physicists responsible for filling this gap in knowledge must stay ...
Cited by 4 Related articles All 3 versions Cite More

The use of **adaptive radiation therapy** to reduce setup error: a prospective clinical study
D Yan, E Ziaja, D Jaffray, J Wong, D Brabbins... - ... Journal of **Radiation** ..., 1998 - Elsevier
Purpose: **Adaptive Radiation Therapy** (ART) is a feedback treatment process that optimizes a patient's treatment according to the patient specific information measured during the course of treatment. Utilizing an electronic portal imaging device (EPID) and a computer- ...
Cited by 117 Related articles All 7 versions Cite

Deformable registration of the planning image (kVCT) and the daily images (MVCT) for **adaptive radiation therapy** [PDF] from researchgate.net
W Lu, GH Olivera, Q Chen, KJ Ruchala... - Physics in medicine ..., 2006 - iopscience.iop.org
Abstract The incorporation of daily images into the radiotherapy process leads to **adaptive radiation therapy** (ART), in which the treatment is evaluated periodically and the plan is adaptively modified for the remaining course of radiotherapy. Deformable registration ...
Cited by 85 Related articles All 7 versions Cite

Comparison of 12 deformable registration strategies in **adaptive radiation therapy** for the treatment of head and neck tumors [HTML] from thegreenjournal.com
P Castadot, JA Lee, A Parraga, X Geets, B Macq... - Radiotherapy and ..., 2008 - Elsevier
BACKGROUND AND PURPOSE: Weight loss, tumor shrinkage, and tissue edema induce substantial modification of patient's anatomy during head and neck (HN) radiotherapy (RT) or chemo-radiotherapy. These modifications may impact on the dose distribution to both ...
Cited by 74 Related articles All 5 versions Cite

On-line re-optimization of prostate IMRT plans for **adaptive radiation therapy**
QJ Wu, D Thongphiew, Z Wang... - Physics in medicine ..., 2008 - iopscience.iop.org
Abstract For intermediate and high risk prostate cancer, both the prostate gland and seminal vesicles are included in the clinical target volume. Internal motion patterns of these two organs vary, presenting a challenge for **adaptive** treatment. **Adaptive** techniques such as ...
Cited by 62 Related articles All 7 versions Cite

Adaptive radiation therapy for compensation of errors in patient setup and treatment delivery
H Rehbinder, C Forsgren, J Löf - Medical physics, 2004 - link.aip.org
In this paper, an **adaptive radiation therapy** algorithm is derived and evaluated using numerical simulations. Patient setup errors are considered and an off-line **adaptive** method to compensate for the effect of these is provided. The method consists of two parts, one for ...
Cited by 44 Related articles All 6 versions Cite

Formulating **adaptive radiation therapy** (ART) treatment planning into a closed-loop control framework [PDF] from northwestern.edu
A de la Zerda, B Armbruster, L Xing - Physics in medicine and ..., 2007 - iopscience.iop.org
Abstract While ART has been studied for years, the specific quantitative implementation details have not. In order for this new scheme of **radiation therapy** (RT) to reach its potential, an effective ART treatment planning strategy capable of taking into account the dose ...
Cited by 50 Related articles All 13 versions Cite

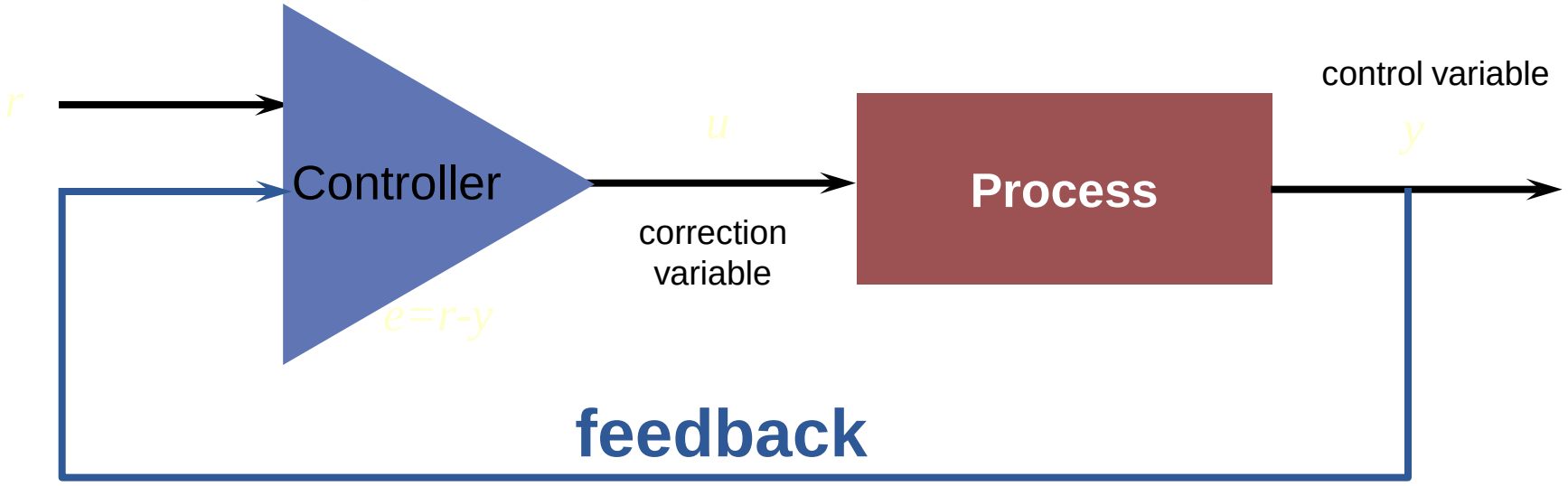
Image-guided **adaptive radiation therapy** (IGART): Radiobiological and dose escalation considerations for localized carcinoma of the prostate
W Song, B Schaly, G Bauman, J Battista, J Van Dyk - Medical physics, 2005 - link.aip.org
The goal of this work was to evaluate the efficacy of various image-guided **adaptive radiation therapy** (IGART) techniques to deliver and escalate dose to the prostate in the presence of geometric uncertainties. Five prostate patients with 15–16 treatment CT studies each were ...
Cited by 46 Related articles All 7 versions Cite

Effects of exercise on fatigue, physical functioning, and emotional distress during **radiation therapy** for breast cancer.
V Mock, KH Dow, CJ Meares, PM Grimm... - Oncology nursing ..., 1997 - ncbi.nlm.nih.gov

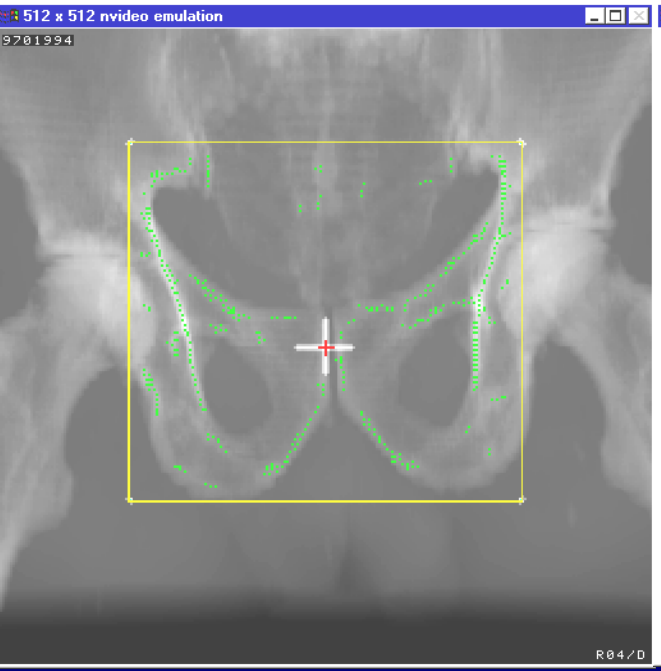
Adaptive Concept

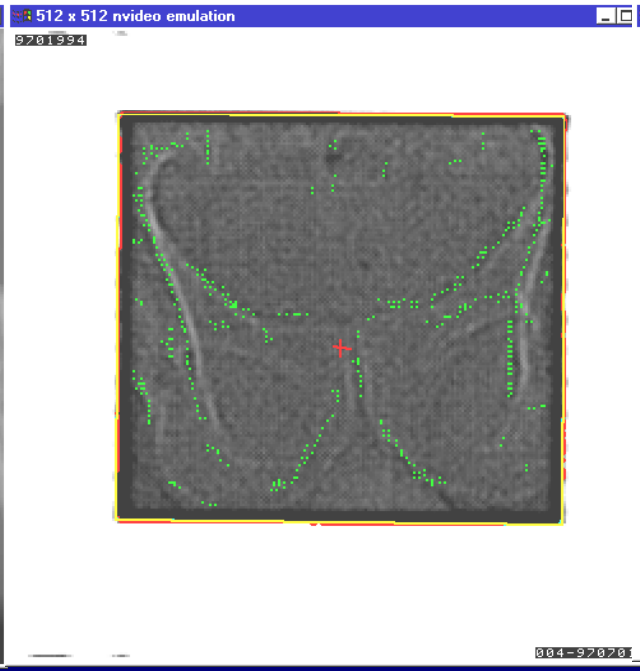
Yan et al., Sem. Rad. Oncol 20(2) 79-83 (2010)

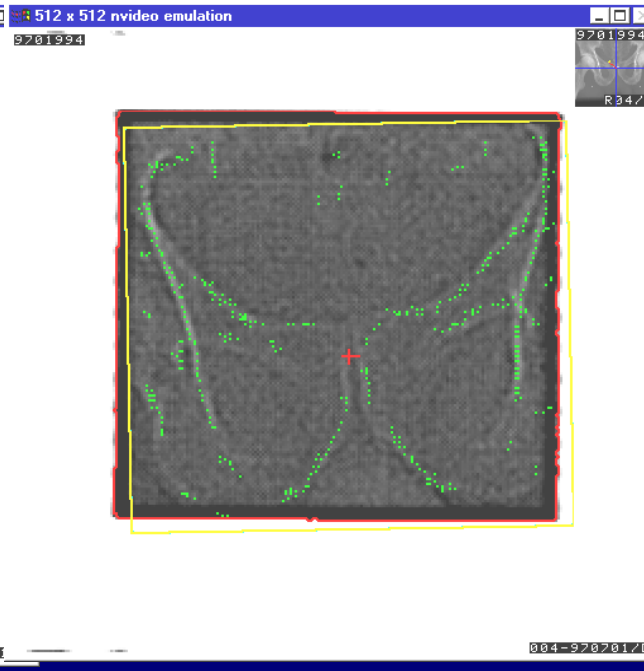
- Origins are informatics and modern control theory.
- IGRT provides *feedback*, statistical treatment deviations are observed.
- Use knowledge to predict and address anatomical (and biological) variation over time.



Portal image analysis - 2D







Reference image Match field edge Match anatomy

Correction procedures

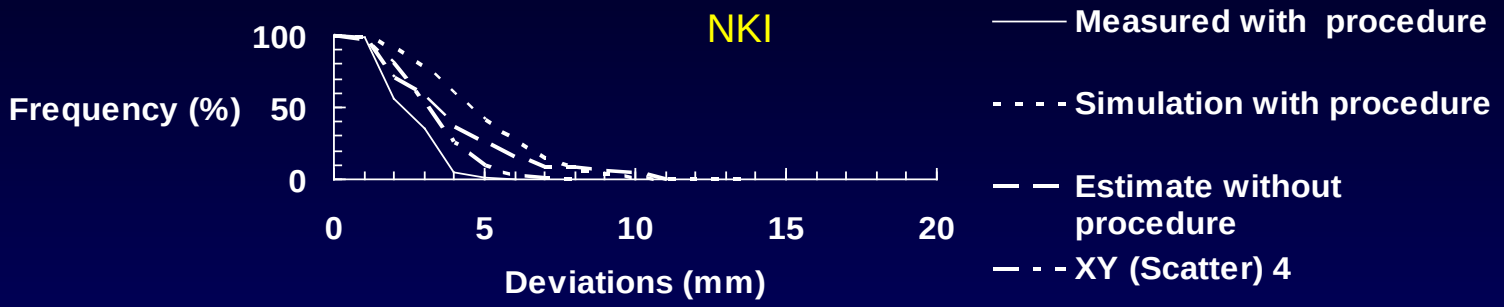
- No corrections (monitoring)
  - Aimed at determining accuracy of clinical practice
- Ad-hoc corrections
  - danger of overcorrection
- Off-line correction protocols
  - Aimed at correcting inter-treatment/systematic errors ← •ART
- On-line correction protocols
  - Aimed at correcting day to day variations

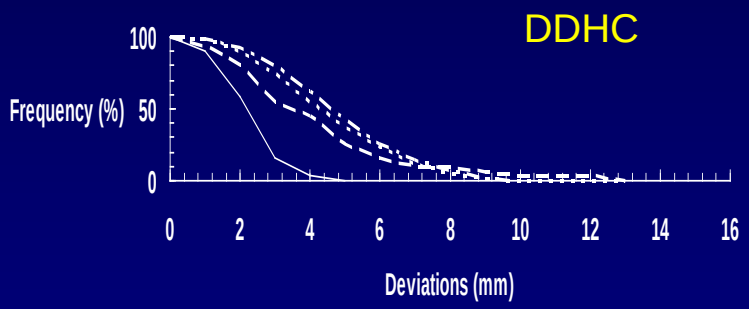
Shrinking action level protocol

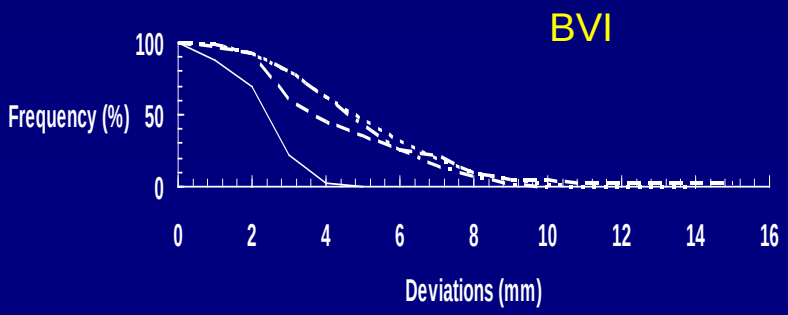
- Correct after first fraction if setup error exceeds 6 mm (vector length)
- Correct after second fraction if average error of first and second fraction exceeds 4 mm
- Restart procedure after correction
- Weekly imaging after second uncorrected fraction

•Bel et al, 1995

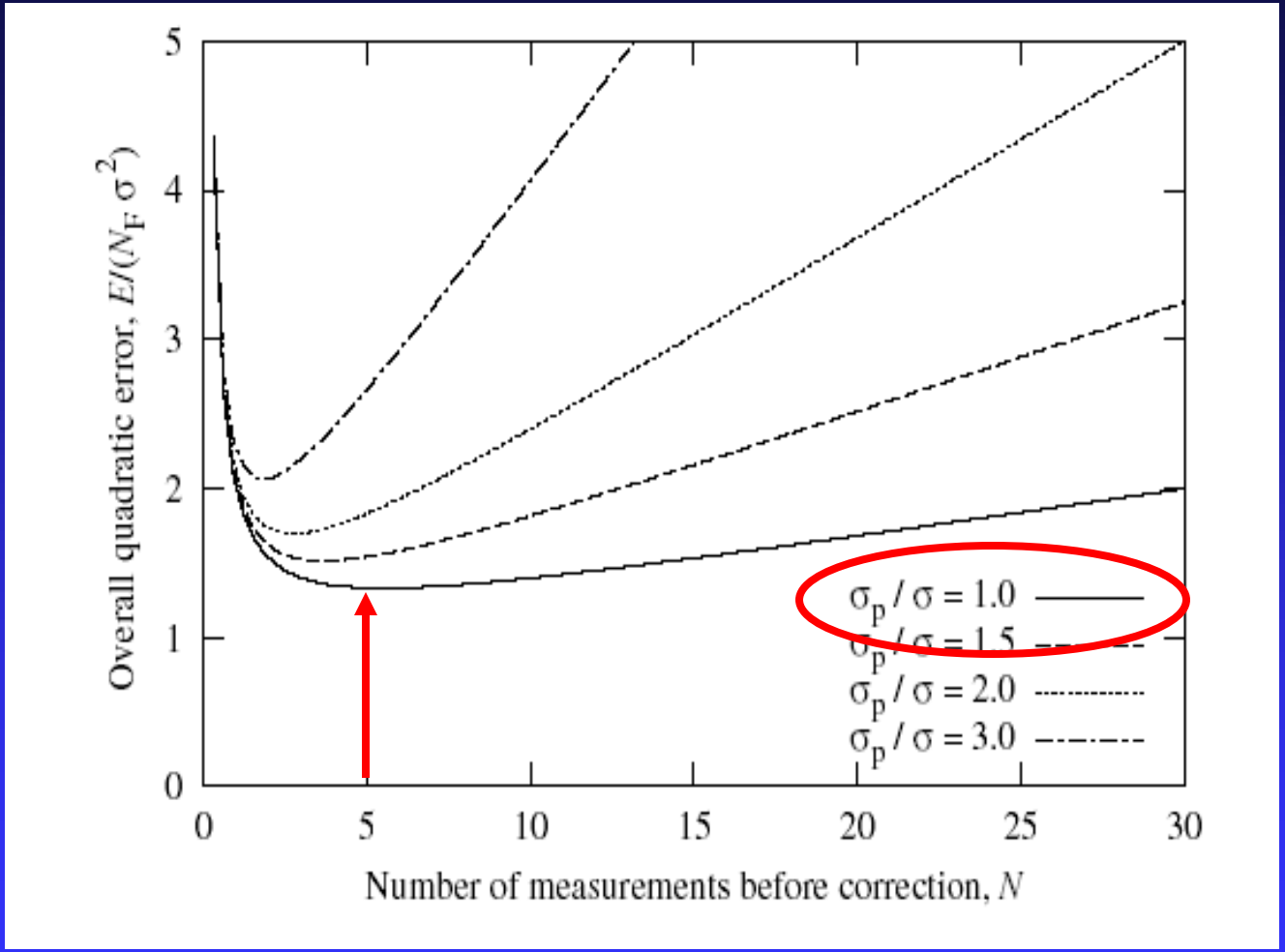
Results of correction procedure (150 prostate cases)







When to correct ?



Bortfeld at al, PBM 2002

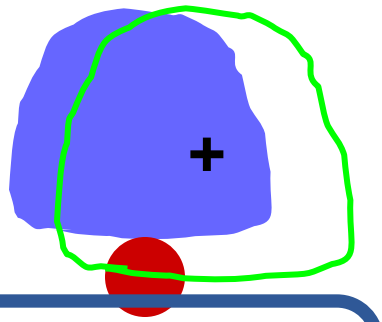
Adaptive Radiation Therapy (Beaumont Strategy)

Yan et al., PMB 1997 Jan;42(1):123-32

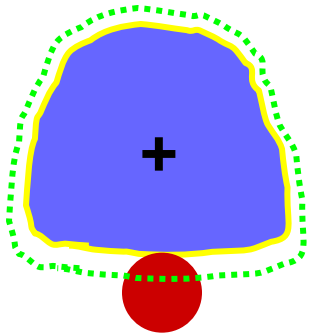
- Extended off-line strategy to account for setup error & organ motion.
- Combine information from EPIDs & multiple CT scans obtained in the first week of treatment.
- Obtain good sense of the average position of organs & targets, replan with personalized margins.

The Evolving Role of IGRT

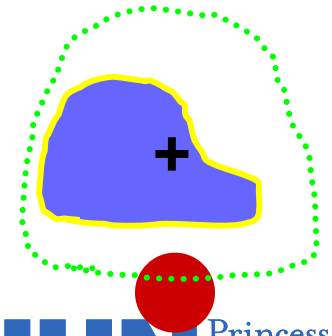
- Accurate:
  - verify target location and extent



- Precise:
  - tailor PTV margins (patient-specific)

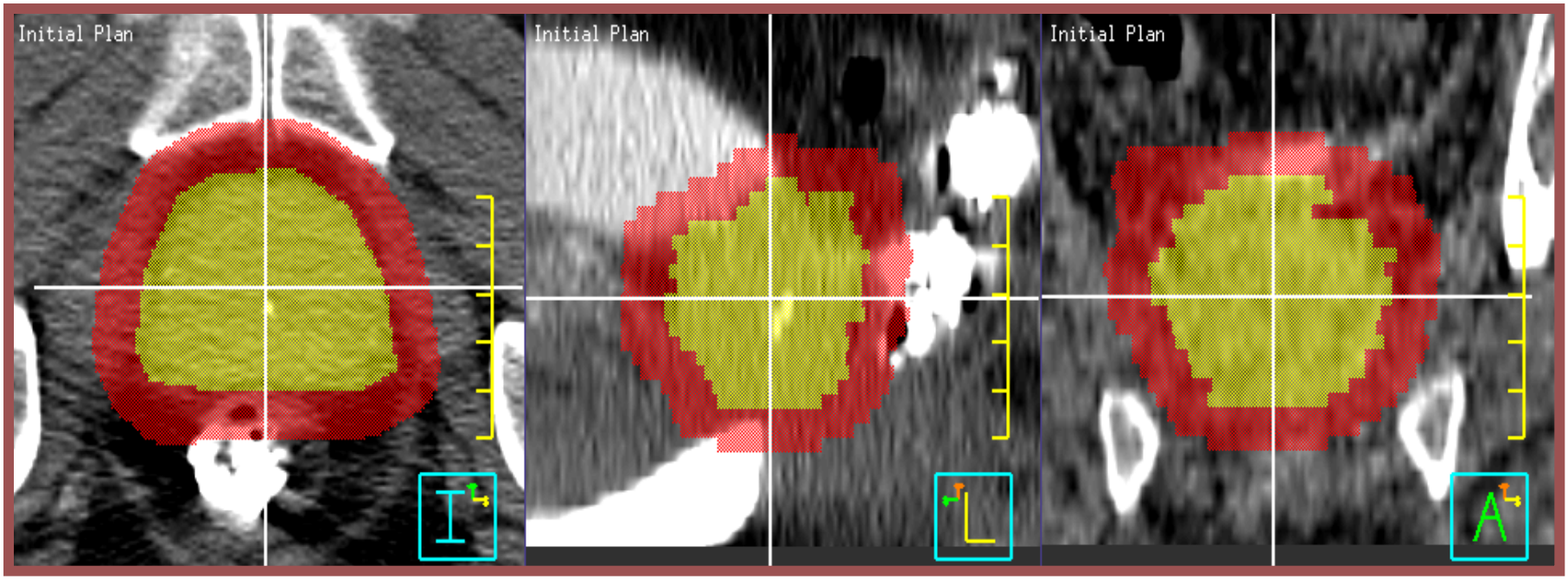


- Adapt
  - Assess and respond to anatomical change on-treatment.



Initial PTV

transverse sagittal coronal



Initial CTV + 10 mm = Initial PTV

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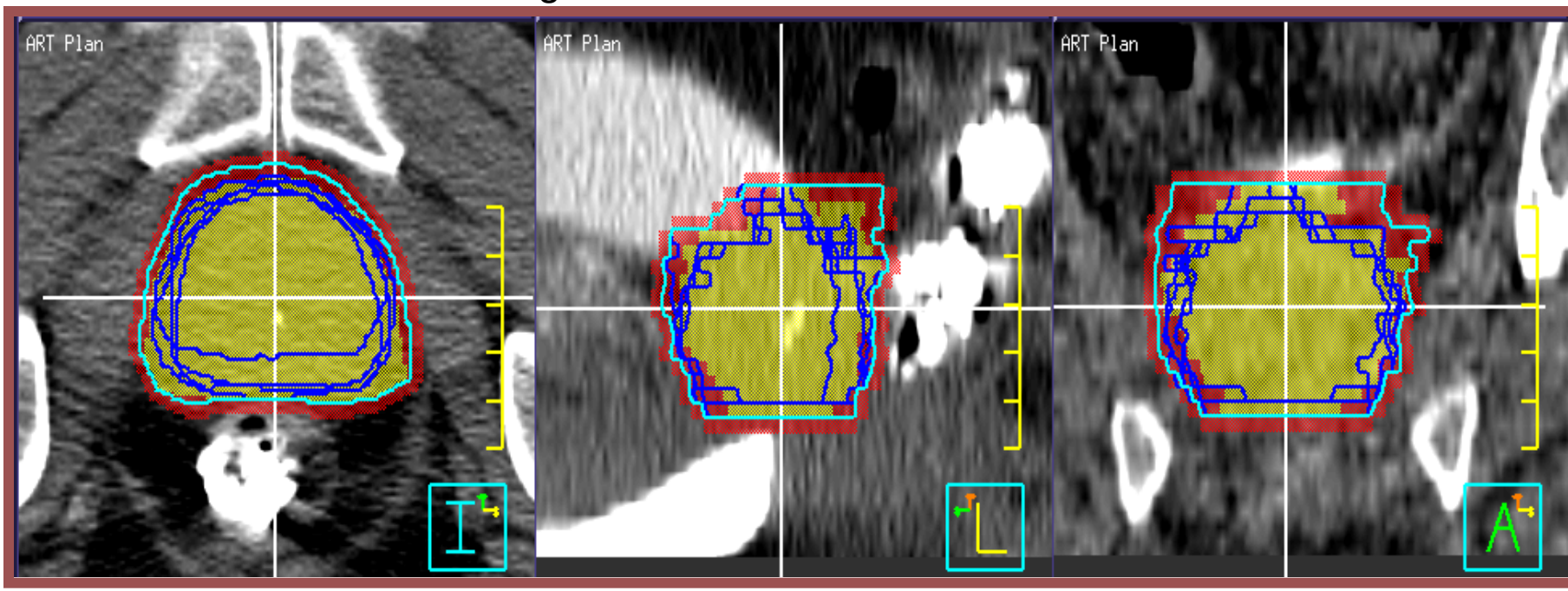
Confidence-Limited PTV (cl-PTV)

transverse sagittal coronal



Initial CTV + 4 CTV_s = ITV (Organ Motion PTV)

ITV + Random Setup Error & Measurement Uncertainty = cl-PTV

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Volume Difference: PTV vs cl-PTV

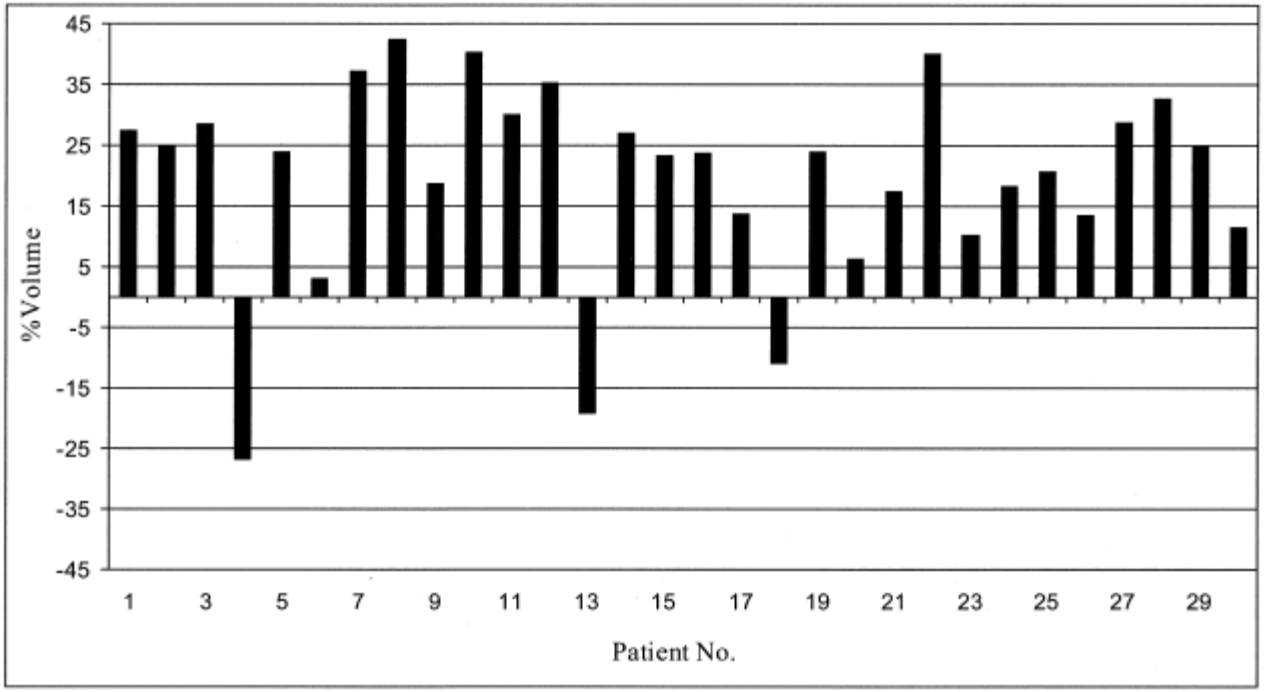

Fig. 5. Distribution of % volume difference between the generic planning target volume (PTV) and the patient-specific confidence-limited planning target volume (cl-PTV, normalizing to the generic PTV).

Martinez, Yan *et al* IJROBP 50, 1226–1234, 2001

Initial PTV & cl-PTV Do NOT Overlap

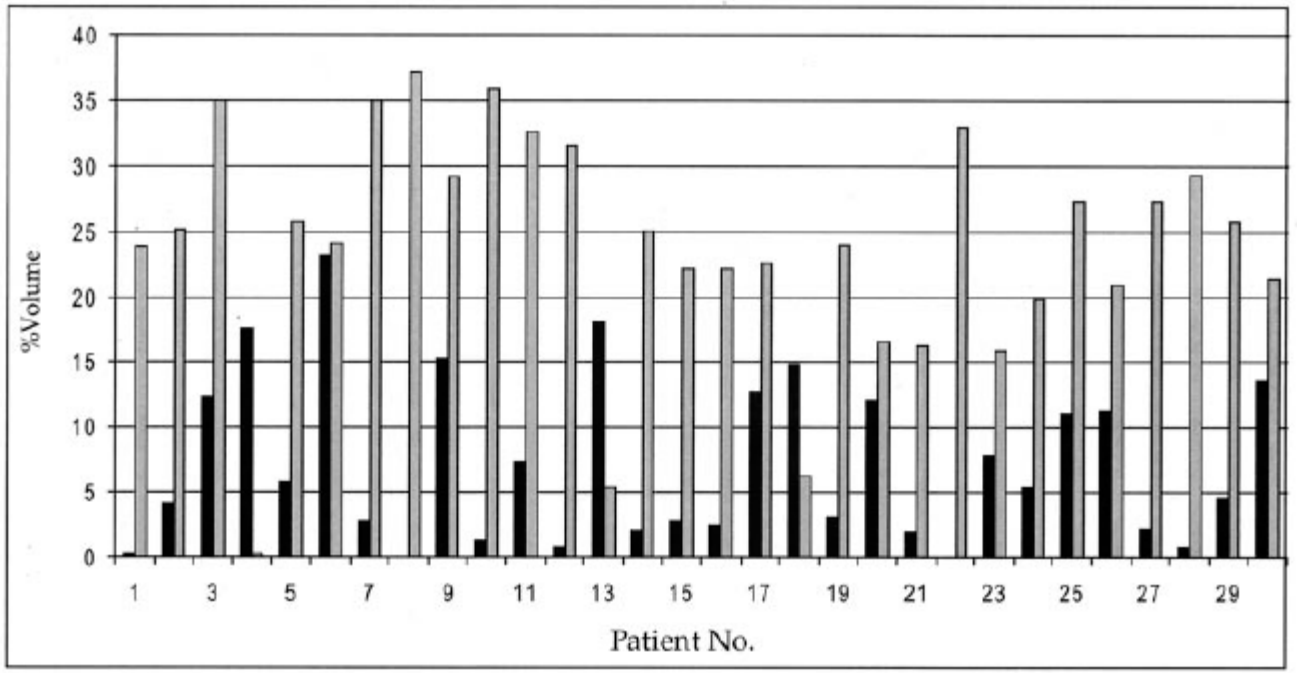

Fig. 6. Solid bars represent the % volume in the confidence-limited planning target volume (cl-PTV) but not in the generic PTV (normalizing to the cl-PTV). The shaded bars represent the % volume in the generic PTV but not in the cl-PTV (normalizing to the generic PTV).

Martinez, Yan *et al* IJROBP 50, 1226–1234, 2001

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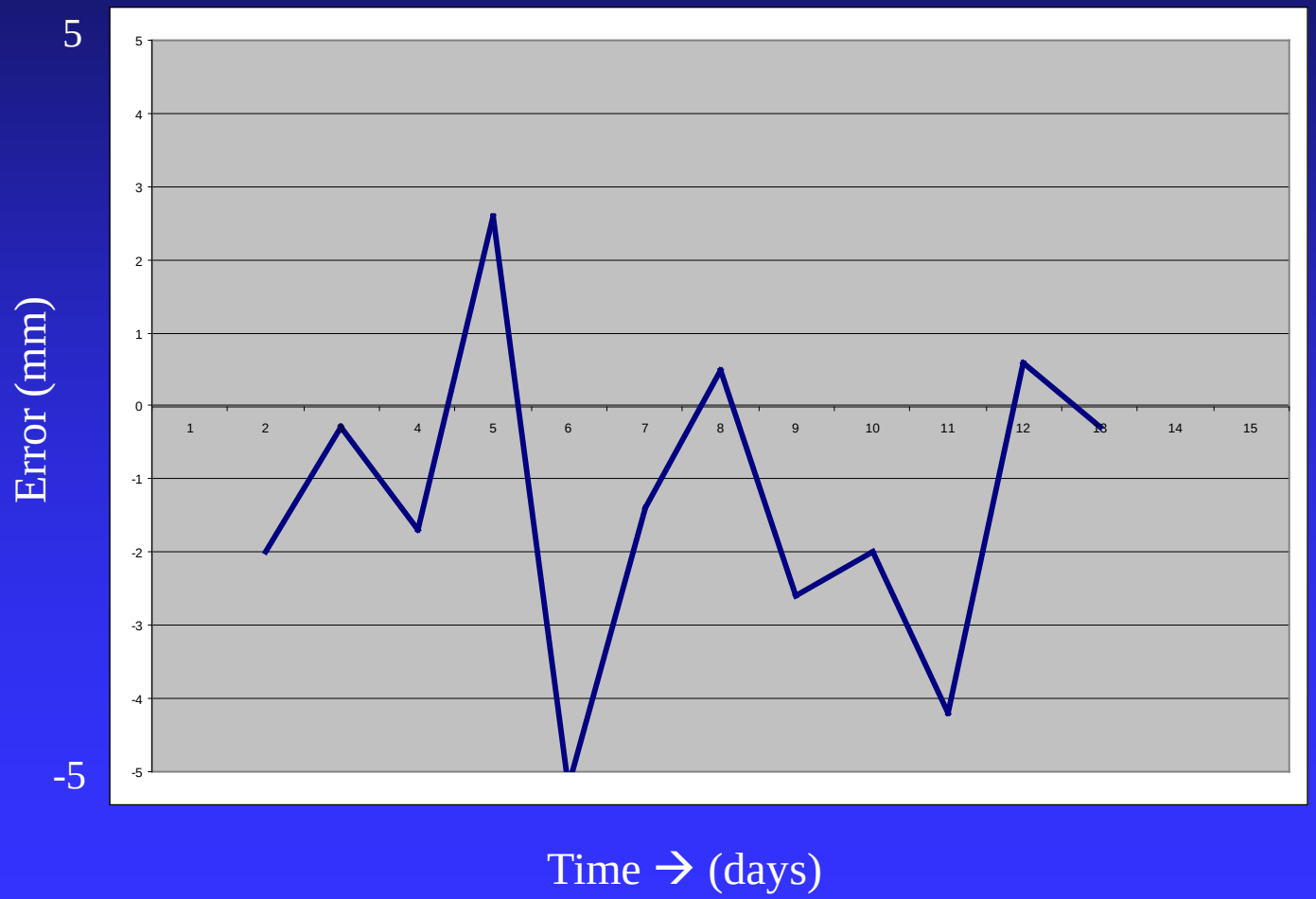
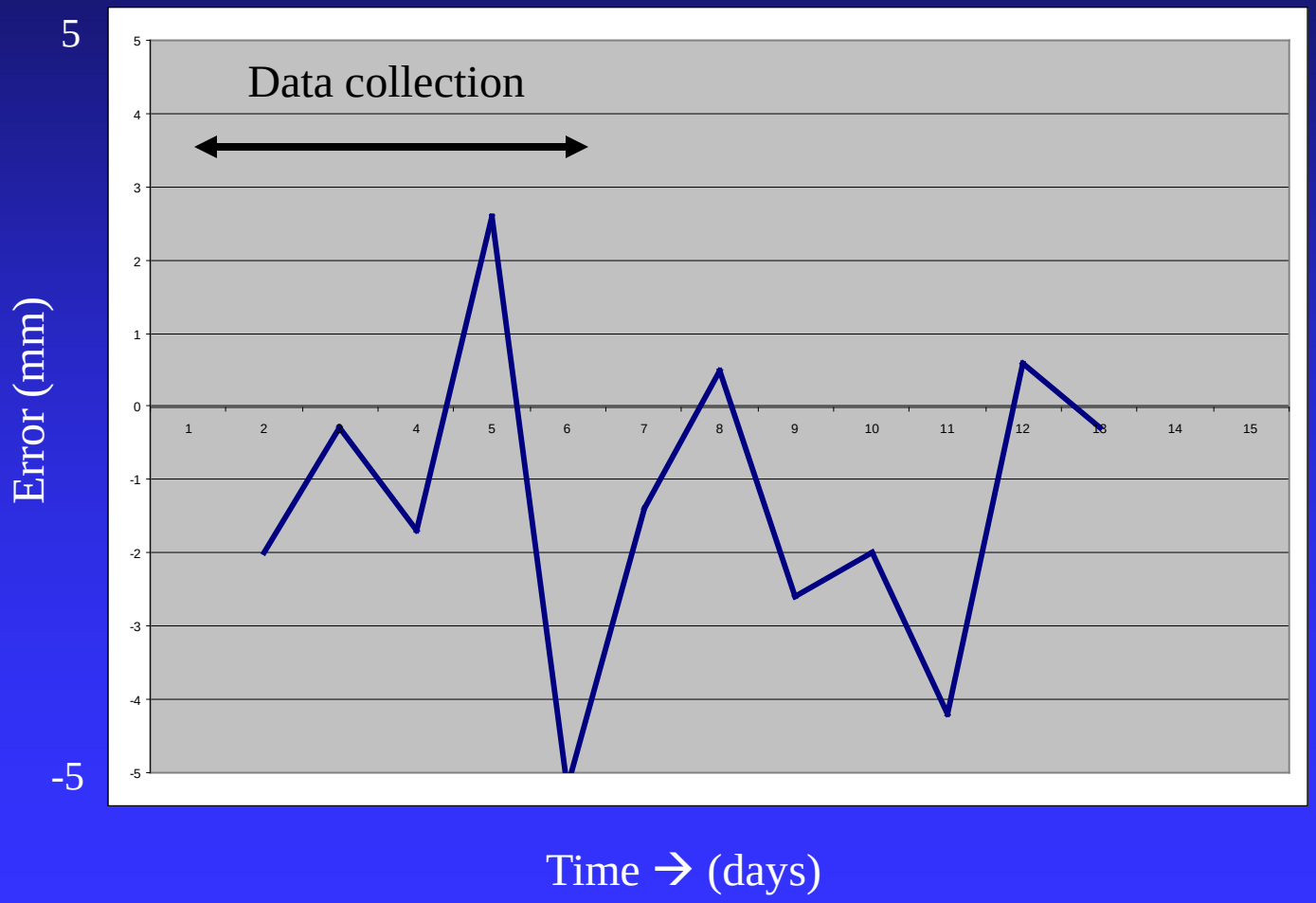
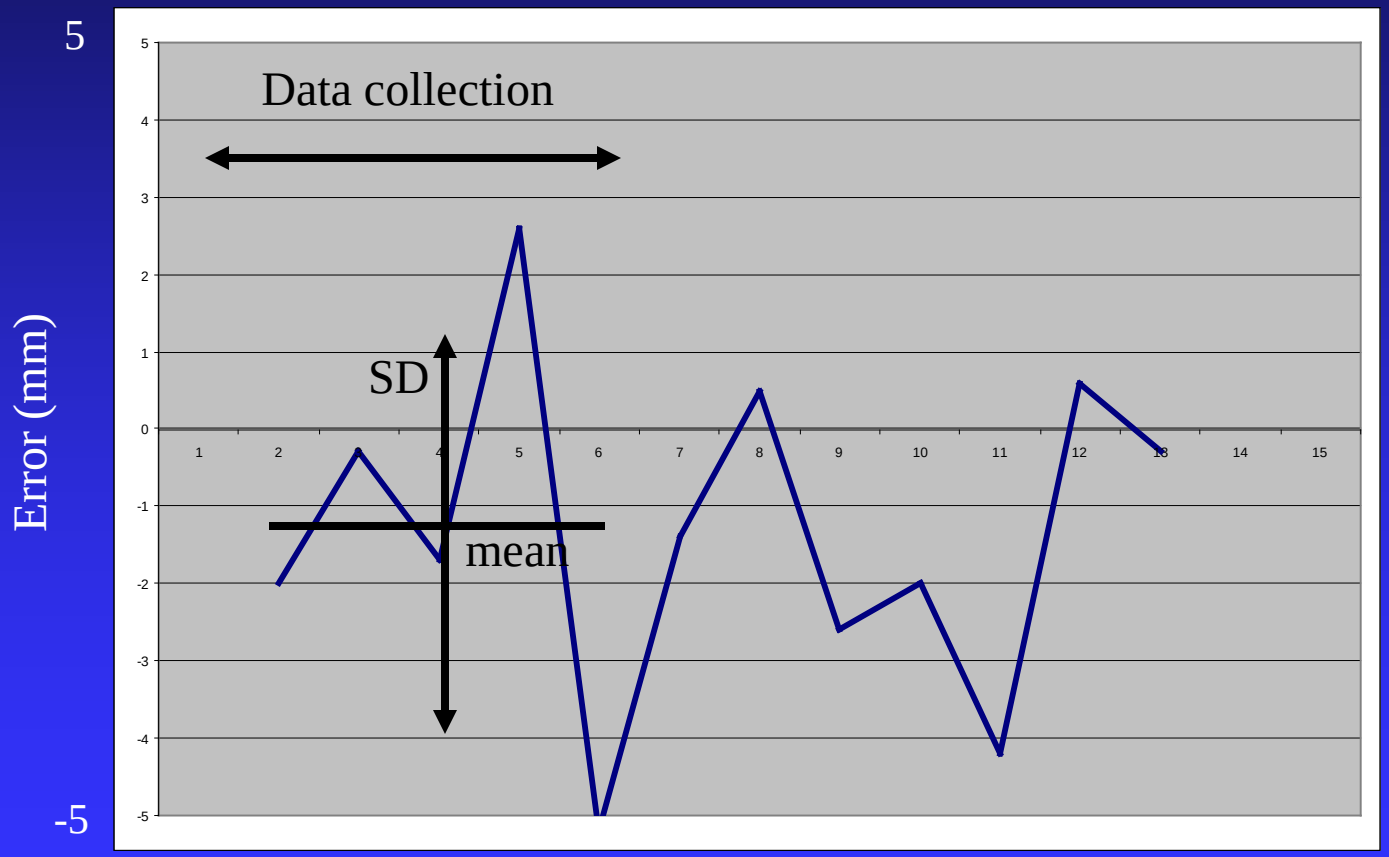
Reality check: setup error pattern



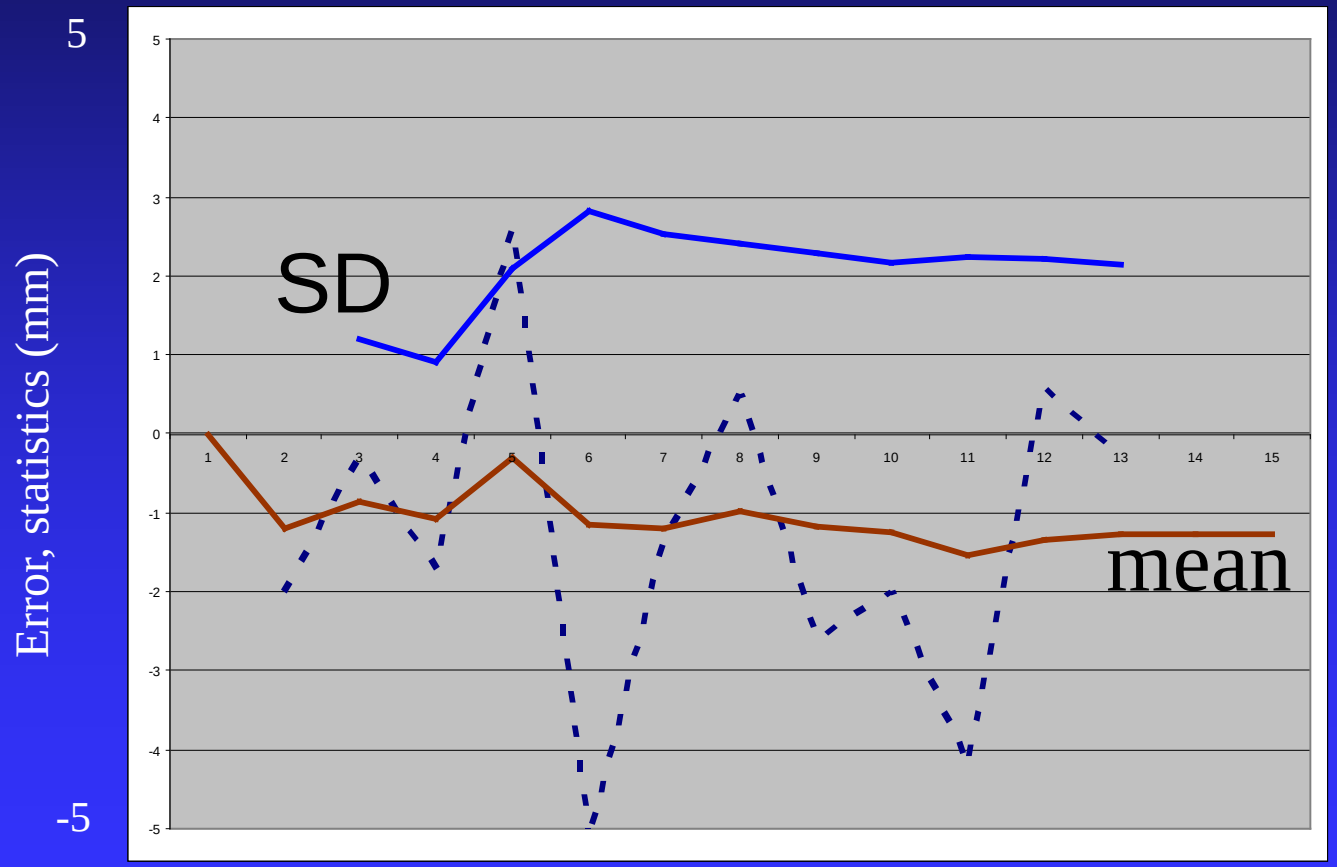
Adaptive radiotherapy



Adaptive radiotherapy (naïve summary after 5 fractions)

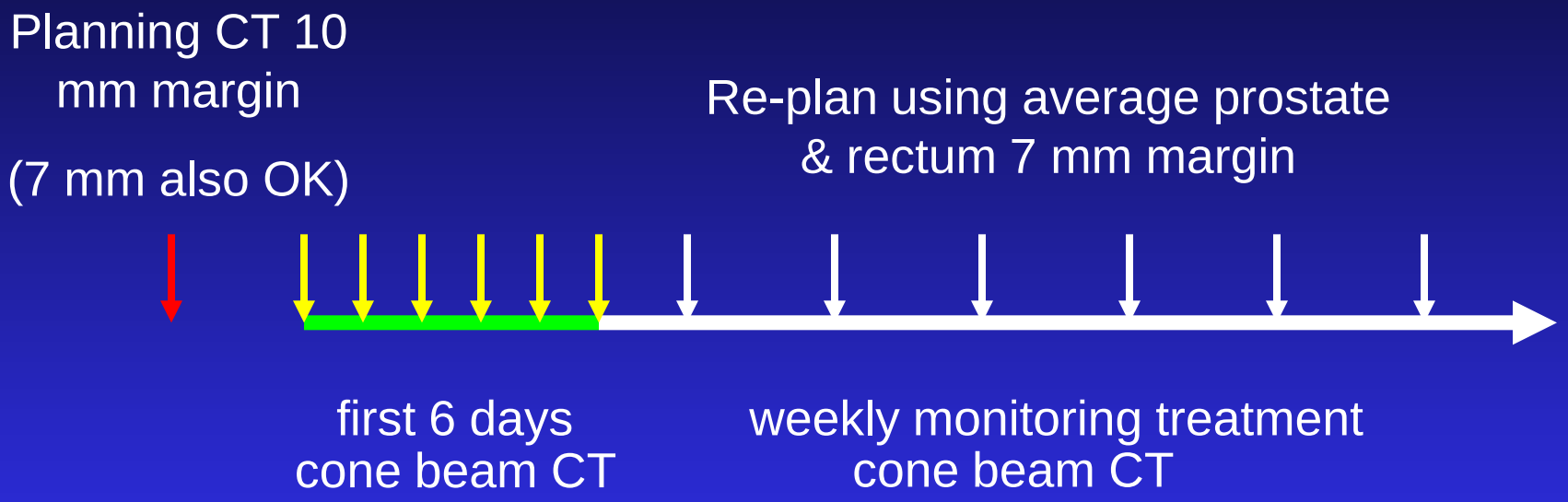


Naïve running estimates



Estimates of mean and σ are unreliable themselves: residual errors in mean and margin

Prostate Adaptive Radiation Therapy



Margin derived from simulation with follow-up CT data of 19 patients (11 scans per patient)*:

Similar results (good target coverage and rectum sparing):

Average prostate + 7 mm ← chosen

Convex hull of all prostates + 4 mm

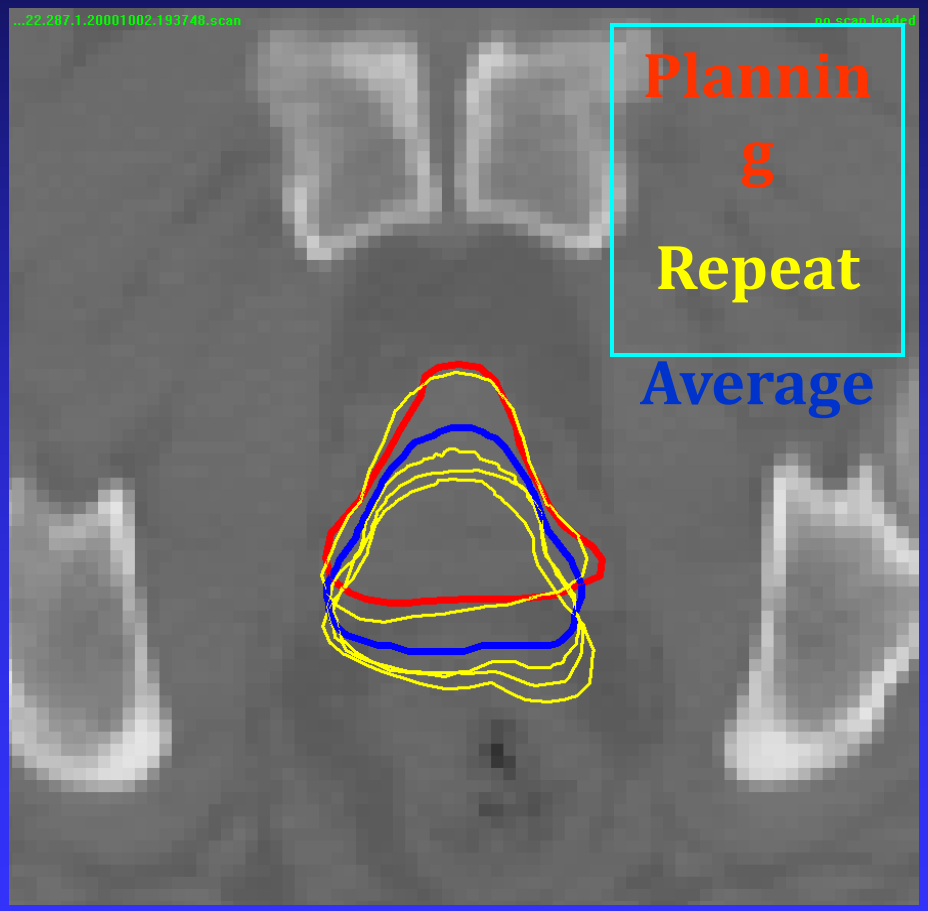
Nuver et al, IJROPB 2007

Methods: average prostate

- Plan → CBCT1: T1/R1
- Plan → CBCT2: T2/R2
- …
- Plan → CBCT6: T6/R6

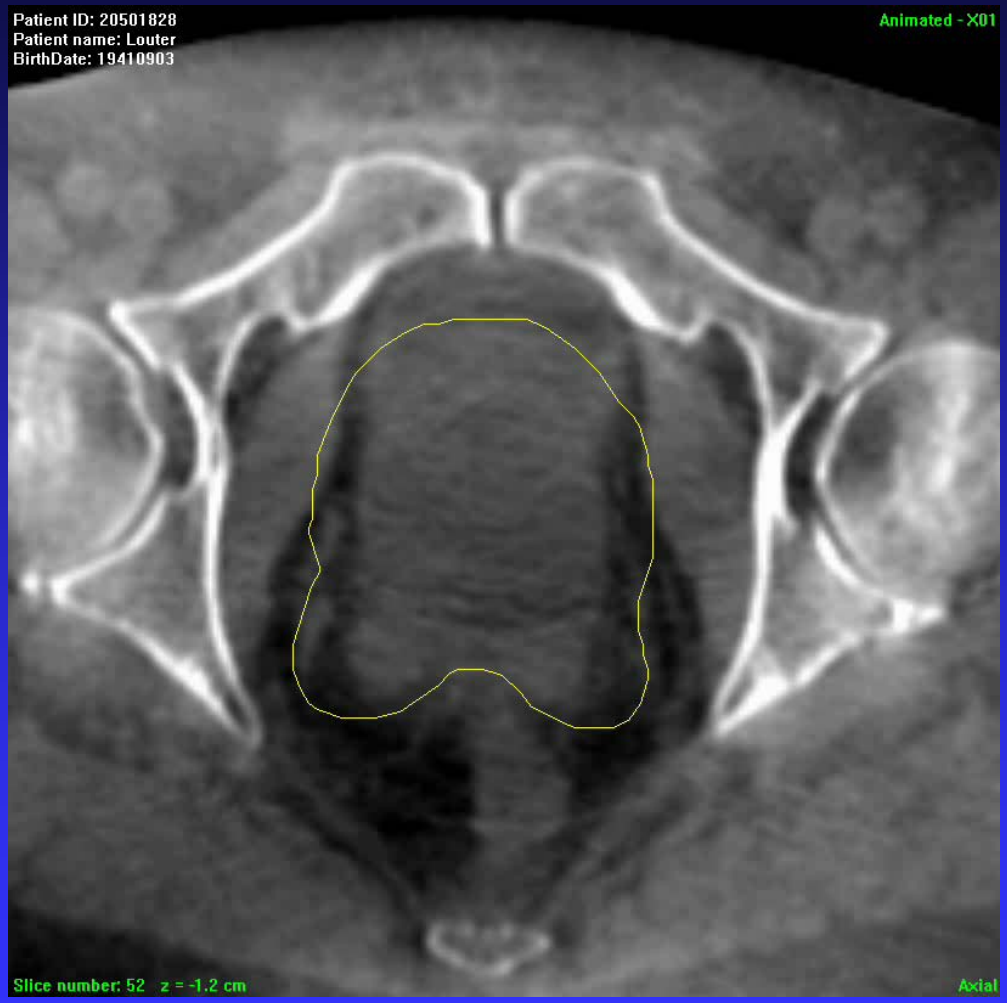
T_{AVG} / R_{AVG}

T_{AVG} / R_{AVG} puts prostate from plan CT in average position



- With this CTV the margin can be safely reduced from 10 mm to 7 mm

Results: monitoring the treatment



average CTV + 7 mm margin

Nijkamp et al, IJROPB 2007

Results

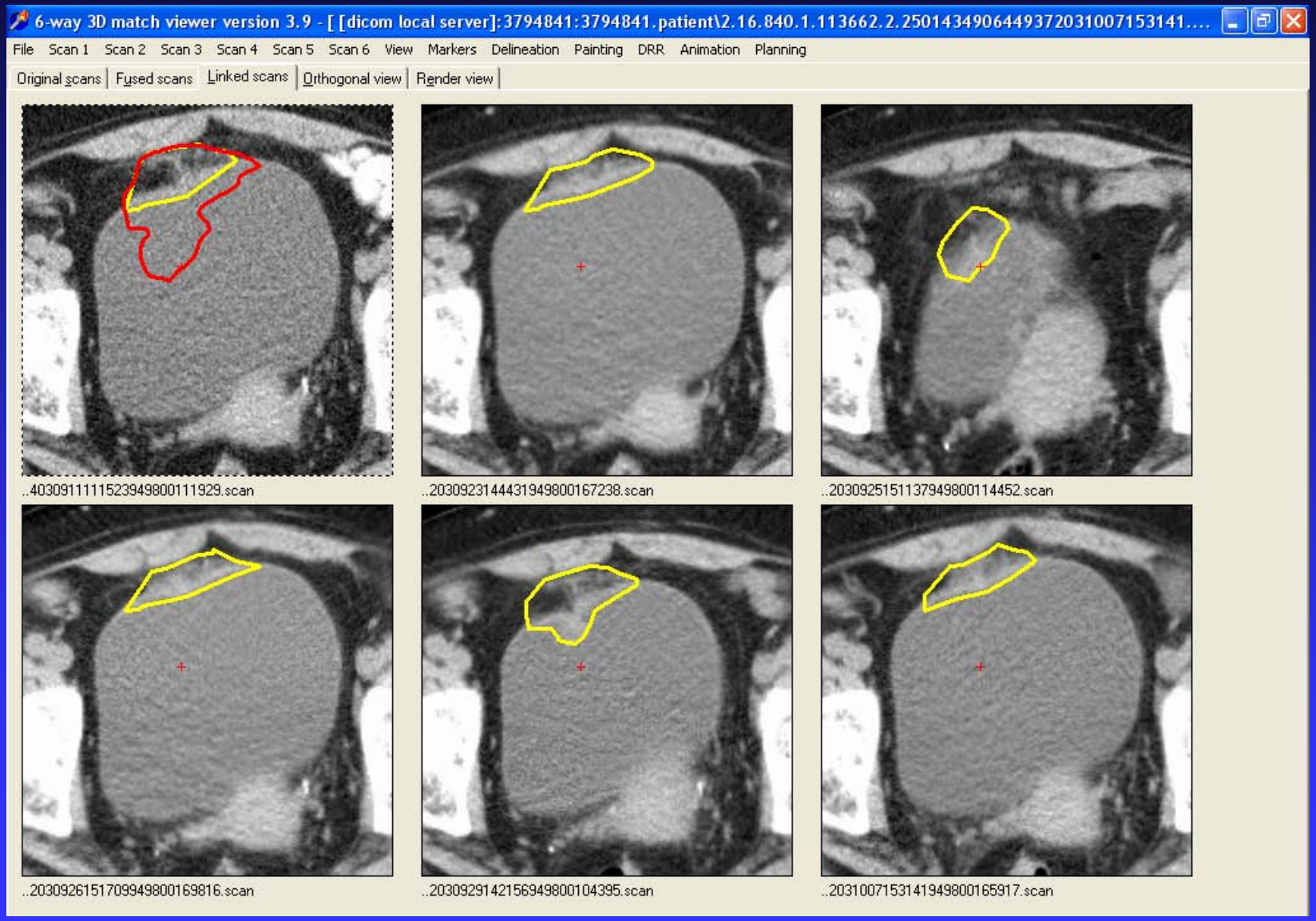
- 472 out of 483 (98%) follow-up CBCT scans GTV within PTV
- Only 5 out of 67 patients (7%) not enough useful CBCT scans in the first week (moving gas/technical problems)

Downside:

- Procedure took approximately 7 hours extra per patient
  - Prostate registration (0.5 hours)
  - ~~Delineation of rectums on CBCT (2 hours)~~
  - Planning and paperwork (4 hours)
  - Follow-up (0.5 hours)

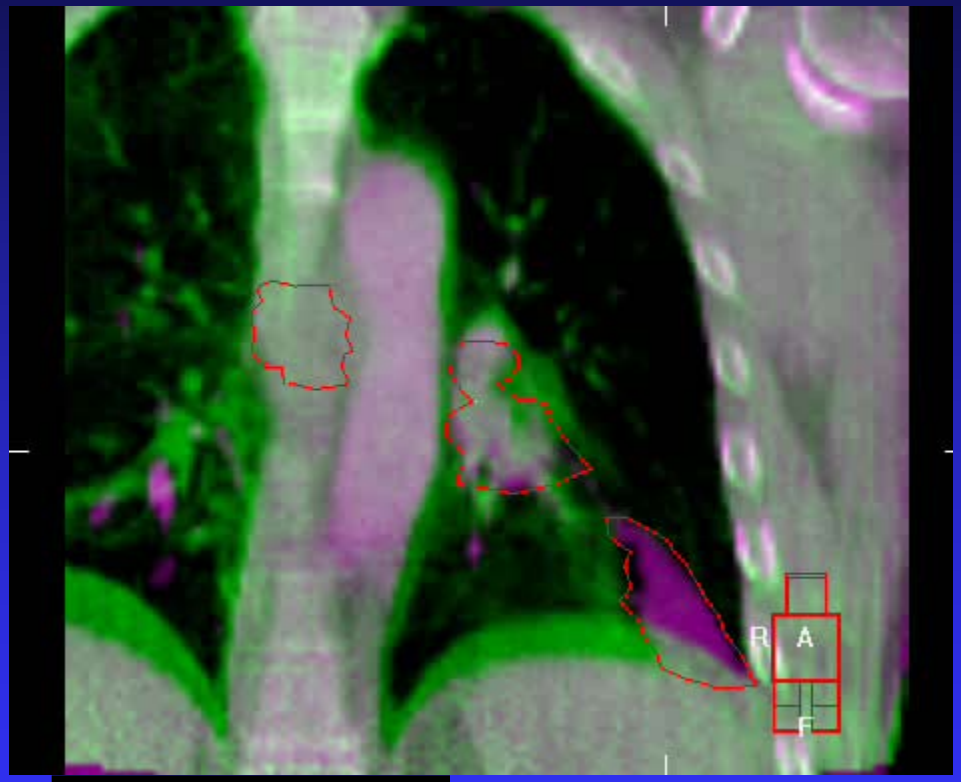
- Maximum of 1 patient per week

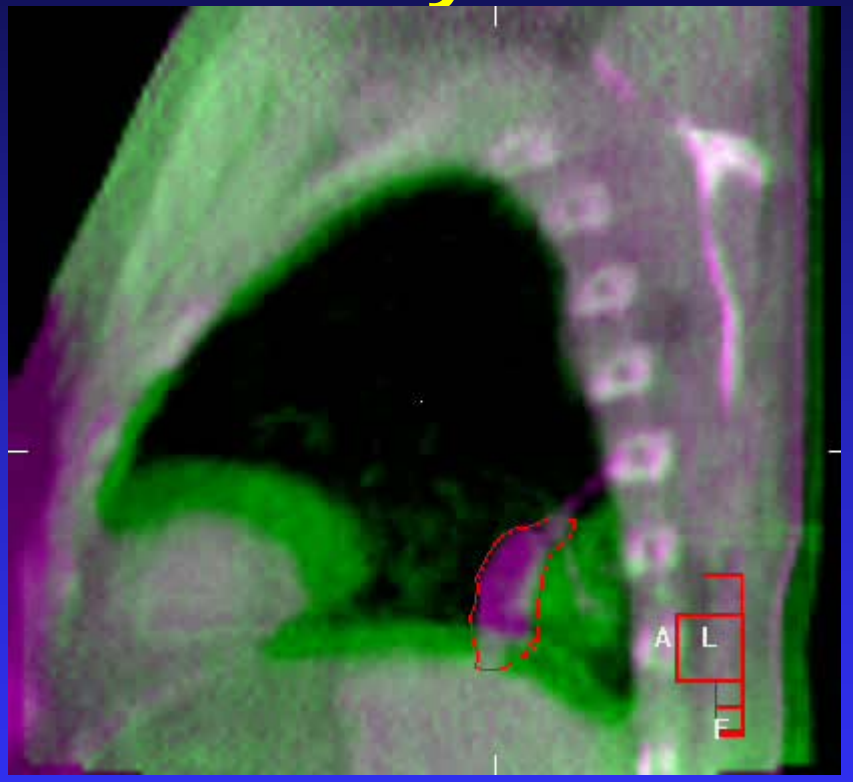
ART for bladder cancer: $GTV_{1\text{-}6}$ construction



•Pos et al 2005

Differential Variability





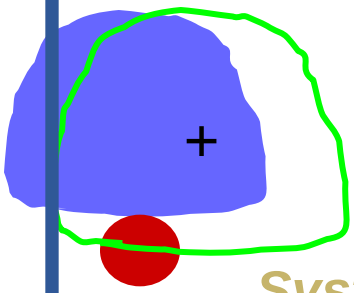
Planning CT

4D-CBCT

CTV

No couch correction can solve this problem

Benefits of Daily IG-IMRT



Accuracy

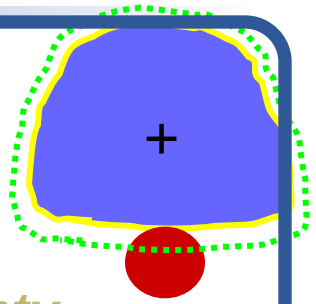
Reduce

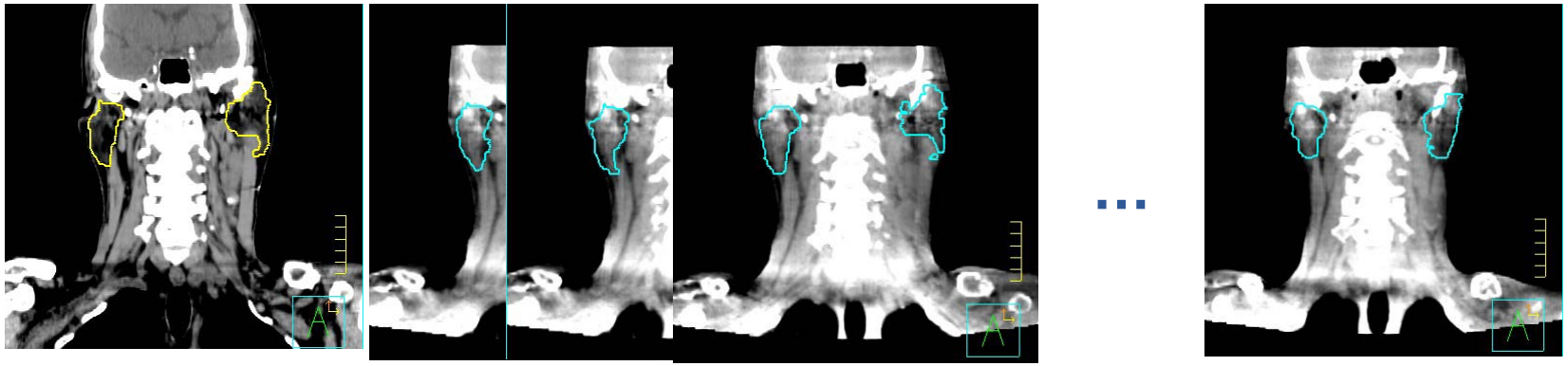
Systematic uncertainty

Precision

Match PTV to

random uncertainty

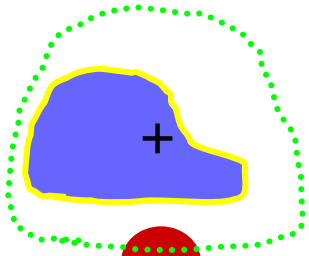




Adaptation

Assess anatomical

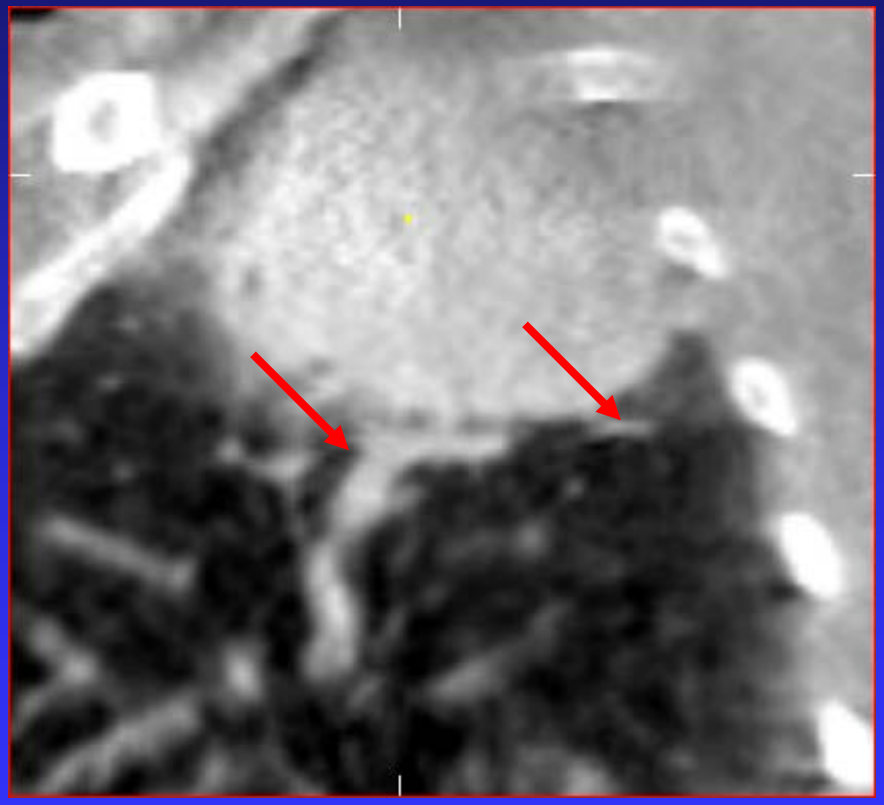
changes & update plan

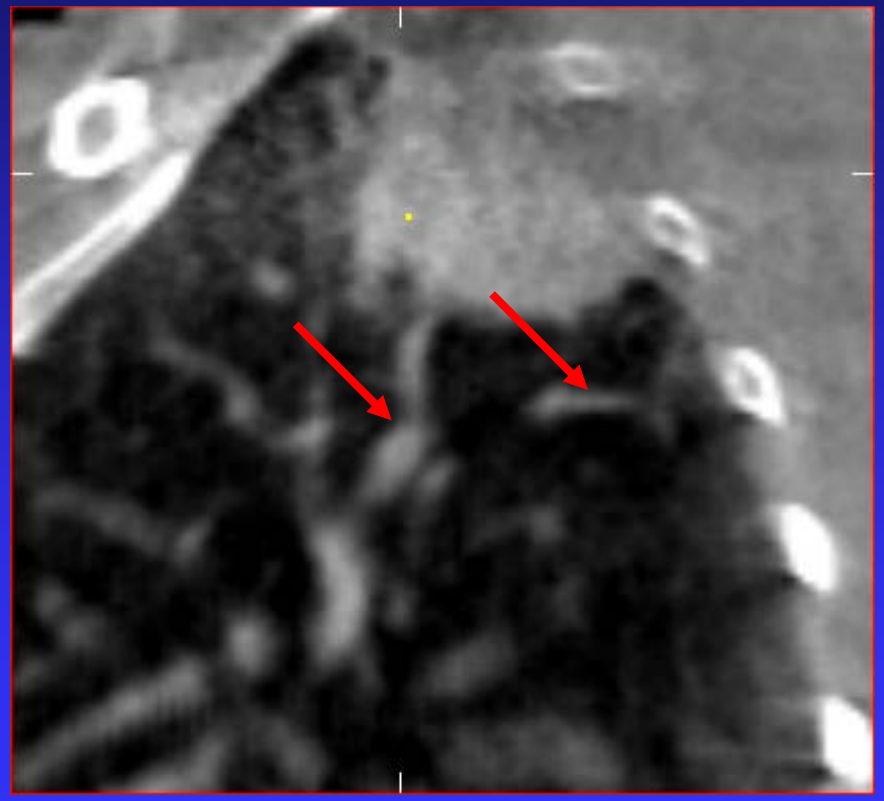


ESTRO School

UHN Princess Margaret Cancer Centre

Tumour Regression





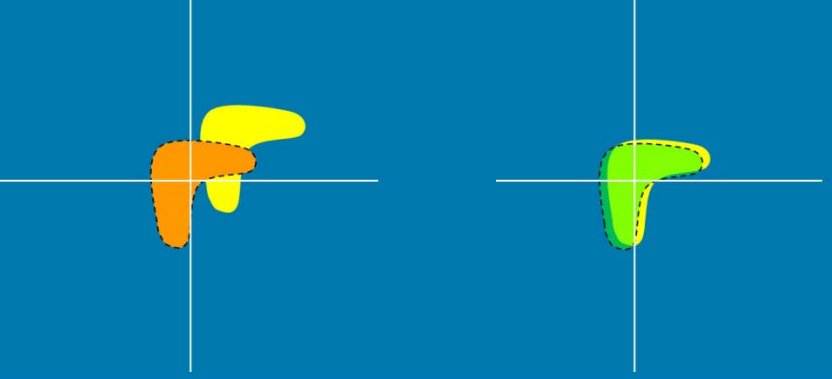
Summary

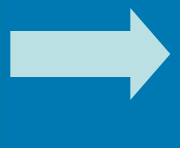
- Frequent soft-tissue imaging provides feedback & and opportunity to adapt to changing conditions.
- On-line correction combined with off-line adaptation is desirable, but may not be sufficient.
- Adaptive schemes may permit PTV margin reduction, and other opportunities to improve treatment:
  - Assure minimum target dose.
  - Spare more normal tissue volume.

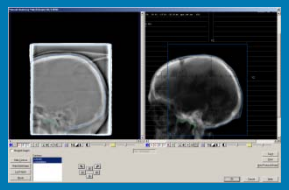
Library planning

Gert Meijer

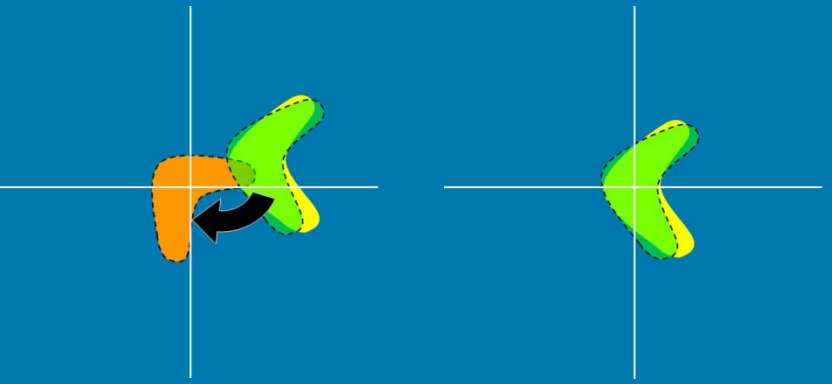
ESTRO
European Society for Therapeutic Radiology and Oncology

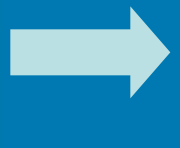


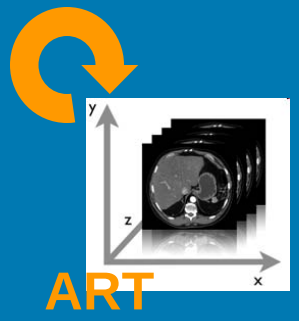




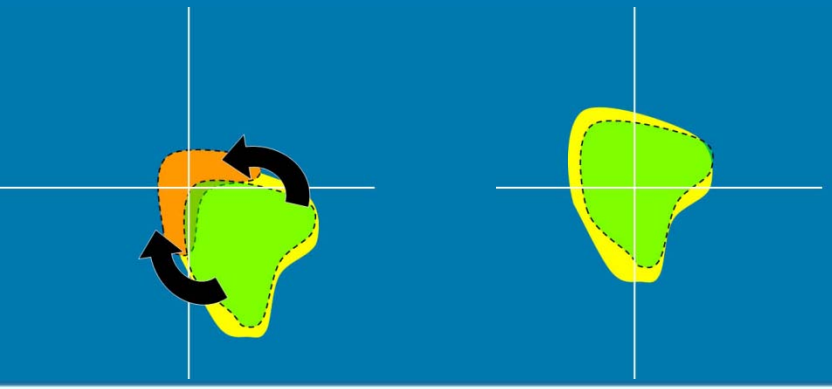
single plan

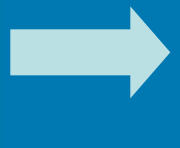






new plan





?

plan of the day

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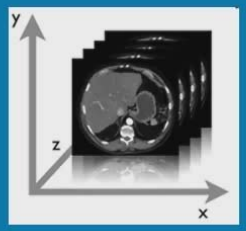
plan of the day

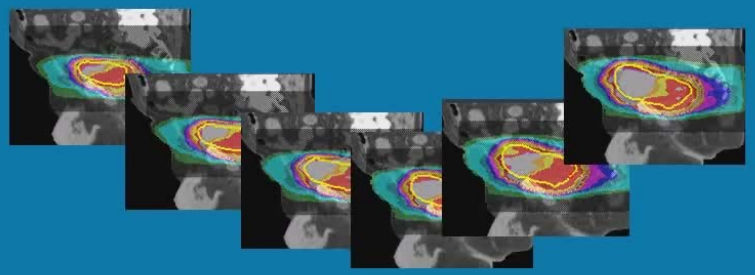
1

online (re)planning



2

library of plans

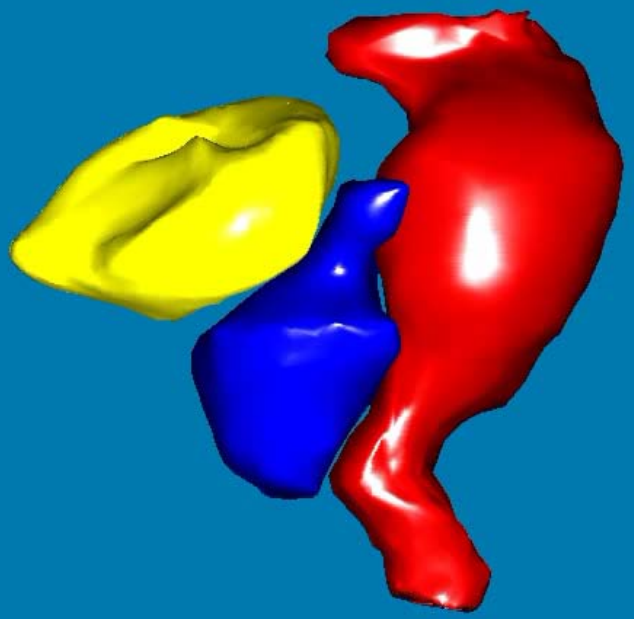


issues with library planning delivery

- how to prospectively generate a set of plans?
  - sampling prior to treatment
  - sampling during treatment
- target visualisation during treatment
- shift in responsibilities
  - who will select the plan of the day?

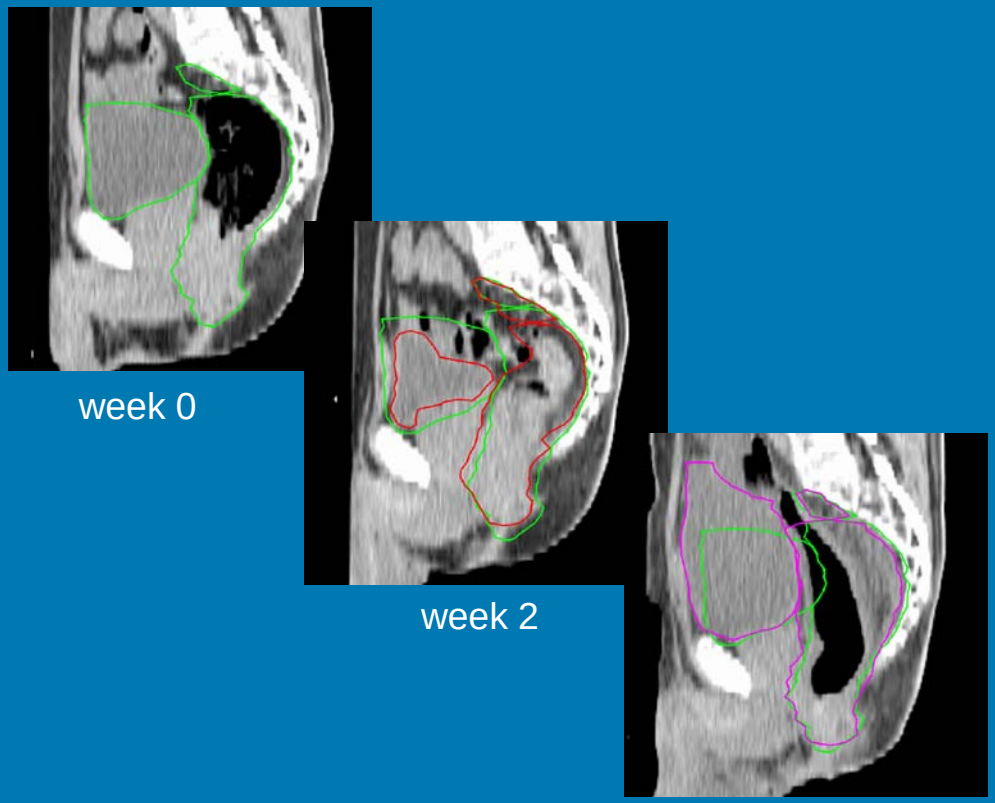
potential tumour sites for online adaptive strategies

- **prostate cancer**
- rectal cancer
- cervical cancer
- bladder cancer



potential tumour sites for online adaptive strategies

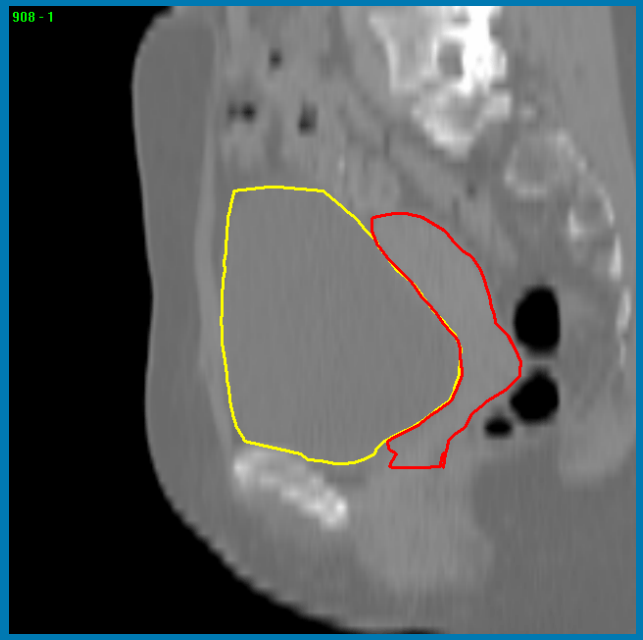
- prostate cancer
- **rectal cancer**
- cervical cancer
- bladder cancer



courtesy of Jasper Nijkamp, NKI

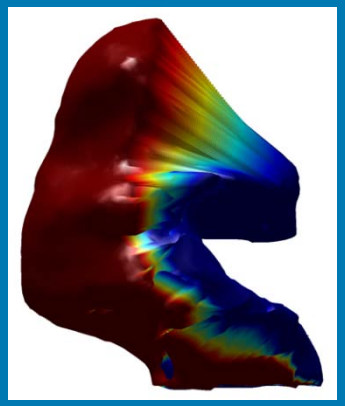
potential tumour sites for online adaptive strategies

- prostate cancer
- rectal cancer
- **cervical cancer**
- bladder cancer

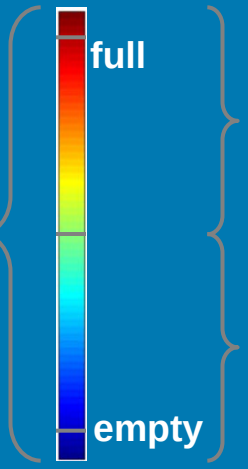


cervical cancer

bladder volume as a surrogate for uterus geometry

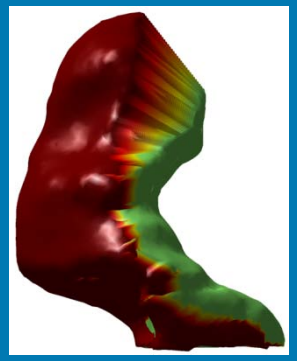


ITV

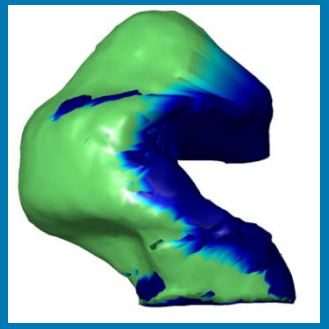


ITV1

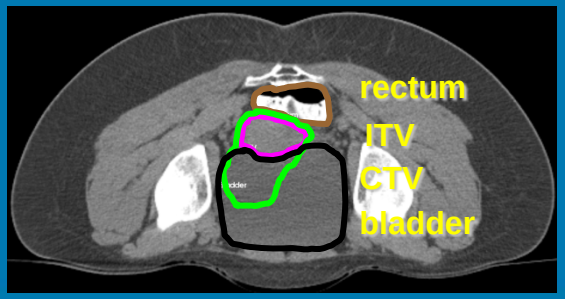
ITV2

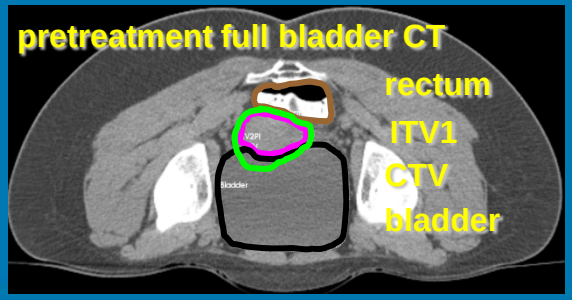


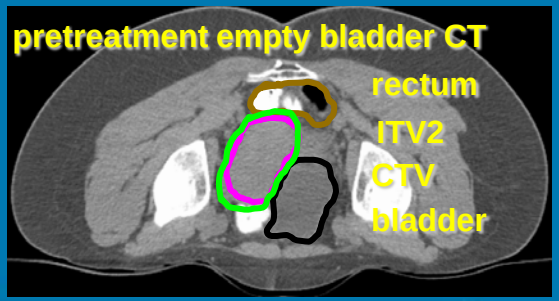
ITV1- large bladders



ITV2- small bladders







Luiza Bondar *et al*, Rotterdam

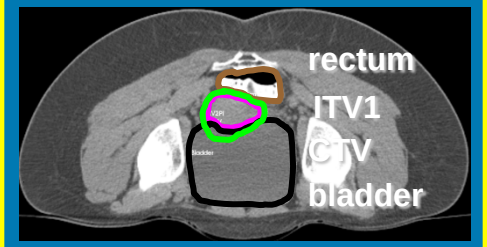
bladder volume used for plan of the day selection

full

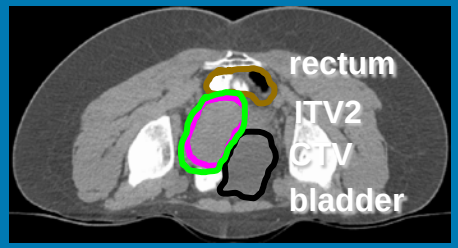
empty

ITV1

ITV2

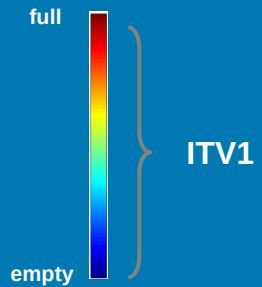


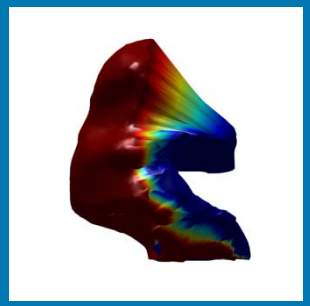
ITV1 - large bladders

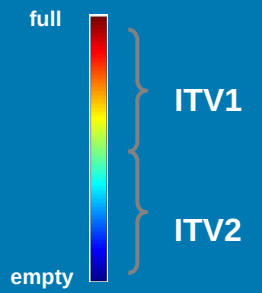


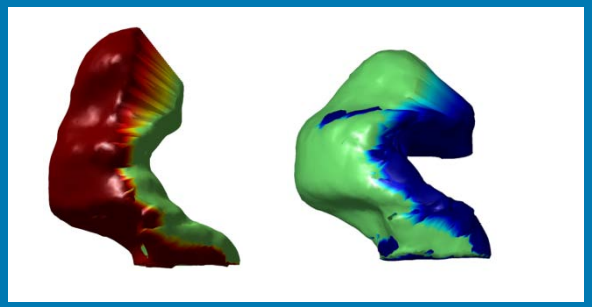
ITV2 - small bladders

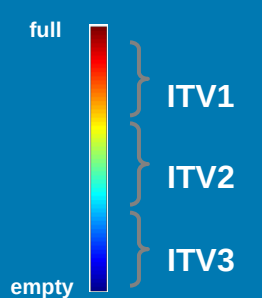
with courtesy of Luiza Bondar Erasmus MC

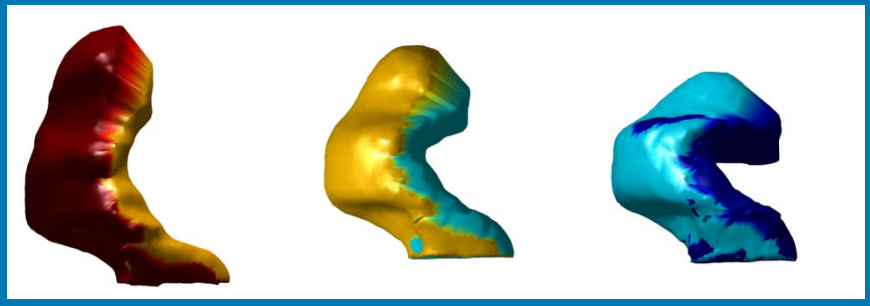








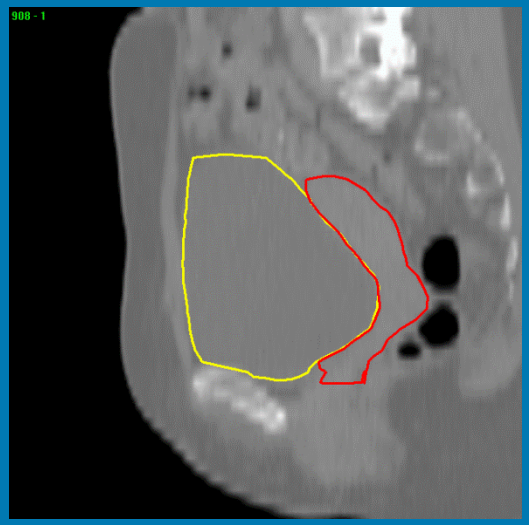




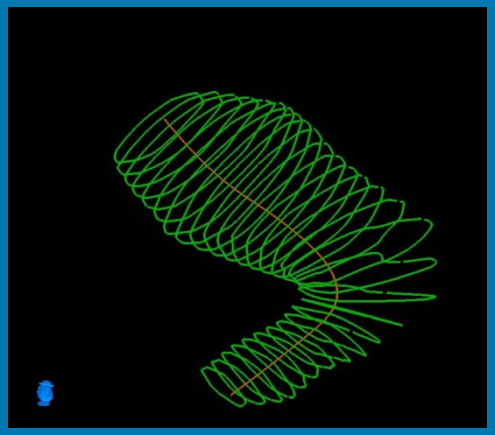
with courtesy of Luiza Bondar Erasmus MC

cervical cancer

library of plans based on patterns of motion in *population* using principal component analysis methods



multiple patients
multiple fracions



courtesy of Simon van Kranen

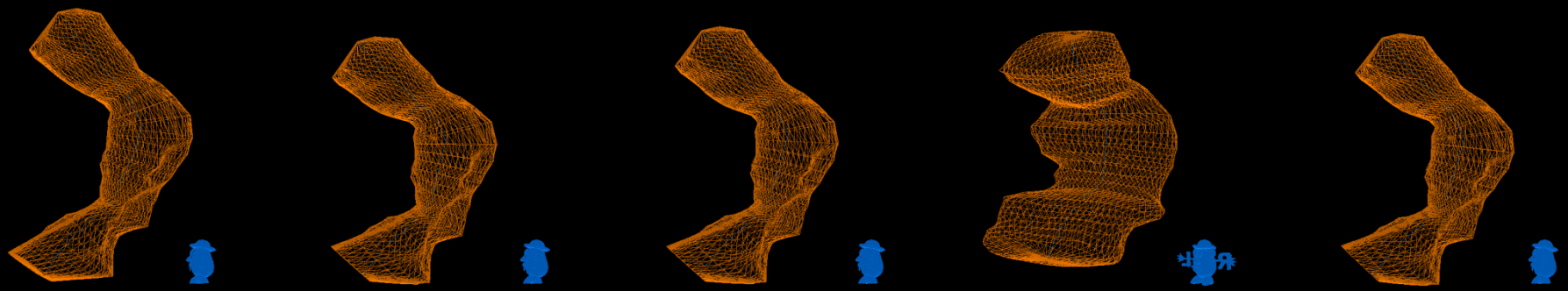
Mean

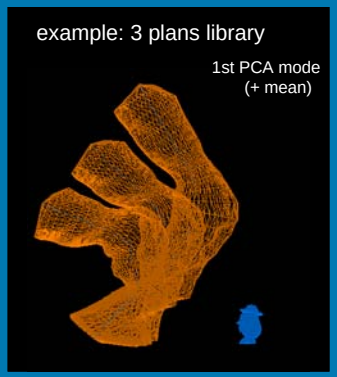
1 - 49%
bladder

2 - 26%
bladder

3 - 10%
LR motion

4 - 6%
rectal filling

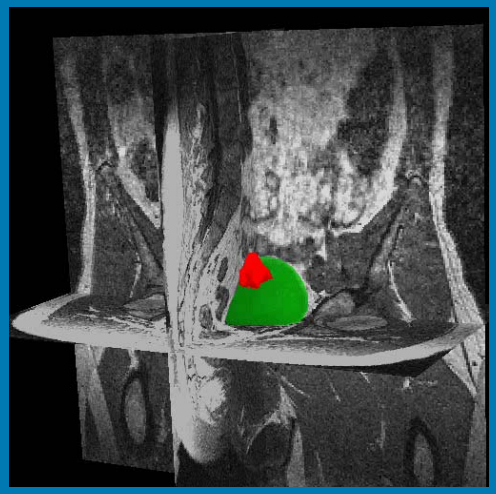


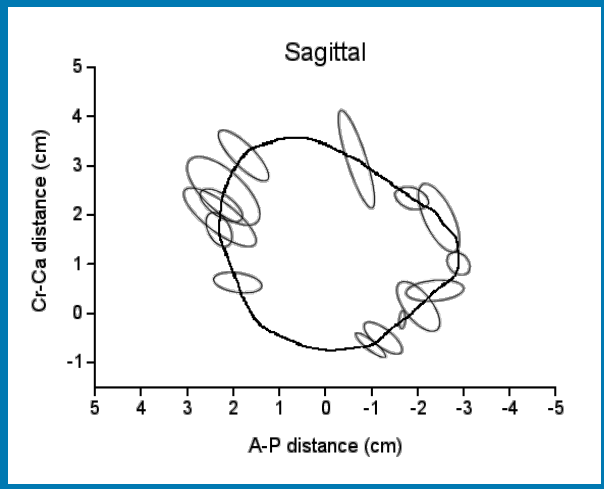


courtesy of Simon van Kranen

potential tumour sites for online adaptive strategies

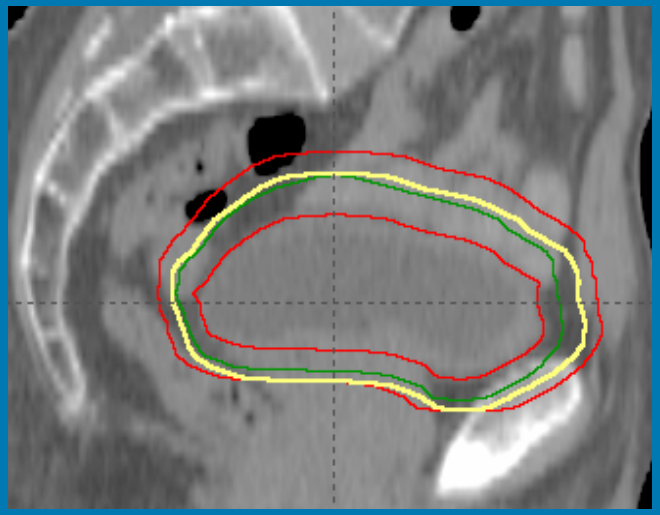
- prostate cancer
- rectal cancer
- cervical cancer
- **bladder cancer**





Lotz *et al.* IJROBP 2003

bladder cancer



library based on different margins

library generation

# CT scans	#CBCT scans	groups
1	**0**	**Vestergaard, Aarhus** **Burridge, Christy Hospital**
1	multiple	Vestergaard & Wright, Aarhus
multiple	0	Lalondrelle, Royal Marsden Meijer, Catharina

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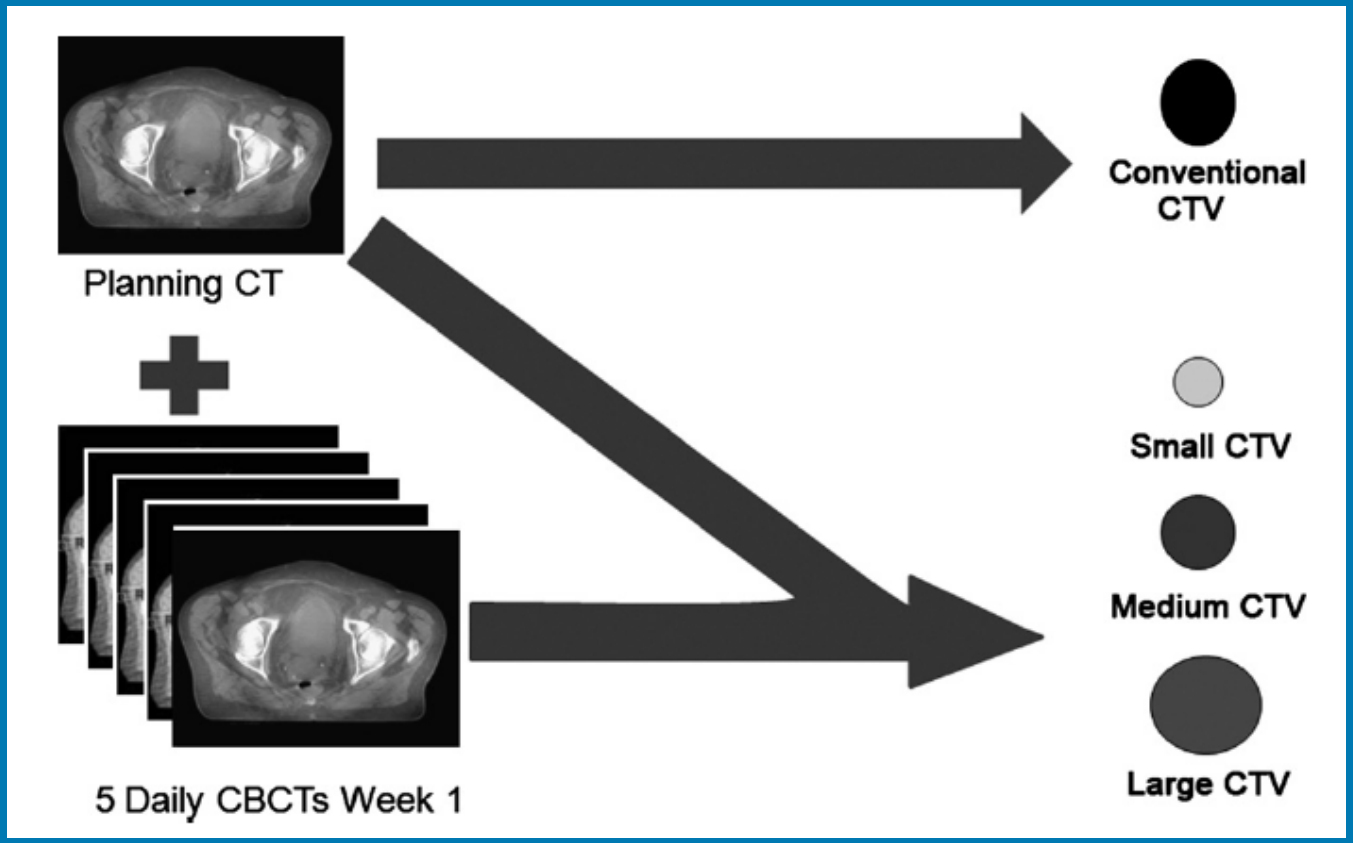

+ 1.5 cm margin

+ 0.5 cm margin

manual

summation

Foroudi *et al.* (IJROBP 2010)

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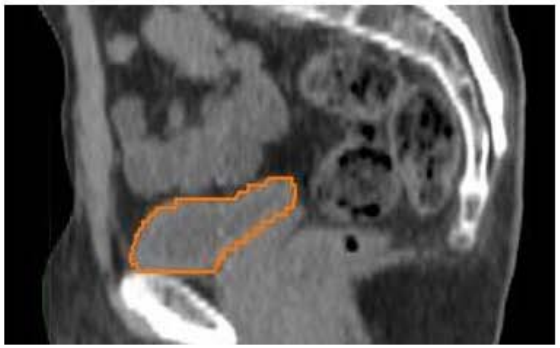
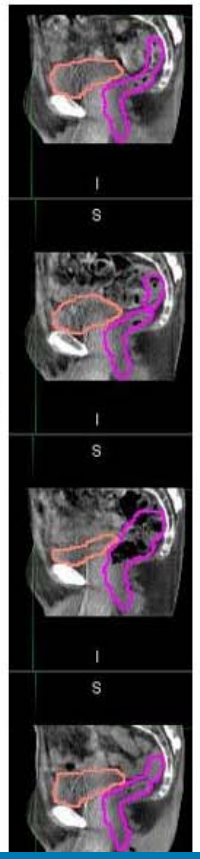
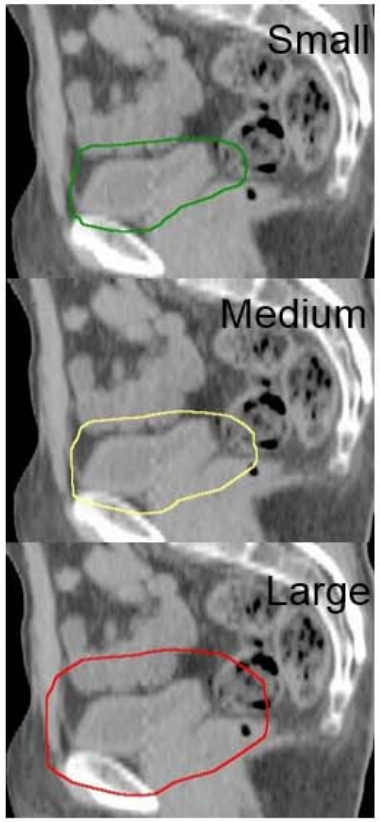
Planning CT prior to treatment

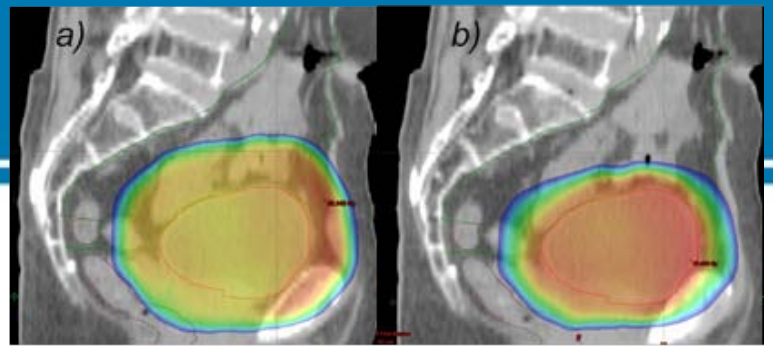


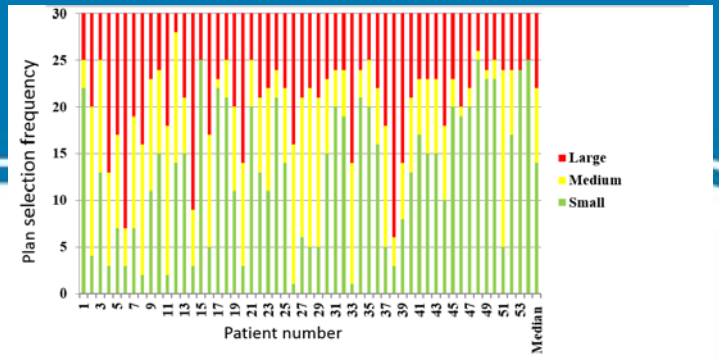


Library of dose plans



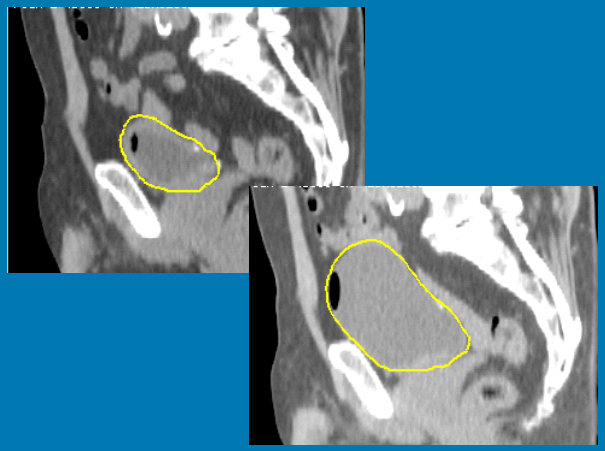
Aarhus group





olume ratio of course averaged PTV: PTV_{ART} /PTV_{nonART} Median 0.68[0.43;0.93]

bladder cancer



prospectively generating target volumes

library generation

# CT scans	#CBCT scans	groups
1	0	Vestergaard, Aarhus Burridge, Christy Hospital
1	multiple	Vestergaard & Wright, Aarhus
multiple	**0**	**Lalondrelle, Royal Marsden** **Meijer, Catharina**

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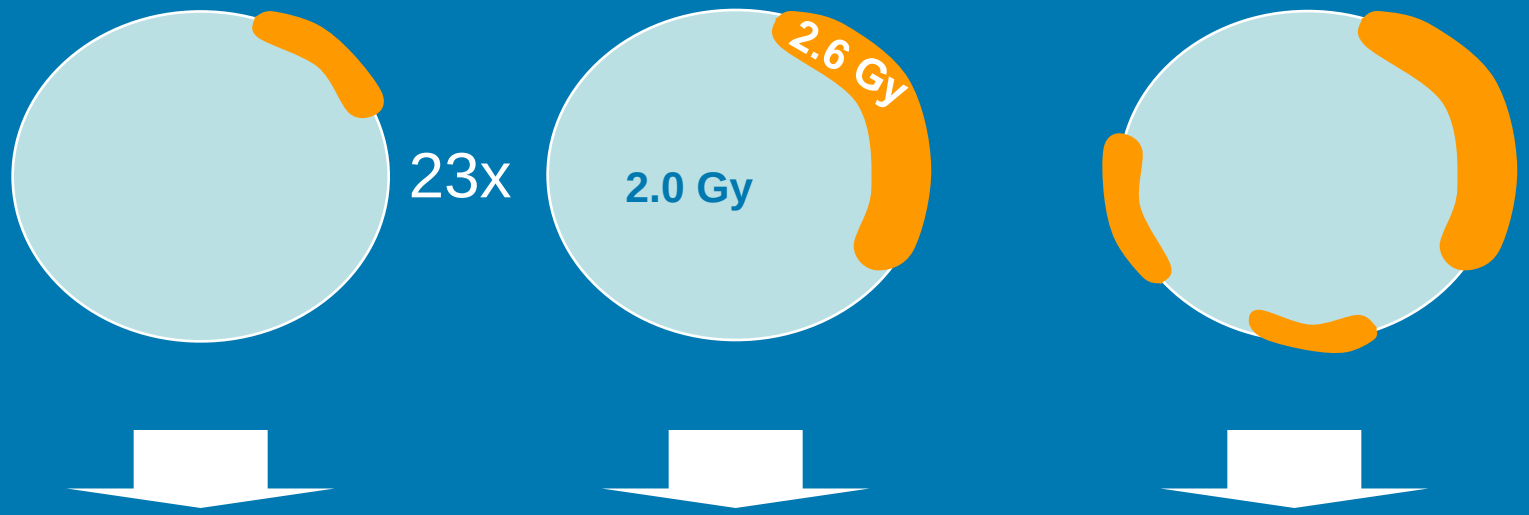
Bladder RT at Catharina Hospital

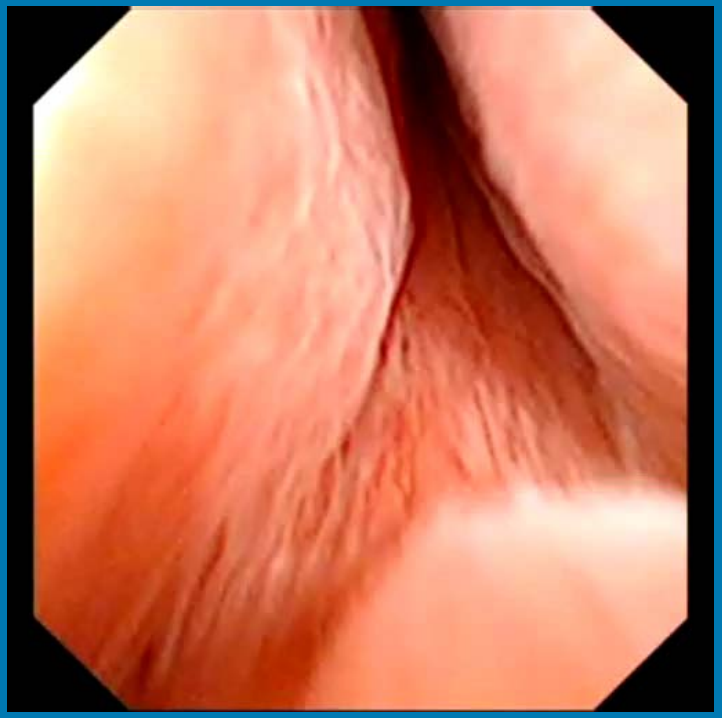


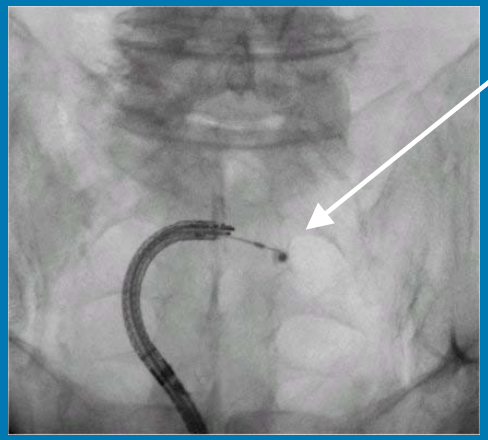
brachytherapy

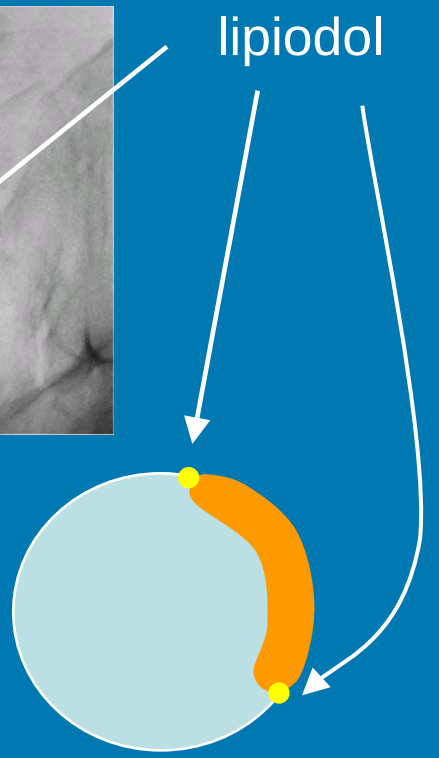
IGART
concomitant boost

EBT whole bladder

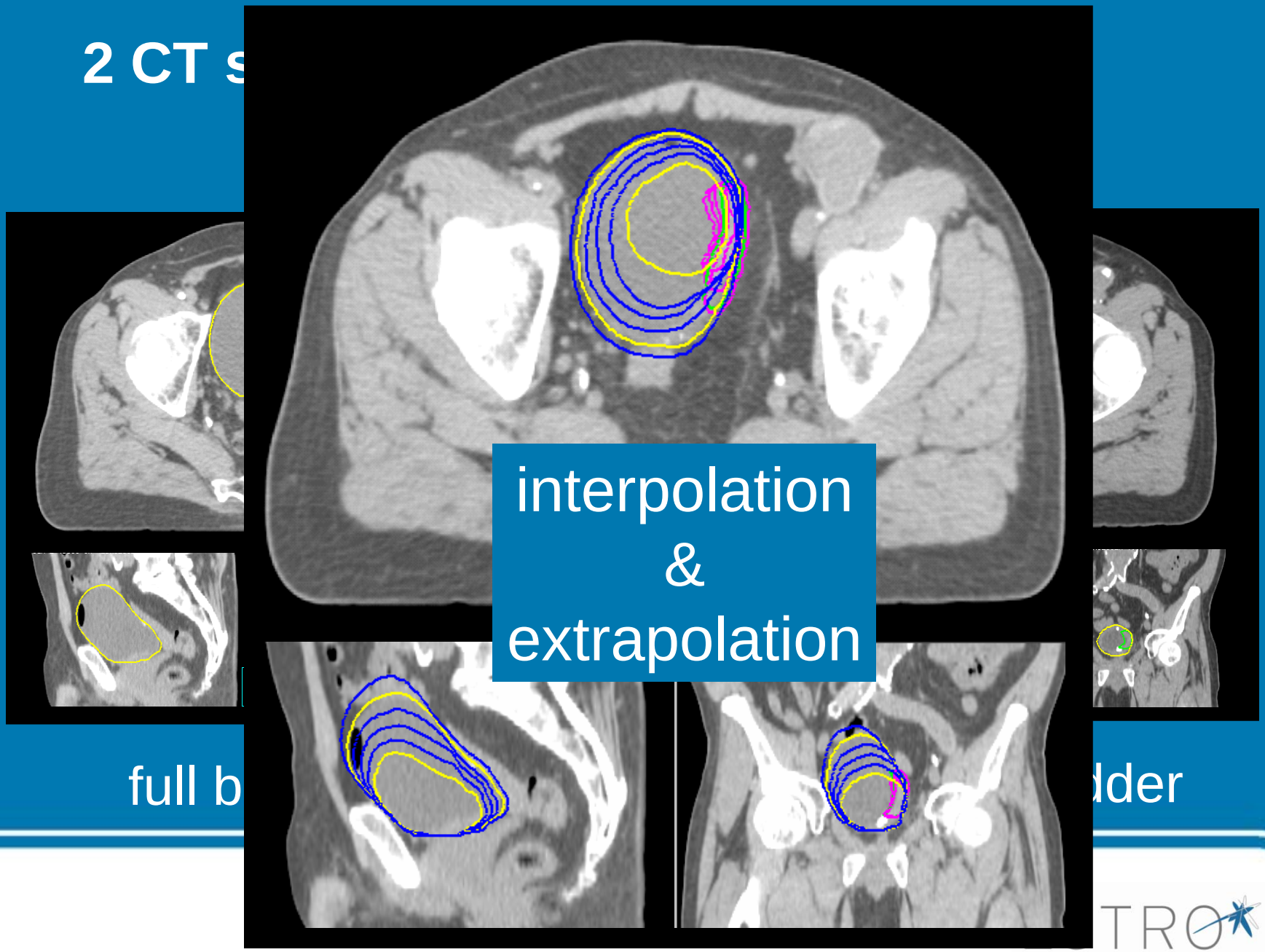
Endoscopic lipiodol demarcation of the GTV







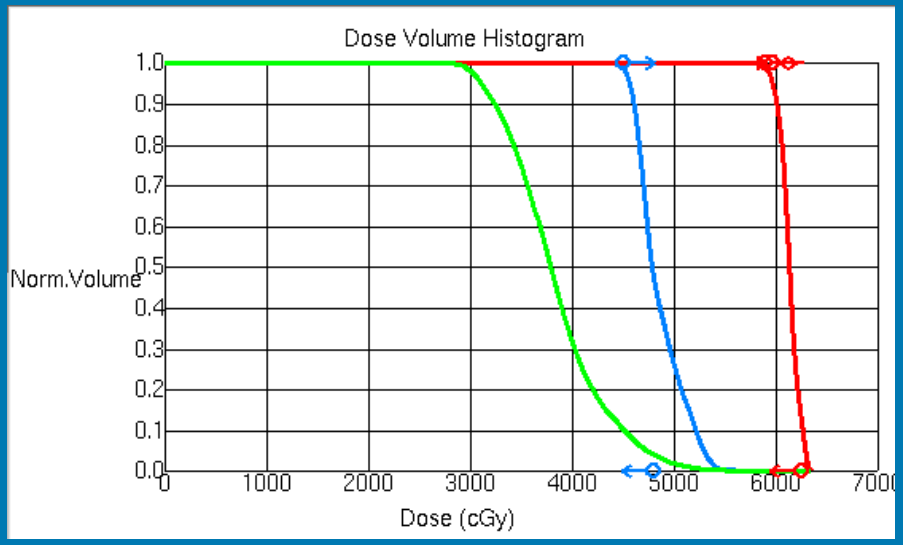
2 CT s

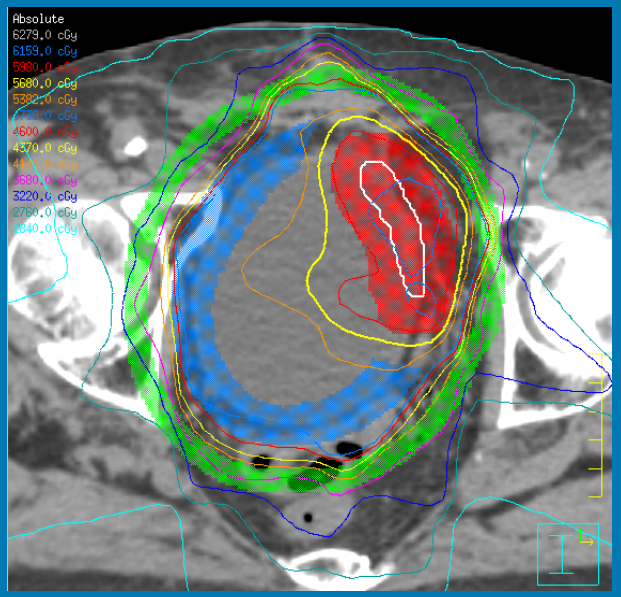


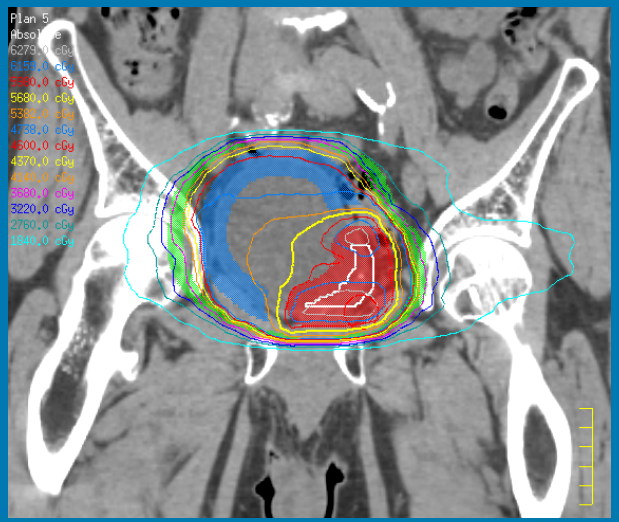
full b

dder

automated planning







PTV GTV	min dose 100	59.0 Gy	
PTV GTV	max dose	62.5 Gy	30
PTV GTV	uni dose	59.8 Gy	1
PTV Bladder*	min dose 100	45.0 Gy	
Ring	Min EUD (a=5)	59Gy	1

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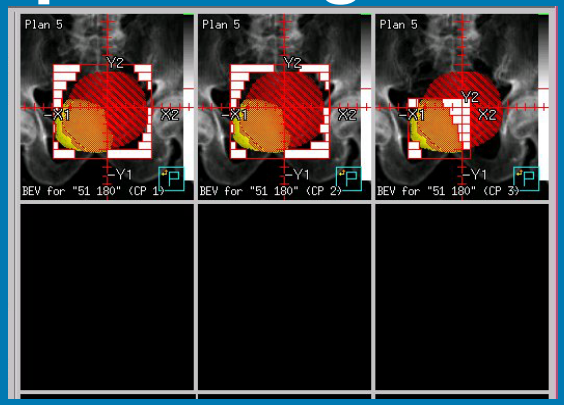
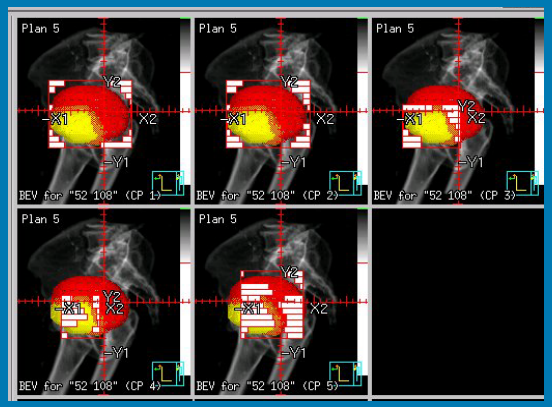
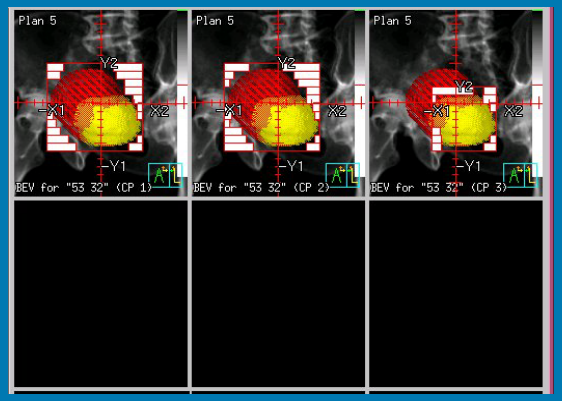
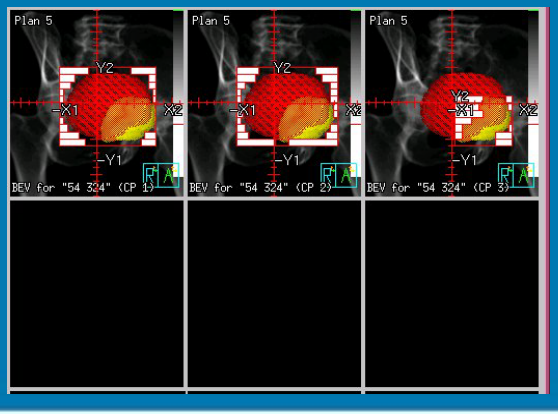
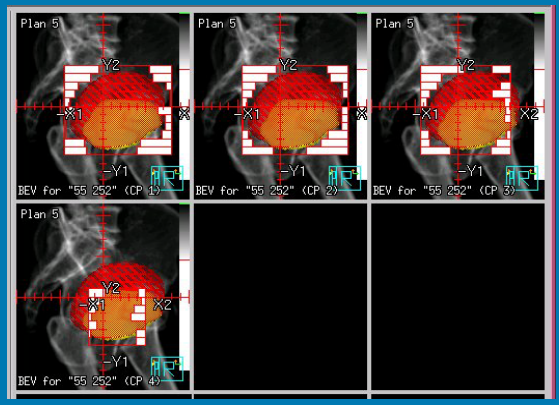
automated planning











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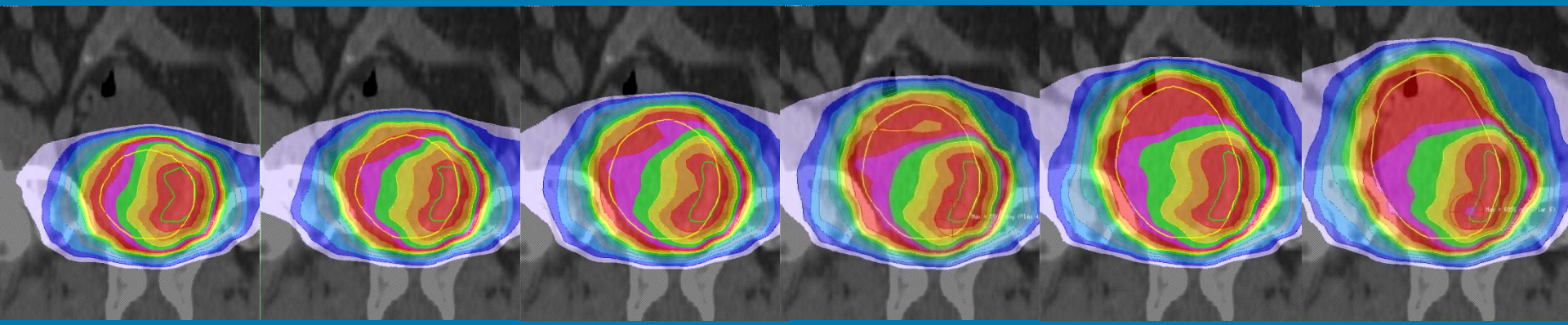
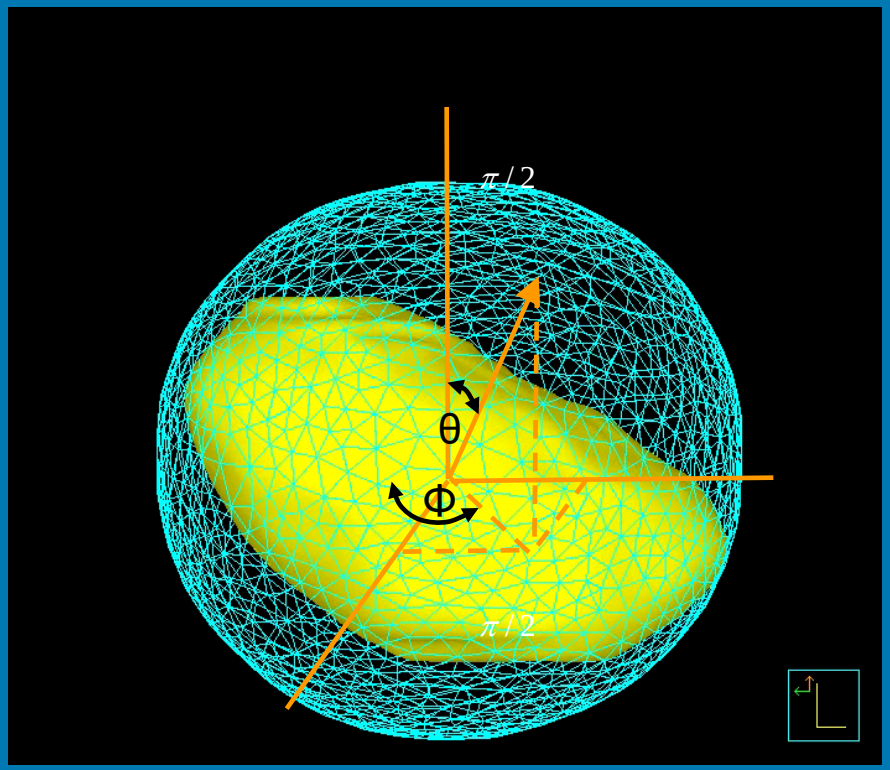
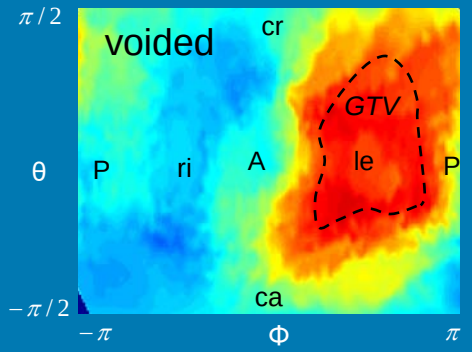
multiple ‘simple’ IMRT plans

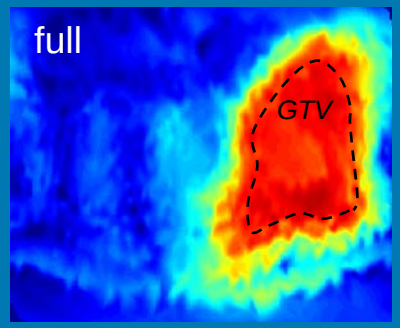


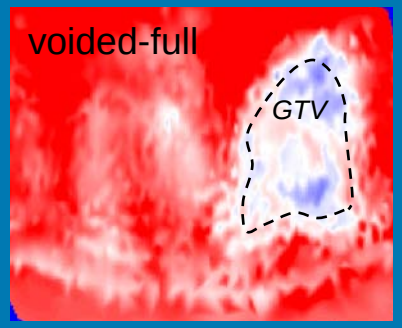
coronal views

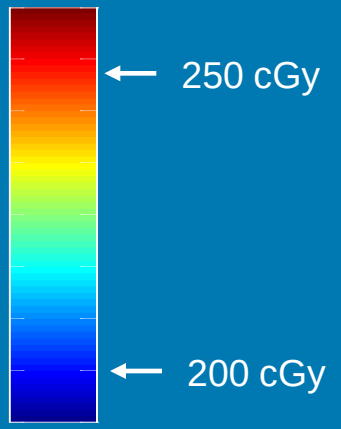
dose wall maps of voided and full bladder plans

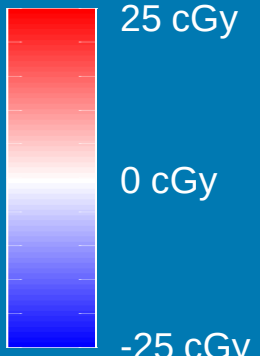












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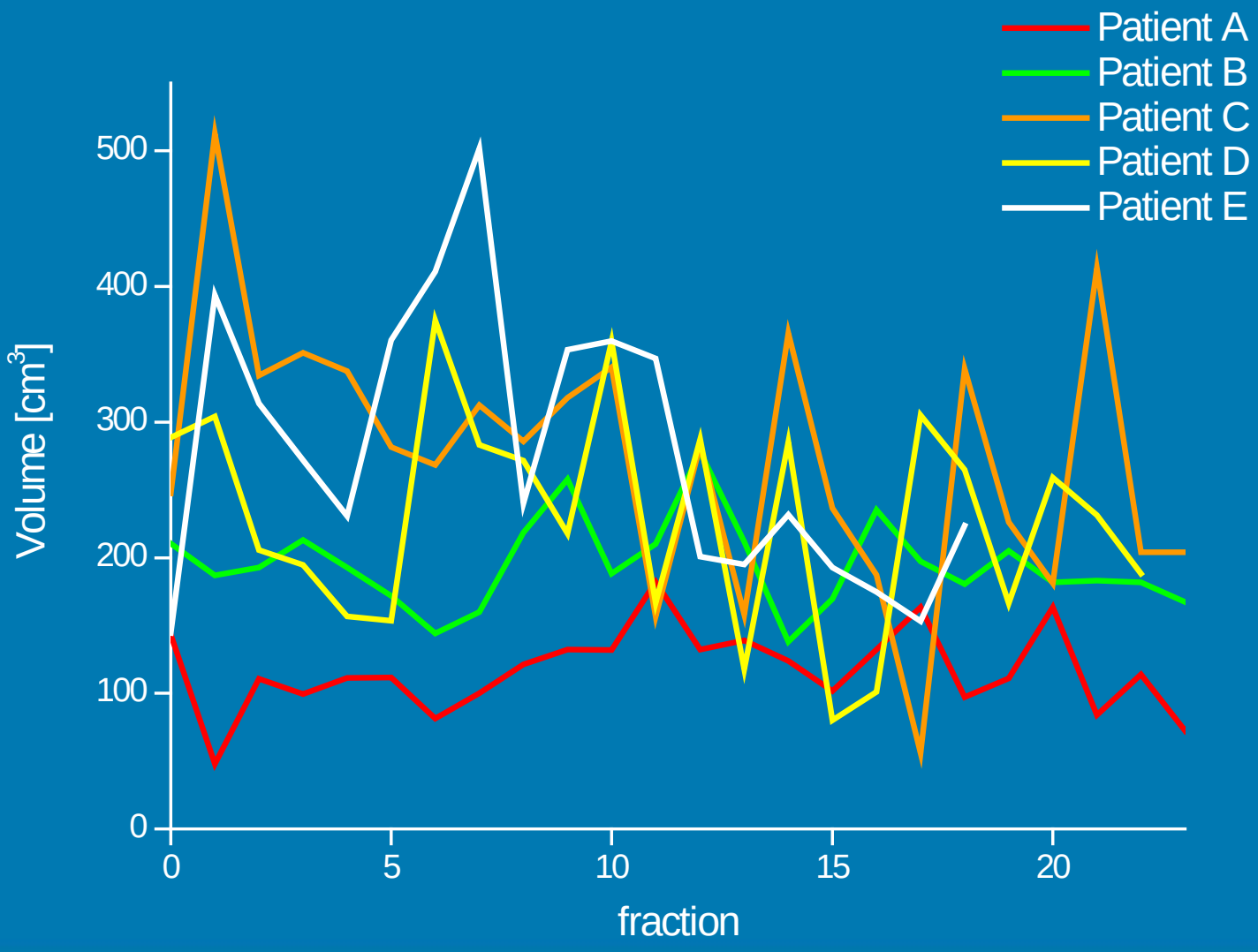
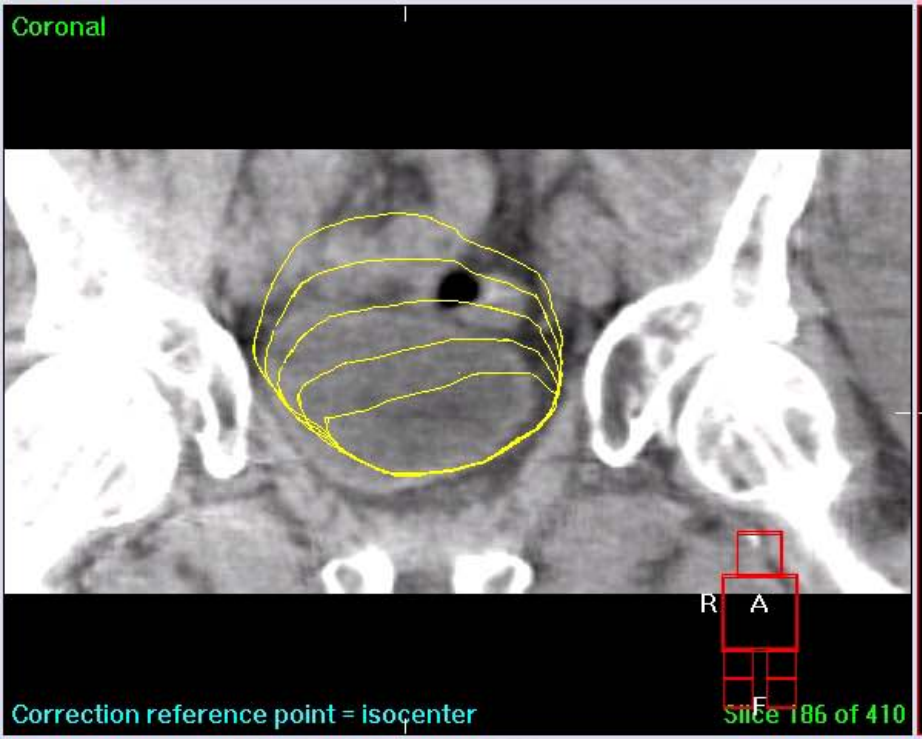
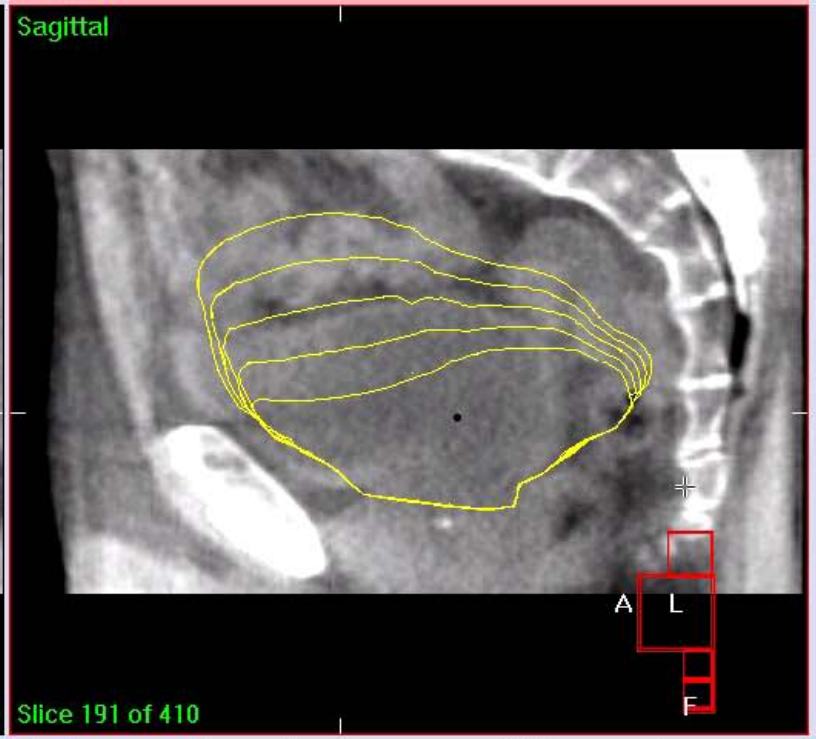






Image

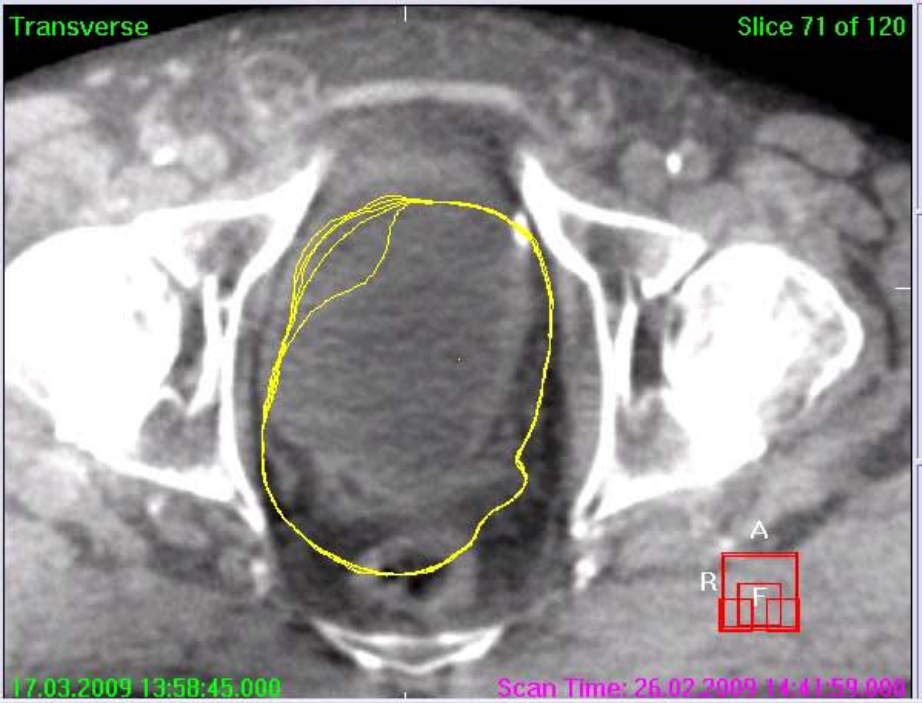
Slice Averaging

none

Display Mode

Localization on

GoTo ..



Reference Preset

Cor Ref Point ..

Scan

Alignment Clipbox

Structures ..

Alignment

Automatic

Bone

Reset

Convert To Correction

Position Error

Translation (cm)

X	0.00
Y	0.00
Z	0.00

Rotation (dg)

X	0.0
Y	0.0
Z	0.0

Table Correction

(cm)

Lateral -

Longitudinal -

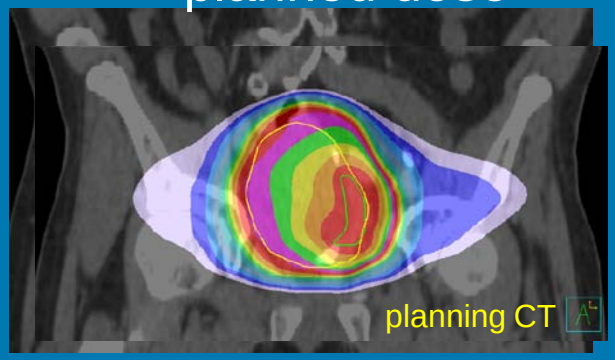
Vertical -

Dismiss

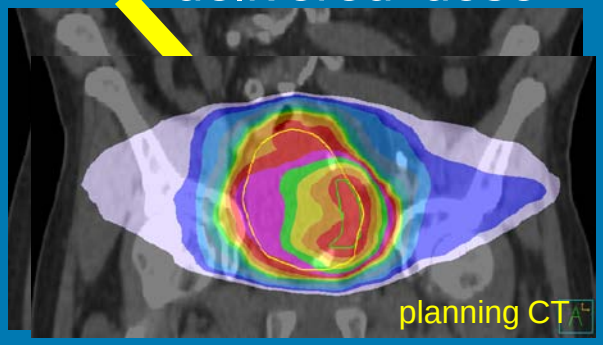
Accept

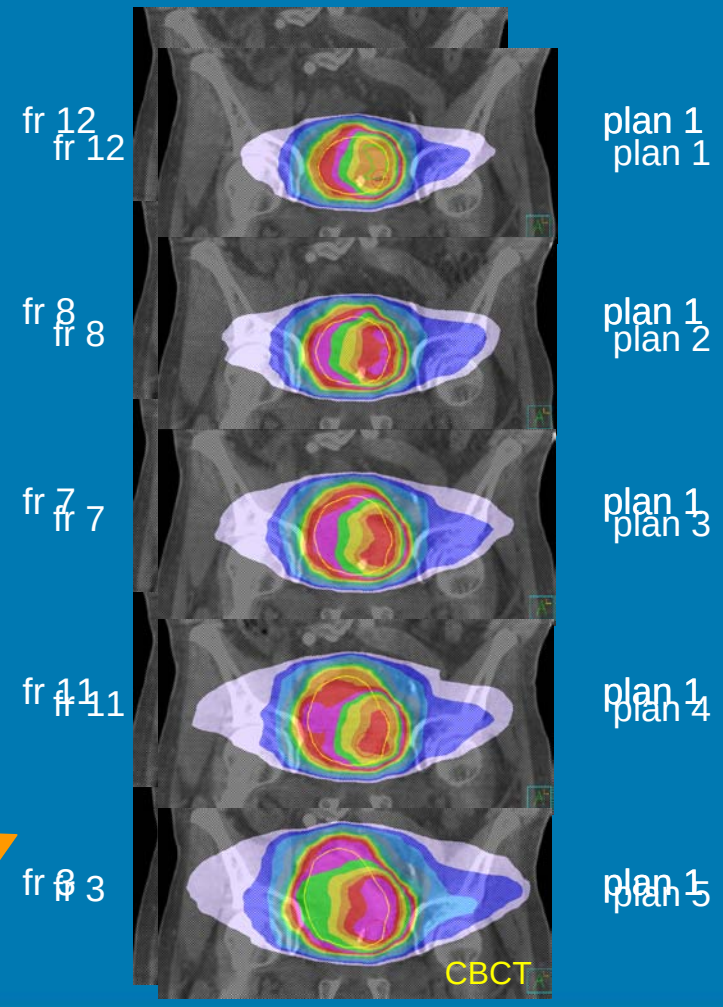
Dose warping of SIB-IMRT provided by Pinnacle 8.1x

planned dose



'delivered' dose





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Conclusions

- Library planning delivery rarely implemented in the clinical routine
  - but ….
- Online plan adaptation helps us to steer the right dose to the right tissues in highly deforming target volumes

Acknowledgements:
Luiza Bondar from the Erasmus Medical Center Rotterdam
Anne Vestergaard from the Århus Universitetshospital
Simon van Kranen and Jasper Nijkamp from the Netherlands Cancer Institute

Probabilistic planning

Marcel van Herk
Includes slides by Michael Sharpe

Institute of Cancer Sciences
Manchester University
The Christie NHS Trust

(Formerly at the Netherlands Cancer Institute)

Simplified PTV margin recipe for dose - probability

To cover the CTV for 90% of the patients with the 95% isodose (analytical solution) :

PTV margin = 2.5 Σ + 0.7 σ

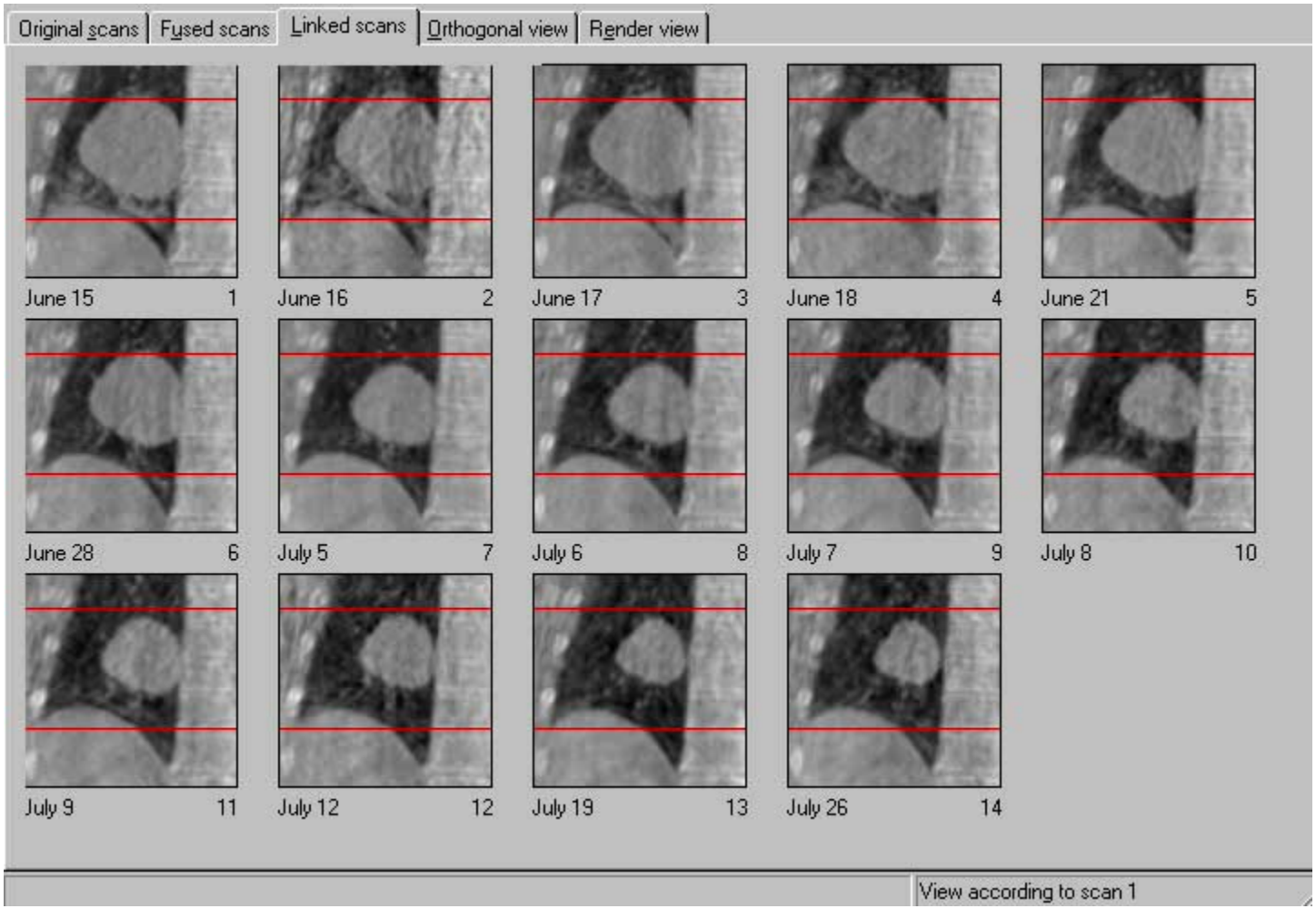
Σ = quadratic sum of SD of all preparation (systematic) errors
σ = quadratic sum of SD of all execution (random) errors

(van Herk et al, IJROBP 47: 1121-1135, 2000)

*For a big CTV with smooth shape, penumbra 5 mm

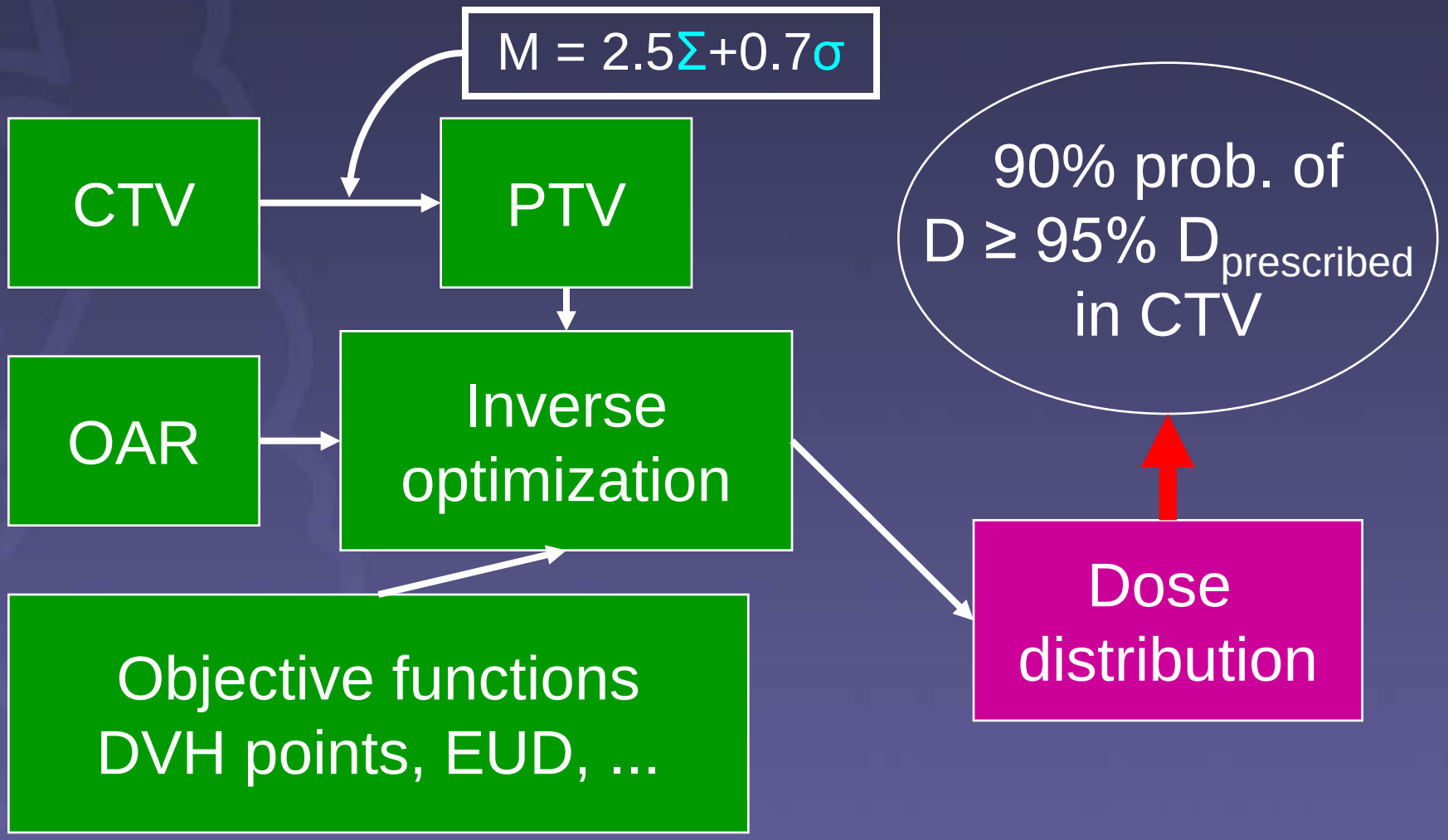
Variability in Repeated 4D CBCT

Day 1 →

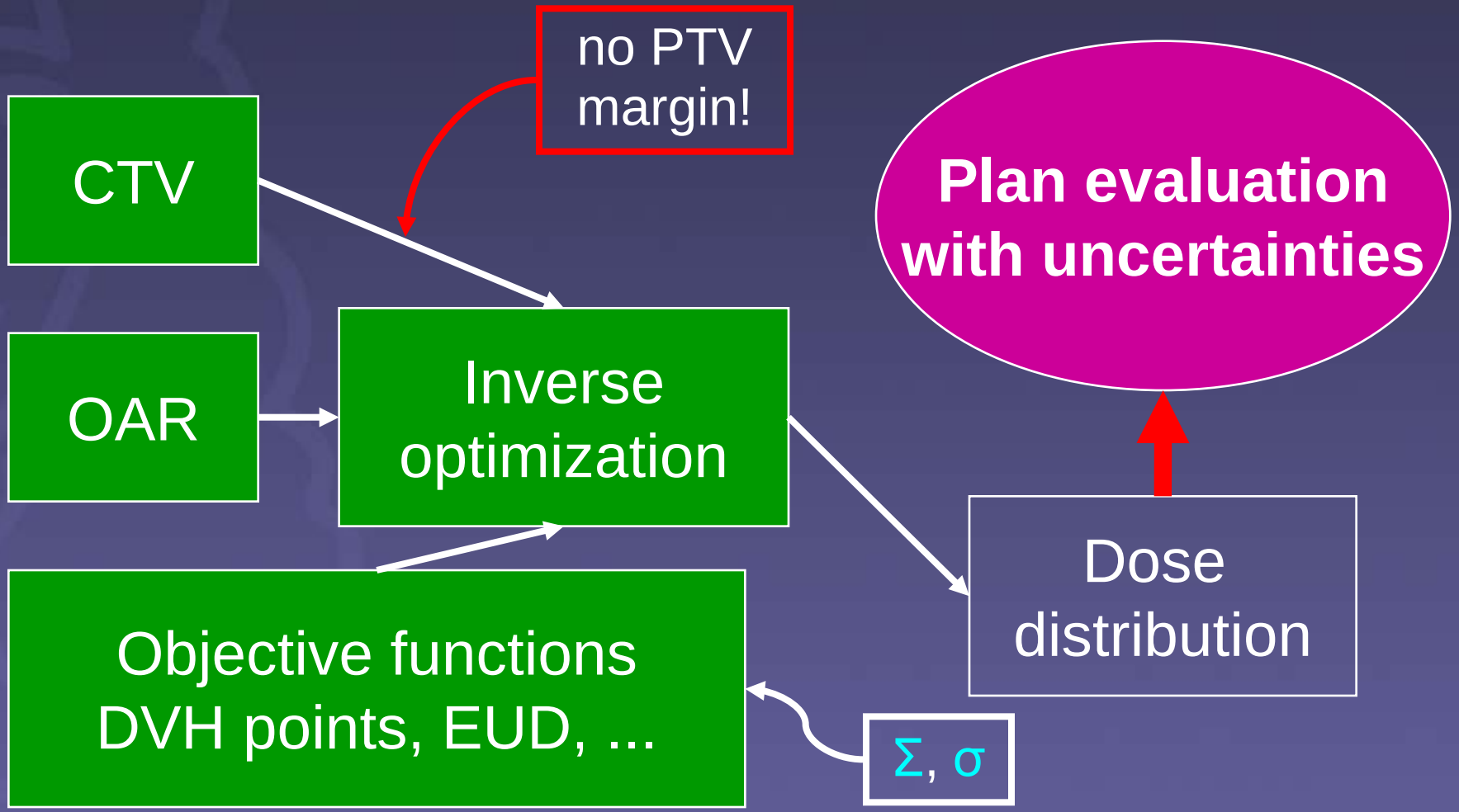


Day 11

Uncertainty management: Conventional IMRT planning with margin



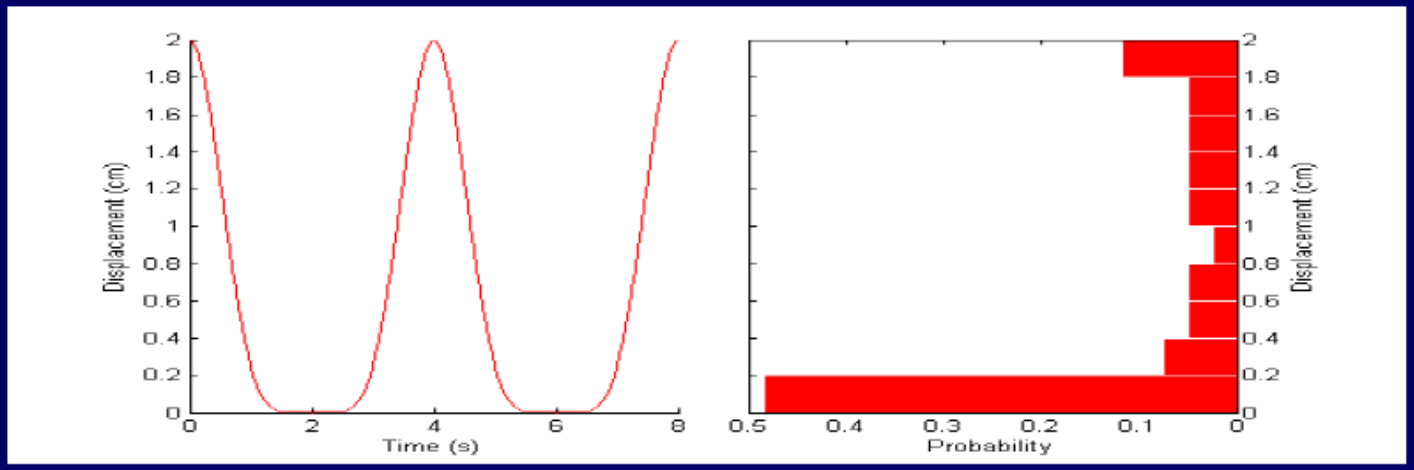
Uncertainty management: Probabilistic IMRT planning without margin



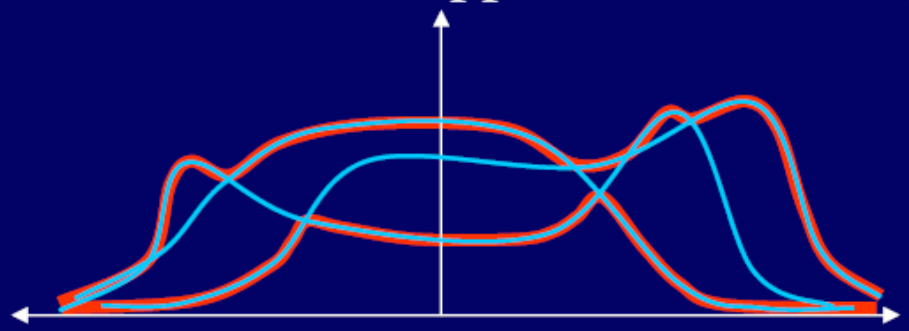
Random errors & breathing

Statistical Model of Breathing Motion

- We can get a pmf from sinusoidal data by "horizontal binning"



- We can get "error bars" as upper/lower envelopes of many pmfs



Phys. Med. Biol. **51** (2006) 2567–2583

Variability in Motion Day-to-Day Revisted

Planned (nominal) vs delivered (realized)

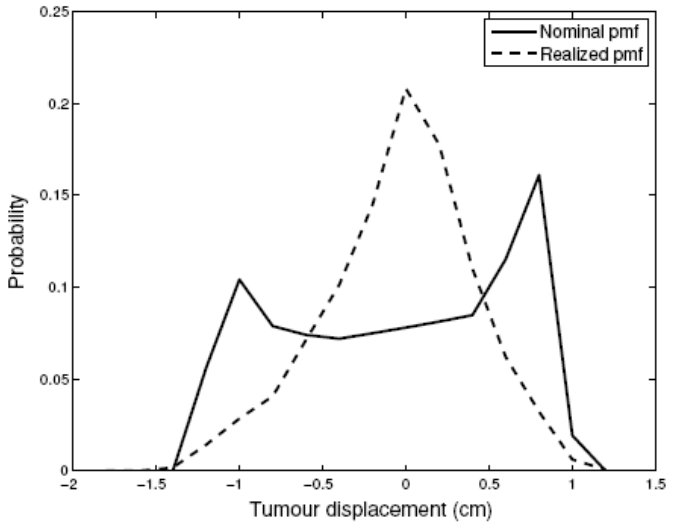


Figure 5. The pmfs used in the nominal, margin and robust formulation illustrations.

Robust model

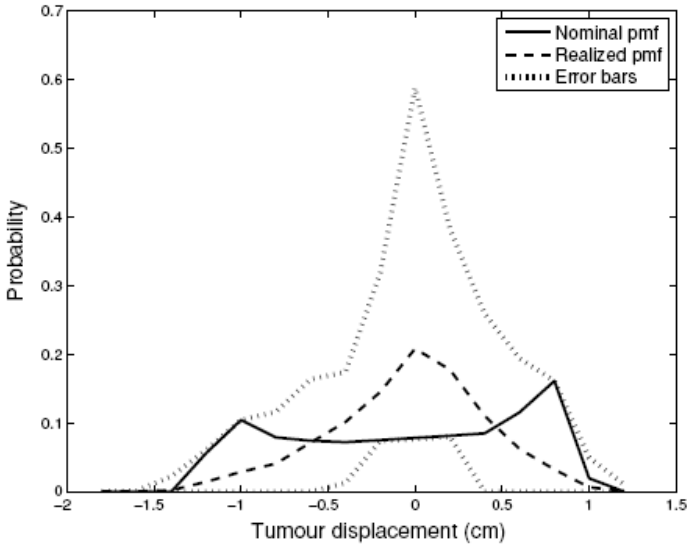
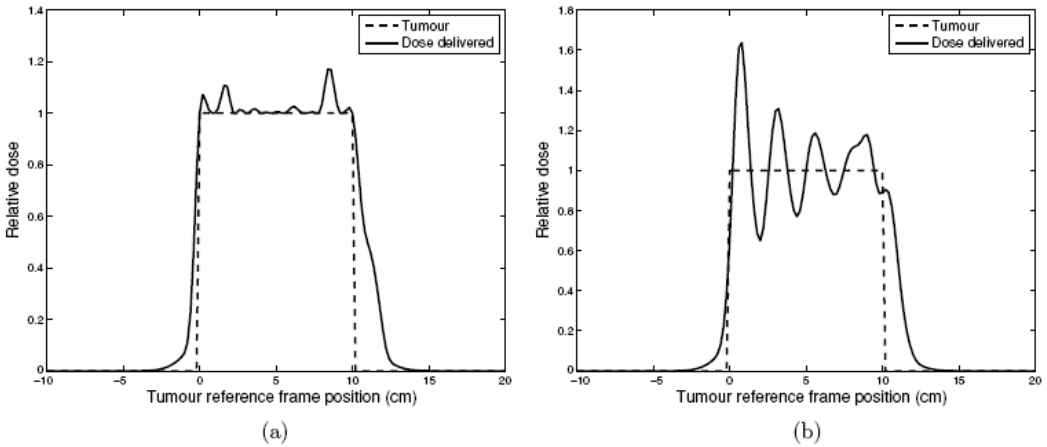


Figure 8. The pmfs and error bars used in the robust formulation illustrati

Phys. Med. Biol. **51** (2006) 2567–2583

Variability in Motion Day-to-Day Revisited

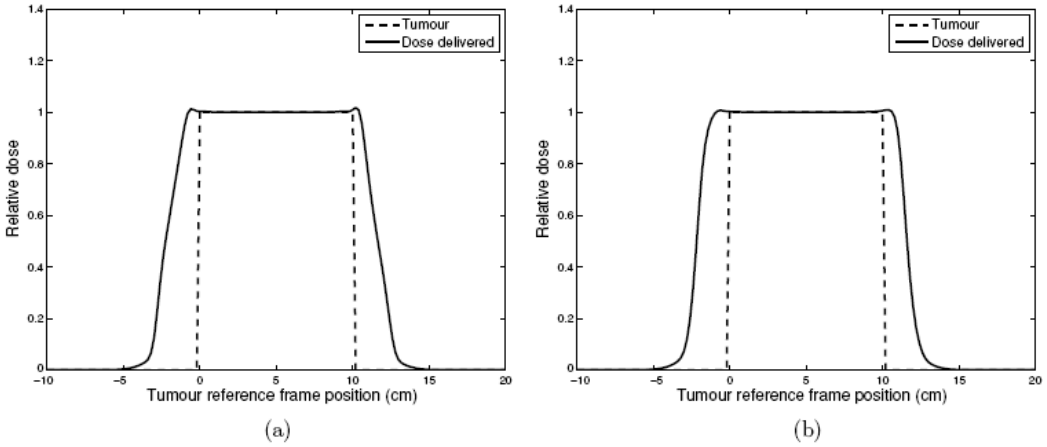
Motion modeling: Nominal plan



Motion modeling: delivered

Figure 6. Dose distribution of nominal solution using the pmfs from figure 5. (a) Nominal pmf. (b) Realized pmf.

Using Margins: Nominal plan

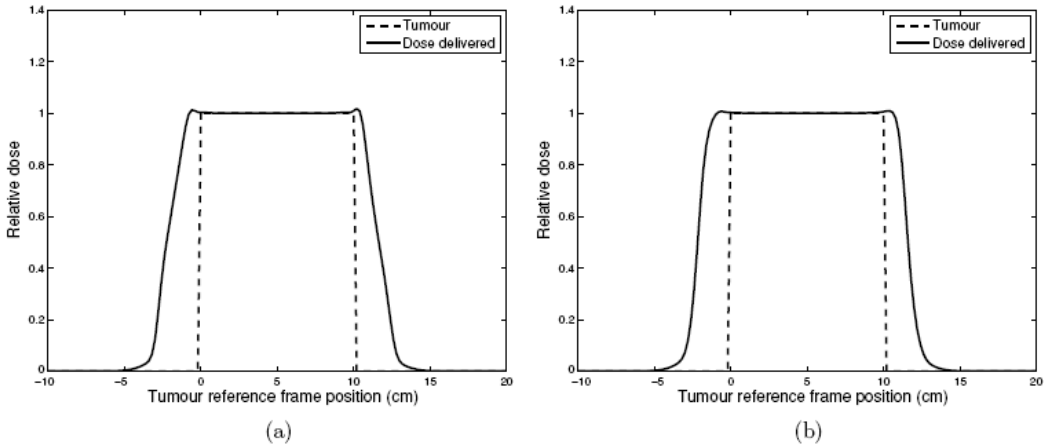


Using Margins: delivered

Figure 7. Dose distribution of margin solution using the pmfs from figure 5. (a) Nominal pmf. (b) Realized pmf.

Variability in Motion Day-to-Day Revisited

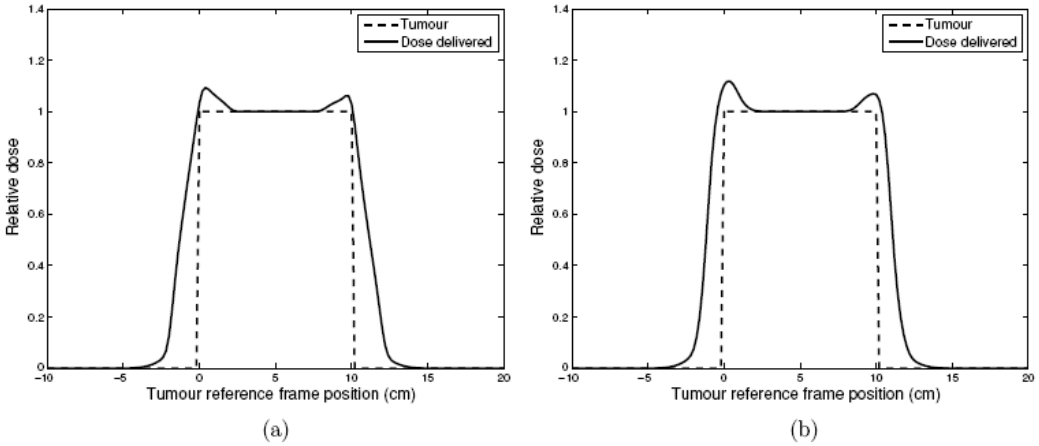
Using Margins: Nominal plan



Using Margins: delivered

Figure 7. Dose distribution of margin solution using the pmfs from figure 5. (a) Nominal pmf. (b) Realized pmf.

Motion modeling: Nominal plan



Robust modeling: delivered

Figure 9. Dose distribution of robust solution using the pmfs and error bars from figure 8. (a) Nominal pmf. (b) Realized pmf.

Clinical Lung Case

- Tumour in left lung
- Critical structures: left lung, esophagus, spinal cord, heart
- Approx. 100,000 voxels, 1600 beamlets
- Minimize dose to healthy tissue
- Lower bound and upper bound on dose to tumour

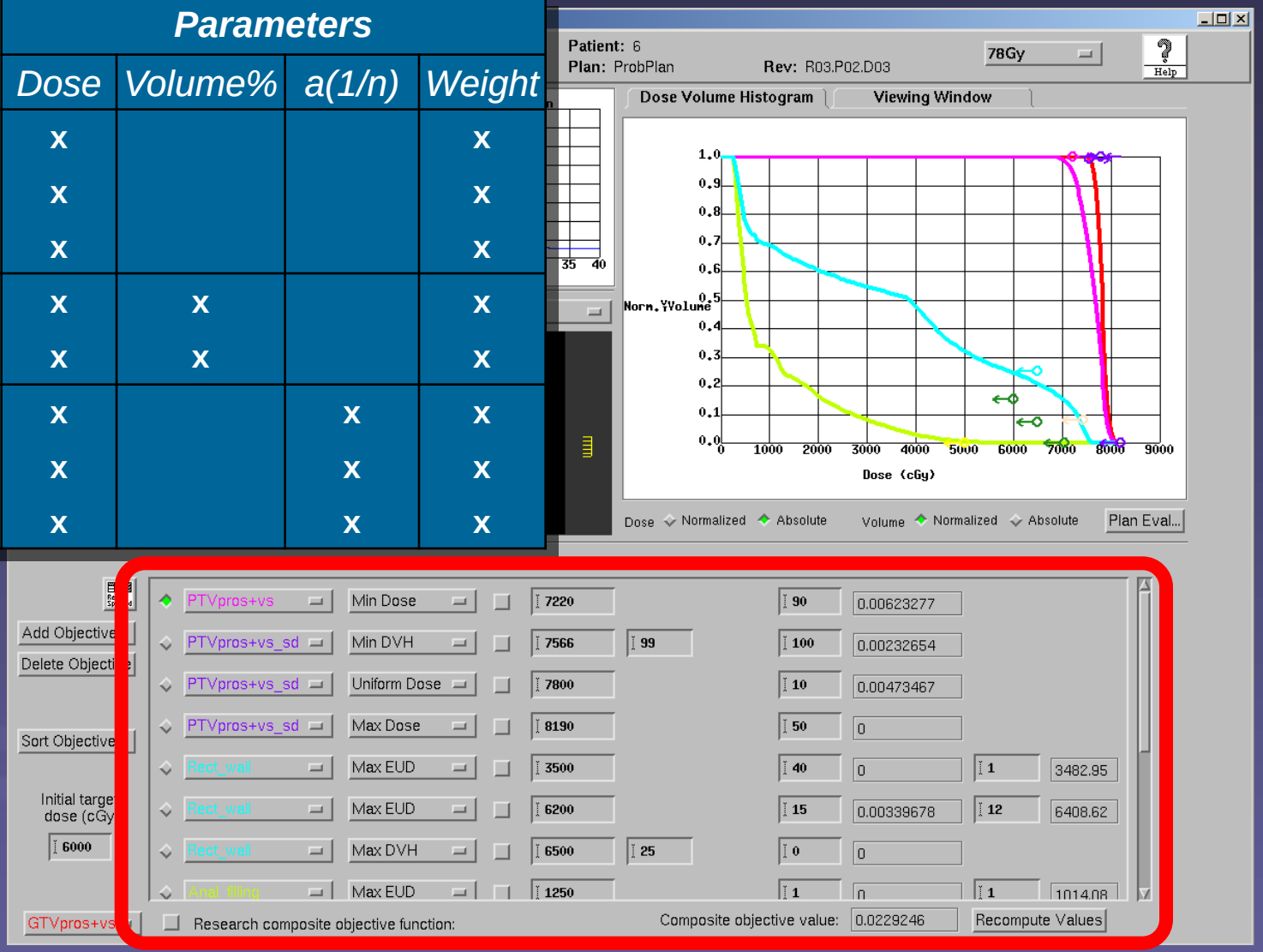
- Simulate delivery of optimal solution with 78 “realized pdfs”

Full probabilistic planning must include systematic errors

Bohoslavsky et al. PMB 2013

Regular planning objective functions

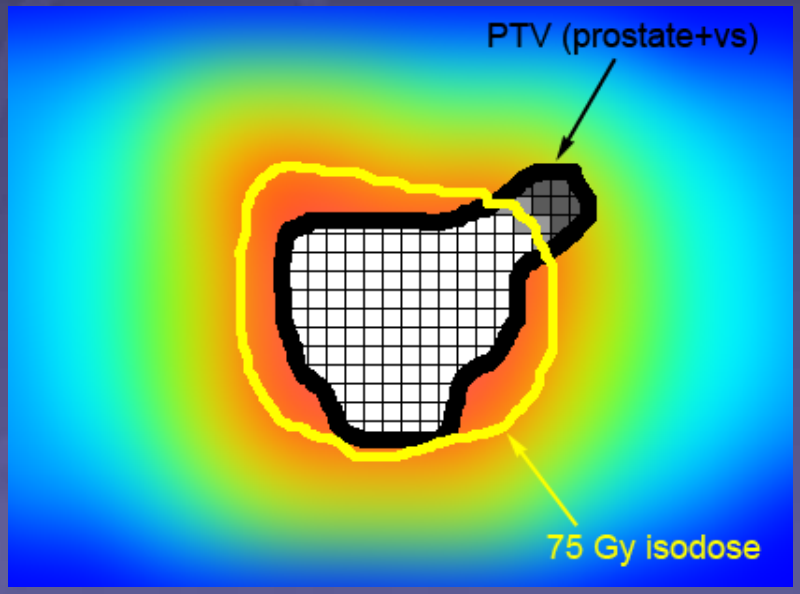
	Parameters			
	Dose	*Volume%*	*a(1/n)*	*Weight*
Minimum Dose	x			x
Maximum Dose	x			x
Uniform Dose	x			x
Minimum DVH	x	x		x
Maximum DVH	x	x		x
Target EUD	x		x	x
Minimum EUD	x		x	x
Maximum EUD	x		x	x

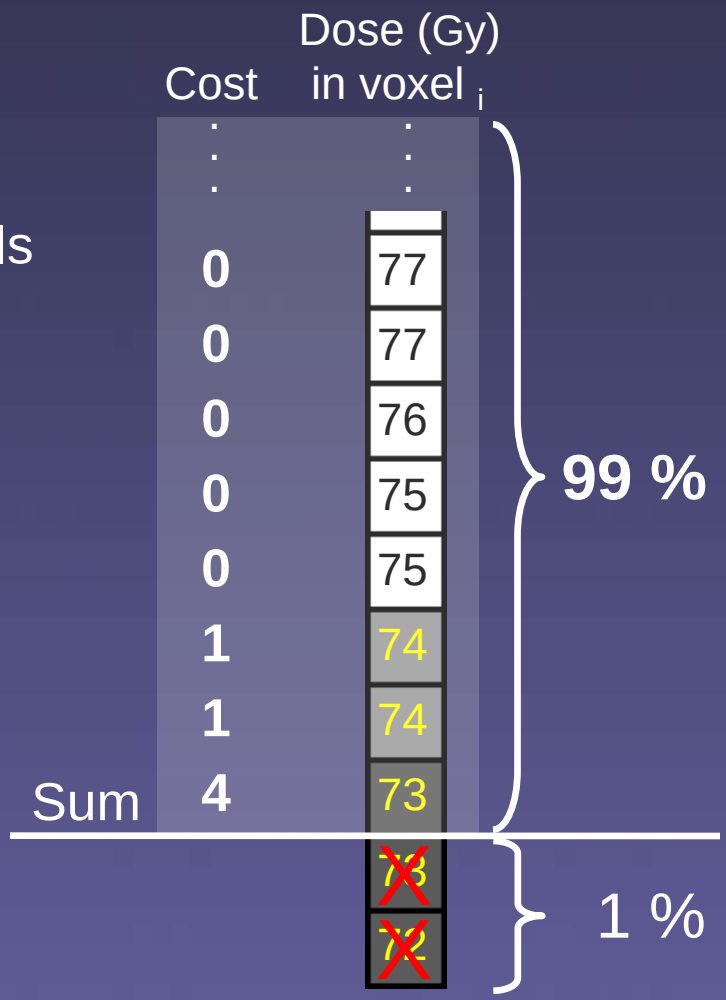


How DVH cost functions are calculated

PTV: MinDVH d=75Gy vol=99%

1. Sort voxels by dose
2. MinDVH: select highest 99% of voxels
3. Compute and add costs





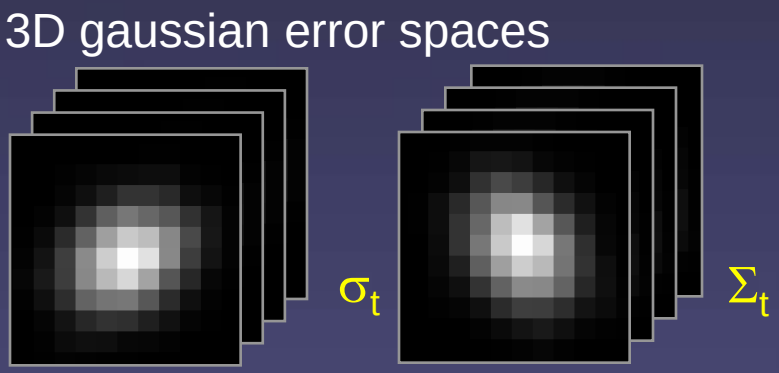
Probabilistic form of exactly the same cost functions

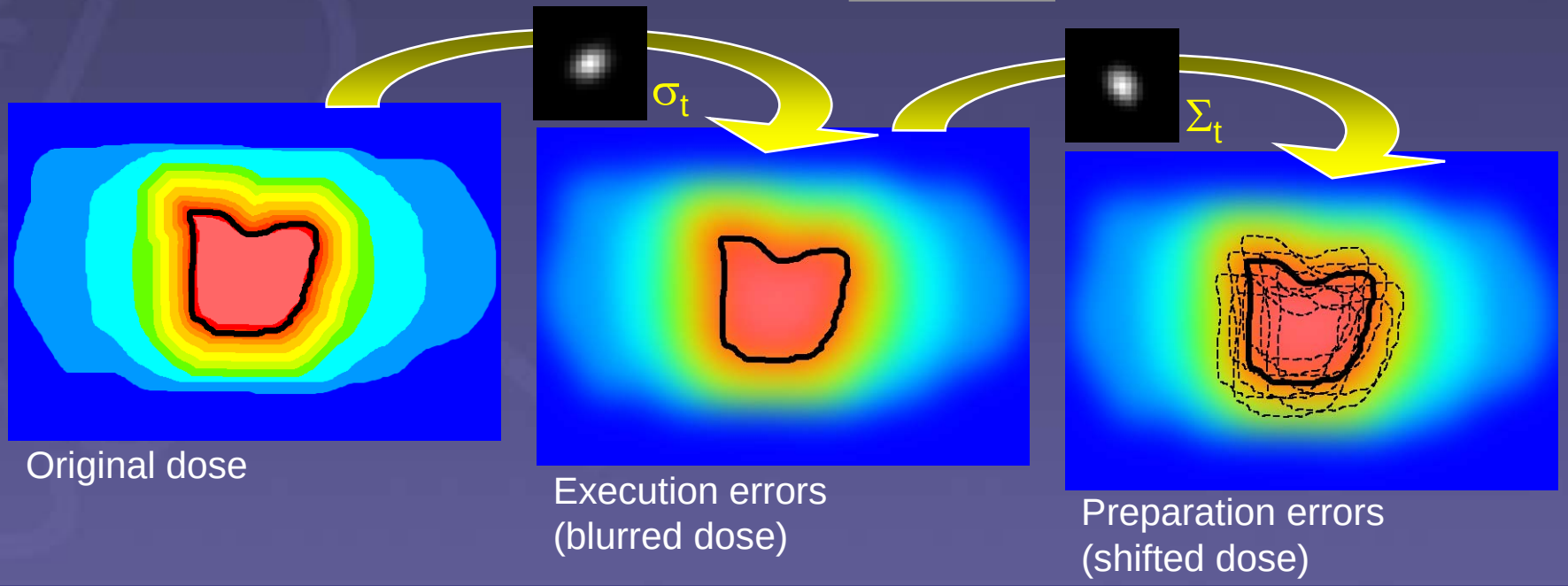
Pinnacle 8.1v research version

Inclusion of uncertainties in plan optimization

Translation errors

- Execution (random) errors → σ_t
- Preparation (systematic) errors → Σ_t





Robust vs probabilistic optimization

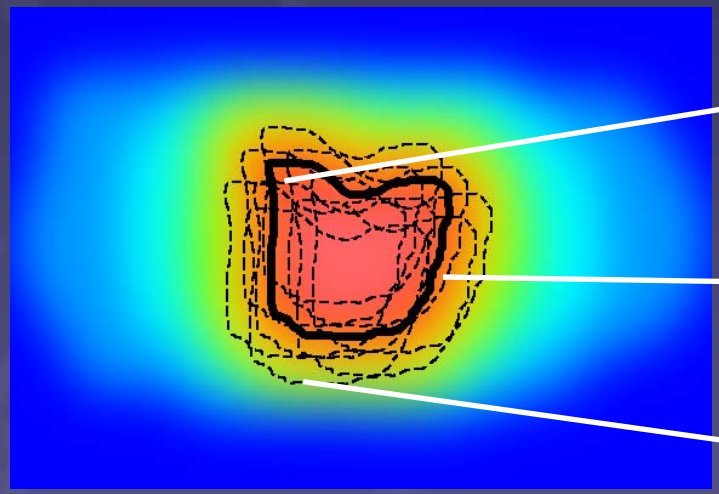
- Robust:
  - Typical 8 error scenarios
  - Weighted average of cost functions
  - Do not separate random and systematic errors

Commercial →

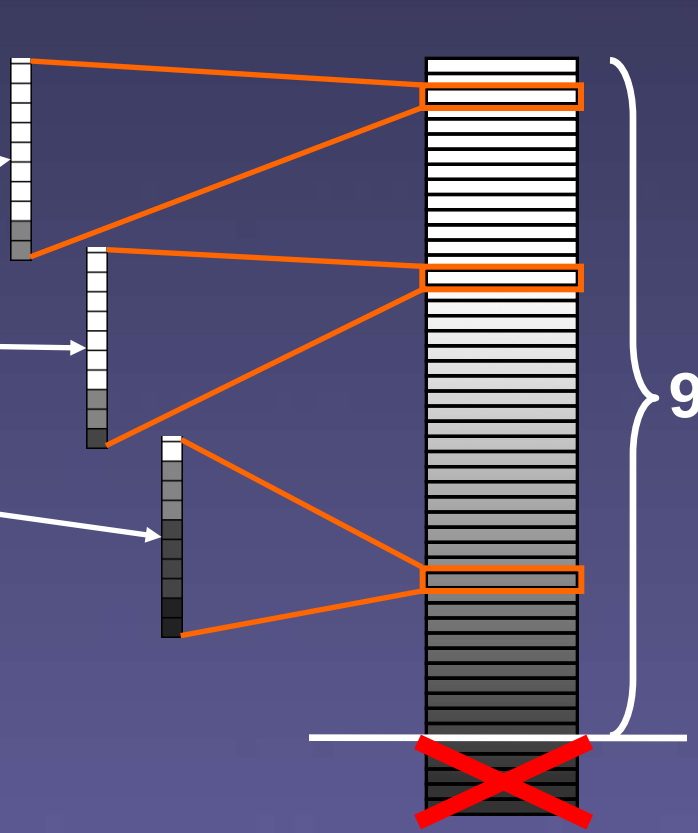
- Probabilistic:
  - Hundreds of error scenarios
  - Optimize on probability of meeting constraint
  - Include random and systematic errors

Confidence level of objective functions

1. Systematic error simulations are sorted by cost
2. The best (lowest cost) cases are selected



e.g.: MinDVH 75Gy for
90% of the population



Materials and Methods

Six prostate cases were replanned using probabilistic objective functions aiming for identical target coverage

All plans were evaluated using independent geometrical uncertainties simulation software (UNCERT)

- 10.000 patients x 39 fractions simulated per plan

Uncertainty values (1SD): setup errors + organ motion

Translation errors (mm)	LR	AP	SI
Preparation (systematic) Σ_k	2.6	3.5	2.4
Execution (random) σ_k	2.0	3.0	2.4

prostate
and
rectum

Objectives for treatment plans

Clinical plan objectives

ROI	Objective	Dose (cGy)	Vol (%)	a (1/n)	Weight
PTVpros+vs	Min Dose	7220			90
PTVpros+vs_sd	M				
PTVpros+vs_sd	U				
PTVpros+vs_sd	M				
Rect_wall	M				
Rect_wall	M				
Rect_wall	M				
Anal_filling	M				
PTV72min78	M				
PTVring	M				
PTVring	M				
PTVring	M				
Hip_R	M				
Hip_L	M				

Probabilistic planning objectives

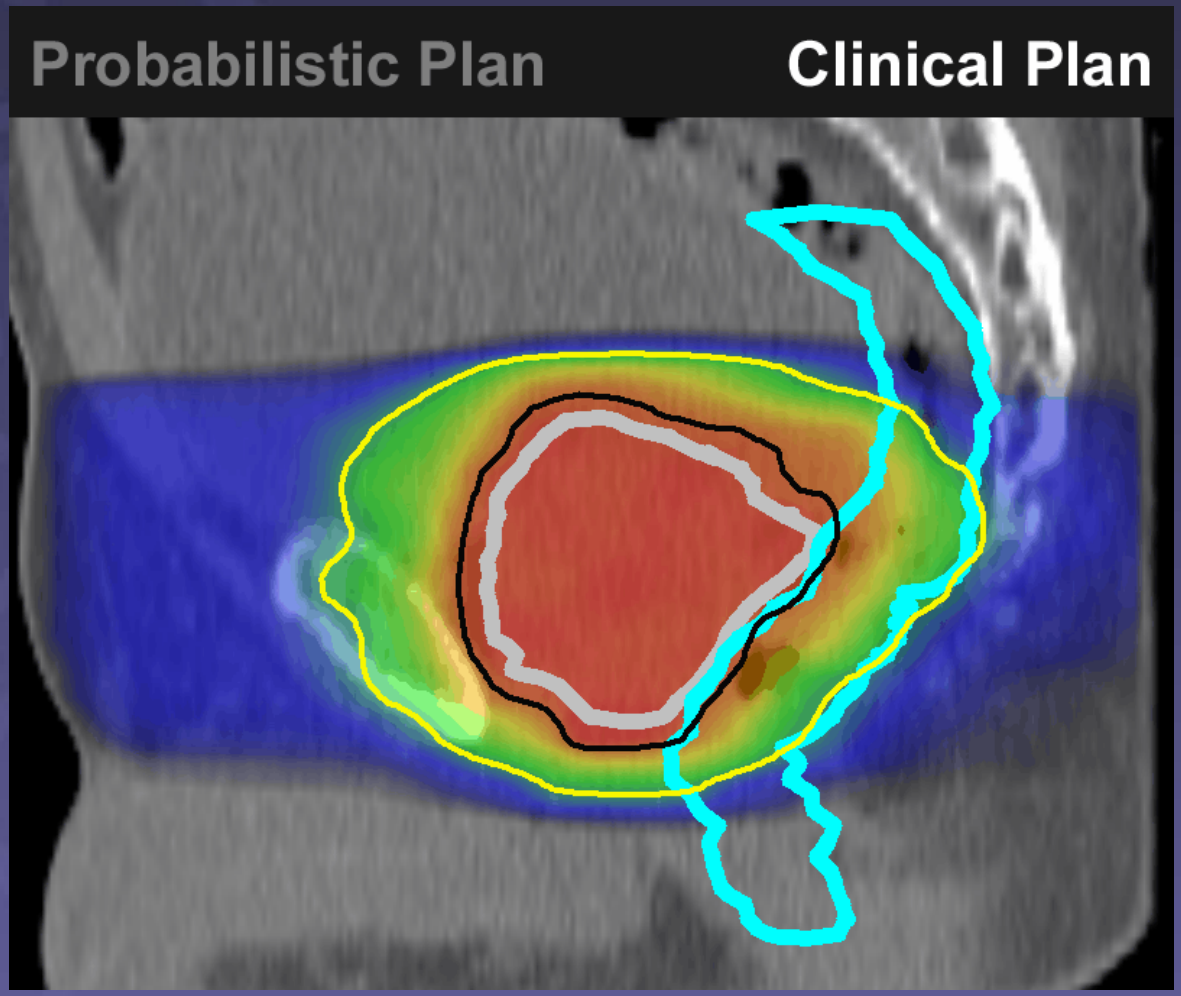
ROI	Objective	Dose (cGy)	Vol (%)	a (1/n)	Weight	Pop (%)	Kernel
GTVpros+vs	Min EUD	7820		1	100	92	sig
						92	sig
						92	sig
						--- (100)	env
						--- (100)	env
						92	sig
						92	sig
						92	sig
						--- (100)	---

GTV instead of PTV

No PTV boost

Less objectives

Effect of probabilistic planning



GTV

Rectum

95% isodose (74.1 Gy)

50% isodose (39.0 Gy)

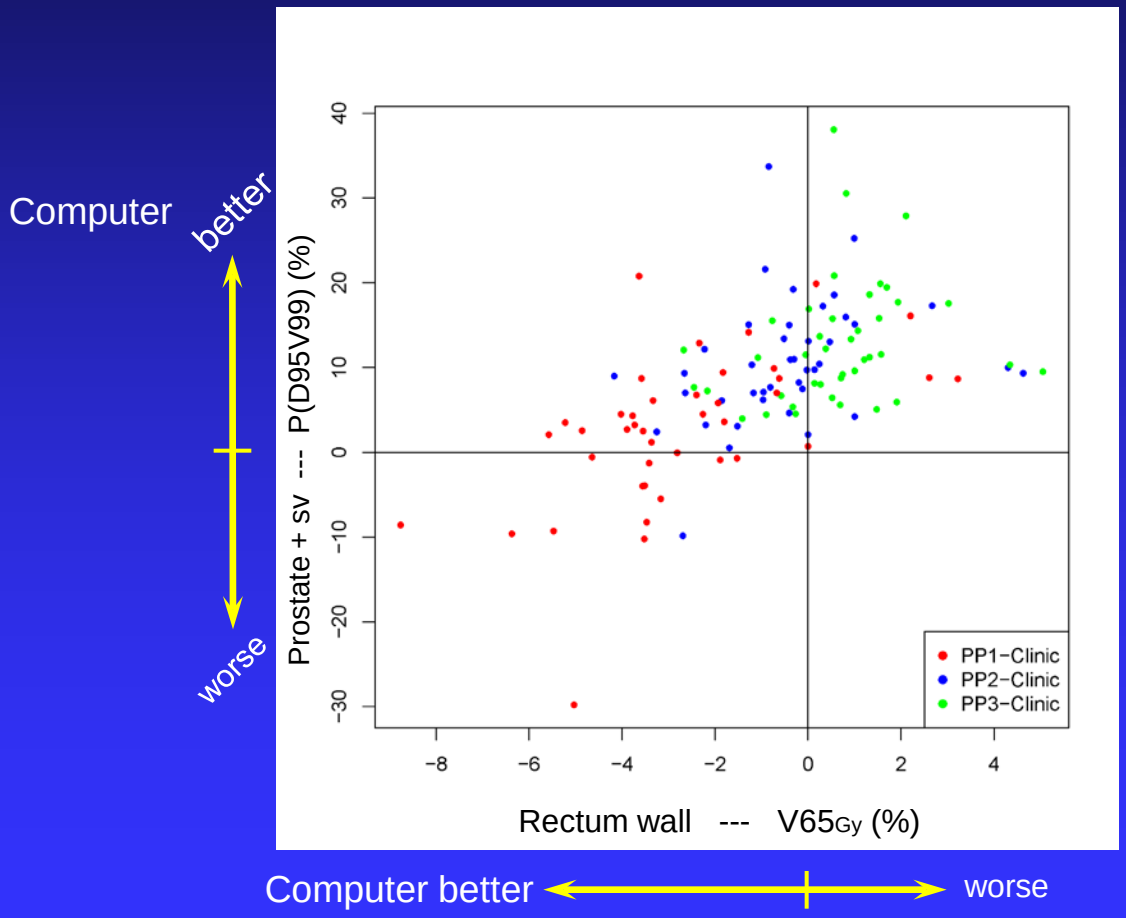
Prescribed dose to the target: 78 Gy

Results

		Plan Averages		Δ(Prob. , Clinic)
		Prob.	Clinic	Mean (1SD)
GTV pros+vs	Dmean (Gy)	78.1	77.3	0.8 (0.2)
	V95 (%)	95.0	93.8	1.2 (1.1)
Rectum wall	Dmean (Gy)	34.6	37.8	– 3.2 (1.5)
	V70.0 (%)	14.4	18.6	– 4.2 (0.7)
	$_{g}$EUD (Gy) (n=0.11)	62.3	63.5	– 1.2 (0.2)

All dose – volume parameters evaluated at a 90% confidence level

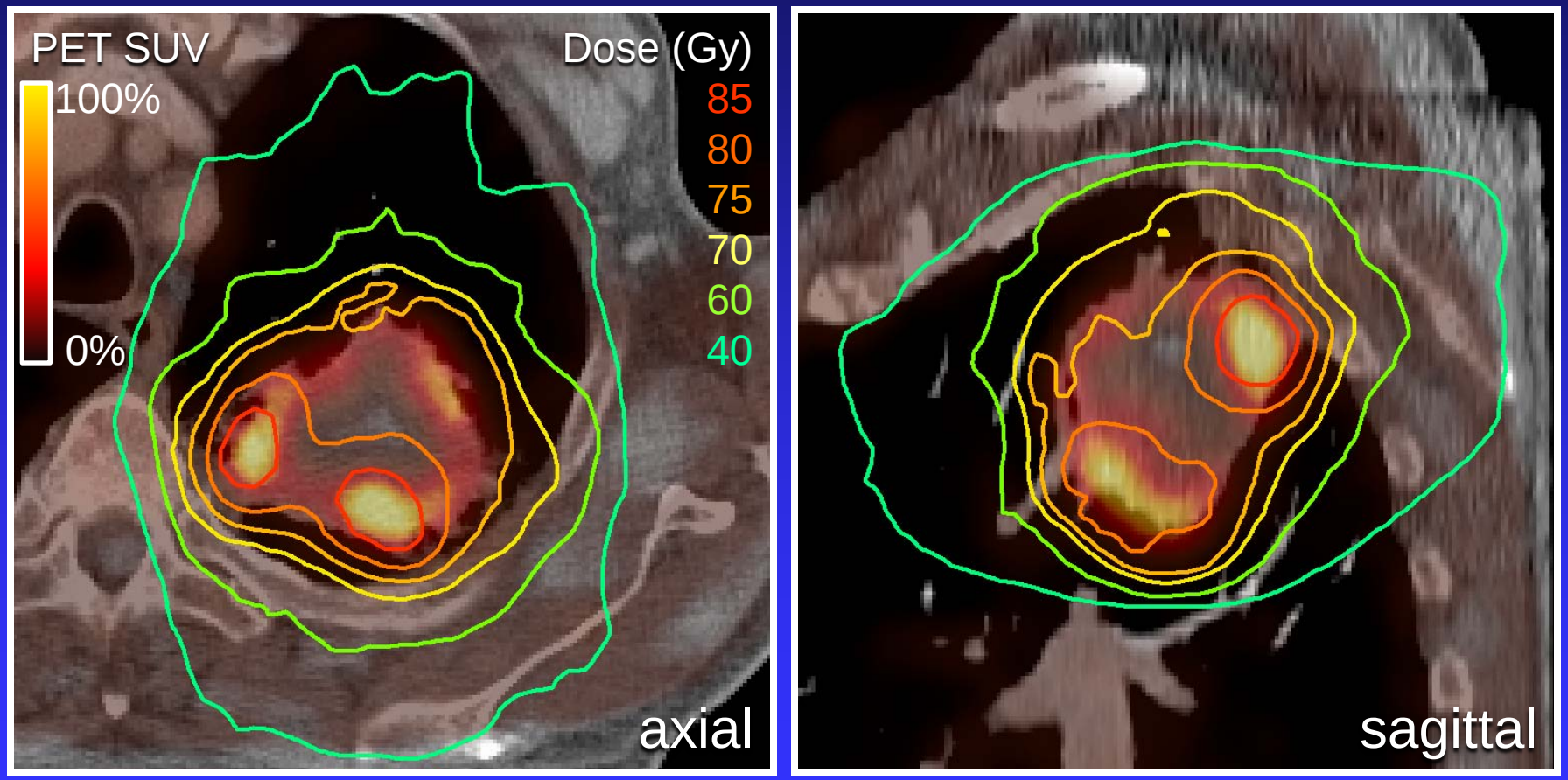
Results: automated probabilistic planning beats manual plan tweaking every time



Computer – manual

- Toxicity reducing
- Balanced
- Coverage improving

Probabilistic dose painting `by numbers'



Conclusions

Margin-less treatment planning is feasible

- Equal or higher target coverage
- Equal or lower dosage to OARs
- Small increase in optimization time
- Reduced number of objective functions
- No boost volume with smaller margin required

Potentially solves the buildup problem if you evaluate multiple anatomies, dose is never evaluated outside the tumor

Open issues: Vendors, implement it!

Dose painted planning

Gert Meijer

ESTRO
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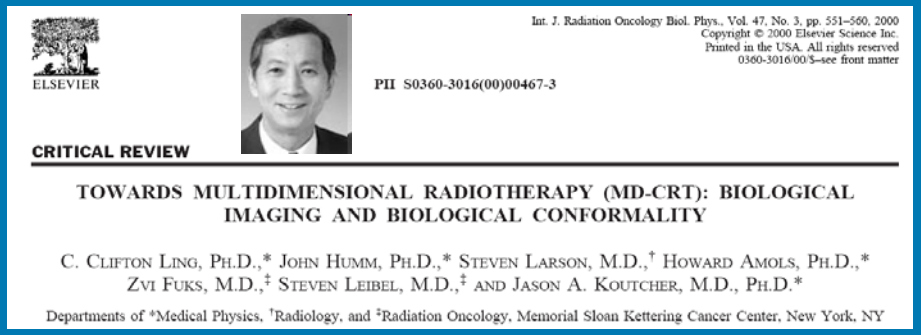
Wilfried De Neve (2008):

The vision is clear

- Tumors are heterogeneous
- CTV is more heterogeneous
- PTV is even more heterogeneous
- Homogeneous PTV dose distributions
  - Planning goal
  - Dogmatic
  - Stupid?



ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 47, No. 3, pp. 551–560, 2000

0360-3016/00/$–see front matter

PII S0360-3016(00)00467-3

CRITICAL REVIEW

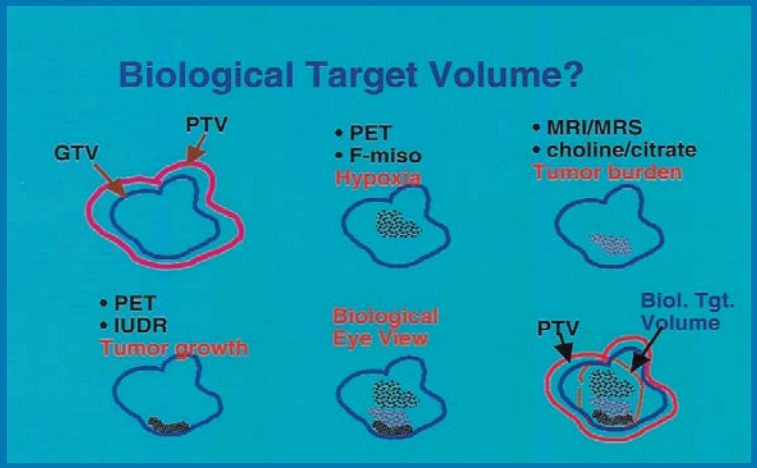
TOWARDS MULTIDIMENSIONAL RADIOTHERAPY (MD-CRT): BIOLOGICAL IMAGING AND BIOLOGICAL CONFORMALITY

C. Clifton Ling, Ph.D.,* John Humm, Ph.D.,* Steven Larson, M.D.,† Howard Amols, Ph.D.,*
Zvi Fuks, M.D.,‡ Steven Leibel, M.D.,‡ and Jason A. Koutcher, M.D., Ph.D.*

Departments of *Medical Physics, †Radiology, and ‡Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY

An engineering approach to cancer treatment?

- Radiation therapy was developed in the heyday of "modern" physics – and, arguably, the greatest progress in the last century has been in physics and technology
- Most of the disease concepts applied in radiotherapy today date back to the 1920's
- Characteristically, we treat VOLUMES rather than DISEASE PROCESSES



Søren Bentzen (ESTRO 2010)

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Dose painting is the prescription of a non-uniform radiation dose distribution to the target volume based on functional or molecular images shown to indicate the local risk of relapse

Hypothesis 1:
Local recurrence is related to resistant areas not eradicated by currently precribed and delivered uniform doses

Hypothesis 2:
Non-invasive functional and molecular imaging allows mapping the target in terms of radioresistance

biological caveats

what parameters?

sensitivity/ specificity?

intensity to dose?

3D fractionation?

4D heterogeneity?

physical caveats

image resolution?

delivery resolution?

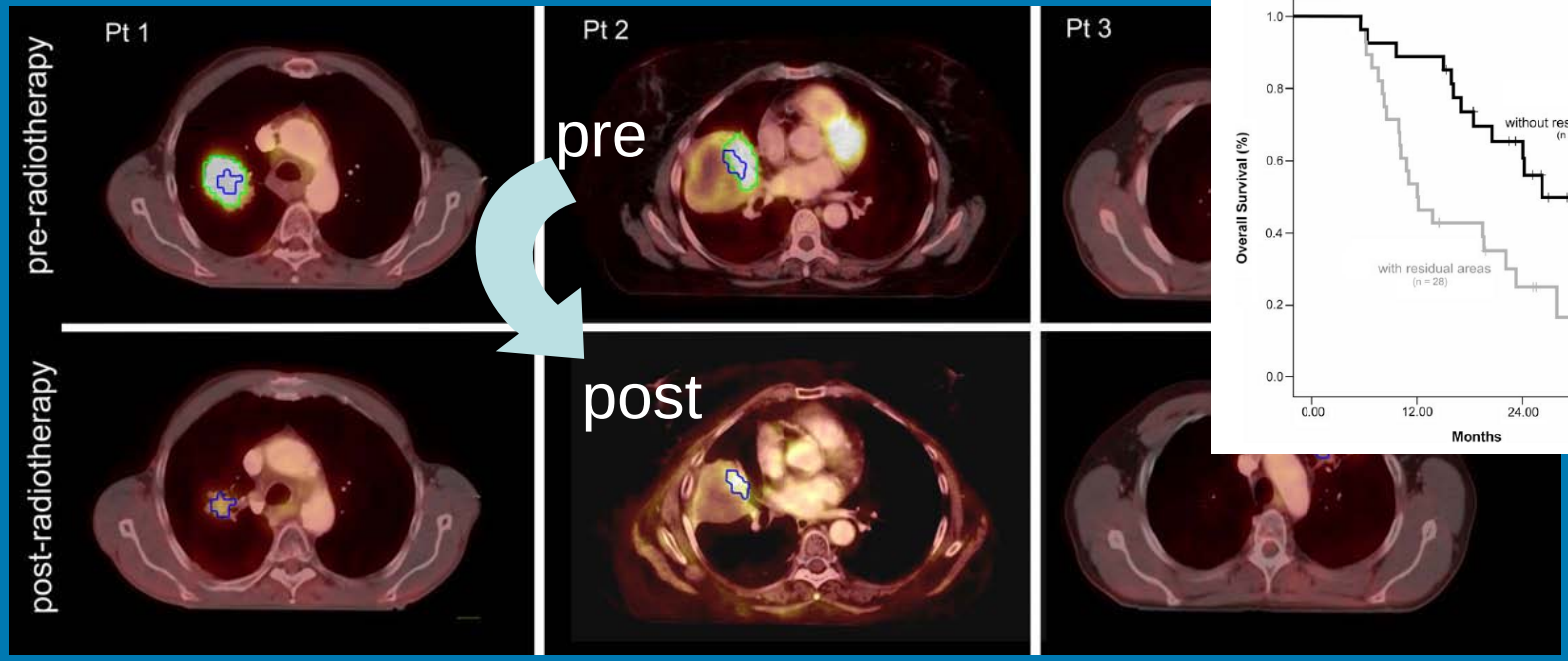
planning?

plan evaluation?

tumour movements?

image guidance?

phenomenological relationships do matter !!



Aerts *et al.* R&O 2009

confirmed by the Dresden group and PMH

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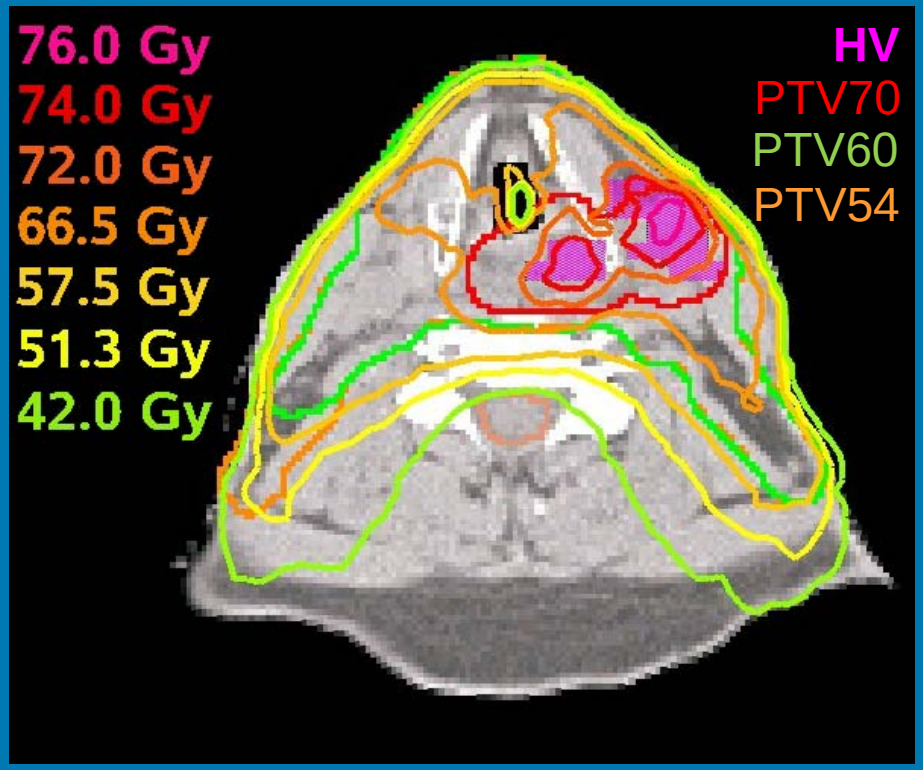
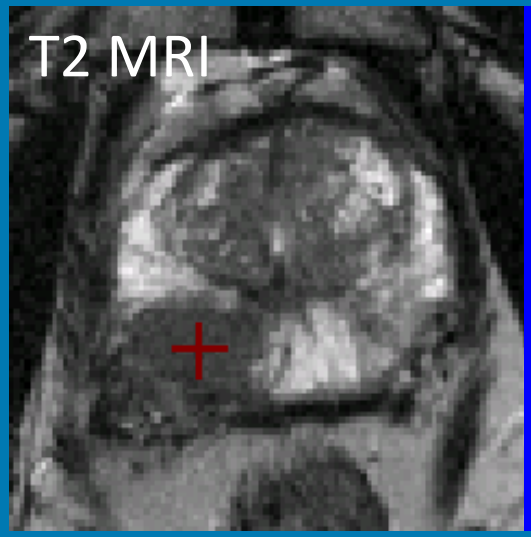
Hypoxia Dose Painting Trail in Tübingen, Germany

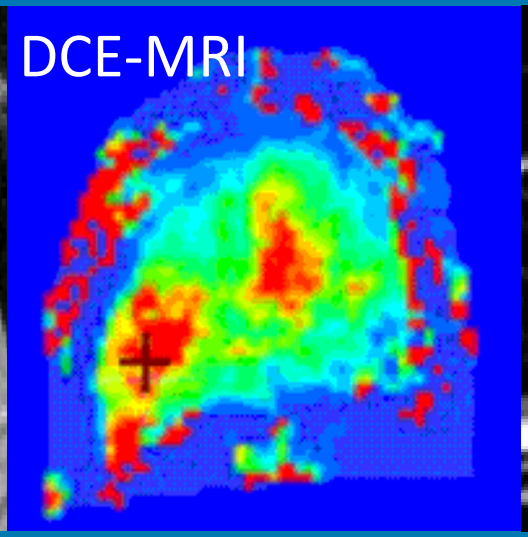
- Definition of hypoxic volume (HV) according to [^{18}F]-FMISO PET/CT
- Dose escalation of 10% (77Gy) in the HV inside the PTV70 in the experimental treatment arm
- Isotoxic approach!
- So far n=26 patients included.

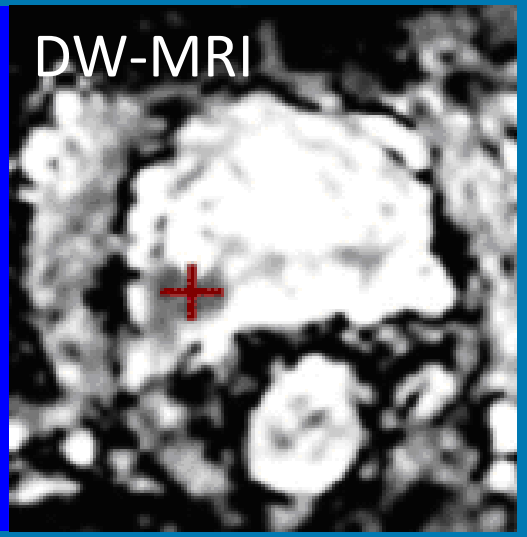


IMRT plan for patient #3 in the HDP trial.

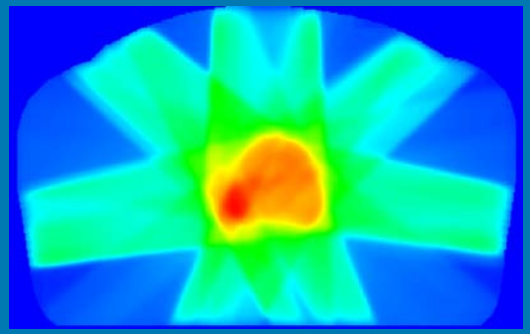
the FLAME trial: Focal Lesion Ablative Microboost







FLAME



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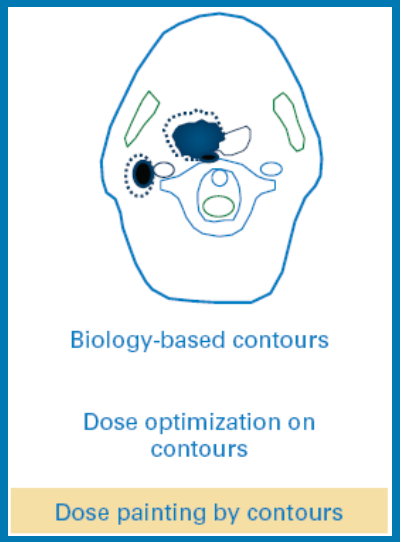
Commercial planning systems do not support dose painting

- objectives based on DVH parameters
  - max dose
  - min dose
  - max DVH
  - EUD
  - NTCP
  - TCP

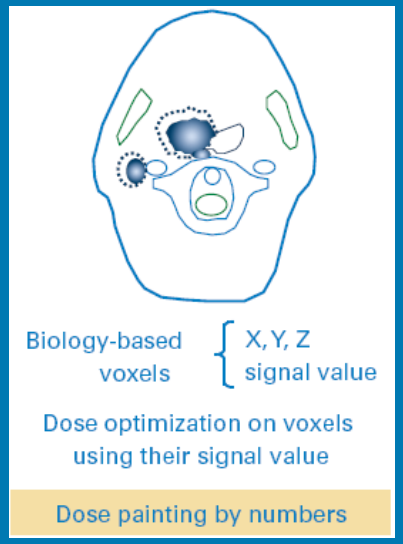
How?

dose painting by contours



Xing (PMB 2002), Chao (IJROBP 2001)
Madani (IJROBP 2007), De Ruysscher (R&O 2006)

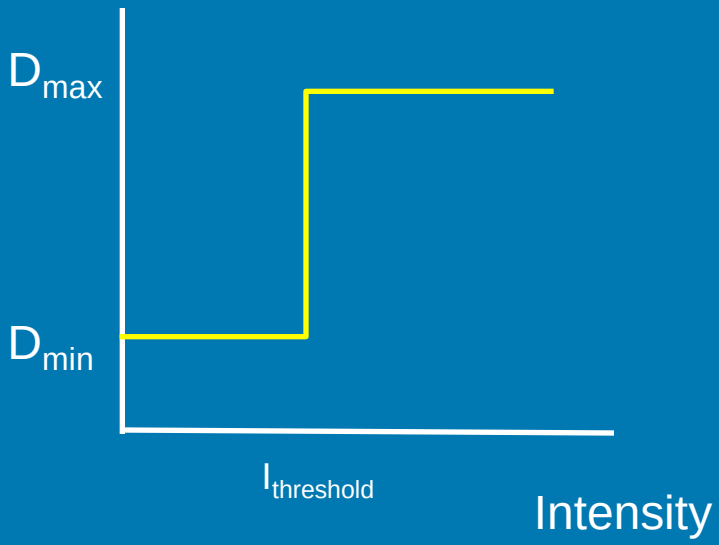
dose painting by numbers



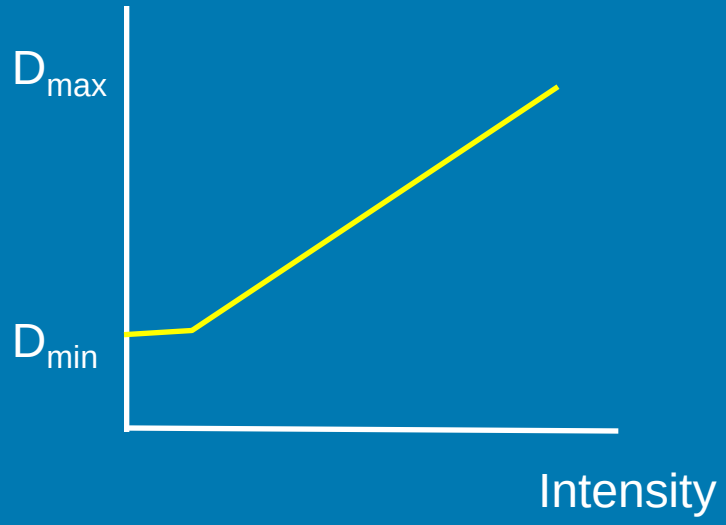
Bentzen (Lancet Oncol 2005), Thorwarth (IJROBP 2007)
Vanderstraeten (PMB 2006)

How?

dose painting by contours



dose painting by numbers



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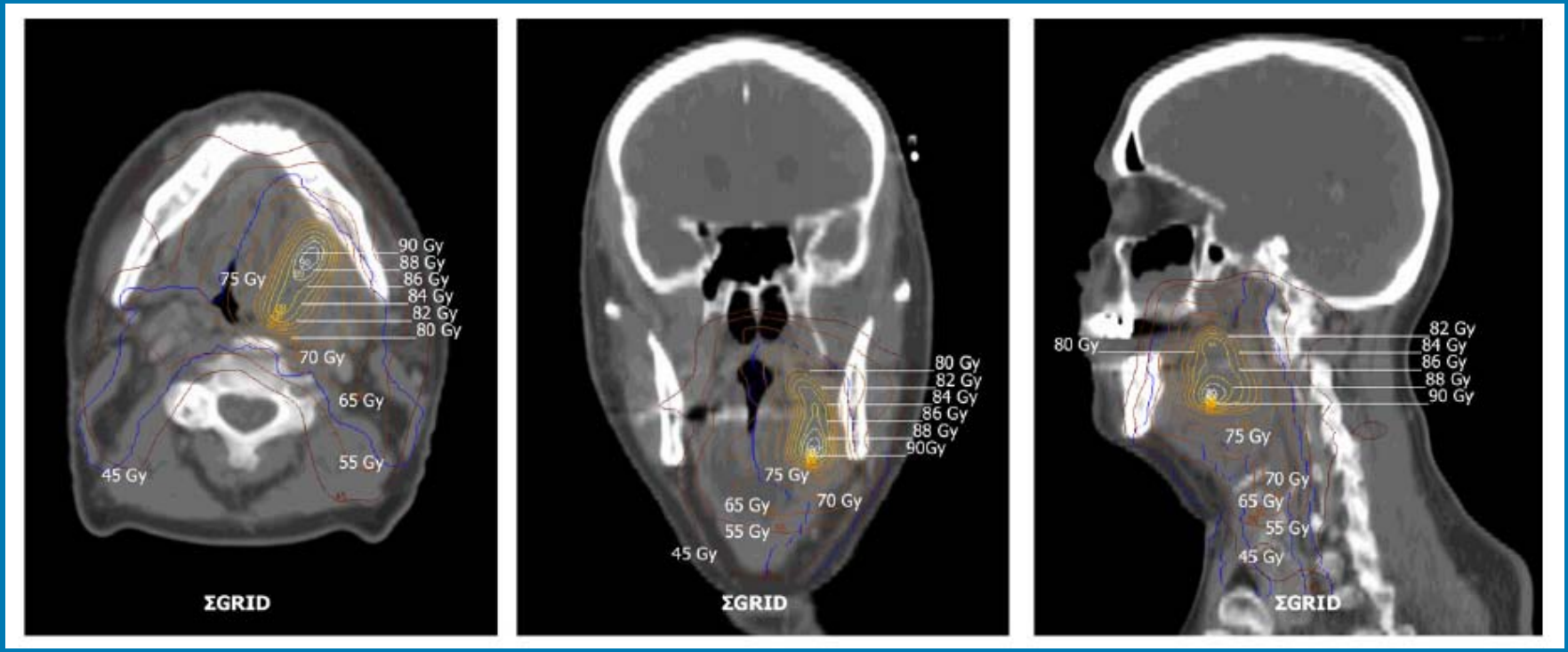


Frederic Duprez *et al.* (IJROBP 2010)

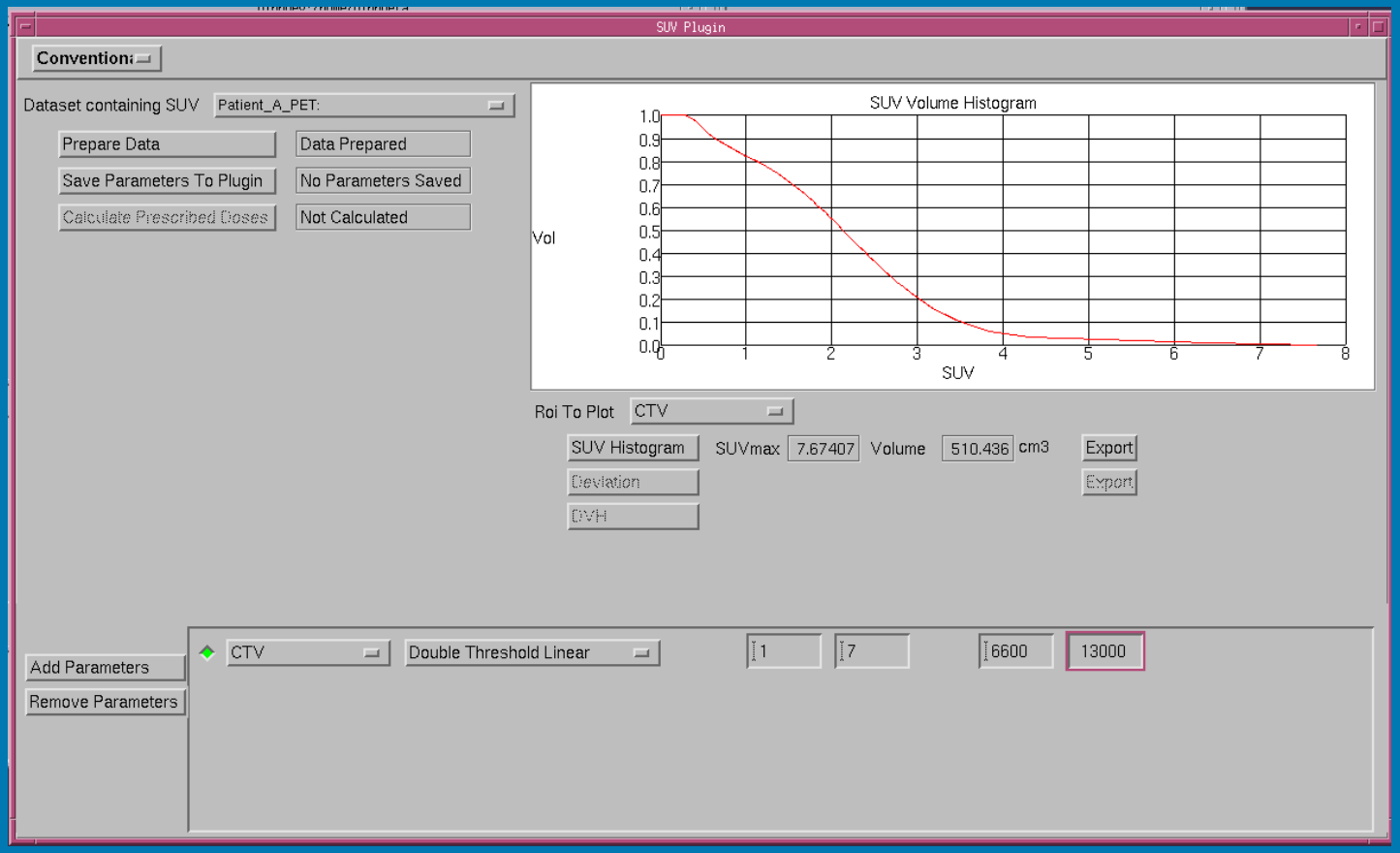
How?

dose painting by contours

- standard software
- allows for margin expansion
- based on thresholding
- evaluation based on DVHs

dose painting by numbers

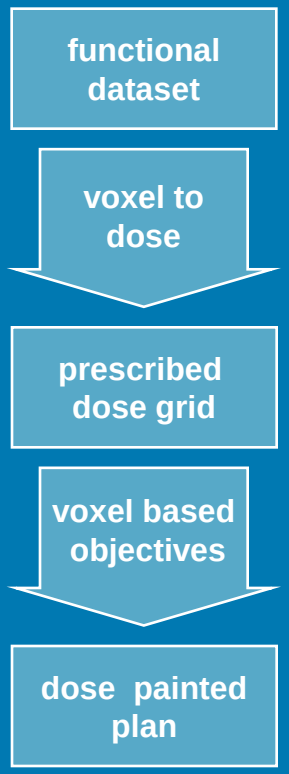
- research software
- no margins
- ‘no’ thresholding
- evaluation based on new descriptors



How?

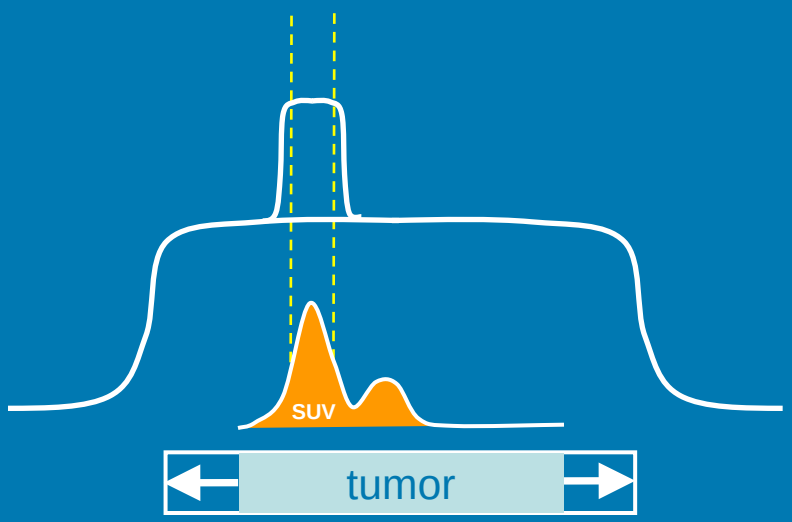
dose painting by contours

dose painting by numbers

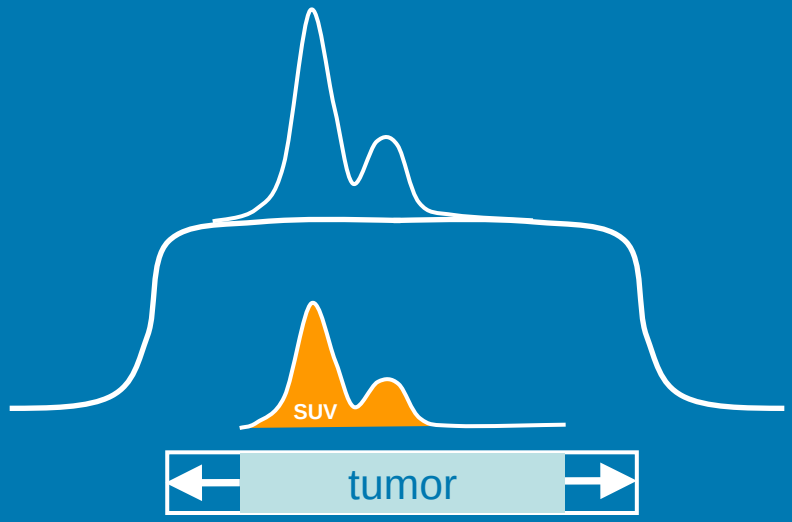


How?

dose painting by contours



dose painting by numbers



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- standard software
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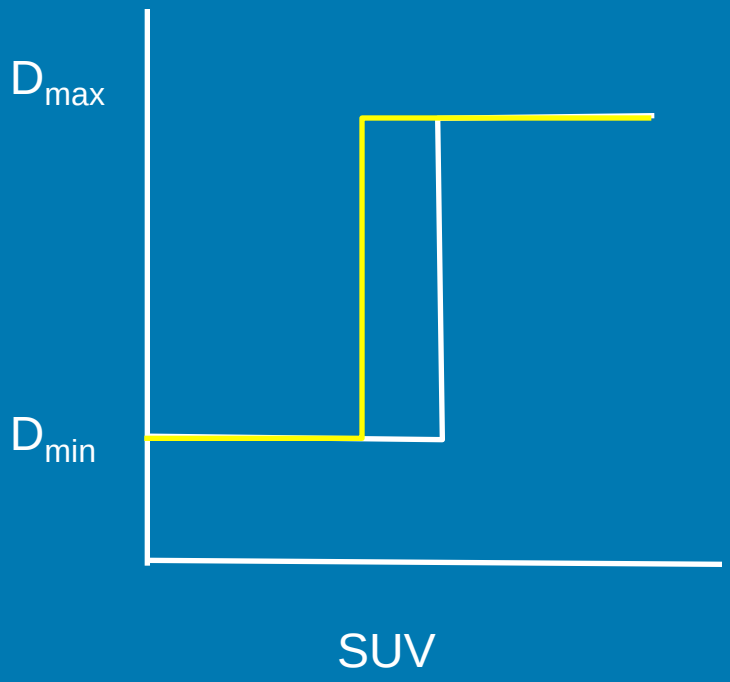
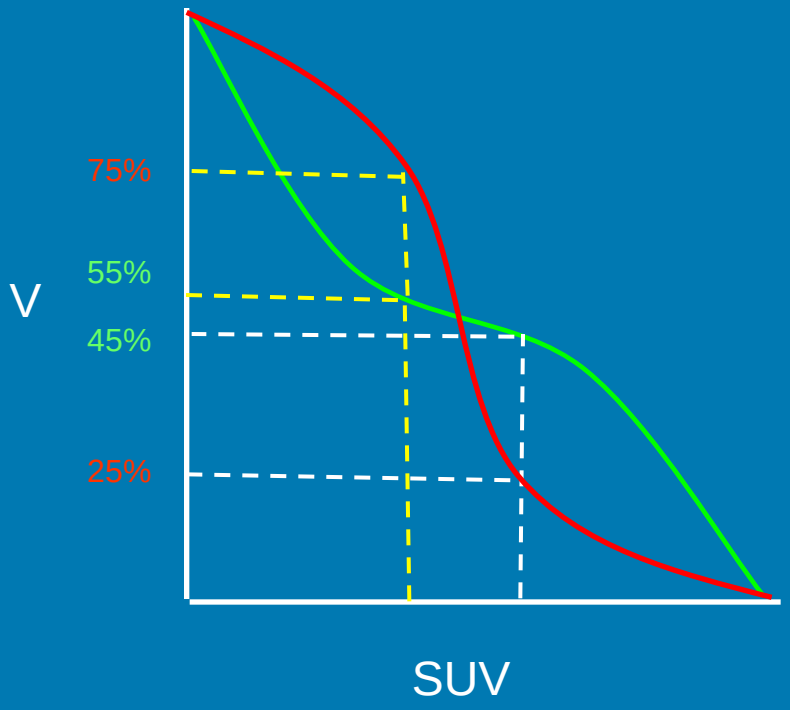
- evaluation based on new descriptors

thresholding might be tricky





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dose painting by numbers

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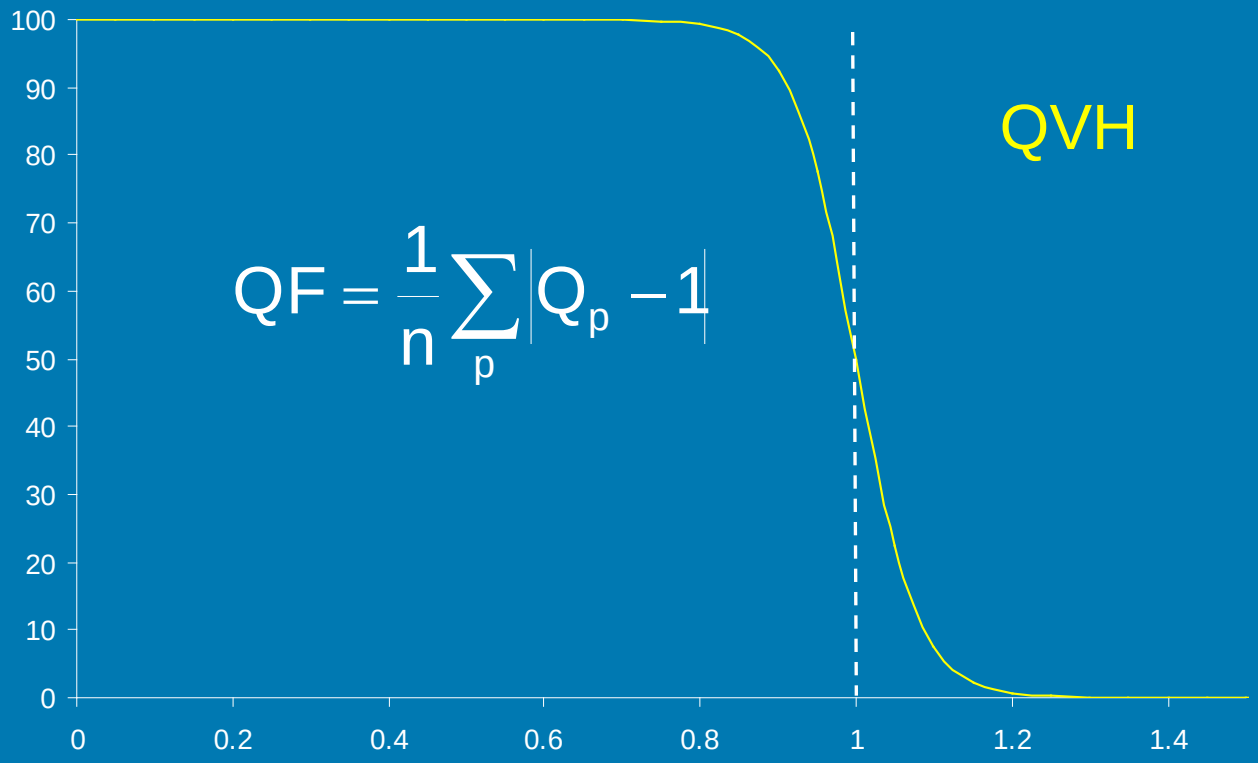
Treatment plan evaluation



QVH

Barbara Vanderstraeten *et al* (PMB 2006)

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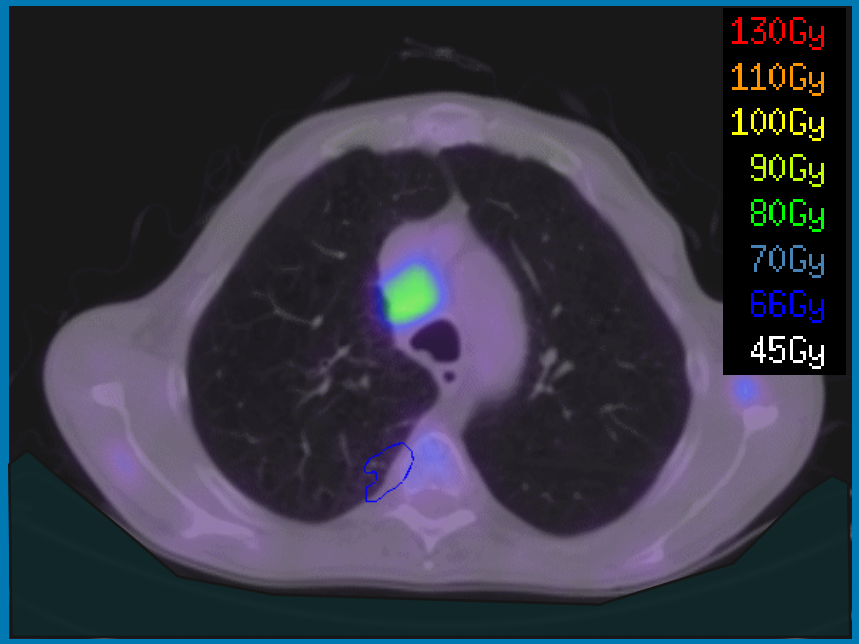
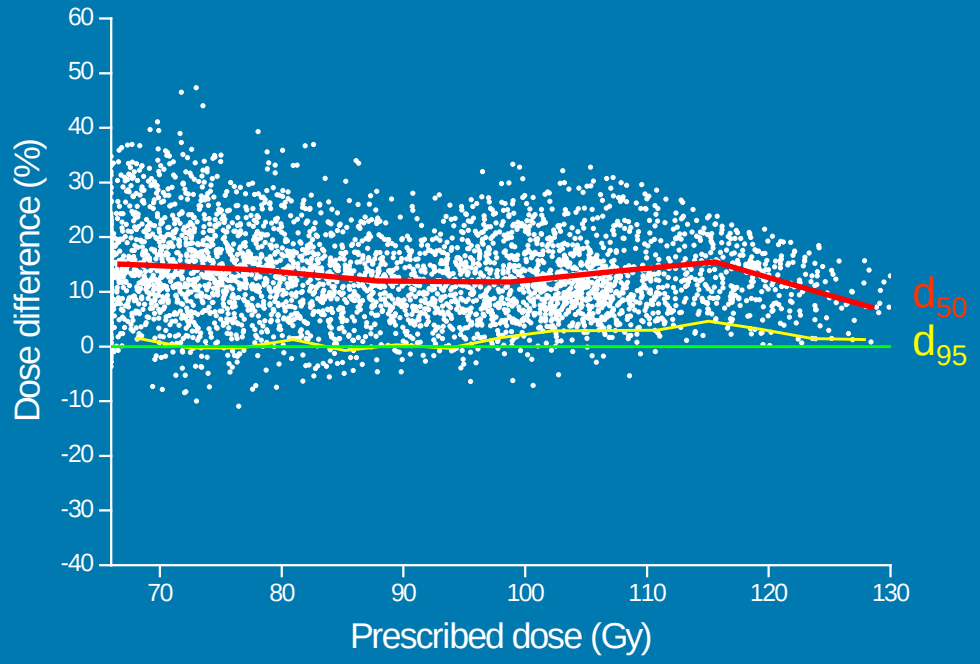
Treatment plan evaluation





7 beams 60 segments

biological gradients match the dose gradients reasonably well

Zwanenburg *et al.* ICCR 2010

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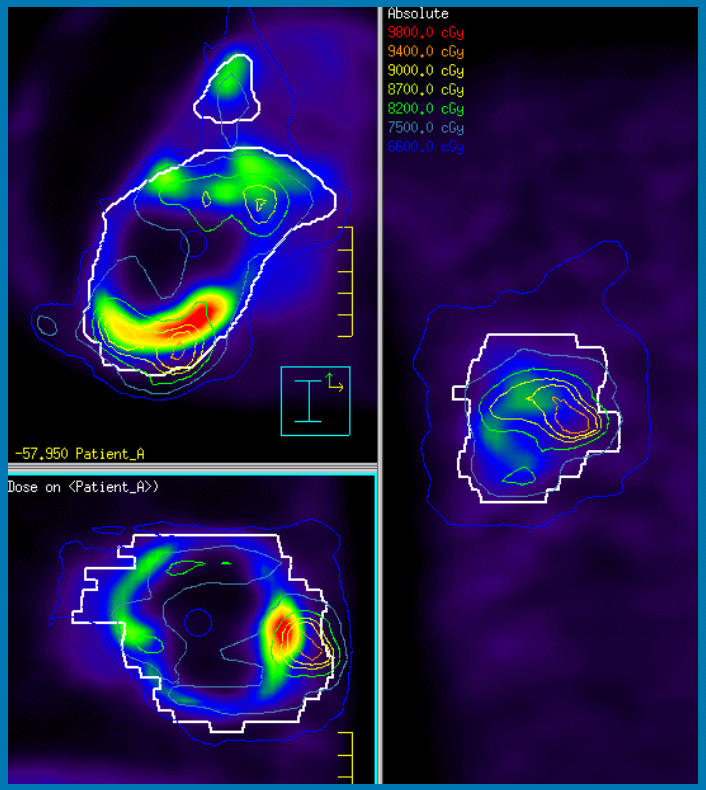
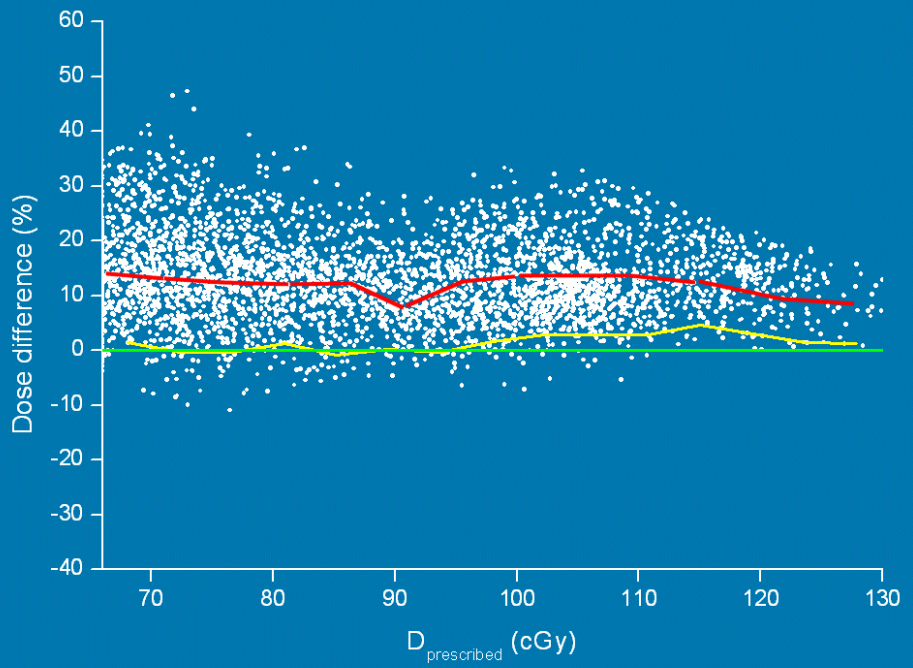
Treatment plan evaluation





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Conclusions

- dose painting is feasible
  - highly conformal delivery technique
  - functional imaging (robust in time and geometry)
  - a sensible relationship between image intensity and high-risk tumor characteristics
- dose painting by contours can be done using conventional treatment planning systems
- for dose painting by numbers you'll need to have acces to dedicated software tools

Rigid and deformable registration

Marcel van Herk

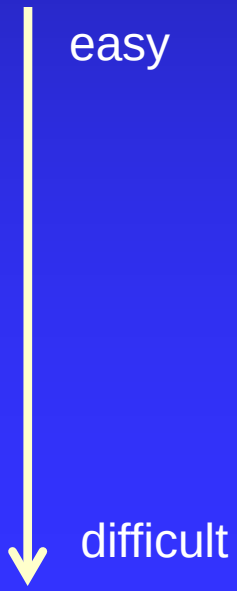
on behalf of the imaging group

Institute of Cancer Sciences,
University of Manchester / The Christie

With slides from:
Netherlands Cancer Institute
Academic Medical Center

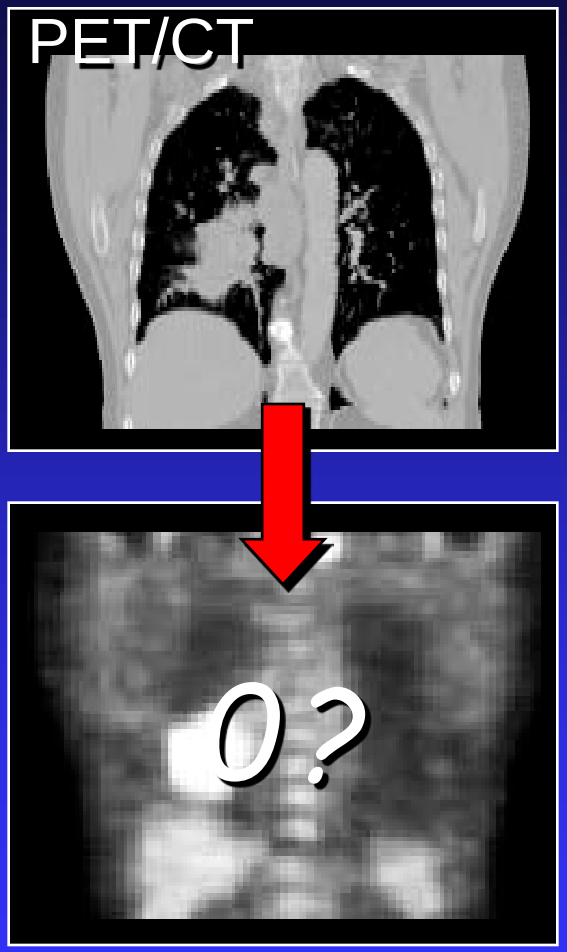
Image registration

- Find translation….deformation to align two 2D..4D data sets (2 .. 1000000+ degrees of freedom)
- Allows combination of scans on a point by point basis
- Applications:
  - Complementary data
  - Motion tracking and compensation (imaging)
  - Image guidance
  - Adaptive radiotherapy
  - Response monitoring
  - Dose accumulation
  - Data mining

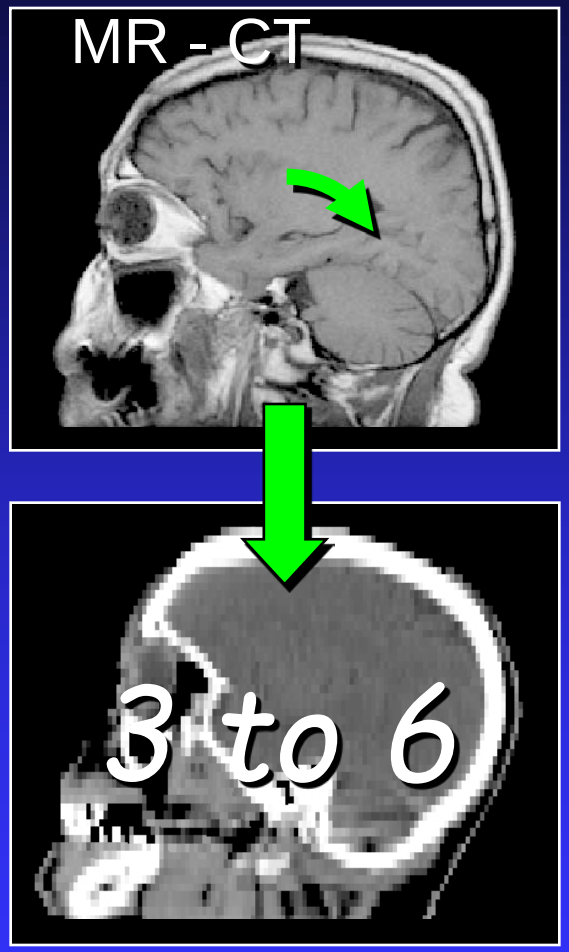


Marc Kessler / UM

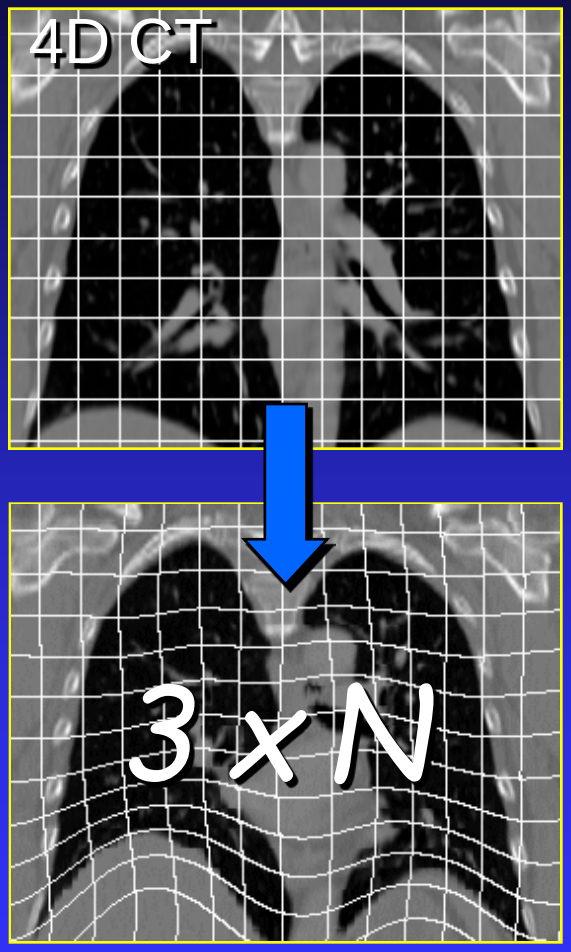
Degrees of Freedom



None ?



Few

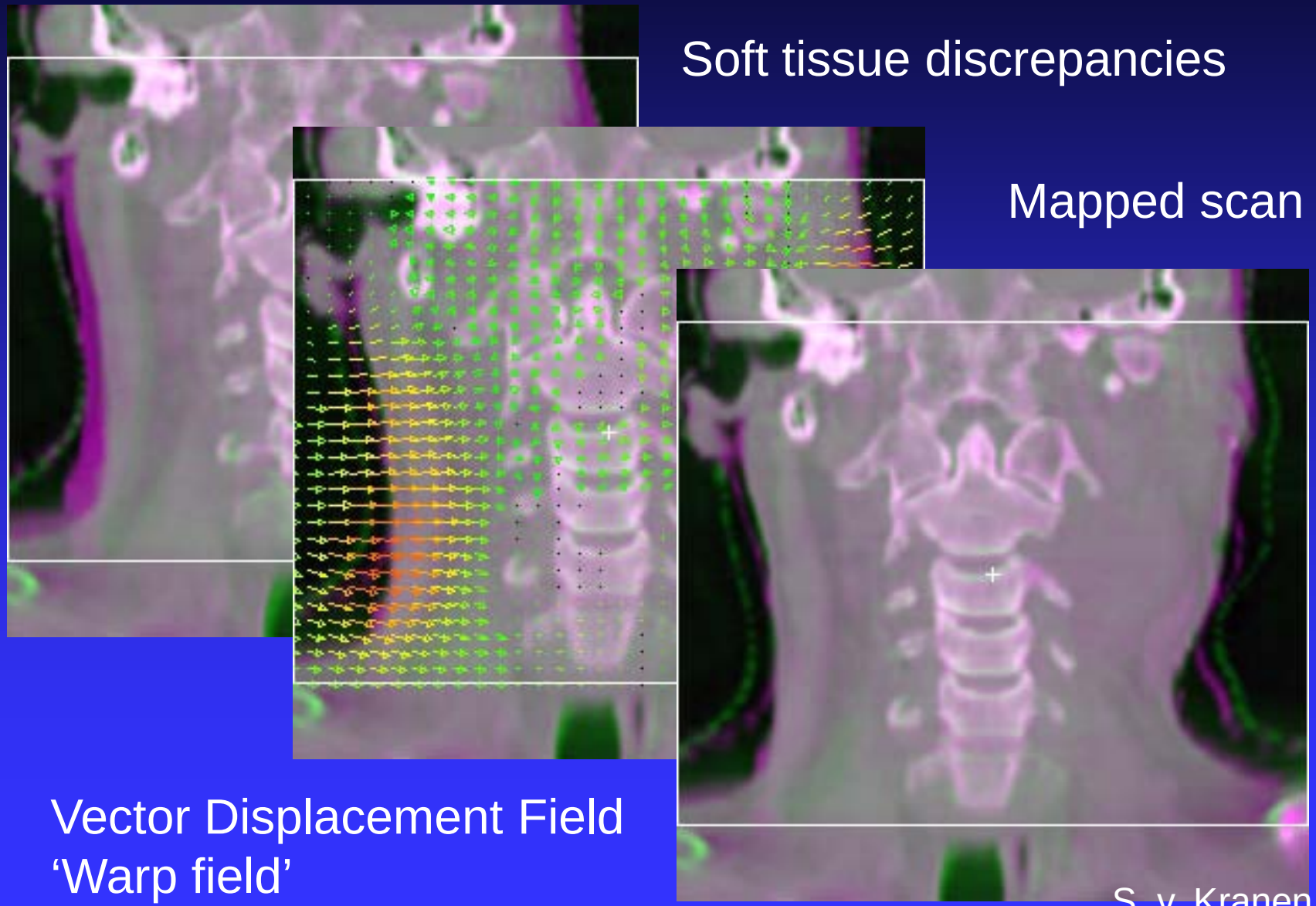


Many

By enforcing smoothness the optimization becomes tractable

Demo rigid registration

Deformation vector fields



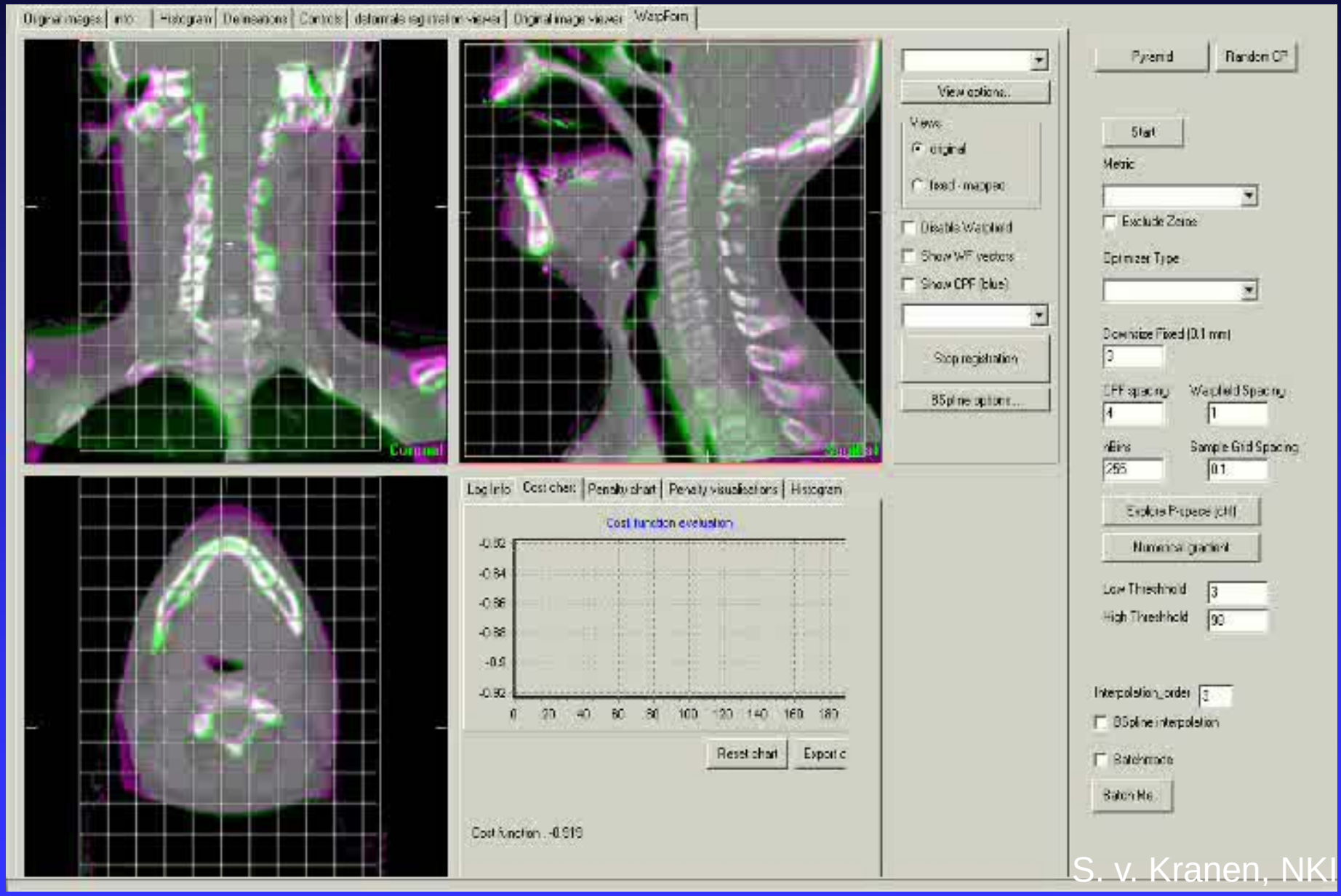
Soft tissue discrepancies

Mapped scan

Vector Displacement Field
‘Warp field’

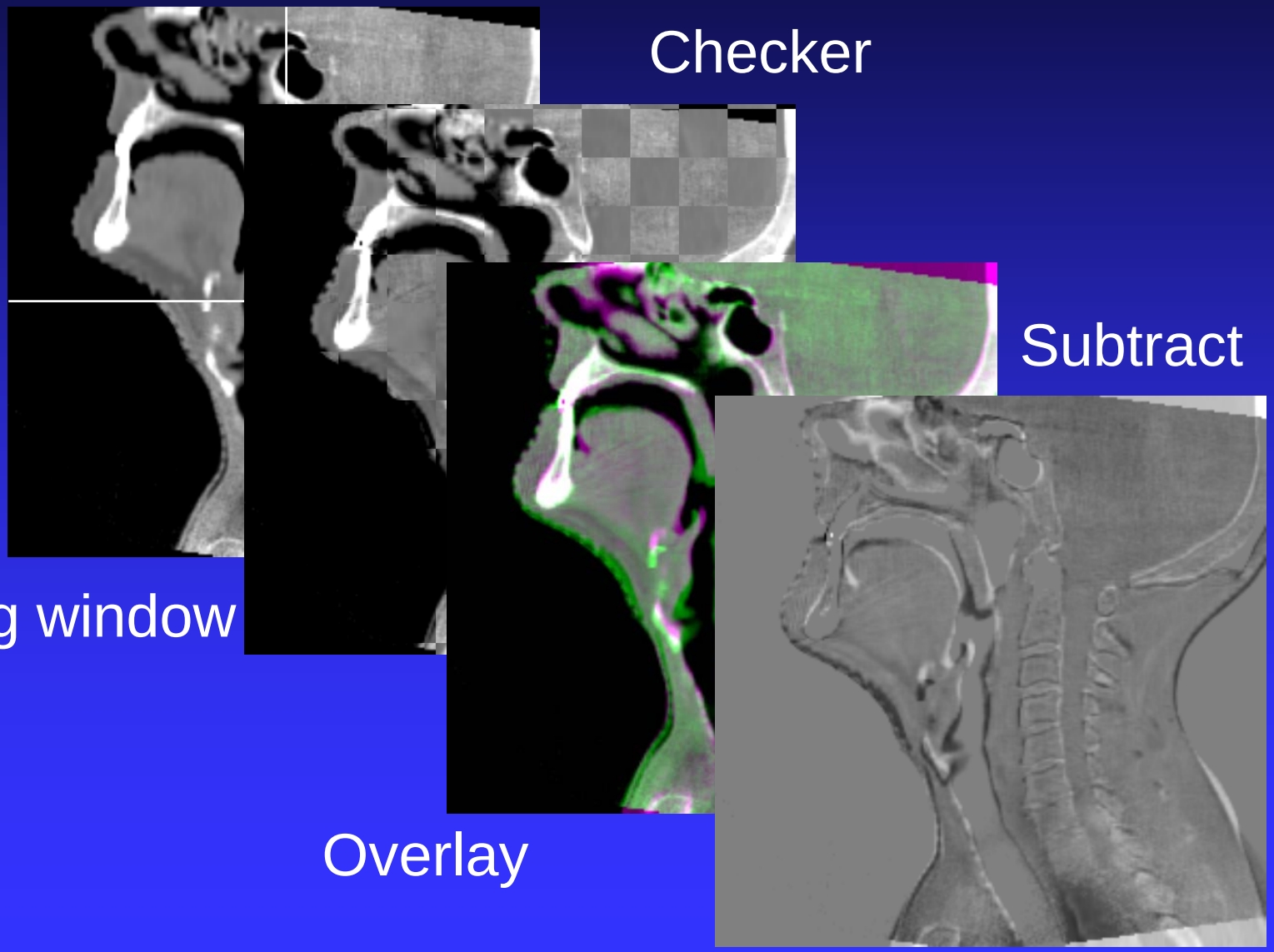
S. v. Kranen, NKI

Deformable registration example

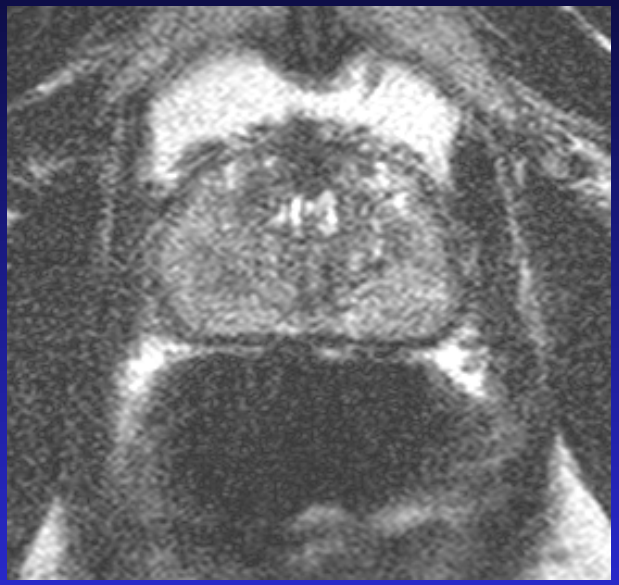


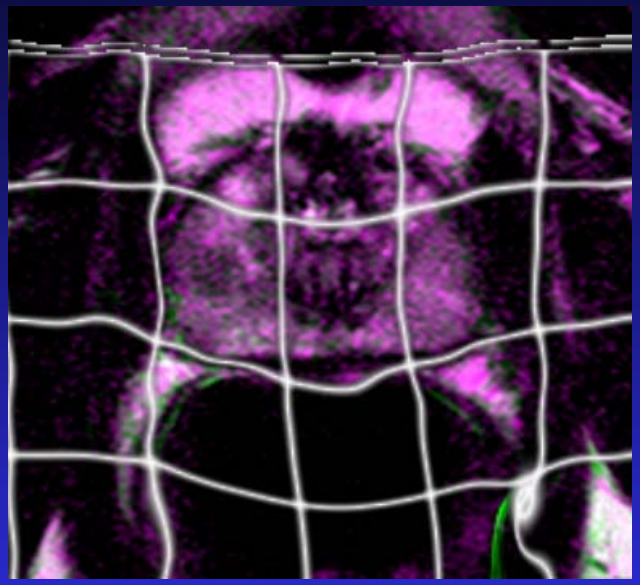
S. v. Kranen, NKI

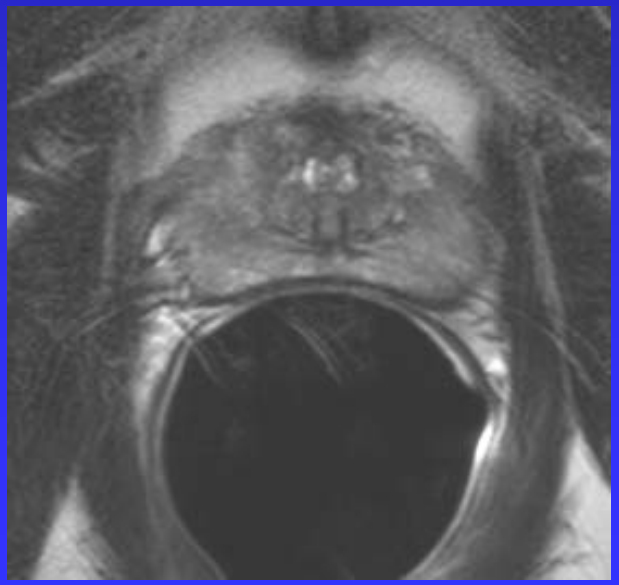
Visual verification

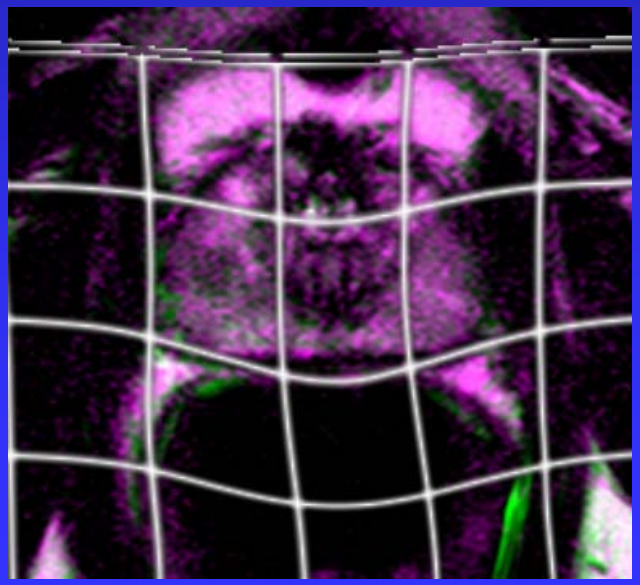


Prostate MRI w/wo Endo Rectal Coil









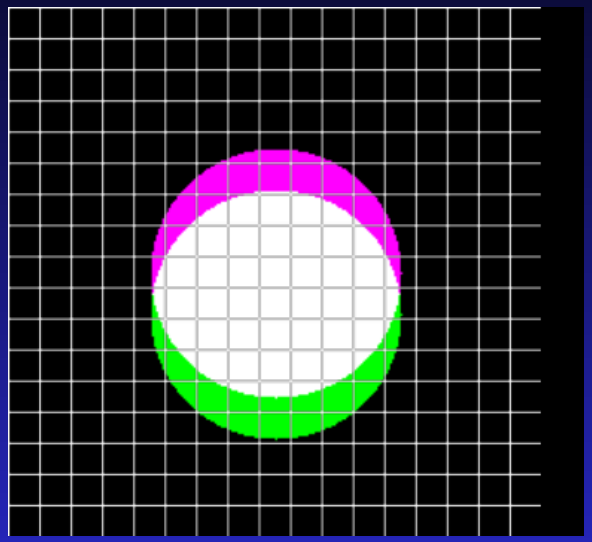
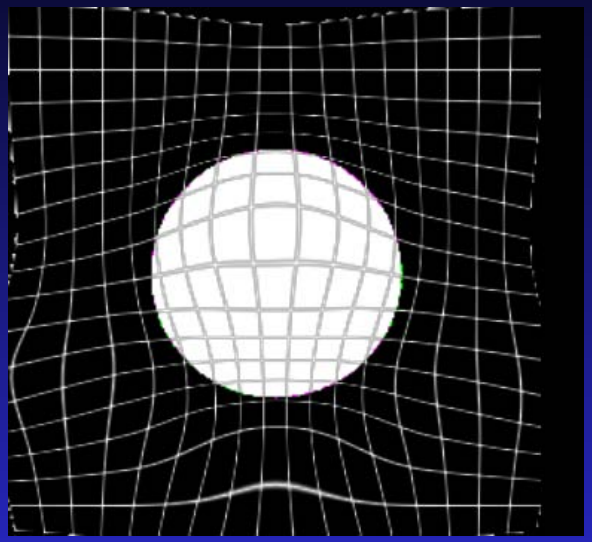
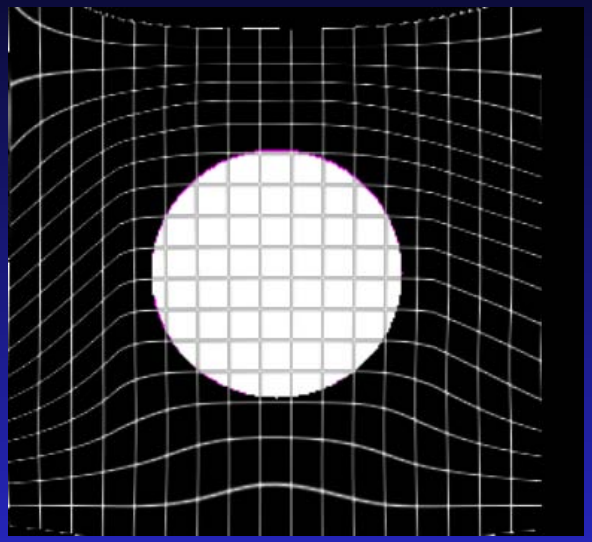
Large effect of parameters on deformable registration

Both solutions are visually correct

Which answer is right?

S van Kranen,
C Kamerling, NKI

Deformable registration classes

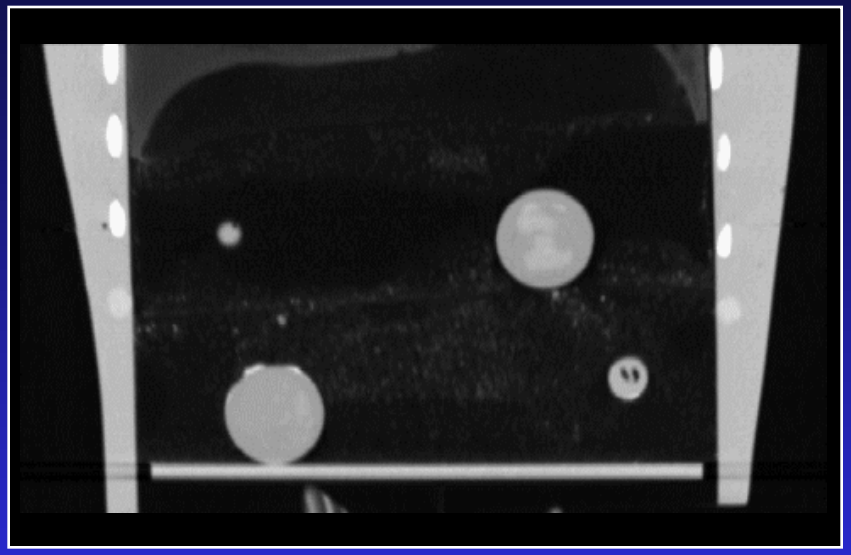
Different DVF provide same visual registration result

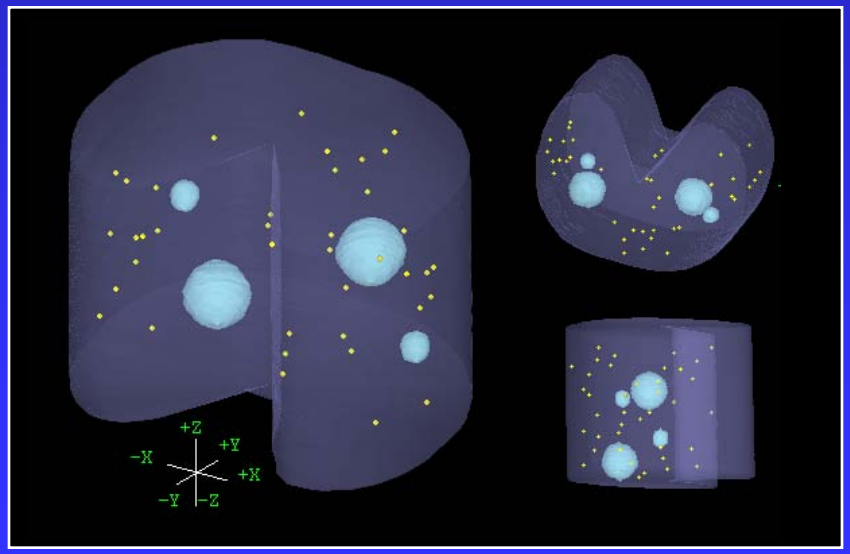
- Descriptive: it must look good
  - e.g. contour propagation
- Quantitative: it must be an anatomically correct, also inside and at surface of homogeneous organ
  - e.g. dose accumulation

QA methods

- The algorithm works technically
  - Use phantom or simulated data
- The program works in general
  - Best: use patients with implanted markers (data scarce)
  - Second: compare with human observers
- The program works for this patient
  - Visual verification
  - Consistency, plausibility

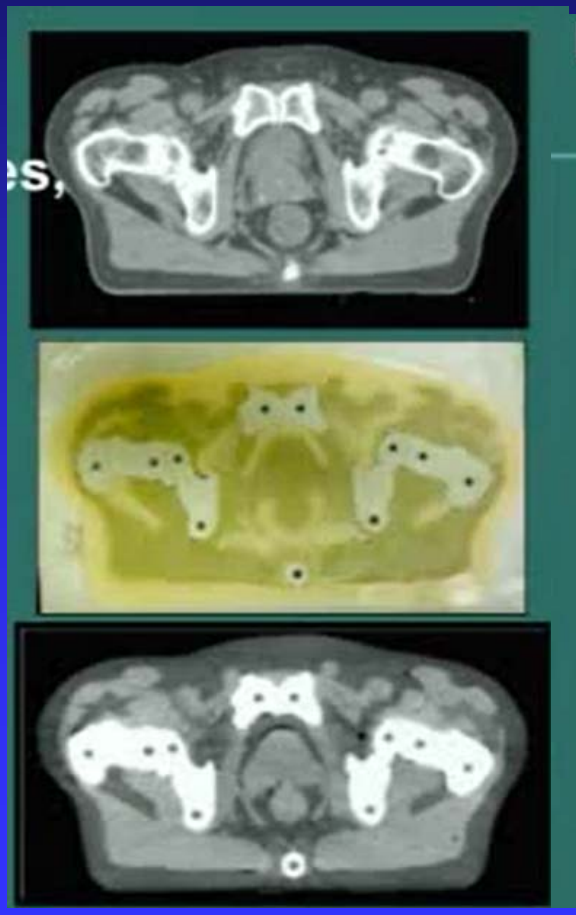
4D Phantoms





		RL[a] (cm)	AP[b] (cm)	SI[c] (cm)	3-D distance (cm)
Affine	Average	−0.01	0.00	0.05	0.38
	Stdev[d]	0.04	0.04	0.44	0.22
	Max[e]	−0.12	−0.13	0.90	0.90
B-splines	Average	−0.02	−0.01	0.05	0.18
	Stdev[d]	0.08	0.06	0.22	0.16
	Max[e]	−0.42	0.19	0.67	0.81
Thin-plate splines	Average	−0.07	−0.15	−0.14	0.37
	Stdev[d]	0.12	0.19	0.28	0.19
	Max[e]	−0.56	−0.58	−0.74	0.75

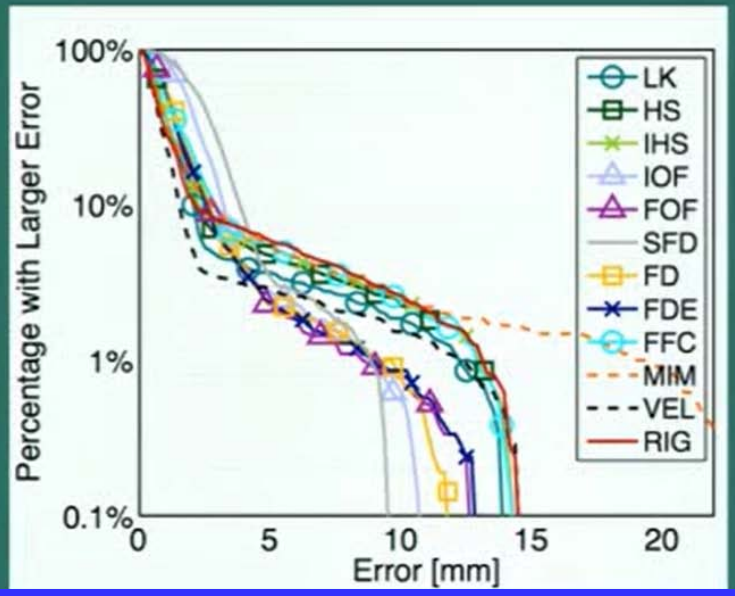
Registration of anatomically realistic phantom in pelvis

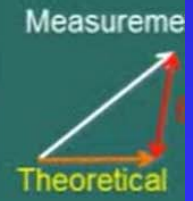


UCSF University of California San Francisco

DIR Error Distribution

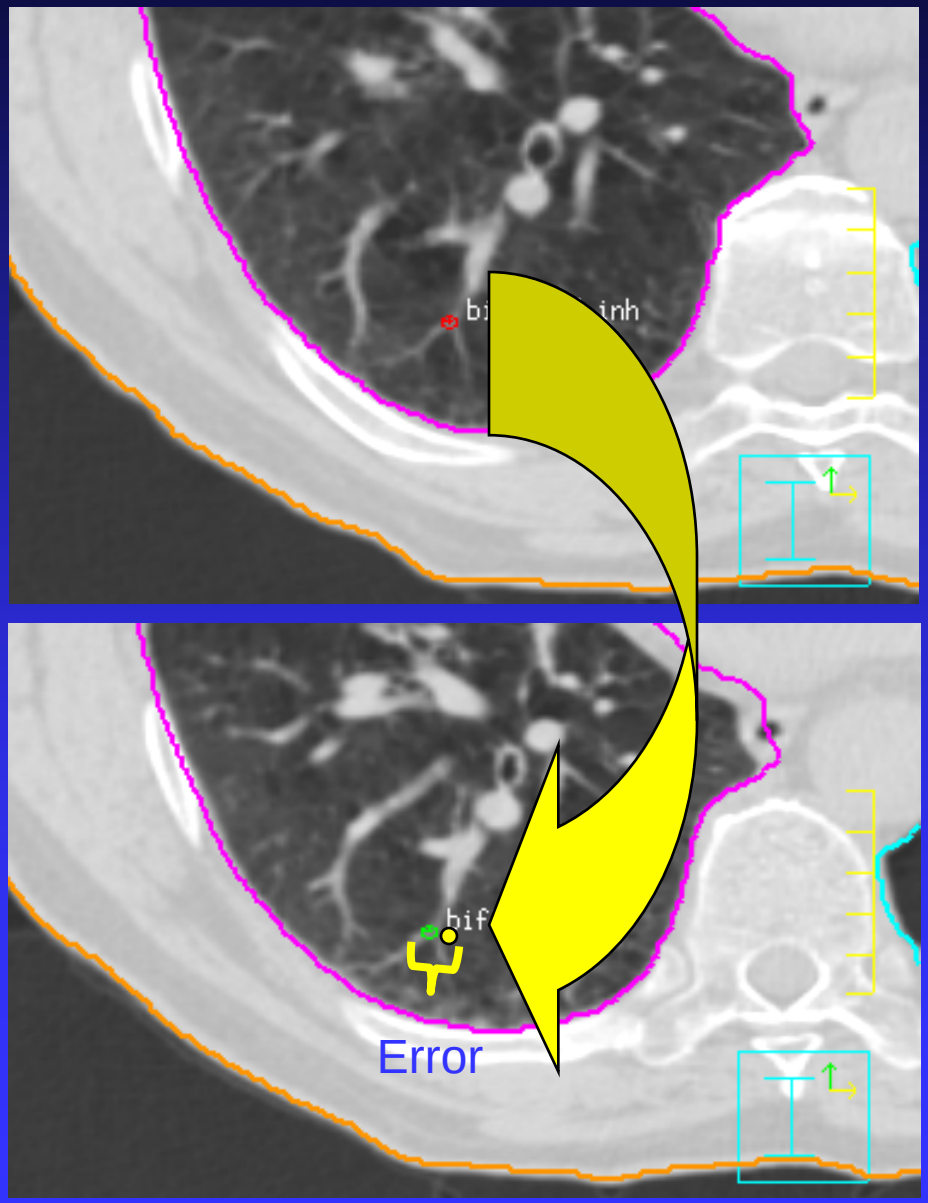
The fraction of markers with a distance to agreement larger than a given error as a function of error.





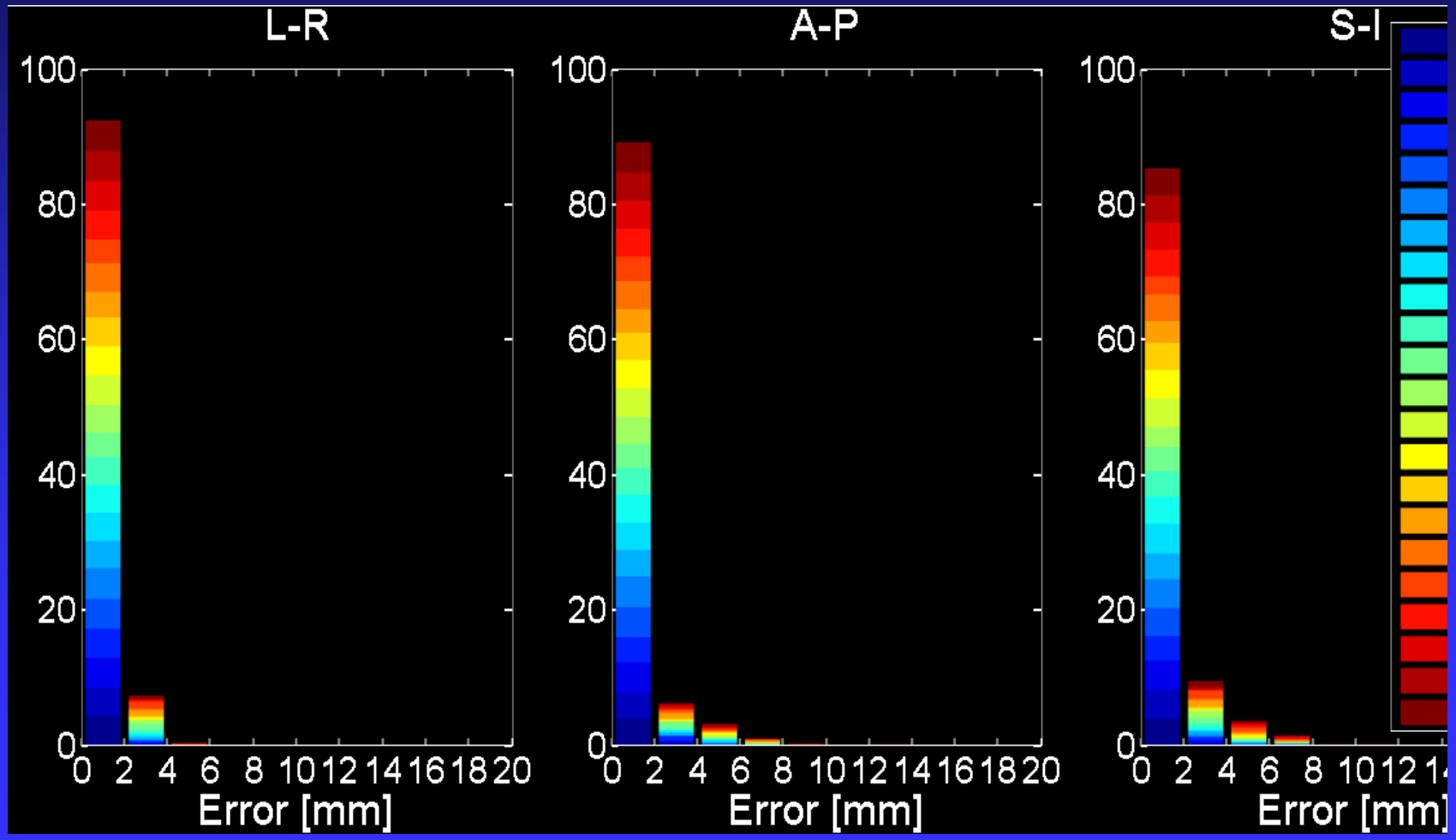
J Pouliot, UCSF

Natural Fiducials

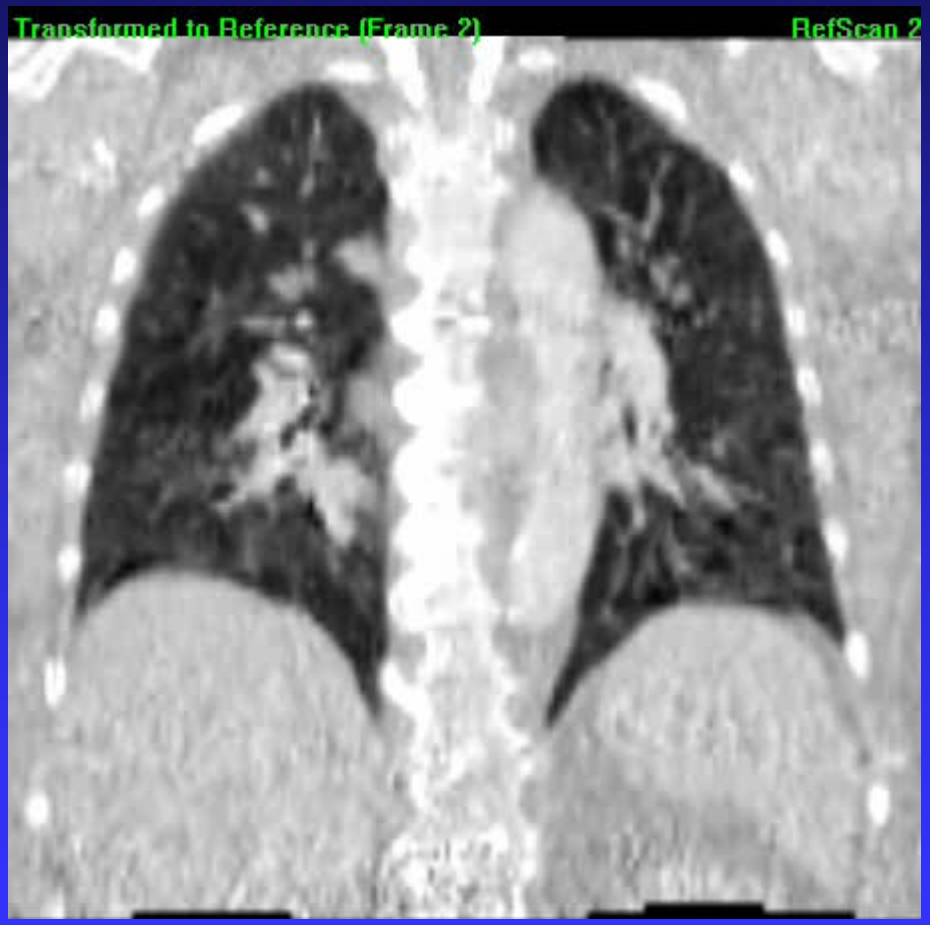


Results: Lung 4D CT (22)

% Bifurcation Points

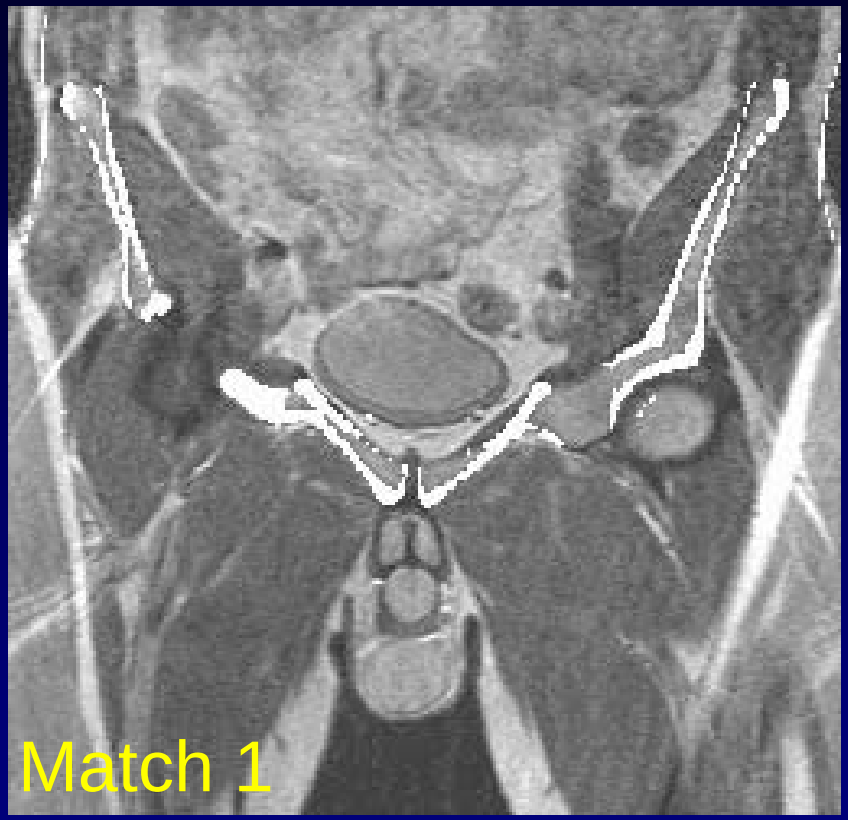


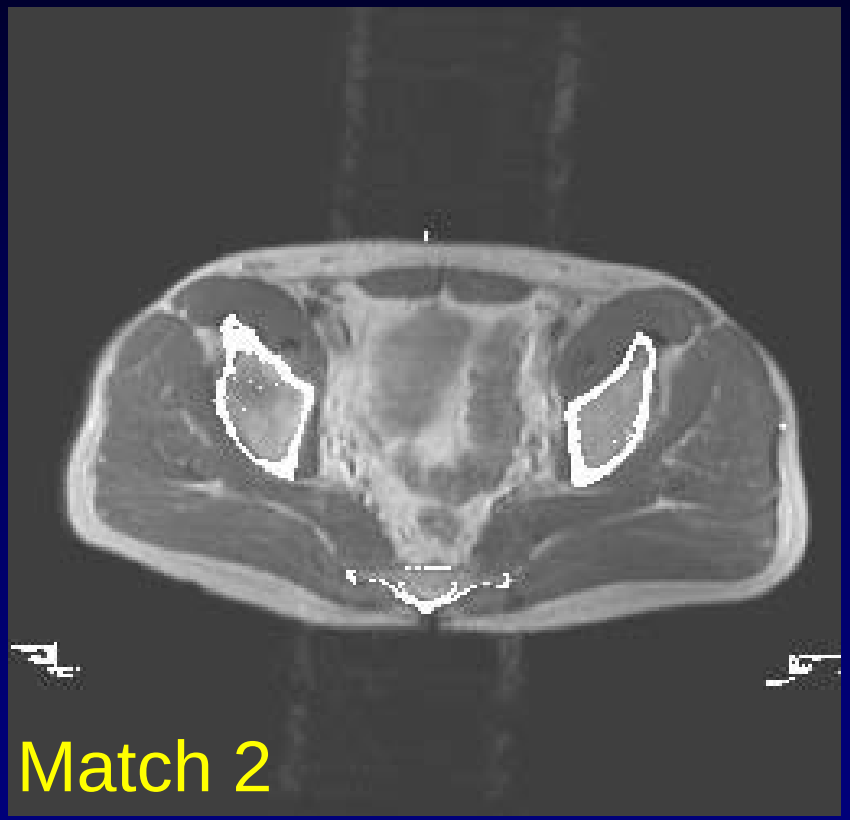
Lung deformable registration easy ?



J Wolthaus, NKI

Consistency check as QA tool



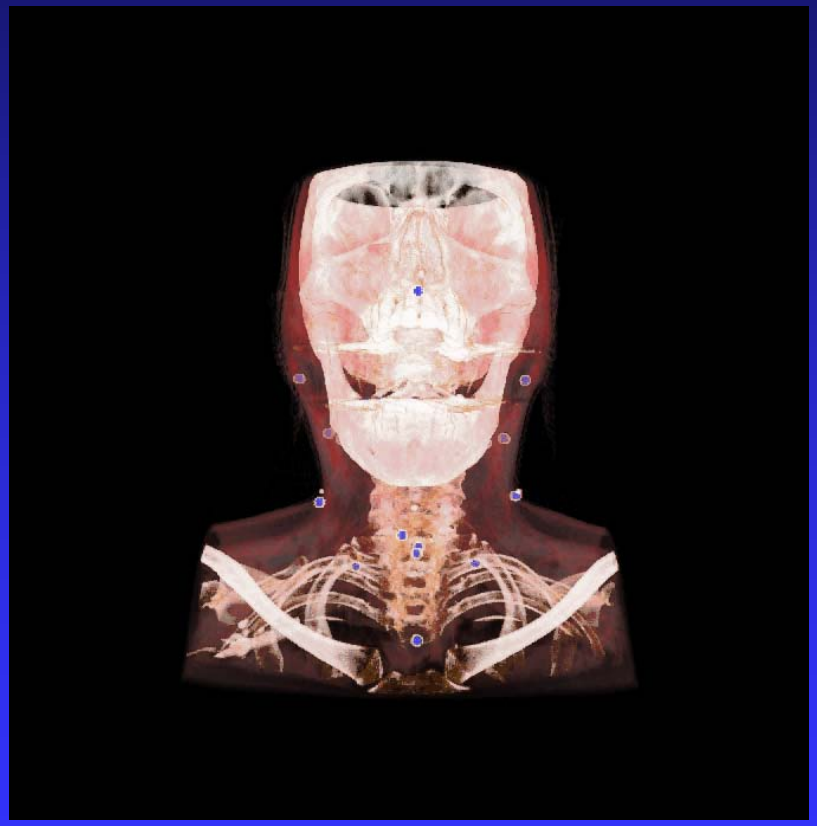


Deviation	Δ x (L-R)	Δ y (A-P)	Δ z (C-C)	Δ rx (L-R)	Δ ry (A-P)	Δ rz (C-C)
between match 1 and 2	-0.5 mm	2.0 mm	-1.6 mm	-0.9 dg	-0.8 dg	-0.7 dg

Van Herk et al, 1998

Landmark QA, analysis of variance

- Landmark validation
- 7 patients, 7 - 8 fractions
- 23 landmarks per CBCT, two human observers
- B-spline deformable registration for landmark propagation
- Use of ANOVA method to correct for observer variation



A. Mencarelli, NKI

Analysis of variance

Observer places O_1, Observer places O_2 Computer places O_3

Measure distances for many scans and landmarks

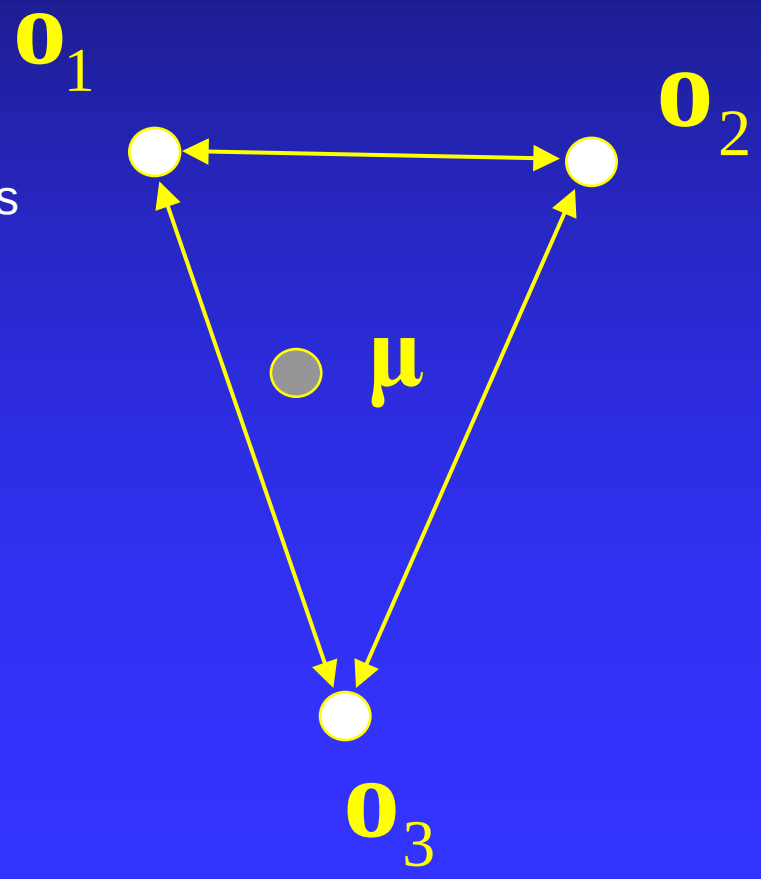
Compute standard deviations of differences

Solve for standard deviation of individual observers

$$\sigma_1^2 = (\sigma_{2-1}^2 + \sigma_{3-1}^2 - \sigma_{3-2}^2)/2$$

$$\sigma_2^2 = (\sigma_{3-2}^2 + \sigma_{2-1}^2 - \sigma_{3-1}^2)/2$$

$$\sigma_3^2 = (\sigma_{3-1}^2 + \sigma_{3-2}^2 - \sigma_{2-1}^2)/2$$

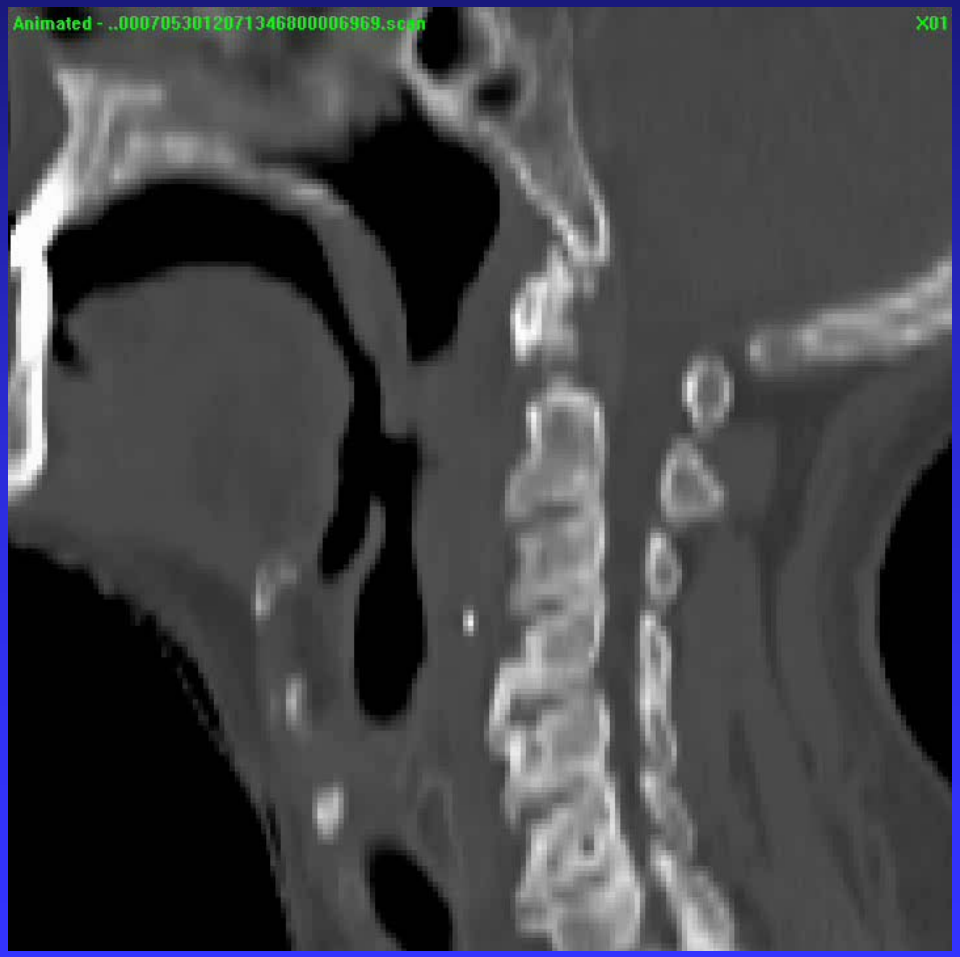


Results: head and neck CT-CBCT

Method	Accuracy (1SD mm)		
	SD_{LR}	SD_{CC}	SD_{AP}
Rigid registration	**1.8**	**2.0**	**1.7**
B-spline *No penalties*	**1.4**	**1.5**	**1.1**
B-spline + *penalties*	**0.9**	**1.0**	**0.9**

A. Mencarelli, NKI

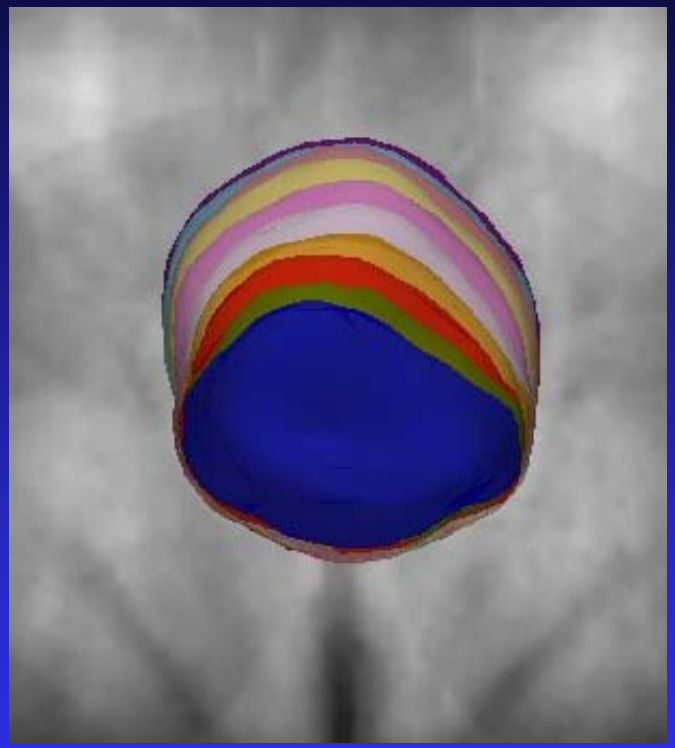
Can you see all anatomical changes ?

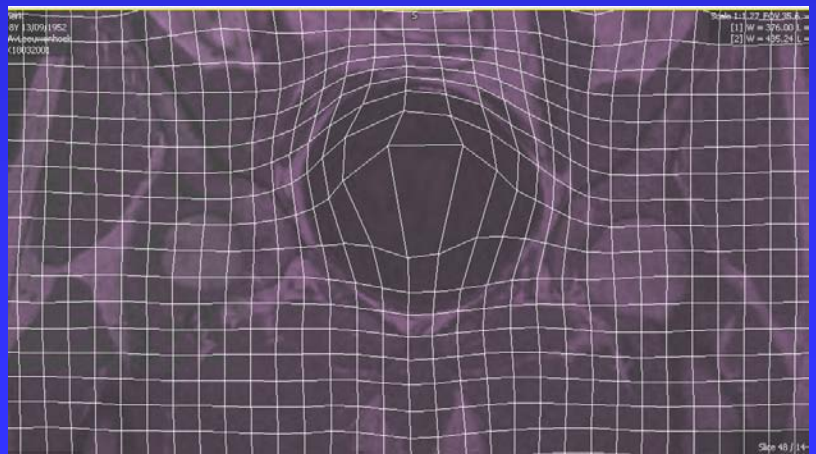


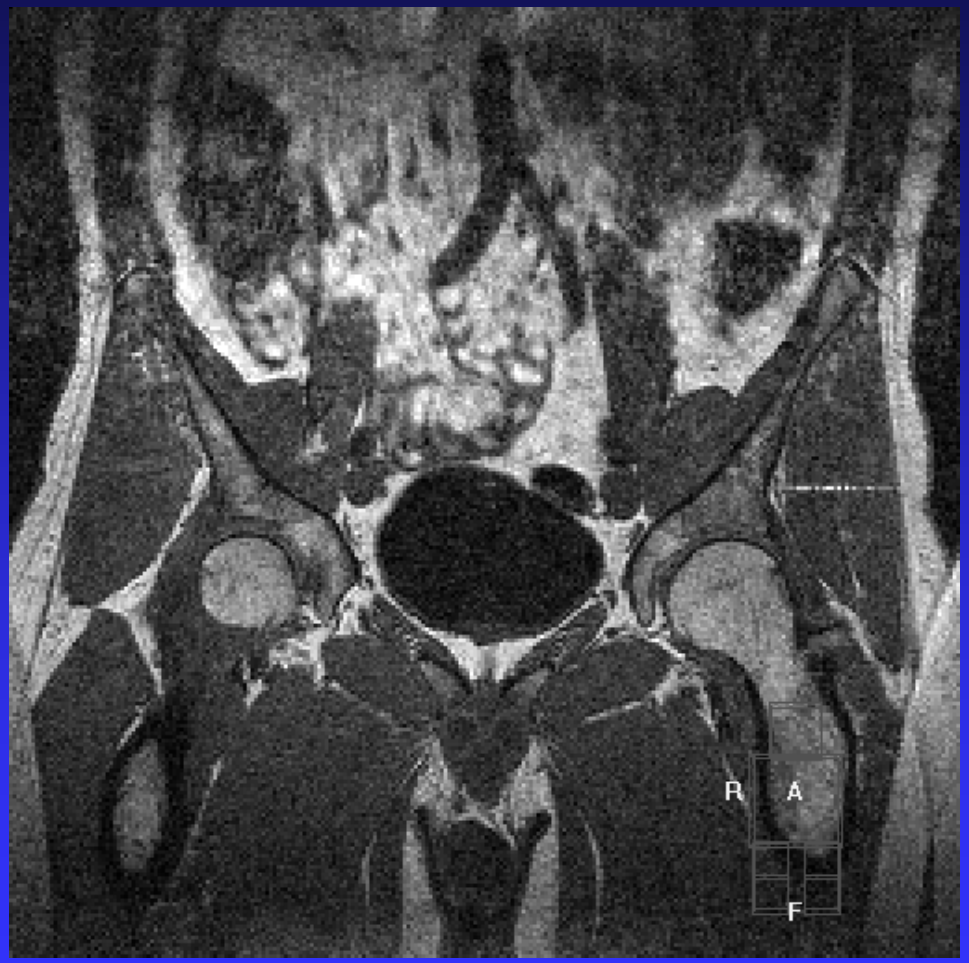
Deformable registration will not pick up motion parallel to interfaces

O Hamming, NKI

Easy deformable registration of the bladder?

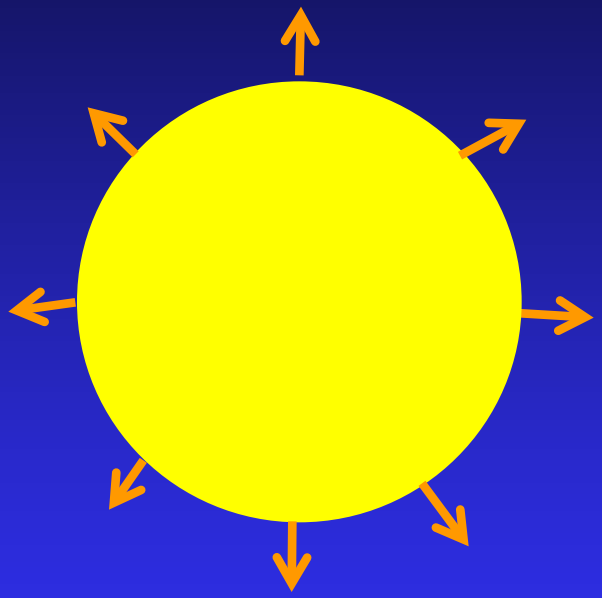


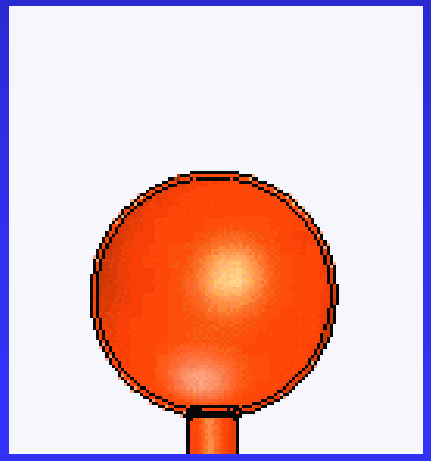


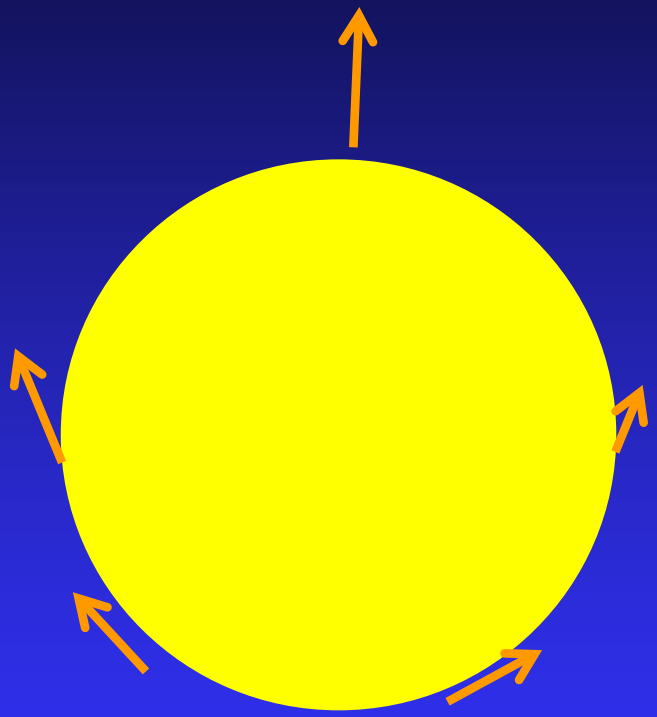


Very high contrast but does software ‘understand’ the anatomy ?

The bladder is a balloon in a box with stuff – it expands isotropic constrained by the organs around it







You get the contours right, but not the tissue cells → danger for dose accumulation

Landmark validation of contour-based bladder registration

Control over structure-specific flexibility improves anatomical accuracy for point-based deformable registration in bladder cancer radiotherapy

S. Wognum, L. Bondar, A. G. Zolnay, X. Chai, M. C. C. M. Hulshof, M. S. Hoogeman, and A. Bel

Citation: Medical Physics **40**, 021702 (2013); doi: 10.1118/1.4773040

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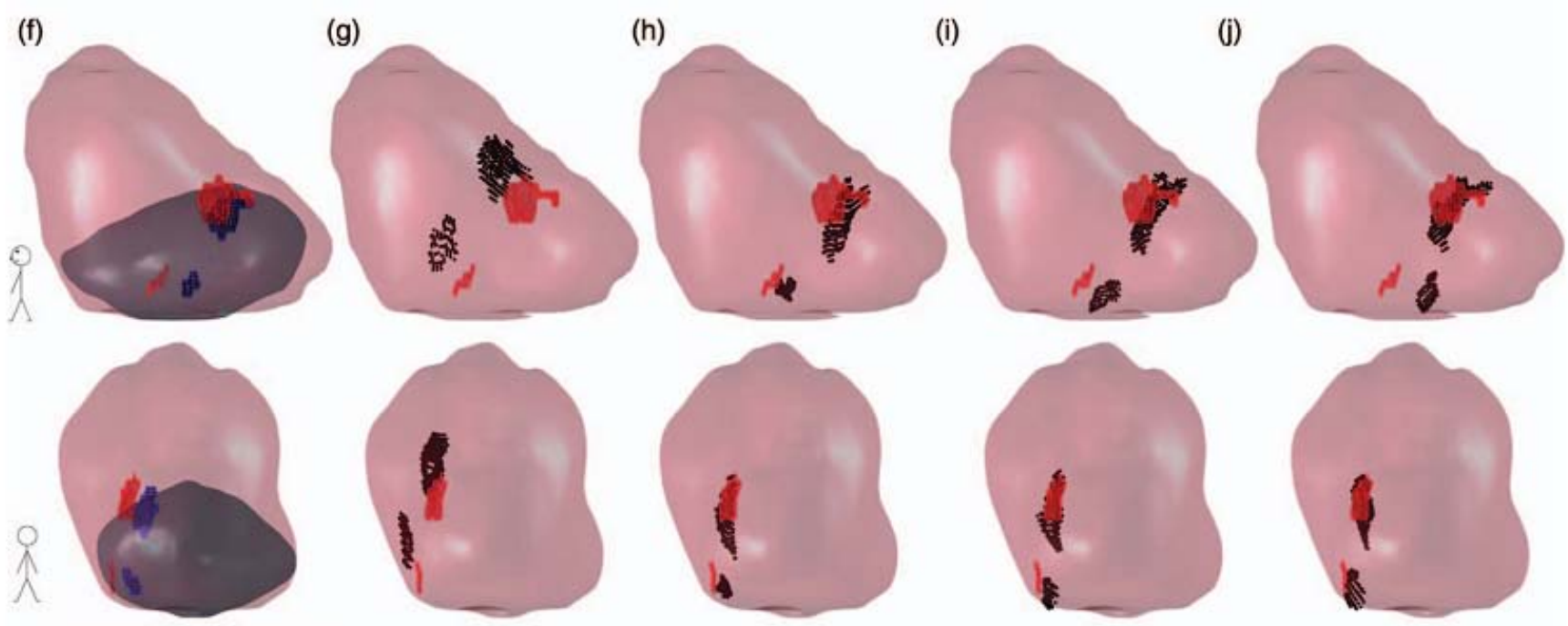
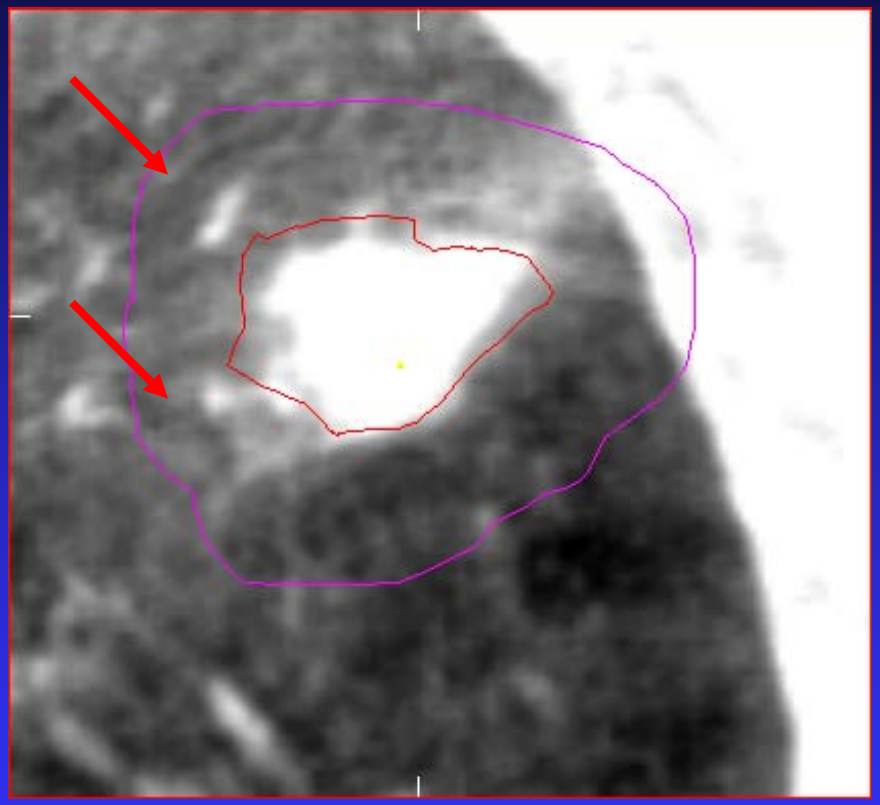


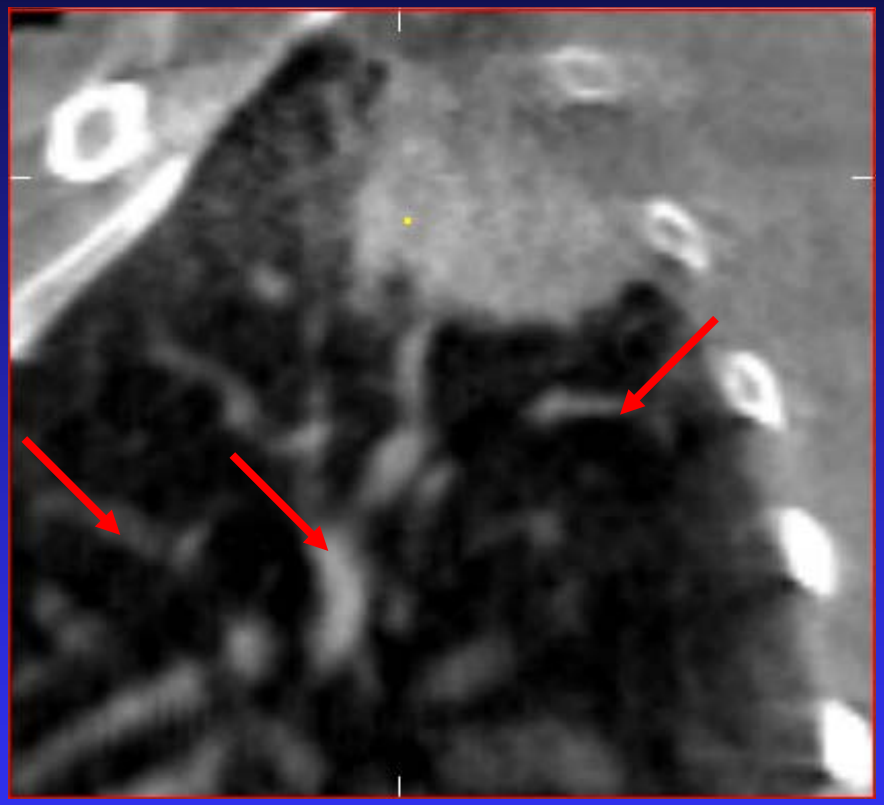
RDE lipiodol (mm)

1	5.9	6.4	3.6	3.1	2.2
2	11.8	8.9	4.0	8.6	14.1

Registration of shrinking tumor ?



‘elastic’
Deformable registation OK



‘erosion’
Deformable registration will fail
→ Potential under-dosage of residual tumor

S. v. Kranen,
JJ Sonke NKI

Overconfidence in commercial systems

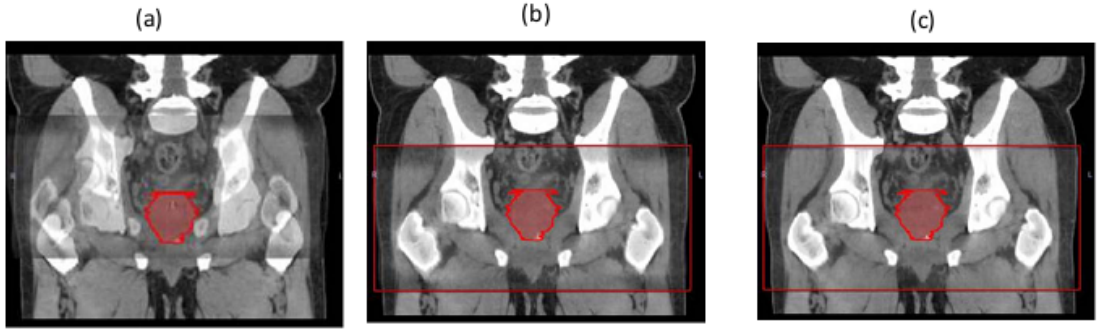
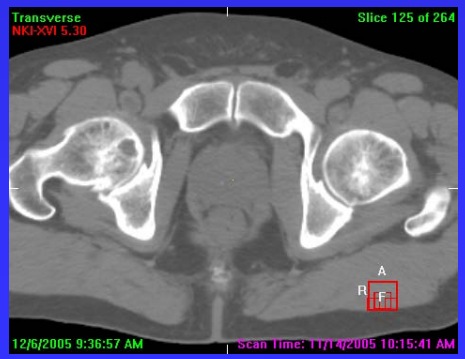
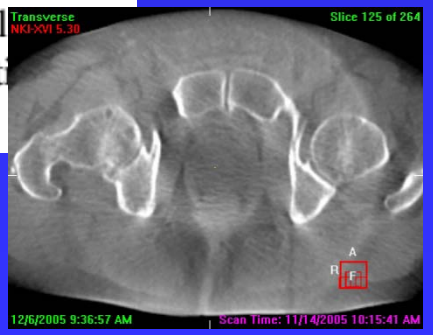


FIG. 1. An example of the registration process in the coronal plane. The rectangular box is the region of interest, which includes the entire CBCT. The contoured structure is the CTV. In (a), CBCT and SimCT were not registered. In (b), rigid registration was performed for CBCT into SimCT based on pelvic bones and fiducial markers. In (c), CBCT is deform

Fiducial markers were used to evaluate the registration for each case. The error in the prostate alignment was defined as the average distance between the markers on CBCT and the corresponding SimCT datasets. Alignment error less than 2 mm was considered acceptable. Figure 2 illustrates the workflow with regard to image registration and data anal
As shown, out of 200 CBCT-to-CT deformable registrati
107 showed alignment agreement within 2 mm.





Conclusions

- QA of deformable image registration is complex
- Deformable image registrations is unsolved problem; algorithms lack biological and biomechanical knowledge
  - Sliding tissue
  - Tumor growth and regression
- This is OK to make pretty pictures and propagate OAR contours
- This is **not OK** for dose accumulation: it is unsafe to estimate you know where previous dose went
- This is **not OK** for adaptation around ‘shrinking’ tumors
- I therefore strongly suggest no to optimize dose on top of ‘accumulated’ dose

Thank you for your attention!

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UNIVERSITÀ CATTOLICA del Sacro Cuore

Radiotherapy & Physics department

Policlinico A. Gemelli, Rome (Italy)

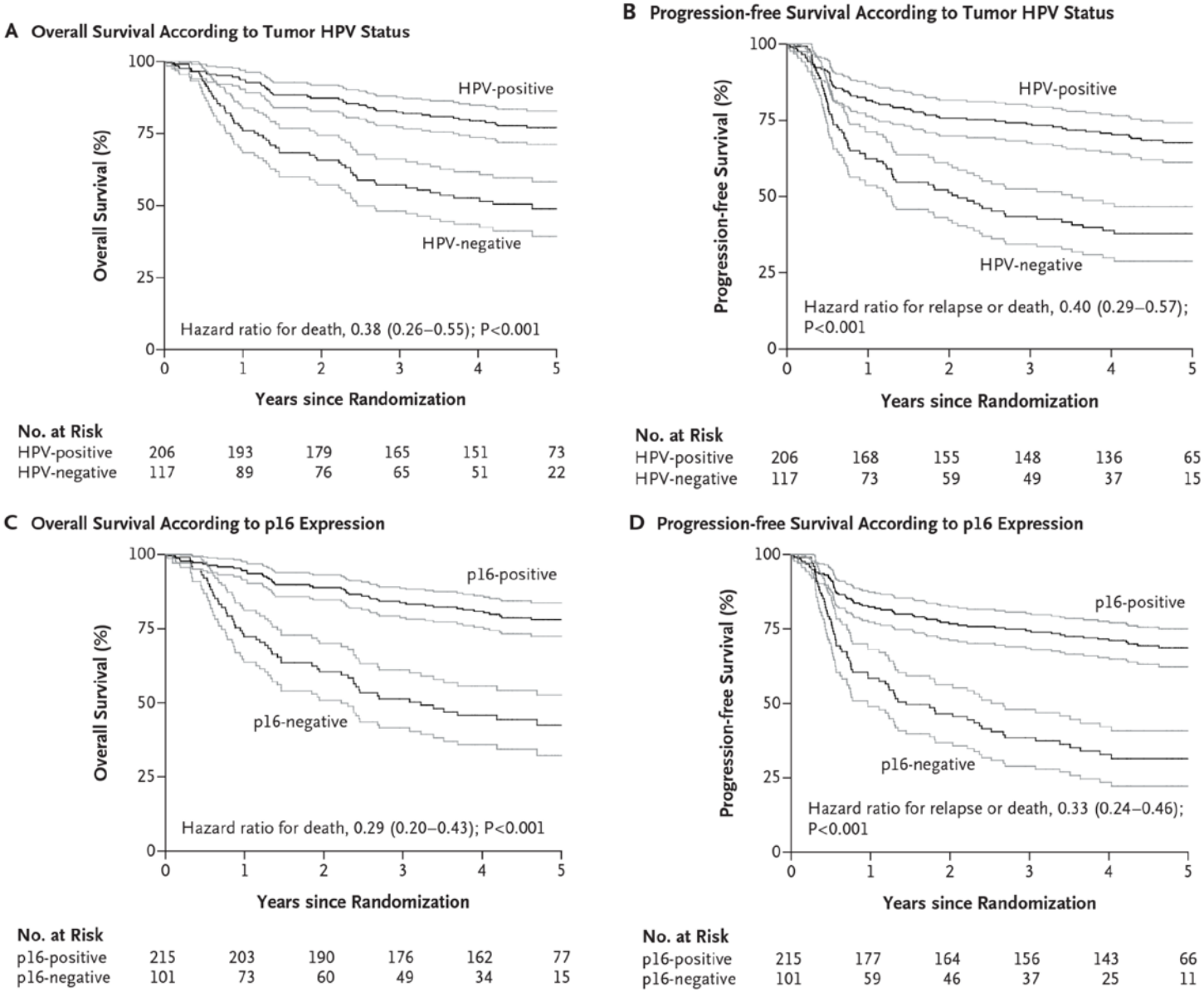
Introduction to Case 5: Bilateral Oropharynx

N. Dinapoli

Staging

- Male patient, 52 years old
- Stage: T3 (T ≥ 4.1 cm) N2b M0 (stage IVa)
- Primary starts from the left tonsil, spreads down to the pre-epiglottic space, soft palate involvement
- Positive nodes in the same side of the tumor (left LC space) and upper retro-pharyngeal space
- Evaluation of HPV status: positive

HPV status (needed for prognosis)



Ang KK et al. Human Papillomavirus and Survival of Patients with Oropharyngeal Cancer. N Engl J Med 2010;363:24-35.

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PTV prescription: SIB treatment

- 1) **Primary + Positive lymph nods** (Left LC and RP)
  - PTVp_7000, PTVn_L_7000, PTVnLRP_7000: **70 Gy @ 2 Gy/fr**

- 2) **Lymph nodes potentially site of microscopic spread**
  - PTVn_L_5425, PTVn_R_5425: **54.25 Gy @ 1.55 Gy/fr**

THE LANCET
www.thelancet.com

Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial

*Christopher M Nutting, James P Morden, Kevin J Harrington, Teresa Guerrero Urbano, Shreerang A Bhide, Catharine Clark, Elizabeth A Miles, Aisha B Miah, Kate Newbold, MaryAnne Tanay, Fawzi Adab, Sarah J Jefferies, Christopher Scrase, Beng K Yap, Roger P A'Hern, Mark A Sydenham, Marie Emson, Emma Hall, on behalf of the PARSPORT trial management group**

Lancet Oncology. 2011;12:127-36.

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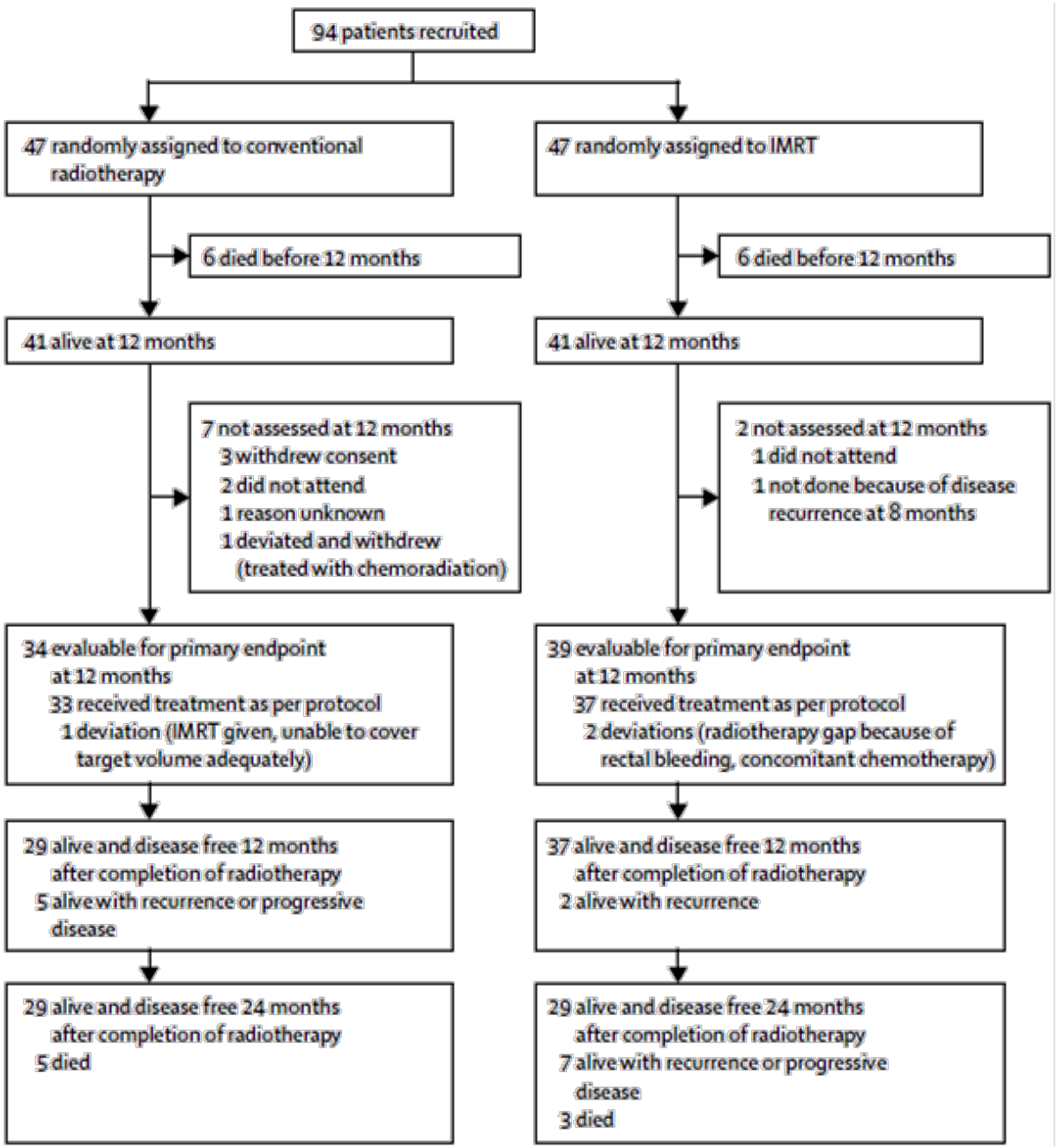

Lancet Oncology. 2011;12:127-36.

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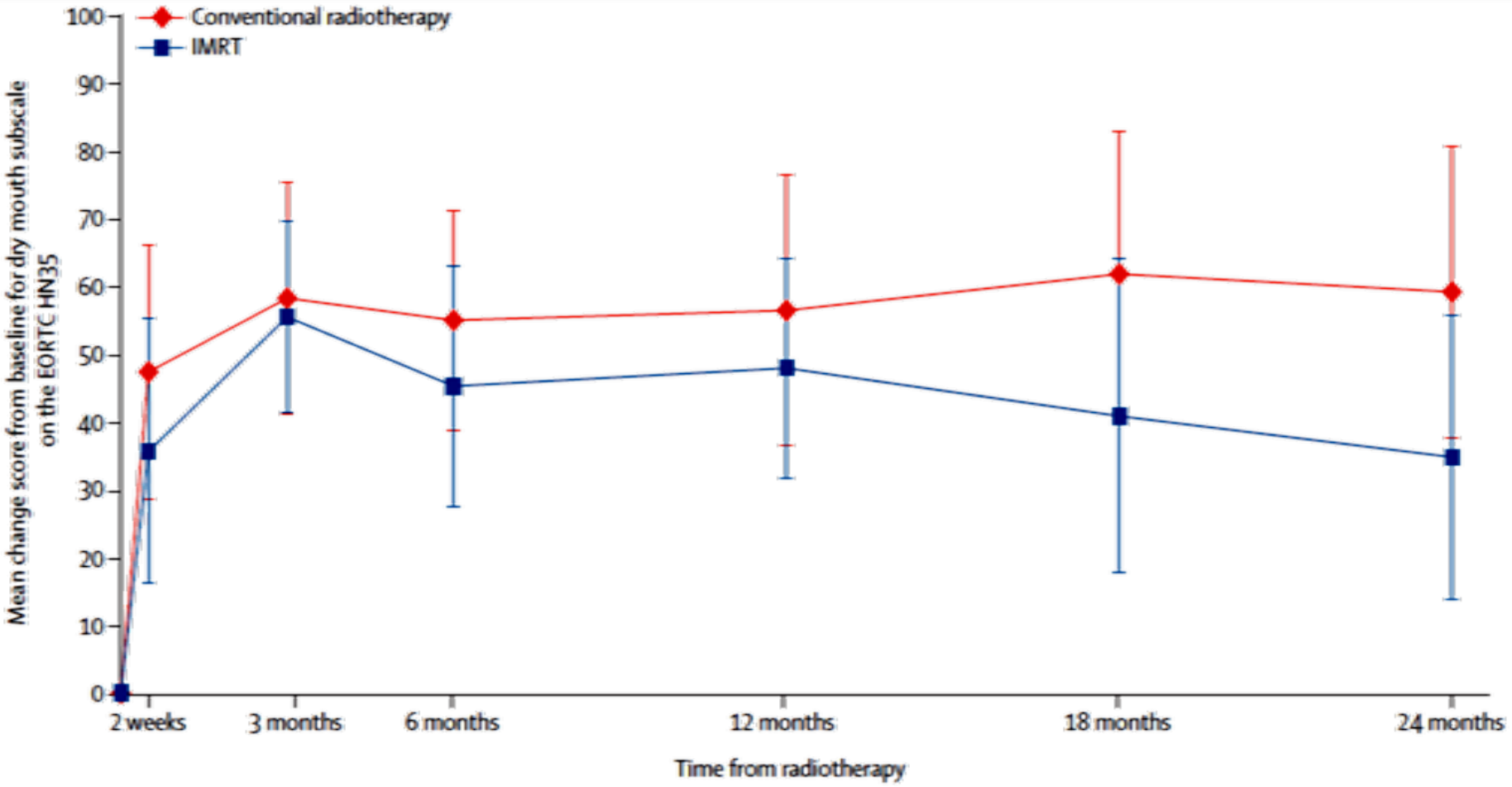

Conventional radiotherapy	26	24	23	23	21	18
IMRT	28	30	25	25	22	22
Difference in mean (99% CI)	11·7 (−14·4 to 37·8)	2·8 (−18·4 to 24·0)	9·7 (−13·5 to 32·9)	8·5 (−15·9 to 33·0)	21·0 (−8·9 to 50·9)	24·4 (−4·3 to 53·2)

Lancet Oncology. 2011;12:127-36.

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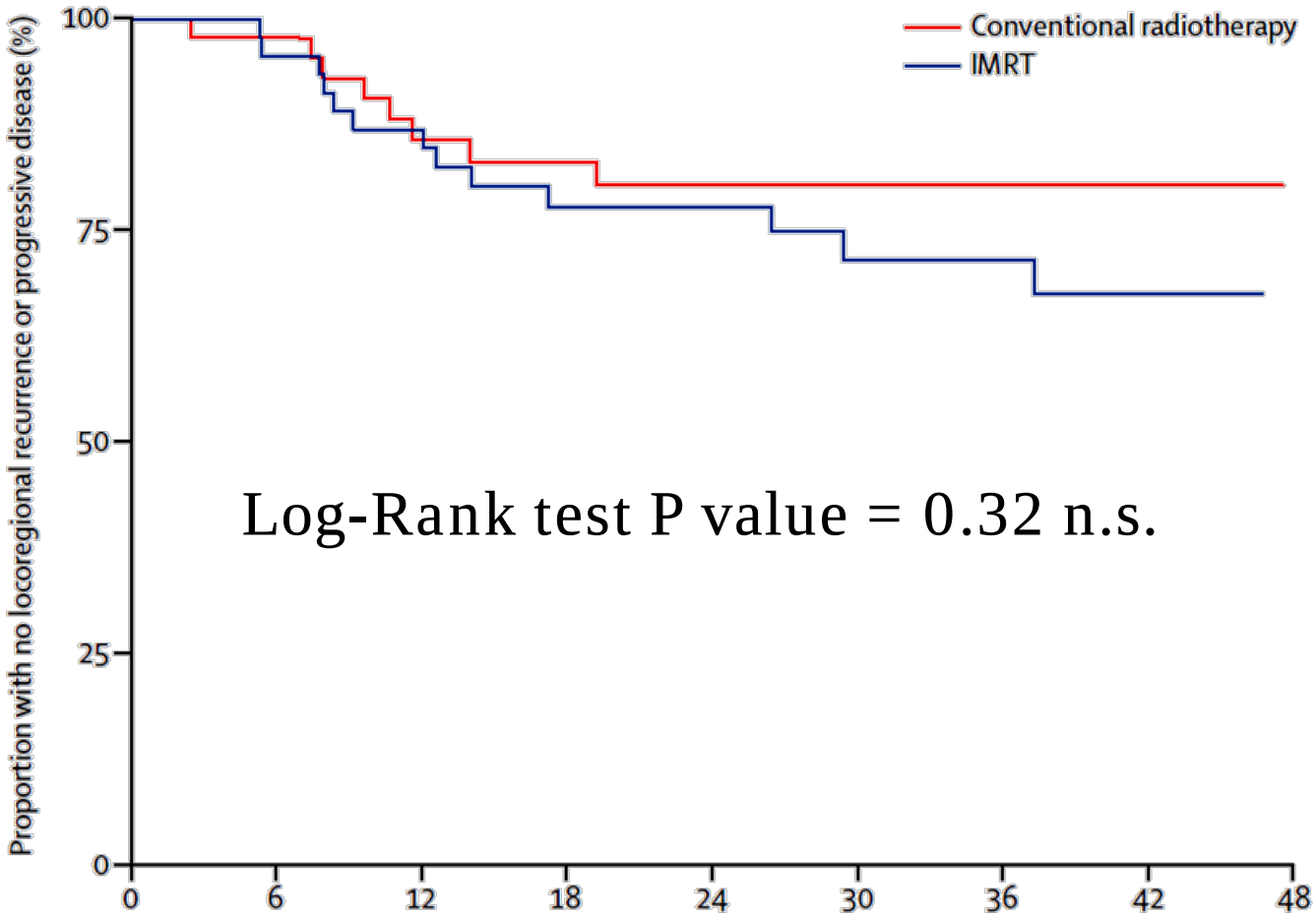

Log-Rank test P value = 0.32 n.s.

Number of events/at risk									
Conventional radiotherapy	0/47	1/42	5/34	1/30	1/29	0/23	0/19	0/15	0/8
IMRT	0/47	2/44	4/39	4/31	0/28	2/22	0/18	1/15	0/11

Lancet Oncology. 2011;12:127-36.

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Recommendations for IMRT use

1) If the **reduction of xerostomia** and improved quality of life are the main outcomes of interest, then **IMRT** is the **recommended** treatment

2) If **blindness** is to be minimized or avoided, **IMRT** is **indicated** in the definitive or adjuvant radiotherapy setting for nasal and paranasal sinus cancers

3) If **osteoradionecrosis** is to be minimized or avoided, **IMRT** is **indicated** in the definitive or adjuvant radio- therapy of tumours in the oral cavity, oropharynx, paranasal sinuses and nasopharynx

4) If **treatment-related outcomes** (local control, overall survival) are the main outcomes of interest, there are **no randomized data to support or refute a recommendation of IMRT** over two- or three-dimensional EBRT in any head and neck site

O'Sullivan, B., Rumble, R. B., & Warde, P. (2012). Intensity-modulated Radiotherapy in the Treatment of Head and Neck Cancer. Clinical Oncology, 24(7), 474–487

OARs constraints

- Create your workflow!
  - 1) Dose at PTV 70 Gy, Dmax to spinal cord
  - 2) Dose at PTV 54.25 Gy, Dmean to parotids
  - 3) Decide if spare only one parotid gland (controlateral to the tumor) or both
  - 4) (Un)balance the dose between the two parotids

OARs constraints

- Create your workflow:
  - Be careful of Hot Spots! (**Overall Dmax ≤ 110%**)
  - Find the location of hot spots (skull base is worse than neck base or PTV)

OARs constraints

- Parotid sparing: one or two?

Parameters for clinical outcome: Salivary glands

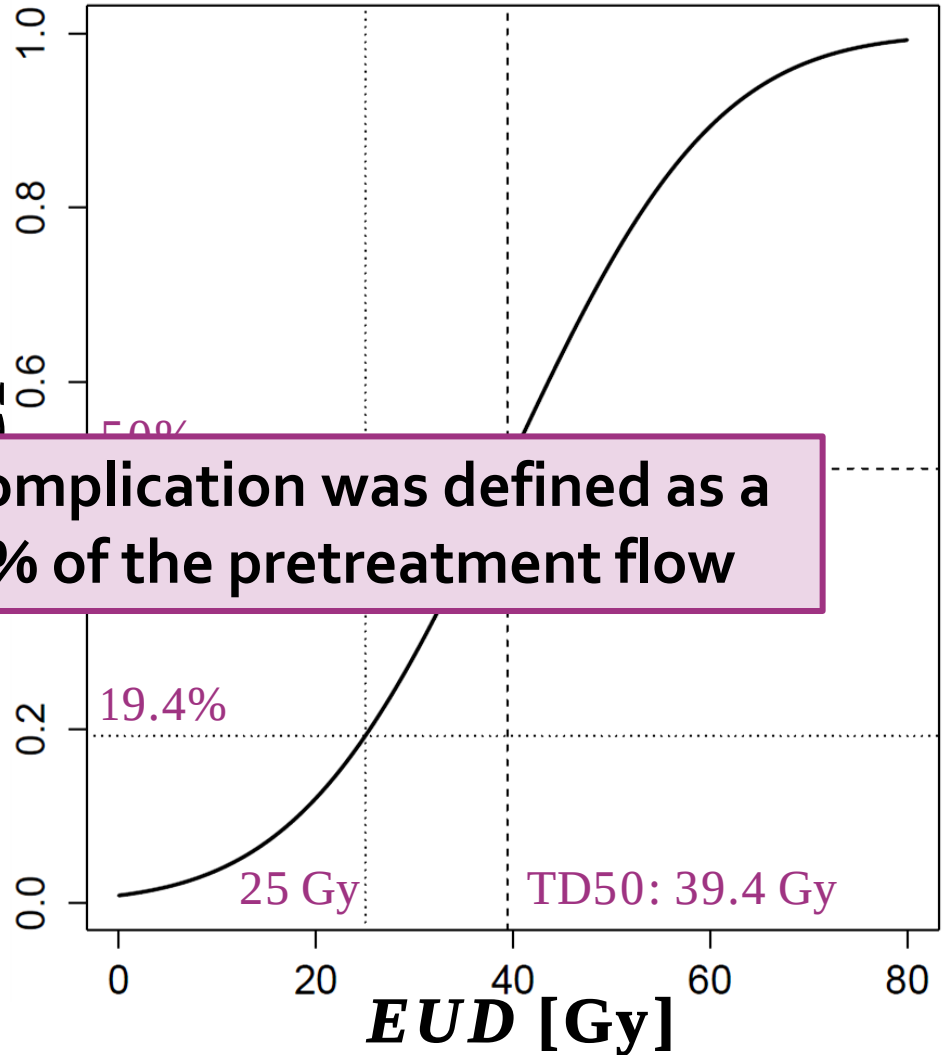
NTCP dose-response models evaluation for analysis of parotid gland function:

Table 2. Model parameters and goodness of fit values of the models

Model	Parameter	Value	95% CI	Δ_{LL}	Monte Carlo
LKB	n	1.13	0.75–14.25	340.63	0.51
	TD_{50}	39.4	33.8–41.8		
	m	0.42	0.36–0.58		
Mean dose	TD_{50}	39.9	37.3–42.8	339.19	0.59
	m	0.40	0.34–0.51		
Relative seriality	s	0.08	0.00–0.65	342.56	0.71
	TD	38.8	36.5–43.5		
Critic					
	N_{FSU}	219	18–298		
Parallel FSU	D_{50}	32.5	15.0–95.0	336.44	0.55
	k	2.75	0.50–4.50		
	TD_{50}	37.0	32.0–44.0		
	m	0.35	0.30–0.60		
V_{Dth}	D_{th}	30.5	25.0–37.0	342.98	0.58
	rdV_{50}	0.68	0.60–0.80		
	m	0.48	0.35–0.65		

Abbreviations: CI = confidence interval; Δ_{LL} = deviance.

For each individual parotid gland, a complication was defined as a reduction in salivary flow to below 25% of the pretreatment flow



Houweling AC et al. A comparison of dose-response models for the parotid gland in a large group of head-and-neck cancer patients. Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 4, pp. 1259–1265, 2010.

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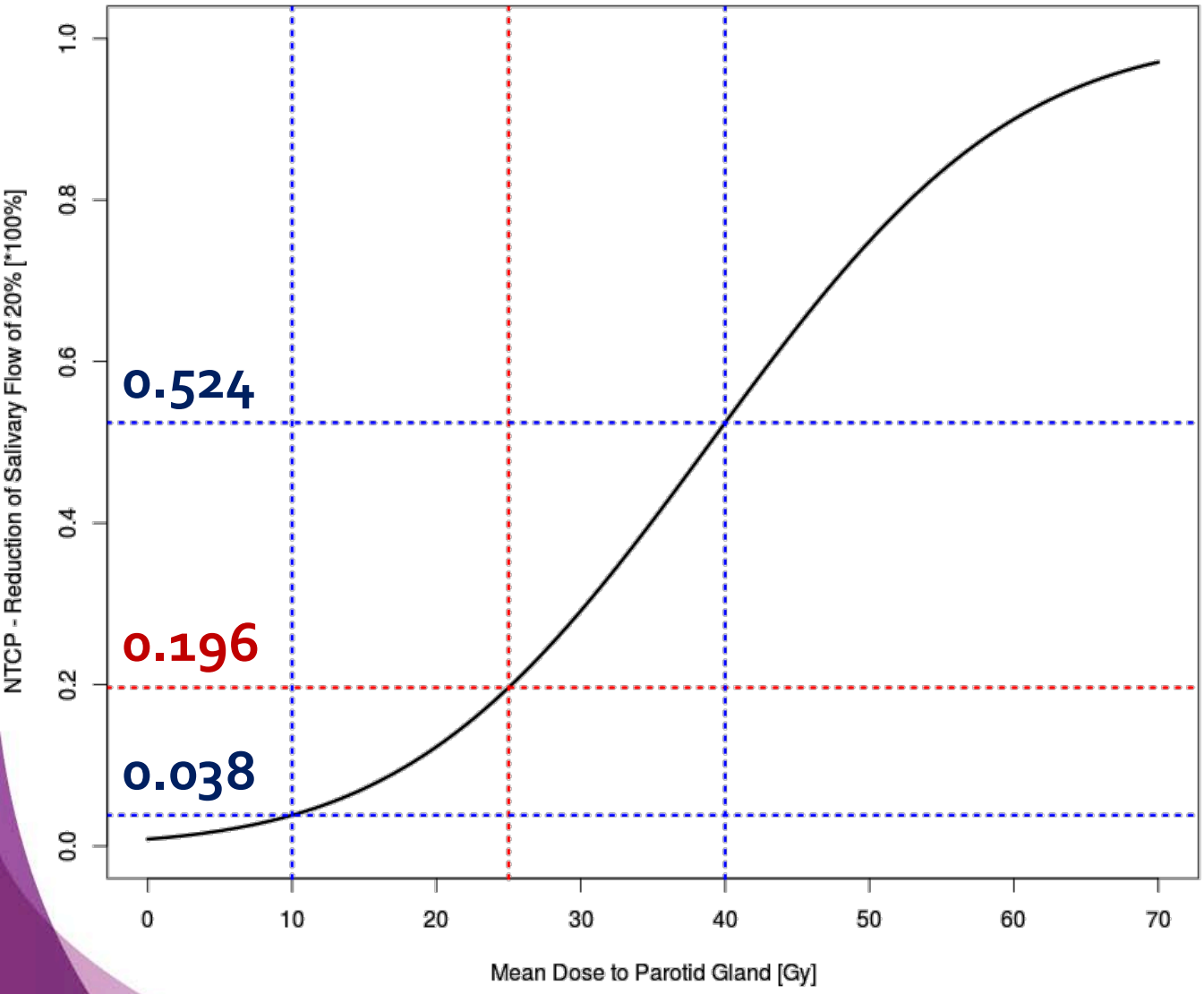
Mean dose to both parotids 25 Gy

Assumption: both parotid have the same volume



$NTCP_{asym}$ = 0.524 * 0.038 = 0.02

$NTCP_{sym}$ = 0.196 * 0.196 = 0.038

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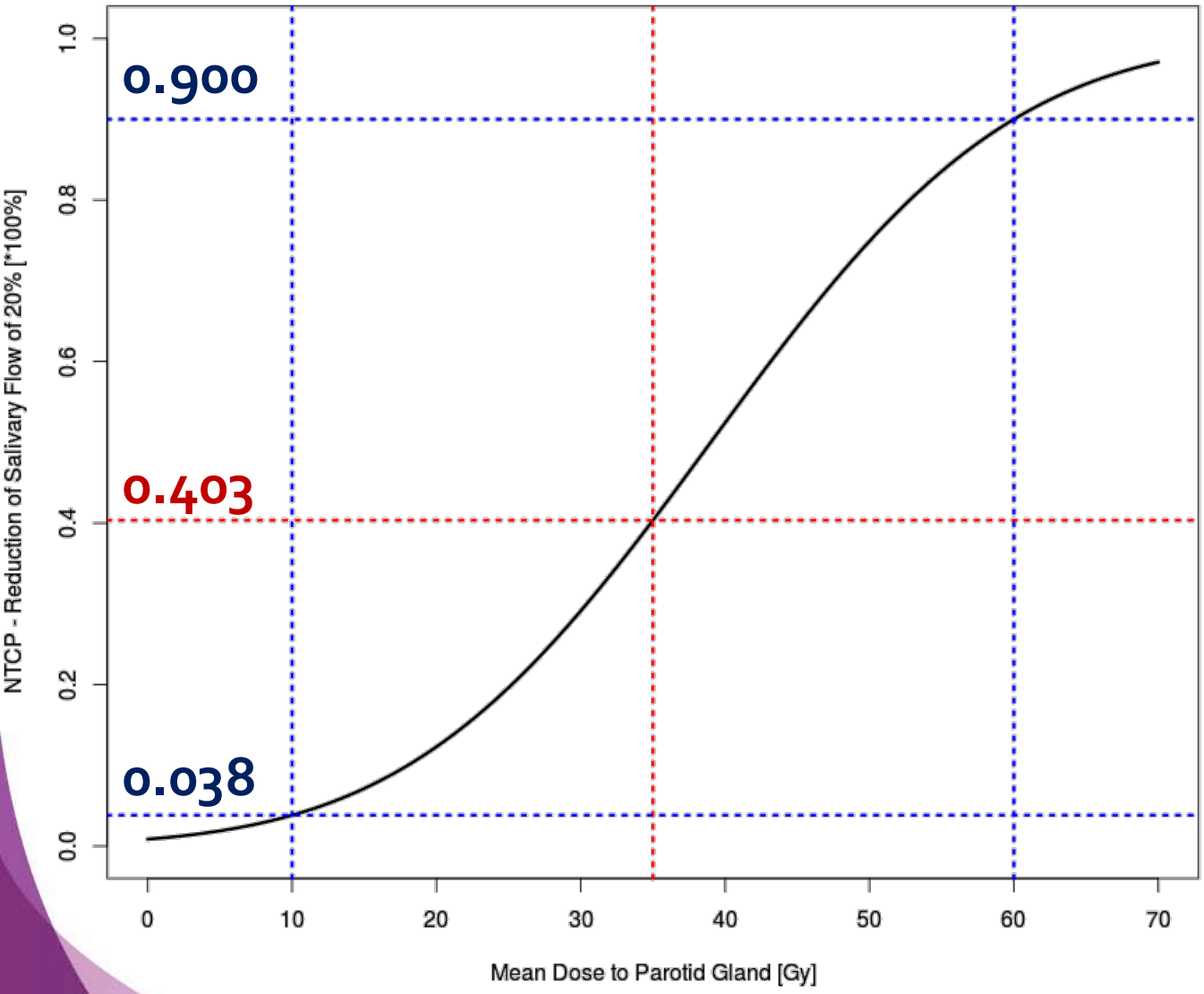
Mean dose to both parotids 35 Gy

Assumption: both parotid have the same volume



$NTCP_{asym}$= 0.900 * 0.038 = 0.034

$NTCP_{sym}$= 0.403 * 0.403 = 0.162

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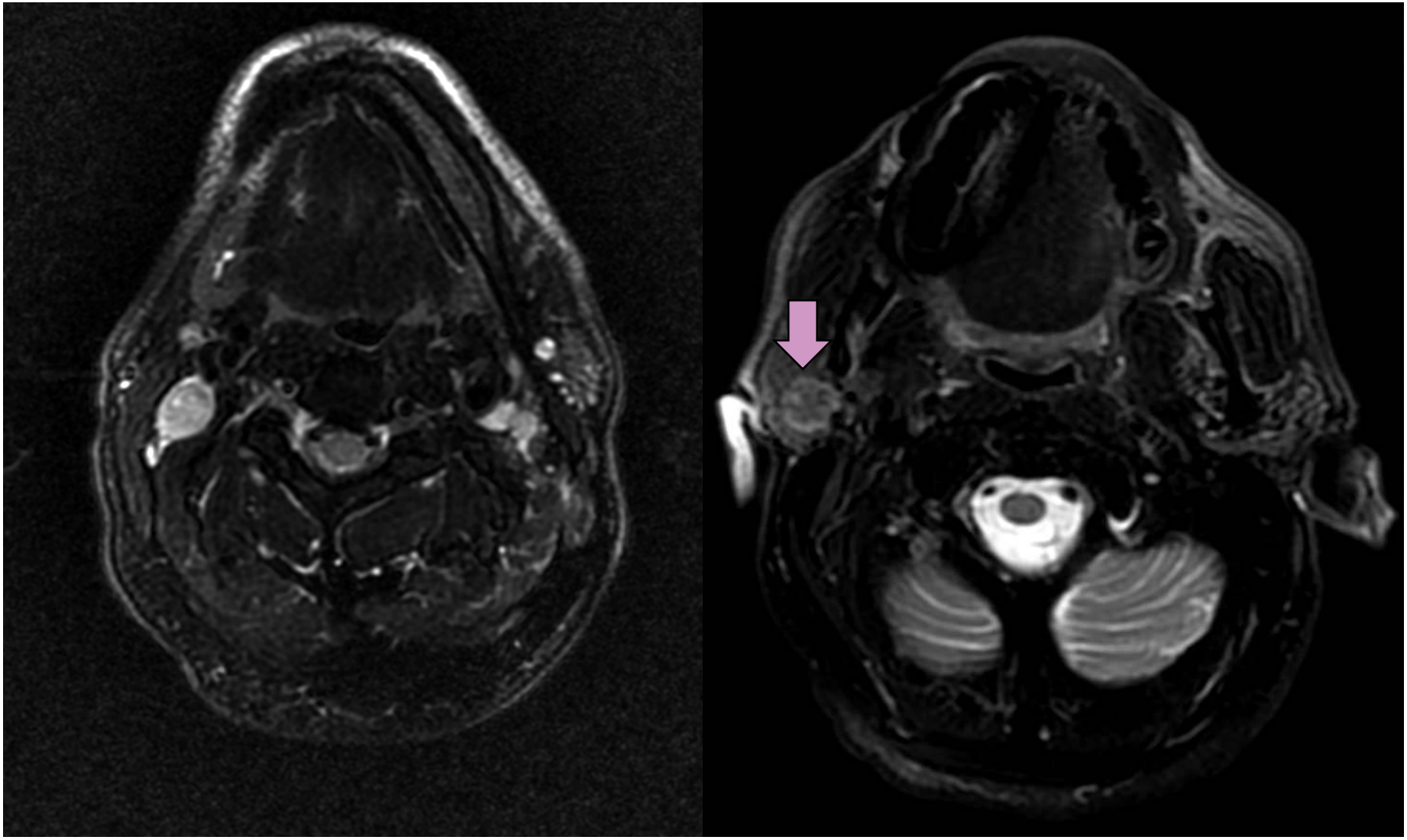
OARs constraints

- Parotid sparing: one or two?
  - Try both, if you get **Dmean > 25 Gy** on both try to sacrifice the omolater gland
  - In case of **bulky lymph nodes** involving one gland please sacrifice it (and try to spare the controlateral)

OARs constraints



N Dinapoli, R Autorino, et al. Recurrence in region of spared parotid gland in patient receiving defi nitive intensity-modulated radiotherapy for nasopharyngeal cancer: A case report. Acta Oncol. 2012 Apr 23.

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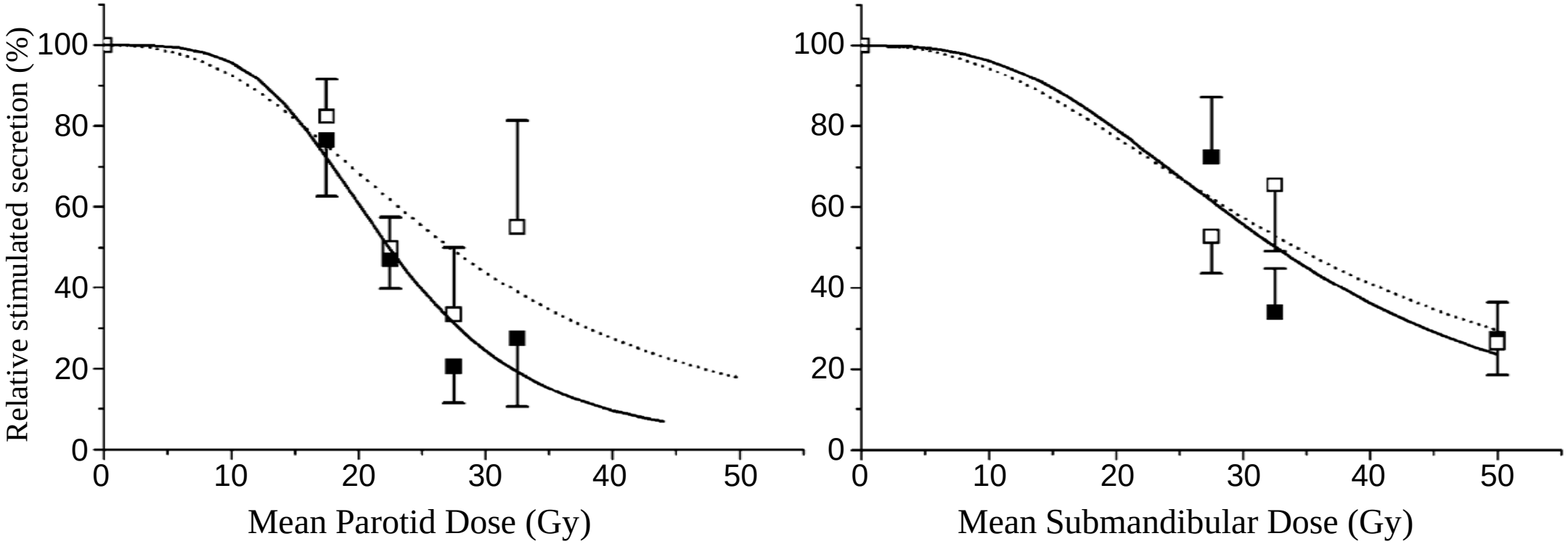
Parameters for clinical outcome: Salivary gland



K Saarilahtia et al. Sparing of the submandibular glands by intensity modulated radiotherapy in the treatment of head and neck cancer. Radiotherapy and Oncology, 78 (2006) 270–275.

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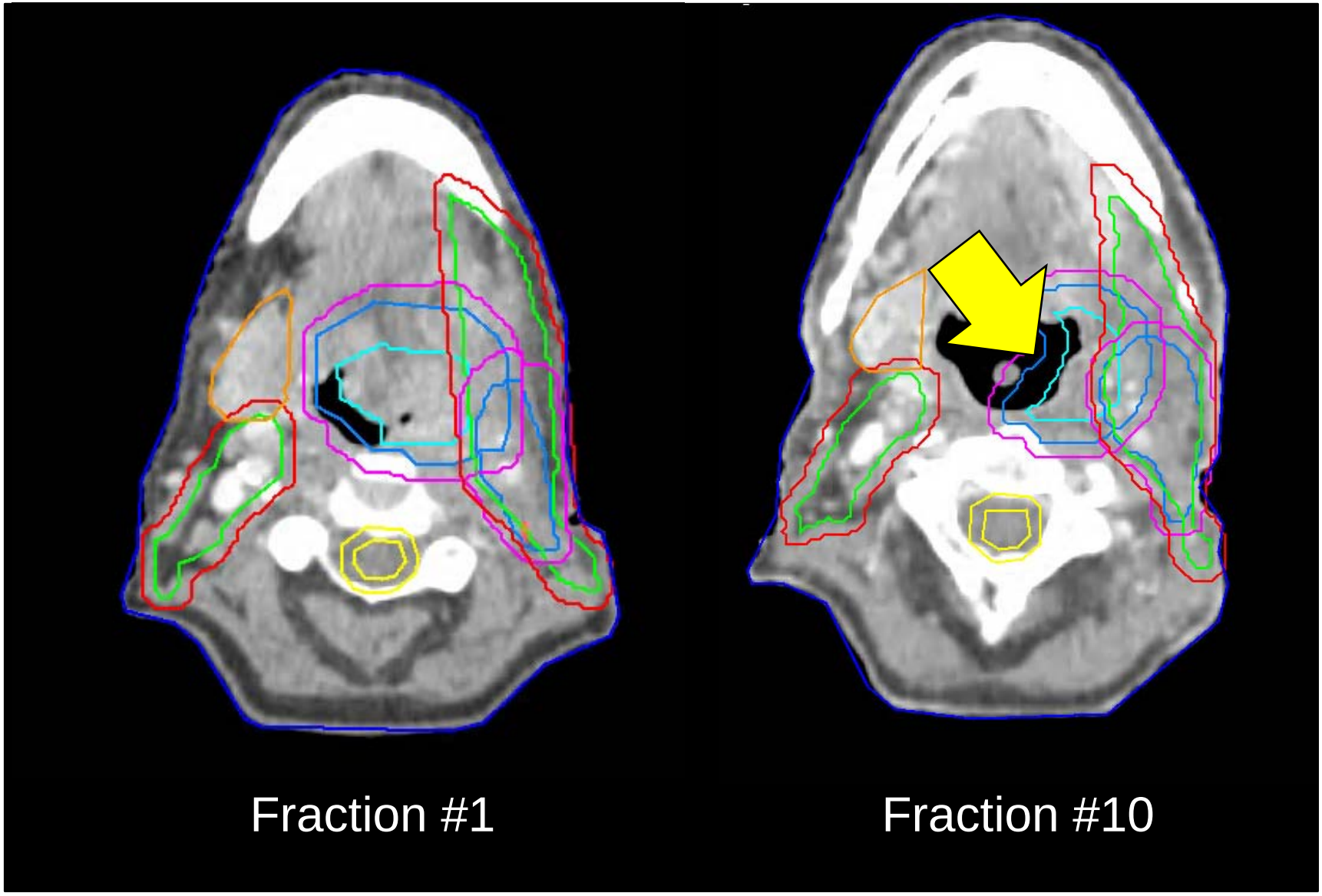
OARs constraints/objectives

- **Constraints (C), Objectives (O)**
- Spinal_Cord: Dmax <42 Gy (C)
- Spinal_Cord_03: <47 Gy (C)
- Parotid glands: both glands Mean Dose ≤25 Gy (O)
- single gland Mean Dose ≤39 Gy (O)
- Submand_R (not comprised in the PTV): as Parotid (O)
- Cochlea: Mean Dose ≤ 45 Gy (O)
- Brainstem: D1 cc < 55 Gy (C)

Replanning H&N IMRT patients



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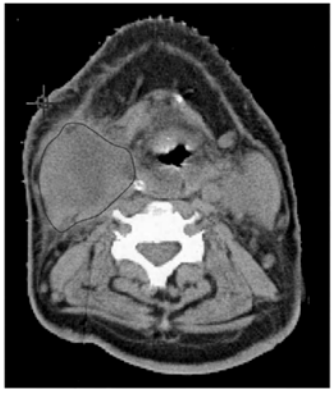
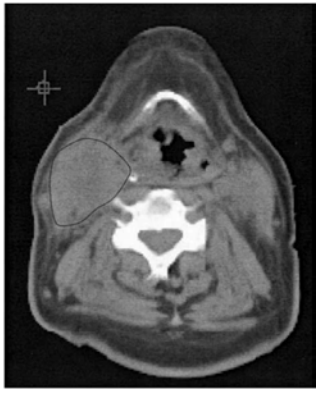
Replanning H&N IMRT patients

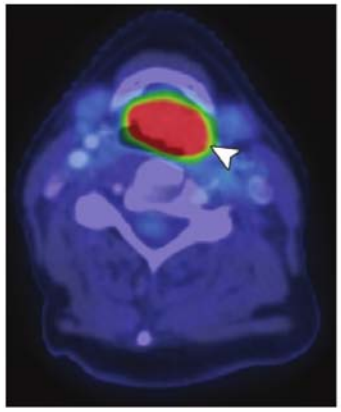


Planning CT

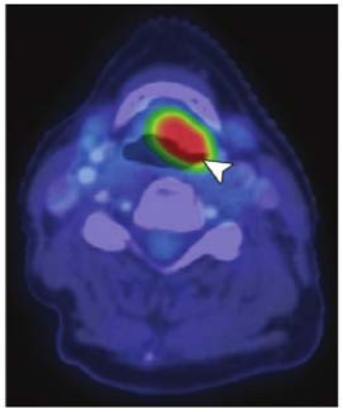


After 3 weeks

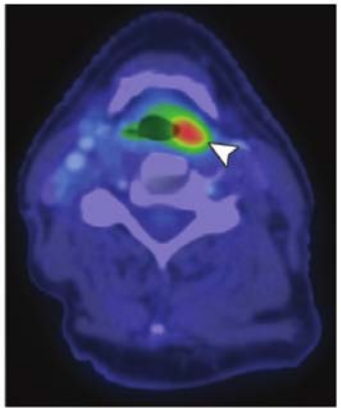
Barker, J. L. *et al.* Quantification of volumetric and geometric changes occurring during fractionated radiotherapy for head-and-neck cancer using an integrated CT/linear accelerator system. *Int. J. Radiat. Oncol. Biol. Phys.* **59,** 960–970 (2004).



Planning PET-CT



11 fractions later



21 fractions later

Bhatnagar, P., Subesinghe, M., Patel, C., Prestwich, R. & Scarsbrook, A. F. Functional imaging for radiation treatment planning, response assessment, and adaptive therapy in head and neck cancer. *Radiographics* **33,** 1909–29 (2013).

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Replanning H&N IMRT patients

- Causes of anatomy variations:
  - Tumor shrinkage
  - Weight loss (mucositis, reduced caloric intake)
  - Radiation induced anatomical changes (parotid glands)

- Significant variations for dose to OAR (generally increased)
- Variations of target coverage

Adaptive RT

Castadot, P., Lee, J. a., Geets, X. & Grégoire, V. Adaptive Radiotherapy of Head and Neck Cancer. Semin. Radiat. Oncol. 20, 84–93 (2010).

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Replanning H&N IMRT patients

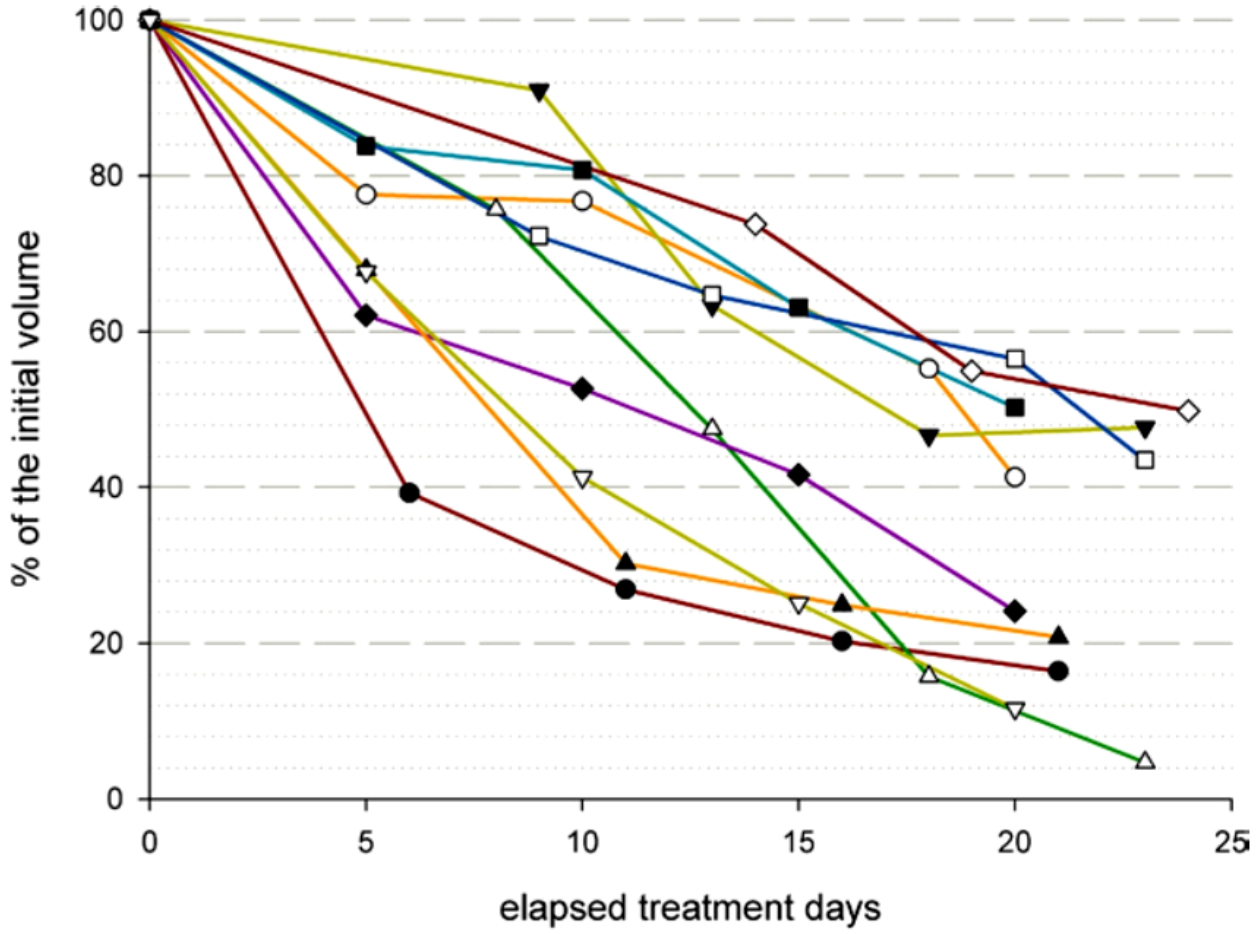

Figure 2 Volumetric changes in the primary tumor gross tumor volume (GTV) during treatment of pharyngolaryngeal tumors.

Castadot, P., Lee, J. a., Geets, X. & Grégoire, V. Adaptive Radiotherapy of Head and Neck Cancer. Semin. Radiat. Oncol. 20, 84–93 (2010).

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Author	No. of Patients	Per-Treatment Imaging	Image Registration	Volume Analysis	Shape and Positional Analysis
Barker et al (2004)[6]	14	In-room CT-on-rail 3 times/wk; no iv contrast	Rigid	Reduction of: • GTV: 1.8% per treatment day • PGs: 0.6%/treatment day	• GTV: COM displacement: 3.3 mm (asymmetric shrinkage) • PG: COM shift medially by 3.1 mm
Geets et al (2007)[50]	10	CT scan at mean doses of 14, 25, 35, and 45 Gy; iv contrast	Rigid	After a mean dose of 45 Gy: • GTV_T: mean decrease of 65.5% • High dose CTV_T: mean decrease of 50.9% • High dose PTV_T: mean decrease of 47.9%	NA
Han et al (2008)[43]	5	Daily helical MVCT	Rigid	At the end of treatment: PGs had decreased from 20.5 to 13.2 cm^3, ie, an average decrease of 0.21 cm^3/treatment day or 1.1%/treatment day	NA
Vasquez Osorio et al (2008)[51]	10	CT scan at 46 Gy; iv contrast	Deformable	Reduction after 46 Gy: • GTV: 25 ± 15% • Homolat PG: 17 ± 7% • Heterolat PG: 5 ± 4% • Homolat SMG: 20 ± 10% • Heterolat SMG: 11 ± 7%	After 46 Gy: • Lateral and inferior regions of homolat PG: medial and posterior shift (3 mm) • Homolat SMG: medial, cranial, and posterior shift (4 mm)
Hansen et al (2006)[52]	13	CT scan after a mean dose of 38 Gy	Rigid	Reduction: • GTV: no change • Right PG: 15.6% • Left PG: 21.5%	NA
Robar et al (2007)[53]	15	Weekly CT scans; no iv constrast	Rigid	Reduction of superficial regions of both PGs: 4.9%/wk	Superficial regions show medial translation of: left PGs: medial shift of 0.91 ± 0.9 mm/wk right PGs: medial shift of 0.78 ± 0.13 mm/wk
Castadot et al (2008)	10	CT scan at mean doses of 14, 25, 35, and 45 Gy; iv contrast	Deformable	Reduction of • GTV_T: 3.2%/treatment day • GTV_N: 2.1%/treatment day • Homolateral PG: 0.9%/treatment day • Heterolat PG: 1.0%/treatment day • Low dose homolat CTV_N: 0.5%/treatment day • low dose heterolat CTV_N: 0.4%/treatment day	After 5 treatment wks: • Homolat PG: medial shift of 3.4 mm • GTV_T: lateral shift of 1.3 mm • GTV_N: medial shift of 0.9 mm • Low dose homolat CTV_N: medial shift of 1.8 mm No shift for the heterolat PG and heterolat low dose CTV_N.

CT, computerized tomography; GTV, gross tumor volume; CTV, clinical target volume; PTV, planning target volume; PG, parotid gland; COM, center of mass; MV, mega-voltage; SMG, submandibular gland; homolat, homolateral; heterolat, heterolateral; CTV_T, primary tumor CTV; PTV_T, primary tumor PTV; CTV_N, nodal CTV; GTV_T, primary tumor GTV; GTV_N, nodal GTV; NA, not applicable.

Anatomical modifications

Castadot, P., Lee, J. a., Geets, X. & Grégoire, V. Adaptive Radiotherapy of Head and Neck Cancer. Semin. Radiat. Oncol. 20, 84–93 (2010).

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Author	No. of Patients	Per-Treatment Imaging	Image Registration	Results	Comments
O'Daniel et al (2007)[44]	11	In-room CT-on-rail scans twice/wk; no iv contrast	Deformable	Cumulative PG dose greater than planned; median dose increase: 1 Gy No impact on tumor dose coverage	If no image-guidance for daily setup error correction, cumulative PG dose greater than planned; median dose increase: 3 Gy for homolat PG and 1 Gy for heterolat PG
Hansen et al (2006)[52]	13	CT scan after a mean dose of 38 Gy	Rigid	• High dose PTV D_{99}, D_{95}, $V_{93\%}$ decreased by 12.1, 12.2 Gy, and 7%, respectively • Low dose PTV D_{99}, D_{95}, $V_{93\%}$ decreased by 12.6, 11.3 Gy, and 8.2%, respectively • Right PG V_{26Gy} increased by 10.9% • Mandible V_{60Gy} increased by 7.2%	If replanning; significant improvement of: • Low and high dose PTVs D_{99} D_{95} and $V_{93\%}$ • Spinal cord D_{max}, D_{1cc} • Brainstem D_{max} • Right parotid PG D_{mean}, D_{50}, and V_{26Gy} • Mandible D_{max} and V_{60Gy}
Robar et al (2007)[53]	15	Weekly CT scan; no iv contrast	NA	• Left PG D_{mean} increased by 2.6 ± 4.3%, V_{26Gy} increased by 3.5 ± 5.2% • Right PG D_{mean} increased by 0.2 ± 4.0%, V_{26Gy} increased by 0.3 ± 4.7%	
Han et al (2008)[43]	5	Daily helical MVCT	Rigid	PG D_{median} increased from 0.83 to 1.42 Gy with an average increase rate of 0.17 Gy/treatment day corresponding to an average increase of 2.2%/treatment day	Strong correlation between the volume and the median parotid dose during the treatment (correlation coefficient, −0.95)
Lee et al (2008)[56]	10	Daily helical MVCT	Deformable	• PG daily D_{mean} differed from the planned dose by an average of 15% • PG cumulative D_{mean}: planned: 29.7 Gy actual: 32.7 Gy (110% of planned dose)	• Changes in the distance between the COMs of the left and right PGs correlated strongly with the mean parotid dose changes (R^2 = 0.88) • Correlation between the relative weight loss and higher parotid mean doses (R^2 = 0.58)
Castadot et al (2009)	10	CT scan at mean doses of 14, 25, 35, and 45 Gy; iv contrast	Deformable	• PGs D_{mean}: planned: 17.9 Gy, actual 18.7 Gy • SMGs D_{mean}: planned 51.9 Gy, actual: 52.8 Gy • OC D_{mean}: planned 26.0 Gy, actual 26.7 Gy • SC D_2: planned 40.1 Gy, actual: 41.0 Gy • Skin V_{60}: planned 17.2 Gy, actual 18.3 Gy • No difference in PTV or CTV coverage	

OC, oral cavity; SC, spinal cord; D_x, dose to x% of the volume; D_{max}, maximum dose; D_{1cc}, dose to 1 cc.; D_{mean}, mean dose; D_{median}, dose to 50% of the volume; V_x, volume receiving a dose of x Gy or x% of the prescribed dose.

Dosimetric modifications

Castadot, P., Lee, J. a., Geets, X. & Grégoire, V. Adaptive Radiotherapy of Head and Neck Cancer. Semin. Radiat. Oncol. 20, 84–93 (2010).

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Patient monitoring: challenges for replanning

- **Single institutions** papers
- Average number of patients **11.1**!
- **Different imaging** equipments
  - (2 CT on rail, 2 MV CBCT, 7 Kv CT)
- **Different registration** techniques
  - (8 rigid, 2 deformable, 1 NA)
- Completely **different timings** for imaging acquisition!
  - (from one acquisition at a given dose level up to daily CBCT)

Patient monitoring: challenges for replanning

- **Take home messages:**
- **Do replanning**
- At least once during the treatment
- Most important changes occur after before 2nd, 3rd treatment week (20 – 30 Gy delivered dose)
- Consider monitoring weight loss or additive risks (mucositis, chemo, absence of feeding tube)

Good work!!!

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Adaptive Re-Planning for Head and Neck

Advanced Treatment Planning Course

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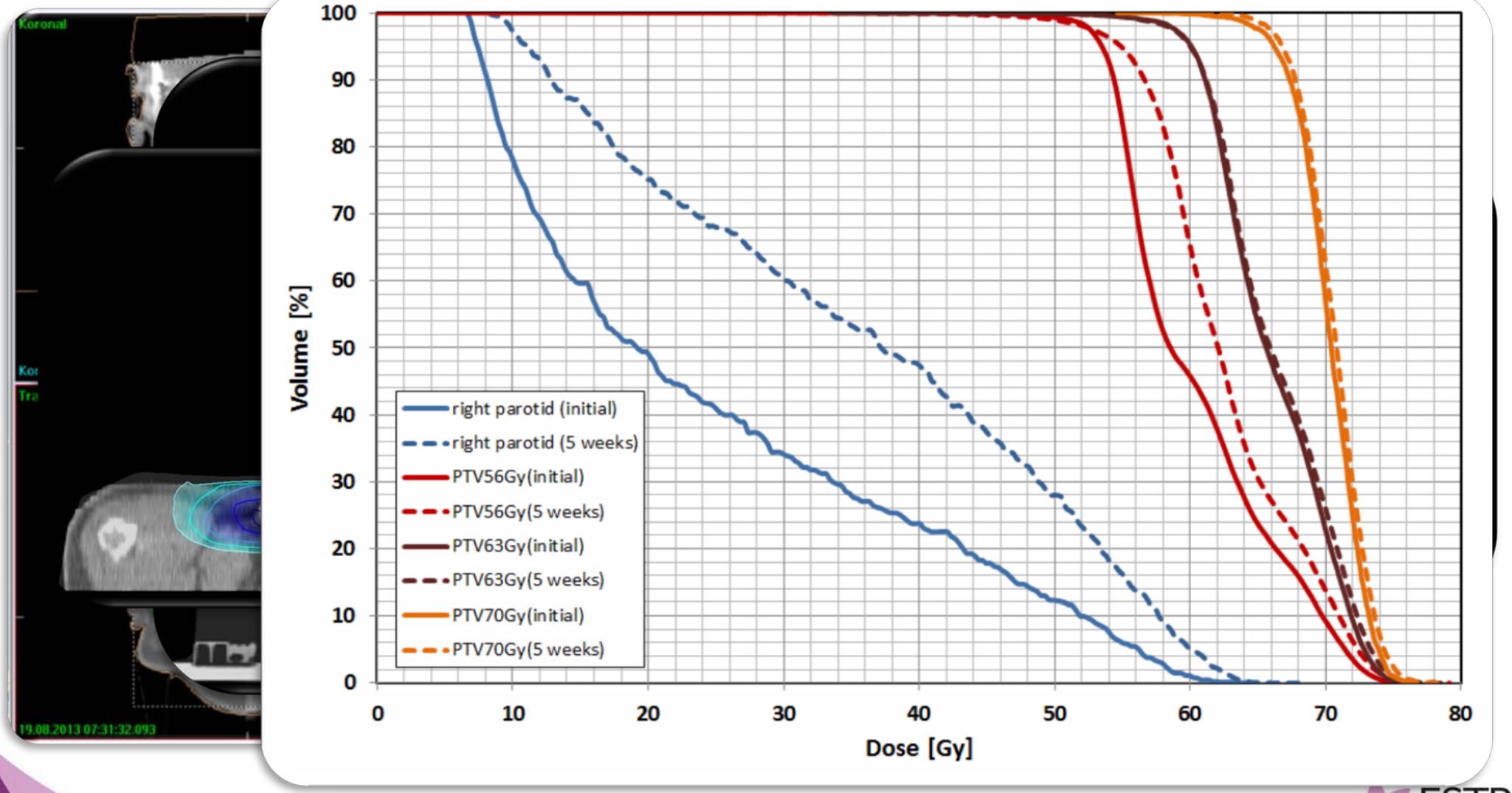
Clinical example

- After five weeks of treatment



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Conventional IGRT Workflow

Imaging

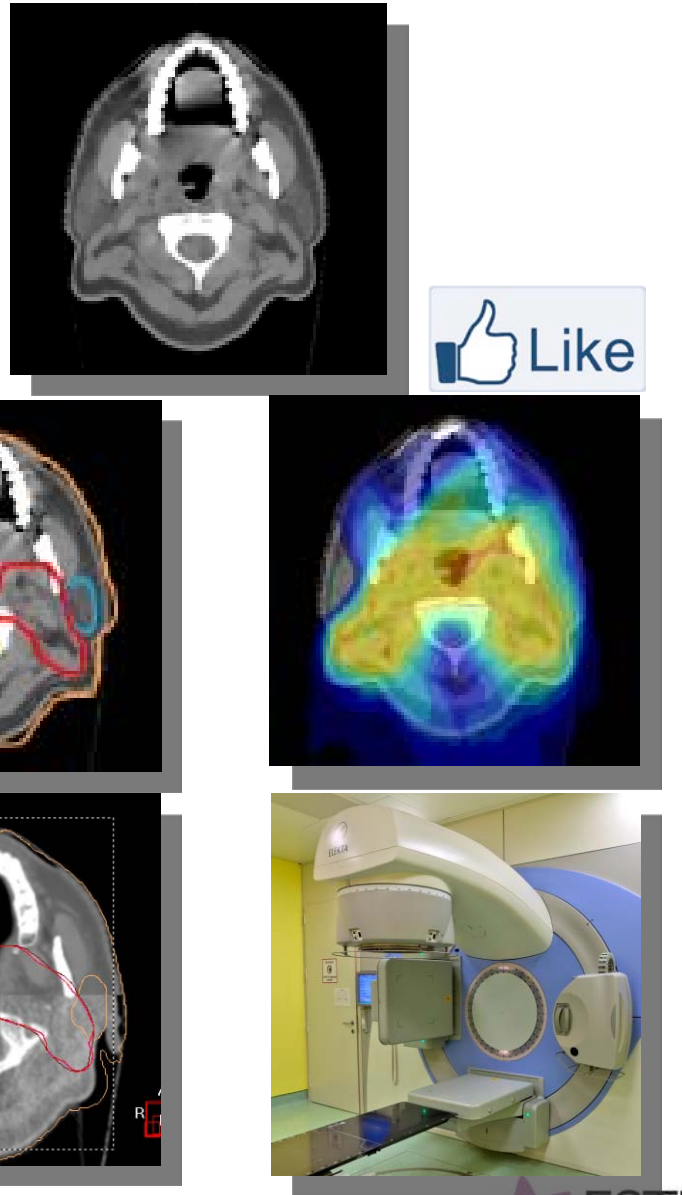
CT | MR, PET

Planning

Contours | Dose

Treatment

Imaging | Dose Application



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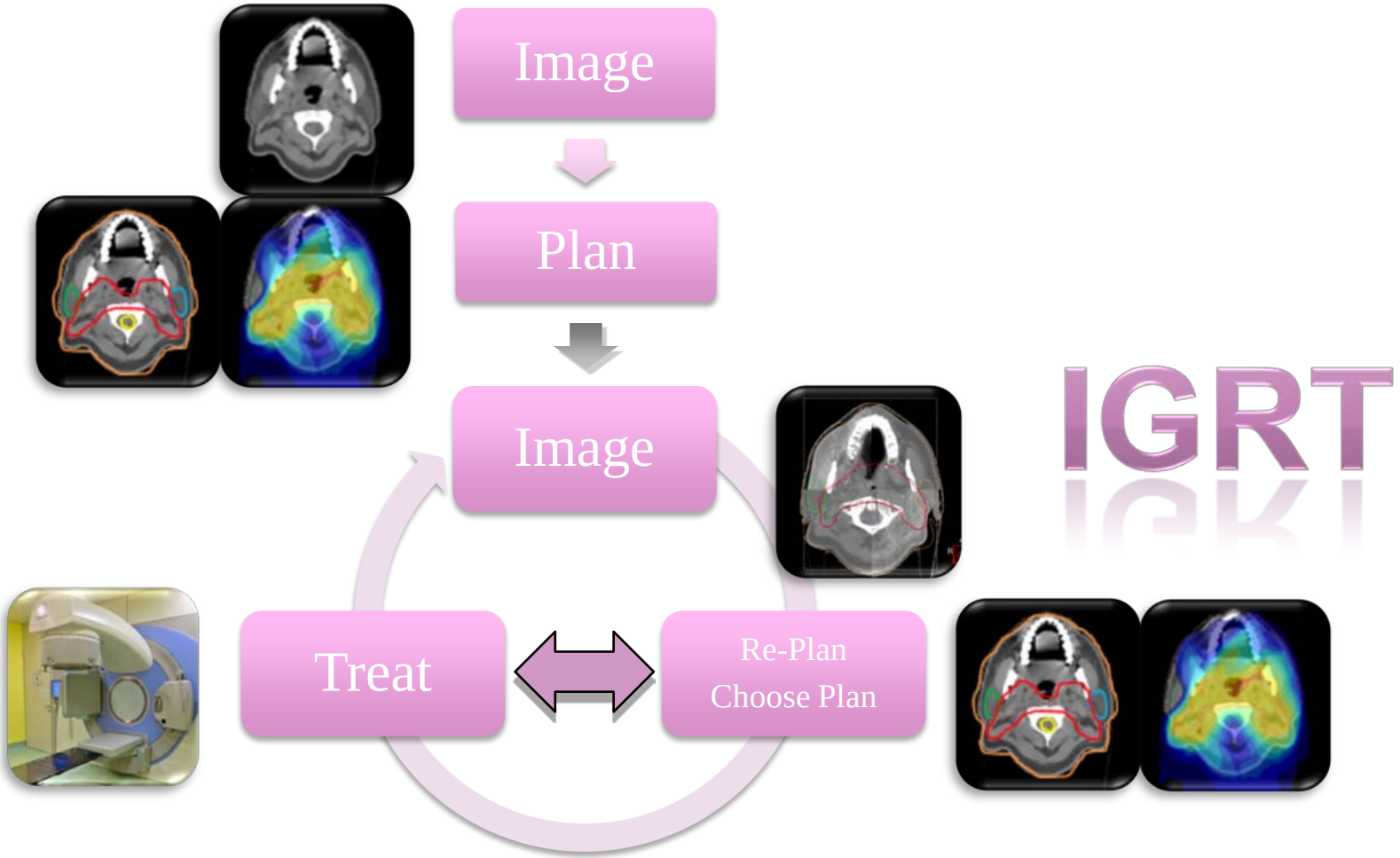
IGART Workflow/Closed loop principle



Decades old concept, but technical limitations have held back integration of ART into routine care → staff input must be replaced by automated processes to make IGART practical

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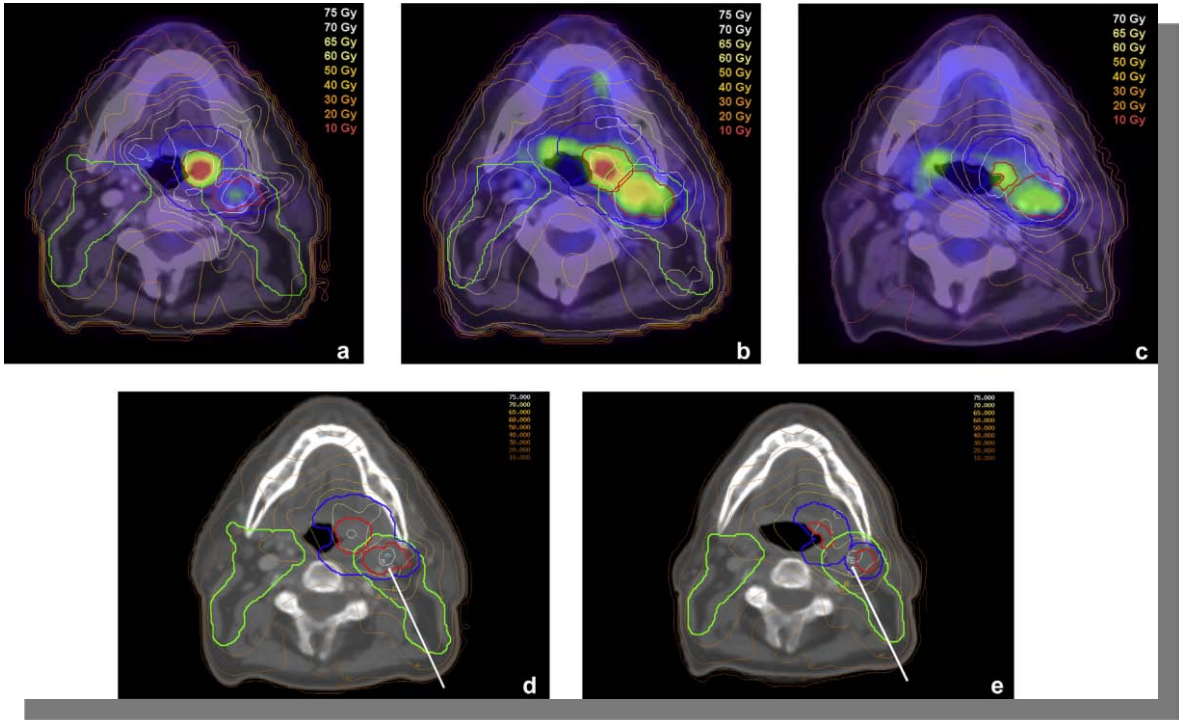
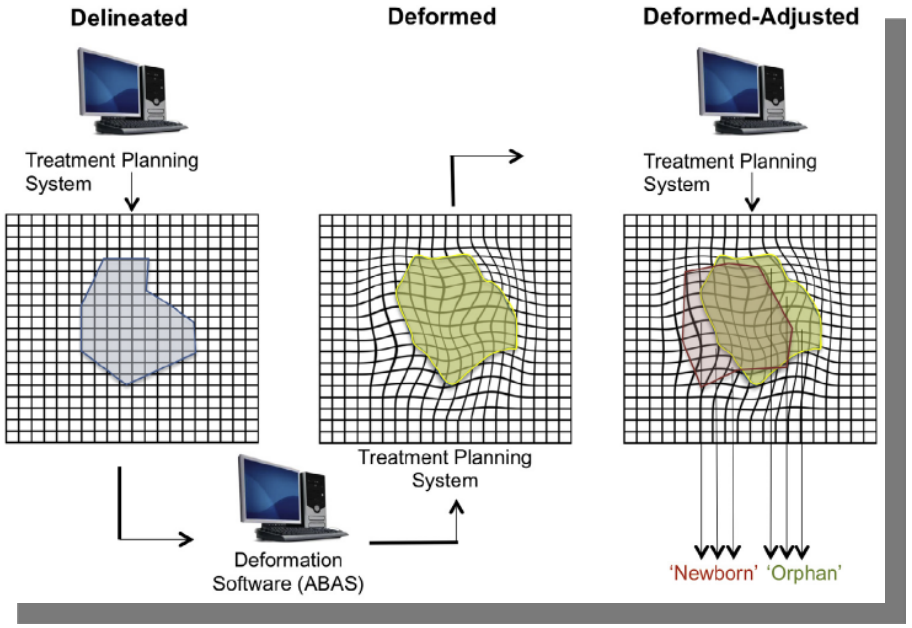
How to finally evaluate?

- Dose accumulation needed for
  - Plan library, PTV adaptation, offline/online re-planning
  - Deformation field necessary, more accurate dose-effect expected





Berwouts et al – Radiother Oncol 2013

- Realtime re-planning even more sophisticated

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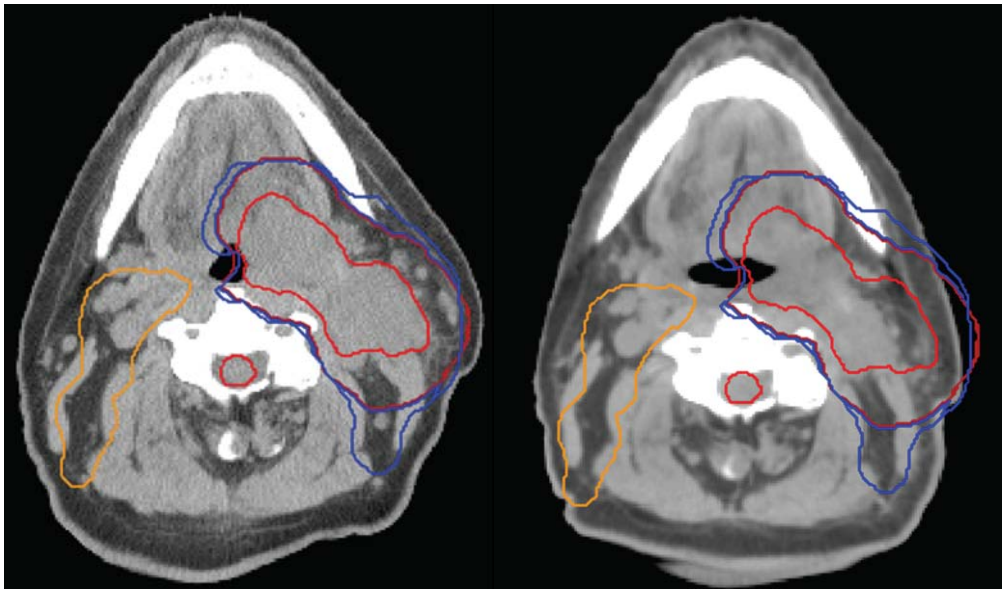
ART for head and neck cancer

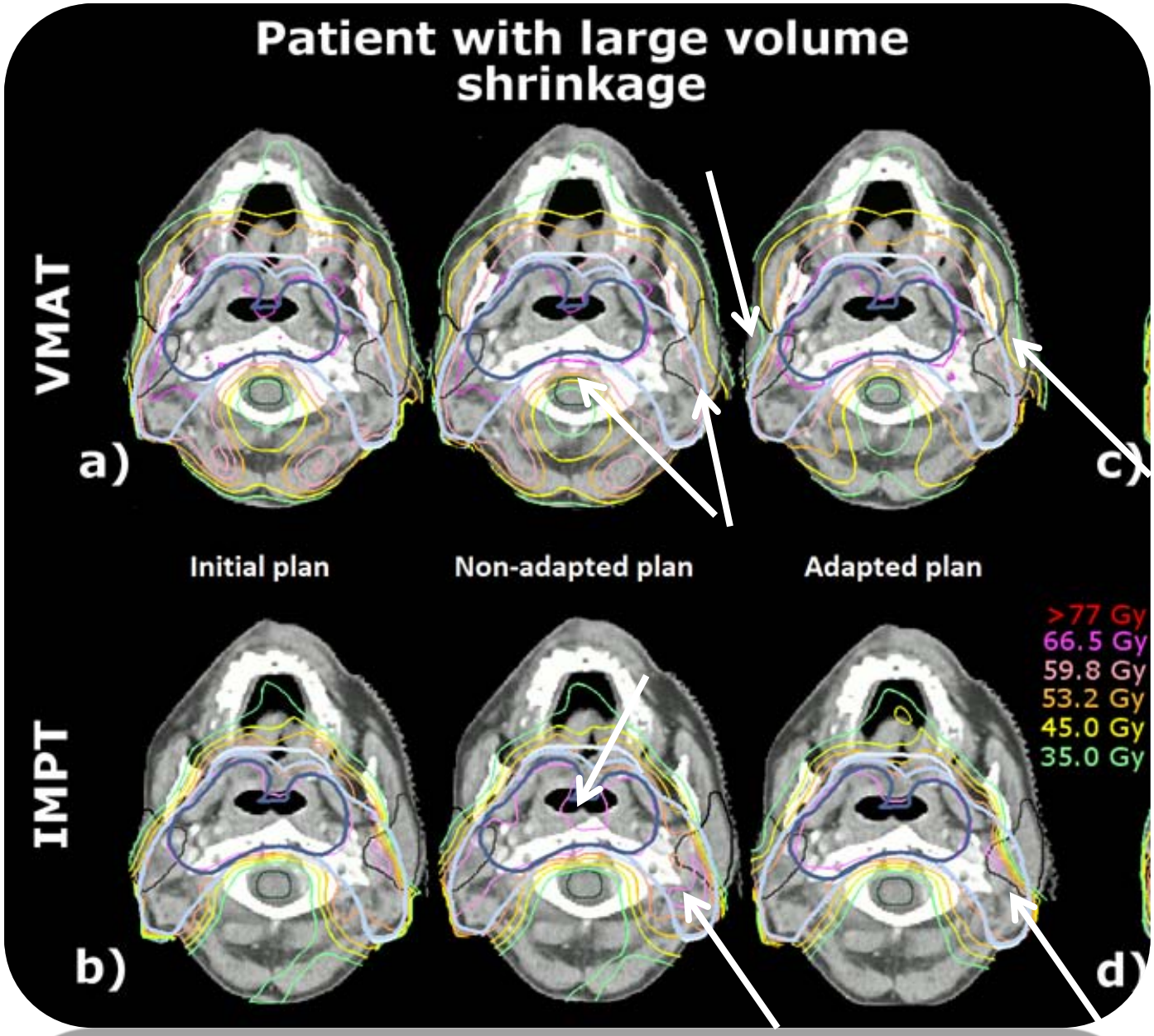
- decrease in weight (avg 7%), tumour volume, OAR
- E.g. parotid gland
  - Shrinkage 1% per day
  - Displacement 3–4 mm (up to 1 cm) at end of treatment toward mid-sagittal plane



Schwartz et al, J Oncol 2011

- E.g. nodal and primary-tumour
  - 2–3% per treatment day (up to 90%)

Results - adaptation vs non-adaptation



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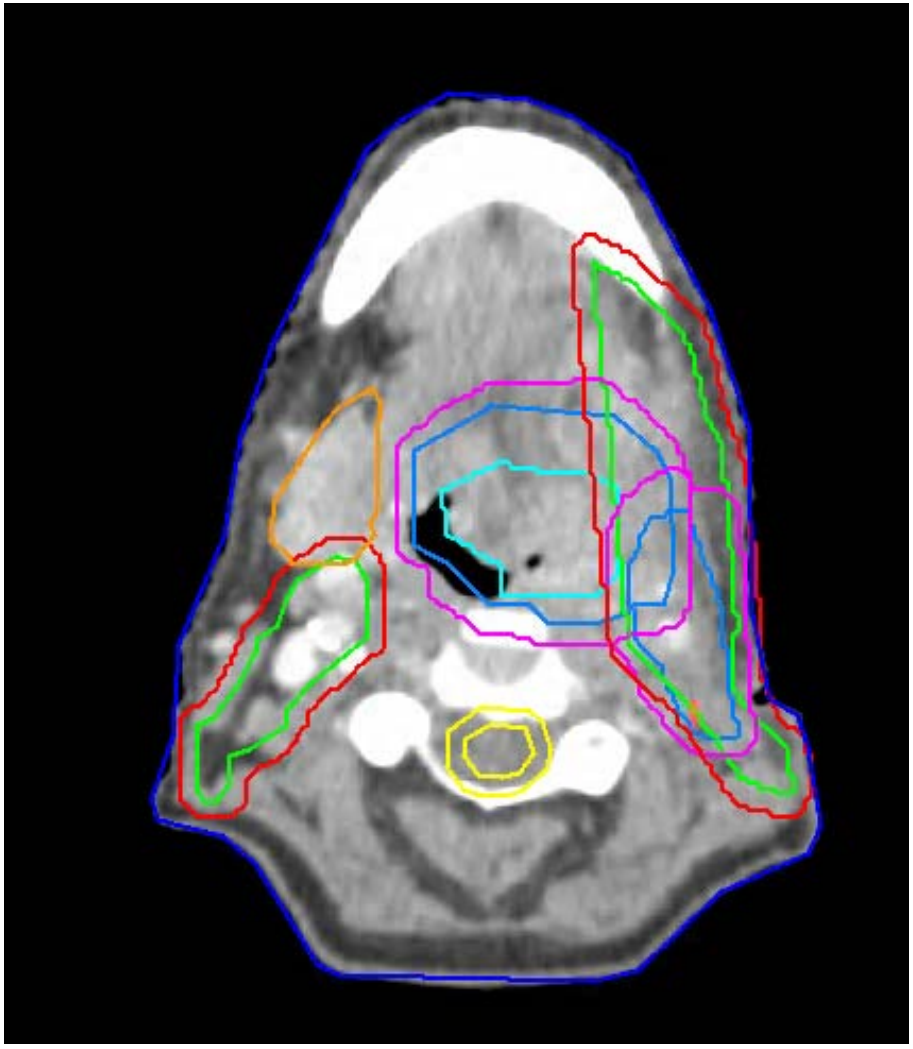
H&N case

- Number of beams?? ……. at least 7? or VMAT? Single arc? Energy?



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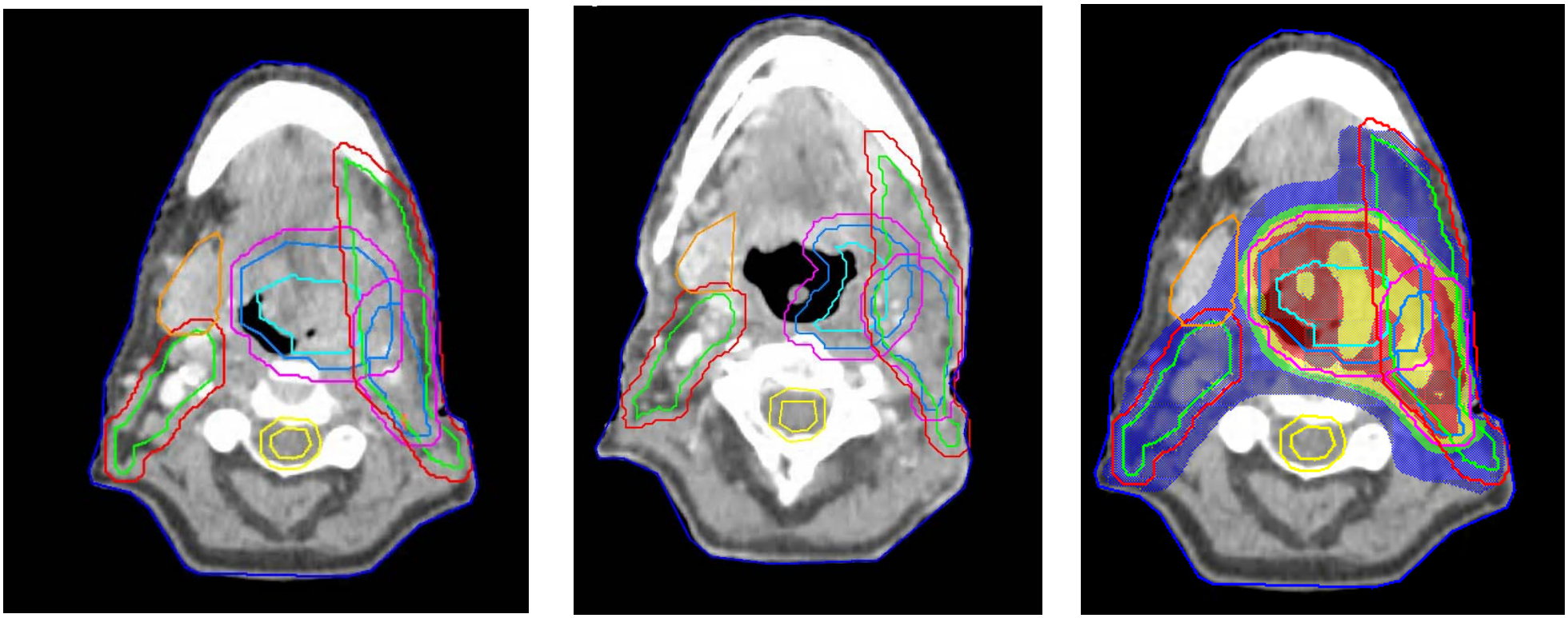
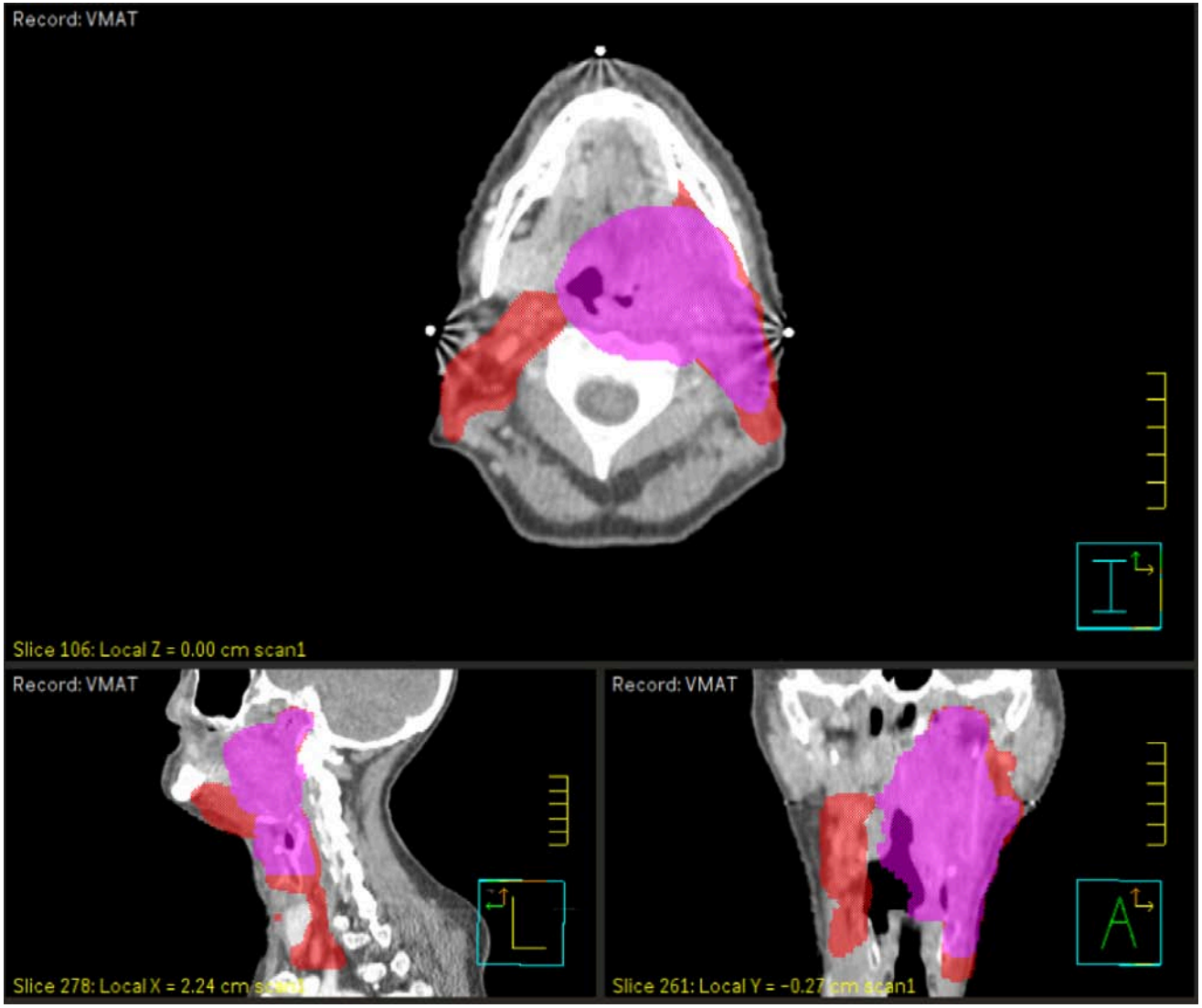
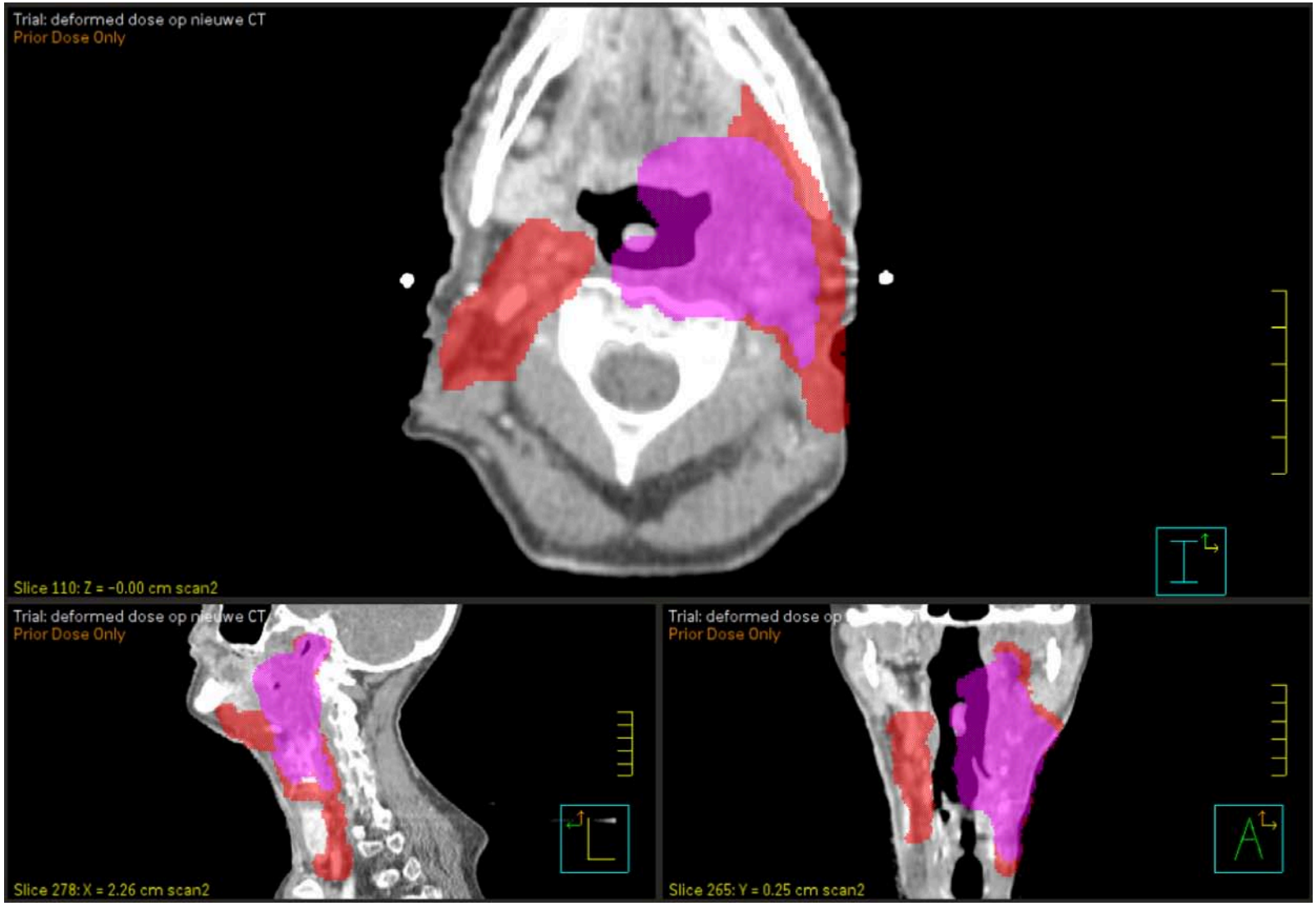
Control Scan after 10 fractions



CT1 + originial ROIs



CT2 + new ROIs



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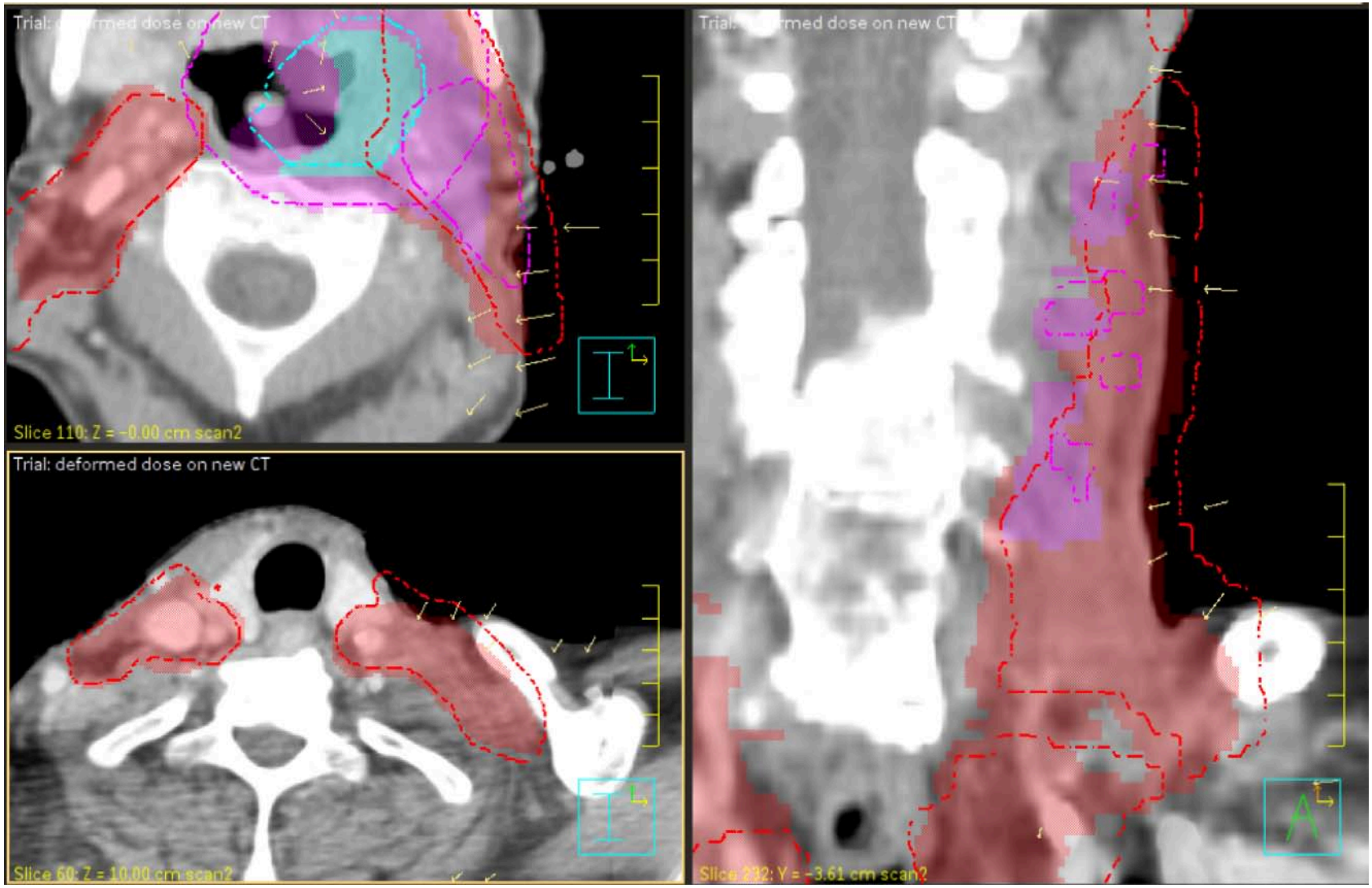
Deformations



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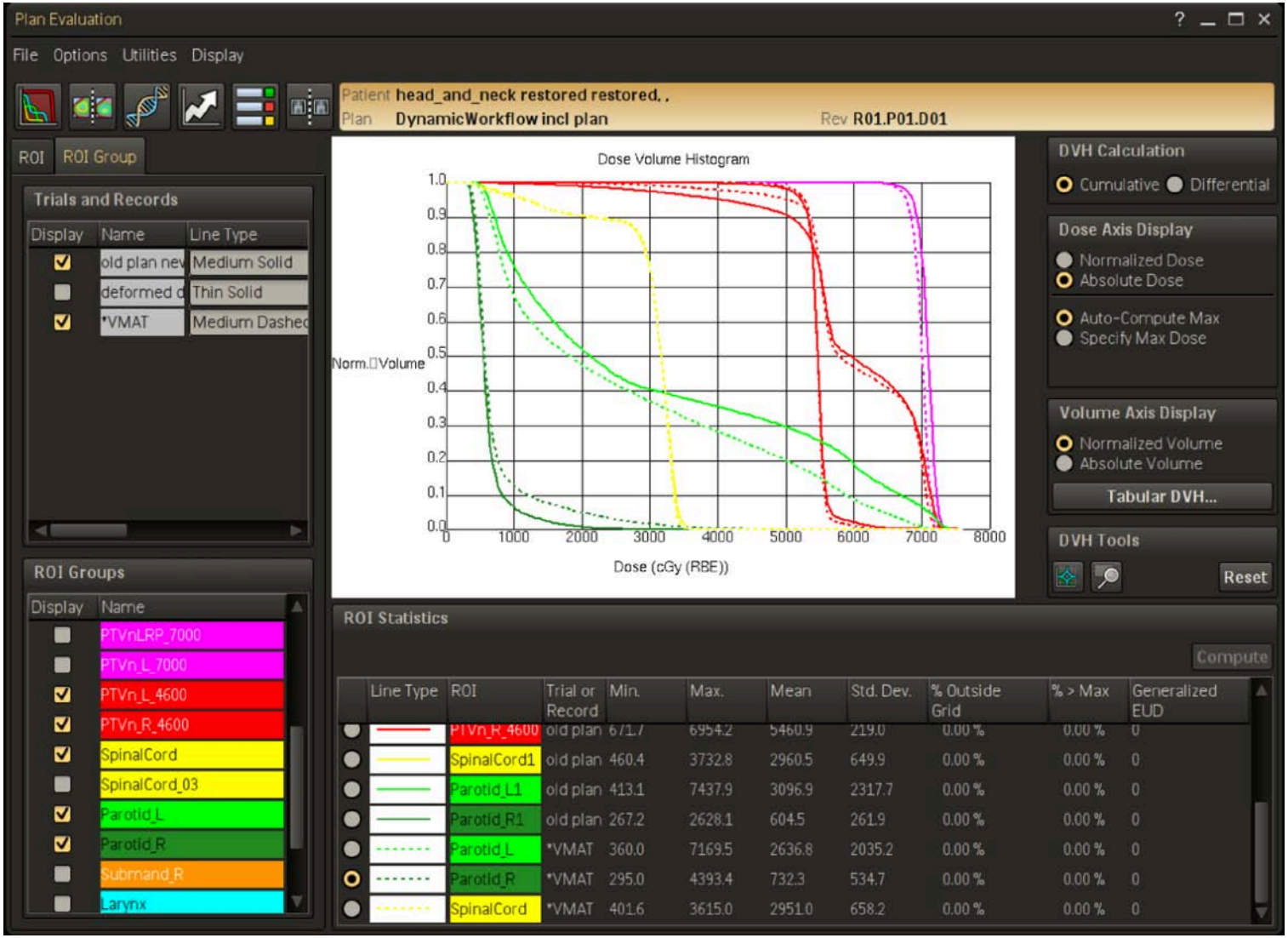
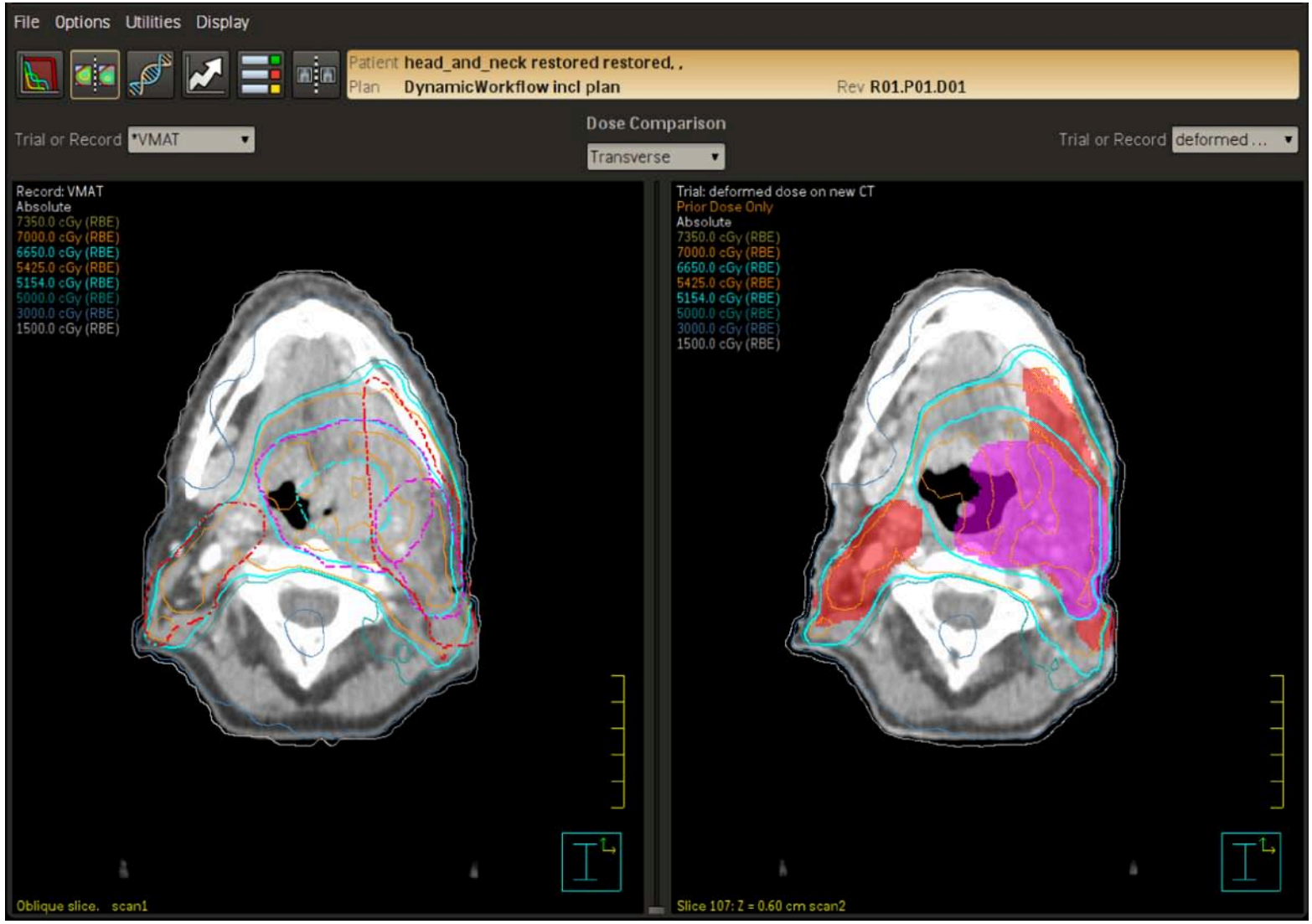
Initial plan on CT1&2



Deformed dose on CT2



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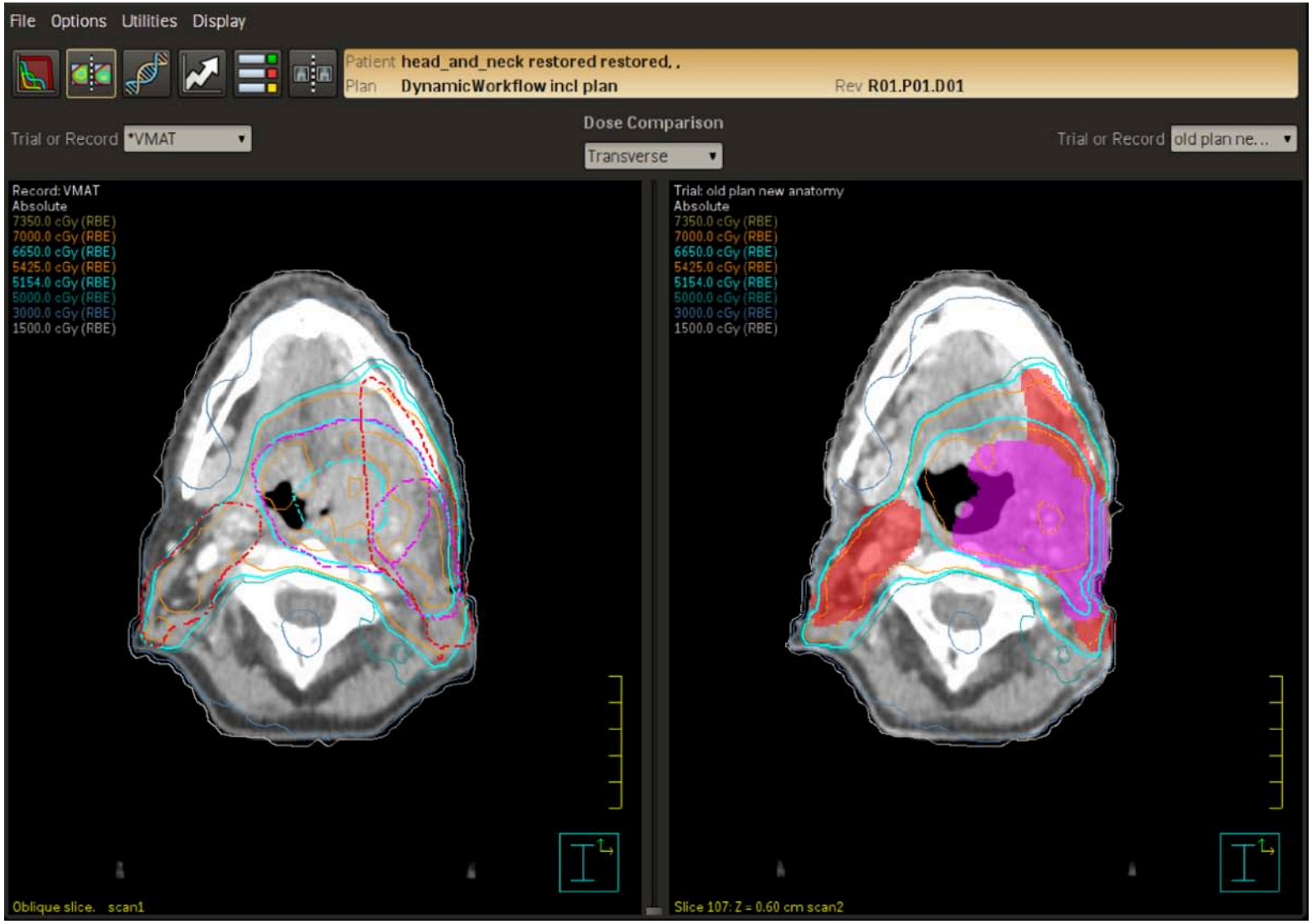
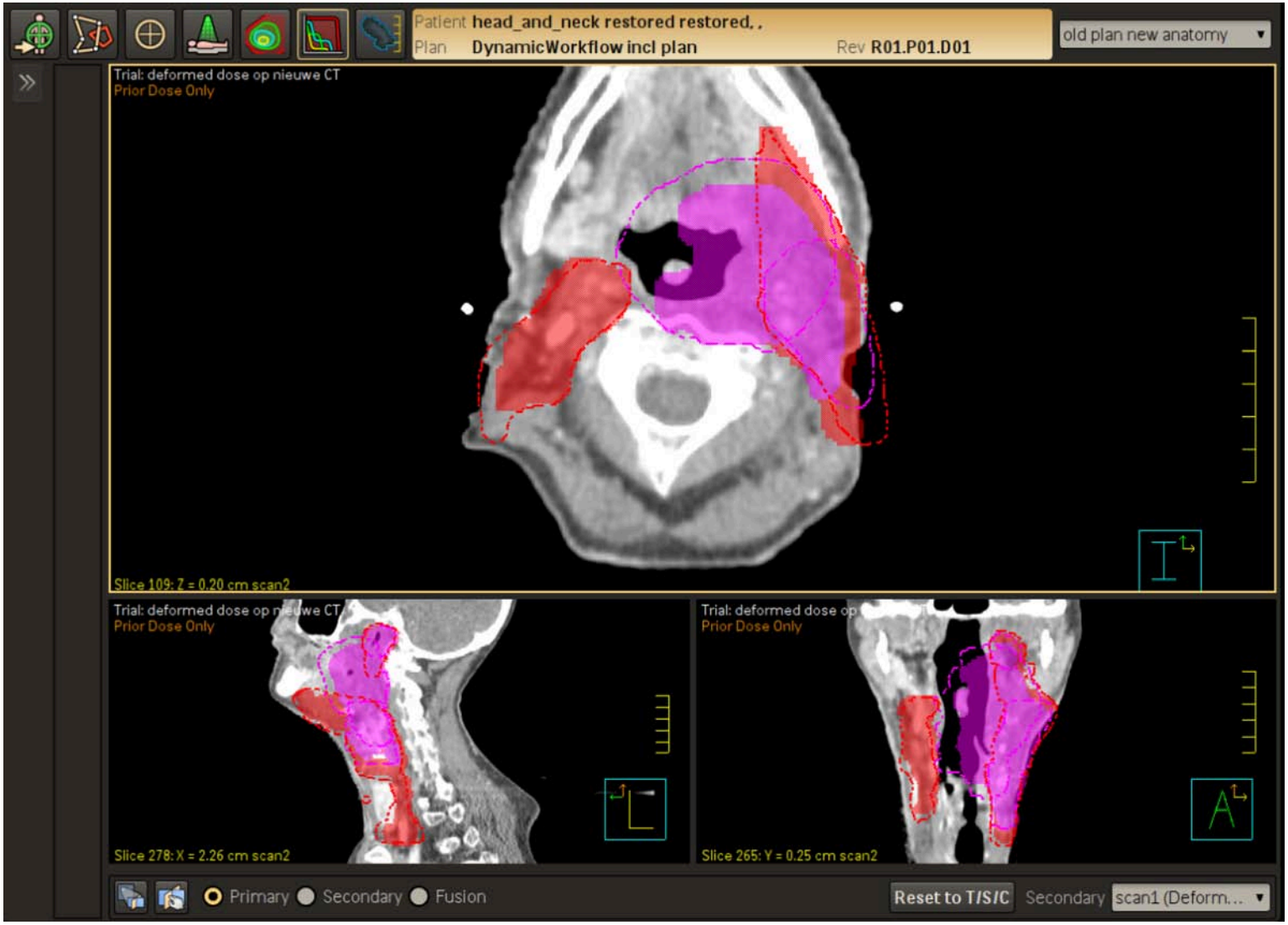
Original plan CT1&2



Old and new ROIs on CT2



H&N case

- Primary tumor: 35 x 2.0 Gy (median dose!)
- Neck levels: 35 x 1.55 Gy (median dose!)

- Constraints :
  - For PTVs: V95 > 95%
  - Spinal cord: max dose < 42 Gy
  - Spinal cord – PRV 3mm: < 47 Gy
  - Parotid glands : both glands < 25 Gy (NTCP 20%)
    : single gland < 39 Gy (NTCP 50 %)
  - SMG not in PTV - as parotids
  - Cochlea: mean dose < 45 Gy
  - Brainstem: D1cc < 55Gy

H&N case

- Group 1 (RaySearch, Pinnacle, Monaco)
  - Use 10 Gy with plan 1 as baseline data
    - Deformed dose from CT1 on CT2
  - Create adapted plan and plan 25 fractions till 70Gy

- Group 2 (Accuray, Eclipse, OMP)
  - Plan 35 fractions on new CT

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PTV prescription: SIB treatment

- 1) **Primary + Positive lymph nods** (Left LC and RP)
  - PTVp_7000, PTVn_L_7000, PTVnLRP_7000: **70 Gy @ 2 Gy/fr**

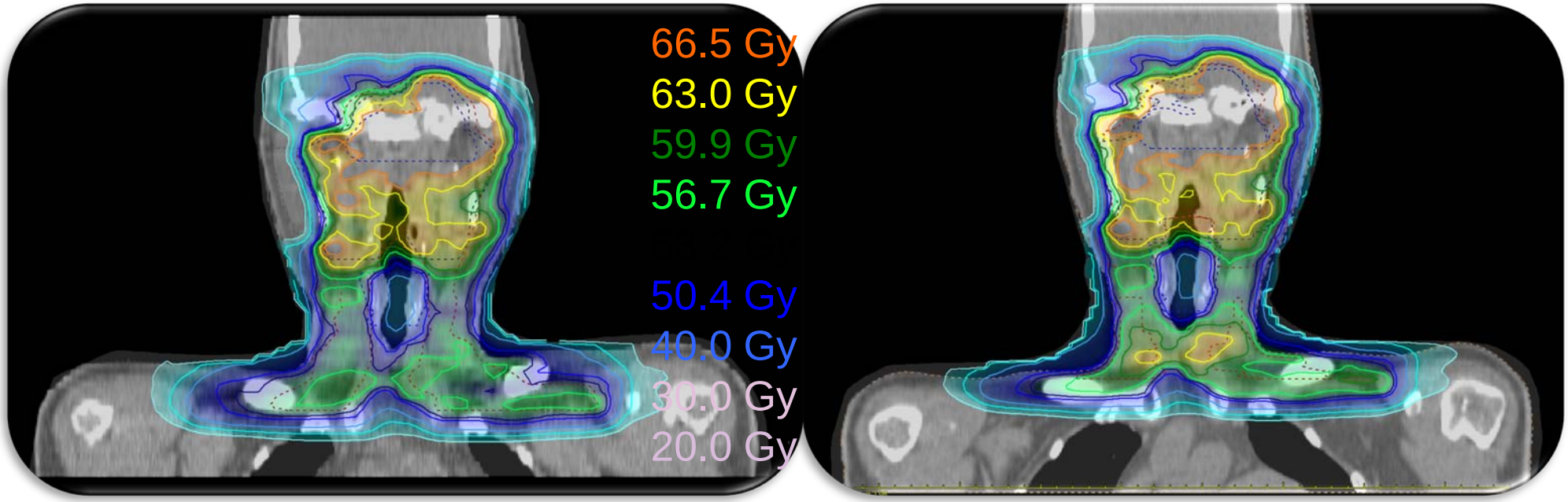
- 2) **Lymph nodes potentially site of microscopic spread**
  - PTVn_L_5425, PTVn_R_5425: **54.25 Gy @ 1.55 Gy/fr**

OARs constraints/objectives

- **Constraints (C), Objectives (O)**
- Spinal_Cord: Dmax <42 Gy (C)
- Spinal_Cord_03: <47 Gy (C)
- Parotid glands: both glands Mean Dose ≤25 Gy (O)
- single gland Mean Dose ≤39 Gy (O)
- Submand_R (not comprised in the PTV): as Parotid (O)
- Cochlea: Mean Dose ≤ 45 Gy (O)
- Brainstem: D1 cc < 55 Gy (C)

Points of discussion

Bias dose



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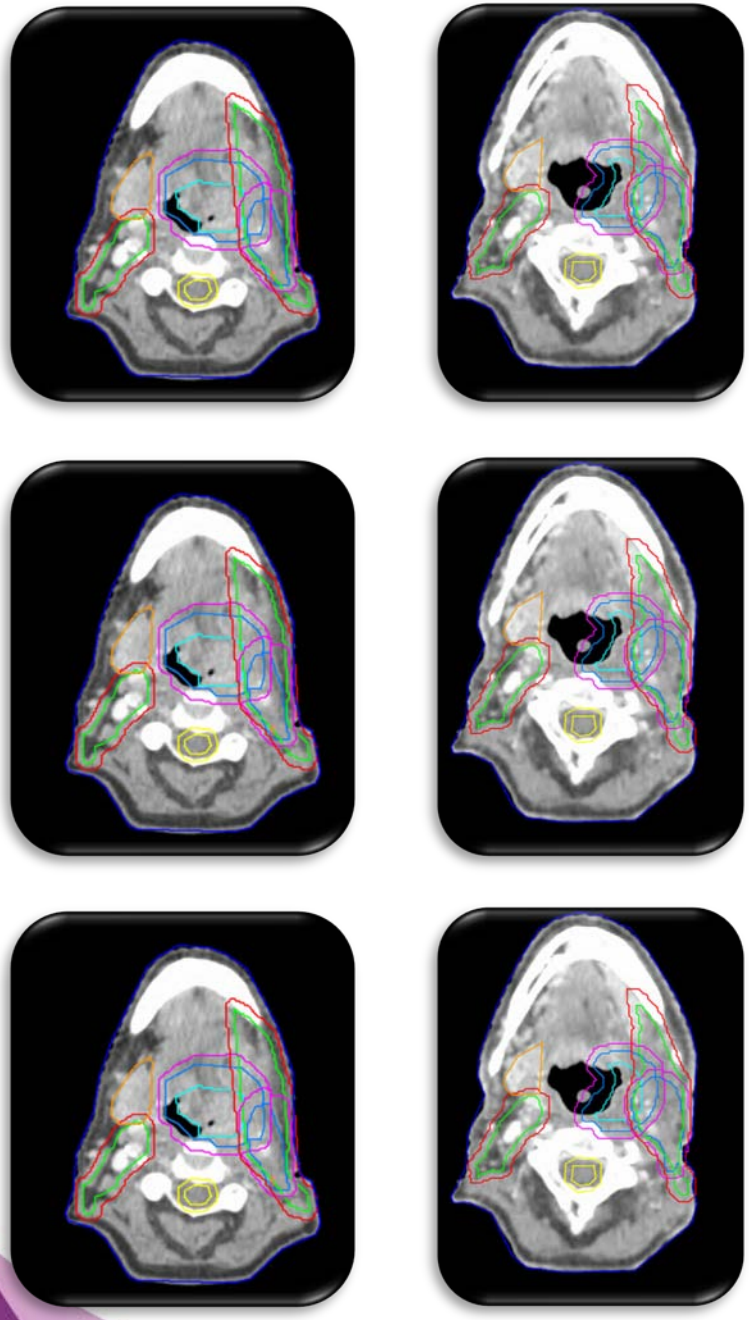
Different scenarios

CT 1 CT2



Scenario 1: New plan on CT without considering prior dose

Scenario 2: Initial plan calculated on CT2 and taken as a prior/background dose

Scenario 3: Warp dose from CT1 to CT2 and use it as a prior/background

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Pareto front analysis in clinical practice: what is it, and what is the gain?

Advanced Treatment Planning Course
14-18 September 2016 – Cambridge, UK

Markus Stock

MedAustron

ESTRO School

Content

- Background: '*planning problem*' in terms of trade off
- *Sweeping* the dose
- Pareto front versus Pareto surface
- Exploring the 'planning problem': Pareto navigation tools
- Published Pareto navigation tools

What is the pareto principle

- The **Pareto principle** (also known as the **80–20 rule**) states that, for many events, roughly 80% of the effects come from 20% of the causes.
- named after Italian economist **Vilfredo Pareto -** showed that approximately 80% of the land in Italy was owned by 20% of the population; Pareto developed the principle by observing that 20% of the peapods in his garden contained 80% of the peas
- Microsoft noted that by fixing the top 20% of the most-reported bugs, 80% of the related errors and crashes in a given system would be eliminated
- **Pareto optimality -** state of allocation of resources in which it is impossible to make any one individual better off without making at least one individual worse off.

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‘Planning problem’: trade off coverage / sparing

In every treatment plan:

- conflicting OARs ….. how to prioritize / weight them ?
- dose fall off

Ultimate goal of treatment plan:

- ‘optimal’ dose coverage
- optimal sparing: as low as possible

Planning problem in manual planning

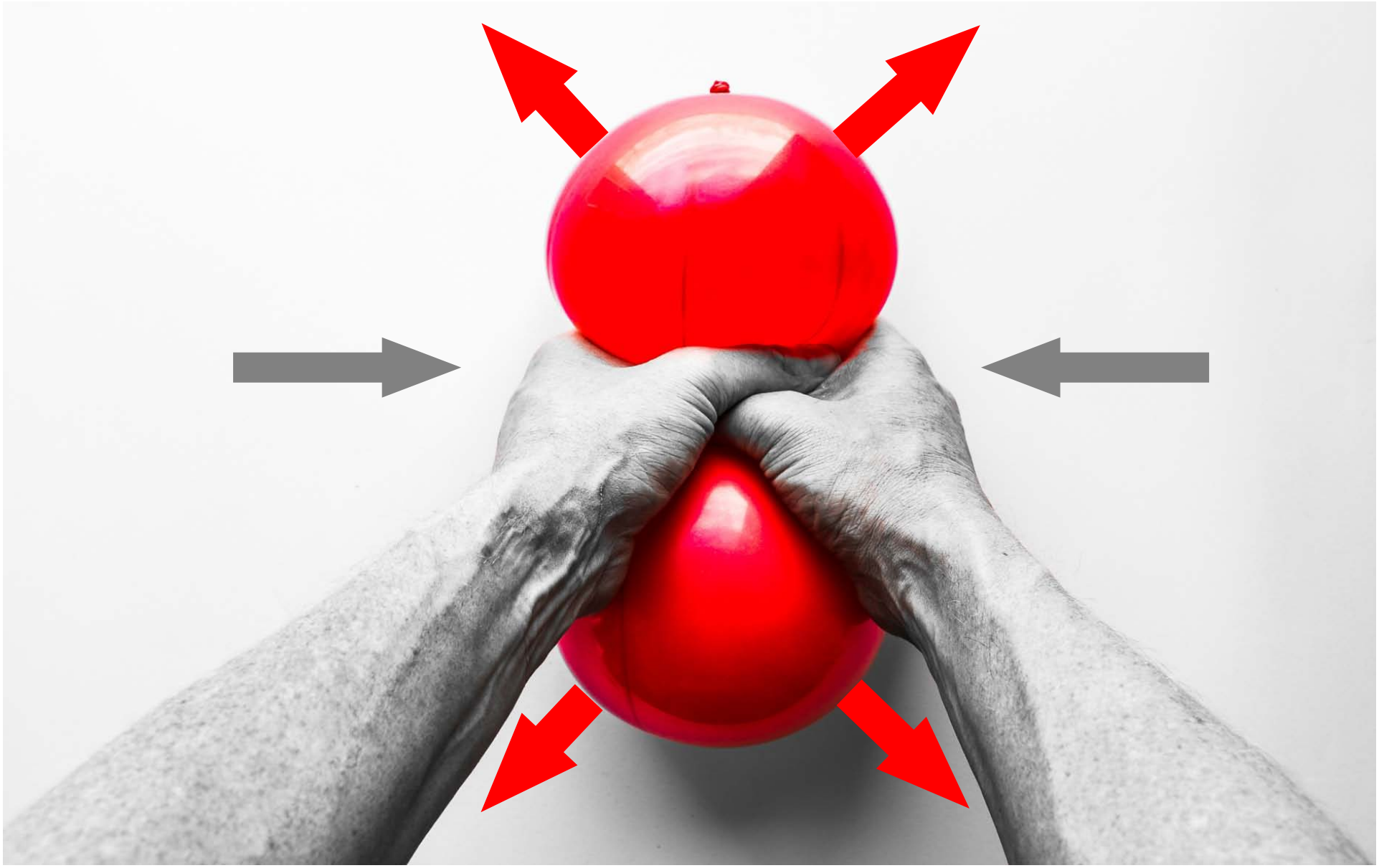
- It’s difficult to make a good estimation of what is achievable in solving the planning problem

- when manually optimizing IMRT plans, one is never sure about the exact quality of the final plan ….. How far away from the ‘best’ plan,
- and what is defined as the best plan?

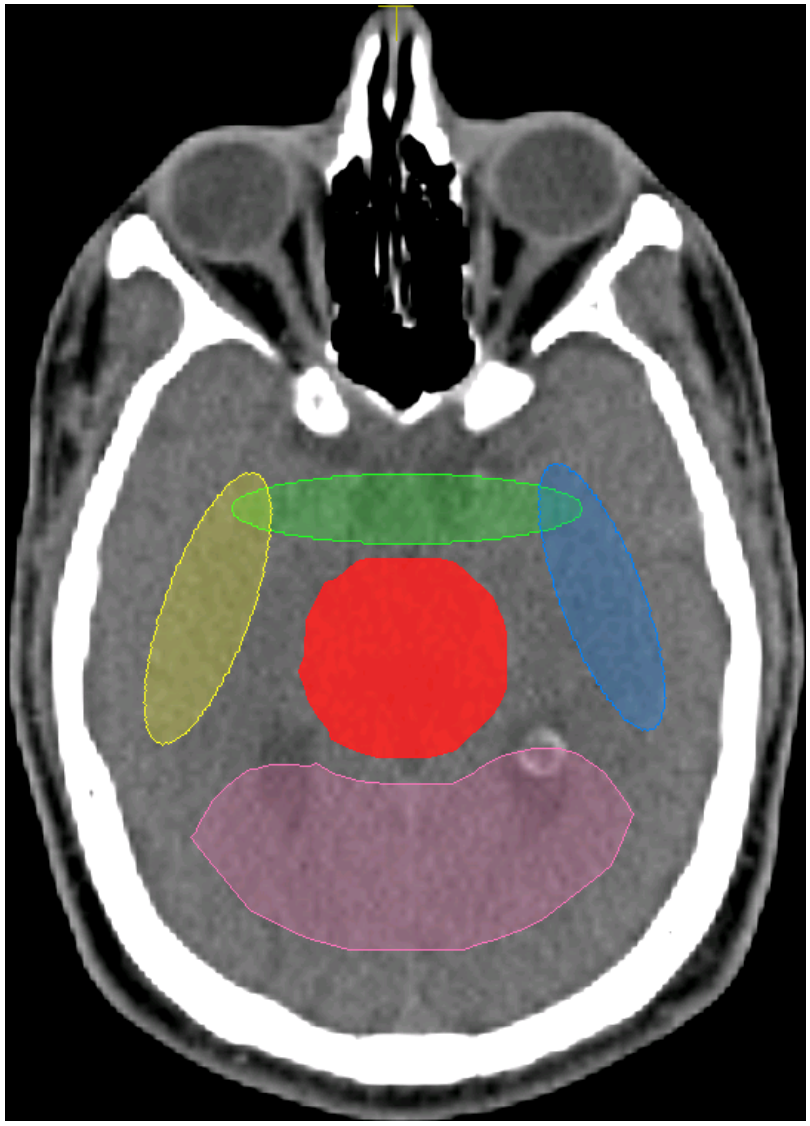
Sweeping dose

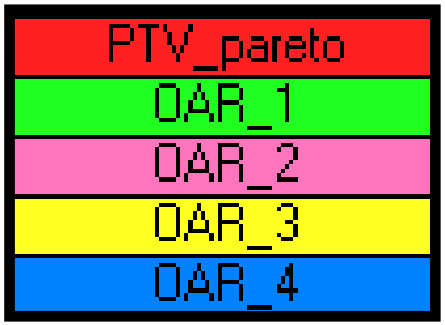
- Applying IMRT is nothing more than sweeping dose away from places you put constraints on …..
- So your IMRT prescription is nothing more than a
- In which you tell the optimizer what to spare

Sweeping the dose : dose *shaping*



Sweeping dose theoretical example





Prescription:
PTV = 50 Gy
OAR1-4 = minimize mean dose

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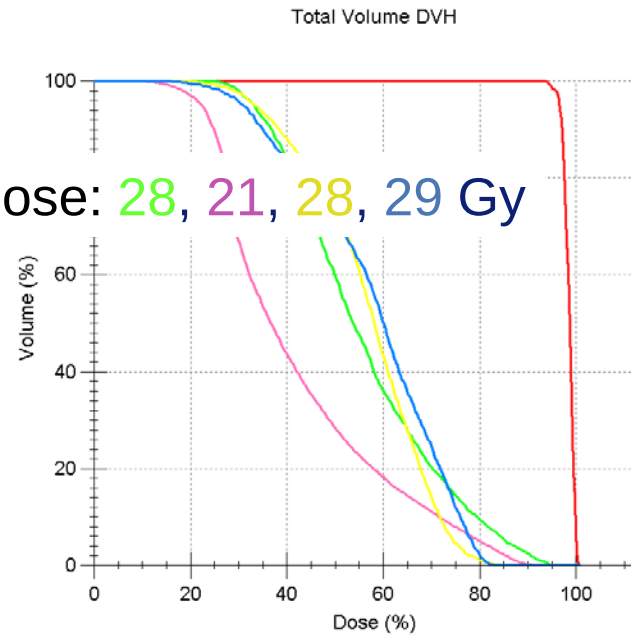
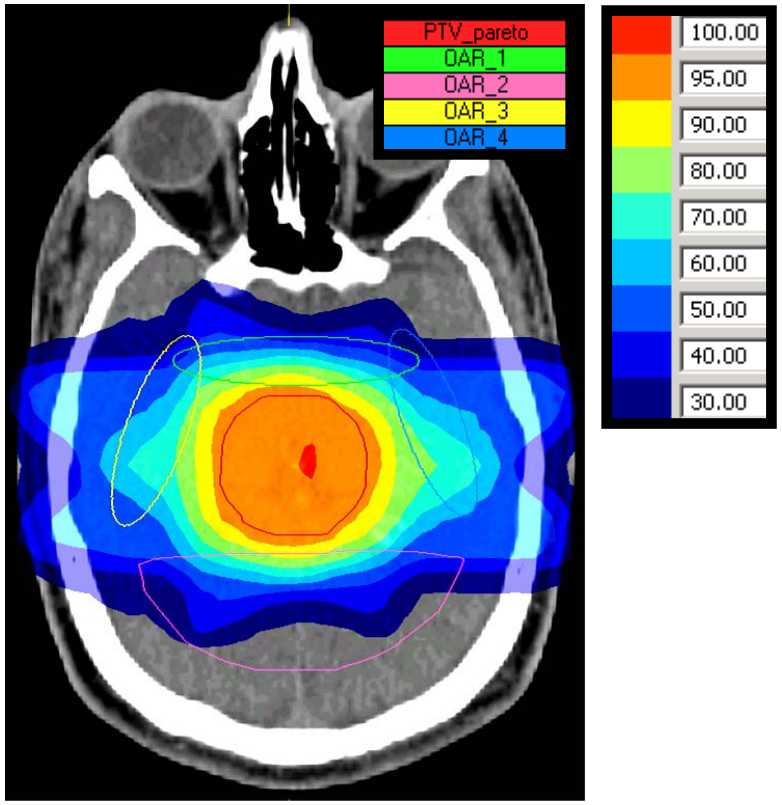
Sweeping dose theoretical example

Option 1:
Conformal dose around PTV, no constraints on individual OAR's

'*Completely random*' shape of dose distribution in surrounding OAR's



Mean dose: 28, 21, 28, 29 Gy



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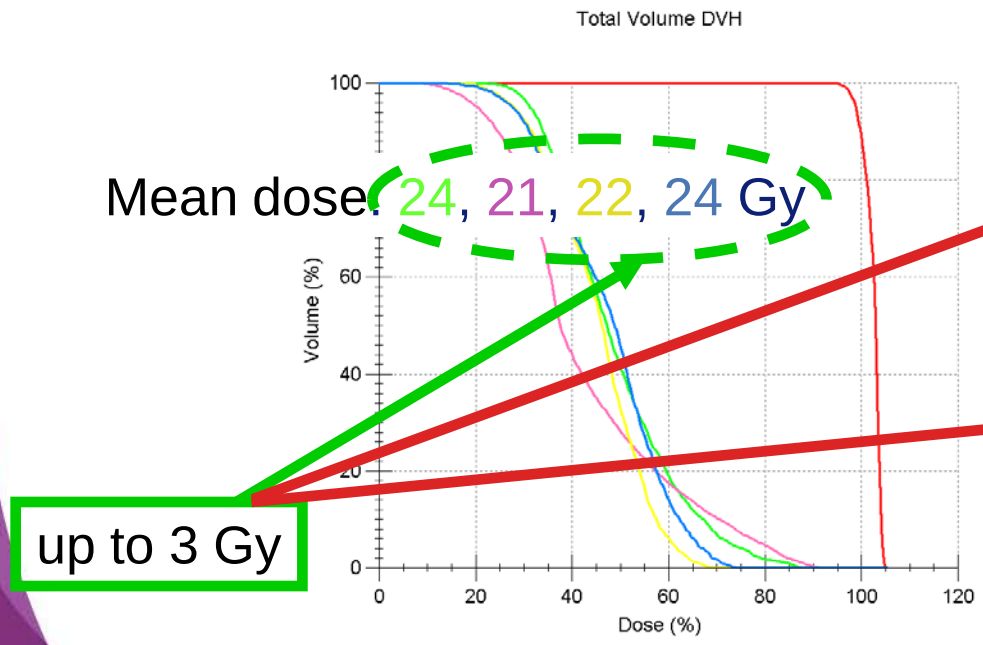
Sweeping dose theoretical example

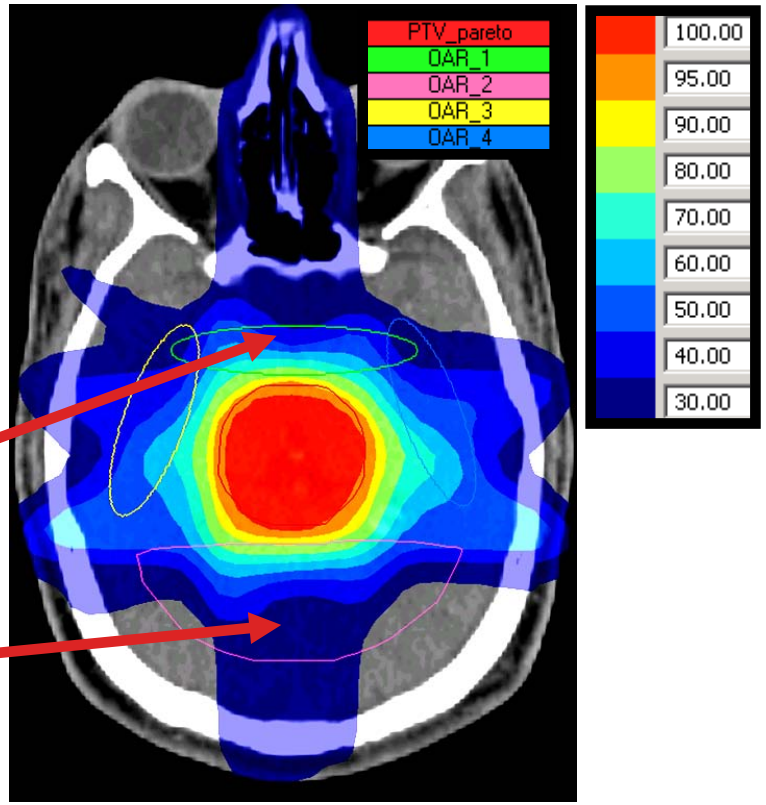
Option 2:
Conformal dose around PTV, equally weighted constraints on all OAR's (mean dose = 25 Gy)

Equally weighted in terms of input, does not result in equally distributed doses…



Mean dose: 24, 21, 22, 24 Gy

up to 3 Gy



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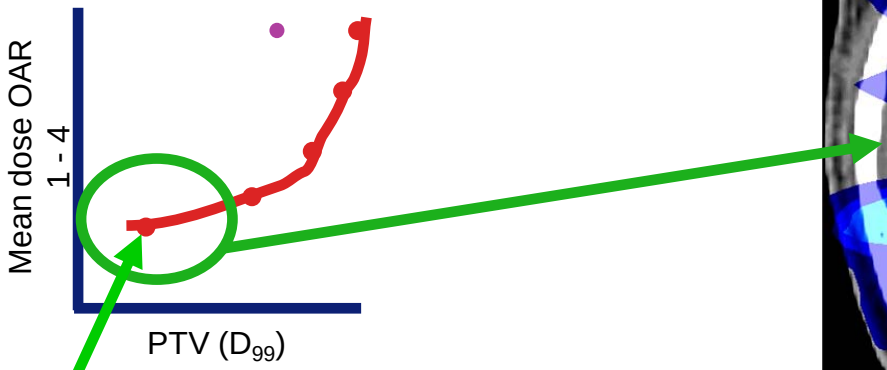
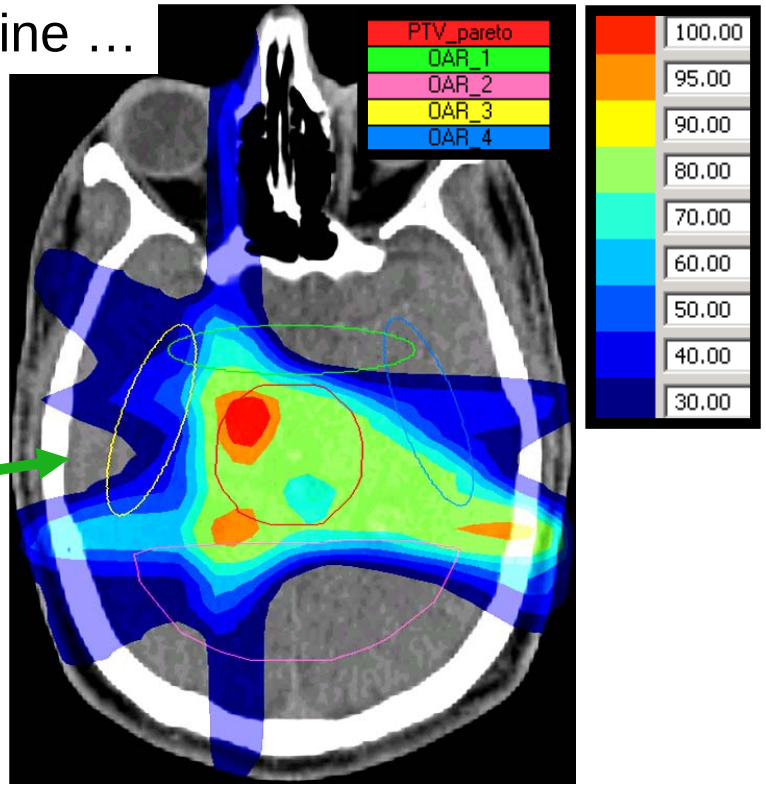
Sweeping dose theoretical example

Option 3:
Conformal dose around PTV, equally weighted constraints on all OAR's (mean dose = 20 Gy)

So, we obviously went too far along the line …





Pareto optimal plan? Sure!
Optimal? No!

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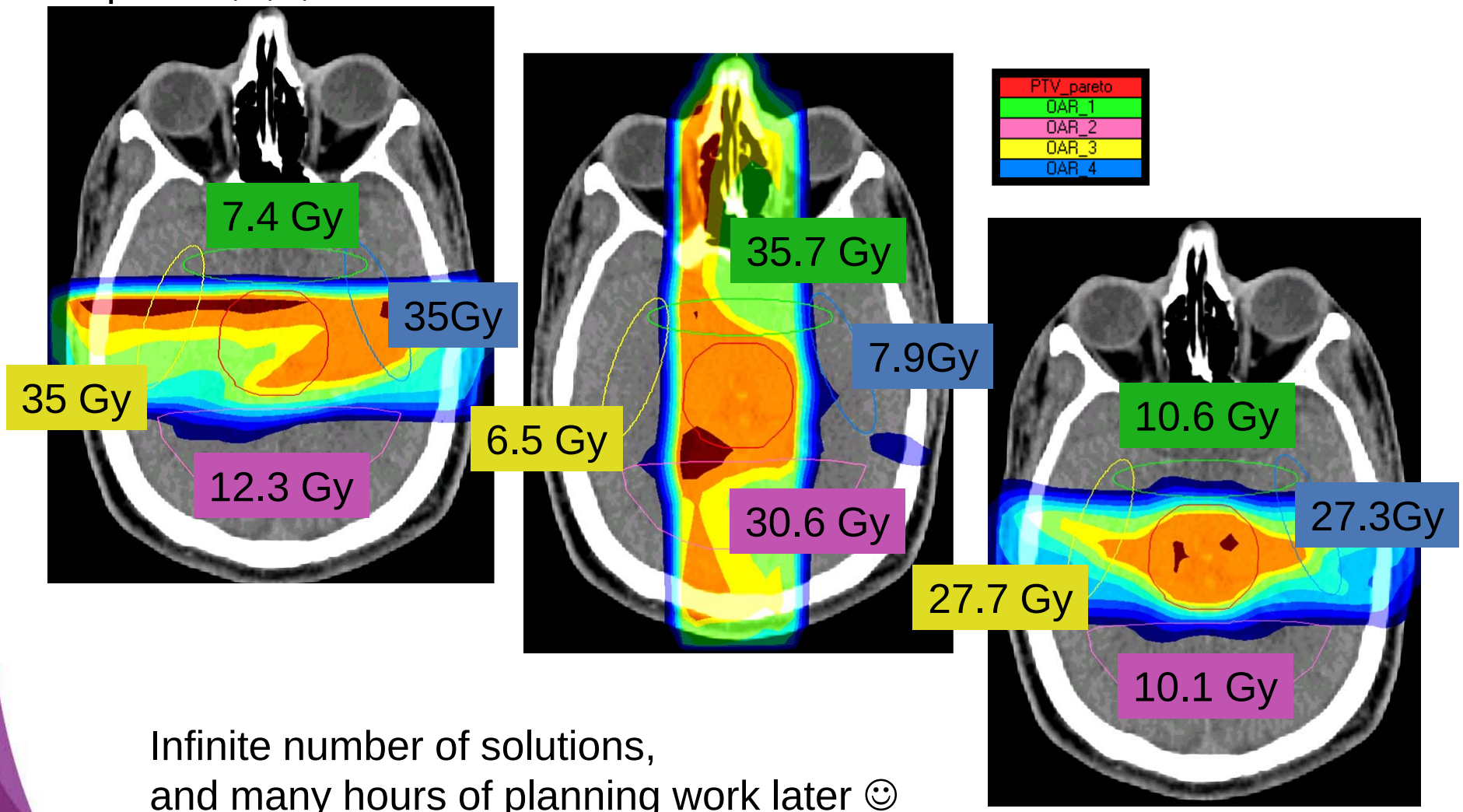
Sweeping dose theoretical example, many options …

Option 4,5,6, ……. :



Infinite number of solutions,
and many hours of planning work later ☺

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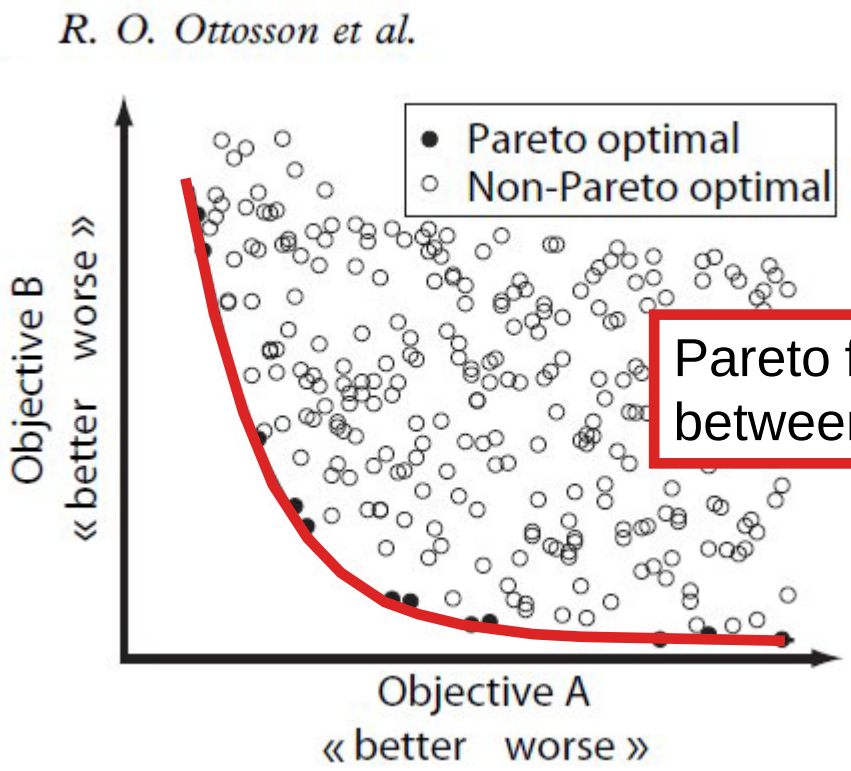
Pareto front



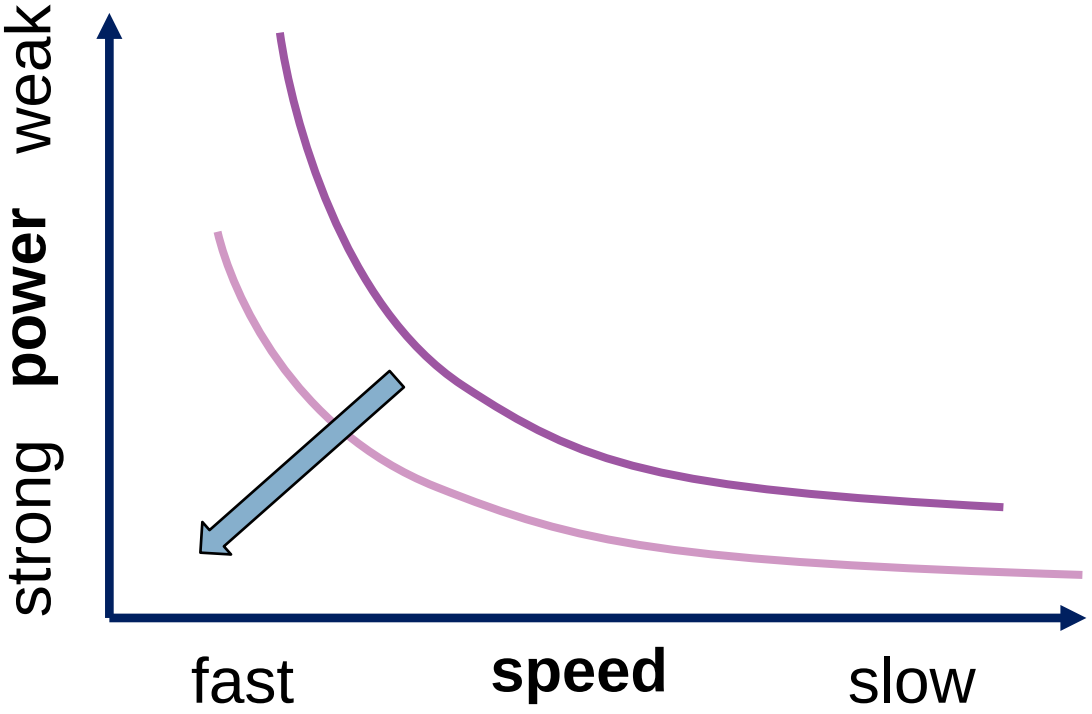
Pareto front = line of Pareto optimal points between two contradicting objectives

For two mutually contradicting objectives an endless number of solution exists

The solutions where one of the objectives can not be improved without deteriorating the other are *Pareto optimal*

All Pareto optimal solutions lie on the Pareto front

Mnemonic for Pareto front



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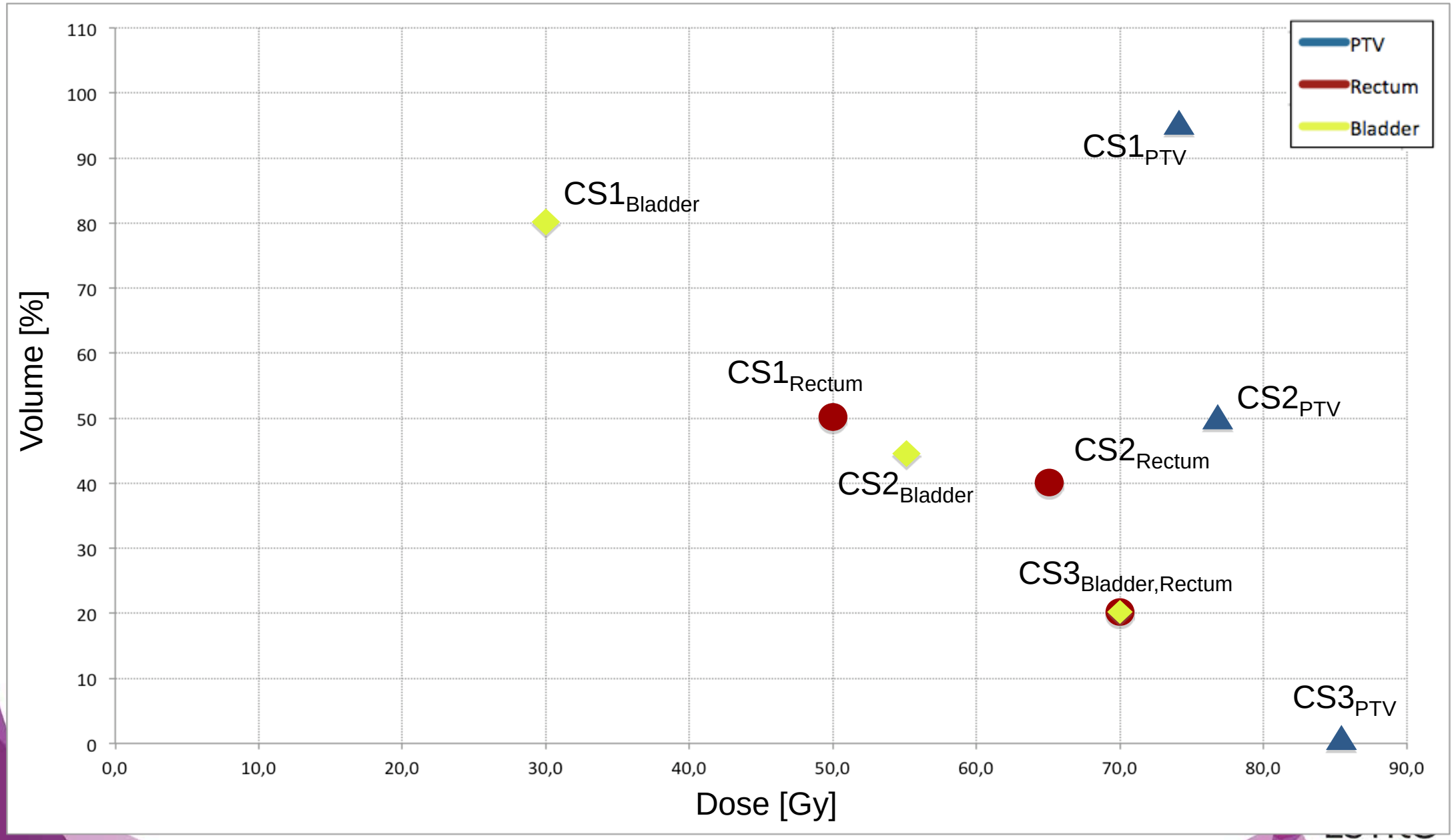
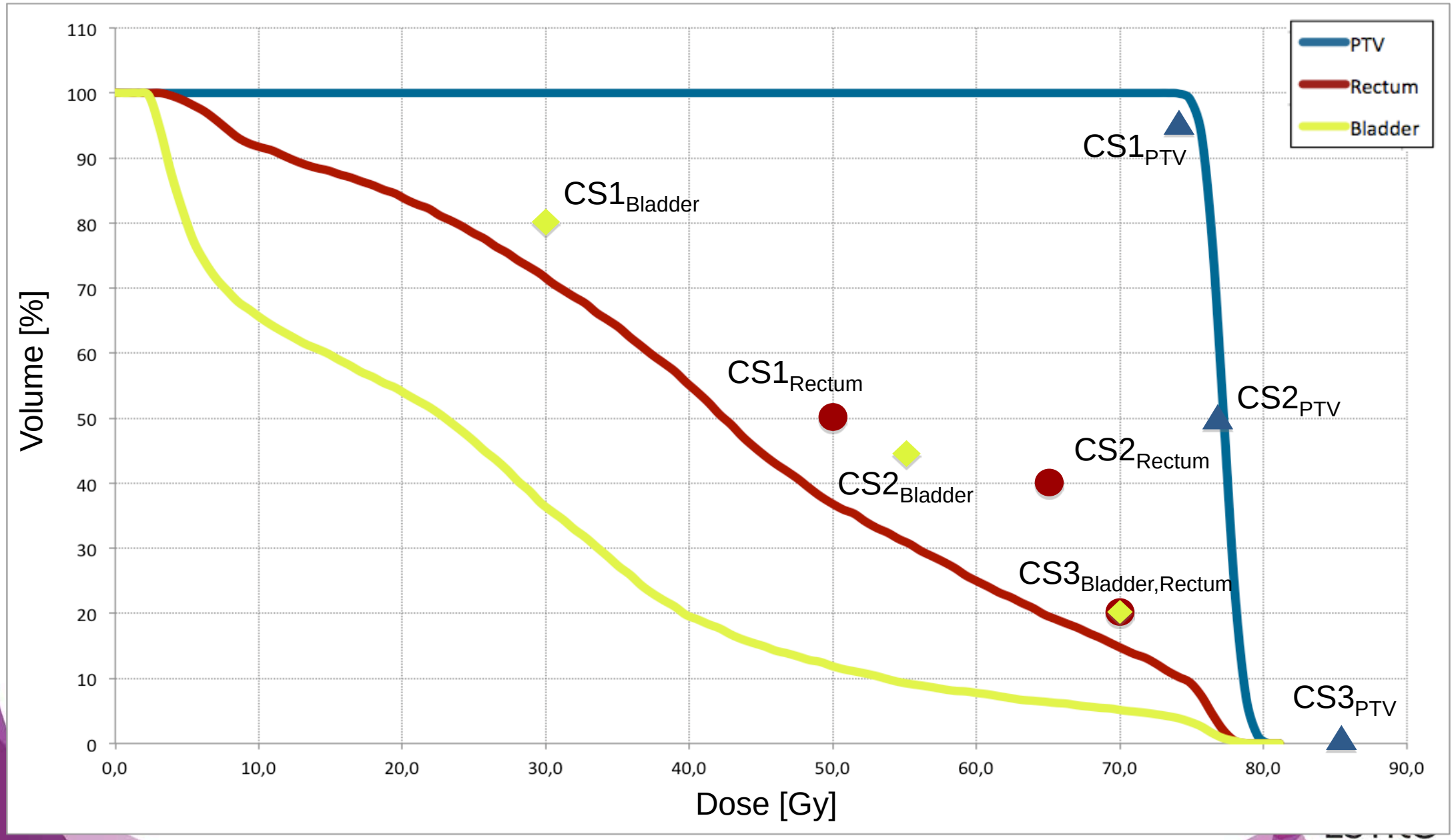
The „manual“ way to get there




PTV
Rectum
Bladder
CS1PTV
CS1Bladder
CS1Rectum
CS2PTV
CS2Rectum
CS2Bladder
CS3Bladder,Rectum
CS3PTV
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Dose [Gy]
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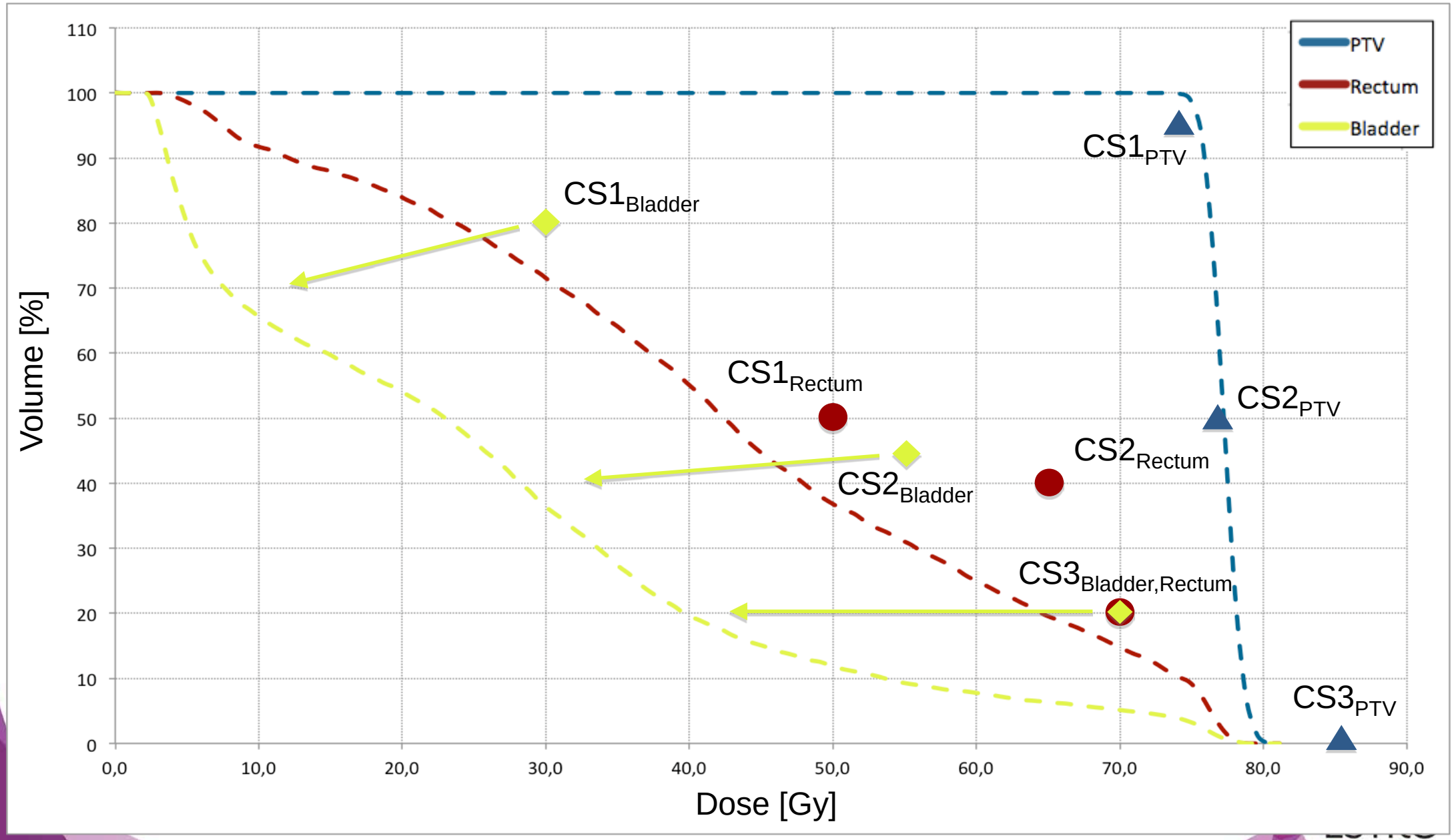
PTV
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CS1Bladder
CS1Rectum
CS2PTV
CS2Rectum
CS2Bladder
CS3Bladder,Rectum
CS3PTV
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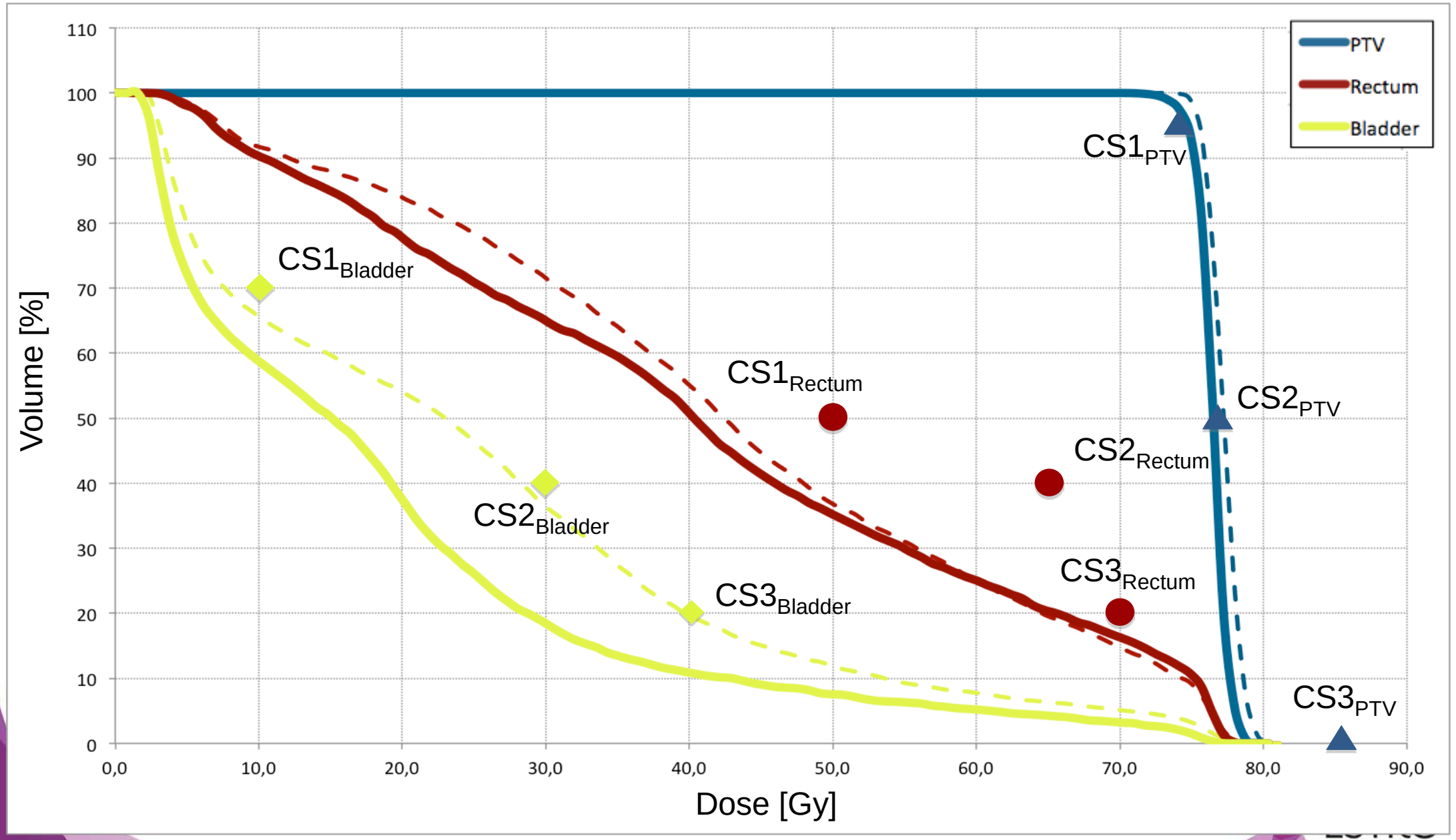
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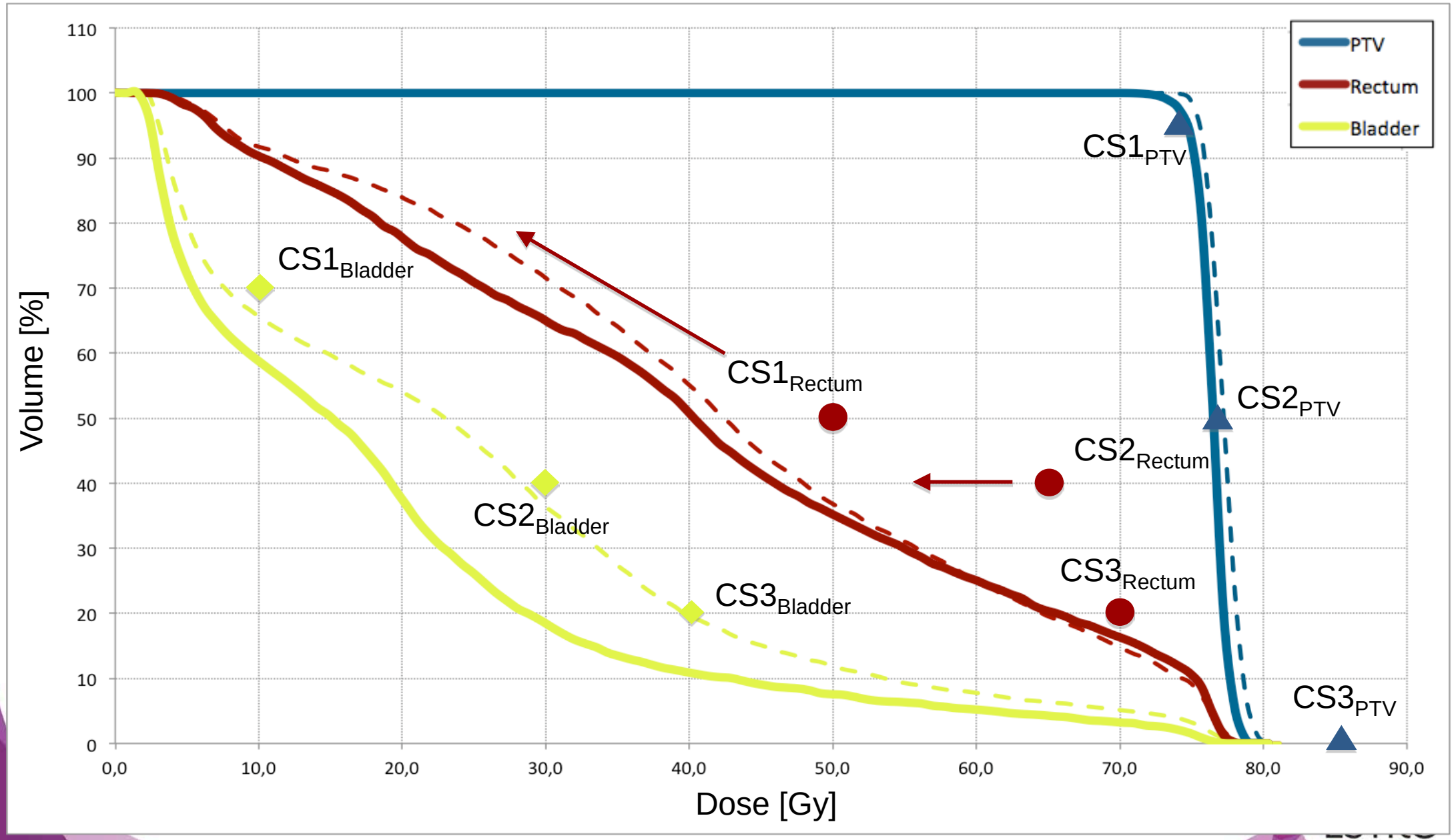
CS1PTV
CS2PTV
CS3PTV
CS1Bladder
CS2Bladder
CS3Bladder
CS1Rectum
CS2Rectum
CS3Rectum


PTV
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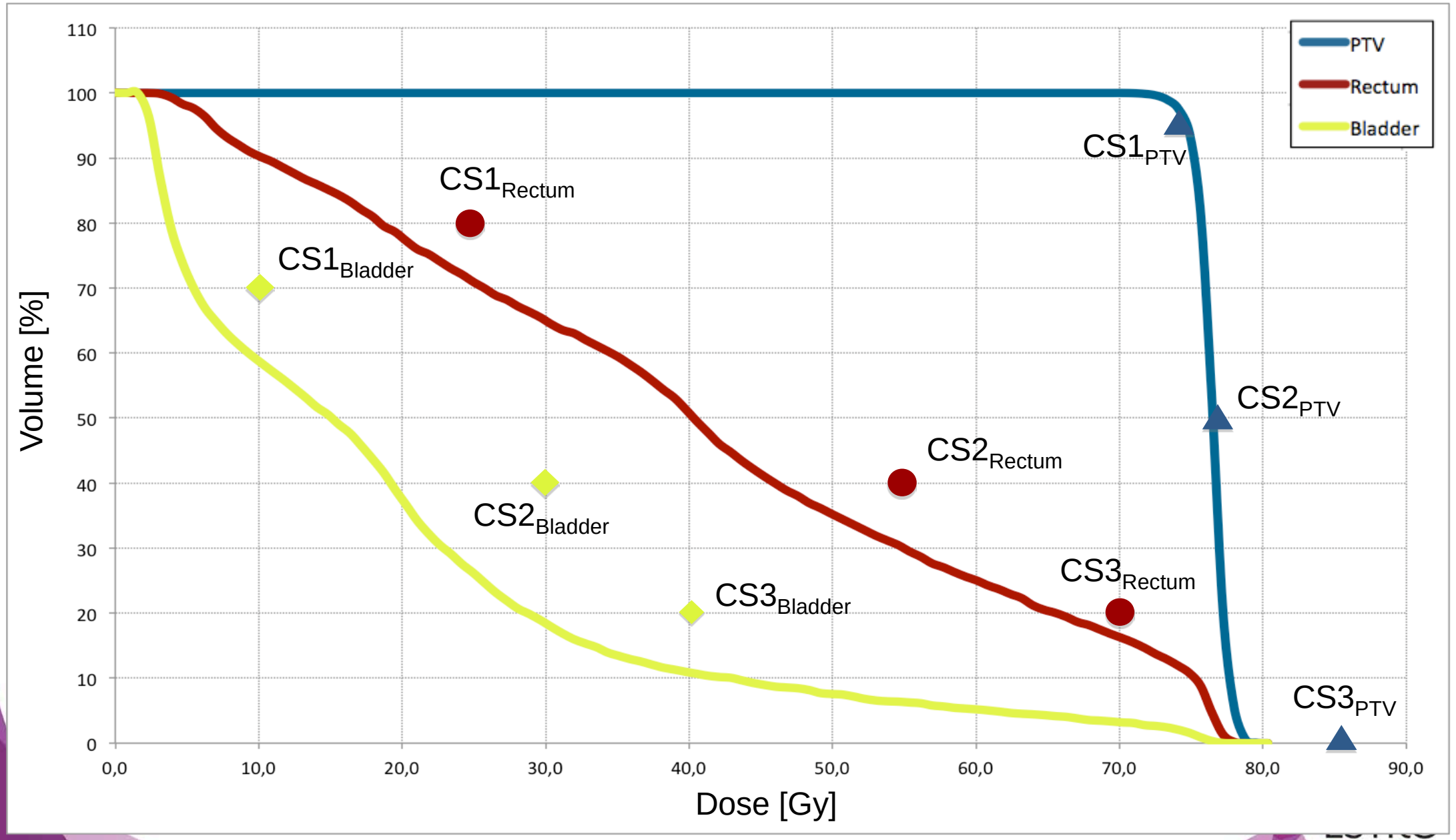
CS1PTV
CS1Bladder
CS1Rectum
CS2PTV
CS2Rectum
CS2Bladder
CS3Rectum
CS3Bladder
CS3PTV


PTV
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CS1Bladder
CS2PTV
CS2Rectum
CS2Bladder
CS3Rectum
CS3Bladder
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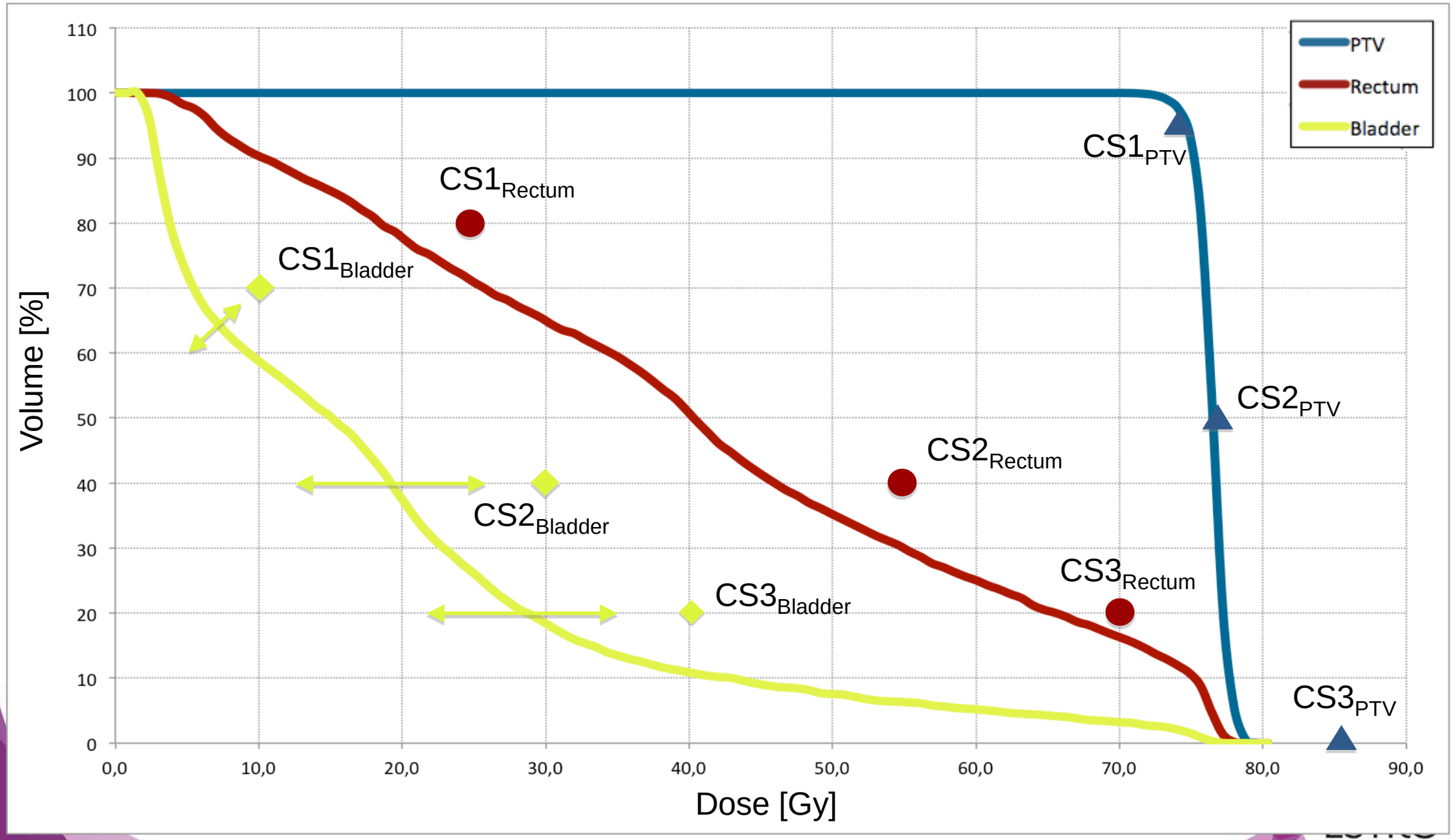
PTV
Rectum
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Volume [%]
Dose [Gy]
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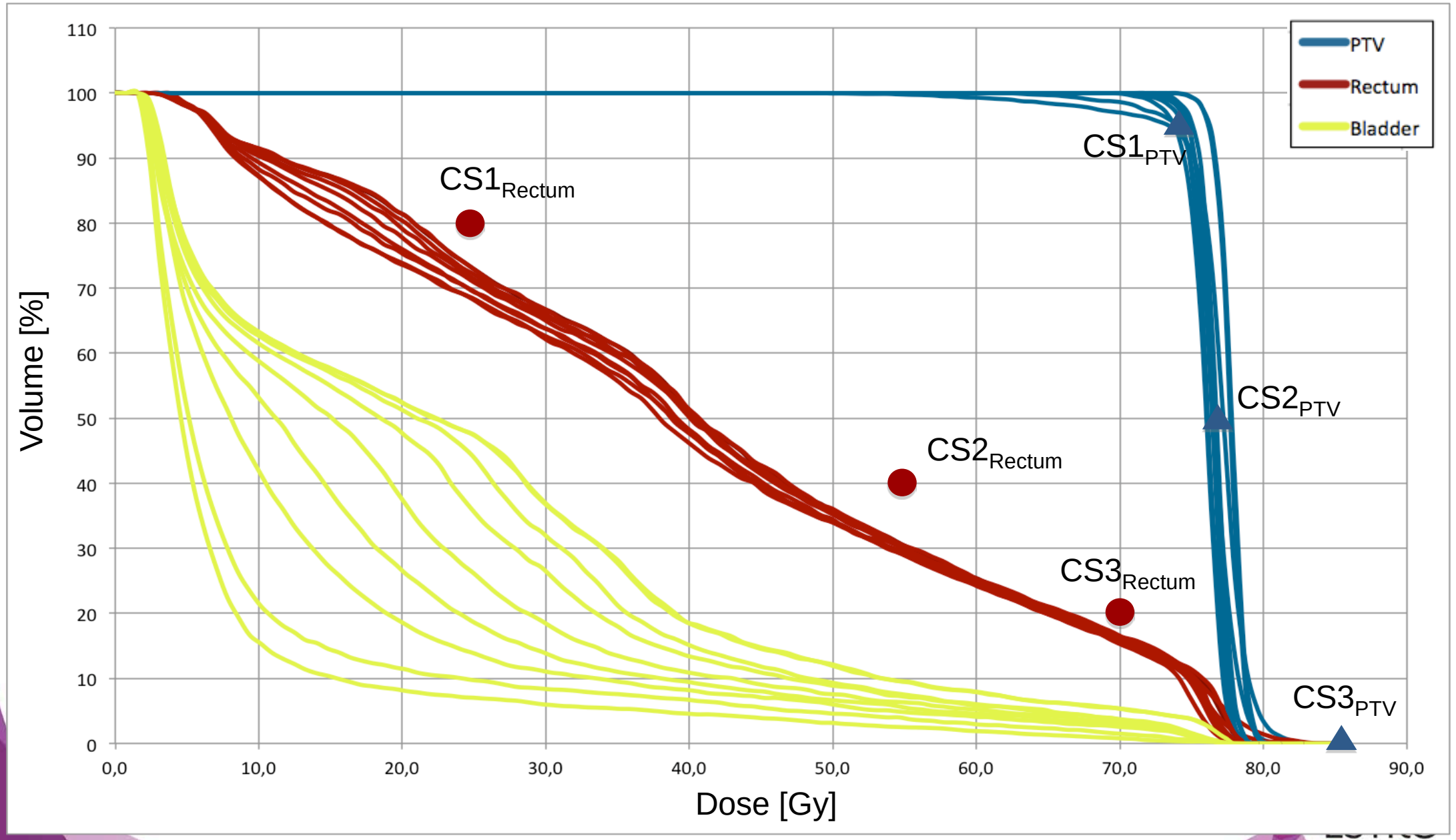
CS1Rectum
CS1Bladder
CS1PTV
CS2PTV
CS2Rectum
CS2Bladder
CS3Rectum
CS3Bladder
CS3PTV


PTV
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Bladder
Volume [%]
Dose [Gy]
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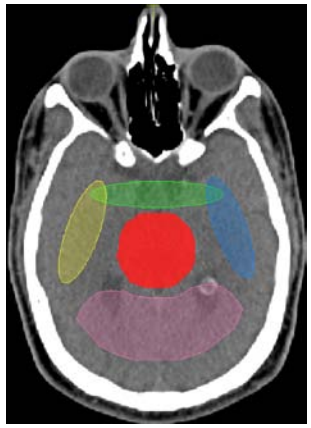
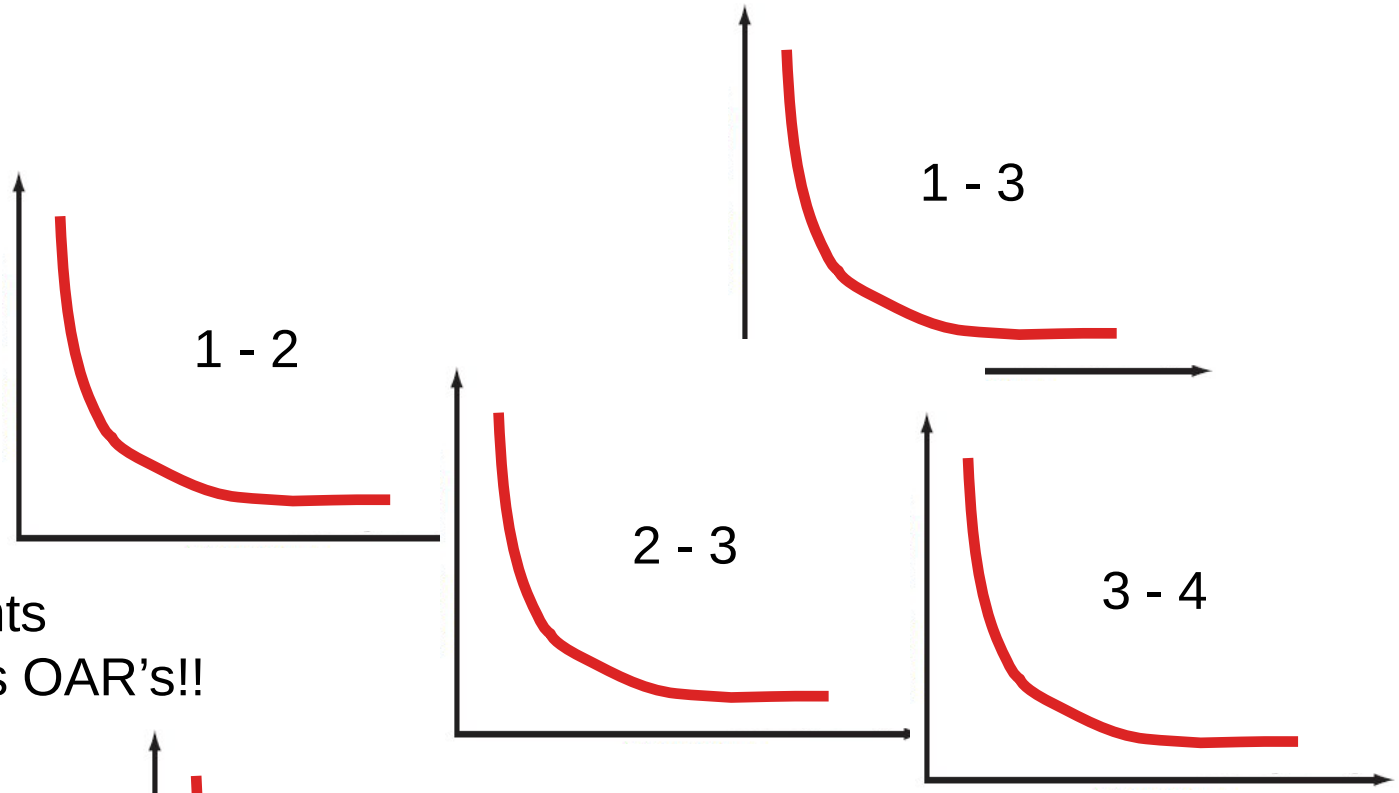
50,0
60,0
70,0
80,0
90,0
CS1Rectum
CS1PTV
CS2Rectum
CS2PTV
CS3Rectum
CS3PTV

Pareto front versus Pareto surface

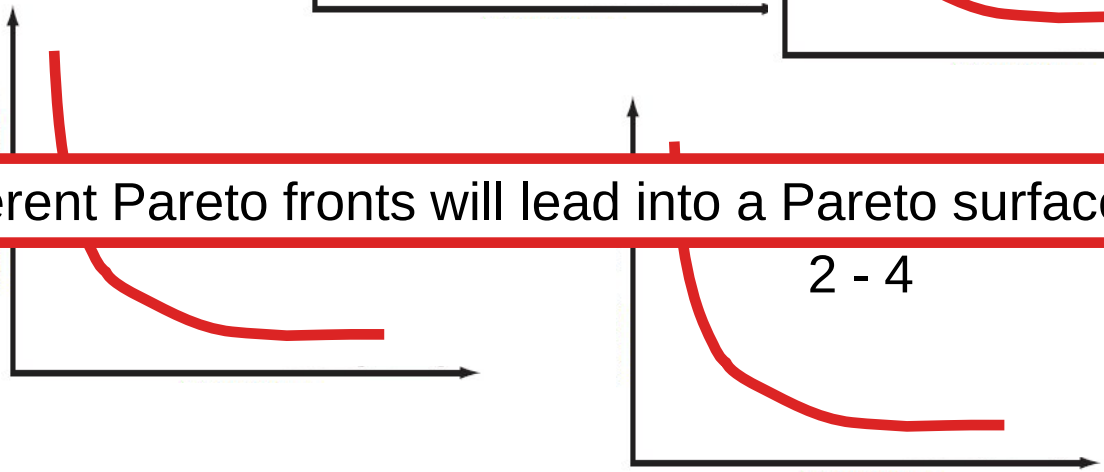
OAR's 1,2,3,4



Another set of fronts
With Target versus OAR's!!



Combination of different Pareto fronts will lead into a Pareto surface



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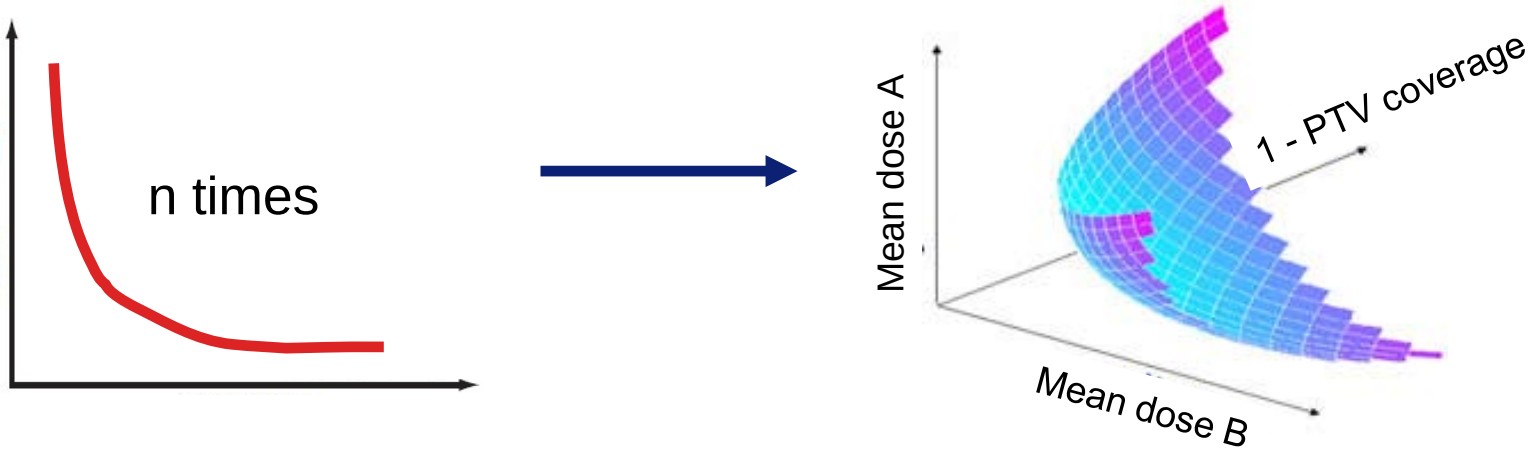
Pareto front versus Pareto surface

Pareto surface is a multi dimensional non linear ‘landscape’ of Pareto optimal solutions

We need tools to *visualize* the landscape and *navigate*



Pareto front

Pareto surface 3 dimensions

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Pareto front navigation in multi-criteria optimization?

To be able to navigate through the landscape we need library of plans
“as fine as possible” resolution of the landscape (= many plans)

All ‘corner’ plans should be part of the library with enough data points along
the Pareto surface (so among all individual Pareto fronts),
so that any interpolated plan should be as close as possible to an already calculated plan

Pareto front navigation works fine for fluence optimization
as long as the landscape is defined with enough detail

Plan library ‘around’ a class solution

Radiotherapy and Oncology 97 (2010) 561–566

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journal homepage: www.thegreenjournal.com

Quality assurance

A practical approach to assess clinical planning tradeoffs in the design of individualized IMRT treatment plans

René Monshouwer *, Aswin L. Hoffmann, Martina Kunze-Busch, Johan Bussink, Johannes H.A.M. Kaanders, Henk Huizenga

Department of Radiation Oncology, Radboud University Nijmegen Medical Centre, The Netherlands

The starting point for building the library of plans was the plan of the initial IMRT class solution. Subsequently, the IMRT parameters (weights and dose levels) of all objective functions, including the PTV, were kept constant and only parameters of the objective functions of the lungs and the oesophagus were varied. The range in which the parameters were varied was chosen such that a broad, but clinically relevant range of IMRT plans was generated.

Class solution = 6 beam configuration divided among ipsi-lateral side

Plan library ‘around’ a class solution

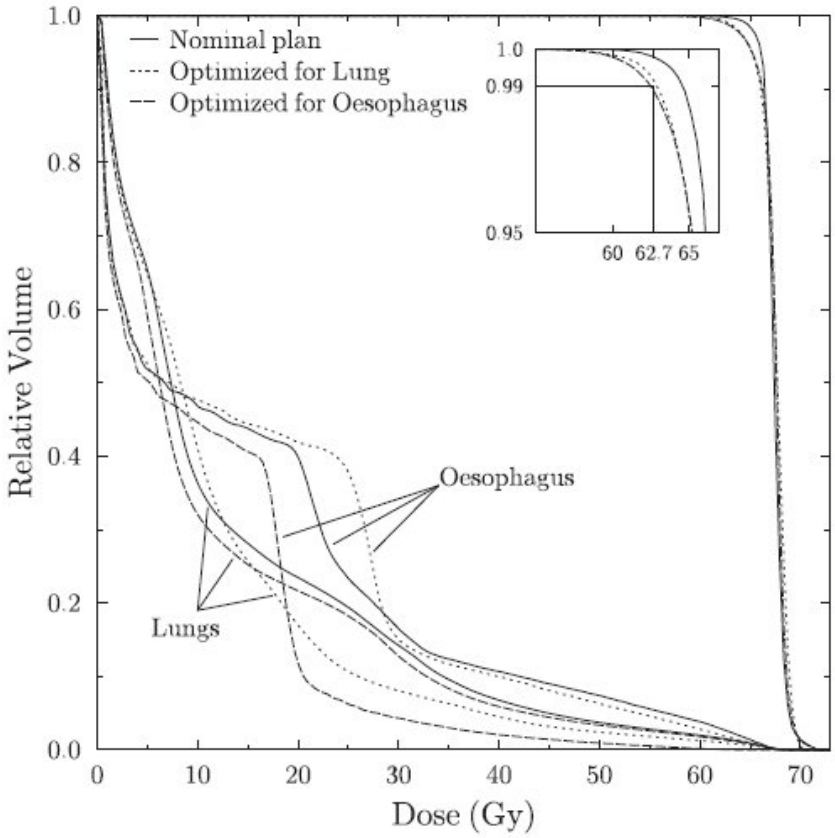

Fig. 1. DVH curves for three different IMRT plans of the same patient (see legend). For the plan optimized for lung sparing, the weight of the lung objective was increased from 1 to 50. For the plan optimized for oesophagus sparing, the dose level of the oesophagus objective function was lowered from 42 to 18 Gy (see text). The inset shows the DVH enlarged around 62.7 Gy (95% of the prescribed dose).

‘simple’ navigation software, based on DVH’s

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Another approach to build a library of plans

Simultaneous navigation of multiple Pareto surfaces, with an application to multicriteria IMRT planning with multiple beam angle configurations

David Craft[a)]
Department of Radiation Oncology, Massachusetts General Hospital, Boston, Massachusetts 02114

Michael Monz
Department of Optimization, Fraunhofer Institute for Industrial Mathematics, Fraunhofer Platz 1, 67663 Kaiserslautern, Germany

(Received 11 September 2009; revised 19 December 2009; accepted for publication 22 December 2009; published 22 January 2010)

Purpose: To introduce a method to simultaneously explore a collection of Pareto surfaces. The method will allow radiotherapy treatment planners to interactively explore treatment plans for different beam angle configurations as well as different treatment modalities.

[DOI: 10.1118/1.3292636]

‘Pareto front navigation-tools’ of RaySearch TPS:
Based on the work of the groups from Boston and Kaiserslautern

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Another approach to build a library of plans

A database of plans is automatically generated

- First *n+1* points calculated on the individual Pareto fronts are the ‘anchor-plans’ : the best you can do in each objective individually

- The user navigates across the Pareto surface by increasing or decreasing the allowed limits of the objectives

- Beam angle configurations (no optimization!):
    - different beam configurations have different Pareto surfaces
    - based on current point and distance to an other Pareto surface (beam configuration), navigation is switched to the new surface.

How to build a library of plans?

Radiotherapy and Oncology 85 (2007) 292–298
www.thegreenjournal.com

Treatment planning

A new concept for interactive radiotherapy planning with multicriteria optimization: First clinical evaluation ☆

Christian Thieke[a,b,*], Karl-Heinz Küfer[c], Michael Monz[c], Alexander Scherrer[c], Fernando Alonso[c], Uwe Oelfke[d], Peter E. Huber[a,b], Jürgen Debus[b], Thomas Bortfeld[e]

[a]*Department of Radiation Oncology, Deutsches Krebsforschungszentrum, Heidelberg, Germany,* [b]*Department of Radiooncology and Radiation Therapy, University Clinic, Heidelberg, Germany,* [c]*Department of Optimization, Fraunhofer-Institute for Industrial Mathematics, Kaiserslautern, Germany,* [d]*Department of Medical Physics in Radiation Oncology, Deutsches Krebsforschungszentrum, Heidelberg, Germany,* [e]*Department of Radiation Oncology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA*

- library of multi-criteria optimized plans are automatically calculated
- treatment beams (number and direction) are manually selected
- Pareto front analysis tool ☺ ☺

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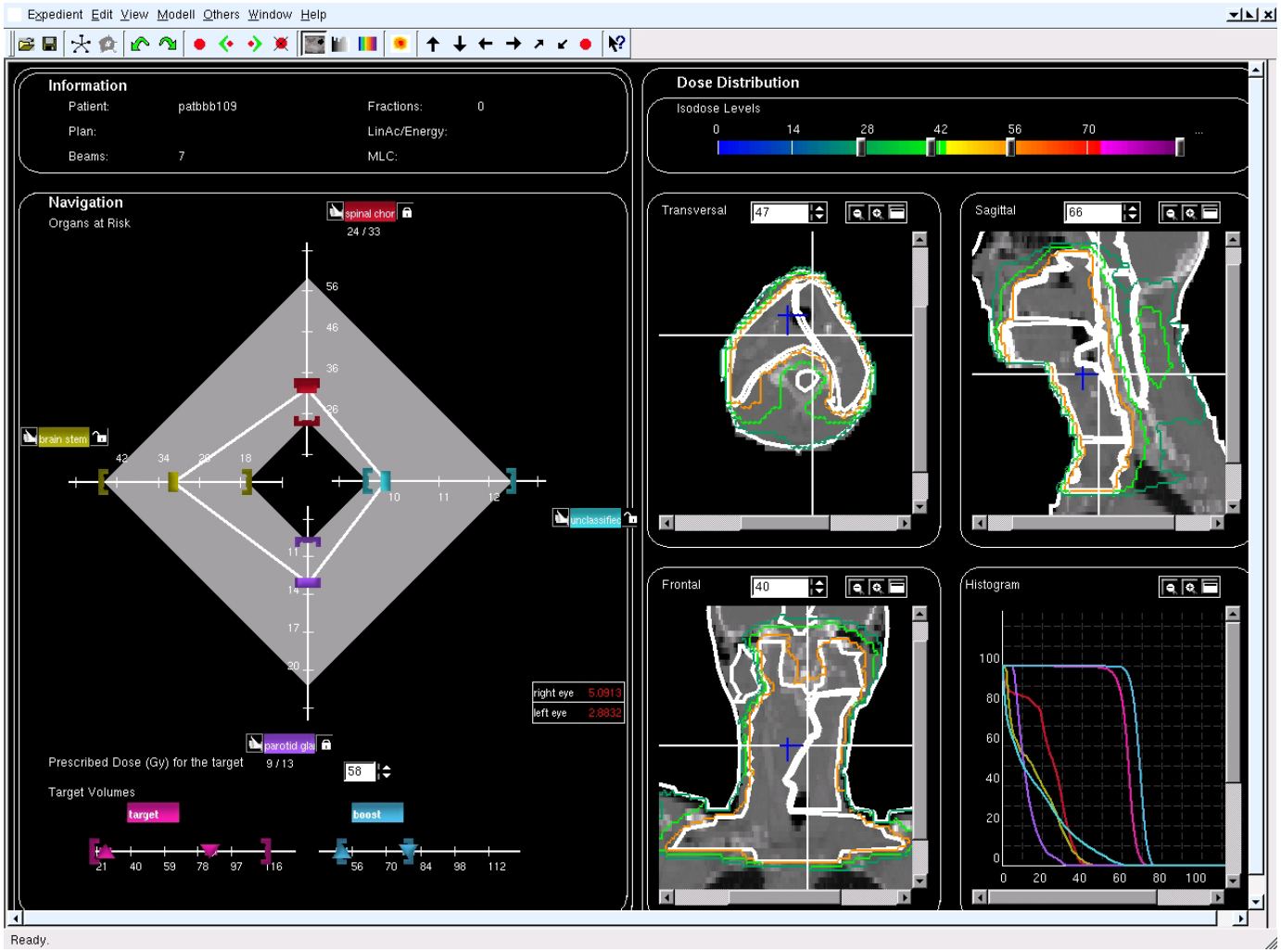
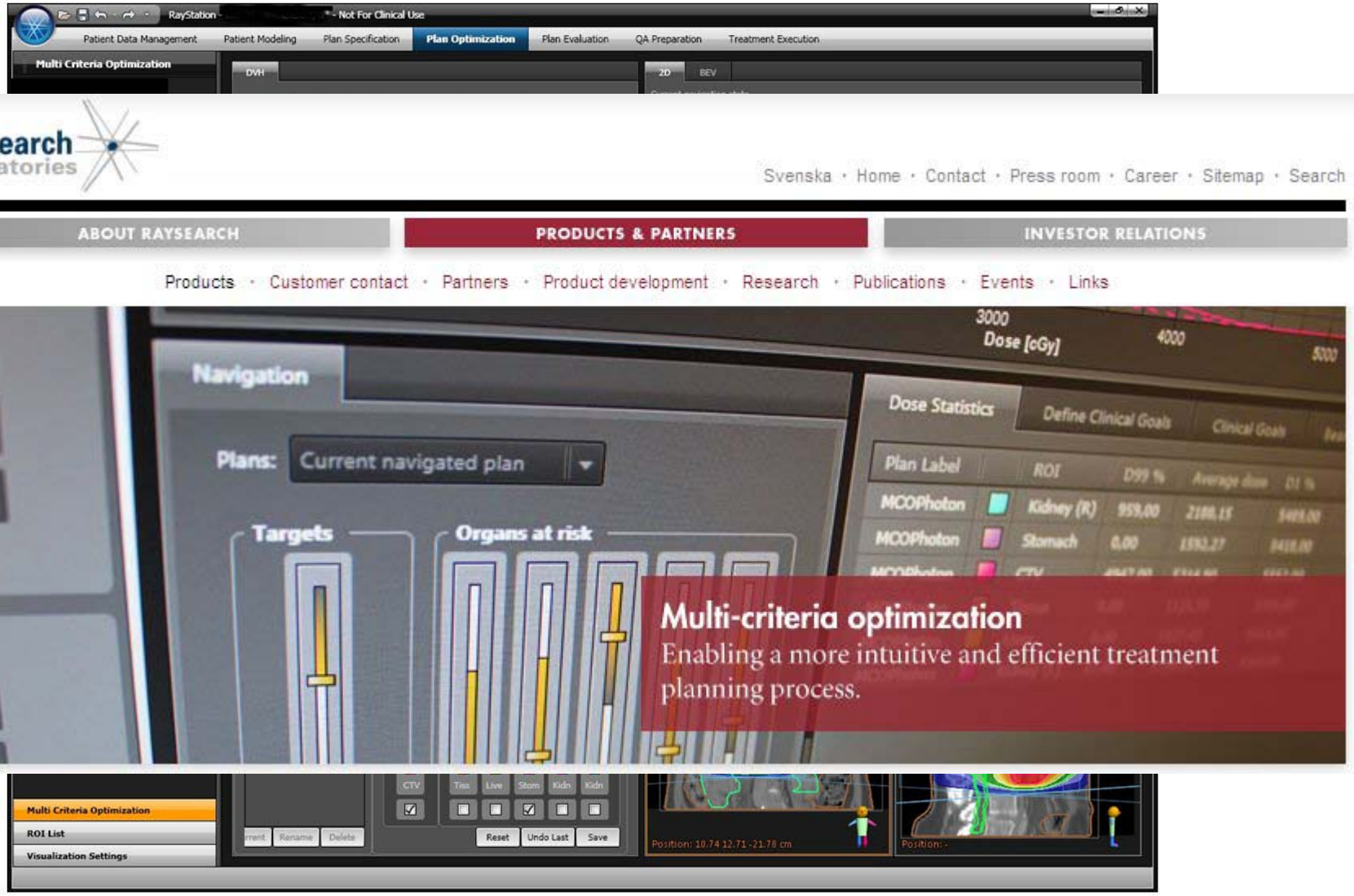
Pareto navigation tool



Courtesy to K.H. Küfer, (FHG-ITWM)

Navigation should be sensitive !!

RaySearch TPS: Pareto navigation

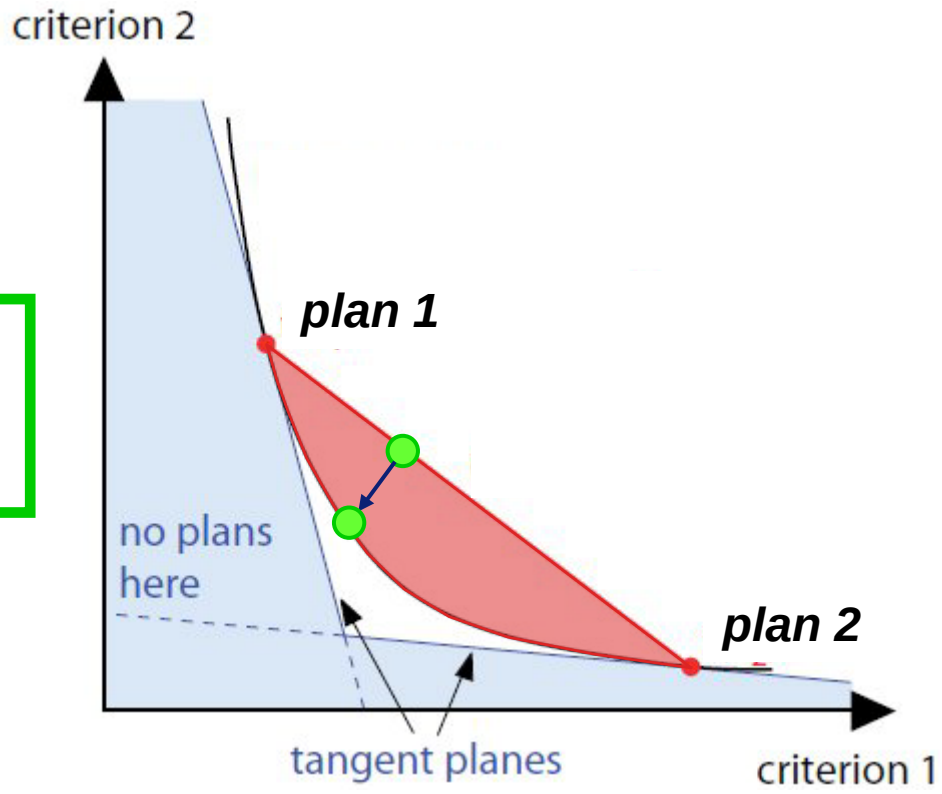


RaySearch TPS: plan library

Reduced workload in making plan database
Only making the achor-plans in the range of acceptable treatment plans

Navigation between plans results in plans in shaded region

Fast algorithm to project the interpolated point back on the real Pareto front



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Comparative analysis of Pareto surfaces in multi-criteria IMRT planning

K Teichert[1], P Süss[1], J I Serna[1], M Monz[1], K H Küfer[1] and C Thieke[2,3]

[1] Department of Optimization, Fraunhofer Institute for Industrial Mathematics (ITWM), Fraunhofer Platz 1, 67663 Kaiserslautern, Germany
[2] Clinical Cooperation Unit Radiation Oncology, German Cancer Research Center, Im Neuenheimer Feld 280, 69120 Heidelberg, Germany
[3] Department of Radiation Oncology, University Clinic Heidelberg, 69120 Heidelberg, Germany

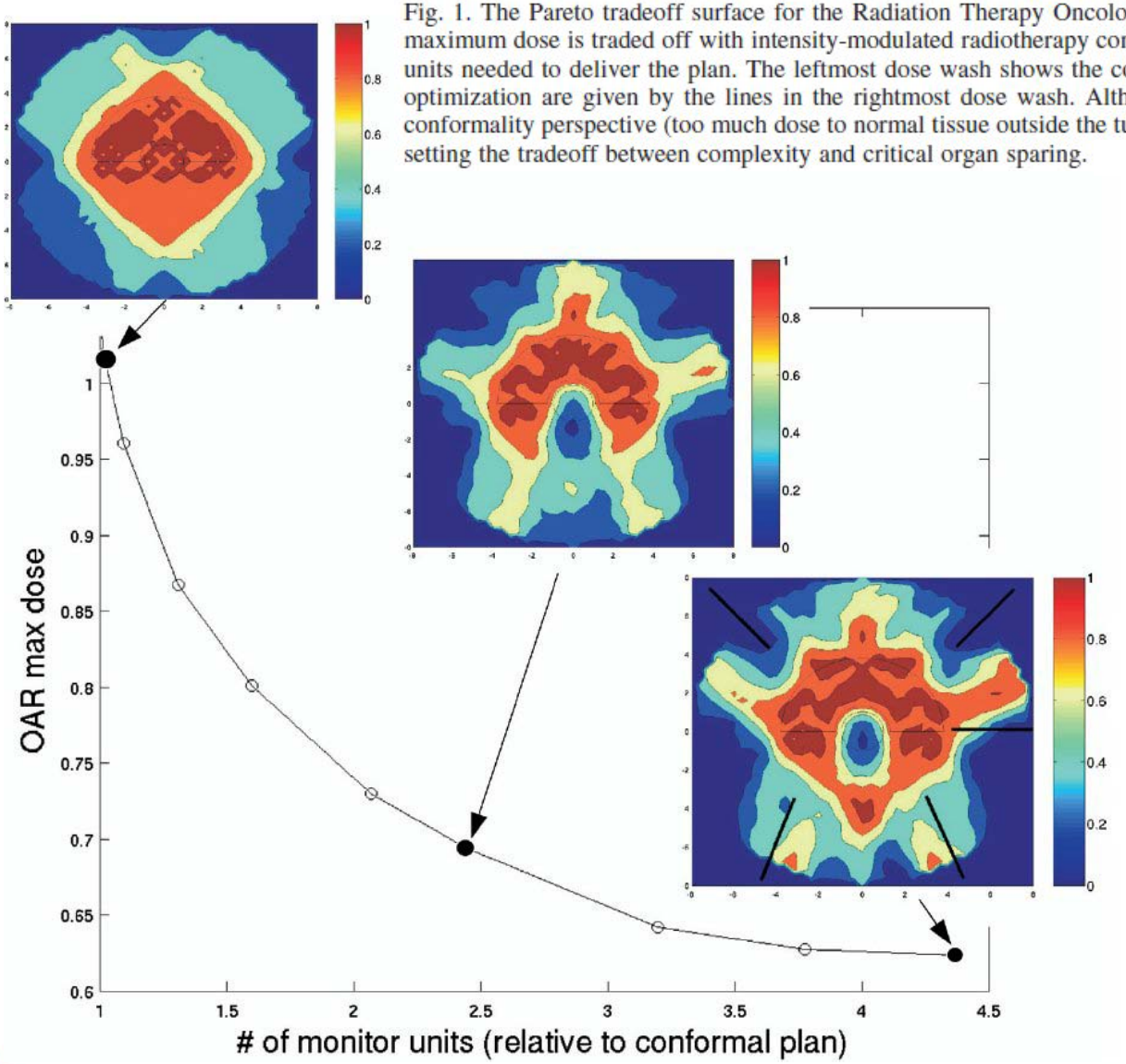
E-mail: katrin.teichert@itwm.fhg.de

Pareto fronts using multiple beam angle configurations

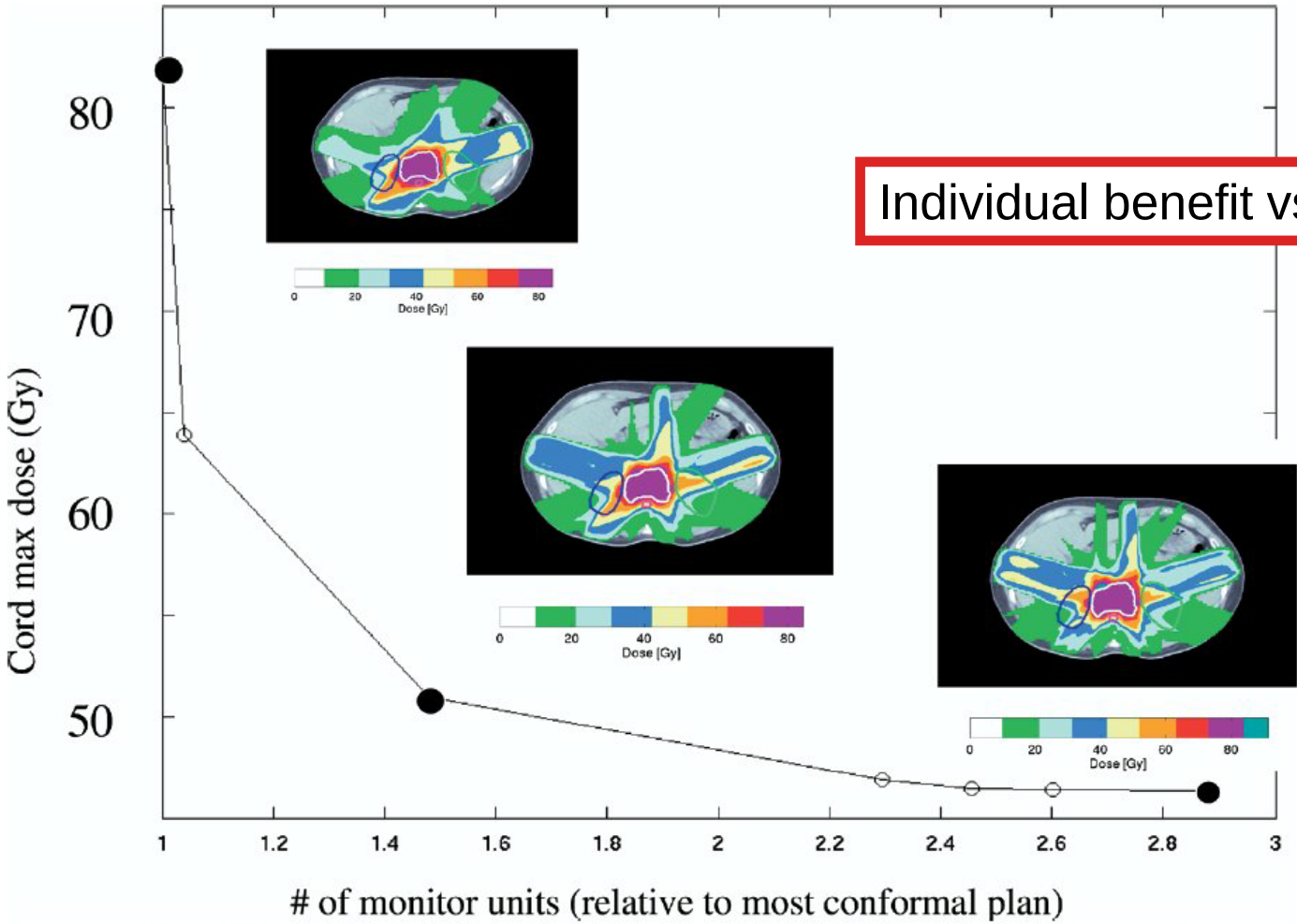
Phys.Med.Biol.56(2011) 3669-3684

Plan quality versus treatment delivery time

Fig. 1. The Pareto tradeoff surface for the Radiation Therapy Oncology Group phantom study. Organ at risk (OAR) maximum dose is traded off with intensity-modulated radiotherapy complexity, as measured by the number of monitor units needed to deliver the plan. The leftmost dose wash shows the conformal plan. The beam directions used in this optimization are given by the lines in the rightmost dose wash. Although none of these plans is acceptable from a conformality perspective (too much dose to normal tissue outside the tumor), this example demonstrates in the simplest setting the tradeoff between complexity and critical organ sparing.



Plan quality versus treatment delivery time



Individual benefit vs group

Fig. 3. The tradeoff between spinal cord sparing and intensity-modulated radiotherapy complexity. Dose contours for three points on the Pareto surface show that added complexity is needed to avoid the spinal cord. The clinical target volume is contoured in white.

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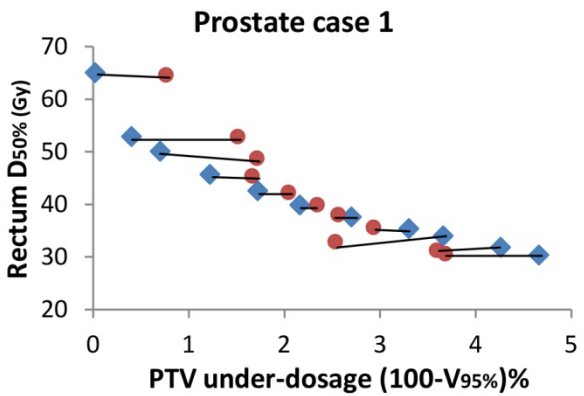
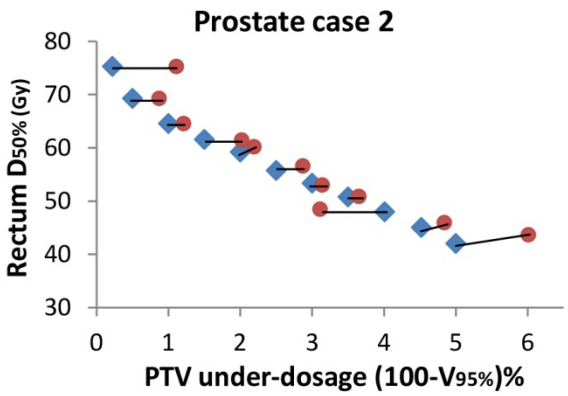
Limitations of this approach

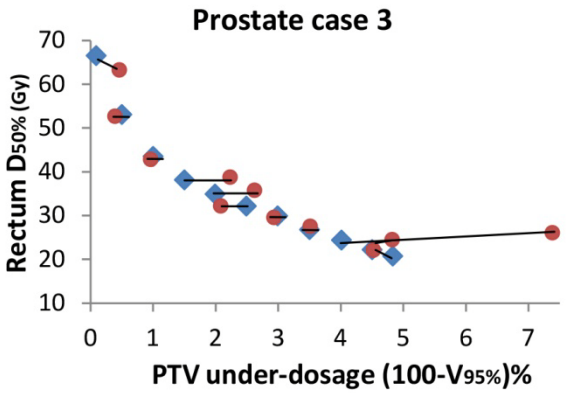
Difference between navigated and delivered plans?

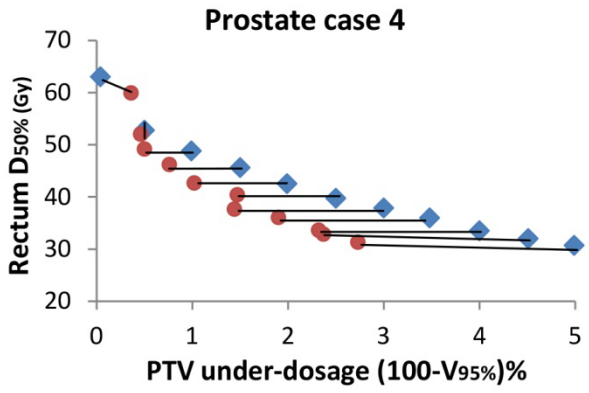
e.g. 5 prostate patients

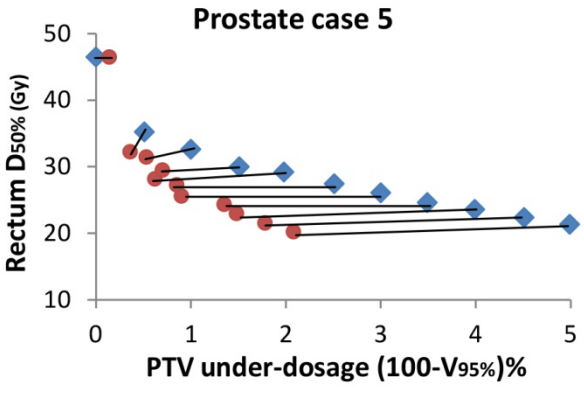
improvement was achieved partly by compromising other parameters, such as increasing doses to other OARs or by creating small “hotspots”











- Pareto plans
- Deliverable plans

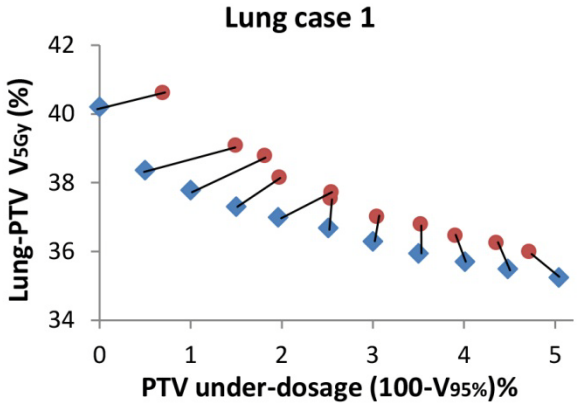
Limitations of this approach

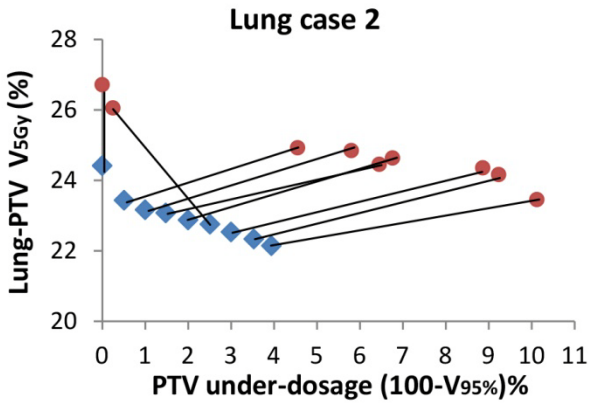
e.g. 5 lung patients

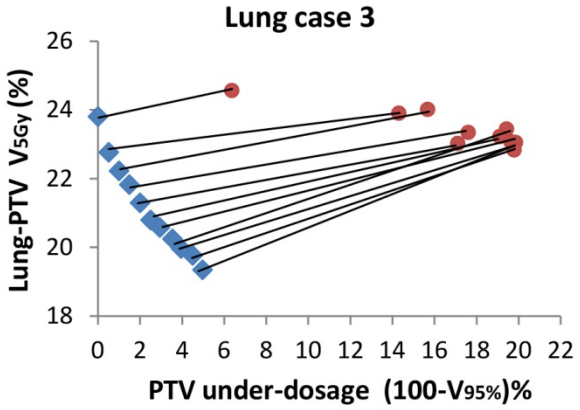
Deliverable plans systematically worse than pareto plans

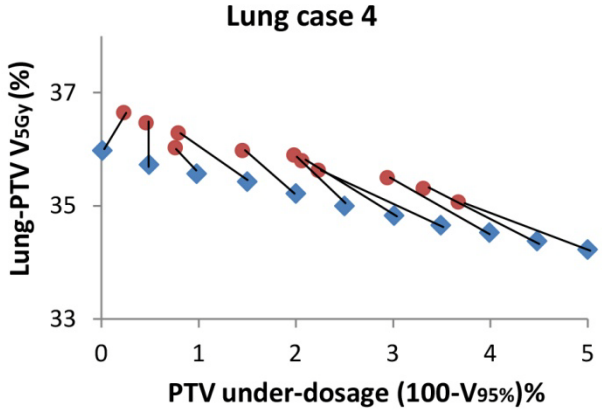
fluence-based treatment plans does not take into account the effect of lateral electron transport in the presence of heterogeneities

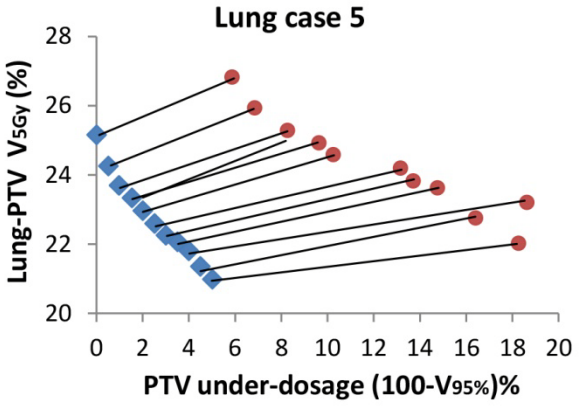
Small PTVs provided bigger differences











- Pareto plans
- Deliverable plans

Conclusion

Finding the ‘best’ plan is a real challenge

Treatment delivery time should be part of Pareto navigation

Pareto navigation tools are very helpful in exploring the solution area, however, navigation should be done in a sensitive way

Keep track of the end result of each navigation to improve the standard input

Lack of systematic differences between navigated and deliverable plans makes it difficult to predict the dosimetric change, its direction and its magnitude.

Physicist’s perspective

Gert Meijer

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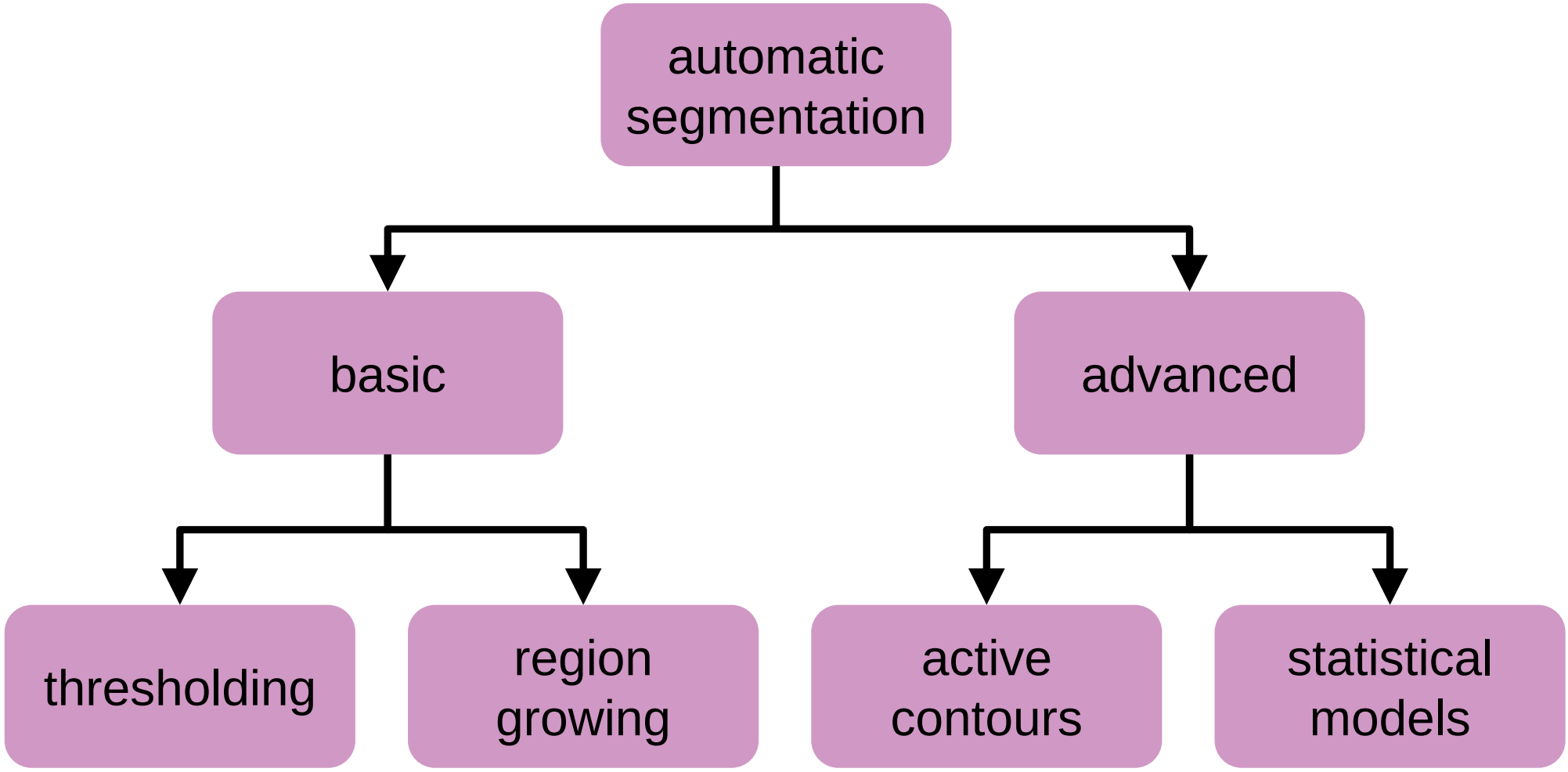
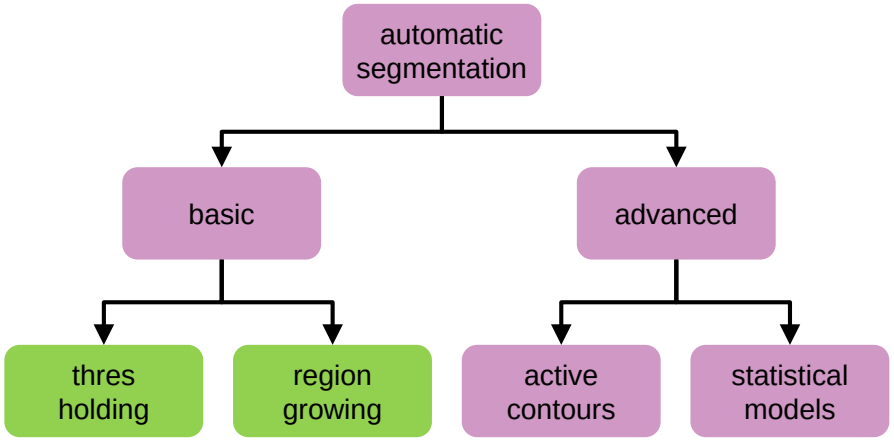
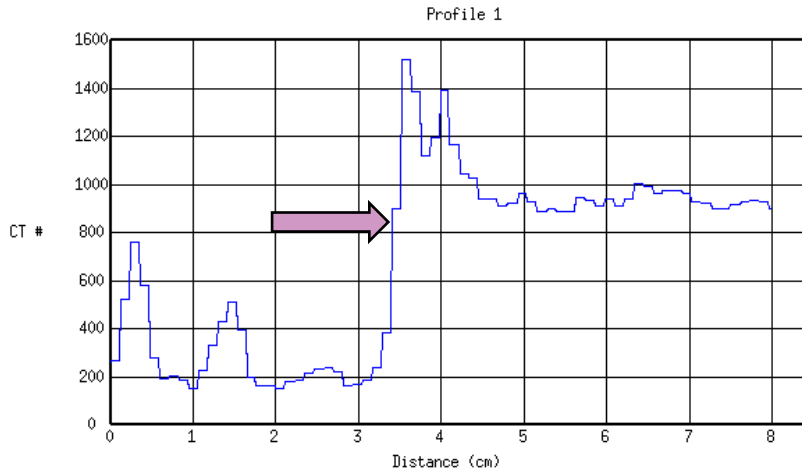
Emerging topics

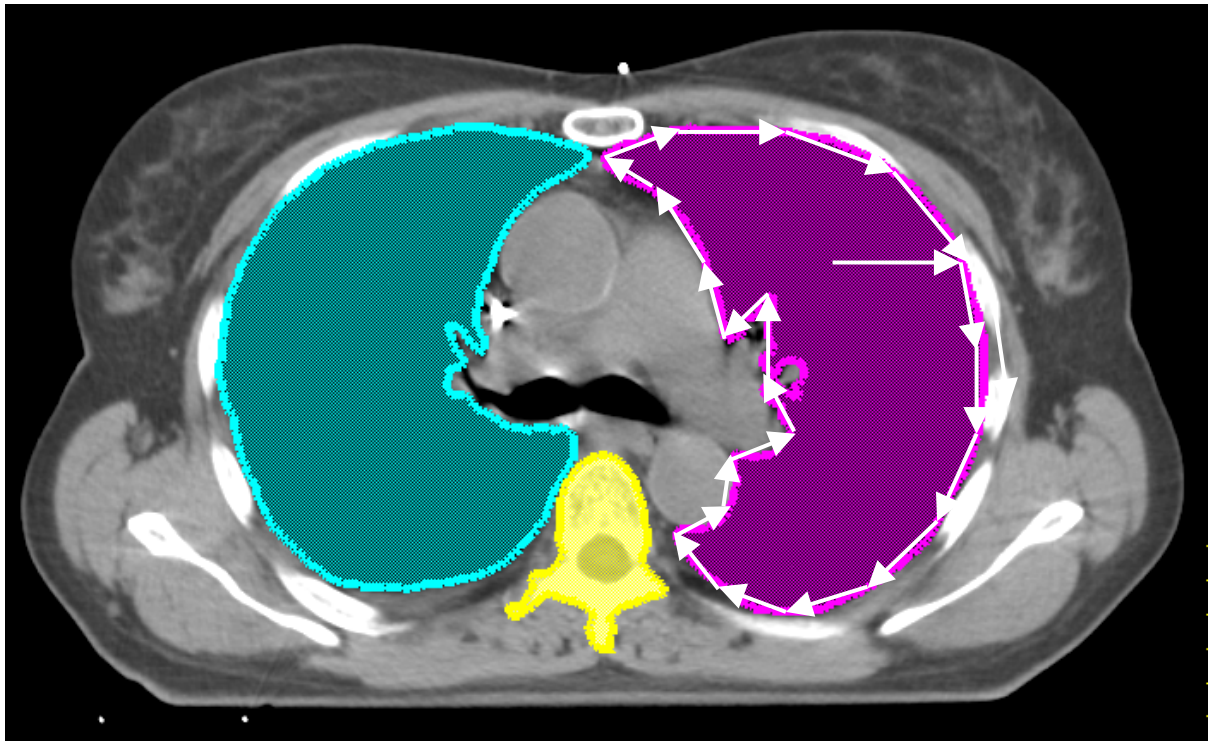
- Normal tissue segmentation
- Plan quality prediction & Automated planning
- Online (MRI linac) planning

Automatic normal tissue segmentation









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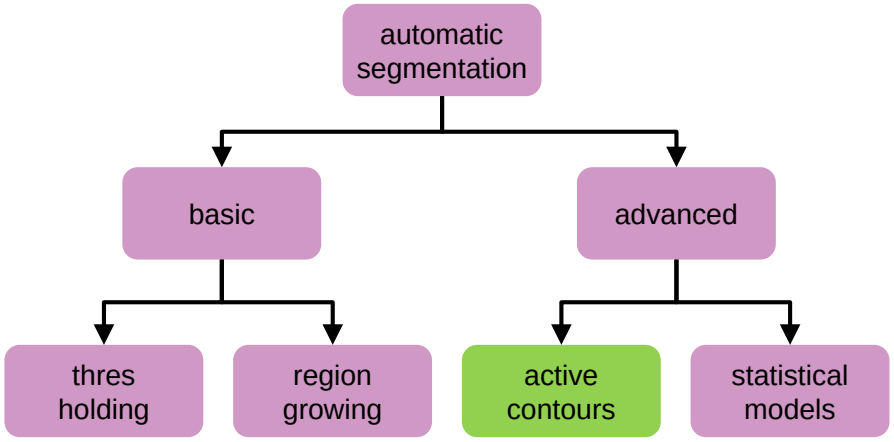
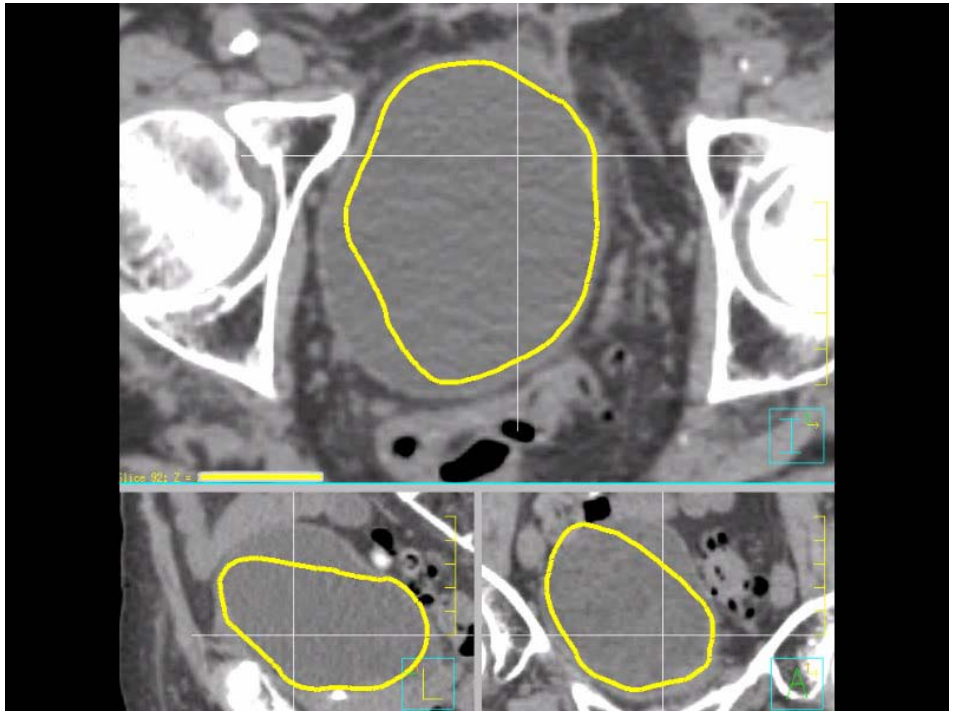
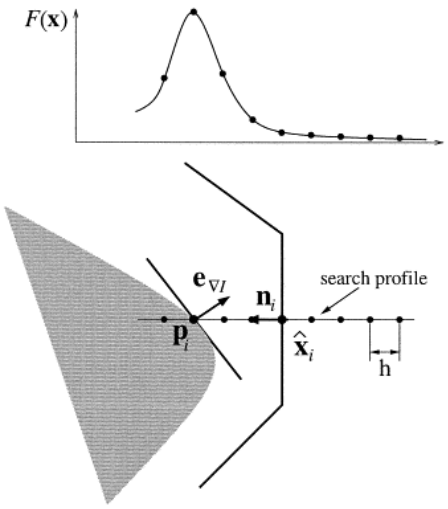
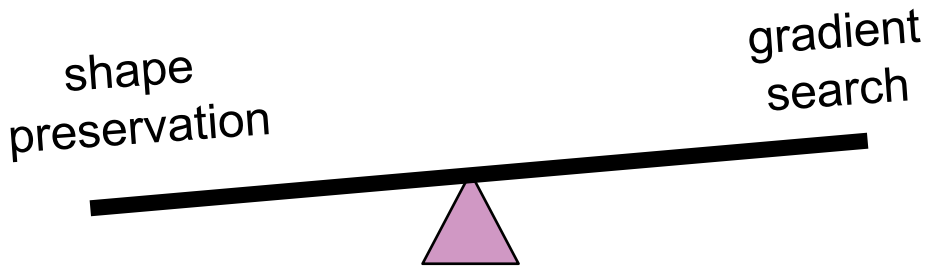






Pekar *et al.* 2004 IJROBP 60(3)



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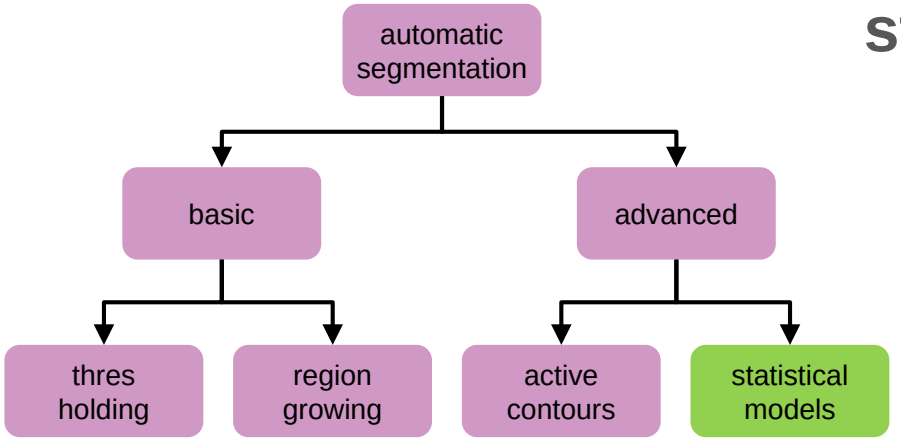
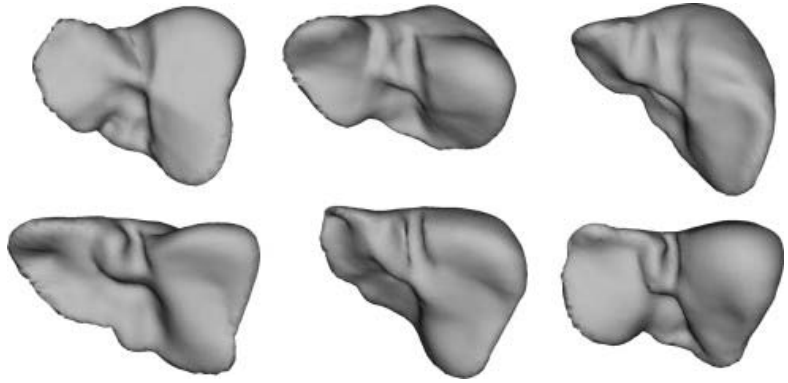
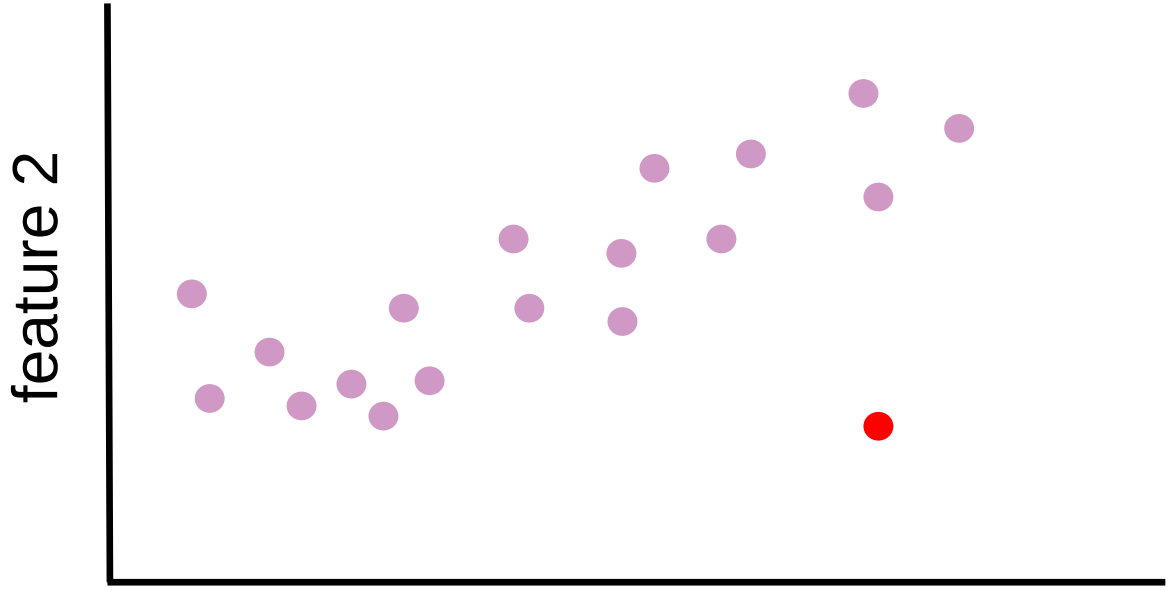
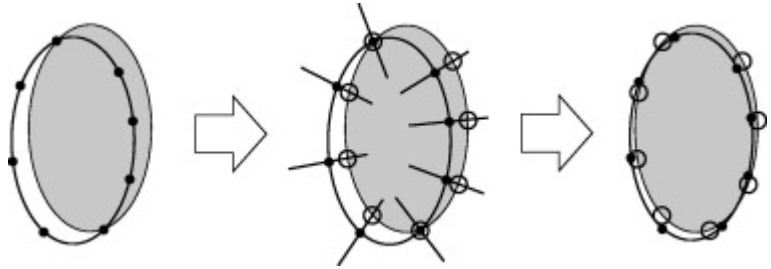
statistical shape models





principal modes liver





Heimann & Meizner Medical image analysis 13(4) 2009

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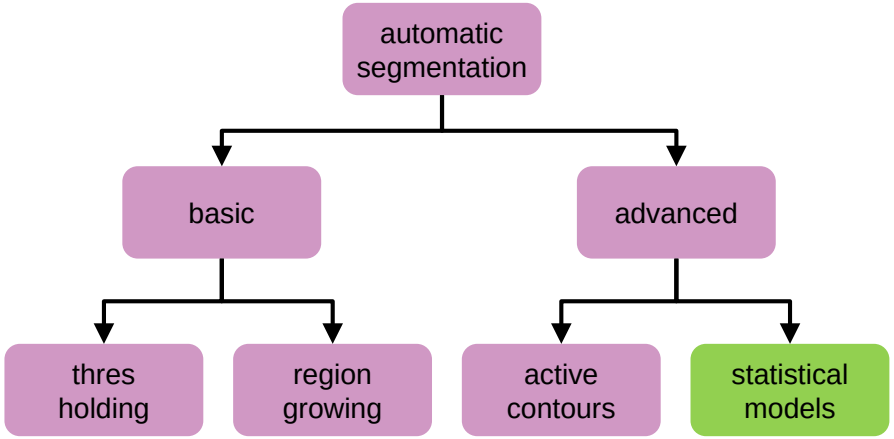
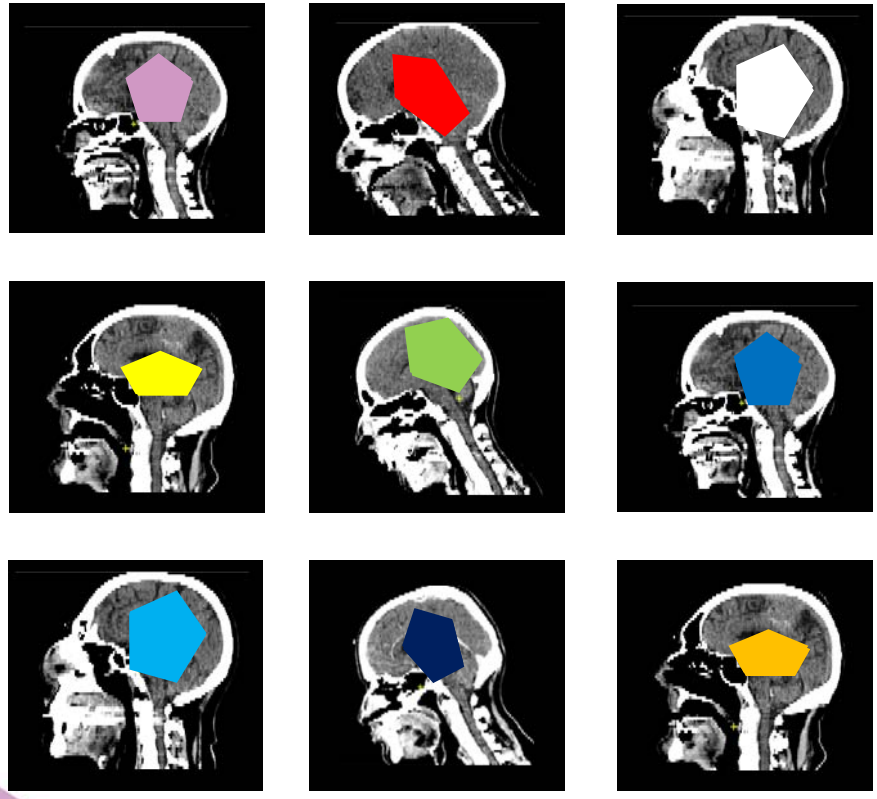
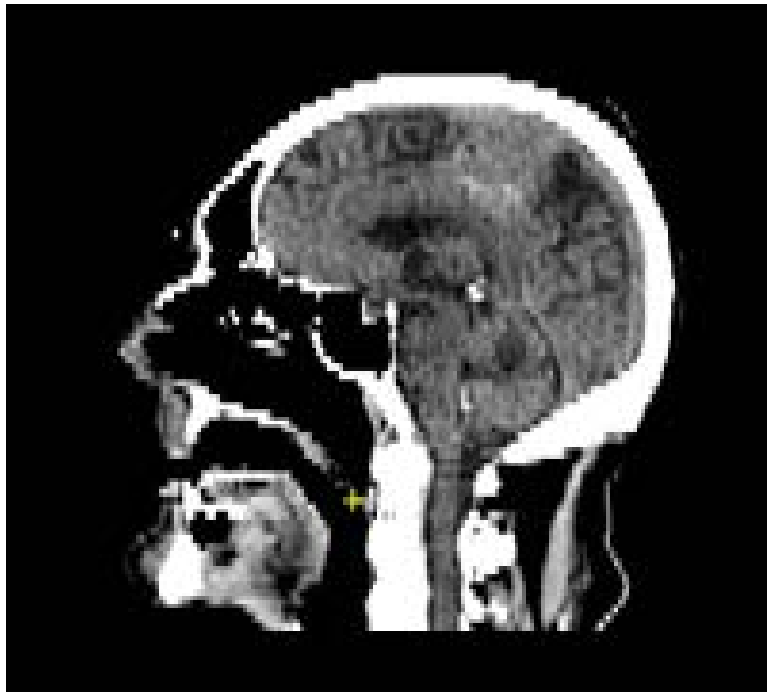
atlas based models





atlas set

non-rigid registration



remove outliers based on estimated performance (e.g. DICE)

Langerak *et al. IEEE Trans Med Imaging. 2010 Dec;29(12)*

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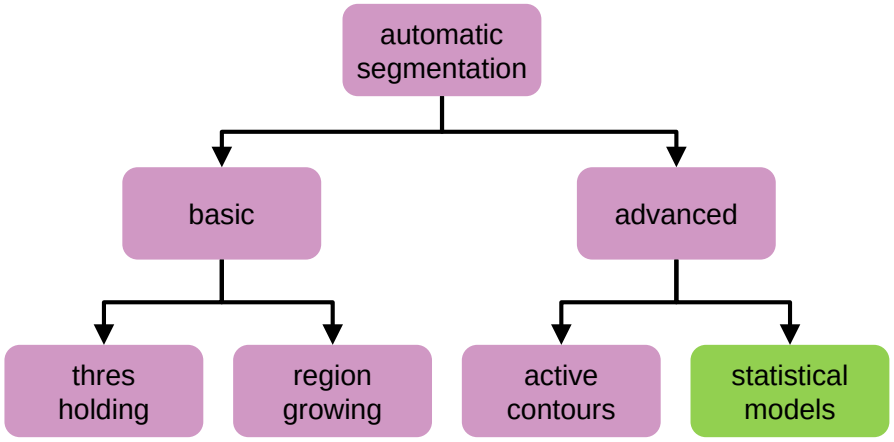
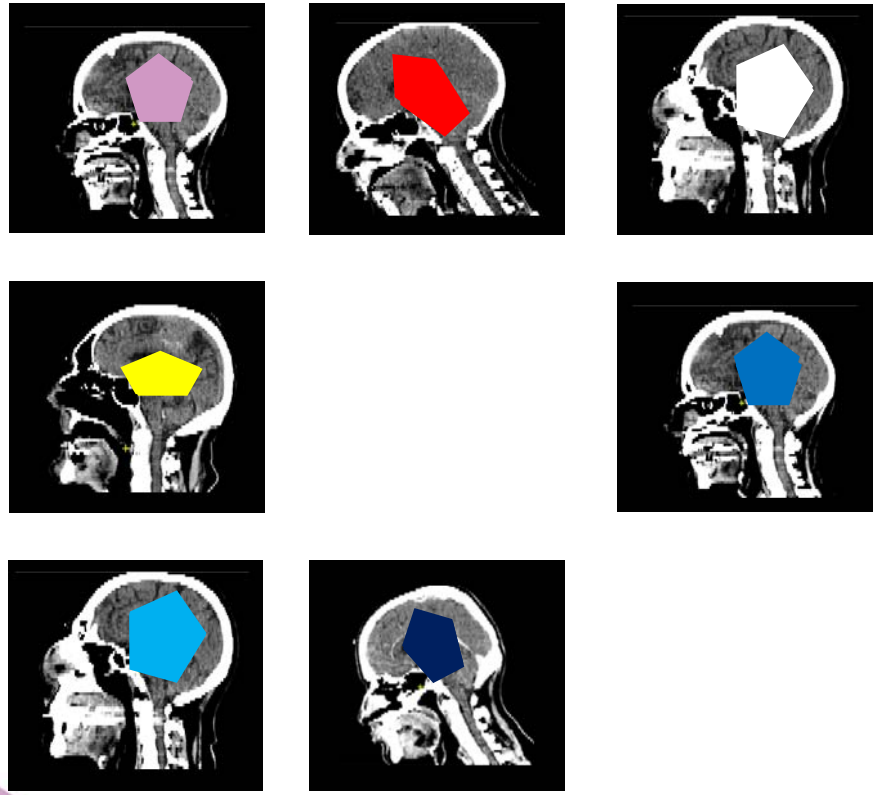
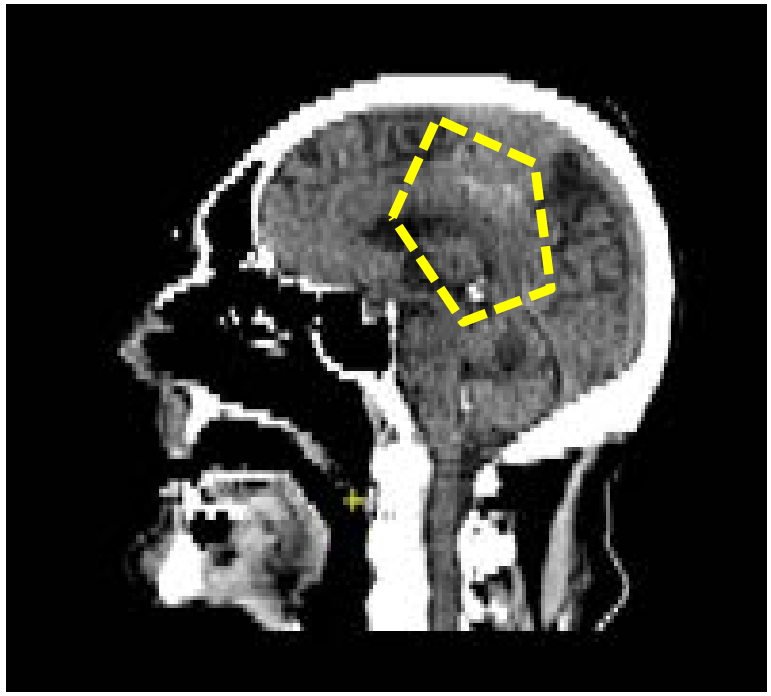
atlas based models





atlas set

non-rigid registration



majority vote

Langerak *et al. IEEE Trans Med Imaging. 2010 Dec;29(12)*

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Summary

- Many methods available!
- Statistical models and atlas-based are the most suitable for normal tissue segmentation.
- But... they require training data or atlas
- Manual validation of experts is still used as golden truth

the planning time to complete a (complex) H&N case is typically

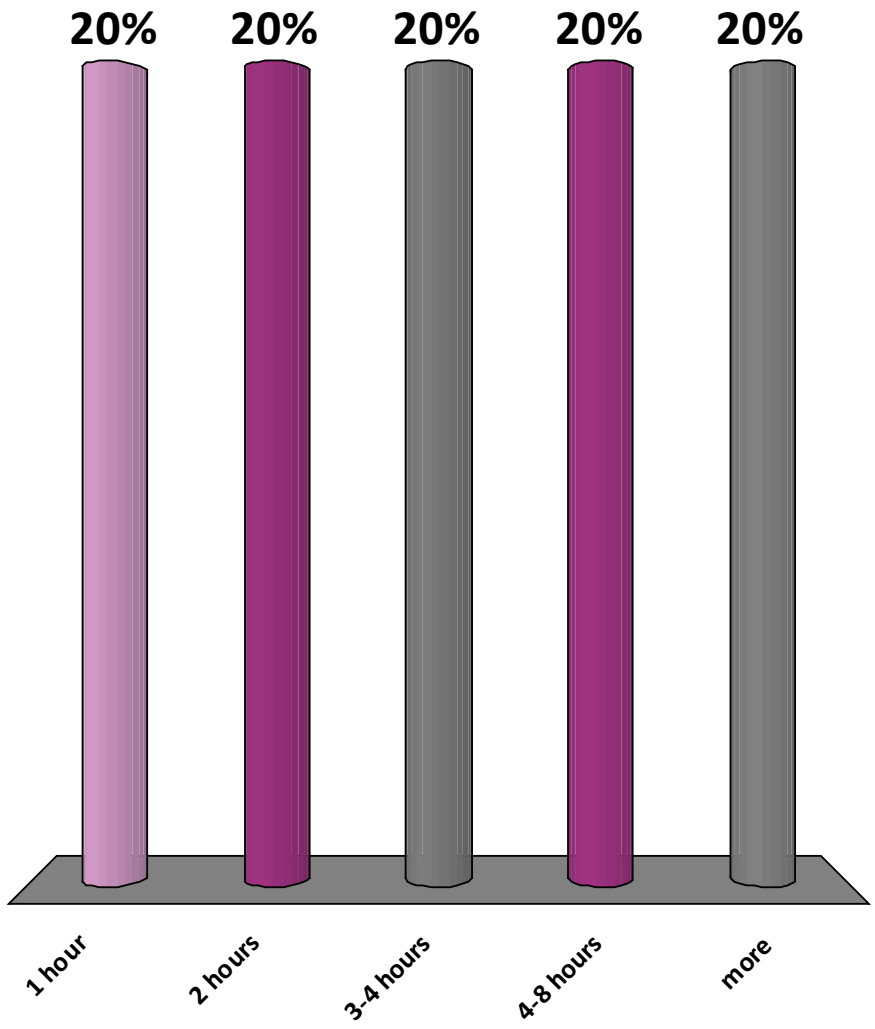
A. 1 hour

B. 2 hours

C. 3-4 hours

D. 4-8 hours

E. more



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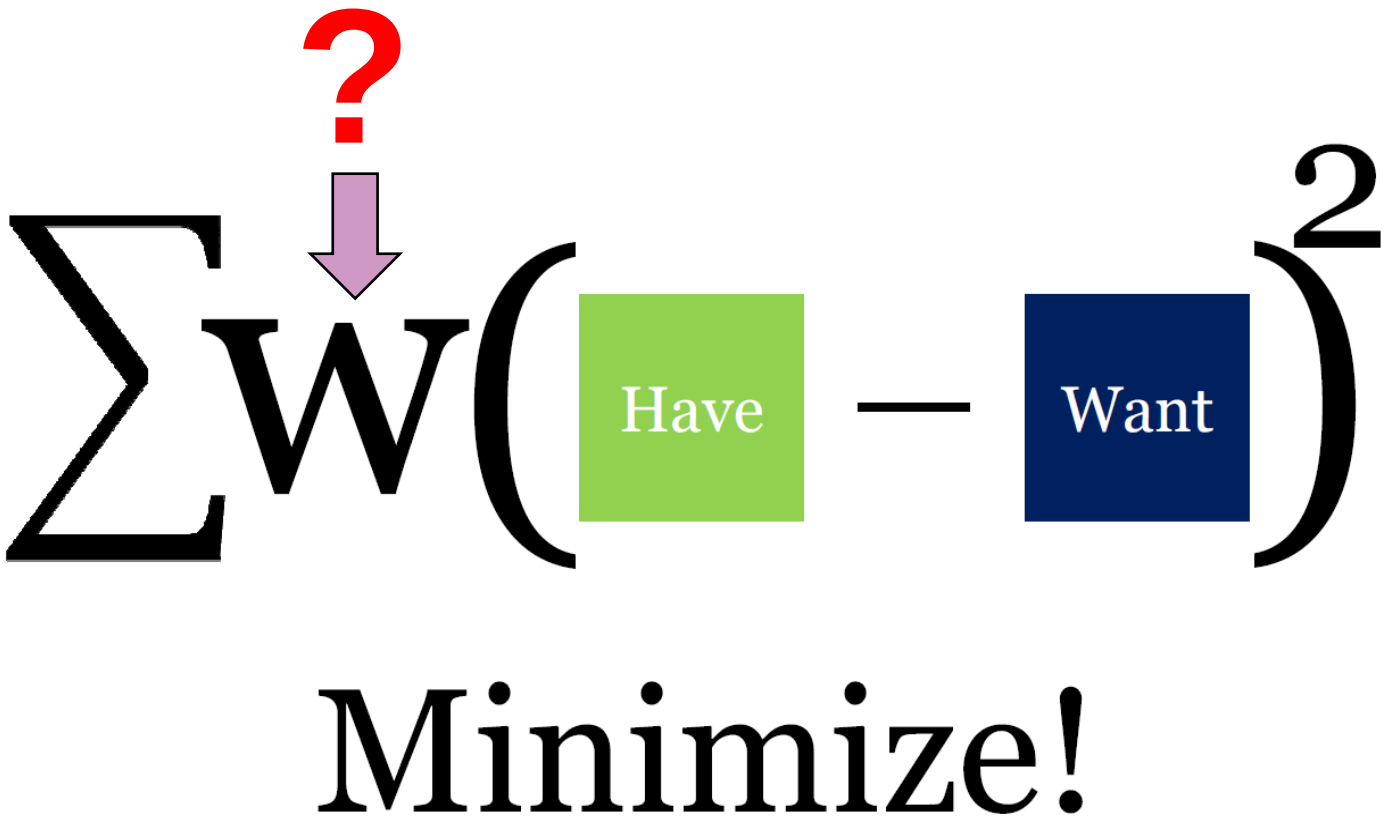
Templates and Automated Plan Generation



Sebastian Breedveld
Treatment planning workshop
ESTRO 2014 Vienna

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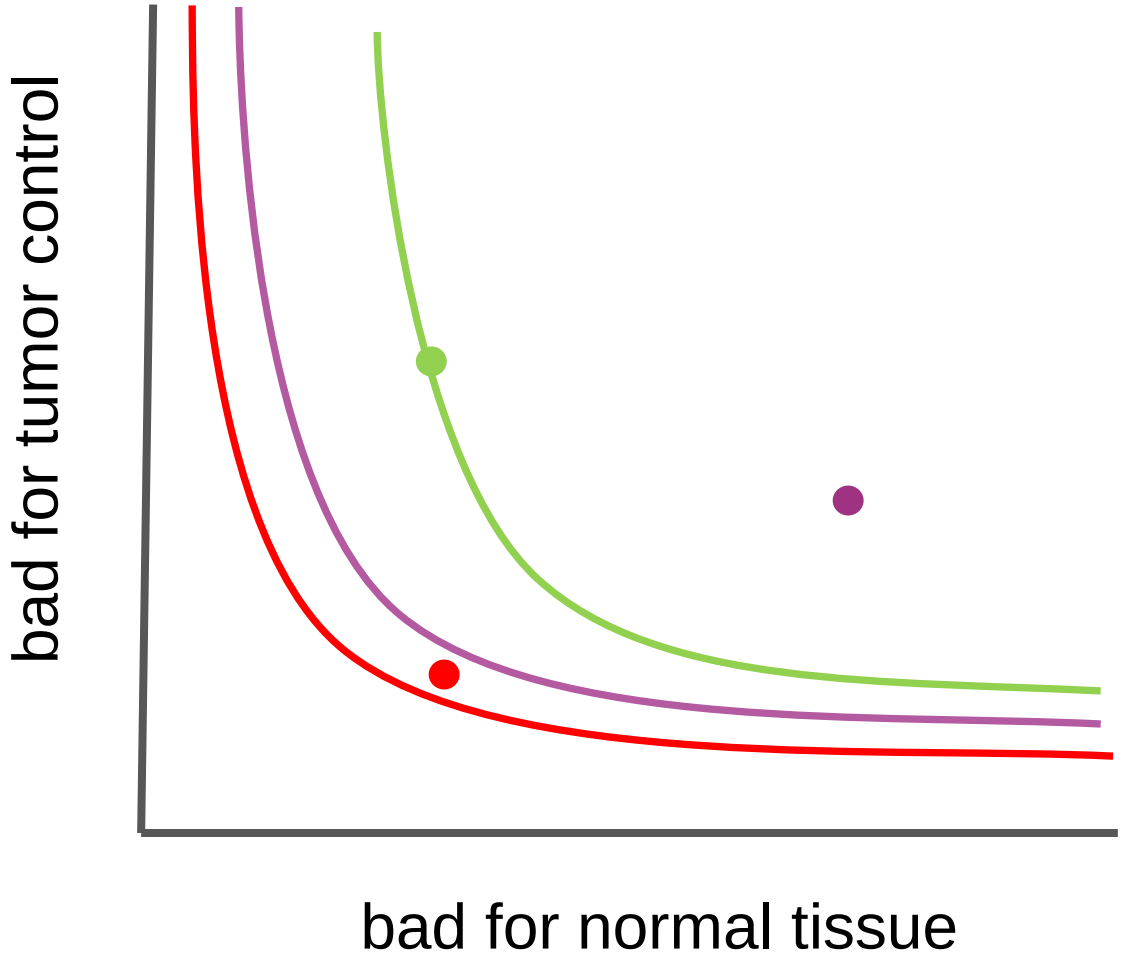
Templates and Automated Plan Generation



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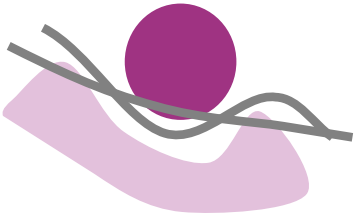
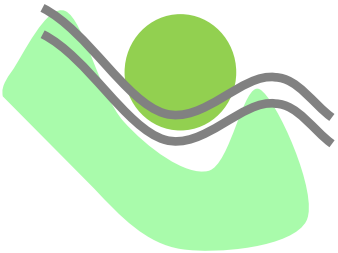
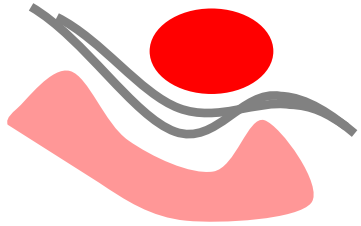


pat 2



pat 3



How to create a good set of objectives?

Knowledge-based

large database
find similar case
extract objectives
reproduce plan

Automated planning

automate decision making
wish-list
define and *prioritize* objectives
iteratively navigate towards
and over pareto surface

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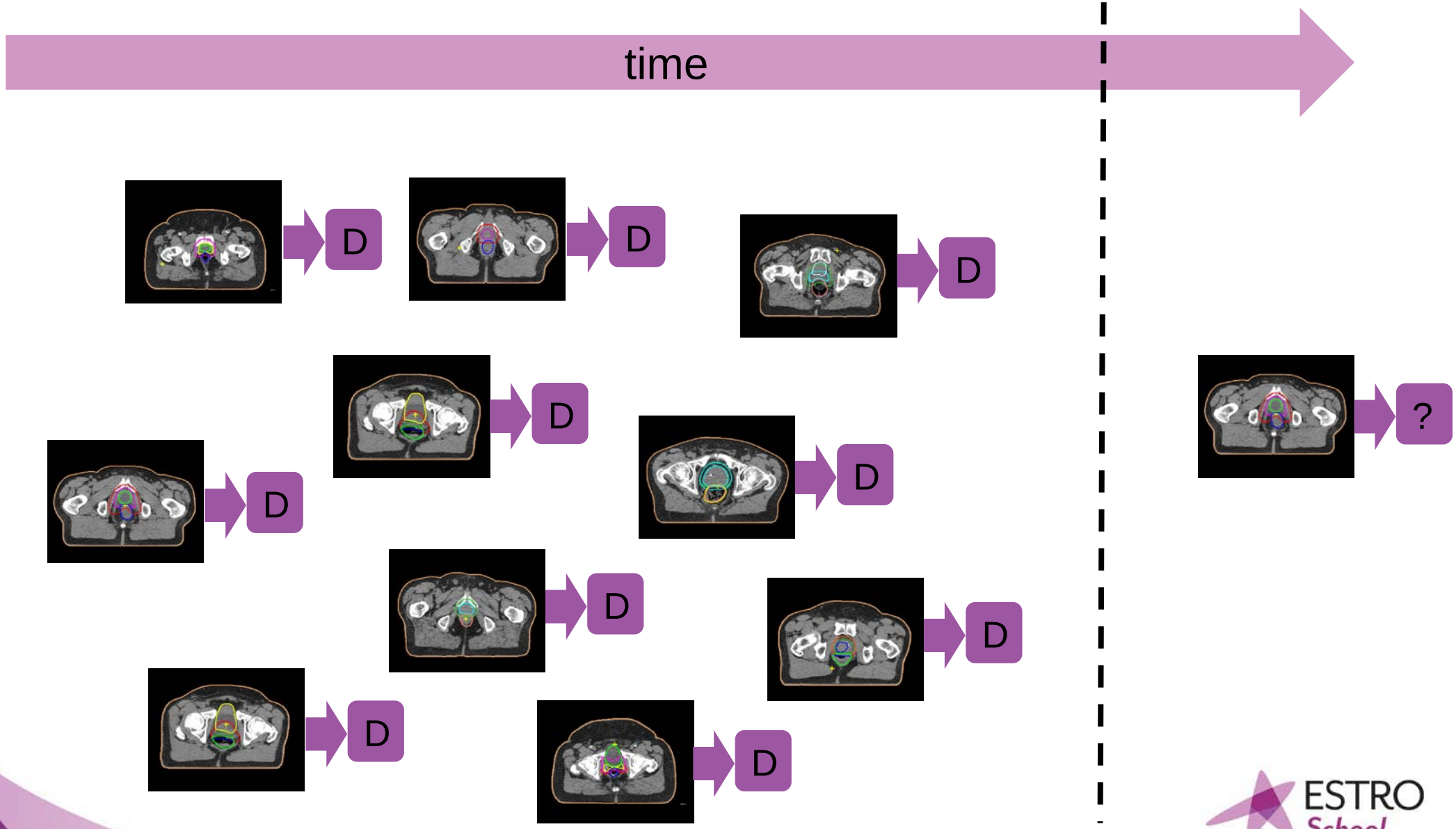
Knowledge-based approach



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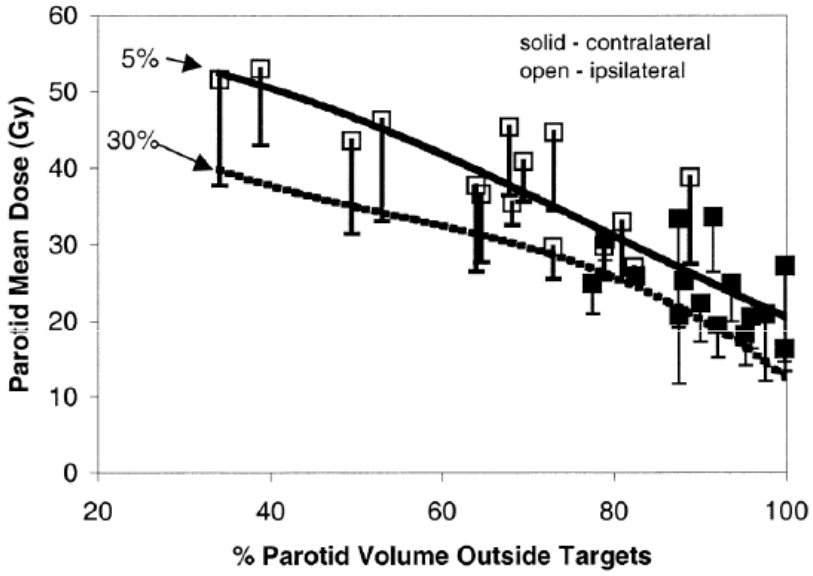
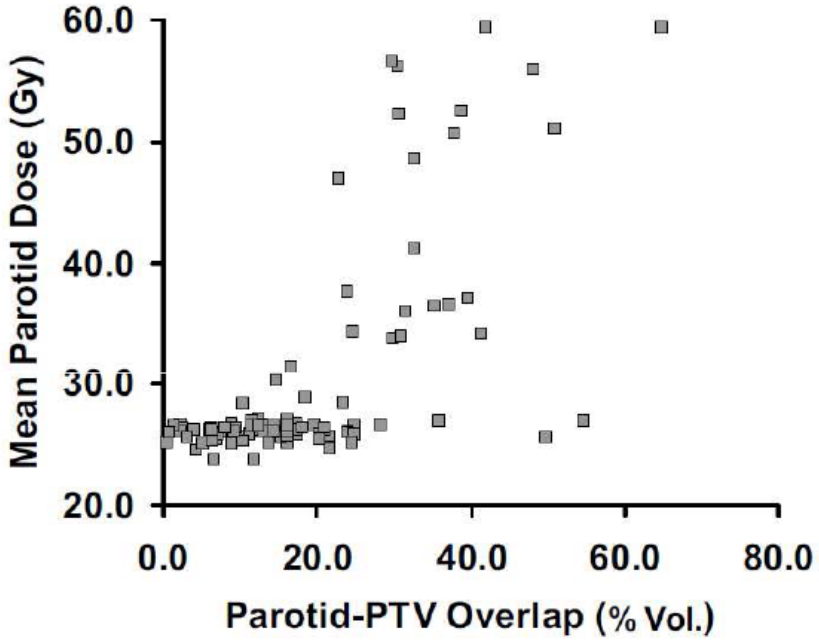
geometric quantification = dosimetric quantification

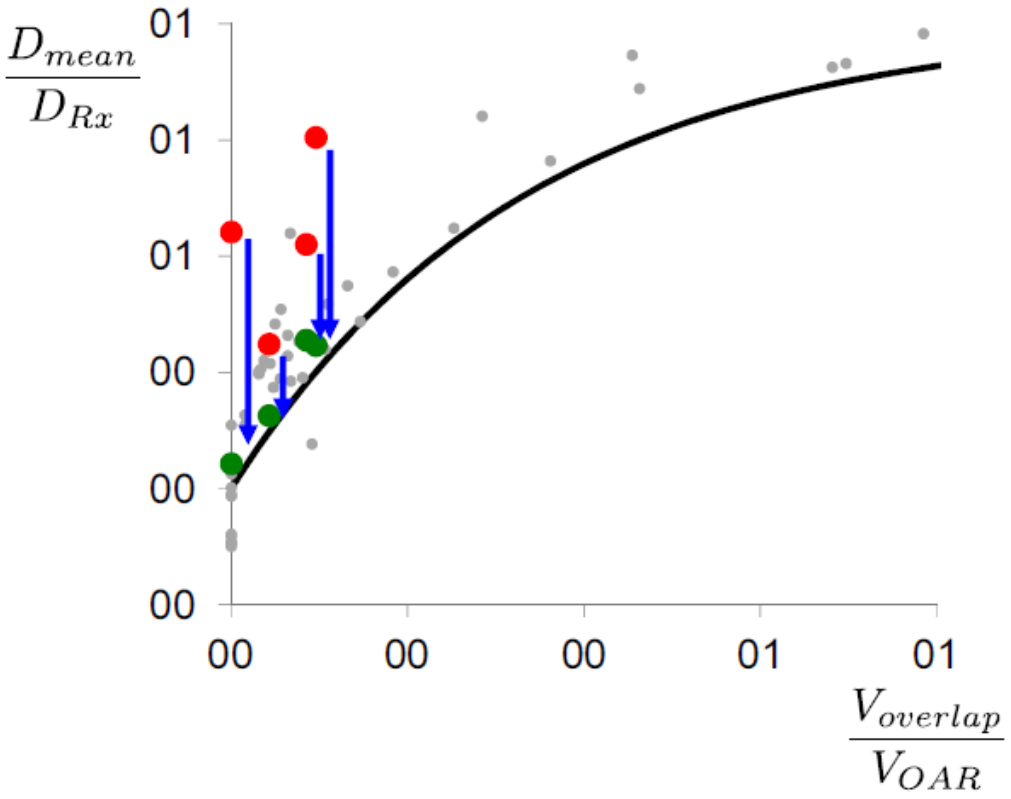


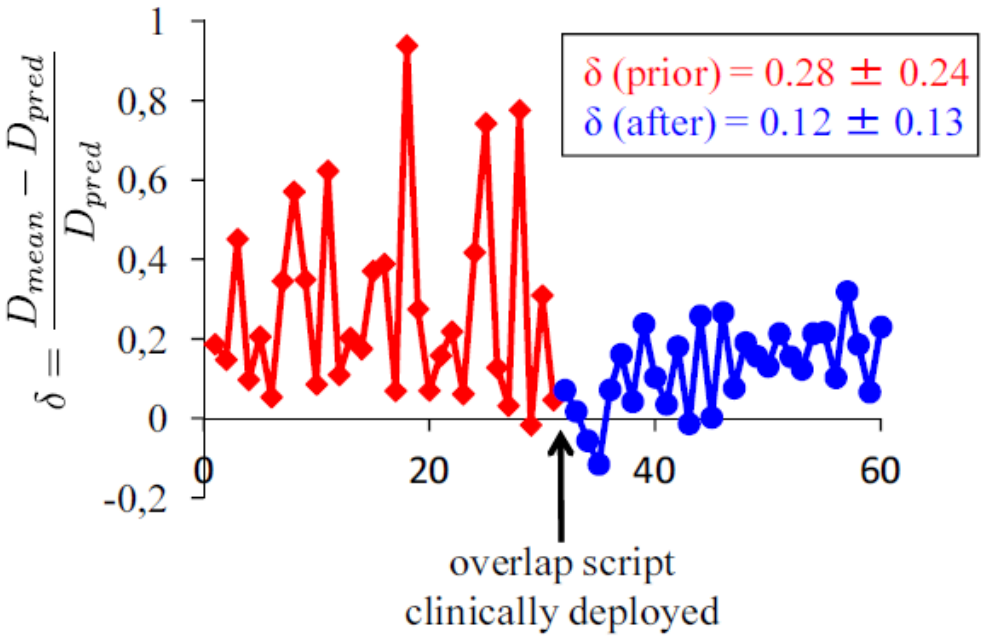
Vineberg, K. A. *et al*. Is uniform target dose possible in IMRT plans in the head and neck? *Int J Radiat Oncol Biol Phys* 52 (5):1159-72 (2002)



Hunt, M.A. *et al.* Geometric factors influencing dosimetric sparing of the parotid glands using IMRT, *Int J Radiat Oncol Biol Phys* 66 (1):296-304 (2006)

catch and correct suspected outliers





KL Moore *et al.*, IJROBP 81 (2010)

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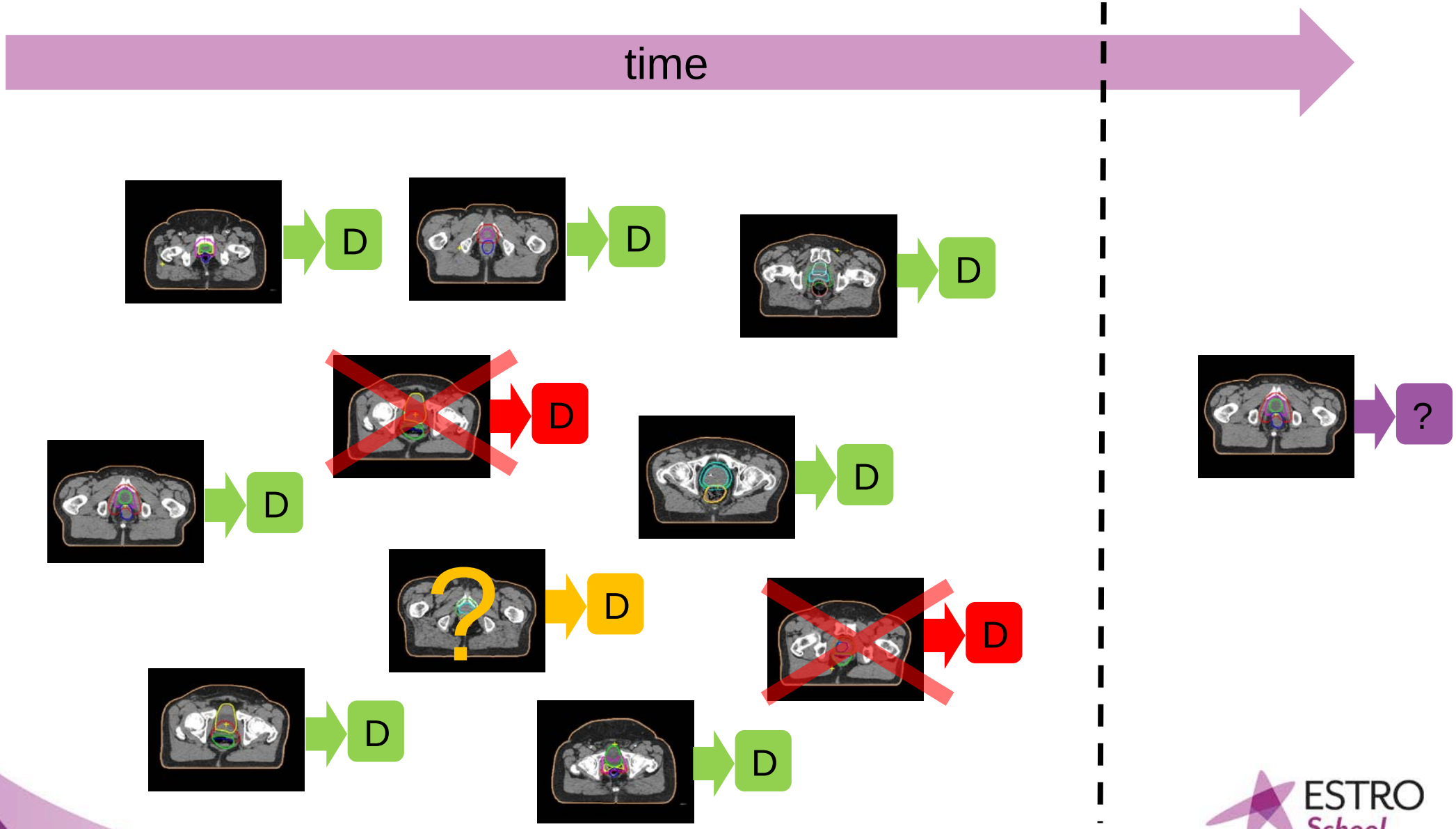
Knowledge-based approach



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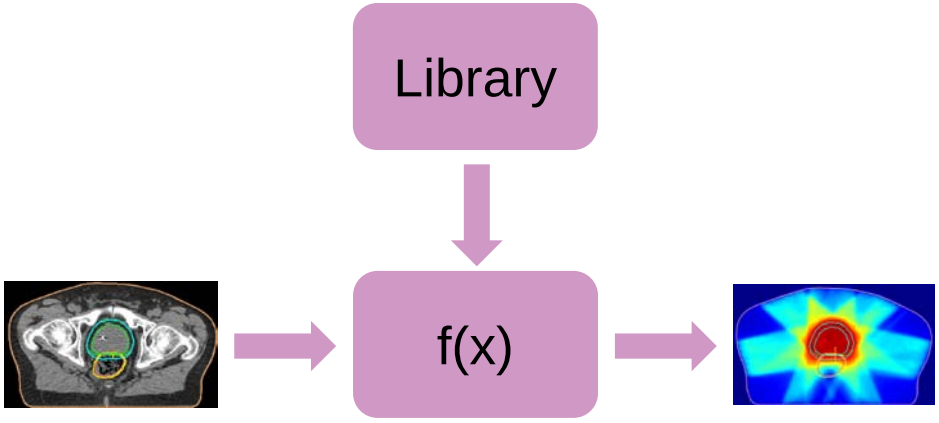

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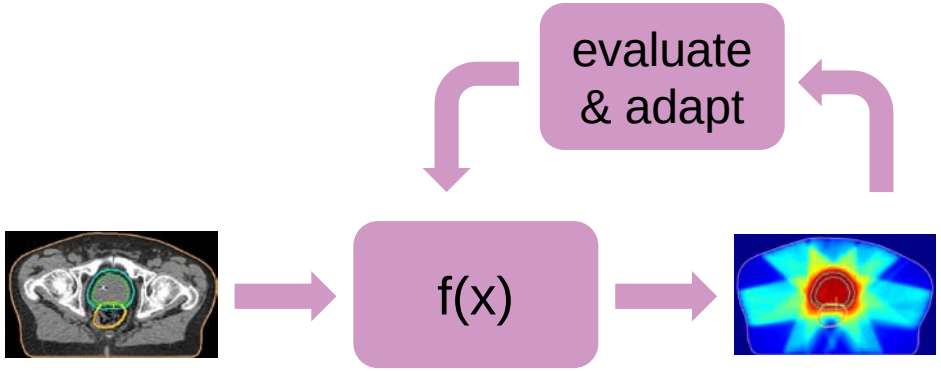

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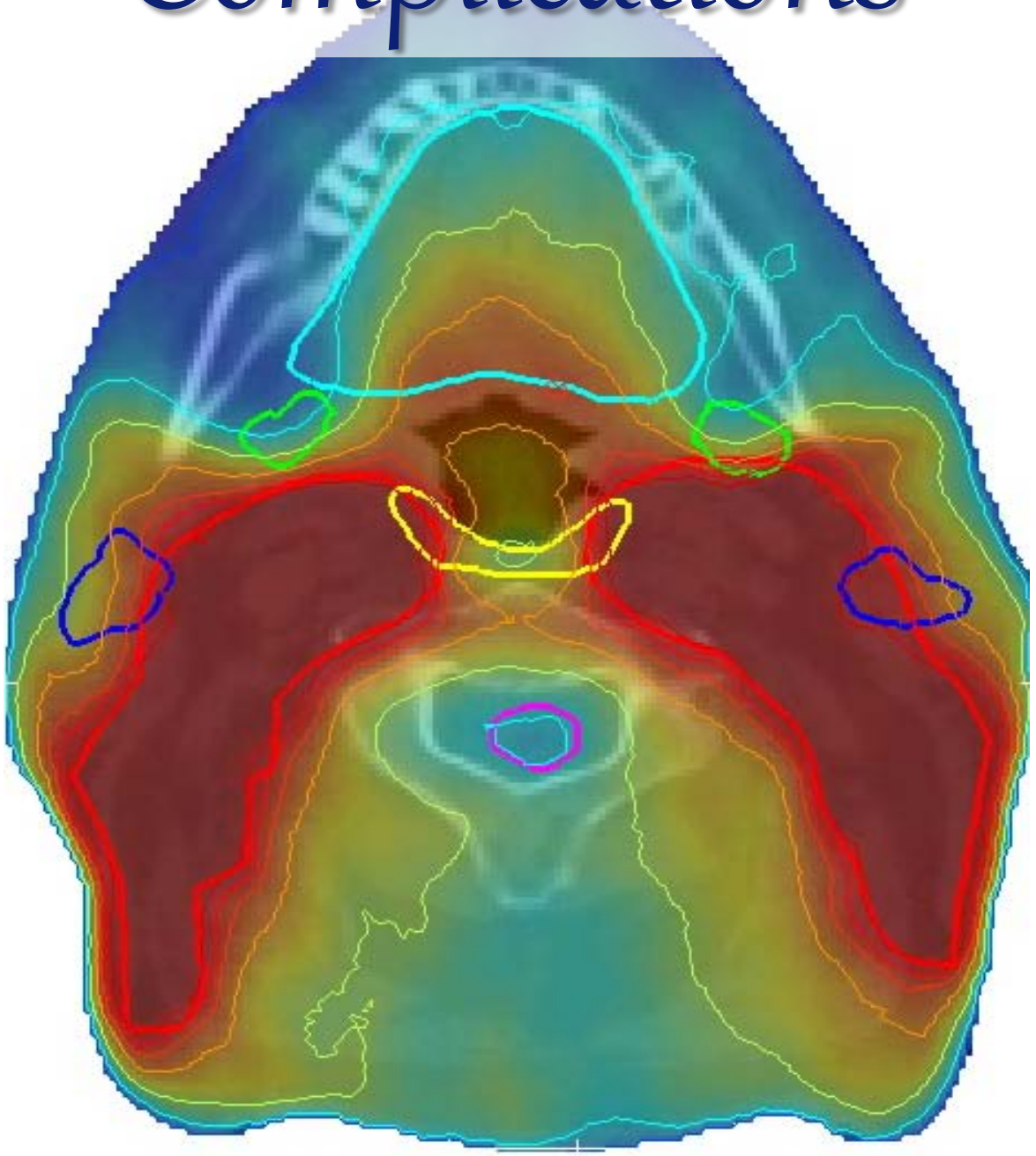
Source: enjoylocations.com

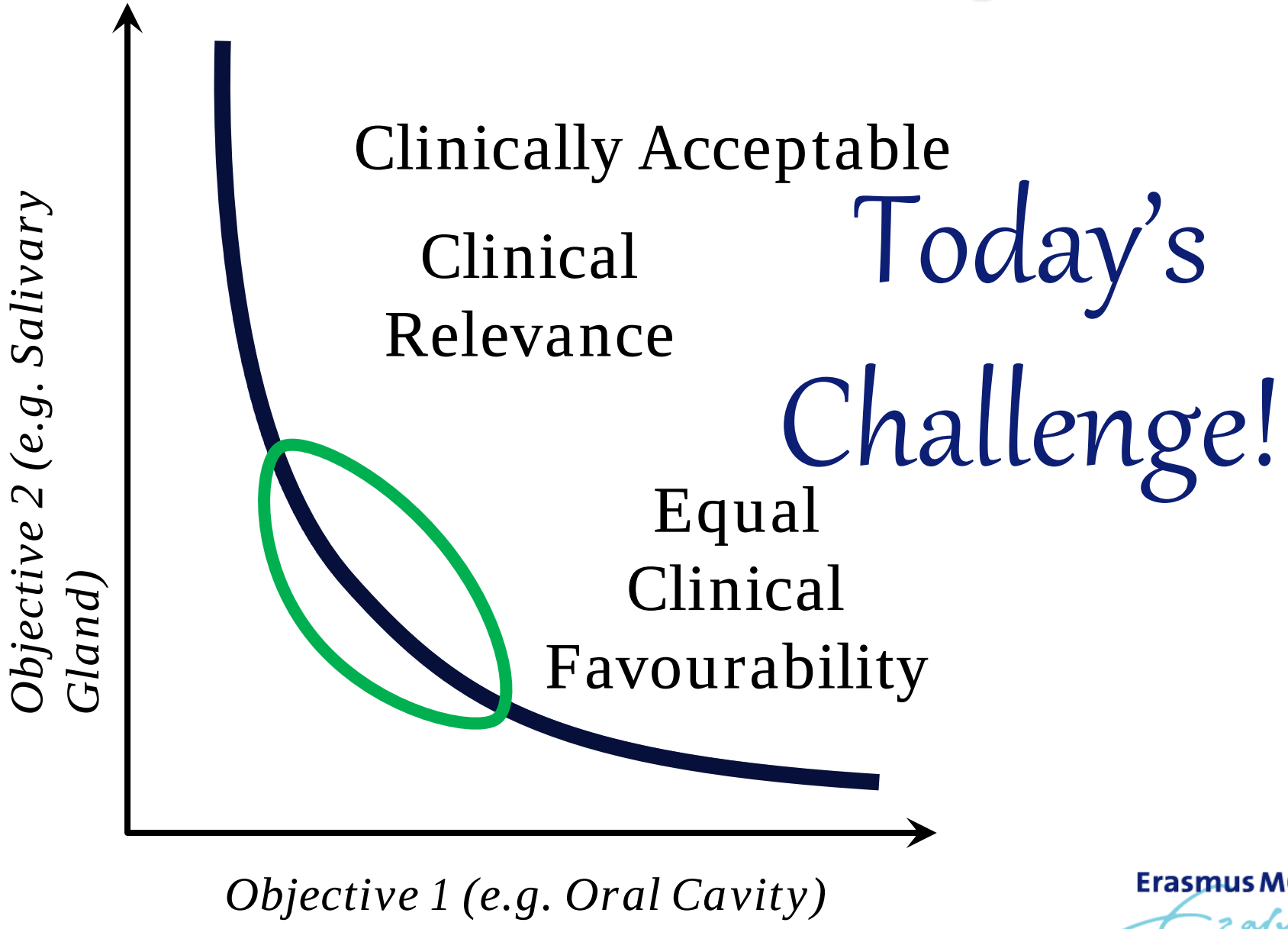
Complications



Acknowledgements: Sebastian Breedveld

Erasmus MC

Clinical Favourability



Acknowledgements: Sebastian Breedveld

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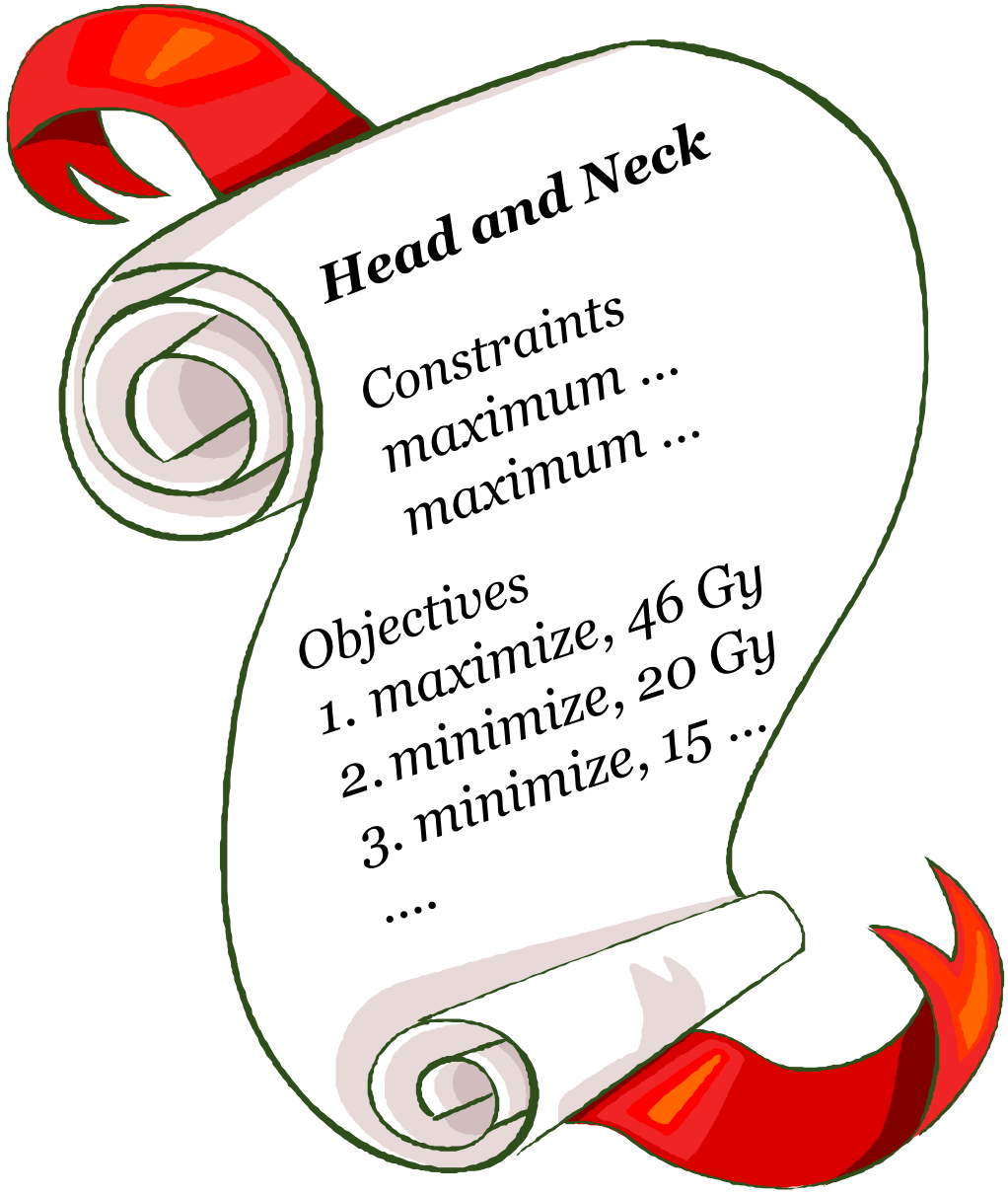
Wish-list: Formalised DM



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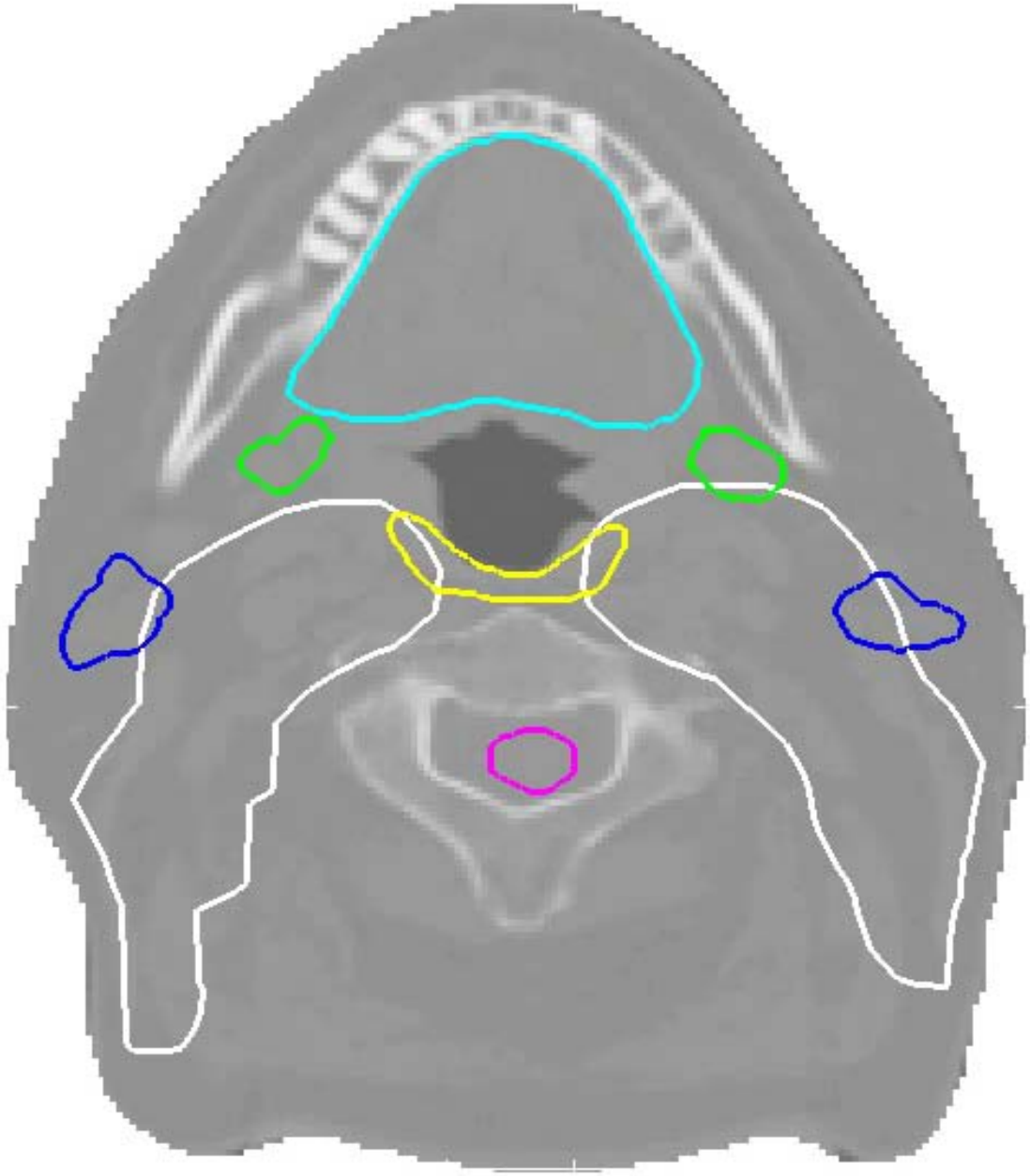

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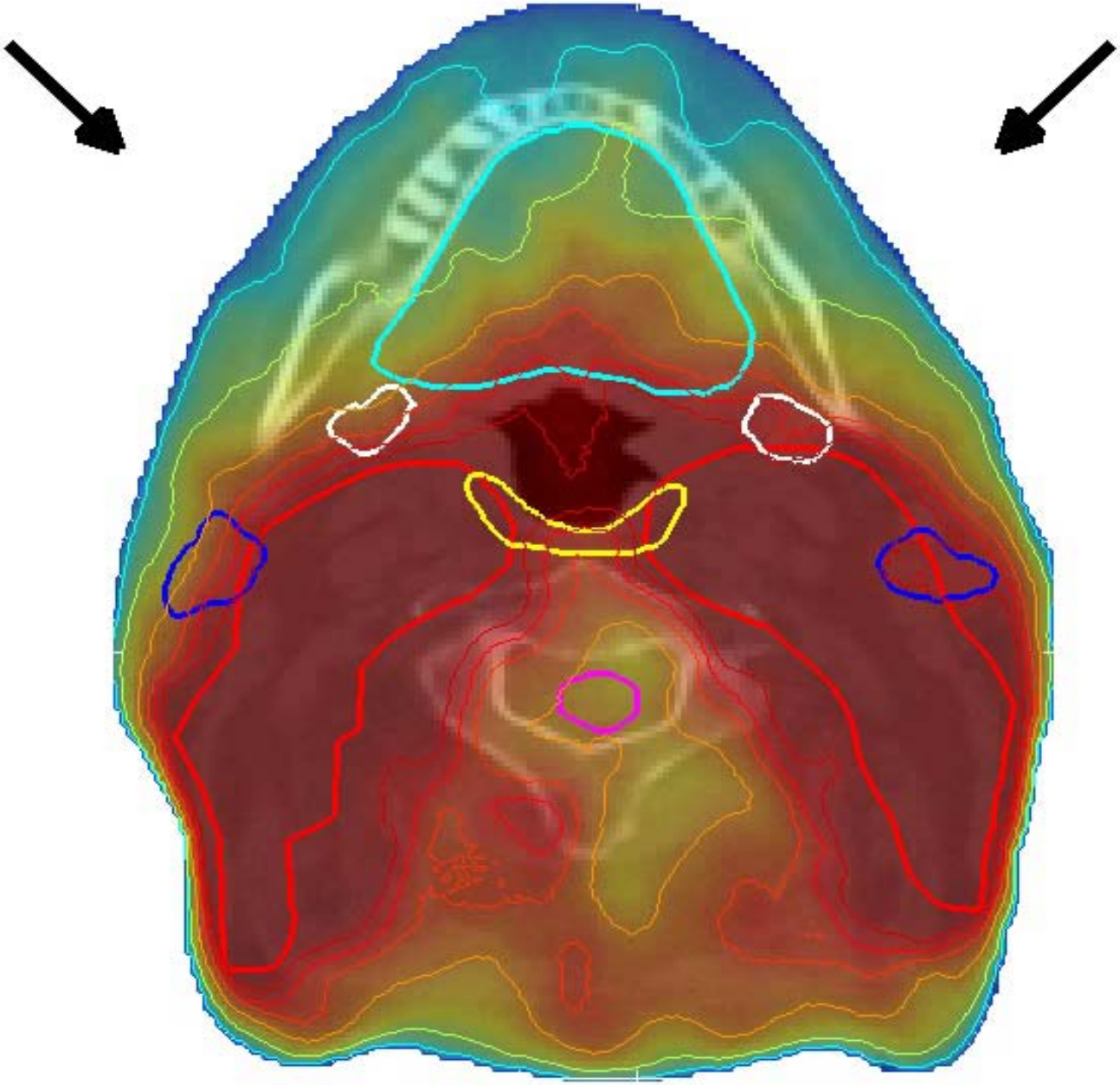

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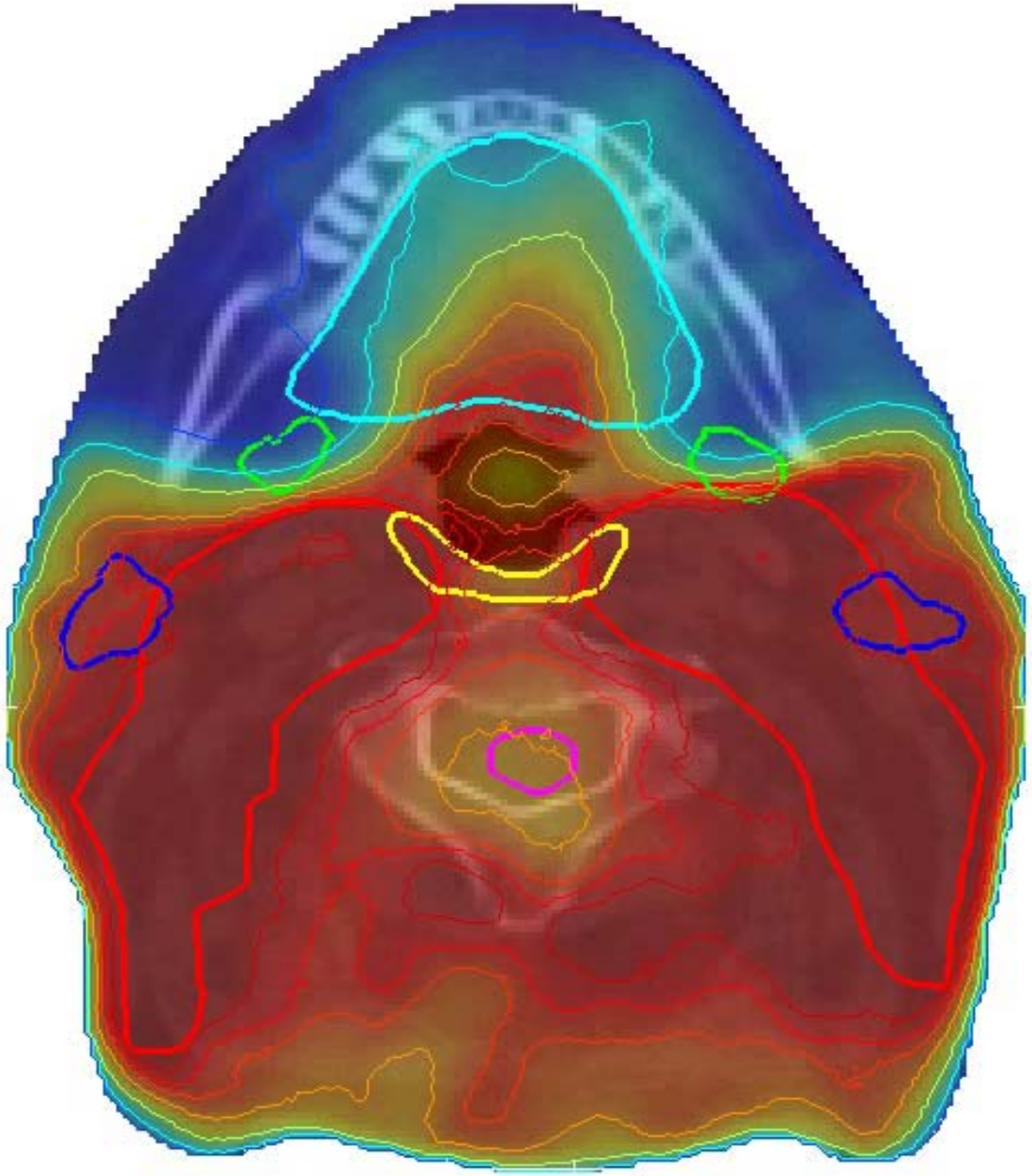

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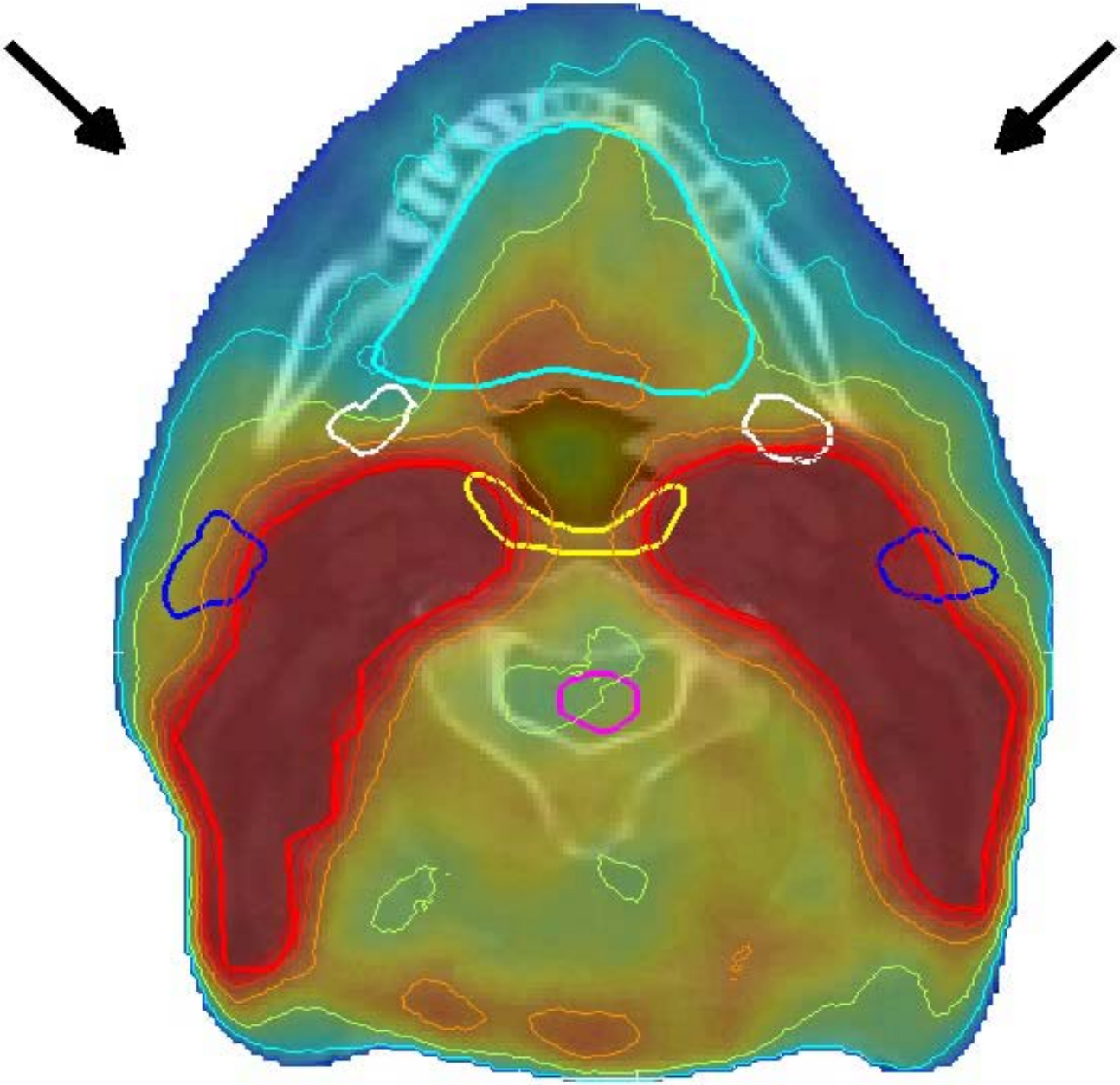

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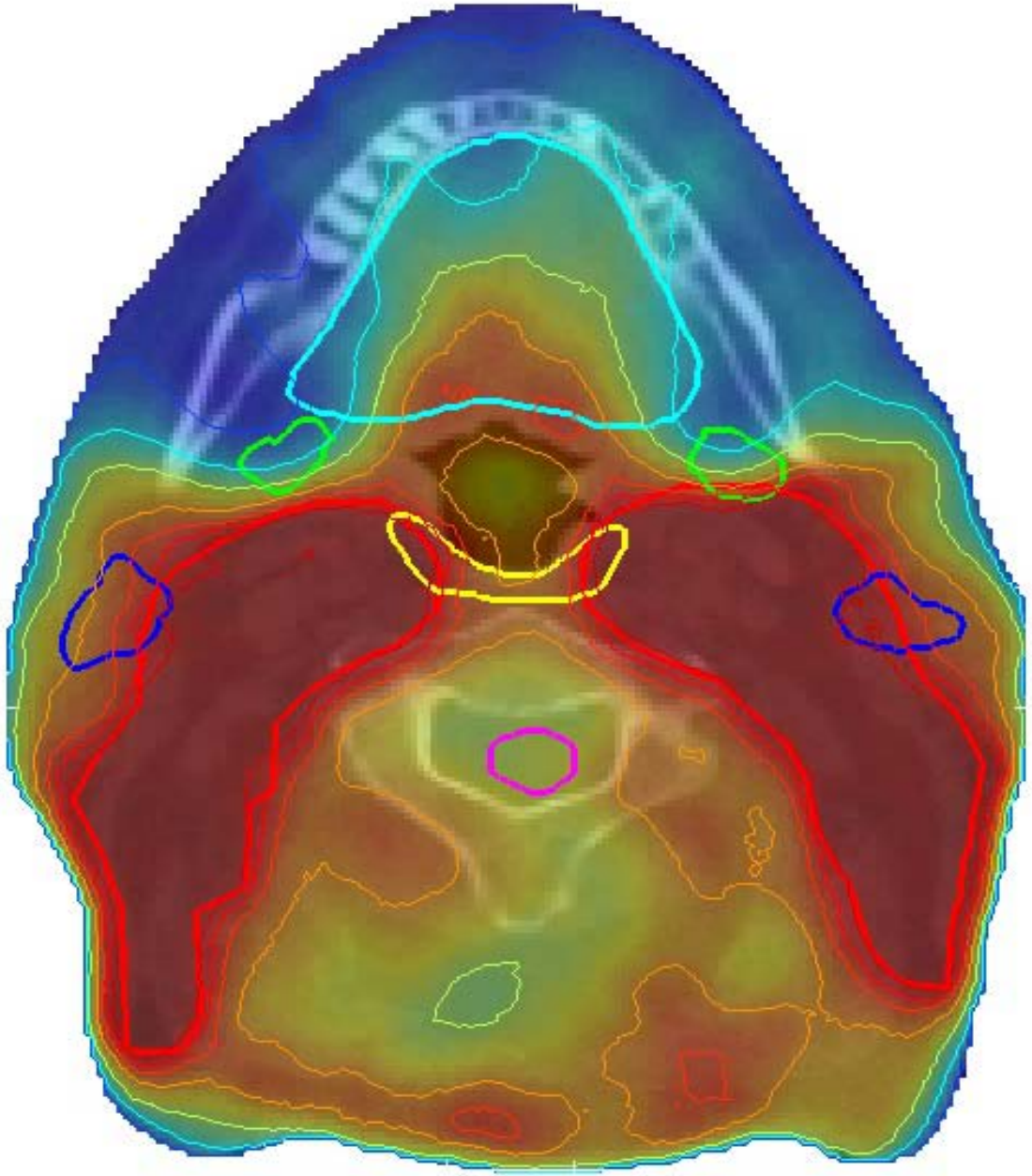

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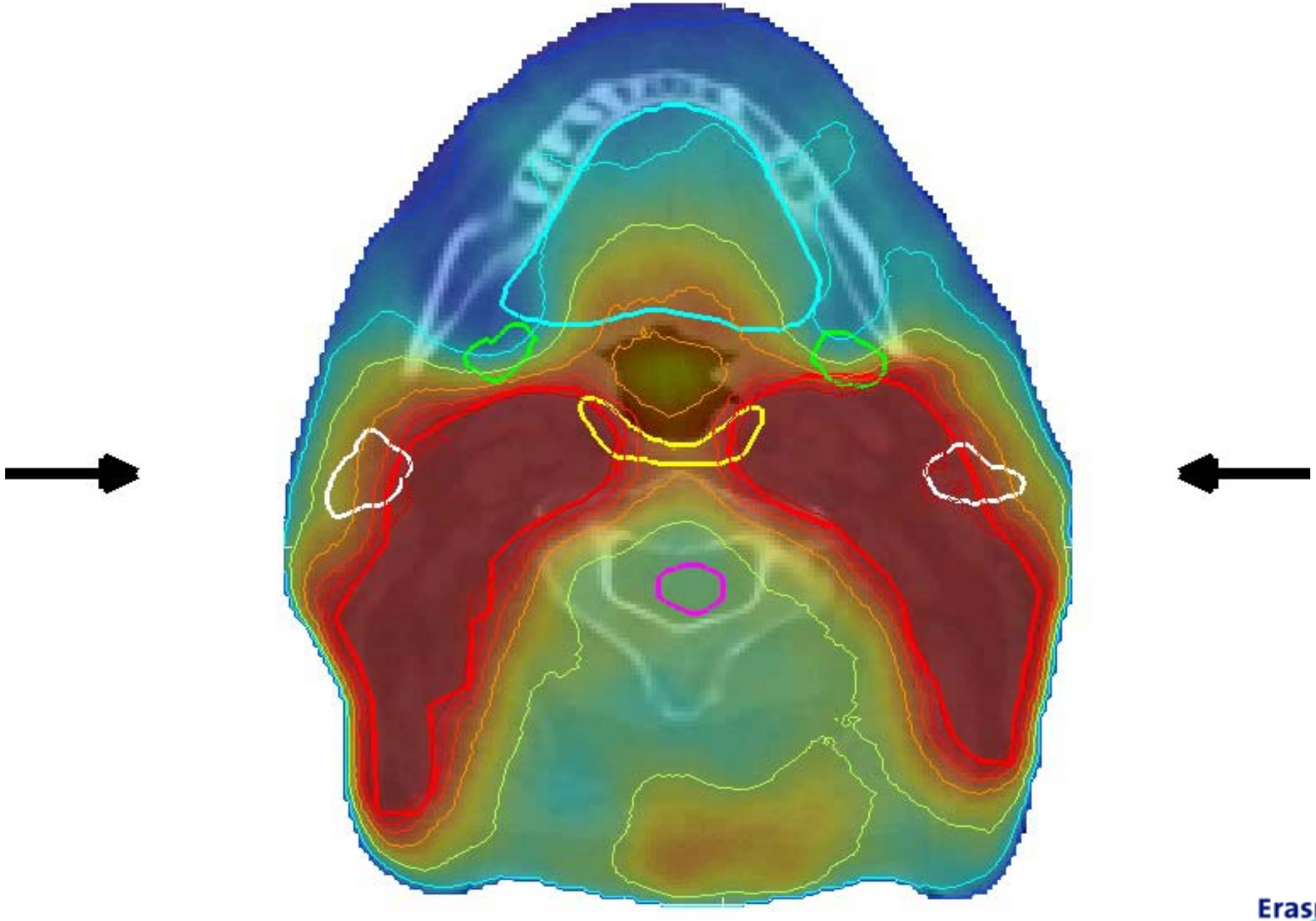

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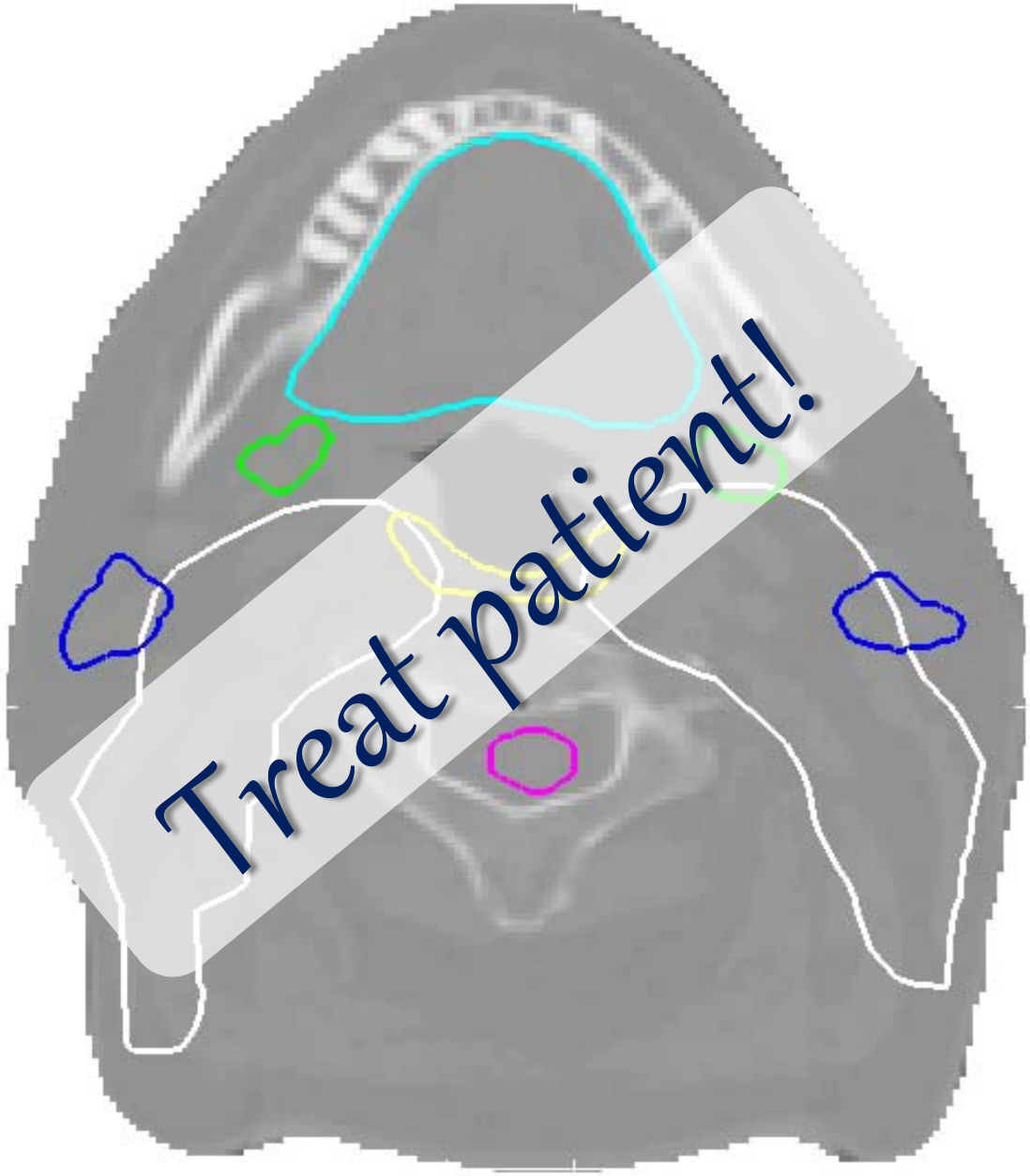

Acknowledgements: Sebastian Breedveld

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Automated planning

- may take longer, but can run overnight immediately after the contouring process
- may result in improved plan quality (computer doesn’t mind ‘drinking another cup of coffee’)
- does general require an extensive hierarchical list of priorities
- output can be used as an input for manual optimization
- reduces the interobserver variability

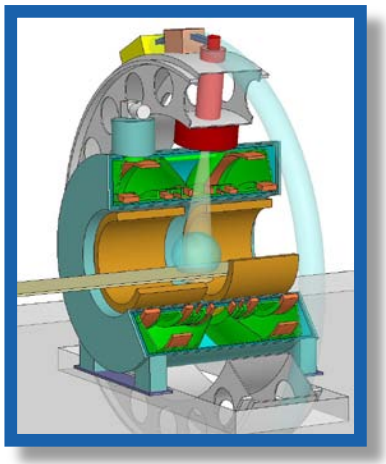

220 oral

MRI guided radiotherapy:

a MRI based linear accelerator

J.J.W. Lagendijk[1], C.J.G. Bakker[2]

[1]University Medical Center Utrecht,



1999	2004	2009	2012	now!
invention	design	1st prototype	2nd prototype	3rd prototype (clinical)

in collaboration Elekta en Philips

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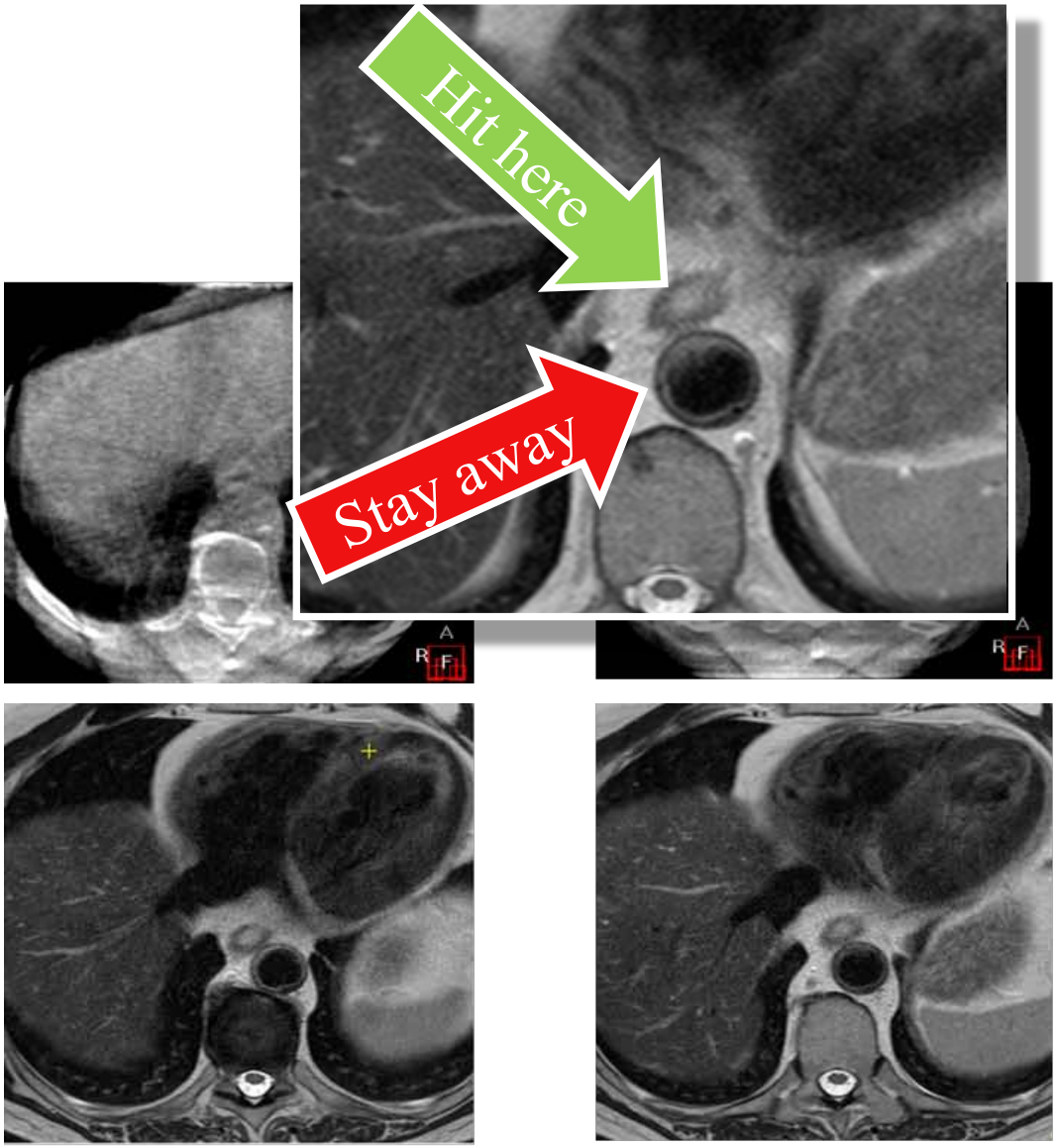
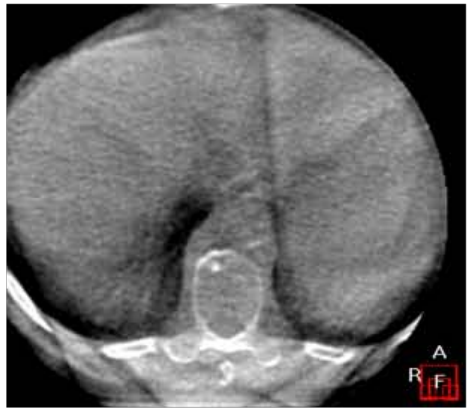
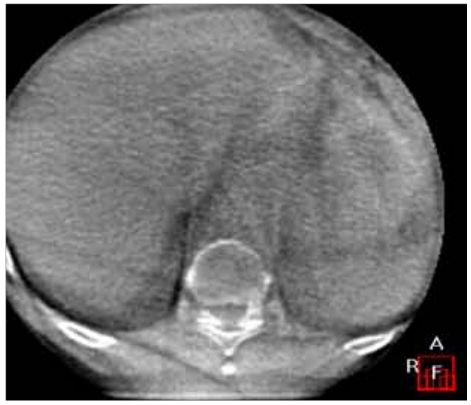
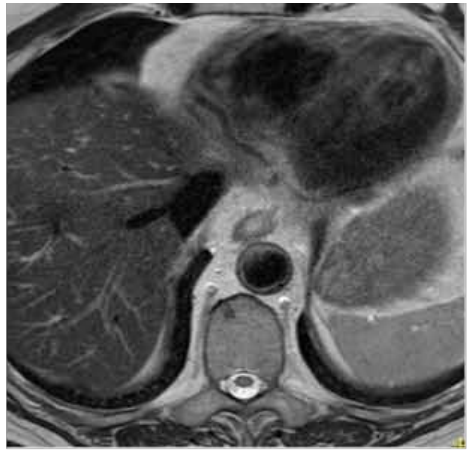
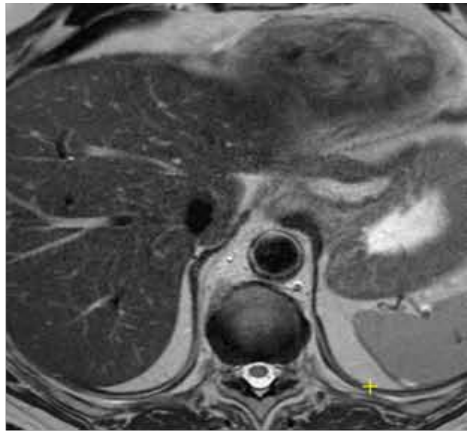
Online MR guidance











With online MR guidance we see GTV, “CTV” and risk organs

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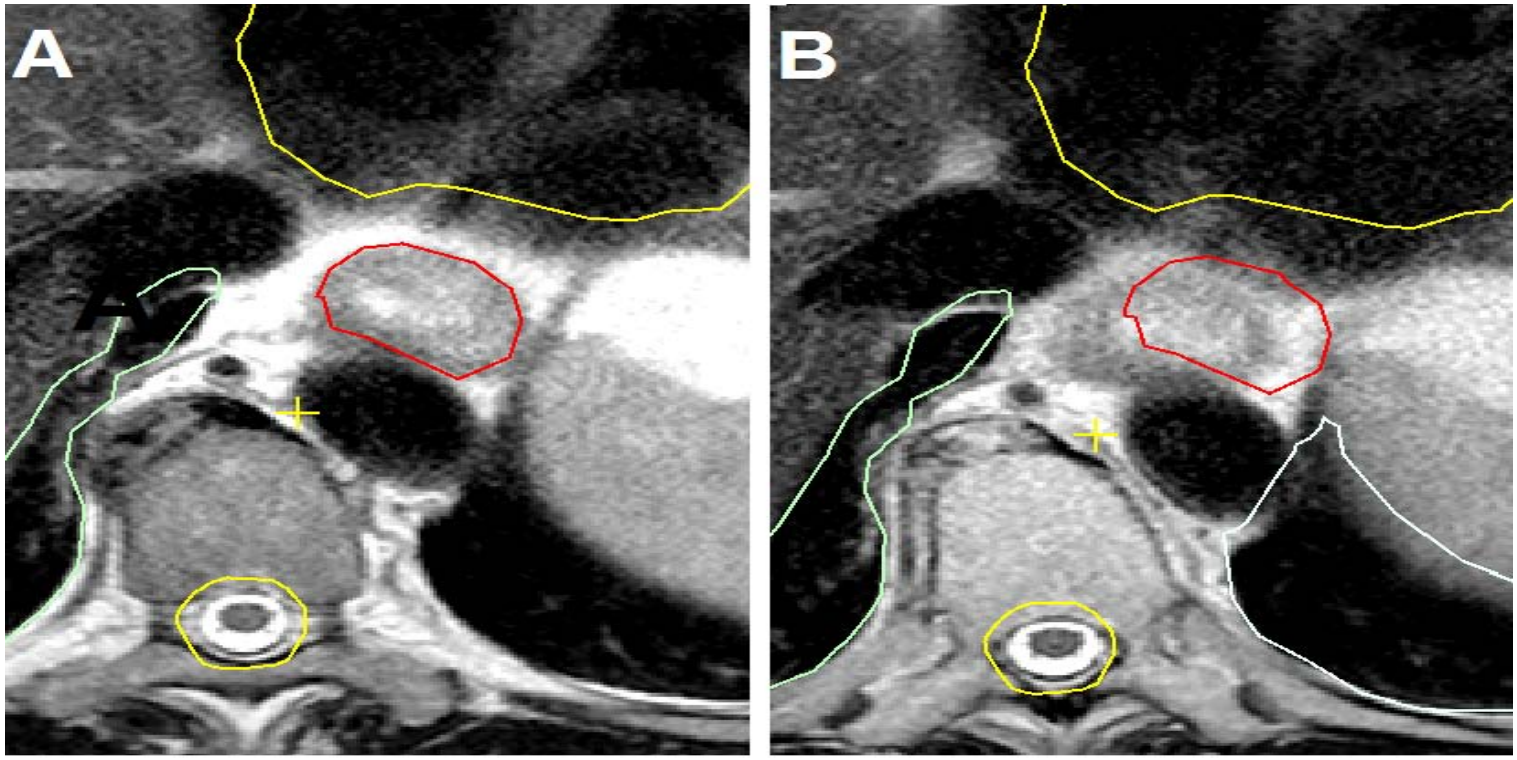
1 MRI guidance for identifying changes in anatomy



Day 1 **Day 4**

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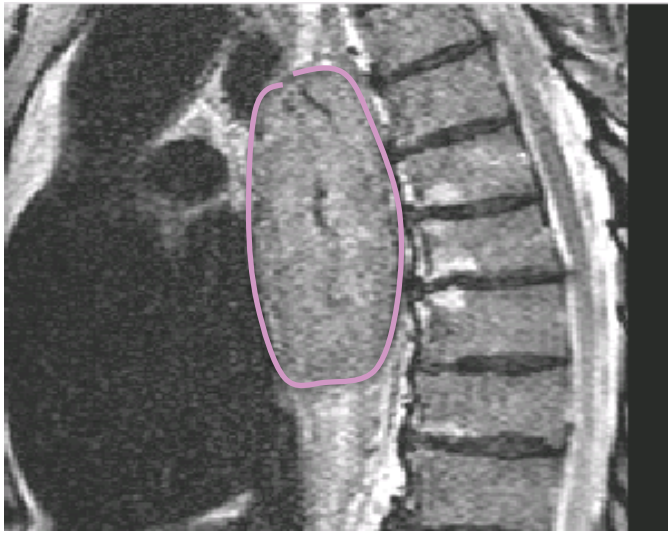
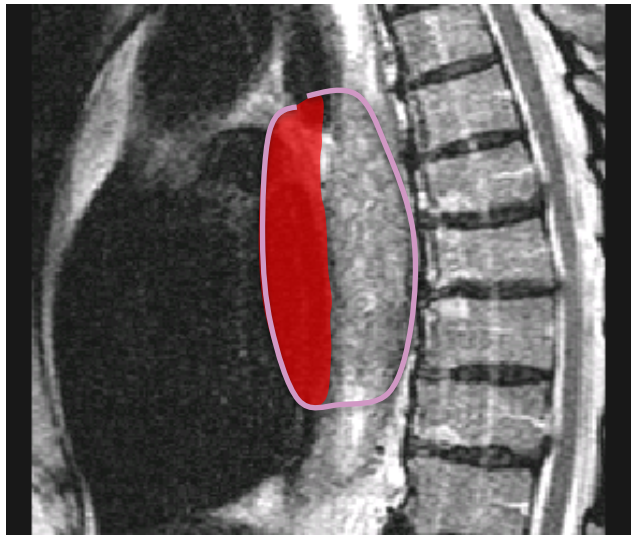
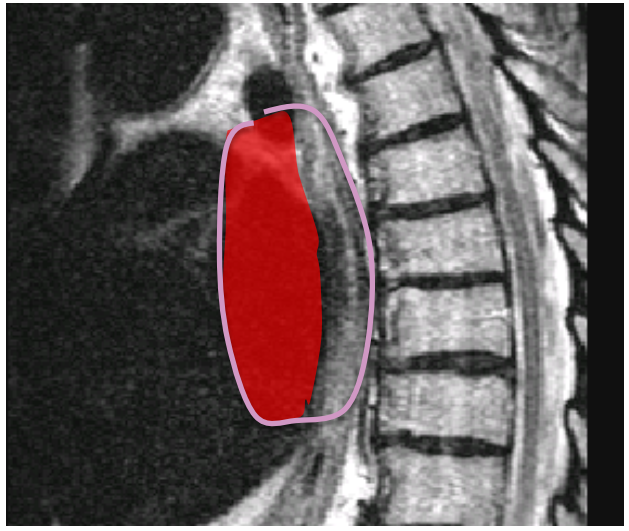
2 MRI guidance for identifying tumor shrinkage



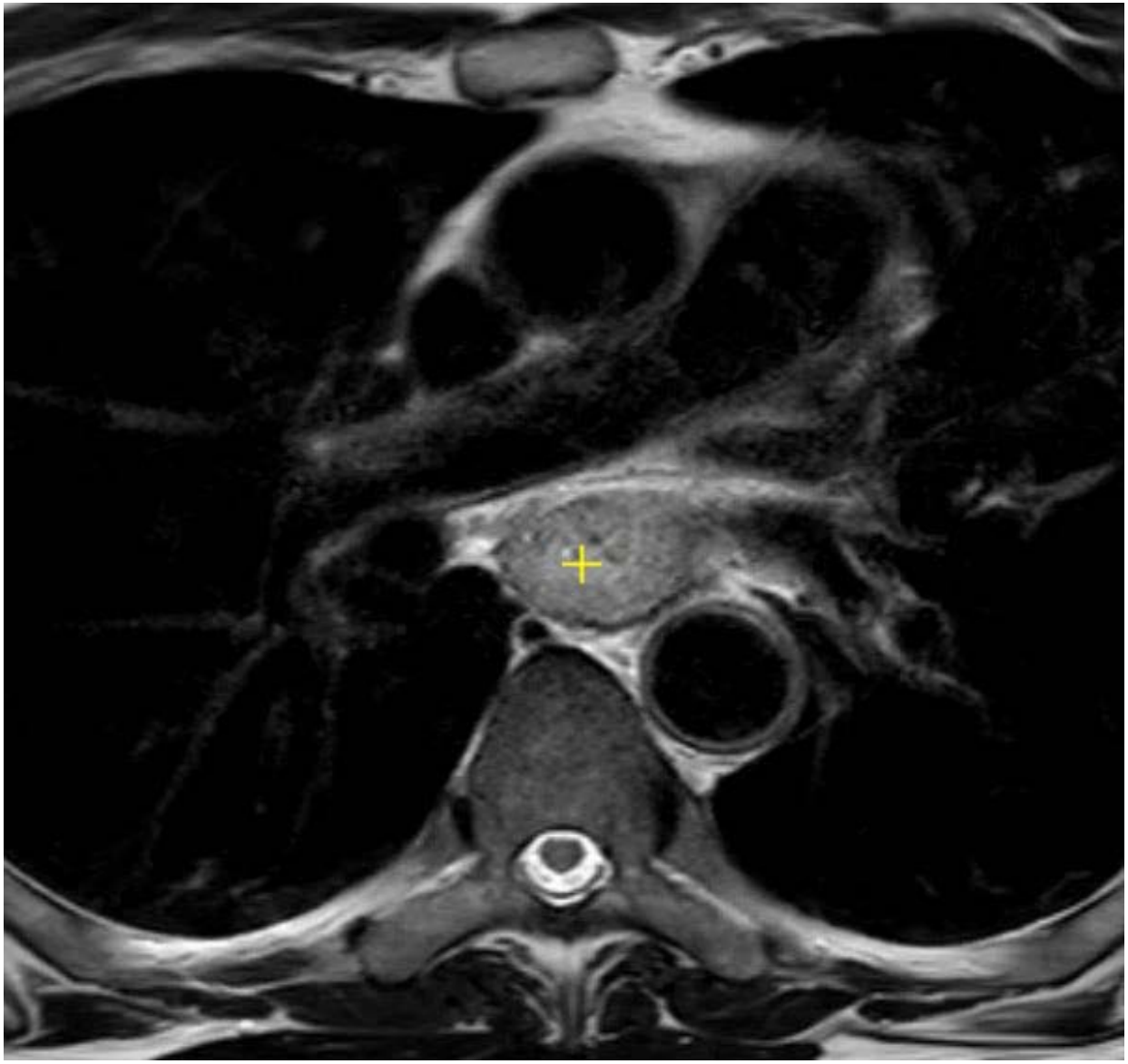
Day 0

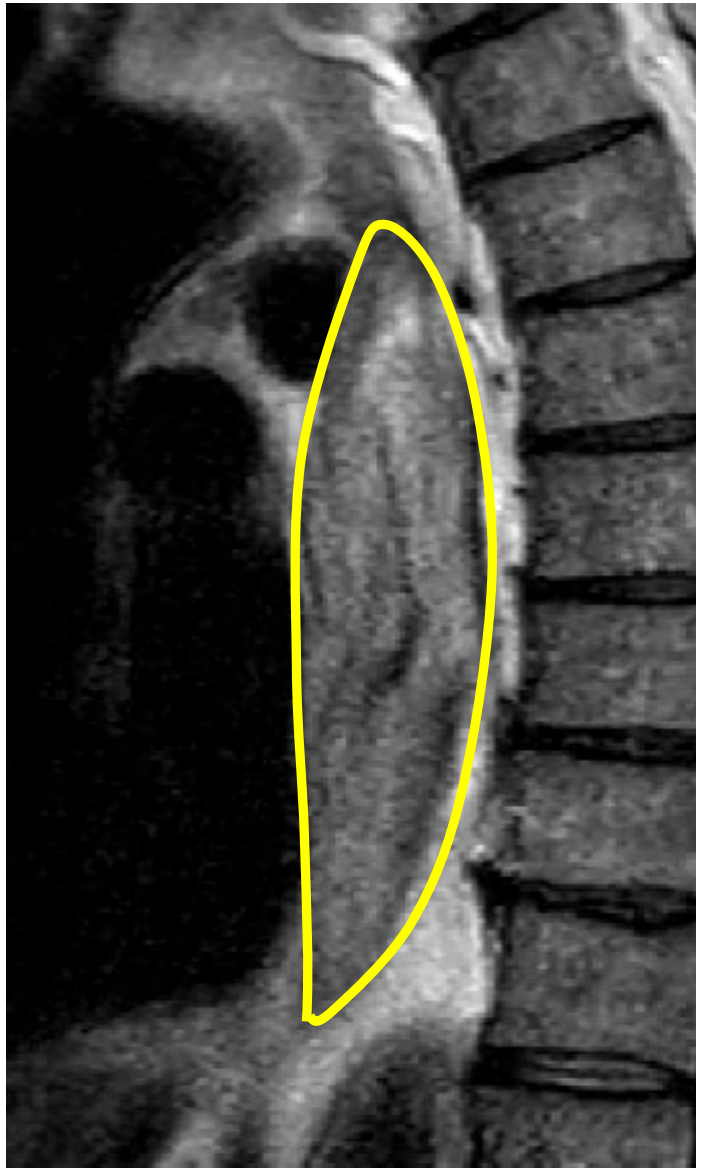


Day 10



Day 20





First patient with weekly repeat imaging

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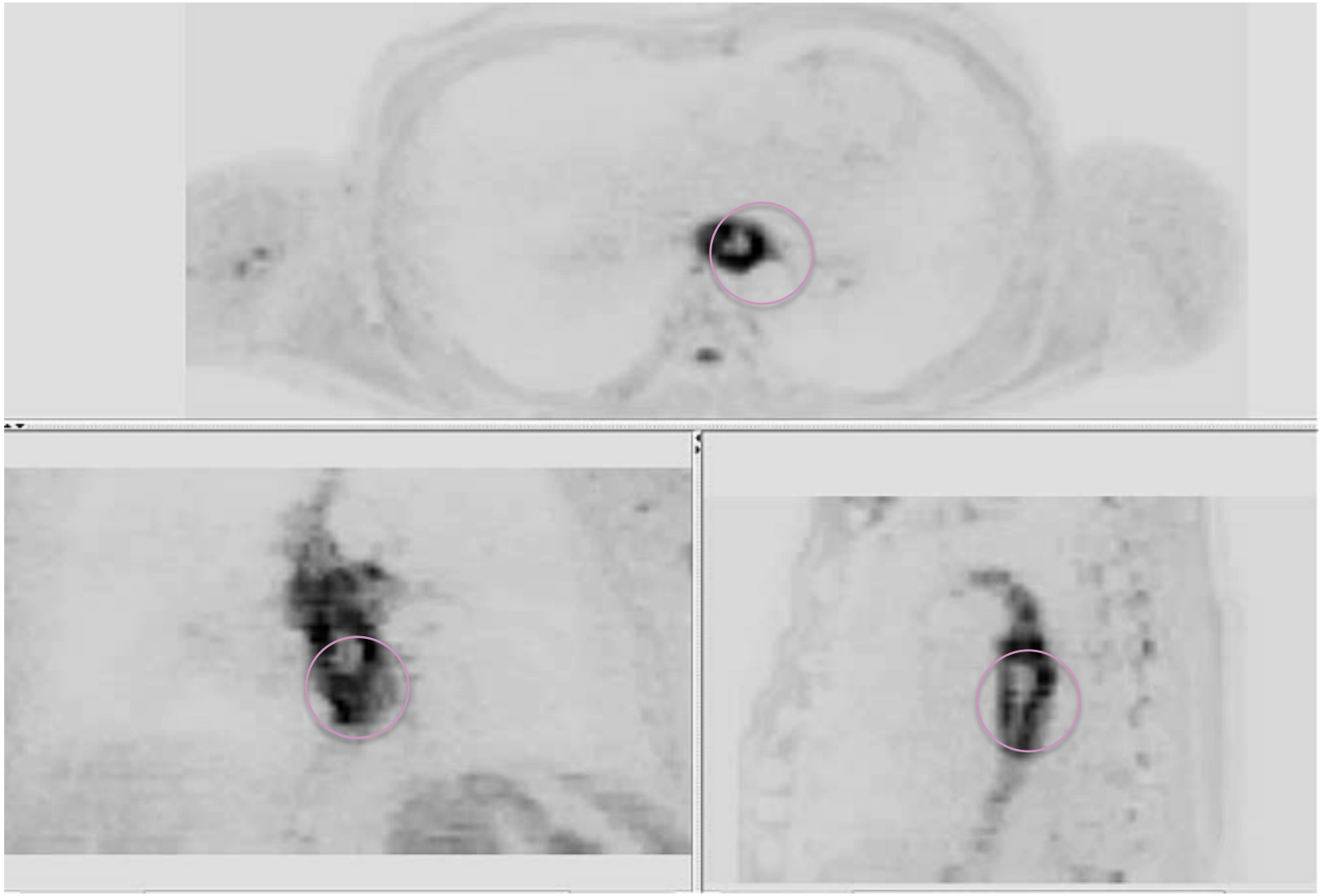
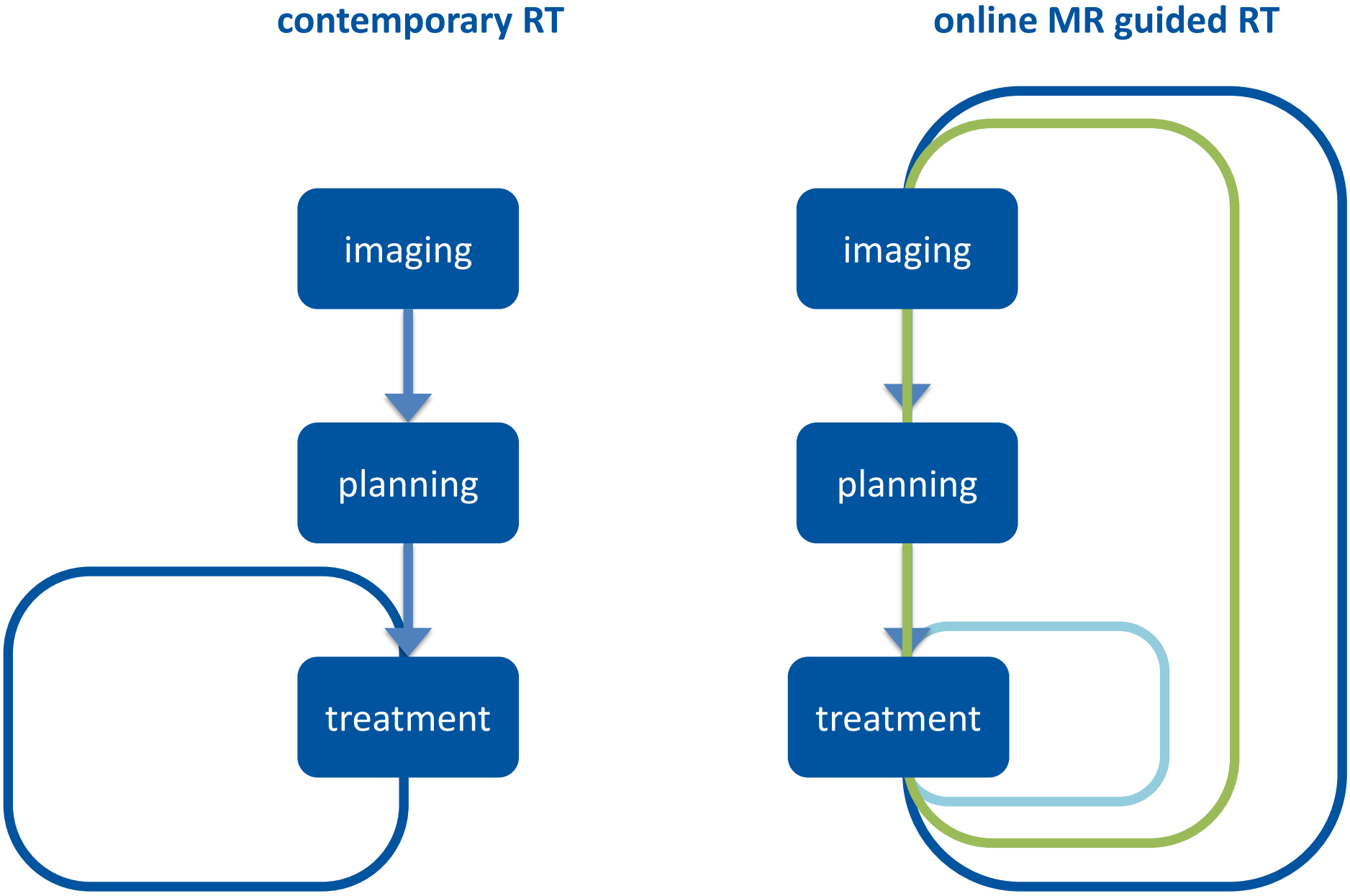
functional changes over time




contemporary RT
online MR guided RT
imaging
planning
treatment
imaging
planning
treatment

the times they are a changin’

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The doctor's perspective

Neil Burnet

University of Cambridge Department of Oncology,
Oncology Centre, Addenbrooke's Hospital,
Cambridge, UK

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Summary

- Small dose differences make a difference (clinically)
  - (MR linac)
  - (Proton Beam Therapy)
- Keep talking – dialogue = 2 way conversation
- Multi-criteria optimisation (MCO) – improved individualisation
- More data needed on normal tissue toxicity dose response

- Dose accumulation – VoxTox
  - Needs automatic OAR segmentation & other computing
- Biological variation in normal tissue sensitivity
  - Could we convolve a ***biological*** measure of individual normal tissue radiosensitivity with the ***physical*** dose plan

Use the best tools for the job !

- “If you want to treat a complex shape ... like this shell ... then you need IMRT”

Jason and Lucy discussing RT techniques ...

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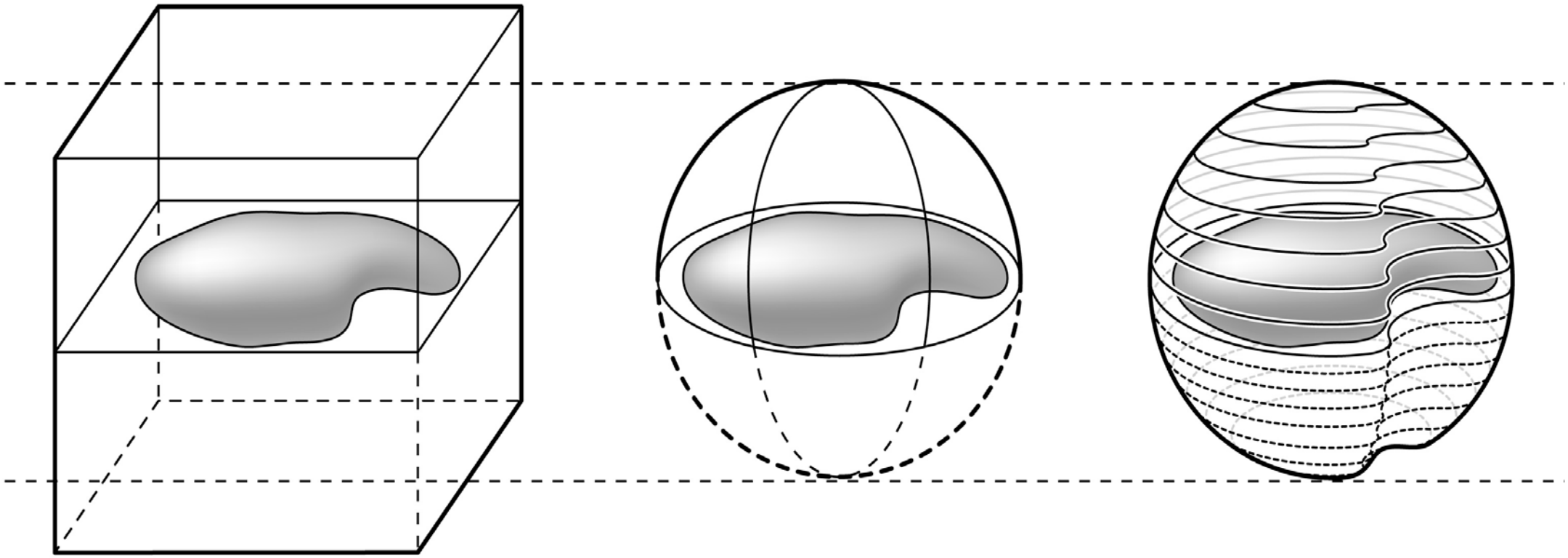
Treatment volumes compared



Conventional ‘square’ plan

3D CRT plan

IMRT plan

Treatment volumes compared

- Use of IMRT does not guarantee accuracy
- Need image guidance with rational PTV margins

Treatment volumes compared

- Use of IMRT does not guarantee accuracy
- Need image guidance with rational PTV margins

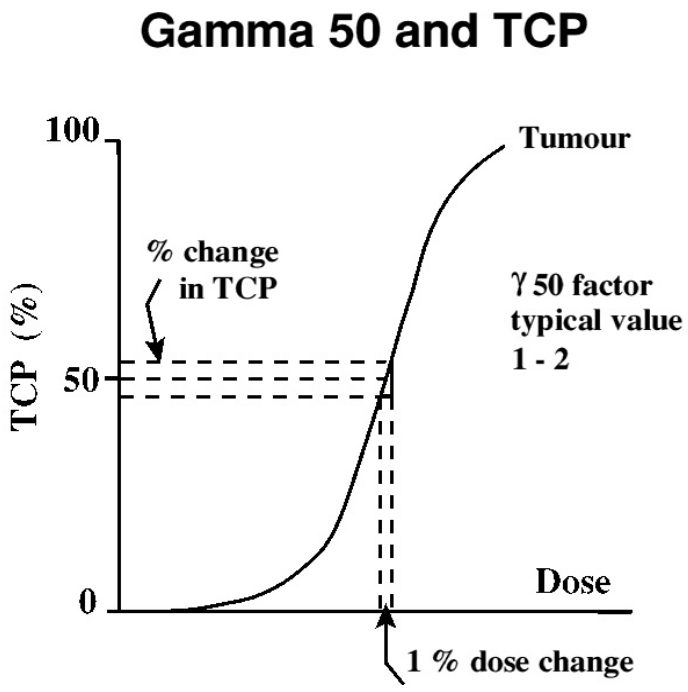
Small dose differences matter

- Get the details right – it's worth it!

- Dose response curves are steep
  - For tumour
  - For normal tissue

- A dose change of 5% can lead to a change in <u>TCP of 5 - 10%</u>

- Small differences are important
  - To the individual patient
  - To society



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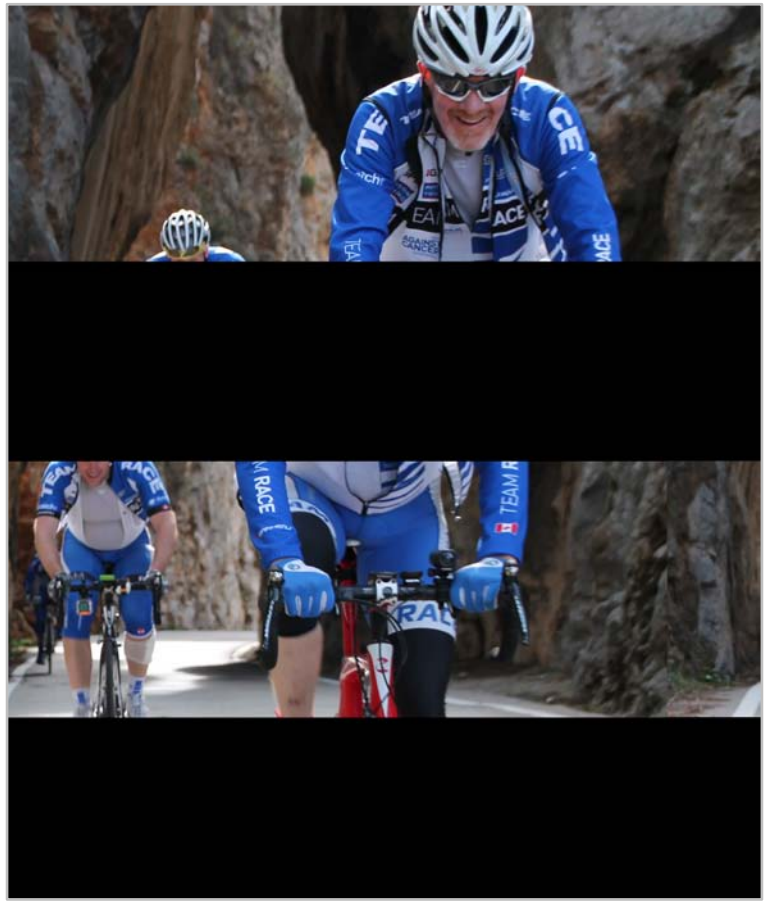
Marginal gains

- Small differences matter
- Application of the concept has been shown to be *very* successful in cycling
- The same applies to what we do ...
- Attention to details will benefit patients



Mike on the bike

Dialogue – a key component of happy planning

Dialogue – a key component of happy planning

- As work flows become busier and more tightly programmed, it is less easy to discuss cases

- Often difficult to set Objectives and Constraints perfectly

- Plan review meeting
  - provides review after completion of the plan
  - It does *not* facilitate discussion *during* its preparation

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Dialogue – a key component of happy planning

- Talk to your colleagues ...

... and at least I always get an intelligent answer!

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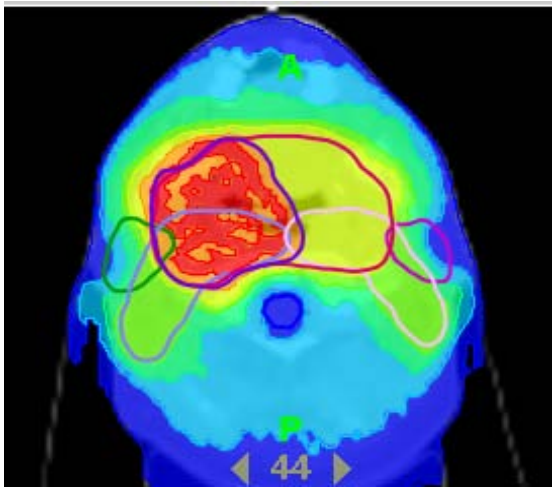
Multi-criteria optimisation (MCO)

Multi-criteria optimisation (MCO)

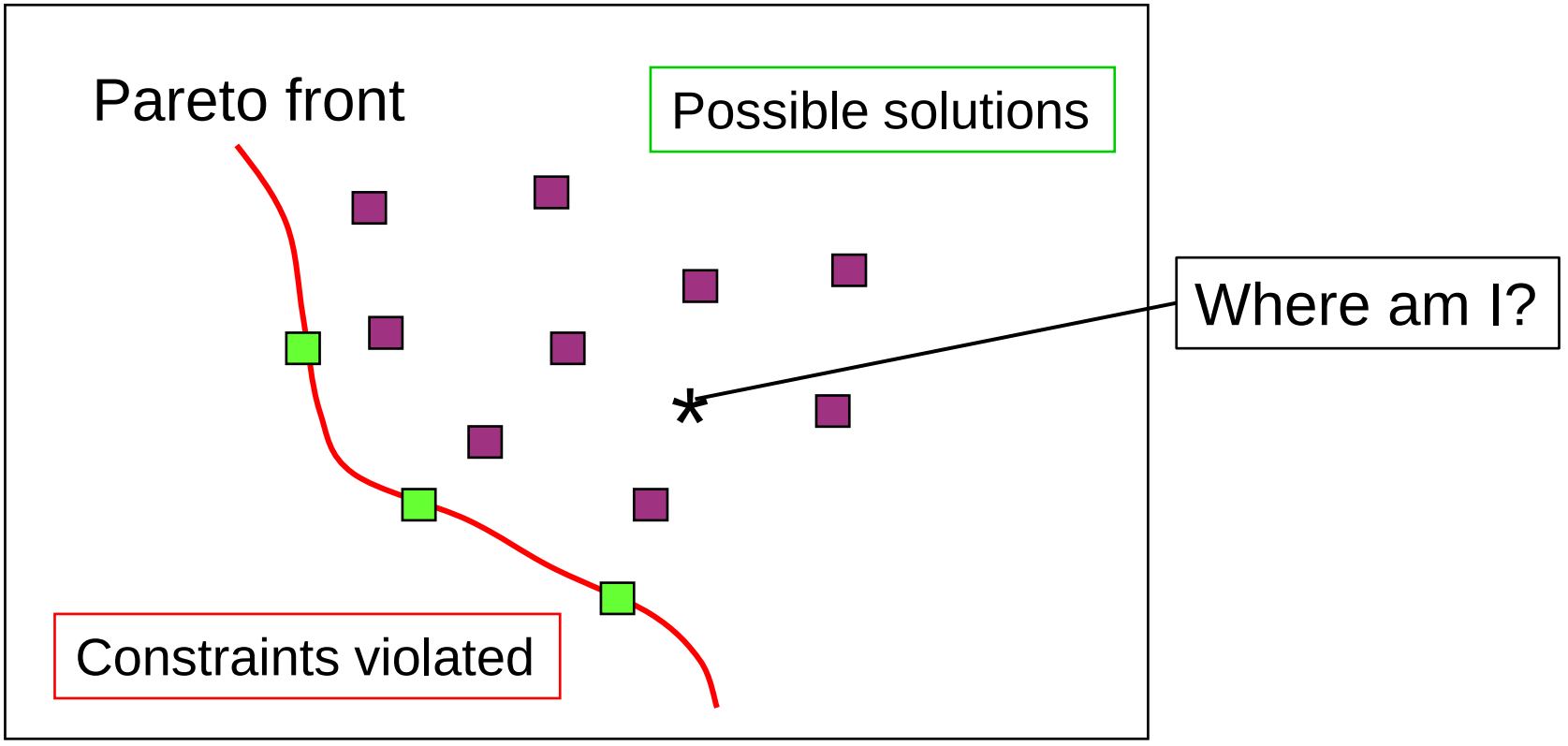
- Multi-criteria (MCO) – prospect of improved individualisation

- Pareto optimisation is basis for IMRT
- Normally have 1 plan from within solution space
- MCO allows real-time examination of solution space

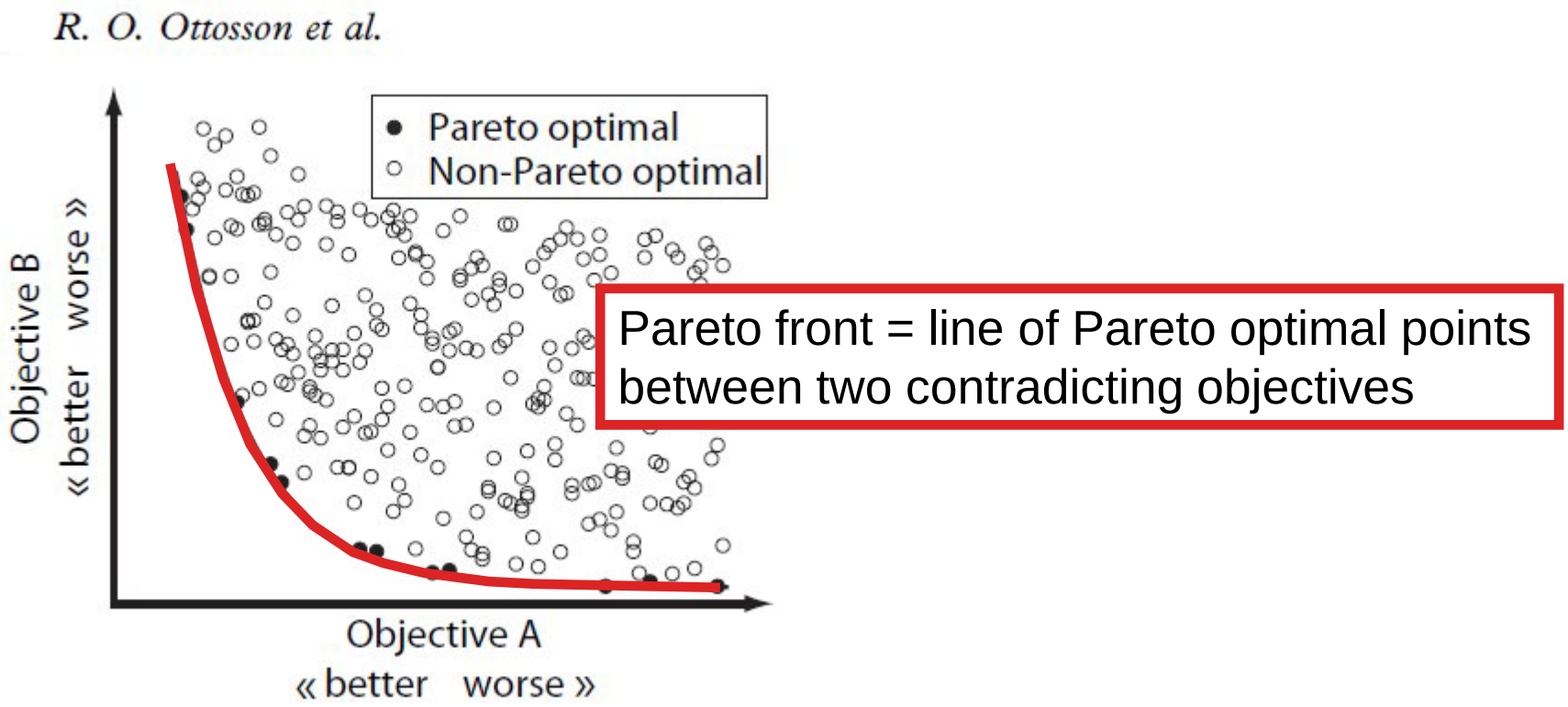
- This might allow (small) improvements in dose plan for individual patients



IMRT – Optimisation



Pareto front



Pareto front = line of Pareto optimal points between two contradicting objectives

For two mutually contradicting objectives an endless number of solution exists

The solutions where one of the objectives can not be improved without deteriorating the other are *Pareto optimal*

All Pareto optimal solutions lie on the Pareto front

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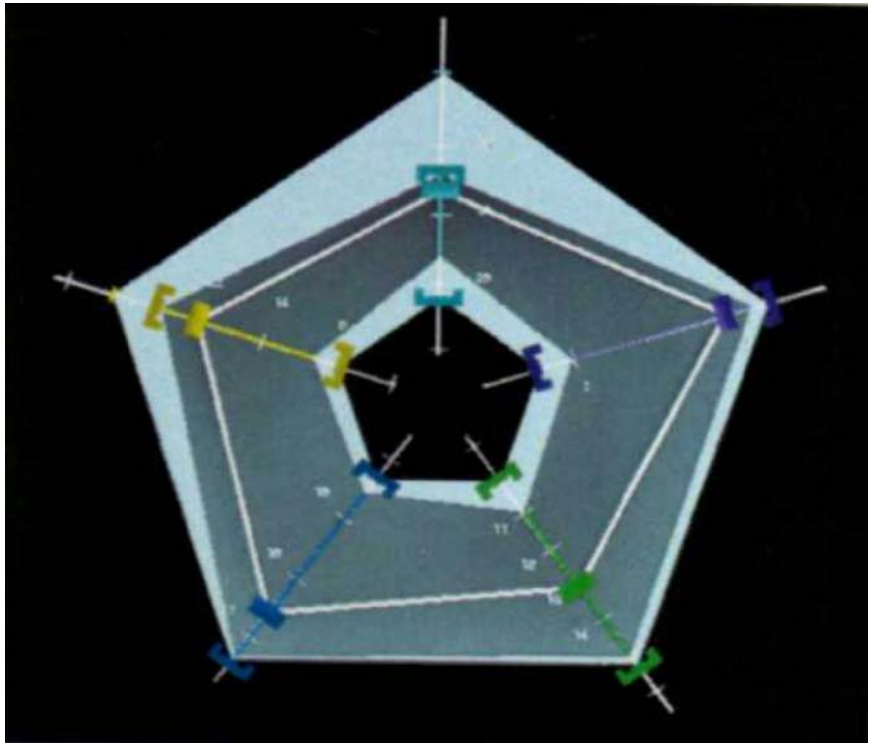
Multi-criteria optimisation (MCO)

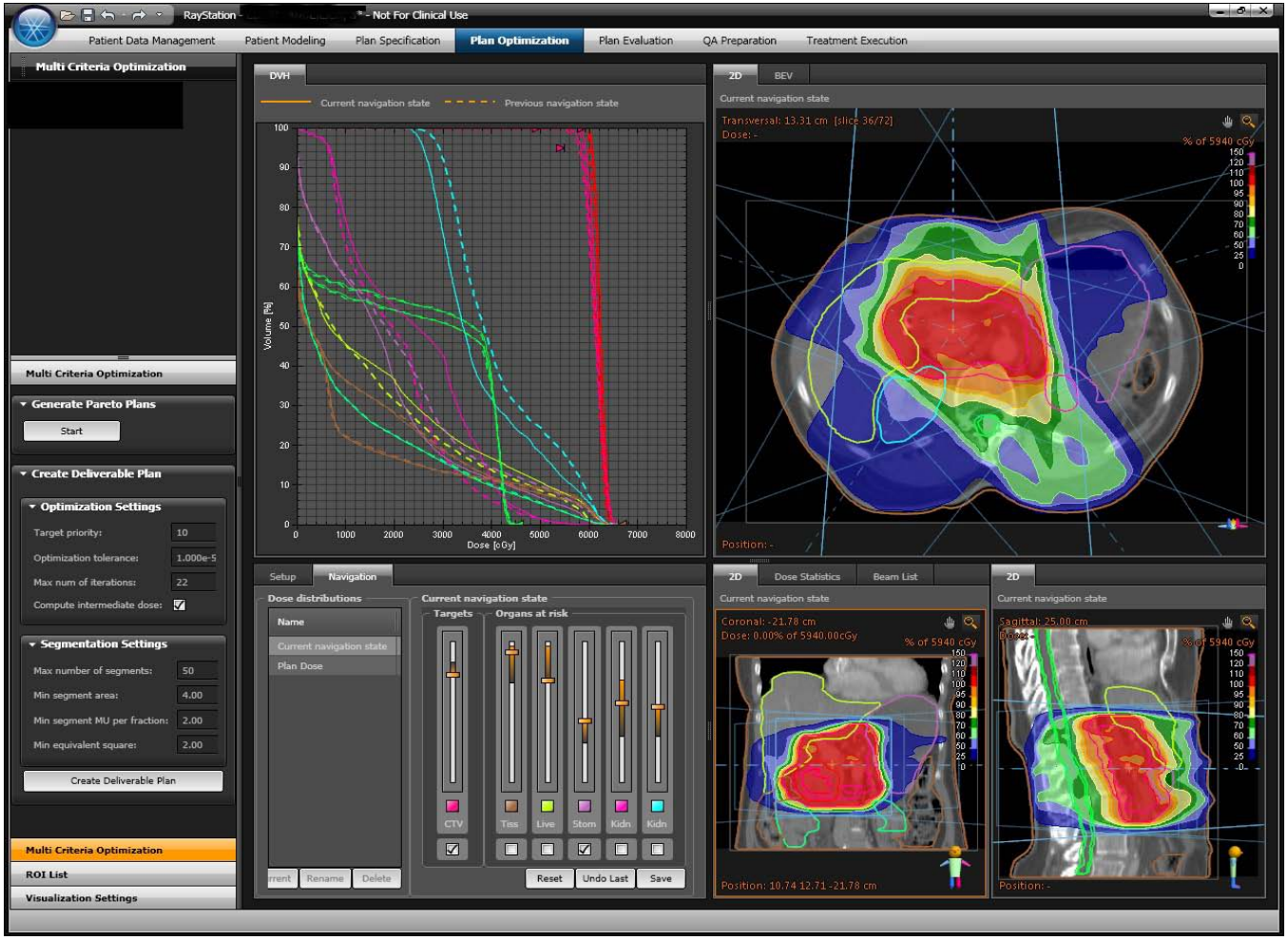
- Developmental version of MCO system
  - Shows normal tissue structures
  - Bounded limits on dose within solution space
- Real-time exploration possible
- Commercial systems becoming available
- Full value not yet known



Courtesy of Fraunhofer Institute

Multi-criteria optimisation (MCO)

- MCO system from RayStation



Picture courtesy of Google

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Normal tissue response data

Normal tissue response data

- More data needed on normal tissue toxicity dose response

- The details of dose response are not known as well as we need
  - Variation in data is considerable
  - Many organs relatively unknown

Normal tissue response data

- Spinal cord - need to avoid events which define tolerance threshold

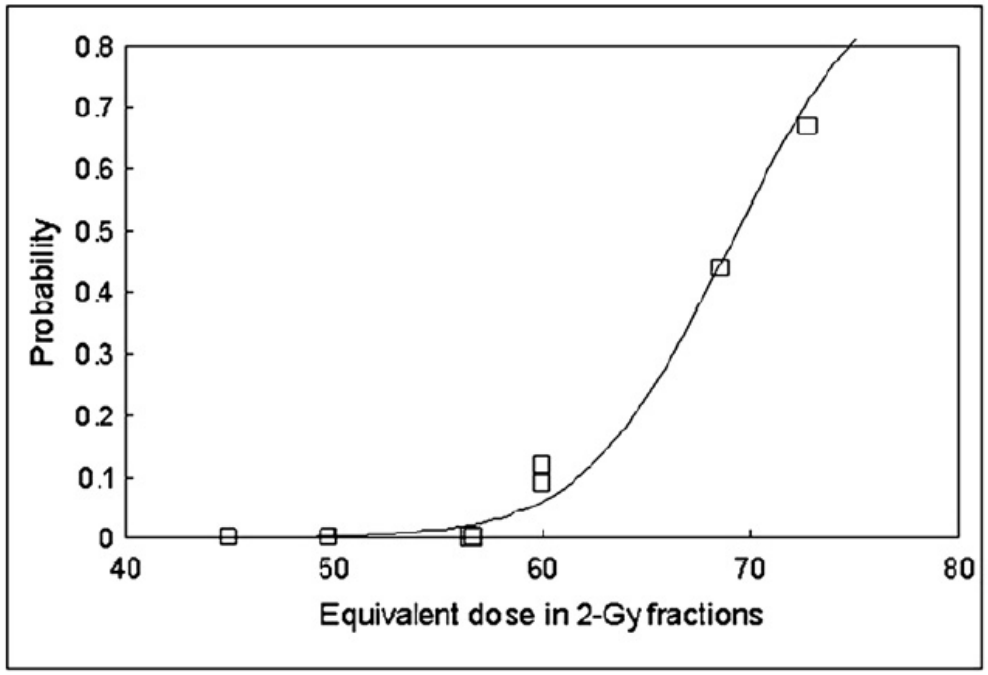


Fig. 1. The dose–response function for the myelopathy of the cervical spinal cord and data points (□) derived from Table 1. The probability of myelopathy was calculated from the data in Table 1, adjusted for estimated overall survival per (18).

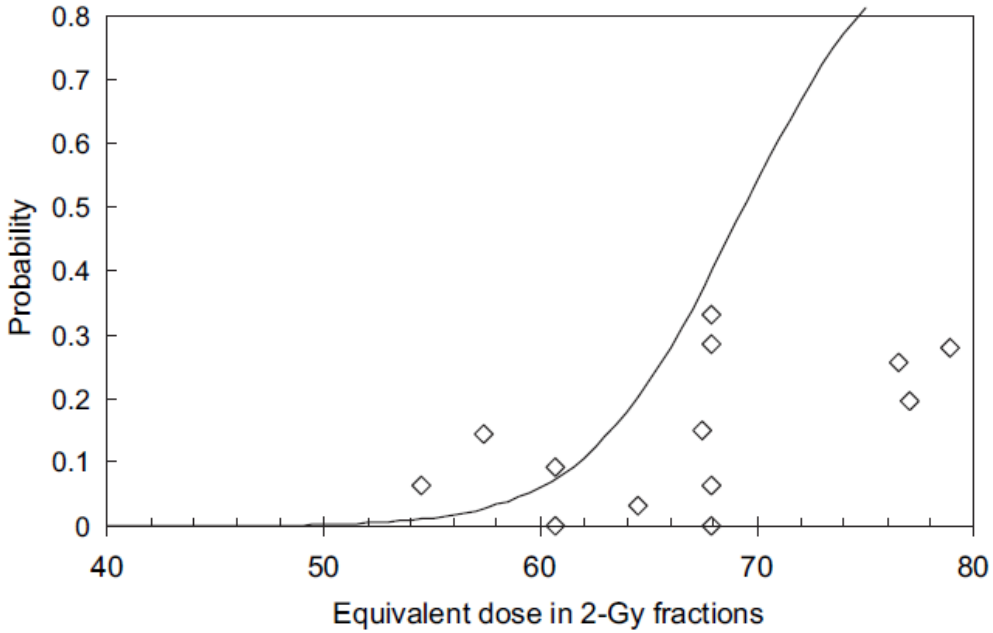


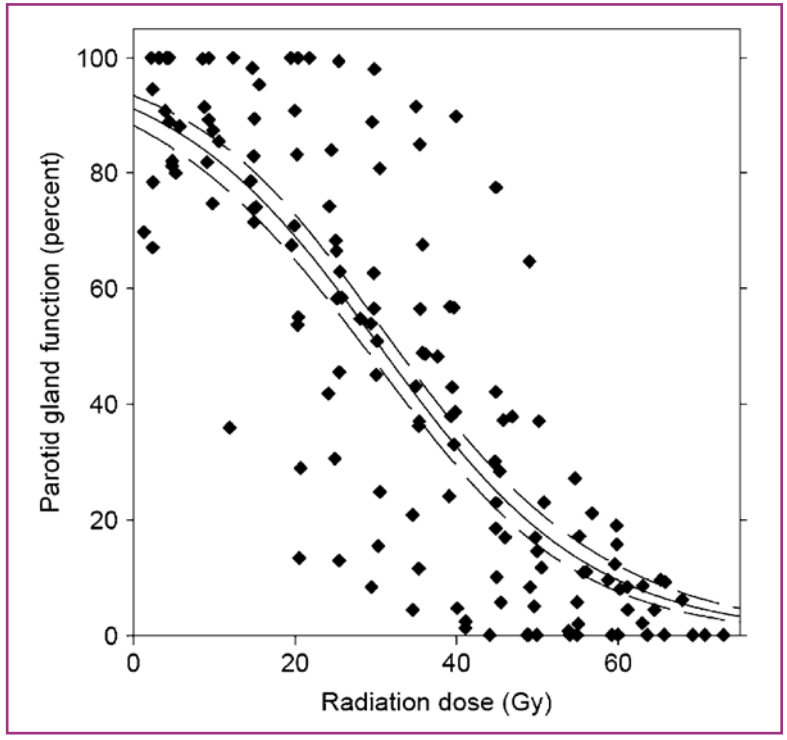
Fig. 2. The dose–response function for myelopathy of the cervical cord (solid line) and data points for the thoracic spinal cord (◇) derived from Table 2. The probability of myelopathy was calculated from the data in Tables 1 and 2, adjusted for estimated overall survival per (18).

- QUANTEC - Kirkpatrick et al. IJROBP 2010; 76(3): S42-49

Normal tissue response data

- More data needed on normal tissue toxicity dose response

- The details of dose response are not known as well as we need
  - Variation in data is considerable
  - Many organs relatively unknown



- Parotid dose-response

- Scatter ...

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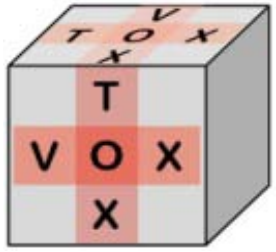
Dose accumulation

Dose accumulation

- Standard dose plans are a good approximation to delivered dose
- Dose differences of 10-15% can be detected (eg in trials)

- Further individualisation possible with measurement (estimate) of accumulated dose D_A

- Our research programme is trying to do just this
  - VoxTox – linking dose at the voxel level with toxicity
  - Consider rectal toxicity ...



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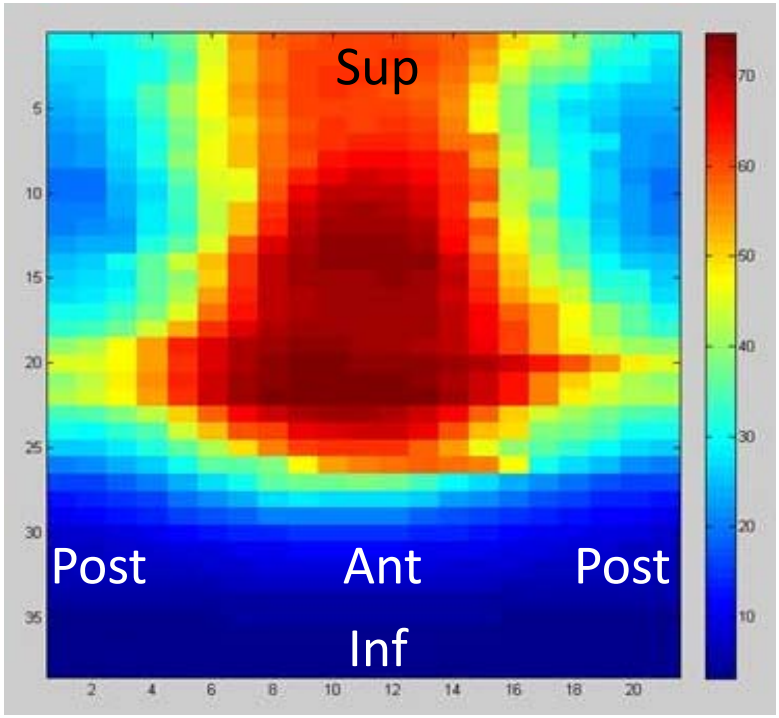
Dose accumulation

- Rectum dose-surface map (DSM) for prostate RT

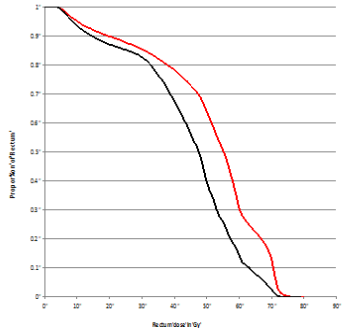


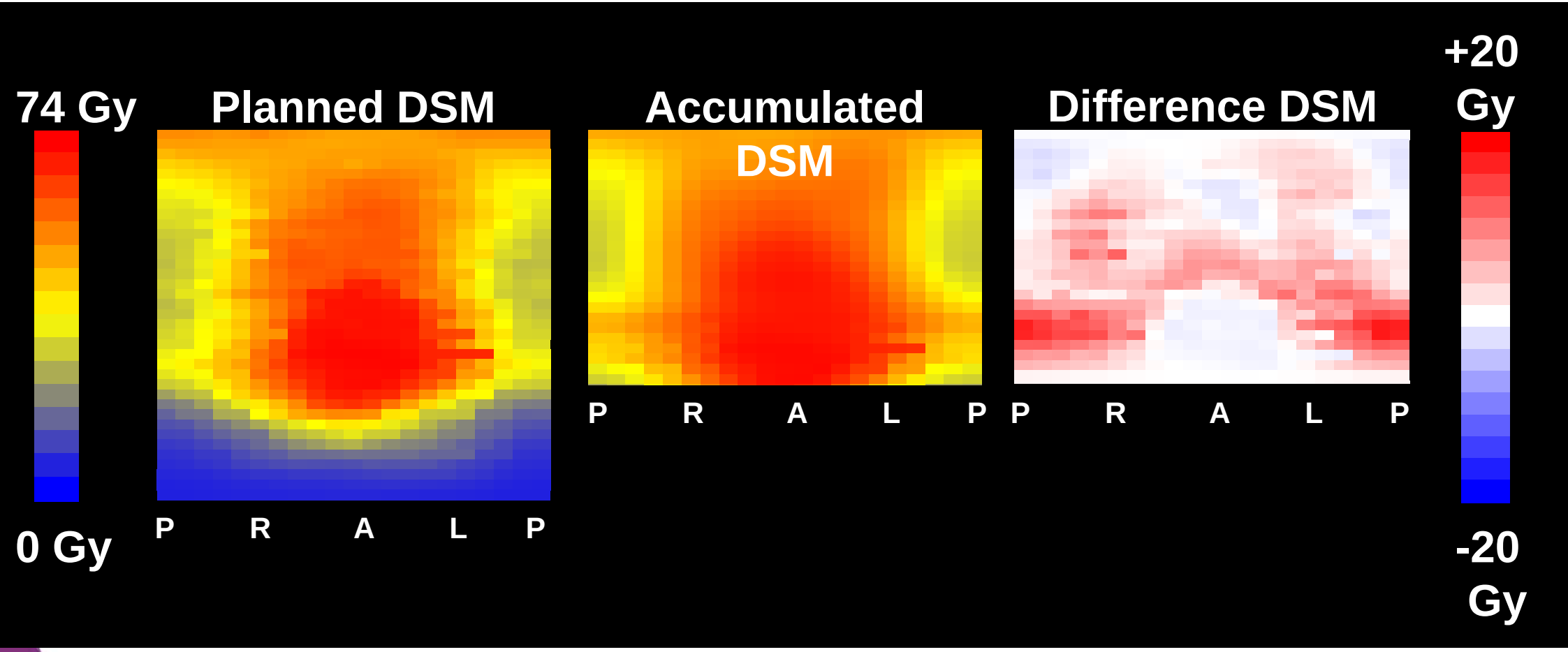
Plan

- Early stage only ...

Work-in-progress courtesy of Dr Jessica Scaife

DSM for highest accumulated dose compared with planned





Courtesy of Dr Jessica Scaife BJR 2015 Aug 11:20150243

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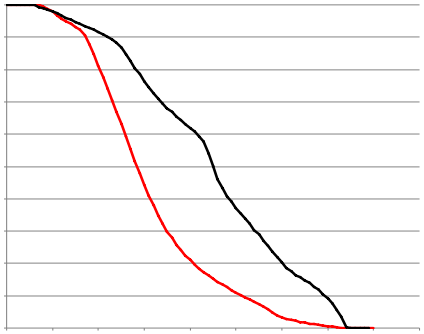
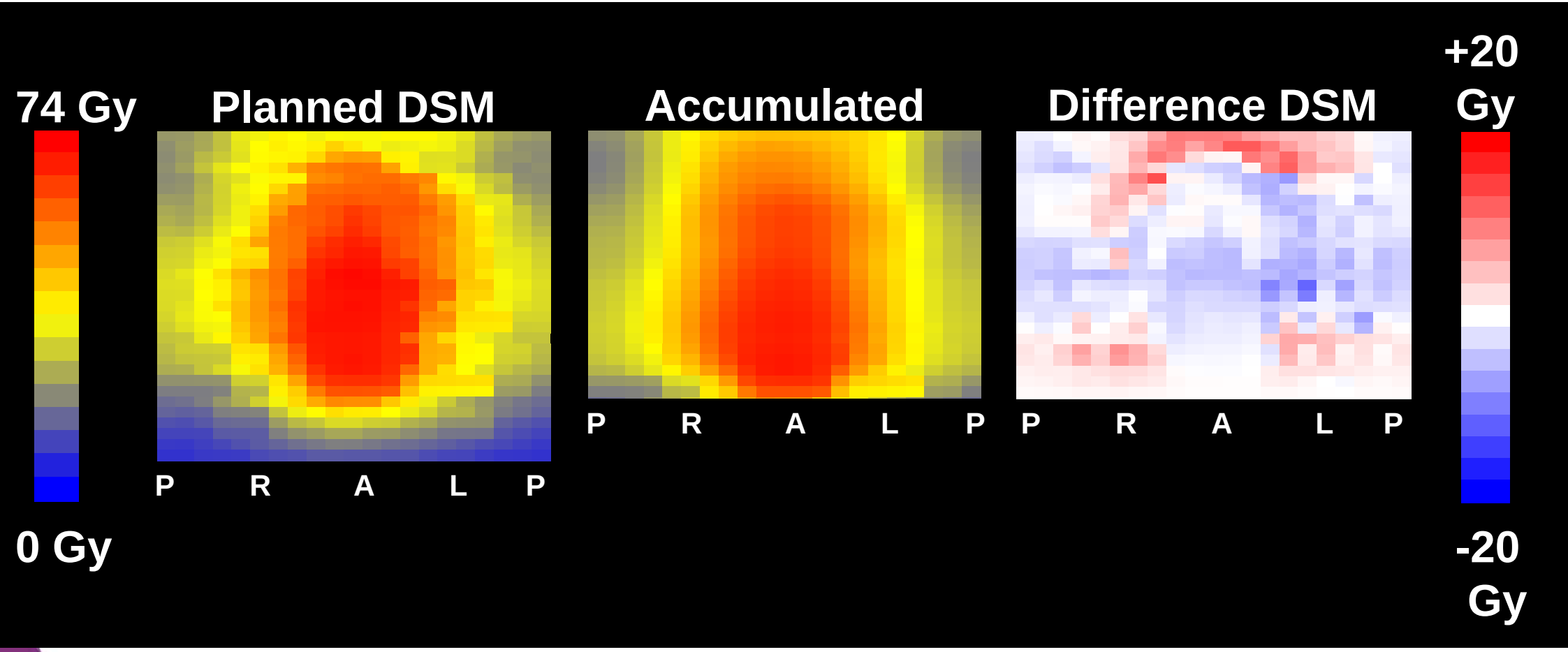
DSM for lowest accumulated dose compared with planned





Courtesy of Dr Jessica Scaife BJR 2015 Aug 11:20150243

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Dose accumulation

- Our VoxTox research programme is trying to quantify accumulated dose D_A

- There are 500,000 contours to draw
  - Not possible for human!
  - Computational solutions needed

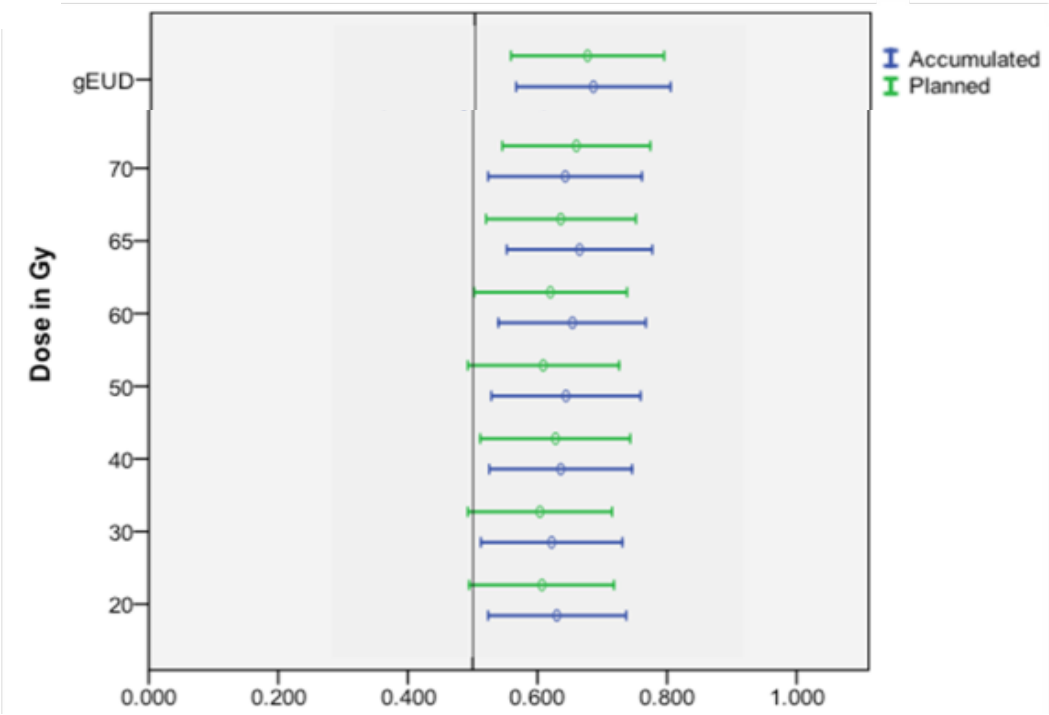
- Further computing developments will need to be incorporated into work flow

Dose accumulation

- Initial run of 109 prostate patients
  - Rectum auto-contoured on 4033 scans
  - D_A recalculated on daily image guidance MV CT scans

VoxTox - results

Dose Surface Map analysis



Result significant if:
- Mean > 0.6
- CI > 0.5

- DSM D_A predictors mostly better than planned dose
  - EUD accumulated dose (D_A) best predictors

ROC AUC for rectal bleeding (CTCAE Grade ≥ 2)

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Dose accumulation

- Our VoxTox programme is investigating the hypothesis that accumulated dose D_A is a better predictor of toxicity than planned dose

- And we need some computational solutions too !

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Individual variation in normal tissue sensitivity

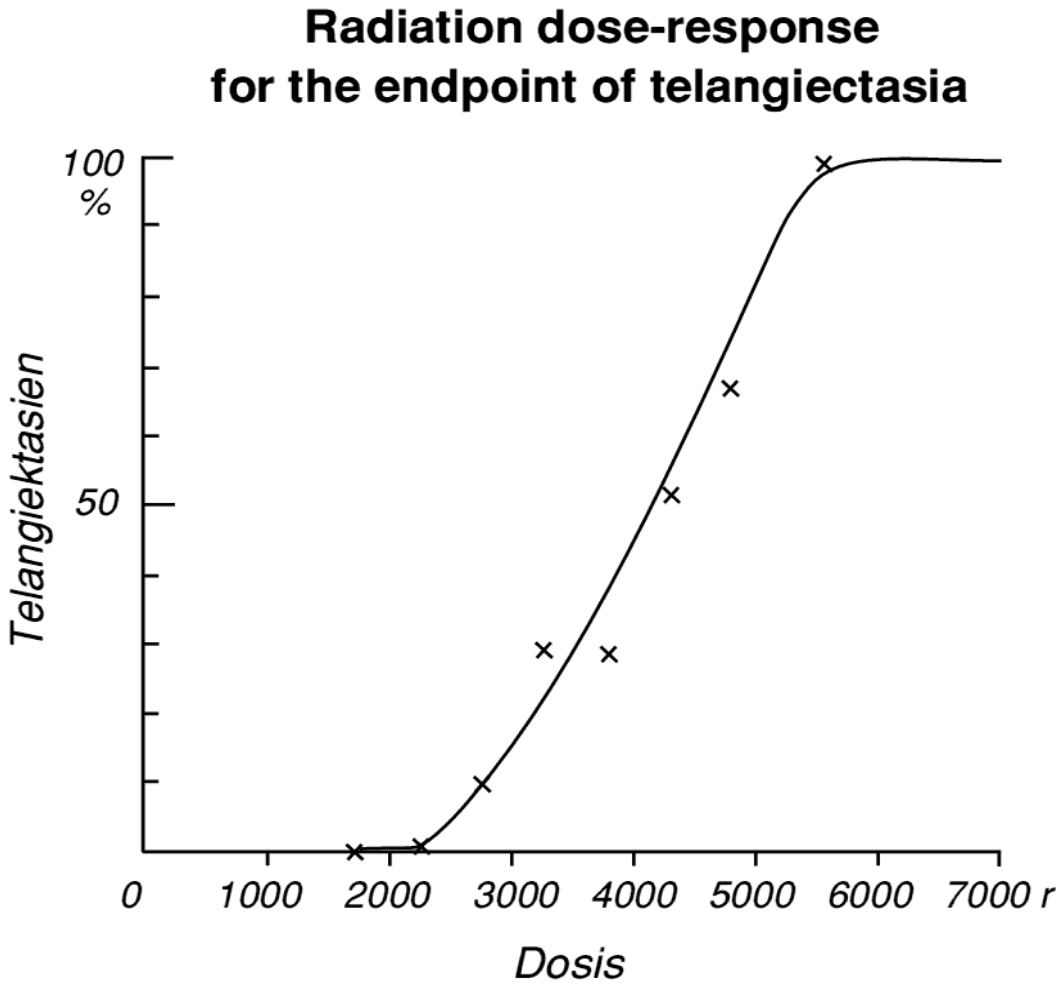
Individual variation in normal tissue sensitivity

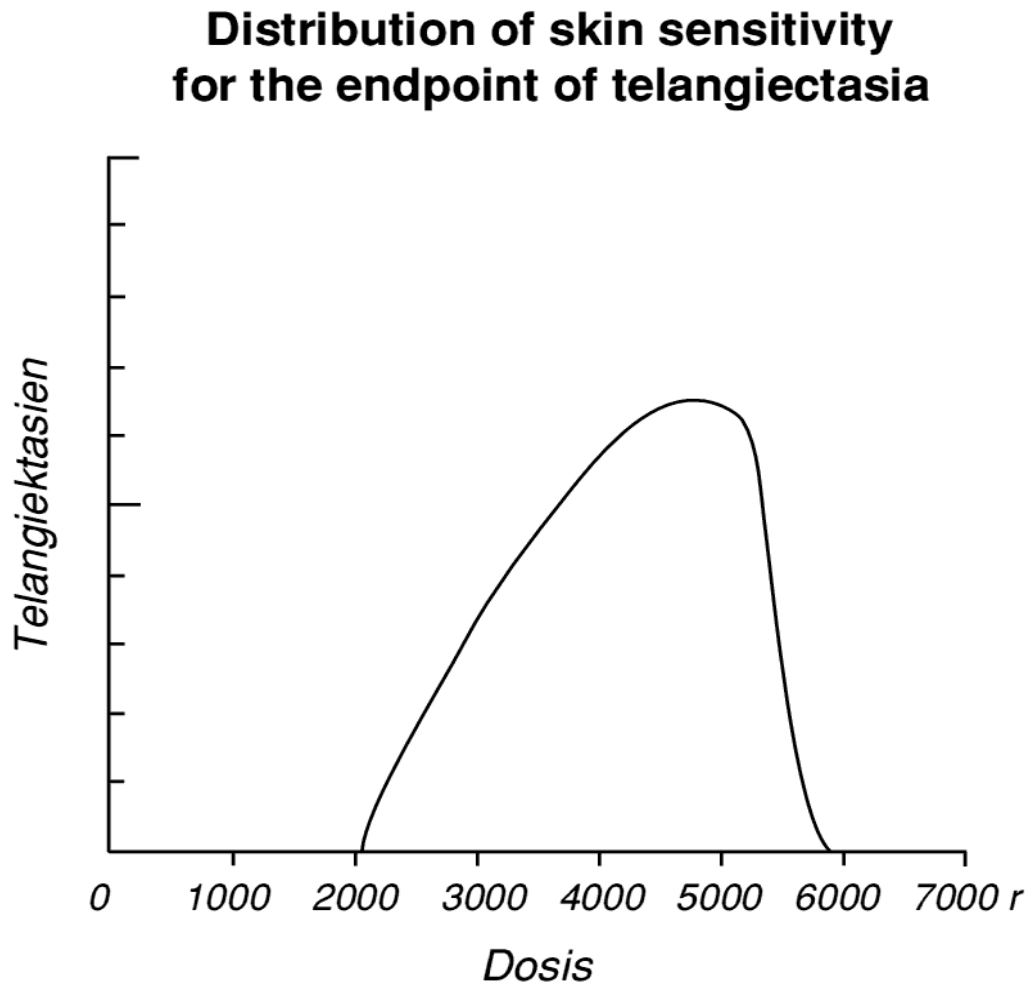
- First formally described in 1936 by Holthusen
  - Original of the sigmoid dose response curve

- Matches clinical experience since

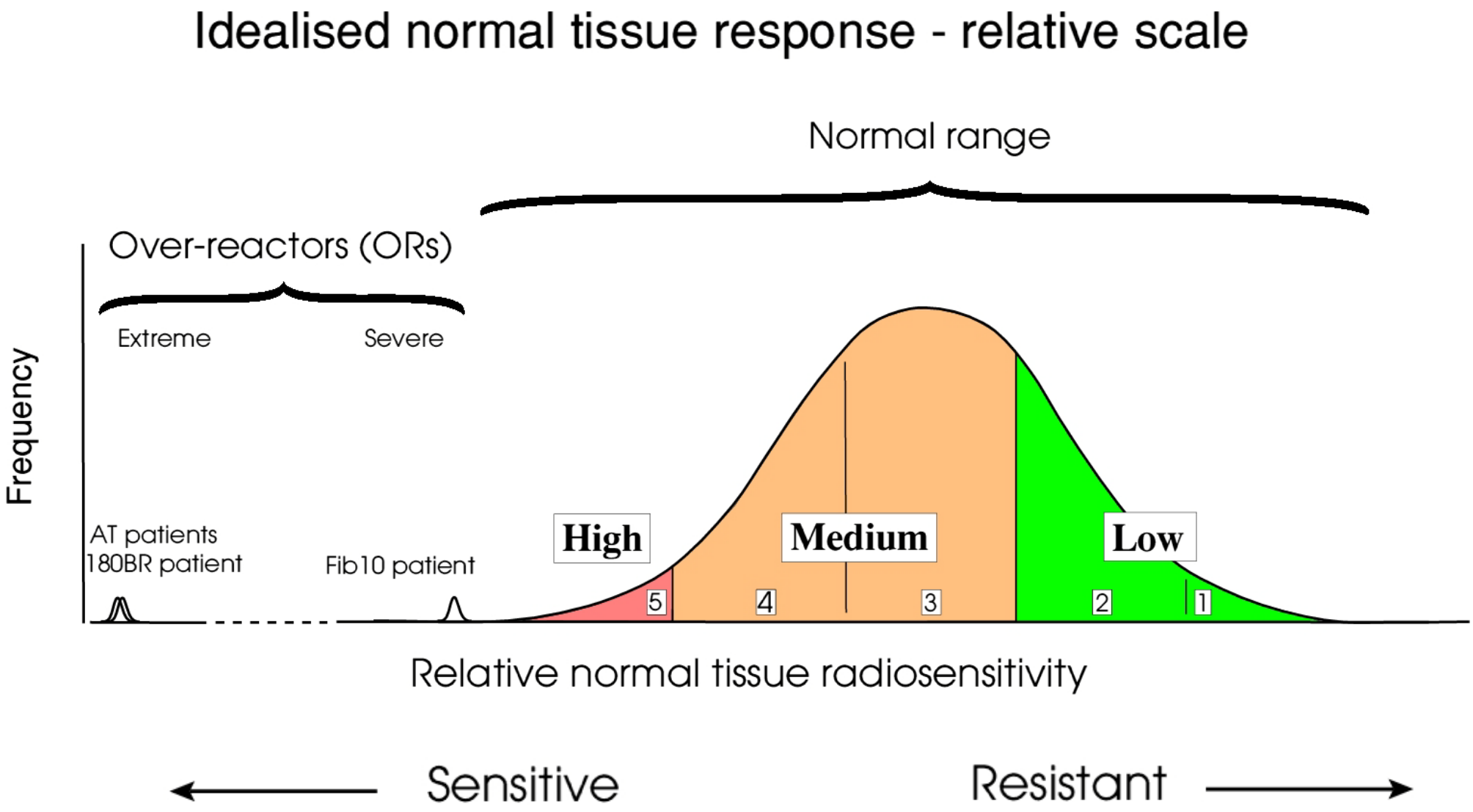
Individual variation in normal tissue sensitivity

Holthusen - Strahlentherapie & Onkologie 1936





Individual variation in normal tissue sensitivity



Individual variation in normal tissue sensitivity

- Variation in response harder to observe with mega-voltage beams because of skin sparing

- Could be exploited
  - To avoid toxicity in sensitive patients
    - 5% of patients
  - To dose escalate resistant patients
    - 40% of patients - dose escalate up to ~15%

- Other methods to measure normal tissue response are needed

Individual variation in normal tissue sensitivity

- Definite evidence that *normal* genetic variation is linked to variation in tissue response or toxicity
- Developments in last 2 years
- Not yet ready for clinical application

Individual variation in normal tissue sensitivity

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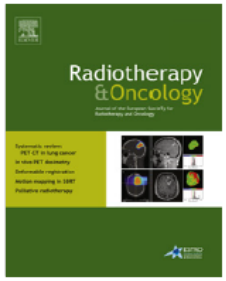

Original article

Individual patient data meta-analysis shows a significant association between the *ATM* rs1801516 SNP and toxicity after radiotherapy in 5456 breast and prostate cancer patients

- Convincingly shows significant association between specific allele in *ATM* gene and increased risk of normal tissue toxicity from RT

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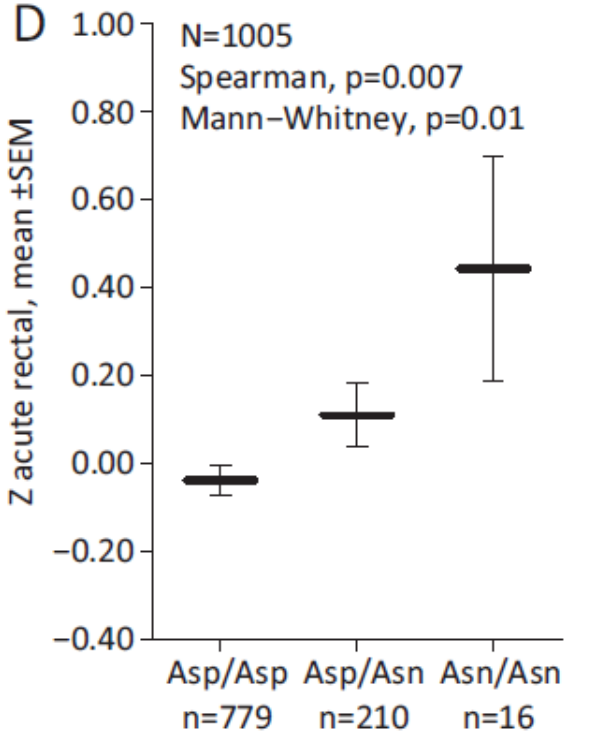
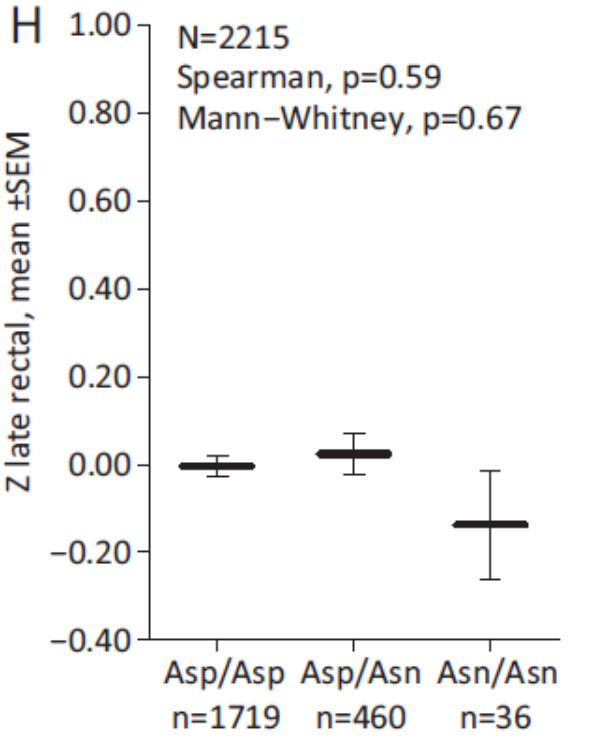
Synergy from physics and biology

Acute rectal toxicity



Late rectal toxicity



- Single SNP change in *ATM* gene
- Association with 7 of 8 endpoints – but *not* late rectal toxicity
- Emphasises complexity in biological responses

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Convolving individual radiosensitivity & individual dose accumulation

- Could we put together a ‘signature’ of individual normal tissue radiosensitivity and an individual estimate of dose accumulation (D_A) ?

- This develop the concept of individualisation (or personalisation) even more
  - Biology meets physics (+ physics)

Convolving individual radiosensitivity & individual dose accumulation

Percentages of patient in different risk categories

Sensitivity	Dose difference (Planned - DA)		
	D_A worse (30%)	D_A same (30%)	D_A lower (40%)
Most sensitive (10%)	3%	3%	4%
Average (50%)	15%	15%	20%
Most resistant (40%)	12%	12%	16%

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Doctor’s perspective

- Radiotherapy has a crucial role in cancer care
- Many developments still required
- There is always still the physics
- There is always still the margin maths
- Small differences make a difference
- Ultimately we are working towards improving patients’ outcomes

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Doctor’s perspective

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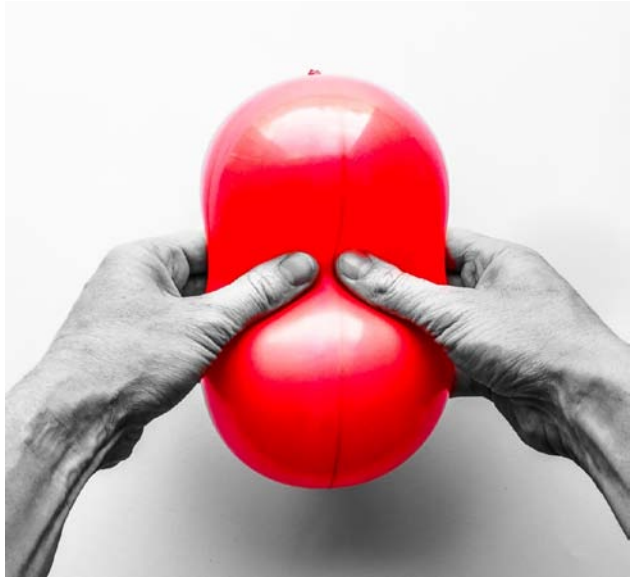

- Ultimately we are working towards improving patients’ outcomes

Doctor’s perspective

Our first IG-IMRT patient - 31st October 2007