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Broadening the therapeutic band width

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ATP Barcelona 2017

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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

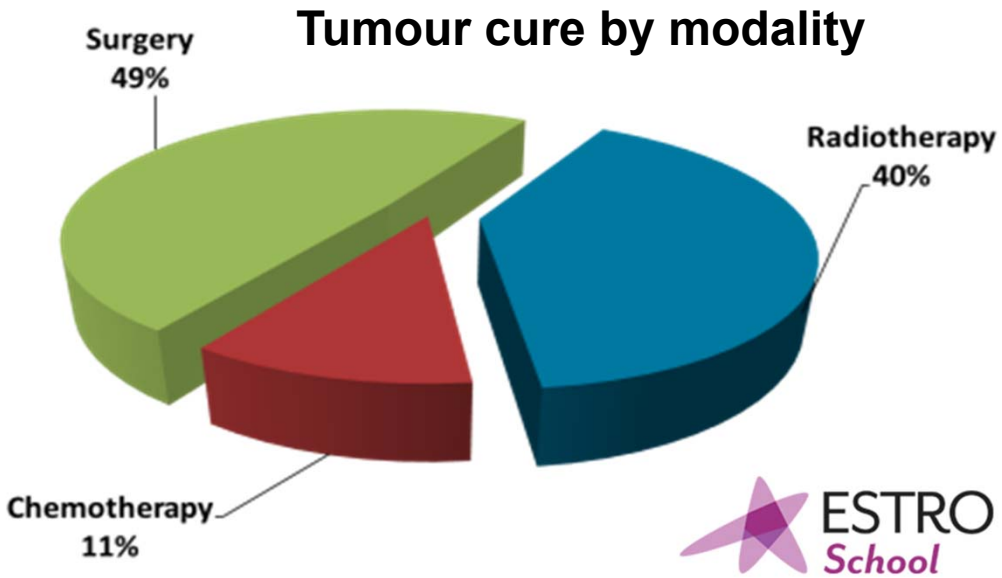
Introduction

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

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

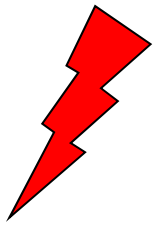
Critical Impact of Radiotherapy Protocol Compliance and Quality in the Treatment of Advanced Head and Neck Cancer: Results From TROG 02.02

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

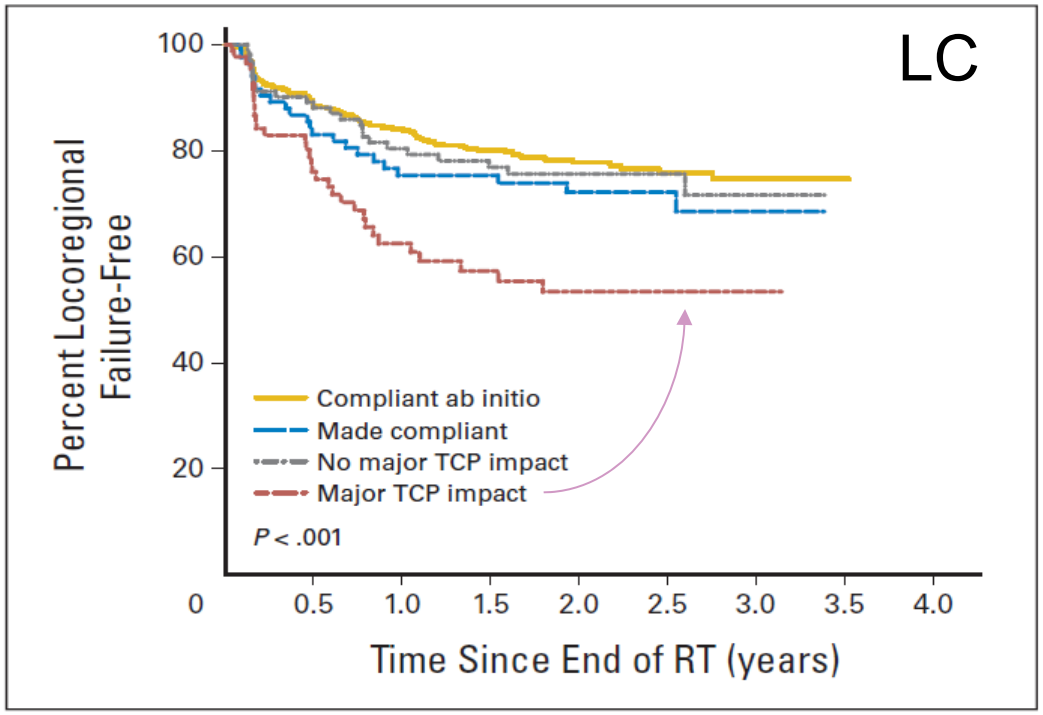

Fig 3. Time to locoregional failure by deviation status

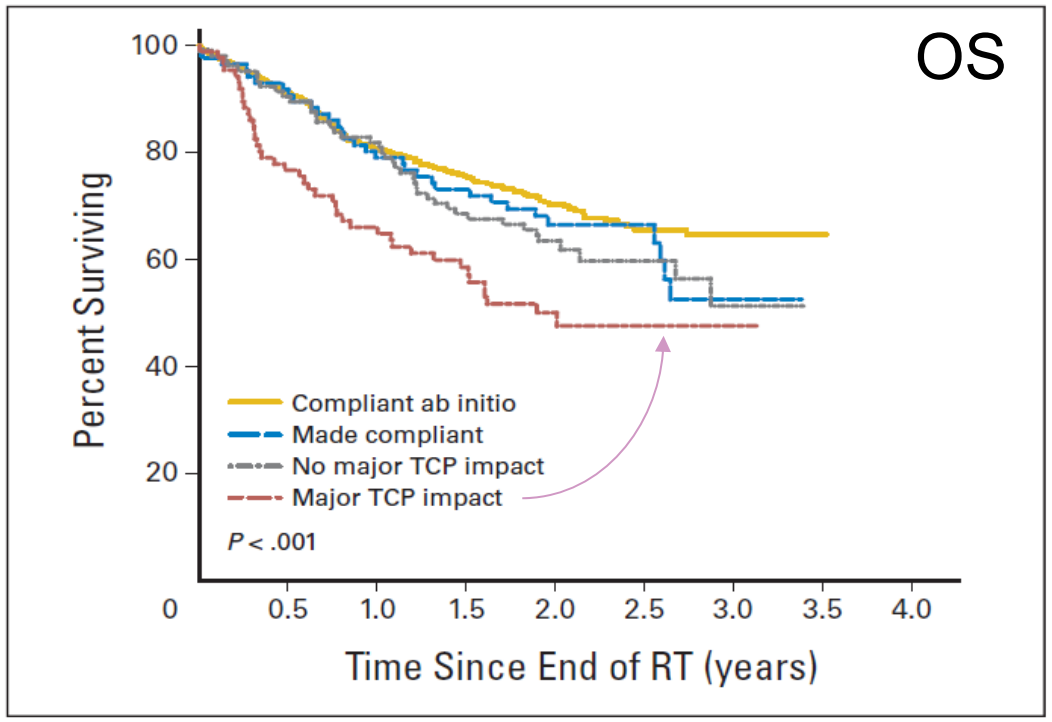

Fig 2. Overall survival by deviation status:

- 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

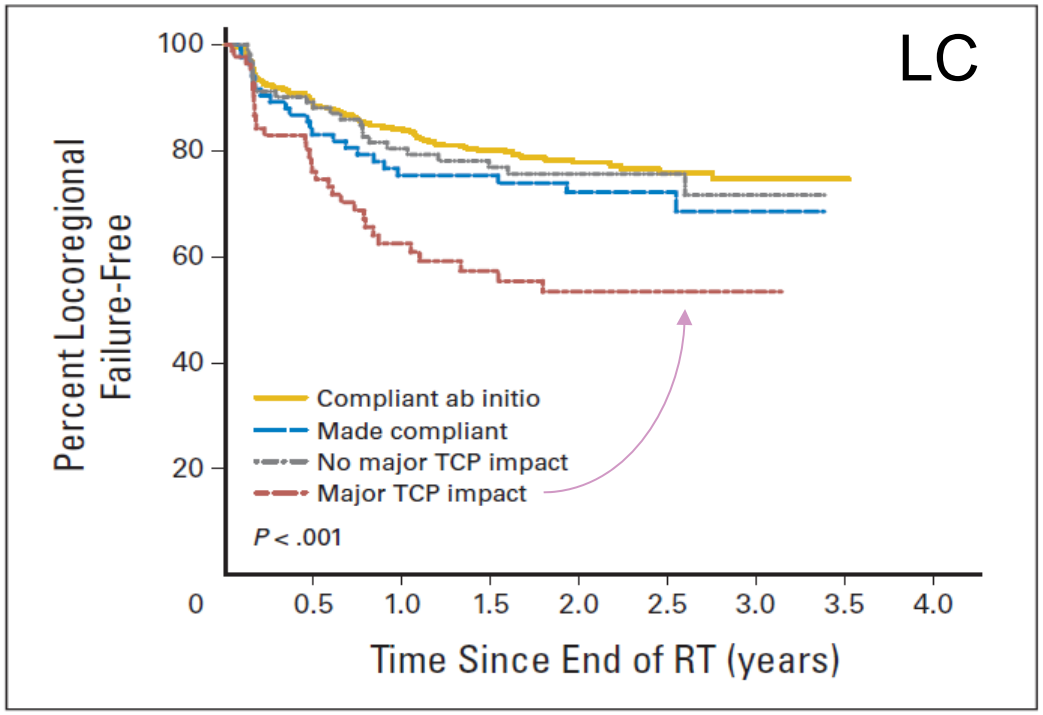

Fig 3. Time to locoregional failure by deviation status

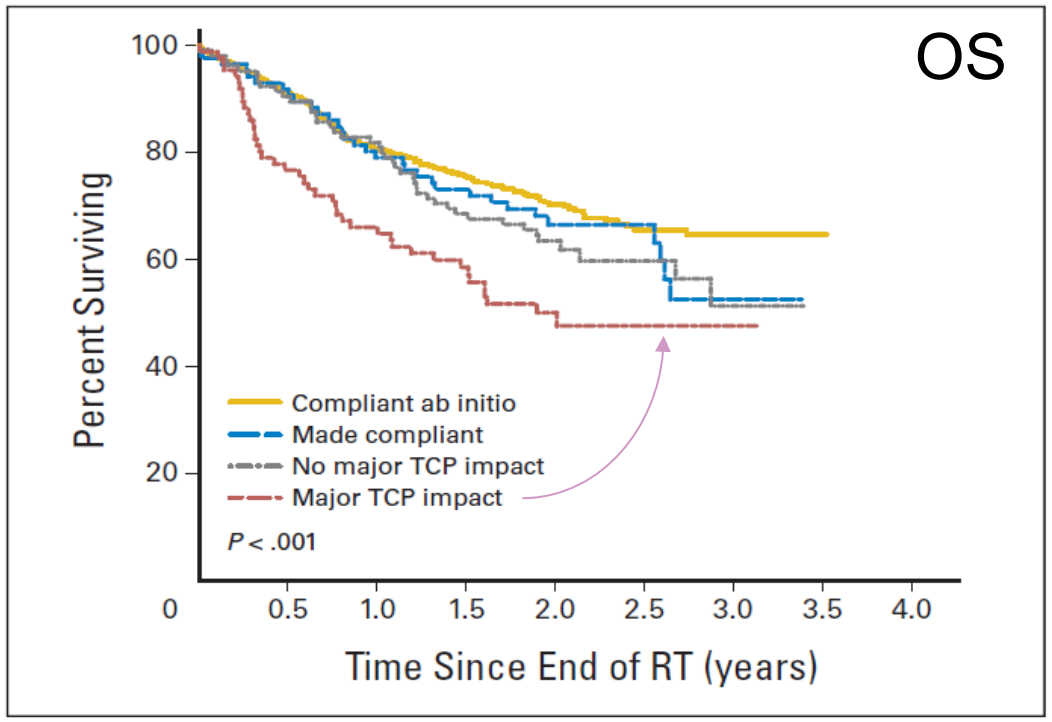

Fig 2. Overall survival by deviation status:

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

Broadening RT band width

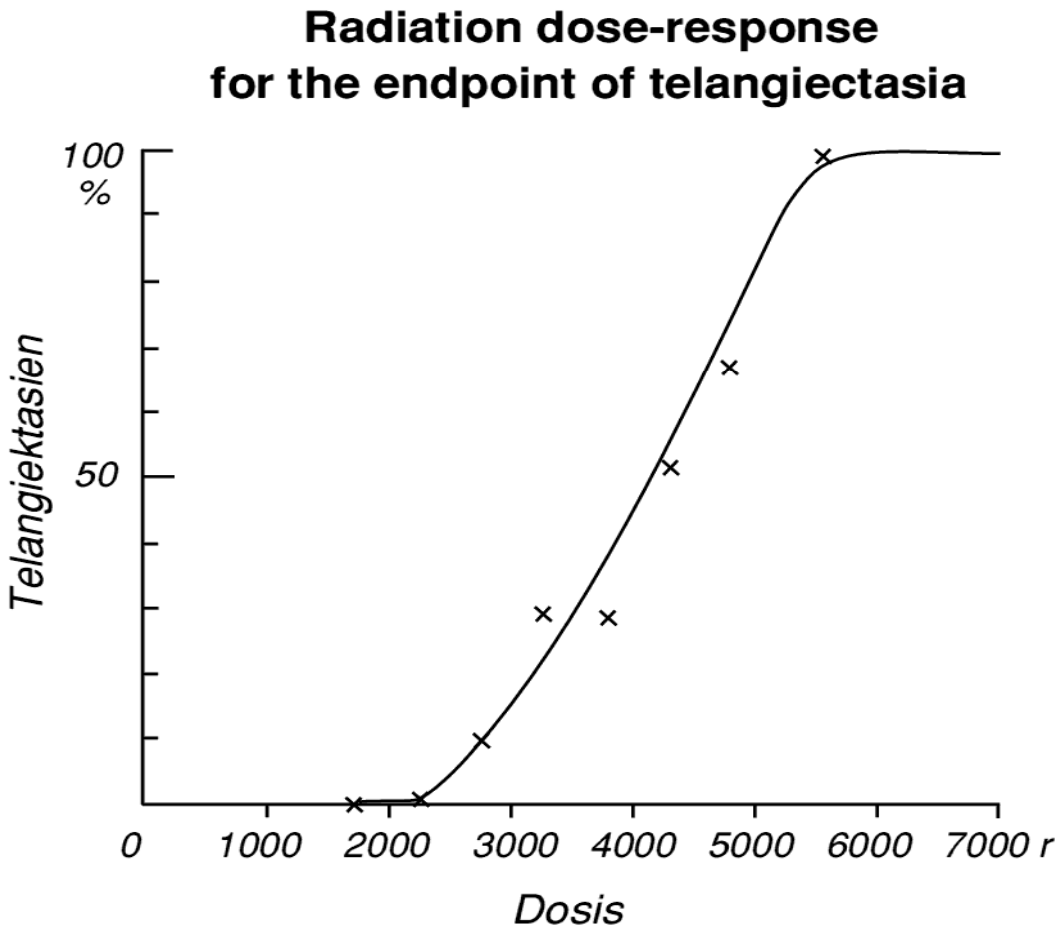
- Local control will translate into overall cure in many patients
  - For breast –1 life saved for every 4 recurrences prevented

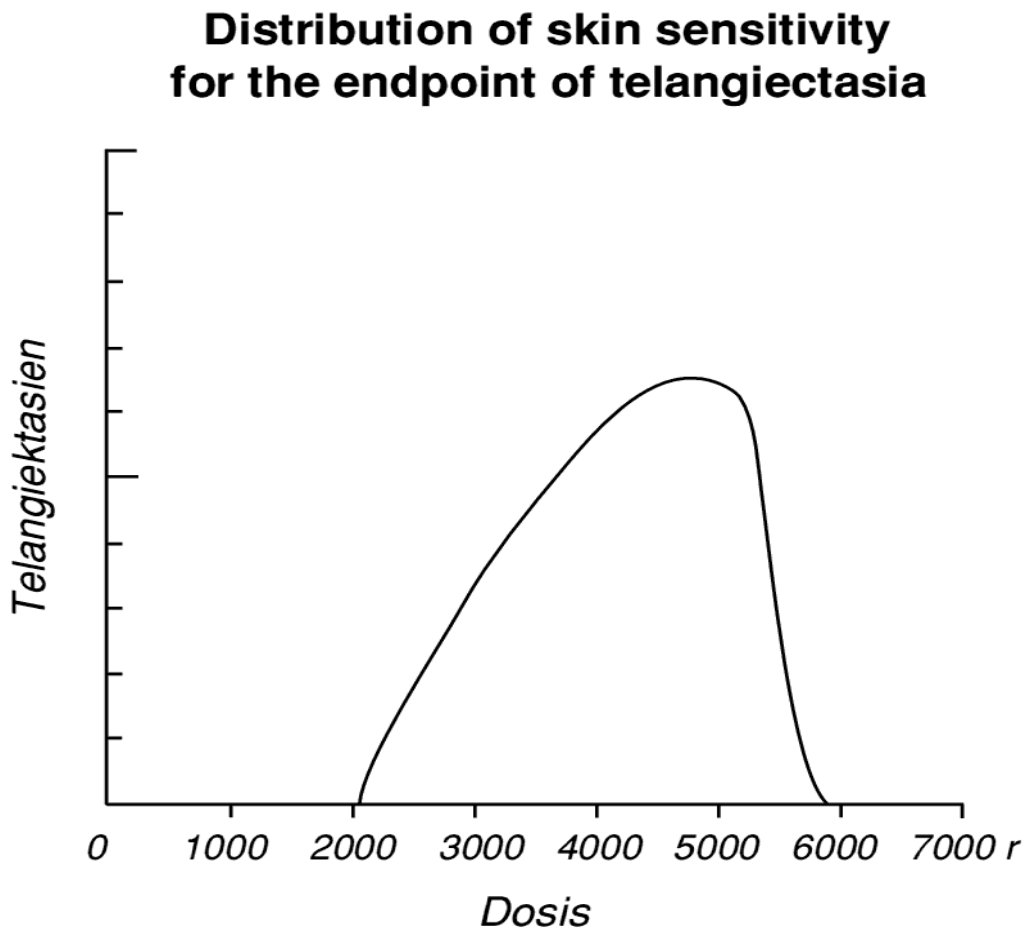
- Three variations on improved therapeutic ratio
  - Same cure, lower toxicity
  - Higher cure, same toxicity
  - Higher cure, lower toxicity (if we can !)

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

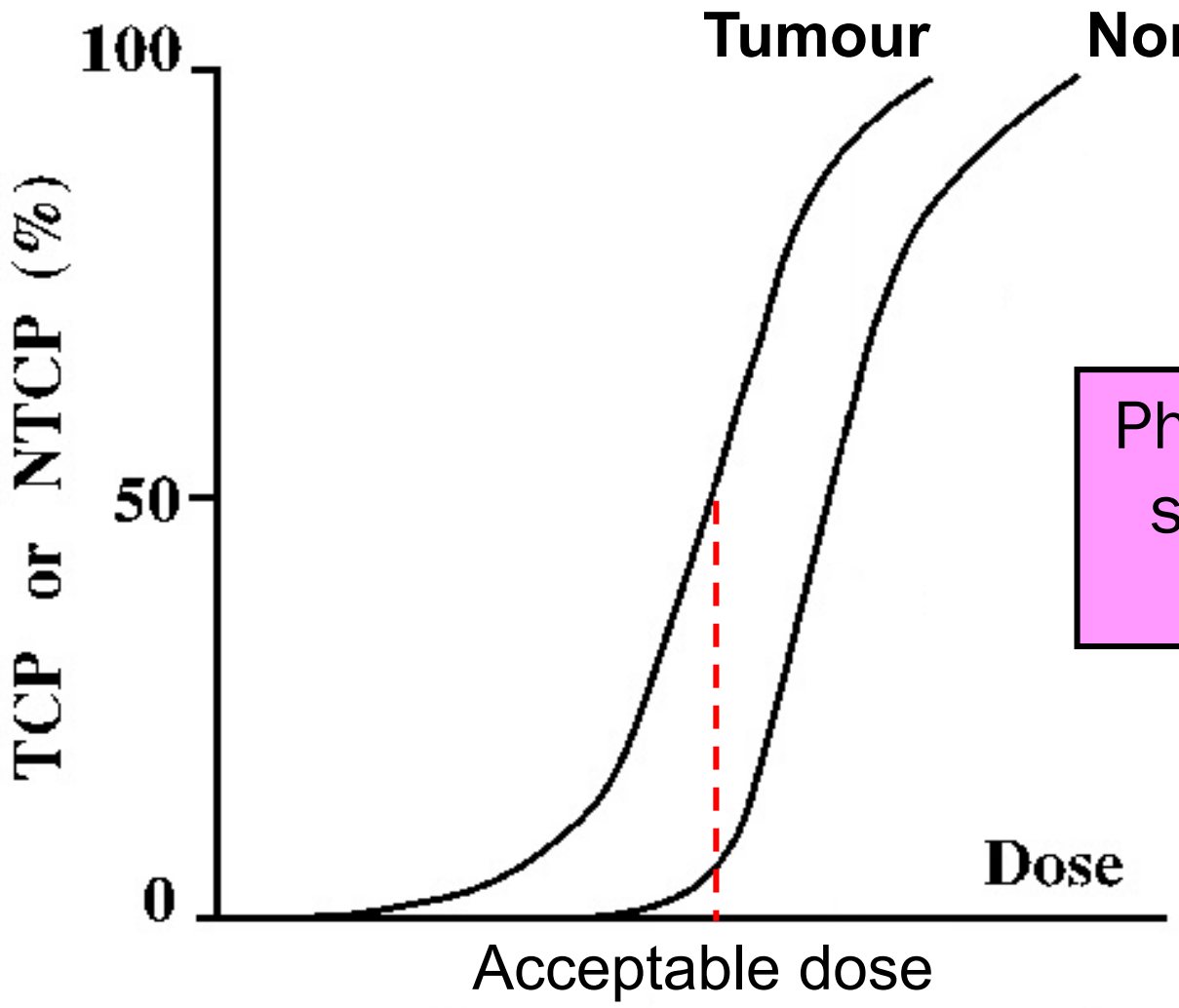
The first normal tissue dose response curve

Holthusen - Strahlentherapie 1936



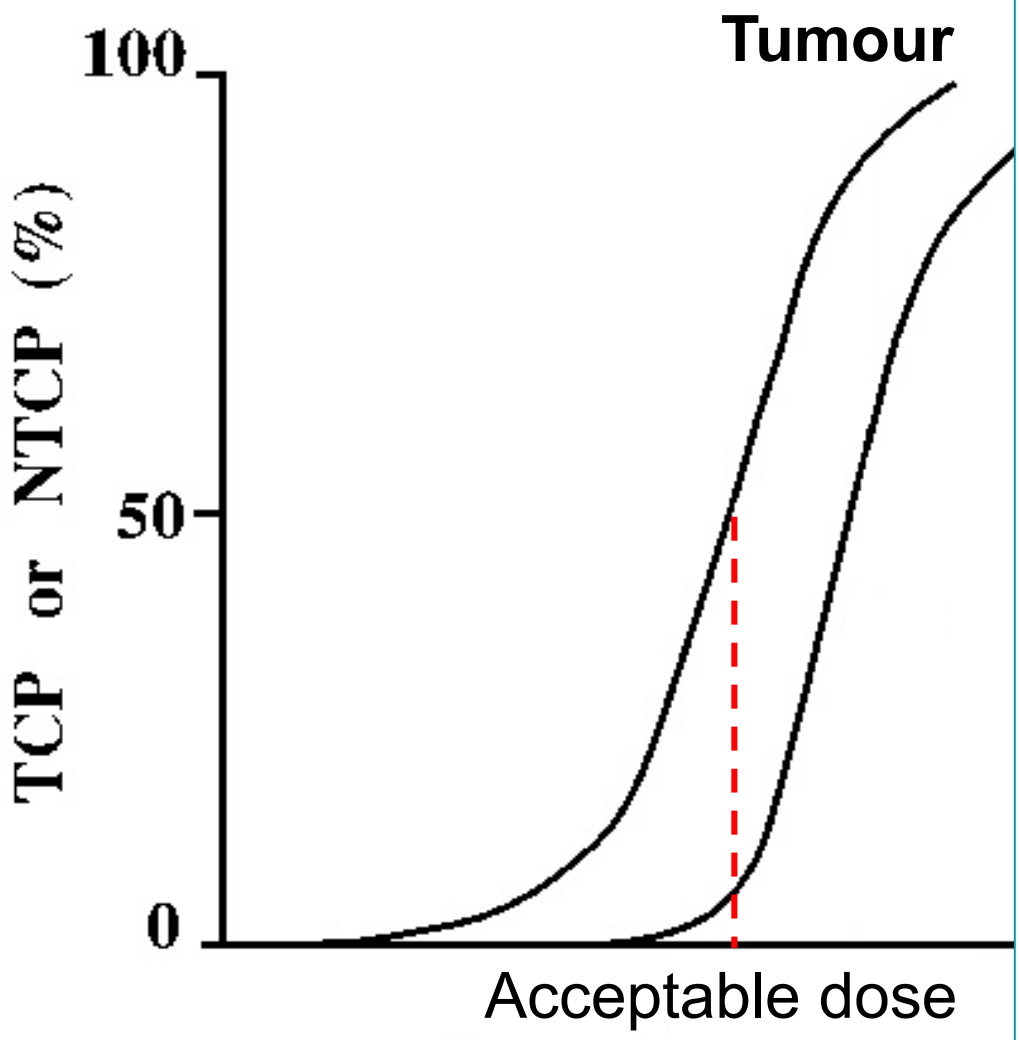


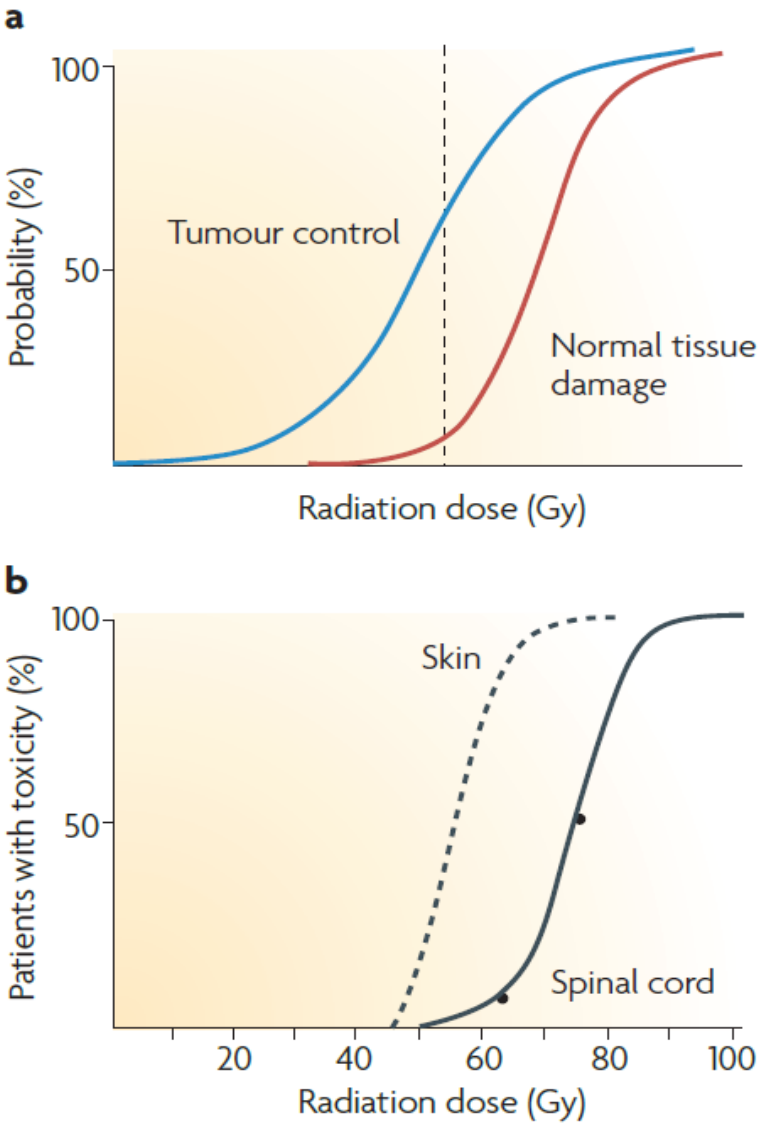
Increase the therapeutic ratio



Physical *and* biological strategies can move the curves apart

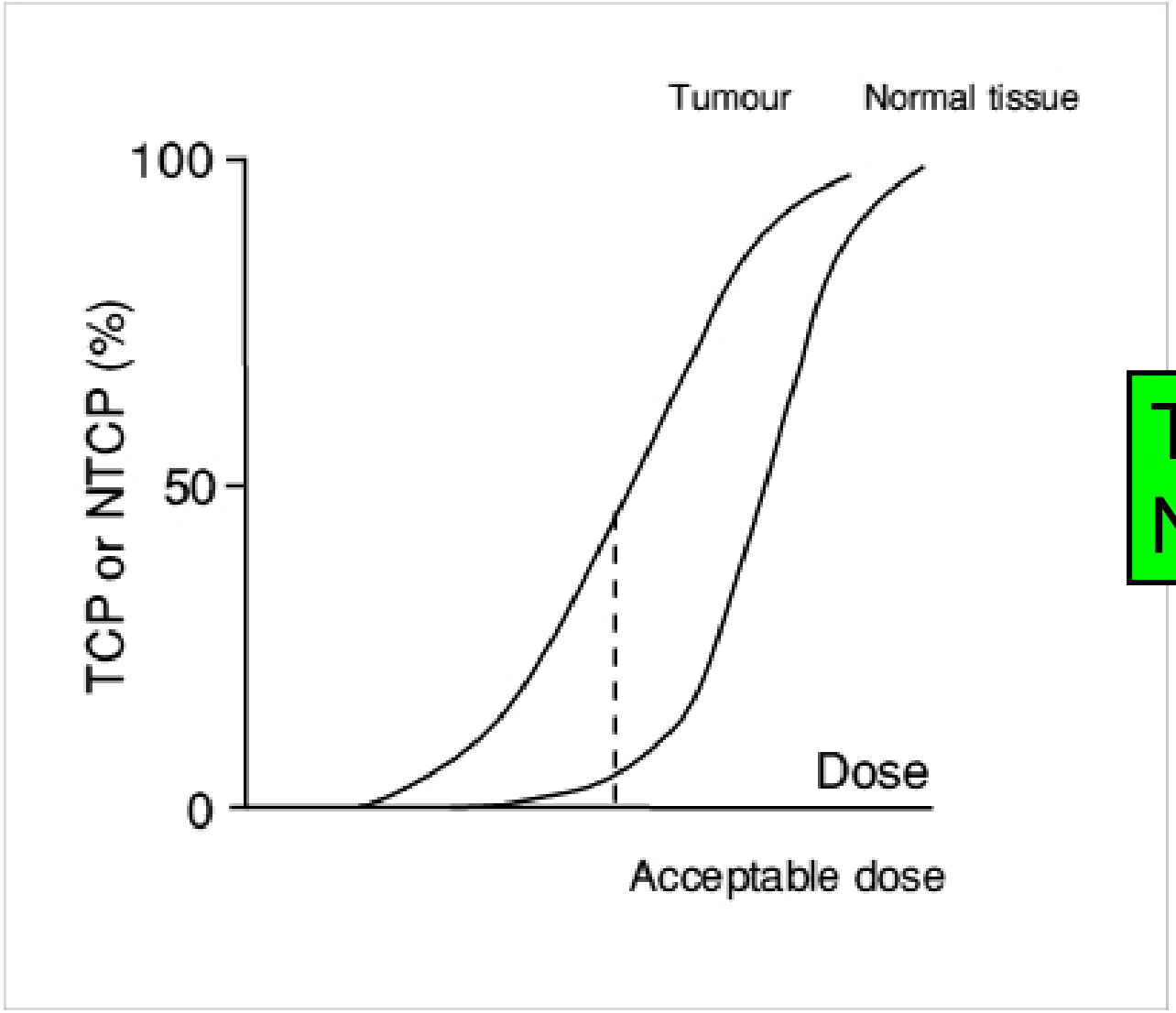
Increase the therapeutic ratio





Barnett et al. Nat Rev Cancer 2009; 9(2): 134-42

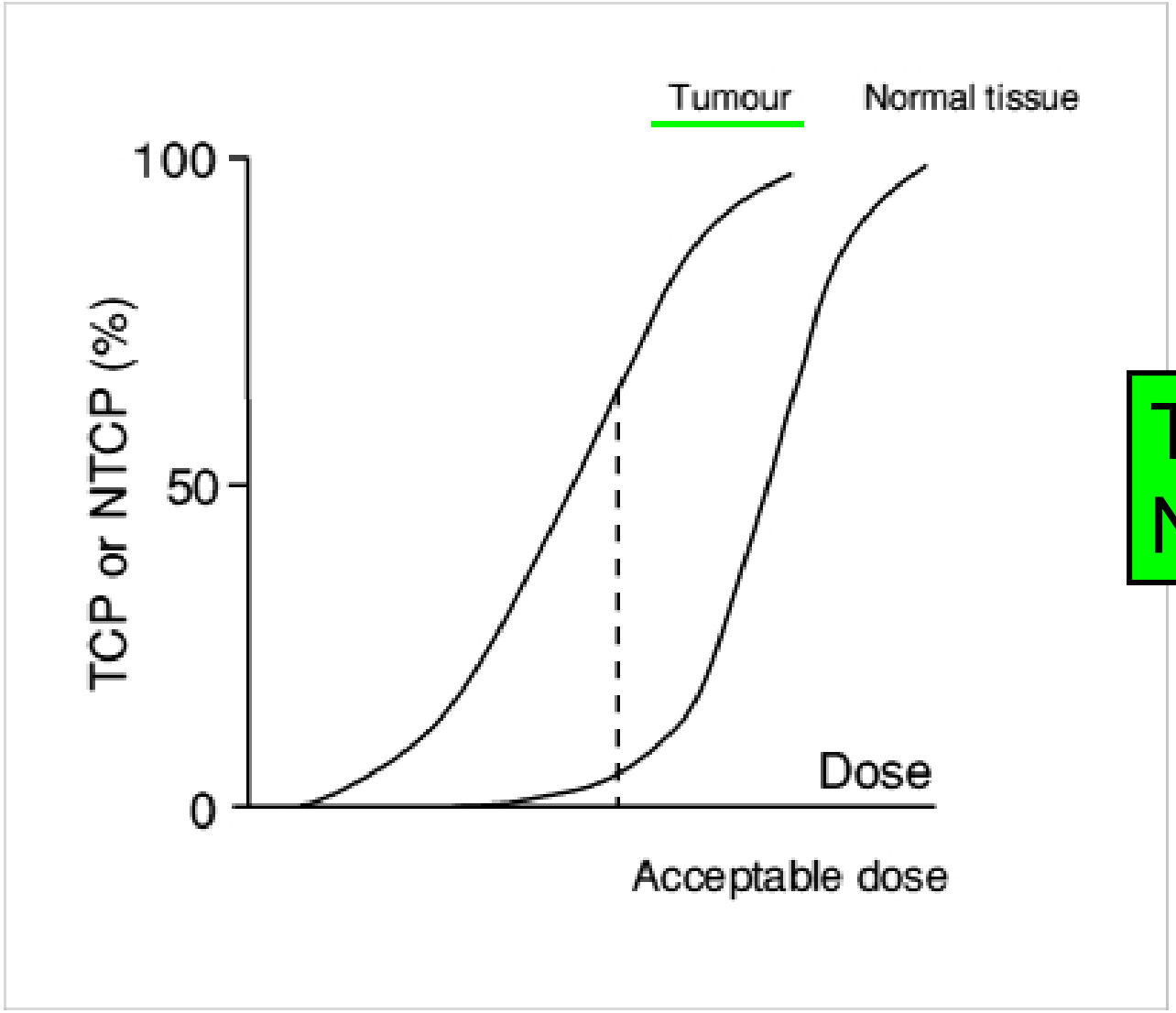
Increase the therapeutic ratio



TCP 50%
NTCP 5%

(a)

Increase the therapeutic ratio



(b)

TCP 70%
NTCP 5%

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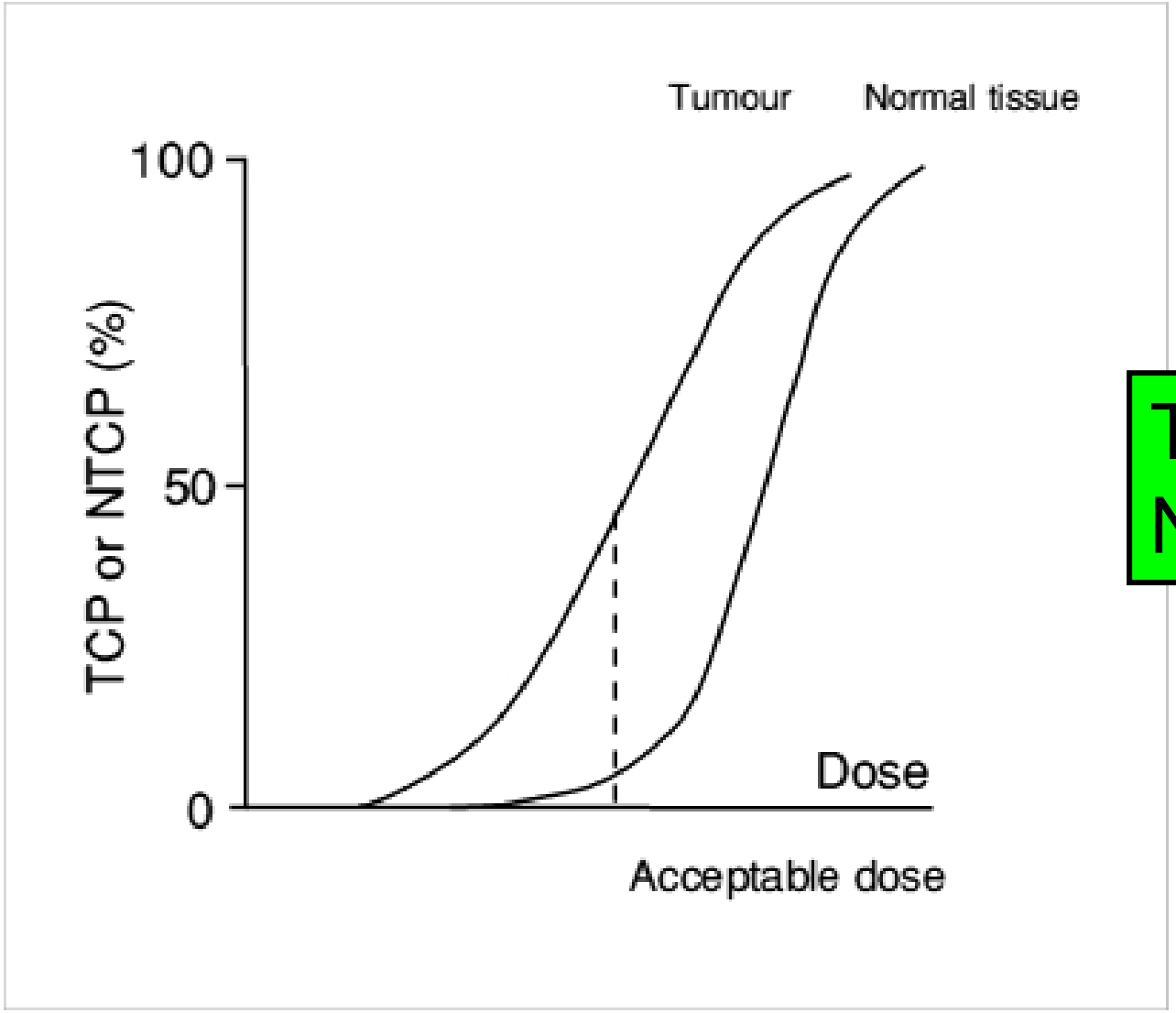
Increase the therapeutic ratio

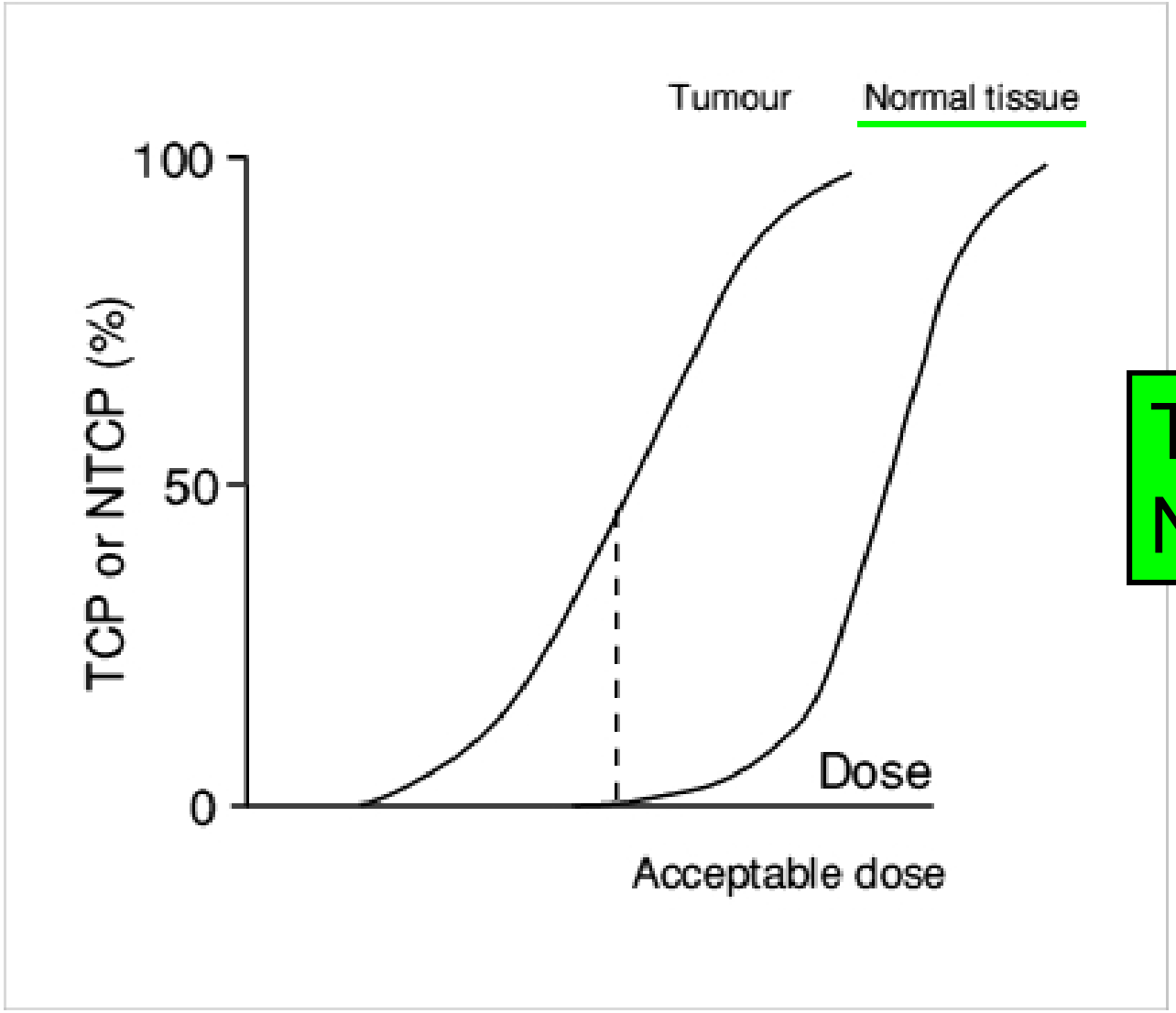


TCP 50%
NTCP 5%

(a)

Back to the beginning

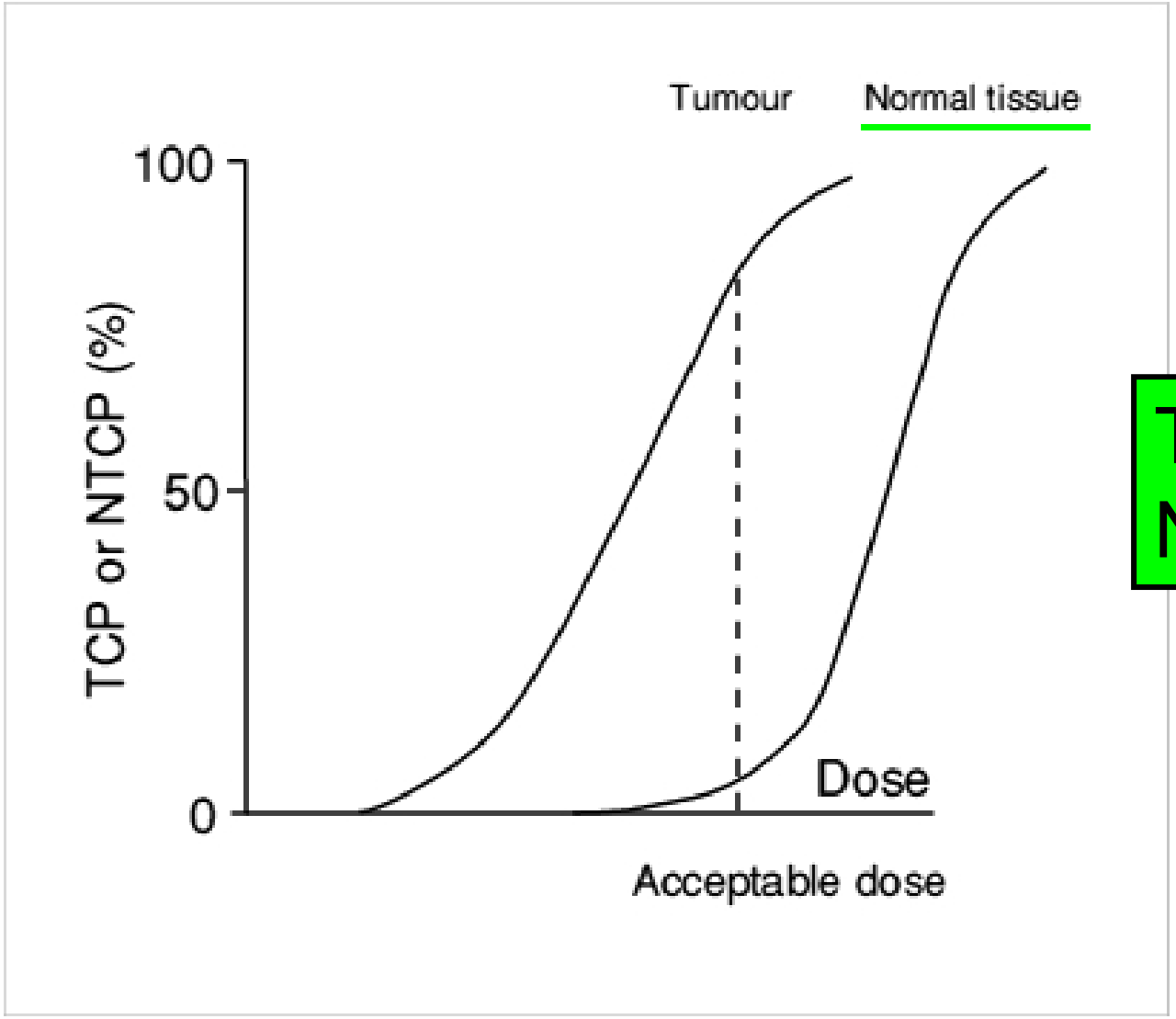
Increase the therapeutic ratio



TCP 50%
NTCP ~0%

(c)

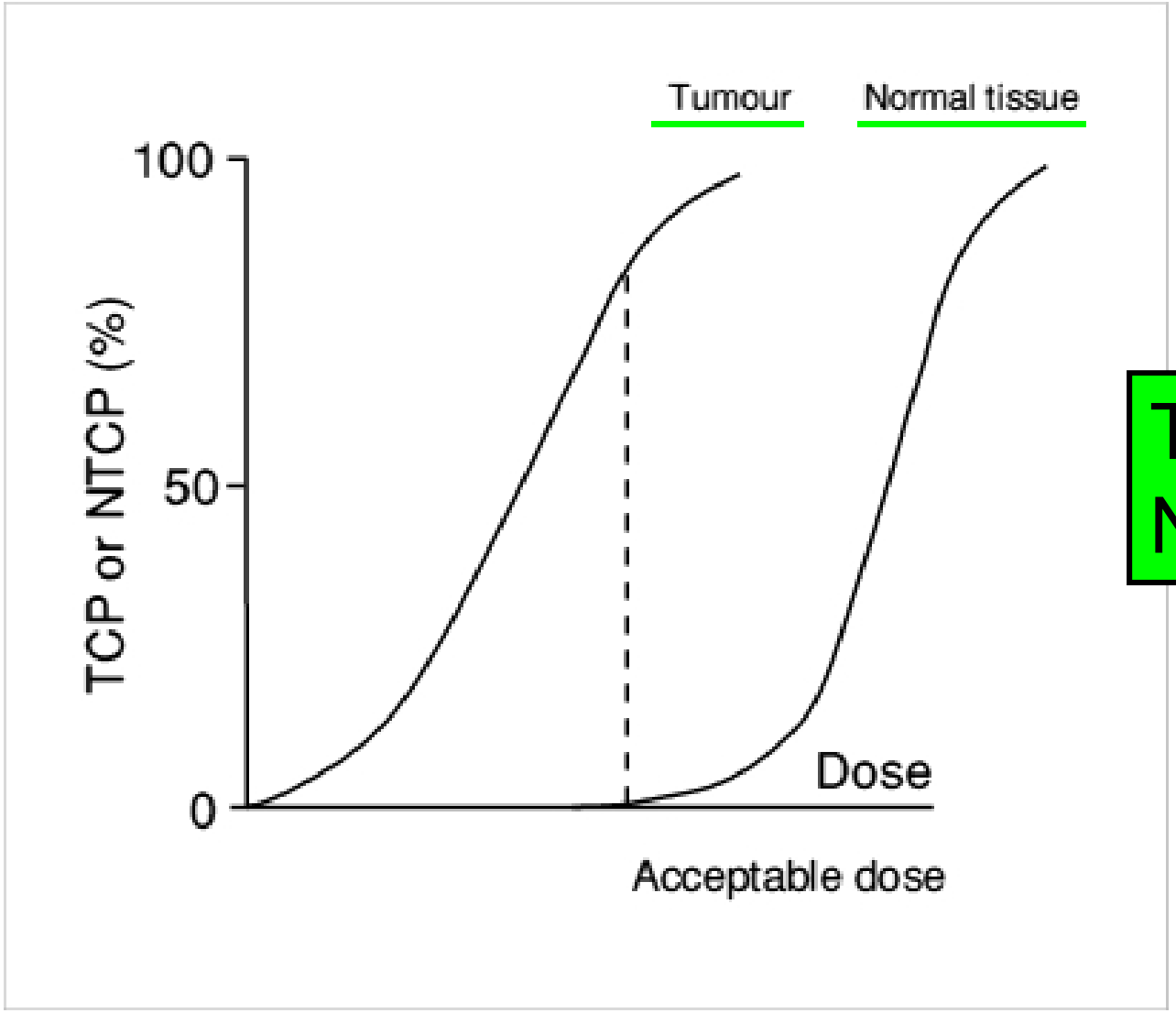
Increase the therapeutic ratio



TCP 80%
NTCP 5%

(d)

Increase the therapeutic ratio



TCP 80%
NTCP ~0%

(e)

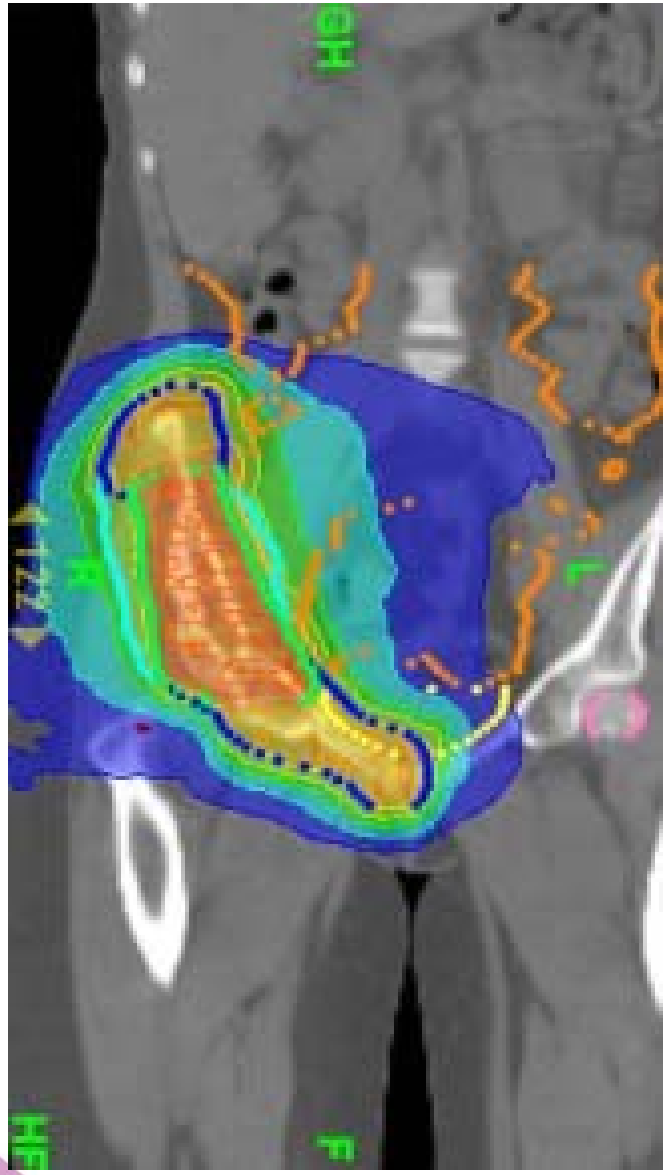
Normal tissue toxicities

- Toxicity largely relates to **late normal tissue effects**
  - Tissue specific

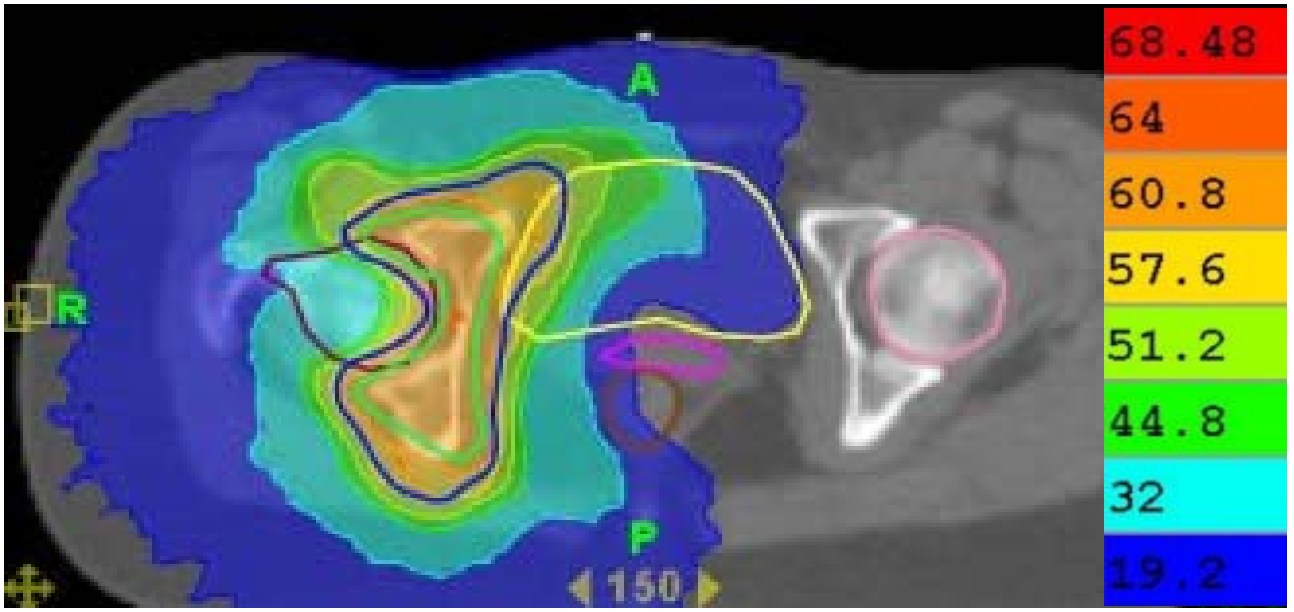
- Some **acute toxicities** also important
  - Especially applies to concurrent chemo-RT

- **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

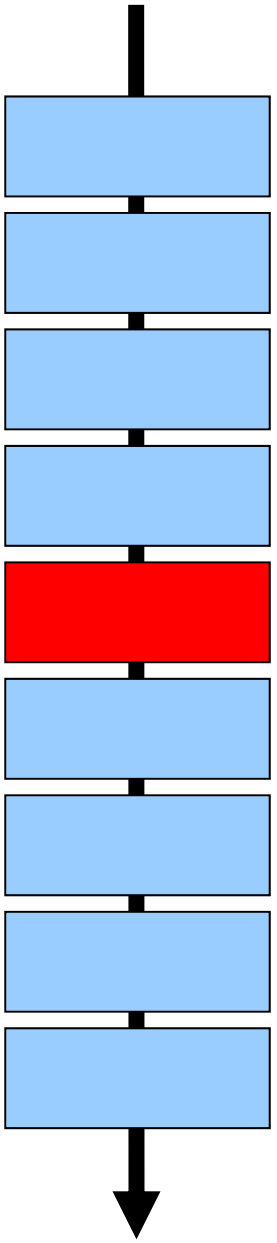
- Serial organ

- Damage to 1 part causes failure
- Serious clinical consequence

- High dose most important

- For example ...

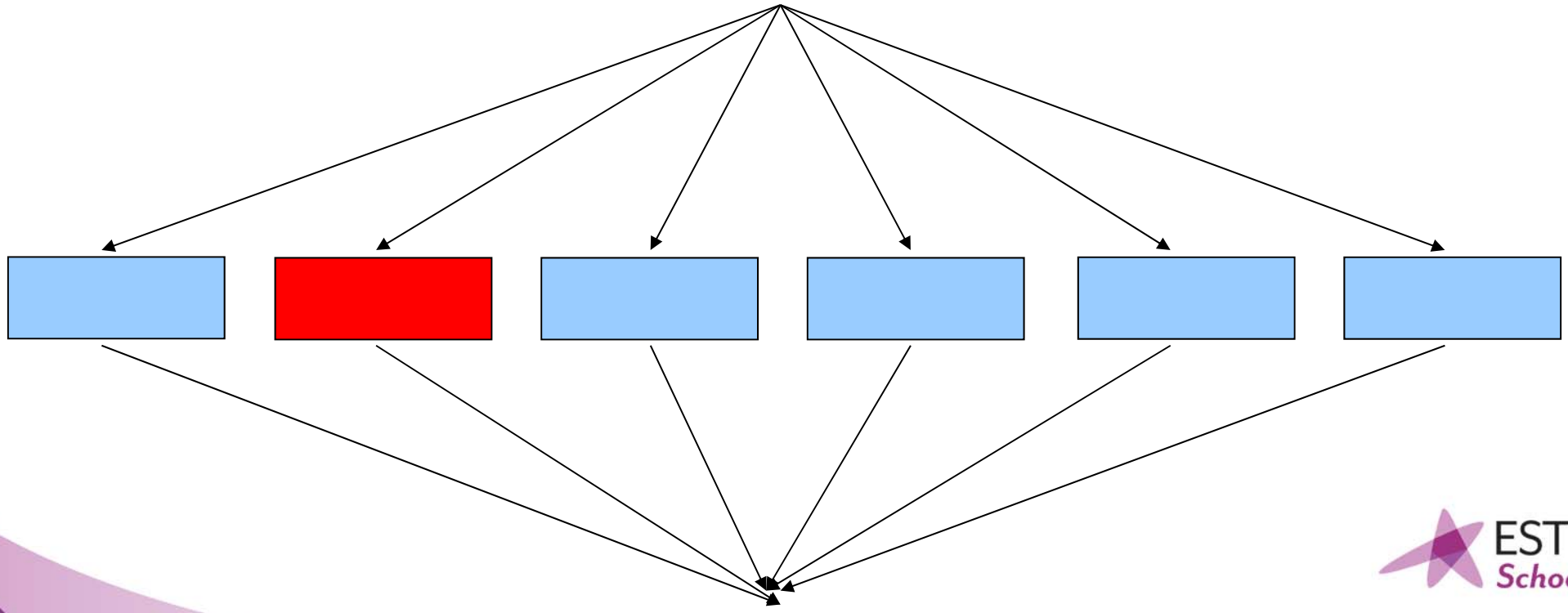
... spinal cord



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

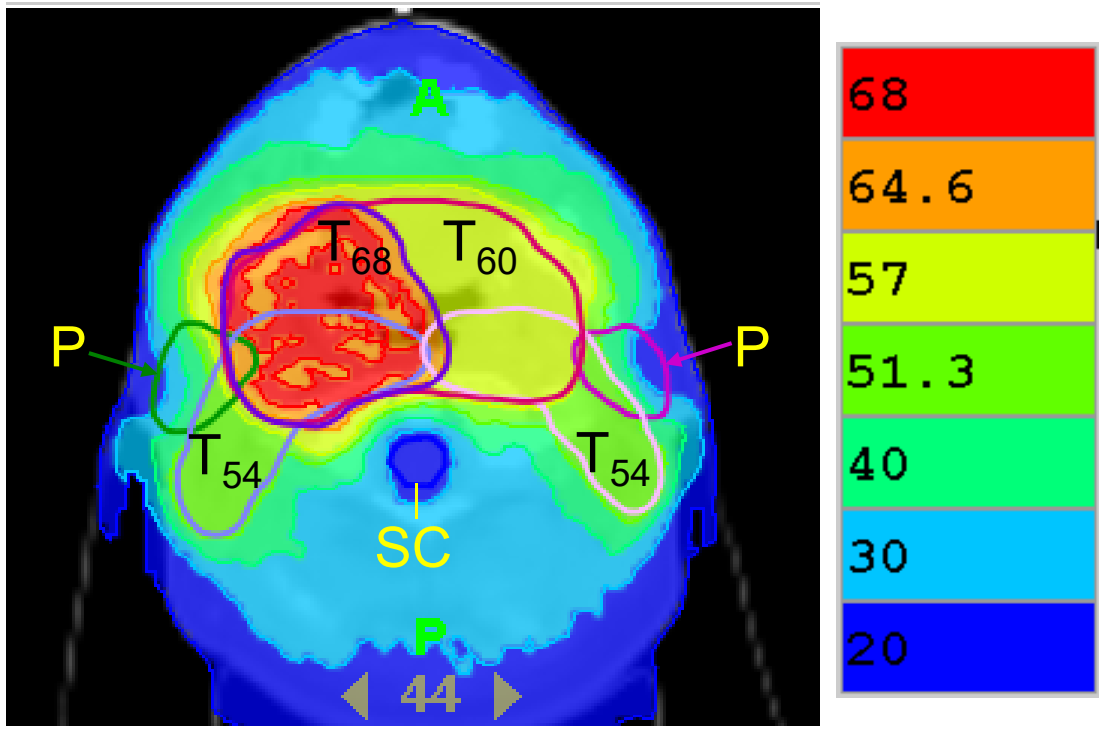
- Volume and architecture important

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

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

Broadening the band width

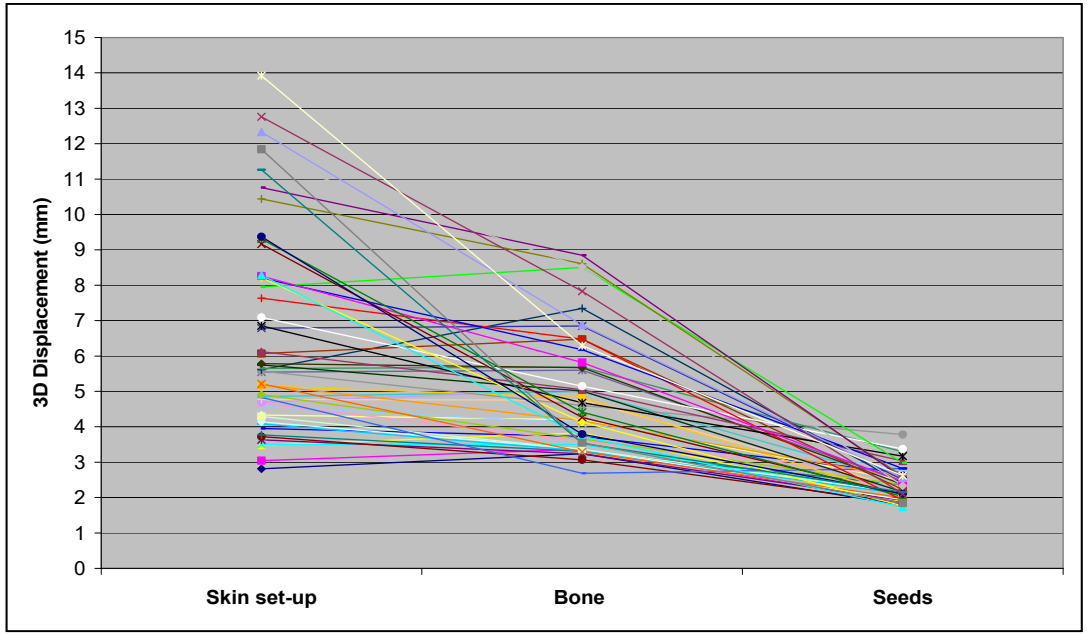
- IMRT for Head and neck cancer
- Sparing parotids reduces toxicity ¶
- Restricting dose to spinal cord allows high dose



¶ 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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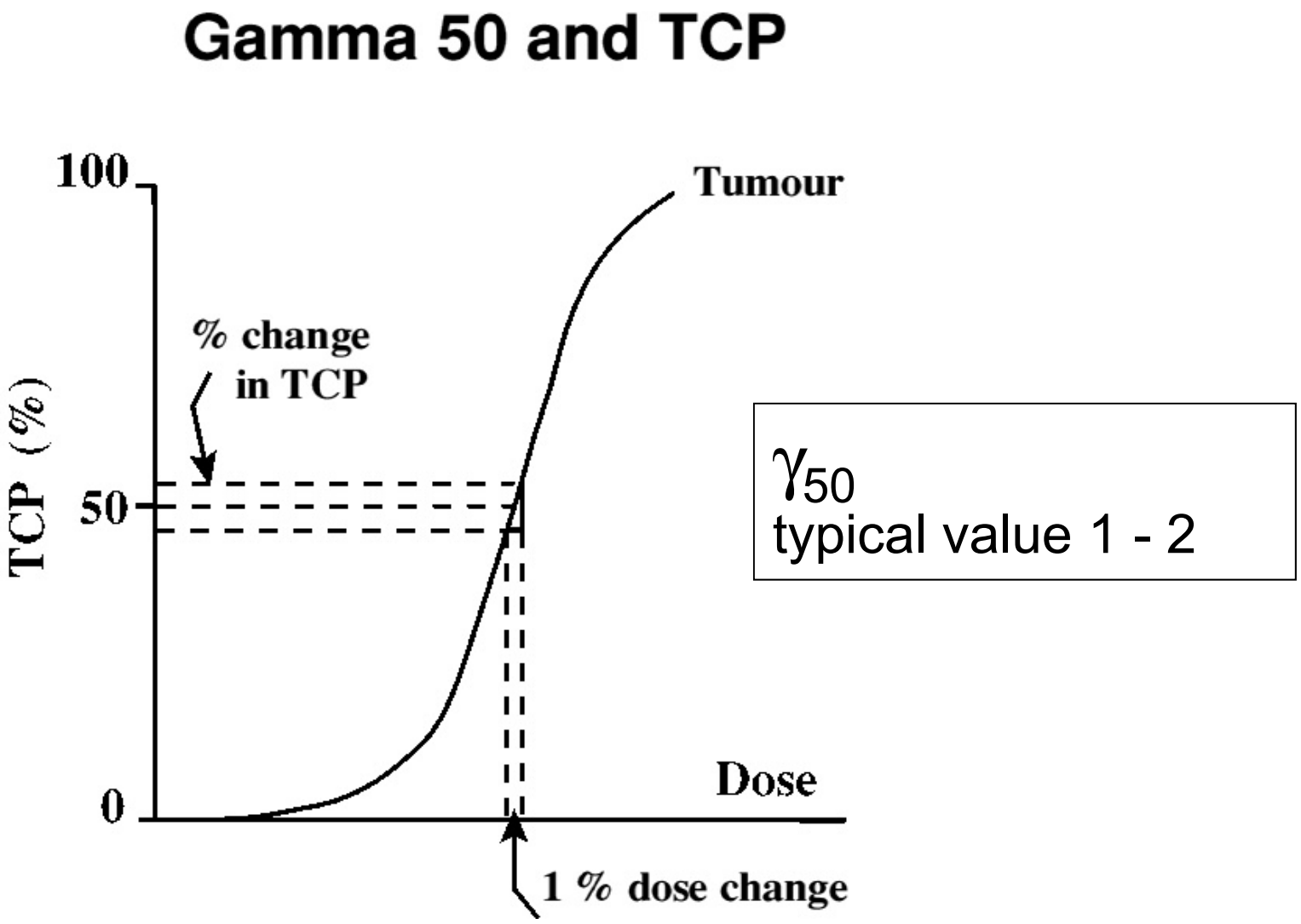
Broadening the band width

- 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



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

- Small differences matter
- Concept of ‘marginal gains’

- 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

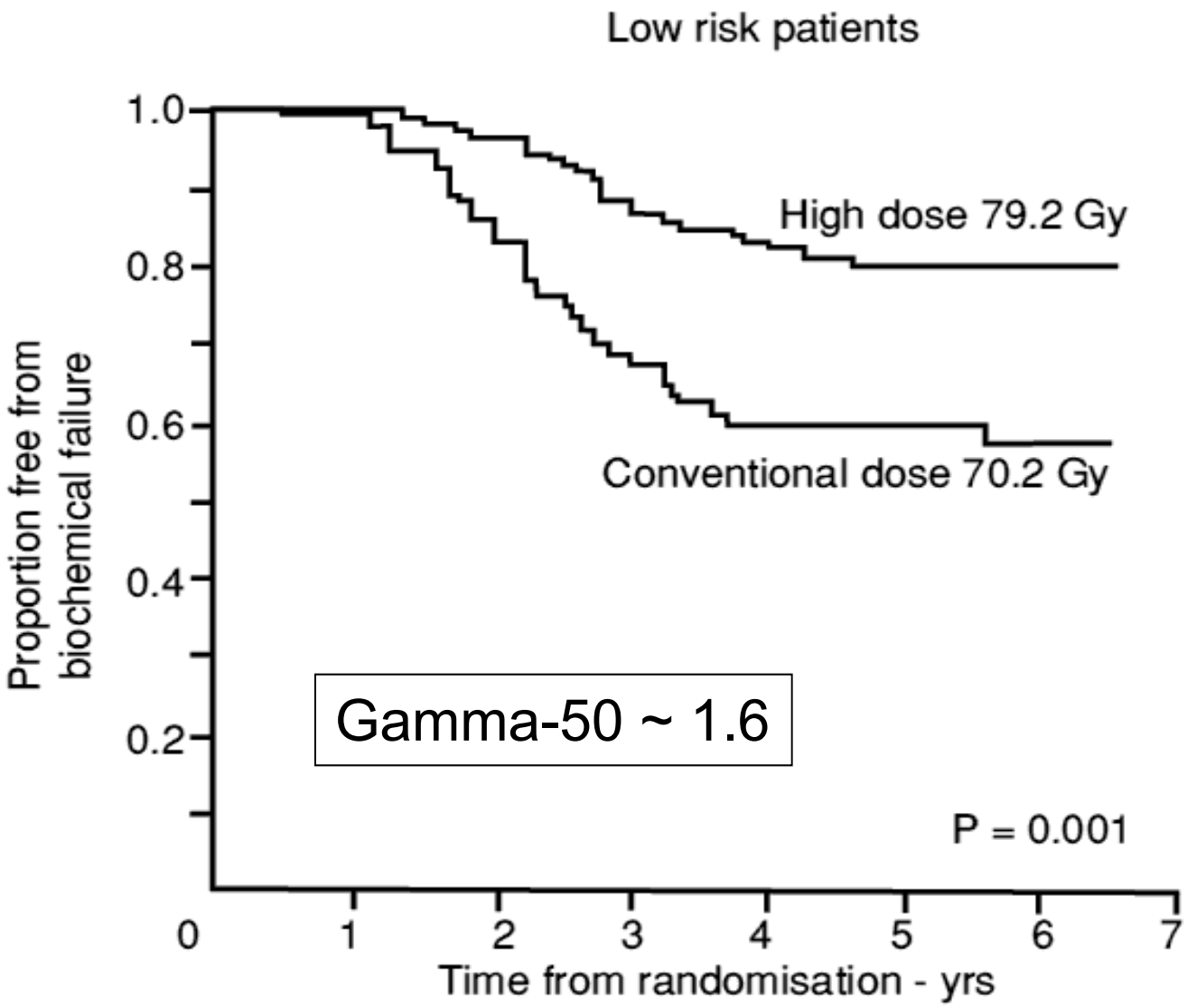
Mike Sharpe
‘Mike on his bike’

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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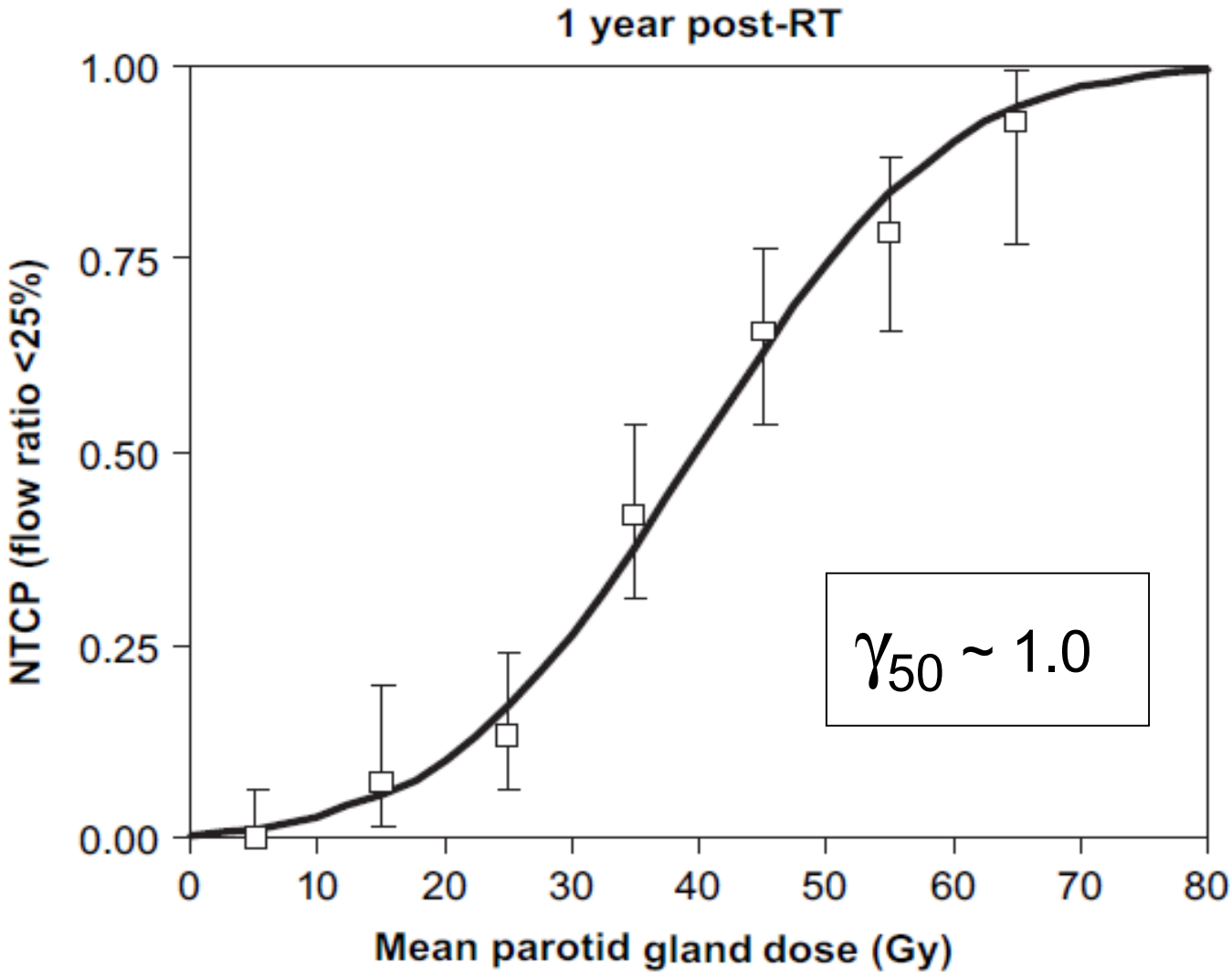
Broadening the band width

Parotid toxicity



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

Combined Michigan & Utrecht data

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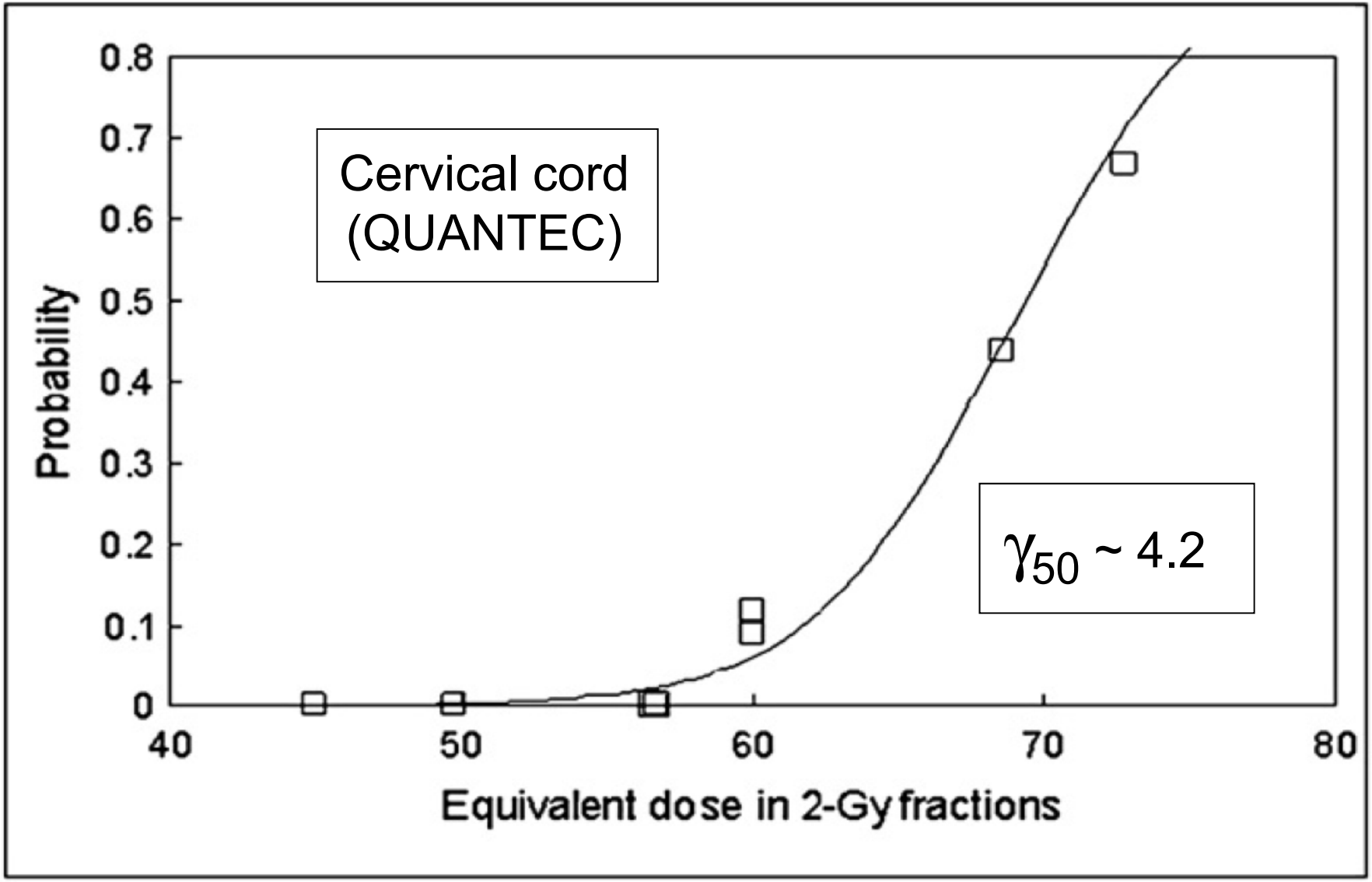
Broadening the band width



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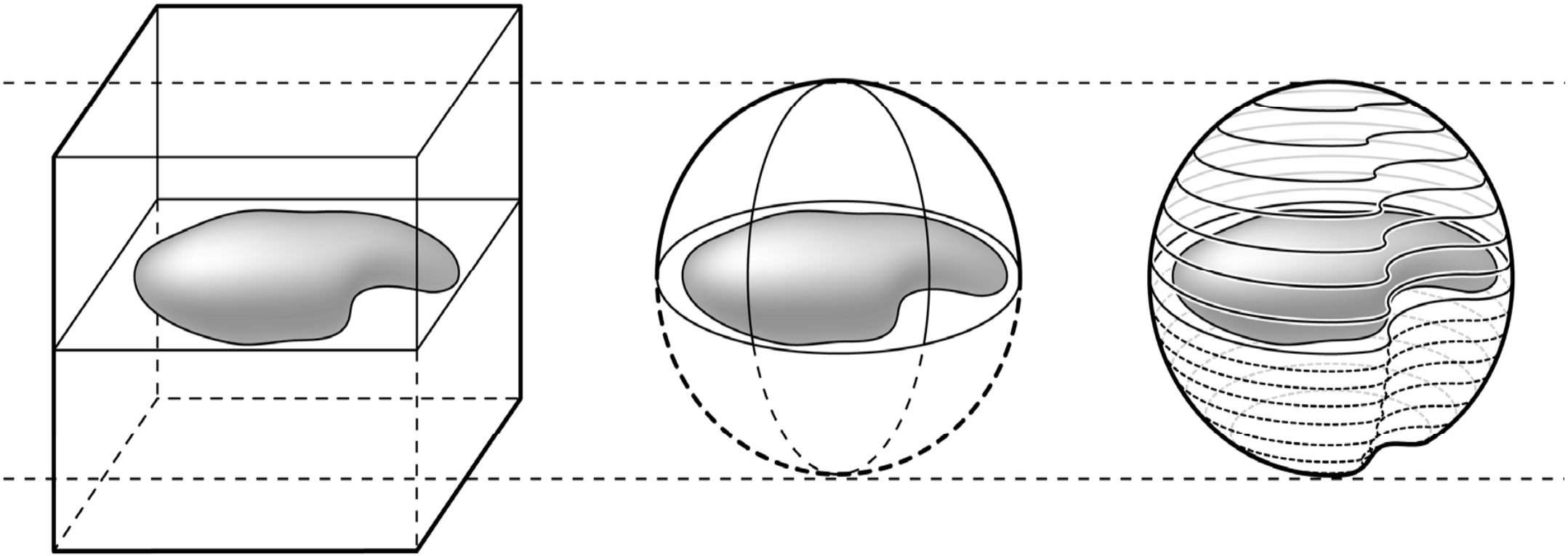
Treatment volumes compared



Conventional ‘square’ plan

3D CRT plan

IMRT plan

Use the best equipment you can!

- Old equipment
- Poor maintenance
- Bad choice!

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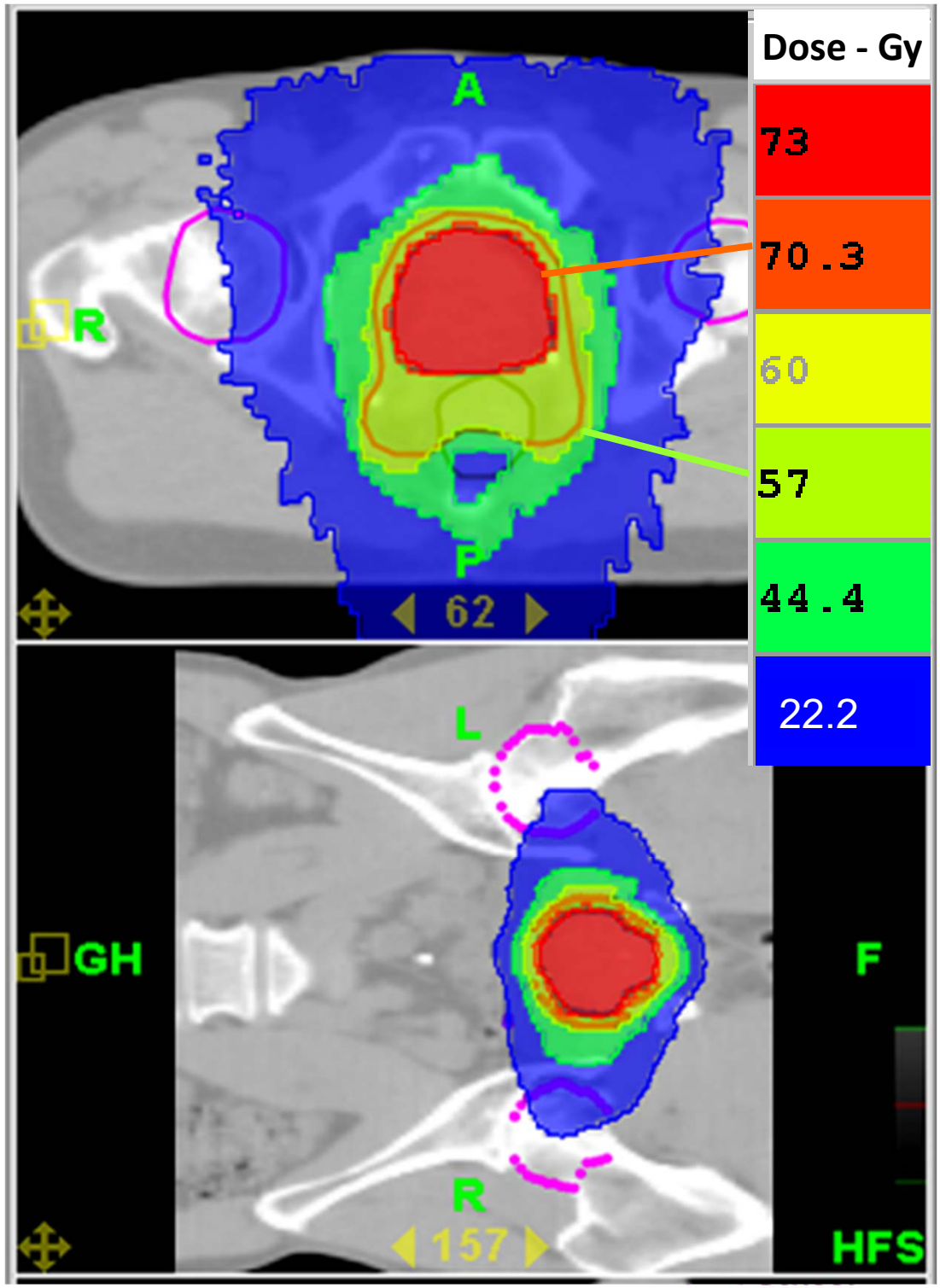
Ca prostate

- Ca prostate

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

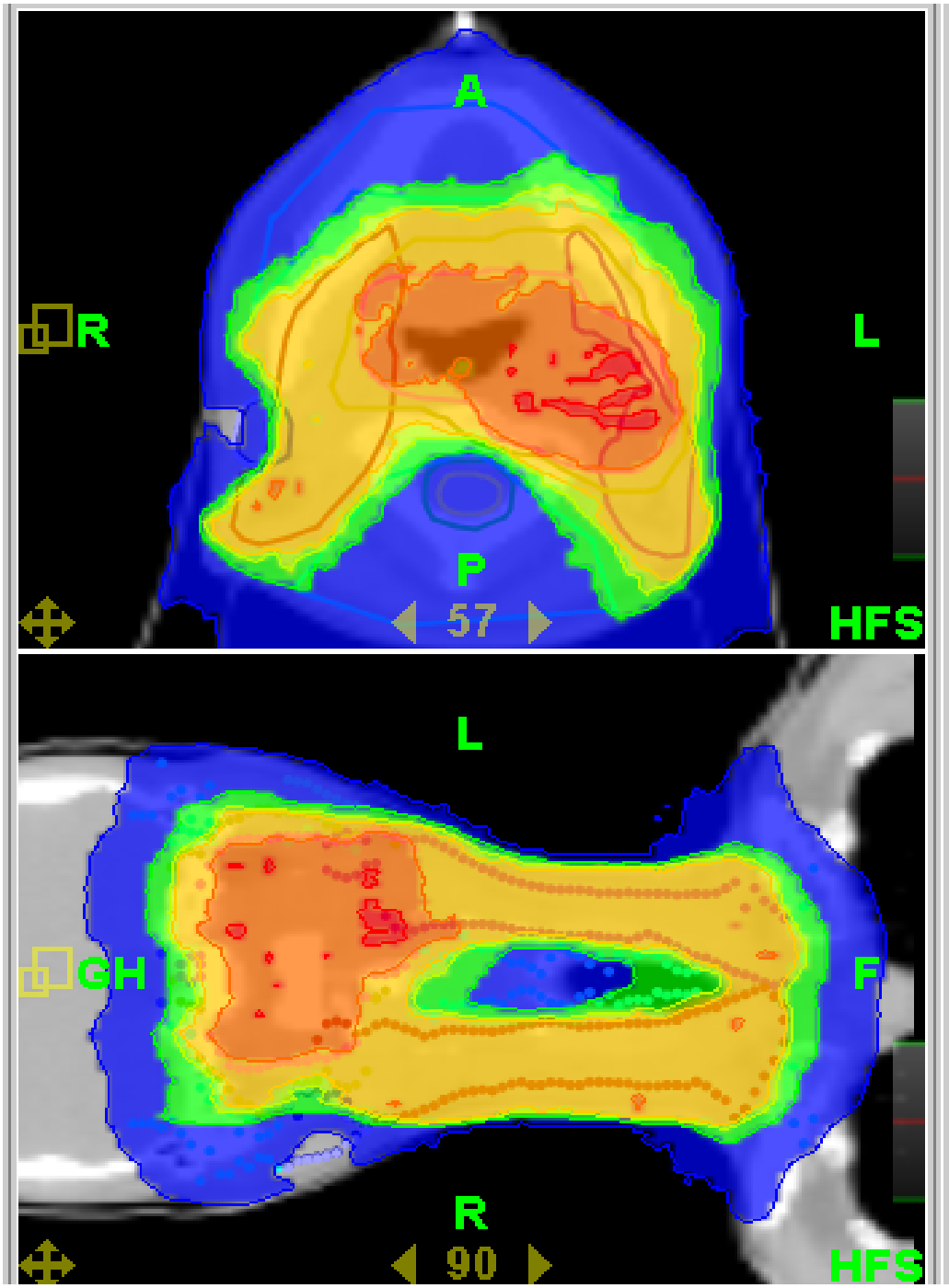
- Rectal sparing behind PTV



Ca nasopharynx

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

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



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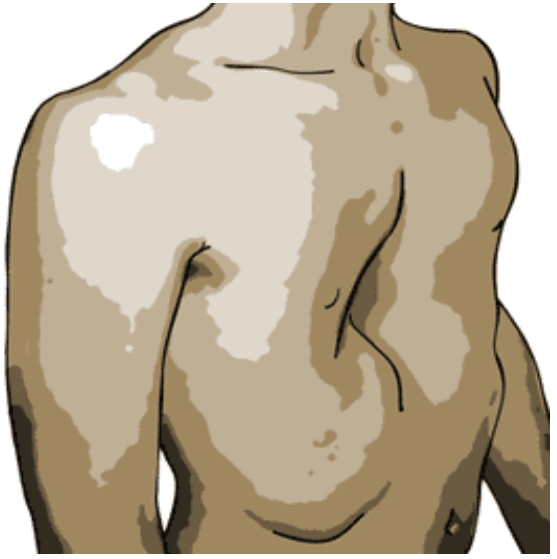
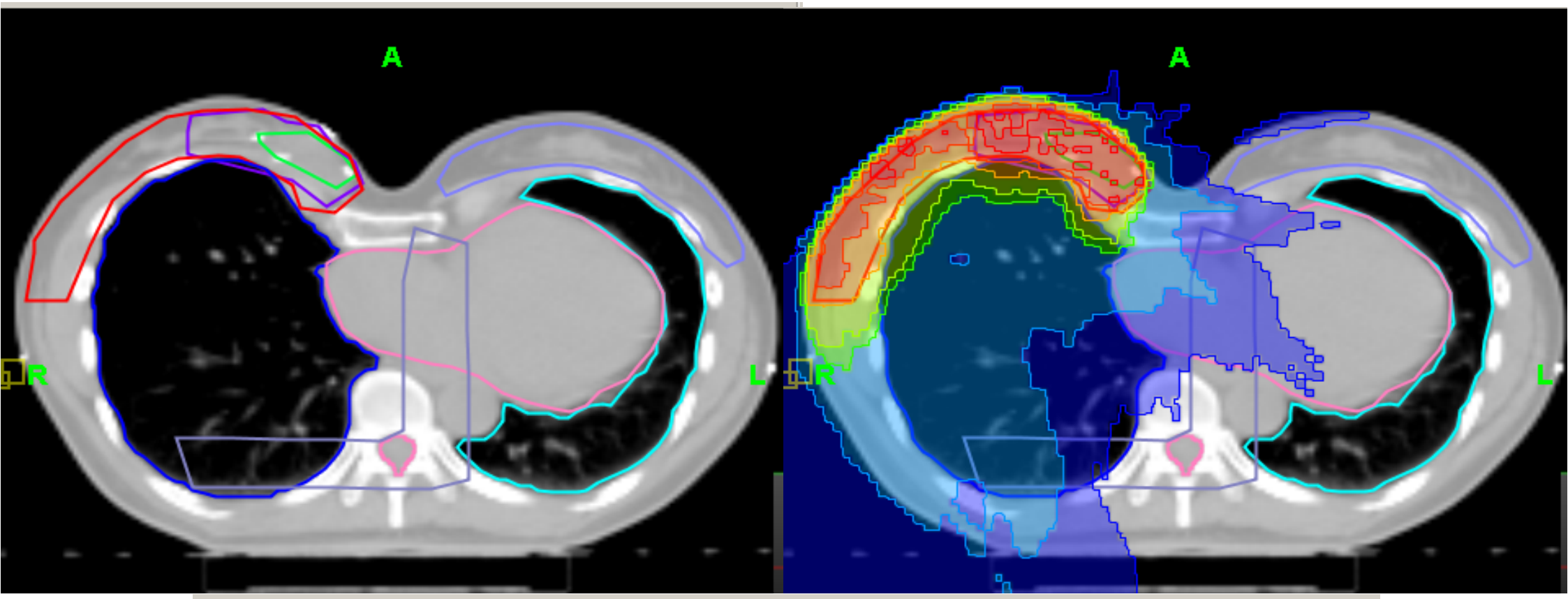
Ca breast

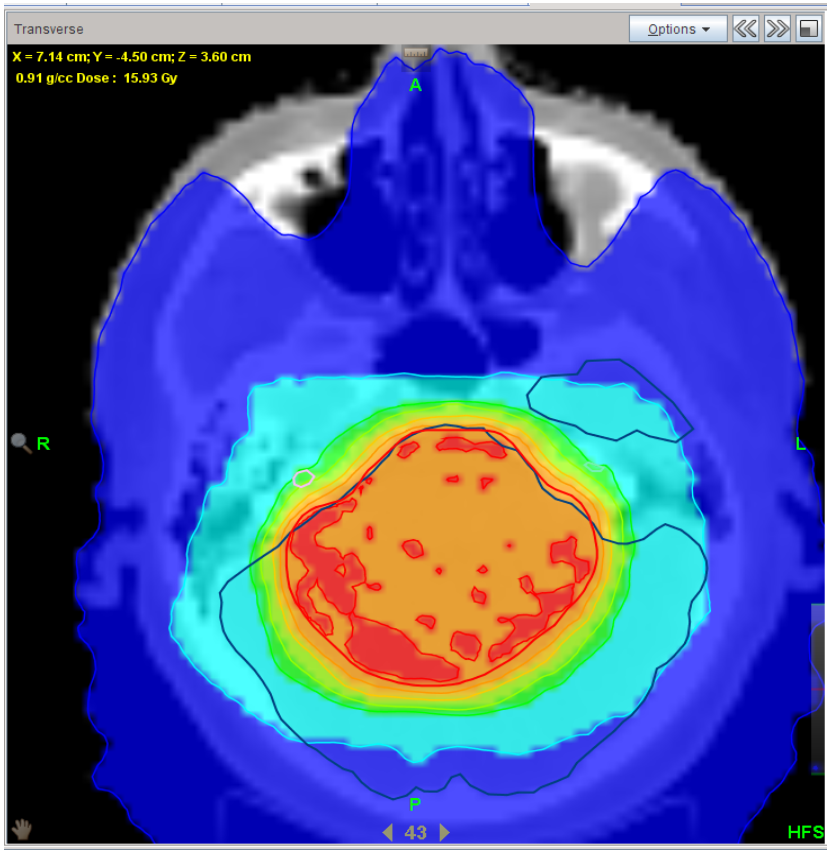
- Ca breast
- Pectus excavatum
- 40 Gy / 15 #

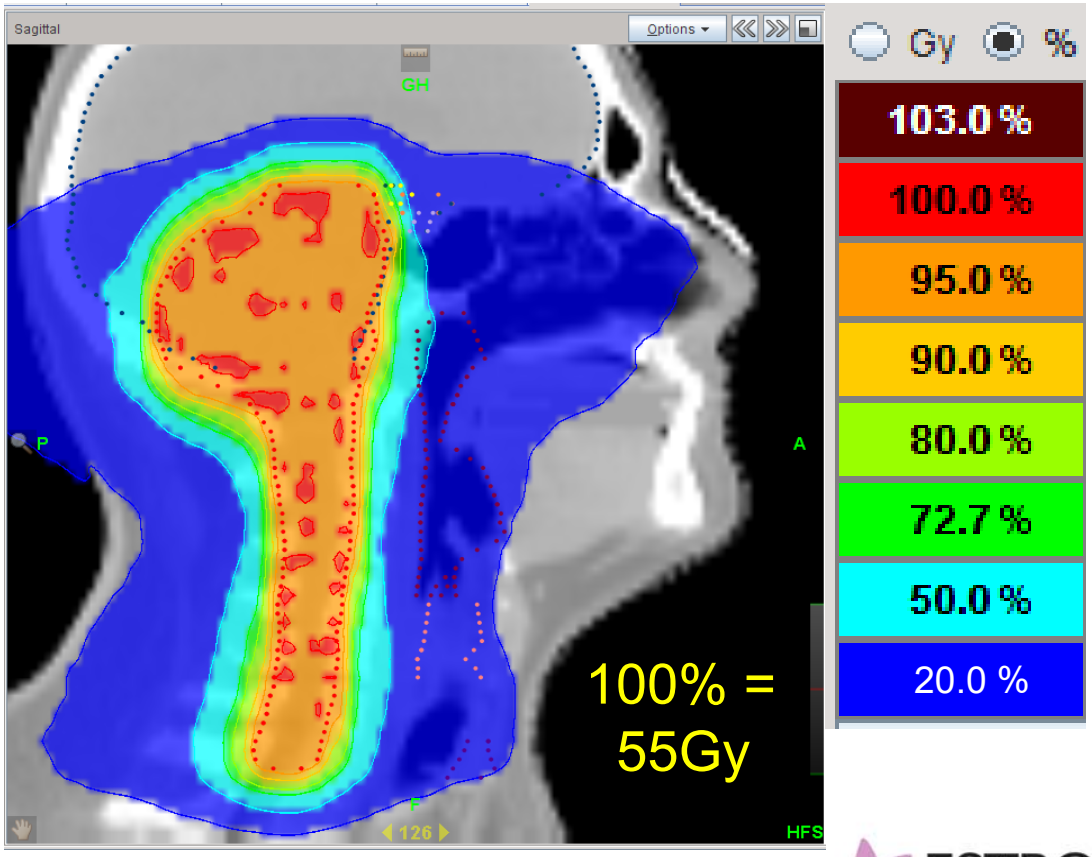




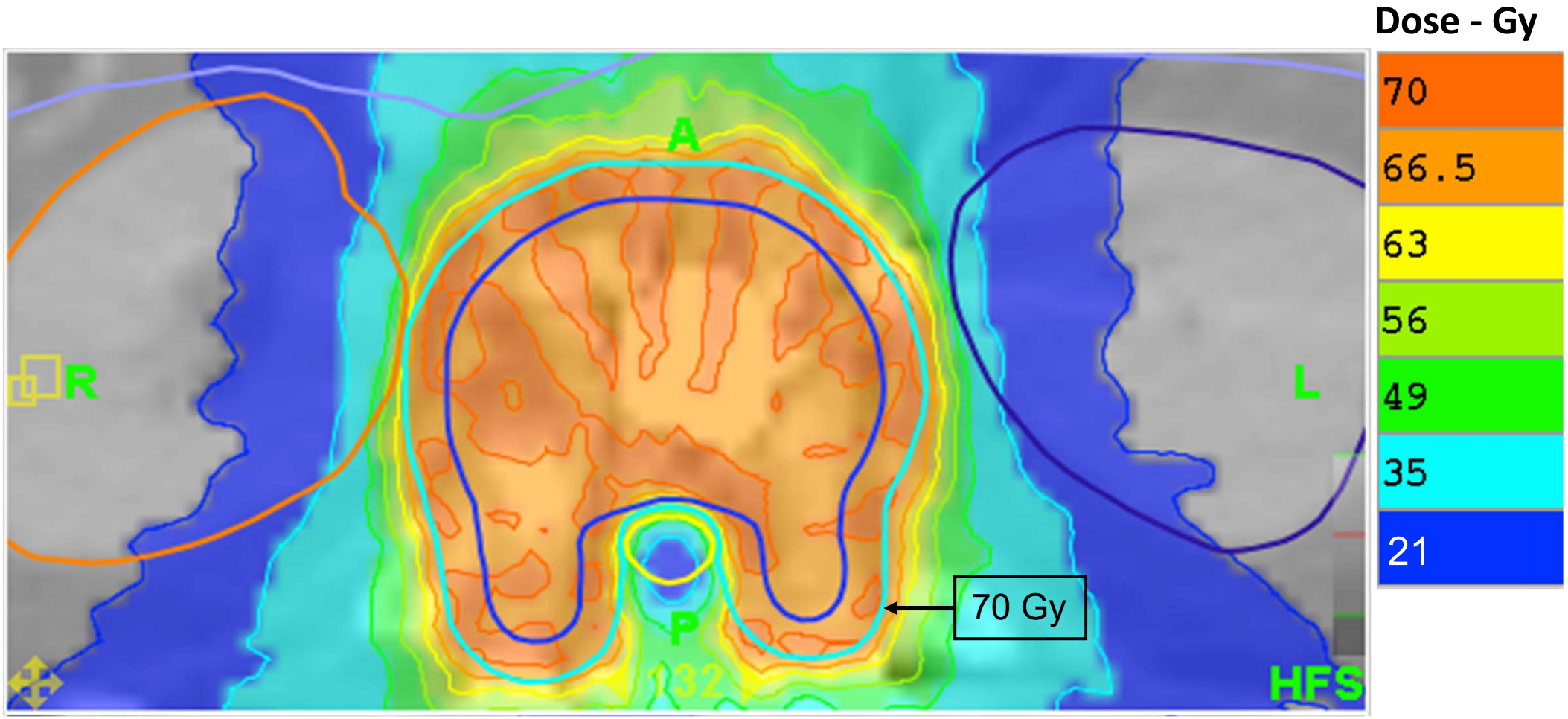
Brainstem + upper cord glioma

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





IMRT for chordoma



CTV

PTV-PRV

PRV cord

70 Gy / 39#

(+ IGRT)

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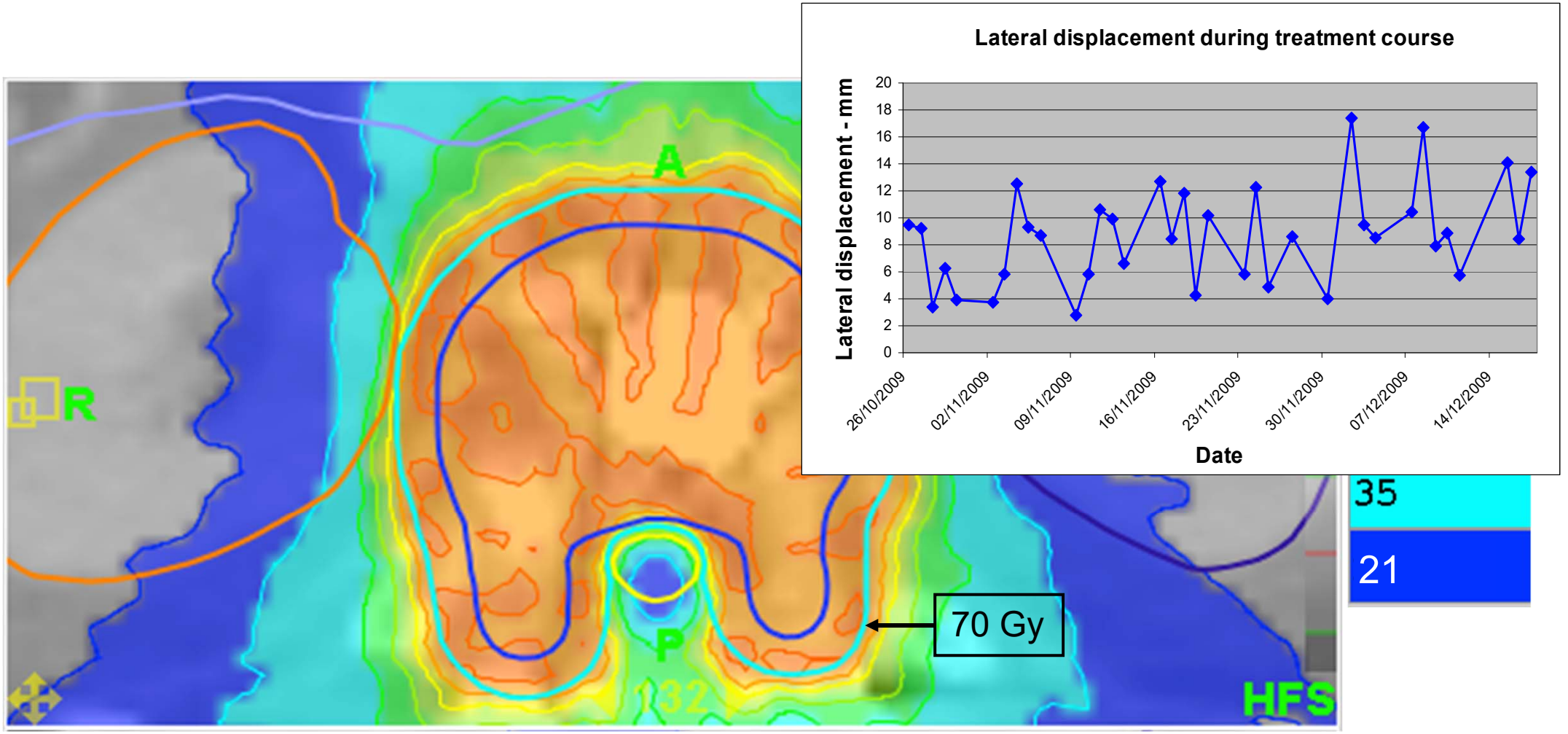
IMRT for chordoma



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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Extras

- Values of LKB parameter ‘n’
- Describes architecture
- Small value = serial
- Large value = parallel
- Spinal cord n = 0.05
- Lung n = 0.87

Table 1. Normal tissue end points and tolerance parameters

	Fit parameters				
Organ	V_{ref}	n	m	TD_{50}	End point
Bladder	Whole organ	0.5	0.11	80	Symptomatic bladder contracture and volume loss
Brachial plexus	Whole organ	0.03	0.12	75	Clinically apparent nerve damage
Brain	Whole organ	0.25	0.15	60	Necrosis/infarction
Brain stem	Whole organ	0.16	0.14	65	Necrosis/infarction
Cauda equina	Whole organ	0.03	0.12	75	Clinically apparent nerve damage
Colon	Whole organ	0.17	0.11	55	Obstruction/perforation/ulceration/fistula
Ear (middle/ external	Whole organ	0.01	0.15	40	Acute serous otitis
Ear (middle/ external	Whole organ	0.01	0.095	65	Chronic serous otitis
Esophagus	Whole organ	0.06	0.11	68	Clinical stricture/perforation
Femoral head and neck	Whole organ	0.25	0.12	65	Necrosis
Heart	Whole organ	0.35	0.10	48	Pericarditis
Kidney	Whole organ	0.70	0.10	28	Clinical nephritis
Larynx	Whole organ	0.11	0.075	80	Cartilage necrosis
Larynx	Whole organ	0.08	0.17	70	Laryngeal edema
Lens	Whole organ	0.30	0.27	18	Cataract requiring intervention
Liver	Whole organ	0.32	0.15	40	Liver failure
Lung	Whole organ	0.87	0.18	24.5	Pneumonitis
Optic nerve	Whole organ	0.25	0.14	65	Blindness
Optic chiasma	Whole organ	0.25	0.14	65	Blindness
Parotid	Whole organ	0.70	0.18	46	Xerostomia
Rectum	Whole organ	0.12	0.15	80	Severe proctitis/necrosis /stenosis/fistula
Retina	Whole organ	0.20	0.19	65	Blindness
Rib cage	Whole organ	0.10	0.21	68	Pathologic fracture
Skin	100 cm^2	0.10	0.12	70.0	Necrosis/ulceration
Small intestine	Whole organ	0.15	0.16	55	Obstruction/perforation
Spinal cord	20 cm	0.05	0.175	66.5	Myelitis/necrosis
Stomach	Whole organ	0.15	0.14	65	Ulceration/perforation
Thyroid	Whole organ	0.22	0.26	80	Clinical thyroiditis
TM joint and mandible	Whole organ	0.07	0.10	72	Marked limitation of joint function

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Dose calculation algorithms & their differrences in clinical impact

Advanced Treatment Planning Course
3-7 September 2017 – Barcelona, Spain

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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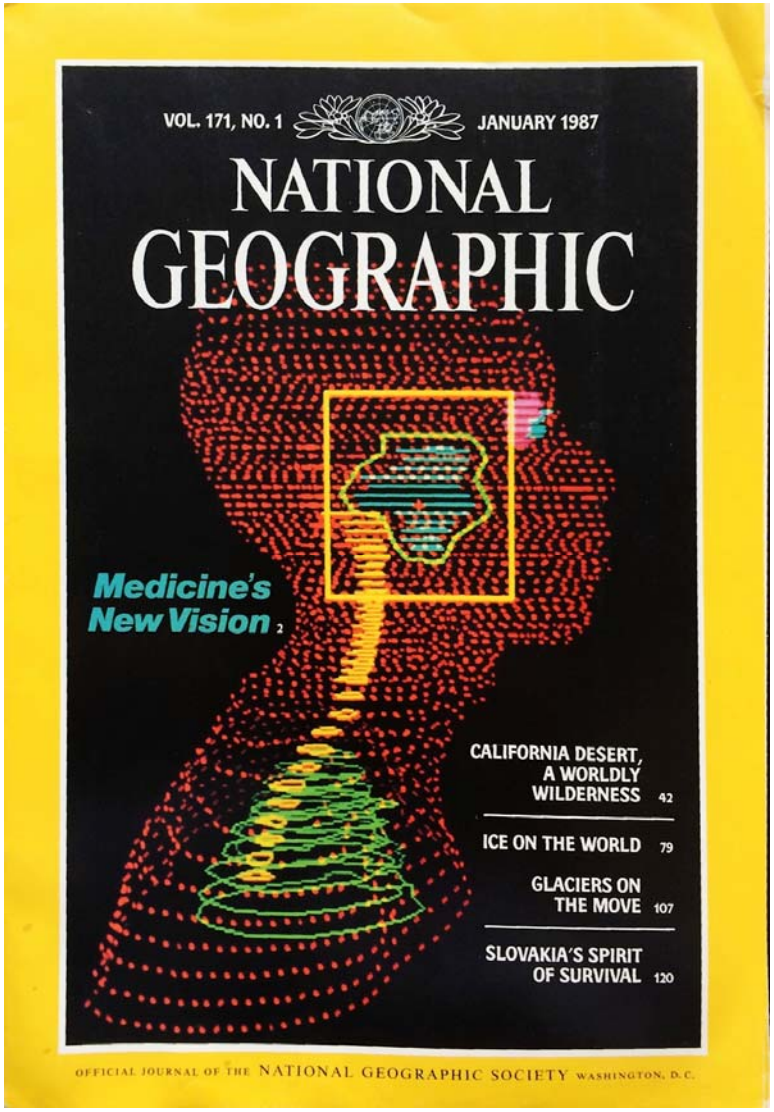
Computer-Aided Treatment Planning

- 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.



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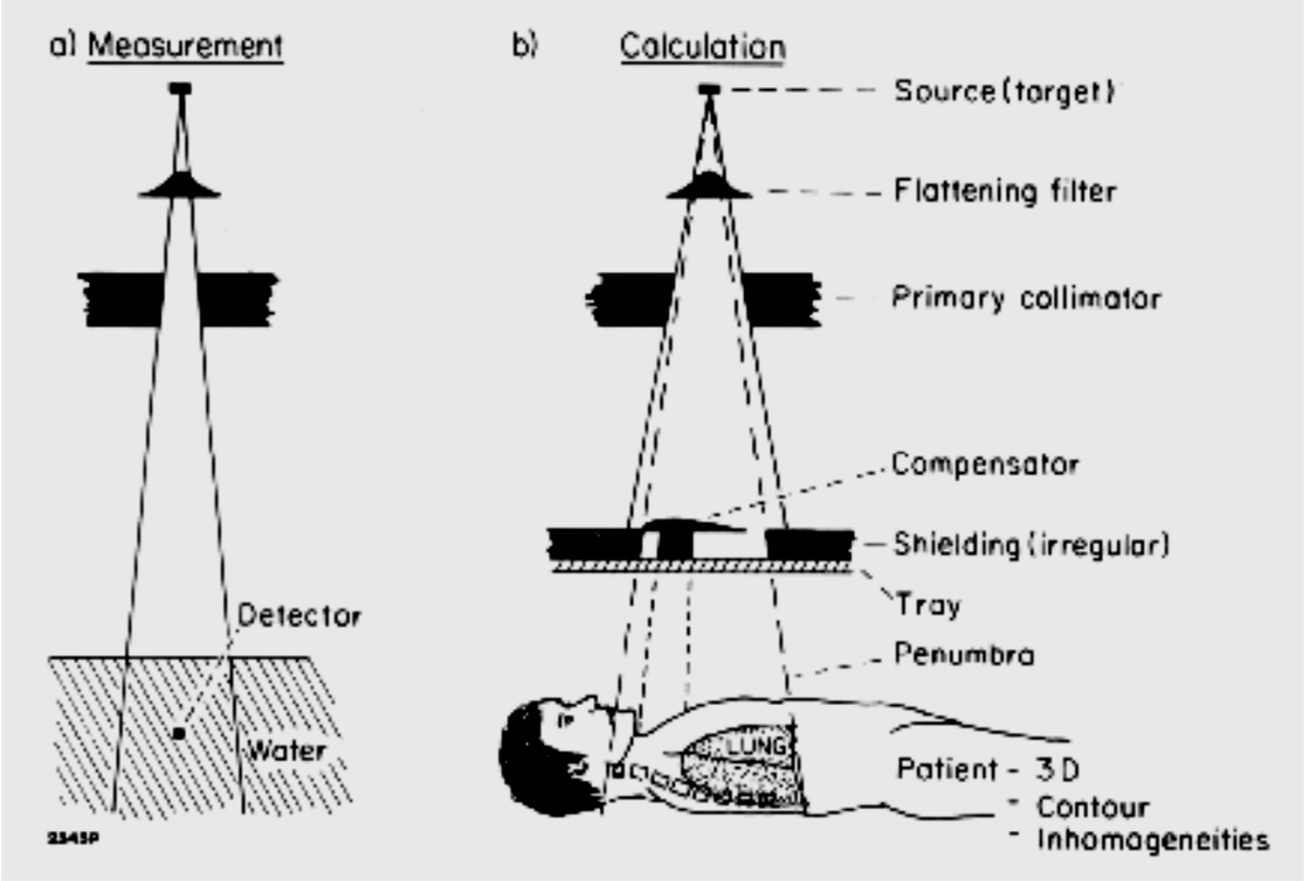
Dose Calculation Problem

Relate dose calculation in patient to beam calibration conditions



Papanikolaou, et al- 2004 - AAPM Task Group 65

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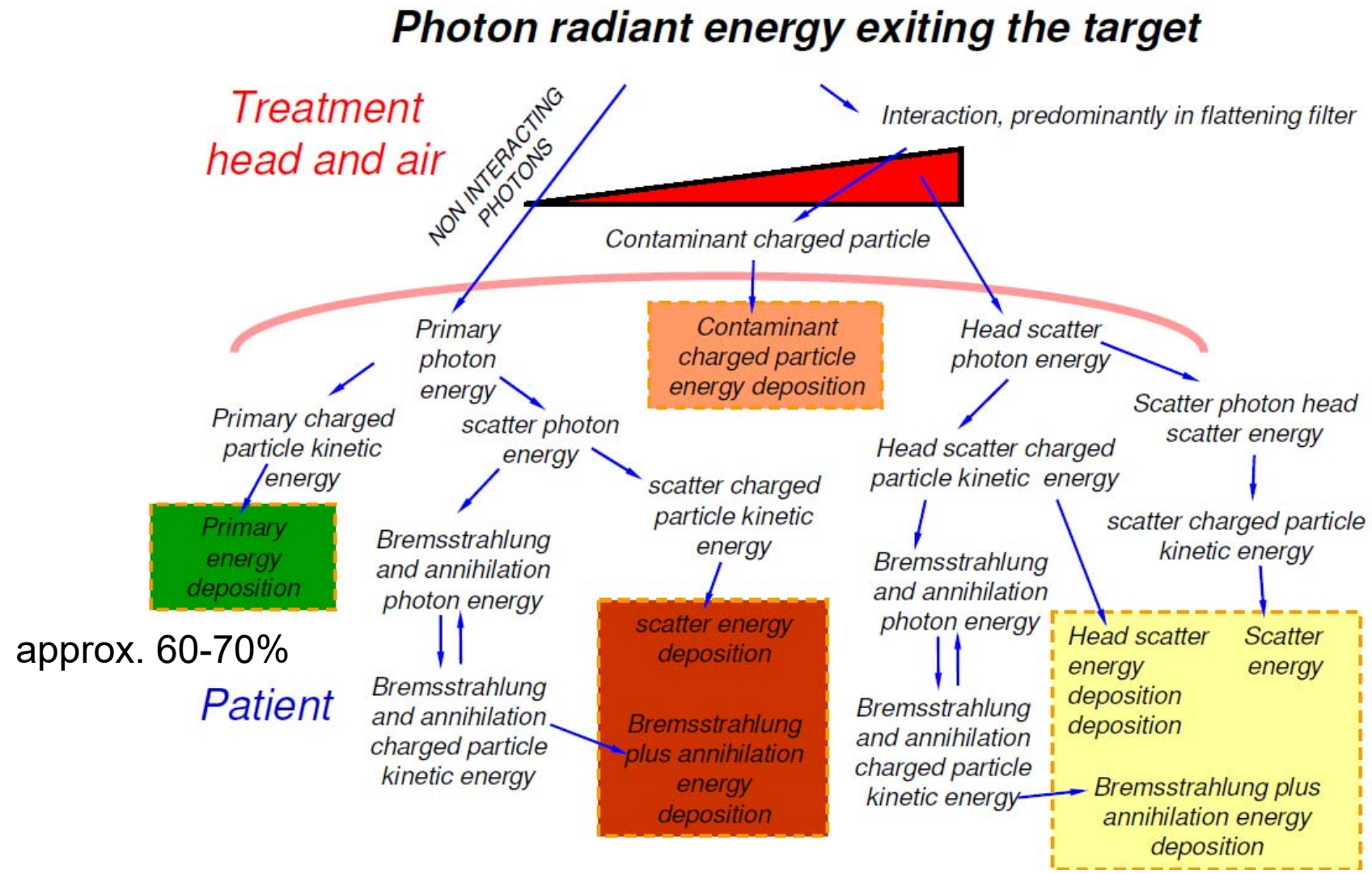
Complexity of dose calculation



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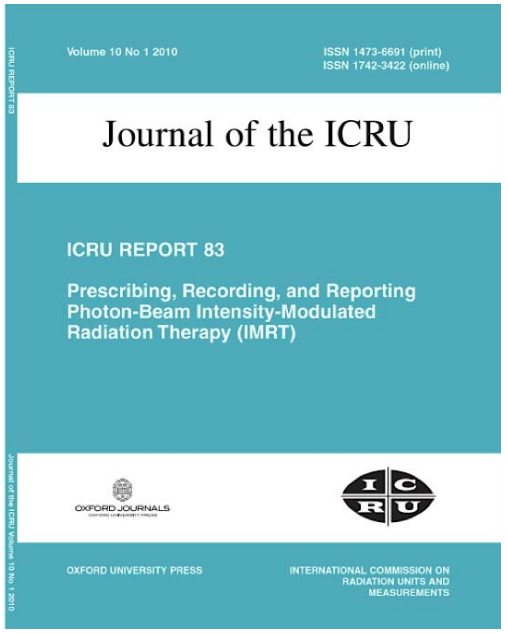
Expectations

- *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

Reconstitute distribution in water by distance, depth, & field size

Apply correction factors (inhomogeneity, contour)

Model & fit parameters to emulate measurements

Compute dose directly from beam geometry & CT images

"Correction" based methods

"Model" based methods

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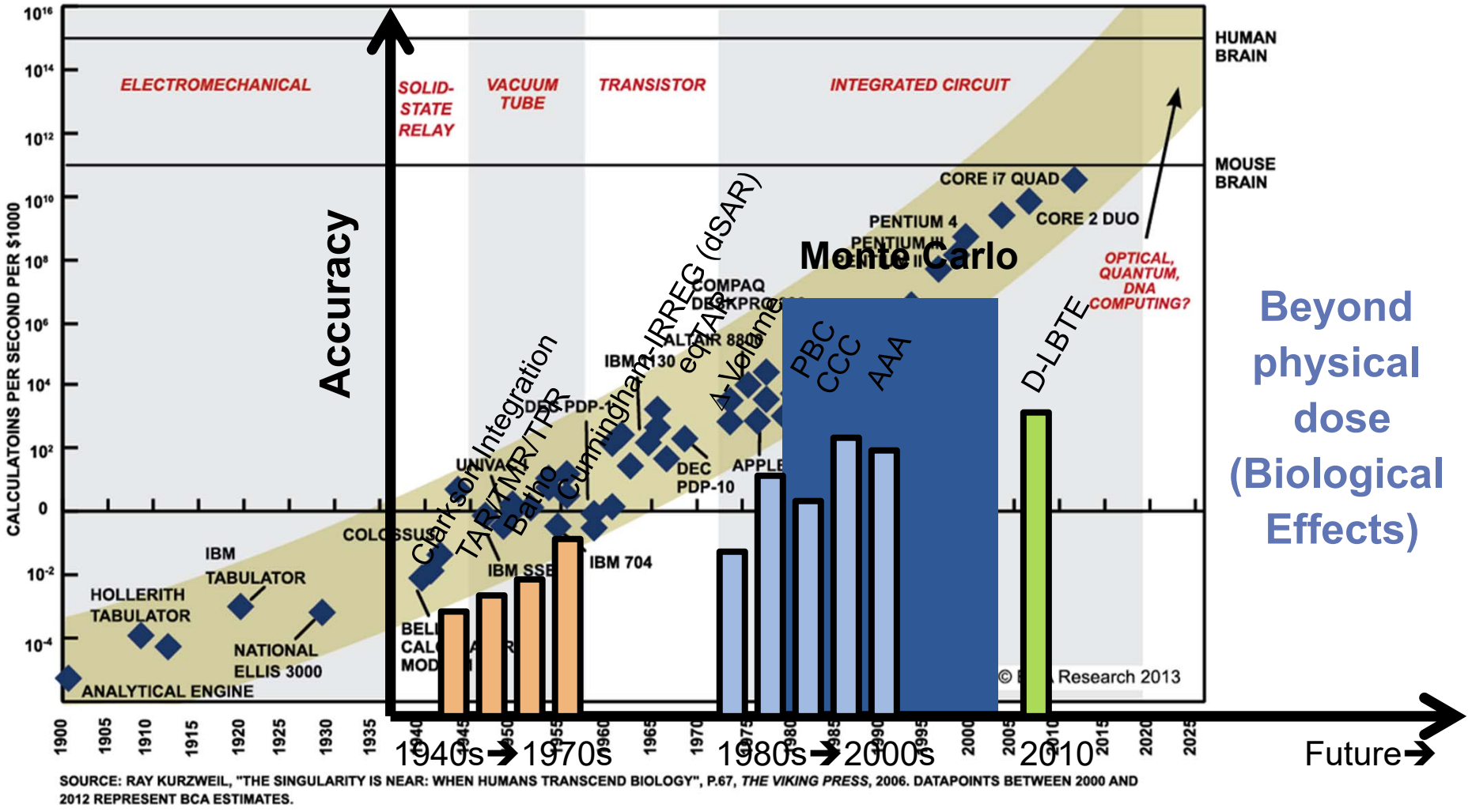
Evolution of Photon Beam Dose Algorithms

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



SOURCE: RAY KURZWEIL, "THE SINGULARITY IS NEAR: WHEN HUMANS TRANSCEND BIOLOGY", P.67, *THE VIKING PRESS*, 2006. DATAPOINTS BETWEEN 2000 AND 2012 REPRESENT BCA ESTIMATES.

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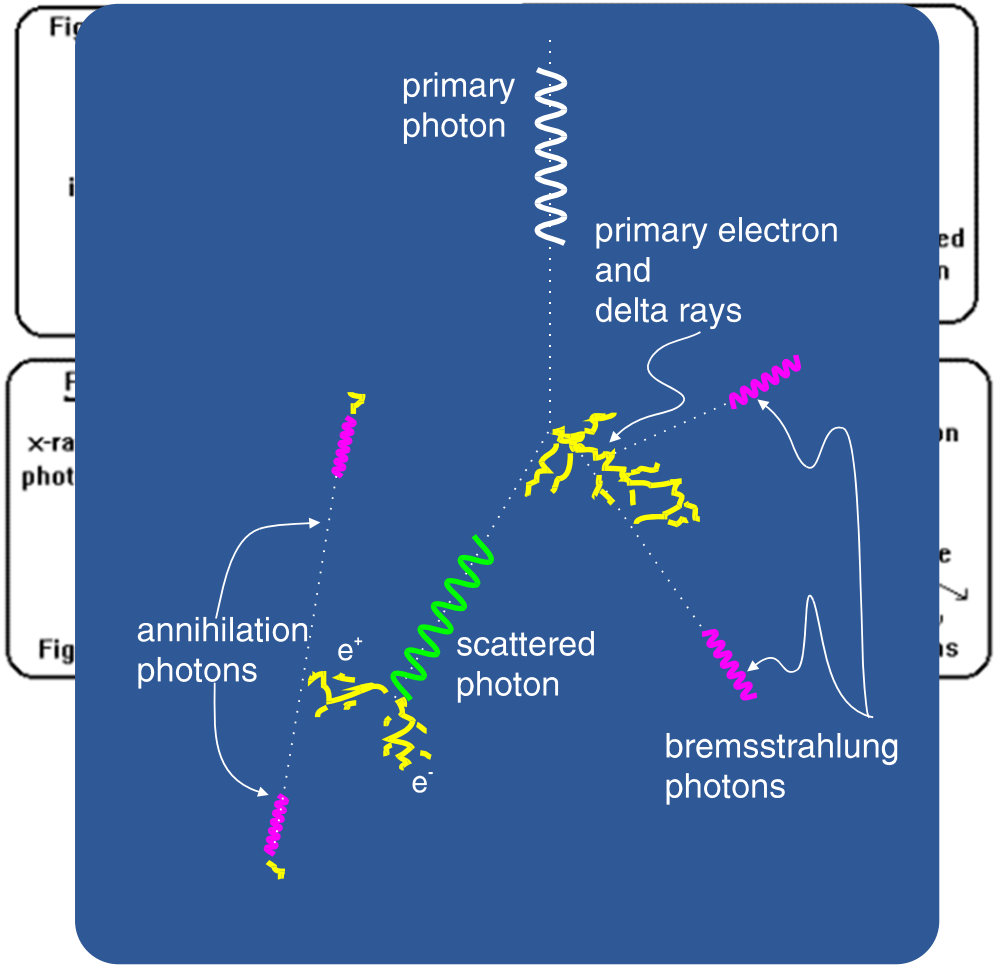
X-Rays: Energy Deposition in a Nutshell

- 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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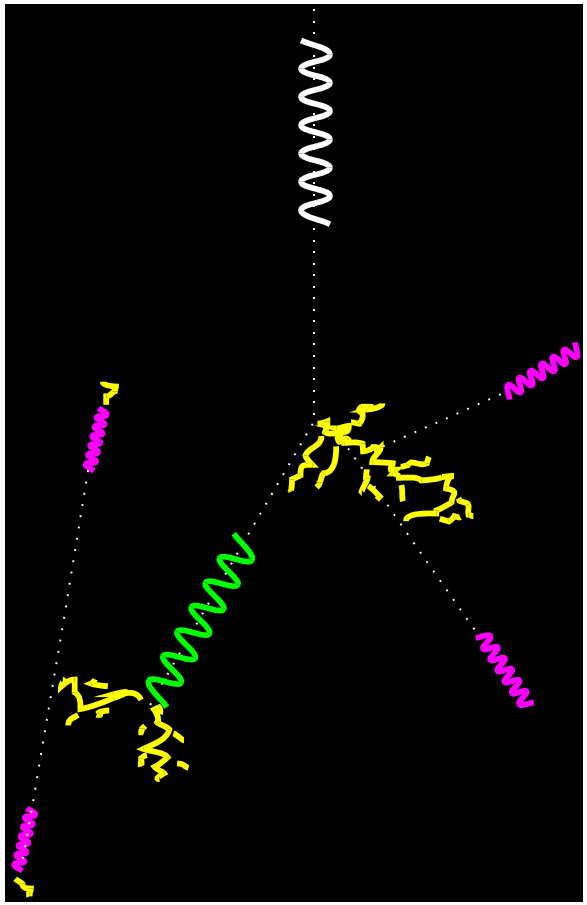
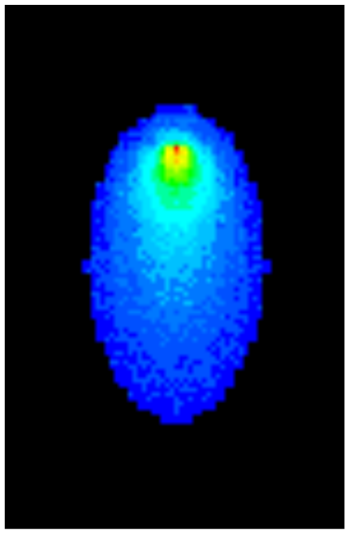
Dose Spread Kernel

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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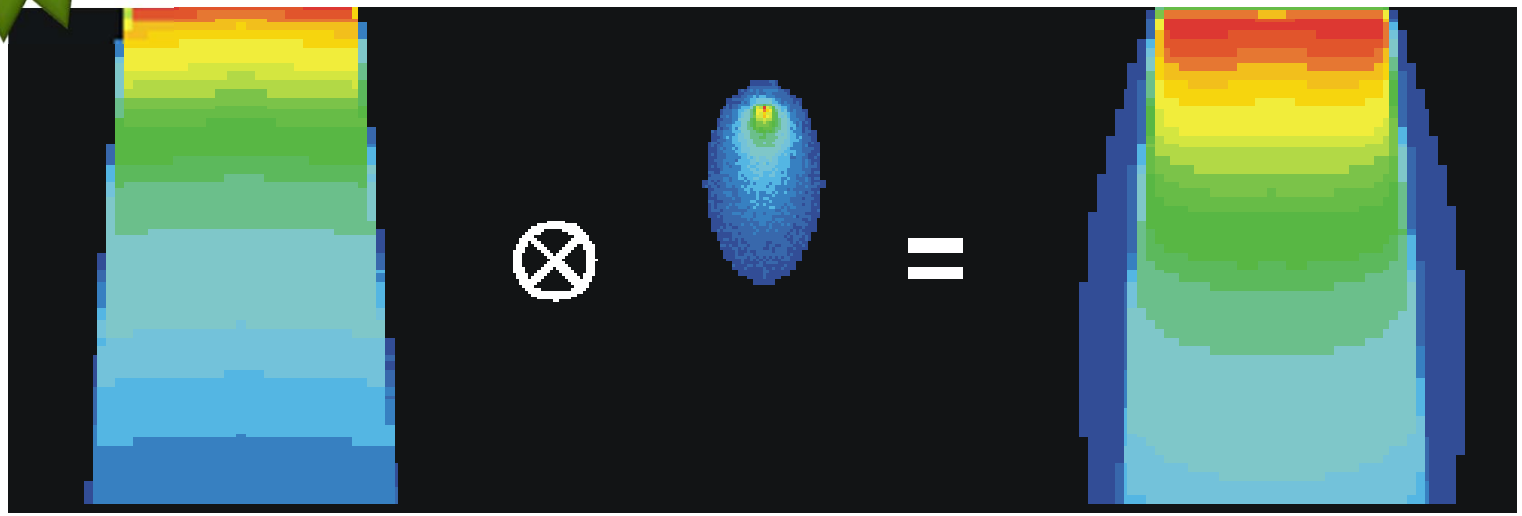
Method: Convolution/Superposition

Ideal Conditions Only

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



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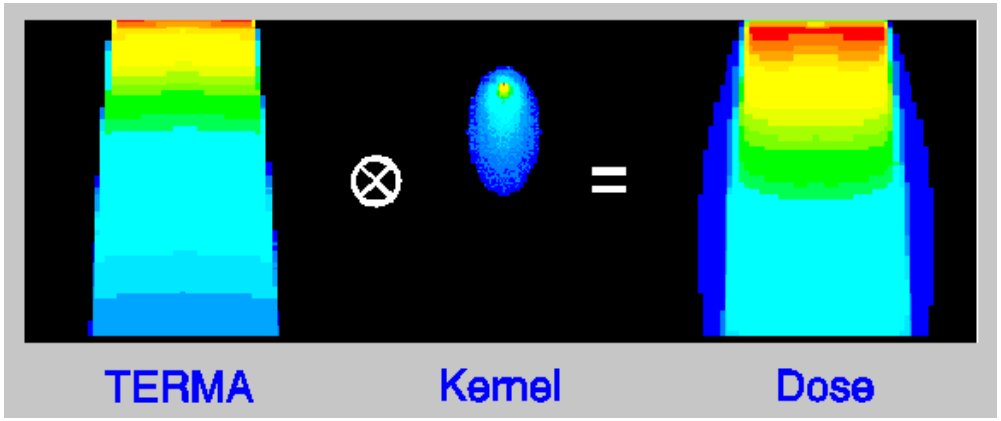
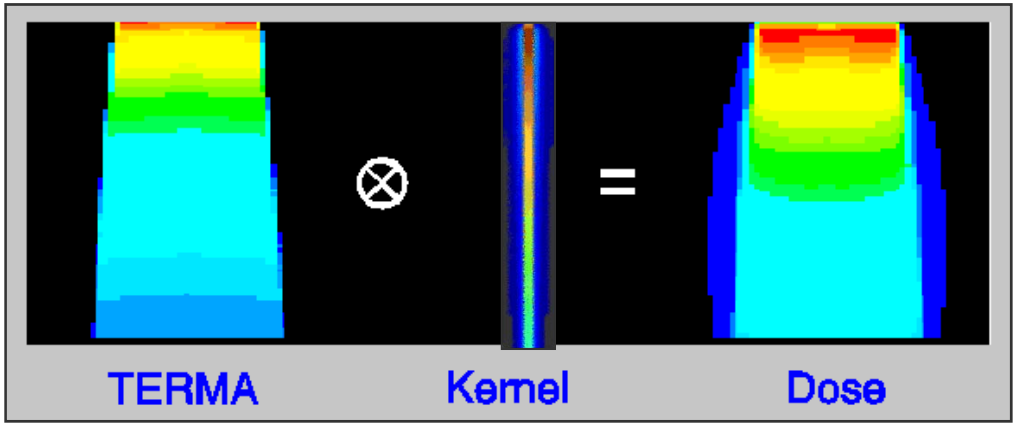
Convolution - Point Kernel

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



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



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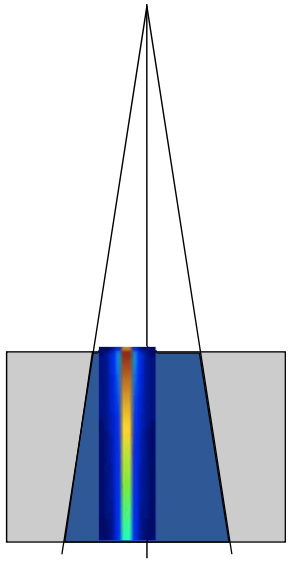
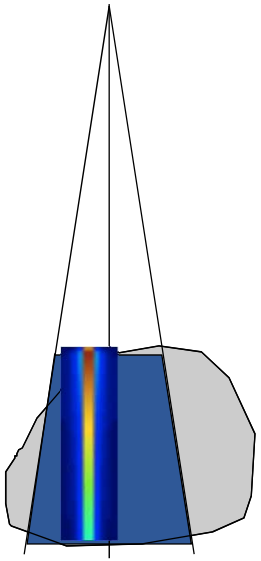
Pencil Kernel Integration

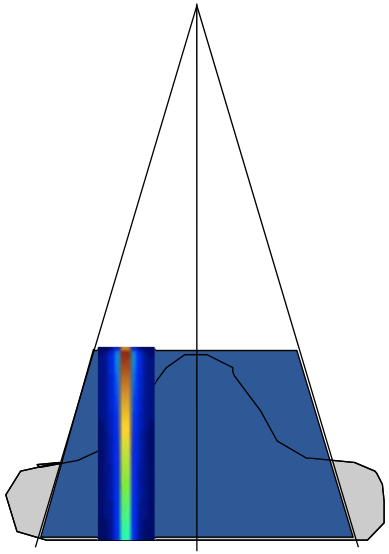
- Pencil kernel methods account for heterogeneity effects along the beam direction but not for lateral effects (penumbra broadening in lungs not modeled).



Correct



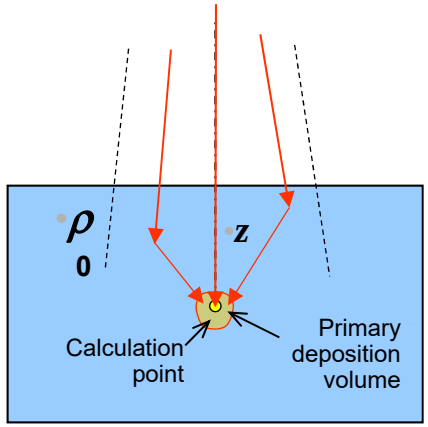
Approximately correct
(error cancels)



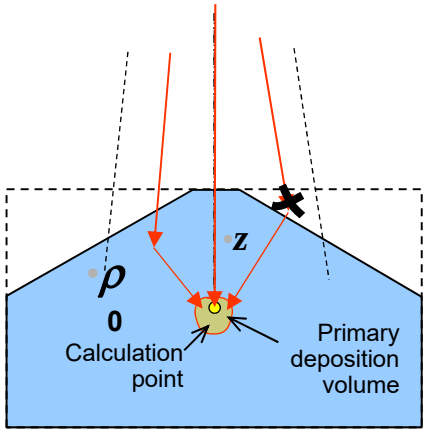
Scatter is
overestimated

Pencil beam kernel

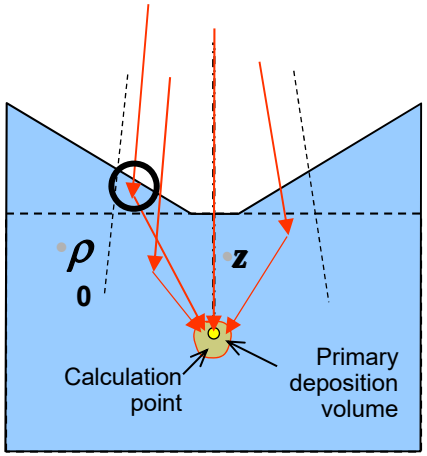
- Calculation object approximations



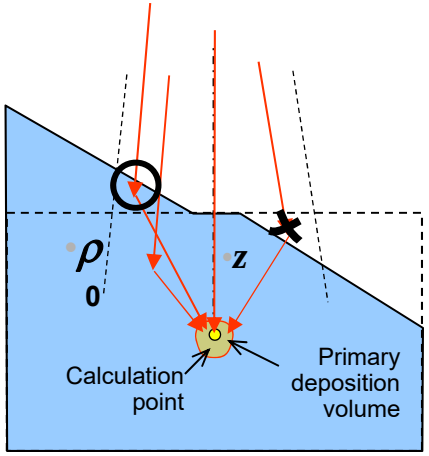
The depth (z) is generally assumed to be constant within the lateral integration plane during calculation of the scatter dose to a point.



Scatter overestimated



Scatter underestimated



Errors cancel (roughly)

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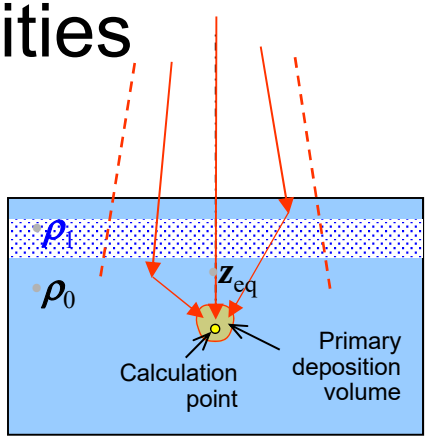
Pencil beam kernel

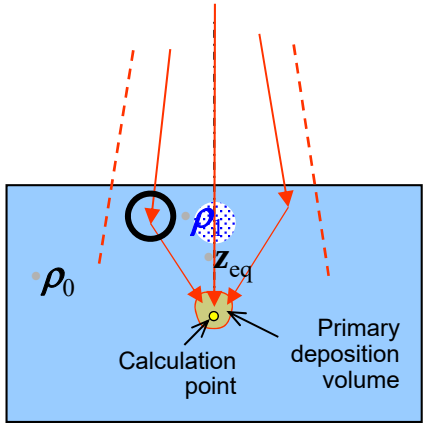
- Calculation object approximations with heterogeneities



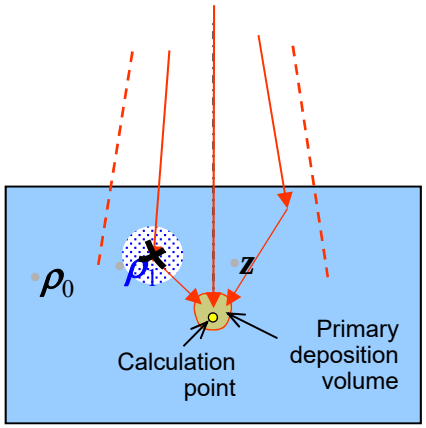
Heterogeneous slab phantom

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

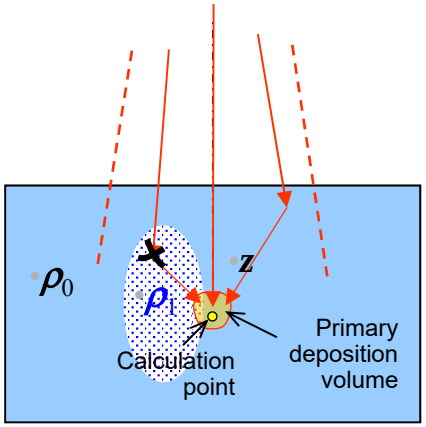
- Effects of heterogeneities are generally modelled in pencil kernel algorithms through depth scaling along rayline (and no lateral scaling). Correct handling of heterogeneities requires proper 3D modelling of the secondary particle transport.



Scatter underestimated



Scatter overestimated



Scatter and primary overestimated

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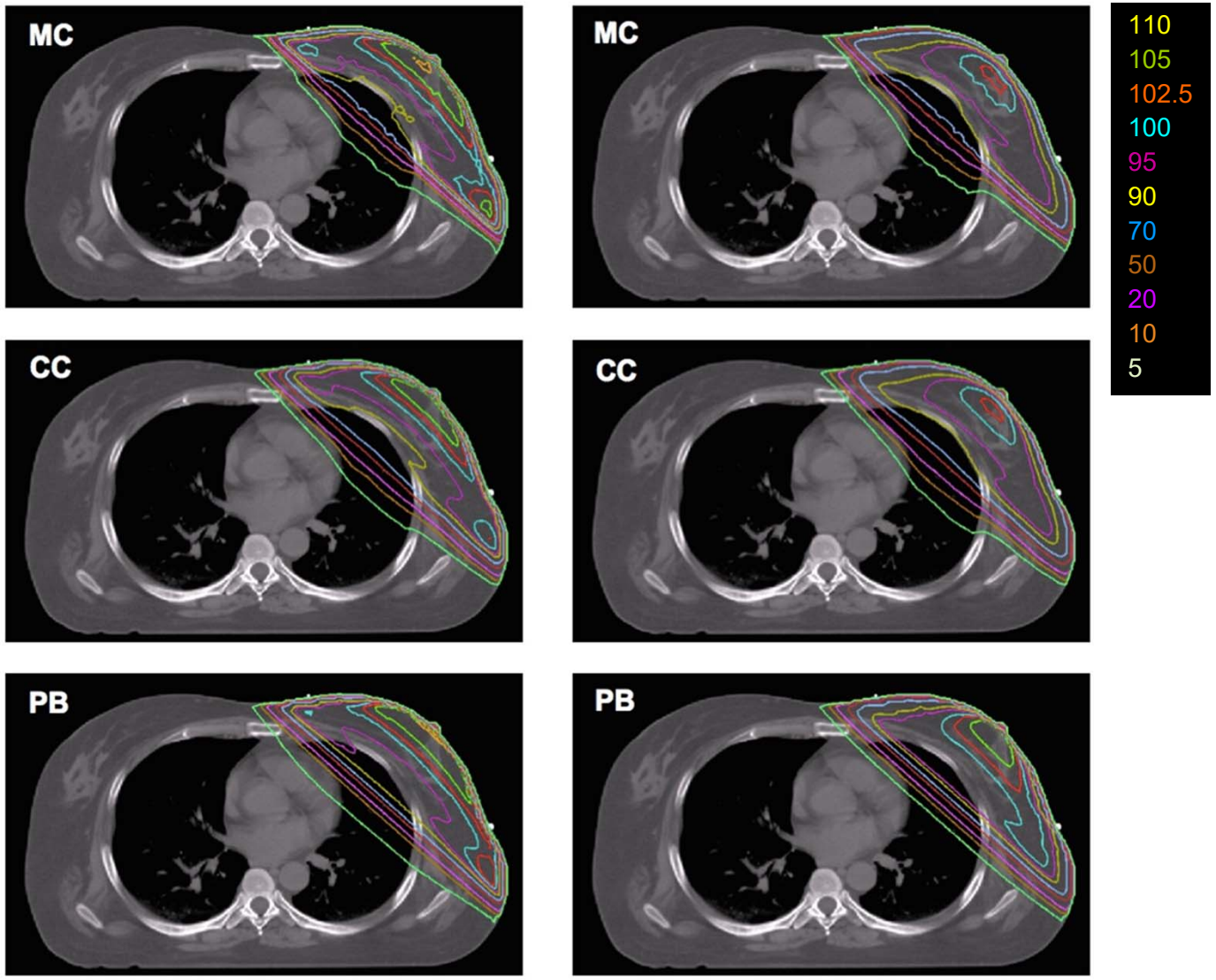
Breast Tangent Example



6 MV

18 MV

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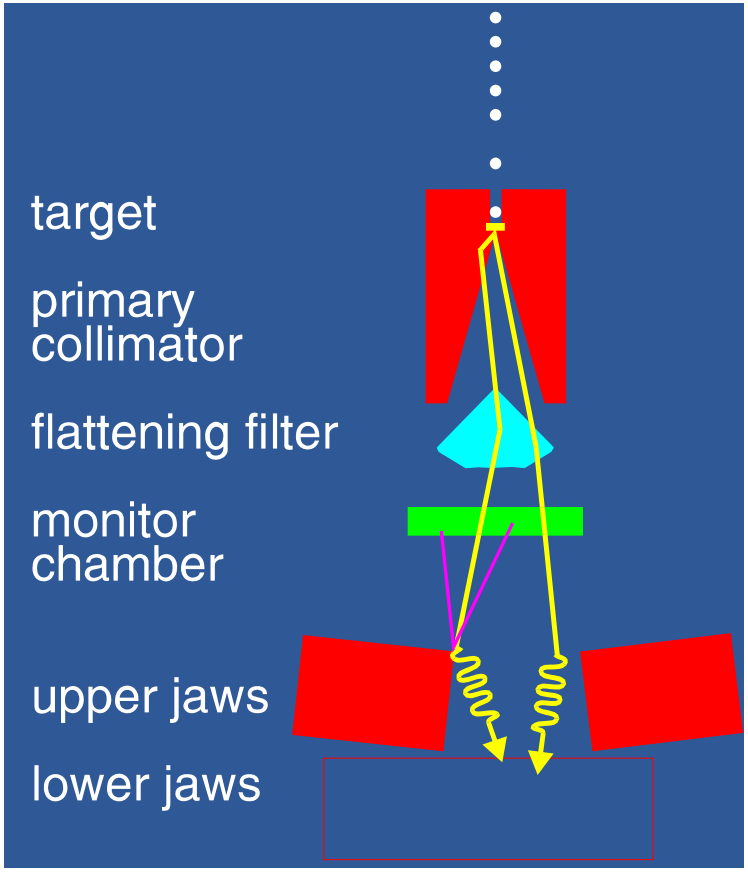
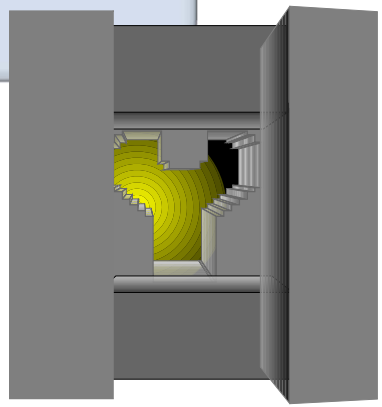
Total Energy Released per MAss (TERMA)

- 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

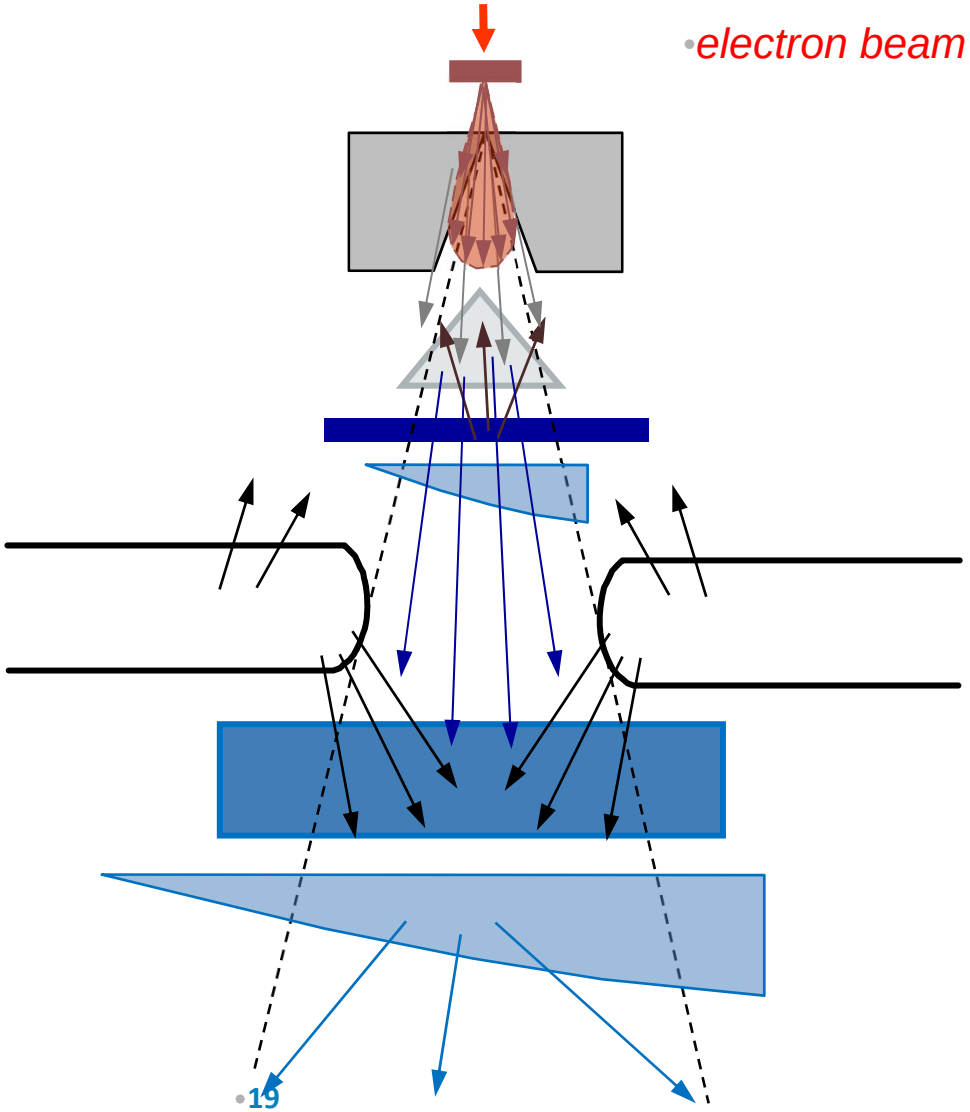
SCATTER SOURCES

- 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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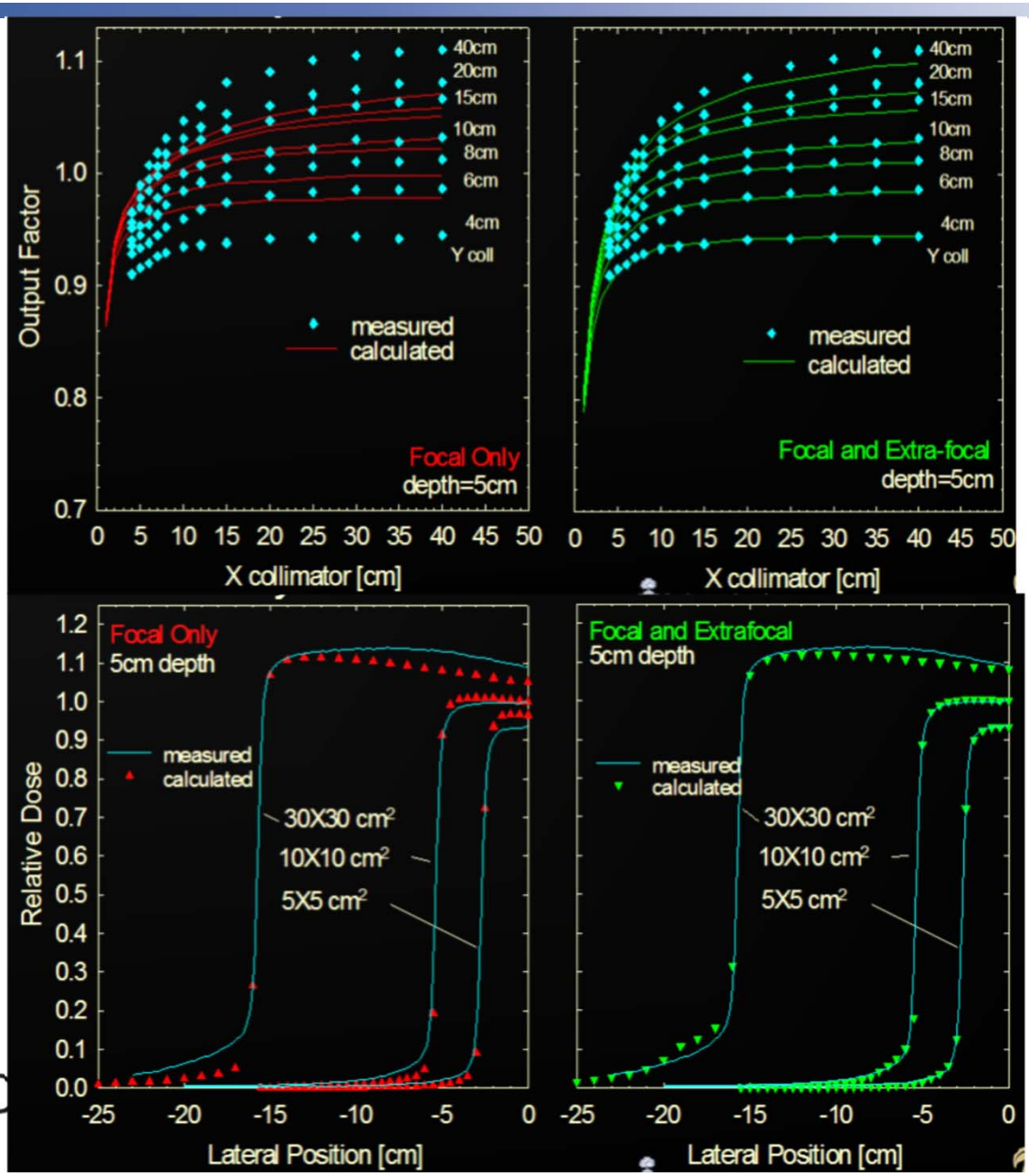
Influence of Head Scatter



Dose Rate

Dose Profile

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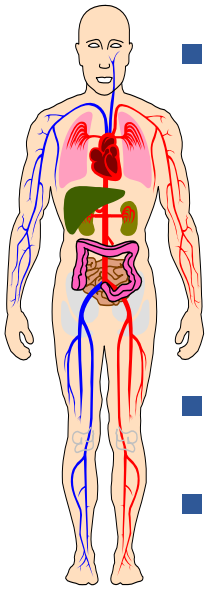
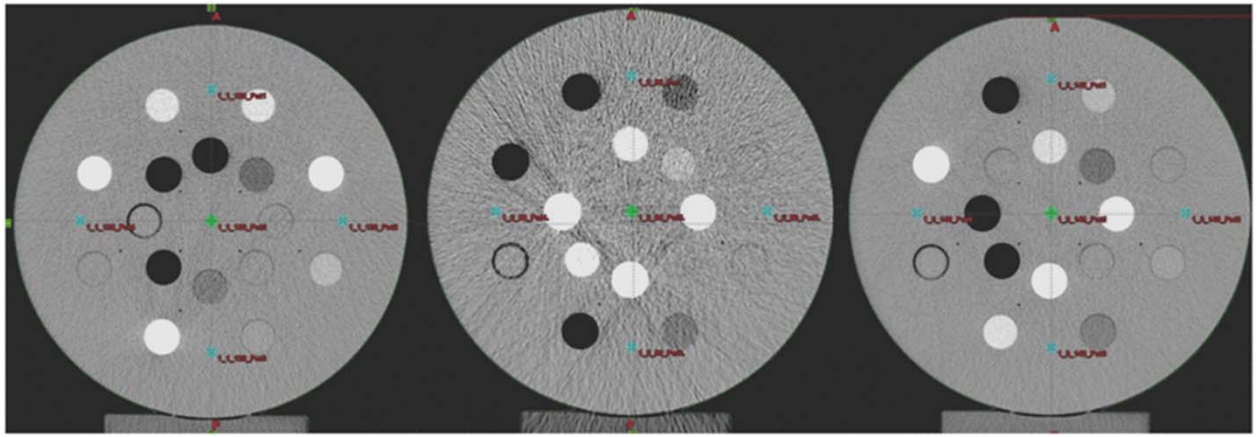
CT Data to Tissue Properties



- 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

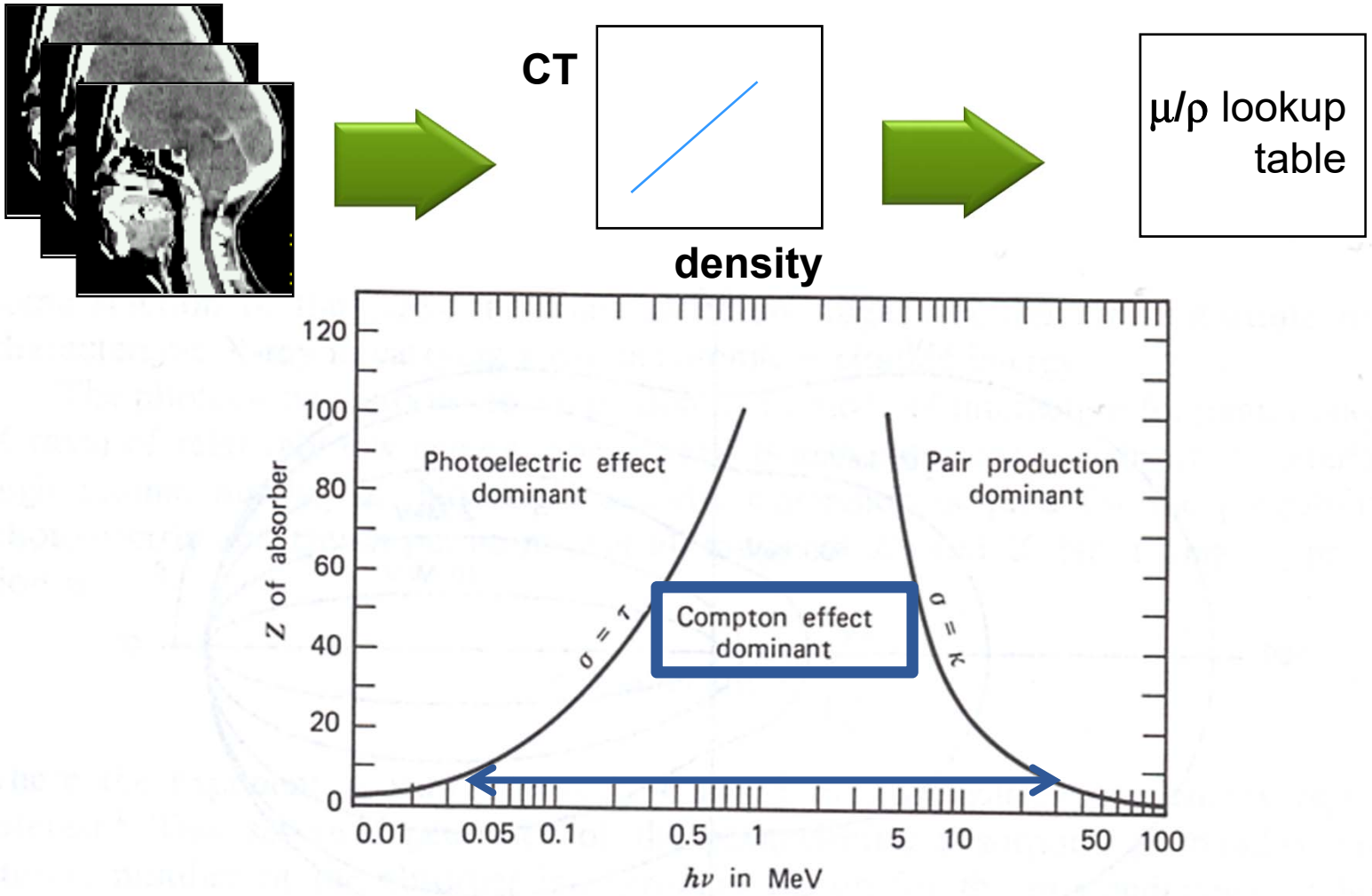
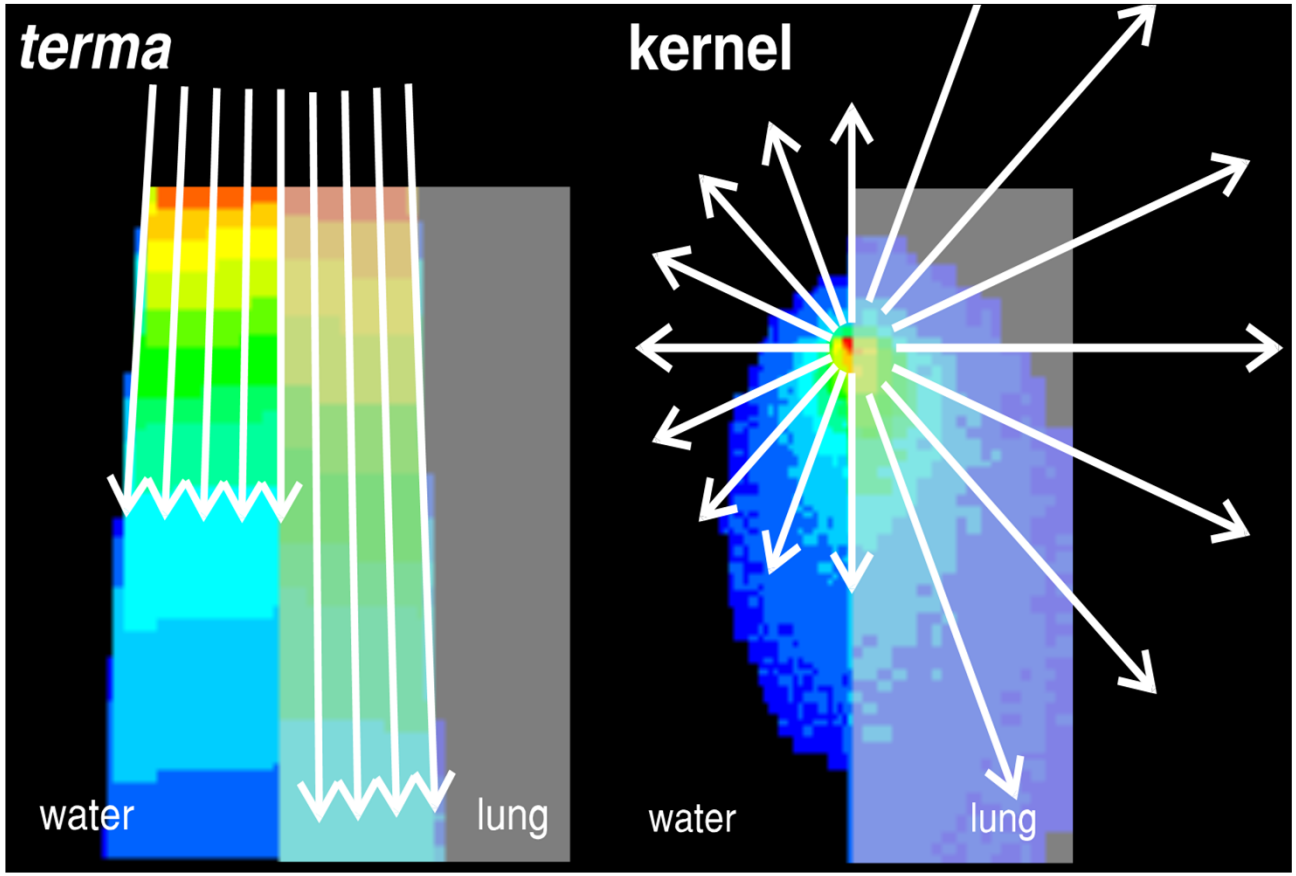


Figure 2-20 The relative importance of the three major types of gamma-ray interaction. The lines show the values of Z and $h\nu$ for which the two neighboring effects are just equal. (From *The Atomic Nucleus* by R. D. Evans. Copyright 1955 by the McGraw-Hill Book Company. Used with permission.)

Density Scaling Approximation

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



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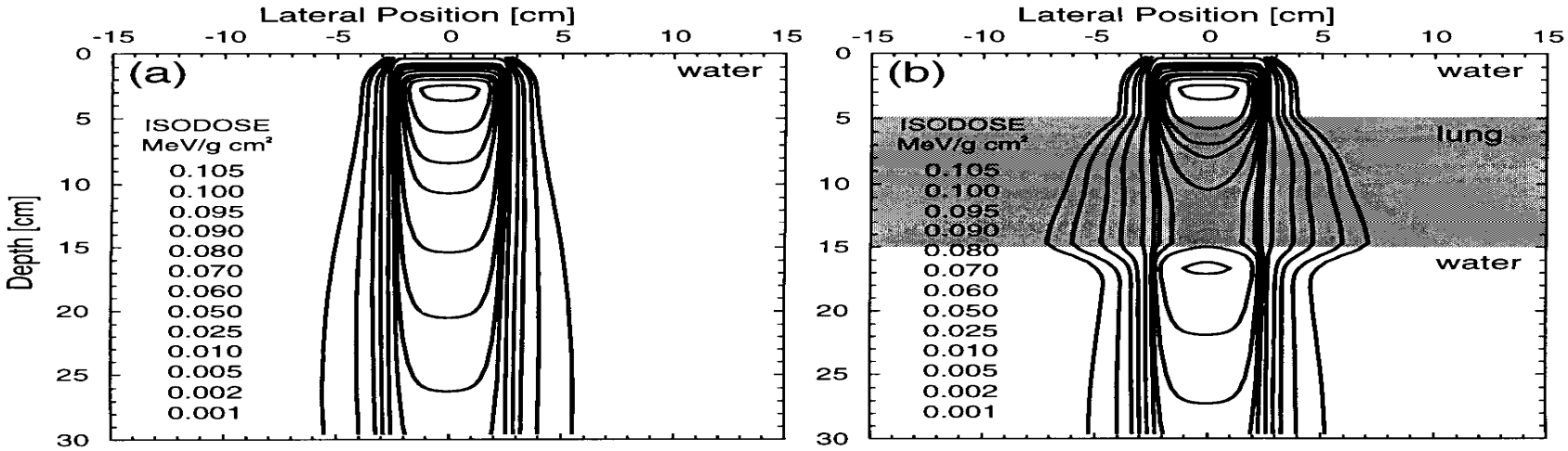
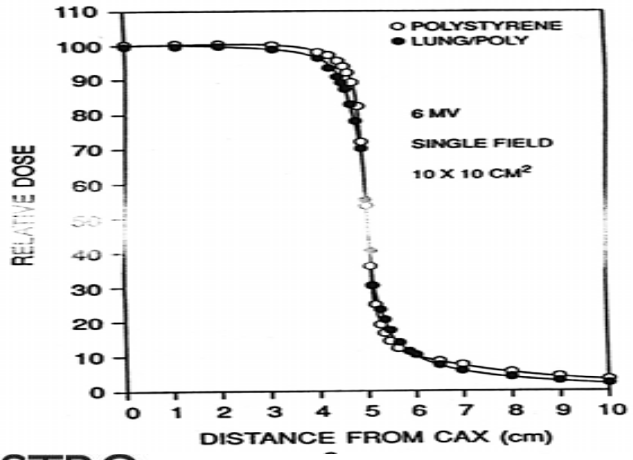
Calculated Data

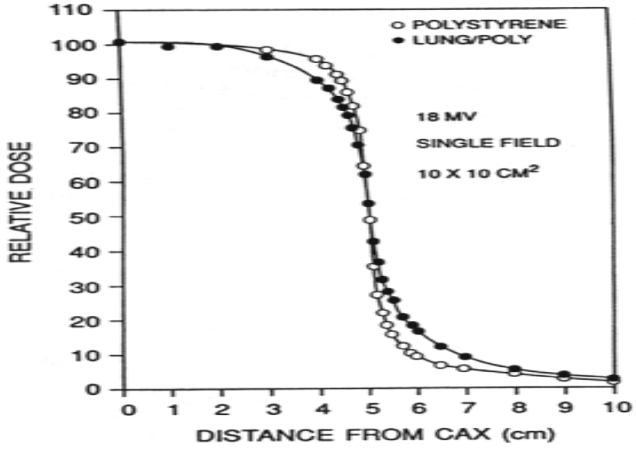
Papanikolaou et al, AAPM Report 85 (2004)



Measured Data

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





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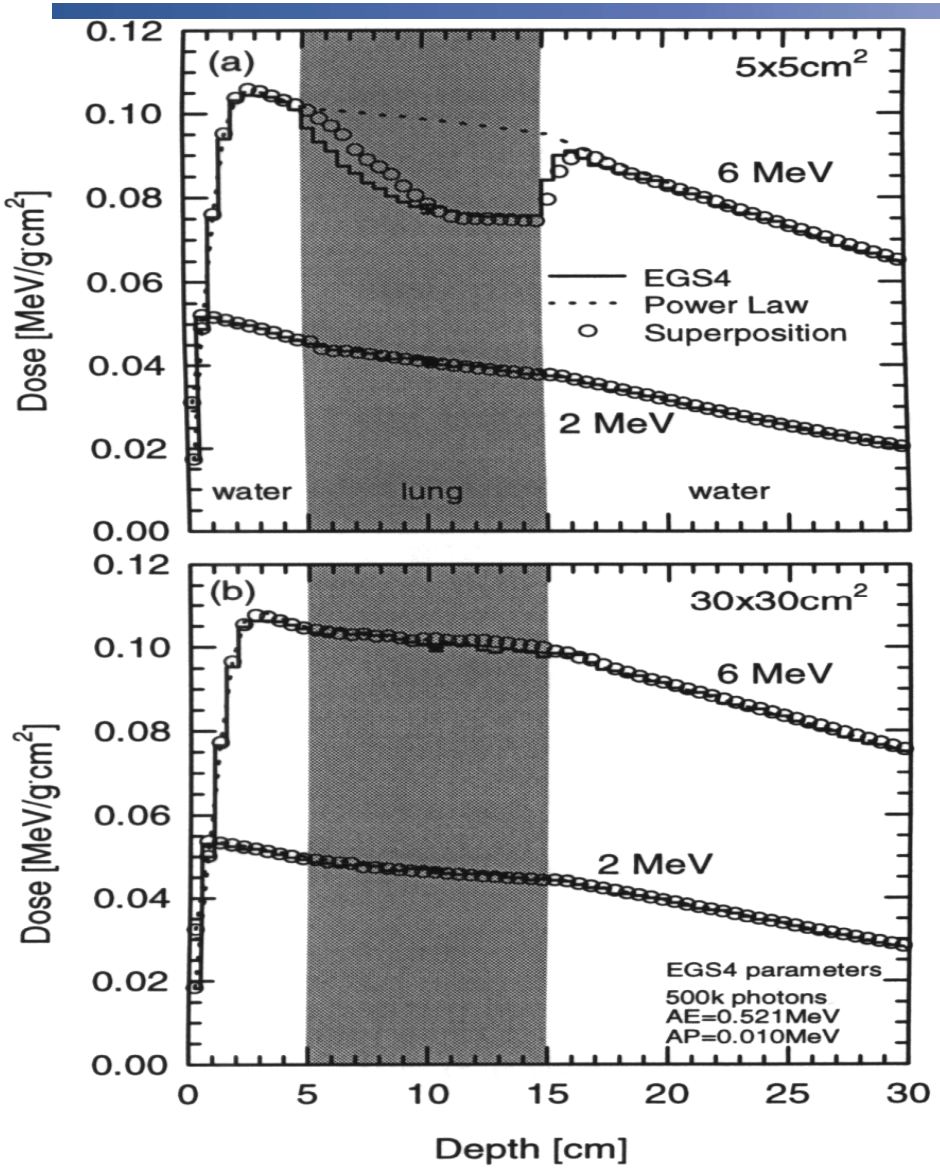
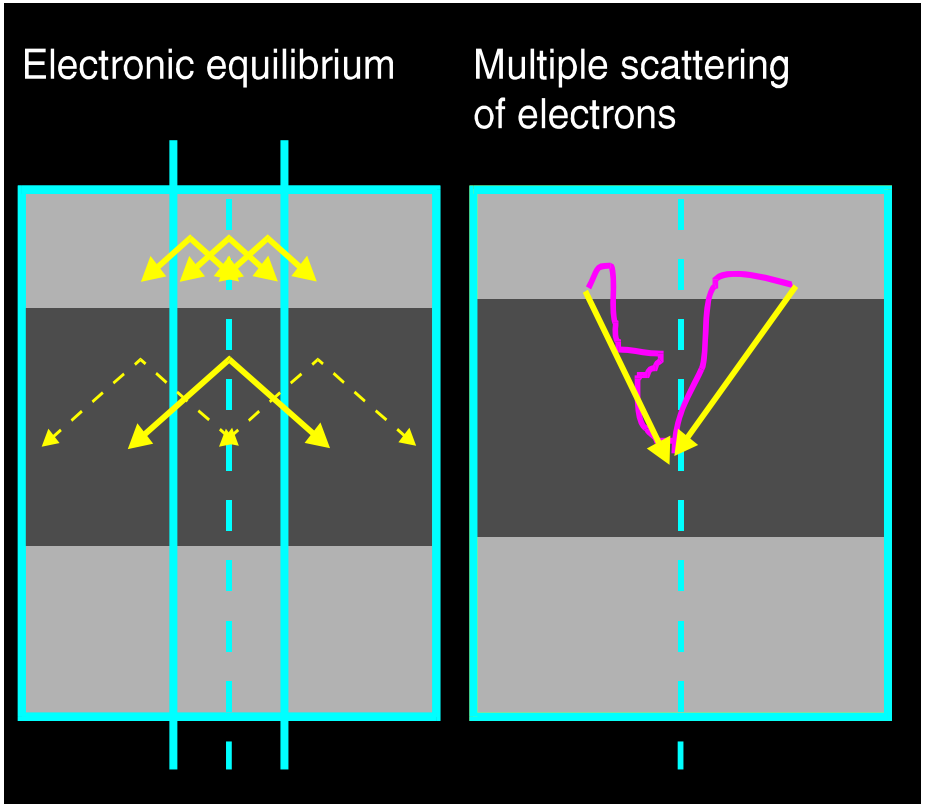
Electronic Disequilibrium





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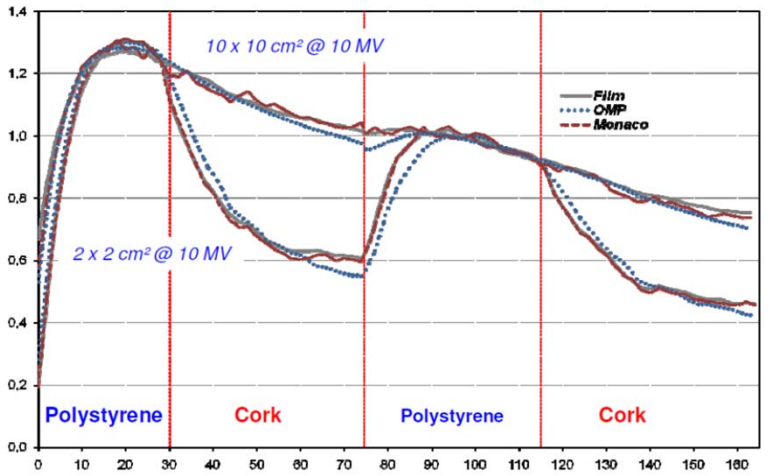
Summary model based & MC approaches

- 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

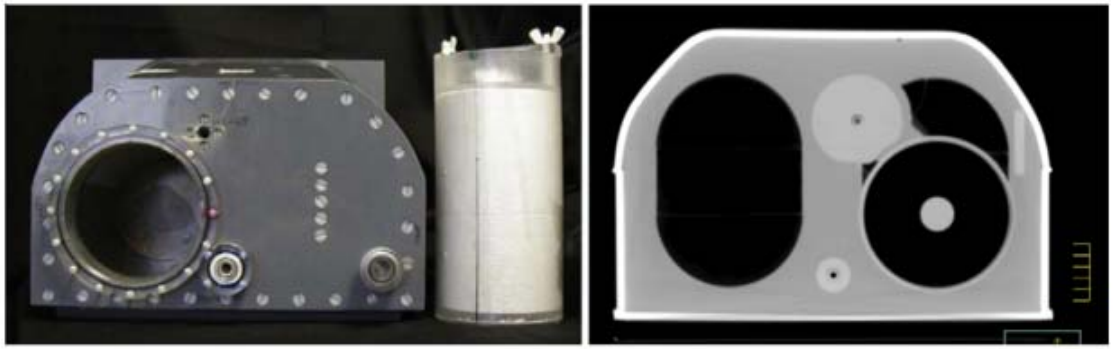
📖 I Fontina et al, Radio & Oncol 93 (2009) 645–653

- 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



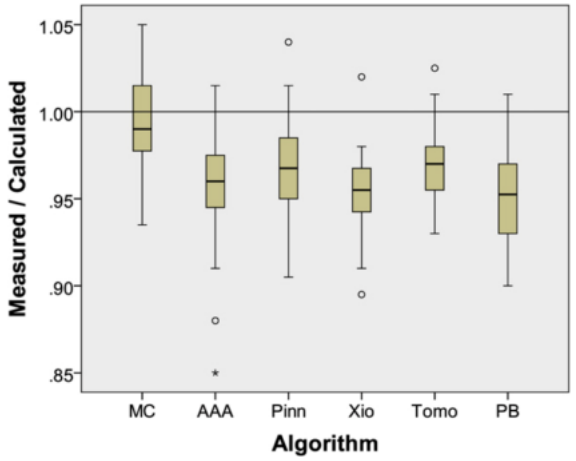


Fig. 2. Ratio of the in-phantom-measured dose to the planning system-calculated dose to the center of the lung target by treatment planning algorithm. Algorithms are Monte Carlo (MC), Eclipse AAA (AAA), Pinnacle CS (Pinn), CMS Xio CS (Xio), Hi-ART Tomotherapy CS (Tomo), and pencil beam (PB).

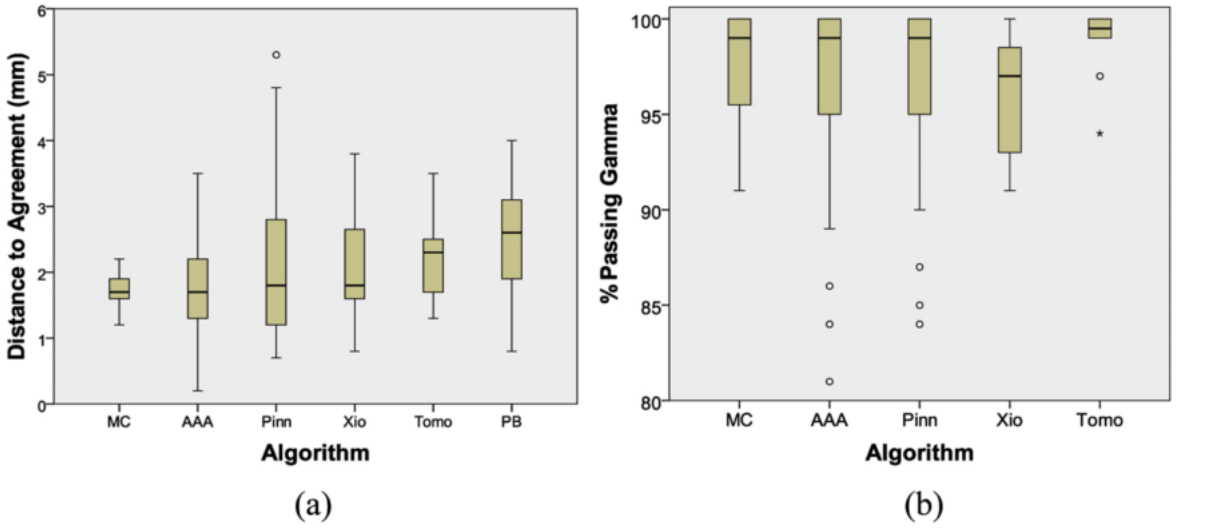


Fig. 3. Two-dimensional agreement between the in-phantom-measured dose and the planning system-calculated dose, based on distance-to-agreement criteria (a) or the percentage of pixels passing the gamma criterion (b). Algorithms are Monte Carlo (MC), Eclipse AAA (AAA), Pinnacle CS (Pinn), CMS Xio CS (Xio),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

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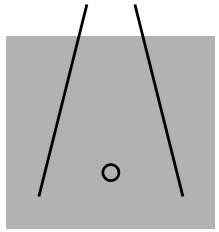
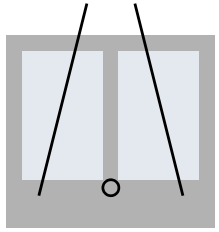
A Simple Algorithm Check

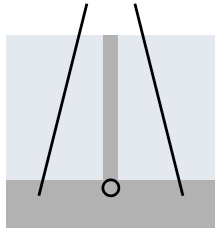
IMRT: the State of the Art, AAPM Monograph 29 pg 449-473 (2003)



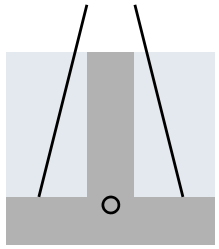
- 20 X 20 cm^2 field, 18MV
- 50 X 50 X 50cm^3 water phantom
- 200cGy to 22cm depth



- 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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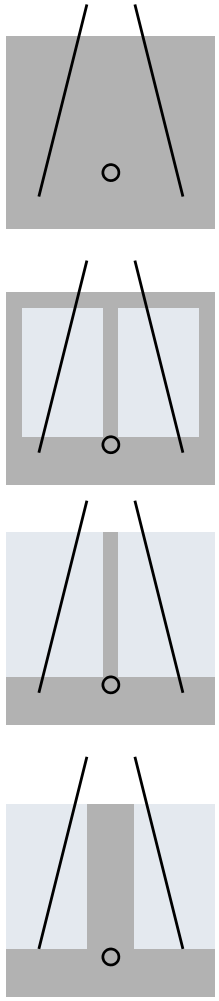
A Simple Algorithm Check: MU's

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:

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

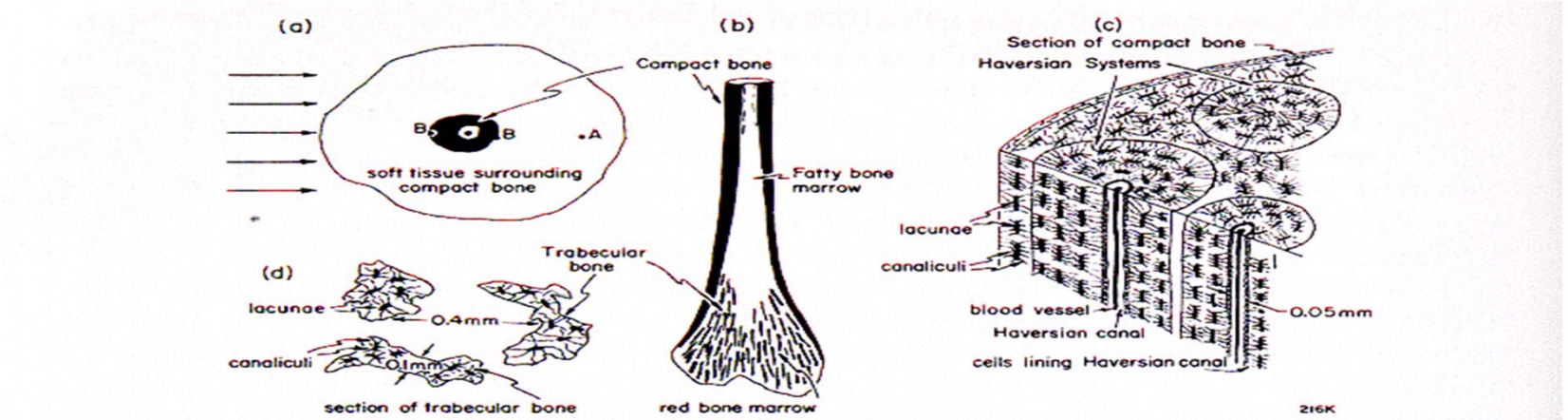

Figure 11-10. (a) Cross section of long bone imbedded in soft tissue. (b) Longitudinal view of lower end of femur. (c) Schematic diagram of Haversian system adapted from Ham (H13). (d) Cross section of trabecular bone.

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Energy Absorbed by an Inhomogeneity

BONE

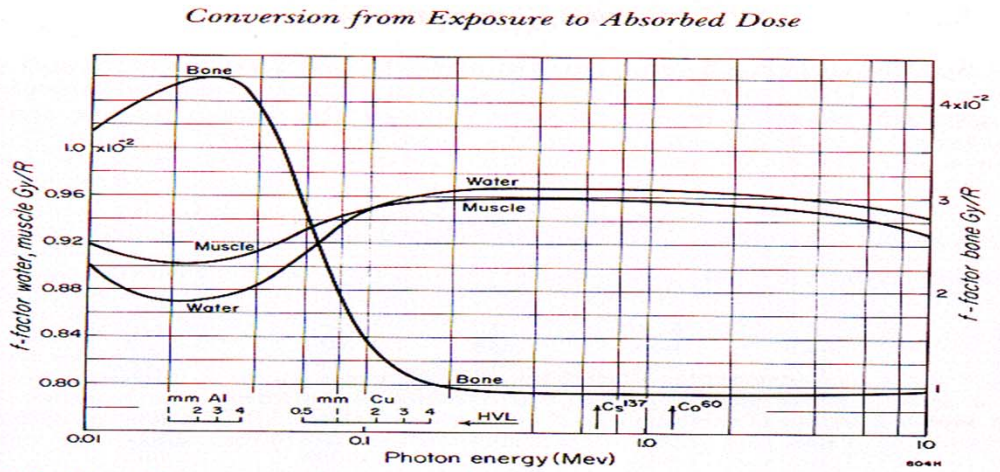

Figure 8-10. The f-factor as a function of photon energy for water, muscle, and bone taken from data in Table A-7. The auxiliary scale relates the HVL in A1 and Cu to the energy scale.

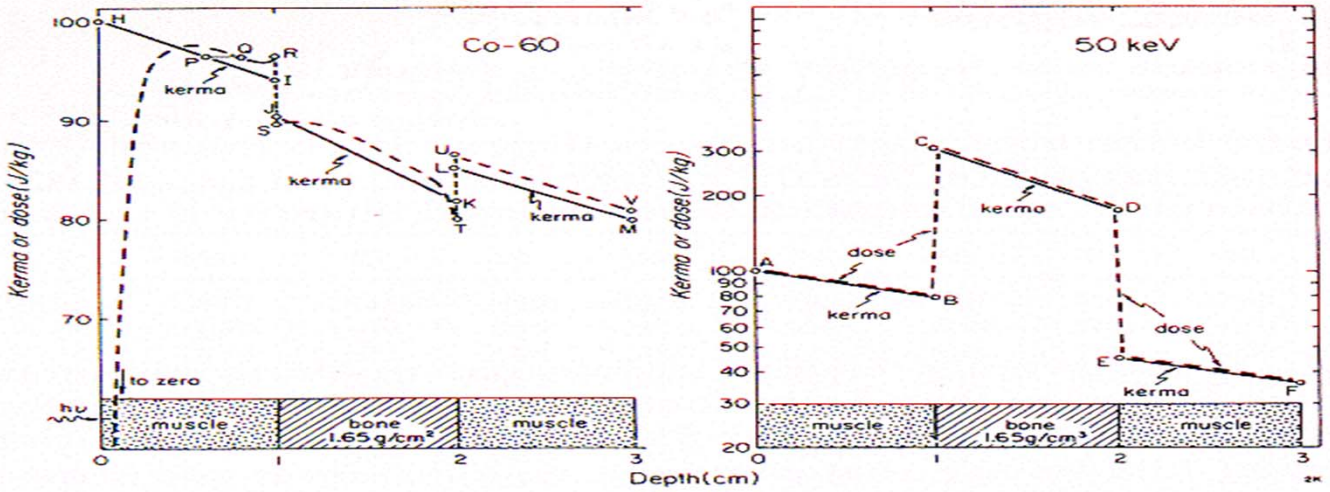

Figure 7-13. Diagram showing kerma and dose in a composite phantom irradiated from the left by cobalt 60 radiation and 50 keV radiation.

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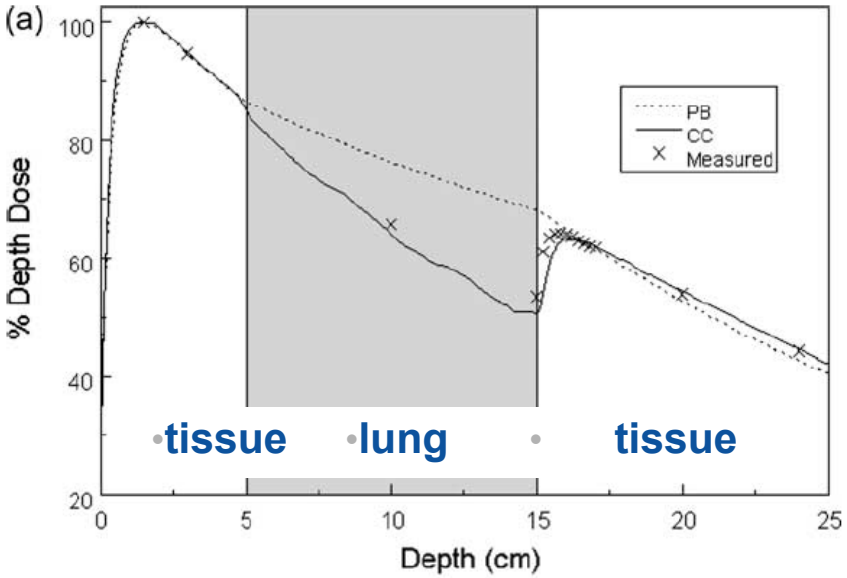
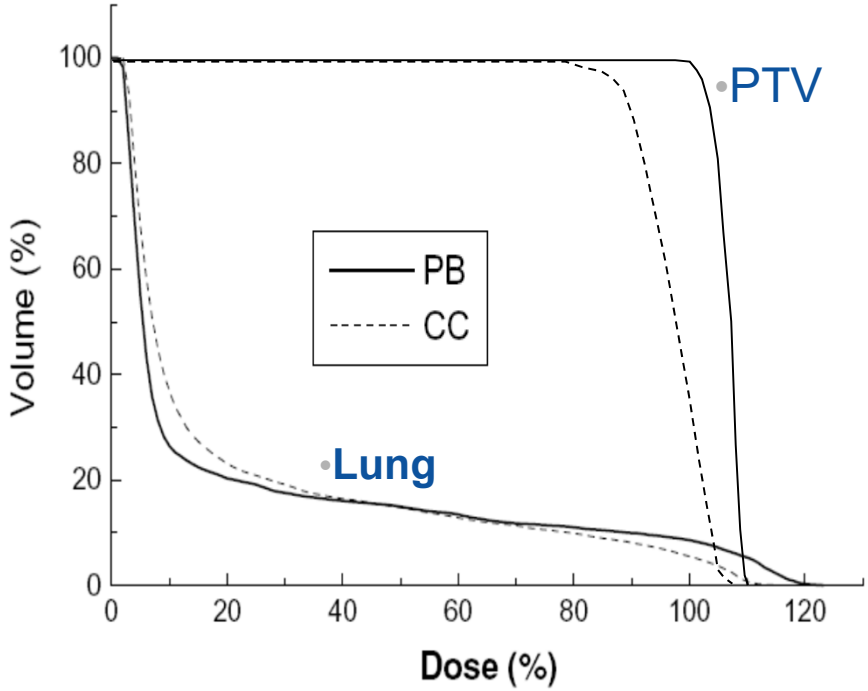
Clinical impact of dose calculation

- 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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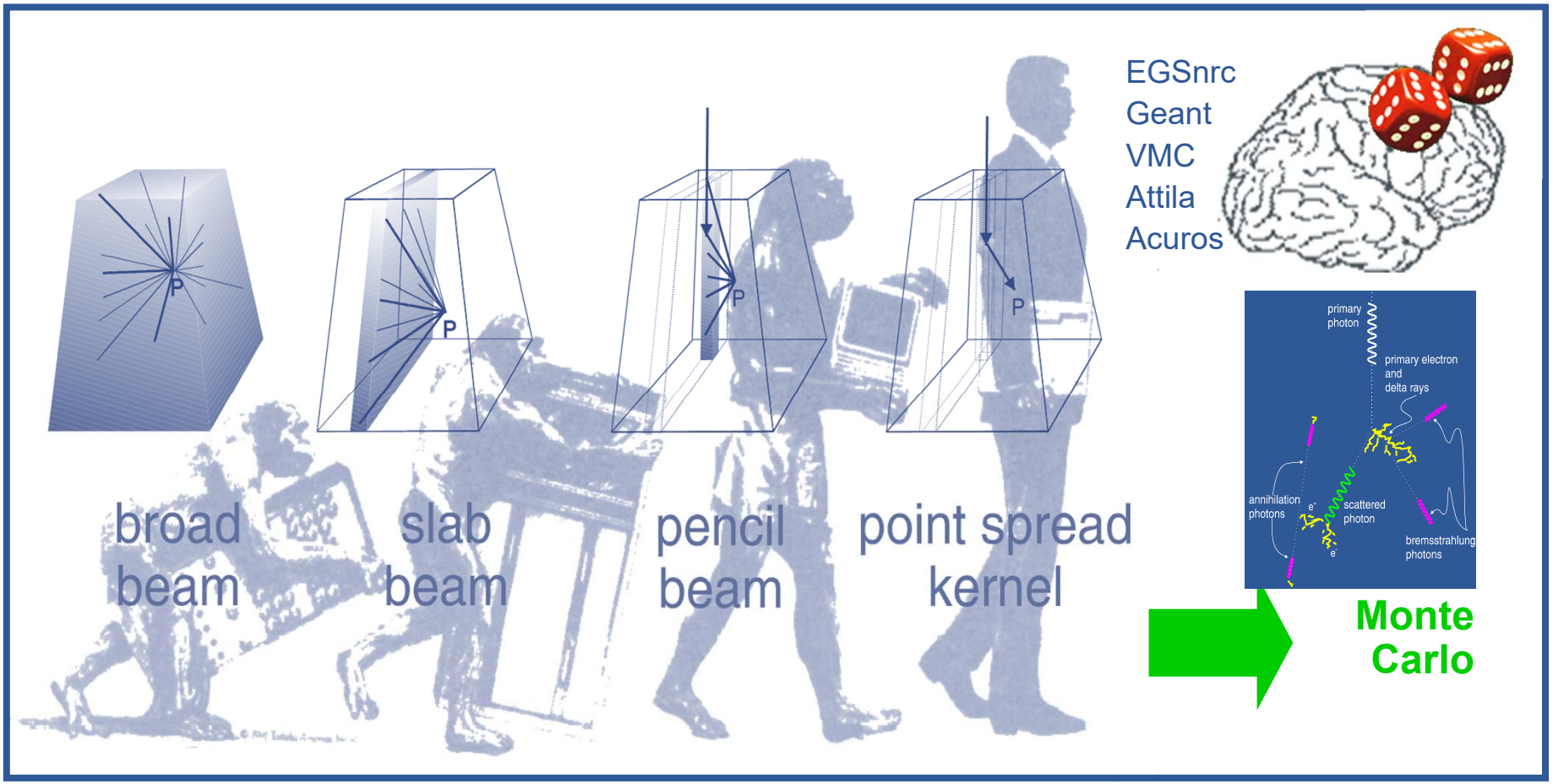
Summary – Evolution, not Revolution

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



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ICRU guidance on planning and prescribing

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Cambridge, UK

ATP Barcelona 2017

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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

The history of radiotherapy

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

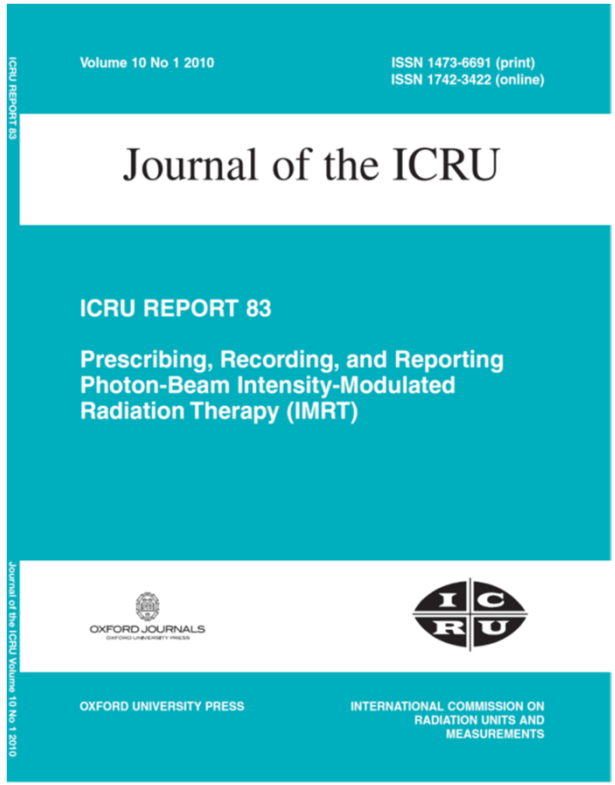
- 100+ years later the technology has changed!
- ICRU reports are here to help us

- 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

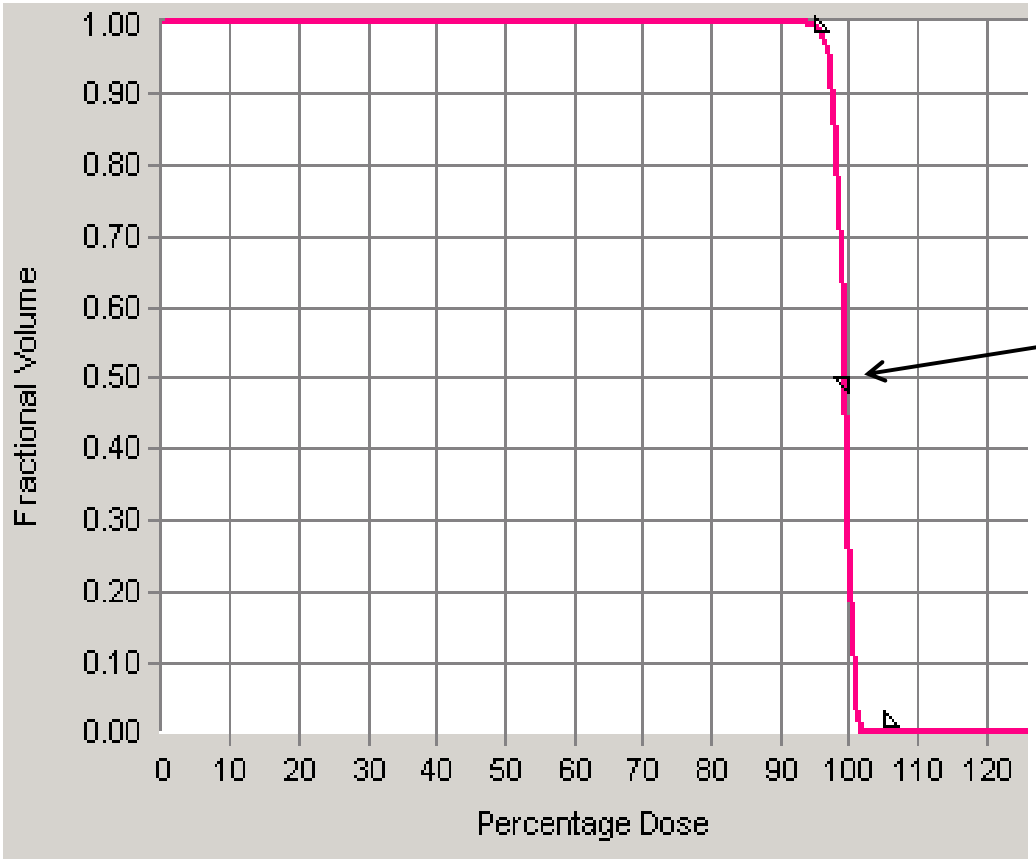
- Specify median dose - $D_{median} = D_{50\ \%}$
  - Corresponds best to previous ICRU reference point dose (≈ isocentre dose)
  - Often close to mean dose
  - Not influenced by 'tails' on the DVH
  - Accurately calculated in TPSs

  - 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

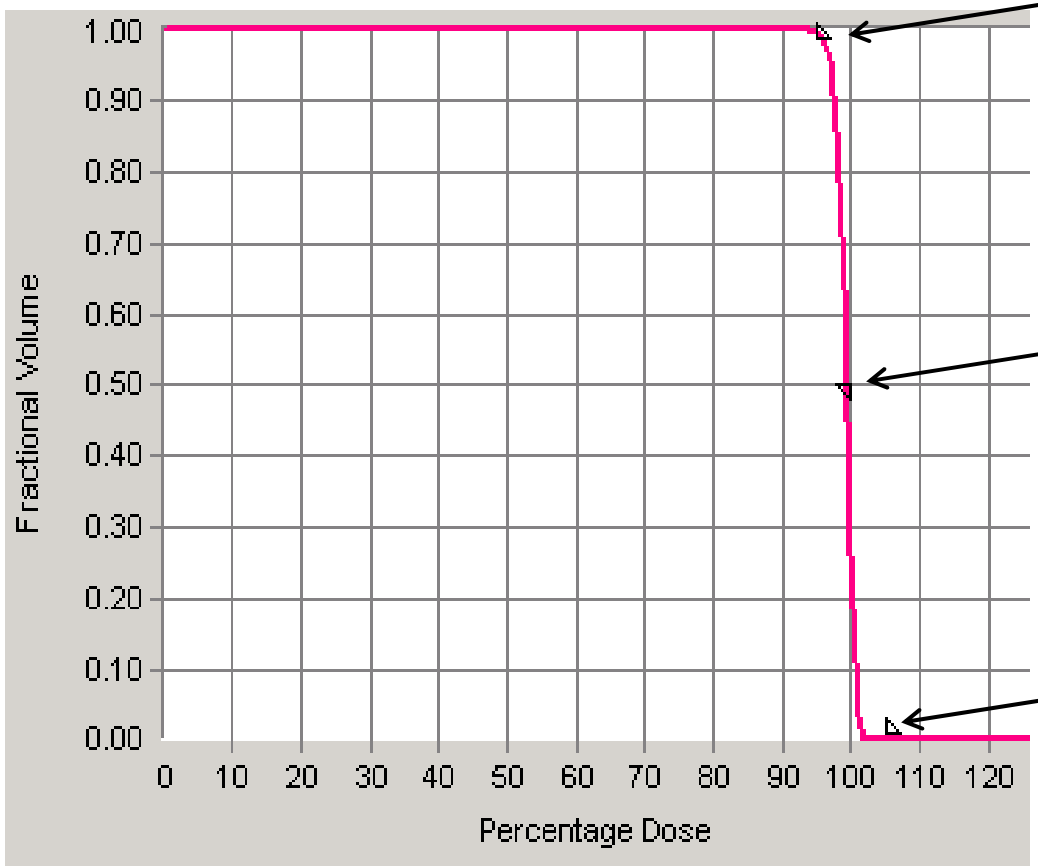
- Prescribing to median dose without some restriction on the slope of the target DVH could allow a shallow slope and low target minimum dose

- 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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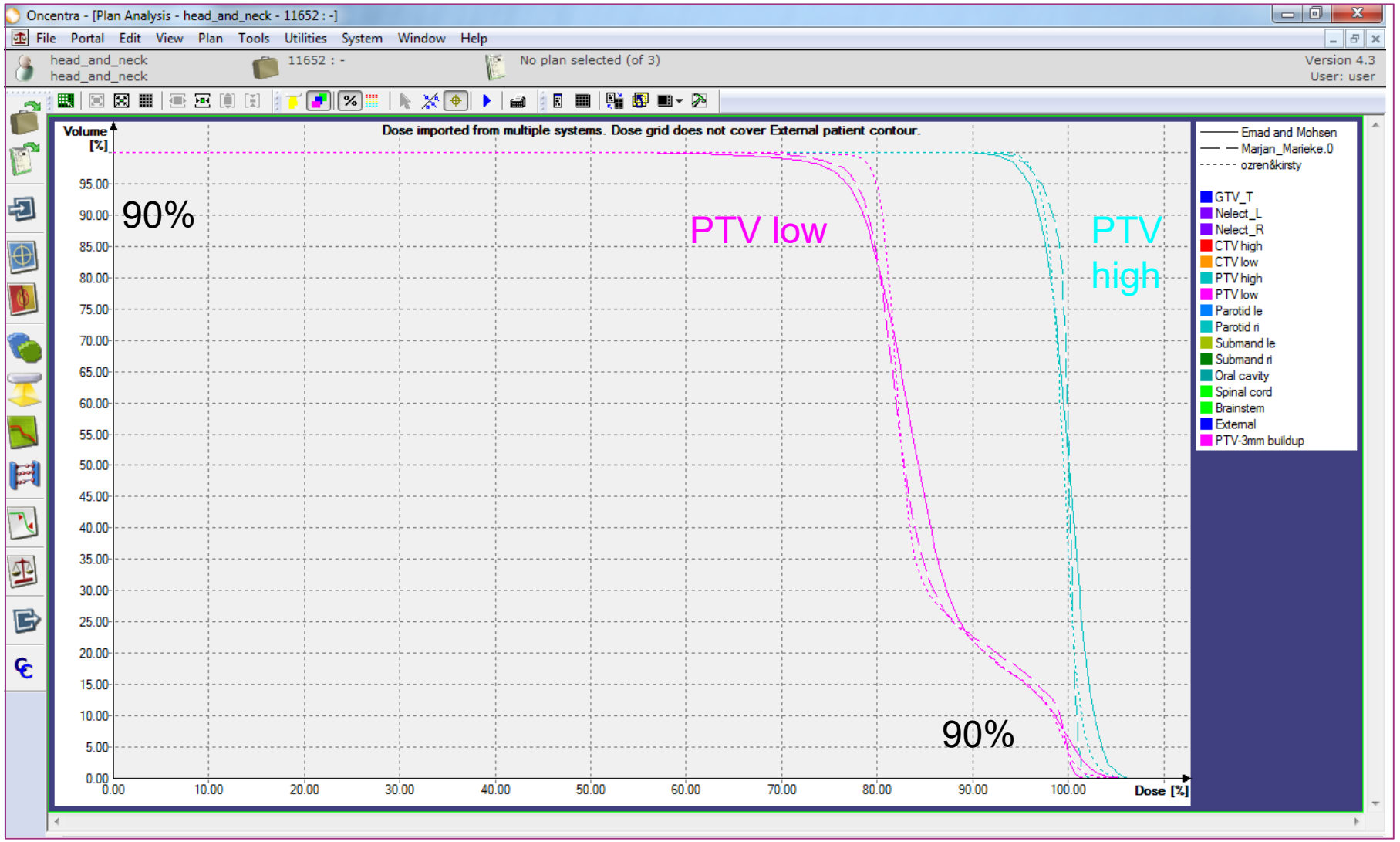
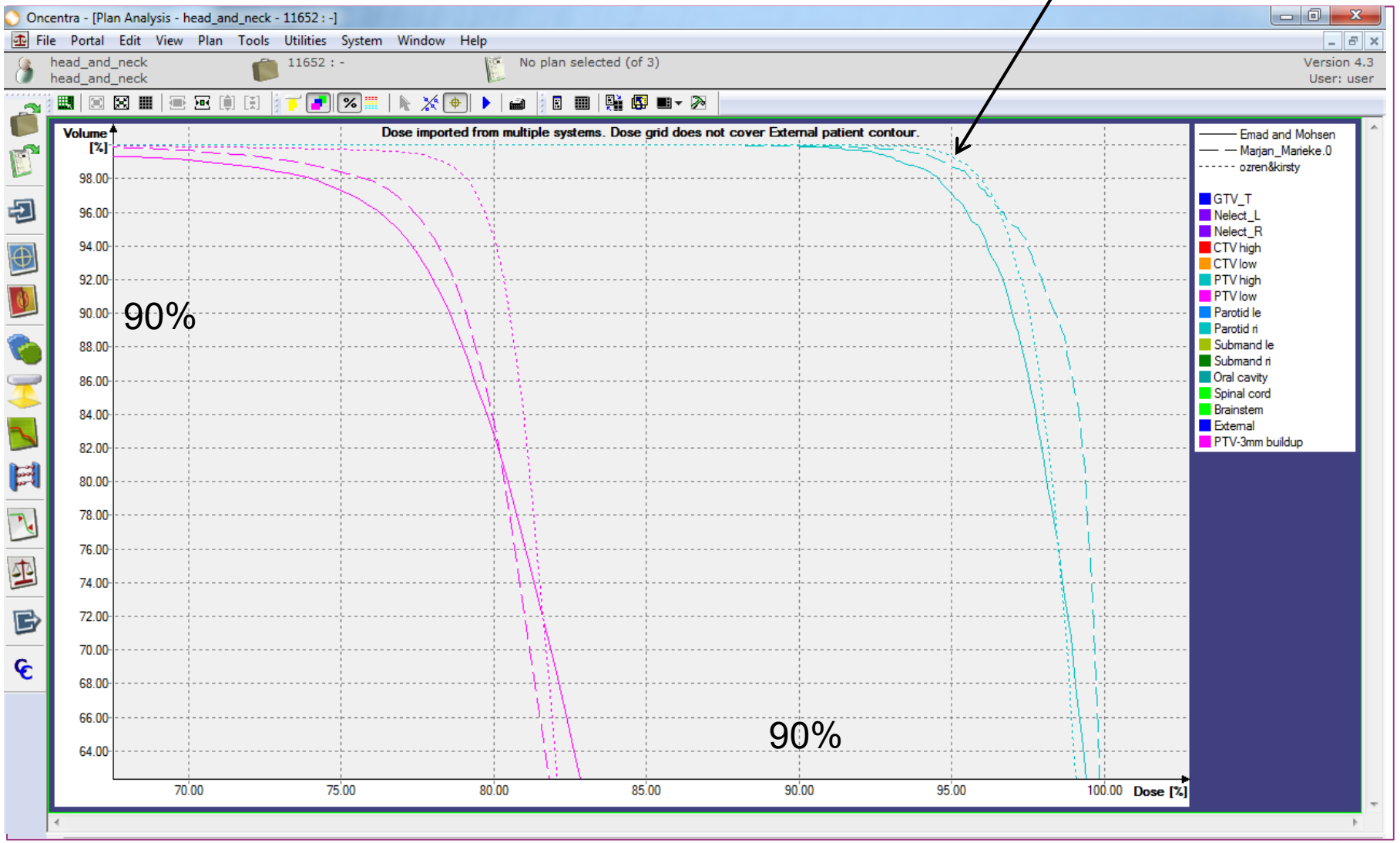
Prescribing



Prescribing

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



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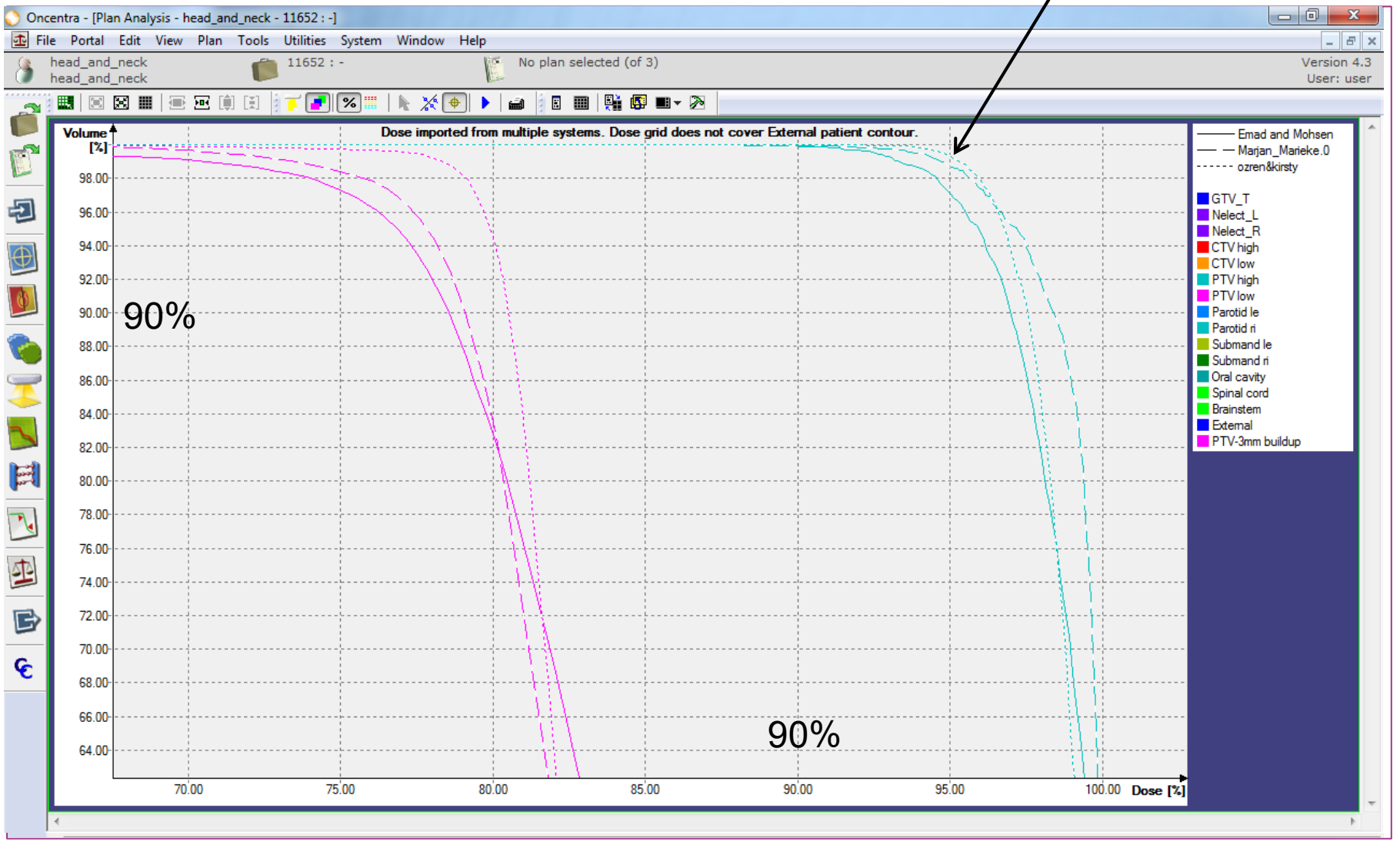
Prescribing

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

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



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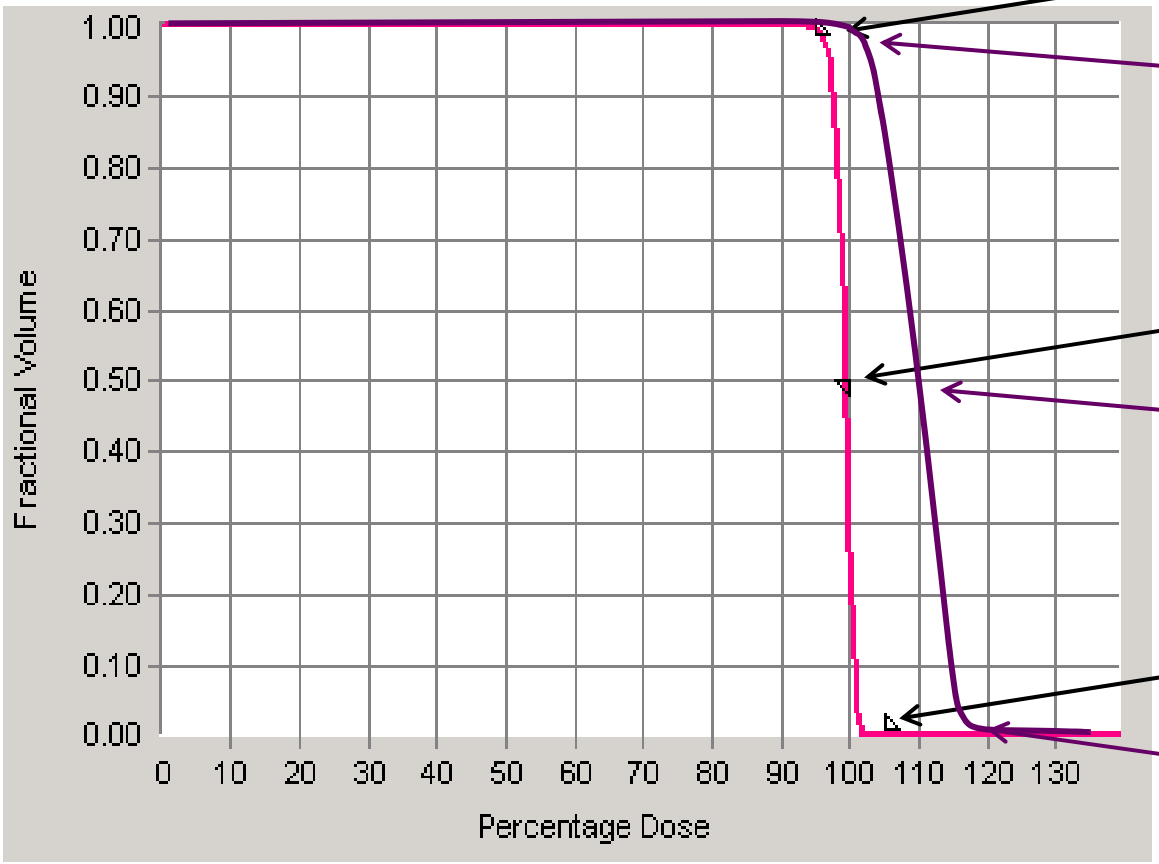
Prescribing

- 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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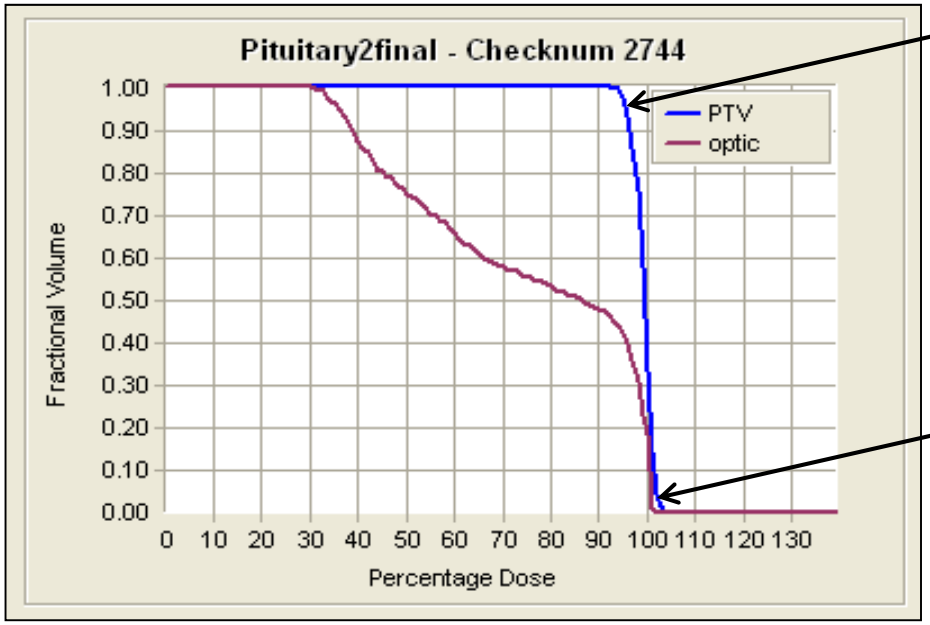
Prescribing

- 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

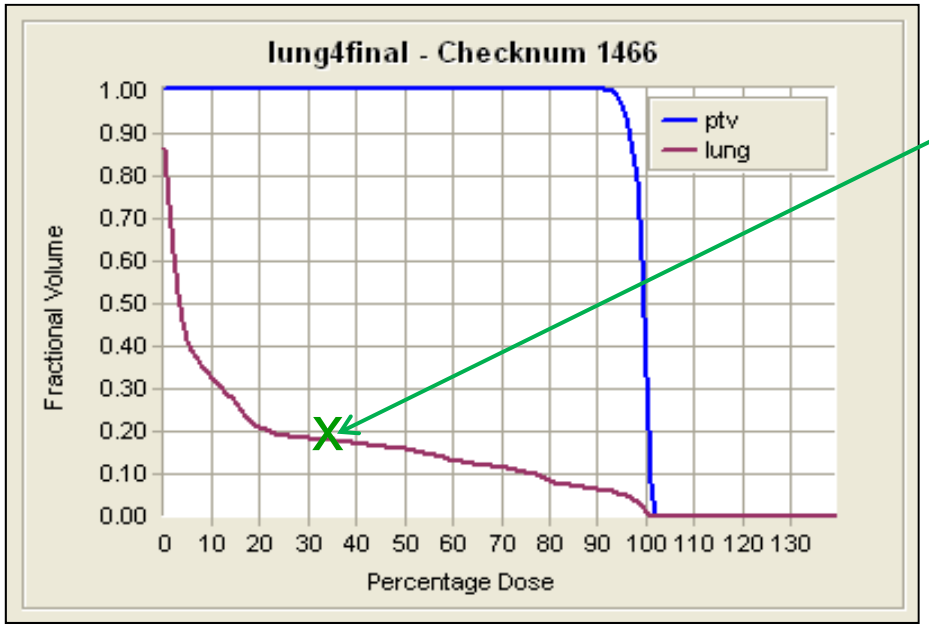
Prescribing

- 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

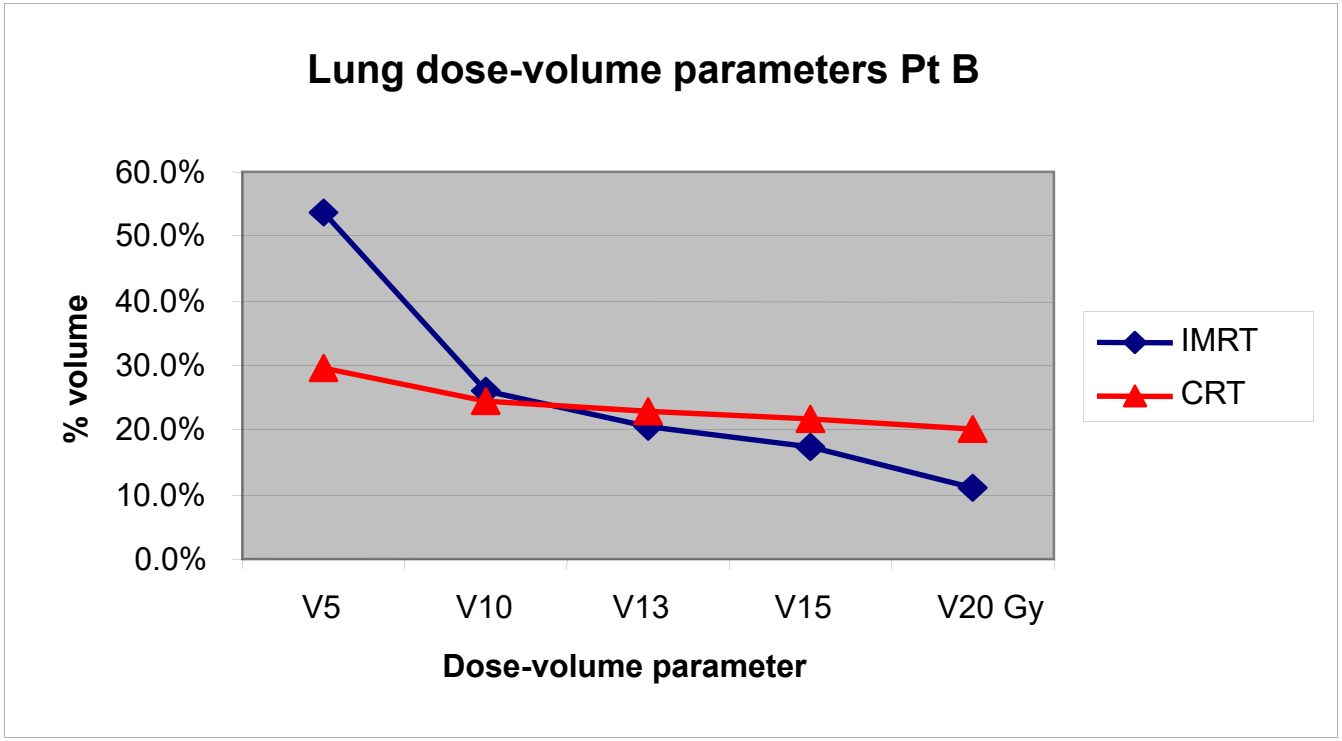
- Add volume parameters where relevant
  - e.g. $V_{20\ Gy}$ for lung

- 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



Prescribing

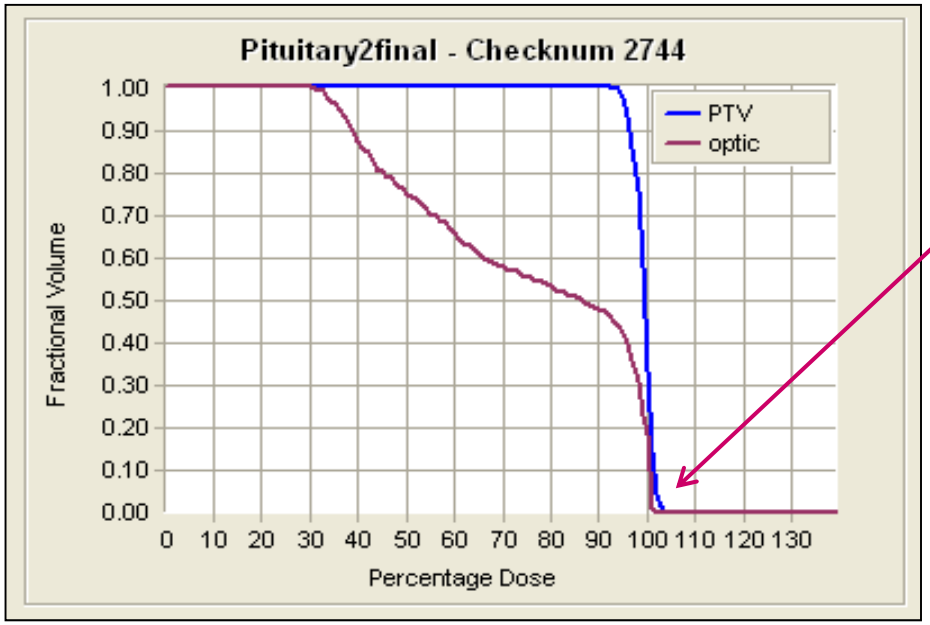
- For serial organs, maximum (near-max) dose is relevant parameter
  - ICRU recommends $D_{2\%}$ rather than D_{Max} ($D_{0\%}$)
  - Overcomes problem of defining (knowing!) what volume of the structure is important

  - 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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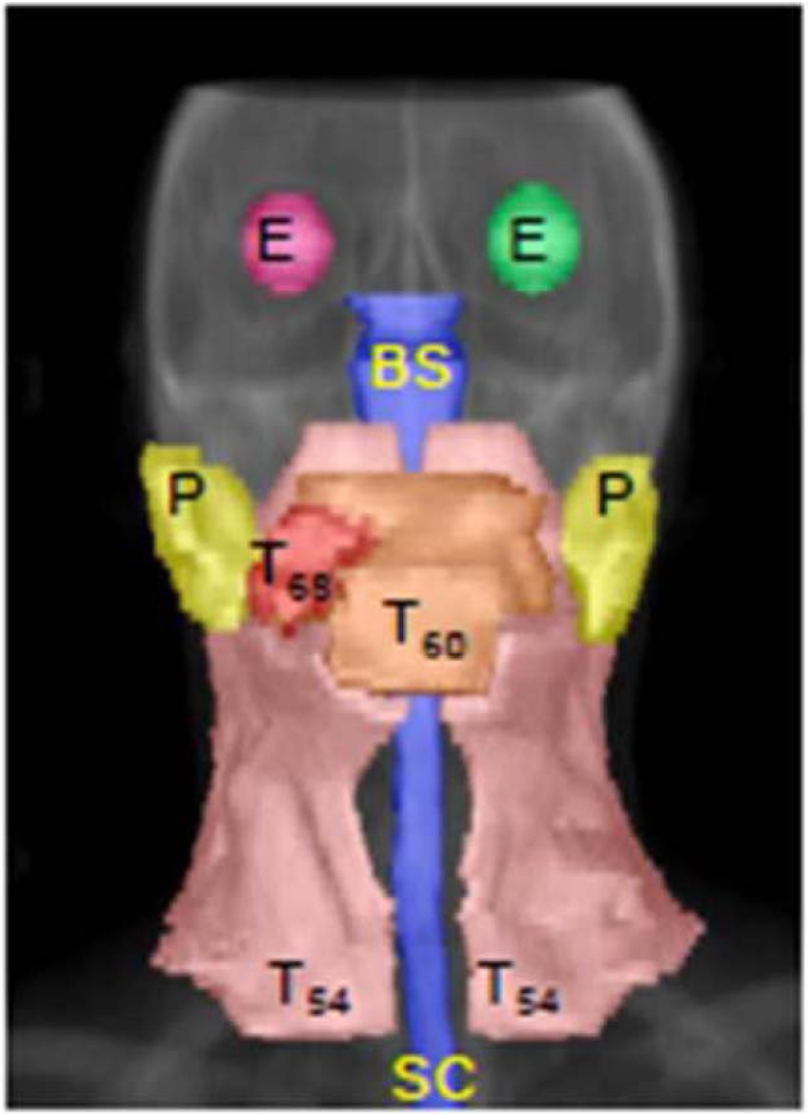
ICRU guidance

- 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)

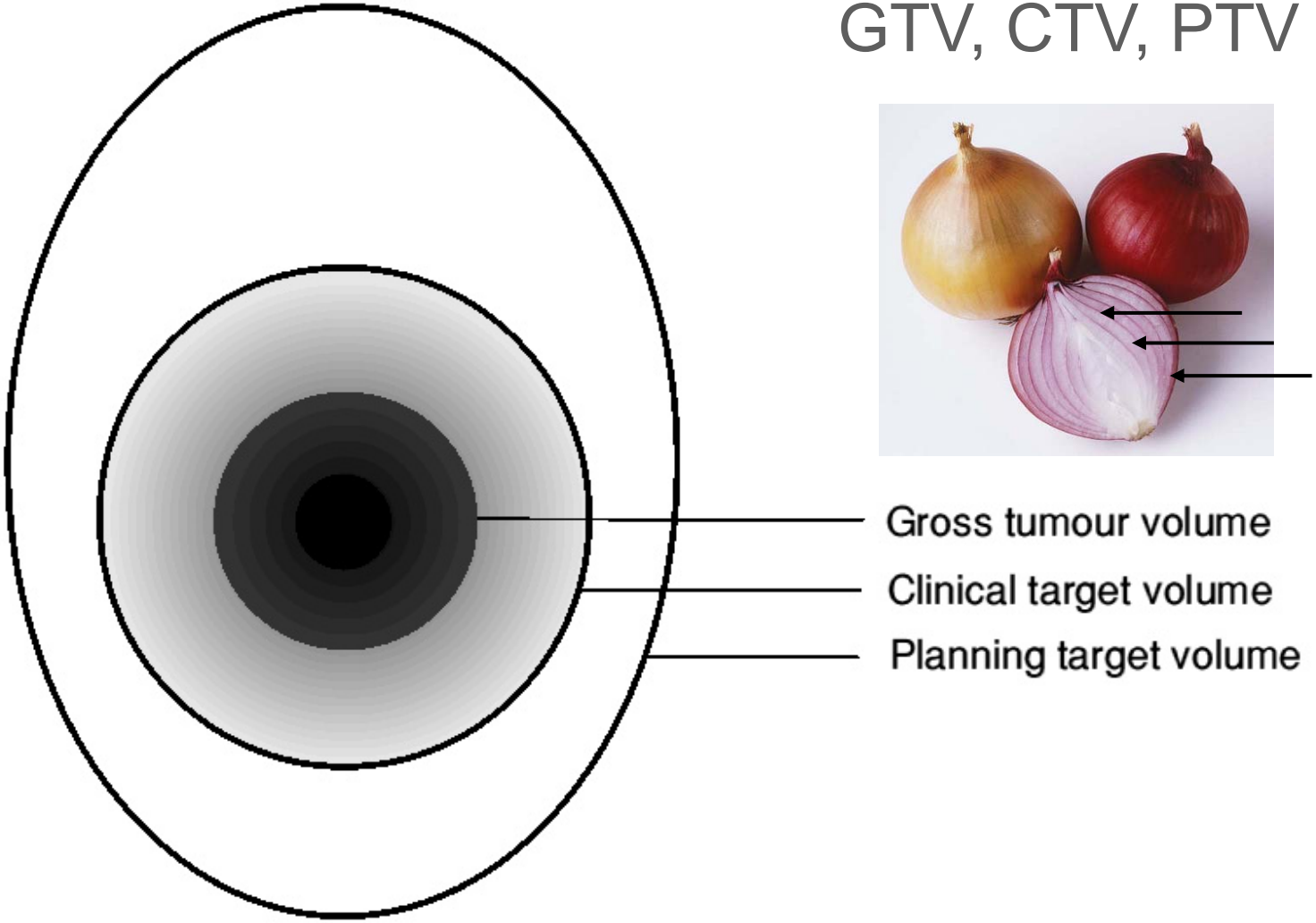
- Some details at end of lecture notes

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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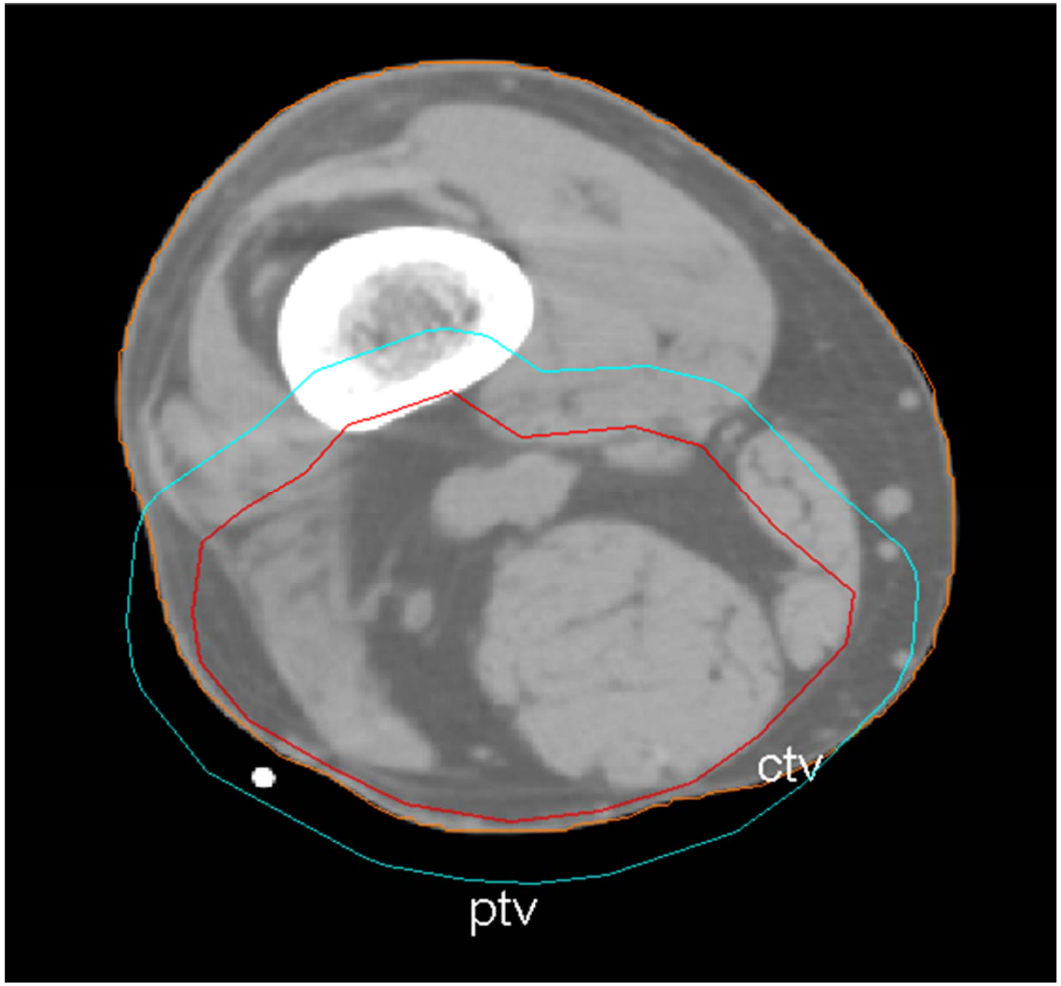
Target volumes - PTV

- 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

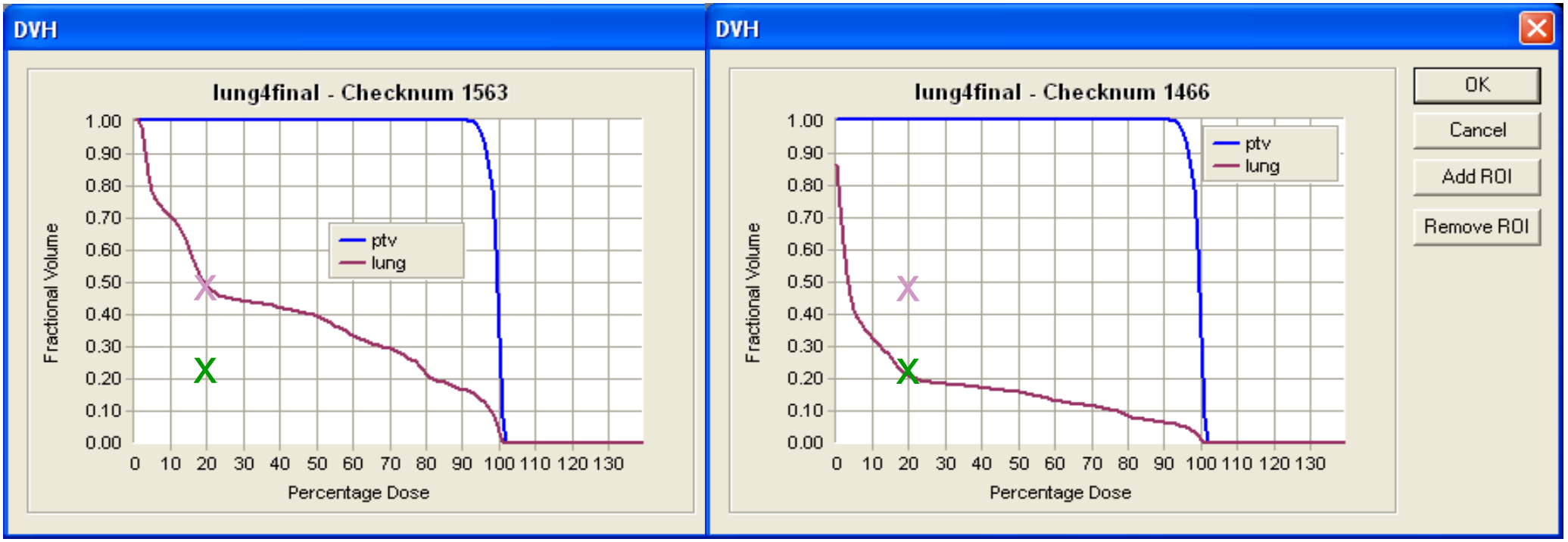
Target volumes – OARs

- 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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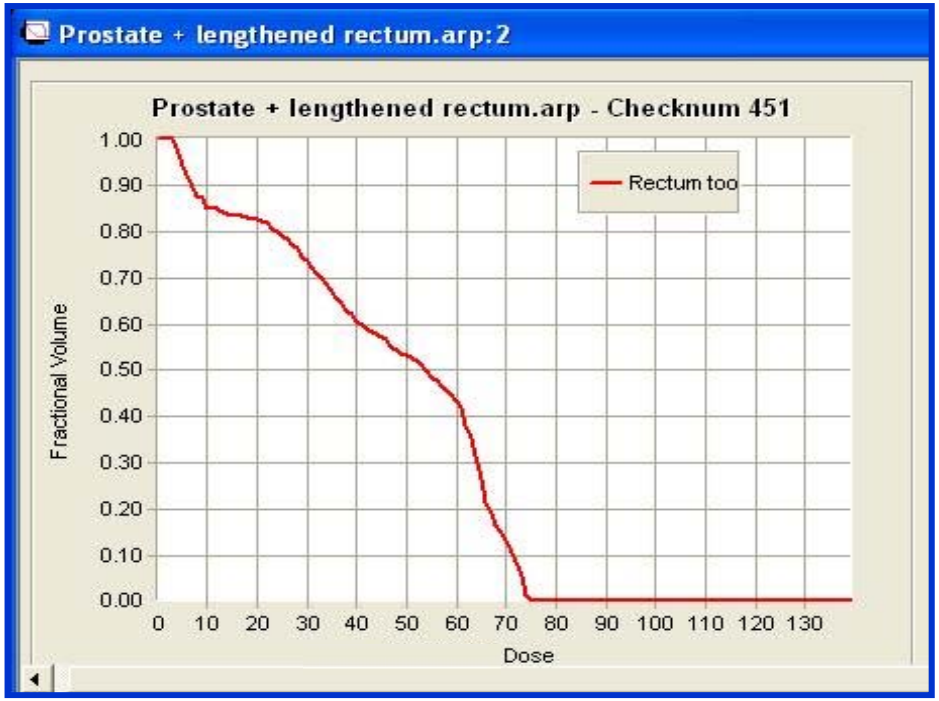
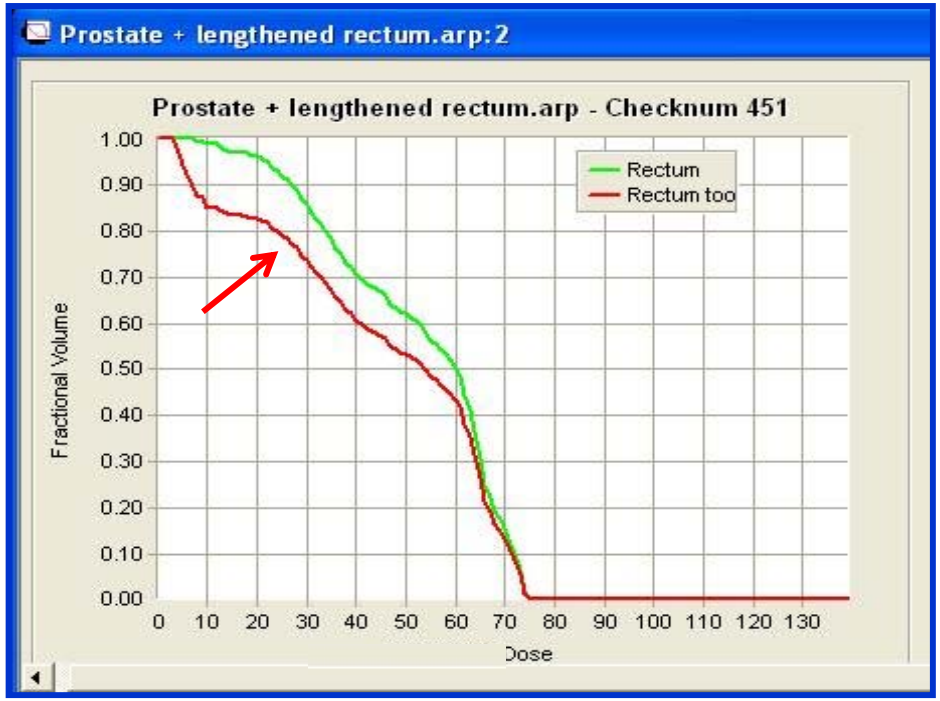
Target volumes – OARs

- 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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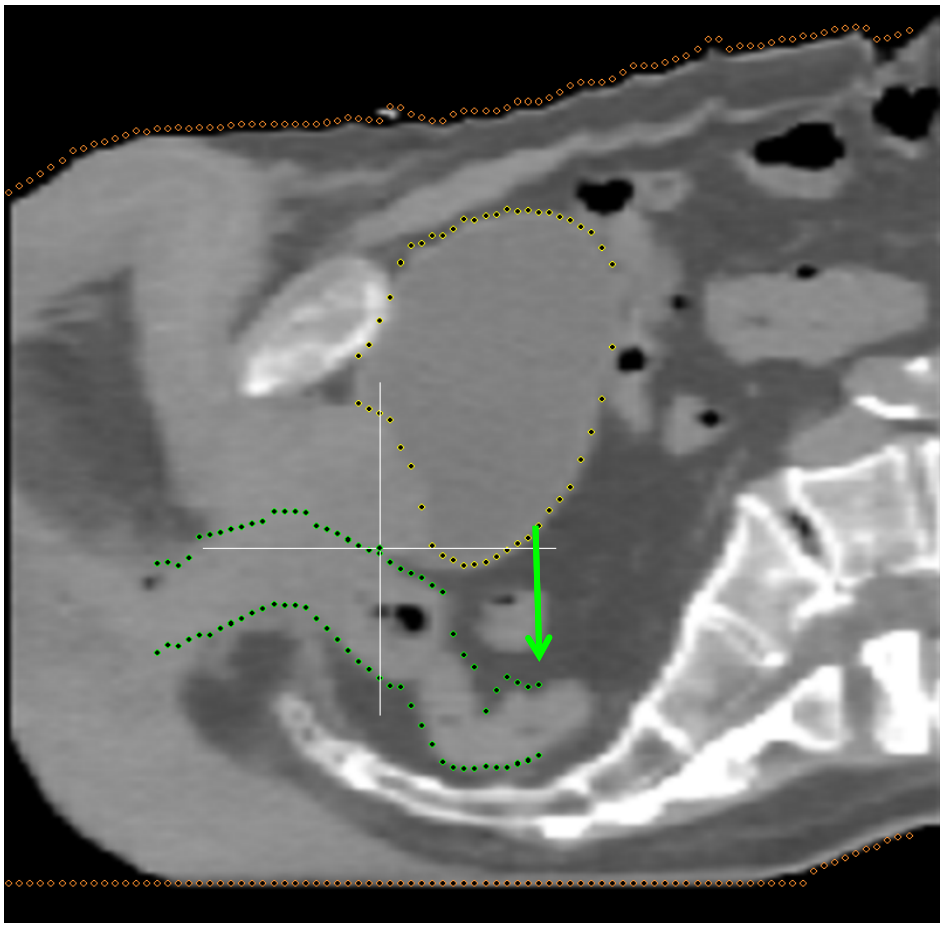
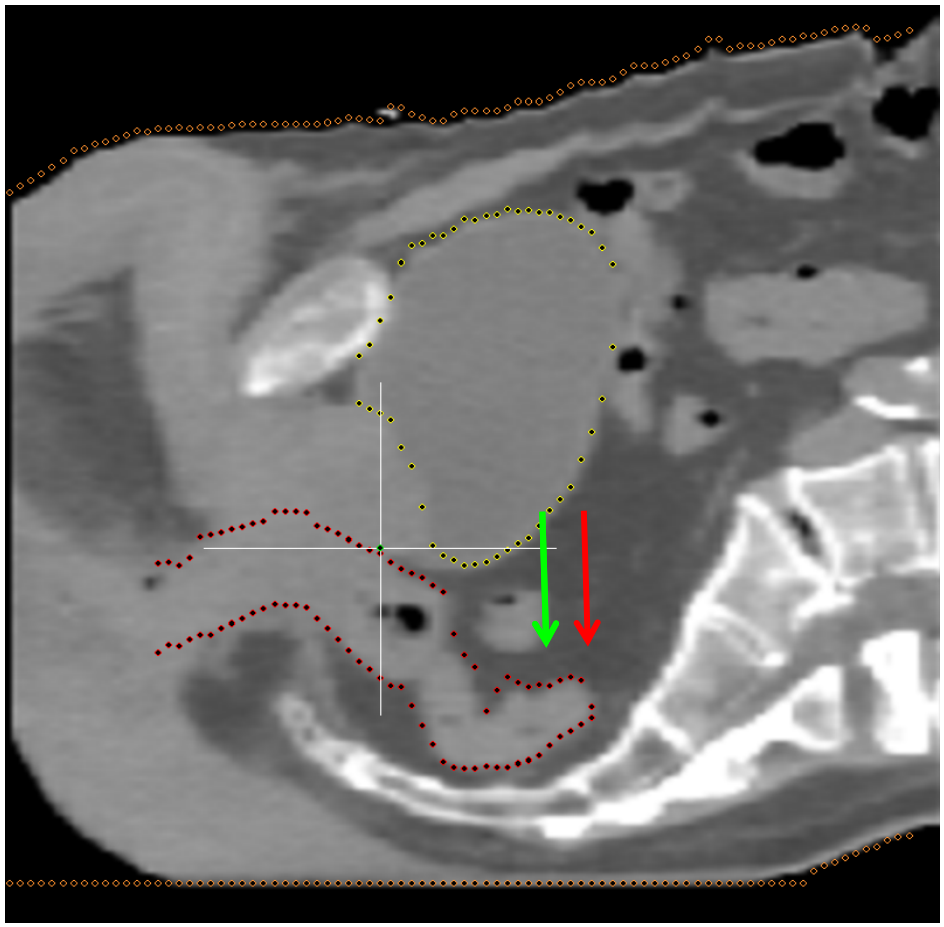
Target volumes – OARs

- Rectum–clear delineation, according to an agreed protocol



- Rectum correct



- Rectum on 4 slices more

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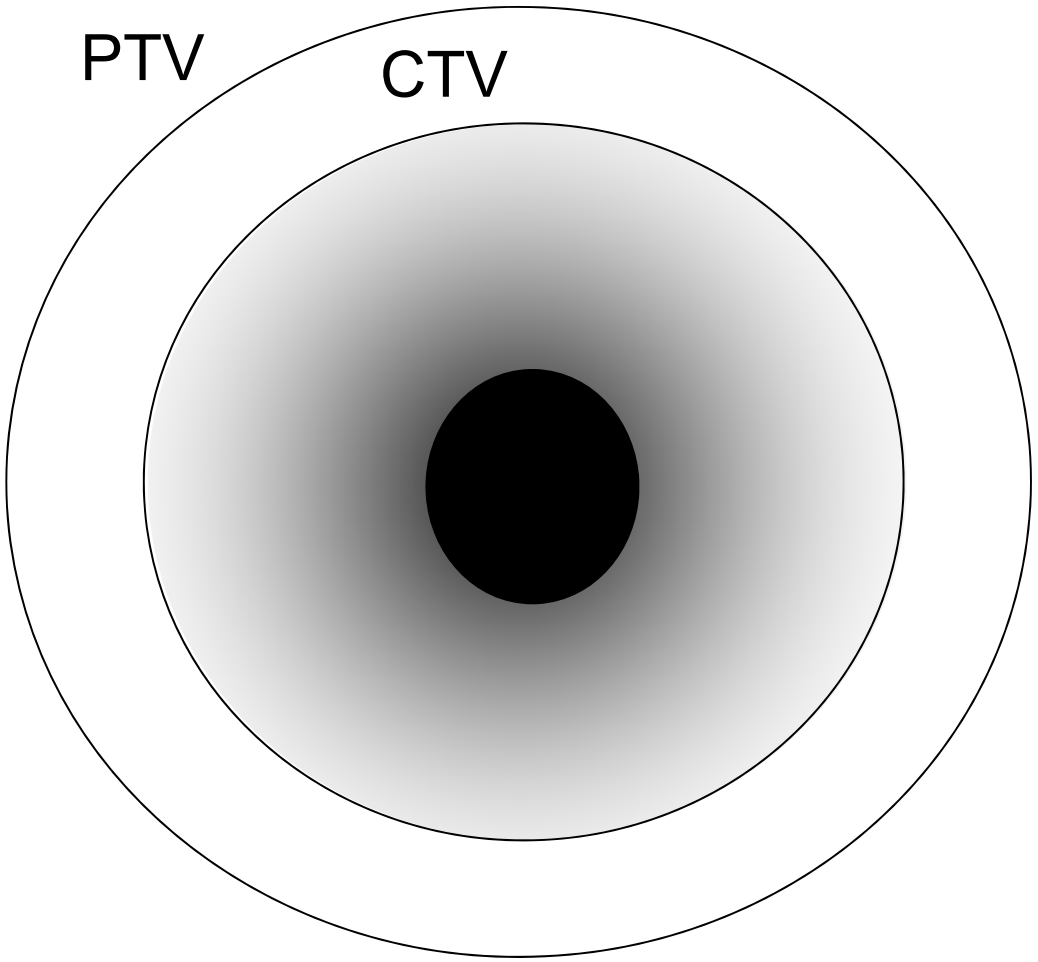
Target volumes – OARs + PRVs

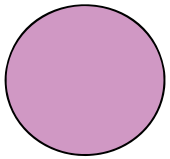
- Uncertainties apply to the OAR … so a 'PTV margin' can be added around it - to give the Planning organ at Risk Volume (PRV)

- 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

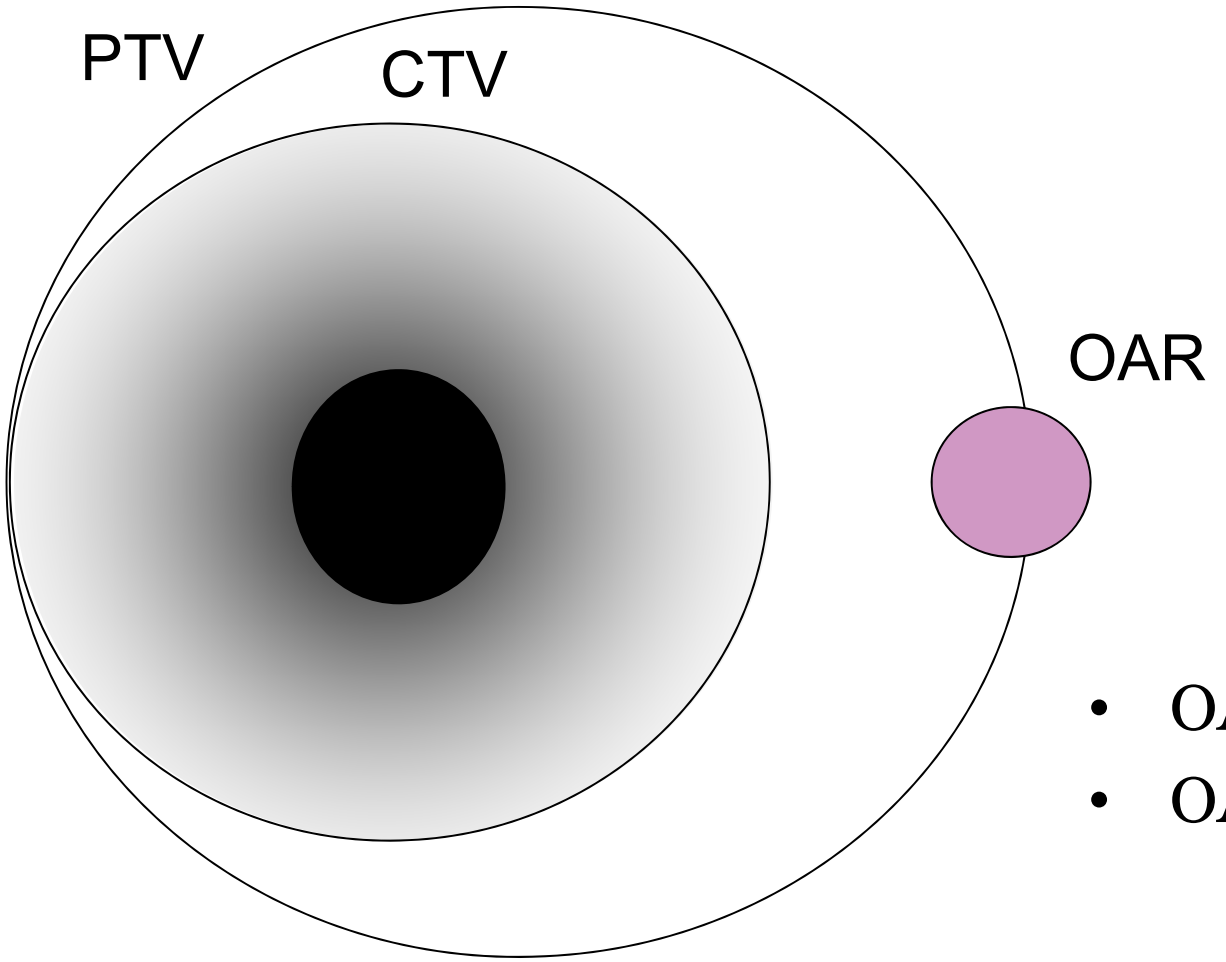
Target volumes – OARs + PRVs





- OAR clear of PTV
- OAR safe …

Target volumes – OARs + PRVs



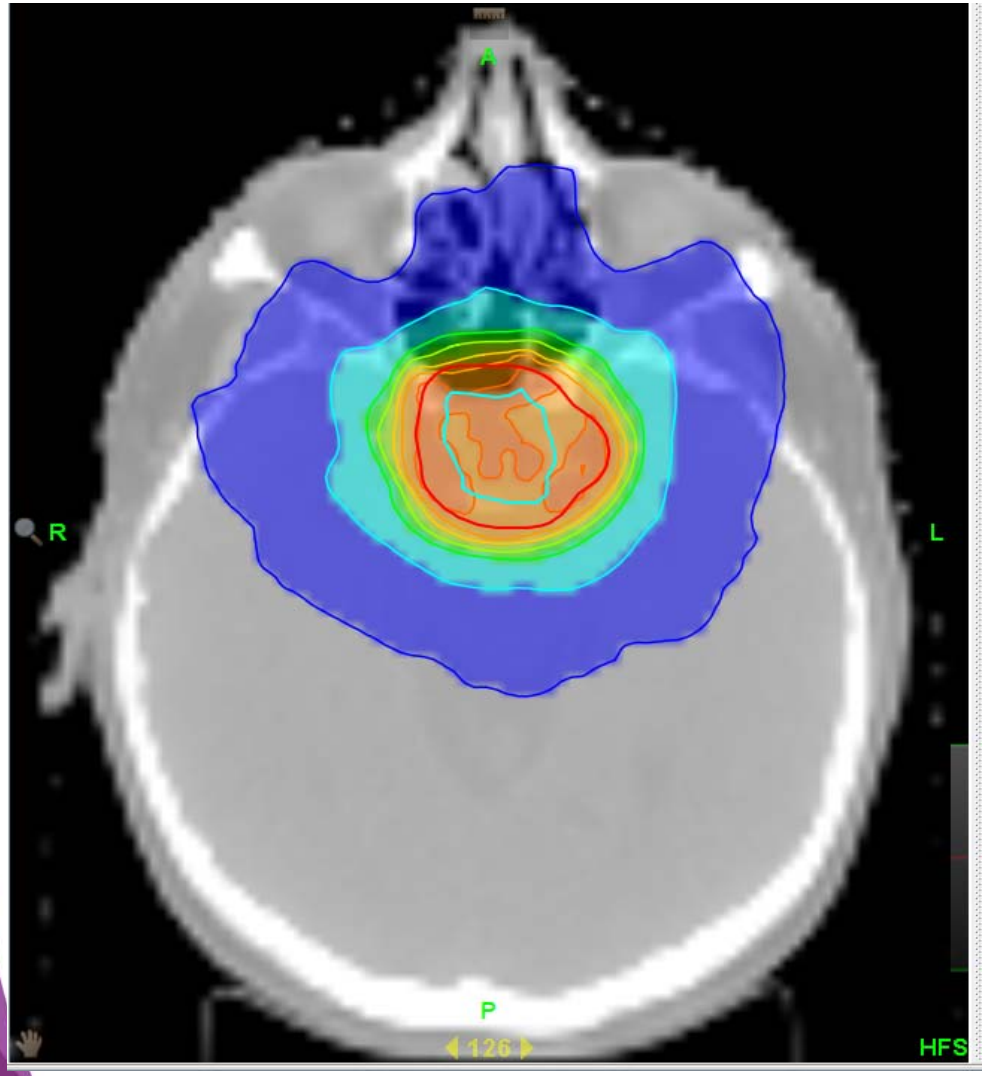
- OAR moves with CTV
- OAR not so safe …

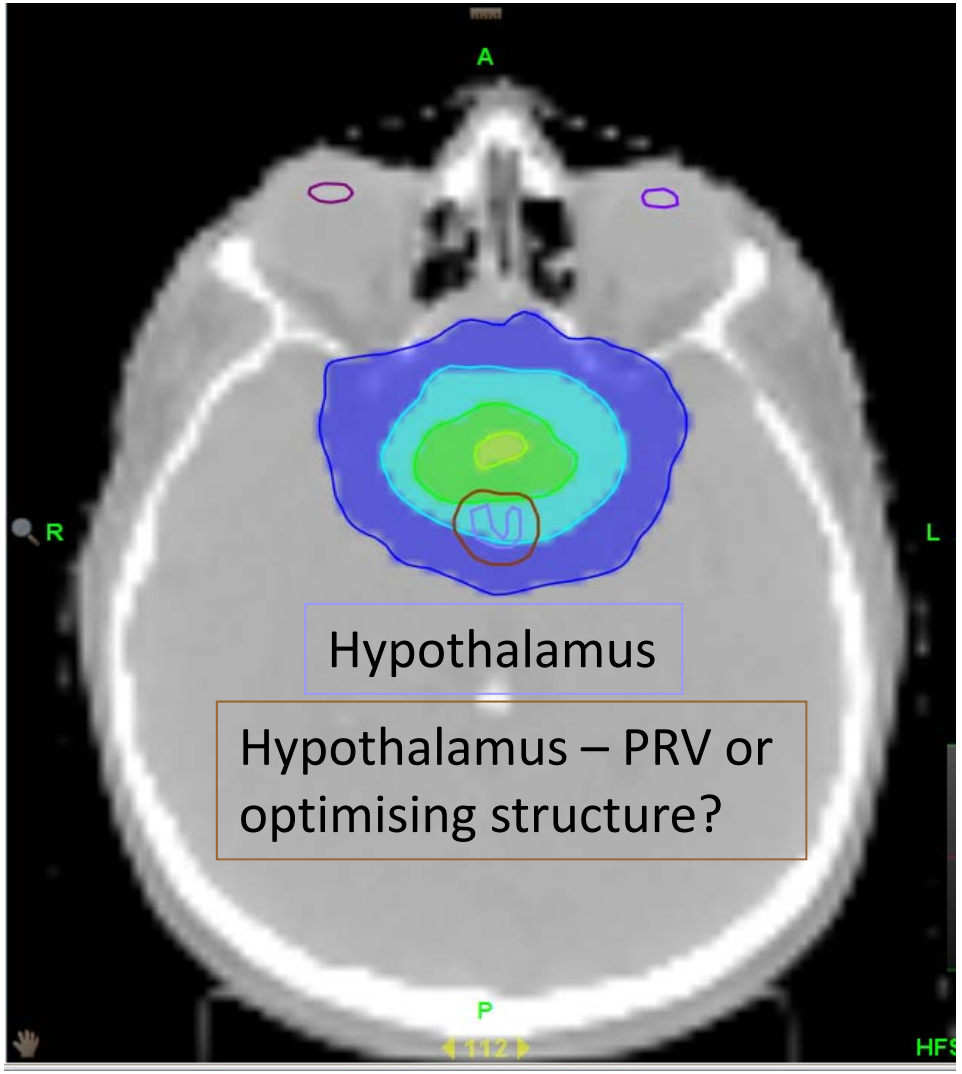
Target volumes – PRV

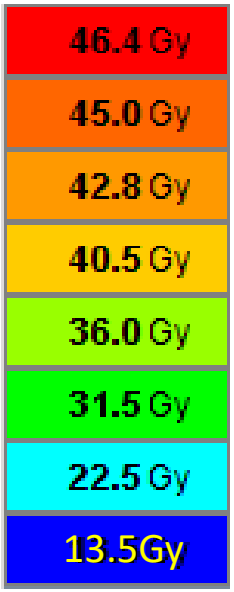
- The use of a PRV around an Organ at Risk is relevant for OARs whose damage is especially dangerous
- This applies to organs where loss of a ***small*** amount of tissue would produce a ***severe*** clinical manifestation
- A PRV is relevant for an OAR with serial organisation (almost exclusively)
  - 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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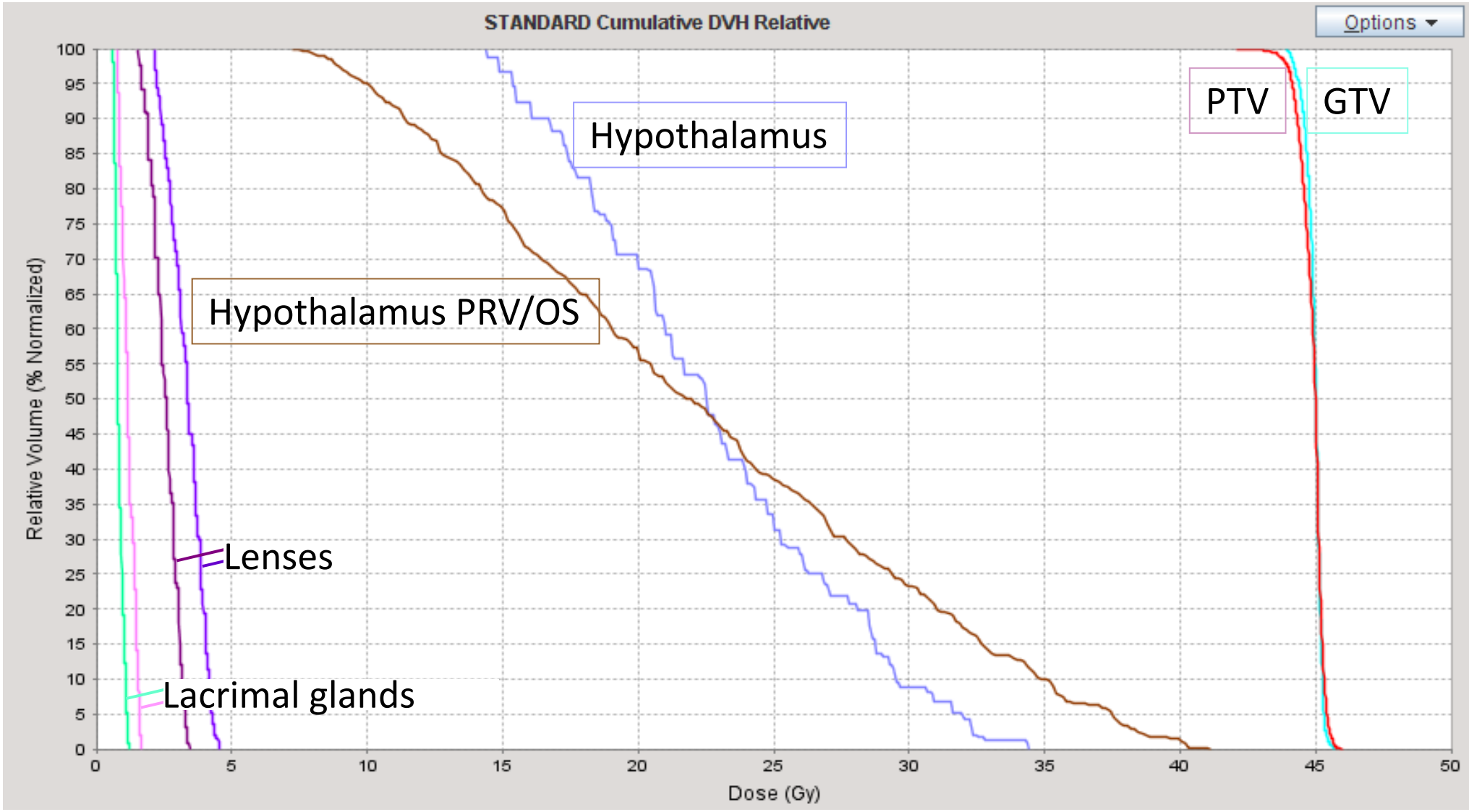
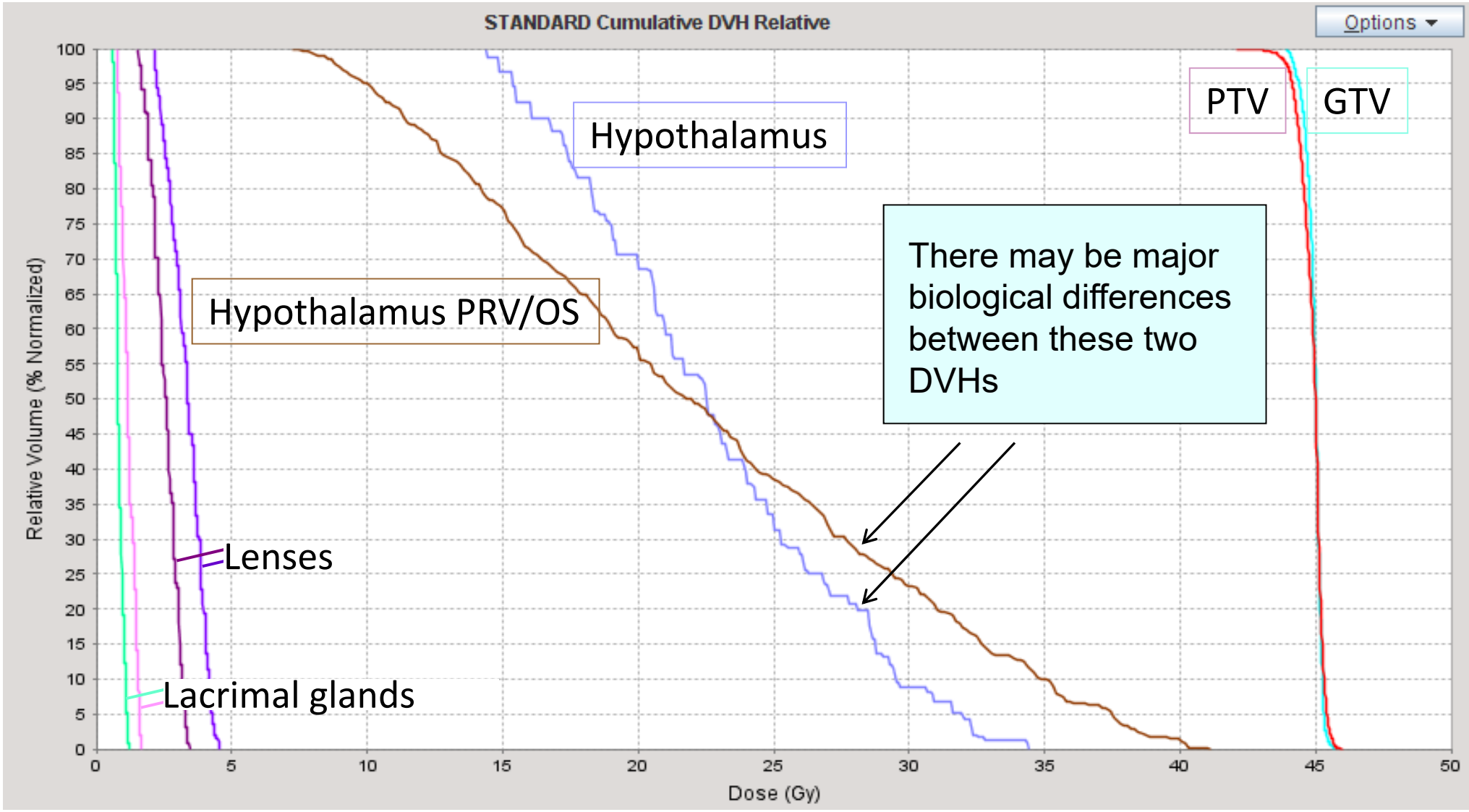
Hypothalamus DVHs



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

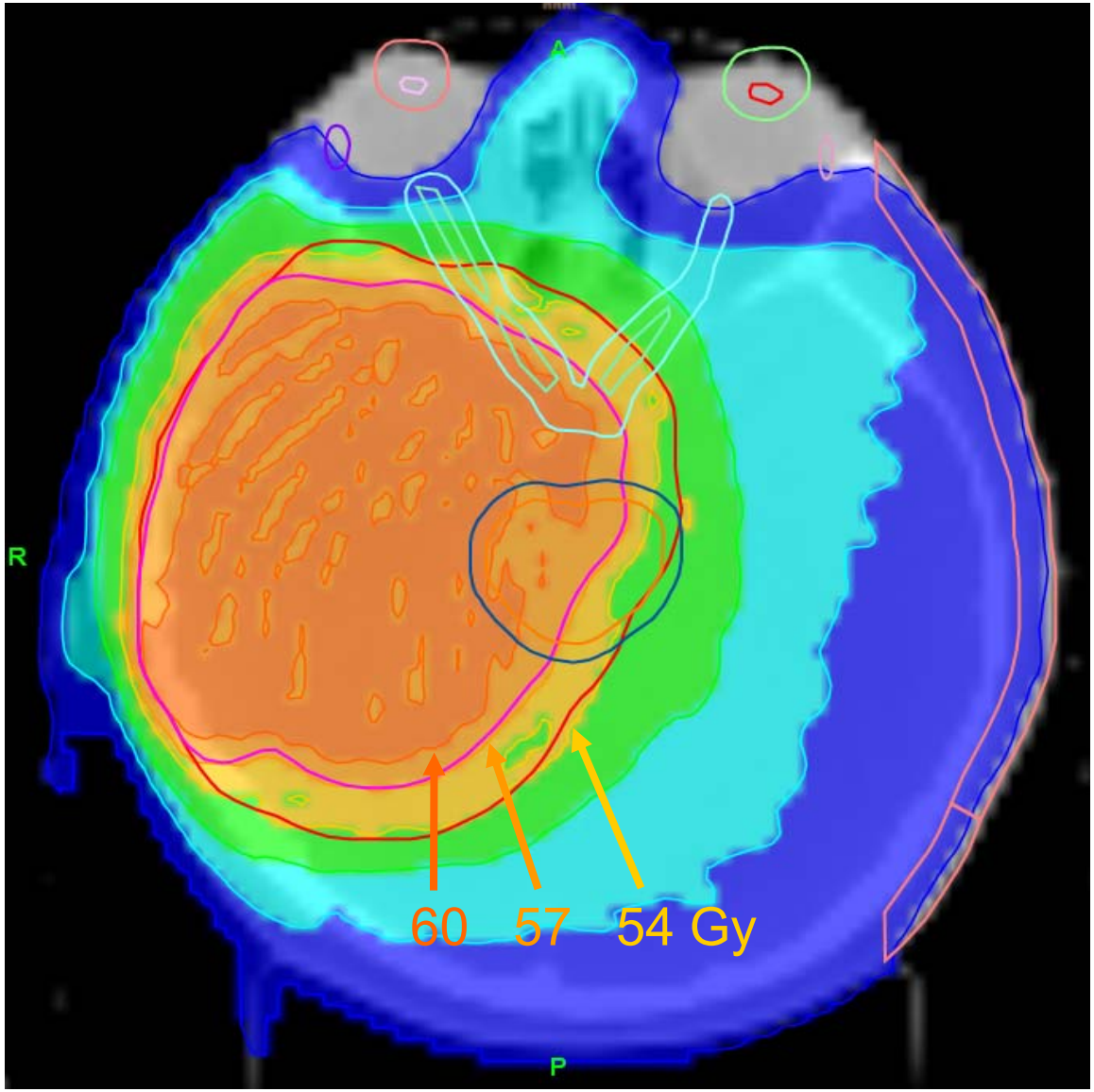
SP		ProSoma Comment	

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

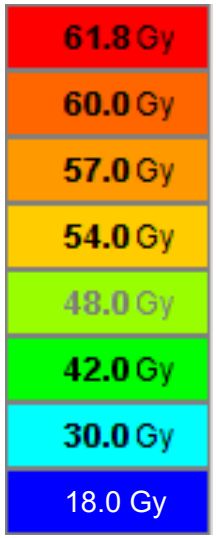
Use?	Organ	Objective (Gy)	Absolute (Gy)
☐	PRV Spinal Cord	48	50
☐	PRV Brainstem	50	52
☐	PRV –Optic Chiasm	50	54
☐	PRV Lt Optic Nerve	50	54
☐	PRV Rt Optic Nerve	50	54
☐	Hippocampus / Eloquent cortex (1cc)		
☐	Pituitary		
☐	Lt Globe	40	45
☐	Rt Globe	40	45
☐	Lt Lens	6	
☐	Rt Lens	6	
☐	Lt Cornea	30	
☐	Rt 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



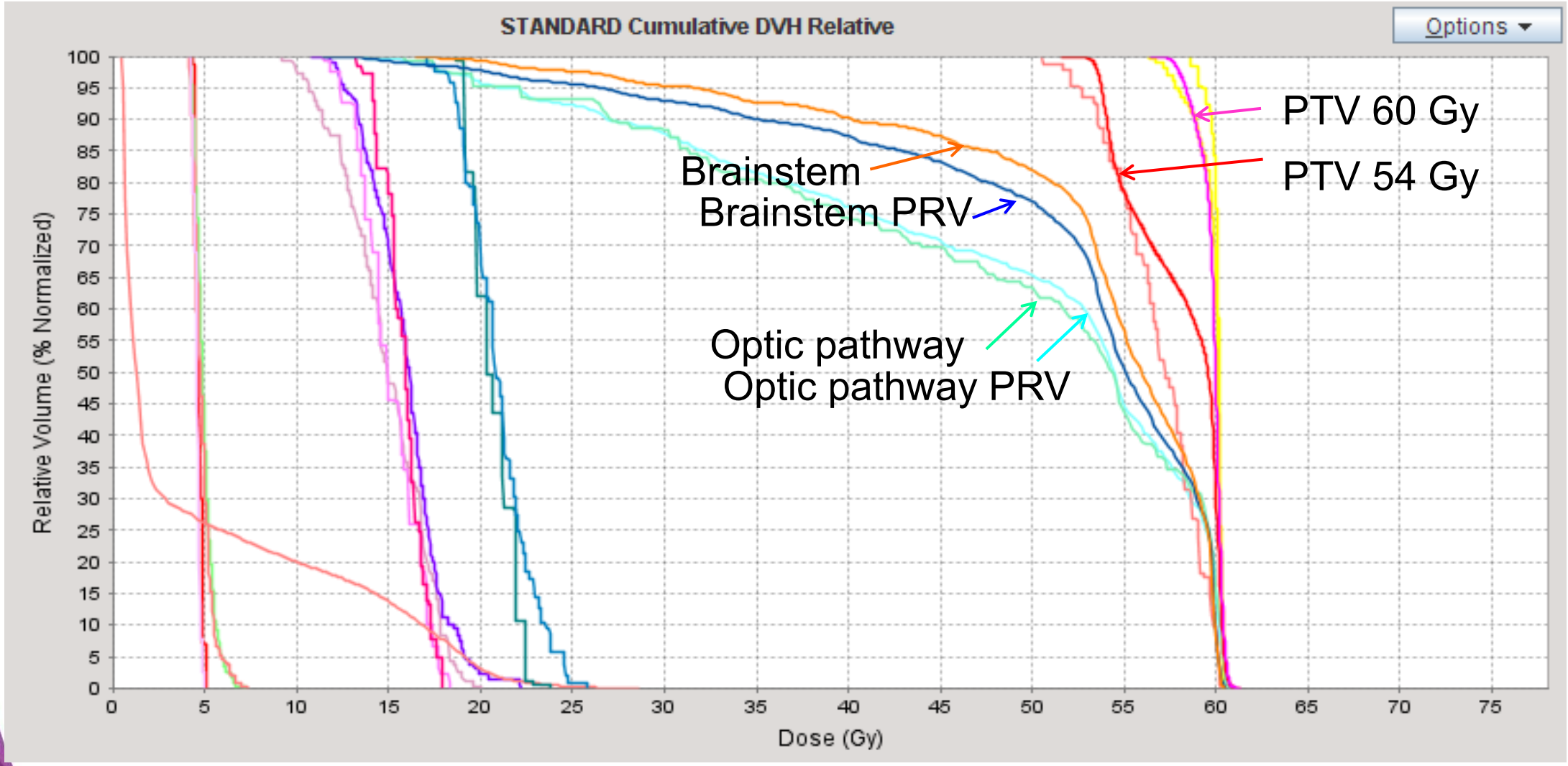
Glioblastoma

Dose - Gy



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

GBM - IMRT plan DVHs



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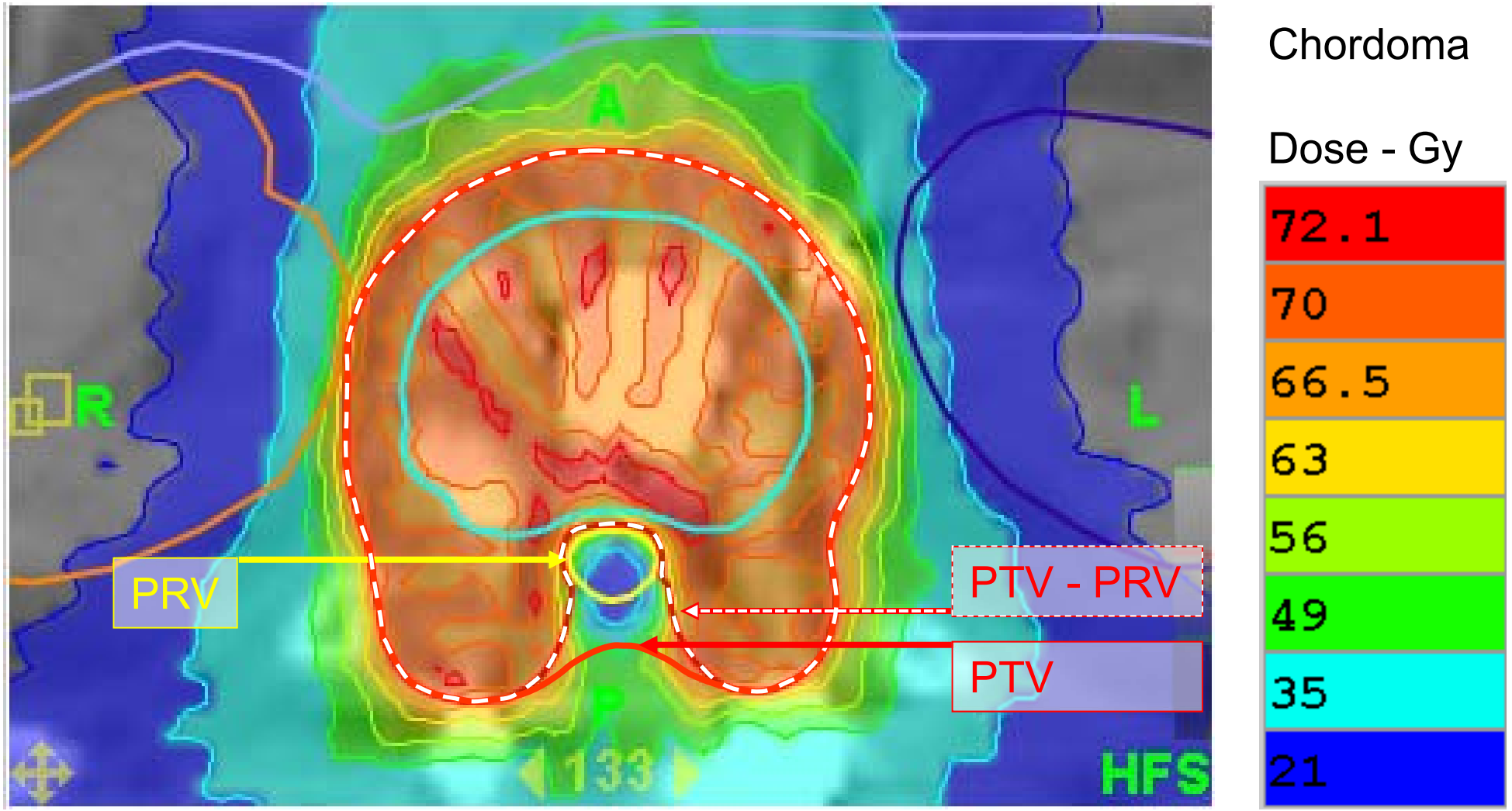
Constraints and Priorities



- 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

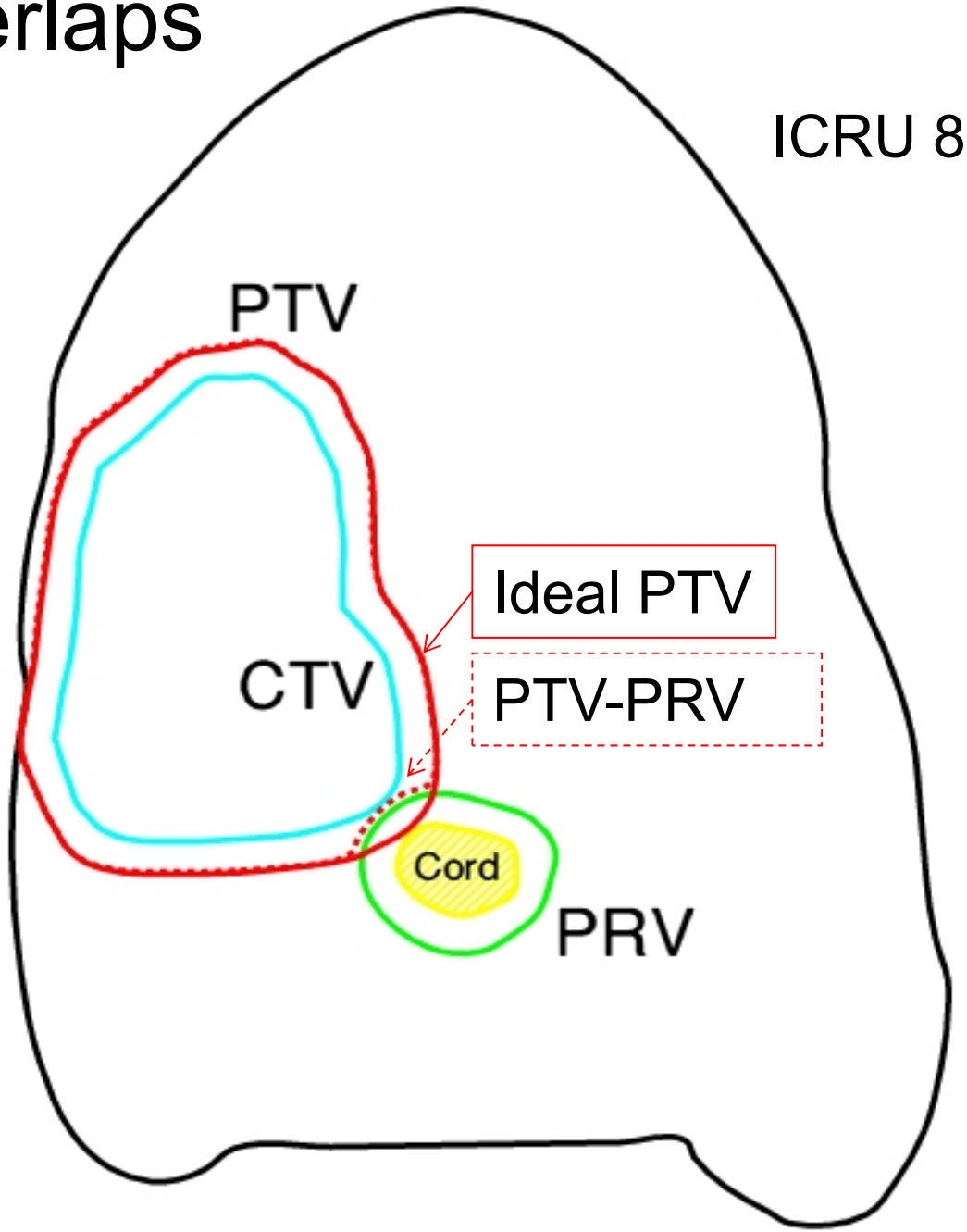
- There are always occasions when the PTV and OARs/PRVs overlap
- What is the best strategy?

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

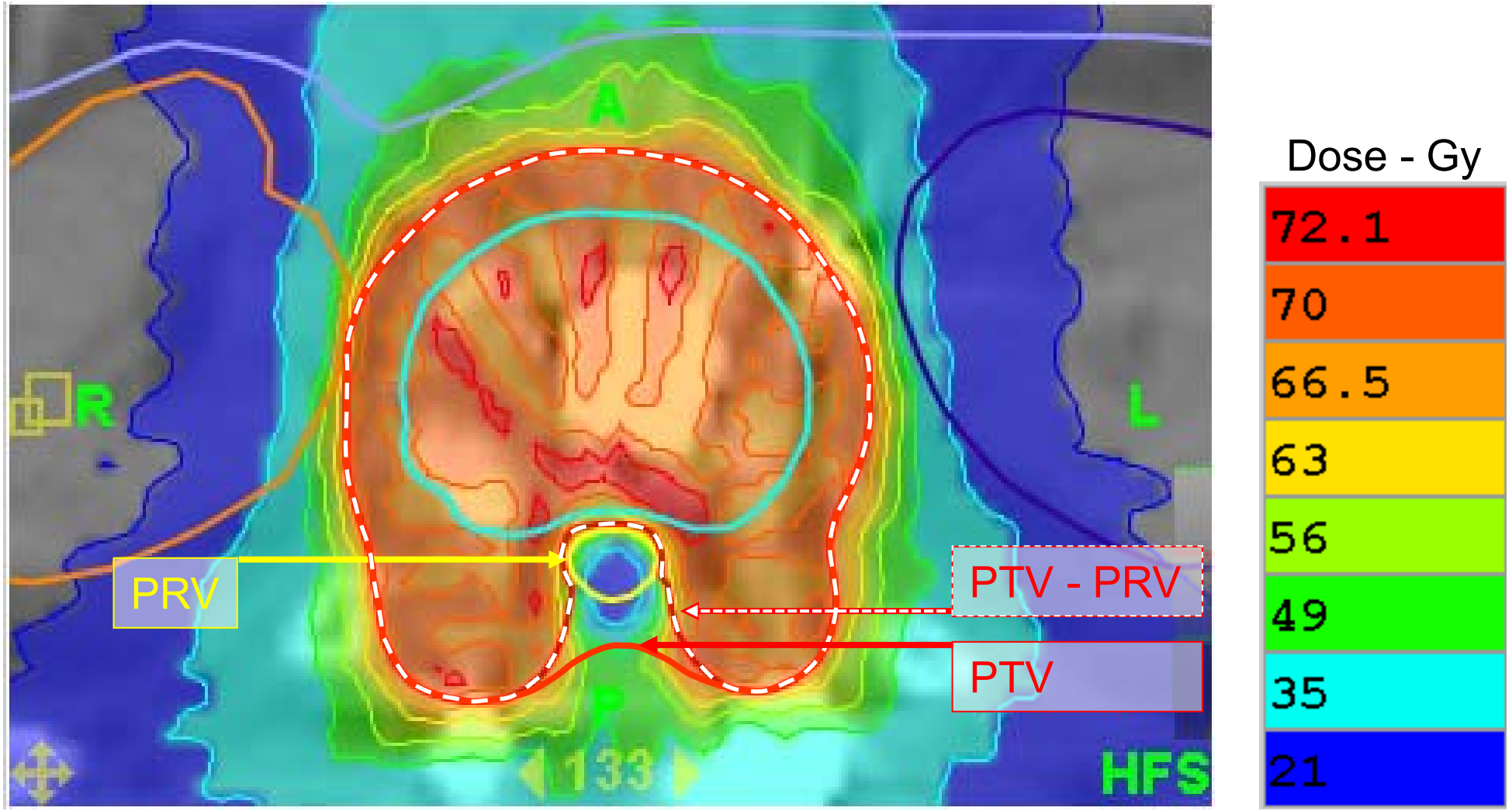
- ICRU 62 – edit PTV (even CTV) – fine for CRT
- ICRU 83 – ***do not*** edit – better for IMRT

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

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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 !

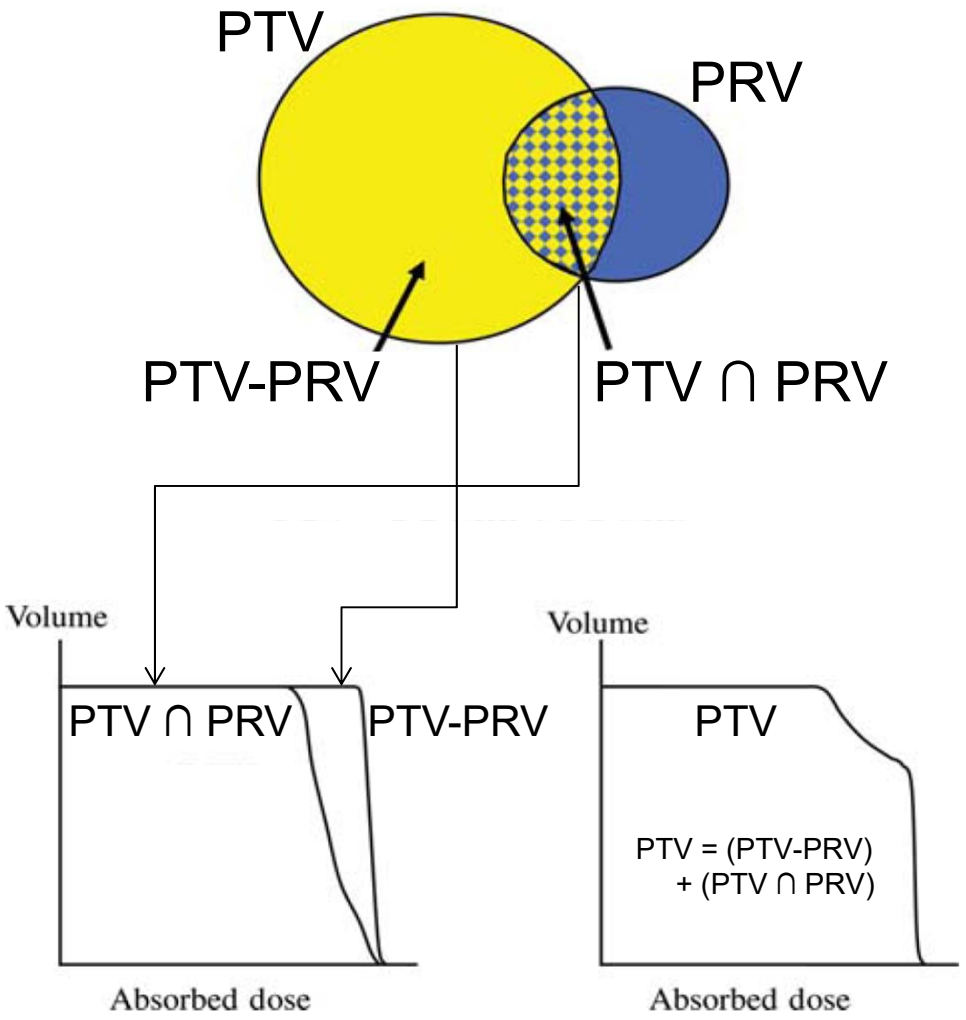
  - Use of optimiser to deliver different doses to different parts of the target

  - 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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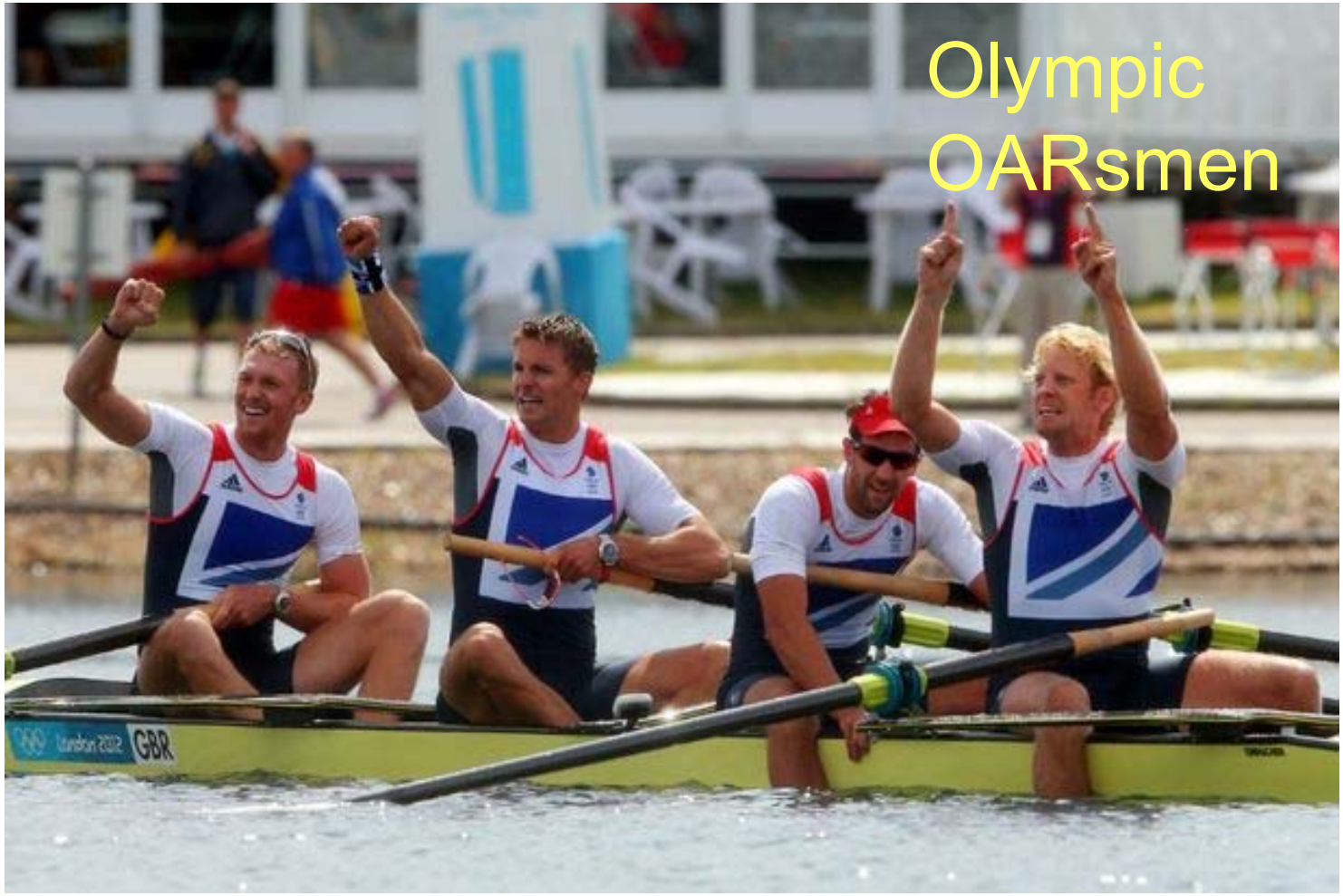
Take home messages

- 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

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

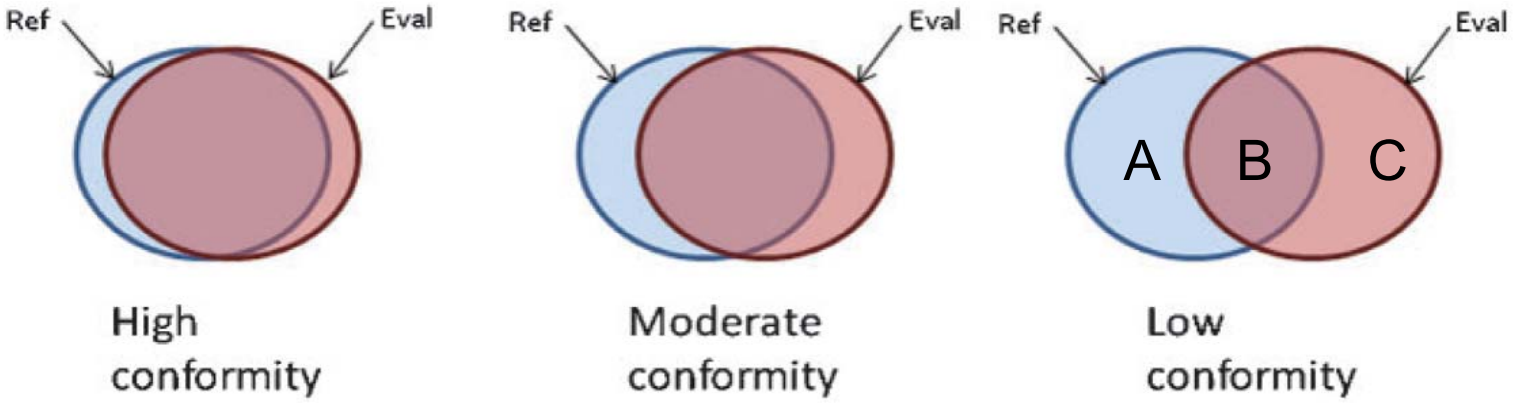
- Designed to show level of homogeneity

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

- 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

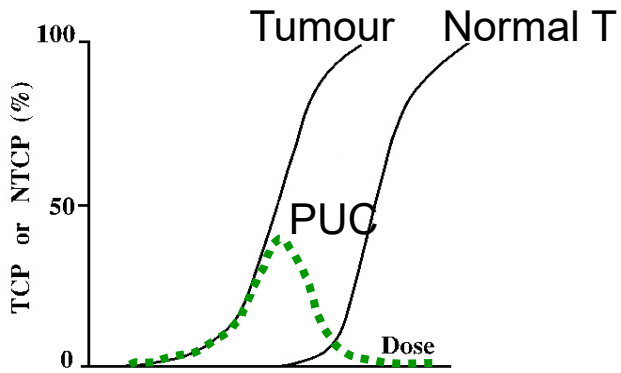
- For normal tissues ‘a’ is positive
  - Parallel - near 1
  - Serial – larger e.g. up to 20 for spinal cord

  - ‘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



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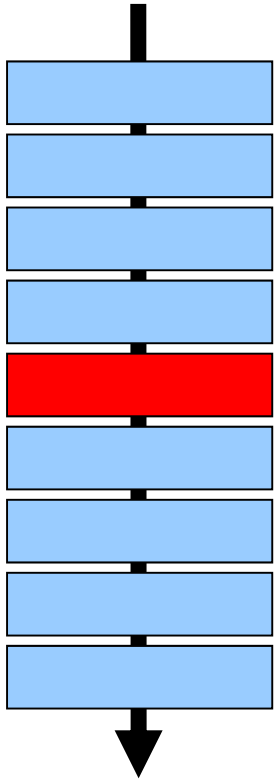
Extra slides

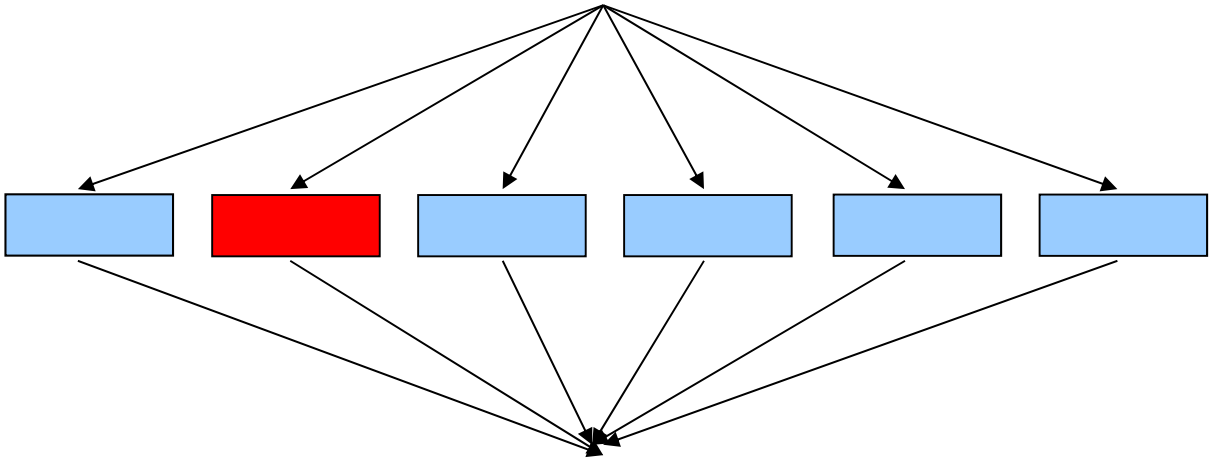
Tissue architecture

- 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

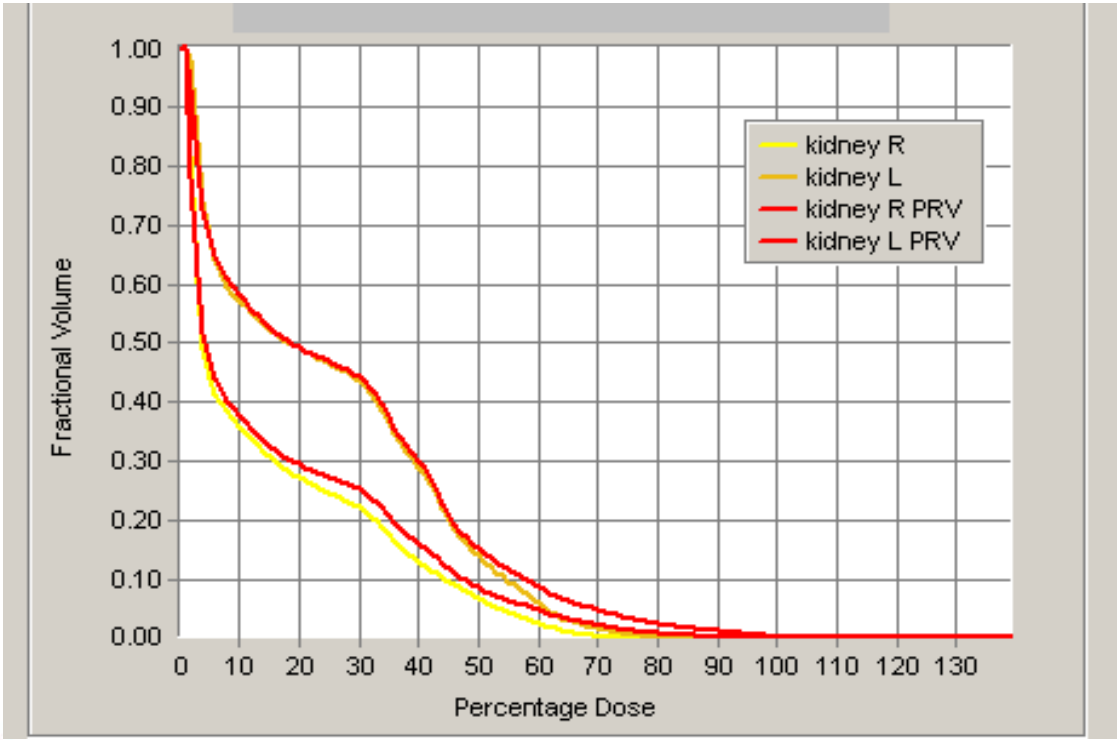
- Spinal cord & optic nerves/chiasm are perfect examples where a PRV may be helpful
  - serial tissue organisation
  - damage is clinically catastrophic
  - Add a PRV, especially if high doses are planned

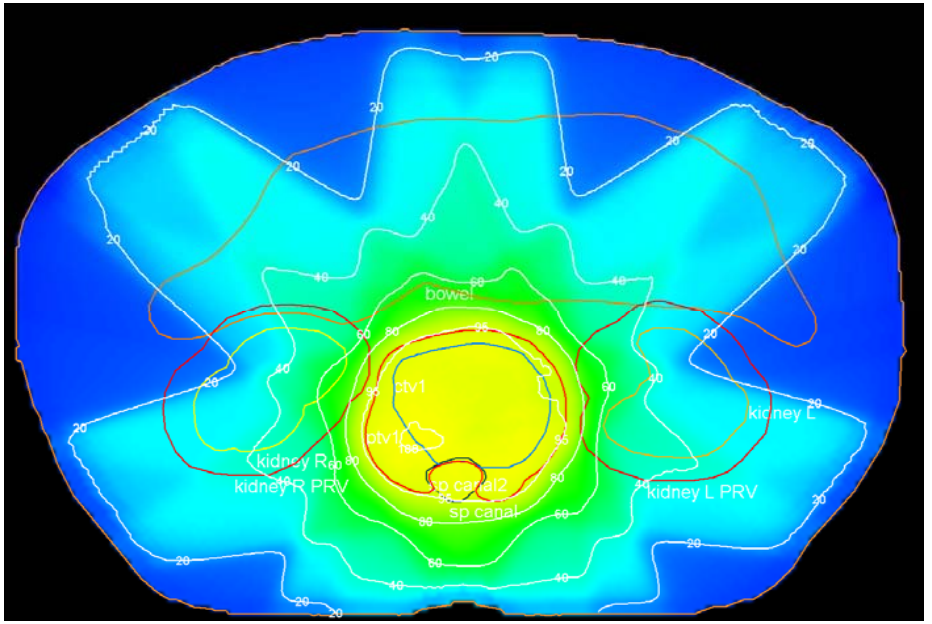
- Almost no other OARs where a PRV is needed
- PRV may be misleading for parallel organs

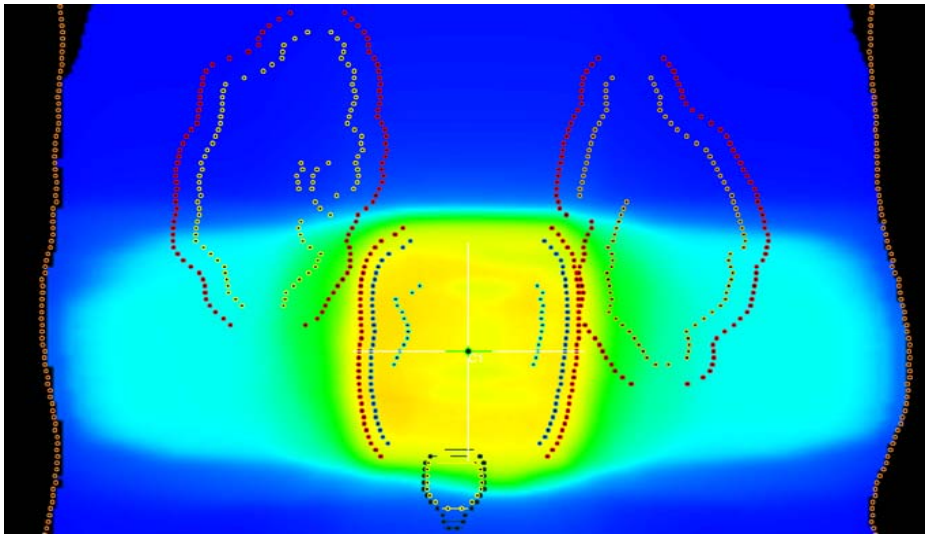
- Question of PRV for mixed parallel-serial structures

Target volumes – PRV

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

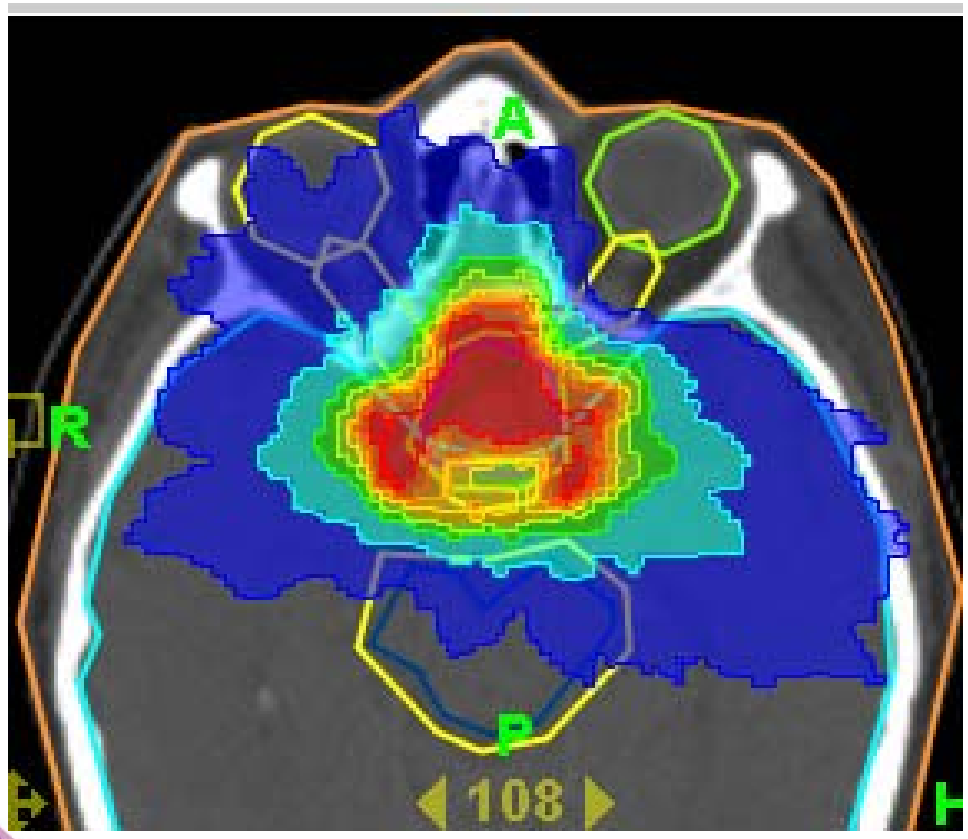


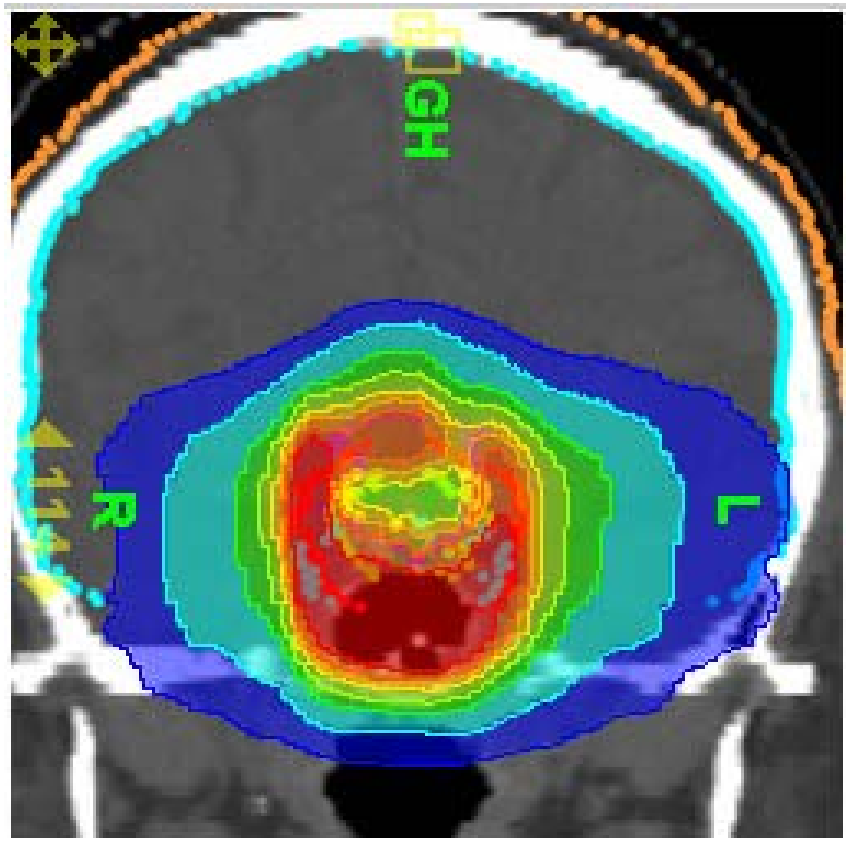




Target volumes – PRV

- 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
3-7 September 2017 – Barcelona, Spain

Markus Stock

MedAustron

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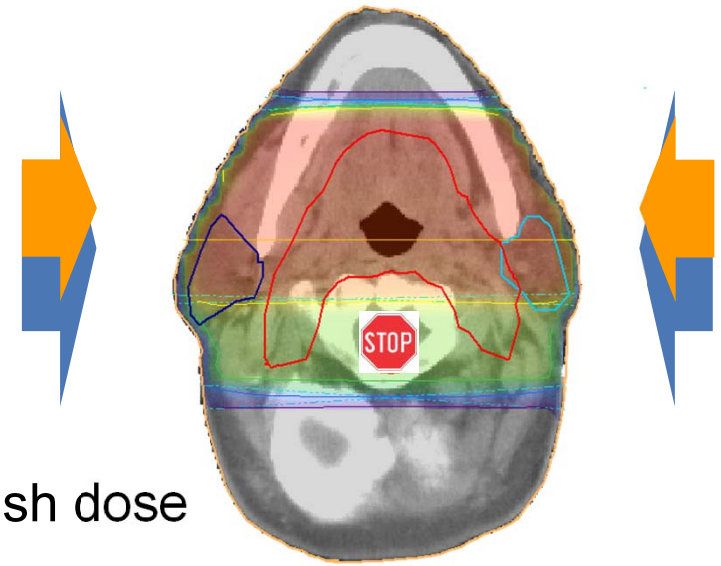
Content

- 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*

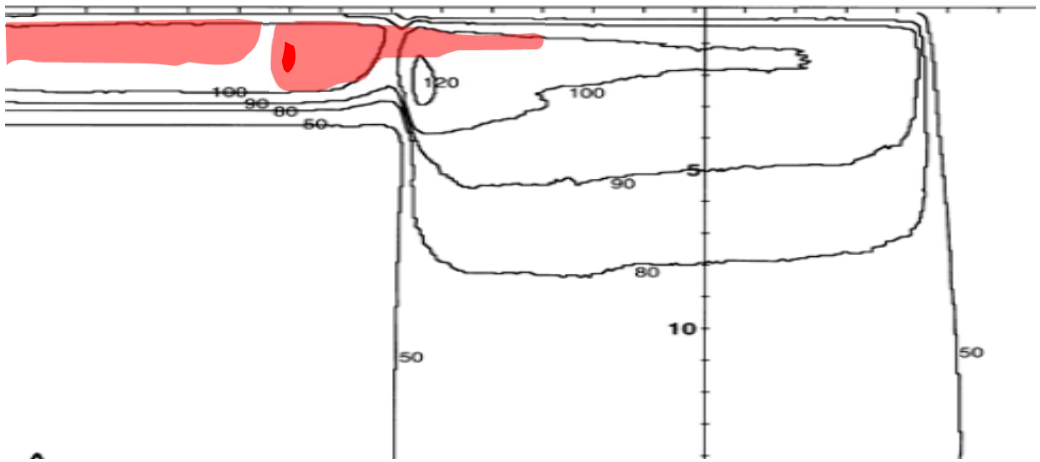
Courtesy Marika Enmark

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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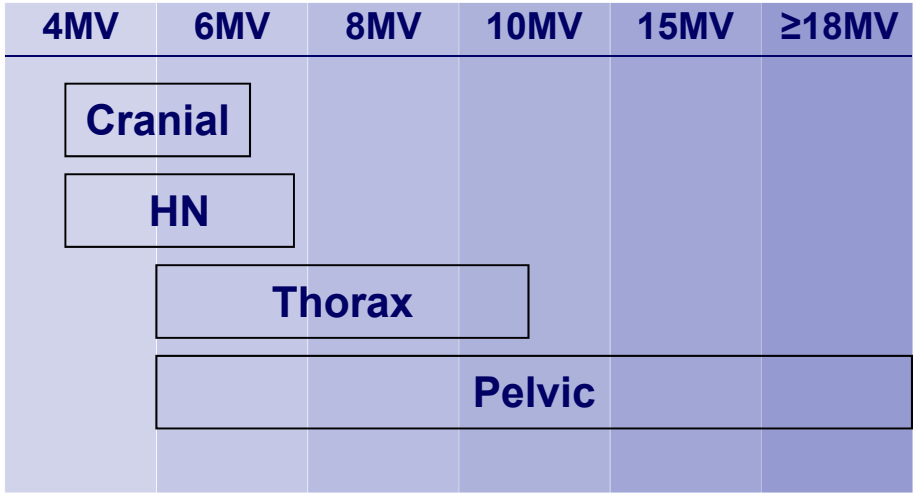
Choice of optimal beam energy

Aspects

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



Higher energy in low density regions

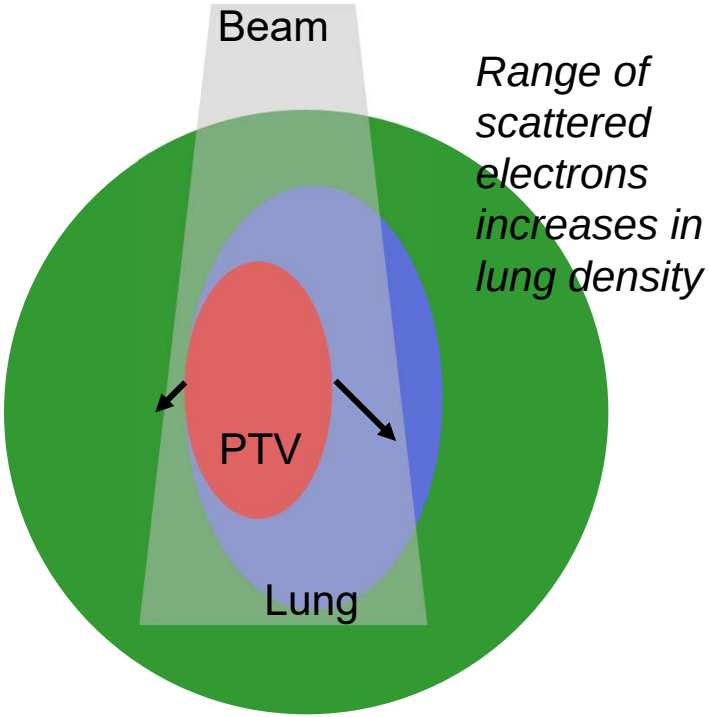
- higher energies means larger penumbra due to increase in lateral electron transport (≥10MV)
- sufficiently accurate planning calculation algorithms are required for decisions on optimal beam energy

Choice of optimal beam energy in the thorax region

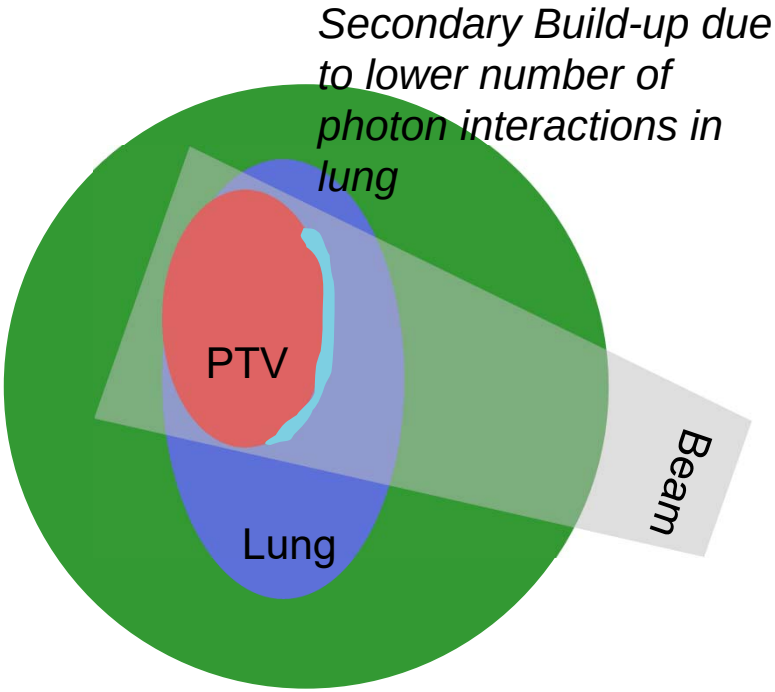
- Low energy beam is preferable
  - tighter margins, sharp dose gradient
  - no significant difference between 6 and 18MV treatment plan (# beams!)
- High energy may be used
  - central tumor location or consolidated lung

Interface effects

- Broadening penumbra in low density area



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



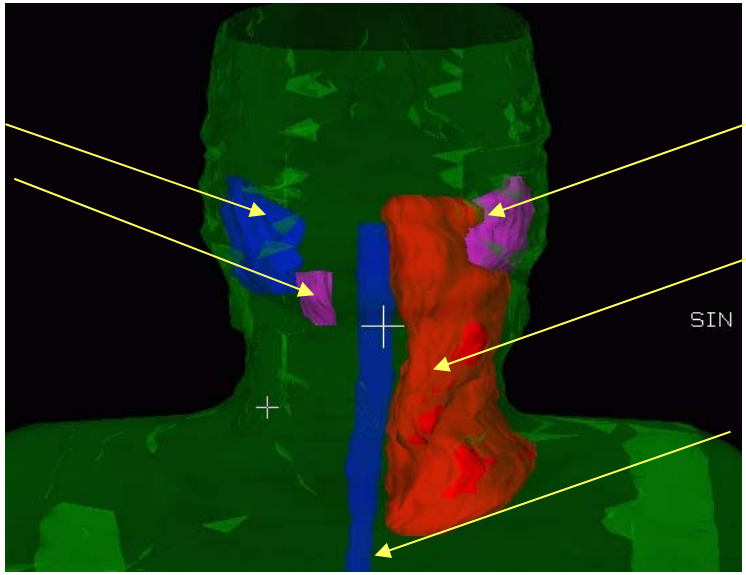
Head & Neck 3D

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



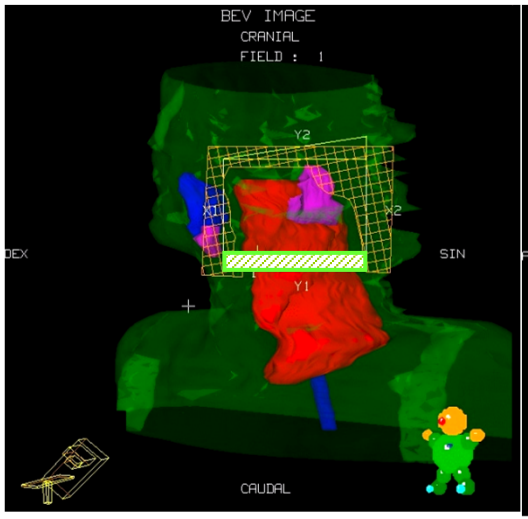
left parotid gland

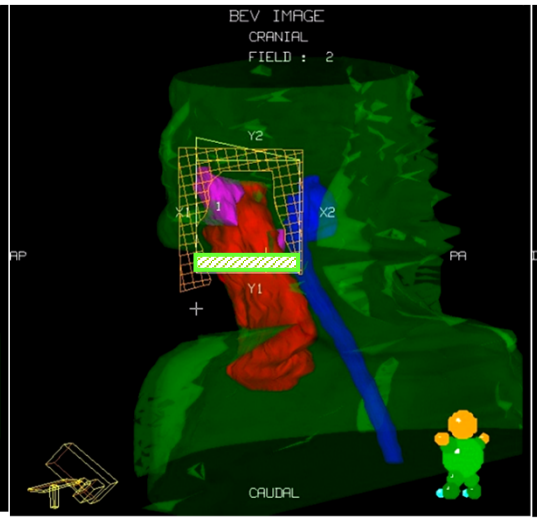
PTV 0-46 Gy

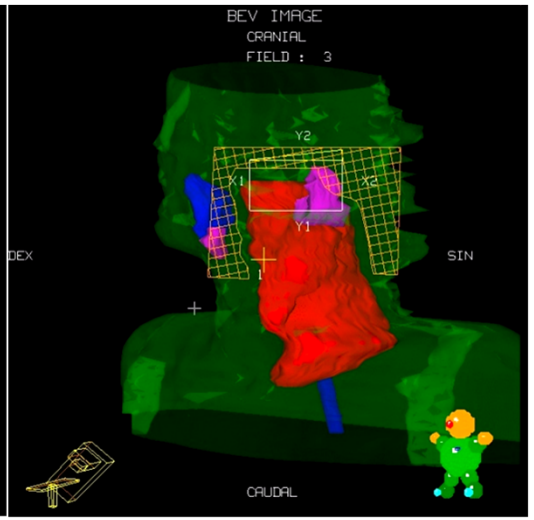
spinal cord

‘simple’ 3D CRT plan

Head and neck: Tonsillar fossa Ca.

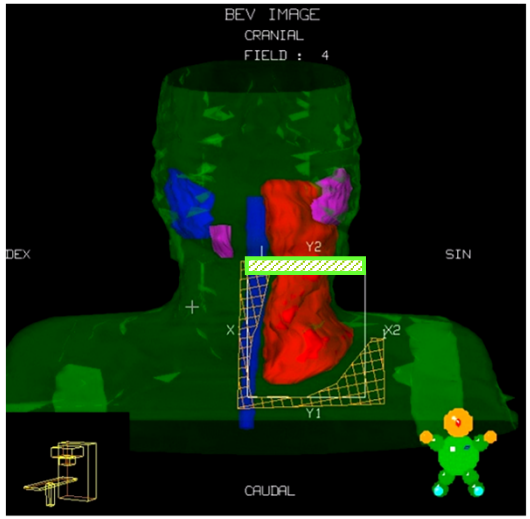


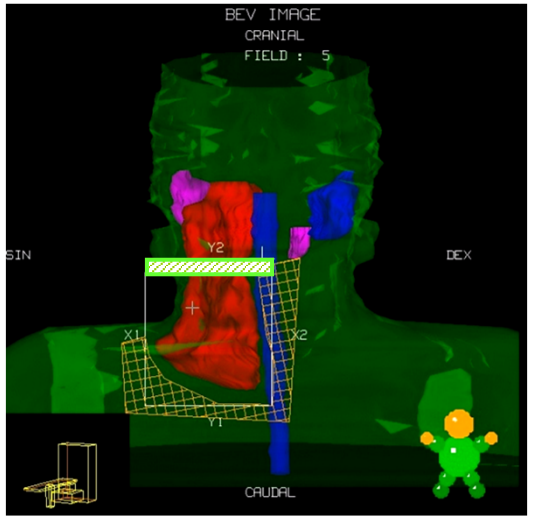




5 fields:
3 cranial fields
2 caudal fields
sliding junction

} *





* total: 9 fields

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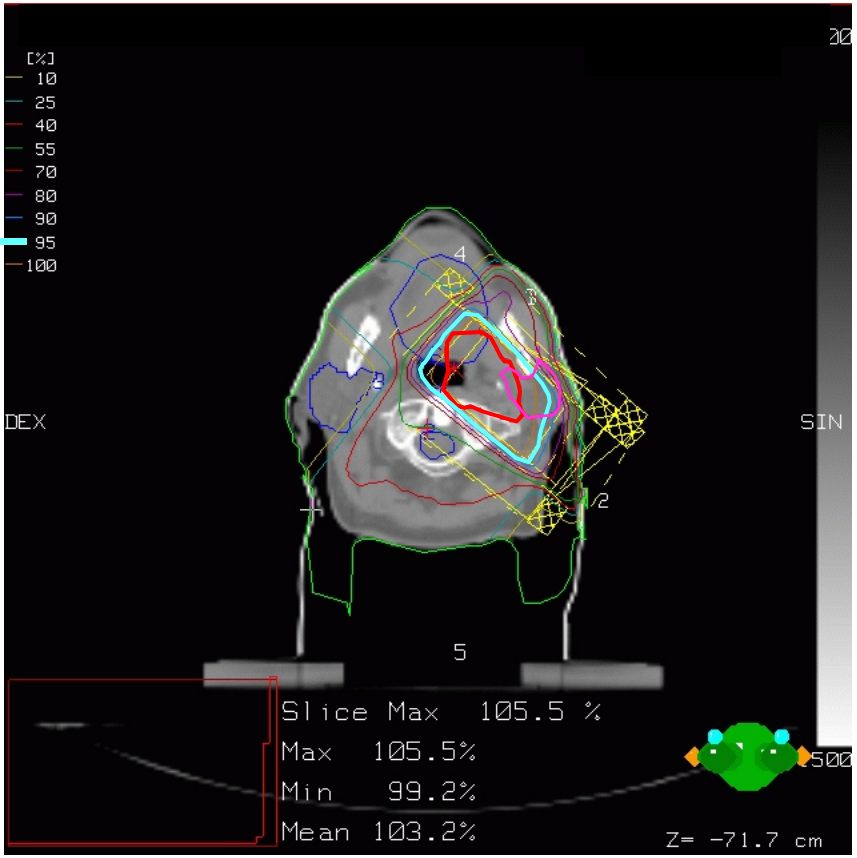
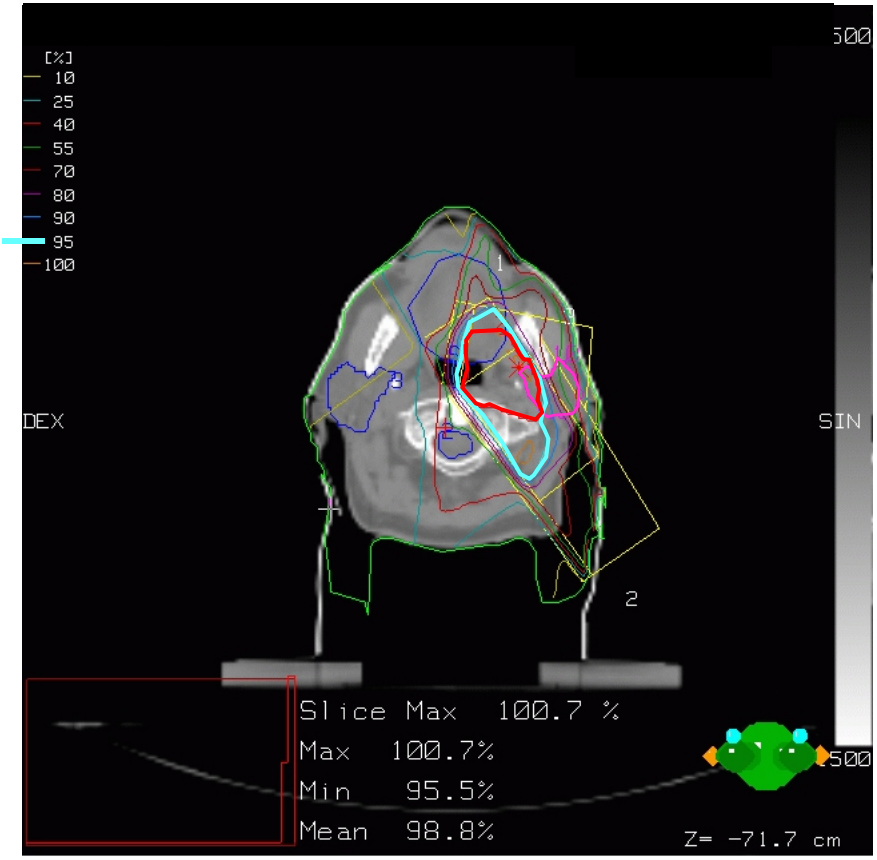
Head and neck: Tonsillar fossa Ca.

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.

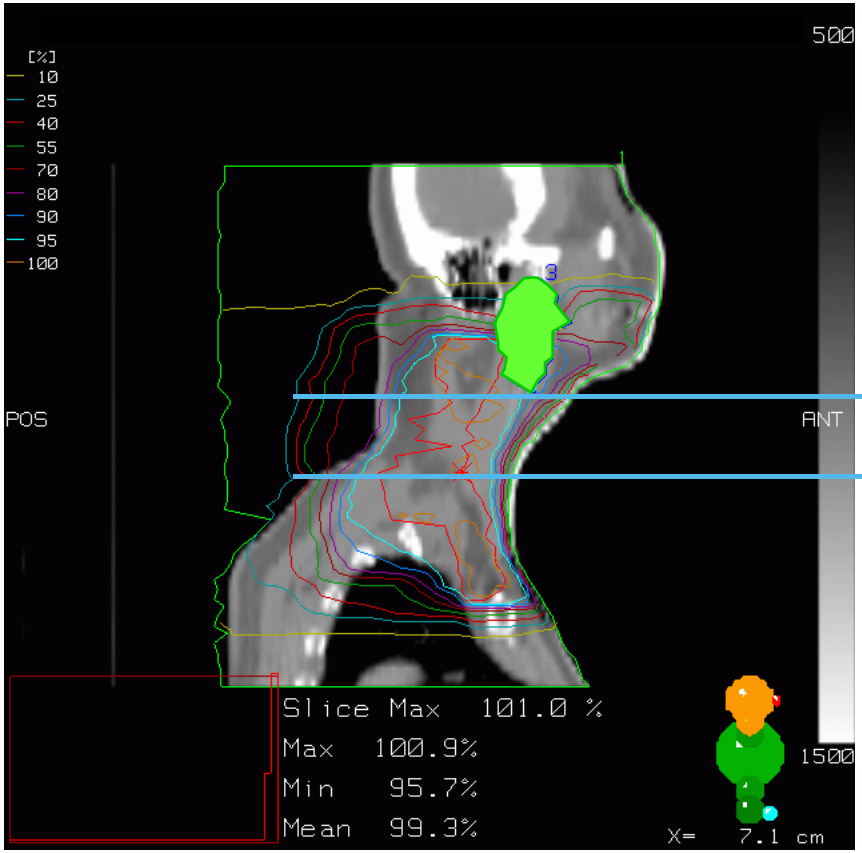
do we <u>really</u> need IMRT for this case?

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

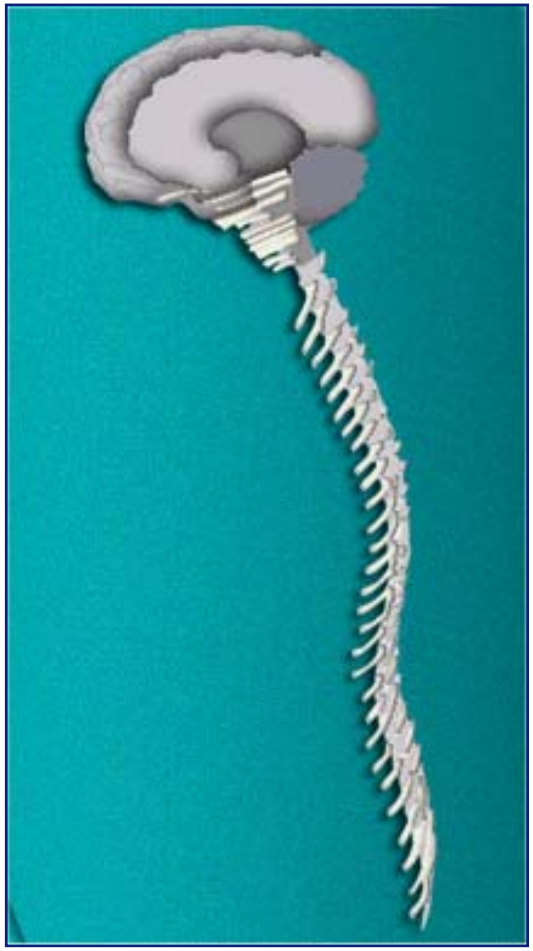
mean dose parotid 27 Gy

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

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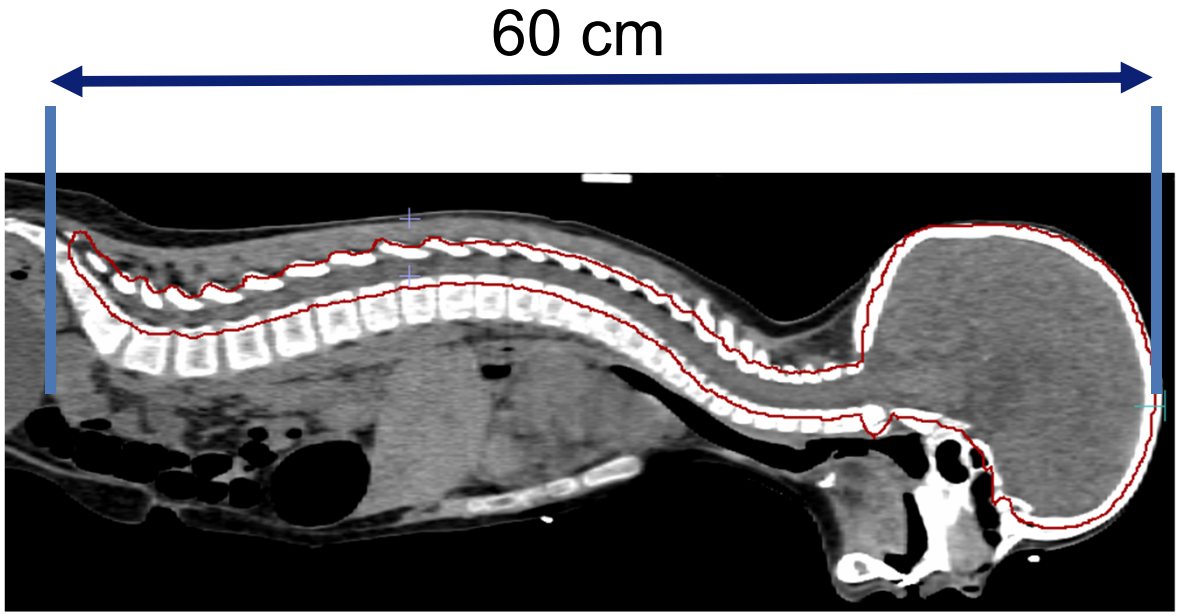
Cranio-spinal lesions

- 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?



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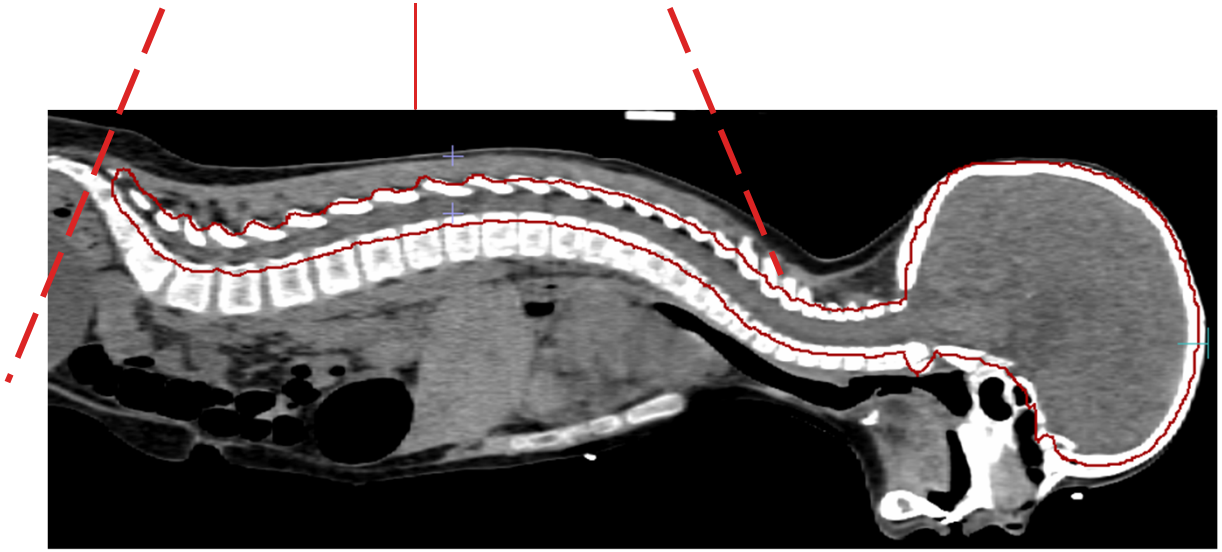
Cranio-spinal lesions

Challenges spinal field:

maximum field size:

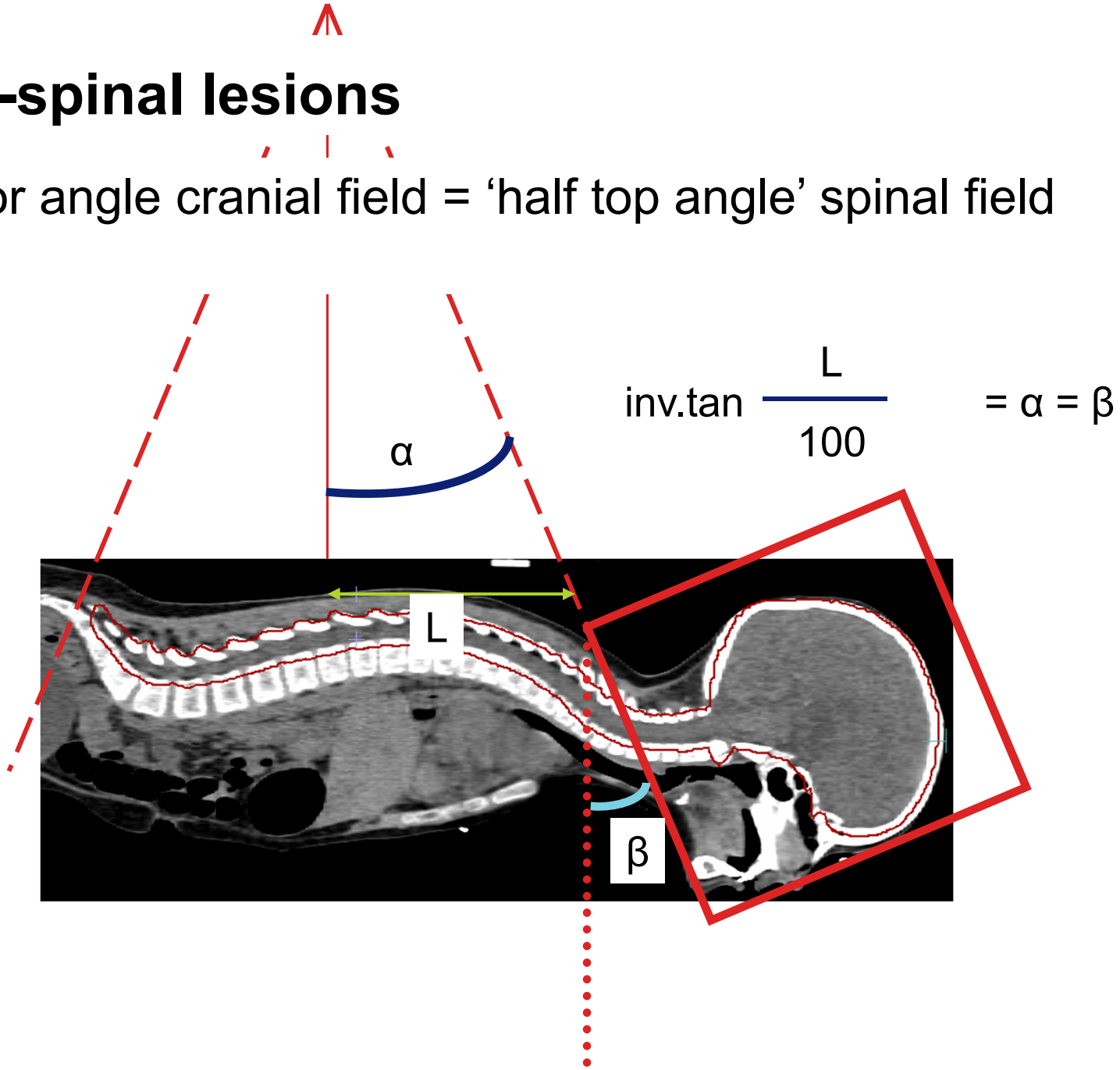
40 cm at focus isocenter distance 100 cm

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



Cranio-spinal lesions

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

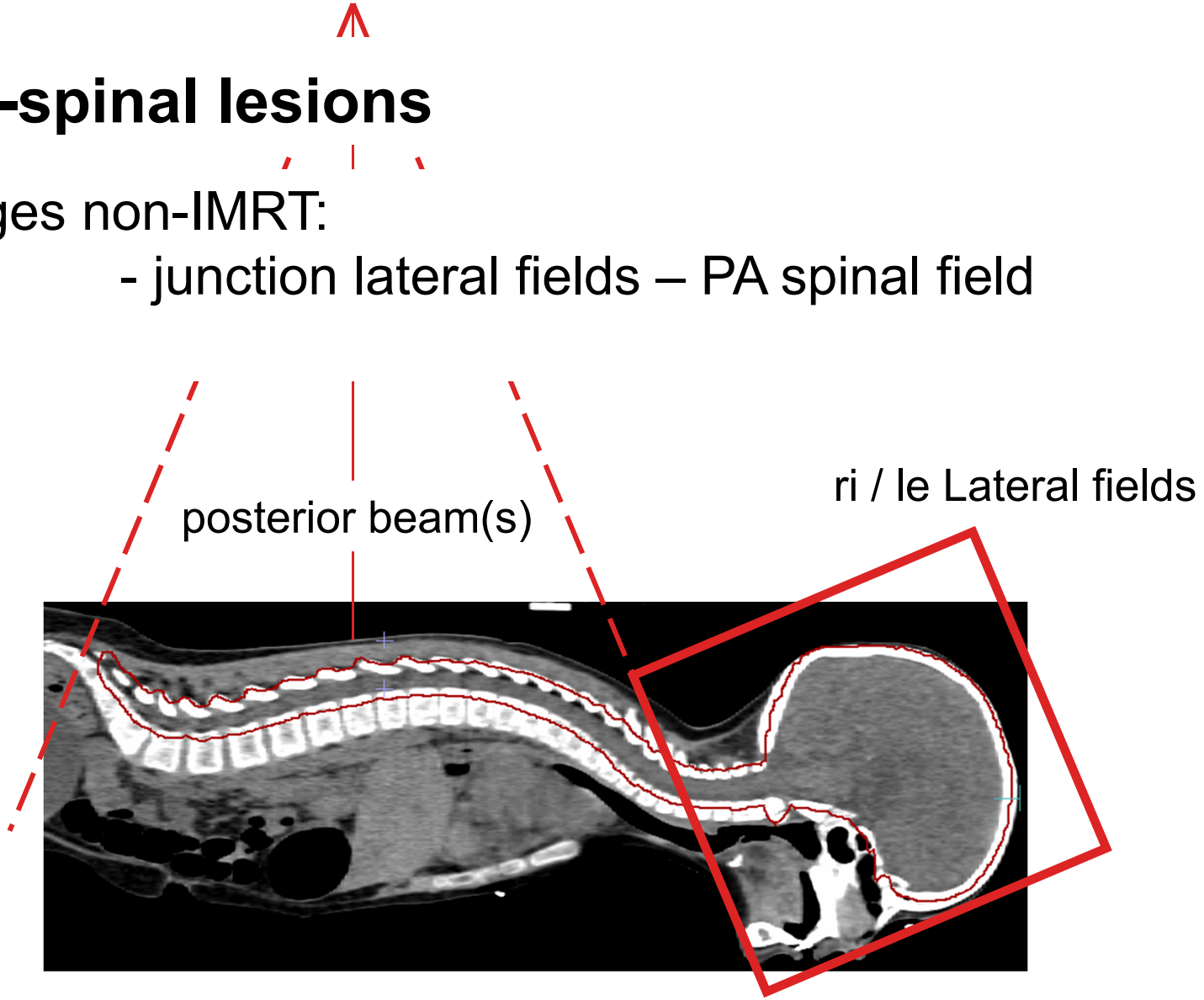


$$\text{inv.tan}\ \frac{L}{100} = \alpha = \beta$$

Cranio-spinal lesions

Challenges non-IMRT:

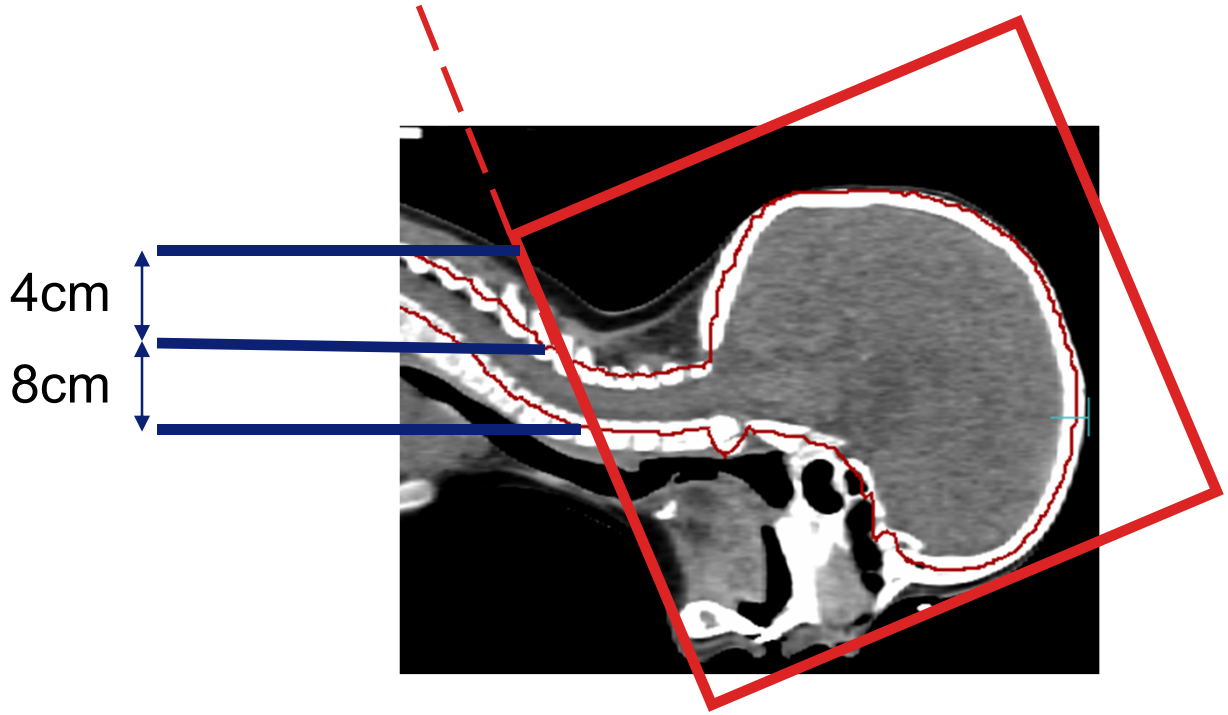
- junction lateral fields – PA spinal field



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?

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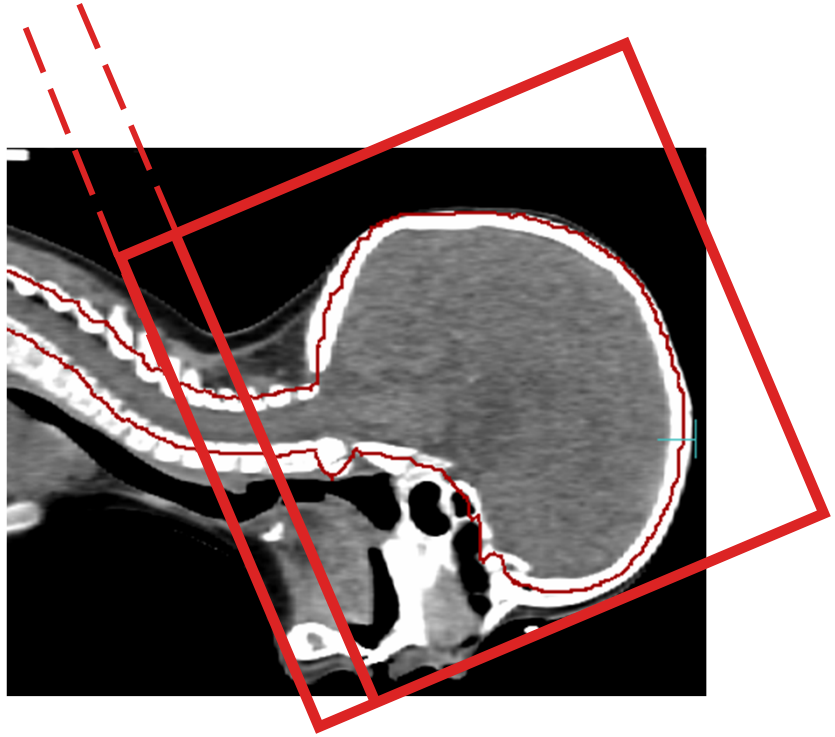
Cranio-spinal lesions: cranial fields

Challenges non-IMRT:

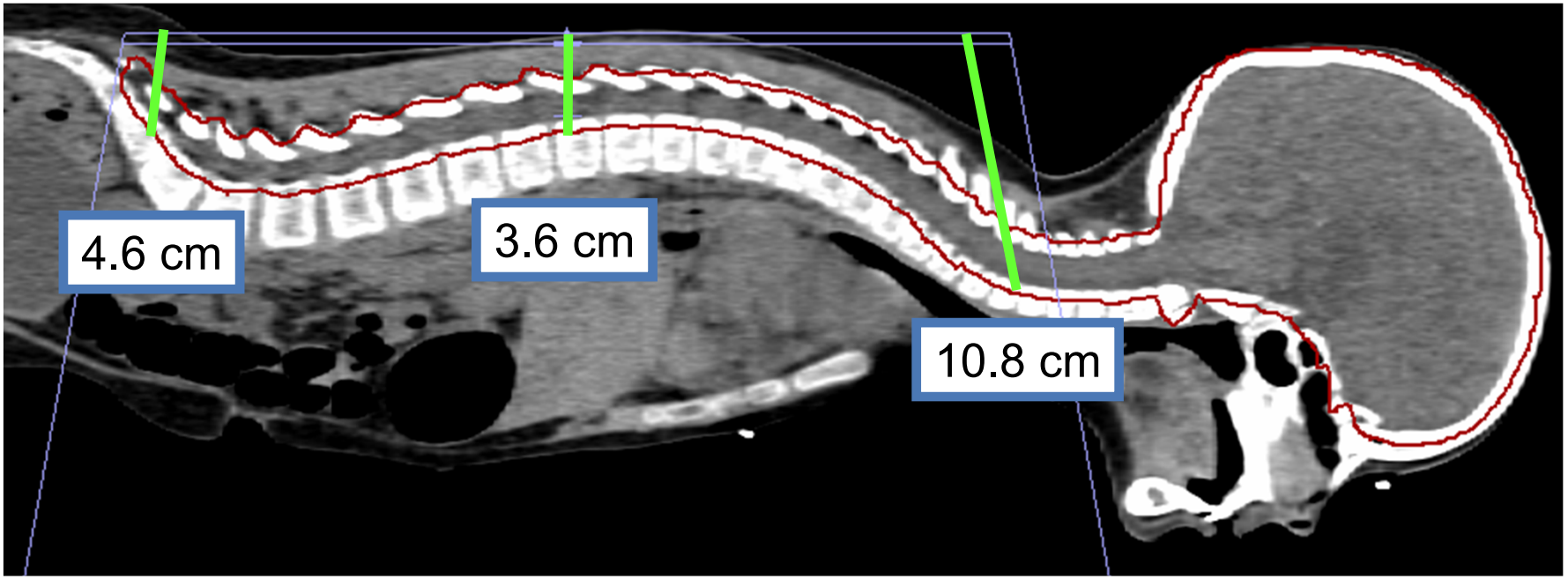
- junction lateral fields – PA spinal field
  better dose-distribution in junction, broader penumbra
  → sliding junction



Cranio-spinal lesions: spinal field

Challenges Non-IMRT:

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

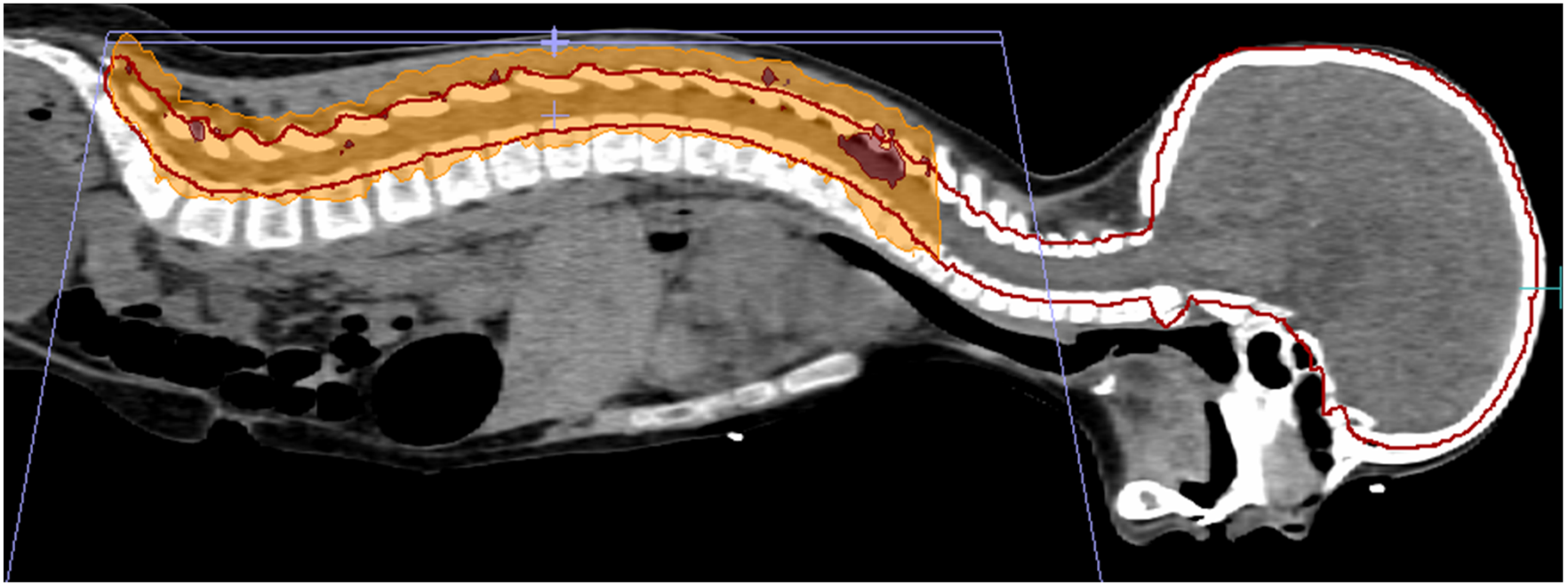


prescribing dose at mean depth, or additional sub-fields needed
multiple energy fields

Cranio-spinal lesions: need for IMRT??

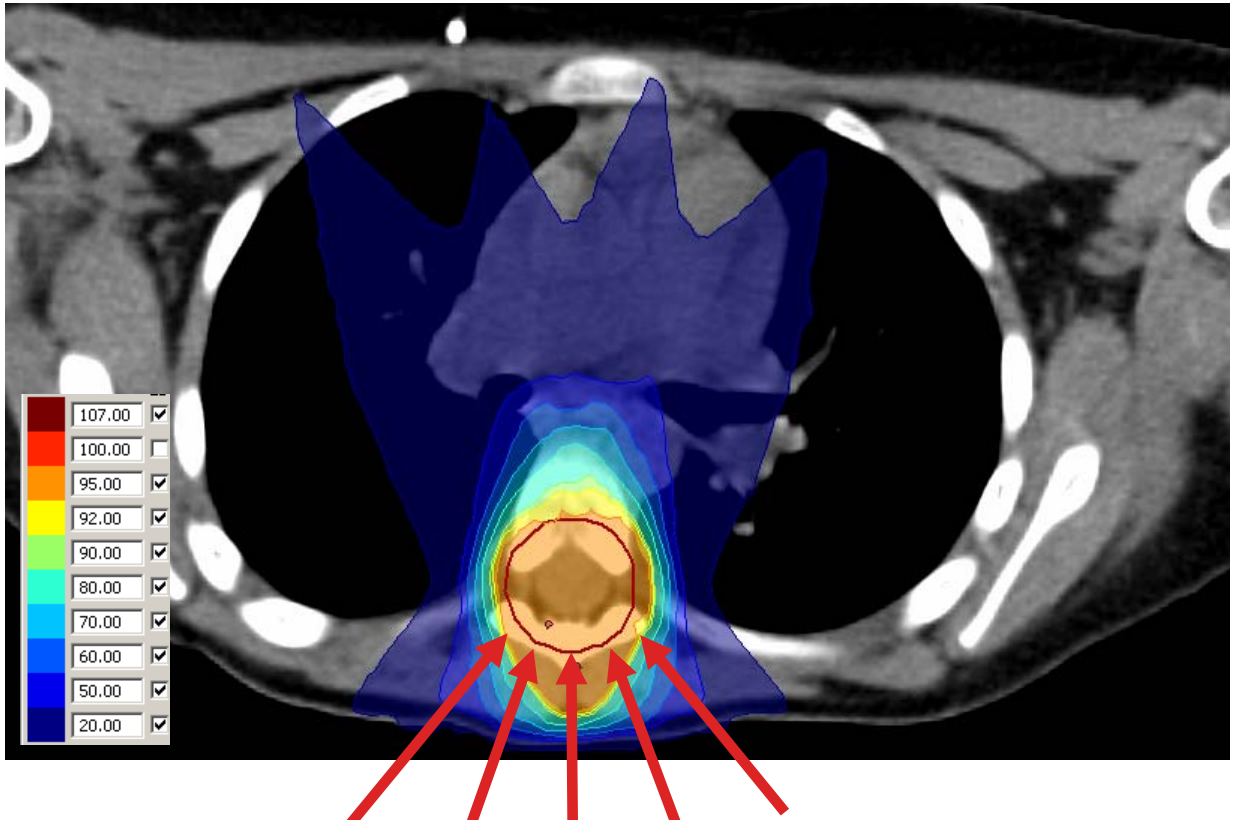
IMRT planning:

- 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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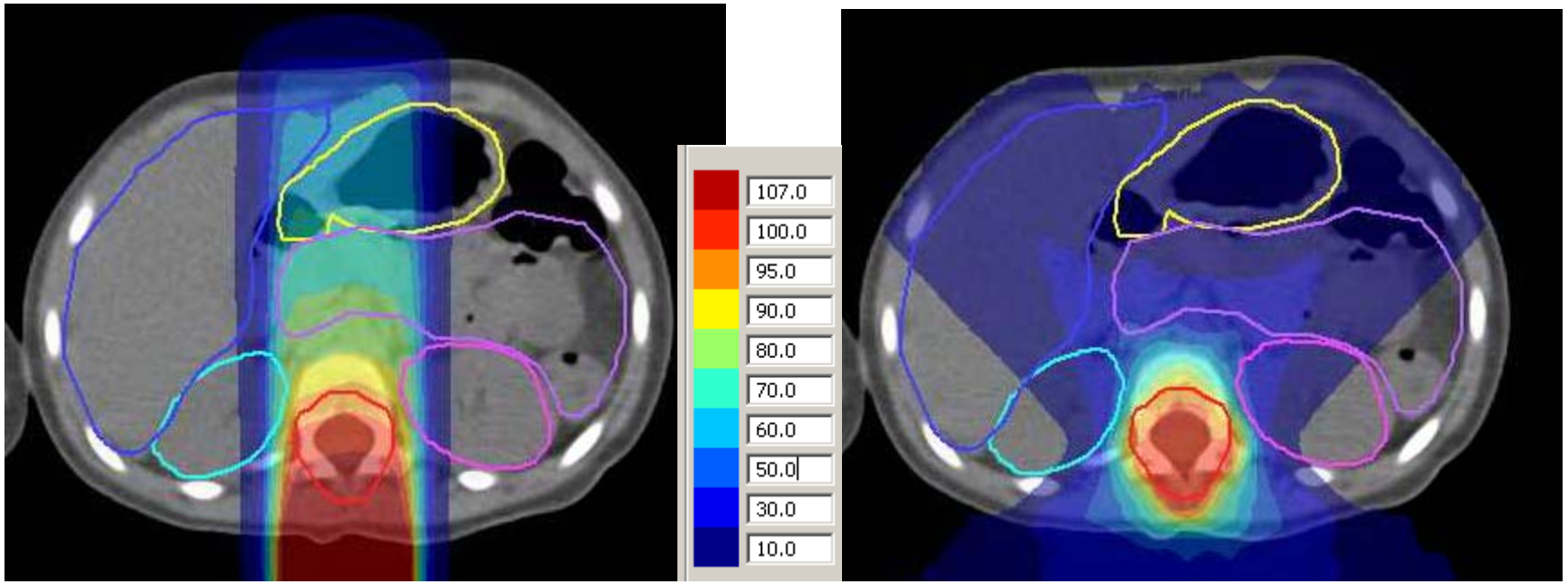
Cranio-spinal lesions: 3D-CRT vs IMRT

‘simple’ 3D-CRT

5 field IMRT / 3D-CRT



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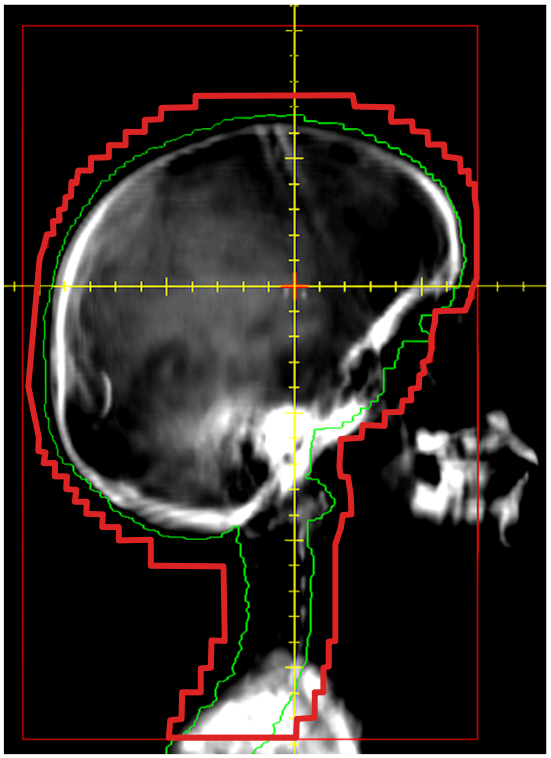
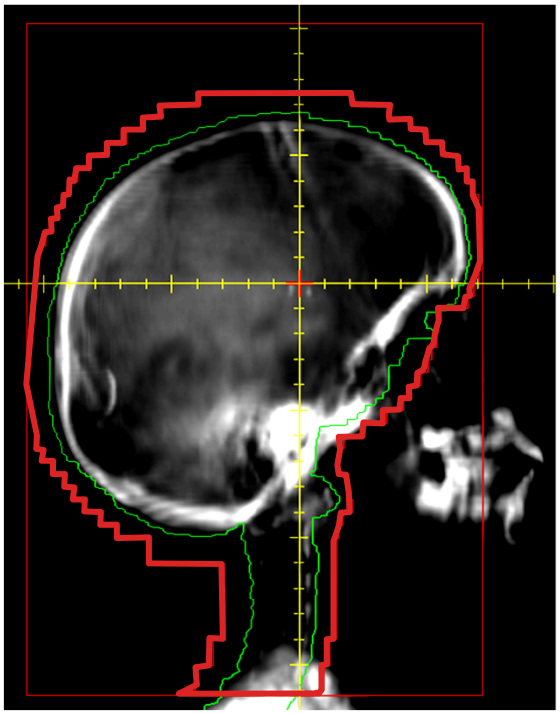
Cranio-spinal lesions: junction with lateral cranial beams

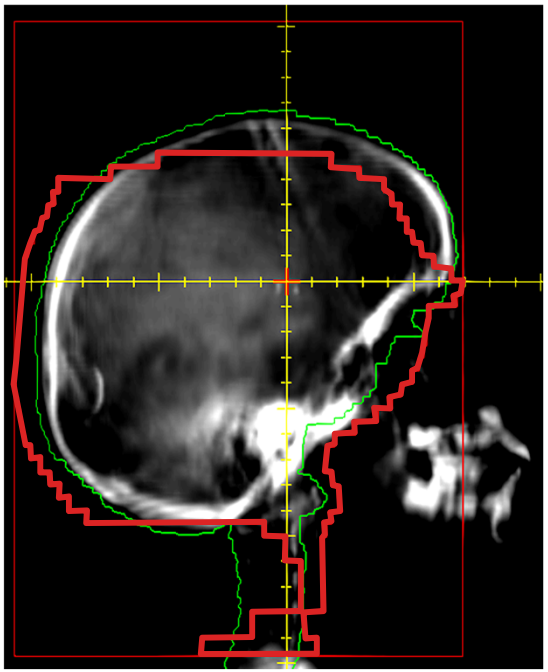
3D-CRT cranial plan with a broad caudal penumbra



ri lat: 1a

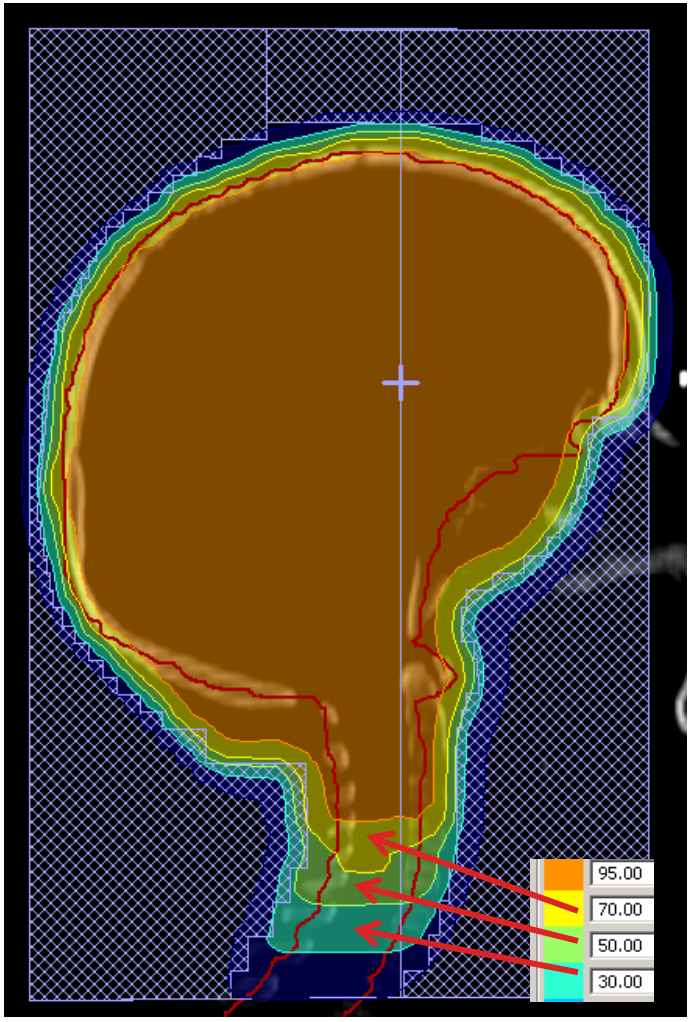


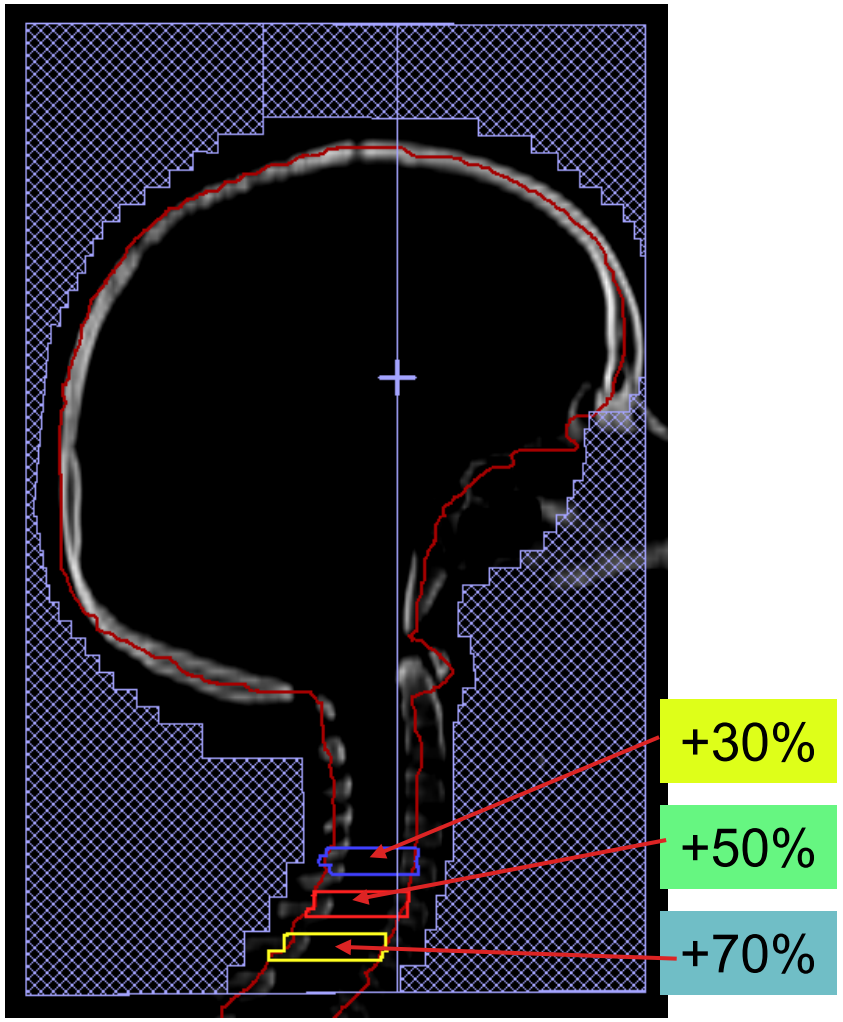
ri lat: 1b



ri lat: 1c

Cranio-spinal lesions: junction with lateral cranial beams





'dose modulation volumes'

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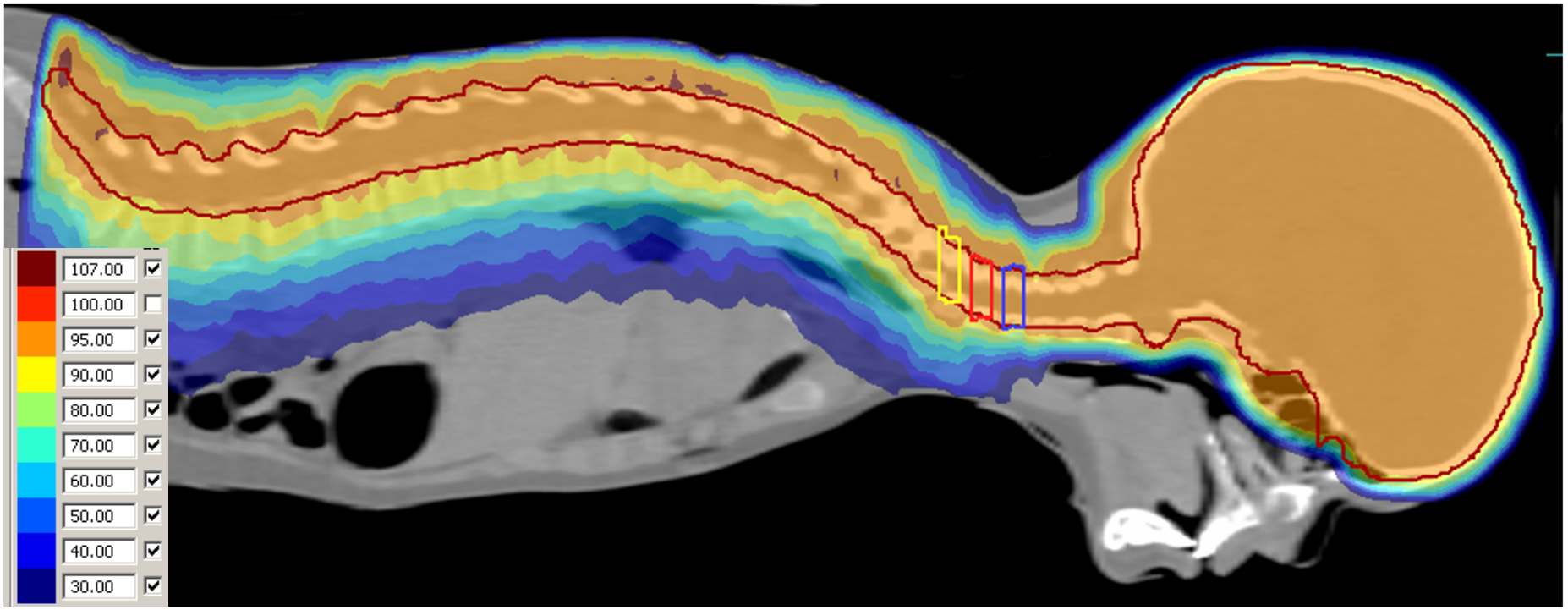
Cranio-spinal lesions: 3D-CRT solution

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



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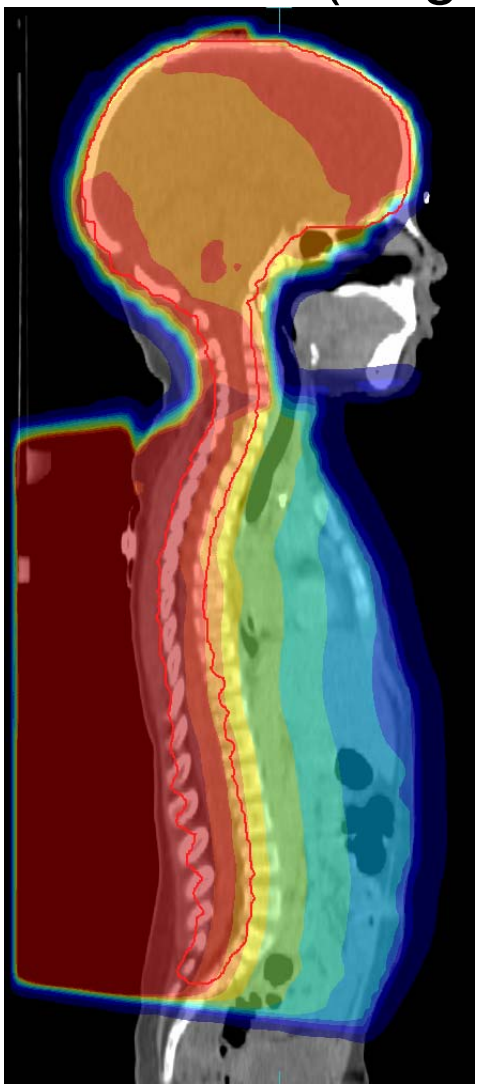
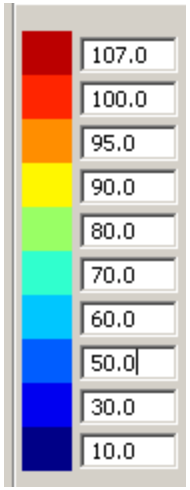
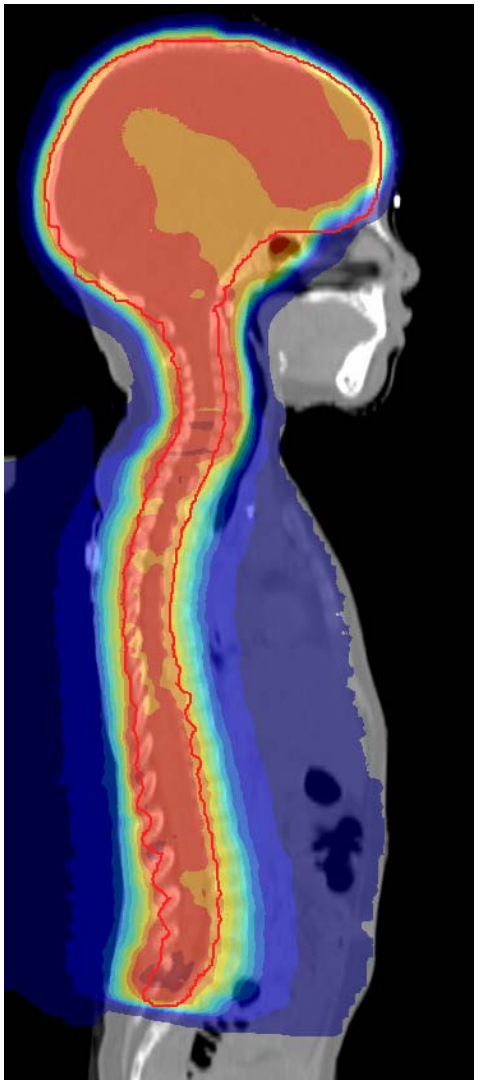
Cranio-spinal lesions: 3D-CRT old vs new

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

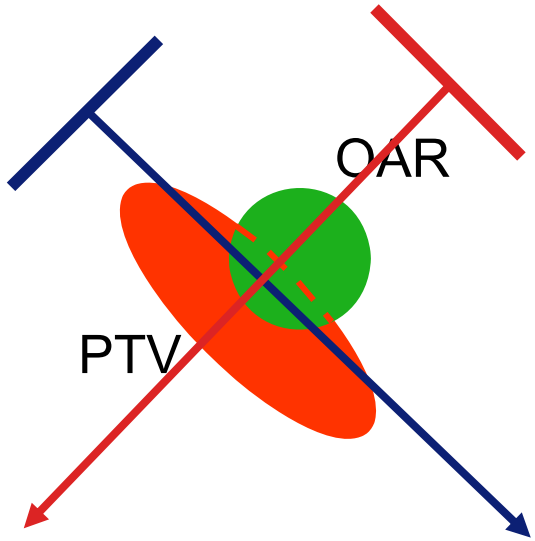
  - isocenter position outside the high dose region often results in a more complicated plan

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

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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JOURNAL OF THE EUROPEAN SOCIETY FOR THERAPEUTIC RADIOLOGY AND ONCOLOGY

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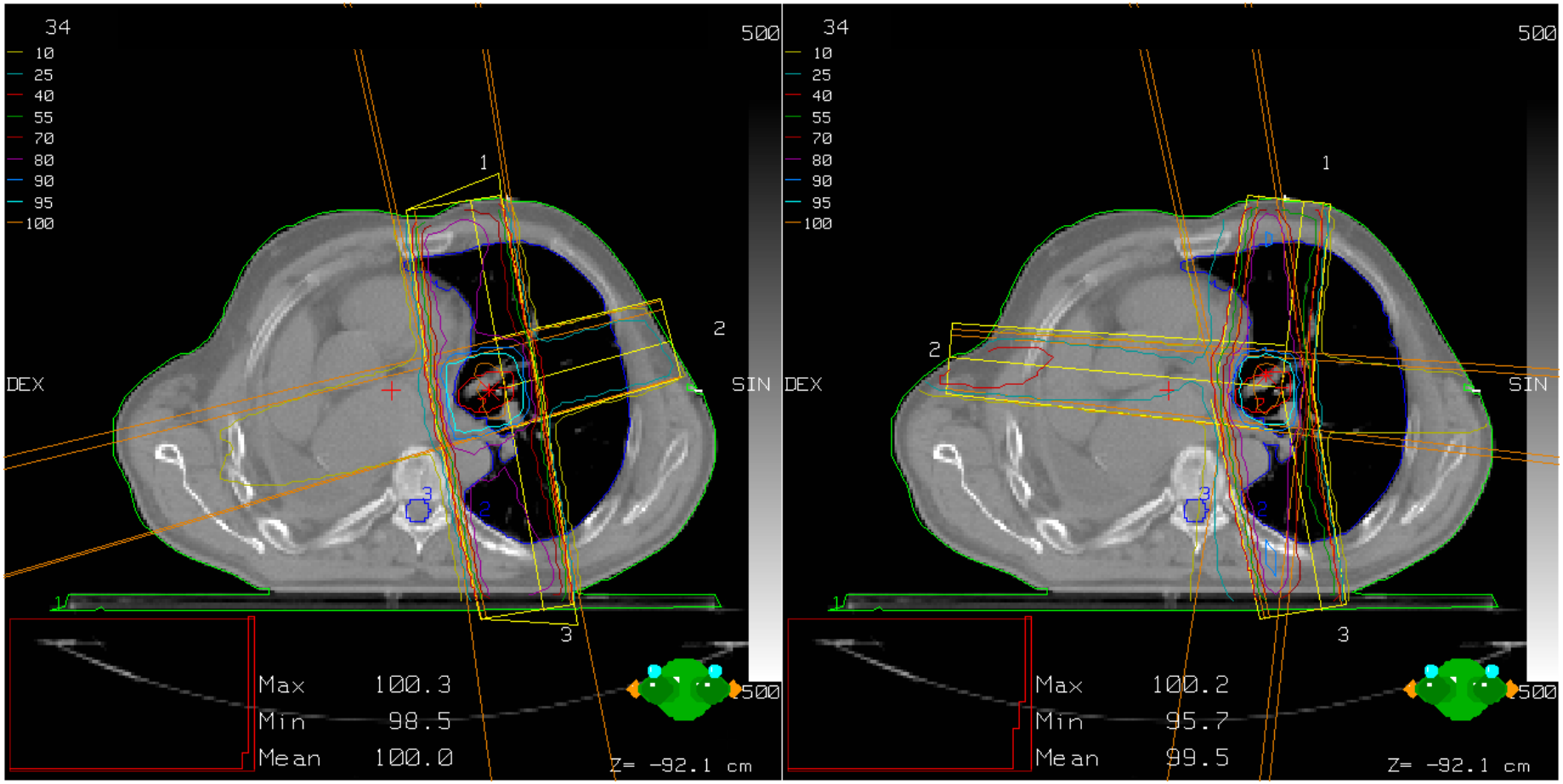
Curative radiotherapy for a second primary lung cancer arising after pneumonectomy — techniques and results☆

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

Received 15 May 2001; received in revised form 20 July 2001; accepted 7 August 2001

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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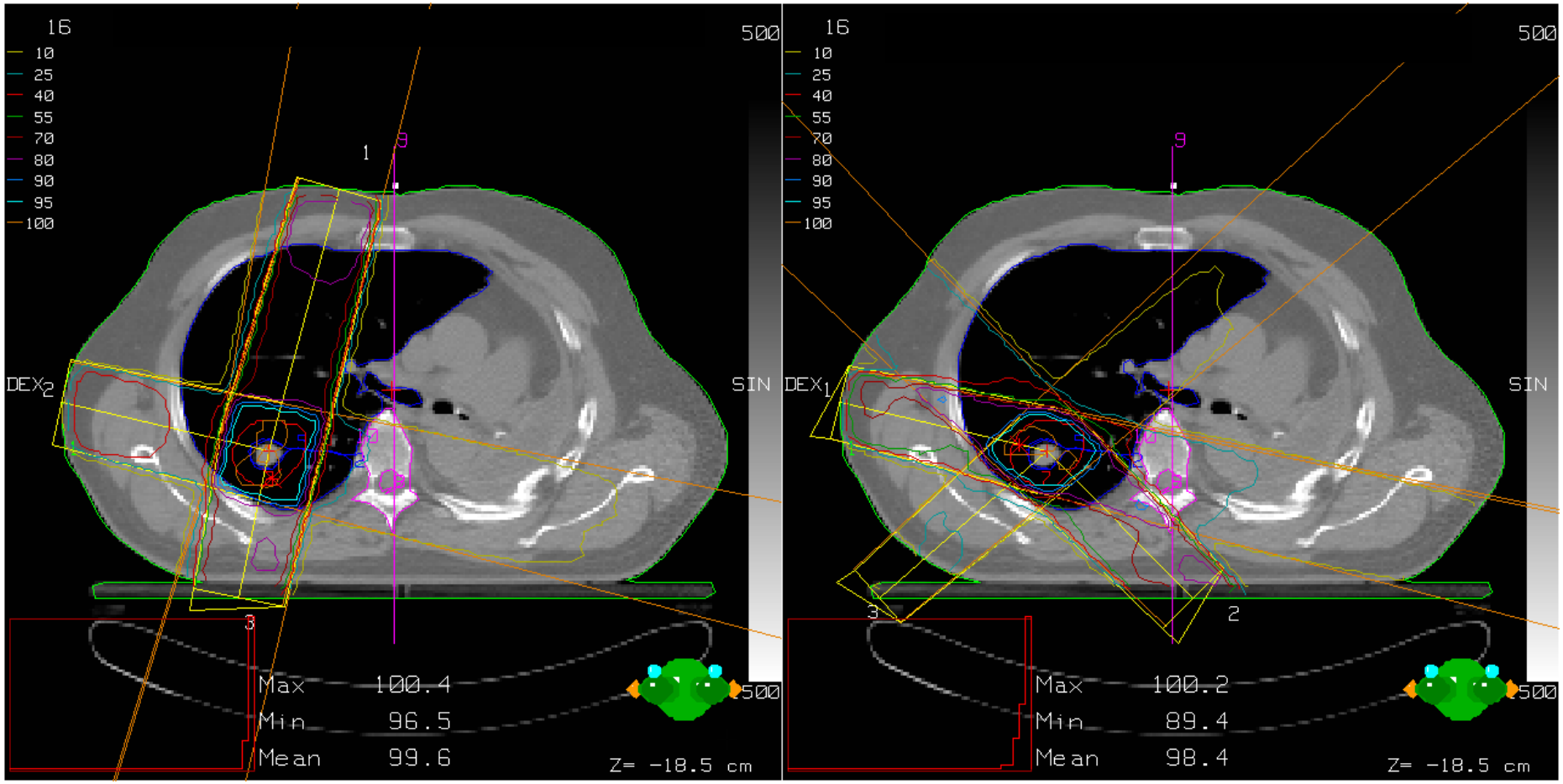
How to select the proper beam angles? Single Lung:



$V_{20} = 27\ \%$

$V_{20} = 15\ \%$

Lagerwaard et al: R&O, 2001

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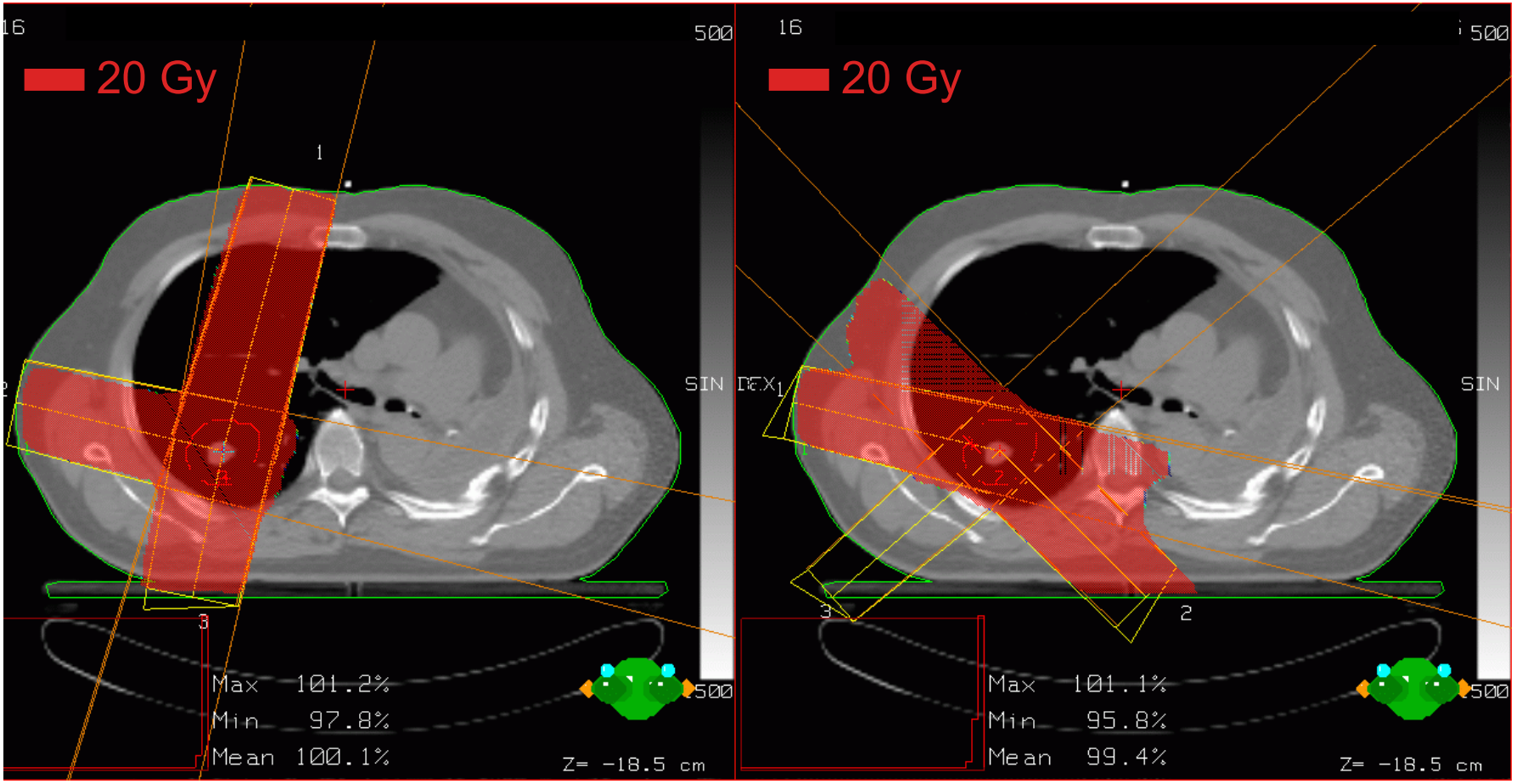
How to select the proper beam angles? Single Lung:



$V_{20} = 27\ \%$

$V_{20} = 15\ \%$

Lagerwaard et al: R&O, 2001

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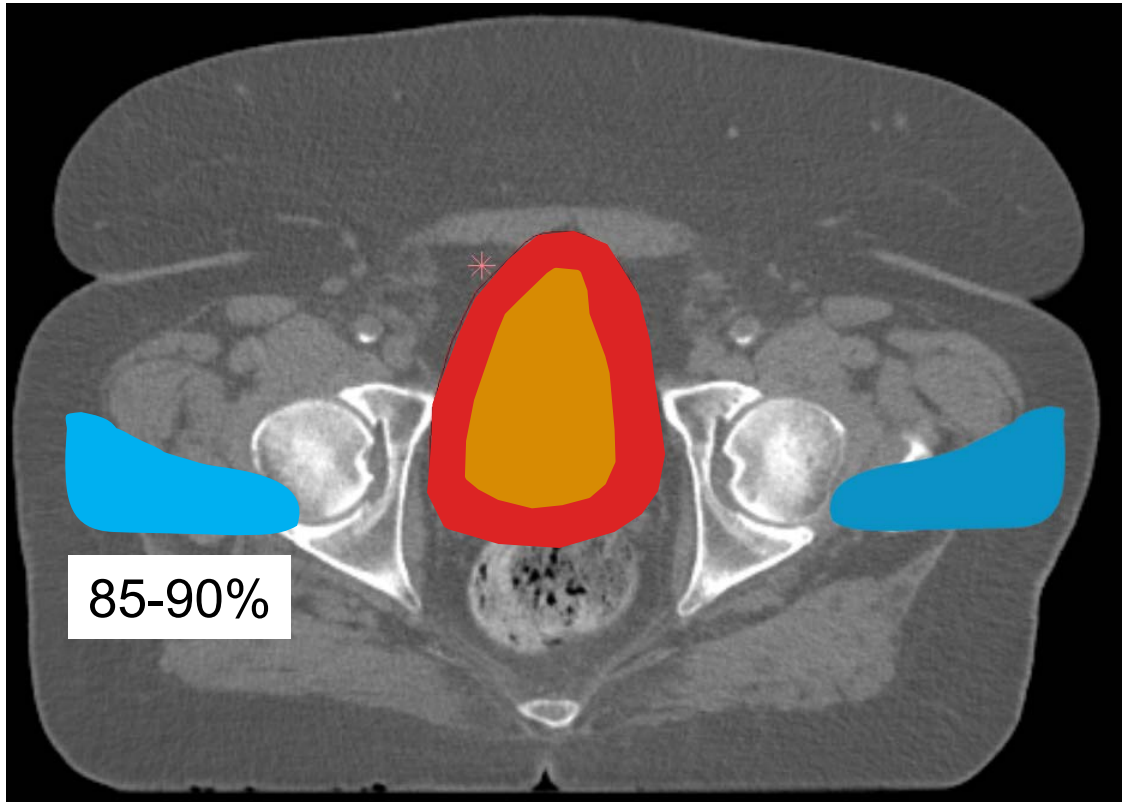
How many fields?

- 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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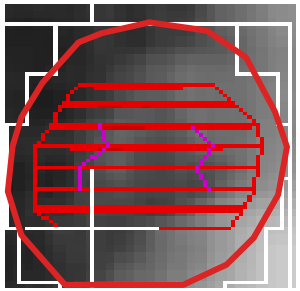
MLC versus Cerrobend blocking

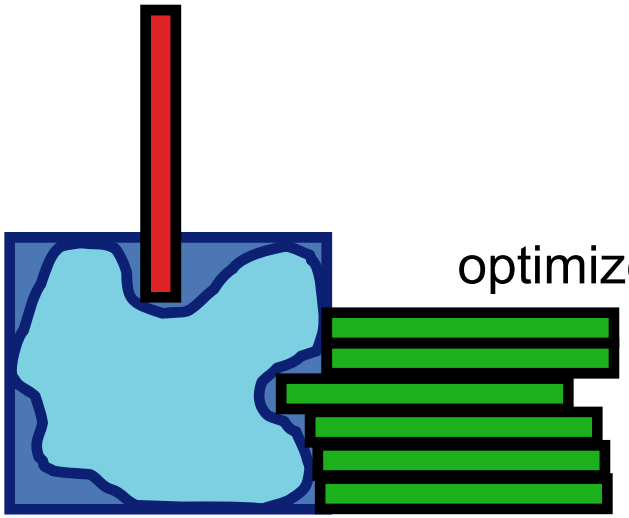


shielding by using cerrobend blocks is always the best

Δ quality with MLC shielding depends on :

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

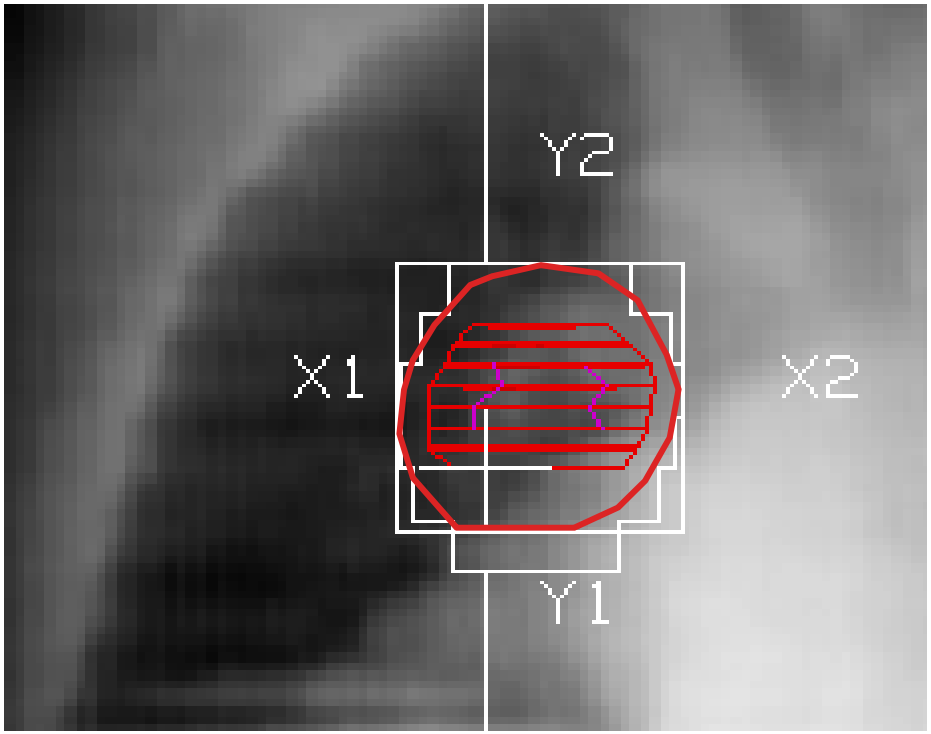
'normally' MLC will do just fine, but be aware of it's limitations



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

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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

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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

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Radiotherapy & Physics department
Policlinico A. Gemelli, Rome (Italy)

Relationships between 3D dose distributions and clinical toxicities (H&N and Pelvis)

N. Dinapoli

Dosimetry, Biology and Clinic

- **Dosimetry: planning related data**
  - Dose distribution
  - Fractionation
  - Volume irradiated
  - Hot-Cold spots
  - DVH (and related indicators)

  V-values
  D-values
  Mean dose
  Maximum dose
  Minimum dose
- **Biology: OAR**
  - Dose/Response models (Lyman, Log-Logistic…)
  - Volume effect
  - Reliability of radiobiological prediction
- **Clinic: factors that can affect the outcome**
  - Patient related: Age, Smoke, HPV status (for H&N), comorbidities…
  - Treatment related: chemo, hormonal therapy…
  - Prognosis, treatment aim (definitive, local control, palliation)

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Dose volume histograms

1st time shown in 1979!

Proton Radiation as Boost Therapy for Localized Prostatic Carcinoma
William U. Shipley. JAMA 241: 1912-1915, 1979

*…A **quantitative analysis** of the posterior rectal-wall dose received by the two treatment techniques is shown in Fig 3…*

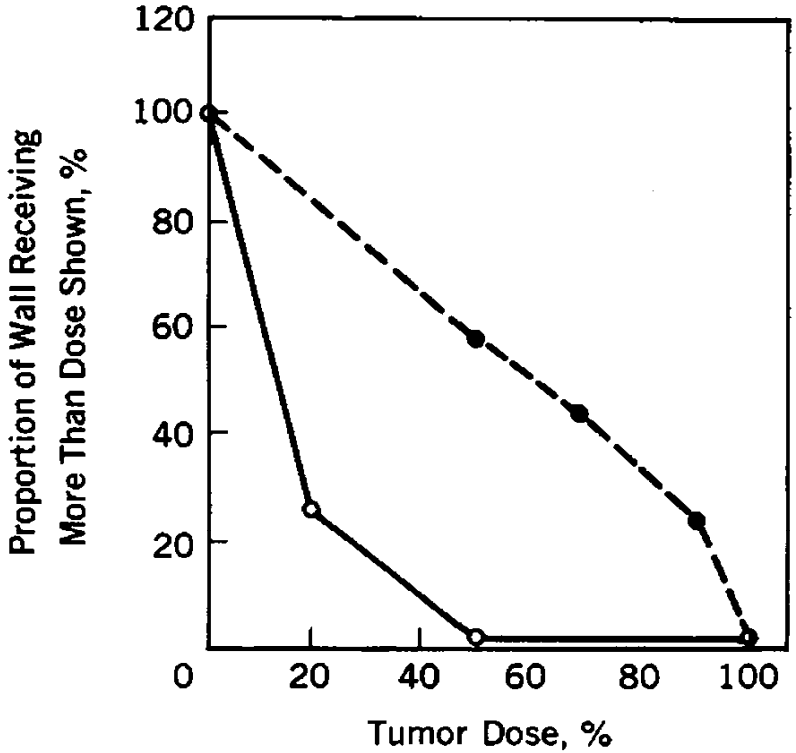
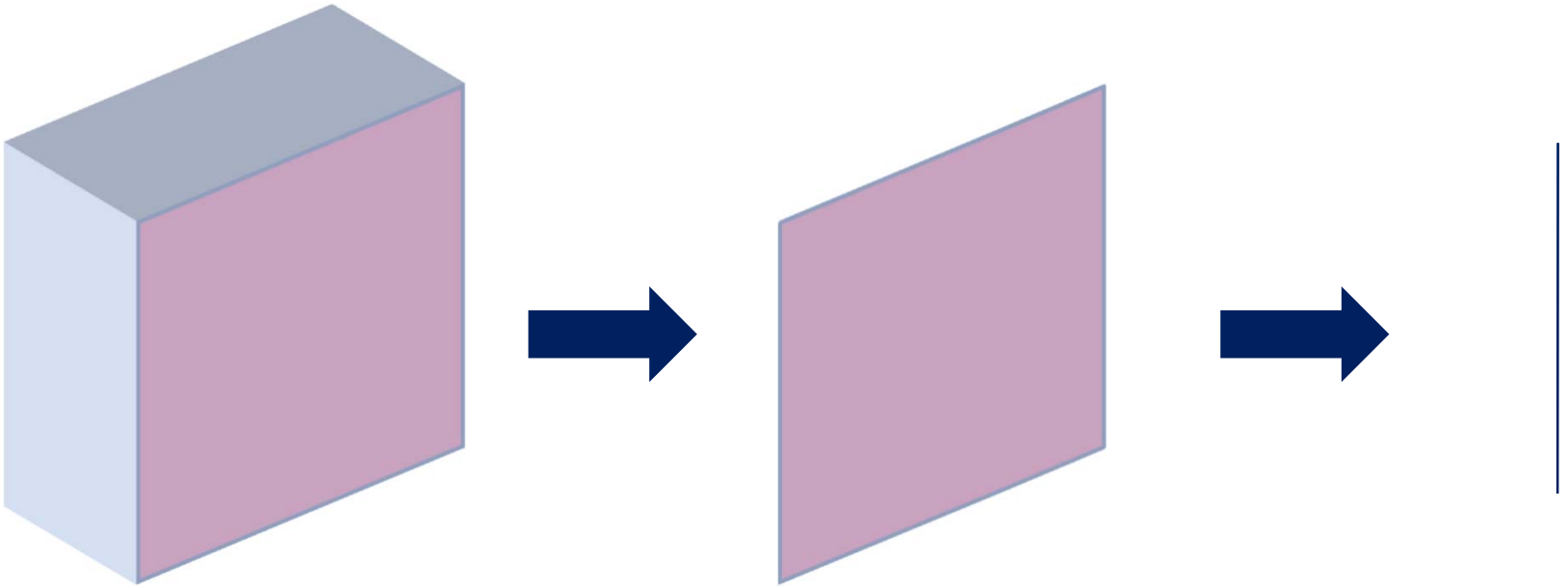


Fig 3.—Comparison of radiation dose to posterior rectal wall by 10-MV x-rays and 160-MV protons. Proportion of the wall is plotted vs dose it received. Dose is expressed as percentage of tumor dose. Solid line indicates protons; dashed line, 10-MV x-rays.

DVH related indicators



- **3D**
  - **Dose distribution**
- **2D**
  - **DVH**
- **1D**
  - **Mean Dose**
  - **Max, Min dose**
  - **$V_{[dose]}$, $D_{[volume]}$**

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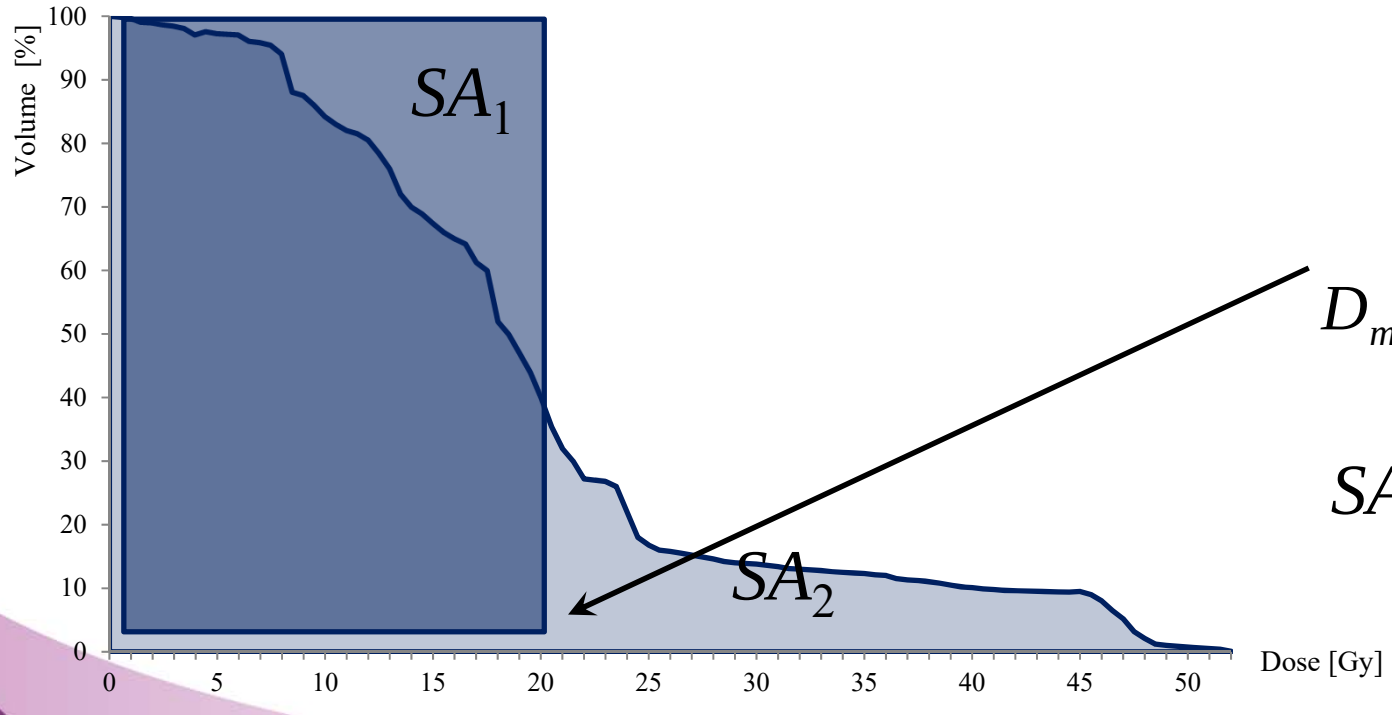
DVH related indicators: mean dose in the OAR

- Mean Dose
  - It "sums" all contributions of the heterogeneous dose distribution
  - It is useful for organs where the impact of the dose is strongly influenced by a **parallel radiobiological organization**



$$D_{mean} = \frac{\sum_{v_0}^{v_i} (D_i \cdot v_i)}{V_{total}}$$

$$SA_1 = SA_2$$

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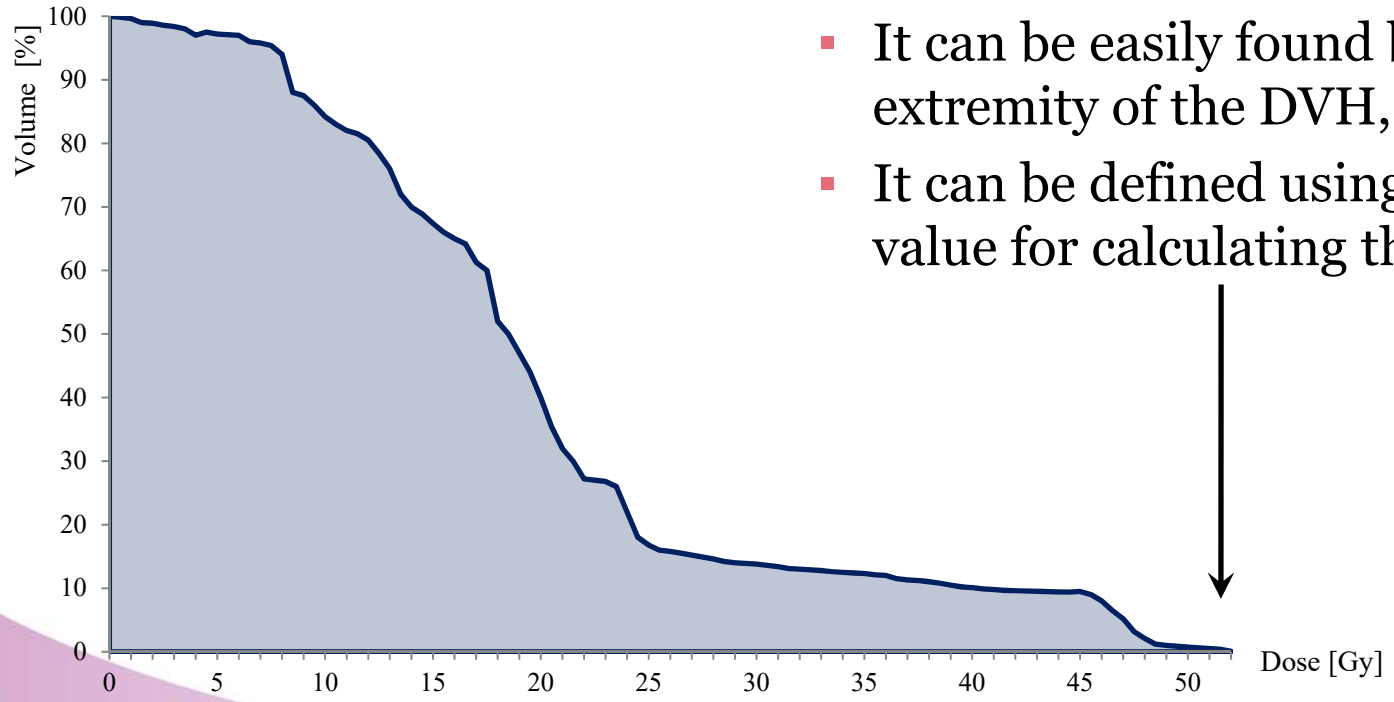
DVH related indicators: max dose in the OAR

- (Near) Maximum Dose
  - It is used when the value of the value of **dose** is **critical relatively independently from the volume**
  - It is useful for organs where the impact of the dose is strongly influenced by a **serial radiobiological organization**



- It can be easily found by viewing the right extremity of the DVH, in this case 52.5 Gy
- It can be defined using a very small volume value for calculating the $D_{[Volume]}$

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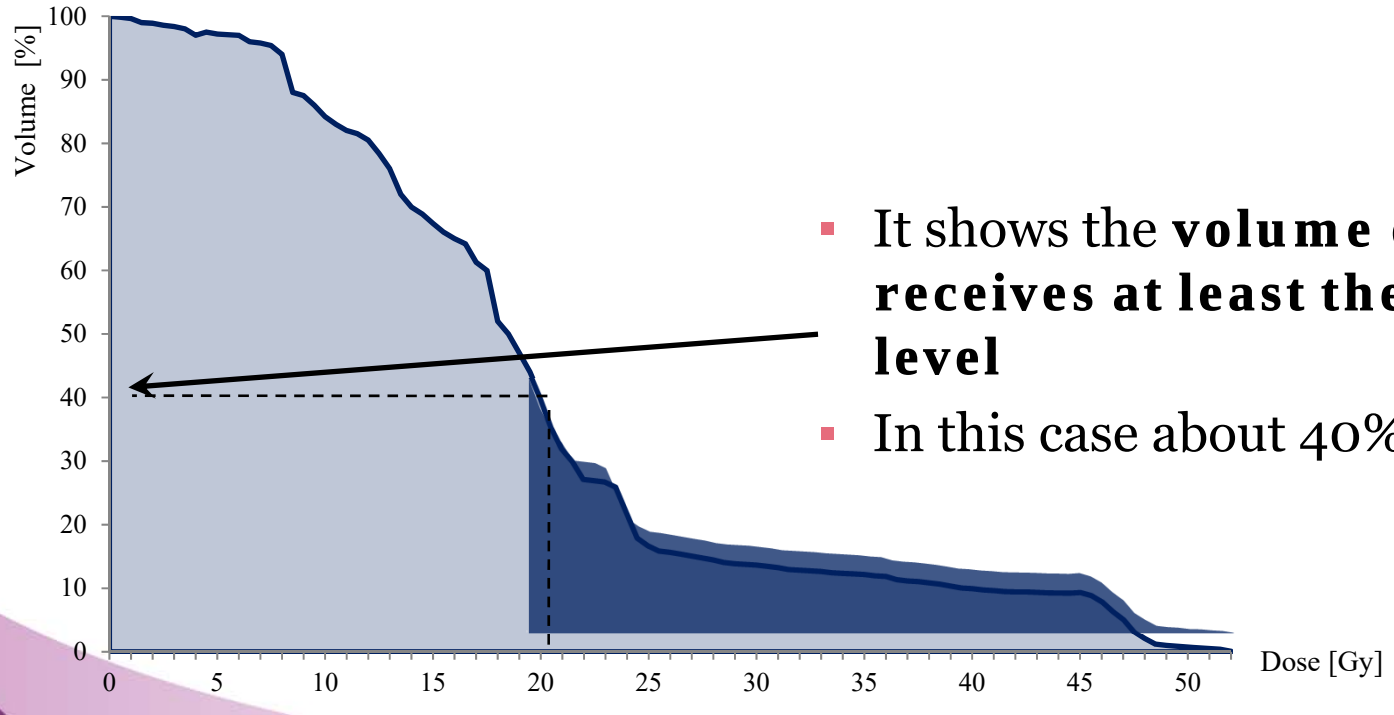
DVH related indicators: V[Gy] dose in the OAR

- V[Gy] Dose
  - It is an indicator that is useful when **critical dose levels**, where the clinical effect begins to be significant for the irradiated organ, **are known**
  - It is useful for organ with **parallel organization**



- It shows the **volume of the organ that receives at least the [Dose] chosen as level**
- In this case about 40% of volume

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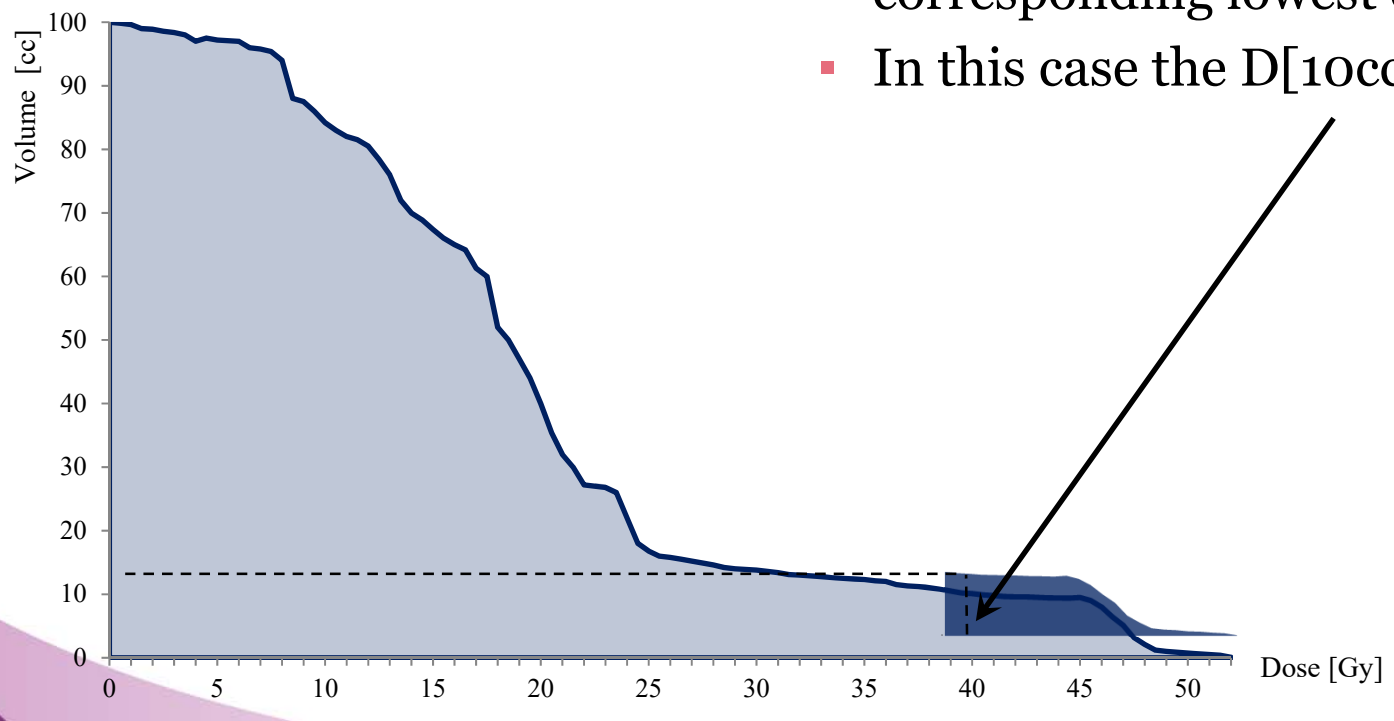
DVH related indicators: D[cc/%] volume in the OAR

- D[cc/%] Volume
  - Minimum dose received by the "hottest" x% (or x cc's) of the organ. Usually measured with absolute Volume scale [cc]

- Useful for organ with **serial organization**
- After choosing the **threshold volume** the corresponding lowest dose is measured
- In this case the D[10cc] is 39.5 Gy



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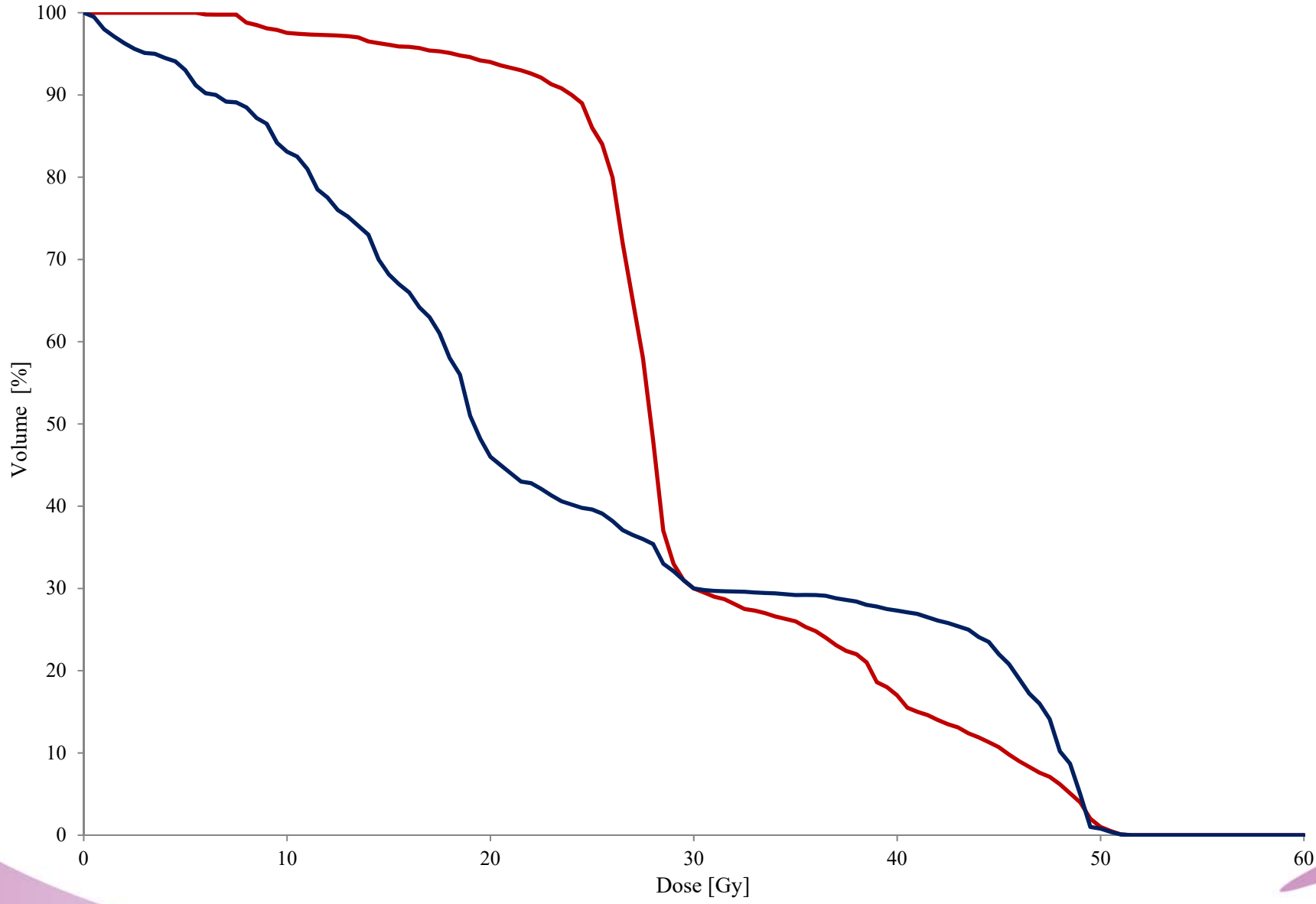
Be careful using single point indicators…



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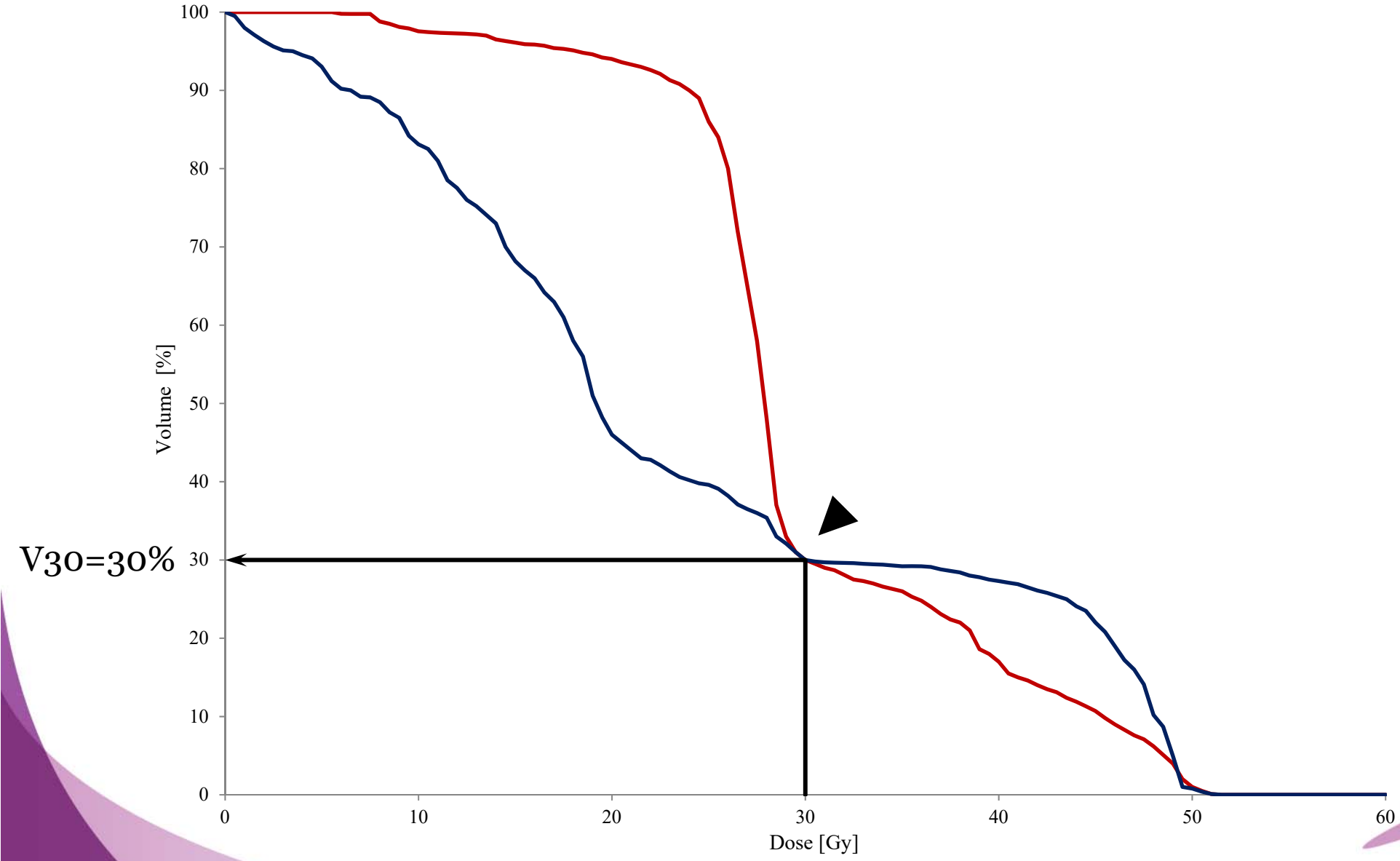

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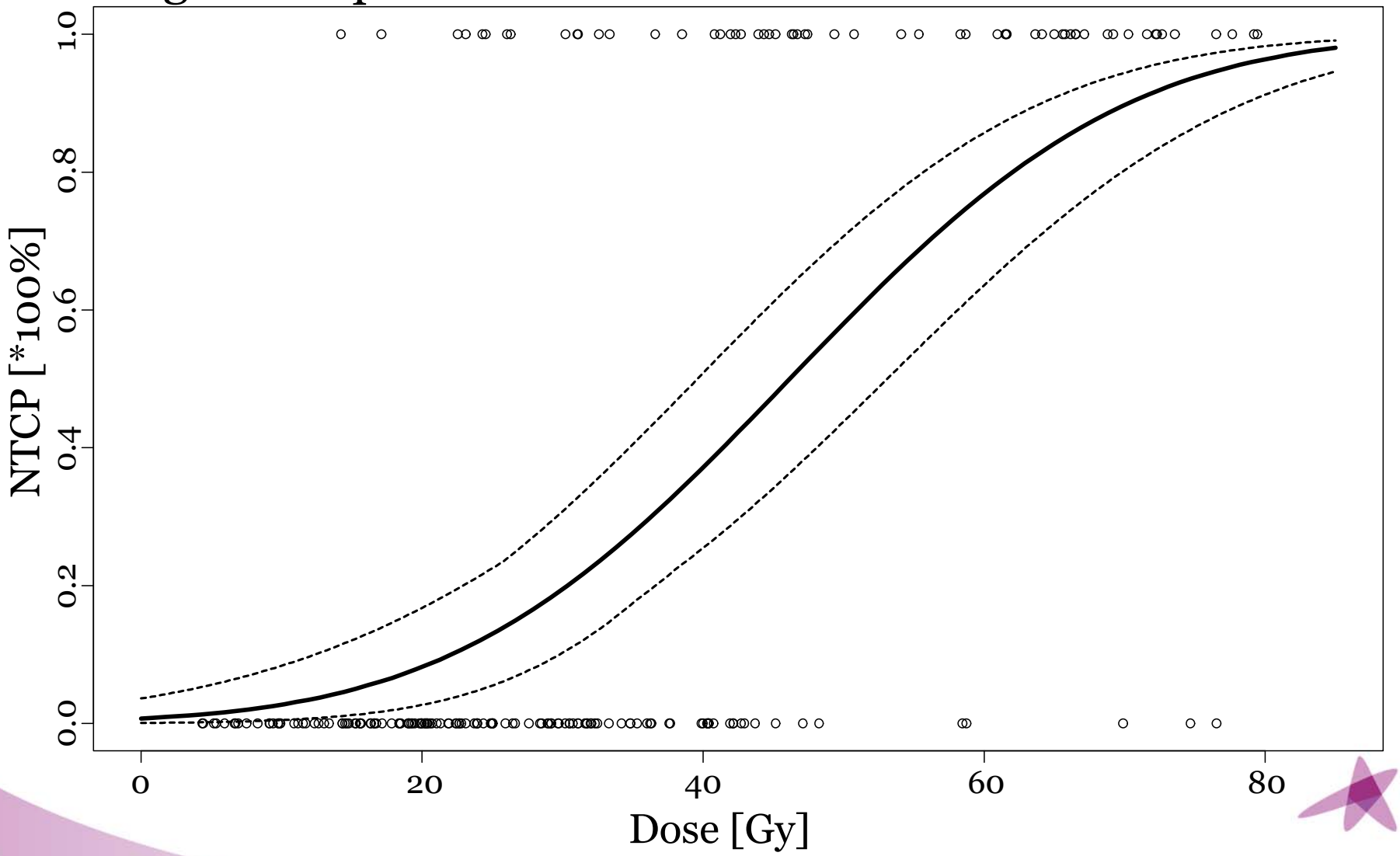
Dose/response models

- Dose-response models are binary model where the observer has to define some kind of **outcome** that has to be fitted to a sigmoid equation



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Radiobiology for OAR - NTCP

- There are mechanistic derived models for predicting TCP (based on probability of tumor stem cells lost during the treatment)
- There are not convincing mechanistic models for describing all side effect onset
  - Stem cells loss (dry mouth, myelopathy)
  - Abnormal cell growth (fibrosis, telangiectasia)
- Likelihood of side effects onset is proportional to the administered dose
  - Using the probability density function of normal distribution (probit)
  - Using the probability density function of other statistical distribution (logit – Log dose)

Deriving NTCP models from dose/outcome data

- *Probit*:
  Lyman

$$NTCP = \frac{1}{2\sqrt{\pi}} \int_{-\infty}^{t} e^{-\frac{x^2}{2}} dx \quad t = \frac{D - D_{50}}{D_{50}} \cdot \left(\gamma_{50} \sqrt{2\pi}\right)$$

- *Logistic* (log *dose*):
  Niemierko

$$NTCP = \frac{1}{1 + \left(\frac{D}{D_{50}}\right)^{4\gamma_{50}}}$$

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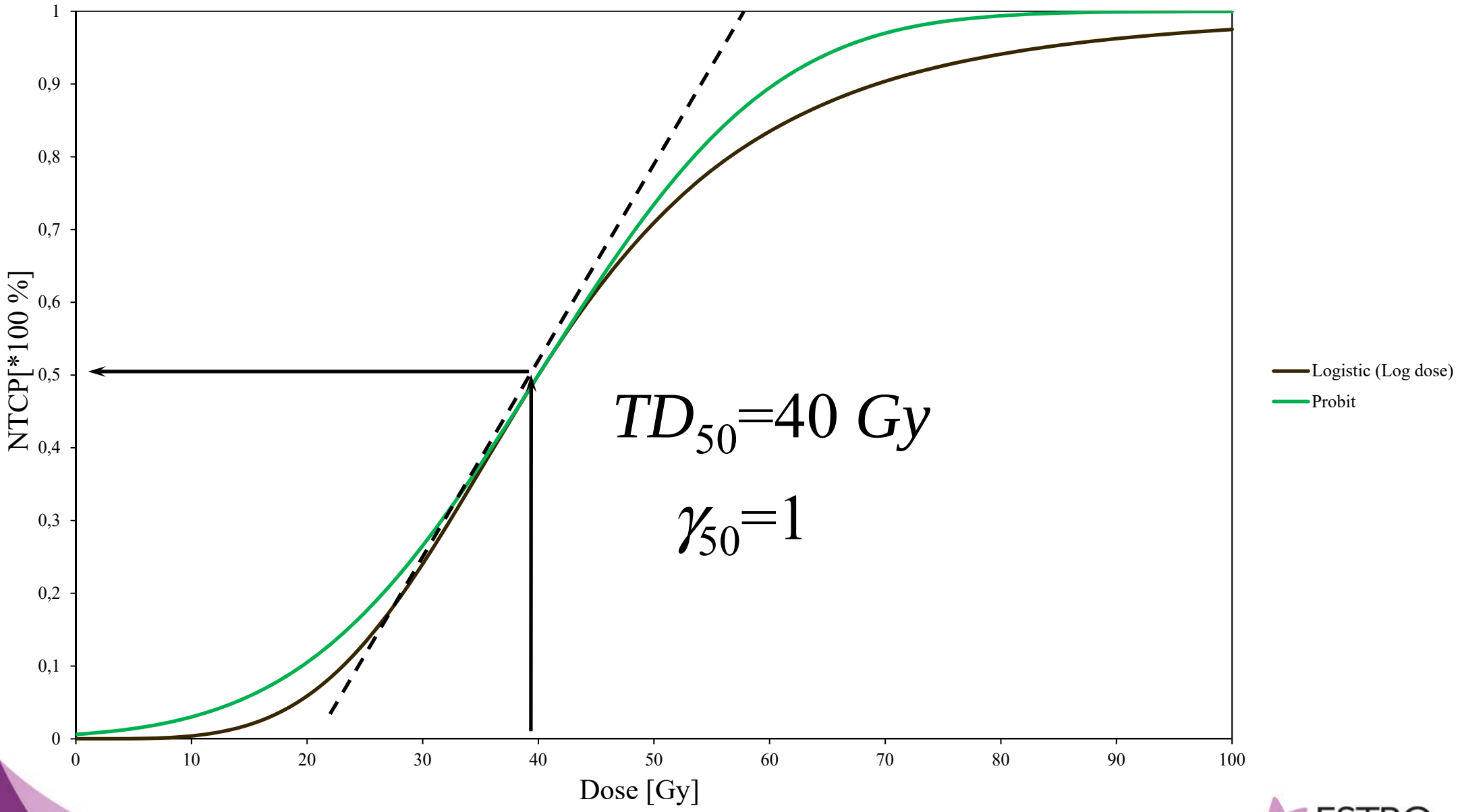
NTCP models



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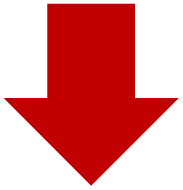
Which dose should be used within NTCP models?

- Dose in OAR is usually heterogeneous
- Dose/response relation in OAR changes with the organ considered
- Need to define a number that can summarize the different contribution of dose in the OAR volume



Equivalent Uniform Dose

Equivalent Uniform Dose

- The **EUD** is base on the assumption that **two dose distributions are equivalent if they produce the same radiobiological or clinical effect** (end-point)
- D_j : the dose in the volum bin
- v_j : volum bin
- a : parameter that describes the serial/parallel structure of the organ

$$EUD = \left(\sum_{j=1} v_j D_j^a \right)^{\frac{1}{a}}$$

Niemierko A. A Concept of Equivalent Uniform Dose (EUD). Volume & Kinetics in Tumor Control & Normal Tissue Complications. 5th International Conference on Dose, Time and Fractionation in Radiation Oncology. 1998

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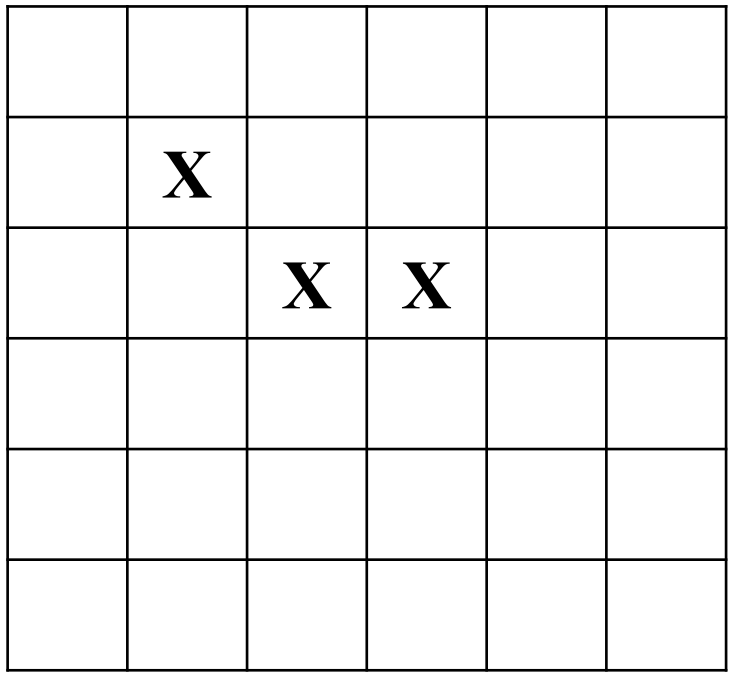
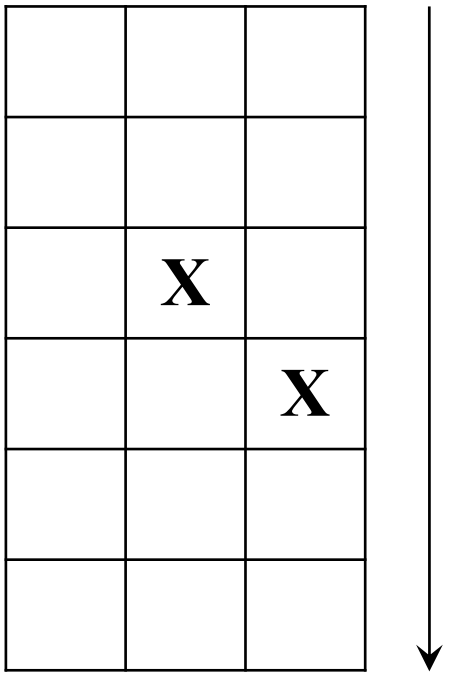
The Volume Effect in OAR

Parallel structure of functional subunits



Serial structure of functional subunits



Withers HR. et al. Treatment volume and tissue tolerance. Int. J. Radiat. Oncol. Biol. Phys. 1988 (14): 751-759.

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The Volume Effect in OAR

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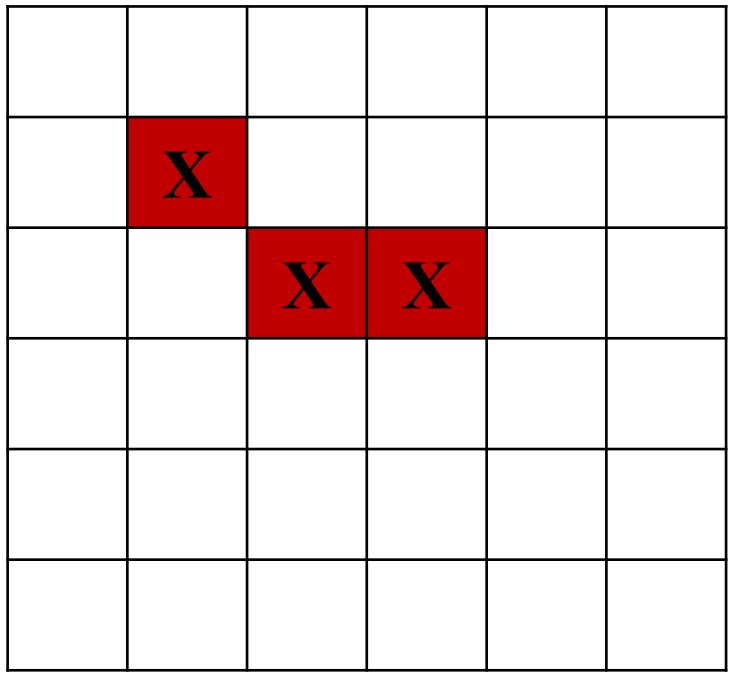
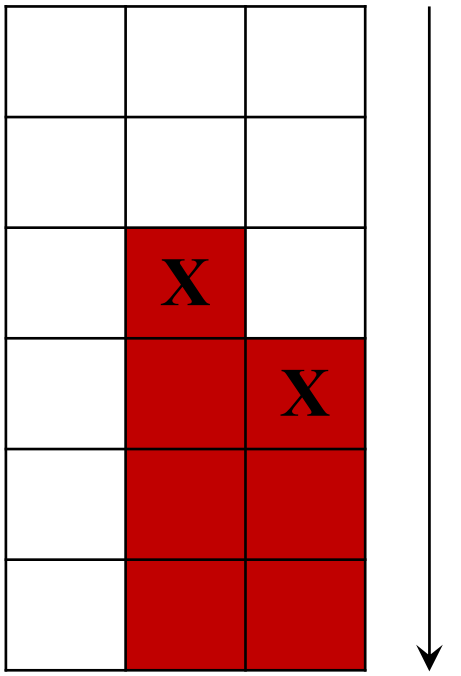


Lung, liver, kidney

Serial structure of functional subunits



Spine, bowel loops

Withers HR. et al. Treatment volume and tissue tolerance. Int. J. Radiat. Oncol. Biol. Phys. 1988 (14): 751-759.

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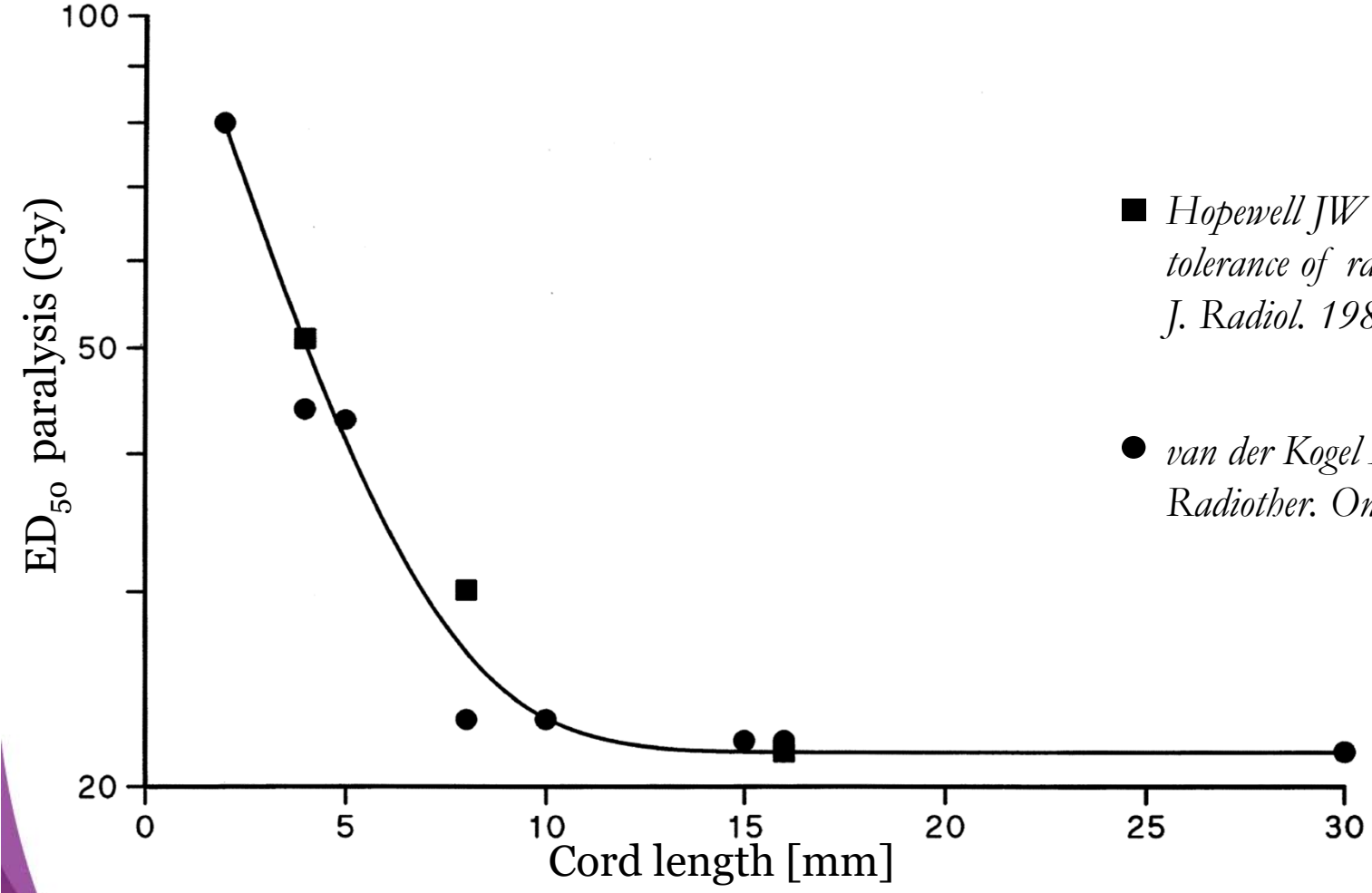
The Volume Effect in OAR

Rat spinal cord: endpoint white matter necrosis



- *Hopewell JW et al. The influence of field size on the late tolerance of rat spinal cord to single doses of X-rays. Br. J. Radiol. 1987(60):1099-1108.*
- *van der Kogel AJ. Dose volume effects in the spinal cord. Radiother. Oncol. 1993(29):105-109.*

Hopewell JW, Trott KR. Volume effects in radiobiology as applied to radiotherapy. Radiater. Oncol. 2000 (56): 283-288.

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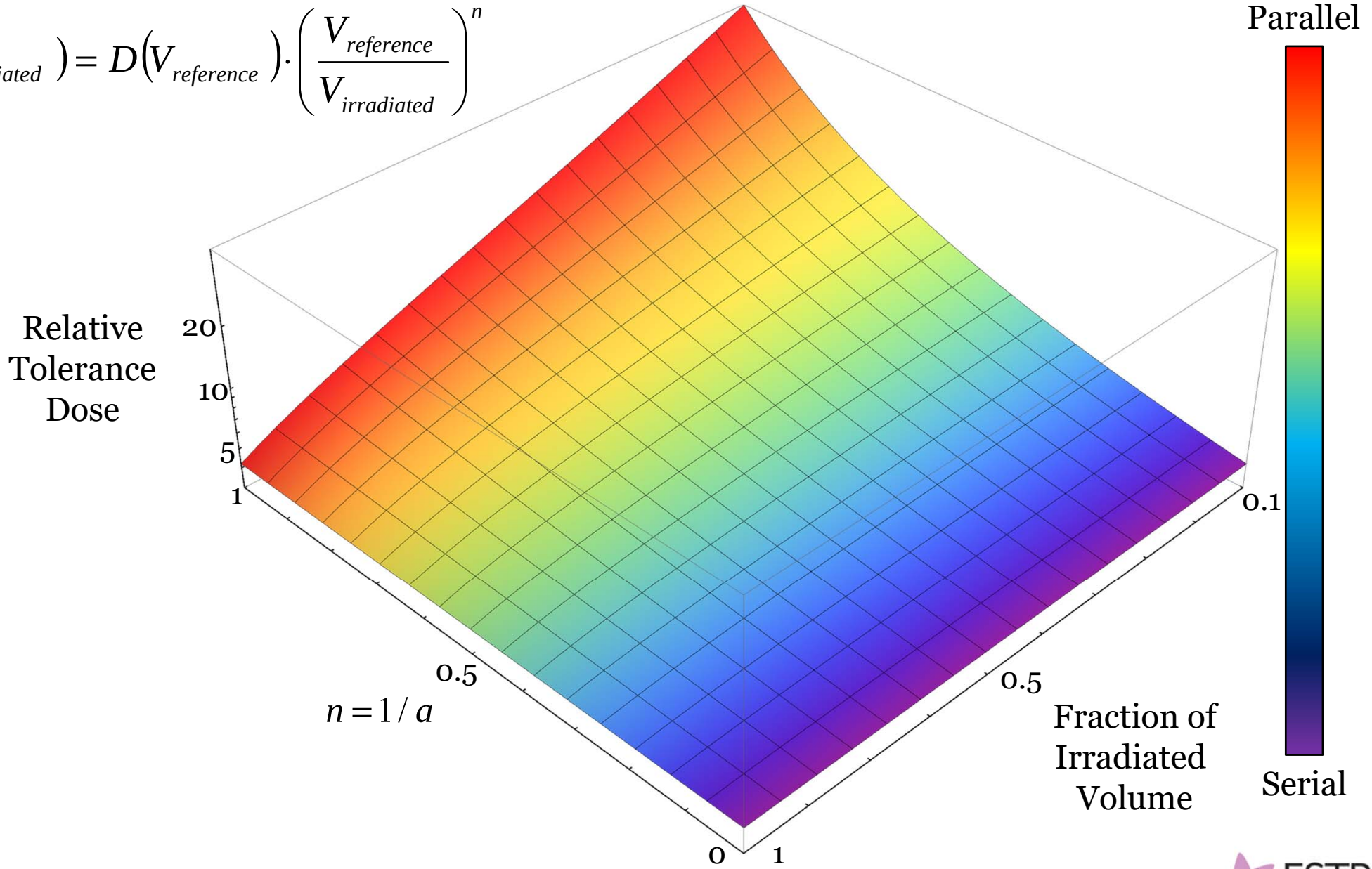
The Volume Effect in OAR

$$D(V_{irradiated}) = D(V_{reference}) \cdot \left(\frac{V_{reference}}{V_{irradiated}} \right)^{n}$$



Adapted and redrawn from: *Marks LB, et al. Use of normal tissue complication probability models in the clinic. Int. J. Radiat. Oncol. Biol. Phys. 2010 (76-3): S10-S19.*

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The Volume Effect in OAR

$$D(V_{irradiated}) = D(V_{reference}) \cdot \left(\frac{V_{reference}}{V_{irradiated}} \right)^{n}$$

1. *n* value is function of the structure:
   - ▲ Lung
   - ▼ Spinal cord
2. Within a structure *n* can be function of the effect:
   - ▲ Proctitis (Rectum)
   - ▼ Rectal Bleeding (Rectum)
   - ▲ Dementia (Brain)
   - ▼ Necrosis (Brain)
3. Within a structure *n* can be function of the anatomy

Marks LB, et al. Use of normal tissue complication probability models in the clinic. Int. J. Radiat. Oncol. Biol. Phys. 2010 (76-3): S10-S19.

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   - ▲ Proctitis (Rectum)
   - ▼ Rectal Bleeding (Rectum)
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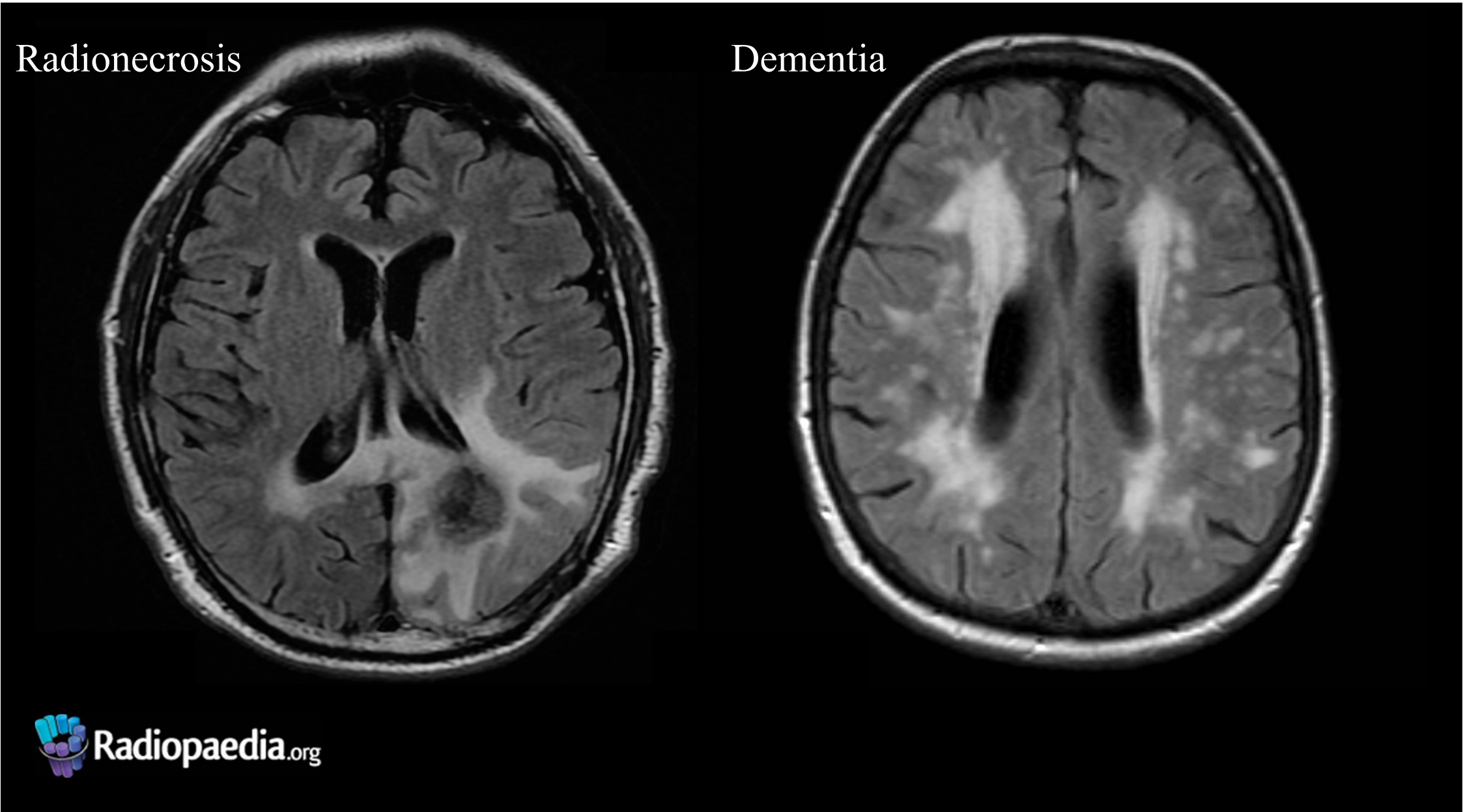
The Volume Effect in OAR



The Volume Effect in OAR

$$D(V_{irradiated}) = D(V_{reference}) \cdot \left(\frac{V_{reference}}{V_{irradiated}} \right)^{n}$$

1. *n* value is function of the structure:
   - ▲ Lung
   - ▼ Spine
2. Within a structure *n* can be function of the effect:
   - ▲ Proctitis (Rectum)
   - ▼ Rectal Bleeding (Rectum)
   - ▲ Dementia (Brain)
   - ▼ Necrosis (Brain)
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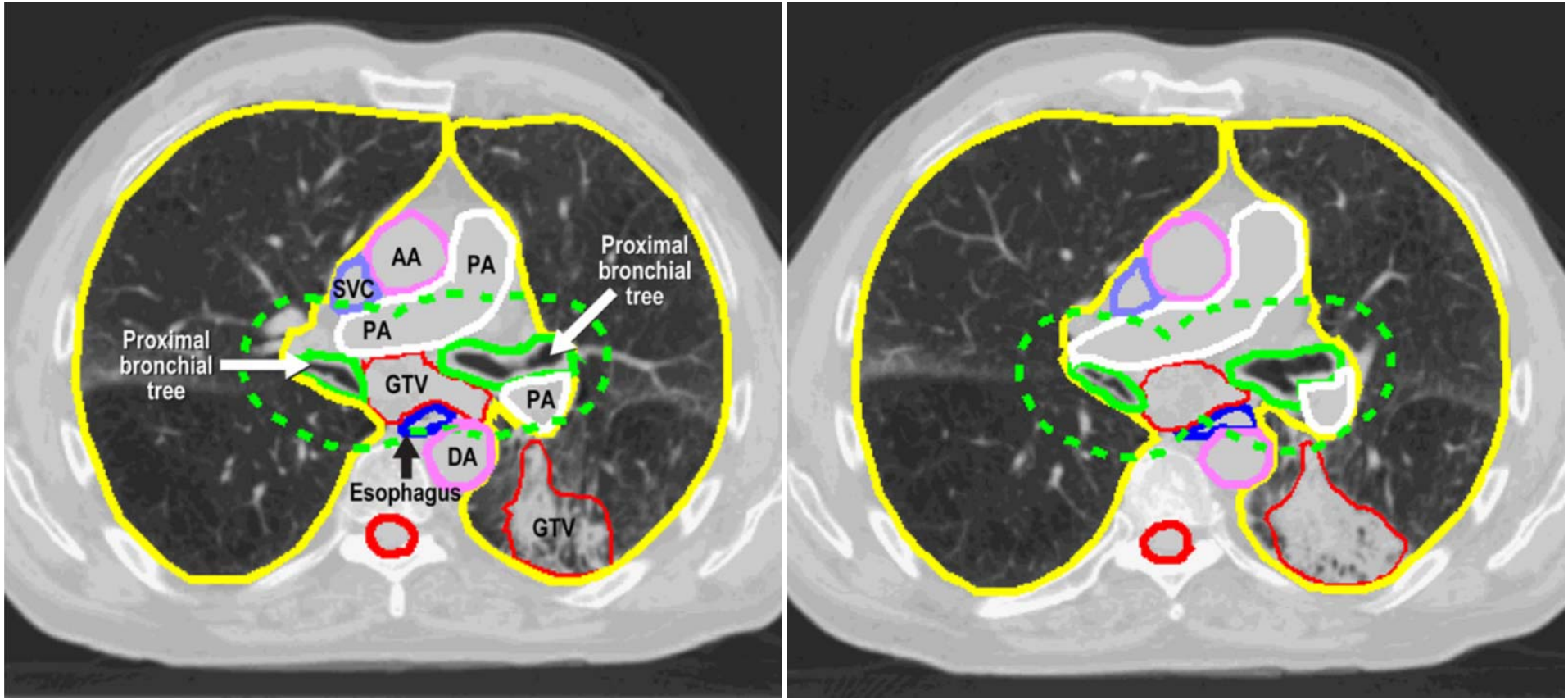

Kong FM et al. Consideration of dose limits for organs at risk of thoracic radiotherapy: Atlas for lung, proximal bronchial tree, esophagus, spinal cord, ribs, and brachial plexus. Int J Radiat Oncol Biol Phys 2011;81:1442–57.

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How to consider the volume effect in dose-response models?

- *Probit*: $NTCP = \frac{1}{2\sqrt{\pi}} \int_{-\infty}^{t} e^{-\frac{x^2}{2}} dx \qquad t = \frac{D - D_{50}}{D_{50}} \cdot \left(\gamma_{50} \sqrt{2\pi}\right)$

  Lyman

$$EUD = \left(\sum_{j=1} v_j D_j^a \right)^{\frac{1}{a}}$$

- *Logistic* (log *dose*): $NTCP = \frac{1}{1 + \left(\frac{D}{D_{50}} \right)^{4\gamma_{50}}}$

  Niemierko

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Are DVHs (and DVHs derived indicators) the best tool for evaluating treatments?

Medical Physics
The International Journal of Medical Physics Research and Practice

Evaluation of treatment plans using target and normal tissue DVHs is no longer appropriate

Christopher F. Njeh, Brent C. Parker, and Colin G. Orton

Citation: Medical Physics **42**, 2099 (2015); doi: 10.1118/1.4903902
View online: http://dx.doi.org/10.1118/1.4903902
View Table of Contents: http://scitation.aip.org/content/aapm/journal/medphys/42/5?ver=pdfcov
Published by the American Association of Physicists in Medicine

Are DVHs (and DVHs derived indicators) the best tool for evaluating treatments?

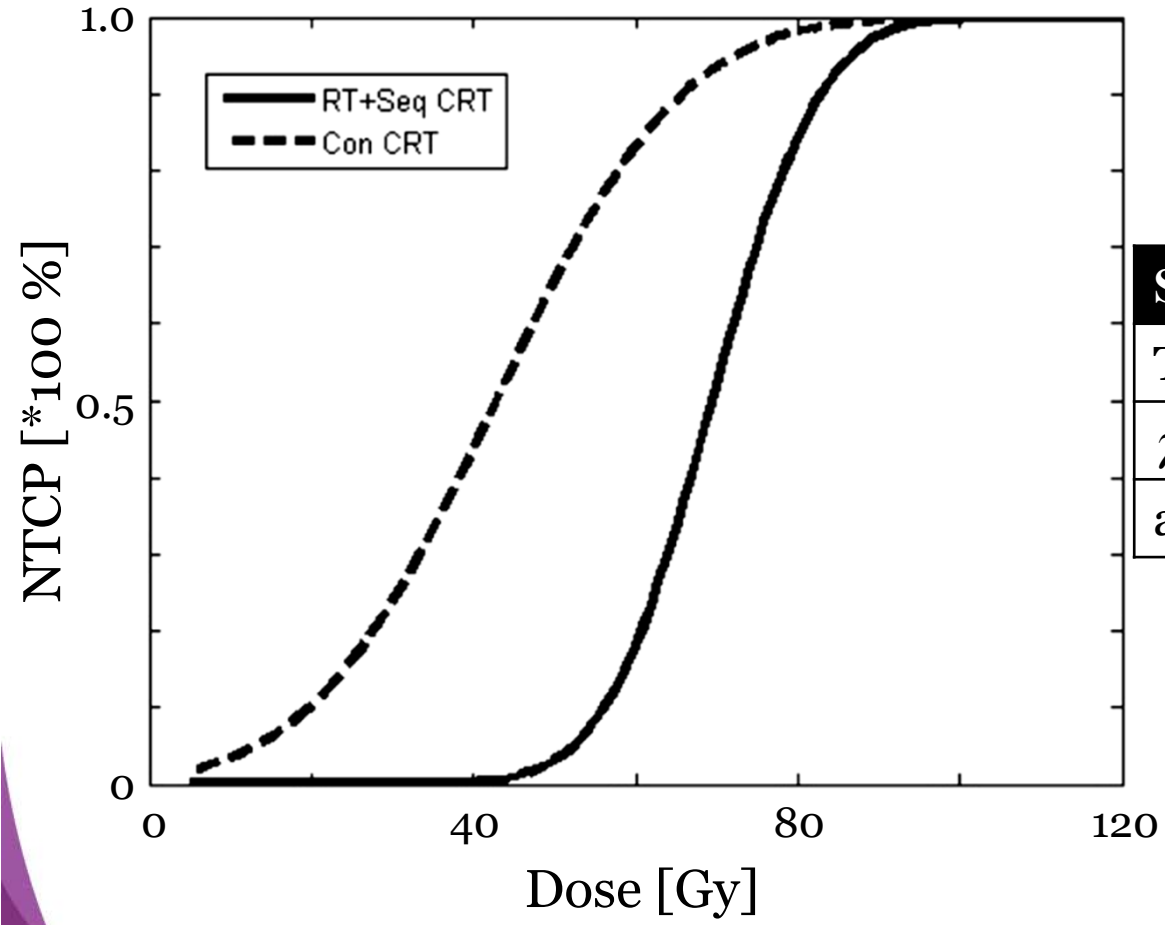
- Point:
  - Long history and huge literature
  - IGRT and modern high precision techniques can be helpful in making DVH estimation more stable
  - Deformable registration could improve the DVH accuracy during treatment
  - Many biological metrics (considered very useful) are substantially based on (differential) DVH data
  - The DVH is not *the* appropriate choice for plan evaluation but it is still *an* appropriate choice
- Counterpoint:
  - Loss of spatial information (from 3D to 2D)
  - The calculation of DVH strongly depends from delineation accuracy (and OAR choices by the doctors)
  - For some structures (e.g. bladder) different metrics can be used (DSH) because of the lack of importance of irradiation of organ content
  - Interpretation of the plot might be subjective
  - It can't carry clinical informations about conditions that could affect the outcome

Beyond the DVHs

- DVHs are based only on **anatomy** (knowledge and interpretation) and **dose distribution** reduced to a 2D estimate
- Dose-response model based on few geometrical parameters could **omit clinical conditions** differentiating the patients
- When referring **outcome prediction** on parameters derived from literature try to compare your evaluation to the **same conditions** used by publications authors (if available!)
- New methods for **patients classification** are required to achieve a robust and reliable evaluation

Reliability of radiobiological evaluation

- Solution 1: different populations, different parameters to be used in dose-response model (Lyman)



Sequential CRT		Concomitant CRT	
TD_{50}	46 (42 – 50)	TD_{50}	36 (34 – 56)
γ_{50}	2.7 (1.25 – 5)	γ_{50}	0.95 (0.71 – 1.11)
a	3.4 (2.4 – 5)	a	11.1 (1.3 – 14.3)

J Zhu et al. Analysis of acute radiation-induced esophagitis in non-small-cell lung cancer patients using the Lyman NTCP model. Radiother Oncol (2010) 449–454.

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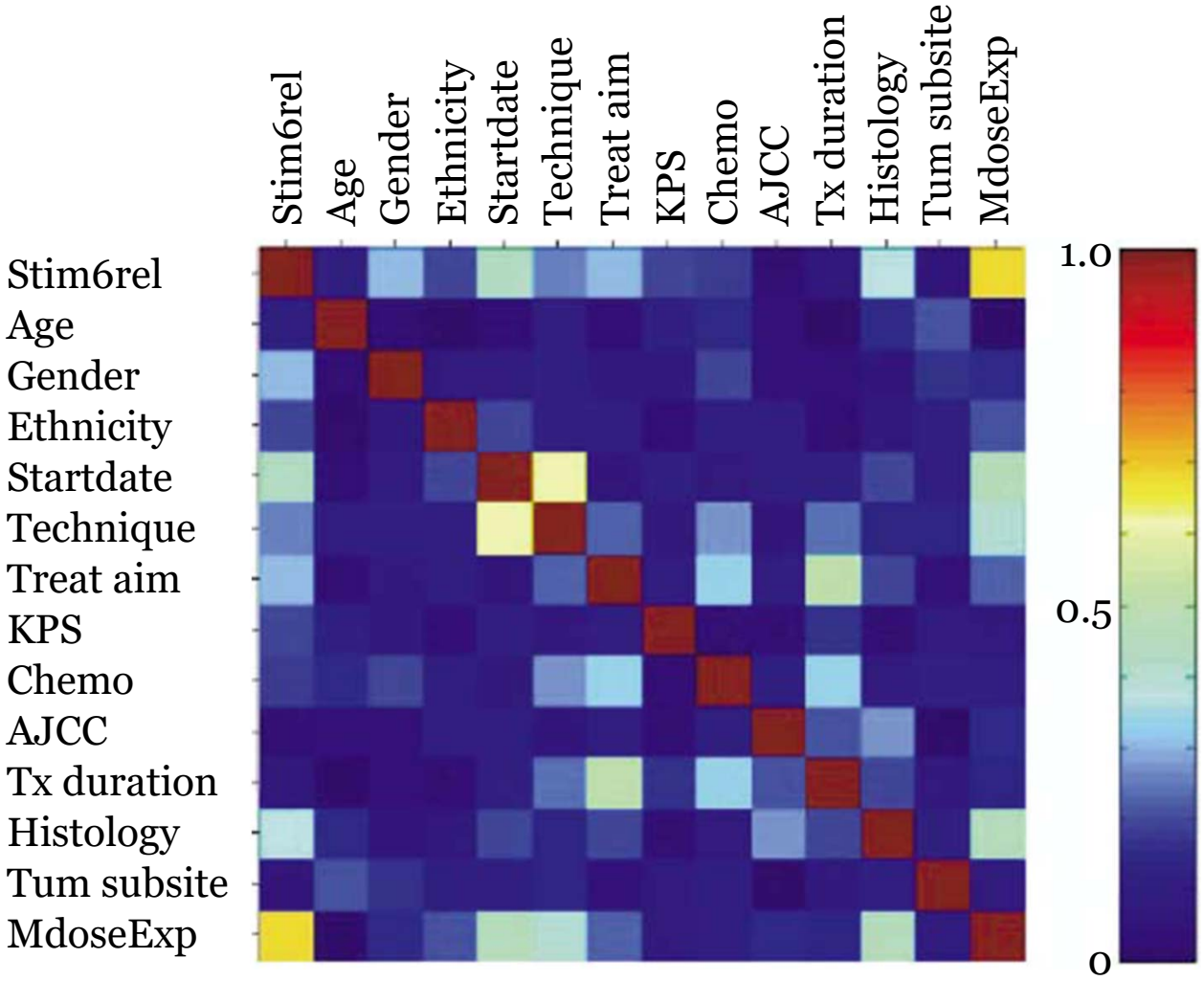
Reliability of radiobiological evaluation

- Solution 2: multivariate regression modeling



Creation of a correlation matrix to establish the relationships among different analyzed factors

J El Naqa et al. Multivariable modeling of radiotherapy outcomes, including dose-volume and clinical factors. Int J Radiat Oncol Biol Phys. 64, (4), 1275–1286, 2006.

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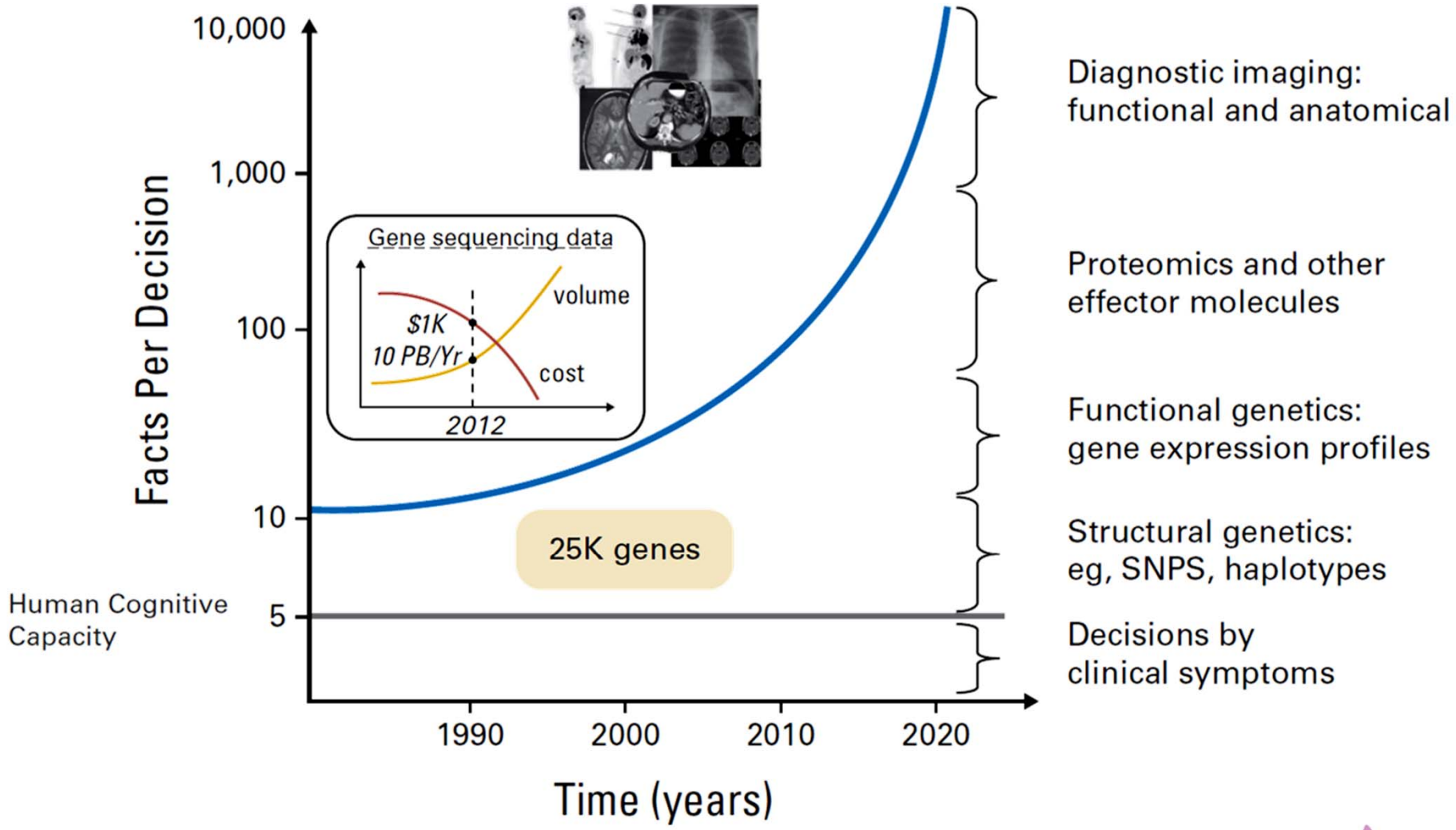
Reliability of radiobiological evaluation

- How many variables can be analyzed for treatment evaluation and outcome prediction?



AP Abernethy et al. Rapid-Learning System for Cancer Care. J Clin Oncol 28:4268-4274. 2010

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Reliability of radiobiological evaluation

- Possible solutions:

1. "Large database" modeling
2. Use of automatic computer bots
3. Multiparametric modeling
   - Inferential statistics
   - Bayesian approach
   - Use of support-vector-machines
   - Other…
4. Extension of data-mining in multi-centric perspective
5. Definition of multi-centric "ontology" for data classification and collection minimizing errors

JO Deasy et al. Improving normal tissue complication probability models: the need to adopt a "data-pooling" culture. Int J Radiat Onc Biol Phys. 76, (3), S151–S154, 2010

V Valentini, N Dinapoli, A Damiani. The future of predictive models in radiation oncology: from extensive data mining to reliable modeling of the results. Future Oncol. (2013) 9(3), 311–313

Beyond the theory… QUANTEC

INTRODUCTORY PAPER

GUEST EDITOR'S INTRODUCTION TO QUANTEC: A USERS GUIDE

LAWRENCE B. MARKS, M.D.,* RANDALL K. TEN HAKEN, PH.D.,† GUEST EDITORS,
AND MARY K. MARTEL, PH.D.,‡ ASSOCIATE GUEST EDITOR

*University of North Carolina, Chapel Hill, North Carolina; †University of Michigan, Ann Arbor, Michigan; and ‡M. D. Anderson Cancer Center, Houston, Texas

…this special issue of the International Journal of Radiation Oncology & Biology & Physics, (is) dedicated to the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC)…

Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, Supplement, pp. S1–S160, 2010.

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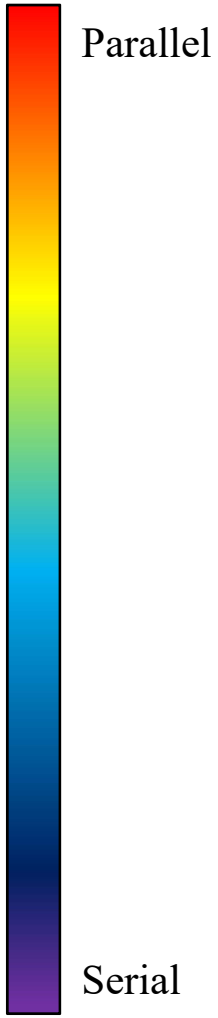
Parameters for clinical outcome prediction and planning evaluation

- Mean Dose
- V[Gy] Dose
- D[cc/%] Volume
- Maximum Dose



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Clinical evaluation: comparison of toxicity data from different protocols

- Biologically Effective Dose
  - A parameter that is independent from the fractionation
  - It doesn't express a real delivered dose

$$① \quad \frac{D_2}{D_1} = \frac{d_1 + \alpha/\beta}{d_2 + \alpha/\beta} \qquad ② \quad \frac{BED}{D_1} = \frac{d_1 + \alpha/\beta}{0 + \alpha/\beta}$$

$$③ \quad BED = D_1\left(\frac{d_1}{\alpha/\beta} + 1\right) = N \cdot d_1\left(\frac{d_1}{\alpha/\beta} + 1\right)$$

N: fraction number α/β: alfa-beta ratio
d_1: fraction number for the given effect

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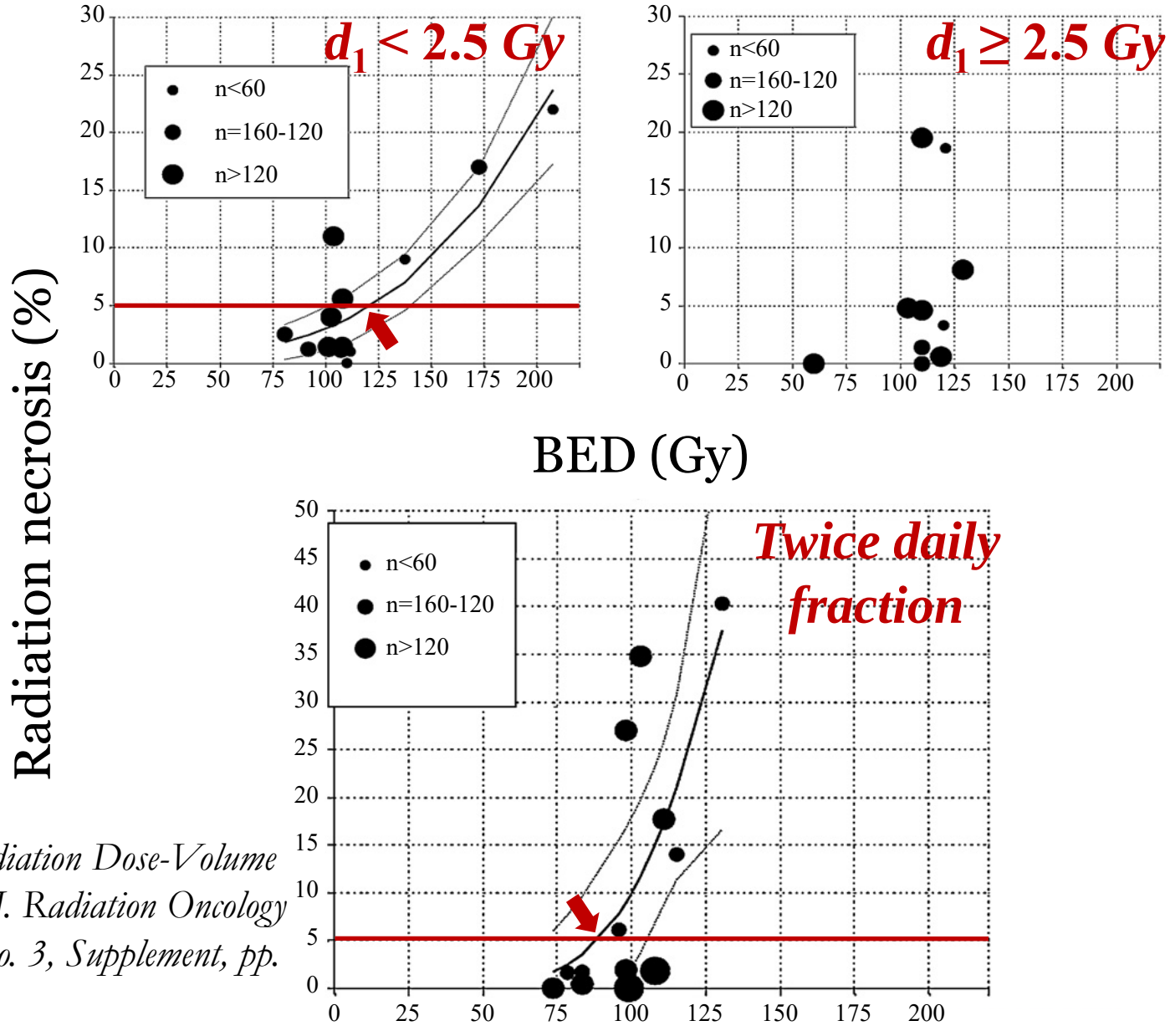
Parameters for clinical outcome: Brain

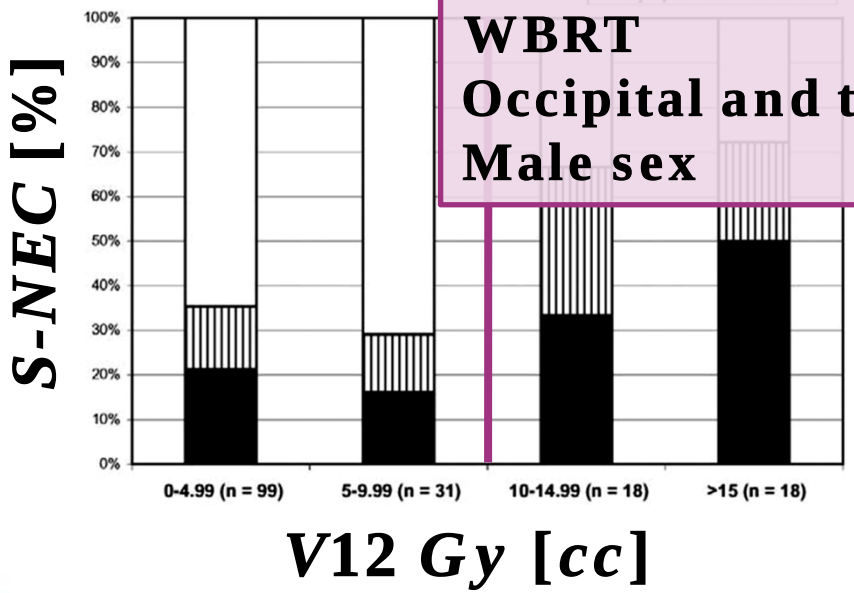


Lawrence YR et al. Radiation Dose-Volume effects in the brain. Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, Supplement, pp. S20–S27, 2010.

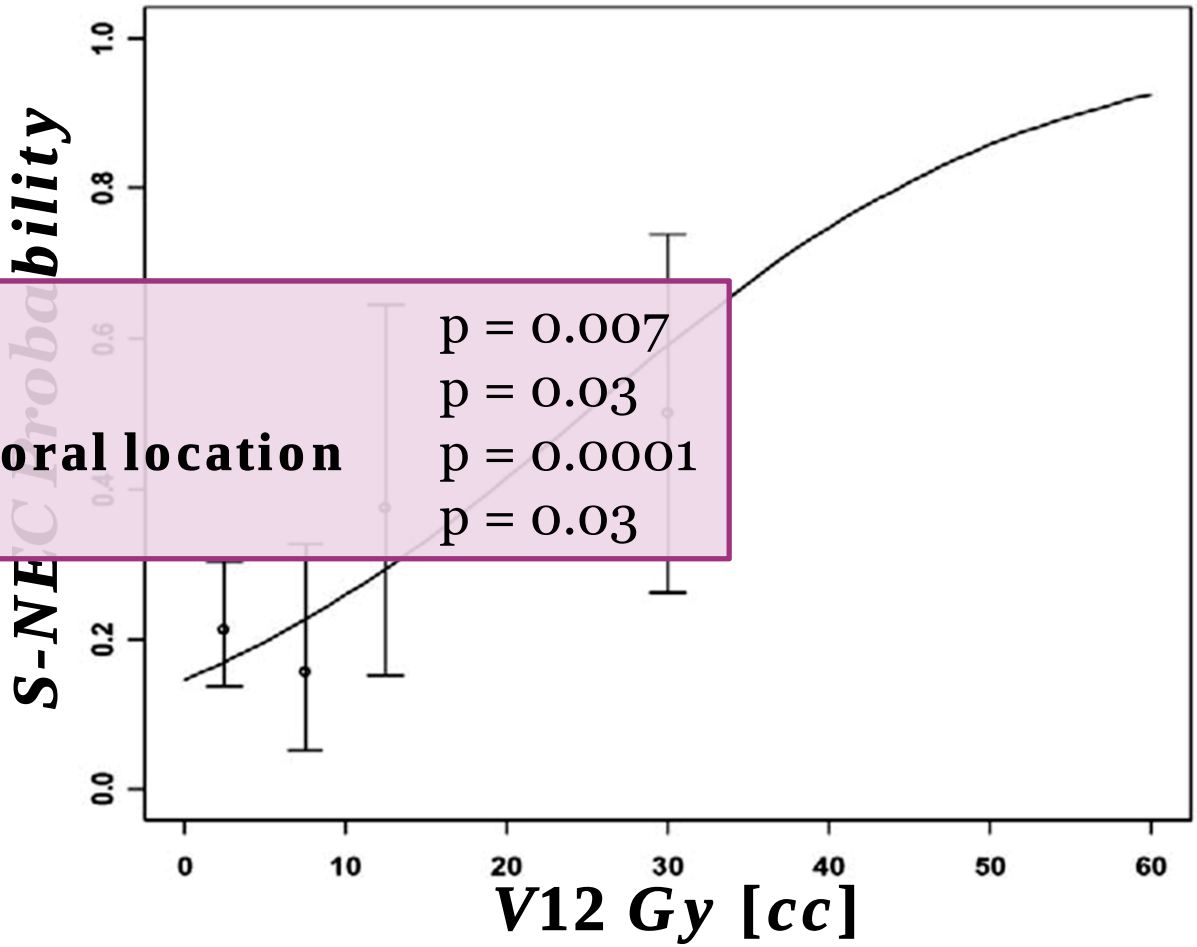
Parameters for clinical outcome: Brain

Endpoint: Symptomatic necrosis vs Asymptomatic necrosis

- 129 patients with 198 separate not-AVM
- Radiosurgery technique (gamma-knife)
- Median prescribed max dose 34.6 Gy (range 22 Gy – 50 Gy)
- Logistic regression



V12 Gy	p = 0.007
WBRT	p = 0.03
Occipital and temporal location	p = 0.0001
Male sex	p = 0.03



T Korytko et al. 12 Gy gamma knife radiosurgical volume is a predictor for radiation necrosis in non-AVM intracranial tumors. Int. J. Radiation Oncology Biol. Phys., Vol. 64, No. 2, pp. 419–424, 2006

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Parameters for clinical outcome: Brain

Volume segmented	Irradiation type (partial organ unless otherwise stated)	Endpoint	Dose (Gy), or dose/volume parameters	Rate (%)	Notes on dose/volume parameters
Whole organ	3D-CRT	Symptomatic necrosis	Dmax <60 Dmax = 72 Dmax = 90	<3 5 10	Data at 72 and 90 Gy, extrapolated from BED models
Whole organ	SRS (single fraction)	Symptomatic necrosis	V12 <5–10 cc	<20	Rapid rise when V12 > 5–10 cc

$$BED = N \cdot d_1\left(\frac{d_1}{\alpha/\beta}+1\right) \Rightarrow 120 = D_1\left(\frac{2}{2}+1\right) \Rightarrow D_1 = 120/2 = 60Gy$$

- High sensitivity for **fraction doses > 2 Gy**
- High sensitivity for **multi fractions** per day treatments
- Evidence for neurocognitive injury is weak in adults
- For **children** the cutoff for **neurocognitive injury** is about **18-24 Gy** (whole brain irradiation for medulloblastoma)

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Parameters for clinical outcome: Brain

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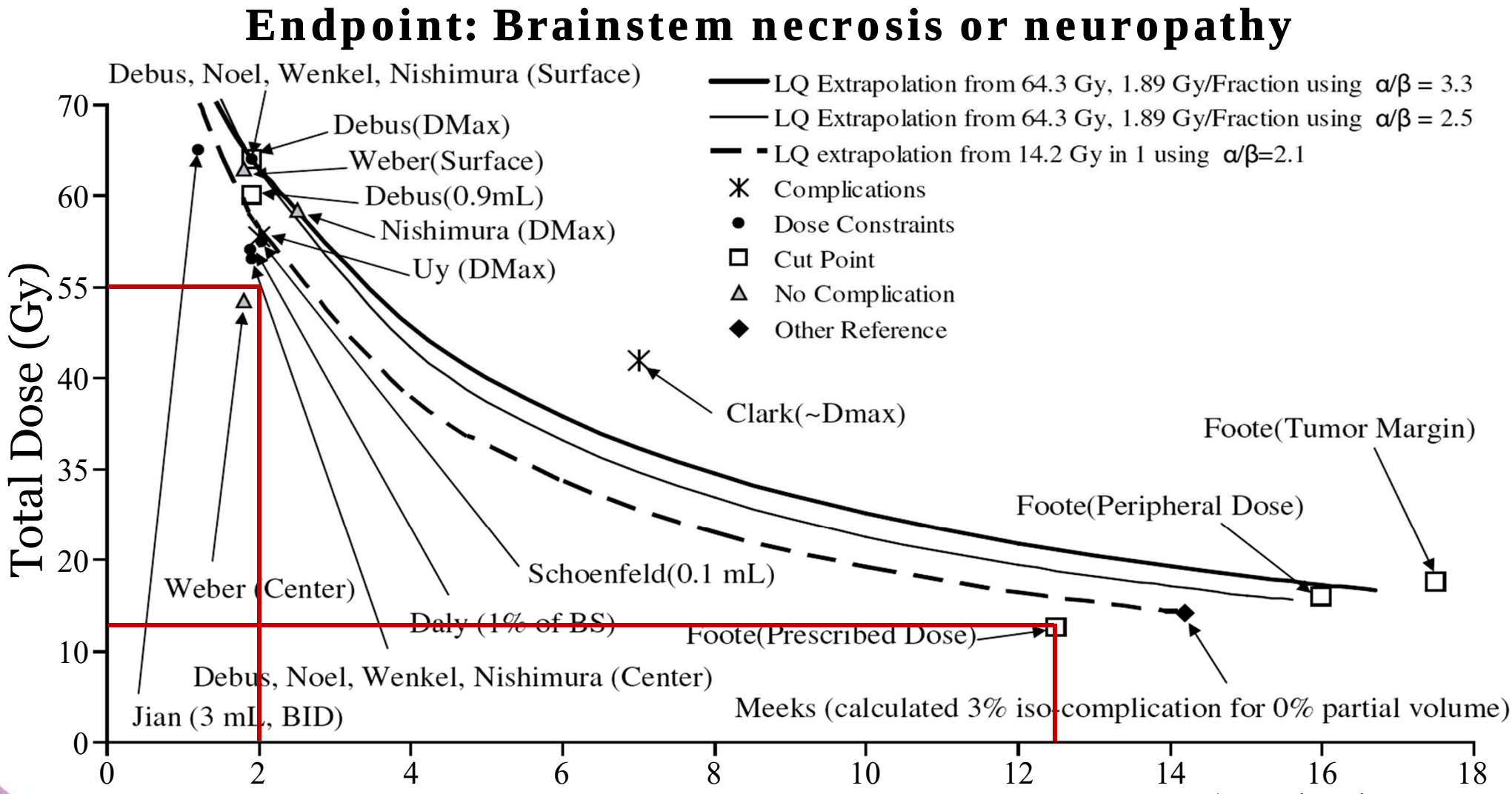
Parameters for clinical outcome: Brainstem



Mayo C et al. Radiation associated brainstem injury. Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, Supplement, pp. S36–S41, 2010.

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Parameters for clinical outcome: Brainstem

Volume segmented	Irradiation type (partial organ unless otherwise stated)	Endpoint	Dose (Gy), or dose/volume parameters	Rate (%)	Notes on dose/volume parameters
Whole organ	Whole organ 3D-CRT	Permanent cranial neuropathy or necrosis	Dmax <54 D1–10 cc ≤ 59	<5 <5	
Whole organ	3D-CRT	Permanent cranial neuropathy or necrosis	Dmax <64	<5	Point dose <<1 cc
Whole organ	SRS (single fraction)	Permanent cranial neuropathy or necrosis	Dmax <12.5	<5	For patients with acoustic tumors

- Lack of information for dose per fraction in the 4 to 8 Gy range and so **there are not affordable recommendations to be followed in the middle fractionations area**
- The extrapolation of LQ model to the highest doses may however be incorrect

Mayo C et al. Radiation associated brainstem injury. Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, Supplement, pp. S36–S41, 2010.

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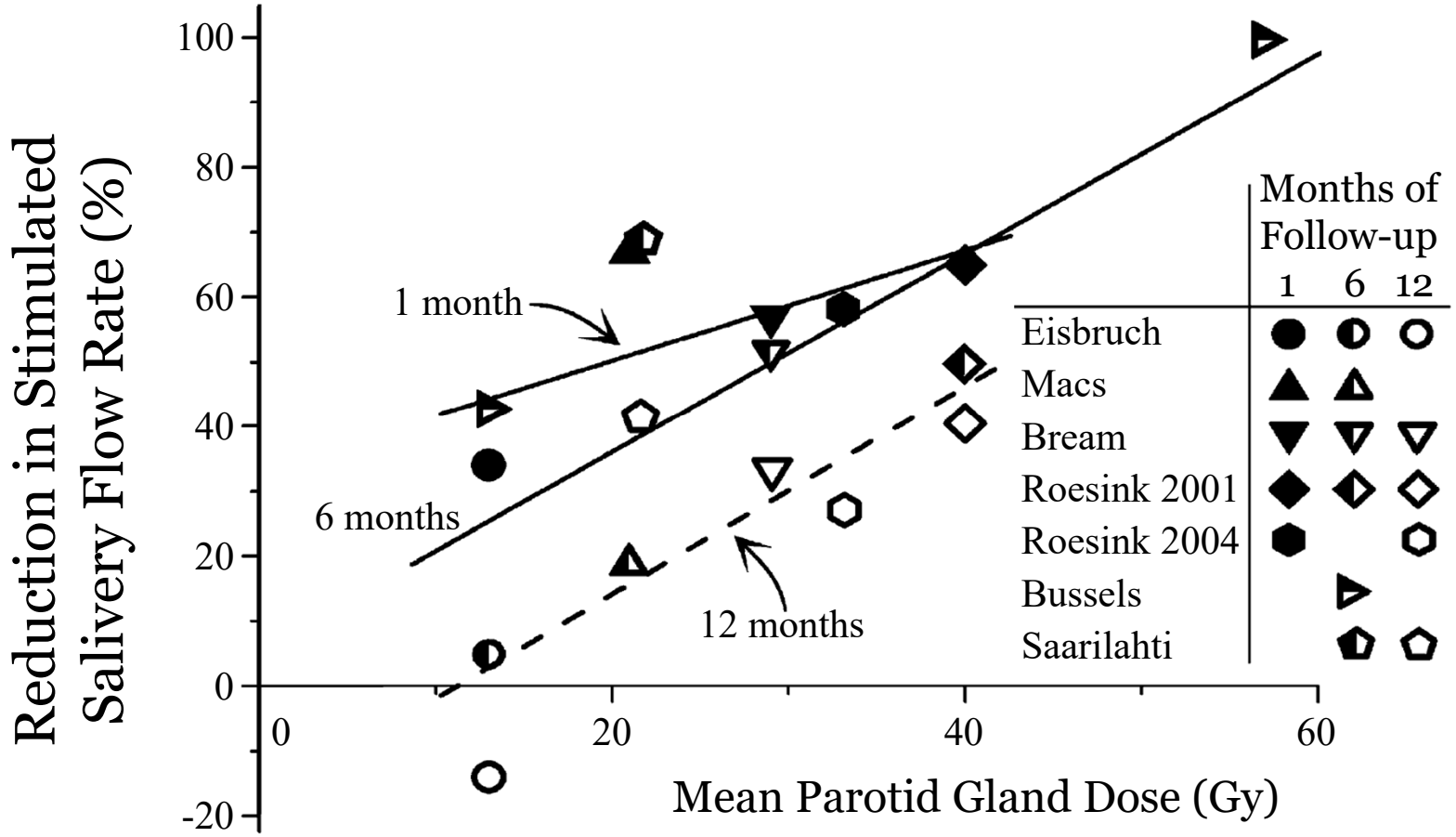
Parameters for clinical outcome: Salivary glands

Mean percentage of reduction in stimulated salivery flow rate vs. mean parotid gland dose for different follow-up durations



Deasy JO et al. Radiation Dose-Volume effects on the salivary gland function. Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, Supplement, pp. S58–S63, 2010.

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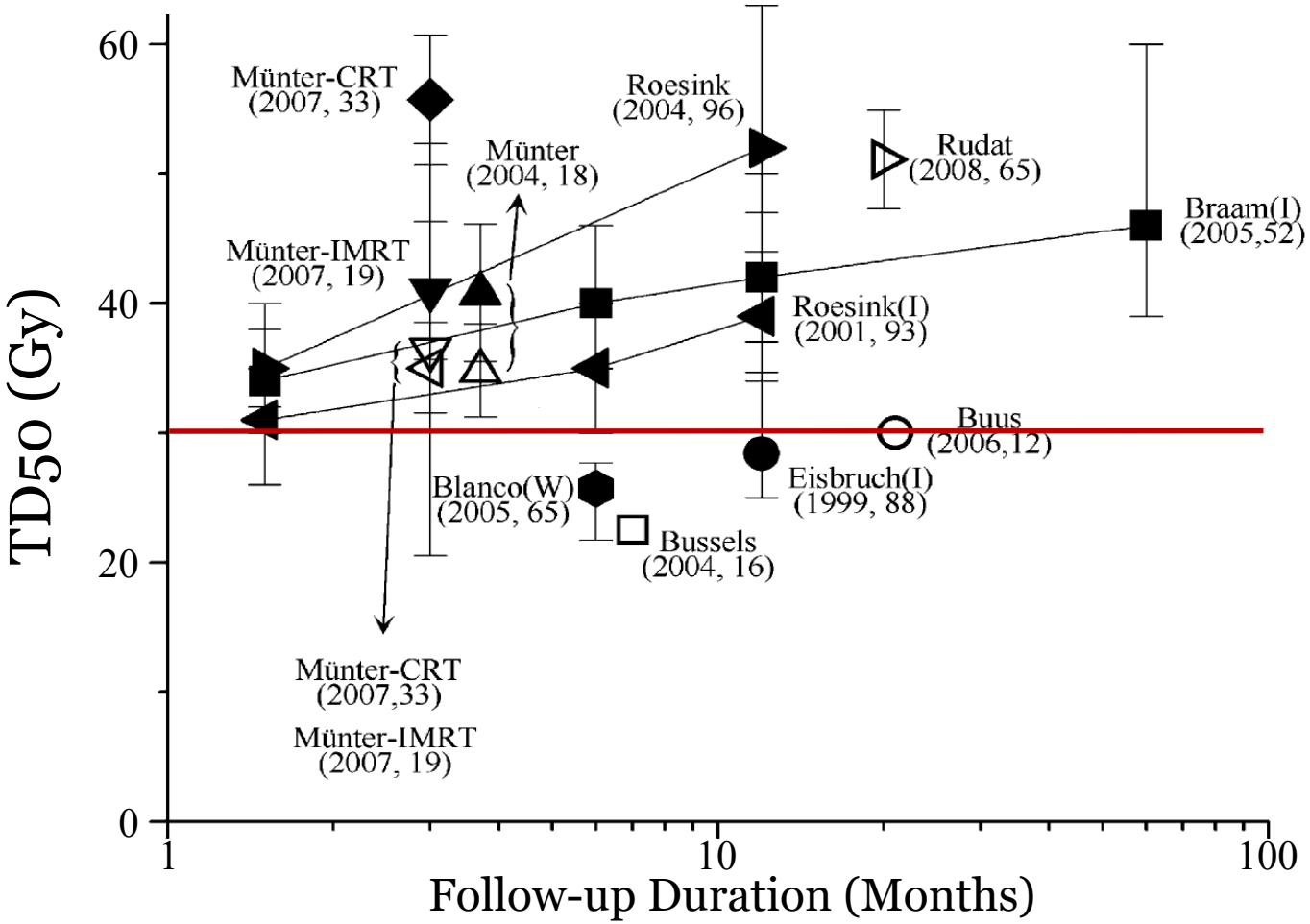
Parameters for clinical outcome: Salivary glands

Reported tissue dose required for 50% response for loss of stimulated saliva flow after radiotherapy for <u>single parotid gland</u>



Deasy JO et al. Radiation Dose-Volume effects on the salivary gland function. Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, Supplement, pp. S58–S63, 2010.

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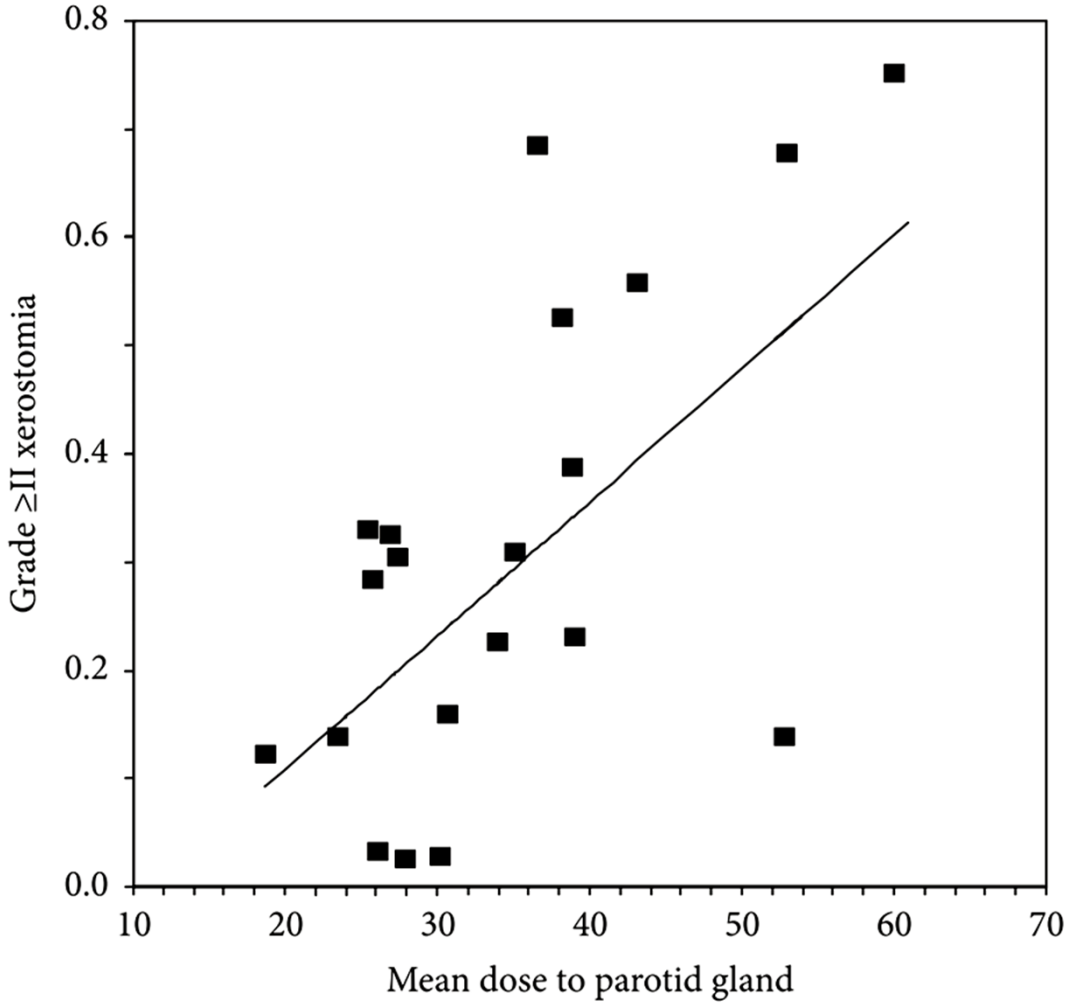
Parameters for clinical outcome: Salivary glands

Clinical estimation of RTOG grade 2 (moderate dryness of mouth; poor response on stimulation): toxicity related to mean parotid glands dose



Kouloulias V et al. The treatment outcome and radiation-induced toxicity for patients with head and neck carcinoma in the IMRT era: a systematic review with dosimetric and clinical parameters. BioMed Research International, Volume 2013, Article ID 401261.

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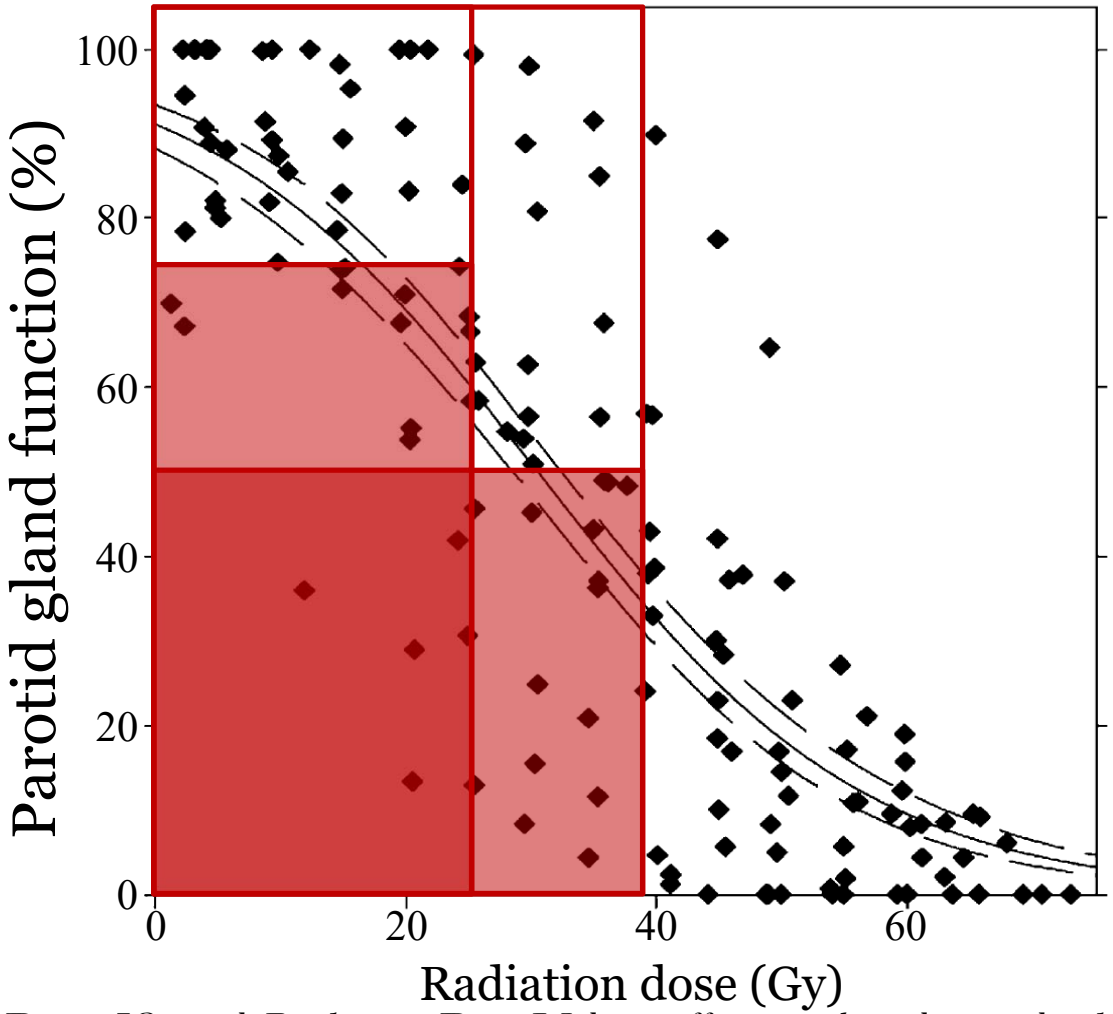
Parameters for clinical outcome: Salivary glands

Population-based dose vs. local function response (salivary function on rest) from imaging study



Dmean < **39 Gy**
Parotid gland function reduction of 25% < **30%**

Deasy JO et al. Radiation Dose-Volume effects on the salivary gland function. Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, Supplement, pp. S58–S63, 2010.

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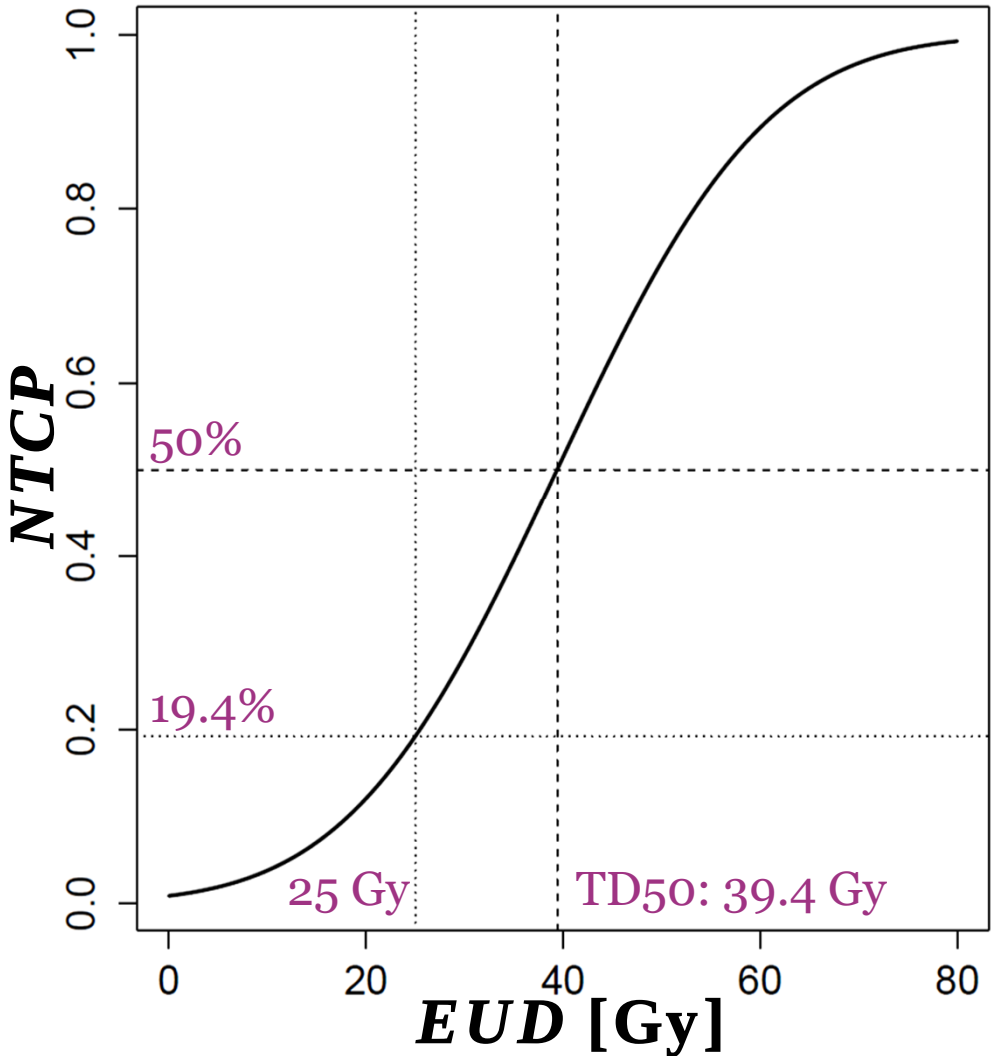
Parameters for clinical outcome: Salivary glands

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_{50}	38.8	36.5–43.5		
	γ	0.95	0.70–1.30		
Critical volume	α	0.03	0.06–0.20	357.73	0.66
	N_0	1	2–32		
	λ	0.65	0.60–0.90		
	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.



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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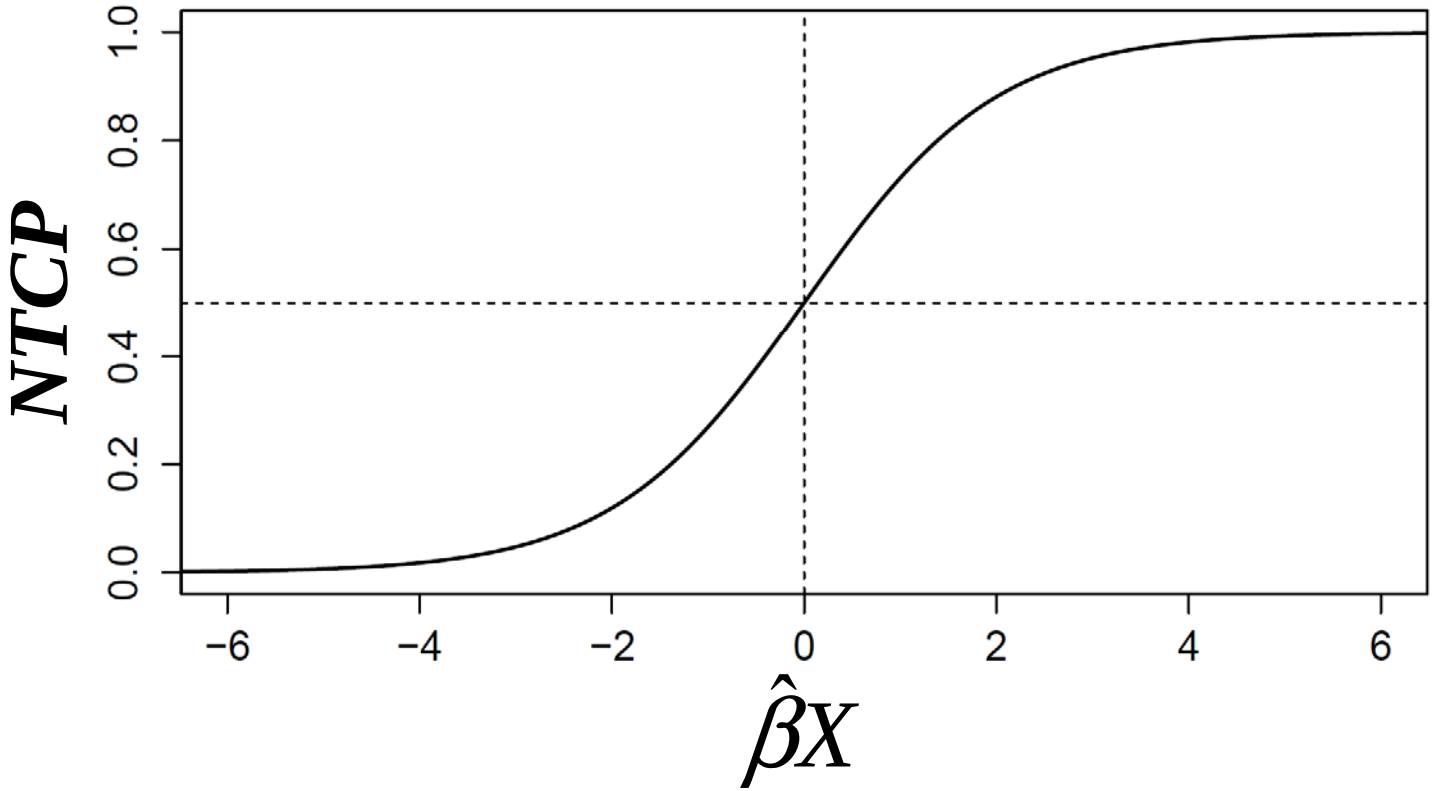
Parameters for clinical outcome: Salivary glands

Multivariate NTCP model:
use of logistic regression for fitting different covariates (in addition to dose):

$$NTCP = \frac{1}{1+e^{-\hat{\beta}X}} \qquad \hat{\beta}X = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_n x_n$$



Beetz I et al. Development of NTCP models for head and neck cancer patients treated with three-dimensional conformal radiotherapy for xerostomia and sticky saliva: The role of dosimetric and clinical factors. Radiother. Oncol. Volume 105, Issue 1, Pages 86–93.

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Parameters for clinical outcome: Salivary glands

Multivariate NTCP model:
Analysis of covariates:

Predictor	Xerostomia					Sticky saliva				
	β	OR	95% CI	p-value	AUC	β	OR	95% CI	p-value	AUC
Mean dose parotid glands (Gy)	0.06	1.06	1.04–1.08	<0.01	0.79	0.03	1.03	1.02–1.05	<0.01	0.69
Mean dose submandibular glands (Gy)	0.05	1.05	1.03–1.07	<0.01	0.75	0.04	1.04	1.02–1.05	<0.01	0.68
Mean dose sublingual glands (Gy)	0.02	1.02	1.01–1.04	<0.01	0.72	0.00	1.00	0.99–1.01	0.67	0.57
Mean dose cheeks (Gy)	0.04	1.04	1.02–1.07	<0.01	0.72	0.00	1.00	0.99–1.02	0.77	0.55
Mean dose inner surface lower lip (Gy)	0.02	1.02	1.00–1.05	0.07	0.67	−0.13	0.99	0.97–1.01	0.21	0.51
Mean dose inner surface upper lip (Gy)	0.03	1.03	1.00–1.07	0.06	0.65	−0.15	0.99	0.96–1.01	0.30	0.52
Mean dose soft palate (Gy)	0.03	1.03	1.02–1.05	<0.01	0.75	0.01	1.01	1.00–1.02	0.06	0.61
Sex	0.24	1.27	0.67–2.40	0.46	0.56	0.31	1.37	0.68–2.74	0.38	0.53
Age	0.01	1.01	0.98–1.04	0.54	0.51	0.03	1.03	1.00–1.06	0.06	0.57
Chemotherapy	0.93	2.53	1.15–5.58	0.02	0.58	0.21	1.24	0.59–2.59	0.57	0.52
Accelerated radiotherapy	−0.29	0.75	0.40–1.42	0.38	0.53	0.02	1.02	0.54–1.91	0.96	0.50
Baseline xerostomia score	1.01	2.75	1.39–5.47	<0.01	0.61	0.63	1.87	1.15–3.04	0.01	0.61
Baseline sticky saliva score	0.59	1.81	1.01–3.23	0.05	0.57	0.94	2.57	1.27–5.17	<0.01	0.59
Bilateral neck irradiation	1.80	6.06	2.90–12.66	<0.01	0.68	1.97	7.15	3.19–16.01	<0.01	0.69
Medical centre (UMCG vs. VUMC)	1.09	2.98	1.43–6.21	<0.01	0.60	1.54	4.67	2.0–10.9	<0.01	0.63

Beetz I et al. Development of NTCP models for head and neck cancer patients treated with three-dimensional conformal radiotherapy for xerostomia and sticky saliva: The role of dosimetric and clinical factors. Radiother. Oncol. Volume 105, Issue 1, Pages 86–93.

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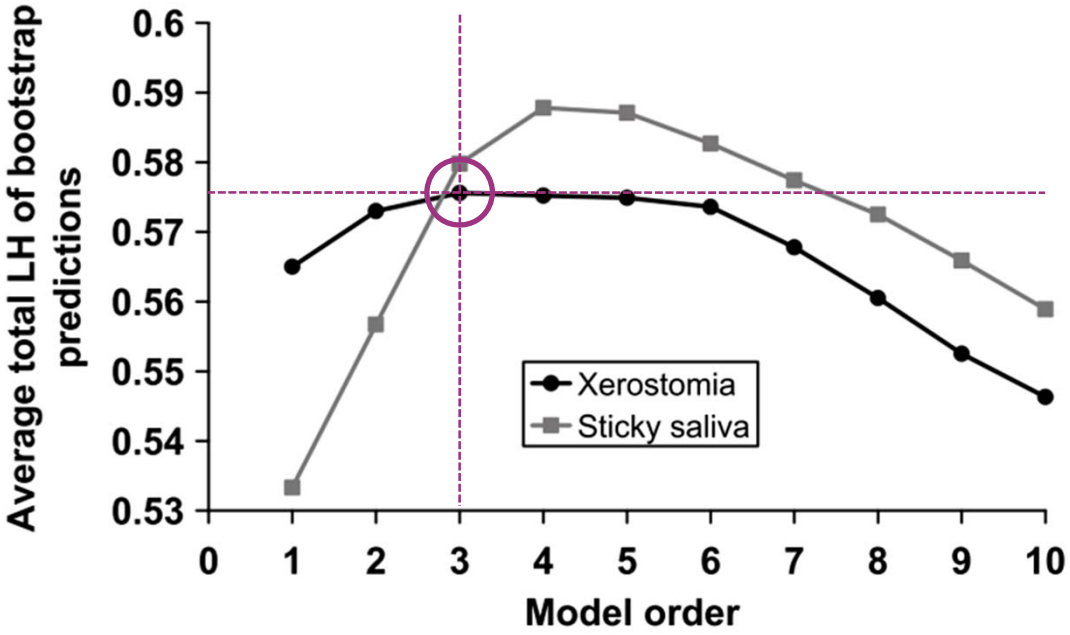
Parameters for clinical outcome: Salivary glands

Multivariate NTCP model:

Selection of covariates:



Final model:

$$NTCP = \frac{1}{1+e^{-\hat{\beta}X}}$$

$$\hat{\beta}X = \text{-5.27 + 0.066*mean dose parotid glands + + 0.05*age + 0.916*baseline xerostomia score}$$

Baseline xerostomia score is a simple clinical evaluation before the treatment (dummy covariate):

0: no xerostomia

1: a bit of xerostomia

Beetz I et al. Development of NTCP models for head and neck cancer patients treated with three-dimensional conformal radiotherapy for xerostomia and sticky saliva: The role of dosimetric and clinical factors. Radiother. Oncol. Volume 105, Issue 1, Pages 86–93.

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Parameters for clinical outcome: Salivary glands

Volume segmented	Irradiation type (partial organ unless otherwise stated)	Endpoint	Dose (Gy), or dose/volume parameters	Rate (%)	Notes on dose/volume parameters
Bilateral whole parotid glands	3D-CRT	Long term parotid salivary function reduced to <25% of pre-RT level	Mean dose <25	<20	For combined parotid glands
Unilateral whole parotid gland	3D-CRT	Long term parotid salivary function reduced to <25% of pre-RT level	Mean dose <20	<20	For single parotid gland. At least one parotid gland spared to <20 Gy
Bilateral whole parotid glands	3D-CRT	Long term parotid salivary function reduced to <25% of pre-RT level	Mean dose <39	<50	For combined parotid glands

- Severe xerostomia is related to additional factors including the doses to the submandibular glands
- But submandibular glands should be included in the CTV for Ib nodes irradiation (oropharynx, oral cavity, N3)

Deasy JO et al. Radiation Dose-Volume effects on the salivary gland function. Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, Supplement, pp. S58–S63, 2010.

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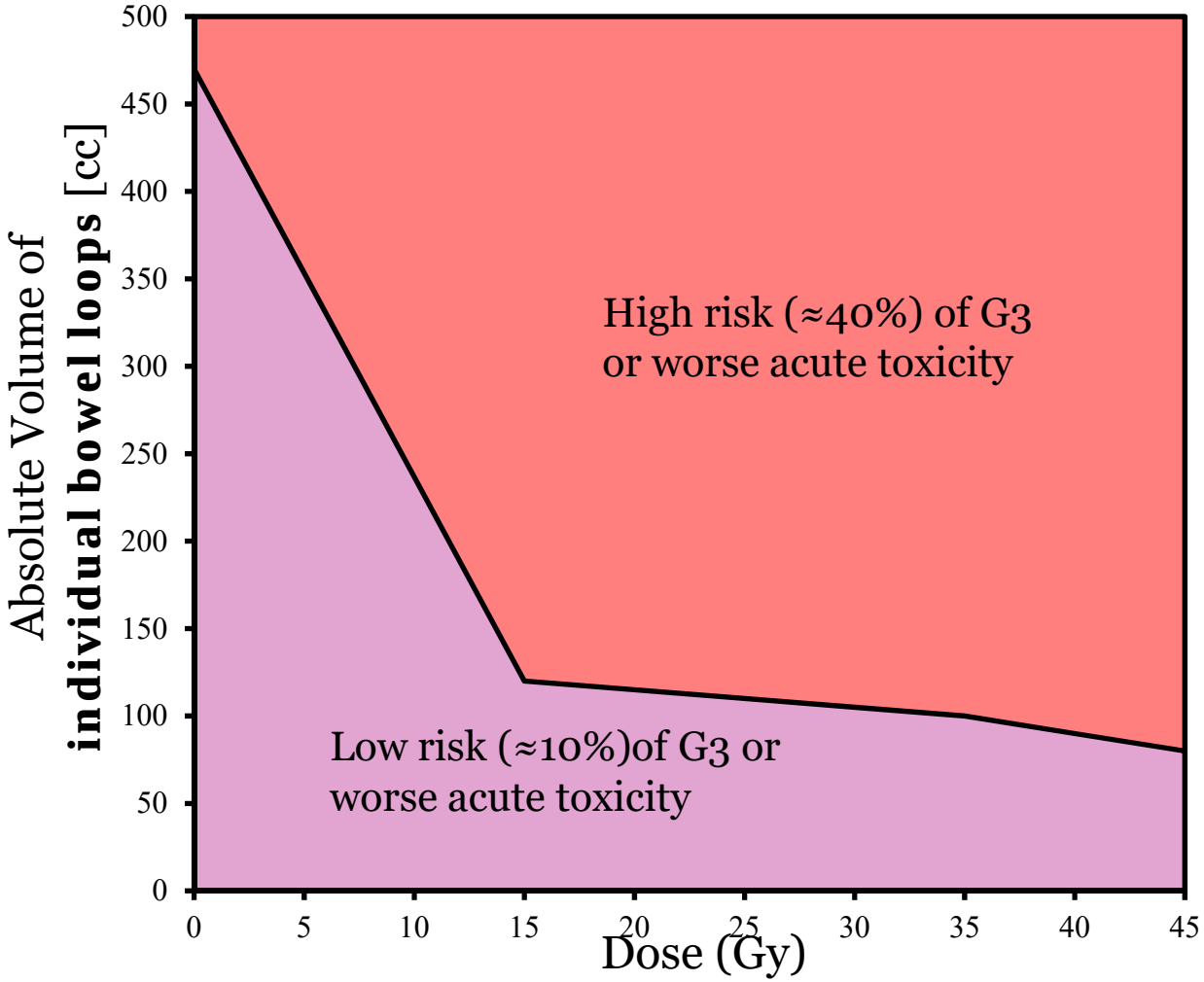
Parameters for clinical outcome: Small bowel

Baglan-Robertson threshold model for risk of acute small bowel toxicity



CTCAE G3: Abdominal pain, fever, change in bowel habits with ileus; peritoneal signs

Kavanagh BD et al. Radiation Dose-Volume effects in the stomach and small bowel. Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, Supplement, pp. S101–S107, 2010.

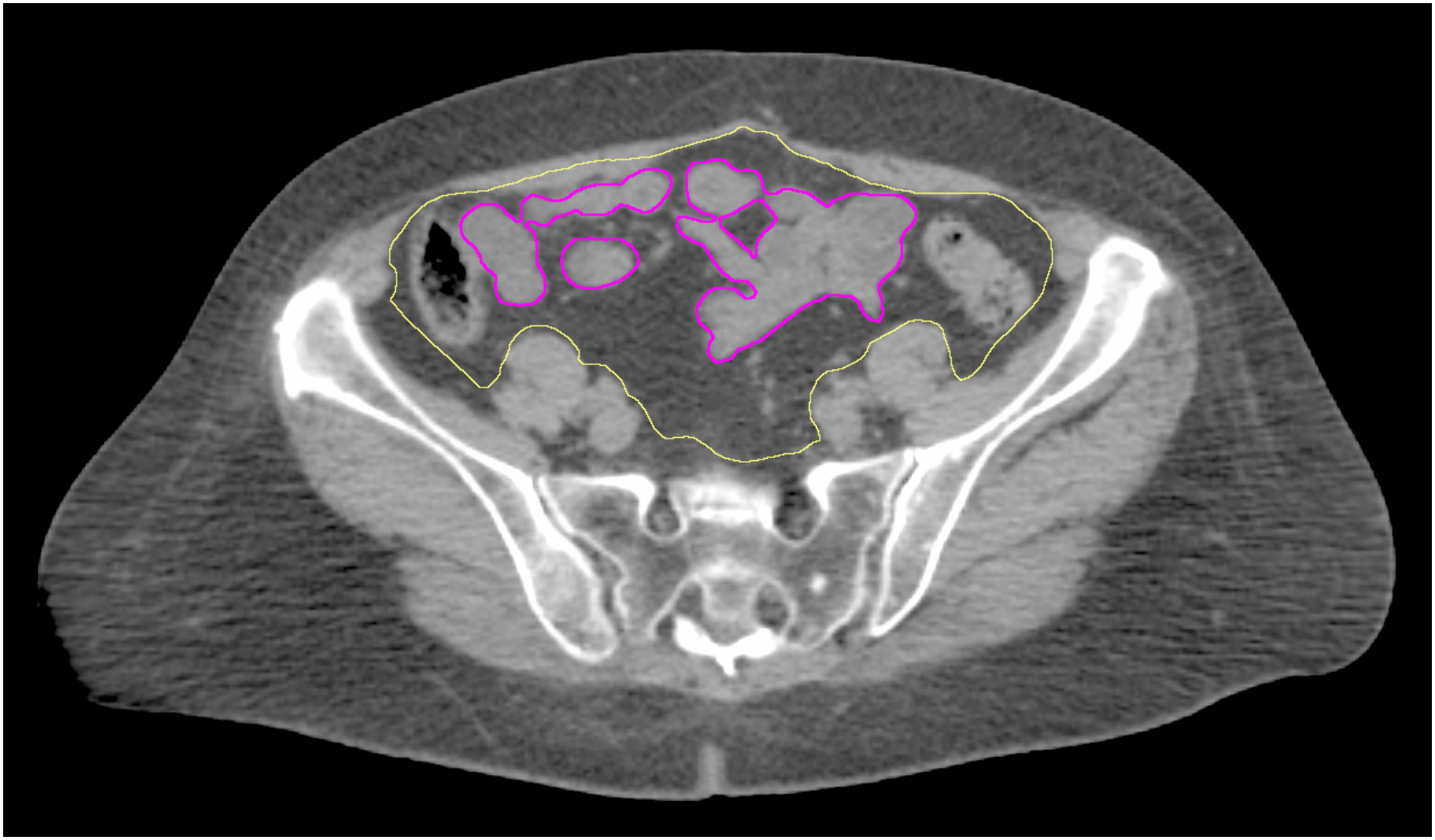
ESTRO School

Parameters for clinical outcome: Small bowel

Problems in evaluating small bowel toxicity:

1) Different types of treatment can involve small bowel according the **primary tumor site** (gastric, pancreas, rectum, prostate, cervical cancer)
2) Different types of **combined treatment** according to the primary site
    1) Chemotherapy (5-Fu, CDDP, Capecitabine, Gemcitabine)
3) Intrinsic **movements of small bowel** (filling, emptying, peristalsis)
4) Presence of **surgery** (before radiotherapy)
    1) Fixed bowel loops
    2) Bowel loops hypovascularization
    3) Bowel loops injury

Parameters for clinical outcome: Small bowel



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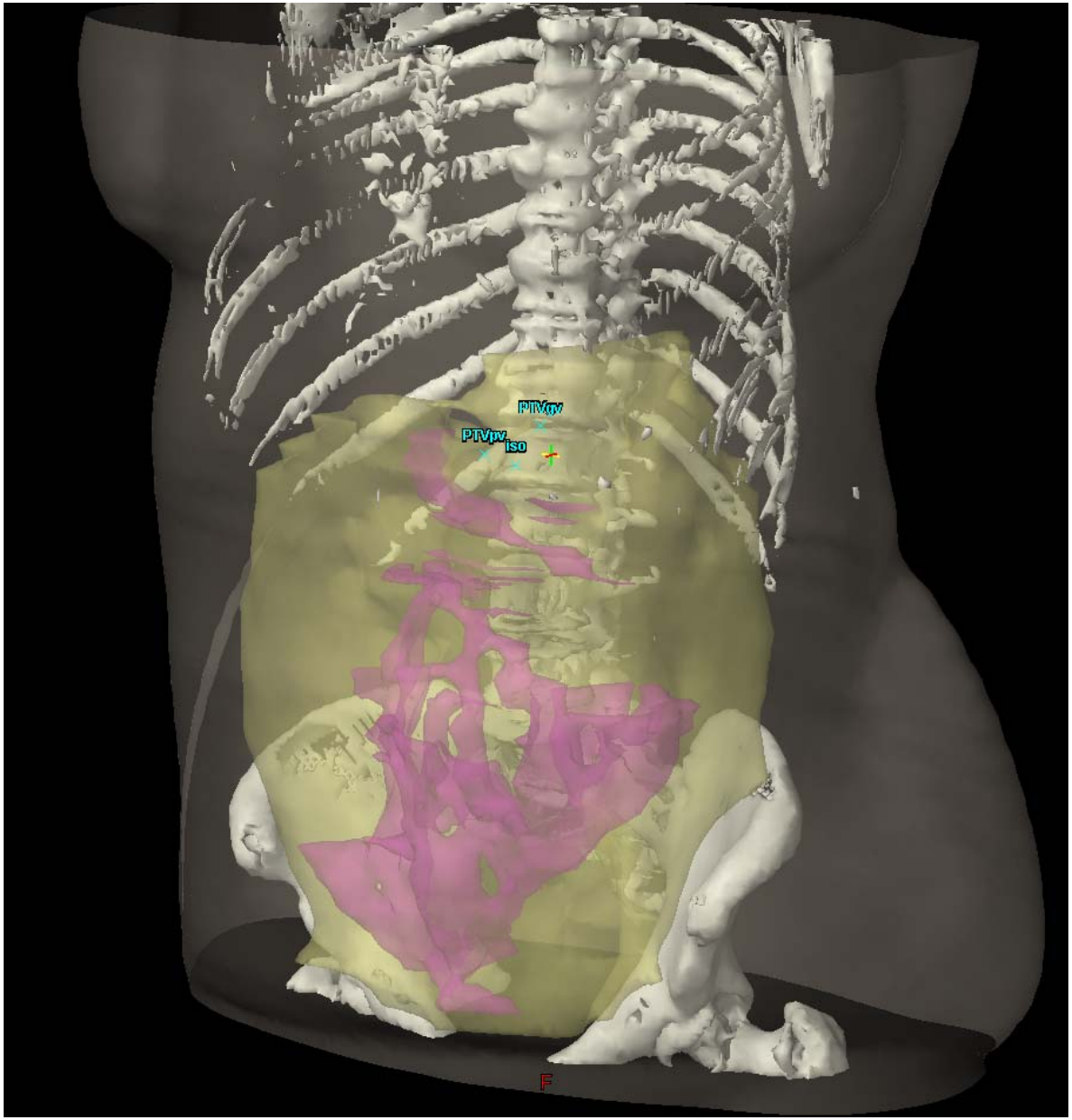
Parameters for clinical outcome: Small bowel



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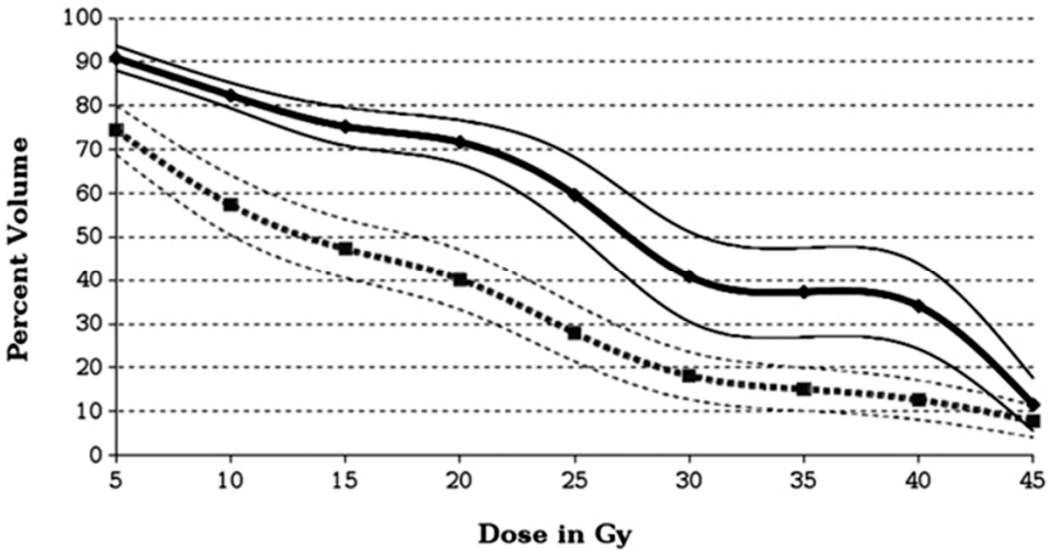
Parameters for clinical outcome: Small bowel

Small bowel toxicity (G0-2 ····· vs G≥3 ———) different OAR delineation procedures



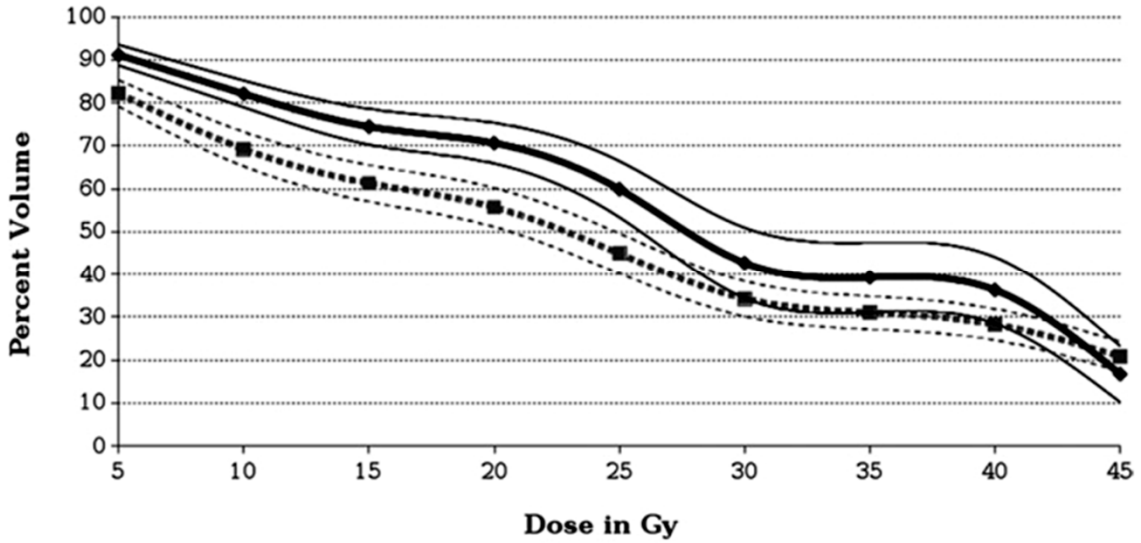


Table 3 ROC analysis for small bowel and peritoneal space volumes and association with grade ≥3 acute small bowel toxicity

Small bowel	AUC	SE	*P* value	Peritoneal space	AUC	SE	*P* value
SB V5	.937	.033	.000	PS V5	.865	.046	.000
SB V10	.946	.031	.000	PS V10	.883	.043	.000
SB V15	.951	.026	.000	PS V15	.883	.050	.000
SB V20	.955	.025	.000	PS V20	.881	.053	.000
SB V25	.964	.021	.000	PS V25	.896	.045	.000
SB V30	.948	.028	.000	PS V30	.839	.062	.000
SB V35	.943	.030	.000	PS V35	.847	.061	.000
SB V40	.950	.028	.000	PS V40	.844	.062	.000
SB V45	.812	.073	.001	PS V45	.567	.094	.488

Abbreviations: AUC = area under the curve; SB = small bowel; SE = standard error; PS = peritoneal space.

R Banerjee et al. Small Bowel Dose Parameters Predicting Grade ≥3 Acute Toxicity in Rectal Cancer Patients Treated With Neoadjuvant Chemoradiation: An Independent Validation Study Comparing Peritoneal Space Versus Small Bowel Loop Contouring Techniques Int. J. Radiation Oncology Biol. Phys., Vol. 85, No. 5, pp. 1226–1231, 2013.

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Parameters for clinical outcome: Small bowel

Small bowel toxicity in patients with GYN tumors undergone or not to abdominal surgery:

1) 95 patients with GYN malignancies
2) 34 patients after surgery, 61 patients without prior surgery
3) Use of LASSO for modeling logistic regression over Vdose parameters

$$NTCP = \frac{1}{1+e^{-\hat{\beta}X}} = \left[1+\left(\frac{TV_{50}}{V}\right)^{4\gamma}\right]^{-1}$$

TV_{50} = tolerance volume corresponding to 50% incidence of complications

V = volume of small bowel receiving a given dose level

γ = normalized slope of the volume response curve

TF Lee et al. The Different Dose-Volume Effects of Normal Tissue Complication Probability Using LASSO for Acute Small-Bowel Toxicity during Radiotherapy in Gynecological Patients with or without Prior Abdominal Surgery. BioMed Research International Volume 2014, Article ID 143020.

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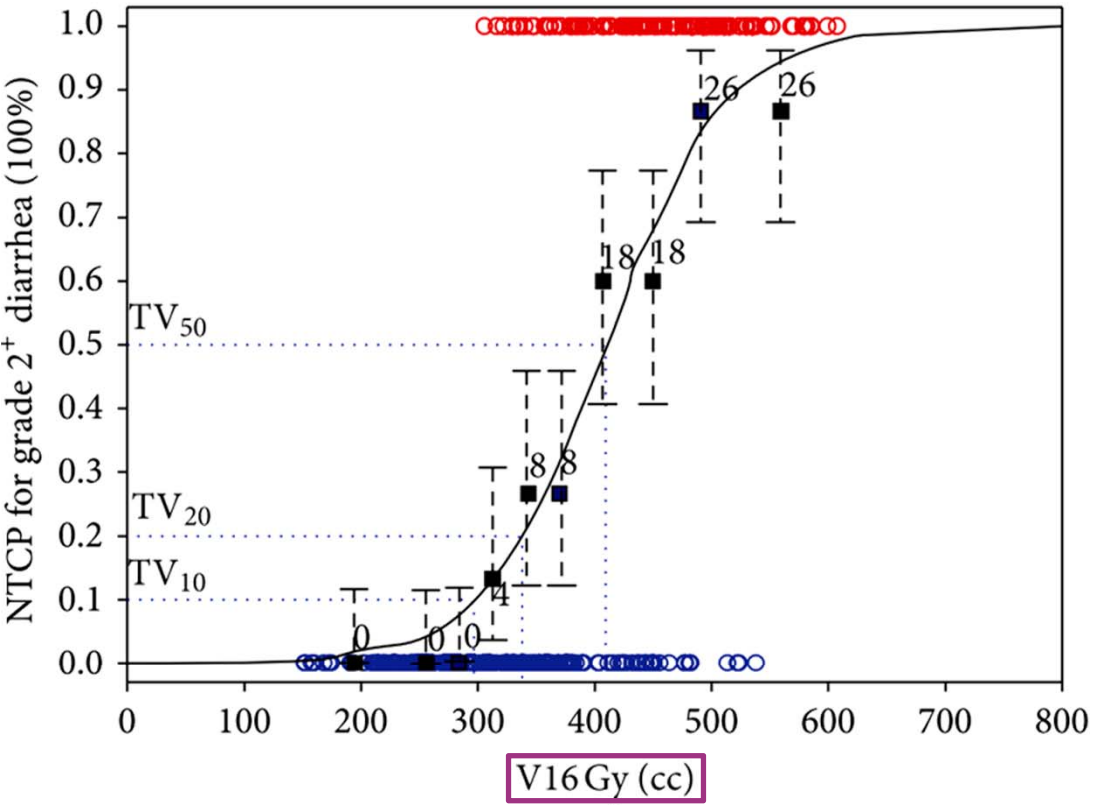
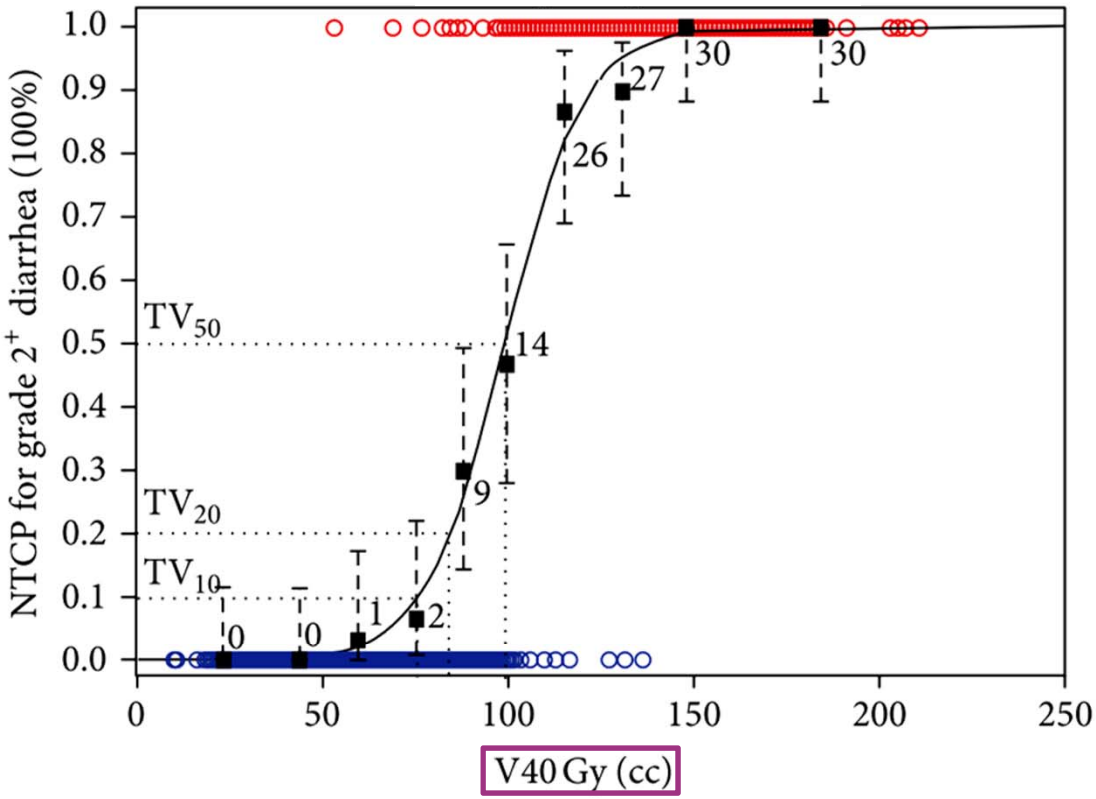
Parameters for clinical outcome: Small bowel

Surgery -



—— TV_{50} = 409.44 (391.13–427.74), γ = 1.99 (1.36–2.62)
TV_{20} = 338.11 (310.22–362.25), TV_{10} = 296.38 (261.12–331.91)
■ Toxicity rates = $N/30$, bin size = 30

Surgery +



—— TV_{50} = 99.03 (96.60–101.46), γ = 2.34 (1.85–2.83)
TV_{20} = 84.37 (80.49–87.87), TV_{10} = 75.80 (70.76–80.93)
■ Toxicity rates = $N/30$, bin size = 30

TF Lee et al. The Different Dose-Volume Effects of Normal Tissue Complication Probability Using LASSO for Acute Small-Bowel Toxicity during Radiotherapy in Gynecological Patients with or without Prior Abdominal Surgery. BioMed Research International Volume 2014, Article ID 143020.

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Parameters for clinical outcome: Small bowel

Volume segmented	Irradiation type (partial organ unless otherwise stated)	Endpoint	Dose (Gy), or dose/volume parameters	Rate (%)	Notes on dose/volume parameters
Individual small bowel loops	3D-CRT	Grade ≥ 3 acute toxicity	V15 <120 cc	<10	Volume based on segmentation of the **individual loops of bowel,** not the entire potential peritoneal space
Entire potential space within peritoneal cavity	3D-CRT	Grade ≥ 3 acute toxicity	V45 <195 cc	<10	Volume based on the **entire potential space within the peritoneal cavity**

- All data based on series with **concurrent chemotherapy**
- For single fraction **SBRT** (25 Gy) **data are poor**, but the cutoff seems to set down to V12.5<30 cc without bowel toxicity

Kavanagh BD et al. Radiation Dose-Volume effects in the stomach and small bowel. Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, Supplement, pp. S101–S107, 2010.

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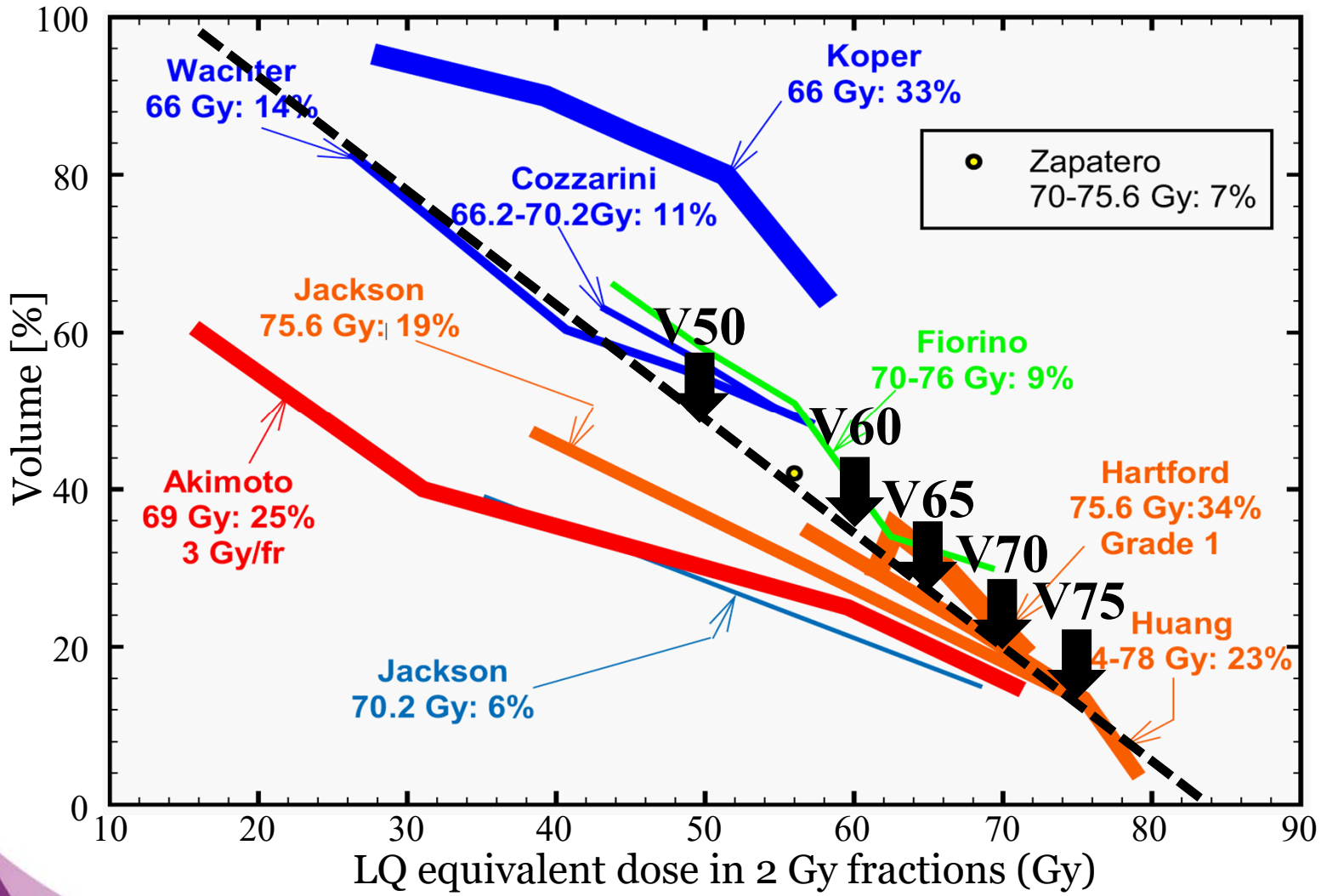
Parameters for clinical outcome: Rectum

Dose-Volume limits for ≥ G2 rectal toxicity with LQ corrected doses (α/β = 3 Gy)



RTOG G2: Increase of 4-6 stools/day, or nocturnal stools, or moderate cramping

CTCAE G2: Symptoms not interfering with ADL; medical intervention indicated

Michalski JM et al. Radiation Dose-Volume effects in radiation-induced rectal injury. Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, Supplement, pp. S123–S129, 2010.

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Parameters for clinical outcome: Rectum

Volume segmented	Irradiation type (partial organ unless otherwise stated)	Endpoint	Dose (Gy), or dose/volume parameters	Rate (%)	Notes on dose/volume parameters
Whole organ	3D-CRT	Grade ≥ 2 late rectal toxicity,	V50 <50%	<15	Prostate cancer treatment
		Grade ≥ 3 late rectal toxicity		<10	
Whole organ	3D-CRT	Grade ≥ 2 late rectal toxicity,	V60 <35%	<15	
		Grade ≥ 3 late rectal toxicity		<10	
Whole organ	3D-CRT	Grade ≥ 2 late rectal toxicity,	V65 <25%	<15	
		Grade ≥ 3 late rectal toxicity		<10	
Whole organ	3D-CRT	Grade ≥ 2 late rectal toxicity,	V70 <20%	<15	
		Grade ≥ 3 late rectal toxicity		<10	
Whole organ	3D-CRT	Grade ≥ 2 late rectal toxicity,	V75 <15%	<15	
		Grade ≥ 3 late rectal toxicity		<10	

- Rectal segmentation from above the anal verge to the turn into sigmoid colon
- The evaluation of **rectal bleeding** seems to have a *n* value lower than other endpoints (0.09)
- The reduction of V75 from 15% to 10% is more effective than reduction of V50 from 50% to 45% respectively

Michalski JM et al. Radiation Dose-Volume effects in radiation-induced rectal injury. Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, Supplement, pp. S123–S129, 2010.

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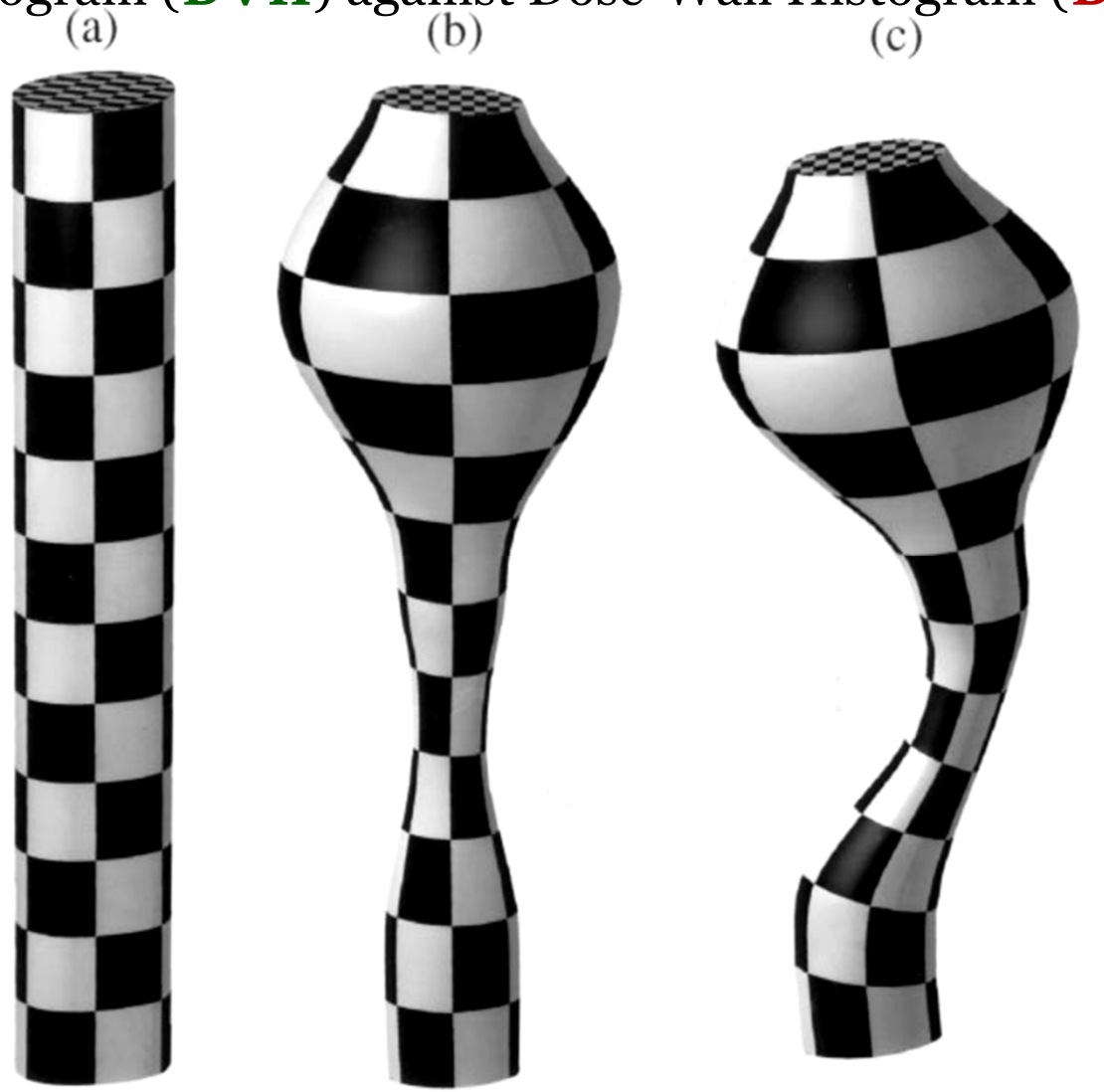
Parameters for clinical outcome: Rectum

- Dose-Volume histogram (**DVH**) against Dose-Wall Histogram (**DWH**)



Meijer GJ et al. Dose-wall histograms and normalized dose-surface histograms for the rectum: A new method to analyze the dose distribution over the rectum in conformal radiotherapy. Int J Radiat Oncol Biol Phys 1999;45:1073–80.

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Parameters for clinical outcome: Rectum

- Dose-Volume histogram (**DVH**) against Dose-Wall Histogram (**DWH**)

Model	Parameter	DVH data	DWH data
Lyman	$\log_{10} n$	0.013 (−1.55, 5.47)	4.95 (−0.35, 5.50)
	m	0.160 (0.039, 0.398)	0.167 (0.089, 0.300)
	D_{50} (Gy)	55.9 (49.0, 75.8)	48.6 (46.1, 58.4)
	LL	−60.47	−57.72
Mean dose	MD_{50} (Gy)	56.0 (53.1, 63.2)	53.2 (51.2, 57.7)
	s (Gy^{-1})	0.112 (0.056, 0.174)	0.154 (0.083, 0.230)
	LL	−60.47	−58.48
Cutoff dose	D_c (Gy)	44.8 (29.4, 76.8)	32.4 (28.2, 47.1)
	VD_c (50) (%)	69.7 (17.8, 97.9)	81.7 (56.0, 92.4)
	s	4.91 (2.38, 7.91)	7.11 (3.67, 10.9)
	LL	−60.90	−57.92
Parallel model	S_D (Gy^{-1})	0.008 (0, ∞)	0.132 (0.003, ∞)
	D_{50} (Gy)	4.92 (0, ∞)	32.7 (0, ∞)
	s_f	38.0 (2.69, ∞)	8.80 (3.84, ∞)
	f_{50}	0.655 (0.510, 1)	0.795 (0.076, 0.924)
	LL	−60.46	−57.83

Abbreviations: DVH = dose–volume histogram; DWH = dose–wall histogram; NTCP = normal tissue complication probability.

Model	AIC		AUC	
	DVH	DWH	DVH	DWH
Lyman model	126.9	121.4	0.731	0.763
Mean-dose model	124.9	121.0	0.733	0.765
Cutoff-dose model	127.8	121.8	0.727	0.761
Parallel model	128.9	123.7	0.731	0.759

Abbreviations: AIC = Akaike Information Criterion; AUC = area under curve; DVH = dose–volume histogram; DWH = dose–wall histogram; ROC = receiver operating characteristic.

- Toxicity scored with a modified RTOG score
- Endpoint G2 or higher within 2 years from the end of the treatment

Tucker SL et al. Comparison of rectal dose-wall histogram versus dose-volume histogram for modeling the incidence of late rectal bleeding after radiotherapy. Int J Radiat Oncol Biol Phys 2004;60:1589–601.

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Parameters for clinical outcome: Rectum

Multivariate modeling for detecting rectal toxicity (G3 late rectal bleeding)

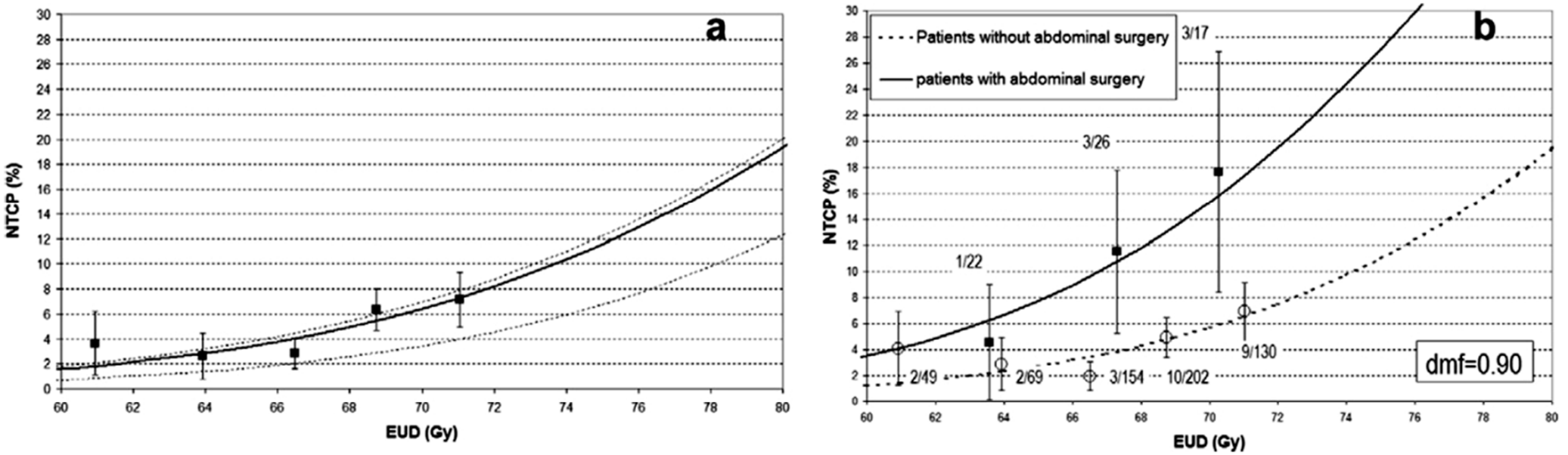

Fig. 2. Incidence of G3 late rectal bleeding vs EUD: (a) unmodified model (without inclusion of clinical risk factor), solid curve predicted NTCP curve, dashed curves 68% confidence interval, see text for the definition of confidence interval; (b) inclusion of previous abdominal surgery. Observed complication rates [symbols] and predicted NTCP curve [continuous lines] are plotted. Description of symbols: (a) solid squares (■) = all patients; (b) open circles (○) = patients without abdominal surgery, solid squares (■) = patients with abdominal surgery.

Logistic regression: $NTCP = \frac{1}{1+\left(\frac{TD_{50}}{EUD}\right)^{k}}$; $EUD = \left(\sum_i v_i \cdot D_i^{\frac{1}{n}}\right)^n$

		TD_{50}:	82.5 Gy
n:	0.046		
TD_{50}:	93.1 Gy	TD_{50}:	91.7 Gy
k:	10.4		

T Rancati et al. Inclusion of clinical risk factors into NTCP modeling of late rectal toxicity after high dose radiotherapy for prostate cancer. Radiother Oncol 100 (2011) 124–130.

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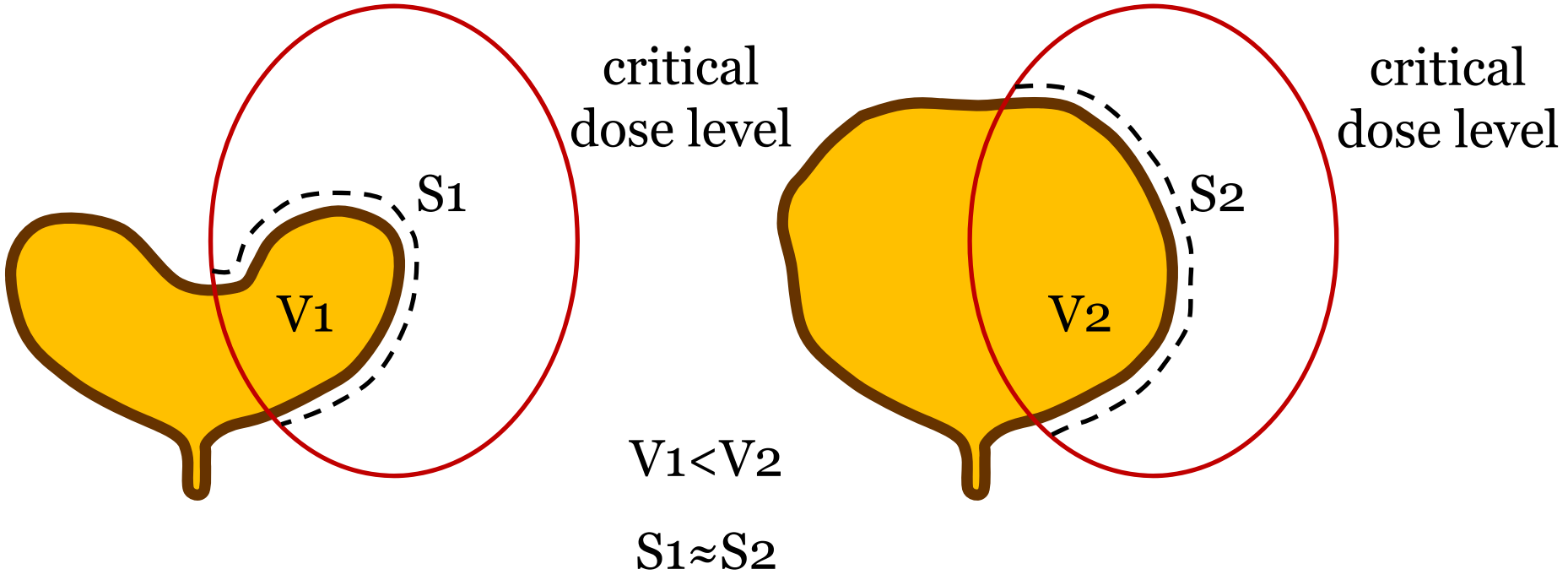
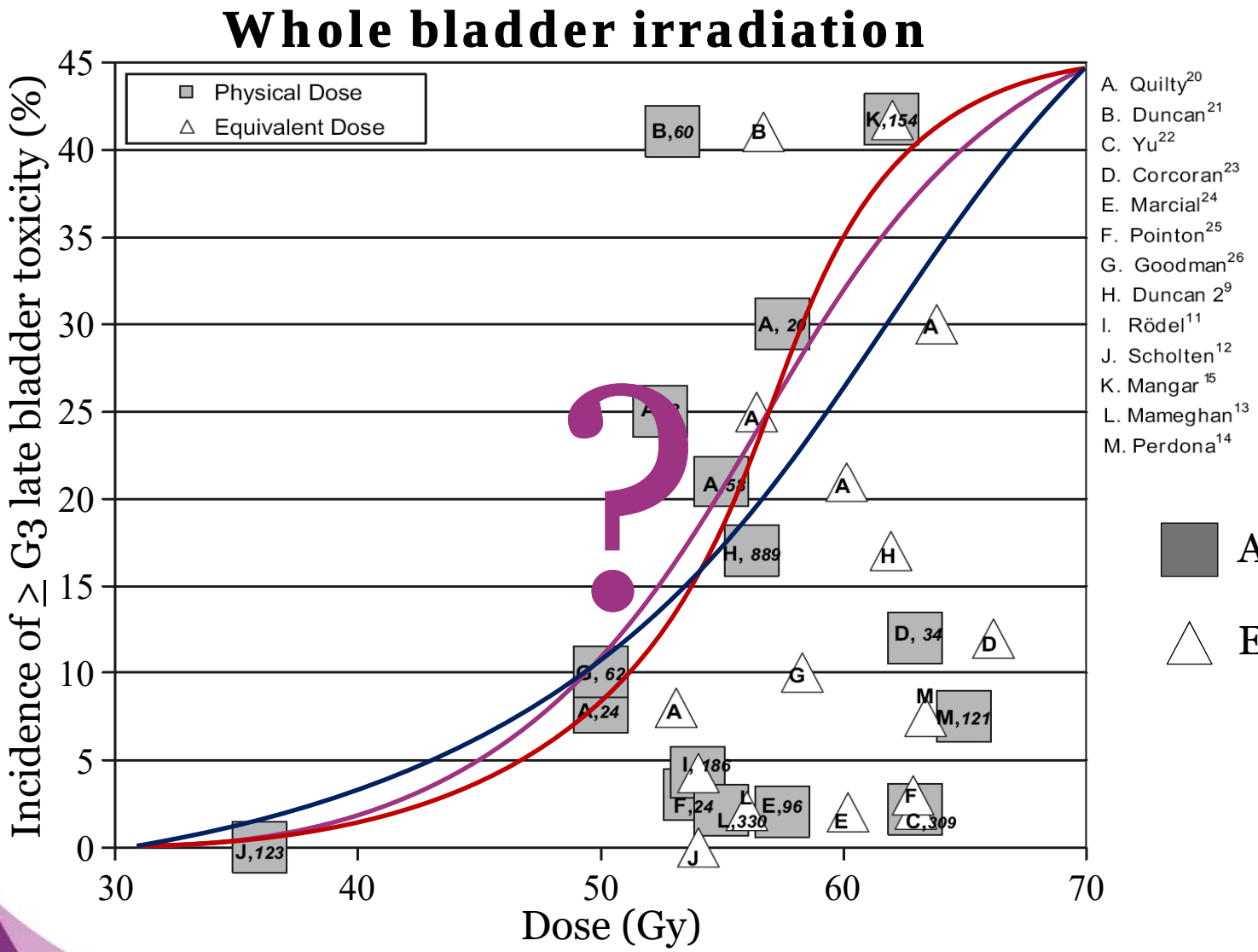
Parameters for clinical outcome: Urinary bladder

Problems in urinary bladder toxicity evaluation:

1) Heterogeneous evidences
2) Poor reliability
3) Problems in volume stability during treatment duration:
   Definition of Vdose and Dvolume not reliable with a single CT scan



Parameters for clinical outcome: Urinary bladder



RTOG G3: gross hematuria/no clots

Average dose

EQD2 dose ($\alpha/\beta = 6$ Gy)

Viswanathan AN et al. Radiation Dose-Volume effects of the urinary bladder. Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, Supplement, pp. S116–S122, 2010.

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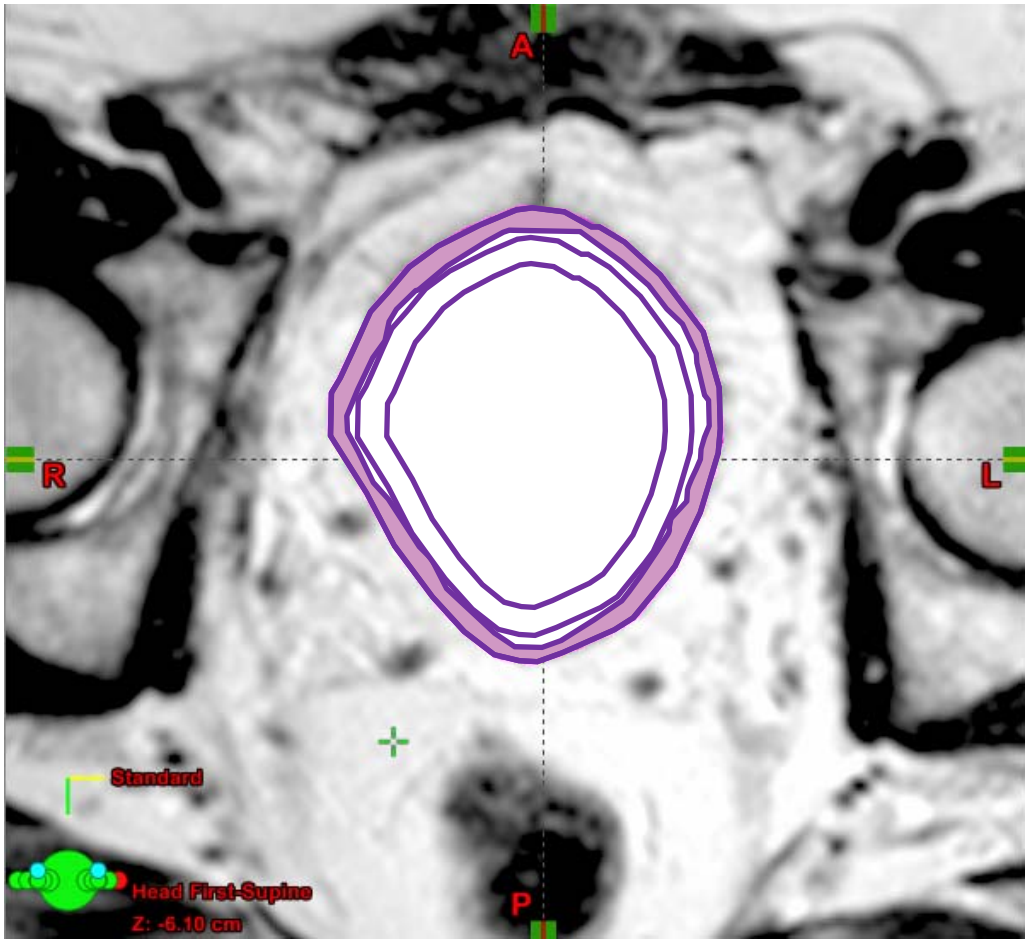
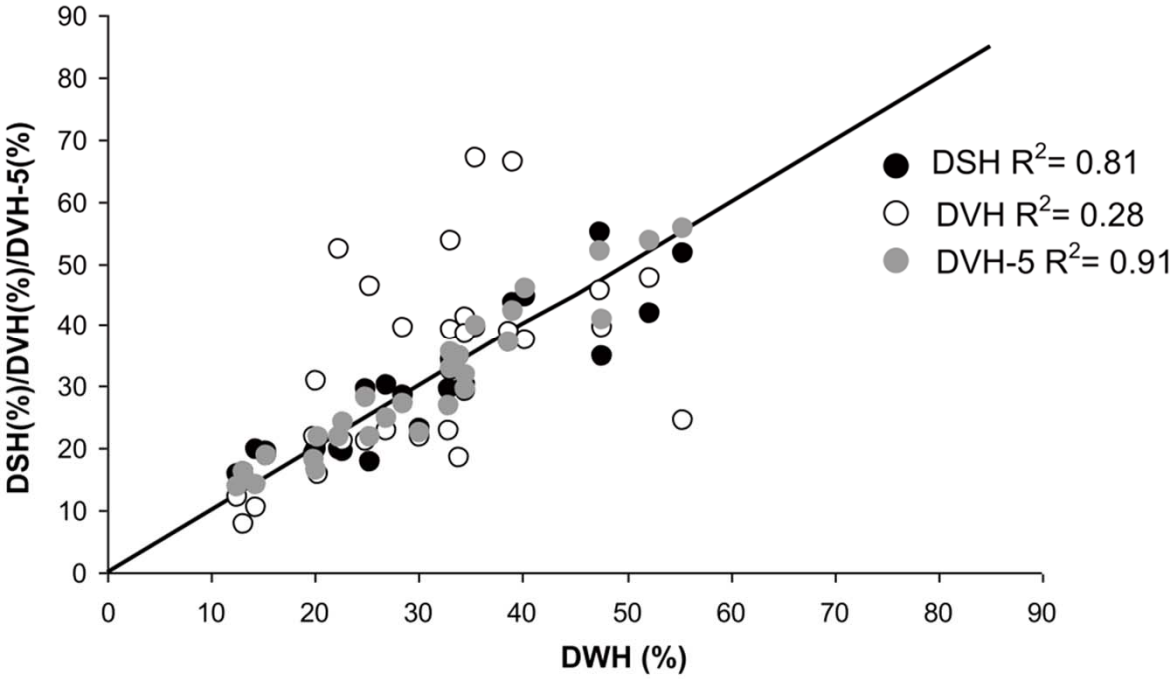
Is the DVH a good predictor of toxicity in bladder?





Carillo V et al. Correlation between surrogates of bladder dosimetry and dose-volume histograms of the bladder wall defined on MRI in prostate cancer radiotherapy. Radiother Oncol 2012;105:180–3.

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Parameters for clinical outcome: Urinary bladder

Multivariate bladder toxicity modeling over clinical factors, DSH and DVH

Table 2
Results of the multivariate logistic analysis for the whole population, endpoint IPSS15end. Discriminative values of the models as measured by the areas under the receiver operating characteristic curve (AUCs) are reported.

	Variable	Coefficient	Std. Error	*p*	OR	95% CI
Surface	*Clinical variables + absolute weekly dose–surface histograms*					
	Overall $p < 0.0001$	Apparent AUC = 0.78 (95% CI 0.72–0.83)	AUC after boostrapping = 0.76		Optimism = 2%	
	Use of anti-hypertensives (yes vs no)	0.55	0.33	0.09	1.7	0.9–3.3
	Stage (T2–3 vs T1)	0.49	0.32	0.13	1.6	0.9–3.1
	Baseline IPSS (discrete variable)	0.19	0.035	<0.001	1.2	1.1–1.3
	s8.5w abs, (continuous variable)	0.007	0.004	0.09	1.01	1.00–1.02
	s12.5w abs (continuous variable)	0.028	0.013	0.03	1.03	1.00–1.06
Volume	*Clinical variables + absolute weekly dose–volume histograms*					
	Overall $p < 0.0001$	Apparent AUC = 0.77 (95% CI 0.71–0.82)	AUC after boostrapping = 0.75		Optimism = 2%	
	Use of anti-hypertensives (yes vs no)	0.58	0.33	0.08	1.8	0.9–3.4
	Stage (T2–3 vs T1)	0.57	0.32	0.088	1.8	0.9–3.3
	Baseline IPSS (discrete variable)	0.19	0.034	<0.001	1.2	1.1–1.3
	v8.5w abs (continuous variable)	0.010	0.005	0.05	1.01	1.00–1.02
	v12.5w abs (continuous variable)	0.023	0.017	0.16	1.02	0.99–1.06
Surface	*Clinical variables + absolute dose–volume histograms corrected for fractionation*					
	Overall $p < 0.0001$	Apparent AUC = 0.77 (95% CI 0.72–0.83)	AUC after boostrapping = 0.76		Optimism = 1%	
	Use of anti-hypertensives (yes vs no)	0.63	0.33	0.06	1.9	1.0–3.6
	Stage (T2–3 vs T1)	0.55	0.32	0.09	1.7	0.9–3.2
	Baseline IPSS (discrete variable)	0.18	0.034	<0.001	1.2	1.1–1.3
	v80c abs (continuous variable)	0.043	0.013	0.001	1.04	1.02–1.07
Volume	*Clinical variables + absolute dose–surface histograms corrected for fractionation*					
	Overall $p < 0.0001$	Apparent AUC = 0.78 (95% CI 0.72–0.83)	AUC after boostrapping = 0.76		Optimism = 1%	
	Use of anti-hypertensives (yes vs no)	0.63	0.33	0.06	1.9	1.0–3.6
	Stage (T2–3 vs T1)	0.50	0.32	0.12	1.7	0.9–3.1
	Baseline IPSS (discrete variable)	0.19	0.035	<0.001	1.2	1.1–1.3
	s80c abs (continuous variable)	0.040	0.011	<0.001	1.04	1.02to 1.06

IPSS = International Prostate Symptoms Score; v8.5w abs/v12.5w abs = absolute bladder volume receiving ⩾8.5/12.5 Gy/week; s8.5w abs/s12.5w abs = absolute bladder surface receiving ⩾8.5/12.5 Gy/week; v80c abs = absolute bladder volume receiving ⩾80 Gy 2 Gy-equivalent; s80c abs = absolute surface volume receiving ⩾80 Gy 2 Gy-equivalent; CI = confidence interval.

V Carillo et al. Relationships between bladder dose–volume/surface histograms and acute urinary toxicity after radiotherapy for prostate cancer. Radiotherapy and Oncology 111 (2014) 100–105.

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Parameters for clinical outcome: Urinary bladder

Volume segmented	Irradiation type (partial organ unless otherwise stated)	Endpoint	Dose (Gy), or dose/volume parameters	Rate (%)	Notes on dose/volume parameters
Whole organ	3D-CRT	Grade ≥ 3 late RTOG	Dmax <65	<6	Bladder cancer treatment. Variations in bladder size/shape/ location during RT hamper ability to generate accurate data
Whole organ	3D-CRT	Grade ≥3 late RTOG	V65 ≤50 % V70 ≤35 % V75 ≤25 % V80 ≤15 %	?	Prostate cancer treatment Based on current RTOG 0415 recommendation

- In the absence of any reliable data, clinicians might consider the dose limits listed in the conventional fractionation arm of the **Radiation Therapy Oncology Group (RTOG) 0415 study**

Viswanathan AN et al. Radiation Dose-Volume effects of the urinary bladder. Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, Supplement, pp. S116–S122, 2010.

Thank you!

Grazie!

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Kliniken Maria Hilf
Mönchengladbach

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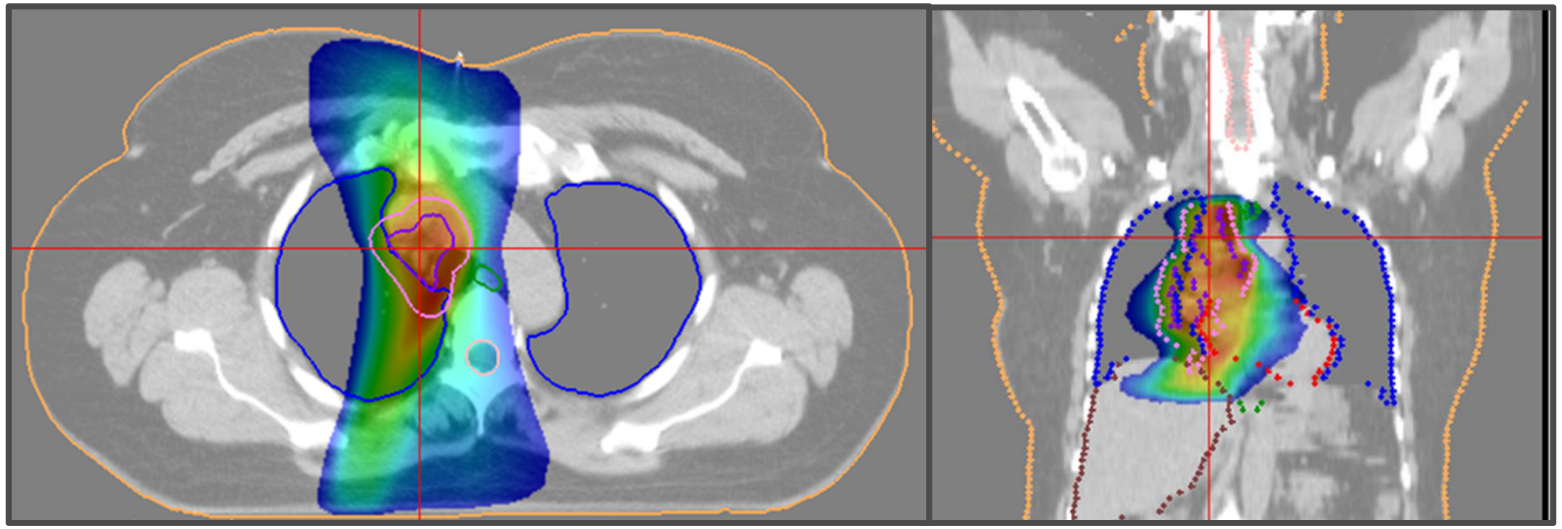
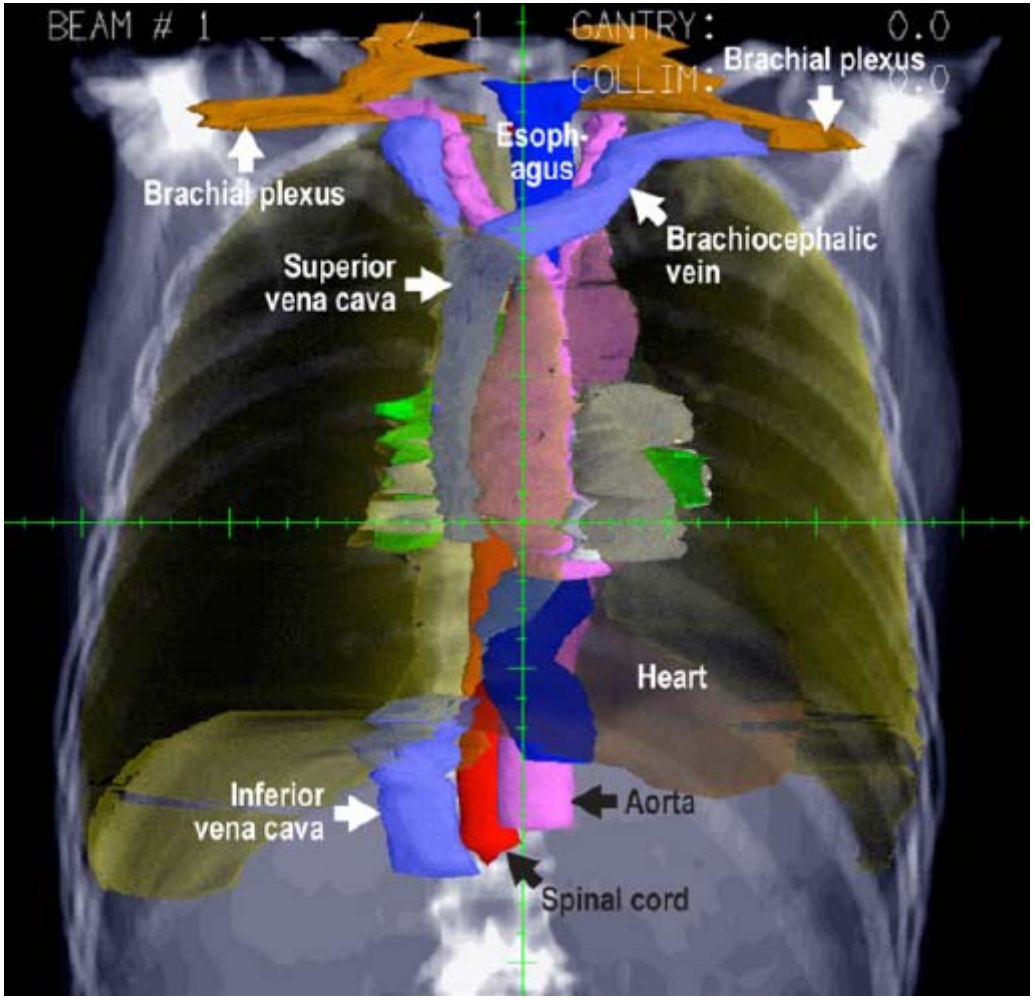


Relationships between 3D dose distributions and clinical toxicities - Chest

Ursula Nestle

KMH Mönchengladbach
and UK Freiburg, Germany

Normal tissues in the chest



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Mönchengladbach

Kong, IJROBP 2011; 81(5); 1442-57

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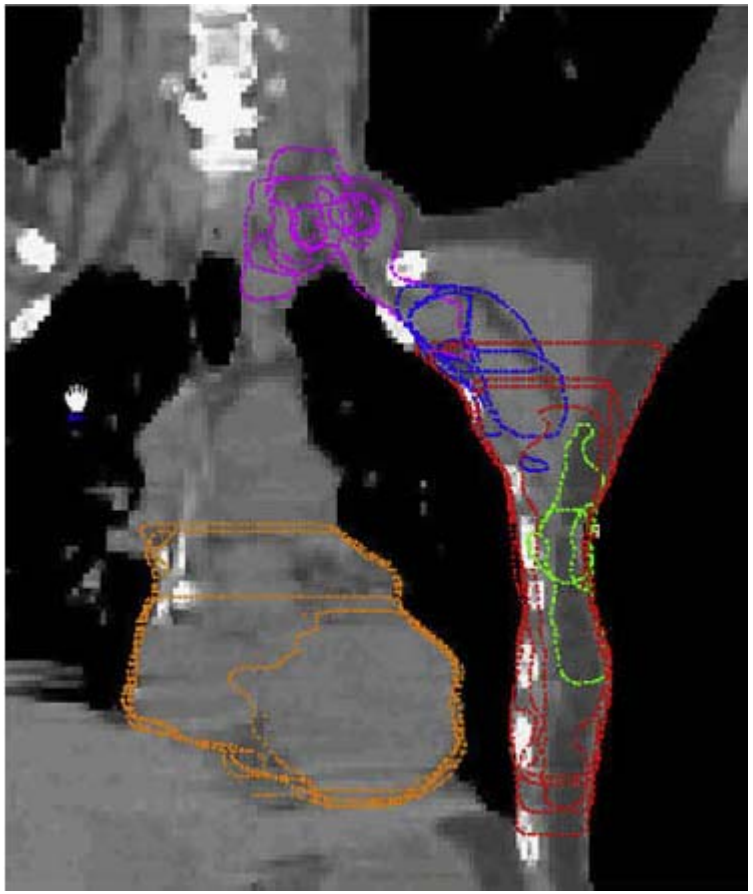
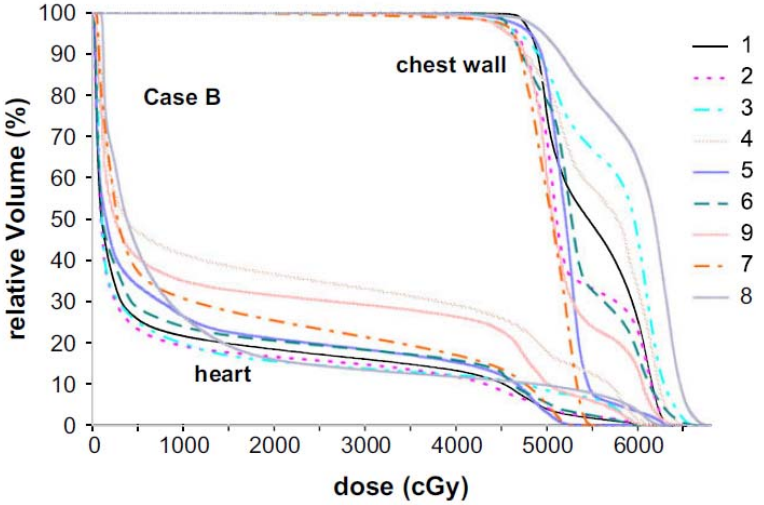
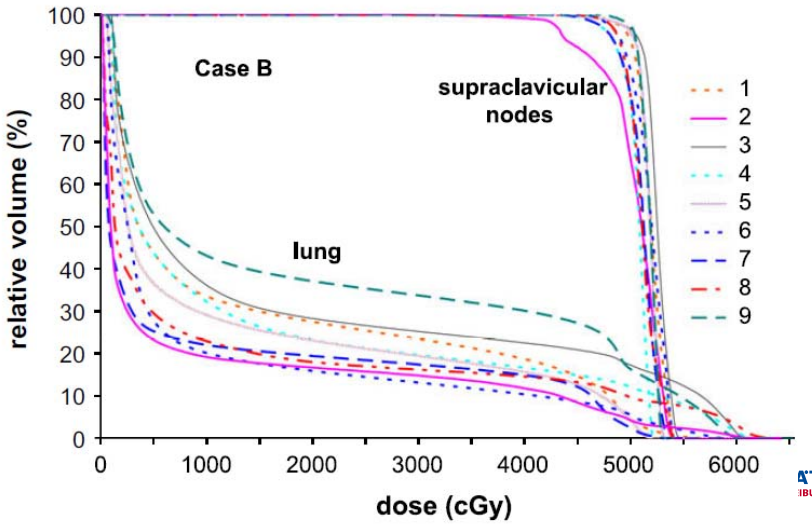
IOV in NT contouring: impact on dose calculation and plan optimisation







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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

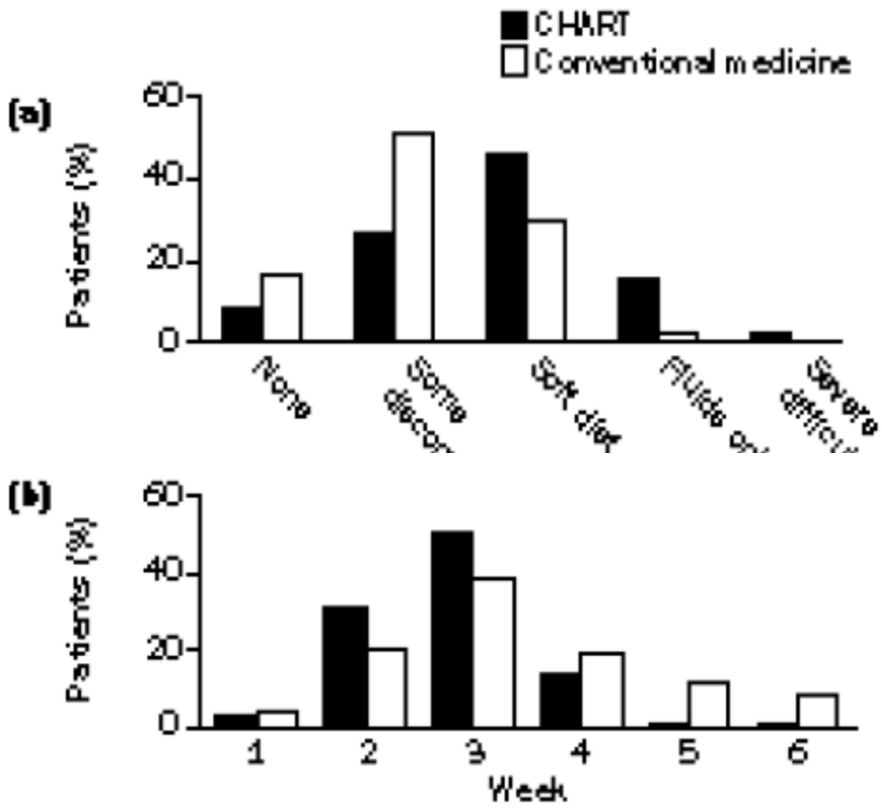
Kong, IJROBP 2011; 81(5); 1442-57

Esophagus: acute reactions

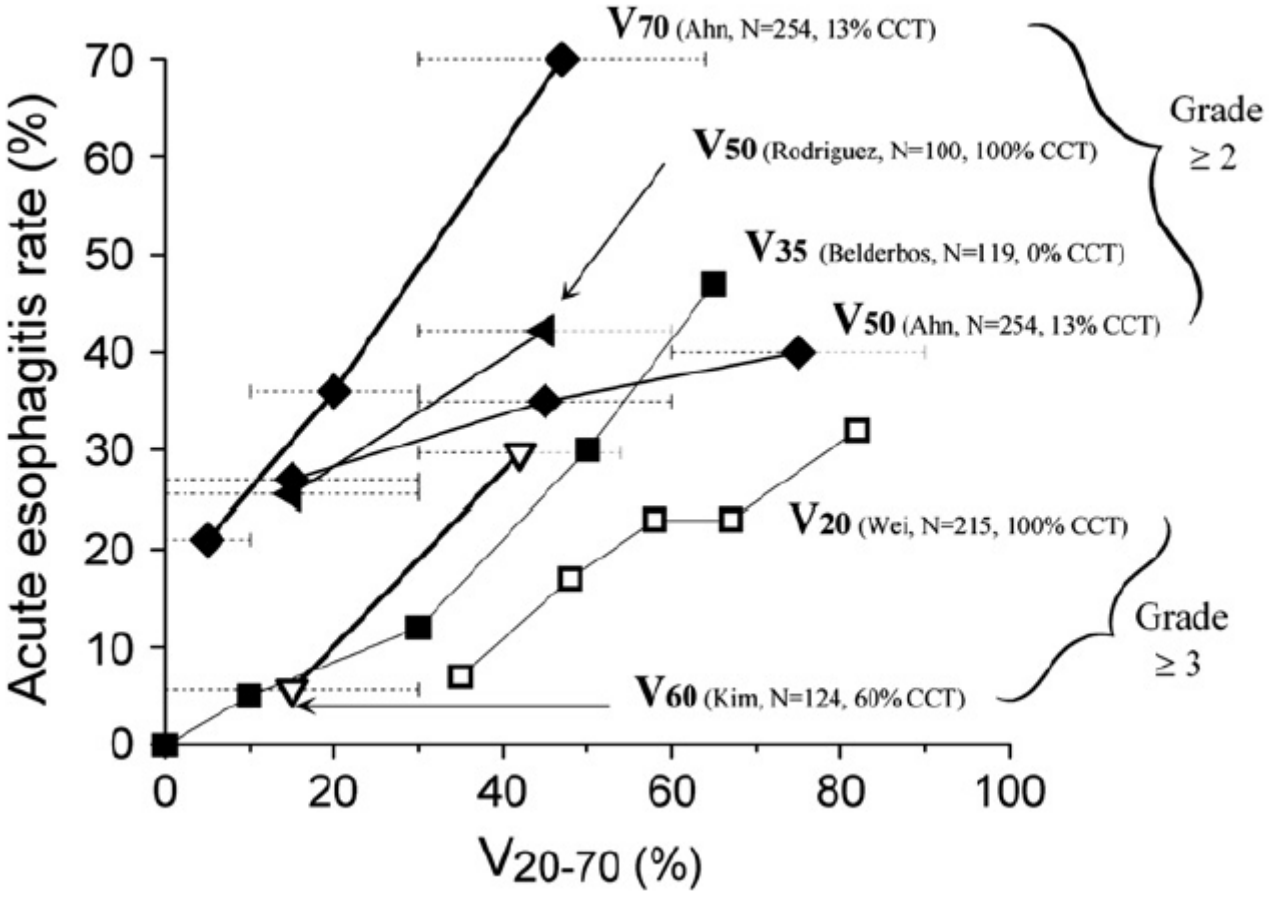
Acute esophagitis
- from ca. 30 Gy/2 Gy
- ca. 3%/ 60 Gy fluid only

Influencing factors:
- Dose
- Fractionation
- Chemotherapy

Therapy:
- symptomatic



Acute esophagitis: dose/volume effects



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Werner-Wasik IRJOBP 2010 76(3) Suppl., S86-S93

Esophagus: late reactions

Fibrosis

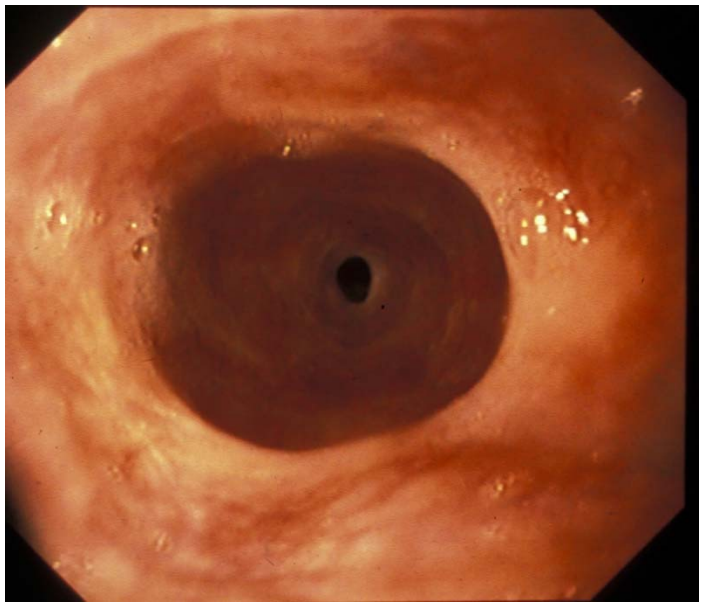
Stricture < 2% < 60 Gy

Influence factors:

- Dose
- Fractionation
- Volume

Therapy:

symptomatic



Thanks to M. Baumann

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):

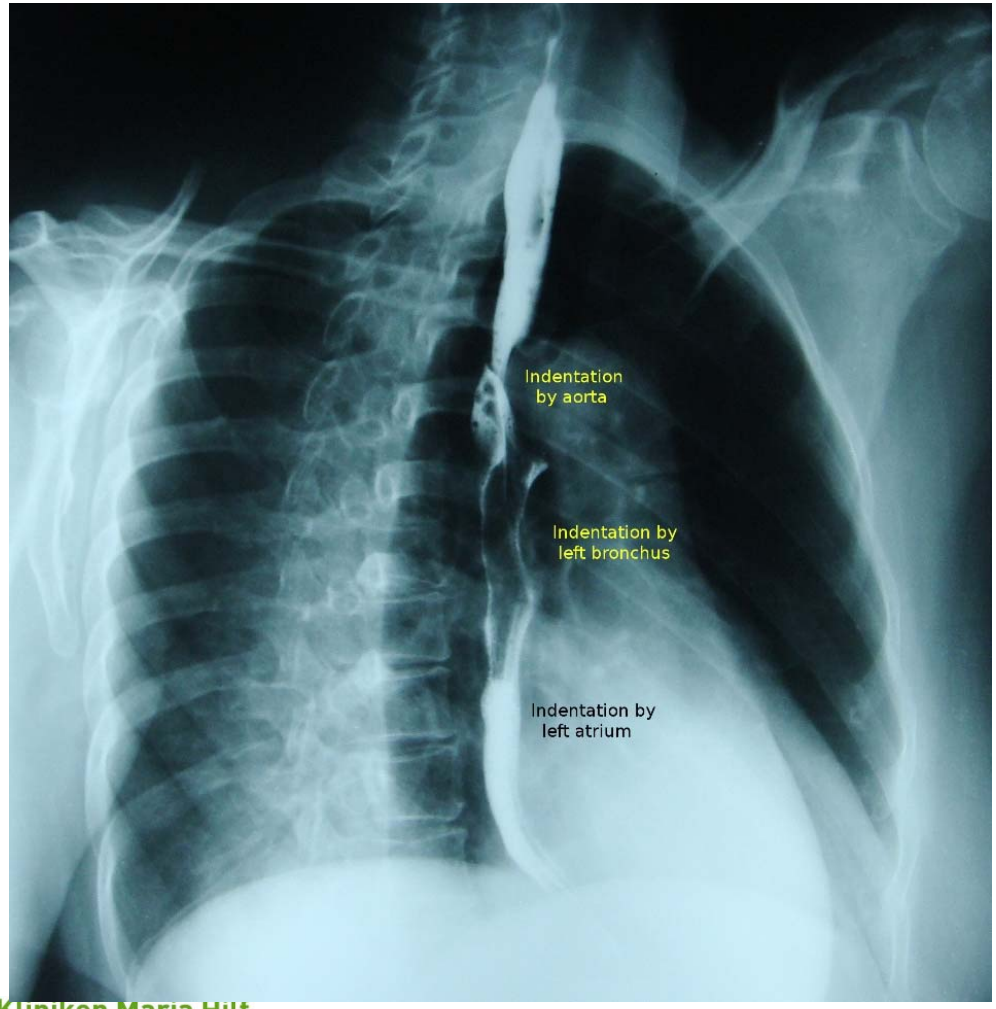
- esophagus dose should not exceed prescription dose
- mean dose < 34 Gy
- max dose up to 74 Gy/ 2Gy + CHT

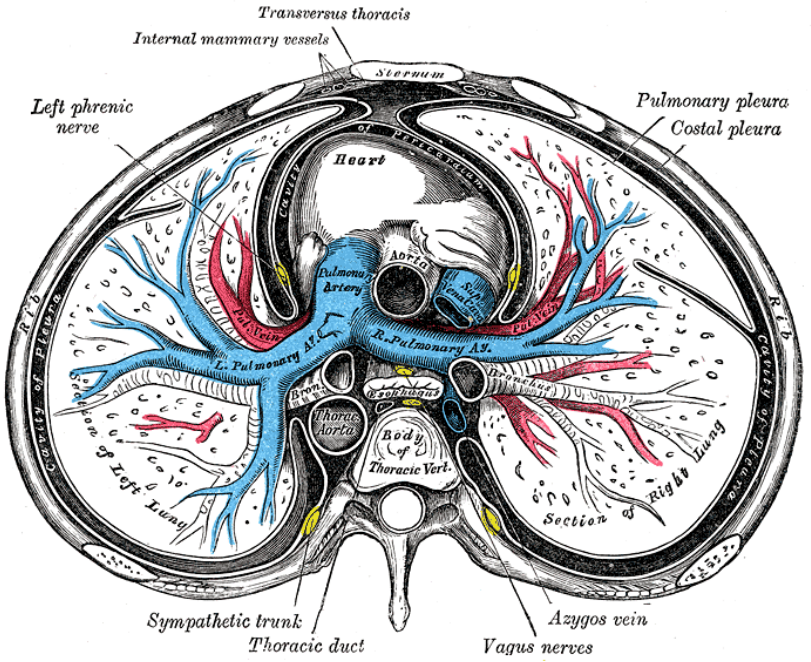
SBRT

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

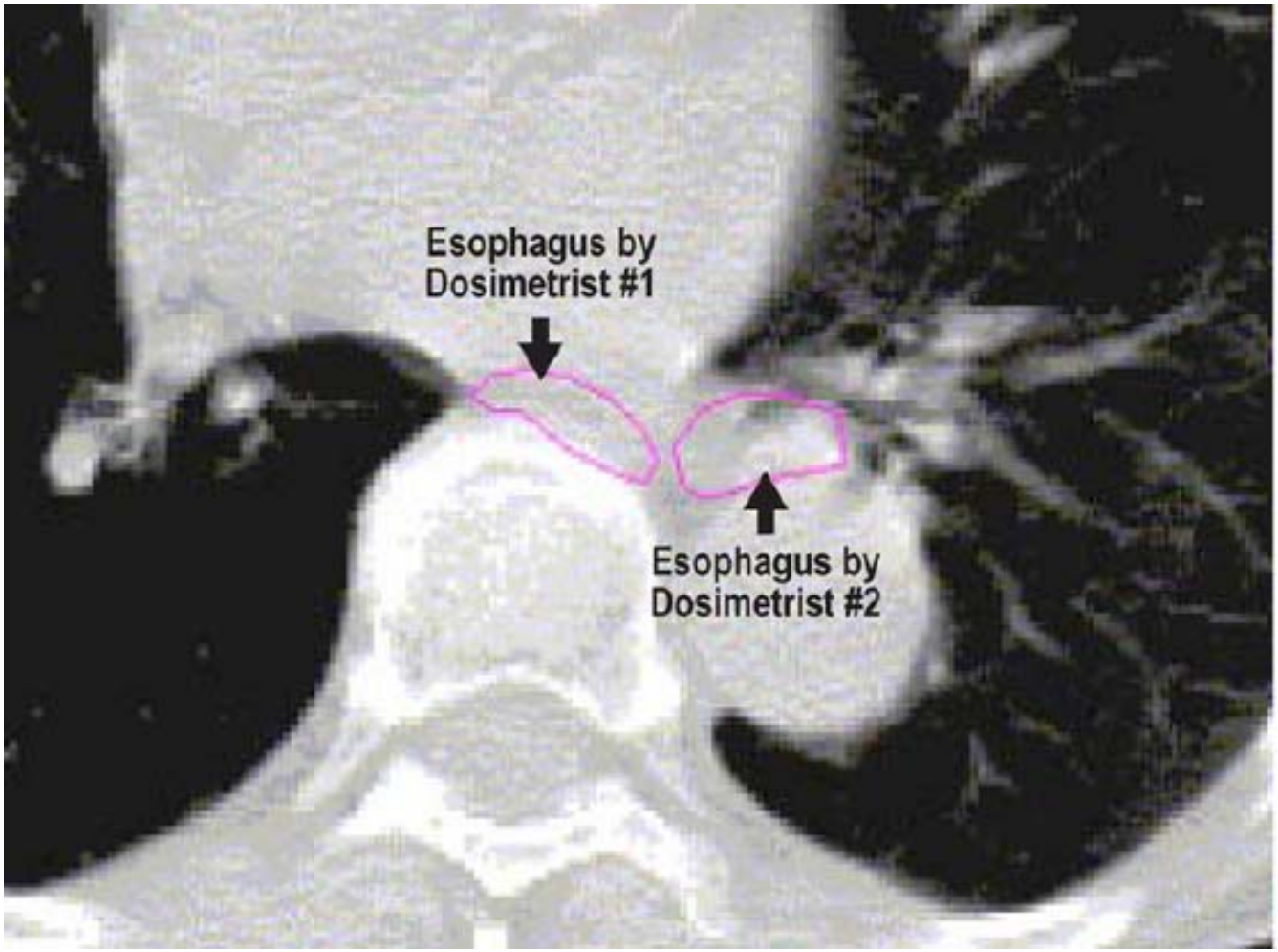
Challenges:

may be difficult to find (search for air)

varying filling

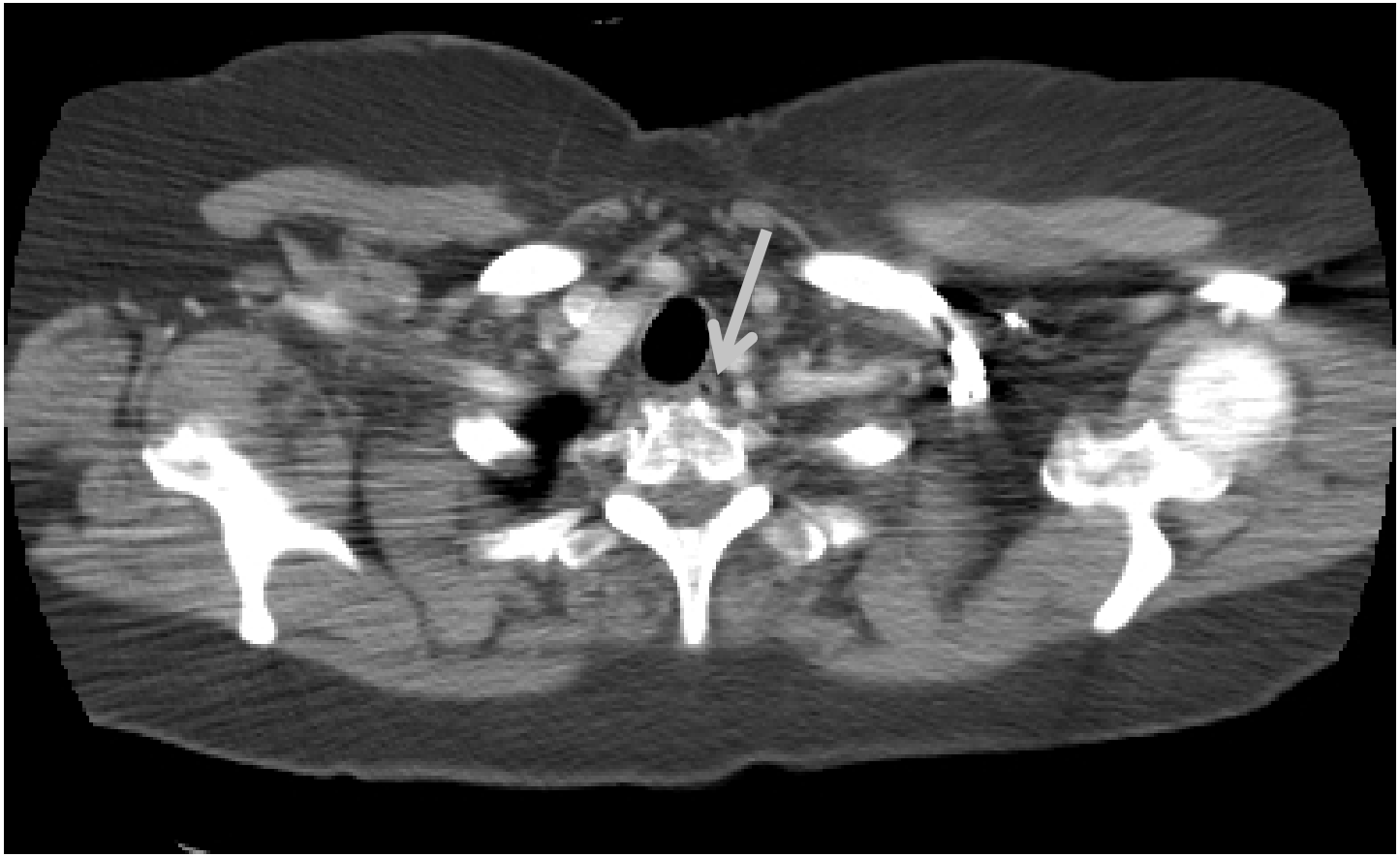
often collapsed (barium swallow or interpolation may help)

Esophagus: geographic miss

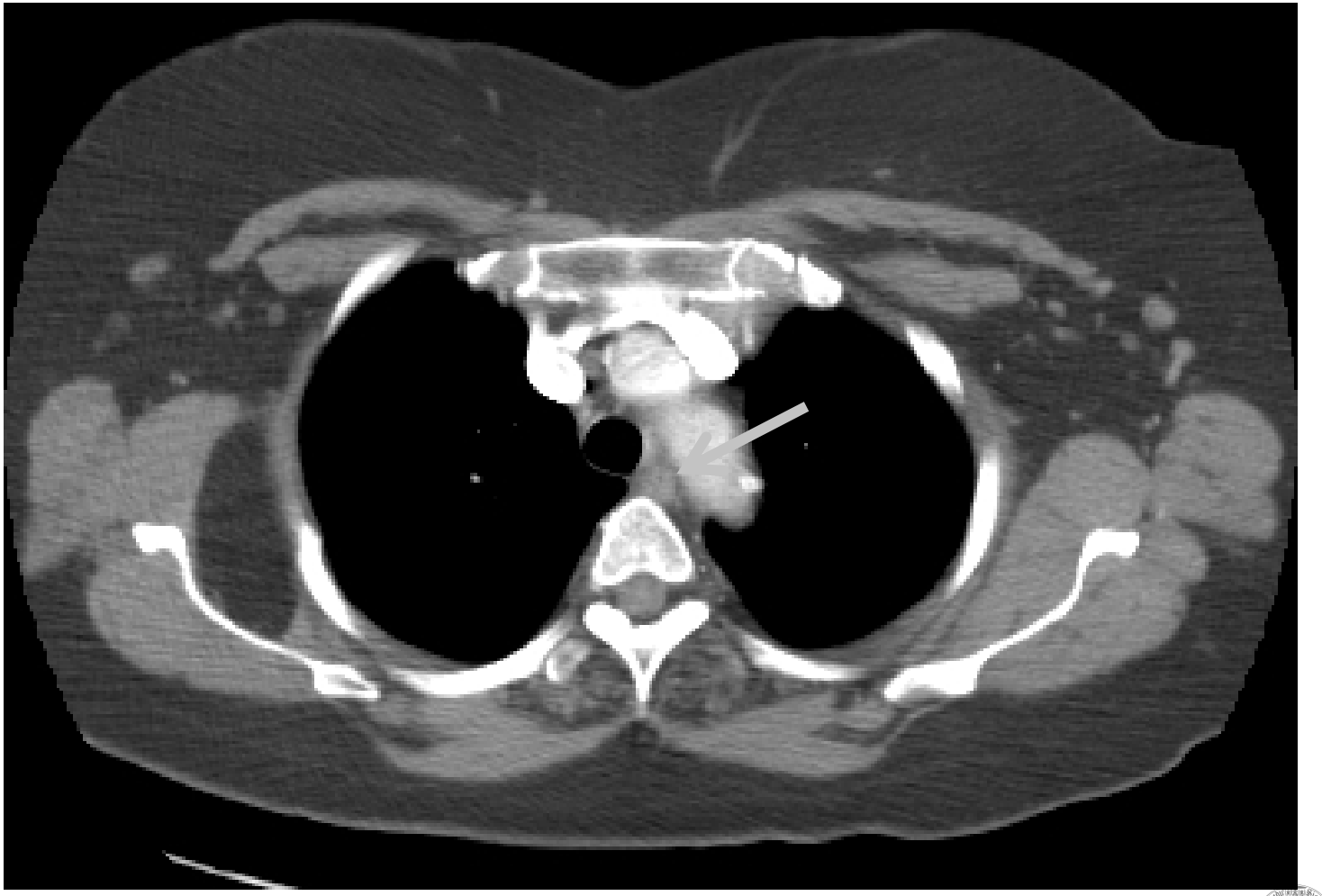


Collier 2003 JACMP 4; 17-24

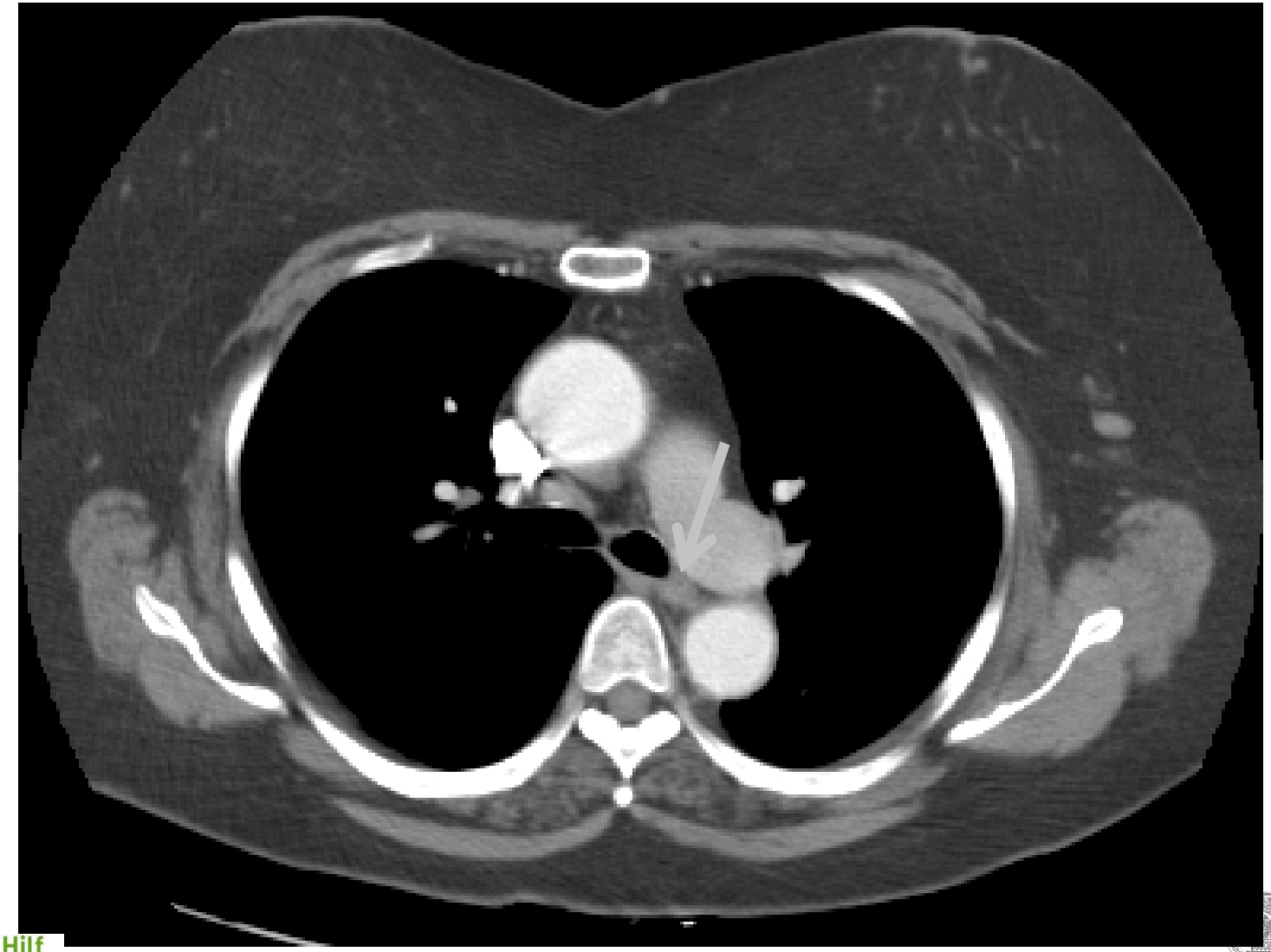
Find the esophagus



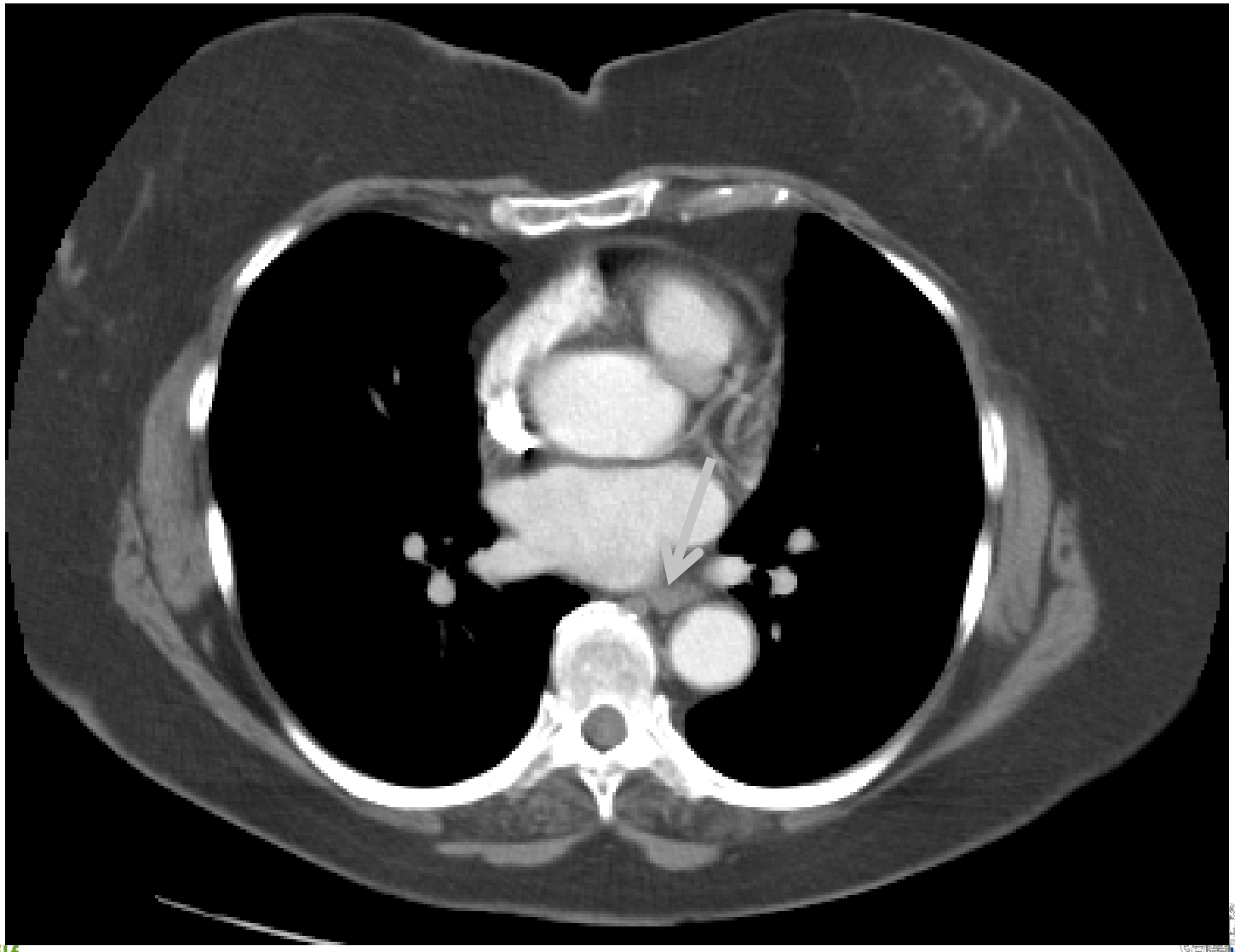
Find the esophagus



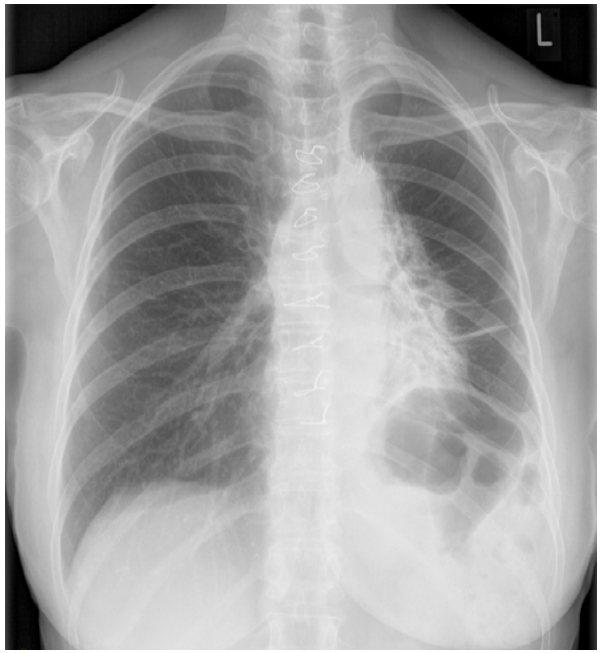
Find the esophagus



Find the esophagus

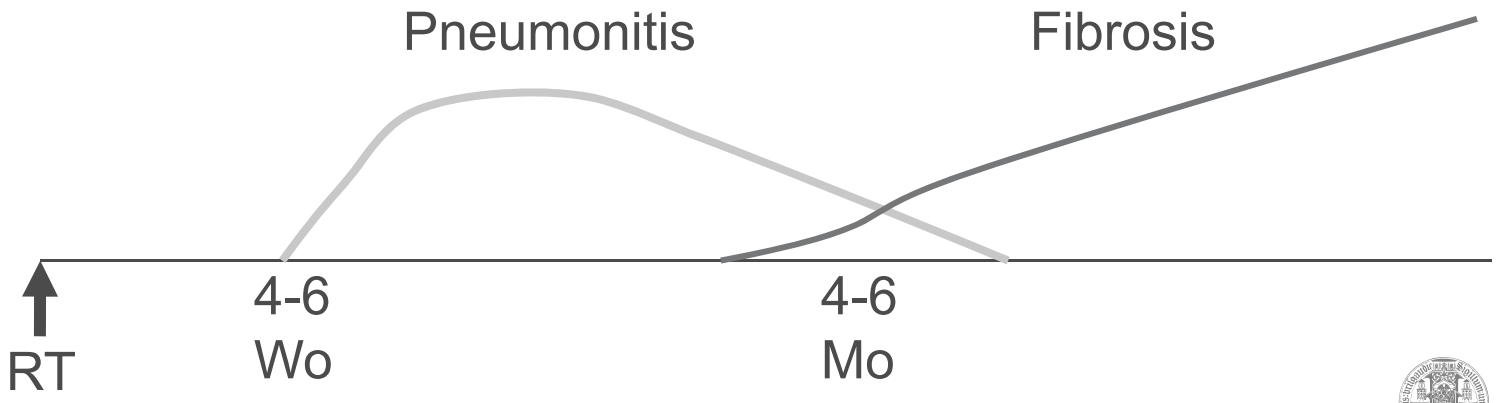


Lung (RILD)



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

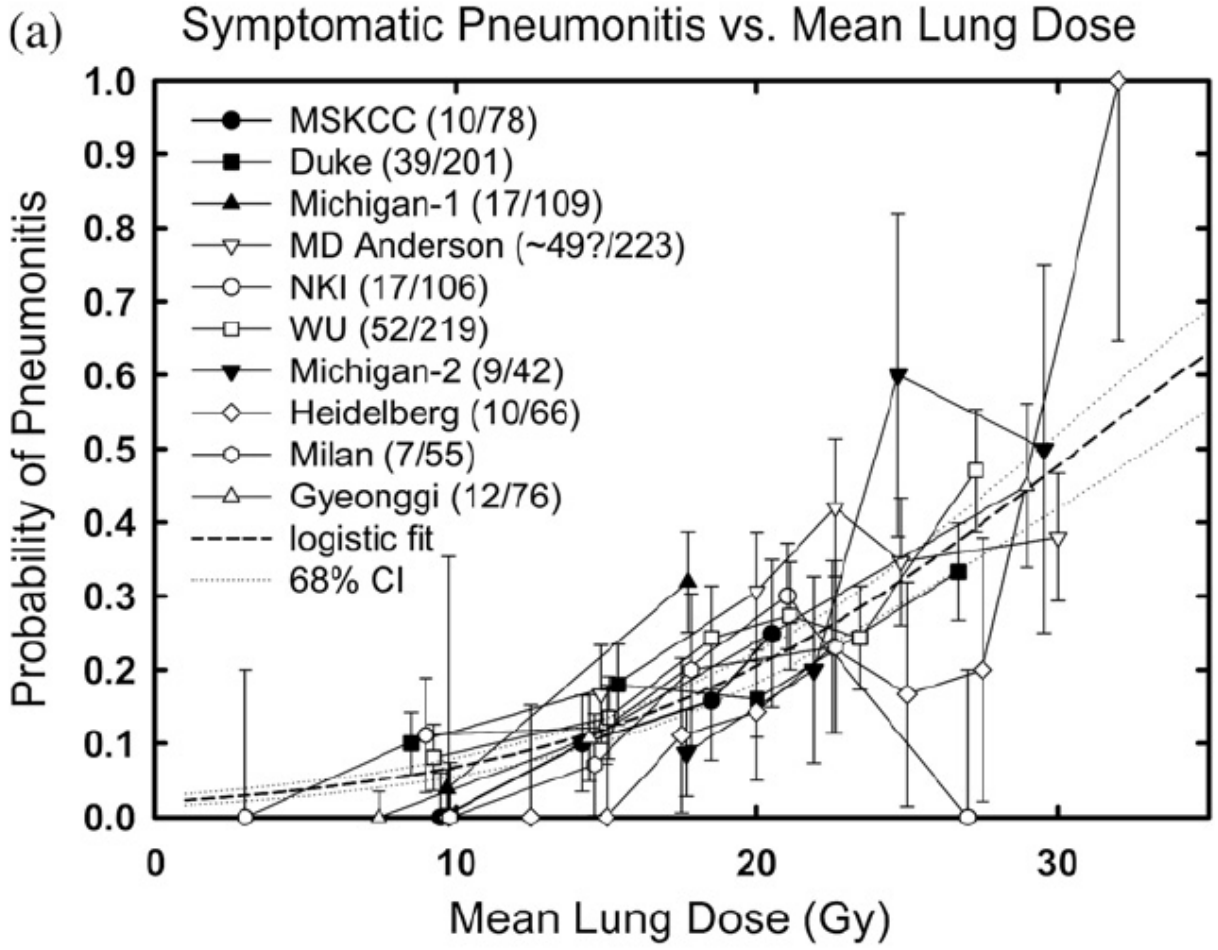
Graham et al. IJROBP1999:

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



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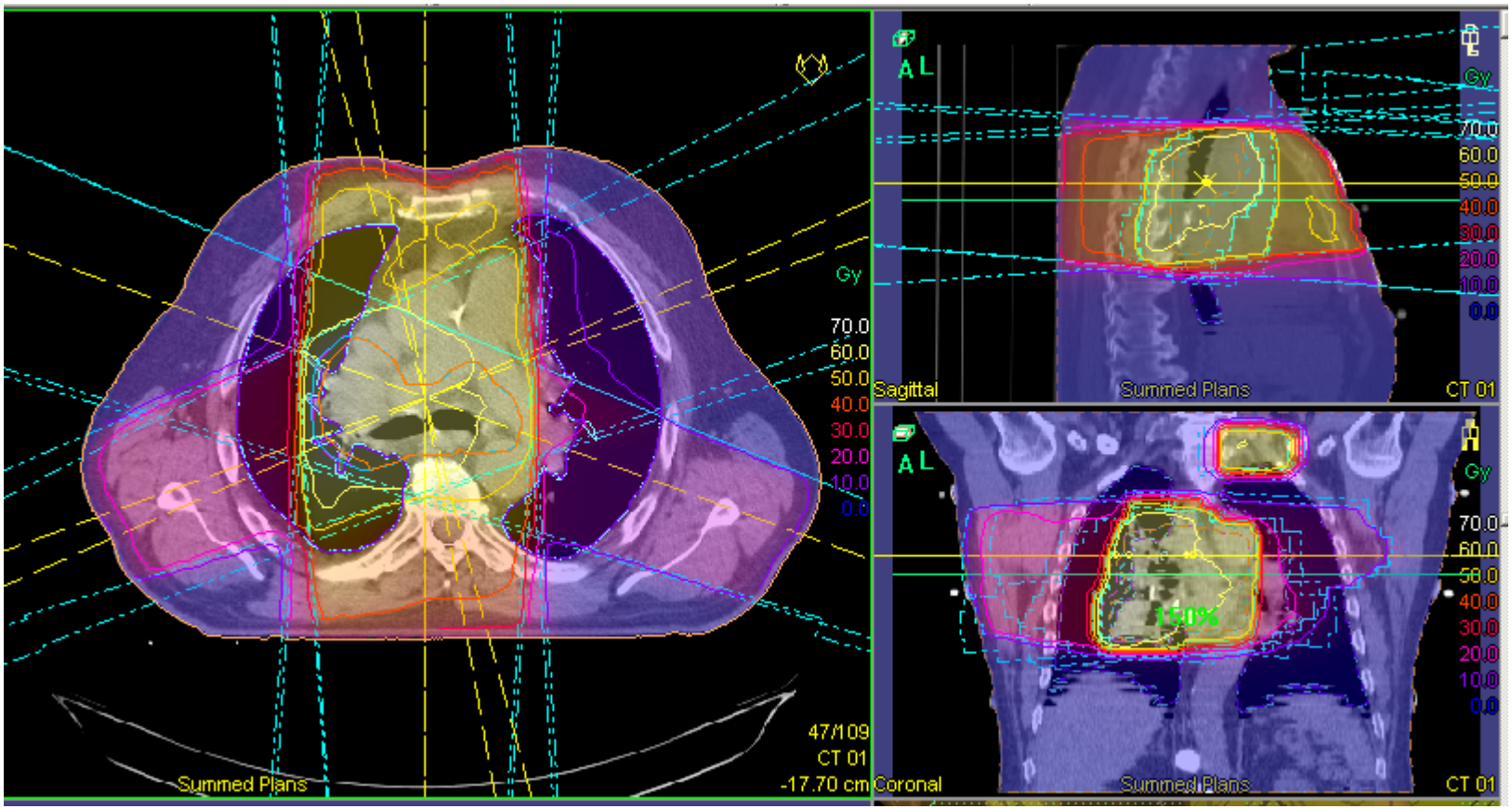
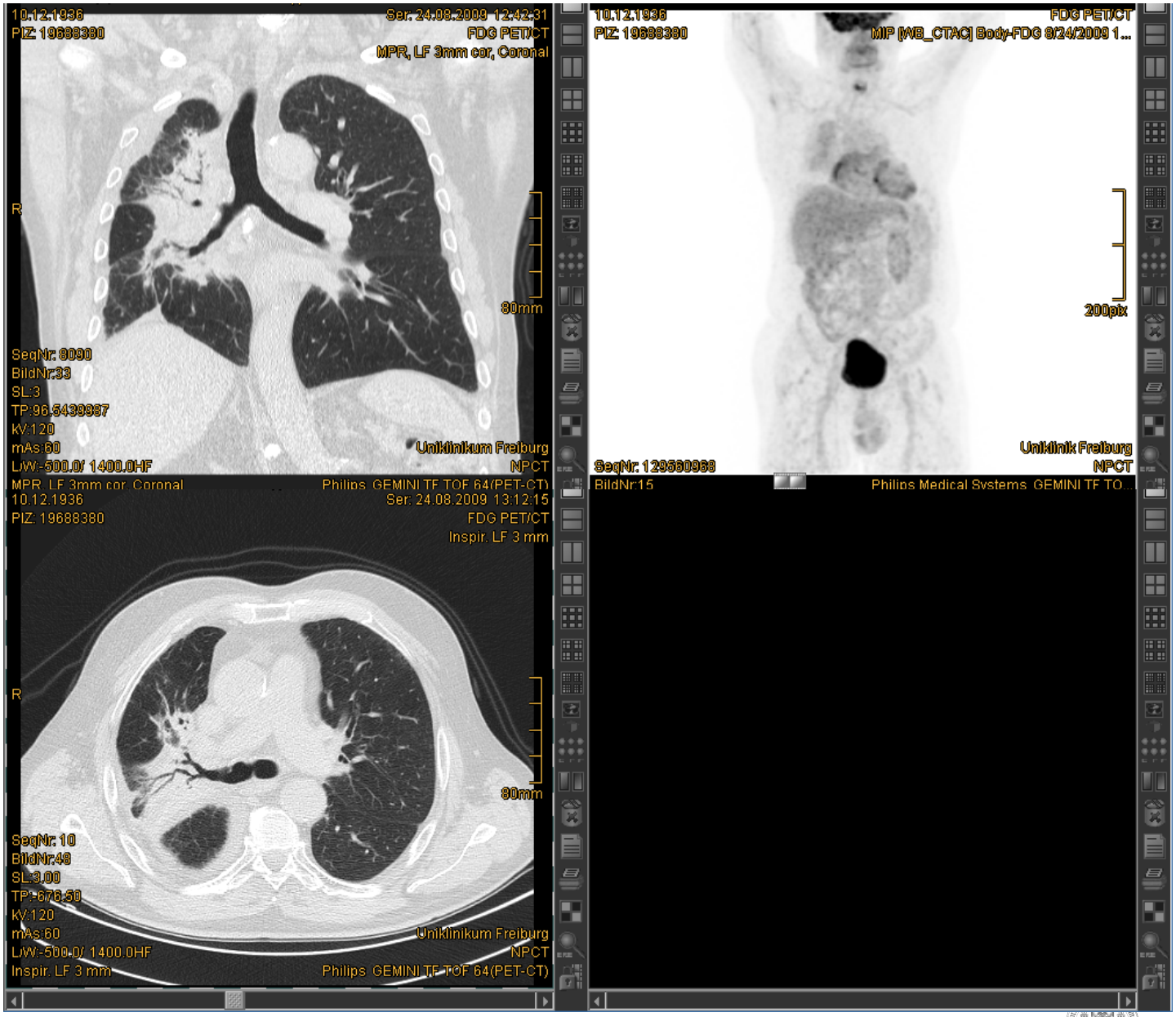
Marks, IJRBOP 76(3) S70-S76 2010



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.

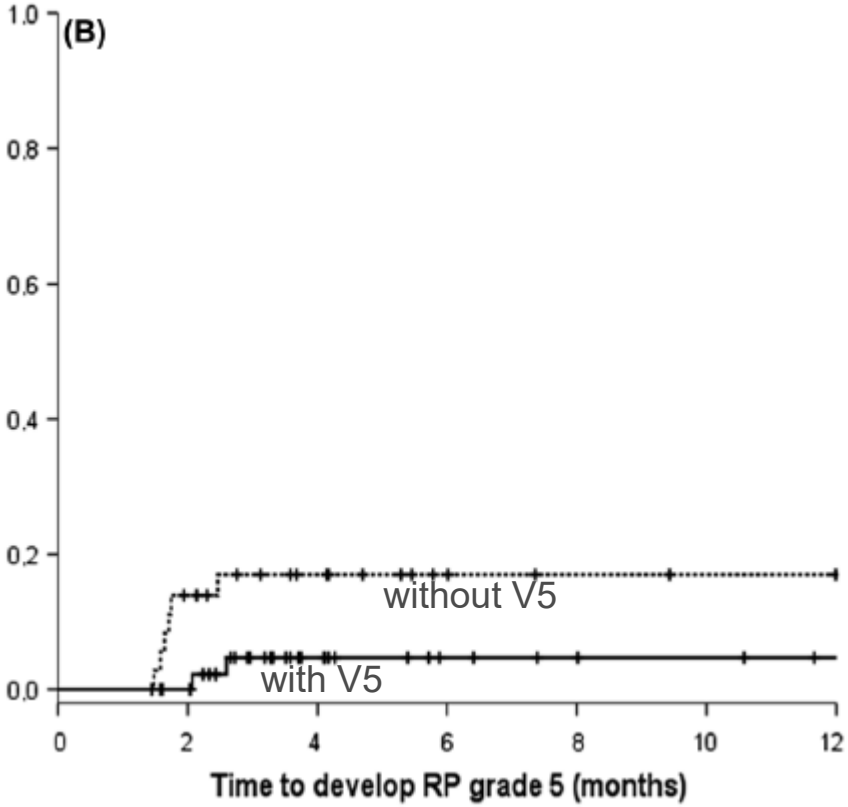
Lung: what about low doses?

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.

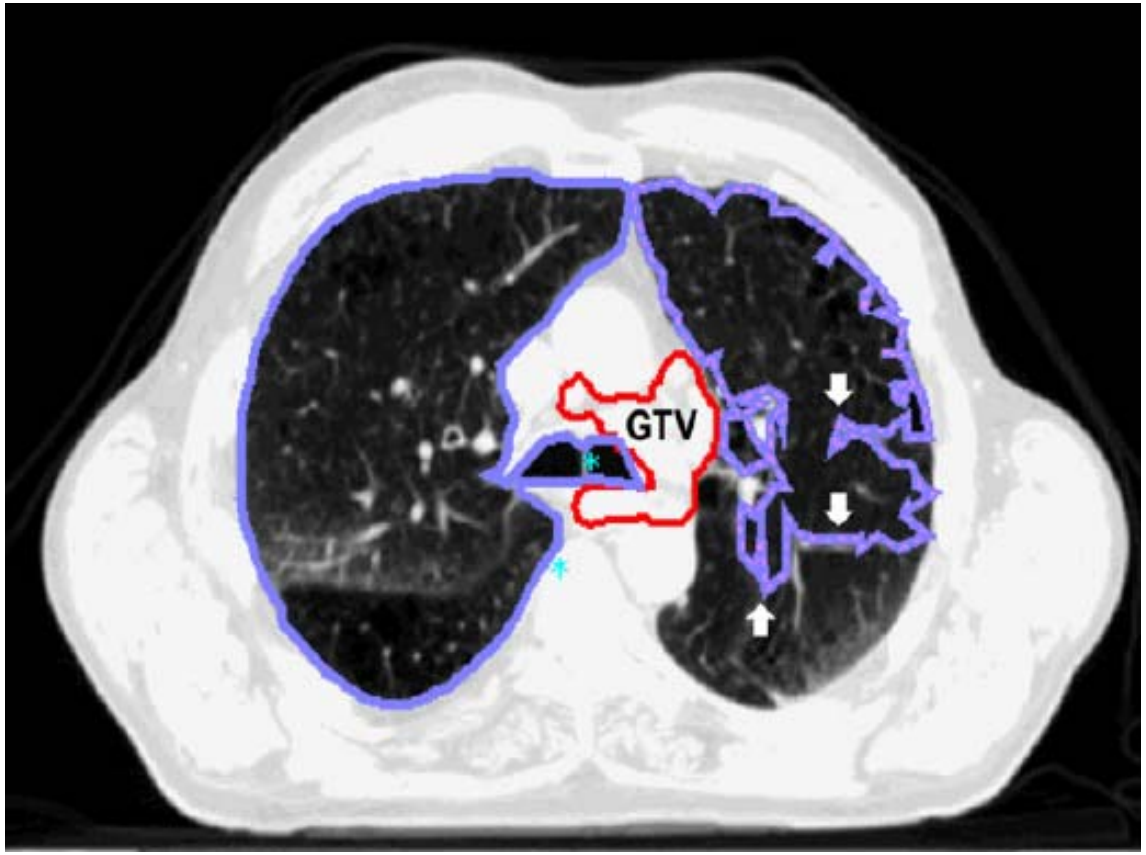
Lung: planning constraints II

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

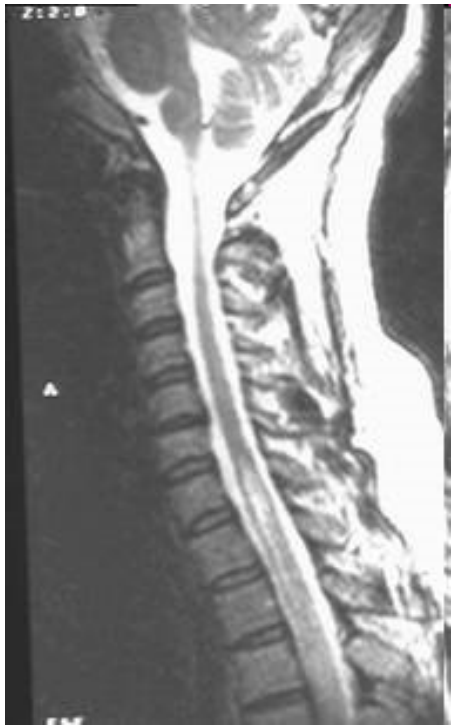


Check complete volume after automatic contouring!

exclude bronchi, bullae, non-lung air

Kong, IJROBP 2011; 81(5); 1442-57

Spinal cord



Tersteeg, Cancer Therapy 2004

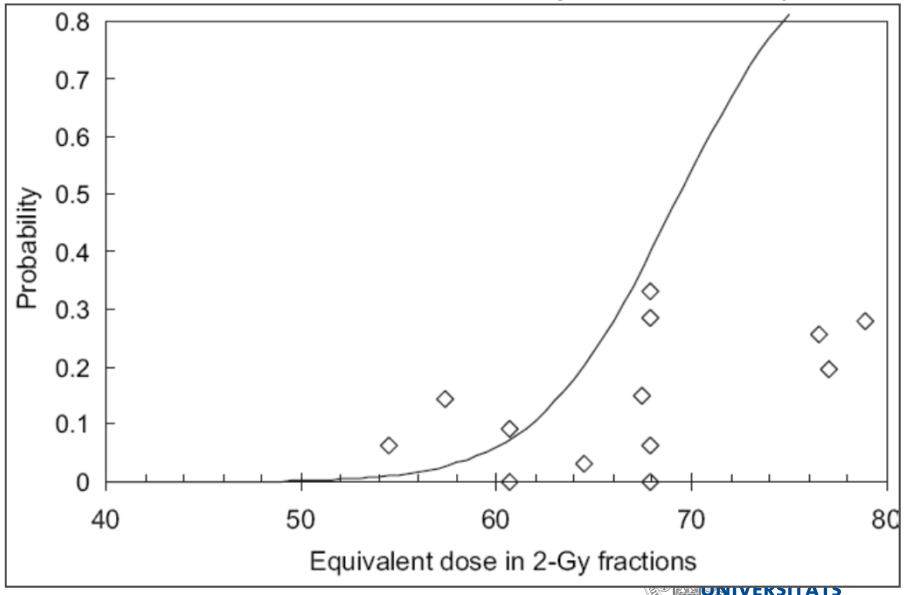
Late effect: Myelitis

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.

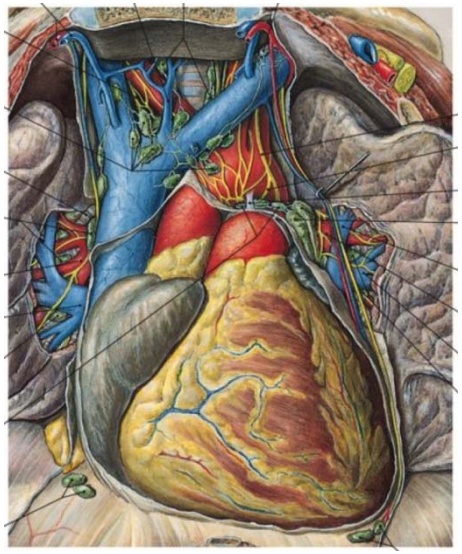
Kong, IJROBP 2011; 81(5); 1442-57

Heart

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)

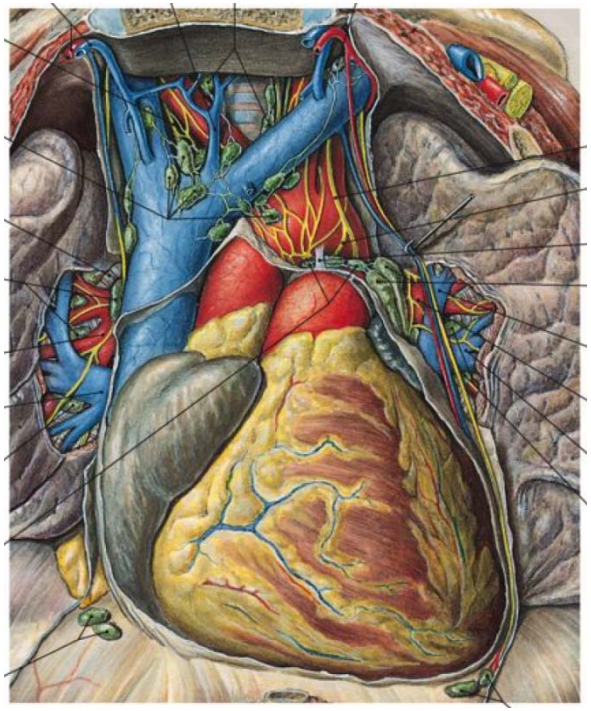


OAR: whole myocardium, coronary arteries, Pericardium…

Gagliardi, IJROBP 2010

Heart

Quantec:
„old“ tolerance dose
for clinically relevant endpoints
40 Gy/ 2 Gy ?

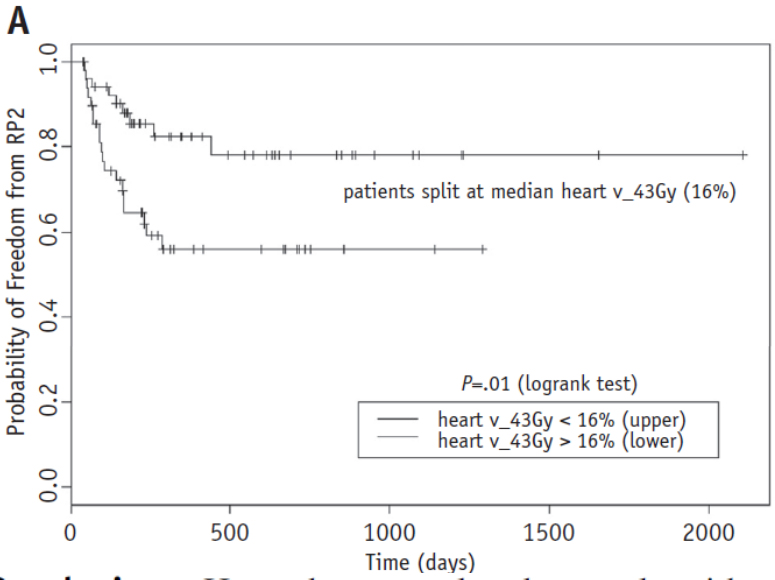


Darby (breast cancer patients):
no threshold
7%/Gy increased risk

AB survivors registry:
increasing risk for CAD from mSv doses

Treatment: symptomatic

Heart: confusing news



Clinical Investigation

Heart Dosimetry is Correlated With Risk of Radiation Pneumonitis After Lung-Sparing Hemithoracic Pleural Intensity Modulated Radiation Therapy for Malignant Pleural Mesothelioma

Ellen D. Yorke, PhD,* Andrew Jackson, PhD,* Li Cheng Kuo, MS,* Anthonia Ojo, BS,† Kelly Panchoo, BA,† Prasad Adusumilli, MD,‡ Marjorie G. Zauderer, MD,§ Valerie W. Rusch, MD,‡ Annemarie Shepherd, MD,† and Andreas Rimner, MD†

*Departments of *Medical Physics, †Radiation Oncology, ‡Surgery, and §Medicine, Memorial Sloan Kettering Cancer Center, New York, New York*

Conclusions: Heart dose correlated strongly with symptomatic RP in this large cohort of MPM patients with 2 lungs treated with IMPRINT. Planning constraints to reduce future heart doses are suggested. Int J Radiation Oncol Biol Phys, Vol. 99, No. 1, pp. 61–69, 2017

Radiation-induced heart disease in lung cancer radiotherapy

A dosimetric update

Xin Ming, MS[a], Yuanming Feng, PhD[a,b], Jun Deng, PhD[c,*]

Medicine (2016) 95:41(e5051)

Table 1

The reported cardiac toxicity after radiotherapy of lung cancer.

Study	Cancer information	Time range	Data scale	Age	Treatment	Follow-up, years	Endpoint	Treatment-associated cardiac toxicity (n)	Dosimetric parameters to the heart
Lally et al[7]	NSCLC	1983–1993	6148	64	PORT	2.1	Cardiac death	Mortality: 6%	Not available
Hardy et al[8]	Stage I–IV NSCLC	1991–2002	34,209	≥65	RT	0.2–1.4	Cardiac death	Mortality: 33%	Not available
Schytte et al[9]	Stage I–III NSCLC	1995–2007	250	–	RT 60–80 Gy	7.9	Cardiac event	38 (15%)	MHD_{up} = 24.7 Gy for whole group
Belliere et al[10]	NSCLC	1998–2002	50	63	RT 68–74 Gy	2.3	Cardiac event	3 (6%) Mortality: 4%	Mean heart V20 = 42–52%
Milano et al[11]	NSCLC/oligometastases	2001–2007	53	–	SBRT 30–63 Gy	0.8	Cardiac event	1 (1.9%)	V40 = 5%, V30 = 10%
Nishimura et al[12]	NSCLC/unproven/ metastasis	2005–2012	133	78	SBRT 40–60 Gy/5 fx	2.8	Cardiac event	None	69 received greater than 25 Gy irradiation to the heart. Median of maximum dose is 45.3 Gy
Modh et al[13]	Stage I–II NSCLC/metastasis	2006–2011	125		SBRT 36–60 Gy/2–5 fx	1.5	Cardiac event	3 (2.4%)	Not available
Haasbeek et al[14]	Lung cancer	2003–2009	63	74	SART	–	Cardiac death	5 (7.9%)	Not available

Result: Cardiac toxicity has been found highly relevant in lung cancer radiotherapy. So far, the crude incidence of cardiac complications in the lung cancer patients after radiotherapy has been up to 33%.

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Mönchengladbach

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

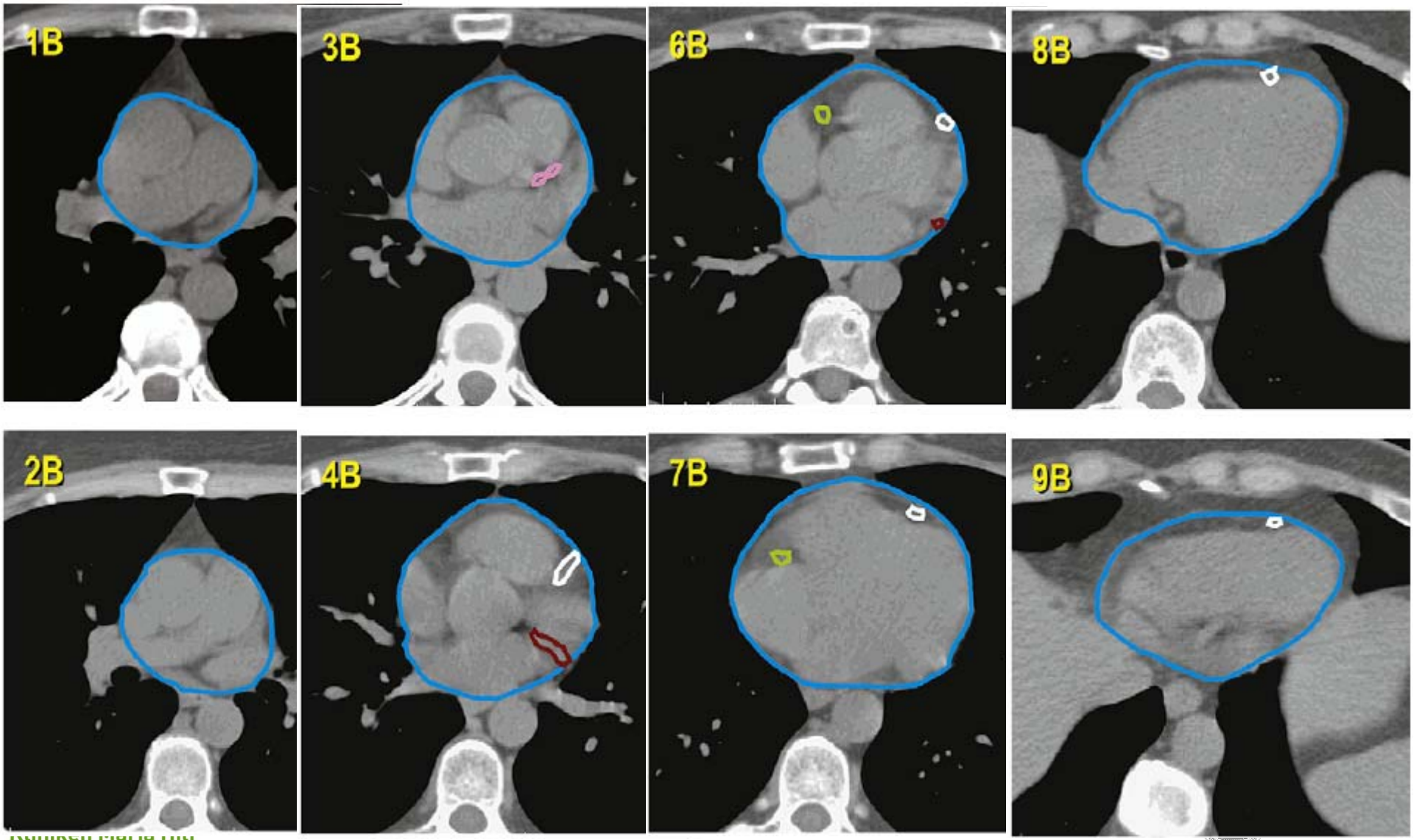
problem: no subvolumes available for further optimisation

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



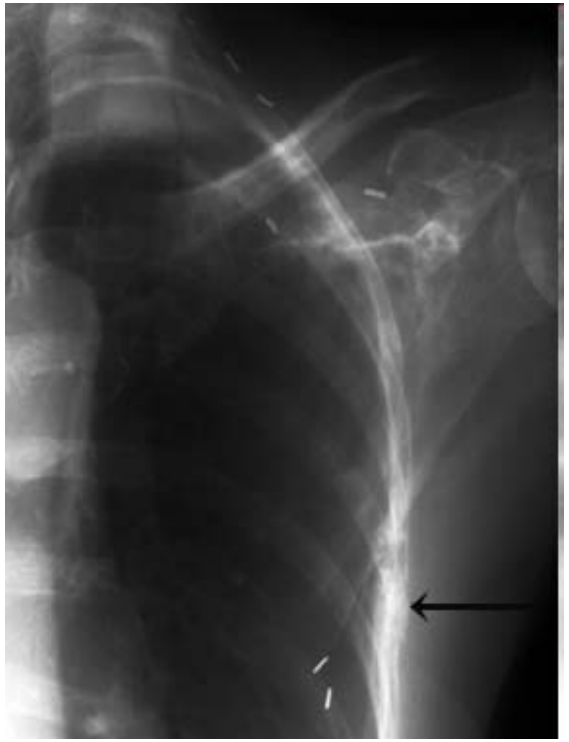
Feng IJRBOP 2011 79(1) 10-18

Bone

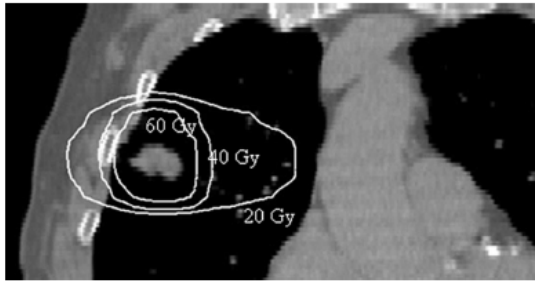
late effect
    Osteoradionecrosis

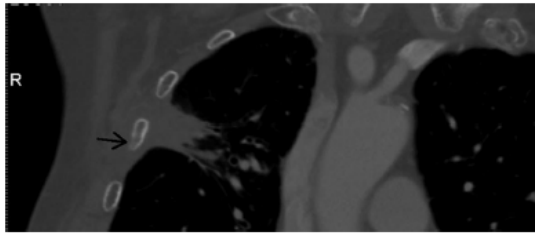
Tolerance dose
    ca. 60 Gy/2 Gy

treatment:
    symptomatic



Predictors of Radiotherapy Induced Bone Injury (RIBI) after stereotactic lung radiotherapy





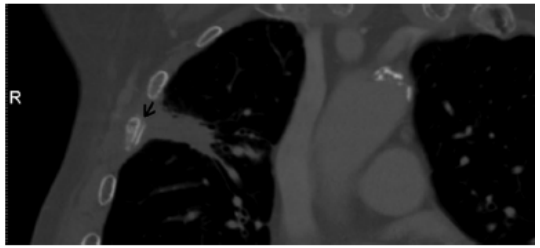


Table 5 Univariate and multivariate analysis on predictors for rib fractures (repeated measures have been taken into consideration)

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

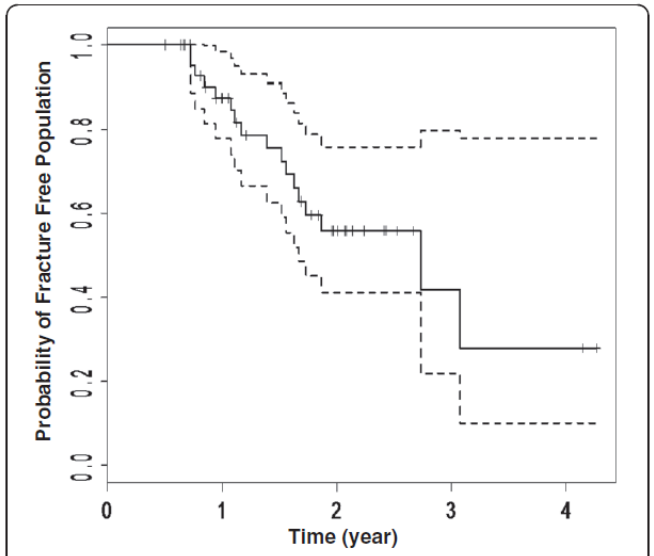


Figure 2 Kaplan Meier curve for fractured rib as an event (n = 46 patients). Dashed lines indicate 95% confidence intervals.

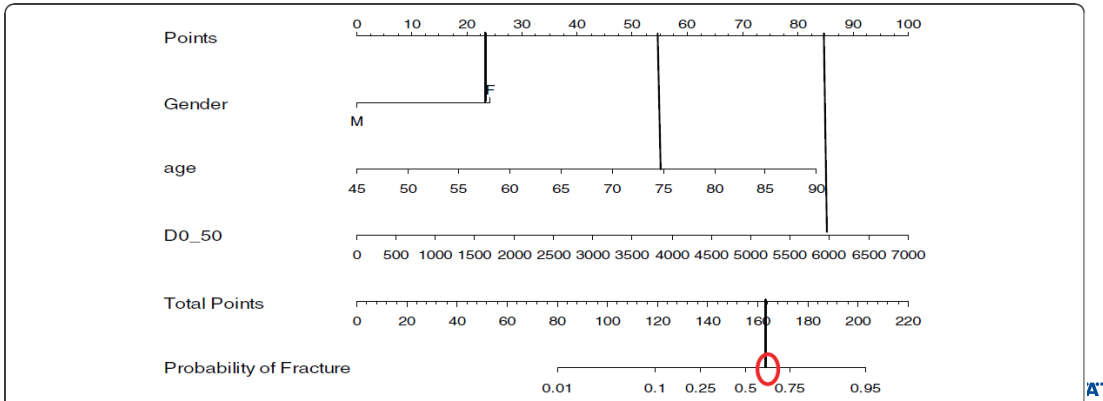
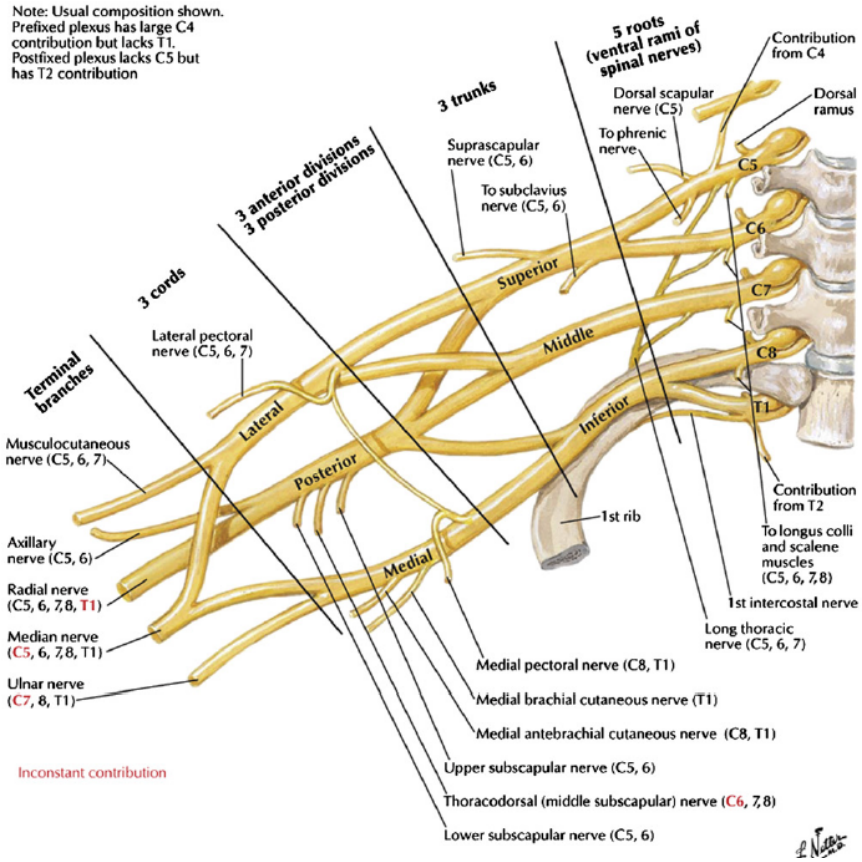
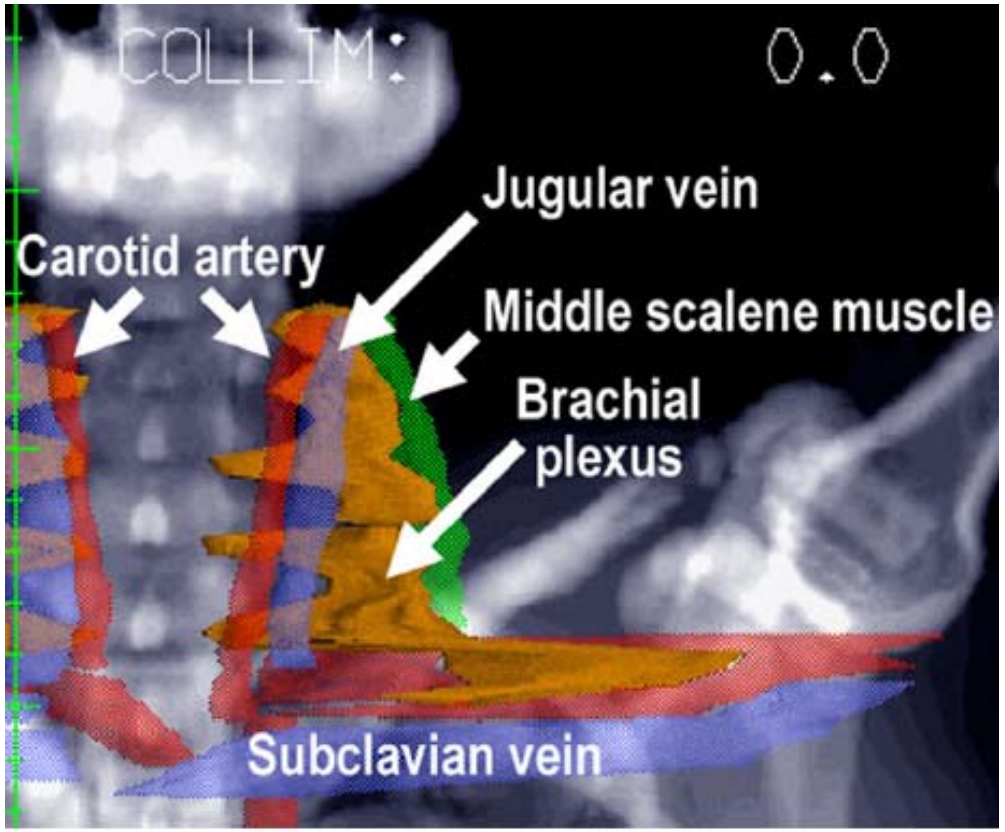


Figure 6 RIBI nomogram based on gender, age and $D_{0.5}$ in 46 patients treated with SBRT at Princess Margaret Hospital (Estimating risk of rib fracture at median follow up of 25 month). Risk of rib fracture in a 75 year old lady treated with 54 Gy in 3 fractions and D0.5 of 60 Gy (within a median FU of 2 years)is about 65%.

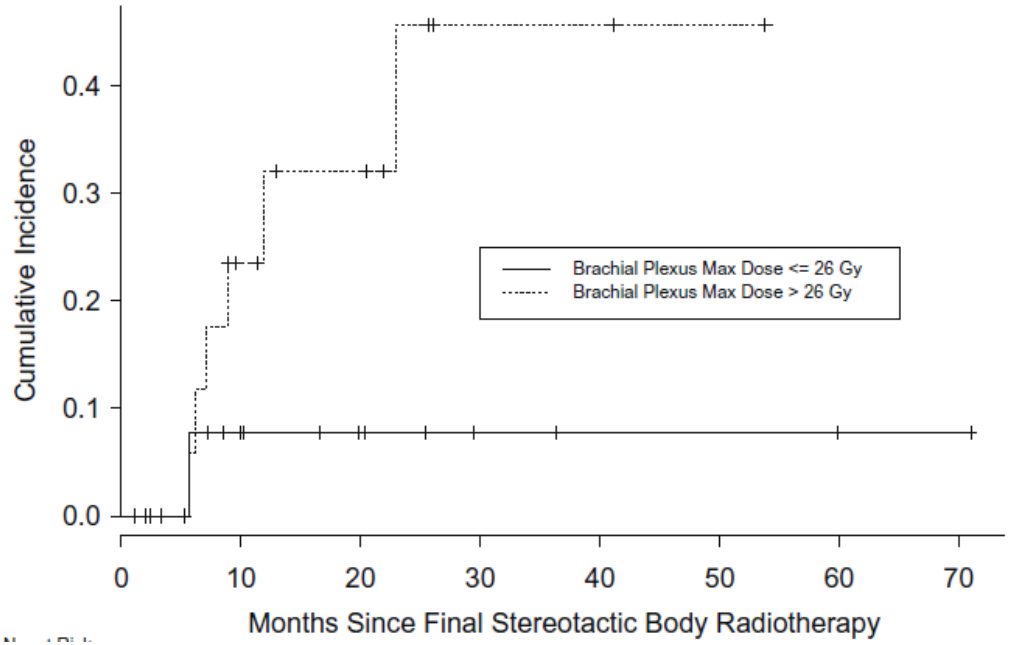
Brachial plexus

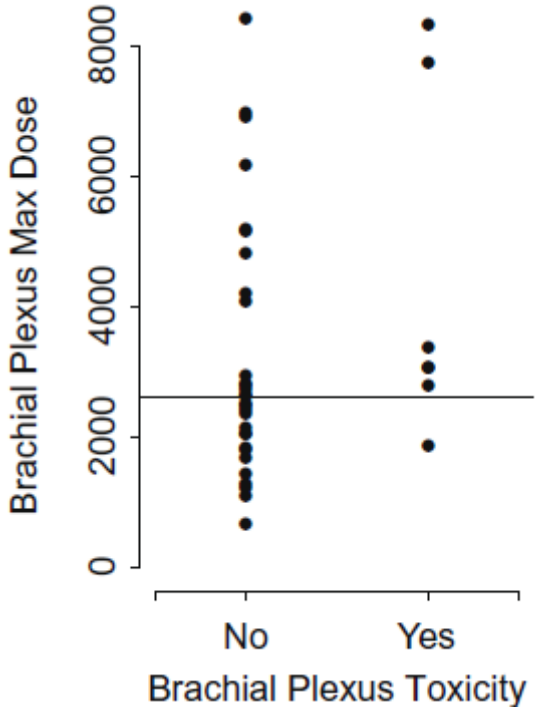




Kong, IJROBP 2011; 81(5); 1442-57

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

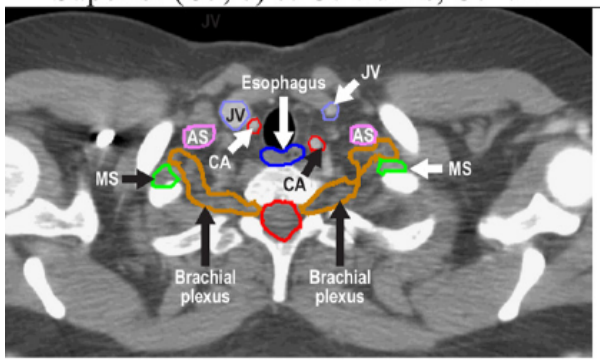
Contouring the brachial plexus

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

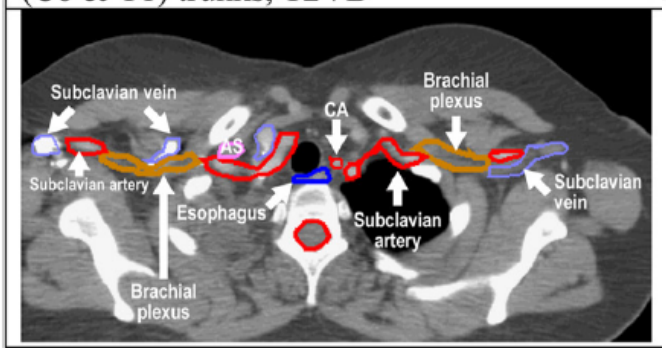
Kong, IJROBP 2011; 81(5); 1442-57

Contouring the brachial plexus

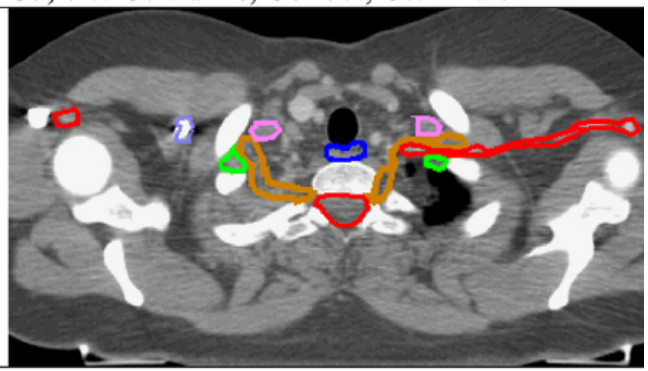
Superior (C5, 6) & C7 trunks, C7 VB



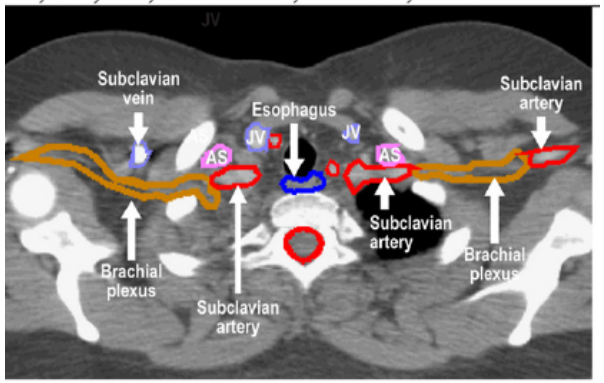
Superior (C5, C6), middle (C7), and inferior (C8 & T1) trunks, T2VB



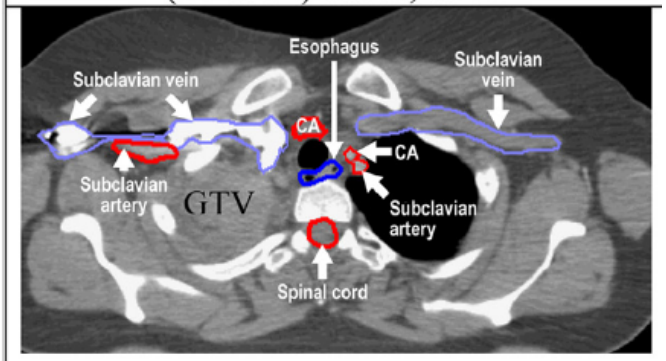
C5, 6 & C7 trunks, C8 root, C7/T1 disk



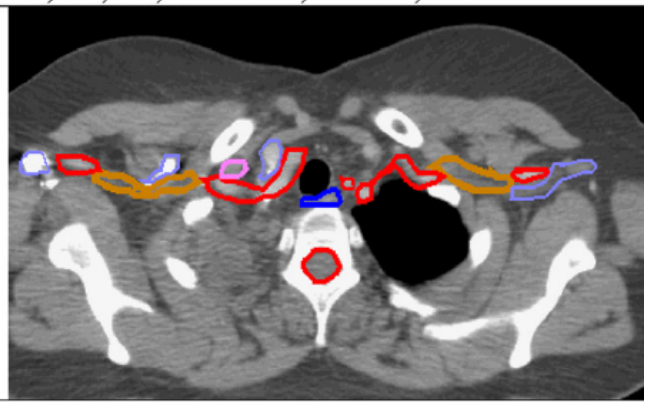
C5, C6, C7, C8 trunks, T1 root, T1VB



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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Practical aspects of IMRT planning part 2

Advanced Treatment Planning Course
3-7 September 2017 – Barcelona, Spain

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!

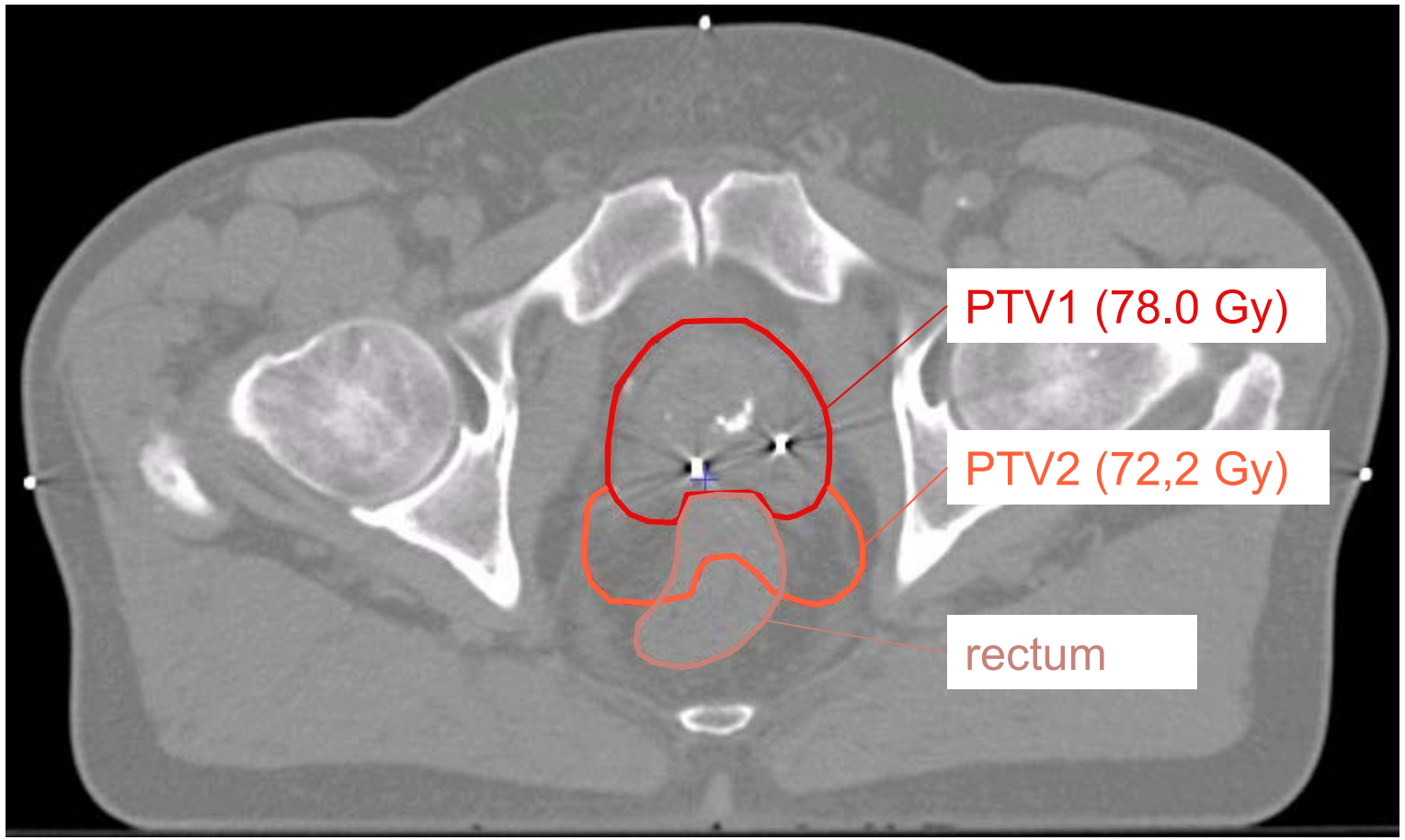
  more beams results in:

  - 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



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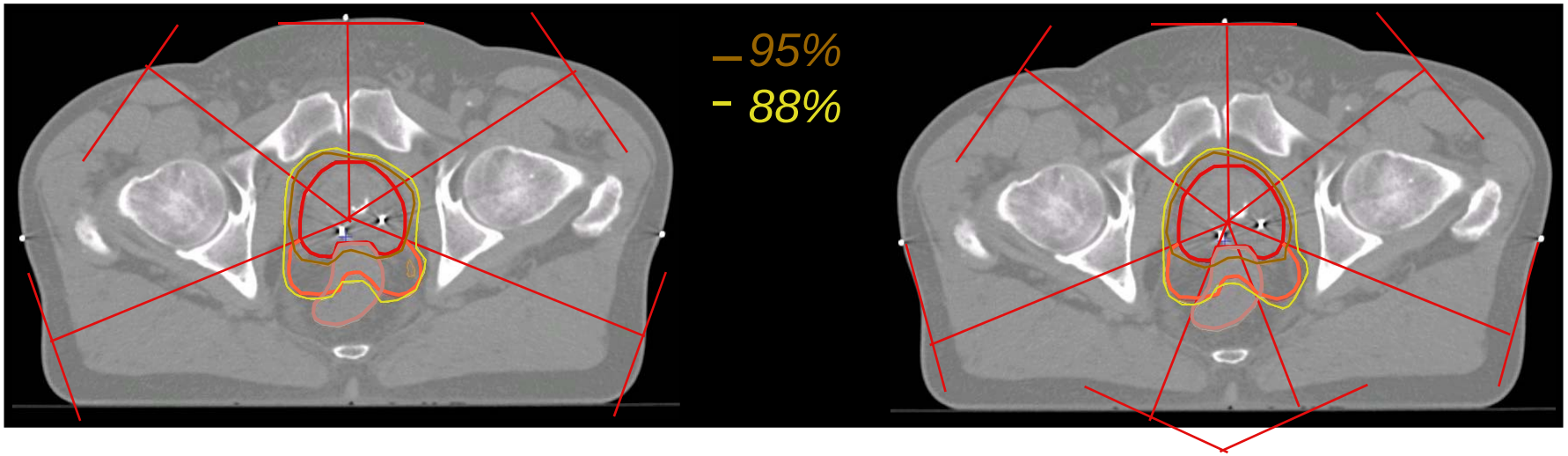
prostate planning: 5 vs 7 beams

5 beams

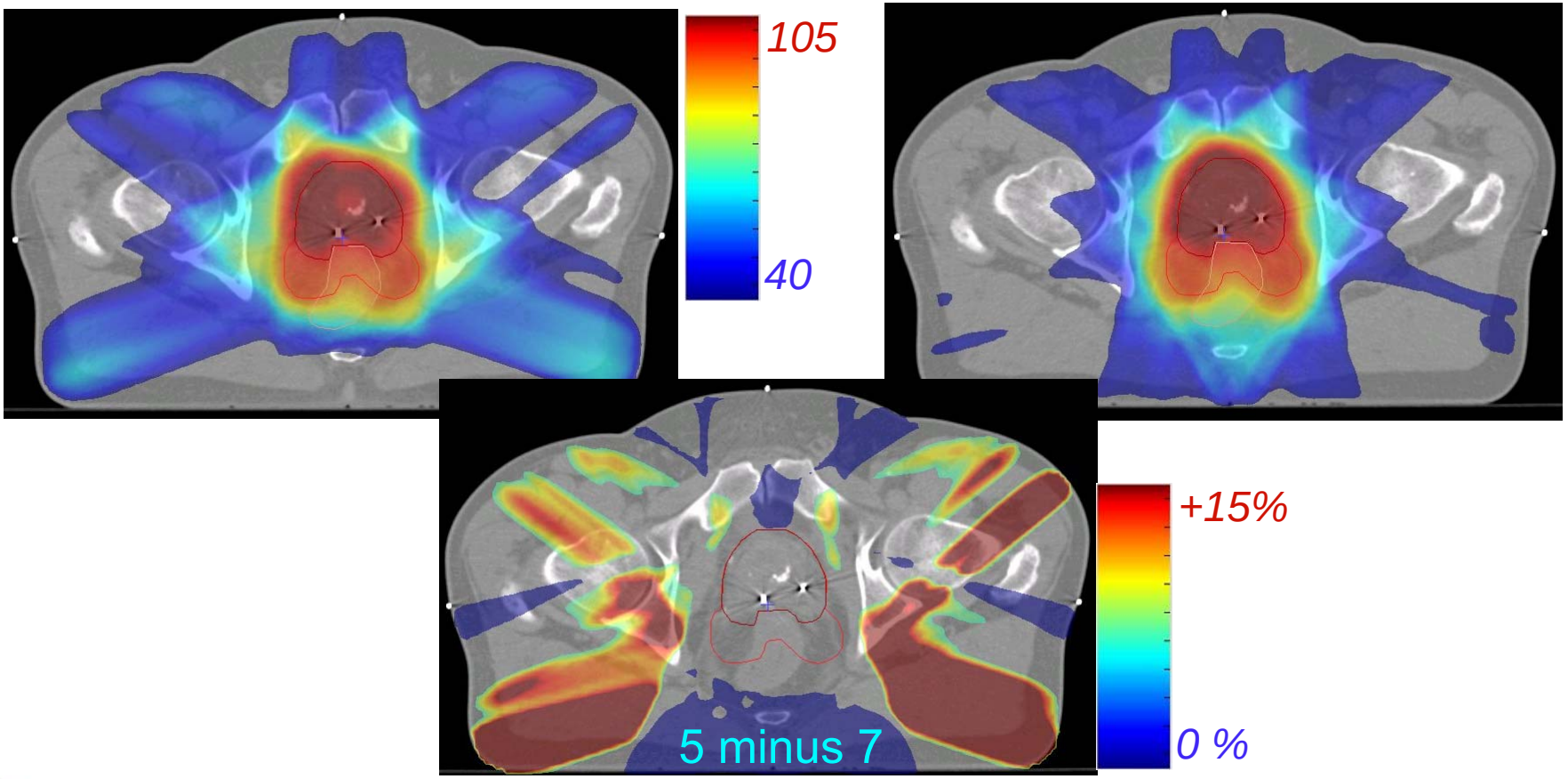
7 beams



prostate planning: 5 vs 7 beams

5 beams

7 beams



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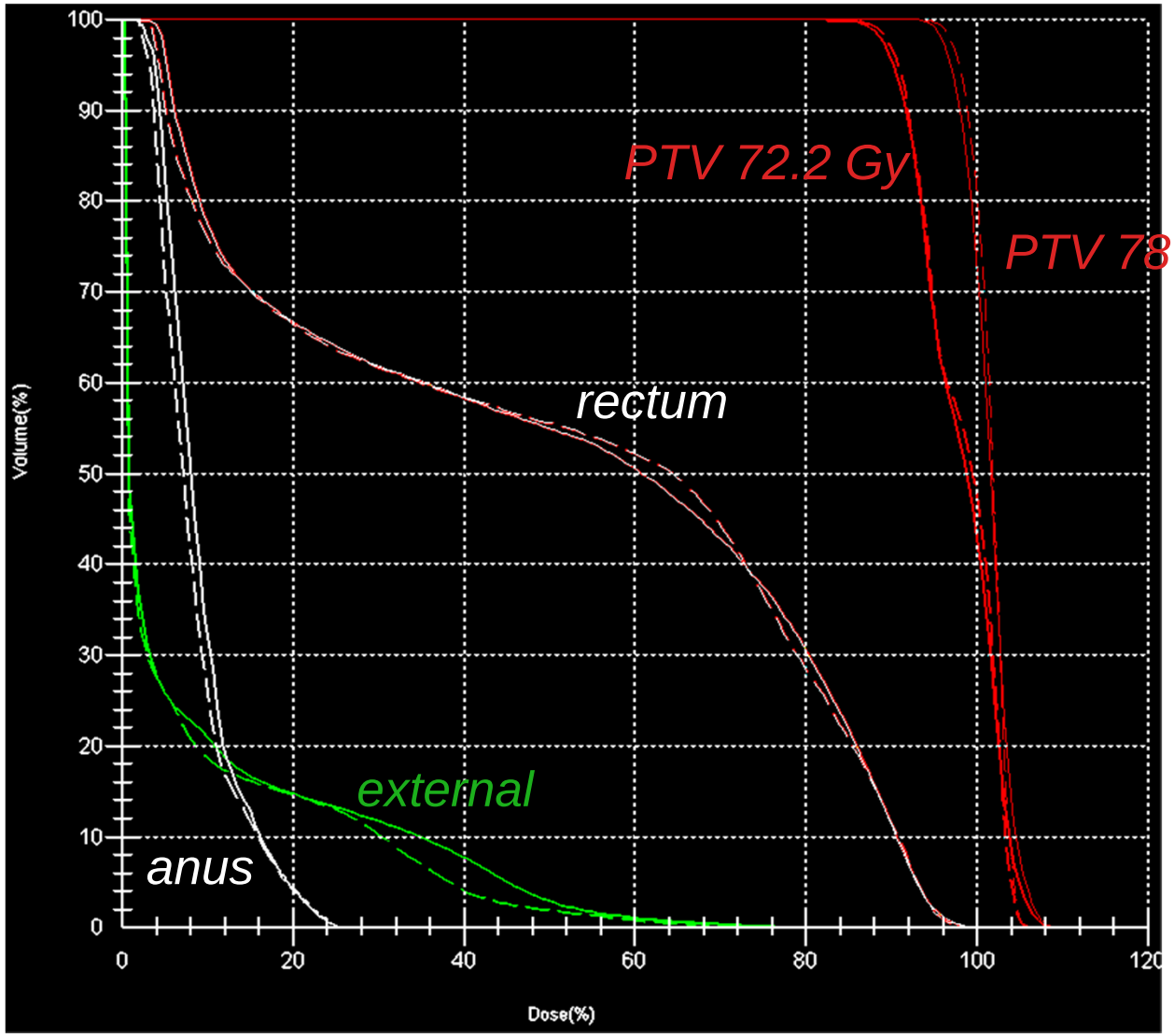
prostate planning: 5 vs 7 beams



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

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Beam angle optimization

Rotterdam:

- Several 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.

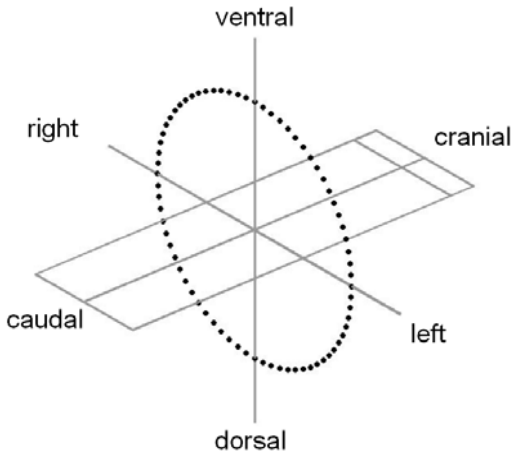
iCycle: Integrated, multicriterial beam angle, and profile optimization for generation of coplanar and noncoplanar IMRT plans.

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

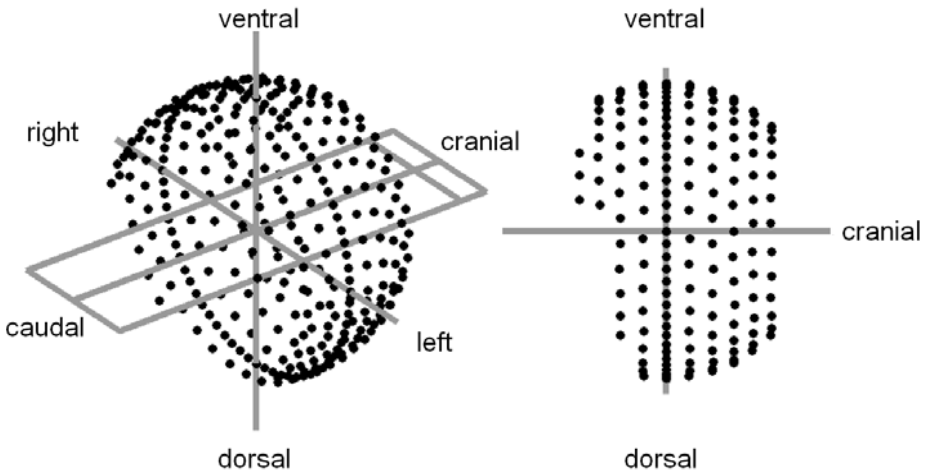
Department of Radiation Oncology, Erasmus MC Rotterdam, Groene Hilledijk 301, 3075 EA Rotterdam, The Netherlands. s.breedveld@erasmusmc.nl

Erasmus-iCycle: main features

- 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

gain per added beam →

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

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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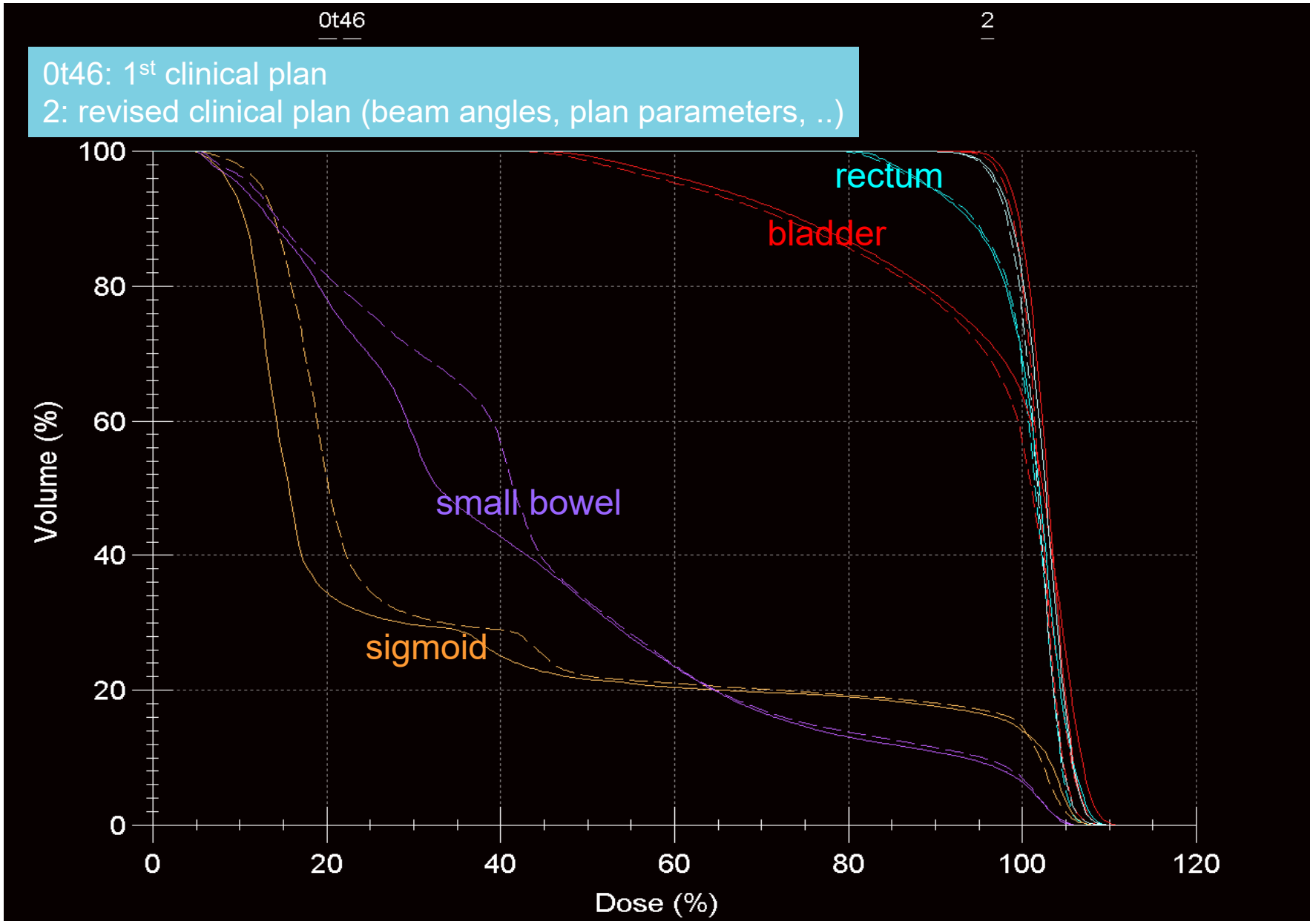
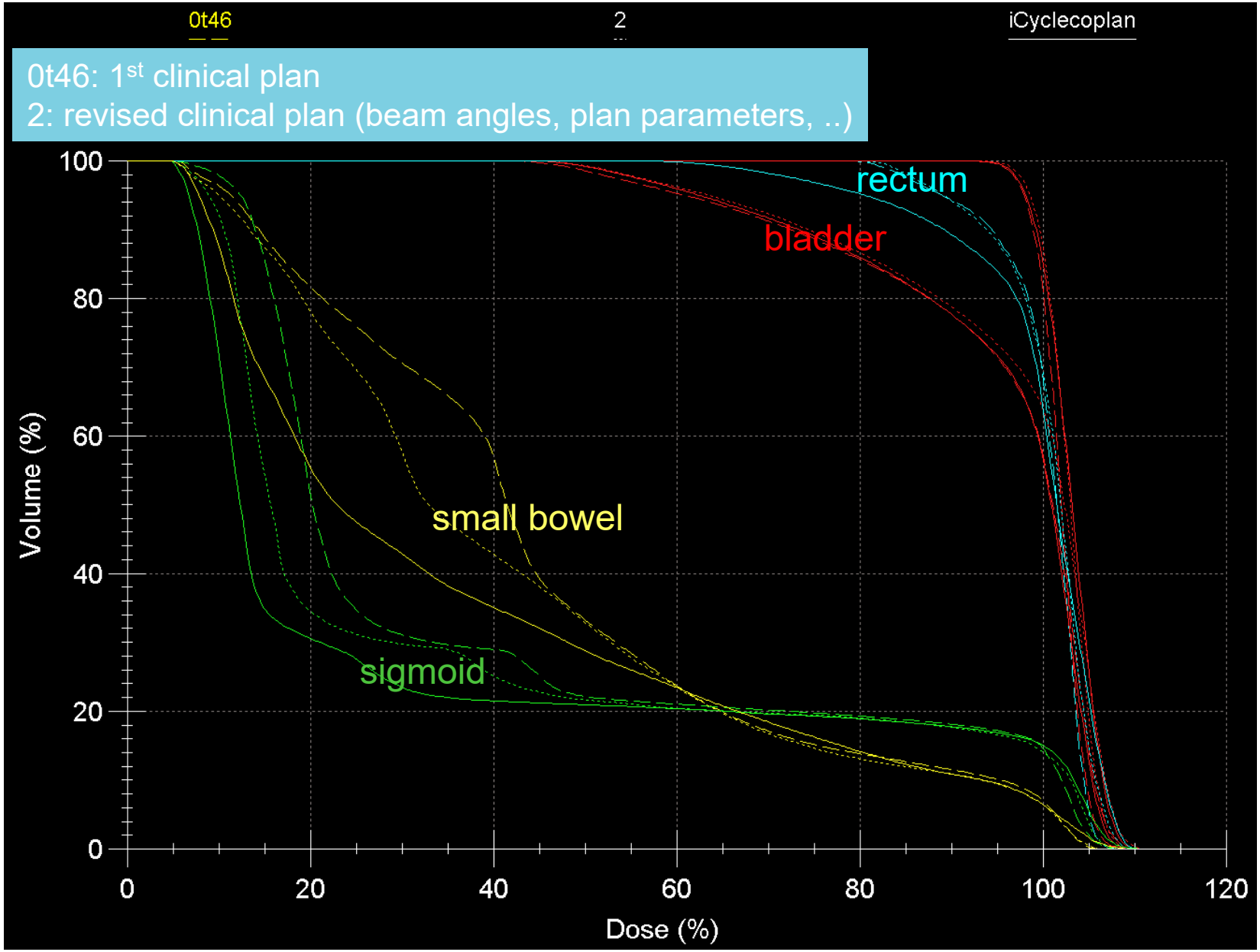
Example: Cervix IMRT Monaco patient



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

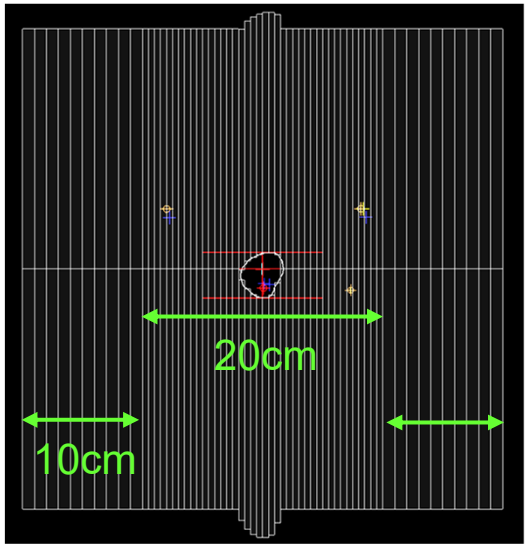
  - 6 MV in pelvic region??

  - combination of different energies is a good option

    (computer based choice?)

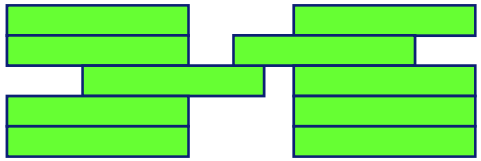
MLC geometry: Varian (millenium MLC)

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



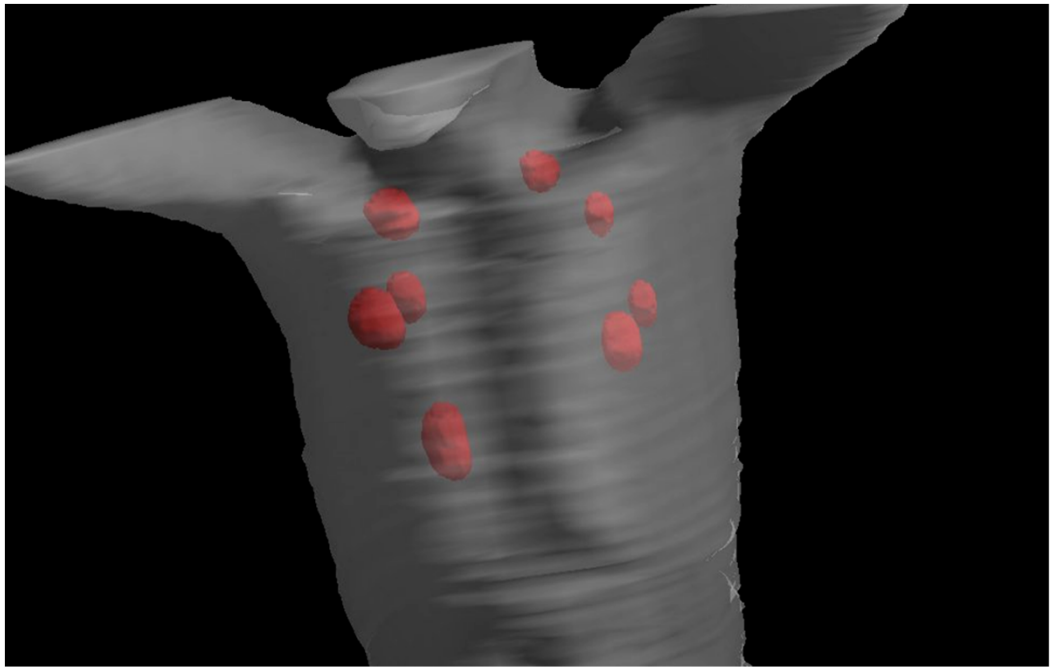
- maximum overtravel in (IMRT) fields is 14.3 cm:
  - so, if an IMRT field width ≥ 14.3 cm ⟶ splitting beam
  - field width ≈ 28 cm ⟶ splitting again (‘*carriage positions*’)

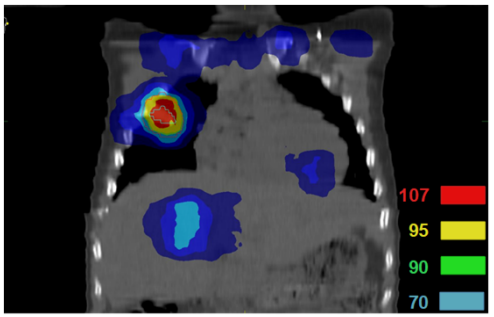
- inter-digitating MLC’s
- closing opposing leaf-pairs

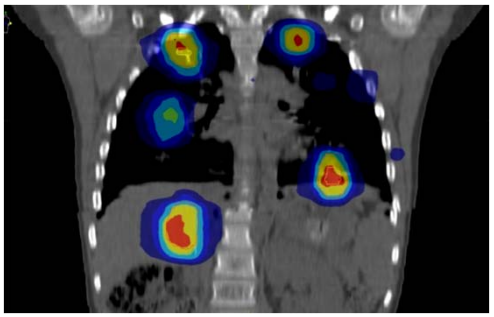


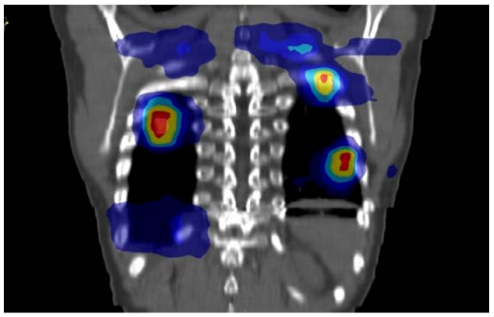
Clinical example multiple PTV case

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

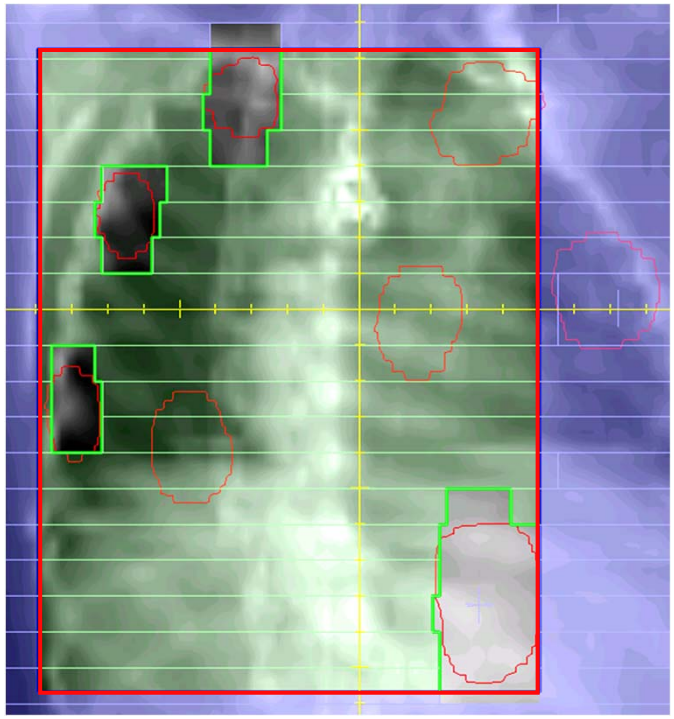








Example multiple PTV (8!) IMRT plan: Varian



segment 1

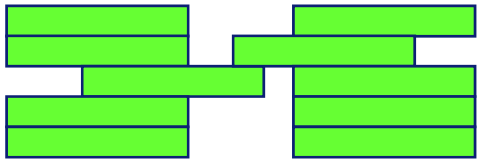
segment x

1.8 Gy / fraction
8 fields
38 segments, 555 MU

MLC geometry: Elekta (MLCi, MLCi2)

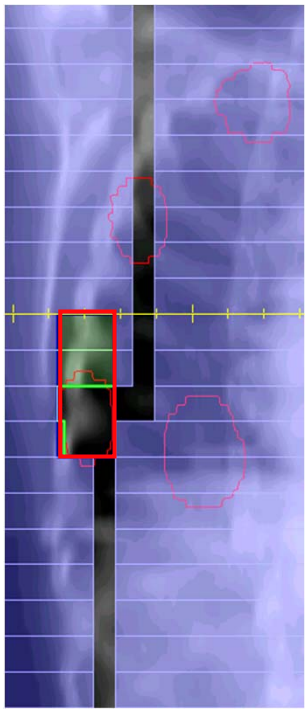
- no splitting of beams

- MLCi : no interdigitating leafs
- MLCi2 : interdigitating leafs

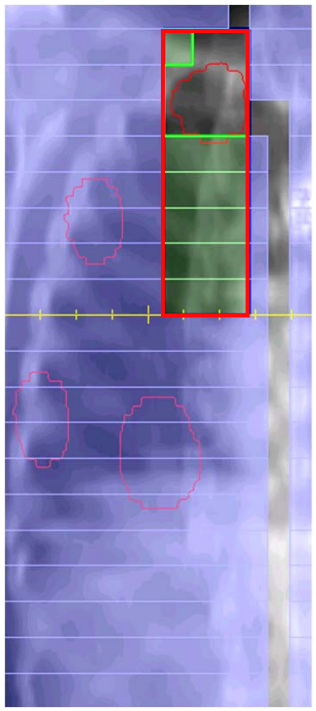


- minimum gap for opposing leaf pairs : 5 mm (MLCi , MLCi2)
- No overtravel on Y-jaws (MLCi , MLCi2)

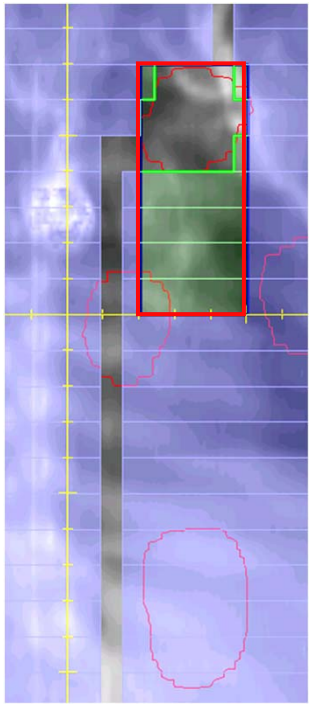
Example multiple PTV IMRT plan: Elekta , MLCi



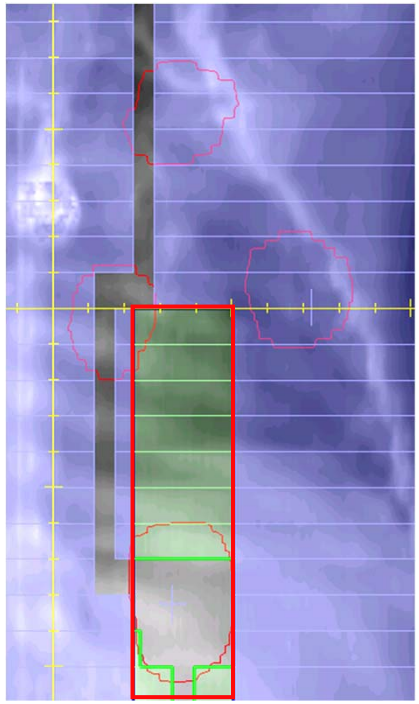
segment 1



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

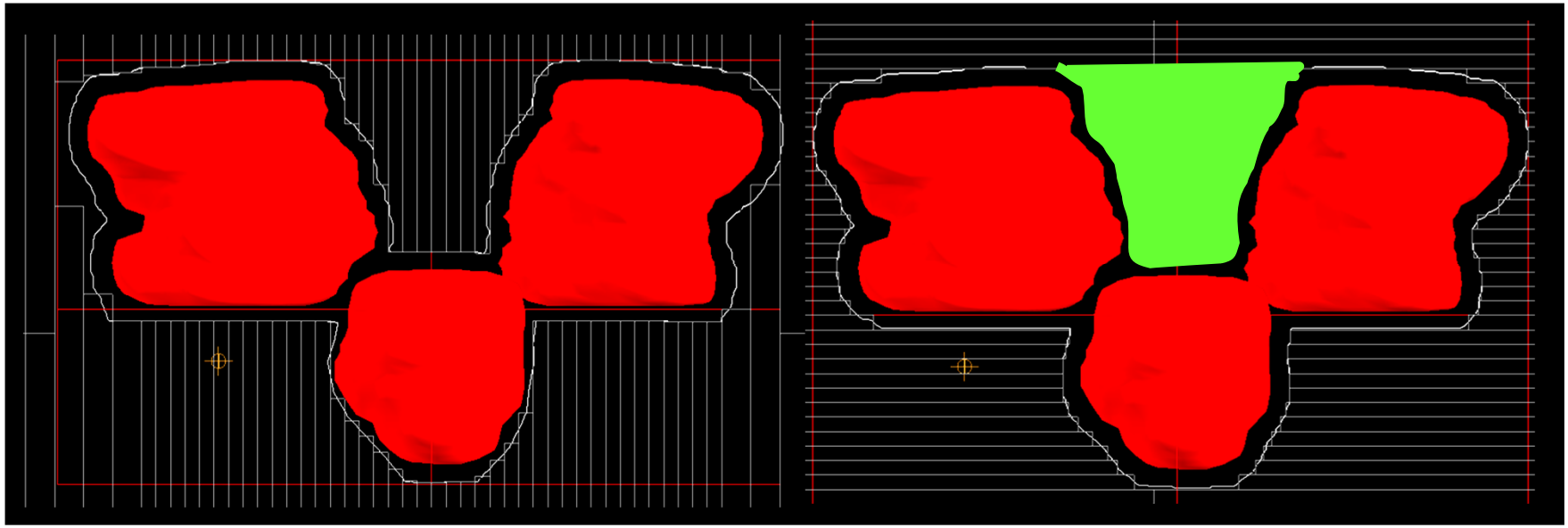
- in this example the MLC limitations resulted in large differences.

  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

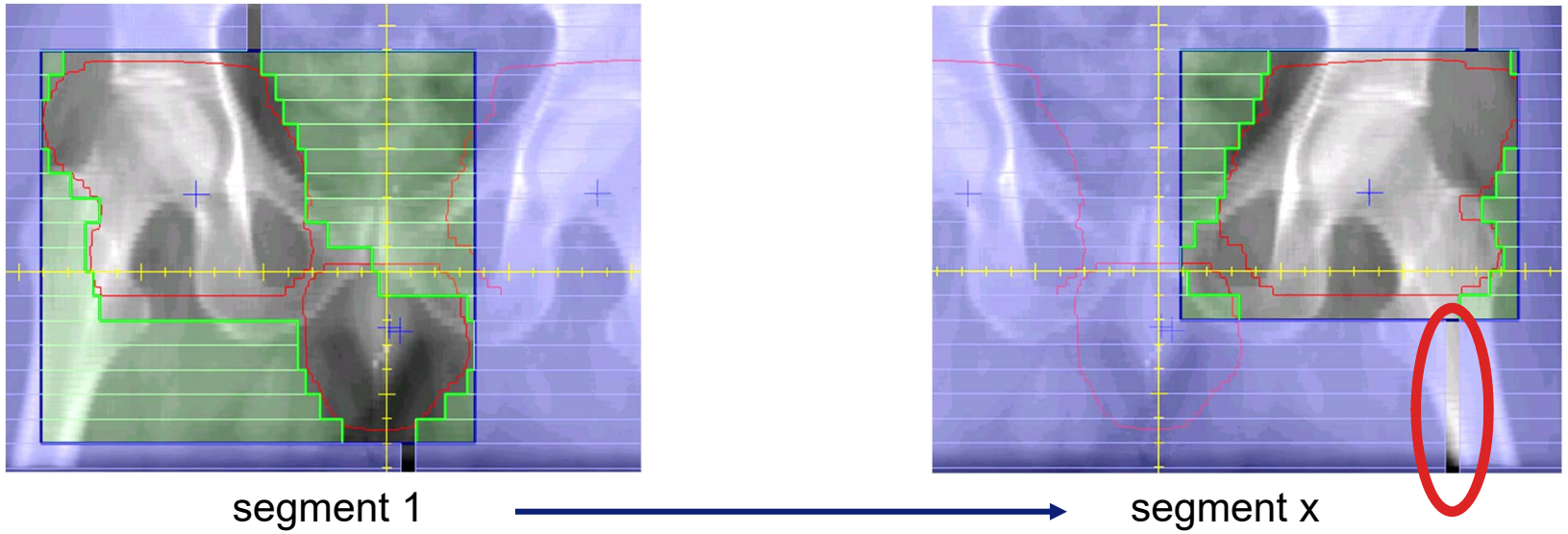


Collimator 90º

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*’

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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

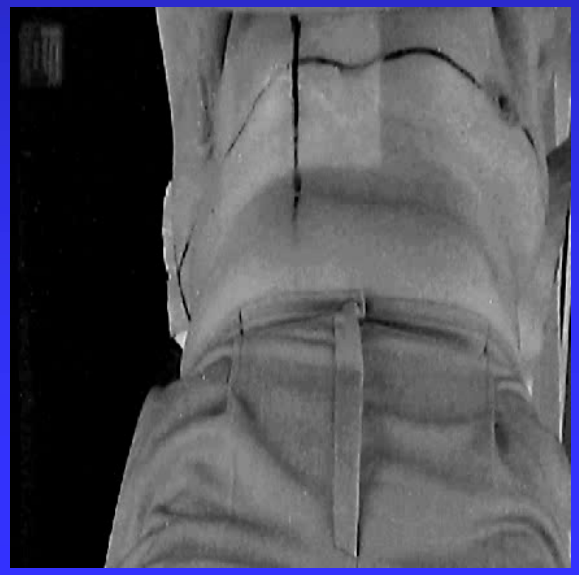
Problems in radiotherapy:

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

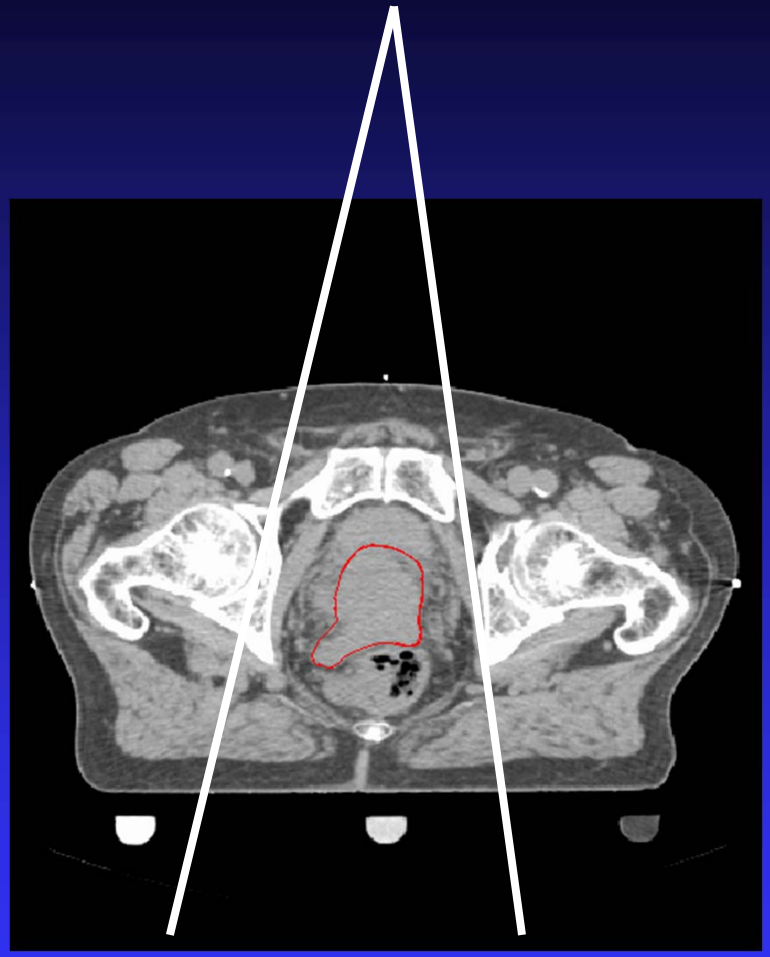
The physician was in a rush when drawing the target volume

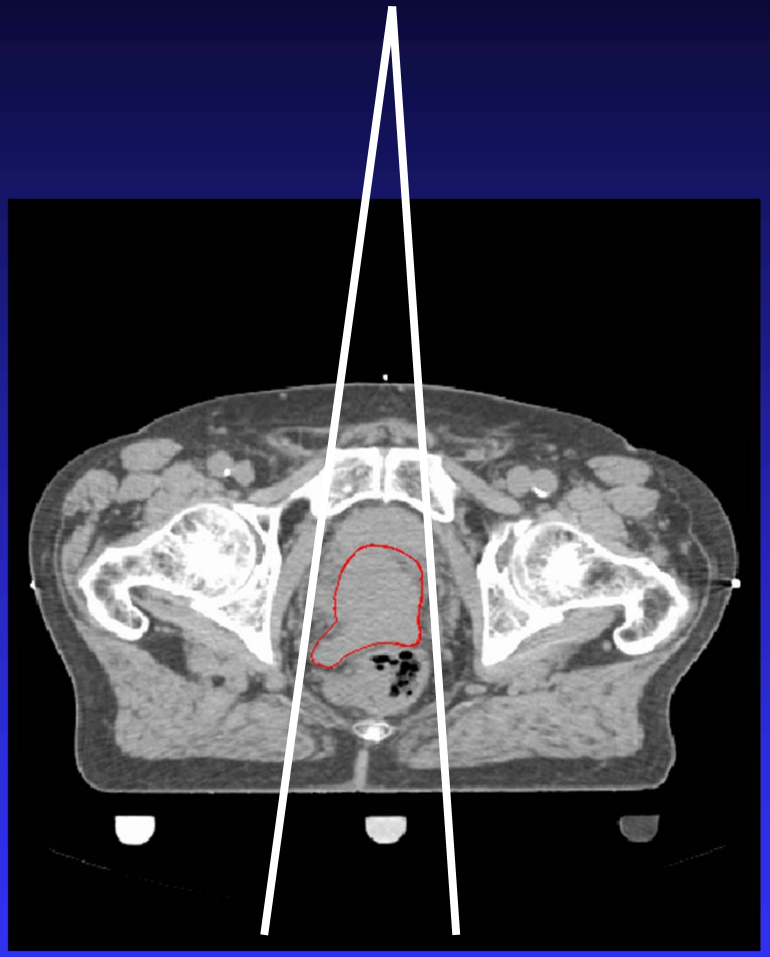
The patients belly flopped from day to day, letting the skin marks move all over the place

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

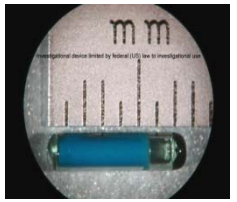
Image guidance does not solve all geometrical uncertainties and variations *and introduces new ones*

IGRT Technologies

Ultrasound

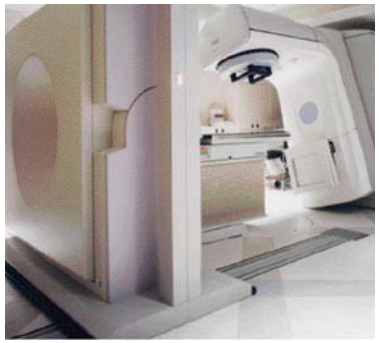
kV Radiographic

Portal Imaging



Markers

(Active and Passive)



Siemens
PRIMATOM™

kV CT

TomoTherapy
Hi-Art™

MV CT

Elekta Synergy

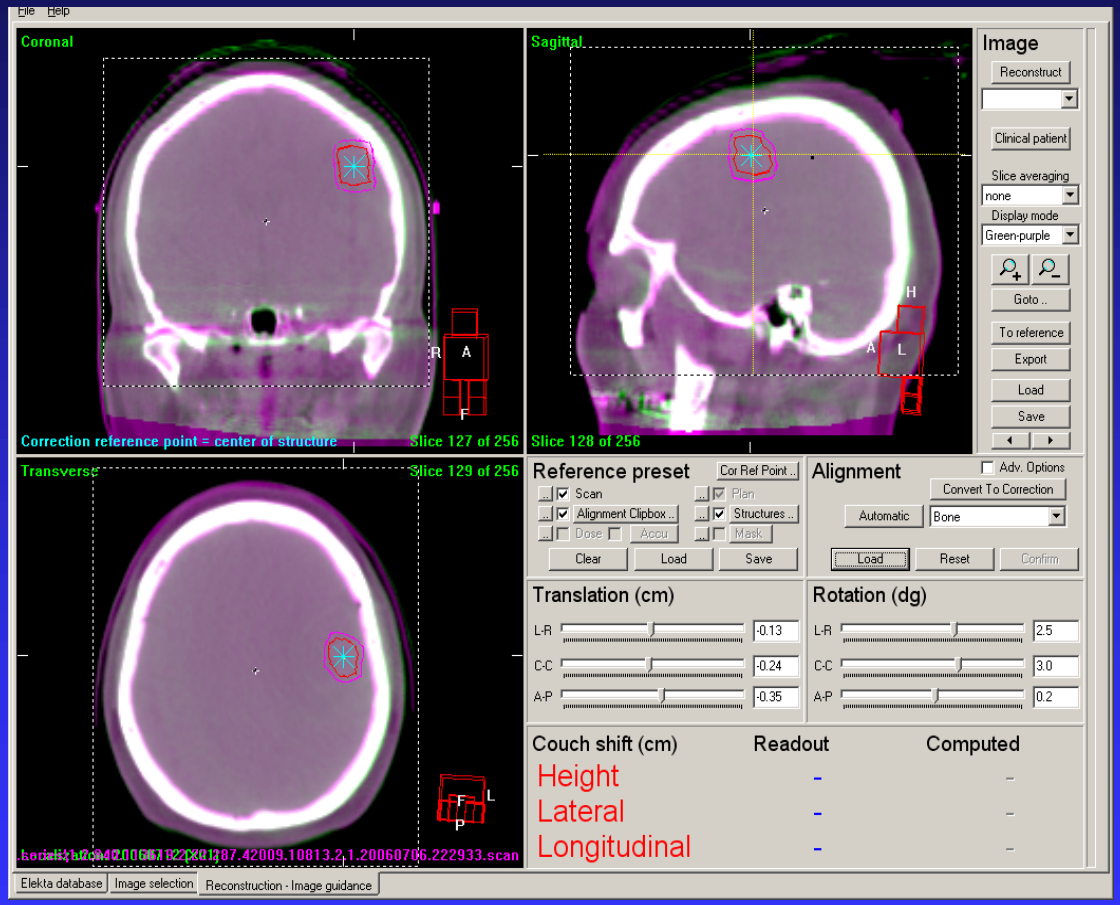
Varian OBI™

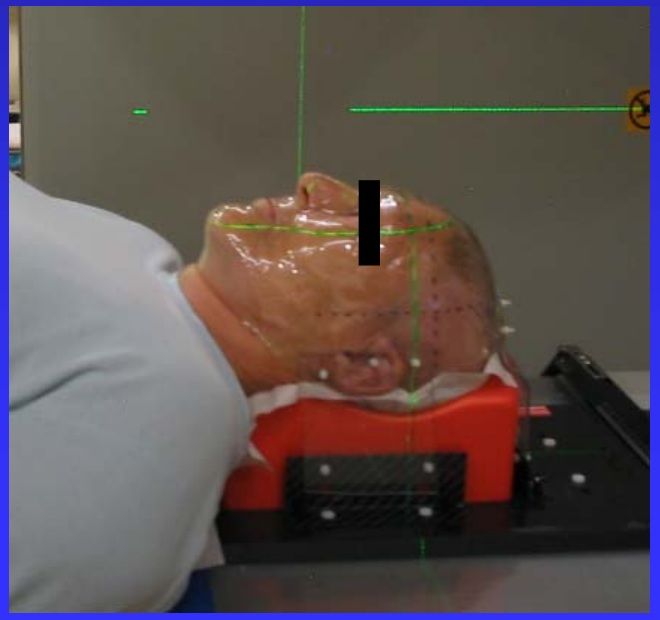
kV and MV Cone-beam CT

School

Cancer Centre

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

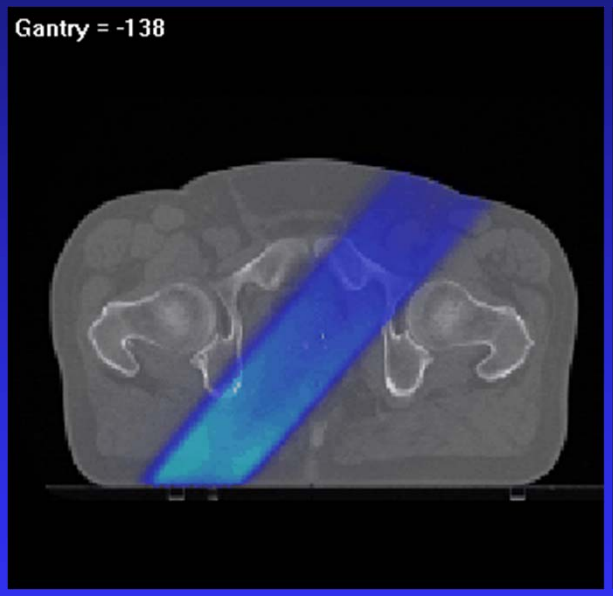
- Gross error: mistakes, transcription errors, software faults:
  - must be caught by QA
- Error: difference between planned value and its true value during treatment, however small
- Uncertainty: the fact that unpredictable errors occur – quantified by standard deviations
- Variation: the fact that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

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

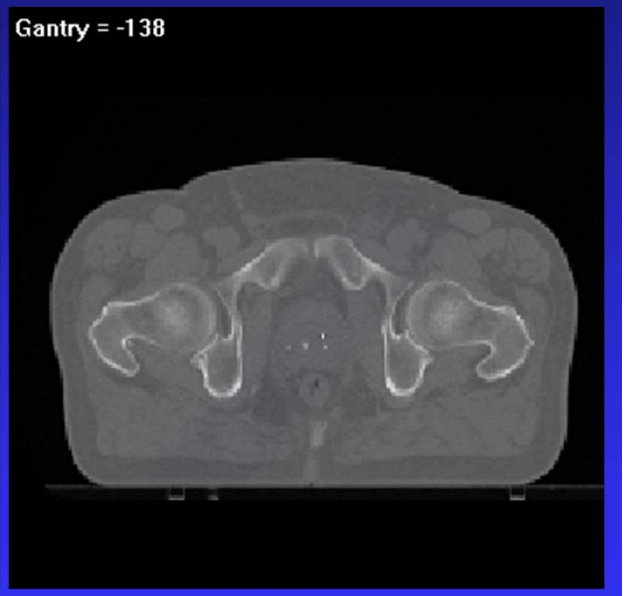
EPID movie

-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 !!

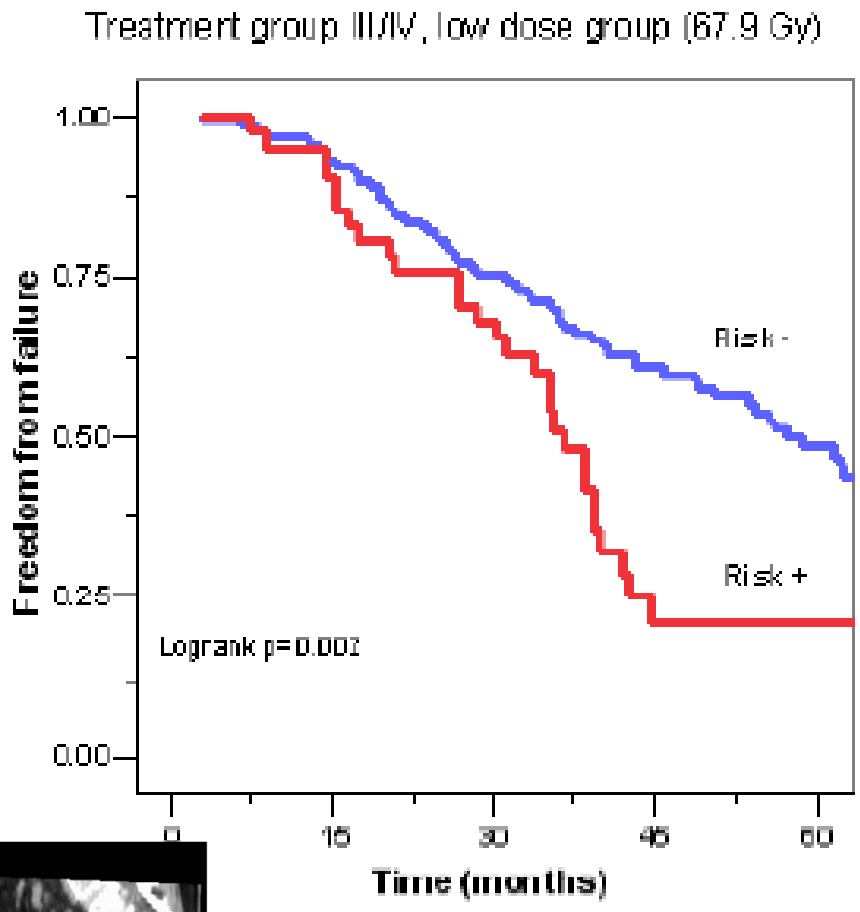
Mans et al, 2010

What happens in the other 99.6% ?

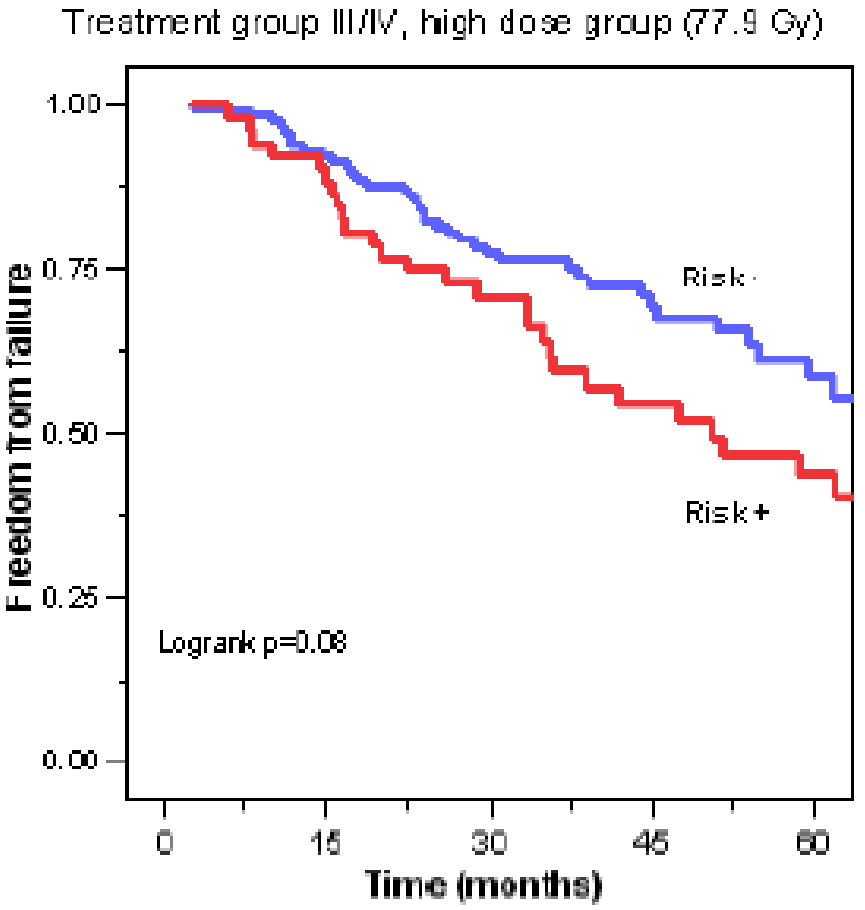
- There are many small unavoidable errors (mm size) in all steps of radiotherapy
  - In some cases many of these small errors point in the same direction
  - I.e., in some patients large (cm) errors occur(ed)
- This is not a fault, this is purely statistics
- What effect does this have on treatment?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

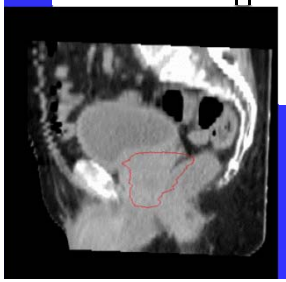
Motion counts? Prostate trial data (1996)

N=185 (42 risk+)



N=168 (52 risk+)





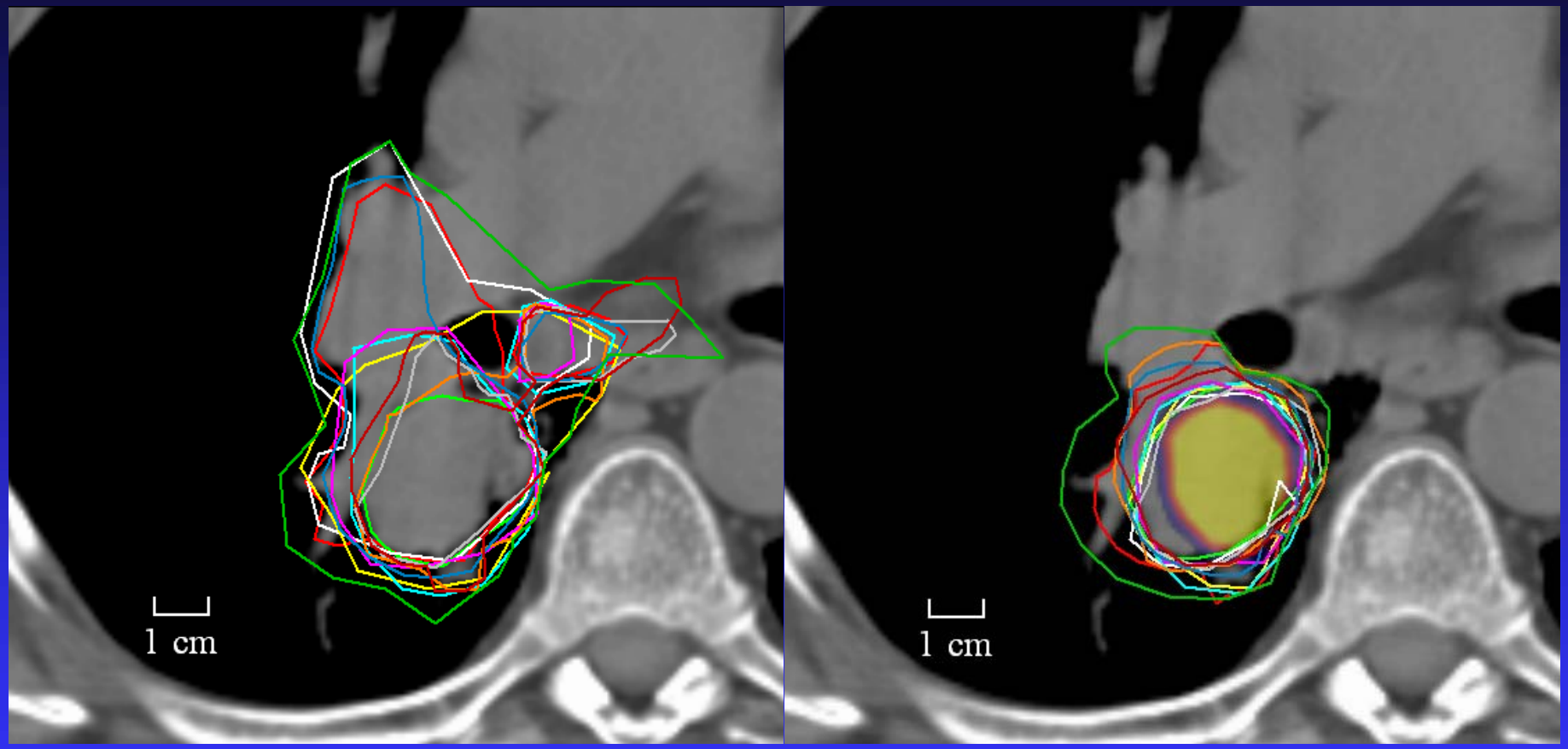
Risk+: initial full rectum, later diarrhea

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

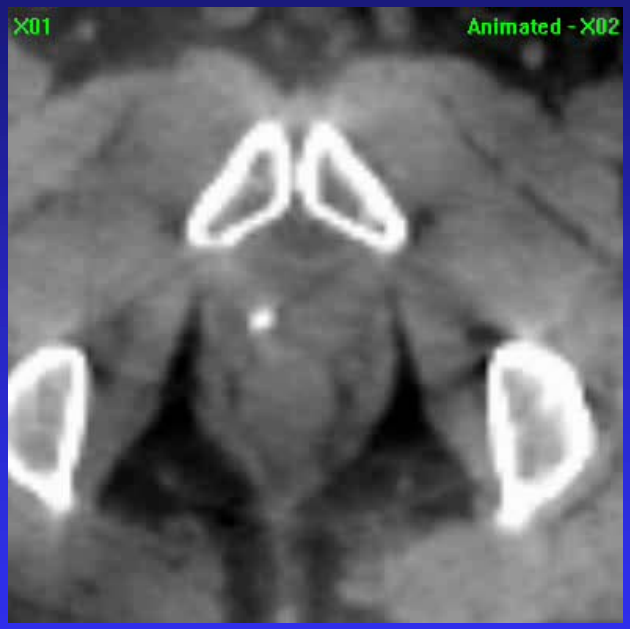
CT + PET (T_2N_1)

SD 3.5 mm

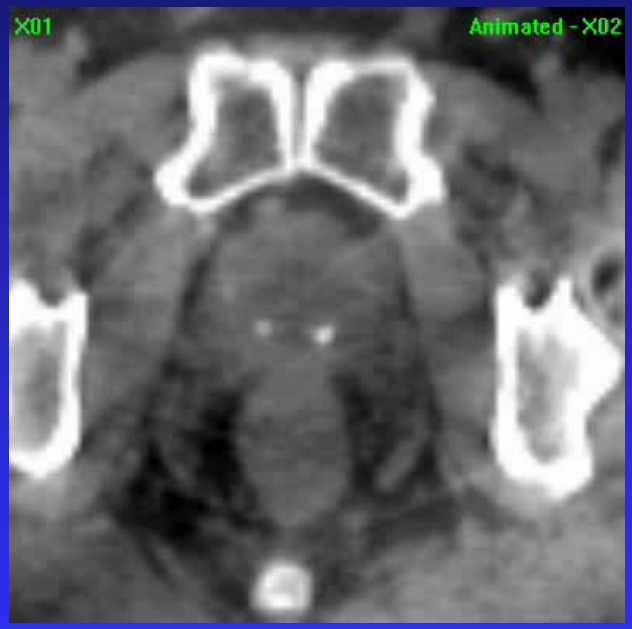
Consistency is imperative to gather clinical evidence!

Steenbakkers et al, IJROBP 2005

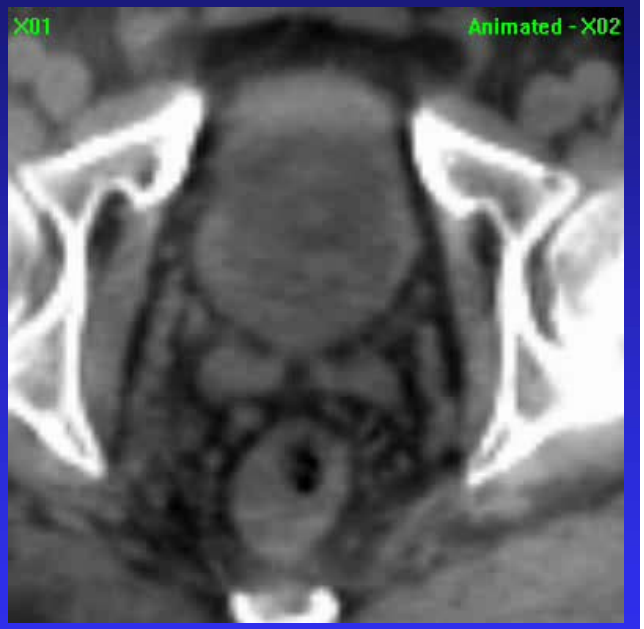
Are prostate markers perfect ?



Apex



Base



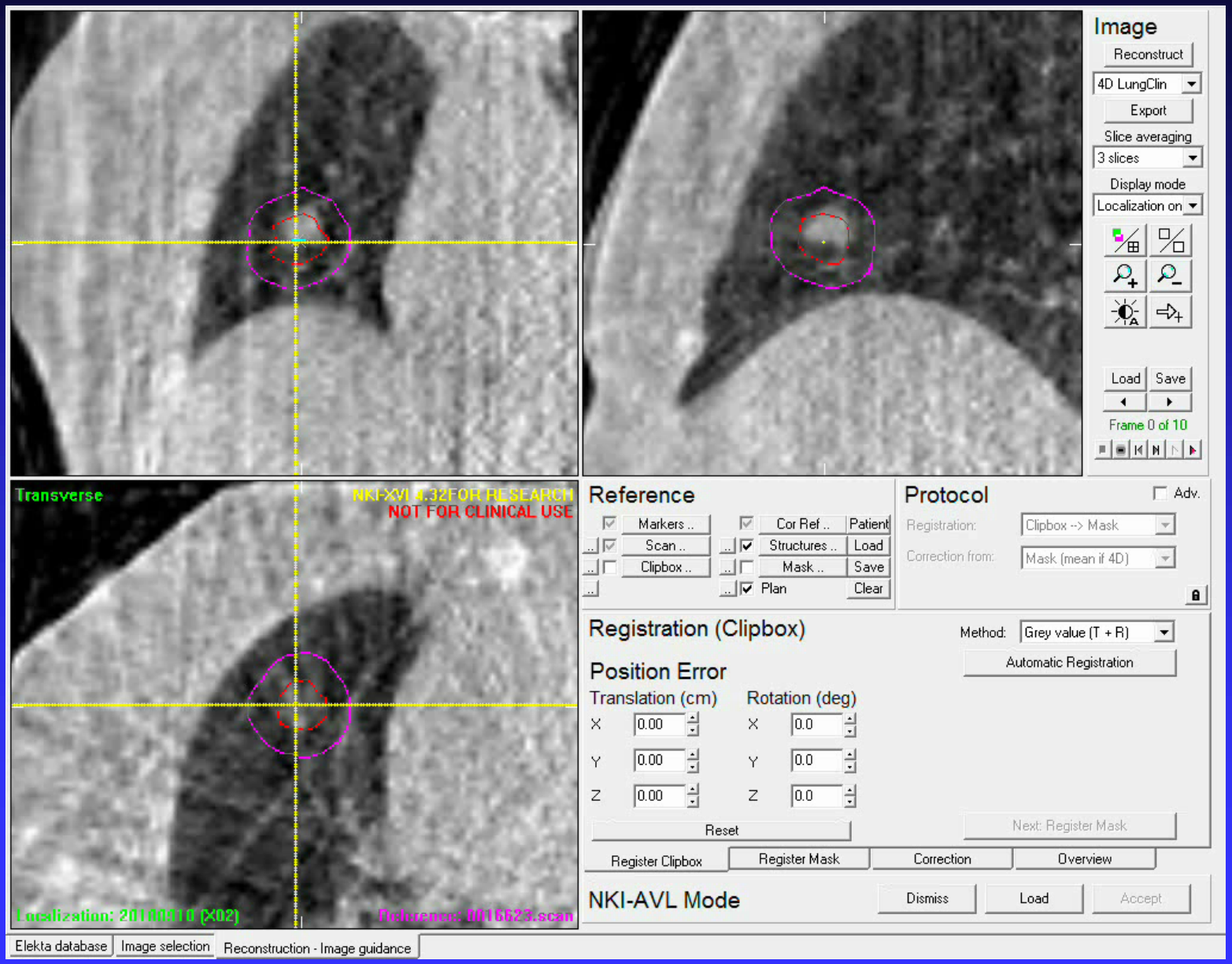
Sem. Vesicles

→ +/-1 cm margin required

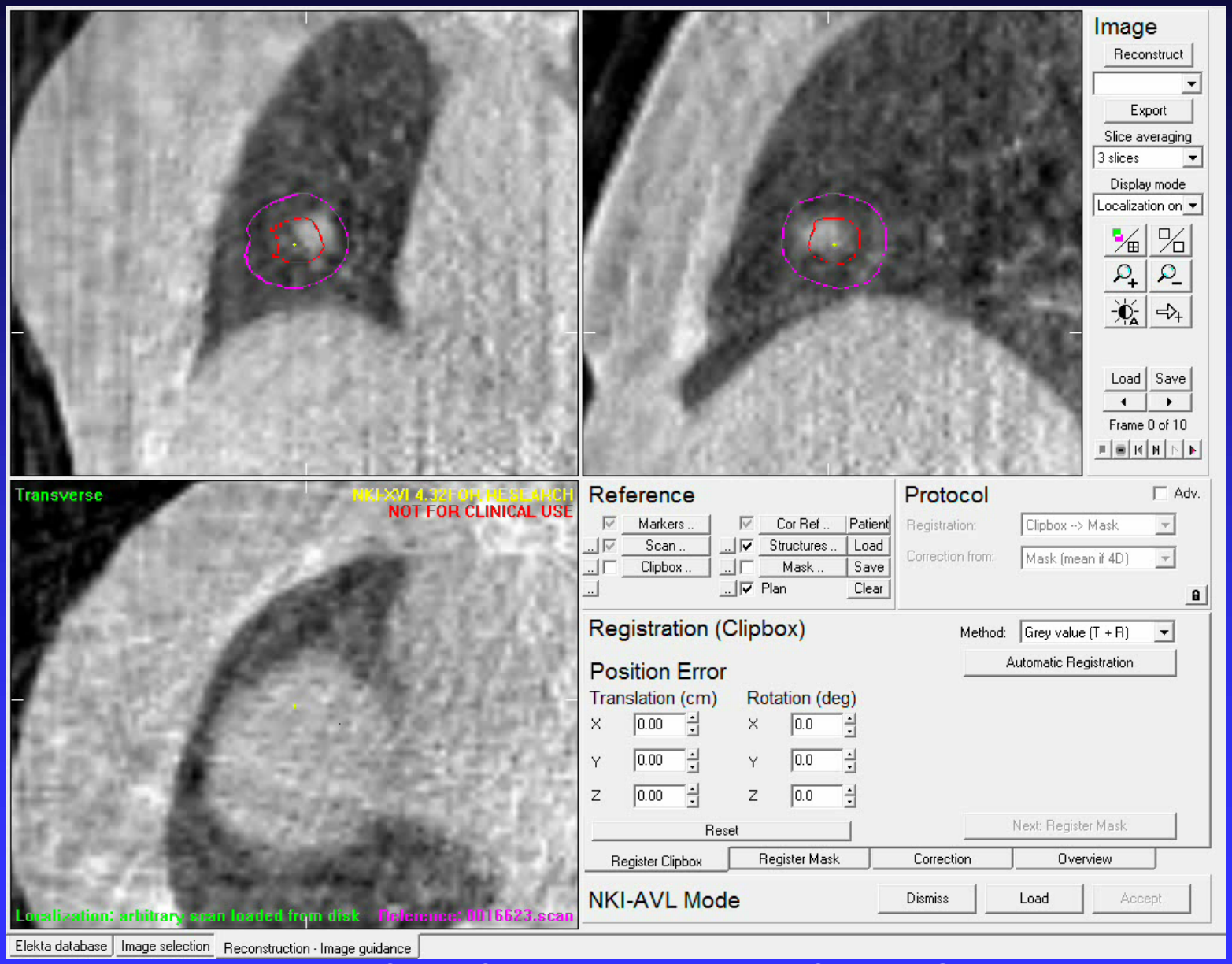
Best: combine markers with low dose CBCT

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

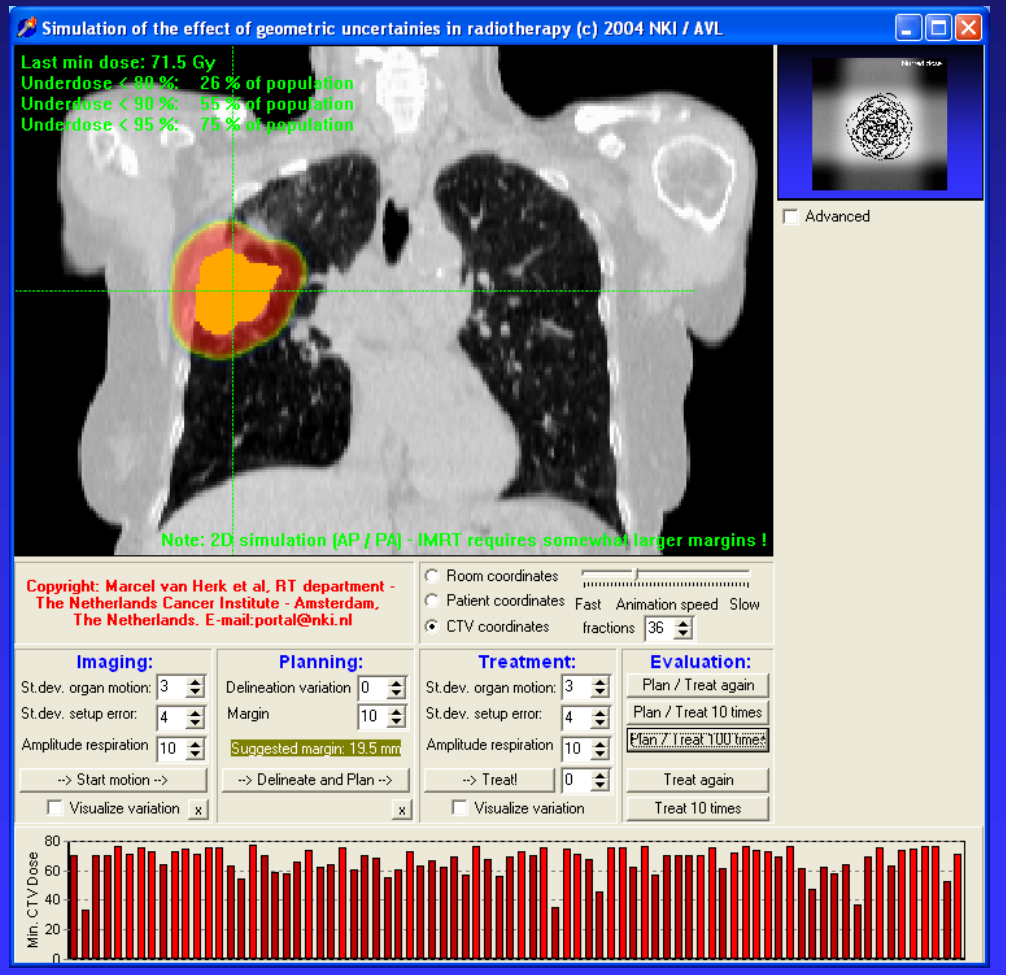
σf = standard deviation of the intra-fraction motion

van Herk et al, Sem Rad Onc 2004

Demonstration – errors in RT

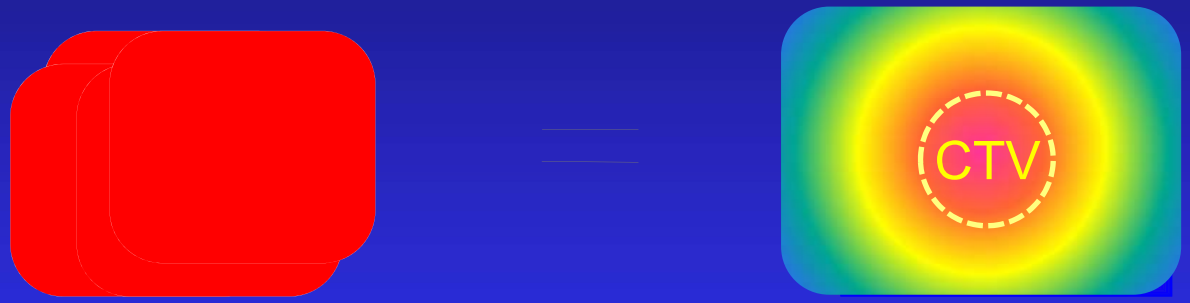
- Margin between CTV and PTV: 10 mm

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

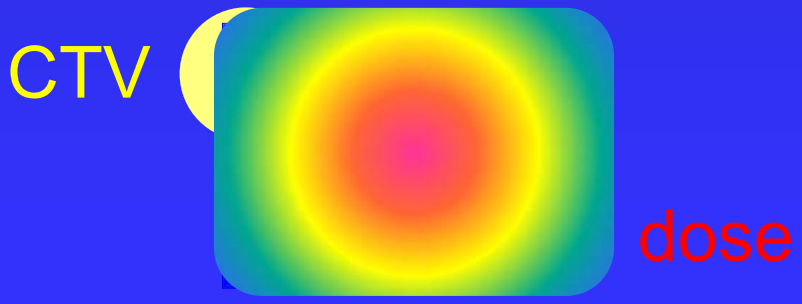


What is the effect of geometrical errors on the CTV dose ?

Random: Breathing, intrafraction motion, IGRT inaccuracy



Systematic: delineation, intrafraction motion, IGRT inaccuracy

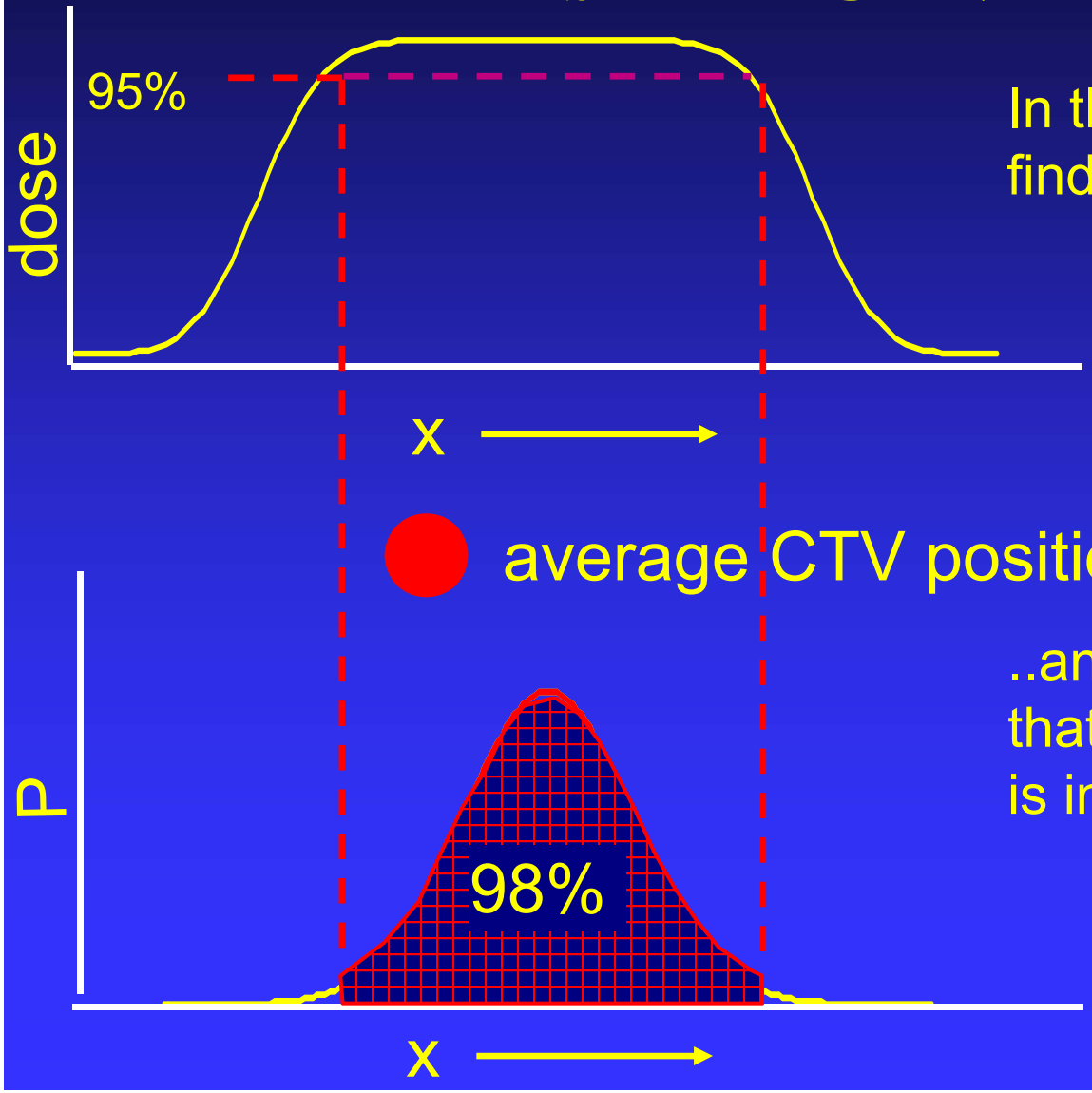


Analysis of CTV dose probability

- 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

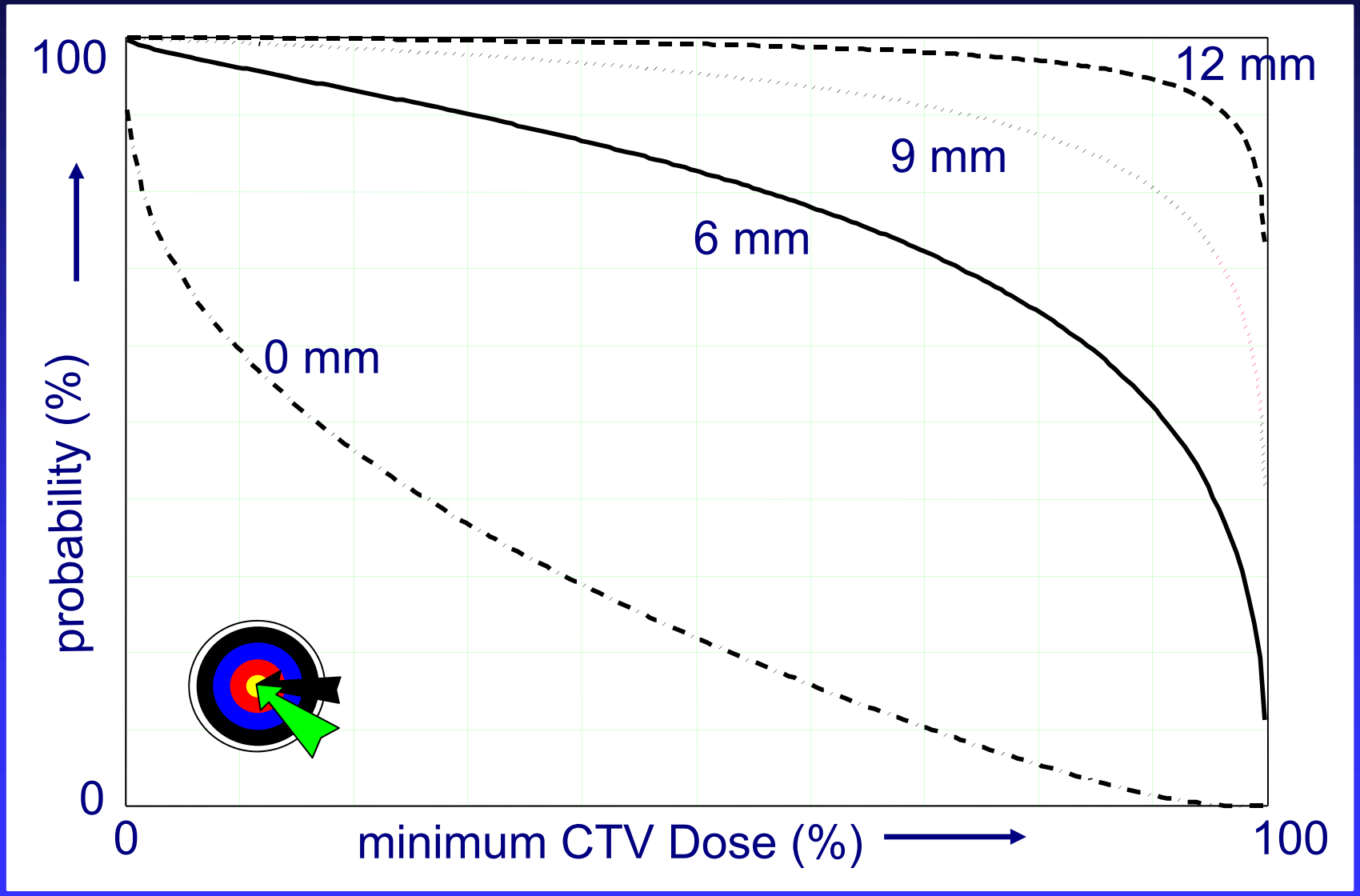
Computation of the dose probability for a small CTV in 1D



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

..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

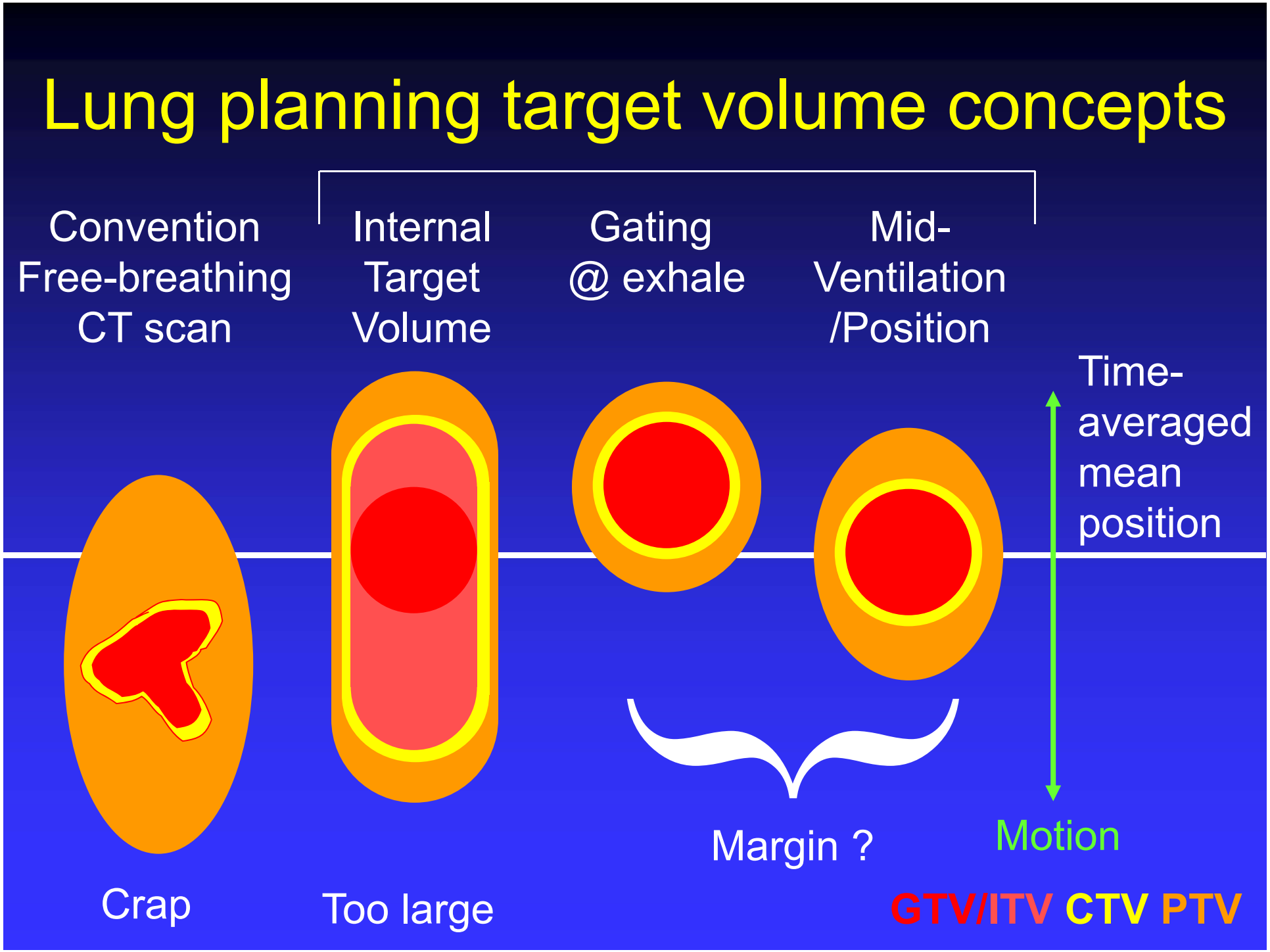
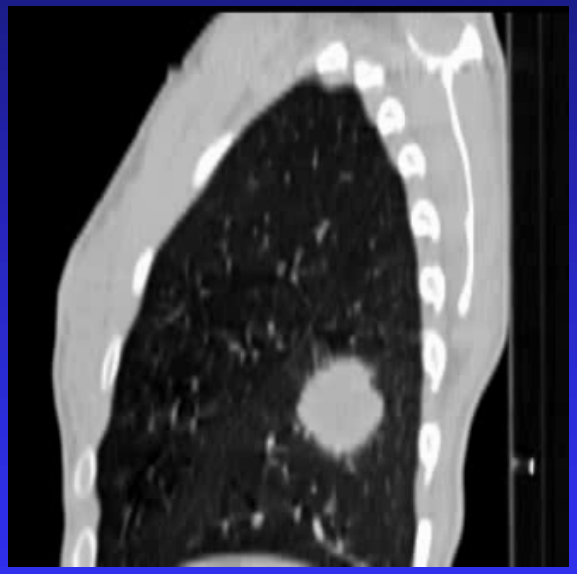
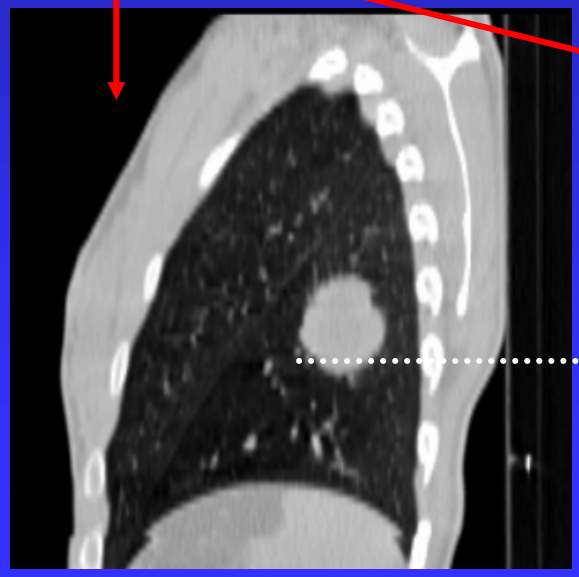


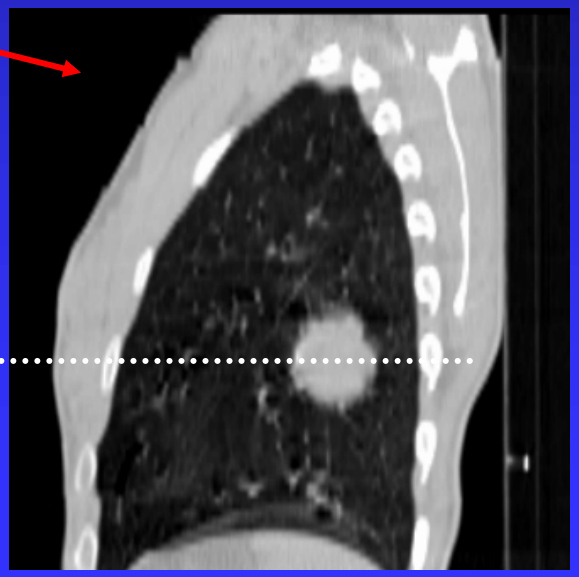
Image *selection* approaches to derive representative 3D data



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**			

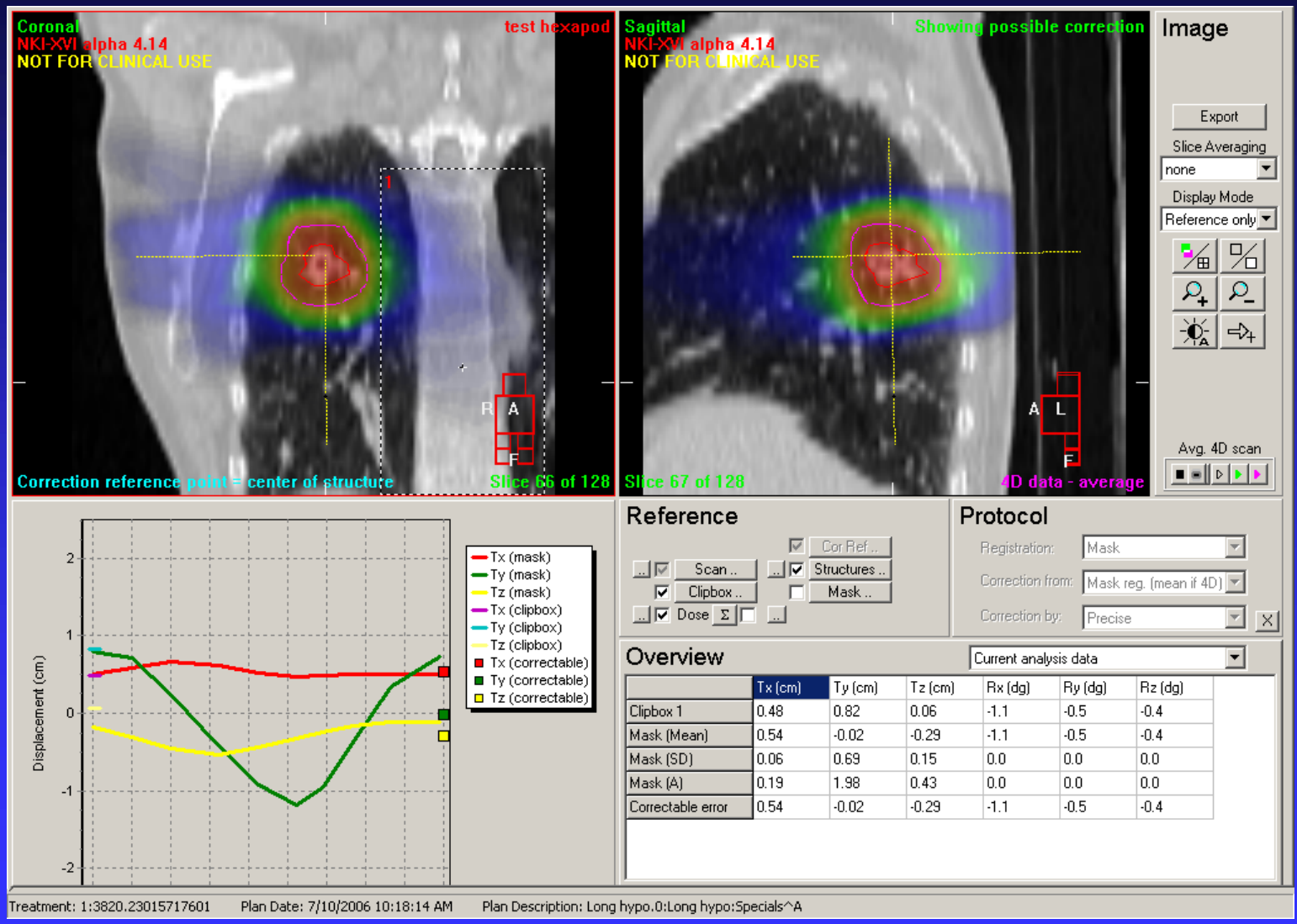
Using conventional fractionation, prescription at 95% isodose line in lung

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**			

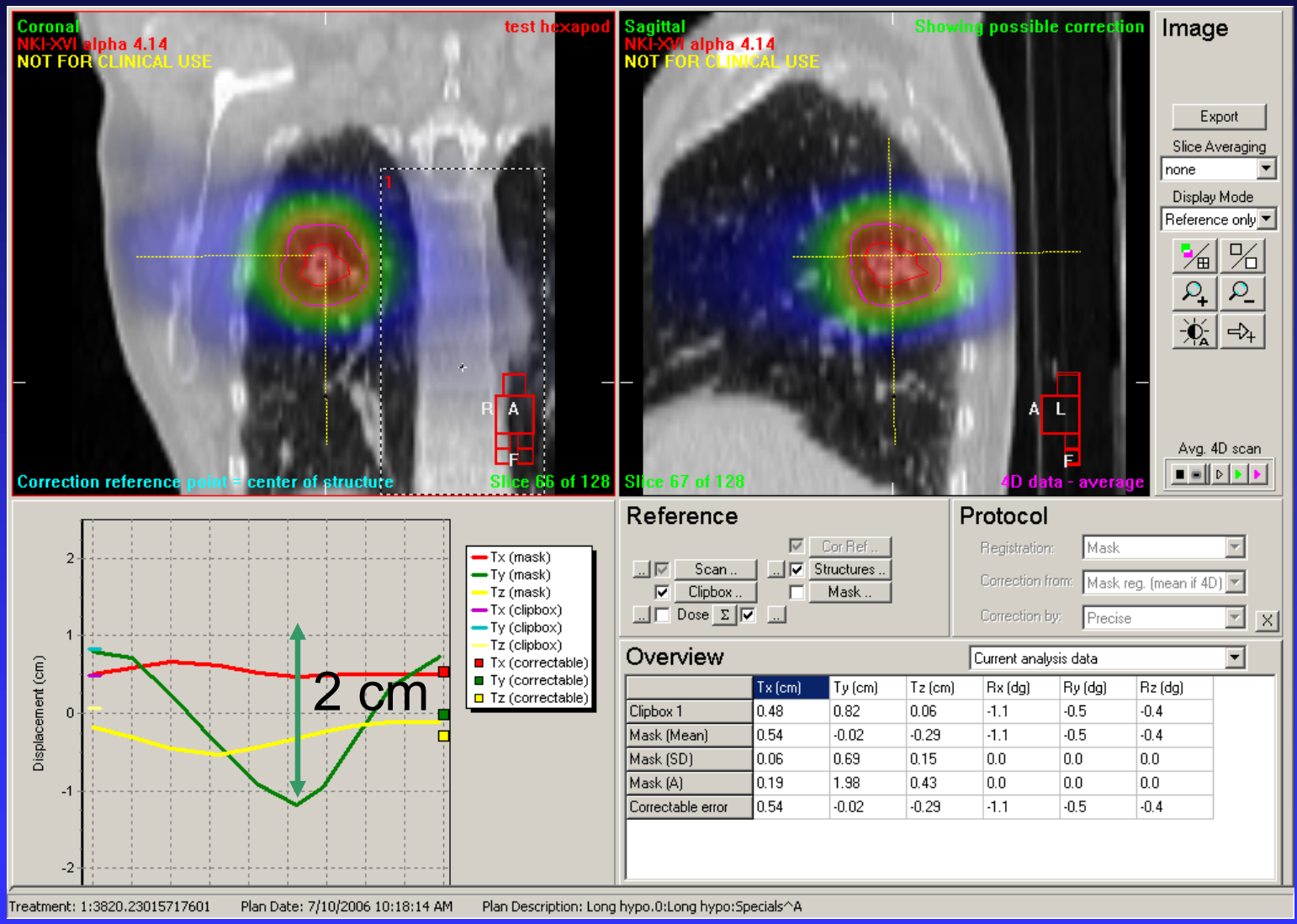
Using hypo-fractionation, prescription at 80% isodose line in lung

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)



	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

9 mm margin is adequate even with 2 cm intrafraction motion

Clinical results with mid-V

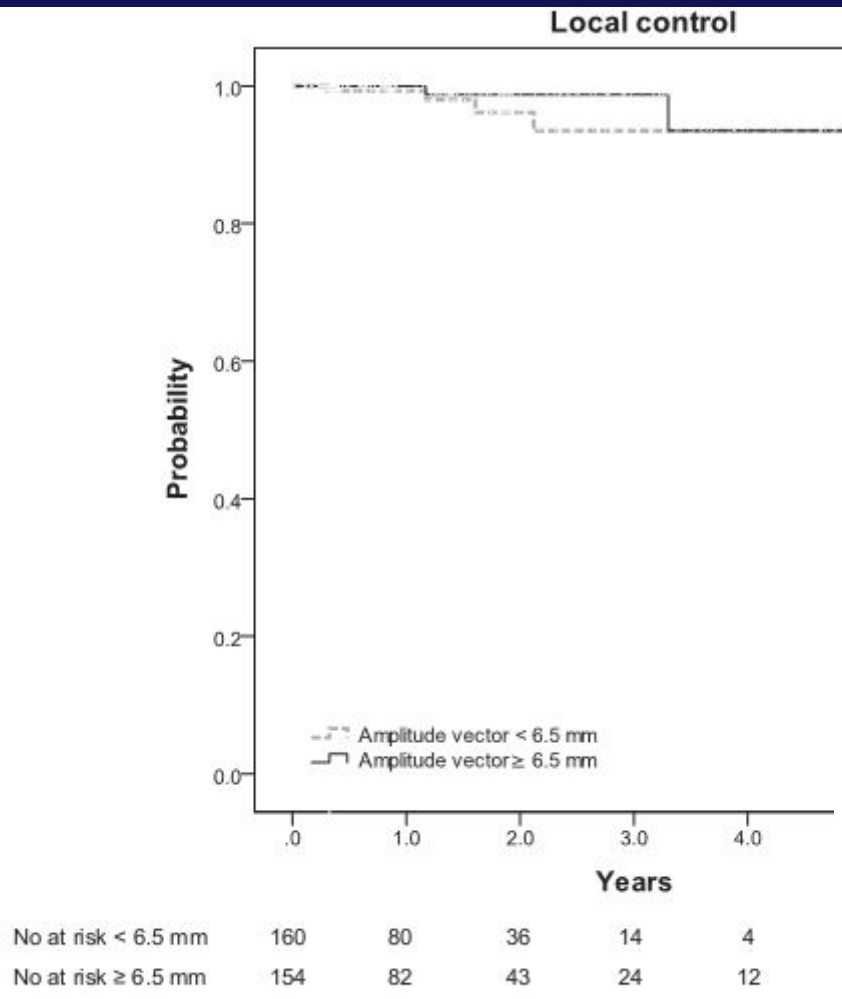


Fig. 3. Local control analyzed per tumor according to respiratory tumor ar

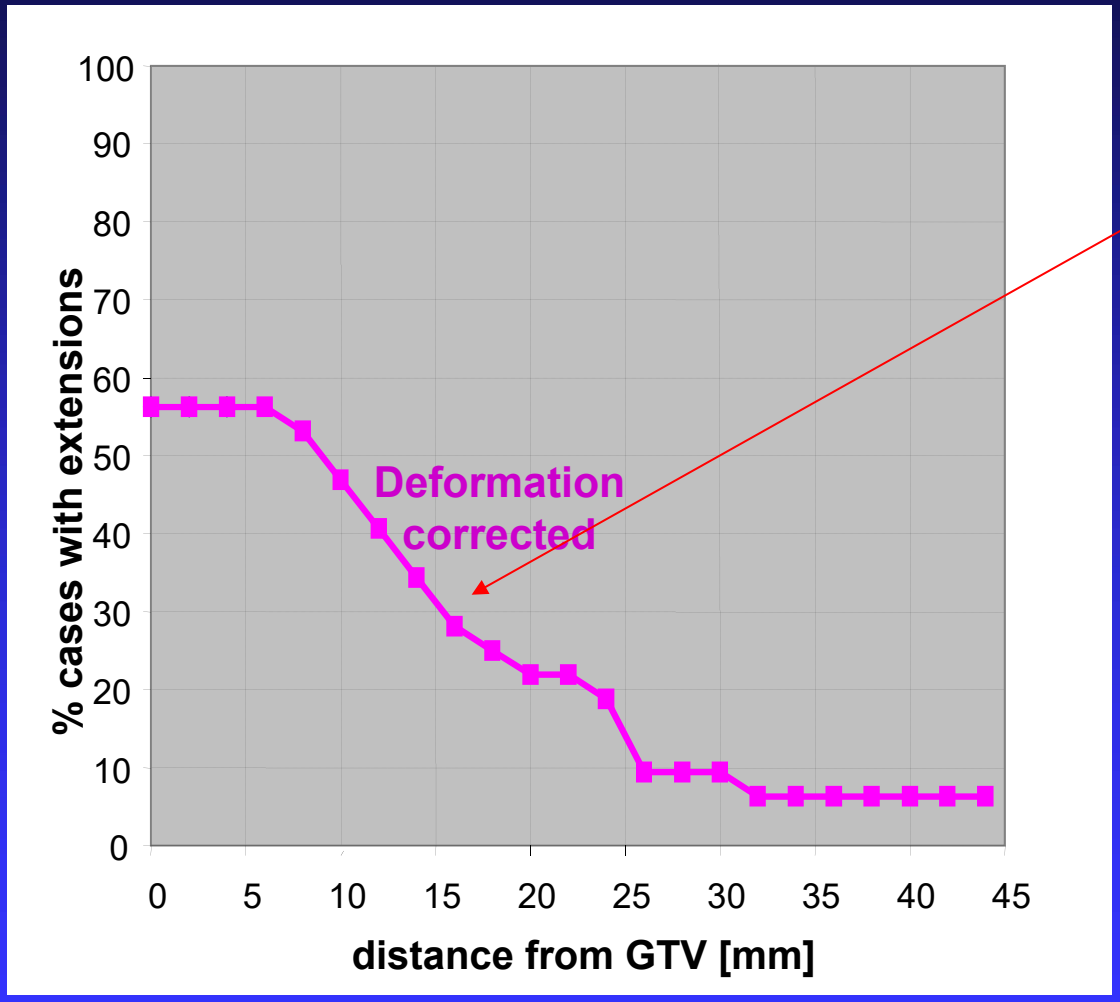
and 3 mm (range 0–18 mm), respectively. The median amplitude vector was 6.5 mm (range 0–39 mm) for all tumors as well as for the locally controlled tumors. In case of local recurrence, the median amplitude vector was significantly *smaller*: 3.0 mm (range 1–8.1 mm) ($p = 0.04$). In patients with a local 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

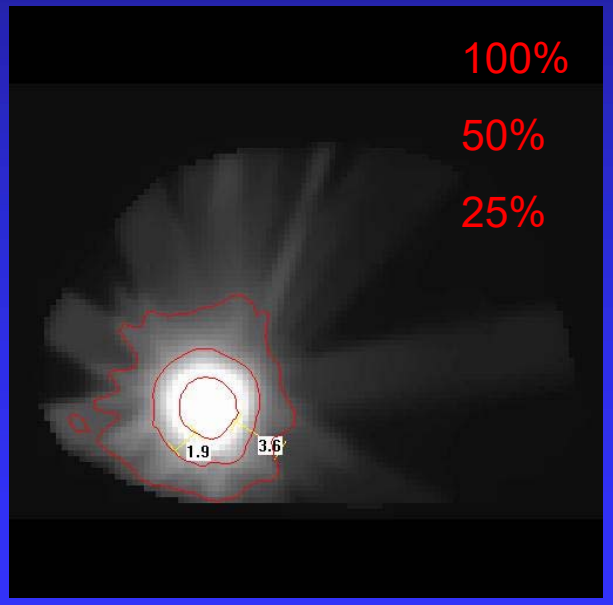
But what about the CTV ?

- 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

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Particle therapy planning

Advanced Treatment Planning Course
3-7 September 2017 – Barcelona, Spain

Markus Stock

MedAustron

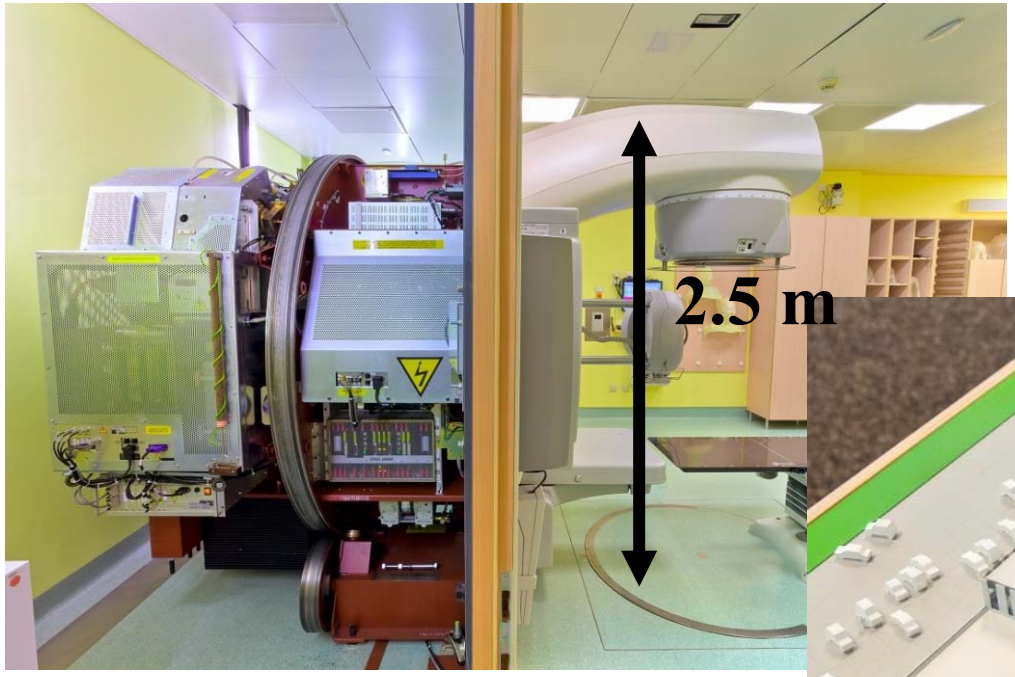
ESTRO School

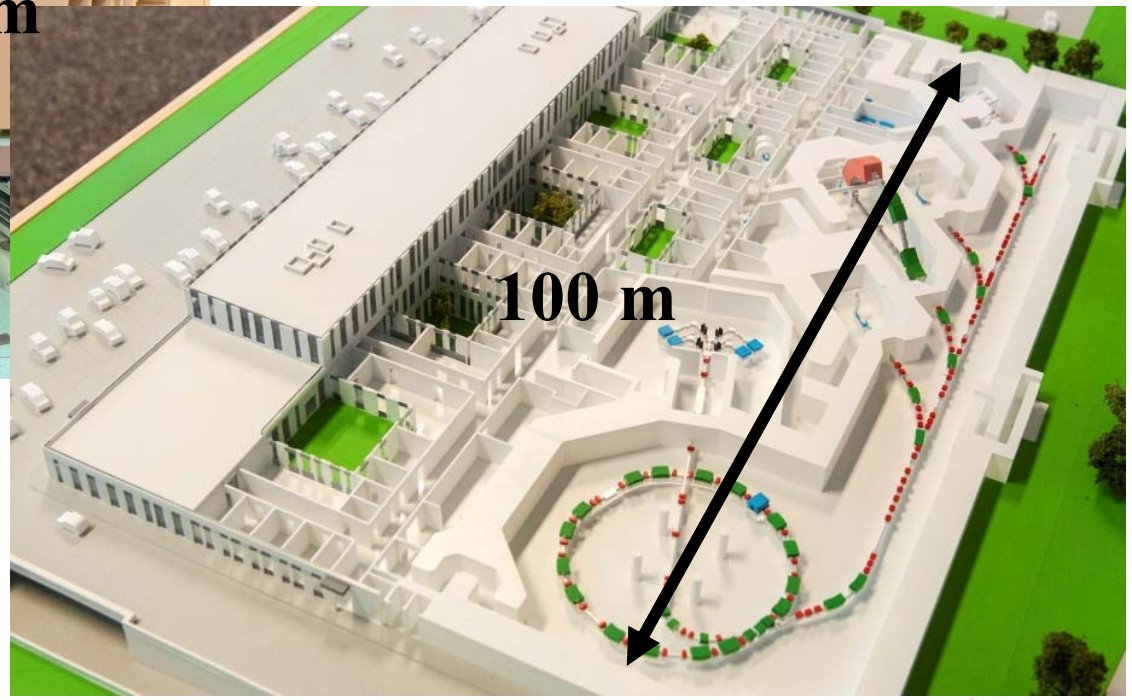
Content

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

Beam Production

Electron Linear Accelerator vs. p, C Synchrotron





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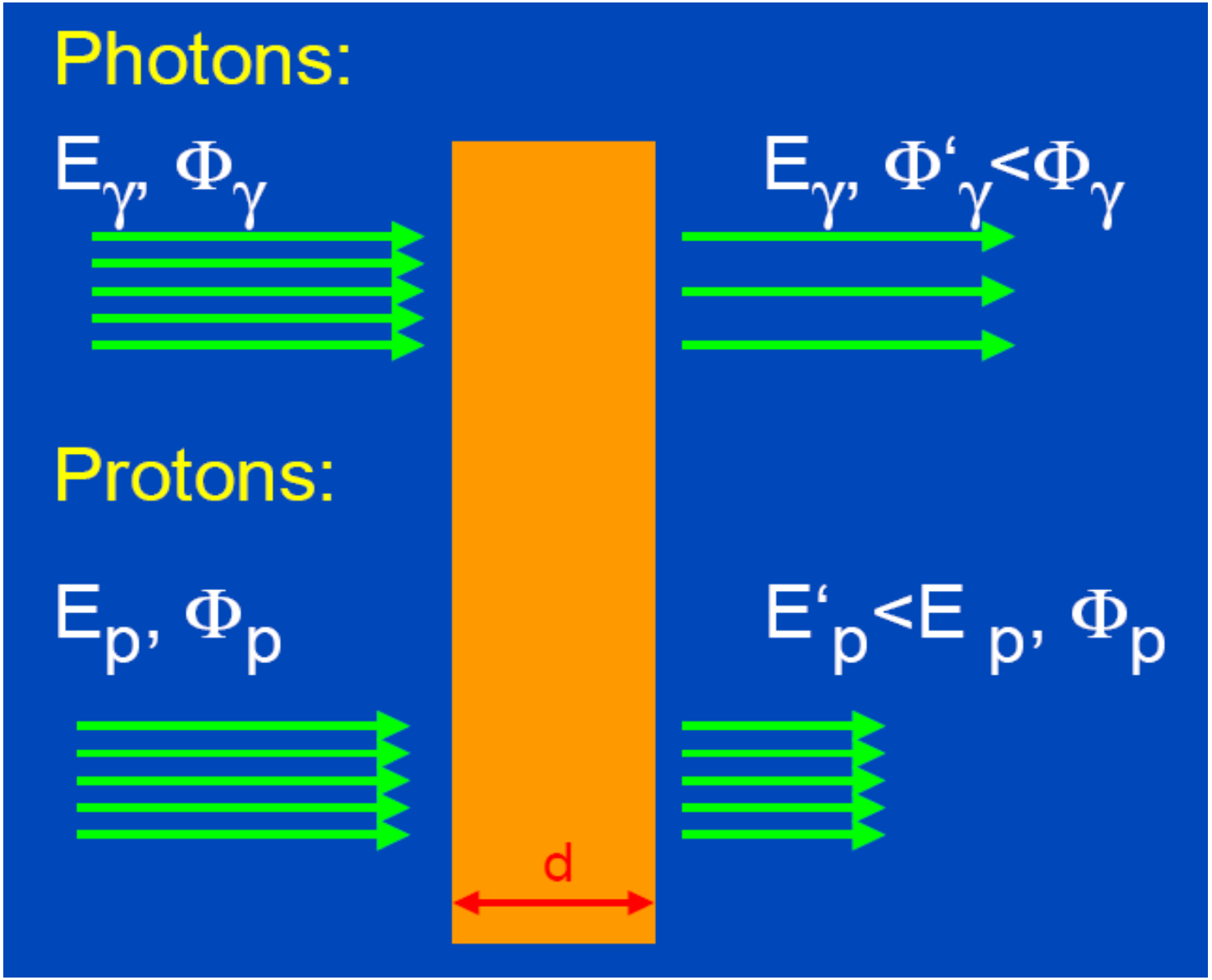
Fundamental Difference in Penetration



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Energy lost = Dose deposition

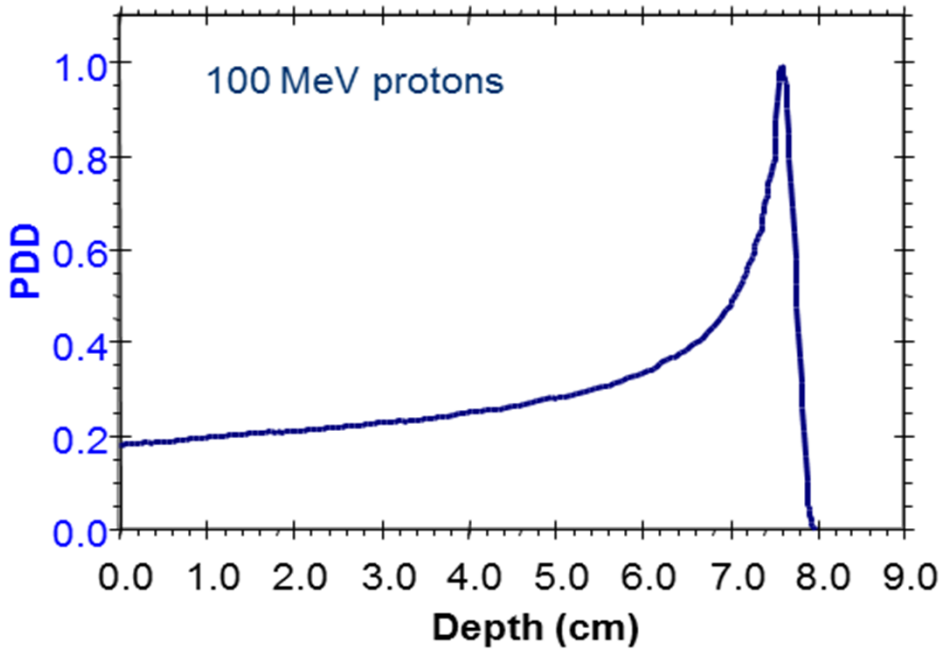
H. Bethe: Annalen der Physik. 397, Nr. 3, 1930

- 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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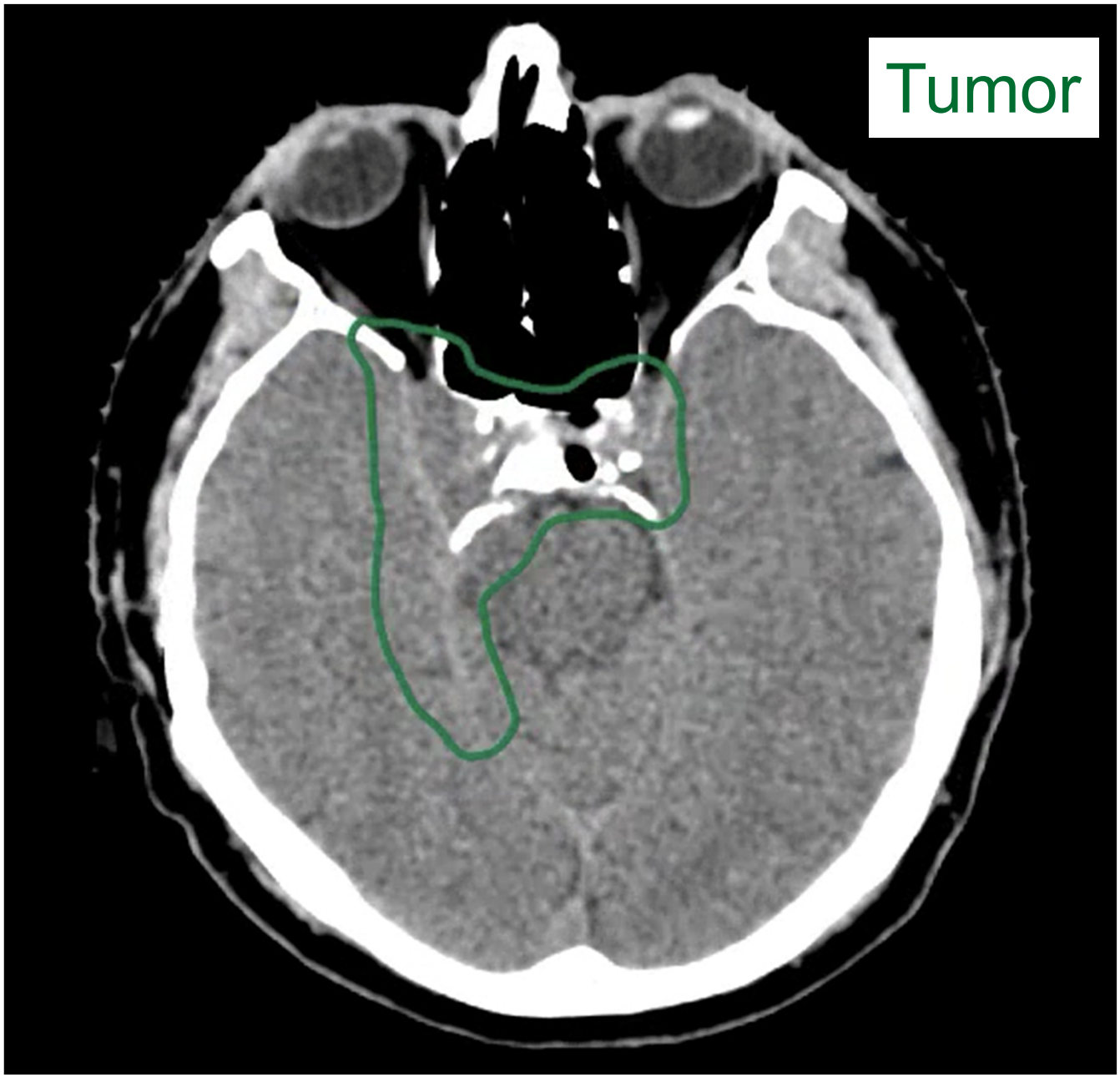
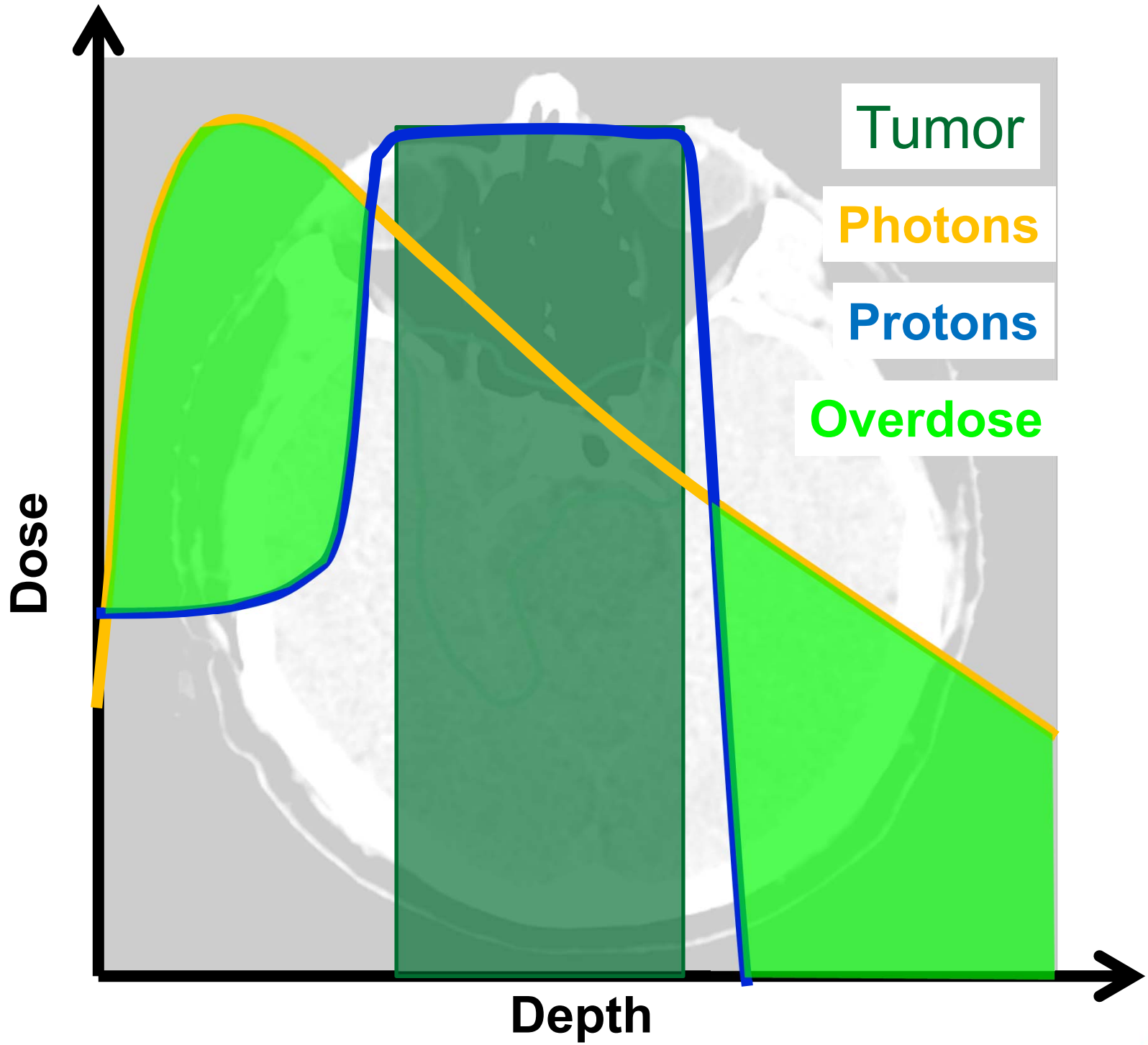
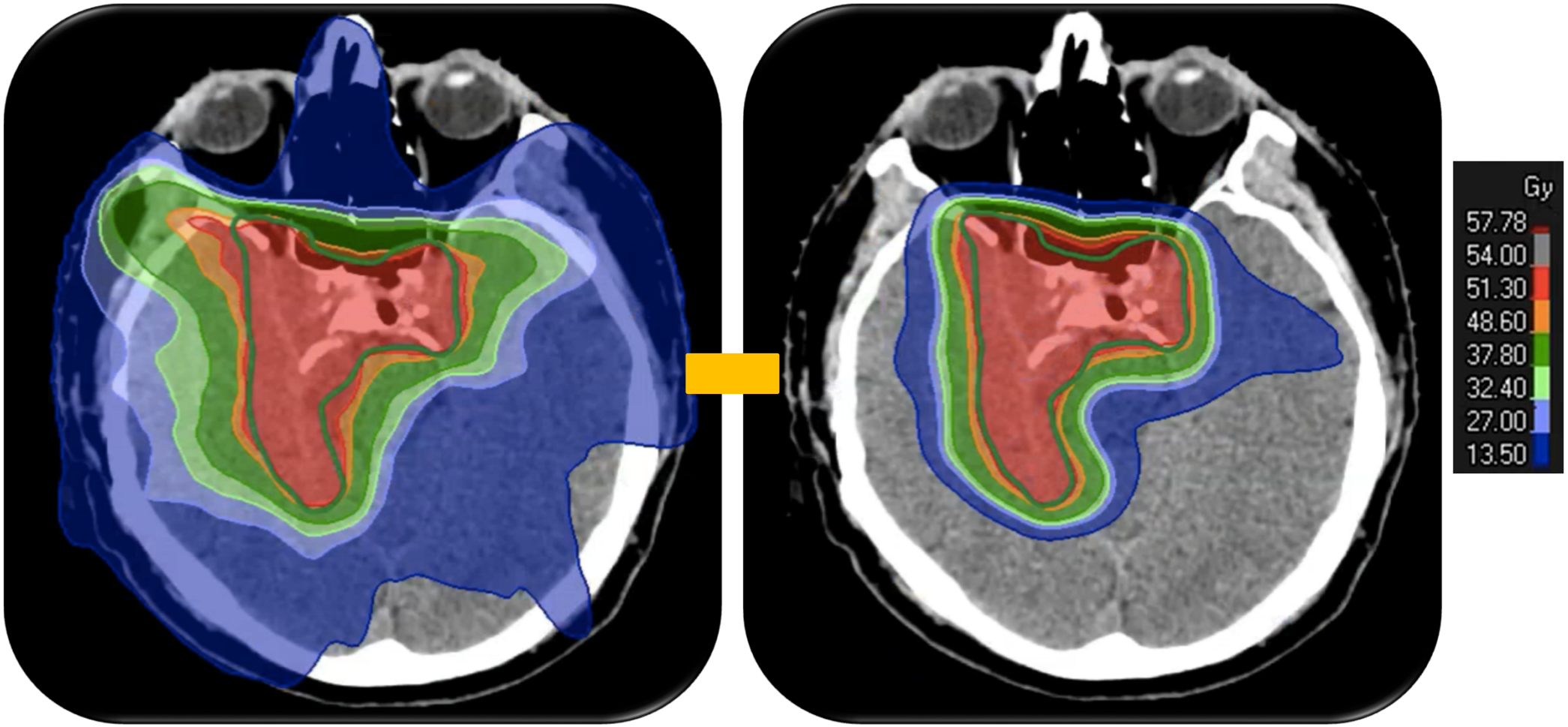

Tumor


Tumor
Photons
Protons
Overdose
Dose
Depth

Photons vs protons



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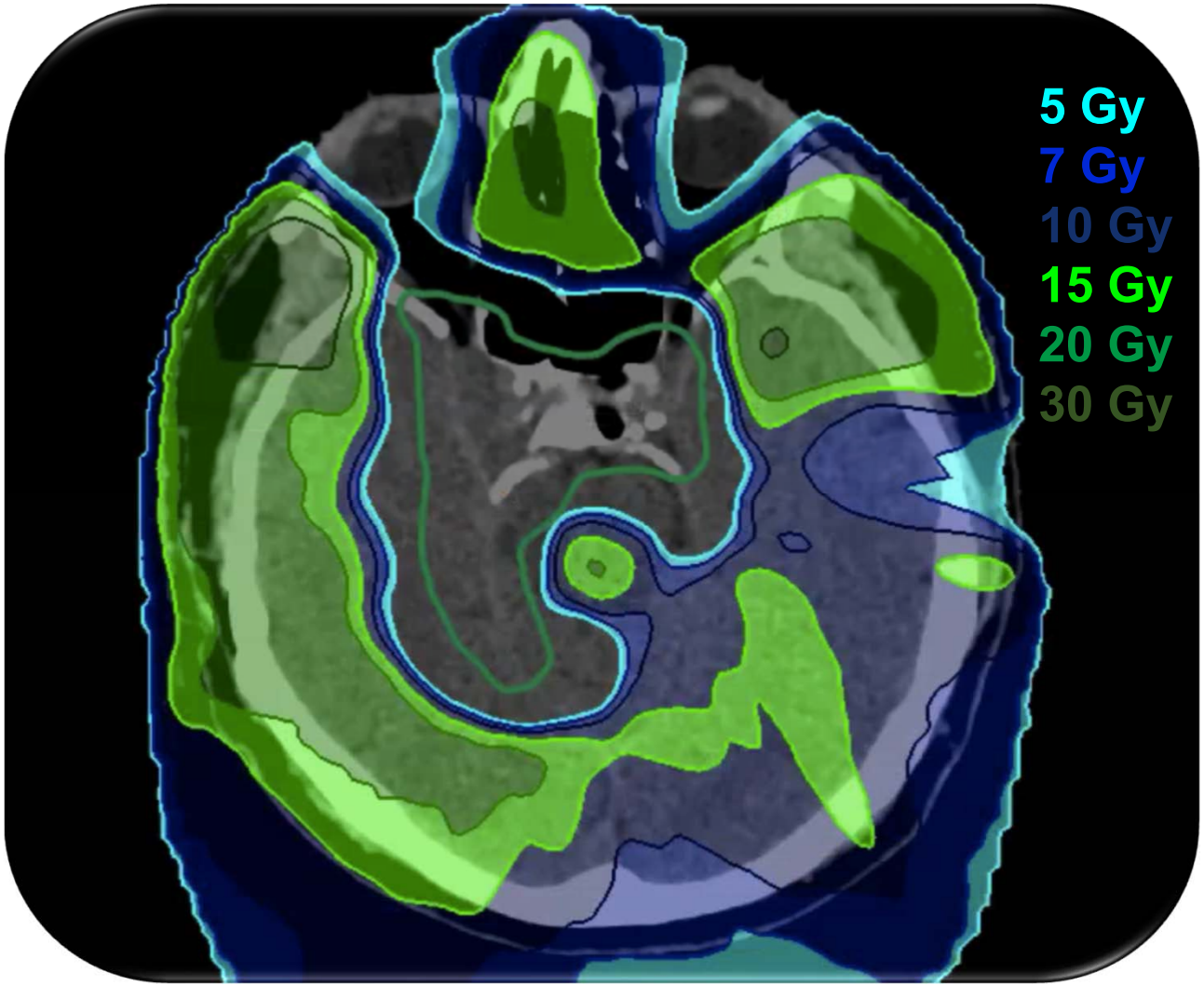
Difference (unwanted dose)



Photons - Protons

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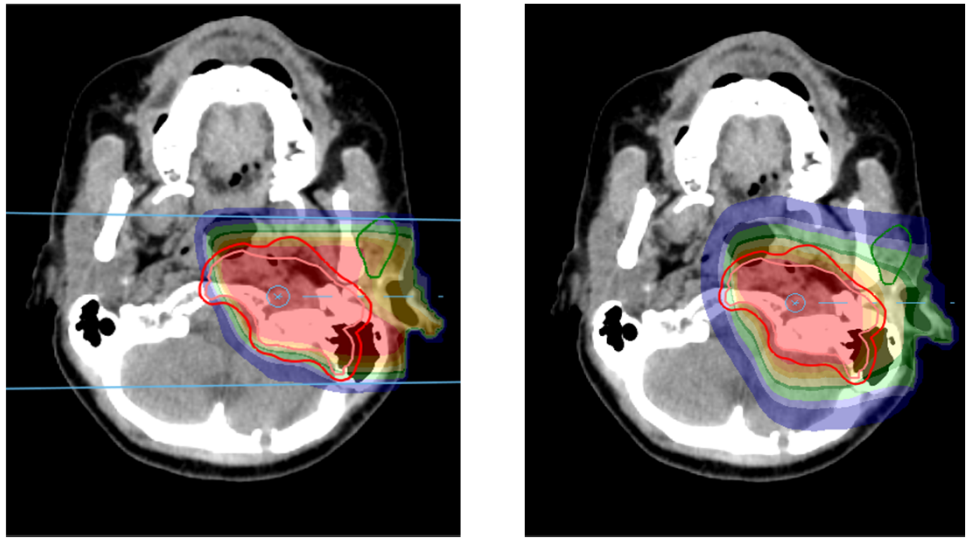
Passive vs. active particle beam delivery

- 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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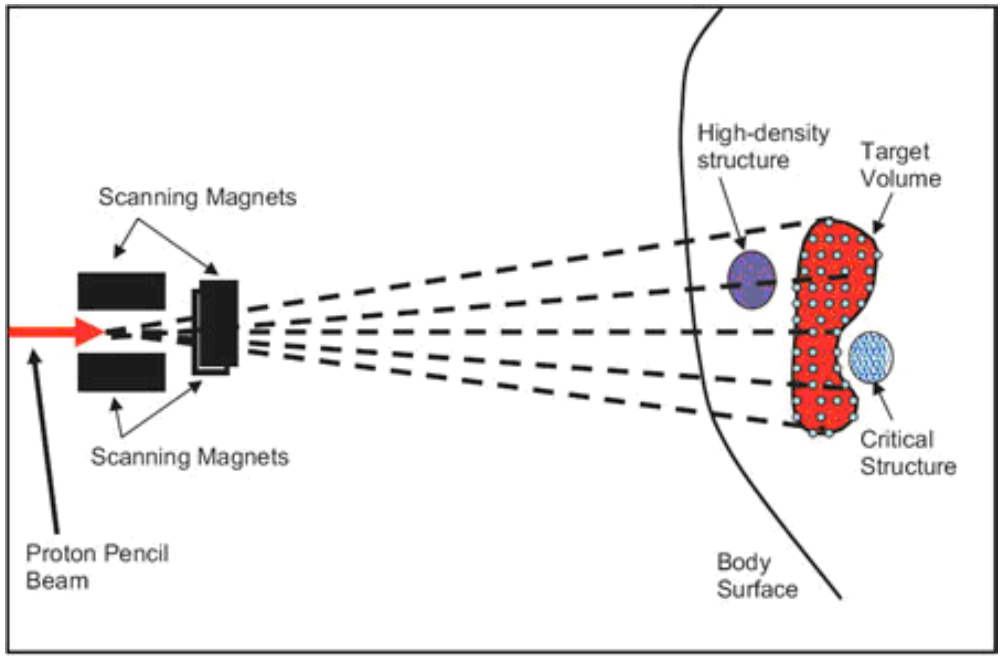
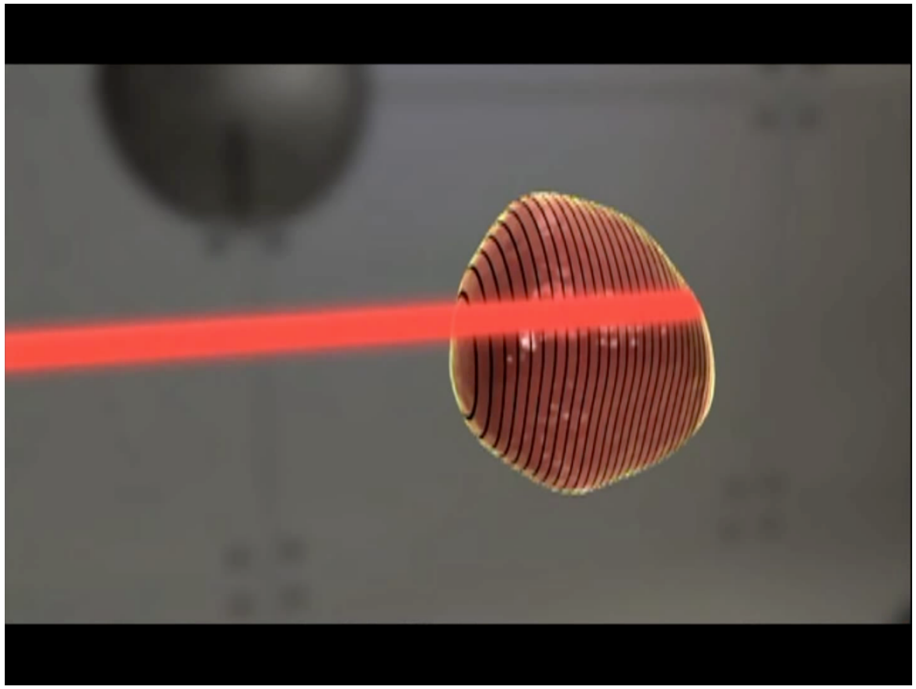
Pencil beam scanning



Courtesy MD Anderson



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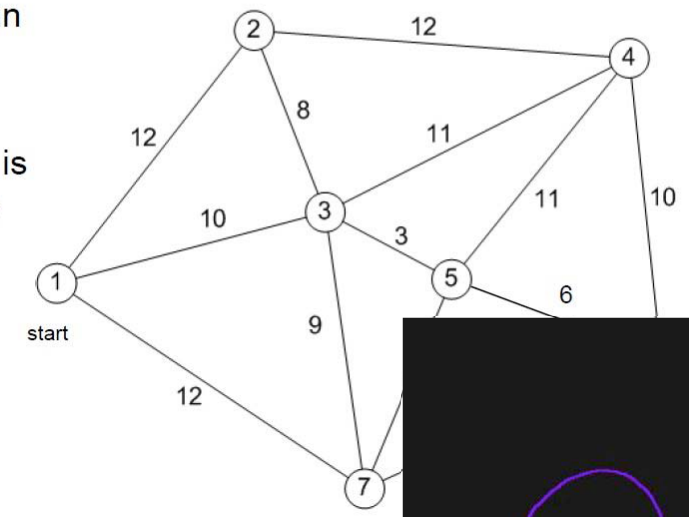
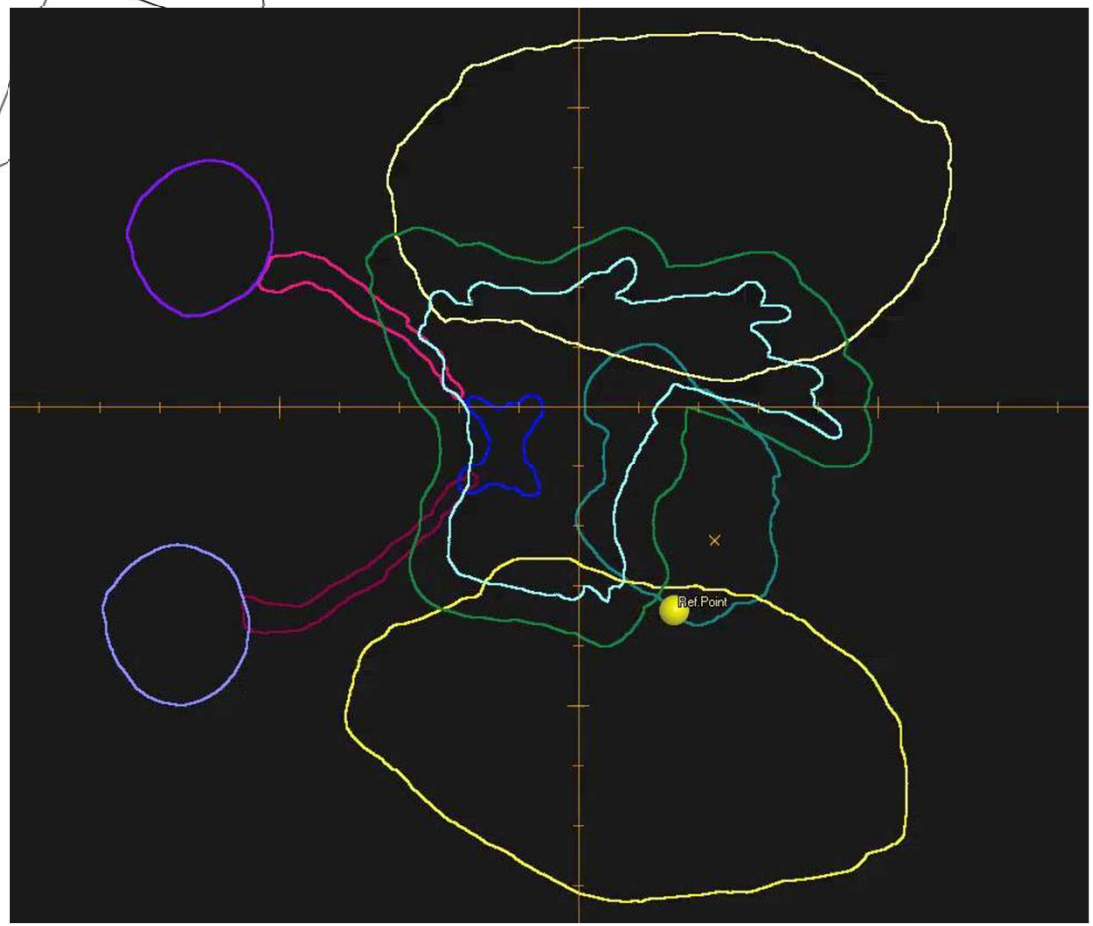
The Traveling Salesman Problem

- Starting from city 1, the salesman must travel to all cities once before returning home
- The distance between each city is given, and is assumed to be the same in both directions
- Only the links shown are to be used
- Objective - Minimize the total distance to be travelled





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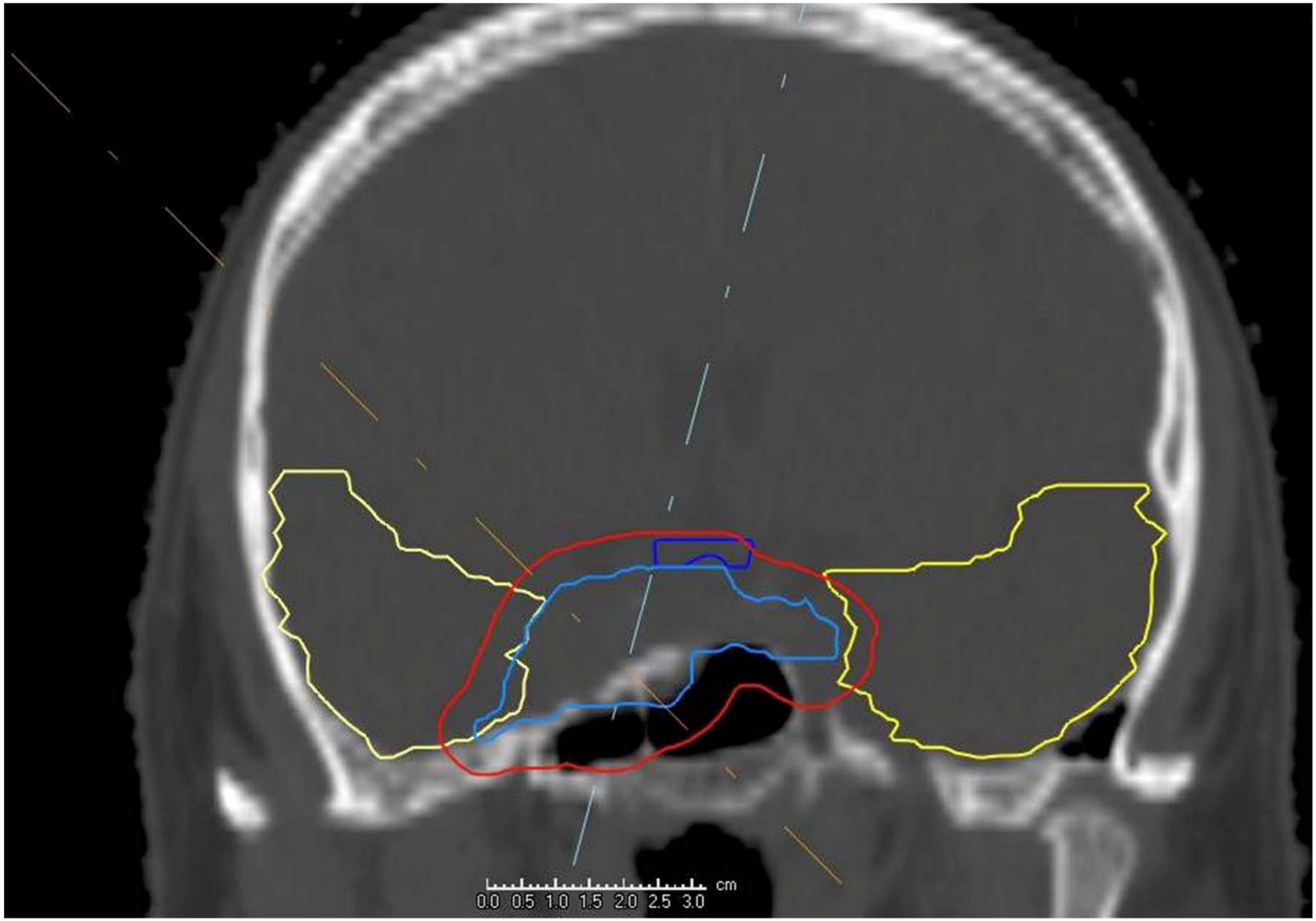
Pencil beam scanning



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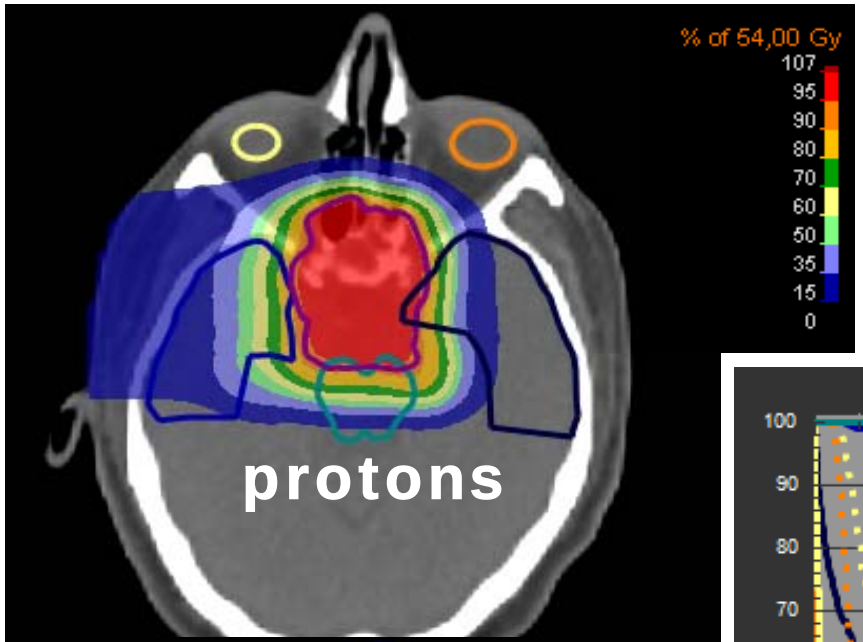
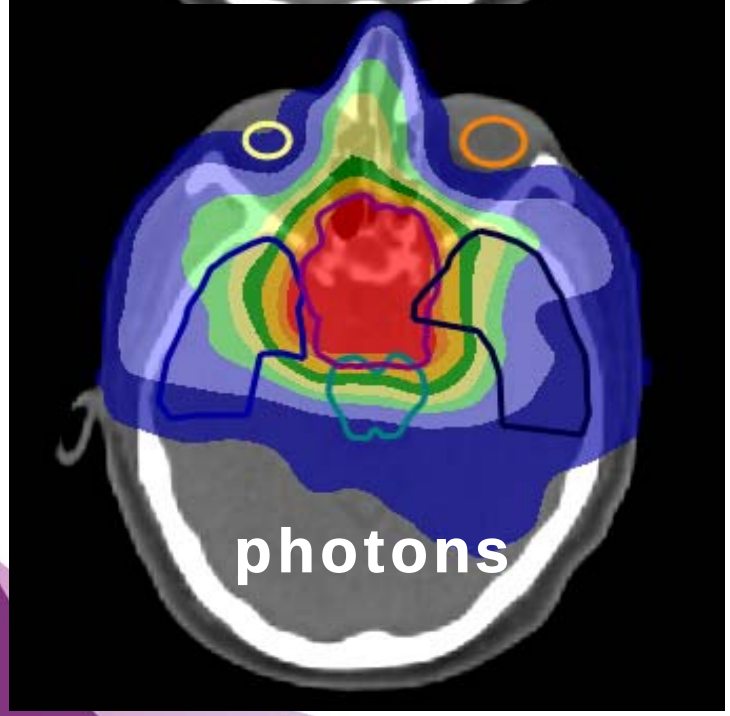
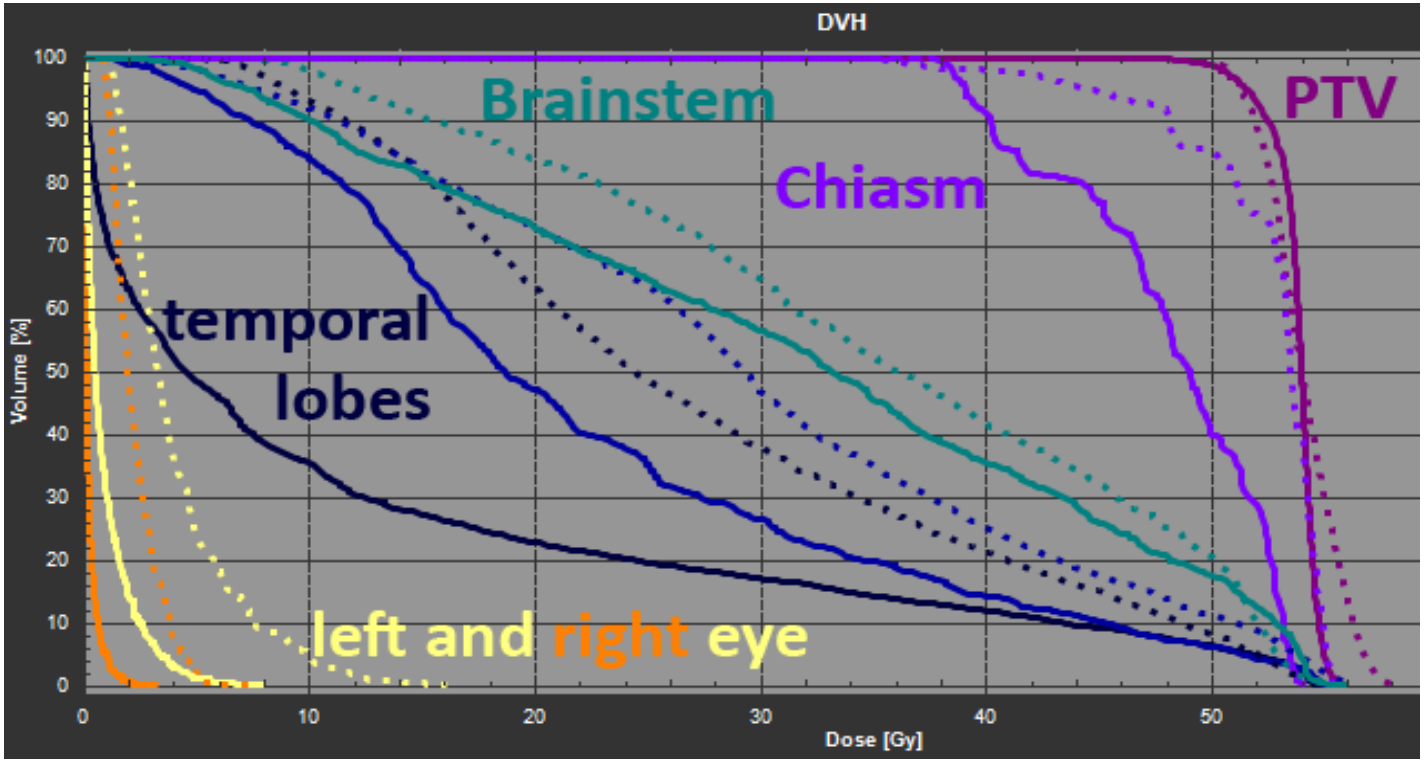
Skull base chordoma





Solid: protons (IMPT)

Dotted: photons (VMAT)



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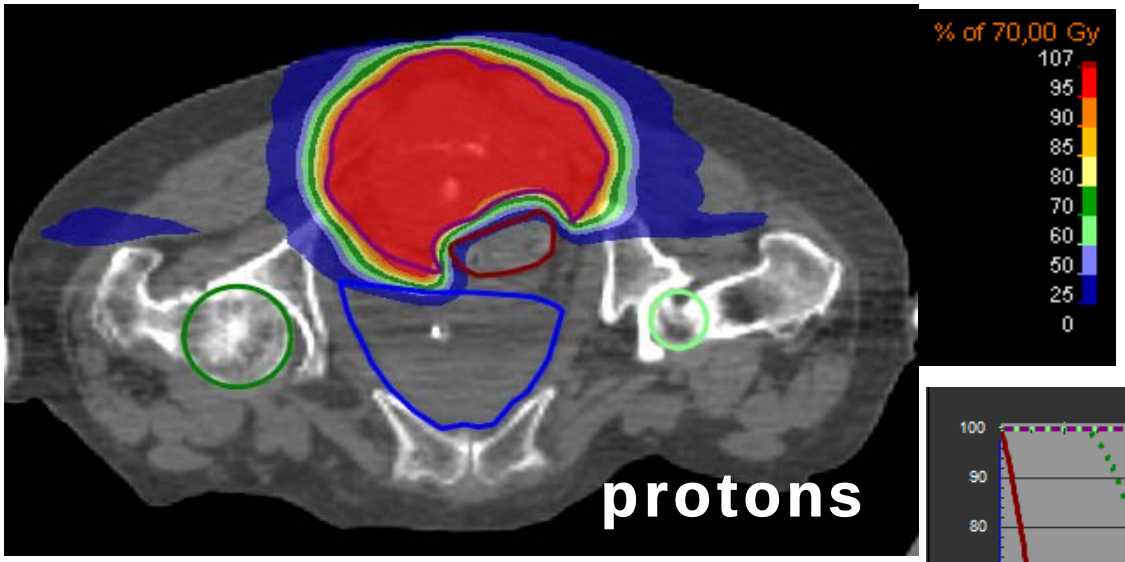
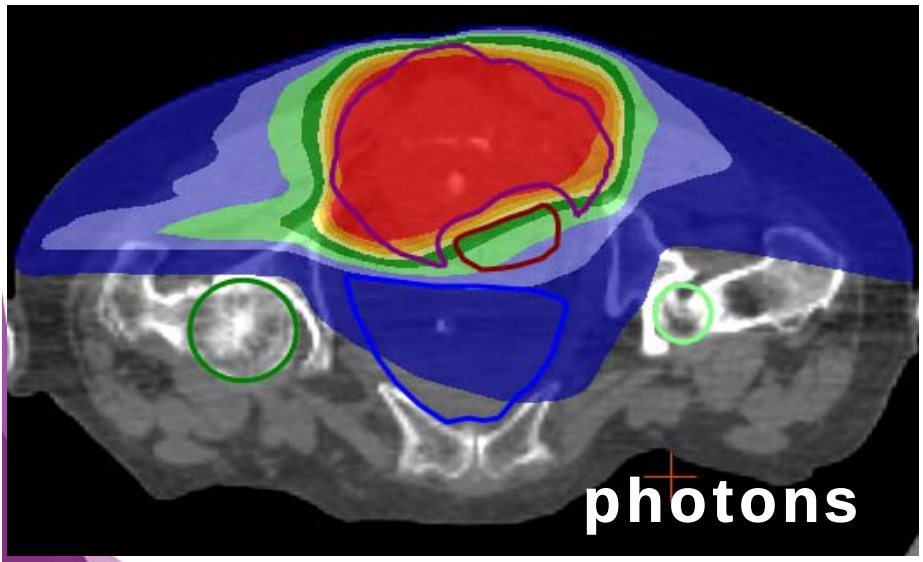
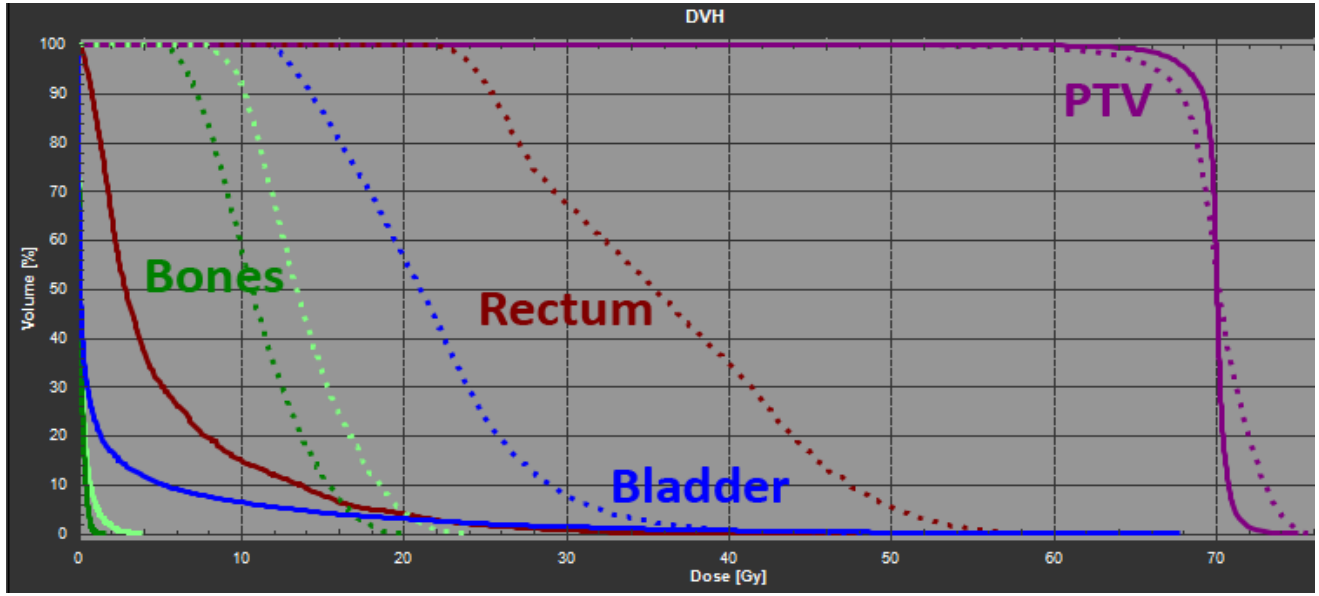
Sacrum chordoma





Solid: protons (IMPT)

Dotted: photons (VMAT)



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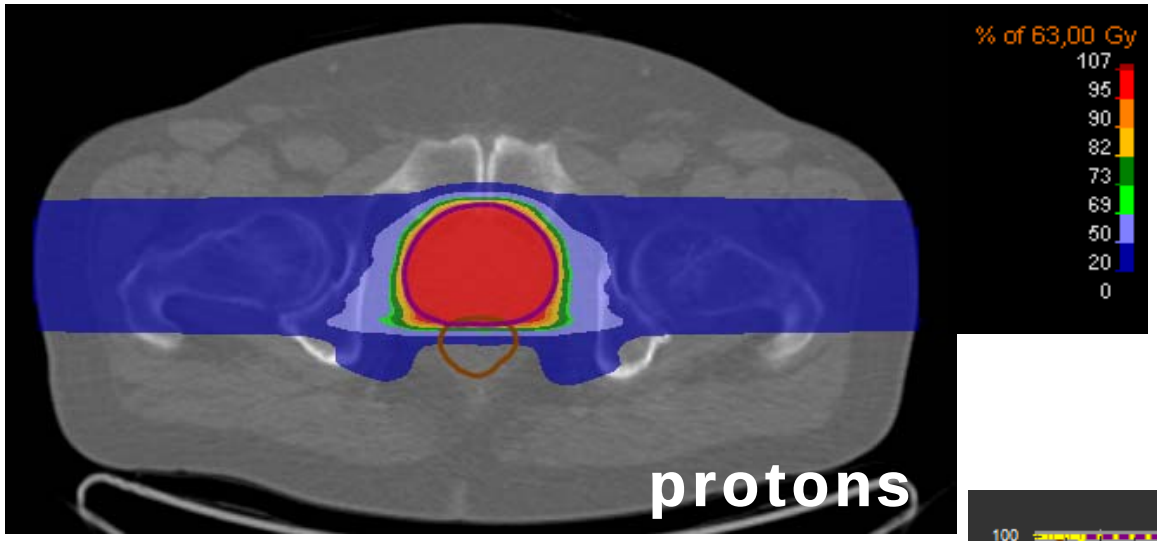
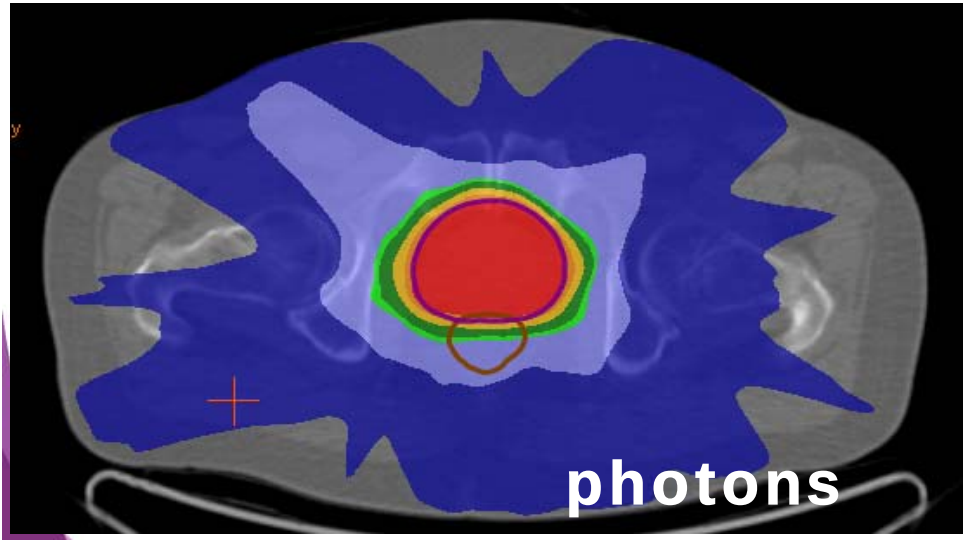
Prostate





Solid: protons (IMPT)

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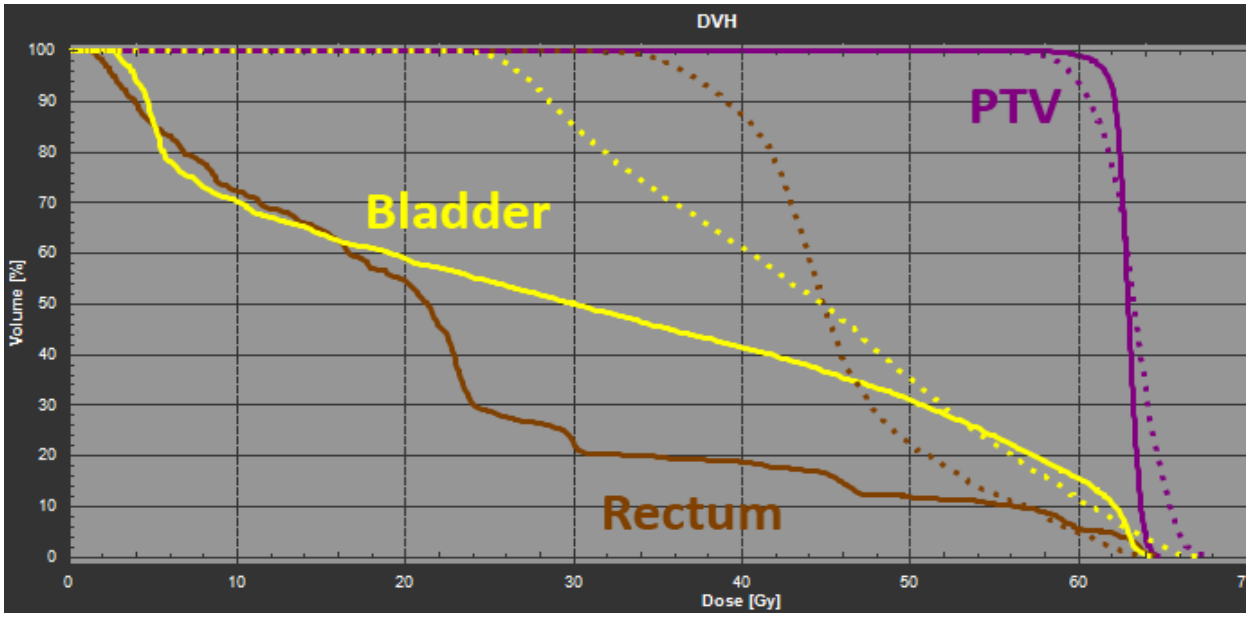

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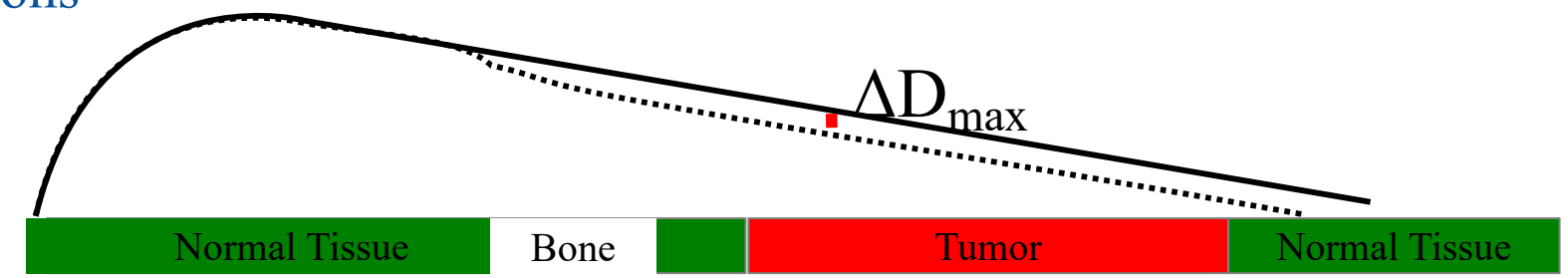
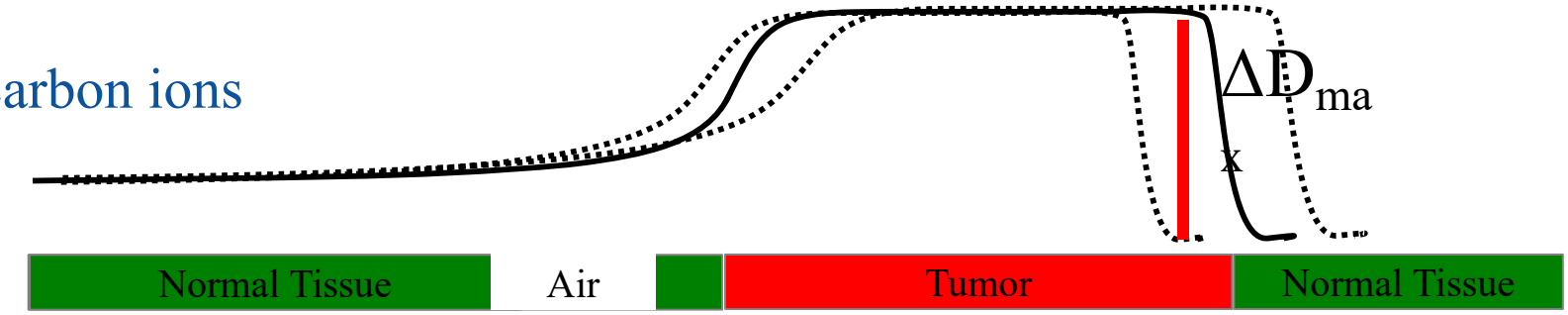
Effect of range uncertainties

MV photons



Protons/carbon ions



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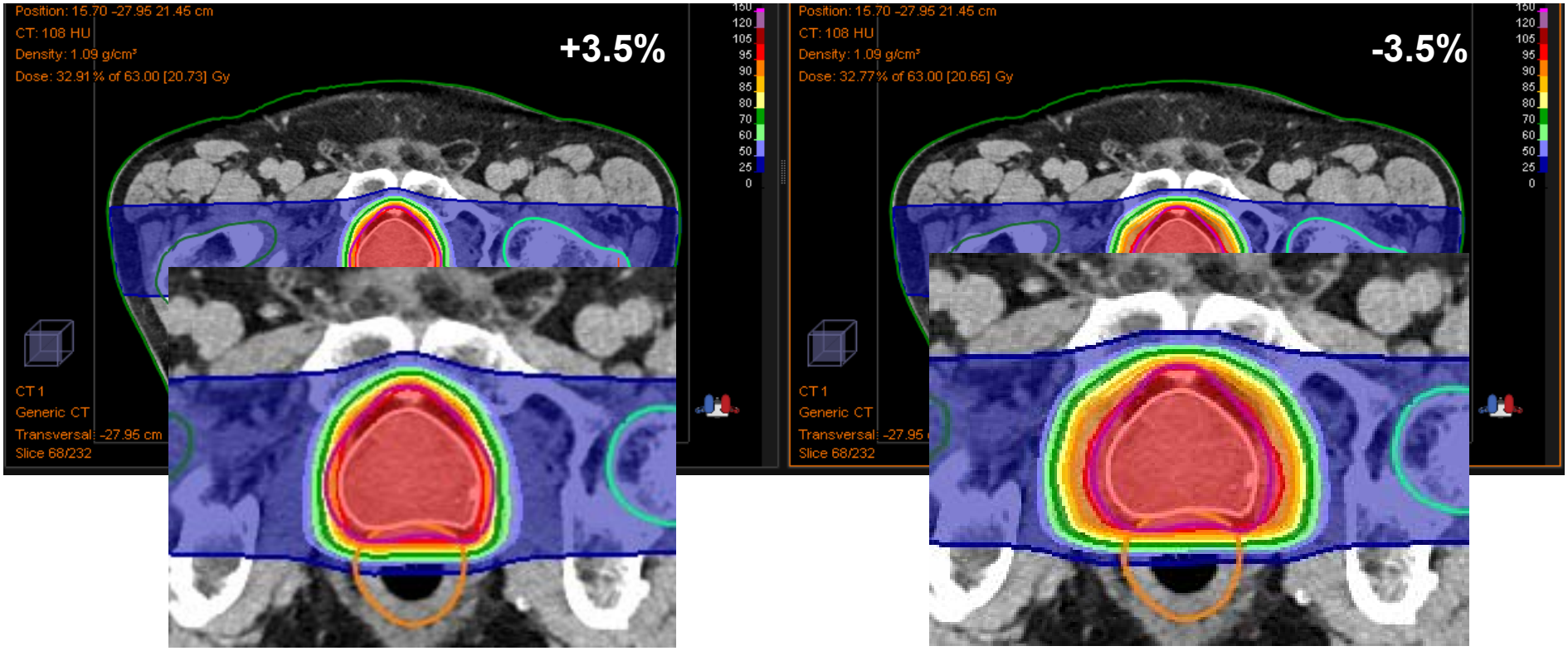
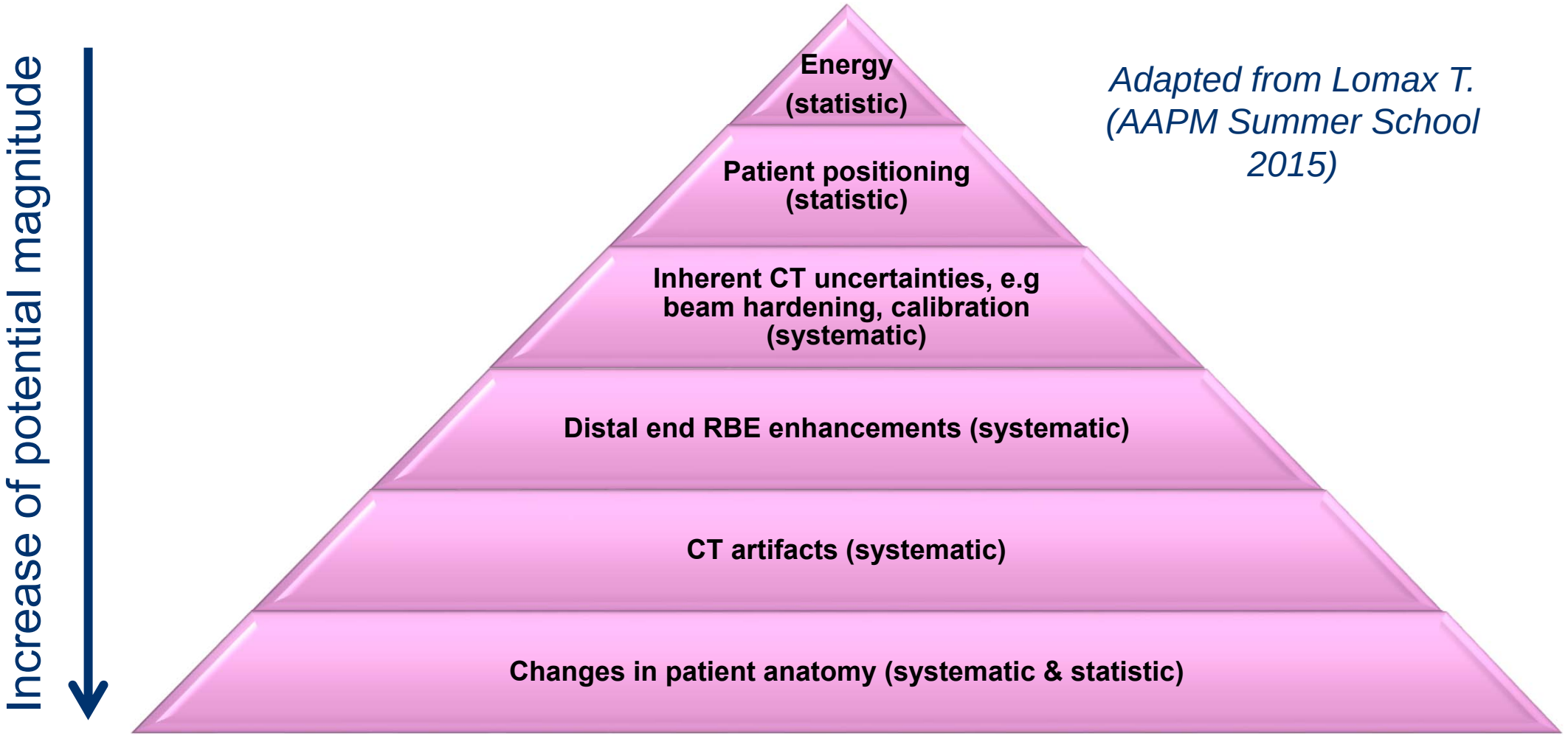
Effect of range uncertainties

Simulation of range uncertainty by HU scaling



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!)

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

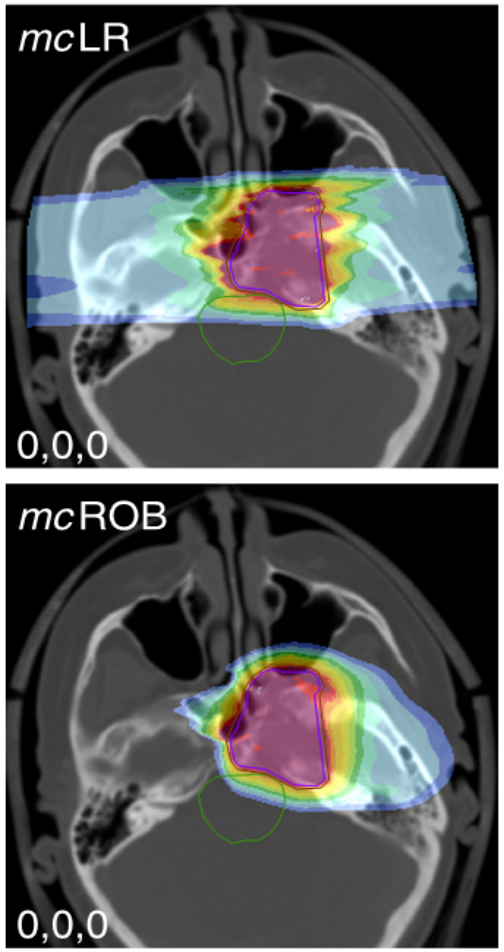
Assessing robustness against set-up errors and patient or organ motion by simulating these variation and their influence on dose distribution

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

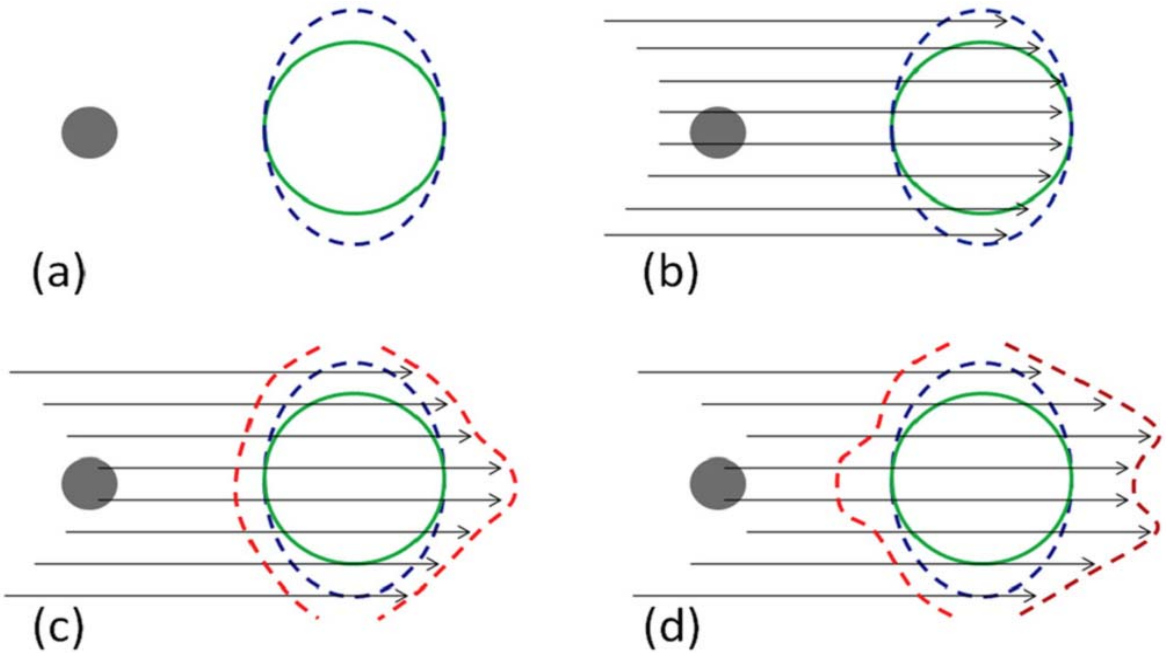
- dose homogeneity: ***choose beam angles avoiding*** large ***density interfaces*** along the beam axis
- range uncertainty: ***avoid*** placing ***Bragg peaks proximal to*** critical ***OARs***
  - beam incidence parallel to OARs
  - spot positioning margins/restrictions around OARs



Ammazalorso et al. Radiat Oncol 9 (2014)

Beam specific margins

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

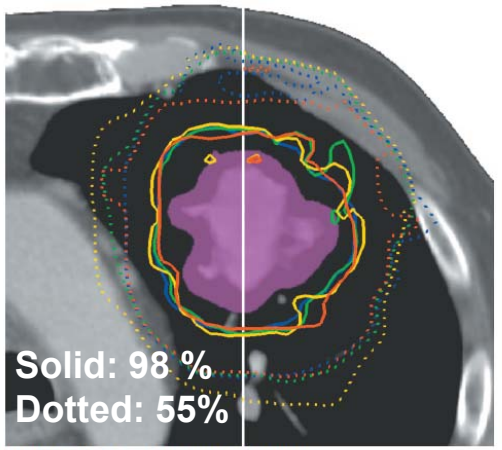


Park et al (2012) IJROBP 82(2):e329-36

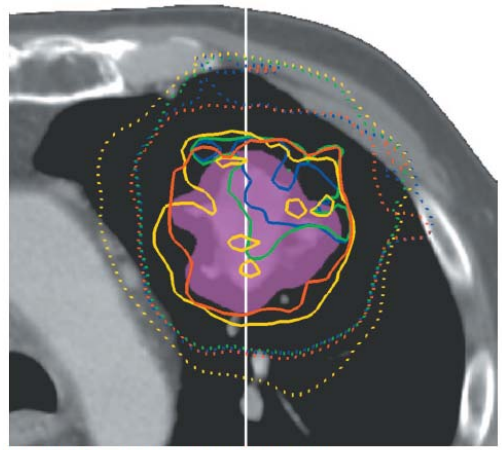
Robust optimisation

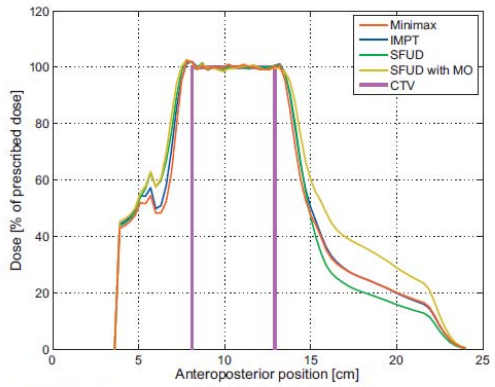
MinMax Optimization

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

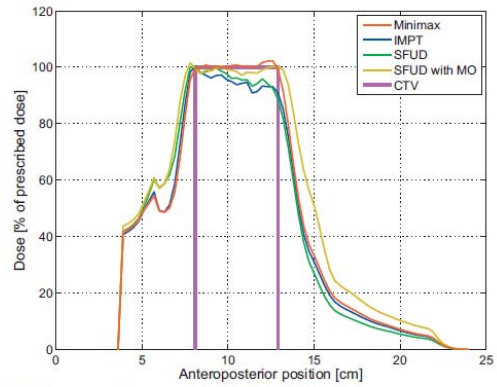


(a) Nominal scenario isodose curves


(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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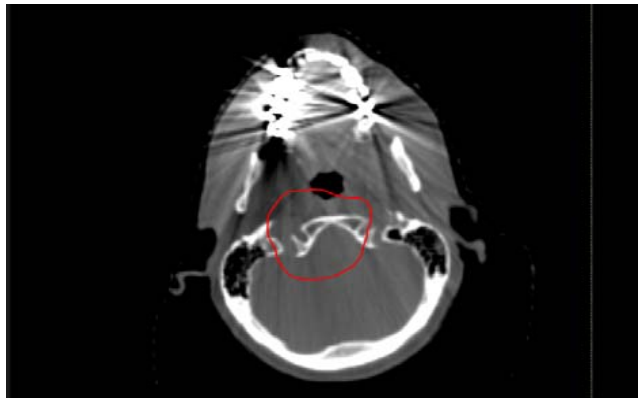
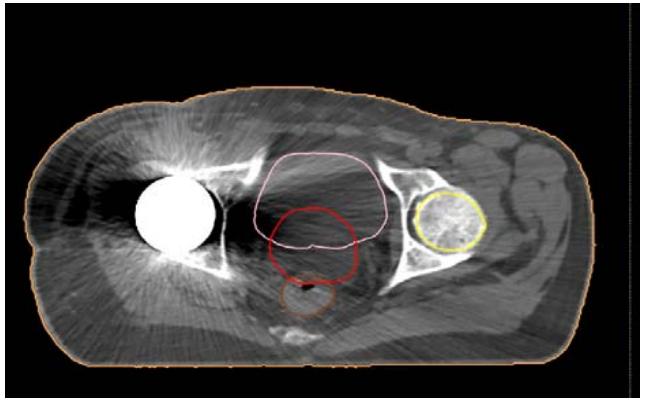
CT artefacts due to metallic implants

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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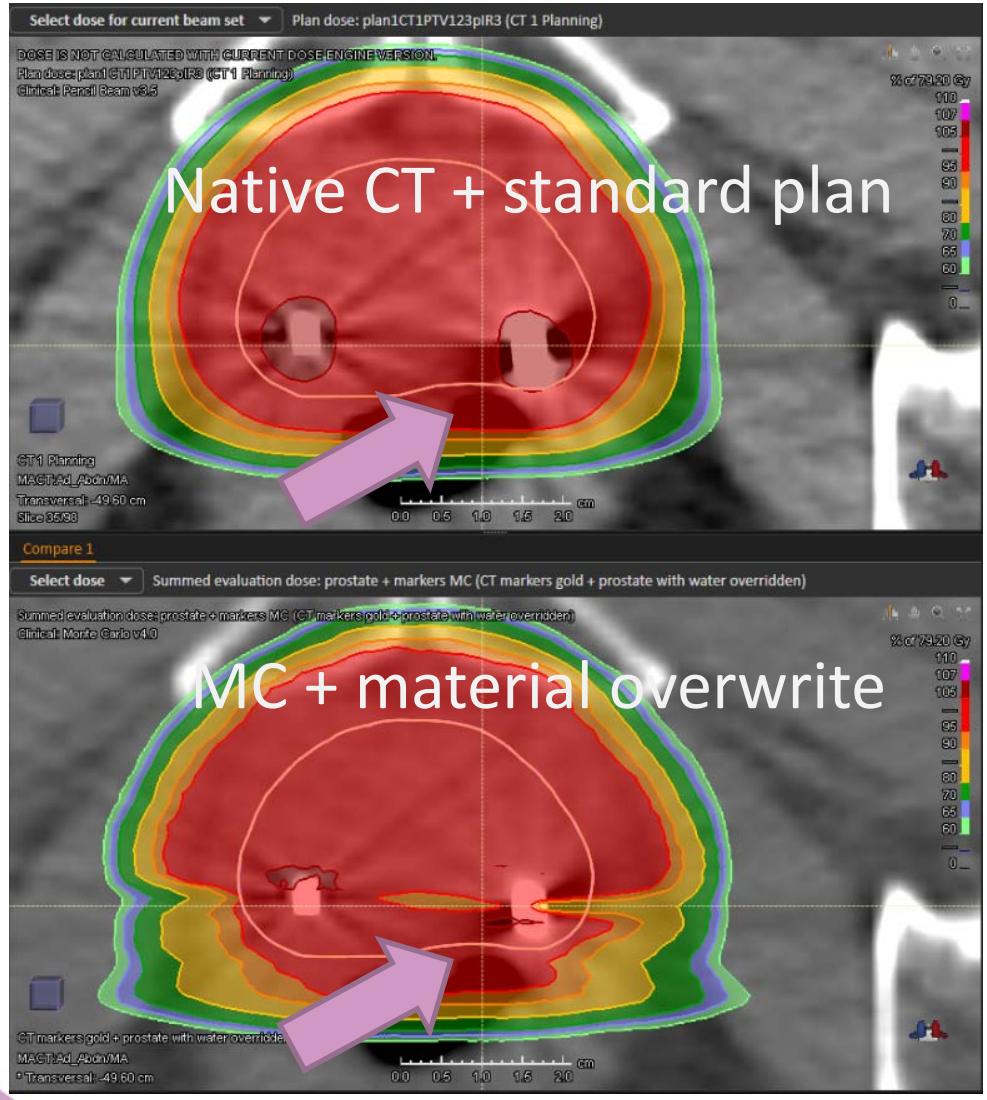
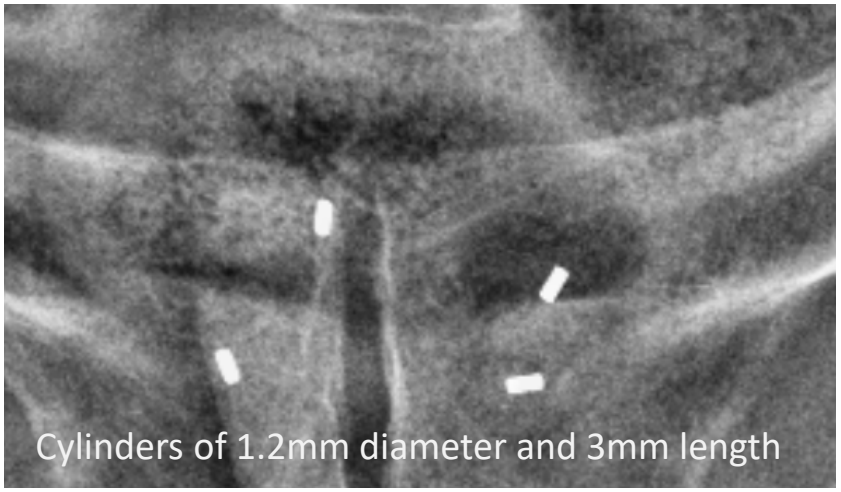
Prostate gold markers





For a standard planning approach evaluated with material overwrite + MC to cause 'dose shadows'

Positioning and orientation of the gold markers quite stable during fx-delivery, but a little smearing due to rotations

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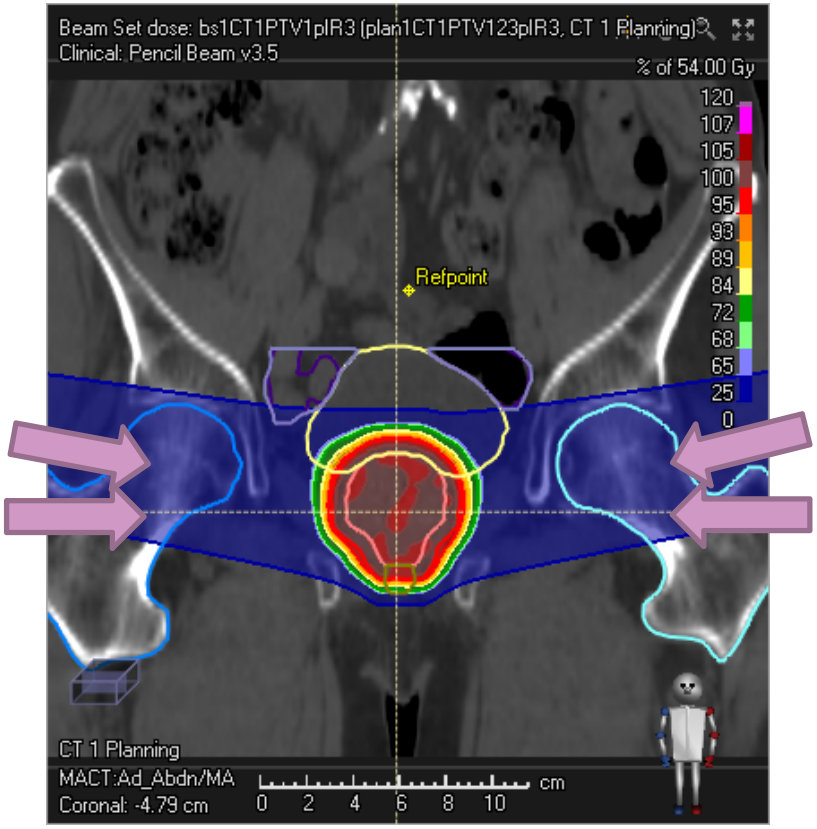
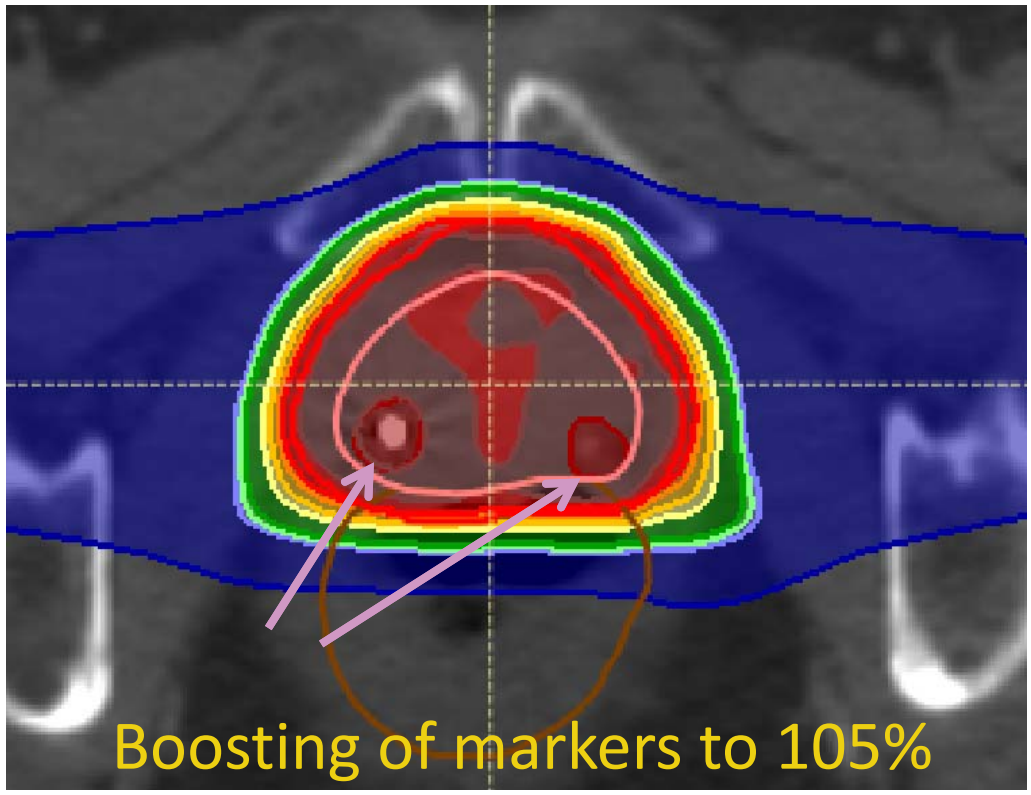
Prostate gold markers





- Using opposite + tilted beams
- Boosting the markers to 105% of prescription

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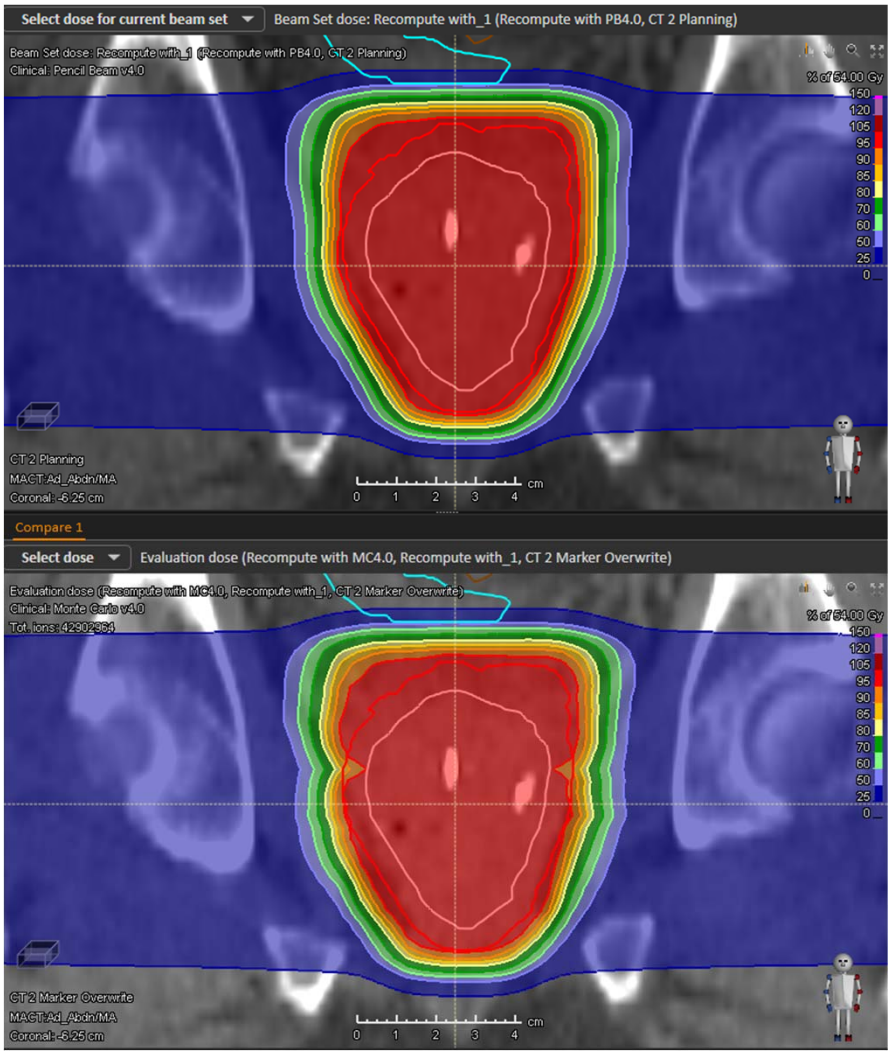
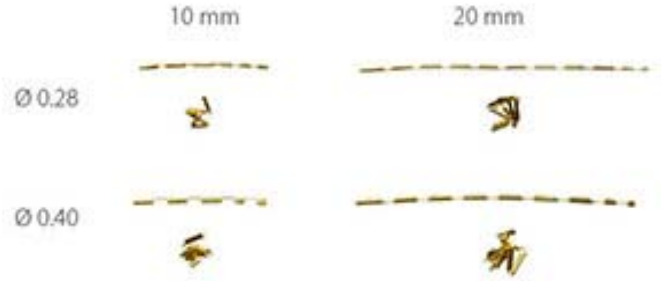
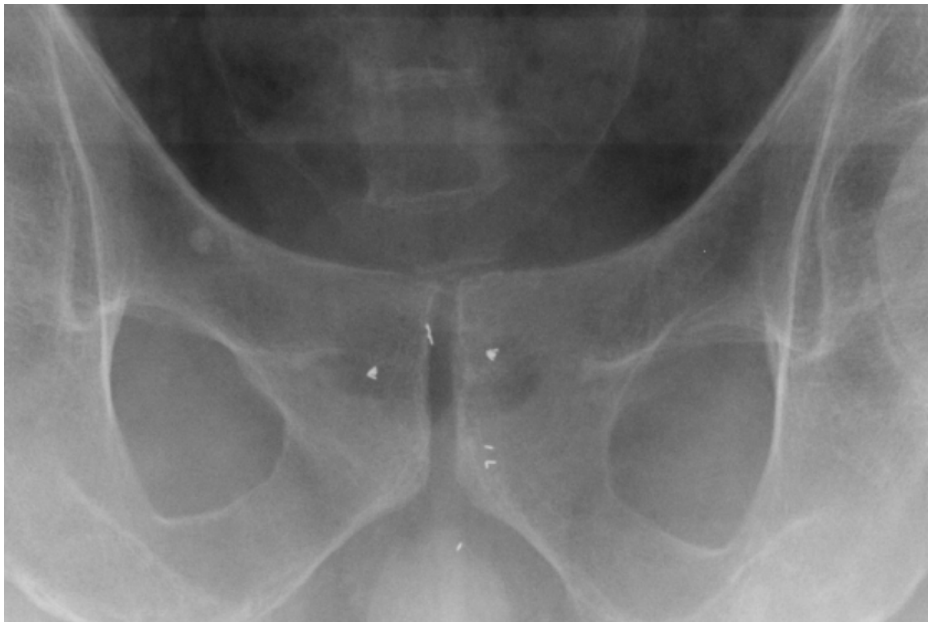
Impact of markers for PT







- Nominal PB plan vs MC recomputation with material overwrite of gold for markers

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SBO (SFUD) and MBO (IMPT)

SBO: Single beam optimization

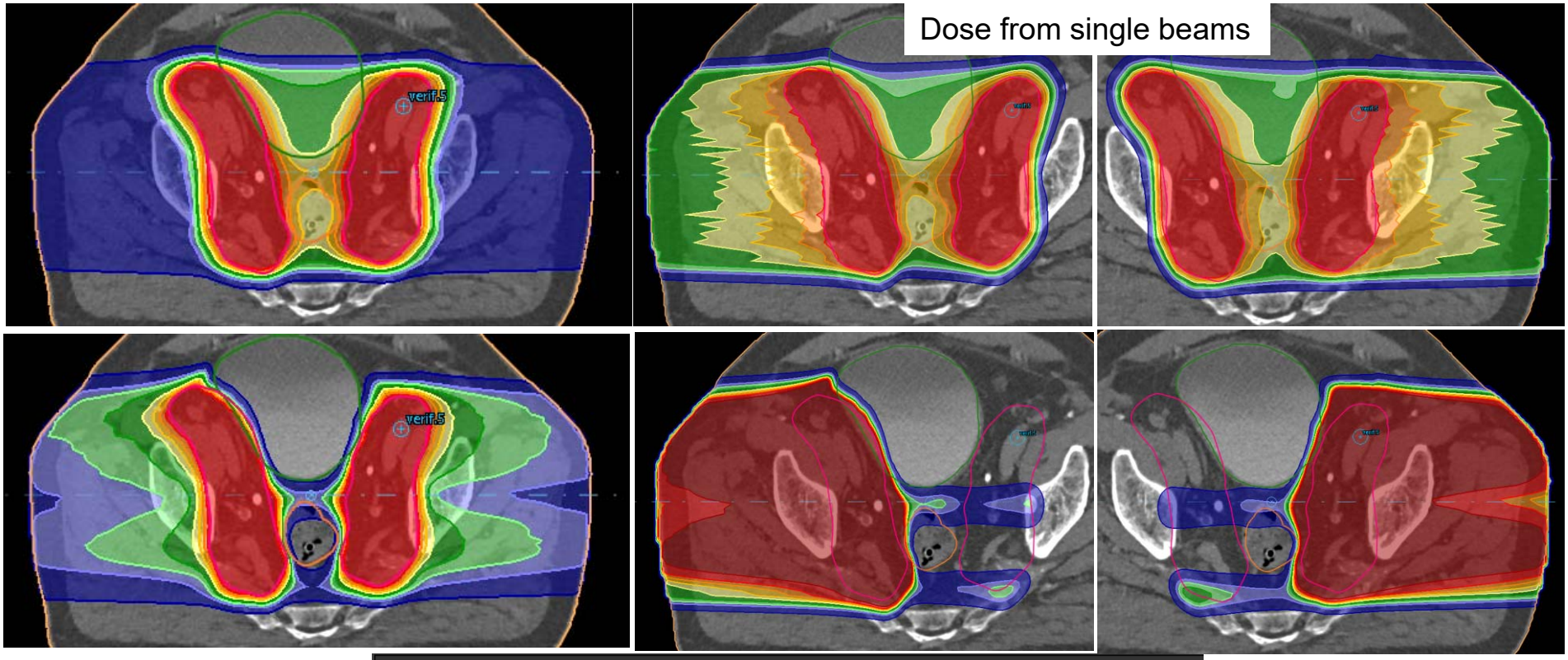
- Possible with passive scattering and active scanning technology
- Spots are weighted in order to achieve a homogenous target dose for every single beam
- OAR sparing only possible by using help structures
- More robust treatment plans

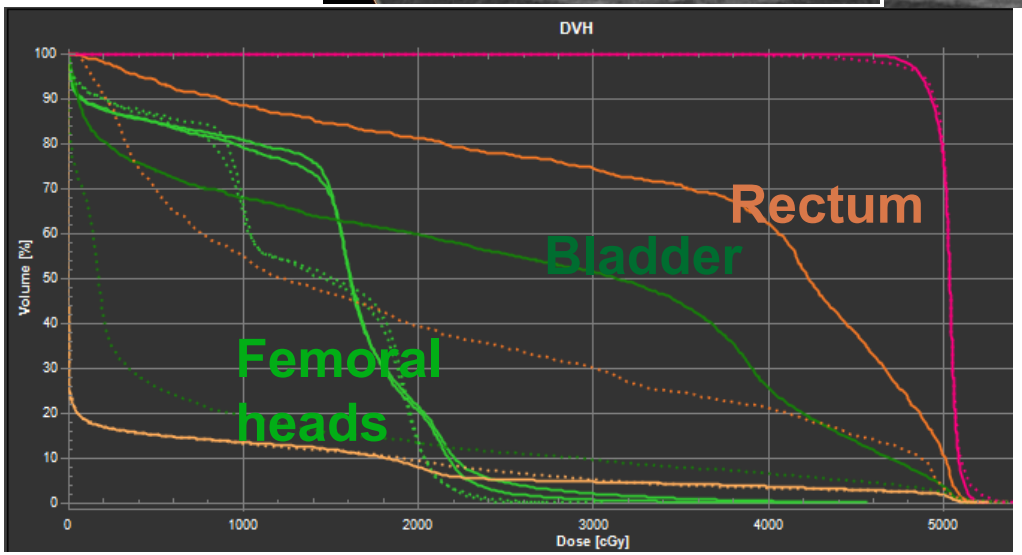
MBO: Multi Beam Optimization

- 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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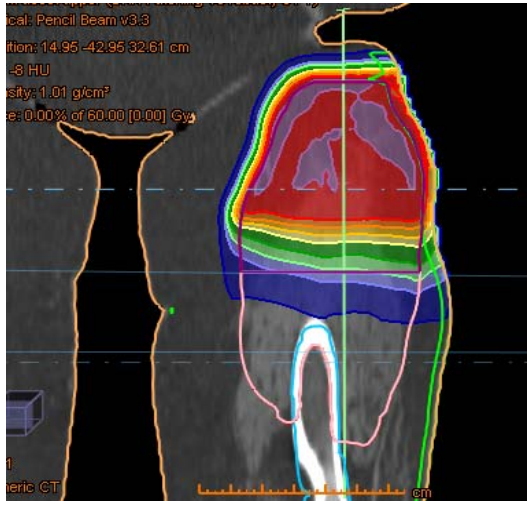
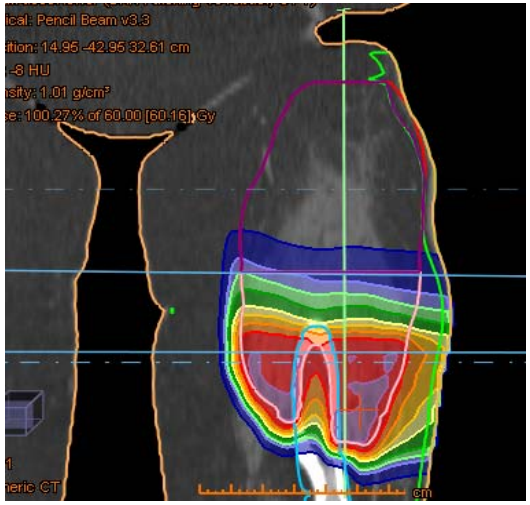
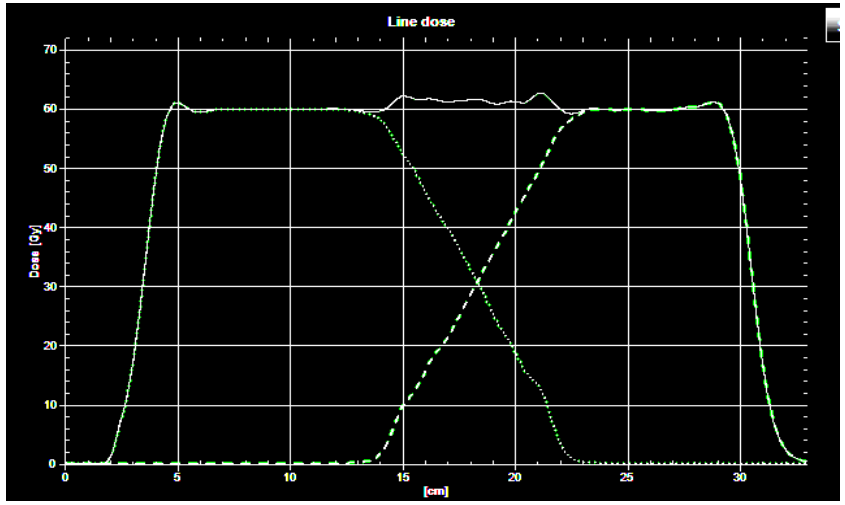
Field matching

- robust optimization for independent beams

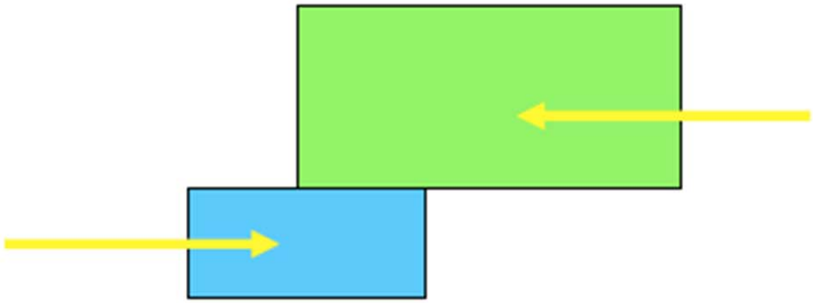






Particle planning basics

Abbuting fields

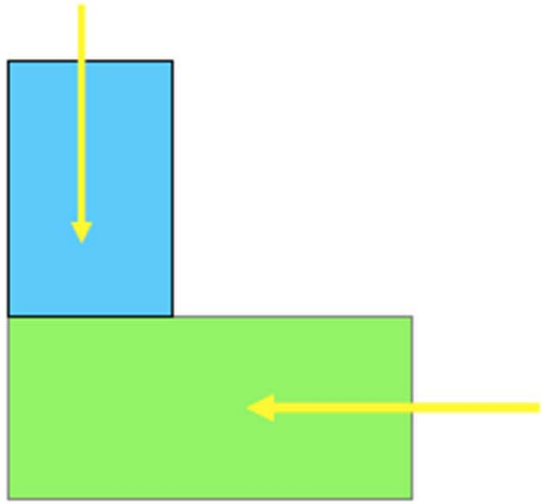


Lateral penumbra

+

Lateral penumbra

Patch fields



Distal penumbra

+

Lateral/distal penumbra

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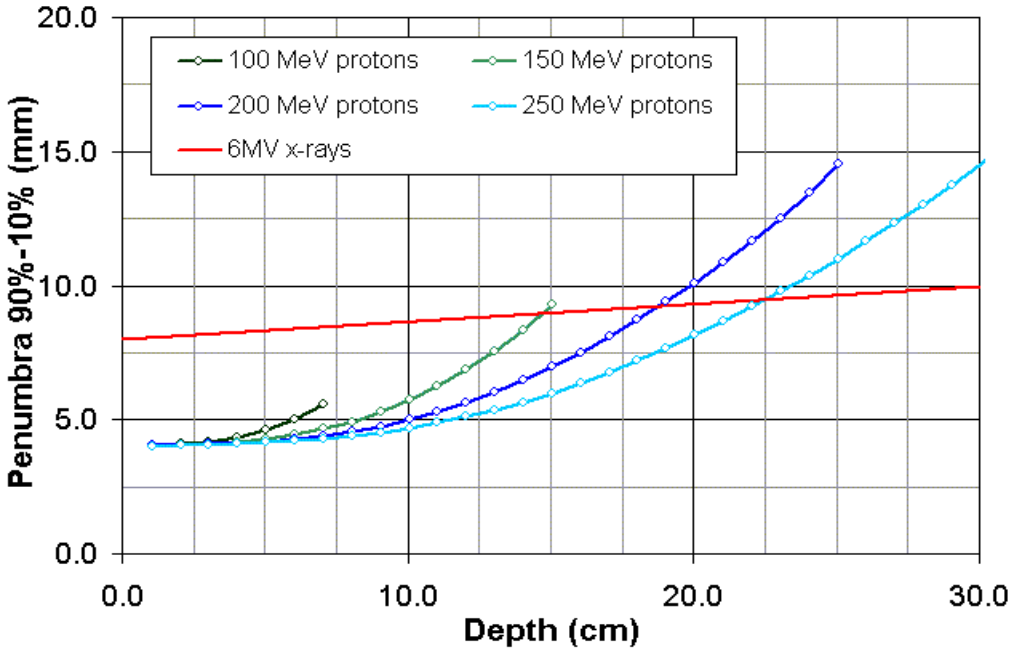
Penumbra

Lateral scattering:

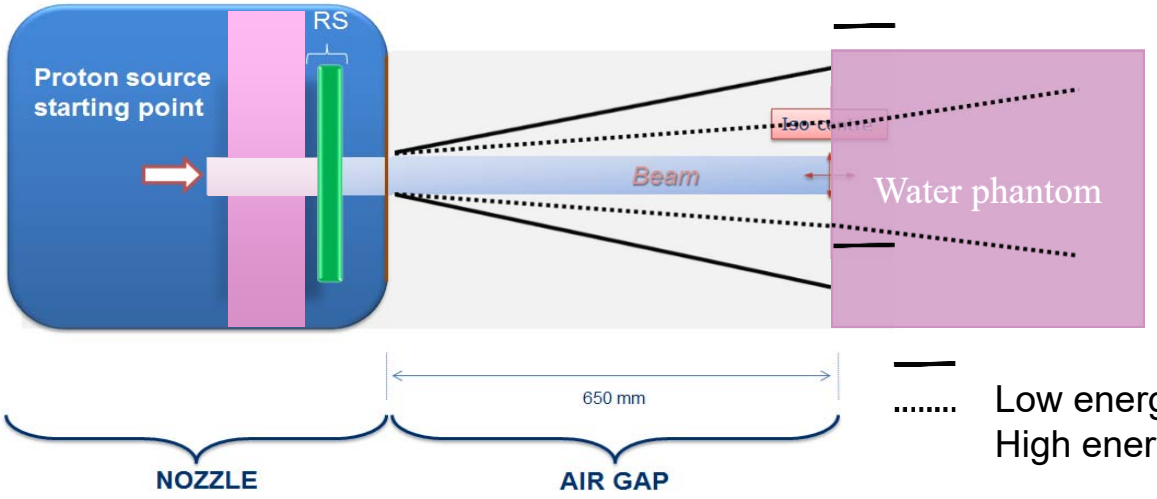
- MCS: penumbra increases with increasing penetration depth.
- Exceeds penumbra of photons at some point.



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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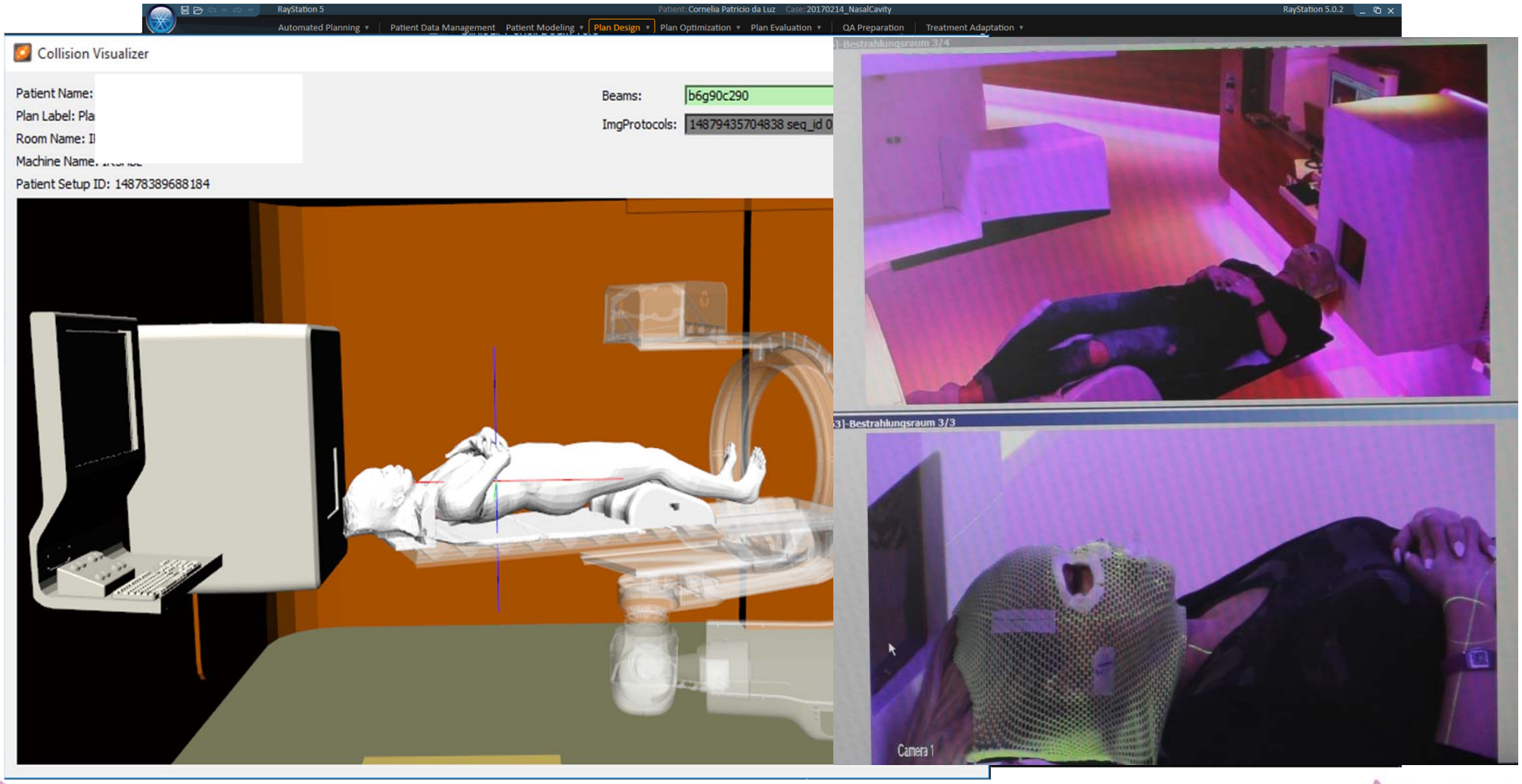
Reduction of air gap

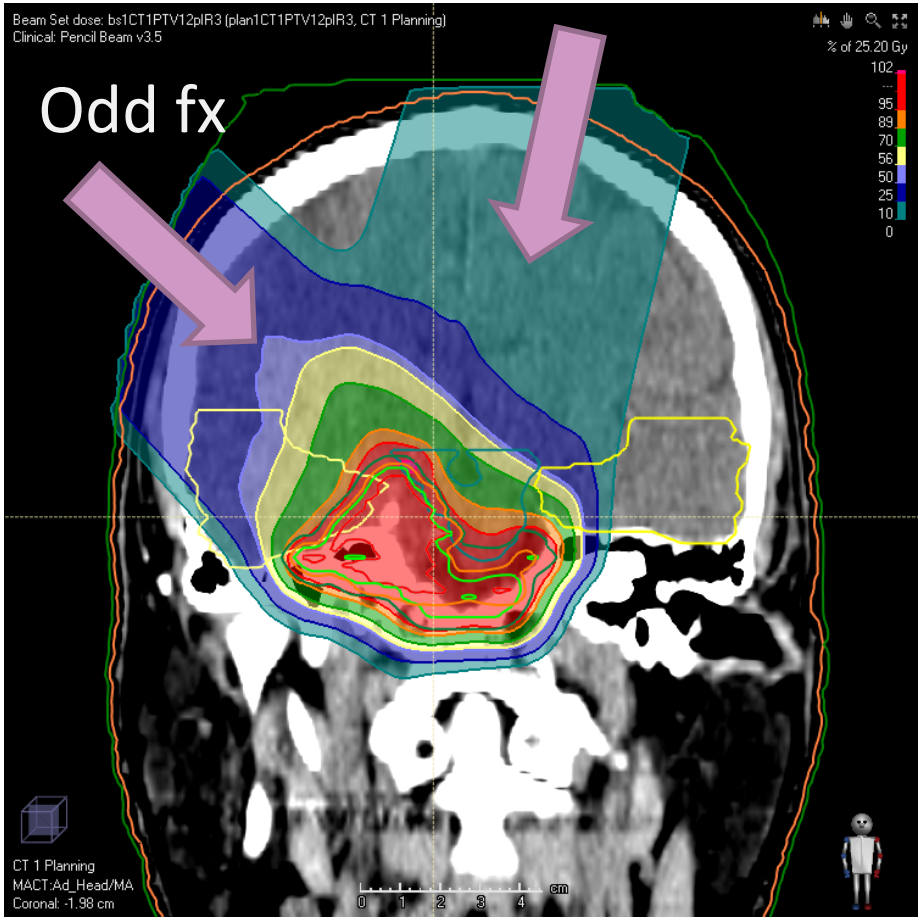
- efficient workflow supported by TPS based modelling of room, robot and patient geometries

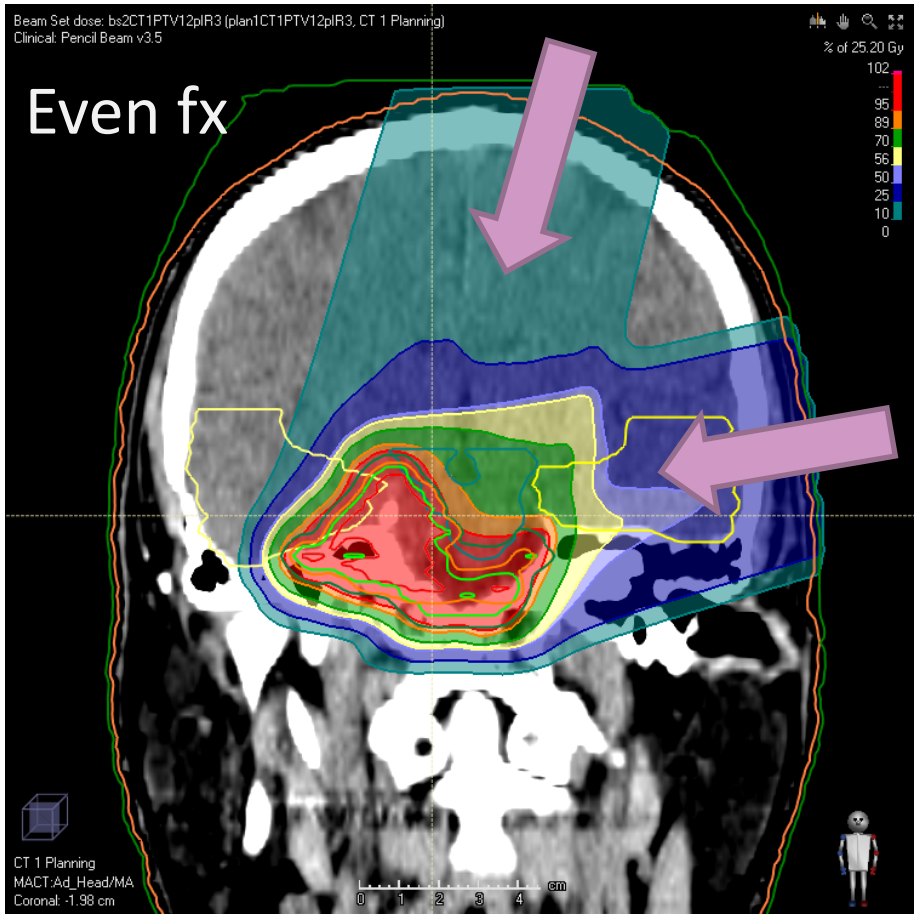


Optimize delivery time per fx

Limited beam angles with horizontal nozzle only

Usage of alternating beam sets with each 2 beams





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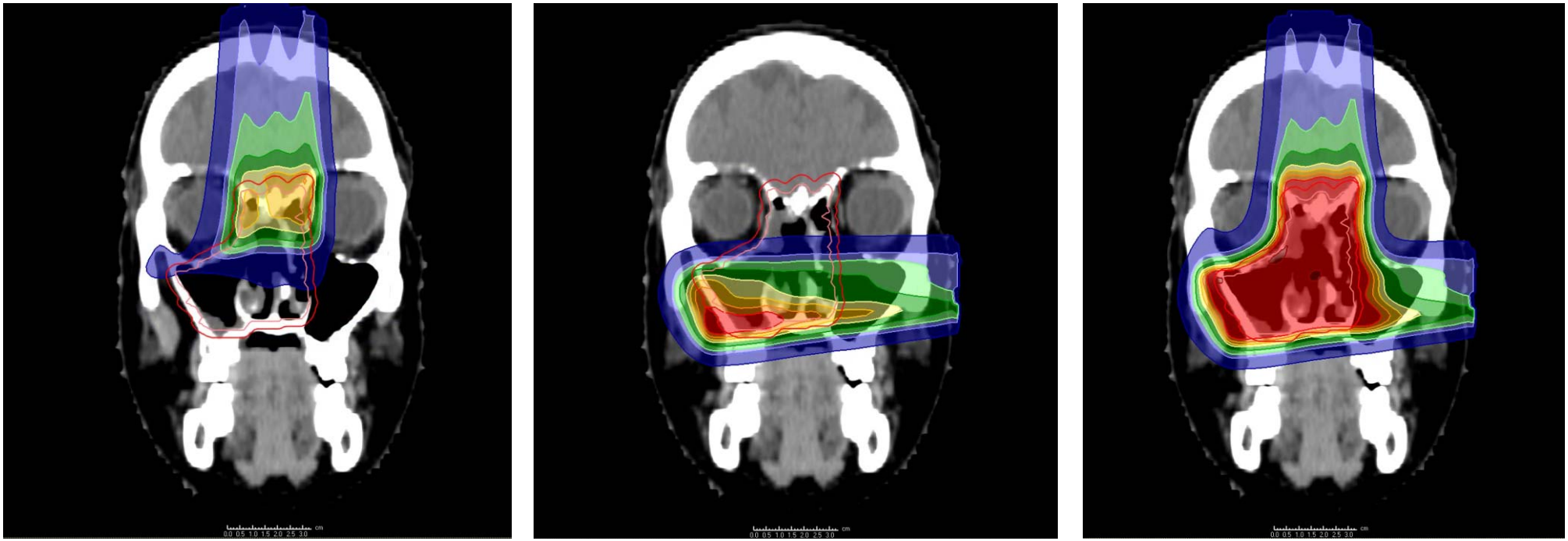
Inter-Ocular Nasal Cavities with horizontal beam only



Patching with smooth matching-gradient + multiple beam sets

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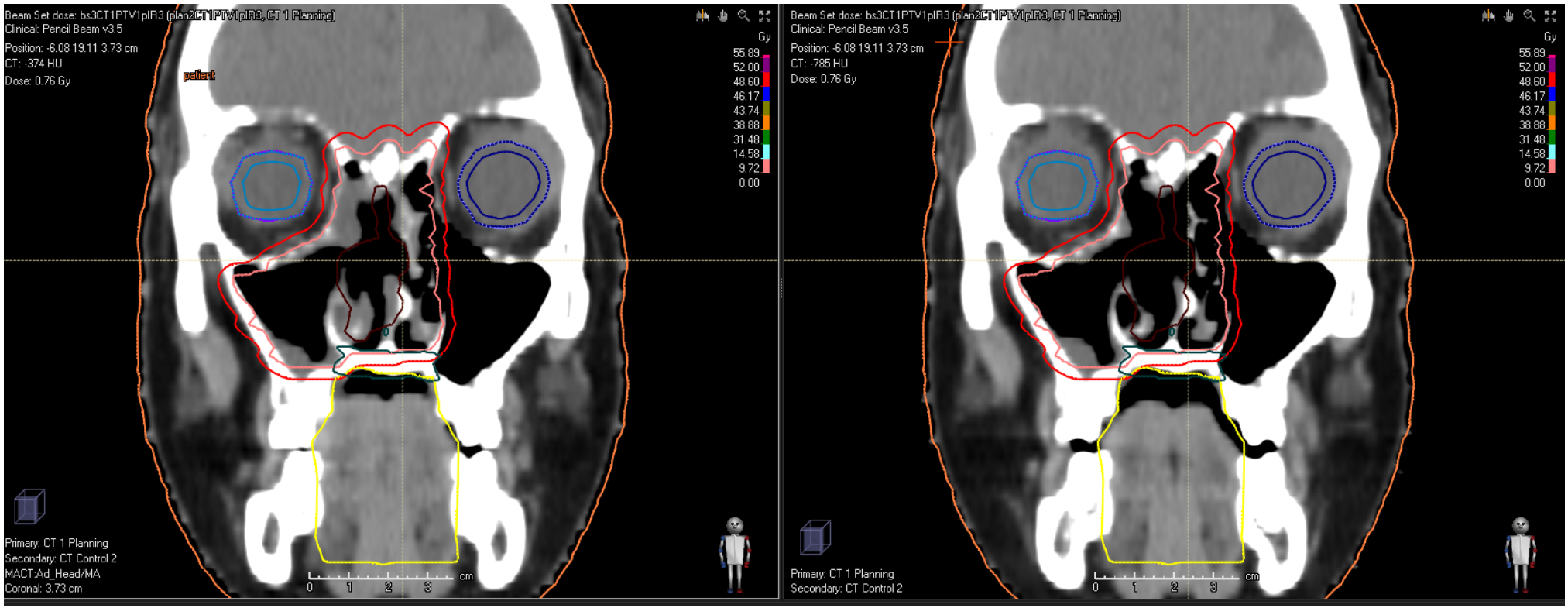
INTER-fx: Nasal Cavity Filling



Monitoring filling by control CTs + dose recomputation

Alters ranges and dose distribution?

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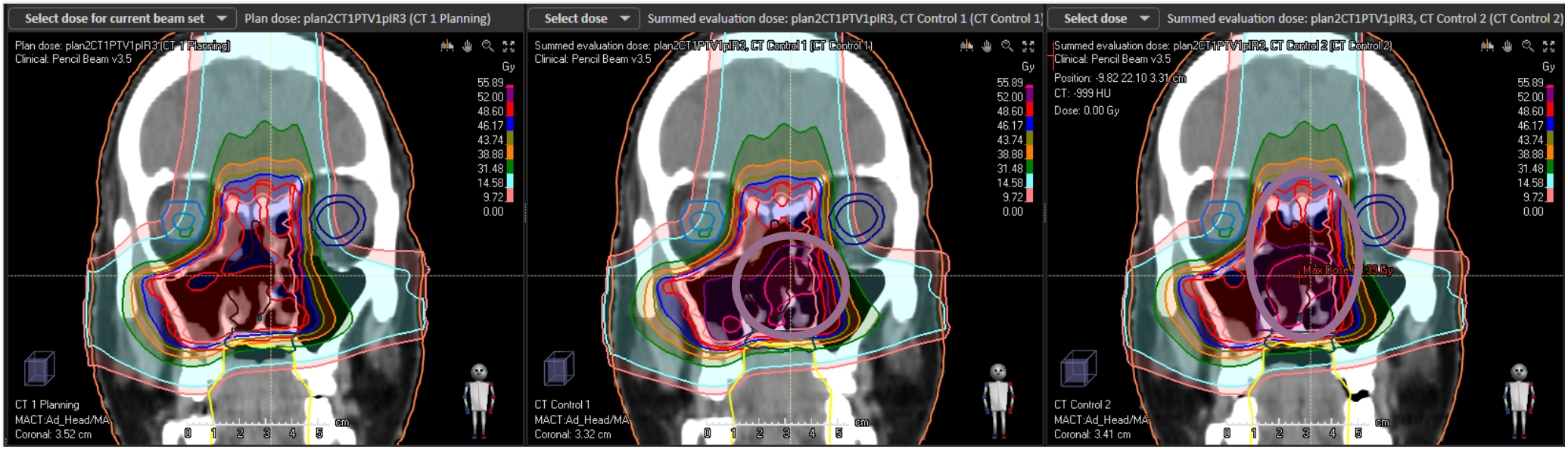
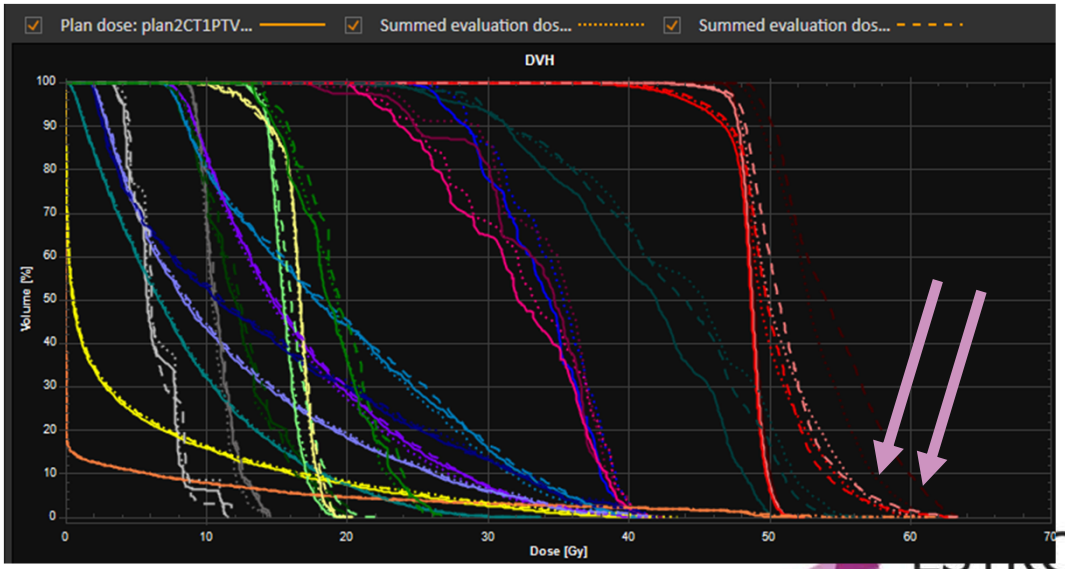
INTER-FX: Nasal Cavity Filling



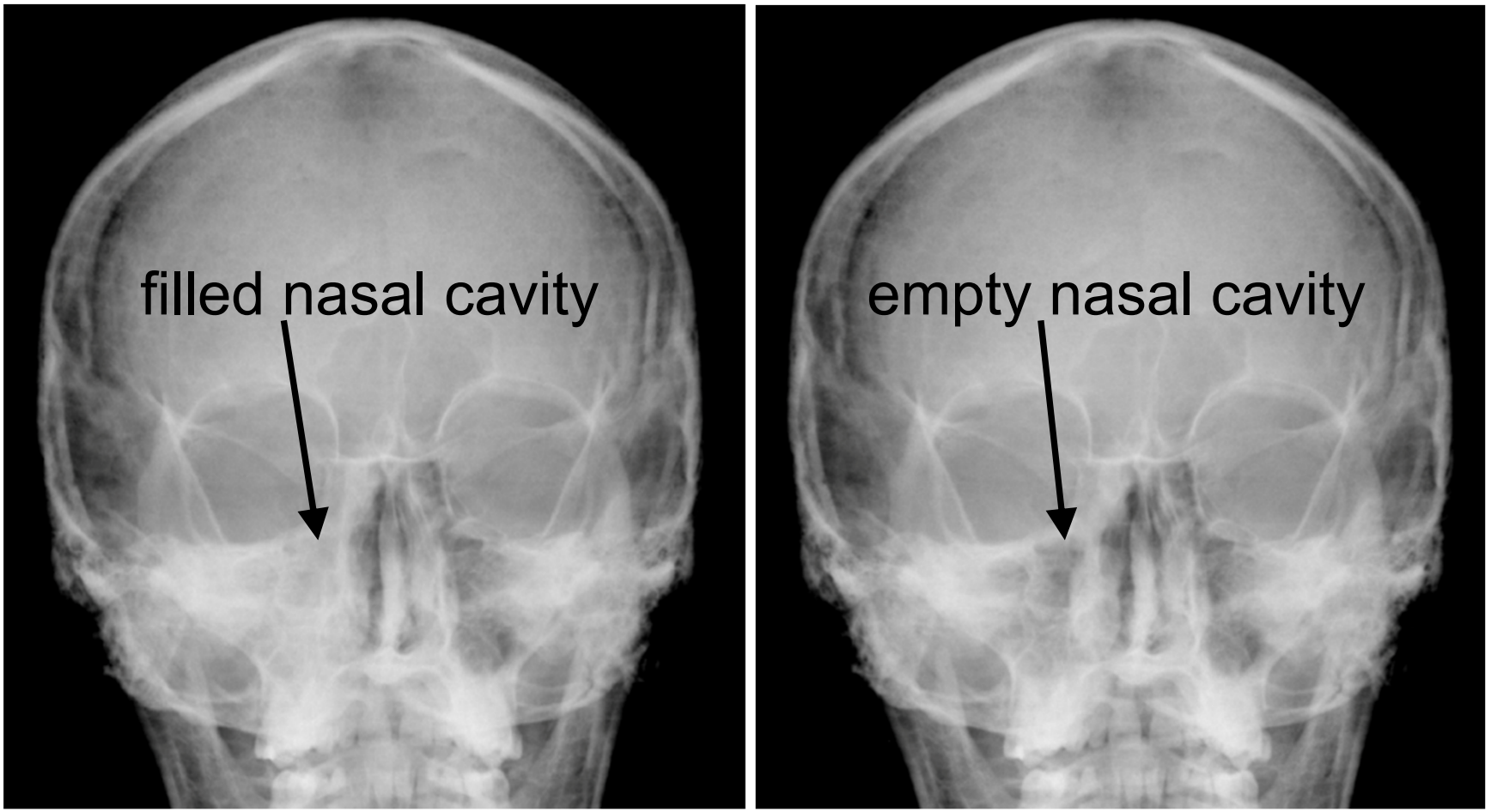


Dosimetric impact evaluation

Palate exposed to higher doses

Plan adaption + compensation

High quality planar imaging



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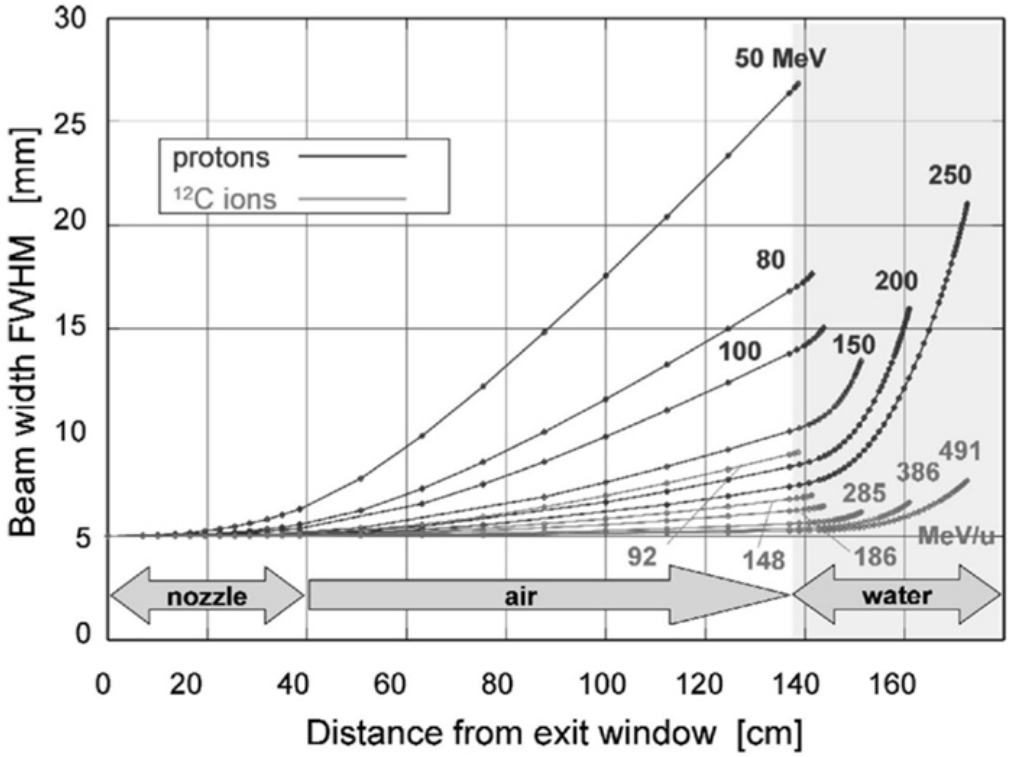
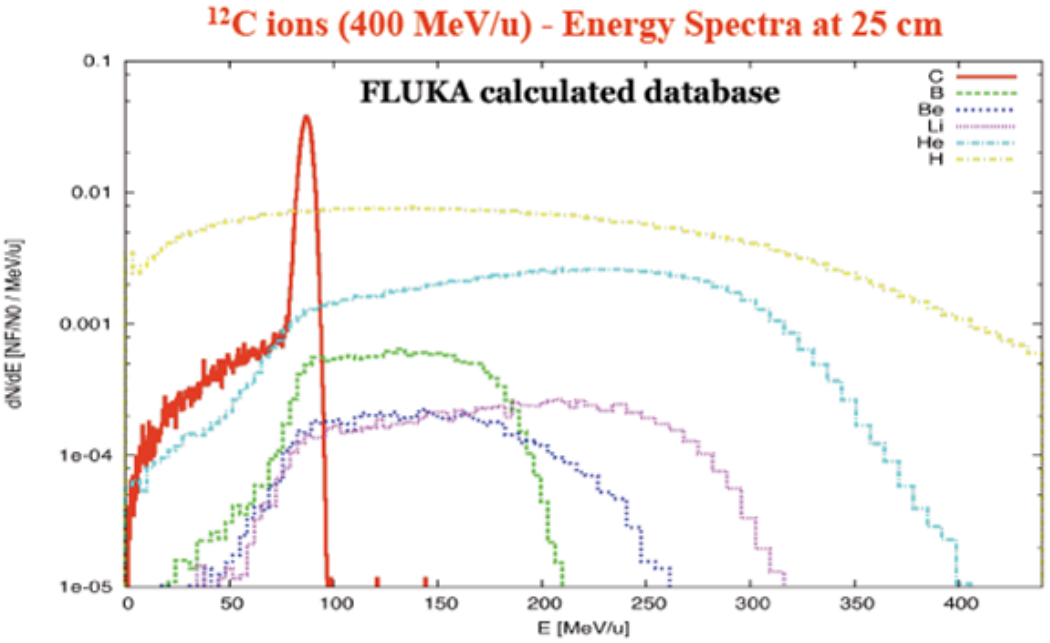
CIBT wrt PT: Some important differences for TP

- 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

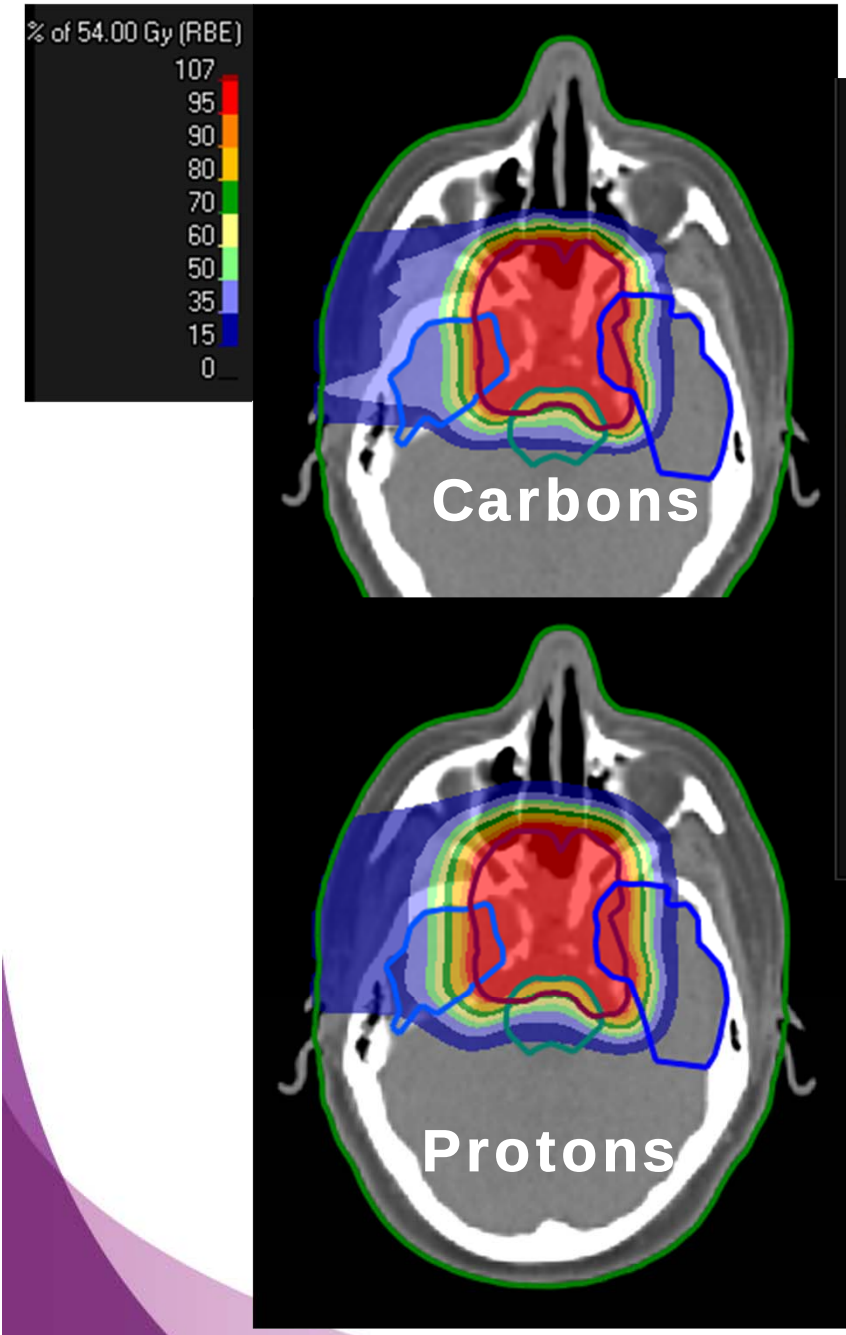
CIBT wrt PT: Some important differences for TP

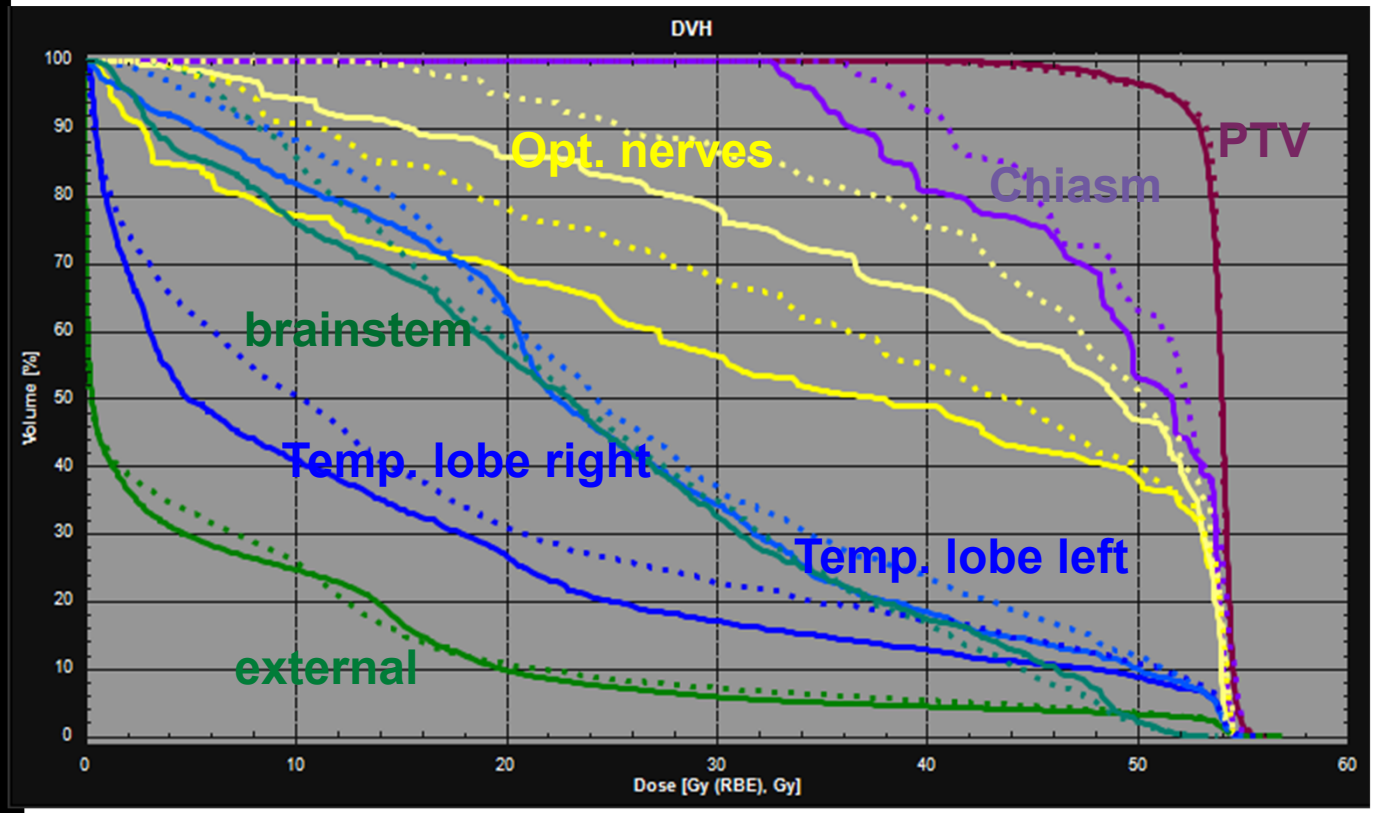
Peculiarities of carbon ion RBE and implications

- 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

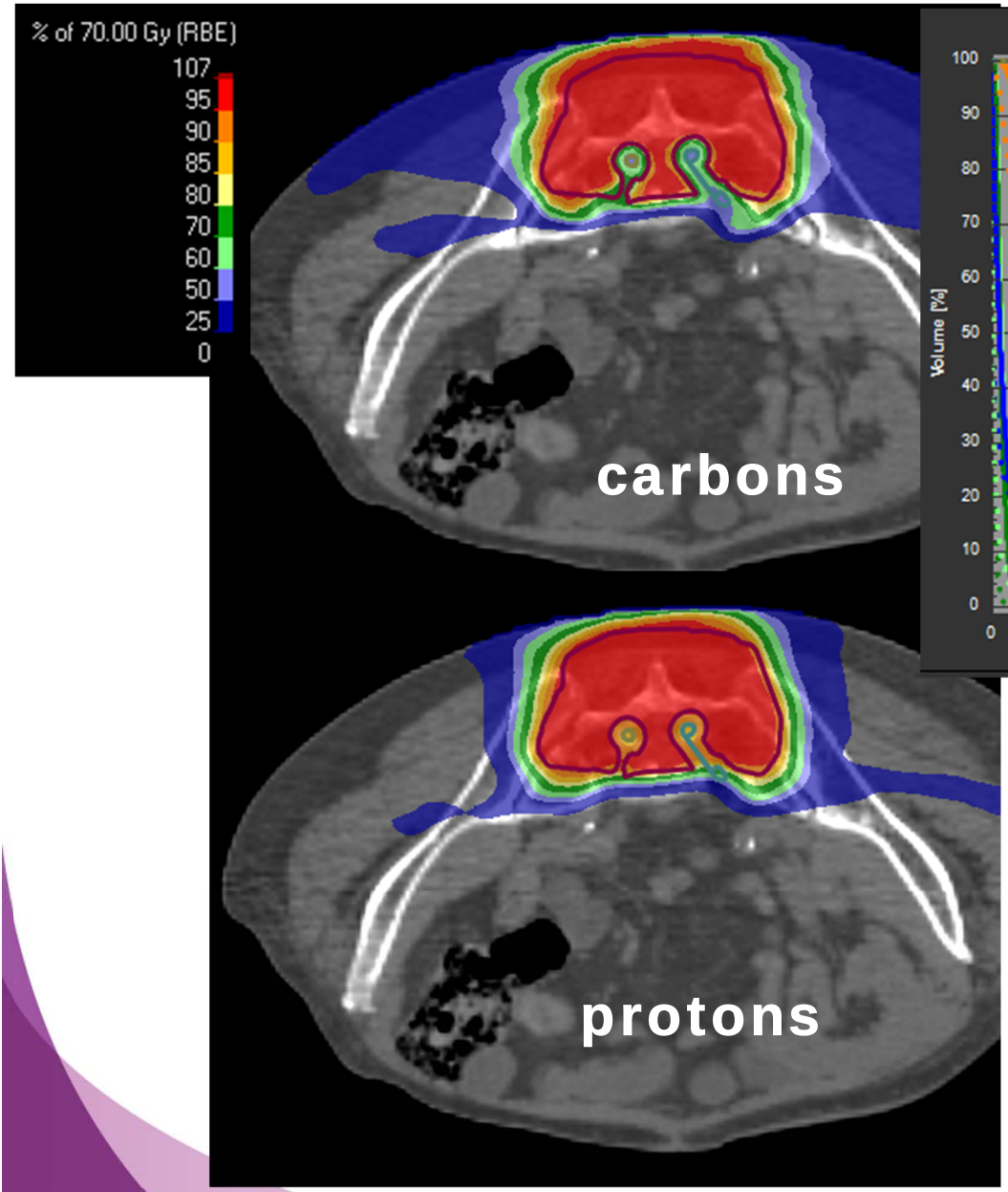


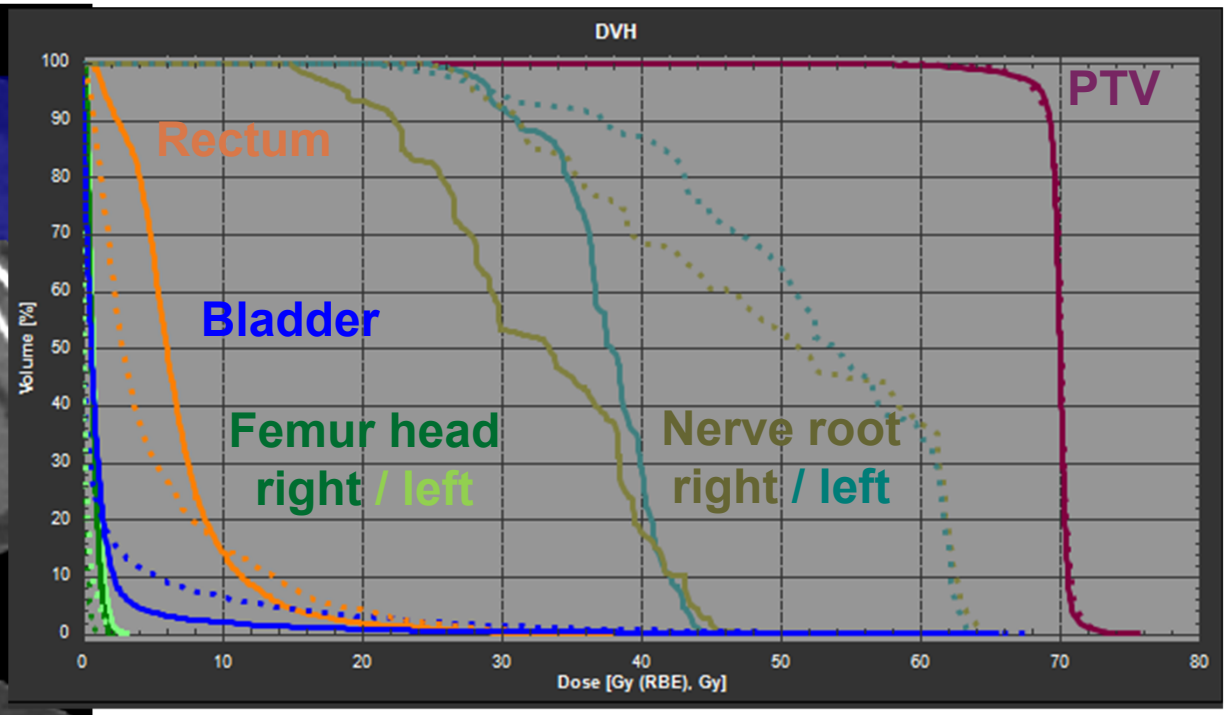


Solid: C

Dotted: p

C vs p: Sacrum





Solid: C

Dotted: p

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Some practical aspect in ion beam planning

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

Basic principles of rotational IMRT planning

Gert Meijer

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Rotational IMRT not really new

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

perated irradia- It must angle of e direct radiated -lateral circum- rotation l phan- in the 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

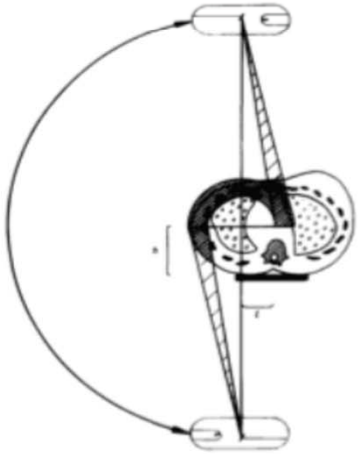

FIG. 1.

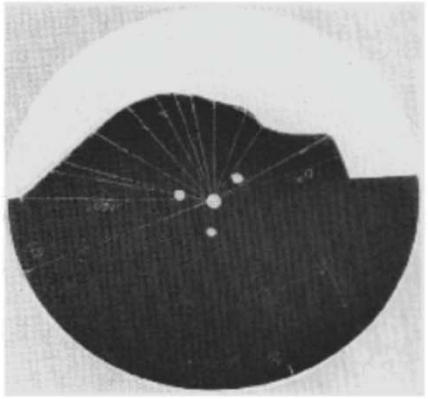

FIG. 2.

British Journal of Radiology, 1956

(1944, Wachsmann, Pendulum unit)

Courstesy of Dirk Verellen

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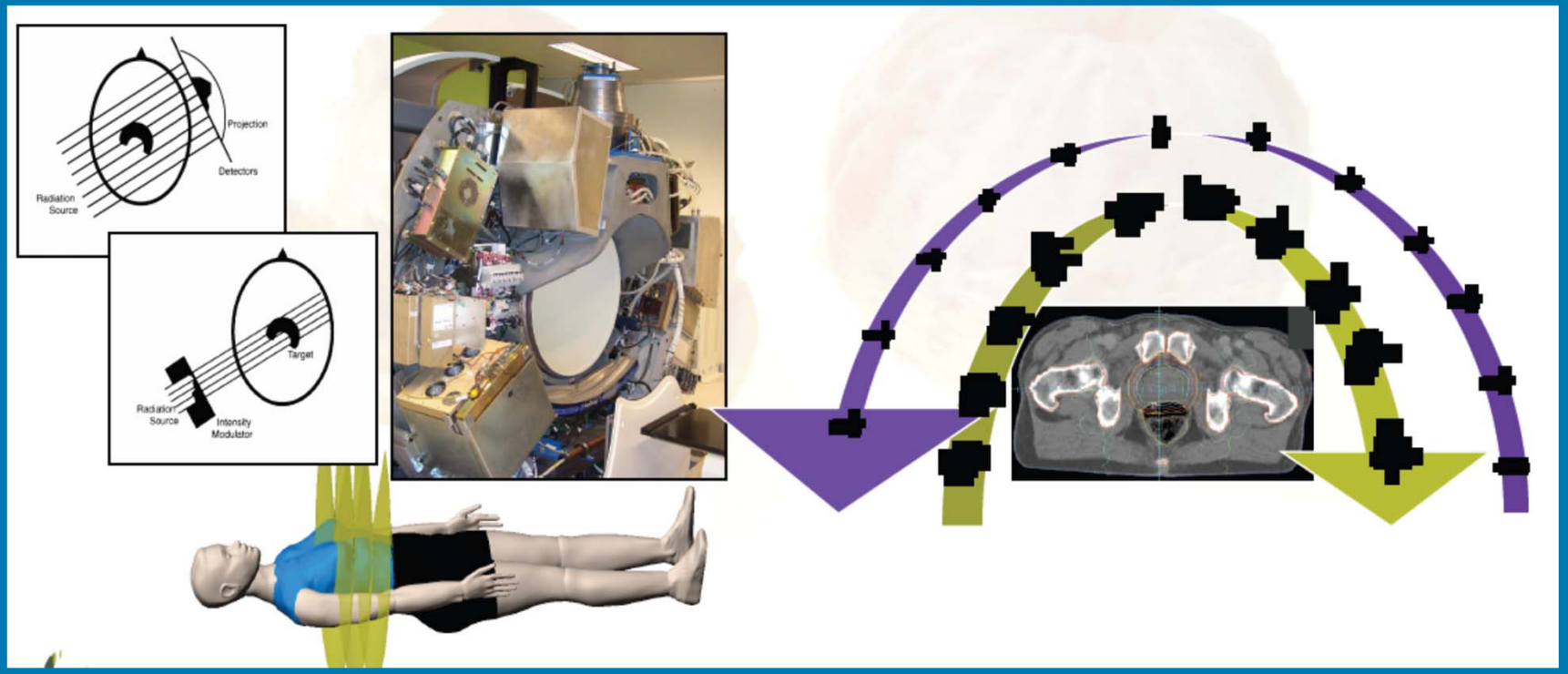
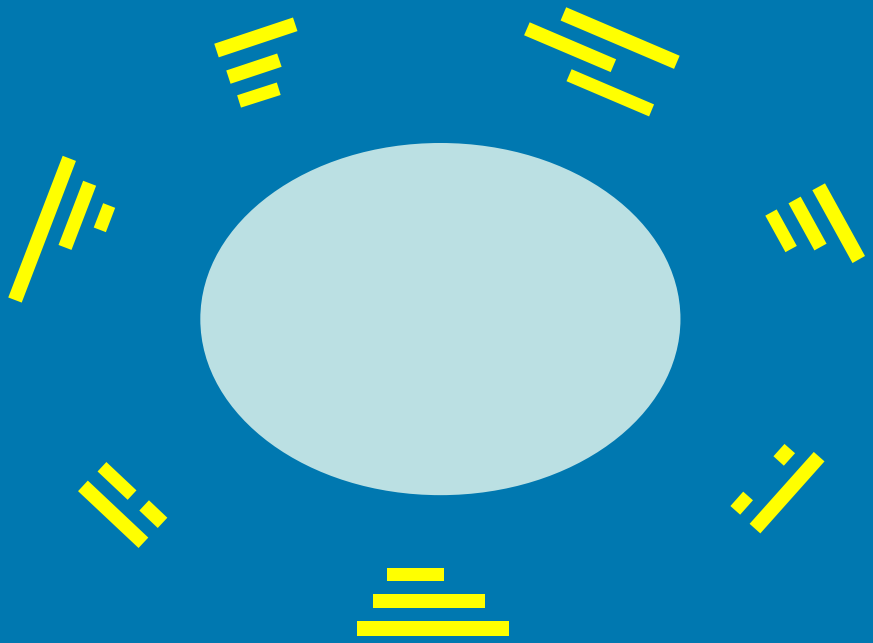
fan beam vs cone beam

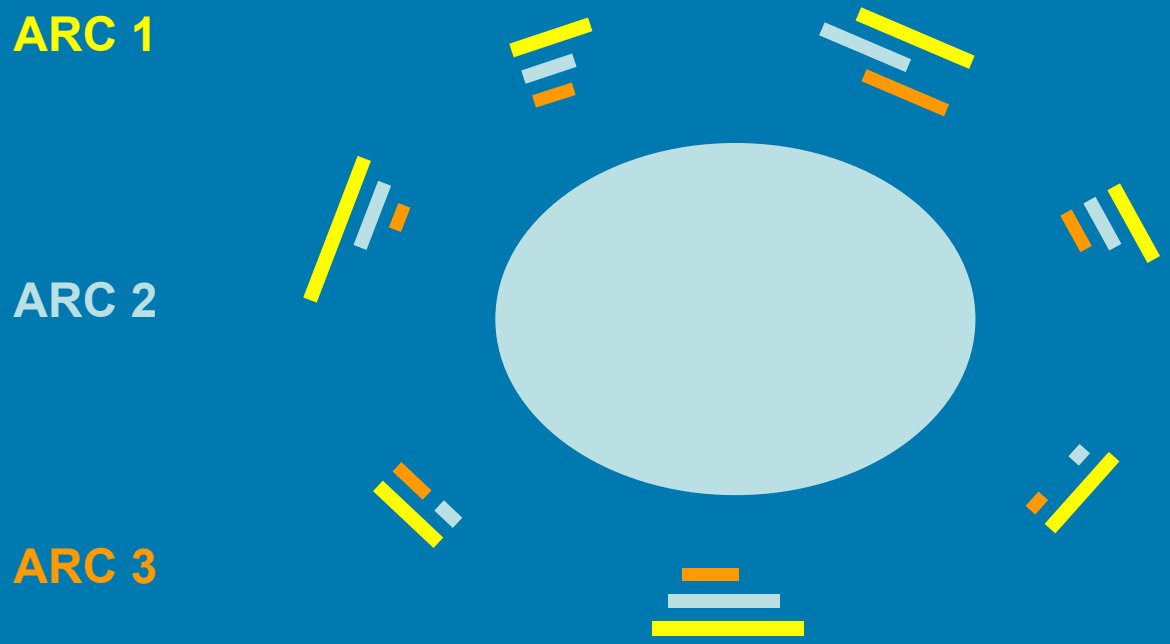


Courstesy of Dirk Verellen

IMRT

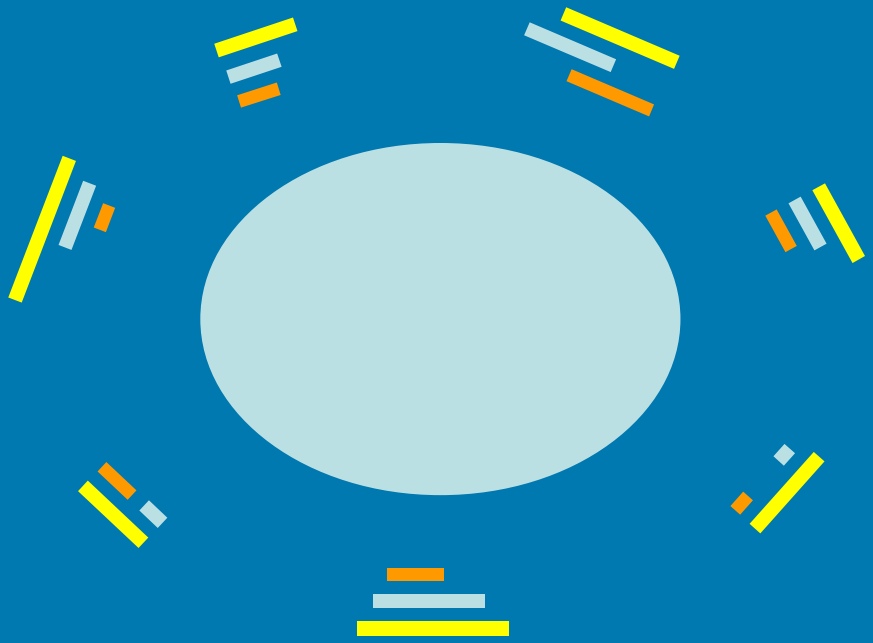


IMAT



from 3 arcs to a single arc

moving from stacked to spaced



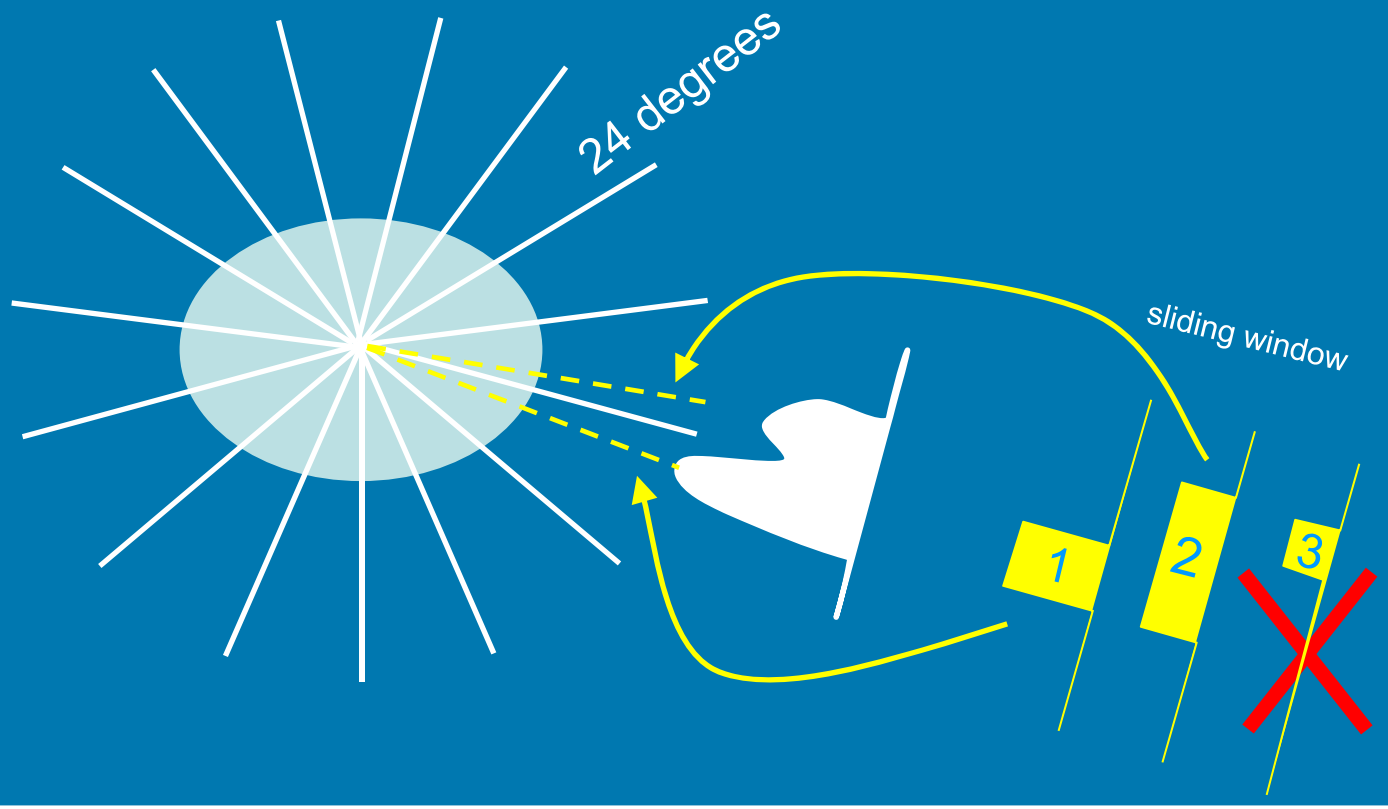
Tang *et al.* (IJROBP 2007)

So….

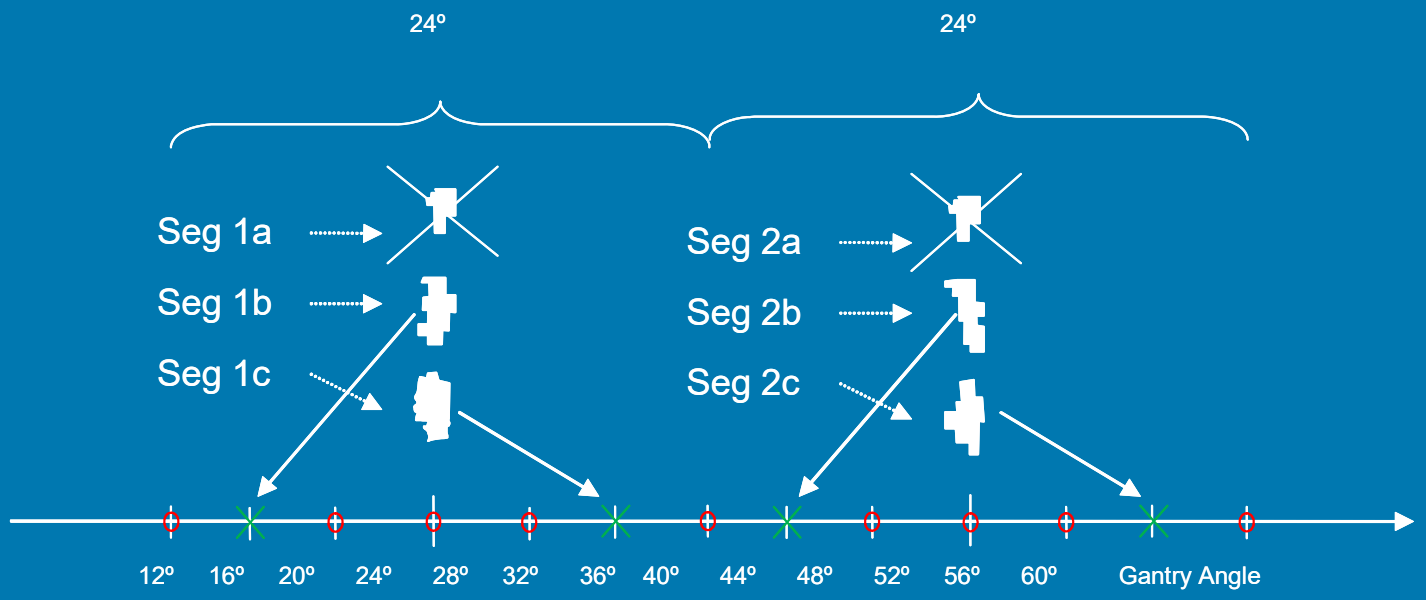
rotational therapy is rather insensitive to angle deviations

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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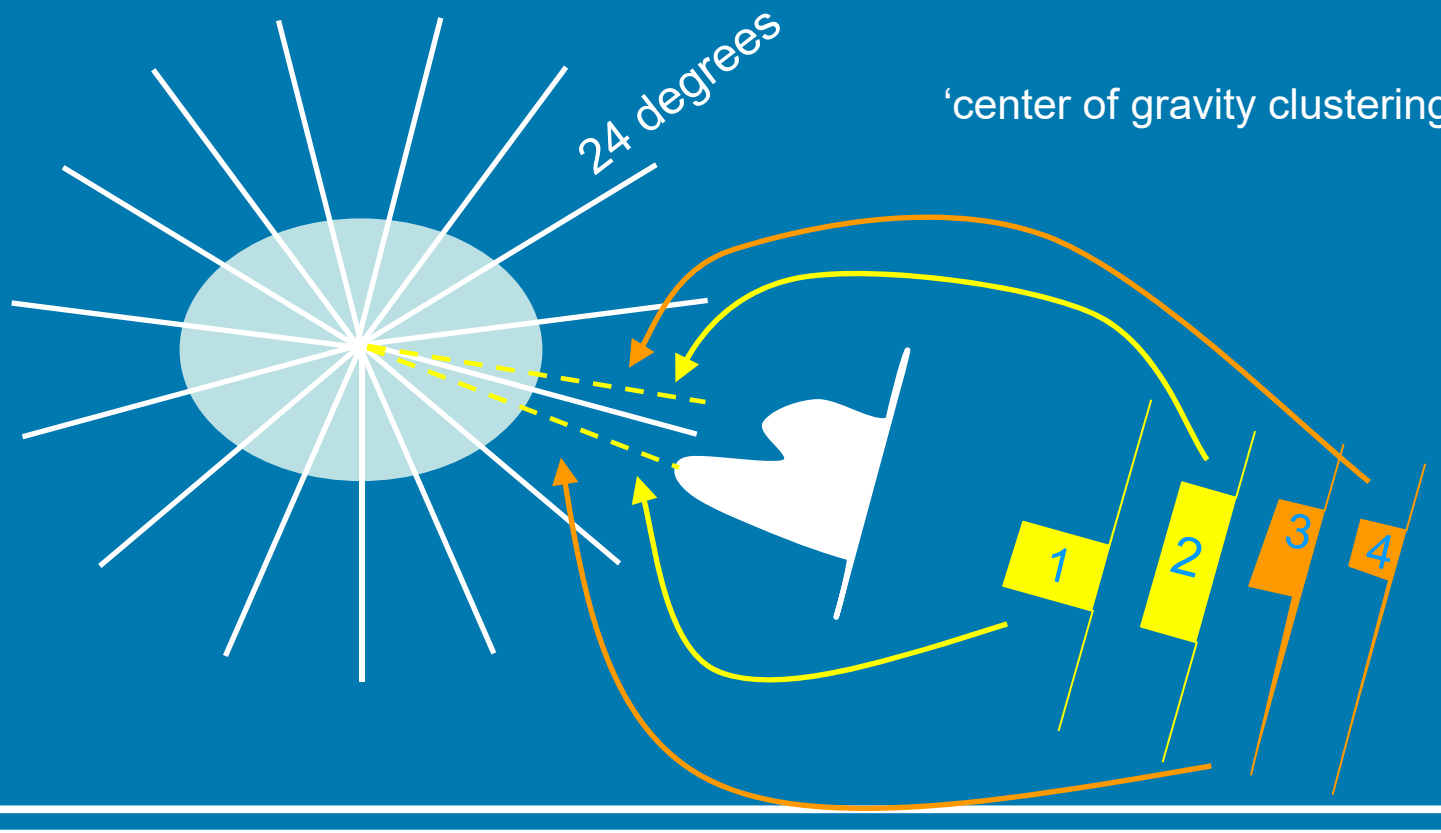
How about dual arcs?




IMRT
VMAT

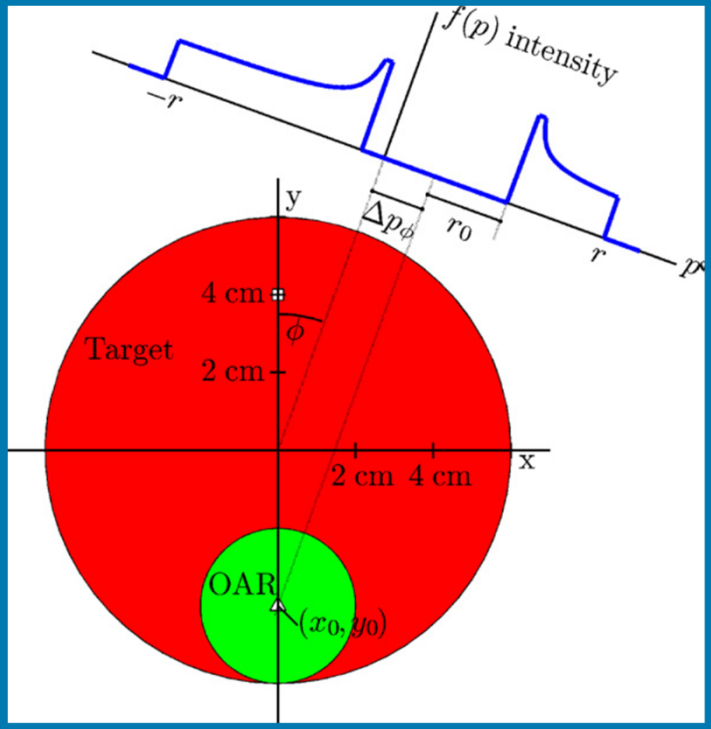
Static IMRT vs VMAT - Conceptual issues

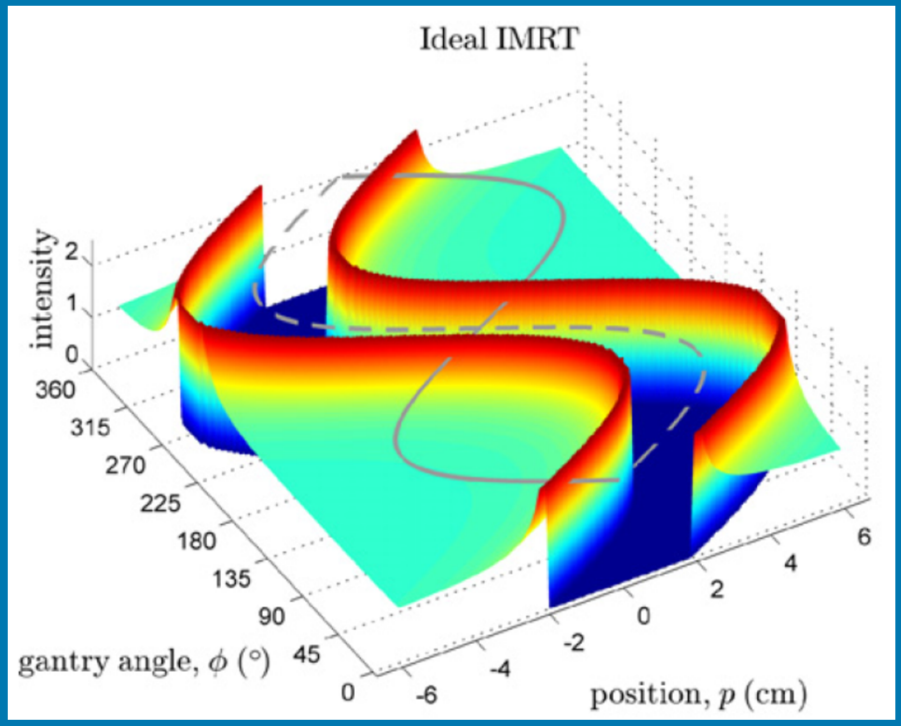
Is there any difference between static IMRT and VMAT?

- 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

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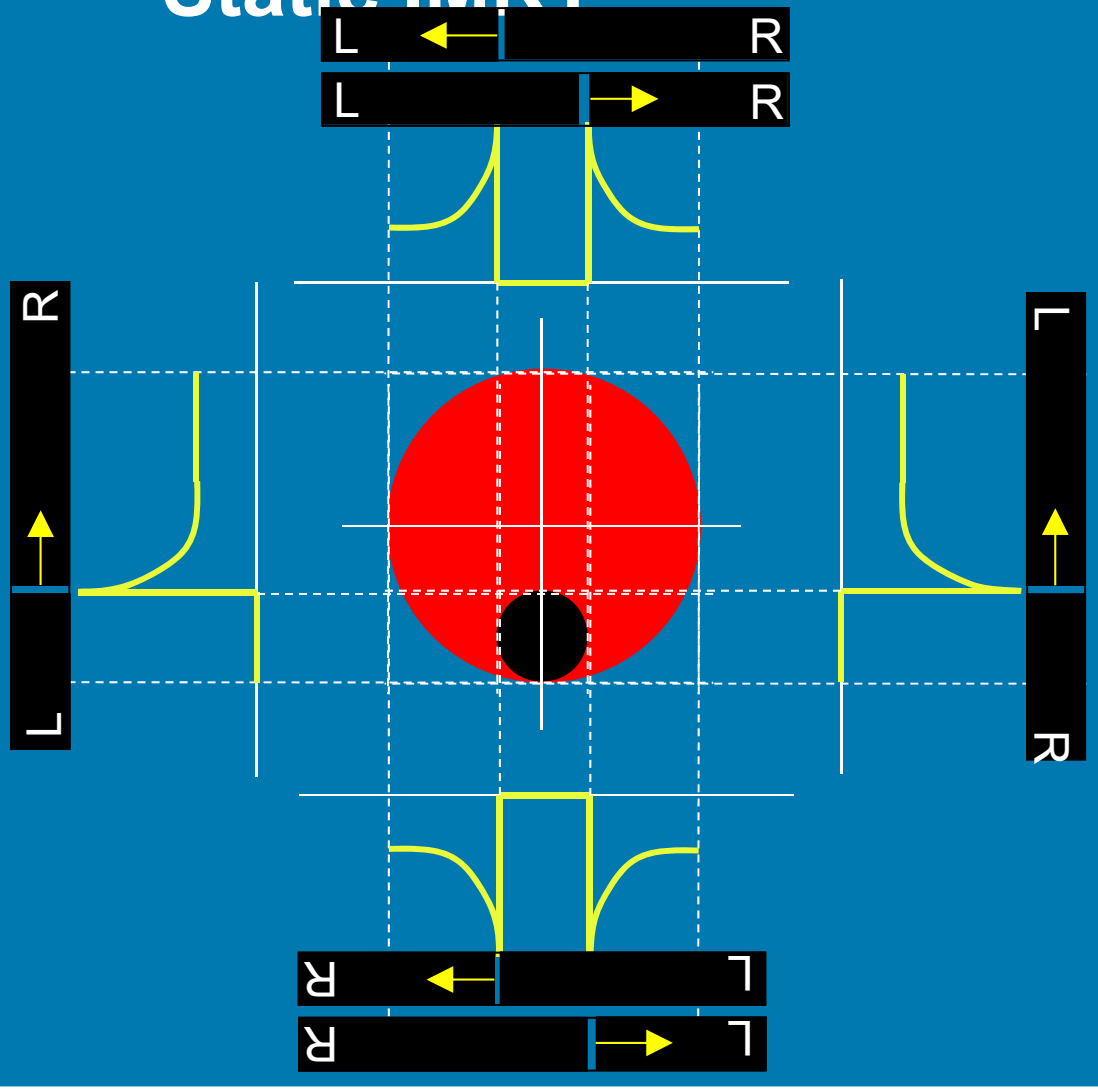
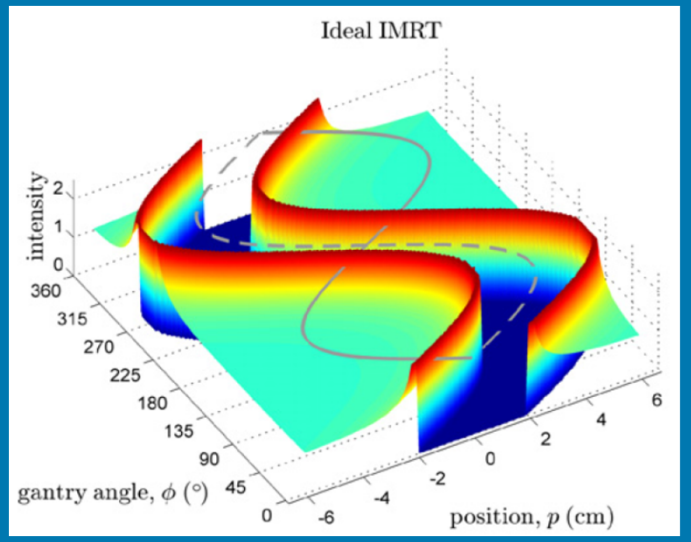
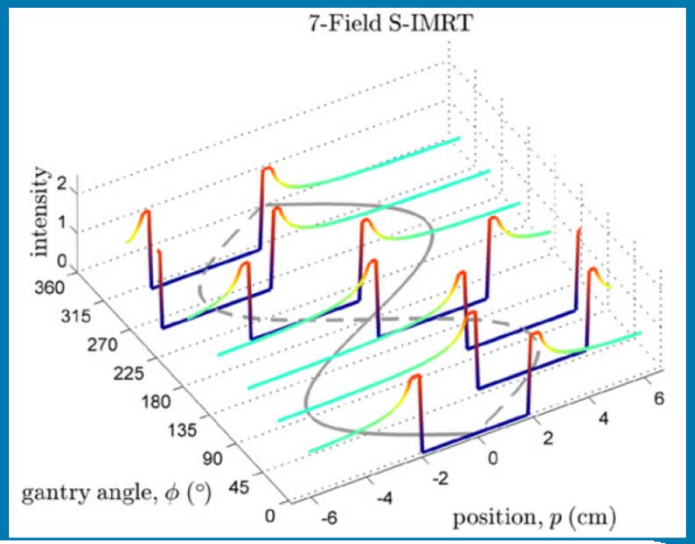
Static IMRT







Courstesy of Jochem Wolthaus

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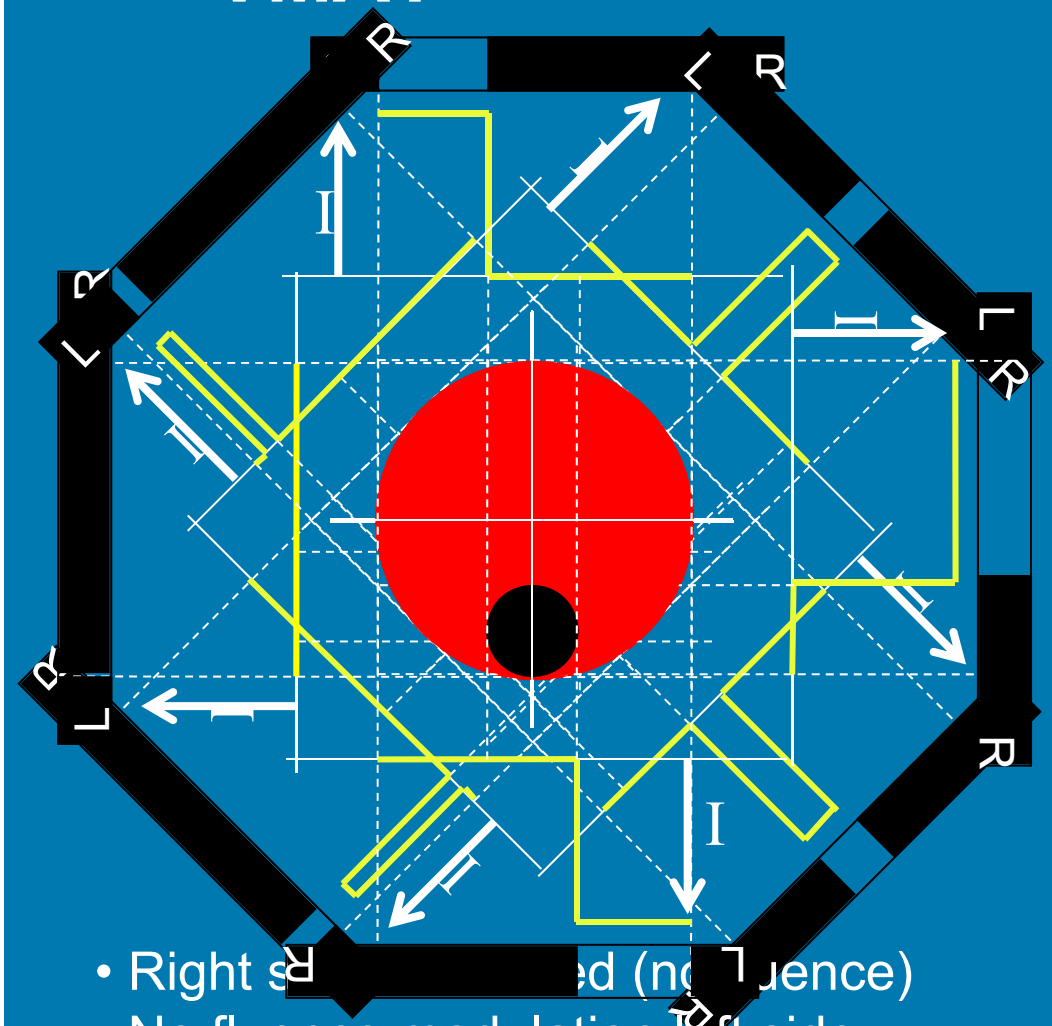
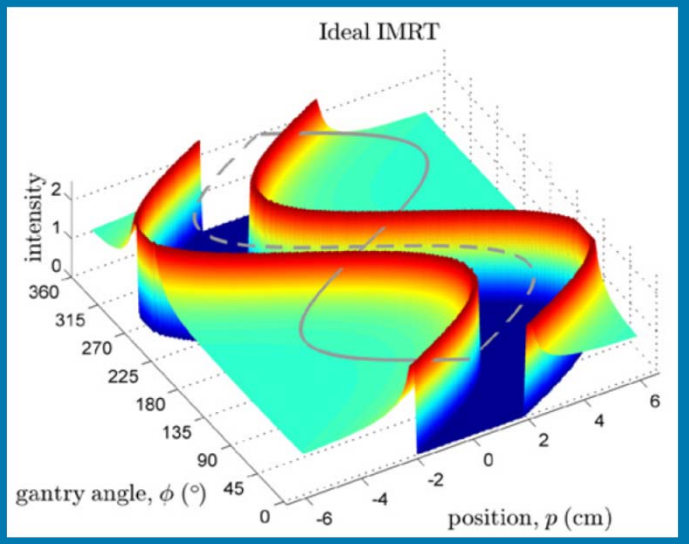
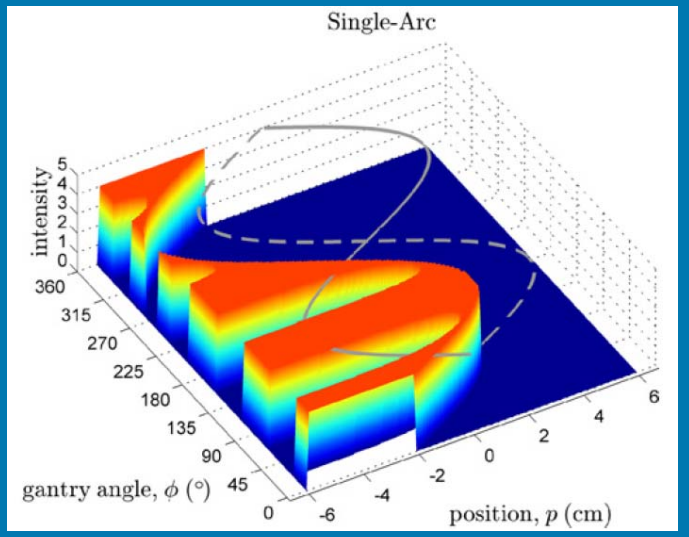
VMAT



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





Courstesy of Jochem Wolthaus

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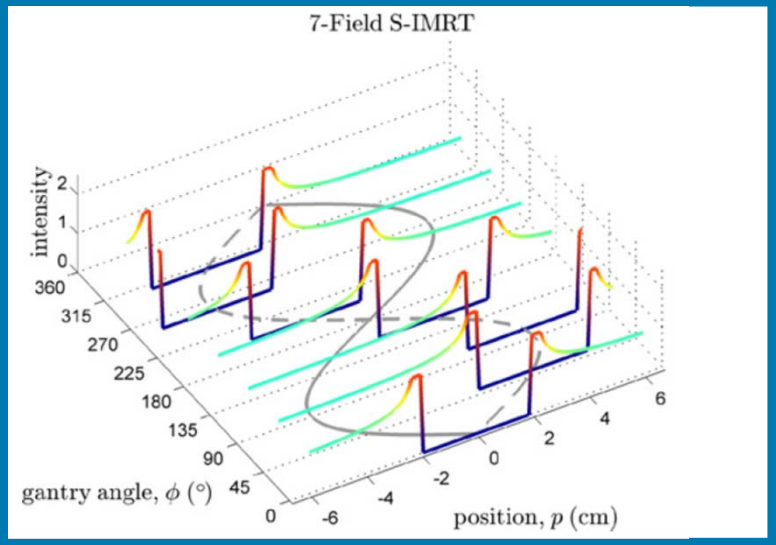
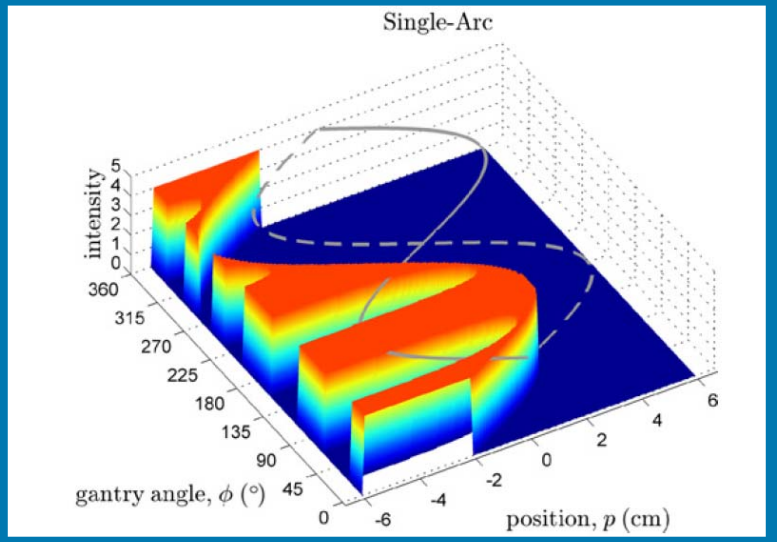
IMRT vs. VMAT - Conceptual differences





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

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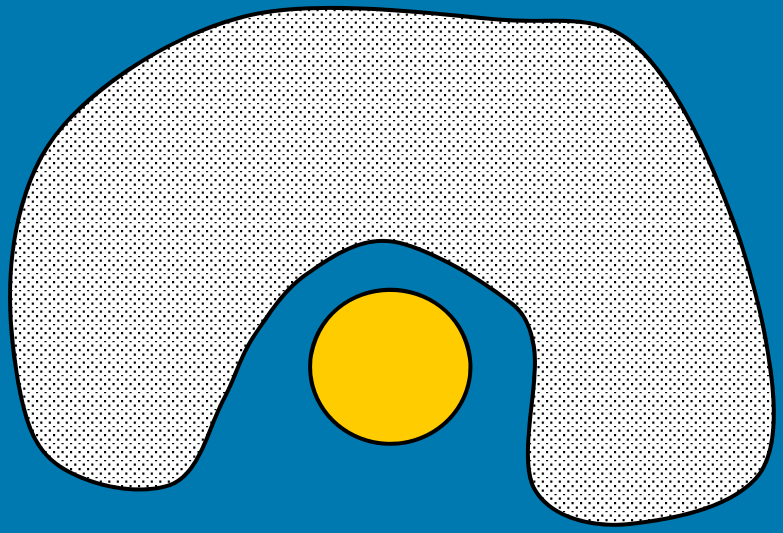
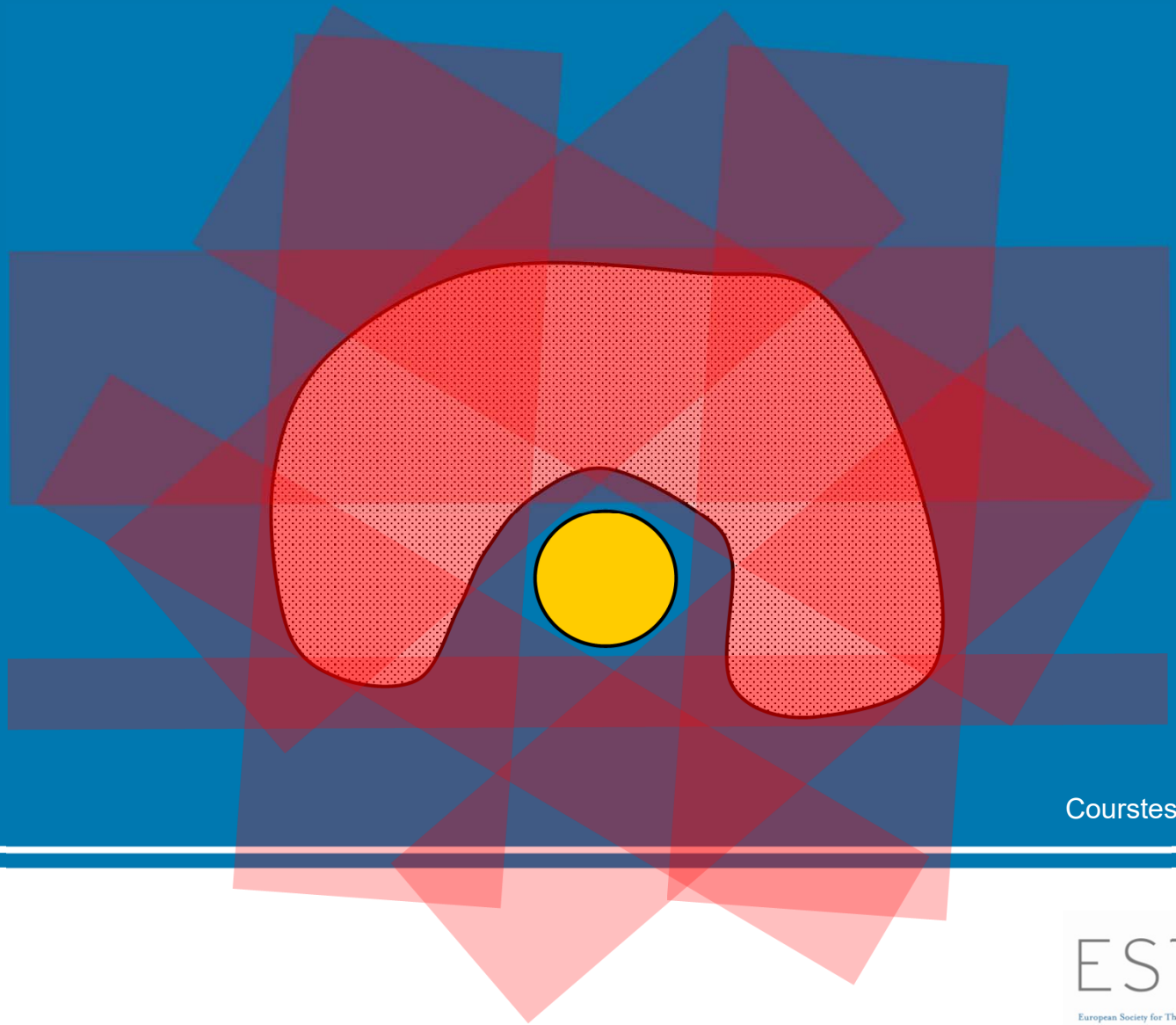
Why need multiple arcs??



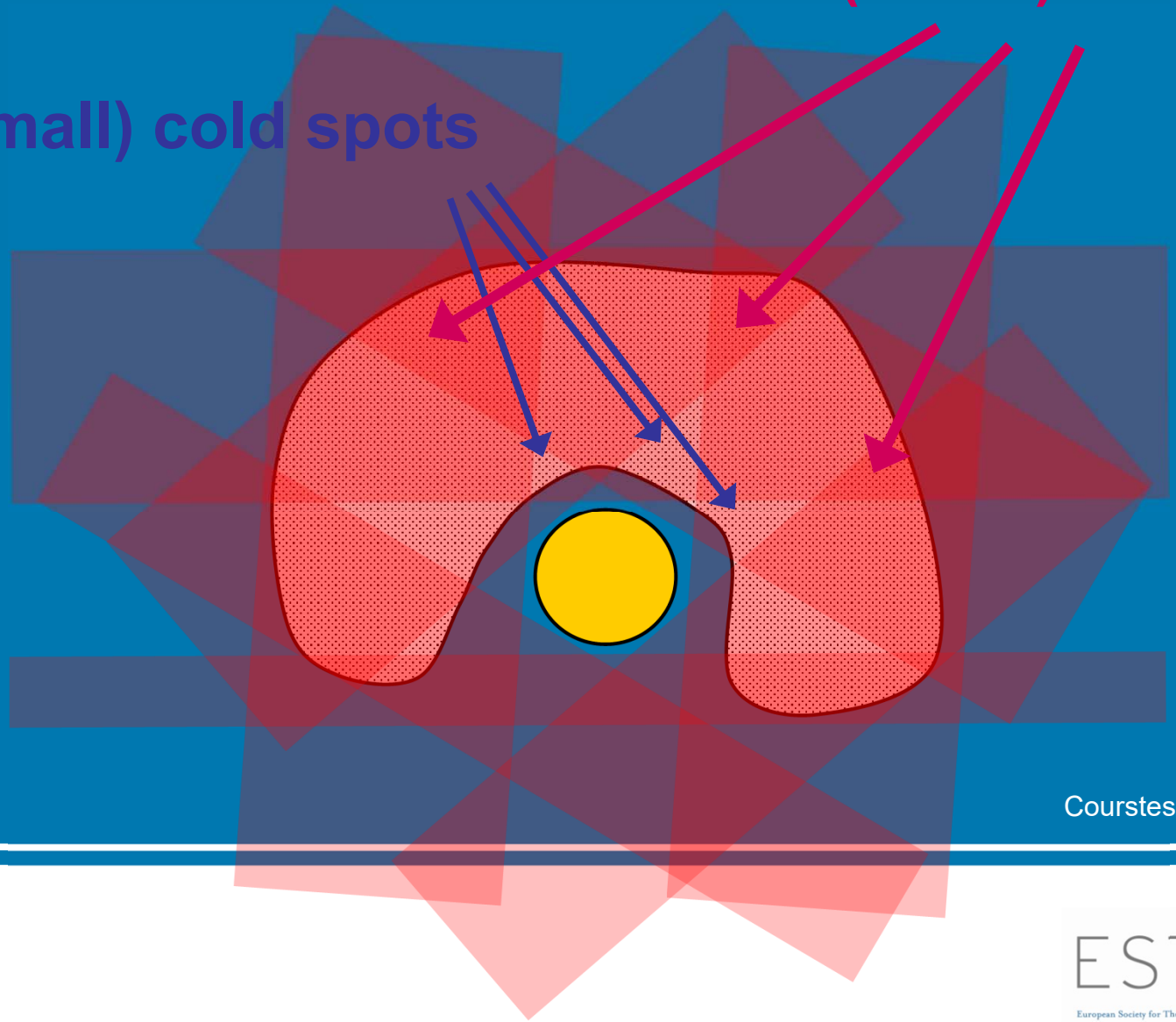
Courstesy of Markus Alber

Start with 4 beam angles



Courstesy of Markus Alber

Start with 4 beam angles



Courstesy of Markus Alber

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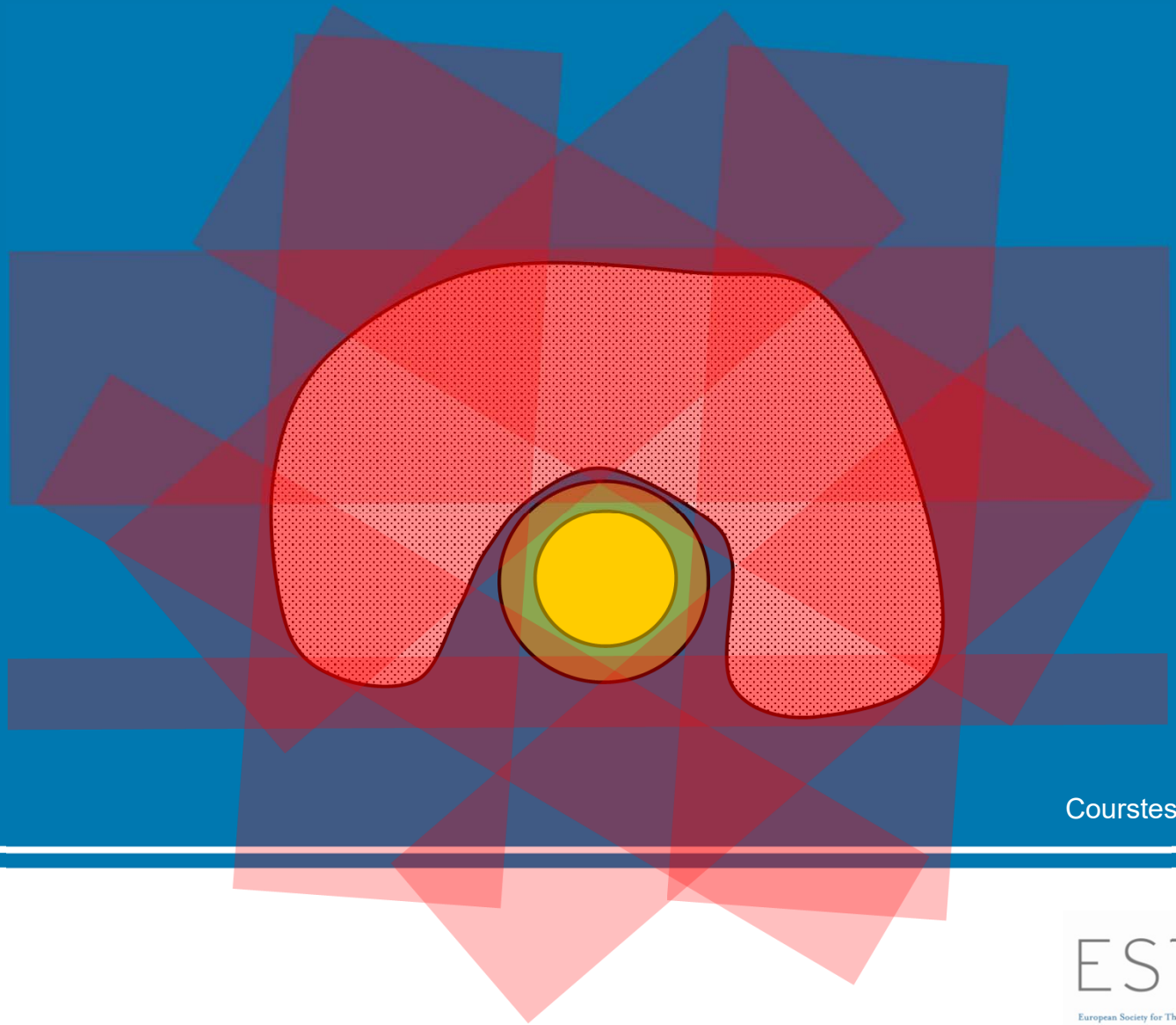
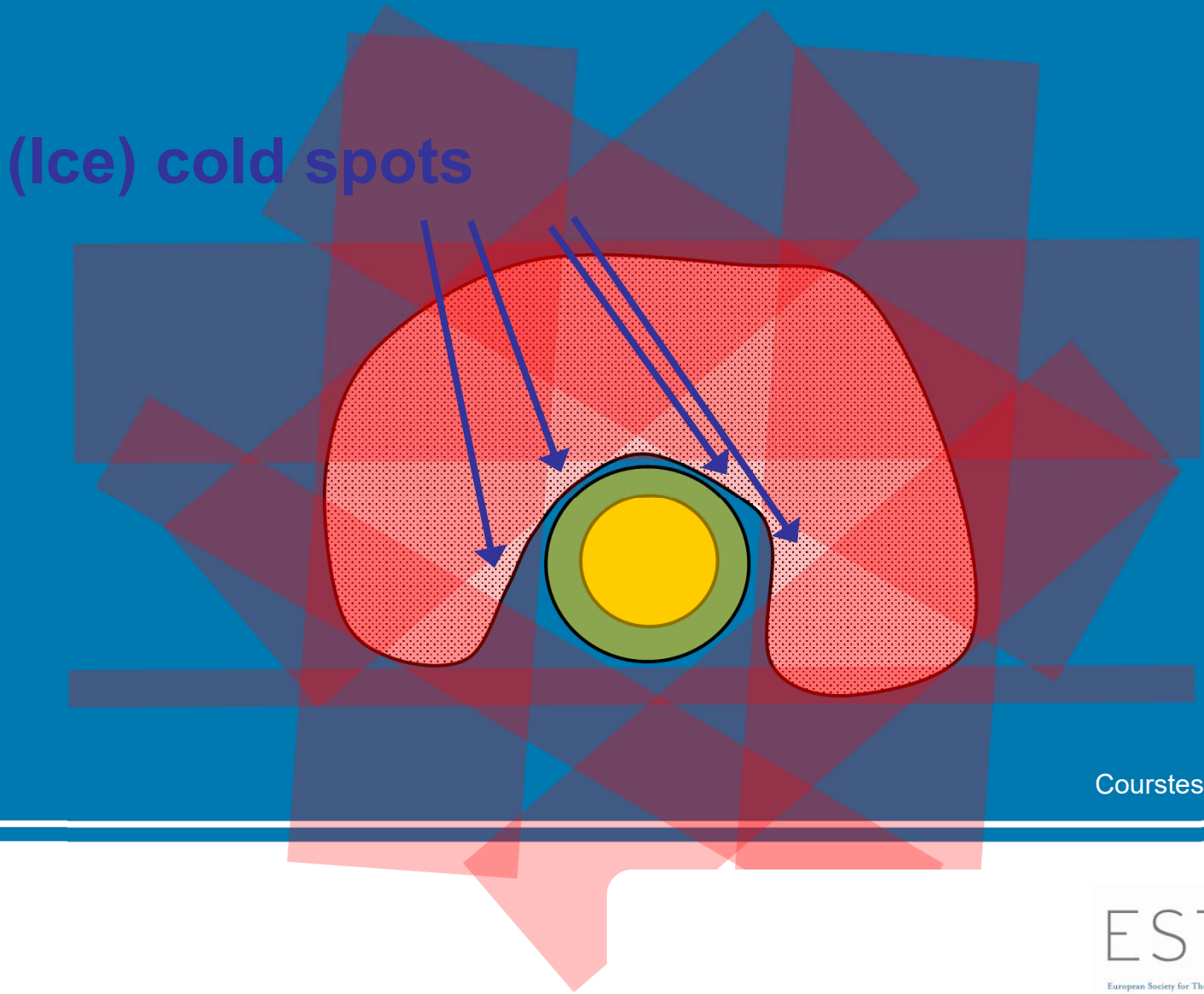
What if the gradient has to be tighter?



Courstesy of Markus Alber

What if the gradient has to be tighter?



Courstesy of Markus Alber

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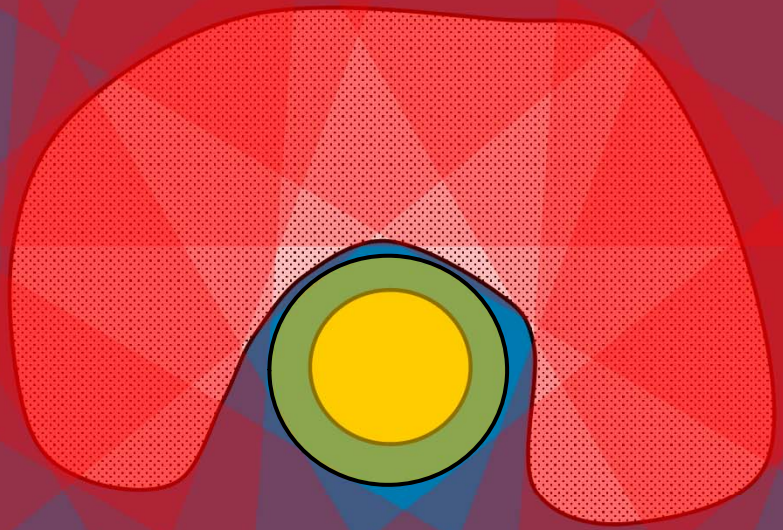
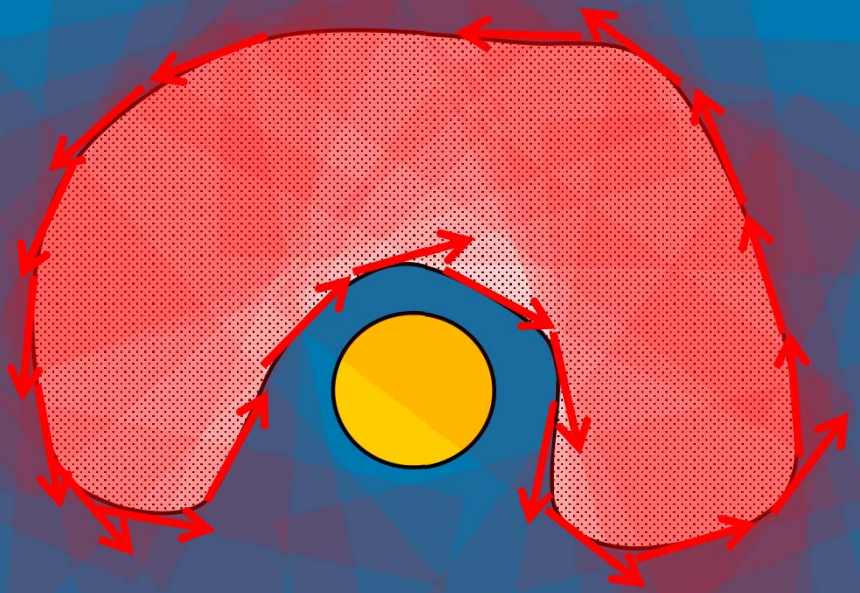
Use more beam angles!



Courstesy of Markus Alber

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



Courstesy of Markus Alber

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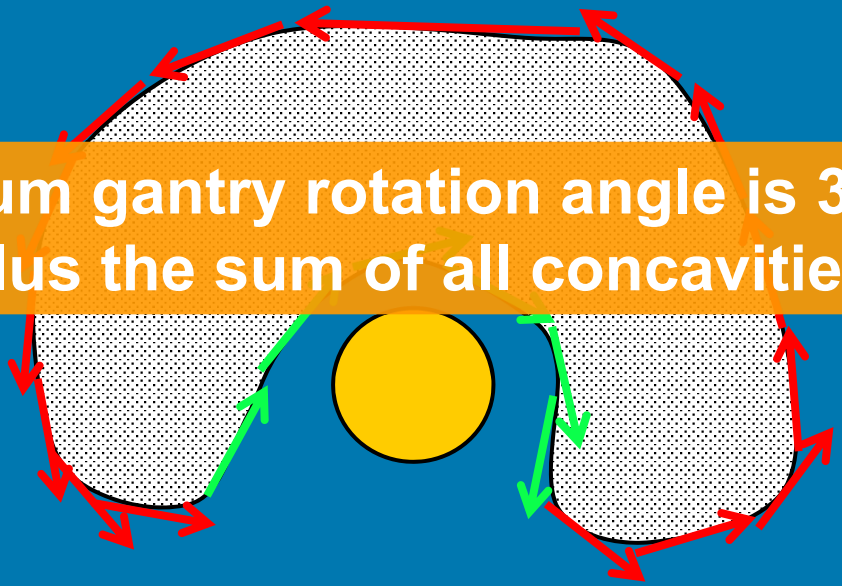
What is the maximum gantry rotation angle needed to paint all gradients for this target??

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

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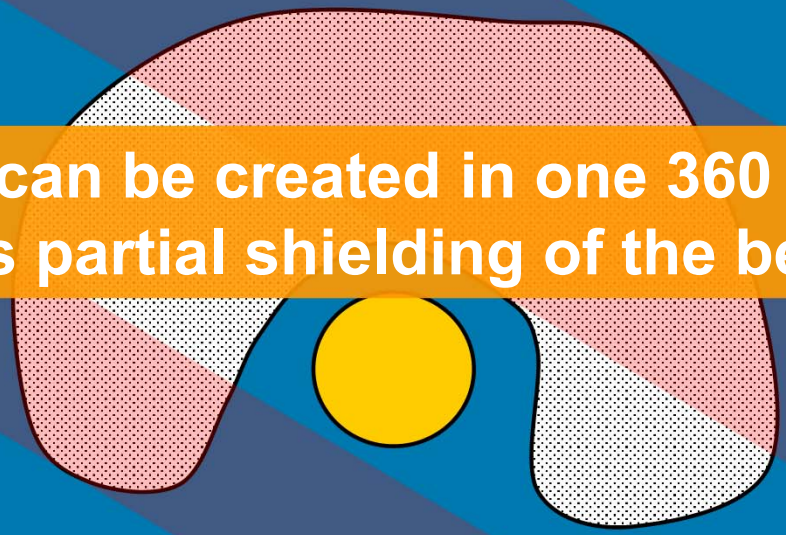
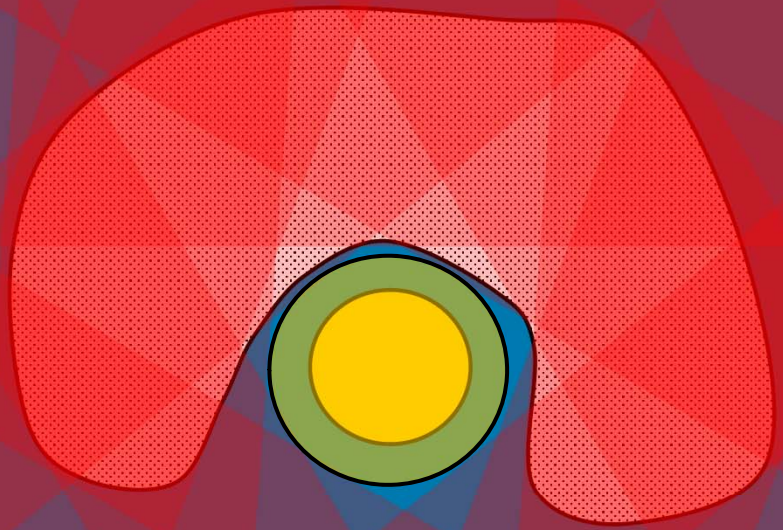
Alternatively:



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

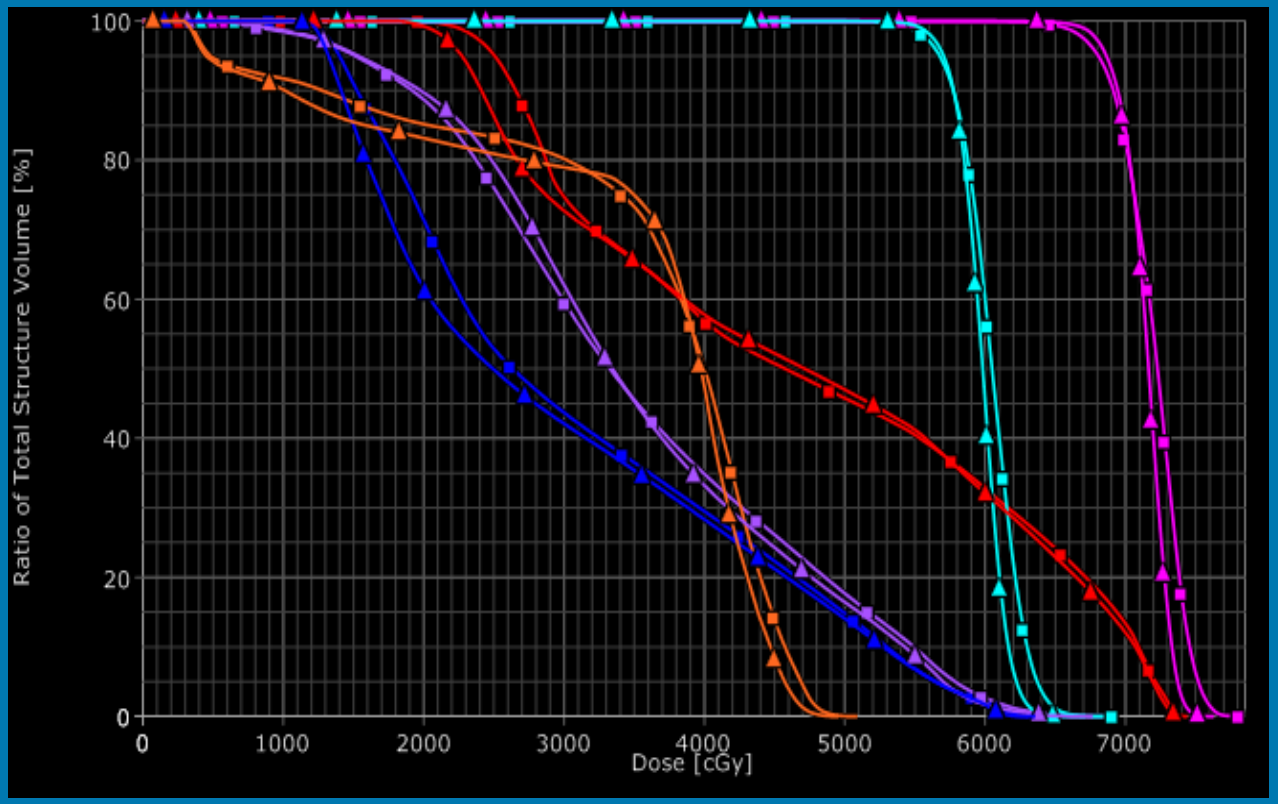
Courstesy of Markus Alber

Alternatively:

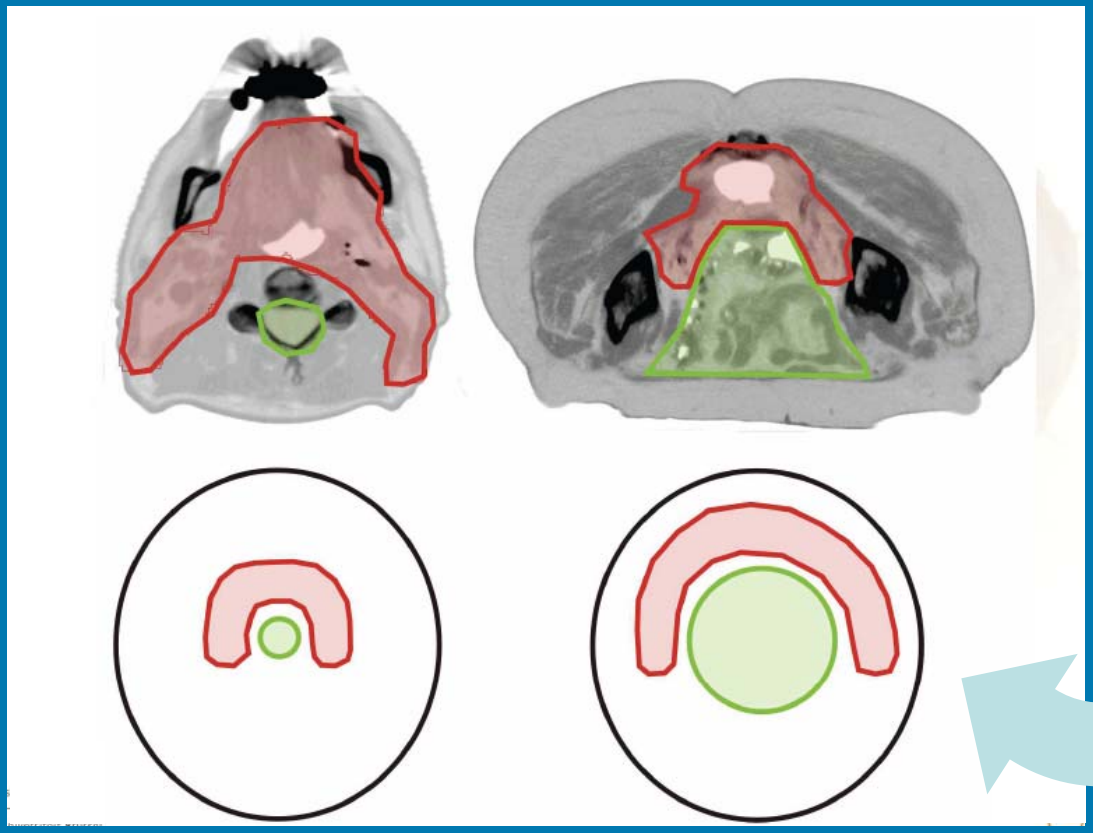


Courstesy of Markus Alber

RapidArc single arc versus double arc

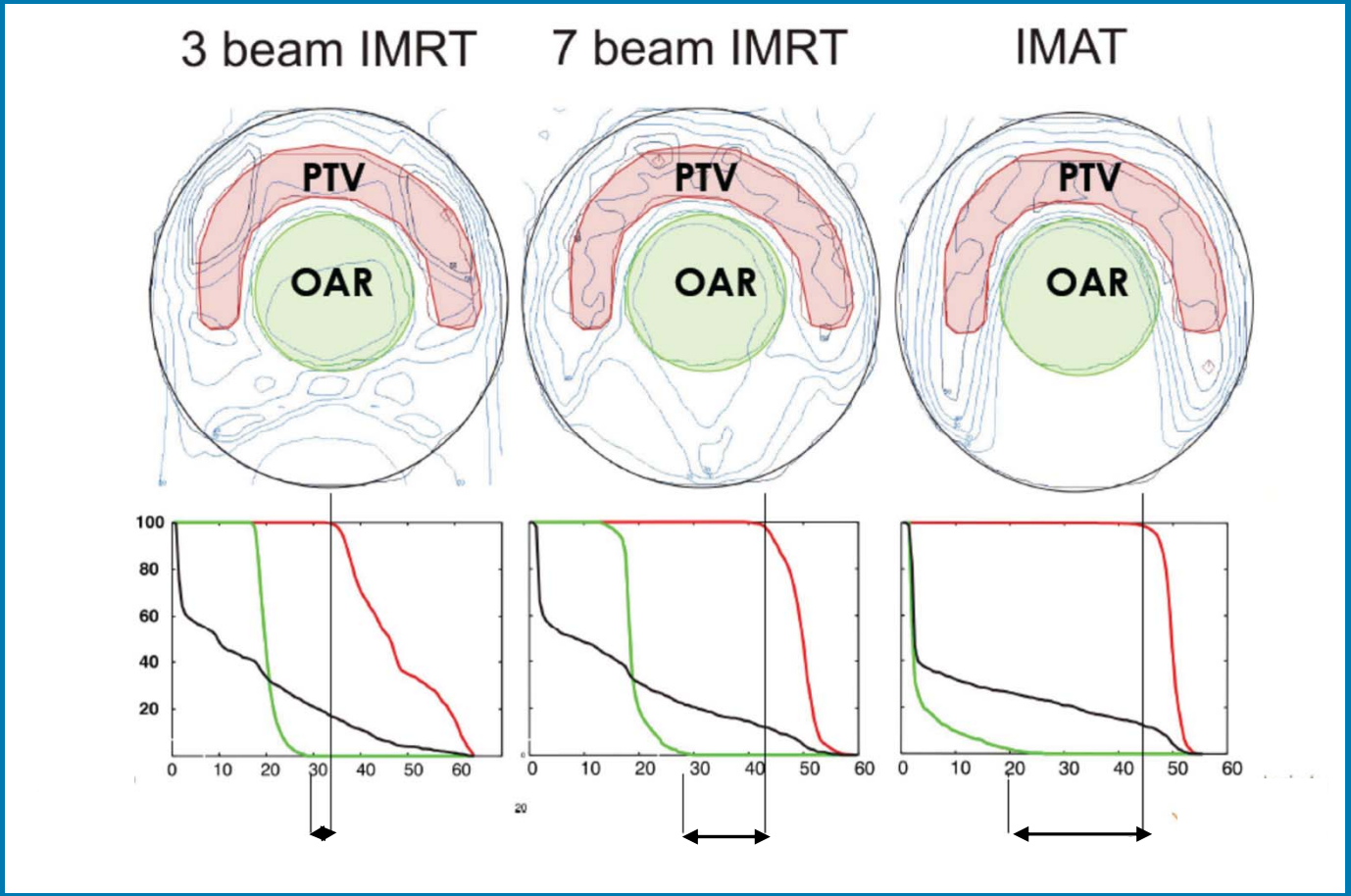


Courtesy of Wilko Verbakel



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

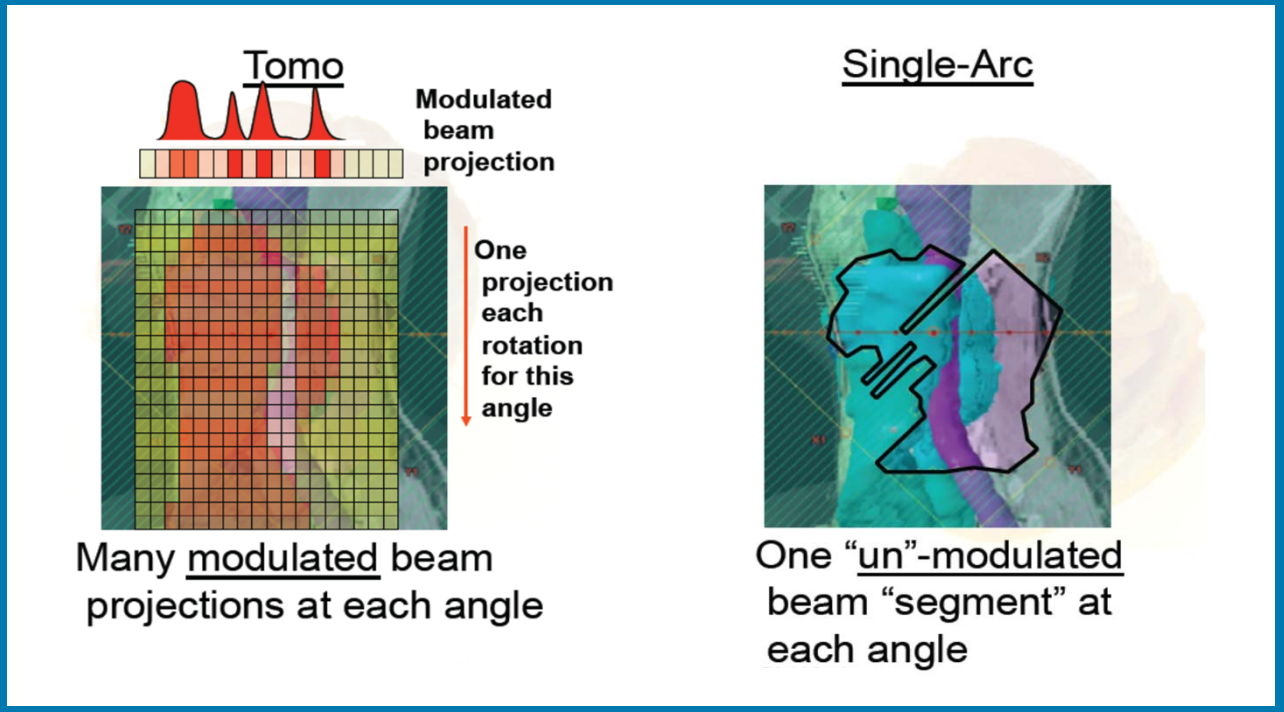
binary leaves

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

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Adaptive radiotherapy

Marcel van Herk

Includes slides by Michael Sharpe and Alan McWilliam

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

geometry-based replan

Two-phase replan

Scholar

About 92,800 results (**0.05** sec)

Articles

Legal documents

Any time
Since 2013
Since 2012
Since 2009
Custom range...

Sort by relevance
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include patents
include citations

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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

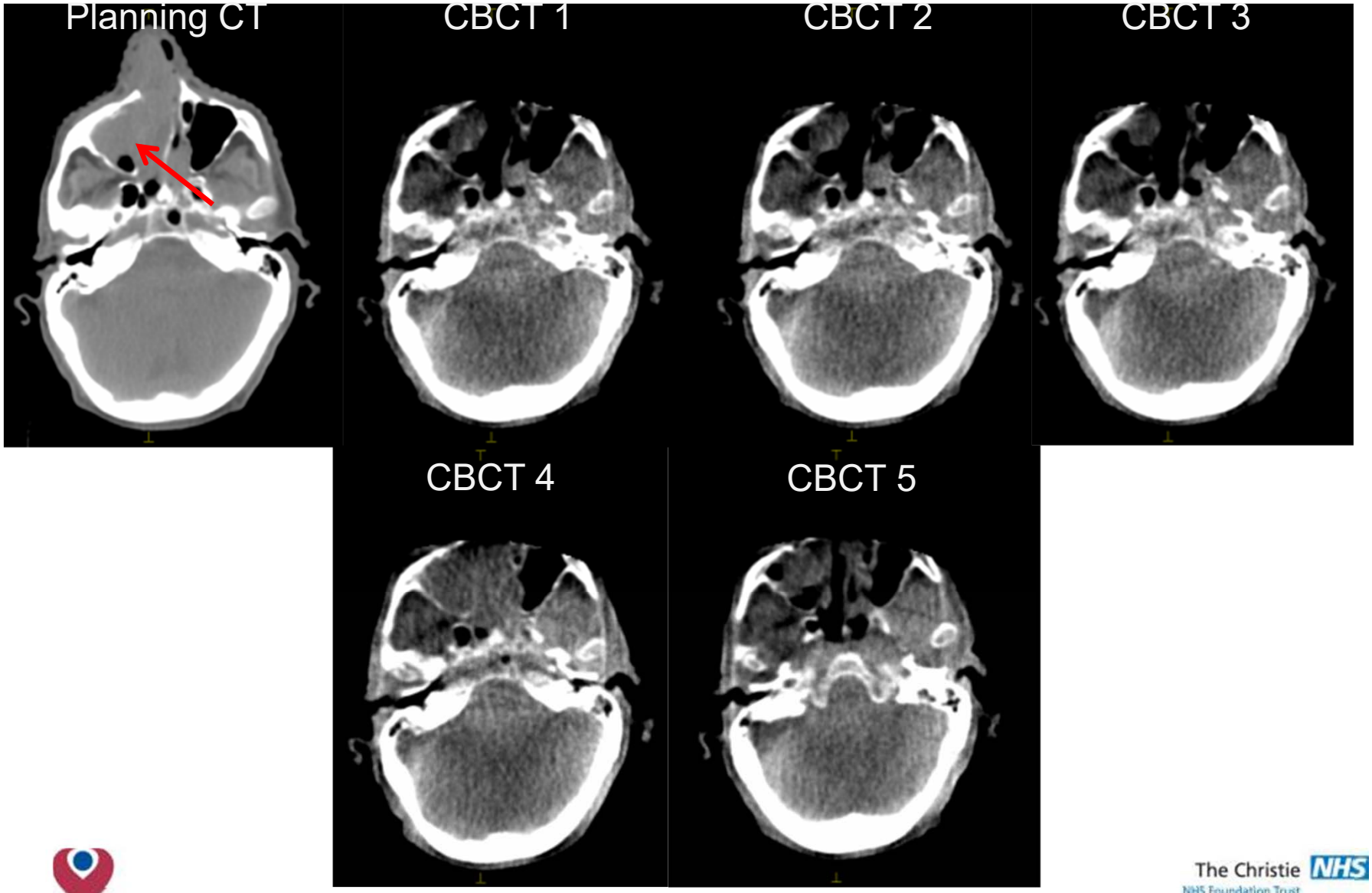
Ad-hoc adaptive radiotherapy

- In the Christie dose is recalculated on CBCT (with density override) based after visual analysis in ~7% of patients
  - mostly lung and H&N

- Actual adaptation in ~1% of patients
  - taking a new CT scan
  - independent new plan

- No special software is used to do this in the clinic – just the planning system

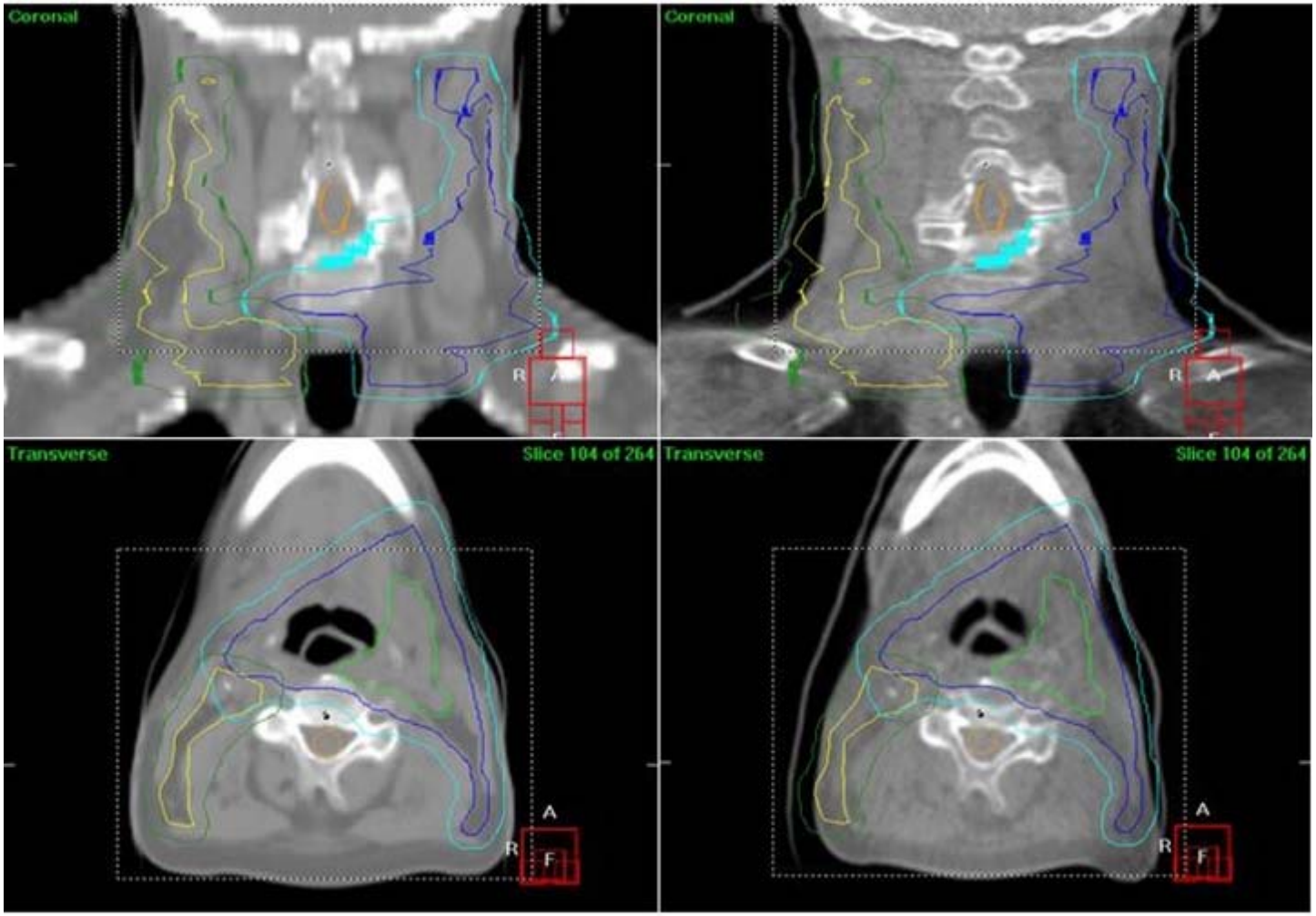
Sinus filling and emptying



The Christie NHS
NHS Foundation Trust

No need for adaptation in photons, but really important in protons

Weight loss in H&N patient



Adaptation can be done to improve delivery,

but also because the mask no longer fits

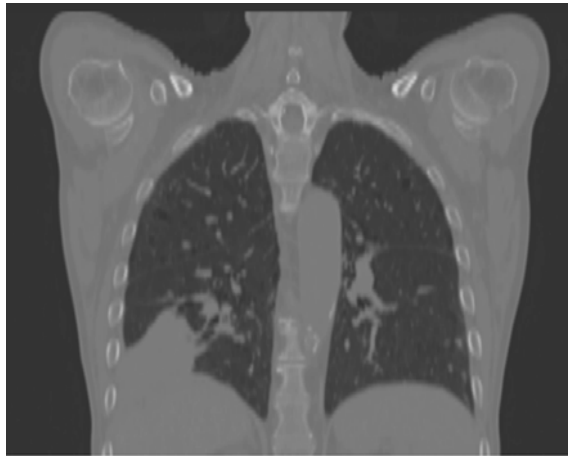
The Christie NHS
NHS Foundation Trust

Software for adaptive RT

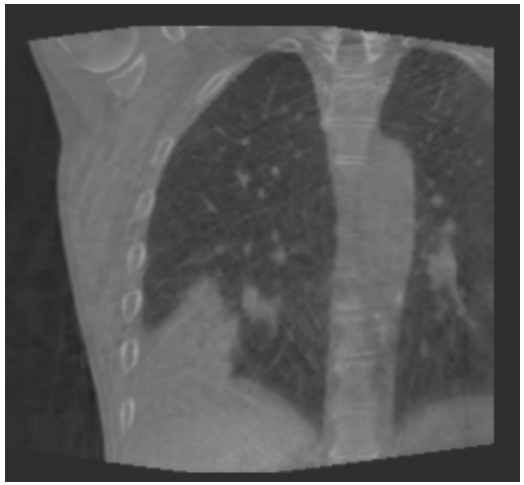
- To fix the HU of CBCT
  - Density override
  - Deform planning CT to CBCT
  - Shading correction based on planning CT

Modify CT to CBCT anatomy

CT



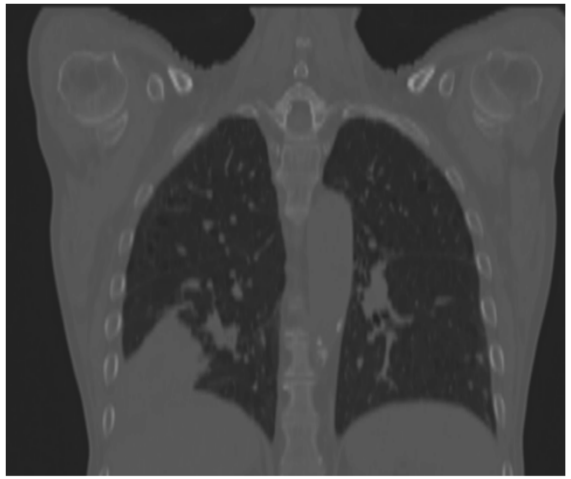
CBCT



Deformable image registration

modified CT (mCT)

(CT numbers + CBCT anatomy)



Make CBCT suitable for dose calculation

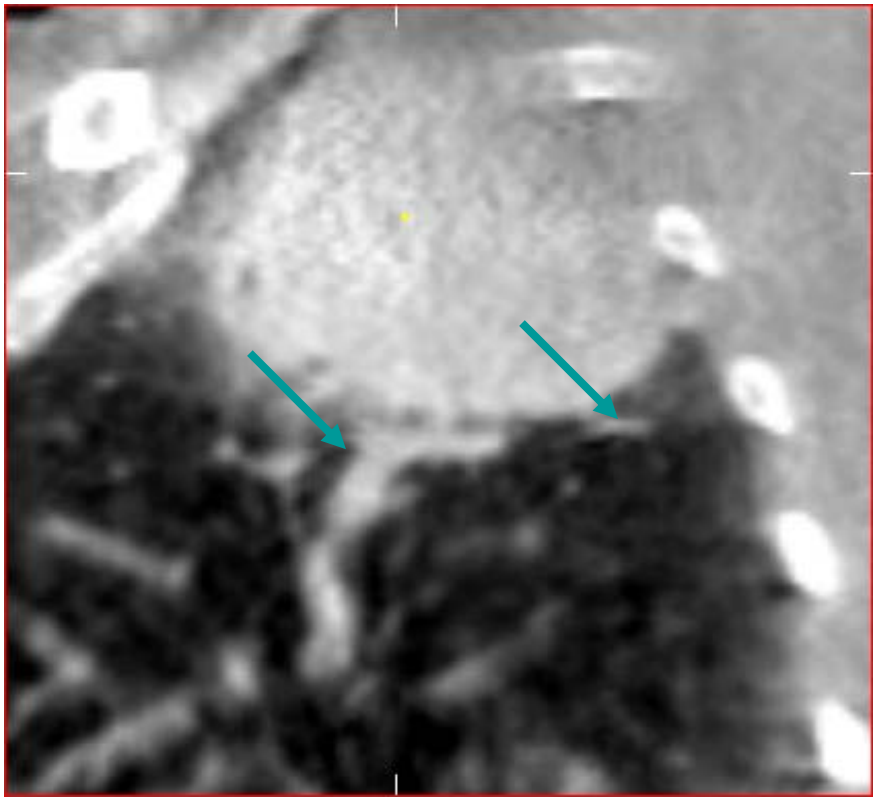
Szeto et al, NK1I 2016

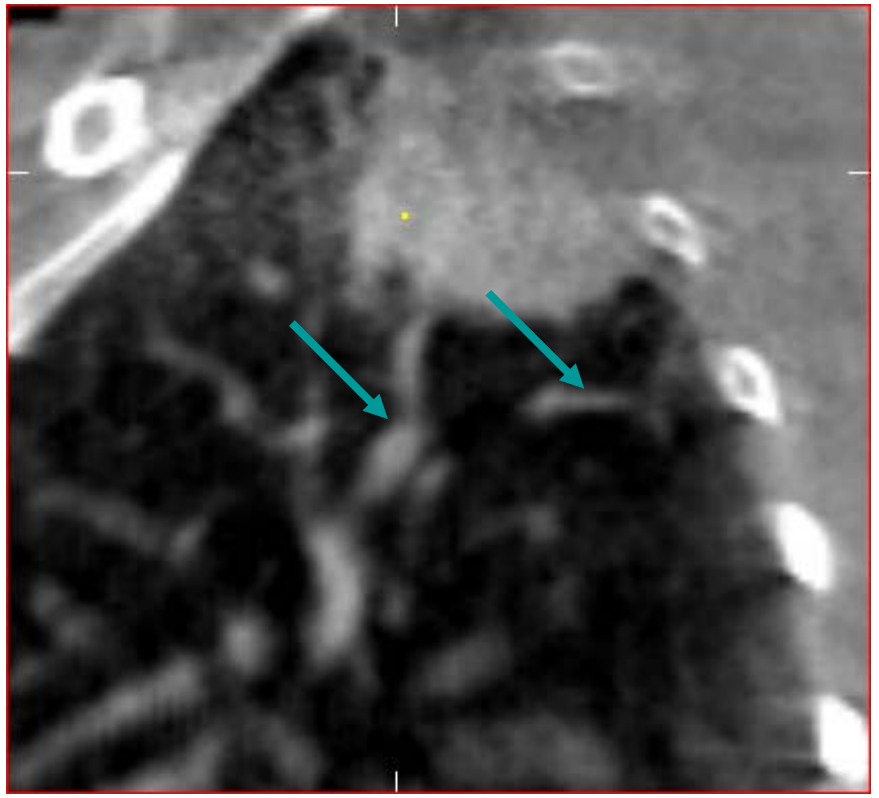
The Christie NHS
NHS Foundation Trust

Contour propagation

- Based on deformable registration between planning CT and repeat CT
- May be useful for OAR contours
    - Editing often needed
- Take extreme care with GTV and CTV contours
    - Use rigid propagation if unsure

Non-elastic tumour regression





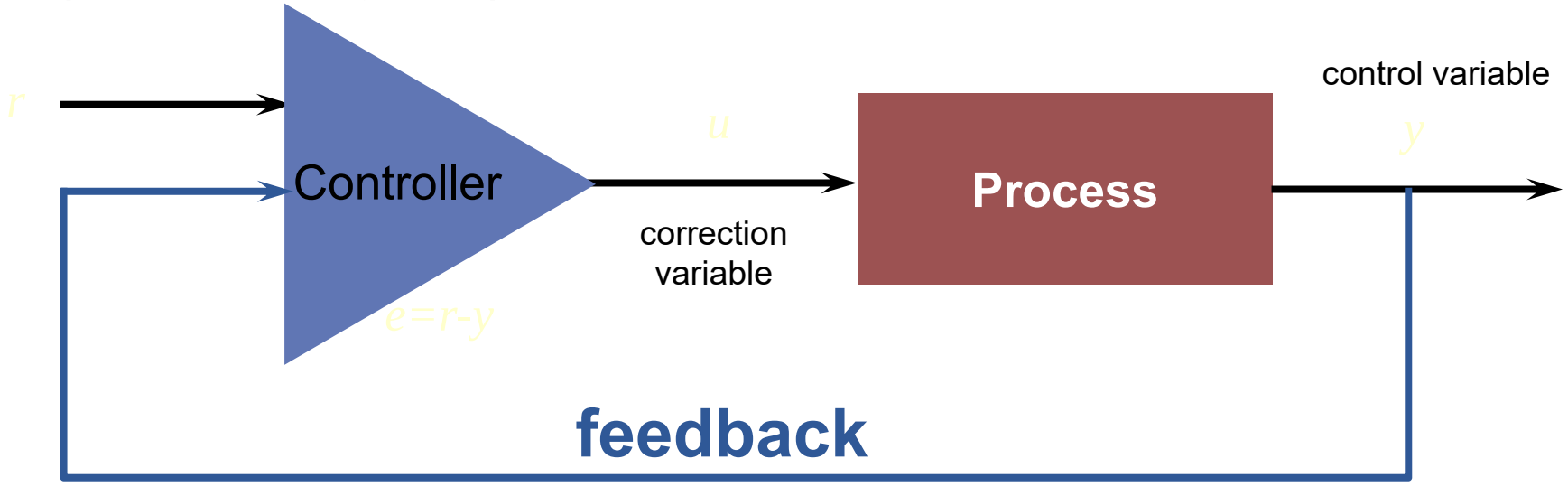
JJ Sonke NKI

The Christie NHS
NHS Foundation Trust

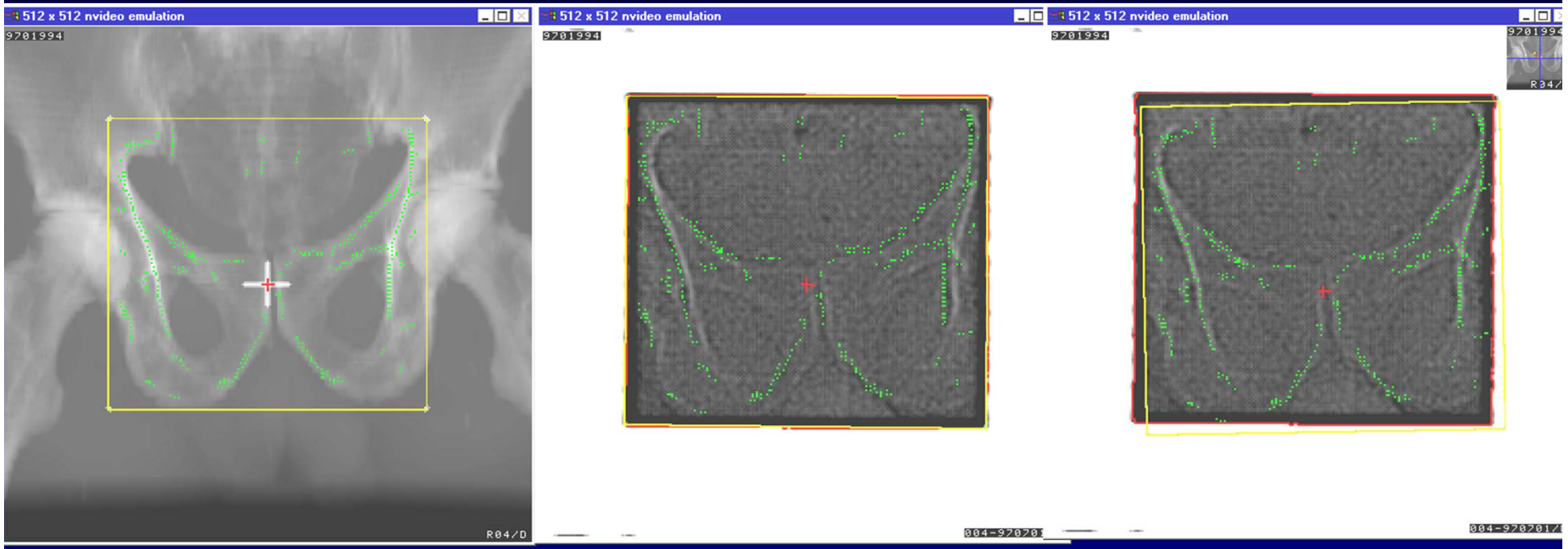
Formal Adaptive Concept

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

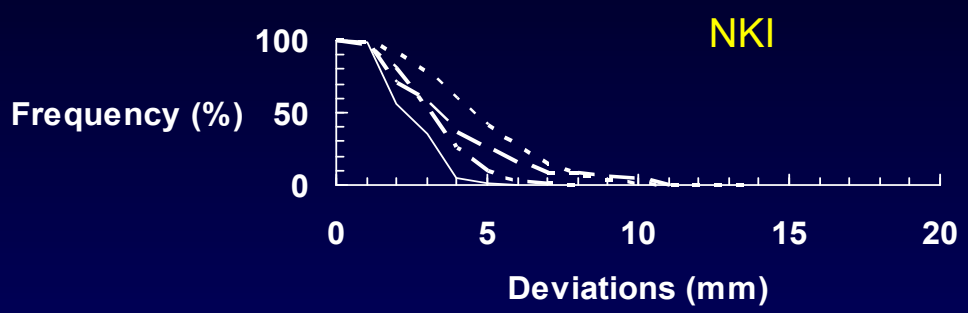
- No corrections (monitoring)
  - Aimed at determining accuracy of clinical practice
- Ad-hoc corrections
  - danger of overcorrection
- Off-line correction protocols
  - Aimed at correcting inter-treatment/systematic errors ← ART
- On-line correction protocols
  - Aimed at correcting day to day variations

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; Bel at el 1997)

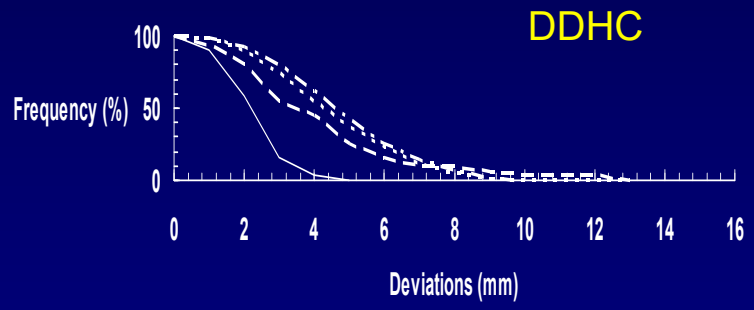


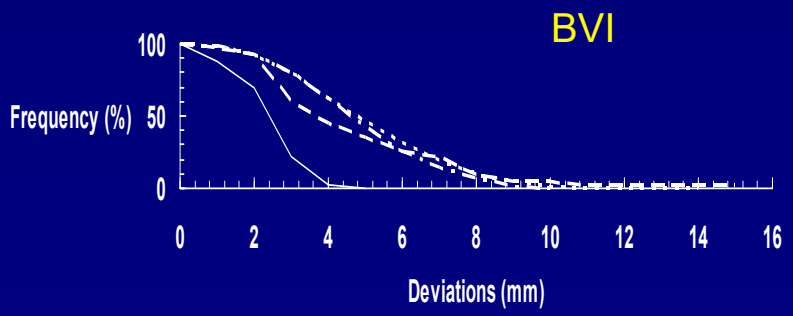
Measured with procedure

Simulation with procedure

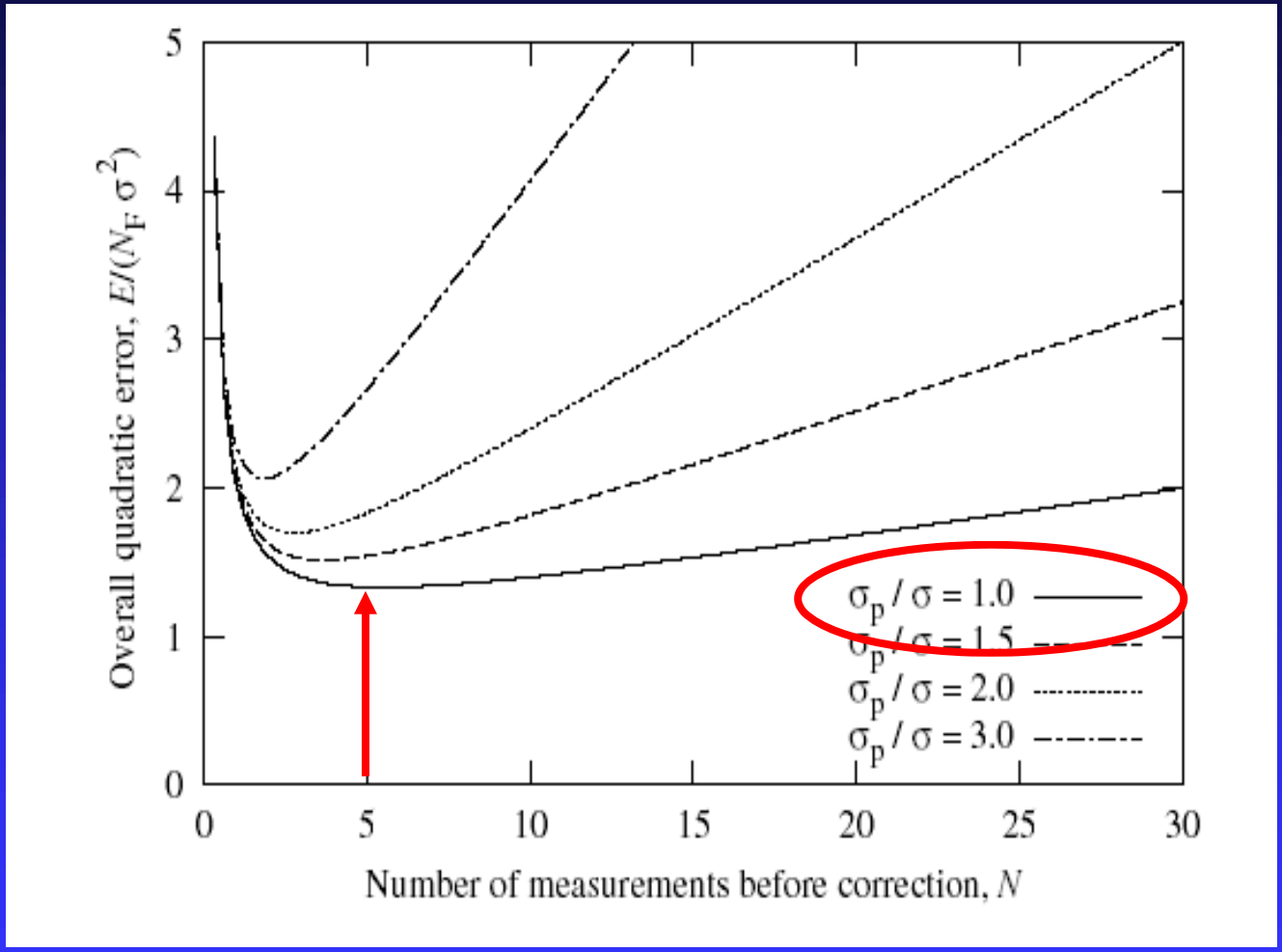
Estimate without procedure

XY (Scatter) 4





When to correct ?



Bortfeld at al, PBM 2002

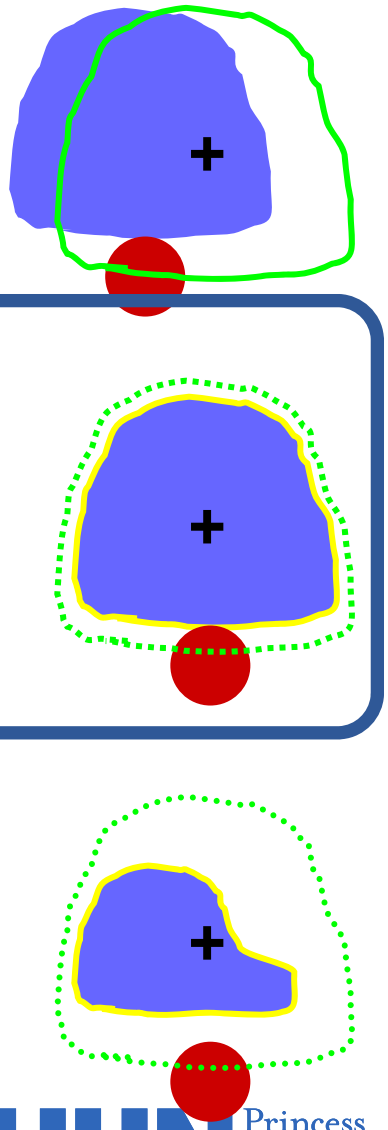
Adaptive Radiation Therapy (Beaumont Strategy)

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.
- 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.



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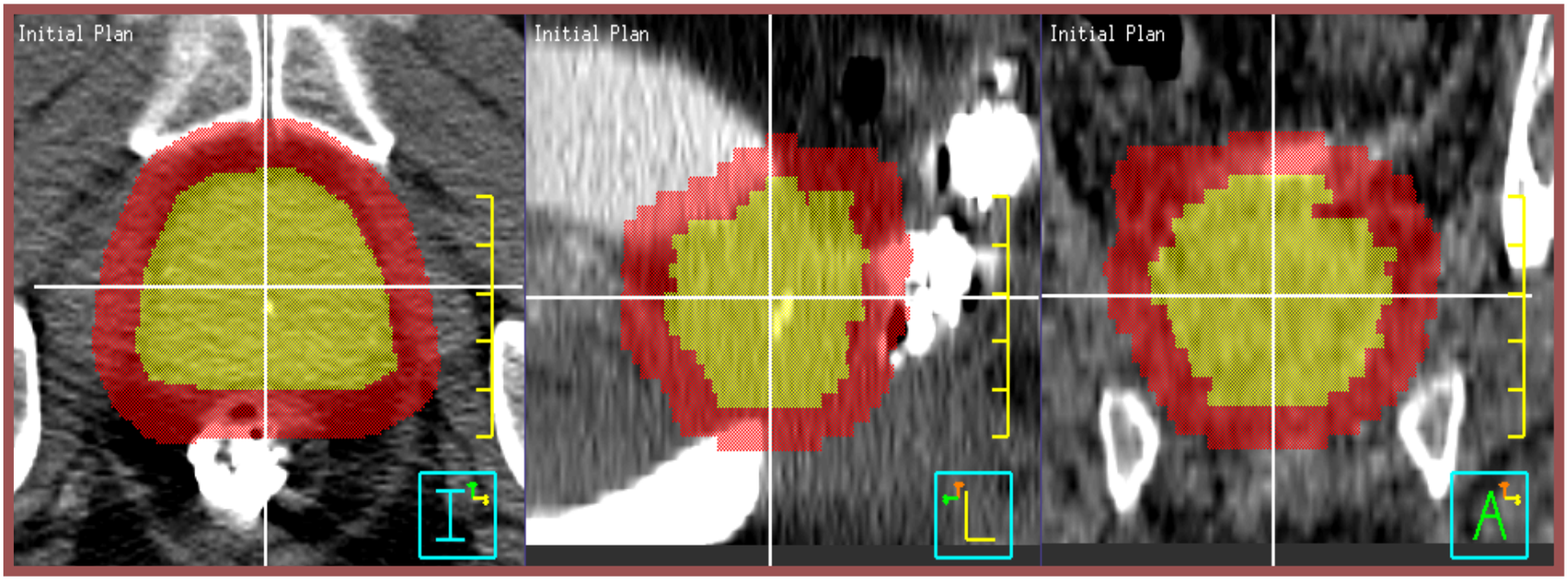
Initial PTV

transverse sagittal coronal



Initial CTV + 10 mm = Initial PTV

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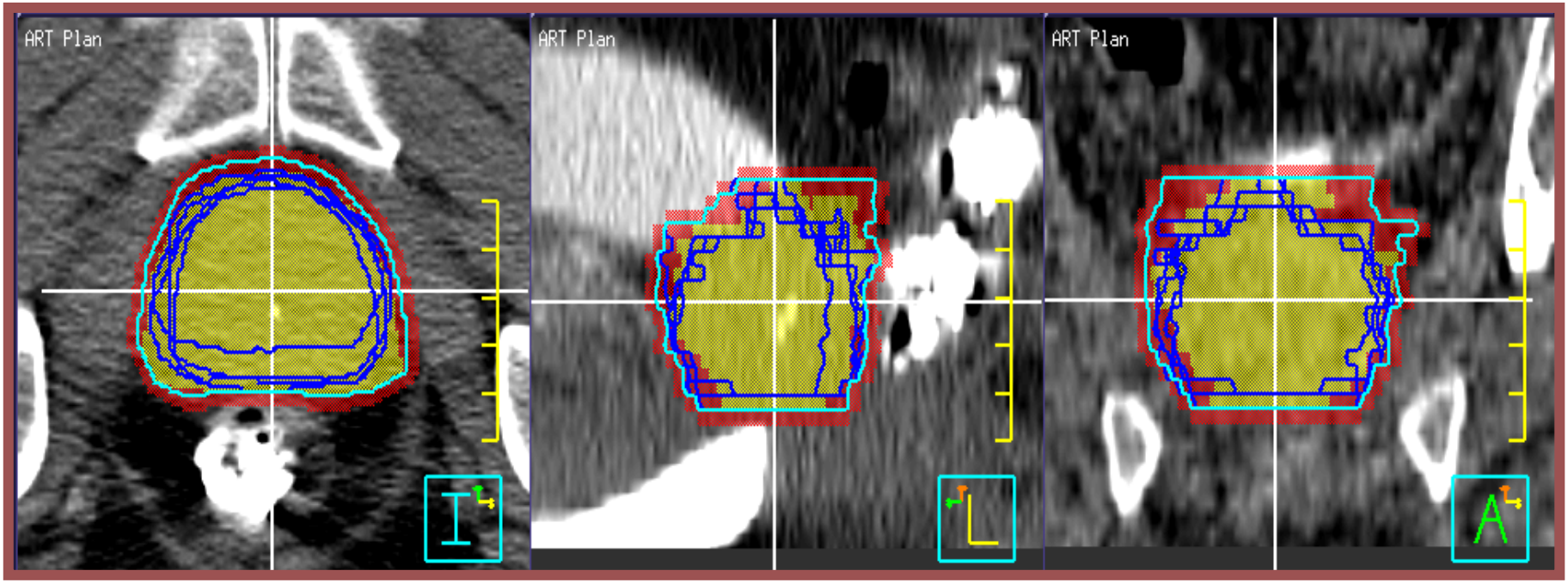
Confidence-Limited PTV (cI-PTV)

transverse sagittal coronal



Initial CTV + 4 CTV_s = ITV (Organ Motion PTV)

ITV + Random Setup Error & Measurement Uncertainty = cI-PTV

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Volume Difference: PTV vs cI-PTV

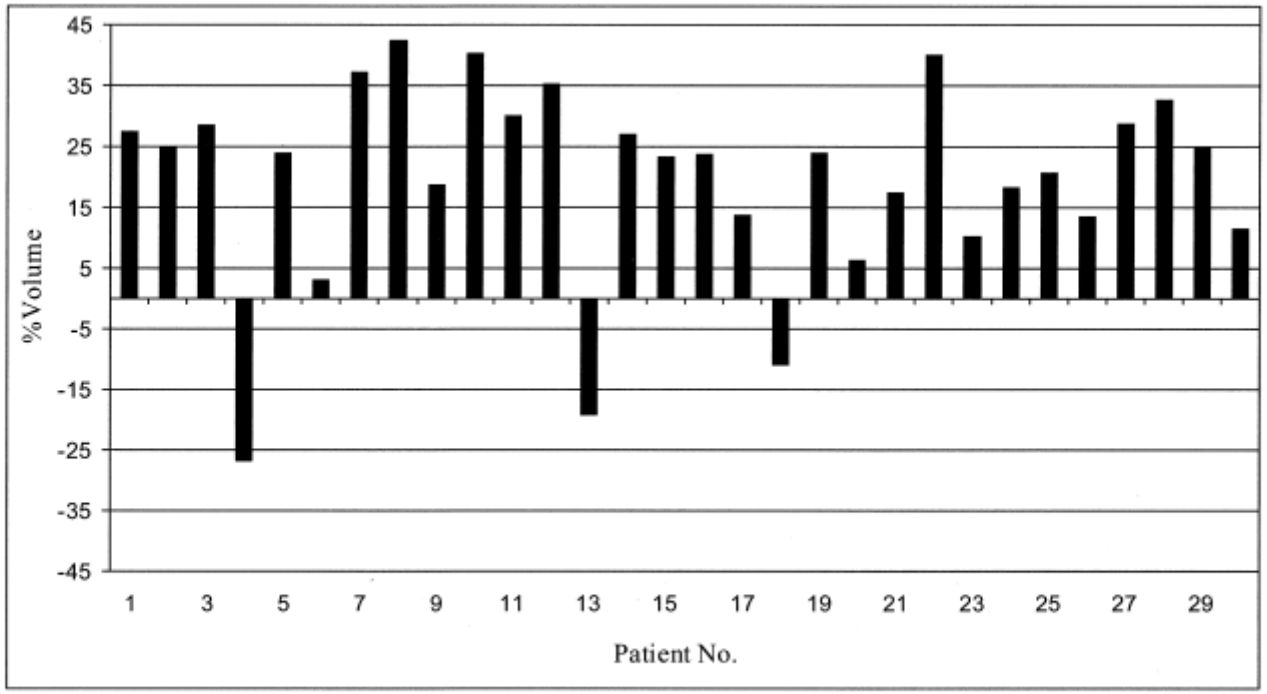

Fig. 5. Distribution of % volume difference between the generic planning target volume (PTV) and the patient-specific confidence-limited planning target volume (cI-PTV, normalizing to the generic PTV).

Martinez, Yan *et al* IJROBP 50, 1226–1234, 2001

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Initial PTV & cI-PTV Do NOT Overlap

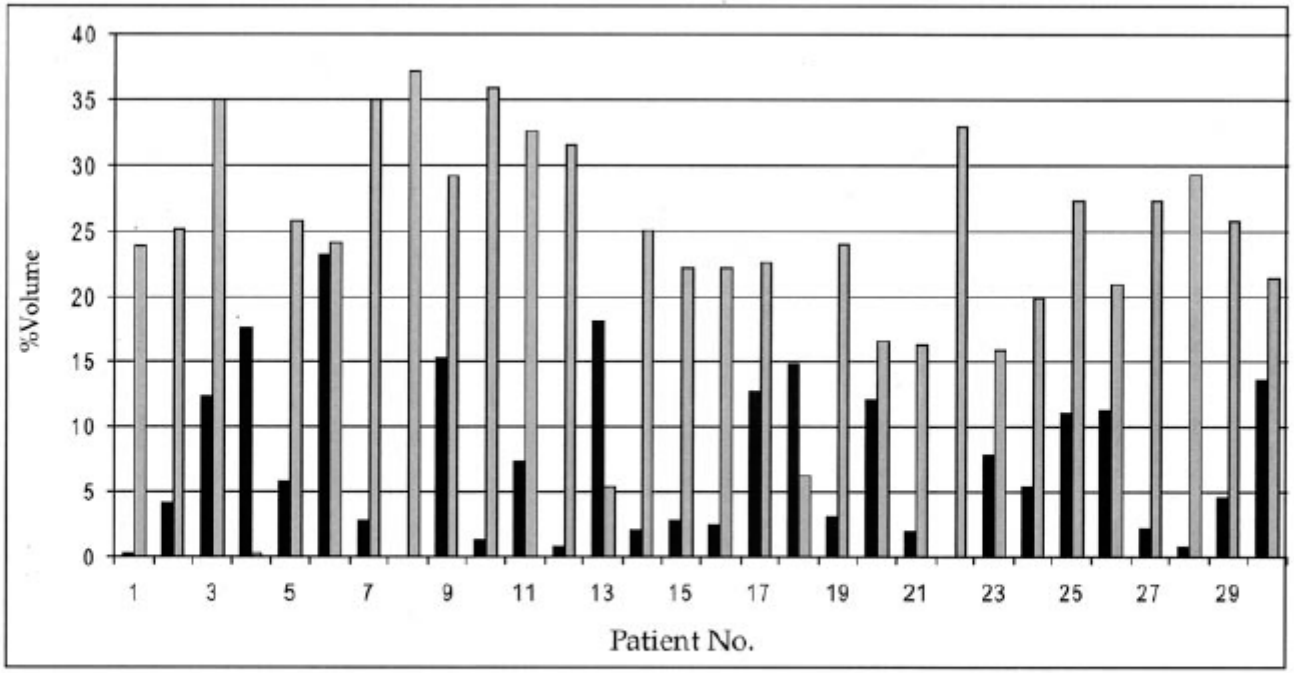

Fig. 6. Solid bars represent the % volume in the confidence-limited planning target volume (cl-PTV) but not in the generic PTV (normalizing to the cl-PTV). The shaded bars represent the % volume in the generic PTV but not in the cl-PTV (normalizing to the generic PTV).

Martinez, Yan *et al* IJROBP 50, 1226–1234, 2001

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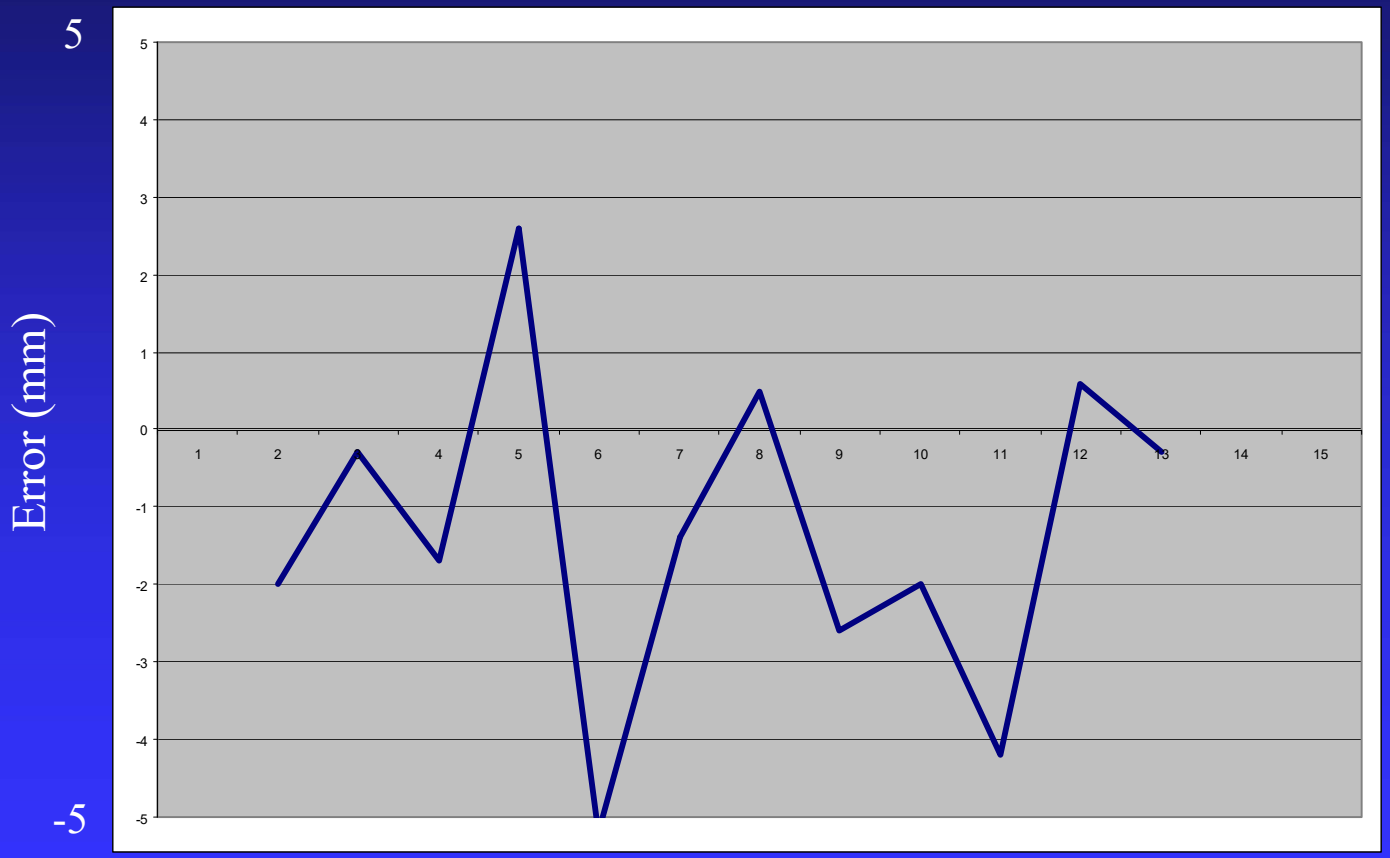
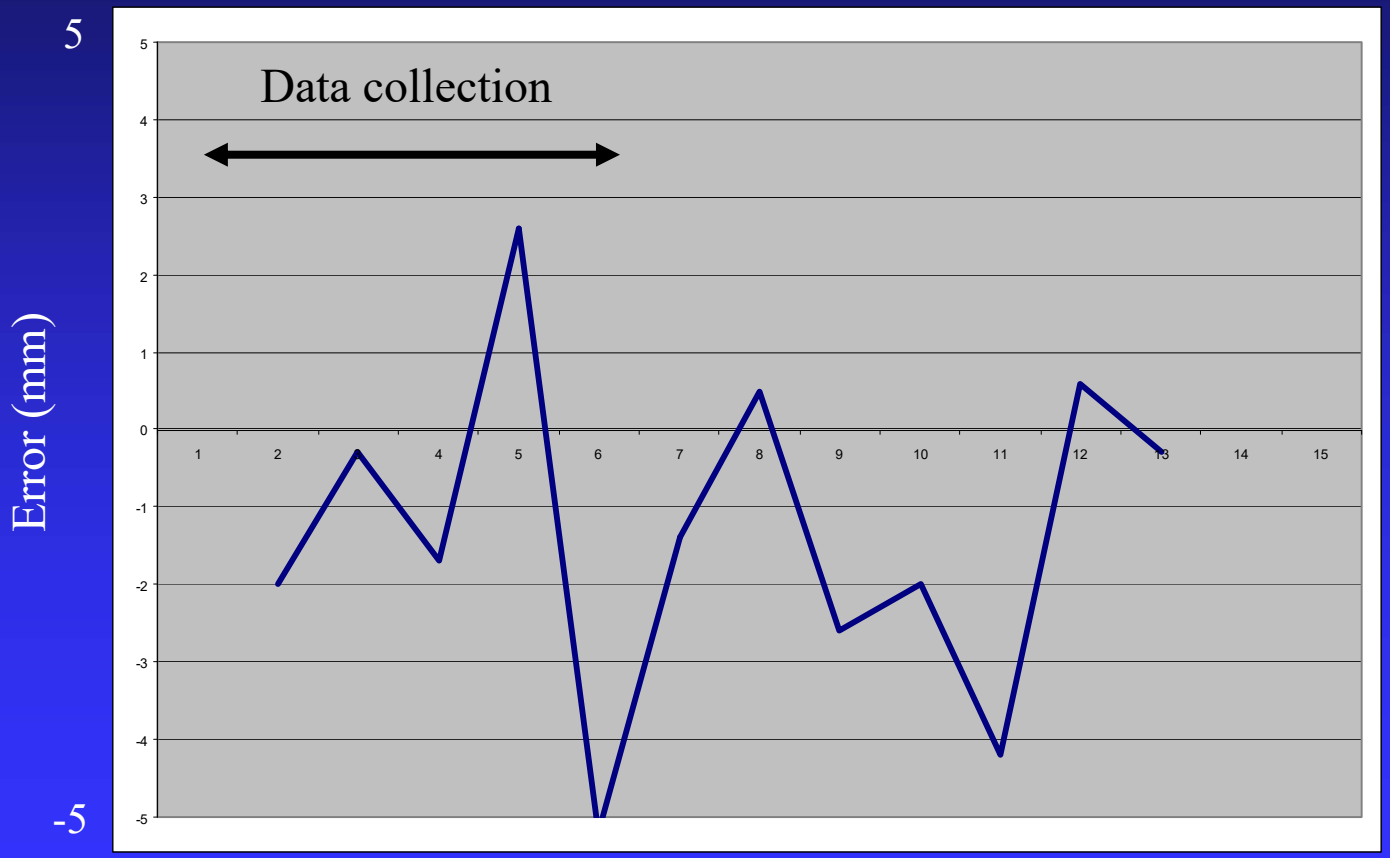
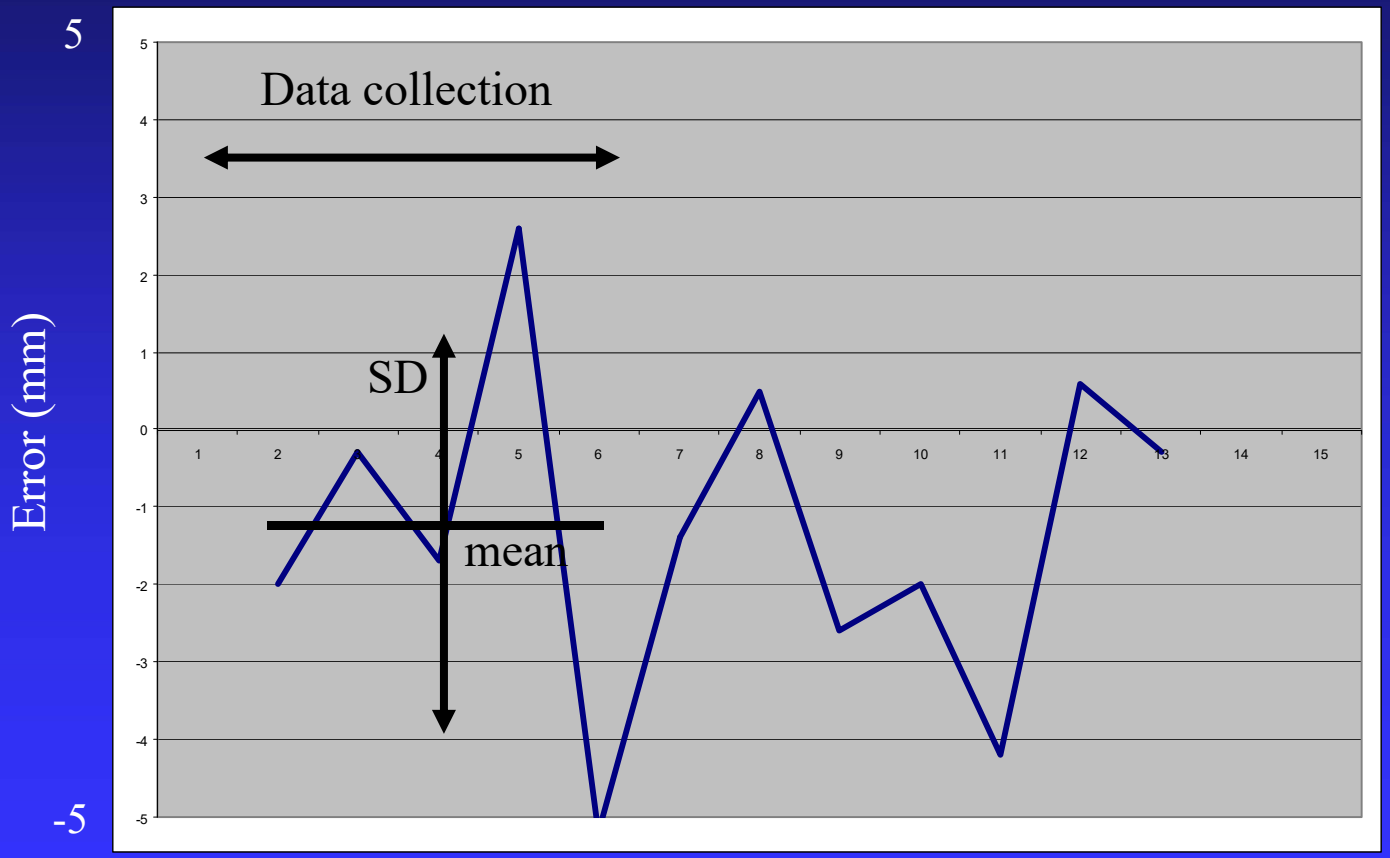
Reality check: example setup error pattern



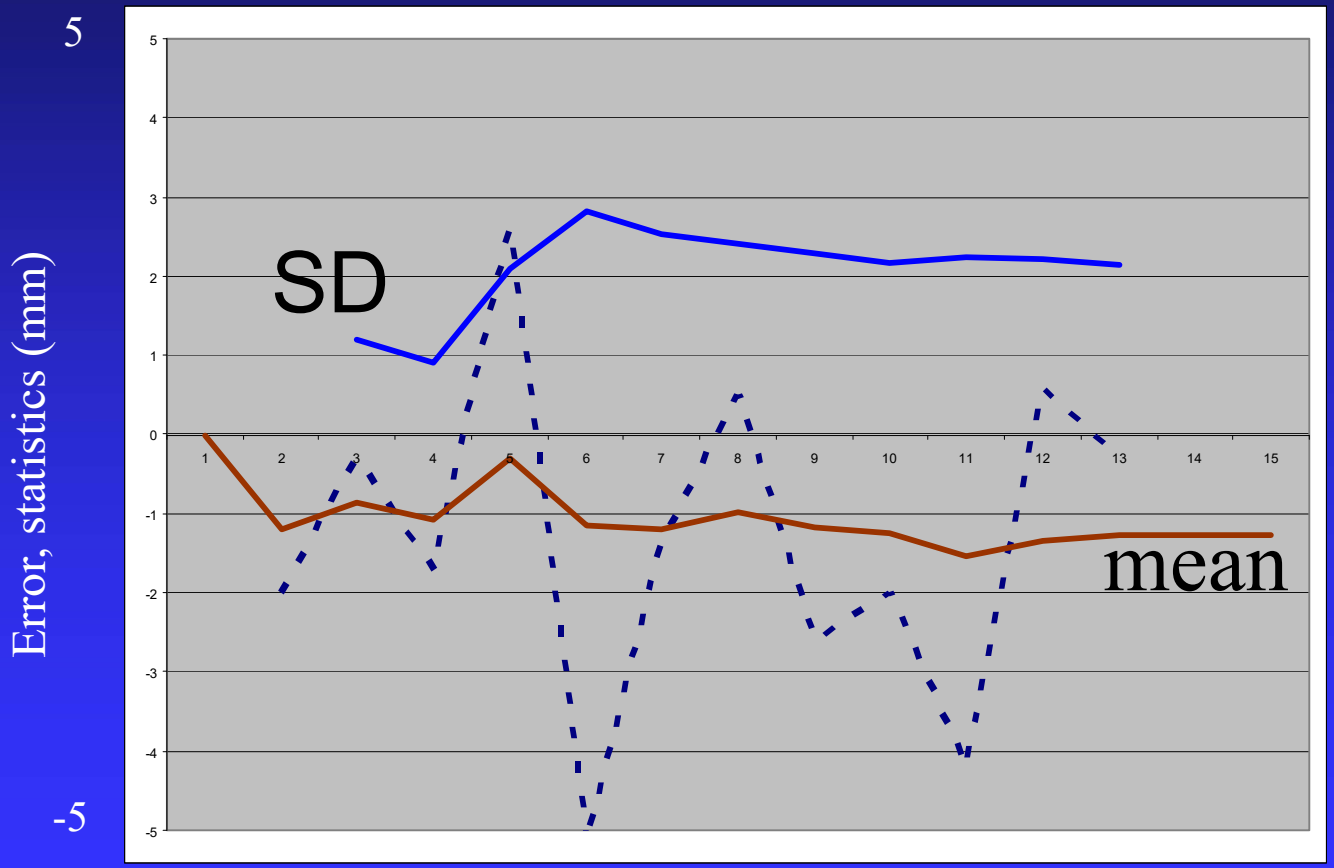
Adaptive radiotherapy



Adaptive radiotherapy (naïve summary after 5 fractions)

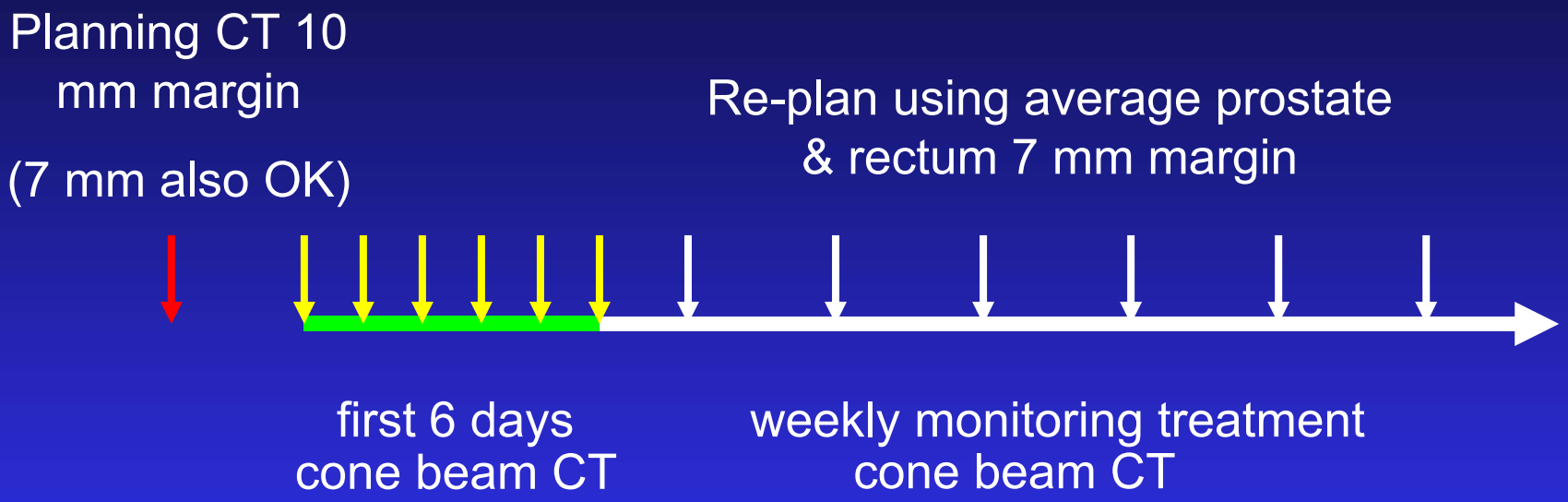


Naïve running estimates



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)*:

Identical results (good target coverage and rectum sparing) for:

Average prostate + 7 mm ← chosen

Convex hull of all prostates + 4 mm

Nuver et al, IJROPB 2007

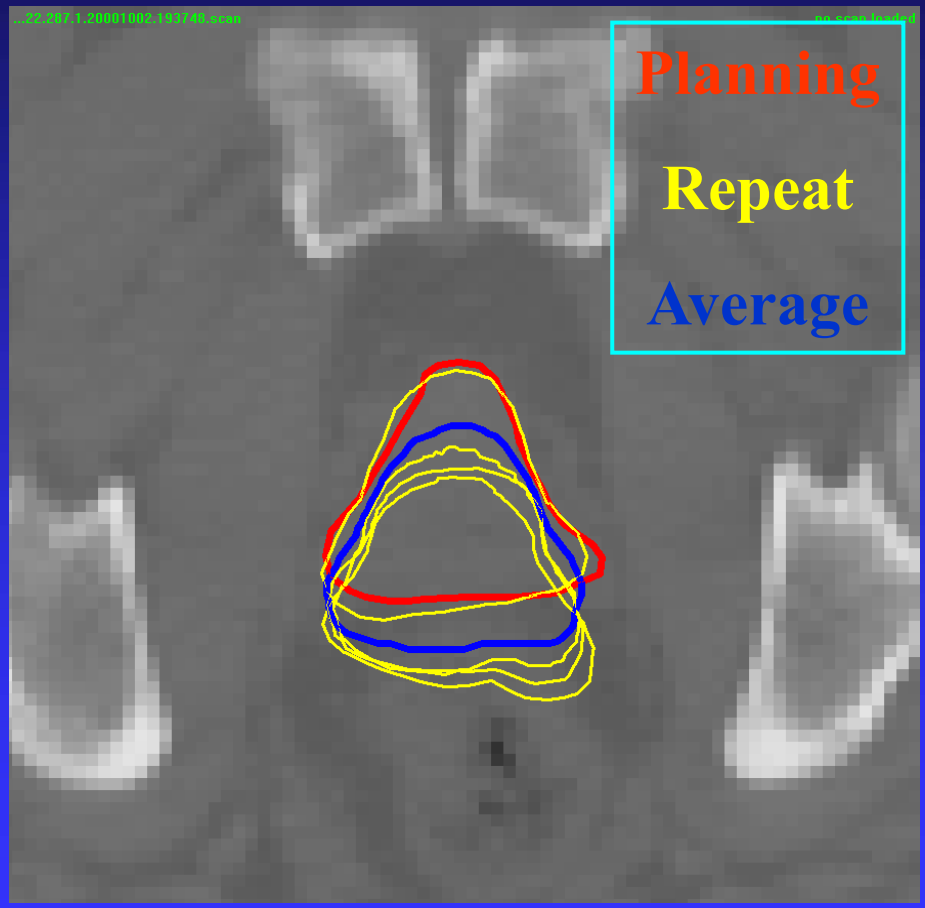
Methods: average prostate

- Plan → CBCT1: T1/R1
- Plan → CBCT2: T2/R2
- …
- Plan → CBCT6: T6/R6

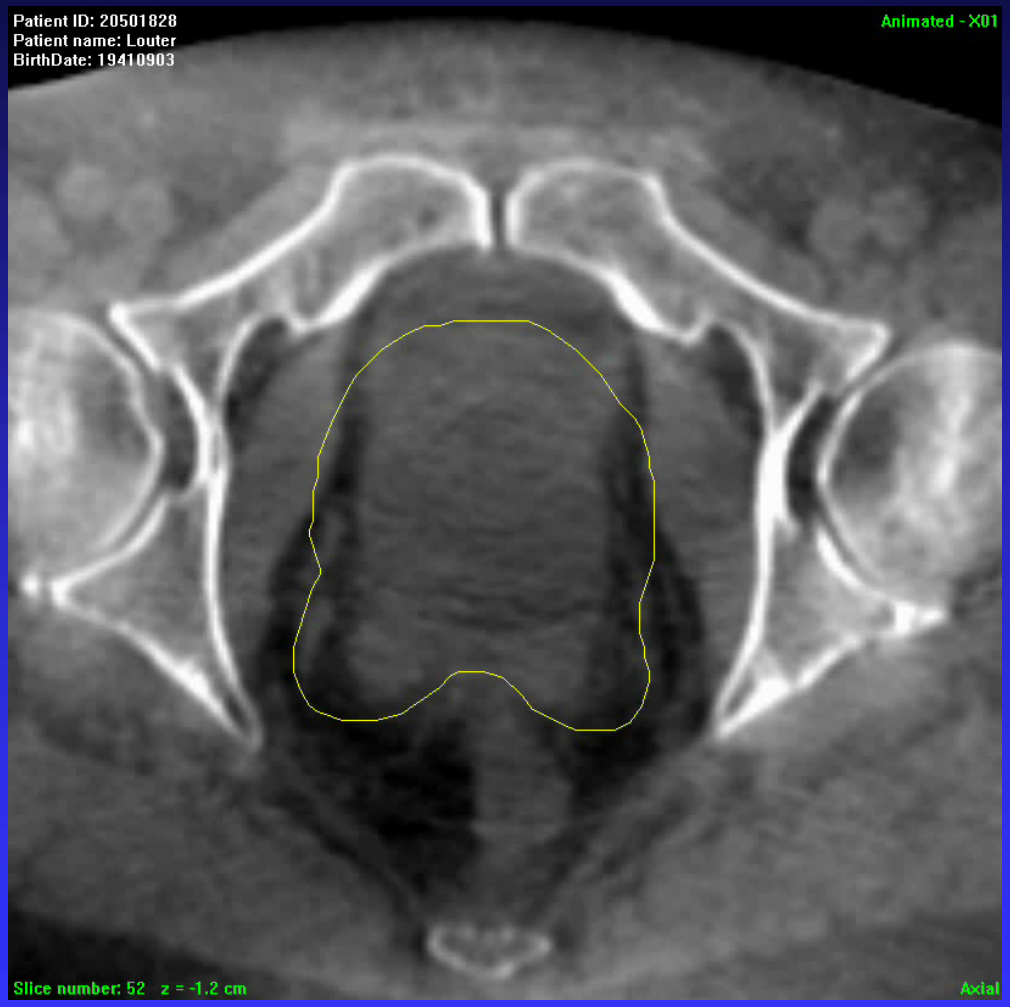
T_{AVG} / R_{AVG}

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

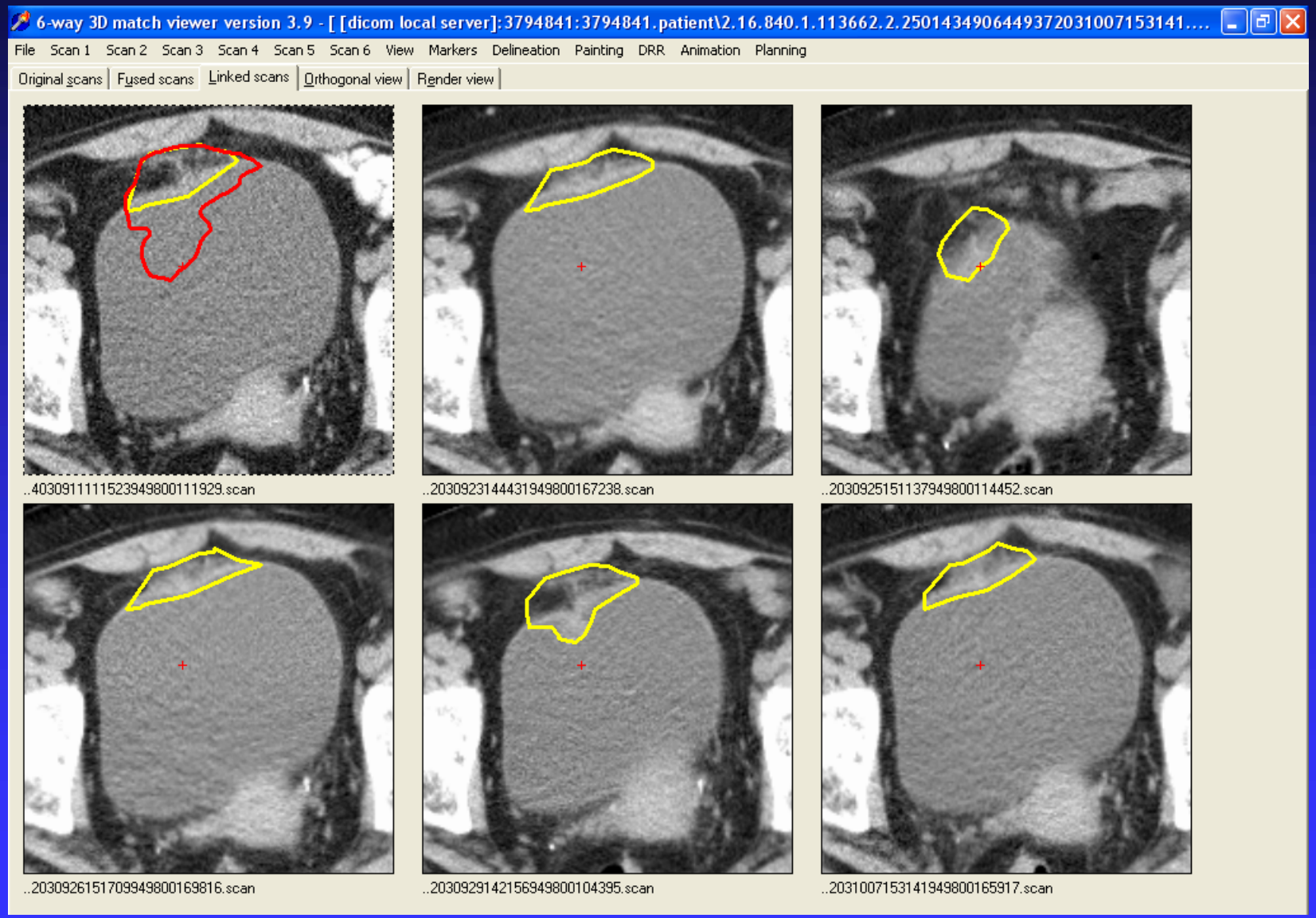
Results

- 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

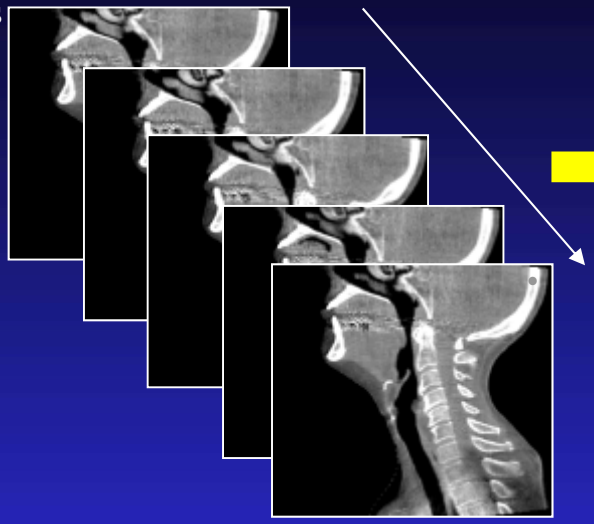
ART for bladder cancer: GTV_{1-6} construction



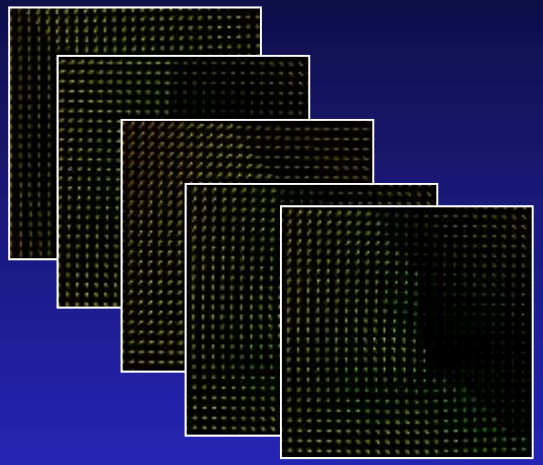
Pos et al 2005

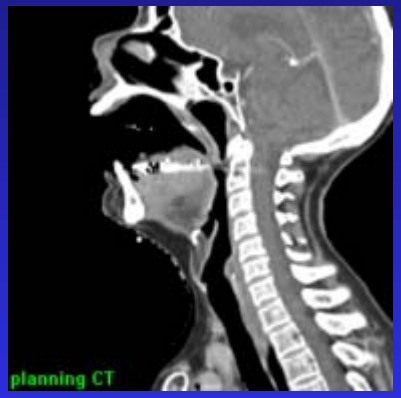
Adaptive replanning on average anatomy

- daily CBCTs

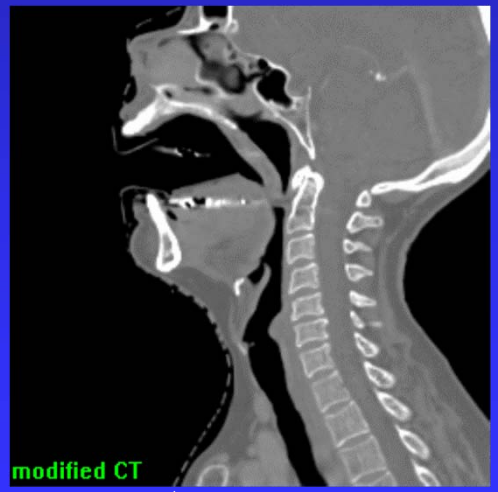


- deformation vector fields

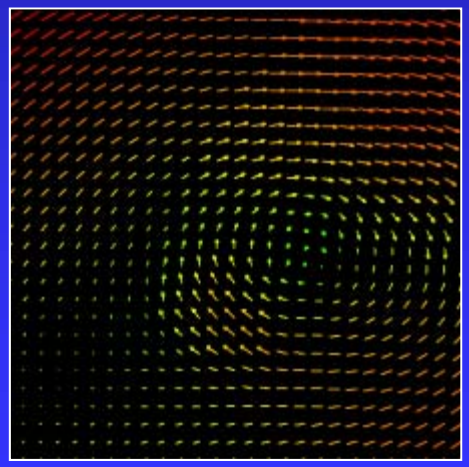




- Planning CT



- Average anatomy



- systematic deformations

Kranen et al, IJROBP 2016

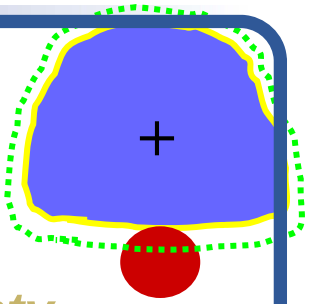
Benefits of Daily IG-IMRT

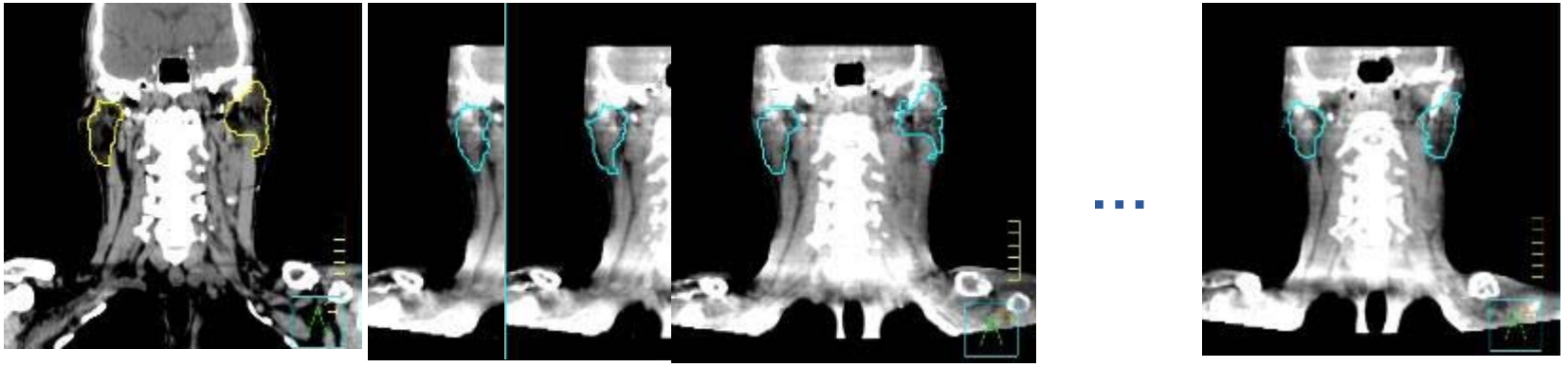
Accuracy

Reduce
Systematic uncertainty

Precision

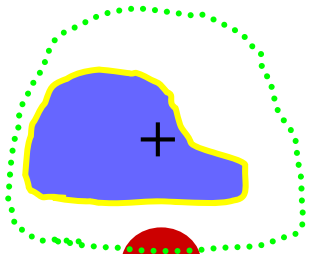
Match PTV to
random uncertainty





Adaptation

Assess anatomical
changes & update plan



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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.


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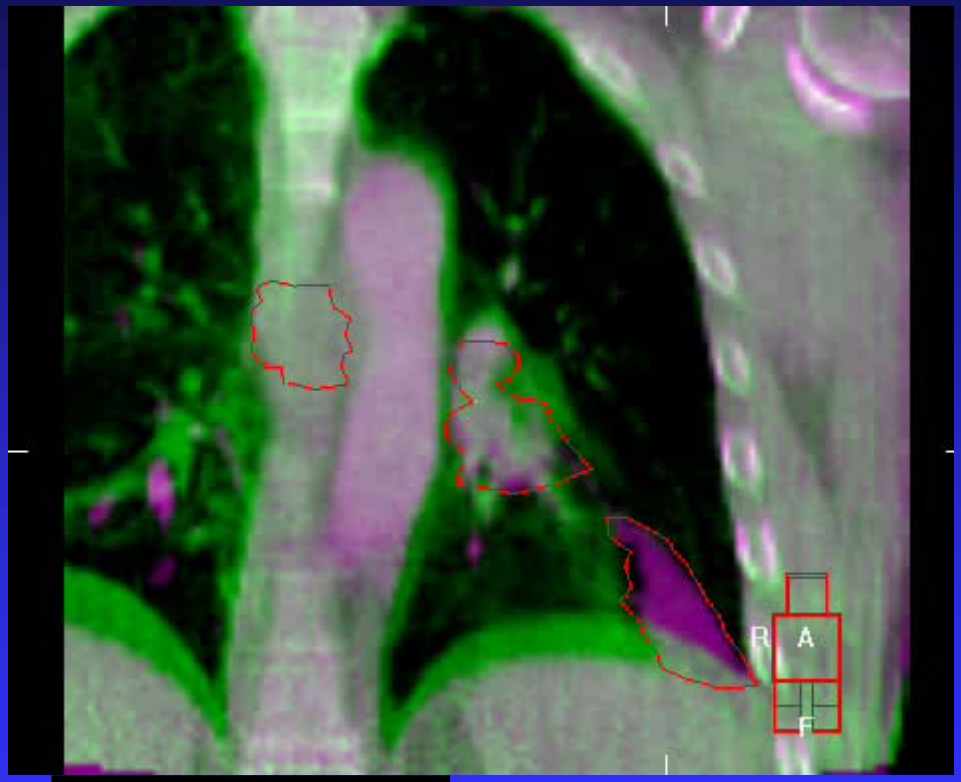
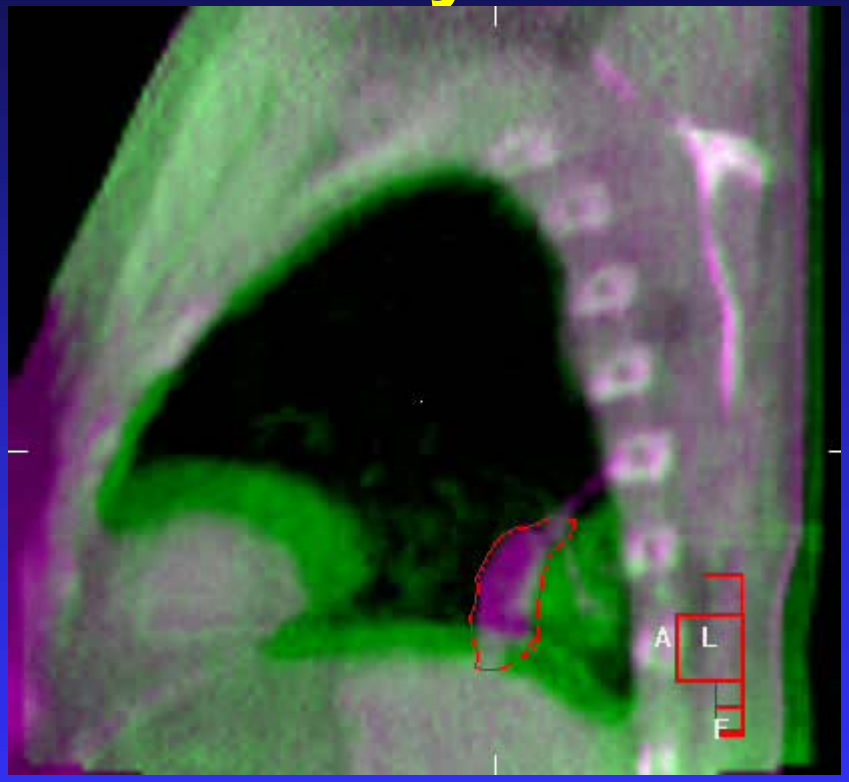
Differential Variability





Planning CT

4D-CBCT

CTV

No couch correction can solve this problem

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

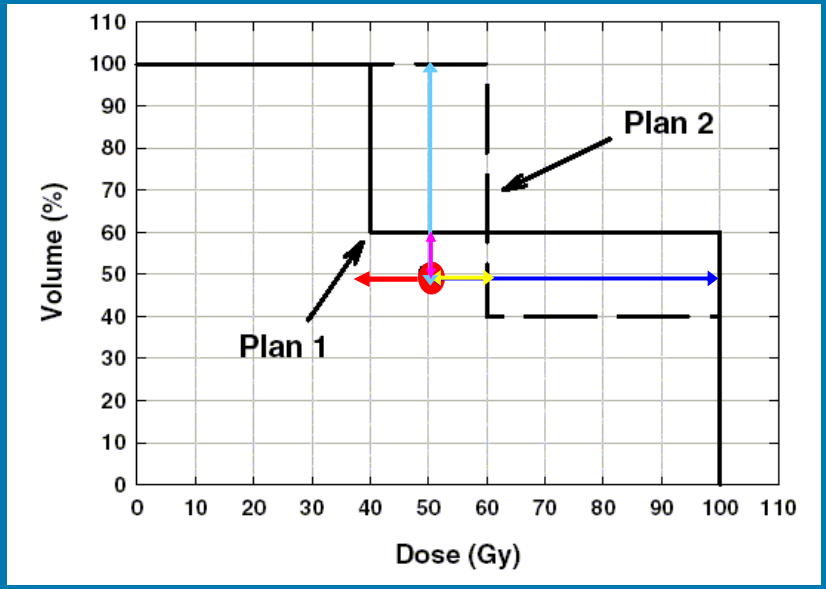
- Quadratic dose difference may not reflect clinical objective
- Properly ranking plans based on dose-volume objectives may fail

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

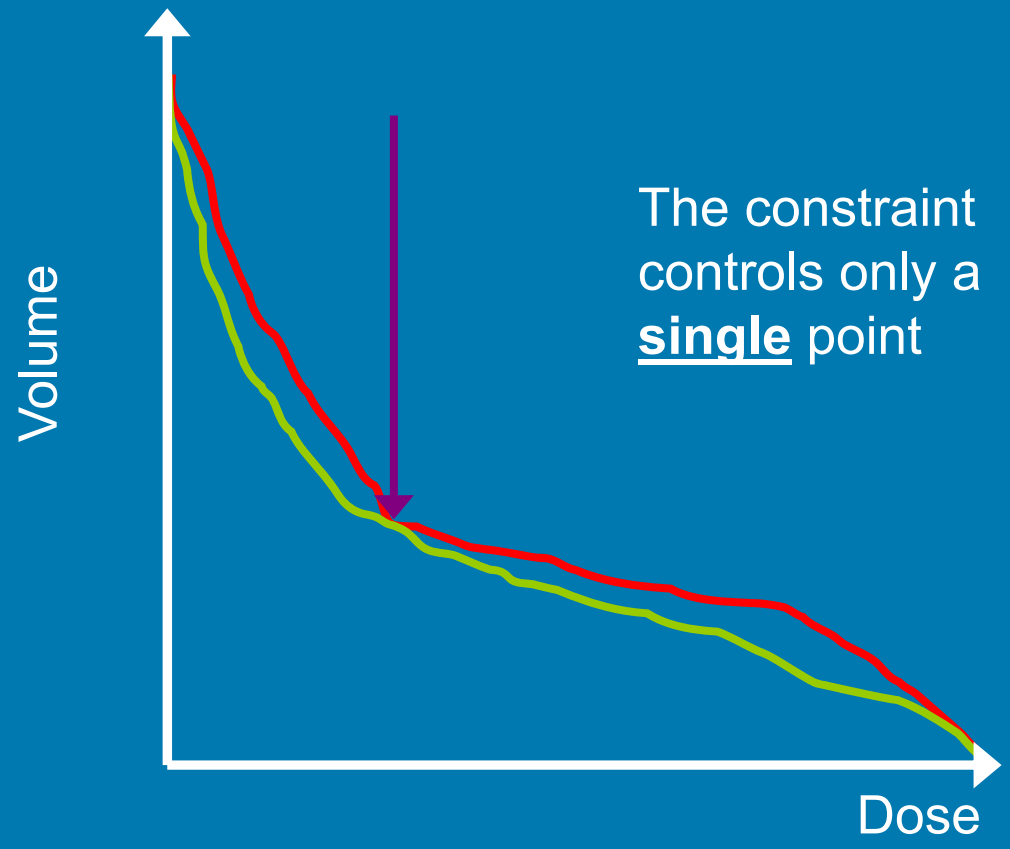
Physical optimisations

- 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

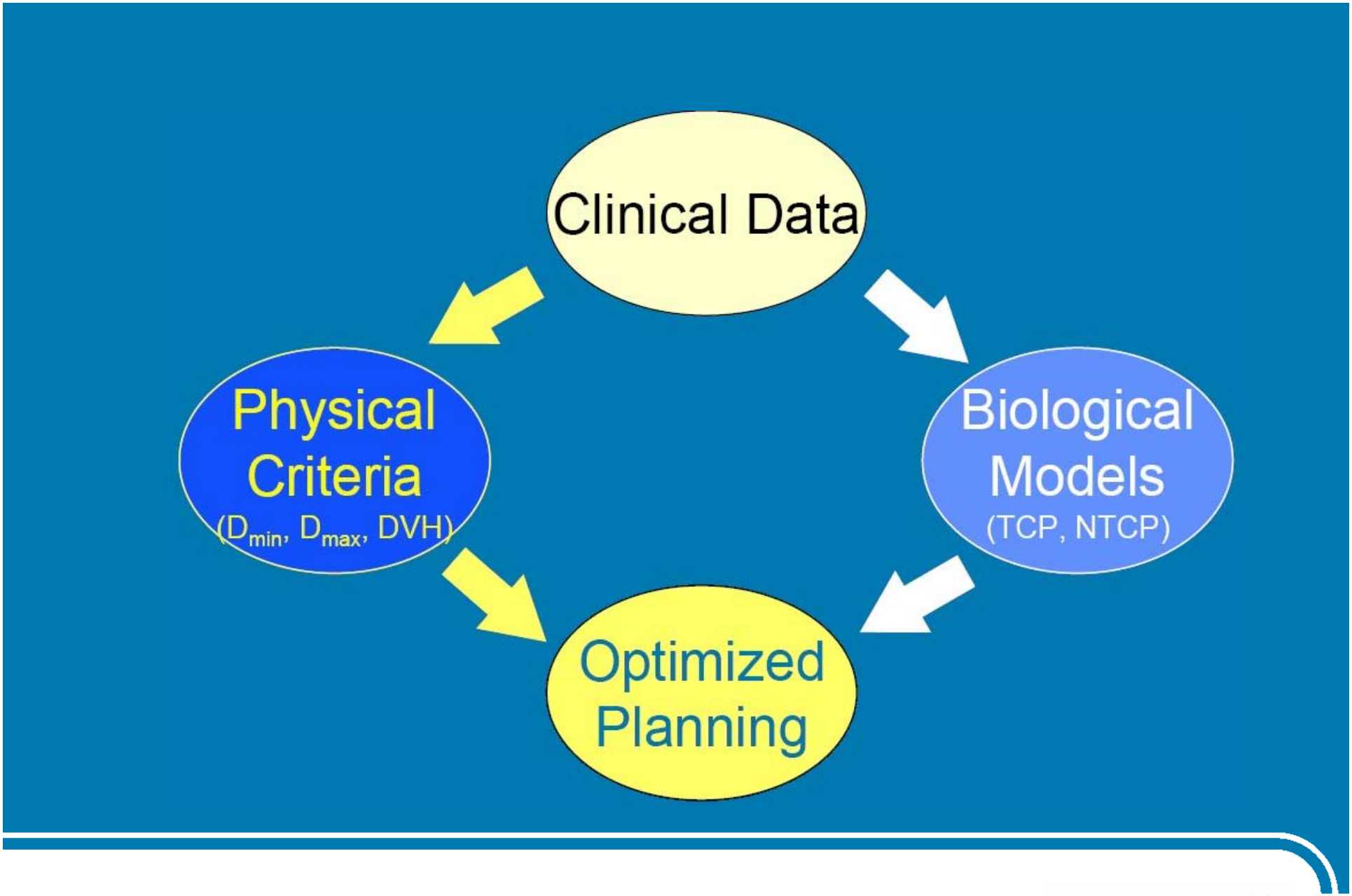
- **Method:** Use an adequate model to quantify the biological effect of dose deposition

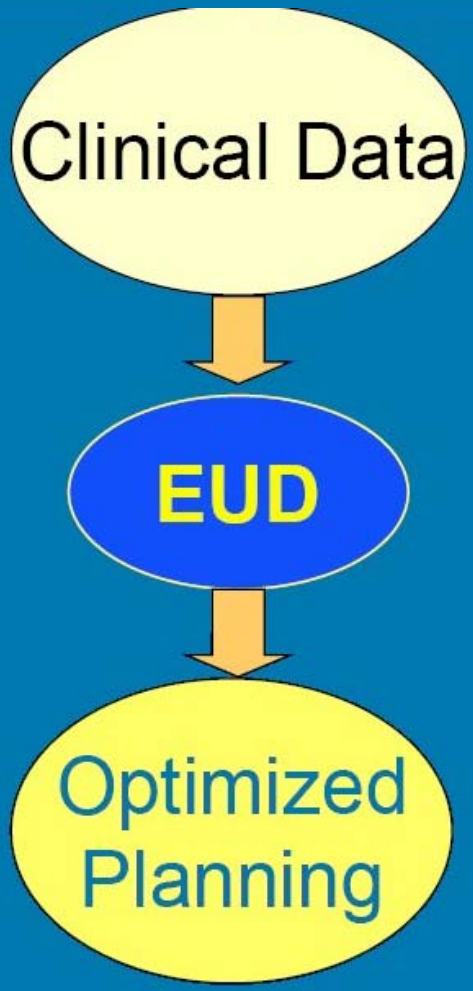
Radiobiological dose-response models

- **Mechanistic models**: radiobiological basis
  - energy deposition in tissue → clinical/biologic
  - 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”

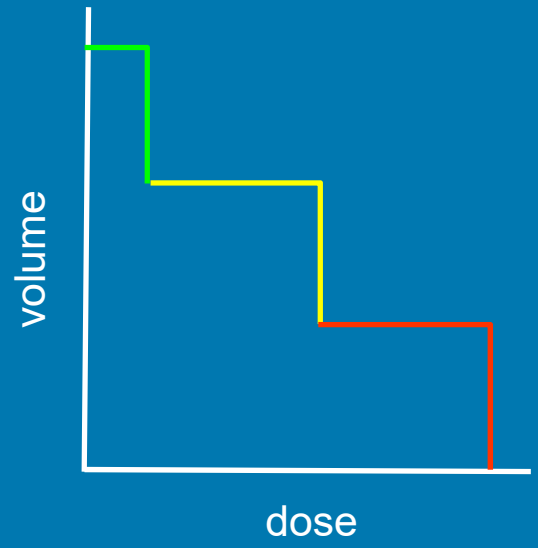


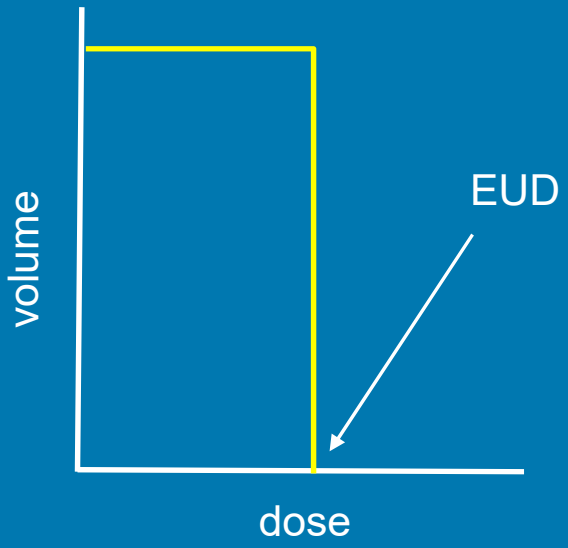


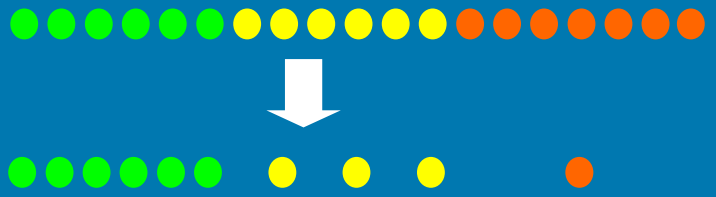
Equivalent uniform dose

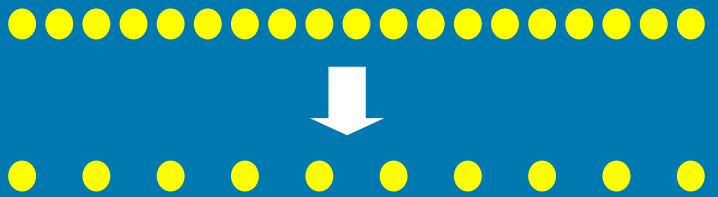
the EUD represents a uniform dose,
which leads to the same probability
of a radiobiological effect as
the corresponding inhomogeneous dose

Equivalent uniform dose

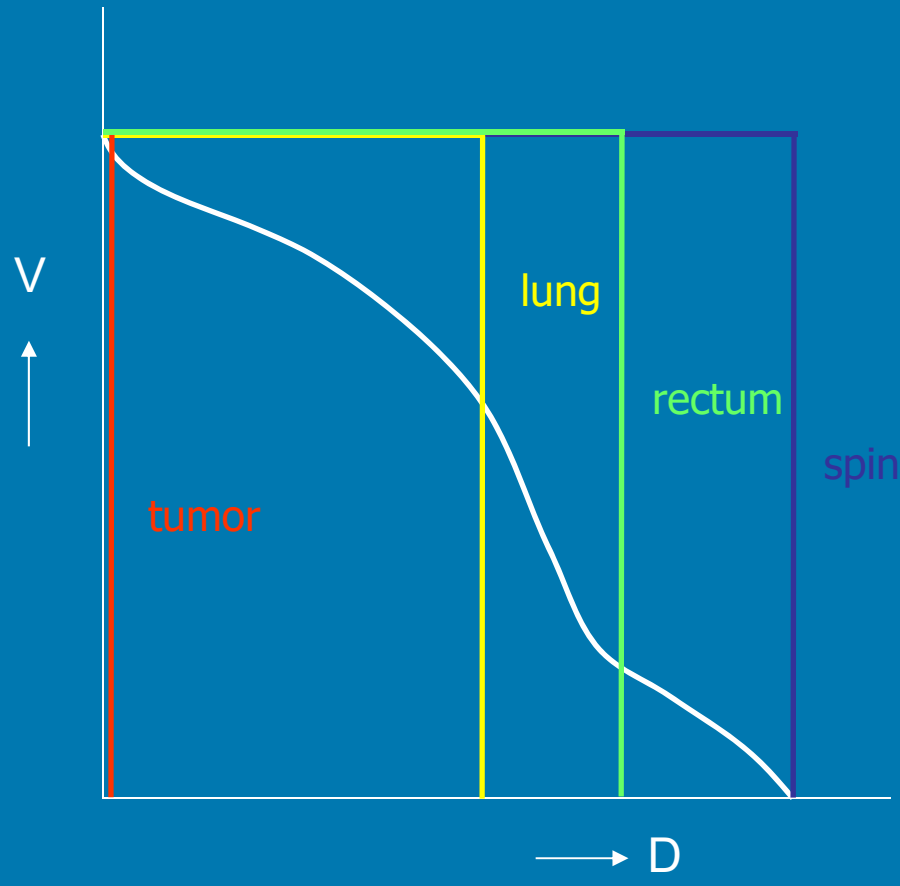








Equivalent uniform dose



Question:

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

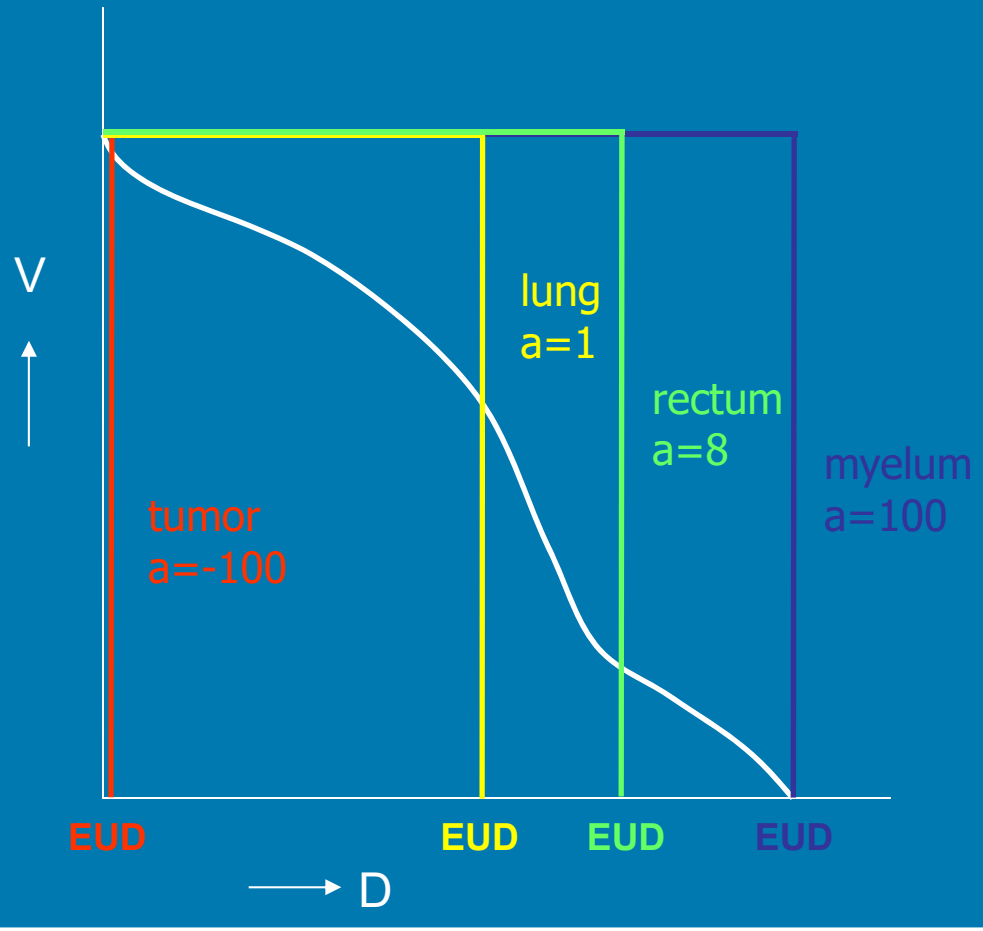
Equivalent uniform dose

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

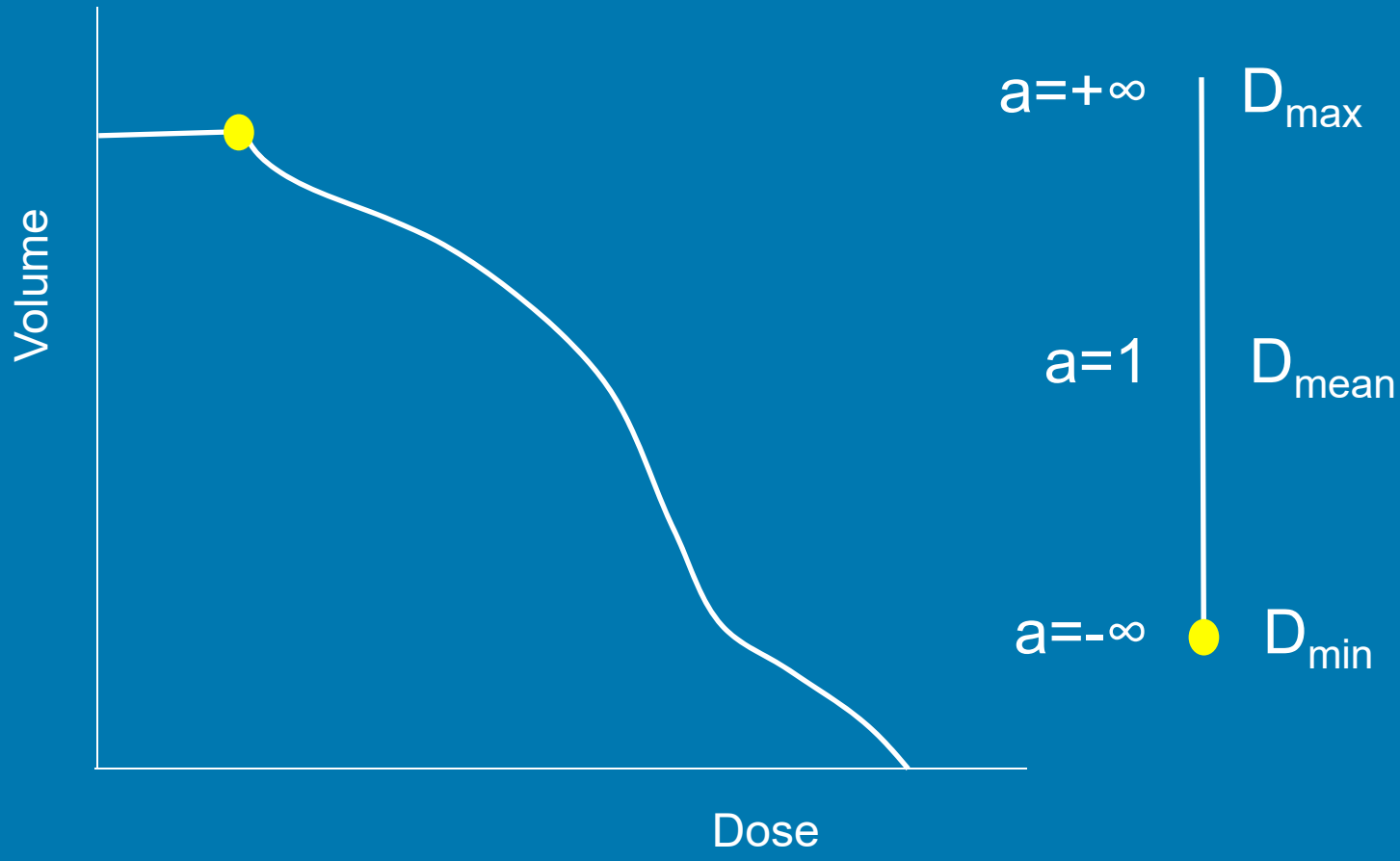
$$EUD = \frac{1}{N} \sum_{i=1}^{N} d_i$$

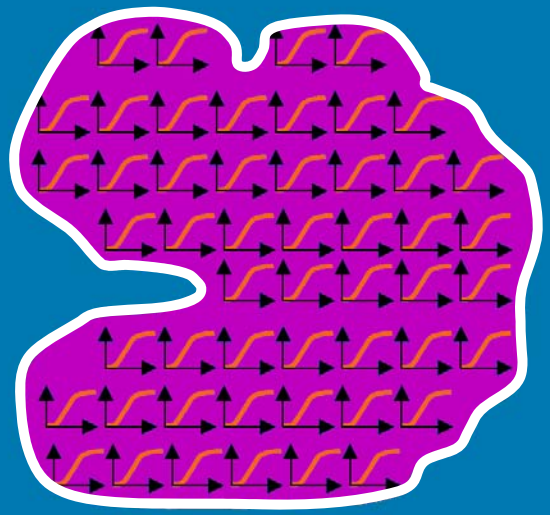
	Effect	Suitable organs
$a < 1$	Lower doses are given higher weight, so that cold spots affect the EUD to a large extent.	Targets.
$a = 1$	This corresponds to the mean dose. Cold and hot spots are given equal weight.	Parallel organized normal tissue, such as lung and liver.
$a > 1$	Larger doses are given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

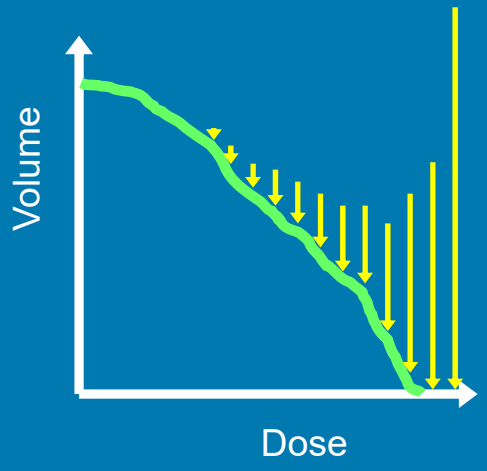
Equivalent uniform dose



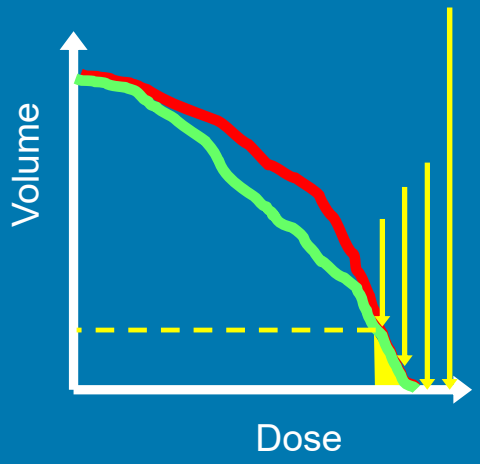
Equivalent uniform dose







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

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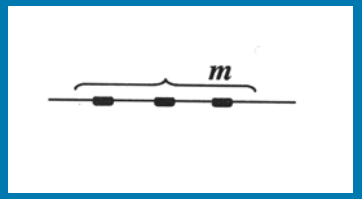
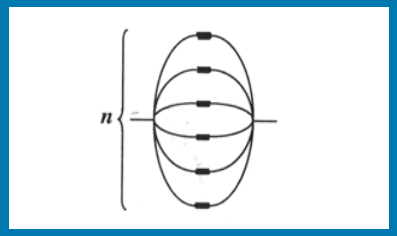
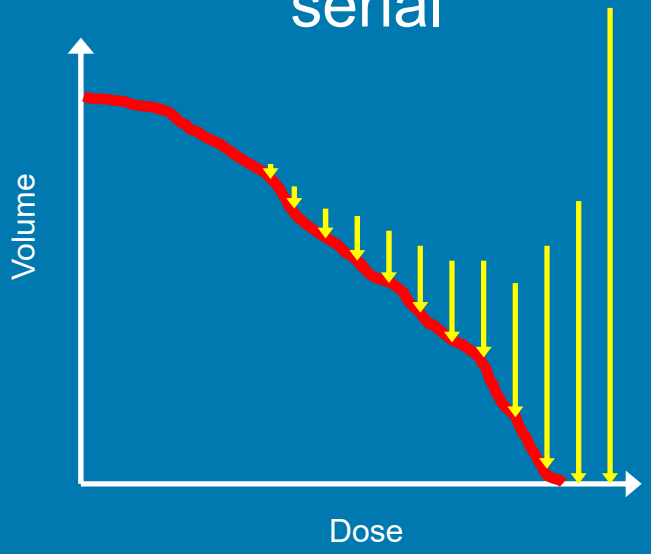
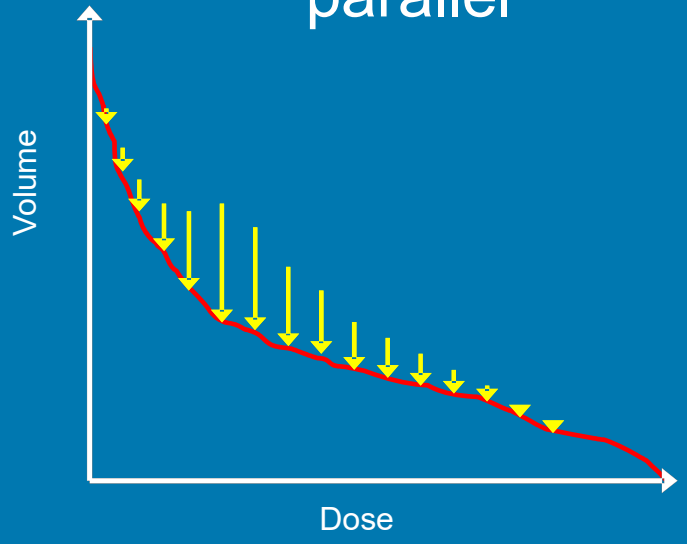




serial



parallel



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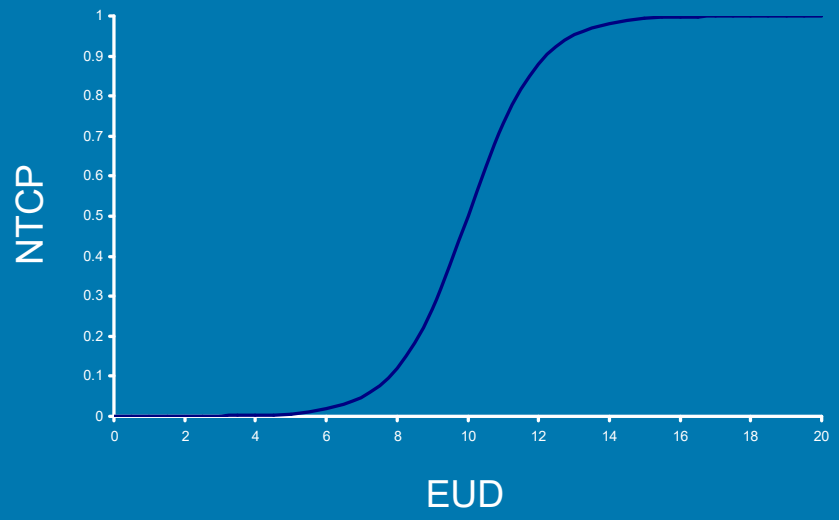
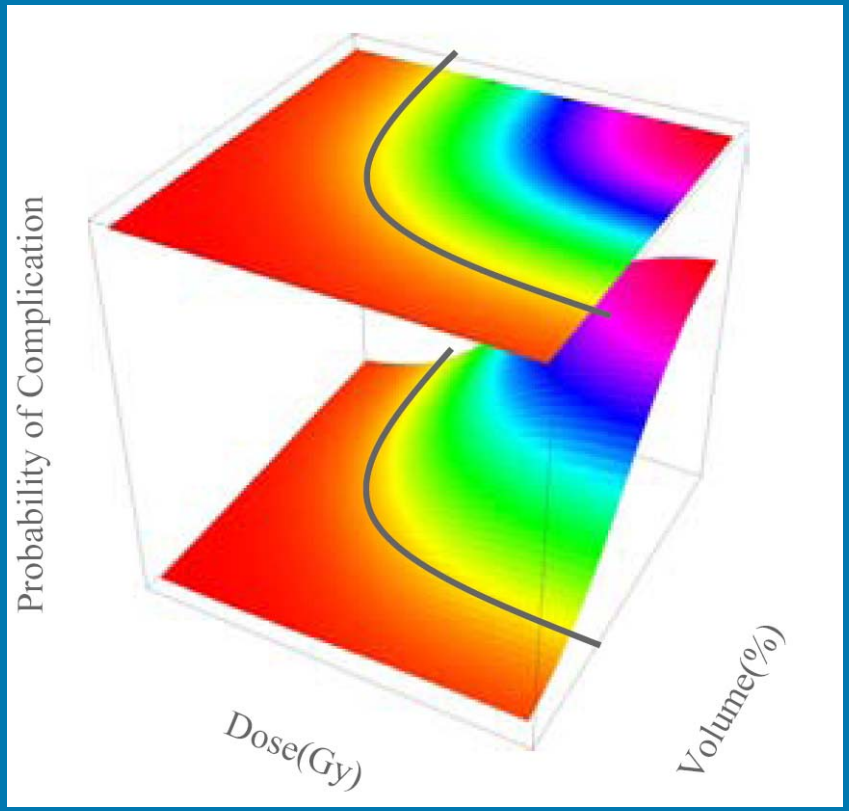
Can we go beyond EUD?

NTCP =
normal tissue complication probability





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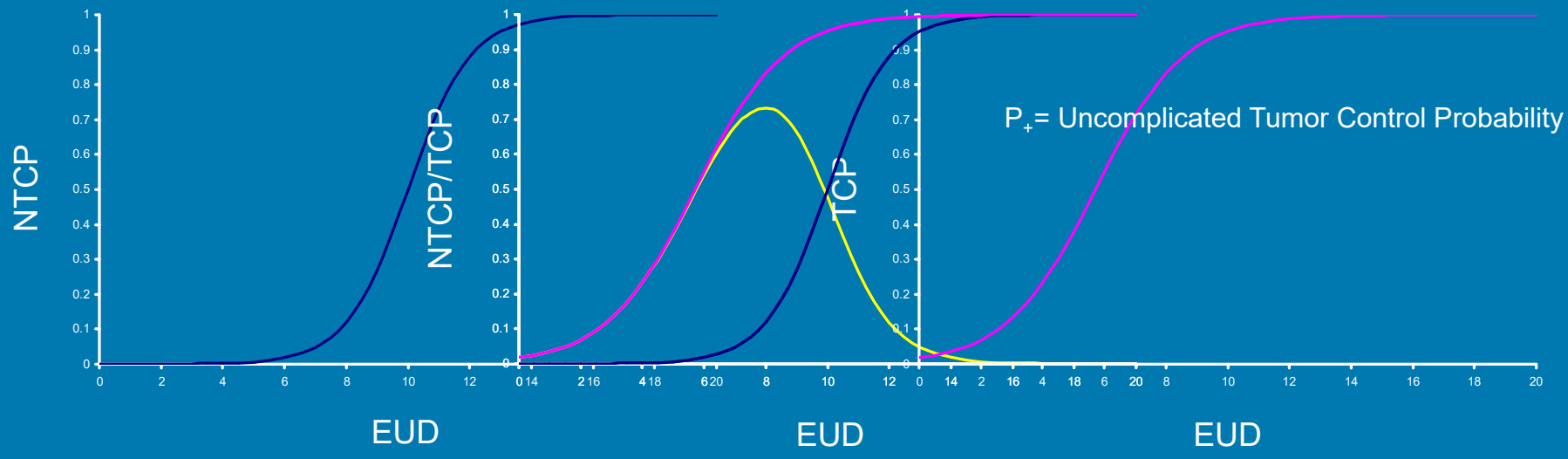
Can we go beyond EUD?



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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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Radiotherapy & Physics department
Policlinico A. Gemelli, Rome (Italy)

MRI in treatment planning

N. Dinapoli

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?

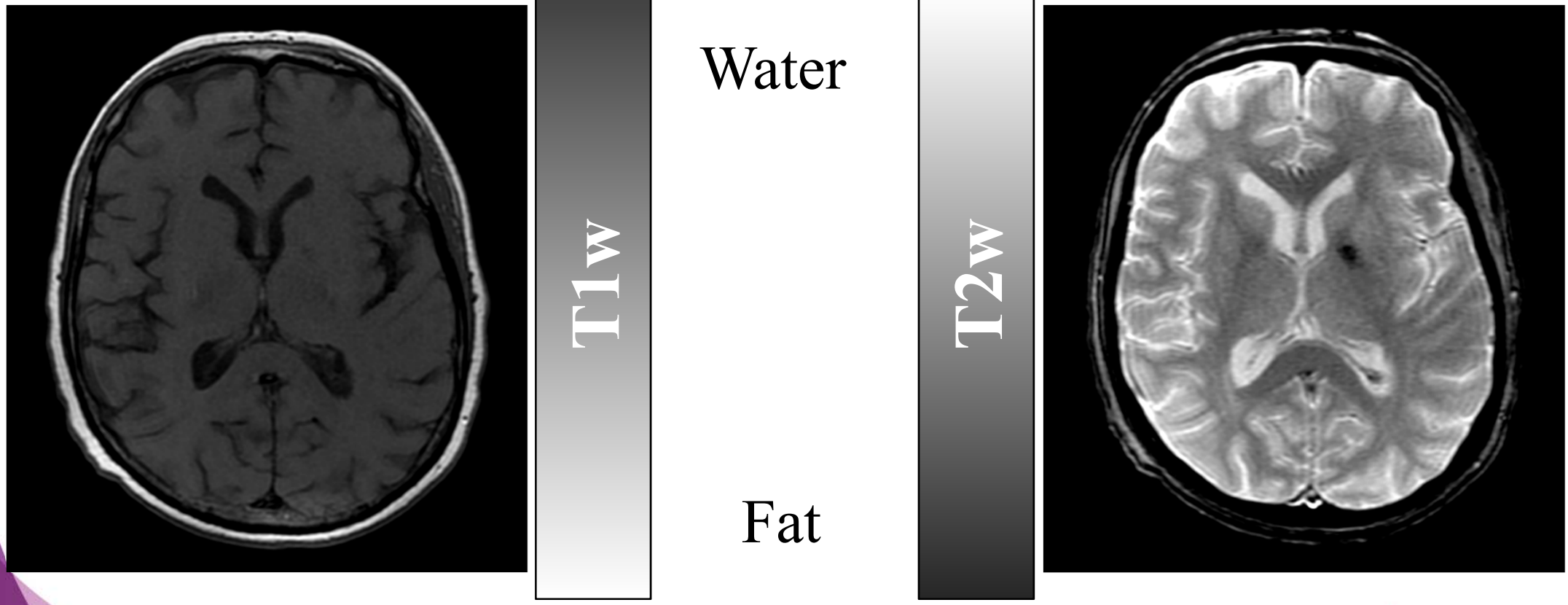
- **Advantages of MRI:**
  - Better contrast definition
  - Better “chemical” description of the matter structure
  - Better definition of **functional** aspects of the tissues (tumor and OAR) that is **physiology** of the tissues

Introduction:
MRI – why, where, when?

- **MRI sequences**
  - **Traditional** (relaxation time)**:**
    - **T1w**
    - **T2w**
  - **Functional** (post-processing)**:**
    - **DWI**
    - **DTI**
    - **PWI**
    - **SMR**

Introduction:
MRI – why, where, when?

- MRI T1w T2w images:



No signal: air, cortical bone

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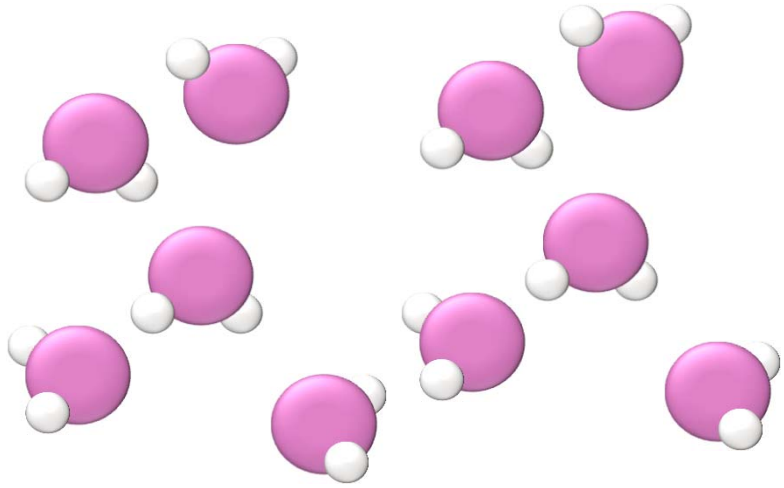
Functional imaging modalities in MRI

- 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**

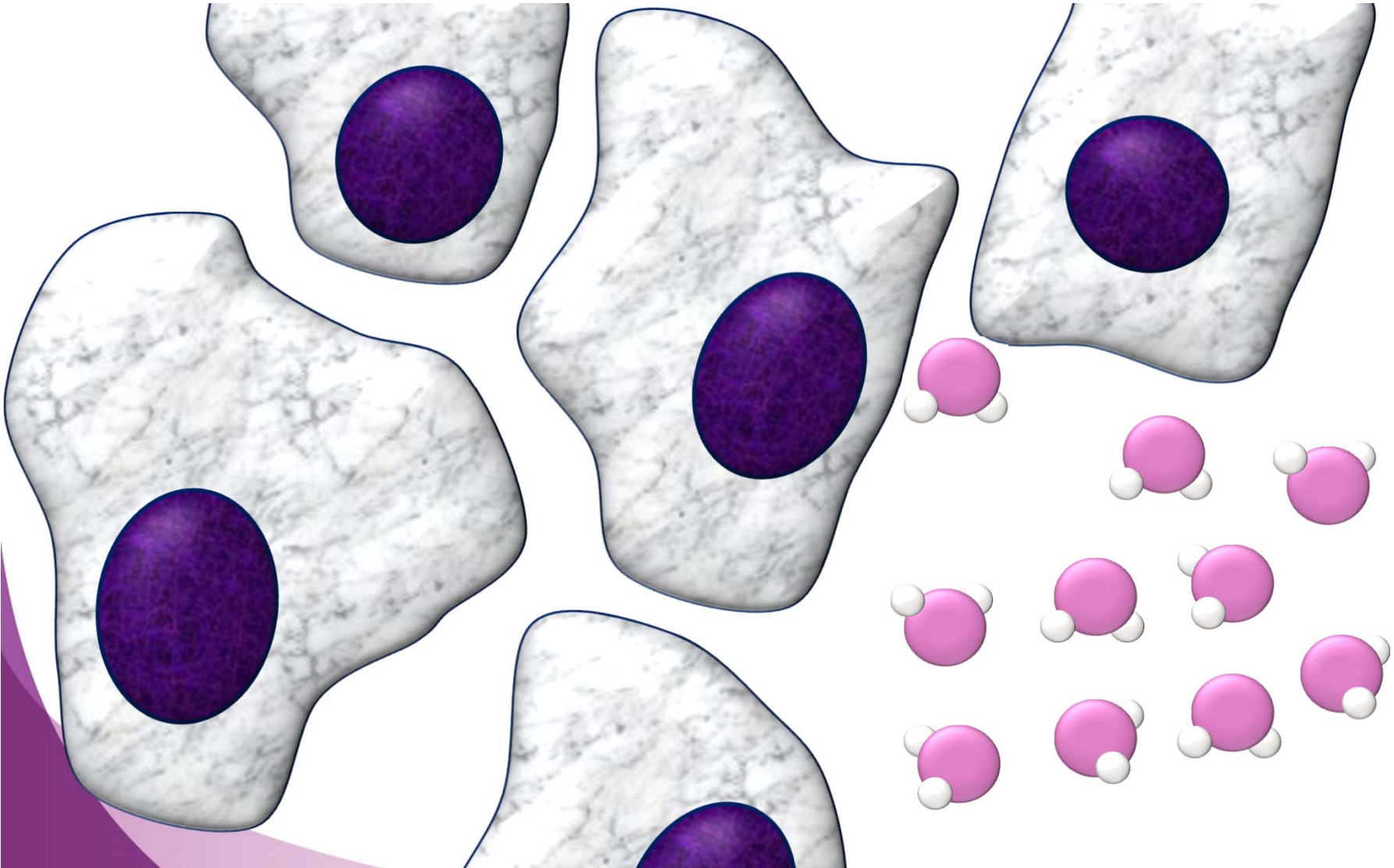
DWI images

- 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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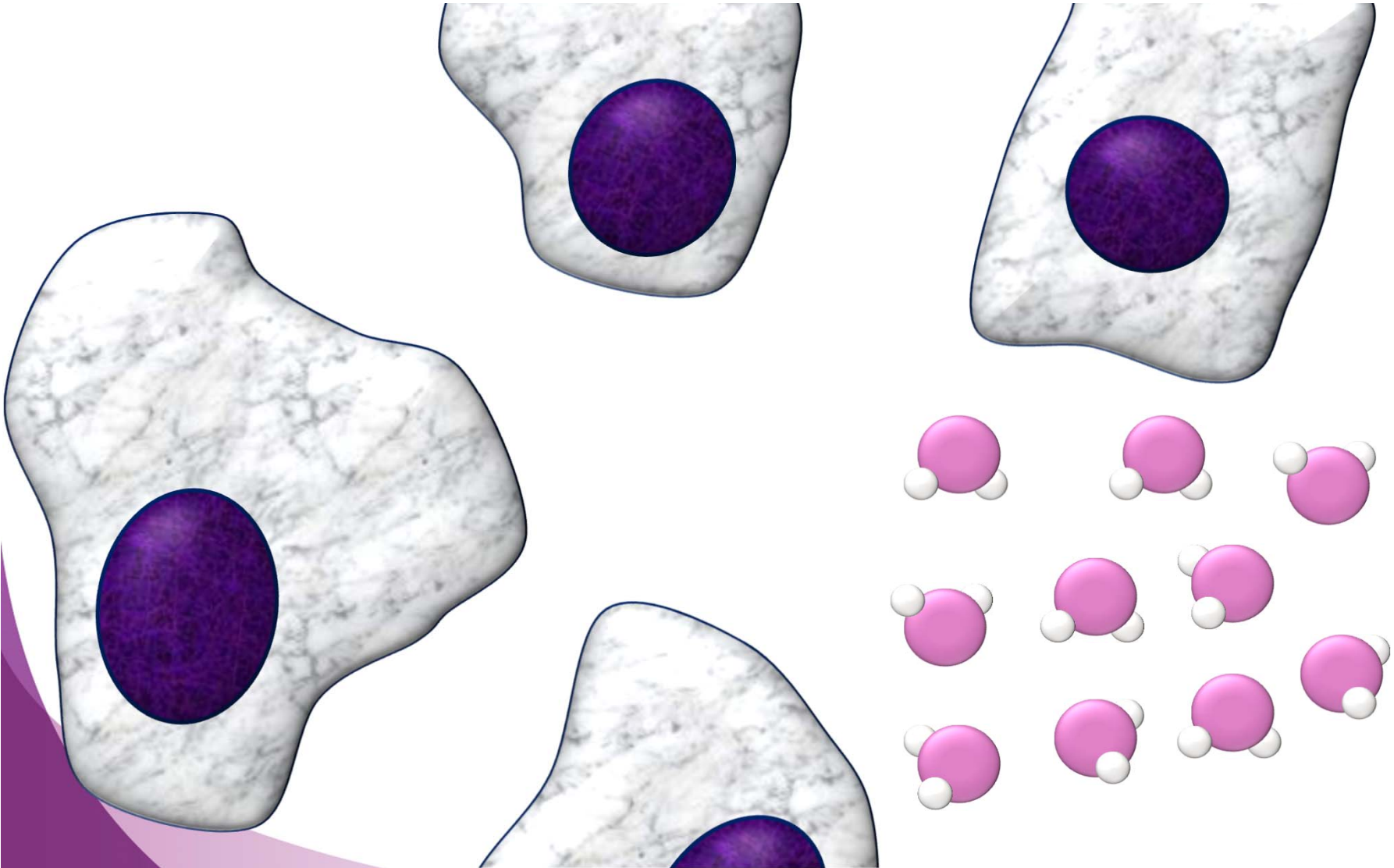
DWI images – ADC maps

- Low cellularity – Higher Apparent Diffusion Coefficient (ADC)



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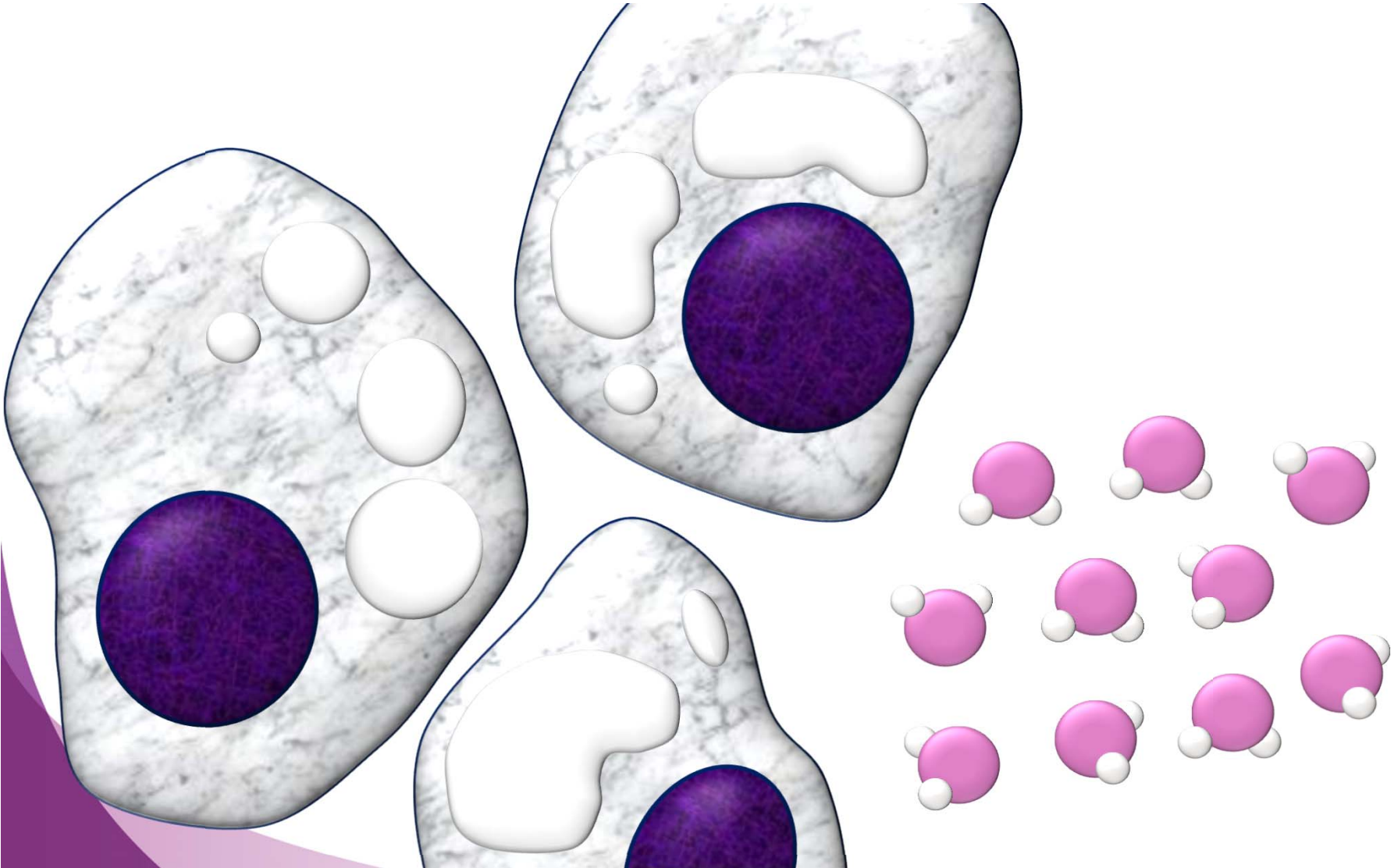
DWI images – ADC maps

- Intracellular edema – Lower Apparent Diffusion Coefficient (ADC)



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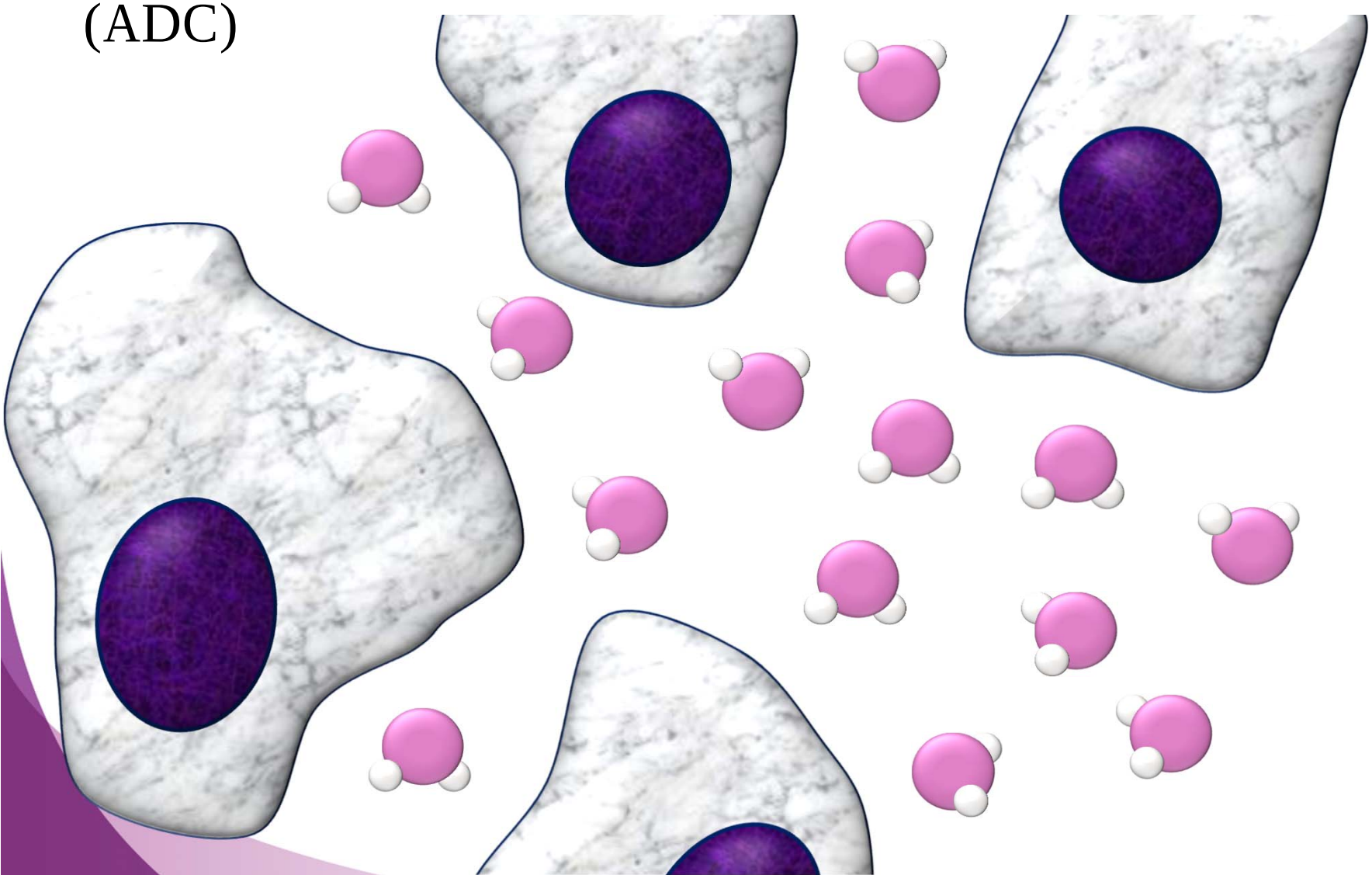
DWI images – ADC maps

- 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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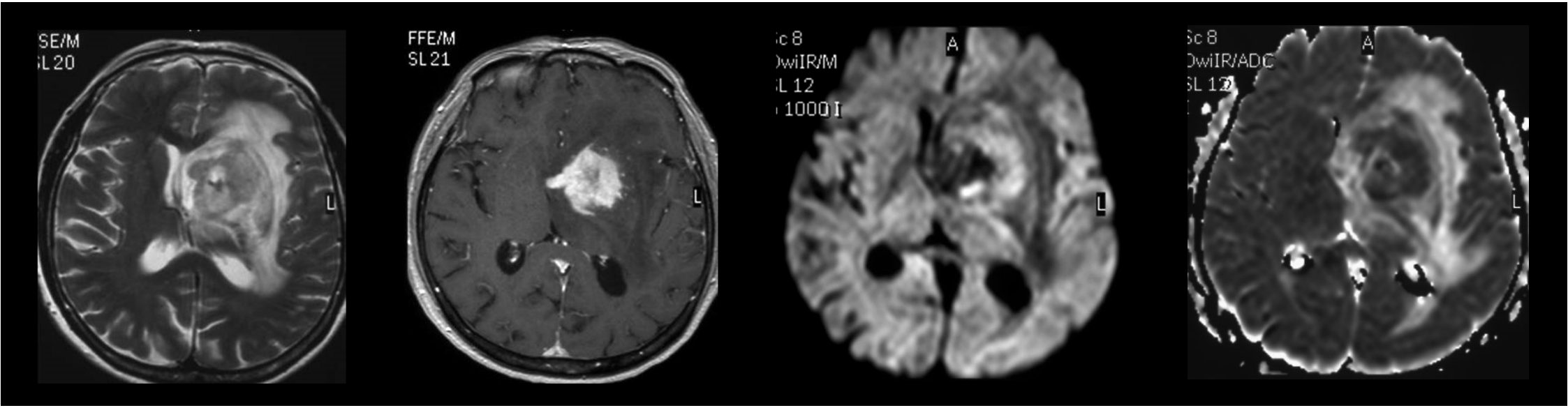
DWI images – ADC maps

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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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**)

     ⇩

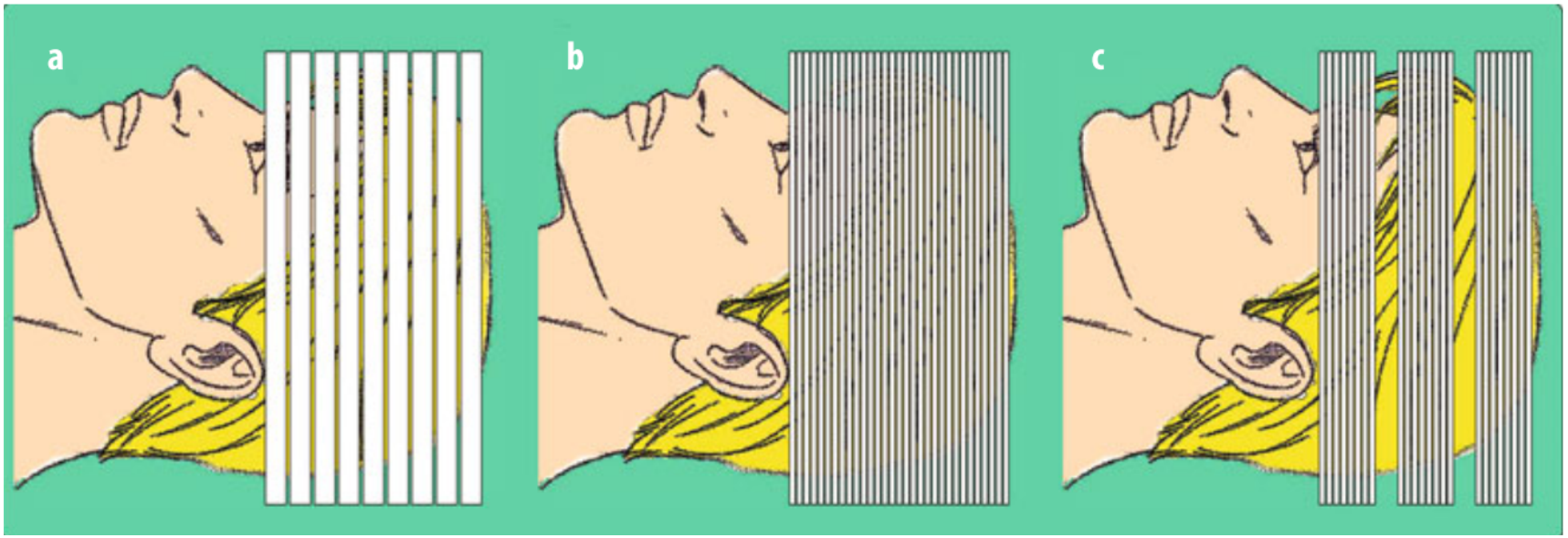
     - Dose escalation protocols

     ⇩

     - Dose distribution-imaging adaptation for simultaneous or sequential boost treatments
  2. Direct **planning** on MRI images
  3. Hybrid machines

Is there a specific image sequence useful for planning?

- Images for planning procedures require:
  - Correct geometry
  - Adequate spatial resolution
  - Visibility and enhancement of GTV



2D 3D 3D - multislab

Coriasco M, et al., Elementi di Risonanza Magnetica, Springer, 2014

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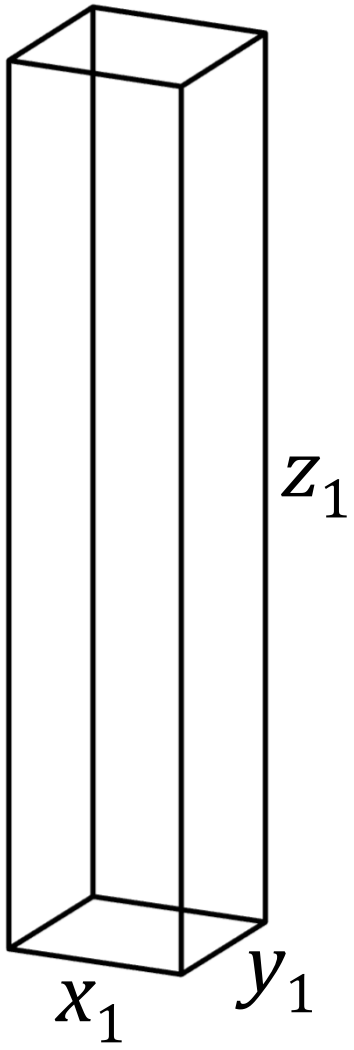
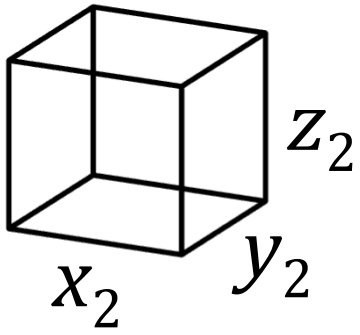
Is there a specific image sequence useful for planning?

z_1? x_1, y_1

$z_2 = x_2, y_2$



$x_1 < x_2$



2D

3D

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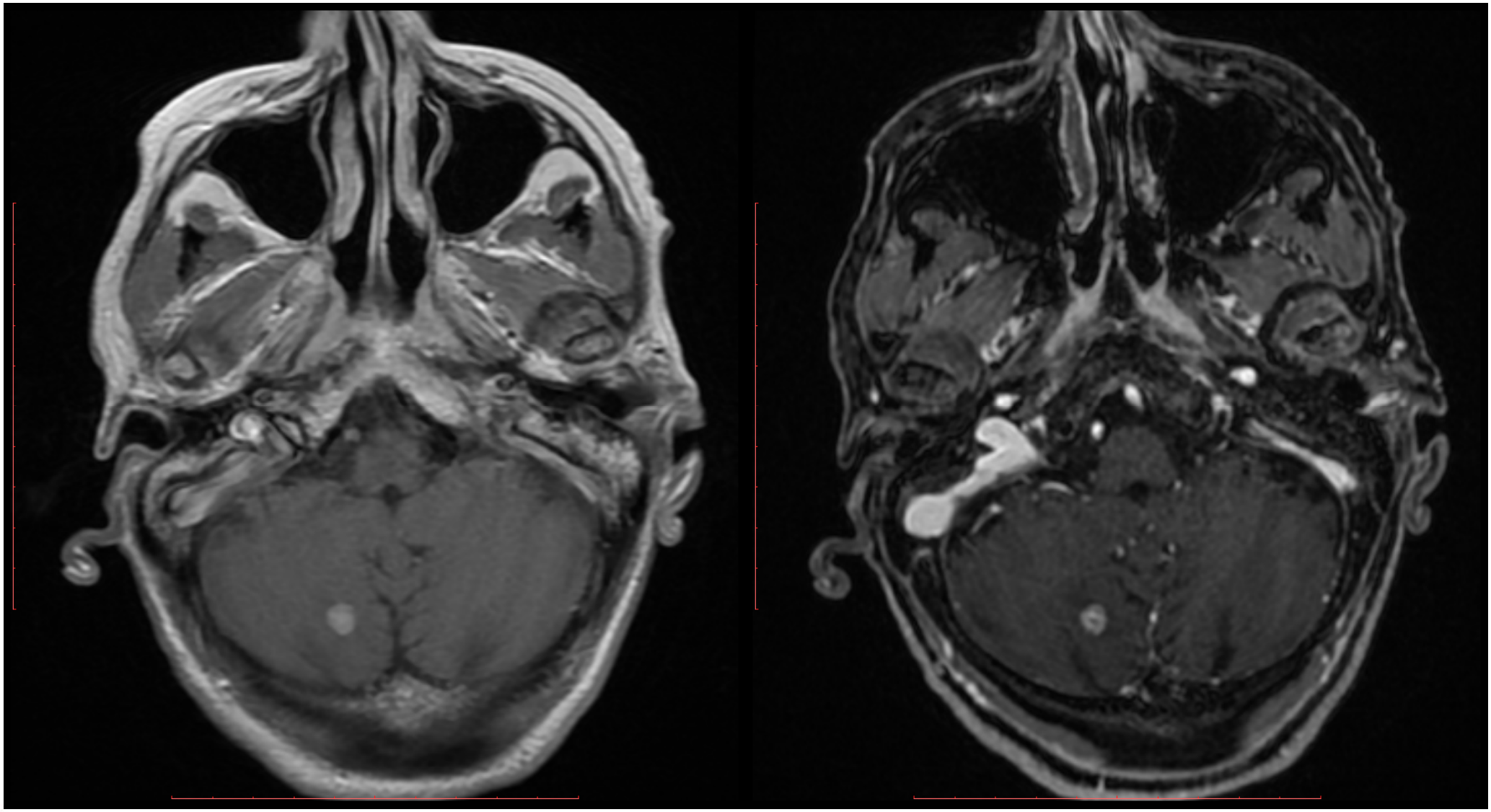
Is there a specific image sequence useful for planning?

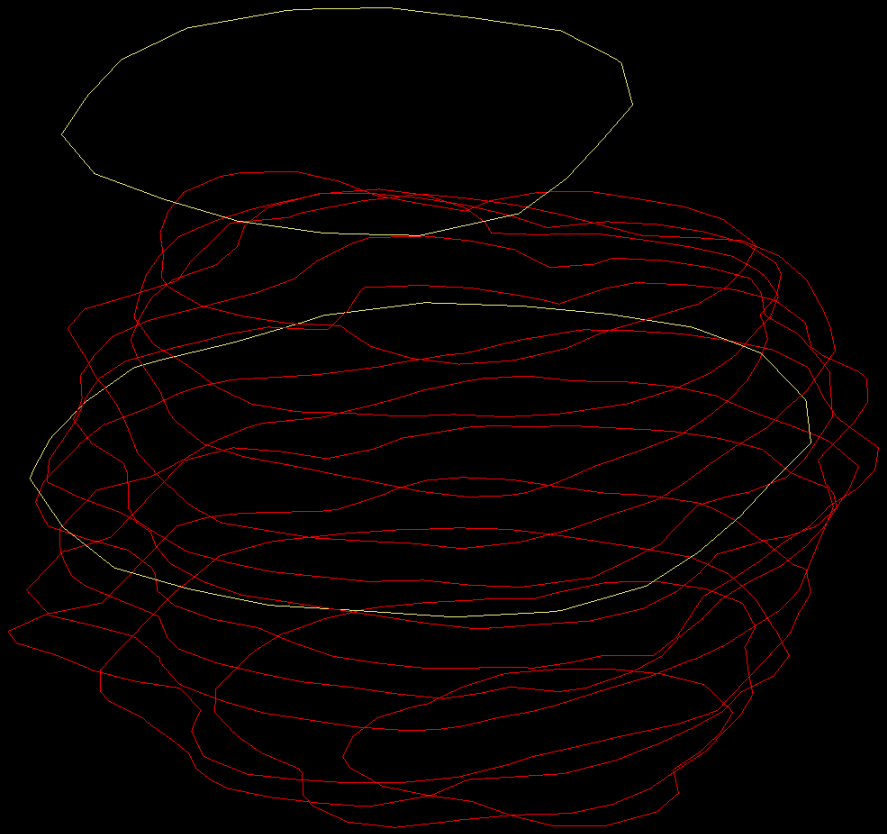


2D – T1c

3D – FSPGR
(fast spoiled gradient echo)

Is there a specific image modality useful for planning?

- Switch screen



Wires

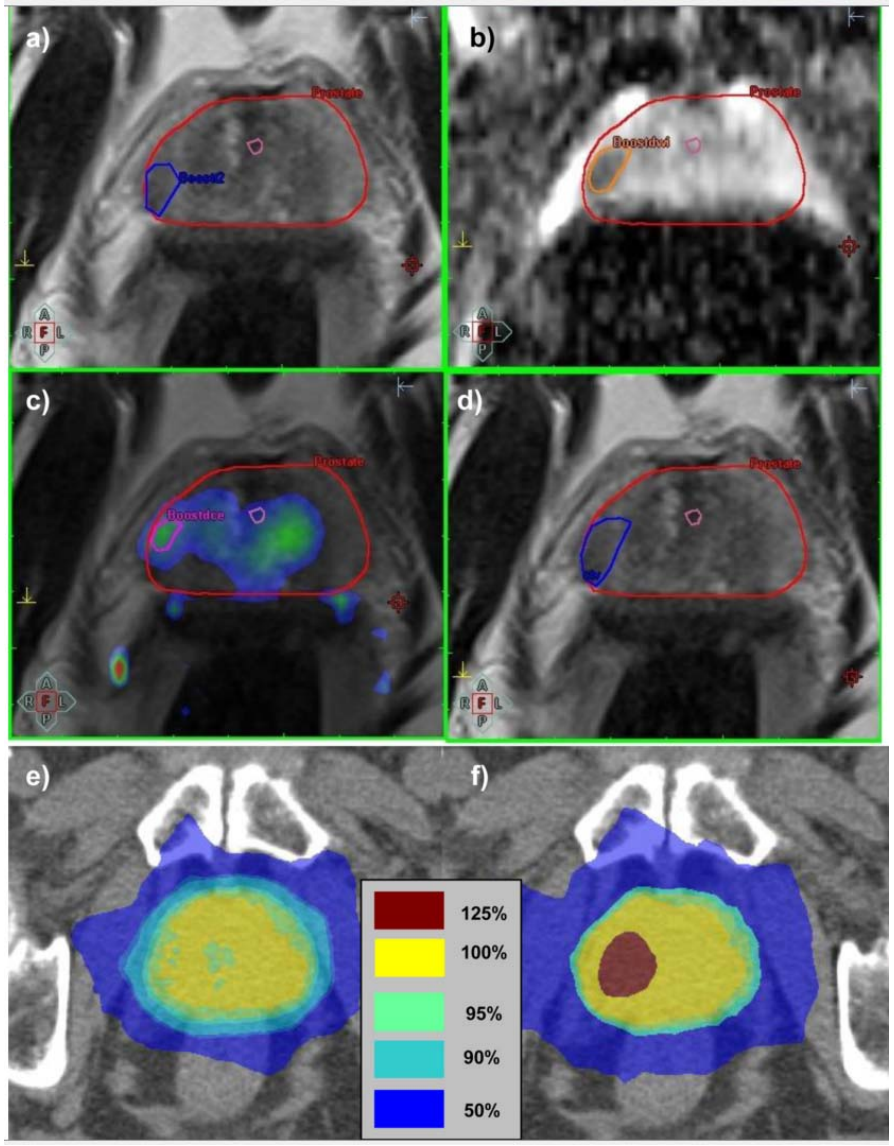
3D model

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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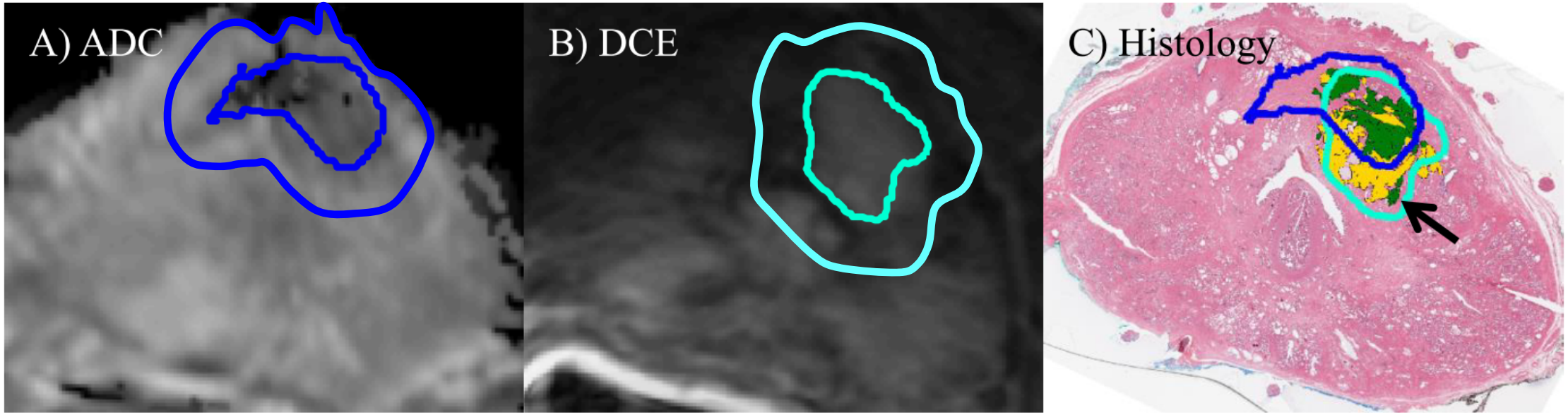
1. MRI for targeting: prostate



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

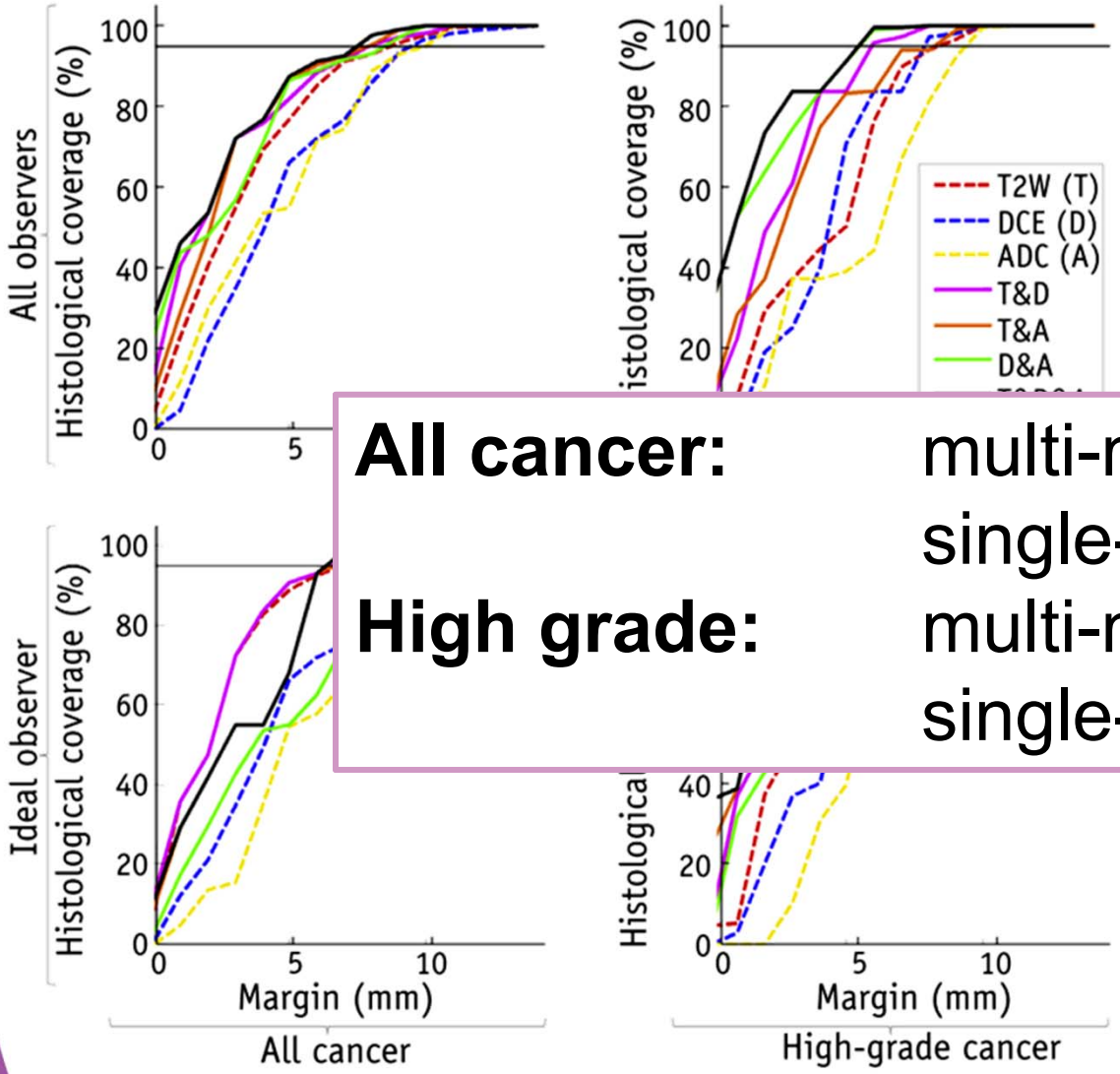

Table 2 Isotropic margins to cover 95% of histologic cancer for prospective case and proportion of prostate tissue spared by CTVs with such margins

	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
			9	55-68
			6	71-81
			6	70-80
			9	60-71
			9	53-67
			8	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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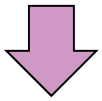
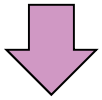
New MRI imaging modalities and radiotherapy planning

- 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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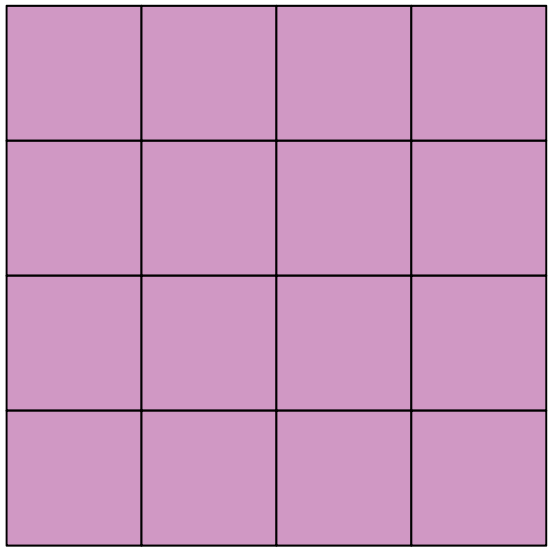
2. Direct planning on MRI images

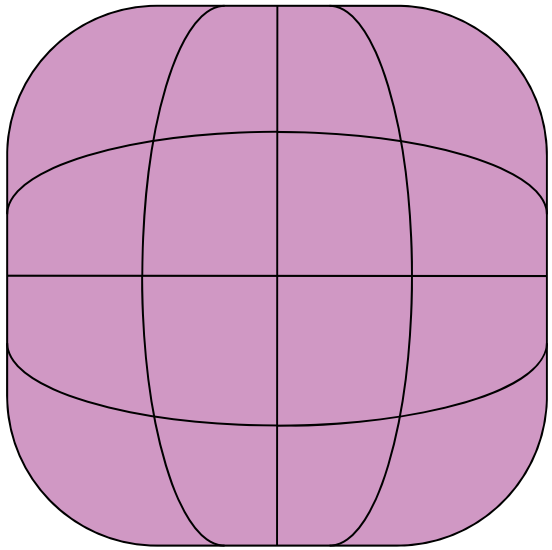
- Problems in using only MRI for planning
  1. Image **distortion**
  2. Dose calculation (lacking informations needed to recontruct **electron density maps**)

2. Direct planning on MRI images

- Strategies for reduce geometry artifact due MRI images acquisition process



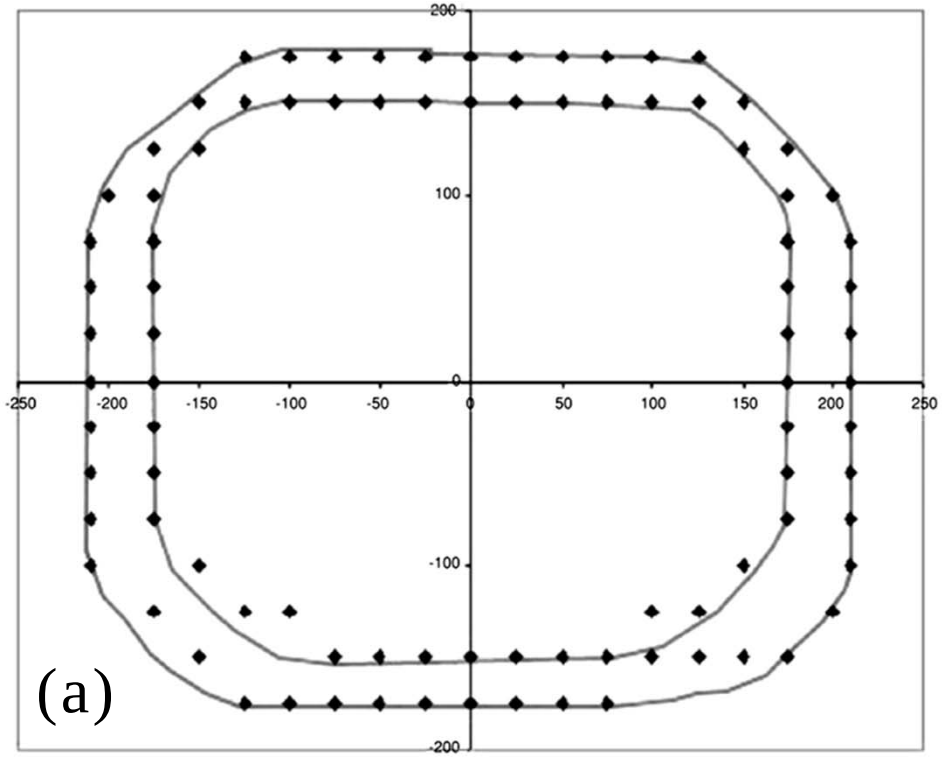
CT

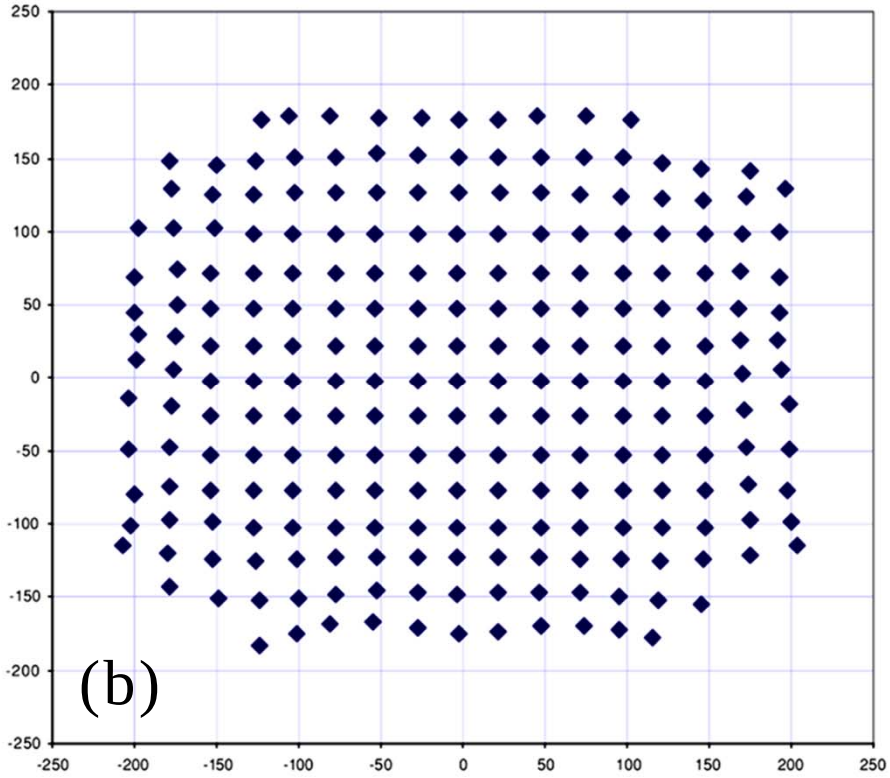


MRI

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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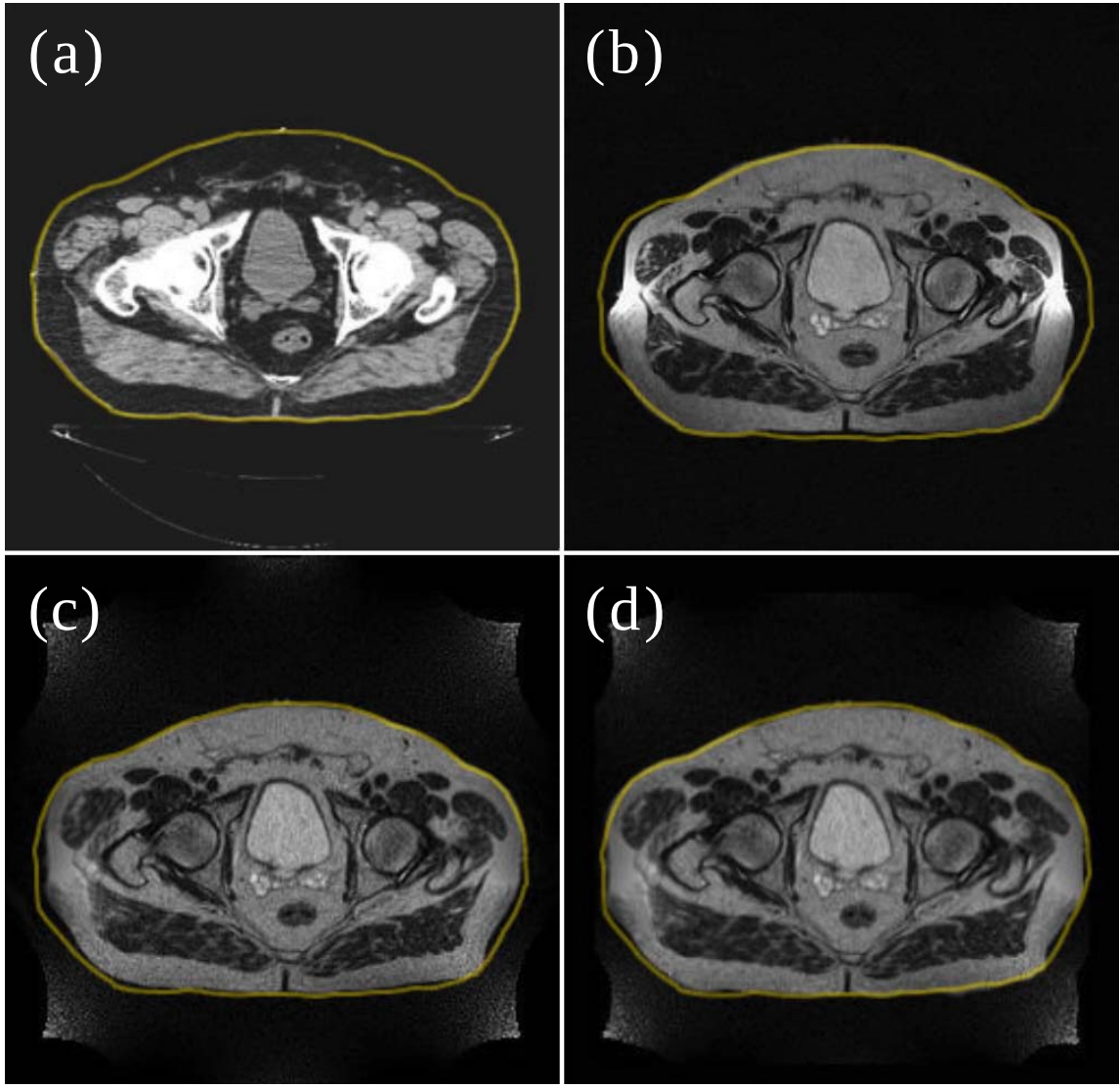
2. Direct planning on MRI images

- 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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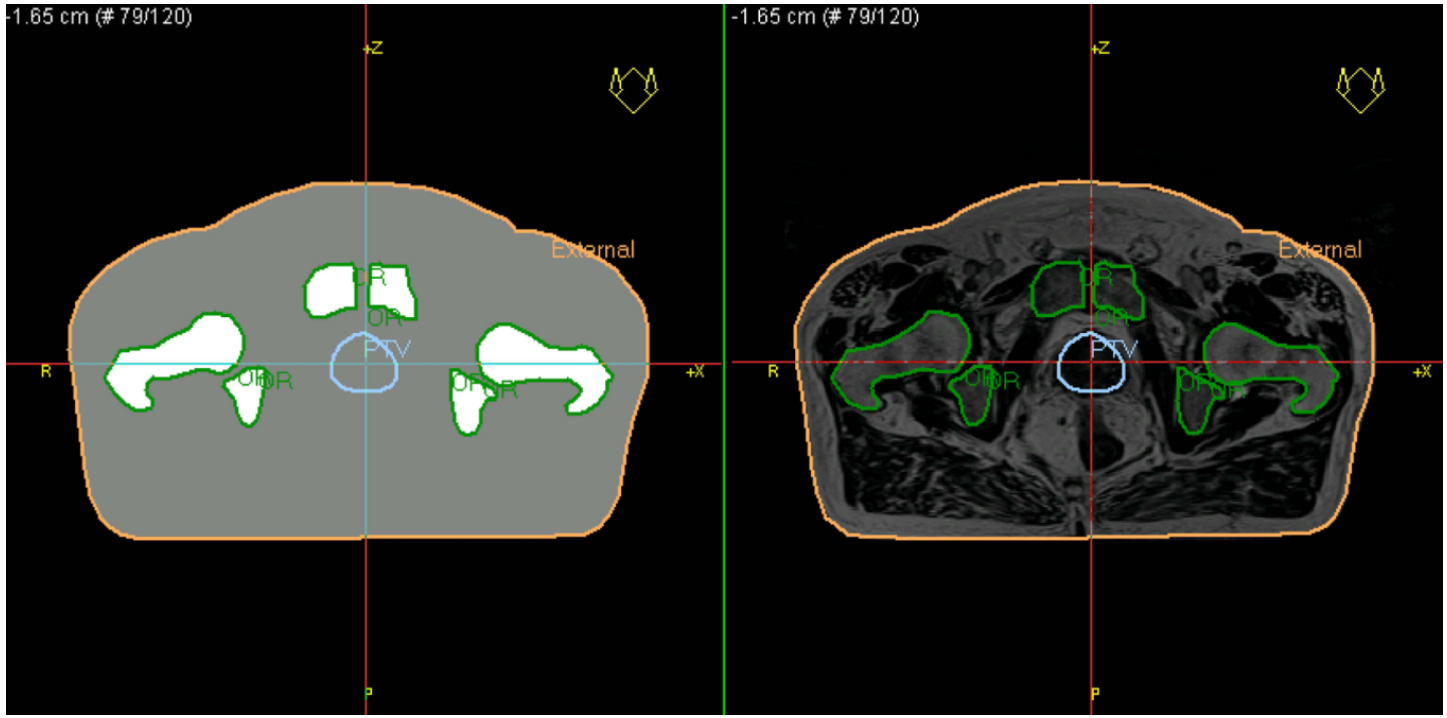
2. Direct planning on MRI images

- 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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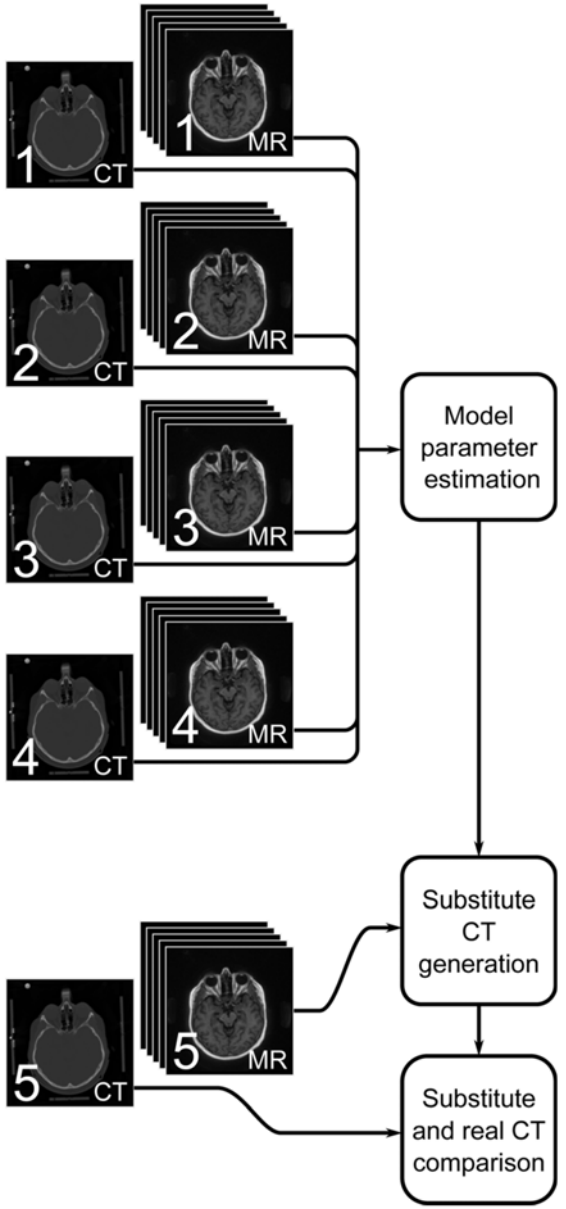
2. Direct planning on MRI images

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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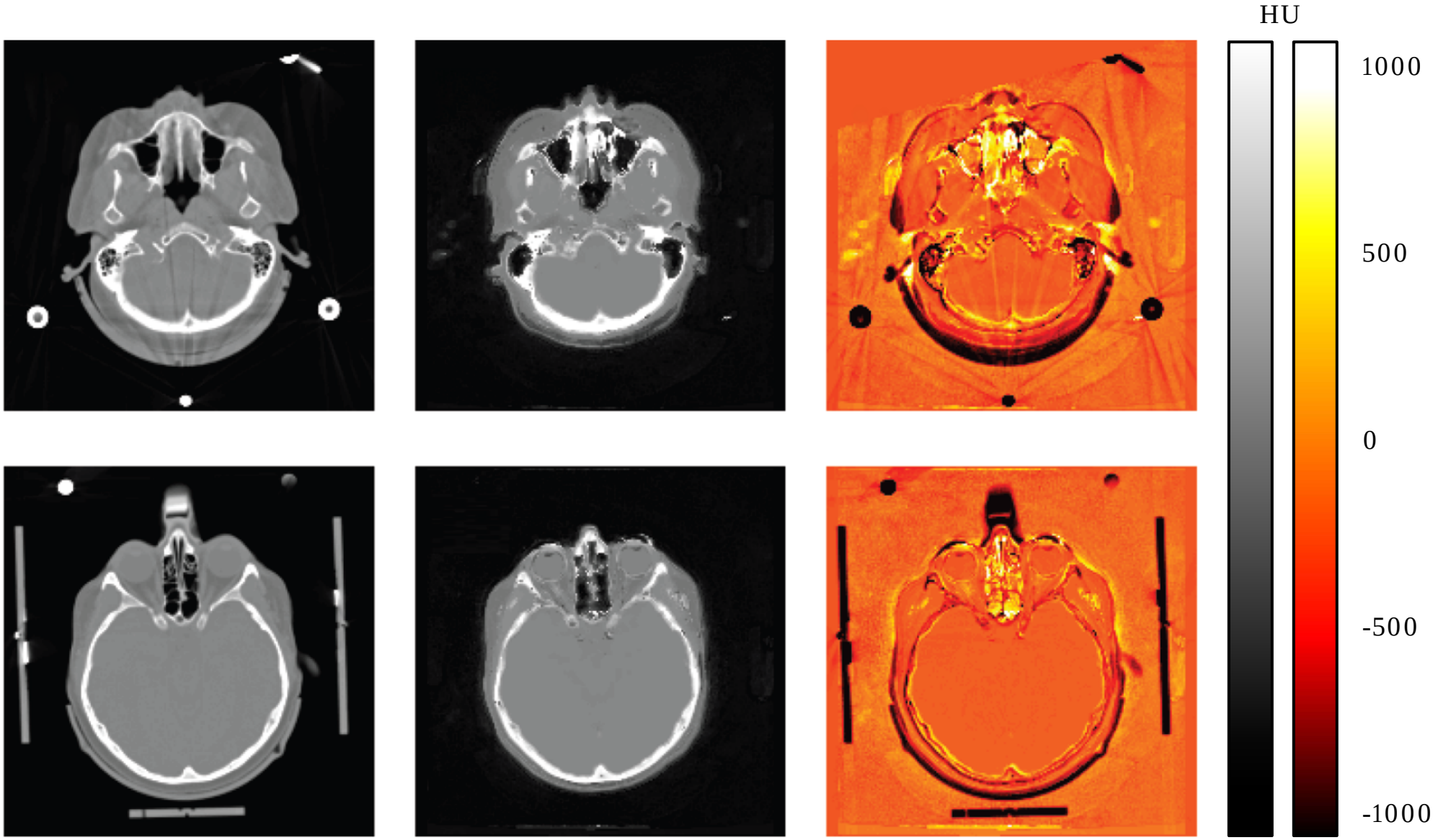
2. Direct planning on MRI images



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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

MR-Linac

6 MV Linac
(350-600 cGy/min)

+

MRPhilips @ 1,5 T

Raaymakers BW, et al Integrating a 1.5 T MRI scanner with a 6 MV accelerator: proof of concept. Phys Med Biol. 2009 Jun 21;54(12):N229-37.

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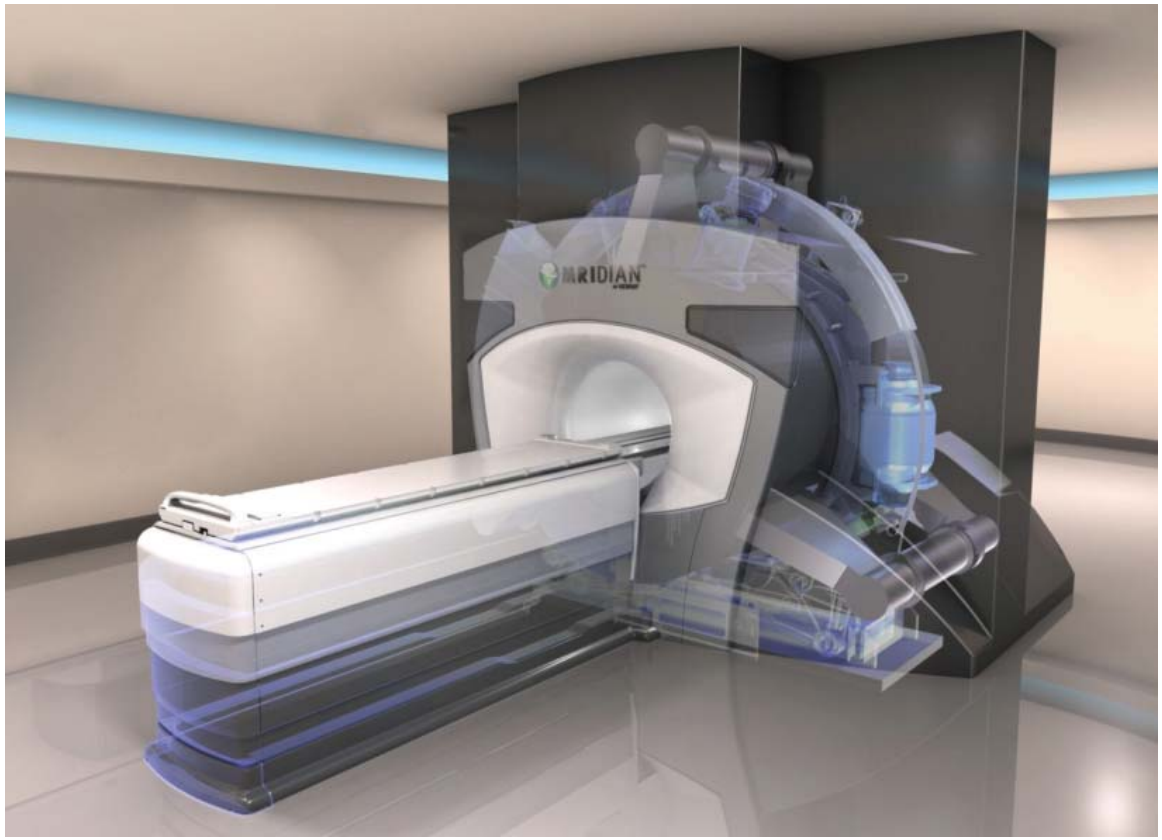
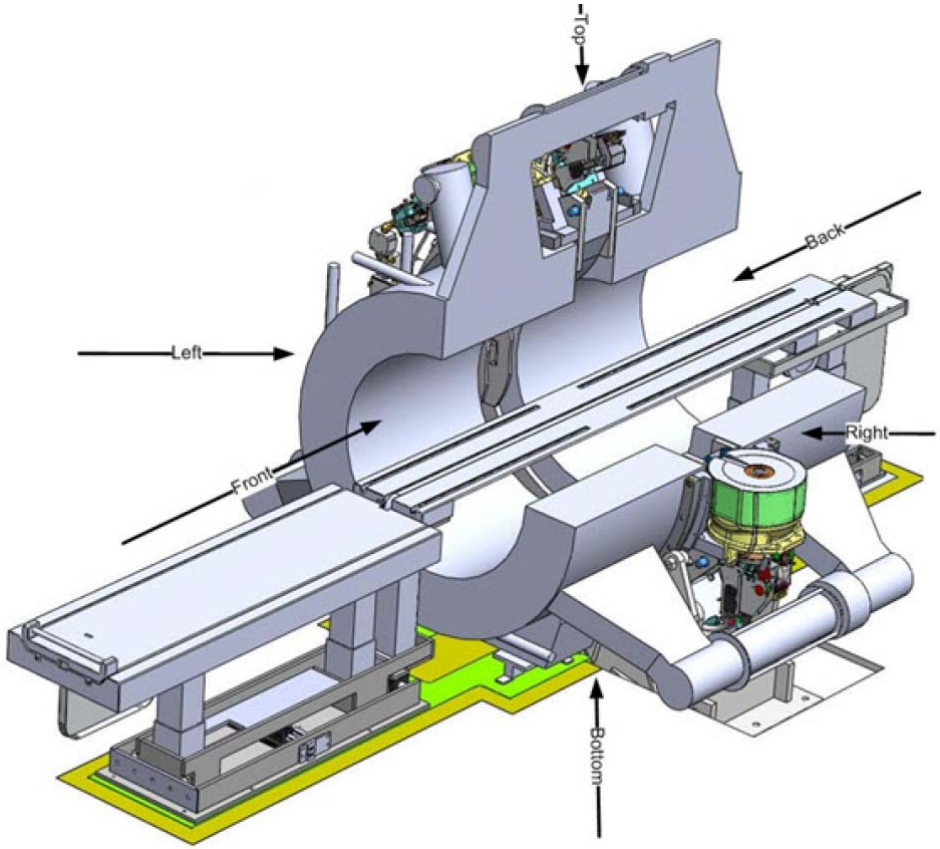
Low Tesla MR-^{60}Co





MR Siemens @ 0.35T

3 ^{60}Co heads on a ring gantry

Mutic, S. & Dempsey J. F. (2014). The ViewRay System: Magnetic Resonance–Guided and Controlled Radiotherapy. Seminars in Radiation Oncology, 24(3), 196-199.

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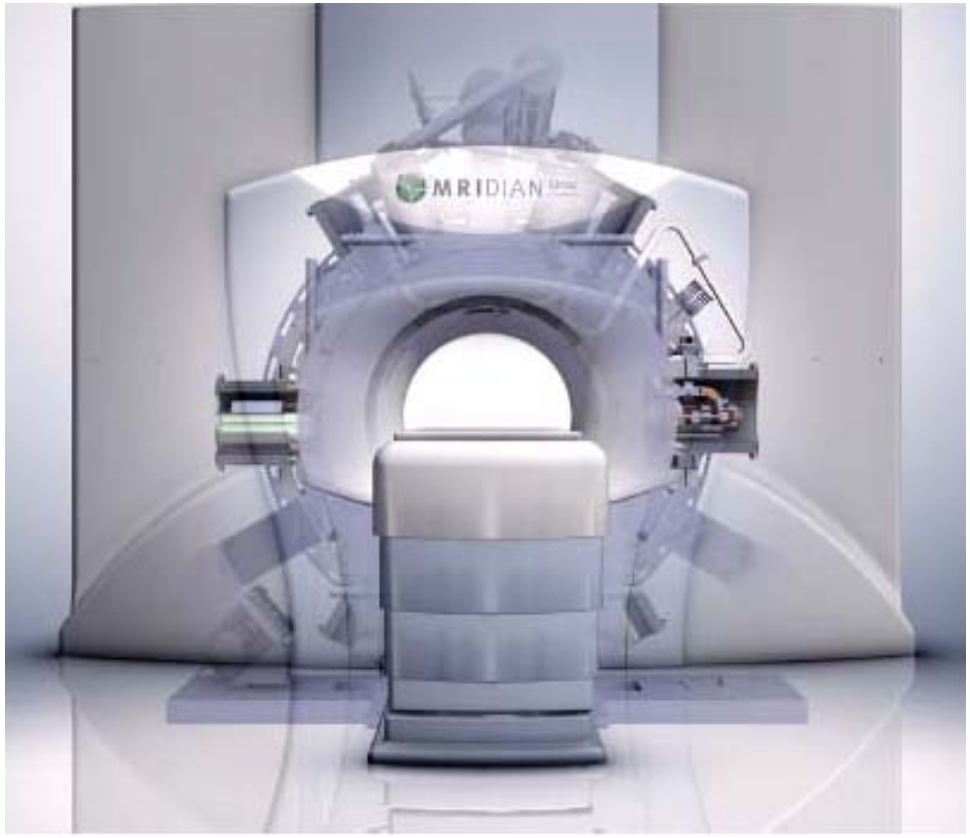
Low Tesla MR – 6 MV Linac



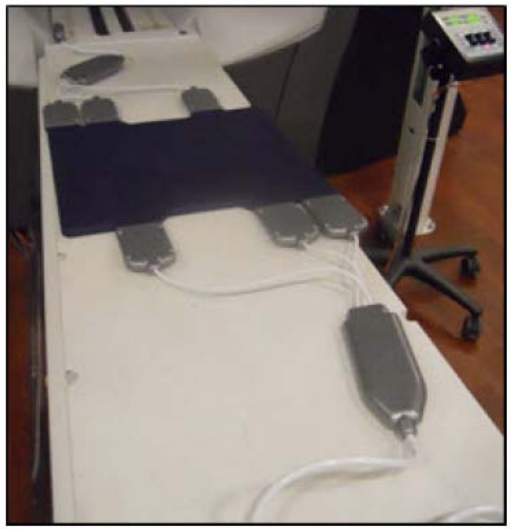
6 MV Linac
(FFF; Drate = 600 cGy/min)

+

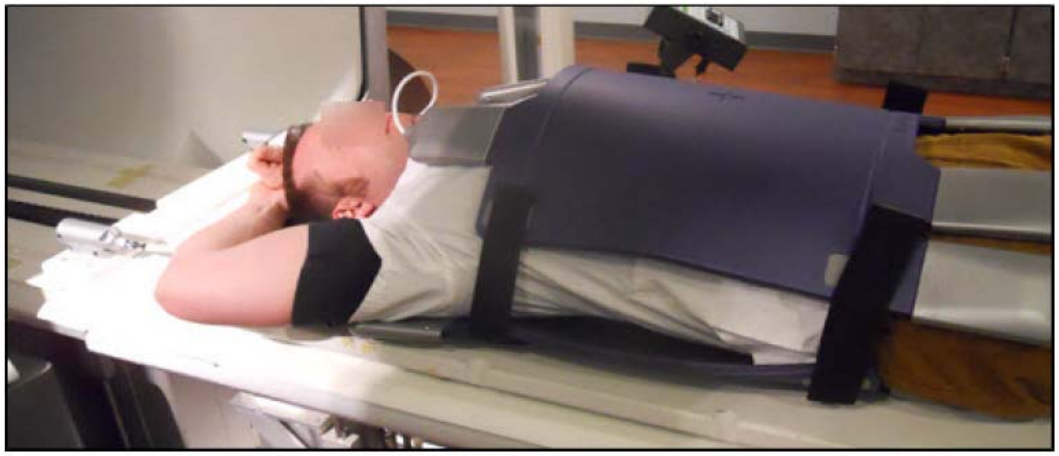
MR Siemens @ 0,35 T

MRI – ^{60}Co: imaging features

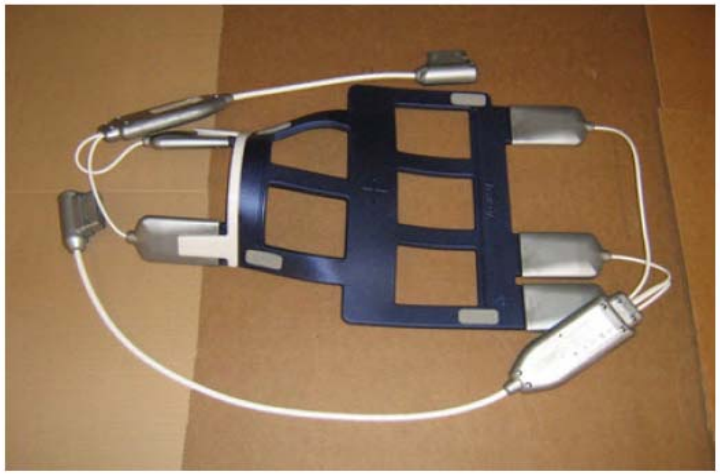
Torso Coil half



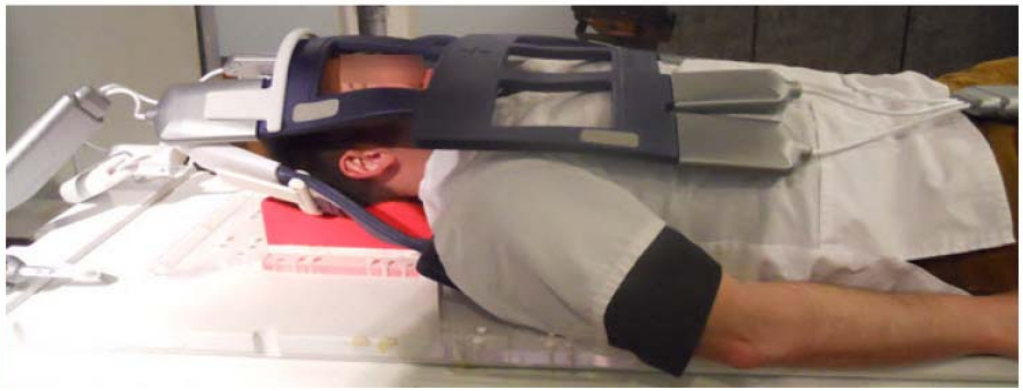
Torso Coils in place



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

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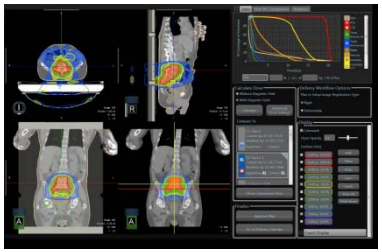
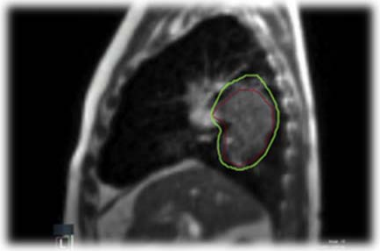
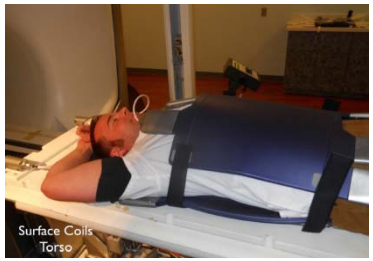
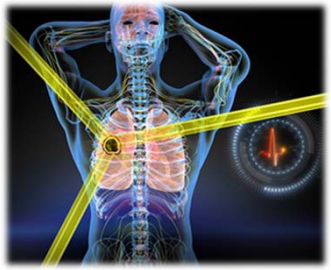
ViewRay workflow

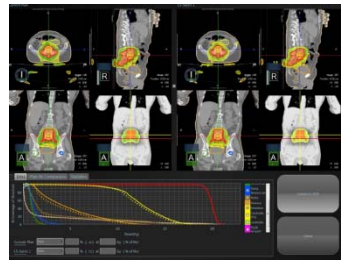




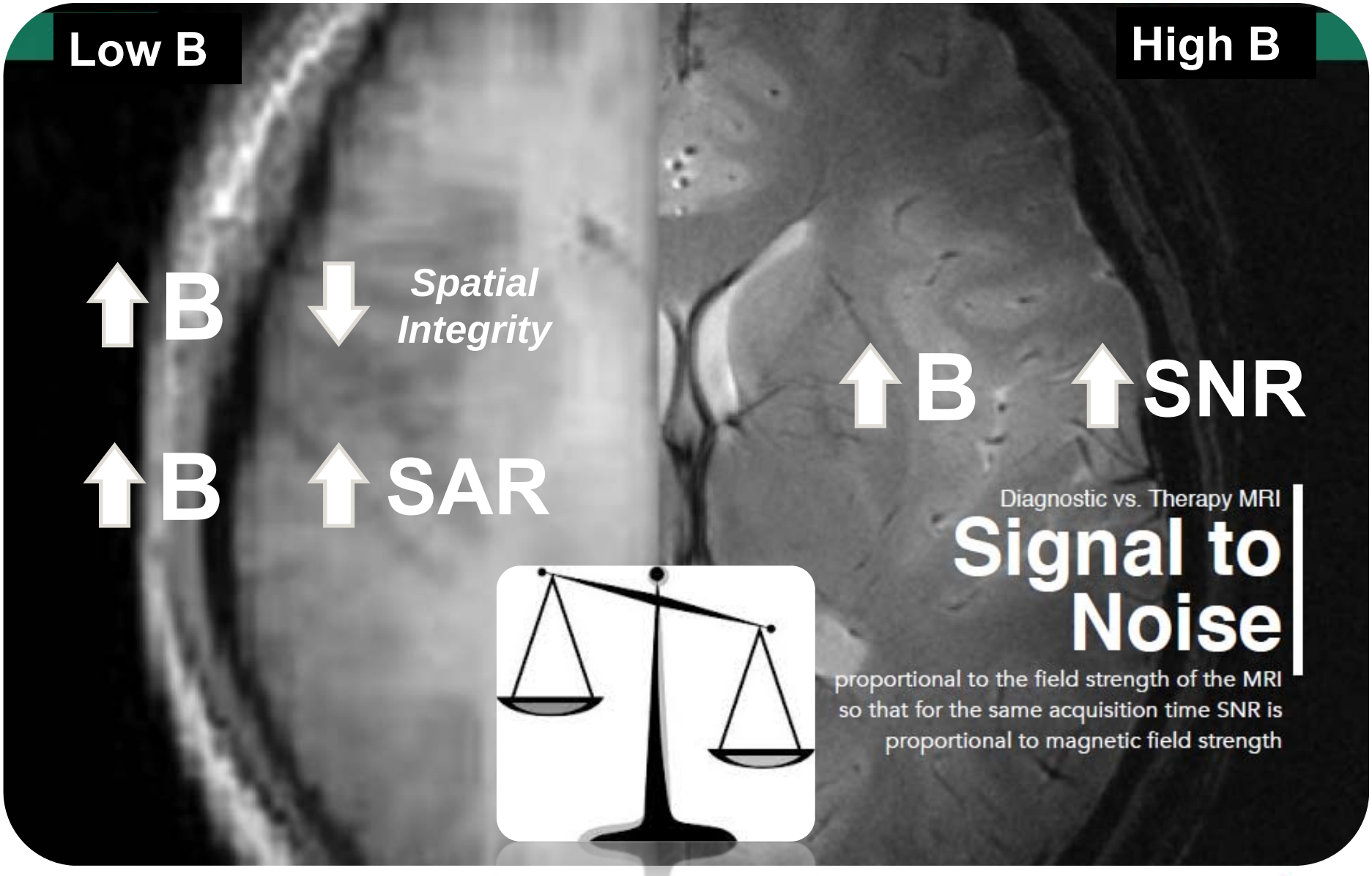
Simulation	Planning	Adaptive	Delivery	Dose Evaluation
• *MR* • *ITV estimation* • *CT*	• *Fusion* • *Contouring* • *ED Transfer* • *Planning* • *Dose Calculation* • *QA*	• *MR Imaging* • *Coregistration* • *Dose Prediction* • *Re-contouring* • *Re-planning* • *Online QA*	• *Tracking* • *Gating* ***IMRT Step & Shoot***	• *DVH sum* • *Dose Accumulation*







MR for planning



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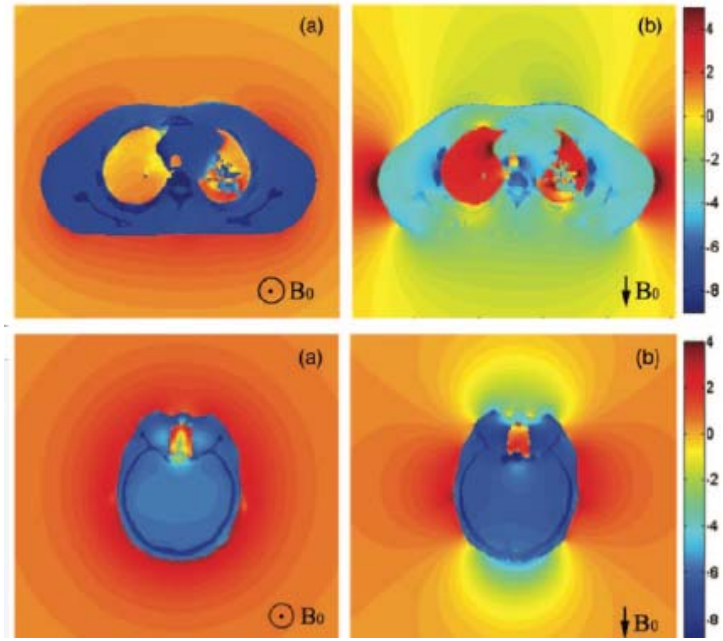
Spatial integrity

Magnetic suscettibility artifacts

Presence of human body

changes B uniformity

$$\Delta x \propto ppm \cdot B$$



Higher spatial artifacts can affect planning process

Stanescu, Wachowicz, & Jaffray Med. Phys. 39 (12), December 2012 pp7185-7193

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Spatial integrity

Chemical Shift

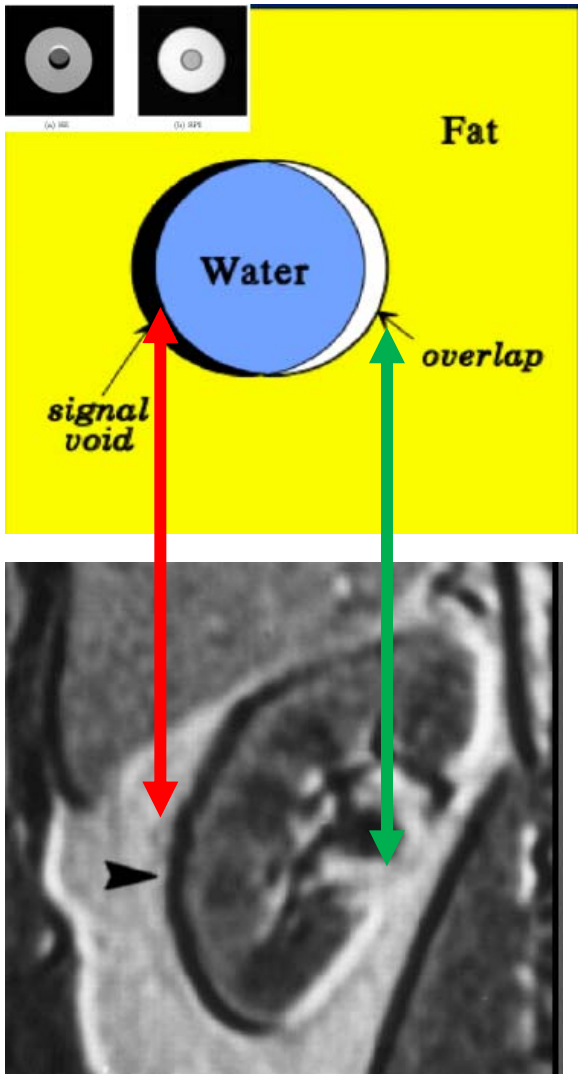
Chemical environment can modify protons precession f producing artifacts in interfaces (water-fat)

This effect depends from B

~ mm → 224 Hz @ 1,5 T

51 Hz @ 0,35 T

< 1 mm



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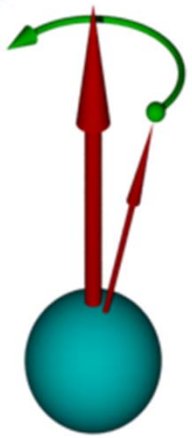
SAR

SAR : Specific Absorbition Rate

Energy absorbed during time in one element having mass m

$$SAR = \frac{1}{t}\frac{E}{m} \left[\frac{W}{kg}\right]$$



In MR absorbition is due to Larmor frequence (protons precession frequence due to B)

14,7 MHz @ 0.35 T

63.86 MHz @ 1.5 T

$$SAR(0.35\,T) = \frac{1}{10} SAR(1,5\,T)$$

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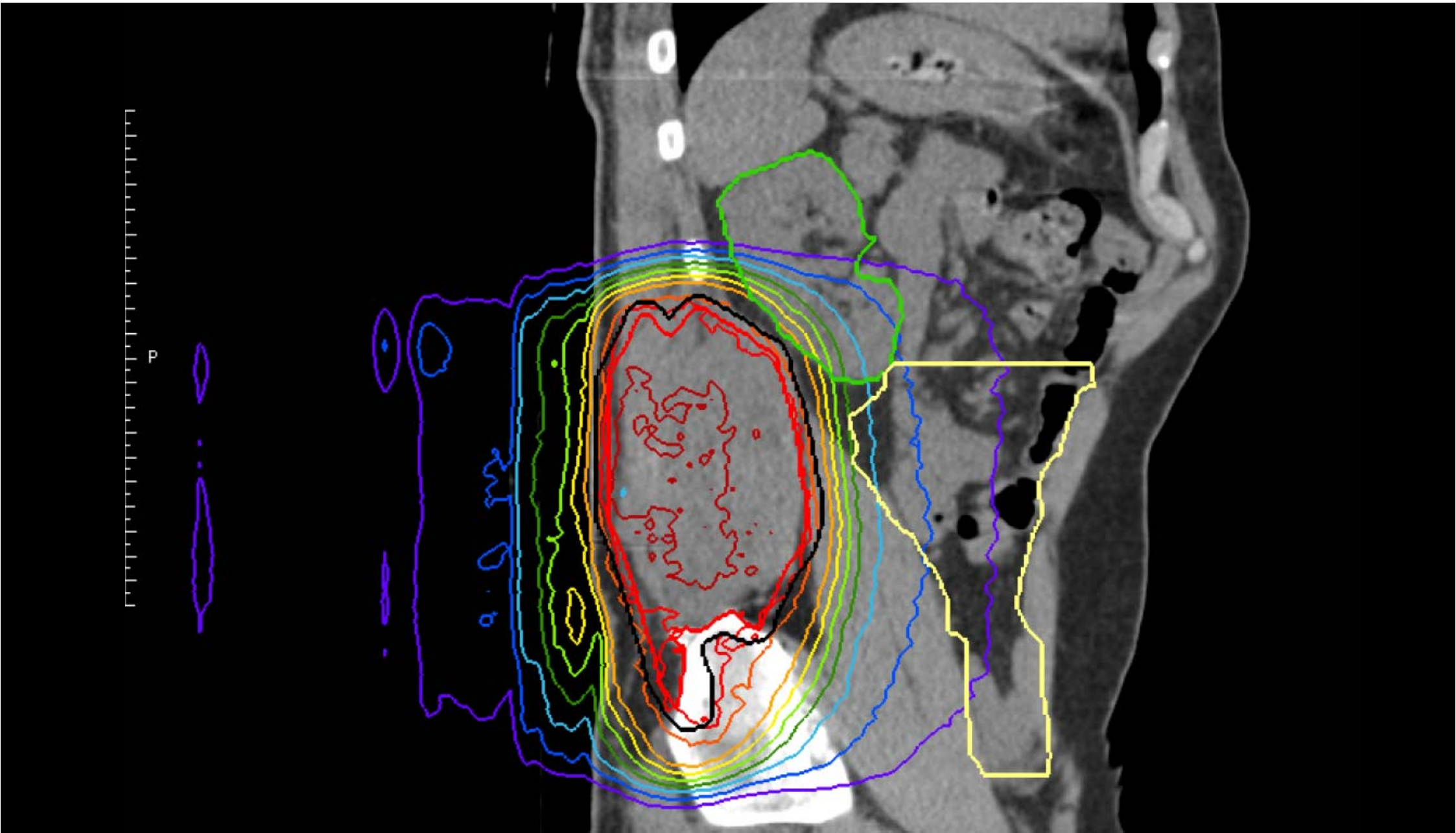
Gating treatment for target movements or target volume shape changes (air)

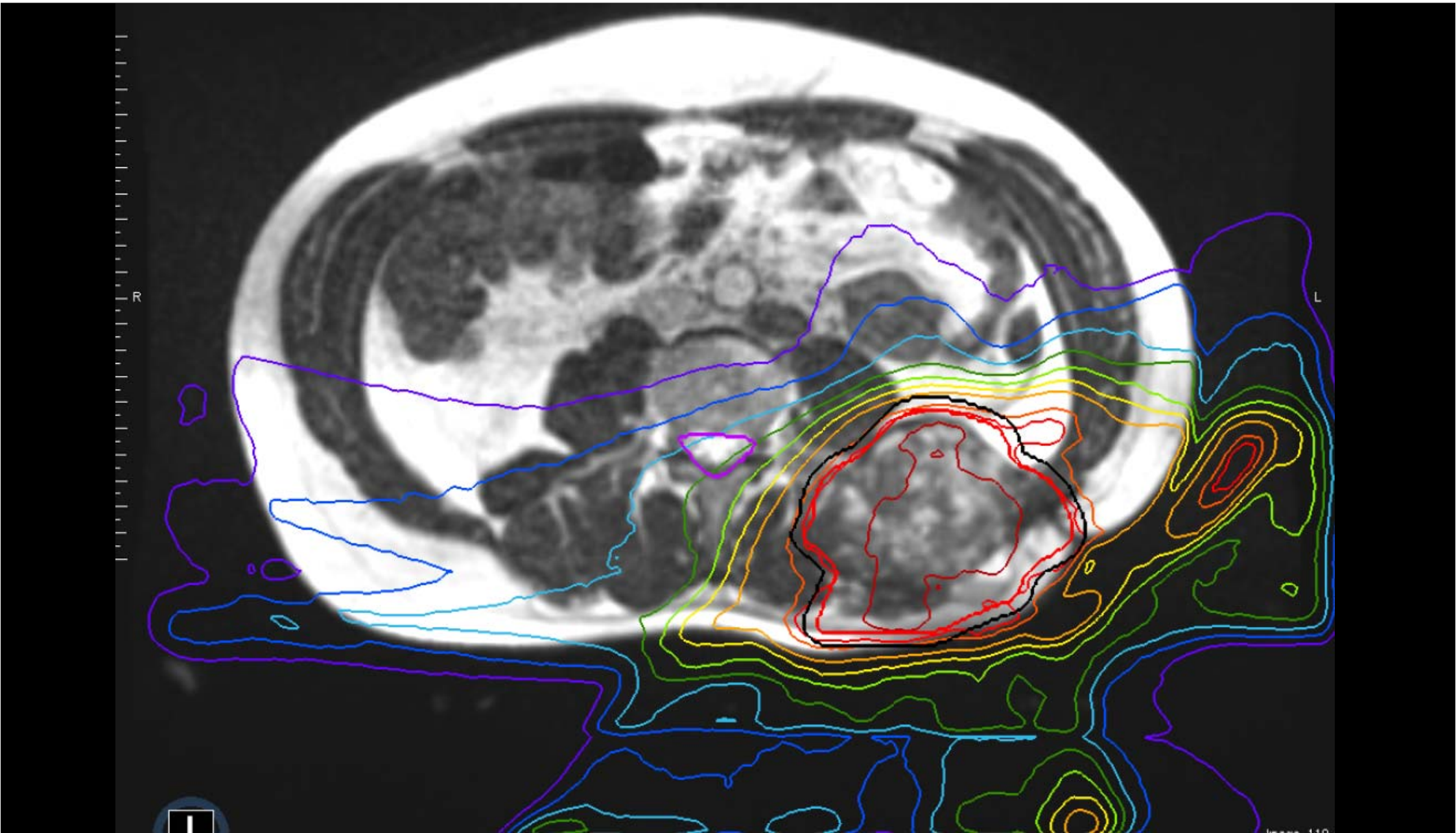
Gating treatment for OAR movements or for PRV boundaries definition

Rhabdomyosarcoma of the back recurrence, near the left kidney

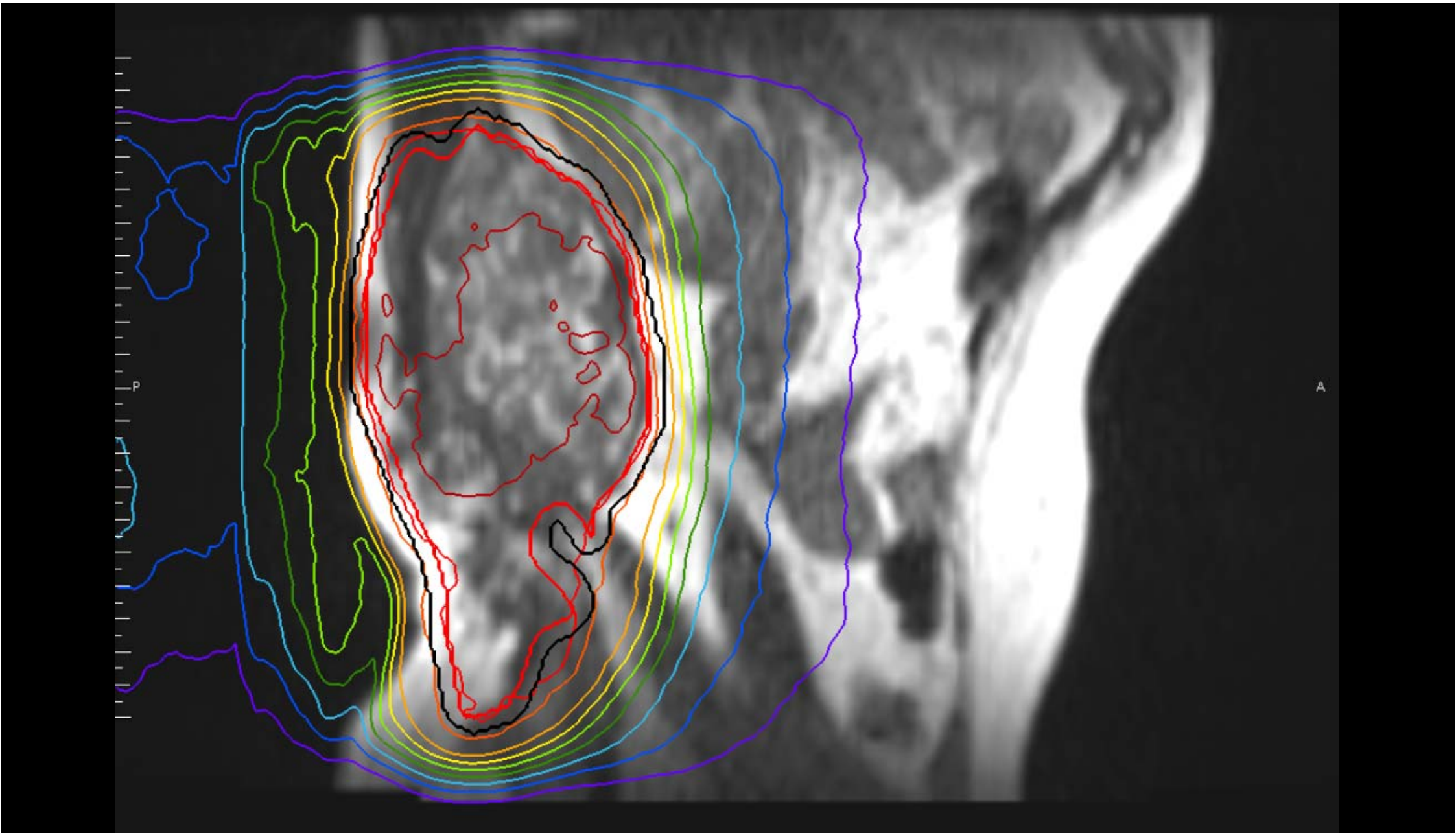
Gating treatment for OAR movements or for PRV boundaries definition



Gating treatment for OAR movements or for PRV boundaries definition



Gating treatment for OAR movements or for PRV boundaries definition

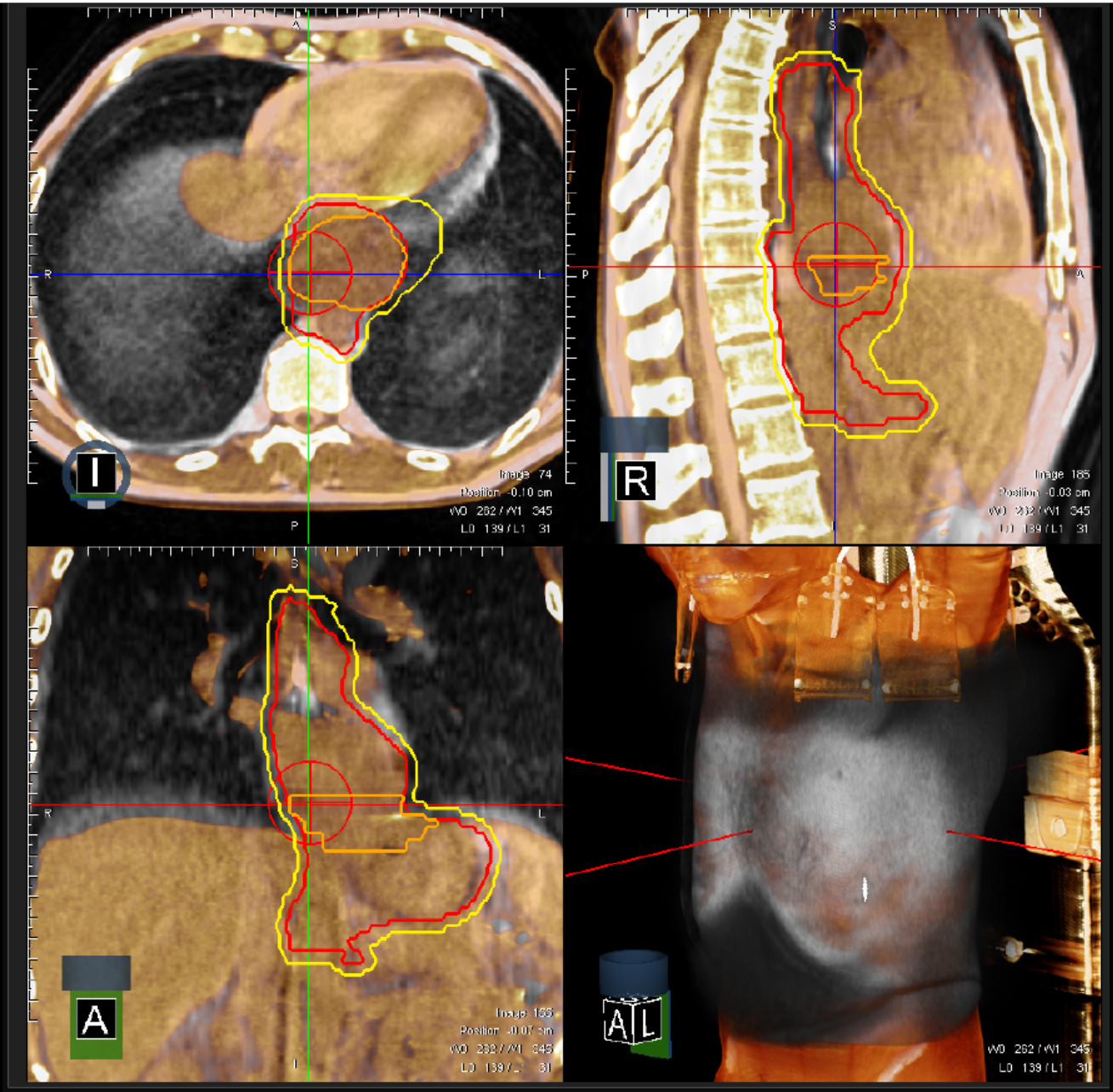


MR for Replanning treatment

Esophageal cancer after 17 fractions

MR for Replanning treatment

Day 1



Thank you!

Grazie!

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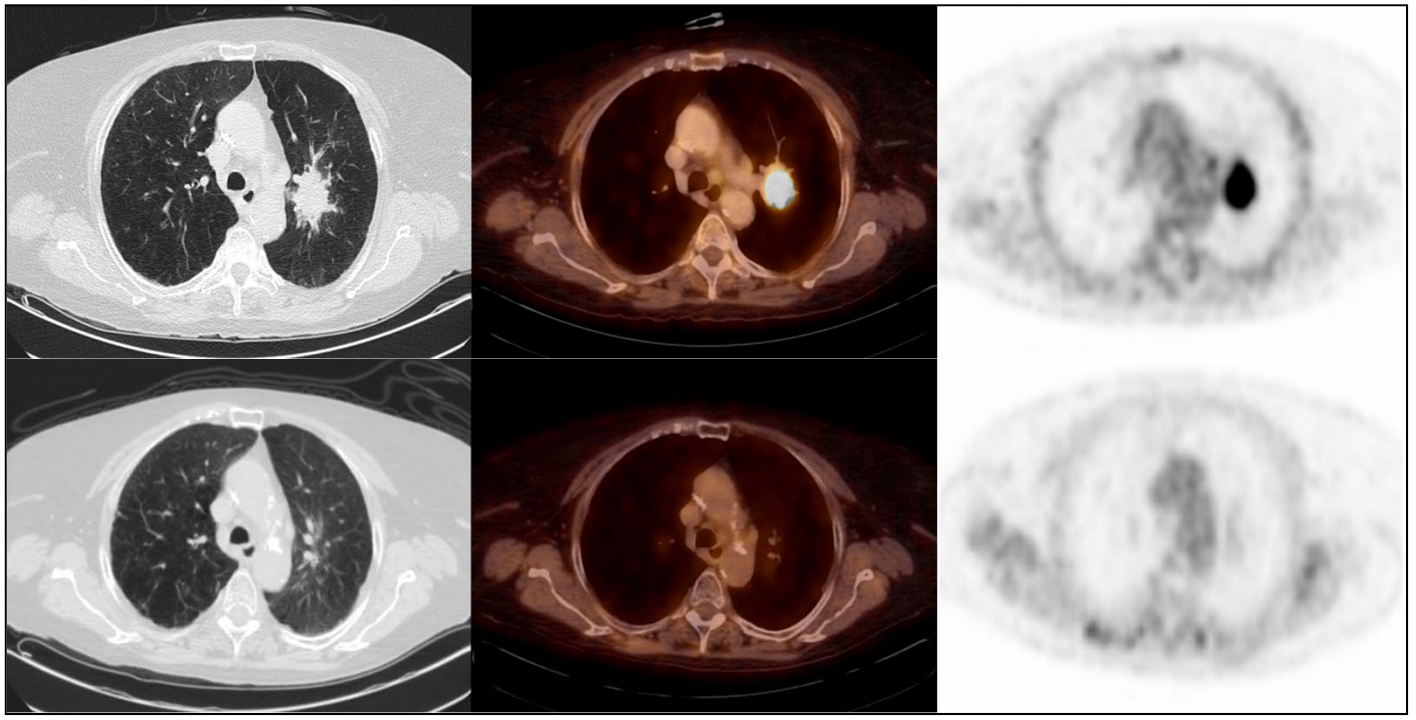
WWW.ESTRO.ORG/SCHOOL

Kliniken Maria Hilf
Mönchengladbach

UNIVERSITÄTS KLINIKUM FREIBURG

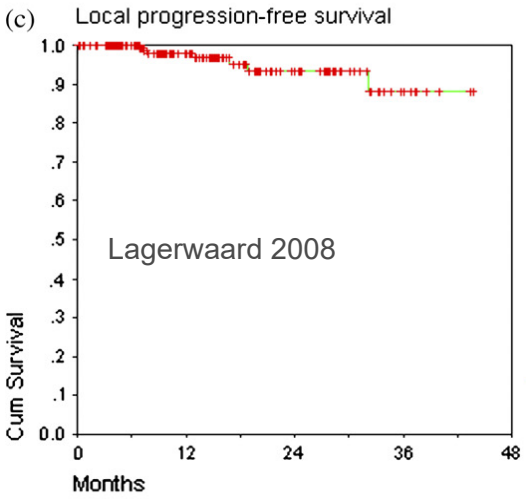


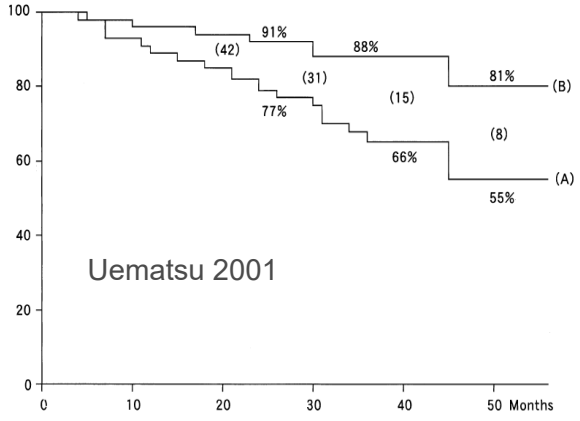
Advanced planning strategies for lung cancer

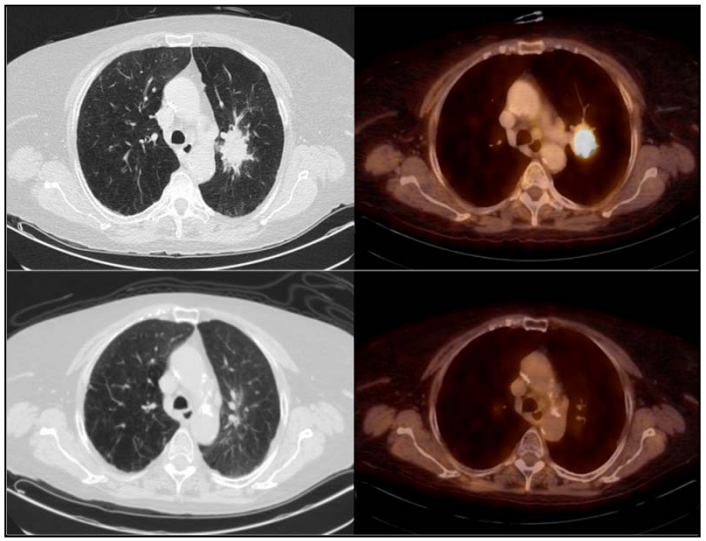
Example: SBRT for lung tumors

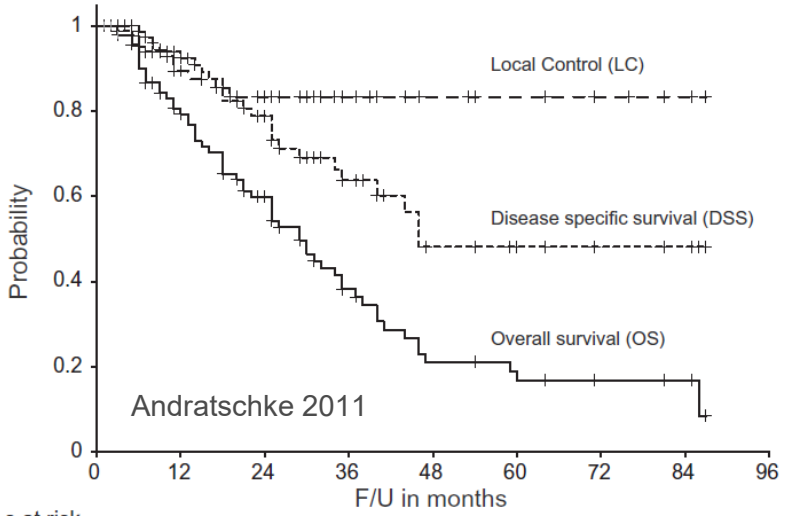
Ursula Nestle

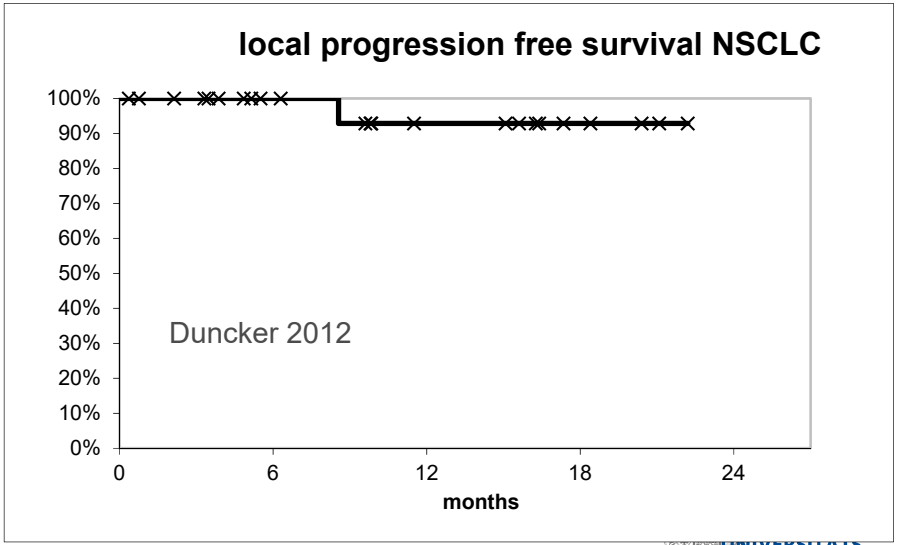
SBRT: success story





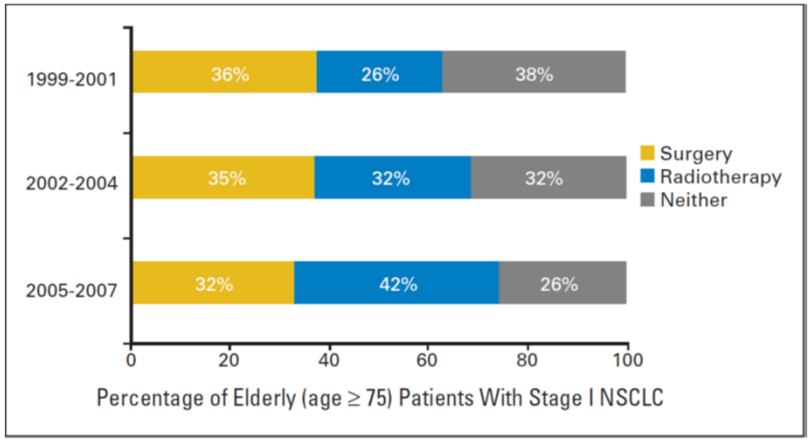




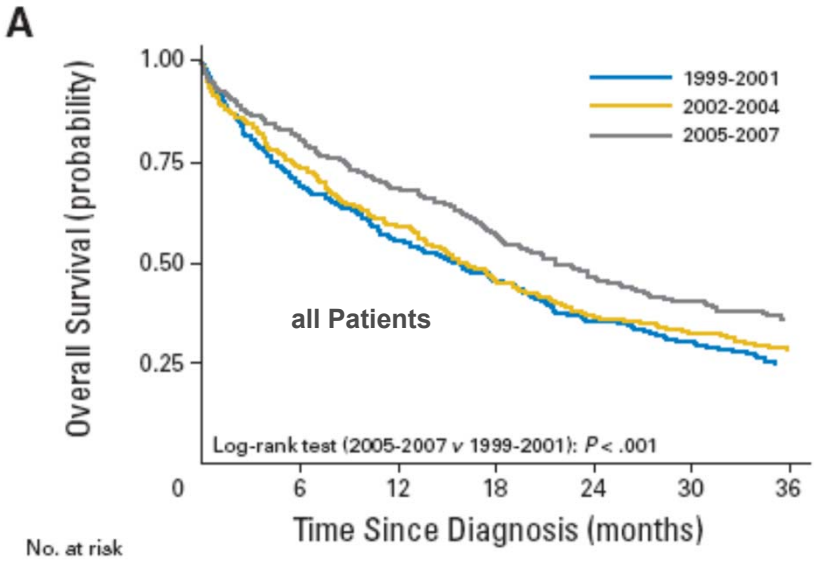


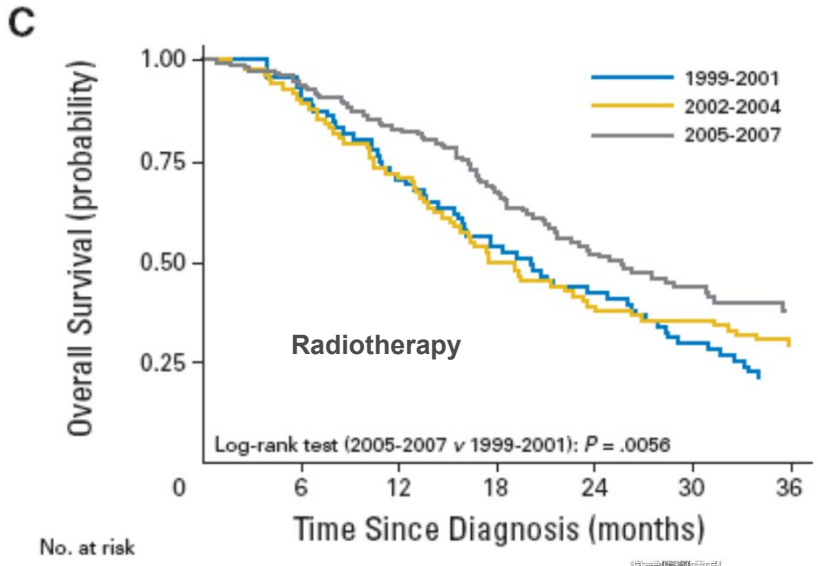
SBRT: improving outcomes stage I LC

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?

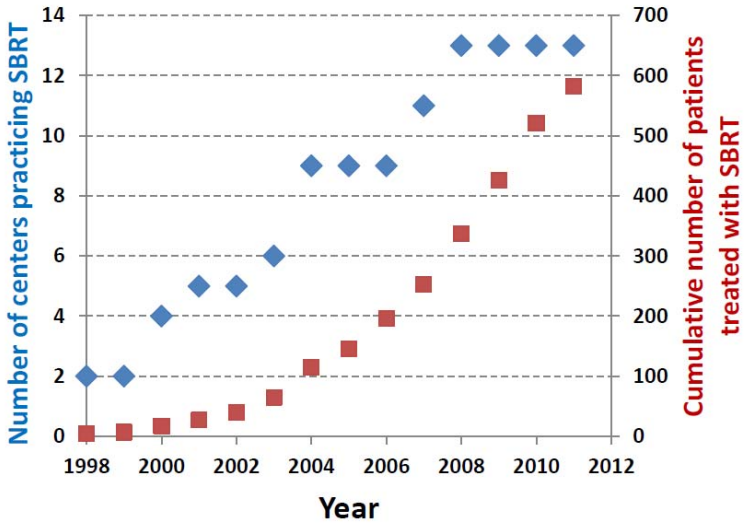
Author	fractionation	dose prescription on % isodose	dose encompassing the PTV	BED for tumor (prescribed dose)	BED on 100%
van Baardwijk [22]	10 x 6 Gy	100%	60 Gy	96 Gy	
Haasbeek [45]	8 x 7.5 Gy	100%	60 Gy	105 Gy	
Mc Garry [16]	3 x 8 Gy	80%	24 Gy	43 Gy	
Mc Garry [16]	3 x 20 Gy	80%	60 Gy		262 Gy
Mc Garry [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

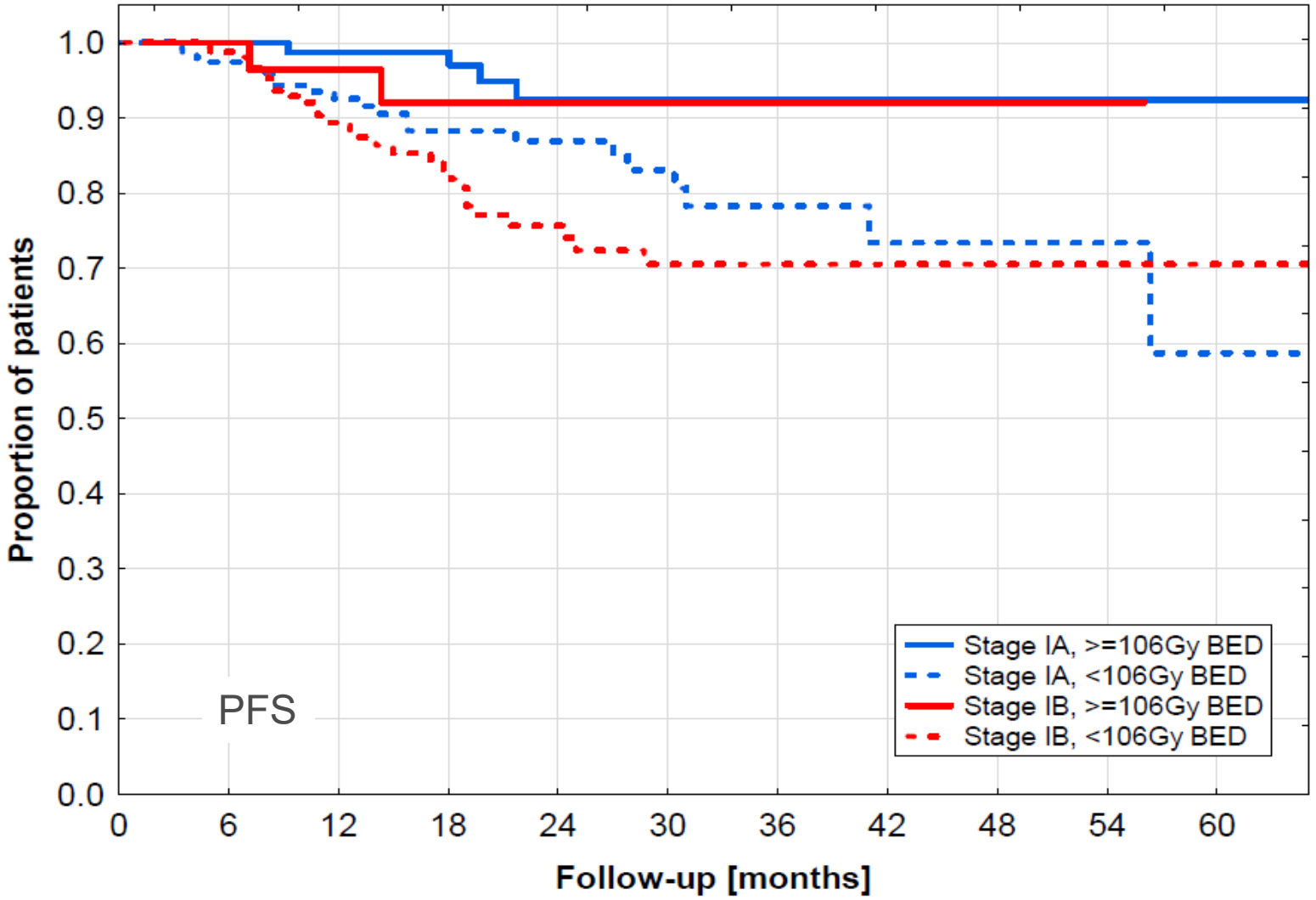
SBRT: wide use, high heterogeneity

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

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

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

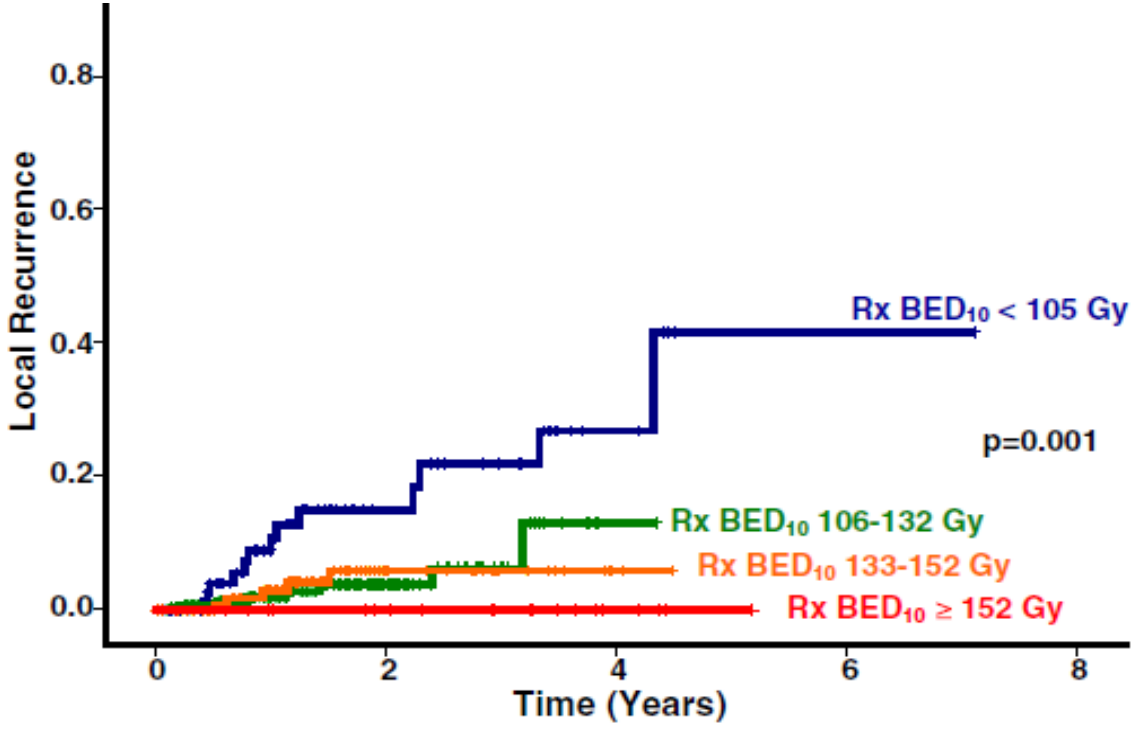
prescriptions (median: 54 Gy/3 fx):

- 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

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

J. Nyman et al. world lung 2015

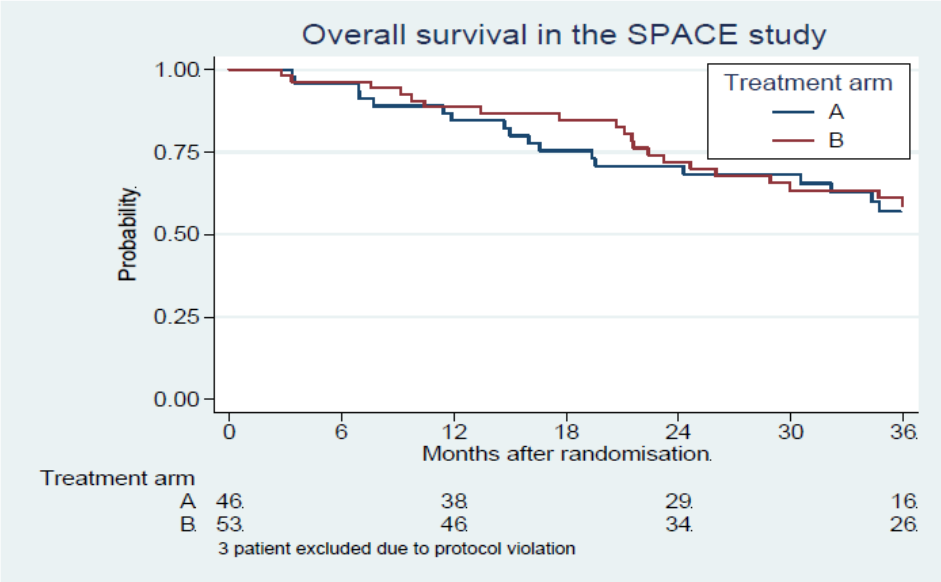
102 patients,
(T1-2N0M0) NSCLC,
significant comorbidity

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

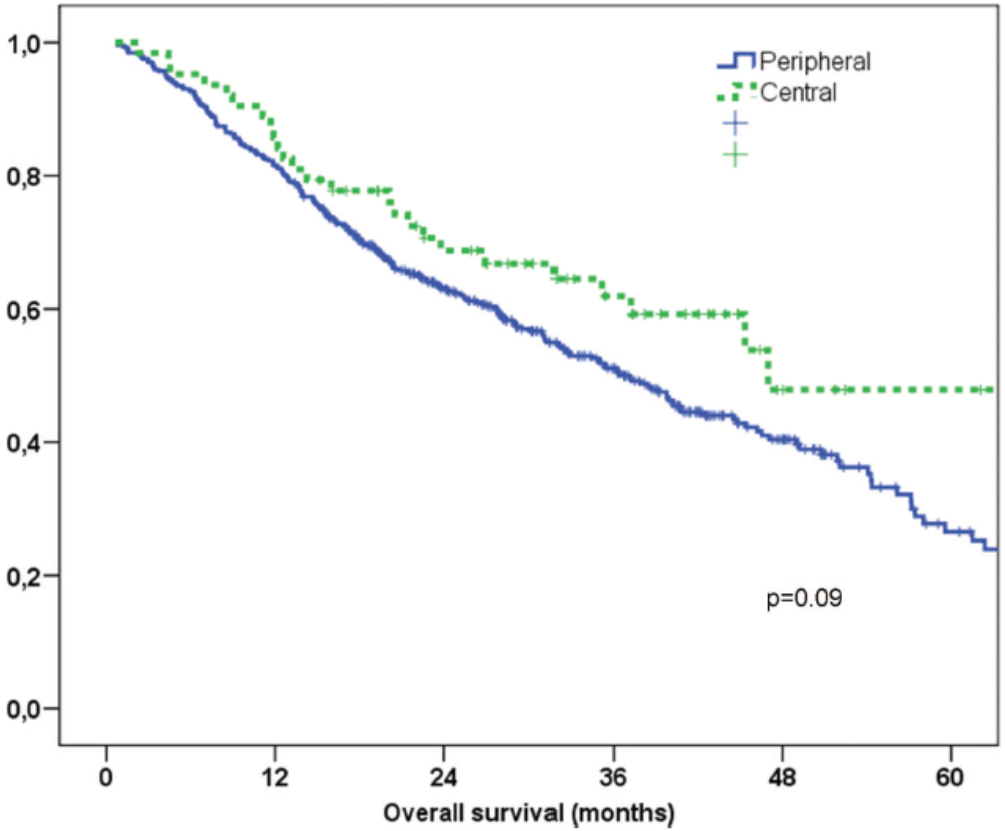
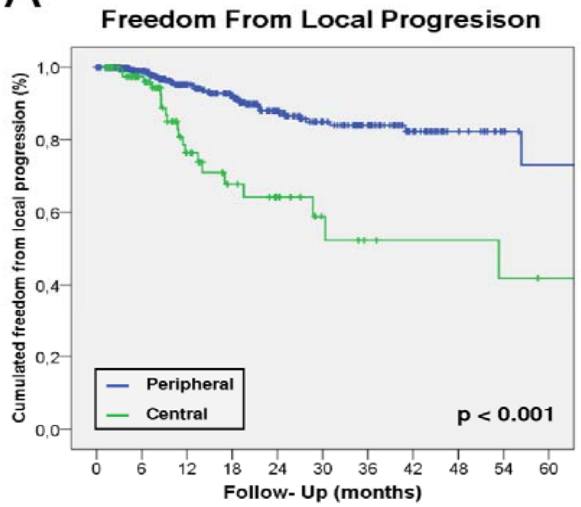


FIGURE 3. Overall survival for central and peripheral early-stage lung tumors after stereotactic ablative radiotherapy (SABR).

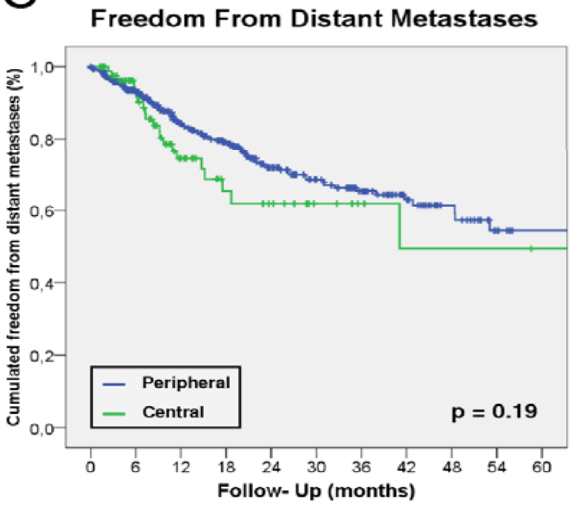
Haasbeek JTO 2011, BED_{10}=105 Gy

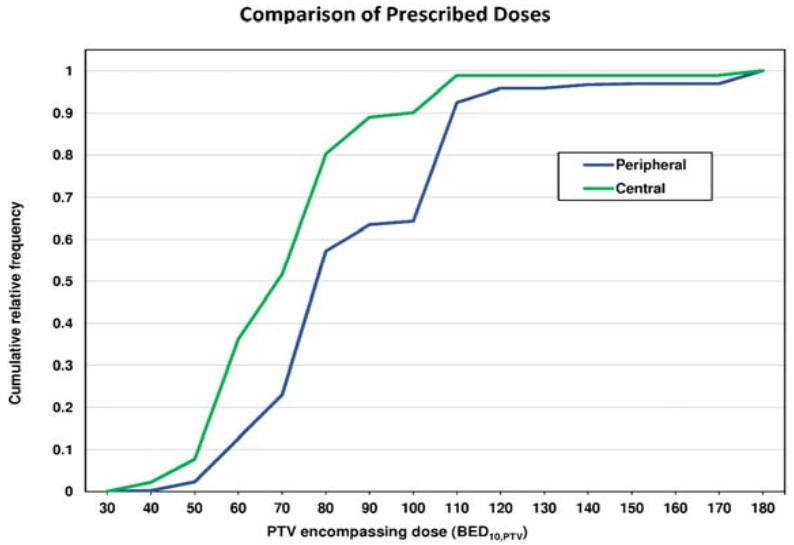
Central tumors, multicenter database

A



C





"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

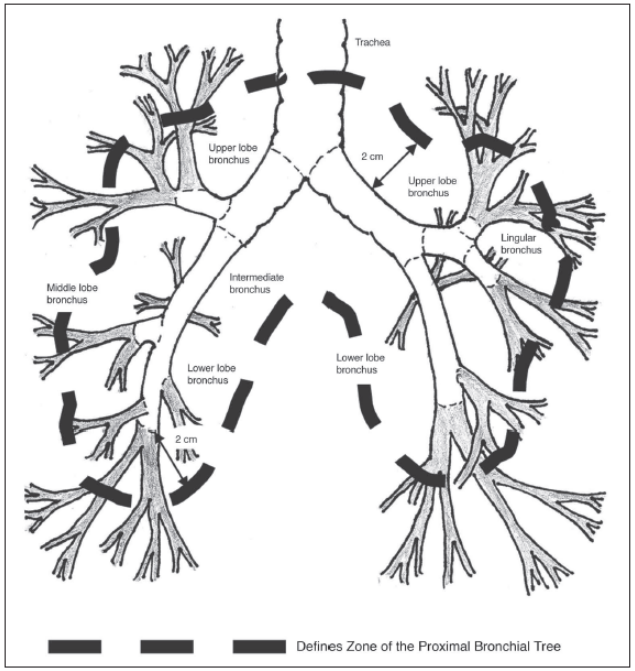
Toxicity!

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

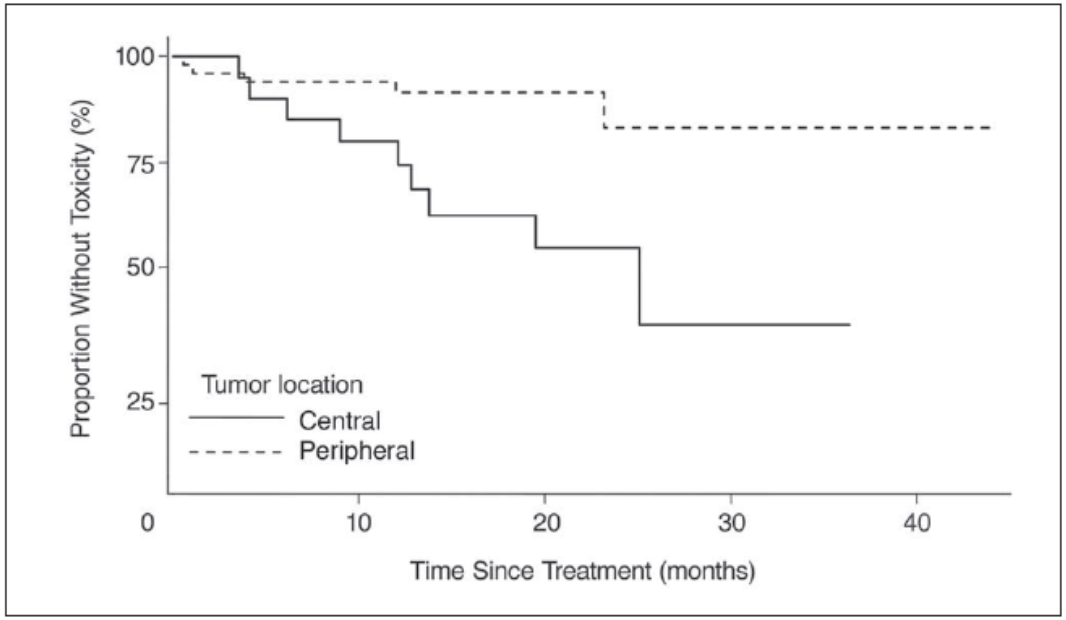
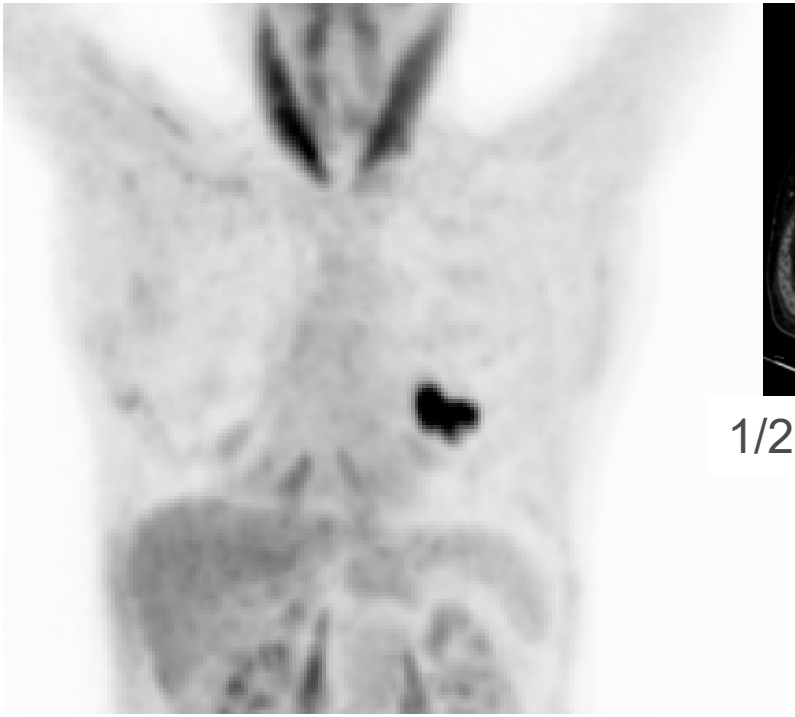
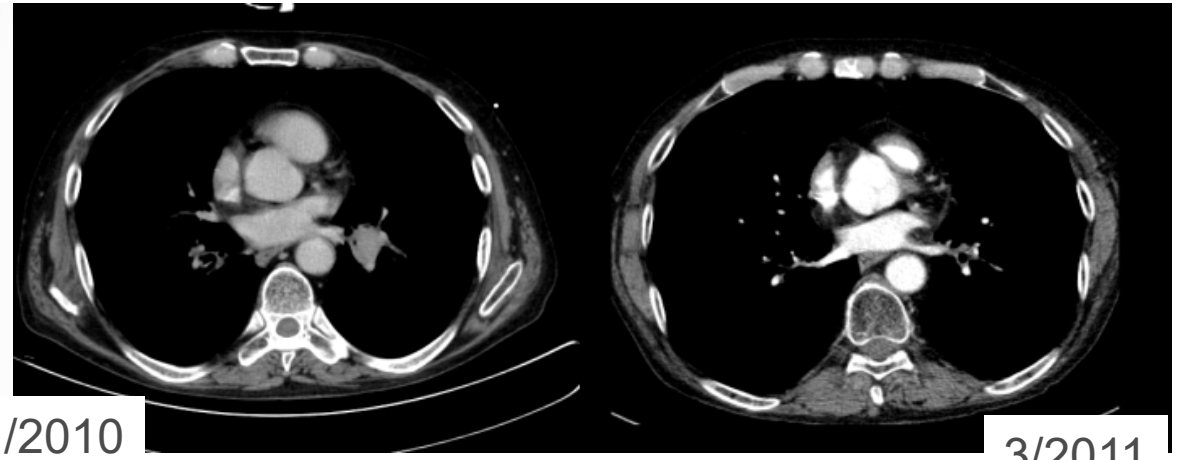


Fig 4. Kaplan-Meier plot of time from treatment until grade 3 to 5 treatment related toxicity comparing patients with tumors in the central (perihilar and central mediastinal) regions from those with more peripheral tumors.

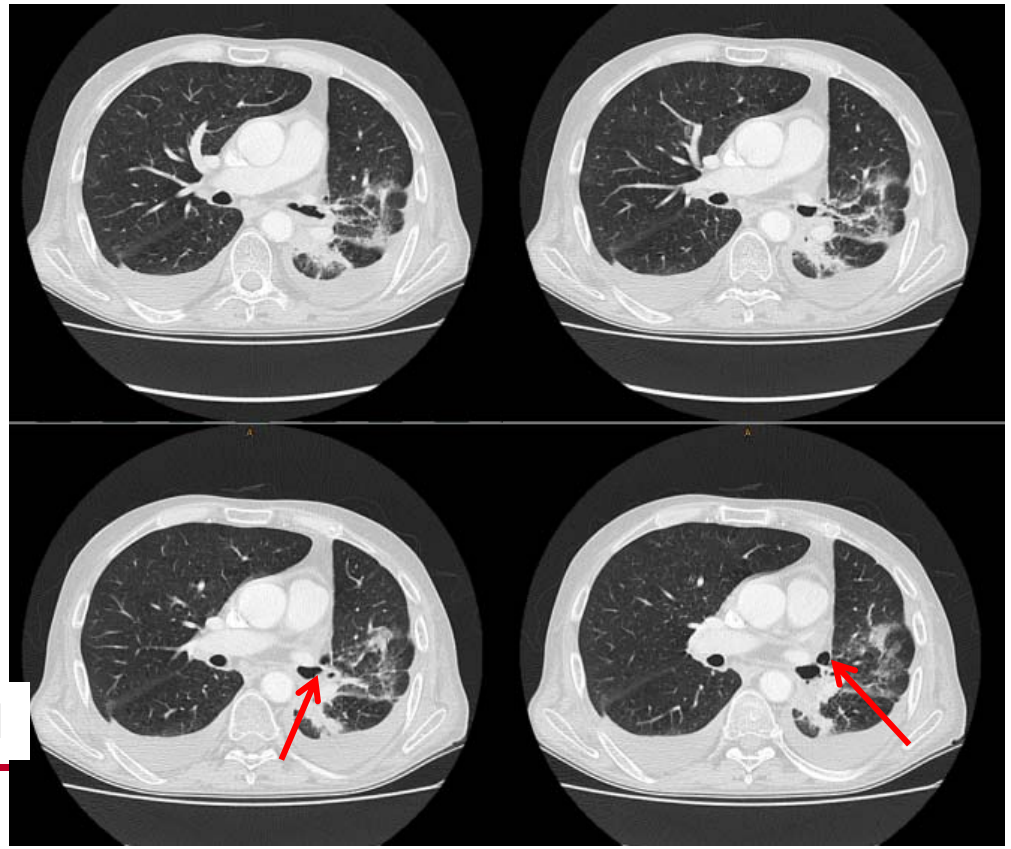
Pat. S.D. *1943, SCC

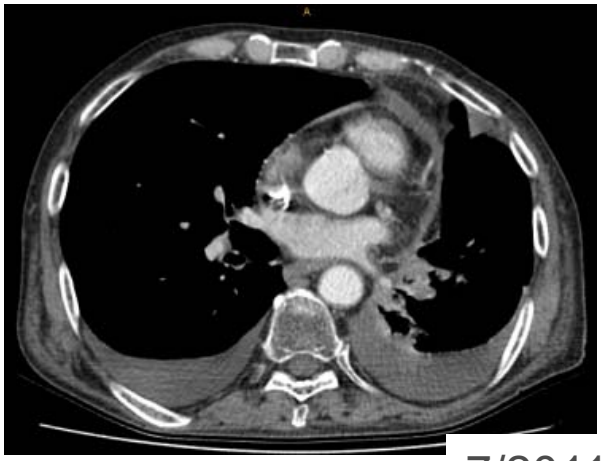




1/2010

3/2011



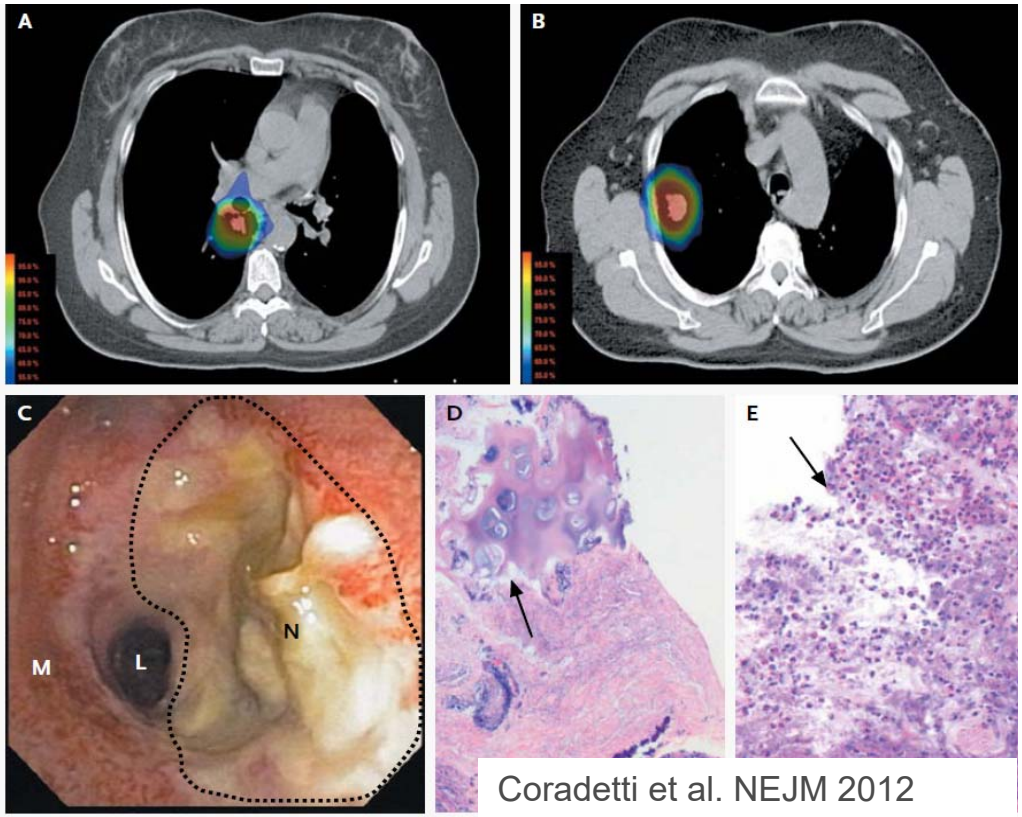


7/2011

Another fatal necrosis after central SBRT…

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

SBRT: a knife without suture

Differences in physiological NT-reaction to high dose RT:

Fibrosis (lung, liver), necrosis (brain, bone), strictures (esophagus, bronchi)

Difference in clinical consequences:

Parallel vs. serial organs

Parallel (lung, liver):

small volume of damage no problem (fibrosis)

Serial (esophagus, vessel):

small volume of damage

may cause life threatening effects

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

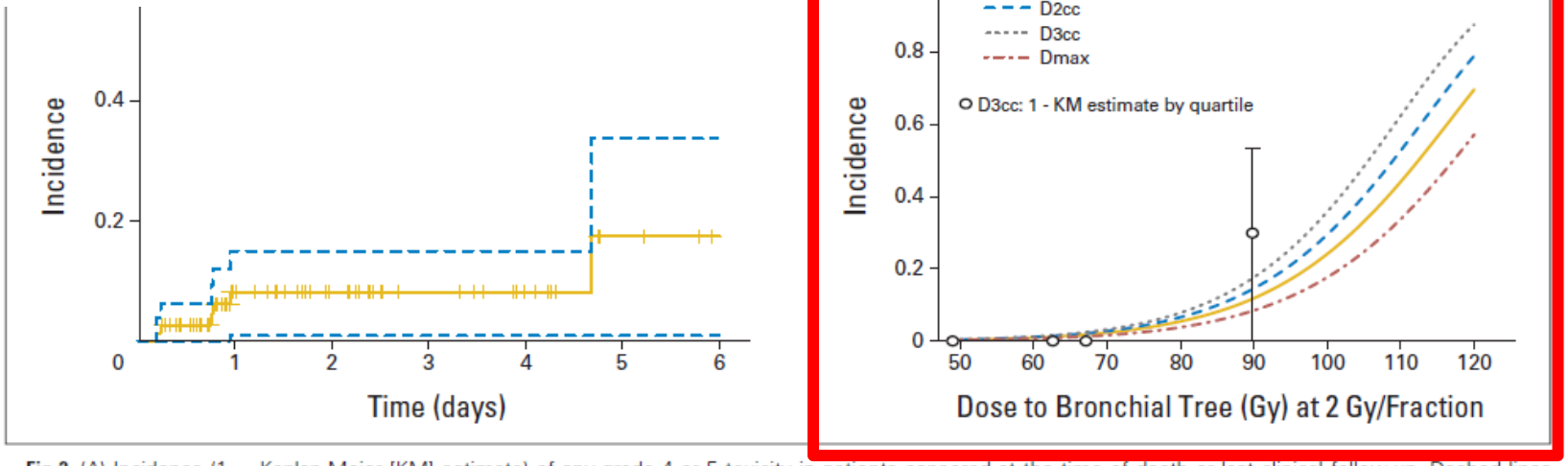
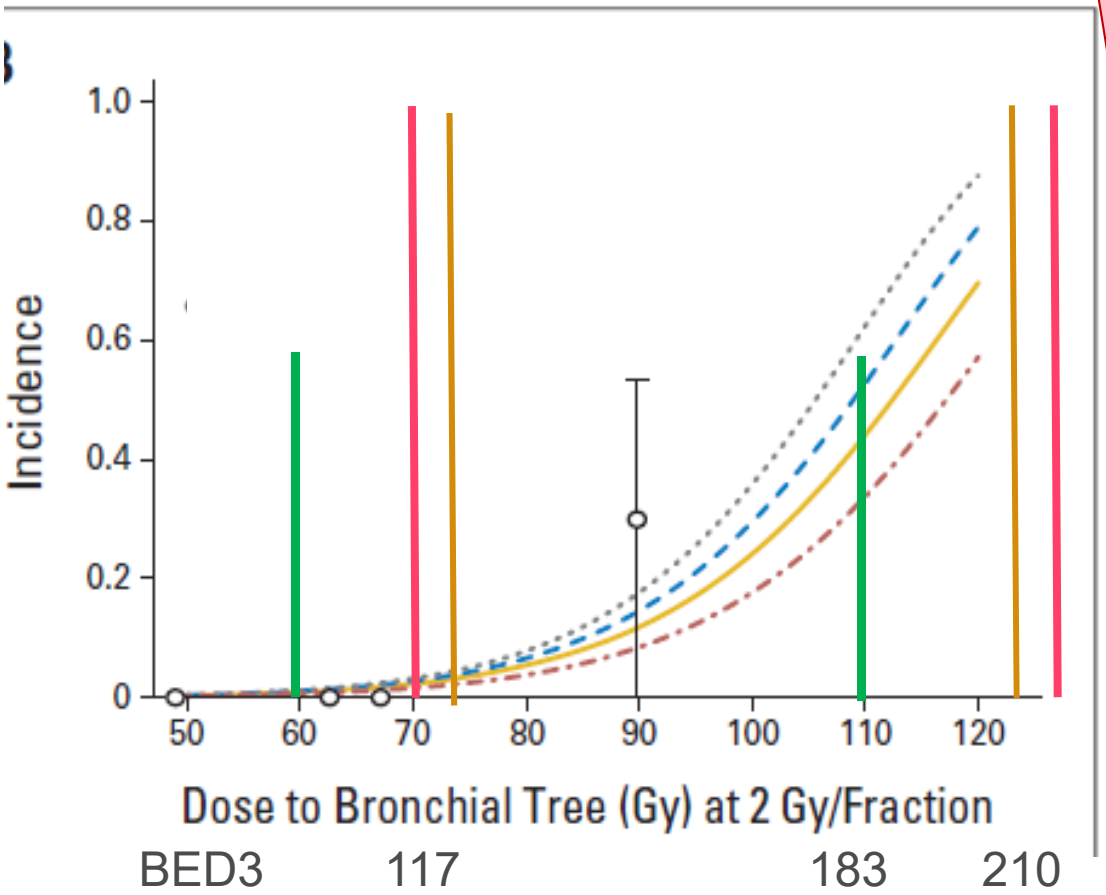


Fig 2. (A) Incidence (1 − Kaplan-Meier [KM] estimate) of any grade 4 or 5 toxicity in patients censored at the time of death or last clinical follow-up. Dashed lines represent the 95% CI. (B) Two-year probabilities of late grade 4 or 5 toxicity according to dose-per-fraction normalized dose (EQD2) to 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.

What is the dangerous SBRT dose to the central mediastinum?

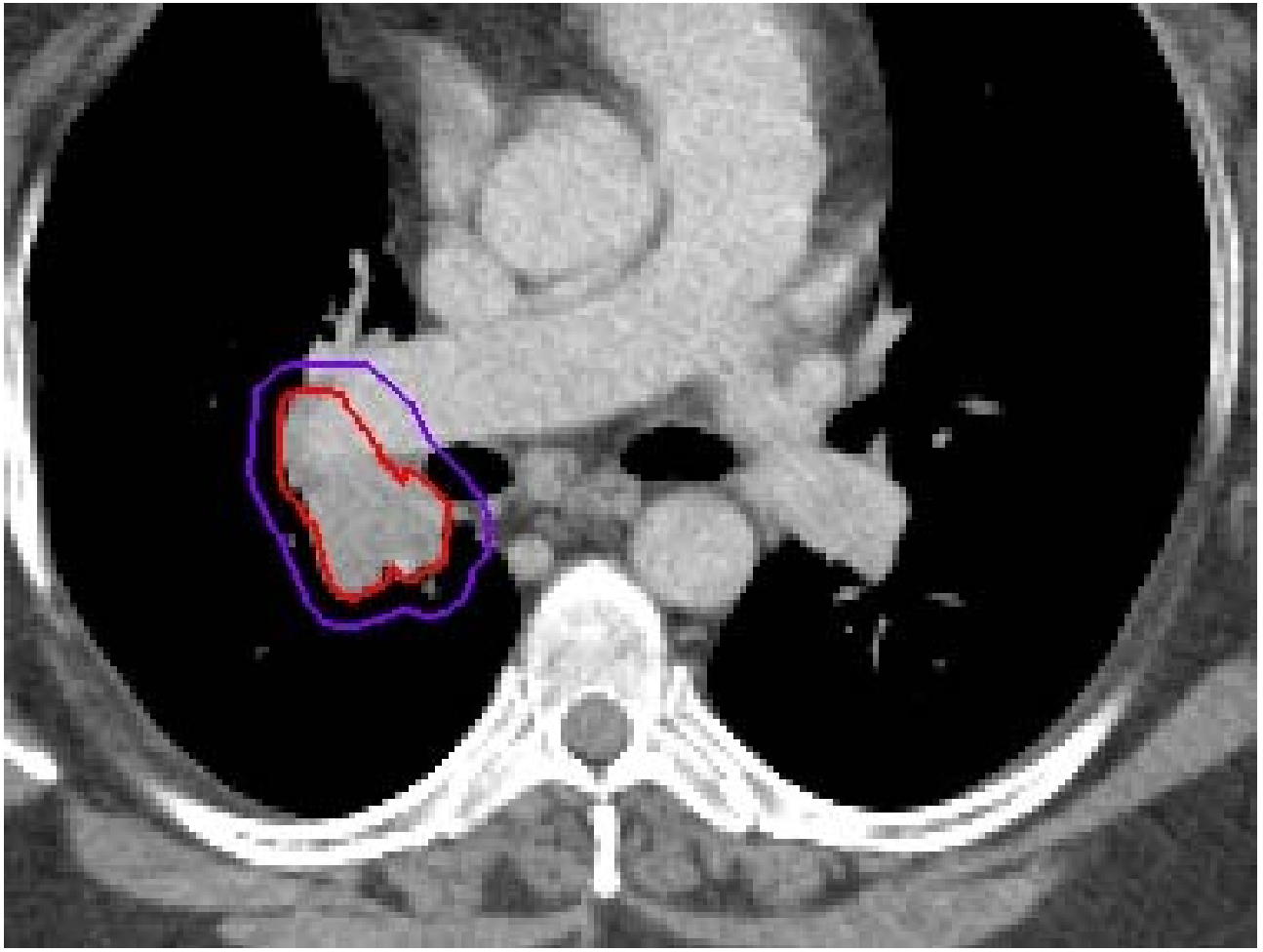
MTD of 83 Gy/ 2Gy
= „magic“ BED_{10} of 100 Gy,
Narrow therapeutic corridor



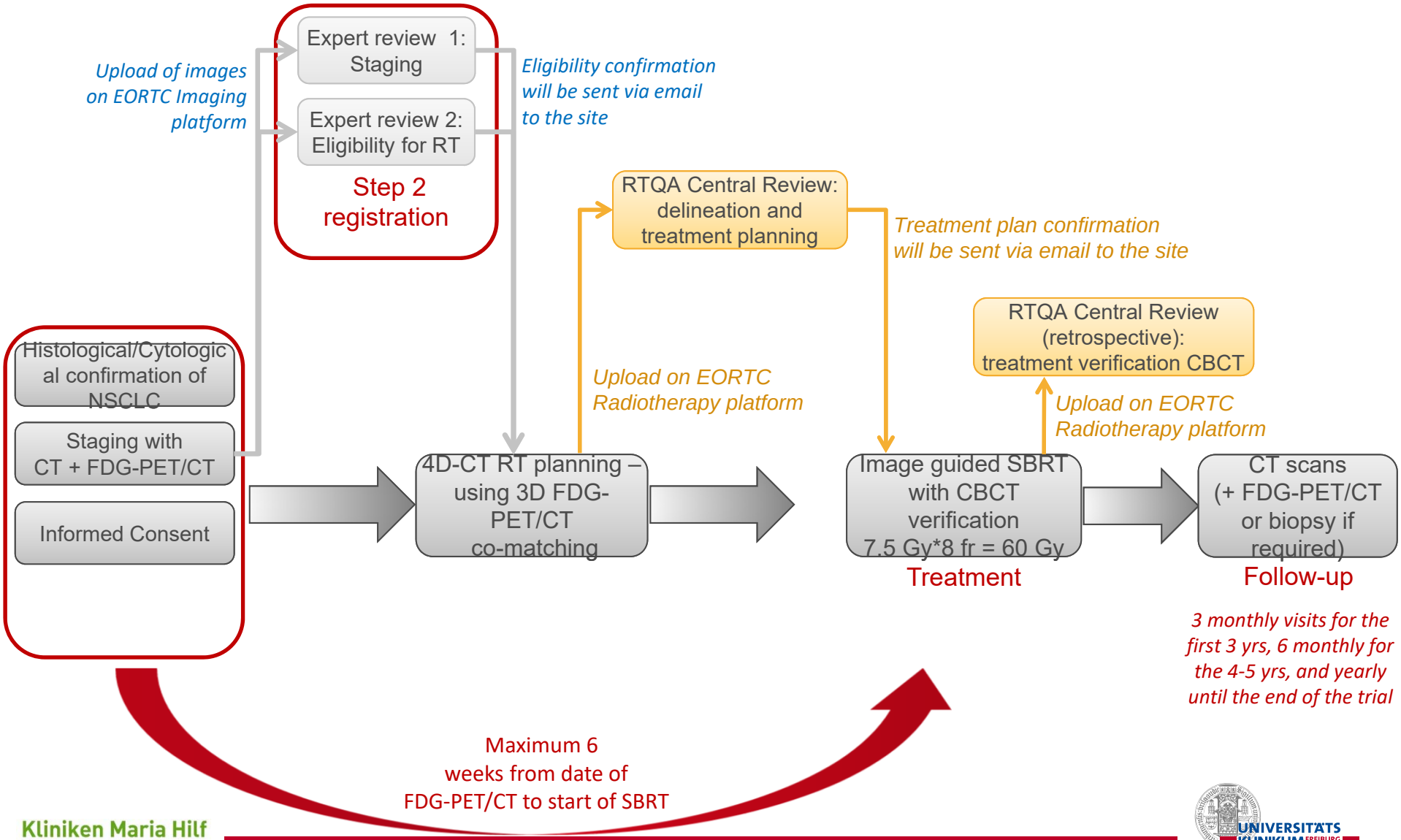
prescribed by	physical dose Gy	EQD2 Gy (αβ=3)
Cannon min.	25x2.28	60
max.	25x3.42	110
Timmerman	3x18	226
VU prescription	8x7.5	126
VU restriction	8x5.5	74.8
Coradetti patient	5x10	130
Freiburg patient encompassing	5x7	70
maximum	5x11.6	130

Need for a more detailed view on doses and volumes..

“competing risk”:
Tumor invasion of bronchus and vessel



22113 – 08113 Trial design



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.

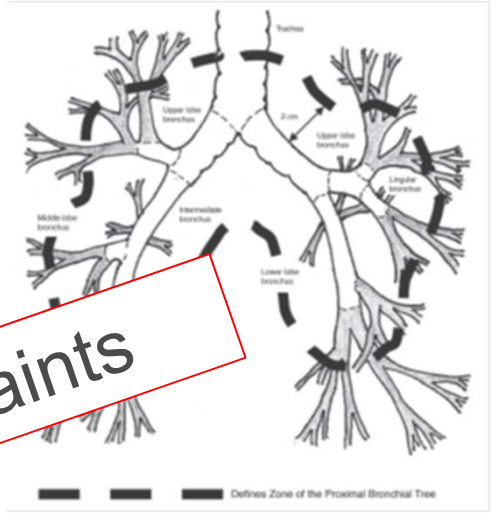
LUNGTECH – KEY NOTES

- *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 l pping rules)
  - patt d distant recurrence
  - ove ival and causes of death

… need to define NT constraints

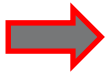


Timmerman et al , JCO 2006

- *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

Received May 9, 2013, and in revised form Jul 14, 2013. Accepted for publication Jul 17, 2013

International Journal of Radiation Oncology biology • physics

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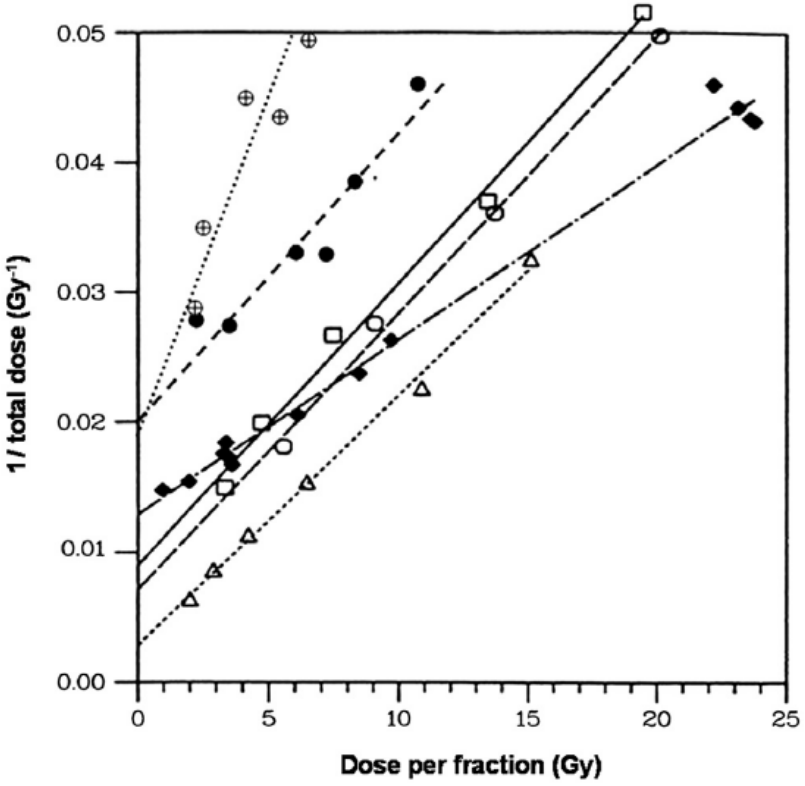


"Thus, we suggest that for most tumors, the standard radiobiology concepts of the 5 Rs are sufficient to explain the clinical data …"

"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/fractionation*
Timmerman (50)	70	1	r	with 19.5
Fakiris (50)				ns),
M				
Os				
Br				
Ung				
Canc	73*	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)**

Gy) #

Gy, **EqD2 not applicable**)

EqD2: 140 Gy) #

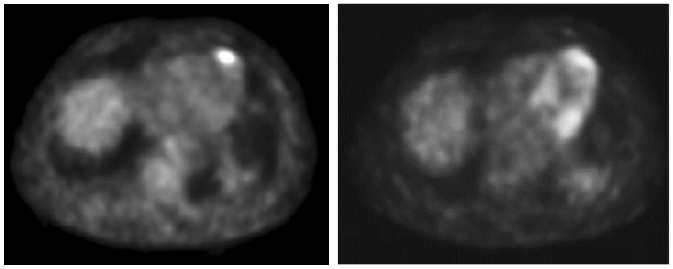
…cessively fatal hemoptysis after stent insert, 4x15Gy=60Gy (**EqD2:**

1 x bronchial fistula, mainstem bronchus received a maximum point dose of 49 Gy (**EqD2 not applicable**)

Adebahr et al , BJR 2015

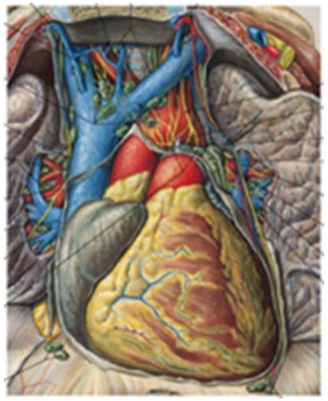
DOSE CONSTRAINTS: **HEART**

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

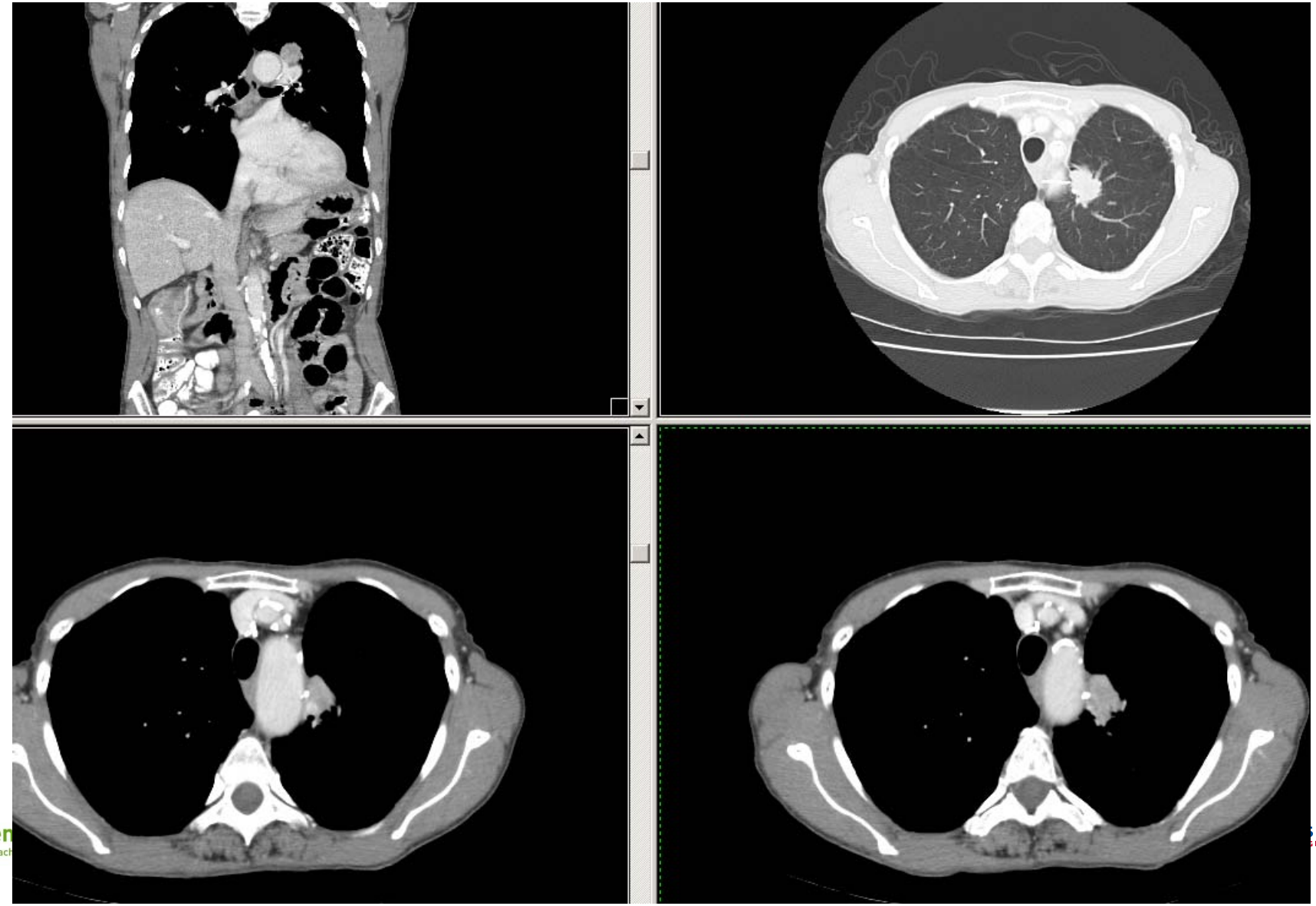
Adebahr et al , BJR 2015

Great vessels: a case from A. Bezjak

59 yr old lady, 2.2 cm adenoca, SUV 8

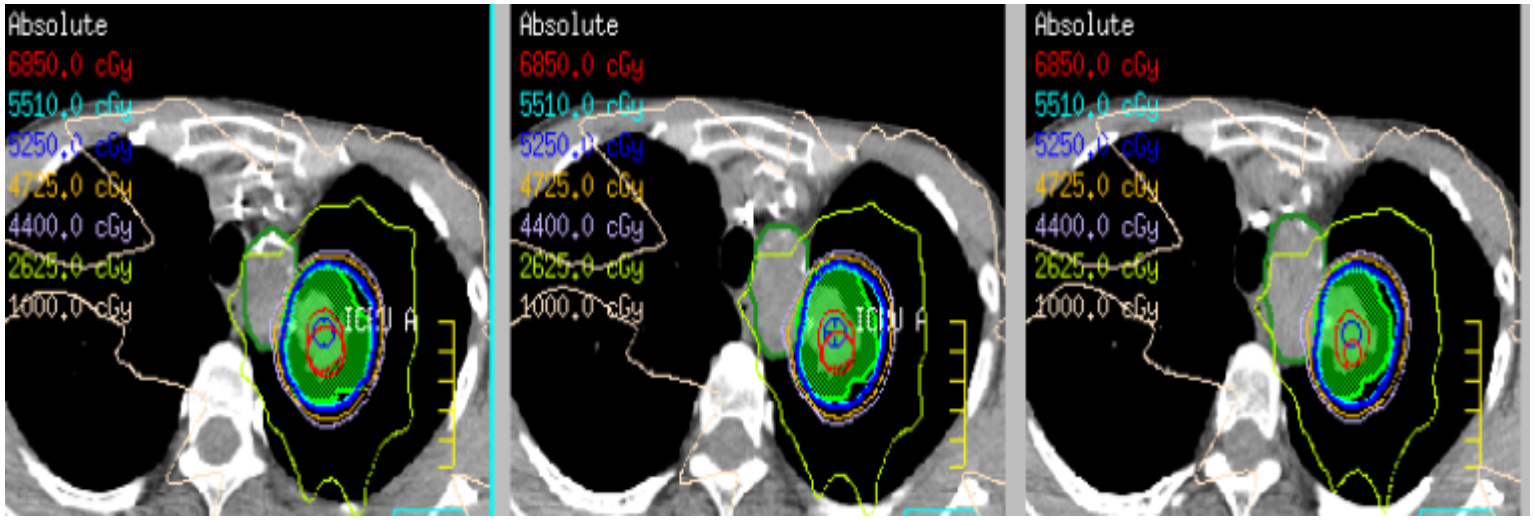
previous RUL and LUL lobectomies 4 and 6 yrs prior

b2

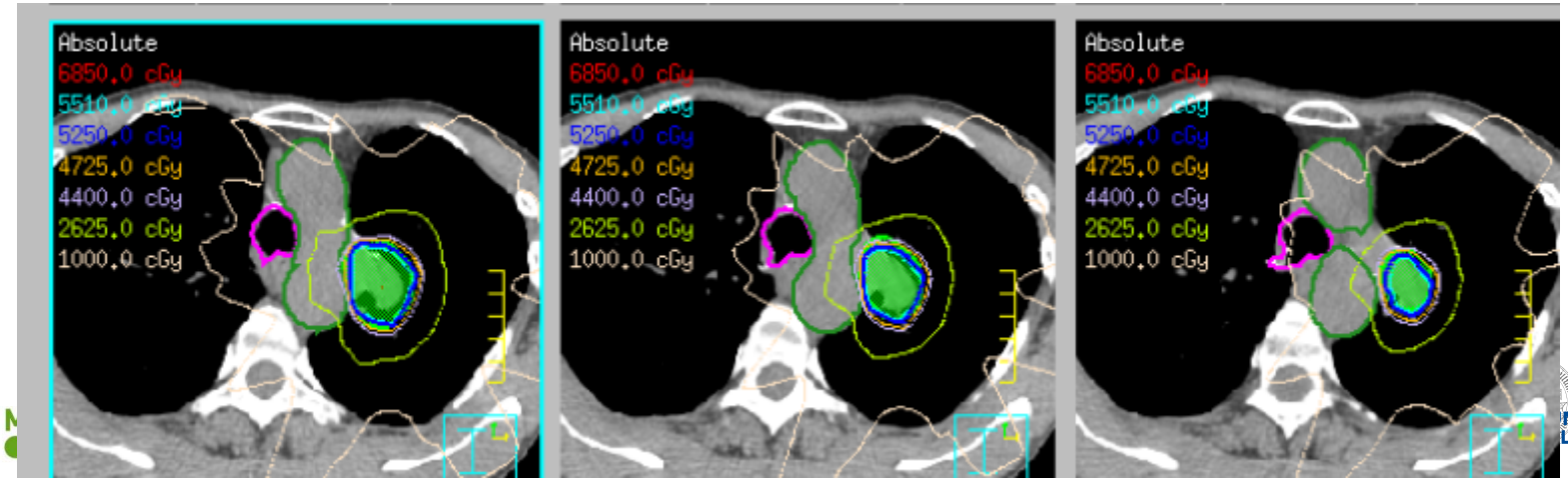


Slide 28

b2 bezjaka; 08-06-11



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

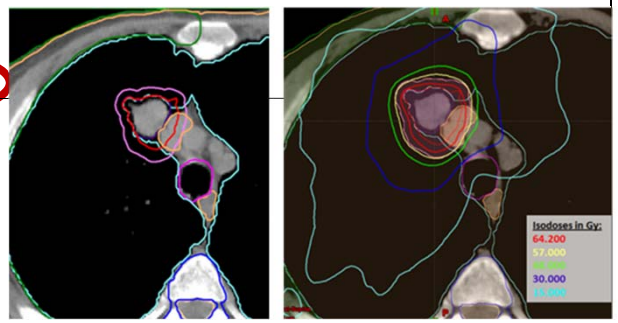
Next day blood - ? coughed or vomited – called ambulance – pt arrested within minutes of ambulance arrival –resuscitation attempts unsuccessful

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

Esophageal toxicity

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 2015

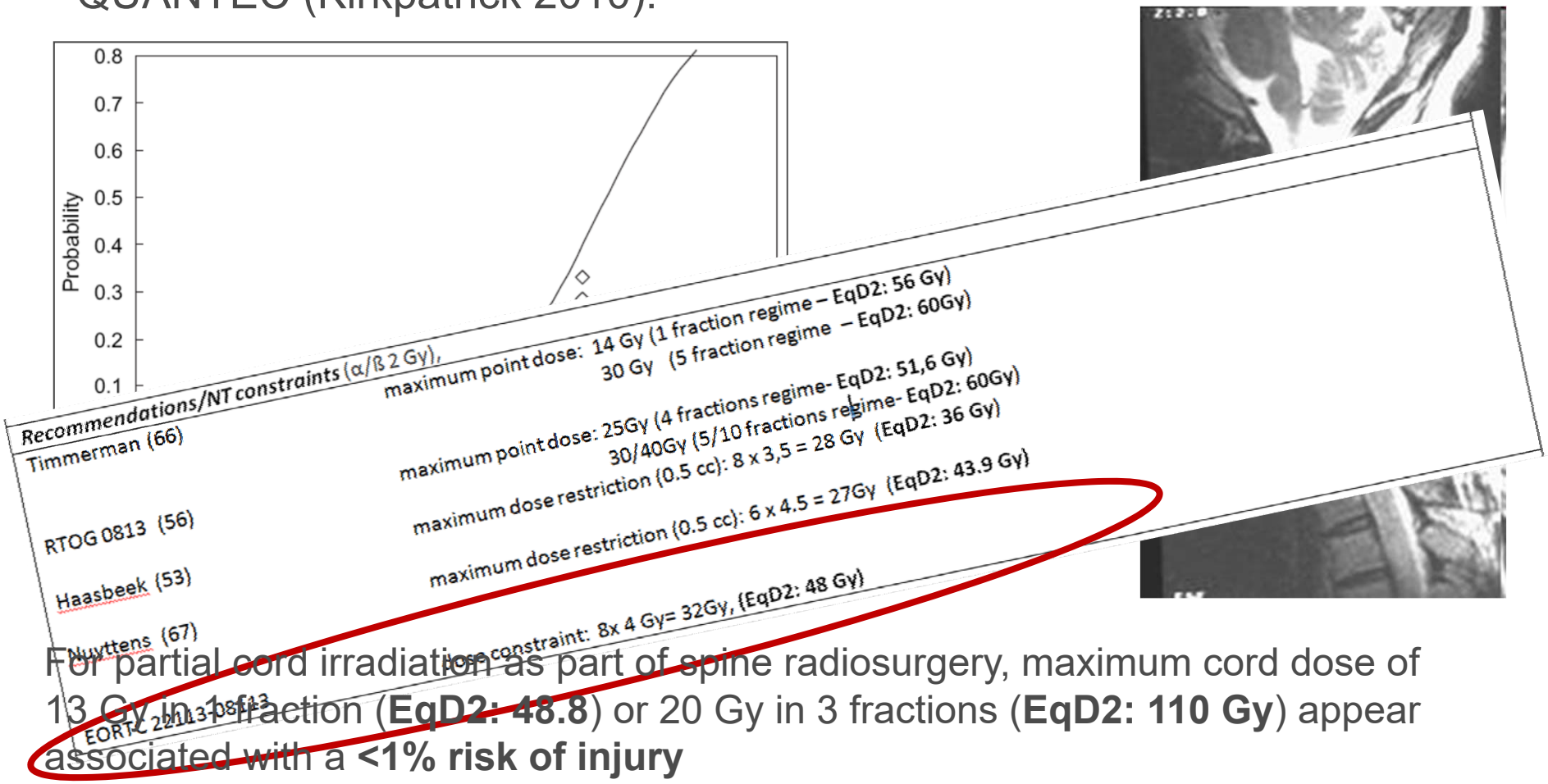
DOSE CONSTRAINTS: OAR IN „PERIPHERAL“ SBRT

- spinal cord
- brachial plexus
- lung
- chest wall

advantage: some larger series available

DOSE CONSTRAINTS: **SPINAL CORD**

QUANTEC (Kirkpatrick 2010):



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

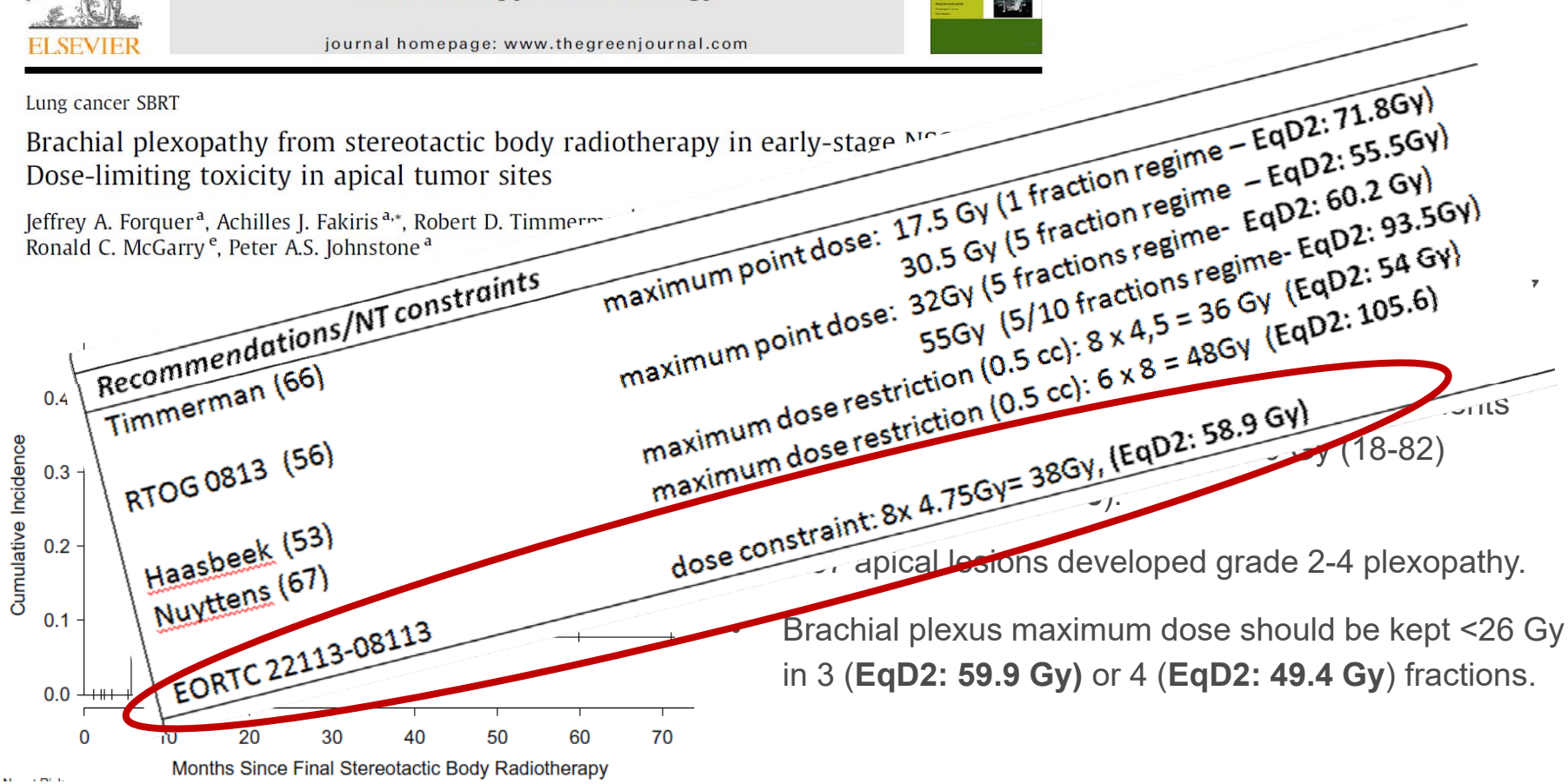
Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Lung cancer SBRT

Brachial plexopathy from stereotactic body radiotherapy in early-stage N
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.

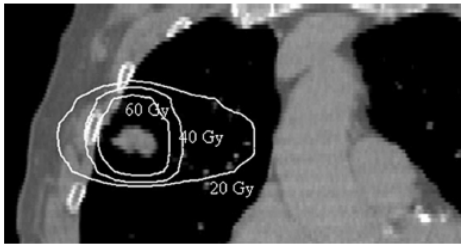
Brachial plexus maximum dose should be kept <26 Gy in 3 (**EqD2: 59.9 Gy)** or 4 (**EqD2: 49.4 Gy**) fractions.

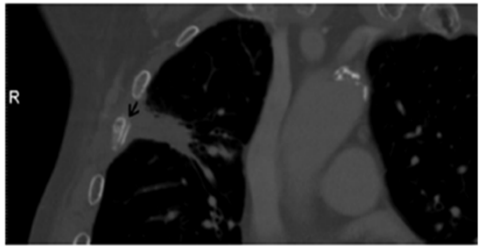
DOSE CONSTRAINTS: LUNGS

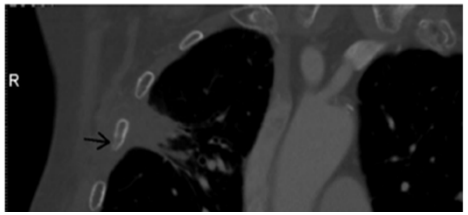
Lungs (α/ß 3 Gy), potential side effects: radiation induced pneumonitis, fibrosis and decrease in lung function, atelectasis, pneumonia (s. bronchus) and abscess				
Reference	*Number of reported patients (treated tumours)*	*Number of centres*	*Pro (p)-/ retro(r)-spective*	*Results (max. point dose or 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

DOSE CONSTRAINTS: **CHEST WALL**







Taremi et al , Radiat Oncol. 2012

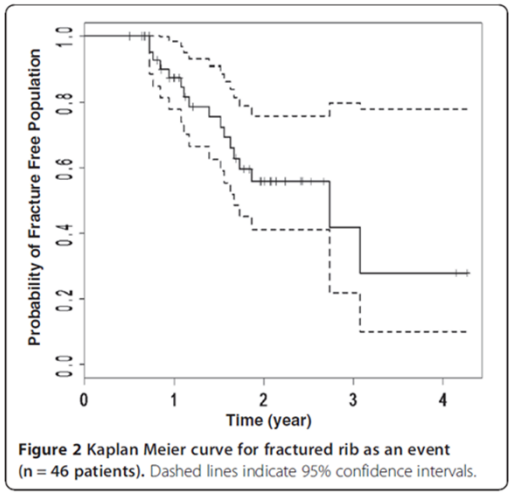


Figure 2 Kaplan Meier curve for fractured rib as an event (n = 46 patients). Dashed lines indicate 95% confidence intervals.

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

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

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?

Advanced planning strategies for lung tumours

physical aspects

Gert Meijer

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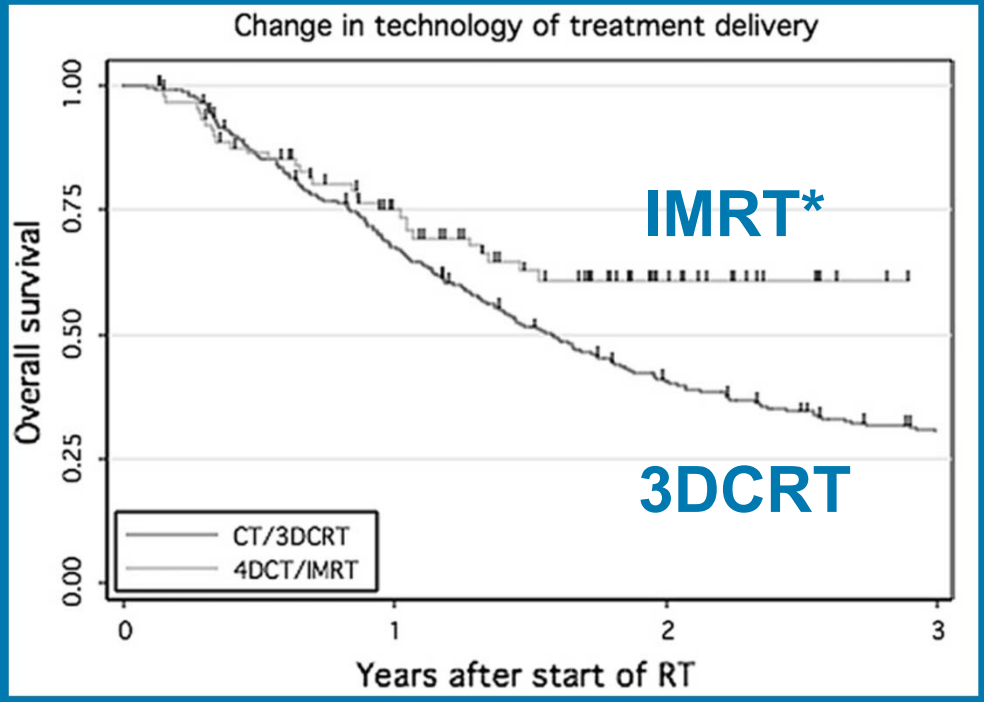
Why use IMRT in lung

- better survival
- better local control
- less pneumonitis



* in combination with IGRT and 4DCT

Liao *et al.* (IJROBP 2010)

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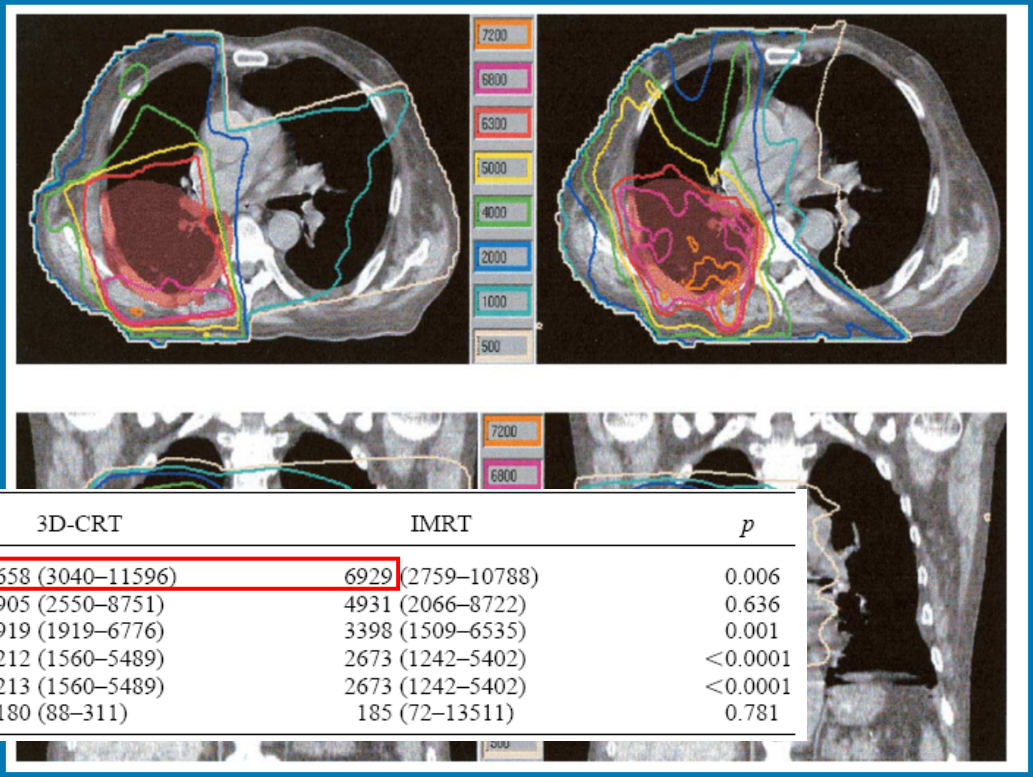
Why use IMRT in lung

43 patients

- more conformal
- better sparing OARs
- lower dose to all lung parameters except V5

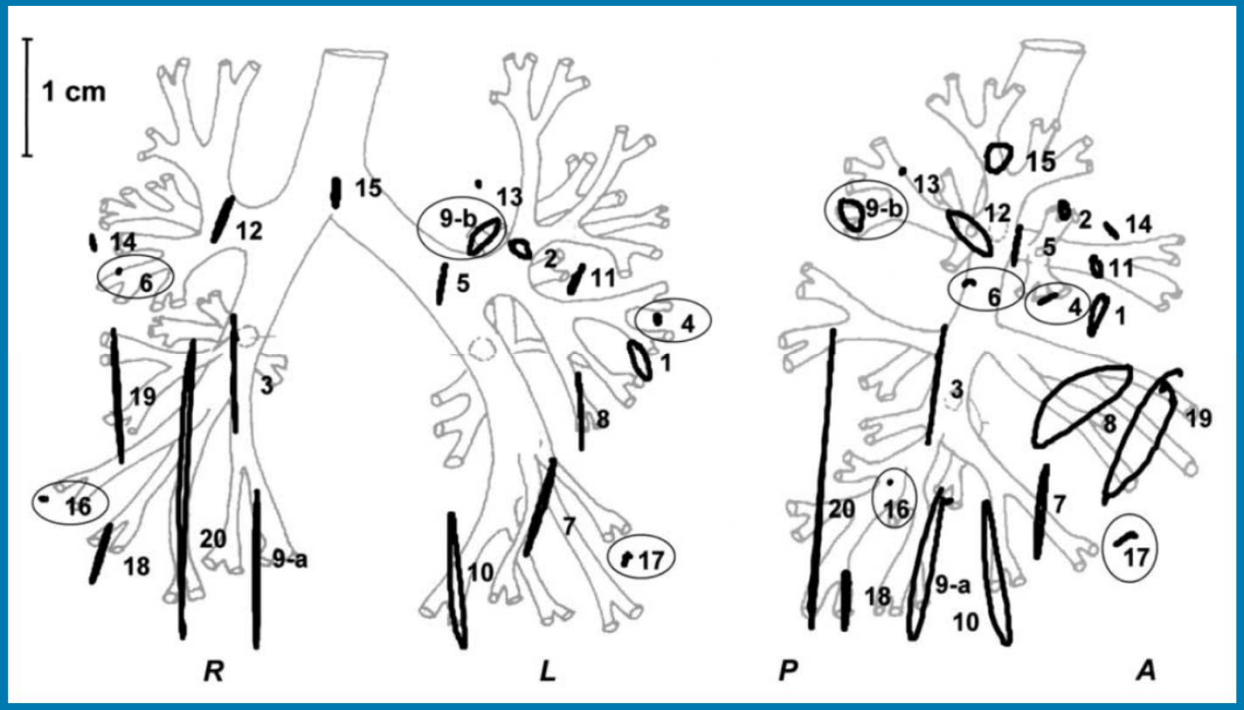


Parameter	3D-CRT	IMRT	*p*
Thoracic normal tissue V_5 (cm^3)	5658 (3040–11596)	6929 (2759–10788)	0.006
Thoracic Normal Tissue V_{10} (cm^3)	4905 (2550–8751)	4931 (2066–8722)	0.636
Thoracic Normal Tissue V_{20} (cm^3)	3919 (1919–6776)	3398 (1509–6535)	0.001
Thoracic Normal Tissue V_{30} (cm^3)	3212 (1560–5489)	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)

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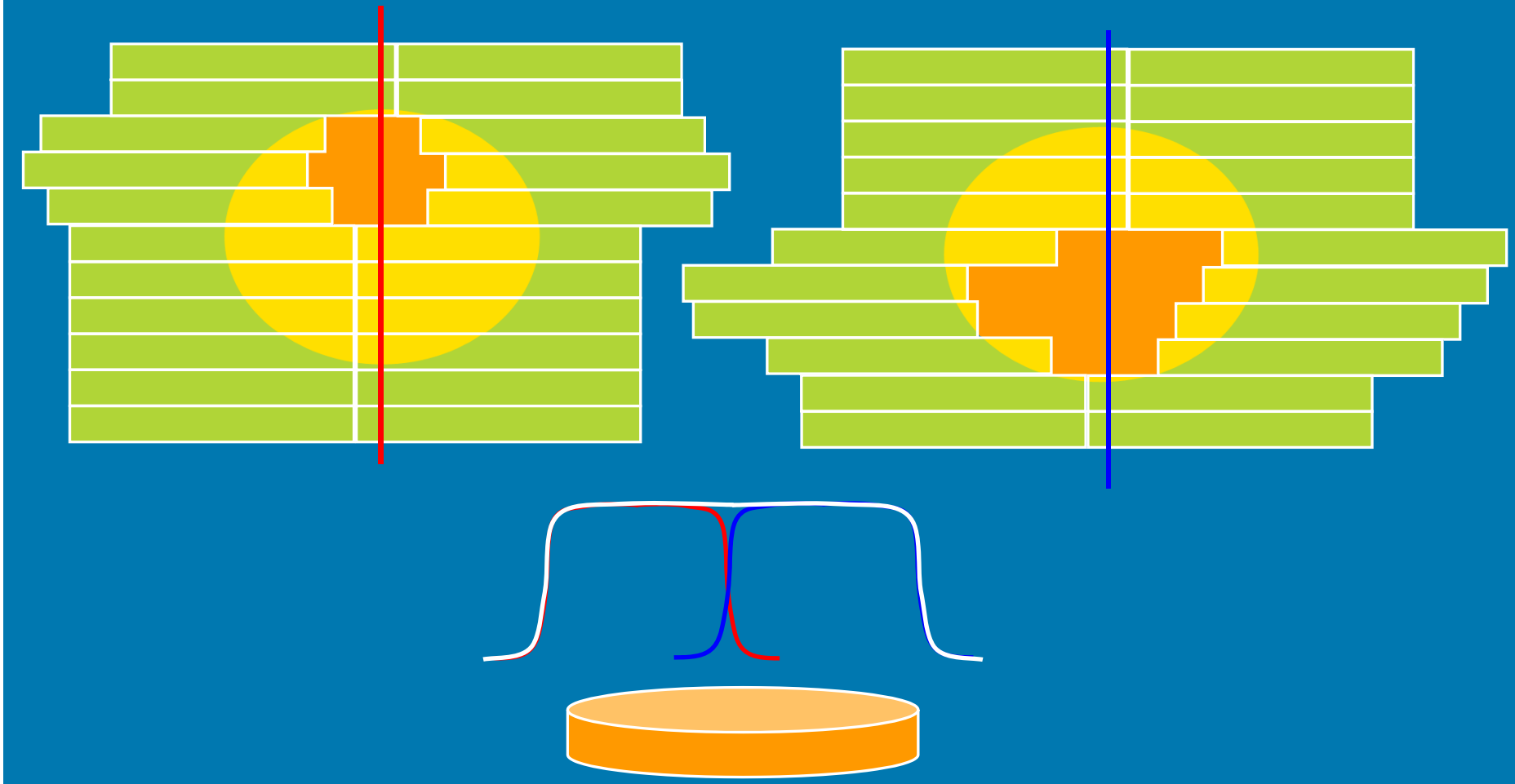
Why not use IMRT in lung



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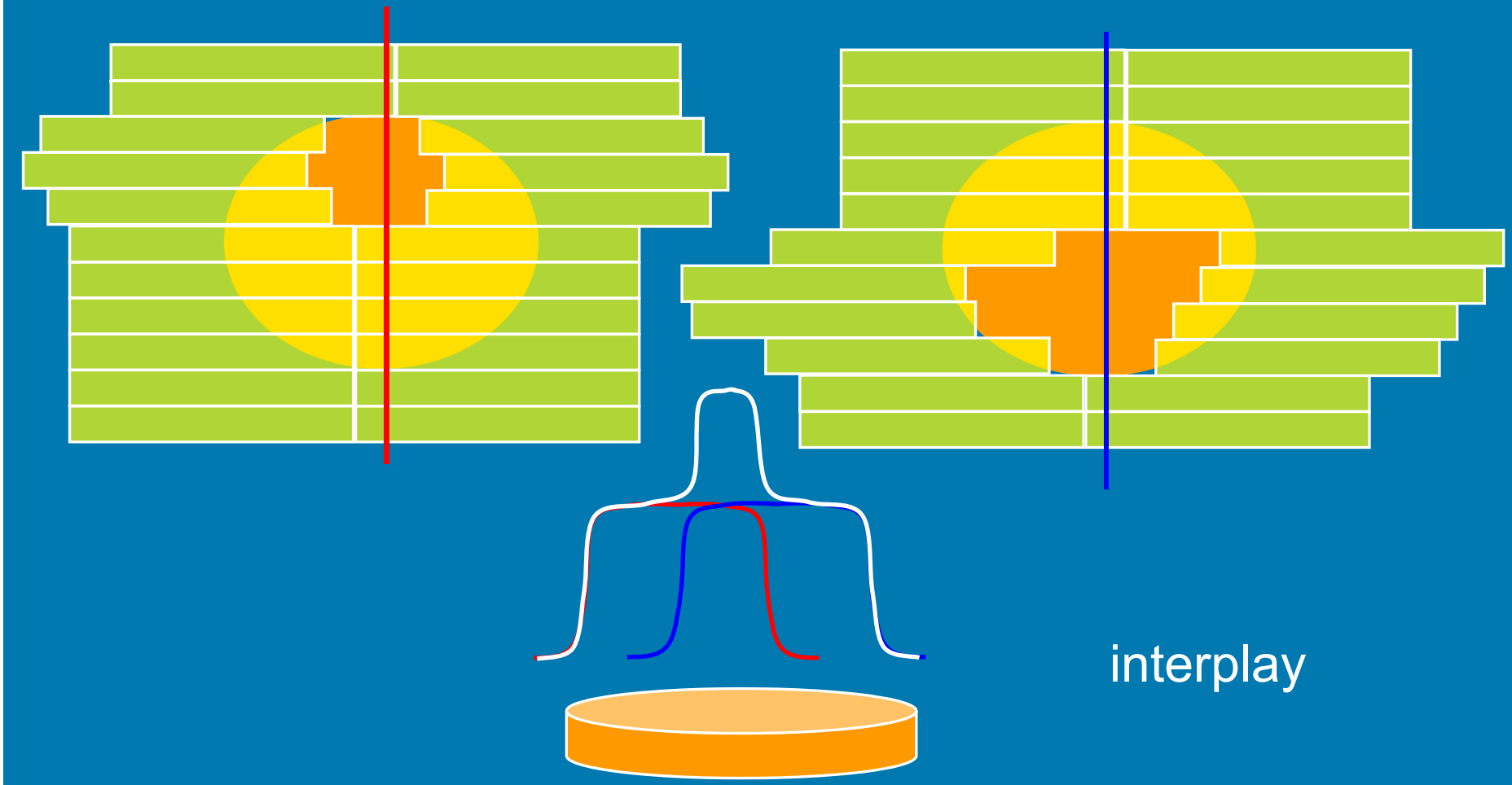
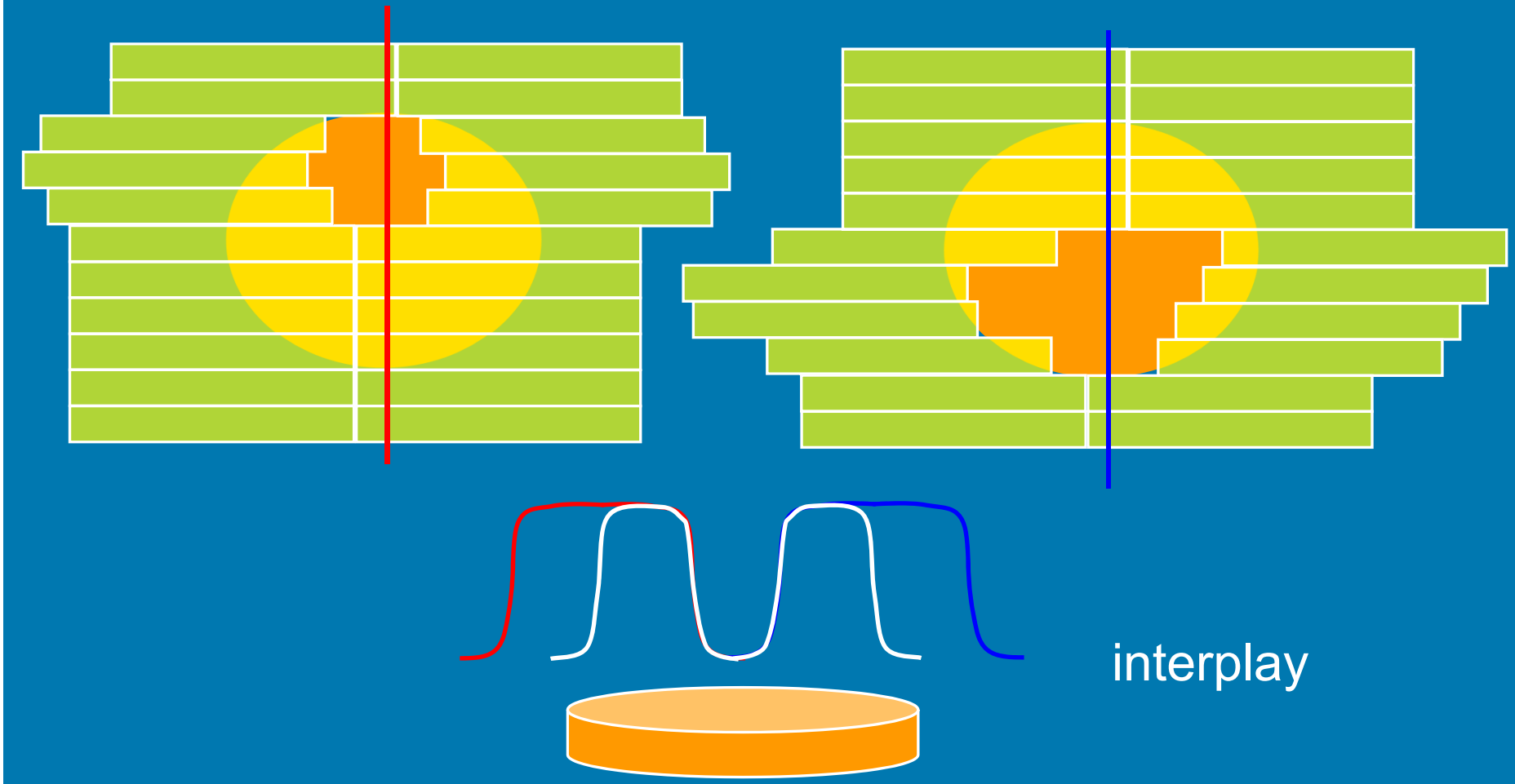
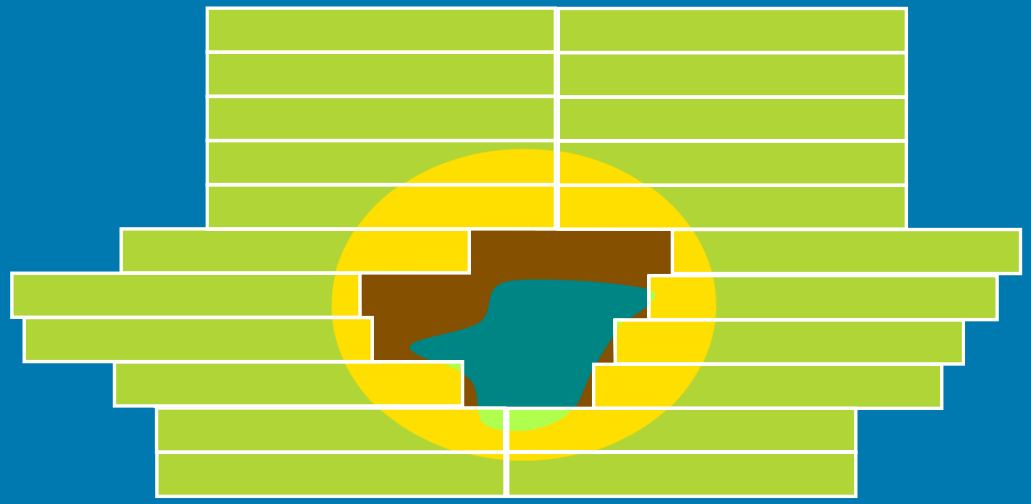
Why not use IMRT in lung



Why not use IMRT in lung

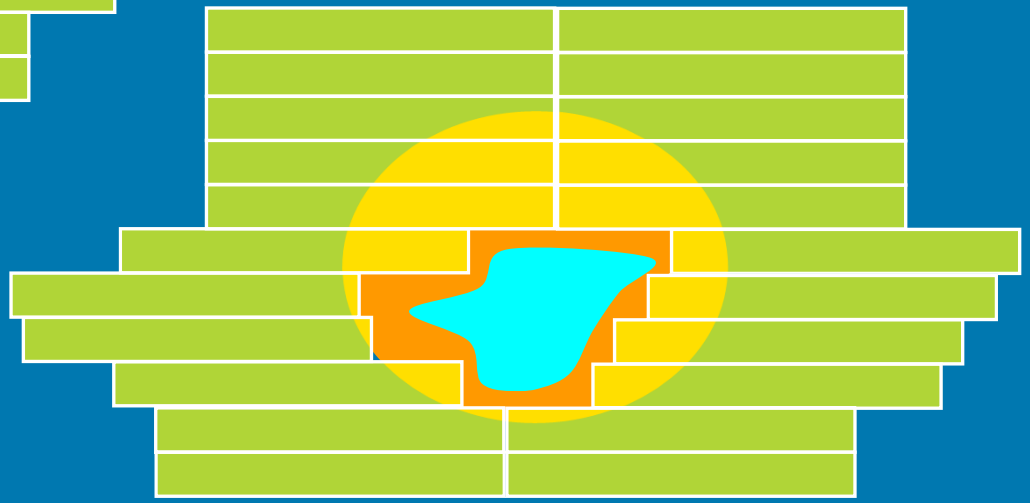


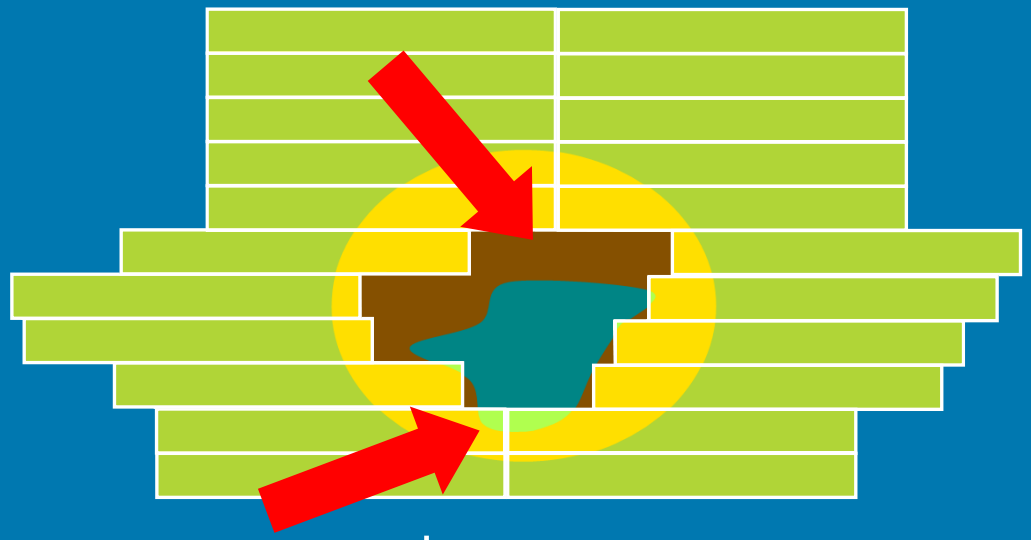


beam on
beam off

gating

‘breathing leaves’



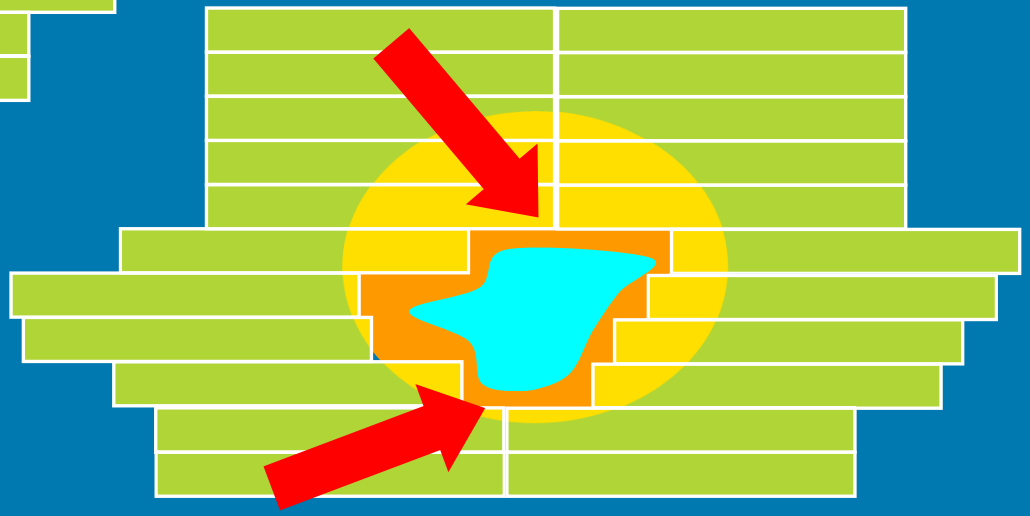


beam on
beam off

gating

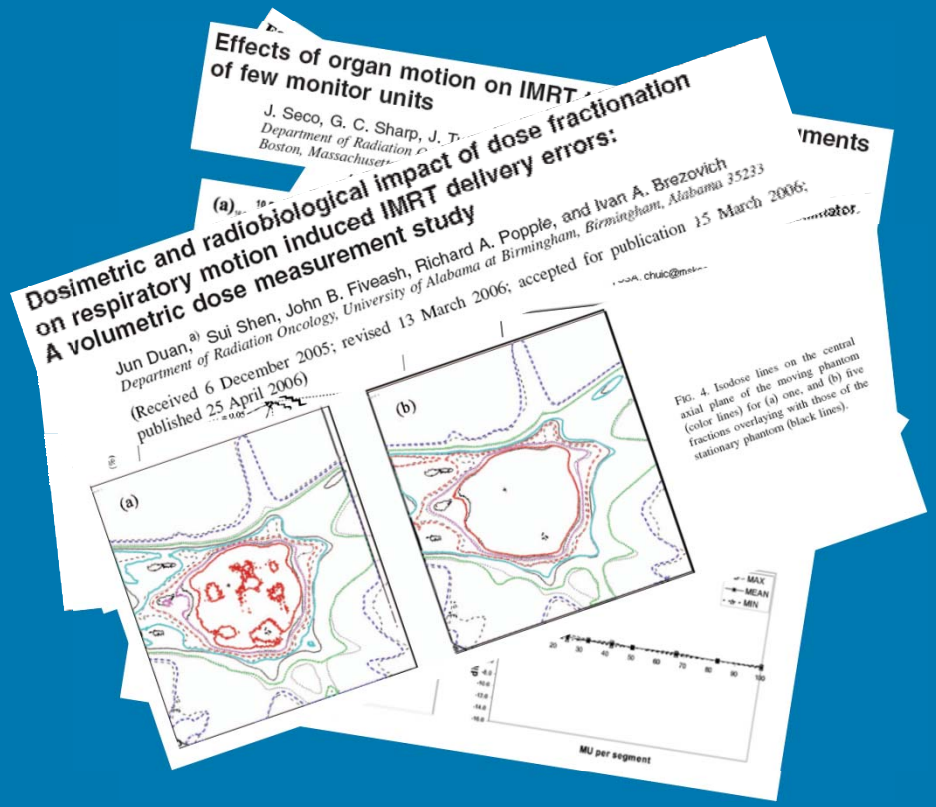
bad synchronisation

‘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**

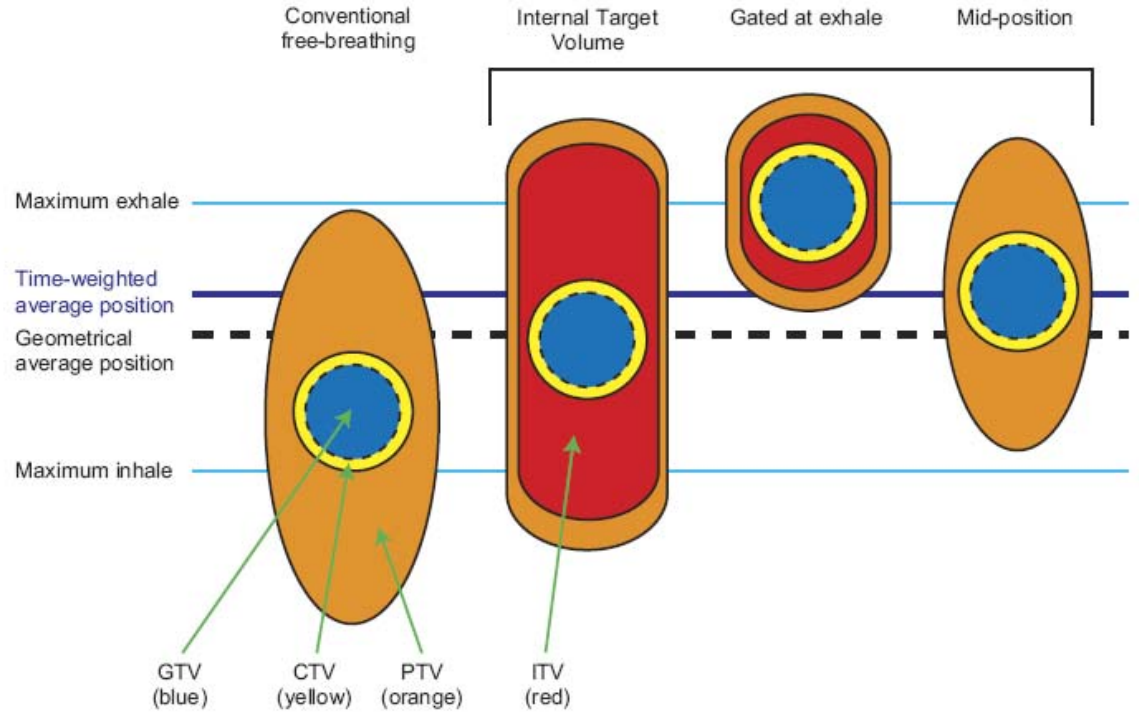
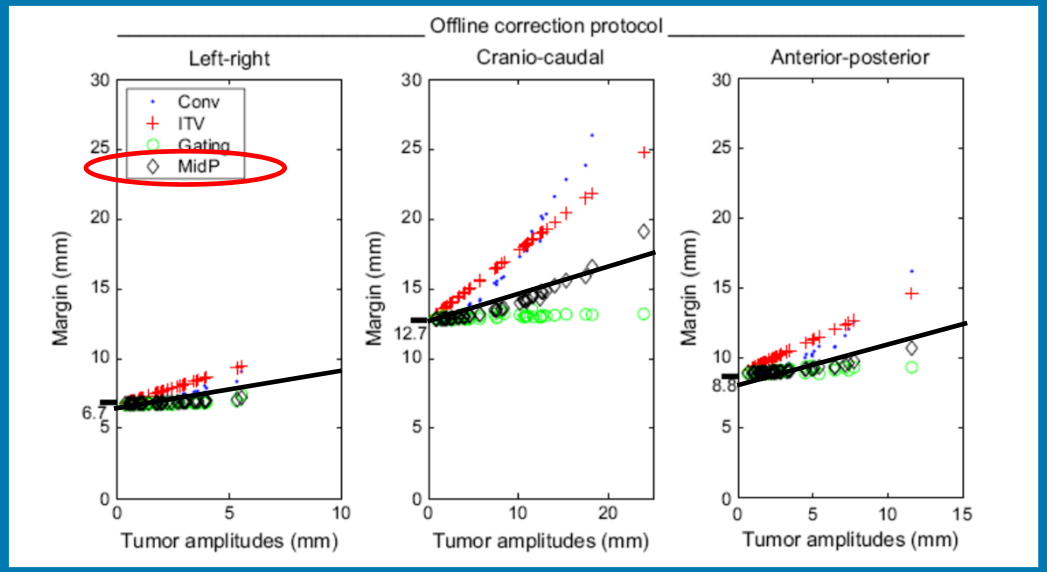


Fig. 1. Schematic overview of different treatment-planning concepts: conventional free-breathing, internal target volume (ITV), gating (at exhale), and mid-position. GTV = gross tumor volume; CTV = clinical target volume; PTV = planning target volume.

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

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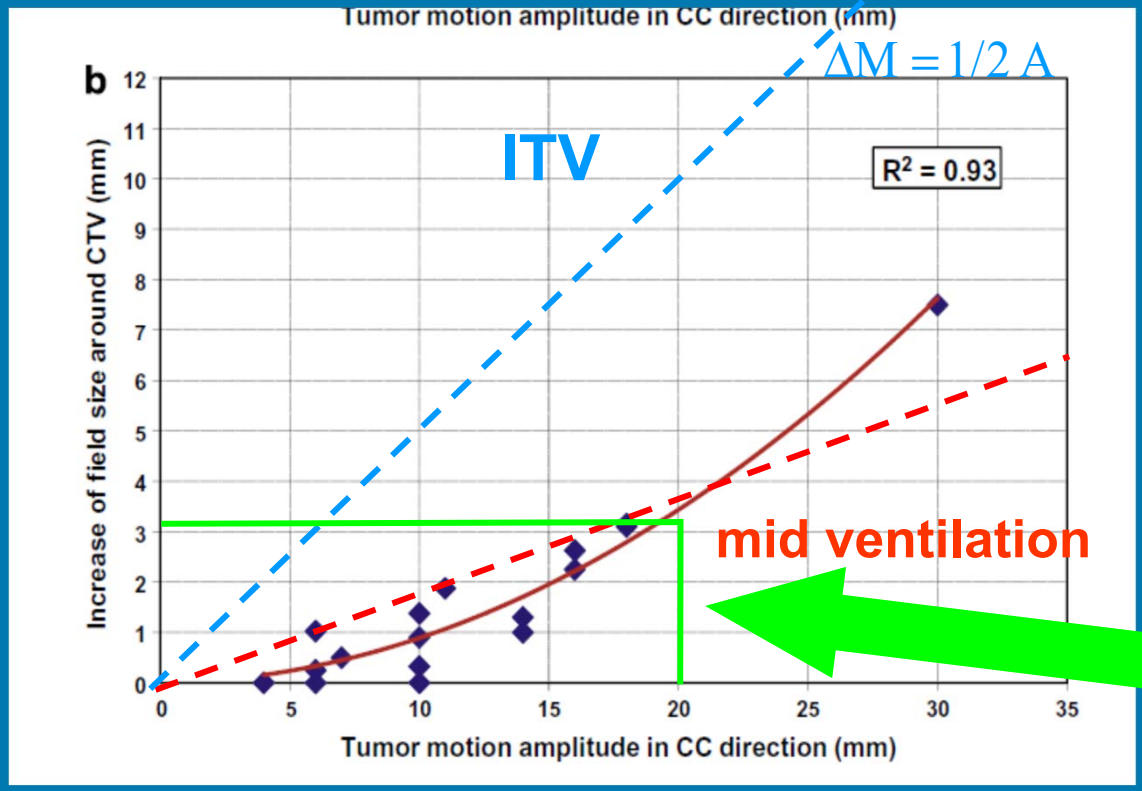
SBRT



ΔM = 1/4 A

mid ventilation

do not gate!

Guckenberger *et al*. (R&O 2009)

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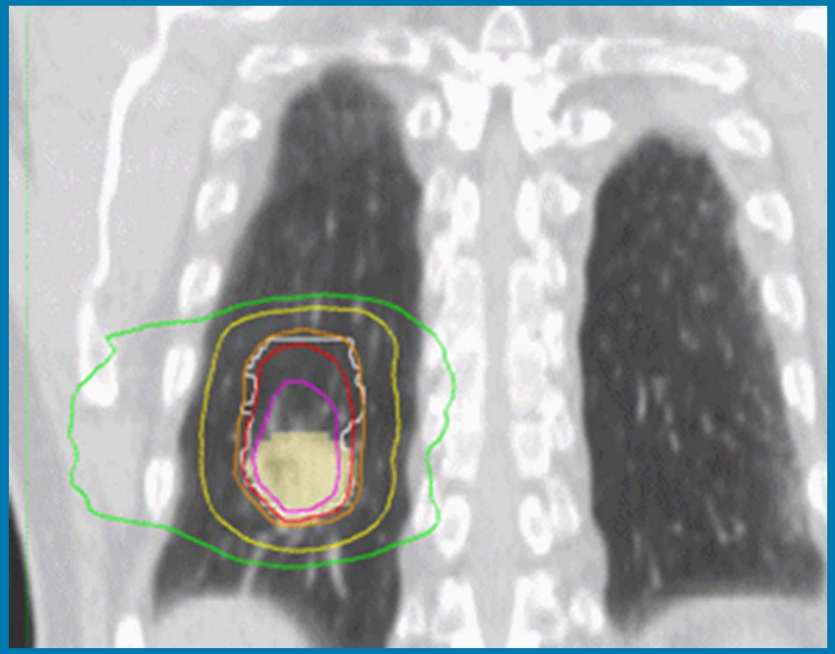
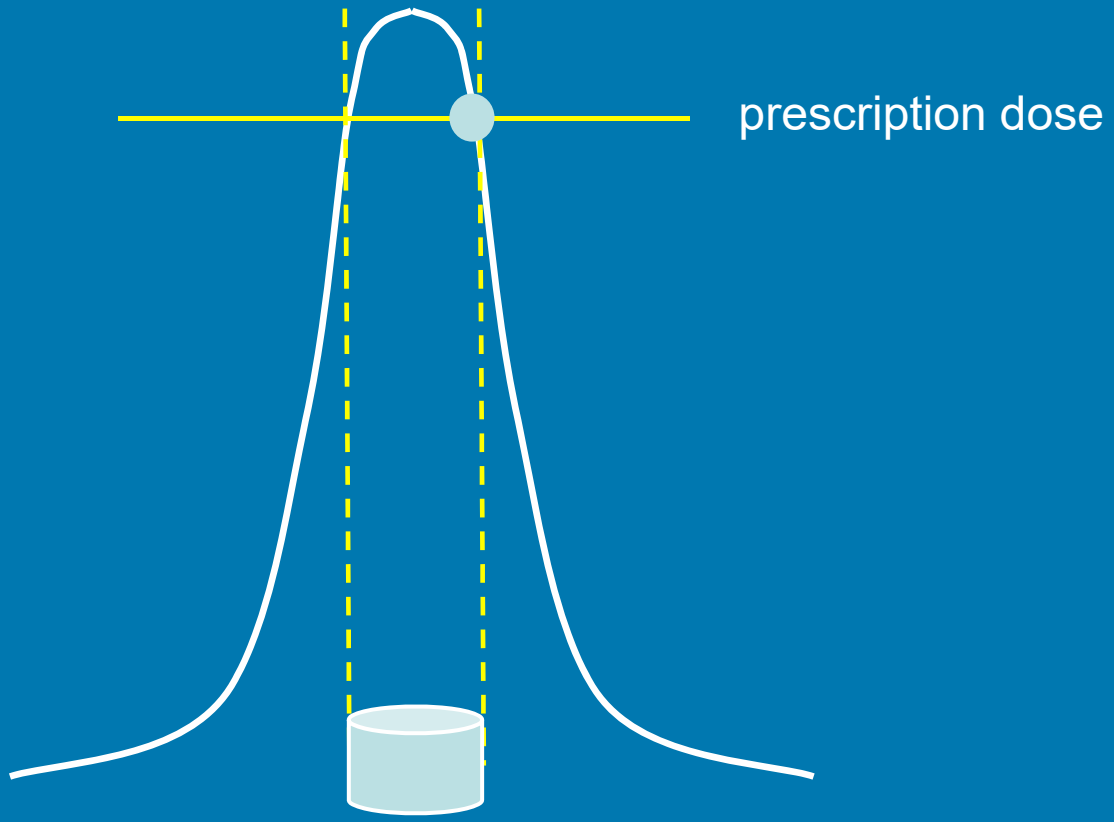
Why? 1

Admiraal *et al*. (R&O 2008)



because high dose regions move along with the tumour

Why? 2



So .....

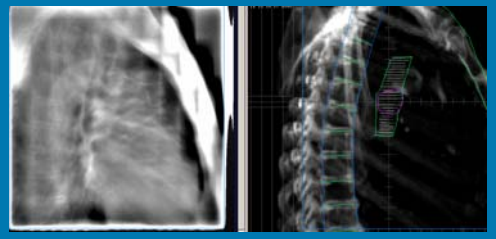
- extra margin for respiration is about ¼ of the breathing amplitude

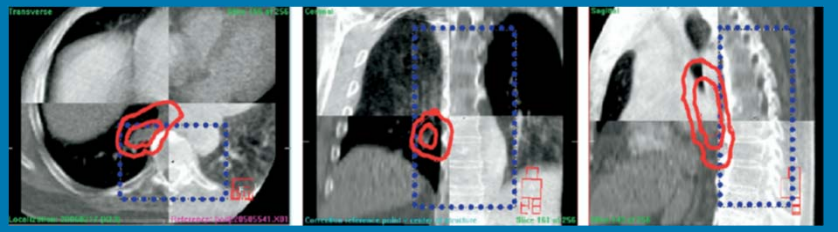
- how about the other uncertainties?

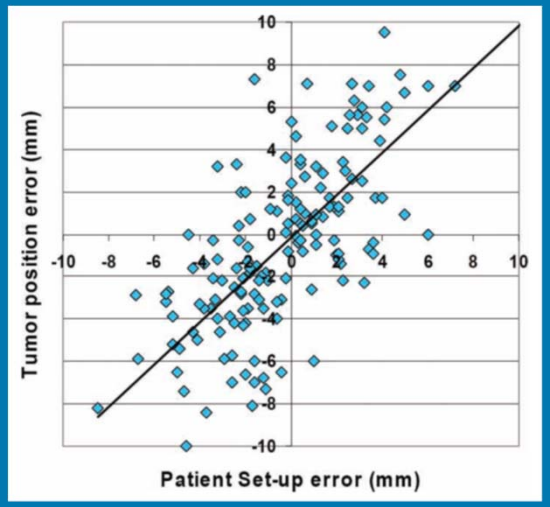
IGRT (not addressed in this course) **is key here**

- 4DCT
  - unblurred target delineation
  - tumour movement

- CBCT
  - 3D soft tissue matching superior to regular 2D bony anatomy matching

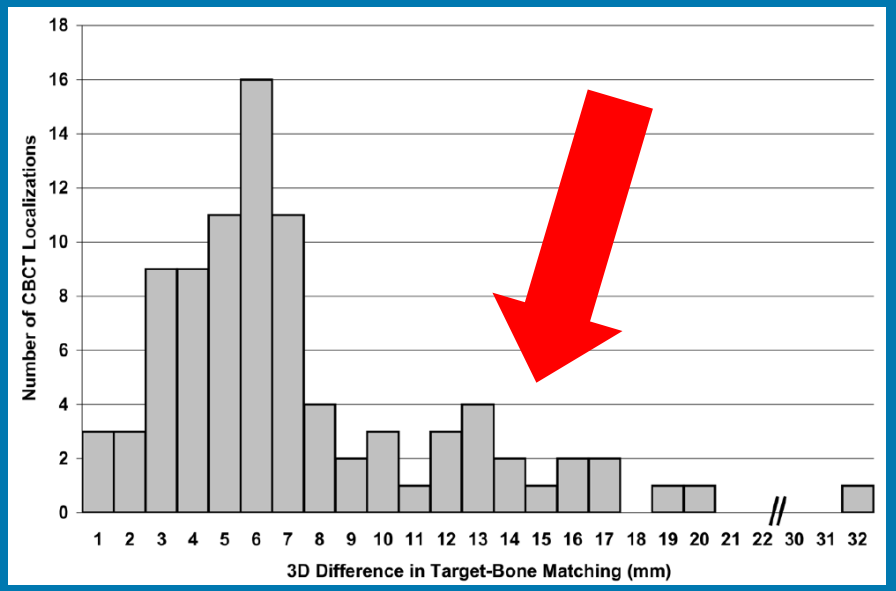






	Sys. ± rand. error	Group mean error	Max. error
SI	2.1 ± 1.1	0.3 (superior)	8.2
AP	3.3 ± 1.3	1.7 (posterior)	9.1
LR	2.2 ± 1.1	0.7 (left)	6.4

Guckenberger *et al.* (ActaOncol 2006)



Purdie *et al.* (IJROBP2007)

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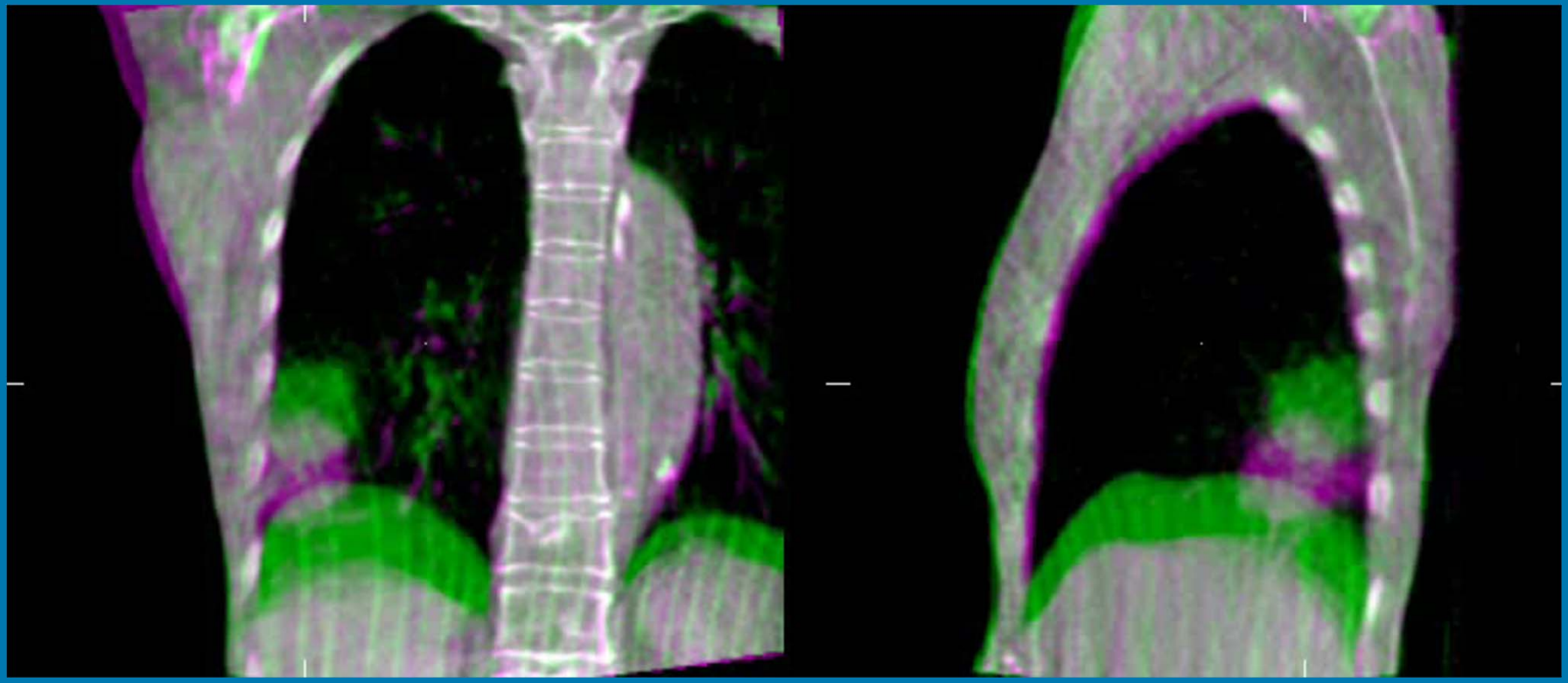
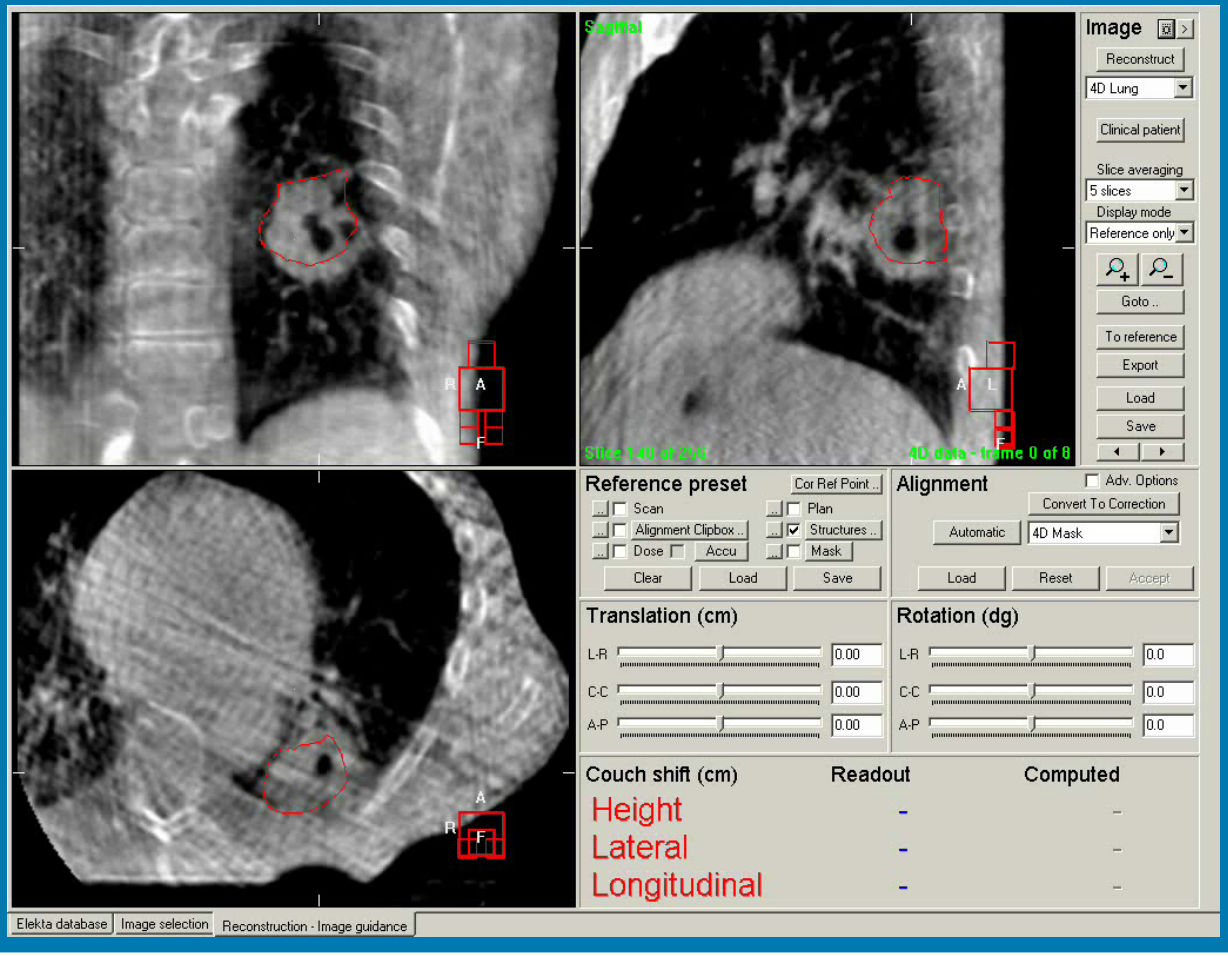
Baseline shifts



Sonke *et al.* IJROBP 2008

4D CBCT + GTV Contour



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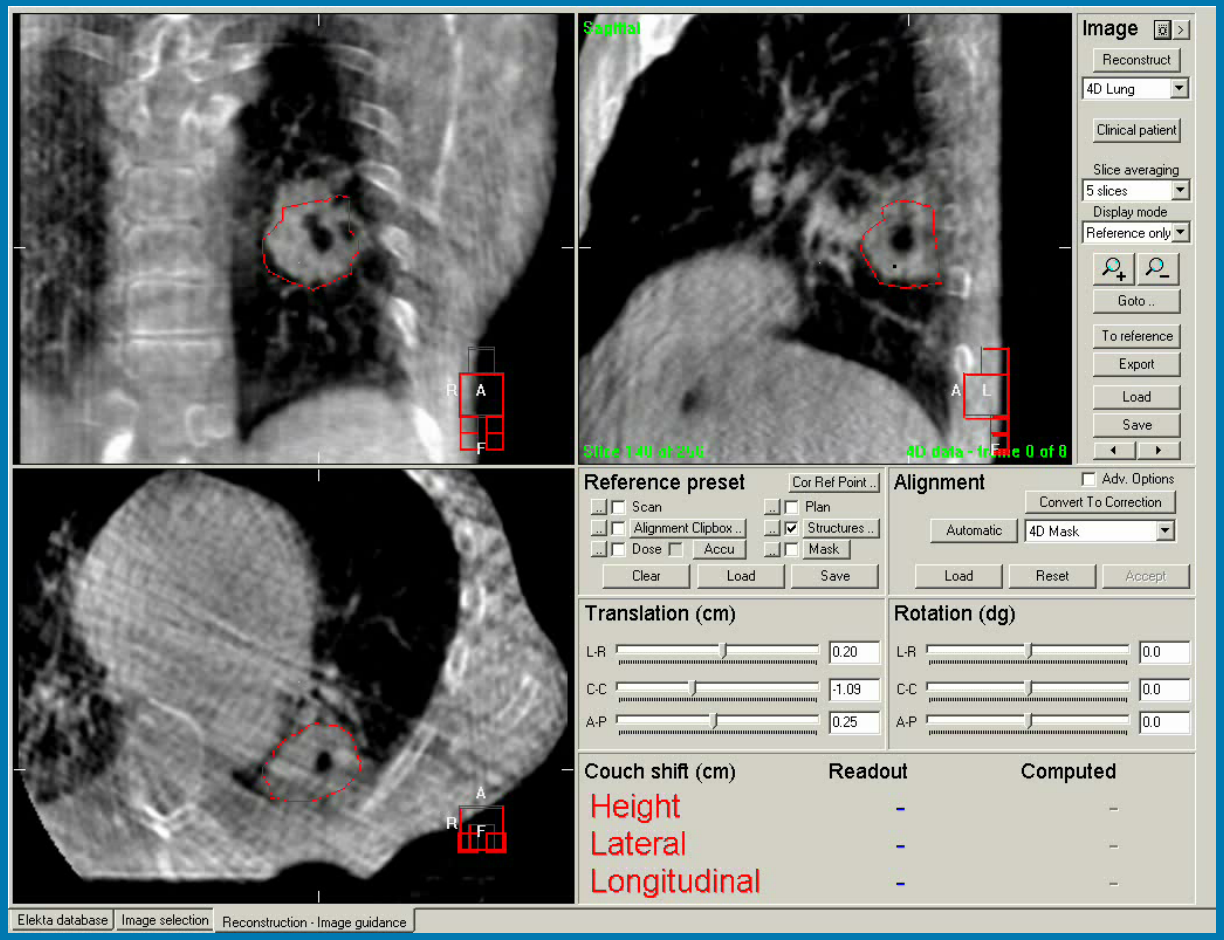
Apply Correction



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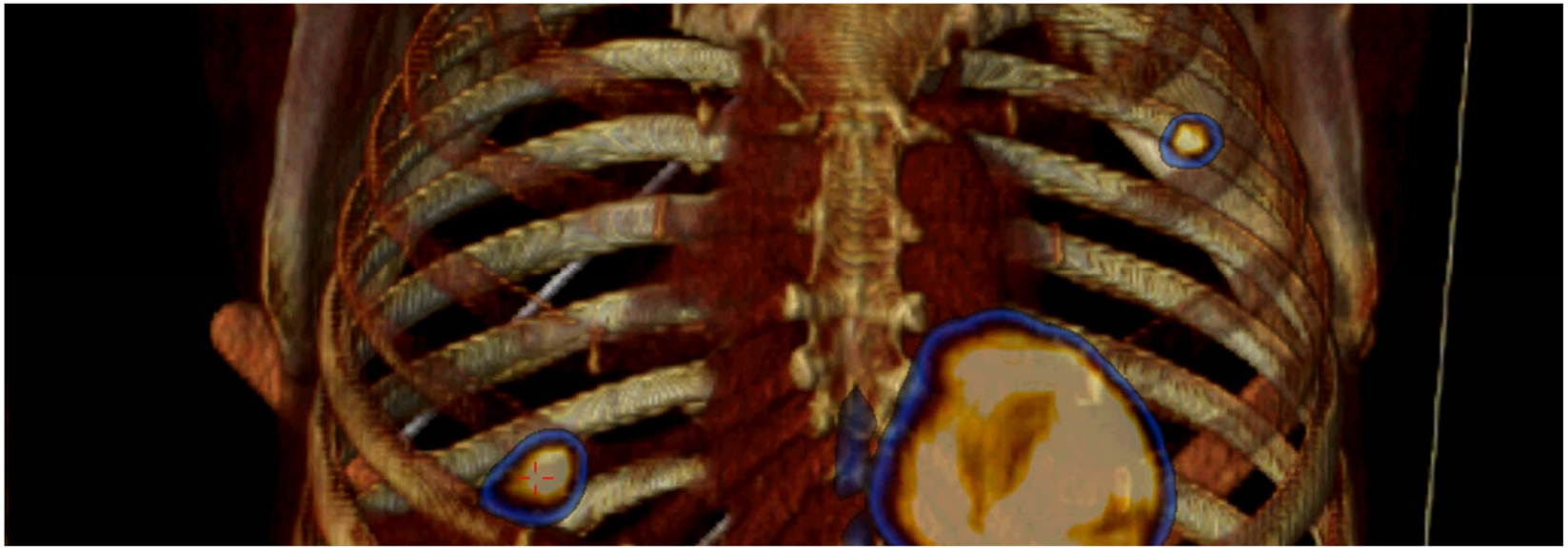
Conclusions

- 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)
- Sound IGRT protocols are crucial

Kliniken Maria Hilf
Mönchengladbach

UNIVERSITÄTS KLINIKUM FREIBURG



Molecular imaging in treatment planning

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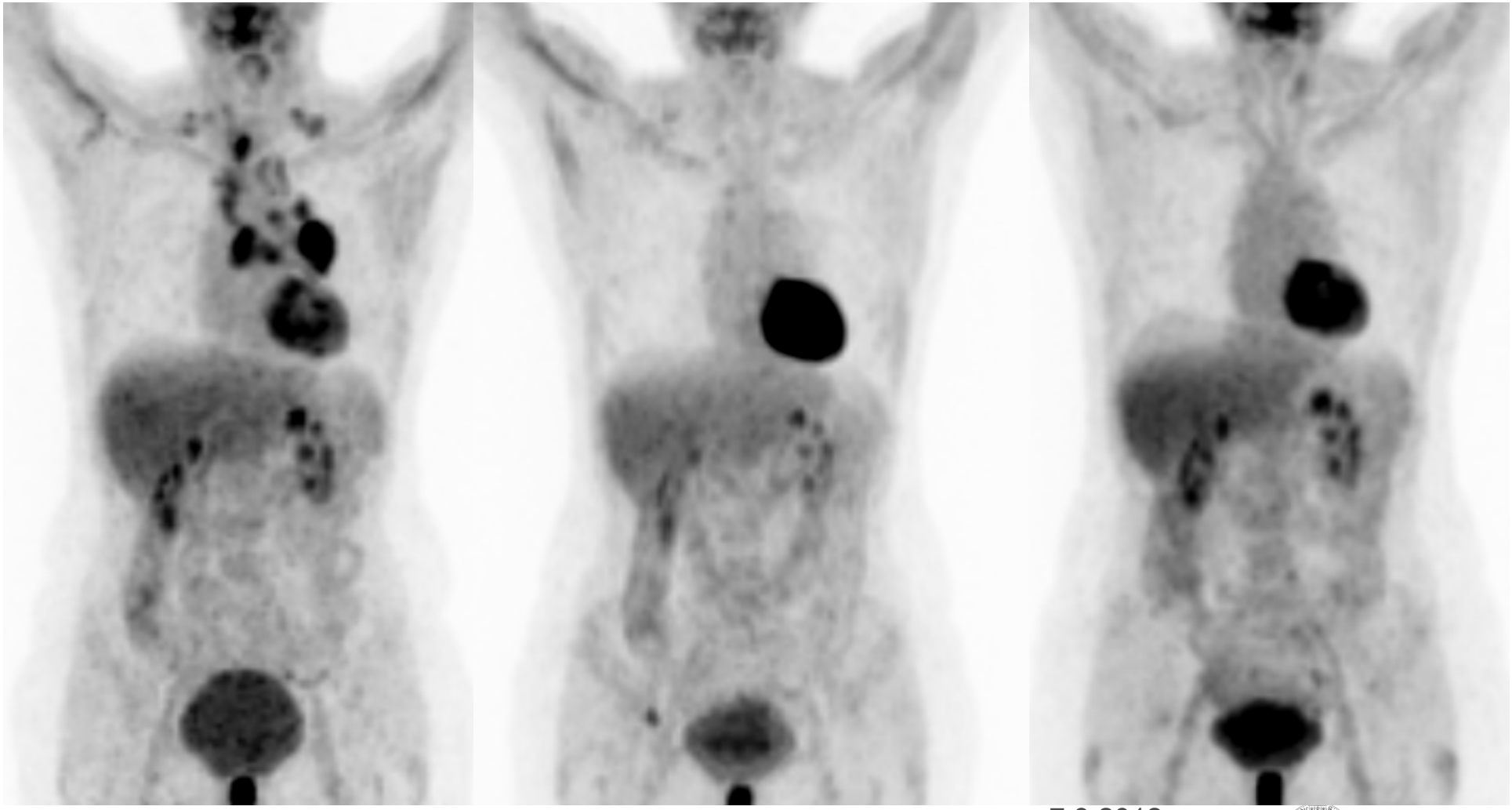
ESTRO ATP Barcelona 2017

Cure with the help of multimodal imaging …



9.3.2010 20.12.2010 7.3.2012

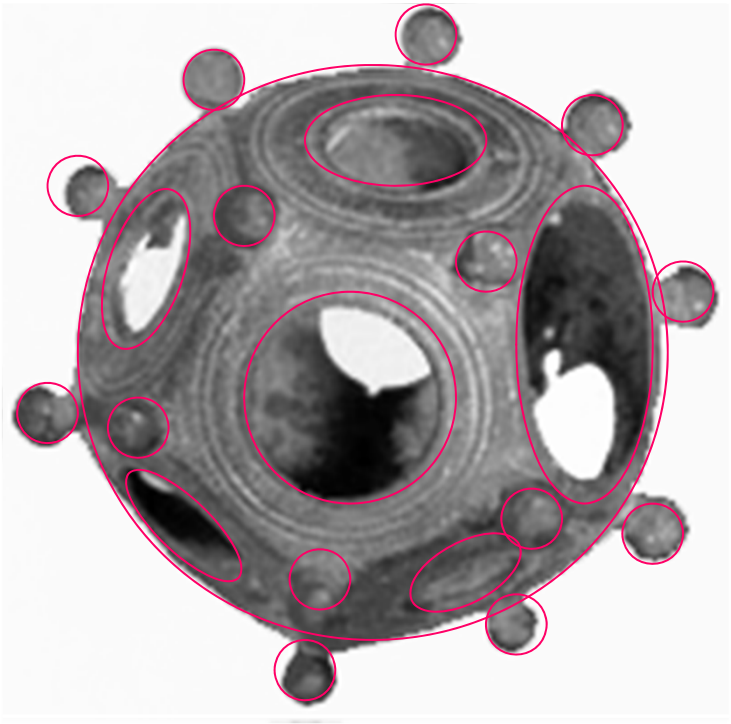
Applications of multimodal imaging in radiation therapy: outline

- Primary tumor: GTV
- Nodal volumes: CTV
- Movements: PTV
- Perspectives, caveats

Applications of multimodal imaging in radiation therapy: outline

- **Primary tumor: GTV**
- Nodal volumes: CTV
- Movements: PTV
- Perspectives, caveats

Imaging for GTV-Definition



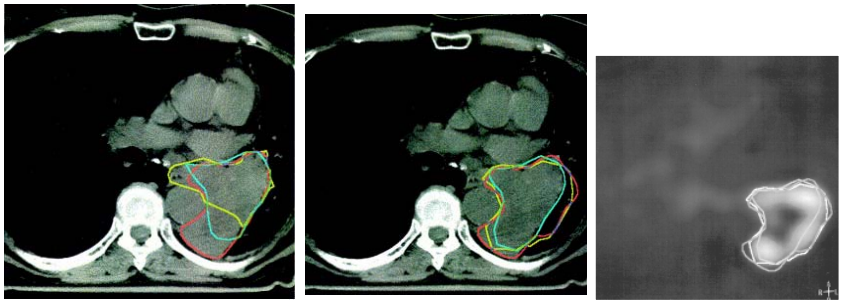
diagnostic imaging:

What is that?

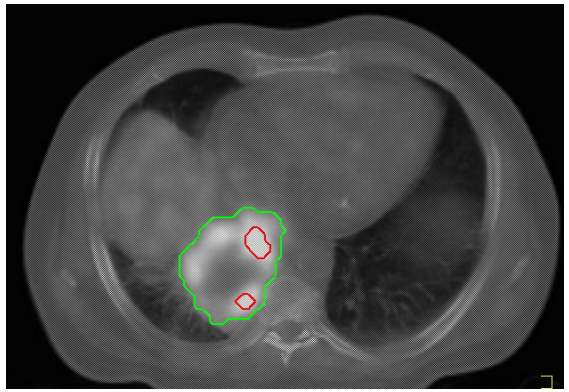
Treatment planning:

Where is that?

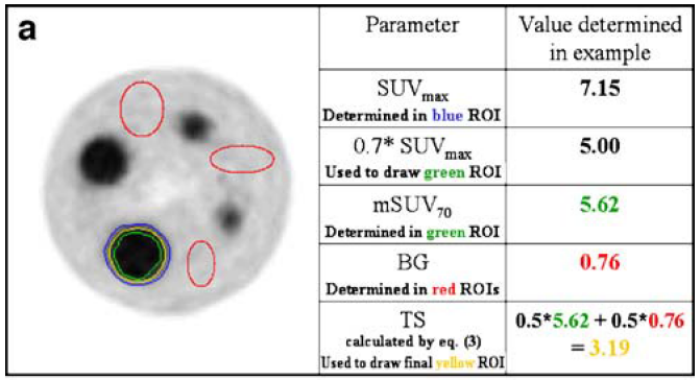
Volume definition using molecular imaging-data: Chance and Challenge



Caldwell, C. et al. IJROBP 2001

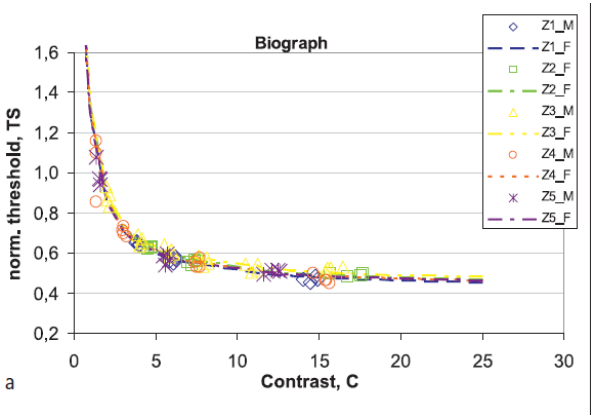


Nestle, U. et al; JNM 2005



Parameter	Value determined in example
SUV_{max} Determined in blue ROI	7.15
0.7* SUV_{max} Used to draw green ROI	5.00
$mSUV_{70}$ Determined in green ROI	5.62
BG Determined in red ROIs	0.76
TS calculated by eq. (3) Used to draw final yellow ROI	0.5*5.62 + 0.5*0.76 = 3.19

Schaefer, A … Nestle, U.; EJNMMI 2008



Schaefer, A, Nestle, U. et al.; Nuklearmedizin 2012

label	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

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	26
Φ	13	PL	8.5	29.5

Shepherd, T. et al. IEEE 2013

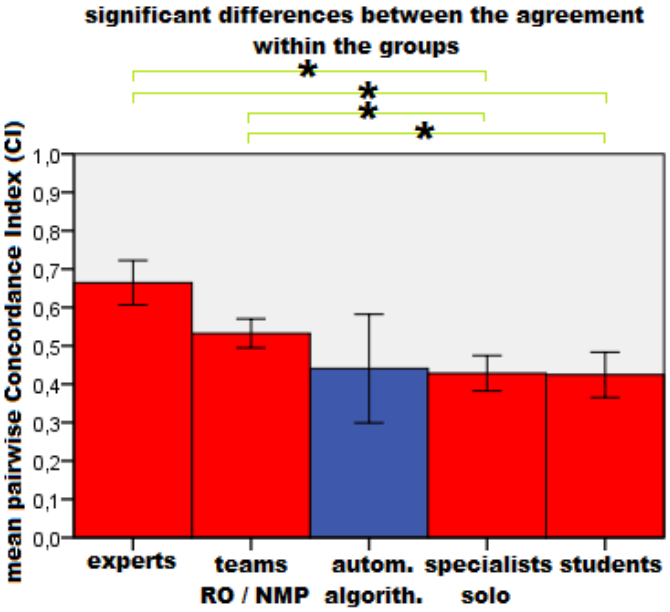
Observer variability vs. method variability

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

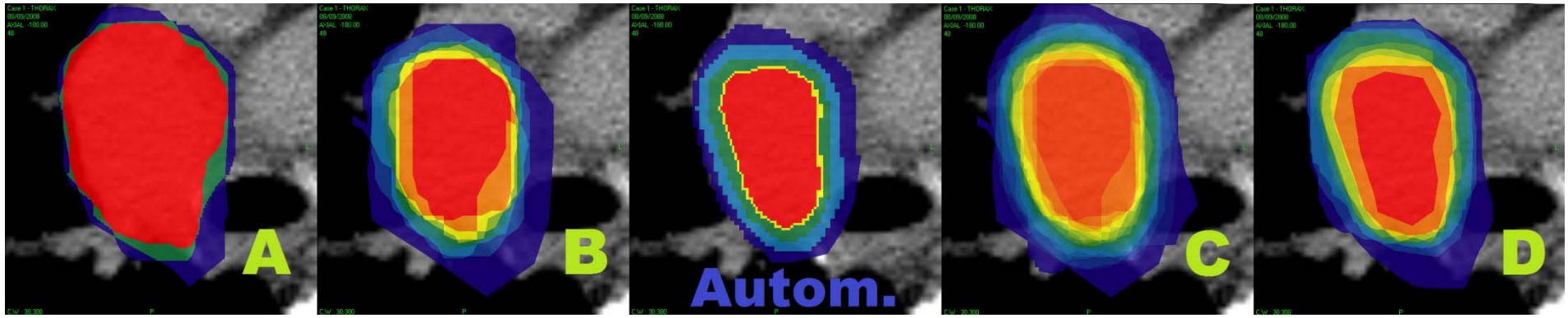
- IOV Specialists (**C**) vs. students (**D**): n.s.
- „PET-years“ n.s.

- IMV of automatic algorithms = IOV of students

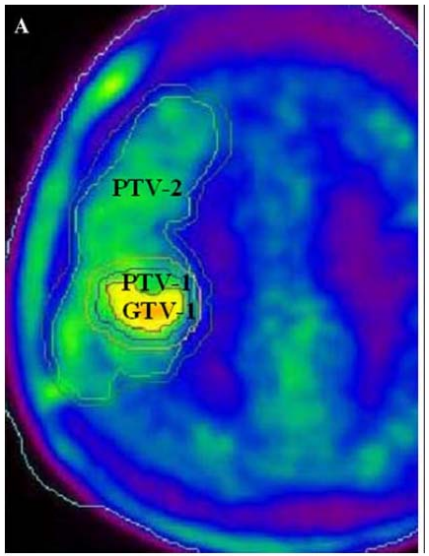
C. Doll et al. Strahlentherapie 2012

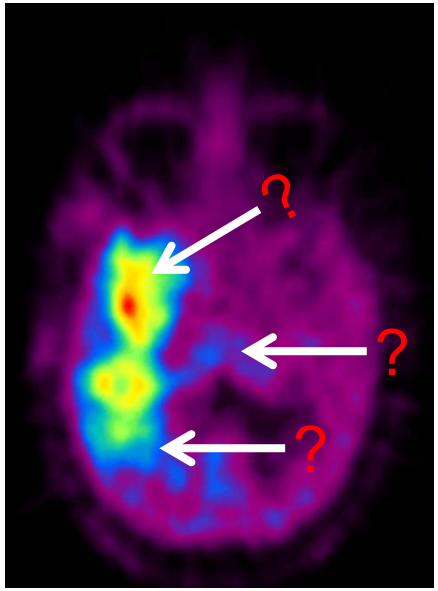


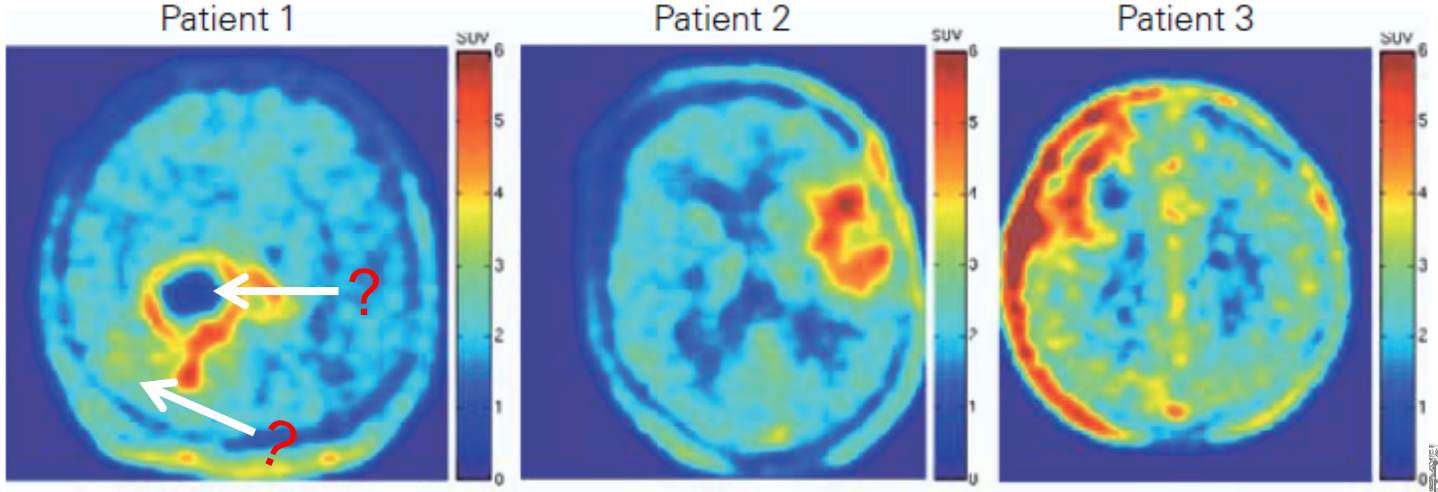
	A	B		C	D
C I	0,67	0,53	0,44	0,43	0,42
Kappa Index	0,80	0,69	0,59	0,57	0,57



Problem: what the hell is the GTV?







Problem: Ground truth

To calibrate a correct contouring method, the knowldedge on the correct tumor borders is essential, e.g. from:

- Phantom-measurements
  Problem: usually homogenous spheres, glass wall, homogenous background
  = not representative for tumors
- simulated images
  Problem: extremely harmful to produce, proximity to reality depends on assumptions
- image data with histopathology correlation
  not many datasets available, all have shortcomings: shrinking, distortion, problem of coregistration, diffuse infiltration
- tumor size known from other imaging
  Problem: reason for second imaging? other problems in size determination

possible surrogates:

- comparison with expert contours, ideally consistent in multiple observers
- visual or mathematical consensus-contour of different methods

Classification and evaluation strategies of auto-segmentation approaches for PET: Report of AAPM Task Group No. 211

M. Hatt[1], J. Lee[2], C.R. Schmidtlein[3], I. El Naqa[4], C. Caldwell[5], E. De Bernardi[6], W. Lu[3], S. Das[7], X. Geets[2], V. Gregoire[2], R. Jeraj[8], M. MacManus[9], O. Mawlawi[10], U. Nestle[11], A. Pugachev[12], H. Schöder[3], T. Shepherd[13], E. Spezi[14], D. Visvikis[1],H. Zaidi[15], A.S. Kirov[3*]

Conclusions: Based on the large number of published PET-AS algorithms and their relative lack of validation, selecting and recommending an algorithm from among those available is challenging. Available comparison studies suggest that PET-AS algorithms relying on advanced image paradigms perform generally better than simple threshold-based approaches, particularly in realistic configurations. However, this may not be the case for situations with a narrower range of parameters (e.g., a particular body site and/or tumor type), where simpler (e.g., adaptive threshold) methods also may perform well. In either case PET-AS contours need to be critically inspected and edited by a physician. Another

Med Phys, accepted 2017

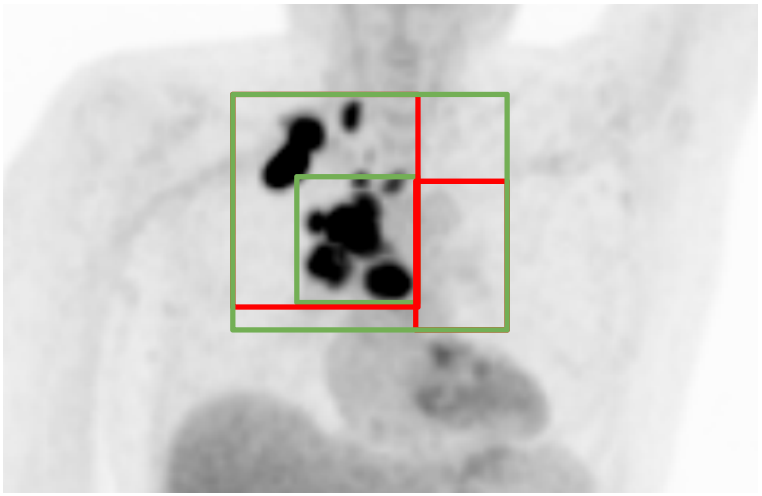
What have we learned after >10 years searching the holy grail for PET based GTV-segmentation?

- Using molecular imaging for GTV delineation **at all** is more important than finding the right method to include the last voxel
- Maybe drawing one line is not what resembles the information needed for future RT planning
- If we need one line, **visual** delineation is not a bad idea, institutional standardisation makes sense
- Automatic delineation (by something else than simple thresholding) **speeds up** the contouring process but should be used as a starting point for user review
- The use **4D** imaging for TVD will not be possible without automation

Applications of multimodal imaging in radiation therapy: outline

- Primary tumor: GTV
- **Nodal volumes: CTV**
- Movements: PTV
- Perspectives, caveats

CTV: where are the nodes?



diagnostic imaging:

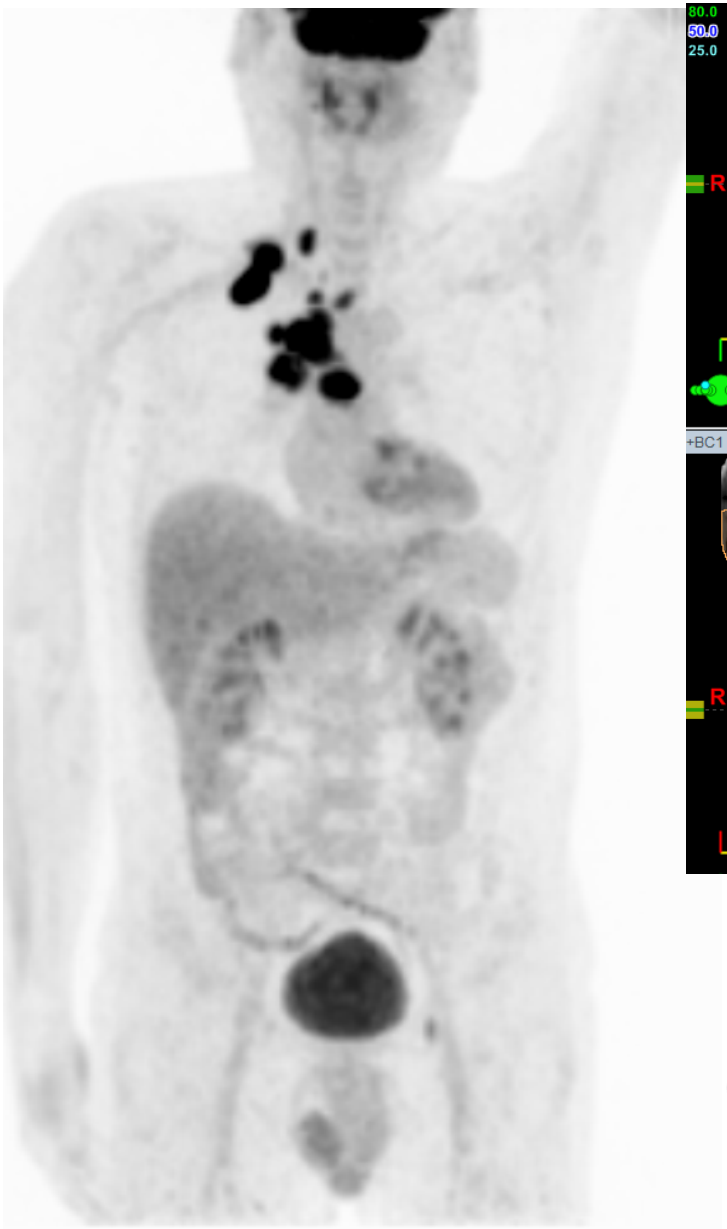
N2

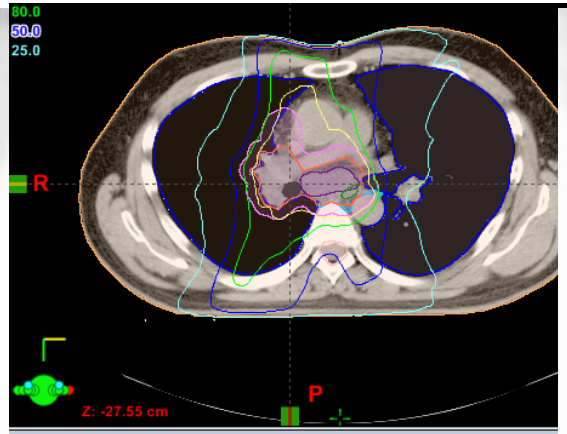
RT treatment planning:

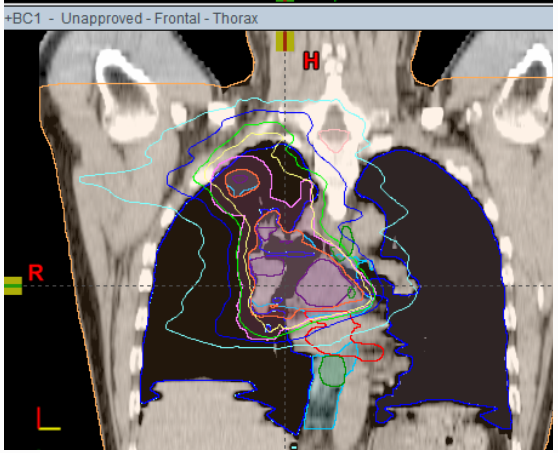
Treat what?

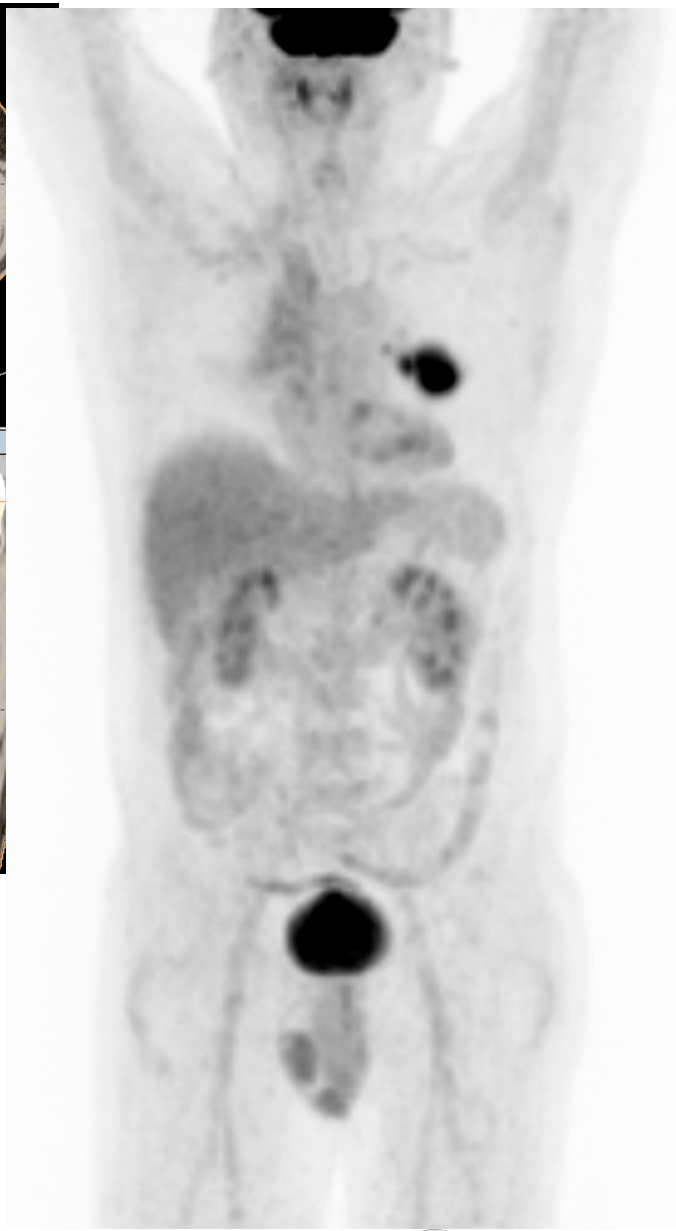
19.4.2012

14.12.2012



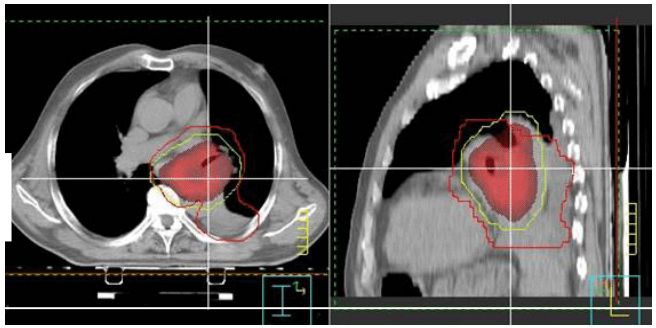






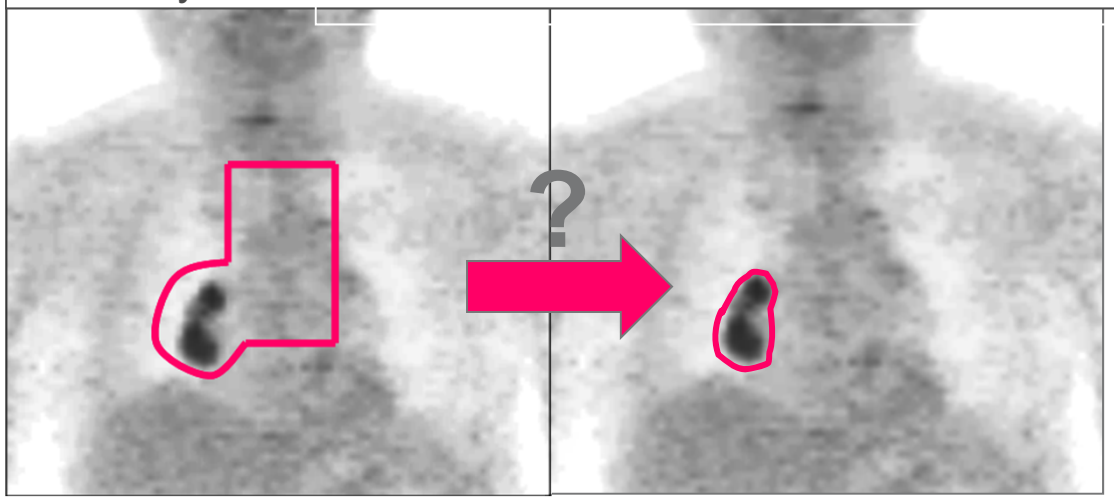
NSCLC (SCC) IIIb;
RCT 07/2012; Platin,
66 Gy/2 Gy

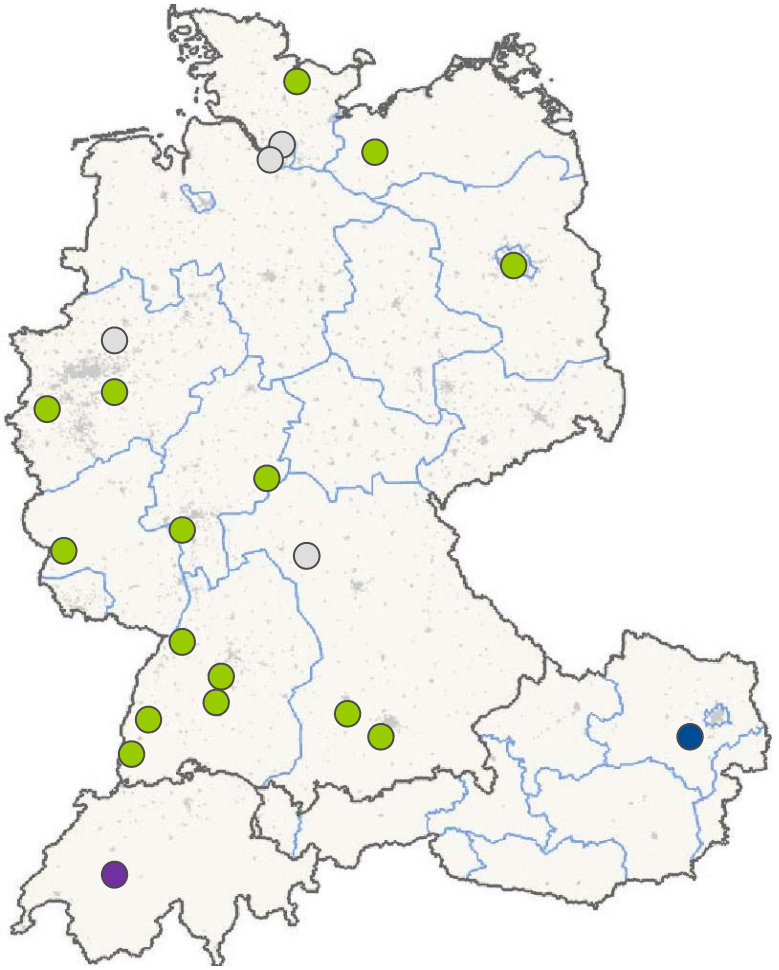
gefördert durch die Deutsche Krebshilfe

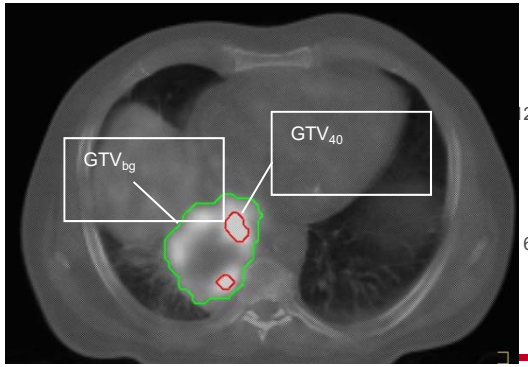


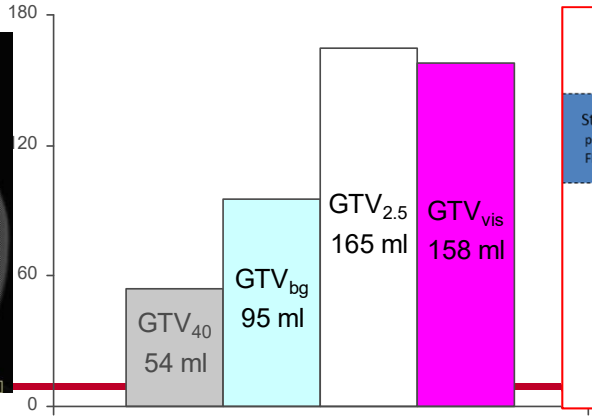
PI: U. Nestle, Freiburg, Germany

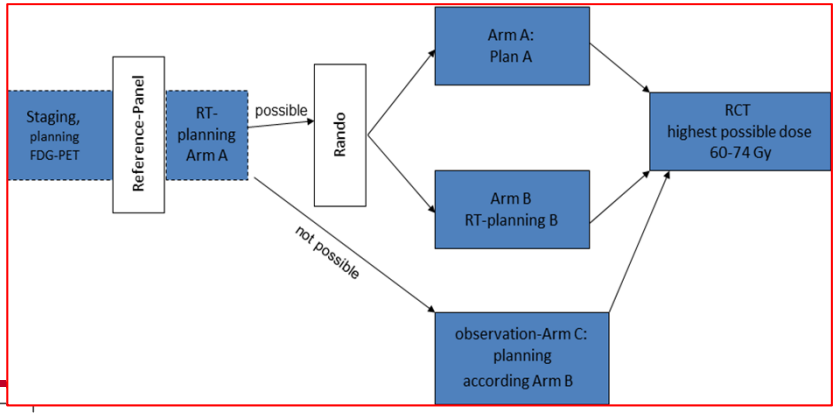
PET - Plan



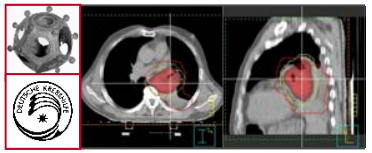


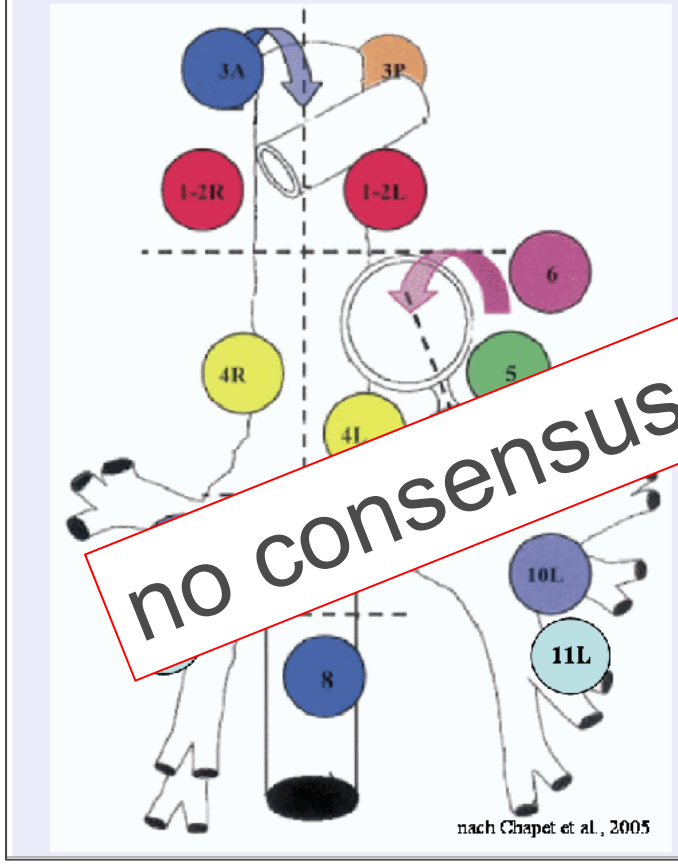






PET-Plan Study: diagnostic expert-panel



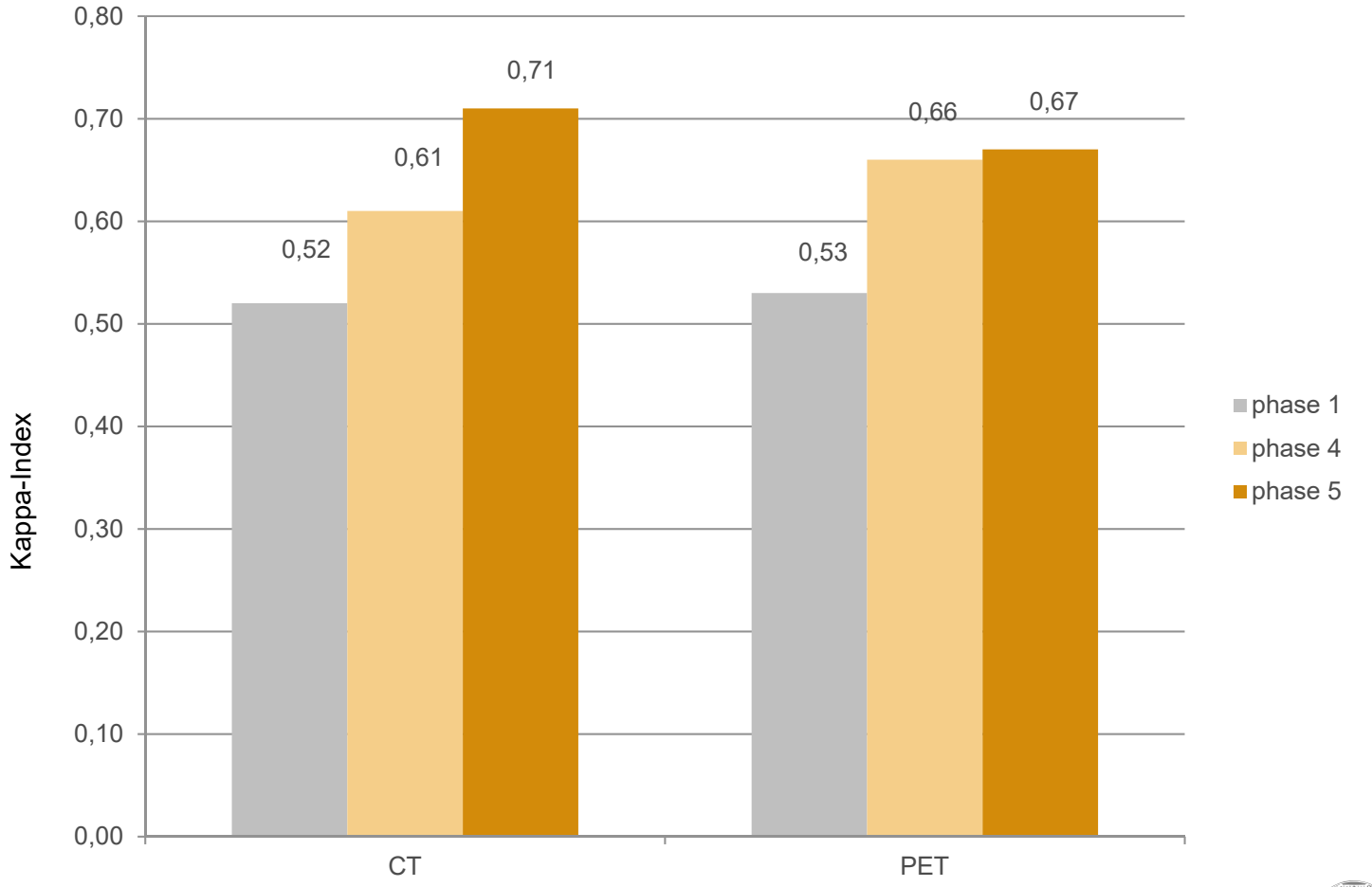


Station	Findings study center	Findings Review 1	Findings Review 2	Consensus Reviewer 3
1R*	neg	neg	pos	
1L*	neg	neg	neg	
2R*	pos	pos		
2L*	neg			pos
3A*	neg		neg	neg
3P*			neg	neg
4R*		pos	pos	pos
4L*		pos	neg	pos
5*	neg	neg	pos	neg
6*	neg	neg	neg	neg
7*	pos	pos	pos	pos
8*	neg	neg	neg	neg
10R*	neg	pos	pos	neg
10L*	pos	pos	pos	pos
11R*	neg	neg	neg	neg
11L*	neg	pos	neg	neg

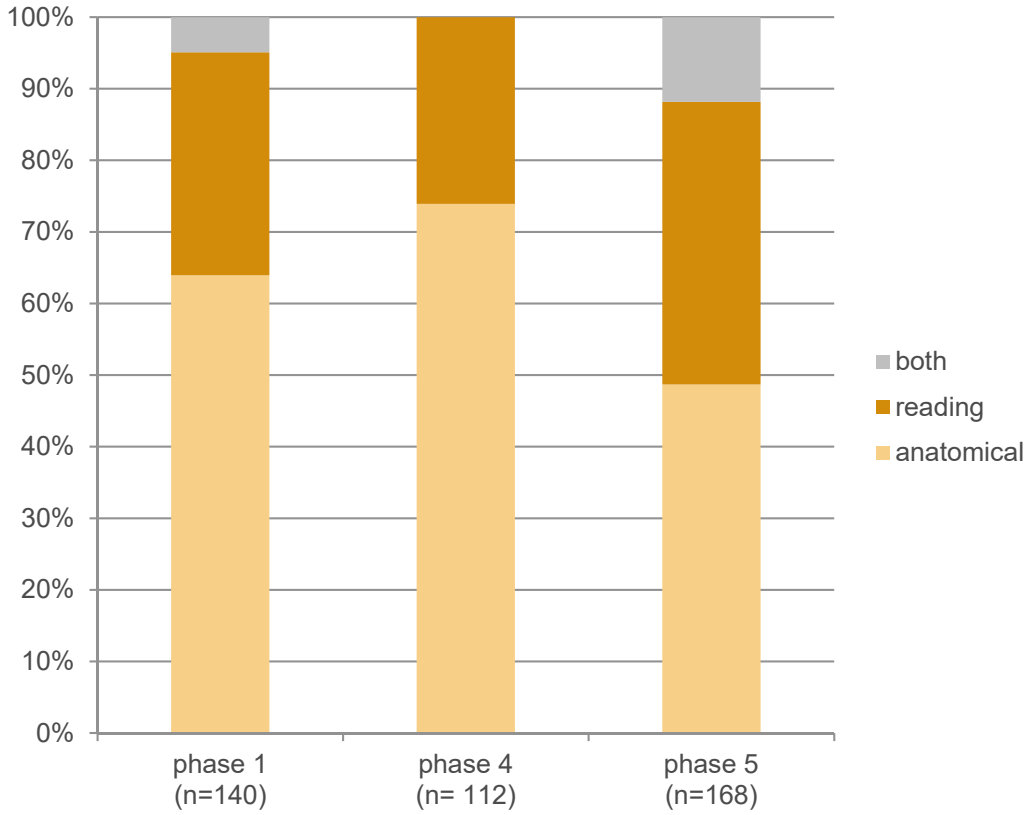
no consensus in first 10 cases ...

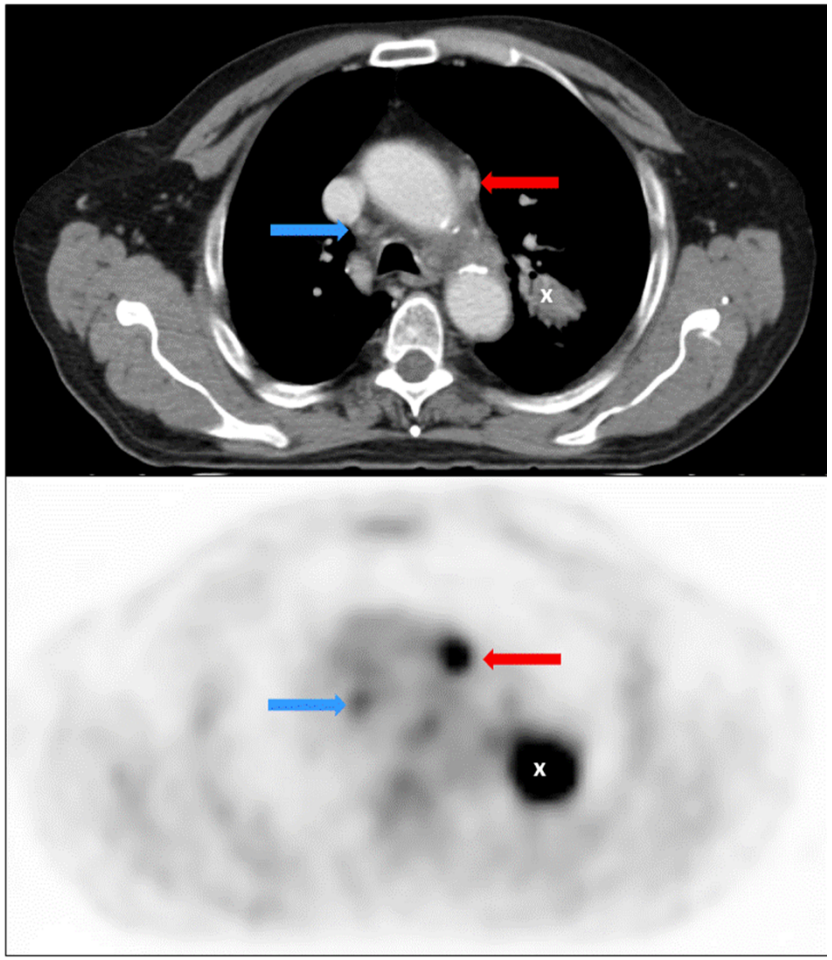
32 LN-reports for PET (16) and CT (16) to be entered at each review step

PET-Plan Panel: overall observer agreement by phase



What are the reasons for reporting disagreements?





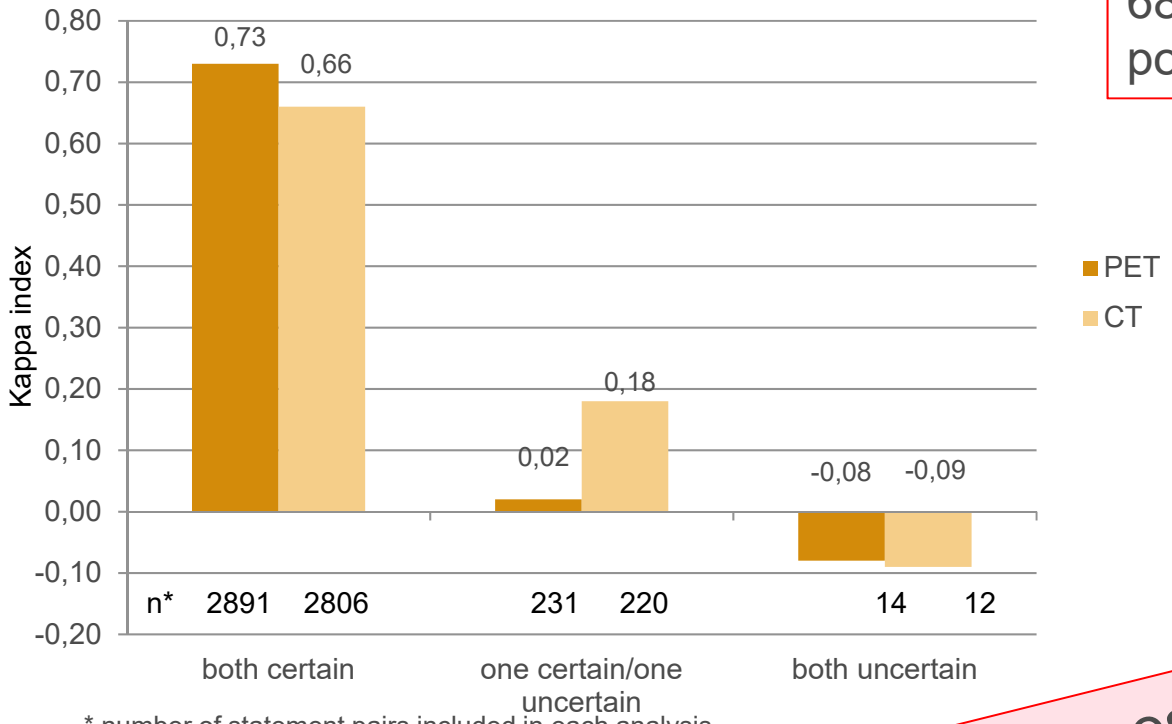
Kliniken Maria Hilf Mönchengladbach

UNIVERSITÄTS KLINIKUM FREIBURG

Nestle et al. EJC 2015

Are you sure about your finding?

Association of subjective certainty of observers with inter observer agreement



* number of statement pairs included in each analysis

comparison with biopsy:

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

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

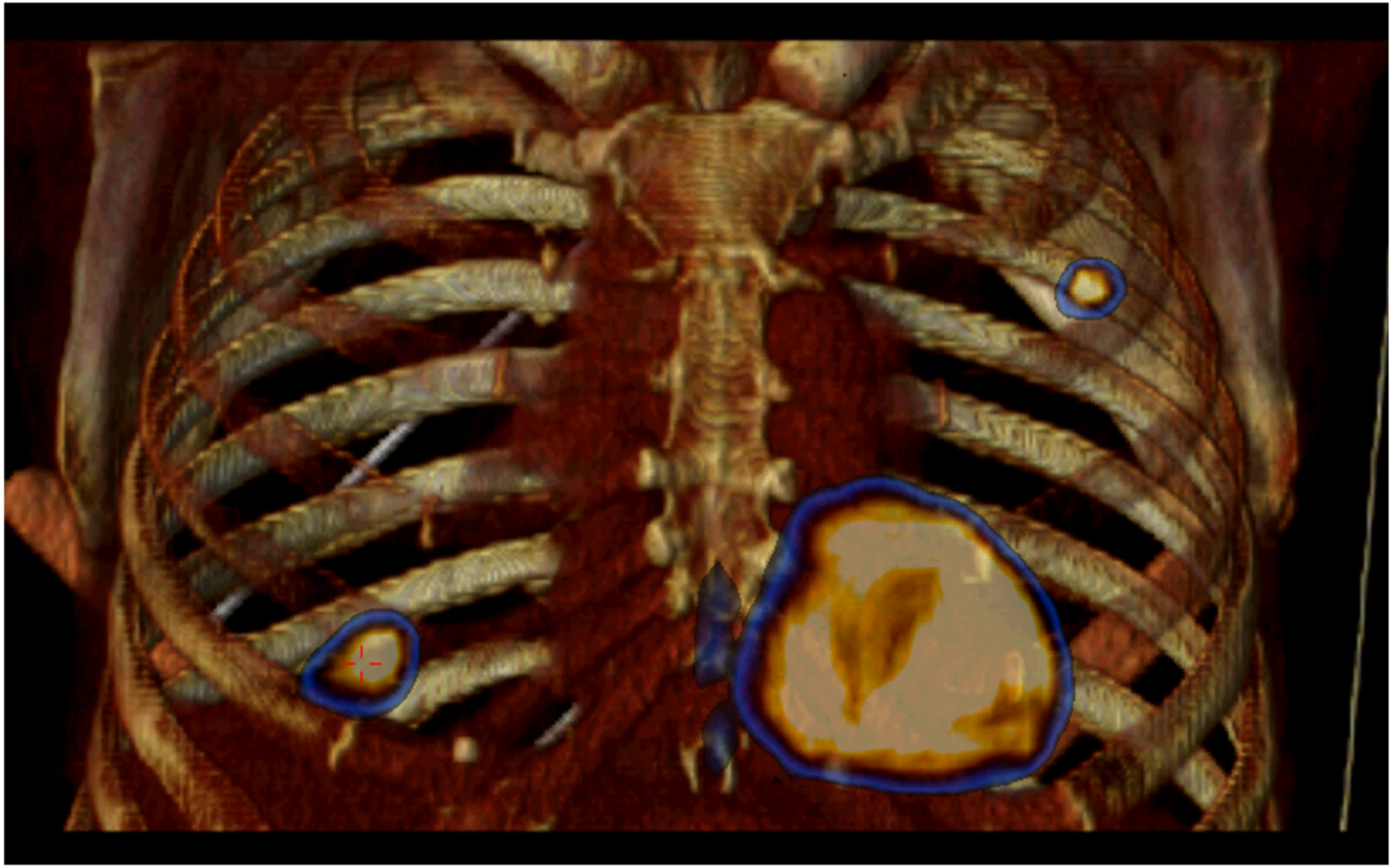
Kliniken Maria Hilf Mönchengladbach

UNIVERSITÄTS KLINIKUM FREIBURG

Applications of multimodal imaging in radiation therapy: outline

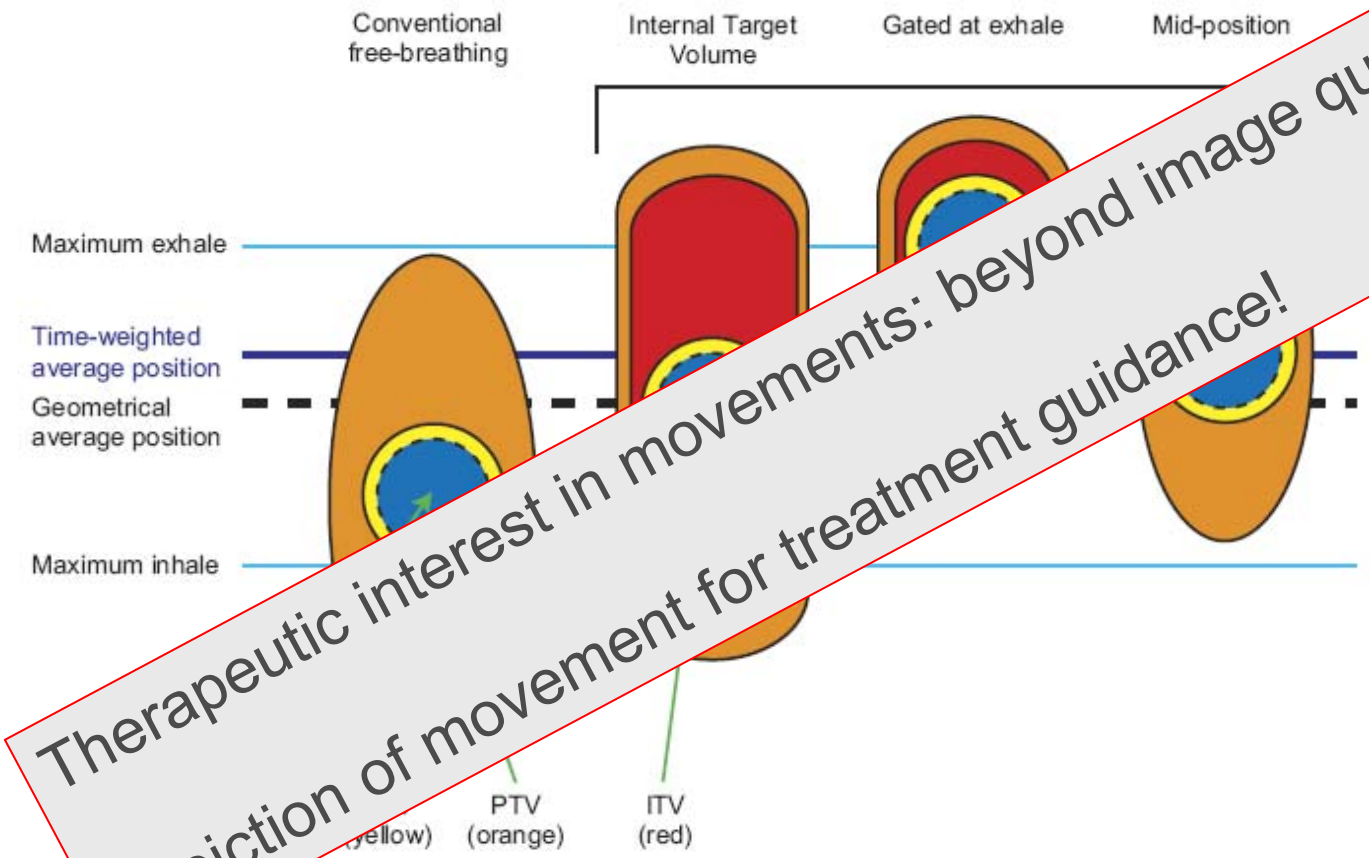
- Primary tumor: GTV
- Nodal volumes: CTV
- **Movements: PTV**
- Perspectives, caveats

Movements:
more than just disturbing image quality…



Thanks to M. Mix

Movement: important information for the planning of high precision radiotherapy



Therapeutic interest in movements: beyond image quality:

depiction of movement for treatment guidance!

Fig. 1. Schem… …w of different treatment-planning concepts: conventional free-breathing, internal target volume (ITV), gating (a… …hale), and mid-position. GTV = gross tumor volume; CTV = clinical target volume; PTV = planning target volume.

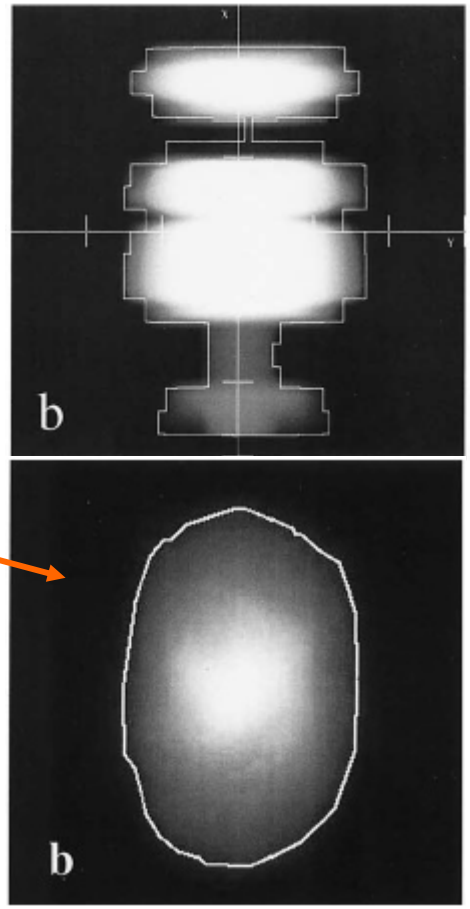
Wolthaus *et al.* (IJROBP 2008)

ITV: PET and breathing movements

Phantom measurements with moving spheres
in ungated PET and CT

CT: significant distortion

PET: image similar to ideal capsular shape
depicting sphere + motion



→ Possibility of exact imaging of 4-D-tumor volume

→ Reduction of risk for topographical miss
from „snapshot“-CT

Caldwell IJROBP 2003 55; 1381-1393

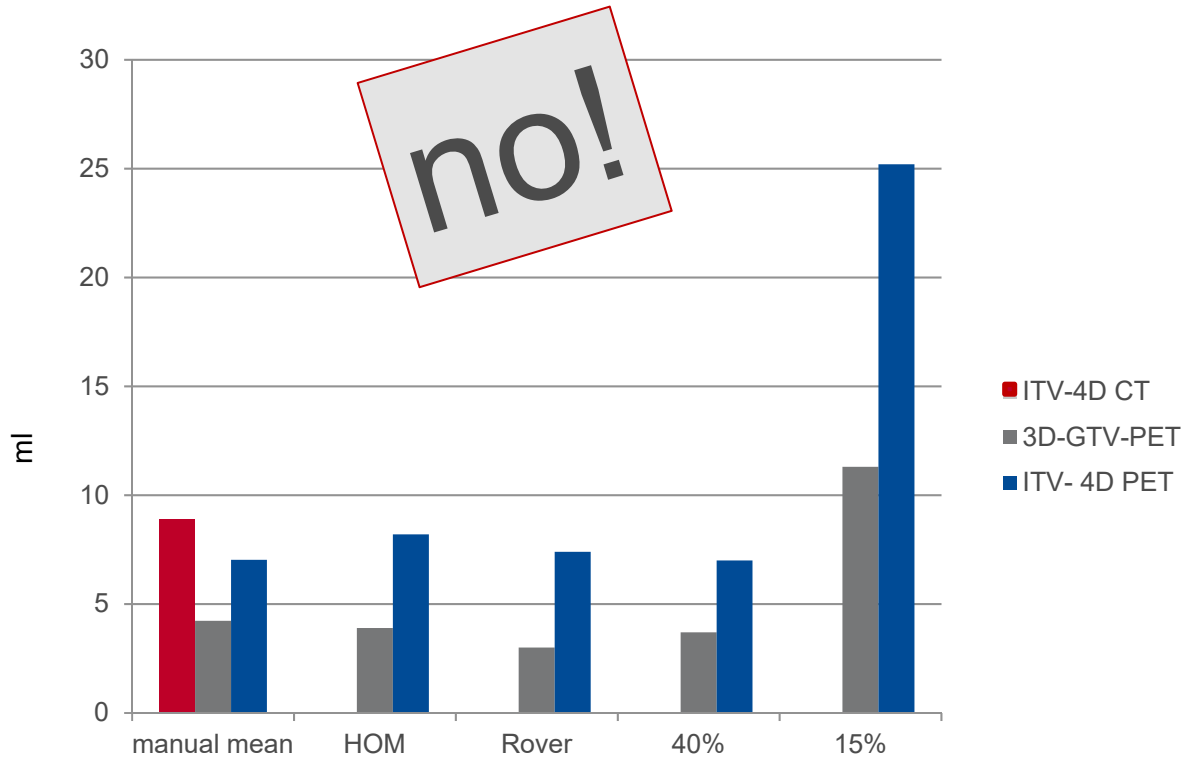
Can we derive an internal target volume from 3D PET?

12 NSCLC scheduled for SBRT; 4D PET/CTs, 4 observers:

1. ITV in 4D CT „gold standard“

2. „GTVs“ in 3D PET
3. ITVs from 4D PET

- manual
- Homburg algorithm
- Rover algorithm
- 40% SUVmax
- 15% SUVmax

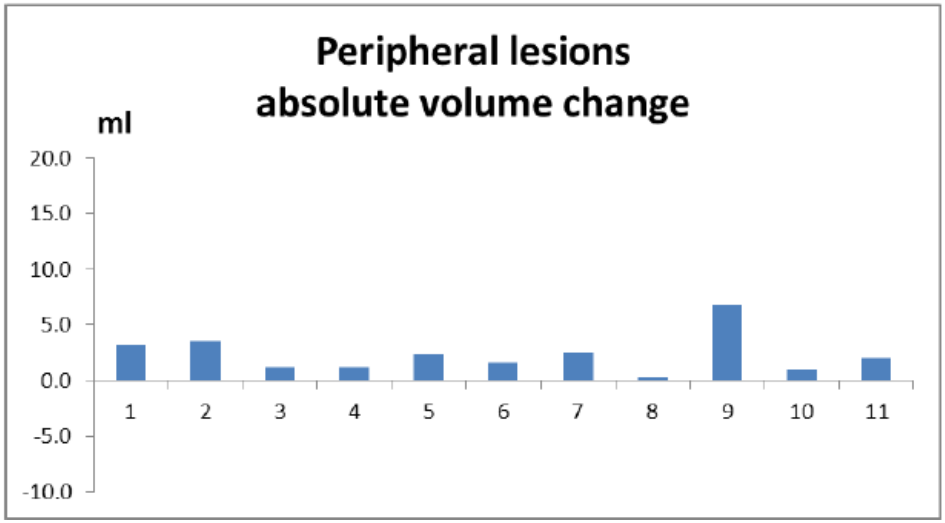


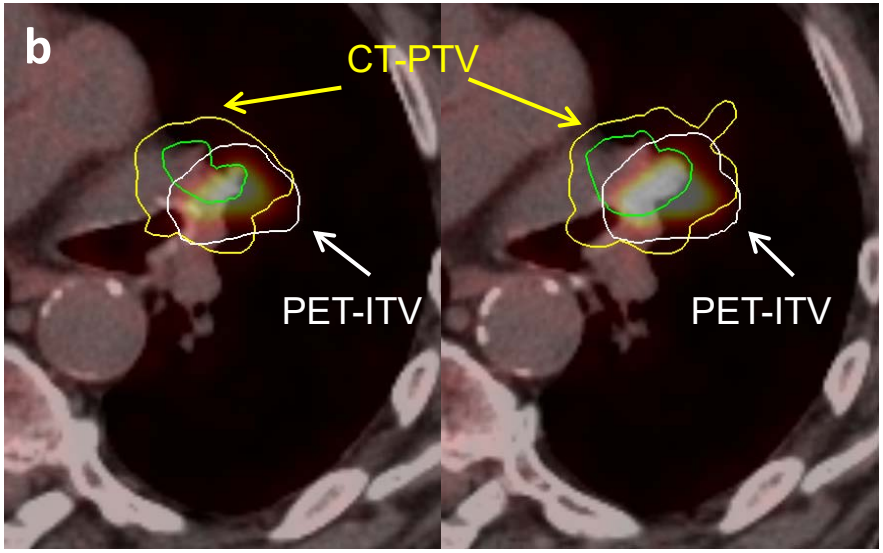
Impact of 4D PET-CT in SBRT-planning

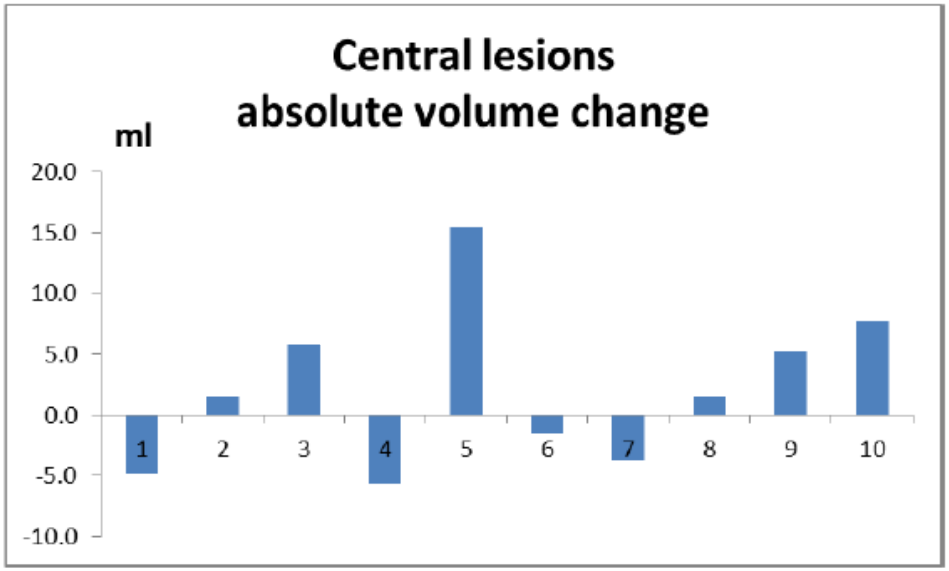
central (n = 10) vs. peripheral (n=11) NSCLC

contouring ITV, 4 observers:

1. in 4D CT, PET-viewing side by side
2. in coregistered 4D PET/CT

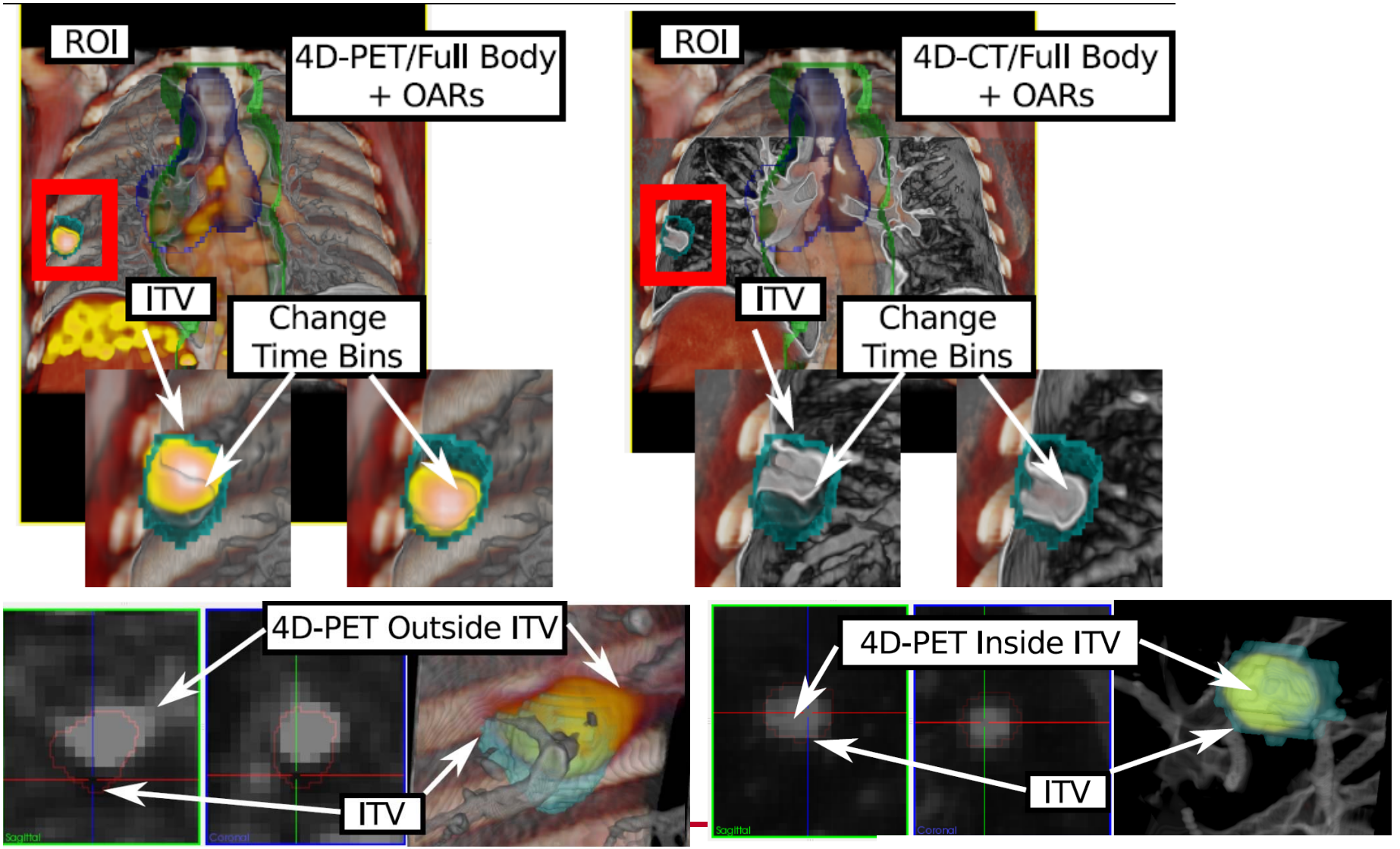






Chirindel et al. R&O 2015

4D PET/CT Delineation: needs automation…

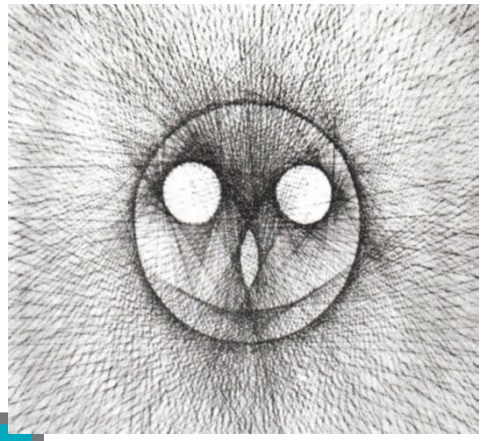


Schlachter, M., et al.IEEE TMI 2017

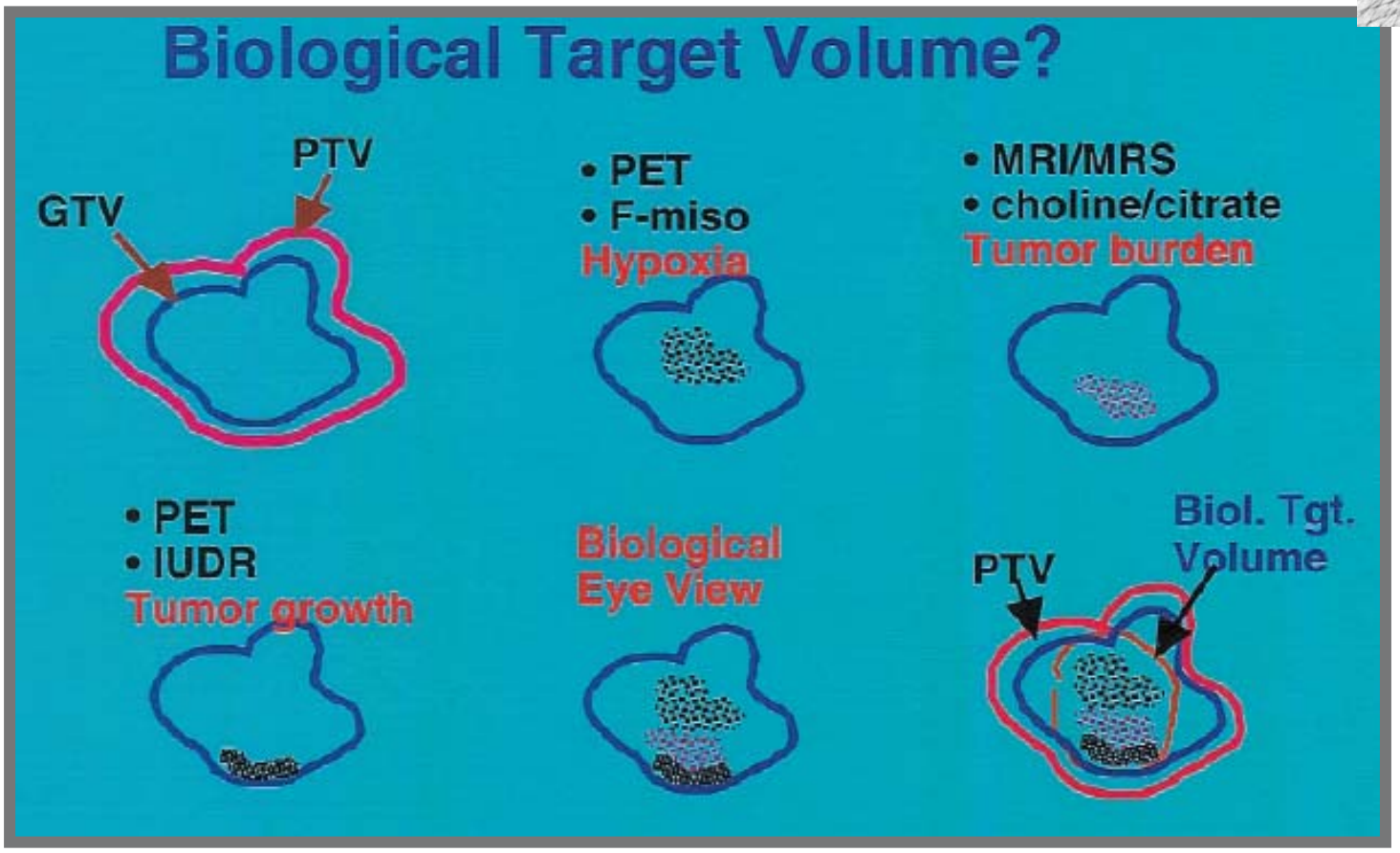
Applications of multimodal imaging in radiation therapy: outline

- Primary tumor: GTV
- Nodal volumes: CTV
- Movements: PTV
- **Perspectives, caveats**

... dose painting

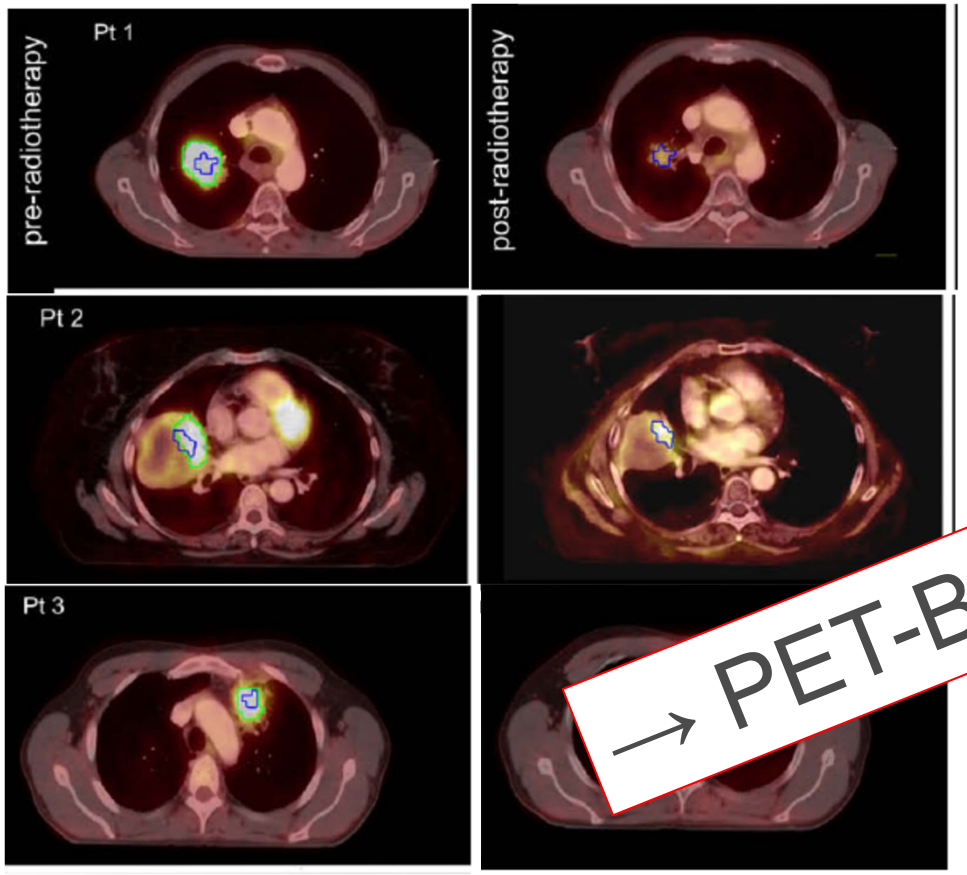


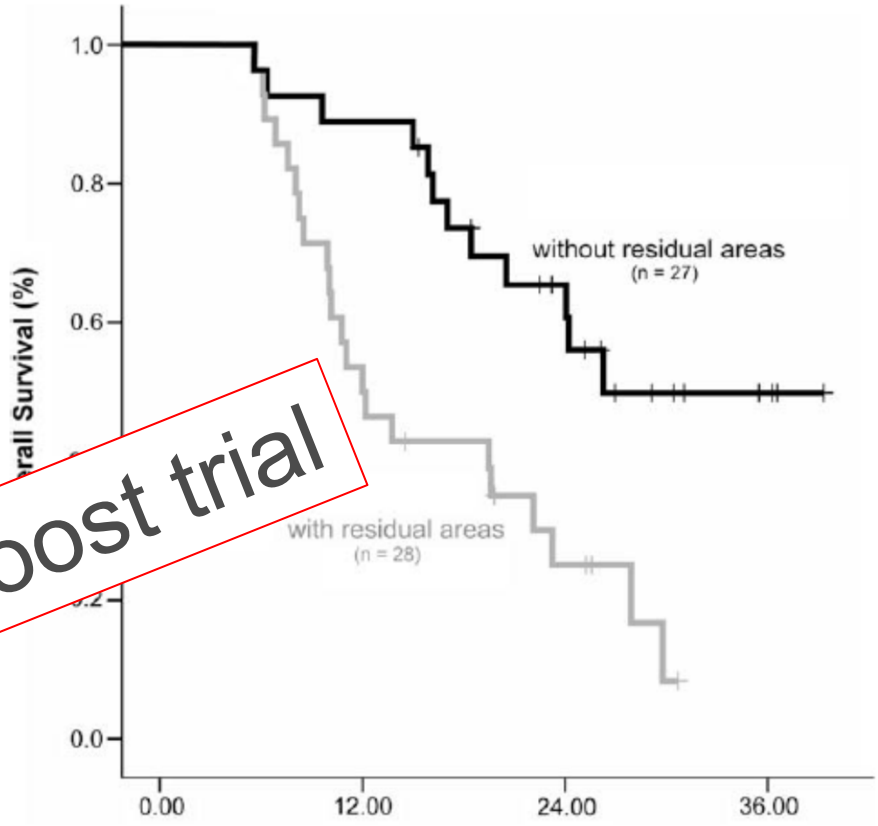
Birkhoff G 1940.



Ling 2000

PET in RT planning: beyond GTV





→ PET-Boost trial

55 pts., FDG-PET pre/post RT

Aerts, R&O 2009

Contents lists available at ScienceDirect

Radiotherapy and Oncology

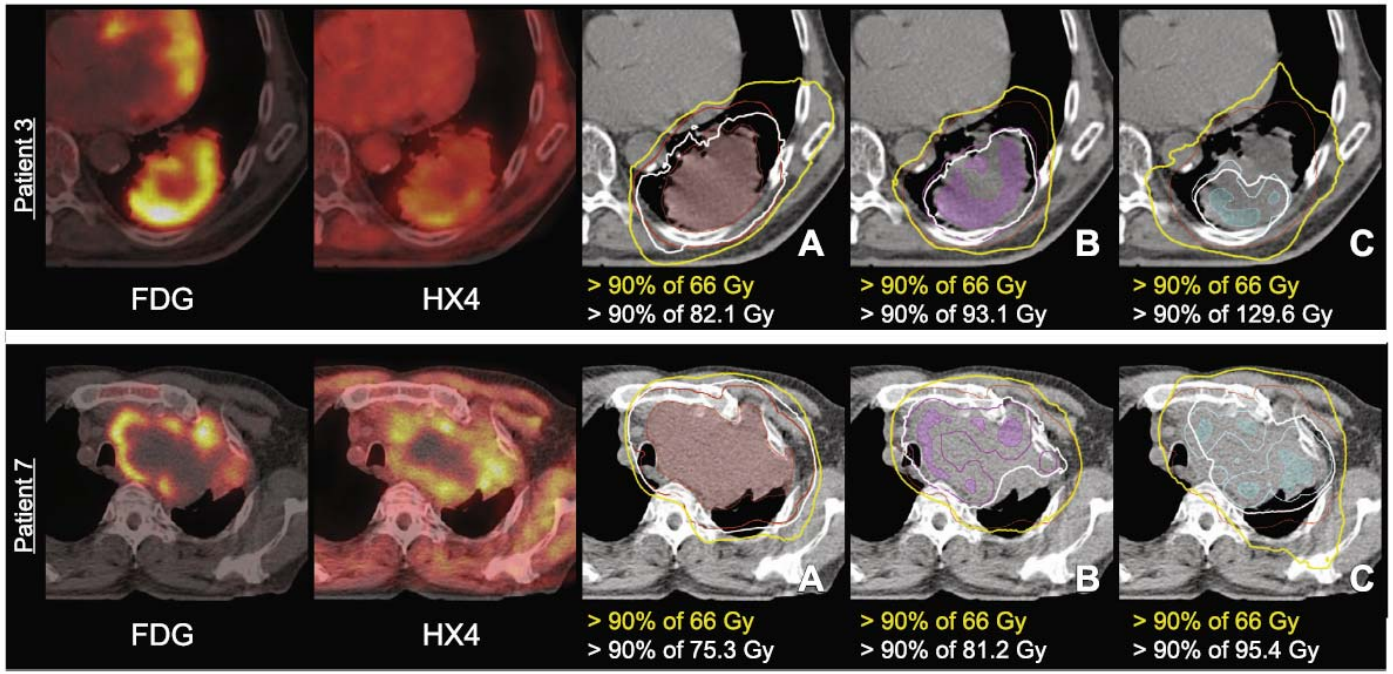
journal homepage: www.thegreenjournal.com

Dose painting in lung cancer

PET-based dose painting in non-small cell lung cancer: Comparing uniform dose escalation with boosting hypoxic and metabolically active sub-volumes

Aniek J.G. Even [a,*], Judith van der Stoep [a], Catharina M.L. Zegers [a], Bart Reymen [a], Esther G.C. Troost [a,b], Philippe Lambin [a], Wouter van Elmpt [a]

[a] *Department of Radiation Oncology (MAASTRO), GROW – School for Oncology and Developmental Biology, Maastricht University Medical Centre, The Netherlands; and* [b] *Institute of Radiooncology, Helmholtz-Zentrum Dresden-Rossendorf, Germany*



Conclusions: Dose escalation based on metabolic sub-volumes, hypoxic sub-volumes and the entire tumour is feasible. Highest dose was achieved for hypoxia plans, without increasing dose to OAR. For most patients, boosting the metabolic sub-volume also resulted in boosting the hypoxic volume, although to a lower dose, but not *vice versa*.

Imaging during conventional radiochemotherapy

Results:

Patient, Tumor & Response characteristics	
Age (median)	66 (47-84) years
	Number (percentage)
Sex	
Female	13 (33,3%)
Male	26 (66,6%)
Histo-/Cytology	
Squamous cell carcinoma	23 (59%)
Adenocarcinoma	12 (31%)
Other	4 (10%)
Stage (UICC, V7, 2009)	
IIa	2 (5%)
IIIa	20 (51%)
IIIb	17 (44%)
Primary tumor	
GTV size (median)	58 (15-923) ml
Total dose (average)	68 (58-76) Gy
SUVmax	
RP PET/CT (median)	14 (5,5 – 28,3)
1.R-PET/CT (median)	10,5 (3,4 – 23,7)
2.R-PET/CT (median)	5,45 (1,4 – 14,3)
	Number (percentage)
Primary tumor PMR	
Patients with PT-PMR1	14/33 (42%)
Patients with PT-PMR2	22/30 (73%)
Patients with PT-PMR1+2	9/29 (31%)
2-year-Overall Survival	
PT-PMR1+2: yes	54%
PT-PMR1+2: no	75%

Schimek-Jasch et al. ESTRO 2016

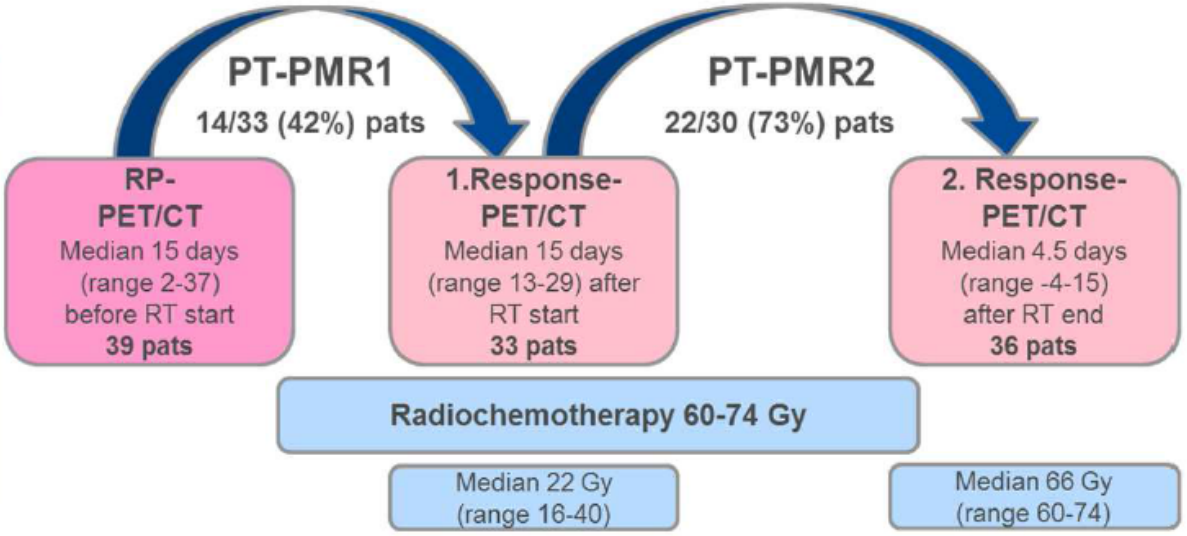


Figure 1: Flowchart of PET/CTs in timely relation to radiotherapy, including number of patients and median irradiation dose at the respective (R-)PET/CT, as well as partial metabolic response of the primary tumor at first and second R-PET/CT.

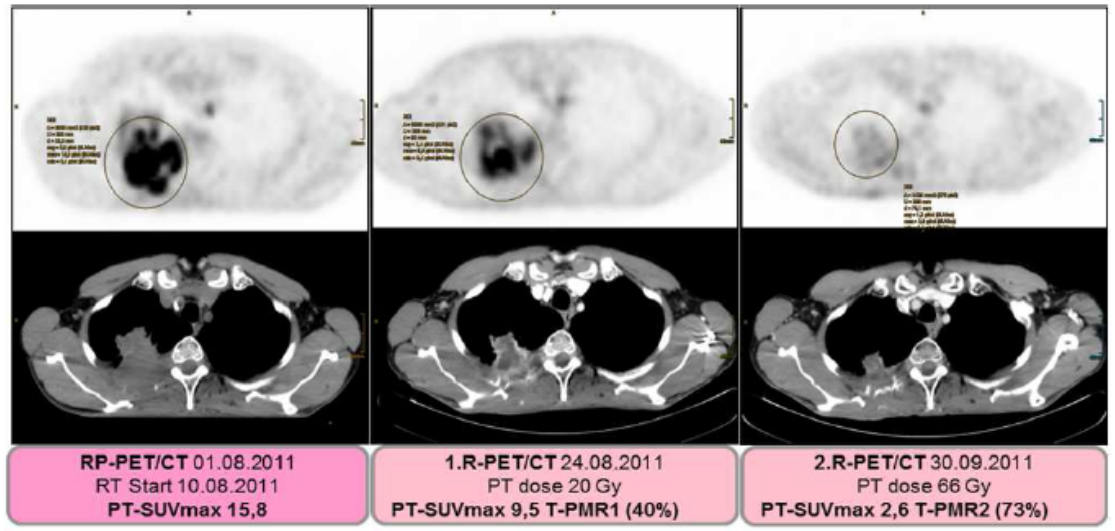


Figure 2: Patient example depicting PR-PET/CT and R-PET/CTs, together with irradiation dose, time points and response of primary tumor (SUXmax and partial metabolic response).

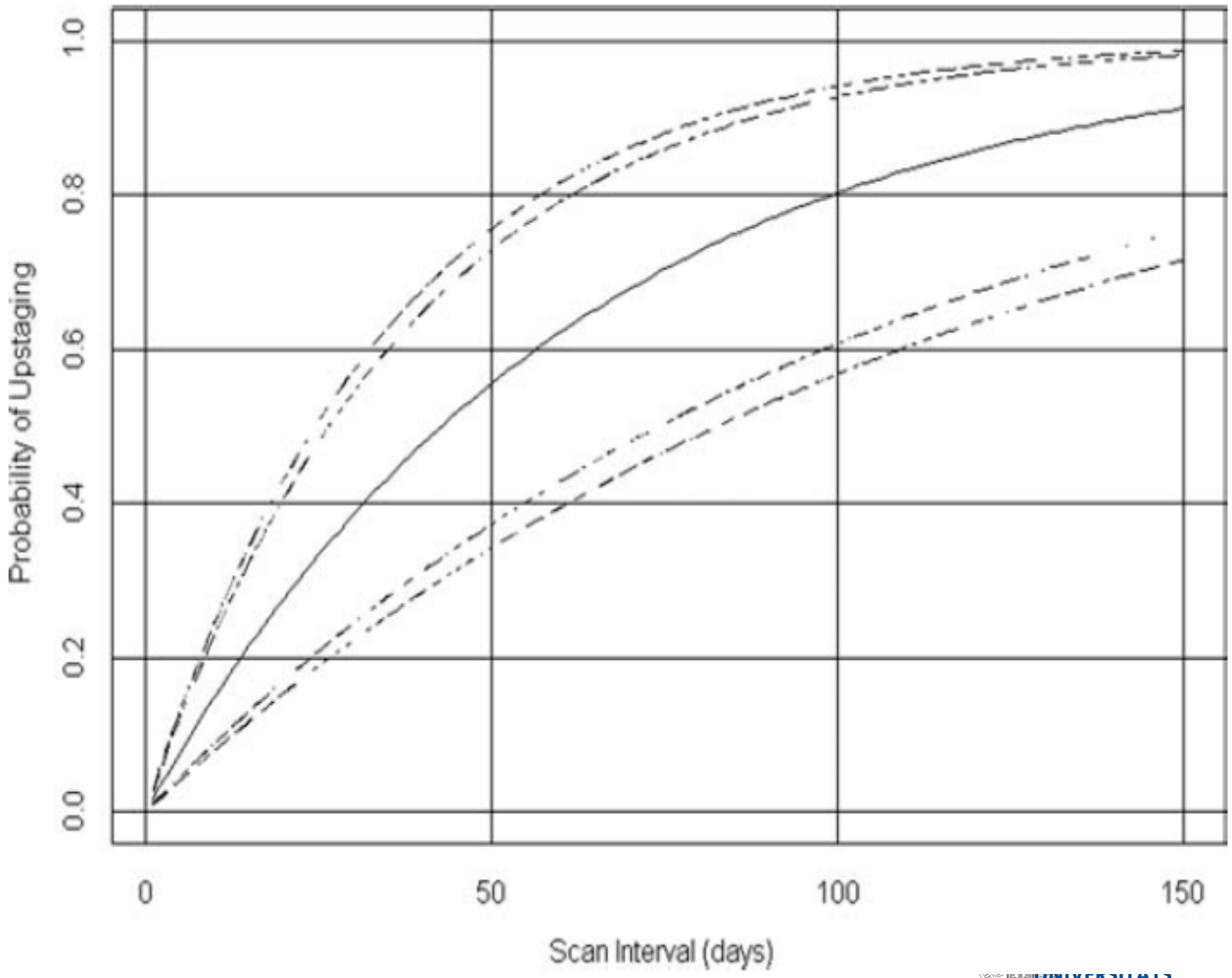
Imaging for RT-planning: soon before treatment!

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

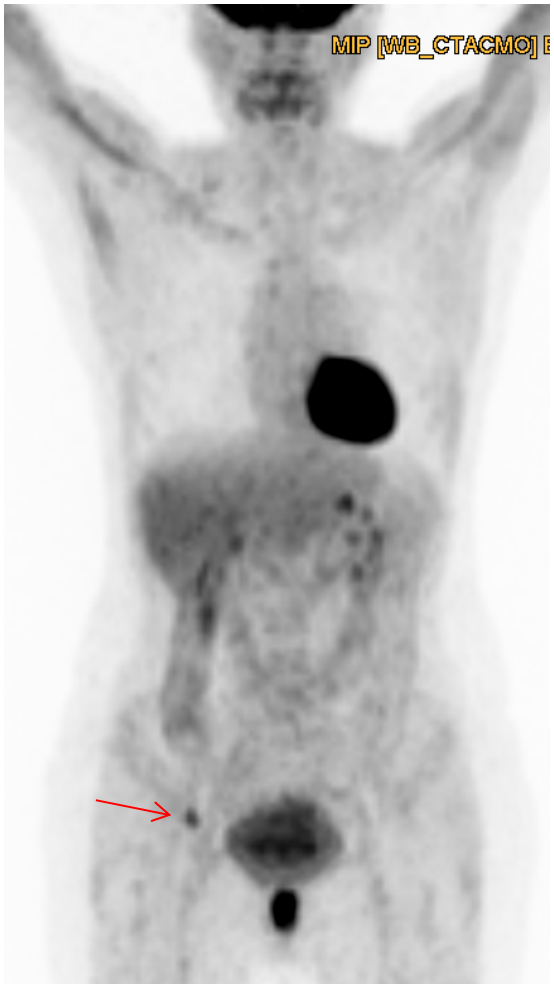
progression in 39%

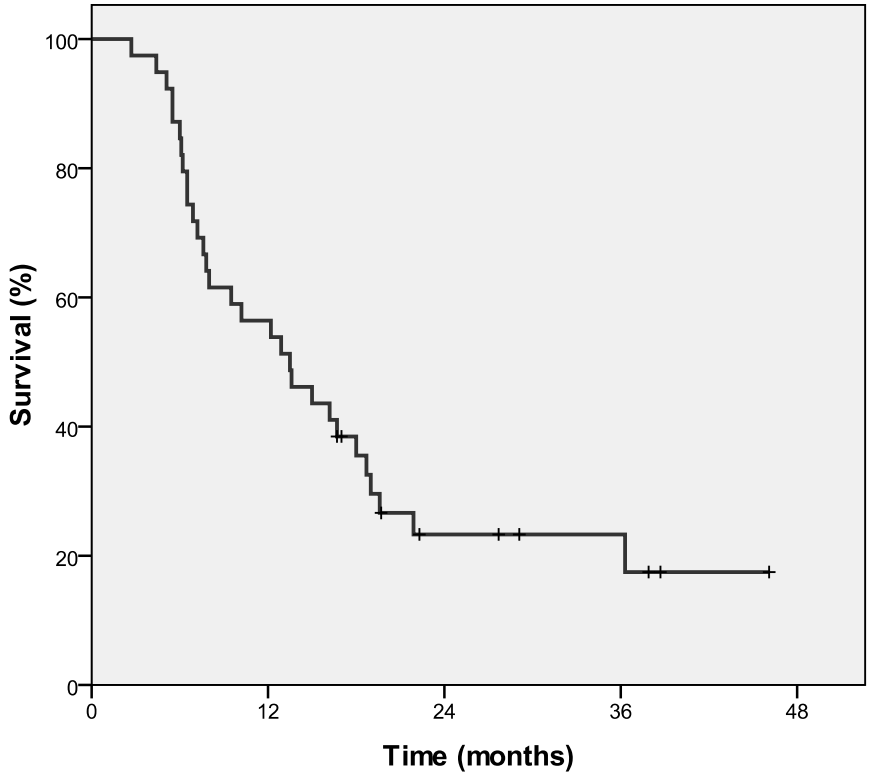
upstaging probability
within 24 days: **32%**

Everitt, S. et al.
Cancer 2010



Accurate imaging of tumor load: New chance for oligometastatic patients?





n=39, UICC IV, RCT + adj CHT + RT M1

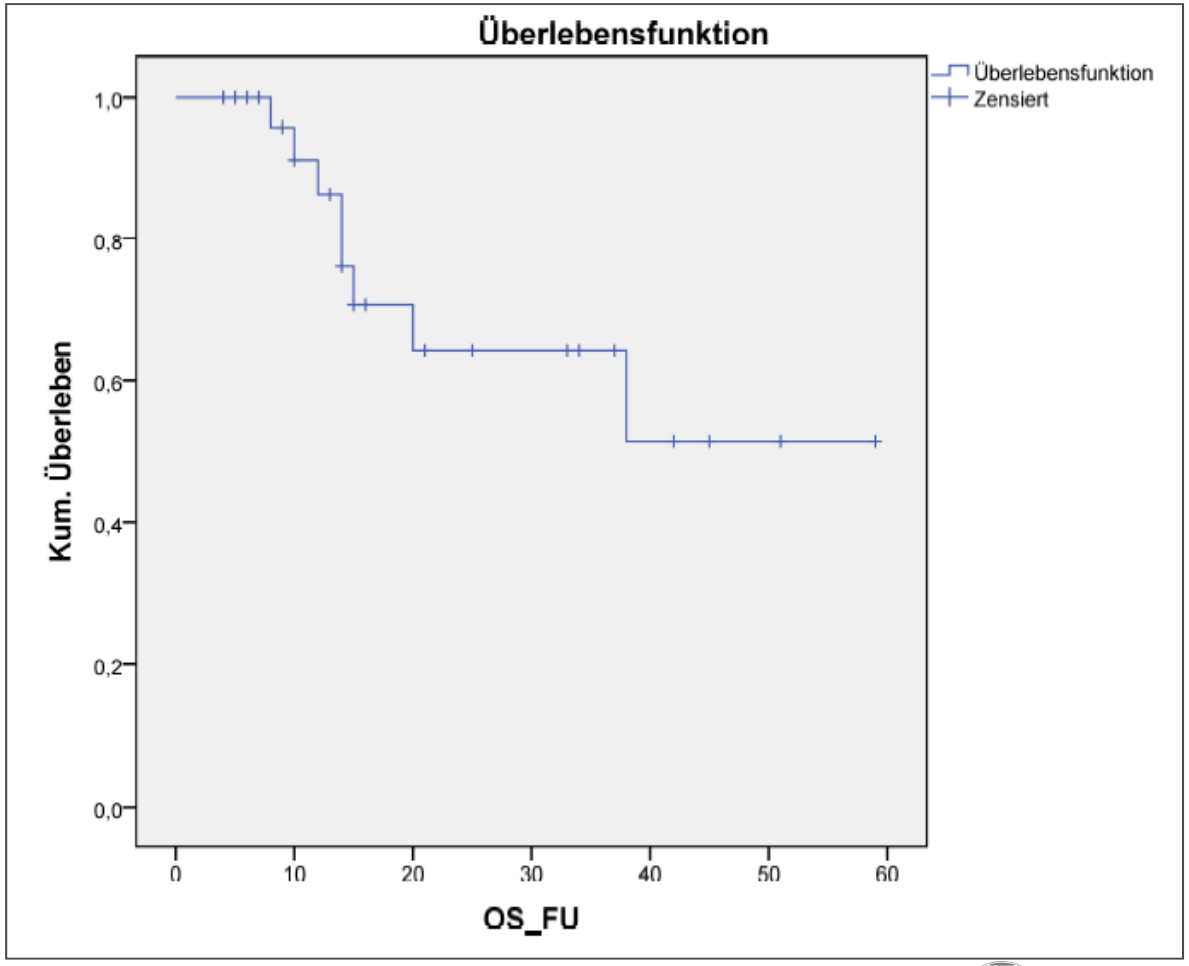
D. DeRuysscher, JTO 2012

Encouraging outcome of patients with oligometastatic NSCLC through intrathoracic radical approach

D.H. Schanne et al. ECCO 2013

n=29/1083
NSCLC, UICC stage IV
Tumorboard FR,
2008 - ज़ज़ह्नट
“radical approach”
<5 distant metastases

brain (ढ़ज़प), lung (ह्नगप),
distant lymph nodes (ह्नठ%),
adrenal glands (ह्नठ%),
other (ण्प)



Summary

Radiation Oncology is being revolutionized by new technologies and those are crucially dependent on imaging

Prerequisites for changing concepts are a clinical need and the superiority of the new imaging to traditional methods and may vary significantly between tumors, tracers and clinical scenarios

To seriously show patients benefit by the use of new imaging modalities in different clinical situations, clinical trials are mandatory

Beyond target volume definition, other areas of the use of hybrid imaging in radiotherapy (response assessment, NT-monitoring …) are presently being investigated

Robust and 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)

Put more emphasis on robust planning

- Less on breathing stuff

Simplified PTV margin recipe for dose - probability

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

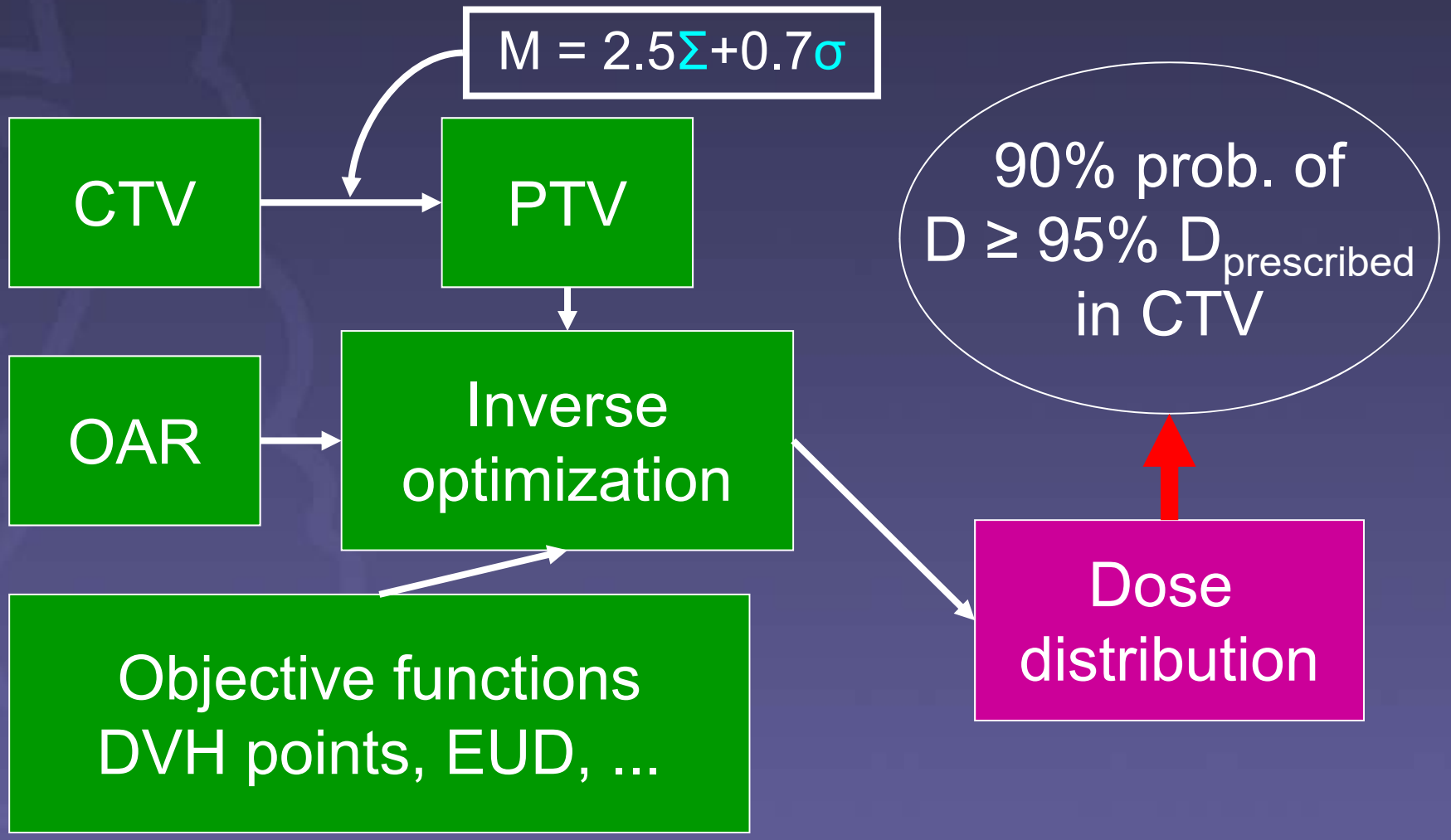
PTV margin = 2.5 Σ + 0.7 σ

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

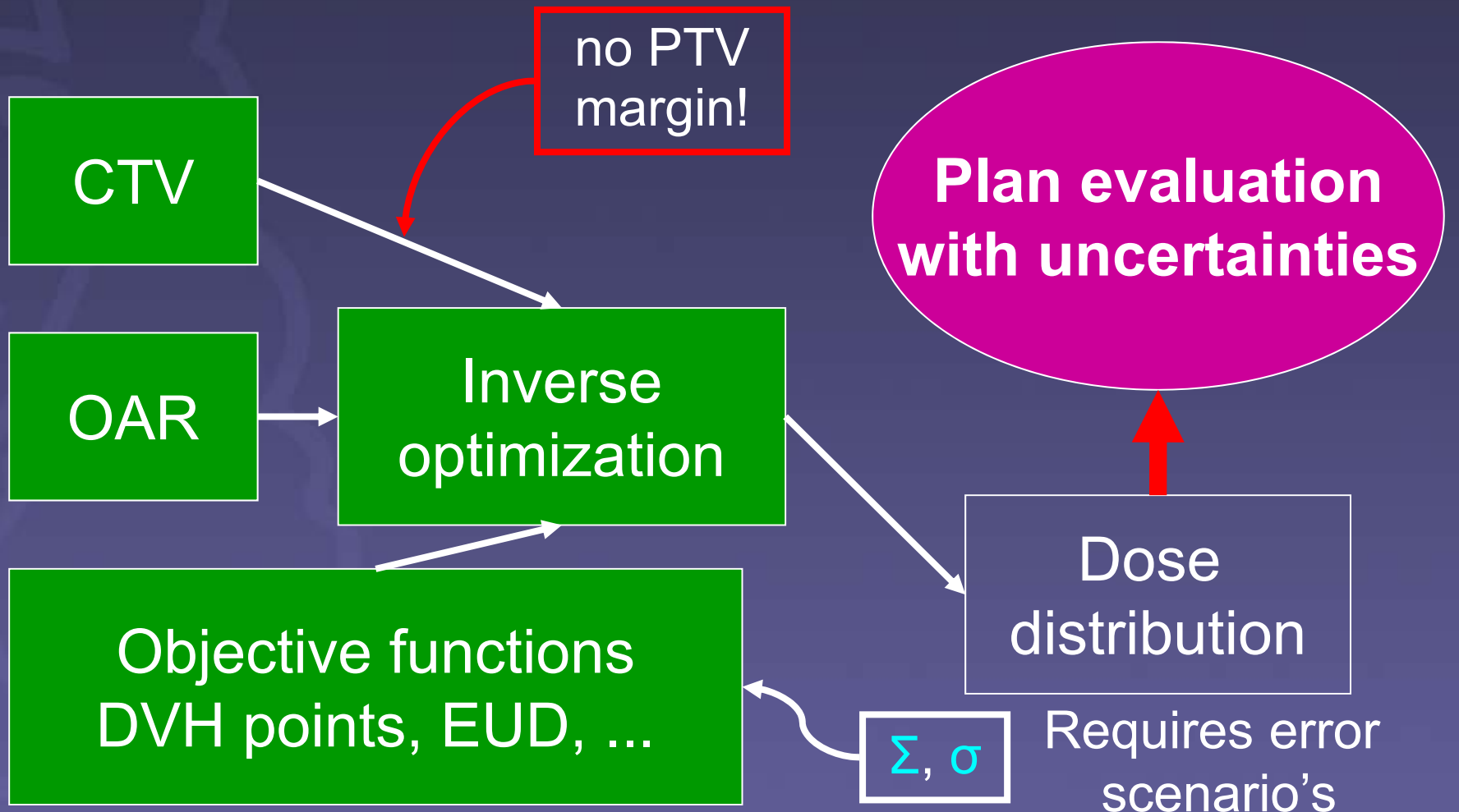
(van Herk et al, IJROBP 47: 1121-1135, 2000)

Margins are an implicit trade off between target coverage and OAR: can we make this explicit?

Uncertainty management: Conventional IMRT planning with margin

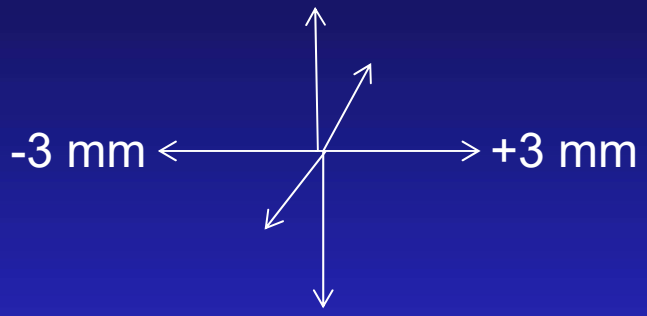


Uncertainty management: Probabilistic IMRT planning without margin



Robust vs probabistic planning

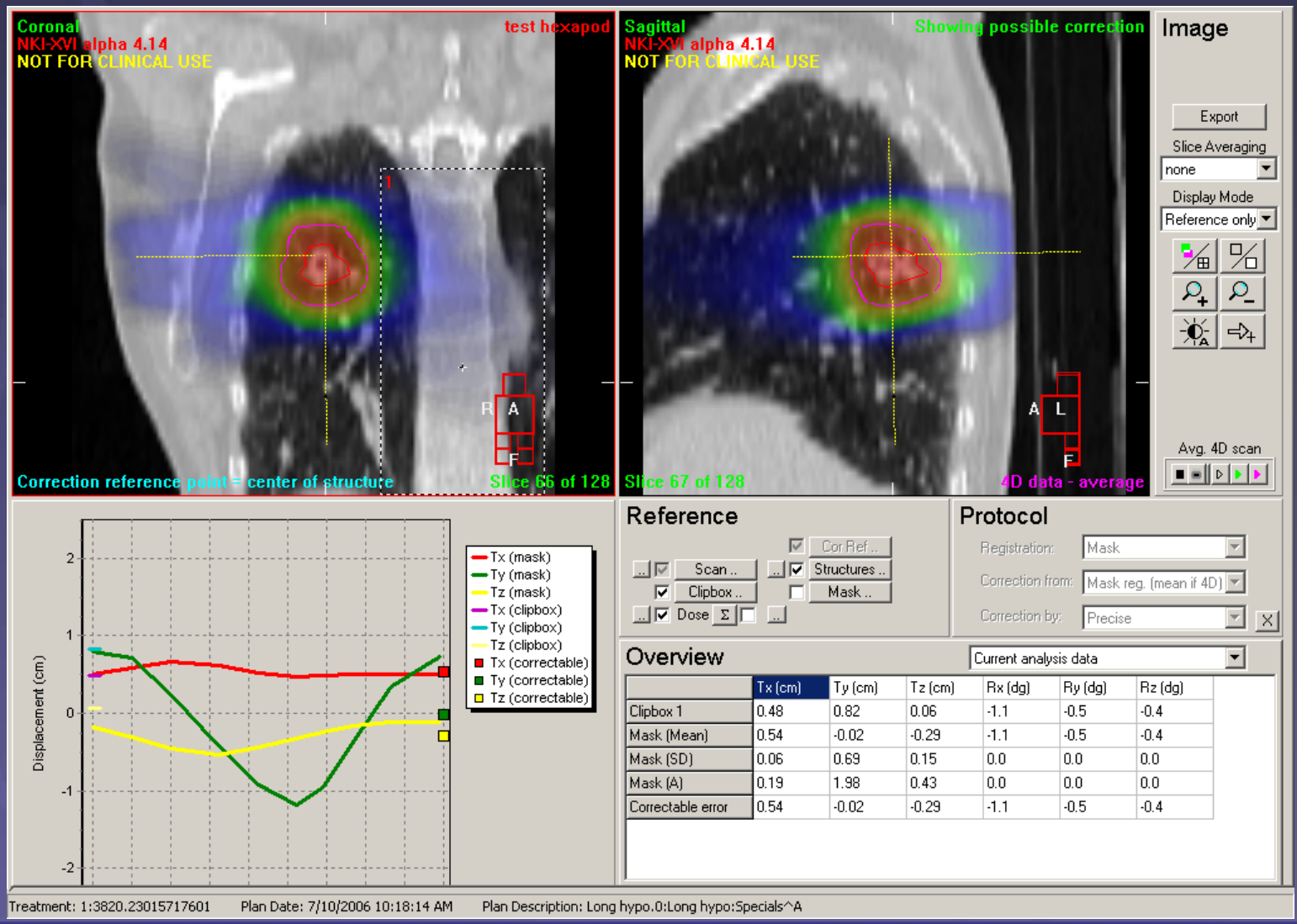
- Robust planning:
  - Few error scenarios
  - Worst case optimization
  - No differentiation random/systematic errors



- Probabilistic planning
  - Hundreds of error scenarios
  - Include both random and systematic errors
  - Optimize on probability

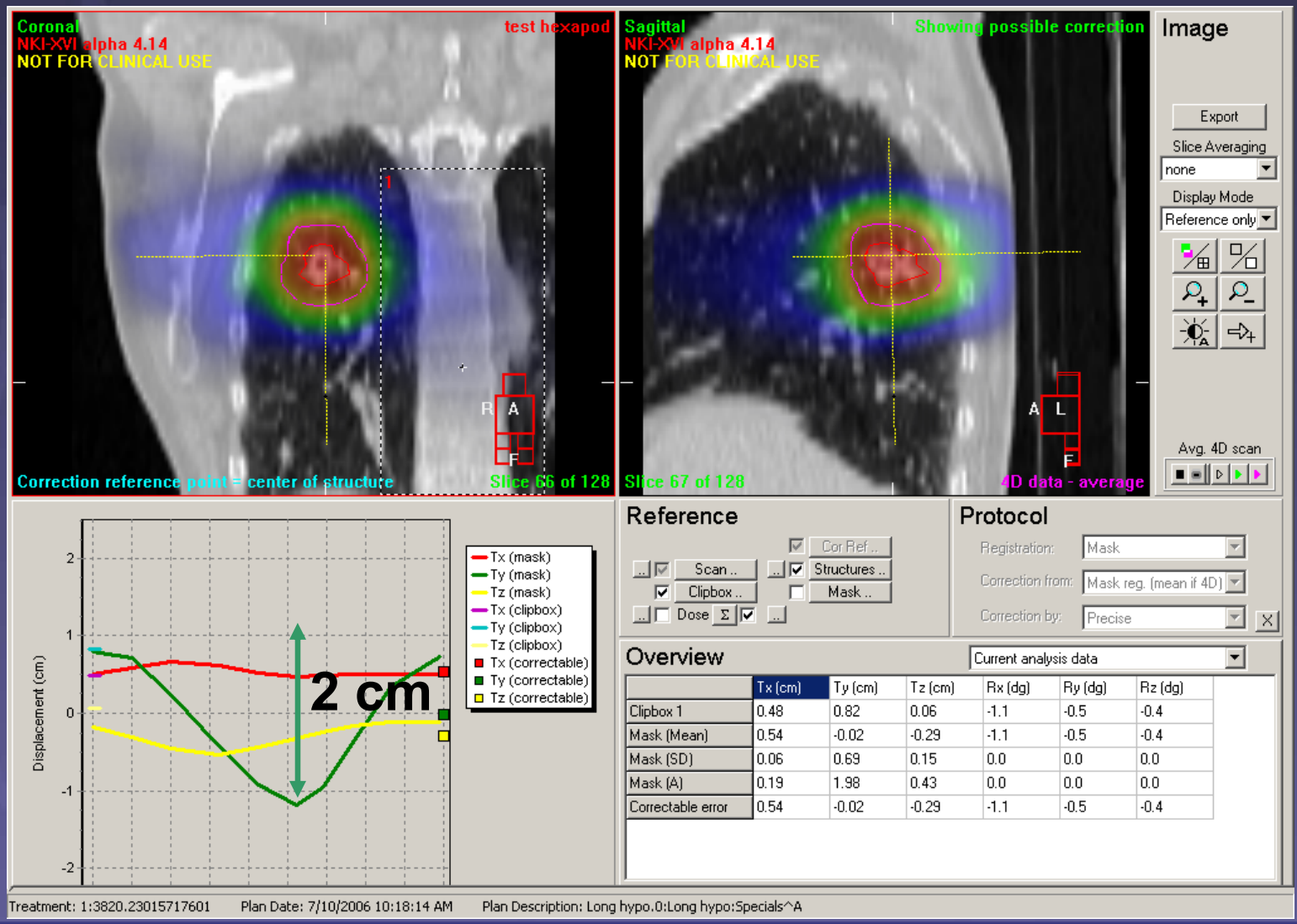
Random errors & breathing

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)



	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
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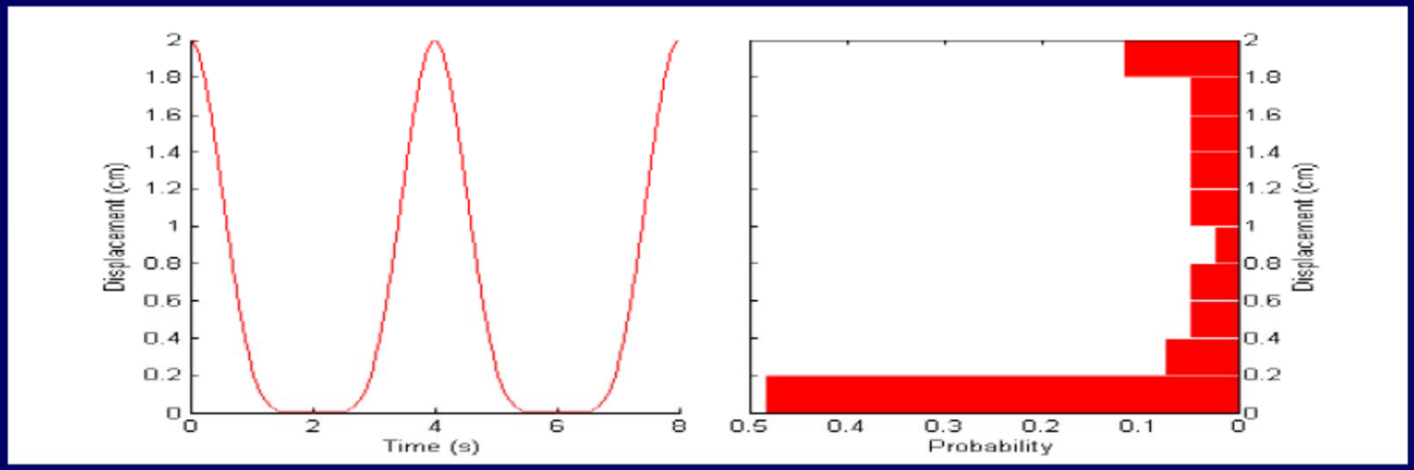
Correctable error	0.54	-0.02	-0.29	-1.1	-0.5	-0.4

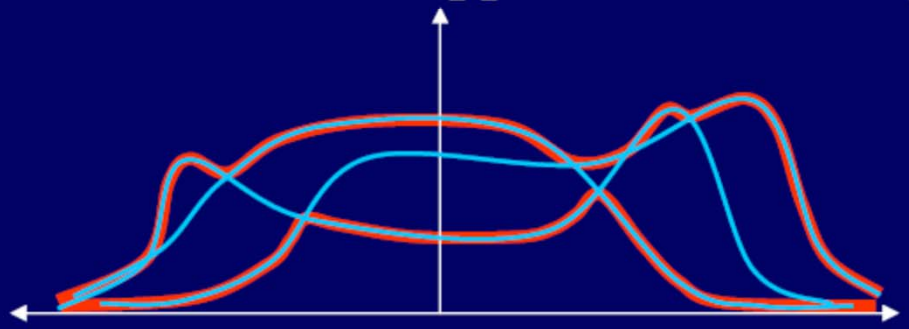
Respiratory motion causes dose blurring – can it be deblurred ?

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

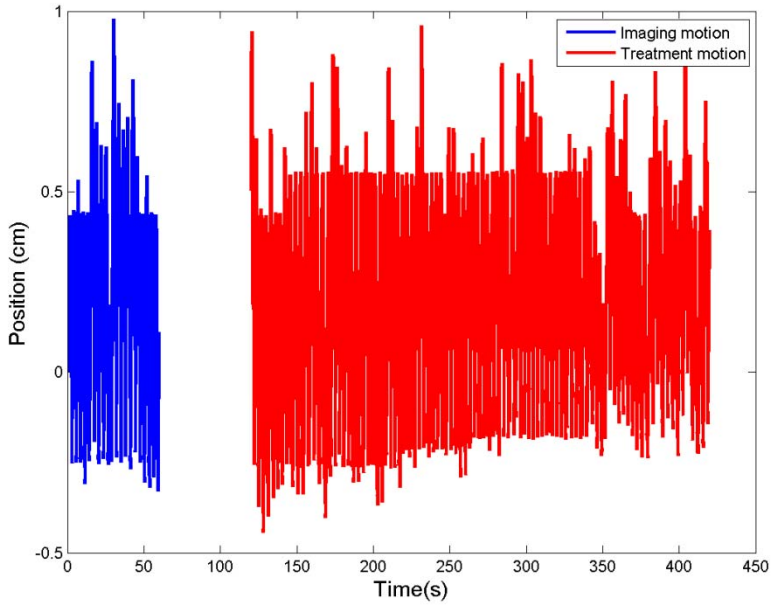


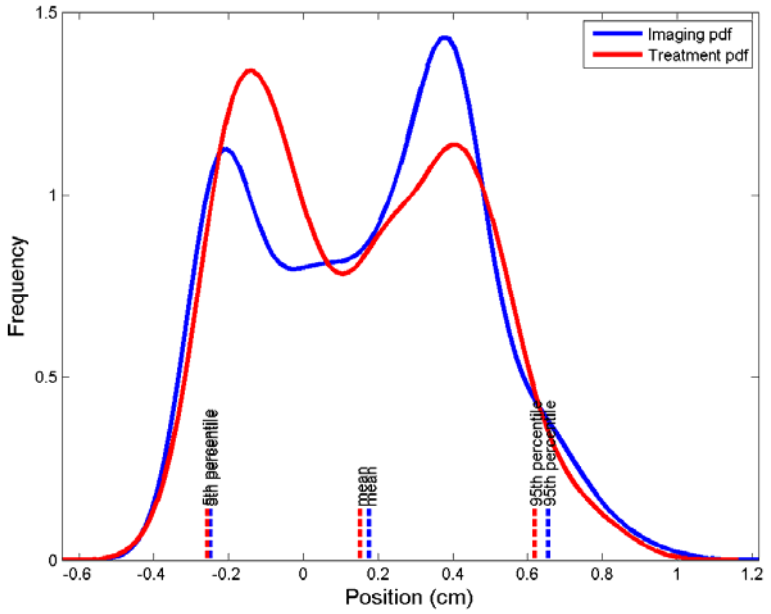
Phys. Med. Biol. **51** (2006) 2567–2583

Statistical Model of Breathing Motion

Similar imaging and treatment motion distribution

courtesy of Paul Keall





Motion traces

Probability density functions

Imaging
Treatment

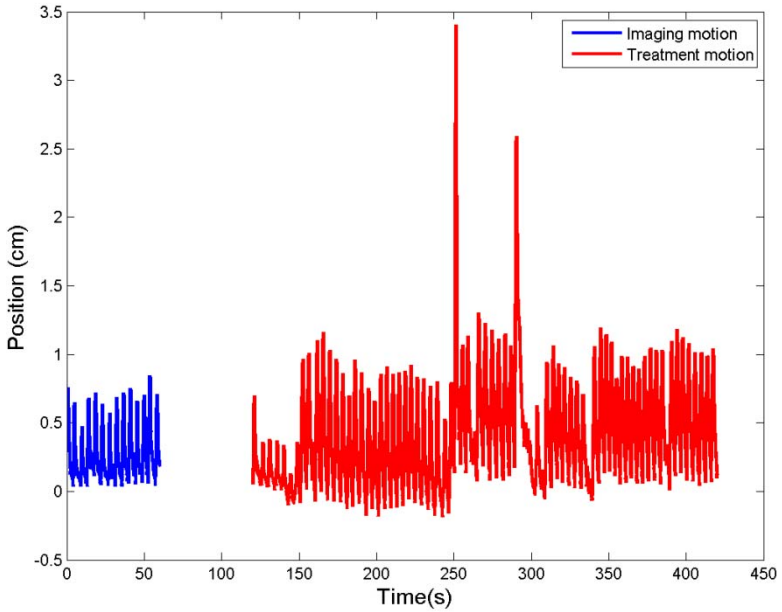
ESTRO School

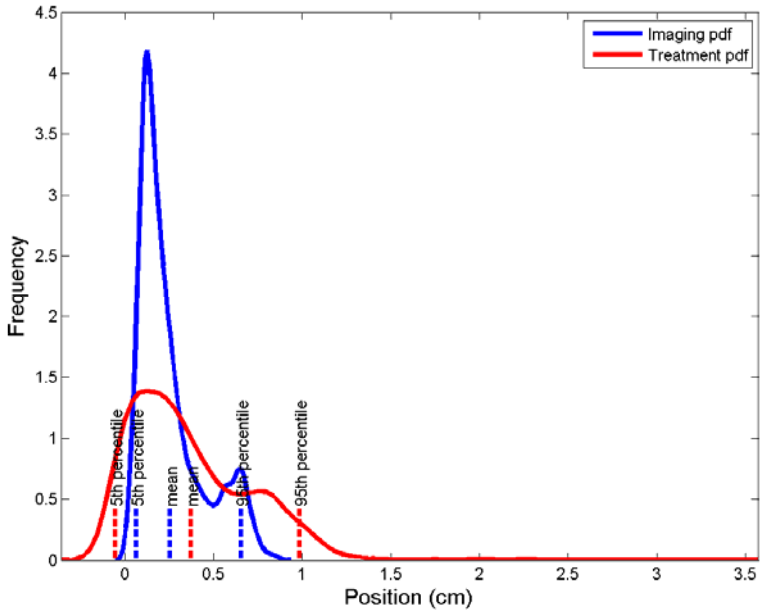
UHN Princess Margaret Cancer Centre

Statistical Model of Breathing Motion

Similar mean, larger range during treatment

courtesy of Paul Keall





Motion traces

Probability density functions

Imaging
Treatment

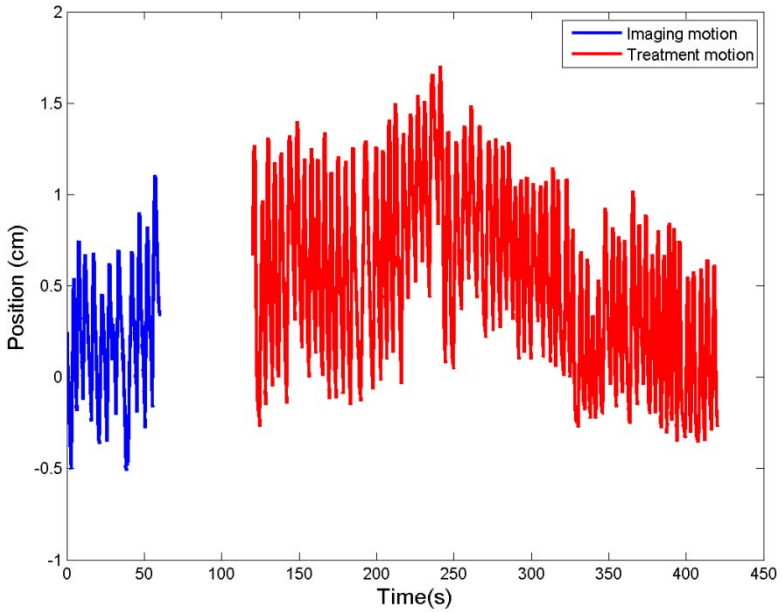
ESTRO School

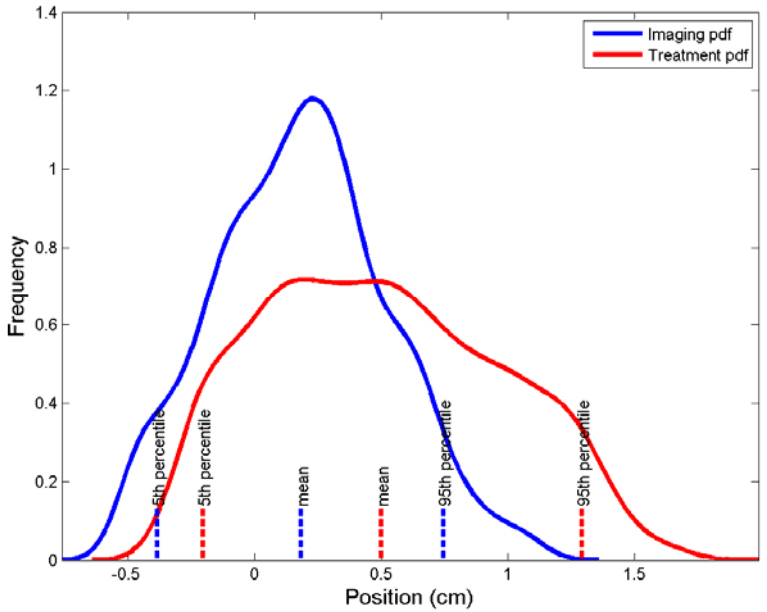
UHN Princess Margaret Cancer Centre

Statistical Model of Breathing Motion

Different mean and distribution width

courtesy of Paul Keall





Motion traces

Probability density functions

Imaging
Treatment

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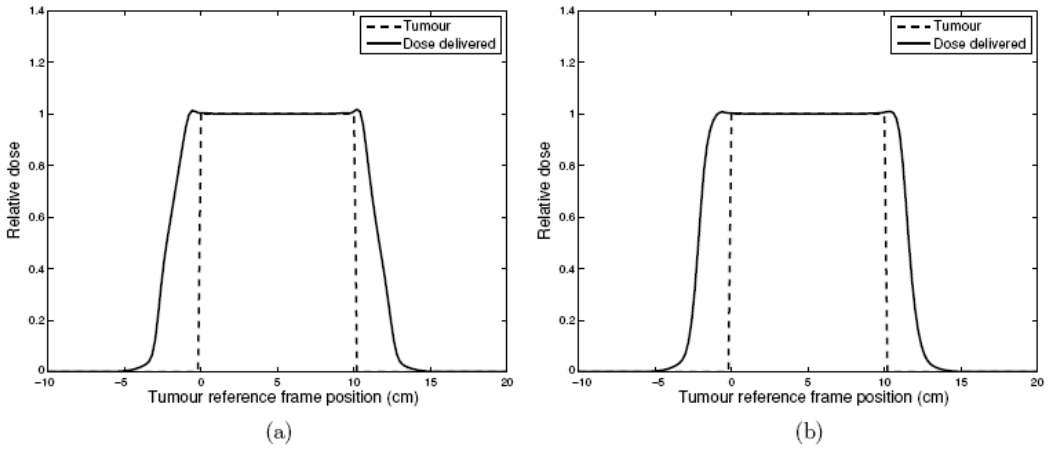
Variability in Motion Day-to-Day Revisited

Using Margins:
Nominal plan

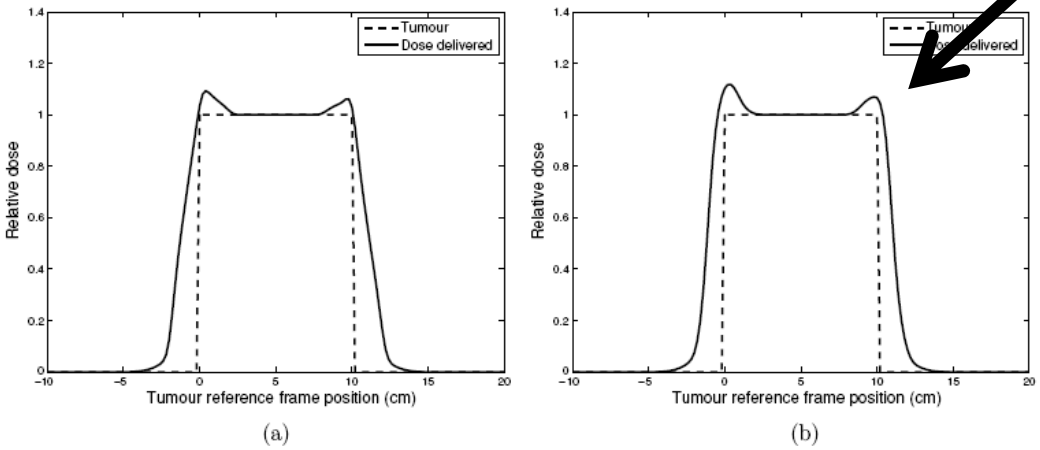


Using Margins:
delivered

Figure 7. Dose distribution of margin solution using the pmfs from figure 5. (a) Nominal pmf. (b) Realized pmf.

'horns' typically disappear

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”

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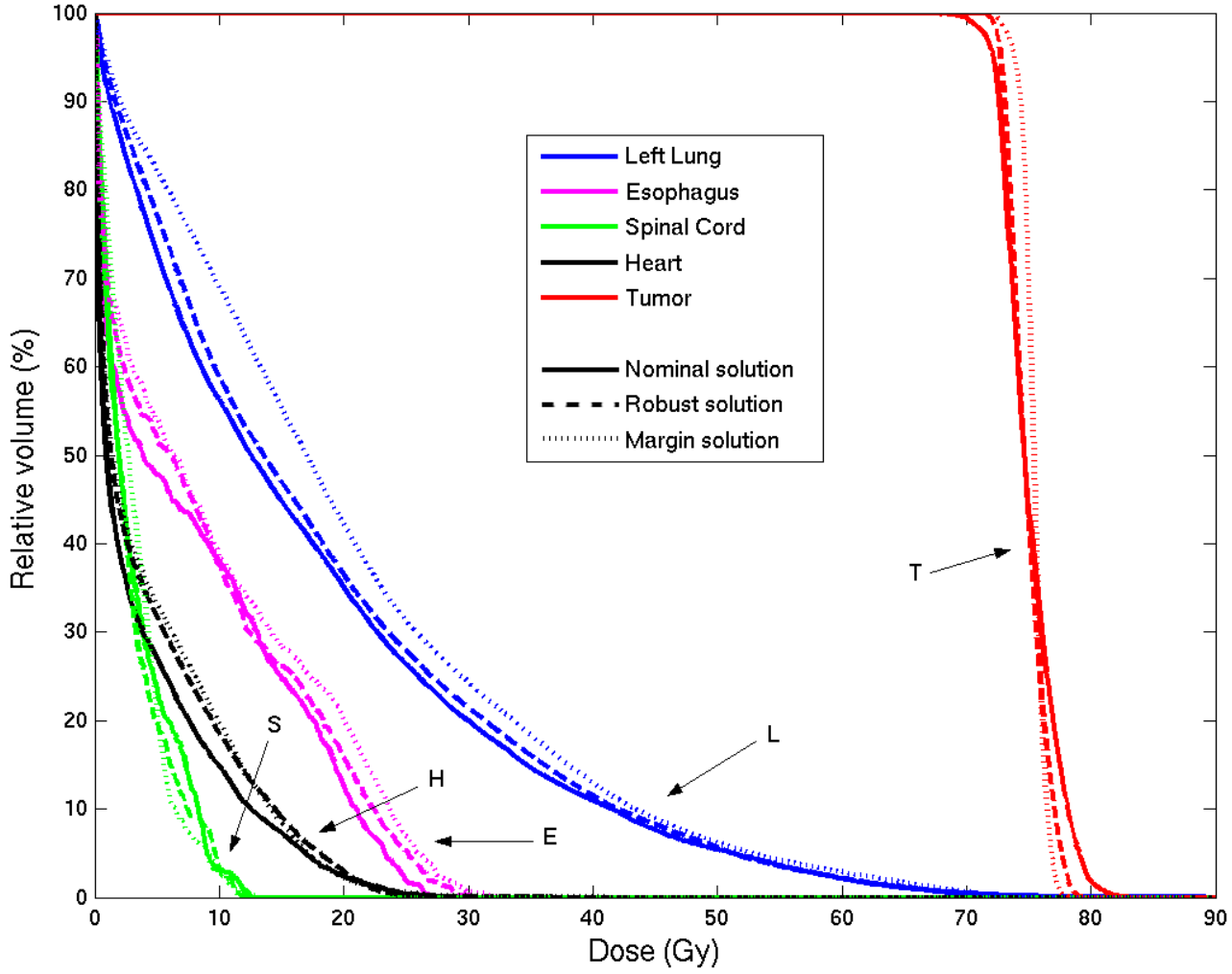
Breathing: Margin vs Robust formulation



Courtesy of Tim Chan MIT/MGH

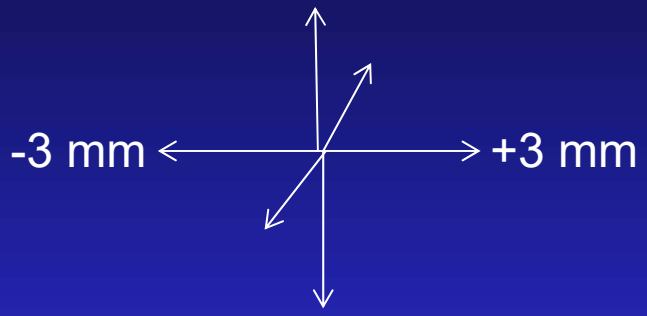
Small gain by taking ‘random’ motion into account in planning

Systematic errors are much more important - probabilistic planning must include systematic errors

Bohoslavsky et al. PMB 2013

Robust vs probabistic planning

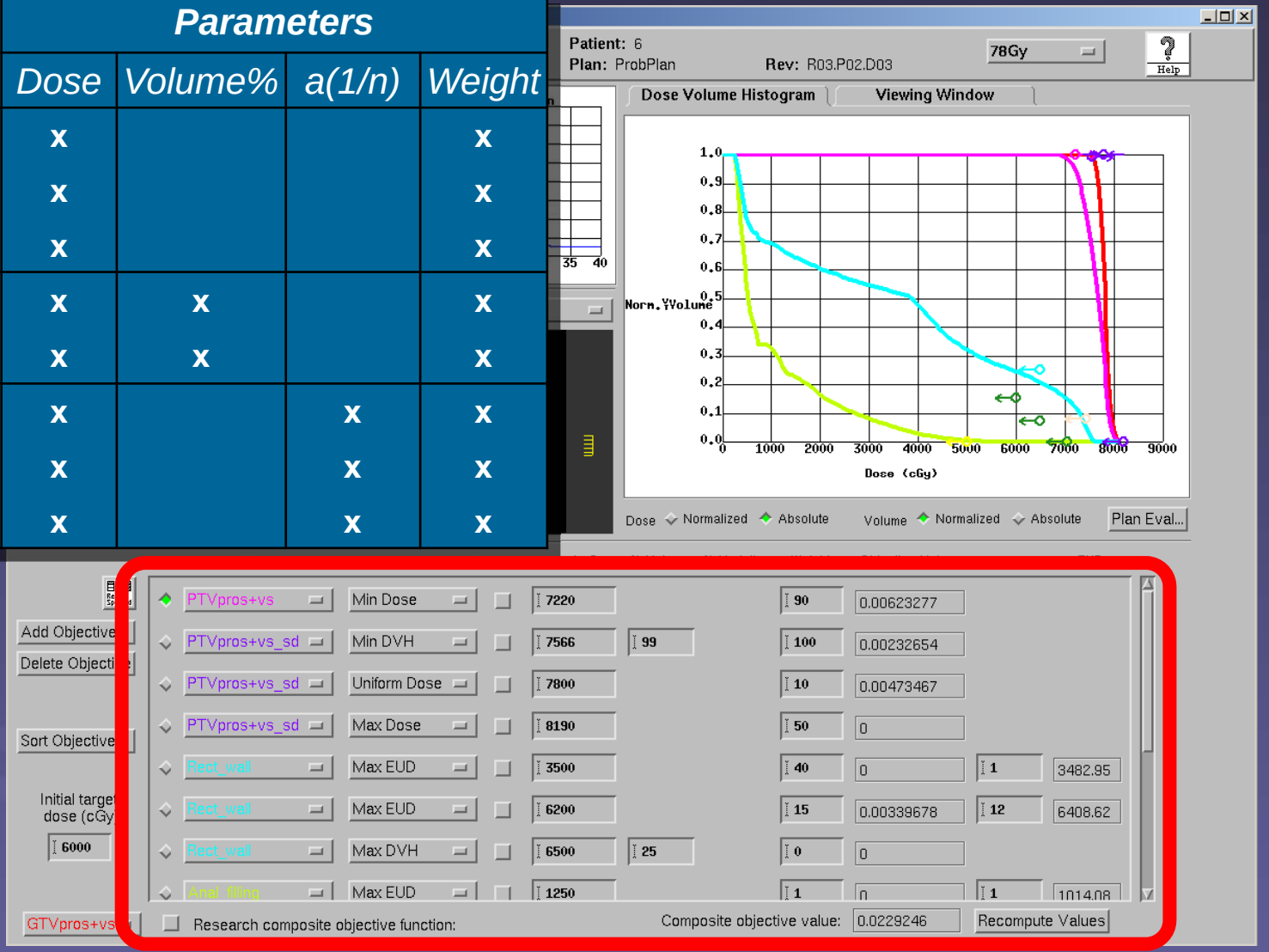
- Robust planning:
  - Few error scenarios
  - Worst case optimization
  - No differentiation random/systematic errors



- Probabilistic planning
  - Hundreds of error scenarios
  - Include both random and systematic errors
  - Optimize on probability

Regular planning objective functions

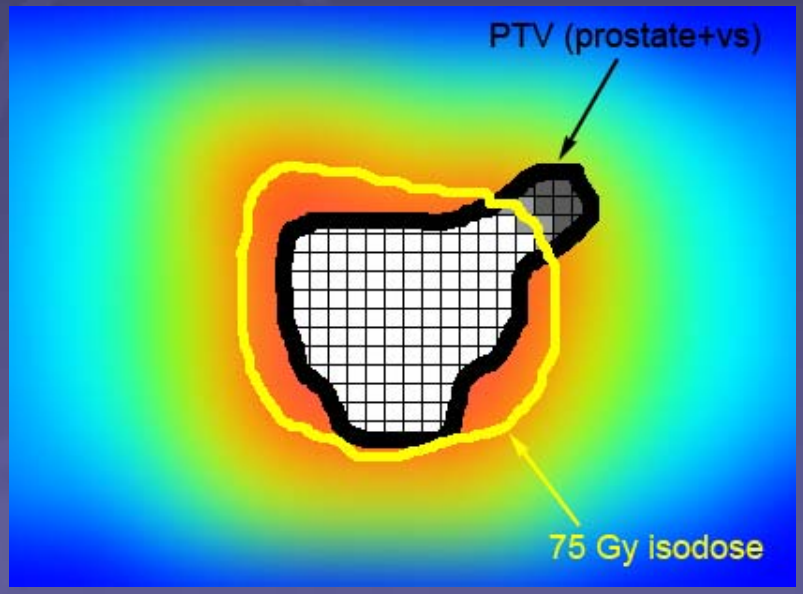
	Parameters			
	Dose	*Volume%*	*a(1/n)*	*Weight*
Minimum Dose	x			x
Maximum Dose	x			x
Uniform Dose	x			x
Minimum DVH	x	x		x
Maximum DVH	x	x		x
Target EUD	x		x	x
Minimum EUD	x		x	x
Maximum EUD	x		x	x

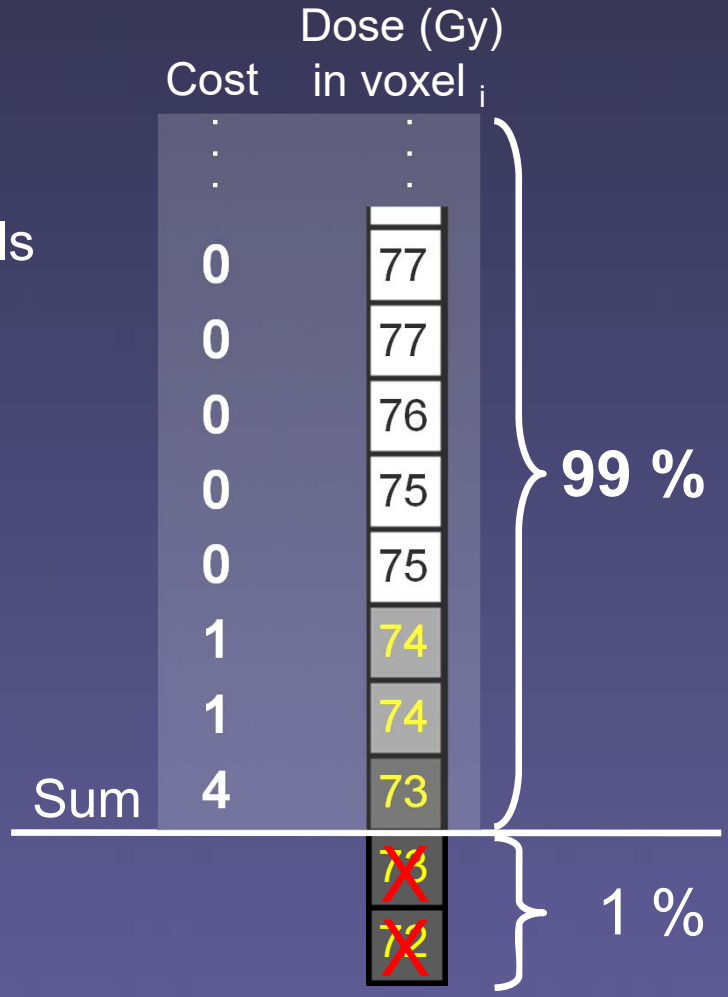


How DVH cost functions are calculated

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

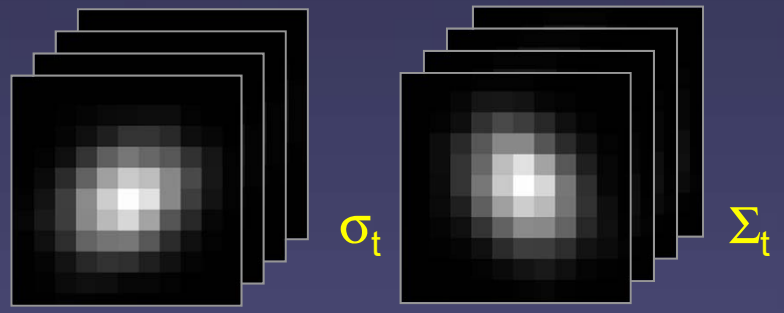
Pinnacle 8.1v research version

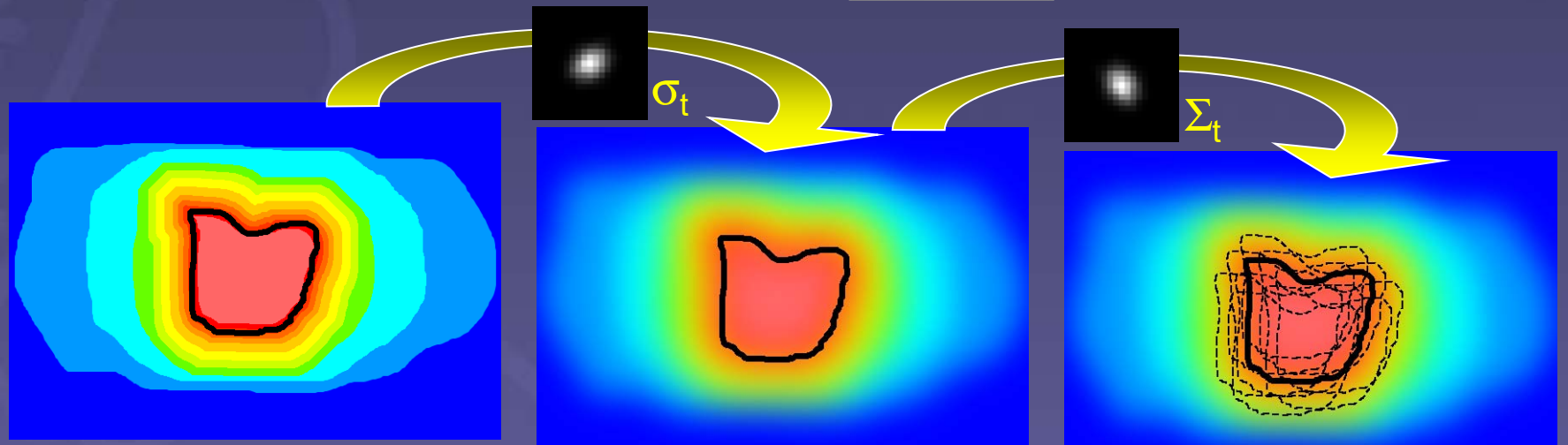
Inclusion of uncertainties in plan optimization

Translation errors

- Execution (random) errors → σ_t
- Preparation (systematic) errors → Σ_t

3D gaussian error spaces





Original dose

Execution errors (blurred dose)

Preparation errors (shifted dose)

Robust vs probabilistic optimization

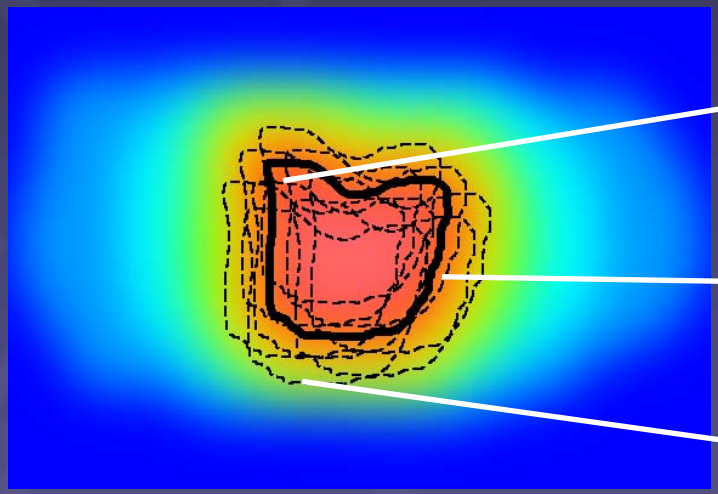
- Robust:
  - Typical 8-24 error scenarios
  - Weighted average of cost functions
  - Do not separate random and systematic errors

Commercial →

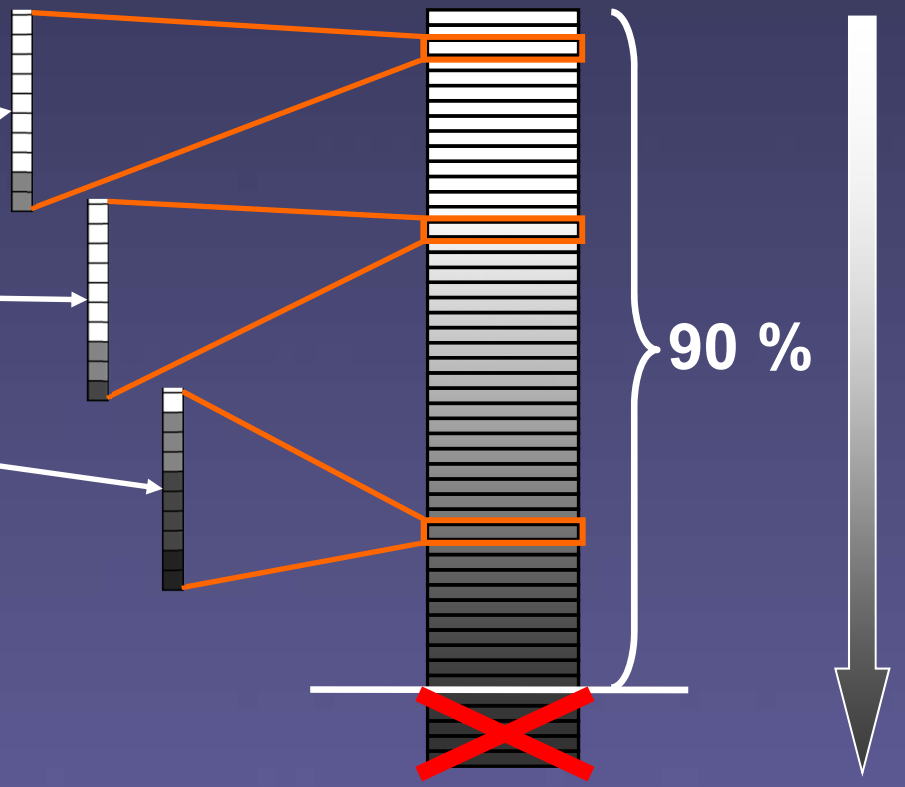
- Probabilistic:
  - Hundreds of error scenarios
  - Optimize on probability of meeting constraint
  - Include random and systematic errors

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

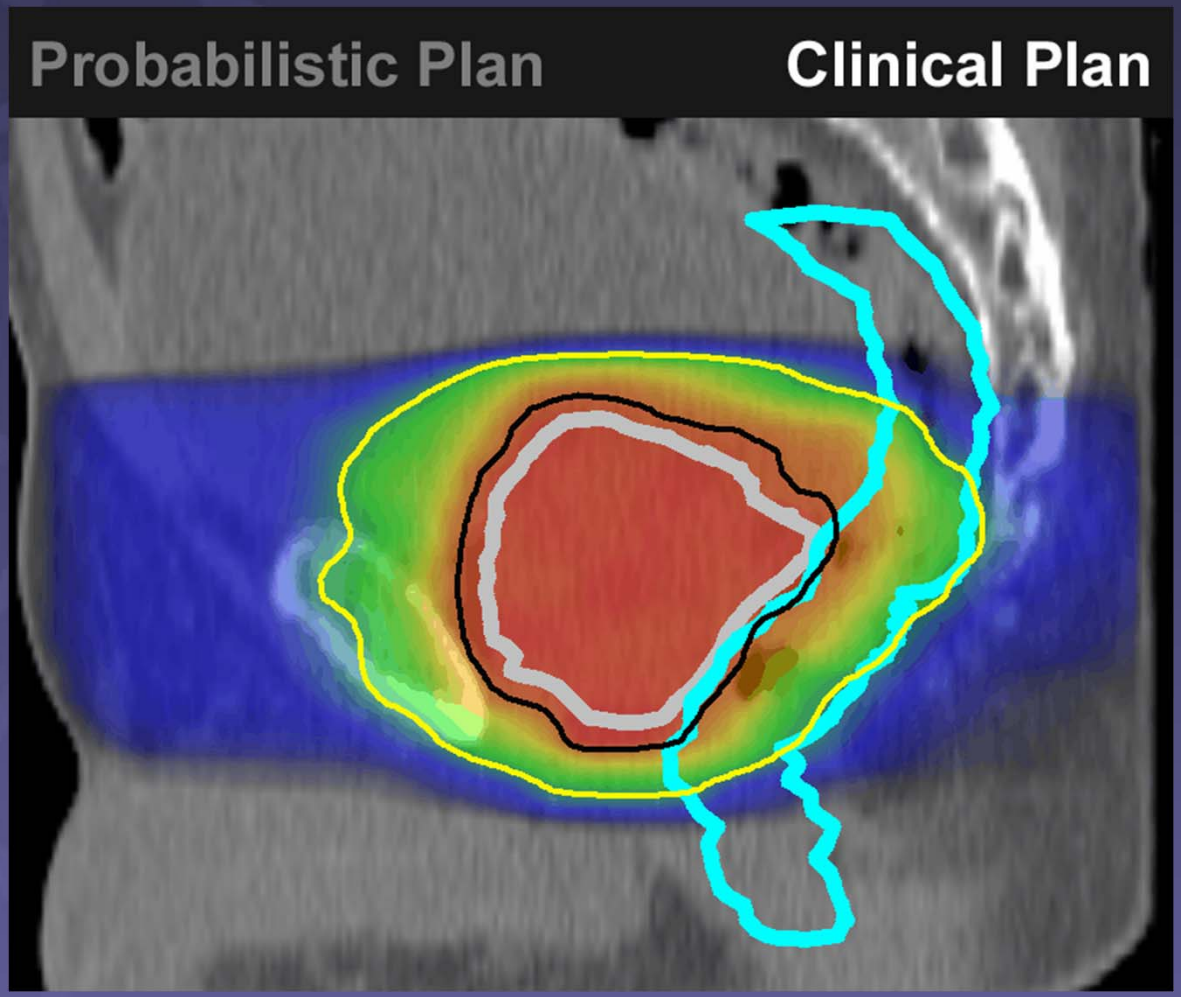
ROI	Objective	Dose (cGy)	Vol (%)	a (1/n)	Weight	Pop (%)	Kernel
GTVpros+vs	Min EUD	7820		1	100	92	sig
					0	92	sig
					0	92	sig
					0	--- (100)	env
					1	--- (100)	env
					2	92	sig
					0	92	sig
					3	92	sig
					0	--- (100)	---

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)

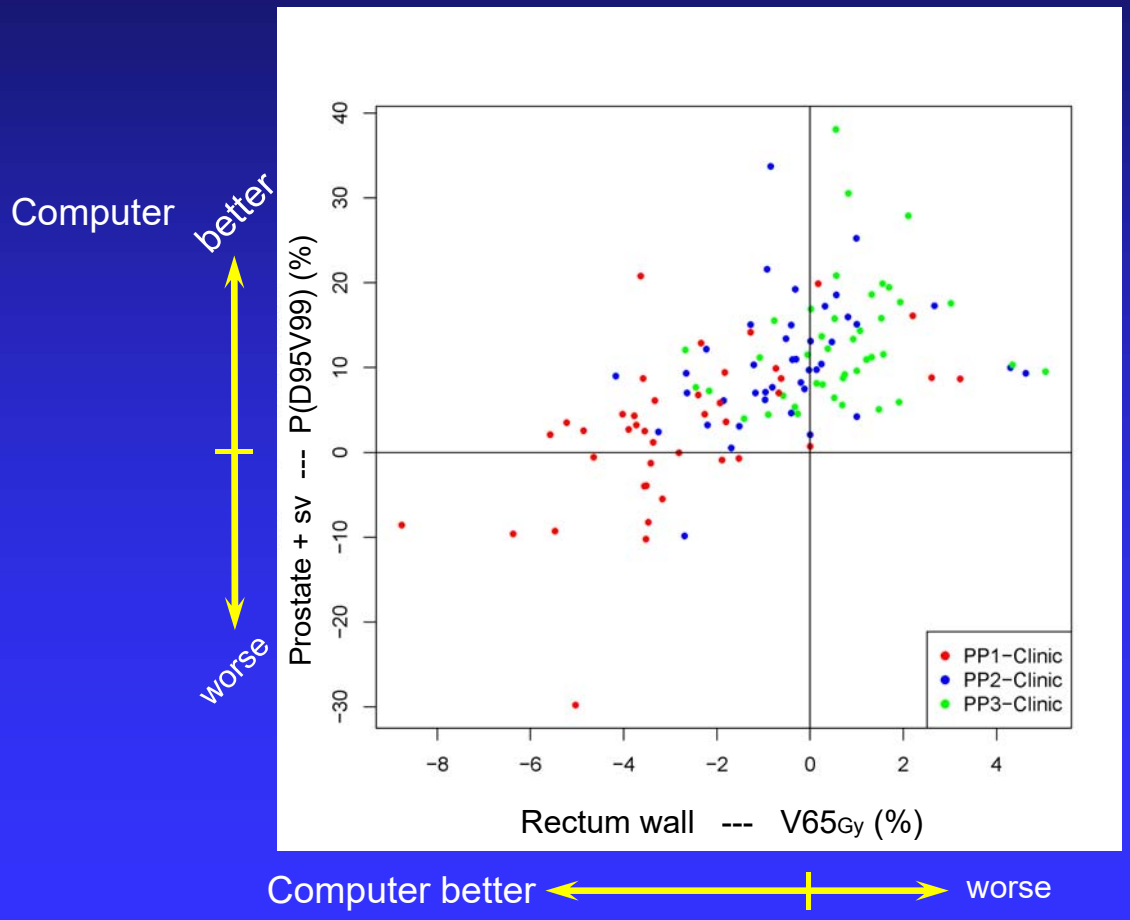
Prescribed dose to the target: 78 Gy

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

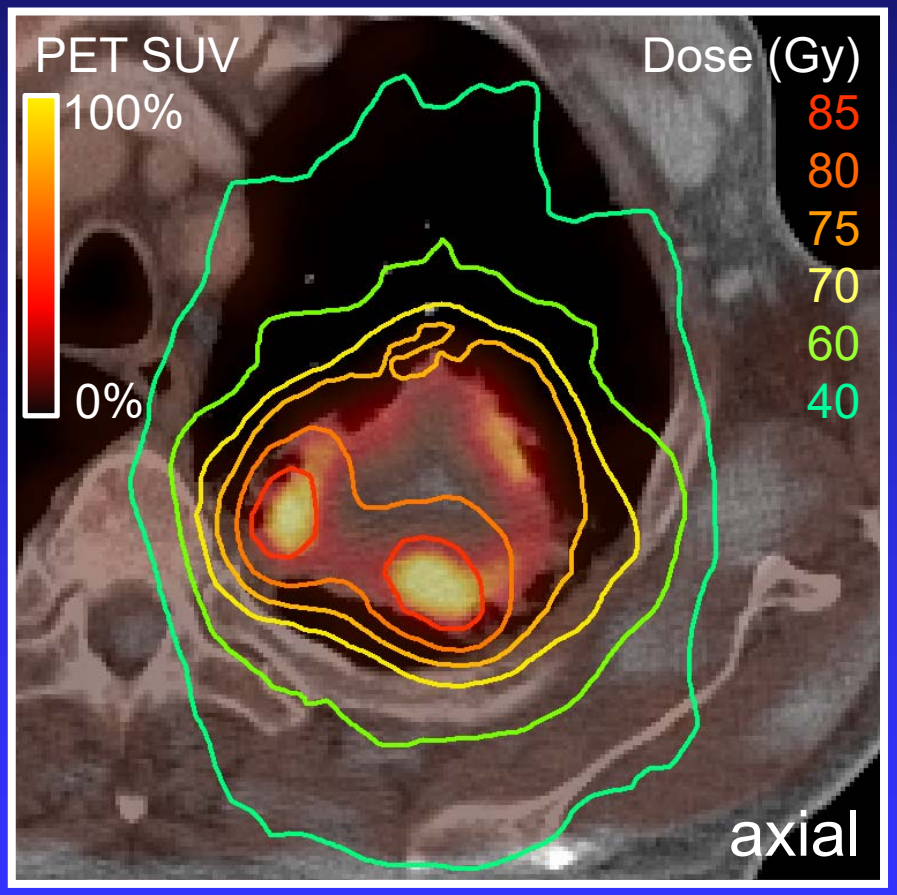
Results: automated probabilistic planning beats manual plan tweaking every time

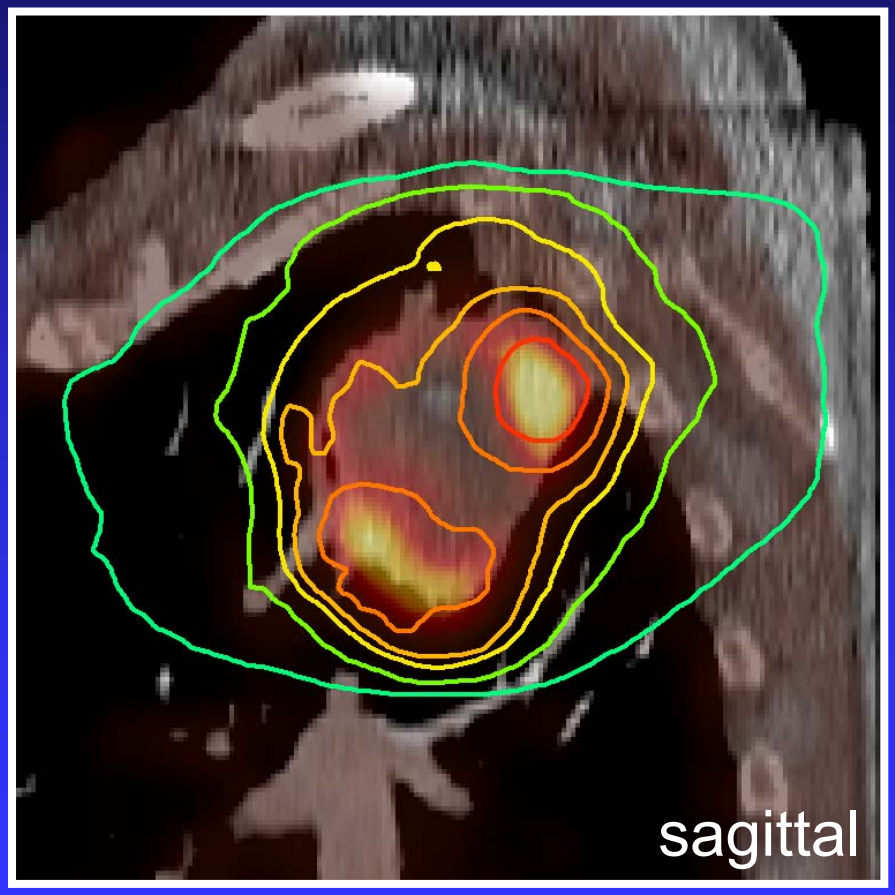


Computer – manual

- Toxicity reducing
- Balanced
- Coverage improving

Probabilistic dose painting `by numbers'





Witte et al NKI

Conclusions

Small gain of including breathing motion in treatment optimization

- Off course, better than using ITV

Margin-less treatment planning is feasible

- Better target coverage and lower dose to OARs
- Reduced number of objective functions
- No CTV boost required

Open issues: Vendors, implement it!

Variability in Motion Day-to-Day Revisted

Planned (nominal) vs delivered (realized)

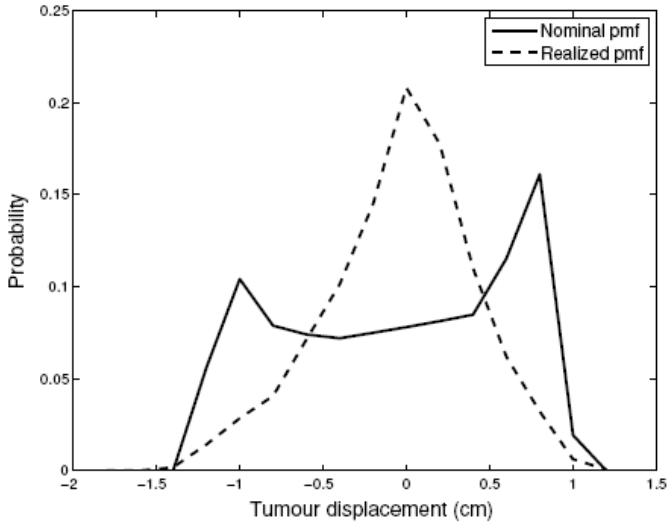


Figure 5. The pmfs used in the nominal, margin and robust formulation illustrations.

Robust model

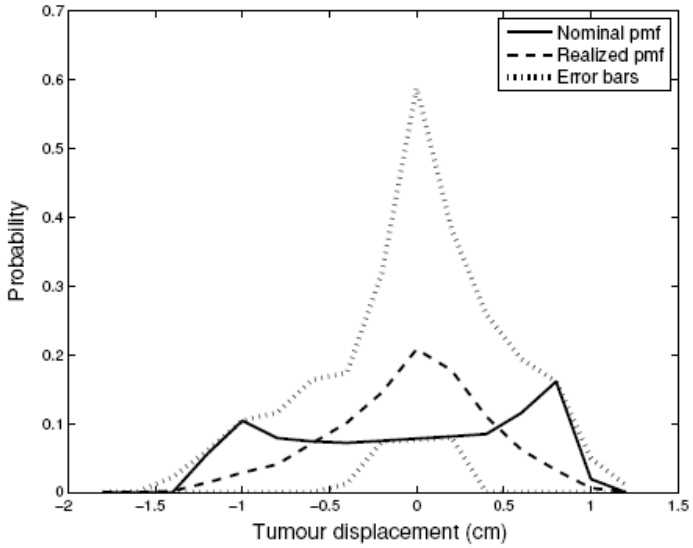
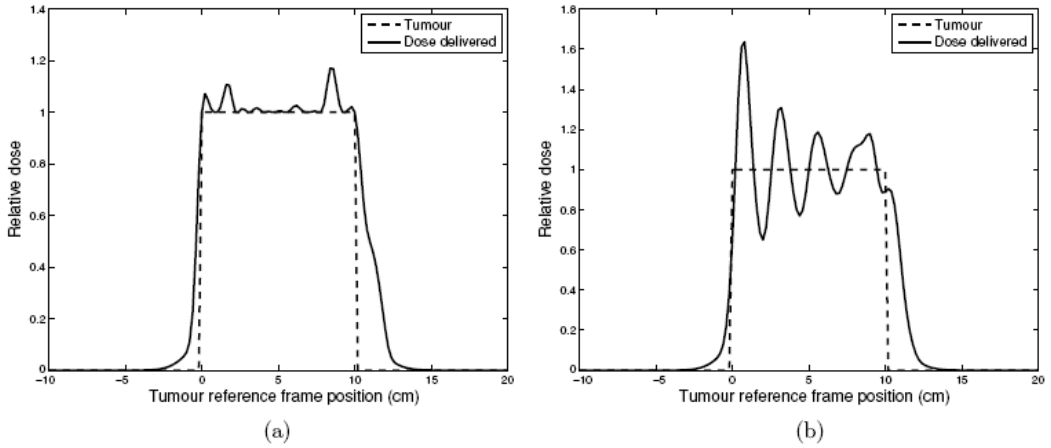


Figure 8. The pmfs and error bars used in the robust formulation illustrati

Variability in Motion Day-to-Day Revisited

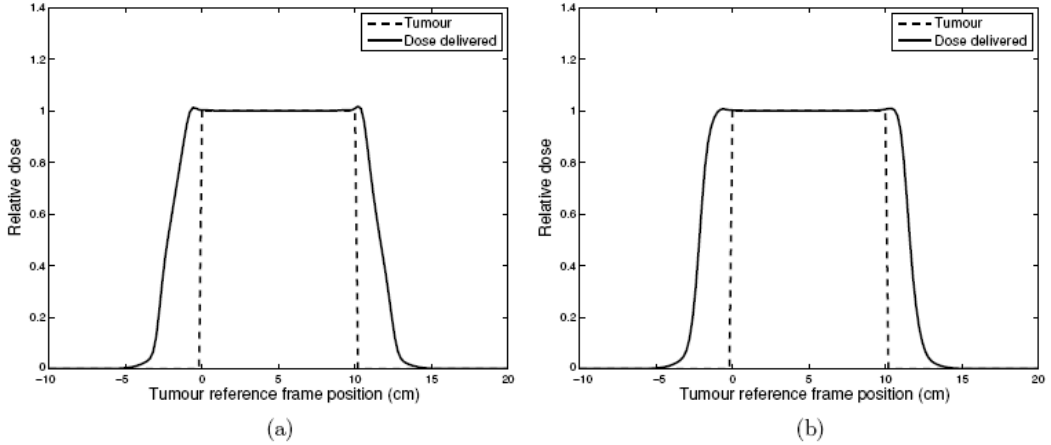
Motion modeling:
Nominal plan



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



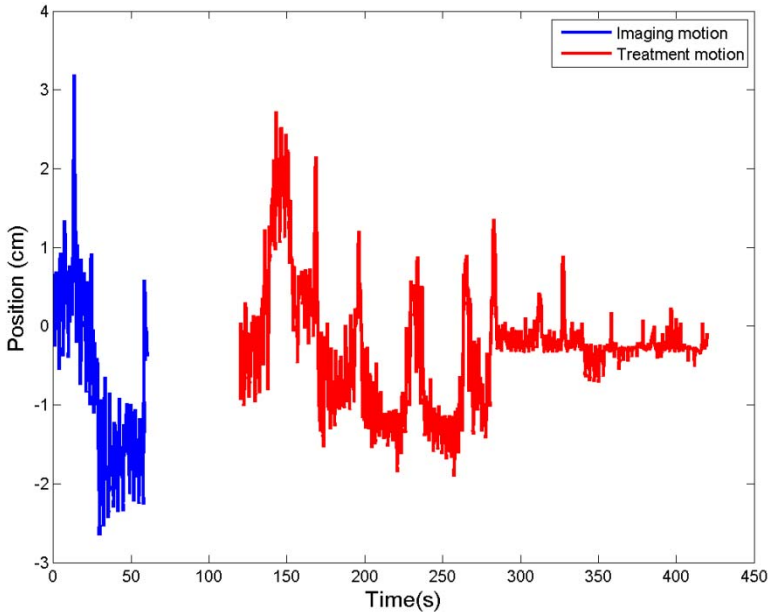
Using Margins:
delivered

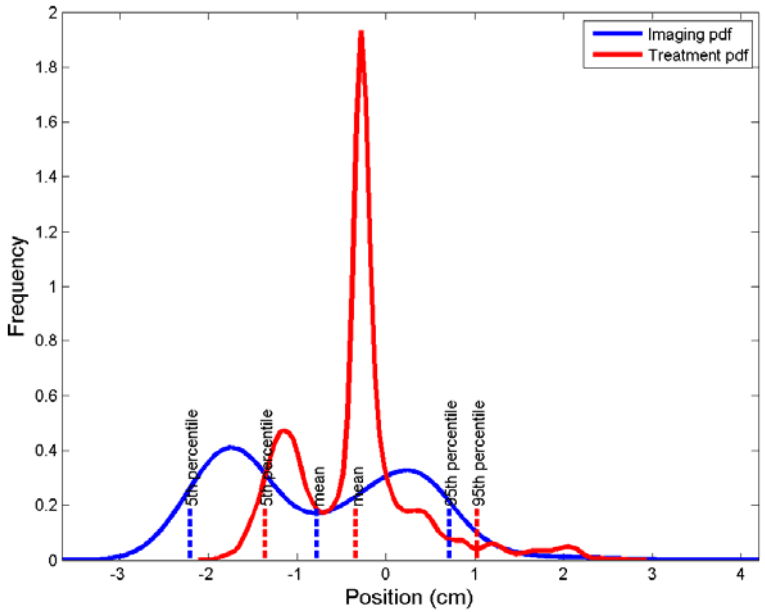
Figure 7. Dose distribution of margin solution using the pmfs from figure 5. (a) Nominal pmf. (b) Realized pmf.

Statistical Model of Breathing Motion

Different mean, similar width during imaging and treatment

courtesy of Paul Keall





Motion traces

Probability density functions

Imaging
Treatment

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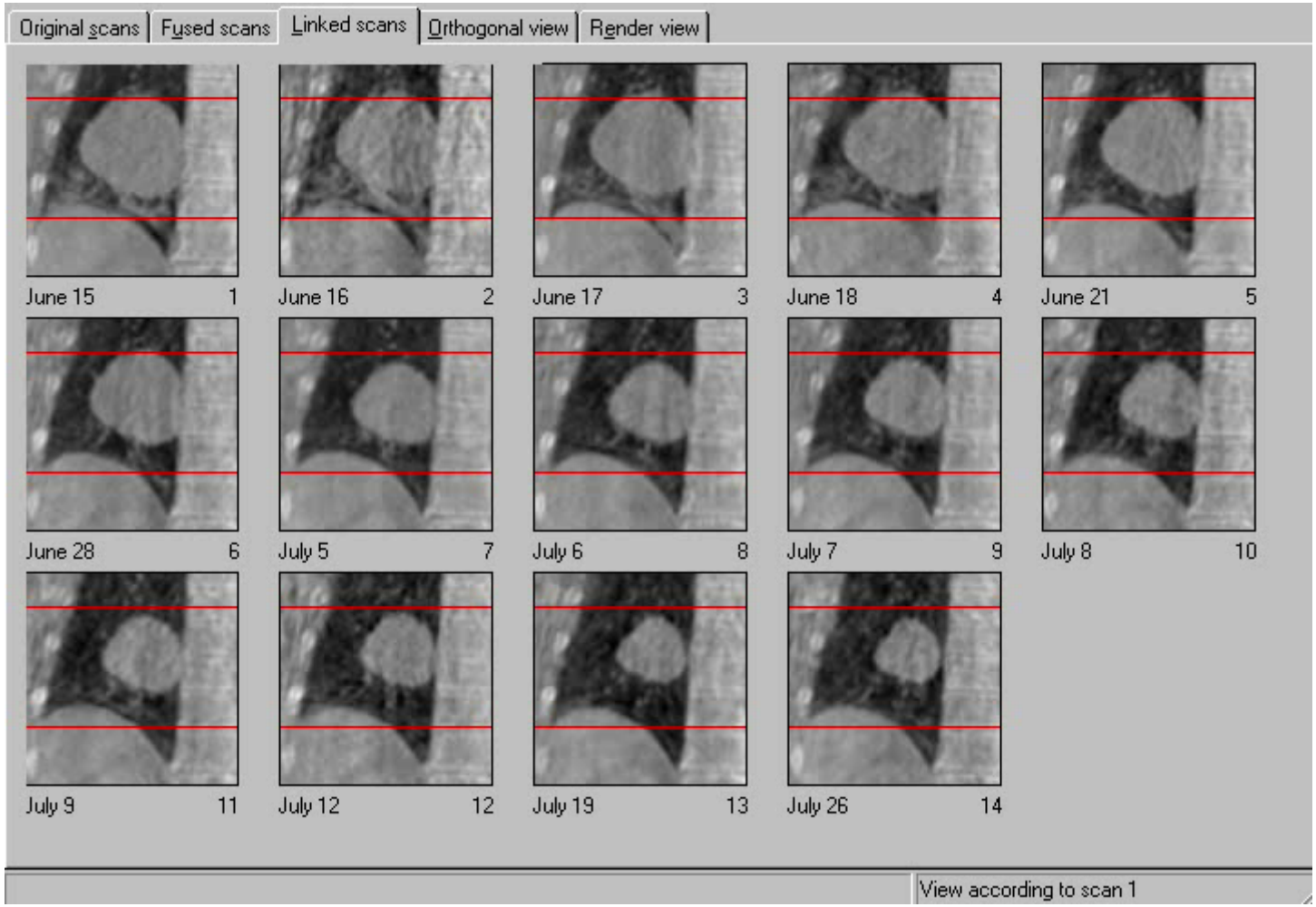
Variability in Repeated 4D CBCT

Day 1 →



Day 11

Rigid and deformable registration

Marcel van Herk

on behalf of the imaging group

Institute of Cancer Sciences,
University of Manchester / The Christie

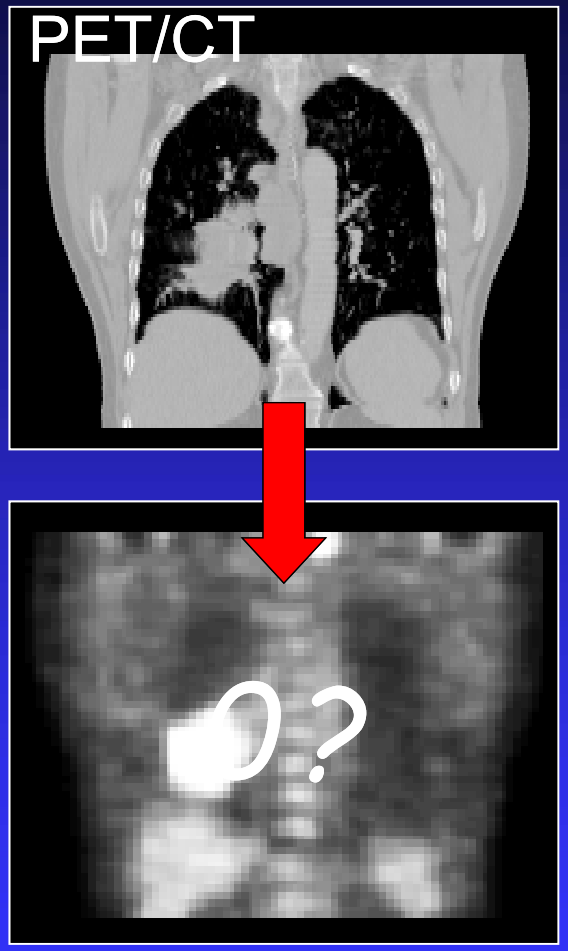
With slides from:
Netherlands Cancer Institute
Academic Medical Center

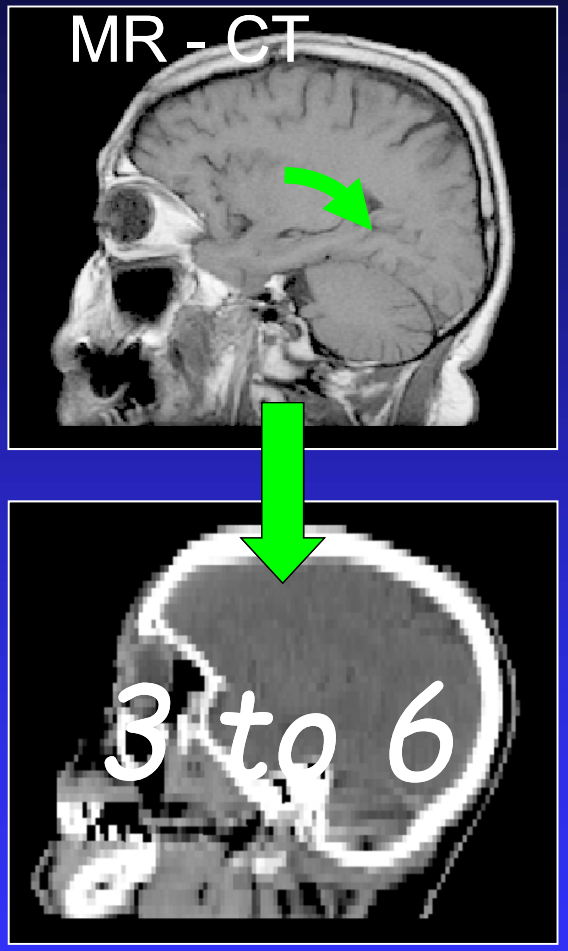
Image registration

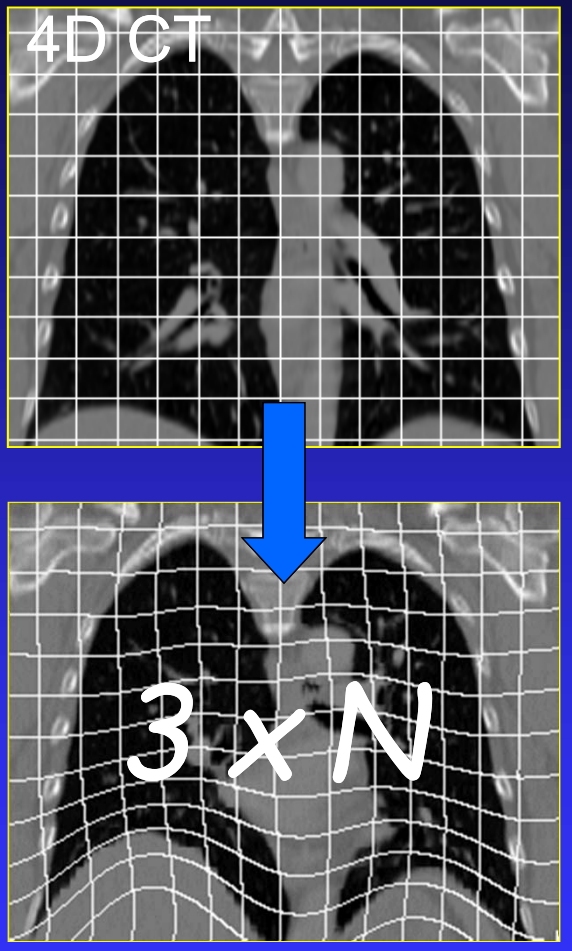
- Find translation….deformation to align two 2D..4D data sets (2 .. 1000000+ degrees of freedom)
- Allows combination of scans on a point by point basis
- Applications:
  - Complementary data
  - Motion tracking and compensation (imaging)
  - Image guidance
  - Adaptive radiotherapy
  - Response monitoring
  - Dose accumulation
  - Data mining

Marc Kessler / UM

Degrees of Freedom







None ?

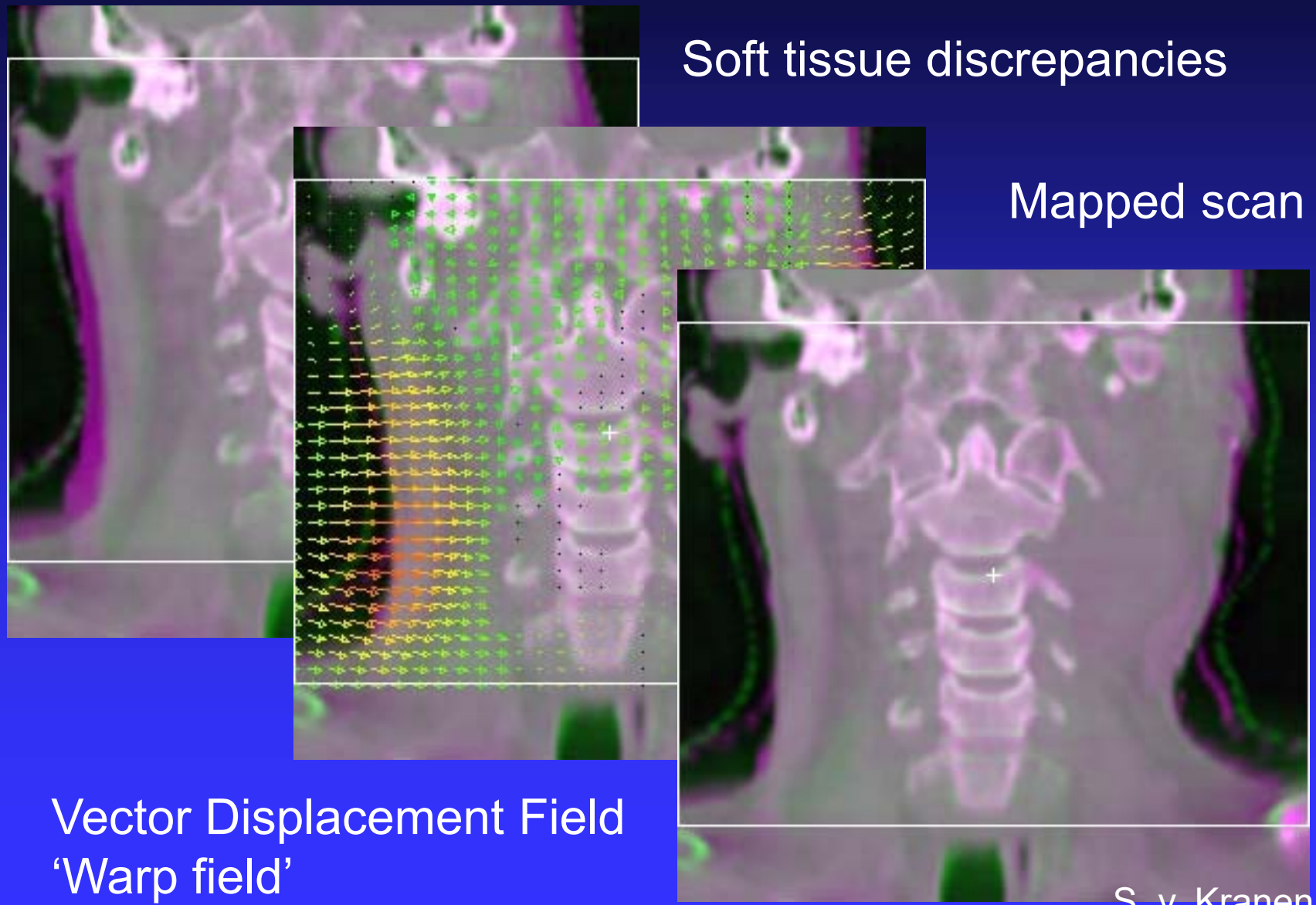
Few

Many

By enforcing smoothness the optimization becomes tractable

Demo rigid registration

Deformation vector fields



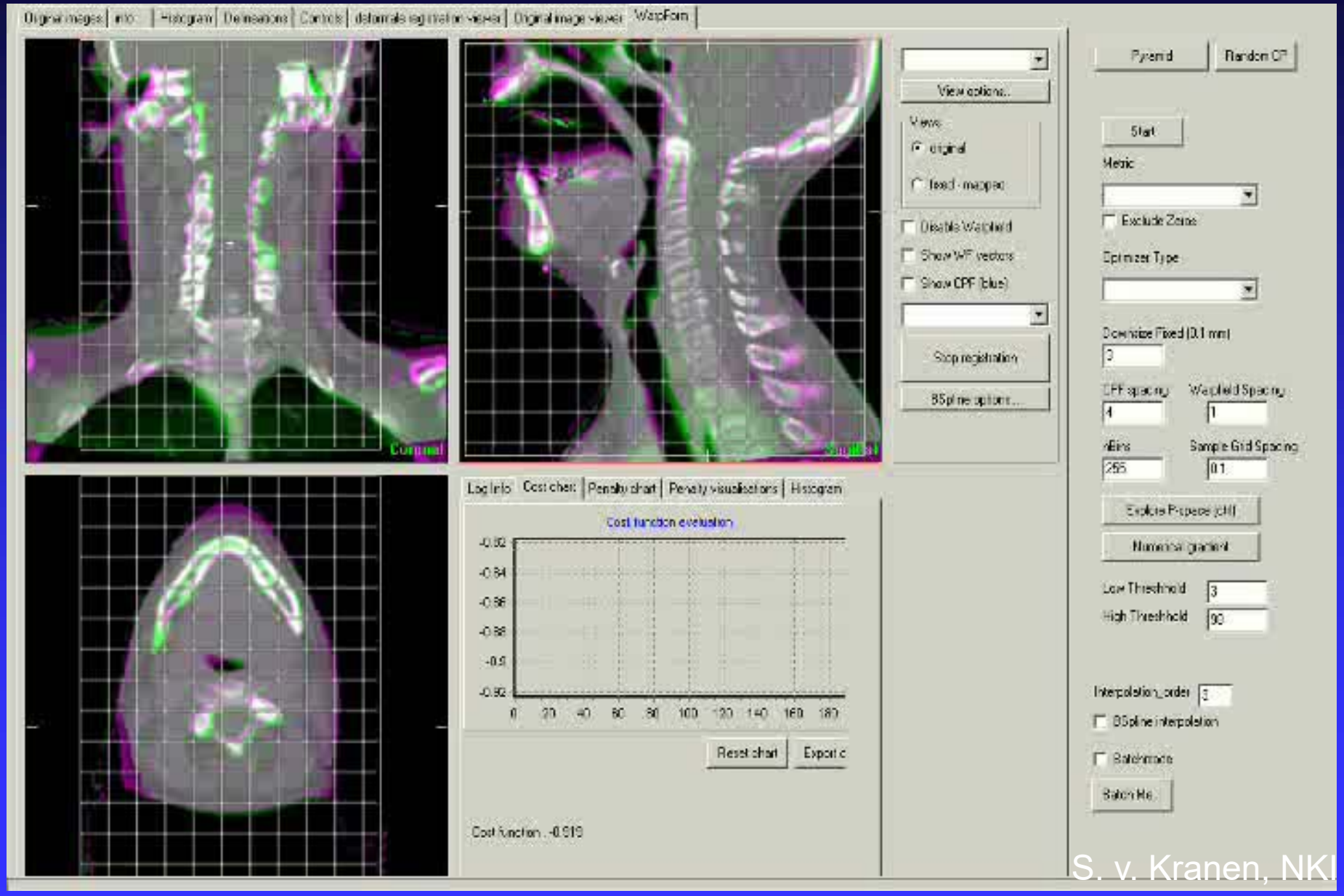
Soft tissue discrepancies

Mapped scan

Vector Displacement Field
‘Warp field’

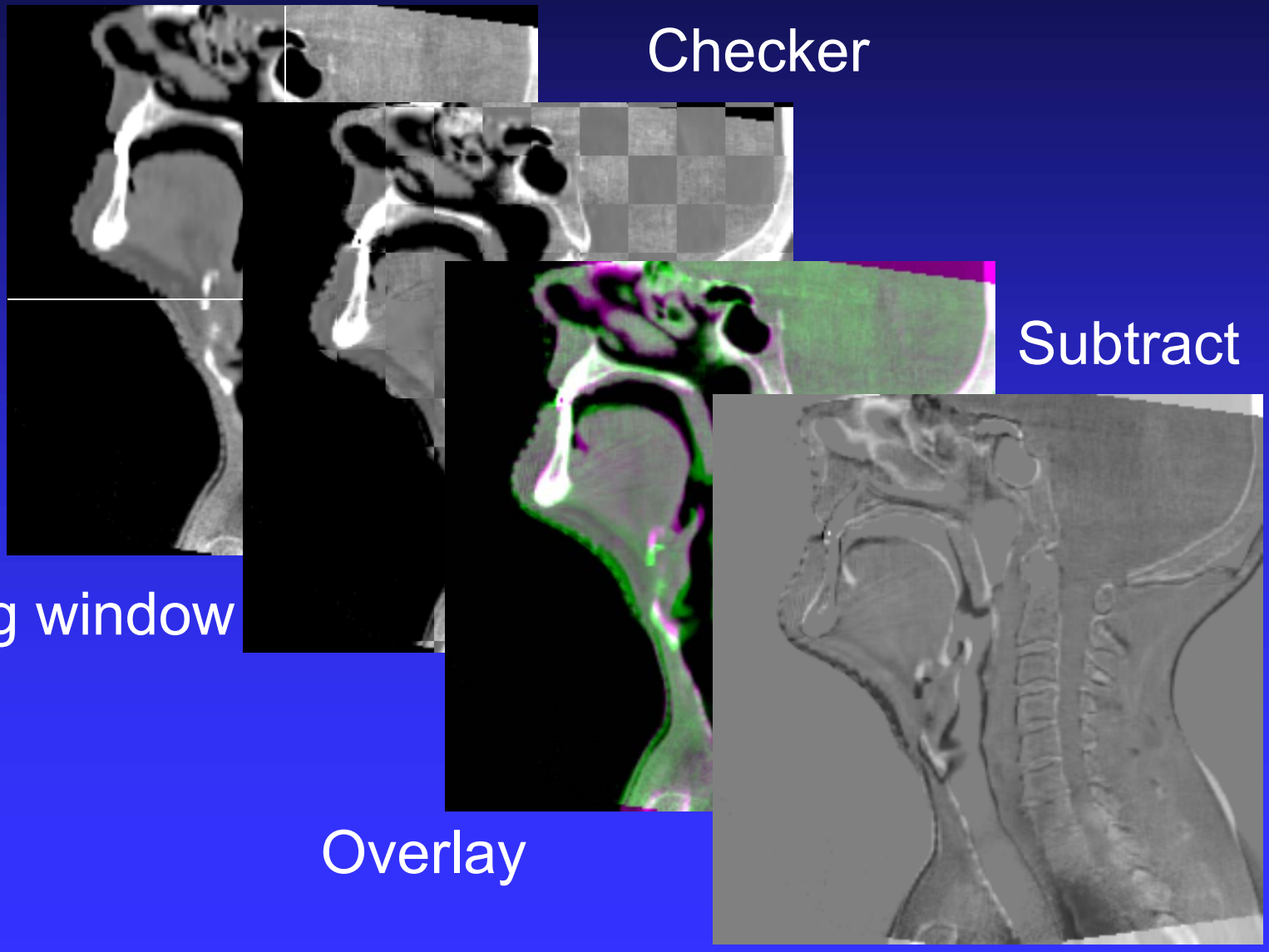
S. v. Kranen, NKI

Deformable registration example

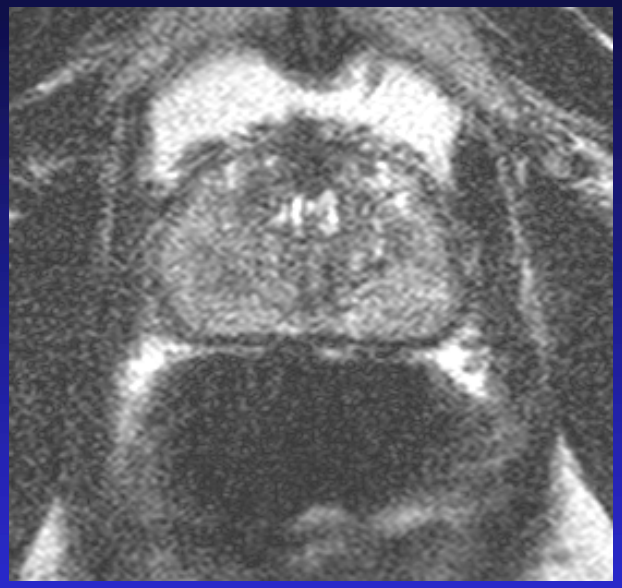


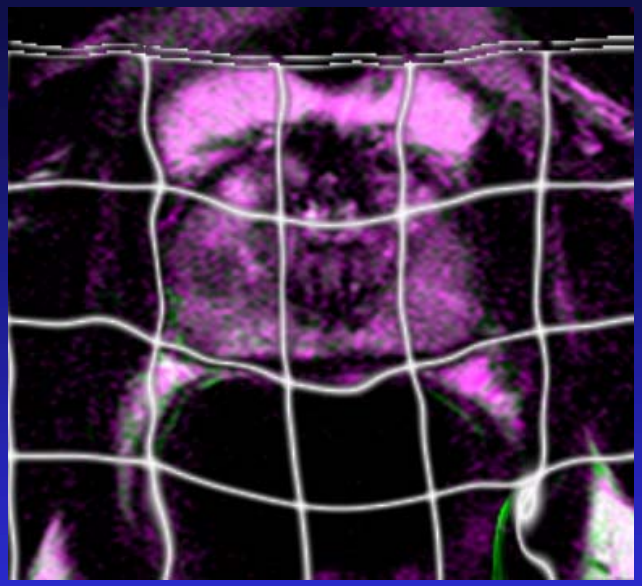
S. v. Kranen, NKI

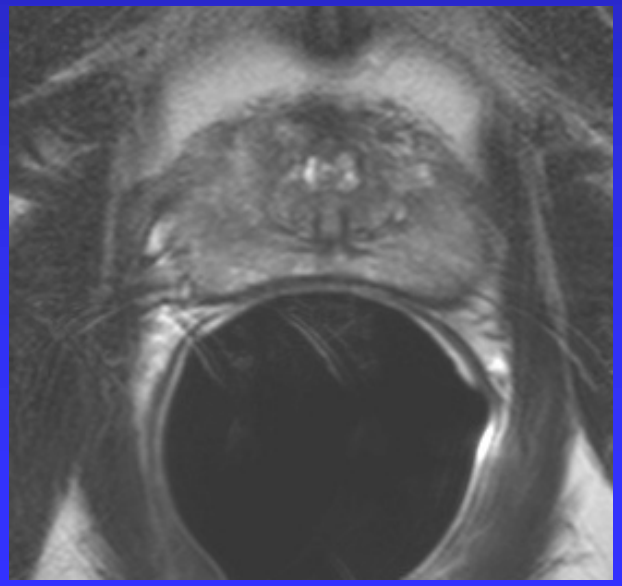
Visual verification

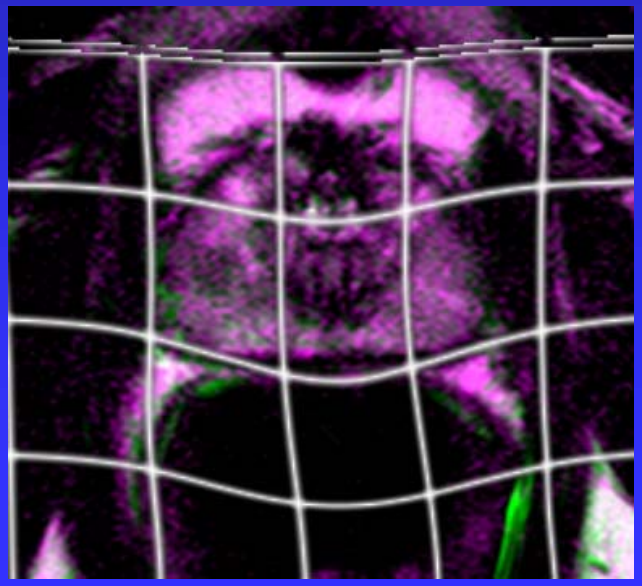


Prostate MRI w/wo Endo Rectal Coil









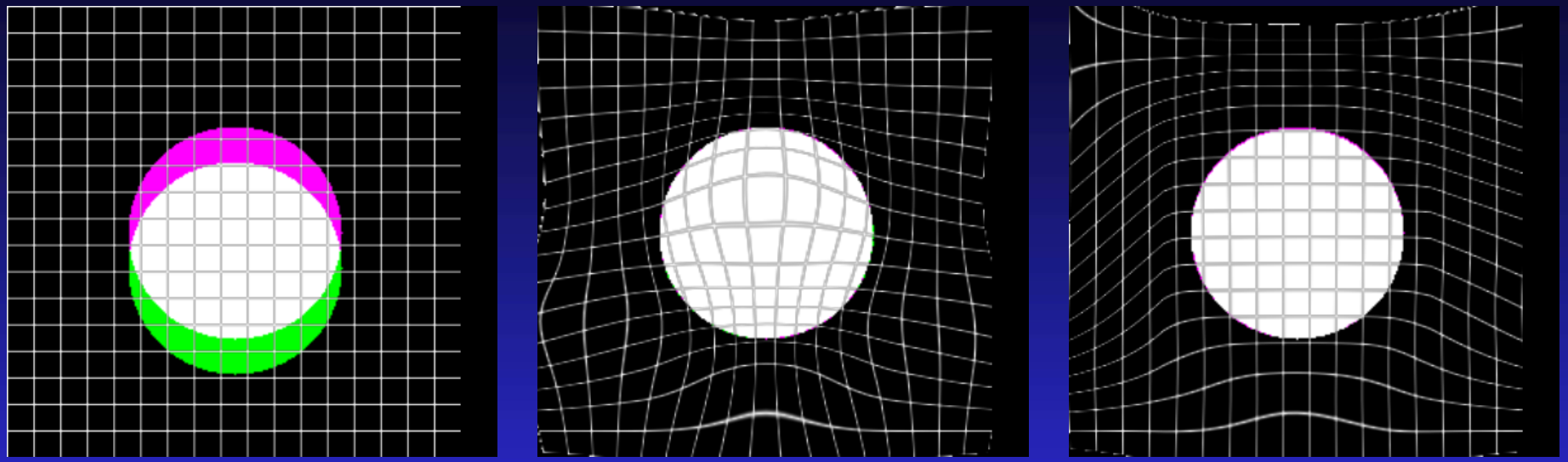
Large effect of parameters on deformable registration

Both solutions are visually correct

Which answer is right?

S van Kranen,
C Kamerling, NKI

Deformable registration classes



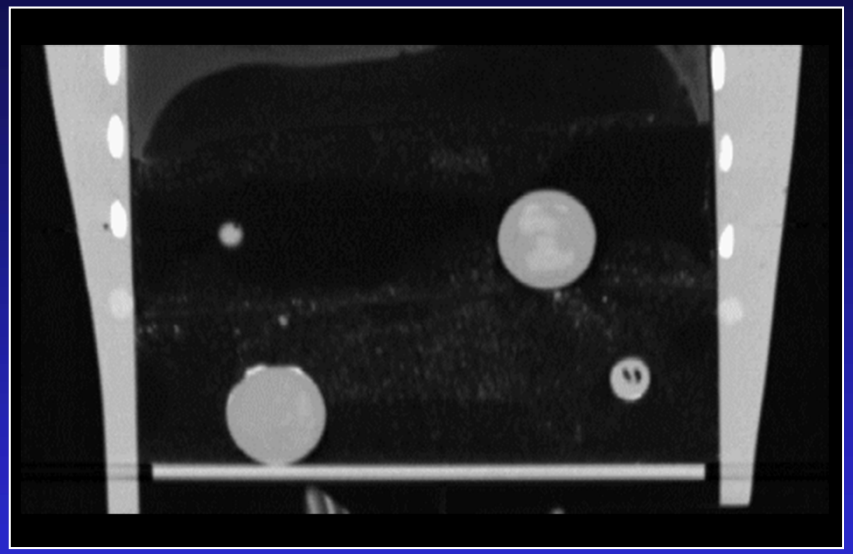
Different DVF provide same visual registration result

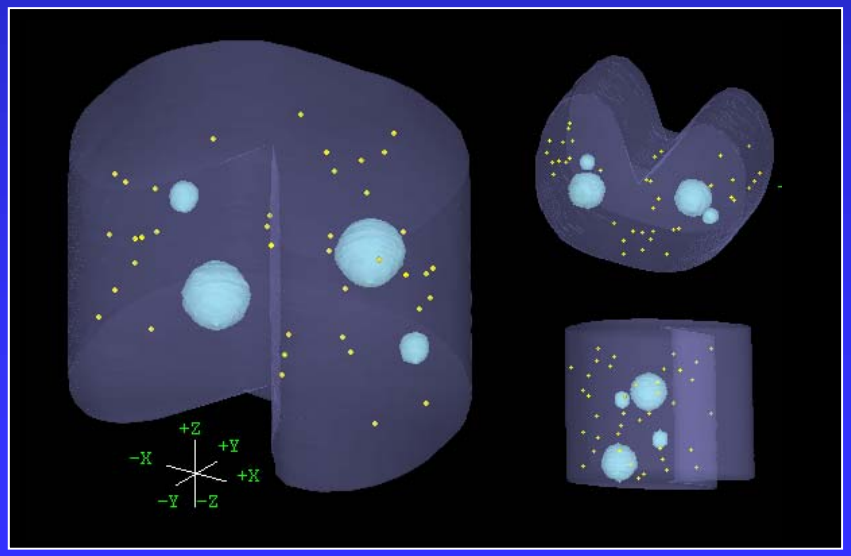
- Descriptive: it must look good
  - e.g. contour propagation
- Quantitative: it must be an anatomically correct, also inside and at surface of homogeneous organ
  - e.g. dose accumulation

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

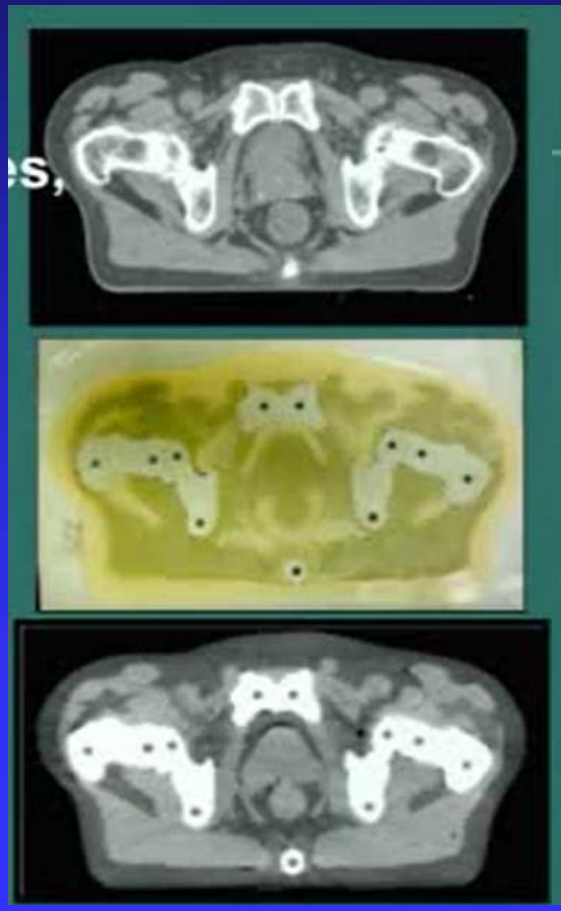
4D Phantoms





		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

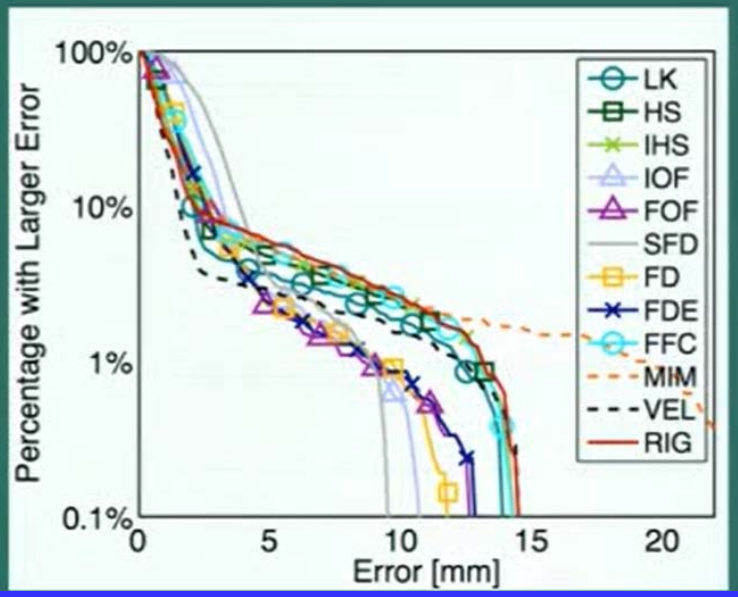
Registration of anatomically realistic phantom in pelvis



UCSF University of California San Francisco

DIR Error Distribution

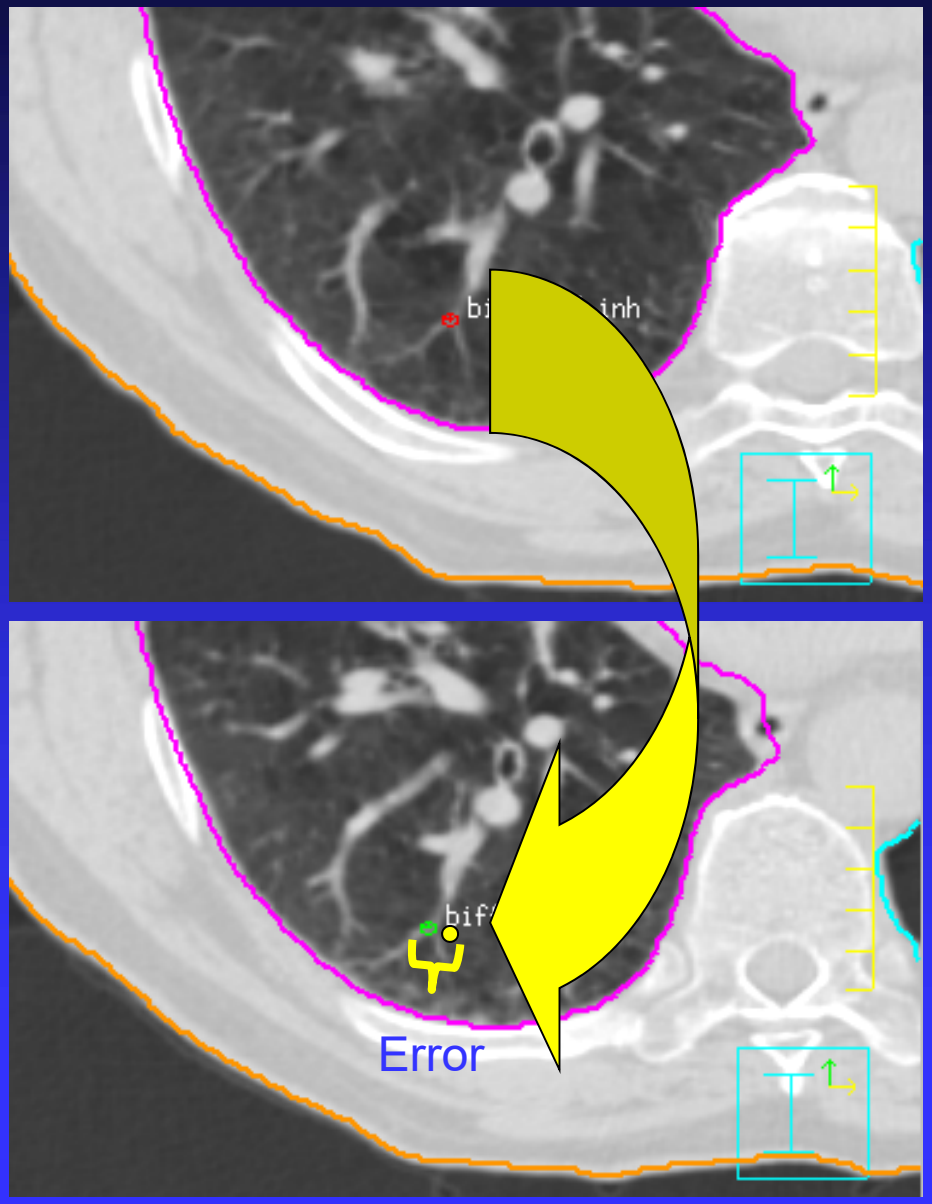
The fraction of markers with a distance to agreement larger than a given error as a function of error.



J Pouliot, UCSF

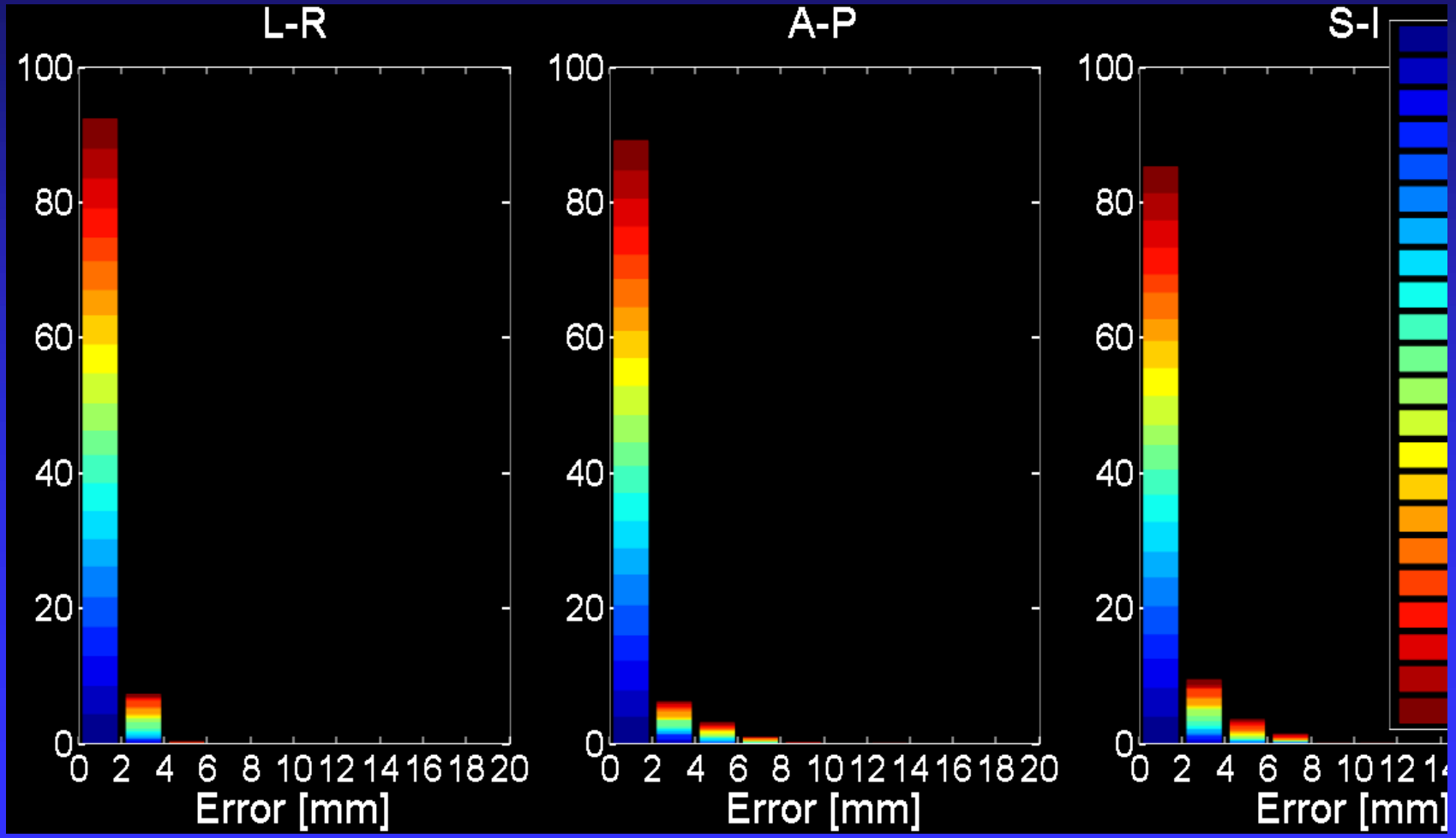
Kristy Brock / PMH

Natural Fiducials

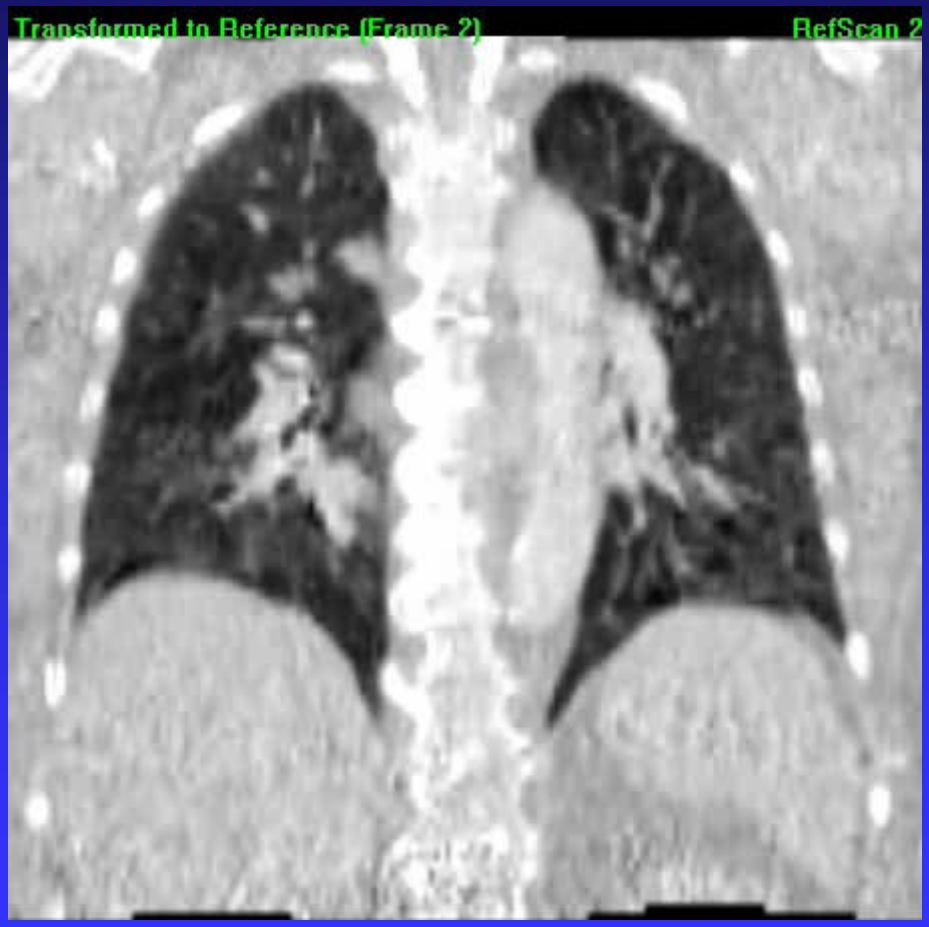


Kristy Brock / PMH

Results: Lung 4D CT (22)
% Bifurcation Points

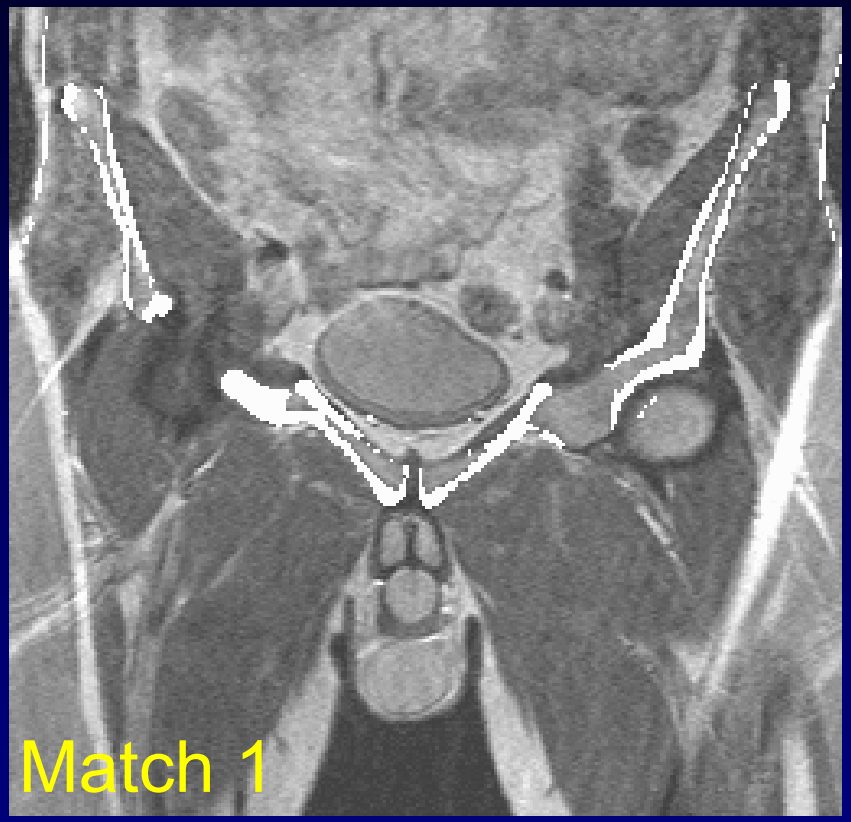


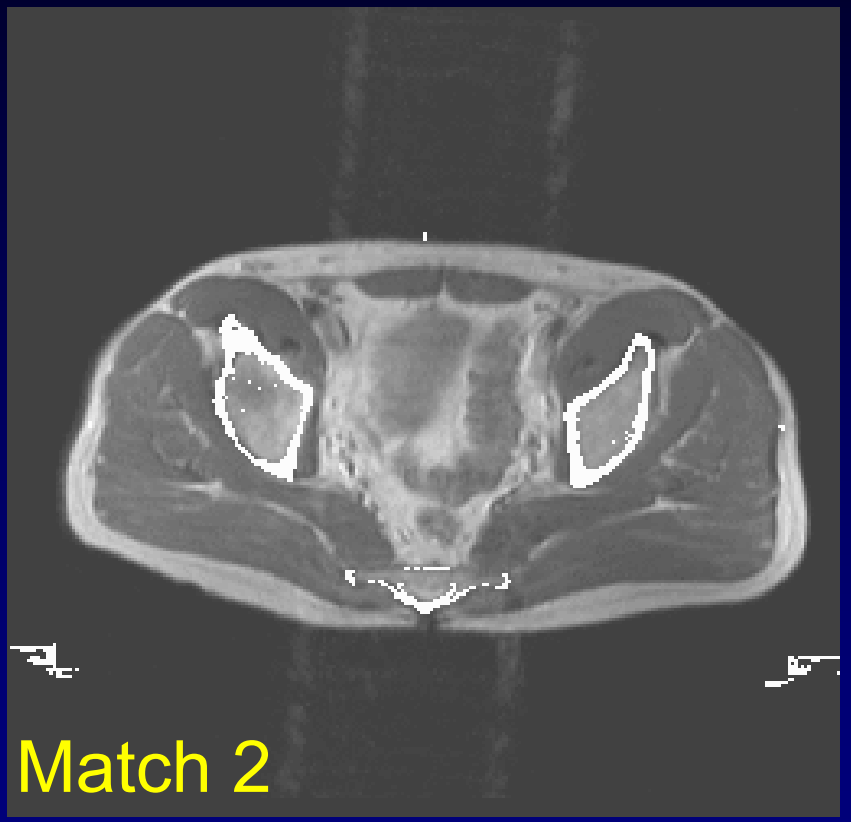
Lung deformable registration easy ?



J Wolthaus, NKI

Consistency check as QA tool



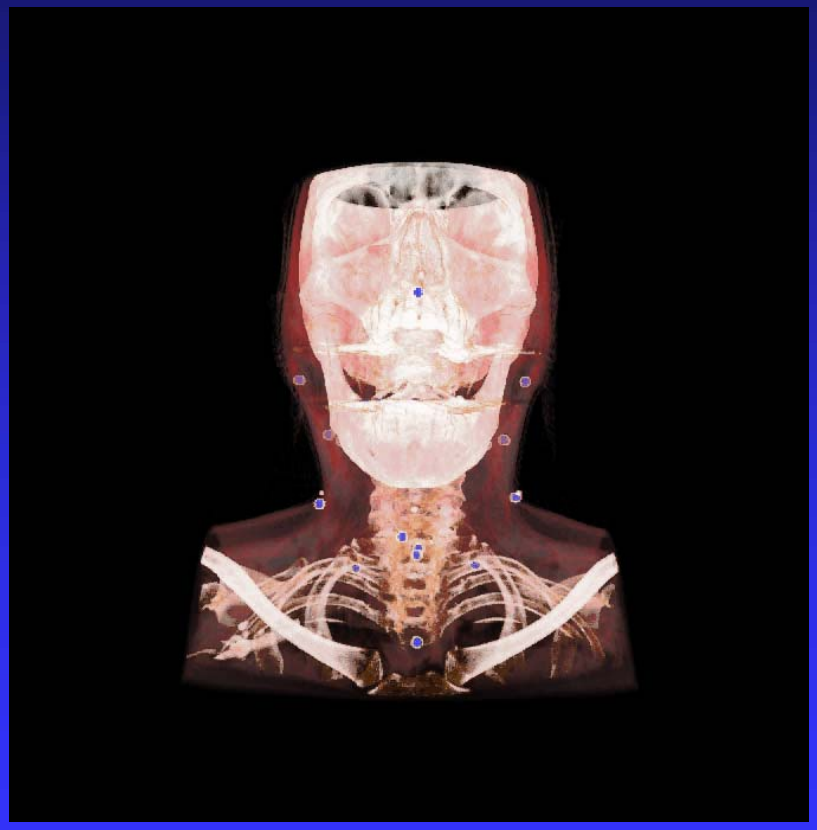


Deviation	Δ x (L-R)	Δ y (A-P)	Δ z (C-C)	Δ rx (L-R)	Δ ry (A-P)	Δ rz (C-C)
between match 1 and 2	-0.5 mm	2.0 mm	-1.6 mm	-0.9 dg	-0.8 dg	-0.7 dg

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

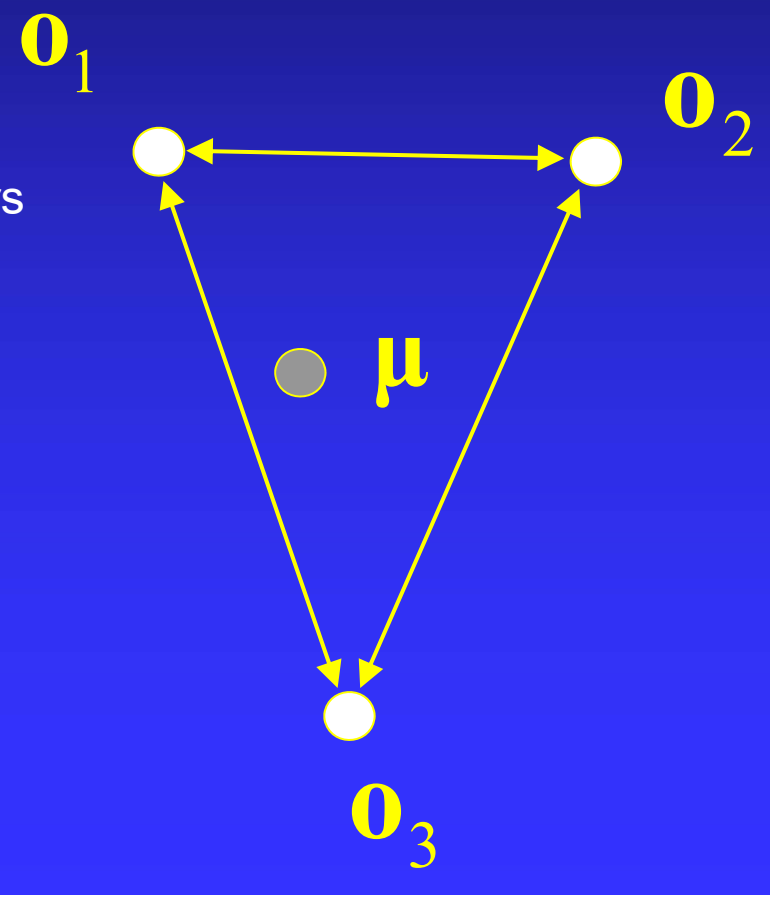
Compute standard deviations of differences

Solve for standard deviation of individual observers

$$\sigma_1^2 = (\sigma_{2-1}^2 + \sigma_{3-1}^2 - \sigma_{3-2}^2)/2$$

$$\sigma_2^2 = (\sigma_{3-2}^2 + \sigma_{2-1}^2 - \sigma_{3-1}^2)/2$$

$$\sigma_3^2 = (\sigma_{3-1}^2 + \sigma_{3-2}^2 - \sigma_{2-1}^2)/2$$

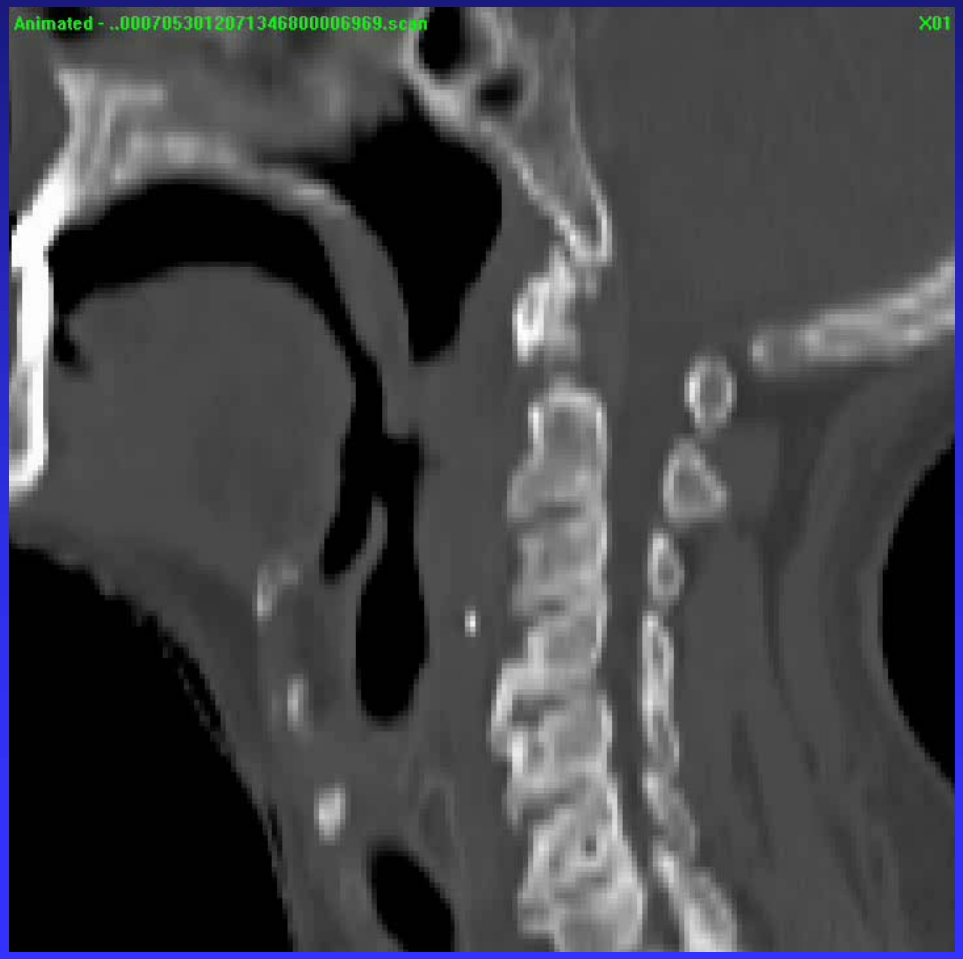


Results: head and neck CT-CBCT

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

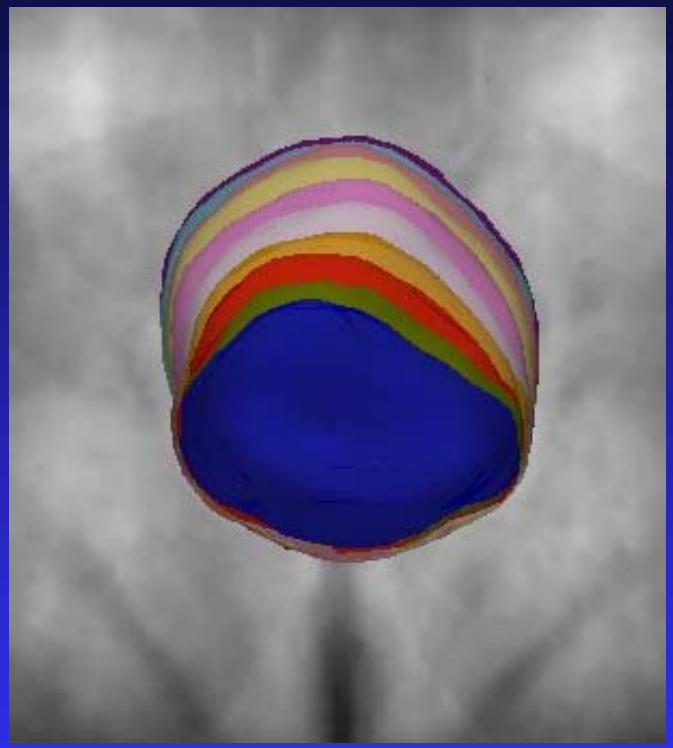
Can you see all anatomical changes ?

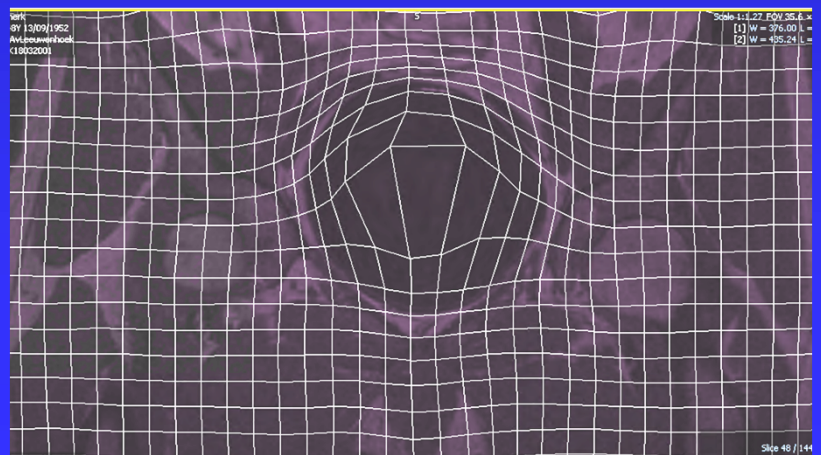


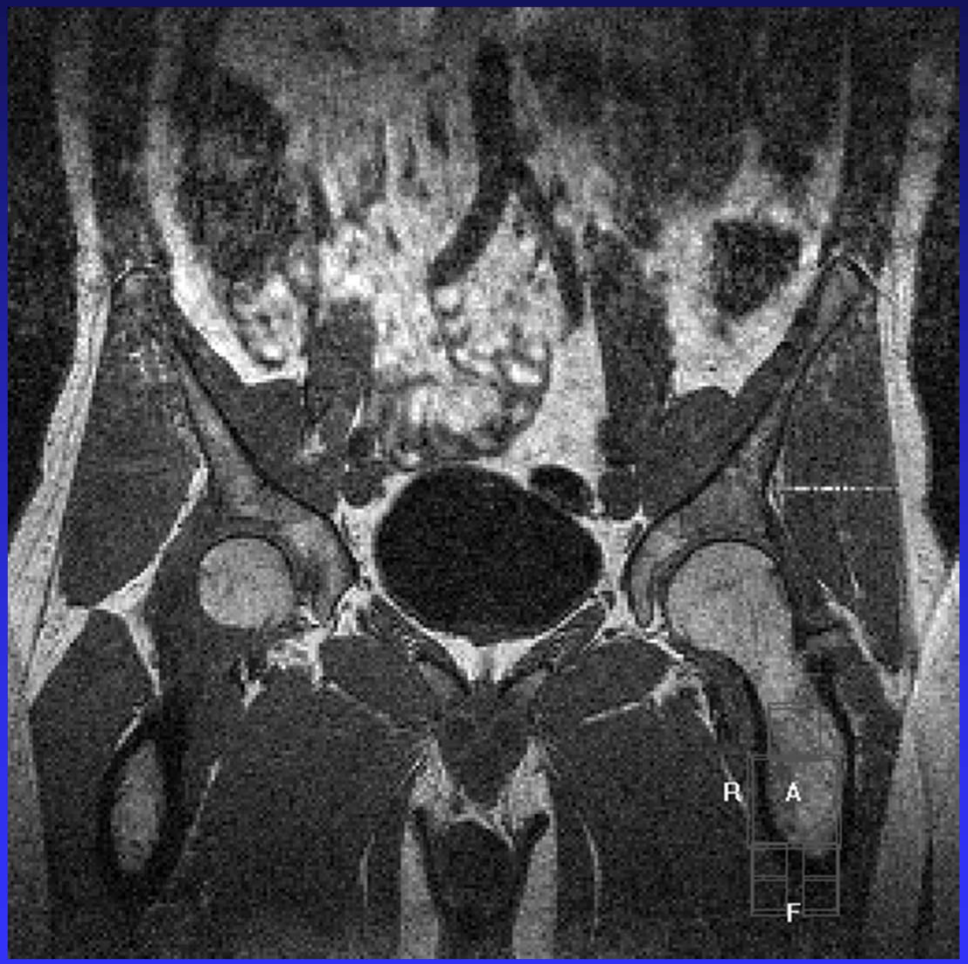
Deformable registration will not pick up motion parallel to interfaces

O Hamming, NKI

Easy deformable registration of the bladder?

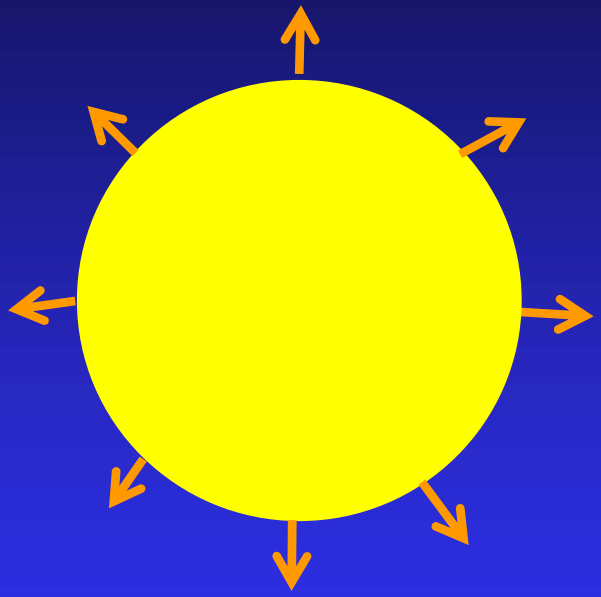


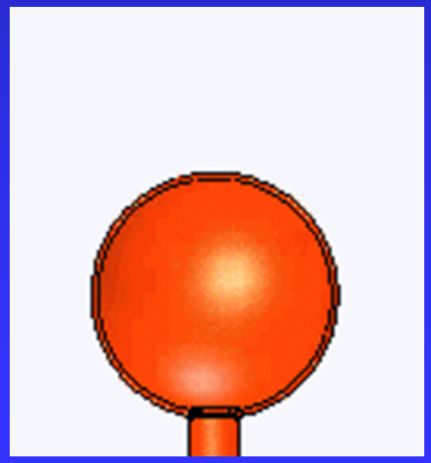


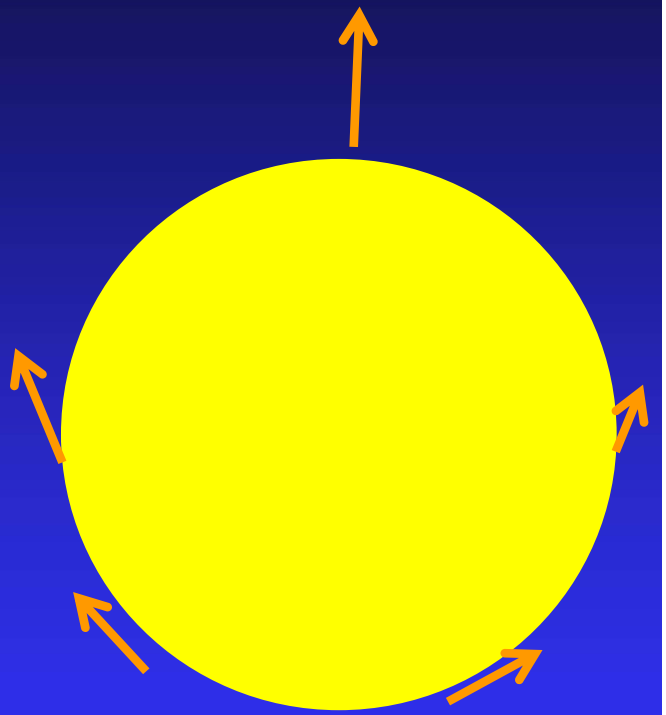


Very high contrast but does software ‘understand’ the anatomy ?

The bladder is a balloon in a box with stuff – it expands isotropic constrained by the organs around it

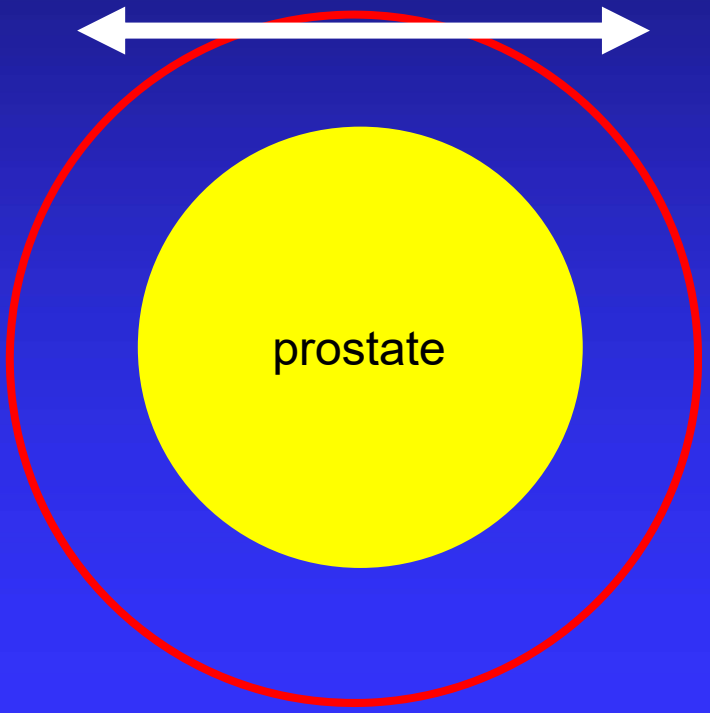




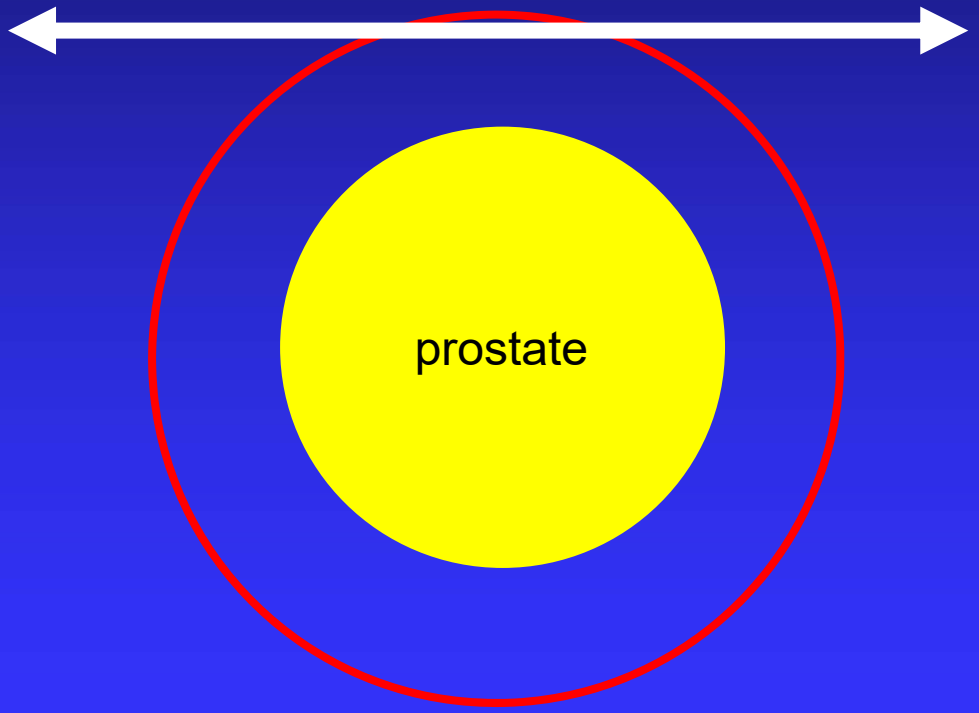


You get the contours right, but not the tissue cells → danger for dose accumulation

Effect of bladder stretching on dose to the bladder neck in prostate RT



50% get high dose



25% get high dose

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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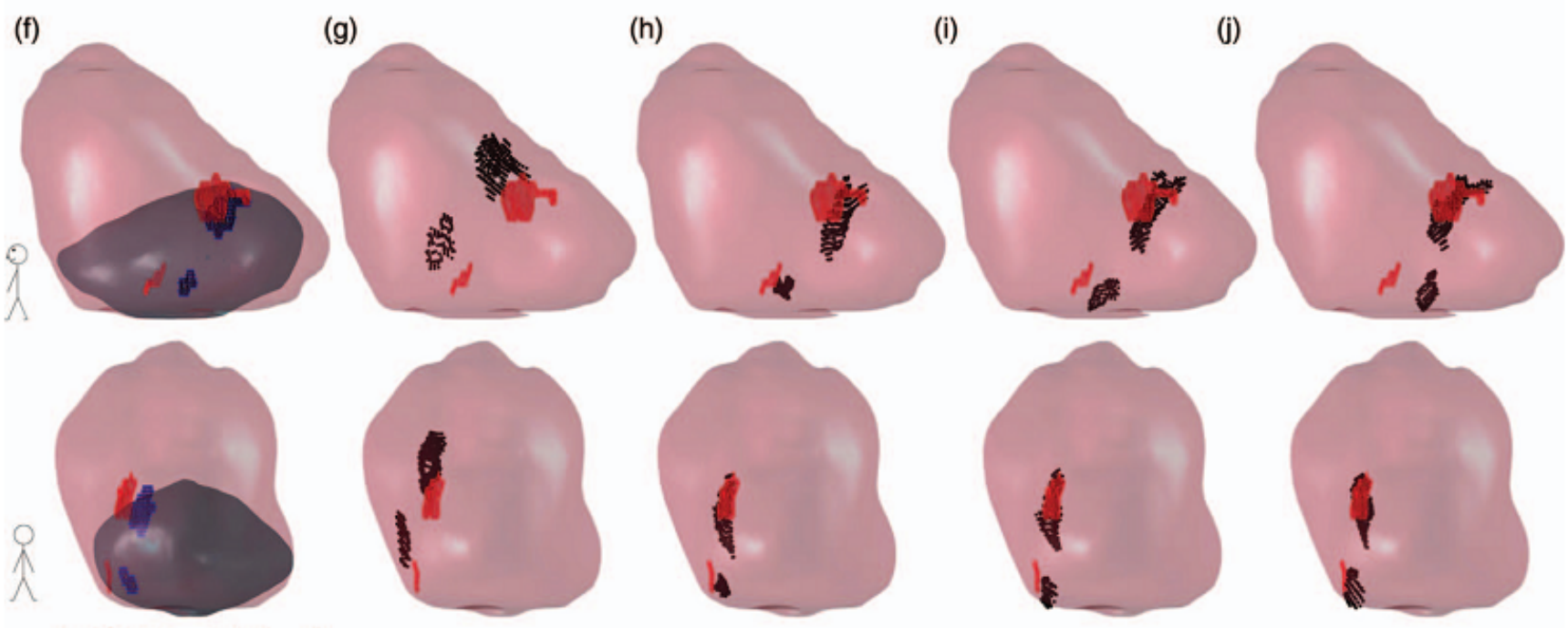
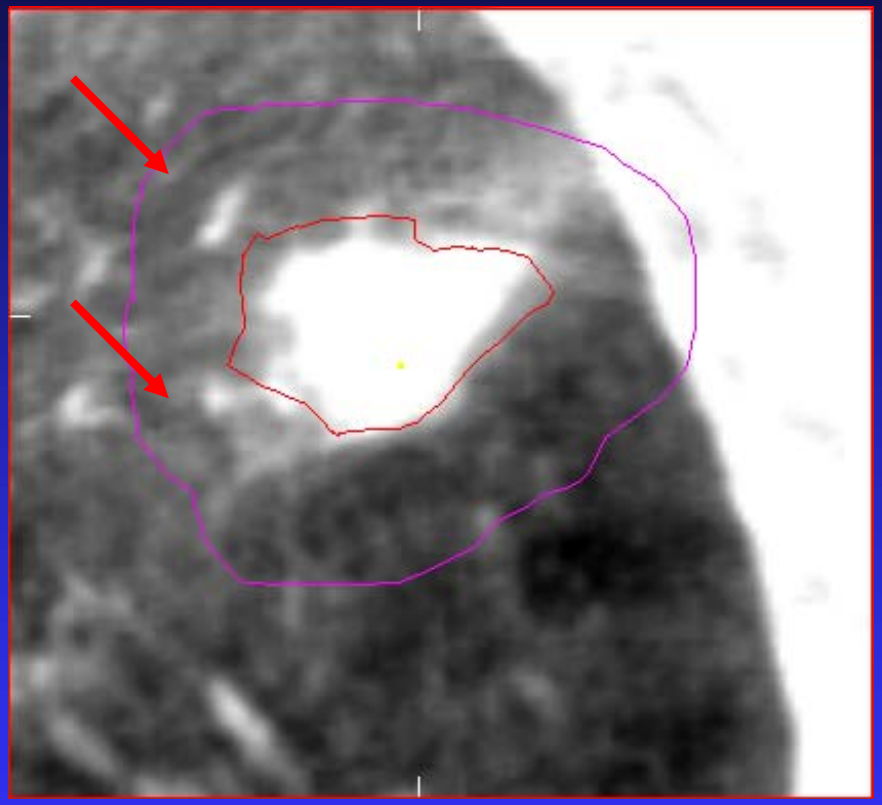


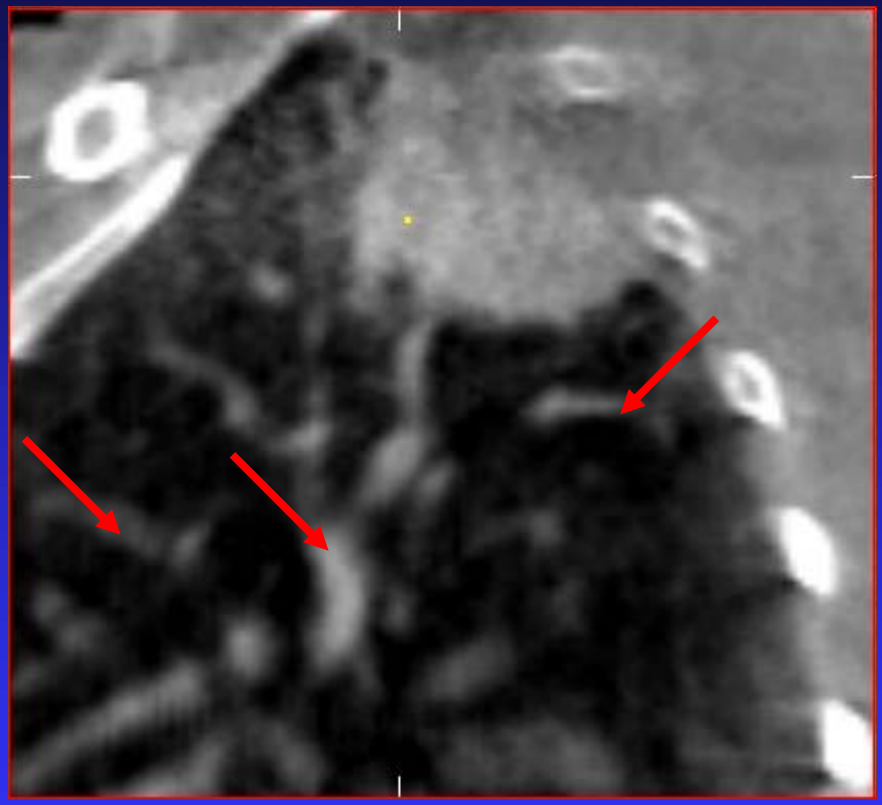
RDE lipiodol (mm)

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

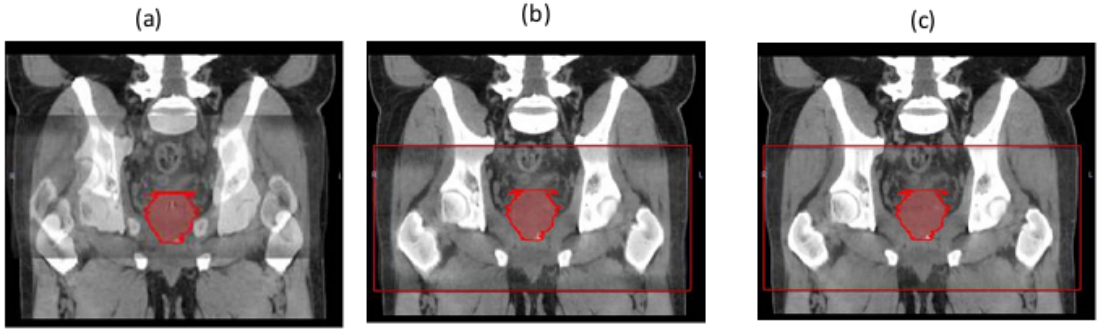
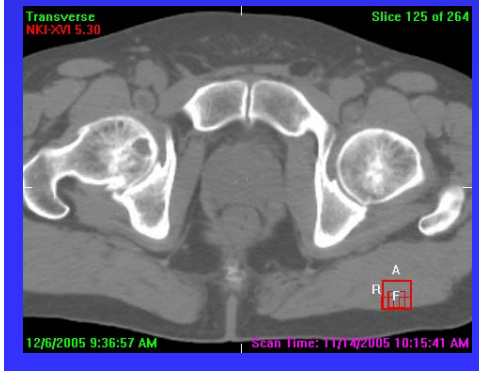
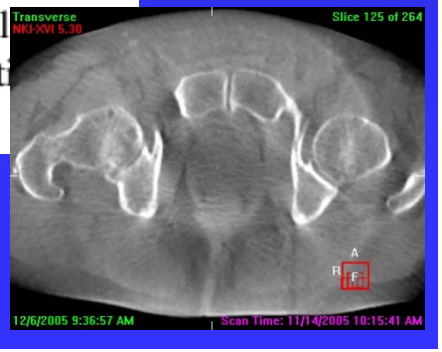


FIG. 1. An example of the registration process in the coronal plane. The rectangular box is the region of interest, which includes the entire CBCT. The contoured structure is the CTV. In (a), CBCT and SimCT were not registered. In (b), rigid registration was performed for CBCT into SimCT based on pelvic 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 registrat
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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Pareto front analysis in clinical practice: what is it, and what is the gain?

Advanced Treatment Planning Course
3-7 September 2017 – Barcelona, Spain

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 without** making **at least one individual worse**.

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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

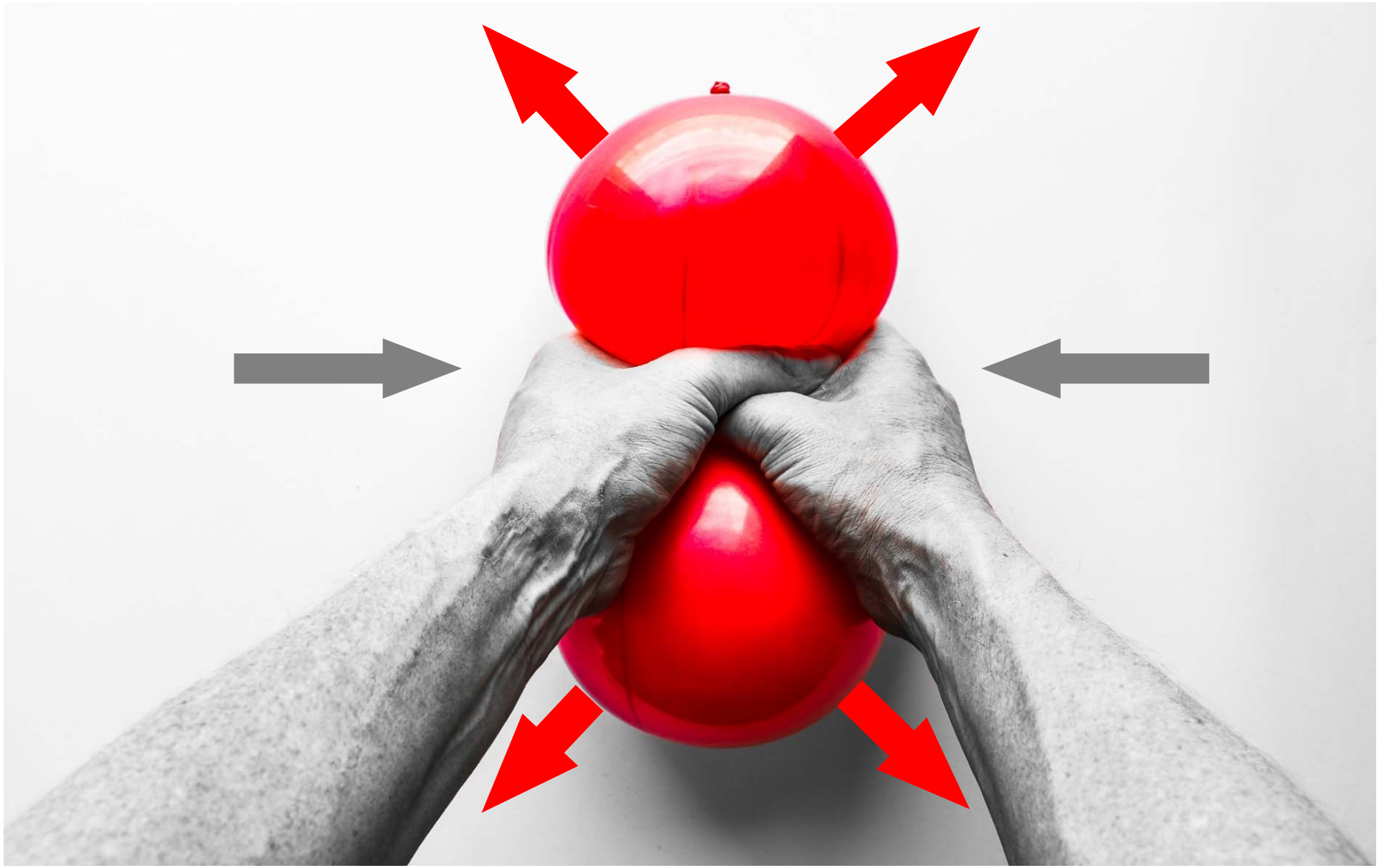
- It's difficult to make a good estimation of what is achievable in solving the planning problem

- 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?

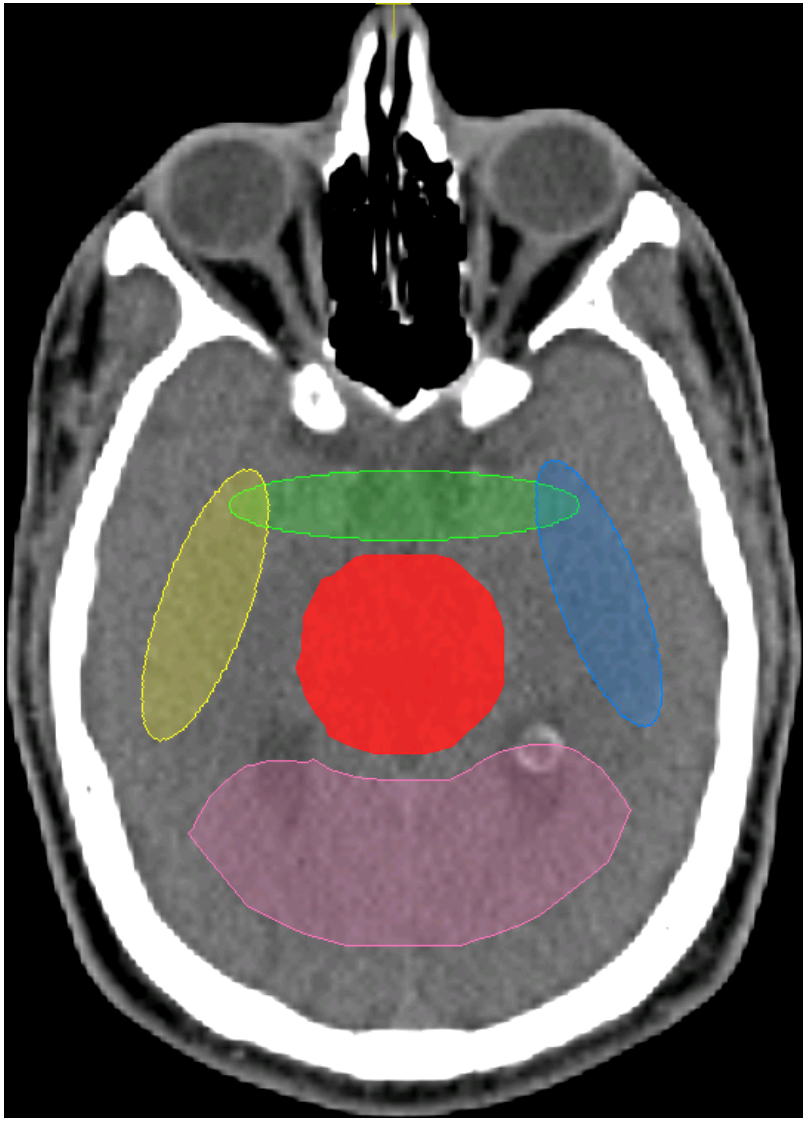
Sweeping dose

- 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

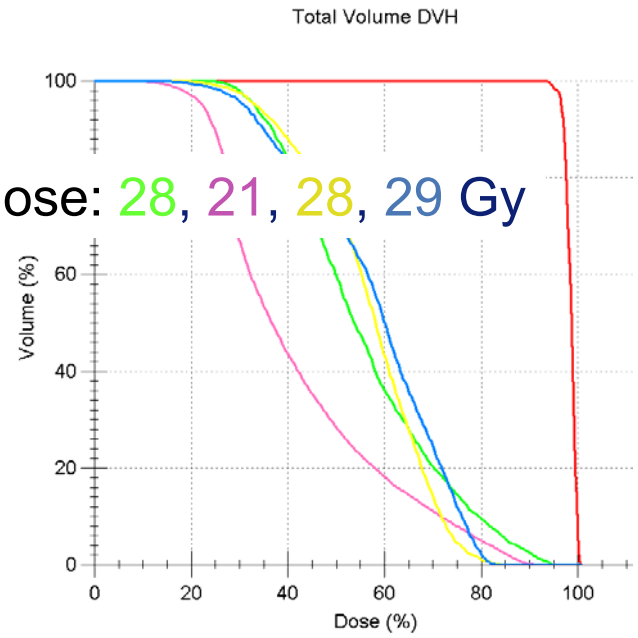


Prescription:
PTV = 50 Gy
OAR1-4 = minimize mean dose

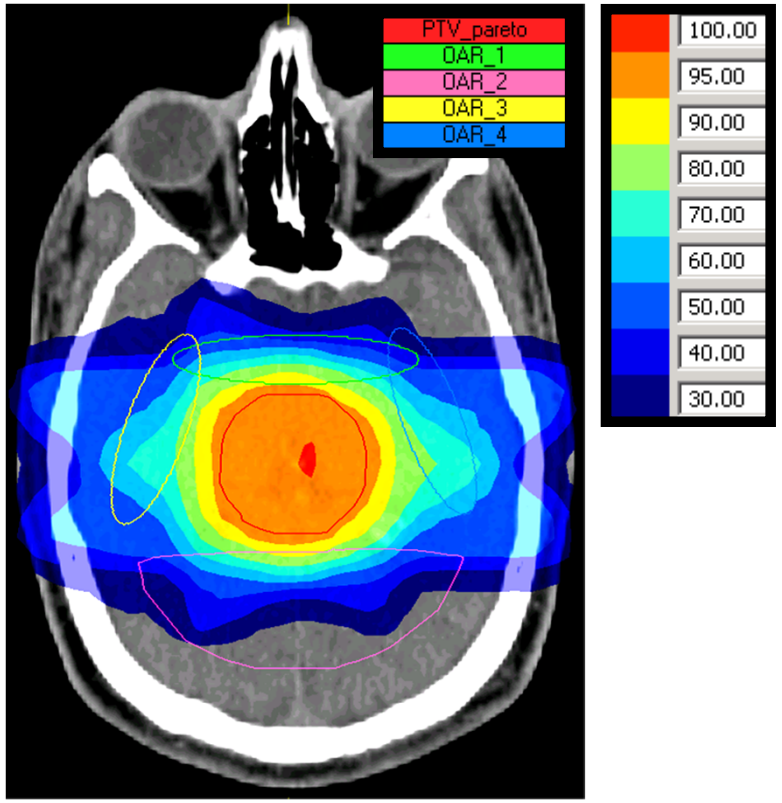
Sweeping dose theoretical example

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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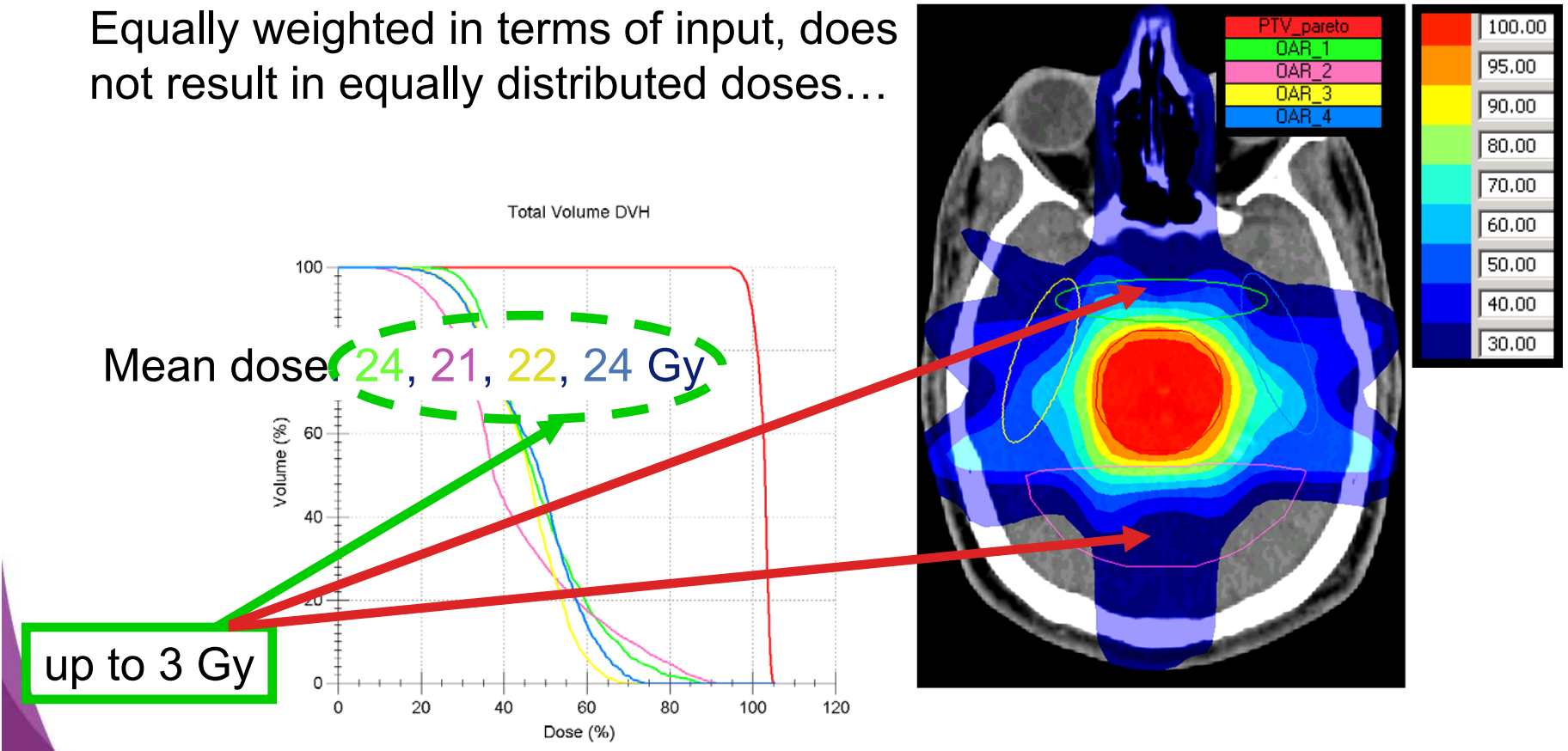
Sweeping dose theoretical example

Option 2:
Conformal dose around PTV, equally weighted constraints on all OAR's (mean dose = 25 Gy)

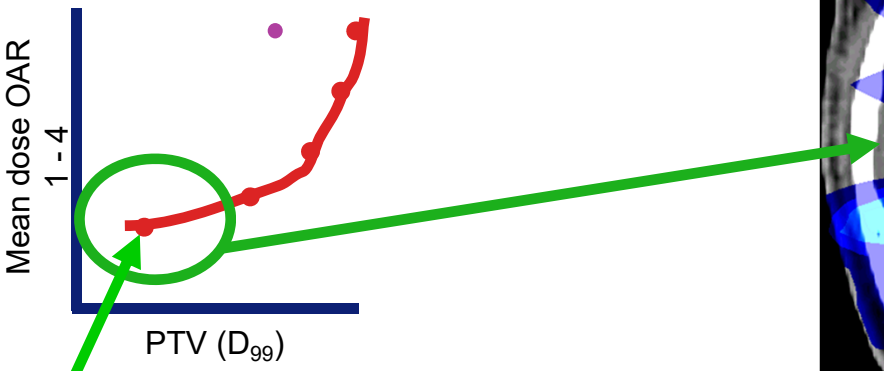
Equally weighted in terms of input, does not result in equally distributed doses…

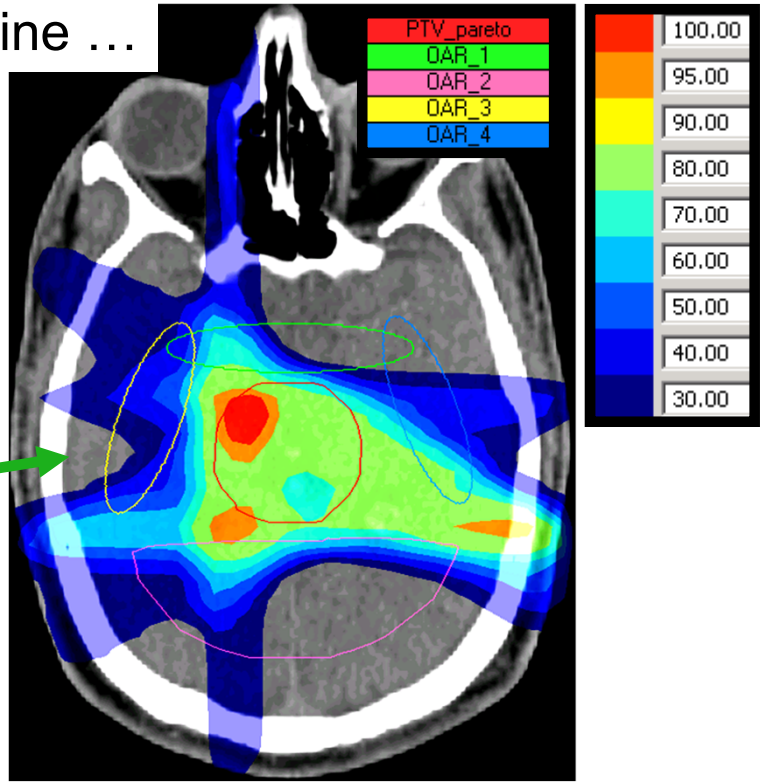


Sweeping dose theoretical example

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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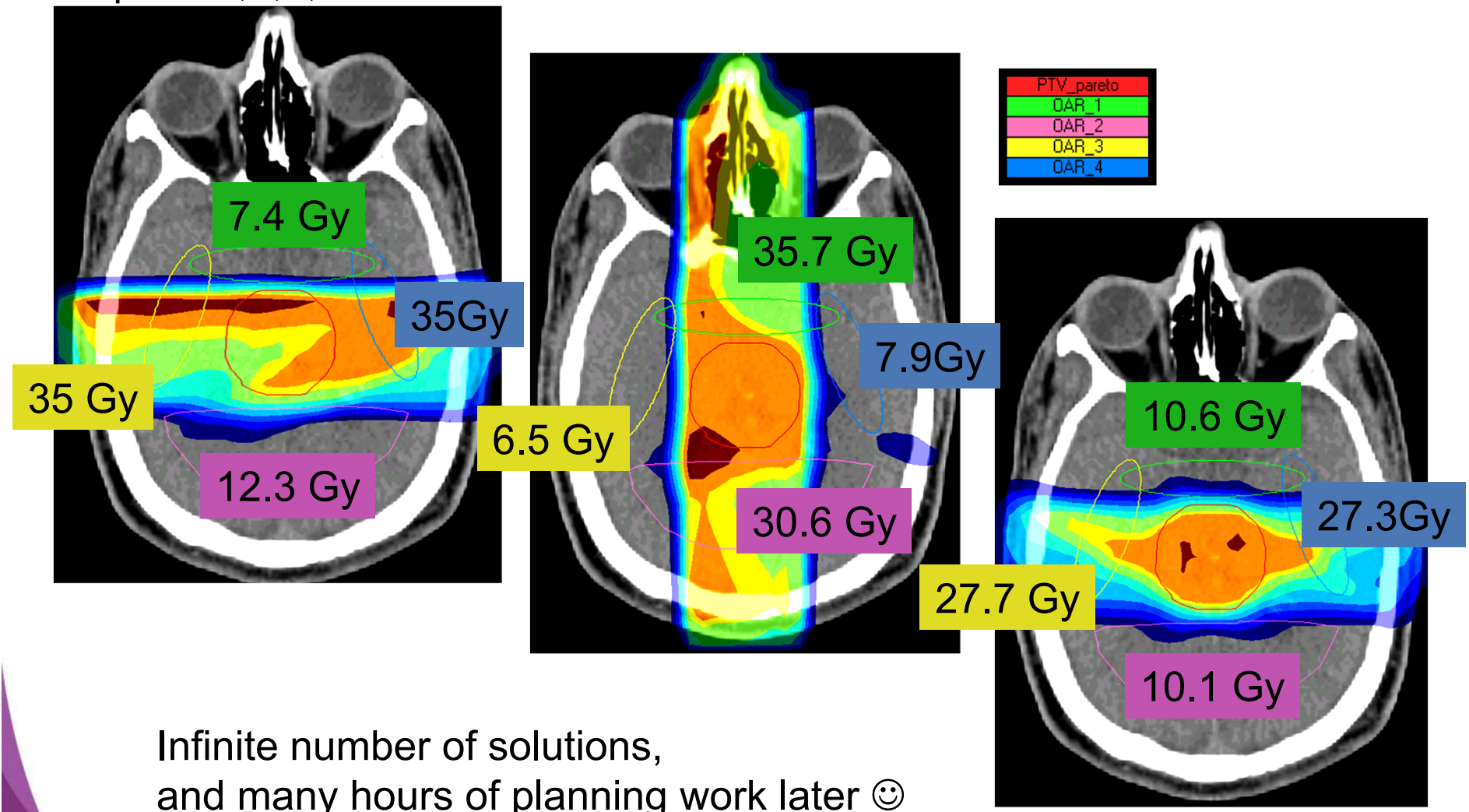
Sweeping dose theoretical example, many options …

Option 4,5,6, ……. :



Infinite number of solutions,
and many hours of planning work later ☺

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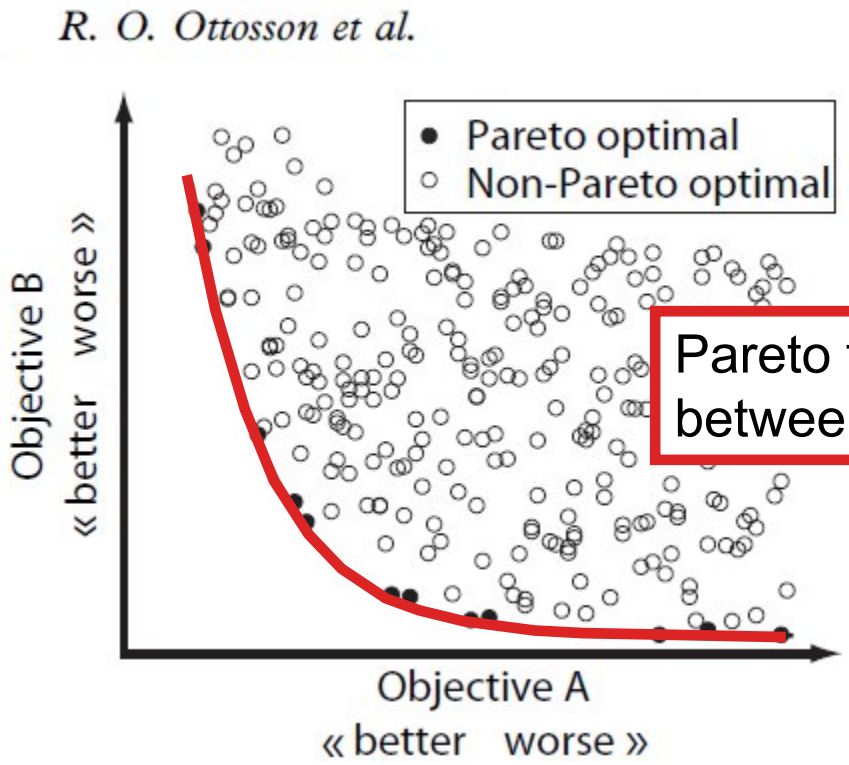
Pareto front



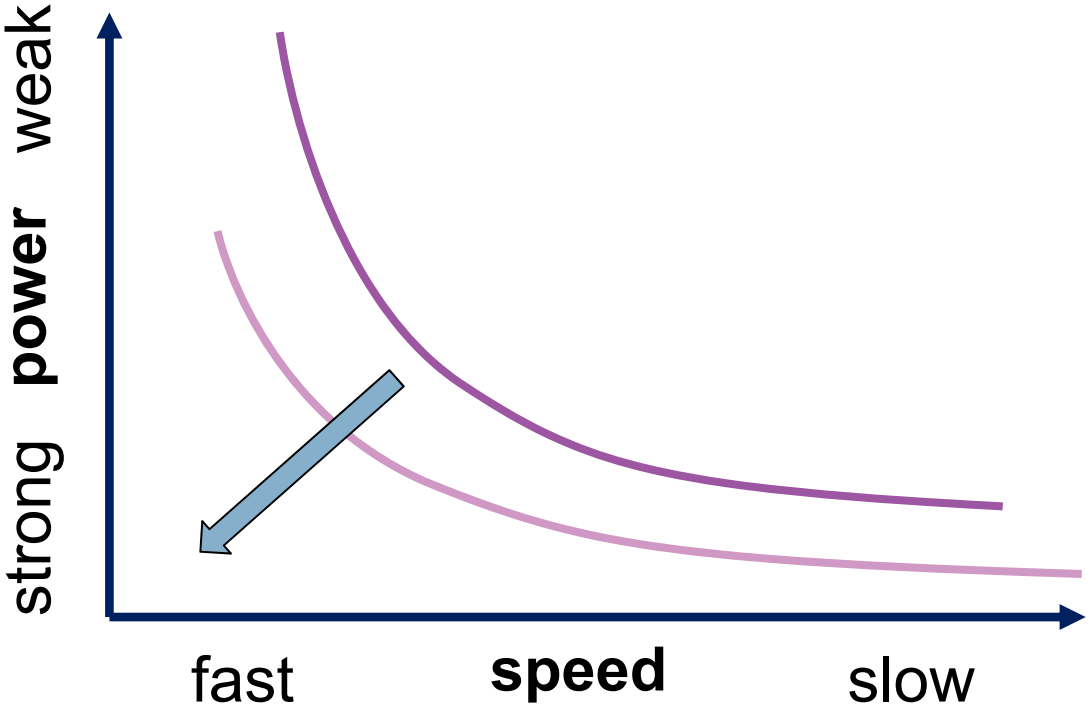
Pareto front = line of Pareto optimal points between two contradicting objectives

For two mutually contradicting objectives an endless number of solution exists

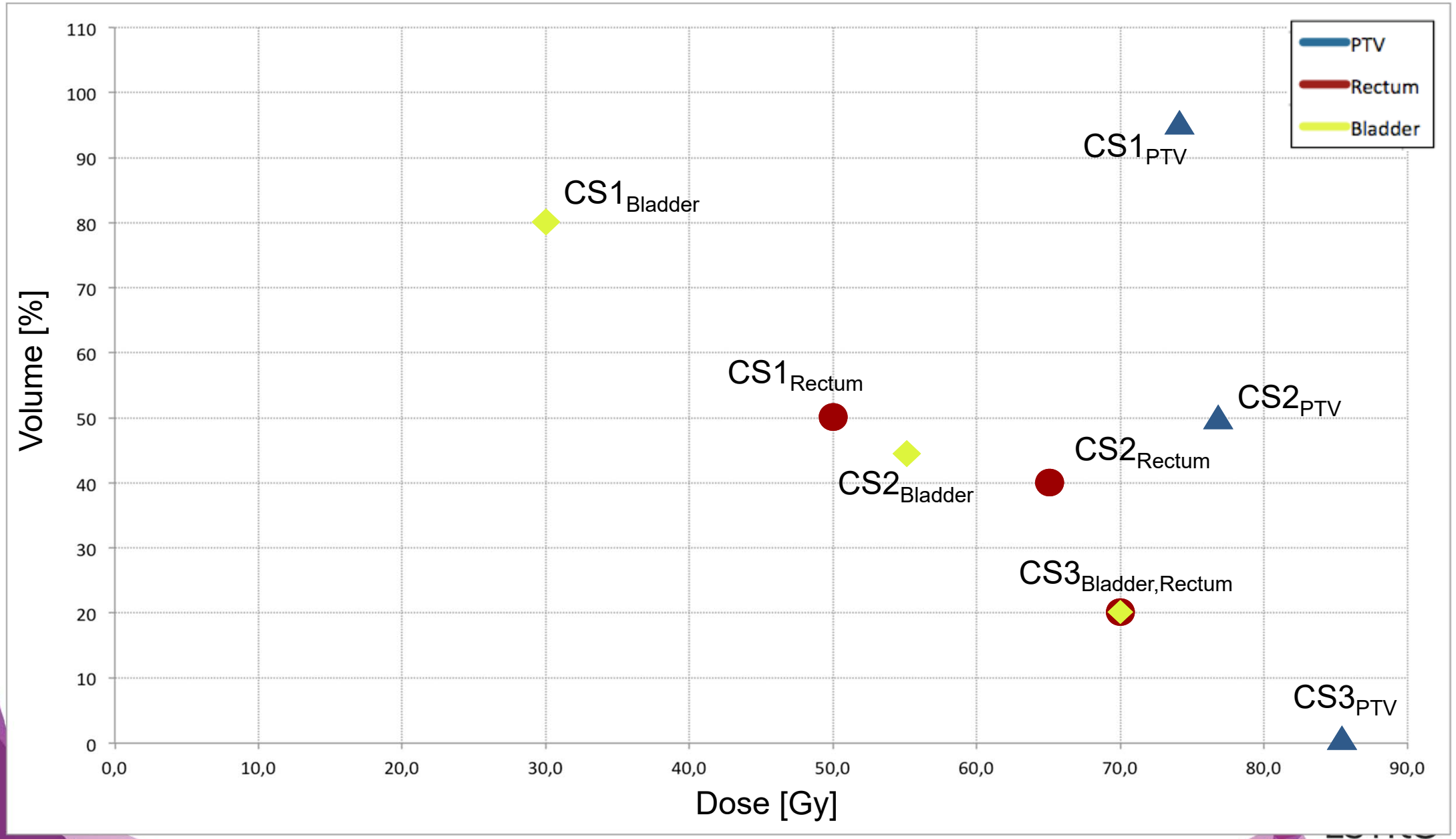
The solutions where one of the objectives can not be improved without deteriorating the other are *Pareto optimal*

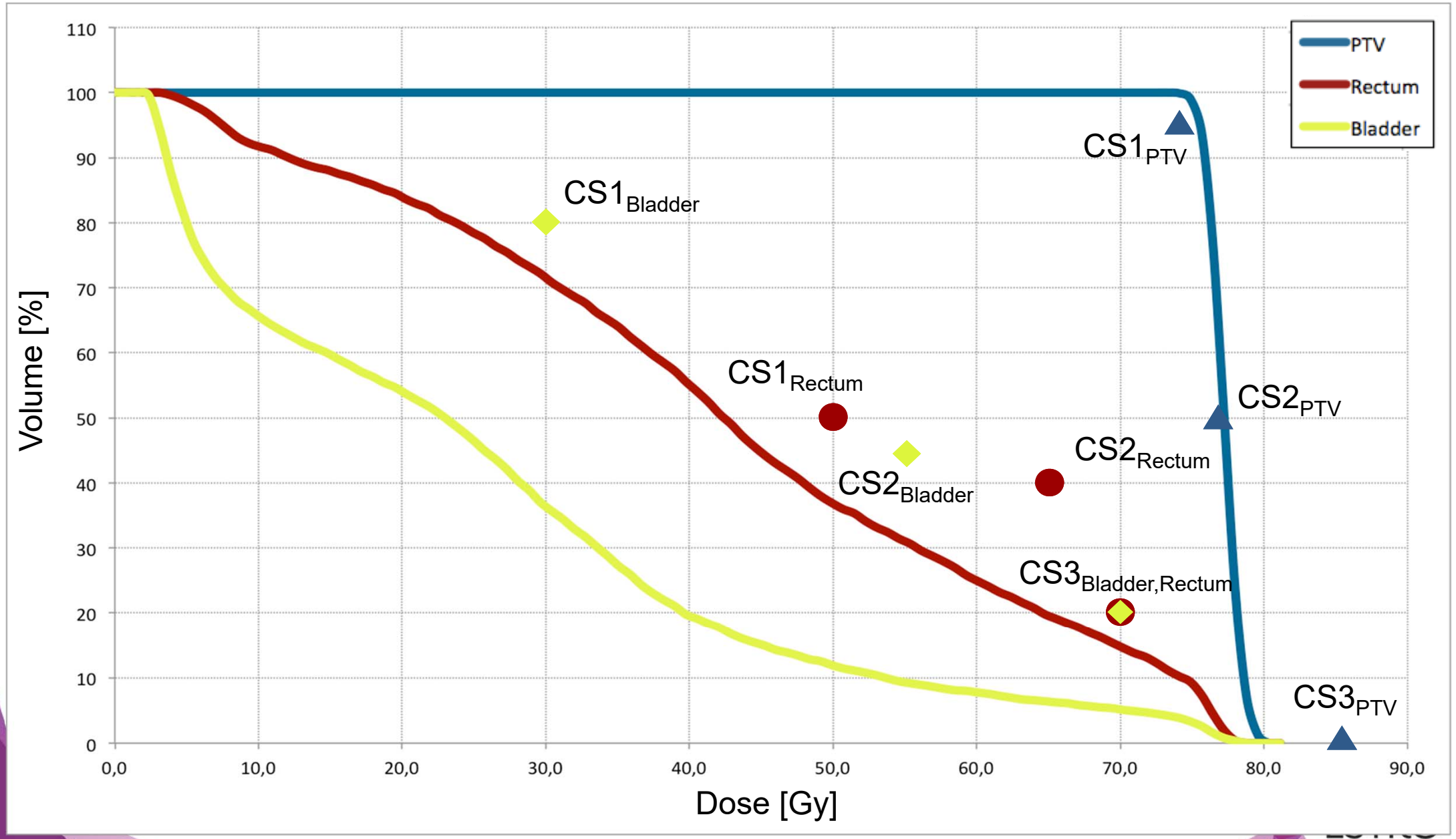
All Pareto optimal solutions lie on the Pareto front

Mnemonic for Pareto front



The „manual“ way to get there

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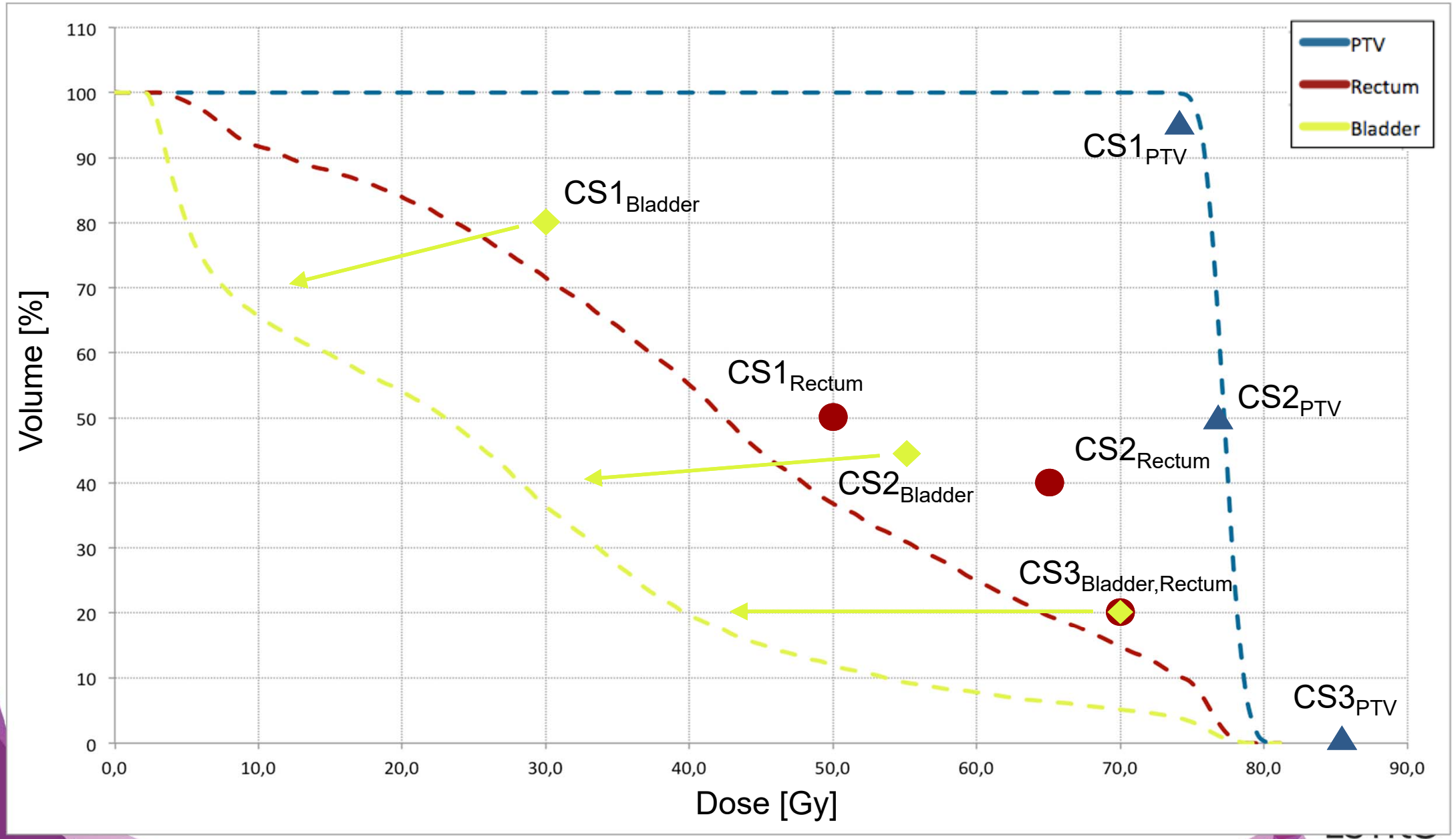
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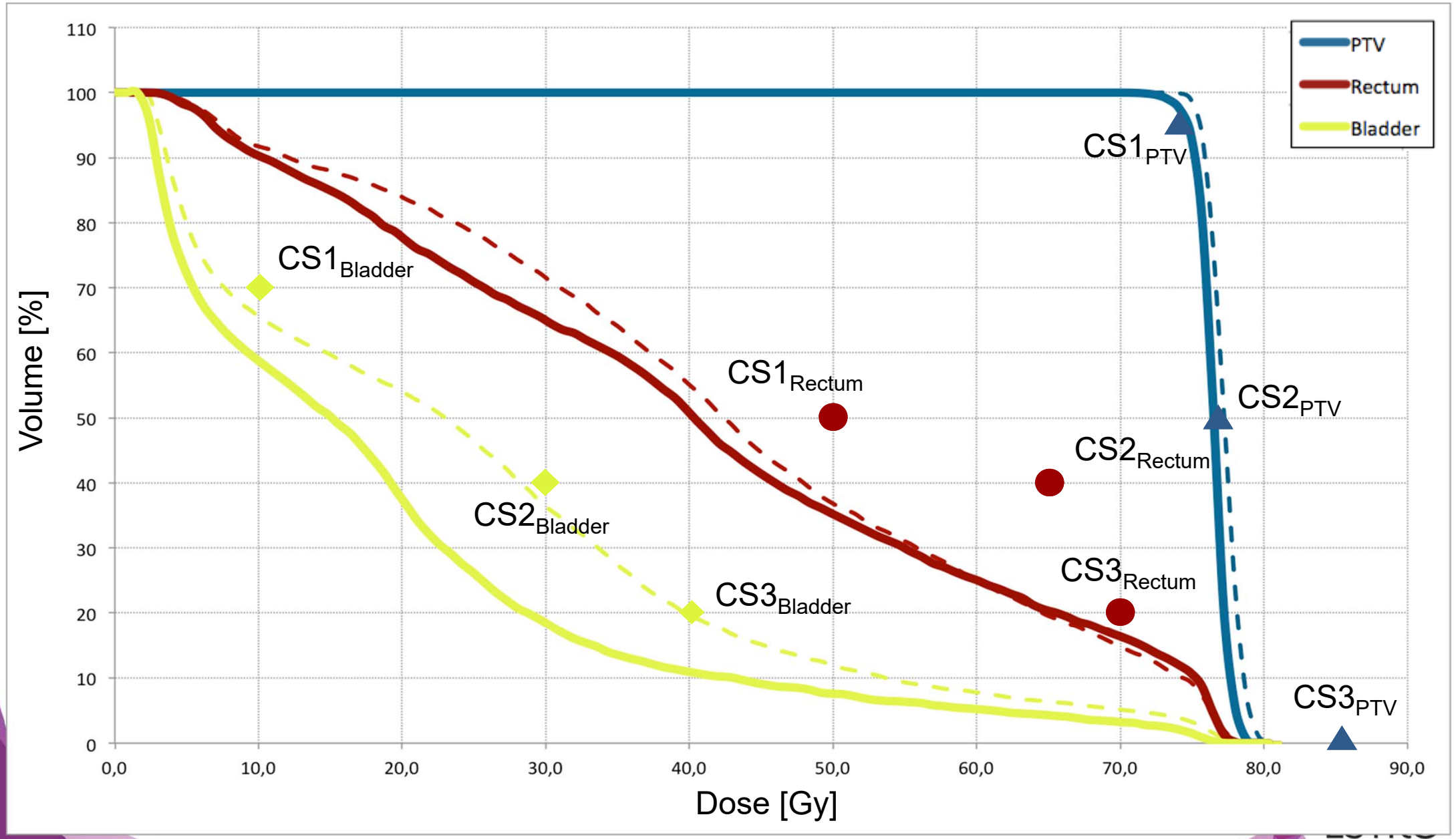
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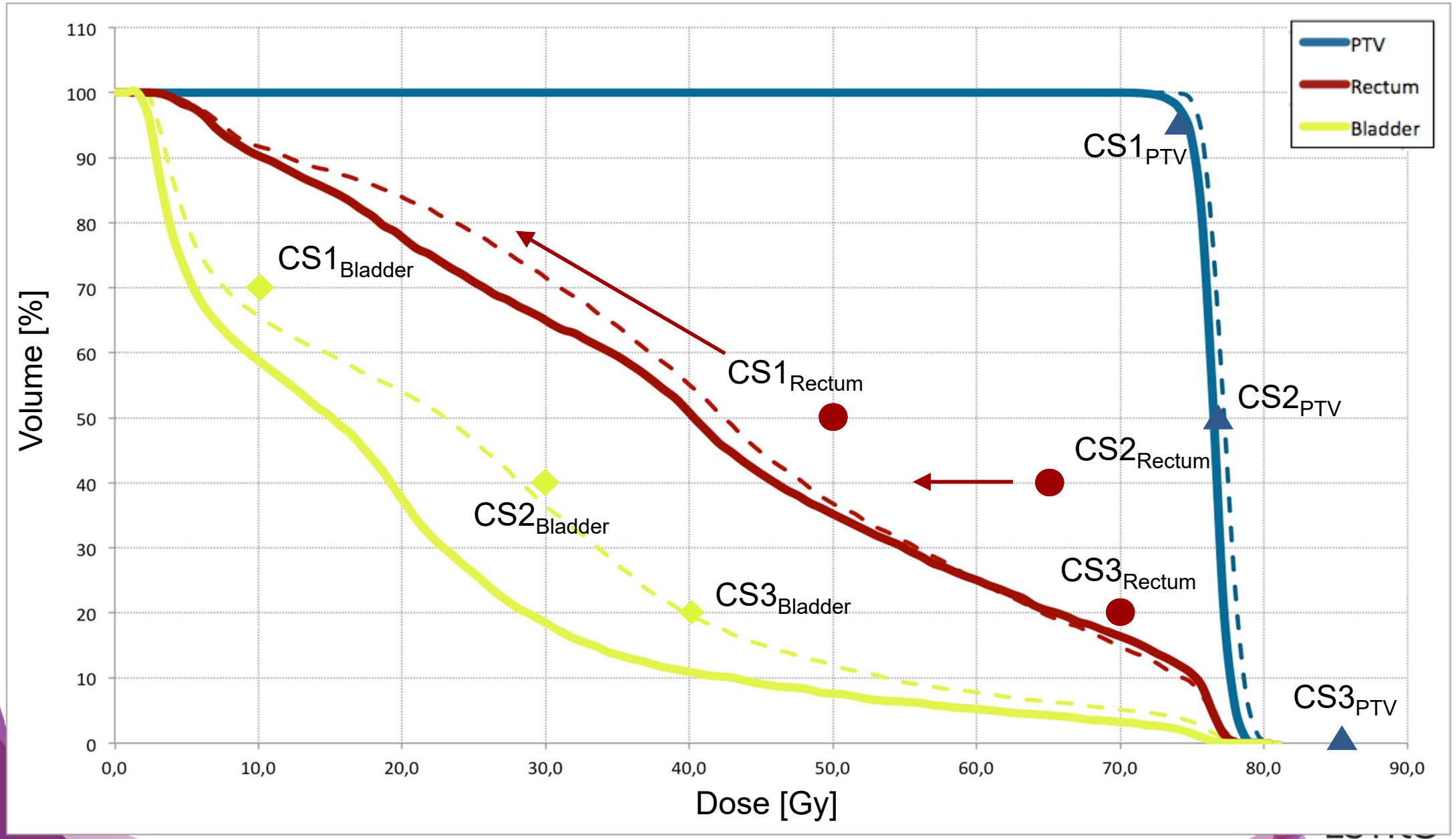
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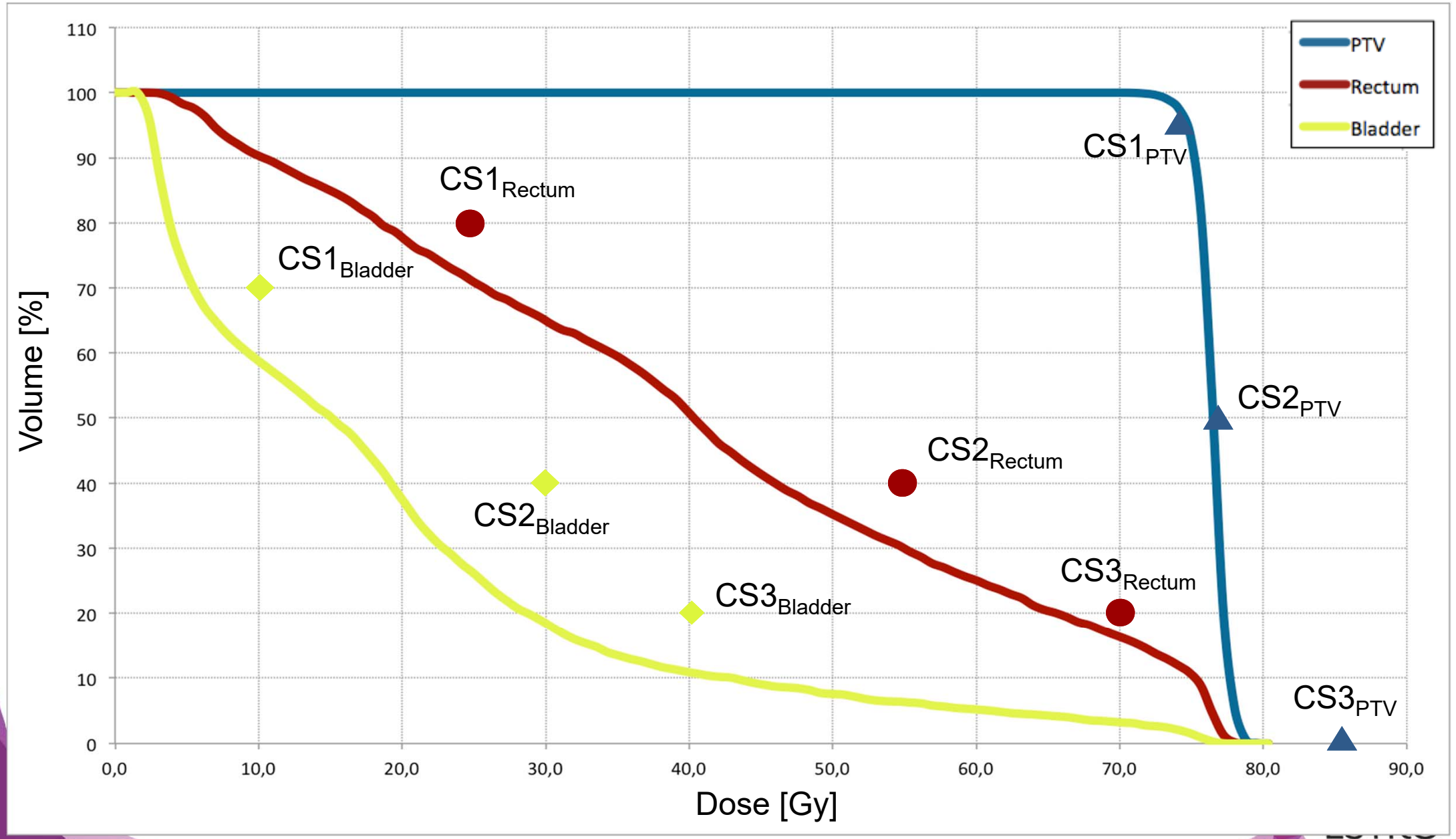
CS3Bladder
CS3PTV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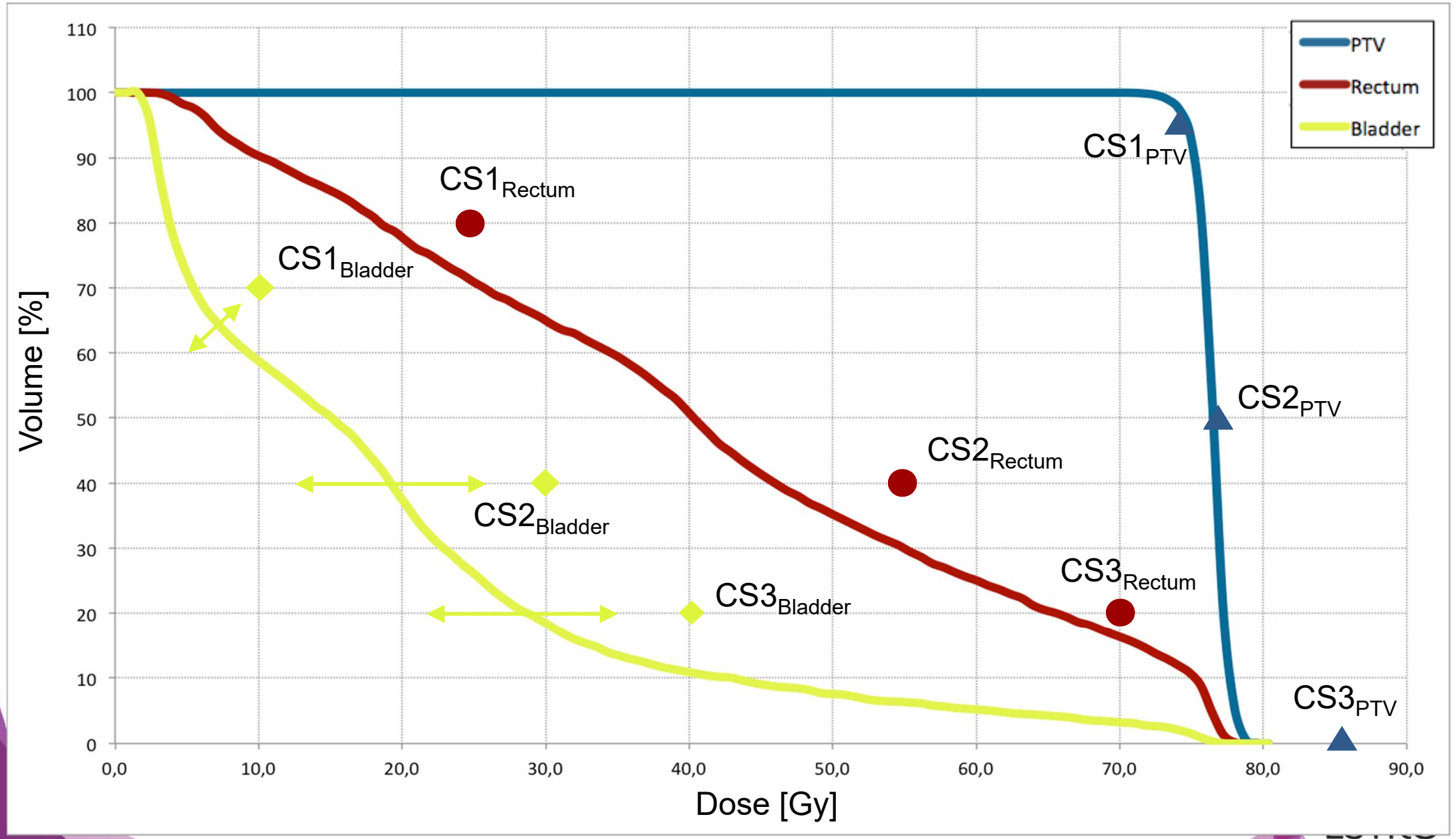
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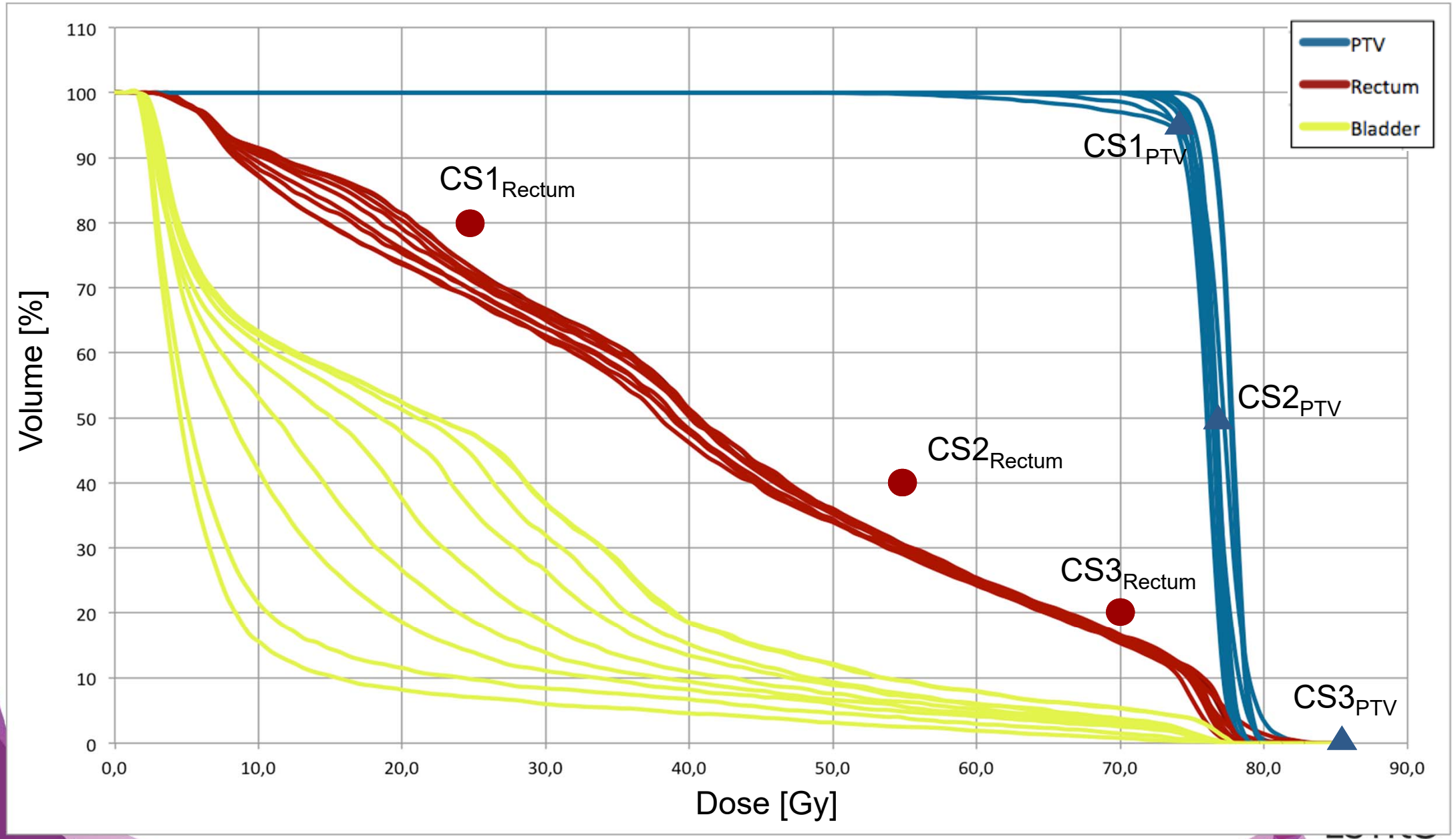
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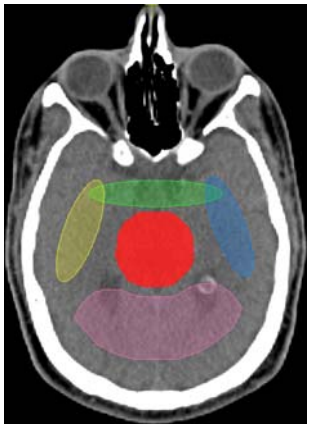
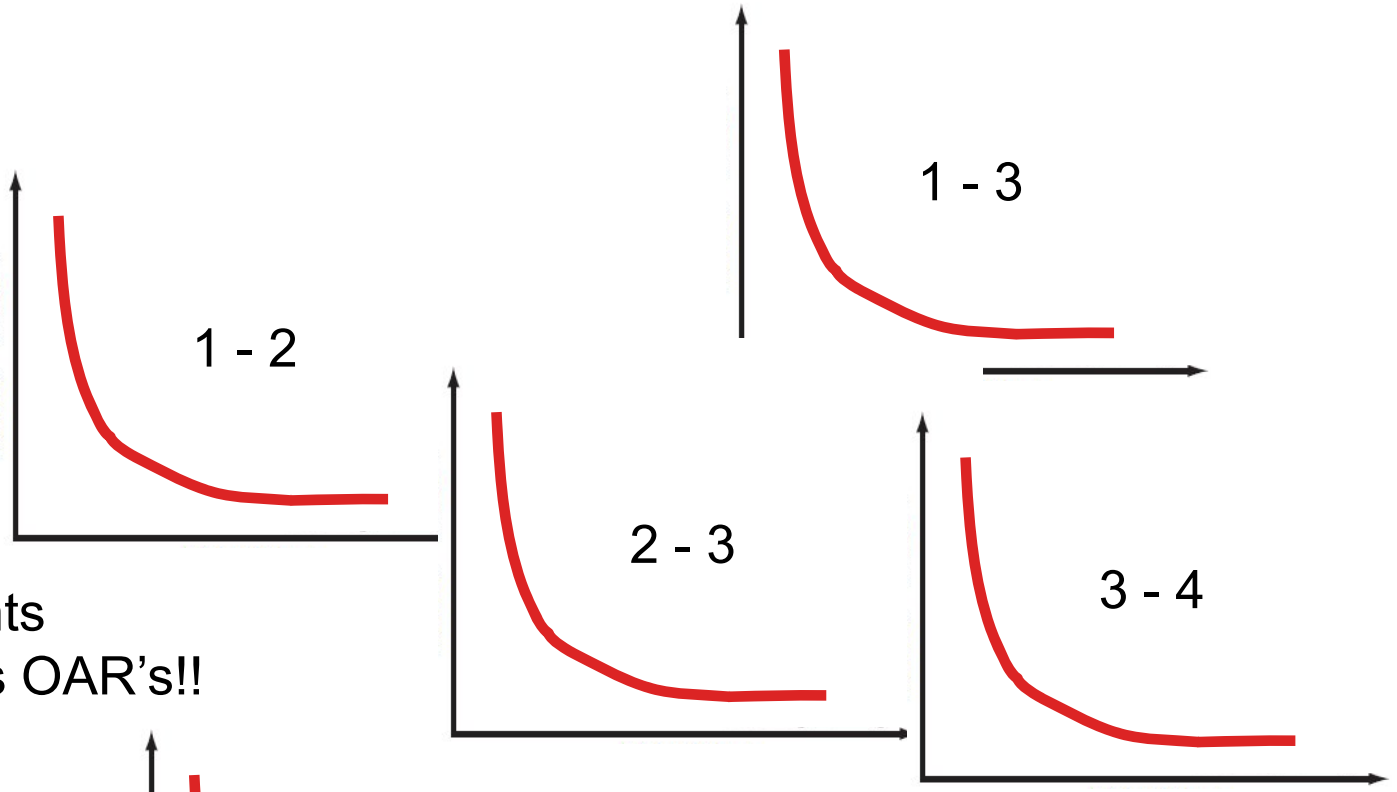
Pareto front versus Pareto surface

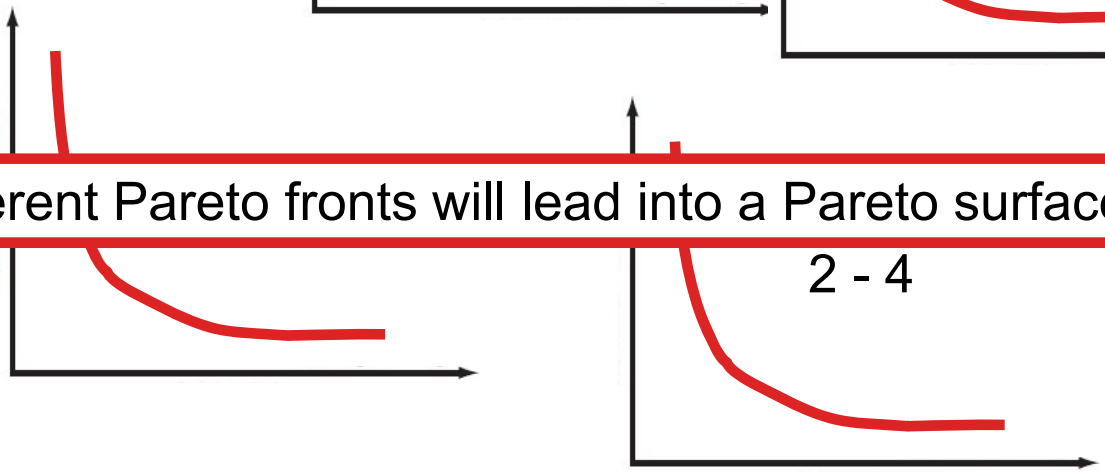
OAR's 1,2,3,4



Another set of fronts
With Target versus OAR's!!



Combination of different Pareto fronts will lead into a Pareto surface



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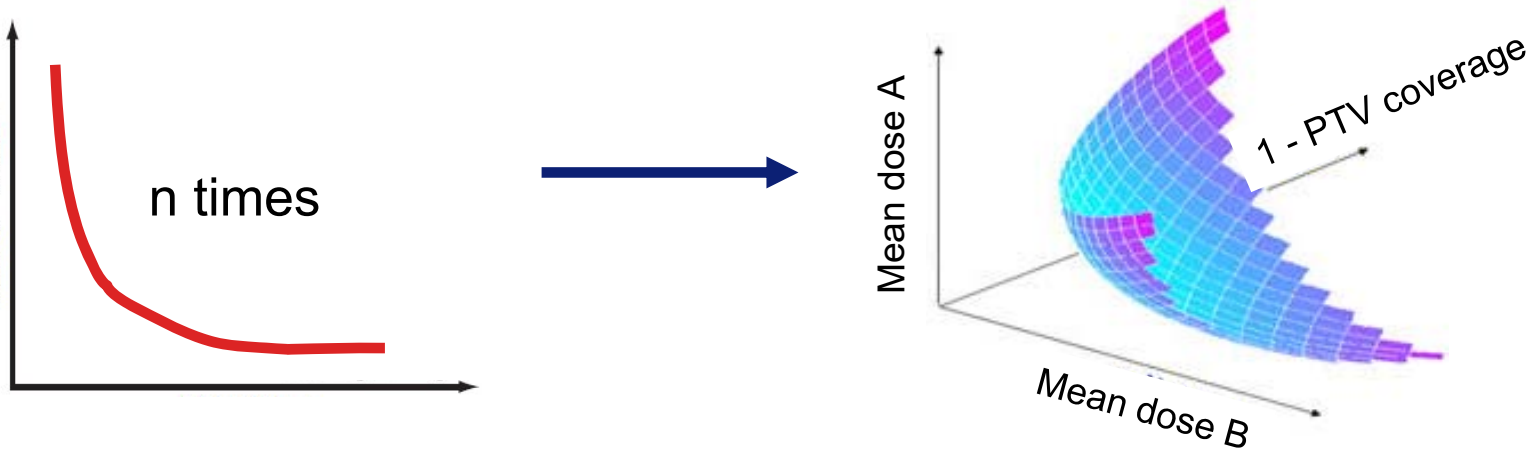
Pareto front versus Pareto surface

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

Contents lists available at ScienceDirect

Radiotherapy and Oncology

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

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Plan library ‘around’ a class solution

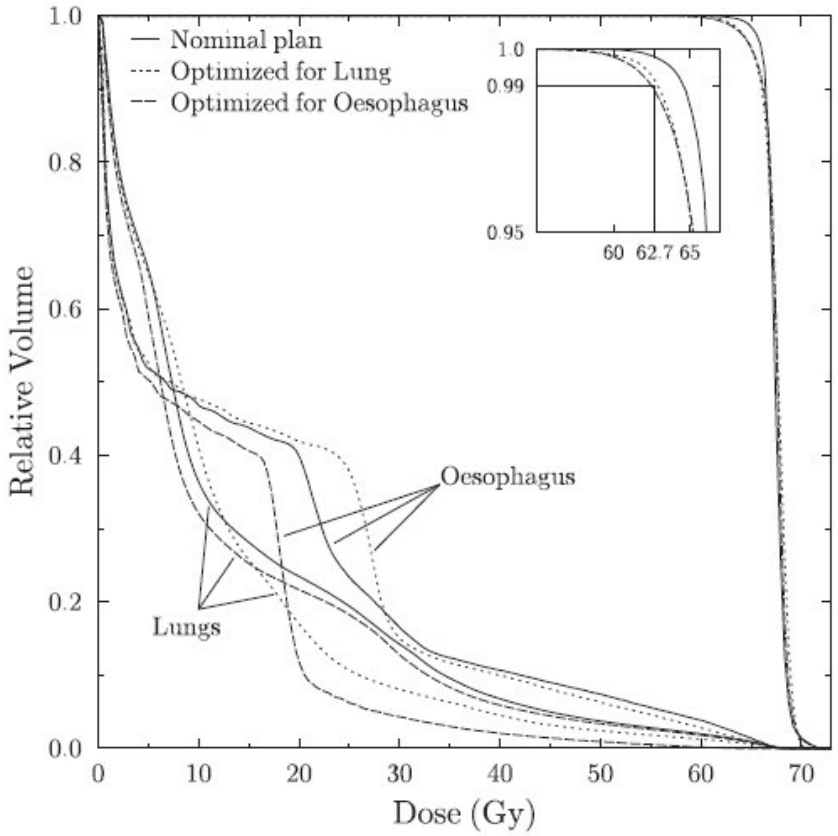

Fig. 1. DVH curves for three different IMRT plans of the same patient (see legend). For the plan optimized for lung sparing, the weight of the lung objective was increased from 1 to 50. For the plan optimized for oesophagus sparing, the dose level of the oesophagus objective function was lowered from 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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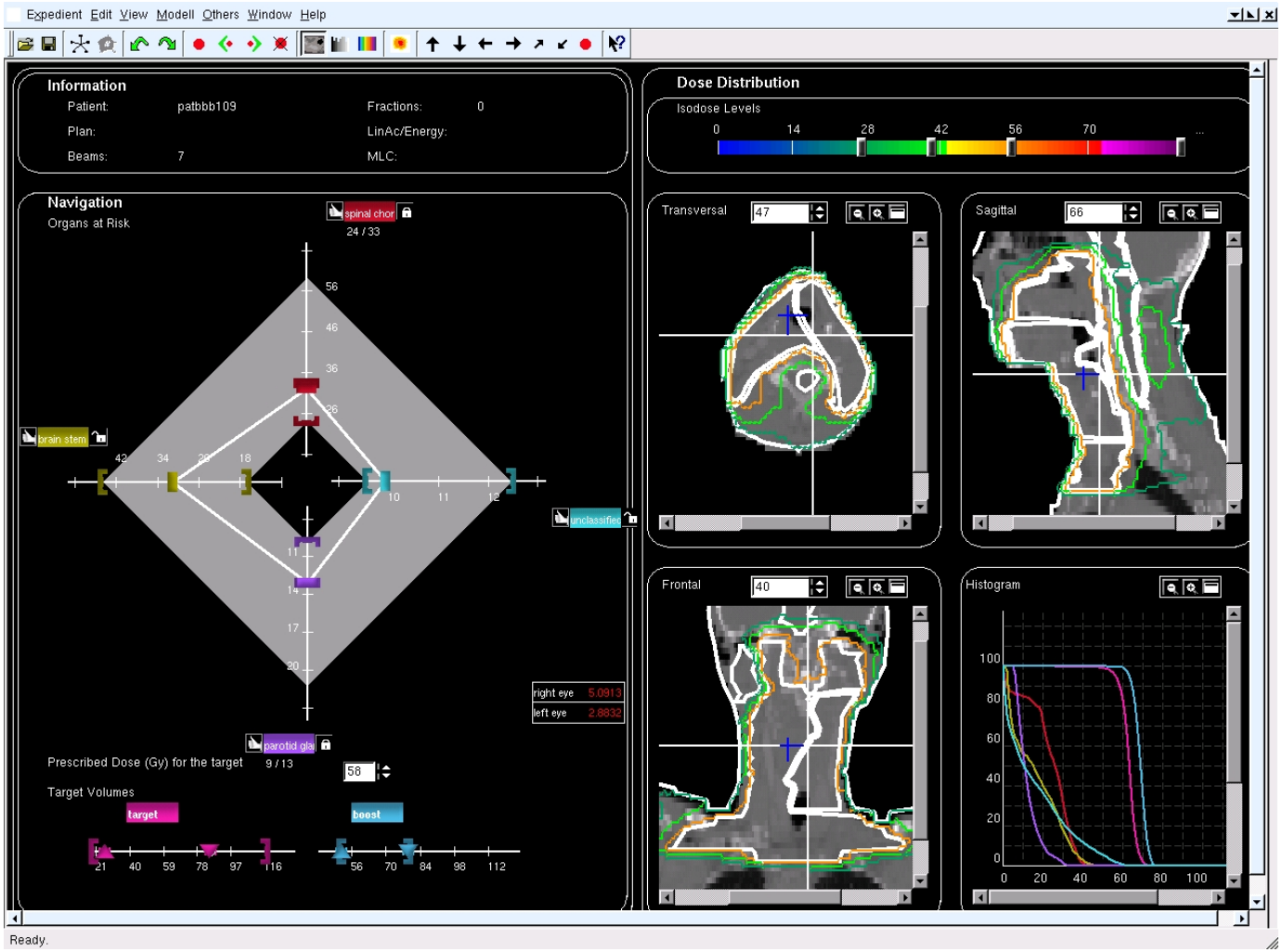
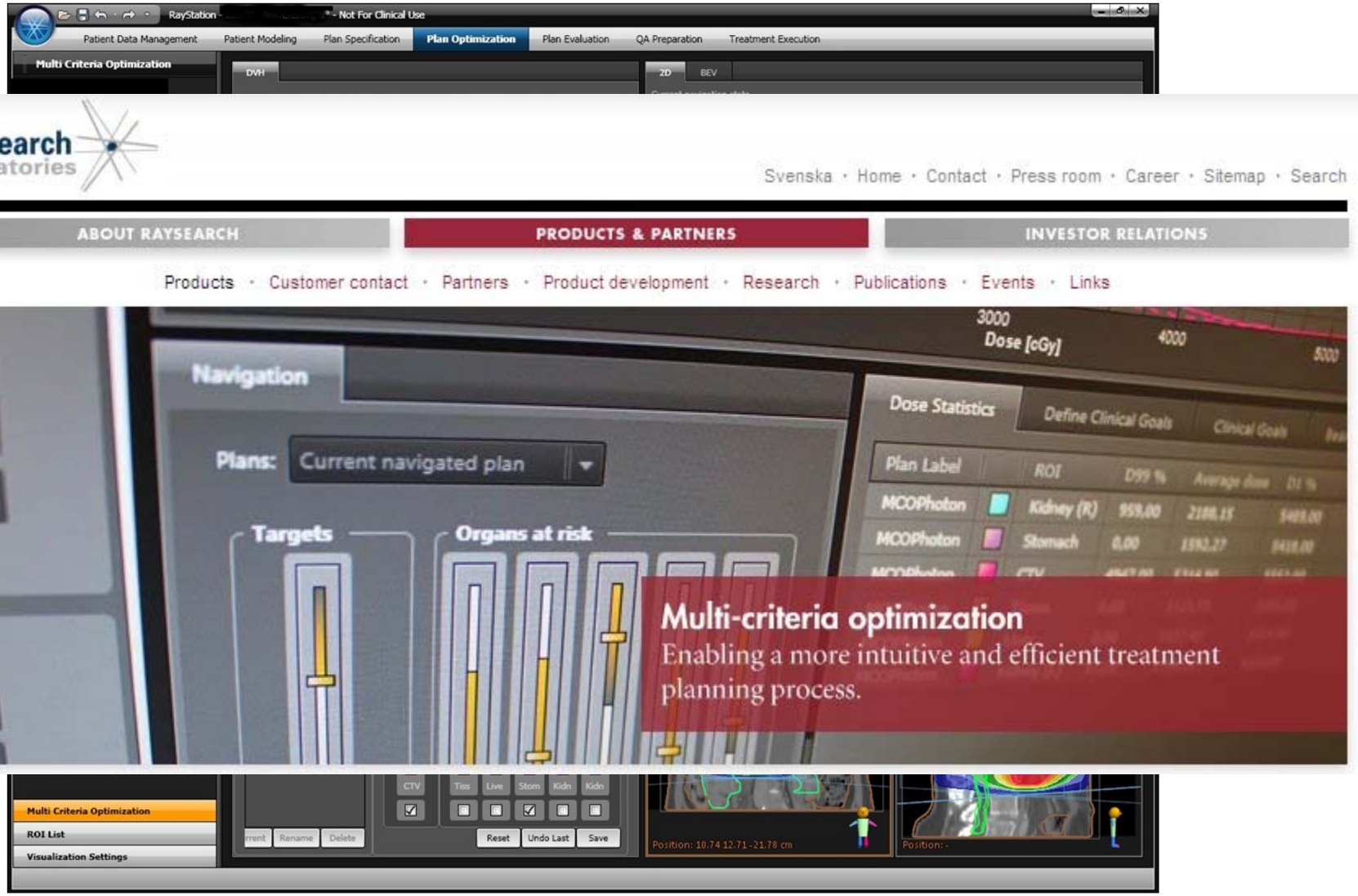
Pareto navigation tool



Courtesy to K.H. Küfer, (FHG-ITWM)

Navigation should be sensitive !!

RaySearch TPS: Pareto navigation



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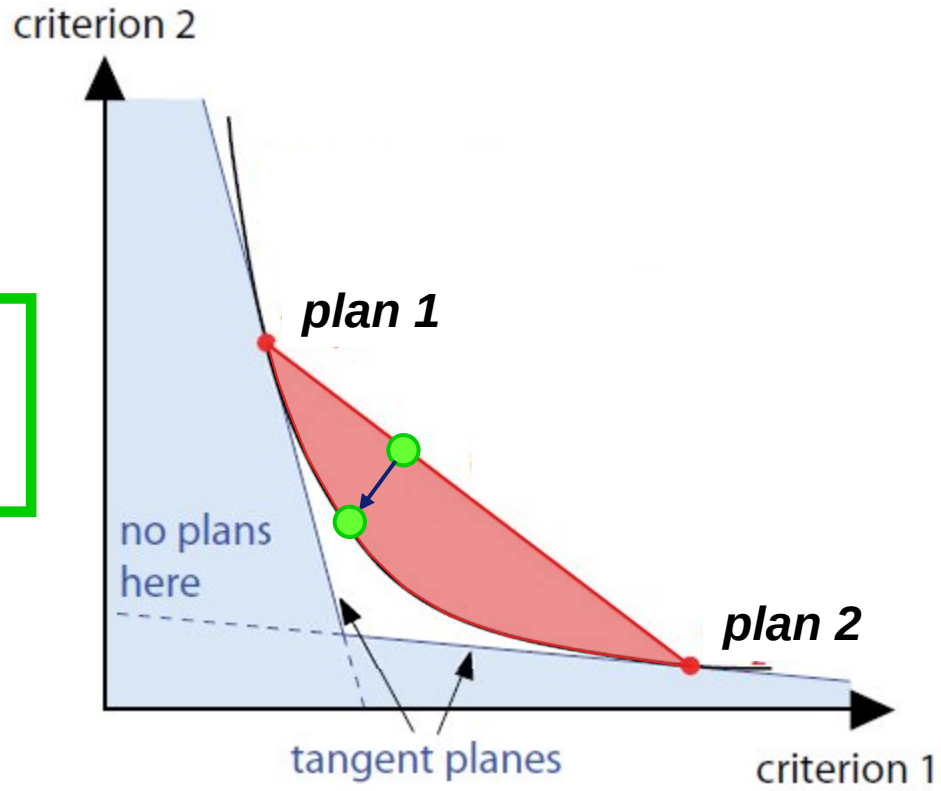
RaySearch TPS: plan library

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

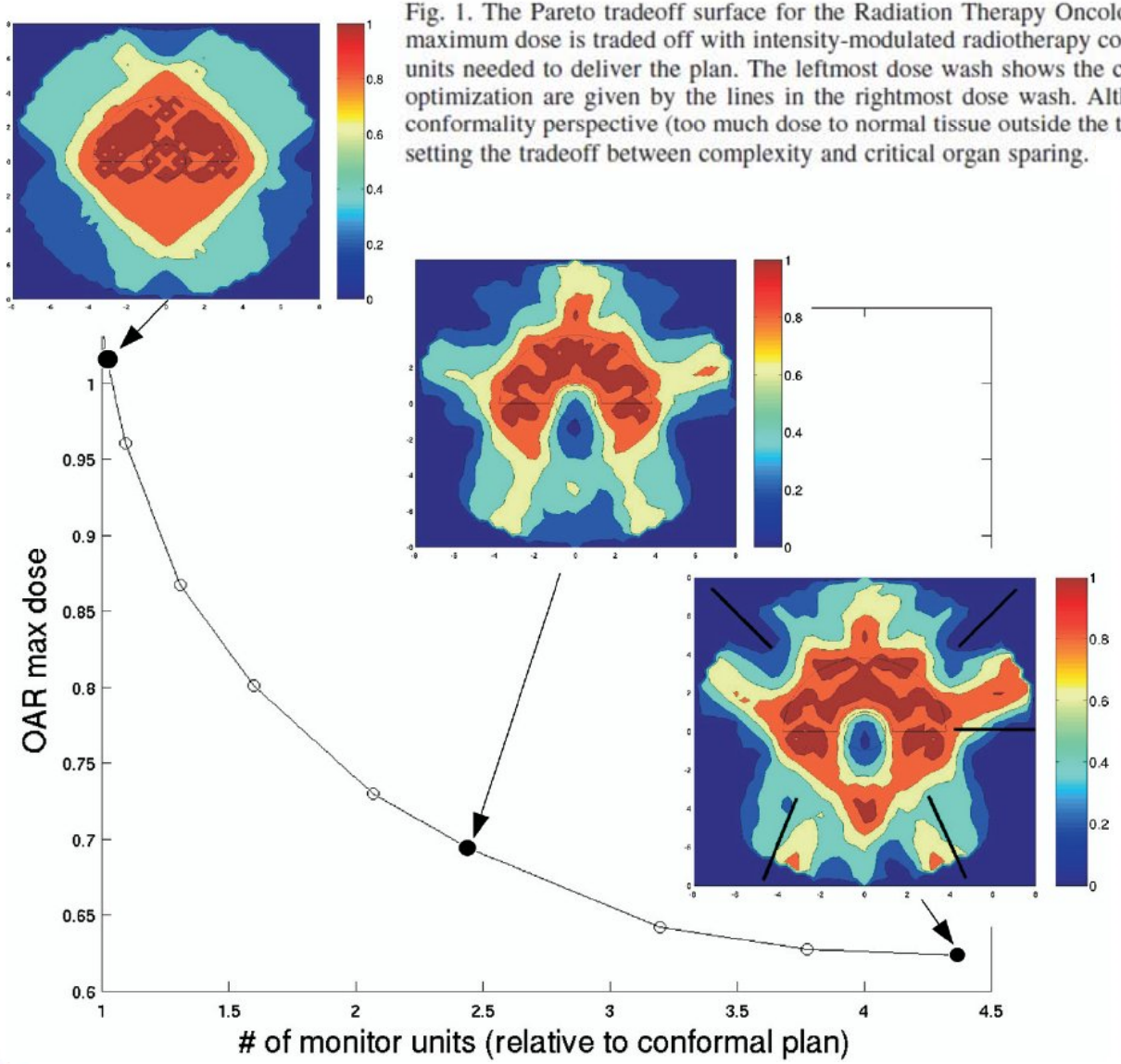
E-mail: katrin.teichert@itwm.fhg.de

Pareto fronts using multiple beam angle configurations

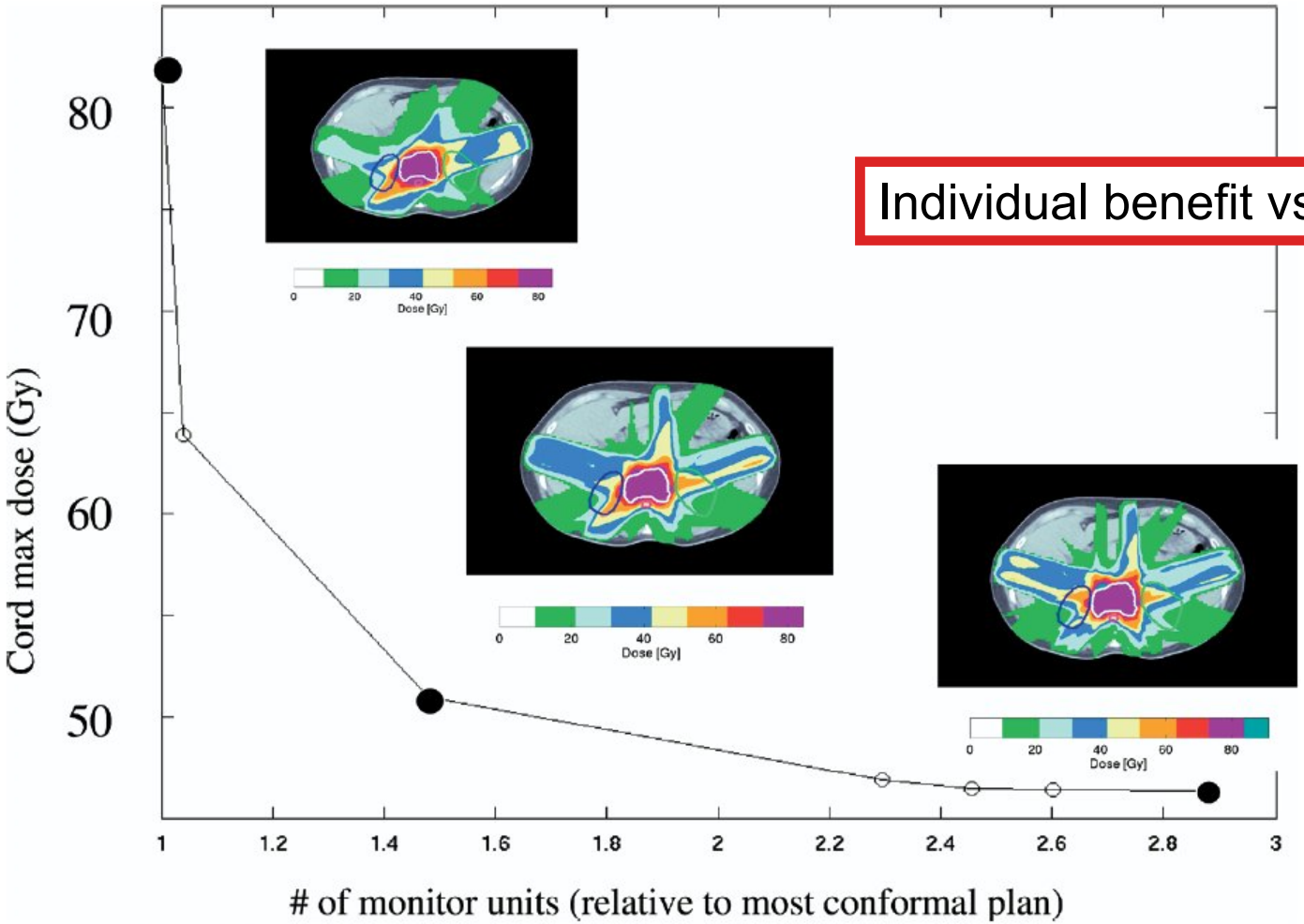
Phys.Med.Biol.56(2011) 3669-3684

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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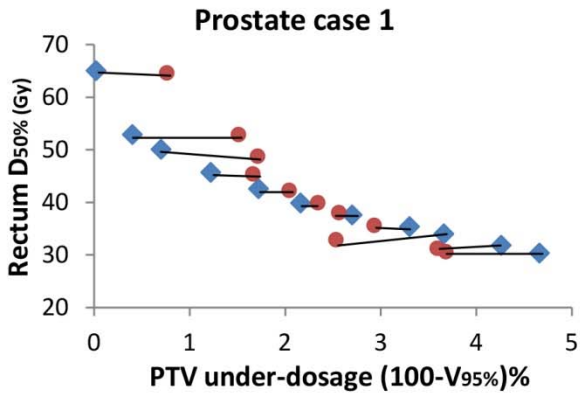
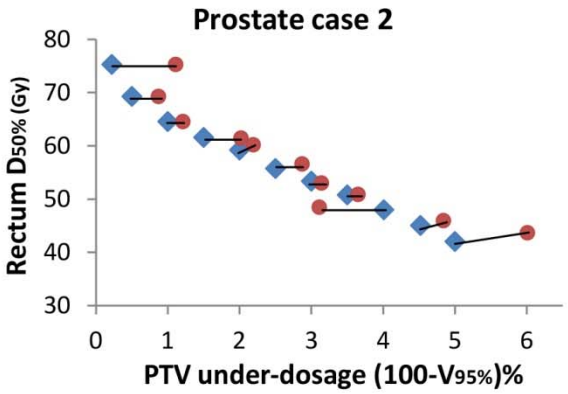
Limitations of this approach

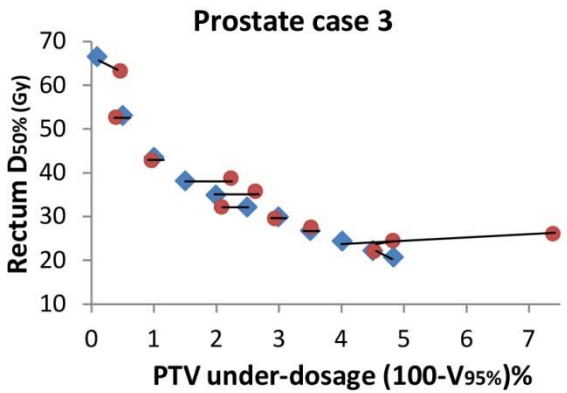
Difference between navigated and delivered plans?

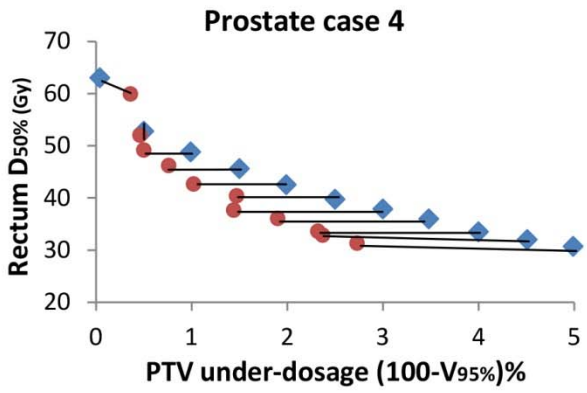
e.g. 5 prostate patients

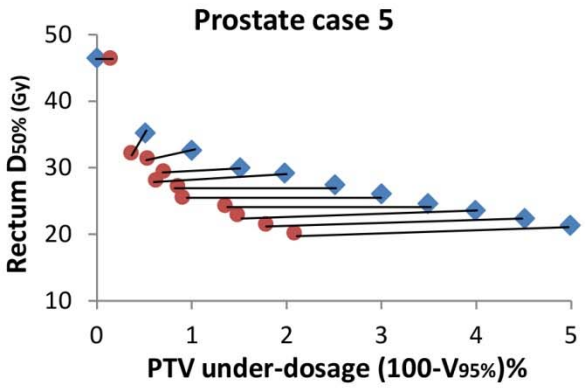
improvement was achieved partly by compromising other parameters, such as increasing doses to other OARs or by creating small “hotspots”











- Pareto plans
- Deliverable plans

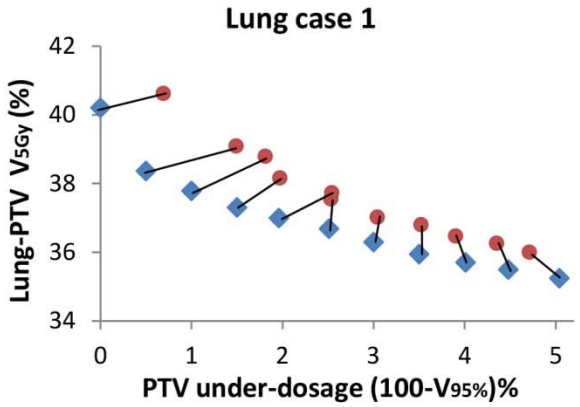
Limitations of this approach

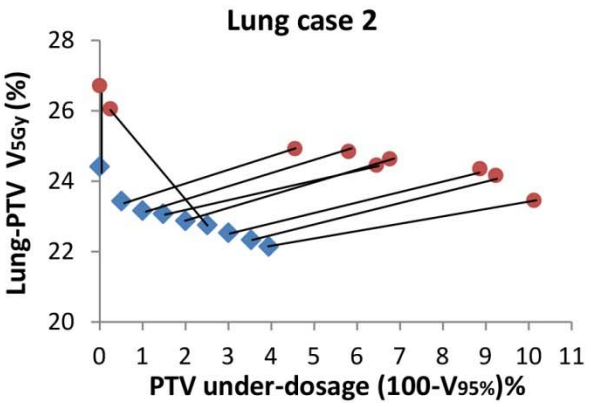
e.g. 5 lung patients

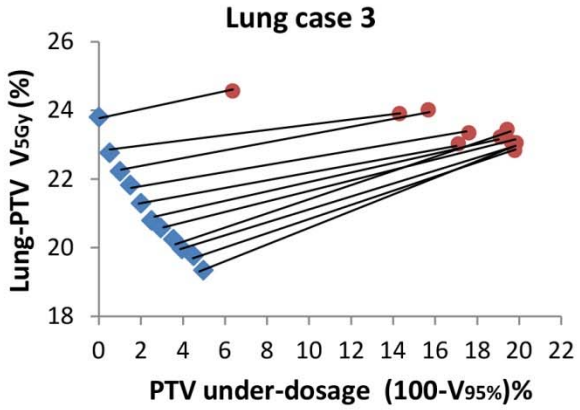
Deliverable plans systematically worse than pareto plans

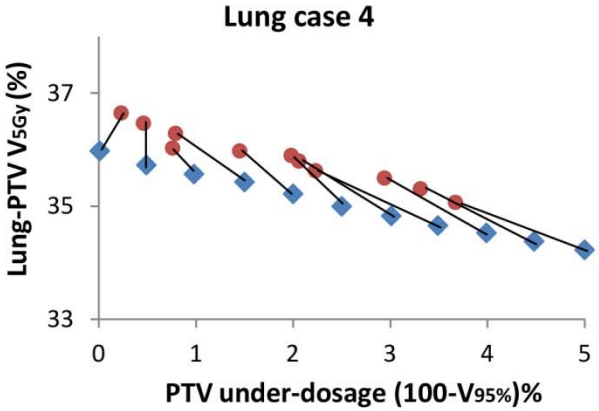
fluence-based treatment plans does not take into account the effect of lateral electron transport in the presence of heterogeneities

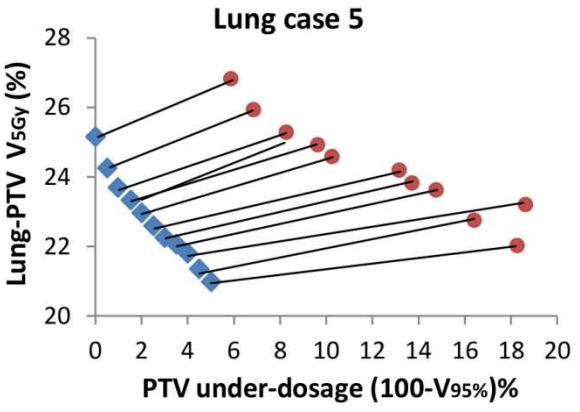
Small PTVs provided bigger differences











- 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.

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The doctor's perspective

Neil Burnet

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

ATP Barcelona 2017

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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 …

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 …

- And for really good IMRT you also need image guidance

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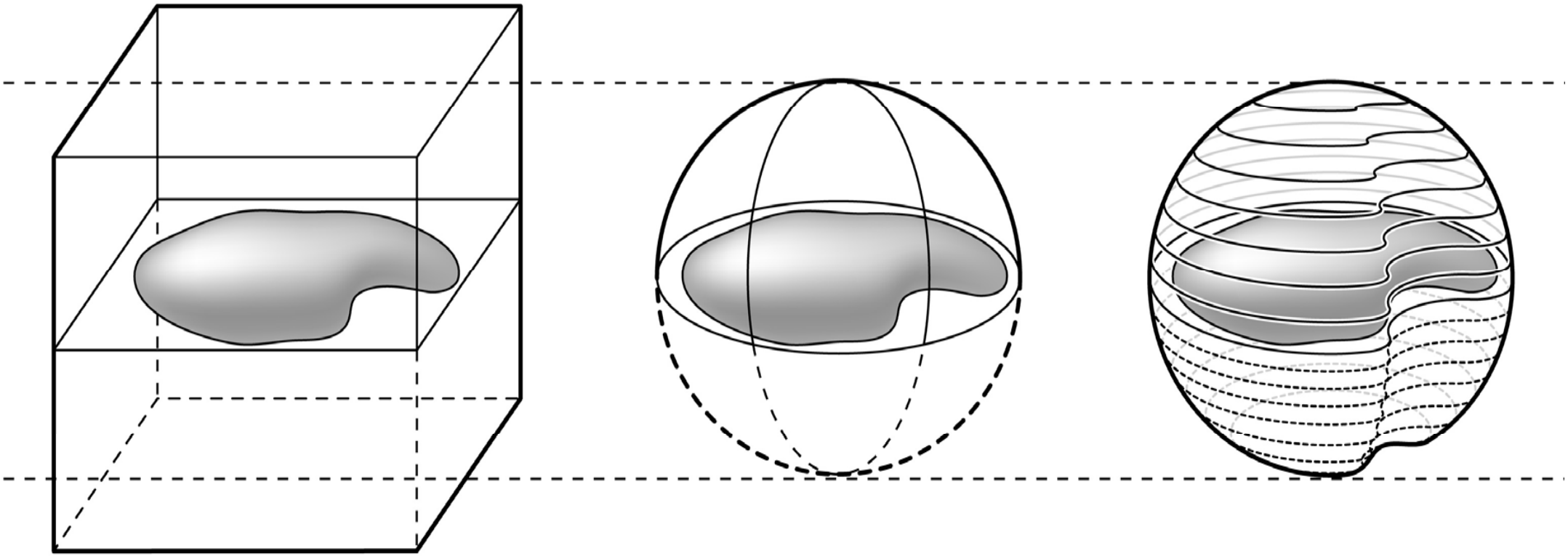
Treatment volumes compared



Conventional ‘square’ plan

3D CRT plan

IMRT plan

Treatment volumes compared

- Imaginative use of different beam and arc directions can sometimes improve IMRT plans

Treatment volumes compared

- Imaginative use of different beam and arc directions can sometimes improve IMRT plans

- The Mohawk arc !

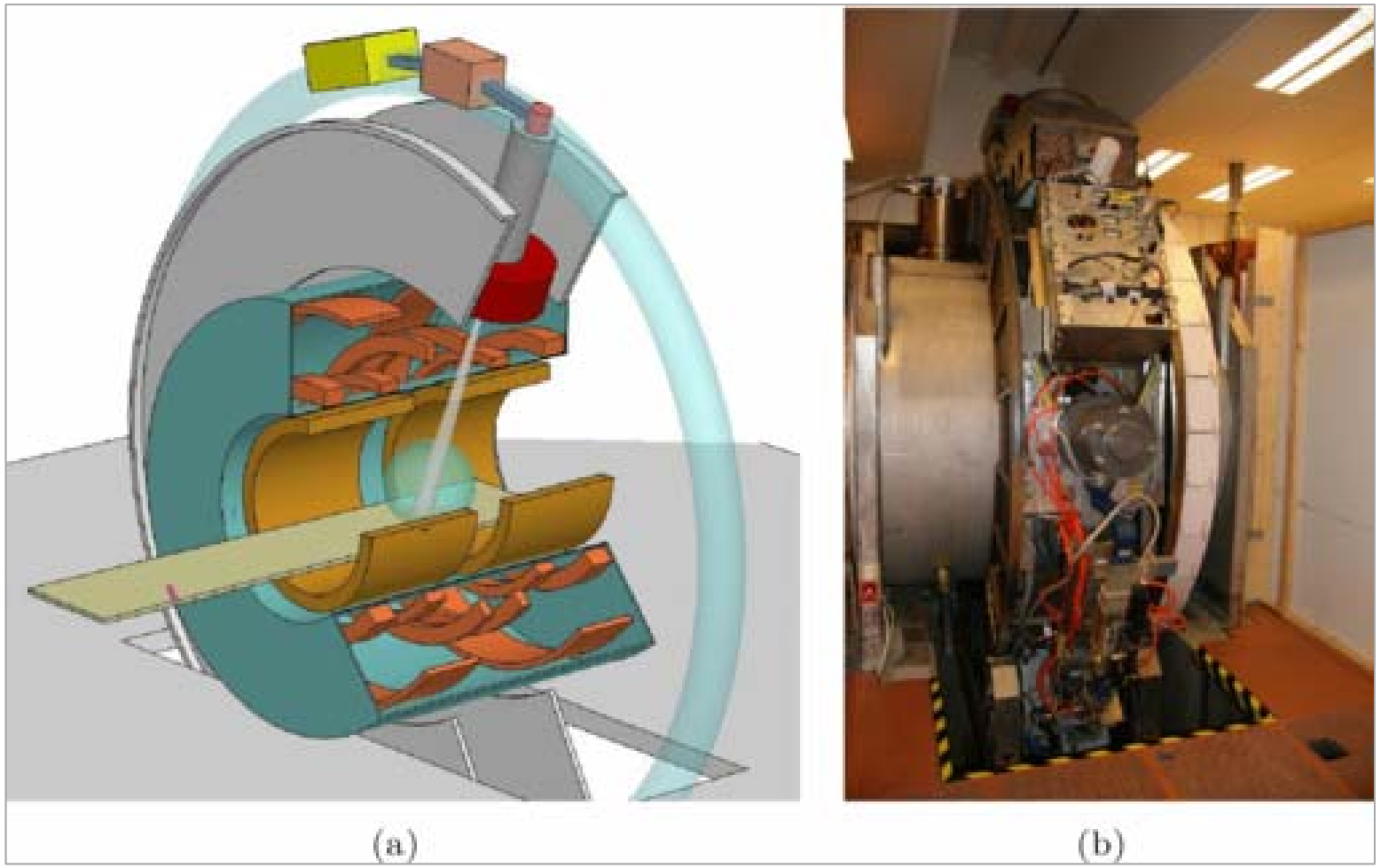
Treatment volumes compared

- 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

Image guidance - MR linac



Crijns S, Raaymakers B. From static to dynamic 1.5T MRI-linac prototype: impact of gantry position related magnetic field variation on image fidelity. *Phys Med Biol*. 2014 Jul 7;59(13):3241-7

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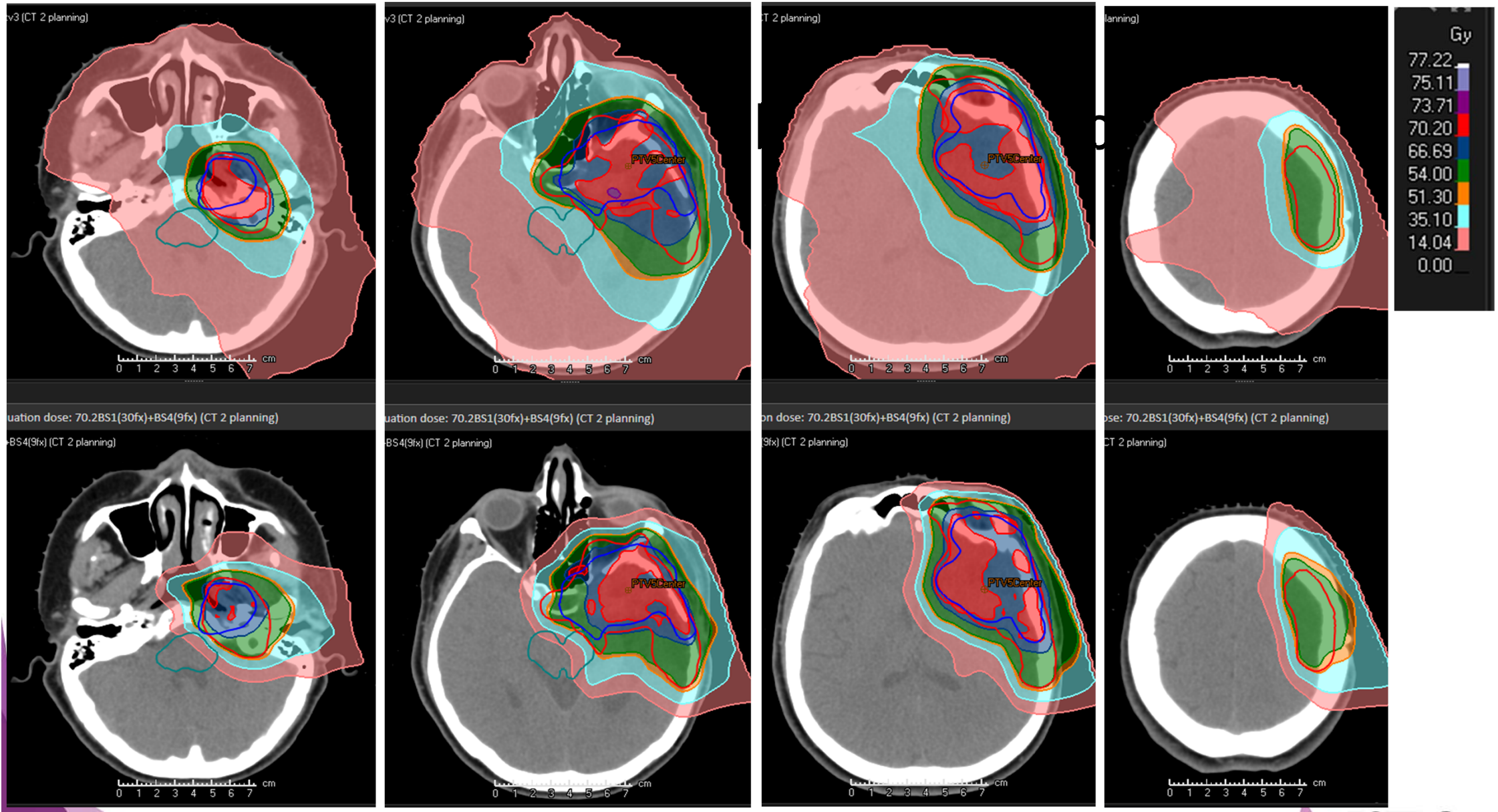
Proton Beam Therapy



- Much work still needed

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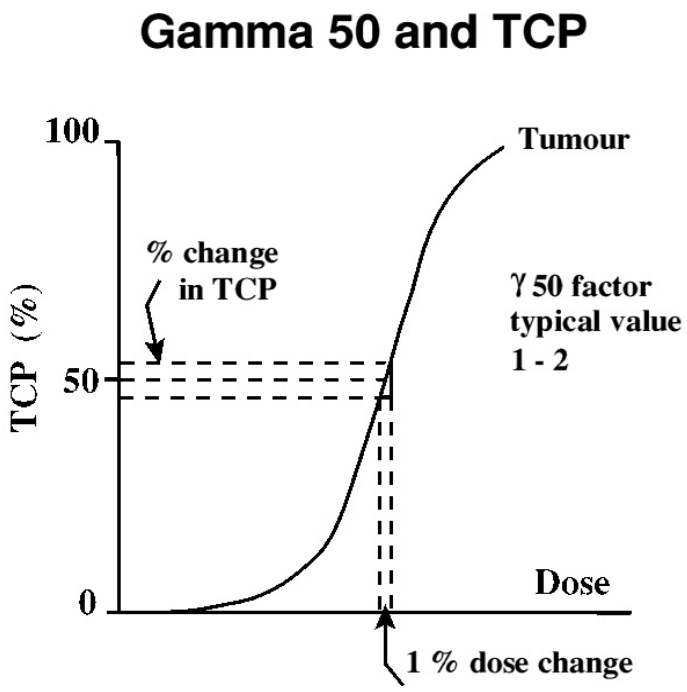
Small dose differences matter

- 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



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 his 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
- Discussions – like our course – are always valuable

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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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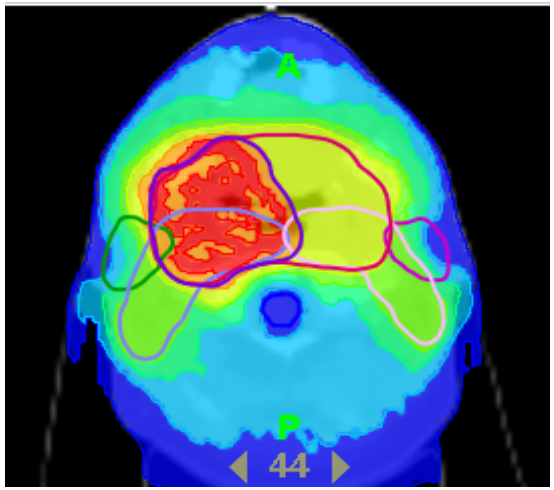
Multi-criteria optimisation (MCO)

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



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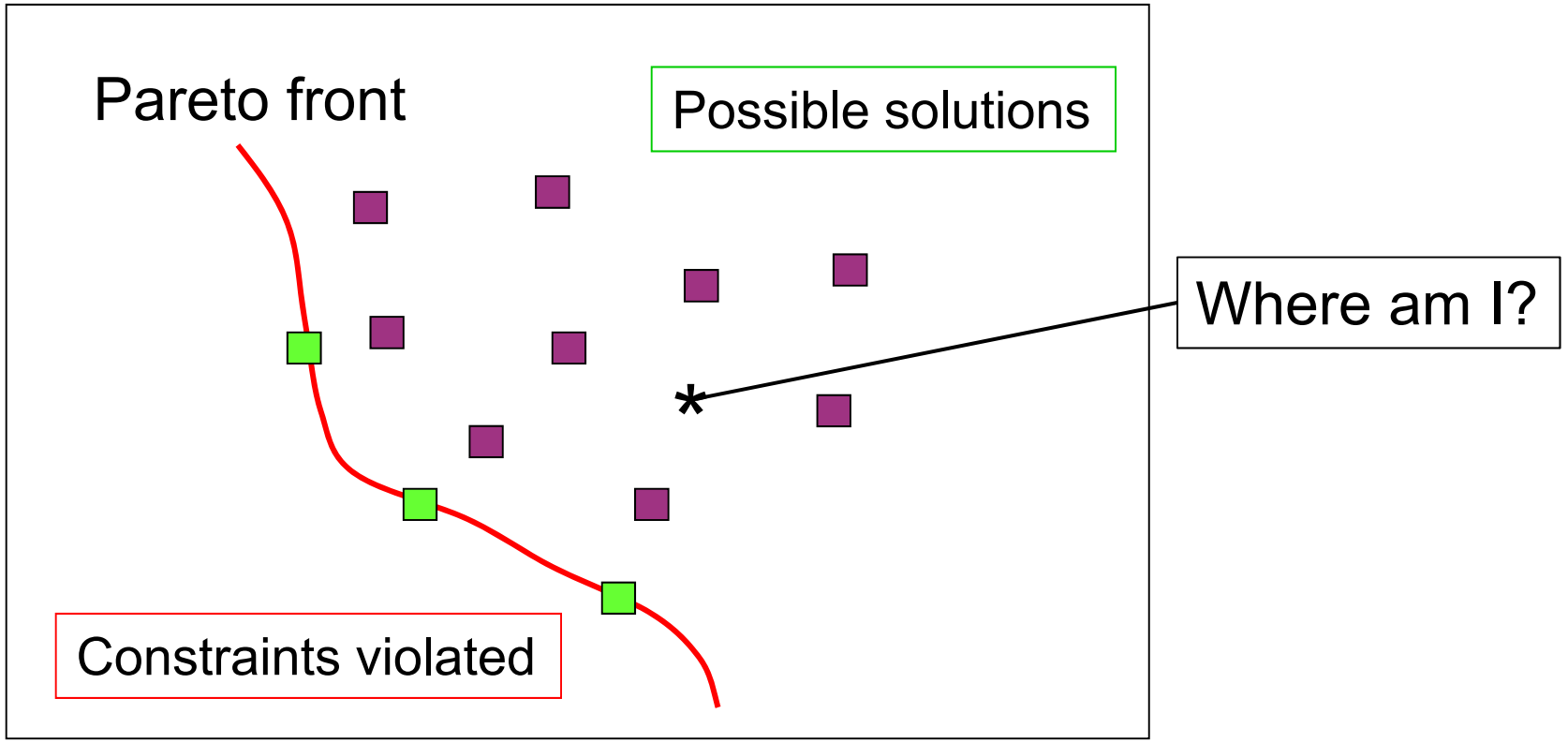
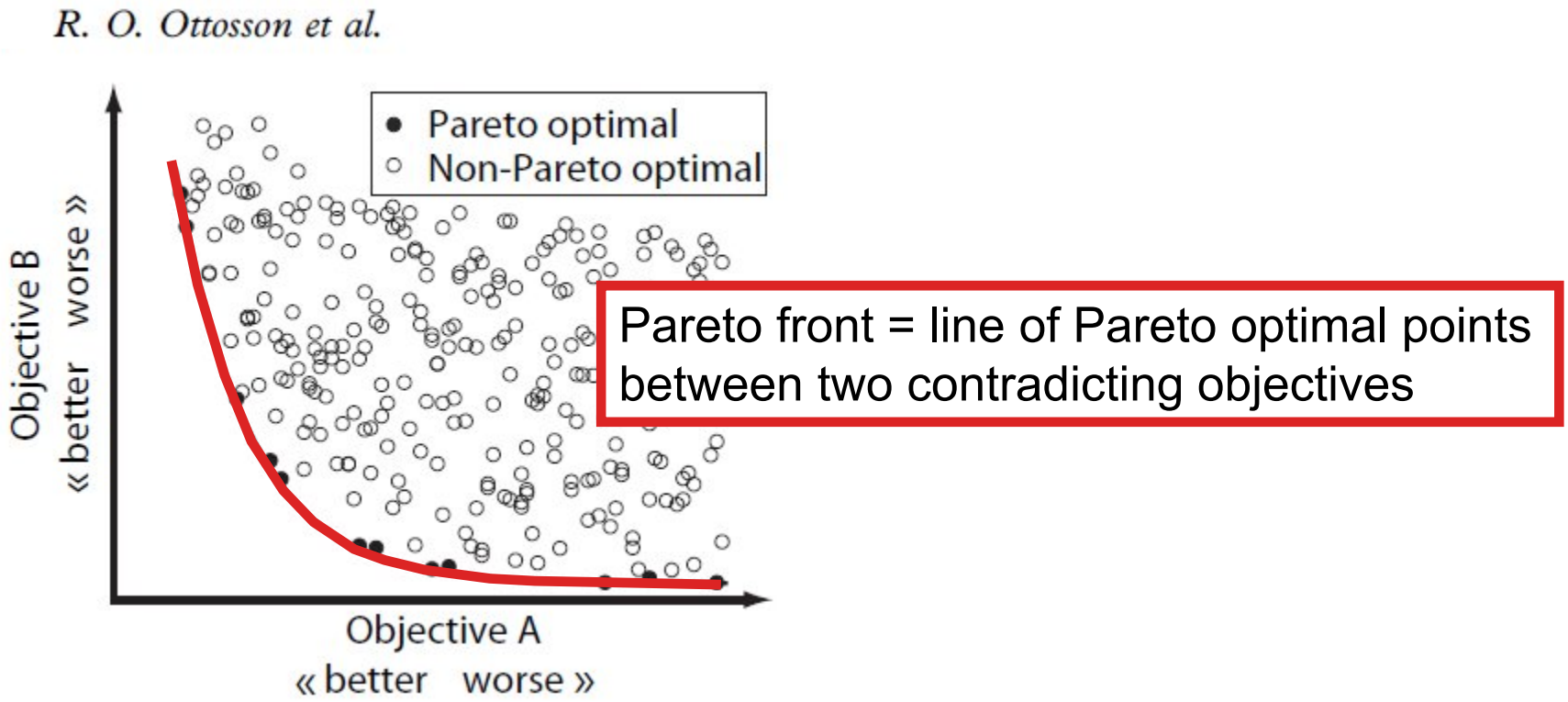
IMRT – Optimisation



Pareto front



Pareto front = line of Pareto optimal points between two contradicting objectives

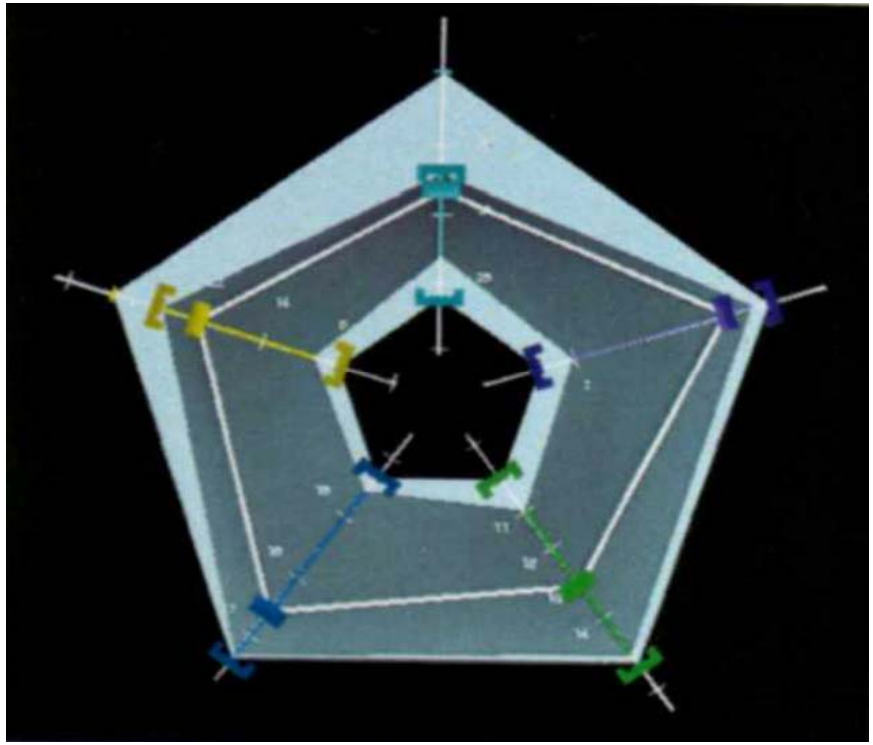
For two mutually contradicting objectives an endless number of solutions exists

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

Multi-criteria optimisation (MCO)

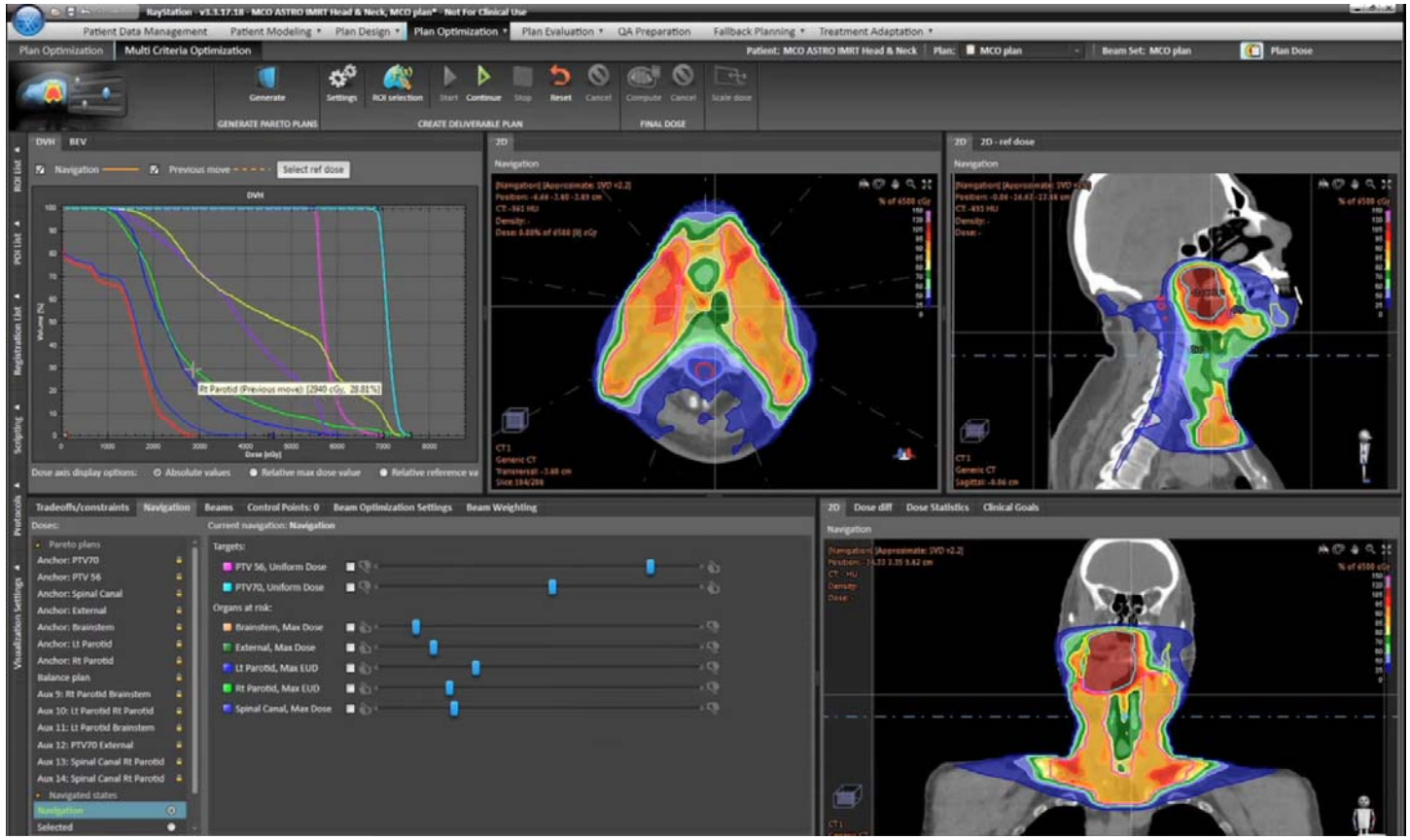
- Developmental version of MCO system
  - Shows normal tissue structures
  - Bounded limits on dose within solution space
- Real-time exploration possible
- Commercial systems becoming available
- Full value not yet known



Courtesy of Fraunhofer Institute

Multi-criteria optimisation (MCO)

- Clinical MCO system from RaySearch



- Possibility to refine individualisation of the plan

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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

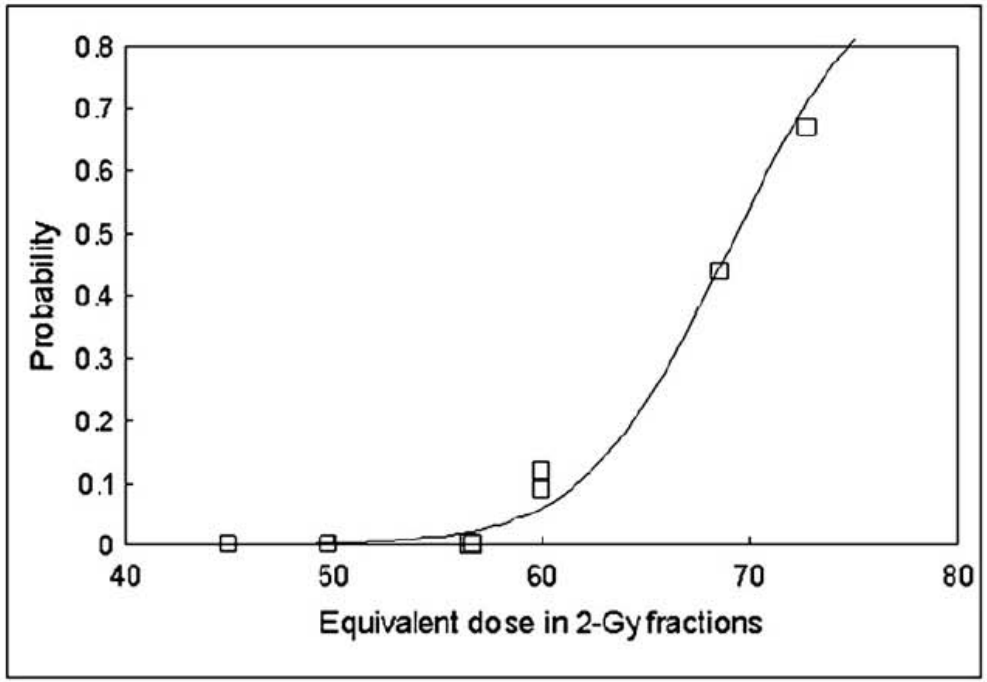


Fig. 1. The dose–response function for the myelopathy of the cervical spinal cord and data points (□) derived from Table 1. The probability of myelopathy was calculated from the data in Table 1, adjusted for estimated overall survival per (18).

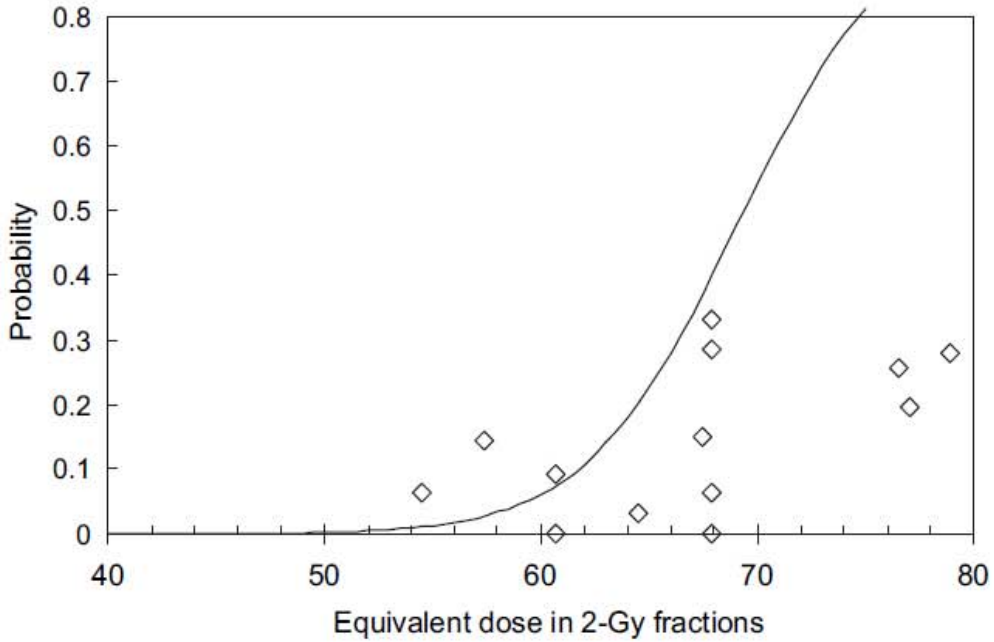


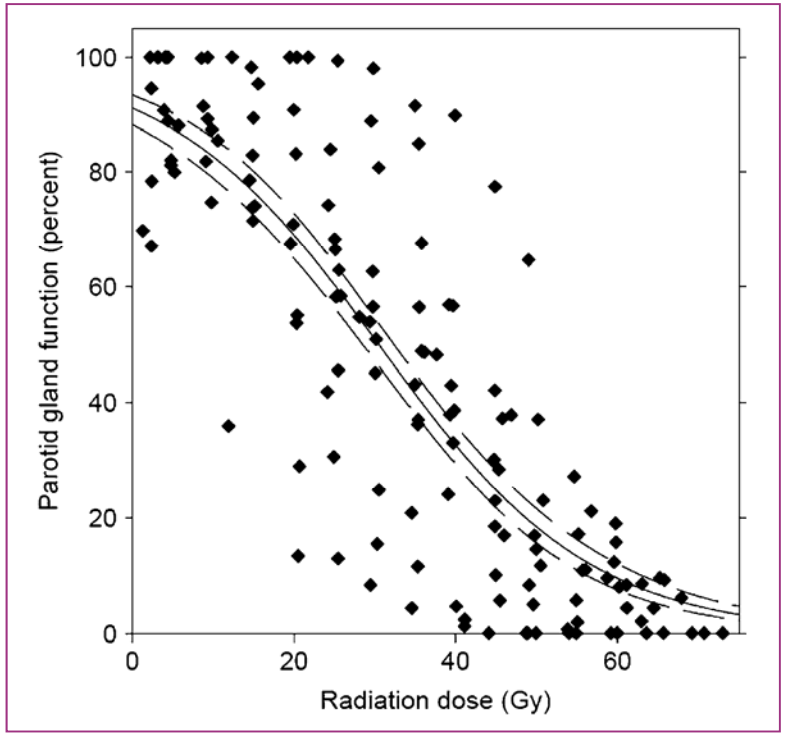
Fig. 2. The dose–response function for myelopathy of the cervical cord (solid line) and data points for the thoracic spinal cord (◇) derived from Table 2. The probability of myelopathy was calculated from the data in Tables 1 and 2, adjusted for estimated overall survival per (18).

- 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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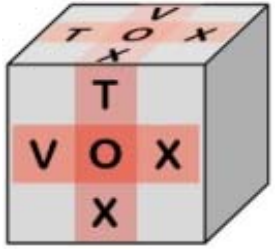
Dose accumulation

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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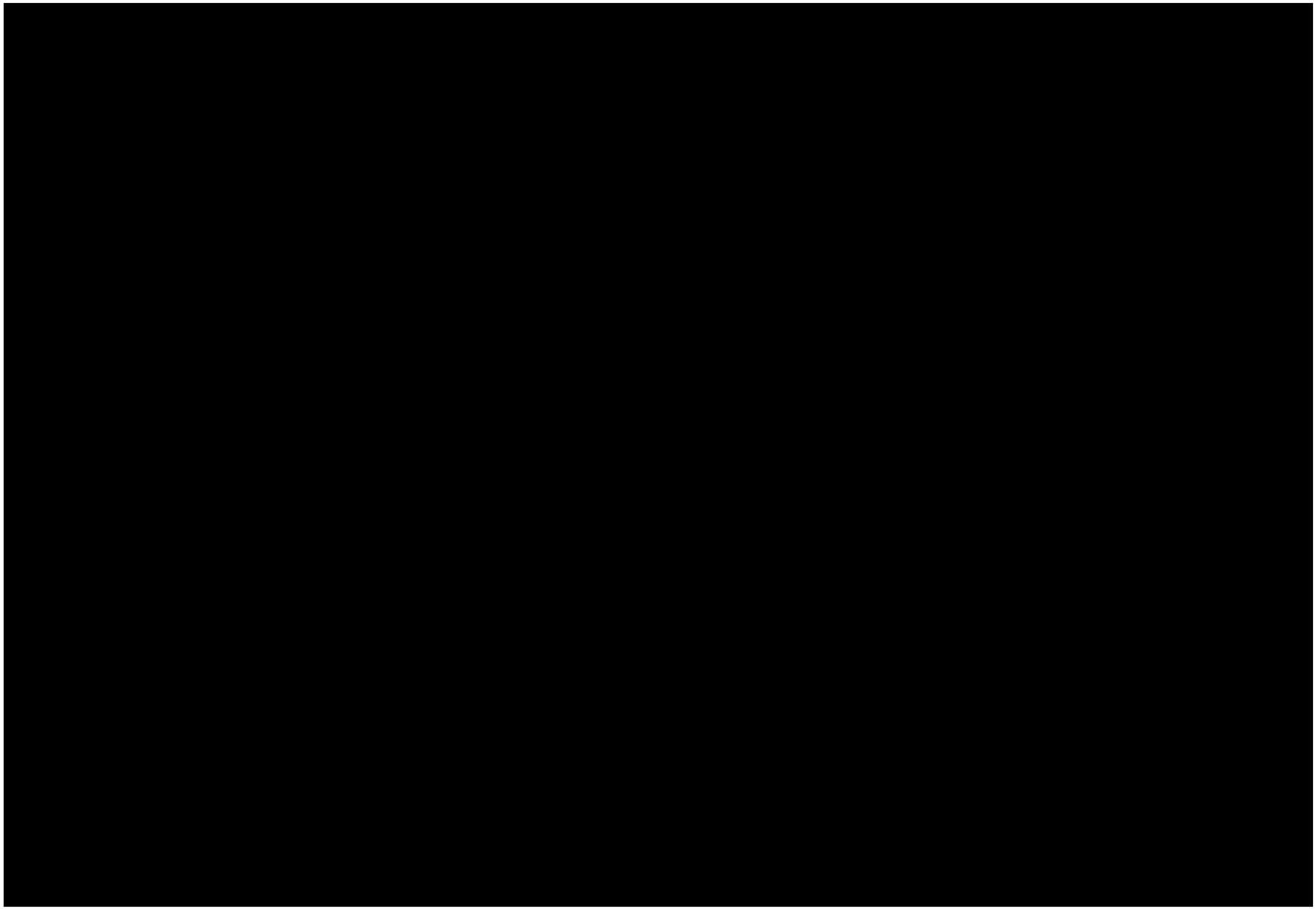
Dose accumulation



Time 01:12

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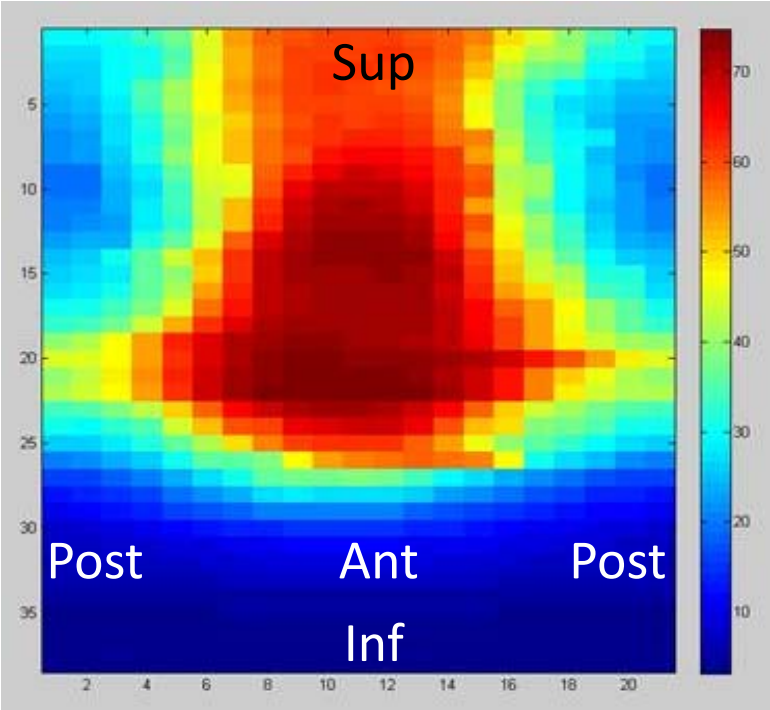
Dose accumulation

- Rectum dose-surface map (DSM) for prostate RT



Plan

- Early stage only …

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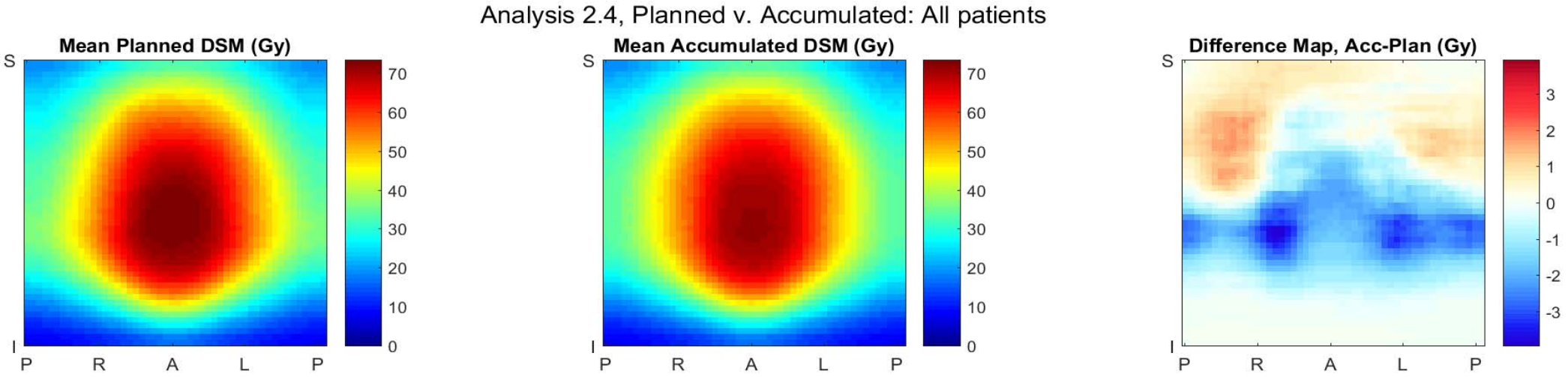
Planned vs Accumulated dose

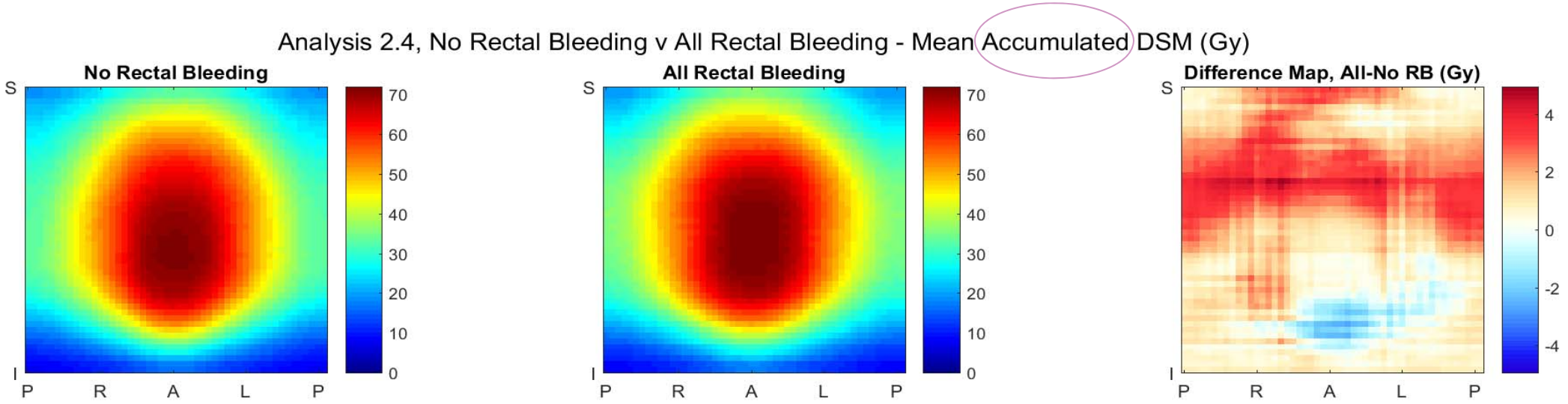
- Compare dose surface maps (DSMs)
  - Planned dose vs Accumulated dose (D_A)



  - Band of dose difference in upper half
  - Postero- lateral in rectal wall

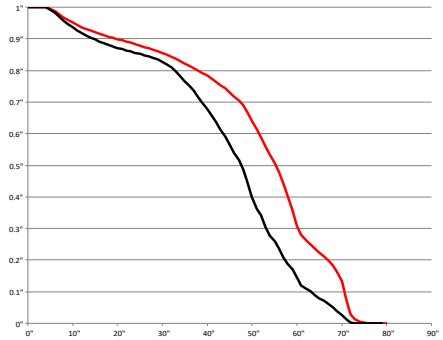
Accumulated dose DSMs

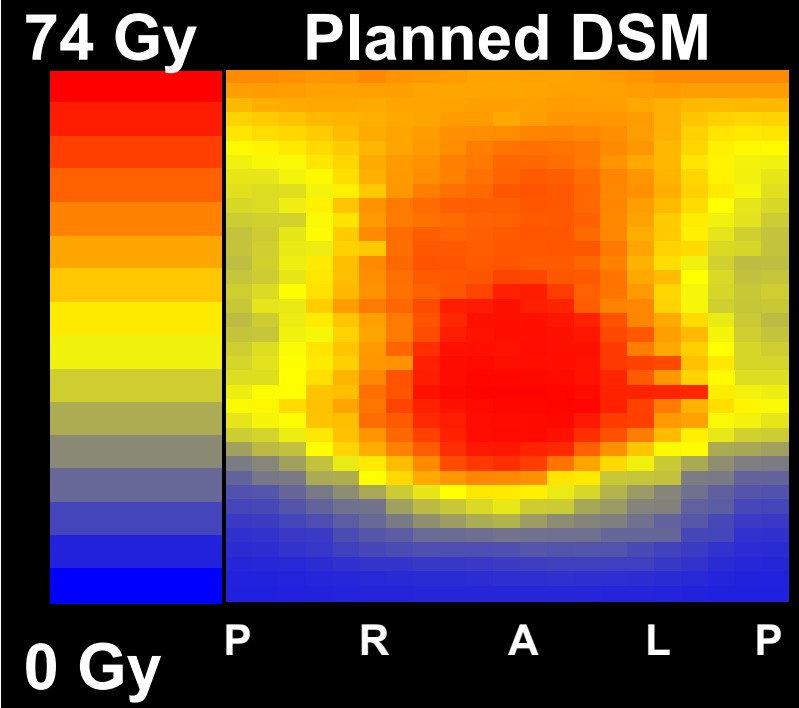
- Compare average D_A
  - No rectal bleeding vs All rectal bleeding

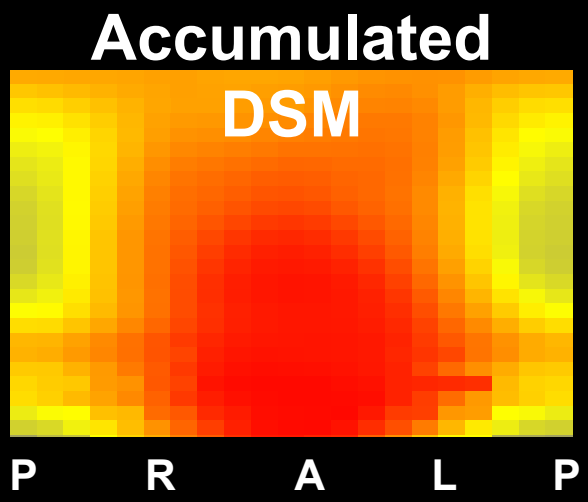


  - Band of dose difference in upper half
  - Includes lateral and posterior rectal wall

DSM for highest accumulated compared with planned







Median difference in dose **+1.7** Gy

Maximum increase in dose **+18.2** Gy

Maximum decrease in dose -2.8 Gy

Courtesy of Dr Jessica Scaife BJR 2015 Aug 11:20150243

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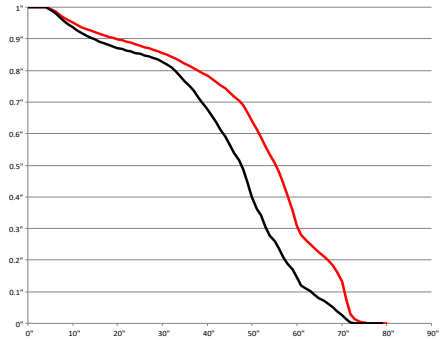
DSM for highest accumulated dose compared with planned



74 Gy

Planned DSM

Accumulated DSM

Difference DSM

+20 Gy

P R A L P

P R A L P

P R A L P

0 Gy

-20 Gy

Courtesy of Dr Jessica Scaife BJR 2015 Aug 11:20150243

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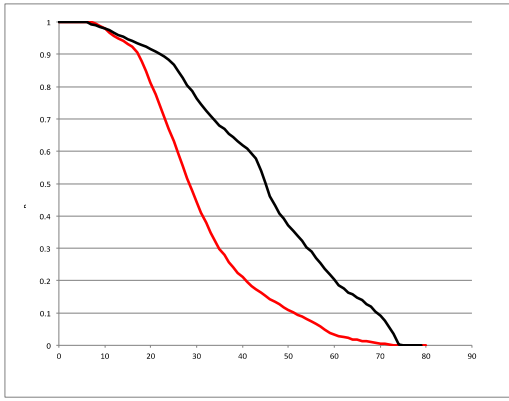
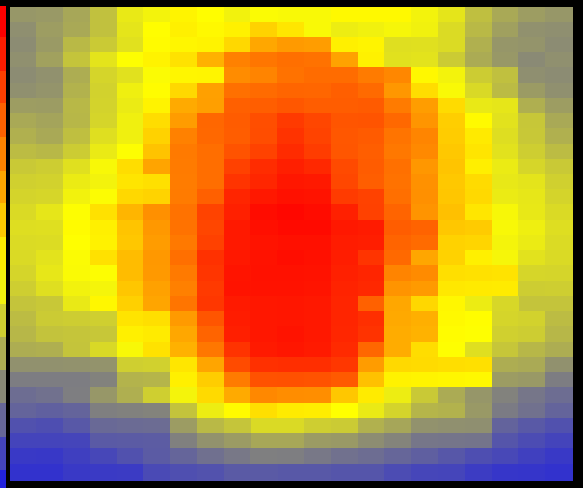
DSM for lowest accumulated compared with planned



74 Gy

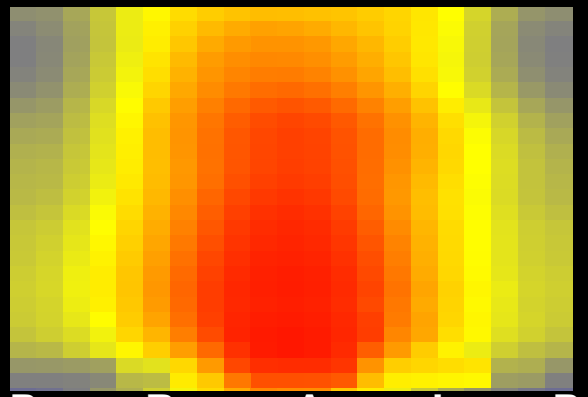
0 Gy

Planned DSM



P R A L P

Accumulated



P R A L P

Median difference in dose **-0.8** Gy

Maximum decrease in dose **-12.0** Gy

Maximum increase in dose +13.9 Gy

Courtesy of Dr Jessica Scaife BJR 2015 Aug 11:20150243

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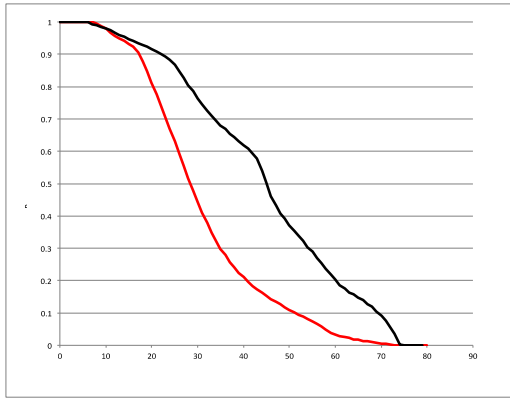
DSM for lowest accumulated compared with planned



74 Gy

0 Gy

Planned DSM

P R A L P

Accumulated

P R A L P

Median difference in dose -0.8 Gy

Maximum decrease in dose -12.0 Gy

Maximum increase in dose **+13.9** Gy

Courtesy of Dr Jessica Scaife BJR 2015 Aug 11:20150243

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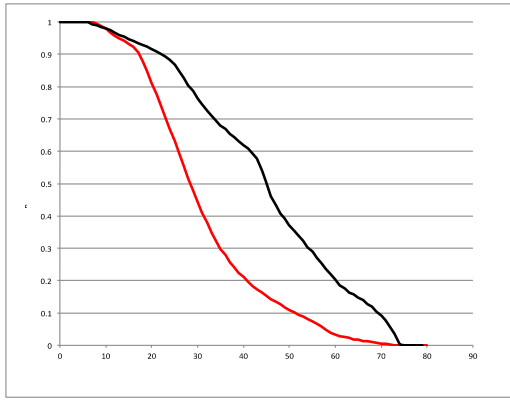
DSM for lowest accumulated dose compared with planned



74 Gy

Planned DSM

P R A L P

Accumulated

P R A L P

Difference DSM

+20 Gy

0 Gy

-20 Gy

Courtesy of Dr Jessica Scaife BJR 2015 Aug 11:20150243

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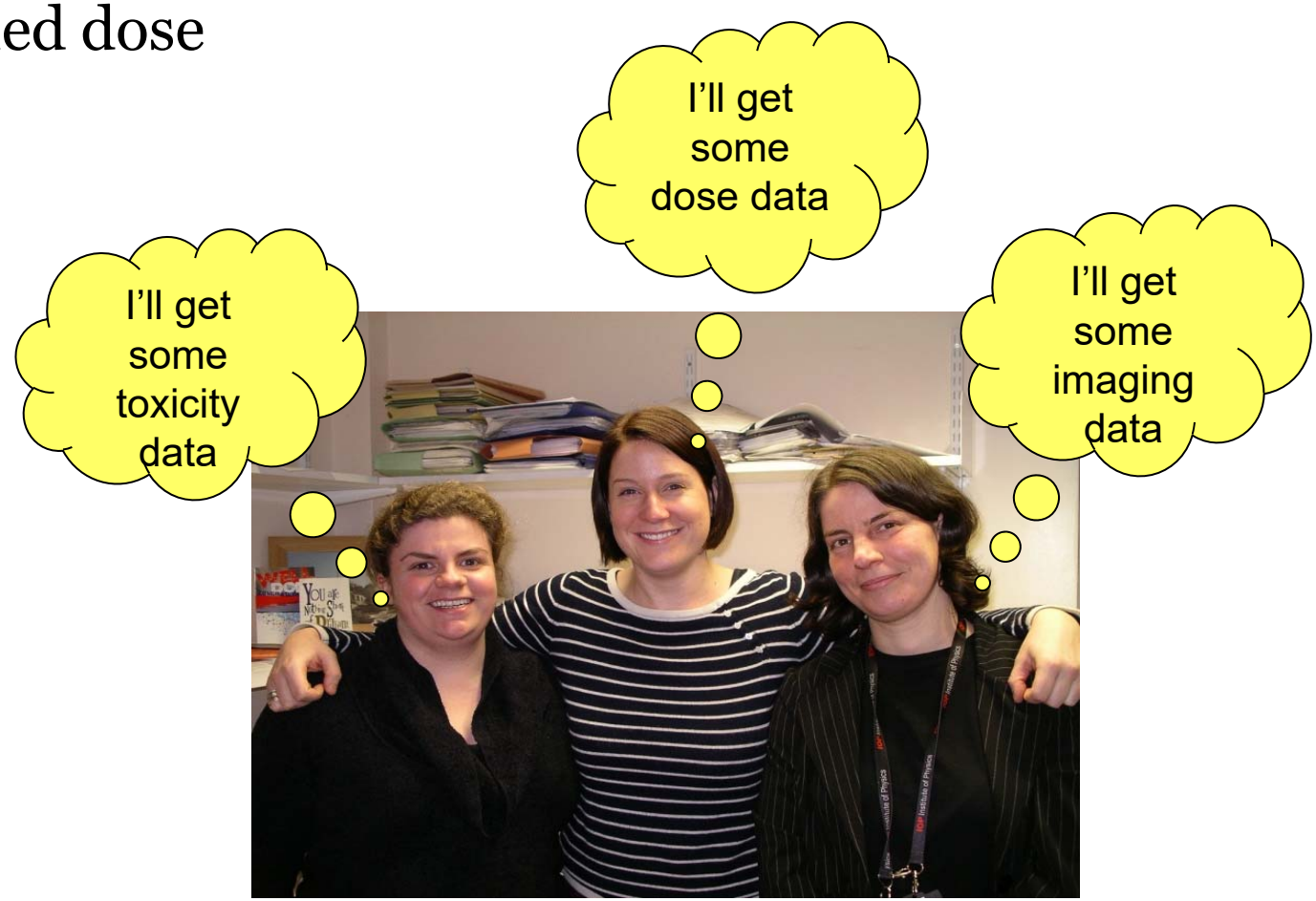
Dose accumulation

- 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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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

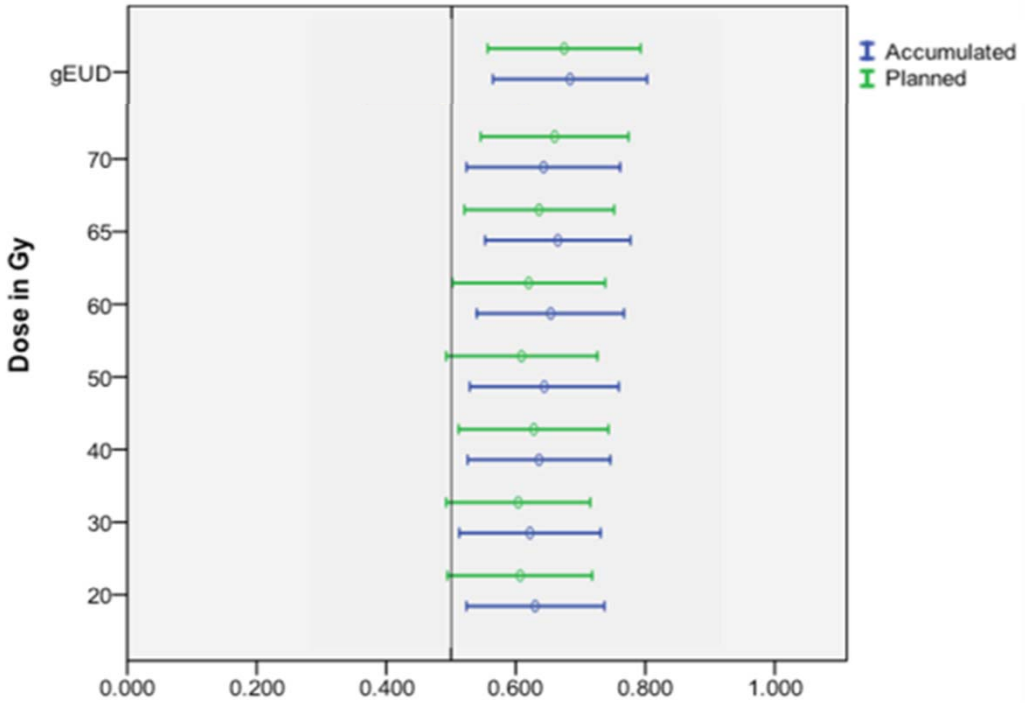
- Further computing developments will need to be incorporated into work flow

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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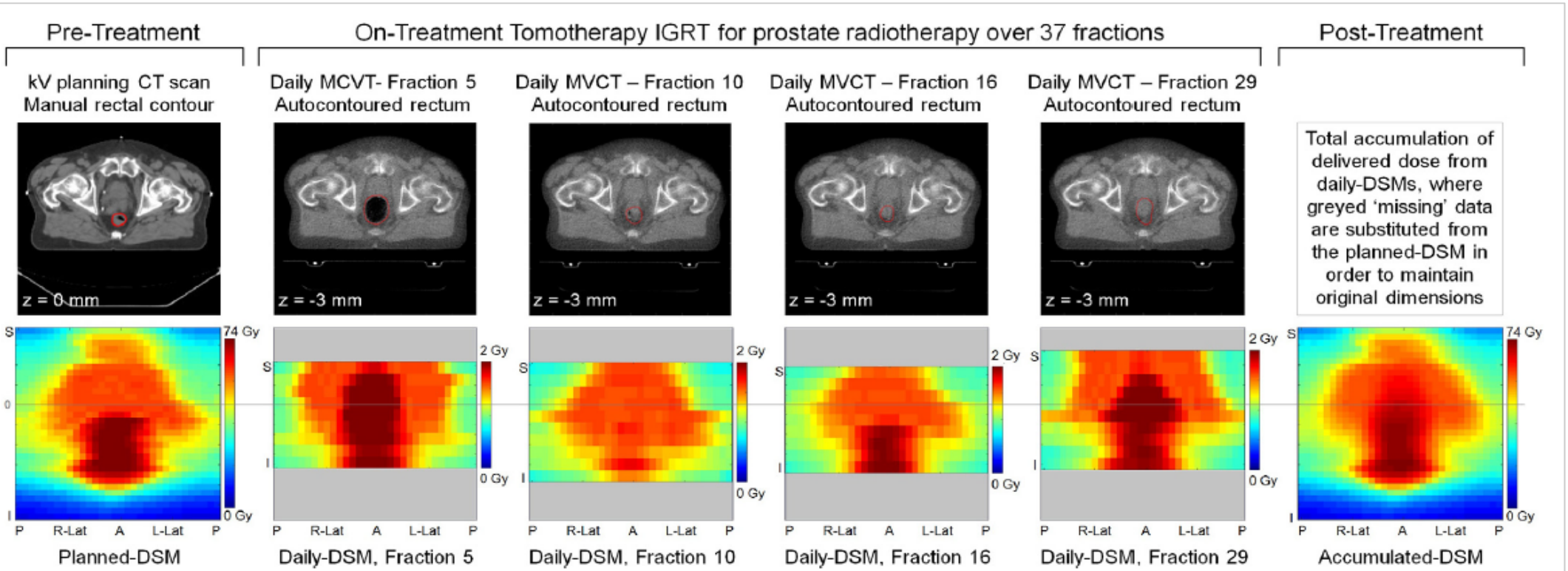

Fig. 1. Generation of planned, daily and accumulated dose surface maps.

- For rectal bleeding

Dose Level (Gy)	Mean AUC (Planned)	Mean AUC (Accumulated)
EUD	0.673	**0.682**

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Radiotherapy and Oncology 123 (2017) 466–471

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Prostate cancer radiotherapy

Delivered dose can be a better predictor of rectal toxicity than planned dose in prostate radiotherapy

L.E.A. Shelley [a,b,c,*], J.E. Scaife [a,d], M. Romanchikova [a,b], K. Harrison [a,f], J.R. Forman [a,e], A.M. Bates [a,d], D.J. Noble [a,d], R. Jena [a,d], M.A. Parker [a,f], M.P.F. Sutcliffe [a,c], S.J. Thomas [a,b], N.G. Burnet [a,d]

Conclusions: Dosimetric parameters extracted from accumulated DSMs have demonstrated stronger correlations with rectal bleeding and proctitis than planned DSMs.

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Individual variation in normal tissue sensitivity

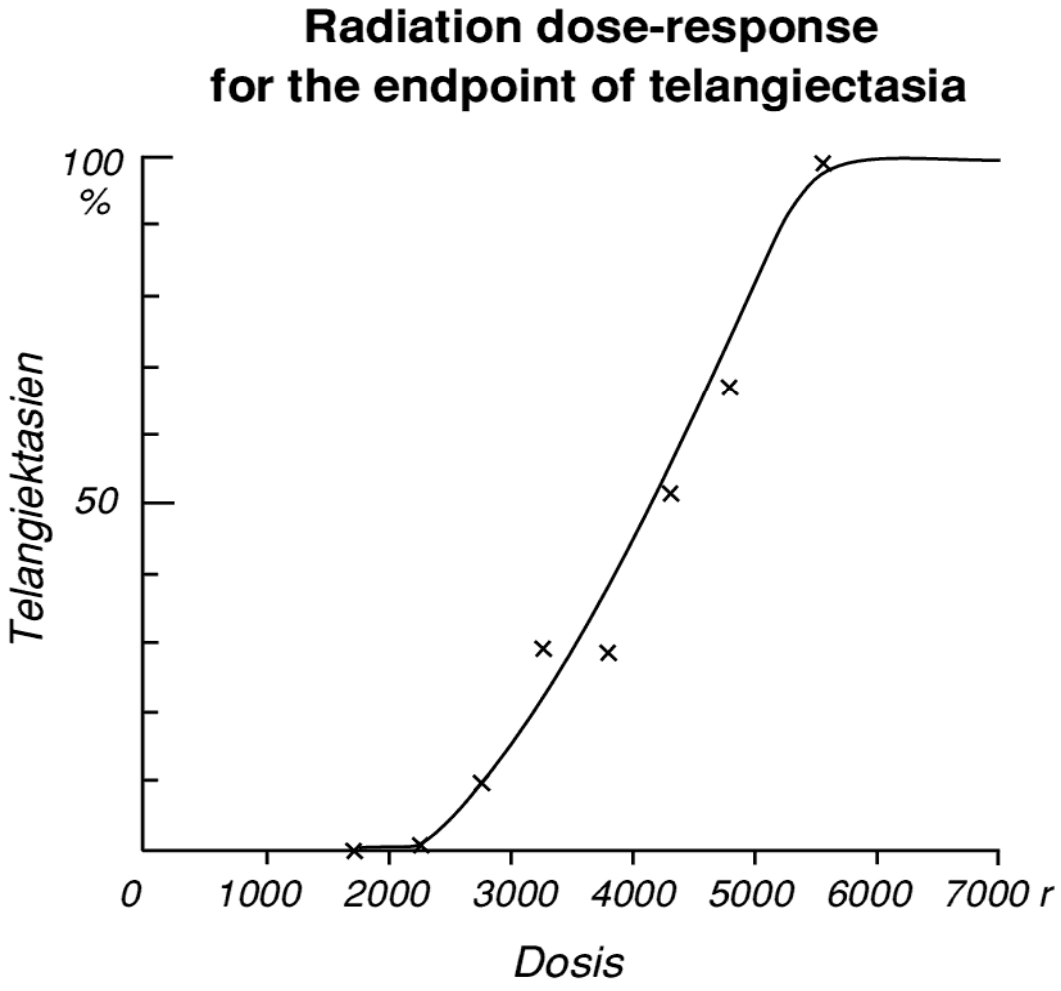
Individual variation in normal tissue sensitivity

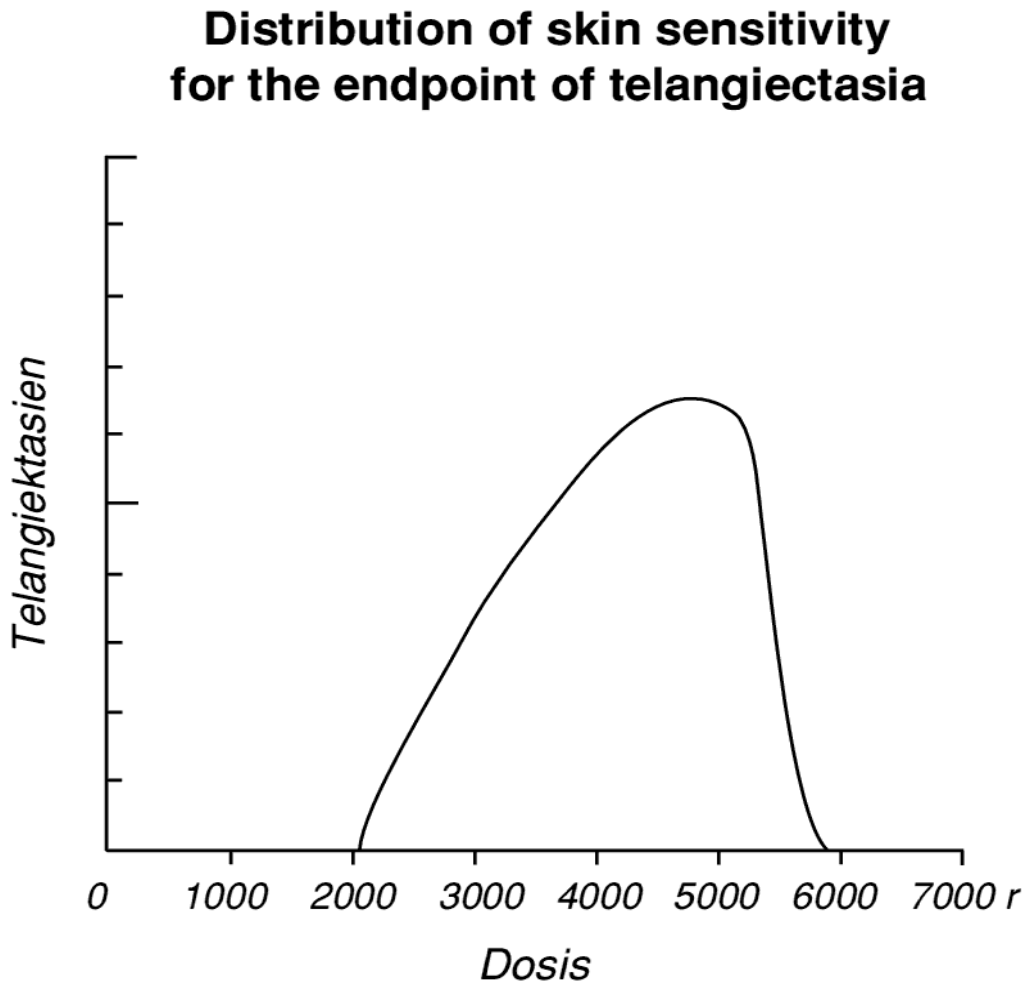
- First formally described in 1936 by Holthusen
  - Original of the sigmoid dose response curve

- Matches clinical experience since

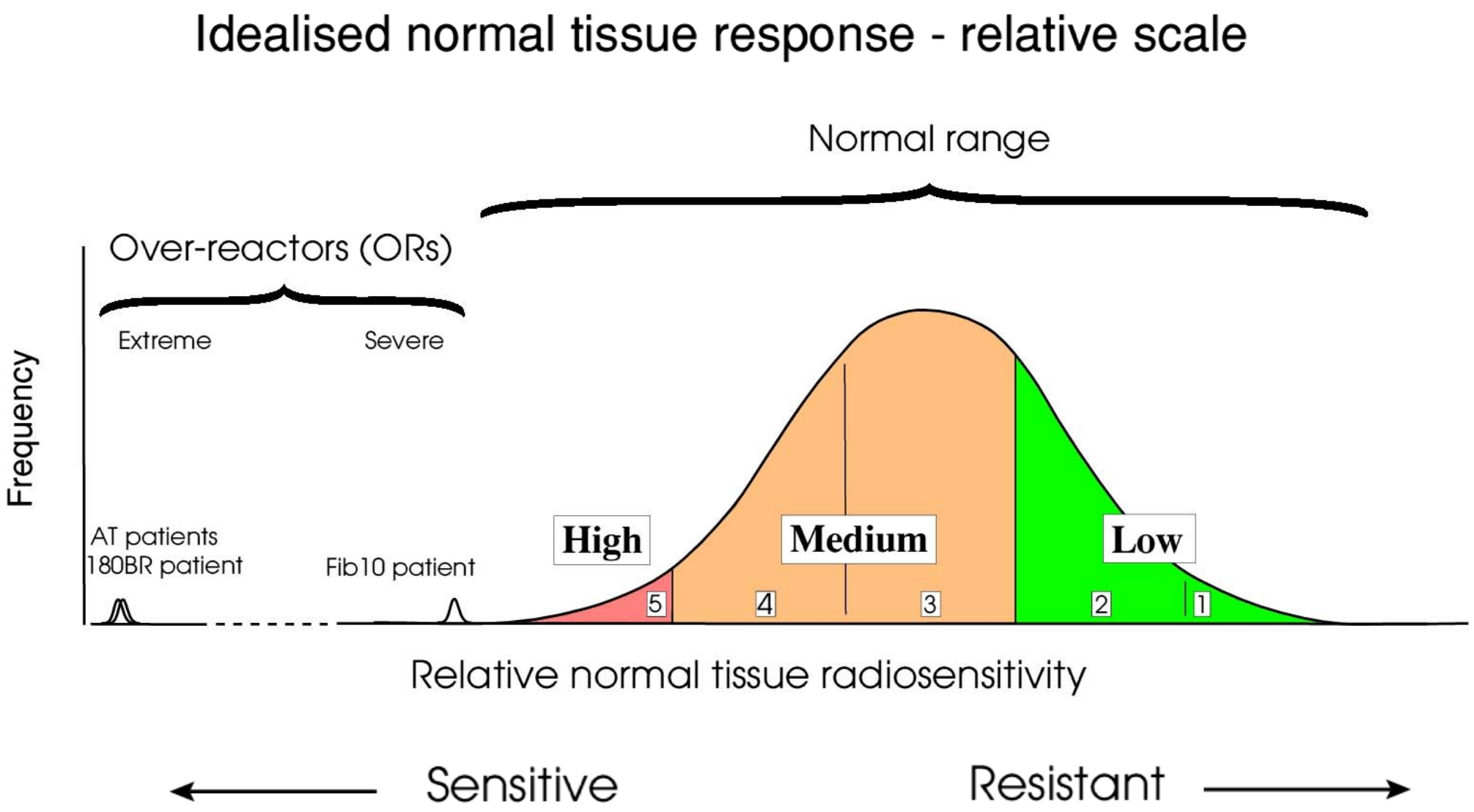
Individual variation in normal tissue sensitivity

Holthusen - Strahlentherapie & Onkologie 1936





Individual variation in normal tissue sensitivity



Individual variation in normal tissue sensitivity

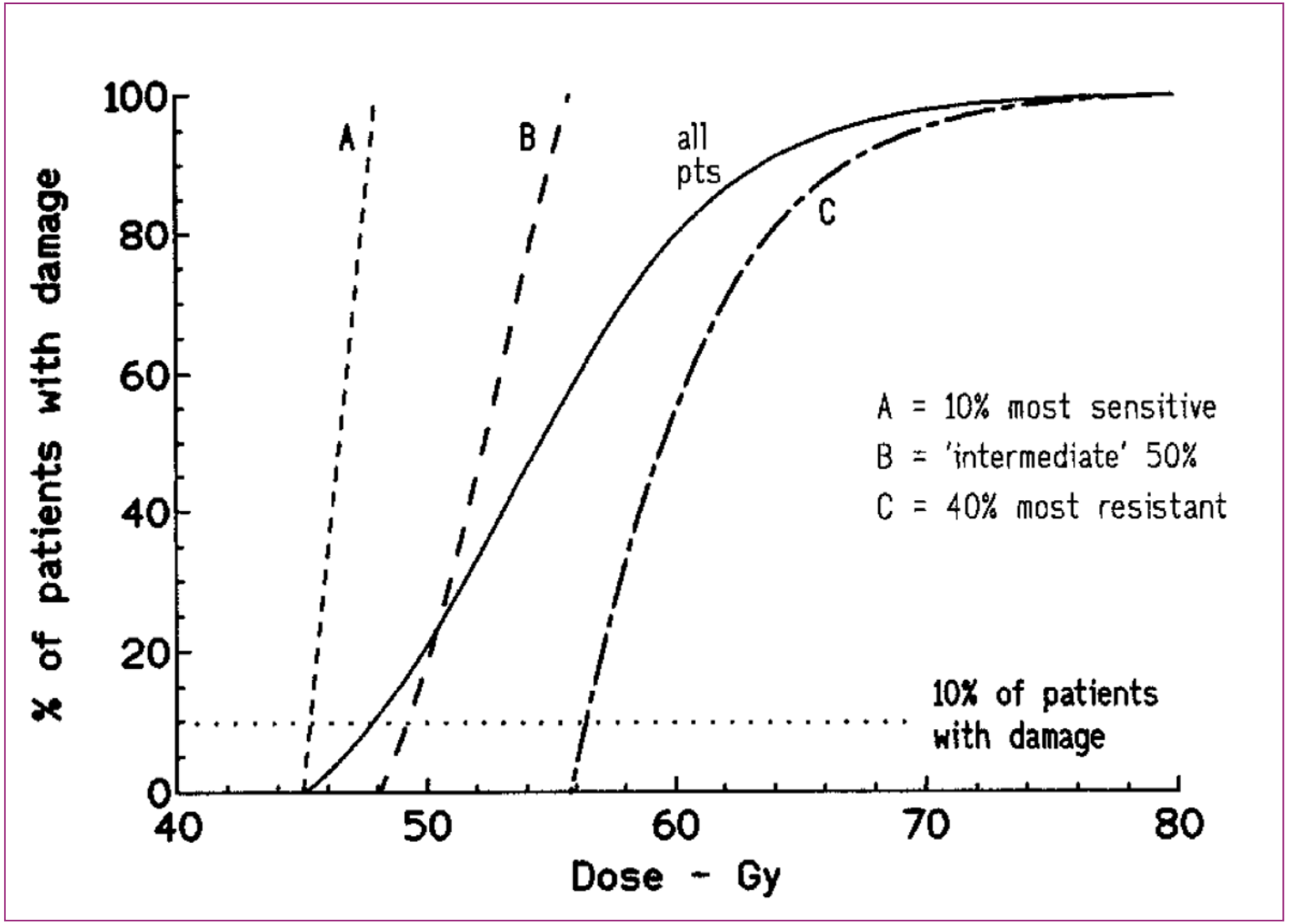
- Variation in response harder to observe with mega-voltage beams because of skin sparing

- 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, to produce more & better dose response data

Individual variation in normal tissue sensitivity

- Example data
- Skin telangiectasia



- Data from Ingela Turesson, Göteborg

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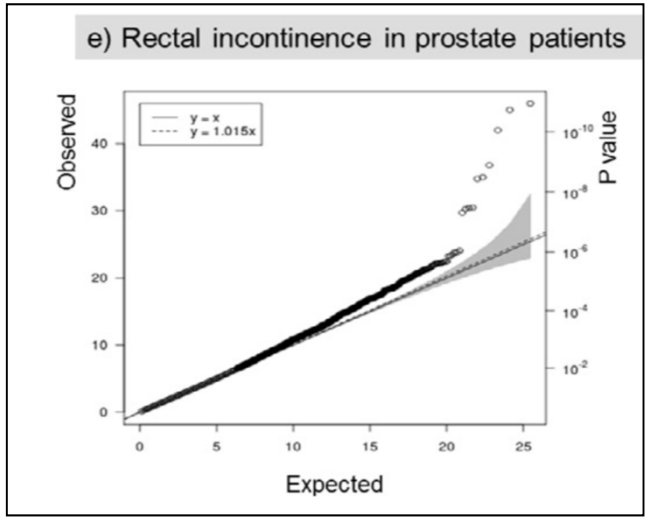
Individual variation in normal tissue sensitivity

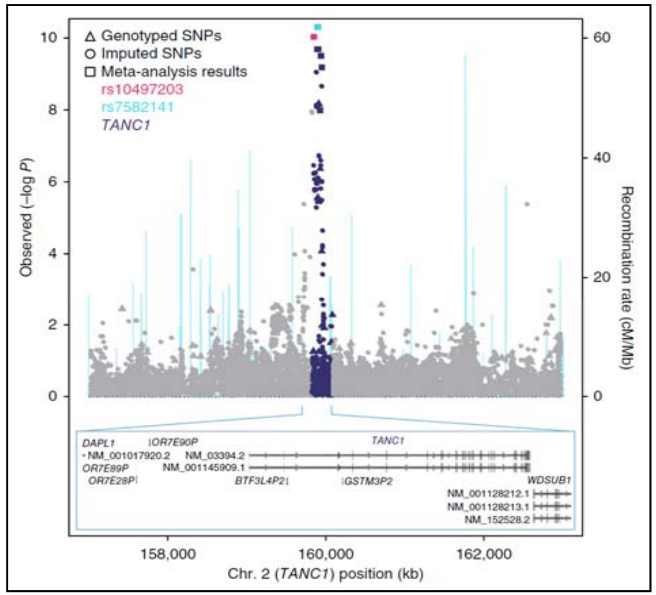
- Definite evidence that *normal* genetic variation is linked to variation in tissue response or toxicity
- Major developments in last 3 years
- Not yet ready for clinical application

Individual variation in normal tissue sensitivity

- Radiogenomics of normal tissue toxicity
- Definite evidence of true association between common genetic variants and toxicity [1]



- GWAS in prostate cancer [2]
- Variation at 1 locus linked to toxicity
- $P = 4.6 \times 10^{-11}$



1. Barnett GC et al. Radiother Oncol 2014; 111(2): 178-185
2. Fachal L et al. Nature Genetics 2014 Aug; 46(8): 891-4

Individual variation in normal tissue sensitivity

Radiotherapy and Oncology 2016 Dec;121(3):431-439.

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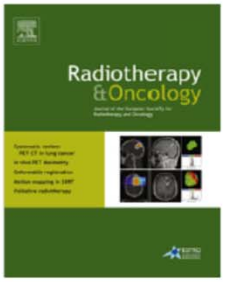

Original article

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

- Andreassen CN et al. for International Radiogenomics Consortium
- Convincingly shows significant association between specific allele in *ATM* gene and increased risk of normal tissue toxicity from RT

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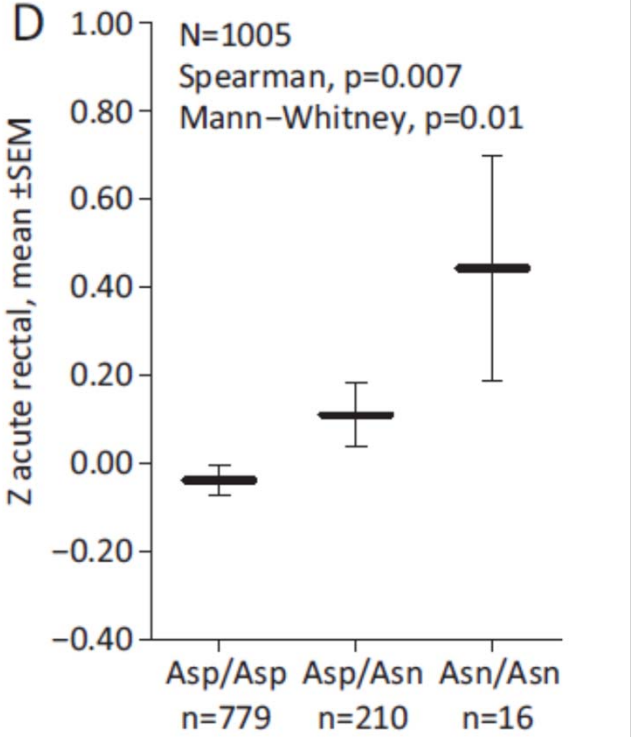
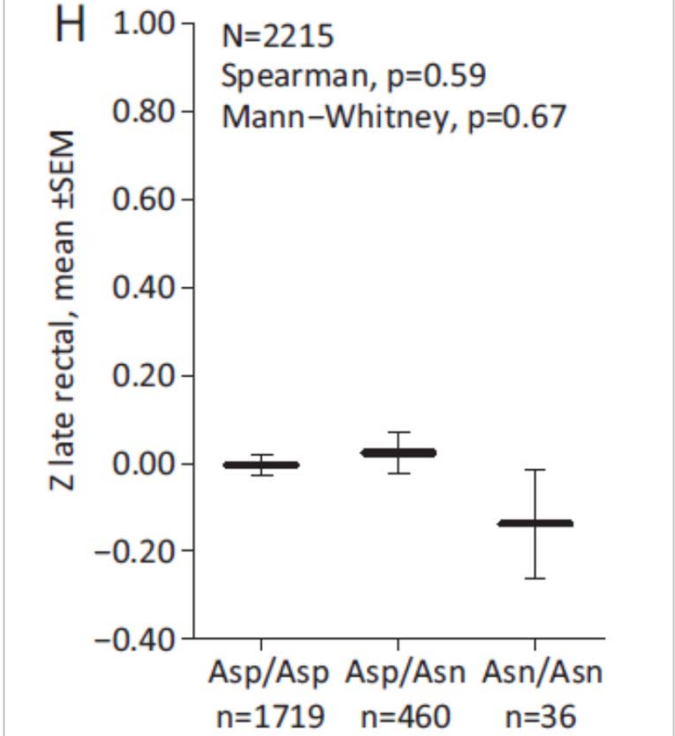
Synergy from physics and biology

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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Individual variation in normal tissue sensitivity

- Much work still do to identify a ‘signature’ that might be useable clinically

- Objective is to ***combine*** individual normal tissue sensitivity measure with individual physical dose plan
  - Biology meets physics

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 develops the concept of individualisation (or personalisation) even more
  - Biology meets more 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%

Scaife JE et al. *Brit J Radiol.* 2015 ; 88: 20150172

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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 – getting more probabilistic
- Small differences make a difference
- Ultimately we are working towards improving patients' outcomes

Doctor's perspective

Better radiotherapy for our patients – a real **team effort**

Our first IG-IMRT patient - 31st October 2007

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Extras

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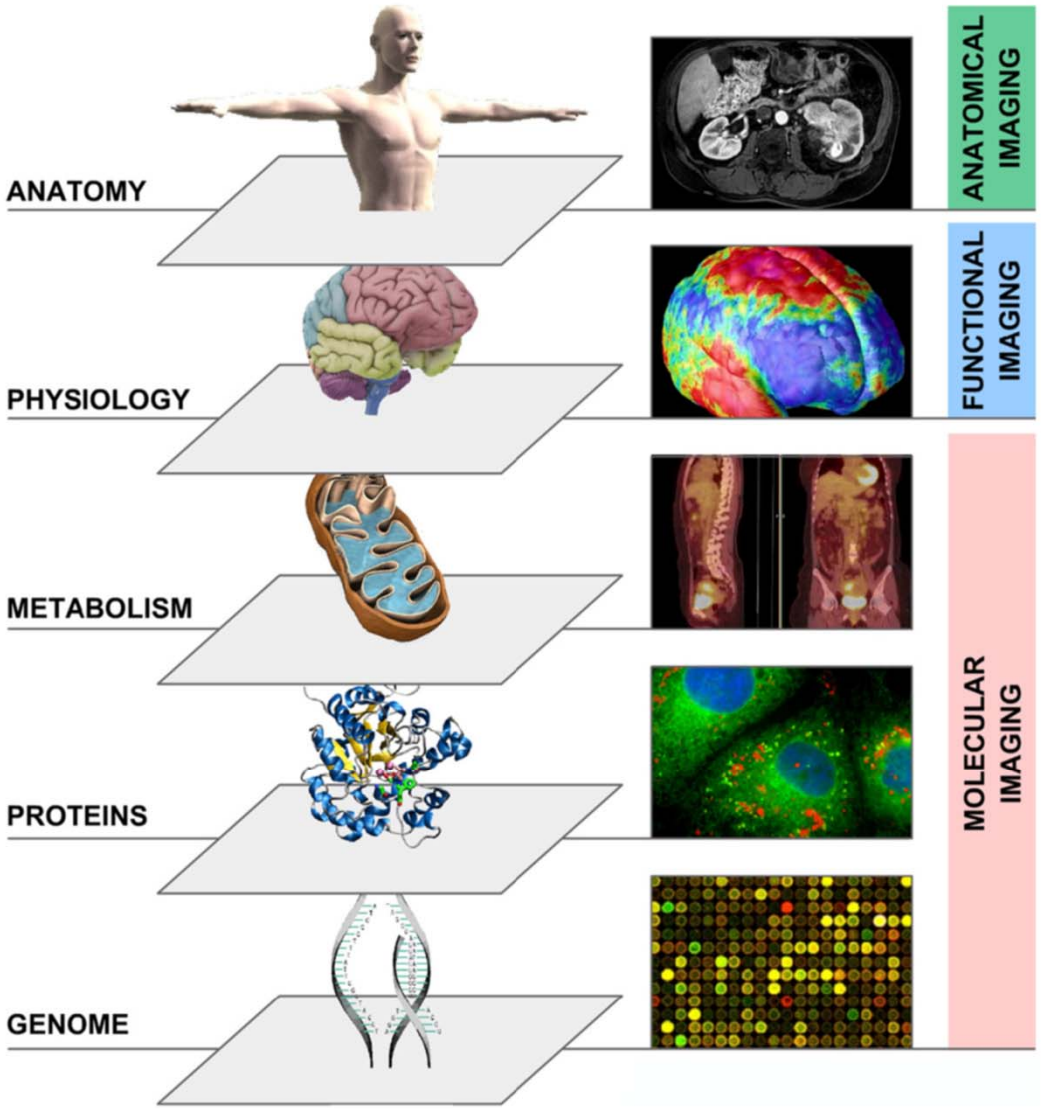


Fig. 2. Multilevel imaging: anatomical, functional, and molecular imaging.

European Journal of Cancer (2012) 48, 441–446

Available at www.sciencedirect.com

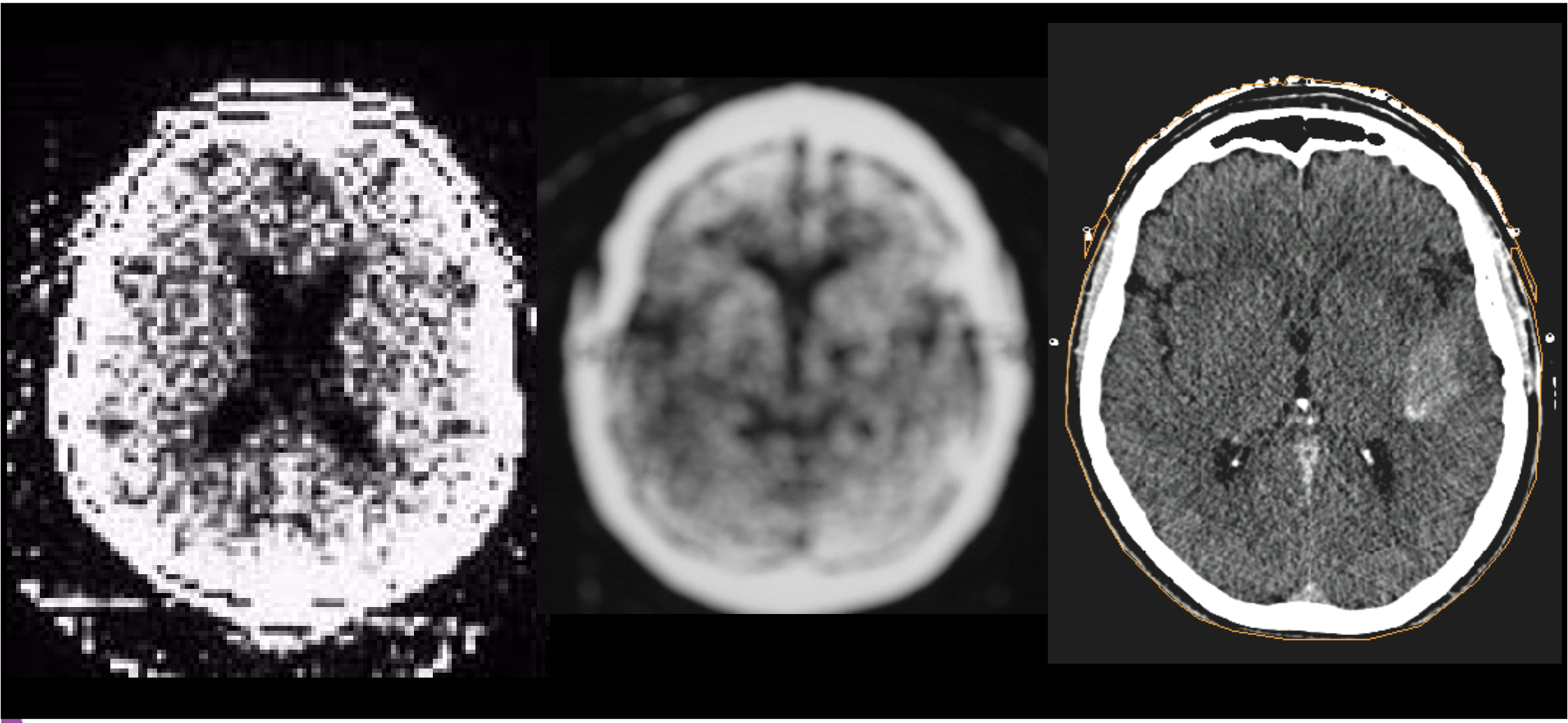
SciVerse ScienceDirect

journal homepage: www.ejconline.com

Radiomics: Extracting more information from medical images using advanced feature analysis

Philippe Lambin [a,*,e,f], Emmanuel Rios-Velazquez [a,e], Ralph Leijenaar [a,e], Sara Carvalho [a,e], Ruud G.P.M. van Stiphout [a,e], Patrick Granton [a,e], Catharina M.L. Zegers [a,e], Robert Gillies [b,e], Ronald Boellard [c,e], André Dekker [a,e], Hugo J.W.L. Aerts [a,d,e]

Imaging



Late 1970s 1980s 2003

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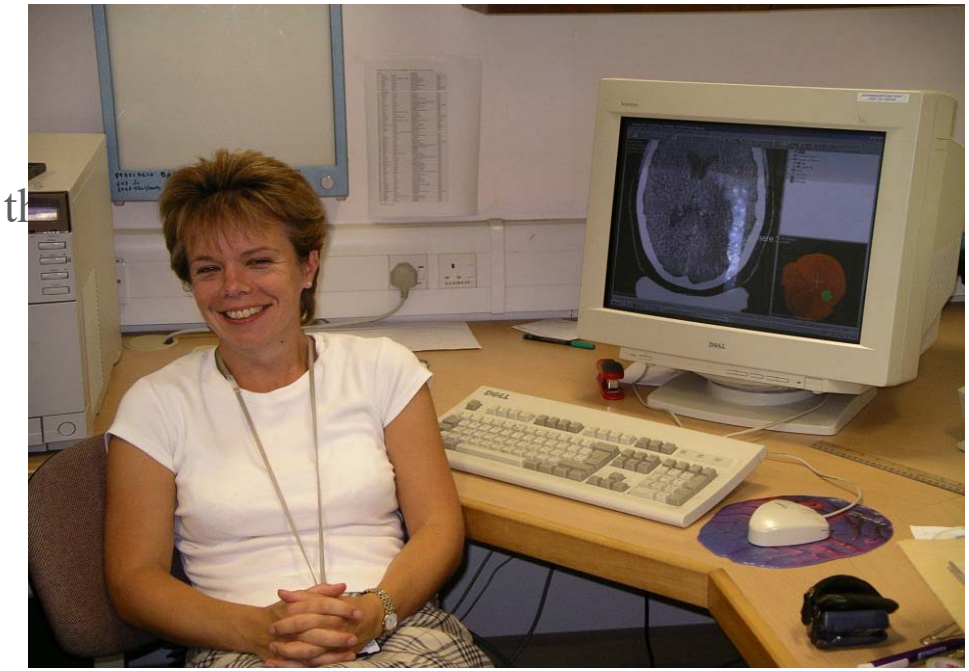
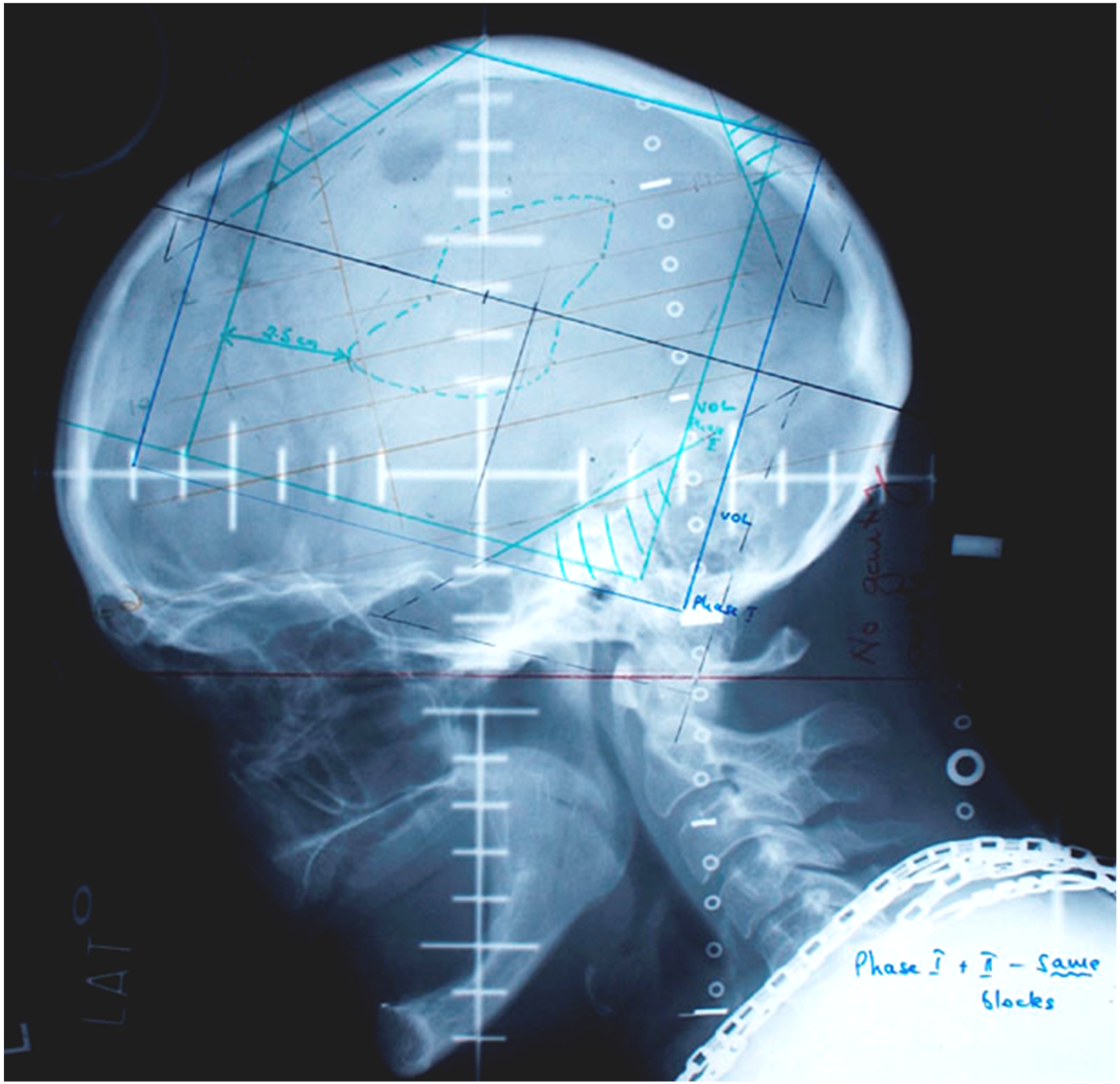
Target volume delineation

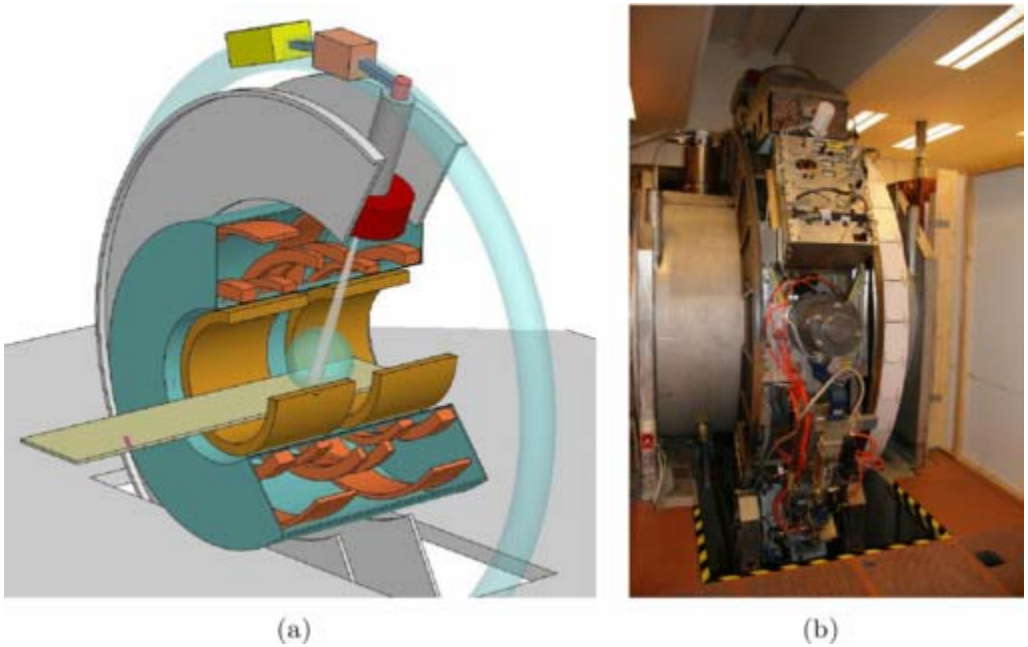
encils th



Old ‘square’ planning



MR linac



Crijns S, Raaymakers B.
From static to dynamic 1.5T MRI-linac prototype: impact of gantry position related magnetic field variation on image fidelity.
Phys Med Biol. 2014 Jul 7;59(13):3241-7

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MD Anderson

Protons

- St Clair et al
- IJROBP 2004; 58(3) 7

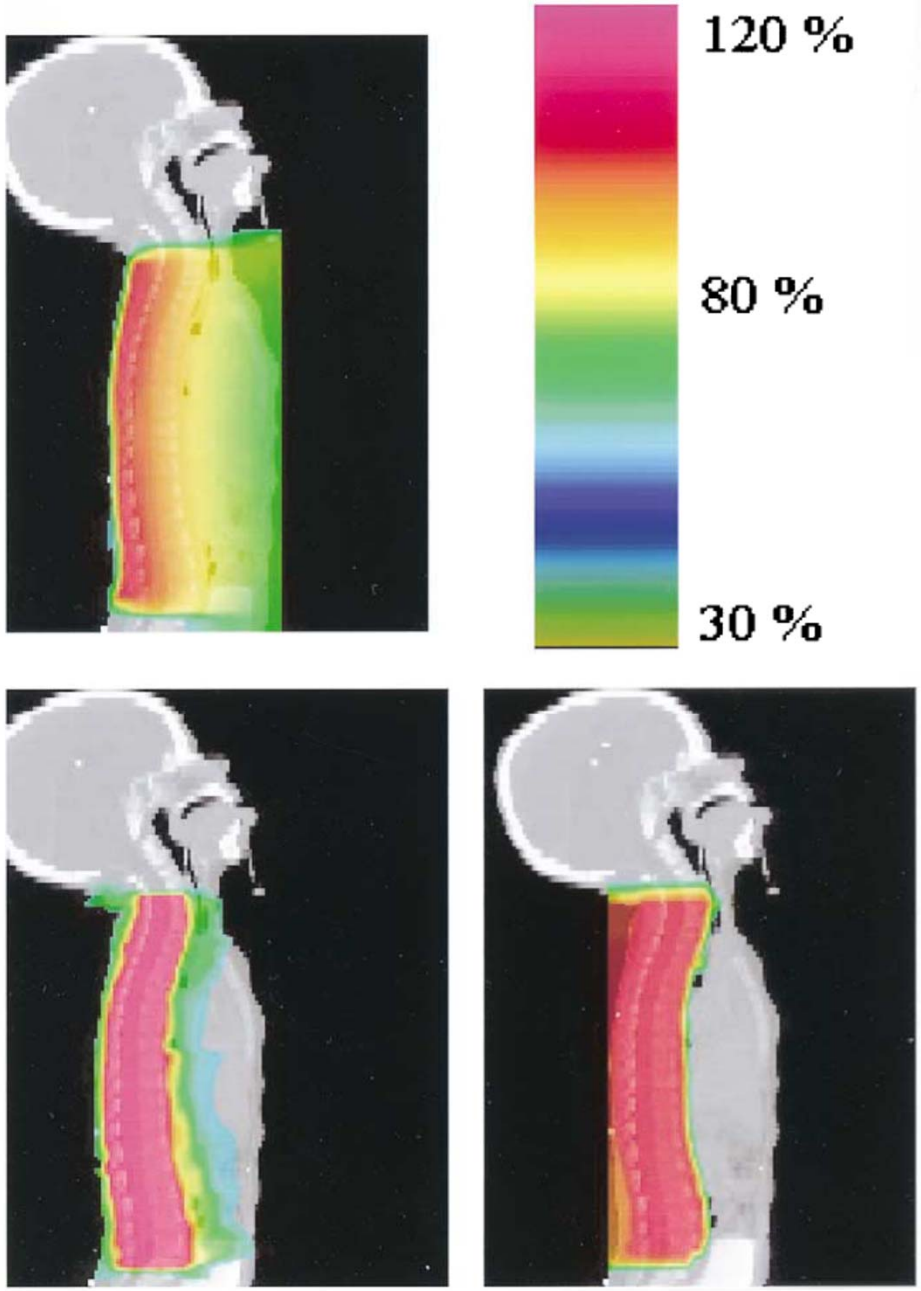

Fig. 3. Isodose distribution in the sagittal projection along the spinal column for (left) X-rays, (center) IMRT, and (right) protons.

Protons

- Proton beam therapy (PBT) can deliver
  - Lower exit doses – ideal for children
  - Possibly higher doses close to dose-limiting structures
    - Used for skull base and spinal chordoma

- Dose plans 'less tolerant' of variation in shape or density
  - Needs consideration of robustness

- Careful comparison is needed

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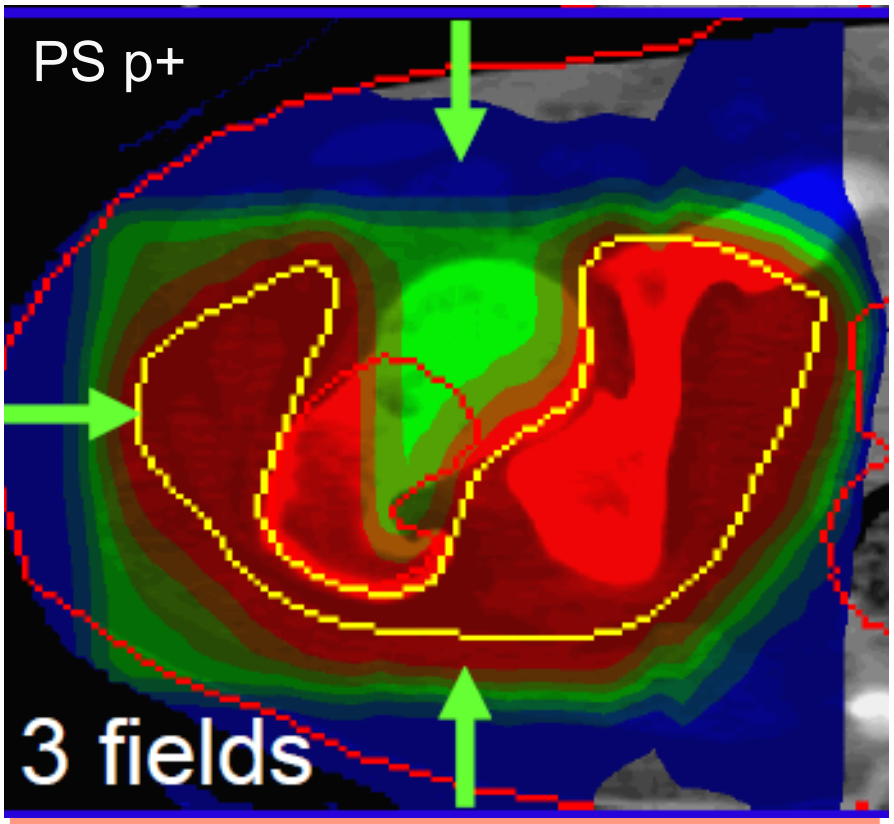
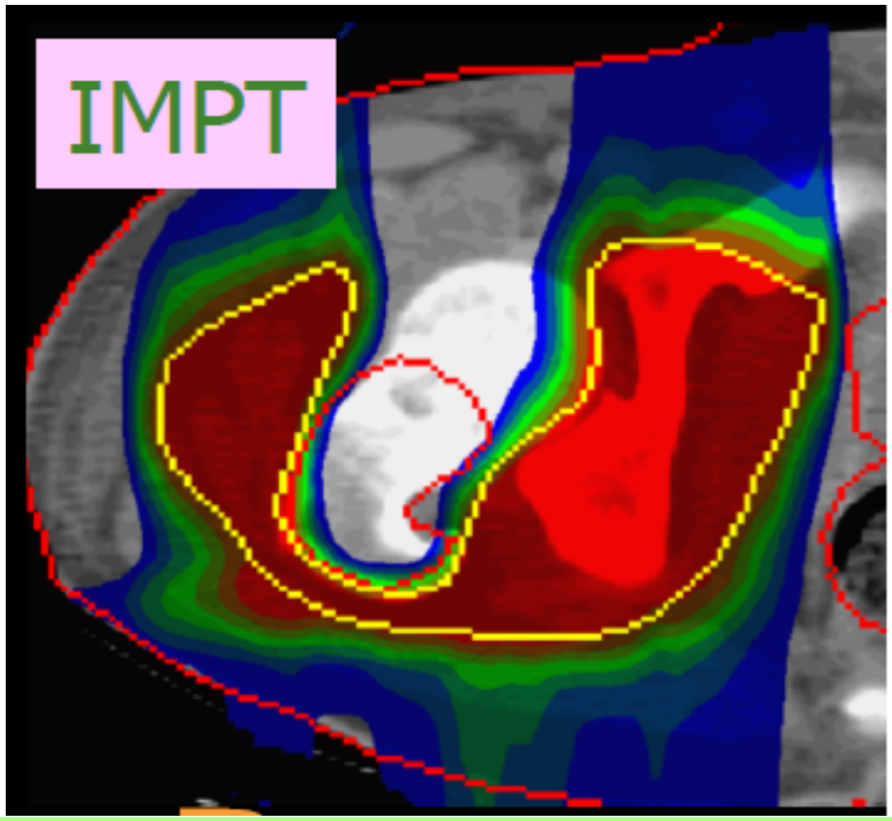
Proton RT plans

- Ewing's sarcoma



Passive scattered proton therapy

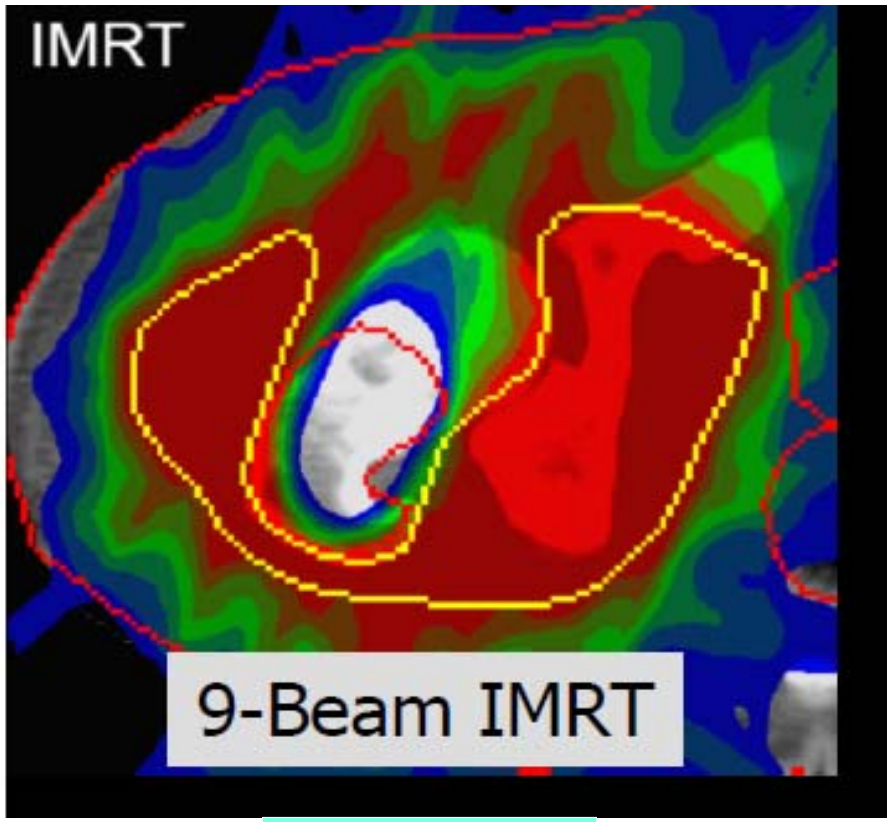


Intensity modulated proton therapy

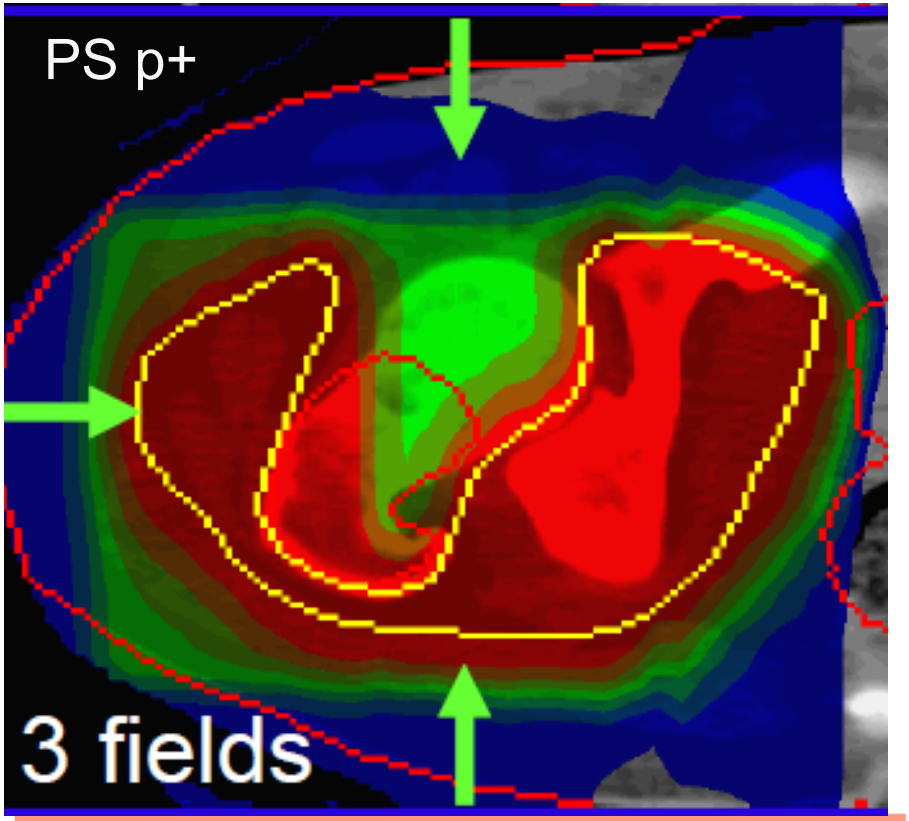
Courtesy of Prof Tony Lomax

Proton RT plans

- Ewing's sarcoma



X-ray IMRT



Passive scattered proton therapy

Courtesy of Prof Tony Lomax

Proton RT plans

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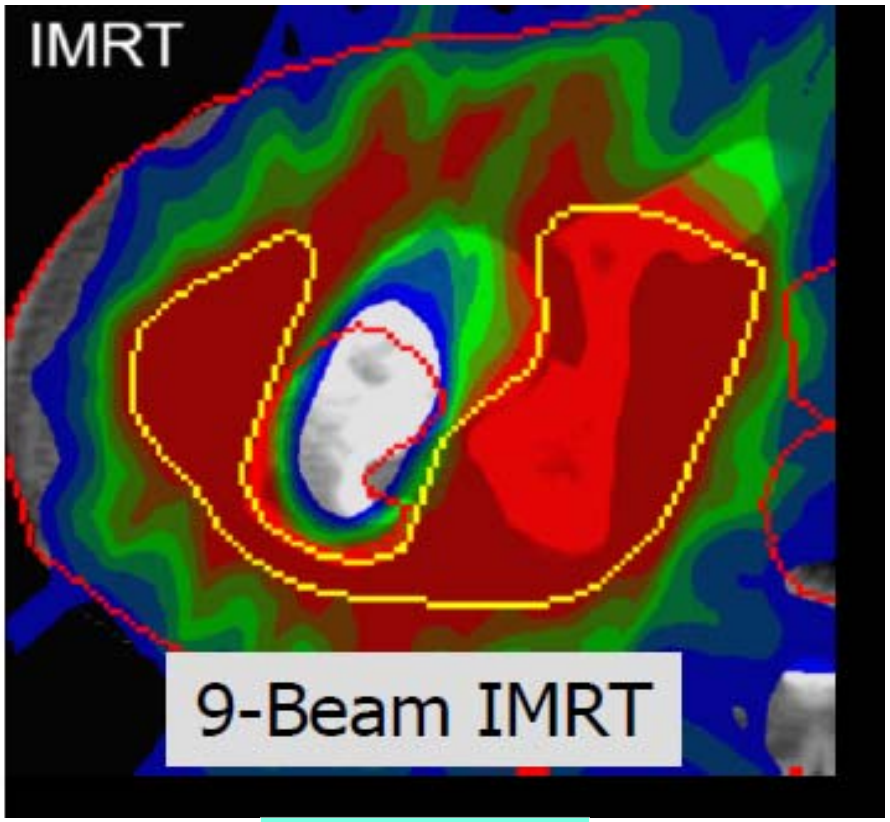
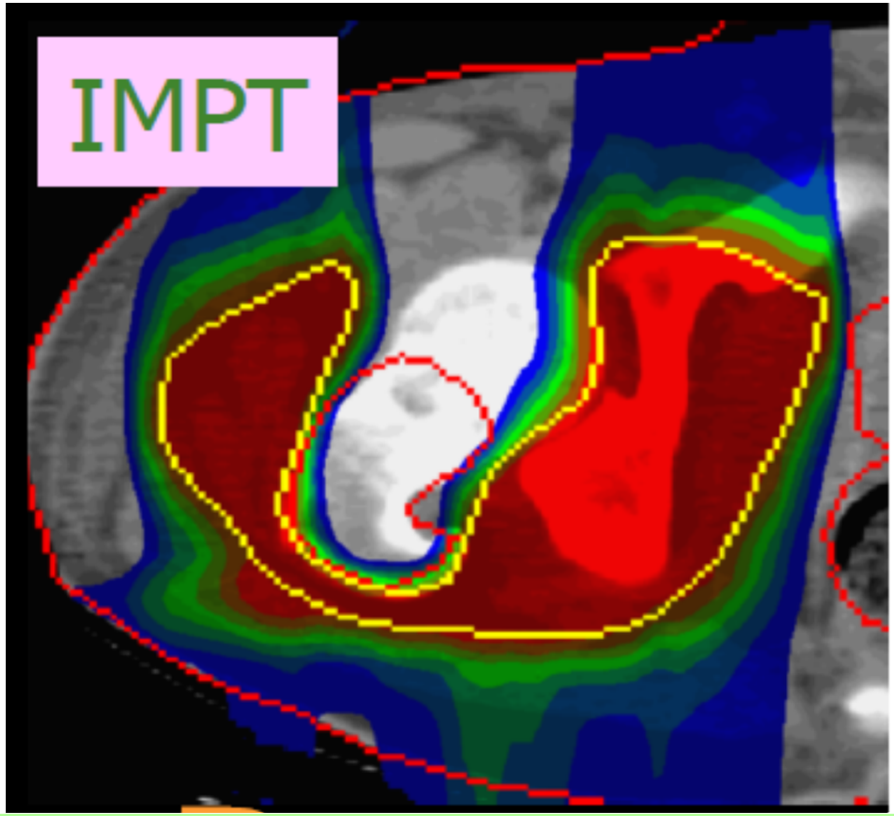


X-ray IMRT



Intensity modulated proton therapy

Courtesy of Prof Tony Lomax

CERN IdeaSquare Journal of Experimental Innovation, 2017; 1(1): 3
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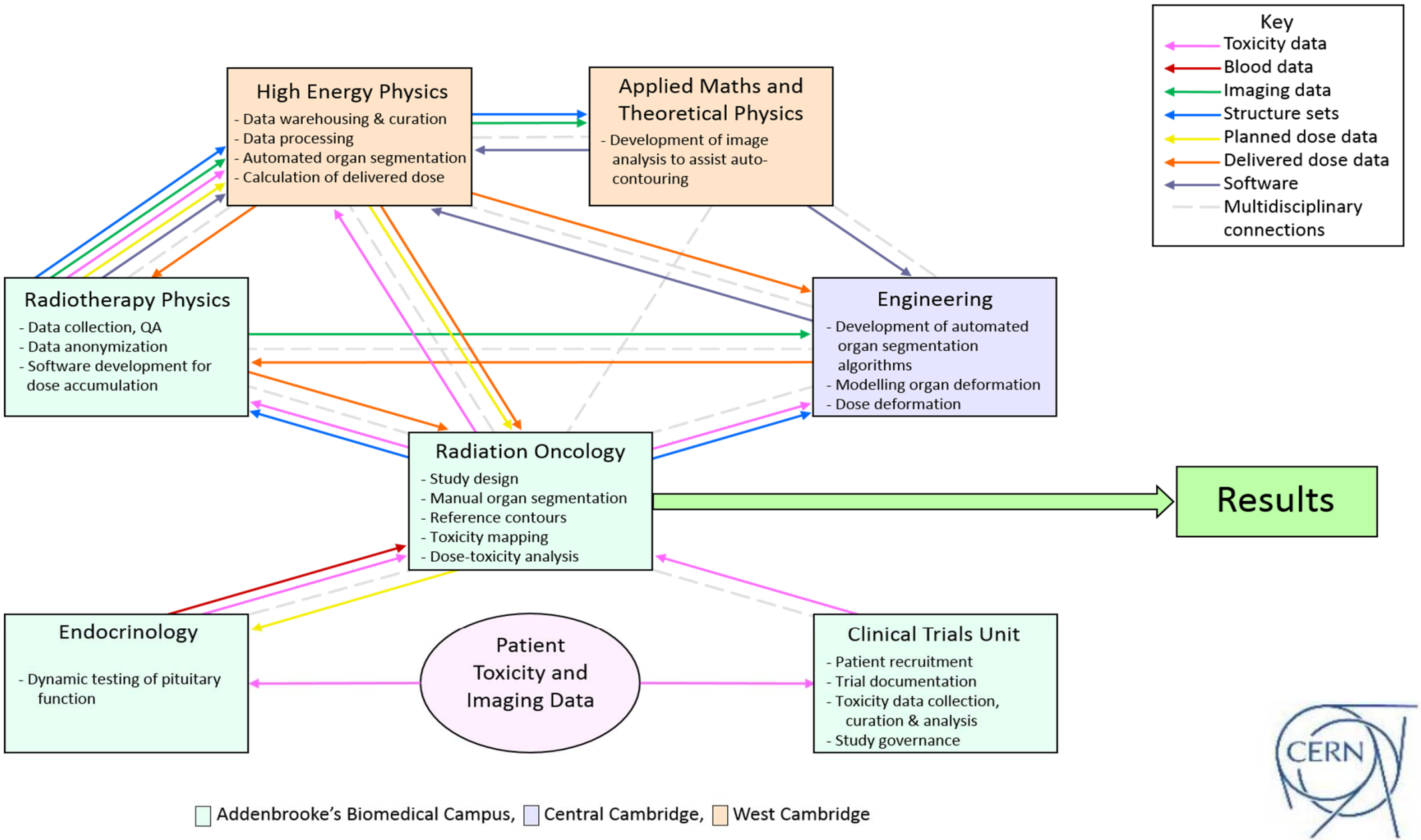
ORIGINAL ARTICLE

Applying physical science techniques and CERN technology to an unsolved problem in radiation treatment for cancer: the multidisciplinary 'VoxTox' research programme

Neil G Burnet[*1,2], Jessica E Scaife[1,2], Marina Romanchikova[1,3], Simon J Thomas[1,3], Amy M Bates[1,4], Emma Wong[1,4], David J Noble[1,4], Leila EA Shelley[1,5], Simon J Bond[1,6], Julia R Forman[1,6], Andrew CF Hoole[1,3], Gillian C Barnett[1,4], Frederic M Brochu[1,7], Michael PD Simmons[1,7], Raj Jena[1,2], Karl Harrison[1,7], Ping Lin Yeap[1,7], Amelia Drew[1,7], Emma Silvester[1,7], Patrick Elwood[1,7], Hannah Pullen[1,7], Andrew Sultana[1,7], Shannon YK Seah[1,7], Megan Z Wilson[1,7], Simon G Russell[1,4], Richard J Benson[1,4], Yvonne L Rimmer[1,4], Sarah J Jefferies[1,4], Nicolette Taku[1,2], Mark Gurnell[1,8], Andrew S Powlson[1,8], Carola-Bibiane Schönlieb[1,9], Xiaohao Cai[1,10], Michael PF Sutcliffe[1,7], Michael A Parker[1,7]

- Published as the first paper in the inaugural edition

VoxTox multi-disciplinary relationships



CERN

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- 33 patients, 30 fractions each
- Spinal cord autocontoured

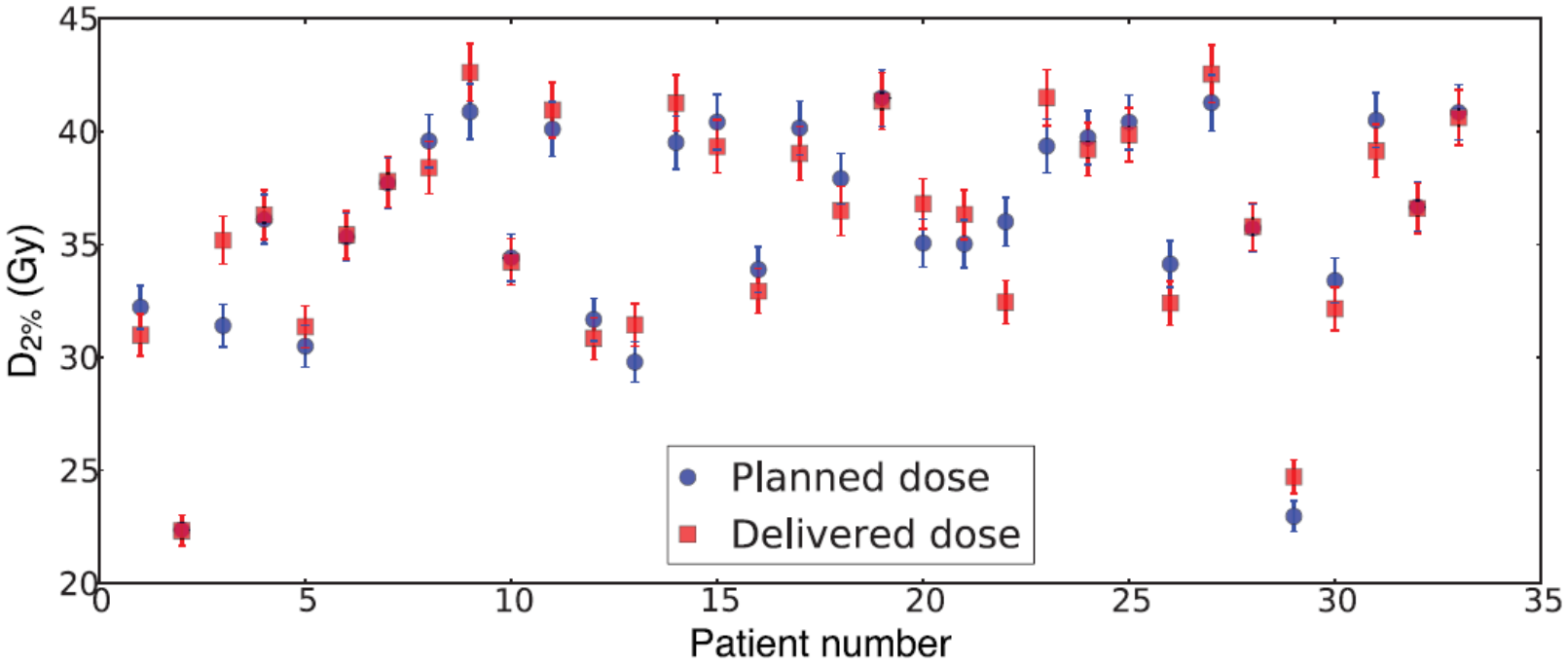
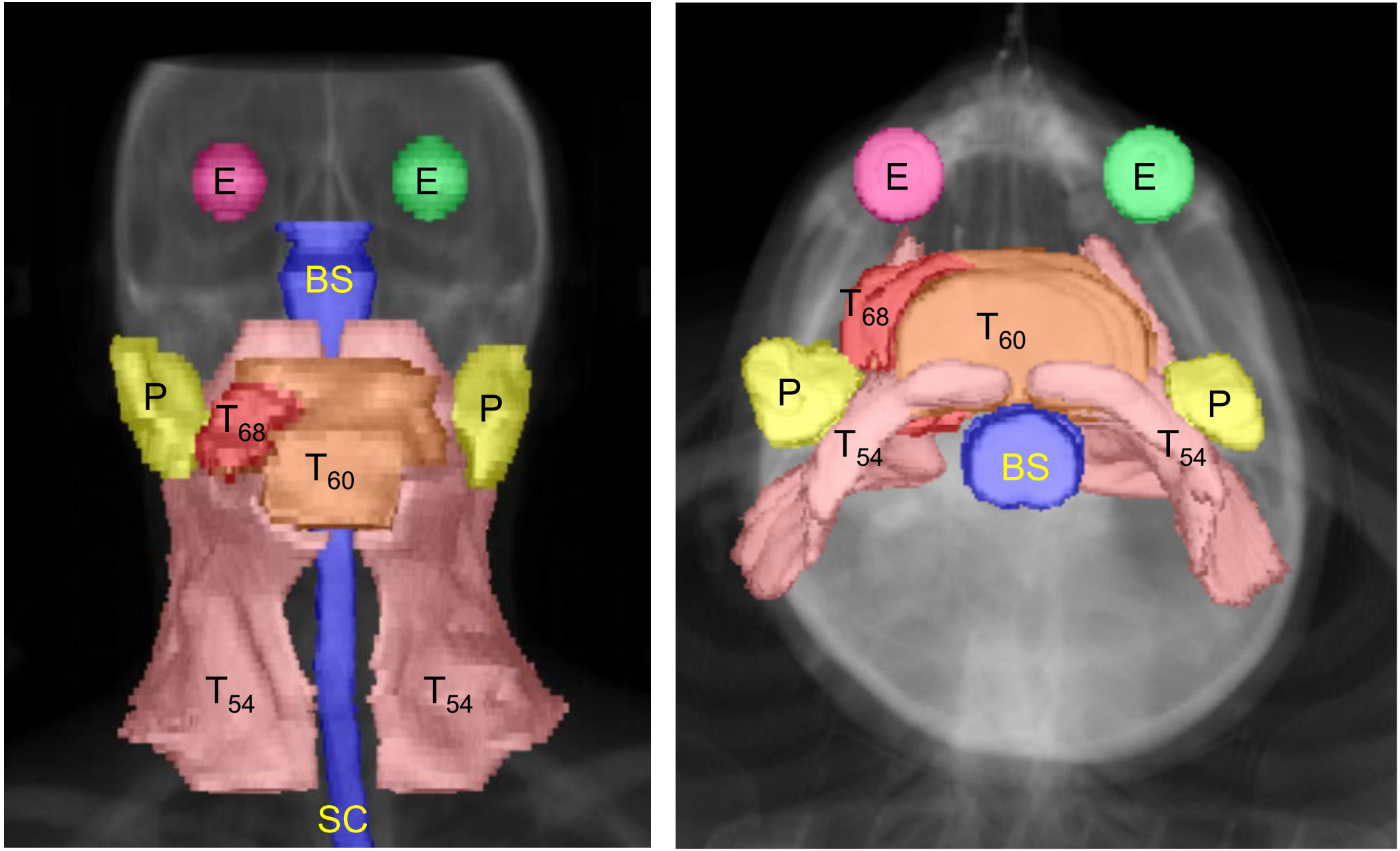


Figure 5. Near-maximum dose, $D_{2\%}$, to the spinal cord, as planned (blue circles) and as delivered (red squares), for 33 patients who underwent radiotherapy for head-and-neck cancers.



E	eye	T_{68}	target 68 Gy - primary
BS	brain stem	T_{60}	target 60 Gy - high risk adjacent to primary
SC	spinal cord	T_{54}	target 54 Gy - nodal areas
P	parotid gland		

Spares

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

- Case example
  - Pituitary adenoma (ie benign)
  - Absolute dose constraint - lens dose <6 Gy
  - Plan would deliver 7.5 Gy
  - "Oh, I thought we used 8 Gy, so I thought you didn't mean it"
  - Outcome …

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Underpinning science

- Finally
  - There is always still the physics …
  - There is always still the maths of margins too

Use the best tools for the job !

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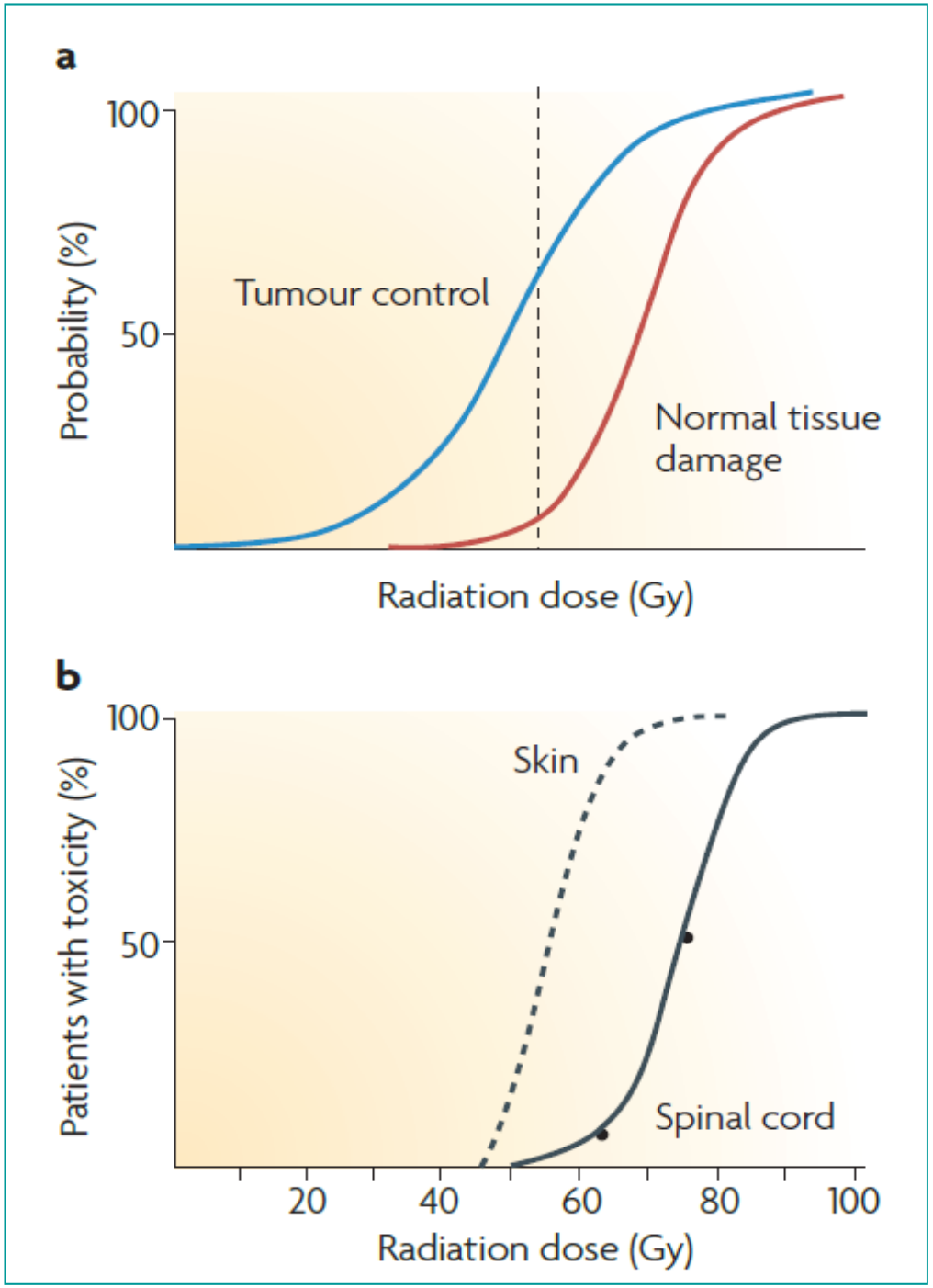
Marginal gains

- Small differences matter
  - To tumour
  - To normal tissues too

- Dose response curves are even steeper for many normal tissues than for tumours



- Barnett et al. Nat Rev Cancer 2009; 9(2): 134-42

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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%

- Red – danger !
  - Alter RT
- Yellow – some risk
  - ?
- White – balanced
  - Same
- Green –
  - ↑ dose
- Dark green
  - ↑↑ dose

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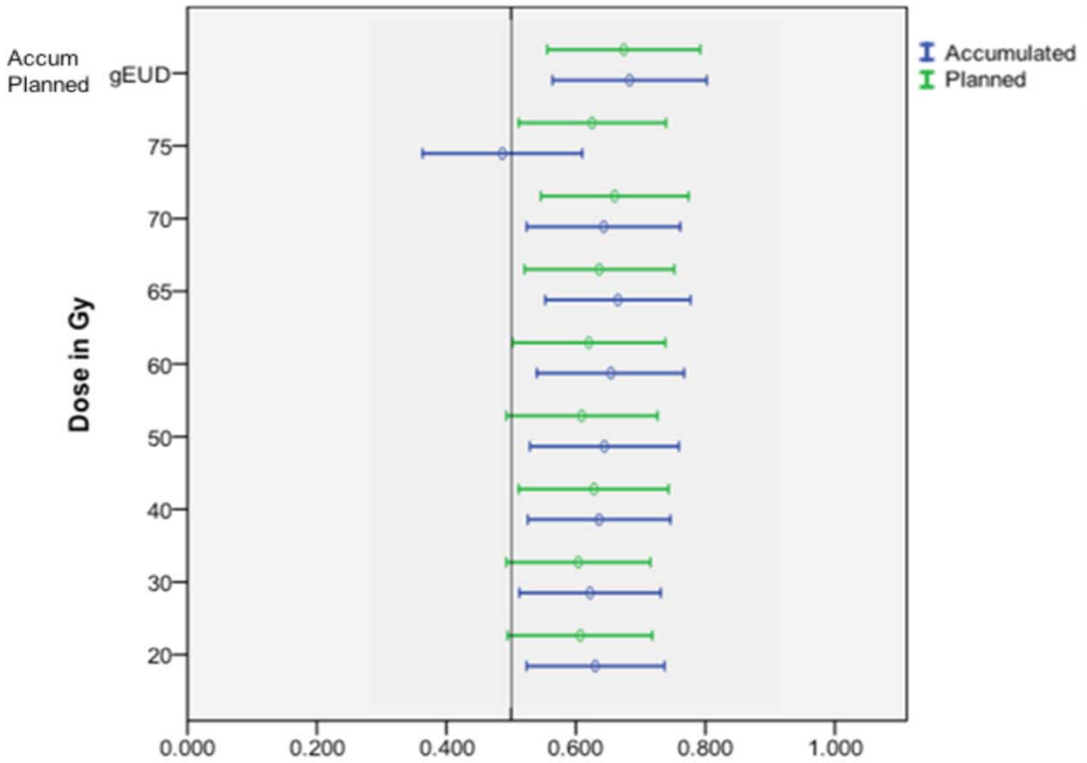
VoxTox - results

Dose Surface Map analysis



Result significant if:
- Mean > 0.6
- CI > 0.5

- DSM predictors better and D_A mostly better than planned
- DVH analysis *not* effective - poor prediction of bleeding

ROC AUC for rectal bleeding (CTCAE Grade ≥ 2)

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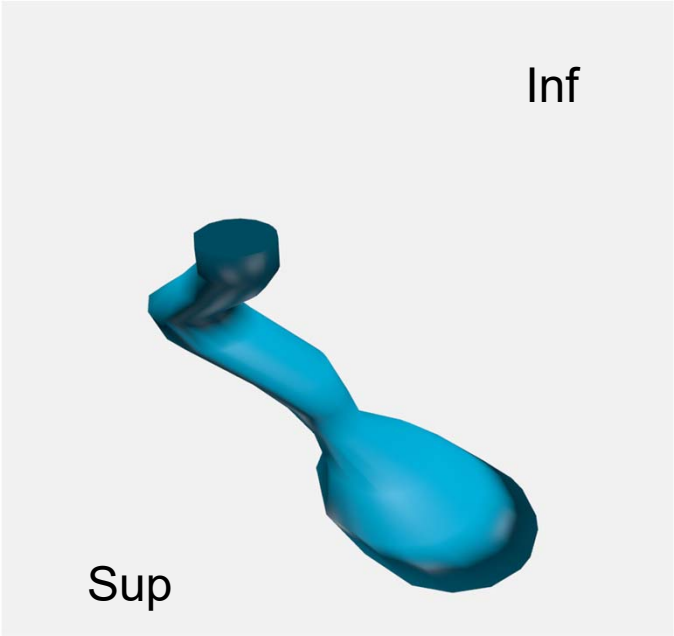
Understanding Delivered Dose

- Useful to understand more about the difference between the dose planned and the dose actually delivered

- Looking at the position of the rectum each day for the course of 37 fractions …



Inferior oblique view

'The Dancing Rectum'

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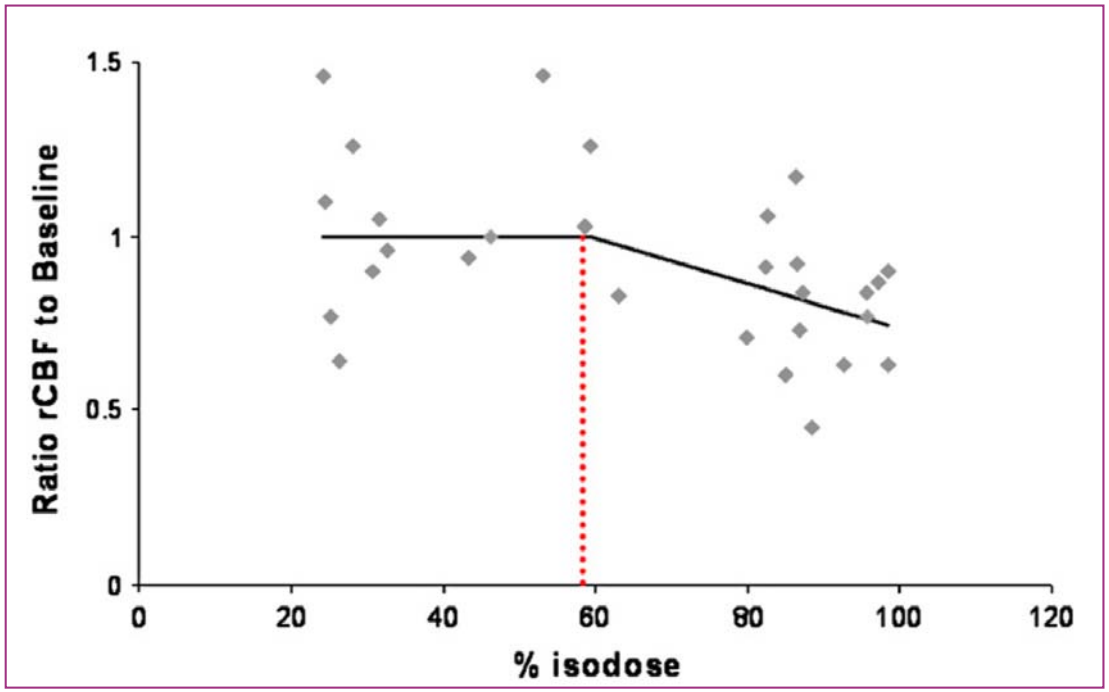
Normal tissue response data

- Investigating normal brain response



- Possible threshold at ~30Gy (in 30 fractions)

Price SJ et al. Clinical Oncology 2007; 19: 577-587

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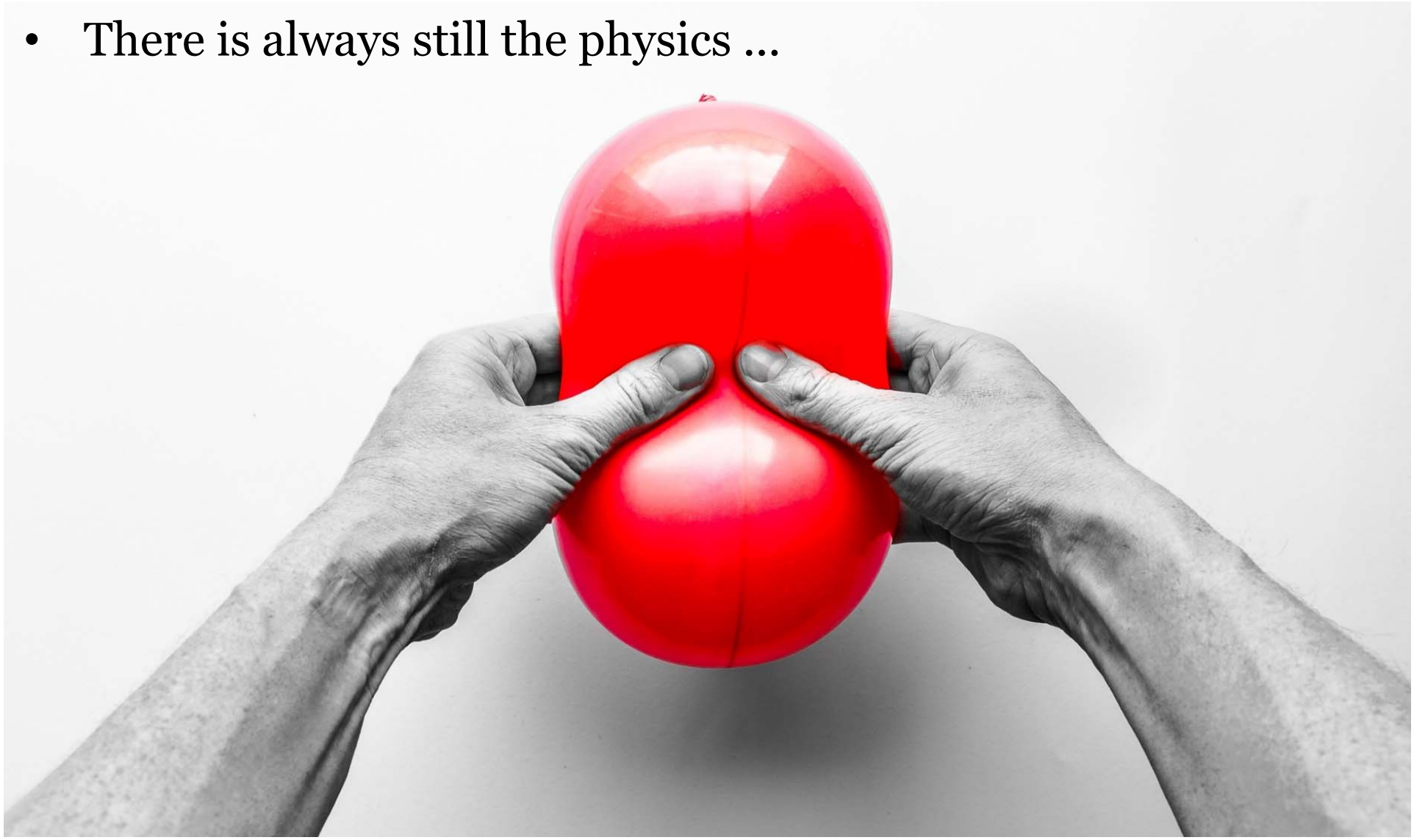
There is always still the physics ...

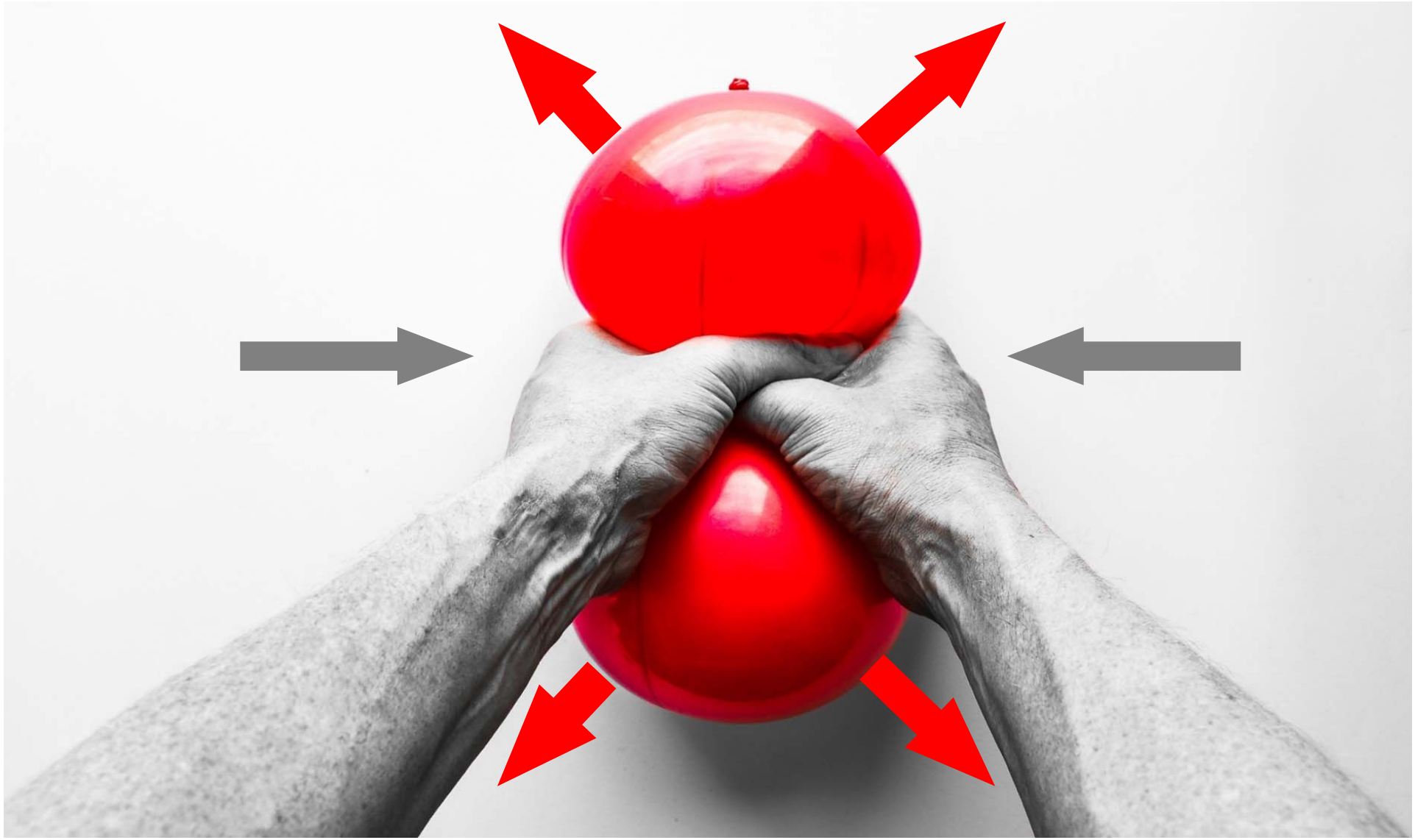
Sweeping the dose : dose *shaping*

- There is always still the physics …



Courtesy of Peter Voet

Sweeping the dose : dose *shaping*



Courtesy of Peter Voet

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